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Reactions of α-Substituted Glycine Derivatives with Stannanes in the Presence of Disulfides

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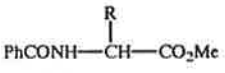
Abstract

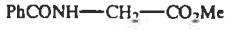
Reactions of α-bromo-, α-benzoyloxy- and α-methoxy-substituted glycine derivatives with stannanes afforded the corresponding α-centred glycinyl radical, which reacted with di-t-butyl disulfide and diphenyl disulfide by homolytic substitution to give the corresponding α-t-butylthio- and α-phenylthio-substituted glycine derivatives, respectively. The glycinyl radical reacted with dibenzyl disulfide by displacement of benzyl radical to give a mixed disulfide, which was subsequently reduced to the corresponding α-benzylthio-substituted glycine derivative. In related reactions of a cystine derivative the corresponding *S*-glycinylcysteine derivative was produced, indicating that, while the chemical integrity of disulfide bonds in cystine derivatives is likely to be affected in radical reactions of peptides, the reactions are suitable for exploitation in the synthesis of cross-linked amino acid derivatives.

Introduction

Recently we reported reactions of the α-substituted glycine derivatives (1b,c) with tributyltin hydride and allyltributyltin to give the reduced product (2) and the allylglycine derivative (3), respectively.[1] The products are the same as those obtained from analogous reactions of the α-bromoglycine derivative (1a)[2,3] but the benzoate (1b) and the methoxide (1c) have the comparative advantage of much greater stability. Although there had been two earlier reports of reduction of benzoates with tributyltin hydride,[4,5] to the best of our knowledge the reaction of the methoxide (1c) to give the reduced product (2) is the first example of



(1a) R = Br
(1b) R = OCOPh
(1c) R = OMe



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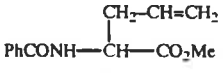

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[1] Easton, C. J., and Peters, S. C., *Tetrahedron Lett.*, 1992, **33**, 5581.
[2] Easton, C. J., Scharfbillig, I. M., and Tan, E. W., *Tetrahedron Lett.*, 1988, **29**, 1565.
[3] Baldwin, J. E., Adlington, R. M., Lowe, C., O'Neil, I. A., Sanders, G. L., Schofield, C. J., and Sweeney, J. B., *J. Chem. Soc., Chem. Commun.*, 1988, 1030; Easton, C. J., and Scharfbillig, I. M., *J. Org. Chem.*, 1990, **55**, 384.
[4] Khoo, L. E., and Lee, H. H., *Tetrahedron Lett.*, 1968, 4351.
[5] Redlich, H., Neumann, H.-J., and Paulsen, H., *Chem. Ber.*, 1977, **110**, 2911.

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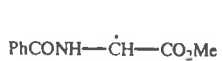
reduction of an ether with a stannane. In view of the unusual nature of the reactions of the glycine derivatives (1b,c) with stannanes we have now examined reactions of this type in more detail.

In preliminary work,[1] evidence of formation of the glycinyl radical (4) in reactions of the glycine derivatives (1b,c) with stannanes was obtained from reactions involving hexabutylditin and disulfides. More comprehensive studies in this area now confirm most of our earlier mechanistic hypotheses, but indicate that a conclusion regarding reaction of the radical (4) with dibenzyl disulfide was erroneous. The present work establishes that radical reactions of amino acid derivatives are likely to compromise the chemical integrity of disulfide links, which are important determinants of the three-dimensional structure of peptides, but reactions of this type can be exploited to produce new cross-linked amino acid derivatives.



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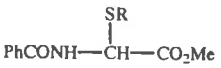
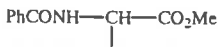


(5a) R = CMe_3
(5b) R = Ph
(5c) R = CH_2Ph
(5d) R = SCH_2Ph



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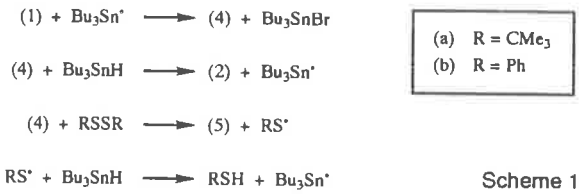
Results and Discussion

On treatment of the bromide (1a)[6] with tributyltin hydride (0·77 equiv.) and di-t-butyl disulfide (20 equiv.), in the presence of trimethyl benzene-1,3,5-tricarboxylate as an internal standard, analysis of the crude reaction mixture by h.p.l.c. and ^1H n.m.r. spectroscopy indicated that the reduced product (2) and the thioether (5a) were formed in yields of 85 and 5%, respectively. When diphenyl disulfide was used instead of di-t-butyl disulfide, the corresponding thioether (5b) was the predominant product. The ratio of production of the thioether (5b) to the glycine derivative (2) varied as a function of the concentration of diphenyl disulfide used in the reaction, halving four times consecutively as the concentration of the disulfide was halved successively.



Scheme 1

Presumably the mechanism of formation of the glycine derivative (2) is as shown in Scheme 1, involving the radical (4) as an intermediate. Formation of the thioethers (5a,b) is consistent with reaction of the radical (4) by homolytic substitution at sulfur in the corresponding disulfides, with abstraction of hydrogen atom by t-butylthio and phenylthio radical from tributyltin hydride completing the

[6] Kober, R., Papadopoulos, K., Miltz, W., Enders, D., Steglich, W., Reuter, H., and Puff, H., *Tetrahedron*, 1985, **41**, 1693.

radical chain processes (Scheme 1). As the concentration of diphenyl disulfide is reduced, reaction of the radical (4) by hydrogen atom abstraction from tributyltin hydride competes more effectively with that involving substitution of the disulfide. The yield of the phenyl thioether (5b) is greater than that of the t-butyl thioether (5a), from reactions carried out under comparable conditions, because substitution of the radical (4) at sulfur in diphenyl disulfide is more facile than the corresponding reaction with di-t-butyl disulfide, due to steric constraints.[7,8] The low yield of the thioether (5a) indicates that hydrogen abstraction by the radical (4) competes favourably with substitution of di-t-butyl disulfide, even in the presence of a large excess of the disulfide. In a separate experiment, the reduced product (2) was obtained in high yield by treatment of the thioether (5b) with tributyltin hydride but it is unlikely that it forms indirectly in this manner in the reactions of the bromide (1a) described above. That would require 2 mole equiv. of the stannane, whereas the yields of the products (2) and (5b) preclude that possibility, and the ratio of the thioether (5b) to the reduced product (2) would not depend directly on the concentration of diphenyl disulfide in the manner observed.

To increase the yield of the thioether (5a), hexabutylditin was used instead of tributyltin hydride in reactions with the bromide (1a) and di-t-butyl disulfide, in order to prevent the competing reduction process. Irradiation of the bromide (1a) in the presence of the disulfide (4 equiv.) and hexabutylditin (1 equiv.) gave the thioether (5a) in 50% yield, together with a 31% yield of a 1:1 mixture of the diastereomers of the dimer (6). The ratio of the thioether (5a) to the dimer (6) decreased to 6:7 when the concentration of the disulfide used in the reaction was quartered, and decreased further to 1:2 when one-eighth the concentration of the disulfide was used. Trace amounts of the reduced product (2) were also formed in these reactions.

The α-substituted glycine derivatives (1b) and (1c) were obtained by treatment of the bromide (1a) with benzoic acid and methanol, respectively, in the presence of triethylamine.[1] They each reacted with hexabutylditin and di-t-butyl disulfide, under photolysis, to give the thioether (5a) and the dimer (6). The reaction of the methoxide (1c) also afforded a low yield of the reduced product (2).

Production of the dimer (6) in these reactions is strong evidence of formation of the radical (4) through reaction of the α-substituted glycine derivatives (1a–c) with tributylstannyl radical, and indicates that coupling of the radical (4) competes with its reaction with the disulfide. The effect of the concentration of the disulfide used in the reaction on the ratio of the products (5a) and (6) is consistent with competing processes in which the rates of formation of the thioether (5a) and the dimer (6) are first and second order, respectively, with respect to the concentration of the radical (4). Presumably the reduced product (2) forms through hydrogen atom abstraction from the disulfide by the radical (4).[7]

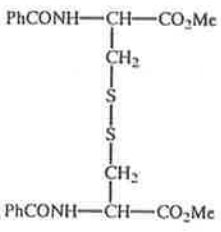
Earlier[1] we observed that photolysis of mixtures of either the benzoate (1b) or the methoxide (1c) with hexabutylditin and dibenzyl disulfide gave the thioether (5c). Production of the thioether (5c) was attributed to reaction of

[7] Pryor, W. A., and Platt, P. K., *J. Am. Chem. Soc.*, 1963, **85**, 1496.
[8] Pryor, W. A., and Guard, H., *J. Am. Chem. Soc.*, 1964, **86**, 1150; Ingold, K. U., and Roberts, B. P., 'Free Radical Substitution Reactions' (John Wiley: New York 1971).

the glycinyl radical (4) by substitution at sulfur of the disulfide but a more detailed examination of reactions involving this disulfide showed that conclusion to be incorrect. Treatment of the bromide (1a) with dibenzyl disulfide (5 equiv.) and tributyltin hydride (0·78 equiv.) gave the thioether (5c) in 4% yield and the reduced product (2) in 56% yield. When the concentration of the disulfide was repeatedly doubled, the ratio of the products (5c) and (2) did not double successively; this indicated that the products (2) and (5c) do not arise from competing processes analogous to those involved in reactions of di-t-butyl disulfide.

To investigate this anomaly the radical (4) was generated in an alternative manner, through hydrogen atom transfer to t-butoxy radical. Accordingly, a mixture of the glycine derivative (2), dibenzyl disulfide (0·2 equiv.) and excess di-t-butyl peroxide was photolysed. The reaction gave the dimer (6) and the mixed disulfide (5d), *albeit* in low yield, but there was no evidence of formation of the thioether (5c). Production of the dimer (6) indicates that the glycinyl radical (4) forms through hydrogen abstraction from the glycine derivative (2) by t-butoxy radical, and formation of the mixed disulfide (5d) can be attributed to homolytic displacement of benzyl radical from dibenzyl disulfide by the radical (4). The ratio of formation of the dimer (6) and the mixed disulfide (5d) was inversely proportional to the concentration of dibenzyl disulfide used in the reaction, consistent with the proposed reaction mechanism. The rate of reaction of the radical (4) to give the mixed disulfide (5d) depends on the concentration of dibenzyl disulfide, while the rate of dimerization of the radical (4) is independent of dibenzyl disulfide.

The radical (4) reacts with diphenyl and di-t-butyl disulfide with sulfur–sulfur bond homolysis, but with dibenzyl disulfide by carbon–sulfur bond scission. The different reaction pathways can be attributed to the relative stability and ease of formation of the corresponding carbon- and sulfur-centred radicals. Benzyl radical from dibenzyl disulfide is more stable than phenyl and t-butyl radical, while phenylthio radical from diphenyl disulfide is more stable than t-butylthio and benzylthio radical. It is thus apparent that the thioether (5c) does not form by direct reaction of the radical (4) with dibenzyl disulfide. Instead it now seems likely that the thioether (5c) forms via the mixed disulfide (5d), because photolysis of a mixture of hexabutylditin and the mixed disulfide (5d) gave the thioether (5c) in addition to the dimer (6) and the reduced product (2), but the exact mechanism of production of the thioether (5c) remains unclear.



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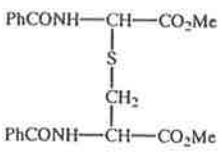

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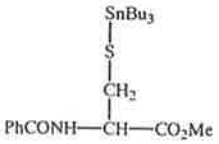

(9)

From the processes discussed above it is clear that disulfide links in peptides are likely to be susceptible to reaction with amino acid radicals. To investigate this more directly, each of the α-substituted glycine derivatives (1a–c) was photolysed

with hexabutylditin in the presence of the cystine derivative (7). Reaction of the bromide (1a) gave the thioether (8) in 37% yield and the dimer (6) in 27% yield; the benzoate (1b) gave the thioether (8) in 73% yield and the stannyl thioether (9), but none of the dimer (6), while the methoxide (1c) was inert under the reaction conditions, but the stannyl thioether (9) was also produced in this case. It is apparent that the bromide (1a) and the benzoate (1b) each react with photochemically generated tributylstannyl radical to give the glycinyl radical (4), which reacts by substitution with the cystine derivative (7) to give the thioether (8). The dimer (6) is formed through coupling of the glycyl radical (4) in the reaction of the bromide (1a). Presumably the dimer (6) does not form in the reaction of the benzoate (1b) because the concentration of the radical (4) is lower in this case, due to the reduced reactivity of the benzoate (1b) compared to the bromide (1a). The methoxide (1c) is the least reactive of the α-substituted glycine derivatives (1a–c), and in that case tributylstannyl radical reacts by substitution with the cystine derivative (7) to give the stannyl thioether (9), in preference to reaction with the methoxide (1c). The relative reactivity of the α-substituted glycine derivatives (1a–c) was confirmed in competitive experiments. The bromide (1a) reacted selectively on treatment of a mixture of the bromide (1a) and the benzoate (1b) with tributyltin hydride, while the benzoate (1b) was the more reactive when a mixture of the benzoate (1b) and the methoxide (1c) was treated with the stannane.

Khoo and Lee reported[4] that the ease of reduction of benzoates with tributyltin hydride depended on the stability of the radical intermediates. This is likely to be an important factor in the reactions of the benzoate (1b) with stannanes, and in the novel but analogous reactions of the methoxide (1c), because the radical (4) belongs to that class known as captodative,[9] merostabilized,[10] or push–pull stabilized[11] radicals. In addition, it is likely that the proactive effect of the amido and methoxycarbonyl substituents, to delocalize charge as well as unpaired spin density[12] that develops at the α-centre of the glycine derivatives (1b,c) in the transition states of their reactions with stannanes, plays an important role.

Experimental

General experimental details have been reported previously.[13] Unless otherwise stated, mass spectra were recorded in the electron impact mode. Organic solutions were dried with $MgSO_4$. Photolyses were performed in quartz reaction vessels by using a Philips 300-W sunlamp unless otherwise indicated. H.p.l.c. analyses were performed by using a Waters Z-module with either a Waters Nova-Pak C_{18} cartridge (10 cm by 8 mm) (column 1), eluting with methanol/water, or a μ-Porasil Radial-Pak cartridge (10 cm by 8 mm) (column 2), eluting with ethyl acetate/light petroleum.

[9] Viehe, H. G., Merenyi, R., Stella, L., and Janousek, Z., *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 917; Viehe, H. G., Janousek, Z., and Merenyi, R., *Acc. Chem. Res.*, 1985, **18**, 148.
[10] Baldock, R. W., Hudson, P., Katritzky, A. R., and Soti, F., *Heterocycles*, 1973, **1**, 67; *J. Chem. Soc., Perkin Trans. 1*, 1974, 1422.
[11] Balaban, A. T., *Rev. Roum. Chim.*, 1971, **16**, 725.
[12] Easton, C. J., Hutton, C. A., Rositano, G., and Tan, E. W., *J. Org. Chem.*, 1991, **56**, 5614.
[13] Easton, C. J., and Peters, S. C., *Aust. J. Chem.*, 1990, **43**, 87.

Reaction of N-*Benzoyl-α-bromoglycine Methyl Ester (1a) with Di-t-butyl Disulfide and Tributyltin Hydride*

A mixture of *N*-benzoyl-α-bromoglycine methyl ester (1a) (0·71 g, 2·6 mmol), di-t-butyl disulfide (10·0 ml, 52 mmol), tributyltin hydride (0·54 ml, 2·0 mmol), azobisisobutyronitrile (43 mg, 0·26 mmol) and trimethyl benzene-1,3,5-tricarboxylate (125 mg, 0·50 mmol) was heated at reflux in benzene (50 ml) for 16 h under an atmosphere of nitrogen; then it was concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy and h.p.l.c. (column 1), with reference to trimethyl benzene-1,3,5-tricarboxylate which was inert under the reaction conditions and was used as an internal standard, to establish the production of *N*-benzoylglycine methyl ester (2)[14] (85%) and *N*-benzoyl-α-t-butylthioglycine methyl ester (5a) (5%). The thioether (5a) was identified by comparison with an authentic sample, obtained as described below.

N-*Benzoyl-α-t-butylthioglycine Methyl Ester (5a)*

To an ice-cooled solution of the bromide (1a)[6] (0·40 g, 1·48 mmol) in dichloromethane (20 ml) was added 2-methylpropane-2-thiol (0·17 ml, 1·48 mmol). The reaction mixture was stirred in the cold for 0·25 h, then it was concentrated under reduced pressure. The residual oil was chromatographed on silica to give N-*benzoyl-α-t-butylthioglycine methyl ester* (5a), as colourless crystals from ethyl acetate/light petroleum (0·19 g, 46%), m.p. 89–91° (Found: C, 59·9; H, 6·9; N, 5·0. $C_{14}H_{19}NO_3S$ requires C, 59·8; H, 6·8; N, 5·0%). ^{1}H n.m.r. δ 1·45, s, 9H, CMe_3; 3·81, s, 3H, OMe; 5·79, d, *J* 9 Hz, 1H, Hα; 6·83, br d, *J* 9 Hz, 1H, NH; 7·43–7·82, m, 5H, ArH. Mass spectrum *m/z* 281 (M, 2%), 225 (43), 192 (29), 166 (19), 120 (9), 105 (100), 77 (86), 57 (48), 51 (33). ν_{max} 3340, 1748, 1640 cm^{-1}.

Reaction of N-Benzoyl-α-bromoglycine Methyl Ester (1a) with Diphenyl Disulfide and Tributyltin Hydride

A mixture of the bromide (1a) (0·7 g, 2·6 mmol), tributyltin hydride (0·54 ml, 2·0 mmol), diphenyl disulfide (2·69 g, 13 mmol), azobisisobutyronitrile (43 mg, 0·26 mmol) and methyl benzoate (0·19 g, 1·4 mmol) was heated at reflux in benzene (50 ml) for 16 h under an atmosphere of nitrogen; then it was concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy and h.p.l.c. (column 2), with reference to methyl benzoate which was inert under the reaction conditions and was used as an internal standard, to establish the production of *N*-benzoyl-α-phenylthioglycine methyl ester (5b) (25%) and *N*-benzoylglycine methyl ester (2) (70%). When the reaction was repeated with half the quantity of diphenyl disulfide (6·5 mmol) the ratio of formation of the thioether (5b) to the glycine derivative (2) decreased to 1:5·2; with double the quantity of the disulfide (26 mmol) the ratio increased to 1:1·4, and with quadruple the quantity of the disulfide (52 mmol) the ratio was 1:0·7. The thioether (5b) was identified by comparison with an authentic sample, obtained as described below.

N-*Benzoyl-α-phenylthioglycine Methyl Ester (5b)*

Triethylamine (0·36 g, 2·6 mmol) was added dropwise to a solution of the bromide (1a) (0·71 g, 2·6 mmol) and benzenethiol (0·27 ml, 2·6 mmol) in dichloromethane (25 ml). The mixture was stirred for 0·25 h, then it was washed with dilute hydrochloric acid (2×20 ml) and water (2×20 ml), dried and concentrated under reduced pressure. Distillation of the oil that formed on heating the residual solid gave N-*benzoyl-α-phenylthioglycine methyl ester* (5b), as colourless crystals after recrystallization from ethyl acetate/light petroleum (0·40 g, 51%), b.p. 250°/0·05 mm (block), m.p. 77·5–78° (Found: C, 63·7; H, 5·2; N, 4·7. $C_{16}H_{15}NO_3S$ requires C, 63·8; H, 5·0; N, 4·7%). ^{1}H n.m.r. δ 3·80, s, 3H, OMe; 5·95, d, *J* 8·5 Hz, 1H, Hα; 6·91, d, *J* 8·5 Hz, 1H, NH; 7·32–7·74, m, 10H, ArH. Mass spectrum *m/z* 301 (M, 2%), 192 (17), 105 (100), 77 (30). ν_{max} 3314, 1736, 1648 cm^{-1}.

[14] Burgess, V. A., Easton, C. J., Hay, M. P., and Steel, P. J., *Aust. J. Chem.*, 1988, **41**, 701.

Reaction of N-*Benzoyl-α-bromoglycine Methyl Ester (1a) with Di-t-butyl Disulfide and Hexabutylditin*

A mixture of the bromide (1a) (1·41 g, 5·2 mmol), di-t-butyl disulfide (4 ml, 21 mmol), hexabutylditin (1·8 ml, 5·2 mmol) and trimethyl benzene-1,3,5-tricarboxylate (0·50 g, 2·0 mmol) was irradiated at reflux in benzene (25 ml) for 14 h under an atmosphere of nitrogen; then it was cooled and concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy and h.p.l.c. (column 1), with reference to trimethyl benzene-1,3,5-tricarboxylate which was inert under the reaction conditions and was used as an internal standard, to establish the production of *N*-benzoyl-α-t-butylthioglycine methyl ester (5a) (50%), a 1 : 1 mixture of the diastereomers of dimethyl 2,3-dibenzamidobutanedioate (6)[14] (31%) and *N*-benzoylglycine methyl ester (2) (1%). When the reaction was repeated with one-quarter the quantity of di-t-butyl disulfide (5·2 mmol), the thioether (5a) (29%), the dimer (6) (35%) and the glycine derivative (2) (2%) were detected. Again halving the concentration of di-t-butyl disulfide (2·6 mmol) resulted in the formation of the thioether (5a) (22%), the dimer (6) (45%) and the glycine derivative (2) (2%).

N-*Benzoyl-α-benzoyloxyglycine Methyl Ester (1b)*

To a solution of the bromide (1a) (1·41 g, 5·2 mmol) and benzoic acid (0·63 g, 5·2 mmol) in carbon tetrachloride (50 ml) was added triethylamine (0·72 ml, 5·2 mmol). The mixture was stirred at room temperature for 0·25 h, then it was washed with dilute hydrochloric acid (2×80 ml) and water (100 ml), dried and concentrated under reduced pressure. The residual oil crystallized from ethyl acetate/light petroleum to afford *N*-benzoyl-α-benzoyloxyglycine methyl ester (1b) as colourless needles (1·26 g, 77%), m.p. 120–122° (lit.[15] 109–110°). ^{1}H n.m.r. δ 3·87, s, 3H, Me; 6·84, d, *J* 9 Hz, 1H, Hα; 7·4–8·1, m, 11H, NH and ArH. Mass spectrum *m/z* 313 (M, 0·1%), 254 (3), 122 (39), 105 (98), 77 (100), 51 (30). ν_{max} 3350, 1760, 1730, 1660 cm^{-1}.

Reaction of N-*Benzoyl-α-benzoyloxyglycine Methyl Ester (1b) with Di-t-butyl Disulfide and Hexabutylditin*

A mixture of the benzoate (1b) (0·40 g, 1·28 mmol), di-t-butyl disulfide (0·25 ml, 1·28 mmol) and hexabutylditin (0·65 ml, 1·28 mmol) was irradiated at reflux in benzene (25 ml) for 14 h under an atmosphere of nitrogen; then it was cooled and concentrated under reduced pressure. Chromatography of the residual oil, with ethyl acetate/light petroleum as eluent, afforded the thioether (5a) (0·10 g, 29%) and a 1 : 1 mixture of the diastereomers of the dimer (6) (60 mg, 24%).

N-Benzoyl-α-methoxyglycine Methyl Ester (1c)

To a solution of the bromide (1a) (4·2 g, 15·5 mmol) in methanol (50 ml) was added triethylamine (2·4 ml, 17·3 mmol), and the mixture was stirred at room temperature for 0·25 h, then it was concentrated under reduced pressure. The residual oil was dissolved in chloroform (50 ml); the solution was washed with dilute hydrochloric acid (2×75 ml) and water (75 ml), then dried and concentrated. The residual oil was distilled to give *N*-benzoyl-α-methoxyglycine methyl ester (1c) as a colourless solid (2·9 g, 84%), m.p. 86–87·5° (lit.[16] 86–87°). ^{1}H n.m.r. δ 3·55, s, 3H, α-OMe; 3·86, s, 3H, CO_2Me; 5·78, d, *J* 9 Hz, 1H, Hα; 7·1–7·9, m, 6H, NH and ArH.

Reaction of N-*Benzoyl-α-methoxyglycine Methyl Ester (1c) with Di-t-butyl Disulfide and Hexabutylditin*

A mixture of the methoxide (1c) (0·22 g, 1 mmol), di-t-butyl disulfide (0·19 ml, 1 mmol) and hexabutylditin (0·59 ml, 1 mmol) in benzene (30 ml) was irradiated for 14 h under an

[15] Bundgaard, H., and Buur, A., *Int. J. Pharm.*, 1987, **37**, 185.
[16] Zoller, U., and Ben-Ishai, D., *Tetrahedron*, 1975, **31**, 863.

atmosphere of nitrogen; then it was concentrated under reduced pressure. Chromatography of the residual oil, with ethyl acetate/light petroleum as eluent, afforded the thioether (5a) (51 mg, 19%), unreacted staring material (1c) (83 mg, 37%), the glycine derivative (2) (7 mg, 4%) and a 1:1 mixture of the diastereomers of the dimer (6) (23 mg, 12%).

Reaction of N-*Benzoyl-α-bromoglycine Methyl Ester (1a) with Dibenzyl Disulfide and Tributyltin Hydride*

A mixture of the bromide (1a) (0·71 g, 2·6 mmol), dibenzyl disulfide (3·19 g, 13·0 mmol), tributyltin hydride (0·54 ml, 2·0 mmol) and trimethyl benzene-1,3,5-tricarboxylate (0·13 g, 0·50 mmol) was heated at reflux in benzene (50 ml) for 16 h under an atmosphere of nitrogen; then it was cooled and concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy and h.p.l.c. (column 2), with reference to trimethyl benzene-1,3,5-tricarboxylate which was inert under the reaction conditions and was used as an internal standard, to establish the production of *N*-benzoylglycine methyl ester (2) (56%) and *N*-benzoyl-α-benzylthioglycine methyl ester (5c) (4%). When the reaction was repeated with double the quantity of dibenzyl disulfide (26 mmol), the thioether (5c) (18%) and the glycine derivative (2) (45%) were detected. Doubling again the concentration of the disulfide (52 mmol) resulted in the formation of the thioether (5c) (18%) and the glycine derivative (2) (67%). The thioether (5c) was identified by comparison with an authentic sample, obtained as described below.

N-*Benzoyl-α-benzylthioglycine Methyl Ester (5c)*

A solution of the bromide (1a) (0·46 g, 1·7 mmol) and phenylmethanethiol (0·20 ml, 1·7 mmol) in dichloromethane (15 ml) was purged with nitrogen for 5 h, then it was concentrated. The residual solid was recrystallized from dichloromethane/light petroleum to afford *N*-benzoyl-α-benzylthioglycine methyl ester (5c) as colourless needles (0·22 g, 41%), m.p. 69–70° (lit.[16] 67–69°). ^{1}H n.m.r. δ 3·79, s, 3H, Me; 3·91, d, *J* 14 Hz, 1H, SCH; 4·03, d, *J* 14 Hz, 1H, SCH′; 5·78, d, *J* 9 Hz, 1H, Hα; 6·80, d, *J* 9 Hz, 1H, NH; 7·21–7·65, m, 10H, ArH. Mass spectrum *m/z* 316 (M, 1%), 256 (24), 224 (59), 193 (27), 161 (34), 123 (13), 121 (12), 105 (100), 92 (61), 77 (84).

Reaction of N-*Benzoylglycine Methyl Ester (2) with Di-t-butyl Peroxide and Dibenzyl Disulfide*

A mixture of *N*-benzoylglycine methyl ester (2) (1·0 g, 5·2 mmol), di-t-butyl peroxide (4·4 ml, 24 mmol) and dibenzyl disulfide (0·26 ml, 1·0 mmol) in benzene (50 ml) under an atmosphere of nitrogen was photolysed in a Rayonet photochemical reactor fitted with 8 RPR 3500 lamps for 15 h; then it was concentrated under reduced pressure. Chromatography of the residual oil gave the unreacted starting material (2) (0·53 g, 53%) and *N*-benzoyl-α-benzyldithioglycine methyl ester (5d) as a colourless solid (7 mg, 2%), m.p. 99–116° (dec.) [Found: *m/z* 282·115 ($M^+ - HS_2$). $C_{17}H_{16}NO_3$ requires *m/z* 282·113]. ^{1}H n.m.r. δ 3·87, s, 3H, Me; 3·92, s, 2H, CH_2; 5·80, d, *J* 8 Hz, 1H, Hα; 7·1–7·6, m, 10H, ArH; 7·84, d, *J* 8 Hz, 1H, NH. Mass spectrum *m/z* 347 (M, 1%), 314 (2), 282 (6), 193 (2), 192 (4), 121 (17), 105 (100), 91 (59), 77 (93), 51 (71). Mass spectrum (fast atom bombardment) *m/z* 348 (M+1, 0·6%), 282 (2), 192 (7), 121 (5), 105 (100), 91 (27), 77 (20). ν_{max} 3074, 3052, 1744, 1674, 1604, 1517 cm^{-1}. Further chromatography afforded a 1:1 mixture of the diastereomers of the dimer (6) (120 mg, 12%).

In order to study the effect of the concentration of dibenzyl disulfide on the reaction, a mixture of *N*-benzoylglycine methyl ester (2) (80 mg, 0·4 mmol), di-t-butyl peroxide (0·35 ml, 1·9 mmol), dibenzyl disulfide (51 mg, 0·21 mmol) and trimethyl benzene-1,3,5-tricarboxylate (25 mg, 0·10 mmol) in benzene (4 ml) was treated as described above; then it was concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy, and the spectrum was integrated with reference to trimethyl benzene-1,3,5-tricarboxylate, which was inert under the reaction conditions and was used as an internal standard, to establish the production of the mixed disulfide (5d) (2%) and the dimer (6) (4%). When the reaction was repeated with double the quantity of dibenzyl disulfide (0·41 mmol), the mixed disulfide

(2%) and the dimer (1%) were detected. Reducing the concentration of dibenzyl disulfide (0·08 mmol) gave the mixed disulfide (2%) and the dimer (15%).

Reaction of N-*Benzoyl-α-benzyldithioglycine Methyl Ester (5d) with Hexabutylditin*

A mixture of *N*-benzoyl-α-benzyldithioglycine methyl ester (5d) (5 mg, 14 μmol), hexabutylditin (20 μl, 36 μmol) and trimethyl benzene-1,3,5-tricarboxylate (1 mg, 4 μmol) in benzene (1 ml) under an atmosphere of nitrogen was irradiated for 6 h, then it was concentrated under reduced pressure. Analysis of the residual oil by using ^{1}H n.m.r. spectroscopy and the trimethyl benzene-1,3,5-tricarboxylate as an internal standard indicated the formation of the thioether (5c) (55%), the dimer (6) (10%) and the reduced product (2) (25%).

Reaction of N-*Benzoyl-α-bromoglycine Methyl Ester (1a) with* N,N′-*Dibenzoylcystine Dimethyl Diester (7) and Hexabutylditin*

A mixture of the bromide (1a) (0·14 g, 0·52 mmol), *N,N′*-dibenzoylcystine dimethyl diester (7)[17] (0·37 g, 0·73 mmol), hexabutylditin (0·18 ml, 0·35 mmol) and trimethyl benzene-1,3,5-tricarboxylate (33 mg, 0·13 mmol) in benzene (30 ml) was irradiated at reflux under an atmosphere of nitrogen for 16 h; then it was cooled and concentrated under reduced pressure. The residual oil was analysed by using ^{1}H n.m.r. spectroscopy and h.p.l.c. (column 2), with reference to trimethyl benzene-1,3,5-tricarboxylate which was inert under the reaction conditions and was used as an internal standard, to establish the production of dimethyl 2,5-dibenzamido-3-thiahexanedioate (8)[13] (37%) and the dimer (6) (27%), each as a 1:1 mixture of diastereomers.

Reaction of N-*Benzoyl-α-benzoyloxyglycine Methyl Ester (1b) with* N,N′-*Dibenzoylcystine Dimethyl Diester (7) and Hexabutylditin*

A mixture of the benzoate (1b) (93 mg, 0·30 mmol), *N,N′*-dibenzoylcystine dimethyl diester (7) (0·21 g, 0·45 mmol) and hexabutylditin (0·10 ml, 0·20 mmol) at reflux in benzene (20 ml) under an atmosphere of nitrogen was irradiated for 15 h; then it was cooled and concentrated under reduced pressure. Chromatography of the residual oil afforded 2-benzamido-2-(methoxycarbonyl)ethylthiotributyltin (9) as a colourless oil (71 mg, 34%) [Found: *m/z* 472·099 ($M^+ - C_4H_9$). $C_{19}H_{30}NO_3SSn$ requires *m/z* 472·097]. ^{1}H n.m.r. δ 0·85–1·58, m, 27H, butyl H; 3·09, dd, *J* 4, 13 Hz, 1H, SCH; 3·18, dd, *J* 4, 13 Hz, 1H, SCH′; 3·81, s, 3H, OMe; 5·04, ddd, *J* 4, 4, 7 Hz, 1H, Hα; 7·13, d, *J* 7 Hz, 1H, NH; 7·42–7·86, m, 5H, ArH. Mass spectrum *m/z* 472 ($M - C_4H_9$, 7%), 269 (39), 177 (20), 105 (100), 77 (60). Further chromatography gave the thioether (8) as a 1:1 mixture of diastereomers (94 mg, 73%).

Treatment of N-*Benzoyl-α-methoxyglycine Methyl Ester (1c) with* N,N′-*Dibenzoylcystine Dimethyl Diester (7) and Hexabutylditin*

A mixture of the methoxide (1c) (0·26 g, 1·17 mmol), *N,N′*-dibenzoylcystine dimethyl diester (7) (0·83 g, 1·95 mmol) and hexabutylditin (0·40 ml, 0·78 mmol) at reflux in benzene (70 ml) under an atmosphere of nitrogen was irradiated for 15 h; then it was cooled and concentrated under reduced pressure. Analysis of the residual oil by using ^{1}H n.m.r. spectroscopy showed the presence of the unreacted starting materials (1c) and (7), and the stannyl thioether (9), but none of the thioether (8) or the dimer (6).

Competitive Reaction of N-*Benzoyl-α-bromoglycine Methyl Ester (1a) and* N-*Benzoyl-α-benzoyloxyglycine Methyl Ester (1b) with Tributyltin Hydride*

When a mixture of the bromide (1a) (7 mg, 26 μmol), the benzoate (1b) (2 mg, 6 μmol) and tributyltin hydride (7·0 μl, 27 μmol) was heated at reflux in benzene (0·5 ml) for 14 h,

[17] Lustus, E. L., *J. Org. Chem.*, 1967, **32**, 3425.

^{1}H n.m.r. spectroscopic analysis of the residue after concentration showed the presence of only *N*-benzoylglycine methyl ester (2) and unreacted benzoate (1b).

Competitive Reaction of N-Benzoyl-α-benzoyloxyglycine Methyl Ester (1b) and N-Benzoyl-α-methoxyglycine Methyl Ester (1c) with Tributyltin Hydride

When a mixture of the benzoate (1b) (4 mg, 13 μmol), the methoxide (1c) (3 mg, 13 μmol) and tributyltin hydride (5 μl, 19 μmol) was heated at reflux in benzene (5 ml) for 16 h, ^{1}H n.m.r. spectroscopic analysis of the residue after concentration showed the presence of only *N*-benzoylglycine methyl ester (2) and unreacted methoxide (1c).

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Reversal of Regiochemistry in the Synthesis of Isoxazoles by Nitrile Oxide Cycloadditions

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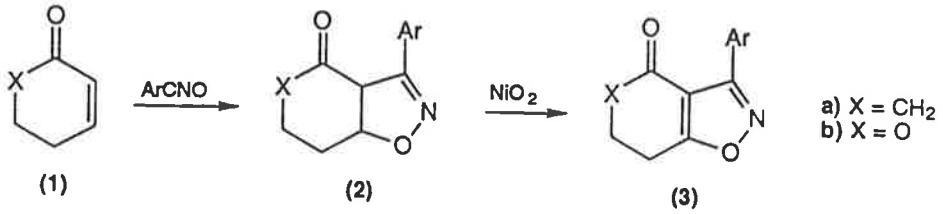
Abstract: The isoxazolines **2a**, **2b** and **8** obtained from nitrile oxide cycloadditions to cyclohex-2-enone **1a** and its analogues **1b** and **7** reacted with nickel peroxide to give the isoxazoles **3a**, **3b** and **9**. In contrast, the corresponding 2-bromocyclohex-2-enones **4a**, **4b** and **10**, prepared by bromination of the corresponding alkenes **1a**, **1b** and **7**, underwent nitrile oxide cycloadditions to afford the regioisomeric isoxazoles **6a**, **6b** and **12**, respectively.

Isoxazoles can be obtained by cycloaddition of nitrile oxides with alkynes or by dehydrogenation of the corresponding Δ^2-isoxazolines.[1] The latter method is particularly useful in ring systems where the alkynes are inaccessible. Using this approach we prepared the isoxazoline **2a** by reaction of 2,6-dichlorobenzonitrile oxide with cyclohex-2-enone **1a**.[2] The isoxazoline **2a** did not react with DDQ[3] or chloranil[4] under standard conditions used to dehydrogenate Δ^2-isoxazolines. However, nickel peroxide was found to be a mild and effective reagent for the preparation of the isoxazole **3a**[5] (Scheme 1).

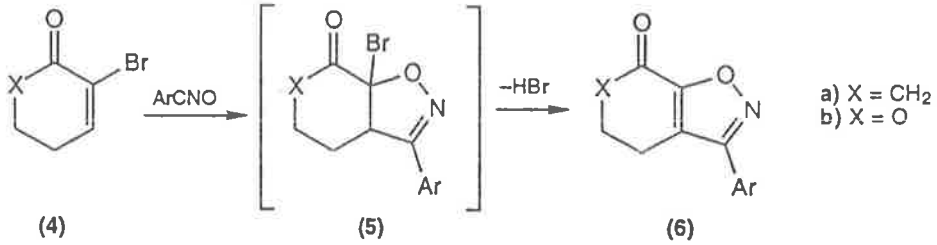


Scheme 1

The nitrile oxide cycloaddition to give the isoxazoline **2a** was regiospecific and the regiochemistry may be attributed to the electronic effect of the carbonyl substituent.[1] In order to obtain the regioisomeric isoxazole **6a** it was necessary to reverse the regiochemistry of the cycloaddition. We now report that the introduction of an α-bromo substituent on the alkene **1a** achieves this reversal. The regiocontrolled synthesis of each of the isoxazoles **3a**, **3b** and **9**, and **6a**, **6b** and **12** demonstrates the synthetic utility of this finding.

By a modification of Posner's method,[6] reaction of the alkene **1a** with bromine in dichloromethane at room temperature, followed by addition of triethylamine, gave the crystalline bromide **4a**.[7] Cycloaddition of

2,6-dichlorobenzonitrile oxide with this bromide **4a** led directly, and regiospecifically, to the isoxazole **6a**, the regioisomer of **3a**. Presumably the reaction proceeds through the cycloadduct **5a** which undergoes spontaneous dehydrobromination (Scheme 2).



Scheme 2

The structures of the isoxazoles **3a** and **6a** were confirmed by X-ray crystallographic analysis[8,9] (Figure 1) (See Table 1 for selected physical and spectroscopic data of key compounds).

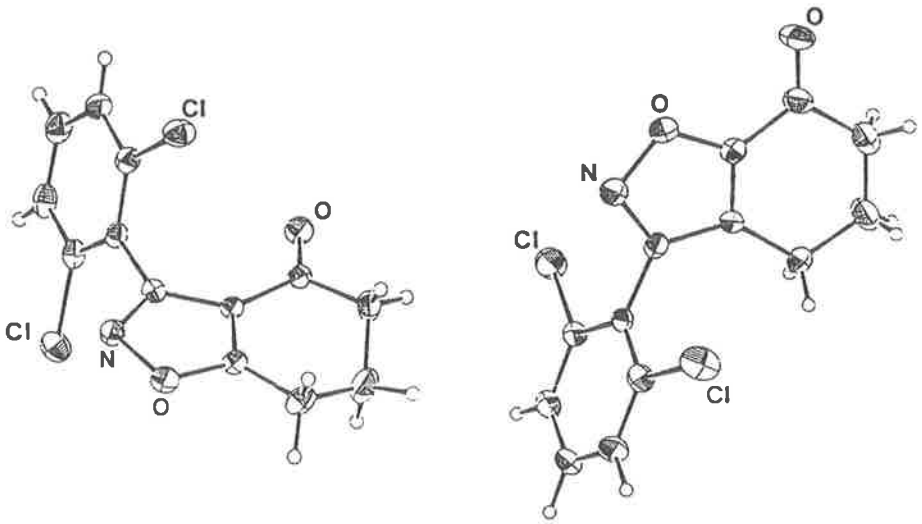


Figure 1. Molecular structures of **3a** and **6a**

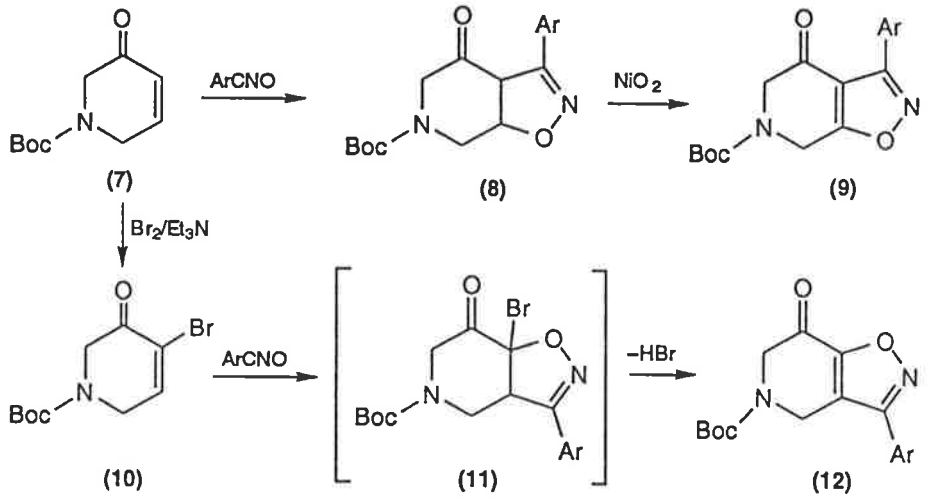
Presumably the steric influence of the bromo substituent of the alkene **4a** directs the regiochemistry of the cycloaddition of this compound, the reverse to that observed with the enone **1a**.

In further examples of this novel methodology (Schemes 1-3), the dihydropyranone **1b** and the dihydropyridinone **7**[10] underwent regiospecific cycloaddition to give the corresponding isoxazolines **2b** and **8**. Nickel peroxide again proved an effective dehydrogenating agent to convert the isoxazolines **2b** and **8** to the isoxazoles **3b** and **9**, respectively. Bromination[6] of the alkenes **1b** and **7** afforded the corresponding bromoalkenes **4b** and **10**. Each of these underwent regiospecific nitrile oxide cycloaddition to give the corresponding cycloadducts **5b** and **11**. The unisolated cycloadducts underwent spontaneous dehydrobromination to give the isoxazoles **6b** and **12**, which are regioisomers of the isoxazoles **3b** and **9** respectively.

Table 1. Selected physical and spectral data of key compounds

No.*	Yield%	M.p. (°C)	^{1}H n.m.r. δ ($CDCl_3$)
2a	40	150-1	1.7-2.7, m, 6H; 4.53, d, *J* 11.0 Hz, 1H; 5.26, dt, *J* 4.5, 11.0 Hz, 1H; 7.3-7.4, m, 3H
2b	64	159-62	2.26, m, 2H; 4.46, m, 1H; 4.69, ddd, *J* 3.0, 11.0, 11.0 Hz, 1H; 4.47, d, *J* 11.0 Hz, 1H; 5.32, m, 1H; 7.3-7.4, m, 3H
3a	65	166-9	2.31, m, *J* 6.0 Hz, 2H; 2.56, t, *J* 6.0 Hz, 2H; 3.14, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
3b	69	175-7	3.34, t, *J* 6.5 Hz, 2H; 4.69, t, *J* 6.5 Hz, 2H; 7.4-7.5, m, 3H
4b	75	32-4	2.57, dt, *J* 4.5, 6.0 Hz, 2H; 4.49, t, *J* 6.0 Hz, 2H; 7.30, t, *J* 4.5 Hz, 1H
6a	53	109-11	2.24, m, *J* 6.0 Hz, 2H; 2.63, t, *J* 6.0 Hz, 2H; 2.73, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
6b	50	106-7	2.89, t, *J* 6.0 Hz, 2H; 4.68, t, *J* 6.0 Hz, 2H; 7.4-7.5, m, 3H
7	56	oil	1.40, s, 9H; 4.05, s, 2H; 4.15, t, *J* 5.2 Hz, 2H; 6.10, dt, *J* 10.3, 5.2 Hz, 1H; 7.0, br, 1H
8	43	gum	1.52, s, 9H; 3.59, dd, *J* 15.1, 3.7 Hz, 1H; 3.90, d, *J* 19.0 Hz, 1H; 4.22, dd, *J* 15.1, 3.7 Hz, 1H; 4.53, m, 1H; 4.57, d, *J* 11.2 Hz, 1H; 5.26, dt, 11.2, 3.7 Hz, 1H; 7.25-7.45, m, 3H
9	87	75-78	1.52, s, 9H; 4.22, s, 2H; 5.00, s, 2H; 7.43, m, 3H
10	42	oil	1.48, s, 9H; 4.31, s, 4H; 7.42, m, 1H
12	25	foam	1.45, s, 9H; 4.38, s, 2H; 4.58, s, 2H; 7.45, m, 3H

* All new compounds gave satisfactory elemental analysis and spectral data



Scheme 3

In conclusion nickel peroxide has been shown to be a new reagent for the conversion of Δ^2-isoxazolines to isoxazoles, and α-bromination of cyclohex-2-enone and its analogues has been used to reverse the regiochemistry of cycloadditions with nitrile oxides providing direct regiocontrolled access to isoxazoles.

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8. Molecular structure of **3a**: monoclinic, $P2_1/c$, a = 10.065(2), b = 12.924(2), c = 10.369(2) Å, β = 107.99(1)°, Z = 4, R = 0.071 for 1172 observed data. Structural data have been submitted for publication in *Z. Krist.*
9. Molecular structure of **6a**: mono Cc, a = 21.688(4), b = 7.804(2), c = 14.921(2) Å, β = 103.14(1)°, Z = 8, R = 0.037 for 1515 observed data; absolute structure determined. Structural data have been submitted for publication in *Z. Krist.*
10. Prepared as follows: ethyl 3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (Imanishi, T.; Shin, H.; Hanaoka, M.; Momose, T.; Imanishi, I. *Chem. Pharm. Bull.* **1982**, *30*, 3617) was treated with sodium hydroxide in ethanol to afford the parent amine. This amine reacted with di-*tert*-butyl dicarbonate and triethylamine in dichloromethane to give the N-Boc protected compound which was then oxidised with PCC in chloroform to give **7**.

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Stereocontrolled Synthesis of β-Hydroxyphenylalanine and β-Hydroxytyrosine Derivatives

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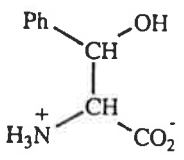
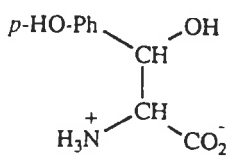
Abstract: Side-chain bromination of *N*-phthaloyl-(*S*)-phenylalanine and tyrosine derivatives, followed by treatment of the product bromides with silver nitrate in aqueous acetone, affords the corresponding (2*S*,3*R*)-β-hydroxy-α-amino acids, enantiospecifically and diastereoselectively. The diastereoselectivity depends on the carboxyl protecting group. *tert*-Butyl esters display greater stereoselectivity than the corresponding methyl esters, presumably as a result of a steric effect, while *N*-*tert*-butylamides react diastereospecifically due to a combination of steric and electronic effects.

INTRODUCTION

β-Hydroxyphenylalanine **1** and β-hydroxytyrosine **2** are important naturally occurring amino acids. They have been implicated as precursors in the biosynthesis of the hypertensive agents adrenalin and noradrenalin,[1] and of the antibiotic chloramphenicol,[2] and as components of peptidases[3] and esterases.[4] They have also been identified as components of biologically active cyclic peptides. As examples, vancomycin contains two residues of β-hydroxytyrosine **2**, one with the (2*S*,3*R*)-stereochemistry and the other with the (2*R*,3*R*)-stereochemistry,[5] lysobactin[6] contains β-hydroxyphenylalanine **1** of the (2*S*,3*R*)-stereochemistry, while phomopsin A[7] contains β-hydroxyphenylalanine **1** and bouvardin[8] contains a residue of β-hydroxytyrosine **2**, each with the (2*S*,3*S*)-stereochemistry. Hydroxy amino acids are also of interest as enzyme inhibitors.[9-11] For example, β-hydroxyphenylalanine **1** has been shown to inhibit *Neisseria gonorrhoeae* bacterial strains[10] and the lactose operon in *Escherichia coli*.[11]

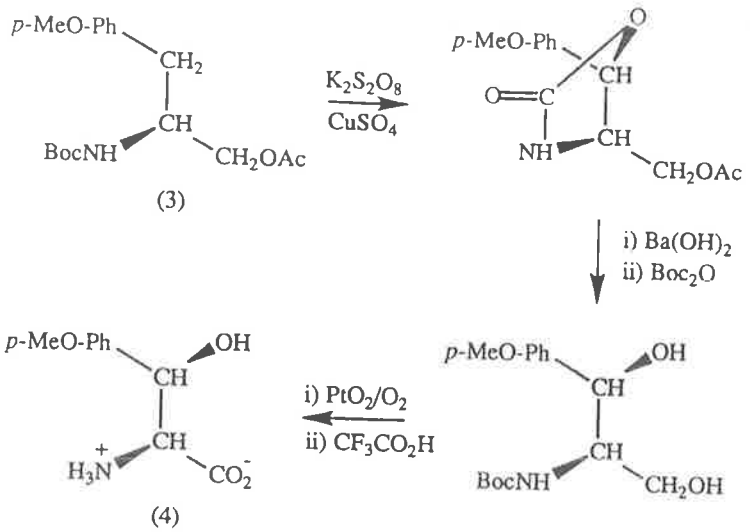


(1)



(2)

As a consequence of their biochemical activity, there is considerable interest in efficient routes for the stereocontrolled synthesis of the hydroxy amino acids **1** and **2**, and related compounds. Many asymmetric syntheses of β-hydroxy amino acids *via* condensation of glycine equivalents with aldehydes have been reported.[12-15] General and versatile methods have been developed by Schöllkopf *et al.*,[13] by Seebach and co-workers[14] and by Evans and Weber.[15] Although these procedures give products of high enantiomeric excess,



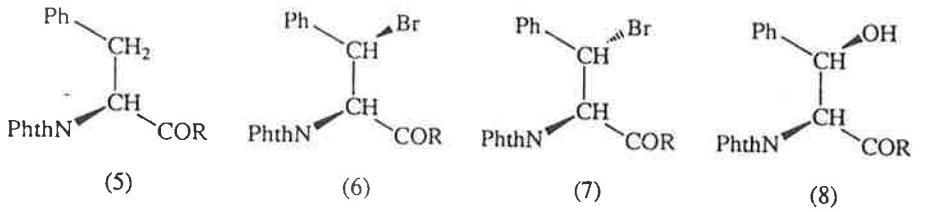
Scheme 1

there remains a strong demand for compounds which are enantiomerically pure. A method for the enantiospecific synthesis of β-hydroxy-α-amino acids from D-glucose has been reported by Rao *et al.*,[16] but the procedure involves many steps. Shimamoto and Ohfune[17] have developed a novel synthesis of (2*S*,3*R*)-β-hydroxy-*O*-methyltyrosine **4**, by direct benzylic oxidation of the *N*-*tert*-butoxycarbonyltyrosinol derivative **3** (Scheme 1). This procedure is limited by its lack of generality, however, with attempts to synthesize the (2*S*,3*R*)-isomer of β-hydroxyphenylalanine **1** *via* an analogous pathway being unsuccessful.[17]

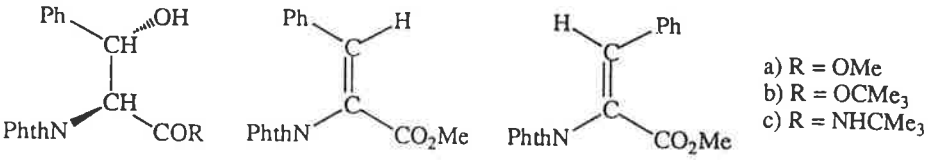
Recently we reported[18] preliminary details of a complementary method for the enantiospecific and diastereoselective synthesis of β-hydroxy-α-amino acids, which involved direct side-chain bromination of amino acid derivatives[19,20] followed by treatment of the product bromides with aqueous silver nitrate. For example, the phenylalanine derivative **5a** gave a 1:1 mixture of the diastereomeric bromides **6a** and **7a**, and that mixture gave a 5:1 mixture of the (2*S*,3*R*)-hydroxyphenylalanine derivative **8a** and the (2*S*,3*S*)-diastereomer **9a**. We now report our investigation of the origin of the stereoselectivity of the hydrolysis, together with full details of our earlier work. We also describe an unusual substituent effect which results in the enantiospecific and diastereospecific synthesis of derivatives of β-hydroxyphenylalanine and β-hydroxytyrosine.

RESULTS AND DISCUSSION

As previously reported,[20,21] treatment of the phenylalaninamide **5c** with *N*-bromosuccinimide gave a 1:1 mixture of the diastereomeric bromides **6c** and **7c**, which were separated by fractional crystallization. The absolute stereochemistry of the bromides **6c** and **7c** is predetermined by that of the phenylalanine derivative **5c**, while their relative stereochemistry has been determined previously, for each of the corresponding racemates, through their *anti*-elimination to dehydro amino acid derivatives on treatment with potassium fluoride.[21]



(5) (6) (7) (8)

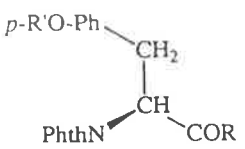


(9) (10) (11)

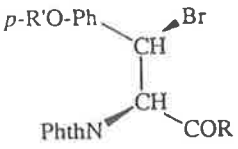
a) R = OMe
b) R = $OCMe_3$
c) R = $NHCMe_3$

Bromination of the ester **5a** gave a 1:1 mixture of the bromides **6a** and **7a**, which were separated by fractional crystallization. The relative stereochemistry of each of the bromo esters **6a** and **7a** was determined using the procedure reported[21] for determining the stereochemistry of the corresponding bromo amides **6c** and **7c**. Treatment of the bromo ester **6a** with potassium fluoride produced the (*Z*)-dehydrophenylalanine derivative **10** in 88% yield, but none of the (*E*)-isomer **11**. The structure and stereochemistry of the (*Z*)-alkene **10** was confirmed through X-ray crystallographic analysis.[22] Treatment of the bromide **7a** with potassium fluoride gave a 2:1 mixture of the (*E*)-dehydrophenylalanine derivative **11** and the (*Z*)-alkene **10**. The stereochemistry of the (*E*)-alkene **11** was confirmed by comparison of its ^{1}H NMR spectrum with that of the (*Z*)-isomer **10**, where the signal due to the vinylic proton of the (*E*)-alkene **11** occurred 0.9 ppm upfield from that of the (*Z*)-isomer **10**.[21,23] Presumably the bromides **6a** and **7a** undergo selective *anti*-elimination, on which basis the bromide **6a** that gave only the (*Z*)-alkene **10** can be assigned the (2*R*,3*R*)-stereochemistry, while the bromide **7a** which gave mainly the (*E*)-alkene **11** can be assigned the (2*R*,3*S*)-stereochemistry. Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **6a** and **7a** is reversed by comparison with that of the precursor **5a**, due to the change in the priority of substituents.

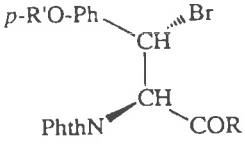
The *tert*-butyl ester **5b** and the tyrosine derivatives **12a** and **12b** reacted with *N*-bromosuccinimide to give the corresponding benzylic bromides **6b** and **7b**, **13a** and **14a**, and **13b** and **14b**. The diastereomeric bromophenylalanine derivatives **6b** and **7b** were separated by fractional crystallization. Although the diastereomeric tyrosine derivatives **13a** and **14a**, and **13b** and **14b**, were not completely separated, due to their instability, samples enriched in each stereoisomer were obtained by chromatography. The relative stereochemistry of the bromides **6b**, **7b**, **13a,b** and **14a,b** was determined by comparison of their ^{1}H NMR spectra with those of the bromides **6a,c** and **7a,c** (Table 1), which follow a general trend. The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2*R*,3*R*)-diastereomers **6a-c** and **13a,b** than for the corresponding (2*R*,3*S*)-diastereomers **7a-c** and **14a,b**. Also, the (2*R*,3*R*)-stereoisomers **6a-c** and **13a,b** exhibit the β-proton signal at higher chemical shift, the α-proton signal at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding (2*R*,3*S*)-diastereomers **7a-c** and **14a,b**. The cause of these effects may be explained by considering, as an example, the preferred conformation of each of the bromides **6a** and **7a** (Figure 1). It can be seen that with the



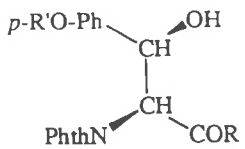
(12)



(13)



(14)



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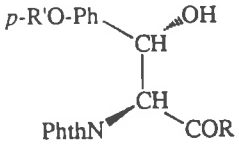


(16)

a) R = OMe, R' = Ac
b) R = $NHCMe_3$, R' = Ac
c) R = OMe, R' = H
d) R = $NHCMe_3$, R' = H

(2*R*,3*R*)-isomer **6a**, the phenyl group is situated close to the ester moiety, and the shielding effect of the phenyl group may explain the lower chemical shift of the signal due to the ester group protons. In the case of the (2*R*,3*S*)-bromide **7a**, π,π-stacking between the phthalimido and phenyl groups would cause rotation about the Cα-Cβ bond, such that the dihedral angle between the α- and β-protons would be less than 180°, thereby explaining the lower coupling constant observed between the α- and β-protons for the (2*R*,3*S*)-diastereomer **7a** than for the (2*R*,3*R*)-diastereomer **6a**.[24]

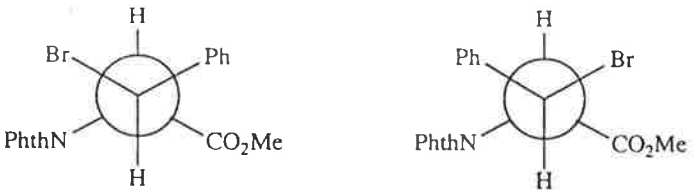
The reactions of the amino acid derivatives **5a-c** and **12a,b** to give the corresponding bromides **6a-c** and **7a-c**, and **13a,b** and **14a,b** occur without discernible asymmetric induction, presumably as a result of the low activation energy for halogen transfer to the intermediate benzylic radicals.[25]

Treatment of the (2*R*,3*R*)-bromophenylalanine derivative **6a** with silver nitrate in acetone/water[26] gave a

Table 1. ^{1}H NMR Spectral Data of the Bromides **6a-c**, **7a-c**, **13a,b** and **14a,b**.

Compound	Stereochemistry	Chemical shift (δ) / *J* (Hz)				
		α-H	β-H	$J_{\alpha,\beta}$	Carboxyl protecting group	OAc
6a	2*R*,3*R*	5.42	5.95	11.2	3.50	-
7a	2*R*,3*S*	5.55[a]	5.92[a]	10.5	3.80	-
6b	2*R*,3*R*	5.47	6.06	11.4	1.16	-
7b	2*R*,3*S*	5.49	5.85	10.4	1.48	-
6c	2*R*,3*R*	5.28	6.25	11.8	1.03	-
7c	2*R*,3*S*	5.32	6.04	11.4	1.43	-
13a	2*R*,3*R*	5.46	6.03	11.2	3.56	2.30
14a	2*R*,3*S*	5.56	5.93	10.4	3.81	2.19
13b	2*R*,3*R*	5.17	6.22	11.8	1.05	2.31
14b	2*R*,3*S*	5.30	6.08	11.5	1.38	2.20

[a]Assigned with the aid of proton-carbon heterocorrelation NMR spectroscopy.

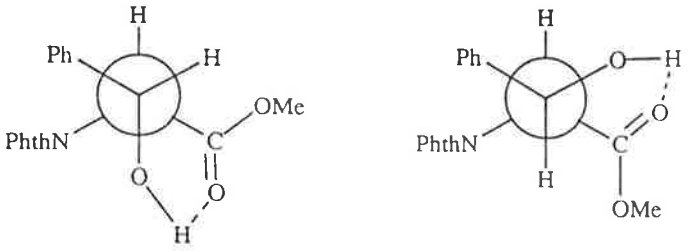


(6a) (7a)

Figure 1. Preferred Conformation of each of the Bromides **6a** and **7a**.

2:1 mixture of the (2*S*,3*R*)-β-hydroxyphenylalanine derivative **8a** and the (2*S*,3*S*)-diastereomer **9a**. The ratio of the diastereomers **8a** and **9a** was determined through analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Recrystallization of the crude product gave the (2*S*,3*R*)-β-hydroxyphenylalanine derivative **8a**, in 75% yield, the stereochemistry of which was determined using X-ray crystallographic analysis.[27] Purification of the (2*S*,3*S*)-alcohol **9a** in the recrystallization mother liquor was achieved using HPLC. Treatment of the (2*R*,3*S*)-bromide **7a** under the same conditions as described for the hydrolysis of the (2*R*,3*R*)-bromide **6a** gave only the (2*S*,3*R*)-hydroxyphenylalanine derivative **8a**, in 93% yield.

The ^{1}H NMR spectra of the hydroxyphenylalanine derivatives **8a** and **9a** follow a general trend displayed in the spectra of the alcohols **8a-c**, **9a-c**, **15a,c** and **16a,c**, described herein (Table 2). The chemical shifts of the signals due to the α– and β–protons and the carboxyl protecting groups of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** are significantly higher than those of the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**. Also, the (2*S*,3*R*)-isomers **8a-c** and **15a,c** each exhibit a smaller coupling constant between their α- and β-protons than is observed for the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**. The correlation of the coupling constants with the stereochemistry may be attributed to the alcohols **8a-c**, **9a-c**, **15a,c** and **16a,c** adopting hydrogen-bonded conformations, as shown in Figure 2 for the phenylalanine derivatives **8a** and **9a**. The dihedral angle between the α- and β-protons of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** in these conformations would be approximately 60°, whereas that angle would be approximately 180° for the (2*S*,3*S*)-isomers **9a-c** and **16a,c**, hence the coupling constant between the α- and β-protons of each of the (2*S*,3*R*)-isomers **8a-c** and **15a,c** would be smaller than that observed for each of the corresponding (2*S*,3*S*)-isomers **9a-c** and **16a,c**.



(8a) (9a)

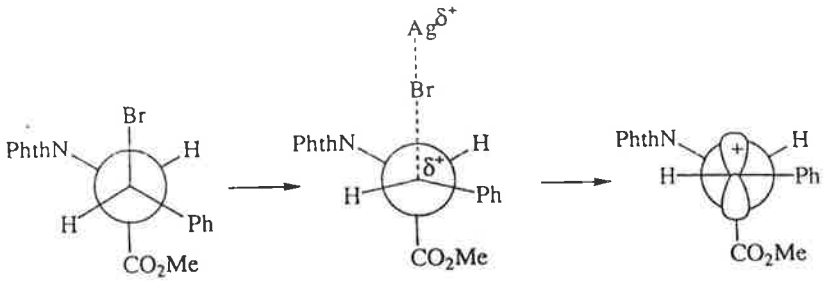
Figure 2. Hydrogen-bonded Conformation of each of the Alcohols **8a** and **9a**.

Table 2. ^{1}H NMR Spectral Data of the Alcohols **8a-c**, **9a-c**, **15a-d** and **16a,c**.

Compound	Stereochemistry	Chemical shift (δ) / *J* (Hz)				
		α-H	β-H	$J_{\alpha,\beta}$	Carboxyl protecting group	OAc
8a	2*S*,3*R*	5.51	5.71	4.6	3.86	-
9a	2*S*,3*S*	5.02	5.52	8.4	3.79	-
8b	2*S*,3*R*	5.44	5.67	4.6	1.52	-
9b	2*S*,3*S*	4.95	5.49	8.0	1.28	-
8c	2*S*,3*R*	5.11	5.63	6.2	1.30	-
9c	2*S*,3*S*	4.61	5.39	8.3	1.15	-
15a	2*S*,3*R*	5.48	5.67	5.0	3.78	2.19
16a	2*S*,3*S*	5.02	5.54	8.2	3.74	2.17
15b	2*S*,3*R*	5.08	5.63	6.3	1.31	2.26
15c	2*S*,3*R*	5.44	5.64	4.8	3.85	-
16c	2*S*,3*S*	4.97	5.49	8.6	3.78	-
15d	2*S*,3*R*	5.11	5.62	6.9	1.27	-

The stereochemical courses of the substitution reactions of the bromides **6a** and **7a** indicate that they occur *via* different mechanisms. It appears that the (2*R*,3*R*)-bromide **6a** reacts *via* the carbocation **17a**, while the (2*R*,3*S*)-bromide **7a** undergoes an S_N2 reaction. This variation in the mechanisms and the stereochemical courses of the reactions can be rationalized by considering the preferred conformation of each of the bromides **6a** and **7a** (Figure 1). In the preferred conformation of the (2*R*,3*R*)-bromide **6a**, the phenyl and β-hydrogen substituents are already in the orientation required to form the most stable conformation of the carbocation **17a** (Figure 3). This orientation also allows for delocalization of the developing positive charge by the ester carbonyl group, as the ester moiety is situated in the plane of the developing unoccupied orbital. S_N2 substitution is disfavored for this conformation of the bromide **6a**, as the ester moiety blocks attack of water from behind the carbon-bromine bond. For these reasons, the carbocation **17a** forms, with subsequent nucleophilic attack of water preferentially from the less hindered face, opposite the ester group, giving rise to the alcohols **8a** and **9a** in a 2:1 ratio. In its preferred conformation, the (2*R*,3*S*)-bromide **7a** is not aligned to lead directly to the most stable conformation of the carbocation **17a**. In fact, the bromide **7a** can only react to give the carbocation **17a** either initially in a less stable conformation or without delocalization of the developing positive charge by the ester carbonyl group. These processes are energetically less favourable than the reaction of the bromide **6a** to give the carbocation **17a** and, instead, the bromide **7a** reacts *via* the S_N2 pathway with inversion of configuration.

Subsequent hydrolyses were performed using 1:1 mixtures of the diastereomeric bromides **6b,c** and **7b,c**, and **13a,b** and **14a,b**, thereby avoiding their separation. For comparison, reaction of a 1:1 mixture of the bromides **6a** and **7a** gave the alcohols **8a** and **9a** in the expected 5:1 ratio. Initially, the reaction of the *tert*-butyl esters **6b** and **7b** was examined, because it was envisaged that the more bulky ester group would increase the stereoselectivity of the reaction. In the event, the alcohols **8b** and **9b** were formed in an 8:1 ratio, as



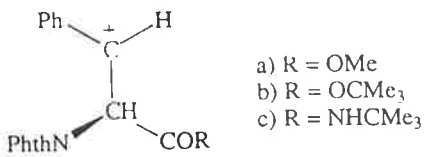
(6a) (17a)

Figure 3. Direct Formation of the Most Stable Conformation of the Carbocation **17a** from the Preferred Conformation of the Bromide **6a**.

determined through analysis of the ^1H NMR spectrum of the crude reaction mixture. The (2*S*,3*R*)-isomer **8b** was isolated in 81% yield, after recrystallization of the crude product. Presumably, by analogy with the reaction of the methyl ester **7a**, the reaction of the (2*R*,3*S*)-bromide **7b** occurs with complete inversion of stereochemistry. The reaction of the (2*R*,3*R*)-bromide **6b** must therefore occur to give an approximately 3.5:1 ratio of the alcohols **8a** and **9a**. The increased selectivity of the reaction of the *tert*-butyl ester **6b**, compared to that of the methyl ester **6a**, can be attributed to the relative extent of the steric effects of the respective ester moieties, blocking one face of each of the corresponding intermediate carbocations **17b** and **17a**.

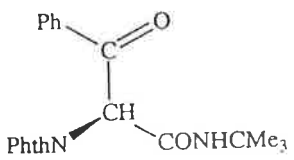
Treatment of a mixture of the phenylalaninamides **6c** and **7c** with silver nitrate in acetone/water gave only the (2*S*,3*R*)-alcohol **8c**, in 93% yield. In order to determine that none of the stereoisomer **9c** was produced in this reaction, an authentic sample was prepared. Oxidation of the alcohol **8c** with Jones reagent[28] gave the ketone **18**, which was reduced with sodium borohydride in ethanol to give a 1.2:1 mixture of the alcohols **8c** and **9c**. It is possible that some racemization occurred during this oxidation-reduction sequence, but the absolute stereochemistry of the alcohol **9c** is of no consequence in determining the diastereoselectivity of the reaction of the bromides **6c** and **7c**. When the ^1H NMR spectrum of the crude reaction mixture obtained from the hydrolysis of the bromides **6c** and **7c** was compared with that of the alcohol **9c**, the former showed no signal corresponding to the *tert*-butyl group of the alcohol **9c**, even though the ^{13}C satellite peaks of that signal for the alcohol **8c** (J_{CH} = 126.7 Hz) were clearly visible, with a signal to noise ratio of greater than 10:1. On that basis the hydrolysis of the mixture of the bromides **6c** and **7c** gave the (2*S*,3*R*)-alcohol **8c** in >99.9% diastereomeric excess.

The diastereoselectivity of the hydrolysis of the mixture of the bromo amides **6c** and **7c** is at least 100-fold greater than that for the reaction of the bromo esters **6b** and **7b**. This may be attributed to the relative



a) R = OMe
b) R = $OCMe_3$
c) R = $NHCMe_3$

(17)



(18)

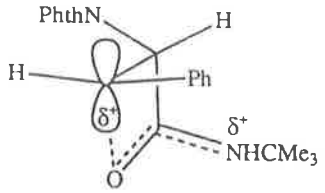


Figure 4. Stabilization of the Carbocation **17c** by the Amido Substituent.

extent of conformational preference of the carbocations **17b** and **17c**. A carbonyl oxygen of an amido group is approximately six orders of magnitude more basic than that of an ester,[29] therefore the extent of interaction of the amido substituent with the unoccupied orbital of the carbocation **17c** (Figure 4) is likely to be much greater than the analogous interaction of the ester group in the carbocation **17b**. This will result in a greater conformational preference of the carbocation **17c** and a greater tendency for approach of the nucleophile to the face of the carbocation **17c** opposite to that through which the amido group stabilization occurs.

A substituent effect analogous to that observed in the reactions of the phenylalanine derivatives **6a,c** and **7a,c** was also observed with the corresponding tyrosine derivatives **13a,b** and **14a,b**. Treatment of a 1:1 mixture of the diastereomeric esters **13a** and **14a** under the standard hydrolysis conditions gave a 6:1 mixture of the alcohols **15a** and **16a**, in 86% yield. The hydroxytyrosine derivatives **15a** and **16a** were unstable and deacetylated slowly on exposure to moisture. Hence, the crude product was completely deacetylated by treatment with a catalytic amount of *p*-toluenesulfonic acid in methanol, to give a 6:1 ratio of the alcohols **15c** and **16c**, from which the (2*S*,3*R*)-isomer **15c** was isolated, in 72% yield, by recrystallization. HPLC of the mother liquor afforded a pure sample of the (2*S*,3*S*)-alcohol **16c**. Reaction of a 1:1 mixture of the tyrosinamides **13b** and **14b** gave only the (2*S*,3*R*)-stereoisomer **15b**, in 88% yield, which on deacetylation afforded only the alcohol **15d**, in 93% yield. Within the limits of detection using ^{1}H NMR spectroscopy, the reaction of the mixture of the bromides **13b** and **14b** was diastereospecific, as there was no evidence of formation of either of the alcohols **16b** or **16d**.

The reactions of the amino acid derivatives **5a-c** and **12a,b** with *N*-bromosuccinimide, and the subsequent treatment of the product bromides **6a-c**, **7a-c**, **13a,b** and **14a,b** with silver nitrate in aqueous acetone, described above, exemplify an efficient route for the stereocontrolled synthesis of hydroxy amino acid derivatives. The alcohols **8a** and **8c** were also used to prepare the (2*S*,3*R*)-stereoisomer of the corresponding free amino acid **1**. Treatment of the ester **8a** with hydrazine to remove the phthaloyl group,[30] followed by acid-catalysed hydrolysis of the ester moiety, gave the hydrochloride salt of the (2*S*,3*R*)-stereoisomer of β-hydroxyphenylalanine **1**. Alternatively, the salt was obtained by treatment of the ester **8a** with a 2:1 mixture of 6N hydrochloric acid and glacial acetic acid, at reflux. In each case the free amino acid was prepared from the hydrochloride salt by crystallization from aniline in ethanol. Treatment of the amide **8c** with a 2:1 mixture of 6N hydrochloric acid and glacial acetic acid, at reflux, followed by crystallization of the crude product from aniline in ethanol, also gave the corresponding free amino acid, in 78% yield. The relative and absolute stereochemistry of samples of the free amino acid, prepared from the amino acid derivatives **8a** and **8c**, was established by comparison of their ^{1}H NMR spectra[31] and optical rotation properties[32] with literature data. This confirmed that the syntheses of the (2*S*,3*R*)-diastereomer of the alcohol **1** from (*S*)-phenylalanine occurred with

retention of chirality at the α-position. It follows that identical procedures could be used in the elaboration of (*R*)-amino acids. Thus, the procedures described above are suitable for the enantiospecific and diastereospecific synthesis of β-hydroxy-α-amino acids and their derivatives, particularly the (2*S*,3*R*)- and (2*R*,3*S*)-stereoisomers.

EXPERIMENTAL

General. General experimental details have been reported previously.[20] ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in deuteriochloroform unless otherwise stated. Infrared spectra were recorded as solutions in dichloromethane. Organic solutions were dried by stirring over anhydrous magnesium sulfate.

(*S*)-Phenylalanine and (*S*)-tyrosine were purchased from Sigma Chemical Co., and used to prepare the amino acid derivatives **5a-c** and **12a,b**, respectively, using standard procedures.[20,21,33]

Bromination of the Amino Acid Derivatives 5a-c and 12a,b. Reactions of the amino acid derivatives **5a-c** and **12a,b** with *N*-bromosuccinimide were carried out as described previously[20,21] for the bromination of the racemate of the amide **5c**, except that the reactions of the esters **5a,b** and **12a** were performed in carbon tetrachloride, instead of the 3:1 mixture of carbon tetrachloride/dichloromethane that was used with the amides **5c** and **12b**. The reactions gave 1:1 mixtures of the diastereomeric bromides **6a-c** and **7a-c**, and **13a,b** and **14a,b**, which were separated by fractional crystallization in the cases of the phenylalanine derivatives **6a-c** and **7a-c**, from hexane/dichloromethane in the cases of **6a,b** and **7a,b**, and from hexane/2-propanol in the case of **6c** and **7c**.

(2*R*,3*R*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester (6a): 42%; mp 142-143 °C; ν_{max} 1778, 1755, 1709, 708 cm^{-1}; MS (EI) *m/e* 389 and 387 (M^+, 6%), 330 (8), 328 (8), 308 (65), 307 (18), 276 (89), 249 (92), 248 (100), 242 (32), 240 (32), 218 (59), 190 (46), 162 (39), 130 (22), 105 (46), 103 (28), 77 (17). Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.8; H, 3.7; N, 3.6. Found: C, 55.7; H, 3.7; N, 3.6.

(2*R*,3*S*)-3-Bromo-*N*-phthaloylphenylalanine Methyl Ester (7a): 40%; mp 121-122 °C; ^{13}C NMR δ 47.6, 53.1, 57.0, 123.6, 128.1, 128.6, 128.9, 130.9, 134.3, 137.1, 166.3, 167.2; ν_{max} 1774, 1758, 1718, 727 cm^{-1}; MS (EI) *m/e* 389 and 387 (M^+, 2%), 330 (5), 328 (5), 308 (32), 276 (59), 249 (79), 248 (85), 242 (24), 240 (24), 218 (56), 190 (62), 169 (11), 167 (11), 161 (26), 130 (33), 104 (82), 102 (64), 76 (100). Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.8; H, 3.7; N, 3.6. Found: C, 56.2; H, 3.7; N, 3.7.

(2*R*,3*R*)-3-Bromo-*N*-phthaloylphenylalanine *tert*-Butyl Ester (6b): 41%; mp 152-153 °C; ν_{max} 1780, 1738, 1720, 1420, 1390, 1050, 840, 710 cm^{-1}; MS (EI) *m/e* 431 and 429 (M^+, 0.02%), 375 (9), 373 (9), 330 (11), 328 (11), 294 (4), 276 (2), 249 (93), 248 (94), 232 (15), 220 (10), 204 (44), 165 (7), 130 (8), 104 (38), 102 (32), 76 (36), 57 (100).

(2*R*,3*S*)-3-Bromo-*N*-phthaloylphenylalanine *tert*-Butyl Ester (7b): 39%; mp 118-119 °C; ν_{max} 1780, 1748, 1726, 1390, 715 cm^{-1}; MS (EI) *m/e* 431 and 429 (M^+, 0.01%), 375 (7), 373 (7), 330 (10), 328 (10), 294 (6), 276 (3), 249 (75), 248 (100), 232 (11), 220 (8), 204 (28), 165 (5), 130 (6), 104 (27), 102 (25), 76 (26), 57 (66).

(2*R*,3*R*)-3-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (6c): 43%; mp 208-209 °C; ν_{max} 3350, 1700, 1530, 1450, 1365, 710 cm^{-1}; MS (EI) *m/e* 430 and 428 (M^+, 5%), 415 (0.2), 413 (0.2), 375 (0.6), 373 (0.6), 330 (2), 328 (2), 249 (100), 232 (6), 220 (3), 204 (5), 165 (2), 130 (3), 104 (8), 102 (7), 76 (6). Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5. Found: C, 58.6; H, 5.0; N, 6.8.

(2*R*,3*S*)-3-Bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloylphenylalaninamide (7c): 41%; mp 188-191 °C; ν_{max} 3375, 1775, 1705, 1530, 1380, 720 cm^{-1}; MS (EI) *m/e* 430 and 428 (M^+, 1%), 415 (0.1), 413 (0.1), 375 (0.2), 373 (0.2), 330 (1), 328 (1), 249 (100), 232 (10), 220 (3), 204 (4), 165 (2), 130 (3), 104 (12), 102 (10), 76 (13). Anal. Calcd for $C_{21}H_{21}BrN_2O_3$: C, 58.8; H, 4.9; N, 6.5. Found: C, 58.8; H, 4.9; N, 6.6.

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester (13a) and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-phthaloyltyrosine Methyl Ester (14a): 1:1 mixture; 97%; MS (EI) *m/e* 447 and 445 (M^+, 0.3%), 405 (0.3), 403 (0.3), 388 (0.6), 386 (0.6), 366 (8), 334 (17), 324 (5), 306 (5), 292 (16), 264 (100), 218 (12), 187 (7), 163 (9), 147 (10), 138 (14), 121 (35), 104 (22), 86 (38), 76 (19); MS (EI) *m/e* 445.018 (M^+). Calc. for $C_{20}H_{16}BrNO_6$: *m/e* 445.016.

(2*R*,3*R*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyltyrosinamide (13b) and (2*R*,3*S*)-*O*-Acetyl-3-bromo-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyltyrosinamide (14b): 1:1 mixture; 97%; ν_{max} 1780, 1726, 1675, 1608, 1394, 1160, 720 cm^{-1}; MS (EI) *m/e* 488 and 486 (M^+, 2%), 446 (1), 444 (1), 403 (14), 388 (1), 386 (1), 361 (10), 308 (31), 265 (100), 248 (5), 121 (11), 118 (10), 104 (14), 76 (9); MS (EI) *m/e* 486.080 (M^+). Calc. for $C_{23}H_{23}BrN_2O_5$: *m/e* 486.079.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloylphenylalanine Methyl Ester (8a) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloylphenylalanine Methyl Ester (9a). To a solution of a 1:1 mixture of the bromides **6a** and **7a** (1.0 g, 2.6 mmol) in acetone (40 ml) was added a solution of silver nitrate (0.66 g, 3.9 mmol) in water (40 ml), and the resultant mixture was stirred in the dark at rt for 24 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane, and the organic solution was dried and then concentrated under reduced pressure, to give a 5:1 mixture of the alcohols **8a** and **9a** (0.77 g, 92%), as determined from the ^{1}H NMR spectrum. Recrystallization of the mixture from hexane/dichloromethane gave the alcohol **8a** as colourless crystals (0.63 g, 75%): mp 185-186 °C; $[\alpha]_D^{16}$ -67.0° (c, 0.6 in EtOH); ν_{max} 3580, 3420, 1780, 1745, 1715, 1390, 1215, 1020, 720 cm^{-1}; MS (FAB) *m/e* 326 ($M+H^+$, 77%), 308 (100), 248 (54), 219 (19), 160 (27), 149 (23), 131 (21), 105 (48), 104 (33), 91 (42). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.5; H, 4.7; N, 4.3. Found: C, 66.7; H, 4.7; N, 4.4.

The structure of the alcohol **8a** was confirmed through X-ray crystallographic analysis.[27]

Reactions of the bromides 6b,c and 7b,c, and 13a,b and 14a,b, with silver nitrate in aqueous acetone. These reactions were performed using the procedure described above for the reaction of the mixture of the bromides **6a** and **7a**.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloylphenylalanine *tert*-Butyl Ester (8b) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloylphenylalanine *tert*-Butyl Ester (9b). Reaction of a 1:1 mixture of the bromides **6b** and **7b** gave an 8:1 mixture of the alcohols **8b** and **9b**. The ratio of the diastereomers **8b** and **9b** was determined from the ^{1}H NMR spectrum of the mixture. Recrystallization of the mixture from hexane/dichloromethane gave the alcohol **8b** as colourless crystals: 81%; mp 125-127 °C; ν_{max} 3440, 1785, 1738, 1712, 1604, 1552, 1392, 1194, 1108, 844, 720 cm^{-1}; MS (FAB) *m/e* 368 ($M+H^+$, 8%), 312 (44), 294

(55), 276 (23), 266 (10), 250 (100), 232 (11), 205 (13), 160 (19), 105 (21), 91 (20), 87 (25), 57 (93). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.7; H, 5.8; N, 3.8. Found: C, 68.7; H, 5.9; N, 3.8.

(2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (8c). Reaction of a 1:1 mixture of the bromides **6c** and **7c** gave the alcohol **8c**, as colourless crystals from hexane/dichloromethane: 93%; mp 195-197 °C; ν_{max} 3352, 3275, 1778, 1704, 1644, 717 cm^{-1}; MS (FAB) *m/e* 367 ($M+H^+$, 68%), 307 (3), 289 (2), 266 (4), 260 (18), 250 (100), 232 (7), 187 (10), 160 (17), 154 (24), 136 (18), 107 (8), 105 (6), 77 (6). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.8; H, 6.1; N, 7.7. Found: C, 68.8; H, 6.0; N, 7.7.

(2*S*,3*R*)-3-Hydroxy-*N*-phthaloyltyrosine Methyl Ester (15c) and (2*S*,3*S*)-3-Hydroxy-*N*-phthaloyltyrosine Methyl Ester (16c). Reaction of a 1:1 mixture of the bromides **13a** and **14a** gave an 86% yield of a 6:1 mixture of the alcohols **15a** and **16a**: ν_{max} 3580, 3410, 1775, 1752, 1712, 1552, 1392, 1184, 1118, 852, 710 cm^{-1}; MS (FAB) *m/e* 384 ($M+H^+$, 13%), 366 (79), 334 (100), 324 (7), 306 (35), 292 (38), 264 (58), 219 (34), 187 (23), 160 (15), 154 (37), 136 (33), 107 (17), 105 (13), 104 (12), 89 (17), 77 (19); MS *m/e* 365.090 (M^+). Calc. for $C_{20}H_{15}NO_6$: *m/e* 365.090. The ratio of the diastereomers **15a** and **16a** was determined from the ^1H NMR spectrum of the mixture.

The acetate moieties of the alcohols **15a** and **16a** were found to hydrolyse slowly on exposure to moisture and the mixture was therefore deacetylated without further purification. A mixture of the acetates **15a** and **16a** (0.87 g, 2.27 mmol), *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) and water (1 ml) in methanol (20 ml) was stirred at rt for 6 h, then it was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic phase was separated and washed with 10% aqueous sodium carbonate, then it was dried and concentrated under reduced pressure, to give a 6:1 mixture of the alcohols **15c** and **16c** (0.74 g, 96%). The ratio of the diastereomers **15c** and **16c** was determined from the ^1H NMR spectrum of the mixture. Recrystallization of the mixture from hexane/ethyl acetate gave the alcohol **15c** as a white solid (556 mg, 72%); mp 200-201 °C; $[\alpha]_D^{16}$ -70.7° (c, 0.4 in EtOH); ν_{max} 3582, 3405, 1775, 1750, 1714, 1516, 1392, 1172, 850, 715 cm^{-1}. MS (FAB) *m/e* 342 ($M+H^+$, 2%), 324 (10), 307 (12), 292 (11), 289 (7), 264 (5), 232 (14), 231 (17), 219 (9), 154 (100), 137 (63), 136 (77), 107 (30), 105 (12), 89 (29), 77 (31). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.3; H, 4.4; N, 4.1. Found: C, 63.3; H, 4.4; N, 4.0.

(2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyltyrosinamide (15d). Reaction of a 1:1 mixture of the bromides **13b** and **14b** gave the alcohol **15b** as colourless crystals; 88%; mp 202-204 °C; ν_{max} 3600, 3440, 3390, 1775, 1710, 1685, 1515, 1390, 1220, 860, 720 cm^{-1}; MS (FAB) *m/e* 425 ($M+H^+$, 43%), 308 (67), 266 (100), 248 (4), 187 (16), 160 (26), 154 (23), 136 (37), 107 (18), 105 (10), 89 (17), 77 (22); MS *m/e* 406.154 (M^+-H_2O). Calc. for $C_{23}H_{22}N_2O_5$: *m/e* 406.153.

The acetate **15b** was hydrolysed, as described above for the hydrolysis of the mixture of the acetates **15a** and **16a**, to give a 93% yield of the alcohol **15d**, as a colourless solid after recrystallization from hexane/chloroform: mp 214-215 °C; ν_{max} 3590, 3546, 3410, 1772, 1712, 1685, 1366, 855, 717 cm^{-1}; MS (FAB) *m/e* 383 ($M+H^+$, 18%), 307 (3), 289 (4), 267 (48), 266 (100), 260 (16), 187 (15), 160 (15), 154 (26), 136 (17), 107 (8), 105 (8), 91 (10), 77 (9). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.8; N, 7.3. Found: C, 65.7; H, 5.8; N, 7.2.

Isomerization of (2*S*,3*R*)-3-Hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide (8c). Jones reagent[28] (*ca.* 0.5 ml) was added dropwise to a vigorously stirred solution of the alcohol **8c** (0.5 g, 1.37 mmol) in acetone (20 ml), until the red/brown colour persisted. The reaction mixture was stirred

for a further 15 min at rt, then it was concentrated under reduced pressure. The residual oil was partitioned between dichloromethane and water. The organic layer was separated and washed with 10% aqueous sodium carbonate and with water, then it was dried and concentrated under reduced pressure. The residual oil was chromatographed on silica, eluting with ethyl acetate, to give the crude ketone **18**, which recrystallized from hexane/ethyl acetate as a colourless solid (0.33 g, 67%); ^{1}H NMR δ 1.34 (9H, s), 6.04 (1H, s), 7.21-7.56 (5H, m), 7.73-7.90 (4H, m); MS (EI) *m/e* 364 (M^+, 2%), 308 (1), 291 (2), 265 (40), 221 (6), 147 (72), 105 (43), 104 (87), 103 (58), 76 (100).

To a solution of the crude ketone **18** (100 mg, 0.27 mmol) in ethanol (5 ml) was added sodium borohydride (10 mg, 0.26 mmol). The mixture was stirred at rt for 10 min, then the reaction was quenched by the addition of dilute hydrochloric acid (*ca.* 1 ml). The mixture was concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water. The organic layer was washed with 10% aqueous sodium carbonate and with water, then it was dried and concentrated under reduced pressure. Chromatography of the residual oil on silica gave a 1:1.2 mixture of **(2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloylphenylalaninamide** (**9c**) and the diastereomer **8c** (84 mg, 84%), as determined from the ^{1}H NMR spectrum.

Reaction of the Bromide 6a with Potassium Fluoride. Treatment of the bromide **6a** with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described previously[21] for the synthesis of *(Z)*-*N*-*tert*-butyl-N^{α}-phthaloyl-2,3-dehydrophenylalaninamide from the bromo amide **6c**, afforded *(Z)*-*N*-phthaloyl-2,3-dehydrophenylalanine methyl ester (**10**) as colourless crystals: 88%; mp 136-137 °C; ^{1}H NMR δ 3.82 (3H, s), 7.26-7.42 (5H, m), 7.78-7.90 (4H, m), 8.12 (1H, s); ν_{max} 1780, 1720, 1640, 1600 cm^{-1}; MS (EI) *m/e* 307 (M^+, 100%), 279 (52), 248 (27), 247 (34). Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.3; N, 4.6. Found: C, 70.6; H, 4.2; N, 4.4.

The structure of the alkene **10** was confirmed through X-ray crystallographic analysis.[22]

Reaction of the Bromide 7a with Potassium Fluoride. Treatment of the bromide **7a** with the 18-crown-6 complex of potassium fluoride in acetonitrile, as described for the reaction of the bromide **6a**, afforded a 2:1 mixture of *(E)*-*N*-phthaloyl-2,3-dehydrophenylalanine methyl ester **11** and the (*Z*)-isomer **10**, in 82% yield. Recrystallization of the mixture from hexane/ethyl acetate gave the *(Z)*-alkene **10** in 18% yield, while concentration of the recrystallization mother liquor afforded a 47% yield of a 5:1 mixture of the alkenes **11** and **10**, as a clear oil; ν_{max} 1780, 1724, 1645, 1600, 1560 cm^{-1}; MS (EI) *m/e* 307 (M^+, 100%), 279 (49), 248 (12), 247 (27); ^{1}H NMR (**11**) δ 3.74 (3H, s), 7.23 (1H, s), 7.29-7.49 (5H, m), 7.80-7.93 (4H, m).

(2*S*,3*R*)-3-Hydroxyphenylalanine. A solution of the hydroxy ester **8a** (0.25 g, 0.77 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 ml) was heated at reflux for 5 h, then it was cooled and concentrated under reduced pressure. The residue was taken up in water (10 ml) and the suspension was filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in a mixture of ethanol (7 ml), aniline (0.7 ml) and dichloromethane (10 ml). The mixture was stored at 0 °C for 16 h, and the precipitate that formed was collected by filtration, to give the (2*S*,3*R*)-isomer of the free amino acid **1**, as a white powder (129 mg, 93%); mp 192-195 °C (lit.[32] 183-186 °C); $[\alpha]_D^{16}$ -49.7±0.5° (c, 0.4 in 6N HCl) (lit.[32]

$[\alpha]_D^{20}$ -50.2±2° (c, 2 in 6N HCl)); ^{1}H NMR (D_2O) δ 3.95 (1H, d, J = 4.4 Hz), 5.29 (1H, d, J = 4.4 Hz), 7.47 (5H, m). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.9; H, 6.1; N, 7.8.

Treatment of the hydroxy amide **8c** with hydrochloric acid and acetic acid, as described above for the hydrolysis of the hydroxy ester **8a**, also gave the (2*S*,3*R*)-isomer of the free amino acid **1**, in 78% yield.

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Yeast-catalysed Reductive Ring-opening of Isoxazoles

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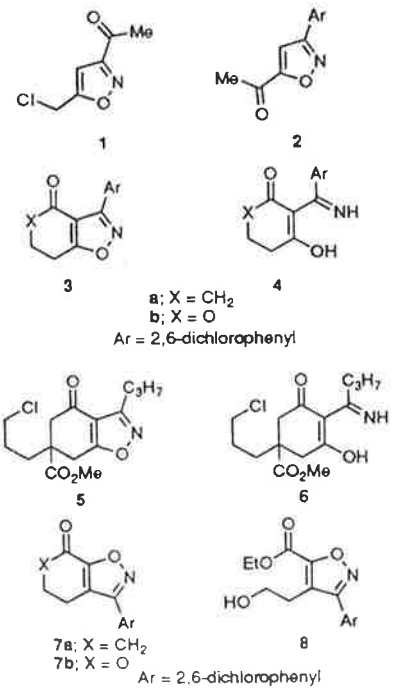
A novel reductive cleavage of the N–O bond of the isoxazoles **3a, b** and **5**, using actively fermenting baker's yeast, is described.

The use of actively fermenting baker's yeast (sp. *Saccharomyces cerevisiae*) is now a well established technique in organic chemistry.[1,2] Numerous synthetic transformations have been reported, including ester hydrolysis, condensations, and of particular importance the reduction of carbonyl compounds. The latter has been exploited in isoxazole chemistry, in the enantioselective reduction of the carbonyl groups of compounds such as the 3- and 5-acetyl-substituted isoxazoles **1** and **2**.[3] By contrast, we have now observed that the isoxazoles **3a, b**[4] and **5** undergo reductive ring-opening to give **4a, b** and **6**, respectively, under analogous conditions. This is the first example of a yeast-catalysed reductive cleavage of either an aromatic ring or a single bond.

The isoxazole **3a** (0.5 g) was added to a fermenting mixture prepared from dried baker's yeast (Fermipan, Gist-brocades Holland, 10 g) and sucrose (75 g) in water (400 ml) at 37 °C. After 24 h, standard work-up gave the ring-opened product **4a** [0.12 g; ^{1}H NMR ($CDCl_3$) δ 1.92 (br s, 1H), 1.97 (quint., *J* 6.5 Hz, 2H), 2.43 (t, *J* 6.5 Hz, 2H), 2.65 (t, *J* 6.5 Hz, 2H), 6.06 (br s, 1H), 7.35 (m, 3H)].† X-Ray crystallographic analysis established that the product **4a** exists as the dione–enamine tautomer in the solid state, the difference between the solution and solid structures being attributable to intermolecular hydrogen bonding in the crystal form.[5]



1 **2** **3** **4**

a; X = CH_2
b; X = O
Ar = 2,6-dichlorophenyl

5 **6** **7a**; X = CH_2 **7b**; X = O **8**

Ar = 2,6-dichlorophenyl

Although the absolute yield of **4a** was only modest, the process yield was 75%, based on recovered starting material (0.34 g), and these conditions were found to be optimal for the quantity of yeast, sucrose and the substrate **3a**, and the reaction time. Other strains of yeast (*e.g.*, Munich lager yeast and Balmoral ale yeast) also catalysed the conversion of **3a** to **4a** but the product was more difficult to isolate from organic material contained by the yeasts. The isoxazoles **3b** and **5** also underwent reductive ring-opening to give **4b** and **6** respectively. In each case the absolute and process yields were similar to that of **4a**.

Incubation of the isoxazoles **7a, b**,[4] regioisomers of **3a, b**, with baker's yeast gave only recovered starting material (67%) in the former case, and starting material (27%) and the transesterification product **8** (2%) in the latter; there was no evidence of reductive ring cleavage. Although there is no obvious explanation for the difference in reactivity of **3a, b** compared with **7a, b**, it is interesting to note that the compounds **3a, b** with the lower reduction potentials underwent reductive ring cleavage. The reduction potentials of **3a, b** and **7a, b** were measured in acetonitrile, with Ag/AgCl as the reference electrode, and found to be −2.15, −2.2, −2.5 and −2.5 V, respectively.

The reductive cleavage of isoxazoles is an important method for the construction of β-diketones, β-ketoimines and β-ketoesters and their derivatives, and is normally carried out by metal-catalysed (nickel, palladium) hydrogenolysis.[6] These methods fail when other sensitive groups or catalyst poisons are present in the molecule. Now, baker's yeast provides an alternative method for this transformation.

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Footnote

† All new compounds were fully characterised.

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Complementary Diastereoselectivity in the Synthesis and Hydrolysis of Acylated Cyclodextrins

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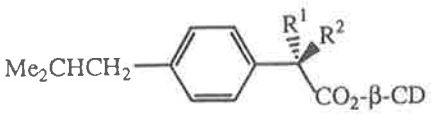
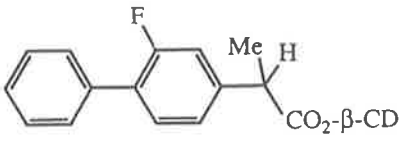
The diastereoselectivity of acylation of β-cyclodextrin with the acid chlorides of Ibuprofen, Flurbiprofen and 2-phenylpropanoic acid is complementary, in absolute and relative terms, to that observed in the hydrolysis of the corresponding cyclodextrin esters.

Acylation and deacylation reactions of cyclic oligomers of D-glucopyranose, or cyclodextrins, have been studied extensively as models of covalent catalysis by enzymes.[1] In this area, there have been several reports of the enantioselective acylation of cyclodextrins and of the stereoselective hydrolysis of esters catalysed by cyclodextrins.[2] This selectivity has been attributed to the inherent chirality of cyclodextrins and their ability to form diastereomeric inclusion complexes with chiral guests. Recently we reported[3] the first example of diastereoselectivity in the deacylation of a cyclodextrin derivative. At 37 °C in 0.1 mol dm^{-3} sodium carbonate buffer at pH 11.5, the pseudo first-order rate constants for the hydrolysis of the diastereomers of 6^{A}-O-{2-[4-(2-methylpropyl)phenyl]propanoyl}-β-cyclodextrin (**1**), to give Ibuprofen {2-[4-(2-methylpropyl)phenyl]propanoic acid} and β-cyclodextrin, were found to be 2.97×10^{-5} s^{-1} and 3.16×10^{-4} s^{-1}, with the diastereomer **1a** derived from (*R*)-Ibuprofen being the most susceptible to hydrolysis. We now report that the synthesis of the ester **1**, through reaction of the acid chloride of Ibuprofen with β-cyclodextrin, is also diastereoselective, and the stereoselectivity of the acylation is complementary to that of the hydrolysis of the ester **1**. We also describe three other examples of diastereoselective deacylation of cyclodextrin derivatives, in the hydrolysis of the esters **2-4**, and the complementary stereoselective acylation of β-cyclodextrin, in the synthesis of the esters **2** and **3**.

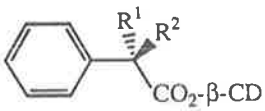
The esters **2-4** were obtained, each as a 1:1 mixture of the diastereomers, by treatment of 6^{A}-O-(4-methylphenylsulfonyl)-β-cyclodextrin[4] with the racemic caesium salts of Flurbiprofen {2-[(3-fluoro-4-phenyl)phenyl]propanoic acid}, 2-phenylpropanoic acid and *N*-acetylphenylalanine, respectively, in *N*,*N*-dimethylformamide at 100 °C for 24 h.[5] The diastereomers of the ester **2**, derived from Flurbiprofen, had HPLC retention times of 0.30 and 0.34 relative to β-cyclodextrin, when analysed using a Waters Carbohydrate



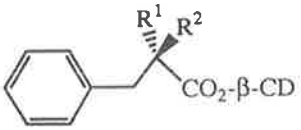
(1)
a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H



(2)



(3)
a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H



(4)
a) R^1 = H, R^2 = NHCOMe
b) R^1 = NHCOMe, R^2 = H

β-CD = 6^A-deoxy-β-cyclodextrin

Analysis column (3.9 x 300 mm) with 70% aqueous acetonitrile as eluent, and their ^{1}H NMR spectra [300 MHz, $(CD_3)_2SO$] showed doublet resonances at δ 1.42 (*J* 8 Hz) and δ 1.45 (*J* 8 Hz), attributable to the methyl groups of the Flurbiprofen moieties. The absolute stereochemistry of the diastereomers of the ester **2** was not determined. The diastereomers of the ester **3**, derived from 2-phenylpropanoic acid, were indistinguishable using ^{1}H NMR spectroscopy, but they were separable using HPLC, having retention times of 0.45 and 0.48 relative to β-cyclodextrin. The more rapidly eluting compound was found to be the diastereomer **3a**, through independent synthesis from the caesium salt of (*R*)-2-phenylpropanoic acid. The HPLC retention times of the diastereomers of the ester **4** were found to be 0.54 and 0.65 relative to β-cyclodextrin. Independent synthesis was used to establish that the diastereomer **4b**, derived from (*S*)-*N*-acetylphenylalanine, had the shorter retention time.

Hydrolysis of the esters **2**-**4** to give β-cyclodextrin and the corresponding acids, Flurbiprofen, 2-phenylpropanoic acid and *N*-acetylphenylalanine, was studied in sodium carbonate buffer at 37 °C, using HPLC and ^{1}H NMR spectroscopic analysis (Table 1). At pH 11.5, the diastereomer of the ester **2** with the longer HPLC retention time (**2i**) hydrolysed with a pseudo first-order rate constant of 2.3 x 10^{-4} s^{-1}. The other diastereomer (**2ii**) hydrolysed more rapidly, making it difficult to accurately determine the rate constant for this process through analysis of samples taken from the reaction mixture. At lower pH, each of the diastereomers of the ester **2** hydrolysed more slowly,[1,6] and at pH 10.5 the diastereoselectivity of the hydrolysis was *ca.* 7:1 in favour of the isomer **2ii**. Hydrolysis of the ester **3** was found to be less stereoselective and, in sodium carbonate buffer at pH 11.5, the ratio of the rates of hydrolysis of the diastereomers **3a** and **3b** was *ca.* 2:1. The

Table 1. Pseudo first-order rate constants[a] for hydrolysis of the esters **1-4** in 0.1 M sodium carbonate buffer at 37 °C

Ester	pH	Rate Constants	
		$k_{(R)}$	$k_{(S)}$
1	11.5	3.16×10^{-4} s^{-1} [b]	2.97×10^{-5} s^{-1} [b]
2	10.5	4.8×10^{-4} s^{-1} [c]	7.1×10^{-5} s^{-1} [c]
3	11.5	1.0×10^{-4} s^{-1}	5.2×10^{-5} s^{-1}
4	10.0	7.7×10^{-5} s^{-1}	4.8×10^{-4} s^{-1}

a) Calculated from data with $r^2 > 0.982$; r = linear correlation coefficient.
b) Data from reference 3.
c) Absolute stereochemistry was not determined in this case.

diastereoselectivity displayed in the hydrolysis of the ester **4** was similar in magnitude to that observed with the ester **2** and, at pH 10.0, the ester **4b** derived from (*S*)-*N*-acetylphenylalanine hydrolysed *ca.* 6 times more rapidly than the diastereomer **4a**. These results, combined with our earlier study[3] of the hydrolysis of the ester **1**, indicate that diastereoselectivity in the deacylation of cyclodextrin derivatives is a general phenomenon.

To examine the relationship between the diastereoselectivity of hydrolysis of the esters **1-3** and of acylation of β-cyclodextrin to give the esters **1-3**, β-cyclodextrin (0.2 M) was treated with a six-fold molar excess of the acid chlorides of (*RS*)-Ibuprofen, (*RS*)-Flurbiprofen and (*RS*)-2-phenylpropanoic acid. The reactions were carried out at room temperature in 0.1 M sodium phosphate buffer, at pH 6.0 in order to minimize hydrolysis of the product esters **1-3**.[1,6] Under these conditions only a portion of the β-cyclodextrin reacts because the major reaction of the acid chlorides is hydrolysis to the corresponding acids. The acid chloride of *N*-acetylphenylalanine is unstable and was therefore unsuitable for use in this study. The esters **1-3** were each obtained as a mixture of diastereomers in approximately 5% yield, and the diastereoselectivity was complementary, in absolute and relative terms, to that of the corresponding deacylation (Table 2), as determined by HPLC analysis of the crude product mixtures. Results were invariant for reaction times between 1-2 hours. The diastereomers of the ester **1** were obtained as a *ca.* 5:1 mixture, with the diastereomer **1a** derived from (*R*)-Ibuprofen being predominant, the ratio of diastereomers of the ester **2** was

Table 2. Diastereoselectivity of synthesis and hydrolysis of the esters **1-3**

Ester	Diastereoselectivity	
	Synthesis	Hydrolysis
1a/1b	5	10
2i/2ii	1.7	7
3a/3b	1.3	2

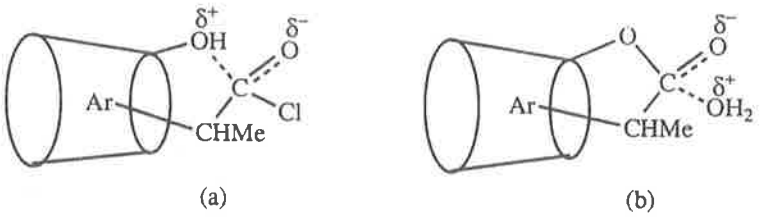


Fig. 1. Transition states (a) for the formation and (b) for the hydrolysis of the esters **1-3**.

ca. 1.7:1, with the major isomer being the one (**2ii**) that hydrolysed more readily, and the diastereomers **3a** and **3b** were produced in the ratio *ca.* 1.3:1. Thus the diastereoselectivity of synthesis and hydrolysis of the esters **1-3** decreases in numerical order. Although the correlation is based on a limited sample, there appears to be direct relationship between the stereoselectivity of the acylation and deacylation reactions. This may reflect similarities between the transition states of these reactions (Fig. 1), in which factors which affect the diastereoselectivity are common to both processes.

For the combined synthesis and hydrolysis of the ester **1**, the overall chiral discrimination in favour of the (*R*)-enantiomer of Ibuprofen is a factor of *ca.* 50. Unfortunately the low yield (5%) for the preparation of the ester **1** from the acid chloride of Ibuprofen limits the synthetic utility of this resolution procedure.

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Crystal structure of 7-(2,6-dichlorophenyl)-8-aza-9-oxa-[4.3.0]-bicyclonon-1,7-diene-2-one, $C_{13}H_9Cl_2NO_2$

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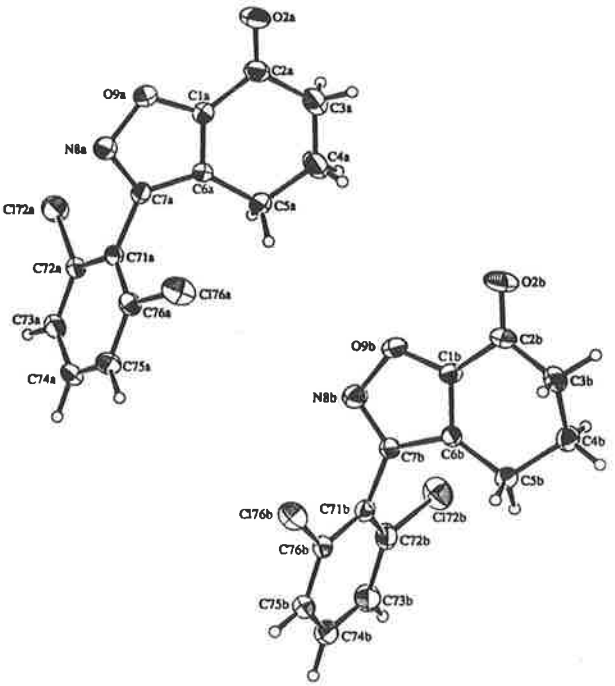

Source of material: see ref. 1; recrystallized from ethyl acetate/light petroleum (313 - 333 K) as colorless crystals with m.p. 381.5 - 383.5 K.

The study shows that the aryl group and oxo function (O(2)) lie on opposite sides of the molecule. The five-membered ring is planar to 0.004 Å (for both independent molecules) and forms a dihedral angle of 103.4° (98.0° for molecule b) with the aryl ring. The two independent molecules have relatively small differences in conformations with the most notable being associated with the C(2)/C(3)/C(4)/C(5) torsion angles of 21(2)° and -54(1)°, respectively.

$C_{13}H_9Cl_2NO_2$, monoclinic, Cc (No. 9), a = 21.688(4) Å, b = 7.804(2) Å, c = 14.921(2) Å, β = 103.14(1)°, V = 2459.3 Å^3, Z = 8, $R(F)$ = 0.037, $R_w(F)$ = 0.033.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless, spherical crystal with diameter 0.29 mm
Wave length:	Mo $K\alpha$ radiation (0.7107 Å)
μ:	5.18 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{measurement}$:	293 K
$2\theta_{max}$:	27.5°
$N(hkl)_{unique}$:	3149
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	323
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(3a1)	4a	0.20506	0.77858	0.41845	0.09546
H(3a2)	4a	0.19773	0.76525	0.31062	0.09546
H(3b1)	4a	0.45577	1.16528	0.42951	0.07815
H(3b2)	4a	0.44277	0.96648	0.41439	0.15076
H(4a1)	4a	0.11365	0.79714	0.38522	0.15076
H(4a2)	4a	0.10828	0.71396	0.28692	0.15076
H(4b1)	4a	0.36376	1.20064	0.47493	0.07604
H(4b2)	4a	0.34877	1.10534	0.37869	0.07144
H(5a1)	4a	0.07743	0.58836	0.43372	0.07144
H(5a2)	4a	0.0543	0.53603	0.32888	0.07144
H(5b1)	4a	0.29601	0.99061	0.49172	0.06308
H(5b2)	4a	0.33149	0.85358	0.44337	0.06308
H(73a)	4a	−0.02292	0.04844	0.57393	0.07915
H(73b)	4a	0.1627	0.85351	0.68986	0.07915
H(74a)	4a	−0.10247	0.00827	0.44266	0.07862
H(74b)	4a	0.14025	0.56647	0.65087	0.07862
H(75a)	4a	−0.08278	0.0558	0.29848	0.09546
H(75b)	4a	0.21813	0.38741	0.61752	0.07497

References

1. Easton, C.J., Hughes, C.M., Tiekink, E.R.T., Lubin, C.E., Savage, G.P., Simpson, W.: Reversal of regiochemistry in the synthesis of isoxazoles by nitrile oxide cycloadditions. Tetrahedron Lett. **35** (1994) 3589-3592.

Table 3. Final atomic coordinates and displacement parameters (in $Å^2$)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(72)	4*a*	0.1001	0.1615(3)	0.6049	0.083(1)	0.096(2)	0.062(1)	−0.019(1)	−0.005(1)	0.015(1)
Cl(72)	4*a*	0.2713(1)	1.0534(3)	0.7027(2)	0.099(2)	0.062(2)	0.133(2)	0.017(2)	0.045(2)	0.002(1)
Cl(76)	4*a*	0.3418(1)	0.4347(3)	0.6109(2)	0.089(1)	0.065(1)	0.082(1)	−0.005(1)	0.030(1)	−0.013(1)
Cl(76)	4*a*	0.0217(1)	0.1771(4)	0.2398(2)	0.091(2)	0.122(2)	0.058(1)	−0.023(2)	0.021(1)	−0.015(1)
O(2a)	4*a*	0.2835(3)	0.5407(9)	0.3751(4)	0.050(3)	0.117(5)	0.109(5)	−0.016(4)	0.021(3)	0.015(3)
O(2b)	4*a*	0.5278(2)	1.0673(8)	0.5755(4)	0.048(3)	0.121(5)	0.099(4)	−0.029(4)	0.022(3)	−0.011(3)
O(9b)	4*a*	0.4600(2)	0.8822(7)	0.6862(4)	0.046(3)	0.089(4)	0.064(4)	−0.011(3)	−0.003(3)	0.012(3)
O(9a)	4*a*	0.2158(2)	0.2447(7)	0.4114(4)	0.048(3)	0.070(4)	0.103(4)	0.008(3)	0.019(3)	0.016(3)
N(8b)	4*a*	0.4117(3)	0.7968(9)	0.7161(4)	0.059(4)	0.080(5)	0.055(4)	−0.006(4)	0.008(3)	0.009(4)
N(8a)	4*a*	0.1667(3)	0.1364(8)	0.4242(5)	0.057(4)	0.053(4)	0.100(5)	0.004(4)	0.017(4)	0.006(3)
C(1a)	4*a*	0.1911(3)	0.4032(9)	0.3946(5)	0.052(4)	0.053(5)	0.051(4)	0.001(4)	0.008(3)	0.004(4)
C(1b)	4*a*	0.4368(3)	0.9416(9)	0.6017(5)	0.043(4)	0.059(5)	0.045(4)	−0.003(4)	0.007(3)	−0.002(4)
C(2a)	4*a*	0.2282(4)	0.548(1)	0.3774(5)	0.053(4)	0.080(6)	0.059(5)	−0.014(5)	0.007(4)	0.004(5)
C(2b)	4*a*	0.4739(3)	1.0311(9)	0.5458(5)	0.043(4)	0.059(5)	0.067(5)	−0.009(4)	0.017(4)	−0.010(4)
C(3a)	4*a*	0.1896(4)	0.708(1)	0.3645(7)	0.084(6)	0.063(6)	0.114(8)	−0.015(6)	0.029(5)	0.009(5)
C(3b)	4*a*	0.4380(4)	1.065(1)	0.4522(5)	0.069(5)	0.063(5)	0.067(5)	−0.007(5)	0.026(4)	0.010(4)
C(4a)	4*a*	0.1251(5)	0.699(1)	0.352(1)	0.078(6)	0.063(6)	0.27(1)	0.006(8)	0.070(8)	0.049(5)
C(4b)	4*a*	0.3690(4)	1.095(1)	0.4435(5)	0.062(5)	0.081(6)	0.060(5)	0.002(4)	0.017(4)	0.018(4)
C(5a)	4*a*	0.0911(3)	0.5586(9)	0.3782(5)	0.051(4)	0.050(5)	0.079(6)	0.008(4)	0.014(4)	0.005(4)
C(5b)	4*a*	0.3370(3)	0.952(1)	0.4842(5)	0.047(4)	0.057(5)	0.053(4)	0.002(4)	0.008(3)	0.004(4)
C(6b)	4*a*	0.3759(3)	0.9034(8)	0.5733(5)	0.045(4)	0.043(4)	0.048(4)	−0.001(4)	0.012(3)	0.003(3)
C(6a)	4*a*	0.1301(3)	0.4022(9)	0.3955(5)	0.040(3)	0.045(5)	0.051(4)	−0.002(4)	0.008(3)	0.002(3)
C(7a)	4*a*	0.1166(3)	0.2328(9)	0.4133(5)	0.050(4)	0.044(5)	0.050(4)	0.005(4)	0.008(3)	0.004(3)
C(7b)	4*a*	0.3623(3)	0.8122(9)	0.6490(5)	0.045(4)	0.051(5)	0.043(4)	−0.003(4)	0.009(3)	0.004(3)
C(71b)	4*a*	0.3010(3)	0.740(1)	0.6551(5)	0.053(4)	0.056(5)	0.040(4)	0.003(4)	0.009(3)	0.010(4)
C(71a)	4*a*	0.0556(3)	0.1608(7)	0.4224(6)	0.044(3)	0.031(4)	0.064(4)	0.002(4)	0.012(3)	0.002(3)
C(72b)	4*a*	0.2549(4)	0.843(1)	0.6765(5)	0.066(5)	0.057(5)	0.073(5)	0.007(4)	0.018(4)	0.017(4)
C(72a)	4*a*	0.0429(3)	0.1281(9)	0.5068(5)	0.048(4)	0.050(5)	0.055(5)	−0.005(4)	0.005(3)	0.012(3)
C(73b)	4*a*	0.1950(4)	0.780(1)	0.6751(6)	0.057(5)	0.087(7)	0.102(7)	0.011(6)	0.031(5)	0.025(5)
C(73a)	4*a*	−0.0147(4)	0.072(1)	0.5138(5)	0.066(5)	0.054(5)	0.066(5)	−0.009(4)	0.015(4)	0.009(4)
C(74b)	4*a*	0.1822(4)	0.612(2)	0.6527(7)	0.056(5)	0.107(8)	0.084(7)	−0.009(6)	0.011(4)	0.041(5)
C(74a)	4*a*	−0.0610(3)	0.047(1)	0.4372(6)	0.053(4)	0.054(5)	0.089(6)	−0.013(5)	0.019(4)	0.006(4)
C(75b)	4*a*	0.2275(4)	0.507(1)	0.6329(6)	0.063(4)	0.067(6)	0.065(5)	−0.014(4)	0.005(4)	0.015(4)
C(75a)	4*a*	−0.0498(3)	0.076(1)	0.3534(5)	0.057(4)	0.059(5)	0.067(5)	−0.015(5)	0.003(4)	−0.010(4)
C(76b)	4*a*	0.2855(3)	0.571(1)	0.6349(5)	0.057(4)	0.054(5)	0.046(4)	−0.007(4)	0.008(3)	0.011(4)
C(76a)	4*a*	0.0086(3)	0.1344(9)	0.3464(5)	0.060(4)	0.049(5)	0.055(5)	−0.005(4)	0.017(4)	−0.005(4)

Zeitschrift für Kristallographie 209, 771–772 771

Crystal structure of 9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-1,8-diene-2-one, $C_{13}H_{11}Cl_2NO_2$

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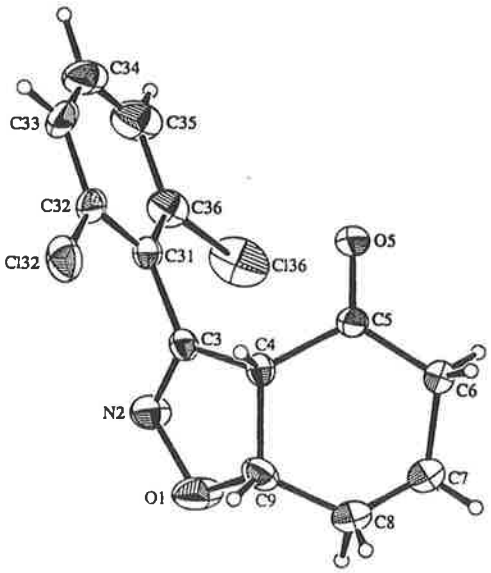

Source of material: see ref. 1; crystals obtained from ethyl acetate/light petroleum (313 - 333 K) with m. p. 439 - 442 K. The determination shows that the aryl group lies to the same side of the molecule as the oxo (O(5)) function. The five-membered ring, the mean deviation of the atoms is 0.033 Å, forms a dihedral angle of 71.4° with the aryl group. The six-membered ring of the fused system adopts a flattened chair conformation.

$C_{13}H_{11}Cl_2NO_2$, monoclinic, $P2_1/c$ (No. 14),
a = 10.056(2) Å, b = 12.924(2) Å, c = 10.369(2) Å,
β = 107.99(1)°, V = 1281.7 Å^3, Z = 4, $R(F)$ = 0.071,
$R_w(F)$ = 0.060.

References

1. Easton, C.J., Hughes, C.M., Tiekink, E.R.T., Lubin, C.E., Savage, G.P., Simpson, G.W.: Reversal of regiochemistry in the synthesis of isoxazoles by nitrile oxide cycloadditions. Tetrahedron Lett. **35** (1994) 3589-3592.

Table 1. Parameters used for the X-ray data collection

Crystal:	multifaceted, colorless crystal, size 0.24 x 0.24 x 0.33 mm
Wave length:	Mo $K\alpha$ radiation (0.7107 Å)
μ:	4.98 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
$N(hkl)_{unique}$:	3212
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	164
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(4)	4*e*	0.19053	0.71649	0.06719	0.04932
H(6a)	4*e*	–0.12033	0.52978	–0.22506	0.07413
H(6b)	4*e*	–0.10185	0.59253	–0.08942	0.07413
H(7a)	4*e*	–0.19434	0.65588	–0.34788	0.14582
H(7b)	4*e*	–0.23788	0.69315	–0.22105	0.14582
H(8a)	4*e*	–0.14237	0.78873	–0.35148	0.15572
H(8b)	4*e*	–0.13626	0.8098	–0.19928	0.15572
H(9)	4*e*	0.06632	0.84439	–0.16322	0.07523
H(33)	4*e*	0.66478	0.58208	–0.01851	0.13925
H(34)	4*e*	0.6497	0.44308	–0.15698	0.13739
H(35)	4*e*	0.45358	0.41577	–0.34576	0.1652

Table 3. Final atomic coordinates and displacement parameters (in $Å^2$)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(32)	4*e*	0.4834(2)	0.7402(2)	–0.0104(2)	0.099(2)	0.121(2)	0.111(2)	–0.041(1)	0.009(1)	0.001(1)
Cl(36)	4*e*	0.1967(4)	0.5157(2)	–0.4367(3)	0.224(3)	0.120(2)	0.101(2)	–0.001(2)	0.029(2)	–0.041(2)
O(1)	4*e*	0.0819(6)	0.8081(5)	–0.3407(6)	0.133(5)	0.135(5)	0.104(4)	0.063(4)	0.056(4)	0.052(4)
O(5)	4*e*	0.1358(5)	0.5192(4)	–0.1213(6)	0.080(4)	0.079(4)	0.184(6)	0.023(4)	0.064(4)	0.046(3)
N(2)	4*e*	0.2008(7)	0.7524(5)	–0.3395(6)	0.105(5)	0.100(5)	0.081(4)	0.027(4)	0.048(4)	0.024(4)
C(3)	4*e*	0.2317(6)	0.6910(5)	–0.2421(6)	0.063(4)	0.062(4)	0.054(4)	–0.006(3)	0.023(3)	0.006(3)
C(4)	4*e*	0.1365(6)	0.6962(5)	–0.1584(6)	0.063(4)	0.065(4)	0.053(4)	–0.008(3)	0.024(3)	0.000(4)
C(5)	4*e*	0.0666(7)	0.5950(6)	–0.1509(7)	0.063(4)	0.067(5)	0.076(5)	0.008(4)	0.032(4)	0.013(4)
C(6)	4*e*	–0.0842(7)	0.5930(6)	–0.1762(8)	0.061(5)	0.076(5)	0.108(6)	–0.001(4)	0.027(4)	0.013(4)
C(7)	4*e*	–0.1596(9)	0.6796(9)	–0.255(1)	0.067(6)	0.119(8)	0.23(1)	0.013(9)	0.022(7)	0.068(6)
C(8)	4*e*	–0.103(1)	0.765(1)	–0.258(2)	0.074(7)	0.15(1)	0.37(2)	0.03(1)	0.036(9)	0.142(7)
C(9)	4*e*	0.0437(9)	0.7853(5)	–0.2239(8)	0.104(6)	0.052(4)	0.099(6)	0.003(4)	0.041(5)	0.003(4)
C(31)	4*e*	0.3507(7)	0.6226(5)	–0.2230(7)	0.066(4)	0.073(5)	0.070(4)	0.003(4)	0.038(4)	0.013(4)
C(32)	4*e*	0.4734(8)	0.6377(6)	–0.1172(8)	0.065(5)	0.102(6)	0.102(6)	0.009(5)	0.048(5)	0.035(5)
C(33)	4*e*	0.5809(9)	0.571(1)	–0.094(1)	0.060(6)	0.15(1)	0.16(1)	0.020(8)	0.057(6)	0.063(7)
C(34)	4*e*	0.572(1)	0.491(1)	–0.176(2)	0.14(1)	0.14(1)	0.20(2)	0.07(1)	0.12(1)	0.08(1)
C(35)	4*e*	0.457(2)	0.4735(9)	–0.285(1)	0.18(1)	0.114(9)	0.16(1)	0.051(8)	0.11(1)	0.02(1)
C(36)	4*e*	0.3468(9)	0.5406(7)	–0.3044(8)	0.118(7)	0.087(6)	0.092(6)	0.013(5)	0.054(6)	–0.004(6)

J. CHEM. SOC. PERKIN TRANS. 1 1994

Synthesis of Each Stereoisomer of [3-$^2H_1$]Phenylalanine and Evaluation of the Stereochemical Course of the Reaction of (*R*)-Phenylalanine with (*S*)-Phenylalanine Ammonia-lyase

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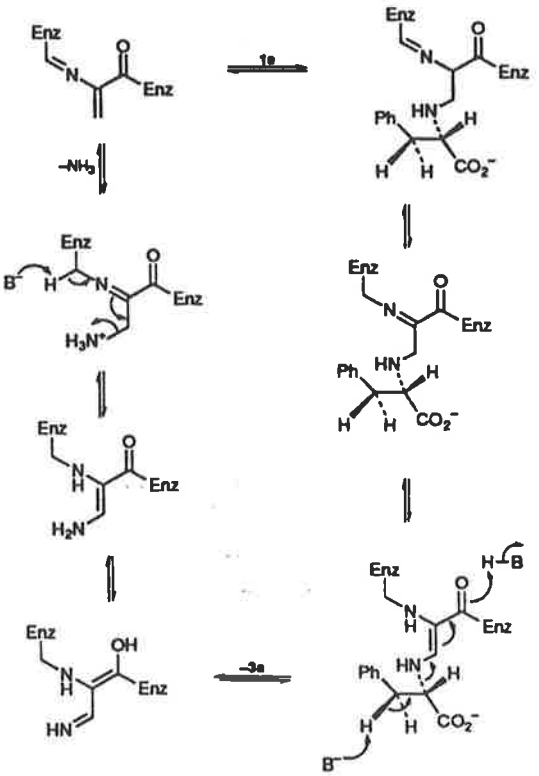
The four stereoisomers of [3-$^2H_1$]phenylalanine have been prepared, each as a single enantiomer in *ca.* 98% diastereoisomeric excess and with *ca.* 99% deuterium incorporation, by side-chain bromination of phenylalanine derivatives, followed by deuteriolysis of each of the diastereoisomeric product bromides with deuterium over 5% palladium-on-carbon. The latter reactions proceeded with retention of configuration. (2*R*,3*S*)-[3-$^2H_1$]Phenylalanine reacted with (*S*)-phenylalanine ammonia-lyase to give [3-$^2H_1$]-*trans*-cinnamic acid, with 92% deuterium incorporation, while the (2*R*,3*R*)-stereoisomer of the deuteriated phenylalanine gave [3-$^2H_1$]-*trans*-cinnamic acid with 27% deuterium incorporation. These results indicate that reaction of (*R*)-phenylalanine with the enzyme involves mainly loss of the 3-*pro*-*R* hydrogen and ammonia, in an antiperiplanar elimination process analogous to that previously reported for (*S*)-phenylalanine, while a minor pathway for reaction of (*R*)-phenylalanine is either isomerization to (*S*)-phenylalanine, before elimination, or synperiplanar elimination.

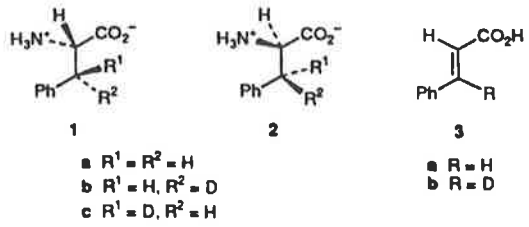
(*S*)-Phenylalanine ammonia-lyase (PAL) catalyses the elimination of ammonia and a proton from (*S*)-phenylalanine **1a**, to give *trans*-cinnamic acid **3a**, in a transformation that has been studied extensively and is thought to occur as shown in Scheme 1.[1-4] Battersby and his co-workers[1] examined the stereoselectivity of the proton transfer from the substrate. They observed that (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** underwent the enzyme-catalysed reaction to give [3-$^2H_1$]-*trans*-cinnamic acid **3b**, while (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** gave the unlabelled acid **3a**, establishing that PAL removes the 3-*pro*-*S* hydrogen from (*S*)-phenylalanine **1a** in an antiperiplanar elimination process.

(*R*)-Phenylalanine **2a** is a competitive inhibitor of PAL and a poor substrate of the enzyme, being converted into *trans*-cinnamic acid **3a** at a rate $\leqslant$1/5000th of that for reaction of (*S*)-phenylalanine **1a**.[2] No studies of the stereochemical course of the reaction of PAL with (*R*)-phenylalanine **2a** have been reported and we were intrigued to determine how the enzyme catalyses the reaction of this compound having the opposite stereochemistry to that of the natural substrate **1a**. We have, therefore, investigated the interaction of PAL with (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** and the corresponding (2*R*,3*R*)-isomer **2c**.

Although a variety of methods have been reported for the stereoselective synthesis of the [3-$^2H_1$]phenylalanine isomers **1b**, **c** and **2b**, **c**,[1,5] they are indirect and involve the use of enzymes either to introduce chirality or to separate enantiomers. We chose to develop an alternative route for the synthesis of the deuteriated phenylalanine derivatives **1b**, **c** and **2b**, **c**, by direct elaboration of the corresponding phenylalanine enantiomers **1a** and **2a**. The procedure is based on our previous studies of the side-chain halogenation of *N*-phthaloylamino acid derivatives, with retention of chirality at the α-position.[6]



Scheme 1



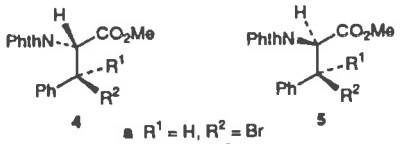
1 **2** **3**

a $R^1 = R^2 = H$
b $R^1 = H, R^2 = D$
c $R^1 = D, R^2 = H$

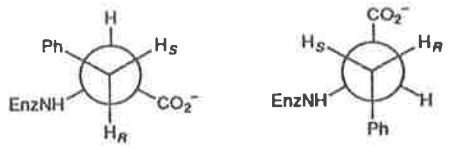
a R = H
b R = D

Results and Discussion

The (2*R*,3*S*)-β-bromophenylalanine derivative **4a** and the (2*R*,3*R*)-diastereoisomer **4b** were prepared from (*S*)-phenylalanine **1a** as previously reported.[6] The corresponding (2*S*,3*S*)-bromide **5a** and the (2*S*,3*R*)-isomer **5b** were obtained in an identical fashion from (*R*)-phenylalanine **2a**, and had spectral and physical properties comparable to those of their respective enantiomers **4b** and **4a**.



a $R^1 = H, R^2 = Br$
b $R^1 = Br, R^2 = H$
c $R^1 = H, R^2 = D$
d $R^1 = D, R^2 = H$



(*a*) (*b*)

Fig. 1 Newman projections of the preferred conformation of (*a*) (*S*)-phenylalanine **1a** and (*b*) (*R*)-phenylalanine **2a** bound to PAL

A variety of methods for the stereocontrolled synthesis of the deuteriated phenylalanine derivatives **4c**, **d** and **5c**, **d**, from the respective bromides **4a**, **b** and **5a**, **b**, was investigated. Reactions with tributyltin deuteride occurred with only low stereoselectivity. Sodium borodeuteride was found to be an unsuitable reagent for the interconversion because the bromide **4a** reacted with sodium borohydride by reduction of the imide functionality,[7] instead of by substitution of the benzylic halide.[8] The zinc chloride complex of sodium cyanoborohydride is reported[9] to reduce benzylic halides without affecting amides or imides, but the bromide **4a** was inert to treatment with this reagent. Finally, the deuterides **4c**, **d** and **5c**, **d** were prepared in a stereocontrolled manner by deuteriolysis of the corresponding bromides **4a**, **b** and **5a**, **b**, with 5% palladium-on-carbon as the catalyst, under an atmosphere of deuterium. The stereoselectivity of the reduction depended on the reaction conditions. In a mixture of tetrahydrofuran and deuterium oxide, the bromide **4a** gave a 13:1 mixture of the deuteriated phenylalanine derivatives **4c** and **4d** when the reaction was conducted at 25 °C, while the product ratio increased to 27:1 when the reaction was performed at 5 °C. At −20 °C, changing to methan[$^2H_1$]ol as the solvent in order to prevent freezing, the deuteride **4c** was obtained in *ca.* 98% diastereoisomeric excess, and with *ca.* 99% $^2H_1$ incorporation regiospecifically at the β-position. At lower temperatures the bromide **4a** failed to react. These conditions for the stereocontrolled synthesis of the deuteride **4c** from the bromide **4a** were used to prepare the deuteriated phenylalanine derivatives **4d** and **5c**, **d** from the bromides **4b** and **5a**, **b**, respectively, each in *ca.* 98% diastereoisomeric excess and with *ca.* 99% $^2H_1$ incorporation. The extent of deuterium incorporation in each of the phenylalanine derivatives **4c**, **d** and **5c**, **d** was determined using ^1H NMR spectroscopy and mass spectrometry. ^1H NMR spectroscopy was used to measure the diastereoisomeric excess, with each of the deuterides **4c** and **5d** giving rise to a doublet resonance at δ 3.53 (J 11.7 Hz) due to the β-proton, while the corresponding signal for the stereoisomers **4d** and **5c** appeared at δ 3.59 (J 4.8 Hz).

The deuterides **4c**, **d** and **5c**, **d** were each hydrolysed in a 2:1 mixture of 6 mol dm^{-3} hydrochloric acid and acetic acid, with subsequent treatment with aniline in ethanol giving the corresponding free amino acids **1c**, **b** and **2b**, **c**, without loss of stereochemical integrity or deuterium content. The diastereoisomeric excess of each of the free amino acids **1b**, **c** and **2b**, **c** was determined using ^1H NMR spectroscopy. The spectra of the deuterides **1b** and **2b** showed doublet signals at δ 3.92 and 3.21, with a coupling constant of 4.9 Hz, corresponding to the α- and β-protons, respectively. The corresponding signals for the diastereoisomers **1c** and **2c** appeared at δ 3.92 and 3.03, with a coupling constant of 7.9 Hz. By comparison of their ^1H NMR spectra with literature data,[1,5] it was possible to assign the relative stereochemistry of the deuterides **1b**, **c** and **2b**, **c**, while their absolute stereochemistry is predetermined by that of the starting phenylalanine enantiomers **1a** and **2a**. From these stereochemical assignments it is clear that deuteriolysis of the bromides **4a**, **b** and **5a**, **b** proceeds with retention of configuration, consistent with other reports of hydrogenolysis of benzylic halides.[10]

With the deuteriated phenylalanine derivatives **1b**, **c** and **2b**, **c** in hand, their interaction with PAL was investigated. In accord with Battersby's studies,[1] the reaction of (2*S*,3*R*)-[3-$^2H_1$]-phenylalanine **1b**, in sodium borate buffer at pH 8.7, gave [3-$^2H_1$]-*trans*-cinnamic acid **3b**, with 98% deuterium incorporation. The deuterium content was determined by integration of the ^1H NMR signals at δ 6.47 (J 16.0 Hz) and 7.81 (J 16.0 Hz), corresponding to the α-and β-protons, respectively, of the unlabelled acid **3a**, and the broad singlet signal at δ 6.47, for the α-proton of the deuteriated species **3b**. The outcome of the reaction is consistent with stereospecific loss of the 3-*pro*-*S* hydrogen in the reaction of (*S*)-phenylalanine **1a**.[1] Production of the 2% unlabelled contaminant **3a** in the deuteriated acid **3b** can be attributed to reaction of the 1% unlabelled (*S*)-phenylalanine **1a** and the 1% (2*S*,3*S*)-[3-$^2H_1$]-phenylalanine **1c** impurities in the (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b**. Thus, this result confirms the stereochemical assignment, diastereoisomeric excess and deuterium content of the deuteride **1b** and, by analogy, the stereoisomers **1c** and **2b**, **c**, since they were prepared using the same procedures.

Treatment of (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** with PAL gave the unlabelled acid **3a**. Again this result is in accord with Battersby's studies and consistent with stereospecific loss of the 3-*pro*-*S* hydrogen in the reaction of (*S*)-phenylalanine **1a**.[1] A contaminant of *ca.* 1% of the labelled material **3b** would be expected in the acid **3a** produced from the reaction of the phenylalanine derivative **1c**, due to the presence of the 1% impurity of the stereoisomer **1b** in the starting material, but this was not detected in the ^1H NMR spectrum, presumably because the signals were masked by those of the dominant product **3a**.

When (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** was treated with PAL, [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation was obtained, whereas the reaction of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** with the enzyme gave the labelled acid **3b** with 27% deuterium incorporation. These results establish that while the loss of hydrogen from (*R*)-phenylalanine **2a** in the conversion to *trans*-cinnamic acid **3a** is not stereospecific, the enzyme preferentially abstracts the 3-*pro*-*R* hydrogen from this substrate. It is thus apparent that the reversal of stereochemistry of the substrate, from (*S*)-phenylalanine **1a** to the (*R*)-enantiomer **2a**, results in a reversal of the stereoselectivity of β-hydrogen abstraction.

This outcome can be explained by considering the likely orientation of the substrates **1a** and **2a** in the enzyme active site. It is reasonable to assume that the conformation of (*S*)-phenylalanine **1a** bound to the enzyme is as shown in Fig. 1a, where the amino, carboxyl and phenyl substituents, and the 3-*pro*-*S* hydrogen which is abstracted, are coplanar, and the carboxyl and phenyl substituents are antiperiplanar, as are the 3-*pro*-*S* hydrogen and the amino substituent. The antiperiplanar orientation of the carboxyl and phenyl substituents is consistent with the observation that *trans*-cinnamic acid **3a** binds very effectively to the enzyme active site,[2] while the spatial arrangement of the amino substituent and the 3-*pro*-*S* hydrogen facilitates their elimination. It is likely that with (*R*)-

phenylalanine **2a**, the phenyl, carboxyl and amino substituents interact with the enzyme *via* the same recognition sites involved in binding (*S*)-phenylalanine **1a**, and therefore adopt a coplanar orientation with the phenyl and carboxyl groups antiperiplanar (Fig. 1b). In this conformation, since the 3-*pro-R* hydrogen is located in the plane of the phenyl, carboxyl and amino substituents, and antiperiplanar to the amino substituent, it is located near that of the 3-*pro-S* hydrogen of bound (*S*)-phenylalanine **1a** and is removed in the enzyme-catalysed elimination.

There are two possible explanations for the lack of stereospecificity in the reactions of the deuteriated phenylalanine derivatives **2b** and **2c**. In a synperiplanar elimination, abstraction of the 3-*pro-S* hydrogen from (*R*)-phenylalanine **2a** may compete with loss of the 3-*pro-R* hydrogen. If the extent of this reaction is *ca.* 15%, a deuterium isotope effect of *ca.* 1.8 would account for the reaction of (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** to give [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation and of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** to give the acid **3b** with 27% deuterium incorporation. Alternatively, reversible abstraction of the α-hydrogen from (*R*)-phenylalanine **2a**, and racemization, may compete with loss of the 3-*pro-R* hydrogen. There was no evidence of racemization in partially reacted samples of (*R*)-phenylalanine **2a**, but it is unlikely that the concentration of the product (*S*)-phenylalanine **1a** would build up to detectable levels under these circumstances. Instead, being a better substrate for the enzyme, (*S*)-phenylalanine **1a** would be converted rapidly into *trans*-cinnamic acid **3a**, with loss of the 3-*pro-S* hydrogen. Based on this hypothesis, the reaction of (2*R*,3*S*)-[3-$^2H_1$]phenylalanine **2b** to give [3-$^2H_1$]-*trans*-cinnamic acid **3b** with 92% deuterium incorporation indicates a selectivity of *ca.* 11.5:1 for loss of the 3-*pro-R* hydrogen over racemization, while the comparison with the reaction of (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** to give the acid **3b** with 27% deuterium incorporation reflects a deuterium isotope effect of *ca.* 3.4 for loss of the β-hydrogen.

In any event, the primary response of PAL to the change in stereochemistry of the substrate, from (*S*)-phenylalanine **1a** to the (*R*)-enantiomer **2a**, is to reverse the stereoselectivity of β-hydrogen abstraction. Accordingly, the loss of a hydrogen and ammonia from each of the phenylalanine enantiomers **1a** and **2a** involves mainly antiperiplanar elimination.

Experimental

General experimental details have been reported previously.[6] PAL (Grade 1 from *Rhodotorula glutinis*; solution in 60% glycerol, 3 mmol dm^{-3} Tris-HCl, pH 7.5) was purchased from Sigma Chemical Co., and used without further purification. The brominated phenylalanine derivatives **4a**, **b** and **5a**, **b** were synthesized from the corresponding phenylalanine enantiomers **1a** and **2a**, using literature procedures.[6]

(2S,3S)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **4c**.—A mixture of the bromide **4a** (1.0 g, 2.6 mmol) and 5% palladium-on-carbon (100 mg) in methan[$^2H_1$]ol (99.5% deuteriated; 20 cm^3) was stirred at −20 °C under an atmosphere of deuterium gas for 72 h, after which it was filtered and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in dichloromethane and the solution was washed with 10% aqueous sodium carbonate, dried and concentrated under reduced pressure. Crystallization of the residual oil from hexane–ethyl acetate gave the deuteride **4c** as colourless prisms (717 mg, 90%), m.p. 125–127 °C; δ($CDCl_3$) 3.53 (d, *J* 11.7, 1 H), 3.77 (s, 3 H), 5.16 (d, *J* 11.7, 1 H), 7.11–7.19 (m, 5 H) and 7.65–7.78 (m, 4 H); *m/z* 310 (M^+, 99% $^2H_1$). The ^1H NMR spectrum showed that the deuteride **4c** was contaminated with *ca.* 1% of the diastereoisomer **4d**.

(2S,3R)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **4d**.—The deuteride **4d**, prepared in 91% yield from **4b** as described above for the synthesis of the diastereoisomer **4c**, had m.p. 124–126 °C; δ($CDCl_3$) 3.59 (d, *J* 4.8, 1 H), 3.77 (s, 3 H), 5.16 (d, *J* 4.8, 1 H), 7.11–7.19 (m, 5 H) and 7.65–7.78 (m, 4 H); *m/z* 310 (M^+, 99% $^2H_1$). The ^1H NMR spectrum showed that the deuteride **4d** was contaminated with *ca.* 1% of the diastereoisomer **4c**.

(2R,3S)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **5c** *and* (2R,3R)-[3-$^2H_1$]-N-*Phthaloylphenylalanine Methyl Ester* **5d**.—The deuterides **5c** and **5d**, prepared from the corresponding bromides **5a** and **5b** as described above for the synthesis of the deuteride **4c**, had spectral and physical properties comparable to those of the corresponding enantiomers **4d** and **4c**.

(2S,3R)-[3-$^2H_1$]*Phenylalanine* **1b**.—A solution of the deuteride **4d** (500 mg, 1.6 mmol) in 6 mol dm^{-3} hydrochloric acid–acetic acid (2:1; 30 cm^3) was heated at reflux for 6 h, after which it was cooled and concentrated under reduced pressure. Water (30 cm^3) was added to the residual oil and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in a dry mixture of aniline (1.5 cm^3) and ethanol (15 cm^3). The precipitate that formed over 96 h was filtered off and washed with acetone to give (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** as a colourless powder (223 mg, 83%), m.p. 272–276 °C; δ(D_2O) 3.21 (d, *J* 4.9, 1 H), 3.92 (d, *J* 4.9, 1 H) and 7.24–7.38 (m, 5 H); *m/z* 167 (M^+ + 1, 99% $^2H_1$). This spectral data is consistent with that reported.[1,5] The ^1H NMR spectrum showed that the deuteride **1b** was contaminated with *ca.* 1% of the diastereoisomer **1c**.

(2S,3S)-[3-$^2H_1$]*Phenylalanine* **1c**.—The deuteride **1c**, prepared in 85% yield from **4c** as described above for the synthesis of diastereoisomer **1b**, had m.p. 270–275 °C; δ(D_2O) 3.03 (d, *J* 7.9, 1 H), 3.92 (d, *J* 7.9, 1 H) and 7.24–7.38 (m, 5 H); *m/z* 167 (M^+ + 1, 99% $^2H_1$). This spectral data is consistent with that reported.[1,5] The ^1H NMR spectrum showed that the deuteride **1c** was contaminated with *ca.* 1% of the diastereoisomer **1b**.

(2R,3S)-[3-$^2H_1$]*Phenylalanine* **2b** *and* (2R,3R)-[3-$^2H_1$]-*Phenylalanine* **2c**.—The free amino acids **2b** and **2c**, prepared from the corresponding protected derivatives **5c** and **5d** as described above for the synthesis of the deuteride **1b**, had spectral and physical properties comparable to those of the corresponding enantiomers **1b** and **1c**.

Reaction of (2S,3R)-[3-$^2H_1$]*Phenylalanine* **1b** *Catalysed by PAL*.—A solution of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** (33 mg, 0.20 mmol) and PAL (0.2 cm^3, 0.5 units) in sodium borate buffer (0.04 mol dm^{-3}, pH 8.7; 25 cm^3) was stirred at 30 °C for 20 h, after which it was acidified to pH 1, by adding concentrated hydrochloric acid, and extracted with dichloromethane (2 × 25 cm^3). The combined extracts were dried and concentrated under reduced pressure and crystallization of the residual oil gave [3-$^2H_1$]-*trans*-cinnamic acid **3b** (15.9 mg, 54%), m.p. 135–137 °C; δ($CDCl_3$) 6.47 (br s, 1 H), 7.41–7.44 (m, 3 H) and 7.55–7.58 (m, 2 H). The ^1H NMR spectrum showed that the deuteriated acid **3b** was contaminated with *ca.* 2% of the unlabelled material **3a**.

Reaction of (2S,3S)-[3-$^2H_1$]*Phenylalanine* **1c** *Catalysed by PAL*.—Treatment of (2*S*,3*S*)-[3-$^2H_1$]phenylalanine **1c** with PAL, as described above for the reaction of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b**, gave *trans*-cinnamic acid **3a** (17.8 mg, 60%), m.p. 134–136 °C (lit.,[11] 132 °C); δ($CDCl_3$) 6.47 (d, *J* 16.0, 1 H), 7.41–7.44 (m, 3 H), 7.55–7.58 (m, 2 H) and 7.81 (d, *J* 16.0, 1 H).

Reaction of (2R,3S)-[3-$^2H_1$]*Phenylalanine* **2b** *and* (2R,3R)-[3-$^2H_1$]*Phenylalanine* **2c** *Catalysed by PAL.*—(2*R*,3*S*)-[3-$^2H_1$]Phenylalanine **2b** and (2*R*,3*R*)-[3-$^2H_1$]phenylalanine **2c** were each treated with PAL, as described above for the reaction of (2*S*,3*R*)-[3-$^2H_1$]phenylalanine **1b** except that the mixtures were each allowed to react for 8 days, and gave [3-$^2H_1$]-*trans*-cinnamic acid **3b**, in yields of 70% (92% $^2H_1$) and 59% (27% $^2H_1$), respectively, with spectral and physical properties comparable with those of the sample obtained as described above. In each case the deuterium content was determined from the ratio of signals due to the acid **3a** and the labelled species **3b** in the ^1H NMR spectrum.

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Cycloaddition Reactions of Nitrile Oxides with Alkenes

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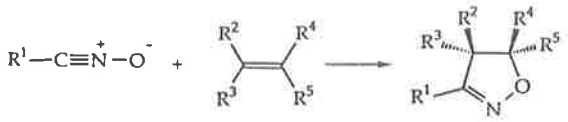
I. Introduction

Reactions of nitrile oxides with alkenes to give Δ^2-isoxazolines (hereinafter referred to as isoxazolines) (Scheme 1) have continued to attract attention since the pioneering work of Werner and Buss in 1894 (1894CB2193), Wieland in 1907 (07CB418, 07CB1667) and Quilico *et al.* in 1950 [50G479, 50N(L)226]. Huisgen categorized these processes as being members of the broad class of [3 + 2] cycloaddition reactions [61MI1; 63AG(E)565, 63AG(E)633]. Their mechanistic aspects have been the subject of considerable debate and, more recently, their synthetic potential has been the object of intensive study.

The extent and diversity of research in this area have led to earlier reviews (64MI1; 71MI1; 75ACR361; 77MI1; 83MI1; 84MI1; 88MI1; 91HC1). Caramella and Grünanger summarized work to 1980 as part of a review of the chemistry of nitrile oxides and imines (84MI1). Later, Grünanger and Vita-Finzi reviewed the synthesis of isoxazolines to 1984 (91HC1). Torssell surveyed the literature relating to the use of nitrile oxides, nitrones, and nitronates in organic synthesis to 1985, with an addendum incorporating work published before August 1987 (88MI1). The

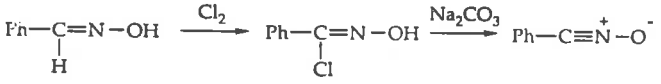


SCHEME 1

publication of more than two hundred papers since 1987 on reactions of nitrile oxides with alkenes is testament to the continued interest in the field and has prompted the current review, which covers literature published between 1985 and 1992. Some work from 1993 and unpublished material are also discussed. Earlier work has been included only where it is required to put more recent developments in context. Research trends are illustrated with representative rather than exhaustive examples. Particular attention is given to dramatic improvements in the degree of stereocontrol that has been attained in intermolecular reactions and to developments in the use of intramolecular nitrile oxide cycloaddition (INOC) reactions, where the predisposition of the reacting groups within a molecule greatly enhances the regio- and stereo-selectivity.

II. Nitrile Oxide Synthesis

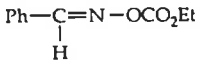
The synthesis of benzonitrile oxide (**3**) by chlorination of benzaldoxime (**1**) to give benzhydroximinoyl chloride (**2**), followed by dehydrohalogenation with sodium carbonate (Scheme 2), as established by Werner and Buss (1894CB2193), formed the basis of what remains the most common approach for synthesis of nitrile oxides. Chlorination has been accomplished using chlorine, although ring chlorination occurs with aryl systems that are substituted with electron-donating groups (89CPB2519). Alternative chlorinating agents include nitrosyl chloride (27LA161), *N*-chlorosuccinimide (80JOC3916), hypochlorite (86SC763; 87TL3189), chloramine-T (*N*-chloro-*N*-sodio-4-methylbenzenesulfonamide) (89S57), 1-chlorobenzotriazole (90SC1373), iodobenzene dichloride (91SC1625), and hydrogen chloride in DMF/OXONE (92JOC1088). Tertiary amines, particularly triethylamine, are commonly used in place of carbonate [61AG656, 61TL583; 78JCS(P2)607]. Aluminium oxide (85T5569), Flori-



(1) (2) (3)

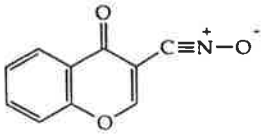
SCHEME 2

sil (85T5569), molecular sieves (90H1693), hexabutylditin (87SC1199), bis(tributyltin) oxide (91CC17), tetraphenyltin (91CC17), tributyltin hydride (91CC1671), and alkali metal fluorides (91H477) have also been used as dehydrohalogenating agents. Other variations include bromination instead of chlorination, using hypobromite (65JOC2809), sodium bromite with a catalytic amount of tributyltin chloride (89TL3987), or *N*-bromosuccinimide (68JOC476), and thermal dehydrohalogenation of the hydroximinoyl halide (63BSB719; 86MI1; 89JOC2209). Thermolysis has also been used to generate the nitrile oxide from the *O*-ethoxycarbonylaldoxime (**4**) (91BCJ318). Nitrile oxides have also been obtained through electrolysis of aldoximes in methanol containing sodium chloride (89JOC2249; 90MI1) and by oxidation of aldoximes with dimethyl dioxirane (92NKK420) or mercuric acetate (92OPP91).

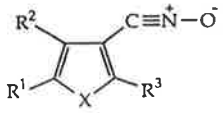


(4)

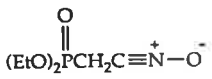
Examples of the variety of nitrile oxides that can be prepared from the corresponding aldoximes include the chromone derivative (**5**) (88H1127), the thiophene derivatives (**6a**) (88KGS1034; 89KGS1620; 91CCC1315), the furan derivatives (**6b**) (91CCC1315), the phosphorus-functionalized nitrile oxide (**7**) (86CL183; 87BCJ2463; 88BCJ2133; 89BCJ171), and the ribose derivative (**8**) (89TL3675). Dibromoformaldoxime gave the nitrile oxide (**9**) in water, for direct reaction with water soluble olefins (92TL3113). Metal-chelated nitrile oxides (**10**) were obtained by treat-



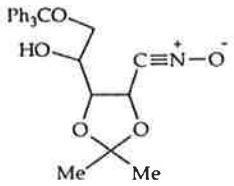
(5)



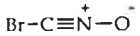
(6)
a) X = S
b) X = O



(7)



(8)



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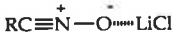

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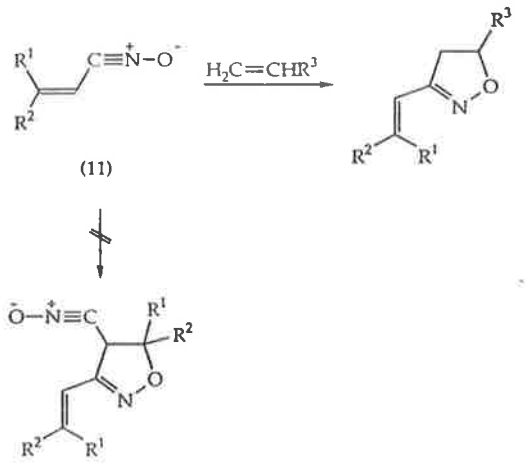
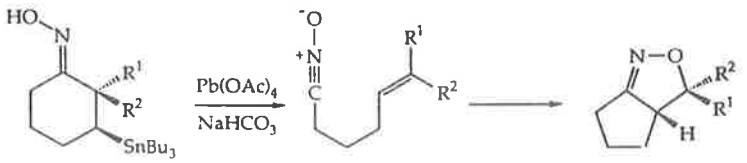


(11)

SCHEME 3

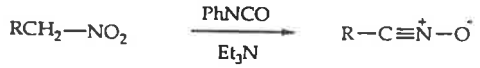
ment of benzhydroximinoyl chloride (**2**) with organometallics, and used to advantage in cycloaddition reactions, where complexation of the metal with the alkene improved the regio- and stereo-selectivity (91TL6367; 92TL1357). Of particular interest, the α,β-unsaturated nitrile oxides (**11**) were prepared by treating the corresponding aldoximes with *N*-chlorosuccinimide/triethylamine and used in cycloaddition reactions without competing self-condensation (Scheme 3) (90ACS806). A novel method of nitrile oxide synthesis was devised by Nishiyama *et al.* (85JA5310), whereby oxidative fragmentation of β-stannyl oximes gave nitrile oxides and alkenes simultaneously, with control of stereochemistry of the alkenes (Scheme 4).

An alternative common method of nitrile oxide synthesis, frequently referred to as the Mukaiyama method (60JA5339), involves dehydration of primary nitroalkanes using, for example, phenyl isocyanate in the presence of a catalytic amount of triethylamine (Scheme 5). Phosphorus oxychloride (73OS59; 90S817), chloroformate esters (86BCJ2827), aryl



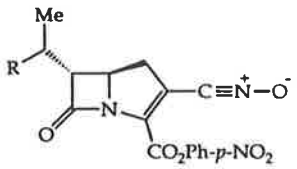
R^1 = Me, R^2 = H
or R^1 = H, R^2 = Me

SCHEME 4

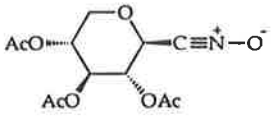


SCHEME 5

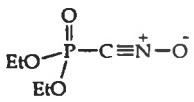
(86BCJ2827, 86M1091) and alkyl sulfonyl chlorides (89MI1), and acetic acid and anhydride (89MI1) have also been used as dehydrating agents, and thionyl chloride has been used with nitroacetamides (89TL3193). The versatility of the method using methyl chloroformate/triethylamine was illustrated through application with the labile carbapenem derivatives (**12**) (84CC1513). The nitrile oxide (**13**) was obtained from the corresponding nitromethylxylose by treatment with tolylene diisocyanate (88CC1339). The nitrile oxide (**14**) was produced from diethylnitromethylphosphonate using phosphorus oxychloride (90S817). The Mukaiyama method is preferable with substrates such as sulfides, which are susceptible to oxidation. Accordingly, nitrile oxides such as (**15**) (88BCJ3973) and (**16**) (90JOC5505, 90TL743) have been prepared from the corresponding nitroalkanes.



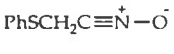
(12)



(13)



(14)



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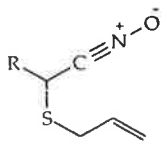
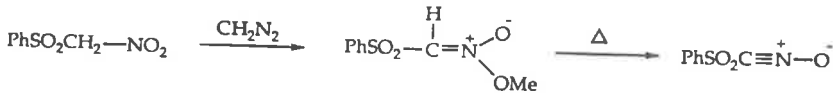


(16)

In related procedures acetyl chloride and acetic anhydride have been used to prepare nitrile oxides from lithium nitronates (86T3825), whereas the nitronic ester (**18**), prepared by *O*-alkylation of the nitroalkane (**17**), underwent thermal elimination of methanol to generate benzenesulfonylnitrile oxide (**19**) (Scheme 6) (84H2187). The latter procedure is potentially HAZARDOUS, as the nitronic ester (**18**) has been reported to be EXPLOSIVE (85JMC1109), and base-induced elimination of methanol from the



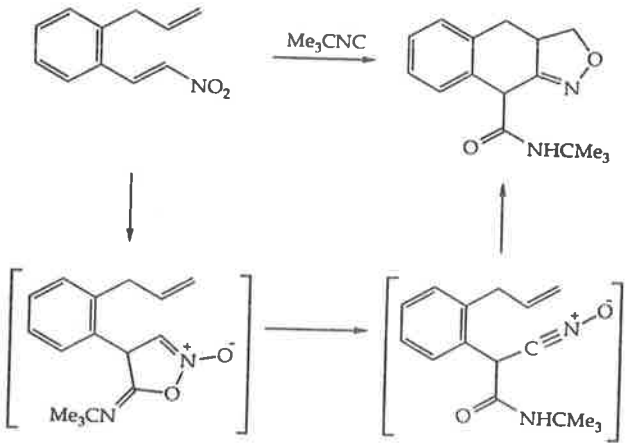
(17) (18) (19)

SCHEME 6

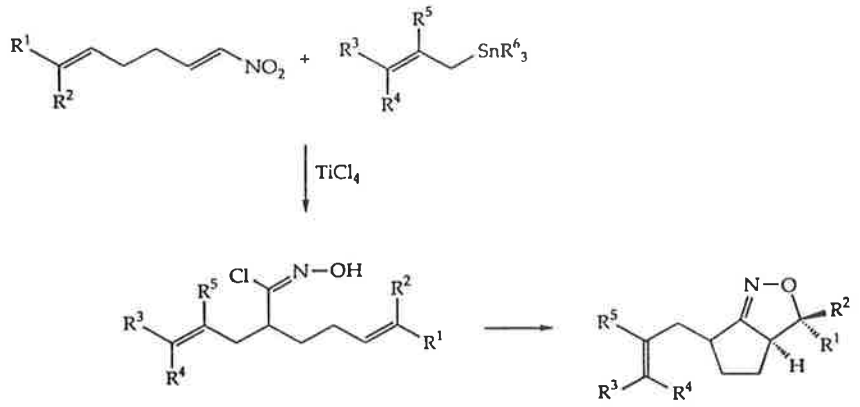
ester (**18**) (85JMC1109) or other standard methods to generate the nitrile oxide (**19**) (81TL3371; 83TL743) are preferable.

Nitroalkenes gave nitrile oxides by conjugate addition with *tert*-butyl isocyanide, followed by intramolecular rearrangement (Scheme 7) (87CC189), or by titanium tetrachloride-mediated conjugate addition of allylstannanes, followed by treatment with base (Scheme 8) [87S471; 89JCS(P1)289]. In each case conjugate addition is concomitant with nitrile oxide formation.

Nitrile oxides are generally unstable and readily undergo dimerization to give the corresponding oxadiazole *N*-oxides (Scheme 9), which are commonly referred to as furazans N-oxides or furoxans. Aryl nitrile oxides usually have a half-life of several hours, whereas aliphatic and acyl nitrile oxides are much more reactive. The dimerization of aryl nitrile oxides is retarded by electron-donating substituents and by bulky groups at the 2- and 6-positions (65JOC2809). Usually, only aryl nitrile oxides such as 2,4,6-trimethyl- and 2,6-dichloro-benzonitrile oxide are sufficiently unreactive to be stored (71MI1); however, other nitrile oxides have been stabilized with tris-(4-bromophenyl)-aminium hexachloroantimonate (93TL4363). Interestingly, 4-methoxy-2,6-dimethylbenzonitrile oxide is



SCHEME 7

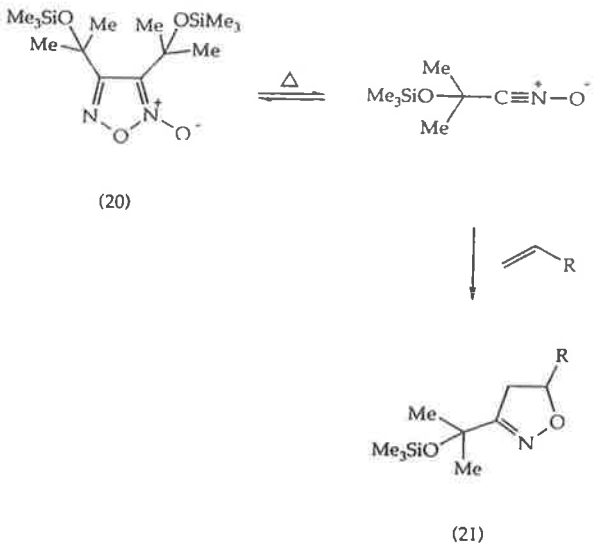


SCHEME 8

sufficiently stable that its structure has been determined through X-ray crystallographic analysis (68CC1409). To diminish competing dimerization, nitrile oxides are generally generated *in situ*, [63AG(E)565] in the presence of excess alkene. Low reaction temperatures and slow addition of reagents have also been used to control the rate of nitrile oxide formation [63AG(E)565; 71MI1]. In this manner, rearrangements of the nitrile oxides (71MI1) are also limited.

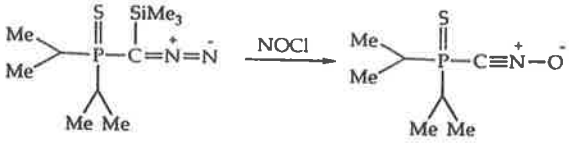
Cycloreversion of furoxans has also been used to generate nitrile oxides *in situ* under thermolytic conditions [72JCS(P1)1587; 76CC240; 79JCR(S)314, 79S36, 79TL2443; 81TL3371]. Of course, dimerization of nitrile oxides becomes inconsequential under these conditions but this procedure is limited by the tendency of nitrile oxides to rearrange to isocyanates, and by the cycloreversion of isoxazoline products, particularly at elevated temperatures [79AG(E)721; 85CB4203]. Curran and Fenk (85JA6023; 86TL4865) performed the thermolysis with bis-[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan) (**20**) and a clean conversion to the isoxazolines (**21**) was observed (Scheme 10). Unprotected hydroxy groups on the alkene were shown to survive the procedure, which is not the case with the Mukaiyama method of nitrile oxide formation, and the cycloaddition with relatively unreactive alkenes proceeded in good yield.

SCHEME 9



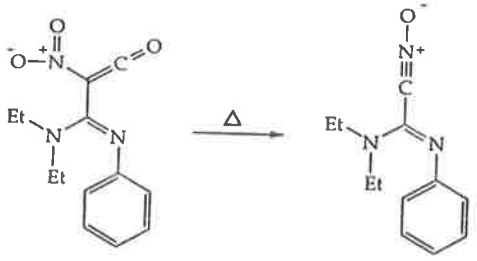
(20) (21)

SCHEME 10



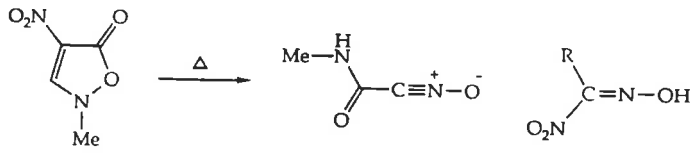
(22) (23)

SCHEME 11



(24) (25)

SCHEME 12



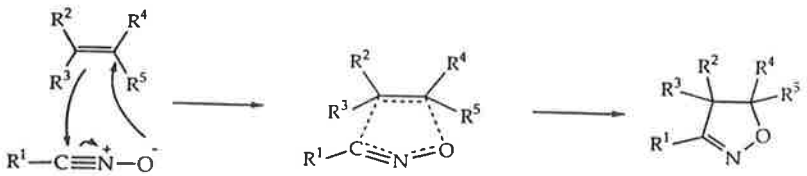
(26) (27) (28)

SCHEME 13

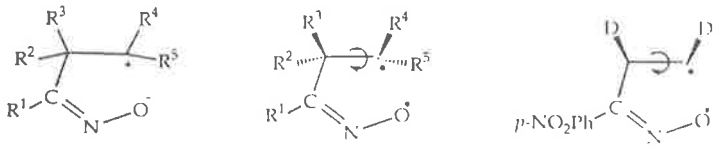
Nitrile oxides have also been identified in several mechanistic studies, although the synthetic utility of these procedures has yet to be examined. Reaction of the trimethylsilylated diazo compound (**22**) with nitrosyl chloride gave the nitrile oxide (**23**) (Scheme 11) (88AG289). The nitrile oxide (**25**) formed on thermolysis of the nitroketene (**24**) (Scheme 12) (92CC485). Heating the nitroisoxazolone (**26**) gave *N*-methylcarbamoylformonitrile oxide (**27**) (Scheme 13) [92H(34)1511]. Nitrile oxides were formed in reactions of arylsulfonyl halides with nitronate ions [88JCS(P2)725], through reactions of nitrolic acids (**28**) with base [91JCS(P2)249] and on treatment of substituted dinitromethane salts with dinitrogen tetroxide (92T6059).

III. Mechanism

The reactions of nitrile oxides with alkenes are 1,3-dipolar cycloadditions and their mechanism has been the subject of numerous investigations. Apart from a one-step concerted mechanism (Scheme 14) (68JOC2291; 76JOC403), stepwise mechanisms proceeding via a zwitterionic intermediate (**29**) (71MI1) or via a diradical (**30**) (68JOC2285) have been proposed. Although there is no direct proof of any of these mechanistic possibilities, there is considerable evidence to suggest that the cyclic electron redistribution is substantially concerted. The configuration of the alkene is retained in the cycloadduct (76JOC403) and the reaction thermodynamics exhibit moderate enthalpy of activation and strongly negative entropy of activation, as expected for a concerted process. Solvent effects have been



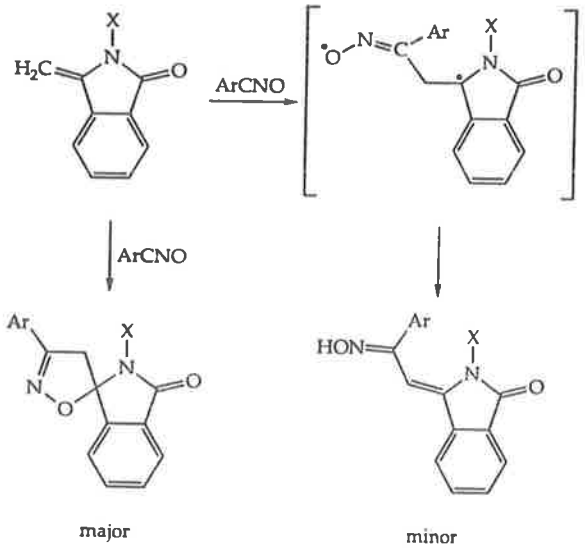
SCHEME 14



(29) (30) (31)

observed for cycloaddition reactions but these are regarded incompatible with the concept of highly polar intermediates (91BCJ3079). Instead they are likely to reflect aggregation of the reactants in solvents in which they have only limited solubility.

As mentioned above, the retention of configuration of the alkene in the cycloadduct is a compelling argument for the concerted mechanism (68JOC2291; 76JOC403) but this assumes that bond rotation in the putative diradical intermediate (**30**) is faster than cyclization (68JOC2285). In support of this assumption, Houk *et al.* (85JA7227) examined the stereoselectivity of the reactions of *cis*- and *trans*-1,2-dideuterioethylene with *p*-nitrobenzonitrile oxide. They calculated that the activation energy for isomerization of the diradical (**31**) would have to be 2.3 kcal mol^{-1} higher than that for cyclization, which is contrary to expectation that the activation barrier for isomerization of the radical would be ≤ 0.4 kcal mol^{-1}—the cycloaddition would have a negative activation energy! There is evidence



SCHEME 15

to suggest, however, that the concerted process may be asynchronous [63AG(E)633; 90JOC4603], and a slower stepwise mechanism cannot be precluded (85JA7227). Diradical intermediates could account for the formation of oximes as by-products in some cycloaddition reactions (Scheme 15) (89JOC5012; 90JOC4603).

IV. Reactivity

Cycloaddition rates range over several orders of magnitude and to predict the likely success of a reaction, when alternative reaction pathways such as nitrile oxide dimerization are possible, it is necessary to understand the reactivity of the system.

The Sustmann frontier molecular orbital (FMO) theory (71TL2717; 74PAC569) has continued to be the basis used to rationalize reactivity (84JHC1397; 85JOC1278, 85MI1; 86JHC1539; 89JHC553; 90CCC2481; 91JHC605, 91M821). According to this model cycloadditions can be divided into three categories (Fig. 1), as follows:

Type I: The cycloaddition involves interaction between the highest occupied molecular orbital (HOMO) of the nitrile oxide and the lowest unoccupied molecular orbital (LUMO) of the olefin.

Type II: The reaction involves both the interaction between the HOMO of the nitrile oxide and the LUMO of the olefin and between the LUMO of the nitrile oxide and the HOMO of the olefin.

Type III: This is the opposite to Type I and involves interaction between the LUMO of the nitrile oxide and the HOMO of the olefin.

In each reaction category the reactivity is inversely proportional to the difference in energy between the interacting orbitals (69BCJ3399; 70FCF85). Electron-donating substituents raise the olefin's FMO energies,

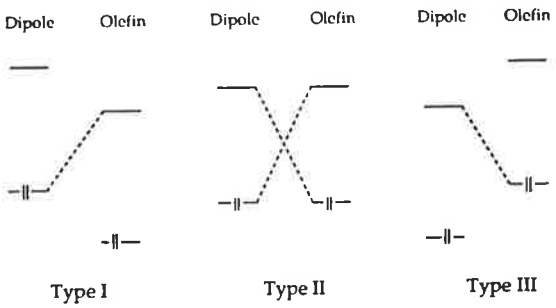


FIG. 1. Sustmann classification of the FMOs for the interaction of nitrile oxides with olefins.

decreasing the reactivity in Type I systems and increasing the reactivity in Type III systems. Conversely, electron-withdrawing substituents lower the olefin's FMO energies, increasing the reactivity in Type I systems and decreasing the reactivity in Type III systems. The effect of olefin substituents on Type II systems depends on which orbital interaction becomes dominant by substitution. With substituents of opposite types, each moderates the effect of the other. Conjugating substituents raise an olefin's HOMO and lower its LUMO, increasing the reactivity of Type I, Type II, and Type III systems. Accordingly, a carbonyl group increases the reactivity of an olefin. The effect of substituents on the nitrile oxide can be rationalized in a similar manner. Electron-donating substituents favor Type I reactivity, whereas electron-acceptor substituents increase the reactivity of Type III systems. Consequently Type III cycloaddition is favored with benzenesulfonyl and acyl nitrile oxides. The relative ease of dimerization of nitrile oxides is often used as a competitive standard to compare the reactivity of alkenes [84JCR(S)36, 84JCR(S)362, 84JHC1397] but this argument is simplistic, as it ignores the effect of the FMO energies of the nitrile oxides on reactivity (84BCJ1643). The utility of the Sustmann classification is widespread, particularly because substituent effects on FMO energies can often be estimated without the need for precise calculations.

Steric affects are not accommodated by the Sustmann classification. The steric effect of a single alkyl substituent on an alkene decreases reactivity, while the rate-enhancing effect of a conjugating substituent is greater than the retarding steric effect. The steric effect becomes dominant with more highly substituted olefins. With disubstituted alkenes the reactivity is generally retarded, more so with 1,2- than 1,1-disubstitution, although the electronic effects of both substituents still affect reactivity. *trans*-disubstituted alkenes are generally more reactive than the corresponding *cis*-isomers, presumably as a result of the greater steric compression of the *cis*-substituents during the cycloaddition [63AG(E)633]. Trisubstituted alkenes are even less reactive and steric effects dominate. Nitrile oxide dimerization is a particular problem in reactions of nitrile oxides with unreactive alkenes, such as unactivated di- and tri-substituted alkenes.

The degree of strain in cyclic olefins (62T3) and their ease of deformation to form cycloaddition transition states (80JA3951; 81JA2436, 81JA2438) also affect reactivity. Thus, for example, cyclopropenes (73TL1139; 74ZOR1669; 81S322; 90ZOR102), cyclobutenes [74JCS(P1)137; 76CC246; 85JOC1278], methylenecyclopropane (85CC1518), norbornene (62T3; 73LA2038), and benzvalene (86CB950) are highly reactive dipolarophiles. As expected, aromatic compounds such as benzene and napthalene do not react with nitrile oxides (84MI1), due to the loss of resonance energy

that would accompany cycloaddition. Heteroaromatics undergo cycloaddition but at much reduced rates compared to those of their nonaromatic analogues. Accordingly, furan and thiophene are much less reactive than 2,3-dihydrofuran and 2,3-dihydrothiophene, respectively (84T441).

With 1-phenylsulfinyl- (85SC663), 1-fluoro- (90T7991), and 1,1-difluoro-substituted allenes (85MI1; 90T7991), the least substituted double bond reacts selectively. However, the α,β-bond of a nitrogen-substituted allene is the more reactive, presumably as a result of activation of that bond by the electron-donating substituent [90JCS(P1)533; 91JCS(P1)1843]. 1,3-Dienes follow the general trends, with the less substituted double bond reacting selectively [85T5569; 91JCS(P1)765; 92T6059], except in the case of some alkoxy-substituted dienes (88ZOR944) where the activating electronic effect of the alkoxy substituent balances the deactivating steric effect. With 1,2,3-trienes the terminal double bonds react selectively (86CB563).

As mentioned above, solvent effects have been observed for cycloaddition processes. Reactions of aryl nitrile oxides with substituted *p*-benzoquinones exhibited a 14-fold rate enhancement in water/ethanol (40 : 60) when compared with chloroform (91BCJ3079), presumably as a result of reactant aggregation in the water/ethanol mixture. Hydrogen bonding between nitrile oxides and hydroxyl- and amino-substituted alkenes increases reactivity, as does metal chelation of nitrile oxides and alkenes (92TL1357; 93TL4011). It has also been reported that cycloaddition reactions can be accelerated significantly by the use of ultrasound (91TL4171) and are catalyzed by baker's yeast (90TL899). The rates of reactions of nitrile oxides with alkenes are decreased by adding Lewis acids, presumably because the nitrile oxides are good Lewis bases and complexation effectively inhibits cycloaddition (87JOC2137).

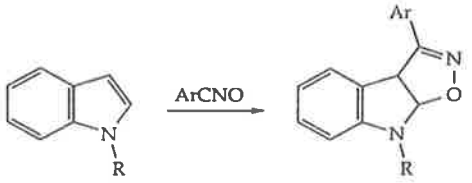
V. Regioselectivity

With unsymmetrical olefins, the direction of addition of the nitrile oxide must be considered. Monosubstituted alkenes afford 5-substituted isoxazolines almost exclusively, regardless of the electron-withdrawing or -donating nature of the substituent. This trend was studied by Martin and Dupré (83TL1337) and is illustrated by numerous examples [86CL183; 87JHC701, 87S998; 88KGS1034; 89JHC255, 89JOC3073, 89SC2237, 89ZOR1901; 90CCC2481, 90CJC1271, 90JHC557, 90JOC283, 90KGS1250, 90MI2, 90T1975; 91ACS736, 91BCJ375, 91JCS(P1)2801, 91JOC1812, 91MI2, 91TL683, 91TL4171; 92CC939, 92TL6811; 93TL2831, 93TL3169]. In the majority of cases with 1,1-disubstituted and trisubstituted olefins,

the oxygen of the nitrile oxide becomes attached to the more sterically hindered end of the double bond [84JHC1121; 85JOC903, 85JOC1278; 86LA1863; 87H755; 89CC986; 89JOC5585, 89JOC5883, 89TL1477; 90JCR(S)202, 90JHC2097, 90JOC3045, 90JOC4603, 90JOC4732, 90LA1097, 90ZOR1274; 91JCR(S)81, 91JHC605, 91JHC1945, 91M821; 92BCJ2484, 92H(34)1703, 92JIC282; 92LA591, 92T6059, 92TL4879].

A mixture of regioisomers is usually obtained with 1,2-disubstituted alkenes and where they are reactive, tetrasubstituted alkenes, although electron-donating amino (86BCJ3631; 89JOC5585; 90JHC1931), alkoxy (84T441), and alkylthiyl (84T441) substituents tend to orientate the cycloaddition such that they are at the 5-position in the cycloadducts. Consistent with this trend, indole and its *N*-substituted derivatives react mainly as shown in Scheme 16 but electron-withdrawing substituents on the indole nitrogen reduce the regioselectivity of the cycloaddition, presumably as a result of reduced polarization of the double bond [84JCR(S)36]. Acyl (85TL4105; 86CL1925, 86JHC1681; 87CCC1315; 91BCJ3274, 91M165; 92T8053) and sulfinyl (91TL3699) substituents direct the oxygen of the nitrile oxide such that they are at the 4-position of the cycloadduct. The combined effects of the alkoxy and acyl substituents resulted in the highly regioselective addition of nitrile oxides to the 1,2-disubstituted alkene (**32**) (Scheme 17) (91JHC429), while the substituents of the uracil (**33**) acted in a similar manner (Scheme 18) (92JOC1088). Reaction of benzonitrile oxide (**3**) with the allylic alcohol (**34**) in the presence of *n*-butoxymagnesium bromide, to give the isoxazolines (**35**) and (**36**) (Scheme 19) in the ratio 99 : 1, can be attributed to metal chelation in the transition state (Fig. 2) (92TL1357) and indicates the potential of this approach in the control of regioselectivity of cycloadditions. β-Cyclodextrin was also used to control the regioselectivity of cycloadditions (90TL899; 92PAC1141).

The reaction of (**37**) with (**38**) to give (**39**) (Scheme 20) in high yield is a good example of exploitation of alkene reactivity and regioselectivity in synthesis (88TL1307). Only the monosubstituted double bond reacts, with the nitrile oxide oxygen adding to the most hindered end of that double bond. The regioselectivity of nitrile oxide cycloadditions with dipo-



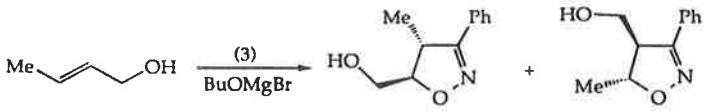
SCHEME 16

(32)

SCHEME 17

(33)

SCHEME 18



(34) (35) (36)

SCHEME 19

larophiles such as methylenecyclopropane (85CC1518; 86CC813; 88JOC2426; 92JOC4206, 92T3323; 93MI1), analogues with electron-withdrawing substituents on the methylene group (87TL3845) or with ring substituents (88JOC2426; 91CB1619; 92JOC4206), and methylenecyclobutane and its derivatives (92T5283) is consistent with the guidelines outlined above, but alkylidene and arylidene cyclopropanes show an unexplained tendency for the cyclopropyl substituent to be at C-4 in the product isoxazoline (87TL3845; 92T3323; 93MI1). In other rare cases the nitrile oxide

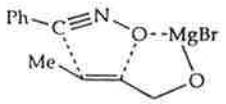
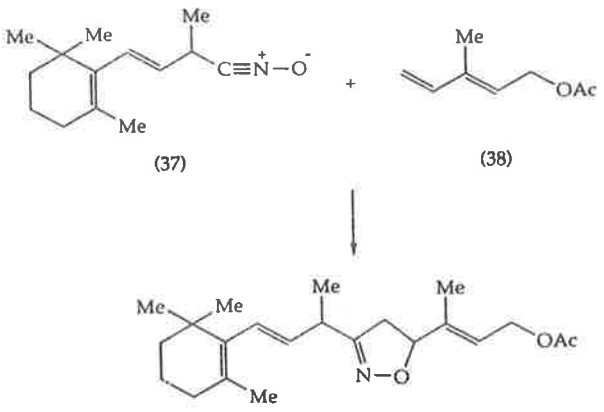


FIG. 2. Metal chelation in the transition state of the cycloaddition of benzonitrile oxide (3) with (*E*)-2-butenol.



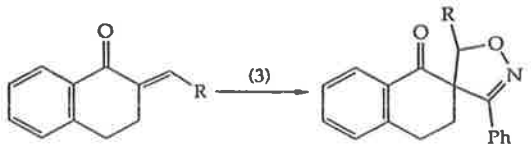
(37) (38)

(39)

SCHEME 20

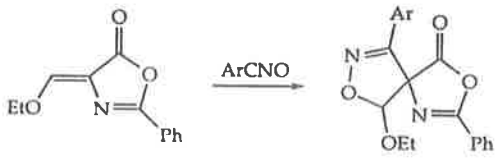
oxygen bonds to the less hindered carbon of the alkene. Apparently this was the case in reactions of the ketones (**40**) (Scheme 21) (86JIC1002). The regioselective reaction of the oxazolone (**41**) (Scheme 22) (92JHC251) can be attributed to the dominance of electronic factors over steric effects.

With 1-phenylsulfinylallene, the residual double bond is found mainly at the 5-position in the cycloadduct (85SC663), whereas nitrogen-substituted allenes afford mainly 4-methylene-substituted isoxazolines [90JCS(P1)533; 91JCS(P1)1843]. The regioselectivity of addition to 1-fluoro- and 1,1-difluoro-allene depends on the nitrile oxide and is thought to reflect the



(40)

SCHEME 21



(41)

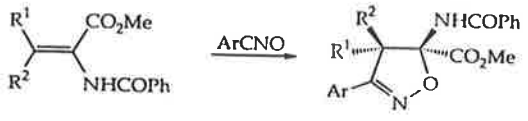
SCHEME 22

extent of electrostatic repulsion between the reactants (85MI1; 90T7991). The nitrile oxide oxygen reacts at C-2 of 1,3-butadienes [85T5569; 88ZOR944; 91JCS(P1)765] and at C-1 and C-4 of tetrasubstituted 1,2,3-trienes (86CB563).

VI. Stereoselectivity

Aspects of the stereoselectivity of nitrile oxide cycloaddition reactions have been reviewed (89G253). The most obvious stereochemical consequence of the cycloaddition is that the configuration of the alkene is retained in the product isoxazoline and this feature continues to be exploited in asymmetric synthesis. For example, the dehydrophenylalanine derivatives (**42**) gave the corresponding isoxazolines (**43**), stereospecifically (Scheme 23) (91JHC1945).

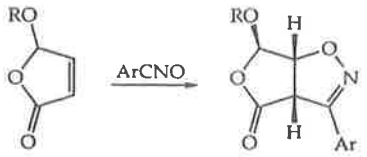
When the faces of the alkene are nonequivalent, reactions often display considerable diastereoselectivity. This is particularly apparent in cyclic systems (88CC1339; 89JOC2209; 90BCJ3300; 92T8053). The stereoselectivity is highly sensitive to steric factors, as illustrated in the *anti*-addition of nitrile oxides to 5-alkoxy- and 5-acyloxy-2(5*H*)-furanones (Scheme 24) (87CCC1315; 91M165). In contrast, the hydroxyfuranone (**44a**) and the corresponding lactam (**44b**) gave approximately equal quantities of the products of *syn*- and *anti*-addition (Scheme 25) (87CCC1315). Since there was no interconversion of the isomers of the cycloadducts under the reaction conditions, the stereoselectivity must occur in the cycloaddition and presumably results from a balance of hydrogen bonding, between benzonitrile oxide (**3**) and the alkenes (**44**), and steric interactions. Similar effects have been observed in reactions of 3-substituted cyclopentenes, where nitrile oxides generally add to the *anti* face (75TL3543; 78JA105). Hydrogen bonding between the nitrile oxide and the alkene can also outweigh these steric effects, however, such that 3-hydroxycyclopentene (74TL229) and, to a greater extent, the cyclopentenyl amides (**45**) react



(42) (43)

R^1 = H, R^2 = Ph
or R^1 = Ph, R^2 = H

SCHEME 23



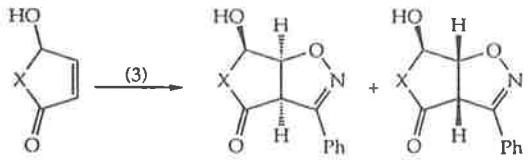
R = alkyl *or* acyl

SCHEME 24

by *syn* addition (Scheme 26) with a high degree of regioselectivity (90JOC3710).

2-substituted methylenecyclopropanes react by *anti*-addition with a high degree of stereoselectivity (Scheme 27) (88JOC2426, 88JOC2430; 90JOC1762; 93MI1), but analogous methylenecyclobutanes show little diastereoselectivity in their reactions (92T5283). This can be attributed to the greater flexibility of the cyclobutane ring, which can adopt a conformation where there are minimal steric interactions between the substituent and the incoming nitrile oxide.

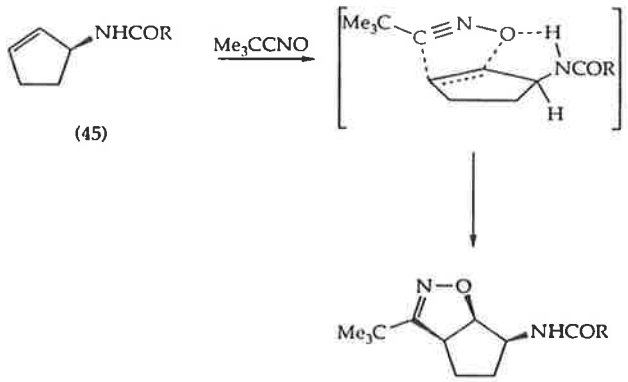
The diastereoselectivity is generally less with acyclic than cyclic alkenes. A number of groups have reported modestly diastereoselective nitrile oxide cycloadditions to chiral allyl ethers and alcohols (Scheme 28) [74JCS(P1)137, 74TL229; 76CC246; 78JA105; 81JCS(P1)3048; 82JA5788, 82TL4563; 83T2247, 83TL5501; 84JOC4674]. Reactions slightly favor the *syn* isomer for allyl alcohols (R^1 = H) and, to a greater extent, the *anti* isomer for allyl ethers (R^1 = alkyl, aryl). Houk *et al.* (84JA3880) combined experimental results and theoretical studies to rationalize this stereoselectivity in terms of a preferred conformation of the transition state (Fig. 3), in which alkyl substituents at the chiral center prefer the sterically less crowded "anti" conformation, an allylic hydroxyl group prefers the "outside" position to maximize hydrogen bonding with the nitrile oxide oxygen, and an ether prefers the "inside" conformation, due to secondary orbital interactions. This concept has been subsequently referred to as



(44)

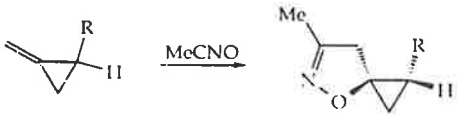
a) X = O
b) X = NH

SCHEME 25

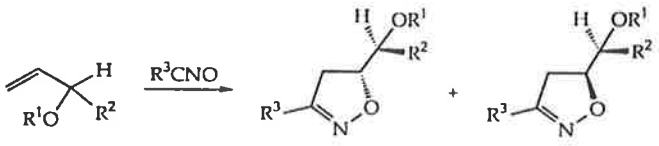


(45)

SCHEME 26



SCHEME 27



SCHEME 28

the "inside alkoxy" effect. In later studies where the groups attached to the stereogenic centre varied only in size (Scheme 29), it was determined that the largest group (L) assumed the "anti" position, the medium-sized group (M) the "inside" position, and the smallest group (S) the "outside" position, as a result of steric interactions (86JA2754). It follows that the

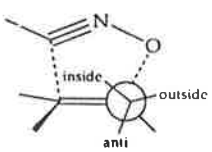
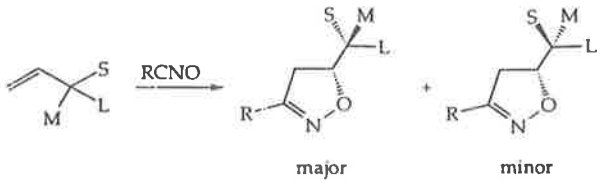


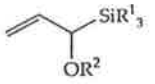
FIG. 3. Houk's "inside alkoxy" model for the reaction of nitrile oxides with chiral allylic alcohols and ethers.



SCHEME 29

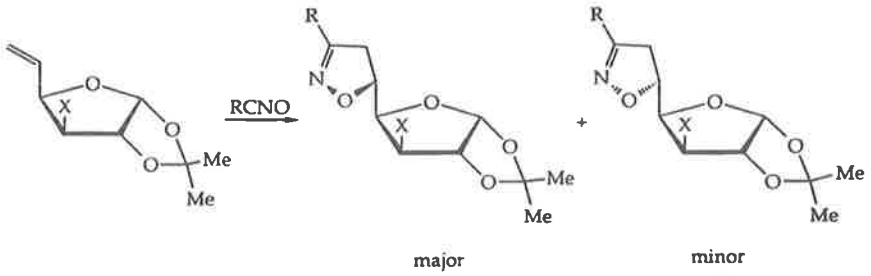
"inside alkoxy" effect is a combination of steric repulsion and secondary orbital interactions (86JA2754).

Houk's model has been used to account for diastereoselectivity observed in nitrile oxide cycloadditions with the (α-oxyallyl)silanes (**46**) (88T3945). The direction and magnitude of asymmetric induction was

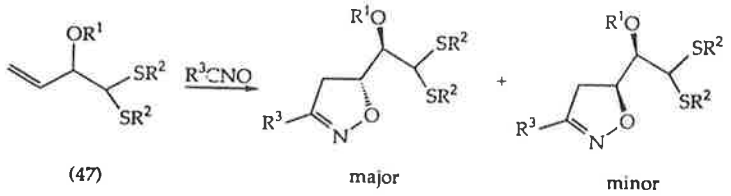


(46)

found to depend on the allylic oxygen substituent. It was found that a free hydroxy substituent provided a modest excess of the *syn* diastereomer, silyl ethers showed modest to good selectivity for the *anti* diastereomer, and various acyl derivatives showed low diastereoselectivity. The diastereoselectivity observed in reactions of unsaturated sugars (Scheme 30) (89JOC793; 91CCC132, 91MI2; 93TL2831) has also been rationalized in terms of the "inside alkoxy" effect (89JOC793). Interestingly, the *syn* selectivity in reactions of chiral allyl alcohols with nitrile oxides was increased through metal chelation of the reactants (91TL6367). Reactions of chiral allyl ethers (**47**) derived from 1,1-dithio-3-buten-2-ols displayed consistently high (>10 : 1) diastereoselectivity (Scheme 31), presumably as a result of the "inside alkoxy" effect and steric interactions associated with the bulky dithioacetal moiety (88T4645).



SCHEME 30

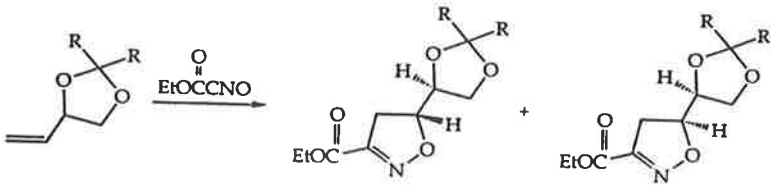


(47) major minor

SCHEME 31

Diastereoselective reactions of the dioxolanes (**48**) have been reported by several groups (84ACR410, 84JOC2762, 84T2199; 85JOC778; 90S556, 90T1975; 92JOC2825). For example, the dioxolane (**48b**) gave the adducts (**49b**) and (**50b**) in the ratio 4 : 1 (Scheme 32) (84JOC2762). The diastereoselectivity has been rationalized in terms of the Felkin–Anh (80MI1; 82JA1106; 83TL2231) transition state model, as illustrated in Fig. 4 (84JOC2762), but the results are also consistent with Houk's model. Reactions of the silyl ether (**51**) (Scheme 33) have also been discussed (84JOC2762) in terms of the Felkin–Anh model but are better accommodated using the "inside alkoxy" theory.

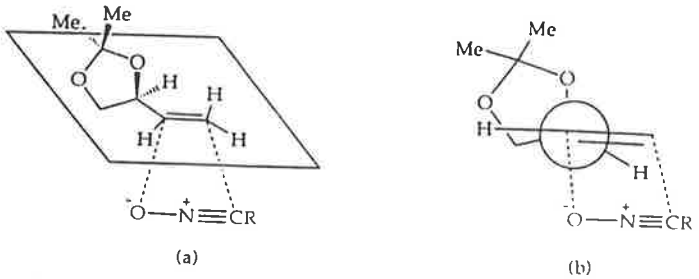
Encouraged by the stereoselectivity observed in nitrile oxide cycloadditions to the dioxolanes (**48**), Wade *et al.* (84T601) studied reactions of



(48) (49) (50)

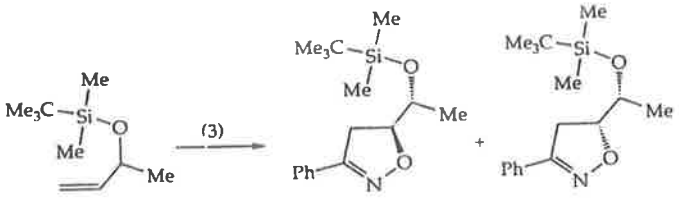
a) R = $-(CH_2)_3-$
b) R = Me

SCHEME 32



(a) (b)

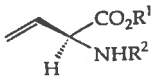
FIG. 4. Houk's transition state model (a) and the Felkin–Ahn transition state model (b) for the reaction of the dioxolane (**48**) with nitrile oxides.



(51)

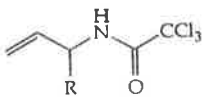
SCHEME 33

derivatives of vinylglycine (**52a**) but the diastereoselectivity was generally poor, ranging from 0 to 40% diastereomeric excess. Similar results were reported by Fushiya *et al.* (87CL2229), for reaction of the vinylglycine derivative (**52b**) with acetonitrile oxide, whereas the cyclic vinylglycine derivative (**53**) gave mainly the diastereomer (**54**) on treatment with nitrile oxides (Scheme 34) (92MI1). Halling *et al.* (91ACS736) reported little stereoselectivity in the cycloaddition of chloronitrile oxide to the *N*-allyltrichloroacetamides (**55**). Curran and Kim (86S312) observed that cycloaddition of benzonitrile oxide (**3**) with the (α-methylallyl)silane (**56**) also occurred with only poor selectivity (Scheme 35). Methylphenylvinylphosphine oxide (**57**) gave cycloadducts with approximately 40% diastereomeric excess (Scheme 36) (89JOC3073). The diphenylphosphine oxide (**58**) reacted with nitrile oxides to give mainly the *anti*-cycloadducts (**59**) (Scheme 37), consistent with Houk's transition state model (91TL4171). Recently, (*S*)-1-(2-naphthyl)ethyl vinyl ether was shown to react with nitrile oxides with a modest degree of diastereoselectivity [93JCS (P1)1277].



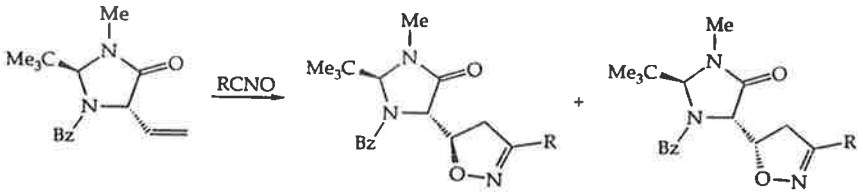
(52)

a) $R^1 = R^2 = H$
b) R^1 = Me, R^2 = OCOPh



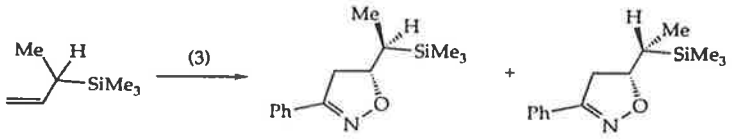
(55)

a) R = CH(Me)Et
b) R = Ph



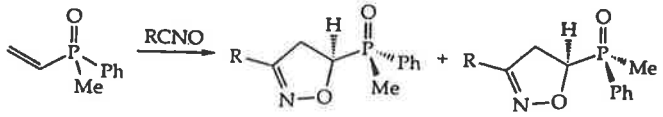
(53) (54) major minor

SCHEME 34



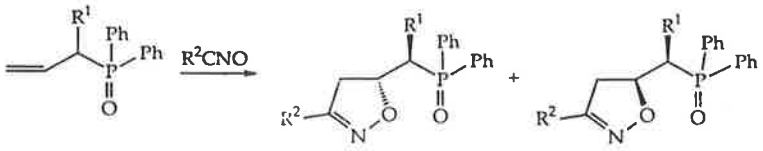
(56) 1.5 : 1

SCHEME 35



(57) major minor

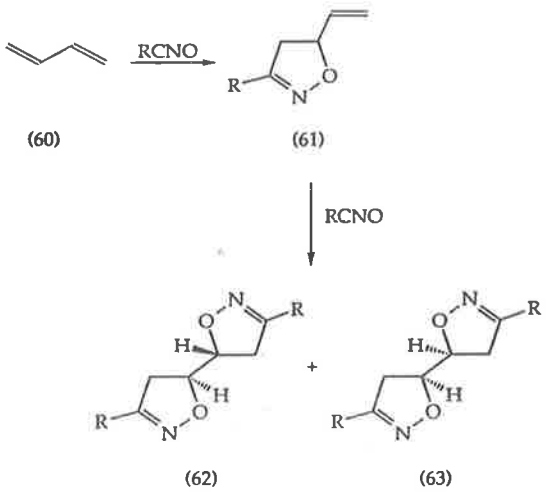
SCHEME 36



(58) (59)

SCHEME 37

Reactions of vinylisoxazolines have also been studied. In reactions of 1,3-butadiene (**60**) with nitrile oxides, the *erythro* adducts (**62**) were formed in preference to the corresponding *threo* isomers (**63**) (Scheme 38) (83T2247; 85T5569), the isomer ratios ranging from 2.7 : 1 to 6.7 : 1. The



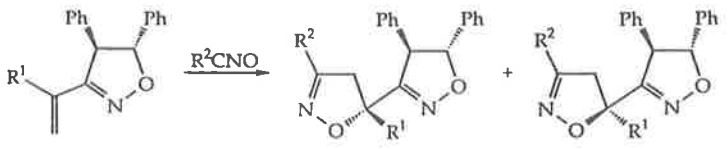
(60) (61) (62) (63)

SCHEME 38

isomer ratios reflect the diastereoselectivity of nitrile oxide addition to the 5-vinylisoxazolines (**61**). The 3-vinylisoxazolines (**64**) gave the cycloadducts (**65**) and (**66**) with diastereomeric excesses ranging from 10 to 45% (Scheme 39) (90JOC3045).

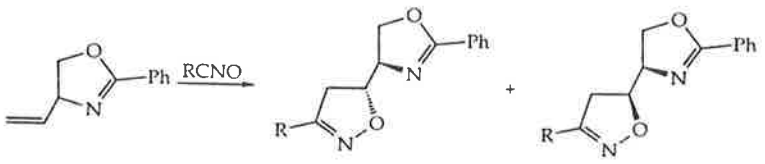
The 4-vinyloxazoline (**67**) and the 4-vinyloxazolidine (**70**) gave mixtures of the isoxazolines (**68**) and (**69**), and (**71**) and (**72**), respectively, in which the *erythro* products (**69**) and (**72**) were formed in 32–64% diastereomeric excess (Schemes 40 and 41) (93TL3169). The results were interpreted by analogy with the "inside alkoxy" effect. Reactions of the acyclic analogue (**73**) were less stereoselective and favored the *threo* cycloadducts (**74**). The reversed selectivity was attributed to hydrogen bonding between the oxygen of the nitrile oxide and the hydroxy substituent of the alkene (**73**) (93TL3169).

Whereas the studies described above involve reactions of chiral alkenes with achiral nitrile oxides, the stereoselectivity of reactions of chiral nitrile oxides has also been studied. The nitrile oxide (**75**) reacted with *cis*-but-



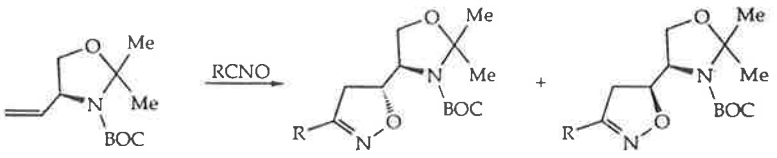
(64) (65) (66)

SCHEME 39



(67) (68) (69)

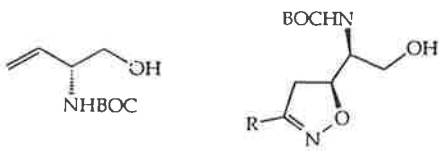
SCHEME 40



(70) (71) (72)

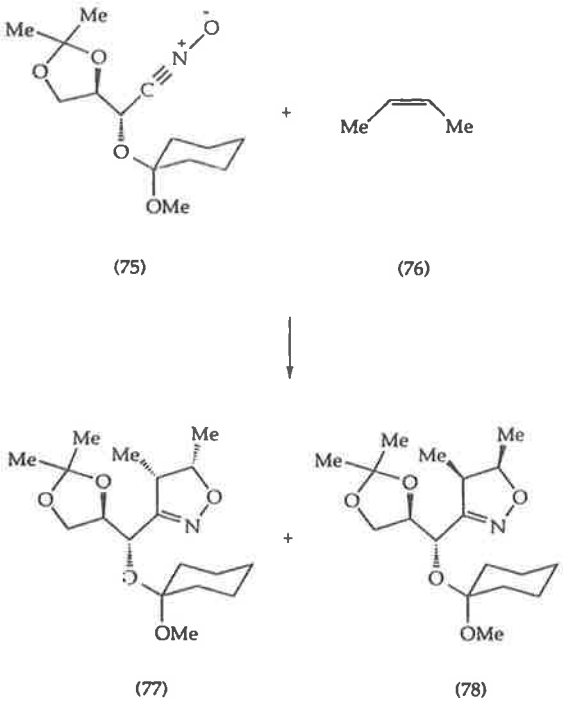
SCHEME 41

2-ene (**76**) to give a 2.9 : 1 mixture of the isoxazolines (**77**) and (**78**) (Scheme 42) (83CC1460). *trans*-But-2-ene and cyclopentene also reacted stereoselectively but styrene (**80**) and vinylcyclohexane did not, indicating that stereocontrol derives from the interaction between the chiral auxiliary and the substituent at C4 of the developing isoxazoline. By a similar argument, the low stereoselectivity reported for the reaction of the chiral oxazoline (**79**) with styrene (**80**) (Scheme 43) is not surprising (93TL3169). The dioxolanes (**81**) reacted with dimethyl maleate and cyclopentene with modest diastereoselectivity but reactions with styrene and dimethyl fumarate gave equal mixtures of diastereomeric cycloadducts (84T177). The bislactim ether (**82**) reacted with alkenes without stereocontrol (92T5607).



(73) (74)

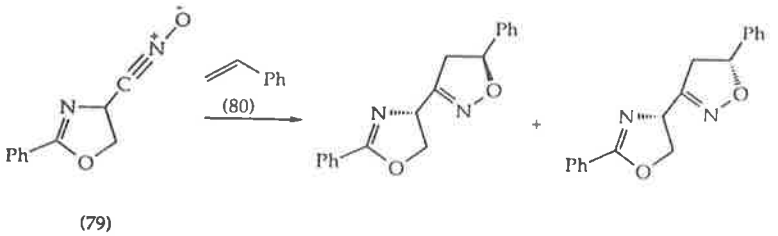
The homochiral nitrile oxide (**83**) reacted with the chiral dioxolane (*R*)-(**48b**) to give the cycloadducts (**84**) and (**85**) as a 4 : 1 mixture (Scheme 44). The degree of diastereoselectivity was similar to that observed in reactions of the dioxolanes (**48**) with achiral nitrile oxides, indicating that the chirality of the nitrile oxide (**83**) had little effect on the stereochemical course of the reaction (84JOC2762). A similar conclusion was reached to



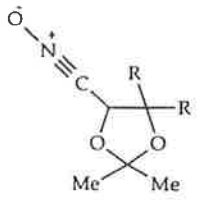
SCHEME 42

explain the diastereoselectivity in the synthesis of the isoxazolines (**87**) (Scheme 45), as the reaction of the nitrile oxide (**86**) with butyl allyl ether was much less stereoselective (87TL3189). The dioxolane (**88**) has been used in the synthesis of sugars (Scheme 46), but again the diastereocontrol most likely derives from the dipolarophile (**89**) (91CC132, 91MI2; 93TL2831).

The approach of using chiral auxiliaries to control stereoselectivity has been investigated by a number of groups. Curran *et al.* (89JA9238) noted that development of chiral auxiliaries in these systems is a particular

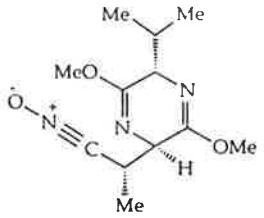


SCHEME 43



(81)

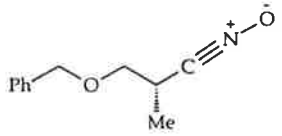
a) R = H
b) R = Me



(82)

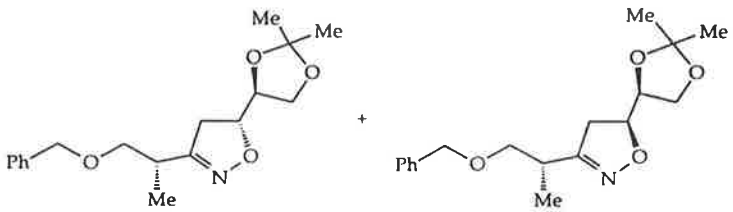
challenge because the geometry of the transition state limits their effects. Although asymmetric induction can be enhanced in other cycloaddition reactions by using Lewis acid catalysts, this option is not available in nitrile oxide cycloadditions because the nitrile oxides act as Lewis bases.

Reactions of *p*-nitrobenzonitrile oxide with the menthyl acrylate (**90a**), the corresponding menthyl allyl ether (**90b**), and the acrylate (**91**) gave adducts with less than 10% diastereoselectivity (84TL2191; 87JOC2137). Reactions of the sulfonamides (**92**) were more stereoselective and that of the dicyclohexyl derivative (**92b**) with benzonitrile oxide (**3**) gave the diastereomers (**93b**) and (**94b**) (Scheme 47) in a ratio of ca. 4 : 1 (87JOC2137). The bornyl crotonates (**95a**) gave only *trans*-4,5-substituted cycloadducts and mainly the regioisomers (**96a**) (Scheme 48) with diaste-



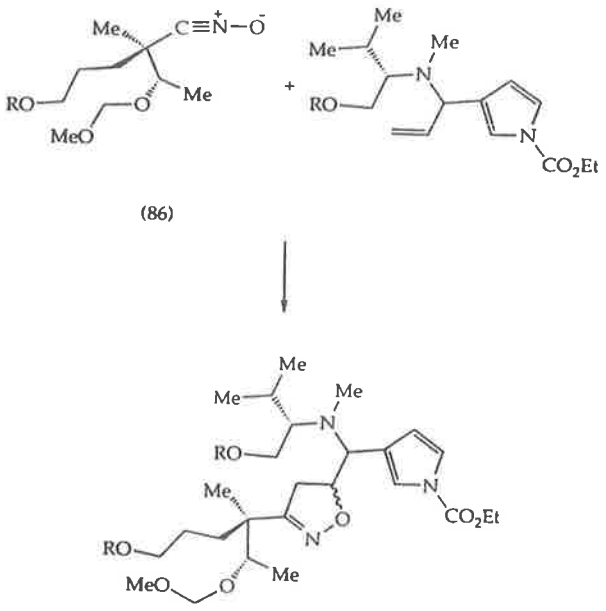
(83)

(*S*)-(48b)



(84) (85)

SCHEME 44

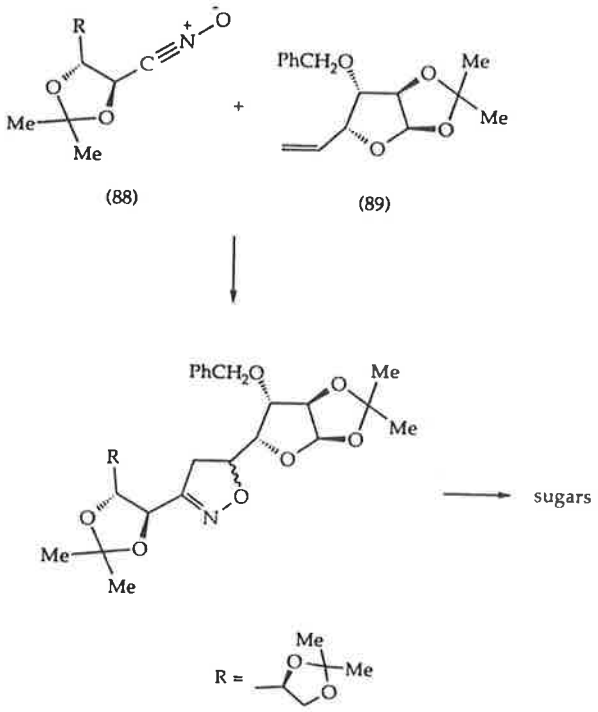


SCHEME 45

reomeric excesses ranging from 5% (R^1 = naphthyl, R^3 = Ph) to 54% (R^1 = Ph, R^3 = Me) (88JOC2468). The stereoselectivity of formation of the minor regioisomers (**97a**) was generally greater and ranged from 12% (R^1 = H, R^3 = Ph) to 80% (R^1 = naphthyl, R^3 = Ph). The bornyl acrylates (**95b**) reacted regioselectively, as expected, with a degree of stereoselectivity similar to that for the reactions of the crotonates (**95a**) (90T2473). The esters (**96**) and (**97**) were easily cleaved and the chiral auxiliaries retrieved.

Acryloyl esters bearing *chiro*-inositol derivatives as chiral auxiliaries reacted with a consistently high degree of stereoselectivity (92TL5763). For example, the *tert*-butyldiphenylsilylether (**98**) reacted with benzonitrile oxide (**3**) to give the cycloadduct (**99**) in 90% diastereomeric excess (Scheme 49). The stereochemical outcome of the reaction indicates *si*-face attack to the *s-cis* conformer of the acrylate (**98**). The chiral auxiliary was recovered after treatment of the isoxazoline (**99**) with L-Selectride.

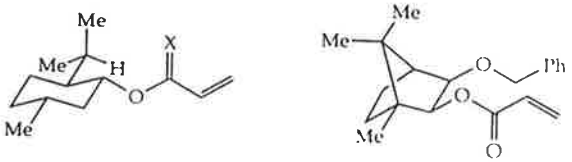
Reactions of the Oppolzer's chiral sultam derivative (**100a**) with nitrile oxides showed considerable diastereoselectivity [88TL3555; 90JOC4585;



(88) (89)

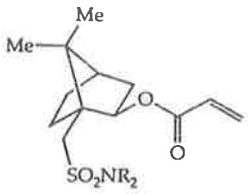
SCHEME 46

91JCS(P1)2627; 92TL6811]. For example, the cycloadduct (**101a**) was obtained in 90% diastereomeric excess (Scheme 50) (88TL3555). The stereoselectivity is consistent with reaction of *tert*-butylnitrile oxide with the *s-cis* conformation of the sultam (**100a**). The α-methacryloyl sultam (**100b**) was less reactive than the acrylamide (**100a**) and its reactions showed less stereoselectivity, whereas reactions of the crotonyl sultam (**100c**) displayed stereoselectivity analogous to that of the acrylamide (**100a**), but afforded mixtures of regioisomers (90JOC4585). The greater selectivity in the reactions of the sultam (**100a**) compared to that for reactions of esters



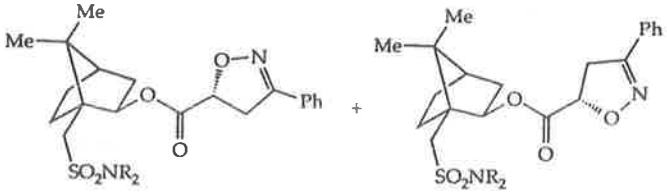
(90) (91)

a) X = O
or b) X = H_2



(92)

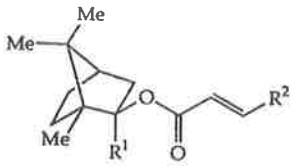
(3)



(93) (94)

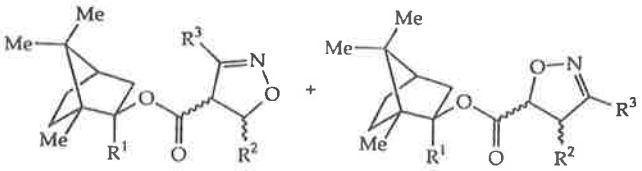
a) R = $CHMe_2$
b) R = cyclohexyl

SCHEME 47



(95)

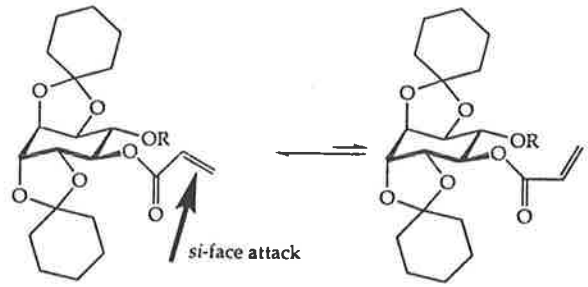
R^3CNO



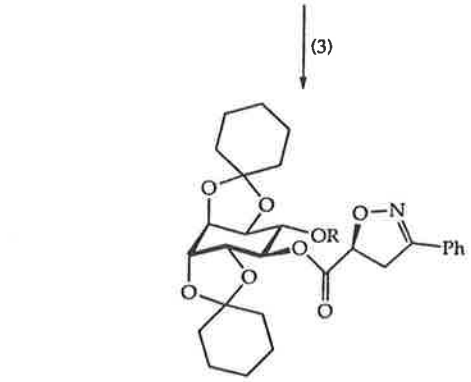
(96) (97)

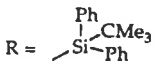
a) R^2 = Me
b) R^2 = H

SCHEME 48



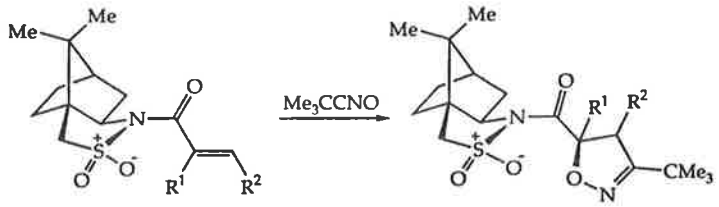
(98)





(99)

SCHEME 49

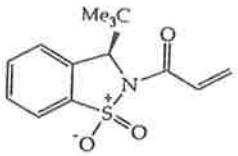


(100) (101)

a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = H$, $R^2 = Me$

SCHEME 50

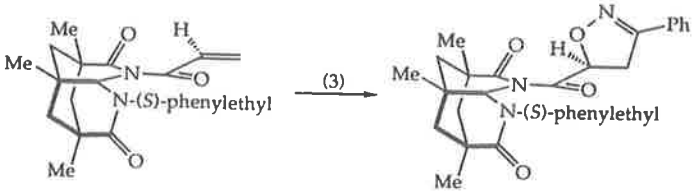
described above is consistent with a greater conformational preference of the sultam (**100a**) (88TL3555). Oppolzer *et al.* (91TL4893) reported the synthesis of the acryloyl sultam (**102**) and its enantiomer. Their reactions with nitrile oxides proceeded stereoselectively, with the ratios of diastereomeric products ranging from 95 : 5 to 98 : 2.



(102)

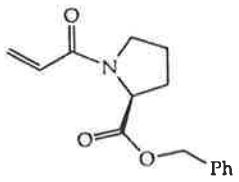
Even greater stereoselectivity was obtained using derivatives of Kemp's triacid (81JOC5140) as chiral auxiliaries. Accordingly the chiral acrylimide (**103**) gave the corresponding isoxazoline (**104**) (Scheme 51) in greater than 98% diastereomeric excess (89JA9238; 93T995). A diastereomer of the imide (**103**) was used to reverse the stereocontrol (89JA9238; 93T995). The *N*-acryloylproline derivative (**105**) reacted with nitrile oxides to give isoxazolines in diastereomeric ratios of ca. 3 : 1 (90LA1013). The chiral auxiliaries of the bis-proline derivative (**106**) displayed synergistic stereocontrol and gave 9 : 1 mixtures of diastereomers of cycloadducts (90LA1013).

The imidazolines (**107**) and (**108**) reacted with nitrile oxides with modest to high stereoselectivity, but low regioselectivity (91BCJ3274). Diastereoselective reactions of the oxazolidines (**109**) and the imidazoline (**110**) have also been reported (91BCJ3274, 91TA1185). As a representative example, the imidazoline (**110**) reacted with benzonitrile oxide (**3**) at room temperature to give the adducts (**111**) and (**112**) in the ratio 4 : 1. After separation

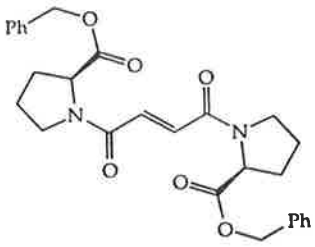


(103) (104)

SCHEME 51



(105)



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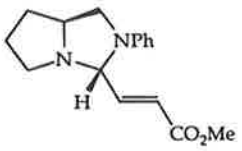
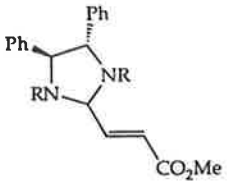
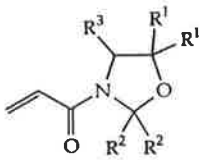


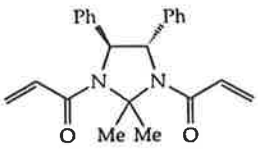
(107)



(108)

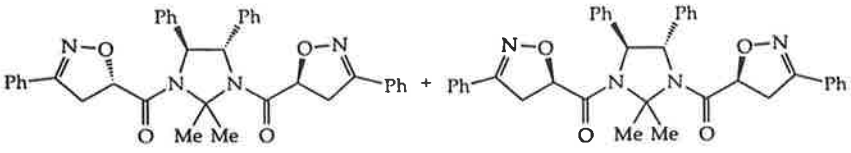


(109)



(110)

(3)



(111) (112)

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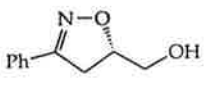
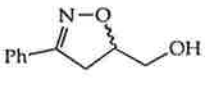


(113)



(114)

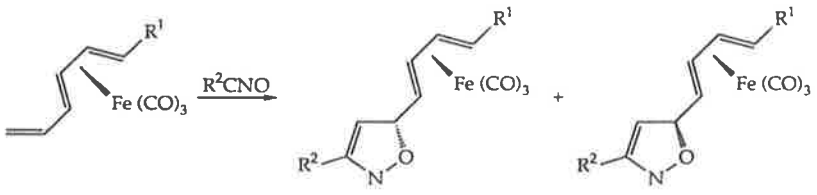
SCHEME 52

and reduction with lithium triethylborohydride, the adduct (**111**) gave the homochiral alcohol (**113**), while the diastereomer (**112**) gave the corresponding racemate (**114**) (Scheme 52).

Another method used in the diastereoselective synthesis of isoxazolines involved reactions of the iron complexed trienes (**115**) with nitrile oxides to give the cycloadducts (**116**) and (**117**) in a ratio of ca. 9 : 1 (Scheme 53) (89TL6517). There have been reports on the use of baker's yeast in the enantioselective synthesis of isoxazolines from 4-vinylpyridine and arylnitrile oxides, and of the enhancement of that selectivity using β-cyclodextrin (90TL3201; 92PAC1141).

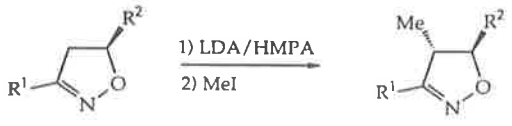
Stereocontrolled modification of isoxazolines provides an alternative to their stereoselective synthesis. For example, alkylation of 5-substituted isoxazolines afforded only the *trans*-4,5-substituted isomers (Scheme 54) (84JOC2762). Conceptually these isoxazolines are accessible from *trans*-1,2-disubstituted alkenes but reactions of that type are complicated by a lack of regioselectivity. Alkylation of 3,4,5-substituted isoxazolines occurred on the 3-substituent with a high degree of regioselectivity (84JOC2762) and modest to good stereoselectivity (87JA3036; 90SC3575, 90T7325), as illustrated in reactions of the 3-ethyl-substituted isoxazoline (**118**) where the electrophile added opposite the 4-substituent (Scheme 55). Hydroxylation of the isoxazoline (**119**) gave only the alcohol (**120**) (Scheme 56) (90S556).

Reactions of the 5-acylisoxazolines (**121**) with L-Selectride were highly stereoselective and gave mainly the *syn*-5-(α-hydroxyethyl)isoxazolines (**122**) (Scheme 57) [91JCS(P1)2613]. Yeast reduction of racemic 5-acetylisoxazolines gave the diastereomeric alcohols (**123**) and (**124**), each

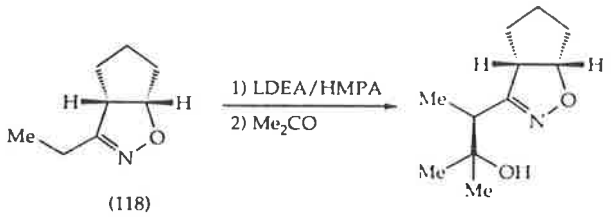


(115) (116) (117)

SCHEME 53

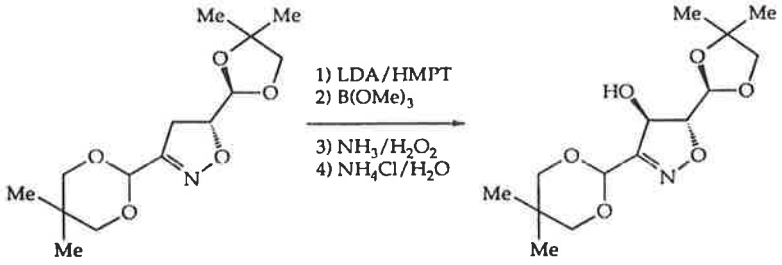


SCHEME 54



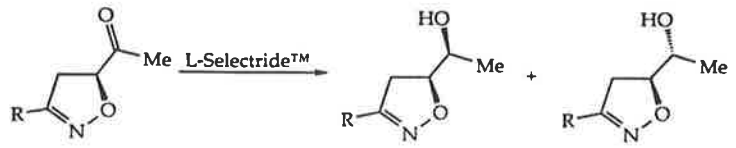
(118)

SCHEME 55



(119) (120)

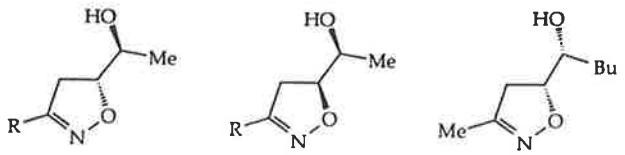
SCHEME 56



(121) *syn* (122)

SCHEME 57

in 97–98% enantiomeric excess (88TL6167; 89LA1257). With Grignard reagents, 5-acyl- and 5-formyl-isoxazolines reacted stereoselectively, according to a conformation determined by metal chelation for the former (Fig. 5) and a Felkin–Anh model in the latter (Fig. 6) [91JCS(P1)2613]. This approach has been used in conjunction with the achiral synthesis of



(123) (124) (125)

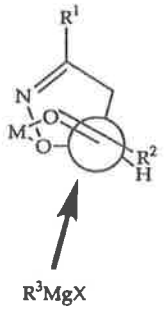


FIG. 5. Metal chelation in Grignard addition to 5-acyl-2-isoxazolines.

isoxazolines from the sultam (**100a**), to obtain the alcohol (**125**) as a single enantiomer [91JCS(P1)2627].

Oxidation of the furoisoxazolines (**127**) with *m*-chloroperbenzoic acid in methanol to give the hydroxyethers (**128**) and with osmium tetroxide to give the diols (**126**) (Scheme 58) proceeded, in each case, with a high degree of diastereoselectivity (85T3519). Similar reactions have been reported with 3-vinylisoxazolines (85T5569; 90JOC3045). Esterases have been used to resolve isoxazolines. Modest discrimination between the enantiomers of the ester (**129**) was accomplished using pig liver esterase (90LA1013). The alcohol (**130**) was prepared in >90% enantiomeric excess through lipase-PS-catalyzed hydrolysis of butyl esters (92JOC2825).

VII. Uses of Isoxazolines

Isoxazolines have attracted interest in their own right. (*R,S*)-4,5-Dihydromuscimol (**132**) is a potent GABA agonist (79MI1) and has been obtained through cycloaddition of bromonitrile oxide (**9**) with *N*-BOC-allylamine (**131**) (Scheme 59) (86TL4651; 90T1975). The individual enantiomers of the isoxazoline (**132**) were synthesized via reaction of bromonitrile oxide (**9**) with the dioxolane (*R*)-(**48b**) and separation of the diastereomeric products (90T1975). The structurally similar isoxazoline (**133**) was

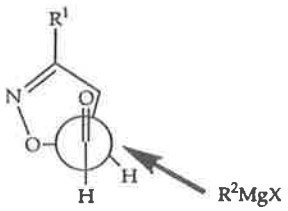
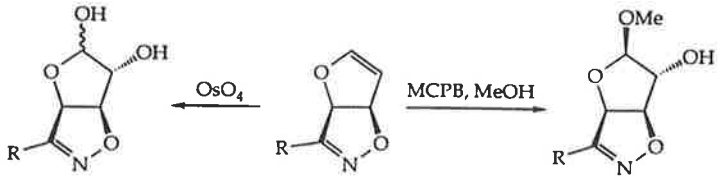


FIG. 6. Felkin–Ahn model for Grignard addition to 5-formyl-2-isoxazolines.



(126) (127) (128)

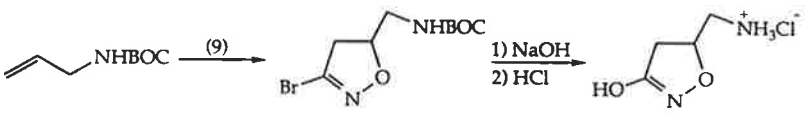
SCHEME 58

shown to be void of GABAergic activity (85JMC1109). The isoxazolines (**134**) display antifungal activity (91CCC1315, 91MI3). Others were investigated as antibiotics (90MI2), chemotherapeutic agents (91JOC1812), and peptide surrogates (92TL6811) and as analogues of prostaglandins (87MI1), steroids (90ZOR1274), and cocaine (91MI4), whereas the isoxazoline (**135**) is of interest in boron neutron capture therapy (92CC939).

(129) (130)

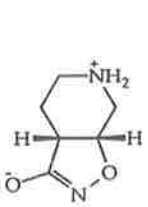
Much of the interest in isoxazolines stems from their use in the synthesis of other compounds. Work in this area has been reviewed (84ACR410; 84MI1; 90H719). Compound types previously obtained from isoxazolines (Scheme 60) continue to be accessed in this manner. Accordingly, syntheses of γ-amino alcohols (85CL1047, 85SC663; 89SC2237), β-hydroxy ketones [84JOC3474; 85TL4047; 86MI2; 87TL3189; 88ACS(B)303, 88BCJ2133, 88BCJ3973, 88KGS972, 88TL1307; 89BCJ171; 90JHC557; 91IZV969, 91TL683], α,β-unsaturated ketones (85SC663; 88TL2051) and β-hydroxy nitriles (90JOC3045), acids (84JOC3474), and esters (84JOC3474) have been reported.

Steinmeyer and Neef (92TL4879) have used nitrile oxide cycloaddition, followed by ring-opening of the cycloadduct (**138**), to give the β-hydroxy ketone (**139**), and subsequent retroaldol cleavage to the ketone

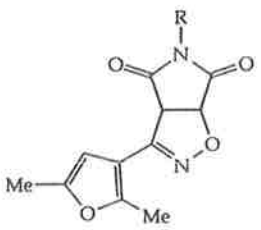


(131) (132)

SCHEME 59

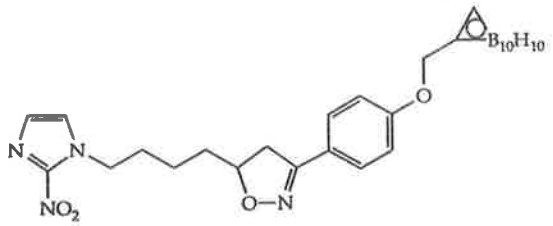


(133)



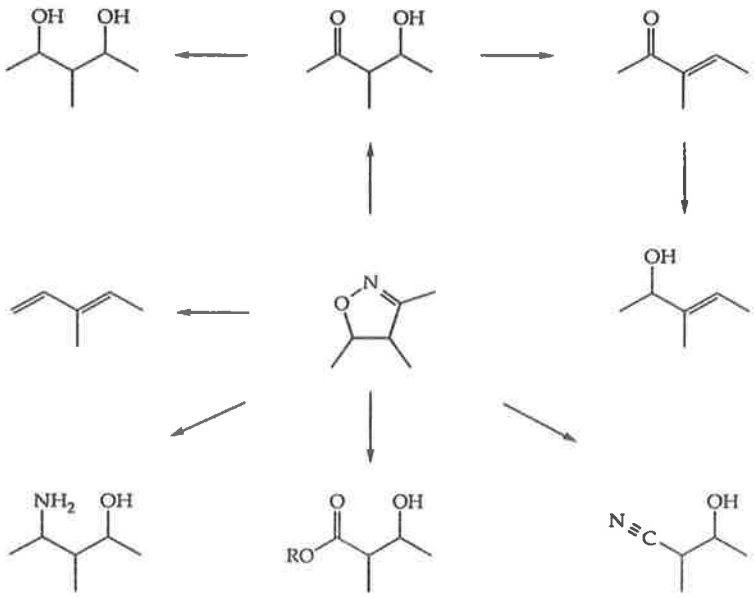
(134)

a) R = *p*-ClPh
or b) R = *o,o'*-Me_2Ph

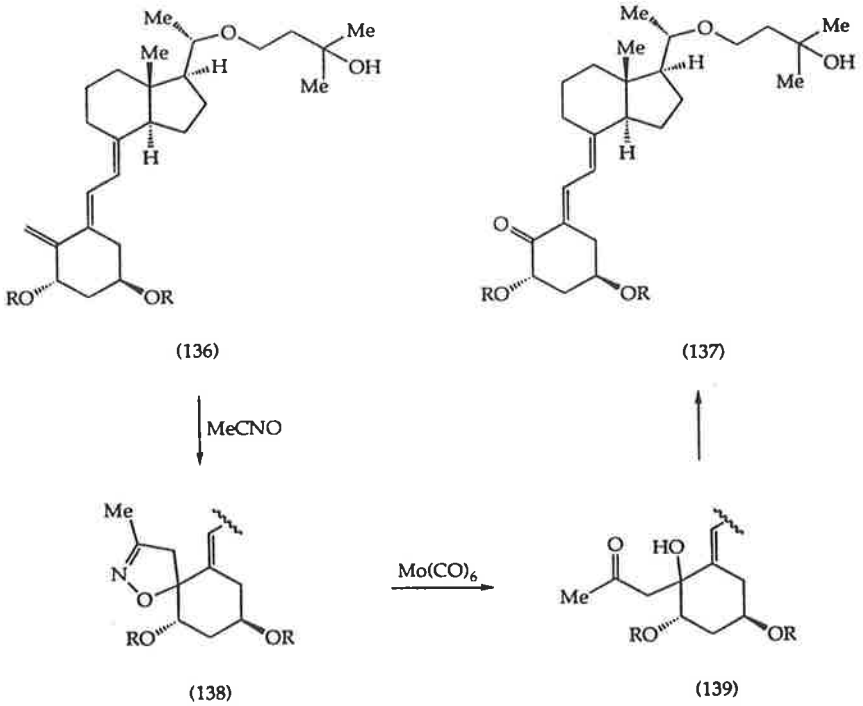


(135)

(137), to accomplish selective oxidation of the exocyclic methylene in the triene (136) (Scheme 61). The selectivity of this process is determined by the relative reactivity of alkenes toward cycloaddition with nitrile oxides.



SCHEME 60

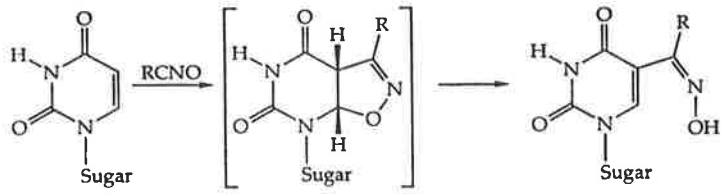


(136) (137) (138) (139)

SCHEME 61

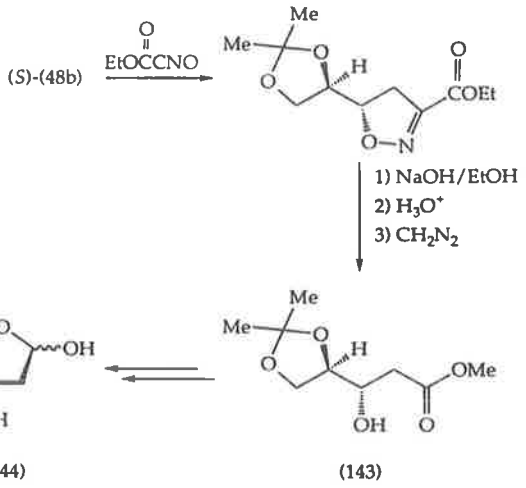
Cycloaddition of the nucleosides (**140**) followed by spontaneous ring-opening of the cycloadducts (**141**) gave the α,β-unsaturated oximes (**142**) (Scheme 62) (92JOC1088).

Much of the more recent work using isoxazolines involves stereocontrolled synthesis. Kozikowski and Ghosh (84JOC2762) used nitrile oxide cycloaddition to prepare the β-hydroxyester (**143**) and the β-hydroxyketone (**145**) from the dioxolane (*S*)-(**48b**) (Schemes 63 and 64). The ester (**143**) and ketone (**145**) are masked triols, suitable for use in the synthesis of sugars, as shown through the elaboration of the ester (**143**)

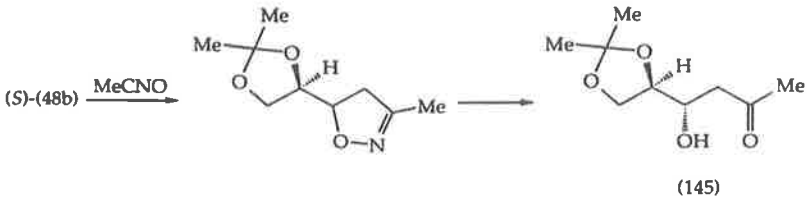


(140) (141) (142)

SCHEME 62

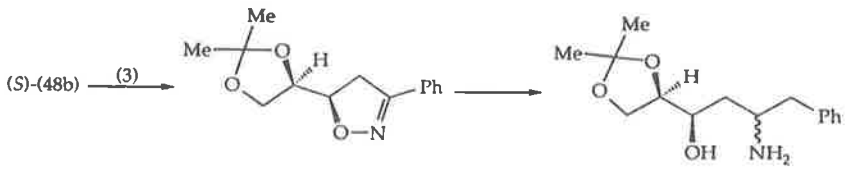


SCHEME 63

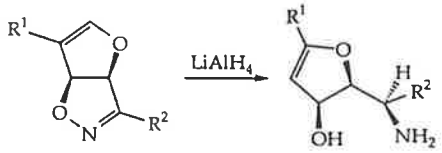


SCHEME 64

to 2-deoxy-D-ribose (**144**) (84JOC2762). Jäger and Schohe (84T2199) used the dioxolane (*S*)-(**48b**) in the stereocontrolled synthesis of γ-amino alcohols via isoxazolines (Scheme 65). The amino alcohols were then converted to amino sugars. Analogous elaboration of furoisoxazolines, coupled with stereoselective oxidation of the dihydrofuran ring, was used in the stereoselective synthesis of aminodeoxy furanosides (Scheme 66) (85T3519). Related syntheses involved a thiazole-substituted isoxazoline (88T3215) and stereocontrolled hydroxylation of the intermediate isoxazoline, before elaboration to the γ-amino alcohol (90S556). Stereoselective cycloaddition to the silyl ether (**146**) and alkylation of the cycloadduct



SCHEME 65

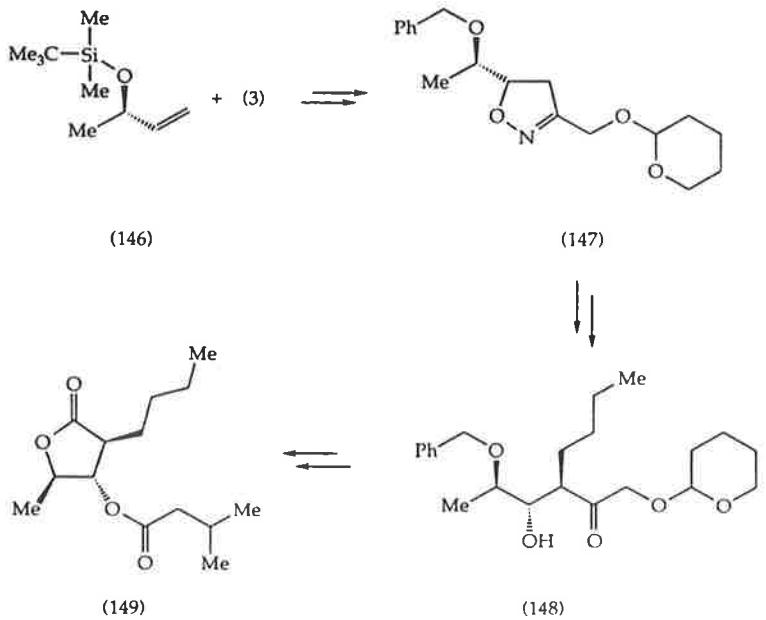


SCHEME 66

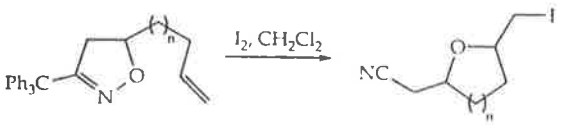
(**147**) followed by reduction gave the masked α,β',γ'-trihydroxyketone (**148**), which was used in the stereocontrolled synthesis of (±)-Blastmycinone (**149**) (Scheme 67) (84JOC2762).

Other stereocontrolled syntheses of γ-amino alcohols [91JCS(P1)2627, 91TL4171; 93TL2831], β-hydroxy ketones [85JOC778; 86S312; 87CL2229, 87JA3036; 88CC1339, 88TL6167; 89JOC2209; 90SC3575; 91CC132, 91JCS(P1)2627; 92MI2; 93JOC2173, 93TL2831], 1,3-diols (88TL6167; 91CC132; 93TL2831), and β-hydroxy nitriles (86TL3099), acids (91ACS736), and esters (91ACS736), via isoxazolines, have also been reported.

Elaboration of isoxazolines has been used in the synthesis of other heterocycles. Electrophilic cyclization reactions of 5-alkenyl-substituted isoxazolines (**150**) have been used in the synthesis of cyclic ethers (Scheme 68) (87JA7577; 90JOC283). Hydrogenolysis and decarboxylation of the



SCHEME 67

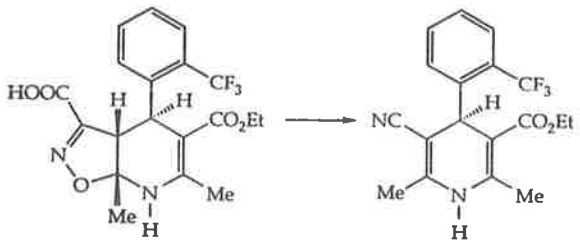


(150)

SCHEME 68

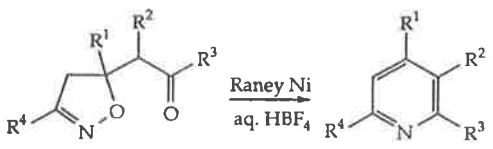
isoxazoline (**151**) gave the dihydropyridine derivative (**152**) (Scheme 69) (83JOC366; 89JOC5585). Reduction of 3-(β-ketoalkyl)-substituted isoxazolines (**153**) has been used in the synthesis of pyridines (Scheme 70) (91BCJ375). Thermolysis of the isoxazolines (**155**), prepared by cycloaddition of nitrile oxides with methylenecyclopropane (**154**), affords 5,6-dihydro-4-pyridone derivatives (**156**), presumably through initial homolysis of the nitrogen—oxygen bond of the isoxazolines (**155**) (Scheme 71) (85CC1518; 86CC813; 88JOC2426; 93MI1). The corresponding spirocyclobutylisoxazolines (**157**) afford azepin-4-ones (**158**) and *N*-alkenylpyrrolidin-2-ones (**159**) (Scheme 72) (86TL5271; 92T5283; 93MI1). Photolytic cleavage of the nitrogen—oxygen bond in the isoxazolines (**160**) resulted in rearrangement to the azabicyclo[4.3.0]nonadienedicarboxylates (**161**) (Scheme 73) (90CCC512).

Although isoxazoles can be obtained by cycloaddition of nitrile oxides to alkynes (Scheme 74), they are also accessible via the corresponding isoxazolines. Dehydrogenation of isoxazolines has been carried out



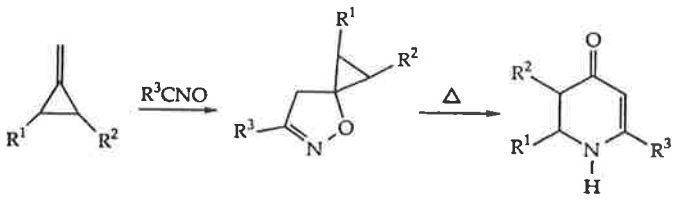
(151) (152)

SCHEME 69



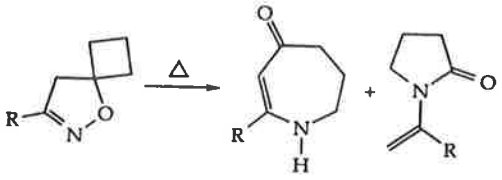
(153)

SCHEME 70



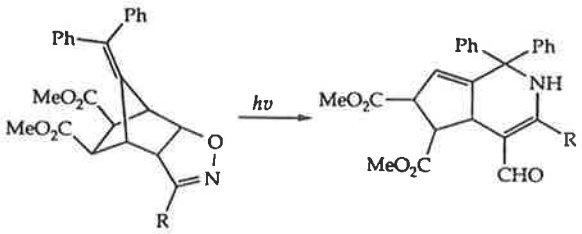
(154) (155) (156)

SCHEME 71



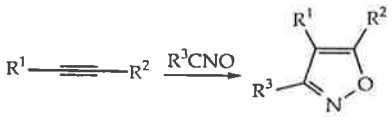
(157) (158) (159)

SCHEME 72



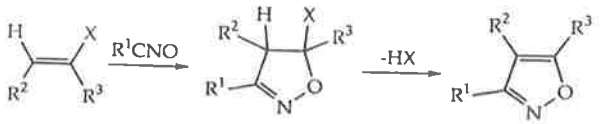
(160) (161)

SCHEME 73

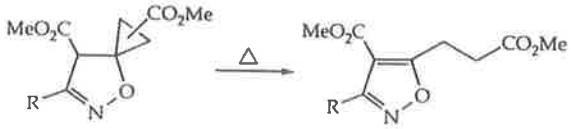


SCHEME 74

using chromic acid (1896JPC405), potassium permanganate (60JOC 1160; 79ZOR2436, 79ZOR2437), *N*-bromosuccinimide (65T817), Chloranil (74T3765; 76TL3983), 2,3-dichloro-5,6-dicyanobenzoquinone [79JCR(S)311], γ-active manganese dioxide (77S837; 78SC219), and air oxidation (74JCS(P1)1757; 83H2181; 93TL4281). Alternatively, isoxazolines have been constructed with leaving groups suitable for subsequent elimination. Thus, chloro- (84BCJ1643), alkoxy- [84BCJ2216; 88ACS(B)303; 91JHC429; 92JHC251], methylthiyl- [84JCR(S)402], amino- [84JHC949, 84JHC1121; 85JHC797; 88ACS(B)303], trimethylsilyloxy- (85CL1047, 85CL1049), bromo- (87BCJ2463), imino- (90JHC2097), thiobenzamido- (90LA1013), acyloxy- (85JOC903; 90CJC1271, 90ZOR1274), vinylsulfonyl- [91JCS(P1)2801], benzamido- (91JHC1945), *tert*-butyl- (92BCJ2484), and hydroxy-substituted [92H(34)1703] alkenes gave 5-substituted isoxazolines, which reacted by elimination to give the corresponding isoxazoles (Scheme 75). In unusual rearrangements, the spirocyclopropylisoxazoline (**162**) gave the isoxazole (**163**) on thermolysis (Scheme 76) (92T3323), and the cycloadducts (**165**) obtained from reaction of the allenes (**164**) with nitrile oxides underwent a Claisen-type rearrangement to give the corresponding isomers (**166**) (Scheme 77) [91JCS(P1)1843]. The synthesis of isoxazoles via isoxazolines is particularly useful where the corresponding alkynes are inaccessible, as is the case, for example, with small ring systems, and positioning of the substituent of the alkene can be used to control the regioselectivity of the cycloaddition. Accordingly, the bromocyclohexenones (**167**) and (**169**) gave the corresponding regioisomeric cycloadducts (**168**) and (**170**) (Schemes 78 and 79) (94UP1).

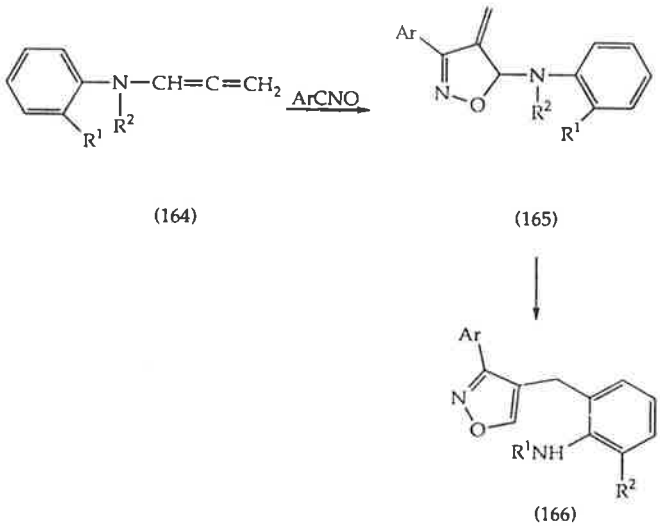


SCHEME 75



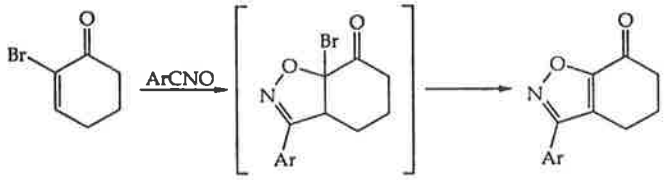
(162) (163)

SCHEME 76



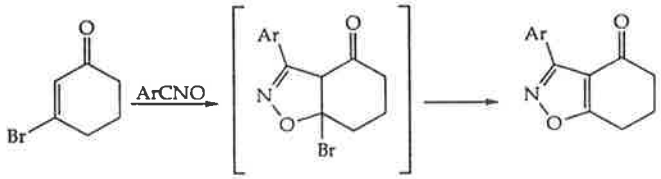
(164) (165) (166)

SCHEME 77



(167) (168)

SCHEME 78



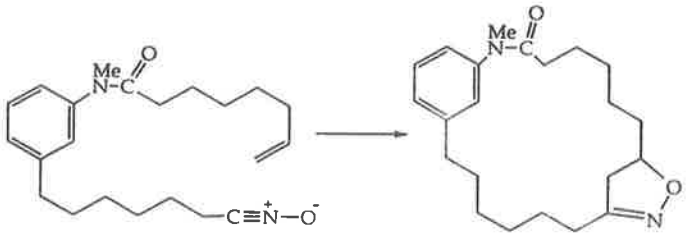
(169) (170)

SCHEME 79

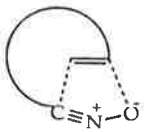
VIII. Intramolecular Nitrile Oxide Cycloadditions

Much of the recent work on nitrile oxide cycloaddition reactions with alkenes has involved intramolecular (INOC) processes. Whereas many aspects of the chemistry of INOC reactions are identical to those of the intermolecular analogues, others differ significantly as a result of the proximity of the reacting groups. Nitrile oxides are usually generated in similar fashion for use in intermolecular and intramolecular reactions; however, the predisposition of the alkene and the nitrile oxide within a molecule limits competing dimerization of the nitrile oxide in the latter case, with the result that less reactive alkenes undergo cycloaddition. Accordingly unactivated trisubstituted alkenes readily undergo INOC reactions (85CC847; 86CC757; 87CC189).

INOC reactions have been used in the synthesis of macrocycles (Scheme 80) (84TL947; 85BCJ2145, 85T3511). In these examples cycloaddition occurs in the *endo* mode (Fig. 7) and the nitrile oxide oxygen adds to the substituted carbon of the terminal alkene, as is the case with intermolecular reactions of monosubstituted alkenes. With most INOC reactions the regioselectivity is determined by geometric constraints, however, and reaction occurs in the *exo* mode (Fig. 8). Accordingly, ω-hexenyl [84ACR410, 84JOC2301; 85JA5310, 85TL2031; 87CC189, 87JA5280, 87JOC4674, 87T2369, 87TL4097; 88JOC50, 88JOC5590, 88TL715, 88TL4169; 89JA8954, 89JOC5277, 89T1517, 89TL5013; 90JOC5505, 90TL743; 91CB1181, 91JOC896, 91JOC5281, 91T3869, 91TL4259, 91TL5363; 93TL3017], heptenyl [84ACR410, 84JA1845, 84T2345; 85CC847, 85JA5310; 85JOC1564, 85TL43; 86CC757, 86TL1407; 87CC189, 87CC529, 87JOC3541, 87JOC4674, 87TL4097; 88JOC50, 88S342, 88TL715, 88TL4169; 89CC1093, 89JOC5277, 89TL5013; 90H597, 90JCS(P1)2481, 90JOC5505, 90TL743; 91CB1181, 91H1327, 91JOC896, 91MI1, 91T3869, 91T6635, 91T7537, 91TL3605, 91TL4259; 92H(33)73, 92H(33)161, 92TL4589], octenyl (84ACR410; 87CC189, 87TL4097; 88JOC50; 91CB1181, 91JOC896; 92TL1059), and decenyl (88CC198) nitrile



SCHEME 80

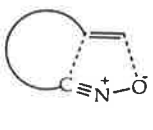


endo

FIG. 7. The INOC reaction occurring in the *endo* mode.

oxides give solely the products of *exo* cycloaddition, irrespective of the degree of substitution of the alkene or of heteroatoms or the degree of hybridization in the alkyl chain. The transition states of INOC reactions of ω-hexenyl and heptenyl nitrile oxides have been modeled using a variety of methods (92JOC4862). Although there has been no systematic study of the geometrical constraints that result in *exo* cycloaddition and the minimum chain length required for the *endo* process, the ω-decenyl nitrile oxide (**171**) reacted solely in the *exo* mode (Scheme 81) (88CC198), whereas the ω-dodecenyl nitrile oxide (**172**) reacted only by *endo* cycloaddition (Scheme 82) (85BCJ2145). Formation of the fused cyclooctane (**173**) instead of the cyclohexane (**174**) is consistent with the effect of bond polarization to increase reactivity (Scheme 83) (84JA1845).

As is the case with their intermolecular counterparts, the stereochemistry of the alkene is retained in INOC reactions [84ACR410, 84T2345; 85JA5310; 87JOC4674, 87T2369; 90JCS(P1)533; 91TL3605]; this is illustrated in the reactions shown in Scheme 4 (85JA5310). The cyclic nitrile oxide (**175**) gave the tricyclic product (**176**) with complete control of stereochemistry at both new stereogenic centers (Scheme 84) (90H597). The latter reaction also involves face selectivity in the approach of the nitrile oxide to the alkene, which occurs commonly in the case of INOC reactions where the reactant is constrained by a preexisting ring (84ACR410, 84JA1845, 84JOC2301; 85TL43, 85TL2031; 86TL1407; 87JA5280, 87JOC3541; 89JOC5277, 89T1517; 91MI1, 91TL3605; 93TL3017). Accordingly, the nitrile oxides (**177**), (**179**), and (**181**) gave only the isoxazolines (**178**) (85TL43), (**180**) (86TL1407), and (**182**) (91TL3605), respectively (Schemes 85–87).

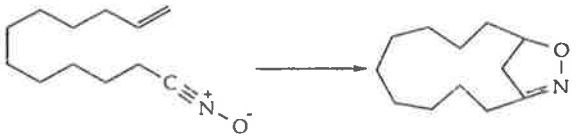


exo

FIG. 8. The INOC reaction occurring in the *exo* mode.

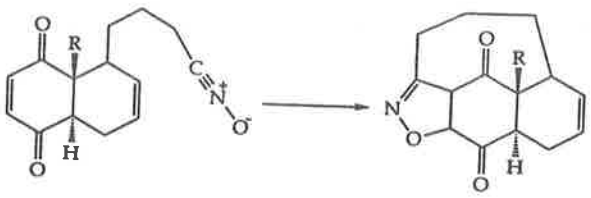
(171)

SCHEME 81

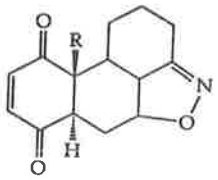


(172)

SCHEME 82

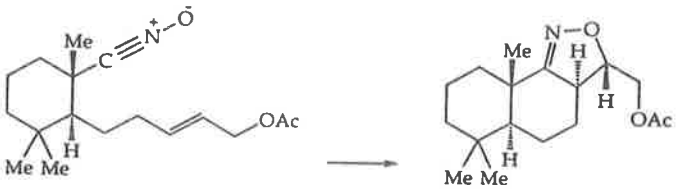


(173)



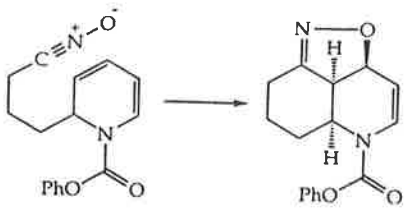
(174)

SCHEME 83



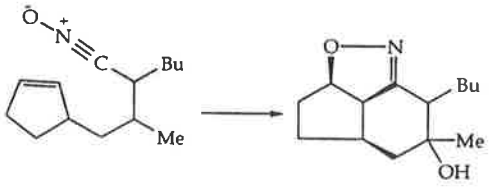
(175) (176)

SCHEME 84



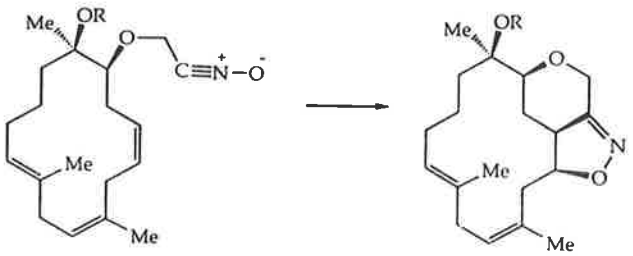
(177) (178)

SCHEME 85



(179) (180)

SCHEME 86

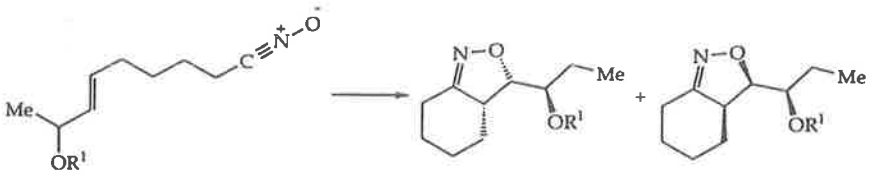


(181) (182)

R = $Si(Me)_2CMe_3$

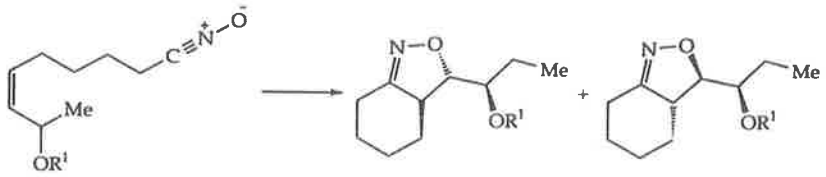
SCHEME 87

Annunziata *et al.* (87CC529, 87JOC4674, 87T2369) have examined the stereochemical outcome of INOC reactions where the alkene possesses a chiral allylic substituent remote from the nitrile oxide group. For example, the (*E*)-alkene (**183**) gave an 86 : 14 mixture of the diastereomers (**184**) and (**185**) (Scheme 88), whereas the corresponding (*Z*)-alkene (**186**) afforded the cycloadducts (**187**) and (**188**) in the same ratio (Scheme 89) (87CC529, 87JOC4674). Theoretical calculations have been used to ratio-



(183) (184) (185)

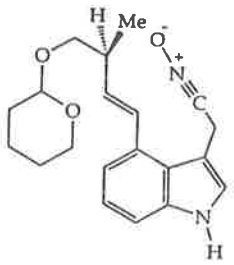
SCHEME 88



(186) (187) (188)

SCHEME 89

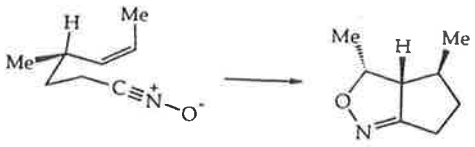
nalize the stereoselectivity observed in reactions of this type (87JOC4674; 92TL4409). The degree of stereoselectivity in these systems is quite variable, however, being negligible in the reaction of the nitrile oxide (**189**) (84T2345).



(189)

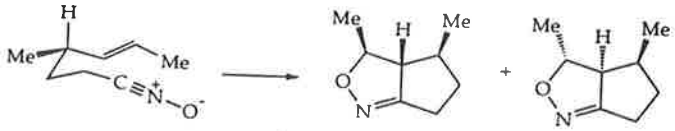
An allylic chiral center between the nitrile oxide and alkene groups can also affect the stereochemistry of INOC reactions. For example, the production of only the cycloadduct (**191**) in the reaction of the (*Z*)-nitroalkene (**190**) (Scheme 90), compared to the formation of a 3 : 1 mixture of the isoxazolines (**193**) and (**194**) from the (*E*)-isomer (**192**) (Scheme 91) (84ACR410) is a dramatic example of the influence of allylic 1,3-strain (89CRV1841) on these processes.

A chiral center adjacent to the nitrile oxide is also known to affect INOC reactions, as illustrated in the formation of the isoxazoline (**195a**),



(190) (191)

SCHEME 90



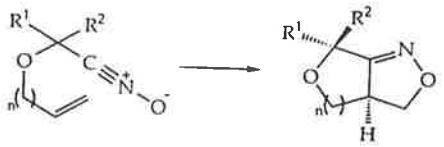
(192) (193) (194)

SCHEME 91

as a single diastereomer (Scheme 92) (88TL4169). By comparison, the homologue (**195b**) was obtained in 70% diasteromeric excess (Scheme 92) (89JOC5277). Theoretical calculations were used to rationalize the opposite stereochemical outcome of these reactions and similar observations in related systems (90JOC5505, 90TL743; 91CB1181; 92TL4405). Remote substituents can affect the diastereoselectivity of these processes, as illustrated in the production of only the isoxazolines (**197**) and (**198**), as an 11 : 1 mixture, in the reaction of the diene (**196**) (Scheme 93) (91TL4259).

INOC reactions of substrates with multiple chiral centers have also been reported [88JOC5590; 92H(33)161]. The heptose derivative (**199**) gave the cycloadducts (**200**) and (**201**) (Scheme 94) as a 64 : 36 mixture, whereas the diastereomeric nitrile oxide (**202**) gave only the isoxazoline (**203**) (Scheme 95) (91T7537). The phthalimide (**204**) gave only a single product (Scheme 96) (91TL5363), whereas the pyranose derivative (**205**) gave the isoxazoline (**206**) (Scheme 97) in 89% diastereomeric excess (92TL1059).

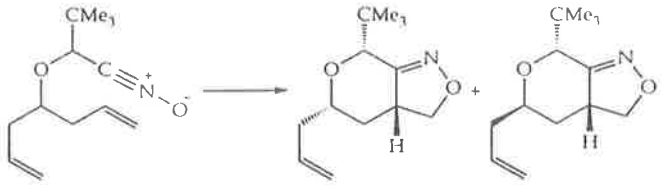
Hassner *et al.* have investigated the stereochemical consequences of cyclization of vinyl-substituted azetidines and azetidinones. The vinylazet-



(195)

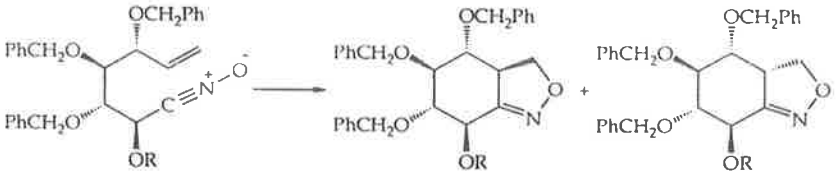
a) R^1 = Ph, R^2 = H, n = 1
b) R^1 = H, R^2 = Ph, n = 2

SCHEME 92



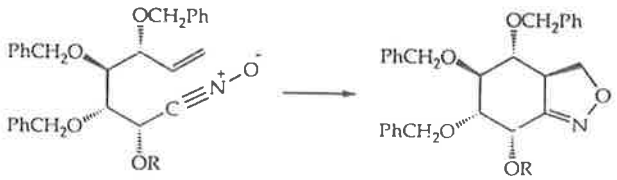
(196) (197) (198)

SCHEME 93



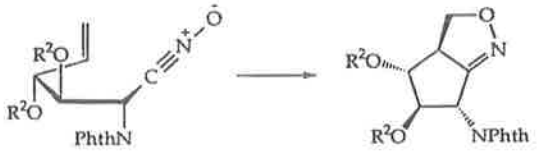
(199) (200) (201)

SCHEME 94



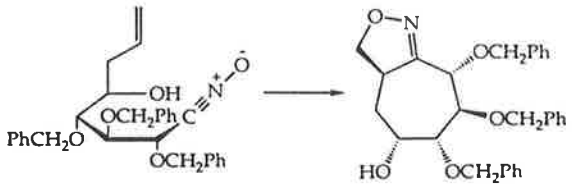
(202) (203)

SCHEME 95



(204)

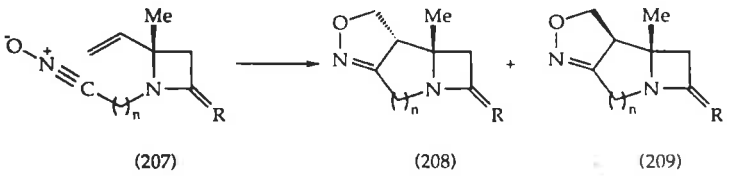
SCHEME 96



(205) (206)

SCHEME 97

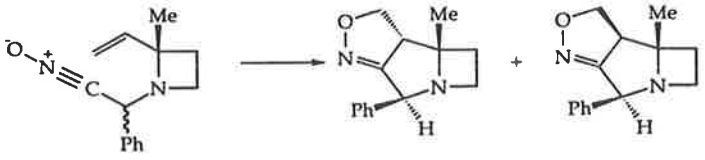
idine (**207a**) gave a 2 : 1 mixture of the fused cyclopentanes (**208a**) and (**209a**) (Scheme 98) (87TL4097). The azetidinones (**207b**) and (**207e**) failed to cyclize, the cyclohexane (**209c**) was produced as a single diastereomer, and the fused cycloheptanes (**208d**) and (**209d**) were obtained as a 2 : 3 mixture (Scheme 98) (88JOC5063). The stereospecific formation of the cyclohexane (**209c**) is consistent with reaction via a chair transition state, whereas the poor stereoselectivity in the reactions to give the cycloheptanes (**208d**) and (**209d**) reflects the greater flexibility in the corresponding transition states. In the case of the azetidine (**210**), only the diastereomer leading to the isoxazolines (**211**) and (**212**) underwent cycloaddition (Scheme 99) (87TL4097). Chair-like transition states have been used to rationalize the stereochemical outcome of a variety of other INOC reac-



(207) (208) (209)

a) R = H_2, n = 1
or b) R = O, n = 1
or c) R = O, n = 2
or d) R = O, n = 3
or e) R = O, n = 4

SCHEME 98



(210) (211) (212)

SCHEME 99

tions that afford fused cyclohexanes [90H597, 90JCS(P1)2481, 90JOC4497; 91T6635].

A major impetus for continued interest in INOC reactions has been their utility in synthesis. Accordingly, γ-hydroxy amines (84ACR410, 84T2345; 90JOC5505; 93TL3017), β-hydroxy imines (86CC757, 86TL4865; 89T1517), β-hydroxy ketones [84JOC2301, 84TL947; 85BCJ2145, 85CC847, 85JOC1564, 85T3511, 85TL43, 85TL2031; 86CC757, 86TL1407, 86TL4865; 87CC189, 87JA5280, 87JOC3541, 87T2369; 88JOC5590; 89BCJ602, 89CC1093, 89T1517; 90H597, 90JCS(P1)2481, 90JOC4497; 91H1327, 91JOC5281, 91MI1, 91T6635, 91TL3605, 91TL5363; 92H(33)161, 92TL1059, 92TL4589], and α,β-unsaturated ketones (86TL1407; 87JA5280, 87JOC3541; 88CC198; 89JA8954) have been reported in this manner.

In this chapter we have attempted to summarize recent trends in nitrile oxide cycloaddition reactions of alkenes. We hope that this overview will stimulate and encourage continued work in the field.

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Aryl Nitrile Oxide Cycloaddition Reactions in the Presence of Baker's Yeast and β-Cyclodextrin

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Abstract: Contrary to recent reports, baker's yeast is not required for reactions of nitrile oxides with either ethyl cinnamate or 4-vinylpyridine to give isoxazolines. β-Cyclodextrin may alter the ratio of isomers isolated from the reactions of the cinnamate but only at concentrations of reactants much lower than those reported, and this effect is most likely due to selective product complexation rather than selective product formation.

In recent articles,[1-5] that have often been cited,[6] it has been reported that baker's yeast catalyses 1,3-dipolar cycloaddition reactions of nitrile oxides with cinnamates,[1,2] vinylpyridines,[2,3] acrylates[4] and vinylcarbazoles,[5] furthermore β-cyclodextrin (βCD) influences the regioselectivity and stereoselectivity of some of these reactions.[1-3] Our interest in the chemistry of nitrile oxide cycloadditions,[7-9] yeast-catalysed reactions,[10] and cyclodextrins,[11] led us to examine these effects. We began by repeating a selection of the reported[1,2] experiments with ethyl cinnamate 2. The results of these studies and comparable literature data are shown in Table 1, together with results of experiments performed in the absence of yeast but otherwise under identical conditions.[12]

Table 1. Ratio of the Cycloadducts 3 and 4 Formed in Reactions of the Nitrile Oxides 1 with Ethyl Cinnamate 2.

Nitrile Oxide	Ratio of the Cycloadducts 3:4[a]			
	Yeast[b] No βCD	No Yeast No βCD	Yeast[b] βCD	No Yeast βCD
1a	94:6 (100:0)[c]	87:13	97:3 (100:0)[c]	87:13
1b	57:43 (65:35)[c]	61:39	59:41 (0:100)[c]	60:40

[a] Determined by integration of 200 MHz ^{1}H NMR spectra.[13]
[b] Fermipan®, Gist-brocades, Holland (*sp. Saccharomyces cerevisiae*).
[c] Data from reference 1 shown in brackets.

Contrary to specific reported statements that cycloaddition reactions of the nitrile oxides **1a** and **1b** with ethyl cinnamate **2** (Scheme 1) do not proceed in aqueous media in the absence of yeast,[1,2] we found that yeast was not required for these reactions. Further, yeast had little effect on the ratio of the regioisomeric cycloadducts **3** and **4** or on the yields of these reactions, which were consistently of the order of 50%.[14] Our results are in accord with earlier literature reports describing cycloadditions of nitrile oxides with cinnamates and acrylates occurring without the need for a biocatalyst.[15,16]

(1) (2) (±)-(3) (±)-(4)

a) Ar = 2,6-dichlorophenyl
b) Ar = 2,4,6-trimethylphenyl

Scheme 1

We observed formation of the cycloadduct **4a**, in addition to the regioisomer **3a** reported previously.[1,2] Using X-ray crystallographic analysis, the regioisomer **3a** (Figure 1)[17] was confirmed to be that previously proposed[1,2] on the basis of ^{1}H NMR spectral data.[15] In the absence of yeast we observed the reported effect of βCD,[1,2] to alter the ratio of the cycloadducts **3b** and **4b** isolated from the reaction of 2,4,6-trimethylbenzonitrile oxide **1b** with ethyl cinnamate **2**. The magnitude of the effect was less than that reported, however, unless much reduced concentrations of the reactants **1b** and **2** were used (Table 2). In the present study, βCD also changed the observed ratio of the isolated cycloadducts **3a** and **4a**.

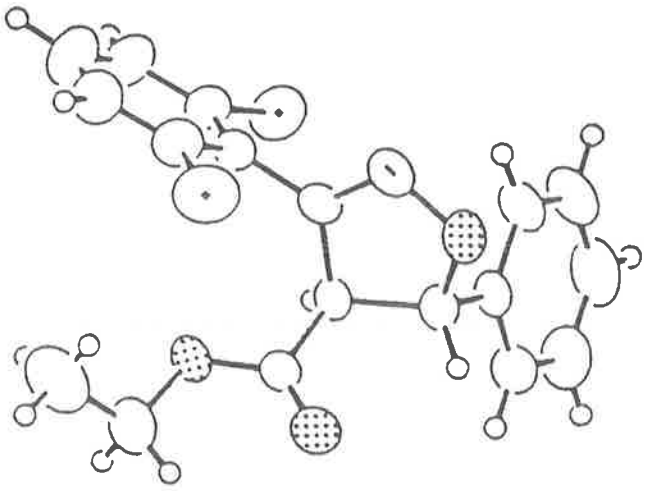


Figure 1. Molecular structure of **3a**

Table 2. Effect of Varying the Ratio of the Reagents 1 and 2[a] to βCD[b] on the Ratio of the Cycloadducts 3 and 4.

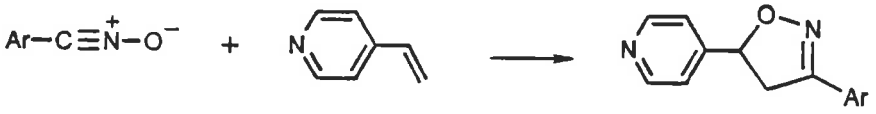
Nitrile Oxide (mmol)	Ratio 3:4
1a (1.5)	87:13
1a (0.25)	80:20
1b (1.5)	60:40
1b (1.0)	46:54
1b (0.25)	26:74

[a] Mole ratio of 1:2 – 1:1.
[b] The amount of βCD was 1.5 mmol in each experiment.

In a separate experiment, we treated a *ca.* 1:1 mixture of the regioisomers **3b** and **4b** (0.1 mmol) with βCD (1.5 mmol) under the conditions used for the cycloadditions. The sample recovered through work-up in the usual manner[12] was a 1:4 mixture of the regioisomers **3b** and **4b**, however, further extractions of the aqueous βCD solution with chloroform, then ethyl acetate, afforded samples increasingly enriched in the cycloadduct **3b**. The final ethyl acetate extracts contained only the regioisomer **3b**. On this basis, the effect of βCD on the ratio of the isomers **3b** and **4b** obtained from the reactions of the nitrile oxide **1b** with the cinnamate **2** can be solely attributed to the isolation procedure, and it is unlikely that βCD affects the ratio of formation of the products **3b** and **4b**.[1,2]

Mixtures of the regioisomers **3** and **4** (0.1 mmol) were treated with yeast under the conditions used for the cycloadditions. In recovered material the ratio of **3a** to **4a** had increased but the ratio of **3b** to **4b** was not affected. This probably results from the yeast either selectively consuming the isoxazoline **4a** or affecting the relative ease with which the isomers **3a** and **4a** are extracted from the aqueous solution.

In our hands the nitrile oxides **1a** and **1b** reacted with 4-vinylpyridine **5** (Scheme 2) in the absence of yeast. Further, the products **6a** and **6b** from reactions carried out in the presence of either yeast, βCD or both, were optically inactive. Again these results are in contrast to the literature[2,3] where it is stated that yeast is required for this reaction to proceed, that reaction in the presence of yeast gives optically active products, and that the optical activity of the products is enhanced by conducting the reactions in the presence of β-cyclodextrin.



(1) (5) (6)

a) Ar = 2,6-dichlorophenyl
b) Ar = 2,4,6-trimethylphenyl

Scheme 2

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12. A solution of the nitrile oxide **1** (*ca.* 1.5 mmol), ethyl cinnamate **2** (1 mole equiv.) and βCD (1 mole equiv.) in 30% aqueous ethanol (20 ml) was added to a mixture of yeast (0.5 g) in phosphate buffer (0.5 M, pH 7.2, 12.5 ml). The suspension was incubated at 37 °C with gentle stirring for 30 h, then it was extracted with chloroform (2 x 20 ml). The extracts were combined and dried ($MgSO_4$), then concentrated under reduced pressure to give the crude product.
13. ^1H NMR ($CDCl_3$) data for the isoxazoline ring hydrogens: **3a**, δ 4.57 and 6.26, J = 9 Hz; **4a**, δ 5.24 and 5.27, J = 6 Hz; **3b**, δ 4.37 and 6.10, J = 9.5 Hz; **4b**, δ 4.81 and 5.32, J = 4 Hz.
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Complexes of Fluorinated Amino Acid Derivatives and Hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin† in Aqueous Solution. A Fluorine-19 Nuclear Magnetic Resonance Study

J. Chem. Research (S), 1995, 2
J. Chem. Research (M), 1995, 0173–0184

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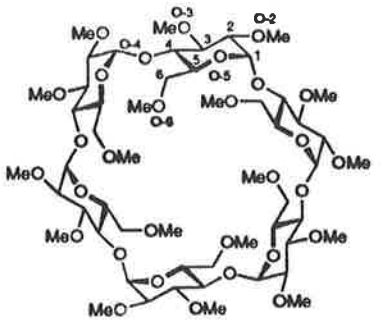
Department of Chemistry, University of Adelaide, South Australia 5005, Australia

The formation of complexes by hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD) and (*RS*)-fluorinated amino acid derivatives in 10% aqueous D_2O solution has been studied by ^{19}F NMR spectroscopy; in each case the stability of the TMαCD complex and the ^{19}F chemical shift induced in the complexed amino acid derivative are substantially greater than those of its cyclodextrin analogue.

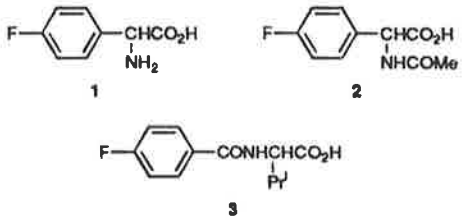
The diastereoisomeric complexes formed between D-hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD)[1] and (*RS*)-fluorinated amino acid derivatives in 10% aqueous D_2O solution are characterized by different ^{19}F (282.35 MHz) chemical shifts from which their stability constants K_R and K_S may be separately determined. Thus, K_R and K_S (dm^3 mol^{-1}) = 54 ± 3 and 59 ± 4 for protonated α-(*p*-fluorophenyl)glycine (**1** + H), 49 ± 3 and 55 ± 3 for deprotonated



TMαCD

α-(*p*-fluorophenyl)glycine (**1** − H), 451 ± 7 and 434 ± 7 for *N*-acetyl-[α-(*p*-fluorophenyl)]glycine (**2**), 80 ± 3 and 77 ± 3 for deprotonated *N*-acetyl-[α-(*p*-fluorophenyl)]glycine (**2** − H), 142 ± 6 and 155 ± 6 for *N*-(*p*-fluorobenzoyl)valine (**3**), and 143 ± 6 and 153 ± 6 for deprotonated *N*-(*p*-fluorobenzoyl)valine (**3** − H) at 295.5 K and I = 0.10 mol dm^{-3}, where the first and second of each pair of values refers to the diastereoisomeric complex formed between TMαCD and the *R* and *S* enantiomers of the fluorinated amino acid derivatives, respectively. The order of complex stability is broadly consistent with the most hydrophobic guest forming the most stable TMαCD complex, subject to the spatial requirements of the TMαCD annulus. In every case the stability of the TMαCD complex and the ^{19}F chemical shift induced in the complexed amino acid derivative are substantially greater than those of its α-cyclodextrin (αCD) analogue.[10]

The hydrophobic annulus of D-hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD) is delineated by six C-6 methoxy groups at its narrow end and twelve C-2 and C-3 methoxy groups at its wide end.[1] In contrast, the annulus of αCD is delineated by six and twelve hydroxy groups at its



1 **2**

3

narrow and wide ends, respectively, and it is only the annulus interior, composed of methylene, methine and ether groups, which is hydrophobic. The greater magnitudes of stabilities of the TMαCD complexes, by comparison with those of their αCD analogues, probably reflect (*i*) the deeper guest penetration into the larger and more hydrophobic TMαCD annulus which results in greater hydrophobic and van der Waals interactions, and a correspondingly larger stabilizing influence on complex formation; (*ii*) the absence of significant hydrogen bonding between the ends of the TMαCD annulus and water such that the extent of dehydration of the guests and its stabilizing effect on complexation are greater in the TMαCD complexes; and (*iii*) the greater flexibility of TMαCD which allows a more ready conformational change to accommodate a guest and increase complex stability.[1]

Technique used: ^{19}F NMR spectroscopy

References: 18

Scheme: 1

Fig. 1: Structure of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD)

Fig. 2: The variation of ^{19}F NMR δ_{obs} for racemic *N*-acetyl-[α-(*p*-fluorophenyl)]glycine (**2**) and deprotonated racemic *N*-acetyl-[α-(*p*-fluorophenyl)]glycine (**2** − H) with [TMαCD]

Table 1: Stability constants and ^{19}F chemical shifts of α-cyclodextrin- and hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin-amino acid derivative diastereoisomeric complexes in 10% aqueous D_2O

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* To receive any correspondence.
† Hexakis(2,3,6-tri-*O*-methyl)cyclohexamaltaose.

Aust. J. Chem., 1995, **48**, 269–277

Amino Substituents as a Probe of Reactions of Phenyl Acetates with Cyclodextrins*

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Abstract

The effects of α- and β-cyclodextrin and 6^A-amino-6^A-deoxy-α- and -β-cyclodextrin on the rates of reactions of *m*- and *p*-nitrophenyl acetate, in borate buffer at pH 10·0 and 298·2 K, show that the amino substituents of the modified cyclodextrins have only a modest influence on the dissociation constants of the complexes formed with each ester and the first-order rate constants for the reactions of complexed *m*-nitrophenyl acetate. By contrast, the amino substituents significantly increase the rate constants for the reactions of complexes of *p*-nitrophenyl acetate. These results indicate that one mode of inclusion of *p*-nitrophenyl acetate in α- and β-cyclodextrin has the ester oxycarbonyl group in the vicinity of the cyclodextrin primary hydroxy groups. While this mode of inclusion in the unmodified cyclodextrins does not lead to reaction and has not been detected previously for that reason, in analogous complexes of the amino-substituted cyclodextrins, the nucleophilic amino group is proximate to the carboxy group of the ester and reaction proceeds. There is no kinetic evidence for this mode of inclusion of *m*-nitrophenyl acetate. This interpretation of the kinetic effects is consistent with the extent of acetamide formation in reactions of the esters with the amino-substituted cyclodextrins.

Introduction

The catalysis by cyclodextrins of the alkaline hydrolysis of phenyl esters has been studied as a model of covalent catalysis by enzymes.[1–4] The reaction of *m*-nitrophenyl acetate (1) in the presence of α-cyclodextrin occurs as outlined in Scheme 1.[1,5] The aryloxy group of the ester (1) is included in the cyclodextrin annulus, in an orientation where the oxycarbonyl group of ester (1) is located close to, and reacts with, a deprotonated secondary hydroxy group of the cyclodextrin. The reaction gives *m*-nitrophenoxide ion, which is liberated from the complex, and

* Dedicated to Athel Beckwith in recognition of his contribution to chemistry.

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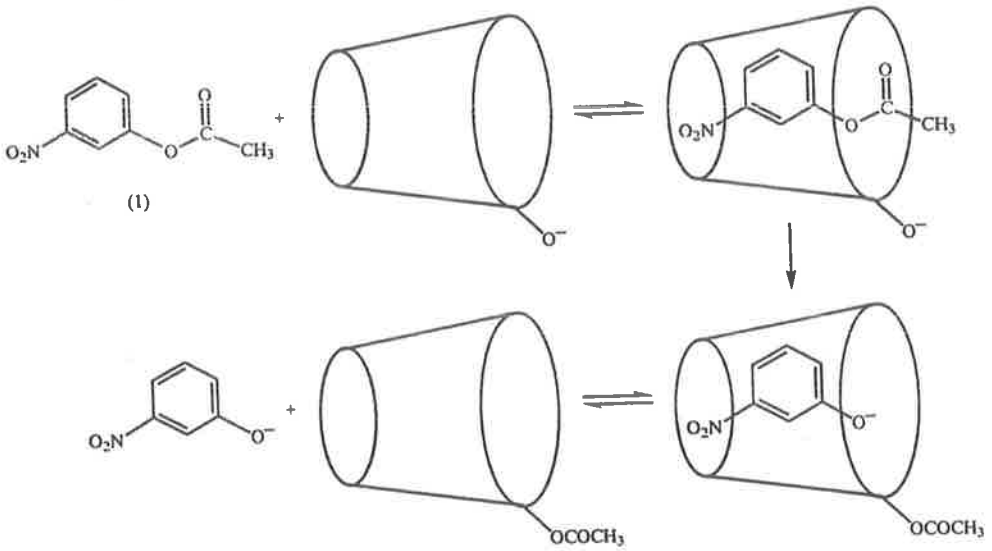
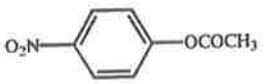
acylated cyclodextrin, which undergoes hydrolysis to regenerate α-cyclodextrin, in a catalytic cycle.



Scheme 1. A truncated cone is used to represent a cyclodextrin. Substituents drawn at the wide end of the cone indicate that they replace secondary hydroxy groups.

While analogous processes are involved in the hydrolysis of the ester (1) catalysed by β-cyclodextrin,[5,6] and in the cyclodextrin-catalysed hydrolysis of other *meta*-substituted phenyl esters,[2,5] recent studies have indicated that related reactions of *para*-substituted phenyl esters do not involve inclusion of the ester aryloxy group in the cavity of the cyclodextrin.[5–8] Instead, it has been suggested that the reaction of *p*-nitrophenyl acetate (2) with β-cyclodextrin takes place outside the cyclodextrin cavity, although this process still involves prior association of the ester (2) with the cyclodextrin.[6] With other *p*-nitrophenyl alkanoates it appears that the acyl group is included in the cavity of the cyclodextrin.[5,7,8]



(2)

In all of the studies so far reported, the reactions involve cyclodextrin secondary hydroxy groups.[1,2,4,6] It follows that reaction occurs when the ester oxycarbonyl group is in close proximity to the wider end of the cyclodextrin annulus, where the secondary hydroxy groups are located. It is not necessarily true that the orientation for reaction is also the preferred orientation of an ester in the cavity of a cyclodextrin, as complexation and reaction of an ester are distinct processes that need not be related.[1,2,5,6] The possibility of complexation of phenyl esters

[6] Tee, O. S., and Hoeven, J. J., *J. Am. Chem. Soc.*, 1989, **111**, 8318.
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with their oxycarbonyl groups in the vicinity of the narrow end of the cyclodextrin annulus, located close to the cyclodextrin primary hydroxy groups, has not been explored. The primary and secondary hydroxy groups of cyclodextrins have pK_a values near 15–16,[1,9] and 12·2,[1,10] respectively. Under the alkaline conditions used in the earlier studies, the extent of deprotonation of the secondary hydroxy groups would have been far more extensive than that of the primary hydroxy groups, providing the secondary hydroxy groups with a distinct kinetic advantage.

In order to obtain a more complete picture of the complexation of phenyl esters by cyclodextrins, we have investigated the interactions of *m*-nitrophenyl acetate (1) and the *para*-substituted isomer (2) with 6^A-amino-6^A-deoxy-α- and -β-cyclodextrin, and compared these systems with those involving unmodified α- and β-cyclodextrin. In each of the modified cyclodextrins a single primary hydroxy group has been replaced by an amino substituent with a pK_a of approximately 8·7.[11] We expected that the nucleophilic potential of these amino substituents could be exploited as a kinetic probe, to detect complexes with the oxycarbonyl groups of the esters (1) and (2) located in the vicinity of the narrow end of cyclodextrin annuli, near the primary hydroxy groups.

Results and Discussion

Reactions of the esters (1) and (2) were followed by monitoring changes in their ultraviolet spectra, at 272 nm, accompanying release of the substituted phenol groups. In order to provide optimal conditions to observe a kinetic effect with the amino-substituted cyclodextrins, the reactions were investigated at pH 10·0, in 0·10 mol dm^{-3} borate buffer at 298·2 K, and under otherwise the same conditions in the presence of either α- or β-cyclodextrin or one of the modified cyclodextrins. Under these conditions approximately 95% of each of the amino-substituted cyclodextrins is in the free-base form. More acidic conditions would be less suitable as more of each amine would be protonated, thus masking the nucleophilic potential of these substituents, whereas under more basic conditions deprotonation of the cyclodextrin secondary hydroxy groups would be more extensive, increasing the concentration of alkoxide competitive nucleophiles.

The effect of each cyclodextrin was examined by using a range of cyclodextrin concentations from 0·002 to 0·010 mol dm^{-3}, with the cyclodextrin in at least 50-fold molar excess compared to the initial concentration of the ester (1) or (2). The reactions followed first-order kinetics, when monitored through to at least 90% completion, as determined from the linearity of the variation of the logarithm of the change in ultraviolet absorbance as a function of time. The pseudo-first-order rate constant (k_{obs}) for each reaction was calculated from this correlation.

The effect of varying cyclodextrin concentration on the k_{obs} values followed Michaelis–Menten kinetics. The data were treated according to a variant of

[9] Rong, D., and D'Souza, V. T., *Tetrahedron Lett.*, 1990, **31**, 4275.
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[11] Brown, S. E., Coates, J. H., Coghlan, D. R., Easton, C. J., van Eyk, S. J., Janowski, W., Lepore, A., Lincoln, S. F., Luo, Y., May, B. L., Schiesser, D. S., Wang, P., and Williams, M. L., *Aust. J. Chem.*, 1993, **46**, 953.

Michaelis–Menten kinetics previously employed for investigation of reactions involving complex formation. By plotting the reciprocal of the difference between the k_{obs} values and the rate constant for hydrolysis in the absence of cyclodextrin (k_{un}) against the reciprocal of the cyclodextrin concentration, a straight line was obtained having a slope equal to the dissociation constant of the complex (K_{diss}) divided by the rate constant for reaction of the entirely complexed ester (1) or (2) (k_c) and a Y intercept equal to $1/k_c$.[1,12] The K_{diss} and k_c values obtained in this manner are presented in Table 1, together with comparable literature data.

Table 1. Dissociation constants for complexes and rate constants for reactions of the esters (1) and (2)

Literature data are shown in parentheses

Cyclodextrin	Ester (1)		Ester (2)	
	k_{un} (s^{-1})		k_{un} (s^{-1})	
—	0·0022[A] (0·00464)[B] (0·0014)[C] (0·086)[D]		0·0023[A] (0·00694)[B] (0·096)[D] (0·00175)[E]	
	k_c (s^{-1})	K_{diss} (mol dm^{-3})	k_c (s^{-1})	K_{diss} (mol dm^{-3})
α-Cyclodextrin	0·17±0·03[A] (0·425)[C] (25)[D] —	0·012±0·001[A] (0·019)[C] (0·025)[D] —	— (0·0243)[B] (0·27)[D] (0·00565)[E]	— (0·012)[B] (0·010)[D] (0·0105)[E]
6[A]-Amino-6[A]-deoxy-α-cyclodextrin	0·12±0·04[A]	0·008±0·001[A]	0·0092±0·0019[A]	0·011±0·001[A]
β-Cyclodextrin	0·050±0·004[A] (0·444)[B] (5·3)[D] —	0·006±0·001[A] (0·008)[B] (0·012)[D] —	0·012±0·003[A] (0·0634)[B] (0·78)[D] (0·0213)[E]	0·009±0·001[A] (0·0061)[B] (0·0078)[D] (0·0065)[E]
6[A]-Amino-6[A]-deoxy-β-cyclodextrin	0·035±0·002[A]	0·003±0·0005[A]	0·048±0·004[A]	0·008±0·001[A]

[A] In 0·10 mol dm^{-3} borate buffer at pH 10·0 and 298·2 K. Duplicate experiments gave k_{un} values which varied by less than 5%. Quoted errors are the calculated standard deviations.
[B] At pH 10·6, 298·2 K.[1]
[C] At pH 10·01, 298·2 K.[1]
[D] At pH 11·7, 298·2 K.[5]
[E] At pH 10·4, 298·2 K.[7]

There are only minor variations between the literature data[1,5,7] and results obtained in this work for the K_{diss} values of *m*-nitrophenyl acetate (1) with α- and β-cyclodextrin, and of the *para*-substituted phenyl ester (2) with β-cyclodextrin, even though the measurements were performed under a range of experimental conditions. It appears that the K_{diss} values vary little between pH 10·0 and 11·7. The differences between the k_{un} and k_c values determined in the present study and those reported in the literature,[1,5,7] for reaction of the esters (1) and (2) in buffer and when complexed to α- and β-cyclodextrin, may be attributed to the range of pH values of the solutions used in the various experiments. The k_{un} and k_c values increase with pH, as expected for processes involving hydroxide and cyclodextrin secondary hydroxy groups having a pK_a near 12·2,[1,10] respectively. Thus the results of the present study are quite consistent with earlier reports.

The K_{diss} values for the complexes of the ester (1) with the amino-substituted cyclodextrins are sufficiently similar to those of the corresponding natural

[12] Lineweaver, H., and Burk, D., *J. Am. Chem. Soc.*, 1934, **56**, 658.

cyclodextrins to indicate that the amino substituents do not induce a major change in the orientation of complexation of the ester (1). The k_c values for reactions of the ester (1) complexed by the amino-substituted cyclodextrins are approximately 30% less than those for the corresponding complexes of the unmodified cyclodextrins, contrary to the result that would be expected if the amino substituents reacted directly with the complexed ester (1). This observation is in accord with the hypothesis, originally proposed by VanEtten *et al.*,[1,2] that catalysis of the reaction of the ester (1) by either α- or β-cyclodextrin involves an inclusion complex in which the oxycarbonyl group of the ester (1) is in the vicinity of the wider end of the cyclodextrin annulus, where it reacts with a deprotonated secondary hydroxy group of the cyclodextrin (Scheme 1). The amino substituents located at the other end of the annuli of the modified cyclodextrins therefore have little effect on the rate of reaction of the complexed ester (1).

By contrast with the situation with the ester (1), the amino substituent of the modified β-cyclodextrin markedly increases the rate of reaction of the complexed ester (2), with k_c for the reaction being four times higher than is observed for the complex of the ester (2) with β-cyclodextrin. The similarity between the K_{diss} values of the complexes of the ester (2) with β-cyclodextrin and the corresponding amine indicates that the amino substituent has little effect on the complexation process. The simplest interpretation of these results is that one mode of inclusion of the ester (2) in the cavity of β-cyclodextrin is as shown in Fig. 1, where the oxycarbonyl group of the ester (2) is in the vicinity of the primary hydroxy groups of the cyclodextrin. While this complex of β-cyclodextrin is catalytically inactive and hitherto has remained undetected for that reason, in the analogous complex of the amino-substituted β-cyclodextrin, the nucleophilic amino group is in close proximity to the oxycarbonyl group of the ester (2) and reaction proceeds.

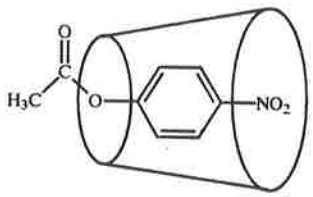

Fig. 1. Inclusion of *p*-nitrophenyl acetate (2) in the cavity of a cyclodextrin.

The effect of α-cyclodextrin on the reaction of *p*-nitrophenyl acetate (2) was less than that of any of the other cyclodextrins, or of any of the cyclodextrins on reaction of the *meta*-substituted phenyl ester (1). It was too small to measure accurately as a function of α-cyclodextrin concentration from 0·002 to 0·010 mol dm^{-3}, as the 0·010 mol dm^{-3} concentration of α-cyclodextrin only increased k_{obs} for hydrolysis of the ester (2) by 40% beyond k_{un}. By comparison, a 0·010 mol dm^{-3} concentration of the amino-substituted α-cyclodextrin increased k_{obs} for hydrolysis of the ester (2) by 180% beyond k_{un}, and the effect of β-cyclodextrin and the corresponding amine on the reaction of the ester (2), and of each cyclodextrin on the reaction of the ester (1), was even greater. The effect of higher concentrations of α-cyclodextrin on the hydrolysis of the ester (2) was inconsistent with Michaelis–Menten kinetics, k_{obs} decreasing with

increasing cyclodextrin concentration, presumably because the ester (2) forms less reactive 2:1 host–guest complexes under these conditions. For this reason it was not possible to determine accurately either K_{diss} for the complex of the ester (2) with α-cyclodextrin, or k_c for the reaction of the ester (2). Nevertheless, K_{diss} of the complex of the ester (2) with the amino-substituted α-cyclodextrin, as determined in this study, is very similar to that reported previously for the analogous complex with α-cyclodextrin.[1,5,7] On this basis it appears that the amino substituent has little effect on the complexation. As the greater effect of the 0·010 mol dm^{-3} concentration of the amino-substituted α-cyclodextrin, than the same concentration of α-cyclodextrin, on k_{obs} of the ester (2), reflects a combination of the differences between the K_{diss} and k_c values of the complexes and reactions of the ester (2), it follows that k_c of the ester (2) complexed by the amino-substituted cyclodextrin is between four and five times larger than that of the corresponding complex of α-cyclodextrin.

At pH 10·4, a k_c of $5{\cdot}65\times10^{-3}$ s^{-1} for hydrolysis of the ester (2) complexed by α-cyclodextrin has been reported,[7] and under less alkaline conditions, at pH 10·0, the reaction would be expected to occur less readily. By comparison, the value of k_c for hydrolysis of the ester (2) complexed by the amino-substituted

Table 2. Effect of cyclodextrins, adamantanecarboxylic acid and undecanoic acid on the rates of reaction of the esters (1) and (2)

Duplicate experiments gave k_{un} values which varied by less than 5%

Cyclodextrin (concentration)	Ester (1)		Ester (2)	
	k_{un} (s^{-1})		k_{un} (s^{-1})	
—	0·0022[A]	0·0018[B]	0·0023[A]	0·0022[C]
	$k_{obs}-k_{un}$ (s^{-1})		$k_{obs}-k_{un}$ (s^{-1})	
α-Cyclodextrin (2·4 mmol dm^{-3})	0·030[A]	0·0004[B]	—	—
6[A]-Amino-6[A]-deoxy-α-cyclodextrin (2·5 mmol dm^{-3})	0·028[A]	0·0009[B]	—	—
6[A]-Amino-6[A]-deoxy-α-cyclodextrin (6·1 mmol dm^{-3})	—	—	0·0034[A]	0·0016[C]
	k_{un} (s^{-1})		k_{un} (s^{-1})	
—	0·0022[A]	0·0015[D]	0·0023[A]	0·0018[D]
	$k_{obs}-k_{un}$ (s^{-1})		$k_{obs}-k_{un}$ (s^{-1})	
β-Cyclodextrin (2·3 mmol dm^{-3})	0·013[A]	0·00088[D]	0·0022[A]	0·000008[D]
6[A]-Amino-6[A]-deoxy-β-cyclodextrin (2·1 mmol dm^{-3})	0·0098[A]	0·00066[D]	0·0104[A]	0·0011[D]

[A] At pH 10·0 and 298·2 K.
[B] At pH 10·0 and 298·2 K, with 6×10^{-3} mol dm^{-3} undecanoic acid.
[C] At pH 10·0 and 298·2 K, with 10×10^{-3} mol dm^{-3} undecanoic acid.
[D] At pH 10·0 and 298·2 K, with 7×10^{-3} mol dm^{-3} adamantanecarboxylic acid.

α-cyclodextrin at pH 10·0 is $9{\cdot}2\times10^{-3}$ s^{-1}, again indicating that the reaction of the ester (2) complexed by the amine is considerably faster than in the complex of α-cyclodextrin. This situation is the same as that observed with the complexes of the ester (2) with β-cyclodextrin and the corresponding amine, and the results clearly indicate that one mode of interaction of the ester (2) with α-cyclodextrin is as shown in Fig. 1 and discussed above for β-cyclodextrin. The ester (2) is included in the cavity of the cyclodextrin with its oxycarbonyl group in the vicinity of the cyclodextrin primary hydroxy groups. In the corresponding complex of the modified α-cyclodextrin, the amino substituent reacts with the ester (2), and k_c for reaction of the ester (2) is increased.

The effect of β-cyclodextrin and the corresponding amine on the rates of reaction of the esters (1) and (2) was reduced by more than 80% through the addition of 7 mmol dm^{-3} adamantanecarboxylic acid to the reaction mixtures (Table 2). A similar reduction in the effect of α-cyclodextrin and the corresponding amine on the rates of reaction of the ester (1) and a 50% reduction in the effect of the amine on the rate of reaction of the ester (2) was observed when those reactions were carried out in the presence of undecanoic acid (Table 2). These results establish clearly that adamantanecarboxylic acid and undecanoic acid compete effectively with the esters (1) and (2), to complex with the cyclodextrins, and that the cyclodextrins enhance the rates of reaction of the esters (1) and (2) through complexation.[1,6]

While acylation of the cyclodextrin hydroxy groups in reactions with the esters (1) and (2) affords transient species that hydrolyse to the cyclodextrin and the corresponding carboxylic acid, analogous reactions involving the amino substituents of the modified cyclodextrins give acetamides that are stable under the conditions used in the experiments. As an independent measurement of the involvement of the amino substituents in the reactions of the modified cyclodextrins with the esters (1) and (2), the extent of amide formation as a function of the mole ratio of cyclodextrin to ester (1) or (2) was examined. Authentic samples of the acetamides were obtained by treatment of the amino-substituted cyclodextrins with acetic anhydride.[13]

In the reactions of the *meta*-substituted ester (1) with the amino-substituted cyclodextrins, a 1:1 mole ratio of the ester (1) to cyclodextrin resulted in the production of 4% of the corresponding acetamido-substituted α-cyclodextrin and 10% of the corresponding β-cyclodextrin derivative. By contrast, a 1:1 mole ratio of the ester (2) to amino-substituted cyclodextrin gave the corresponding acetamido-substituted α- and β-cyclodextrin derivatives in yields of 85 and 71%, respectively. These results confirm that the reactions of the ester (1) complexed by the amino-substituted cyclodextrins occur with little direct involvement of the amino substituents, while those substituents are intimately involved in the reactions of the complexed ester (2). The amino substituent of the modified β-cyclodextrin increases k_c of the ester (2) by a factor of 3 beyond that for reaction of the ester (2) complexed by unmodified β-cyclodextrin (Table 1). If that rate acceleration was due solely to reaction of the amino substituent of the modified cyclodextrin, then a 1:1 mole ratio of ester (2) to amino-substituted β-cyclodextrin would be

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predicted to result in a 75% conversion into the corresponding acetamide. This prediction is in close agreement with the experimental observation.

The results of the analysis of the formation of acetamides in the reactions of the esters (1) and (2) with the amino-substituted cyclodextrins reaffirm the conclusions derived from the studies of the kinetics of the reactions of the esters (1) and (2) (Table 1). The reactions of the ester (1) in the presence of cyclodextrins involve complexes where the oxycarbonyl group of the ester (1) is in the vicinity of the wider end of the cyclodextrin annulus, where it reacts with a deprotonated secondary hydroxy group of the cyclodextrin. In analogous orientations of the ester (1) complexed with the amino-substituted cyclodextrins, the amino substituent is too distant from the oxycarbonyl group of the ester (1) for them to react. By contrast, one mode of complexation of the ester (2) by cyclodextrins has the oxycarbonyl group of the ester (2) in the vicinity of the narrow end of the cyclodextrin annulus (Fig. 1); with complexes of this type involving the amino-substituted cyclodextrins, the amino substituent is located close to the oxycarbonyl group of the ester (2), and reaction occurs.

From the results of the studies of reactions of the ester (2) described above, it is not possible to determine the relative contribution of structures such as that shown in Fig. 1 to the overall complexation of the ester (2) with either α- or β-cyclodextrin or the corresponding amines. Indeed, the present study highlights the need for caution in relating kinetic data for reactions of complexed species to the orientation of complexation, as complexes of the type shown in Fig. 1 have not been detected in the past, merely because they are unreactive. Nevertheless, the contribution is likely to be substantial, as it is so obviously manifest from the kinetic effects and product studies. In any event the results presented in this report clearly establish the existence of cyclodextrin–phenyl ester complexes with the ester oxycarbonyl groups near the narrow end of the cyclodextrin annuli, in the vicinity of the primary hydroxy groups of the cyclodextrins.

Experimental

General experimental details have been reported previously.[11,14] The esters (1) and (2) were prepared by treatment of the corresponding nitrophenols with acetyl chloride, and they had physical and spectral properties consistent with those reported previously.[15] 6^A-Amino-6^A-deoxy-α- and -β-cyclodextrin were prepared according to the reported procedure,[11] from α- and β-cyclodextrin that had been purchased from Nihon Shokuhin Kako Co. Before use each cyclodextrin was dried to constant weight under reduced pressure over phosphorus pentoxide.

Kinetics of Reactions of m-*Nitrophenyl Acetate (1) and* p-*Nitrophenyl Acetate (2)*

Stock methanolic solutions of the esters (1) and (2) (4×10^{-3} mol dm^{-3}) were diluted (1:100) with 0·010 mol dm^{-3} sodium borate buffer at pH 10·0, and placed in the cell holder of a Pye Unicam SP8-100 spectrophotometer, thermostatted at 298·2 K. The reactions were followed by monitoring the spectrophotometric change, at 272 nm, accompanying the release of the corresponding nitrophenols.

The pH of the solutions did not change during the reactions, which followed pseudo-first-order kinetics. The infinite absorbance values were taken after at least 8 half-lives, and reactions

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were monitored through to at least 90% completion. The rate constants for the reactions (k_{un}) were calculated from the plot of the logarithm of the change in ultraviolet absorbance as a function of time. Duplicate experiments gave k_{un} values which varied by less than 5%.

The reactions in the presence of α- and β-cyclodextrin and 6^A-amino-6^A-deoxy-α- and -β-cyclodextrin were studied in a similar fashion, by diluting the stock methanolic solutions of the esters (1) and (2) with buffer containing the cyclodextrin at concentrations spanning 0·002–0·010 mol dm^{-3}. The reciprocal of the difference between the first-order rate constants for these reactions (k_{obs}), determined for at least five cyclodextrin concentrations, and k_{un} was plotted against the reciprocal of the cyclodextrin concentration. The rate constants for reaction of the esters (1) and (2) complexed by the cyclodextrins (k_c) were determined from the reciprocal of the Y intercept of that plot, while the dissociation constants of the complexes of the esters (1) and (2) with the cyclodextrins (K_{diss}) were determined from the slope of the plot multiplied by k_c. Quoted errors are the calculated standard deviations.

The effect of adamantanecarboxylic acid and undecanoic acid on the reactions was studied by adding these carboxylic acids to the borate buffer, with and without the cyclodextrin, before adding the stock methanolic solutions of the esters (1) and (2).

Products of Reactions of m-*Nitrophenyl Acetate (1) and* p-*Nitrophenyl Acetate (2) with* 6^A-*Amino-*6^A-*deoxy-α- and -β-cyclodextrin*

Mixtures of either 6^A-amino-6^A-deoxy-α- or -β-cyclodextrin (5×10^{-5} mol dm^{-3}) and either of the esters (1) or (2) (5×10^{-5} mol dm^{-3}), in 0·010 mol dm^{-3} sodium borate buffer at pH 10·0, were stirred at 298·2 K for 16 h. H.p.l.c. of the product mixtures, on a Waters carbohydrate analysis column (3·9 by 300 mm), with 65% acetonitrile/water as elutent, and comparison with authentic samples of N-acetyl-6^A-amino-6^A-deoxy-α- and -β-cyclodextrin, which were prepared by treatment of the corresponding amines with acetic anhydride,[13] were used to determine the extent of conversion of the amino-substituted cyclodextrins into the corresponding acetamides. The acetamido-substituted α- and β-cyclodextrin derivatives had refractive index detector response ratios of 0·90 and 0·86, compared to those of the corresponding amines. Each acetamide had a retention time of 0·70 relative to that of the corresponding amine.

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Complexation of Fluorinated Amino Acid Derivatives by β- and γ-Cyclodextrin in Aqueous Solution. A ^{19}F Nuclear Magnetic Resonance Study

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Abstract

A ^{19}F n.m.r. study shows that the β-cyclodextrin complexes of deprotonated α-(*p*-fluorophenyl)glycine, *N*-acetyl-α-(*p*-fluorophenyl)glycine, deprotonated *N*-acetyl-α-(*p*-fluorophenyl)glycine, and *N*-(*p*-fluorobenzoyl)valine are characterized by stability constants K_R/dm^3 mol^{-1} and K_S/dm^3 mol^{-1} = 13±2 and 21±3, 34±1 and 35±2, 12±1 and 12±1, and 84±2 and 93±2, respectively, where the first and second of each pair of values refers to the complex formed by the *R* and *S* enantiomers of the fluorinated amino acid derivatives, respectively, in 10% aqueous D_2O solution at 295·5 K and I = 0·10 mol dm^{-3}. A comparison of these data and the associated ^{19}F chemical shift data with those for the analogous α- and γ-cyclodextrin complexes provides an insight into the factors affecting the stabilities and structures of these complexes.

Introduction

Naturally occurring α-, β- and γ-cyclodextrin (αCD, βCD and γCD) are, respectively, the α-1,4-linked cyclic hexamer, heptamer and octamer of D-glucopyranose. They have annular structures whose narrow and wide ends are delineated by six, seven and eight C6 primary hydroxy groups and twelve, fourteen and sixteen C2 and C3 secondary hydroxy groups, respectively, as exemplified by βCD in Fig. 1.[1–4] The internal annular diameters of αCD, βCD and γCD are 470–520, 600–640 and 750–830 pm, respectively,[3] where the smaller values refer to rings of hydrogen atoms bonded to C5, and the larger values refer to rings of hydrogen atoms bonded to C3 as measured from Corey–Pauling–Koltun (CPK) molecular models.[5] The annular depth is 530–540 pm from the C3 to the C5 hydrogens, and 790–800 pm from the primary to the secondary hydroxy hydrogens.

The ability of cyclodextrins to form host–guest complexes through the inclusion of aromatic guests in their annuli is well established.[1–6] Such guests tend to align their hydrophobic aromatic regions in the vicinity of the hydrophobic interiors of the cyclodextrin annuli while their hydrophilic regions are aligned in the

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vicinity of the hydrophilic hydroxy groups. A combination of the variations in the intensity of the host–guest secondary bonding interactions coinciding with these alignments and the variation in annular size sometimes results in size-selective enantioselective guest complexation.[2,7–11]

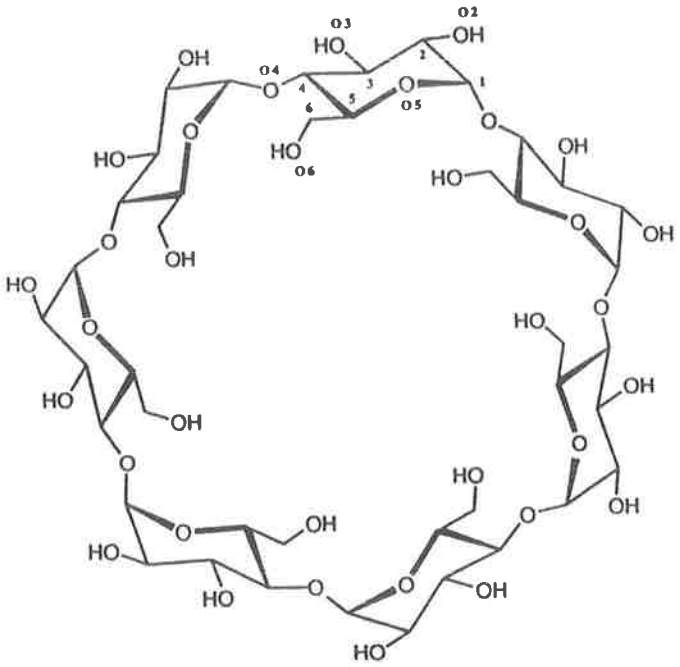

Fig. 1. β-Cyclodextrin.

In a recent ^{19}F n.m.r. study we found that the diastereomeric complexes formed by αCD with protonated and deprotonated α-(*p*-fluorophenyl)glycine [(1)+H and (1)−H, respectively], *N*-acetyl-α-(*p*-fluorophenyl)glycine (2) and *N*-(*p*-fluorobenzoyl)valine (3) and their deprotonated forms [(2)−H and (3)−H, respectively], whose structures are shown in Fig. 2, were characterized by different stabilities in some cases and different ^{19}F chemical shifts in all cases.[9] The studies now reported represent a systematic attempt to assess the effect of cyclodextrin annular size on complex stability and structure through a study of the same guests by βCD and γCD.

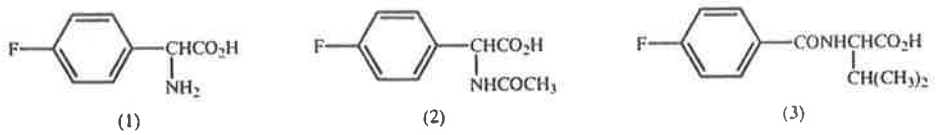

Fig. 2. Amino acid derivative structures.

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Experimental

βCD and γCD (Cyclolab) were dried to constant weight and stored over P_2O_5 in a vacuum desiccator. (*RS*)-*N*-(*p*-Fluorobenzoyl)valine and the analogous (*S*)-derivative were prepared by reaction of *p*-fluorobenzoyl chloride with the appropriate free amino acids.[12,13] (*RS*)-α-(*p*-Fluorophenyl)glycine was prepared by condensation of *p*-fluorobenzaldehyde with chloroform and ammonia,[14,15] and resolved by treatment of the corresponding *N*-acetyl derivative with hog renal acylase 1.[16] The *N*-acetyl derivatives of (*RS*)- and (*S*)-α-(*p*-fluorophenyl)glycine were prepared by reaction with acetic anhydride.[17] All other reagents were of analytical grade. Solutions for ^{19}F n.m.r. studies at pH 1·3, 6·9 and 10·8 were buffered with KCl/HCl, KH_2PO_4/Na_2HPO_4 and glycine/NaOH buffers prepared as in the literature.[18] An ionic strength of 0·10 mol dm^{-3} was maintained by the buffers. Deionized water was purified with a MilliQ-Reagent system to produce water with a resistance of >15 MΩ cm, and D_2O was added to give a 10% mixture in each solution studied by ^{19}F n.m.r. Solutions were made up by weight, and the molar concentrations of the solutes were calculated from the density of each solution, which was determined by standard procedures with pycnometers. The βCD and γCD concentrations were varied within the ranges 0–0·0163 and 0–0·129 dm^3 mol^{-1}, respectively. Because of its low solubility βCD (1·85 g/100 cm^3 in water at 298·2 K)[3] was studied over a smaller concentration range than the more soluble γCD (23·2 g/100 cm^3 in water at 298·2 K).[3] Fluorinated guest concentrations were held constant at $1{\cdot}1\times10^{-3}$ mol dm^{-3}.

^{1}H broad-band decoupled ^{19}F n.m.r. spectra of solutions of a guest and either βCD or γCD in 5-mm tubes were recorded on a Bruker CXP 300 spectrometer at 282·35 MHz locked on the deuterium frequency of D_2O, and an average of 2000 transients was accumulated in an 8192-point data base for each spectrum. Chemical shifts were measured from a 2% CF_3COONa/D_2O external reference solution. Solution temperature (295·5±0·3 K) was controlled by a Bruker B-VT1000 variable-temperature controller.

Results

The complexation of a guest enantiomer (E) by a cyclodextrin (CD) may be expressed as in equation *(1)*:

$$\mathrm{E} + \mathrm{CD} \overset{K_R \text{ or } K_S}{\rightleftharpoons} \mathrm{E.CD} \qquad (1)$$

When exchange of the enantiomer between the free (E) and complexed (E.CD) environments is in the fast exchange limit of the ^{19}F n.m.r. time scale, as in this study, a single environmentally averaged ^{19}F resonance is observed whose chemical shift is the weighted mean of the populations of the two environments. Thus, the environmentally averaged chemical shift of an *R* enantiomer (*R*E) is given by equation *(2)*

$$\delta_{\mathrm{obs}} = (\delta_{\mathrm{F}}[R\mathrm{E}] + \delta_R[R\mathrm{E.CD}])/([R\mathrm{E}] + [R\mathrm{E.CD}]) \qquad (2)$$

where δ_{obs} is the observed shift, δ_{F} is the shift of free *R*E and δ_R is the shift of *R*E.CD, and a similar equation holds for *S*E and δ_S. The concentrations in equation *(2)* are directly related to the stability constants K_R and K_S (where, for *R*E, $K_R = [R\mathrm{E.CD}][R\mathrm{E}]^{-1}[\mathrm{CD}]^{-1}$, and an equivalent expression holds for *S*E and K_S).

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Table 1. Stability constants and ^{19}F chemical shifts of αCD, βCD and γCD amino acid derivative diastereomeric complexes in 10% aqueous D_2O at 295·5 K and $I = 0·10$ mol dm^{-3} (buffer)

Cyclodextrin	Amino acid derivative Species	Charge	pH	Buffer components	K_R and K_S[A]/ dm^3 mol^{-1}	δ_R, δ_S and δ_F[A,B]	$\Delta\delta$
αCD[C]	(1)+H	1+	1·3	KCl/HCl	$K_R = 8·3\pm0·4$ $K_S = 8·7\pm0·4$	$\delta_R = -37·04\pm0·04$ $\delta_S = -37·10\pm0·04$ $\delta_F = -35·752\pm0·004$	$\delta_R-\delta_F = -1·29\pm0·04$ $\delta_S-\delta_F = -1·35\pm0·04$ $\delta_R-\delta_S = 0·06\pm0·08$
αCD[C]	(1)−H	1−	10·8	glycine/NaOH	$K_R = 21·8\pm0·5$ $K_S = 22·9\pm0·5$	$\delta_R = -41·21\pm0·01$ $\delta_S = -41·12\pm0·01$ $\delta_F = -40·123\pm0·004$	$\delta_R-\delta_F = -1·09\pm0·01$ $\delta_S-\delta_F = -1·00\pm0·01$ $\delta_R-\delta_S = -0·09\pm0·02$
βCD[D]	(1)−H	1−	10·8	glycine/NaOH	$K_R = 13\pm2$ $K_S = 21\pm3$	$\delta_R = -41·5\pm0·2$ $\delta_S = -41·0\pm0·1$ $\delta_F = -40·151\pm0·004$	$\delta_R-\delta_F = -1·3\pm0·2$ $\delta_S-\delta_F = -1·8\pm0·1$ $\delta_R-\delta_S = -0·5\pm0·3$
γCD[D]	(1)−H	1−	10·8	glycine/NaOH	$K_{RS} = 7·4\pm0·4$	$\delta_{RS} = -39·52\pm0·03$ $\delta_F = -40·154\pm0·004$	$\delta_{RS}-\delta_F = 0·63\pm0·03$
αCD[C]	(2)	0	1·3	KCl/HCl	$K_R = 14·6\pm0·1$ $K_S = 14·8\pm0·1$	$\delta_R = -39·235\pm0·007$ $\delta_S = -39·325\pm0·007$ $\delta_F = -37·779\pm0·004$	$\delta_R-\delta_F = -1·456\pm0·008$ $\delta_S-\delta_F = -1·546\pm0·008$ $\delta_R-\delta_S = 0·09\pm0·016$
βCD[D]	(2)	0	1·3	KCl/HCl	$K_R = 34\pm1$ $K_S = 35\pm2$	$\delta_R = -38·80\pm0·02$ $\delta_S = -38·83\pm0·04$ $\delta_F = -37·741\pm0·004$	$\delta_R-\delta_F = -1·06\pm0·02$ $\delta_S-\delta_F = -1·09\pm0·04$ $\delta_R-\delta_S = 0·03\pm0·06$
γCD[D]	(2)	0	1·3	KCl/HCl	$K_{RS} = 7·1\pm0·1$	$\delta_{RS} = -36·66\pm0·01$ $\delta_F = -37·764\pm0·004$	$\delta_{RS}-\delta_F = 1·10\pm0·01$
αCD[D]	(2)−H	1−	6·9	KH_2PO_4/Na_2HPO_4	$K_R = 13·0\pm0·3$ $K_S = 14·1\pm0·3$	$\delta_R = -40·99\pm0·02$ $\delta_S = -40·83\pm0·02$ $\delta_F = -39·355\pm0·004$	$\delta_R-\delta_F = -1·64\pm0·02$ $\delta_S-\delta_F = -1·48\pm0·02$ $\delta_R-\delta_S = -0·16\pm0·04$

Table 1 *(Continued)*

Cyclo-dextrin	Amino acid derivative Species	Charge	pH	Buffer components	K_R and K_S[A] / $dm^3\ mol^{-1}$	δ_R, δ_S and δ_F[A,B]	$\Delta\delta$
βCD[D]	(2)–H	1–	6·9	KH_2PO_4/Na_2HPO_4	$K_R = 12\pm1$ $K_S = 12\pm1$	$\delta_R = -40\cdot9\pm0\cdot1$ $\delta_S = -40\cdot7\pm0\cdot1$ $\delta_F = -39\cdot358\pm0\cdot004$	$\delta_R-\delta_F = -1\cdot5\pm0\cdot1$ $\delta_S-\delta_F = -1\cdot3\pm0\cdot1$ $\delta_R-\delta_S = -0\cdot2\pm0\cdot2$
αCD[C]	(3)	0	1·3	KCl/HCl	$K_{R,S} = 8\cdot5\pm0\cdot3$	$\delta_{R,S} = -32\cdot99\pm0\cdot02$ $\delta_F = -32\cdot308\pm0\cdot004$	$\delta_{R,S}-\delta_F = -0\cdot68\pm0\cdot02$
βCD[D]	(3)	0	1·3	KCl/HCl	$K_R = 84\pm2$ $K_S = 93\pm2$	$\delta_R = -31\cdot56\pm0\cdot01$ $\delta_S = -31\cdot55\pm0\cdot01$ $\delta_F = -32\cdot345\pm0\cdot004$	$\delta_R-\delta_F = 0\cdot79\pm0\cdot01$ $\delta_S-\delta_F = 0\cdot80\pm0\cdot01$ $\delta_R-\delta_S = -0\cdot01\pm0\cdot02$
γCD[D]	(3)	0	1·3	KCl/HCl	$K_R = 13\cdot1\pm0\cdot1$ $K_S = 14\cdot0\pm0\cdot1$	$\delta_R = -31\cdot458\pm0\cdot005$ $\delta_S = -31\cdot454\pm0\cdot004$ $\delta_F = -32\cdot299\pm0\cdot004$	$\delta_R-\delta_F = 0\cdot841\pm0\cdot006$ $\delta_S-\delta_F = 0\cdot845\pm0\cdot006$ $\delta_R-\delta_S = -0\cdot004\pm0\cdot012$
αCD[C]	(3) -H	1–	6·9	KH_2PO_4/Na_2HPO_4	$K_R = 11\cdot9\pm0\cdot3$ $K_S = 10\cdot0\pm0\cdot3$	$\delta_R = -33\cdot69\pm0\cdot01$ $\delta_S = -33\cdot53\pm0\cdot01$ $\delta_F = -32\cdot823\pm0\cdot004$	$\delta_R-\delta_F = -0\cdot87\pm0\cdot01$ $\delta_S-\delta_F = -0\cdot71\pm0\cdot01$ $\delta_R-\delta_S = -0\cdot16\pm0\cdot02$
γCD[D]	(3)–H	1–	6·9	KH_2PO_4/Na_2HPO_4	$K_{RS} = 5\cdot39\pm0\cdot09$	$\delta_{RS} = -31\cdot92\pm0\cdot01$ $\delta_F = -32\cdot830\pm0\cdot004$	$\delta_{RS}-\delta_F = 0\cdot91\pm0\cdot01$

[A] Errors represent one standard deviation derived from a least-squares fit of the data to equation *(2)*, except for δ_F where the error represents the digital resolution of the spectrum. No corrections for medium effects were incorporated into the stability constant calculations.
[B] Chemical shifts referenced to external 2% CF_3COONa in D_2O which was assigned a shift of zero. Thus the more negative the value the further is δ upfield from the reference.
[C] A small density correction, inadvertently omitted in ref. 9, has been made to these data (Brown, S. E., Easton, C. J., and Lincoln, S. F., *J. Chem. Res.*, in press); this slightly alters the values reported in ref. 9, but does not alter the data interpretation therein.
[D] This work.

Complexation between either βCD or γCD and each of the conjugate acid and base forms of the guests [the pK_a values for (1)+H, (1), (2) and (3) are 2·3, 8·8, 2·8 and 3·4, respectively, under the conditions of this study[9]] should result in seven βCD and seven γCD 1:1 complexes. In practice derivative (1) is insufficiently soluble for quantitative ^{19}F n.m.r. studies, and sufficiently large δ_{obs} from which stability constants could be calculated were observed only for (1)–H, (2), (2)–H and (3) in the presence of βCD and for (1)–H, (2), (3) and (3)–H in the presence of γCD. The variation of δ_{obs} for each of these systems fitted equation *(2)* according to a non-linear regression analysis, and the derived K_R, K_S, δ_R and δ_S appear in Table 1. Separate ^{19}F resonances were observed for the *R*- and *S*-(3)–H enantiomers in the presence of βCD indicating the formation of diastereomeric complexes, although δ_{obs} was too small for the determination of reliable stability constants.

It is seen from Figs 3 and 4, respectively, that the ^{19}F resonances of *R*- and *S*-(3) move downfield with increasing [βCD] and [γCD]. Similar monophasic δ_{obs} variations, consistent with the predominant formation of 1:1 complexes, were also observed for the other systems for which stability constants are given in Table 1. While downfield shifts were observed for βCD.(3) and all four γCD systems, upfield shifts were observed for (1)–H, (2) and (2)–H in the presence of βCD. Identification of the enantiomer ^{19}F resonances was made by the addition of the pure *S*-guest to a solution of the racemic guest in the presence of either βCD or γCD and observing which of the two ^{19}F resonances increased in intensity. Separate resonances were not observed for *R* and *S* enantiomers of (1)–H, (2) and (3)–H in the presence of γCD, and as a result the stabilities of the diastereomeric complexes are indistinguishable and are denoted as K_{RS}.

The observation of a change in the chemical shift of the guest molecule is not necessarily indicative of complexation as 0·02 mol dm^{-3} non-cyclic maltotriose induces upfield ^{19}F chemical shifts in the range 0·04–0·08 ppm for the guests studied; this may result from either a loose complexation or a general medium effect.[19] If this represents a general medium effect and it is incorporated into the stability constant calculations, the values listed for αCD in Table 1 are decreased by up to 40%; for βCD the values for the (1)–H, (2) and (2)–H complexes decrease by 30%, and that of the (3) complex increases by 30%. When a similar medium effect is included in the γCD calculations, a 2–4-fold increase in the stability constants listed in Table 1 results. While this causes a degree of uncertainty in making quantitative comparisons between the complex stability constants characterizing the α-, β- and δ-cyclodextrin complexes of the same guest, the qualitative comparisons of stabilities and the interpretation of the δ_{obs} variations which follow are little affected.

Discussion

The observation that αCD and γCD induce upfield and downfield shifts of the ^{19}F resonances of the guests, respectively, whereas βCD induces upfield shifts for (1)–H, (2) and (2)–H, but a downfield shift for (3) (Table 1), infers that the structures of the complexes formed differ significantly. The change in the ^{19}F chemical shift is largely a result of a change in the immediate environment of the

[19] Brown, S. E., Easton, C. J., and Lincoln, S. F., *J. Chem. Res.*, in press.

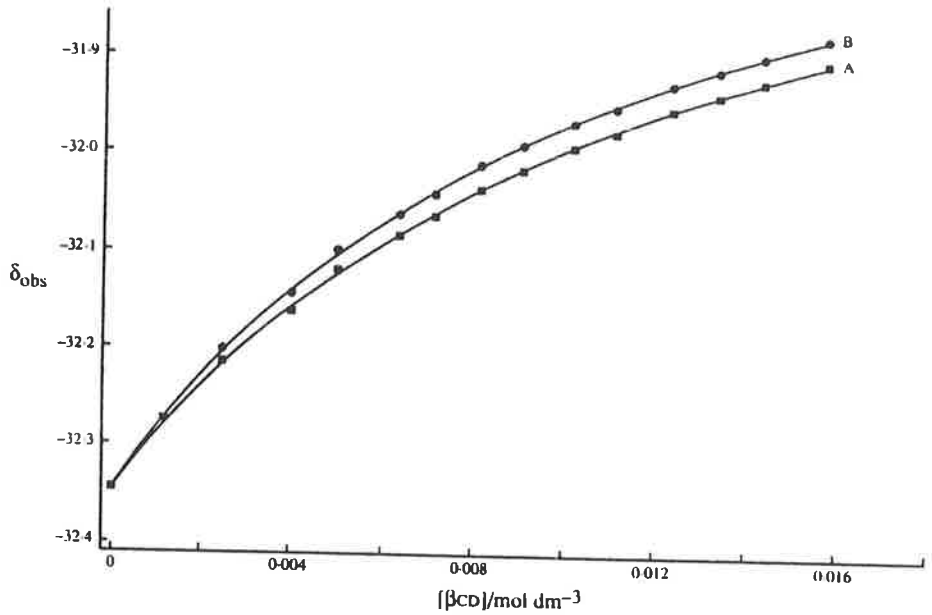

Fig. 3. The variation of ^{19}F n.m.r. δ_{obs} for $1 \cdot 10 \times 10^{-3}$ mol dm^{-3} racemic (3) at pH 1·3 with [βCD] at 295·5 K and $I = 0 \cdot 10$ mol dm^{-3} (KCl/HCl). The solid curves A and B represent the best fit between δ_{obs} and equation *(2)* for *R*-(3) and an analogous equation for *S*-(3), respectively.

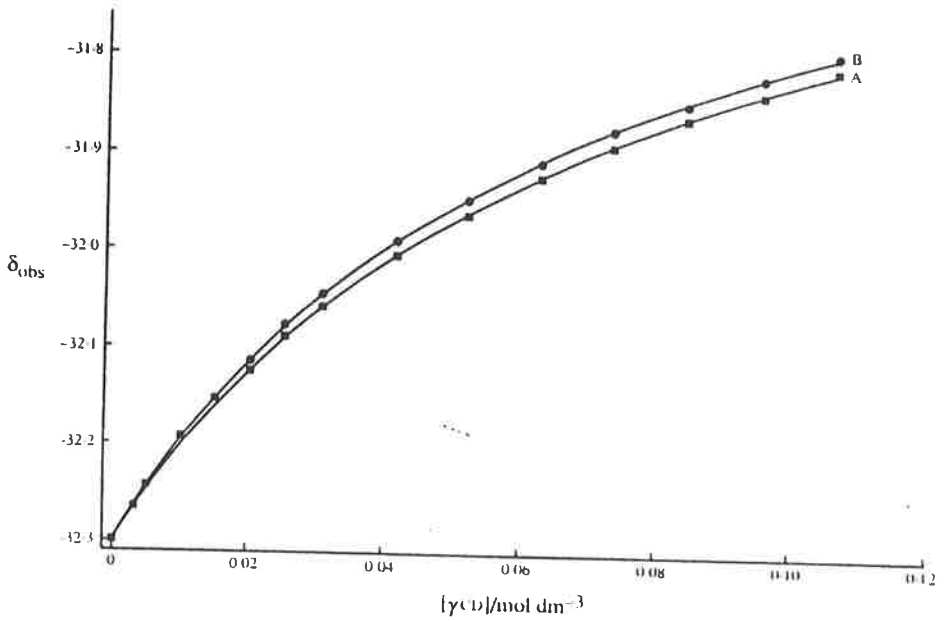

Fig. 4. The variation of ^{19}F n.m.r. δ_{obs} for $1 \cdot 10 \times 10^{-3}$ mol dm^{-3} racemic (3) at pH 1·3 with [γCD] at 295·5 K and $I = 0 \cdot 10$ mol dm^{-3} (KCl/HCl). The solid curves A and B represent the best fit between δ_{obs} and equation *(2)* for *R*-(3) and an analogous equation for *S*-(3), respectively.

p-fluoro substituent with a small influence arising from the overall environmental change experienced by the guest. Upon complexation, the *p*-fluoro substituent may experience either of two environments in the cyclodextrin annulus. The first is the hydrophobic environment in the centre of the annulus which a number of studies indicate induces an upfield shift by comparison with that observed in an aqueous enviroment.[8,9,20] The second is the hydrophilic environment in the vicinity of the rings of hydroxy groups at either end of the cyclodextrin annulus whose restricted motion may lead to a greater degree of hydrogen bonding than that occurring in a solely aqueous environment and thereby induce a downfield shift.

CPK models show that, when the *p*-fluorophenyl moieties of the complexed guests are positioned inside the αCD annulus, the *p*-fluoro substituent is restricted to the hydrophobic region consistent with the upfield shift induced in the ^{19}F resonances of all of the guests listed in Table 1.[9] [The substantially larger upfield shifts induced through complexation by hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD), which has a more extensive hydrophobic annulus, supports this identification of the cause of an upfield shift of the ^{19}F resonance as an increase in the hydrophobicity of the environment.[19]]

The upfield shifts of the ^{19}F resonances of the (1)−H, (2) and (2)−H complexes of βCD are also consistent with this interpretation, but the downfield shift of (3) indicates that the *p*-fluoro substituent is probably hydrogen-bonded to a βCD hydroxy group. This may be rationalized in terms of the larger internal diameter of the βCD annulus permitting deeper penetration of the guest into the annulus than is the case with αCD. It is expected that the position of the guest relative to the βCD annulus is one which maximizes the complex stabilizing effects of the interaction of the *p*-fluorophenyl moiety with the hydrophobic interior of the annulus and of hydrogen bonding between the βCD hydroxy groups and the amino acid substituent. Maximizing the latter interaction for (3) appears to place its *p*-fluoro substituent in the vicinity of βCD primary hydroxy groups; this induces a downfield ^{19}F shift in contrast to the substantially shorter (1)−H, (2) and (2)−H whose *p*-fluoro substituents reside in the hydrophobic region of the βCD annulus. [The argument that the ^{19}F shift of the (3).βCD complex may be rationalized in these terms is given some support from the observation that it is the most stable of the complexes in Table 1.]

Similar hydrophobic and hydrophilic interactions are important in the γCD complexes, but the downfield ^{19}F shifts characterizing the γCD complexes suggest that the larger size of the γCD annulus may allow another ^{19}F shift-determining factor to become important. The γCD annulus is sufficiently large to accommodate water as well as the guest, with the result that the *p*-fluoro substituent may hydrogen bond with water even when positioned in the centre of the annulus. Because such water in the hydrophobic region of the annulus can only hydrogen bond to the guest *p*-fluoro substituent, it is probably more persistent than that in aqueous solution and thereby generates a downfield ^{19}F shift.

The variation of complex stability in the sequene αCD < βCD > γCD seen in Table 1 (this persists after the assumption of medium effects based on the shifts induced by maltotriose as discussed above) when the neutral guest is either (2) or

[20] Hansen, P. E., Dettman, H. D., and Sykes, B. D., *J. Magn. Reson.* 1985, **62**, 487.

(3) is consistent with the βCD annulus being closest to optimum size to maximize the combined stabilizing effects of hydrophobic and hydrophilic interactions in the complexation of these guests. This, together with the observation that the stabilities of the (1)–H, (2), (2)–H and (3) complexes of αCD vary by a factor of <3, whereas those of the analogous βCD complexes vary by a factor of >7, indicates that the combination of the differing depths of guest penetration into the annulus of the two cyclodextrins and the consequently differing degrees of interaction of the guest amino acid function with the CD hydroxy groups and extent of hydration of the guest substantially determines the variation of complex stability. The complexes of the completely hydrophobic TMαCD[19] are 2–30-fold more stable than their analogues in Table 1; this illustrates the considerable importance of hydrophobic interactions in stabilizing these complexes.

While most of the systems studied show separate ^{19}F resonances for the *S* and *R* enantiomers consistent with these guests experiencing different magnetic environments in the diastereomeric complexes, thermodynamic enantioselectivity is small. Thus, αCD selectively complexes *S*-(2)–H and *R*-(3)–H, βCD shows enantioselectivity for *S*-(1)–H and *S*-(3), and γCD is enantioselective for *S*-(3). By comparison, enantioselectivities of 5 and 10 arise in the acylation and deacylation of (*R*)-6^{A}-*O*-{2-[4-(2-methylpropyl)phenyl]propanoyl}-β-cyclodextrin, respectively, over those of its *S* diastereomer,[21,22] and (*S*)-tryptophan anion is complexed 10-fold preferentially by 6^{A}-(3-aminopropylamino)-6^{A}-deoxy-β-cyclodextrinnickel(II) by comparison to the complexation of (*R*)-tryptophan anion.[23,24] These observations indicate that under favourable conditions a higher enantioselectivity is engendered by the stronger orientating forces present in systems involving primary bonding than is the case in the complexes considered in this study where only relatively weak secondary bonding occurs.

Acknowledgments

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J. CHEM. SOC. FARADAY TRANS., 1995, 91(6), 1013–1018

Complexation of Phenylalanine and Histidine by β-Cyclodextrin,† 6^A-(3-Aminopropylamino)-6^A-deoxy-β-cyclodextrin and its Metallocyclodextrins in Aqueous Solution

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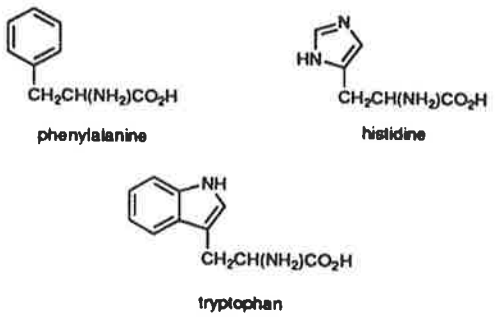
A pH titration study shows that for the complexation of phenylalanine anion [(*R*)- and (*S*)-Phe$^-$] by β-cyclodextrin (βCD), $\log(K_{1R}/dm^3\ mol^{-1}) = 2.91 \pm 0.08$ and $\log(K_{1S}/dm^3\ mol^{-1}) = 2.83 \pm 0.06$, and that by 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin (βCDpn) is characterized by $\log(K_{2R}/dm^3\ mol^{-1}) = 2.51 \pm 0.07$ and $\log(K_{2S}/dm^3\ mol^{-1}) = 2.74 \pm 0.05$. No complexation of histidine (HisH) by βCD was detected, but for the complexation of histidine anion (His$^-$) by βCDpnH$^+$ $\log(K_{3R}/dm^3\ mol^{-1}) = 2.50 \pm 0.02$ and $\log(K_{3S}/dm^3\ mol^{-1}) = 2.37 \pm 0.09$; and for the complexation of HisH by βCDpnH$^+$ $\log(K_{4R}/dm^3\ mol^{-1}) = 2.31 \pm 0.05$ and $\log(K_{4S}/dm^3\ mol^{-1}) = 2.18 \pm 0.05$. For the complexation of Phe$^-$ by the metallocyclodextrin, [M(βCDpn)]$^{2+}$, $\log(K_{11R}/dm^3\ mol^{-1})$ and $\log(K_{11S}/dm^3\ mol^{-1}) = 3.6 \pm 0.2$ and 3.69 ± 0.06, <3.6 and 4.4 ± 0.1, 7.2 ± 0.1 and 6.9 ± 0.1, 4.7 ± 0.1 and 4.7 ± 0.2, when $M^{2+} = Co^{2+}$, Ni^{2+}, Cu^{2+} and Zn^{2+}, respectively. For the complexation of His$^-$ by [Cu(βCDpn)]$^{2+}$, $\log(K_{11R}/dm^3\ mol^{-1}) = 8.38 \pm 0.04$ and $\log(K_{11S}/dm^3\ mol^{-1}) = 8.42 \pm 0.02$, and for the complexation of a second His$^-$ $\log(K_{12R}/dm^3\ mol^{-1}) = 7.75 \pm 0.05$ and $\log(K_{12S}/dm^3\ mol^{-1}) = 7.6 \pm 0.1$. The roles of the cyclodextrins, divalent metal ions and amino acids affecting complexation are discussed.

Naturally occurring and modified cyclomaltaoses, or cyclodextrins, form host–guest complexes whose structures and thermodynamic stabilities vary with the nature of the cyclodextrin and the guest.[1–5] The most stable complexes are usually formed with guests possessing some aromatic character. When the guest is enantiomeric, two diastereomeric complexes form as a consequence of the single chirality of cyclodextrins and sometimes such complexation is enantioselective as a result of selective interaction of the cyclodextrin with one of the guest enantiomers,[6–11] and a similar phenomenon has been observed with metallocyclodextrins.[12–15] As part of our studies in this area, we have shown that β-cyclodextrin (βCD) and 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin (βCDpn) complex the tryptophan anion (Trp$^-$), and that βCDpn forms metallocyclodextrins, [M(βCDpn)]$^{2+}$, which are enantioselective for (*S*)-Trp$^-$ over (*R*)-Trp$^-$ in forming [M(βCDpn)(*S*)-Trp]$^+$ and [M(βCDpn)(*R*)-Trp]$^+$ when $M^{2+} = Co^{2+}$, Ni^{2+} and Cu^{2+}, but which exhibit no enantioselectivity when $M^{2+} = Zn^{2+}$.[14,15] Several factors affect the stability and enantioselectivity of these cyclodextrin–amino acid complexes and warrant further investigation. Accordingly, we now report a study in which the complexation of phenylalanine and histidine by βCD, βCDpn and [M(βCDpn)]$^{2+}$ is explored. These guests promise significant comparisons with the complexation of tryptophan because they are smaller, and phenylalanine retains the phenyl ring of tryptophan, whereas histidine possesses a five-membered polar aromatic ring which resembles that of tryptophan.

Experimental

Preparation of Materials

β-Cyclodextrin (Sigma), 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin prepared as in the literature,[14] (*R*)-, (*S*)- and



(*RS*)-phenylalanine† (Sigma), and (*R*)-, (*S*)- and (*RS*)-histidine† (Sigma) were dried to constant weight and stored in the dark over P_2O_5 in a vacuum desiccator prior to use. The enantiomeric purities of (*R*)- and (*S*)-PheH were determined to be ≥99% after HPLC analysis (Pirkle covalent L-phenylglycine column) of their respective *N*-benzoyl methyl esters, and those of (*R*)- and (*S*)-HisH were determined to be ≥99% from optical rotation determinations. Metal perchlorates (Fluka) were twice recrystallized from water, and were dried and stored over P_2O_5 under vacuum. (Caution: Anhydrous perchlorate salts are potentially powerful oxidants and should be handled with care.) Deionized water purified with a MilliQ-Reagent system to produce water with a resistivity of >15 MΩ cm, which was then boiled to remove CO_2, was used in the preparation of all solutions.

Equilibrium Studies

Titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer, and an Orion 8172 Ross Sureflow combination pH electrode which was

† IUPAC recommended name cyclomaltoheptaose.

† Monoprotonated phenylalanine, phenylalanine zwitterion and phenylalanine anion are denoted as $PheH_2^+$, PheH and Phe$^-$, respectively, prefixed by (*R*)- or (*S*)- as appropriate. Diprotonated histidine, monoprotonated histidine, histidine zwitterion and histidine anion are denoted as $HisH_3^{2+}$, $HisH_2^+$, HisH and His$^-$, respectively, prefixed by (*R*)- or (*S*)- as appropriate.

filled with 0.10 mol dm^{-3} $NaClO_4$. During all titrations a stream of fine nitrogen bubbles (previously passed through aqueous 0.10 mol dm^{-3} $NaClO_4$) was passed through the titration solution which was magnetically stirred and maintained at 298.2 ± 0.1 K in a water-jacketted 20 cm^3 titration vessel which was closed to the atmosphere with the exception of a small exit for nitrogen.

The 0.1 mol dm^{-3} $Ni(ClO_4)_2$, $Cu(ClO_4)_2$ and $Zn(ClO_4)_2$ stock solutions were standardized by EDTA (ethylenediaminetetraacetic acid) titration in the presence of Murexide indicator in the first two cases and Eriochrome Black T in the case of $Zn(ClO_4)_2$.[16] Ion exchange of Co^{2+} on an Amberlite HRC-120 cation-exchange column in the acid form followed by back titration of the liberated acid was used as the standardization method for the 0.100 mol dm^{-3} $Co(ClO_4)_2$ stock solution.

In all titrations, standardized 0.100 mol dm^{-3} NaOH was titrated against the species of interest in solutions of 0.010 mol dm^{-3} in $HClO_4$ and 0.090 mol dm^{-3} in $NaClO_4$. Thus the pK_a values of $PheH_2^+$ and $HisH_3^{2+}$ were determined from titrations of 10.00 cm^3 aliquots of their 0.001 and 0.002 mol dm^{-3} solutions, respectively. The stability constants for the formation of the βCD·(*R*)-Phe^- and βCD·(*S*)-Phe^- complexes, and the βCDpn·(*R*)-Phe^- and βCDpn·(*S*)-Phe^- complexes, were determined by titration of 5.00 cm^3 each of 0.001 mol dm^{-3} solutions of either (*R*)-$PheH_2^+$ or (*S*)-$PheH_2^+$ and βCD or $\beta CDpnH_2^{2+}$. Stability constants for the formation of the βCDpn complexes of histidine were similarly determined from 0.002 mol dm^{-3} $HisH_3^{2+}$ and $\beta CDpnH_2^{2+}$ solutions. The stability constants for the formation of the metal amino acid complexes were determined by titration of 10.00 cm^3 aliquots of 0.001 mol dm^{-3} solutions of $PheH_2^+$, with either 0.095 cm^3 or 0.045 cm^3 of 0.1 mol dm^{-3} $M(ClO_4)_2$, and $HisH_3^{2+}$ with 0.098 cm^3 of 0.1 mol dm^{-3} $Cu(ClO_4)_2$ solution added. The stability constants for the formation of $[M(\beta CDpn)(R)\text{-Phe}]^+$ and $[M(\beta CDpn)(S)\text{-Phe}]^+$ and related complexes were determined by titration of 5.00 mol dm^{-3} each of 0.001 mol dm^{-3} solutions of either (*R*)-$PheH_2^+$ or (*S*)-$PheH_2^+$ and $\beta CDpnH_2^{2+}$ with 0.045 cm^3 of $M(ClO_4)_2$ solution added. Stability constants for the formation of the analogous complexes of histidine were similarly determined from 0.002 mol dm^{-3} $HisH_3^{2+}$ and $\beta CDpnH_2^{2+}$ solutions with 0.098 cm^3 of $Cu(ClO_4)_2$ solution added. E_0 and pK_w values were determined by titration of 0.010 mol dm^{-3} $HClO_4$ (0.090 mol dm^{-3} in $NaClO_4$) against 0.100 mol dm^{-3} NaOH. Derivations of the stability constants were carried out using the program SUPERQUAD.[17] At least three runs were performed for each system, and at least two of these runs were averaged; the criterion for selection for this averaging being that X^2 for each run was < 12.6 at the 95% confidence level.[15]

Results

In the 2.0–11.5 pH range, several complexes formed in the aqueous solutions of βCD, βCDpn, M^{2+}, phenylalanine and histidine, and their stabilities were calculated from the differences between the pH profiles arising from titration against NaOH of solutions containing different combinations of the complexing species using the program SUPERQUAD.[17] The sequence of these titrations was: (i) pK_a determinations of the amino acids followed by determination of the stability constants of complexes in solutions of (ii) either βCD or $\beta CDpnH_2^{2+}$ and either (*R*)- or (*S*)-amino acid, (iii) M^{2+} and the amino acid and (iv) M^{2+}, $\beta CDpnH_2^{2+}$ and either (*R*)- or (*S*)-amino acid. The pK_as determined in (i) together with the pK_as of $\beta CDpnH_2^{2+}$ and the stability constants for $[M(\beta CDpn)]^{2+}$ determined under the same conditions and reported in our earlier studies[14,15] were used as constants in the determination of stability constants in (ii)–(iv). The stability constants determined in (ii) and (iii) were employed as constants in the determination of stability constants in (iv). The titration data were fitted to equilibria containing the minimum number of species required for a good fit, and any newly determined species found to be <5% of the total cyclodextrin or amino acid concentrations were considered to be insignificant. Two such pH titration profiles are shown in Fig. 1. A plot of the major Cu^{2+} species present in the Cu^{2+}–βCDpn–(*S*)-histidine system is shown in Fig. 2. The effect of enantioselectivity on Cu^{2+} species concentration in the Cu^{2+}–βCDpn–(*R*)- or (*S*)-phenylalanine system is shown in Fig. 3. The stability constants of the major M^{2+} complexes

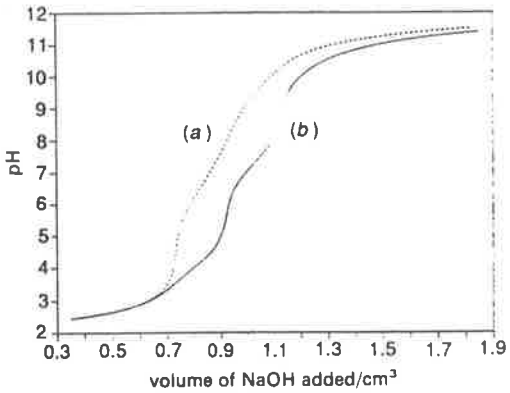


Fig. 1 Titration profiles for (*a*) $\beta CDpnH_2^{2+}$ (1.00×10^{-3} mol dm^{-3}) and (*S*)-$HisH_3^{2+}$ (1.00×10^{-3} mol dm^{-3}), and (*b*) $\beta CDpnH_2^{2+}$ (1.00×10^{-3} mol dm^{-3}), (*S*)-$HisH_3^{2+}$ (1.00×10^{-3} mol dm^{-3}) and $Cu(ClO_4)_2$ (9.98×10^{-4} mol dm^{-3}), each in aqueous 0.010 mol dm^{-3} $HClO_4$ and 0.090 mol dm^{-3} $NaClO_4$ titrated against 0.101 mol dm^{-3} NaOH at 298.2 K

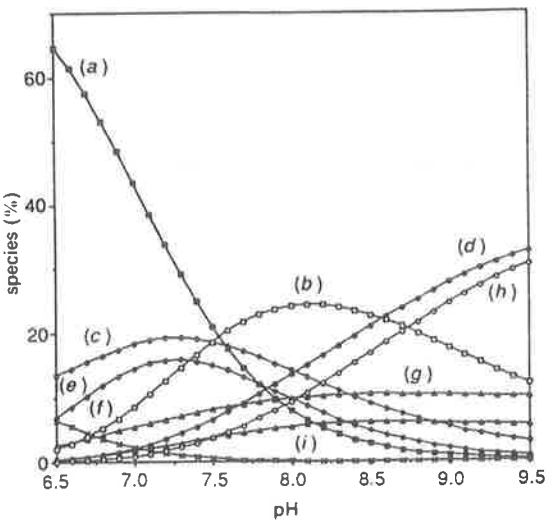


Fig. 2 Percentage of Cu^{2+} species in a solution containing 9.98×10^{-4}, 1.00×10^{-3} and 1.00×10^{-3} mol dm^{-3} total Cu^{2+}, βCDpn and (*S*)-histidine, respectively, plotted relative to $[\beta CDpn]_{total} = [(S)\text{-histidine}]_{total} = 100\%$. (*a*) $[Cu\{(S)\text{-His}\}]^+$, (*b*) $[Cu(\beta CDpn)(S)\text{-His}]^+$, (*c*) $[Cu\{(S)\text{-His}\}_2]$, (*d*) $[Cu(\beta CDpn)OH]^+$, (*e*) $[Cu(\beta CDpn)]^{2+}$, (*f*) Cu^{2+}, (*g*) $[Cu\{(S)\text{-His}\}OH]$, (*h*) $[Cu(\beta CDpn)\{(S)\text{-His}\}_2]$, (*i*) $[Cu\{(S)\text{-His}\}OH]_2$.

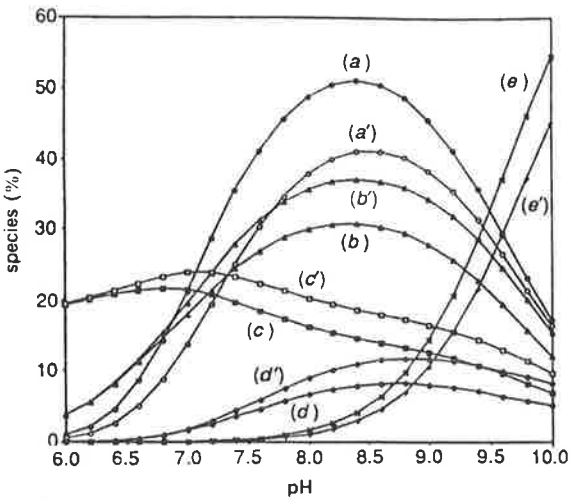


Fig. 3 Percentage of selected species in a solution of 0.000 95, 0.001 and 0.001 mol dm^{-3} total Cu^{2+}, βCDpn and either (*R*)- or (*S*)-PheH (latter indicated by prime on curve labels) concentrations, respectively, plotted relative to $[\beta CDpn]_{total}$ = either $[(R)\text{-PheH}]_{total}$ or $[(S)\text{-PheH}]_{total}$ = 100%. (*a*) $[Cu(\beta CDpn)(R)\text{-Phe}]^+$, (*a'*) $[Cu(\beta CDpn)(S)\text{-Phe}]^+$, (*b*, *b'*) $\beta CDpnH^+$, (*c*) $[Cu\{(R)\text{-Phe}\}_2]$, (*c'*) $[Cu\{(S)\text{-Phe}\}_2]$, (*d*, *d'*) $[Cu(\beta CDpn)OH]^+$, (*e*) $[Cu(\beta CDpn)\{(R)\text{-Phe}\}OH]$ and (*e'*) $[Cu(\beta CDpn)\{(S)\text{-Phe}\}OH]$.

appear in Table 1, and those for other species appear in the text.

For the acid dissociations of $PheH_2^+$, $pK_{a1} = 2.3 \pm 0.2$ and $pK_{a2} = 9.08 \pm 0.08$, and were derived from data obtained in the pH range 2.0–10.5. For $HisH_3^{2+}$, $pK_{a1} = 2.1 \pm 0.2$, $pK_{a2} = 6.04 \pm 0.05$ and $pK_{a3} = 9.07 \pm 0.02$ and were derived from data obtained in the pH range 2.5–11.5. These pK_a values are similar to those in the literature,[18] and may be compared with $pK_{a1} = 2.40 \pm 0.02$ and $pK_{a2} = 9.28 \pm 0.01$ for diprotonated tryptophan, $TrpH_2^+$.[15] For $\beta CDpnH_2^{2+}$, $pK_{a1} = 7.39 \pm 0.04$ and $pK_{a2} = 9.9 \pm 0.1$.[15]

Discussion

Cyclodextrin Equilibria

For the complexation of either (*R*)-Phe^- or (*S*)-Phe^- by βCD:

$$\beta CD + (R)\text{-Phe}^- \overset{K_{1R}}{\rightleftharpoons} \beta CD\cdot(R)\text{-Phe}^- \quad (1)$$

$$\beta CD + (S)\text{-Phe}^- \overset{K_{1S}}{\rightleftharpoons} \beta CD\cdot(S)\text{-Phe}^- \quad (2)$$

$\log(K_{1R}/dm^3\ mol^{-1}) = 2.91 \pm 0.08$ (0.1) and $\log(K_{1S}/dm^3\ mol^{-1}) = 2.83 \pm 0.06$ (0.1) were derived from data in the pH range 8.0–10.0, where the first and second errors are calculated on the basis of phenylalanine being 100 and 99% pure, respectively. These values compare with $\log(K_{1R}/dm^3\ mol^{-1}) = 2.33 \pm 0.06$ (0.2) and $\log(K_{1S}/dm^3\ mol^{-1}) = 2.33 \pm 0.08$ (0.2), for the analogous complexation of tryptophan anion (Trp^-). The phenyl moieties of Phe^- and Trp^- probably reside largely within the hydrophobic region of the βCD annulus in the βCD·Phe^- and βCD·Trp^- complexes as has been shown to be the case for a range of cyclodextrin complexes formed with other aromatic guests.[1–5] The greater stability of βCD·Phe^- by comparison with that of βCD·Trp^- may indicate that the amino acid moiety of Trp^- extends further from the annulus into the aqueous environment than does that of Phe^- such that Trp^- is more hydrated and the stability of βCD·Trp^- is lowered by comparison with that of βCD·Phe^-. No complexation of His^- by βCD was detected. It appears that although the His^- ring is flat and possesses aromatic character, the ability of both the ring and the amino acid function of His^- to hydrogen bond with water, and possibly the smaller size of the ring, engender insufficient stability in βCD·His^- for its detection in this study.

For the complexation of (*R*)-Phe^- and (*S*)-Phe^- by βCDpn:

$$\beta CDpn + (R)\text{-Phe}^- \overset{K_{2R}}{\rightleftharpoons} \beta CDpn\cdot(R)\text{-Phe}^- \quad (3)$$

$$\beta CDpn + (S)\text{-Phe}^- \overset{K_{2S}}{\rightleftharpoons} \beta CDpn\cdot(S)\text{-Phe}^- \quad (4)$$

Table 1 Stability constants $\log(K/dm^3\ mol^{-1})^a$ for metallo-6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrins and related complexes in aqueous solution at 298.2 K and $I = 0.10$ ($NaClO_4$)

	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}
K_5[b]	4.22 ± 0.02	5.2 ± 0.1	7.35 ± 0.04	4.96 ± 0.08
K_6[b]	2.5 ± 0.2	3.1 ± 0.1	3.09 ± 0.04	3.0 ± 0.1
			phenylalanine[c]	
K_7	4.19 ± 0.03	5.09 ± 0.05	7.8 ± 0.1	4.59 ± 0.04
K_8	3.38 ± 0.07	4.3 ± 0.1	6.9 ± 0.1	not detected
K_{11R}	3.6 ± 0.2 (0.2)	< 3.6[d]	7.2 ± 0.1 (0.1)	4.7 ± 0.1 (0.1)
K_{11S}	3.69 ± 0.06 (0.1)	4.4 ± 0.1 (0.1)	6.9 ± 0.1 (0.1)	4.7 ± 0.2 (0.2)
			tryptophan[b]	
K_7	4.41 ± 0.05	5.42 ± 0.03	8.11 ± 0.03	4.90 ± 0.04
K_8	4.01 ± 0.08	4.67 ± 0.03	7.20 ± 0.07	not detected
K_{11R}	4.04 ± 0.03 (0.1)	4.1 ± 0.2 (0.2)	7.85 ± 0.07 (0.07)	5.3 ± 0.1 (0.1)
K_{11S}	4.32 ± 0.05 (0.09)	5.1 ± 0.2 (0.2)	8.09 ± 0.05 (0.06)	5.3 ± 0.1 (0.1)
			histidine[c]	
K_7			9.95 ± 0.03	
K_8			8.27 ± 0.04	
K_{11R}			8.38 ± 0.04	
K_{11S}			8.42 ± 0.02	
K_{12R}			7.75 ± 0.05	
K_{12S}			7.6 ± 0.1	

[a] Errors quoted for K (mean of N runs) represent the standard deviation. Phenylalanine: standard deviation $\sigma = \sqrt{\{[\sum(K_i - K)^2]/(N-1)\}}$ where K_i is a value from a single run for the best fit of the variation of pH with added volume of NaOH titrant obtained through SUPERQUAD and $i = 1, 2, \ldots, N$. When a K derived in this way was employed as a constant in the subsequent derivation of another K, the error associated with the first K was propagated in the derivation of the second K. For the diastereomers, the first and second errors quoted are calculated assuming 100 and 99% enantiomeric purity of the amino acid, respectively. [b] Ref. 15. [c] This work. [d] Limit corresponding to the stability constant that would result in the formation of 5–10% of the ternary species $[Ni(\beta CDpn)(R)\text{-Phe}]^+$. This ternary species was not detected at a significant concentration and so, K_{11R} must be less than this value, allowing an upper limit to be placed on the value of K_{11R}.

$\log(K_{2R}/dm^3\ mol^{-1}) = 2.51 \pm 0.07$ (0.2) and $\log(K_{2S}/dm^3\ mol^{-1}) = 2.74 \pm 0.05$ (0.1) were derived from data in the pH range 8.5–11.5, where the errors quoted have the same significance as above. It is seen that βCDpn is slightly enantioselective in complexing (*S*)-Phe^- over (*R*)-Phe^-. The corresponding values reported for the complexation of Trp^- by βCDpn are $\log(K_{2R}/dm^3\ mol^{-1}) = 3.41 \pm 0.02$ (0.05) and $\log(K_{2S}/dm^3\ mol^{-1}) = 3.40 \pm 0.07$ (0.1).[15]

The relative stabilities of the βCD and βCDpn complexes decreased in the sequence: βCDpn·(*R*)-Trp^- = βCDpn·(*S*)-Trp^- > βCD·(*R*)-Phe^- = βCD·(*S*)-Phe^- > βCDpn·(*R*)-Phe^- = βCDpn·(*S*)-Phe^- > βCD·(*R*)-Trp^- = βCD·(*S*)-Trp^-. The most probable structures for βCDpn·Trp^- and βCDpn·Phe^- place the phenyl group inside the cyclodextrin annulus where hydrophobic interactions occur, and the amino acid moieties in the vicinity of the 3-aminopropylamino substituent of βCDpn where hydrogen-bonding interactions occur. The ten-fold greater stability of βCDpn·Trp^-, relative to that of βCD·Trp^-, is consistent with these two interactions being additive in stabilizing βCDpn·Trp^-. In contrast, βCD·Phe^- is more stable than βCDpn·Phe^- consistent with these interactions not being additive in their contributions to the stability of βCDpn·Phe^-. This may be attributed to the greater length of Trp^- allowing an optimization of the two interactions in βCDpn·Trp^- while the shorter Phe^- constrains the interactions in βCDpn·Phe^- to be less favourable.

Although His^- and βCDpn coexist at significant concentrations under the conditions of this study, no βCDpn·His^- complex was detected in the pH range 6.9–11.1. However, βCDpnH·His and βCDpnH·$HisH^-$ were detected and their formation may be expressed through the equilibria:

$$\beta CDpnH^+ + (R)\text{-}His^- \overset{K_{3R}}{\rightleftharpoons} \beta CDpnH\cdot(R)\text{-}His \quad (5)$$

$$\beta CDpnH^+ + (S)\text{-}His^- \overset{K_{3S}}{\rightleftharpoons} \beta CDpnH\cdot(S)\text{-}His \quad (6)$$

$$\beta CDpnH^+ + (R)\text{-}HisH \overset{K_{4R}}{\rightleftharpoons} \beta CDpnH\cdot(R)\text{-}HisH^+ \quad (7)$$

$$\beta CDpnH^+ + (S)\text{-}HisH \overset{K_{4S}}{\rightleftharpoons} \beta CDpnH\cdot(S)\text{-}HisH^+ \quad (8)$$

for which $\log(K_{3R}/dm^3\ mol^{-1}) = 2.50 \pm 0.02$, $\log(K_{3S}/dm^3\ mol^{-1}) = 3.37 \pm 0.09$, $\log(K_{4R}/dm^3\ mol^{-1}) = 2.31 \pm 0.05$ and $\log(K_{4S}/dm^3\ mol^{-1} = 2.18 \pm 0.05$, where all errors are estimated assuming (*R*)- and (*S*)-histidine to be 100% enantiomerically pure. [Equilibria (5) and (6) may be alternatively expressed as between βCDpn and HisH, and equilibria (7) and (8) may be expressed as between either $\beta CDpnH_2^{2+}$ and His^- or βCDpn and $HisH_2^+$.] As $pK_{a2} = 9.9$ for $\beta CDpnH^+$ and $pK_{a3} = 9.07$ for HisH in the free states, it is probable that the aminopropylamino substituent of βCDpn is protonated in both βCDpnH·His and βCDpnH·$HisH^+$. The greater stability of βCDpnH·His over that of βCDpn·His^- may arise from the positive charge on $\beta CDpnH^+$ producing a greater dipole moment (by comparison with that of βCDpn) and providing an increased electrostatic interaction with His^-, and the neutralization of charge in the complex decreasing hydration, such that their combined effects stabilize the complex. The stabilization of βCDpnH·$HisH^+$ is less readily rationalized. Complexes analogous to those in equilibria (5)–(8) were not detected in the phenylalanine and tryptophan systems, a difference in behaviour which appears to be at least partially associated with the absence of a phenyl ring in histidine as demonstrated by the βCD complexations discussed above.

Complexation of βCDpn and Amino Acid Ligands by Divalent Metal Ions

The formation of the metallocyclodextrin $[M(\beta CDpn)]^{2+}$:

$$M^{2+} + \beta CDpn \overset{K_5}{\rightleftharpoons} [M(\beta CDpn)]^{2+} \quad (9)$$

has been previously studied,[14,15] and the variation of the magnitude of K_5 in the sequence $Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$ (Table 1) is as anticipated from the Irving–Williams series.[19] The formation of $[M(\beta CDpnH)]^{3+}$:

$$M^{2+} + \beta CDpnH^+ \overset{K_6}{\rightleftharpoons} [M(\beta CDpnH)]^{3+} \quad (10)$$

is less favoured (Table 1) as anticipated from the charged and monodentate nature of $\beta CDpnH^+$. The pK_a of $[M(\beta CDpnH)]^{3+}$ is 8.3 ± 0.1, 7.83 ± 0.02, 5.74 ± 0.05 and 8.1 ± 0.1, when $M^{2+} = Co^{2+}$, Ni^{2+}, Cu^{2+} and Zn^{2+}, respectively. These values probably characterize the deprotonation of the monoprotonated aminopropylamino substituents of $\beta CDpnH^+$ in the metallocyclodextrins. A further deprotonation of $[M(\beta CDpn)]^{2+}$ to produce $[M(\beta CDpn)OH]^+$ has been reported for $M^{2+} = Ni^{2+}$ and Cu^{2+} for which $pK_a = 9.20 \pm 0.04$ and 7.84 ± 0.03, respectively.

The formation of $[M(Phe)]^+$ and $[M(Phe)_2]$ also occurs:

$$M^{2+} + Phe^- \overset{K_7}{\rightleftharpoons} [M(Phe)]^+ \quad (11)$$

$$[M(Phe)]^+ + Phe^- \overset{K_8}{\rightleftharpoons} [M(Phe)_2] \quad (12)$$

The stability constants determined in this study (Table 1) are in reasonable agreement with those in the literature,[18] and also exhibit variations anticipated from the Irving–Williams series.[19] A pK_a of 7.46 ± 0.05 was determined for $[Cu(Phe)]^+$ which probably corresponds to the deprotonation of water bound to the metal centre. Similar deprotonations were not reliably detected for the Co^{2+}, Ni^{2+} and Zn^{2+} analogues, because the precipitation of a metal hydroxide species above pH = 8.5, 9.0 and 7.5, respectively, interfered with the titrations. The stability constants K_7 and K_8 were derived from data obtained in the pH ranges 6.5–8.5, 5.5–8.0, 4.0–7.0 and 5.5–7.5 when $M^{2+} = Co^{2+}$, Ni^{2+}, Cu^{2+} and Zn^{2+}, respectively. The analogous formation of $[Cu(His)]^+$ and $[Cu(His)_2]$ is characterized by K_7 and K_8 given in Table 1, and the greater magnitude of K_7 may indicate a different mode of binding of His^- to Cu^{2+} by comparison with that occurring with Phe^- and Trp^-. The latter two ligands probably coordinate as a five-membered chelate ring through a carboxylate oxygen and the amine nitrogen. While this may also occur with His^-, the alternative coordination as a six-membered chelate ring through the imidazole nitrogen and the amine nitrogen of His^- is more likely.[20] In all three systems $K_7 > K_8$ as anticipated for sequential binding of ligands.

In addition, $[Cu(HisH)]^{2+}$ and $[Cu(HisH)_2]^{2+}$ are formed:

$$Cu^{2+} + HisH \overset{K_9}{\rightleftharpoons} [Cu(HisH)]^{2+} \quad (13)$$

$$[Cu(HisH)]^{2+} + HisH \overset{K_{10}}{\rightleftharpoons} [Cu(HisH)_2]^{2+} \quad (14)$$

for which $\log(K_9/dm^3\ mol^{-1}) = 4.78 \pm 0.04$ and $\log(K_{10}/dm^3\ mol^{-1}) = 4.88 \pm 0.04$, respectively, determined in the pH range 3.5–8.0. The relationship $K_9 < K_{10}$ suggests that the coordination geometry of Cu^{2+} may have changed from a six-coordinated tetragonally distorted stereochemistry in $[Cu(HisH)]^{2+}$ to either a four-coordinate square planar or a tetrahedral stereochemistry in $[Cu(HisH)_2]^{2+}$. The smaller values of K_9 and K_{10} for complexation of HisH by compari-

son with K_7 and K_8, respectively, for complexation of His^- probably reflect the lesser electrostatic interaction between the metal centre and the uncharged HisH. {The proton dissociation of $(Cu(His)H_20]^+$ ($pK_a = 7.92 \pm 0.08$) yields [Cu(His)OH] and the dimerization of this species yields $[Cu(His)OH]_2$ for which $\log K_{dim} = 3.8 \pm 0.1$. A minor species, $[Cu(HisH)(His)]^+$ for which $\log K = 9.90 \pm 0.03$, also appeared to be formed by the addition of His^- to $[Cu(HisH)]^{2+}$, but it did not exceed 5% of the total species concentration and is not shown in Fig. 2.}

Complexation of (*R*)- and (*S*)-Phe^- and His^- Anions by Divalent Metallocyclodextrins of βCDpn

The stability constants for the complexations shown in equilibria (15) and (16), derived from data obtained in the pH ranges 7.5–8.5, 7.5–9.5, 6.0–10.0 and 6.5–7.5 when $M^{2+} = Co^{2+}$, Ni^{2+}, Cu^{2+} and Zn^{2+}, respectively, show that the complexes formed by $[Cu(\beta CDpn)]^{2+}$ are the most stable. However, $[Ni(\beta CDpn)]^{2+}$ is the most enantioselective complex showing a greater than six-fold enantioselectivity for (*S*)-Phe^- (Table 1) while its Cu^{2+} analogue is less enantioselective. It is also the case that $[Ni(\beta CDpn)]^{2+}$ is the most enantioselective metallocyclodextrin for (*S*)-Trp^-.[14,15] The Co^{2+} and Cu^{2+} analogues show a significant, but lesser, enantioselectivity for (*S*)-Trp^-.

$$[M(\beta CDpn)]^{2+} + (R)\text{-}Phe^- \underset{}{\overset{K_{11R}}{\rightleftharpoons}} [M(\beta CDpn)(R)\text{-}Phe]^+ \quad (15)$$

$$[M(\beta CDpn)]^{2+} + (S)\text{-}Phe^- \underset{}{\overset{K_{11S}}{\rightleftharpoons}} [M(\beta CDpn)(S)\text{-}Phe]^+ \quad (16)$$

The higher stabilities of $[M(\beta CDpn)(R)\text{-}Phe]^+$ and $[M(\beta CDpn)(S)\text{-}Phe]^+$ (K_{11R} and K_{11S}) by comparison with those of $\beta CDpn \cdot (R)\text{-}Phe^-$ and $\beta CDpn \cdot (S)\text{-}Phe^-$ (K_{2R} and K_{2S}), demonstrate that coordination to M^{2+} strengthens the complexation of Phe^-. Nevertheless, the lower stabilities of $[M(\beta CDpn)(R)\text{-}Phe]^+$ and $[M(\beta CDpn)(S)\text{-}Phe]^+$ by comparison with those of $[M(Phe)]^+$ (K_7) when $M^{2+} = Co^{2+}$, Ni^{2+} and Cu^{2+}, indicate that the factors stabilizing complexation of (*R*)-Phe^- and (*S*)-Phe^- by βCDpn and M^{2+} in $[M(\beta CDpn)(R)\text{-}Phe]^+$ and $[M(\beta CDpn)(S)\text{-}Phe]^+$ do not reinforce each other. A similar situation prevails in the analogous tryptophan systems.[14,15] In contrast, $[Zn(\beta CDpn)(R)\text{-}Phe]^+$, $[Zn(\beta CDpn)(S)\text{-}Phe]^+$ and $[Zn(Phe)]^+$ are of similar stability, and $[Zn(\beta CDpn)(R)\text{-}Trp]^+$ and $[Zn(\beta CDpn)(S)\text{-}Trp]^+$ are more stable than $[Zn(Trp)]^+$ which indicates that Zn^{2+} is more able to accommodate the complex stabilizing effects of βCDpn in the diastereomers.

The influence of M^{2+} and βCDpn on the stabilities of $[M(\beta CDpn)(R)\text{-}Phe]^+$ and $[M(\beta CDpn)(S)\text{-}Phe]^+$ may be rationalized through the structure shown in Fig. 4. The phenyl moiety of Phe^- is inside the cyclodextrin annulus with the Phe^- chiral centre in the vicinity of the primary hydroxy groups of the cyclodextrin, and the Phe^- amine and carboxylate groups coordinated to M^{2+}. The variation of stability with the nature of M^{2+} coincides with the variation of the ionic radii of six-coordinate Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}, which are 0.745, 0.69, 0.73 and 0.74 Å,[21] respectively, the geometric constraints arising from ligand-field effects in Co^{2+}, Ni^{2+} and Cu^{2+}, and the lack of such constraints arising from d^{10} Zn^{2+}.[22] While $[Ni(\beta CDpn)(R)\text{-}Phe]^+$ and $[Ni(\beta CDpn)(S)\text{-}Phe]^+$ differ substantially in stability, the analogous diastereomers for the other three metals are of similar stability. Evidently the size of Ni^{2+} and its octahedral stereochemistry are particularly appropriate in engendering

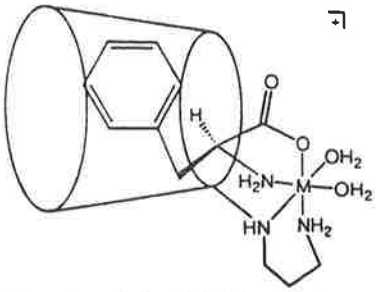


Fig. 4 Structure proposed for $[M(\beta CDpn)(S)\text{-}Phe]^+$. The cyclodextrin annulus is shown as a truncated cone with the narrow and wide ends representing the circles delineated by primary and secondary hydroxy groups, respectively. The two aqua ligands may either occupy the *cis* positions shown, or the aqua ligand *trans* to the secondary amine group of the 3-aminopropylamino substituent may be interchanged with that of the Phe^- carboxylate oxygen.

enantioselectivity for (*S*)-Phe^- over (*R*)-Phe^- and for (*S*)-Trp^- over (*R*)-Trp^- resulting from the interaction of their chiral centres with βCDpn in the metallocyclodextrin. The smaller enantioselectivity observed in the more stable $[Cu(\beta CDpn)(R)\text{-}Phe]^+$ and $[Cu(\beta CDpn)(S)\text{-}Phe]^+$ demonstrates that increasing complex stability does not necessarily induce a corresponding increase in enantioselectivity. The pK_as of 9.56 ± 0.04 (0.05) and 9.6 ± 0.1 (0.2) for deprotonation of $[Cu(\beta CDpn)(R)\text{-}Phe]^+$ and $[Cu(\beta CDpn)(S)\text{-}Phe]^+$, respectively, probably characterize the deprotonation of coordinated water. These reactions were not detected with $M^{2+} = Co^{2+}$, Ni^{2+} and Zn^{2+}.

Studies were limited to complexation of histidine by $[Cu(\beta CDpn)]^+$ because the three titratable protons of $HisH_3^{2+}$ (see Results) generate more protonic and complexation equilibria which result in more minor species than is the case with tryptophan and phenylalanine, and it was considered that the higher metal complex stabilities associated with Cu^{2+} presented the best opportunity for their detection. The K_{11R} and K_{11S}, derived from data in the pH range 6.5–9.5, for the complexation of His^- to form $[Cu(\beta CDpn)(R)\text{-}His]^+$ and $[Cu(\beta CDpn)(S)\text{-}His]^+$ in equilibria analogous to equilibria (15) and (16) are greater than those for the Phe^- and Trp^- complexes (Table 1). This is attributable to bidentate Phe^- and Trp^- coordinating through their carboxylate and amine groups, while bidentate His^- coordinates through a ring nitrogen and an amine group. A second His^- coordinates to form $[Cu(\beta CDpn)\{(R)\text{-}His\}_2]$ and $[Cu(\beta CDpn)\{(S)\text{-}His\}_2]$ (characterized by K_{12R} and K_{12S} in Table 1), but the formation of complexes with analogous stoichiometry was not observed for Phe^- and Trp^-. This probably reflects the smaller size of His^-, its different coordination mode and its weaker interaction with the βCDpn annulus, all of which should favour the coordination of a second His^- over either a second Phe^- or Trp^-.

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Crystal structure of α-amino-α-(2,6-dichlorophenyl)-cyclohexane-2,6-dione, $C_{13}H_{11}Cl_2NO_2$

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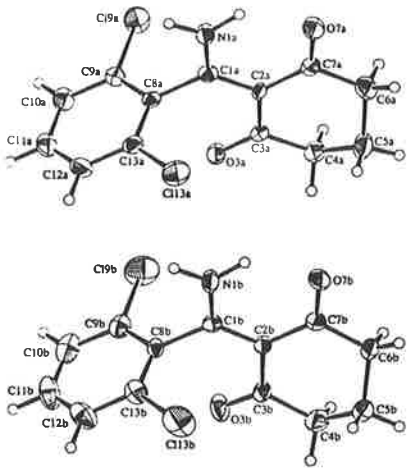

Source of material: see ref. 1.

The molecule has been shown to exist as the ketoenol-imine tautomer in solution (see ref. 1) whereas in the solid state the dione-eneimine tautomer is found. This is rationalized in terms of the intermolecular H bonding: the NH...O(3)′ interaction (1.84 Å for molecule a and 1.79 Å for molecule b) leaves the N atom electron rich and thereby is stabilized by the H atom that otherwise would have resided on the O(7) atom. There are also intramolecular interactions such that NH... O(7) is 1.83 Å and 1.84 Å for molecules a and b, respectively. The main difference between the two molecules comprising the asymmetric unit is found in the values of 3(1)° and 14(1)° for the O(3)/C(3)/C(2)/C(1) torsion angle for molecules a and b, respectively.

$C_{13}H_{11}Cl_2NO_2$, monoclinic, $P2_1/c$ (No. 14),
a = 17.139(3) Å, b = 11.605(2) Å, c = 12.915(4) Å,
β = 93.63(2)°. V = 2563.6 Å^3, Z = 8, $R(F)$ = 0.046,
$R_w(F)$ = 0.032.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless, size 0.03 x 0.16 x 0.48 mm
Wavelength:	Mo K_α radiation (0.7107 Å)
μ:	4.98 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
$N(hkl)_{unique}$:	6416
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	325
Program:	TEXSAN-TEXRAY

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1a2)	4e	0.4907	0.2702	0.6871	0.0583
H(1a1)	4e	0.40066	0.24478	0.63284	0.0583
H(1b1)	4e	0.10457	−0.09859	0.82621	0.07111
H(1b2)	4e	0.01696	−0.10732	0.76057	0.07502
H(4a1)	4e	0.34757	−0.23342	0.72255	0.06448
H(4a2)	4e	0.28861	−0.14583	0.77004	0.06448
H(4b1)	4e	0.17491	0.3802	0.80498	0.06799
H(4b2)	4e	0.17335	0.34136	0.9224	0.06799
H(5b1)	4e	0.25948	0.23618	0.77168	0.06205
H(5b2)	4e	0.29443	0.30403	0.87043	0.06205
H(5a1)	4e	0.32307	−0.15696	0.56074	0.07314
H(5a2)	4e	0.24185	−0.18913	0.60525	0.07314
H(6b1)	4e	0.30075	0.10529	0.8972	0.06431
H(6b2)	4e	0.24858	0.16589	0.97827	0.06431
H(6a1)	4e	0.24214	−0.00591	0.52693	0.0662
H(6a2)	4e	0.21751	−0.00325	0.64306	0.0662
H(10a)	4e	0.60629	0.11347	1.00712	0.07294
H(10b)	4e	−0.20026	0.14872	0.76916	0.07795
H(11a)	4e	0.70928	0.02464	0.92709	0.07741
H(11b)	4e	−0.19991	0.20471	0.59649	0.07891
H(12b)	4e	−0.08528	0.18826	0.50821	0.09927
H(12a)	4e	0.69606	−0.02022	0.75073	0.07541

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(9b)	4e	−0.0884(2)	0.0647(2)	0.9100(2)	0.117(2)	0.131(2)	0.089(2)	−0.003(2)	0.043(2)	0.008(2)
Cl(13)	4e	0.0647(2)	0.1156(2)	0.5692(2)	0.102(2)	0.168(3)	0.077(2)	0.023(2)	0.031(2)	0.023(2)
Cl(9a)	4e	0.4579(1)	0.1821(2)	0.9347(2)	0.075(2)	0.104(2)	0.052(1)	0.007(1)	0.010(1)	−0.019(2)
Cl(13)	4e	0.5763(1)	0.0044(2)	0.5995(2)	0.088(2)	0.101(2)	0.074(2)	0.010(2)	0.015(1)	−0.034(2)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(3a)	4e	0.4449(3)	−0.1027(4)	0.8026(4)	0.057(4)	0.035(4)	0.071(3)	−0.005(3)	−0.018(3)	0.009(3)
O(3b)	4e	0.0446(3)	0.2880(4)	0.8050(5)	0.057(4)	0.045(4)	0.126(5)	0.009(4)	−0.036(4)	−0.000(3)
O(7a)	4e	0.3129(3)	0.1654(5)	0.5871(4)	0.069(4)	0.044(4)	0.068(4)	0.003(3)	−0.024(3)	0.015(3)
O(7b)	4e	0.1953(3)	−0.0353(5)	0.8850(4)	0.060(4)	0.037(4)	0.082(4)	0.003(3)	−0.015(3)	0.010(3)
N(1a)	4e	0.4465(3)	0.2188(5)	0.6741(4)	0.048(5)	0.039(5)	0.057(4)	−0.008(4)	−0.009(3)	0.011(4)
N(1b)	4e	0.0592(3)	−0.0613(6)	0.7924(5)	0.043(5)	0.041(5)	0.097(5)	−0.004(4)	−0.022(4)	0.005(4)
C(1a)	4e	0.4489(4)	0.1161(7)	0.7113(5)	0.051(6)	0.030(5)	0.037(4)	0.003(4)	−0.001(4)	0.007(5)
C(1b)	4e	0.0551(5)	0.0497(7)	0.7897(6)	0.048(6)	0.023(5)	0.054(5)	−0.002(4)	−0.002(4)	0.000(5)
C(2a)	4e	0.3880(4)	0.0379(6)	0.6918(5)	0.035(5)	0.027(5)	0.036(4)	−0.006(4)	−0.007(4)	−0.002(4)
C(2b)	4e	0.1149(4)	0.1187(7)	0.8301(5)	0.038(5)	0.024(5)	0.055(5)	−0.000(4)	−0.004(4)	−0.002(5)
C(3a)	4e	0.3916(4)	−0.0732(7)	0.7403(5)	0.042(6)	0.032(6)	0.046(5)	0.002(4)	−0.004(4)	−0.008(5)
C(3b)	4e	0.1061(5)	0.2421(7)	0.8247(6)	0.046(6)	0.033(6)	0.060(5)	−0.010(5)	−0.012(5)	−0.005(5)
C(4a)	4e	0.3268(5)	−0.1558(7)	0.7184(6)	0.056(6)	0.039(6)	0.068(6)	−0.006(5)	−0.005(4)	0.005(5)
C(4b)	4e	0.1762(5)	0.3146(7)	0.8515(6)	0.063(6)	0.040(6)	0.087(6)	−0.001(5)	0.004(5)	0.001(6)
C(5b)	4e	0.2522(5)	0.2546(7)	0.8438(6)	0.050(6)	0.054(6)	0.072(5)	−0.009(5)	−0.002(5)	0.005(5)
C(5a)	4e	0.2868(5)	−0.1384(8)	0.6130(6)	0.059(7)	0.063(7)	0.084(6)	−0.022(6)	−0.019(5)	0.000(5)
C(6b)	4e	0.2522(4)	0.1460(7)	0.9058(6)	0.042(6)	0.049(6)	0.081(6)	−0.011(5)	−0.014(5)	0.008(5)
C(6a)	4e	0.2604(5)	−0.0164(8)	0.5990(5)	0.062(6)	0.056(7)	0.071(5)	0.007(5)	−0.018(4)	0.011(6)
C(7b)	4e	0.1858(5)	0.0687(7)	0.8735(5)	0.044(6)	0.039(6)	0.053(5)	0.001(5)	0.001(4)	0.006(5)
C(7a)	4e	0.3227(5)	0.0703(7)	0.6254(5)	0.049(6)	0.039(6)	0.045(5)	0.001(5)	−0.004(4)	−0.006(5)
C(8b)	4e	−0.0182(4)	0.0943(6)	0.7350(6)	0.034(5)	0.028(5)	0.052(5)	−0.001(4)	−0.009(4)	−0.008(4)
C(8a)	4e	0.5236(4)	0.0885(6)	0.7732(5)	0.042(5)	0.022(5)	0.039(5)	−0.003(4)	0.002(4)	0.003(4)
C(9a)	4e	0.5332(4)	0.1178(6)	0.8765(5)	0.041(5)	0.041(5)	0.042(5)	−0.001(4)	0.007(4)	0.003(4)
C(9b)	4e	−0.0860(5)	0.1029(7)	0.7830(6)	0.050(6)	0.044(6)	0.072(6)	−0.000(5)	0.004(5)	−0.009(5)
C(10b)	4e	−0.1526(6)	0.1432(8)	0.7327(8)	0.055(7)	0.055(7)	0.124(8)	0.003(7)	0.005(7)	−0.030(6)
C(10a)	4e	0.6009(5)	0.0940(7)	0.9340(5)	0.063(6)	0.051(6)	0.056(5)	−0.003(5)	−0.010(5)	0.012(5)
C(11b)	4e	−0.1525(6)	0.1751(8)	0.6320(9)	0.064(8)	0.065(7)	0.112(9)	0.026(7)	−0.031(7)	−0.035(6)
C(11a)	4e	0.6609(5)	0.0422(7)	0.8871(7)	0.058(7)	0.045(7)	0.085(7)	−0.004(5)	−0.021(6)	0.018(5)
C(12a)	4e	0.6531(5)	0.0152(7)	0.7844(7)	0.041(6)	0.048(6)	0.100(7)	0.005(6)	0.007(5)	−0.005(5)
C(12b)	4e	−0.0860(7)	0.1657(8)	0.5804(6)	0.104(9)	0.052(7)	0.075(7)	0.017(5)	−0.025(7)	−0.008(7)
C(13b)	4e	−0.0192(5)	0.1235(7)	0.6329(6)	0.063(7)	0.060(7)	0.053(6)	0.005(5)	−0.001(5)	−0.008(5)
C(13a)	4e	0.5849(5)	0.0379(6)	0.7292(6)	0.044(6)	0.037(6)	0.060(5)	−0.005(4)	0.009(4)	−0.007(5)

Reference

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Zeitschrift für Kristallographie 210, 233 - 234

Crystal structure of (*Z*)-*N*-phthaloyl-2,3-dehydrophenylalanine methyl ester, $C_{18}H_{13}NO_4$

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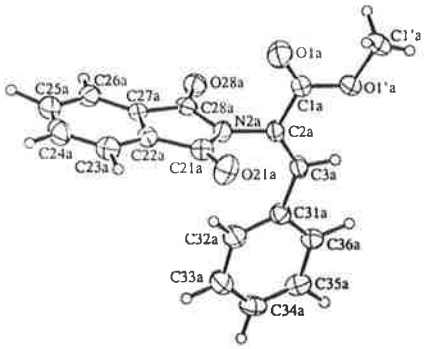

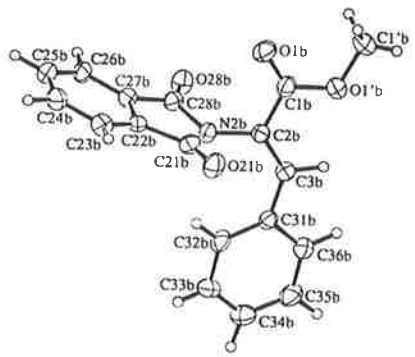

Source of material: see ref. 1.

The analysis confirms that this compound exists as the (*Z*)-isomer (see ref. 1). There are two molecules in the asymmetric unit which differ in their torsion angle about the N(2)–C(2) bond, i.e. the C(2)/N(2)/C(21)/O(21) torsion angle is -5.7(9)° for molecule a and -16.7(8)° for molecule b.

$C_{18}H_{13}NO_4$, triclinic, $P\bar{1}$ (No. 2), a = 11.249(2) Å, b = 14.082(3) Å, c = 11.159(3) Å, α = 112.63(2)°, β = 114.82(2)°, γ = 76.36(2)°, V = 1475.1 Å^3, Z = 4, $R(F)$ = 0.040, $R_w(F)$ = 0.031.

Table 1. Parameters used for the X-ray data collection

Crystal:	fragment with diameter of ca. 0.11 mm
Wavelength:	Mo $K\alpha$ radiation (0.7107 Å)
μ:	0.99 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
$N(hkl)_{unique}$:	5395
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	519
Program:	TEXSAN-TEXRAY

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1'a)	2*i*	0.859(4)	0.545(4)	0.556(5)	0.08(1)
H(1'b)	2*i*	0.707(6)	0.567(5)	0.425(6)	0.160(9)
H(1'c)	2*i*	0.730(6)	0.504(5)	0.533(6)	0.11(1)
H(1'd)	2*i*	0.959(6)	0.074(5)	0.755(6)	0.12(1)
H(1'e)	2*i*	0.955(5)	0.039(4)	0.598(5)	0.12(1)
H(1'f)	2*i*	0.982(7)	0.147(6)	0.689(8)	0.181(8)
H(3a)	2*i*	0.783(3)	0.247(3)	0.267(4)	0.04(1)
H(3b)	2*i*	0.594(4)	0.128(3)	0.645(4)	0.04(1)
H(23a)	2*i*	0.754(5)	0.382(4)	−0.276(5)	0.10(1)
H(23b)	2*i*	0.477(4)	0.464(3)	0.277(4)	0.04(1)
H(24b)	2*i*	0.432(4)	0.440(3)	0.044(4)	0.06(1)
H(24a)	2*i*	0.933(4)	0.385(4)	−0.344(5)	0.08(1)
H(25b)	2*i*	0.439(4)	0.272(3)	−0.103(4)	0.07(1)
H(25a)	2*i*	1.168(5)	0.374(4)	−0.183(5)	0.12(1)
H(26a)	2*i*	1.196(4)	0.338(3)	0.017(4)	0.06(1)
H(26b)	2*i*	0.476(4)	0.128(3)	−0.029(4)	0.06(1)
H(32a)	2*i*	0.807(5)	0.158(4)	−0.074(5)	0.09(1)
H(32b)	2*i*	0.309(3)	0.234(3)	0.405(3)	0.02(1)
H(33a)	2*i*	0.804(5)	−0.011(4)	−0.226(5)	0.12(1)
H(33b)	2*i*	0.105(4)	0.252(4)	0.400(5)	0.06(1)
H(34a)	2*i*	0.803(4)	−0.143(3)	−0.138(4)	0.06(1)
H(34b)	2*i*	0.051(4)	0.181(4)	0.514(5)	0.07(1)
H(35a)	2*i*	0.782(4)	−0.094(3)	0.084(4)	0.06(1)
H(35b)	2*i*	0.220(5)	0.088(4)	0.666(5)	0.10(1)
H(36a)	2*i*	0.792(4)	0.076(3)	0.236(4)	0.08(1)
H(36b)	2*i*	0.437(4)	0.082(3)	0.680(4)	0.03(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1a)	2*i*	0.8415(5)	0.5033(3)	0.2898(5)	0.186(5)	0.048(3)	0.138(4)	−0.024(3)	0.112(4)	0.014(3)
O(1'a)	2*i*	0.7836(3)	0.4207(3)	0.3862(4)	0.079(3)	0.048(3)	0.059(3)	−0.011(2)	0.035(2)	0.004(2)
O(1'b)	2*i*	0.7957(4)	0.1167(3)	0.6411(4)	0.047(3)	0.090(3)	0.060(3)	0.002(2)	0.017(2)	0.038(2)
O(1b)	2*i*	0.7914(3)	0.1619(3)	0.4695(4)	0.061(3)	0.096(3)	0.061(3)	−0.013(2)	0.029(2)	0.029(2)
O(21a)	2*i*	0.6689(4)	0.3671(3)	−0.0729(4)	0.048(3)	0.111(3)	0.096(3)	0.004(3)	0.020(3)	0.057(3)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(21b)	2*i*	0.5405(4)	0.3760(3)	0.5081(4)	0.093(3)	0.049(3)	0.046(2)	−0.000(2)	0.028(2)	0.006(2)
O(28b)	2*i*	0.5356(3)	0.0514(3)	0.2077(3)	0.079(3)	0.038(2)	0.046(2)	−0.010(2)	0.018(2)	0.006(2)
O(28a)	2*i*	1.0910(3)	0.3194(3)	0.2087(4)	0.058(3)	0.078(3)	0.052(2)	−0.011(2)	0.015(2)	0.021(2)
N(2a)	2*i*	0.8698(4)	0.3315(3)	0.0862(4)	0.046(3)	0.056(3)	0.051(3)	−0.004(2)	0.022(3)	0.018(3)
N(2b)	2*i*	0.5285(4)	0.2041(3)	0.3808(4)	0.050(3)	0.042(3)	0.034(3)	−0.005(2)	0.015(2)	0.012(2)
C(1a)	2*i*	0.8192(6)	0.4263(5)	0.2911(6)	0.071(4)	0.059(5)	0.056(4)	−0.012(4)	0.033(3)	0.010(4)
C(1′a)	2*i*	0.7639(8)	0.5187(5)	0.4877(8)	0.112(7)	0.059(5)	0.074(6)	−0.013(4)	0.054(5)	−0.006(5)
C(1b)	2*i*	0.7358(6)	0.1481(4)	0.5310(5)	0.057(5)	0.054(4)	0.038(4)	−0.005(3)	0.017(3)	0.013(3)
C(1′b)	2*i*	0.9366(6)	0.0971(6)	0.6833(8)	0.045(5)	0.108(7)	0.078(5)	0.002(5)	0.015(4)	0.044(4)
C(2a)	2*i*	0.8275(5)	0.3258(4)	0.1856(5)	0.053(4)	0.049(4)	0.051(4)	−0.002(3)	0.031(3)	0.013(3)
C(2b)	2*i*	0.5927(5)	0.1667(4)	0.4958(5)	0.041(4)	0.046(3)	0.034(3)	−0.001(3)	0.012(3)	0.009(3)
C(3b)	2*i*	0.5327(5)	0.1482(4)	0.5627(5)	0.048(4)	0.050(4)	0.043(4)	−0.001(3)	0.019(3)	0.013(3)
C(3a)	2*i*	0.8041(5)	0.2392(4)	0.1865(6)	0.059(4)	0.053(4)	0.051(4)	−0.000(3)	0.032(3)	0.015(3)
C(21a)	2*i*	0.7853(6)	0.3560(4)	−0.0352(6)	0.053(4)	0.050(4)	0.054(4)	−0.001(3)	0.016(4)	0.021(4)
C(21b)	2*i*	0.5213(5)	0.3087(4)	0.3992(5)	0.054(4)	0.041(4)	0.047(4)	−0.004(3)	0.022(3)	0.009(3)
C(22b)	2*i*	0.4891(4)	0.3139(4)	0.2596(5)	0.034(3)	0.050(4)	0.042(3)	−0.003(3)	0.016(3)	0.018(3)
C(22a)	2*i*	0.8740(6)	0.3638(4)	−0.0970(6)	0.056(4)	0.041(3)	0.050(4)	0.000(3)	0.022(3)	0.018(3)
C(23a)	2*i*	0.8448(6)	0.3801(5)	−0.2202(6)	0.070(5)	0.060(4)	0.059(5)	−0.005(4)	0.017(4)	0.025(4)
C(23b)	2*i*	0.4684(5)	0.3978(4)	0.2173(6)	0.053(4)	0.047(4)	0.053(4)	−0.013(4)	0.013(3)	0.011(3)
C(24b)	2*i*	0.4508(5)	0.3799(5)	0.0815(6)	0.059(4)	0.058(4)	0.060(4)	0.001(4)	0.021(3)	0.030(3)
C(24a)	2*i*	0.9501(8)	0.3819(5)	−0.2520(7)	0.111(7)	0.072(5)	0.060(5)	−0.008(4)	0.040(5)	0.029(5)
C(25a)	2*i*	1.0761(8)	0.3671(5)	−0.1686(7)	0.089(6)	0.066(4)	0.069(5)	−0.015(4)	0.041(4)	0.016(4)
C(25b)	2*i*	0.4525(5)	0.2819(5)	−0.0085(6)	0.056(4)	0.068(5)	0.044(4)	−0.004(4)	0.020(3)	0.022(3)
C(26b)	2*i*	0.4696(5)	0.1973(5)	0.0319(5)	0.054(4)	0.051(4)	0.034(4)	−0.006(3)	0.013(3)	0.009(3)
C(26a)	2*i*	1.1049(6)	0.3513(4)	−0.0447(6)	0.052(4)	0.060(4)	0.065(5)	−0.009(3)	0.023(4)	0.015(4)
C(27a)	2*i*	1.0006(6)	0.3490(4)	−0.0131(5)	0.050(4)	0.041(3)	0.043(3)	−0.011(3)	0.019(3)	0.008(3)
C(27b)	2*i*	0.4889(5)	0.2151(4)	0.1675(5)	0.043(3)	0.039(3)	0.036(3)	−0.009(3)	0.012(3)	0.007(3)
C(28a)	2*i*	0.9999(6)	0.3319(4)	0.1082(5)	0.058(5)	0.041(4)	0.043(4)	−0.010(3)	0.016(3)	0.005(3)
C(28b)	2*i*	0.5204(5)	0.1430(4)	0.2446(5)	0.044(4)	0.048(4)	0.041(4)	−0.010(3)	0.016(3)	0.009(3)
C(31a)	2*i*	0.8046(5)	0.1348(4)	0.0919(6)	0.052(4)	0.050(4)	0.054(4)	−0.003(3)	0.022(3)	0.016(3)
C(31b)	2*i*	0.3961(5)	0.1586(4)	0.5448(5)	0.054(4)	0.039(3)	0.040(3)	0.002(3)	0.023(3)	0.013(3)
C(32a)	2*i*	0.8078(7)	0.1066(5)	−0.0397(7)	0.127(6)	0.053(5)	0.077(5)	−0.026(4)	0.053(5)	0.011(5)
C(32b)	2*i*	0.2935(6)	0.2062(4)	0.4594(6)	0.069(5)	0.061(4)	0.056(4)	−0.005(3)	0.030(4)	0.030(4)
C(33b)	2*i*	0.1675(6)	0.2121(5)	0.4508(6)	0.049(5)	0.075(5)	0.075(5)	0.005(4)	0.032(4)	0.028(4)
C(33a)	2*i*	0.8035(7)	0.0054(6)	−0.1246(7)	0.121(6)	0.066(5)	0.077(5)	−0.020(4)	0.056(5)	0.006(4)
C(34a)	2*i*	0.7984(6)	−0.0683(5)	−0.0776(7)	0.070(4)	0.038(4)	0.073(5)	−0.005(4)	0.021(4)	0.005(3)
C(34b)	2*i*	0.1403(6)	0.1705(5)	0.5268(7)	0.058(5)	0.074(5)	0.077(5)	−0.007(4)	0.035(4)	0.025(4)
C(35b)	2*i*	0.2395(7)	0.1236(5)	0.6126(6)	0.075(5)	0.076(5)	0.069(5)	−0.005(4)	0.039(4)	0.034(4)
C(35a)	2*i*	0.7952(6)	−0.0436(5)	0.0497(7)	0.064(4)	0.060(5)	0.069(5)	−0.015(4)	0.014(4)	0.023(4)
C(36a)	2*i*	0.7980(5)	0.0576(5)	0.1352(6)	0.052(4)	0.053(4)	0.050(4)	−0.008(4)	0.014(3)	0.015(3)
C(36b)	2*i*	0.3653(6)	0.1176(4)	0.6216(6)	0.058(5)	0.059(4)	0.054(4)	0.002(3)	0.023(3)	0.025(4)

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1. Easton, C.J., Hutton, C.A., Roselt, P.D., Tiekink, E.R.T.: Stereocontrolled synthesis of β-hydroxyphenylalanine and betahydroxytyrosine derivatives. Tetrahedron **50** (1994) 7327-7340.

Aust. J. Chem., 1995, 48, 1065–1070

Copper-Catalysed Reactions of Penicillin Derivatives with t-Butyl Perbenzoate

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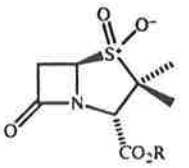
Abstract

The benzoyloxylation of penicillin derivatives at C5, on treatment with t-butyl perbenzoate in the presence of a copper catalyst, is facilitated by a phthalimido group at C6 when the substituents on the lactam ring are in the *cis* orientation, but hindered when the groups are *trans* substituted. In the absence of a C6 substituent, a competing reaction occurs in which the thiazolidine ring is cleaved.

Introduction



(1a) R = H
(1b) R = Me

Penicillin derivatives such as the sulfone (1a), in which the β-lactam ring bears a substituent that can act as a good leaving group, are of interest in the treatment of penicillin-resistant bacterial infections.[1] 4-Acyloxy-substituted β-lactams have attracted particular attention in the synthesis of penicillins and cephalosporins.[2] The report of Matsumura *et al.*[3] of the direct benzoyloxylation at C5 of the 6β-phthalimidopenicillinate esters (2), on treatment with t-butyl perbenzoate in the presence of a copper catalyst (Scheme 1), has considerable potential in each of these areas. Consequently, we decided to examine the scope of the reaction in more detail.

[1] English, A. R., Retsema, J. A., Girard, A. E., Lynch, J. E., and Barth, W. E., *Antimicrob. Agents Chemother.*, 1978, **14**, 414; Foulds, C. D., Kasmirak, M., and Sammes, P. G., *J. Chem. Soc., Perkin Trans. 1*, 1985, 963; Fisher, J., Charnas, R. L., Bradley, S. M., and Knowles, J. R., *Biochemistry*, 1981, **20**, 2726; Brenner, D. G., and Knowles, J. R., *Biochemistry*, 1981, **20**, 3680; Kemal, C., and Knowles, J. R., *Biochemistry*, 1981, **20**, 3688.

[2] Clauss, K., Grimm, D., and Prossel, G., *Justus Liebigs Ann. Chem.*, 1974, 359; Brown, A. G., Corbett, D. F., and Howarth, T. T., *J. Chem. Soc., Chem. Commun.*, 1977, 359; Mickel, S., *Aldrichimica Acta*, 1985, **18**, 95; Georg, G. I., and Kant, J., *J. Org. Chem.*, 1988, **53**, 692; Wagle, D. R., Garai, C., Monteleone, M. G., and Bose, A. K., *Tetrahedron Lett.*, 1988, **29**, 1649.

[3] Matsumura, H., Yano, T., Ueyama, M., Tori, K., and Nagata, W., *J. Chem. Soc., Chem. Commun.*, 1979, 485.

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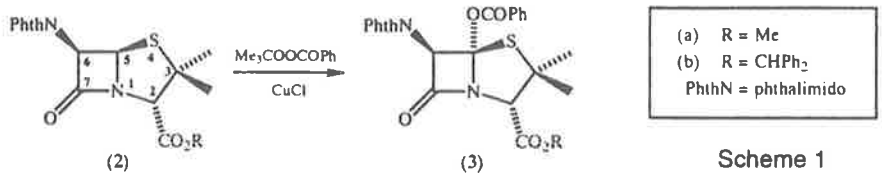
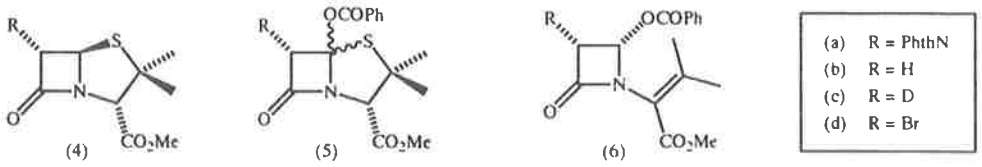


Scheme 1

Results and Discussion

Following the reported procedure,[3] a mixture of methyl 6β-phthalimidopenicillinate (2a), t-butyl perbenzoate (3 mole equiv.) and a catalytic amount of cuprous chloride, in benzene, was heated at reflux under nitrogen for 6 h. Analysis of the crude product mixture by ^{1}H n.m.r. spectroscopy showed the presence of the starting material (2a), the benzoate (3a) and methyl benzoate, in the ratio 1 : 2 : 5. Chromatography of the mixture afforded the benzoate (3a) in 43% yield. By contrast, treatment of methyl 6α-phthalimidopenicillinate (4a) under identical conditions afforded only the starting material (4a) and methyl benzoate. Even when the penicillin derivative (4a) was treated with 15 mole equiv. of t-butyl perbenzoate, there was no evidence of formation of the benzoate (5a). When methyl penicillinate (4b) was treated with t-butyl perbenzoate (3 mole equiv.) in an analogous manner, the product mixture contained the starting material (4b), the benzoates (5b) and (6b), and methyl benzoate, in the ratio 8 : 1 : 2 : 20. That ratio became 1 : 1 : 2 : 20 when the reaction was repeated with 10 mole equiv. of the peroxy ester, and chromatography of that mixture afforded the benzoates (5b) and (6b), in yields of 24 and 41%, respectively.



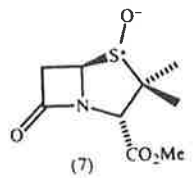
Presumably the mechanism of formation of the benzoates (3a) and (5b) involves hydrogen atom transfer from the corresponding penicillinates (2a) and (4b) to t-butoxy radical, followed by electron transfer and incorporation of benzoate at the site of hydrogen abstraction.[4,5] It is evident from the different outcomes of the reactions of the penicillin derivatives (2a) and (4a) that hydrogen atom abstraction by t-butoxy radical from the *cis*-disubstituted β-lactam (2a) occurs much more readily than the corresponding process involving the *trans*-isomer (4a). Two factors are likely to contribute to this effect. The C 6 substituent probably hinders the approach of t-butoxy radical to the C 5 position of the *trans*-isomer (4a), while facilitating the reaction of the *cis*-isomer (2a), where the hydrogen transfer is accompanied by relief of steric interactions between the C 5 and C 6

[4] Rawlinson, D. J., and Sosnovsky, G., *Synthesis*, 1972, 1.
[5] Sosnovsky, G., *J. Org. Chem.*, 1961, **26**, 281; Sosnovsky, G., and O'Neill, H. J., *J. Org. Chem.*, 1962, **27**, 3469; Sosnovsky, G., *Tetrahedron*, 1962, **18**, 15.

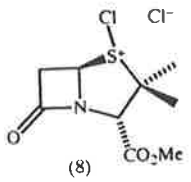
substituents. Consistent with this interpretation of the results, the reactivity of methyl penicillinate (4b), which has no C6 substituent, is intermediate between that of the phthalimides (2a) and (4a), as indicated by the extent of formation of the corresponding benzoates (5b), (3a) and (5a) per mole of t-butyl perbenzoate used in the reactions.

In order to investigate the mechanism of formation of the benzoate (6b) in the reaction of the penicillinate (4b), methyl (6α-D)penicillinate (4c) was prepared by treatment of methyl 6α-bromopenicillinate (4d) with tributyltin deuteride. The stereochemistry of the β-lactam ring in the deuteride (4c) was determined by ^{1}H n.m.r. spectroscopy, which showed a coupling constant of 1·5 Hz for the interaction between C5 and C6 hydrogens, consistent with the *trans* orientation.[6] Presumably, the reaction of the bromide (4d) affords the *trans*-deuteride (4c) because the stannane delivers the deuterium to the less hindered face of the intermediate radical, opposite the C5 substituent. When the deuteride (4c) was treated with t-butyl perbenzoate, the product benzoate (6c) contained the deuterium in a *cis* orientation with respect to the benzoyloxy substituent. The ^{1}H n.m.r. spectrum of the benzoate (6c) showed a coupling constant of 4·0 Hz for the interaction between the hydrogens of the lactam ring, confirming the stereochemistry.[6]

The reaction of the deuteride (4c) to give the benzoate (6c) shows that the benzoyloxy group replaces the sulfanyl substituent with inversion of stereochemistry, and it is on this basis that the stereochemistry of the benzoate (6b) was assigned. The mechanism of the reaction is likely to involve oxidation at sulfur of the penicillinate (4b), then incorporation of benzoate in an S_N2 process. Related rearrangements of penicillin derivatives on treatment with oxidizing reagents have been reported;[7] however, neither oxidation on sulfur nor carbon–sulfur bond cleavage has been observed in previous studies of copper-catalysed reactions of t-butyl peroxy esters with sulfides.[5] There was no evidence of formation of products analogous to the benzoate (6b) in the reactions of the phthalimides (2a) and (4a). Presumably, the steric effect of the C6 substituent of the phthalimide (4a) restricts backside displacement of the sulfanyl group in that compound, while the alternative reaction of the 6β-isomer (2a), to give the benzoate (3a), is the preferred mode of reaction in that case.



(7)



(8)

A number of alternative experiments were performed in attempts to produce the benzoate (6b) by first oxidizing methyl penicillinate (4b) on sulfur. The diastereomers of the sulfoxide (7)[8] and the sulfone (1b)[8] each failed to react to give the benzoate

[6] Barrow, K. D., and Spotswood, T. M., *Tetrahedron Lett.*, 1965, 3325.
[7] Somazoa, C., and Mascaretti, O. A., *Tetrahedron*, 1988, **44**, 7007; Kang, J., Im, W. B., Choi, S., Lim, D., Choi, Y. R., Cho, H. G., and Lee, J. H., *Heterocycles*, 1989, **29**, 209.
[8] Micetich, R. G., Maiti, S. N., Tanaka, M., Yamazaki, T., and Ogawa, K., *J. Org. Chem.*, 1986, **51**, 853.

(6b) on treatment with benzoate anion under a range of conditions. Finally the chlorosulfonium chloride salt (8) was prepared by treatment of methyl penicillinate (4b) with sulfuryl chloride in carbon tetrachloride. On treatment of the salt (8) with benzoic acid and triethylamine, the benzoate (6b) was produced in 27% yield. The analogy between this reaction and the production of the benzoate (6b) in the reaction of methyl penicillinate (4b) provides support for the mechanism proposed above for the latter process.

Experimental

Melting points are uncorrected. Light petroleum refers to the fraction with b.p. 66–68°. Chromatography was carried out on a Chromatotron 7924T (Harrison Research, Palo Alto/TC Research, Norwich) by using Merck silica gel 60 PF_{254}, eluting with a gradient of light petroleum/ethyl acetate. ^1H n.m.r. spectra were recorded on either a Bruker CXP-300 or a Varian XL-300 spectrometer, as dilute solutions in (D)chloroform, with tetramethylsilane as internal standard. Electron impact mass spectra were recorded on either an AEI MS-902 or an AEI MS-3010 spectrometer. Microanalyses were performed by the Canadian Microanalytical Service Ltd., Vancouver.

6β-Aminopenicillanic acid was purchased from Sigma Chemical Company and treated with *N*-ethoxycarbonylphthalimide,[9] then methyl iodide in the presence of sodium carbonate,[10] to produce methyl 6β-phthalimidopenicillinate (2a).[9] Methyl 6α-phthalimidopenicillinate (4a) was prepared from the corresponding β-isomer (2a) by treatment with 1,5-diazabicyclo[4.3.0]non-5-ene.[11] Diazotization of 6β-aminopenicillanic acid with sodium nitrite in the presence of bromine, under acidic conditions, gave 6,6-dibromopenicillanic acid.[12] Hydrogenolysis of the dibromide over 5% palladium on charcoal, in aqueous sodium bicarbonate, afforded penicillanic acid,[10] from which methyl penicillinate (4b) was prepared by treatment with methyl iodide in the presence of sodium carbonate.[10] Methyl 6α-bromopenicillinate (4d) was prepared by diazotization of 6β-aminopenicillanic acid with sodium nitrite in the presence of sodium bromide under acidic conditions,[13] followed by esterification with methyl iodide in the presence of sodium carbonate.[10,13]

General Procedure for Reactions of the Penicillin Derivatives (2a) and (4a–c) with t-Butyl Perbenzoate

A mixture of the penicillin derivative (2a), (4a), (4b) or (4c) (*c.* 3 mmol), t-butyl perbenzoate and cuprous chloride (*c.* 5 mg), in benzene (25 ml), was heated at reflux under nitrogen for 6 h; then it was cooled, washed with saturated aqueous sodium metabisulfite (2×20 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Components in the crude product mixture were identified by ^1H n.m.r. spectroscopy, and separated by means of chromatography.

Treatment of Methyl 6β-Phthalimidopenicillinate (2a) with t-Butyl Perbenzoate

The reaction was carried out according to the general procedure, 3 mole equiv. of t-butyl perbenzoate being used. The ^1H n.m.r. spectrum of the crude product mixture showed the presence of the starting material (2a) (δ 3·81, s, 3H), the benzoate (3a) (δ 3·90, s, 3H) and methyl benzoate (δ 3·96, s, 3H), in the ratio 1:2:5. Chromatography of the mixture afforded methyl 5α-benzoyloxy-6β-phthalimidopenicillinate (3a) in 43% yield, m.p. 176–177°. ^1H n.m.r. δ 1·50, s, 3H; 1·83, s, 3H; 3·90, s, 3H; 4·85, s, 1H; 5·65, s, 1H; 7·2–8·0, m, 9H. Other spectral characteristics were consistent with those reported previously.[3]

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[10] Clayton, J. P., *J. Chem. Soc. C*, 1969, 2123.
[11] Denerley, P. M., and Thomas, E. J., *J. Chem. Soc., Perkin Trans. 1*, 1979, 3175.
[12] Volkmann, R. A., Carrol, R. D., Drolet, R. B., Elliot, M. L., and Moore, B. S., *J. Org. Chem.*, 1982, **47**, 3344.
[13] Cignarella, G., Pifferi, G., and Testa, E., *J. Org. Chem.*, 1962, **27**, 2668; Brennan, J., and Hussain, H. S., *Synthesis*, 1985, **8**, 749.

Treatment of Methyl 6α-Phthalimidopenicillinate (4a) with t-Butyl Perbenzoate

The reaction was carried out according to the general procedure, first by using 3 mole equiv. of t-butyl perbenzoate, then by using 15 mole equiv. of the peroxy ester. In each case the ^{1}H n.m.r. spectrum of the crude product mixture showed the presence of the starting material (4a) (δ 3·80, s, 3H) and methyl benzoate (δ 3·96, s, 3H).

Treatment of Methyl Penicillinate (4b) with t-Butyl Perbenzoate

The reaction was carried out according to the general procedure, with 3 mole equiv. of t-butyl perbenzoate, then repeated with 10 mole equiv. of the peroxy ester. The ^{1}H n.m.r. spectra of the crude product mixtures showed the presence of the starting material (4b) (δ 3·80, s, 3H), the benzoates (5b) (δ 3·86, s, 3H) and (6b) (δ 3·78, s, 3H) and methyl benzoate (δ 3·96, s, 3H), in the ratio 8:1:2:20 in the former reaction and 1:1:2:20 in the latter case. Chromatography of the product mixture obtained from the latter reaction afforded *methyl 5-benzoyloxypenicillinate* (5b) m.p. 91–93°, in 24% yield after recrystallization from light petroleum [Found: *m/z* 335·083. $C_{16}H_{17}NO_5S$ (M) requires *m/z* 335·083]. ^{1}H n.m.r. δ 1·60, s, 3H; 1·71, s, 3H; 3·59, d, *J* 17 Hz, 1H; 3·79, d, *J* 17 Hz, 1H; 3·86, s, 3H; 4·54, s, 1H; 7·2–7·8, m, 5H.

Continued chromatography gave *methyl (2S)-2-benzoyloxy-α-isopropylidene-4-oxoazetidine-1-acetate* (6b), m.p. 133–134·5°, in 41% yield after recrystallization from light petroleum (Found: C, 63·0; H, 5·8; N, 4·5. $C_{16}H_{17}NO_5$ requires C, 63·4; H, 5·6; N, 4·6%). ^{1}H n.m.r. δ 1·99, s, 3H; 2·24, s, 3H; 3·10, dd, *J* 1·5, 15·5 Hz, 1H; 3·46, dd, *J* 4, 15·5 Hz, 1H; 3·78, s, 3H; 6·46, dd, *J* 1·5, 4 Hz, 1H; 7·3–7·8, m, 5H. Mass spectrum *m/z* 303 (M, 0·5%), 233 (4), 201 (2), 198 (2), 181 (25), 105 (100), 77 (42).

Treatment of Methyl (6α-D)Penicillinate (4c) with t-Butyl Perbenzoate

The reaction was carried out according to the general procedure, 10 mole equiv. of t-butyl perbenzoate being used. Chromatography of the crude product mixture afforded methyl (2*S*,3*R*)-2-benzoyloxy-α-isopropylidene-4-oxo(3-D)azetidine-1-acetate (6c), m.p. 132–134°, in 28% yield after recrystallization from light petroleum. ^{1}H n.m.r. δ 2·00, s, 3H; 2·24, s, 3H; 3·44, d, *J* 4 Hz, 1H; 3·78, s, 3H; 6·45, d, *J* 4 Hz, 1H; 7·2–7·8, m, 5H. Mass spectrum *m/z* 304 (M, 98% D). These properties and other spectral characteristics were consistent with those found for the non-deuterated analogue (6b).

Methyl (6α-D)Penicillinate (4c)

A mixture of methyl 6α-bromopenicillinate (4d) (0·2 g, 0·69 mmol), tributyltin deuteride (0·29 g, 1·0 mmol) and azobisisobutyronitrile (*c.* 5 mg) in benzene (25 ml) was heated at 65–70° for 12 h; then it was cooled and concentrated under reduced pressure. The residue was dissolved in acetonitrile (60 ml), and the solution was washed with light petroleum (3×70 ml); then it was dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residual oil afforded methyl (6α-D)penicillinate (4c) (82 mg, 55%), m.p. 50–52°. ^{1}H n.m.r. δ 1·50, s, 3H; 1·70, s, 3H; 3·08, d, *J* 1·5 Hz, 1H; 3·80, s, 3H; 4·49, s, 1H; 5·32, d, *J* 1·5 Hz, 1H. Mass spectrum *m/z* 216 (M, 98% D). These properties and other spectral characteristics were consistent with those found for the non-deuterated analogue (4b).

Methyl (2S)-2-Benzoyloxy-α-isopropylidene-4-oxoazetidine-1-acetate (6b)

Sulfuryl chloride (40 mg, 0·28 mmol) was added to a solution of methyl penicillinate (4b) (60 mg, 0·28 mmol) in carbon tetrachloride (5 ml). After 0·25 h at room temperature the solution was concentrated under reduced pressure to give the chlorosulfonium chloride salt (8) as a yellow oil (^{1}H n.m.r. δ 1·54, s, 3H; 1·66, s, 3H; 3·18, dd, *J* 2, 16 Hz, 1H; 3·67, dd, *J* 4, 16 Hz, 1H; 3·79, s, 3H; 4·23, s, 1H; 5·89, dd, *J* 2, 4 Hz, 1H) which was used without further purification. The oil was dissolved in carbon tetrachloride (5 ml); then benzoic acid (100 mg, 0·81 mmol) and triethylamine (300 mg, 2·97 mmol) were added. The mixture was stirred at

room temperature for 18 h, then it was washed with dilute hydrochloric acid (2×5 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residual oil gave methyl (2*S*)-2-benzoyloxy-α-isopropylidene-4-oxoazetidine-1-acetate (6b) in 27% yield, identical in all respects to the sample obtained as described above.

Acknowledgment

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Complexation of Benzoic, 4-Methylbenzoic, and (*R*)- and (*S*)-2-Phenylpropanoic Acids and Their Conjugate Bases by 3^A-Amino-3^A-deoxy-($2^A S$,$3^A S$)-β-cyclodextrin in Aqueous Solution

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Abstract

A potentiometric titration study of the complexation of benzoic, 4-methylbenzoic, and (*R*)- and (*S*)-2-phenylpropanoic acids and their conjugate bases by 3^A-amino-3^A-deoxy-($2^A S$,$3^A S$)-β-cyclodextrin, βCD3NH$_2$, in which the amino group may be protonated to produce a singly charged species, βCD3NH$_3^+$, is reported. In aqueous solution at 298·2 K and $I = 0{\cdot}10$ mol dm^{-3} (KCl), the complexation constants for the complexes indicated have the values (in dm^3 mol^{-1}) shown in parentheses: benzoic acid.βCD3NH$_3^+$ (K_{HA} = 110±10); benzoate.βCD3NH$_3^+$ (K_A = 19±2); 4-methylbenzoic acid.βCD3NH$_3^+$ (K_{HA} = 210±10); 4-methylbenzoate.βCD3NH$_3^+$ (K_A = 21±3); (*R*)- and (*S*)-2-phenylpropanoic acid.βCD3NH$_3^+$ (K_{RHA} = 64±8, K_{SHA} = 57±5); (*R*)- and (*S*)-2-phenylpropanoate.βCD3NH$_3^+$ (K_{RA} = 51±6, K_{SA} = 32±6); and (*R*)- and (*S*)-2-phenylpropanoate.βCD3NH$_2$ (K_{RA}' = 13±7; K_{SA}' is too small to quantify reliably). These complexation constants are substantially less than those for the host–guest complexes formed by the isomeric 6^A-amino-6^A-deoxy-β-cyclodextrin and also for those formed by β-cyclodextrin. The origins of these differences are discussed.

Introduction

The chiral α-1,4-linked cyclic oligomers of D-glucopyranose, or cyclodextrins, act as hosts in the formation of host–guest complexes with a wide range of guests.[1–10] Such complexation processes are modified by the substitution of

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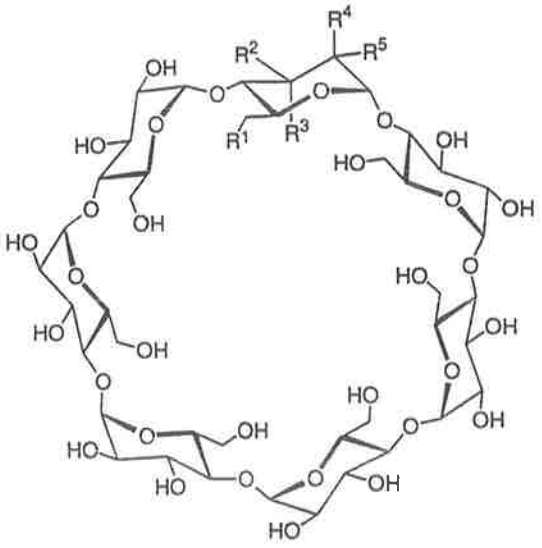
a cyclodextrin hydroxy group by another group, but there are few reported determinations of the stabilities of the host–guest complexes formed by the modified cyclodextrin,[11–15] and none in which the influence of the position of substitution has been systematically studied. Accordingly we have selected 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin, βCD3NH$_2$,[16] in which a C 3 hydroxy group of β-cyclodextrin (βCD) is substituted by an amino group, to compare its complexing properties with those reported for 6^A-amino-6^A-deoxy-β-cyclodextrin, βCD6NH$_2$,[12] in which a C 6 hydroxy group of βCD is replaced by an amino group, and also with those of βCD (Fig. 1). The conjugate acids of βCD6NH$_2$ and βCD3NH$_2$, βCD6NH$_3^+$ and βCD3NH$_3^+$, respectively, provide an opportunity to study the effect of positive charges localized at opposite ends of the βCD annulus on complexation. The guests benzoic acid, 4-methylbenzoic acid, (*R*)- and (*S*)-2-phenylpropanoic acids, and their conjugate bases embody the phenyl moiety usually necessary to confer significant stability in cyclodextrin host–guest complexes, and provide convenient conjugate acid–base pairs to test the effect of varying the guest size and changing the guest charge from neutral to negative on complexation. The chirality of (*R*)- and (*S*)-2-phenylpropanoic acids provides an opportunity to observe any enantioselective complexation.[8–10,12]



	R^1	R^2	R^3	R^4	R^5
βCD	OH	OH	H	H	OH
βCD6NH$_2$	NH$_2$	OH	H	H	OH
βCD3NH$_2$	OH	H	NH$_2$	OH	H

Fig. 1. β-Cyclodextrin (βCD), 6^A-amino-6^A-deoxy-β-cyclodextrin (βCD6NH$_2$) and 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin (βCD3NH$_2$).

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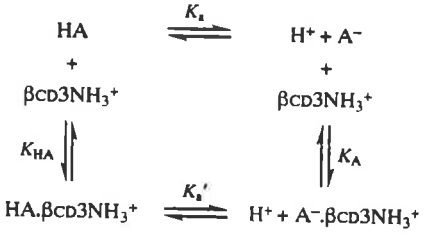
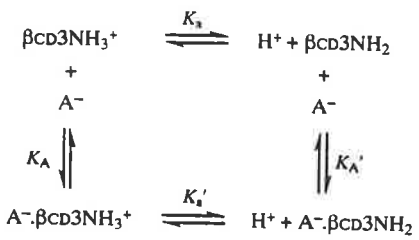
Experimental

βCD3NH$_2$, prepared as in the literature,[16] was dried to constant weight and stored over P_2O_5 in a vacuum desiccator prior to use. The carboxylic acids (Sigma) were used as received. Deionized water was purified with a MilliQ-Reagent system to produce water with a specific resistance of >15 MΩ cm, which was then boiled to render it CO_2-free. All solutions were prepared from this water, and were 0·100 mol dm^{-3} in KCl which acted as the supporting electrolyte. Titrations were performed by using a Metrohm Dosimat E665 Titrimator, an Orion SA 720 potentiometer, and an Orion 8103 Ross combination pH electrode which was filled with 0·100 mol dm^{-3} KCl and calibrated before use with appropriate buffer solutions. Fifteen minutes prior to and during a titration a stream of fine nitrogen bubbles (previously passed through aqueous 0·100 mol dm^{-3} KCl) was passed through the titration solution which was magnetically stirred and thermostatted at 298·2±0·1 K in a water-jacketed titration vessel which was closed to the atmosphere apart from a small exit for nitrogen. A pK_w value was determined by titration of 1·00×10^{-2} mol dm^{-3} HCl (2·0 cm^3) with standardized 5·00×10^{-2} mol dm^{-3} NaOH. The pK_a of βCD3NH$_3^+$ was determined by titration of 2·00×10^{-3} mol dm^{-3} aqueous solutions (2·0 cm^3) with standardized 5·00×10^{-2} mol dm^{-3} NaOH.

To determine the stability constants for the complexation of benzoic, 4-methylbenzoic, and (*R*)- and (*S*)-2-phenylpropanoic acids and their conjugate bases by βCD3NH$_3^+$, the burette contained a solution of 1·44×10^{-2} mol dm^{-3} βCD3NH$_3^+$ at pH 5·0. The pH of each 2·00×10^{-3}–3·00×10^{-3} mol dm^{-3} carboxylic acid solution (2·0 cm^3) in the titration vessel was adjusted to a value within 0·1 pH unit of the pK_a of the carboxylic acid. Up to 3·0 cm^3 of βCD3NH$_3^+$ solution were added to the titration vessel in increments not greater than 0·05 cm^3, and the pH increased by approximately 0·3 pH units in total. To determine the stability constants for the complexation of a guest carboxylate with βCD3NH$_3^+$ and its conjugate base βCD3NH$_2$, the burette contained a solution of 1·00×10^{-2} mol dm^{-3} carboxylate at pH 7·0. The pH of each 2·00×10^{-3} mol dm^{-3} βCD3NH$_2$ solution (2·0 cm^3) in the titration vessel was adjusted to 7·5, a value near the pK_a of βCD3NH$_2$. Up to 3·0 cm^3 of carboxylate solution were added to the titration vessel in increments not greater than 0·05 cm^3, and the pH increased by 0·2–0·4 pH units, depending on the carboxylic acid being studied. At least three similar titrations were performed for each carboxylic acid system studied.



Scheme 1



Scheme 2

Results

The complexation of a carboxylic acid (HA) and its carboxylate (A^-) by βCD3NH$_3^+$ may be expressed as in Scheme 1, where K_a and K_a' are the acid dissociation constants for the carboxylic acid in the free state and in the complex, respectively. The complexation of HA and A^- is characterized by complexation constants K_{HA} and K_A, respectively. In addition to the minor changes accompanying the mixing of the titrants, the variation of the pH of an (*R*)-2-phenylpropanoic acid/(*R*)-2-phenylpropanoate solution in the vicinity of the pK_a of (*R*)-2-phenylpropanoic acid as it is titrated with βCD3NH$_3^+$ solution

(Fig. 2) arises because either $pK_a \neq pK_a'$ or $K_{HA} \neq K_A$ or both inequalities hold. (Analogous inequalities hold for the other titrations discussed herein.) The best fit of the data by expressions for K_{HA}, and K_A, employing the independently determined value of K_a and using program SUPERQUAD,[17] yielded the curve through the data points in Fig. 2 and the constants in Table 1. Similar pH curves were obtained for the titration of benzoic acid/benzoate, 4-methylbenzoic acid/4-methylbenzoate and (*S*)-2-phenylpropanoic acid/(*S*)-2-phenylpropanoate by βCD3NH_3^+, and the data were similarly fitted. The constants derived for these systems also appear in Table 1.

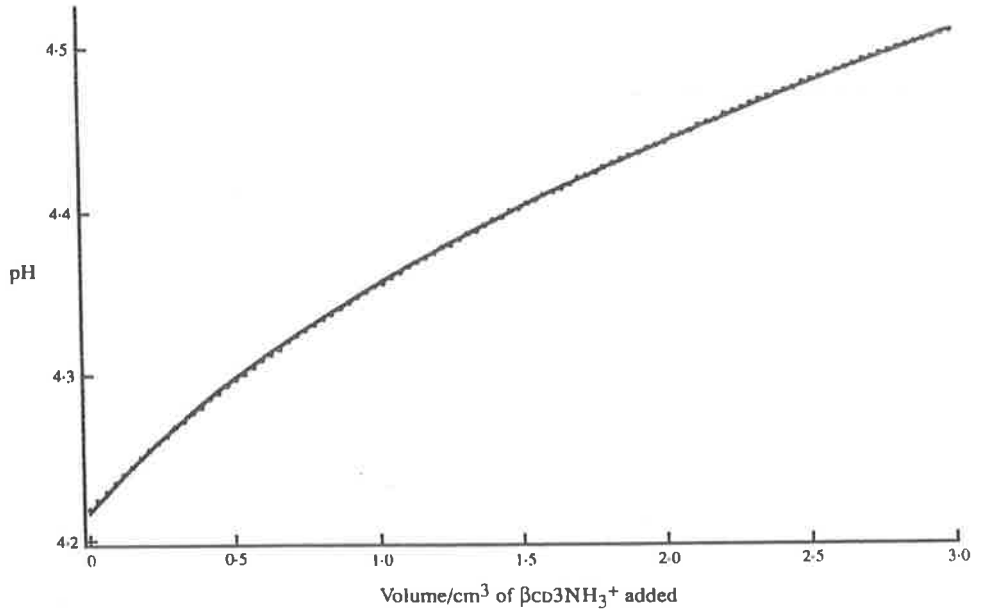


Fig. 2. Variation of the pH of a solution (2·0 cm^3) of (*R*)-2-phenylpropanoic acid/phenylpropanoate ($2{\cdot}00\times10^{-3}$ mol dm^{-3}) with volume of added βCD3NH_3^+ ($1{\cdot}44\times10^{-2}$ mol dm^{-3}) at 298·2 K and $I = 0{\cdot}10$ (KCl). The curve through the data points represents the best fit of the data by the expression for the equilibria shown in Scheme 1 according to program SUPERQUAD.

The complexation of a guest carboxylate (A^-) by βCD3NH_3^+ and its conjugate base, βCD3NH_2, may be expressed as in Scheme 2, where K_a is the acid dissociation constant of βCD3NH_3^+, K_A and K_A' are the stability constants for the complexation of A^- by βCD3NH_3^+ and βCD3NH_2, respectively, and K_a' characterizes βCD3NH_3^+ in the A^-.βCD3NH_3^+ complex.

The increase in pH of solutions of βCD3NH_3^+/βCD3NH_2 in the vicinity of the pK_a of βCD3NH_3^+ as they were titrated within the pH range 7·2–7·8 with solutions of any one of the four carboxylates varied in the range 0·2–0·4 pH units. The best fit of these data by expressions for K_A and K_A',

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employing the independently determined value of K_a, yielded the pK_a' value for βCD3NH$_3^+$ and the K_A and K_A' values, which appear in Table 1, for the complexation of benzoate, 4-methylbenzoate, and (*R*)- and (*S*)-2-phenylpropanoate by βCD3NH$_3^+$ and βCD3NH$_2$. The only βCD3NH$_2$ complex detected was (*R*)-2-phenylpropanoate.βCD3NH$_2$. Speciation plots showing the variation of species concentration with pH may be calculated from the data in Table 1 as is illustrated in Fig. 3 for the βCD3NH$_2$/βCD3NH$_3^+$/(*R*)-2-phenylpropanoic acid/phenylpropanoate system.

The formation of benzoic acid.(βCD3NH$_3^+$)$_2$ as shown in equation (1), and for which $K = 29\pm3$ dm^3 mol^{-1}, was also observed. Complexes of this stoichiometry

Table 1. K, pK_a and pK_a' values for cyclodextrin host–guest complexes, cyclodextrins and guest species at $I = 0{\cdot}10$ (KCl) and 298·2 K

Species	K_{HA} [A] / dm^3 mol^{-1}	K_A and K_A' [A] / dm^3 mol^{-1}	pK_a [B]	pK_a' [C]
Benzoic acid [D]			4·06±0·04	
Benzoic acid.βCD [D]	590±60			5·1±0·1
Benzoate.βCD [D]		60±10		
βCD6NH$_3^+$ [D]			8·49±0·01	
Benzoic acid.βCD6NH$_3^+$ [D]	340±30			4·5±0·1
Benzoate.βCD6NH$_3^+$ [D]		120±20		8·9±0·2
Benzoate.βCD6NH$_2$ [D]		50±20		
βCD3NH$_3^+$ [E]			7·50±0·03	
Benzoic acid.βCD3NH$_3^+$ [E]	110±10			4·8±0·1
Benzoate.βCD3NH$_3^+$ [E]		19±2		
Benzoate.βCD3NH$_2$ [E]		[F]		
4-Methylbenzoic acid [D]			4·20±0·08	
4-Methylbenzoic acid.βCD [D]	1680±90			5·39±0·09
4-Methylbenzoate.βCD [D]		110±1		
4-Methylbenzoic acid.βCD6NH$_3^+$ [D]	910±20			4·6±0·1
4-Methylbenzoate.βCD6NH$_3^+$ [D]		330±20		9·0±0·1
4-Methylbenzoate.βCD6NH$_2$ [D]		100±20		
4-Methylbenzoic acid.βCD3NH$_3^+$ [E]	210±10			
4-Methylbenzoate.βCD3NH$_3^+$ [E]		21±3		
4-Methylbenzoate.βCD3NH$_2$ [E]		[F]		
(*R*)-2-Phenylpropanoic acid [D]			4·23±0·05	
(*R*)-2-Phenylpropanoic acid.βCD [D]	1090±30			5·47±0·08
(*R*)-2-Phenylpropanoate.βCD [D]		63±8		
(*R*)-2-Phenylpropanoic acid.βCD6NH$_3^+$ [D]	580±20			4·82±0·06
(*R*)-2-Phenylpropanoate.βCD6NH$_3^+$ [D]		150±8		9·11±0·08
(*R*)-2-Phenylpropanoate.βCD6NH$_2$ [D]		36±6		
(*R*)-2-Phenylpropanoic acid.βCD3NH$_3^+$ [E]	64±8			
(*R*)-2-Phenylpropanoate.βCD3NH$_3^+$ [E]		51±6		8·09±0·09
(*R*)-2-Phenylpropanoate.βCD3NH$_2$ [E]		13±7		
(*S*)-2-Phenylpropanoic acid [D]			4·23±0·05	
(*S*)-2-Phenylpropanoic acid.βCD [D]	1010±40			5·52±0·07
(*S*)-2-Phenylpropanoate.βCD [D]		52±5		
(*S*)-2-Phenylpropanoic acid.βCD6NH$_3^+$ [D]	480±10			4·87±0·07
(*S*)-2-Phenylpropanoate.βCD6NH$_3^+$ [D]		110±10		9·4±0·4
(*S*)-2-Phenylpropanoate.βCD6NH$_2$ [D]		13±7		
(*S*)-2-Phenylpropanoic acid.βCD3NH$_3^+$ [E]	57±5			4·48±0·08
(*S*)-2-Phenylpropanoate.βCD3NH$_3^+$ [E]		32±6		
(*S*)-2-Phenylpropanoate.βCD3NH$_2$ [E]		[F]		

[A] Errors for either K_{HA}, or K_A or $K_A' = K$ (the mean of N runs) represent the standard deviation. $\sigma = \sqrt{((\Sigma(K_i - K)^2)/(N-1))}$ where K_i is a value from a single run for the best fit of the variation of pH with added volume of cyclodextrin or carboxylic acid/carboxylate titrant obtained through SUPERQUAD, and $i = 1, 2, \ldots, N$.

[B] Errors quoted for pK_a are similarly calculated for the best fit of the variation of pH with added volume of NaOH titrant obtained through SUPERQUAD.

[C] Errors quoted for pK_a' represent those calculated from the propagation of errors associated with pK_a and K.

[D] Ref. 12.

[E] This work.

[F] Not detected.

were not detected in the other systems studied here, but this stoichiometry has been reported for some carboxylic acid/αCD complexes.[3]

$$\text{benzoic acid.}\beta\text{CD3NH}_3^+ + \beta\text{CD3NH}_3^+ \overset{K}{\rightleftharpoons} \text{benzoic acid.}(\beta\text{CD3NH}_3^+)_2 \quad (1)$$

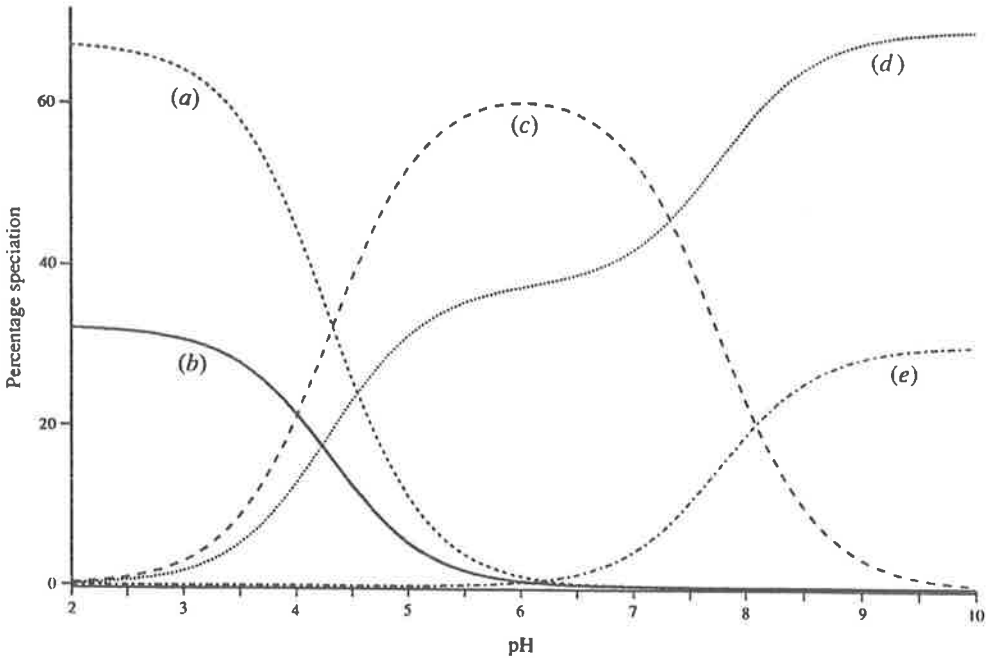

Fig. 3. Speciation plot for the βCD3NH$_2$/βCD3NH$_3^+$/(*R*)-2-phenylpropanoic acid/phenylpropanoate system calculated from pK_a, K_{SHA}, K_{SA} and K_{SA}' (Table 1). The total concentration of (*R*)-2-phenylpropanoic acid/phenylpropanoate is $2{\cdot}00\times10^{-3}$ mol dm^{-3} and the total concentration of βCD3NH$_2$/βCD3NH$_3^+$ is $1{\cdot}44\times10^{-2}$ mol dm^{-3}. The total concentration of (*R*)-2-phenylpropanoic acid/phenylpropanoate is defined as 100% and the free βCDNH$_2$/βCDNH$_3^+$ concentration is not shown. The curves represent: (*a*) (*R*)-2-phenylpropanoic acid.βCD3NH$_3^+$; (*b*) (*R*)-2-phenylpropanoic acid; (*c*) (*R*)-2-phenylpropanoate.βCD3NH$_3^+$; (*d*) (*R*)-2-phenylpropanoate; (*e*) (*R*)-2-phenylpropanoate.βCD3NH$_2$.

Discussion

The formation of a cyclodextrin complex involves varying intensities of van der Waals, dipolar, hydrogen-bonding and solvent interactions, depending on the nature of the cyclodextrin and the guest.[1,2,18] Solid-state X-ray structural studies of cyclodextrin complexes usually show the aromatic moiety of the guest to be in the cyclodextrin annulus in the vicinity of the hydrophobic ring delineated by the ether oxygens,[19–22] with the dipole moment of the guest aligned antiparallel

[18] Gelb, R. I., Schwartz, L. M.. Cardelino, B.. Fuhrman, H. S., Johnson, R. F., and Laufer, D. A., *J. Am. Chem. Soc.*, 1981, **103**, 1750.
[19] Harata, K., *Bull. Chem. Soc. Jpn*, 1975, **48**, 2409.
[20] Harata, K., *Bull. Chem. Soc. Jpn*, 1976, **49**, 1493.
[21] Harata, K., *Bull. Chem. Soc. Jpn*, 1976, **49**, 2066.
[22] Harata, K., *Bull. Chem. Soc. Jpn*, 1977, **50**, 1416.

to that of the cyclodextrin,[23–25] and similar structures are assumed in solution. The cyclodextrin dipole moment is in the range 10–20 D,* with the positive and negative poles adjacent to the primary and secondary hydroxy groups delineating the narrow and wide ends of the cyclodextrin annulus, respectively.[23–25] It has been observed that the carboxylic acid group of 4-hydroxybenzoic acid is in the vicinity of the primary hydroxy groups of αCD (α-cyclodextrin) in the 4-hydroxybenzoic acid.αCD complex consistent with an antiparallel alignment of the αCD and 4-hydroxybenzoic acid dipole moments.[22] A similar influence of the host and guest dipoles on structure is assumed for the complexes appearing in Table 1.

The magnitude of the cyclodextrin complexation constant reflects the competitive abilities of the cyclodextrin to complex the guest species and water to solvate it, and accordingly the data in Table 1 reflect the changes in these abilities as the natures of both the host cyclodextrin and the guest species are varied. Several major trends emerge from the data in Table 1.

(A) The substitution of a βCD C3 hydroxy group by an amino group generally decreases the stability of the complex. Thus, for the complexation of the same carboxylic acid K_{HA} is lower for βCD3NH_3^+ than for βCD6NH_3^+ and βCD. For the complexation of the same carboxylate K_A is lower for βCD3NH_3^+ than for βCD6NH_3^+ and βCD, and for the complexation of the same carboxylate K_A' is lower for βCD3NH_2 than βCD6NH_2. This is probably a consequence of the inversion of stereochemistry at C2 and C3 which occurs during the synthesis[16] of βCD3NH_2 and causes the $-NH_3^+$ and $-NH_2$ groups to project into the βCD3NH_3^+ and βCD3NH_2 annuli. This decreases the annular hydrophobicity and size by comparison with those of the other cyclodextrins and thereby decreases the effectiveness of βCD3NH_3^+ and βCD3NH_2 as hosts. The $-NH_3^+$ group on C3 diminishes, and possibly reverses, the direction of the βCD3NH_3^+ dipole by comparison with those of βCD6NH_3^+, βCD6NH_2 and βCD, so that the orientation of the guests in the βCD3NH_3^+ complexes may also reverse. Such a difference in guest orientation may be a factor in the low K_{HA} values observed for the βCD3NH_3^+ complexes. The carboxylic acid complexes are of higher stability than their carboxylate analogues consistent with the negatively charged carboxylates being more strongly hydrated. The relative stabilities $A^-.\beta$CD3$NH_2 < A^-.\beta$CD3NH_3^+ and $< A^-.\beta$CD6$NH_2 < A^-.\beta$CD6NH_3^+ are attributable to the stabilizing attraction between the positive and negative charges of the host and guest, respectively.

Another effect of the inversion at C2 and C3 is that the $-NH_3^+$ group is less strongly hydrated in the hydrophobic interior of the βCD3NH_3^+ annulus by comparison with the $-NH_3^+$ group of βCD6NH_3^+ which does not project into the annulus. As a consequence βCD3NH_2 is more stabilized relative to its conjugate acid than is the case for βCD6NH_2 so that the pK_a of βCD3NH_3^+ is lower than that of βCD6NH_3^+.

* 1 D = $3{\cdot}33564\times10^{-30}$ C m.

[23] Kitagawa, M., Hoshi, H., Sakurai, M., Inoue, Y., and Chûjô, R., *Carbohydr. Res.*, 1987, **163**, c1.
[24] Sakurai, M., Kitagawa, M., Hoshi, H., Inoue, Y., and Chûjô, R., *Chem. Lett.*, 1988, 895.
[25] Sakurai, M., Kitagawa, M., Hoshi, H., Inoue, Y., and Chûjô, R., *Carbohydr. Res.*, 1990, **198**, 181.

(B) The magnitude of K_{HA} increases with guest in the sequence (*S*)-2-phenylpropanoic acid ≈ (*R*)-2-phenylpropanoic acid < benzoic acid < 4-methylbenzoic acid for the complexes of βCD3NH_3^+, and benzoic acid < (*S*)-2-phenylpropanoic acid ≈ (*R*)-2-phenylpropanoic acid < 4-methylbenzoic acid for βCD6NH_3^+ and βCD. Within each series of complexes, K_{HA} only varies by a factor of approximately 3. Thus, the three cyclodextrins show only minor selectivity in complexation probably because their annular sizes are sufficient to encapsulate substantially the carboxylic acid guests. However, for each guest K_{HA} increases with cyclodextrin in the sequence βCD3NH_3^+ < βCD6NH_3^+ < βCD with corresponding variations of K_{HA} of approximately 17, 8 and 5 for the (*R*)- and (*S*)-2-phenylpropanoic, 4-methylbenzoic and benzoic acids series of complexes, respectively. Thus, the (*R*)- and (*S*)-2-phenylpropanoic acids are more sensitive to the nature of the cyclodextrin than are the 4-methylbenzoic acids. Unlike benzoic acid and 4-methylbenzoic acid, the (*R*)- and (*S*)-2-phenylpropanoic acids are not flat, and this may cause the stabilities of their complexes to be more dependent on cyclodextrin annular geometry.

The relatively high K_{HA} magnitudes characterizing the 4-methylbenzoic acid complexes, compared with those of benzoic acid, are attributable to the increased hydrophobicity caused by the methyl group and the resulting greater interaction with the hydrophobic region of the cyclodextrin annuli. The (*R*)- and (*S*)-2-phenylpropanoic acids are also more hydrophobic than benzoic acid, but they do not exhibit an enhanced stability in their complexes; this reinforces the argument that the geometry of the host–guest interactions assumes a greater importance in their cases.

(C) While no enantioselectivity between (*R*)- and (*S*)-2-phenylpropanoic acid is exhibited by βCD3NH_3^+, a small enantioselectivity in favour of (*R*)-2-phenylpropanoate over the (*S*)-enantiomer is observed. Similarly, βCD6NH_3^+ favours (*R*)-2-phenylpropanoic acid and (*R*)-2-phenylpropanoate over the (*S*)-enantiomers, and βCD6NH_2 favours (*R*)-2-phenylpropanoic acid. A small enantioselectivity for (*R*)-2-phenylpropanoic acid is also observed for the βCD complex. This infers similar chiral interactions in the βCD3NH_3^+, βCD6NH_3^+, βCD6NH_2 and βCD complexes.

(D) For the guest carboxylic acids and for βCD3NH_3^+, $pK_a < pK_a'$; this indicates that in the complex the conjugate base is destabilized relative to the conjugate acid, by comparison with the case in the free state. The charged and more strongly hydrated carboxylate is likely to experience a greater decrease of hydration in the partially hydrophobic βCD3NH_3^+ annulus than is the carboxylic acid, with a consequent destabilization of the carboxylate by comparison with the carboxylic acid.

The decreased acidity of complexed βCD3NH_3^+, by comparison with that of βCD3NH_3^+ alone, may result from a partially hydrophobic guest disrupting the interactions between the $-NH_3^+$ substituent and adjacent hydroxy residues and ether linkages which probably confer its rather low pK_a value in the uncomplexed state.[13] Similar arguments apply to the βCD6NH_3^+/βCD6NH_2 system.

Acknowledgments

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Cyclodextrin and Termethylated Cyclodextrin Complexation of Aromatic Carboxylic Acids and their Conjugate Bases in Aqueous Solution. The Effect of Size, Hydrophobicity and Charge

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Abstract

For α-cyclodextrin (αCD), the complexation constants (K) for the formation of binary host–guest complexes (HA.αCD) are 750±60, 1070±60, 27±3 and 17±4 $dm^3\ mol^{-1}$ when the guests (HA) are benzoic, 4-methylbenzoic and (*R*)- and (*S*)-2-phenylpropanoic acids, respectively, as determined by potentiometric titration in aqueous solution at 298·2 K and $I = 0{\cdot}10\ mol\ dm^{-3}$ (KCl). For the analogous hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin complexes (HA.TMαCD), K = 1580±150, 2890±130, 220±10 and 207±8 $dm^3\ mol^{-1}$, and for the heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin complexes (HA.TMβCD), K = 200±20, 340±30, 129±5 and 170±10 $dm^3\ mol^{-1}$. The binary complexes formed by the corresponding carboxylates (A^-) are much less stable. Ternary host–guest α-cyclodextrin complexes (HA.αCD$_2$) are also formed. These data, together with literature data for β-cyclodextrin, are discussed in terms of the factors influencing complexation.

Introduction

Variations in the size and hydrophobicity of the annuli of the chiral α-1,4-linked cyclic oligomers of D-glucopyranose, or cyclodextrins, and their termethylated analogues (Fig. 1) affect the abilities of these molecules to act as hosts in the formation of host–guest complexes.[1–5] The wide and narrow ends of a cyclodextrin annulus are delineated by a ring of hydrophilic C2 and C3 secondary hydroxy groups and a ring of hydrophilic C6 primary hydroxy groups, respectively, and the interior of the annulus, composed of methylene, methine and ether groups, is hydrophobic. Substitution of all of the hydroxy groups by methoxy groups causes the resulting termethylated cyclodextrin to be completely hydrophobic, to be of increased annular size and to be of more flexible structure through the absence of the inter-hydroxy group hydrogen bonding present in the precursor cyclodextrin. However, there have been few systematic comparisons of the complexation characteristics of cyclodextrins and their termethylated analogues reported, and accordingly such a study of the formation of host–guest complexes

[1] Saenger, W., *Incl. Comp.*, 1984, **2**, 231.
[2] Clarke, R. J., Coates, J. H., and Lincoln, S. F., *Adv. Carbohydr. Chem. Biochem.*, 1989, **46**, 205.
[3] Duchêne, D., 'New Trends in Cyclodextrins and Derivatives' (Editions de Santé: Paris 1991).
[4] Harata, K., *Incl. Comp.*, 1991, **5**, 311.
[5] Brown, S. E., Easton, C. J., and Lincoln, S. F., *J. Chem. Res. (S)*, 1995, 2.

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by α-cyclodextrin (αCD), D-hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMαCD) and D-heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMβCD) has been undertaken.

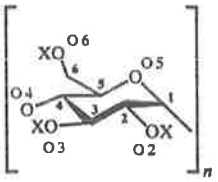


Fig. 1. Cyclodextrin structures: for αCD, $n = 6$, X = H; for TMαCD, $n = 6$, X = CH_3; for βCD, $n = 7$, X = H; and for TMβCD, $n = 7$, X = CH_3.

The guests, benzoic, 4-methylbenzoic and (*R*)- and (*S*)-2-phenylpropanoic acids and their conjugate bases, were selected for study because they embody the phenyl moiety usually necessary to confer significant stability in CD complexes, provide a convenient variation in size to test its effect on complexation and present an opportunity to observe the effect on complexation of changing the guest charge from neutral to negative. In addition, (*R*)- and (*S*)-2-phenylpropanoic acids provide an opportunity to observe any enantioselective complexation.[6–9] The data derived from this study are compared with those from an earlier study of β-cyclodextrin (βCD) complexation in an assessment of the factors controlling complexation.[9]

Experimental

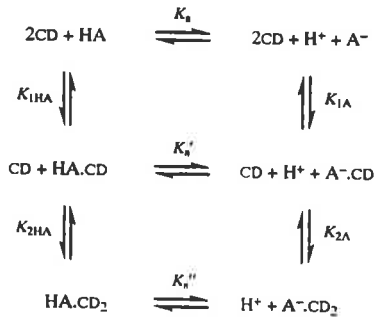
αCD (Sigma), TMαCD and TMβCD (Cyclolab) were dried to constant weight and stored over P_2O_5 in a vacuum desiccator prior to use. The carboxylic acids (Sigma) were used as received. Deionized water was purified with a MilliQ-Reagent system to produce water with a specific resistance of >15 MΩ cm, which was then boiled to render it CO_2-free. All solutions were prepared from this water, and were 0·10 mol dm^{-3} in KCl supporting electrolyte. Titrations were performed by using a Metrohm Dosimat E665 titrimeter, an Orion SA 720 potentiometer, and an Orion 8115 Ross combination pH electrode which was filled with 0·10 mol dm^{-3} KCl and calibrated before use with appropriate buffer solutions. Fifteen minutes prior to and during a titration, a stream of fine nitrogen bubbles (previously passed through aqueous 0·10 mol dm^{-3} KCl) was passed through the magnetically stirred titration solution thermostatted at 298·2±0·1 K in a water-jacketted titration vessel which was closed to the atmosphere apart from a small exit to allow passage of the nitrogen stream. A pK_w value was determined by titration of 5·00×10^{-3} mol dm^{-3} HCl (10·0 cm^3) with standardised 5·00×10^{-2} mol dm^{-3} NaOH.

To determine the stability constants for the complexation of benzoic, 4-methylbenzoic and (*R*)- and (*S*)-2-phenylpropanoic acids and their conjugate bases by αCD, TMαCD and TMβCD, the burette contained a 1·50×10^{-2} mol dm^{-3} solution of the chosen cyclodextrin (CD) at pH 7·0. The pH of each carboxylic acid solution (2·0 cm^3) in the concentration range 2·00×10^{-3}–2·13×10^{-3} mol dm^{-3} in the titration vessel was adjusted to a value within 0·2 pH unit of the pK_a of the carboxylic acid. Up to 3·0 cm^3 of CD solution were added to the titration vessel in increments not greater than 0·05 cm^3, and the pH increased by 0·45–1·12, 0·61–1·32 and 0·17–0·55 pH units in total for the benzoic acid/benzoate, 4-methylbenzoic acid/4-methylbenzoate and (*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate systems, respectively, depending on the CD titrated. Titrations were performed in triplicate for each system.

[6] Greatbanks, D., and Pickford, R., *Magn. Reson. Chem.*, 1987, **25**, 208.
[7] Smith, N. J., Spotswood, T. M., and Lincoln, S. F., *Carbohydr. Res.*, 1989, **192**, 9.
[8] Brown, S. E., Coates, J. H., Lincoln, S. F., Coghlan, D. R., and Easton, C. J., *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 2699.
[9] Brown, S. E., Coates, J. H., Duckworth, P. A., Lincoln, S. F., Easton, C. J., and May, B. L., *J. Chem. Soc., Faraday Trans.*, 1993, **89**, 1035.

Results

The formation of a binary complex between either a carboxylic acid (HA) or its carboxylate (A^-) by a cyclodextrin (CD) may be expressed as in Scheme 1, where K_a and K_a' are the acid dissociation constants for the carboxylic acid in the free state and in the complex, and K_{1HA} and K_{1A} are complexation constants. Depending on the nature of HA, A^- and CD, a second CD may complex either HA or A^- to form ternary complexes, HA.CD_2 and A^-.CD_2, which are characterized by complexation constants K_{2HA} and K_{2A} and pK_a''. When either $pK_a \neq pK_a' \neq pK_a''$ or $K_{1HA} \neq K_{1A}$ and $K_{2HA} \neq K_{2A}$, the formation of binary and ternary complexes produces a change in the pH of a carboxylic acid solution whose initial pH is in the vicinity of its pK_a when it is titrated with a CD solution. (This is in addition to, and much greater than, the minor pH changes arising from the mixing of the titrant solutions alone.) All of the complexes shown in Scheme 1 need not exist in the detectable amounts, but this scheme conveniently shows the equilibria considered and tested for by fitting the titration data to expressions for K_{1HA}, K_{1A}, K_{2HA}, K_{2A} and the independently determined value of pK_a by using the program SUPERQUAD.[10]



Scheme 1

The variation of the pH of (*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate solutions in the vicinity of the acid pK_a as they were titrated with TMβCD solution is shown in Fig. 2. The difference between these two pH variations indicates differing interactions in the diastereomeric (*R*)- and (*S*)-2-phenylpropanoic acid.TMβCD complexes which the best fit of these data, through SUPERQUAD, showed to be the only complexes in solution in significant amounts. The derived K_{R1HA} and K_{S1HA} values for the diastereomers appear in Table 1, and a speciation plot showing the effect of enantioselectivity on species concentration is shown in Fig. 3. Similar pH curves were obtained for the titration of benzoic acid/benzoate and 4-methylbenzoic acid/4-methylbenzoate, and the data were similarly fitted to derive the constants which also appear in Table 1.

Analogous titrations were carried out with αCD and TMαCD, and the resulting data yielded the constants in Table 1. A speciation plot for the αCD/4-methylbenzoic acid/4-methylbenzoate system showing the occurrence of the 4-methylbenzoic acid.αCD_2 ternary complex appears in Fig. 4. Our K_{1HA} values for benzoic acid.αCD and 4-methylbenzoic acid.αCD are close to literature values (Table 1) obtained at $I = 0{\cdot}10$ mol dm^{-3} (NaCl) and 298·2 K.[11]

[10] Gans, P., Sabatini, A., and Vacca, A., *J. Chem. Soc., Dalton Trans.*, 1985, 1195.
[11] Connors, K. A., Lin, S.-H., and Wong, A. B., *J. Pharm. Sci.*, 1982, **71**, 217.

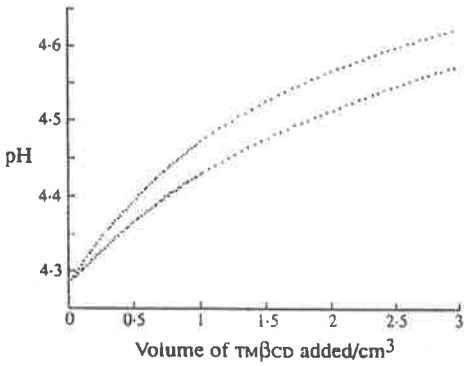


Fig. 2. Variation of the pH of solutions ($2{\cdot}0\ cm^3$, $2{\cdot}00\times10^{-3}$ mol dm^{-3}) of (*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate (lower and upper data sets, respectively) with volume of added TMβCD ($1{\cdot}50\times10^{-2}$ mol dm^{-3}) at 298·2 K and $I = 0{\cdot}10\ dm^3\ mol^{-1}$ (KCl).

Table 1. K_{1HA}, K_{1A}, K_{2HA} and pK_a' values for host–guest complexes at $I = 0{\cdot}10$ (KCl) and 298·2 K

Host CD	Guest acid	K_{1HA}[A]/ $dm^3\ mol^{-1}$	K_{1A}[A]/ $dm^3\ mol^{-1}$	K_{2HA}[A]/ $dm^3\ mol^{-1}$	pK_a'[B]
αCD	benzoic	750±60		9±2	
	$pK_a = 4{\cdot}06\pm0{\cdot}04$[C]	722[D]			
αCD	4-methylbenzoic	1070±60		16±8	
	$pK_a = 4{\cdot}20\pm0{\cdot}08$[C]	1091[D]			
αCD	(*R*)-2-phenylpropanoic	27±3		60±20	
	$pK_a = 4{\cdot}23\pm0{\cdot}05$[C]				
αCD	(*S*)-2-phenylpropanoic	17±4		130±50	
	$pK_a = 4{\cdot}23\pm0{\cdot}05$[C]				
βCD[C]	benzoic	590±60	60±10		5·1±0·1
βCD[C]	4-methylbenzoic	1680±90	110±1		5·39±0·09
βCD[C]	(*R*)-2-phenylpropanoic	1090±30	63±8		5·47±0·08
βCD[C]	(*S*)-2-phenylpropanoic	1010±40	52±5		5·52±0·07
TMαCD	benzoic	1580±150	8·0±0·7		6·35±0·02
TMαCD	4-methylbenzoic	2890±130	38±3		6·10±0·03
TMαCD	(*R*)-2-phenylpropanoic	220±10			
TMαCD	(*S*)-2-phenylpropanoic	207±8			
TMβCD	benzoic	200±20			
TMβCD	4-methylbenzoic	340±30			
TMβCD	(*R*)-2-phenylpropanoic	129±5			
TMβCD	(*S*)-2-phenylpropanoic	170±10			

[A] Errors quoted for either K_{1HA}, K_{1A} or $K_{2HA} \equiv K$ (the mean of N runs) represent the standard deviation, $\sigma = \sqrt{((\Sigma(K_i - K)^2)/(N-1))}$ where K_i is a value from a single run for the best fit of the variation of pH with added volume of cyclodextrin or carboxylic acid/carboxylate titrant obtained through SUPERQUAD, and $i = 1,2,\ldots,N$.
[B] Errors quoted for pK_a' represent those calculated from the propagation of errors associated with pK_a and K.
[C] Ref. 9.
[D] Ref. 11. $I = 0{\cdot}10$ mol dm^{-3} (NaCl) and 298·2 K.

Discussion

The differences in annular dimensions and extent of hydrophobicity between the cyclodextrins are important in interpreting the complexation data in Table 1 and are conveniently estimated from Corey–Pauling–Koltun (CPK) models.[12] Thus, the diameters of the rings of C5 and C3 hydrogens defining the hydrophobic

[12] Koltun, W. L., *Biopolymers*, 1965, **3**, 665.

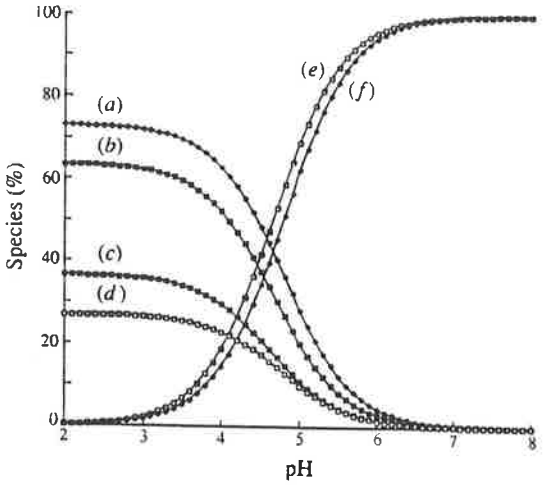


Fig. 3. Speciation plot for the TMβCD/(*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate system calculated from K_{R1HA}, K_{S1HA} and pK_a data in Table 1. The total concentrations of (*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate are both $1{\cdot}00\times10^{-3}$ mol dm^{-3}, and in each case the total concentration of TMβCD is $7{\cdot}50\times10^{-3}$ mol dm^{-3}. The total concentration of (*R*)- and (*S*)-2-phenylpropanoic acid/(*R*)- and (*S*)-2-phenylpropanoate is defined as 100% in each case, and the free TMβCD concentration is not shown. Curves (*a*) and (*b*) represent (*S*)- and (*R*)-2-phenylpropanoic acid.TMβCD, respectively. Curves (*c*) and (*d*) represent (*R*)- and (*S*)-2-phenylpropanoic acid, respectively, and curves (*e*) and (*f*) represent (*R*)- and (*S*)-2-phenylpropanoate, respectively.

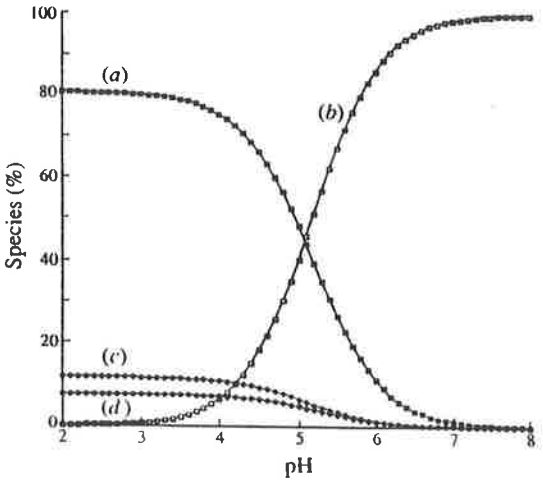


Fig. 4. Speciation plot for the αCD/4-methylbenzoic acid/4-methylbenzoate system calculated from K_{1HA}, K_{2HA} and pK_a data in Table 1. The total concentration of 4-methylbenzoic acid/4-methylbenzoate is $1{\cdot}00\times10^{-3}$ mol dm^{-3} and the total concentration of αCD is $7{\cdot}50\times10^{-3}$ mol dm^{-3}. The total concentration of 4-methylbenzoic acid/4-methylbenzoate is defined as 100% in each case, and the free αCD concentration is not shown. Curves (*a*)–(*d*) represent 4-methylbenzoic acid.αCD, 4-methylbenzoate, 4-methylbenzoic acid and 4-methylbenzoic acid.αCD$_2$, respectively.

regions of the αCD and βCD annuli are approximately 470 and 520 pm, and 600 and 640 pm, respectively, and the depth delineated by them is 530–540 pm. The distance between the hydrogens of the primary and secondary hydroxy groups is 790–800 pm and defines the overall depths of the αCD and βCD annuli. The annuli of TMαCD and TMβCD are approximately 320 and 720, and 400 and 1000 pm in diameter at their narrow and wide ends, respectively, and both are 1000–1040 pm deep, as delineated by the rings of methyl hydrogens.

The stability of a CD complex is dependent to varying extents on van der Waals, dipolar and hydrogen-bonding interactions between the CD and guest, and also on changes in hydration which accompany the complexation process.[1–3,13] Solid-state X-ray structural studies of αCD and βCD complexes show the aromatic moiety of the guest to be in the annulus in the vicinity of the hydrophobic ring delineated by the ether oxygens,[4,14] with the dipole moment of the guest aligned antiparallel to that of the CD, and similar structures are assumed in solution. The αCD dipole moment is in the range 10–20 D* with the positive and negative poles adjacent to the primary and secondary hydroxy groups delineating the narrow and wide annular ends, respectively.[15–17] Thus, the carboxylic acid group is in the vicinity of the αCD primary hydroxy groups in the 4-hydroxybenzoic acid.αCD complex in the solid state consistent with an antiparallel alignment of the αCD and 4-hydroxybenzoic acid dipole moments.[14] A similar dipolar influence on structure is assumed in solution for the αCD and βCD complexes appearing in Table 1. The orientation of guests in TMαCD complexes in the solid state is sometimes reversed by comparison with those in αCD complexes.[4]

The magnitude of the CD complexation constant reflects the competitive abilities of the CD to complex the guest species and of water to hydrate it, and the data in Table 1 reflect the changes in these abilities as the natures of the CD and the guest species are varied. Several trends are seen.

(A) For the αCD, TMαCD, βCD and TMβCD complexes, stability (K_{1HA}) varies with the carboxylic acid by approximately 50-, 14-, 3- and 3-fold,† respectively, consistent with strong, moderate and weak discrimination between the carboxylic acids. This coincides with the carboxylic acids being only partially encapsulated by αCD (as shown by CPK models) and complex stability being more sensitive to changes in the size, hydrophobicity and hydration of the carboxylic acid as a consequence. A lesser sensitivity to these factors is exhibited by the βCD complexes in which the increased annular size results in an increasing degree of carboxylic acid encapsulation. A similar relationship exists between the TMαCD and TMβCD complexes, and it appears that in the latter case annular size has

* $1\ D = 3{\cdot}33564\times10^{-30}$ C m.

† For example, in the case of TMβCD, the K_{1HA} increases approximately threefold, from 129±5 $dm^3\ mol^{-1}$ for (*R*)-2-phenyhlpropanoic acid to 340±30 $dm^3\ mol^{-1}$ for 4-methylbenzoic acid.

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increased to the point at which the fit of the carboxylic acid has become quite loose and K_{1HA} decreases as a consequence.

The lower stabilities of the carboxylate complexes are consistent with the carboxylate negative charge causing a stronger hydration than is the case for the carboxylic acid so that water competes more effectively with the CD for the carboxylate.

(B) For all four cyclodextrins, K_{1HA} is largest for the 4-methylbenzoic complex and increases with CD in the sequence TMβCD < αCD < βCD < TMαCD. The sequence is TMβCD < βCD < αCD < TMαCD for benzoic acid and αCD < TMβCD < TMαCD < βCD for (*R*)- and (*S*)-2-phenylpropanoic acid. For benzoic, 4-methylbenzoic and (*R*)- and (*S*)-2-phenylpropanoic acids, K_{1HA} varies by approximately 8-, 9- and 50-fold, respectively, consistent with the complexation of (*R*)- and (*S*)-2-phenylpropanoic acid being more sensitive to CD interactions than are the other carboxylic acids. Unlike benzoic and 4-methylbenzoic acids, (*R*)- and (*S*)-2-phenylpropanoic acid are not flat and their carboxylic acid groups are one carbon removed from the phenyl ring. Thus, the phenyl moiety projects a considerable distance from the annulus when the carboxylic acid group is in the vicinity of the αCD primary hydroxy groups in an orientation in which the αCD and carboxylic acid dipoles are antiparallel. This decreases the interaction between the phenyl moiety and the hydrophobic annular interior to a greater extent than is the case in the more stable βCD complex in which the greater annular size better accommodates (*R*)- and (*S*)-2-phenylpropanoic acid. The intermediate stabilities of the TMαCD and TMβCD complexes indicate that their greater annular size, by comparison with that of αCD, also increases stability. However, the greater K_{1HA} values of the βCD complexes are consistent with the interactions with the primary hydroxy groups in βCD further stabilizing its complexes with (*R*)- and (*S*)-2-phenylpropanoic acid.

For αCD, TMαCD and TMβCD, K_{1HA} increases in the sequence (*R*)- and (*S*)-2-phenylpropanoic acid < benzoic acid < 4-methylbenzoic acid, while for βCD the sequence is benzoic acid < (*R*)- and (*S*)-2-phenylpropanoic acid < 4-methylbenzoic acid. The higher stabilities of the 4-methylbenzoic acid complexes are attributable to the methyl group increasing guest hydrophobicity and tendency to bind in the hydrophobic CD annuli, without distancing the carboxylic acid group from the phenyl moiety and generating the destabilizing effect observed for (*R*)- and (*S*)-2-phenylpropanoic acid.

(C) A significant enantioselectivity for (*S*)-2-phenylpropanoic acid is exhibited by TMβCD (Fig. 3), but not by TMαCD despite its moderately greater complexing ability for this guest. A small enantioselectivity is shown for (*R*)-2-phenylpropanoic acid by βCD[8] and αCD, although in the latter case the small K_{1HA} values and the coexistence of substantial amounts of the ternary (*R*)- and (*S*)-2-phenylpropanoic acid.αCD_2 complexes render the degree of discrimination less certain. The reversal in enantioselectivity shown by TMβCD by comparison with that of βCD may arise from opposite guest orientations in the different annuli in a similar manner to that observed for some guests in the solid state.[4]

(D) For the guest carboxylic acids, $pK_a < pK_a'$, indicating the destabilization of the conjugate base relative to the conjugate acid in the complex by comparison with the case in the free state. The charged and more strongly hydrated carboxylate is probably more affected by the decreased hydrogen bonding in the

complex than is the carboxylic acid and is relatively destabilized. The pK_a' values are greater for the TMαCD complexes than for the βCD complexes. This may be because the greater hydrophobicity of the TMαCD annulus, relative to that of βCD, causes a greater destabilization of the conjugate base, but data from more CD systems are required to test this interpretation.

(E) Ternary complexes, HA.αCD_2, were only observed for αCD which has the smallest annulus. In HA.αCD, a substantial portion of HA protrudes from the wide end of the annulus, unlike the other CD complexes, and it appears that the formation of HA.αCD_2 completes the encapsulation of HA. While the stabilities of the HA.αCD_2 complexes detected in this study are low, this stoichiometry has been well established in other studies of αCD complexes.[18]

Acknowledgments

We are grateful to the Australian Research Council and the University of Adelaide for supporting this research.

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J. CHEM. SOC., CHEM. COMMUN., 1995

High Enantioselectivity in the Reactions of (*R*)-and (*S*)-1-Phenylethylamine with 6^A-Deoxy-6^A-iodo-β-cyclodextrin

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6^A-Deoxy-6^A-iodo-β-cyclodextrin reacts with (*R*)-1-phenylethylamine one hundred and sixty times faster than it reacts with the corresponding (*S*)-enantiomer of the amine.

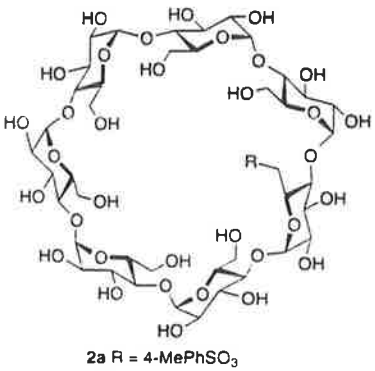
Cyclodextrins and their derivatives are chiral host molecules that are known to exhibit enantioselectivity in reactions with racemic guests. For example, stereoselectivity has been observed in the hydrolysis of esters[1–10] and in the ring opening of oxazolones,[11,12] catalysed by cyclodextrins. The greatest enantioselectivity so far reported for reaction of a cyclodextrin involved the acylation of β-cyclodextrin by the *p*-nitrophenyl ester of a ferrocene derivative, where the rates of reaction of the enantiomers of the ester differed by a factor of 62.6 More recently, a 19-fold enantioselectivity has been reported for the reaction of β-cyclodextrin with the *m*-nitrophenyl ester of 1-phenylpropanoic acid,[7] and complementary diastereoselectivity in the synthesis and hydrolysis of a cyclodextrin ester of Ibuprofen has been observed, with an overall selectivity of 50 : 1.[10] We now report that the reaction of 1-phenylethylamine **1** with 6^A-deoxy-6^A-iodo-β-cyclodextrin **2b** is also enantioselective, with the (*R*)-amine **1a** reacting one hundred and sixty times faster than the corresponding (*S*)-enantiomer **1b**. To the best of our knowledge, this is the highest enantioselectivity reported for reaction of a cyclodextrin.

The iodide **2b** was obtained by treatment of the corresponding tosylate **2a**[13] with sodium iodide.[14] Treatment of the iodide **2b** with (*R*)-1-phenylethylamine **1a** (2 mol equiv.) in *N,N*-dimethylformamide at 343 K for 48 h gave the cyclodextrin derivative **3a** [δ_C (75.5 MHz, 298 K) 26.8 (Me), 40.0 (C-6^A); δ_H (500 MHz, 343 K) 1.75 (d, *J* 6 Hz, 3H, Me); HPLC (Waters Carbohydrate Analysis column with 30% aqueous acetonitrile as eluent) t_R 0.7 relative to β-cyclodextrin] in 44% yield. By comparison, under the same conditions reaction of the iodide **2b** with the amine (*S*)-enantiomer **1b** gave the diastereoisomeric cyclodextrin derivative **3b** [δ_C 26.5 (Me), 40.2 (C-6^A); δ_H 1.72 (*d*, *J* 6 Hz, 3H, Me); HPLC t_R 0.5 relative to β-cyclodextrin] in only 2% yield. More substantial yields of the cyclodextrin derivative **3b** were only obtained after longer reaction times and by using greater molar excesses of the amine **1b**.

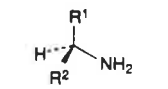
The relative yields of the cyclodextrin derivatives **3a** and **3b**, from experiments carried out under identical conditions, indicate the enantioselectivity of the reaction of the iodide **2b** with the amine **1**. To examine this stereoselectivity in more detail, the iodocyclodextrin **2b** was treated with various mixtures of the amine enantiomers **1a** and **1b**. When the reaction was carried out using the iodide **2b** and 1 mol equiv. of each enantiomer of the amine **1**, only the cyclodextrin derivative **3a**, derived from the (*R*)-enantiomer **1a**, was detected by HPLC and ^{1}H NMR spectroscopic analysis of the product mixture. When the iodide **2b**, the (*R*)-amine **1a** and the (*S*)-enantiomer **1b** were mixed in a 1 : 1 : 100 molar ratio, the cyclodextrin derivatives **3a** and **3b** were produced in the ratio 1.6 : 1. On this basis, the enantioselectivity displayed in the reaction of the iodide **2b** with the amine **1** is a factor of one hundred and sixty.

The reaction of each enantiomer of the amine **1** with the iodocyclodextrin **2b** most likely occurs in two discrete steps. The first involves formation of a host **2b**–guest **1** complex, and the second reaction of the host **2b** with the included guest **1**. In principle the enantioselectivity could derive from either or both of these processes, but the results of the experiments using mixtures of the amine enantiomers **1a** and **1b** described above indicate that the stereoselectivity most likely originates in the latter stage. As the amount of the (*S*)-amine **1b** used in the reactions was increased, the rate of formation of the cyclodextrin derivative **3a** decreased without a similar increase in the rate of production of the diastereoisomer **3b**. This decrease in the rate of formation of the cyclodextrin derivative **3a** shows that the (*S*)-amine **1b** competes with the (*R*)-enantiomer **1a** to complex with the cyclodextrin **2b**, while the fact that the rate of formation of the cyclodextrin derivative **3b** does not increase to the same extent as the rate of production of the diastereoisomer **3a** is reduced indicates that the complex of the (*S*)-amine **1b** with the cyclodextrin **2b** is less reactive.

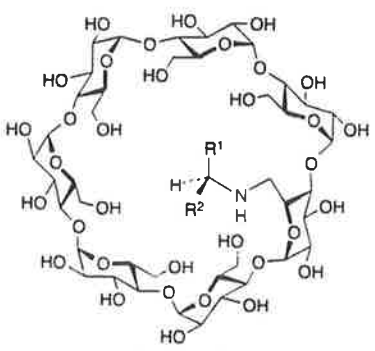
Although there is no obvious explanation for the enantioselectivity, the HPLC retention times of the cyclodextrin derivatives **3a** and **3b** relative to β-cyclodextrin indicate that the diastereoisomer **3b** is the less polar. This may reflect a lower



2a R = 4-MePhSO$_3$
b R = I



1a R^1 = Me, R^2 = Ph
b R^1 = Ph, R^2 = Me



3a R^1 = Me, R^2 = Ph
b R^1 = Ph, R^2 = Me

degree of intramolecular inclusion of the aryl moiety in that compound, which may in turn suggest that the geometry of the inclusion complex formed between the iodide **2b** and the (*S*)-amine **1b** is unlike the product **3b** and therefore unsuitable for reaction. In any event the enantioselectivity displayed by the iodide **2b** is sufficient for a kinetic resolution of the amine **1**, as demonstrated in a preliminary experiment through the enrichment of a racemic sample to give the (*S*)-enantiomer **1b** in 90% enantiomeric excess with no detectable reaction of that isomer. The amine enantiomers **1a** and **1b** were distinguished by HPLC analysis of their diastereoisomeric amide derivatives formed through reaction with (*S*)-2-phenylpropanoic acid.

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Footnote

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Synthesis of Side-chain Functionalized Amino Acid Derivatives Through Reaction of Alkyl Nitronates with α-Bromoglycine Derivatives

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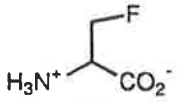
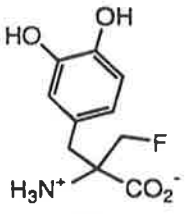
Abstract: Reactions of alkyl nitronates with α-bromoglycine derivatives provide access to a variety of halo-, β-nitro- and α,β-dehydro-α-amino acid derivatives, including β-functionalized α,β-dehydro-amino acid derivatives. The hydrochloride salts of free β-nitro-α-amino acids can also be prepared using this approach.

INTRODUCTION

Interest in the synthesis of halogenated and, in particular, fluorinated amino acid derivatives stems from their activity as enzyme inhibitors and potential as pharmaceutical agents.[1-4] For example, β-fluoroalanine **1** and the dopa analogue **2** have been studied as inhibitors of bacterial alanine racemase[2] and dopa decarboxylase,[3] respectively, while the methotrexate derivative **3** has been investigated for use in anticancer therapy.[4] β-Nitro-[5] and α,β-dehydro-[6] amino acids have also been studied as enzyme inhibitors and used to investigate structure-activity relationships. β-Functionalized α,β-dehydro-amino acid derivatives are of interest in synthesis because they have been shown to undergo addition-elimination reactions, with net substitution of the β-functional group, to give novel dehydro-amino acid derivatives.[7] Several years ago we reported[8] the synthesis of the β-nitro-amino acid derivatives **6a-d** through reaction of *N*-benzoyl-2-bromoglycine methyl ester **4** with the anions of the corresponding nitroalkanes **5a-d** (Scheme 1). We have now applied this procedure to the synthesis of α,β-dehydro-, δ- and ε-halo-β-nitro-, δ- and ε-halo-α,β-dehydro-, δ- and ε-halo-, β-halo-β-nitro-, α,β-dehydro-β-nitro- and α,β-dehydro-β-halo-amino acid derivatives. During the present work we determined that the procedure[8] for the synthesis of the β-nitro-amino acid derivatives **6a-d** was of limited utility in the synthesis of the corresponding free amino acids **7a-d**, however, these compounds have now been obtained using a variation of that method.



(1)



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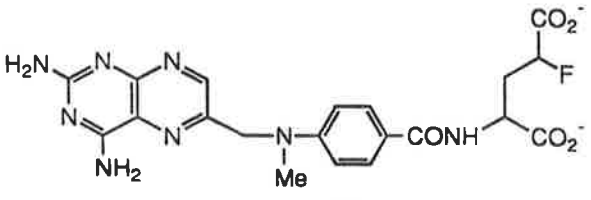
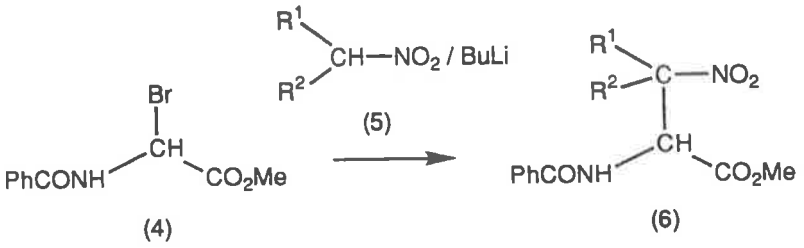


(3)

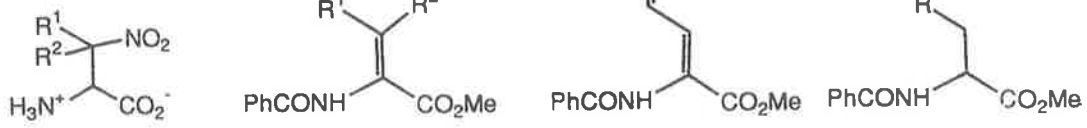
RESULTS AND DISCUSSION

The δ- and ε-halo-β-nitro-amino acid derivatives **6f-h** were prepared as outlined in Scheme 1, by incorporating the halogen into the nitroalkane. 3-Fluoro-1-nitropropane **5f** and 4-fluoro-1-nitrobutane **5g** were synthesized using the method of Pattison and coworkers,[9] by treatment of the corresponding 1-fluoro-ω-iodoalkanes with silver nitrite. 3-Chloro-1-nitropropane **5h** was prepared in a similar manner, by treating the corresponding chloroiodoalkane with silver nitrite. Treatment of the nitronate salt of 3-fluoro-1-nitropropane **5f** with 0.5 mole equivalents of the α-bromoglycine derivative **4**, in tetrahydrofuran/hexamethylphosphoramide (5:1) at -78 °C,[8] afforded the 5-fluoro-3-nitropentanoic acid derivative **6f**, in 64% yield as a 1.5:1 mixture of diastereomers. The diastereomers were separated by chromatography of the mixture on silica and subsequently crystallized from ethyl acetate/light petroleum, in yields of 35% and 23%. Similar treatment of the nitronate salt



a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = Ph$, $R^2 = H$
d) $R^1 = R^2 = Me$
e) $R^1 = Et$, $R^2 = Me$
f) $R^1 = CH_2CH_2F$, $R^2 = H$
g) $R^1 = CH_2CH_2CH_2F$, $R^2 = H$
h) $R^1 = CH_2CH_2Cl$, $R^2 = H$
i) $R^1 = Cl$, $R^2 = H$
j) $R^1 = Cl$, $R^2 = Me$
k) $R^1 = Br$, $R^2 = Me$

Scheme 1



a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = Ph$, $R^2 = H$
d) $R^1 = R^2 = Me$
e) $R^1 = Et$, $R^2 = Me$

a) $R^1 = CH_2CH_2F$, $R^2 = H$
b) $R^1 = CH_2CH_2CH_2F$, $R^2 = H$
c) $R^1 = NO_2$, $R^2 = H$
d) $R^1 = NO_2$, $R^2 = Me$
e) $R^1 = Cl$, $R^2 = Me$

a) $R = CH_2CH_2F$
b) $R = CH_2CH_2CH_2F$

of 4-fluoro-1-nitrobutane **5g** with the bromide **4** gave methyl 2-benzamido-6-fluoro-3-nitrohexanoate **6g**, as a 5:1 mixture of diastereomers, in 72% yield. The major diastereomer was isolated in 41% yield and the minor diastereomer in 7% yield, after chromatography of the mixture on silica and crystallization from ethyl acetate/light petroleum. Reaction of the nitronate salt of 4-chloro-1-nitropropane **5h** with the α-bromoglycine derivative **4** afforded a 3:1 mixture of the diastereomers of the δ-chloro-β-nitro-amino acid derivative **6h**. The diastereomers were separated by chromatography of the mixture on silica and crystallization from ethyl acetate/light petroleum, and isolated in yields of 49% and 14%.

The δ- and ε-fluoro-β-nitro-amino acid derivatives **6f** and **6g** were efficiently converted to the corresponding α,β-dehydro-amino acid derivatives **8a** and **8b**. Treatment of each of the diastereomers of methyl 2-benzamido-5-fluoro-3-nitropentanoate **6f** with one equivalent of di-*iso*-propylamine, in chloroform at room temperature for 16 h, gave methyl (*Z*)-2-benzamido-5-fluoropent-2-enoate **8a** as a colourless oil, in 80% yield in each case. The stereochemistry of the alkene **8a** was assigned on the basis of the ease of interconversion of *E*- and *Z*-dehydro-amino acid derivatives and the greater stability of the *Z*-isomers.[10] The observation that each diastereomer of the nitro-amino acid derivative **6f** gave the same alkene **8a** may reflect either interconversion of the diastereomers of the starting material **6f**, prior to elimination, or isomerization of the product.[10] When treated with a ten-fold excess of di-*iso*-propylamine, the fluoride **6f** afforded the α,β,γ,δ-didehydro-amino acid derivative **9**, as the sole product. Reaction of the major diastereomer of methyl 2-benzamido-6-fluoro-3-nitrohexanoate **6g** with one equivalent of di-*iso*-propylamine gave the α,β-dehydro-amino acid derivative **8b** in 83% yield. The diene **9** and the monoene **8b** are each assumed to have the *Z*-configuration, by analogy with related compounds.[10]

Hydrogenation of methyl (*Z*)-2-benzamido-5-fluoropent-2-enoate **8a** over 10% palladium on carbon gave methyl 2-benzamido-5-fluoropentanoate **10a**, as a colourless solid, in 98% yield. Similar treatment of methyl (*Z*)-2-benzamido-6-fluorohex-2-enoate **8b** afforded the fluoride **10b**, in 94% yield. It is thus evident that β-nitro-amino acid derivatives can be used in the synthesis of α,β-dehydro-amino acid derivatives and the saturated analogues, with retention of fluorine at either the δ- or ε-position. Through asymmetric hydrogenation of α,β-dehydro-amino acid derivatives in the presence of chiral catalysts,[11] this approach should be suitable for the synthesis of the individual enantiomers of the corresponding amino acid derivatives.

In order to prepare β-functionalized α,β-dehydro-amino acid derivatives, reactions of α-halonitroalkanes were investigated. Chloronitromethane **5i** was prepared from nitromethane **5a** and *tert*-butyl hypochlorite, in the presence of styrene, as described by Heasley and coworkers.[12] α-Chloronitroethane **5j** was prepared using the method outlined by Levering,[13] which involved the chlorination of nitroethane **5b**. In a similar manner, α-bromonitroethane **5k** was prepared from nitroethane **5b**. Reaction of the bromoglycine derivative **4** with the nitronate salt of chloronitromethane **5i** gave *N*-benzoyl-β-nitro-α,β-dehydroalanine methyl ester **8c**, as a yellow solid in 42% yield. The structure of the amino acid derivative **8c** was determined using X-ray crystallographic analysis (Figure 1).[14] Similar treatment of the nitronate salt of 1-chloronitroethane **5j** with the bromide **4** gave a 1.4:1 mixture of the diastereomers of the β-chloro-β-nitro-amino acid derivative **6j**, in 48% yield. The β-nitro-α,β-dehydro-amino acid derivative **8d** was also isolated, in 9% yield, and its structure was determined using X-ray crystallographic analysis (Figure 2).[14] The diastereomers of the β-chloro-β-nitro-amino acid derivative **6j** were separated by chromatography on silica. Treatment of the major diastereomer with di-*iso*-propylamine gave a 2:1 mixture of the β-nitro-α,β-dehydro-amino acid derivative **8d** and the β-chloro-α,β-dehydro-amino acid derivative **8e**. The products **8d** and **8e** were separated by

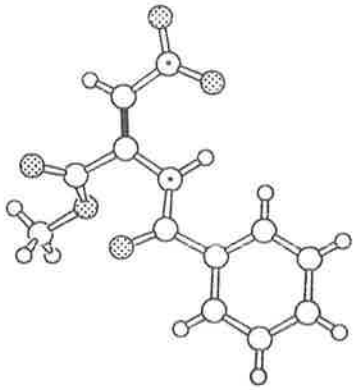


Figure 1. Molecular structure of **8c**.

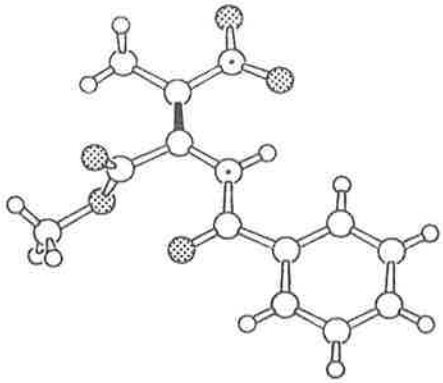


Figure 2. Molecular structure of **8d**.

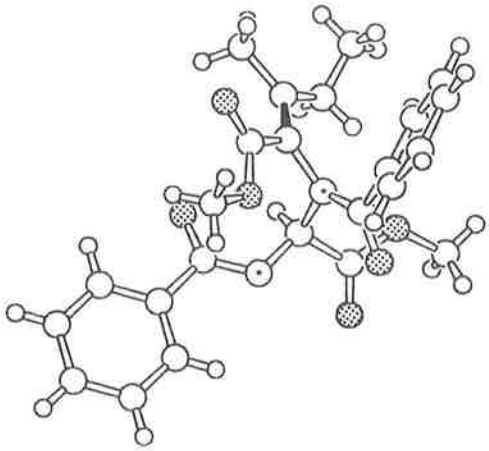


Figure 3. Molecular structure of **11**.

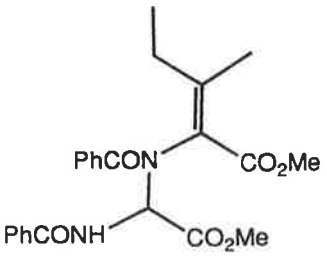
chromatography of the mixture on silica and isolated in yields of 39% and 17%, respectively. Reaction of the minor diastereomer of the β-chloro-β-nitro-amino acid derivative **6j** with di-*iso*-propylamine gave a 1:2 mixture of the nitro-amino acid derivative **8d** and the chloride **8e**. The Z-stereochemistry of the chloride **8e** is assumed by analogy with that of the nitroalkene **8d**.

When α-bromonitroethane **5k** was treated with butyllithium (1 equivalent) and subsequently with 0.5 mole equivalents of the α-bromoglycine derivative **4**, reaction gave a 2:1 mixture of the diastereomers of methyl 2-benzamido-3-nitrobutanoate **6b**.[8] This outcome can be attributed to *trans*-metallation of α-bromonitroethane **5k** having afforded the lithium salt of nitroethane **5b**, which reacted with the α-bromoglycine derivative **4**. Based on an estimation of the relative pK_a values of nitroethane **5b** and α-bromonitroethane **5k**, it was anticipated that the anion of nitroethane **5b** would react with an excess of α-bromonitroethane **5k** to produce the nitronate salt of the latter. Accordingly, reaction of a ten-fold excess of α-bromonitroethane **5k** with

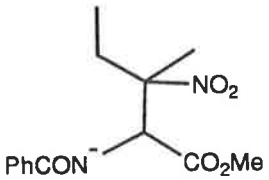
butyllithium, followed by reaction with the α-bromoglycine derivative **4**, afforded the β-bromo-β-nitro-amino acid derivative **6k**, as a single diastereomer in 58% yield. The β-nitro-α,β-dehydro-amino acid derivative **8d** was also isolated, in 6% yield, while the nitrobutanoate **6b** was obtained as a 1:1 mixture of diastereomers, in 13% yield. Treatment of the bromide **6k** with di-*iso*-propylamine gave the β-nitro-α,β-dehydro-amino acid derivative **8d** in 81% yield.

In order to exploit reactions of bromoglycine derivatives with alkyl nitronates in the synthesis of free β-nitro-amino acids, we examined the deprotection of the amino acid derivatives **6a-e**. The nitroalkanes **6a-d** were prepared as reported previously.[8] In an analogous manner, 2-nitrobutane **5e**, prepared by oxidation of 2-aminobutane with *m*-chloroperbenzoic acid,[15] was treated with butyllithium (1 equivalent) and subsequently with 0.5 mole equivalents of the α-bromoglycine derivative **4**, to give *N*-benzoyl-3-nitroisoleucine methyl ester **6e**, in 70% yield as a 1:1.25 mixture of diastereomers. Small samples of each of the diastereomers of the isoleucine derivative **6e** were obtained by normal phase preparative HPLC of the mixture. A by-product of the reaction of the nitronate salt of 2-nitrobutane **5e** with the bromide **4** was the α,β-dehydro-isoleucine derivative **11**, the structure of which was determined using X-ray crystallographic analysis (Figure 3).[14] Based on the mechanism proposed for reactions of alkyl nitronates with the bromide **4**,[8] formation of the by-product **11** can be attributed to addition of the amide anion **12** to the imine **13**, followed by elimination.

Treatment of *N*-benzoyl-3-nitrovaline methyl ester **6d** with 6N HCl at reflux for 1 h gave the hydrochloride salt of β-nitrovaline **7d**, in 84% yield, which was converted to the corresponding free amino acid **7d** by precipitation from a solution of ethanol and aniline (10:1 v/v).[16] The amino acid **7d** was found to be less stable than the corresponding hydrochloride salt, consequently the β-nitro-amino acids **7a-e** prepared as



(11)



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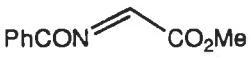
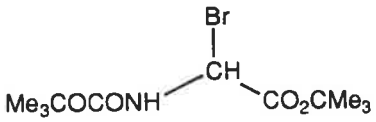
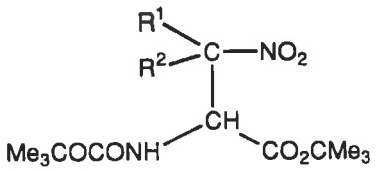


(13)



(14)



(15)

a) $R^1 = R^2 = H$
b) $R^1 = Me$, $R^2 = H$
c) $R^1 = Ph$, $R^2 = H$

described herein were stored and characterized as their hydrochloride salts. Each of the diastereomers of *N*-benzoyl-3-nitroisoleucine methyl ester **6e** reacted with 6N HCl to give the corresponding diastereomer of the hydrochloride salt of β-nitroisoleucine **7e**. There was no evidence of interconversion between the diastereomers of either the starting material **6e** or the product **7e** under the reaction conditions.

The amino acid derivatives **6d** and **6e** were the only ones amenable to deprotection with 6N HCl, however, similar treatment of the analogues **6a-c** giving only decomposition products. The different outcomes may be attributed to the fact that the amino acid derivatives **6a-c** are primary or secondary nitroalkanes, which are known to be susceptible to acid catalysed decomposition.[17] By contrast, tertiary nitroalkanes are not acid labile, explaining why the nitroalkanes **6d** and **6e** hydrolysed without decomposition. In order to obtain the hydrochloride salts of the β-nitro amino acids **7a-c** it was therefore necessary to use amino acid derivatives susceptible to deprotection under less vigorous conditions. Steglich and coworkers[18] reported that the carbamate **14** is suitable for the synthesis of free amino acids. After introduction of the side chain, both the protecting groups are easily removed by treatment with trifluoroacetic acid in chloroform. Consequently, the bromide **14** was prepared[18,19] and used in reactions with alkyl nitronates. Reaction of the bromide **14** with the salt of nitromethane **5a** gave the β-nitroalanine derivative **15a**, in 63% yield. The corresponding reaction using nitroethane **5b** gave a 2:1 mixture of the diastereomers of the β-nitro-α-amino acid derivative **15b**. The diastereomers were separated by chromatography of the mixture on silica. The major diastereomer crystallized from light petroleum as a colourless solid in 34% yield, while the minor diastereomer was isolated as an oil in 17% yield. Reaction of the bromide **14** with the salt of α-nitrotoluene **5c** gave the β-nitrophenylalanine derivative **15c** in 71% yield, as a 1:1 mixture of diastereomers. The diastereomers crystallized from dichloromethane/light petroleum with different shapes, one as spars and the other as clusters, thus enabling partial separation of the diastereomers by mechanical means.

The amino acid derivatives **15a-c** were used to prepare the hydrochloride salts of the corresponding free amino acids **7a-c**. Accordingly, treatment of the β-nitroalanine derivative **15a** with a solution of trifluoroacetic acid in chloroform, at reflux for 0.25 h, followed by treatment with HCl during work-up, gave the salt of β-nitroalanine **7a**, in 63% yield. Each of the diastereomers of the nitrobutanoate derivative **15b** was treated with trifluoroacetic acid, then HCl, to give the corresponding diastereomer of the hydrochloride salt of the amino acid **7b**. Similar reaction of a 1:1 mixture of the diastereomers of the β-nitrophenylalanine derivative **15c** afforded a 1:1 mixture of the diastereomers of the hydrochloride salt of β-nitrophenylalanine **7c**.

It is evident from the synthesis of the β-nitro-amino acid derivatives **7a-e** described above that reaction of alkyl nitronates with α-bromoglycine derivatives is a viable method for the synthesis of the corresponding free amino acids. The reported[5] method for the synthesis of β-nitroalanine **7a** is unsuitable for the preparation of secondary and tertiary nitroalkane analogues. Access to these compounds should provide the opportunity to probe novel aspects of enzyme inhibition, particularly with the tertiary derivatives because they are neither able to form the corresponding alkyl nitronates nor particulary susceptible to elimination, whereas those reaction modes are associated with enzyme inhibition by the alanine derivative **7a**.[5]

EXPERIMENTAL

General. ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on either a Bruker ACP-300 or a Bruker CXP-300 spectrometer, in $CDCl_3$ for protected amino acid

derivatives or D_2O for the free amino acids. With the ^1H and ^{13}C NMR spectra, tetramethylsilane and *tert*-butanol were used as internal standards for the spectra recorded in $CDCl_3$ and D_2O, respectively. Trifluoroacetic acid was used as the internal standard for the ^{19}F NMR spectra. Infrared spectra were recorded on a Jasco IRA-1 spectrometer, as nujol mulls for solids and thin films for oils. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Microanalyses were performed by the Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada.

N-Benzoyl-2-bromoglycine methyl ester **4**,[8] 2-nitrobutane **5e**,[15] 3-fluoro-1-nitropropane **5f**,[9] 4-fluoro-1-nitrobutane **5g**,[9] 3-chloro-1-nitropropane **5h**,[9] chloronitromethane **5i**,[12] 1-chloro-1-nitroethane **5j**,[13] 1-bromo-1-nitroethane **5k**,[13] the β-nitro-amino acid derivatives **6a-d**[8] and 2-bromo-*N*-*tert*-butoxycarbonylglycine *tert*-butyl ester **14**[18] were prepared using literature procedures, and they had physical and spectral properties consistent with those reported previously.

Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM) and HPLC on a Waters μ-Porasil Radial-Pak Cartridge (10 cm x 8 mm), each using ethyl acetate and light petroleum (bp 66-68 °C) as eluants.

General Procedure for Reactions of the α-Bromoglycine Derivative 4 with the Anions of the Nitroalkanes 5e-k. A solution of butyllithium (2.5 M in hexane, 0.42 ml, 1.05 mmol) was added dropwise to a solution of the nitroalkane **5e-k** (1.04 mmol) in tetrahydrofuran (5 ml) and hexamethylphosphoramide (1 ml) maintained at -78 °C. A solution of *N*-benzoyl-2-bromoglycine methyl ester **4** (0.52 mmol) in tetrahydrofuran (2 ml) was then added at -78 °C and, after 4 h at that temperature, acetic acid (3 ml) was added. The reaction mixture was allowed to warm slowly to room temperature and was then concentrated under reduced pressure. The concentrate was diluted with ethyl acetate (25 ml) and the organic solution was washed with water (3 x 10 ml), then concentrated under reduced pressure to give the crude product.

Methyl 2-Benzamido-3-methyl-3-nitropentanoate, 6e and Methyl (*Z*)-3-Aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate 11: Reaction of the bromide **4** with the anion of 2-nitrobutane **5e** gave a crude product which was chromatographed to give methyl 2-benzamido-3-methyl-3-nitropentanoate **6e** as a 1.25:1 mixture of diastereomers in 70% yield. A sample of each of the diastereomers was obtained by HPLC of the mixture. The minor diastereomer had: ^1H NMR δ 1.01 (3H, t, *J* = 7.5 Hz), 1.60 (3H, s), 2.07 (1H, qd, *J* = 7.5 and 15 Hz), 2.42 (1H, qd, *J* = 7.5 and 15 Hz), 3.80 (3H, s), 5.51 (1H, d, *J* = 9 Hz), 6.90 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 8.3, 19.2, 30.2, 53.2, 56.8, 93.5, 127.2, 128.8, 132.4, 133.1, 167.5, 168.9; υ_{max} 3443, 1746, 1671, 1549 cm^{-1}; MS (ei) *m/e* 294 (M^+), 247, 234, 215, 105; MS (ei) *m/e* 294.122 (M^+). Calc. for $C_{14}H_{18}N_2O_5$: *m/e* 294.122. The major diastereomer had: ^1H NMR δ 0.95 (3H, t, *J* = 7.5 Hz), 1.80 (3H, s), 1.93 (1H, qd, *J* = 7.5 and 15 Hz), 2.20 (1H, qd, *J* = 7.5 and 15 Hz), 3.77 (3H, s), 5.31 (1H, d, *J* = 10 Hz), 7.24 (1H, br d, *J* = 10 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 7.9, 20.1, 30.8, 53.1, 57.2, 92.2, 127.2, 128.8, 132.3, 133.0, 167.2, 168.8; υ_{max} 3445, 1744, 1673, 1549 cm^{-1}; MS (ei) *m/e* 294 (M^+), 248, 234, 105; MS (ei) *m/e* 294.122 (M^+). Calc. for $C_{14}H_{18}N_2O_5$: *m/e* 294.122. Continued chromatography of the crude reaction product also afforded a 1.5:1 mixture of methyl (*Z*)-3-aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate **11** and the

corresponding *E*-isomer, in 7% yield, from which a small sample of the *Z*-isomer **11** was obtained by crystallization of the mixture from ethyl acetate/light petroleum. The Z-isomer **11** had: mp 134-135 °C; ^{1}H NMR δ 1.19 (3H, t, *J* = 7.5), 2.12 (3H, s), 2.69 (1H, qd, *J* = 7.5 and 13.5 Hz), 2.97 (1H, qd, *J* = 7.5 and 13.5 Hz), 3.32 (3H, s), 3.87 (3H, s), 5.97 (1H, d, *J* = 9.5 Hz), 7.55 (11H, m); υ_{max} 3332, 1760, 1740, 1650, 1630, 1526 cm^{-1}; MS (ei) *m/e* 439 (M+H$^+$), 379, 247, 215, 142, 105; MS (ei) *m/e* 439.188 (M+H$^+$). Calc. for $C_{24}H_{27}N_2O_6$: *m/e* 439.187. The stereochemistry of the Z-isomer **11** was confirmed through X-ray crystallographic analysis (Figure 3).[14] The ^{1}H NMR spectrum of the mixture of methyl (Z)-3-aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methylhept-4-enoate **11** and the corresponding *E*-isomer showed peaks for the *E*-isomer at δ 1.03 (3H, t, *J* = 7.5 Hz), 2.30 (3H, s), 2.36 (1H, qd, *J* = 7.5 and 12.5 Hz), 2.72 (1H, qd, *J* = 7.5 and 12.5 Hz), 3.30 (3H, s), 3.86 (3H, s), 5.99 (1H, d, *J* = 9.5 Hz), 7.55 (11H, m).

Methyl 2-Benzamido-5-fluoro-3-nitropentanoate 6f: Reaction of the bromide **4** with the anion of 3-fluoro-1-nitropropane gave the title compound **6f** in 64% yield as a 1.5:1 mixture of diastereomers. The diastereomers were separated by chromatography. The minor diastereomer eluted first and crystallized from ethyl acetate/light petroleum: 23%; mp 99-101 °C; ^{1}H NMR δ 2.32 (1H, m), 2.55 (1H, m), 3.84 (3H, s), 4.66 (2H, m, J_F = 46 Hz), 5.44 (2H, m), 7.07 (1H, br d, *J* = 9 Hz), 7.4-7.8 (5H, m); ^{13}C NMR δ 31.9 (d, *J* = 20 Hz), 53.3, 54.3, 80.2 (d, *J* = 167 Hz), 84.5 (d, *J* = 3 Hz), 127.9, 129.4, 133.2, 168.7, 169.4; ^{19}F NMR δ -147.6; υ_{max} 3345, 1754, 1670, 1550 cm^{-1}; MS (ei) *m/e* 298 (M$^+$), 251, 238, 191, 105; MS (ei) *m/e* 298.098 (M$^+$). Calc. for $C_{13}H_{15}FN_2O_5$: *m/e* 298.097. Continued elution gave the major diastereomer which crystallized from ethyl acetate/light petroleum: 35%; mp 112-114 °C; ^{1}H NMR δ 2.58 (2H, m), 3.85 (3H, s), 4.60 (2H, m, J_F = 47 Hz), 5.19 (1H, dt, *J* = 4.5 and 9 Hz), 5.28 (1H, dd, *J* = 4.5 and 7.5 Hz), 7.25 (1H, br d, *J* = 7.5 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 32.0 (d, *J* = 20 Hz), 54.1, 54.9, 80.6 (d, *J* = 168 Hz), 85.4 (d, *J* = 3 Hz), 127.9, 129.3, 133.1, 133.2, 168.0, 169.0; ^{19}F NMR δ -146.5; υ_{max} 3450, 1746, 1658, 1564 cm^{-1}; MS (ei) *m/e* 298 (M$^+$), 251, 238, 191, 105; MS (ei) *m/e* 298.097 (M$^+$). Calc. for $C_{13}H_{15}FN_2O_5$: *m/e* 298.097.

Methyl 2-Benzamido-6-fluoro-3-nitrohexanoate 6g: Reaction of the bromide **4** with the anion of 4-fluoro-1-nitrobutane gave the title compound **6g** as a 5:1 mixture of diastereomers in 72% yield. The diastereomers were partially separated by chromatography, and further purified by fractional crystallization from ethyl acetate/light petroleum. The minor diastereomer was the first to elute from the silica: 7%; mp 119-121 °C; ^{1}H NMR δ 1.88 (2H, m), 2.33 (2H, m), 3.83 (3H, s), 4.52 (2H, m, J_F = 47 Hz), 5.26 (1H, dt, *J* = 3 and 7.5 Hz), 5.43 (1H, dd, *J* = 3 and 9.5 Hz), 7.03 (1H, br d, 9.5 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 26.8 (d, *J* = 21 Hz), 26.9 (d, *J* = 4 Hz), 52.6, 53.5, 82.8 (d, *J* = 167 Hz), 87.2, 127.2, 128.8, 132.4, 132.8, 167.9, 169.0; ^{19}F NMR δ -145.0; υ_{max} 3450, 1753, 1670, 1542 cm^{-1}; MS (ei) *m/e* 313 (M+H$^+$), 266, 253, 205, 160, 121, 105, 77; MS (ei) *m/e* 313.119 (M+H$^+$). Calc. for $C_{14}H_{18}FN_2O_5$: *m/e* 313.120. The major diastereomer was the second to elute from the silica: 41%; mp 120-121 °C; ^{1}H NMR δ 1.88 (2H, m), 2.22 (1H, m), 2.43 (1H, m), 3.89 (3H, s), 4.52 (2H, m, J_F = 47 Hz), 5.04 (1H, dt, *J* = 4.5 and 9 Hz), 5.17 (1H, dd, *J* = 4.5 and 7 Hz), 7.08 (1H, br d, 7 Hz), 7.4-7.8 (5H, m); ^{13}C NMR δ 26.8 (d, *J* = 5 Hz), 27.2 (d, *J* = 20 Hz), 53.5, 54.2, 82.6 (d, *J* = 166 Hz), 88.4, 127.2, 128.8, 132.5, 132.7, 167.2, 168.4; ^{19}F NMR δ -145.6; υ_{max} 3375, 1748, 1652, 1565 cm^{-1}; MS (ei) *m/e* 313 (M+H$^+$), 266, 253, 205, 160, 121, 105, 77; MS (ei) *m/e* 313.120 (M+H$^+$). Calc. for $C_{14}H_{18}FN_2O_5$: *m/e* 313.120.

Methyl 2-Benzamido-5-chloro-3-nitropentanoate 6h: Reaction of the bromide **4** with the anion of 3-chloro-1-nitropropane gave the title compound **6h** as a 3:1 mixture of diastereomers, in 73% yield. The diastereomers were separated by chromatography. The major diastereomer eluted first and crystallized from ethyl acetate/light petroleum: 49%; mp 109-111 °C; ^{1}H NMR δ 2.46 (1H, m), 2.85 (1H, m), 3.63 (1H, ddd, *J* = 5, 9 and 12 Hz), 3.76 (1H, td, *J* = 6 and 12 Hz), 3.89 (3H, s), 5.23 (2H, m), 7.06 (1H, br d, *J* = 6.5 Hz), 7.5-7.9 (5H, m); ^{13}C NMR δ 33.3, 40.4, 53.6, 54.2, 85.5, 127.2, 128.8, 132.5, 132.6, 167.2, 168.3; υ_{max} 3300, 1760, 1650, 1560, 1540 cm^{-1}; MS (ei) *m/e* 316 and 314 (M^+), 270, 268, 256, 254, 207, 105; MS (ei) *m/e* 314.066 (M^+). Calc. for $C_{13}H_{15}{}^{35}ClN_2O_5$: *m/e* 314.067. The minor diastereomer was the second to elute and crystallized from ethyl acetate/light petroleum: 14%; mp 102-107 °C; ^{1}H NMR δ 2.37 (1H, dtd, *J* = 5, 7 and 15 Hz), 2.63 (1H, dtd, *J* = 5, 7 and 15 Hz), 3.72 (1H, ddd, *J* = 5, 7 and 12 Hz), 3.84 (1H, ddd, *J* = 5, 7 and 12 Hz), 3.86 (3H, s), 5.40 (1H, dd, *J* = 3 and 9 Hz), 5.54 (1H, dt, *J* = 3 and 7 Hz), 7.00 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); ^{13}C NMR δ 32.8, 40.3, 52.4, 53.6, 84.6, 127.3, 128.9, 132.5, 132.6, 168.0, 168.7; υ_{max} 3295, 1765, 1650, 1560, 1535 cm^{-1}; MS (ei) *m/e* 316 and 314 (M^+), 270, 268, 256, 254, 207, 105; MS (ei) *m/e* 314.066 (M^+). Calc. for $C_{13}H_{15}{}^{35}ClN_2O_5$: *m/e* 314.067.

Methyl (Z)-2-Benzamido-3-nitroprop-2-enoate 8c: Reaction of the bromide **4** with the anion of chloronitromethane **5i** gave the title compound **8c**: 42%; mp 93-95 °C; ^{1}H NMR δ 3.96 (3H, s), 6.91 (1H, s), 7.4-7.9 (5H, m), 11.17 (1H, br s); MS (ei) *m/e* 205 ($[M+H-NO_2]^+$), 163, 105; MS (ei) *m/e* 205.075 ($[M+H-NO_2]^+$). Calc. for $C_{11}H_{11}NO_3$: *m/e* 205.074. The structure of the dehydro-amino acid derivative **8c** was confirmed through X-ray crystallographic analysis (Figure 1).[14]

Methyl 2-Benzamido-3-chloro-3-nitrobutanoate 6j and Methyl (Z)-2-Benzamido-3-nitrobut-2-enoate 8d: Reaction of the bromide **4** with the anion of 1-chloro-1-nitroethane **5j** gave a crude product which was chromatographed to give methyl 2-benzamido-3-chloro-3-nitrobutanoate **6j** as a 1.4:1 mixture of diastereomers in 48% yield. The diastereomers were separated by further chromatography. The major diastereomer was isolated in 28% yield and had: ^{1}H NMR δ 2.21 (3H, s), 3.80 (3H, s), 6.10 (1H, d, *J* = 9 Hz, 1H), 7.11 (1H, br d, *J* = 9 Hz), 7.4-7.9 (5H, m); υ_{max} 3268, 1746, 1654, 1578, 1522 cm^{-1}; MS (ei) *m/e* 302 and 300 (M^+), 269, 267, 256, 254, 243, 241, 219, 192, 105; MS (ei) *m/e* 300.052 (M^+). Calc. for $C_{12}H_{13}{}^{35}ClN_2O_5$: *m/e* 300.051. The minor diastereomer was isolated in 14% yield and had: ^{1}H NMR δ 2.28 (3H, s), 3.83 (3H, s), 5.87 (1H, d, *J* = 9.5 Hz, 1H), 7.15 (1H, br d, *J* = 9.5 Hz), 7.4-7.9 (5H, m); υ_{max} 3274, 1742, 1656, 1578, 1530 cm^{-1}; MS (ei) *m/e* 302 and 300 (M^+), 269, 267, 256, 254, 243, 241, 219, 192, 105; MS (ei) *m/e* 300.051 (M^+). Calc. for $C_{12}H_{13}{}^{35}ClN_2O_5$: *m/e* 300.051. Continued chromatography of the crude reaction product also afforded methyl (Z)-2-benzamido-3-nitrobut-2-enoate **8d** as a yellow solid in 9% yield: mp 91-92 °C; ^{1}H NMR δ 2.07 (3H, s), 4.04 (3H, s), 7.4-8.0 (5H, m), 11.86 (1H, br s); υ_{max} 3500, 1750, 1700, 1624, 1520 cm^{-1}; MS (ei) *m/e* 264 (M^+), 233, 218, 105; MS (ei) *m/e* 264.075 (M^+). Calc. for $C_{12}H_{12}N_2O_5$: *m/e* 264.075. Anal. Calc. for $C_{12}H_{12}N_2O_5$: C, 54.5; H, 4.6; N, 10.6. Found: C, 54.3; H, 4.8; N, 10.6. The structure of the alkene **8d** was confirmed through X-ray crystallographic analysis (Figure 2).[14]

Methyl 2-Benzamido-3-bromo-3-nitrobutanoate 6k: Reaction of the bromide **4** with the anion of 1-bromo-1-nitroethane **5k**, generated by treating 1-bromo-1-nitroethane with 0.1 mole equivalents of butyllithium, gave a crude product mixture which was chromatographed to give the title compound **6k** as a

single diastereomer: 58%; mp 97-98 °C; ^{1}H NMR δ 2.45 (3H, s), 3.86 (3H, s), 5.88 (1H, d, *J* = 9.5 Hz), 7.04 (1H, br d, *J* = 9.5 Hz), 7.4-8.0 (5H, m); υ_{max} 3272, 1740, 1648, 1562 cm^{-1}; MS (ei) *m/e* 346 and 344 (M$^+$), 300, 298, 286, 284, 192, 105, 77; MS (ei) *m/e* 345.999 (M$^+$). Calc. for $C_{12}H_{13}{}^{81}BrN_2O_5$: *m/e* 345.999. Continued chromatography of the crude reaction product also afforded methyl (Z)-2-benzamido-3-nitrobut-2-enoate **8d** in 6% yield, identical in all respects to the sample obtained as described above, and a 1:1 mixture of the diastereomers of methyl 2-benzamido-3-nitrobutanoate **6b** in 13% yield, identical in all respects to the sample obtained previously.[8]

Methyl (Z)-2-Benzamido-5-fluoropent-2-enoate 8a. Di-*iso*-propylamine (6.8 mg, 0.07 mmol) was added to solution of the major diastereomer of methyl 2-benzamido-5-fluoro-3-nitropentanoate **6f** (20 mg, 0.07mmol) in chloroform (1 ml), and the mixture was stirred at room temperature for 18 h, then it was diluted with chloroform (5 ml), washed with water (2 x 3 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue afforded the title compound **8a** as an oil in 80% yield: ^{1}H NMR δ 2.66 (2H, tdd, *J* = 6, 7 and 28 Hz), 3.83 (3H, s), 4.62 (2H, td, *J* = 6 and 47 Hz), 6.83 (1H, t, *J* = 7 Hz), 7.4-7.6 (3H, m), 7.75 (1H, br s), 7.8-7.9 (2H, m); υ_{max} 3700, 3680, 1720, 1600, 1580, 1490 cm^{-1}; MS (ei) *m/e* 251 (M$^+$), 105, 77; MS (ei) *m/e* 251.097 (M$^+$). Calc. for $C_{13}H_{14}NO_3$: *m/e* 251.096. Treatment of the minor diastereomer of the pentanoate **6f** with di-*iso*-propylamine under analogous conditions also gave the alkene **8a** in 80% yield.

Methyl (Z)-2-Benzamido-6-fluorohex-2-enoate 8b. Treatment of the major diastereomer of the hexanoate **6g** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave the title compound **8b** in 83% yield: mp 89-90 °C; ^{1}H NMR δ 1.92 (2H, pd, *J* = 7.5 and 26 Hz), 2.40 (2H, q, *J* = 7.5 Hz), 3.82 (3H, s), 4.50 (2H, td, *J* = 7.5 and 47 Hz), 6.78 (1H, t, *J* = 7.5 Hz), 7.4-7.6 (3H, m), 7.75 (1H, br s), 7.8-7.9 (2H, m); ^{13}C NMR δ 24.7 (d, *J* = 5 Hz), 28.7 (d, *J* = 20 Hz), 52.4, 83.2 (d, *J* = 165 Hz), 125.9, 127.3, 128.5, 132.0, 133.5, 136.6, 164.9, 165.7; ^{19}F NMR δ -145.6; υ_{max} 3680, 3600, 1730, 1610, 1585, 1490 cm^{-1}; MS (ei) *m/e* 266 (M+H$^+$), 206, 160, 105, 77; MS (ei) *m/e* 266.120 (M+H$^+$). Calc. for $C_{14}H_{17}FNO_3$: *m/e* 266.119.

Reaction of Methyl 2-Benzamido-3-bromo-3-nitrobutanoate 6k with Di-*iso*-propylamine. Treatment of the butanoate **6k** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave the alkene **8d** in 81% yield, identical in all respects to the sample obtained as described above.

Reaction of Methyl 2-Benzamido-3-chloro-3-nitrobutanoate 6j with Di-*iso*-propylamine. Treatment of the major diastereomer of the butanoate **6j** with di-*iso*-propylamine, as described above for the preparation of the alkene **8a** from the pentanoate **6f**, gave a 2:1 mixture of the alkene **8d** and methyl (Z)-2-benzamido-3-chlorobut-2-enoate **8e**. Chromatography of the mixture afforded **8d** in 39% yield, identical in all respects to the sample obtained as described above, and the chloride **8e** in 17% yield: mp 130-132 °C; ^{1}H NMR δ 2.45 (3H, s), 3.85 (3H, s), 7.4-7.6 (3H, m), 7.66 (1H, br s), 7.8-8.0 (2H, m); υ_{max} 3650, 1745, 1620, 1578, 1480 cm^{-1}; MS (ei) *m/e* 255 and 253 (M$^+$), 224, 222, 218, 186, 105; MS (ei) *m/e* 253.051 (M$^+$). Calc. for $C_{12}H_{12}{}^{35}ClNO_3$: *m/e* 253.051. The analogous reaction of the minor diastereomer of

the butanoate **6j** gave a 63% yield of a 1:2 mixture of the alkenes **8d** and **8e**, from which the components were separated by chromatography in yields of 17% and 33%, respectively.

Methyl (Z)-2-Benzamidopenta-2,4-dienoate 9. A mixture of the major diastereomer of methyl (Z)-2-benzamido-5-fluoro-3-nitropentanoate **6f** (40 mg, 0.13 mmol), di-*iso*-propylamine (1 ml) and chloroform (2 ml) was stirred at room temperature for 18 h, then it was diluted with chloroform (10 ml), washed with water (3 x 10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue afforded the title compound **9** (26 mg, 87%) as a colourless oil: ^{1}H NMR δ 3.82 (3H, s), 5.43 (1H, d, *J* = 10.5 Hz), 5.57 (1H, d, *J* = 16.5 Hz), 6.49 (1H, ddd, *J* = 10.5, 11.5 and 16.5 Hz), 7.06 (1H, d, *J* = 11.5 Hz), 7.4-7.6 (3H, m), 7.85 (1H, br s), 7.8-7.9 (2H, m); υ_{max} 3400, 1760, 1730, 1690, 1520, 1500 cm^{-1}; MS (ei) *m/e* 231 (M^+), 105, 77; MS (ei) *m/e* 231.090 (M^+). Calc. for $C_{13}H_{13}NO_3$: *m/e* 231.090.

Methyl 2-Benzamido-5-fluoropentanoate 10a. A mixture of the alkene **8a** (9.3 mg, 0.04 mmol), 10% palladium on activated carbon (7 mg) and ethyl acetate (5 ml) was stirred under hydrogen (25 psi) for 3 h, then it was filtered through celite and the filtrate was concentrated under reduced pressure. Chromatography of the residual oil gave the title compound **10a** (9.2 mg, 98%): mp 53-56 °C, ^{1}H NMR δ 1.83 (2H, m), 2.04 (2H, m), 3.81 (3H, s), 4.49 (2H, td, *J* = 5.5 and 47 Hz), 4.88 (1H, dt, *J* = 5 and 7.5 Hz), 6.77 (1H, br d, *J* = 7.5H), 7.4-7.6 (3H, m), 7.8-7.9 (2H, m); ^{13}C NMR δ 26.4 (d, *J* = 23 Hz), 28.8 (d, *J* = 5 Hz), 52.0, 52.6, 83.2 (d, *J* = 166 Hz), 127.0, 128.6, 131.9, 133.7, 167.1, 172.8; ^{19}F NMR δ -144.4; υ_{max} 3444, 1739, 1666, 1580, 1516 cm^{-1}; MS (ei) *m/e* 254 ($M+H^+$), 253, 194, 105, 77; MS (ei) *m/e* 253.112 (M^+). Calc. for $C_{13}H_{16}FNO_3$: *m/e* 253.111.

Methyl 2-Benzamido-6-fluorohexanoate 10b. Hydrogenation of the alkene **8b** as described above for the preparation of the pentanoate **10a** gave the title compound **10b** in 94% yield, as colourless needles from dichloromethane/light petroleum: mp 73-74 °C; ^{1}H NMR δ 1.7 (6H, m), 3.71 (3H, s), 4.36 (2H, td, *J* = 6 and 47 Hz), 4.77 (1H, dt, *J* = 5.5 and 7.5 Hz), 6.75 (1H, br d, *J* = 7.5 Hz), 7.3-7.5 (3H, m), 7.7-7.8 (2H, m); ^{19}F NMR δ -144.0; υ_{max} 3300, 1746, 1632, 1578, 1532 cm^{-1}; MS (ei) *m/e* 267 (M^+), 208, 193, 161, 105, 77; MS (ei) *m/e* 267.127 (M^+). Calc. for $C_{14}H_{18}FNO_3$: *m/e* 267.127. Anal. Calc. for $C_{14}H_{18}FNO_3$: C, 62.9; H, 6.8; N, 5.2. Found: C, 62.9; H, 6.9; N, 5.2.

3-Nitrovaline 7d. A suspension of the nitrovaline derivative **6d** (0.30 g, 1.0 mmol) in 6N HCl (30 ml) was heated at reflux for 2 h, then it was cooled and concentrated under reduced pressure. The residue dissolved in water and that aqueous solution was washed with ethyl acetate, then concentrated under reduced pressure to give the hydrochloride salt of the title compound **7d** (0.14 g, 70%): mp 143-145 °C; ^{1}H NMR δ 1.79 (3H, s), 1.86 (3H, s), 4.71 (1H, s); ^{13}C NMR δ 25.2, 25.6, 60.4, 89.2, 170.1; υ_{max} 1666, 1601, 1552, 1508 cm^{-1}; MS (fab) *m/e* 163 ($M-Cl^+$), 116, 72, 70.

A solution of the hydrochloride salt of 3-nitrovaline **7d** (0.30 g, 1.5 mmol) in ethanol (30 ml) and aniline (3 ml) was allowed to stand at room temperature for 18 h. The precipitate that formed was collected by filtration and washed with ethanol to give the title compound **7d** (0.11 g, 46%): mp 145-147 °C; ^{1}H NMR δ 1.74 (3H, s), 1.79 (3H, s), 4.34 (1H, s); ^{13}C NMR δ 24.9, 25.9, 62.1, 89.6, 171.6; MS (fab) *m/e* 163 ($M+H^+$), 116, 72, 70.

3-Nitro-*iso*-leucine 7e Hydrochloride Salt. Treatment of the major diastereomer of the *iso*-leucine derivative **6e** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitrovaline **7d** gave the title compound in 70% yield as a single diastereomer: mp 132-133 °C (dec.); ^{1}H NMR δ 0.94 (3H, t, J = 7 Hz), 1.75 (3H, s), 2.08 (1H, qd, J = 7 and 14 Hz), 2.19 (1H, qd, J = 7 and 14 Hz), 4.47 (1H, s); ^{13}C NMR δ 9.3, 20.7, 33.1, 61.2, 93.5, 171.1; υ_{max} 1642, 1601, 1539, 1495 cm^{-1}; MS (fab) *m/e* 177 (M-Cl$^+$), 130, 86, 84. Treatment of the minor diastereomer of the *iso*-leucine derivative **6e** with 6N HCl under analogous conditions afforded the other diastereomer of the title compound in 64% yield: mp 132-135 °C (dec.); ^{1}H NMR δ 0.92 (3H, t, J = 7 Hz), 1.63 (3H, s), 2.20 (1H, qd, J = 7 and 14 Hz), 2.22 (1H, qd, J = 7 and 14 Hz), 4.72 (1H, s); ^{13}C NMR δ 9.2, 19.6, 32.2, 59.9, 93.0, 170.1; υ_{max} 1647, 1608, 1549, 1506 cm^{-1}; MS (fab) *m/e* 177 (M-Cl$^+$), 130, 86, 84.

***N-tert*-Butoxycarbonyl-3-nitroalanine *tert*-Butyl Ester 15a.** Treatment of the bromide **14** with the anion of nitromethane **5a**, as described above for the reactions of the bromide **4**, gave the title compound **15a** in 63% yield: mp 99-100 °C; ^{1}H NMR δ 1.45 (9H, s), 1.48 (9H, s), 4.61 (1H, td, J = 3.5 and 7 Hz), 4.82 (1H, dd, J = 3.5 and 15 Hz), 4.95 (1H, dd, J = 3.5 and 15 Hz), 5.52 (1H, br d, J = 7 Hz); ^{13}C NMR δ 27.5, 28.2, 51.8, 75.7, 80.8, 84.0, 155.2, 167.0; υ_{max} 3436, 1760, 1712, 1562, 1498 cm^{-1}; MS (ei) *m/e* 290 (M$^+$), 234, 178; MS (ei) *m/e* 290.149 (M$^+$). Calc. for $C_{12}H_{22}N_2O_6$: *m/e* 290.148. Anal. Calc. for $C_{12}H_{22}N_2O_6$: C, 49.6; H, 7.6; N, 9.7. Found: C, 49.5; H, 7.8; N, 9.4.

***N-tert*-Butoxycarbonyl-3-methyl-3-nitroalanine *tert*-Butyl Ester 15b.** Treatment of the bromide **14** with the anion of nitroethane **5b**, as described above for the reactions of the bromide **4**, gave the title compound **15b** in 60% yield as a 2:1 mixture of diastereomers. Chromatography of the mixture gave the major diastereomer in 34% yield, as needles from light petroleum: mp 65-66 °C; ^{1}H NMR δ 1.45 (9H, s), 1.49 (9H, s), 1.66 (3H, d, J = 7 Hz), 4.66 (1H, dd, J = 4 and 8 Hz), 4.89 (1H, dq, J = 4 and 7 Hz), 5.42 (1H, br d, J = 8 Hz); ^{13}C NMR δ 15.6, 27.7, 28.1, 56.3, 80.5, 80.7, 83.5, 155.1, 167.0; υ_{max} 3420, 1720, 1550 cm^{-1}; MS (ei) *m/e* 304 (M$^+$), 248, 232, 202, 192, 102; Anal. Calc. for $C_{13}H_{24}N_2O_6$: C, 51.3; H, 8.0; N, 9.2. Found: C, 51.6; H, 8.3; N, 9.0. Continued chromatography gave the minor diastereomer as an oil in 17% yield: ^{1}H NMR δ 1.49 (18H, s), 1.65 (3H, d, J = 7 Hz), 4.64 (1H, dd, J = 3 and 9 Hz), 5.70 (1H, dq, J = 3 and 7 Hz), 5.94 (1H, br d, J = 9 Hz); ^{13}C NMR δ 15.7, 27.7, 28.2, 55.9, 80.6, 82.8, 83.7, 156.0, 167.5; υ_{max} 3420, 1740, 1560 cm^{-1}; MS (ei) *m/e* 305 (M+H$^+$), 249, 232, 202, 192, 102; MS (ei) *m/e* 249.108 (M-$C_4H_7^+$). Calc. for $C_9H_{17}N_2O_6$: *m/e* 249.109.

***N-tert*-Butoxycarbonyl-3-nitrophenylalanine *tert*-Butyl Ester 15c.** Treatment of the bromide **14** with the anion of α-nitrotoluene **5c**, as described above for the reactions of the bromide **4**, gave the title compound **15c** in 71% yield as a 1:1 mixture of diastereomers. Crystallization of the mixture from dichloromethane/light petroleum resulted in the formation of two distinct crystal types, which were partially separated by sorting. One diastereomer of the title compound **15c** crystallized as spars: mp 167-169 °C; ^{1}H NMR δ 1.35 (9H, s), 1.42 (9H, s), 4.99 (1H, t, J = 8 Hz), 5.08 (1H, br d, J = 8 Hz), 6.00 (1H, d, J = 8 Hz), 7.4 (5H, m); υ_{max} 3430, 1740, 1570, 1515 cm^{-1}; MS (ei) *m/e* 367 (M+H$^+$), 311, 255, 230, 219, 208, 175, 164, 163; MS (ei) *m/e* 367.186 (M+H$^+$). Calc. for $C_{18}H_{27}N_2O_6$: *m/e* 367.187. The other diasteromer of the title compound **15c** crystallized as needle clusters: mp 163-166 °C; ^{1}H NMR δ 1.33 (9H, s), 1.39 (9H, s),

4.95 (1H, dd, J = 5.5 and 9.5 Hz), 5.49 (1H, br d, J = 9.5 Hz), 6.03 (1H, d, J = 5.5 Hz), 7.3-7.5 (5H, m); υ_{max} 3410, 1735, 1540, 1505 cm^{-1}; MS (ei) *m/e* 367 ($M+H^+$), 311, 255, 230, 219, 175, 164, 163; MS (ei) *m/e* 367.188 ($M+H^+$). Calc. for $C_{18}H_{27}N_2O_6$: *m/e* 367.187.

3-Nitroalanine 7a Hydrochloride Salt. A solution of the ester **15a** (150 mg, 0.41 mmol) in trifluoroacetic acid (10 ml) and chloroform (10 ml) was heated at reflux for 0.25 h, then it was cooled and concentrated under reduced pressure. The residue was dissolved in 0.1 N HCl, and the solution was washed with ethyl acetate then concentrated under reduced pressure, to give the title compound (34 mg, 63%): mp 125-127 °C; ^1H NMR δ 4.55 (1H, dd, J = 3 and 5.5 Hz), 5.06 (1H, dd, J = 3 and 17 Hz), 5.16 (1H, dd, J = 5.5 and 17 Hz); υ_{max} 1606, 1540 cm^{-1}; ^{13}C NMR δ 53.1, 75.1, 171.1; MS (fab) *m/e* 135 ($M+H^+$), 108, 91, 75.

3-Methyl-3-nitroalanine 7b Hydrochloride Salt. Treatment of the major diastereomer of the β-methylalanine derivative **15b** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitroalanine **7a** gave the title compound in 56% yield as a single diastereomer: ^1H NMR δ 1.63 (3H, d, J = 7 Hz), 4.68 (1H, d, J = 2.5 Hz), 5.23 (1H, dq, J = 2.5 and 7 Hz); ^{13}C NMR δ 16.0, 57.3, 82.6, 170.5; MS (fab) *m/e* 149 ($M+H^+$), 110, 108, 103, 102. Treatment of the minor diastereomer of the methylalanine derivative **15b** with 6N HCl under analogous conditions afforded the other diastereomer of the title compound in 61% yield: ^1H NMR δ 1.79 (3H, d, J = 7.5 Hz), 4.64 (1H, d, J = 4 Hz), 5.35 (1H, dq, J = 4 and 7.5 Hz); ^{13}C NMR δ 16.9, 56.7, 82.0, 170.0; MS (fab) 149 ($M+H^+$), 110, 108, 103, 102.

3-Nitrophenylalanine 7c Hydrochloride Salt. Treatment of a 1:1 mixture of the diastereomers of the phenylalanine derivative **15c** with 6N HCl, as described above for the synthesis of the hydrochloride salt of 3-nitroalanine **7a** gave the title compound in 45% yield as a 1:1 mixture of diastereomers: ^1H NMR δ 4.68 (0.5H, d, J = 5.5 Hz), 5.02 (0.5H, d, J = 5 Hz), 6.41 (0.5H, d, J = 5 Hz), 6.53 (0.5 H, d, J = 5.5 Hz), 7.3-7.5 (5H, m); υ_{max} 1652, 1604, 1560 cm^{-1}; MS (fab) *m/e* 211 ($M+H^+$), 164, 148, 120.

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Directing Bromination of Piperazine-2,5-diones

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Abstract

From intermolecular and intramolecular competition experiments, it has been established that, by comparison with an *N*-methyl substituent, an *N*-acetyl group deactivates glycine residues in piperazine-2,5-diones towards free-radical bromination. Combined with the ease of introduction and removal of *N*-acetyl substituents, the deactivating effect provides a method for regiocontrolled functionalization of these compounds.

Introduction

Interest in the synthesis of piperazine-2,5-diones stems from the wide ranging natural occurrence and biological activity of this class of compounds. For example, albonoursin (1) has been isolated from *Streptomyces albus* var. *fungatus*, *Streptomyces noursei* and *Actinomyces tumemacerance*, and has been found to exhibit antibacterial and antitumour activity,[1] bicyclomycin (2) has been obtained from *Streptomyces sapporonensis* and *Streptomyces aizunensis*, and has been shown to be a broad spectrum antibiotic,[2] while gliotoxin (3) has been isolated from a variety of sources including *Aspergillus fumigatus*, *Gliocladium fimbriatum* and *Penicillium obsurum*, and is known to have antibacterial, antifungal, antiviral and immunosuppressive properties.[3]

[1] Brown, R., and Kelley, C., *Annu. Rep. N.Y. State Dep. Health*, 1957, 10; 1958, 47; 1960, 50; 1960, 52; 1961, 40; Rao, K. V., and Cullen, W. P., *J. Am. Chem. Soc.*, 1960, **82**, 1127; Fukushima, K., Yazawa, K., and Arai, T., *J. Antibiot.*, 1973, **26**, 175.
[2] Miyoshi, T., Miyairi, N., Aoki, H., Kohsaka, M., Sakai, H., and Imanaka, H., *J. Antibiot.*, 1972, **25**, 569; Kamiya, T., Maeno, S., Hashimoto, M., and Mine, Y., *J. Antibiot.*, 1972, **25**, 576; Nishida, M., Mine, Y., and Matsubara, T., *J. Antibiot.*, 1972, **25**, 582; Nishida, M., Mine, Y., Matsubara, T., Goto, S., and Kuwahara, S., *J. Antibiot.*, 1972, **25**, 594; Miyamura, S., Ogasawara, N., Otsuka, H., Niwayama, S., Tanaka, H., Take, T., Uchiyama, T., Ochiai, H., Abe, K., Koizumi, K., Asao, K., Matsuki, K., and Hoshino, T., *J. Antibiot.*, 1972, **25**, 610; Miyamura, S., Ogasawara, N., Otsuka, H., Niwayama, S., Tanaka, H., Take, T., Uchiyama, T., and Ochiai, H., *J. Antibiot.*, 1973, **26**, 479.
[3] Waring, R., and Mullbacher, A., *Med. Res. Rev.*, 1988, **8**, 76; Taylor, A., in 'Microbial Toxins' (Eds S. Kadis, A. Ciegler and S. J. Ajl) Vol. 7, p. 337 (Academic: New York 1971).

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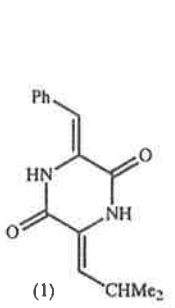
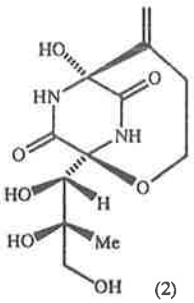
A common approach to the synthesis of the more complex piperazine-2,5-diones is through elaboration of simple precursors derived from proteinogenic amino acids.[4] In this regard, procedures for the regiocontrolled functionalization of piperazine-2,5-diones have considerable potential as many of the target molecules are asymmetrically substituted. The radical bromination of certain symmetric glycine anhydride derivatives with *N*-bromosuccinimide is known,[5–7] but no attempts to direct bromination using different *N*-substituents have been reported. Accordingly, we have now examined the effect of *N*-methyl and *N*-acetyl substituents on the halogenation.



(1)



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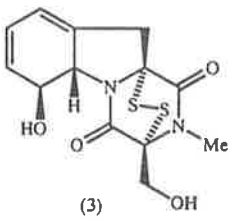


(3)

Results and Discussion

Initially, to gauge the effect of the substituents on reactivity, we examined reactions of sarcosine anhydride (4) and 1,4-diacetylpiperazine-2,5-dione (7). Bromination of the sarcosine derivative (4) to give the corresponding bromides (5a) and (6) has been reported.[5] In a similar fashion, the reaction of 1,4-diacetylpiperazine-2,5-dione (7) with *N*-bromosuccinimide in carbon tetrachloride, initiated with azobisisobutyronitrile, gave the bromides (8a) and (9a). Due to their instability, the bromides (8a) and (9a) were characterized by conversion into the corresponding thioethers (8b) and (9b), through treatment with 4-chlorothiophenol and pyridine. The di(thioether) (9b) was only obtained in 15% yield, presumably as a result of the particular instability of the dibromide (9a). The ^{1}H n.m.r. spectrum of the dibromide (9a) showed only one signal for the methyl group hydrogens, at δ 2·65, and one for the hydrogens attached to C3 and C6, at δ 6·93. Likewise, the spectrum of the di(thioether) (9b) showed only one resonance for each type of hydrogen. On this basis, it appears that the dibromide (9a) and the di(thioether) (9b) were each formed as a single diastereomer. Presumably this

[4] Ganem, B., *Tetrahedron*, 1978, **34**, 3353; Trown, P. W., *Biochem. Biophys. Res. Commun.*, 1968, **33**, 402; Fukuyama, T., Nakatsuka, S., and Kishi, Y., *Tetrahedron*, 1981, **37**, 2045; Williams, R. M., *Tetrahedron Lett.*, 1981, **22**, 2341; Williams, R. M., and Rastetter, W. H., *J. Org. Chem.*, 1980, **45**, 2625.

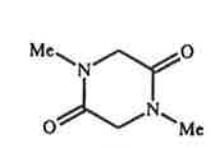
[5] Badran, T. W., and Easton, C. J., *Aust. J. Chem.*, 1990, **43**, 1455.

[6] Chai, C. L. L., and Page, D. M., *Tetrahedron Lett.*, 1993, **34**, 4373.

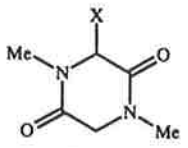
[7] Williams, R. M., Armstrong, R. W., Maruyama, L. K., Dung, J., and Anderson, O. P., *J. Am. Chem. Soc.*, 1985, **107**, 3246; Williams, R. M., and Kwast, A., *J. Org. Chem.*, 1988, **53**, 5785.

reflects the greater thermodynamic stability of the *cis* isomers of 3,6-disubstituted piperazine-2,5-diones.[8]

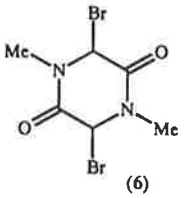
The relative reactivity of the piperazinediones (4) and (7) was determined by reaction of an equimolar mixture of each substrate and *N*-bromosuccinimide, in the presence of *N*-t-butylbenzamide (0·1 mole equiv.) as an internal standard. The crude reaction mixture was cooled and concentrated, and the residue was analysed by means of ^{1}H n.m.r. spectroscopy. Integration of signals for the internal standard (δ 1·44, s, 9H, Me_3, 100%), the piperazinediones (4) (δ 3·96, s, 2×CH_2, 4H, 20%) and (7) (δ 4·66, s, 2×CH_2, 4H, 420%), and the bromides (5a) (δ 6·02, s, H3, 1H, 85%) and (6) (δ 6·13, s, H3,6, 2H, 22%) showed that 5% of the sarcosine anhydride (4) remained and the bromides (5a) and (6) were produced in yields of approximately 75 and 10%, respectively, while 95% of the diacetylpiperazinedione (7) remained unreacted. There was no indication of formation of either of the bromides (8a) or (9a), as indicated by the absence of resonances at δ 6·87 and 6·93, respectively.



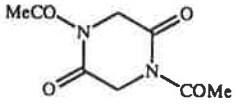
(4)



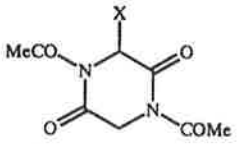
(5a) X = Br
(5b) X = 4-ClC_6H_4S



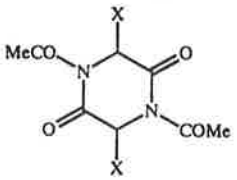
(6)



(7)



(8a) X = Br
(8b) X = 4-ClC_6H_4S



(9a) X = Br
(9b) X = 4-ClC_6H_4S

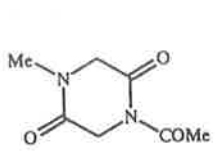
The deactivating effect of the *N*-acetyl substituent was further examined by studying reactions of 1-acetyl-4-methylpiperazine-2,5-dione (10), obtained by acetylation of glycylsarcosine anhydride[9] with acetic anhydride. Reaction of the piperazinedione (10) with *N*-bromosuccinimide under conditions analogous to those described above gave only the unstable bromide (11a), which was characterized by conversion into the thioether (11b) on treatment with 4-chlorothiophenol, and the ether (12) on treatment with methanol. Presumably the reaction of the bromide (11a) with methanol afforded the ether (11c) but the *N*-acetyl substituent of that compound hydrolysed during workup of the reaction mixture and chromatography of the crude product.

The regioselectivity of the halogenation of the piperazinedione (10) was assigned by comparison of the ^{1}H n.m.r. spectrum of the bromide (11a) with those of

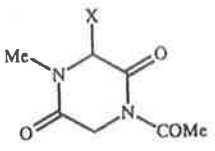
[8] Williams, R. M., Anderson, O. P., Armstrong, R. W., Josey, J., Meyers, H., and Eriksson, C., *J. Am. Chem. Soc.*, 1982, **104**, 6092; Williams, R. M., Armstrong, R. W., Maruyama, L. K., Dung, J., and Anderson, O. P., *J. Am. Chem. Soc.*, 1985, **107**, 3246; Benedetti, E., Marsh, R. E., and Goodman, M., *J. Am. Chem. Soc.*, 1976, **98**, 6676.

[9] Levene, P. A., Bass, L. W., Rothen, A., and Steiger, R. E., *J. Biol. Chem.*, 1954, **81**, 697.

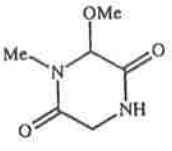
the bromides (5a) and (8a). The C3 proton of the bromide (11a) gave rise to a singlet resonance at δ 5·98. This chemical shift is similar to that of the signal for the C3 proton of the dimethylpiperazinedione (5a), at δ 5·79,[5] but different from that of the corresponding diacetyl derivative (8a), at δ 6·87. The ^{1}H n.m.r. spectra of the thioethers (11b), (5b) and (8b) support the assignment of regioselectivity of functionalization of the piperazinedione (10). The resonance for the C3 proton of the thioether (11b) appeared as a singlet at δ 4·99, with a similar chemical shift to that for the dimethyl derivative (5b) at δ 4·94, but 1·23 ppm upfield from that of the corresponding diacetyl derivative (8b). The thioether (5b) was obtained by treatment of the piperazinedione (4) with *N*-bromosuccinimide, followed by reaction of the crude product bromide (5a) with 4-chlorothiophenol.



(10)



(11a) X = Br
(11b) X = 4-ClC$_6$H$_4$S
(11c) X = OMe



(12)

Confirmation of the regioselectivity of bromination of the piperazinedione (10) was obtained by heating the ether (12) in refluxing 6 N hydrochloric acid, in the presence of alanine as an internal standard. Analysis of the concentrated product mixture by means of ^{1}H n.m.r. spectroscopy showed that glycine was produced in 60% yield, but there was no evidence of the presence of sarcosine.

From the reactions of the piperazinediones (4), (7) and (10), it is clear that, by comparison with an *N*-methyl substituent, an *N*-acetyl group deactivates glycine residues in piperazine-2,5-diones towards free-radical bromination. This effect is analogous to that observed with amino acid derivatives where the amino group is protected as a benzamide or a phthalimide.[10] Relative to the amido substituent, the greater steric bulk and reduced electron-donating capability of the imido group disfavour radical formation at the adjacent position.

An *N*-acetyl substituent is easily introduced on to a piperazinedione and readily removed,[11] as indicated in the synthesis of the piperazinediones (7) and (10) and the interconversion of the bromide (11a) into the ether (12), outlined above. On this basis, there is considerable scope to exploit the effect of the *N*-acetyl substituent, on reactions of piperazinediones with *N*-bromosuccinimide, in the regiocontrolled halogenation and elaboration of these compounds.

Experimental

Melting points are uncorrected. Light petroleum refers to the fraction with b.p. 66–68°. Radial chromatography was carried out on a Chromatotron 7924T (Harrison Research, Palo

[10] Easton, C. J., Tan, E. W., and Hay, M. P., *J. Chem. Soc., Chem. Commun.*, 1989, 385; Easton, C. J., Hutton, C. A., Rositano, G., and Tan, E. W., *J. Org. Chem.*, 1991, **56**, 5614.
[11] Gallina, C., and Liberatori, A., *Tetrahedron*, 1974, **30**, 667; Badran, T. W., Easton, C. J., Horn, E., Kociuba, K., May, B. L., Schliebs, D. M., and Tiekink, E. R. T., *Tetrahedron: Asymmetry*, 1993, **4**, 197.

Alto/TC Research, Norwich) by using Merck silica gel 60 PF_{254}, eluting with a gradient of light petroleum/ethyl acetate. N.m.r. spectra were recorded on either a Bruker CXP-300 or a Varian FT80A spectrometer, as dilute solutions in (D)chloroform, with tetramethylsilane as the internal standard. Electron impact mass spectra were recorded on either an AEI MS-902 or a Hewlett Packard HP-5995C spectrometer. Microanalyses were performed by the Microanalytical Facility, Otago University, New Zealand.

Glycine anhydride and sarcosine anhydride (4) were purchased from Sigma Chemical Co. 1,4-Diacetylpiperazine-2,5-dione (7) was prepared by treatment of glycine anhydride with acetic anhydride.[9]

1,4-Diacetyl-3-(4-chlorophenylthio)piperazine-2,5-dione (8b)

A mixture of the piperazinedione (7) (0·2 g, 1 mmol), *N*-bromosuccinimide (0·18 g, 1 mmol) and azobisisobutyronitrile (17 mg, 0·1 mmol) in dry carbon tetrachloride (10 ml) was heated at reflux under nitrogen for 2 h, then it was cooled and filtered. The filtrate was concentrated under reduced pressure to give a pale yellow oil, the ^{1}H n.m.r. spectrum of which showed the presence of the bromides (8a) and (9a) in the ratio 13:1. Signals for 1,4-diacetyl-3-bromopiperazine-2,5-dione (8a) were observed at δ 2·61, s, 3H; 2·62, s, 3H; 4·30, d, J 19 Hz, 1H; 5·24, d, J 19 Hz, 1H; 6·87, s, 1H.

The crude product of bromination of the piperazinedione (7) was dissolved in dry dichloromethane at 0°, then 4-chlorothiophenol (0·22 g, 1·5 mmol) and pyridine (0·15 g, 1·5 mmol) were added. The mixture was stirred at room temperature for 16 h, before it was washed with dilute hydrochloric acid and brine, then dried and concentrated under reduced pressure. Chromatography of the residual oil afforded a colourless solid which was recrystallized from light petroleum/ethyl acetate to give *1,4-diacetyl-3-(4-chlorophenylthio)piperazine-2,5-dione* (8b) (235 mg, 69%), m.p. 85–87° (Found: C, 49·3; H, 3·8; N, 8·1; S, 9·5. $C_{14}H_{13}ClN_2O_4S$ requires C, 49·3; H, 3·9; N, 8·2; S, 9·4%). ^{1}H n.m.r. δ 2·55, s, 3H; 2·56, s, 3H; 4·09, d, J 18 Hz, 1H; 5·13, d, J 18 Hz, 1H; 6·22, s, 1H; 7·4–7·6, m, 4H.

3-(4-Chlorophenylthio)-1,4-dimethylpiperazine-2,5-dione (5b)

The piperazinedione (4) (0·4 g, 2·81 mmol) was treated with *N*-bromosuccinimide (0·5 g, 2·81 mmol), and that crude product mixture was treated with 4-chlorothiophenol (0·61 g, 4·21 mmol), as described above for the synthesis of the thioether (8b). Chromatography of the crude product afforded a colourless solid which was recrystallized from ethyl acetate/methanol to give *3-(4-chlorophenylthio)-1,4-dimethylpiperazine-2,5-dione* (5b) (54%), m.p. 160–161° [Found: m/z 283·0309. $C_{12}H_{12}{}^{35}ClN_2O_2S$ ($M^{+\bullet} - H$) requires m/z 283·0308]. ^{1}H n.m.r. δ 2·52, d, J 18 Hz, 1H; 2·78, s, 3H; 3·15, s, 3H; 3·46, d, J 18 Hz, 1H; 4·94, s, 1H; 7·3–7·5, m, 4H.

1,4-Diacetyl-3,6-di(4-chlorophenylthio)piperazine-2,5-dione (9b)

The piperazinedione (7) was treated with *N*-bromosuccinimide (2 mole equiv.), and that crude product mixture was treated with 4-chlorothiophenol, as described above for the synthesis of the thioether (8b). The ^{1}H n.m.r. spectrum of the product of bromination showed signals for one diastereomer of 1,4-diacetyl-3,6-dibromopiperazine-2,5-dione (9a) at δ 2·65, s, 6H; 6·93, s, 2H.

Chromatography of the product of the reaction with 4-chlorothiophenol gave one diastereomer of *1,4-diacetyl-3,6-di(4-chlorophenylthio)piperazine-2,5-dione* (9b) (15%) as a white solid after recrystallization from light petroleum/ethyl acetate, m.p. 167–169° (Found: C, 50·0; H, 3·4; N, 5·8; S, 13·3. $C_{20}H_{16}Cl_2N_2O_4S_2$ requires C, 49·7; H, 3·3; N, 5·8; S, 13·3%). ^{1}H n.m.r. δ 2·60, s, 6H; 6·11, s, 2H; 7·3–7·6, m, 8H.

Competitive Reaction of 1,4-Dimethylpiperazine-2,5-dione (4) and 1,4-Diacetylpiperazine-2,5-dione (7) with N-Bromosuccinimide

Treatment of a mixture of the piperazinediones (4) (0·38 g, 2·65 mmol) and (7) (0·52 g, 2·64 mmol) and *N*-t-butylbenzamide (0·047 g, 0·265 mmol) with *N*-bromosuccinimide (0·47 g,

2·64 mmol), as described above for the reactions of the diacetylpiperazinedione (7), afforded a crude product mixture. The ^{1}H n.m.r. spectrum of the mixture indicated the presence of the starting materials (4), (7) and *N*-t-butylbenzamide, and the bromides (5a) and (6), in the ratio 0·05 : 0·95 : 1·0 : 0·75 : 0·10.

1-Acetyl-4-methylpiperazine-2,5-dione (10)

Glycylsarcosine anhydride[9] (200 mg, 1·56 mmol) was dissolved in acetic anhydride (2 ml), and the mixture was heated at reflux for 4 h, then it was cooled and concentrated under reduced pressure. Chromatography of the residual oil afforded a colourless solid which was recrystallized from light petroleum/ethyl acetate to give *1-acetyl-4-methylpiperazine-2,5-dione* (10) (212 mg, 81%), m.p. 60–61° (Found: C, 49·3; H, 5·6; N, 16·4. $C_7H_{10}N_2O_3$ requires C, 49·4; H, 5·9; N, 16·5%). ^{1}H n.m.r. δ 2·56, s, 3H; 3·01, s, 3H; 4·14, s, 2H; 4·37, s, 2H.

1-Acetyl-3-(4-chlorophenylthio)-4-methylpiperazine-2,5-dione (11b)

The piperazinedione (10) was treated with *N*-bromosuccinimide (1 mole equiv.), and that crude product mixture was treated with 4-chlorothiophenol, as described above for the synthesis of the thioether (8b). The ^{1}H n.m.r. spectrum of the product of bromination showed signals for 1-acetyl-3-bromo-4-methylpiperazine-2,5-dione (11a) at δ 2·62, s, 3H; 3·01, s, 3H; 3·82, d, *J* 18 Hz, 1H; 4·99, d, *J* 18 Hz, 1H; 5·98, s, 1H.

Chromatography of the product of the reaction with 4-chlorothiophenol gave *1-acetyl-3-(4-chlorophenylthio)-4-methylpiperazine-2,5-dione* (11b) (74%) as a colourless solid after recrystallization from light petroleum/ethyl acetate, m.p. 115–117° (Found: C, 49·8; H, 4·2; N, 9·1; S, 10·5. $C_{13}H_{13}ClN_2O_3S$ requires C, 49·9; H, 4·2; N, 9·0; S, 10·3%). ^{1}H n.m.r. δ 2·57, s, 3H; 3·13, s, 3H; 3·08, d, *J* 18 Hz, 1H; 4·49, d, *J* 18 Hz, 1H; 4·99, s, 1H; 7·3–7·5, m, 4H.

6-Methoxy-1-methylpiperazine-2,5-dione (12)

A mixture of the piperazinedione (10) (0·57 g, 3·3 mmol), *N*-bromosuccinimide (0·59 g, 3·3 mmol) and azobisisobutyronitrile (5 mg) in carbon tetrachloride (30 ml) was heated at reflux under nitrogen for 0·5 h, then it was cooled. Methanol (1·0 ml) was added and the resultant mixture was stirred at room temperature for 16 h, before it was concentrated under reduced pressure. Chromatography of the residual oil gave *6-methoxy-1-methylpiperazine-2,5-dione* (12) (36%) as an oil, which crystallized from ethyl acetate/light petroleum, in 21% yield, as a colourless solid, m.p. 116–117° (Found: C, 45·7; H, 6·2; N, 17·6. $C_6H_{10}N_2O_3$ requires C, 45·6; H, 6·4; N, 17·7%). ^{1}H n.m.r. δ 3·10, s, 3H; 3·52, s, 3H; 3·96, dd, *J* 4, 17 Hz, 1H; 4·16, d, *J* 17 Hz, 1H; 4·70, s, 1H; 6·3, br, 1H. ^{13}C n.m.r. δ 34·9, 46·8, 58·4, 90·1, 166·5, 167·7.

Hydrolysis of 6-Methoxy-1-methylpiperazine-2,5-dione (12)

A mixture of the piperazinedione (12) (21 mg, 0·13 mmol), alanine (12 mg, 0·13 mmol) and hydrochloric acid (6 N, 10 ml) was heated at reflux for 12 h, then it was cooled and concentrated under reduced pressure. The residue was dissolved in deuterium oxide (3 ml), and the solution was concentrated under reduced pressure. The ^{1}H n.m.r. spectrum (CD_3OD) of that residue showed the presence of alanine (δ 1·56, d, *J* 7 Hz, 3H) and glycine (δ 3·77, s, 2H) in the mole ratio 3 : 2. The presence of glycine and the absence of sarcosine were confirmed by the addition of authentic samples.

Acknowledgments

This work was supported by grants from the Australian Research Council and the Research Fund of Victoria University of Wellington.

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Crystal structure of 4,5-bis(2,6-dichlorophenyl)-1-oxide-2-oxa-1,3-diazole, $C_{14}H_6Cl_4N_2O_2$

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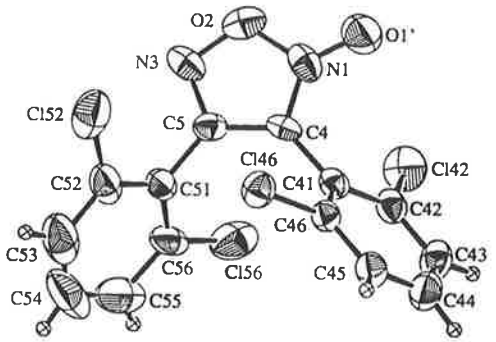

Source of material: The compound is the dimerization product of the parent nitrile oxide; m. pt. 474.5 - 476 K. Lit. m. pt. 474 - 476 K (see ref. 1).

The five-membered ring is planar to +/– 0.003(5) Å and the dihedral angles between this plane and the two aryl rings are 63.1° and 65.6°, respectively. The delocalization of electron density through the five-membered ring is indicated by the following bond distances: d(N(1)–O(1'))=1.115(5)Å, d(N(1)–O(2))= 1.424(6)Å, d(N(1)–C(4))= 1.327(6)Å, d(N(3)–O(2))= 1.351(6)Å, d(N(3)–C(5))= 1.355(6)Å and d(C(4)–C(5))= 1.414(7) Å.

$C_{14}H_6Cl_4N_2O_2$, monoclinic, $P2_1/n$ (No. 14), a =8.391(2) Å, b =18.344(6) Å, c =9.825(2) Å, β =91.21(9)°, V =1512.0 Å^3, Z =4, $R(F)$ =0.056, $R_w(F)$ =0.057.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.24 x 0.24 x 0.32 mm
Wavelength:	Mo K_α radiation (0.7107 Å)
μ:	7.88 cm^{-1}
Diffractometer:	AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
N(hkl)$_{unique}$:	3599
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	223
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(43)	4e	0.152(7)	0.079(3)	0.095(6)	0.11(2)
H(44)	4e	–0.037(7)	0.104(3)	0.255(6)	0.11(2)
H(45)	4e	–0.148(6)	0.010(2)	0.385(5)	0.08(2)
H(53)	4e	0.251(7)	–0.237(3)	0.749(7)	0.11(2)
H(54)	4e	0.47(1)	–0.136(5)	0.770(9)	0.20(2)
H(55)	4e	0.547(6)	–0.078(3)	0.590(6)	0.05(2)

Reference

1. Koopman, H., Daams, J.: Relation between structure and herbicidal activity of substituted benzonitriles. Weed Research 5 (1965) 319-326.

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(42)	4e	0.3203(2)	–0.0407(1)	0.0193(2)	0.094(1)	0.118(1)	0.107(1)	–0.020(1)	0.030(1)	0.017(1)
Cl(46)	4e	–0.0715(2)	–0.13711(8)	0.4102(1)	0.0789(9)	0.0746(9)	0.0744(9)	0.0036(8)	0.0123(7)	0.0095(7)
Cl(52)	4e	0.1381(3)	–0.2962(1)	0.5261(2)	0.156(2)	0.112(1)	0.111(2)	0.042(1)	0.043(1)	0.031(1)
Cl(56)	4e	0.5157(2)	–0.0822(1)	0.3280(3)	0.085(1)	0.093(1)	0.187(2)	–0.006(1)	–0.036(1)	–0.025(1)
O(1')	4e	0.1152(5)	–0.1885(2)	–0.0145(5)	0.120(4)	0.108(3)	0.088(3)	–0.014(3)	–0.004(3)	0.004(3)
O(2)	4e	0.2566(5)	–0.2656(2)	0.1187(5)	0.097(3)	0.070(3)	0.106(4)	–0.006(3)	0.024(3)	–0.019(2)
N(1)	4e	0.1764(6)	–0.1983(3)	0.0949(5)	0.077(3)	0.104(4)	0.055(3)	–0.022(3)	–0.004(3)	0.013(3)
N(3)	4e	0.3179(6)	–0.2671(3)	0.2470(5)	0.089(3)	0.111(4)	0.054(3)	–0.013(3)	0.001(3)	–0.009(3)
C(4)	4e	0.1882(6)	–0.1580(3)	0.2069(5)	0.062(3)	0.069(3)	0.046(3)	–0.014(3)	0.001(2)	–0.018(3)
C(5)	4e	0.2757(6)	–0.2019(3)	0.3001(6)	0.064(3)	0.061(3)	0.065(4)	0.005(3)	0.004(3)	–0.014(3)
C(41)	4e	0.1215(6)	–0.0839(3)	0.2169(5)	0.053(3)	0.066(3)	0.054(3)	–0.007(3)	–0.008(2)	0.001(3)
C(42)	4e	0.1728(6)	–0.0266(3)	0.1360(5)	0.063(3)	0.076(4)	0.067(4)	–0.009(3)	–0.011(3)	0.010(3)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(43)	4*e*	0.1114(8)	0.0431(4)	0.1503(7)	0.082(4)	0.074(4)	0.099(5)	–0.019(4)	–0.013(4)	0.030(4)
C(44)	4*e*	–0.0058(8)	0.0557(4)	0.2433(7)	0.089(5)	0.073(4)	0.098(5)	0.006(4)	–0.015(4)	0.013(4)
C(45)	4*e*	–0.0597(7)	0.0010(3)	0.3229(6)	0.071(4)	0.081(4)	0.066(4)	0.009(3)	–0.004(3)	0.006(3)
C(46)	4*e*	0.0024(6)	–0.0686(3)	0.3092(5)	0.060(3)	0.061(3)	0.059(3)	0.000(3)	–0.008(3)	0.004(3)
C(51)	4*e*	0.3240(8)	–0.1846(3)	0.4386(6)	0.097(5)	0.078(4)	0.062(4)	0.044(4)	–0.021(3)	–0.018(4)
C(52)	4*e*	0.2681(9)	–0.2237(4)	0.5482(8)	0.136(6)	0.117(6)	0.065(5)	0.075(4)	–0.011(4)	–0.010(5)
C(53)	4*e*	0.312(2)	–0.2057(8)	0.679(1)	0.21(1)	0.18(1)	0.084(9)	0.123(8)	–0.011(8)	–0.01(1)
C(54)	4*e*	0.415(2)	–0.151(1)	0.702(1)	0.25(2)	0.25(2)	0.10(1)	0.17(1)	–0.09(1)	–0.07(2)
C(55)	4*e*	0.475(1)	–0.1132(7)	0.599(2)	0.130(9)	0.126(9)	0.19(1)	0.06(1)	–0.09(1)	–0.074(7)
C(56)	4*e*	0.4346(9)	–0.1283(4)	0.4619(8)	0.107(5)	0.095(5)	0.109(6)	0.050(5)	–0.062(5)	–0.048(4)

Complexes of 2- and 4-Fluorobenzoate Anions and the Corresponding Methyl Esters with β-Cyclodextrin and the Conjugate Acids of 6^A-Amino-6^A-deoxy-β-cyclodextrin and 3^A-Amino-3^A-deoxy-(2^A*S*,3^A*S*)-β-cyclodextrin in Aqueous Solution: a Fluorine-19 Nuclear Magnetic Resonance Study

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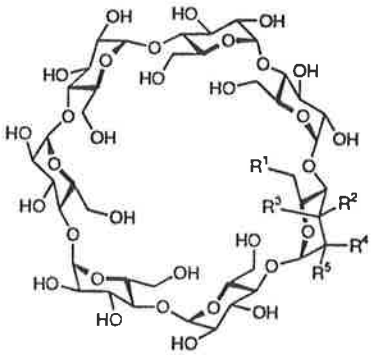
A ^{19}F NMR spectroscopic study shows that inclusion complexes of β-cyclodextrin with aromatic guests are more stable than those of the conjugate acids of 6^A-amino-6^A-deoxy-β-cyclodextrin and 3^A-amino-3^A-deoxy-(2^A*S*,3^A*S*)-β-cyclodextrin, presumably as a result of the effect of the protonated amino substituents of the latter impinging on the character of their hydrophobic cavities.

A ^{19}F NMR spectroscopic study (282.35 MHz) of the formation of inclusion complexes by 2- and 4-fluorobenzoate anions and the corresponding methyl esters with β-cyclodextrin (βCD), in 10% aqueous D_2O solution at pH 6.0, yielded the stability constants K/dm^3 mol^{-1} = 19 ± 3, 50 ± 2, 253 ± 11 and 228 ± 7, respectively. For the corresponding complexes of the fluorinated compounds with the conjugate acid of 6^A-amino-6^A-deoxy-β-cyclodextrin (βCD6NH$_3^+$), K/dm^3 mol^{-1} = 65 ± 2, 69 ± 4, 152 ± 7 and 128 ± 7, respectively, while K/dm^3 mol^{-1} = 32 ± 3, 19 ± 5, 69 ± 2 and 59 ± 2, respectively, for the analogous complexes of the conjugate acid of 3^A-amino-3^A-deoxy-(2^A*S*,3^A*S*)-β-cyclodextrin (βCD3NH$_3^+$).



βCD: $R^1 = R^2 = R^5 = OH$, $R^3 = R^4 = H$
βCD6NH$_3^+$: $R^1 = NH_3^+$, $R^2 = R^5 = OH$, $R^3 = R^4 = H$
βCD3NH$_3^+$: $R^4 = NH_3^+$, $R^1 = R^3 = OH$, $R^2 = R^5 = H$

The stability constants of the complexes formed with βCD vary markedly with the identity of the guest. The complexes of the esters are more than four times more stable than those of the corresponding benzoate anions. This suggests that, although van der Waals interactions between the aromatic moieties of each of the guests and the hydrophobic interior of the cyclodextrin annulus result in complexation, the stronger hydration of the carboxylates destabilises their inclusion complexes. The stability constant of the βCD·*ortho*-ester complex is greater than that of the complex of the *para*-isomer. This may be attributed to the effect of the complementary dipole moments of βCD and the guests on the inclusion complexes. The contribution of the dipole moment of the guest to the stability of the inclusion complex is also evident in the stability constants of the complexes of the esters with the modified cyclodextrins. It is interesting to note the greater stability of the complexes of the anions with βCD6NH$_3^+$ compared to that of the corresponding complexes with βCD and βCD3NH$_3^+$. The extra stabilisation may be attributed to ionic interactions between βCD6NH$_3^+$ and the anions, which are important only with this cyclodextrin, where interaction between charged groups of the cyclodextrin and the guests is compatible with the antiparallel alignment of the dipole moments of the cyclodextrin and the guests in the inclusion complexes.

The complexes of the esters with βCD6NH$_3^+$ are each less stable than those with βCD. This is probably a reflection of the decreased hydrophobicity of the annulus of the modified cyclodextrin, resulting from the effect of hydration of the protonated amino substituent impinging on the character of the cyclodextrin cavity. The stability constants of the complexes of the esters with βCD3NH$_3^+$ are even lower than those with βCD6NH$_3^+$. The synthesis of βCD3NH$_3^+$ occurs with inversion of stereochemistry at C-2 and C-3 of the modified glucopyranose residue,[15] with the result that the protonated amino substituent intrudes into the cavity of the cyclodextrin. The consequent hydration of the substituent will decrease the hydrophobicity of the cyclodextrin annulus, to an even greater extent than for βCD6NH$_3^+$, and the decreased stability of the inclusion complexes of the esters follows.

Techniques used: ^{19}F NMR spectroscopy

References: 20

Fig. 1: The variation in ^{19}F δ_{obs} for (*a*) methyl 2-fluorobenzoate (1.22 mmol dm^{-3}) and (*b*) methyl 4-fluorobenzoate (1.51 mmol dm^{-3}), in the presence of βCD, βCD6NH$_3^+$ and βCD3NH$_3^+$, at pH 6.0, I = 0.40 and 295.5 K

Table 1: Stability constants and ^{19}F chemical shifts of cyclodextrin-fluorinated guest inclusion complexes, in 10% aqueous D_2O at 295.5 K and I = 0.40 mol dm^{-3}

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* To receive any correspondence.

J. CHEM. SOC. PERKIN TRANS. 1 1995

Use of cyclodextrins to limit product inhibition of (*S*)-phenylalanine ammonia lyase

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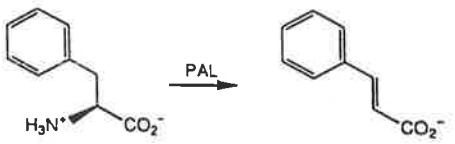
The extent of product inhibition of (*S*)-phenylalanine ammonia lyase, in catalysing the conversion of (*S*)-phenylalanine into *trans*-cinnamate, is reduced, and the efficiency of the reaction increased, through the addition of a cyclodextrin to sequester the cinnamate.

(*S*)-Phenylalanine ammonia lyase (PAL) catalyses the elimination of ammonia and a proton from (*S*)-phenylalanine **1**, to give *trans*-cinnamate **2** (Scheme 1)[1,2] which is a competitive



1 **2**

Scheme 1

inhibitor of the enzyme.[2] While product inhibition of this type is an important form of control of enzyme activity *in vivo*, it limits the utility of enzymes in organic synthesis. In this manuscript we report the use of α- and β-cyclodextrin to limit the effect of the cinnamate **2** on the catalytic activity of PAL, as an illustration of an approach to reduce product inhibition of enzymes.

Reactions of (*S*)-phenylalanine **1** catalysed by PAL (Grade 1 from *Rhodotorula glutinis*, purchased from Sigma Chemical Co.) were followed by monitoring changes in the UV absorbance at 268 nm accompanying formation of the cinnamate **2** (Fig. 1). Comparative experiments using the same quantity of enzyme were carried out with no cyclodextrin and with either α-cyclodextrin or β-cyclodextrin, in the presence and absence of the cinnamate **2**. Owing to its increased solubility in aqueous solutions compared to β-cyclodextrin,[3] it was possible to use α-cyclodextrin at higher concentration.

The results of the experiments show that the addition of the cinnamate **2** increases the extent of reaction over the first 1–3 min, but reduces the extent of reaction in the longer term. The initial increase can be attributed to the effect of the cinnamate **2** to bind competitively to the enzyme and thus slow the negative allosteric effect of the phenylalanine **1**.[4] The later reduction in the extent of each reaction with added cinnamate **2** is a clear illustration of the effect of the cinnamate **2** to inhibit the enzyme, an effect which is also apparent in the reduction in the rate of the reaction as each experiment proceeds and the cinnamate **2** is produced.

At the concentrations used, α- and β-cyclodextrin each marginally reduce the molar UV absorption of the cinnamate **2**.[5] Consequently, the effect of the cyclodextrins to increase the absorption of reaction mixtures clearly demonstrates that both α- and β-cyclodextrin increase the extent of reaction. The obvious interpretation of this effect is that the cyclodextrins complex the cinnamate **2**, irrespective of whether it is only

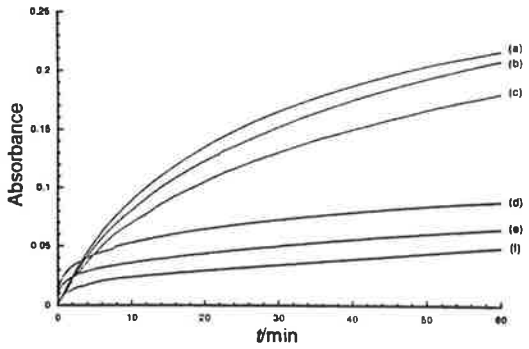


Fig. 1 Change in UV absorbance at 268 nm of solutions containing (*S*)-phenylalanine **1** (0.25×10^{-3} mol dm^{-3}), PAL (*ca.* 70 units dm^{-3}) and either (a) α-cyclodextrin (0.080 mol dm^{-3}), (b) β-cyclodextrin (6.9×10^{-3} mol dm^{-3}), (c) no cyclodextrin, (d) α-cyclodextrin (0.075 mol dm^{-3}) and the cinnamate **2** (0.26×10^{-3} mol dm^{-3}), (e) β-cyclodextrin (6.5×10^{-3} mol dm^{-3}) and the cinnamate **2** (0.26×10^{-3} mol dm^{-3}), or (f) the cinnamate **2** (0.26×10^{-3} mol dm^{-3}) but no cyclodextrin, in 0.05 mol dm^{-3} phosphate buffer at pH 6.9 and 303 K.

produced during the reaction or also added initially. This reduces the concentration of the cinnamate **2** free in solution, thus limiting the inhibitory effect on the enzyme. The results indicate that each cyclodextrin binds the cinnamate **2** in preference to (*S*)-phenylalanine **1**. This is consistent with the reported stability constants of the complexes of α- and β-cyclodextrin with (*S*)-phenylalanine **1**, of 8 and 3 dm^3 mol^{-1}, respectively,[6] and with the cinnamate **2**, of 109 and 313 dm^3 mol^{-1}, respectively.[5] From these stability constants it can be calculated that a solution containing β-cyclodextrin (6.5×10^{-3} mol dm^{-3}) and either the cinnamate **2** (0.26×10^{-3} mol dm^{-3}) or (*S*)-phenylalanine **1** (0.25×10^{-3} mol dm^{-3}) would contain only 34% of the cinnamate **2** or 98% of the phenylalanine **1** free in solution, while in analogous solutions of α-cyclodextrin (0.075 mol dm^{-3}) the amount of the cinnamate **2** and (*S*)-phenylalanine **1** unbound would be 11 and 63%, respectively.

To confirm the above interpretation of the experiments illustrated in Fig. 1, and the effect of the cyclodextrins, the experiments beginning with (*S*)-phenylalanine **1** and the cinnamate **2**, with no cyclodextrin and with either α- or β-cyclodextrin, were repeated using >99% 2-^{13}C-labelled (*S*)-phenylalanine **1** and approximately double the concentration of PAL. After 1 h, each reaction mixture was acidified to pH 1 and extracted with chloroform, and the residue obtained from concentration of the organic extract was analysed by ^{1}H NMR spectroscopy (Fig. 2). In these experiments the unlabelled

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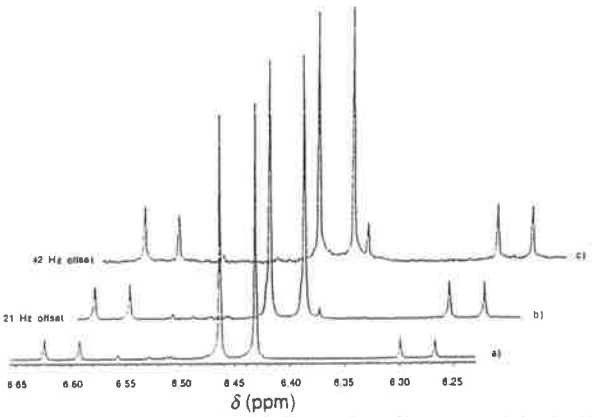

Fig. 2 ^{1}H NMR spectra (500 MHz, $CDCl_3$) of the material obtained by treatment of a solution of 2-^{13}C-labelled (*S*)-phenylalanine **1** (0.25×10^{-3} mol dm^{-3}) and the cinnamate **2** (0.26×10^{-3} mol dm^{-3}), containing either (a) no cyclodextrin, (b) β-cyclodextrin (6.5×10^{-3} mol dm^{-3}), or (c) α-cyclodextrin (0.075 mol dm^{-3}) in 0.05 mol dm^{-3} phosphate buffer at pH 6.9, with PAL at 303 K for 1 h.

cinnamate **2** is an internal standard and the different ratios of unlabelled to labelled cinnamate **2** isolated from the reaction mixtures are a measure of the relative extents of reactions. The ^{1}H NMR spectra show signals due to the ^{13}C-labelled cinnamate **2** produced during reaction, at δ 6.45 (dd, J_H 16 Hz, J_C 164 Hz), and due to the cinnamate **2** added initially to each reaction mixture, at δ 6.45 (d, J_H 16 Hz). Integration of these signals shows that whereas the reaction in the absence of a cyclodextrin proceeded to an extent of 16%, the reaction carried out under otherwise identical conditions, but in the presence of β-cyclodextrin had proceeded to an extent of 29%, while the analogous reaction in the presence of α-cyclodextrin had proceeded even further, to an extent of 41%. These results were confirmed by using gas chromatography–mass spectrometry to determine the ^{13}C-isotope content of the cinnamate **2** recovered from each of the reaction mixtures.

Reducing product inhibition of an enzyme in this manner may be achieved if the cyclodextrins complex a reaction product in preference to a substrate. In a similar manner it may be possible to manipulate enzyme-catalysed equilibrations, or the substrate selectivity in enzyme-catalysed reactions, by selectively complexing components from mixtures. Studies to this effect are underway in our laboratories.

Experimental

Procedures for assaying the effect of cyclodextrins on the catalytic activity of PAL

For UV spectrophotometric studies, aliquots of stock solutions of (*S*)-phenylalanine **1** (5.0×10^{-3} mol dm^{-3} solution in 0.05 mol dm^{-3} pH 6.9 sodium phosphate buffer; 1.0×10^{-5} dm^3) and the cinnamate **2** (5.2×10^{-3} mol dm^{-3} solution in 0.05 mol dm^{-3} pH 6.9 sodium phosphate buffer; 1.0×10^{-5} dm^3), as appropriate, were diluted to 1.6×10^{-4} dm^3 with 0.05 mol dm^{-3} pH 6.9 sodium phosphate buffer containing either no cyclodextrin, α-cyclodextrin (0.107 mol dm^{-3}) or β-cyclodextrin (9.26×10^{-3} mol dm^{-3}). The resulting solutions were equilibrated at 303 K for 10 min and then a thermally pre-equilibrated solution of PAL (4.0×10^{-5} dm^3 of a 30% glycerol, 0.025 mol dm^{-3} pH 6.9 sodium phosphate buffer solution) was added to each one. These mixtures were prepared in a 1 mm path-length cell, and monitored for change in UV absorbance at 268 nm using a Cary 1E spectrophotometer, with the cell-holder thermostatted at 303 K.

For product studies, solutions were prepared as described above, except that >99% 2-^{13}C-labelled (*S*)-phenylalanine **1** was used and the scale of the reactions was increased 50-fold. After incubation at 303 K for 1 h, the solutions were each acidified to pH 1 with concentrated HCl and extracted with $CHCl_3$ (8×0.040 dm^3). For each reaction mixture, the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was analysed using ^{1}H NMR spectroscopy and mass spectrometry.

Acknowledgements

The authors acknowledge the support of Prof. J. A. Elix, the assistance of P. T. Culnane and Dr. J. K. MacLeod in obtaining spectral data, and the award of a Research School of Chemistry Honours Scholarship to J. B. H.

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Crystal structure of 5-(2,6-dichlorophenyl)-4-ethoxycarbonyl-3-phenyl-δ^2-isoxazoline, $C_{18}H_{15}Cl_2NO_3$

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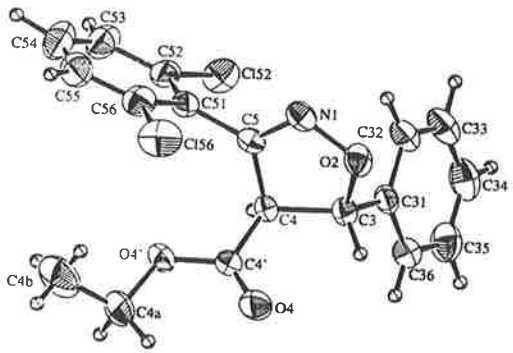

Source of material: see ref. 1.

The deviations of the O(2), N(1), C(3), C(4) and C(5) atoms from the least-squares plane through these atoms are 0.061(3), −0.023(3), −0.143(4), 0.090(4) and −0.033(4) Å, respectively. The substituents at C(3), C(4) and C(5) form dihedral angles of 75.8°, 69.0° and 72.1° with the central five-membered ring, respectively.

$C_{18}H_{15}Cl_2NO_3$, orthorhombic, $P2_12_12_1$ (No. 19), a =10.736(6) Å, b =20.281(7) Å, c =7.977(5) Å, V =1736.9 Å^3, Z =4, $R(F)$ =0.034, $R_w(F)$ =0.030.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.24 x 0.32 x 0.40 mm
Wavelength:	Mo $K\alpha$ radiation (0.7107 Å)
μ:	3.88 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
$N(hkl)_{unique}$:	2322
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	277
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(3)	4*a*	0.083(4)	0.460(2)	0.560(5)	0.06(1)
H(4)	4*a*	0.177(3)	0.458(1)	0.244(4)	0.034(9)
H(4a)	4*a*	0.504(8)	0.428(4)	0.511(9)	0.23(1)
H(4b)	4*a*	0.55(1)	0.449(5)	0.35(2)	0.29(1)
H(4c)	4*a*	0.527(9)	0.331(4)	0.36(1)	0.25(1)
H(4d)	4*a*	0.645(6)	0.355(3)	0.377(9)	0.15(2)
H(4e)	4*a*	0.586(9)	0.367(4)	0.23(1)	0.21(1)
H(32)	4*a*	−0.136(4)	0.422(2)	0.245(5)	0.09(2)
H(33)	4*a*	−0.286(5)	0.496(2)	0.140(6)	0.11(2)
H(34)	4*a*	−0.275(5)	0.606(2)	0.189(6)	0.12(2)
H(35)	4*a*	−0.105(5)	0.648(2)	0.368(6)	0.09(2)
H(36)	4*a*	0.037(4)	0.572(2)	0.472(5)	0.06(1)
H(53)	4*a*	0.228(5)	0.327(2)	−0.277(6)	0.11(2)
H(54)	4*a*	0.358(5)	0.237(2)	−0.218(6)	0.12(2)
H(55)	4*a*	0.398(4)	0.211(2)	0.080(5)	0.08(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(52)	4*a*	0.0742(1)	0.40558(6)	−0.0789(1)	0.093(1)	0.0812(7)	0.0605(6)	0.0113(6)	−0.0101(7)	0.0049(8)
Cl(56)	4*a*	0.3071(2)	0.24973(7)	0.3703(2)	0.112(1)	0.0664(7)	0.107(1)	0.0113(8)	−0.0277(9)	0.0170(8)
O(2)	4*a*	0.0009(3)	0.3799(1)	0.4743(3)	0.062(2)	0.067(2)	0.065(2)	−0.007(2)	0.020(2)	0.009(2)
O(4)	4*a*	0.3020(3)	0.4388(2)	0.5716(4)	0.061(2)	0.105(2)	0.061(2)	−0.008(2)	−0.008(2)	−0.013(2)
O(4')	4*a*	0.3845(3)	0.4159(2)	0.3218(4)	0.036(2)	0.110(3)	0.073(2)	−0.002(2)	−0.004(2)	−0.023(2)
N(1)	4*a*	0.0443(3)	0.3357(2)	0.3521(4)	0.052(2)	0.064(2)	0.066(2)	−0.011(2)	0.003(2)	0.009(2)
C(3)	4*a*	0.0569(4)	0.4443(2)	0.4450(5)	0.044(3)	0.058(2)	0.050(2)	−0.001(2)	0.006(2)	0.003(2)
C(4)	4*a*	0.1686(4)	0.4300(2)	0.3310(5)	0.037(2)	0.048(2)	0.045(2)	−0.000(2)	0.005(2)	0.004(2)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(4')	4*a*	0.2908(4)	0.4294(2)	0.4237(5)	0.046(3)	0.051(2)	0.056(2)	−0.006(2)	0.002(2)	−0.005(2)
C(4a)	4*a*	0.5088(5)	0.4134(4)	0.399(1)	0.037(3)	0.187(8)	0.137(6)	0.027(6)	−0.023(4)	−0.070(4)
C(4b)	4*a*	0.5771(7)	0.3586(4)	0.332(1)	0.067(4)	0.122(6)	0.160(7)	0.019(6)	−0.035(5)	0.013(4)
C(5)	4*a*	0.1332(4)	0.3618(2)	0.2710(5)	0.045(3)	0.046(2)	0.053(2)	−0.007(2)	−0.004(2)	0.005(2)
C(31)	4*a*	−0.0376(4)	0.4911(2)	0.3717(5)	0.038(2)	0.068(3)	0.053(2)	0.000(2)	0.005(2)	−0.000(2)
C(32)	4*a*	−0.1345(4)	0.4688(3)	0.2712(6)	0.043(3)	0.085(3)	0.077(3)	−0.006(3)	−0.003(3)	0.004(3)
C(33)	4*a*	−0.2199(5)	0.5126(3)	0.2086(7)	0.046(3)	0.112(5)	0.086(4)	−0.006(4)	−0.007(3)	0.017(4)
C(34)	4*a*	−0.2106(6)	0.5781(3)	0.2437(8)	0.061(4)	0.105(5)	0.093(4)	0.021(4)	0.008(3)	0.025(4)
C(35)	4*a*	−0.1151(6)	0.6014(3)	0.3384(8)	0.076(4)	0.074(3)	0.105(4)	0.018(4)	0.013(4)	0.007(3)
C(36)	4*a*	−0.0273(5)	0.5577(2)	0.4034(6)	0.052(3)	0.073(3)	0.075(3)	0.002(3)	−0.000(3)	−0.008(3)
C(51)	4*a*	0.1961(4)	0.3252(2)	0.1344(5)	0.048(3)	0.044(2)	0.061(2)	−0.005(2)	0.002(2)	−0.004(2)
C(52)	4*a*	0.1773(4)	0.3429(2)	−0.0331(5)	0.067(3)	0.051(2)	0.064(3)	−0.011(2)	0.008(2)	−0.006(2)
C(53)	4*a*	0.2382(6)	0.3115(3)	−0.1622(7)	0.105(5)	0.080(4)	0.067(3)	−0.010(3)	0.021(3)	−0.014(3)
C(54)	4*a*	0.3206(7)	0.2616(3)	−0.1257(9)	0.114(5)	0.074(4)	0.101(4)	−0.001(4)	0.039(4)	−0.017(4)
C(55)	4*a*	0.3410(6)	0.2432(3)	0.0366(9)	0.077(4)	0.059(3)	0.127(6)	0.008(4)	0.008(4)	−0.015(3)
C(56)	4*a*	0.2786(5)	0.2744(2)	0.1648(6)	0.073(3)	0.050(2)	0.085(3)	0.002(2)	−0.004(3)	−0.002(3)

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Athelstan L. J. Beckwith

This special issue of the Australian Journal of Chemistry has been compiled to celebrate the contributions to chemistry of Professor Athelstan L. J. Beckwith, FRACI, FAA, FRS, and to mark the occasion of his 65th birthday on 20 February 1995.

Born in Perth, Athel received his B.Sc. Hons degree from the University of Western Australia in 1953. He then spent 2 years as a lecturer at the University of Adelaide, before moving to Oxford University where he worked with (the late) Professor W. A. Waters, graduating D.Phil. in 1956. In 1957 Athel returned to Australia as a Research Officer with the CSIRO Division of Industrial Chemistry, in Melbourne; then in 1958 he moved to a lectureship in the Department of Organic Chemistry at the University of Adelaide, where he was promoted to Senior Lecturer in 1962, Reader in 1964, and Professor of Organic Chemistry and Head of Department in 1965. In 1981 he moved to his present position of Professor of Chemistry in the Research School of Chemistry at the Australian National University. At the University of Adelaide, Athel was Dean of the Faculty of Science in 1972–1973. He has also served as South Australian Branch President of the Royal Australian Chemical Institute in 1971–1972, and Federal President of the Institute in 1984–1985. He was Vice-President of the Australian Academy of Science in 1985–1986 and Dean of the Research School of Chemistry in 1989–1991. He has served on various committees of the Australian Research Grants Scheme and the Australian Research Council, and currently he is Chairman of the Board of the Australian Journals of Scientific Research.

Athel is recognized nationally and internationally as an ambassador and statesman of chemistry in Australia. Despite the obstacles imposed by distance he has maintained an exceptionally high profile at international conferences and other meetings. In addition, he has spent periods of study leave at Imperial College London in 1962, at the University of York in 1968, and at Oxford University in 1974 and 1979. Athel's scientific reputation has been acknowledged through the award of the Rennie Memorial Medal of the Royal Australian Chemical Institute in 1960, his receipt of a Carnegie Fellowship in 1968, his election as a Fellow of the Royal Australian Chemical Institute in 1973 and a Fellow of the Australian Academy of Science in 1974, the award of the H. G. Smith Memorial Medal of the Royal Australian Chemical Institute in 1981, his election as a Fellow of the Royal Society in 1989, and his receipt of the inaugural Organic Chemistry Division Medal of the Royal Australian Chemical Institute in 1992 and the Centenary Medal of the Royal Society of Chemistry in 1993.

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Athel's research has covered many areas of chemistry but his main work has been on the physical organic chemistry of free radicals. His work has contributed substantially to our understanding of the factors affecting free-radical reactions, to the point where it is now possible to confidently predict the outcome of many of these processes. In the area of free-radical cyclizations Athel's research has had particular impact and, largely as a result of his pioneering work in this field, these reactions are now being used routinely in synthetic chemistry. The significance of Athel's research is reflected in the fact that his publications were cited more than a thousand times in 1992–1993.

To discuss Athel's contributions to science solely in terms of his research does not do him justice, however, as he is equally admired as a teacher and friend. Fondly regarded by his former and current students, he is a caring and innovative teacher, who inspires others with his natural enthusiam for chemistry. His delight in observing an unusual signal in an e.p.r. spectrum leaves a lasting impression, and many of his students have gained their first real taste for chemistry from his fascination with the unexplained and unexpected. Athel has always recognized the need for teaching to be entertaining, as well as informative, and he is a master of the art of presentation of science.

Over the years, Athel's unfailing support of his past and present students, and his genuine concern for their welfare, and that of their families and friends, have been most appreciated. This support has been extended far beyond his own research collaborators, to colleagues throughout the chemical community. He has always maintained extensive contacts with chemists throughout the private and public sectors, particularly CSIRO and ICI (Australia). During his career, Athel and his students and colleagues have benefited from the constant support shown by Athel's wife, Kaye. The hospitality extended at their family homes, at Belair and then at Kingston, has been most generous.

Through their contributions to this issue, the authors wish to acknowledge Athel's science, as well as his friendship and support. We thank the Australian Journal of Chemistry and the Editor, Dr J. R. Zdysiewicz, for this opportunity.

Adelaide 1994 *Chris J. Easton*

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Functionalisation of Pyrrolidin-2-ones at C4 and C5

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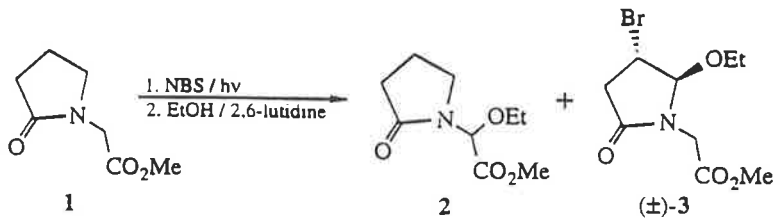
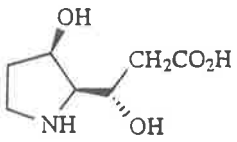
Abstract: Treatment of pyrrolidin-2-ones with *N*-bromosuccinimide affords the corresponding 4,5-dibromo-γ-lactams. The introduced bromo substituents may be selectively displaced in ionic and radical reactions. The synthetic utility of this procedure is illustrated in regioselective elaborations of the dibromides, including the generation of a bicyclic tetrahydrofuropyrrolidinone system.

A variety of methods have been reported for the direct functionalisation of pyrrolidin-2-ones at C5.[1-7] Anodic oxidation of *N*-alkylpyrrolidinones occurs regioselectively at endocyclic carbon adjacent to nitrogen, to give the corresponding 5-hydroxypyrrolidinones and imides,[2] and *N*-unsubstituted pyrrolidinones are similarly oxidised.[3,4] Photochemical oxidation of pyrrolidin-2-ones to their corresponding imides has also been reported.[5,6] Alternatively, free radical benzoyloxylation has been used for the introduction of the synthetically versatile acyloxy group at C5.[7] More recently, we have described reactions with *N*-bromosuccinimide as methodology for functionalisation of *N*-substituted γ-lactams at exocyclic carbon adjacent to nitrogen.[8] For example, the reaction of the pyrrolidinone **1** with *N*-bromosuccinimide, followed by treatment with ethanol, gave mainly the exocyclic substitution product **2** (*Scheme 1*). As part of that study, endocyclic substitution of pyrrolidinones at C4 and C5 was observed as a minor reaction pathway and, in the reaction of the pyrrolidinone **1**, the 4,5-disubstituted γ-lactam **3** was obtained.



Scheme 1

Substituted pyrrolidinones have found widespread use in the synthesis of alkaloids[9-13] and the generation of 4,5-disubstituted pyrrolidinones is of potential interest in this area. Detoxinine (**4**)[14] and retronecine (**5**)[15] are examples of alkaloids bearing a disubstituted pyrrolidine ring. Accordingly, we have examined the



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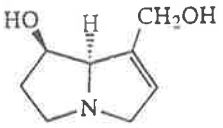

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processes involved in the formation of the 4,5-disubstituted γ-lactam **3** in more detail, and exploited the procedure to develop methodology for the direct endocyclic functionalisation of pyrrolidinones at C4 and C5.

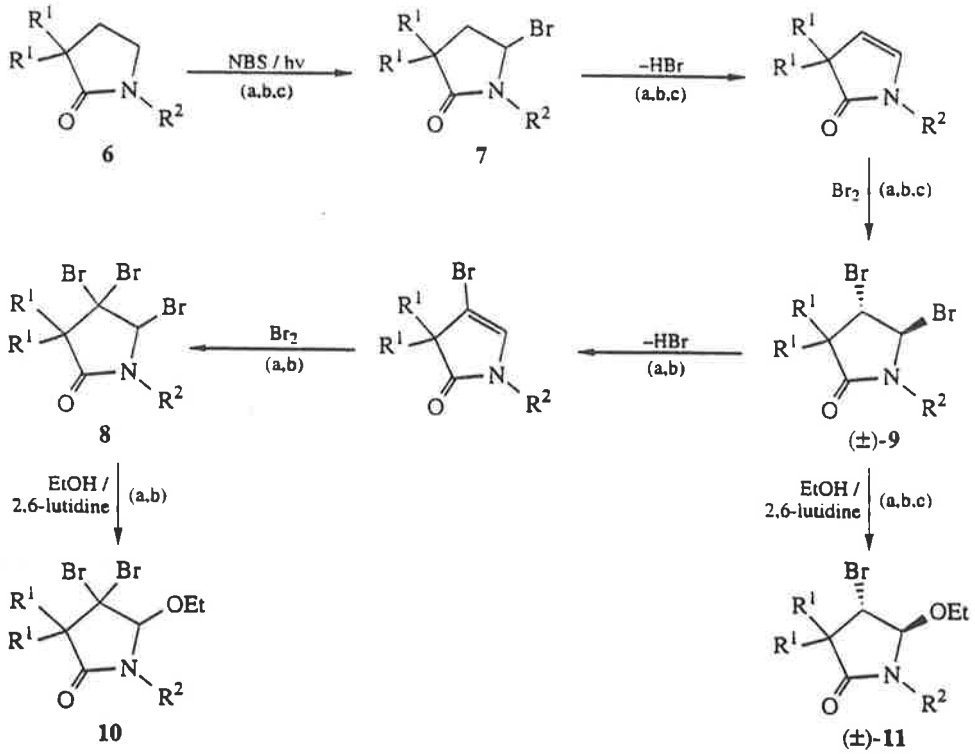
RESULTS AND DISCUSSION

The major reaction of the pyrrolidinone **1** to give the exocyclic substitution product **2** is facilitated by the methoxycarbonyl substituent activating the exocyclic position to hydrogen atom abstraction. Accordingly, we anticipated that in the absence of activating substituents at the exocyclic position, the balance of exo- and endocyclic functionalisation would be altered. We therefore chose to investigate reactions of the *N*-methylpyrrolidinones **6a** and **6b** with *N*-bromosuccinimide. The trimethylpyrrolidinone **6a** was chosen for initial investigation as it was reasoned that the methyl substituents at C3 would block that position to possible side reactions.

1,3,3-Trimethylpyrrolidin-2-one (**6a**) was treated with two mole equivalents of *N*-bromosuccinimide, in carbon tetrachloride at reflux under nitrogen for 10 minutes, with reaction initiated by irradiation with a 300 W mercury lamp. The products of reaction were converted to stable derivatives, for isolation and characterisation, through treatment with two mole equivalents of ethanol and one mole equivalent of 2,6-lutidine. This afforded, after chromatography of the product mixture on silica, the 4-bromo-5-ethoxypyrrolidinone **11a** and the 4,4-dibromo-5-ethoxypyrrolidinone **10a**, in yields of 9 and 14%, respectively. Similar treatment of *N*-methylpyrrolidin-2-one (**6b**) afforded the 4-bromo-5-ethoxypyrrolidinone **11b** and the 4,4-dibromo-5-ethoxypyrrolidinone **10b**, in yields of 9 and 11%, respectively. As comparable yields of products were obtained in these reactions, in the presence and absence of methyl substituents at C3, reaction of 1,3,3-trimethylpyrrolidin-2-one (**6b**) was not investigated further. In each case, no products attributable to bromination of the *N*-methyl substituent were observed.

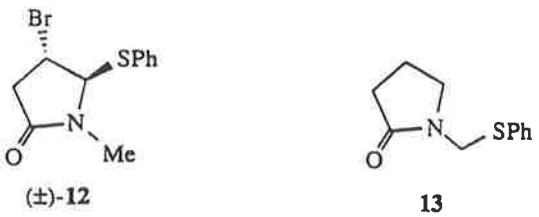
Production of the 4-bromo-5-ethoxylactams **11a** and **11b** and the 4,4-dibromo-5-ethoxylactams **10a** and **10b** may be attributed to initial free radical bromination to give the bromides **7a** and **7b**, which undergo ionic reactions as shown in *Scheme 2* to give the *trans*-dibromides **9a** and **9b** and the tribromides **8a** and **8b**. Indeed, ^{1}H NMR spectroscopic analysis of the crude products of the reaction of *N*-methylpyrrolidin-2-one (**6b**) with *N*-bromosuccinimide indicated formation of a major amount of the *trans*-dibromide **9b** and the tribromide **8b** in an approximately 5:2 ratio.

To maximise the ratio of production of the dibromide **9b** to the tribromide **8b**, from the pyrrolidinone **6b**, AIBN was added to the reaction mixture to increase the efficiency of the radical reaction, and the reaction time was reduced in order to limit subsequent ionic reactions. Coincidentally, conversion of the products of bromination of **6b** to their corresponding phenylthioethers was investigated. Thus, *N*-methylpyrrolidin-2-one (**6b**) was treated with *N*-bromosuccinimide in the presence of a catalytic amount of AIBN, for only 5 minutes, and the product mixture was treated with thiophenol. This reaction afforded the 4-bromo-5-phenylthio-γ-lactam **12**, in 25% yield, and the *N*-phenylthiomethyl-γ-lactam **13**, resulting from exocyclic substitution, in 3% yield.



a: $R^1 = R^2 = Me$
b: $R^1 = H$, $R^2 = Me$
c: $R^1 = H$, $R^2 = p$-MeOPh

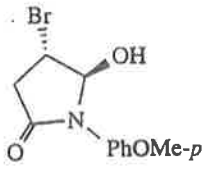
Scheme 2



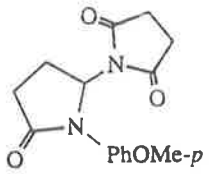
Despite the modest product yields obtained in this reaction, given the ready availability of *N*-methylpyrrolidin-2-one (**6b**), the above reactions illustrate the accessibility of 4,5-difunctionalised γ-lactams through this procedure. In addition, the above examples demonstrate selective substitution of the C5 bromine.

The *N*-(*p*-methoxyphenyl)-substituted pyrrolidinone **6c** was next investigated. Reaction of the lactam **6c** with a slight molar excess of *N*-bromosuccinimide in the presence of a catalytic amount of AIBN for 5 minutes, followed by treatment with ethanol, afforded, after chromatography, the 4-bromo-5-ethoxypyrrolidinone **11c**,

in 38% yield. In addition, 33% of the starting material **6c** was recovered unreacted, and the alcohol **14** and the 5-succinimidopyrrolidinone **15** were obtained as minor products, in yields of 14 and 7%, respectively. The *p*-methoxyphenyl substituent has previously been reported to be amenable to removal from nitrogen of functionalised β-lactams,[16] through oxidative dearylation with ceric ammonium nitrate,[17] so elaboration of the lactam **6c** should provide a route to functionalised *N*-unsubstituted pyrrolidinones.



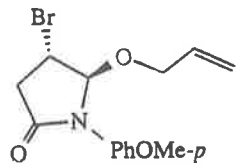
(±)-**14**



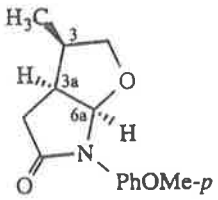
15

This procedure for functionalisation of pyrrolidinones at C4 and C5, and for differential elaboration of the introduced functionality has potential in the synthesis of bicyclic pyrrolidinones. Accordingly, 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) was treated with a slight molar excess of *N*-bromosuccinimide followed by allyl alcohol. Chromatography of the crude product mixture afforded the 5-allyloxy-4-bromo-pyrrolidinone **16** in 29% yield. In addition, 48% of the pyrrolidinone **6c** was recovered unreacted and the alcohol **14** was obtained in 8% yield. The yield of the allyl ether **16** from the pyrrolidinone **6c**, *via* this procedure, was improved to 47% when the reaction was conducted with five mole equivalents of *N*-bromosuccinimide. The alcohol **14** was also obtained, in 9% yield, and 31% of the starting material **6c** was recovered. In each case above, production of a minor amount of the 5-succinimidopyrrolidinone **15** was also detected.

Cyclisation of the 5-allyloxy-4-bromopyrrolidinone **16** was achieved by treatment with tri-*n*-butyltin hydride according to the method reported by Hart and co-workers[12,13] for the intramolecular cyclisation of related systems. Thus a dilute solution of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene was added dropwise to a solution of the bromide **16** in benzene, heated at reflux under nitrogen. Chromatography of the crude product mixture afforded the tetrahydrofuropyrrolidinone **17**, in 38% yield, resulting from 1,5-*exo* cyclization.[18,19] No products resulting from simple reduction of the bromide **16** were detected.



(±)-**16**



(±)-**17**

Both ^{1}H and ^{13}C n.m.r. analyses of the tetrahydrofuropyrrolidinone **17** indicated it to be a single diastereomer. A high degree of stereoselectivity is exhibited in the free radical cyclisation of related systems,[13,20–22] whereby the major diastereomer obtained is invariably that in which the three substituents of the newly formed 5-membered ring are in an all-*cis* geometry. The stereochemical preference may be rationalised as due to reaction *via* a transition state geometry that affords maximal overlap between the semi-

occupied *p*-orbital of the radical centre and the π*-orbital of the alkenyl moiety.[18,21,22] On this basis, the single diastereomer of **17** obtained was assigned as that with the all-*cis* geometry, namely the (3*SR*,3a*RS*,6a*SR*)-diastereomer.

Synthesis of the tetrahydrofuropyrrolidinone **17** from **6c**, whilst exemplifying the viability of the free radical bromination procedure for the synthesis of bicyclic pyrrolidinones, moreover highlights the provision of the free radical bromination procedure for selective elaboration of functionality thus introduced at both C4 and C5 of a pyrrolidinone system. In summary, the procedure described in this paper provides an effective method for the synthesis of 4,5-difunctionalised pyrrolidinones and bears scope for application to the synthesis of pyrrolidine and pyrrolizidine alkaloids.

EXPERIMENTAL

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer as nujol mulls between sodium chloride plates, or as liquid films or solutions as indicated. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on either a Bruker AC-P 300 or CXP 300 spectrometer as dilute solutions in deuterochloroform, using tetramethylsilane as internal standard. Electron impact mass spectra and high resolution mass spectra were recorded on an AEI MS-3010 spectrometer, using an ionising voltage of 70 eV. Elemental analyses were performed by Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada.

Flash column chromatography was carried out using Matrex™ silica gel (pore size 60 Å, particle size 50 μm, No. 84072). Squat column[23] and preparative thin layer chromatographies were carried out using Merck silica gel $60_{PF\text{-}254}$ (Art. 7749). Preparative thin layer chromatographies were carried out on a Chromatotron 7924T (Harrison Research, Palo Alto/ TC Research, Norwich). All organic extracts were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction with b.p. 66 – 69°C. A WOTAN Ultra-Vitalux® 300 W sunlamp was used as the light source in reactions of *N*-bromosuccinimide. *N*-Bromosuccinimide was recrystallised from water and dried under reduced pressure before use.

1,3,3-Trimethylpyrrolidin-2-one (**6a**) was prepared according to the method reported by Gasman and Fox.[24] 1-Methylpyrrolidin-2-one (**6b**) was purchased from Merck (Art. 806072) and used without further purification.

N-(p-Methoxyphenyl)-4-chlorobutyramide. 4-Chlorobutyryl chloride (30 g, 213 mmol) was dissolved in dichloromethane (200 ml) and a solution of freshly recrystallised *p*-anisidine (28.8 g, 266 mmol) in dichloromethane (100 ml) was added dropwise with stirring. After the addition was complete the solution was stirred at room temperature for a further 4 hr. The solution was then washed with water (3 × 100 ml), dried, and evaporated under reduced pressure to give an oil that solidified on standing. The residual solid was recrystallised from ethyl acetate / light petroleum to give *N*-(*p*-methoxyphenyl)-4-chlorobutyramide as a white crystalline solid (23.8 g, 54%): m.p. 85°C; IR (nujol) 3308, 1662, 1620, 1518, 1240, 1024, 840 cm^{-1}; ^{1}H NMR δ 2.13 (2H, tt, *J* 7.2, 6.2 Hz, CH_2CH_2Cl), 2.48 (2H, t, *J* 7.2 Hz, CH_2Cl), 3.59 (2H, t, *J* 6.2 Hz, CH_2CONH), 3.76 (3H, s, OCH_3), 6.80 (2H, m, ArH), 7.38 (2H, m, ArH), 8.06 (1H, broad, NH); ^{13}C NMR δ 169.84, 156.40, 130.70, 121.80, 114.07, 55.44, 44.50, 33.89, 27.94; HRMS calcd for $C_{11}H_{14}{}^{35}ClNO_2$ *m/z* 227.0713 (M^+), found 227.0757. Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.01; H, 6.20; N, 6.15. Found: C, 58.31; H, 5.87; N, 6.14.

1-(p-Methoxyphenyl)pyrrolidin-2-one (6c). A solution of *N*-(*p*-methoxyphenyl)-4-chlorobutyramide (2.28 g, 10 mmol) in dichloromethane (200 ml) was added dropwise over 6 hr, to a stirred suspension of powdered potassium hydroxide (672 mg, 12 mmol) and tetra-*n*-butylammonium chloride (556 mg, 2 mmol) in dichloromethane (200 ml). After the addition was complete, stirring was continued for 30 min. The precipitate was filtered off and washed with dichloromethane (2 × 50 ml). The combined filtrates were dried and concentrated under reduced pressure to give an oil that was chromatographed on a squat column, gradient eluting with light petroleum and ethyl acetate. The resulting solid was recrystallised from ethyl acetate / light petroleum to give 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) as fine transparent leaves (1.19 g, 63%): m.p. 108°C; IR (nujol) 1682, 1612, 1514, 1252, 1032, 830 cm^{-1}; ^1H NMR δ 2.12 (2H, tt, *J* 8.1, 7.0 Hz, C4-H_2), 2.56 (2H, t, *J* 8.1 Hz, C3-H_2), 3.78 (3H, s, OCH_3), 3.80 (2H, t, *J* 7.0 Hz, C5-H_2), 6.89 (2H, m, ArH), 7.48 (2H, m, ArH); ^{13}C NMR δ 173.90, 156.49, 132.53, 121.79, 113.96, 55.41, 49.15, 32.42, 17.98; HRMS calcd for $C_{11}H_{13}NO_2$ *m/z* 191.0946 (M^+), found 191.1005. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.09; H, 6.93; N, 7.35.

trans-*4-Bromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (11a) and 4,4-dibromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (10a).* A mixture of 1,3,3-trimethylpyrrolidin-2-one (**6a**) (252 mg, 1.98 mmol) and *N*-bromosuccinimide (705 mg, 3.96 mmol) in carbon tetrachloride (40 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was cooled to room temperature, dry ethanol (240 µl, 4.09 mmol) and 2,6-lutidine (230 µl, 1.97 mmol) were added and the mixture was stirred under nitrogen for 3 hr. The reaction mixture was filtered and evaporated under reduced pressure and the resultant residue was taken up in ethyl acetate and washed successively with 0.01 M hydrochloric acid, brine, saturated aqueous sodium bicarbonate and brine. The organic layer was dried and concentrated under reduced pressure and flash column chromatography of the residue, eluting with a mixture of light petroleum and ethyl acetate (2:5), then afforded two products, **11a** and **10a**.

trans-4-Bromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (**11a**) as an oil (46 mg, 9%): IR (liquid film) 2972, 1708, 1276, 1064, 760 cm^{-1}; ^1H NMR δ 1.22 (3H, s, C3-CH_3), 1.28 (3H, s, C3-CH_3), 1.29 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.87 (3H, s, NCH_3), 3.74 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 3.80 (1H, dq, *J* 9.4, 7.0 Hz, $CHHCH_3$), 3.98 (1H, d, *J* 3.8 Hz, C4-H), 4.89 (1H, d, *J* 3.8 Hz, C5-H); ^{13}C NMR δ 175.55, 95.57, 65.61, 57.92, 44.84, 27.13, 24.19, 23.95, 15.47; MS *m/z* (relative intensity) 251 (M^+, 6), 249 (M^+, 6), 206 ([M – OEt]$^+$, 66), 204 ([M – OEt]$^+$, 67), 192 (11), 190 (11), 170 ([M – Br]$^+$, 21), 149 (13.5), 147 (14), 113 (100), 85 (81). HRMS calcd for $C_9H_{16}{}^{79}BrNO_2$ *m/z* 249.0364 (M^+), found 249.0355.

4,4-Dibromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (**10a**) as an oil (91 mg, 14%): IR (liquid film) 2976, 1714, 1294, 1064, 770 cm^{-1}; ^1H NMR δ 1.30 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.38 (3H, s, C3-CH_3), 1.42 (3H, s, C3-CH_3), 2.92 (3H, s, NCH_3), 3.81 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 4.11 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 5.02 (1H, s, C5-H); ^{13}C NMR δ 173.52, 98.55, 75.70, 68.39, 51.81, 26.91, 24.54, 24.08, 15.15; MS *m/z* (relative intensity) 331 (M^+, 9), 329 (M^+, 18), 327 (M^+, 9), 286 ([M – OEt]$^+$, 21), 284 ([M – OEt]$^+$, 42), 282 ([M – OEt]$^+$, 21), 250 ([M – Br]$^+$, 5), 248 ([M – Br]$^+$, 5), 206 (31), 204 (32), 165 (98), 163 (100). HRMS calcd for $C_9H_{15}{}^{79}Br_2NO_2$ *m/z* 326.9470 (M^+) found 326.9461.

Treatment of 1-methylpyrrolidin-2-one (6b) with N-*bromosuccinimide.* A mixture of 1-methylpyrrolidin-2-one (**6b**) (230 mg, 2.32 mmol) and *N*-bromosuccinimide (826 mg, 4.64 mmol) in carbon tetrachloride

(20 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The cooled reaction mixture was filtered through glass wool and concentrated under reduced pressure to give an oil containing an approximately 5:2 mixture of *trans*-4,5-dibromo-1-methylpyrrolidin-2-one (**9b**) and 1-methyl-4,4,5-tribromopyrrolidin-2-one (**8b**) as judged by ^{1}H NMR spectroscopic analysis. No discrete products were isolated from this reaction mixture.

trans-4,5-Dibromo-1-methylpyrrolidin-2-one (**9b**): ^{1}H NMR δ 2.90 (3H, s, NCH_3), 3.08 (1H, d, *J* 18.5 Hz, C3-H), 3.29 (1H, dd, *J* 18.5, 5.9 Hz, C3-H'), 4.87 (1H, d, *J* 5.9 Hz, C4-H), 6.12 (1H, s, C5-H).

1-Methyl-4,4,5-tribromopyrrolidin-2-one (**8b**): ^{1}H NMR δ 2.95 (3H, s, NCH_3), 3.39 (1H, d, *J* 17.5 Hz, C3-H), 3.47 (1H, d, *J* 17.5 Hz, C3-H'), 6.34 (1H, s, C5-H).

trans-*4-Bromo-5-ethoxy-1-methylpyrrolidin-2-one (**11b**) and 4,4-dibromo-5-ethoxy-1-methylpyrrolidin-2-one (**10b**).* A mixture of 1-methylpyrrolidin-2-one (**6b**) (169 mg, 1.71 mmol) and *N*-bromosuccinimide (607 mg, 3.41 mmol) in carbon tetrachloride (20 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was cooled to room temperature, dry ethanol (200 µl, 3.41 mmol) and 2,6-lutidine (200 µl, 1.72 mmol) were added and the mixture was stirred under nitrogen for 3 hr. Upon workup, as above for the similar treatment of the pyrrolidinone **6a**, the residue obtained was purified by preparative thin layer chromatography, eluting with a mixture of light petroleum and ethyl acetate (50:50), affording two products, **11b** and **10b**.

trans-4-Bromo-5-ethoxy-1-methylpyrrolidin-2-one (**11b**) as an oil (34 mg, 9%): IR (liquid film) 2976, 1712, 1262, 1068, 708 cm^{-1}; ^{1}H NMR δ 1.26 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.65 (1H, dd, *J* 17.9, 1.4 Hz, C3-H), 2.92 (3H, s, NCH_3), 3.21 (1H, dd, *J* 17.9, 6.8 Hz, C3-H'), 3.63 (1H, dq, *J* 9.2, 7.0 Hz, $OCHHCH_3$), 3.68 (1H, dq, *J* 9.2, 7.0 Hz, $OCHHCH_3$), 4.24 (1H, ddd, *J* 6.8, 1.4, 0.9 Hz, C4-H), 4.97 (1H, d, *J* 0.9 Hz, C5-H); ^{13}C NMR δ 171.29, 97.90, 63.93, 41.64, 39.54, 27.50, 14.98; MS *m/z* (relative intensity) 223 (M^+, 9), 221 (M^+, 9), 178 ([M – OEt]$^+$, 98), 176 ([M – OEt]$^+$, 100), 150 (28), 148 (29), 142 ([M – Br]$^+$, 11); HRMS calcd for $C_7H_{12}{}^{79}BrNO_2$ *m/z* 221.0051 (M^+), found: 221.0058.

4,4-Dibromo-5-ethoxy-1-methylpyrrolidin-2-one (**10b**) as an oil (54 mg, 11%): IR (liquid film) 2976, 1710, 1282, 1072, 752 cm^{-1}; ^{1}H NMR δ 1.32 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.93 (3H, s, NCH_3), 3.36 (1H, d, *J* 17.6 Hz, C3-H), 3.51 (1H, d, *J* 17.6 Hz, C3-H'), 3.80 (1H, dq, *J* 9.3, 7.0 Hz, $OCHHCH_3$), 4.07 (1H, dq, *J* 9.3, 7.0 Hz, $OCHHCH_3$), 5.02 (1H, s, C5-H); ^{13}C NMR δ 168.8, 99.19, 67.16, 57.33, 52.29, 27.64, 14.89; MS *m/z* (relative intensity) 303 (M^+, 18.5), 301 (M^+, 37.5), 299 (M^+, 19), 258 ([M – OEt]$^+$, 49.5), 256 ([M – OEt]$^+$, 100), 254 ([M – OEt]$^+$, 50.5), 230 (9), 228 (18), 226 (9), 222 ([M – Br]$^+$, 7), 220 ([M – Br]$^+$, 7); HRMS calcd for $C_7H_{11}{}^{79}Br_2NO_2$ *m/z* 298.9157 (M^+), found 298.9153.

trans-*4-Bromo-1-methyl-5-phenylthiopyrrolidin-2-one (**12**) and 1-phenylthiomethylpyrrolidin-2-one (**13**).* A mixture of 1-methylpyrrolidin-2-one (**6b**) (195 mg, 1.97 mmol), *N*-bromosuccinimide (740 mg, 4.16 mmol) and a catalytic amount of AIBN in carbon tetrachloride (35 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 5 min. The reaction mixture was immediately cooled to room temperature, thiophenol (410 µl, 3.99 mmol) and 2,6-lutidine (460 µl, 3.95 mmol) were added and the mixture was stirred at room temperature under nitrogen for 2 hr. The residue obtained upon workup was purified by preparative thin layer chromatography, eluting with a mixture of light petroleum and ethyl acetate (50:50) and afforded two products, **12** and **13**.

trans-4-Bromo-1-methyl-5-phenylthiopyrrolidin-2-one (**12**) as an oil (139 mg, 25%): IR (liquid film)

3054, 2934, 1722, 1584, 1476 cm^{-1}; ^1H NMR δ 2.38 (1H, dd, *J* 18.4, 6.5 Hz, C3-H), 2.51 (1H, dd, *J* 18.4, 1.2 Hz, C3-H'), 3.06 (3H, s, NCH_3), 4.53 (1H, ddd, *J* 6.5, 1.2, 1.1 Hz, C4-H), 4.98 (1H, d, *J* 1.1 Hz, C5-H), 7.23 – 7.51 (5H, m, ArH); ^{13}C NMR δ 171.08, 134.55, 134.15, 129.60, 129.36, 77.27, 44.63, 40.20, 28.20; MS *m/z* (relative intensity) 287 (M^+, 3), 285 (M^+, 3), 205 ([M – HBr]$^+$, 45), 177 ([M – PhSH]$^+$, 98), 175 ([M – PhSH]$^+$, 100), 149 (50), 147 (51), 108 (71); HRMS calcd for $C_{11}H_{12}{}^{79}BrNOS$ *m/z* 284.9823 (M^+), found 284.9811.

1-Phenylthiomethylpyrrolidin-2-one (**13**) as an oil (10.4 mg, 3%): IR (liquid film) 3054, 2926, 1696, 1584, 1488 cm^{-1}; ^1H NMR δ 1.96 (2H, tt, *J* 8.1, 7.1 Hz, C4-H_2), 2.30 (2H, t, *J* 8.1 Hz, C3-H_2), 3.44 (2H, t, *J* 7.1 Hz, C5-H_2), 4.77 (2H, s, NCH_2S), 7.27 (3H, m, ArH), 7.44 (2H, m, ArH); ^{13}C NMR δ 174.85, 133.51, 130.87, 129.01, 127.16, 46.65, 45.86, 30.80, 17.54; MS *m/z* (relative intensity) 207 (M^+, 14), 98 ([M – PhS]$^+$, 100), 70 (23); HRMS calcd for $C_{11}H_{13}NOS$ *m/z* 207.0718 (M^+), found 207.0721. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.75. Found: C, 63.66; H, 6.52; N, 7.02.

trans-*4-Bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (11c).* A mixture of 1-(*p*-methoxyphenyl)-pyrrolidin-2-one (**6c**) (92.3 mg, 0.48 mmol), *N*-bromosuccinimide (100 mg, 0.56 mmol) and a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (8:1, 18 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 5 min. The reaction mixture was cooled to room temperature, dry ethanol (60 µl, 1.02 mmol) and 2,6-lutidine (120 µl, 1.03 mmol) were added and the mixture was stirred at room temperature under nitrogen for 2 hr. The residue obtained upon workup was purified by preparative thin layer chromatography, eluting with ethyl acetate, to give *trans*-4-bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**11c**), the alcohol **14**, the 5-succinimidopyrrolidinone **15** and unreacted starting material **6c** (30 mg, 33%).

trans-4-Bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**11c**) as an oil which solidified on standing (58.1 mg, 38%): m.p. 53°C; b.p. 105°C/0.02mm (block); IR (liquid film) 2972, 1722, 1610, 1514, 1250, 1066, 700 cm^{-1}; ^1H NMR δ 1.19 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.82 (1H, dd, *J* 18.2, 1.0 Hz, C3-H), 3.42 (1H, dd, *J* 18.2, 6.4 Hz, C3-H'), 3.54 (1H, dq, *J* 9.3, 7.0 Hz, $OCHHCH_3$), 3.59 (1H, dq, *J* 9.3, 7.0 Hz, $OCHHCH_3$), 3.81 (3H, s, OCH_3), 4.35 (1H, ddd, *J* 6.4, 1.0, 0.9 Hz, C4-H), 5.27 (1H, d, *J* 0.9 Hz, C5-H), 6.93 (2H, m, ArH), 7.34 (2H, m, ArH); ^{13}C NMR δ 171.29, 158.30, 129.35, 125.98, 114.34, 98.37, 64.52, 55.40, 42.57, 40.18, 15.20; MS *m/z* (relative intensity) 315 (M^+, 84), 313 (M^+, 86), 269 ([M – EtOH]$^+$, 42), 267 ([M – EtOH]$^+$, 43), 234 ([M – Br]$^+$, 14), 203 (36), 199 (100); HRMS calcd for $C_{13}H_{16}{}^{79}BrNO_3$ *m/z* 313.0314 (M^+), found 313.0306.

trans-4-Bromo-5-hydroxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**14**) as an oil (19.7 mg, 14%): IR ($CDCl_3$) 3400, 1704, 1610, 1514, 1254, 1034 cm^{-1}; ^1H NMR δ 1.77 (1H, broad, OH), 2.74 (1H, dd, *J* 18.4, 1.4 Hz, C3-H), 3.36 (1H, dd, *J* 18.4, 6.5 Hz, C3-H'), 3.89 (3H, s, OCH_3), 4.23 (1H, ddd, *J* 6.5, 1.4, 1.2 Hz, C4-H), 5.51 (1H, d, *J* 1.2 Hz, C5-H), 6.90 (2H, m, ArH), 7.32 (2H, m, ArH); ^{13}C NMR δ 171.95, 158.39, 129.02, 125.91, 114.40, 92.41, 55.45, 44.70, 40.85; MS *m/z* (relative intensity) 287 (M^+, 54), 285 (M^+, 55), 269 ([M – H_2O]$^+$, 98), 267 ([M – H_2O]$^+$, 100), 254 (29.5), 252 (30), 205 ([M – HBr]$^+$, 23), 160 (61); HRMS calcd for $C_{11}H_{12}{}^{79}BrNO_3$ *m/z* 285.0001 (M^+), found 284.9992.

1-(*p*-Methoxyphenyl)-5-(1-succinimido)pyrrolidin-2-one (**15**) as a white crystalline solid (9.7 mg, 7%): m.p. 77°C; IR (CH_2Cl_2) 2960, 1780, 1712, 1610, 1514 cm^{-1}; ^1H NMR δ 2.23 (1H, m), 2.62 (2H, m), 2.55 (4H, s), 3.05 (1H, m), 3.78 (3H, s, OCH_3), 6.20 (1H, dd, *J* 8.9, 2.2 Hz, C5-H), 6.87 (2H, m, ArH), 7.22 (2H, m, ArH); ^{13}C NMR δ 176.09, 174.62, 158.03, 128.24, 125.83, 114.41, 65.85, 55.34, 30.58, 27.74, 22.57; MS *m/z* (relative intensity) 288 (M^+, 100), 233 (33), 190 ([M – $C_4H_4NO_2$]$^+$, 38), 134

(52), 123 (53); HRMS calcd for $C_{15}H_{16}N_2O_4$ *m/z* 288.1110 (M^+), found 288.1113.

trans-*5-Allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (16).* A mixture of 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) (371 mg, 1.94 mmol), *N*-bromosuccinimide (380 mg, 2.13 mmol) and a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (6:1, 55 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was then cooled to room temperature, allyl alcohol (3 ml, excess) and 2,6-lutidine (450 µl, 3.86 mmol) were added and the mixture was stirred at room temperature under nitrogen overnight. Upon workup, preparative thin layer chromatography of the residue, eluting with a mixture of ethyl acetate and light petroleum (50:50), afforded *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) (181 mg, 29%), the alcohol **14** (46 mg, 8%), unreacted starting material **6c** (177 mg, 48%) and a minor amount of the 5-succinimidopyrrolidinone **15**.

A greater yield of **16** was obtained from **6c** when the pyrrolidinone **6c** was treated with excess *N*-bromosuccinimide. Thus, 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) (108 mg, 0.56 mmol), was treated with *N*-bromosuccinimide (502 mg, 2.82 mmol) in the presence of a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (6:1, 35 ml) as described above. The reaction mixture was then cooled to room temperature, allyl alcohol (1 ml, excess) and 2,6-lutidine (130 µl, 1.12 mmol) were added and the mixture was stirred at room temperature under nitrogen for 4.5 hr. Upon workup, chromatography of the residue, as before, afforded *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) (87.3 mg, 47%), the alcohol **14** (14 mg, 9%), unreacted starting material **6c** (33.8 mg, 31%) and a minor amount of the 5-succinimidopyrrolidinone **15**.

trans-5-Allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) as an oil: IR ($CDCl_3$) 3020, 1714, 1612, 1512, 1224 cm^{-1}; ^1H NMR δ 2.82 (1H, dd, *J* 18.2, 0.9 Hz, C3-H), 3.43 (1H, dd, *J* 18.2, 6.3 Hz, C3-H'), 3.81 (3H, s, OCH_3), 4.00 (1H, dddd, *J* 12.8, 5.7, 1.5, 1.3 Hz, C*H*HCH=CH_2), 4.04 (1H, dddd, *J* 12.8, 5.7, 1.5, 1.3 Hz CH*H*CH=CH_2), 4.37 (1H, ddd, *J* 6.3, 0.9, 0.8 Hz, C4-H), 5.20 (1H, ddt, *J* 10.5, 1.4, 1.3 Hz, CH=C*H*H), 5.22 (1H, dtd, *J* 17.1, 1.5, 1.4 Hz, CH=CH*H*), 5.33 (1H, d, *J* 0.8 Hz, C5-H), 5.81 (1H, ddt, *J* 17.1, 10.5, 5.7 Hz, C*H*=CH_2), 6.94 (2H, m, ArH), 7.33 (2H, m, ArH); ^{13}C NMR δ 171.36, 158.31, 132.90, 129.53, 126.12, 118.29, 114.28, 97.67, 69.64, 55.32, 42.45, 40.02; MS *m/z* (relative intensity) 327 (M^+, 13.5), 325 (M^+, 14), 270 ([M – C_3H_5O]$^+$, 17.5), 268 ([M – C_3H_5O]$^+$, 18), 245 (M – HBr],$^+$ 10), 189 (100); HRMS calcd for $C_{14}H_{16}{}^{79}BrNO_3$ *m/z* 325.0314 (M^+), found 325.0299.

*(3*SR*,3a*RS*,6a*SR*)-6-(*p*-Methoxyphenyl)-3-methyl-5-oxotetrahydrofuro[2,3-*b*]pyrrolidine (17).* A solution of tri-*n*-butyltin hydride (475 µl, 1.77 mmol) and a catalytic amount of AIBN in dry benzene (15 ml) was added dropwise with stirring, over 2.5 hr to a solution of *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)-2-oxopyrrolidine (**16**) (384 mg, 1.18 mmol) in dry benzene (20 ml) heated at reflux. After the addition was complete the reaction mixture was further heated at reflux under nitrogen, overnight. The reaction mixture was then evaporated under reduced pressure and preparative thin layer chromatography of the resultant residue, gradient eluting with a mixture of light petroleum and ethyl acetate gave an oil which solidified on standing. Subsequent recrystallisation from dichloromethane / light petroleum afforded (3*SR*,3a*RS*,6a*SR*)-6-(*p*-methoxyphenyl)-3-methyl-5-oxotetrahydrofuro[2,3-*b*]pyrrolidine (**17**) as a white crystalline solid (111 mg, 38%): m.p. 95°C; IR (CH_2Cl_2) 2960, 1700, 1612, 1514, 1036 cm^{-1}; ^1H NMR δ 1.06 (3H, d, *J* 6.9 Hz, CCH_3), 2.49 (1H, dddq, *J* 11.3, 8.0, 6.9, 6.8 Hz, C3-H), 2.53 (1H, dd, *J* 18.2, 10.0 Hz, C4-H), 2.62 (1H, dd, *J* 18.2, 6.4 Hz, C4-H'), 3.02 (1H, dddd, *J* 10.0, 8.0, 6.4, 6.2 Hz, C3a-H), 3.44 (1H, dd, *J* 11.3, 8.8 Hz, C2-H), 3.80 (3H, s, OCH_3), 3.98 (1H, dd, *J* 8.8, 6.8 Hz, C2-H'), 5.78 (1H, d, *J* 6.2 Hz,

C6a-H), 6.91 (2H, m, ArH), 7.48 (2H, m, ArH); ^{13}C NMR δ 173.43, 157.58, 130.62, 124.71, 114.10, 95.91, 71.50, 55.36, 38.58, 36.01, 30.12, 10.97; HRMS calcd for $C_{14}H_{17}NO_3$ *m/z* 247.1208 (M^+), found 247.1216.

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Formation of Metallo-6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino)-6^A-deoxy-β-cyclodextrins and Their Complexation of Tryptophan in Aqueous Solution

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A pH titration study shows that 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino)-6^A-deoxy-β-cyclodextrin (βCDtren) forms binary metallocyclodextrins, $[M(\beta CDtren)]^{2+}$, for which $\log(K/dm^3\ mol^{-1}) = 11.65 \pm 0.06$, 17.29 ± 0.05, and 12.25 ± 0.03, respectively, when $M^{2+} = Ni^{2+}$, Cu^{2+}, and Zn^{2+}, where K is the stability constant in aqueous solution at 298.2 K and $I = 0.10$ mol dm^{-3} ($NaClO_4$). The ternary metallocyclodextrins $[M(\beta CDtren)Trp]^+$, where Trp^- is the tryptophan anion, are characterized by $\log(K/dm^3\ mol^{-1}) = 8.2 \pm 0.2$ and 8.1 ± 0.2, 9.5 ± 0.3 and 9.4 ± 0.2, and 8.1 ± 0.1 and 8.3 ± 0.1, respectively, where the first and second values represent the stepwise stability constants for the complexation of (*R*)- and (*S*)-Trp^-, respectively, when $M^{2+} = Ni^{2+}$, Cu^{2+}, and Zn^{2+}. From comparisons of stabilities and UV−visible spectra, the binary and ternary metallocyclodextrins appear to be six-coordinate when $M^{2+} = Ni^{2+}$ and Zn^{2+} and five-coordinate when $M^{2+} = Cu^{2+}$. The factors affecting the stoichiometries and stabilities of the metallocyclodextrins, are discussed and comparisons are made with related systems.

Introduction

The formation of a binary metallocyclodextrin through the coordination of a metal ion by a functionalized cyclodextrin, and the formation of a ternary metallocyclodextrin through the binding of a substrate, offers an opportunity to study the effects of metal center and cyclodextrin interactions on metallocyclodextrin stability and substrate binding.[2−17] The ternary metallocyclodextrin annulus can partly encapsulate a substrate which also interacts with the adjacent metal center, and in this respect it resembles the Michaelis complex of some metalloenzymes.[18−21] The catalytic activities of metalloenzymes are very metal center specific, and this may be partly due to the influence of the metal center on the thermodynamic stability of the metalloenzyme and its efficacy in binding substrates. The simpler and more readily manipulated metallocyclodextrins provide an opportunity to study the influence of the metal center on metallocyclodextrin formation and on substrate binding in some detail, and such studies may be relevant to the understanding of some aspects of metalloenzymes. Although a range of metallocyclodextrin studies have appeared,[2−17] only two of these studies incorporate quantitative data on the effect of changing the metal center on binary and ternary metallocyclodextrin formation.[16,17]

We now report a study of the binary metallo-6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino)-6^A-deoxy-β-cyclodextrin, $[M(\beta CDtren)]^{2+}$, where $M^{2+} = Ni^{2+}$, Cu^{2+}, and Zn^{2+}, and the ternary metallocyclodextrins $[M(\beta CDtren)Trp]^+$, where Trp^- is the tryptophan anion. Their protonated analogues have also been studied. (Bound water molecules are generally not shown in the metallocyclodextrin formulas in the text, and tryptophan and its protonated form are indicated by TrpH and $TrpH_2^+$, respectively.) The three M^{2+} were selected because Zn^{2+} frequently acts as a metal center in metalloenzymes,[18−21] and while Ni^{2+} and Cu^{2+} fill this role less often, they are closely related in electronic structure and size to Zn^{2+}. The tetradentate 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino) substituent of βCDtren ensures the formation of stable $[M(\beta CDtren)]^{2+}$. The substrates (*R*)- and (*S*)-Trp^- were chosen for study because their aromatic moieties are of appropriate size to fit into the $[M(\beta CDtren)]^{2+}$ annulus, they bind to metal centers and provide a test for enantioselectivity in $[M(\beta CDtren)Trp]^+$.[16]

It is found that the $M^{2+}/\beta CDtren/Trp^-$ systems exist as a series of labile equilibria, some of which are shown for the Ni^{2+} system in Figure 1. The truncated cone represents the cyclodextrin moiety where the wide end of the annulus is delineated by fourteen secondary hydroxy groups and the narrow end is delineated by six primary hydroxy groups and the secondary

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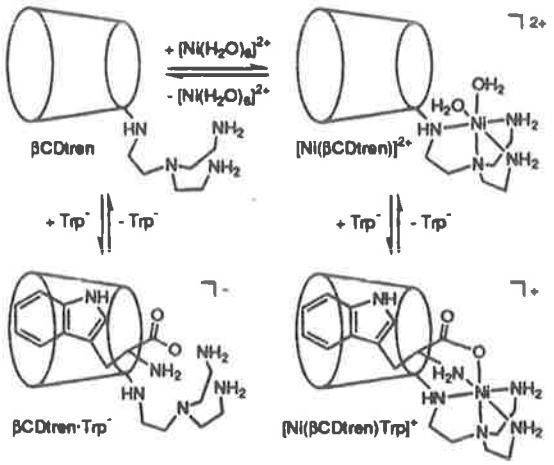

Figure 1. Both $[Ni(\beta CDtren)(H_2O)_2]^{2+}$ and $[Ni(\beta CDtren)Trp]^+$ are six-coordinate, as is probably the case for their Zn^{2+} analogues. It is possible that coordination of a cyclodextrin primary hydroxy group may replace one of the two coordinated water molecules in the Ni^{2+} and Zn^{2+} binary metallocylodextrins. The Cu^{2+} metallocyclodextrins are probably five-coordinate as discussed in the text.

amine group of the 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino) substituent in place of the seventh primary hydroxy group of β-cyclodextrin, βCD. The structures shown for the complex βCDtren·Trp^- and the metallocyclodextrins $[Ni(\beta CDtren)]^{2+}$ and $[Ni(\beta CDtren)Trp]^+$ are deduced from this study.

Experimental Section

Preparation of Materials. The tetrakis(hydrochloric acid) salt of 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino)-6^A-deoxy-β-cyclodextrin (βCDtren$(HCl)_4$) was prepared by stirring 6^A-deoxy-6^A-*O*-((4-methylphenyl)sulfonyl)-β-cyclodextrin[22] (8.0 g, 6.2 mmol) and (2-(bis(2-aminoethyl)amino)ethyl)amine (tren, 0.9 cm^3, 6.02 mmol) in pyridine (60 cm^3) at 333 K for 48 h. The solution was evaporated to dryness under reduced pressure, and the residue was triturated with acetone (3 × 80 cm^3) and dissolved in water (20 cm^3). This solution was added dropwise with stirring to acetone (250 cm^3), and the resulting precipitate was collected by filtration and washed with acetone and ether. The resultant off-white solid was dissolved in water (60 cm^3), and the solution was heated and treated with charcoal (2 g). Filtration of the mixture and evaporation to dryness of the filtrate under reduced pressure gave a white solid that was dissolved in water (200 cm^3) and stirred with Bio-Rex 70 ion-exchange resin in the acid form (50 g) for 16 h at room temperature. The resin was isolated by filtration and was washed with water (1 dm^3) and then aqueous ammonia (10%, v/v, 1 dm^3). The ammonia washings were evaporated to dryness under reduced pressure, the residue was dissolved in water (20 cm^3), and dilute hydrochloric acid (1 cm^3) was added dropwise with stirring. The solution was evaporated to dryness under reduced pressure, and the βCDtren residue was dried to constant weight over P_2O_5 to give βCDtren$(HCl)_4$ as a colorless solid (2.6 g, 31%). Anal. Calcd for $C_{48}H_{90}Cl_4N_4O_{34}$: C, 40.91; H, 6.43; N, 3.97. Found: C, 40.84; H, 6.52; N, 4.06. The tris(methanesulfonic acid) salt of 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino)-6^A-deoxy-β-cyclodextrin, βCDtren$(MeSO_3H)_3$, was prepared by dissolving βCDtren$(HCl)_4$ (2.6 g, 0.15 mmol) in water (15 cm^3), adding methanesulfonic acid (1 cm^3), and adding the mixture to acetone (250 cm^3) with stirring. The resulting off-white precipitate was filtered off, washed with acetone and ether, and dissolved in water (30 cm^3), and the resultant solution was heated with charcoal (1 g). Filtration of the mixture and evaporation to dryness gave $\beta CDtrenH_3(MeSO_3)_3(Me_2CO)_5(H_2O)_8$ as a white solid (2.1 g), which was dried to constant weight and stored over P_2O_5 under vacuum in darkness. Anal. Calcd for $C_{66}H_{144}N_4O_{56}S_3$: C, 39.91; H, 7.26; N, 2.82; S, 4.84. Found: C, 39.85; H, 7.26; N, 2.92; S, 4.99. ^1H NMR (300 MHz, D_2O): δ 2.75 (s, 9H), 2.84 (t, J = 6 Hz, 4H), 2.92 (t, J = 6 Hz, 2H), 3.10 (t, J = 6 Hz, 4H), 3.20 (t, J = 6 Hz, 2H), 3.4−4.0 (m, 42H), 5.03 (m, 7H). ^{13}C NMR (75.8 MHz, D_2O): δ 37.8, 39.8, 46.2, 49.5, 50.0, 51.2, 61.6, 62.1, 68.9, 73.1, 73.2, 73.3, 73.6, 74.1, 74.4, 81.7, 82.4, 82.8, 84.4, 102.4, 103.1.

(*R*)- and (*S*)-tryptophan (Sigma) were dried to constant weight and stored in the dark over P_2O_5 in a vacuum desiccator before use. Their enantiomeric purities were determined to be ≥ 99% after HPLC analysis (Pirkle covalent (*S*)-phenylglycine column) of the esters formed with thionyl chloride pretreated methanol. Metal perchlorates (Fluka) were twice recrystallized from water and were dried and stored over P_2O_5 under vacuum. (***Caution***! Anhydrous perchlorate salts are potentially powerful oxidants and should be handled with care.) Stock 0.100 mol dm^{-3} $Ni(ClO_4)_2$, $Cu(ClO_4)_2$, and $Zn(ClO_4)_2$ solutions were standardized by edta titration in the presence of Murexide indicator in the first two cases and Eriochrome Black T in the last case.[23] Deionized water, purified with a MilliQ reagent system to produce water with a specific resistance of > 15 MΩ cm, was boiled to remove CO_2 and used in the preparation of all solutions.

Equilibrium Studies. Potentiometric titrations were carried out using a Metrohm Dosimat E665 titrimater, an Orion SA 720 potentiometer, and an Orion 8172 Ross Sureflow combination pH electrode that was filled with 0.10 mol dm^{-3} $NaClO_4$. All titration solutions were saturated with nitrogen by passing a fine stream of nitrogen bubbles (previously passed through aqueous 0.10 mol dm^{-3} $NaClO_4$) through them for at least 15 min before commencement of the titration. During the titrations, a similar stream of nitrogen bubbles was passed through the titration solution that was magnetically stirred and thermostated at 298.2 ± 0.1 K in a water-jacketed 20 cm^3 titration vessel closed to the atmosphere except for a small exit for nitrogen.

In all titrations, standardized 0.100 mol dm^{-3} NaOH was titrated against the species of interest in solutions 0.007 mol dm^{-3} in $HClO_4$ and 0.090 mol dm^{-3} in $NaClO_4$. Thus, the protonation constants for βCDtren were determined from titrations of 10.00 cm^3 aliquots of 0.002 mol dm^{-3} $\beta CDtrenH_3(MeSO_3)_3$ solutions. The stability constants for the formation of $[M(\beta CDtren)]^{2+}$ and related complexes were determined by titration of 10.00 cm^3 aliquots of 0.001 mol dm^{-3} $\beta CDtrenH_4^{4+}$ to which 0.075 cm^3 of $M(ClO_4)_2$ solution had been added. The stability constants for the formation of βCDtren·(*R*)-Trp^-, βCDtren·(*S*)-Trp^-, and related complexes were determined by titration of 5.00 cm^3 each of 0.002 mol dm^{-3} solutions of either (*R*)-$TrpH_2^+$ or (*S*)-$TrpH_2^+$ and $\beta CDtrenH_4^{4+}$. The stability constants for the formation of $[M(\beta CDtren)$-(*R*)-$Trp]^+$, $[M(\beta CDtren)$-(*S*)-$Trp]^+$, and related complexes were determined by titration of 5.00 cm^3 each of 0.002 mol dm^{-3} solutions of either (*R*)-$TrpH_2^+$ or (*S*)-$TrpH_2^+$ and $\beta CDtrenH_4^{4+}$ with 0.075 cm^3 of $M(ClO_4)_2$ solution added. E_0 and pK_w values were determined by titration of 0.010 mol dm^{-3} $HClO_4$ (0.090 mol dm^{-3} in $NaClO_4$) against 0.100 mol dm^{-3} NaOH. Derivations of the stability constants were carried out using the program SUPERQUAD.[24] At least three runs were performed for each system, and at least two of these runs were averaged; the criterion for selection for this averaging being that χ^2 for each run was <12.6 at the 95% confidence level.[24]

Spectrophotometric Studies. All spectra were run in duplicate on a Cary 2200 spectrophotometer in 0.025 mol dm^{-3} NaPIPES buffer at pH 7.00 and I = 0.10 mol dm^{-3} ($NaClO_4$) in quartz cells thermostated at 298.2 K against reference solutions containing all components of the solution of interest except the metal salt. The spectra of the Co^{2+} systems were run under nitrogen on solutions prepared under nitrogen in a glovebox.

Results

Several complexes exist in aqueous solutions of βCDtren, M^{2+}, and tryptophan in the pH range 2.0−11.5 (Figure 1 and Tables 1 and 2). Their stabilities were calculated from the differences between the pH profiles arising from titration of

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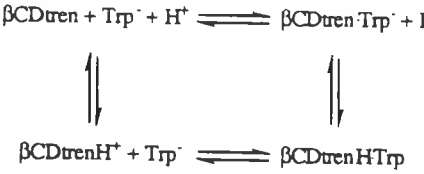
Table 1. Protonation and Stability Constants for 6^A^-((2-(Bis(2-aminoethyl)amino)ethyl)amino)-6^A^-deoxy-β-cyclodextrin (βCDtren) and Its Complexes and Related Species[a] in Aqueous Solution at 298.2 K and I = 0.10 mol dm^{-3} (NaClO4)

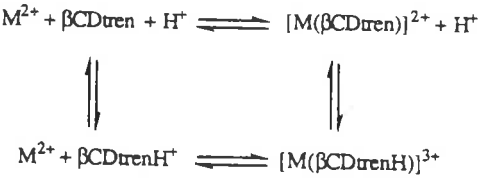
equilibrium	log(K/dm^3 mol^{-1})[b]
βCDtren + H$^+$ ⇌ βCDtrenH$^+$	9.85 ± 0.02 (10.14)[c]
βCDtrenH$^+$ + H$^+$ ⇌ βCDtrenH$_2^{2+}$	8.99 ± 0.09 (9.43)[c]
βCDtrenH$_2^{2+}$ + H$^+$ ⇌ βCDtrenH$_3^{3+}$	6.89 ± 0.05 (8.41)[c]
βCDtrenH$_3^{3+}$ + H$^+$ ⇌ βCDtrenH$_4^{4+}$	2.6 ± 0.3
βCDtren + (*R*)-Trp$^-$ ⇌ βCDtren·(*R*)-Trp$^-$	6.36 ± 0.01
βCDpn + (*R*)-Trp$^-$ ⇌ βCDpn·(*R*)-Trp$^-$ [d]	3.41
βCD + (*R*)-Trp$^-$ ⇌ βCD·(*R*)-Trp$^-$ [d]	2.33
βCDtren + (*S*)-Trp$^-$ ⇌ βCDtren·(*S*)-Trp$^-$	6.5 ± 0.1
βCDpn + (*S*)-Trp$^-$ ⇌ βCDpn·(*S*)-Trp$^-$ [d]	3.40
βCD + (*S*)-Trp$^-$ ⇌ βCD·(*S*)-Trp$^-$ [d]	2.33
βCDtrenH$^+$ + (*R*)-Trp$^-$ ⇌ βCDtrenH·(*R*)-Trp	5.85 ± 0.03
βCDtrenH$^+$ + (*S*)-Trp$^-$ ⇌ βCDtrenH·(*S*)-Trp	5.9 ± 0.1
βCDtren·(*R*)-Trp$^-$ + H$^+$ ⇌ βCDtrenH·(*R*)-Trp	9.34 ± 0.04
βCDtren·(*S*)-Trp$^-$ + H$^+$ ⇌ βCDtrenH·(*S*)-Trp	9.3 ± 0.2
βCDtrenH$^+$ + (*R*)-TrpH ⇌ βCDtrenH·(*R*)-TrpH$^+$	5.59 ± 0.05
βCDtrenH$^+$ + (*S*)-TrpH ⇌ βCDtrenH·(*S*)-TrpH$^+$	5.61 ± 0.08
βCDtrenH·(*R*)-Trp + H$^+$ ⇌ βCDtrenH·(*R*)-TrpH$^+$	8.99 ± 0.07
βCDtrenH·(*S*)-Trp + H$^+$ ⇌ βCDtrenH·(*S*)-TrpH$^+$	8.9 ± 0.2
Trp$^-$ + H$^+$ ⇌ TrpH[d]	9.28
TrpH + H$^+$ ⇌ TrpH$_2^+$ [d]	2.40

[a] β-Cyclodextrin and 6^A^-((3-aminopropyl)amino)-6^A^-deoxy-β-cyclodextrin are represented by βCD and βCDpn, respectively. βCDtrenH$_n^{n+}$ indicates the degree of protonation of the title cyclodextrin, and βCDpnH$_n^{n+}$ has an analogous meaning. Trp$^-$, TrpH, and TrpH$_2^+$ represent the anionic, neutral, and protonated forms of tryptophan. The complex formed between βCDtren and (*R*)-Trp$^-$ is represented by βCDtren·(*R*)-Trp$^-$, and other complexes are represented in a similar manner. [b] This work unless otherwise indicated. Errors quoted for K (the mean of N runs) represent the standard deviation, $\sigma = \sqrt{((\Sigma(K_i - K)^2)/(N-1))}$, where K_i is a value from a single run for the best fit of the variation of pH with added volume of NaOH titrant obtained through SUPERQUAD and i = 1, 2, ... N. [c] Data for the analogous equilibria tren(H)$_n^{n+}$ + H$^+$ ⇌ tren(H)$_{n+1}^{n+1}$ where n = 0, 1, and 2, respectively, from ref 31. [d] References 15 and 16.

Scheme 1



Scheme 2



acidified solutions, containing different combinations of the complexing species, against NaOH using the program SUPERQUAD.[24] The titrimetric technique depends either on the protonation constant of an equilibrium constituent changing on complexation or on the complexation constants for the constituent and its protonated form differing, or both, to produce a pH change. This is exemplified by the βCDtren/Trp$^-$/H$^+$ system (Scheme 1) where the protonation constants of βCDtren and its complex βCDtren·Trp$^-$ differ as do the stability constants of βCDtren·Trp$^-$ and βCDtrenH·Trp (Table 1). Similarly, for the M^{2+}/βCDtren/H$^+$ system (Scheme 2) both the protonation constants of βCDtren and [M(βCDtren)]$^{2+}$ and the stability constants of [M(βCDtren)]$^{2+}$ and [M(βCDtrenH)]$^{3+}$ differ (Tables 1 and 2).

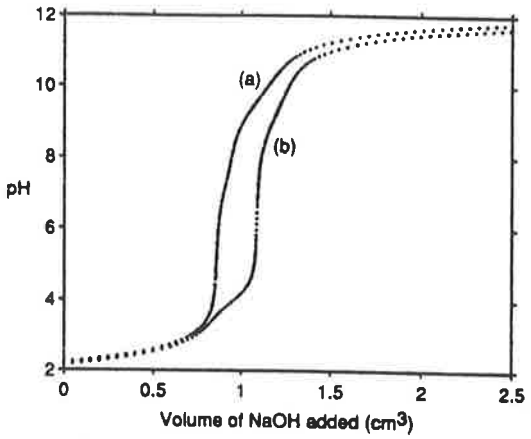


Figure 2. Titration profiles for (a) βCDtrenH$_4^{4+}$ (8.25 × 10^{-4} mol dm^{-3}) and (*R*)-TrpH$_2^+$ (1.03 × 10^{-3} mol dm^{-3}) and (b) βCDtrenH$_4^{4+}$ (8.25 × 10^{-4} mol dm^{-3}), (*R*)-TrpH$_2^+$ (1.03 × 10^{-3} mol dm^{-3}), and Cu(ClO$_4$)$_2$ (7.64 × 10^{-4} mol dm^{-3}), each in aqueous 0.007 mol dm^{-3} HClO$_4$ and 0.090 mol dm^{-3} NaClO$_4$ against 0.101 mol dm^{-3} NaOH at 298.2 K.

The sequence of titrations was (i) protonation constant determinations for βCDtren, followed by determination of the stability constants of the complexes formed from (ii) βCDtren and either (*R*)-Trp$^-$ or (*S*)-Trp$^-$ and their protonated analogues, (iii) M^{2+} and either βCDtren or βCDtrenH$^+$, and (iv) M^{2+} and either βCDtren or βCDtrenH$^+$ and either (*R*)-Trp$^-$ or (*S*)-Trp$^-$ and their protonated analogues. The protonation constants determined in (i), and those previously determined[16] under the same conditions for Trp$^-$, together with the stability constants determined in (ii) and (iii) and those for the complexation of tryptophan by M^{2+} previously determined under the same conditions,[16] were used where appropriate in the determination of stability constants from (ii)–(iv). The pH titration data were fitted to equilibria containing the minimum number of species required for a good fit, and any newly determined species found to be <5% of the total cyclodextrin or amino acid concentrations were considered to be insignificant. Two such pH titration profiles are shown in Figure 2. The protonation and stability constants derived in this study appear in Tables 1 and 2, and the speciation plots of the major species present in the Cu^{2+} system (Figures 3 and 4) exemplify those generated from these data.

Discussion

Formation of 6^A^-((2-(Bis(2-aminoethyl)amino)ethyl)amino)-6^A^-deoxy-β-cyclodextrin tryptophan complexes. The stability constants (Table 1) for βCDtren·(*R*)-Trp$^-$ and βCDtren·(*S*)-Trp$^-$ are ~10^3 times greater than those for βCDpn·(*R*)-Trp$^-$ and βCDpn·(*S*)-Trp$^-$ [16] (where βCDpn is 6^A^-((3-aminopropyl)-amino)-6^A^-deoxy-β-cyclodextrin), which are ~10 times greater than those for βCD·(*R*)-Trp$^-$ and βCD·(*S*)-Trp$^-$.[15] The phenyl moiety of Trp$^-$ probably resides largely within the hydrophobic region of the cyclodextrin annuli of these complexes (Scheme 1), as has been shown to be the case for a range of cyclodextrin complexes formed with other aromatic guests.[25–28] Polar guests tend to align their dipole moments antiparallel to that of the

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Table 2. Protonation and Stability Constants for Metallocyclodextrins of 6^-((2-(Bis(2-aminoethyl)amino)ethyl)amino)-6^-deoxy-β-cyclodextrin (βCDtren) and Related Species[a] in Aqueous Solution at 298.2 K and I = 0.10 mol dm^{-3} (NaClO4)

equilibrium	log(K/dm^3 mol^{-1})[b]		
	$M^{2+} = Ni^{2+}$	$M^{2+} = Cu^{2+}$	$M^{2+} = Zn^{2+}$
$M^{2+} + tren \rightleftharpoons [M(tren)]^{2+}$ [c]	14.6	18.5	14.5
$M^{2+} + pn \rightleftharpoons [M(pn)]^{2+}$ [c]	6.31	9.75	
$M^{2+} + \beta CDtren \rightleftharpoons [M(\beta CDtren)]^{2+}$	11.65 ± 0.06	17.29 ± 0.05	12.25 ± 0.03
$M^{2+} + \beta CDpn \rightleftharpoons [M(\beta CDpn)]^{2+}$ [d]	5.2	7.35	4.96
$M^{2+} + \beta CDtrenH^+ \rightleftharpoons [M(\beta CDtrenH)]^{3+}$	8.46 ± 0.06	11.56 ± 0.02	7.92 ± 0.02
$M^{2+} + \beta CDpnH^+ \rightleftharpoons [M(\beta CDpnH)]^{3+}$ [d]	3.1	3.09	3.0
$[M(\beta CDtren)]^{2+} + H^+ \rightleftharpoons [M(\beta CDtrenH)]^{3+}$	6.65 ± 0.09	4.11 ± 0.05	5.51 ± 0.04
$[M(\beta CDtren)OH]^+ + H^+ \rightleftharpoons [M(\beta CDtren)]^{2+}$	9.68 ± 0.09	8.48 ± 0.04	8.9 ± 0.6
$M^{2+} + Trp^- \rightleftharpoons [M(Trp)]^+$ [d]	5.42	8.11	4.90
$[M(Trp)]^+ + Trp^- \rightleftharpoons [M(Trp)_2]$ [d]	4.67	7.20	
$[M(\beta CDtren)]^{2+} + (R)\text{-}Trp^- \rightleftharpoons [M(\beta CDtren)\text{-}(R)\text{-}Trp]^+$	8.2 ± 0.2	9.5 ± 0.3	8.1 ± 0.1
$[M(\beta CDpn)]^{2+} + (R)\text{-}Trp^- \rightleftharpoons [M(\beta CDpn)\text{-}(R)\text{-}Trp]^+$ [d]	4.1	7.85	5.3
$[M(\beta CDtren)]^{2+} + (S)\text{-}Trp^- \rightleftharpoons [M(\beta CDtren)\text{-}(S)\text{-}Trp]^+$	8.1 ± 0.2	9.4 ± 0.2	8.3 ± 0.1
$[M(\beta CDpn)]^{2+} + (S)\text{-}Trp^- \rightleftharpoons [M(\beta CDpn)\text{-}(S)\text{-}Trp]^+$ [d]	5.1	8.09	5.3
$[M(\beta CDtren)]^{2+} + (R)\text{-}TrpH \rightleftharpoons [M(\beta CDtren)\text{-}(R)\text{-}TrpH]^{2+}$	4.6 ± 0.2	4.3 ± 0.3	
$[M(\beta CDtren)\text{-}(R)\text{-}Trp]^+ + H^+ \rightleftharpoons [M(\beta CDtren)\text{-}(R)\text{-}TrpH]^{2+}$	5.6 ± 0.3	4.0 ± 0.5	
$[M(\beta CDtren)]^{2+} + (S)\text{-}TrpH \rightleftharpoons [M(\beta CDtren)\text{-}(S)\text{-}TrpH]^{2+}$	4.3 ± 0.2	4.2 ± 0.2	
$[M(\beta CDtren)\text{-}(S)\text{-}Trp]^+ + H^+ \rightleftharpoons [M(\beta CDtren)\text{-}(S)\text{-}TrpH]^{2+}$	5.4 ± 0.3	4.0 ± 0.3	
$[M(\beta CDtrenH)]^{3+} + (R)\text{-}TrpH \rightleftharpoons [M(\beta CDtrenH)\text{-}(R)\text{-}TrpH]^{3+}$	3.56 ± 0.07	4.4 ± 0.2	4.82 ± 0.06
$[M(\beta CDtren)\text{-}(R)\text{-}TrpH]^{2+} + H^+ \rightleftharpoons [M(\beta CDtrenH)\text{-}(R)\text{-}TrpH]^{3+}$	5.6 ± 0.3	4.3 ± 0.4	
$[M(\beta CDtrenH)]^{3+} + (S)\text{-}TrpH \rightleftharpoons [M(\beta CDtrenH)\text{-}(S)\text{-}TrpH]^{3+}$	3.6 ± 0.3	4.4 ± 0.2	4.96 ± 0.05
$[M(\beta CDtren)\text{-}(S)\text{-}TrpH]^{2+} + H^+ \rightleftharpoons [M(\beta CDtrenH)\text{-}(S)\text{-}TrpH]^{3+}$	6.0 ± 0.4	4.3 ± 0.3	
$[M(\beta CDtren)((R)\text{-}Trp)OH] + H^+ \rightleftharpoons [M(\beta CDtren)\text{-}(R)\text{-}Trp]^+$	7.86 ± 0.02	8.58 ± 0.02	8.7 ± 0.3
$[M(\beta CDtren)((S)\text{-}Trp)OH] + H^+ \rightleftharpoons [M(\beta CDtren)\text{-}(S)\text{-}Trp]^+$	7.77 ± 0.03	8.53 ± 0.08	8.76 ± 0.08

[a] In addition to the abbreviations given in the footnote to Table 1, the following abbreviations apply: tren = (2-(bis(2-aminoethyl)amino)ethyl)amine, pn = 1,3-diaminopropane, and their complexes are represented by $[M(tren)]^{2+}$ and $[M(pn)]^{2+}$, respectively. The binary metallocyclodextrin formed by the title cyclodextrin is represented by $[M(\beta CDtren)]^{2+}$, and $[M(\beta CDtren)\text{-}(R)\text{-}Trp]^+$ is the ternary cyclodextrin formed with (R)-Trp$^-$. Analogous representations refer to the metallocyclodextrins of 6^-((3-aminopropyl)amino)-6^-deoxy-β-cyclodextrin (βCDpn). Metallocyclodextrin protonation is indicated by the addition of protons to the abbreviations and appropriate changes of charge. [b] This work unless otherwise indicated. Errors quoted for K (the mean of N runs) represent the standard deviation, $\sigma = \sqrt{((\sum(K_i - K)^2)/(N - 1))}$, where K_i is a value from a single run for the best fit of the variation of pH with added volume of NaOH titrant obtained through SUPERQUAD and i = 1, 2, ..., N. [c] Reference 31. [d] Reference 16.

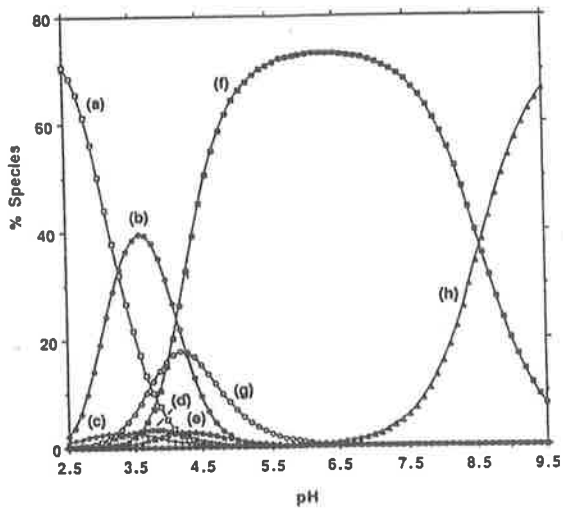

Figure 3. Plot of percentage of Cu^{2+} species in a solution 7.64 × 10^{-4}, 8.25 × 10^{-4}, and 1.03 × 10^{-3} mol dm^{-3} in total Cu^{2+}, βCDtren, and (R)-TrpH, respectively, calculated from the data in Tables 1 and 2 and plotted relative to total [(R)-TrpH] = 100%: (a) Cu^{2+}; (b) [Cu(βCDtrenH)-(R)-TrpH]$^{3+}$; (c) [Cu((R)-Trp)]$^+$; (d) [Cu(βCDtrenH)]$^{3+}$; (e) [Cu(βCDtren)]$^{2+}$; (f) [Cu(βCDtren)-(R)-Trp]$^+$; (g) [Cu(βCDtrenH)-(R)-Trp]$^{2+}$; (h) [Cu(βCDtren)((R)-Trp)OH]. No other Cu^{2+} species are present at >5%.

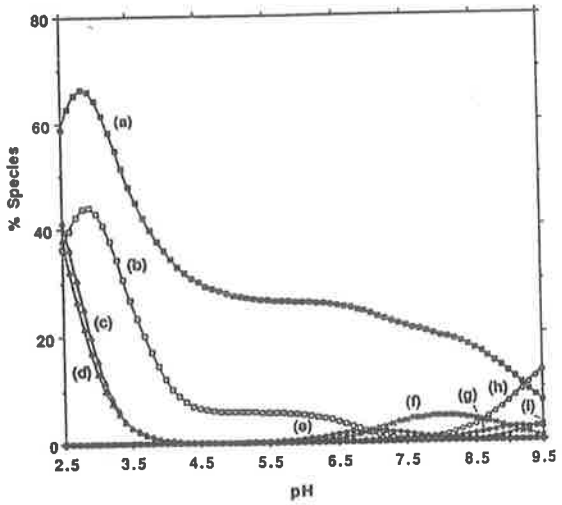

Figure 4. Plot of percentage of non-Cu^{2+} species in a solution 7.64 × 10^{-4}, 8.25 × 10^{-4}, and 1.03 × 10^{-3} mol dm^{-3} in total Cu^{2+}, βCDtren, and (R)-TrpH, respectively, calculated from the data in Tables 1 and 2 and plotted relative to total [(R)-TrpH] = 100%: (a) (R)-TrpH; (b) βCDtrenH$_3^{3+}$; (c) βCDtrenH$_4^{4+}$; (d) (R)-TrpH$_2^-$; (e) βCDtrenH$_2^{2+}$; (f) βCDtrenH·(R)-TrpH$^+$; (g) βCDtrenH·(R)-Trp; (h) (R)-Trp$^-$, (i) βCDtren·(R)-Trp$^-$. No other non-Cu^{2+} species are present at >5%.

cyclodextrin, which for α-cyclodextrin has a magnitude of 10–20 D with the positive and negative poles near the centers of the narrow and wide ends of the annulus, respectively.[29,30]

Similar dipole orientations are assumed for the cyclodextrins considered here. Thus, the increase in stability of the complexes with change in nature of the cyclodextrin in the sequence βCD < βCDpn < βCDtren is attributable to the interaction of the

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Trp^- amino carboxylate group with the narrow end of the cyclodextrin annulus.

The higher stability of the βCDtren complexes may arise because either (i) βCDtren has a greater dipole and a consequently stronger interaction with Trp^-, (ii) the greater bulk of the 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino) substituent hinders egress more than ingress of Trp^-, or (iii) it hydrogen bonds more strongly to Trp^-, or a combination of these factors. As no complexation of Trp^- by (2-(bis(2-aminoethyl)amino)-ethyl)amine (tren) was detected by the pH titrimetric method employed in this study, it appears that the interaction of the phenyl moiety of Trp^- with the interior of the cyclodextrin annulus is the essential contribution to complex stability on which the stabilizing effect of the 6^A-((2-(bis(2-aminoethyl)-amino)ethyl)amino) substituent is superimposed. The similarity of the βCDtren·(*R*)-Trp^- and βCDtren·(*S*)-Trp^- stabilities is also consistent with this interaction dominating the complexation free energy and any free energy differences arising from matching of the opposite chiralities of (*R*)-Trp^- and (*S*)-Trp^- with the homochirality of βCDtren being small by comparison. A similar dominance applies for the analogous βCD and βCDpn complexes.

Protonation decreases the stabilities of βCDtrenH·(*R*)-Trp, βCDtrenH·(*S*)-Trp, βCDtrenH·(*R*)-TrpH$^+$, and βCDtrenH·(*S*)-TrpH$^+$ (Table 1) despite an anticipated increase in the dipolar character of βCDtrenH$^+$. This may reflect either a decreased ability of βCDtrenH$^+$ to hydrogen bond with Trp^- and TrpH or an increased hydration of βCDtrenH$^+$, by comparison with that of βCDtren, diminishing the hydrophobic interaction with the tryptophan phenyl moiety.

Formation of Binary Metallocyclodextrins. The stabilities of the binary metallocyclodextrins, [M(βCDtren)]$^{2+}$, are lower than those of the analogous [M(tren)]$^{2+}$ complexes when M^{2+} = Ni^{2+}, Cu^{2+}, and Zn^{2+} [31] (Table 2). This probably reflects a difference in the electron-donating powers of the secondary amine group in βCDtren and a primary amine group in tren and the greater steric hindrance to metal binding caused by βCDtren. However, the stabilities of [M(βCDtren)]$^{2+}$ are substantially greater than those of [M(βCDpn)]$^{2+}$ because of the tetradentate nature of βCDtren. The stability variations for both binary metallocyclodextrins with the nature of M^{2+} are as anticipated from the Irving–Williams sequence[32] (Ni^{2+} < Cu^{2+} > Zn^{2+}) which arises through a combination of the variation of M^{2+} size and ligand field effects. The stabilities of [M(βCDtrenH)]$^{3+}$ are decreased by comparison with those of [M(βCDtren)]$^{2+}$ because the protonation of an amino group decreases the denticity of βCDtrenH$^+$ to 3 and causes charge repulsion of M^{2+}. The acidity of [M(βCDtrenH)]$^{3+}$ (Table 2) is greatly increased by comparison with that of βCDtrenH$^+$ (Table 1) because of the coordination of M^{2+}. The most acidic is [Cu(βCDtrenH)]$^{3+}$, coincident with its being the most stable of the protonated binary cyclodextrins formed in the equilibria between M^{2+} and βCDtrenH$^+$ (Table 2). The formation of [M(βCDtren)OH]$^+$ arises from the protolysis of a coordinated water molecule that has a pK_a of 9.68, 8.48, and 8.9 when M^{2+} = Ni^{2+}, Cu^{2+}, and Zn^{2+}, respectively.

In aqueous solution, [Ni(tren)(H_2O)$_2$]$^{2+}$ is six-coordinate, but the five-coordinate stoichiometry, [M(tren)H_2O]$^{2+}$, is observed when M^{2+} = Cu^{2+} and Zn^{2+}.[33–35] Over the wavelength range

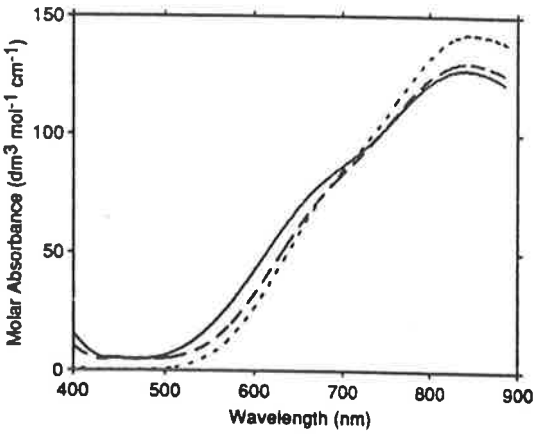

Figure 5. Absorbance spectra for [Cu(tren)H_2O]$^{2+}$ (dotted curve), [Cu-(βCDtren)H_2O]$^{2+}$ (dashed curve), and [Cu(βCDtren)Trp]$^+$ (solid curve) in aqueous 0.025 mol dm^{-3} NaPIPES buffer at pH 7.00 and I = 0.10 mol dm^{-3} ($NaClO_4$) at 298.2 K.

400–900 nm, [Ni(tren)(H_2O)$_2$]$^{2+}$ exhibited a major absorbance maximum at 560 nm with a molar absorbance of 10 dm^3 mol^{-1} cm^{-1} assigned to the $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ transition in reasonable agreement with the literature.[36] The spectra of [Ni(βCDtren)-(H_2O)$_2$]$^{2+}$ and [Ni(βCDtren)Trp]$^+$ differ only slightly in molar absorbance in the range 400–900 nm, and both show maxima at 567 nm with molar absorbances of 6 dm^3 mol^{-1} cm^{-1}, consistent with six-coordination. (It appears that a metal center bound to a polyamine substituent at the 6^A site of a modified cyclodextrin may simultaneously coordinate a cyclodextrin primary hydroxy group, but it was not possible to distinguish between such coordination and that of a water molecule from our data.[7])

The spectrum of [Cu(tren)H_2O]$^{2+}$ (Figure 5) shows a shoulder at ~720 nm and a maximum at 847 nm (molar absorbance = 143 dm^3 mol^{-1} cm^{-1}) assigned to the $^2A_1' \rightarrow {}^2E''$ and $^2A_1' \rightarrow {}^2E'$ transitions, respectively, in reasonable agreement with literature data.[36] The spectra of [Cu(βCDtren)H_2O]$^{2+}$ and [Cu-(βCDtren)Trp]$^+$ exhibit shoulders at ~698 and ~690 nm, respectively, and maxima at 841 nm, with molar absorbances of 131 and 128 dm^3 mol^{-1} cm^{-1}, consistent with Cu^{2+} being five-coordinate in these metallocyclodextrins. UV–visible spectroscopy provides little information about the environment of Zn^{2+} because of its d^{10} electronic configuration. While the formation of five-coordinate [Zn(tren)H_2O]$^{2+}$ in solution[37] indicates the possibility of five-coordinate [Zn(βCDtren)H_2O]$^{2+}$ and [Zn(βCDtren)Trp]$^+$ forming, an analysis of stability data indicates that six-coordination is more probable. Thus, the differences between the log(K/dm^3 mol^{-1}) values for [M(βCDtren)]$^{2+}$ and [M(tren)]$^{2+}$ are 2.95, 1.21, and 2.25 when M^{2+} = Ni^{2+}, Cu^{2+}, and Zn^{2+}, respectively (Table 2). The first difference corresponds to the effect of the βCD substituent on a six-coordinate metal center, whereas the second corresponds to its effect on a five-coordinate metal center. The difference when M^{2+} = Zn^{2+} is intermediate between the other two values, which may result from the βCD substituent causing a change from five- to six-coordination, consistent either with Zn^{2+} in [Zn(βCDtren)H_2O]$^{2+}$ being six-coordinate through the coordination of a cyclodextrin primary hydroxy group as discussed above or with the stoichiometry being [Zn(βCDtren)(H_2O)$_2$]$^{2+}$.

The spectra of solutions of [Co(tren)H_2O]$^{2+}$, Co^{2+}/βCDtren, and Co^{2+}/βCDtren/Trp^- and their protonated analogues ob-

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served under the same saturating nitrogen conditions as those applying in the titrations exhibited significant charge transfer bands extending from 400 to 500 nm, which are absent from the spectra of completely oxygen free solutions of [Co(tren)-H_2O]$^{2+}$.[37] These bands probably arise from the formation of μ-peroxo complexes that are well established for tetra- and pentaamminecobalt(II) complexes.[38] While the proportion of the complex existing as the μ-peroxo form is probably small, the effect of this on the measured stability constants is uncertain, and accordingly the Co^{2+} system is not further discussed.

Formation of Ternary Metallocyclodextrins. The stepwise stability constants for the formation of the ternary metallocyclodextrins [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)-(*S*)-Trp]$^+$ from [M(βCDtren)]$^{2+}$ and (*R*)- and (*S*)-Trp$^-$ are substantially greater than the analogous stability constants for [M(βCDpn)-(*R*)-Trp]$^+$ and [M(βCDpn)-(*S*)-Trp]$^+$. This reflects the differing interactions of Trp$^-$ with the βCDpn and βCDtren that produced the ~10^3-fold greater stability of βCDtren·(*R*)-Trp$^-$ and βCDtren·-(*S*)-Trp$^-$ by comparison with that of βCDpn·(*R*)-Trp$^-$ and βCDpn·(*S*)-Trp$^-$, as discussed above. The probability of substitution of Trp$^-$ on [M(βCDpn)]$^+$ where four water molecules are available for substitution compared to the one or two available in [M(βCDtren)]$^{2+}$, depending on the identity of M^{2+}, should be higher for the former species on a statistical basis. However, this is insufficient to offset the differences in the contributions to ternary metallocyclodextrin stability arising from the interaction of Trp$^-$ with βCDpn and βCDtren.

The stabilities of [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)-(*S*)-Trp]$^+$ are greater than those of the analogous [M(Trp)]$^+$ and βCDtren·Trp$^-$ complexes (Tables 1 and 2). This is consistent with the binding of the Trp$^-$ amino acid moiety by M^{2+} and the hydrophobic interaction between the Trp$^-$ aromatic moiety and the hydrophobic interior of the cyclodextrin annulus (Figure 1) reinforcing each other to stabilize [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)-(*S*)-Trp]$^+$. The variation of the stepwise stability constants for the binding of Trp$^-$ in the ternary metallocyclodextrins with the nature of M^{2+} in the sequence $Ni^{2+} < Cu^{2+} > Zn^{2+}$ is similar to that for the formation of [M(Trp)]$^+$,[31] consistent with the size[39] and electronic configuration[40] of M^{2+} exerting a major influence in this complexation step. The visible spectral data for [Ni(βCDtren)Trp]$^+$ and [Cu-(βCDtren)Trp]$^+$ show that the metal centers are six- and five-coordinate, respectively. In the first case the structure is probably six-coordinated as indicated in Figure 1, but for [Cu-(βCDtren)Trp]$^+$ the possibility arises that either the amine or the carboxylate group of Trp$^-$ may be bound, or both may be bound and one of the amine groups of the 6^A-((2-(bis(2-aminoethyl)amino)ethyl)amino) substituent may not be bound.

The differences between the log(*K*/dm^3 mol^{-1}) values for [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)]$^+$ are 3.45, 7.79, and 4.15, and the analogous data for the (*S*)-Trp$^-$ analogue are 3.55, 7.89, and 3.95 when $M^{2+} = Ni^{2+}$, Cu^{2+}, and Zn^{2+}, respectively (Table 2). In both cases, the first and third values are quite similar, whereas there is about twice the difference in the case of Cu^{2+}. This is consistent with similar coordination changes occurring for [Ni(βCDtren)]$^+$ and [Zn(βCDtren)]$^+$ on complexation of Trp$^-$, and with both metal centers being six-coordinate.

No enantioselectivity was found in the formation of [M(βCDtren)-(*R*)-Trp]$^-$ and [M(βCDtren)-(*S*)-Trp]$^+$. This contrasts with the formation of [M(βCDpn)-(*R*)-Trp]$^+$ and [M(βCDpn)-(*S*)-Trp]$^+$, where a 10-fold enantioselectivity for (*S*)-Trp$^-$ was found when $M^{2+} = Ni^{2+}$ and a lesser enantioselectivity arose when $M^{2+} = Cu^{2+}$ (Table 2).[15,16] (A similar variation was found in the enantioselective complexation of (*R*)- and (*S*)-phenylalanine anions by [M(βCDpn)]$^{2+}$.[17]) Despite the high stabilities of [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)-(*S*)-Trp]$^+$ by comparison with those of [M(βCDpn)-(*R*)-Trp]$^+$ and [M(βCDpn)-(*S*)-Trp]$^+$, the opposed chiralities of (*R*)- and (*S*)-Trp$^-$ generate too small a free energy difference through interaction with the homochiral annulus of the metallocyclodextrin for thermodynamic enantioselectivity to be observed. (Thermodynamic enantioselectivity may reverse with change in the metal binding group as is shown by (6^A-histamino-6^A-deoxy-β-cyclodextrin)copper(II), which forms ternary complexes with (*R*)-Trp$^-$ and the (*R*)-phenylalanine anion that are 2.2 and 1.5 times more stable than those formed with the corresponding (*S*)-enantiomers,[11,14] or it may disappear for the same chiral substrates as is found for (6^A-((2-aminoethyl)amino)-6^A-deoxy-β-cyclodextrin)copper(II).[13])

The pair of protonated species [M(βCDtren)-(*R*)-TrpH]$^{2+}$ and [M(βCDtren)-(*S*)-TrpH]$^{2+}$ are more stable than or similarly stable to the [M(βCDtrenH)-(*R*)-TrpH]$^{3+}$ and [M(βCDtrenH)-(*S*)-TrpH]$^{3+}$ pair when $M^{2+} = Ni^{2+}$ and Cu^{2+}, respectively, or have decreased stabilities by comparison with those of [M(βCDtren)-(*R*)-Trp]$^+$ and [M(βCDtren)-(*S*)-Trp]$^+$. Only [M(βCDtrenH)-(*R*)-TrpH]$^{3+}$ and [M(βCDtren)-(*R*)-Trp]$^+$ and their (*S*) analogues were detected for Zn^{2+}, and the latter metallocyclodextrin is much more stable. These stability variations probably arise because TrpH acts as a monodentate ligand and the major contribution to stability arises from the interaction of the substrate aromatic moiety with the hydrophobic interior of the cyclodextrin annulus.

Conclusions

While the relative stabilities of [M(βCDtren)]$^{2+}$ vary with M^{2+} in the sequence $Ni^{2+} < Cu^{2+} > Zn^{2+}$ and are dominated by the nature of M^{2+}, the subsequent binding of Trp$^-$ is greatly influenced by its interaction with the cyclodextrin annulus. Thus, the combined effects of βCDtren and M^{2+} produce a greater binding of Trp$^-$ in [M(βCDtren)Trp]$^+$ (which also varies with M^{2+} in the sequence $Ni^{2+} < Cu^{2+} > Zn^{2+}$) than that in either [M(Trp)]$^+$ or βCDtren·Trp$^-$, but no enantioselectivity between (*R*)- and (*S*)-Trp$^-$ is observed. The closely related [M(βCDpn)]$^{2+}$ bind (*S*)-Trp$^-$ enantioselectively over (*R*)-Trp$^-$ when $M^{2+} = Ni^{2+}$ and Cu^{2+} but with lower stabilities that also vary with M^{2+} in the sequence $Ni^{2+} < Cu^{2+} > Zn^{2+}$.[16] This enantioselectivity is coincident with the weaker interaction of βCDpn with Trp$^-$ (by comparison with βCDtren) allowing M^{2+} to exert more influence on the binding of Trp$^-$. These observations indicate the subtle relationship between the nature of the cyclodextrin and M^{2+} in substrate binding in ternary metallocyclodextrins. Similarly subtle relationships are probably partly responsible for the high degree of metal ion specificity observed for metalloenzyme activity.

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Crystal structure of 9-(2,6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-1,7-diene-2-one, $C_{13}H_9Cl_2NO_2$

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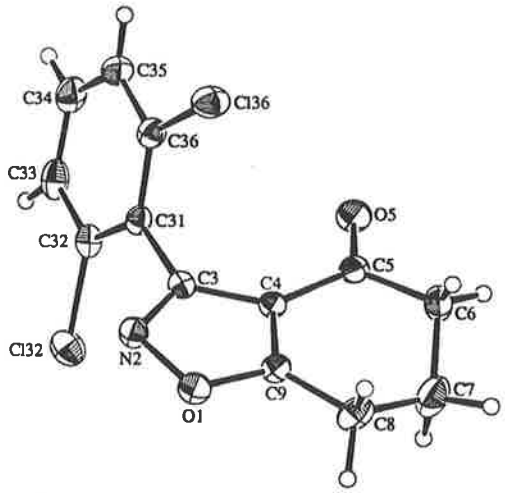

Source of material: Prepared as described in ref. 1.
Some conjugation in the five-membered ring is indicated by the O(1)–N(2), O(1)–C(9), N(2)–C(3), C(3)–C(4) and C(4)–C(9) bond distances of 1.411(3) Å, 1.324(4) Å, 1.289(4) Å, 1.402(4) Å and 1.340(4) Å, respectively. The average deviation of the atoms from their least-squares plane is 0.004 Å and the dihedral angle formed with the aryl ring is 68.9°.
Please note a correction to the title of a related paper (see ref. 2): the name of the compound is 9-(2.6-dichlorophenyl)-8-aza-7-oxa-[4.3.0]-bicyclonon-7-ene-2-one.

$C_{13}H_9Cl_2NO_2$, monoclinic, $P12_1/c1$ (No. 14), a =12.312(2) Å, b =9.733(3) Å, c =10.132(3) Å, β =99.67(2)°, V =1196.9 Å^3, Z =4, $R(F)$ =0.043, $R_w(F)$ =0.040.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless multifaceted prism, size 0.23 x 0.23 x 0.27 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	5.32 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
N(hkl)$_{unique}$:	3027
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	199
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(6a)	4e	0.737(3)	−0.483(4)	0.446(4)	0.06(1)
H(6b)	4e	0.717(4)	−0.466(5)	0.289(5)	0.12(2)
H(7a)	4e	0.932(4)	−0.435(5)	0.435(5)	0.15(2)
H(7b)	4e	0.857(3)	−0.559(4)	0.307(4)	0.08(1)
H(8a)	4e	0.973(3)	−0.378(4)	0.227(4)	0.08(1)
H(8b)	4e	0.851(3)	−0.392(4)	0.158(4)	0.08(1)
H(33)	4e	0.751(3)	0.293(4)	0.611(4)	0.08(1)
H(34)	4e	0.561(3)	0.286(4)	0.553(4)	0.06(1)
H(35)	4e	0.473(3)	0.145(4)	0.393(4)	0.07(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(32)	4e	0.91166(8)	0.1586(1)	0.5177(1)	0.0539(6)	0.0624(6)	0.0615(7)	−0.0119(5)	0.0022(5)	−0.0064(5)
Cl(36)	4e	0.54228(7)	−0.0508(1)	0.2364(1)	0.0467(5)	0.0637(6)	0.0625(7)	0.0006(5)	−0.0011(5)	−0.0142(5)
O(1)	4e	0.8935(2)	−0.1233(2)	0.1948(2)	0.050(1)	0.053(2)	0.043(2)	0.003(1)	0.025(1)	0.001(1)
O(5)	4e	0.6784(2)	−0.2485(3)	0.4941(3)	0.057(2)	0.060(2)	0.056(2)	0.008(1)	0.034(1)	0.011(1)
N(2)	4e	0.8449(2)	−0.0029(3)	0.2363(3)	0.049(2)	0.040(1)	0.041(2)	0.001(1)	0.018(1)	0.002(1)
C(3)	4e	0.7846(2)	−0.0437(3)	0.3210(3)	0.035(2)	0.036(2)	0.032(2)	−0.003(1)	0.004(1)	0.000(1)
C(4)	4e	0.7894(2)	−0.1865(3)	0.3386(3)	0.034(2)	0.036(2)	0.030(2)	0.002(1)	0.011(1)	0.000(1)
C(5)	4e	0.7352(3)	−0.2836(3)	0.4139(4)	0.037(2)	0.041(2)	0.042(2)	0.004(2)	0.008(2)	0.005(2)
C(6)	4e	0.7541(4)	−0.4301(4)	0.3823(5)	0.065(3)	0.039(2)	0.065(3)	−0.002(2)	0.024(2)	0.005(2)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(7)	4*e*	0.8651(4)	−0.4577(4)	0.3465(5)	0.088(3)	0.047(3)	0.084(4)	0.019(3)	0.030(3)	0.005(2)
C(8)	4*e*	0.8909(4)	−0.3699(4)	0.2334(4)	0.062(3)	0.052(2)	0.043(3)	0.018(2)	0.017(2)	−0.004(2)
C(9)	4*e*	0.8574(3)	−0.2294(3)	0.2568(3)	0.041(2)	0.041(2)	0.032(2)	0.005(2)	0.010(1)	0.002(2)
C(31)	4*e*	0.7218(3)	0.0574(3)	0.3853(3)	0.044(2)	0.031(2)	0.035(2)	0.003(2)	0.011(1)	0.003(1)
C(32)	4*e*	0.7704(3)	0.1500(3)	0.4787(3)	0.054(2)	0.034(2)	0.039(2)	−0.002(2)	0.010(2)	0.001(2)
C(33)	4*e*	0.7096(4)	0.2365(4)	0.5440(4)	0.080(3)	0.036(2)	0.046(3)	−0.003(2)	0.016(2)	−0.005(2)
C(34)	4*e*	0.5983(4)	0.2310(4)	0.5151(5)	0.073(3)	0.041(2)	0.066(3)	0.009(2)	0.035(3)	−0.007(2)
C(35)	4*e*	0.5463(3)	0.1445(4)	0.4210(4)	0.048(2)	0.048(2)	0.063(3)	0.007(2)	0.022(2)	0.003(2)
C(36)	4*e*	0.6079(3)	0.0581(3)	0.3570(3)	0.044(2)	0.039(2)	0.041(2)	0.002(2)	0.009(2)	0.001(2)

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Crystal structure of methyl (*Z*)-2-benzamido-3-nitroprop-2-enoate, $C_{11}H_{10}N_2O_5$

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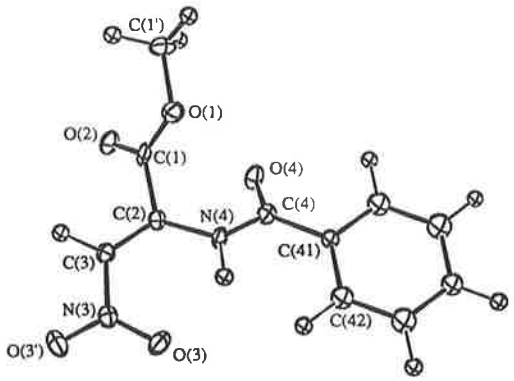

Source of material: Prepared as described in ref. 1.
The conformation about the C(2)–C(3) bond is *Z*. The torsion angles of –0.8°, 122.8° and 22.9° for N(3)/C(3)/C(2)/N(4), O(1)/C(1)/C(2)/C(3) and N(4)/C(4)/C(41)/C(42), respectively indicate significant twists about the C(1)–C(2) and C(4)–C(41) bonds.

$C_{11}H_{10}N_2O_5$, monoclinic. *C*12/*c*1 (No. 15), a =28.517(2) Å, b =4.955(1) Å, c =19.630(2) Å, β =121.40(1)°, V =2367.6 Å^3, Z =8, $R(F)$ =0.079, $R_w(F)$ =0.075.

Reference

1. Easton, C. J.; Roselt, P. D.; Tiekink, E. R. T.: Synthesis of side-chain functionalized amino acid derivatives through reaction of alkyl nitronates with α-bromoglycine derivatives. Tetrahedron **51** (1995) 7809-7822.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless flat prism, size 0.03 x 0.03 x 0.50 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.72 cm^{-1}
Diffractometer:	CAD4F
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
N(hkl)$_{unique}$:	2077
Criterion for F_o:	$F_o > 5\,\sigma(F_o)$
N($param$)$_{refined}$:	126
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1'A)	8*f*	0.3107(3)	–0.205(2)	0.7673(5)	0.16(1)
H(1'B)	8*f*	0.3198(3)	–0.286(2)	0.6969(5)	0.16(1)
H(1'C)	8*f*	0.2807(3)	–0.462(2)	0.7140(5)	0.16(1)
H(3)	8*f*	0.2032(3)	0.049(1)	0.4630(4)	0.16(1)
C(42)	8*f*	0.0457(2)	0.191(1)	0.5772(3)	0.062(2)
C(43)	8*f*	0.0063(2)	0.260(1)	0.5959(3)	0.075(3)
C(44)	8*f*	0.0039(2)	0.120(1)	0.6557(3)	0.059(2)
C(45)	8*f*	0.0408(2)	–0.089(1)	0.6967(3)	0.077(3)
C(46)	8*f*	0.0802(2)	–0.158(1)	0.6780(3)	0.064(2)
C(41)	8*f*	0.0827(2)	–0.018(1)	0.6182(3)	0.038(2)
H(42)	8*f*	0.0474(2)	0.288(1)	0.5356(3)	0.16(1)
H(43)	8*f*	–0.0194(2)	0.405(1)	0.5674(3)	0.16(1)
H(44)	8*f*	–0.0235(2)	0.168(1)	0.6687(3)	0.16(1)
H(45)	8*f*	0.0391(2)	–0.186(1)	0.7383(3)	0.16(1)
H(46)	8*f*	0.1059(2)	–0.303(1)	0.7065(3)	0.16(1)
H(4)	8*f*	0.117(4)	0.25(2)	0.534(6)	0.16(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	8*f*	0.2471(2)	–0.113(1)	0.6593(3)	0.053(3)	0.064(4)	0.055(4)	0.010(3)	0.027(3)	0.001(3)
O(2)	8*f*	0.2306(2)	–0.378(1)	0.5566(3)	0.065(4)	0.046(3)	0.082(4)	0.010(3)	0.051(3)	–0.004(3)
O(3)	8*f*	0.1027(2)	0.410(1)	0.4335(3)	0.060(4)	0.081(5)	0.098(5)	0.025(3)	0.053(4)	0.025(4)
O(3')	8*f*	0.1432(3)	0.393(1)	0.3673(4)	0.111(5)	0.111(6)	0.075(5)	0.026(5)	0.067(4)	0.031(4)
O(4)	8*f*	0.1424(2)	–0.338(1)	0.6117(3)	0.077(4)	0.035(3)	0.098(5)	0.013(3)	0.065(4)	0.012(3)
N(3)	8*f*	0.1381(3)	0.318(1)	0.4222(4)	0.056(4)	0.062(5)	0.060(5)	0.006(4)	0.038(4)	0.012(4)
N(4)	8*f*	0.1376(2)	0.071(1)	0.5586(4)	0.052(4)	0.035(4)	0.064(4)	0.011(3)	0.045(4)	0.007(3)
C(1)	8*f*	0.2192(3)	–0.191(2)	0.5836(5)	0.046(5)	0.045(5)	0.067(6)	0.002(4)	0.045(5)	0.002(5)
C(1')	8*f*	0.2934(3)	–0.280(2)	0.7139(5)	0.060(5)	0.097(7)	0.072(6)	0.025(6)	0.025(5)	0.030(6)
C(2)	8*f*	0.1736(3)	0.006(2)	0.5336(4)	0.046(4)	0.033(4)	0.044(5)	–0.002(4)	0.028(4)	–0.006(4)
C(3)	8*f*	0.1752(3)	0.113(1)	0.4732(4)	0.042(4)	0.042(5)	0.046(5)	0.002(4)	0.026(4)	–0.003(4)
C(4)	8*f*	0.1233(3)	–0.111(2)	0.5981(4)	0.043(4)	0.043(5)	0.045(5)	–0.005(4)	0.022(4)	–0.012(4)

NCS 196 Zeitschrift für Kristallographie 211, 196–197

Crystal structure of methyl (*Z*)-3-aza-2-benzamido-3-benzoyl-4-methoxycarbonyl-5-methyl-hept-4-enoate, $C_{24}H_{26}N_2O_6$

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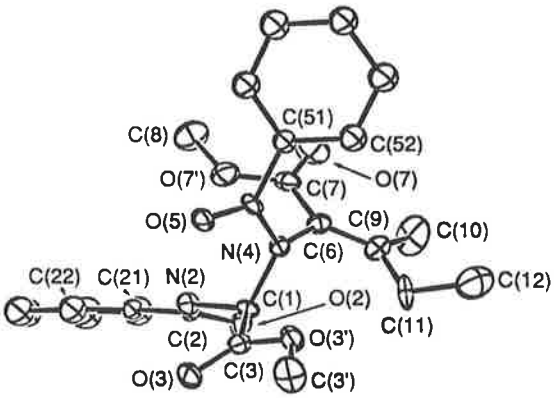

Source of material: Prepared as described in ref. 1.
The conformation about the C(6)–C(9) bond (d =1.43(2) Å) is Z. In the lattice there is a H-bond between N(2)H and O(5) such that N(2)...O(5) is 3.07 Å (H atom not located in study).

$C_{24}H_{26}N_2O_6$, monoclinic, $P12_1/c1$ (No. 14), a =10.288(1) Å, b =13.088(4) Å, c =17.776(6) Å, β =90.91(2)°, V =2393.2 Å^3, Z =4, $R(F)$ =0.068, $R_w(F)$ =0.071.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.40 x 0.40 x 0.40 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.53 cm^{-1}
Diffractometer:	CAD4F
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	45°
$N(hkl)_{unique}$:	3308
Criterion for F_o:	$F_o > 5\,\sigma(F_o)$
$N(param)_{refined}$:	206
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1)	4*e*	0.123(1)	0.9501(9)	0.0256(7)	0.22(2)
H(3'a)	4*e*	0.274(2)	0.977(1)	0.2724(8)	0.22(2)
H(3'b)	4*e*	0.222(2)	1.079(1)	0.2347(8)	0.22(2)
H(3'c)	4*e*	0.370(2)	1.048(1)	0.2268(8)	0.22(2)
H(8a)	4*e*	0.442(2)	0.828(1)	−0.189(1)	0.22(2)
H(8b)	4*e*	0.305(2)	0.781(1)	−0.211(1)	0.22(2)
H(8c)	4*e*	0.414(2)	0.710(1)	−0.175(1)	0.22(2)
H(10a)	4*e*	−0.080(2)	0.648(1)	0.024(1)	0.22(2)
H(10b)	4*e*	0.036(2)	0.600(1)	−0.021(1)	0.22(2)
H(10c)	4*e*	−0.040(2)	0.695(1)	−0.054(1)	0.22(2)
H(11a)	4*e*	−0.017(2)	0.819(1)	0.096(1)	0.22(2)
H(11b)	4*e*	0.129(2)	0.802(1)	0.124(1)	0.22(2)
H(12a)	4*e*	−0.011(2)	0.724(2)	0.201(1)	0.22(2)
H(12b)	4*e*	0.078(2)	0.642(2)	0.160(1)	0.22(2)
H(12c)	4*e*	−0.067(2)	0.660(2)	0.132(1)	0.22(2)
C(22)	4*e*	0.2981(8)	1.1227(8)	−0.1731(5)	0.100(5)
C(23)	4*e*	0.3182(8)	1.1769(8)	−0.2395(5)	0.116(6)
C(24)	4*e*	0.2360(8)	1.1614(8)	−0.3016(5)	0.113(6)
C(25)	4*e*	0.1338(8)	1.0917(8)	−0.2974(5)	0.157(8)
C(26)	4*e*	0.1137(8)	1.0375(8)	−0.2310(5)	0.118(6)
C(21)	4*e*	0.1959(8)	1.0530(8)	−0.1689(5)	0.052(4)
H(22)	4*e*	0.3552(8)	1.1334(8)	−0.1299(5)	0.22(2)
H(23)	4*e*	0.3892(8)	1.2253(8)	−0.2424(5)	0.22(2)
H(24)	4*e*	0.2500(8)	1.1991(8)	−0.3478(5)	0.22(2)
H(25)	4*e*	0.0767(8)	1.0809(8)	−0.3406(5)	0.22(2)
H(26)	4*e*	0.0427(8)	0.9890(8)	−0.2280(5)	0.22(2)
C(52)	4*e*	0.4019(7)	0.6679(7)	0.1075(5)	0.081(5)
C(53)	4*e*	0.4614(7)	0.5735(7)	0.1201(5)	0.093(5)
C(54)	4*e*	0.5753(7)	0.5486(7)	0.0828(5)	0.090(5)
C(55)	4*e*	0.6298(7)	0.6180(7)	0.0328(5)	0.100(5)
C(56)	4*e*	0.5703(7)	0.7124(7)	0.0201(5)	0.083(5)
C(51)	4*e*	0.4563(7)	0.7373(7)	0.0575(5)	0.060(4)
H(52)	4*e*	0.3227(7)	0.6852(7)	0.1335(5)	0.22(2)
H(53)	4*e*	0.4235(7)	0.5252(7)	0.1549(5)	0.22(2)
H(54)	4*e*	0.6167(7)	0.4830(7)	0.0916(5)	0.22(2)
H(55)	4*e*	0.7090(7)	0.6007(7)	0.0068(5)	0.22(2)
H(56)	4*e*	0.6081(7)	0.7607(7)	−0.0147(5)	0.22(2)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(2)	4*e*	0.0592(9)	0.9533(7)	−0.0942(5)	0.049(7)	0.090(8)	0.081(7)	−0.006(6)	−0.002(6)	0.020(6)
O(3)	4*e*	0.2871(9)	1.1086(8)	0.0931(5)	0.110(8)	0.049(6)	0.090(8)	−0.019(7)	0.023(6)	−0.015(6)
O(3')	4*e*	0.2497(9)	0.9669(7)	0.1611(6)	0.108(8)	0.053(7)	0.071(8)	−0.003(6)	0.019(7)	0.004(6)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(5)	4e	0.4693(8)	0.9169(7)	0.0562(5)	0.055(7)	0.043(6)	0.104(8)	−0.007(5)	0.006(5)	0.000(5)
O(7)	4e	0.206(1)	0.660(1)	−0.1082(7)	0.17(1)	0.095(9)	0.14(1)	−0.003(9)	−0.002(9)	−0.046(9)
O(7')	4e	0.330(1)	0.7997(8)	−0.1019(7)	0.108(9)	0.10(1)	0.09(1)	0.018(8)	0.024(7)	−0.011(7)
N(2)	4e	0.251(1)	1.0056(8)	−0.0400(6)	0.063(8)	0.060(8)	0.037(7)	0.009(6)	−0.005(7)	0.014(6)
N(4)	4e	0.270(1)	0.8511(8)	0.0350(5)	0.029(7)	0.047(8)	0.055(8)	−0.001(7)	−0.006(6)	0.004(6)
C(1)	4e	0.217(1)	0.9559(9)	0.0279(7)	0.045(8)	0.035(9)	0.04(1)	0.005(7)	−0.010(7)	−0.014(8)
C(2)	4e	0.165(1)	0.000(1)	−0.0961(8)	0.04(1)	0.05(1)	0.06(1)	0.011(8)	0.021(9)	0.010(8)
C(3)	4e	0.255(1)	1.018(1)	0.096(1)	0.05(1)	0.06(1)	0.09(1)	0.000(9)	0.02(1)	−0.01(1)
C(3')	4e	0.282(2)	1.022(1)	0.2294(8)	0.21(2)	0.10(1)	0.05(1)	−0.04(1)	0.01(1)	−0.04(1)
C(5)	4e	0.400(1)	0.841(1)	0.0464(7)	0.06(1)	0.04(1)	0.06(1)	0.007(9)	−0.010(8)	0.020(8)
C(6)	4e	0.196(2)	0.768(1)	−0.0000(9)	0.05(1)	0.07(1)	0.06(1)	0.01(1)	−0.003(9)	0.00(1)
C(7)	4e	0.238(2)	0.738(1)	−0.074(1)	0.06(1)	0.07(1)	0.10(2)	0.02(1)	−0.01(1)	−0.01(1)
C(8)	4e	0.377(2)	0.778(1)	−0.175(1)	0.26(3)	0.15(2)	0.14(2)	0.03(2)	0.11(2)	−0.04(2)
C(9)	4e	0.085(2)	0.732(1)	0.029(1)	0.07(1)	0.09(1)	0.10(2)	0.01(1)	0.03(1)	−0.00(1)
C(10)	4e	−0.008(2)	0.663(1)	−0.009(1)	0.14(2)	0.19(2)	0.19(2)	−0.12(2)	0.00(1)	−0.09(2)
C(11)	4e	0.053(2)	0.769(1)	0.102(1)	0.14(2)	0.08(1)	0.14(2)	−0.05(1)	0.04(1)	0.05(2)
C(12)	4e	0.010(2)	0.693(2)	0.153(1)	0.20(2)	0.16(2)	0.24(3)	−0.00(2)	0.10(2)	−0.05(2)

Reference

1. Easton, C. F.; Roselt, P. D.; Tiekink, E. R. T.: Synthesis of side-chain functionalized amino acid derivatives through reaction of alkyl nitronates with α-bromoglycine derivatives. Tetrahedron **51** (1995) 7809-7822.

NCS 198 Zeitschrift für Kristallographie 211, 198–199

Crystal structure of 3,6-diethoxycarbonyl-1,4-dimethyl-3,6-epitetrathia-2,5-piperazinedione, $C_{12}H_{16}N_2O_6S_4$

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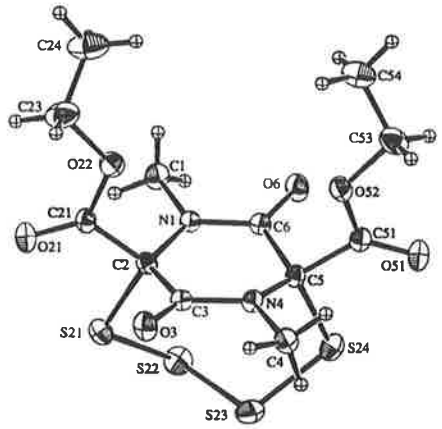

Source of material: Prepared as described in ref. 1; crystals from dichlormethane / light petroleum, m. pt 445 K- 447 K.
The study confirms the presence of the four S atom bridge - the compound is quite unreactive in attempts to form the disulphide, presumably because the disulphide is much more highly strained. The internal S–S bond of 2.076(2) Å is slightly longer than the others of 2.025(2) Å and 2.022(2) Å.

$C_{12}H_{16}N_2O_6S_4$, monoclinic, $C12/c1$ (No. 15), a =11.271(3) Å, b =10.019(3) Å, c =31.883(2) Å, β =96.75(1)°, V =3575.4 Å^3, Z =8, $R(F)$ =0.039, $R_w(F)$ =0.036.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless cube, size 0.11 x 0.11 x 0.11 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	5.61 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
$N(hkl)_{unique}$:	4356
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	281
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1a)	8*f*	–0.112(4)	0.294(4)	0.681(1)	0.09(1)
H(1b)	8*f*	–0.104(4)	0.423(4)	0.655(1)	0.08(1)
H(1c)	8*f*	–0.180(5)	0.300(5)	0.637(2)	0.12(1)
H(4a)	8*f*	0.311(4)	0.058(4)	0.582(1)	0.08(1)
H(4b)	8*f*	0.382(4)	0.152(4)	0.615(1)	0.09(1)
H(4c)	8*f*	0.325(3)	0.206(4)	0.568(1)	0.06(1)
H(23b)	8*f*	0.247(4)	0.533(5)	0.727(1)	0.08(1)
H(23a)	8*f*	0.133(4)	0.518(5)	0.748(1)	0.10(1)
H(24c)	8*f*	0.032(5)	0.659(6)	0.701(2)	0.15(1)
H(24a)	8*f*	0.133(4)	0.740(5)	0.722(1)	0.09(1)
H(24b)	8*f*	0.134(5)	0.686(6)	0.677(2)	0.13(1)
H(53b)	8*f*	0.110(4)	0.499(5)	0.499(1)	0.11(1)
H(53a)	8*f*	0.252(4)	0.499(4)	0.514(1)	0.07(1)
H(54b)	8*f*	0.171(4)	0.709(5)	0.524(2)	0.10(1)
H(54c)	8*f*	0.093(5)	0.649(5)	0.553(2)	0.11(1)
H(54a)	8*f*	0.240(6)	0.644(6)	0.568(2)	0.18(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S(21)	8*f*	0.03945(9)	0.0633(1)	0.69324(3)	0.0509(6)	0.0467(6)	0.0442(5)	–0.0035(4)	0.0078(5)	0.0097(5)
S(22)	8*f*	–0.0603(1)	–0.0243(1)	0.64383(3)	0.0473(7)	0.0537(6)	0.0635(7)	–0.0159(5)	0.0111(5)	–0.0018(6)
S(23)	8*f*	0.0646(1)	–0.0820(1)	0.60442(3)	0.0589(7)	0.0396(6)	0.0654(7)	–0.0014(5)	0.0121(5)	–0.0053(5)
S(24)	8*f*	0.04187(9)	0.0446(1)	0.55473(3)	0.0494(6)	0.0526(6)	0.0435(5)	–0.0067(5)	0.0024(5)	–0.0132(5)
O(3)	8*f*	0.2931(2)	0.1621(3)	0.67505(7)	0.031(2)	0.076(2)	0.042(1)	0.012(1)	–0.003(1)	0.003(1)
O(6)	8*f*	–0.0804(2)	0.3250(3)	0.57222(7)	0.040(2)	0.076(2)	0.038(1)	0.020(1)	–0.003(1)	0.003(2)
O(21)	8*f*	0.1359(2)	0.2824(3)	0.74133(7)	0.065(2)	0.069(2)	0.031(1)	–0.001(1)	0.004(1)	0.002(2)
O(22)	8*f*	0.1403(2)	0.4371(3)	0.69059(8)	0.076(2)	0.042(2)	0.044(2)	–0.006(1)	–0.004(1)	–0.003(1)
O(51)	8*f*	0.1070(2)	0.2547(3)	0.50488(7)	0.063(2)	0.071(2)	0.032(1)	–0.005(1)	0.006(1)	–0.004(2)
O(52)	8*f*	0.1690(2)	0.4075(2)	0.55390(7)	0.064(2)	0.046(2)	0.039(1)	–0.004(1)	0.007(1)	0.005(1)
N(1)	8*f*	–0.0033(2)	0.2768(3)	0.63887(8)	0.024(2)	0.040(2)	0.031(1)	0.006(1)	0.002(1)	0.000(1)
N(4)	8*f*	0.2073(2)	0.1887(3)	0.60802(8)	0.024(2)	0.041(2)	0.033(1)	0.001(1)	0.006(1)	–0.002(1)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	8*f*	–0.1091(4)	0.3316(5)	0.6557(1)	0.034(3)	0.067(3)	0.045(2)	0.018(2)	0.012(2)	0.002(2)
C(2)	8*f*	0.0882(3)	0.2205(3)	0.6679(1)	0.027(2)	0.038(2)	0.033(2)	0.002(1)	0.002(1)	0.004(2)
C(3)	8*f*	0.2057(3)	0.1870(3)	0.6504(1)	0.031(2)	0.033(2)	0.037(2)	–0.000(1)	0.004(2)	–0.001(2)
C(4)	8*f*	0.3184(4)	0.1480(5)	0.5911(1)	0.034(2)	0.056(3)	0.046(2)	0.010(2)	0.012(2)	0.005(2)
C(5)	8*f*	0.1021(3)	0.2061(3)	0.57886(9)	0.031(2)	0.039(2)	0.029(2)	–0.000(1)	0.001(1)	–0.003(2)
C(6)	8*f*	–0.0023(3)	0.2749(3)	0.5966(1)	0.029(2)	0.037(2)	0.035(2)	–0.000(2)	0.003(2)	–0.000(2)
C(21)	8*f*	0.1247(3)	0.3161(4)	0.7053(1)	0.030(2)	0.052(2)	0.031(2)	0.005(2)	0.002(2)	0.000(2)
C(23)	8*f*	0.1712(6)	0.5455(5)	0.7211(2)	0.078(4)	0.053(3)	0.080(4)	0.004(3)	–0.022(3)	–0.021(3)
C(24)	8*f*	0.1138(6)	0.6672(6)	0.7041(2)	0.071(4)	0.053(3)	0.124(5)	0.002(3)	–0.014(4)	–0.016(3)
C(51)	8*f*	0.1260(3)	0.2909(4)	0.5406(1)	0.031(2)	0.051(2)	0.036(2)	0.005(2)	0.004(2)	–0.002(2)
C(53)	8*f*	0.1824(5)	0.5115(5)	0.5224(2)	0.062(3)	0.058(3)	0.065(3)	0.002(2)	0.024(3)	0.019(3)
C(54)	8*f*	0.1684(6)	0.6404(5)	0.5435(2)	0.081(4)	0.050(3)	0.090(4)	–0.000(3)	0.008(3)	0.009(3)

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Anchimeric Assistance in Hydrogen Atom Transfer Reactions on the Side Chains of Amino Acid Derivatives

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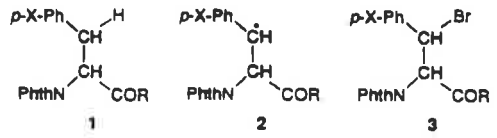
Only a limited range of examples of neighboring group participation in atom transfer reactions have been reported. Anchimeric assistance has been observed in hydrogen atom abstractions, in the vicinal bromination of alkyl bromides,[1,2] and in reactions of *tert*-butoxy radical with Et_4Si, Et_4Ge, and Et_4Sn.[3] Results of studies by Wilt *et al.*,[4] of reactions of β-haloalkylsilanes with stannanes, have also been shown[3] to illustrate neighboring group participation in halogen atom transfer reactions. In each of these systems alkyl radical production is facilitated by a substituent on carbon adjacent to the incipient radical center, through 1,3-participation. We now report strong evidence for anchimeric assistance by an amido substituent, in hydrogen atom transfer reactions, through 1,4-participation. The present work stems from our earlier observations[5] that nucleophilic substitution reactions of **3a−f** to give alcohols are substantially affected through neighboring group participation by the ester and amide groups, particularly in the latter case where the amido substituent can interact more extensively with an electron deficient center developing in a reaction transition state.[6] In that work, **3a−f** were prepared, each as a 1:1 mixture of the diastereomers, by treatment of **1a−f** with NBS. The reverse transformations, of **3a−f** to **1a−f**, have now been accomplished using Ph_3SnH. As these reactions may be assumed to proceed *via* hydrogen and halogen atom transfer, respectively, to give the corresponding radicals **2a−f**, they



(a) X = H, R = OMe
(b) X = H, R = NHt Bu
(c) X = OAc, R = OMe
(d) X = OAc, R = NHt Bu
(e) X = NO_2, R = OMe
(f) X = NO_2, R = NHt Bu

provided the opportunity to probe for anchimeric assistance in atom transfer reactions.

The relative rates of reaction of **1a−f** to give **3a−f** were determined in standard competitive experiments, by measuring the relative rates of consumption of the starting materials and of formation of the products, and in a similar manner the relative rates of reduction of **3a−f** were also determined (Table 1). The effect of the aromatic ring substituents on the reactions of **1a−f** is similar to that previously reported for radical bromination of series of substituted toluene derivatives,[7] with **1a** and **1c**, and **1b** and **1d** reacting much faster than the corresponding nitro-substituted analogues **1e** and **1f**, respectively. This is consistent with the transition state proposed for radical bromination, in which hydrogen transfer to electrophilic bromine atom occurs with the development of an electron deficient center at the site of hydrogen abstraction.[7] In the processes involving Ph_3SnH, the relative rates of reaction reflect the ease with which **3a−f** transfer a bromine atom to the triphenyltin radical. In these processes, the effect of the nitro substituent is the reverse of that seen in the reactions with NBS, with the nitro-substituted compounds **3e** and **3f** reacting much faster than **3a−d**. The relative reactivity of **3a−f** is to be expected, however, as the transition state for a reaction of this type involves transfer of the halogen to the nucleophilic stannyl radical with the development of an electron rich center at the site of halogen abstraction.[8]

Table 1. Relative Rates of Reaction[a] of the Amino Acid Derivatives **1a−f** and **3a−f**

compd	k_{rel}[b]	compd[c]	k_{rel}[d]
1a	8	**3a**	1[e]
1b	40	**3b**	1
1c	9	**3c**	1.2
1d	34	**3d**	1.4
1e	1[e]	**3e**	4
1f	5	**3f**	4

[a] Relative rates of reaction determined in duplicate experiments varied by less than 20%. [b] Reaction with NBS in CCl_4 at reflux under N_2, initiated using a 250 W mercury lamp. [c] Data refers to reaction of the *threo* diastereomer in each case. The diastereoselectivity was less than 1.1 in the reactions of **3a**, **3b**, and **3e** and low in the reactions of **3c**, **3d**, and **3f**, but not possible to accurately quantify in the latter cases due to decomposition of the *erythro* isomers. [d] Reaction with Ph_3SnH in benzene at reflux under N_2, initiated using either AIBN or a 250 W mercury lamp. [e] Assigned as unity within each column.

Whether the carboxyl group is protected as an ester or an amide has very little effect on the relative rates of reaction of **3a−f** with Ph_3SnH, yet in the reactions with NBS, each of the amides **1b**, **1d**, and **1f** reacted approximately 5 times faster than the corresponding ester **1a**, **1c**, and **1e**, respectively. These effects are not consistent with steric constraints resulting from the greater bulk of the amido substituent relative to the ester group, as such factors would be expected to be at least as severe in the reactions of **3a−f**, where the large bromine atom is transferred to the bulky triphenyltin radical. The most obvious interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f**, being more electron rich than the ester group of **1a**, **1c**, and **1e**, facilitates reaction by interacting directly with the electron deficient center in the bromination transition state (Figure 1). The analogous effect would not be expected in the reactions of **3a−f**, where any interaction between the carboxyl group and the electron rich center developing in the transition state would be unfavorable and would therefore be avoided.

Consistent with this interpretation, there was little diastereoselectivity in the reactions of **3a−f** with Ph_3SnH, indicating that the energetics of these processes are little affected by geometrical constraints on interactions between substituents. To examine the possibility of stereoselectivity in the hydrogen transfer

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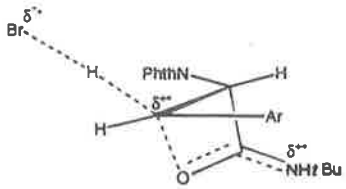
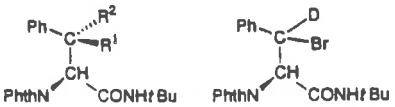


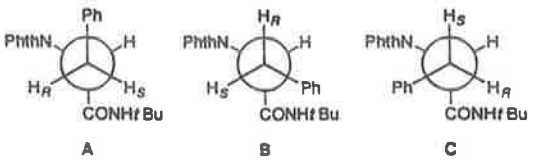
Figure 1. Neighboring group participation by the amido group in the reactions to give the radicals **2b**, **2d**, and **2f**.

reactions, the deuterides **4a** and **4b**[9] were treated with NBS. The (2*S*,3*S*)-deuteride **4a** gave a 1:1 mixture of the diastereomers of **5**, with each diastereomer containing 79% deuterium, whereas the diastereomer **4b** gave **5**, with 66% deuterium retention.



(a) R^1 = H, R^2 = D
(b) R^1 = D, R^2 = H

These results correlate with a deuterium isotope effect of 2.7 for the hydrogen atom transfer[10] and a stereoselectivity of 1.4 for abstraction of the pro-*R* hydrogen. This selectivity is not simply a result of steric effects. The ^{1}H NMR spectra of **4a** and **4b** and the respective coupling constants, $J_{\alpha,\beta}$, of 9.8 and 5.8 Hz indicate that the preferred conformation of the *S*-enantiomer of **1b** is **A**. This is the only staggered conformation which will give rise to the large coupling constant between the α-proton and the pro-*R* β-hydrogen. In this conformation, any steric interactions affecting the hydrogen atom transfer would be expected to result in stereoselective loss of the pro-*S* hydrogen, as this site is the less hindered to the approach of the bromine atom and loss of this hydrogen would relieve steric interactions between the phenyl and phthalimido groups. The stereoselectivity is consistent with neighboring group participation by the amido substituent. Considering the conformations **B** and **C** of **1b** which have the correct orientation to undergo



hydrogen atom transfer with direct interaction between the amide group and the developing electron deficient center, the conformer **B** would be preferred on steric grounds and stereoselective loss of the pro-*R* hydrogen from this conformer would be expected.

Several alternative explanations for the kinetic effects observed in the reactions of **1a**−**f** and **3a**−**f** were considered, but these are inconsistent with the stereoselectivity observed in the reactions of **4a** and **4b**. In principal, the phthalimido group of **1a**−**f** could be involved in neighboring group participation, but this would be expected to result in stereoselective loss of the pro-*S* hydrogen from **1b**. This would occur from the conformer **A**, whereas loss of the pro-*R* hydrogen would involve the conformer **C**. Not only is the conformer **C** of much higher ground-state energy, reaction *via* that conformer would also involve the development of additional steric interactions between the phenyl and amido substituents in the reaction transition state. Another possible interpretation of the results is that the amido substituent of **1b**, **1d**, and **1f** coordinates to the bromine atom involved in the hydrogen atom abstraction [Br∴NH(tBu)COR], thereby facilitating reaction. Similar three-electron-bonded species have been proposed as intermediates, for example, in the reaction of amino acids with hydroxyl radical [HO∴NH_2-$CHRCO_2^-$][11] and in the radical-induced oxidation of sulfides [RR′S∴OCOR″],[12] and sulfide coordination of the bromine atom [R_2S∴Br] has been demonstrated.[13] A third alternative is that the reactions of **1b**, **1d**, and **1f** proceed *via* the corresponding *N*-bromoamides and involve intramolecular 1,4-hydrogen transfer to the amidyl radicals. In these cases, stereoselective loss of the pro-*S* hydrogen from **1b** would be expected, however, as this would involve less steric interactions between the phenyl and phthalimido substituents. To confirm this expectation, the *N*-bromoamides of **4a** and **4b** were prepared by treatment with *tert*-butylhypobromite and photolyzed at reflux in CCl_4. The bromoamide derived from the (2*S*,3*S*)-deuteride **4a** gave a mixture of the diastereomers of **5**, with each diastereomer containing 28% deuterium, whereas the bromoamide of the diastereomer **4b** gave **5**, with 85% deuterium retention. These results correlate with a deuterium isotope effect of 1.5 for the intramolecular 1,4-hydrogen atom transfer[10,14] and a stereoselectivity of 3.8 for abstraction of the pro-*S* hydrogen. Clearly this stereochemical outcome is different to that observed in the reactions of **4a** and **4b** with NBS and precludes the involvement of amidyl radicals as intermediates in the reactions of **1b**, **1d**, and **1f** with NBS.

In conclusion, all of the above evidence indicates that the reactions of **1a**−**f** with NBS involve anchimeric assistance in hydrogen atom abstraction by the bromine atom, through neighboring group participation by an adjacent protected carboxyl group. It appears that this may be a more specific phenomenon than the examples of 1,3-participation in atom transfer reactions reported previously.[1−4] While 1,3-participation occurs in reactions involving either hydrogen or halogen atom abstraction, with correspondingly electron rich or deficient transition states, and is also reflected in the bridging of the product radicals as determined by EPR spectroscopic studies,[15] neighboring group effects observed in the present work are apparently limited to hydrogen transfer reactions and the stabilization of electron deficient reaction transition states.

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(9) Compounds **4a** and **4b** were prepared as previously described for the corresponding methyl esters,[16] each in approximately 98% diastereomeric excess and with approximately 99% D_1 incorporation.

(10) Based on the assumption that the isotope effects for loss of the pro-*R* and pro-*S* hydrogens are identical.

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(14) Although examples of intramolecular 1,4-hydrogen atom transfer are rare,[17] the reactions of the *N*-bromoamides of **1b**, **4a**, and **4b** were shown to be intramolecular by carrying out the photolyses to give the bromides **3b** and **5** in the presence of other potentially reactive substrates.

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Neighbouring Group Effects Promote Substitution Reactions over Elimination and Provide a Stereocontrolled Route to Chloramphenicol

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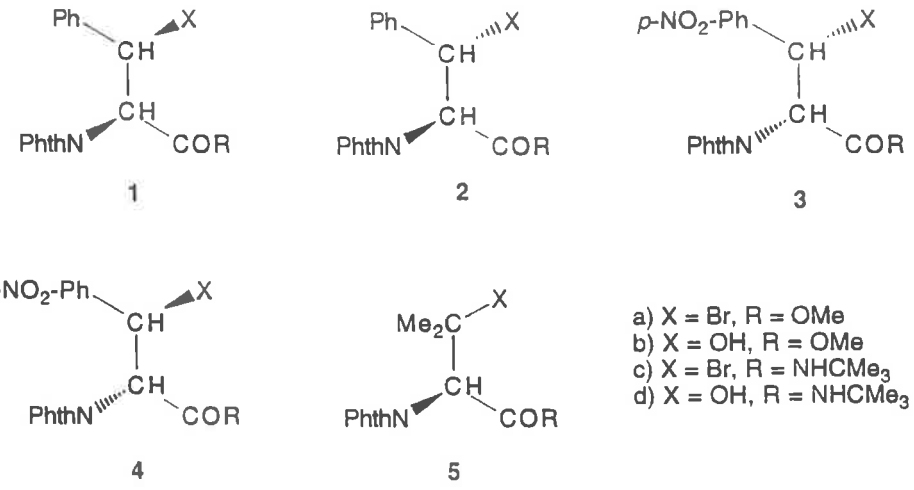
Abstract: In reactions of β-brominated valine and *p*-nitrophenylalanine derivatives to give β-hydroxy amino acid derivatives the carboxyl group, when protected as an amide, exerts a neighbouring group effect to facilitate the substitution process, and reduce competing elimination reactions. As a consequence of the effect, the (2*R*,3*R*)- and (2*R*,3*S*)-stereoisomers of 3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide both react to give (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, providing a stereoconvergent route to chloramphenicol.

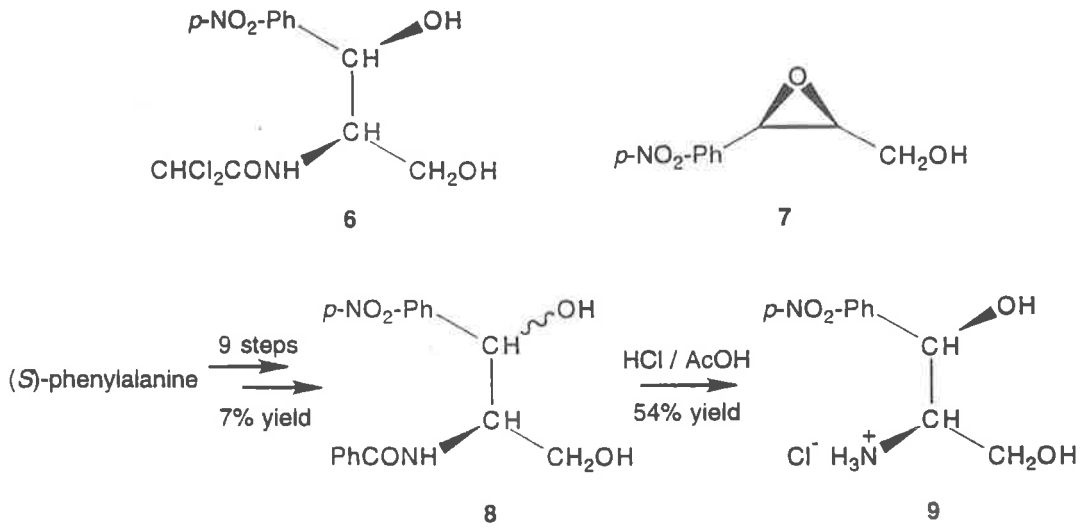
INTRODUCTION

Neighbouring group participation by amido and aminocarbonyl substituents is well known[1] and the chemical and biochemical implications of this phenomenon in reactions of amino acid derivatives have attracted considerable attention.[2-6] For example, it appears that the biochemistry of asparagine incorporated in peptides is influenced by the interaction of the side chain aminocarbonyl moiety with the peptide bonds,[2] while amides derived from either the amino[3,4] or carboxyl group[5] of an amino acid are known to be able to act as nucleophiles or provide anchimeric assistance in solvolysis reactions, *via* 1,5-participation. Recently we reported[7] much greater diastereoselectivity in the synthesis of the hydroxyamides **1d** and **2d** from the bromoamides **1c** and **2c** than in the conversion of the corresponding bromoesters **1a** and **2a** to the hydroxyesters **1b** and **2b**. The enhanced stereoselectivity was attributed to neighbouring group participation by the aminocarbonyl substituent in the reactions of the bromides **1c** and **2c**. Consistent with this proposal, the extent of anchimeric assistance displayed by amides is known to be larger than that shown by esters,[6] although 1,4-participation by amides appears to be unusual. We now report reactions of the bromides **3a,c**-**5a,c**, in which it is apparent that the neighbouring group effect changes the course of reaction, favouring substitution over elimination, as well as controlling the stereochemistry in the conversion of the bromides **3a,c** and **4a,c** to the alcohols **3b,d** and **4b,d**.

During the course of the present work a stereospecific route to chloramphenicol **6** was also developed. The industrial synthesis of this broad spectrum antibiotic involves the condensation of benzaldehyde with β-nitroethanol[8] but a disadvantage of that and other approaches[9] is that they involve the formation of racemic products which need to be resolved. An asymmetric synthesis based on azide ring-opening of the epoxide **7** has been reported.[10] Alternatively, (*S*)-phenylalanine has been used to obtain the chloramphenicol precursor **9**



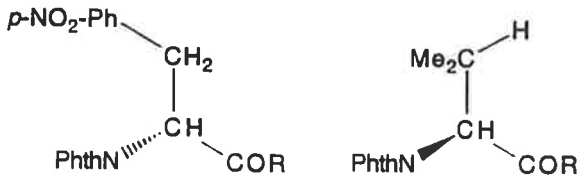
in a multi-step synthesis (Scheme 1), in which diastereocontrol was achieved by utilising 1,5-neighbouring group participation in the hydrolytic rearrangement of the benzamide **8**.[4]



Scheme 1

RESULTS AND DISCUSSION

The *p*-nitrophenylalanine derivatives **10a** and **10b** were prepared using standard procedures, and treated with *N*-bromosuccinimide to give 1:1 mixtures of the diastereomers of the corresponding bromides **3a** and **4a**, and **3c** and **4c**. The bromoesters **3a** and **4a** were separated through fractional crystallisation and their relative stereochemistry was determined through X-ray crystallographic analysis of the (2*S*,3*R*)-diastereomer **4a**.[11] [Note that the Cahn-Ingold-Prelog designation at the α-carbon of the bromides **3a,c-5a,c** is reversed by comparison with that of the corresponding non-halogenated amino acid derivatives **10a,b** and **11a,b**, due to the change in priority of the substituents.] The stereochemistry of the bromoamides **3c** and **4c** was assigned by comparison of the spectral properties of the (2*S*,3*R*)-diastereomer **4c** with those of a racemic sample. That sample was prepared by bromination of the racemic analogue of the nitrophenylalanine derivative **10b**, then separated from its diastereomer by fractional crystallisation and its structure was determined through X-ray crystallographic analysis.[11] The ^{1}H NMR spectra of the bromides **3a,c** and **4a,c** show the same trends as previously observed with the corresponding phenylalanine derivatives **1a,c** and **2a,c**.[7] The signals corresponding to the carboxyl protecting groups occur at lower chemical shift for the (2*S*,3*S*)-diastereomers **3a** and **3c** than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**, while the (2*S*,3*S*)-diastereomers **3a** and **3c** exhibit the β-proton signal at higher chemical shift, the α-proton at lower chemical shift, and a larger coupling constant between the α- and β-protons, than for the corresponding (2*S*,3*R*)-diastereomers **4a** and **4c**. The bromides **5a**[12] and **5c** were prepared by halogenation of the amino acid derivatives **11a** and **11b**, which had each been prepared from (*S*)-valine.



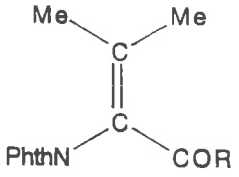
10 **11**

a) R = OMe
b) R = $NHCMe_3$

The valine derivative **5a** reacted with silver nitrate in aqueous acetone, at room temperature for 24 h, to give a crude product containing the alcohol **5b** and the dehydrovaline derivatives **12a** and **13a** in the ratio *ca.* 3.5:1:3.5. Chromatography of the mixture afforded the alcohol **5b** in 43% yield, and the alkenes **12a** and **13a**, in yields of 8 and 34%, respectively. The corresponding reaction of the valinamide **5c** afforded a *ca.* 2:1 mixture of the alcohol **5d** and the alkene **13b**, from which the components were isolated in 63 and 26% yield, respectively. The ^{1}H NMR spectrum of the crude product of the reaction of the valinamide **5c** showed no indication of formation of the alkene **12b**.

The *p*-nitrophenylalanine derivatives **3a,c** and **4a,c** required more vigorous conditions to react. On one occasion, treatment of the bromoester **4a** at 65 °C for 48 h gave the alcohol **3b** in 63% yield, with the dehydrophenylalanine derivatives **14a** and **15a** also being isolated as a 2:3 mixture in 25% yield. Repeated experiments afforded the alcohol **3b** in only 10-30% yield, with higher proportions of the alkenes **14a** and

15a. Under similar conditions, the bromide **3a** gave only the alkene **15a**, in 84% yield, and neither the alcohol **3b** nor the alkene **14a** were detected in the crude product. The analogous reaction of a 1:1 mixture of the bromides **3a** and **4a** carried out using silver sulfate, in place of the nitrate salt, gave mainly the alkene **15a** and only small quantities of either the (*E*)-isomer **14a** or the alcohol **3b**. In contrast, treatment of a 1:1 mixture of



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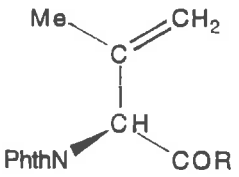
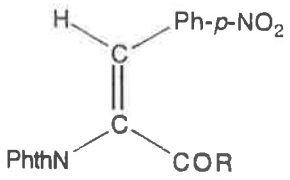


13

a) R = OMe
b) R = $NHCMe_3$

the bromoamides **3c** and **4c** with silver sulfate over 3 days under similar conditions gave only the substitution product **3d** in 64% yield. Reaction of the bromoamides **3c** and **4c** using silver nitrate was complicated by competing formation of a second product, which was tentatively identified as the nitrate **16**. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectra of the crude products obtained from these reactions of the bromoamides **3c** and **4c**.

The stereochemistry of the dehydrophenylalanine derivatives **14a** and **15a** was assigned on the basis of their ^1H NMR spectra, in which the resonance due to the vinylic proton of the (*E*)-isomer **14a** was observed at δ 7.28, 0.85 ppm upfield from that of the corresponding signal for the (*Z*)-alkene **15a**. This is consistent with the general trend displayed by dehydrophenylalanine derivatives.[13] The stereochemistry of the alcohols **3b** and **3d** is apparent from their ^1H NMR spectra, which show a much closer correlation with the spectra of the corresponding hydroxyphenylalanine derivatives **1b** and **1d** than with those of the respective diastereomers **2b** and **2d**. The assignment of stereochemistry of the alcohols **3b** and **3d** is further supported by hydrolysis to the free amino acid **18** and comparison of the physical and spectral properties of that material with literature data.[14-16]



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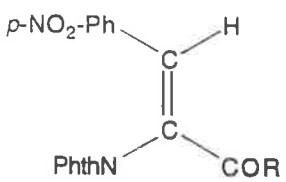

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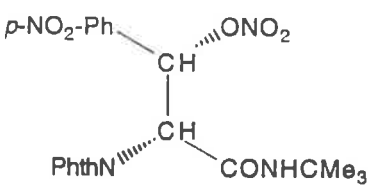
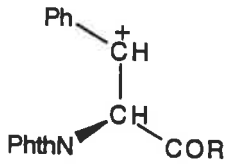


16

a) R = OMe
b) R = $NHCMe_3$

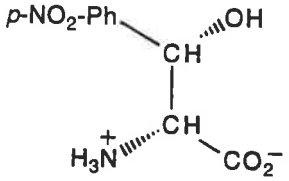
Elimination reactions of the bromovalinate **5a**, to give the alkenes **12a** and **13a**, compete with the substitution reaction, to give the alcohol **5b**. By comparison, the reaction of the bromovalinamide **5c** gives a better yield of the substitution product **5d**. This is not merely a steric effect of the bulky aminocarbonyl substituent to retard elimination. Under these circumstances, the amide **5c** would be expected to react more slowly than the ester **5a**, whereas in competitive experiments the opposite was observed, with the amide **5c**

reacting *ca.* six times faster than the ester **5a**. Instead, the effect of the aminocarbonyl substituent to promote substitution over elimination, and increase the rate of reaction of the bromide **5c**, indicates a neighbouring group effect of the protected carboxyl group to stabilise the carbocation intermediate in the substitution reaction. The neighbouring group effect is also seen in the reactions of the nitrophenylalanine derivatives **3a,c** and **4a,c**, to promote substitution over elimination, and to give the alcohol **3d** with a high degree of stereocontrol from the reaction of the bromoamides **3c** and **4c**. The predominant reaction of the esters **3a** and **4a** is elimination, whereas the amides **3c** and **4c** react by substitution. As shown previously,[7] the bromophenylalanine derivatives **1a,c** and **2a,c** react to give the corresponding alcohols **1b,d** and **2b**. Presumably, in the absense of an electron withdrawing group on the aromatic ring, the carbocations **17a,b** form in the substitution reactions without competing elimination. In that case the only effect of the neighbouring group is to enhance the stereoselectivity in the production of the alcohols **1b,d** and **2b**. The nitrophenylalanine derivatives **3a** and **4a** react predominantly by elimination. When the carboxyl group is protected as an amide, however, the destabilising effect of the nitro substituent on the intermediate carbocation is diminished to the extent that substitution now becomes the favoured reaction pathway.



17

a) R = OMe
b) R = $NHCMe_3$



18

On treament with hydrochloric acid in aqueous acetic acid, the hydroxynitrophenylalanine derivative **3d** hydrolysed to the corresponding free amino acid **18**. The synthetic procedure used to prepare the alcohol **18**, in 29% yield from (*R*)-*p*-nitrophenylalanine, was repeated using racemic *p*-nitrophenylalanine and the (*S*)-enantiomer as starting materials, to obtain the corresponding racemate and the (2*S*,3*R*)-enantiomer of the alcohol **18**. The spectral properties of these compounds were found to be identical to those reported.[14-16] Previously, the racemate of the alcohol **18** has been converted to the corresponding methyl ester, the enantiomers of that compound have been resolved by complexation with tartaric acid, and the (2*S*,3*R*)-stereoisomer has been elaborated to chloramphenicol **6**.[16] Now stereocontrolled access to the (2*S*,3*R*)-enantiomer of the alcohol **18**, as a consequence of neighbouring group participation by an aminocarbonyl substituent to facilitate substitution over elimination and control the stereochemistry of the former, offers a more direct route for synthesis of the antibiotic **6**.

EXPERIMENTAL

General. M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded as nujol mulls, liquid films or as solutions in chloroform, on a Hitachi 270-30 spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Bruker ACP-300 or a GEMINI 300

spectrometer, in $CDCl_3$ with Me_4Si as the internal standard, unless otherwise stated. Electron impact (ei) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Fast atom bombardment (fab) mass spectra were recorded on a VG ZAB 2HF spectrometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over $MgSO_4$.

All solvents were purified and dried using standard methods. (*S*)-Valine, (*RS*)-*p*-nitrophenylalanine, and (*S*)- and (*R*)-*p*-nitrophenylalanine were purchased from Sigma Chemical Co.

*(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine.* A mixture of (*R*)-*p*-nitrophenylalanine monohydrate (1.78 g, 7.81 mmol), phthalic anhydride (1.27 g, 8.58 mmol) and triethylamine (1.1 cm^3, 7.95 mmol) was heated at reflux in toluene (60 cm^3) for 3 h, during which time water was continuously removed using a Dean-Stark condenser. The resultant mixture was cooled in an ice bath and then it was concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with dilute aqueous hydrochloric acid and water, then it was dried and concentrated under reduced pressure. Crystallisation of the solid residue from a mixture of ethyl acetate and light petroleum yielded the title compound as a pale yellow crystalline solid (2.57 g, 97%), m.p. 203-207 °C; $[\alpha]_{578}^{25}$ +234.5° (c, 0.31 in MeOH); δ_H 8.09 (d, *J* 8.7 Hz, 2 H, ArH), 7.72-7.83 (m, 4 H, phth), 7.36 (d, *J* 8.7 Hz, 2 H, ArH), 5.26 (dd, *J* 7.3 and 9.2 Hz, 1 H, α-H) and 3.72 (m, 2 H, β-H).

*(*RS*)-*N*-Phthaloyl-*p*-nitrophenylalanine.* This compound was prepared from (*RS*)-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding (*R*)-isomer, and obtained in 93% yield, m.p. 185-187 °C.

*(*S*)-*N*-Phthaloyl-*p*-nitrophenylalanine.* This compound was prepared from (*S*)-*p*-nitrophenylalanine monohydrate, as described above for the synthesis of the corresponding (*R*)-enantiomer, and obtained in 57% yield, m.p. 200-202 °C (lit.[17] 204.7 °C); $[\alpha]_{578}^{19}$ -230.2° (c, 0.086 in MeOH) (lit.[17] -232.5° (c, 1.55 in MeOH)).

*(*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine Methyl Ester* **10a**. (*R*)-*N*-Phthaloyl-*p*-nitrophenylalanine (2.50 g, 7.35 mmol) was dissolved in dry methanol (50 cm^3) which had been pretreated with thionyl chloride (400 mg, 3.36 mmol). The solution was stirred under anhydrous conditions for 16 h, then it was concentrated under reduced pressure. The residue dissolved in dichloromethane, and the solution was washed with aqueous sodium carbonate and water, then it was dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the title compound **10a** as a colourless solid (2.24 g, 86%), m.p. 121-122 °C; ν_{max}/cm^{-1} 1775, 1750, 1715, 1600, 1520, 1390, 1345, 1240, 860 and 720; δ_H 8.06 (d, *J* 8.6 Hz, 2 H, ArH), 7.72-7.82 (m, 4 H, phth), 7.45 (d, *J* 8.6 Hz, 2 H, ArH), 5.31 (dd, *J* 5.5 and 10.9 Hz, 1 H, α-H), 3.81 (s, 3 H, OMe), 3.77 (dd, *J* 5.5 and 14.3 Hz, 1 H, β-H) and 3.71 (dd, *J* 10.9 and 14.3 Hz, 1 H, β'-H); *m/z* (ei) (%) 354 (M^+, 12), 295 (37), 278 (14), 218 (36), 207 (100), 190 (37), 176 (25), 130 (33), 104 (17) and 76 (21).

*(2*S*,3*S*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester* **3a** *and (2*S*,3*R*)-3-Bromo-*N*-phthaloyl-*p*-nitrophenylalanine Methyl Ester* **4a**. To a solution of (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine methyl ester **10a** (2.20 g, 6.21 mmol) in carbon tetrachloride (40 cm^3), *N*-bromosuccinimide (1.20 g, 6.74 mmol) was added

and the mixture was heated at reflux for 4 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water and dried, then it was concentrated under reduced pressure, to give a 1:1 mixture of the title compounds **3a** and **4a** as a colourless solid (2.69 g, 100%). Fractional recrystallisation of the mixture from a combination of dichloromethane and light petroleum gave the (2*S*,3*S*)-bromide **3a** (1.17 g, 43%), m.p. 198-201 °C; ν_{max}/cm^{-1} 1775, 1750, 1720, 1600, 1525, 1340, 1215, 1100, 820 and 715; δ_H 8.27 (d, *J* 8.8 Hz, 2 H, ArH), 7.82-7.99 (m, 4 H, phth), 7.78 (d, *J* 8.8 Hz, 2 H, ArH), 6.02 (d, *J* 11.2 Hz, 1 H, β-H), 5.51 (d, *J* 11.2 Hz, 1 H, α-H) and 3.59 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 2), 375 (6), 373 (6), 353 (4), 352 (9), 321 (6), 294 (29), 293 (17), 287 (10), 285 (10), 247 (7), 219 (16), 218 (100), 190 (30), 130 (18), 104 (40) and 76 (37) (Found: C, 49.8; H, 3.0; N, 6.5. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). Further recrystallisation gave the (2*S*,3*R*)-bromide **4a** (1.07 g, 40%), m.p. 195-197 °C; ν_{max}/cm^{-1} 1775, 1755, 1720, 1605, 1525, 1390, 1350, 855 and 720; δ_H 8.07 (d, *J* 8.7 Hz, 2 H, ArH), 7.68-7.76 (m, 4 H, phth), 7.56 (d, *J* 8.7 Hz, 2 H, ArH), 5.97 (d, *J* 10.3 Hz, 1 H, β-H), 5.59 (d, *J* 10.3 Hz, 1 H, α-H) and 3.83 (s, 3 H, OMe); *m/z* (ei) (%) 434/432 (M^+, 1), 375 (3), 373 (3), 353 (6), 352 (3), 321 (7), 294 (20), 293 (12), 287 (3), 285 (3), 247 (5), 219 (15), 218 (100), 190 (29), 130 (16), 104 (28) and 76 (26) (Found: C, 49.8; H, 3.0; N, 6.6. Calc. for $C_{18}H_{13}BrN_2O_6$: C, 49.9; H, 3.0; N, 6.5%). The structure of the bromide **4a** was confirmed through X-ray crystallographic analysis.[11]

(RS)-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a suspension of (*RS*)-*N*-phthaloyl-*p*-nitrophenylalanine (2.00 g, 5.88 mmol) in dichloromethane (40 cm^3), triethylamine (0.81 cm^3, 5.85 mmol) was added. The resultant solution was cooled to 0 °C, then ethyl chloroformate (0.56 cm^3, 5.86 mmol) was added. That mixture was stirred for 10 min, then *tert*-butylamine (0.61 cm^3, 5.85 mmol) was added and the solution was warmed to room temperature. After stirring for a further 30 min, the mixture was filtered and the filtrate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate and water, then it was dried and concentrated under reduced pressure. The residue was chromatographed to give the title compound, as a colourless crystalline solid after recrystallisation from a mixture of ethyl acetate and light petroleum (1.26 g, 54%), m.p. 215-216 °C, ν_{max}/cm^{-1} 3316, 2920, 2848, 1774, 1714, 1658, 1554, 1516, 1456, 1382, 1344, 1220, 1088, 1016, 888, 874, 766 and 726; δ_H 8.03 (d, *J* 8.6 Hz, 2 H, ArH), 7.77-7.69 (m, 4 H, phth), 7.33 (d, *J* 8.6 Hz, 2 H, ArH), 5.93 (br s, 1 H, NH), 5.02 (t, *J* 8.4 Hz, 1 H, α-H), 3.65 (d, *J* 8.4 Hz, 2 H, β-H) and 1.33 (s, 9 H, CMe_3); δ_C 29.1, 35.2, 52.4, 56.4, 124.2, 124.3, 130.3, 131.6, 135.1, 145.4, 147.4, 167.1 and 168.3; *m/z* (ei) (%) 395 (M^+, 5), 352 (5), 341 (10), 256 (20), 236 (5) and 213 (10) (Found: C, 63.6; H, 5.3; N, 10.5. Calc. for $C_{21}H_{21}N_3O_5$: C, 63.8; H, 5.3; N, 10.6%).

(R)-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **10b.** This compound was prepared from (*R*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 72% yield, m.p. 230 °C (dec.); $[\alpha]_D^{25}$ +117.0° (c, 0.227 in $CHCl_3$).

(S)-N-tert-*Butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. This compound was prepared from (*S*)-*N*-phthaloyl-*p*-nitrophenylalanine, as described above for the synthesis of the corresponding racemate, and obtained in 79% yield, m.p. 230 °C (dec.); $[\alpha]_D^{21}$ -120.8° (c, 0.418 in $CHCl_3$).

(2RS,3RS)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide and (2RS,3SR)-3-Bromo*-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a solution of (*RS*)-*N*-*tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide (771 mg, 1.95 mmol) in a mixture of carbon tetrachloride and dichloromethane (4:1, 50

cm^3), *N*-bromosuccinimide (695 mg, 3.90 mmol) was added and the mixture was heated at reflux for 3 h, while it was irradiated with a 250 W mercury lamp. The mixture was then allowed to cool, before it was filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give a 1:1 mixture of the title compounds as a colourless solid (905 mg, 98%), m.p. 194-210 °C; ν_{max}/cm^{-1} 3380, 3350, 2950, 2920, 2850, 1775, 1715, 1670, 1520, 1460, 1380, 1350, 1280, 1220, 1110, 1090, 1060, 880, 720 and 700; *m/z* (fab) (%) 476/474 ($M+H^+$, 40%), 420/418 (20), 295 (30), 154 (100) and 136 (90) (Found: C, 53.1; H, 4.2; N, 8.9. Calc. for $C_{21}H_{20}BrN_3O_5$: C, 53.2; H, 4.3; N, 8.9%). Fractional recrystallisation of the mixture of isomers from a combination of dichloromethane and light petroleum afforded a sample of (2*RS*,3*SR*)-3-bromo-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, δ_H 8.08 (d, *J* 8.9 Hz, 2 H, ArH), 7.79-7.64 (m, 4 H, phth), 7.56 (d, *J* 8.9 Hz, 2 H, ArH), 6.23 (br s, 1 H, NH), 6.18 (d, *J* 11.4 Hz, 1 H, β-H), 5.29 (d, *J* 11.4 Hz, 1 H, α-H) and 1.41 (s, 9 H, CMe_3); δ_C 29.1, 46.4, 52.9, 60.7, 124.3, 124.5, 129.3, 129.4, 131.2, 135.1, 145.3, 164.8 and 167.5. The structure of this material was confirmed through X-ray crystallographic analysis.[11] The ^1H and ^{13}C NMR spectra of the mixture of diastereomers showed resonances for the (2*RS*,3*RS*)-isomer, δ_H 8.26 (d, *J* 8.9 Hz, 2 H, ArH), 7.98-7.81 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 6.27 (br s, 1 H, NH), 6.20 (d, *J* 11.7 Hz, 1 H, β-H), 5.19 (d, *J* 11.7 Hz, 1 H, α-H) and 1.11 (s, 9 H, CMe_3); δ_C 28.8, 49.1, 52.4, 62.7, 124.5, 124.6, 130.0, 130.1, 131.6, 135.3, 148.3, 163.9 and 168.3.

(2S,3S)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **3c** *and (2S,3R)-3-Bromo*-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **4c**. A 1:1 mixture of these compounds was prepared from (*R*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 95% yield.

(2R,3R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide and (2R,3S)-3-Bromo*-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. A 1:1 mixture of these compounds was prepared in quantitative yield from (*S*)-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate.

Treatment of (2S,3S)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **3a** *with Silver Nitrate in Aqueous Acetone*. To a solution of the bromide **3a** (50 mg, 0.12 mmol) in acetone (3 cm^3), a solution of silver nitrate (25 mg, 0.15 mmol) in water (2 cm^3) was added. The resultant mixture was stirred at 65 °C in the dark for 48 h, then it was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with dichloromethane and the organic extracts were dried and concentrated under reduced pressure. Recrystallisation of the residue from a mixture of dichloromethane and light petroleum gave the (*Z*)-*p*-nitrophenylalanine derivative **15a** as large colourless prisms (34 mg, 84%), m.p. 133-134 °C; ν_{max}/cm^{-1} 1780, 1720, 1600, 1530 and 1345; δ_H 8.16 (d, *J* 8.8 Hz, 2 H, ArH), 8.13 (s, 1 H, β-H), 7.92-7.83 (m, 4 H, phth), 7.55 (d, *J* 8.8 Hz, 2 H, ArH), 3.87 (s, 3 H, OMe); *m/z* (ei) (%) 352 (M^+, 90), 342 (63), 293 (41), 292 (46), 247 (24), 218 (15), 190 (18), 166 (21), 104 (100) and 76 (73); *m/z* (ei) 352.068 (M^+) [Calc. for $C_{18}H_{12}N_2O_6$ (M^+) *m/z* 352.070]. Neither the alcohol **3b** nor the alkene **14a** were detected in the crude product.

Treatment of (2S,3R)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester* **4a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **4a**, carried out as described above for the reaction of the stereoisomer **3a**, afforded an oil which was chromatographed. Elution afforded a 2:3 mixture of the dehydrophenylalanine derivatives **14a** and **15a** as a viscous oil (25%). The ^1H NMR spectrum of the mixture

showed resonances for the (*Z*)-isomer **15a**, identical to those described above, and signals for the (*E*)-isomer **14a**, δ_H 8.26 (d, *J* 8.7 Hz, 2 H, ArH), 7.80-7.98 (m, 4 H, phth), 7.60 (d, *J* 8.7 Hz, 2 H, ArH), 7.28 (s, 1 H, β-H) and 3.72 (s, 3 H, OMe). Continued elution gave the β-hydroxy-*p*-nitrophenylalanine derivative **3b** as colourless needles (63%), after recrystallisation from a mixture of dichloromethane and light petroleum, m.p. 183-185 °C; ν_{max}/cm^{-1} 3604, 3421, 1779, 1752, 1714, 1614, 1526, 1392, 1352 and 1182; δ_H 8.13 (d, *J* 8.9 Hz, 2 H, ArH), 7.82-7.73 (m, 4 H, phth), 7.54 (d, *J* 8.9 Hz, 2 H, ArH), 5.79 (dd, *J* 4.4 and 10.0 Hz, 1 H, β-H), 5.53 (d, *J* 4.4 Hz, 1 H, α-H), 5.34 (d, *J* 10.0 Hz, 1 H, OH) and 3.89 (s, 3 H, OMe); *m/z* (fab) (%) 371 ($M+H^+$, 9), 353 (3), 321 (3), 307 (11), 289 (9), 219 (3), 154 (100), 137 (66), 136 (79), 107 (28), 89 (33) and 77 (31).

(2RS,3SR)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. To a solution of a 1:1 mixture of (2*RS*,3*RS*)-3-bromo-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide and the (2*RS*,3*SR*)-isomer (265 mg, 0.56 mmol) in acetone (10 cm^3) and water (10 cm^3), silver sulfate (263 mg, 0.84 mmol) was added and the suspension was heated at 65 °C in the dark for 3 days. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue dissolved in dichloromethane and the solution was washed with saturated brine, then it was dried and concentrated under reduced pressure. The residue was chromatographed, to give the title compound as an off-white crystalline solid (154 mg, 67%), m.p. 209-210 °C; ν_{max}/cm^{-1} 3700, 3400, 3160, 3000, 2920, 2270, 1830, 1800, 1720, 1650, 1610, 1570, 1480, 1390 and 1110; δ_H 8.14 (d, *J* 8.8 Hz, 2 H, ArH), 7.81-7.71 (m, 4 H, phth), 7.54 (d, *J* 8.8 Hz, 2 H, ArH), 6.01 (br s, 1 H, NH), 5.68 (dd, *J* 4.9 and 8.3 Hz, 1 H, β-H), 5.17 (d, *J* 4.9 Hz, 1 H, α-H), 4.93 (d, *J* 8.3 Hz, 1 H, OH) and 1.37 (s, 9 H, CMe_3); δ_C 168.6, 164.9, 147.4, 134.7, 131.1, 126.6, 123.9, 123.6, 71.7, 59.9, 52.3 and 28.6; *m/z* (ei) (%) 412 ($M+H^+$, 1), 384 (2), 378 (2), 356 (1), 294 (82), 260 (100) and 204 (30) (Found: C, 61.0; H, 5.3; N, 10.0. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.3; H, 5.2; N, 10.2%).

(2R,3S)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide* **3d**. This compound was prepared from a 1:1 mixture of the bromides **3c** and **4c**, as described above for the synthesis of the corresponding racemate, and obtained in 64% yield, m.p. 226-228 °C; $[\alpha]_D^{25}$ +84.1° (c, 0.453 in $CHCl_3$). There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude reaction mixture.

(2S,3R)-3-Hydroxy-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide*. This compound was prepared from a 1:1 mixture of (2*R*,3*R*)- and (2*R*,3*S*)-3-bromo-*N-tert*-butyl-*N*$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 62% yield, m.p. 220-222 °C; $[\alpha]_D^{20}$ -83.1 (c, 0.083 in $CHCl_3$).

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-*phthaloyl*-p-*nitrophenylalanine Methyl Ester with Silver Sulfate in Aqueous Acetone*. A 1:1 mixture of the title bromides was treated with silver sulfate in aqueous acetone, as described for the reaction of the bromoamides **3c** and **4c**. Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed that the racemate of the alcohol **3a** and the alkenes **14a** and **15a** were present in the ratio *ca.* 1:1:10.

Treatment of (2RS,3RS)- and (2RS,3SR)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloyl*-p-*nitrophenylalaninamide with Silver Nitrate in Aqueous Acetone*. The reaction of a 1:1 mixture of the title bromides, carried out as

described above for the reaction of the bromoester **3a**, afforded an oil which was chromatographed. Elution afforded the nitrate **16** (19%), m.p. 192 °C (dec.); ν_{max}/cm^{-1} 3720, 3460, 3390, 3190, 3020, 2950, 2290, 1830, 1800, 1740, 1670, 1630, 1550, 1490, 1400, 1370, 1320, 1300, 1240, 1190 and 1110; δ_H 8.30 (d, *J* 8.9 Hz, 2 H, ArH), 7.81-7.92 (m, 4 H, phth), 7.77 (d, *J* 8.9 Hz, 2 H, ArH), 7.19 (d, *J* 10.7 Hz, 1 H, β-H), 5.89 (br s, 1 H, NH), 4.90 (d, *J* 10.7 Hz, 1 H, α-H) and 1.14 (s, 9 H, CMe_3); δ_C 167.6, 163.1, 148.6, 141.8, 134.9, 131.2, 129.1, 124.1, 124.1, 78.1, 57.8, 52.2 and 28.3; *m/z* (ei) (%) 457 ($M+H^+$, 30), 393 (15), 307 (40), 286 (100) and 260 (30). Continued elution gave (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (54%), identical to the sample obtained as described above. There was no indication of the presence of either of the alkenes **14b** or **15b** in the ^1H NMR spectrum of the crude product.

(2RS,3SR)-3-Hydroxy-p-*nitrophenylalanine*. A mixture of (2*RS*,3*SR*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide (85 mg, 0.21 mmol) in a 2:1 mixture of 6N hydrochloric acid and acetic acid (10 cm^3) was heated at reflux for 5 h and stirred overnight at room temperature, before it was concentrated under reduced pressure. Water (10 cm^3) was added to the residue, then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (10 cm^3) and to that solution aniline (0.7 cm^3) in dichloromethane (10 cm^3) was added. The mixture was let stand at 4 °C for 24 h and the material which crystallised was separated by filtration and washed with dichloromethane, to give the title compound as an off-white powder (27 mg, 58%), m.p. 192-193 °C (lit.[14] 187-188 °C (dec.)); ν_{max}/cm^{-1} 3550, 3200, 2920, 2870, 1610, 1590, 1530, 1460, 1380, 1350, 1200, 1110, 1010, 865, 855, 740 and 710; δ_H (CF_3CO_2D) 8.33 (d, *J* 8.8 Hz, 2 H, ArH), 7.74 (d, *J* 8.8 Hz, 2 H, ArH), 5.77 (d, *J* 3.9 Hz, 1 H, β-H) and 4.70 (d, *J* 3.9 Hz, 1 H, α-H); δ_C (D_2O) 173.5, 149.6, 149.0, 129.1, 126.0, 72.7 and 62.5; *m/z* (fab) (%) 227 ($M+H^+$). The ^1H NMR spectral data for this compound is consistent with that reported.[14]

(2R,3S)-3-Hydroxy-p-*nitrophenylalanine* **18**. This compound was prepared from the alcohol **3d**, as described above for the synthesis of the corresponding racemate, and obtained in 69% yield, m.p. 200-203 °C (lit.[15] 174-176 °C); $[\alpha]_D^{25}$ +35.3° (c, 0.102 in 1N HCl) (lit.[15] $[\alpha]_D^{25}$ +27° (c, 0.5 in H_2O)).

(2S,3R)-3-Hydroxy-p-*nitrophenylalanine*. This compound was prepared from the (2*S*,3*R*)-3-hydroxy-*N*-*tert*-butyl-N^{α}-phthaloyl-*p*-nitrophenylalaninamide, as described above for the synthesis of the corresponding racemate, and obtained in 54% yield, m.p. 204-205 °C; $[\alpha]_D^{20}$ -36.4° (c, 0.176 in 1N HCl) (lit.[16] $[\alpha]_D^{21.5}$ -33.8° (c, 5 in 1N HCl)).

(S)-N-tert-*Butyl*-N$^{\alpha}$-*phthaloylvalinamide* **11b**. To a suspension of *(S)*-*N*-phthaloylvaline[12] (15.57 g, 63 mmol) in dichloromethane (60 cm^3), triethylamine (6.37 g, 63 mmol) was added. The resulting solution was cooled to 0 °C, then ethyl chloroformate (6.87 g, 63 mmol) was added and the mixture was stirred for 15 min. *tert*-Butylamine (4.60 g, 63 mmol) was added and the mixture was allowed to warm to room temperature, then it was stirred for a further 40 min. The mixture was filtered and the filtrate was washed with water, then it was dried and concentrated under reduced pressure. A portion (*ca.* 4.6 g, 25%) of the residue was chromatographed, to give the title compound **11b** as a colourless crystalline solid (2.60 g), m.p. 144-147 °C; $[\alpha]_D^{21}$ +32.3° (c, 8.7 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3365, 2920, 2850, 1760, 1710, 1680, 1550, 1530, 1470, 1400, 1070 and 715; δ_H 7.81-7.91 (m, 4 H, phth), 7.13 (br s, 1 H, NH), 4.35 (d, *J* 11.3 Hz, 1 H, α-H), 2.88 (m, 1 H, β-H), 1.39 (s, 9 H, CMe_3), 1.15 (d, *J* 6.7 Hz, 3 H, CH_3) and 0.87 (d, *J* 6.5 Hz, 3 H, CH_3'); δ_C 21.6, 21.7, 29.8, 30.6, 53.3, 66.7, 125.6, 133.4, 136.3, 169.9 and 170.5; *m/z* (ei) (%) 303 ($M+H^+$, 1), 275

(1), 260 (5) and 202 (100) (Found: C, 67.3; H, 7.6; N, 9.2%. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.5; H, 7.3; N, 9.3%).

(R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloylvalinamide* **5c**. A mixture of *N*-bromosuccinimide (1.18 g, 6.6 mmol) and the amide **11b** (1.33 g, 4.4 mmol) in carbon tetrachloride (60 cm^3) was heated at reflux for 2 h, while it was irradiated with a 250 W mercury lamp. The mixture was then cooled to 0 °C and filtered. The filtrate was washed with water, then it was dried and concentrated under reduced pressure, to give the title compound **5c** as fine colourless needles, after recrystallisation from a mixture of light petroleum and ether (1.54 g, 92%), m.p. 139-141 °C; $[\alpha]_D^{20}$ +11.6° (c, 3.03 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 2920, 2850, 1710, 1530, 1460, 1380, 1080 and 720; δ_H 7.67 (m, 4 H, phth), 5.28 (s, 1 H, α-H), 2.07 (s, 3 H, CH_3), 1.86 (s, 3 H, CH_3') and 1.30 (s, 9 H, CMe_3); δ_C 30.5, 35.0, 35.4, 54.0, 67.7, 68.1, 125.8, 133.3, 136.6, 166.0 and 170.2; *m/z* (ei) (%) 381/383 ($M+H^+$, 5), 380/382 (5), 279/381 (5), 365/367 (10), 325/327 (15), 308/310 (15) and 301 (100) (Found: C, 53.7; H, 5.5; N, 7.1. Calc. for $C_{17}H_{21}BrN_2O_3$: C, 53.6; H, 5.6; N, 7.3%).

Treatment of (R)-3-Bromo-N-*phthaloylvaline Methyl Ester* **5a** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5a**,[12] carried out at room temperature for 14 h, but otherwise as described above for the reaction of the nitrophenylalanine derivative **3a**, afforded an oil which was chromatographed. Elution gave the α,β-dehydrovaline derivative **12a** (40 mg, 8%), m.p. 81-82 °C; δ_H 7.40-8.10 (m, 4 H, phth), 3.68 (s, 3 H, OMe), 2.43 (s, 3 H, CH_3) and 1.88 (s, 3 H, CH_3') (Found: C, 64.7; H, 5.1; N, 5.4. Calc. for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.1; N, 5.4%). Continued elution afforded the β,γ-dehydrovaline derivative **13a** (0.15 g, 34%); ν_{max}/cm^{-1} 2950, 1780, 1748, 1728, 1470, 1440, 1386, 1293, 1245, 1203, 1113, 915 and 717; δ_H 7.75-7.92 (m, 4 H, phth), 5.38 (br s, 1 H, γ-H), 5.14 (br s, 1 H, γ-H'), 5.11 (s, 1 H, α-H), 3.79 (s, 3 H, OMe) and 1.92 (s, 3 H, β-CH_3); *m/z* (ei) (%) 259 (M^+, 8), 227 (20) and 200 (100). Further elution gave the β-hydroxyvaline derivative **5b** (0.21 g, 43%), m.p. 86-87 °C; ν_{max}/cm^{-1} 3544, 1767, 1725, 1275 and 717; δ_H 7.91-7.80 (m, 4 H, phth), 4.41 (br s, 1 H, OH), 3.77 (s, 3 H, OMe), 1.53 (s, 3 H, CH_3) and 1.31 (s, 3 H, CH_3'); *m/z* (ei) (%) 262 ($M-CH_3^+$, 10), 246 (5), 230 (28), 219 (100), 188 (74), 187 (98) and 160 (74) (Found: C, 60.6; H, 5.5; N, 5.1. Calc. for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.5; N, 5.1%). Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5b** and the alkenes **12a** and **13a** to be present in the ratio *ca.* 3.5 : 1 : 3.5.

Treatment of (R)-3-Bromo-N-tert-*butyl*-N$^{\alpha}$-*phthaloylvalinamide* **5c** *with Silver Nitrate in Aqueous Acetone*. The reaction of the bromide **5c**, carried out as described above for the reaction of the ester **5a**, afforded an oil which was chromatographed. Elution gave the β,γ-dehydrovaline derivative **13b** as a colourless oil (26%); ν_{max}/cm^{-1} 3450, 2975, 2950, 1780, 1710, 1695, 1525, 1460, 1475 and 1385; δ_H 7.89-7.73 (m, 4 H, phth), 6.28 (br s, 1 H, NH), 5.27 (s, 1 H), 5.23 (s, 1H), 5.21 (s, 1H), 1.89 (s, 3 H, CH_3) and 1.43 (s, 9 H, CMe_3); δ_C 169.8, 167.3, 141.6, 136.1, 133.8, 125.4, 119.5, 62.5, 53.7, 30.5 and 22.8; *m/z* (ei) (%) 300 (M^+, 5) and 200 (100) (Found: C, 68.0; H, 7.0; N, 9.0. Calc. for $C_{17}H_{20}N_2O_3$: C, 68.0; H, 6.7; N, 9.3%). Further elution afforded the alcohol **5d**, as colourless crystals after recrystallisation from a mixture of ether and light petroleum (63%), m.p. 135-136 °C; ν_{max}/cm^{-1} 3328, 3084, 2972, 2928, 2248, 1774, 1720, 1660, 1614, 1550, 1470, 1384, 1224, 1176, 1144, 1088, 1048, 992, 956, 912, 878, 788, 774, 724 and 646; δ_H 7.84-7.79 (m, 2 H, phth), 7.73-7.69 (m, 2 H, phth), 7.30 (br s, 1 H, NH), 4.61 (s, 1 H, α-H), 4.25 (br s, 1 H, OH),

1.41 (s, 3 H, CH_3), 1.30 (s, 9 H, CMe_3) and 1.22 (s, 3 H, CH_3); *m/z* (ei) (%) 318 (M^+, 50), 300 (10), 259 (50), 201 (100), 187 (100) and 160 (95) (Found: C, 64.3; H, 7.2; N, 8.7. Calc. for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8%). The structure of the alcohol **5d** was confirmed through X-ray crystallographic analysis.[11] Analysis of the crude reaction mixture by ^1H NMR spectroscopy showed the alcohol **5d** and the alkene **13b** were present in the ratio *ca.* 2 : 1.

Competitive Hydrolysis Reactions of the Bromides **5a** *and* **5c**. The relative rates of reaction of the bromides **5a** and **5c** with silver nitrate were determined by treating an equimolar ratio of the substrates at a concentration of approximately 0.1 mM in aqueous acetone (1:1, v/v) with the silver salt (1.4 equiv.) at room temperature, in the presence of *N-tert*-butylbenzamide (0.5 equiv.) as an internal standard. Aliquots of the reaction mixture were sampled at intervals and worked up as described for the preparative studies, then analysed by ^1H NMR spectroscopy. Integration of peaks characteristic of the residual bromides **5a** and **5c** and the internal standard, and comparison with the spectra of the corresponding starting mixtures, were used to determine the percentage of each substrate remaining, from which the ratios of the logarithms of those percentages were used to calculate the relative rates of reaction. Relative rates of duplicate experiments varied by less than 10%.

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Crystal structure of methyl (*Z*)-2-benzamido-3-nitrobut-2-enoate, $C_{12}H_{12}N_2O_5$

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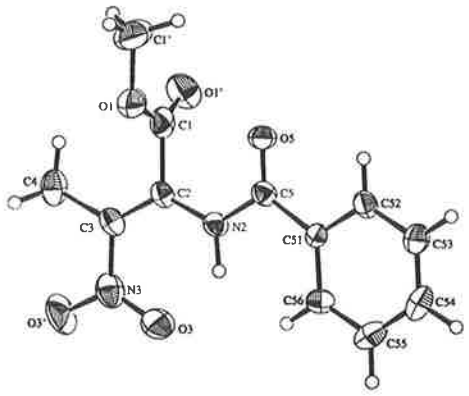

Source of material: see ref. 1.

The conformation about the C(2)=C(3) bond is Z. The molecule is essentially planar except for the CO_2Me group as seen in the torsion angles N(2)/C(2)/C(3)/N(3), C(2)/N(2)/C(5)/C(51) and N(2)/C(5)/C(51)/C(52) of −0.5(8)°, 178.6(5)° and −178.4(5)°, respectively; N(2)/C(2)/C(1)/O(1) is −94.2(6)°.

$C_{12}H_{12}N_2O_5$, monoclinic, $P12_1/c1$ (No. 14), a =7.198(1) Å, b =12.280(2) Å, c =14.073(3) Å, β =98.28(2)°, V =1231.0 Å^3, Z =4. $R(F)$ =0.036, $R_w(F)$ =0.034.

Reference

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Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.07 x 0.13 x 0.45 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	11.27 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
N(hkl)$_{unique}$:	2499
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	173
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1'a)	4*e*	0.01178	0.36585	0.53627	0.13704
H(1'b)	4*e*	−0.03294	0.38930	0.42463	0.13704
H(1'c)	4*e*	−0.19473	0.34962	0.48175	0.13704
H(2)	4*e*	0.28326	−0.03920	0.51025	0.06110
H(4a)	4*e*	0.07056	0.19502	0.27802	0.07790
H(4b)	4*e*	0.18643	0.11916	0.21692	0.07790
H(4c)	4*e*	−0.02353	0.08920	0.22780	0.07790
H(52)	4*e*	0.31070	0.12016	0.78756	0.06316
H(53)	4*e*	0.40904	0.01090	0.92003	0.07882
H(54)	4*e*	0.48549	−0.16909	0.89949	0.07416
H(55)	4*e*	0.45656	−0.24530	0.74585	0.07869
H(56)	4*e*	0.36974	−0.13519	0.61206	0.06111

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	4*e*	−0.0191(6)	0.2316(3)	0.4567(2)	0.092(4)	0.070(3)	0.061(3)	0.017(2)	−0.001(3)	−0.004(3)
O(1')	4*e*	0.2751(7)	0.2779(4)	0.4442(3)	0.125(4)	0.076(3)	0.068(3)	−0.042(2)	0.012(3)	0.011(3)
O(3)	4*e*	0.2697(6)	−0.1154(3)	0.3931(3)	0.117(4)	0.076(3)	0.062(3)	0.018(2)	0.012(3)	−0.015(3)
O(3')	4*e*	0.1614(6)	−0.0890(4)	0.2465(3)	0.130(4)	0.137(4)	0.051(2)	0.015(3)	−0.004(3)	−0.044(4)
O(5)	4*e*	0.2255(6)	0.1710(3)	0.6208(2)	0.126(4)	0.043(3)	0.040(2)	0.012(2)	−0.002(2)	−0.001(3)
N(2)	4*e*	0.2489(6)	0.0365(3)	0.5172(3)	0.066(3)	0.043(3)	0.034(3)	0.000(2)	0.008(2)	−0.003(3)
N(3)	4*e*	0.1975(7)	−0.0559(5)	0.3277(3)	0.064(4)	0.095(5)	0.049(3)	0.002(4)	0.012(3)	−0.013(4)
C(1)	4*e*	0.156(1)	0.2133(6)	0.4482(4)	0.082(6)	0.068(6)	0.032(3)	−0.009(3)	−0.001(4)	0.012(5)
C(1')	4*e*	−0.062(1)	0.3432(6)	0.4764(4)	0.208(9)	0.083(6)	0.079(5)	0.065(4)	0.002(5)	−0.003(6)
C(2)	4*e*	0.1874(7)	0.0933(4)	0.4360(3)	0.044(4)	0.050(4)	0.035(3)	−0.014(3)	0.007(3)	−0.001(3)
C(3)	4*e*	0.1601(7)	0.0561(5)	0.3470(4)	0.047(4)	0.058(4)	0.043(4)	−0.009(3)	0.009(3)	−0.007(4)
C(4)	4*e*	0.0926(8)	0.1204(5)	0.2600(3)	0.063(4)	0.096(5)	0.042(3)	−0.012(3)	0.009(3)	0.011(4)
C(5)	4*e*	0.2657(7)	0.0787(5)	0.6084(4)	0.052(4)	0.044(4)	0.044(3)	−0.008(3)	0.008(3)	−0.002(4)
C(51)	4*e*	0.3309(7)	0.0025(4)	0.6870(3)	0.033(3)	0.040(4)	0.041(3)	−0.004(3)	0.003(3)	0.007(3)
C(52)	4*e*	0.3430(7)	0.0446(4)	0.7785(4)	0.060(4)	0.052(4)	0.040(3)	−0.013(3)	0.000(3)	0.002(3)
C(53)	4*e*	0.3998(9)	−0.0193(5)	0.8558(4)	0.085(5)	0.066(5)	0.041(3)	0.006(3)	−0.002(3)	0.008(4)
C(54)	4*e*	0.4434(9)	−0.1243(6)	0.8438(4)	0.056(5)	0.085(5)	0.061(4)	0.011(4)	0.000(3)	0.026(4)
C(55)	4*e*	0.4291(8)	−0.1688(5)	0.7539(5)	0.065(5)	0.054(4)	0.087(5)	0.012(4)	0.011(4)	0.020(4)
C(56)	4*e*	0.3759(7)	−0.1047(4)	0.6760(3)	0.054(4)	0.045(4)	0.055(4)	0.004(3)	0.014(3)	−0.003(3)

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Crystal structure of (2*RS*, 3*RS*)-3-bromo-N-*tert*-butyl-N$^{\alpha}$-phthaloyl-*p*-nitrophenylalaninamide, $C_{21}H_{20}BrN_3O_5$

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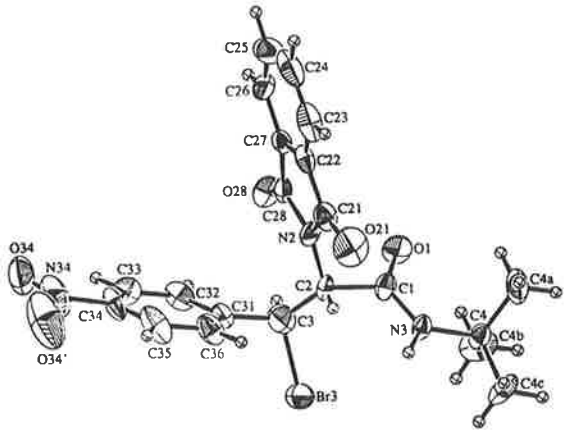

Source of material: see ref. 1.

The dihedral angle between the C(31)–C(36) and phthaloyl groups is 110.6°. Hydrogen bonding the lattice occurs between the N(3)–H and O(28) atoms such that H(3)···O(28) is 2.21 Å and N(3)···O(28) is 3.16(1) Å.

$C_{21}H_{20}BrN_3O_5$, monoclinic, $P12_1/n1$ (No. 14), a =10.900(5) Å, b =11.189(6) Å, c =18.285(4) Å, β =103.10(2)°, V =2172.0 Å^3, Z =4, $R(F)$ =0.047, $R_w(F)$ =0.037.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.07 x 0.16 x 0.36 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	19.35 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
$N(hkl)_{unique}$:	4058
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
$N(param)_{refined}$:	271
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(2)	4*e*	−0.27611	−0.14957	−0.75497	0.10104
H(3')	4*e*	−0.46030	−0.18462	−0.75327	0.09207
H(3)	4*e*	−0.26753	0.05770	−0.81770	0.09406
H(4c)	4*e*	−0.50644	−0.03443	−0.59803	0.09801
H(4d)	4*e*	−0.60326	0.08314	−0.71652	0.10167
H(4e)	4*e*	−0.73425	0.02275	−0.71540	0.10167
H(4f)	4*e*	−0.67814	0.01249	−0.78784	0.10167
H(4g)	4*e*	−0.68504	−0.21079	−0.78710	0.09288
H(4h)	4*e*	−0.74916	−0.20537	−0.71762	0.09288
H(4i)	4*e*	−0.62516	−0.28172	−0.71259	0.12685
H(4a)	4*e*	−0.52359	−0.17503	−0.59839	0.09801
H(4b)	4*e*	−0.64110	−0.09037	−0.60142	0.09801
H(23)	4*e*	0.09440	−0.24695	−0.53057	0.09207
H(24)	4*e*	0.25165	−0.12344	−0.45802	0.09095
H(25)	4*e*	0.27409	0.07115	−0.48074	0.10727
H(26)	4*e*	0.13103	0.16555	−0.57853	0.0784
H(32)	4*e*	−0.12542	0.12761	−0.87005	0.07925
H(33)	4*e*	0.05122	0.10325	−0.91680	0.0889
H(35)	4*e*	0.03505	−0.25429	−0.89274	0.09105
H(36)	4*e*	−0.14418	−0.23138	−0.84222	0.09429

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(3)	4*e*	−0.4198(1)	−0.0577(1)	−0.89881(6)	0.0740(8)	0.0761(8)	0.0662(7)	−0.007(1)	0.0102(5)	−0.004(1)
O(1)	4*e*	−0.3736(7)	0.0567(7)	−0.6764(4)	0.093(6)	0.046(5)	0.104(6)	−0.014(5)	0.033(5)	−0.029(5)
O(21)	4*e*	−0.1494(9)	−0.2462(8)	−0.6522(5)	0.19(1)	0.049(5)	0.152(8)	−0.045(6)	0.072(7)	0.004(6)
O(28)	4*e*	−0.0976(7)	0.1436(6)	−0.7058(4)	0.078(6)	0.041(6)	0.101(7)	−0.003(5)	0.027(5)	0.013(5)
O(34')	4*e*	0.196(2)	−0.192(1)	−0.9519(8)	0.18(1)	0.28(2)	0.17(1)	0.15(1)	0.099(9)	0.08(1)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(34)	4*e*	0.226(1)	−0.000(2)	−0.9453(8)	0.11(1)	0.37(3)	0.086(9)	−0.05(1)	0.042(7)	0.03(1)
N(2)	4*e*	−0.1507(7)	−0.054(1)	−0.6949(4)	0.052(6)	0.057(6)	0.059(6)	−0.021(7)	0.017(5)	0.013(7)
N(3)	4*e*	−0.4719(8)	−0.1123(7)	−0.7264(4)	0.047(6)	0.038(6)	0.070(6)	−0.006(5)	0.032(5)	−0.012(5)
N(34)	4*e*	0.177(2)	−0.091(2)	−0.933(1)	0.13(2)	0.19(3)	0.08(1)	0.05(1)	0.05(1)	0.06(2)
C(1)	4*e*	−0.378(1)	−0.032(1)	−0.7144(6)	0.057(9)	0.05(1)	0.072(9)	−0.009(7)	0.027(7)	0.011(8)
C(2)	4*e*	−0.267(1)	−0.064(1)	−0.7494(7)	0.051(8)	0.14(1)	0.062(8)	−0.04(1)	0.029(7)	−0.002(9)
C(3)	4*e*	−0.267(1)	−0.029(1)	−0.8219(7)	0.068(9)	0.15(1)	0.070(9)	0.00(1)	0.016(8)	−0.004(9)
C(4)	4*e*	−0.589(1)	−0.1001(9)	−0.7025(6)	0.043(8)	0.057(9)	0.073(9)	−0.000(7)	0.022(7)	−0.006(6)
C(4a)	4*e*	−0.563(1)	−0.100(1)	−0.6174(7)	0.083(9)	0.13(1)	0.10(1)	0.003(9)	0.059(8)	−0.001(8)
C(4b)	4*e*	−0.6575(9)	0.015(1)	−0.7334(6)	0.075(9)	0.07(1)	0.14(1)	0.036(8)	0.006(8)	−0.023(8)
C(4c)	4*e*	−0.6695(9)	−0.210(1)	−0.7327(6)	0.048(7)	0.08(1)	0.14(1)	−0.024(8)	0.022(7)	−0.016(7)
C(21)	4*e*	−0.100(1)	−0.149(1)	−0.6478(7)	0.09(1)	0.05(1)	0.066(9)	−0.012(9)	0.037(8)	0.007(9)
C(22)	4*e*	0.013(1)	−0.102(1)	−0.5989(7)	0.06(1)	0.07(1)	0.055(9)	0.015(8)	0.035(7)	0.004(8)
C(23)	4*e*	0.099(2)	−0.162(1)	−0.541(1)	0.13(1)	0.08(1)	0.10(1)	0.02(1)	0.07(1)	0.02(1)
C(24)	4*e*	0.192(2)	−0.088(2)	−0.500(1)	0.10(2)	0.17(2)	0.07(1)	0.05(1)	0.04(1)	0.02(2)
C(25)	4*e*	0.206(2)	0.026(2)	−0.512(1)	0.06(1)	0.21(2)	0.08(1)	−0.00(2)	0.014(9)	−0.05(2)
C(26)	4*e*	0.123(1)	0.081(1)	−0.5688(7)	0.053(8)	0.10(1)	0.087(9)	−0.021(9)	0.033(7)	−0.029(9)
C(27)	4*e*	0.027(1)	0.015(1)	−0.6126(6)	0.067(9)	0.04(1)	0.048(8)	−0.010(7)	0.029(7)	−0.009(7)
C(28)	4*e*	−0.077(1)	0.048(1)	−0.6762(6)	0.053(7)	0.053(9)	0.057(8)	−0.006(9)	0.032(6)	0.00(1)
C(31)	4*e*	−0.154(1)	−0.049(2)	−0.8535(6)	0.065(9)	0.09(1)	0.045(7)	−0.00(1)	0.025(6)	−0.01(1)
C(32)	4*e*	−0.093(2)	0.048(1)	−0.8745(7)	0.09(1)	0.06(1)	0.072(9)	0.03(1)	0.020(8)	−0.01(1)
C(33)	4*e*	0.010(2)	0.034(1)	−0.9012(7)	0.08(1)	0.06(1)	0.09(1)	0.001(9)	0.020(8)	0.00(1)
C(34)	4*e*	0.058(1)	−0.075(2)	−0.9066(7)	0.06(1)	0.14(2)	0.048(7)	0.06(1)	0.027(7)	0.02(1)
C(35)	4*e*	0.002(2)	−0.175(1)	−0.8869(8)	0.15(2)	0.07(1)	0.08(1)	0.052(9)	0.05(1)	0.02(1)
C(36)	4*e*	−0.104(2)	−0.162(2)	−0.8586(7)	0.12(1)	0.06(1)	0.07(1)	0.001(8)	0.041(9)	−0.00(1)

Reference

1. Easton, C. J.; Hutton, C. A.; Merrett, M. C.; Tiekink, E. R. T.: Neighbouring group effects in side chain reactions of amino acid derivatives: a stereocontrolled route to chloramphenicol. Tetrahedron (1996) in press.

Zeitschrift für Kristallographie 211, 289–290 289 NCS

Crystal structure of (*S*)-3-hydroxy-N-*tert*-butyl-N$^{\alpha}$-phthaloylvalinamide, $C_{17}H_{22}N_2O_4$

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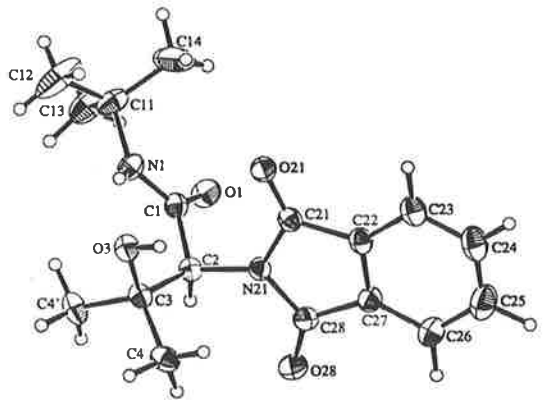

Source of material: see ref. 1; m. pt 408 K - 409 K.
The structure features both intra- and inter-molecular H bonding contacts. The N(1)H···O(3) separation is 2.04(1) Å and in the lattice O(3)H···O(1) is 1.88(3) Å such that O(1)···O(3) is 2.739(3) Å.

$C_{17}H_{22}N_2O_4$, monoclinic, $P12_1/c1$ (No. 14), a =11.242(4) Å, b =10.299(2) Å, c =14.908(3) Å, β =94.76(2)°, V =1720.1 Å^3, Z =4, $R(F)$ =0.038, $R_w(F)$ =0.036.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.24 x 0.40 x 0.56 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.88 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	50°
N(hkl)$_{unique}$:	4092
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	296
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1)	4*e*	0.685(2)	0.146(2)	0.318(2)	0.057(9)
H(2)	4*e*	0.465(2)	0.330(2)	0.329(1)	0.040(6)
H(3)	4*e*	0.510(3)	−0.012(3)	0.331(2)	0.13(1)
H(4'a)	4*e*	0.564(2)	0.156(3)	0.520(2)	0.084(9)
H(4'b)	4*e*	0.650(2)	0.228(3)	0.455(2)	0.080(9)
H(4'c)	4*e*	0.528(2)	0.302(3)	0.482(2)	0.076(9)
H(4a)	4*e*	0.324(2)	0.201(2)	0.419(2)	0.062(8)
H(4b)	4*e*	0.326(2)	0.077(2)	0.363(2)	0.061(8)
H(4c)	4*e*	0.374(2)	0.066(3)	0.464(2)	0.078(9)
H(12a)	4*e*	0.866(3)	0.058(4)	0.283(3)	0.15(2)
H(12b)	4*e*	0.968(3)	0.141(3)	0.293(2)	0.11(1)
H(12c)	4*e*	0.897(3)	0.135(4)	0.374(3)	0.15(2)
H(13a)	4*e*	0.863(3)	0.370(3)	0.359(2)	0.11(1)
H(13b)	4*e*	0.950(2)	0.367(3)	0.281(2)	0.078(9)
H(13c)	4*e*	0.821(3)	0.425(3)	0.265(2)	0.10(1)
H(14a)	4*e*	0.774(6)	0.279(8)	0.127(5)	0.36(1)
H(14b)	4*e*	0.888(3)	0.218(4)	0.137(2)	0.15(1)
H(14c)	4*e*	0.782(4)	0.145(5)	0.149(3)	0.19(2)
H(23)	4*e*	0.350(2)	0.007(2)	−0.004(2)	0.068(9)
H(24)	4*e*	0.161(2)	0.042(3)	−0.073(2)	0.08(1)
H(25)	4*e*	0.019(3)	0.185(3)	−0.021(2)	0.12(1)
H(26)	4*e*	0.076(2)	0.300(3)	0.119(2)	0.10(1)

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	4*e*	0.6120(2)	0.3846(2)	0.2259(1)	0.061(1)	0.065(1)	0.078(1)	0.004(1)	0.011(1)	0.030(1)
O(3)	4*e*	0.5541(2)	0.0381(2)	0.3677(1)	0.065(1)	0.039(1)	0.054(1)	0.0074(9)	−0.001(1)	0.0009(9)
O(21)	4*e*	0.5217(2)	0.0771(2)	0.1528(1)	0.060(1)	0.056(1)	0.054(1)	0.0143(9)	0.0027(9)	−0.004(1)
O(28)	4*e*	0.2572(2)	0.3488(2)	0.2676(1)	0.062(1)	0.079(1)	0.070(1)	0.021(1)	0.006(1)	−0.010(1)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	4*e*	0.7026(2)	0.2153(2)	0.2939(2)	0.047(1)	0.046(2)	0.070(2)	0.002(1)	−0.001(1)	0.002(1)
N(21)	4*e*	0.4083(2)	0.2150(2)	0.2317(1)	0.046(1)	0.045(1)	0.041(1)	0.007(1)	−0.000(1)	−0.003(1)
C(1)	4*e*	0.6089(2)	0.2870(3)	0.2716(2)	0.052(2)	0.044(2)	0.045(2)	0.000(1)	−0.001(1)	0.002(1)
C(2)	4*e*	0.4921(2)	0.2491(2)	0.3074(2)	0.051(2)	0.036(2)	0.045(1)	0.003(1)	0.001(1)	−0.002(1)
C(3)	4*e*	0.4930(2)	0.1546(2)	0.3868(2)	0.060(2)	0.039(1)	0.041(1)	0.004(1)	0.002(1)	−0.001(1)
C(4)	4*e*	0.3685(3)	0.1238(3)	0.4093(2)	0.075(2)	0.049(2)	0.054(2)	0.002(2)	0.016(2)	0.002(2)
C(4')	4*e*	0.5614(3)	0.2150(4)	0.4679(2)	0.095(3)	0.056(2)	0.045(2)	−0.002(2)	−0.005(2)	−0.004(2)
C(11)	4*e*	0.8206(2)	0.2339(3)	0.2627(2)	0.040(2)	0.063(2)	0.101(3)	−0.003(2)	0.004(2)	−0.018(1)
C(12)	4*e*	0.8968(4)	0.1292(5)	0.3068(5)	0.049(2)	0.073(3)	0.262(8)	0.011(4)	−0.011(3)	−0.013(2)
C(13)	4*e*	0.8695(3)	0.3636(4)	0.2924(3)	0.057(2)	0.066(3)	0.126(4)	−0.008(2)	−0.003(2)	−0.005(2)
C(14)	4*e*	0.8110(4)	0.2238(7)	0.1604(3)	0.075(3)	0.226(7)	0.113(4)	−0.031(4)	0.041(3)	−0.080(4)
C(21)	4*e*	0.4298(2)	0.1320(2)	0.1618(2)	0.053(2)	0.042(2)	0.042(2)	0.000(1)	0.004(1)	0.005(1)
C(22)	4*e*	0.3193(2)	0.1315(2)	0.1011(2)	0.055(2)	0.047(2)	0.044(2)	−0.008(1)	−0.001(1)	0.006(1)
C(23)	4*e*	0.2913(3)	0.0659(3)	0.0224(2)	0.074(2)	0.056(2)	0.053(2)	−0.009(2)	−0.004(2)	0.000(2)
C(24)	4*e*	0.1798(3)	0.0882(4)	−0.0199(2)	0.090(3)	0.080(3)	0.061(2)	−0.020(2)	−0.016(2)	−0.005(2)
C(25)	4*e*	0.1020(3)	0.1721(4)	0.0139(3)	0.065(2)	0.103(3)	0.088(3)	−0.011(2)	−0.020(2)	0.002(2)
C(26)	4*e*	0.1311(3)	0.2386(4)	0.0926(2)	0.052(2)	0.094(3)	0.073(2)	−0.002(2)	−0.006(2)	−0.003(2)
C(27)	4*e*	0.2416(2)	0.2162(3)	0.1349(2)	0.043(2)	0.063(2)	0.051(2)	−0.003(1)	−0.000(1)	0.004(1)
C(28)	4*e*	0.2968(2)	0.2712(3)	0.2185(2)	0.049(2)	0.056(2)	0.050(2)	0.005(1)	0.007(1)	0.001(1)

Reference

1. Easton, C. J.; Hutton, C. A.; Merrett M. C.; Tiekink, E. R. T.: Neighbouring group effects in side chain reactions of amino acid derivatives: a stereocontrolled route to chloramphenicol. Tetrahedron (1996) in press.

Zeitschrift für Kristallographie 211, 291–292 291 NCS

Crystal structure of (2*S*,3*S*)-3-bromo-N-phthaloyl-*p*-nitrophenylalanine methyl ester, $C_{18}H_{13}BrN_2O_6$

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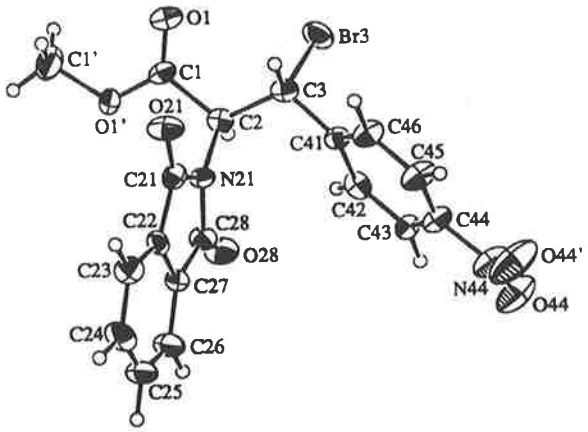


Source of material: see ref. 1; m. pt 471 K - 474 K.
The structure is shown to be *S* at both C(2) and C(3). The dihedral angle between the C(41)–C(46) and phthaloyl groups is 111.7° and a small twist about the C(44)–N(44) bond is noted; C(43)/C(44)/N(44)/ O(44) is 13(1)°.

$C_{18}H_{13}BrN_2O_6$, orthorhombic, $P2_12_12_1$ (No. 19), a =11.299(2) Å, b =19.642(1) Å, c =8.066(2) Å, V =1790.1 Å^3, Z =4. $R(F)$ =0.030, $R_w(F)$ =0.029.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless block, size 0.19 x 0.23 x 0.26 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	23.41 cm^{-1}
Diffractometer:	Rigaku AFC6R
Scan mode:	ω/2θ
$T_{measurement}$:	293 K
$2\theta_{max}$:	55°
N(hkl)$_{unique}$:	2468
Criterion for F_o:	$F_o > 6\,\sigma(F_o)$
N($param$)$_{refined}$:	245
Program:	teXsan

Table 2. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{iso}
H(1'a)	4*a*	0.10208	0.25245	0.0689	0.08696
H(1'b)	4*a*	0.20696	0.21671	−0.02805	0.16837
H(1'c)	4*a*	0.09753	0.17315	0.03372	0.09145
H(2)	4*a*	0.27721	0.13305	0.46611	0.01322
H(3)	4*a*	0.47968	0.08675	0.30149	0.06300
H(23)	4*a*	0.58467	0.37157	0.27821	0.08217
H(24)	4*a*	0.57967	0.46313	0.46874	0.03593
H(25)	4*a*	0.48323	0.45286	0.71846	0.06891
H(26)	4*a*	0.37144	0.35659	0.78193	0.10184
H(42)	4*a*	0.37989	0.09896	0.72279	0.04710
H(43)	4*a*	0.50403	0.10364	0.95324	0.10901
H(45)	4*a*	0.78692	0.08401	0.65124	0.05231
H(46)	4*a*	0.66205	0.08193	0.41865	0.06136

Table 3. Final atomic coordinates and displacement parameters (in Å^2)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(3)	4*a*	0.34492(6)	0.00098(5)	0.4113(1)	0.0695(5)	0.0393(3)	0.0836(6)	−0.0057(8)	−0.0057(6)	−0.0085(7)
O(1)	4*a*	0.3071(4)	0.1116(3)	0.1062(6)	0.064(4)	0.066(3)	0.044(3)	−0.009(3)	−0.000(3)	−0.015(3)
O(1')	4*a*	0.2093(5)	0.1984(3)	0.2157(7)	0.068(4)	0.053(4)	0.040(4)	0.018(3)	−0.011(3)	0.004(3)
O(21)	4*a*	0.4965(5)	0.2285(3)	0.2041(7)	0.078(4)	0.064(3)	0.042(4)	−0.022(3)	0.028(4)	−0.011(3)
O(28)	4*a*	0.2867(5)	0.2226(3)	0.6760(7)	0.081(5)	0.066(4)	0.040(3)	−0.011(3)	0.025(4)	−0.000(3)
O(44)	4*a*	0.6871(6)	0.0824(4)	1.0952(8)	0.101(6)	0.164(7)	0.046(4)	−0.003(5)	−0.012(5)	0.002(5)
O(44')	4*a*	0.8352(6)	0.0930(4)	0.9392(9)	0.065(4)	0.26(1)	0.072(5)	−0.011(7)	−0.016(6)	−0.010(6)
N(21)	4*a*	0.3877(5)	0.2086(3)	0.4349(7)	0.048(4)	0.034(3)	0.029(4)	−0.008(4)	0.003(3)	−0.003(3)
N(44)	4*a*	0.7303(8)	0.0896(4)	0.960(1)	0.077(6)	0.118(7)	0.051(6)	−0.015(5)	−0.014(6)	−0.009(6)
C(1)	4*a*	0.2843(7)	0.1484(4)	0.2180(9)	0.048(5)	0.049(5)	0.033(5)	−0.012(4)	−0.003(4)	−0.004(4)
C(1')	4*a*	0.1489(8)	0.2113(4)	0.060(1)	0.084(7)	0.091(7)	0.055(6)	0.011(6)	−0.011(7)	0.015(6)

Table 3. (Continued)

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(2)	4*a*	0.3401(6)	0.1436(3)	0.3884(9)	0.037(4)	0.042(4)	0.040(5)	−0.005(4)	0.009(5)	−0.001(4)
C(3)	4*a*	0.4310(6)	0.0865(3)	0.401(1)	0.045(5)	0.043(4)	0.042(5)	−0.009(4)	0.005(5)	−0.003(4)
C(21)	4*a*	0.4604(7)	0.2468(4)	0.335(1)	0.035(5)	0.052(5)	0.039(5)	−0.001(5)	−0.001(4)	0.004(4)
C(22)	4*a*	0.4778(6)	0.3109(3)	0.423(1)	0.036(4)	0.034(4)	0.056(5)	0.005(5)	−0.009(5)	−0.002(3)
C(23)	4*a*	0.5408(7)	0.3683(4)	0.381(1)	0.052(5)	0.056(5)	0.059(6)	−0.013(5)	−0.003(5)	0.001(4)
C(24)	4*a*	0.5384(8)	0.4211(4)	0.494(1)	0.062(6)	0.036(5)	0.098(8)	−0.016(5)	−0.012(6)	−0.007(5)
C(25)	4*a*	0.4795(9)	0.4156(5)	0.640(1)	0.079(8)	0.058(6)	0.068(8)	0.004(6)	−0.014(7)	−0.026(6)
C(26)	4*a*	0.4156(7)	0.3595(4)	0.679(1)	0.073(6)	0.049(5)	0.057(6)	−0.001(5)	0.002(5)	−0.016(5)
C(27)	4*a*	0.4162(6)	0.3081(3)	0.569(1)	0.047(5)	0.039(4)	0.037(5)	0.004(4)	0.001(5)	0.004(4)
C(28)	4*a*	0.3528(8)	0.2432(4)	0.576(1)	0.059(5)	0.048(4)	0.031(5)	0.004(4)	0.017(6)	−0.002(5)
C(41)	4*a*	0.5090(6)	0.0906(3)	0.5486(9)	0.043(5)	0.041(4)	0.033(5)	−0.007(4)	0.004(4)	−0.001(4)
C(42)	4*a*	0.4649(7)	0.0962(4)	0.707(1)	0.039(5)	0.043(5)	0.055(6)	−0.002(4)	0.016(5)	0.008(4)
C(43)	4*a*	0.5360(8)	0.0979(4)	0.843(1)	0.064(7)	0.051(6)	0.038(6)	0.002(5)	−0.009(5)	0.000(5)
C(44)	4*a*	0.6544(8)	0.0913(4)	0.816(1)	0.055(5)	0.065(5)	0.037(5)	−0.016(4)	−0.005(6)	0.001(6)
C(45)	4*a*	0.7018(7)	0.0867(5)	0.665(1)	0.037(5)	0.108(7)	0.045(6)	−0.005(6)	0.006(5)	−0.010(5)
C(46)	4*a*	0.6286(7)	0.0859(4)	0.529(1)	0.043(6)	0.071(6)	0.039(6)	−0.009(5)	0.007(5)	−0.000(5)

Reference

1. Easton, C. J.; Hutton, C. A.; Merrett, M. C.; Tiekink, E. R. T.: Neighbouring group effects in side chain reactions of amino acid derivatives: a stereocontrolled route to chloramphenicol. Tetrahedron (1996) in press.

PVC IN PERSPECTIVE

When Sydney was awarded the 2000 Olympic Games, the environmental guidelines adopted for the construction of the site at Homebush Bay precluded the use of chlorine-based products such as PVC. However, this decision was successfully overruled on the grounds that it was not based on sound scientific evidence. **Jenny O'Connell, Chris Easton** *and* **Greg Simpson** *weigh up the evidence.*

The preparations for Sydney's Olympic Games have highlighted the debate about the use of polyvinyl chloride (PVC). The environmental guidelines set for the Games included a recommendation that the use of chlorine-containing materials should be minimised, with specific mention made of PVC. Some groups, principally environmental lobby groups, claim that PVC is associated with undesirable health and environmental risks while the manufacturers maintain that it is a safe, inexpensive and versatile material for which the benefits far outweigh the risks. In the light of these arguments and because of the importance of PVC to the Australian chemical and building industry, this article presents the main issues that have dominated the debate around the use and manufacture of PVC.

Structure and Synthesis

PVC is a thermoplastic produced from the primary feedstocks of chlorine and ethylene. Chlorine is obtained from the electrolysis of sodium chloride while ethylene is a petroleum product. The chlorine and ethylene react to give ethylene dichloride (EDC), which is then cracked in a high temperature furnace to remove hydrogen chloride (HCl) and give vinyl chloride monomer (VCM). The HCl produced in this step is recycled and combined with ethylene in the presence of oxygen to produce more EDC. PVC in Australia is manufactured by the suspension polymerisation system, whereby VCM is suspended as droplets in water and the presence of an initiator starts a free radical chain reaction process (Fig. 1).

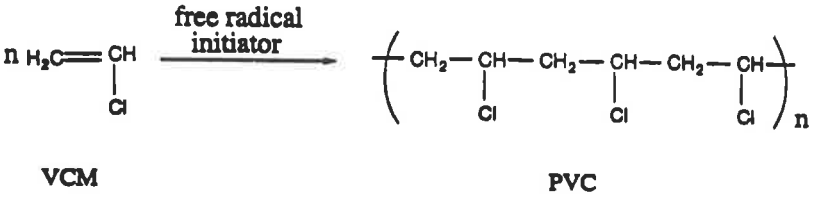


Fig. 1. A free radical initiator polymerises PVC from VCM suspended in water.

The process occurs in a sealed vessel under increased pressure and temperature. Special corrosion-resistant vessels must be used due to the presence of HCl. These vessels are tight and leakproof to maintain the pressure and prevent loss of VCM. Unreacted VCM is removed and reused (Fig. 2).

Engineering Properties

PVC is a tough polymer with many physical properties that make it a useful construction material. It is lightweight, has good weather resistance and requires minimal maintenance, making PVC a good material for window frames, gutters, plumbing pipes and conduit. It is also an excellent electrical insulator and, when combined with plasticisers, it provides a flexible product widely used as cable insulation. PVC has good barrier properties, meaning that it is waterproof and air proof and somewhat chemically resistant. It is not biodegradable and does not burn readily. It is easy to colour and mould and will more readily accept a wider range of additives than other plastics, giving the products greater diversity. Other products from PVC include appliance housing, upholstery, shower cur-

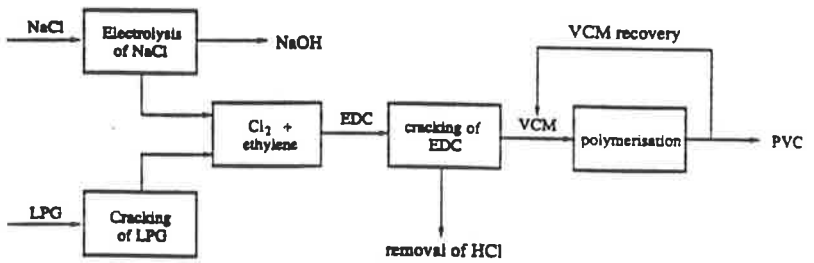


Fig. 2. The production of PVC occurs in a sealed vessel under increased temperature and pressure in corrosion-resistant vessels. Unreacted VCM is removed and reused during the process.

tains, cling wrap, gum boots, garden hose, blood product bags, surgical masks and oxygen tubing.

Australian Manufacture and Market

There are currently three major PVC production sites in Australia. The ICI Botany site produces approximately 50,000 tonnes per annum from chlorine and ethylene produced on site. The ICI Laverton site produces 60,000 tonnes per annum and is expected to increase to 140,000 tonnes per annum by the end of 1996, when the Botany plant will close. The Auseon site at Altona produces 100,000 tonnes per annum using imported VCM. The Altona plant will then use imported VCM as well. The total Australian manufacture of PVC is about 210,000 tonnes per annum, with a large percentage of this being used for the domestic market. More than 60% of Australian PVC goes into the building and construction industry, primarily for pipes and conduit. These are considered long-life products. Approximately 64% of PVC in Australia is used for purposes with a lifetime greater than 15 years, while 12% is used for short lifetime products up to 2 years.

Safety of PVC Manufacture and Use

There has been controversy surrounding the manufacture, use and disposal of PVC in recent years. Is it safe, or should its use be discouraged or even banned because of environmental and health concerns?

The arguments against the use and manufacture of PVC include objections to the use of chlorine, EDC, VCM and presumably PVC itself. Groups that have chosen to campaign for the ban of all anthropogenic chlorine-containing compounds have singled out PVC for particular attention because of its high profile.

The industry argues that PVC is a safe, non-degradable, inexpensive and versatile product that can be used for a wide range of applications. Unlike many alternative polymers it does not burn readily and its production is comparatively energy efficient. Its safety is exemplified by its use as the preferred material for blood product bags and tubing for medical purposes. The industry maintains that the use of hazardous materials in the production of PVC is subject to high standards and responsible work practices.

Chlorine is a toxic gas and a powerful oxidising agent. The use of chlorine and the manufacture of chlorine-containing compounds (organochlorines) is currently the subject of worldwide debate. Chlorine-containing compounds are a diverse group with a broad spectrum of physical, chemical and toxicological properties. There are many compounds that contain chlorine that are hazardous to human health and the environment but the fact that a molecule contains chlorine does not necessarily mean that it is toxic.

PVC appears to have been targeted as an unsafe material because it is part of the chlorine industry rather than due to problems intrinsic to PVC.

The production of chlorine itself poses industrial challenges. Older chlorine plants in Australia still use the amalgam process, requiring mercury, in the electrolytic cell. Losses of mercury in the past occurred where environmental standards and recovery technologies were not as stringent as those currently employed. More modern chlorine plants use either membrane or diaphragm technology that avoid the use of mercury.

VCM is also toxic and has been shown to cause a rare form of liver cancer called angiosarcoma in rats. Studies of health records of people working in this industry found cases of this cancer. There have been no new cases of angiosarcoma attributable to VCM production since changes in work practices have reduced the level of VCM.

PVC Toxicity

PVC is a very stable material. VCM is not produced from it either through decomposition or combustion, although very small amounts of VCM can be trapped in the resin during polymerisation. This has caused some concerns about the dangers of VCM being released from PVC with time. For this reason the National Health and Medical Research Council has set an upper limit of VCM in PVC resin. The industry works within this guideline and con-

■ **PVC is waterproof, airproof and somewhat chemically resistant, and is not biodegradeable or burn easily, making it an ideal material for many uses.**

forms to the Australian Standard for Plastic Material for Food Contact (AS 2070).

Other objections to the use of PVC include concerns about the additives mixed with the polymer to give desirable properties like plasticity and resistance to ultraviolet light, the production of toxic material during combustion and the recycling of PVC. There are concerns that the additives in PVC can migrate from the plastic material into food and water supplies and that degradation of PVC in landfill and pipes will result in the release of dangerous compounds. A study of the degradation of PVC in landfill conducted in Sweden found that: (i) rigid PVC (without plasticiser) does not degrade; and (ii) plasticised PVC will degrade at a rate of 0.1–0.5% over a period of 50–100 years.

The combustion of PVC produces carbon monoxide, carbon dioxide and HCl gas. There is also a concern that dioxins are produced. Whenever there is a fire, toxic gases are produced. The major consideration in a fire is the risk to life. Combustion of common building materials produces carbon dioxide and carbon monoxide. Hydrogen cyanide is produced when nitrogen-containing materials such as nylon, acrylonitrile, polyurethane and wool are present in the fire.

The production of HCl gas in either office or house fires can cause severe irritation of the mucous membranes and was once thought to be a major cause of death in fires. It has since been established that the main causes of death in office and house fires are asphyxiation and cyanide poisoning from carbon monoxide, carbon dioxide and hydrogen cyanide, well ahead of the risk from HCl gas. Another problem with the release of HCl is the extensive structural damage that can result from minor fires. Hydrogen chloride can permeate areas of a building undamaged by fire, causing serious corrosion problems.

Dioxins are a group of chemicals called polychlorinated benzodioxins (PCDD) and usually also includes polychlorinated benzofurans (PCDF) (Fig. 3). PCDDs and PCDFs are produced from the combustion of many organic substances, including wood in wood heaters and barbecues, cigarettes, municipal waste and in naturally occurring bushfires and volcanoes. Some groups argue that the combustion of PVC in either accidental situations or deliberately for disposal purposes causes the production of PCDDs and PCDFs, posing health risks.

PCDDs PCDFs

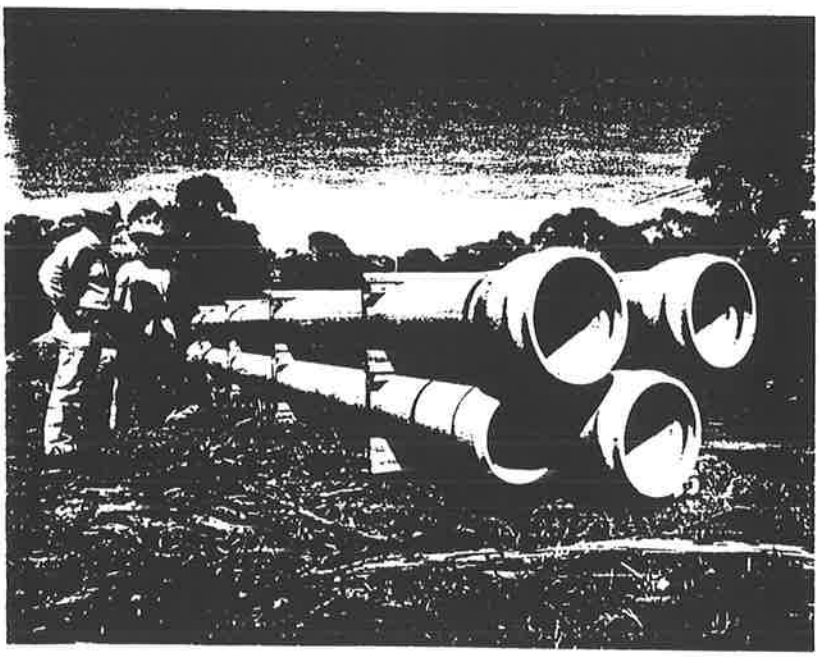
Fig. 3. The chemical structure of PCDDs and PCDFs, which are more commonly known as dioxins. While these pose health risks, there is no conclusive evidence that they are produced when PVC is burned.

The relationship between the PVC content of municipal solid waste (MSW) and the PCDD and PCDF content in incinerator output has been the subject of many studies in Europe and the US. To date the evidence is inconclusive and contradictory, with some studies showing an increase of PCDDs and PCDFs while others show a decrease and a third group show no significant difference within the bounds of experimental error. It cannot be concluded that the inclusion of PVC in MSW will cause the production of PCDDs and PCDFs.

Recycling Issues

For PVC or any other material to be considered environmentally friendly there must be an assessment of the life-cycle of that product. Is the material used for long life products? When it reaches the end of its lifetime is it effectively recycled? There is great potential for recycling of PVC given that it is a thermoforming polymer: that is, it can be reheated and remoulded. Greenpeace claims that more than 4000 additives are used in PVC, making the separation of the different types of PVC based on additive content difficult and subsequent recycling limited by the compatibility of the additives. Faulkner (1996) disputes this figure, claiming that there are only approximately 50 additives used in PVC, excluding the colours.

The major use of PVC in Australia is for long life products such as plumbing pipes and electrical conduit. PVC pipes are not being recycled on a large scale at this stage because they have not reached the end of their life time. ICI Australia



■ **Plumbing pipes made with PVC are not being recycled because the pipes have not reached the end of their life time.**

manufactures a product called Revinyl that is 30% recycled and 70% new polymer. Cryogrind Australia produces a product for Auseon that contains 20% recycled polymer. These recycled polymers are used for applications such as pipes and outdoor furniture.

Alternatives to PVC

Greenpeace recommends that PVC be replaced with other more environmentally sound materials such as polyethylene (PE), polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET), aluminium or suitable synthetic rubbers. Wherever an alternative material is considered it should be subject to the same safety considerations as PVC; a complete assessment of the risk against the benefit must be made. Any replacement considered must demonstrate some kind of health or environmental advantage.

PP and PE are prepared by polymerisation of propylene and ethylene and have some similar properties when compared with PVC, such as toughness, flexibility, impermeability and chemical resistance. PET, another thermoplastic, is made from ethylene glycol and terephthalate. The manufacture of PS involves the use of benzene, styrene and butadiene, all considered to be human carcinogens. A significant disadvantage of these alternative polymers is that they burn readily and are not particularly UV resistant. PE, PP, PS and PET must be treated with a flame retardant for most purposes. Other additives include UV and heat stabilisers, antioxidants and colours, and plasticisers similar to those added to PVC. Rubbers have associated problems with occupational health and provide no significant advantage over the use of PVC. Combustion also produces toxic gases and the environmental impact studies are limited.

Issues for Sydney's Olympic Games

Sydney's bid for the 2000 Olympic Games included strong environmental awareness arguments. The environmental guidelines that were adopted for the construction of the Olympic village include the statement "selection of components that go into new projects being subject to life cycle costing and consideration of environmental implications during manufacture, use and disposal". It is intended that this set the standard for future selection of building materials, both nationally and internationally. The document also stated that Olympic host cities should commit themselves to minimising and ideally avoiding the use of chlorine-based products (organochlorines) such as PVC. This was later altered due to objections from the PVC and construction industries that the argument was not based on sound scientific evidence. The environmental guidelines for the Olympic village were written with assistance from Greenpeace. A major item on the Greenpeace agenda is a worldwide ban of organochlorines.

PVC accounts for 35% of the world's chlorine manufacture, and it is an important product of the Australian chemical industry. Clearly there are concerns about the continued use of PVC in an increasingly environmentally responsible society. The suitability of PVC for continued use must be subject to rigourous scientific debate and analysis. The weight of scientific evidence at this time supports the view that PVC is a responsibly manufactured material that provides much more of a benefit to society than it imposes a risk. PVC appears to have been targeted as an unsafe material because it is part of the chlorine industry rather than due to problems intrinsic to PVC.

The expectation that the building standards used for the Olympic village in Sydney in the year 2000 will provide the guide for future building in this country makes it essential that decisions about the safety of PVC are based on an unbiased and independent assessment of the scientific facts. This is an ongoing process, with organisations such as the CSIRO now taking an active role in the debate. Provided the scientific evidence is fully considered, the result of this debate about the role of chemicals in our life can lead only to an improved quality of life in both the economic and enviromental spheres.

■ **Although chlorine-based products such as PVC were originally banned from use in the construction of Sydney's Olympic village, this decision was later overturned due to objections that the decision was not based on sound scientific evidence.**

Reference

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Cooperative Binding of 6-(*p*-Toluidinyl)naphthalene-2-sulfonate by β-Cyclodextrin Dimers

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A fluorimetric study shows that 6-(*p*-toluidinyl)naphthalene-2-sulfonate (TNS^-) forms binary complexes with dimeric *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin)glutaramide and its succinamide, malonamide, oxalamide, and urea analogues characterized by stability constants 13 010 ± 20, 16 700 ± 20, 11 000 ± 10, 32 640 ± 90, and 45 230 ± 70 $dm^3\ mol^{-1}$, respectively, in aqueous phosphate buffer at pH 7.0, $I = 0.10\ dm^3\ mol^{-1}$ and 298.2 K. These values are substantially greater than that for the β-cyclodextrin·TNS^- complex and are indicative of collaborative binding in the β-cyclodextrin dimer complexes. The factors affecting the stabilities of the cyclodextrin dimer complexes and their fluorescence characteristics are discussed, and comparisons are made with related systems.

Introduction

β-Cyclodextrin, βCD, is the α-1,4 linked heptamer of glucopyranose for which 7 primary and 14 secondary hydroxy groups, respectively, delineate the narrow and wide ends of a macrocyclic annulus whose hydrophobic interior is lined with methine and methylene groups and ether oxygens.[2−4] It acts as the host in the formation of βCD·G host−guest complexes with a wide range of guests (G), most of which contain an aromatic group that is included within the hydrophobic region of the βCD annulus on complexation.[5−7] Considerable interest is currently centered on the extent to which two βCD, joined through a linker (x) in a dimer $(\beta CD)_2x$, may cooperatively bind a guest.[8−18] We now report the effect of a systematic variation of the linker length in *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin)-glutaramide $(\beta CD)_2$gl, and its succinamide $(\beta CD)_2$su, malonamide $(\beta CD)_2$ma, oxalamide $(\beta CD)_2$ox, and urea $(\beta CD)_2$ur analogues[19] on the binding of 6-(*p*-toluidinyl)naphthalene-2-sulfonate, TNS^- (Figure 1). This guest is chosen because its toluidinyl and naphthalene groups constitute separate binding sites, and its fluorescence spectrum is very sensitive to environment[20,21] and should thereby provide structural information about the host−guest complexes formed.

Experimental Section

The dimer β-cyclodextrins, $(\beta CD)_2x$, were prepared by methods reported in the literature[19] and were shown to be >95% pure by microanalysis, TLC, and ^1H and ^{13}C NMR spectroscopy. The minor impurity was βCD. Both $(\beta CD)_2x$ and βCD were dried to constant weight and stored in the dark over P_2O_5 in a vacuum desiccator. Potassium 6-(*p*-toluidinyl)naphthalene-2-sulfonate (Molecular Probes), which was similarly dried and stored, showed only a single TLC spot and was used without further purification. Na_2HPO_4/KH_2PO_4 buffer (pH 7.0, $I = 0.10$ mol dm^{-3}) was prepared as described in the literature.[22] Deionized water, purified with a MilliQ-reagent system to produce water with a specific resistance of > 15 MΩ cm was used in the preparation of all solutions immediately prior to measurement. Exposure of solutions to light was kept to a minimum by wrapping their containers in aluminum foil.

Absorbance spectra were run in 1 cm path length matched quartz cells on a Zeiss DMR 10 spectrophotometer in which the samples were thermostated at 298.2 ± 0.1 K. Fluorescence spectra were run in a 1 cm path length cuvette on a Perkin-Elmer LS 50B fluorometer in which the samples were thermostated at 298.2 ± 0.1 K. An excitation slit width of 5 nm and an emission slit width of 10 nm were used for all systems except for $(\beta CD)_2$ur for which a 5 nm emission slit width was used. The excitation wavelength was selected from within the longest wavelength absorption band to reduce the possibility of reabsorption. This wavelength was either that of an isosbestic point or, in its absence, the wavelength where the absorbance difference between free TNS^- and TNS^- complexed by either βCD or $(\beta CD)_2x$ was at a minimum (Table 1). This was designed to keep the number of photons absorbed similar for TNS^- alone and TNS^- complexed by either βCD or $(\beta CD)_2x$ so that a comparison of the relative fluorescences of free and complexed TNS^- was possible (Table 1). An isosbestic point occurred at the excitation wavelength of 369 nm in the βCD/TNS^- system. For the $(\beta CD)_2$gl/TNS^- system the excitation wavelength was 355 nm and complexed TNS^- absorbed 3% more strongly than free TNS^-, and the corresponding values

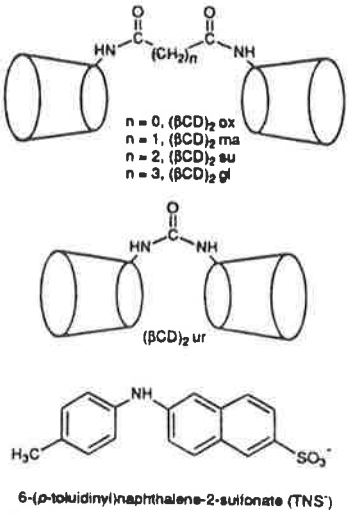

Figure 1. Schematic illustrations of the β-cyclodextrin dimers, $(\beta CD)_2x$, where the cyclodextrin annulus is represented by a truncated cone in which the narrow end is delineated by 6 primary hydroxy groups and a secondary amine group and the wide end is delineated by 14 secondary hydroxy groups. Structure of 6-(*p*-toluidinyl)naphthalene-2-sulfonate, TNS^-, is also shown.

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TABLE 1: Stability Constants for Binary Complexes of Dimer β-Cyclodextrins and TNS⁻ in Aqueous Phosphate Buffer at pH 7.0, I = 0.10 dm³ mol⁻¹, and 298.2 K

species	K_1 or K_2 (dm³ mol⁻¹)[a]	λ_{max} (nm)	excitation λ (nm)	relative intensity[b]
TNS⁻		408, 489		
βCD·TNS⁻	1850 ± 10[c]	458	369	15[e]
βCD·TNS⁻	3140 ± 20[d]	463	369	12[e]
$(\beta CD)_2$·TNS⁻	86 ± 5[d]	446	369	24[e]
$(\beta CD)_2$gl·TNS⁻	13010 ± 20[f]	447	355	47[g]
$(\beta CD)_2$su·TNS⁻	16700 ± 20[f]	440	353	84[g]
$(\beta CD)_2$ma·TNS⁻	11000 ± 10[f]	441	357	133[g]
$(\beta CD)_2$ox·TNS⁻	32640 ± 90[f]	433	346	23[h]
$(\beta CD)_2$ur·TNS⁻	45230 ± 70[f]	434	354	197[h]
$(\beta CD)_2$ur·TNS⁻	45700 ± 300[f]	434	354	177
$((\beta CD)_2ur)_2$·TNS⁻	9300 ± 400[f]	435	354	187

[a] The errors represent one standard deviation. [b] Normalized ratio of integrated areas of the emission spectra of the host−guest complex and TNS⁻ under the same conditions over the wavelength ranges 385−550,[e] 370−530,[g] and 370−550,[h] which take into account the differences in absorbance at the excitation wavelength as discussed in the Experimental Section. [c] Stability constant derived for βCD·TNS⁻ when data were fitted to the algorithm arising from eq 1 (ssr = 1.63 × 10⁴). [d] Stepwise stability constants for βCD·TNS⁻ and $(\beta CD)_2$·TNS⁻, respectively, when data were fitted to the algorithm arising from eqs 1 and 2 together (ssr = 3.66 × 10³). [f] Stability constant derived for $(\beta CD)_2$x·TNS⁻ when data were fitted to the algorithm arising from eq 3 (10^{-4}ssr = 1.22, 5.06, 5.73, 1.25, and 1.08 as the table is descended). [f] Stepwise stability constants for $(\beta CD)_2$x·TNS⁻ and $((\beta CD)_2x)_2$·TNS⁻, respectively, when data were fitted to the algorithm arising from eqs 3 and 4 together (ssr = 2.79 × 10³).

for $(\beta CD)_2$su/TNS⁻ are 353 nm and 2%, for $(\beta CD)_2$ma/TNS⁻ 357 nm and 10%, for $(\beta CD)_2$ox/TNS⁻ 346 nm and 7%, and for $(\beta CD)_2$ur/TNS⁻ 354 nm and 27%. The relative fluorescence of free and complexed TNS⁻ was determined from the integrated area of the fluorescence spectrum of each over the same wavelength range and was normalized by multiplying by the ratio of the absorbance of the free TNS⁻ to that of the complexed TNS⁻ at the excitation wavelength. The $(\beta CD)_2$x species showed a weak fluorescence with a maximum at 420−430 nm. This was subtracted from the fluorescence spectra of all $(\beta CD)_2$x/TNS⁻ solutions prior to data treatment. A smaller correction was required for βCD solutions. Solutions of TNS⁻ alone exhibited a linear dependence of fluorescence on concentration at [TNS⁻] < 10^{-5} mol dm⁻³. At [TNS⁻] > 10^{-5} mol dm⁻³, the increase in fluorescence progressively deviated below a linear dependence on concentration.

Fluorescence spectra were measured for at least 22 different total [βCD] or [$(\beta CD)_2$x] at a constant [TNS⁻] in the range (1.00−1.04) × 10^{-6} mol dm⁻³ for each system. Stability constants were determined from a simultaneous fit of the fluorescence data at 0.5 nm intervals over either the [βCD] or [$(\beta CD)_2$x] ranges and the wavelength ranges, respectively, shown after each of the following systems, where the full wavelength range scanned is shown in parentheses: βCD, 1.50 × 10^{-6} to 5.50 × 10^{-3} mol dm⁻³, 410−520 nm (385−550 nm); $(\beta CD)_2$gl, 3.08 × 10^{-6} to 8.95 × 10^{-4} mol dm⁻³, 400−500 nm (370−530 nm); $(\beta CD)_2$su, 3.00 × 10^{-6} to 1.00 × 10^{-3} mol dm⁻³, 400−500 nm (370−530 nm); $(\beta CD)_2$ma, 2.51 × 10^{-6} to 9.00 × 10^{-4} mol dm⁻³, 400−500 nm (370−530 nm); $(\beta CD)_2$ox, 3.98 × 10^{-6} to 6.03 × 10^{-4} mol dm⁻³, 400−500 nm (370−550 nm); $(\beta CD)_2$ur, 8.32 × 10^{-7} to 3.07 × 10^{-4} mol dm⁻³, 400 500 nm (370−550 nm). Thus, a minimum of 4422 data points were simultaneously used in the derivation of each stability constant and the emission spectrum of each species. All data fitting was carried out on a AcerPower 466d computer using a nonlinear least squares regression routine based on method 5 of Pitha and Jones[23] through our program DATAFIT/SPECFIT, which outputs bestfit parameters and their standard deviations.

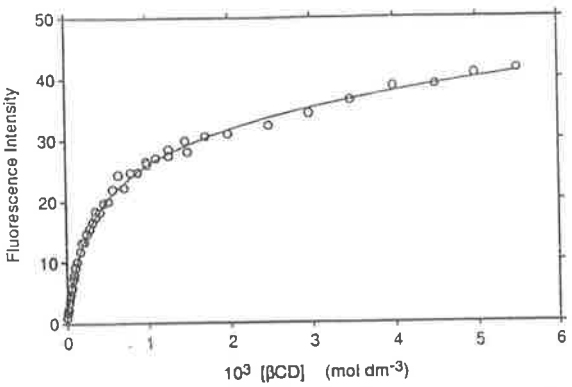

Figure 2. Fluorescence variation of TNS⁻ (1.04 × 10^{-6} mol dm⁻³) at 453 nm with total [βCD] in the range 1.50 × 10^{-6} to 5.50 × 10^{-3} mol dm⁻³ in aqueous phosphate buffer at pH 7.0, I = 0.10 mol dm⁻³, and 298.2 K. Excitation wavelength was 369 nm, and excitation and emission slit widths were 5 and 10 nm, respectively. Solid curve represents the best fit of the data, collected over the range 410−520 nm, to the algorithm arising from the equilibria shown in eqs 1 and 2.

Results and Discussion

Complexation of TNS⁻ by βCD. The complexation of TNS⁻ by βCD is the comparator for the complexation of TNS⁻ by $(\beta CD)_2$x. Several studies of the former[9,15,24−26] have detected only the equilibrium shown in eq 1 and yield K_1 values ranging from 1200 to 3950 dm³ mol⁻¹. Other studies[27−32] have indicated the existence of the two equilibria shown in eqs 1 and 2 and yield values of K_1 and K_2 ranging from 970 to 6650 dm³ mol⁻¹ and from 1.4 to 600 dm³ mol⁻¹, respectively. The experimental conditions and methods and data treatments vary considerably in these studies. Accordingly, the βCD/TNS⁻ system was reinvestigated under the same conditions as the $(\beta CD)_2$x studies described below to provide a basis for the assessment of the degree of cooperative binding in these systems.

$$\beta CD + TNS^- \overset{K_1}{\rightleftharpoons} \beta CD \cdot TNS^- \quad (1)$$

$$\beta CD + \beta CD \cdot TNS^- \overset{K_2}{\rightleftharpoons} (\beta CD)_2 \cdot TNS^- \quad (2)$$

The variation of the TNS⁻ fluorescence intensity with total [βCD] was fitted to the algorithm arising from the equilibrium in eq 1. This yielded K_1 = 1850 ± 10 dm³ mol⁻¹ with a sum of the squares of the residuals (ssr) = 1.63 × 10^4 in aqueous phosphate buffer at pH = 7.0, I = 0.10 dm³ mol⁻¹, and 298.2 K. Fitting to the algorithm for the equilibria shown in eqs 1 and 2 yielded K_1 = 3140 ± 20 dm³ mol⁻¹ and K_2 = 86 ± 5 dm³ mol⁻¹ with a decrease in the ssr to 3.66 × 10^3. (A plot of TNS⁻ fluorescence variation with total [βCD] is shown in Figure 2.) The two models for βCD complexation of TNS⁻ establish upper and lower limits for K_1 characterizing βCD·TNS⁻ under the conditions of this study, and the substantial decrease in the ssr on going from the first to the second model indicates that the latter has validity. Thus, data pertaining to both βCD·TNS⁻ and $(\beta CD)_2$·TNS⁻ are considered. In principle, βCD·TNS⁻ may exist with either of the TNS⁻ aromatic groups included inside the βCD annulus, and $(\beta CD)_2$·TNS⁻ is assumed to exist with each TNS⁻ aromatic group included within a βCD annulus. Within these broad confines a range of host and guest orientations may exist.

The increase in the magnitude of TNS^- fluorescence and its blue shift with increasing total [βCD] (Table 1) is characteristic of the transfer of the TNS^- fluorophore from an aqueous environment to the low-polarity hydrophobic βCD annulus.[20,21] Analysis of the fluorescence variation in the range 385−550 nm shows λ_{max} = 463 and 446 nm, respectively, for $\beta CD \cdot TNS^-$ and $(\beta CD)_2 \cdot TNS^-$, which are 12 and 24 times more fluorescent than TNS^- alone when the integrated intensities in the range 385−550 nm are compared. (In this study, TNS^- exhibited λ_{max} at 408 and 489 nm in agreement with literature values.[21]) The blue shift in λ_{max} and increase in fluorescence for $\beta CD \cdot TNS^-$ and $(\beta CD)_2 \cdot TNS^-$ are consistent with an increasingly hydrophobic environment being experienced by TNS^- similar to that observed when TNS^- is transferred from water to low-polarity solvents or hydrophobic macromolecular environments where λ_{max} in the range 420−460 nm are found.[20,21]

The blue shift may be understood in terms of a recently proposed model for TNS^- fluorescence.[21] This model incorporates excitation (λ_{max} = 290 nm) of a TNS^- S_0 ground state, in which the bridging nitrogen is either protonated or hydrogen bonded, and emission from a charge-transfer excited state ($S_{1-ct,perp}$, λ_{max} emission = 400 nm) in which the planes of the toluidinyl and naphthyl groups are perpendicular to each other. Also incorporated is excitation ($\lambda_{max} \approx$ 330 nm) from a TNS^- S_0 ground state, from which hydrogen bonding and protonation are absent, with emission from a conventional π^* excited state ($S_{1,np}$, λ_{max} emission $\approx$ 453 nm) in which the toluidinyl and naphthyl rings are in a nonplanar orientation, which is favored in low-polarity environments. Electron transfer from the toluidinyl to the naphthyl groups may then occur to give the charge-transfer excited state ($S_{1-ct,np}$, λ_{max} emission $\approx$ 490 nm) in which the toluidinyl and naphthyl rings become coplanar, which is favored in aprotic polar solvents. In water, emission from $S_{1-ct,perp}$ and $S_{1-ct,np}$ dominates TNS^- fluorescence while in low-polarity solvents emission from $S_{1,np}$ becomes important as indicated by a blue shift in the TNS^- emission spectrum. Thus, the blue shifts of the emission spectra of $\beta CD \cdot TNS^-$ and $(\beta CD)_2 \cdot TNS^-$ in water relative to the spectrum of TNS^- are consistent with emission from $S_{1,np}$ becoming dominant for TNS^- in the low-polarity hydrophobic environment of the βCD annulus. A similar interpretation also holds for the blue shift of the TNS^- emission spectrum in its $(\beta CD)_2x \cdot TNS^-$ complexes whose formation is discussed below. (Structural constraints arising from the inclusion of TNS^- in the βCD annulus may induce some further shifts in emission frequency that superimpose on the effect of the more general environmental change discussed above.)

The increased fluorescence of TNS^- in $\beta CD \cdot TNS^-$ and $(\beta CD)_2 \cdot TNS^-$ is consistent with complexation causing decreases in (i) the occurrence of the electron-transfer process leading to the charge-transfer excited states $S_{1-ct,perp}$ and $S_{1-ct,np}$, which are likely to decay more rapidly than the $S_{1,np}$ excited state, (ii) the hydration interactions, which provide a path for energy transfer from the TNS^- excited states to water vibronic modes, and (iii) the TNS^- rotational degrees of freedom, which also provide a path for energy transfer.[33] Thus, the greater fluorescence of complexed TNS^- arises largely because the $S_{1,np}$ excited state is stabilized by the low-polarity environment of the βCD annulus, which also restricts interaction with water and the rotational motion of TNS^-.

Complexation of TNS^- by $(\beta CD)_2x$. By analogy to the βCD system, the equilibria shown in eqs 3 and 4 may exist for the complexation of TNS^- by $(\beta CD)_2x$, and the interaction of two TNS^- with a single $(\beta CD)_2x$ could produce $(\beta CD)_2x \cdot (TNS)_2^{2-}$ as shown in eq 5. With the exception of $(\beta CD)_2ur$, the complexation of TNS^- by $(\beta CD)_2x$ could only be fitted to the algorithm for the TNS^- fluorescence variation with total [$(\beta CD)_2x$] arising from eq 3, consistent with $(\beta CD)_2x \cdot TNS^-$ being the greatly predominant complex formed. The derived K_1 appear in Table 1. The variation of TNS^- fluorescence in the presence of $(\beta CD)_2gl$, which incorporates the longest linker, is shown in Figure 3 and illustrates the change in the TNS^- spectrum caused by the formation of $(\beta CD)_2gl \cdot TNS^-$. The fitting of these data to the algorithm arising from the equilibrium analogous to that shown in eq 3 appears in Figure 4.

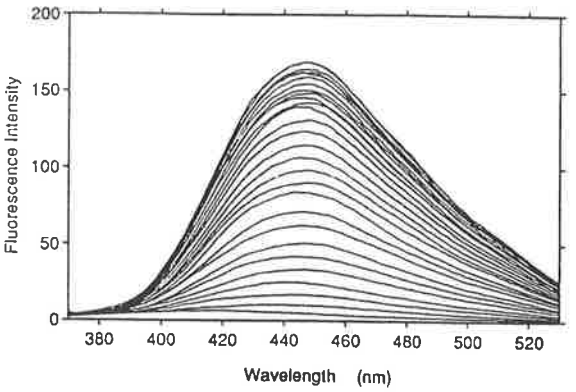

Figure 3. Fluorescence variation of TNS^- (1.01×10^{-6} mol dm^{-3}) with total [$(\beta CD)_2gl$] in the range 3.08×10^{-6} to 8.95×10^{-4} mol dm^{-3} in aqueous phosphate buffer at pH 7.0, I = 0.10 mol dm^{-3}, and 298.2 K. TNS^- spectrum in the absence of $(\beta CD)_2gl$ is the lowest intensity curve in the montage. Excitation wavelength was 355 nm, and excitation and emission slit widths were 5 and 10 nm, respectively.

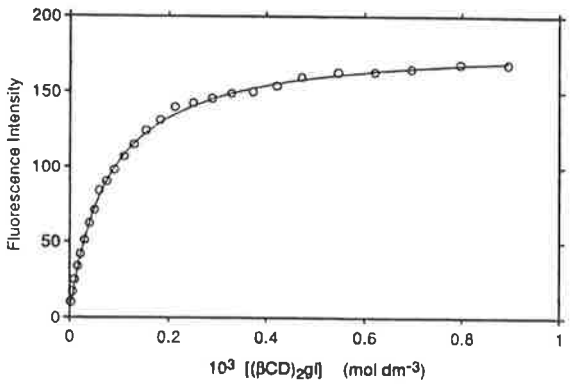

Figure 4. Fluorescence variation of TNS^- with total [$(\beta CD)_2gl$] at 447 nm under the same conditions as for Figure 3. Solid curve represents the best fit of the data, collected over the range 400−500 nm, to the algorithm arising from the equilibrium analogous to that shown in eq 3.

The fluorescence variation of TNS^- with [$(\beta CD)_2ur$] (Figure 5) was fitted to the algorithm arising from eq 3 alone to yield $K_1 = 45\,230 \pm 70$ dm^3 mol^{-1} (ssr = 1.08×10^4) as exemplified by the fit shown in Figure 6. (The increase in TNS^- fluorescence caused by the formation of $(\beta CD)_2ur \cdot TNS^-$ is such that the spectrum of TNS^- alone cannot be distinguished from the base line on the scale of Figure 5.) The data were also fitted to the algorithm for the equilibria shown in eqs 3 and 4 together to give $K_1 = 45\,700 \pm 300$ dm^3 mol^{-1} and $K_2 = 9300 \pm 400$ dm^3 mol^{-1} for the formation of $(\beta CD)_2ur \cdot TNS^-$ and $((\beta CD)_2ur)_2 \cdot TNS^-$, respectively, with an ssr = 2.79×10^3. The error in K_1 is significantly smaller for the fit of the data for the formation of $(\beta CD)_2ur \cdot TNS^-$ alone, but the decrease in ssr on going from the first to the second model is significant. Since both models give similar K_1 values for $(\beta CD)_2ur \cdot TNS^-$, which

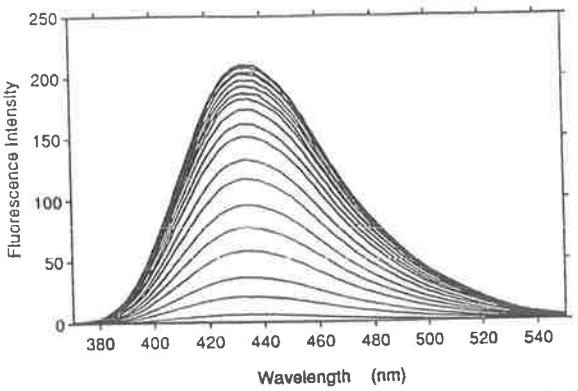

Figure 5. Fluorescence variation of TNS^- (1.00×10^{-6} mol dm^{-3}) with total [$(\beta CD)_2$ur] in the range 8.32×10^{-7} to 3.07×10^{-4} mol dm^{-3} in aqueous phosphate buffer at pH 7.0, $I = 0.10$ mol dm^{-3}, and 298.2 K. TNS^- spectrum in the absence of $(\beta CD)_2$ur is almost coincident with the base line. Excitation wavelength was 354 nm, and excitation and emission slit widths were both 5 nm.

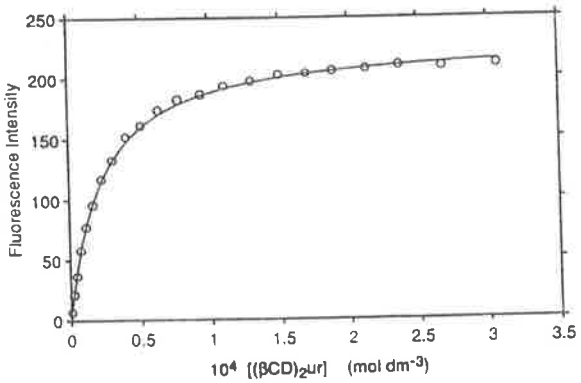

Figure 6. Fluorescence variation of TNS^- with total [$(\beta CD)_2$ur] at 434 nm under the same conditions as for Figure 5. Solid curve represents the best fit of the data, collected over the range 400–500 nm, to the algorithm arising from the equilibrium analogous to that shown in eq 3.

is the complex of prime interest in this study, the probability of the formation of $((\beta CD)_2ur)_2 \cdot TNS^-$ is not further considered. The fluorescence data could not be fitted to algorithms that include the equilibrium shown in eq 5, and it is therefore unlikely that $(\beta CD)_2ur \cdot (TNS)_2^{2-}$ is present in significant amounts.

$$(\beta CD)_2x + TNS^- \overset{K_1}{\rightleftharpoons} (\beta CD)_2x \cdot TNS^- \quad (3)$$

$$(\beta CD)_2x + (\beta CD)_2x \cdot TNS^- \overset{K_2}{\rightleftharpoons} ((\beta CD)_2x)_2 \cdot TNS^- \quad (4)$$

$$(\beta CD)_2x \cdot TNS^- + TNS^- \overset{K_3}{\rightleftharpoons} (\beta CD)_2x \cdot (TNS)_2^{2-} \quad (5)$$

The complexation of a second βCD to form $(\beta CD)_2 \cdot TNS^-$ is weak by comparison with the first βCD complexation probably because of the mutual steric hindrance existing between the βCD in $(\beta CD)_2 \cdot TNS^-$. This, together with the observation that the least stable dimer complex, $(\beta CD)_2$ma$\cdot TNS^-$, is much more than twice as stable as $\beta CD \cdot TNS^-$ indicates substantial cooperativity in the binding of TNS^- in $(\beta CD)_2x \cdot TNS^-$. The most stable complex is $(\beta CD)_2$ur$\cdot TNS^-$, consistent with the shortest linker optimizing the binding interactions within the host–guest complex. Although a shortening of the linker results in a general tendency toward higher $(\beta CD)_2x \cdot TNS^-$ stabilities, the trend is not smooth as illustrated by $(\beta CD)_2$ma$\cdot TNS^-$, which incorporates the intermediate length linker in the series studied, being of lowest stability. These stability variations are probably dominated by a balance between the flexibility of $(\beta CD)_2x$ and the maximizing of the interaction of the TNS^- toluidyl and naphthyl groups with the βCD annuli, which in turn affects the degree to which hydration of TNS^- and $(\beta CD)_2x$ competes with formation of $(\beta CD)_2x \cdot TNS^-$.

The blue shifts of the λ_{max} of TNS^- in $(\beta CD)_2x \cdot TNS^-$ (Table 1) are consistent with both aromatic groups of TNS^- moving from an aqueous environment to a hydrophobic environment and are similar in magnitude to that of $(\beta CD)_2 \cdot TNS^-$ where both aromatic groups of TNS^- are considered to be in the hydrophobic regions of the two βCD annuli. The normalized relative fluorescence intensities (Table 1) indicate a decrease in TNS^- fluorescence quenching in the complexed environment as discussed above. Broadly, the more TNS^- is tightly complexed and shielded from hydration the less the factors i–iii discussed above should quench TNS^- flourescence. Thus, TNS^- in $(\beta CD)_2$ur$\cdot TNS^-$ exhibits the greatest fluorescence by comparison with $(\beta CD)_2$su$\cdot TNS^-$ and $(\beta CD)_2$gl$\cdot TNS^-$, which were excited at similar wavelengths. However, the least stable complex of the series, $(\beta CD)_2$ma$\cdot TNS^-$, exhibits a high fluorescence while the more stable $(\beta CD)_2$ox$\cdot TNS^-$ exhibits a low fluorescence. This indicates that significant variations in the relative contributions of factors i–iii to quenching occurs in the range of $(\beta CD)_2x \cdot TNS^-$ studied.

Comparisons with Related Systems. An interesting comparison may be made between the stability of $(\beta CD)_2$su$\cdot TNS^-$ ($K_1 = 16\,700 \pm 20$ dm^3 mol^{-1}), where the βCD are linked by substitution of a primary hydroxy group by an amide nitrogen, and its isomeric *N,N'*-bis(3^A^-deoxy-3^A^-β-cyclodextrin)succinamide complex, $(\beta CD)_2$su*$\cdot TNS^-$ ($K_1 = 10\,500 \pm 200$ dm^3 mol^{-1}), where the βCD are linked by substitution of a secondary hydroxy group by an amide nitrogen.[16] The major structural difference is that in the first complex the narrow ends of the βCD annuli are adjacent to each other, while in the second the wide ends of the annuli are adjacent to each other. The moderate difference in the stabilities of the two complexes is consistent with the primary stabilizing interaction being that between the βCD annuli and the toluidinyl and naphthyl groups of TNS^- with the orientation of the annuli exerting a secondary influence. A lengthening of the linker in *N,N'*-bis-(3^A^-deoxy-3^A^-β-cyclodextrin)sebacamide ($(\beta CD)_2$se*, where se is $-NHCO(CH_2)_8CONH-$) causes a decrease in stability for $(\beta CD)_2$se*$\cdot TNS^-$ ($K_1 = 6700 \pm 300$ dm^3 mol^{-1}) consistent with the general decrease in stability with increase in linker length observed in the $(\beta CD)_2x$ series in Table 1.

A series of binary BNS^- complexes of dimer βCD in which linking was effected by substitution of a primary hydroxy group by a sulfur of $-S(CH_2)_nS-$, where n varied from 2 to 6, were characterized by a smooth decrease in stability as the linker lengthened such that $K_1 = 8\,200\,000$ and $150\,000$ dm^3 mol^{-1} when $n = 2$ and 6, respectively.[15] (BNS^- = 6-(4-*tert*-butylanilino)naphthalene-2-sulfonate has the same structure as TNS^- except that the methyl group is replaced by a *tert*-butyl group.) However, when $n = 0$, stability decreased as shown by $K_1 = 79\,000$ dm^3 mol^{-1} in contrast to the data reported in this study where the complex with the shortest linker, $(\beta CD)_2$ur$\cdot TNS^-$, is the most stable.

It is apparent that there is an optimum linker length for stabilizing $(\beta CD)_2x \cdot G$ complexes that depends on the nature of the guest species and that the linking of two βCD can lead to significant cooperativity in guest binding.

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Chiral Discrimination by Modified Cyclodextrins

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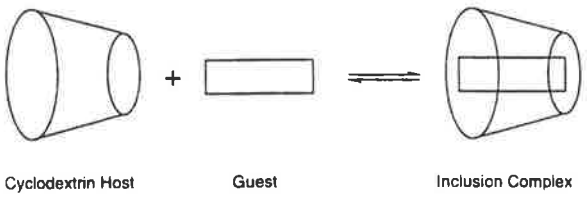
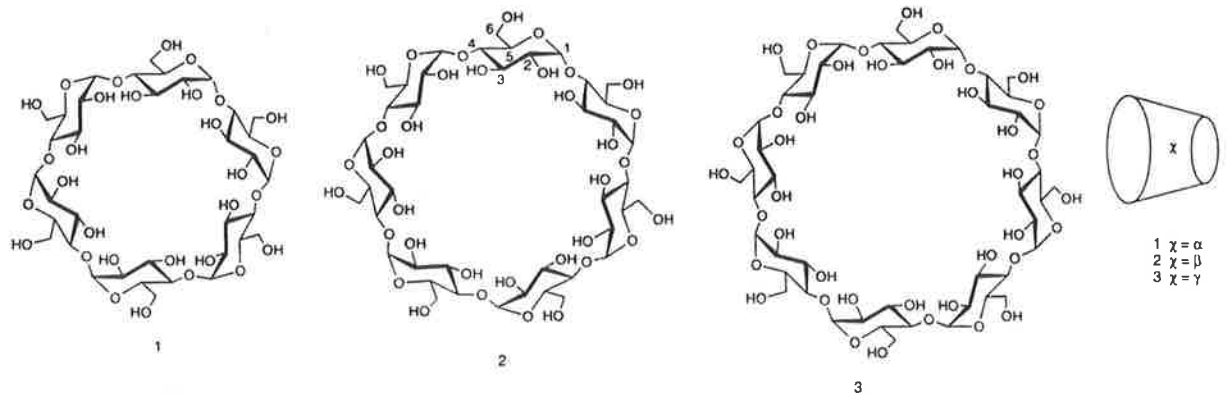
1 Introduction

The naturally occurring α-, β- and γ-cyclodextrins **1**—**3** are cyclic oligosaccharides, consisting of six, seven and eight α-1,4-linked D-glucopyranose units, respectively. Interest in these compounds stems from the fact that they act as host molecules to form inclusion complexes with a wide variety of guests (Scheme 1).[1] The cyclodextrins each exist as a single enantiomer, with the consequence that when they act as host molecules, interaction with a racemic guest may lead to the formation of diastereoisomeric complexes of differing thermodynamic stability. This chiral discrimination by unmodified cyclodextrins has been intensively studied and extensively exploited, most notably through the work of Armstrong *et al.*,[2] in the development of cyclodextrin-based chromatographic systems.

The extent of chiral discrimination displayed by the naturally occurring cyclodextrins is typically quite modest, however, with efficient resolution of racemates only resulting from repeated interactions with a cyclodextrin, as is the case with cyclodextrin-based chromatography. The low enantioselectivity may be attributed to the inherent symmetry of the cyclodextrins, with each having an axis of symmetry. In addition, inclusion complex formation often occurs principally as a result of interaction of the hydrophobic annulus of the cyclodextrin with an achiral hydrophobic portion of



Scheme 1 Inclusion complex association constant K = [inclusion complex]/([cyclodextrin host][guest]).



A truncated cone is often used to represent the torus of a cyclodextrin. A substituent drawn at the narrow end of the cone indicates that it replaces one of the C-6 hydroxy groups in the cyclodextrin, while a substituent drawn at the wide end of the cone indicates that it replaces either a C-2 or a C-3 hydroxy group.

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Stephen Lincoln is head of the department of chemistry at the University of Adelaide where he holds a personal chair. He was born in Suffolk and graduated BSc (Tech) with first class honours from UMIST in 1962. He then decided to see the world and graduated with a PhD from the University of Adelaide in 1966. He went on to a post-doctoral position at Washington State University, returning to Adelaide as a lecturer in 1968. He was awarded a DSc by the University of Manchester in 1984. His research interests include inorganic and bioinorganic mechanisms and molecular recognition chemistry.

a guest, and there is little interaction between the chiral centres of the cyclodextrin and those of the guest. It follows that increased chiral discrimination can be expected with modified cyclodextrins where, through the modification, the degree of asymmetry of the cyclodextrin has been increased and there is the possibility of greater interaction between chiral portions of the cyclodextrins and those of the guests.

Modifying cyclodextrins and their complexing characteristics usually involves substitution of one or more of the C-2, C-3 and C-6 hydroxy groups. The modifications may be divided into two categories. In one, the hydroxy substituents are substituted in a symmetric fashion to give a single modified cyclodextrin (*e.g.*, all the hydroxy groups may be substituted) or at random to give a complex mixture of cyclodextrins in which the average effect is that of a symmetric substitution. As we will show, this tends not to alter the symmetry of the cyclodextrin or the enantioselectivity that it displays. With the other type of modified cyclodextrin, either a single substituent or a specific combination of substituents is introduced. This may induce substantial changes in the asymmetry of the cyclodextrin and result in additional and more specific interactions between the chiral area of the guest and the asymmetry of the host, which restrict the geometry of binding, leading to greater enantioselectivity. The additional interactions between the cyclodextrin substituent and the host may be subdivided into secondary bonding interactions, metal complexation and covalent attachment. Again we will show that as the extent of the interaction between the cyclodextrin substituent and the guest increases, the magnitude of chiral discrimination often becomes greater.

In choosing examples to illustrate this review, we have restricted our selection to those for which thermodynamic and/or kinetic parameters of the homogeneous solution-phase interaction between the cyclodextrin and each enantiomer of the guest have been reported. We have not included results from heterogeneous systems, on the basis that they may depend on factors such as phase solubility and other medium and surface effects, and guest or cyclodextrin aggregate formation, rather than inclusion complex formation. It has been noted previously that little direct correlation exists between the retention times of molecules on cyclodextrin-based chromatography columns and the thermodynamic stability of the inclusion complexes formed in solution between those molecules and cyclodextrins.[3] Spectroscopic discrimination does not necessarily correlate with thermodynamic discrimination, so examples of the former are only discussed where they have been used to measure the thermodynamics of inclusion complex formation. Since our aim is to compare the chiral discrimination displayed by the natural and modified cyclodextrins, we have only included details of enantioselectivity shown by natural cyclodextrins where comparative data with cyclodextrin derivatives are available.

The values for cyclodextrin–guest association constants given herein are quoted directly from the primary literature. It should be noted that these data arise from work in various laboratories, with the result that a range of experimental conditions has been used. For this reason, key experimental parameters are indicated, to show the limits to which results from various studies are directly comparable. Nevertheless, there is remarkable consistency between the various experiments, with most studies being carried out in aqueous solution, at or near 298 K. Most importantly, identical conditions prevailed in all cases where comparisons are made between diastereoisomeric pairs of host–guest complexes.

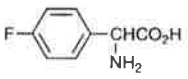
2 Effect of Additional Secondary Bonding Interactions

As mentioned above, symmetrically substituted cyclodextrins tend to show no greater chiral discrimination than the naturally occurring analogues. This holds even where the modification results in more favourable interactions between the racemic guest and cyclodextrin host, as reflected in much higher association constants for the diastereoisomeric inclusion complexes. For example, as shown in Table 1 (entries 1—12), the association constants of the inclusion

Table 1 Association constants of cyclodextrin inclusion complexes

Entry	Cyclodextrin	Guest	K_R/dm^3 mol^{-1}	K_S/dm^{3}mol^{-1}	K_R/K_S[a]	Ref.[b]
1	**1**	**4** + H$^-$	7.7 ± 0.3	8.2 ± 0.3	0.94	4
2	**7**	**4** + H$^-$	54 ± 3	59 ± 4	0.92	5
3	**1**	**4** − H$^-$	21.5 ± 0.4	22.5 ± 0.4	0.96	4
4	**7**	**4** − H$^-$	49 ± 3	55 ± 3	0.89	5
5	**1**	**5**	14.4 ± 0.1	14.6 ± 0.1	0.99	4
6	**7**	**5**	451 ± 7	434 ± 7	1.04	5
7	**1**	**5** − H$^-$	13.1 ± 0.5	14.1 ± 0.5	0.93	4
8	**7**	**5** − H$^-$	80 ± 3	77 ± 3	1.04	5
9	**1**	**6**	8.3 ± 0.3	8.3 ± 0.3	1.00	4
10	**7**	**6**	142 ± 6	155 ± 6	0.92	5
11	**1**	**6** − H$^-$	12.4 ± 0.3	10.6 ± 0.4	1.17	4
12	**7**	**6** − H$^-$	143 ± 6	153 ± 6	0.93	5
13	**1**	**10**	27 ± 3	17 ± 4	1.59	7
14	**2**	**10**	1090 ± 30	1010 ± 40	1.08	6
15	**7**	**10**	220 ± 10	207 ± 8	1.06	7
16	**8**	**10**	129 ± 5	170 ± 10	0.76	7
17	**2**	**10** − H$^-$	63 ± 8	52 ± 5	1.21	6
18	**9**	**10** − H$^-$	36 ± 6	13 ± 7	2.77	6
19	**13**[c]	**16**	14.7	10.8	1.36	11
20	**14**[d]	**16**	54.0 ± 7.6	42.5 ± 7.3	1.27	10,11
21	**15**[d]	**16**	45.5 ± 8.2	34.5 ± 5.7	1.32	10
22	**18**	**17**	295 ± 3	629 ± 10	0.47	13
23	**19**	**17**	160 ± 36	83 ± 28	1.93	12,13
24	**20**	**17**	139 ± 24	231 ± 45	0.60	12,13

[a] These ratios substantiate the trends referred to in the text, but it should be noted that standard deviations in the association constants of the diastereoisomeric pairs of inclusion complexes limit the reliability of the data. [b] Although a range of conditions has been used in measuring the association constants cited herein, in the text comparisons are only made of data recorded under similar conditions. Experimental conditions were as follows: refs. 4 and 5: solvent 10% aqueous D_2O, I = 0.10 mol dm^{-3}, T = 295.5 K; refs. 6 and 7: solvent H_2O, I = 0.10 mol dm^{-3}, T = 298.2 K; refs. 10 and 11: solvent H_2O, $Na_2B_4O_7$ (15.4×10^{-3} mol dm^{-3}) and H_3BO_3 (34.6×10^{-3} mol dm^{-3}), T = 298 K; refs. 12 and 13: solvent H_2O, 0.066 mol dm^{-3} phosphate, T = 298 K. [c] Compound **13** is a mixture of the 6^A,6^B-isomers, in which the primary hydroxy groups of two adjacent glucose residues of the cyclodextrin have been substituted. The association constants are the same for each isomer, within experimental error.[10,11] [d] Compounds **14** and **15** are 6^A,6^B-isomers, in which the primary hydroxy groups of two adjacent glucose residues of the cyclodextrin have been substituted. The structures of the 6^A,6^B-isomers **14** and **15** may be the reverse.[10,11]



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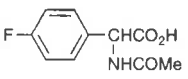

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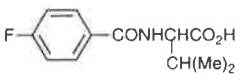

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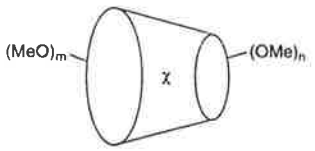
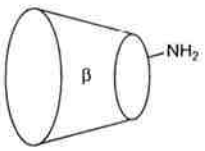


7 $\chi = \alpha$, m = 12, n = 6
8 $\chi = \beta$, m = 14, n = 7



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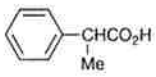

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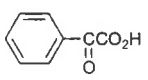
complexes of the variously protonated and deprotonated fluorinated amino acid derivatives **4**—**6** with termethylated α-cyclodextrin **7** are substantially greater than those formed with the parent α-cyclodextrin **1**, yet the enantioselectivity shown by the modified cyclodextrin **7** is little different from that displayed by α-cyclodextrin **1**.[4,5] Similarly, the extent of chiral discrimination displayed by the termethylated cyclodextrins **7** and **8** in the formation of inclusion complexes with the (*R*)- and (*S*)-enantiomers of 2-phenylpropanoic acid **10** is not much different from that exhibited by the natural cyclodextrin analogues **1** and **2** (Table 1, entries 13—16).[6,7] It is worth noting that the methyl substituents of the modified cyclodextrins **7** and **8** increase their flexibility as hosts. This flexibility allows conformational change to occur more easily, to accommodate a guest and increase complex stability, but it is unlikely to favour chiral discrimination. Conversely, lack of flexibility of the host and specific host–guest interactions should lead to increased enantioselectivity, but this is likely to correlate with the formation of less stable complexes. The association constants of the complexes of the enantiomers of the anion of 2-phenylpropanoic acid **10** with β-cyclodextrin **2** and the corresponding amine **9** (Table 1, entries 17 and 18)[6] provide a pertinent illustration. The enantioselectivity displayed by the modified cyclodextrin **9** is significantly greater but the association constants are lower, indicating a specific and unfavourable effect of the amino substituent of the host **9** on complexation of the propanoate guest. The enhanced stereoselectivity displayed by the amino-substituted cyclodextrin **9** in the formation of inclusion complexes is reflected by an increase in asymmetric induction in reactions of included guests.[8,9] While the sodium borohydride reduction of benzoylformic acid **11** in the presence of β-cyclodextrin **2** gave the (*R*)-enantiomer of the alcohol **12** in 4% enantiomeric excess, a 13% excess was obtained when the reaction was performed in the presence of the amino-substituted cyclodextrin **9**. The effect of the modified cyclodextrin **9** was attributed to electrostatic interaction between the amino substituent of the cyclodextrin **9** and the carboxy moiety of benzoylformic acid **11**.



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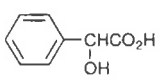

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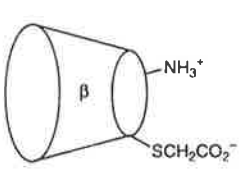
With an increase in the number of interactions between the guest and substituents introduced on to the modified host, greater chiral discrimination by the host could be expected. Tabushi *et al.*,[10,11] synthesised the modified cyclodextrins **13**—**15**, having both positively and negatively charged substituents, and investigated their behaviour as chiral artificial receptors for tryptophan **16** (Fig. 1). Each of the modified cyclodextrins **13**—**15** displayed a modest degree of enantioselectivity (Table 1, entries 19—21). The stability



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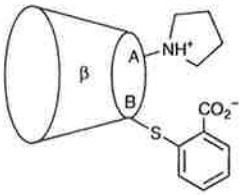

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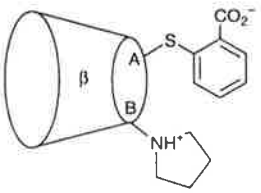

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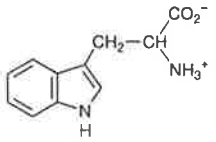

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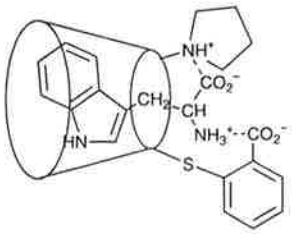
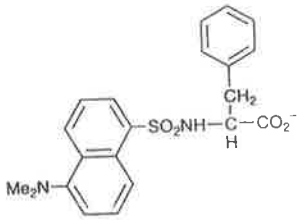


Figure 1 Schematic representation of the complexation of tryptophan **16** by the modified cyclodextrin **14**.

constants of the complexes were found to be larger in the cases of the cyclodextrins **14** and **15**, than those observed with the analogue **13**, and this was attributed to greater polar interactions between the guest and host when the host substituents were in a relatively non-polar environment. The greater polar interactions were not reflected in enhanced chiral discrimination, however, as the enantioselectivity displayed by the cyclodextrins **13**—**15** was quite similar.

An alternative facet of enantioselective guest complexation by a modified cyclodextrin was reported by Takahashi *et al.*[12,13] Amino acid-substituted cyclodextrins formed diastereoisomeric complexes with the *N*-dansylphenylalanine anion **17**; in the case of the tyrosine



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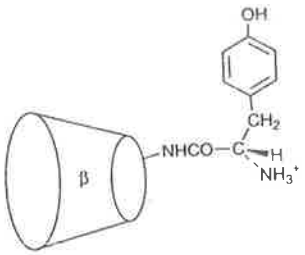

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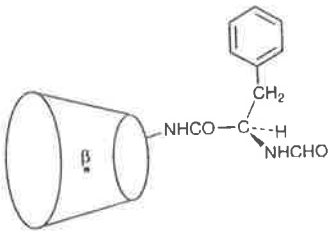

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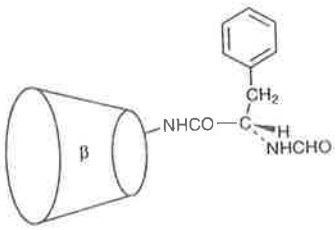

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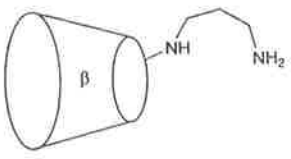
derivative **18** their association constants differed by a factor of 2.13 (Table 1, entry 22). In this case, where the substituent of the modified cyclodextrin is chiral, the cyclodextrin annulus probably serves mainly to bind the guest and contributes little towards the enantioselectivity. Instead stereoselectivity probably results from interactions between the chiral substituent of the cyclodextrin and chiral portions of the guest. Support for this interpretation comes from the observation that the enantioselectivity displayed by the modified cyclodextrin diastereoisomers **19** and **20** in complexing the *N*-dansylphenylalanine anion **17** is similar in magnitude, though reversed in terms of absolute stereochemistry (Table 1, entries 23 and 24).[12,13]

3 Metallocyclodextrins

The examples given above show that secondary bonding interactions between included guests and substituents of modified cyclodextrins can lead to greater stereoselectivity in the formation of inclusion complexes. Nevertheless the association constants of the diastereoisomeric inclusion complexes differ by no greater than a factor of three and generally by much less. Through metal complexation, which further increases the extent of interaction between the cyclodextrin and the guest, the diastereoselectivity can be further improved. This involves the coordination of both the cyclodextrin substituent and the guest to a metal in the host–guest complex, as a result of which the binding geometry can be quite restricted.

The tenfold chiral discrimination displayed by the nickel(II) complex **22** (M = Ni) of 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin **21** in the formation of inclusion complexes with the enantiomers of the anion of tryptophan **16** (Table 2, entry 3) is the largest reported for a metallocyclodextrin.[14,15] Comparison of the association constants of the inclusion complexes of the metallocyclodextrin **22** (M = Ni) with those of the complexes formed in the absence of a metal and with the parent β-cyclodextrin **2** (Table 2, entries 1—3) provides an insight into the origin of this enantioselectivity. There is no chiral discrimination in the formation of the diastereoisomeric inclusion complexes of the enantiomers of the anion of tryptophan **16** with β-cyclodextrin **2** or with the aminopropylamino-substituted cyclodextrin **21**, although the thermodynamic stability of the complexes is greater with the modified cyclodextrin **21**. The thermodynamic stability of the ternary complex of each enantiomer of the anion of tryptophan **16** with the metallocyclodextrin **22** (M = Ni) is even greater, showing the presence of even more favourable interactions. By comparison with the complexation constant for the interaction between the anion of tryptophan **16** and nickel(II) (Table 3, entry 2), the ternary complexes are less stable, however, indicating that the cyclodextrin annulus disrupts coordination of the anion of tryptophan **16** to nickel(II). The extent of these unfavourable interactions appears to depend on the chirality of the anion of tryptophan **16**, thus affecting the enantioselectivity.

The adverse effect of the cyclodextrin on the thermodynamic stability of the ternary complex is also apparent, though less marked, in the interaction of the anion of tryptophan **16** with the cobalt(II) and copper(II) complexes **22** (M = Co) and **22** (M = Cu) of the aminopropylamino-substituted cyclodextrin **21** (Table 2, entries 4 and 5; Table 3, entries 4 and 6).[15] These metallocyclodextrins also display enantioselectivity but to a lesser extent than that displayed by the nickel(II) complex **22** (M = Ni). By contrast, the



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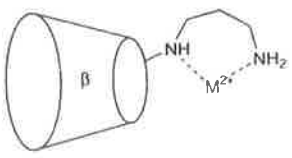

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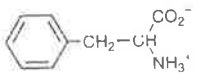

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Table 2 Association constants of metallocyclodextrin inclusion complexes[a]

Entry	Cyclodextrin	Guest	log (K_R/dm^3 mol^{-1})	log (K_S/dm^3 mol^{-1})	K_R/K_S	Ref.
1	**2**	**16** − H$^+$	2.33 ± 0.06	2.33 ± 0.08	1.00	14,15
2	**21**	**16** − H$^+$	3.41 ± 0.05	3.40 ± 0.07	1.00	14,15
3	**22** (M = Ni)	**16** − H$^+$	4.1 ± 0.2	5.1 ± 0.2	0.10	14,15
4	**22** (M = Co)	**16** − H$^+$	4.04 ± 0.03	4.32 ± 0.05	0.53	15
5	**22** (M = Cu)	**16** − H$^+$	7.85 ± 0.07	8.09 ± 0.05	0.58	15
6	**22** (M = Zn)	**16** − H$^+$	5.3 ± 0.1	5.3 ± 0.1	1.00	15
7	**22** (M = Ni)	**23** − H$^+$	< 3.6	4.4 ± 0.1	<0.16	16
8	**22** (M = Co)	**23** − H$^+$	3.6 ± 0.2	3.69 ± 0.06	0.81	16
9	**22** (M = Cu)	**23** − H$^+$	7.2 ± 0.1	6.9 ± 0.1	2.00	16
10	**22** (M = Zn)	**23** − H$^+$	4.7 ± 0.1	4.7 ± 0.1	1.00	16

[a] In H_2O, I = 0.10 mol dm^{-3}, T = 298.2 K.

Table 3 Metal complexation constants[a]

Entry	Metal	Ligand	log (K/dm^3 mol^{-1})	Ref.
1	Ni^{2+}	**21**	5.2 ± 0.1	14,15
2	Ni^{2+}	**16** − H$^+$	5.42 ± 0.03	14,15
3	Co^{2+}	**21**	4.22 ± 0.02	15
4	Co^{2+}	**16** − H$^+$	4.41 ± 0.05	15
5	Cu^{2+}	**21**	7.35 + 0.04	15
6	Cu^{2+}	**16** − H$^+$	8.11 ± 0.03	15
7	Zn^{2+}	**21**	4.96 ± 0.08	15
8	Zn^{2+}	**16** − H$^+$	4.90 ± 0.04	15
9	Ni^{2+}	**23** − H$^+$	5.09 + 0.05	16
10	Co^{2+}	**23** − H$^+$	4.19 ± 0.03	16
11	Cu^{2+}	**23** − H$^+$	7.8 ± 0.1	16
12	Zn^{2+}	**23** − H$^+$	4.59 ± 0.04	16

[a] In H_2O, I = 0.10 mol dm^{-3}, T = 298.2 K.

diastereoisomeric ternary complexes **22** (M = Zn) of the anion of tryptophan **16**, zinc(II) and the modified cyclodextrin **21** are thermodynamically indistinguishable (Table 2, entry 6), but more stable than the binary complexes of zinc(II) with the modified cyclodextrin **21** and of the anion of tryptophan **21** with the metal ion alone (Table 3, entries 7 and 8). It seems that enantioselectivity only results from unfavourable interactions in the ternary complexes which restrict the geometry of binding.

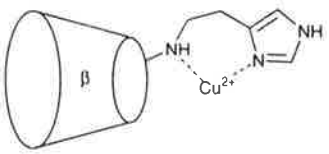
Analogous effects were observed in the formation of ternary complexes of the metallocyclodextrins **22** with the anion of phenylalanine **23** (Table 2, entries 7—10; Table 3, entries 9—12).[16] The enantioselectivity was greatest with the nickel(II) metallocyclodextrin **22** (M = Ni), decreasing in the order nickel(II) > copper(II) ≈ cobalt(II) > zinc(II). Again this order correlates with the extent to which the cyclodextrin disrupts the binding of the guest to the metal. The discrimination displayed by the nickel(II) and cobalt(II) metallocyclodextrins **22** (M = Ni) and **22** (M = Co) favours binding of the (*S*)-enantiomers of the anions of tryptophan **16** and phenylalanine **23**. The discrimination of the copper(II) metallocyclodextrin **22** (M = Cu) favours binding of the (*S*)-enantiomer of the anion of tryptophan **16** and the (*R*)-enantiomer of the anion of phenylalanine **23**.

While the work carried out to date with the metal complexes of the aminopropylamino-substituted cyclodextrin **21** has been mostly limited to studies with the anions of tryptophan **16** and phenylalanine **23** as guests, a more extensive range of amino acids has been used to investigate chiral discrimination by the copper(II) complexed histamine-monofunctionalised β-cyclodextrin **24** (Table 4).[17,18] In this case the metallocyclodextrin **24** displayed enantioselectivity in the complexation of the anions of the aromatic amino acids, tryptophan **16**, phenylalanine **23** and tyrosine **25**, with the stability constant of the complex of the (*R*)-enantiomer being the

Table 4 Association constants of copper(II) ternary complexes of the cyclodextrin **24** with amino acid anions[a]

Entry	Amino acid	log (K_R/ dm^3 mol^{-1})	log (K_S/ dm^3 mol^{-1})	K_R/K_S	Ref.
1	**16** − H$^+$	16.47 ± 0.02	16.12 ± 0.01	2.23	17,18
2	**23** − H$^+$	15.85 ± 0.01	15.68 ± 0.02	1.48	18
3	**25** − H$^+$	15.22 ± 0.01	14.82 ± 0.01	2.51	18
4	**26** − H$^+$	15.51 ± 0.02	15.53 ± 0.04	0.96	17,18
5	**27** − H$^+$	14.87 ± 0.05	14.80 ± 0.02	1.17	18
6	**28** − H$^+$	14.96 ± 0.02	14.89 ± 0.02	1.18	18

[a] In H_2O, I = 0.10 mol dm^{-3}, T = 298 K.



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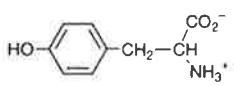

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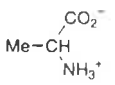

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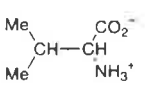

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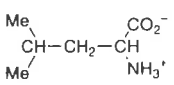

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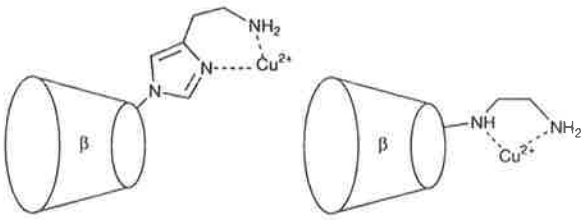
larger in each case. By comparison, the diastereoisomeric pairs of ternary complexes of the anions of the aliphatic amino acids **26**—**28** showed only small differences in thermodynamic stability. In this work, calorimetric studies were carried out in order to examine the factors contributing to the enantioselectivity. The overall complexation process for each of the amino acids was found to be enthalpically and entropically favoured. For the complexes of aromatic amino acids, however, the enthalpy contribution was found to be more favourable for the (*R*)-enantiomers, while the entropy factor was less favourable. This indicates that the geometry of complexation of the (*R*)-enantiomers is more restricted but the binding interactions in the complexes are stronger, and is consistent with a model in which the complexation of the (*R*)-enantiomers is favoured by the preferential inclusion of their aromatic side chains in the cyclodextrin cavity.

The histamine-substituted metallocyclodextrin **24** also displayed spectroscopic and chromatographic chiral discrimination in the complexation of amino acid anions, and the extent of chromatographic discrimination for various amino acids paralleled the thermodynamic enantioselectivity.[17,18] Interestingly the isomeric metallocyclodextrin **29** showed even greater enantioselectivity when used in chromatography with the anion of tryptophan **16**[19] but no thermodynamic data for this discrimination have been reported. The copper(II)-complexed aminoethylamino-substituted cyclodextrin **30** also displayed chromatographic and spectroscopic discrimination in complexing the anion of tryptophan **16**, but there was no thermodynamic enantioselectivity in this case.[20] Again this illustrates the lack of correlation between thermodynamic, and chromatographic and spectroscopic effects. In this regard, while the spectroscopic discrimination displayed by lanthanide–cyclodextrin complexes[21] and the enantiodiscriminating oxygenation of α-pinene using a porphyrin-substituted cyclodextrin[22] are interesting examples of exploitation of the enantioselectivity displayed by metallocyclodextrins, they are difficult to evaluate further in the absence of thermodynamic data.



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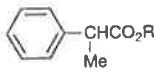
Although only a limited number of studies of chiral discrimination by metallocyclodextrins have been reported, they are sufficient to support the hypothesis, stated above, that coordination of both the cyclodextrin and the guest to a metal, which increases the extent of interaction between the cyclodextrin and the guest, will generally increase the enantiodiscrimination. It is likely that even greater stereoselectivity can be expected where the substituent attached to the cyclodextrin and coordinating the metal is chiral, thus increasing the asymmetry of the complex, though this has yet to be tested.

4 Covalent Interactions

An alternative form of interaction between cyclodextrins and guests, which also leads to enhanced enantioselectivity, involves the formation of a covalent bond between the host and guest in the inclusion complex. The hydrolysis of esters by cyclodextrins has been intensively studied as a model of covalent catalysis by enzymes.[23] The process involves the formation of a host–guest complex between a cyclodextrin and an ester, then transesterification between host and guest, followed by hydrolysis of the acylated cyclodextrin. The interest in cyclodextrins as enzyme mimics stems from the fact that they enhance the rates of reaction of included esters and they show enantioselectivity in the case of chiral derivatives.[24—32] In principal, the chiral discrimination could arise either from stereoselectivity in the formation of the host–guest complexes or from different reactivities of the guests in the diastereoisomeric complexes, or from a combination of these processes. In practice, more substantial stereoselectivity has usually arisen from differences in the reactivity of the complexed species.[25—30] This is illustrated by the association constants for complexation of the phenylpropionates **31** by α- and β-cyclodextrin **1** and **2** and the rate constants for the reactions of the complexed species (Table 5).[26] An overall enantioselectivity of 19.0 was observed for the interaction of the ester **31b** with β-cyclodextrin **2**, that figure comprising factors of 1.2 for the complexation and 15.5 for the reactions of the complexed species.



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a) R = C_6H_4-*p*-NO_2
b) R = C_6H_4-*m*-NO_2

Table 5 Thermodynamic parameters[a] for interaction of the esters **31** with cyclodextrins[26]

Cyclodextrin	Ester	K_R/K_S[b]	k_{cR}/k_{cS}[c]	$(k_{cR}K_R)/(k_{cR}K_S)$
1	**31a**	1.33	1.2	1.6
1	**31b**	1.07	8.7	9.3
2	**31a**	—	9.5	—
2	**31b**	1.22	15.5	19.0

[a] In H_2O, 0.2×10^{-3} mol dm^{-3} sodium carbonate buffer, T = 298 K. [b] Ratio of the association constants for the enantiomers. [c] Ratio of the rate constants for the reactions of the complexed species.

It has been clearly demonstrated that the enantioselectivity displayed by the cyclodextrin depends on the extent to which the geometry of binding and transesterification has been restricted. Trainor and Breslow[28] showed that freezing out residual rotational degrees of freedom in the acylation transition state increased the enantioselectivity shown by the cyclodextrin. The enantiomers **33** and **34** correspond to one of the preferred conformers of the ester **32**, and β-cyclodextrin **2** was found to accelerate their rates of reaction to extents approximately ten times and one half, respectively, of that observed with the ester **32** (Table 6). The esters **35** and **36** correspond to the enantiomers of the other preferred conformer of the ester **32**, and the enantioselectivity observed in their reactions with β-cyclodextrin **2** was much less. A further minor modification to the geometry of the cyclodextrin acylation, in the reactions of the esters **37** and **38**, resulted in a 62-fold enantioselectivity (Table 6).[29] This is the largest reported for hydrolysis of an ester by a cyclodextrin.

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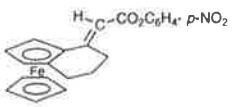

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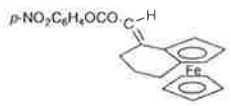

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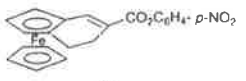

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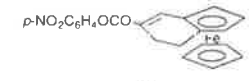

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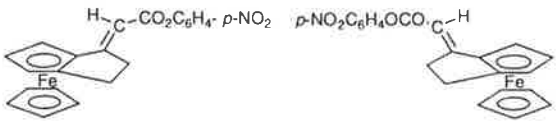
Table 6 Rate accelerations for reactions of esters complexed by β-cyclodextrin **2**[a]

Ester	k_c/k_{un} ($\times 10^{-4}$)	Ref.
32	36	28
33	16	28
34	320	28
35	1.0	28
36	6.6	28
37	590	29
38	9.5	29

[a] In 60% Me_2SO / 40% H_2O (v/v), T = 303 K.



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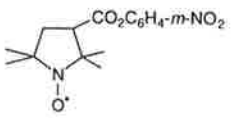
Frequently, studies of the interactions of cyclodextrins with esters have concentrated on the formation of the host–guest complexes and the subsequent transesterification, and the possibility of diastereoselective hydrolysis of the acylated cyclodextrins has often not been examined. Deacylation of the cyclodextrin **40** was investigated as part of a study of the reaction of the ester **39** with α-cyclodextrin **1**.[30]



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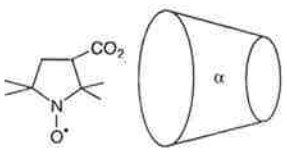

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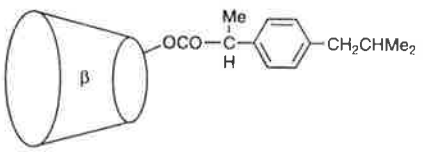

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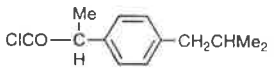
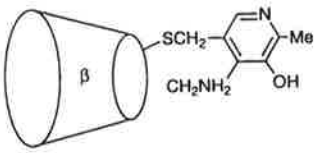


42

The reaction occurred without diastereoselectivity, as was the case with formation of the inclusion complexes between the ester **39** and α-cyclodextrin **1**, although the rates of reaction of the included enantiomers of the ester **39**, to give the acylated cyclodextrin **40**, differed by a factor of 7. More recently, we reported a tenfold diastereoselectivity in the hydrolysis of the cyclodextrin **41**.[31,32] The synthesis of the ester **41** through reaction of the Ibuprofen acid chloride **42** with β-cyclodextrin **2** afforded a 5:1 mixture of the diastereoisomers, in favour of the isomer derived from (*R*)-Ibuprofen, and that diastereoisomer was also the most readily hydrolysed. Consequently the overall stereoselectivity for the two-step reaction of the acid chloride **42** is *ca.* 50:1. The complementary nature of the diastereoselectivity of the synthesis and hydrolysis was attributed to similarities between the reaction transition states. The contrast in diastereoselectivity in the reactions of the esters **40** and **41** is not surprising, given the differences between these systems. The acyl substituents of the esters **40** and **41** are bound *via* secondary and primary hydroxy groups, respectively. In addition, the acyl group of the Ibuprofen derivative **41** is more hydrophobic and is more likely to interact with the cyclodextrin annulus.

Stereoselectivity has also been observed in a variety of other reactions where the guests become covalently bound to the cyclodextrins. Enantioselectivity has been found in the acylation of cyclodextrins with 5(4*H*)-oxazolones,[33,34] in reactions which are mechanistically quite similar to those of esters interacting with cyclodextrins. A variety of Schiff base derivatives of cyclodextrins has been synthesised and studied as models of pyridoxal phosphate-dependent enzymes. Breslow *et al.*,[35] reported the synthesis of the pyridoxamine derivative **43** and showed that in the reaction of this compound with phenylpyruvic acid **44**, phenylalanine **23** was produced as a 5:1 mixture of the (*S*)- and (*R*)-enantiomers. With the related cyclodextrin derivative **45**, Tabushi *et al.*,[11,36] reported much higher stereoselectivity in the reactions of ketoacids, producing the (*S*)-isomers of phenylalanine **23**, tryptophan **16** and phenylglycine **46**, each in at least 90% enantiomeric excess.



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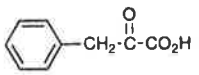

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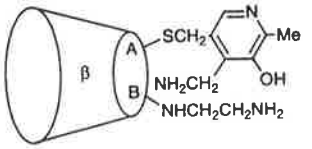

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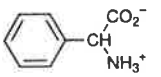

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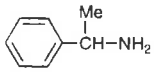
Recently we reported high enantioselectivity in the reactions of 2-phenylethylamine **47** with the iodocyclodextrin **48** to give the diastereoisomers of the amine **49**.[37] In further experiments aimed to elucidate the thermodynamic parameters of those interactions, we have now found that the extent of the stereoselectivity is highly irregular, however, and is generally much less than was observed originally. Currently we are examining the possibility that ternary complexes may be involved in these processes.



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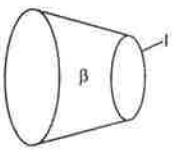

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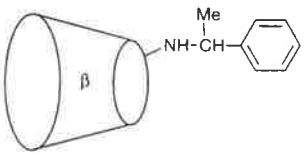

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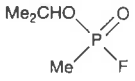

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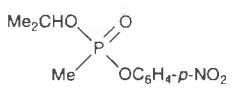

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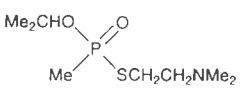

52

With Sarin **50**, the compound used recently in terrorist attacks in Japan, the reaction with α-cyclodextrin **2** proceeds by inclusion complex formation, followed by phosphonylation of the cyclodextrin, and each of these processes is stereoselective (Table 7).[38,39] The reactions of α-cyclodextrin **1** with the related phosphonate **51** and phosphonothioate **52** are also highly stereoselective (Table 7).[39,40] The high enantiomeric selectivity reported in the cleavage of organophosphates may be attributed to the fact that the reaction takes place directly at the chiral centre, further supporting the hypothesis developed throughout this review, that higher stereoselectivity will result from a more intimate interaction between the chiral centres of the cyclodextrins and the guests.

Table 7 Thermodynamic parameters[a] for interaction of α-cyclodextrin **1** with the organophosphorus compounds **50**—**52**[38—40]

Guest	K_R/K_S[b]	k_{cR}/k_{cS}[c]	$(k_{cR}K_R)/(k_{cS}K_S)$
50	0.15	3.5	0.52
51	0.38	≥ 76	≥ 29
52	1.91	> 100	> 191

[a] In H_2O, I = 0.10 mol dm^{-3}, T = 298 K. [b] Ratio of the association constants for the enantiomers. [c] Ratio of the rate constants for the reactions of the complexed species.

5 Conclusion

In summary, it is apparent from the work reviewed here that the naturally occurring cyclodextrins show only limited enantioselectivity in their interactions with chiral guests, because they form inclusion complexes in which there is only minimal interaction between chiral centres of the cyclodextrin and chiral substituents of the guests. As the extent of interaction between these groups is increased, as a result of modification to the cyclodextrin, the stereoselectivity is often increased. The immediate result of this improved stereoselectivity is that, whereas separation of racemic guests using the naturally occurring cyclodextrins requires multiple interactions between the host and guest, more efficient, practical and larger-scale resolutions should be possible with the modified cyclodextrins.

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Stereoselective Synthesis of (2*S*,3*S*)-γ-Hydroxyvaline Utilising an Asymmetric Radical Hydrogen Bromide Addition

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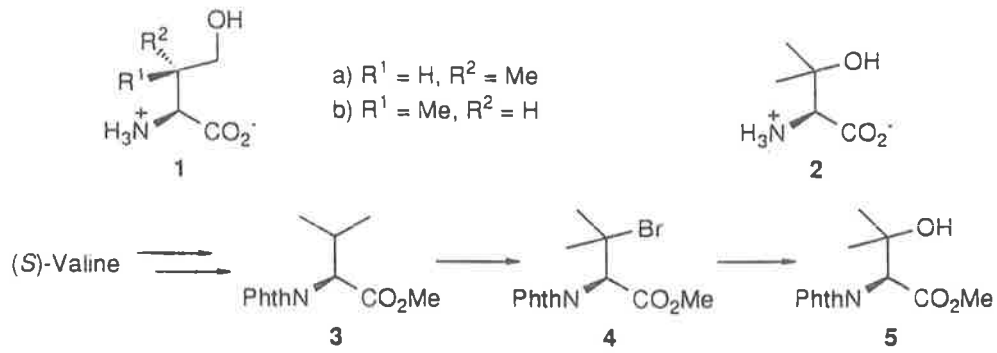
Abstract: (*S*)-Valine has been utilised in the stereocontrolled synthesis of (2*S*,3*S*)-γ-hydroxyvaline. The selectivity was achieved *via* 1,2-asymmetric induction in the *anti*-Markovnikov hydrobromination of a β,γ-dehydrovaline derivative. The relative and absolute stereochemistry of the γ-hydroxyvaline was determined using a variety of methods, including a nuclear Overhauser enhancement experiment with the diastereomeric lactones of γ-hydroxy-*N*-phthaloylvaline, and the synthetic material was shown to be identical to the natural product. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

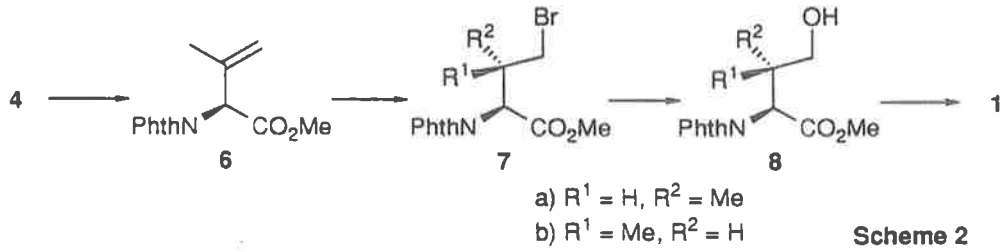
Hydroxy-substituted amino acids are an important class of natural products. They have been used in synthesis,[1] as enzyme inhibitors[2] and as probes in studies of biochemical pathways,[3] and many are constituents of biologically active peptides.[4] As a particular example, γ-hydroxyvaline has been isolated from the plant species *Kalanchoe daigremontiana*,[5] and it has since been used to determine the infidelity of the proof reading mechanism of the amino acylation of tRNA by valyl-tRNA synthetases, from *Saccharomyces cerevisiae* and *Escherichia coli*.[3] Given the importance of hydroxylated amino acids, there is much interest in routes for the stereocontrolled synthesis of these compounds. γ-Hydroxyvaline has been prepared previously.[6-9] One approach involved radical chlorination of (*S*)-valine, using either sulfuryl chloride[6] or chlorine,[9] followed by hydrolysis of the product chlorides to give a mixture of diastereomers of γ-hydroxyvaline.[6] The isomers were separated by crystallisation, affording the (2*S*,3*S*)-isomer **1a** in 6% yield, and the diastereomer **1b** in 0.2% yield.[6] Other syntheses afforded racemic mixtures.[7,8]

Recently it has been shown that treatment of *N*-phthaloyl-protected amino acid derivatives with *N*-bromosuccinimide results in side-chain bromination, and treatment of the product bromides with aqueous silver salts in acetone affords the corresponding hydroxy amino acid derivatives.[10-12] This procedure has been used in the stereocontrolled synthesis of hydroxy amino acid derivatives from readily available proteinogenic precursors, as illustrated by the synthesis of the β-hydroxyvaline derivative **5** from (*S*)-valine (Scheme 1).[12] The regioselectivity of the reaction is determined in the bromination, and is therefore limited to the site of the most stable side chain radical.[12-14] For example, while the derivative **5** of (*S*)-β-hydroxyvaline **2** can be obtained from the corresponding bromide **4**,[12] the derivatives **8a** and **8b** of γ-hydroxyvaline cannot be obtained directly using this approach. One aim of the work presented here was to manipulate the bromovaline derivative **4** for the stereocontrolled synthesis of isomers of γ-hydroxyvaline.



Scheme 1

It was envisaged that the (2*S*,3*S*)-isomer **1a** and the (2*S*,3*R*)-diastereomer **1b** of γ-hydroxyvaline could be obtained as shown in Scheme 2, *via* an elimination reaction of the bromide **4**, followed by an *anti*-Markovnikov hydrogen bromide addition. The latter reaction was also of interest due to the possibility of stereoselectivity. There have been many recent reports of 1,2-stereoinduction in radical reactions.[15,16] The stereochemical outcome of these processes has been attributed to a combination of minimised 1,3-allylic strain (A-strain), torsional strain, stereoelectronic effects and intramolecular hydrogen bonding.[15,16] A final goal of the present work was to determine the stereochemistry of γ-hydroxyvaline from *Kalanchoe daigremontiana*.[5]



Scheme 2

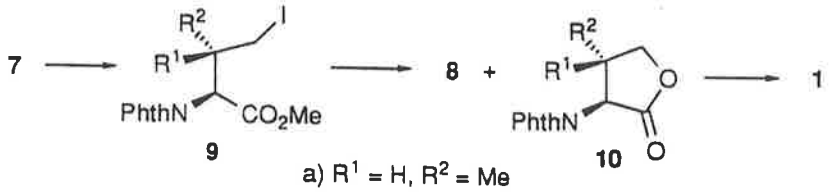
RESULTS AND DISCUSSION

The bromide **4** was prepared as reported previously.[12] A variety of methods were examined for the conversion of the bromide **4** into the alkene **6**. The reactions were complicated by competing formation of the corresponding α,β-dehydrovaline derivative and, in some cases, products of substitution of the bromine. The optimal conditions involved treatment of the bromide **4** with silver nitrate in anhydrous methanol, which gave the β,γ-dehydrovaline derivative **6** in 42% yield, after purification through repeated chromatography. This synthesis of the alkene **6** is complementary to that reported by Griesbeck *et al.*,[17] which involves photolysis of the valine derivative **3**, followed by oxidation. Hydrogen bromide was added to the alkene **6** by passing a dry stream of the gas through a solution of the alkene **6** in carbon tetrachloride at 0 °C, whilst irradiating the mixture with a 250 W mercury sunlamp. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed the presence of the diastereomeric γ-bromides **7a** and **7b**, in a 2.2:1 ratio. The diastereomers **7a** and **7b** were inseparable using chromatography on silica and the crude mixture was therefore used without purification.

Hydrolysis of the bromides **7a** and **7b** to the corresponding alcohols **8a** and **8b** was initially attempted by treatment with aqueous silver nitrate in acetone, first at room temperature, then at reflux, but no reaction occurred. Therefore, to facilitate the substitution reaction, the bromides **7a** and **7b** were converted

into the corresponding iodides **9a** and **9b** using sodium iodide in acetone. Treatment of the crude iodides **9a** and **9b** with aqueous silver nitrate in acetone at room temperature gave a mixture which contained the lactone **10a** and the alcohols **8a** and **8b**. Acidic hydrolysis of the mixture, followed by purification by ion exchange chromatography, gave a 3:1 mixture of the γ-hydroxyvaline diastereomers **1a** and **1b**, in 60% yield from the γ-bromides **7a** and **7b** (Scheme 3). The major isomer **1a** was separated from the mixture by fractional crystallisation, and isolated as a white crystalline solid.

The relative stereochemistry of the γ-hydroxyvaline diastereomers **1a** and **1b** is apparent from comparison of their ^{1}H NMR spectra with literature data.[6] Signals for the methyl group and the α-hydrogen occur as doublets at δ 0.94 and 3.85 for the isomer **1a**, indicating the (2*S*,3*S*)-stereochemistry, while the (2*S*,3*R*)-diastereomer **1b** shows the corresponding resonances at δ 1.02 and 3.74. The absolute stereochemistry of the alcohols **1a** and **1b** was confirmed by the optical rotation of the diastereomer **1a**.[6]



a) R^1 = H, R^2 = Me
b) R^1 = Me, R^2 = H

Scheme 3

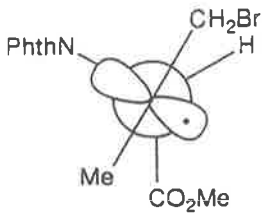
Repeated reactions of the iodides **9a** and **9b** with aqueous silver nitrate afforded various mixtures of the lactones **10a** and **10b** and the alcohols **8a** and **8b**, which were difficult to separate due to incomplete lactonisation of the alcohols **8a** and **8b**. For this reason, crude mixtures were used directly to synthesise the free amino acids **1a** and **1b**. On one occasion, a crude mixture from reaction of the iodides **9a** and **9b** was chromatographed on silica giving a *ca.* 6:1 mixture of the lactones **10a** and **10b**, in 67% yield.

The relative stereochemistry of the lactones **10a** and **10b** was determined using an NOE experiment. In the ^{1}H NMR spectrum, signals due to the H3, H4, H5 and H5' protons of the lactone **10b** occur at δ 5.01 (d, *J* 10.0 Hz), 3.06-2.90 (m), 4.66 (dd, *J* 8.4 and 8.7 Hz) and 4.26 (dd, *J* 8.0 and 8.7 Hz), respectively. Irradiation of the resonance centred at δ 2.98 affected the signals at δ 5.01 by +27%, at δ 4.66 by +0.2% and at δ 4.26 by -4.0%. The H3 and H5 protons of the lactone **10a** give rise to a multiplet at δ 4.66, while the H4 and H5' proton signals of that compound occur at δ 3.27-3.11 (m) and 3.98 (dd, *J* 9.2 and 10.3 Hz), respectively. Irradiation of the resonance at δ 3.20 affected the signals at δ 4.66 by +5.5% and at δ 3.98 by -1.7%. These values indicate a *syn*-relationship between the H3 and H4 protons of the isomer **10b**.

From the mass balance of the reactions, it is clear that the major iodide **9a** is derived from the predominant bromide **7a**, and it is the iodide **9a** which affords the lactone **10a** and the γ-hydroxyvaline **1a**. As expected, therefore, the stereochemistry of the lactone **10a** corresponds to that of the γ-hydroxyvaline **1a**. Using the same reasoning, the stereochemistry of the bromides **7a** and **7b** and the iodides **9a** and **9b** may be inferred from that of the alcohols **1a** and **1b**. The stereoselectivity which arises in hydrogen bromide addition to the alkene **6** can be attributed to delivery of hydrogen atom to the less hindered face of the intermediate radical **11**. The preferred conformation of the radical **11** results from minimising A-strain.[15]

Presumably the production of the 6:1 mixture of the lactones **10a** and **10b** from reaction of a 2.2:1 mixture of the iodides **9a** and **9b** is a consequence of selective lactonisation of the alcohol **8a**. This is in accord with the relative stereochemistry of the alcohols **8a** and **8b**. In the conformation required for lactonisation, unfavourable steric interactions exist between the phthalimido and methyl substituents of the (2*S*,3*S*)-isomer **8a**. In contrast, these unfavourable interactions are not present for the (2*S*,3*R*)-isomer **8b**.

In order to determine the absolute stereochemistry of the natural product, γ-hydroxyvaline was isolated from the plant species *Kalanchoe daigremontiana* using the procedure outlined by Pollard *et al.*[5] This material was determined to be the (2*S*,3*S*)-isomer **1a**, using the procedure outlined above to assign the stereochemistry of the synthetic material. Consequently the synthesis constitutes a stereoselective preparation of the natural isomer **1a**.



11

EXPERIMENTAL

General. M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a GEMINI 300 spectrophotometer, in $CDCl_3$ with Me_4Si as the internal standard, unless otherwise stated. Electron impact mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Optical rotations were measured using a Perkin Elmer 241 polarimeter. Microanalyses were performed by Chemical and Microanalytical Services Pty. Ltd., Melbourne, Australia. Silica chromatography was performed on Merck-Keiselgel 60 (230-400 mesh ASTM), using ethyl acetate and light petroleum (b.p. 66-68 °C) as eluants. Organic solutions were dried over Na_2SO_4. All solvents were purified and dried using standard methods.

(S)-N-Phthaloyl-3,4-dehydrovaline Methyl Ester **6**. Silver nitrate (8.19 g, 48 mmol) was added to a solution of the bromovaline derivative **4**[12] (10.85 g, 32 mmol) in dry methanol (100 ml) over activated 4 Å sieves. The mixture was stirred at room temperature for 36 h in the dark, then saturated brine was added and the mixture was filtered. The filtrate was concentrated under reduced pressure, then the residue was partitioned between dichloromethane and water, and the organic layer was separated and concentrated. A ^{1}H NMR spectrum of the crude product showed that the β,γ-alkene **6** and the corresponding α,β-alkene were present in the ratio *ca.* 5:1. A portion of this material was chromatographed on silica to give the alkene **6** as a colourless oil (3.46 g, 42%). δ_H 7.75-7.92 (m, 4H), 5.38 (s, 1H), 5.14 (s, 1H), 5.11 (s, 1H), 3.79 (s, 3H), 1.92 (s, 3H). The ^{1}H NMR spectral data for this compound are consistent with those reported.[17]

(2S,3S)- and *(2S,3R)-4-Bromo-N-phthaloylvaline Methyl Ester* **7a** and **7b**. Through a solution of the β,γ-dehydrovaline derivative **6** (819 mg, 3.2 mmol) in carbon tetrachloride (50 ml), in an ice-water bath, was passed a dry stream of hydrogen bromide, for 5 mins. During this time, and for a further 40 mins, the solution was irradiated with a 250 W mercury sunlamp. The resultant solution was washed twice with water, then it was dried and concentrated under reduced pressure. The crude product was a colourless oil, which, when analysed using ^{1}H NMR spectrometry, showed a 2.2:1 mixture of the bromides **7a** and **7b** (944 mg, 88%). **7a** δ_H 7.78-7.94 (m, 4H, ArH), 5.02 (d, *J* 8.4 Hz, 1H, α-H), 3.90 (dd, *J* 5.1, 10.2 Hz, 1H, γ-H), 3.66 (dd, *J* 3.9, 10.2 Hz, 1H, γ'-H), 3.73 (s, 3H, OMe), 3.01 (m, 1H, β-H), 1.03 (d, *J* 6.9 Hz, 3H, β-Me); δ_C 168.2, 167.3, 134.2, 131.4, 123.5, 53.9, 52.5, 38.7, 34.8, 15.9; **7b** δ_H 7.78-7.94 (m, 4H, ArH), 4.91 (d, *J* 7.4 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.65 (dd, *J* 3.7, 10.3 Hz, 1H, γ-H), 3.25 (dd, *J* 6.8, 10.3 Hz, 1H, γ'-H), 3.01 (m, 1H, β-H), 1.30 (d, *J* 6.6 Hz, 3H, β-Me); δ_C 168.5, 167.2, 134.0, 131.3, 123.7, 54.7, 52.3, 36.9, 35.3, 16.7; *m/z* (%) 341 ($M^{+\bullet}$, 1%), 339 ($M^{+\bullet}$, 1), 281 (20), 279 (20), 219 (50), 201 (100), 199 (100); *m/z* 339.009 ($M^{+\bullet}$) [Calc. for $C_{14}H_{14}{}^{79}BrNO_4$ ($M^{+\bullet}$) *m/z* 339.016].

(2S,3S)- and *(2S,3R)-4-Iodo-N-phthaloylvaline Methyl Ester* **9a** and **9b**. A solution of a 2.2:1 mixture of the bromides **7a** and **7b** (944 mg, 2.8 mmol) and sodium iodide (1.28 g, 8.5 mmol) in acetone (40 ml) was heated at reflux for 2 h. After cooling to room temperature, the mixture was filtered and the

filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the solution was washed with aqueous sodium metabisulfite solution and water, then it was dried and concentrated under reduced pressure, to give a 2.2:1 mixture of the iodides **9a** and **9b** as a yellow oil. **9a** δ_H 7.76-7.97 (m, 4H, ArH), 4.89 (d, *J* 8.3 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.63 (dd, *J* 5.4, 10.2 Hz, 1H, γ-H), 3.50 (dd, *J* 3.9, 10.2 Hz, 1H, γ'-H), 2.59 (m, 1H, β-H), 0.99 (d, *J* 6.7 Hz, 1H, β-Me); **9b** δ_H 7.76-7.97 (m, 4H, ArH), 4.83 (d, *J* 7.3 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.47 (dd, *J* 3.8, 10.2 Hz, 1H, γ-H), 3.01 (dd, *J* 7.8, 10.2 Hz, 1H, γ'-H), 2.79 (m, 1H, β-H), 1.25 (d, *J* 6.5 Hz, 3H, β-Me). The unstable iodides **9a** and **9b** were not purified and were used in the following reaction without characterisation.

(2S,3S)-4-Hydroxyvaline **1a**. To a stirred solution of the crude iodides **9a** and **9b** in aqueous acetone (30 ml) was added silver nitrate (711 mg, 4.2 mmol). The mixture was stirred at room temperature in darkness for 60 h, then brine was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up in dichloromethane and the resultant solution was washed with brine, then dried and concentrated under reduced pressure. The crude product was analysed using ^{1}H NMR spectroscopy, which showed a mixture of the (3*S*,4*S*)-lactone **10a** and the alcohols **8a** and **8b**. **8a** δ_H 7.93-7.72 (m, 4H, ArH), 5.05 (d, *J* 5.4 Hz, 1H, α-H), 3.74 (s, 3H, OMe), 3.68 (dd, *J* 4.8, 11.8 Hz, 1H, γ-H), 3.39 (dd, *J* 8.3, 11.8 Hz, 1H, γ'-H), 2.82 (m, 1H, β-H), 0.93 (d, *J* 6.6 Hz, 3H, β-Me); **8b** δ_H 7.93-7.72 (m, 4H, ArH), 4.91 (d, *J* 6.3 Hz, 1H, α-H), 3.75 (s, 3H, OMe), 3.57 (dd, *J* 5.0, 12.0 Hz, 1H, γ-H), 3.51 (dd, *J* 6.6, 12.0 Hz, 1H, γ'-H), 2.79 (m, 1H, β-H), 1.10 (d, *J* 7.2 Hz, 3H, β-Me). The ^{1}H NMR spectral data for the lactone **10a** are given in the Results and Discussion.

The mixture containing the lactone **10a** and alcohols **8a** and **8b** was dissolved in a 2:1 mixture of 6 N hydrochloric and glacial acetic acid (25 ml), and the solution was heated at reflux for 4 h. After cooling to room temperature, the solution was concentrated under reduced pressure, then the residue was taken up in water and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in water, then the solution was applied to a column of Amberlite IR 120 cation exchange resin (NH_4^+ form). The column was washed with water (1 L), then eluted with aqueous ammonia solution (1 L). The eluate was boiled until no ammonia could be detected, then concentrated under reduced pressure affording a 3:1 mixture of the diastereomers **1a** and **1b** (223 mg, 60%). **1a** δ_H (D_2O) 3.85 (d, *J* 3.2 Hz, 1H, α-H), 3.69 (dd, *J* 5.2, 11.4 Hz, 1H, γ-H), 3.57 (dd, *J* 6.9, 11.4 Hz, 1H, γ'-H), 2.33 (m, 1H, β-H), 0.94 (d, *J* 7.2 Hz, 3H, Me); **1b** δ_H (D_2O) 3.74 (d, *J* 4.4 Hz, 1H, α-H), 3.64 (d, *J* 5.6 Hz, 2H, CH_2O), 2.17 (m, 1H, β-H), 1.02 (d, *J* 7.0 Hz, 3H, Me). Fractional crystallisation of this mixture from acetone and water afforded the (2*S*,3*S*)-isomer **1a** (94 mg, 25%), m.p. 219-221 °C (dec.) (Lit.[6] 212-214 °C (dec.)); δ_C (D_2O) 176.9, 67.0, 60.2, 38.4, 13.5; $[\alpha]_{365}^{24}$ +24.0° (c, 0.2 in H_2O) (Lit.[6] (2*S*,3*S*)-isomer **1a** +23.3°; (2*S*,3*R*)-isomer **1b** +26.4°); (Found: C, 45.0; H, 8.4; N, 10.5. Calc for $C_5H_{11}NO_3$: C, 45.1; H, 8.3; N, 10.5%).

(3S,4S)- and *(3S,4R)-4-Methyl-3-phthalimido-γ-butyrolactone* **10a** and **10b**. The title compounds were synthesised from a mixture of the iodides **9a** and **9b** by treatment with aqueous silver nitrate, using the procedure described above. In this case, however, the crude mixture was chromatographed on silica affording a *ca.* 6:1 mixture of the lactone diastereomers **10a** and **10b** as a colourless oil (607 mg, 67% from the bromides **7a** and **7b**). ν_{max}(neat)/cm^{-1} 3490, 2970, 1770, 1720, 1620, 1470, 1390, 1340, 1200, 1010. The ^{1}H NMR spectral data for the (3*S*,4*S*)-isomer **10a** and the (3*S*,4*R*)-diastereomer **10b** are given in the Results and Discussion. **10a+10b** *m/z* (%) 245 ($M^{+\bullet}$, 5%), 201 (25), 186 (100). *m/z* 245.070 ($M^{+\bullet}$) [Calc. for $C_{13}H_{11}NO_4$ ($M^{+\bullet}$) *m/z* 245.069]. (Found: C, 63.5; H, 5.0; N, 5.4. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N 5.7%).

Extraction of γ-hydroxyvaline from Kalanchoe diagremontiana. γ-Hydroxyvaline was isolated from the lyophilised leaves and stems (20 g) of *Kalanchoe diagremontiana* using the procedure outlined by Pollard *et al.*,[5] then recrystallised from acetone and water (43 mg, 0.2%), m.p. 208-214 °C (Lit.[6] 212-214 °C). $[\alpha]_{365}^{20}$ +22.0° (c, 0.44 in H_2O) (Lit.[6] (2*S*,3*S*)-isomer **1a** +23.3°; (2*S*,3*R*)-isomer **1b** +26.4°) The ^1H NMR spectral data for this material are identical to those given above for the synthesised (2*S*,3*S*)-isomer **1a**.

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Free-Radical Reactions in the Synthesis of α-Amino Acids and Derivatives

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Contents

I. Introduction

α-Amino acids are one type of the main building blocks of living systems, being the principal components of all naturally occurring peptides and proteins. Although only 20 compounds of this class occur commonly in biological systems, the group is much more diverse, with over 500 α-amino acids having been identified in nature.[1] These compounds and their derivatives display quite diverse physiological and pharmaceutical activity. As a consequence, methods for their synthesis have attracted a considerable amount of attention.[2-4]

In the past, most of the focus of amino acid synthesis has been on the use of ionic procedures. Until recently, free-radical reactions had received little attention, by comparison, in this and in many other areas of chemistry, because the potential to exploit radical reactions to achieve transformations in a controlled manner had not been recognized. Now, the realization that radical reactions can be accomplished in good yield, with a high degree of regio- and stereocontrol,[5-8] has aroused interest in this area. Often the products of the radical processes are quite distinct from those formed in ionic reactions of the same substrates, and under some circumstances the reagents and reaction conditions used in the free-radical procedures are more compatible with the functional groups present and the stability of the compounds involved.

The purpose of this review is to collate examples of the use of free-radical reactions in the synthesis of α-amino acids and their derivatives. The examples have been categorized according to the methods of generation of the amino acid radicals and the types of reactions that the radicals undergo. Reaction mechanisms and other factors governing the processes have been discussed, in order to draw correlations and reach general conclusions.

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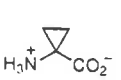
Since the emphasis of the review is on the use of radical reactions of amino acid derivatives in synthesis, examples are only included where reaction products have been isolated and the amino acid moieties have remained intact throughout the transformations. Accordingly, spectroscopic studies have not been surveyed and radiation studies, which result mainly in decarboxylation or deamination of amino acids, have not been incorporated. These aspects of the free-radical chemistry of amino acids have been the subjects of earlier reviews.[9-11] Many biochemical reactions involve amino acid radicals.[12] For example, there is strong evidence that free radicals are intermediates in penicillin and cephalosporin biosynthesis[13-26] and in the bioconversion of the cyclopropyl amino acid **1** to ethylene[27] during the maturation of fruits. Although it could be argued that these reactions involve amino acid radicals in synthesis, processes of this type are only discussed in this review when there has been a deliberate attempt to accomplish a transformation of a novel substrate using an enzyme.



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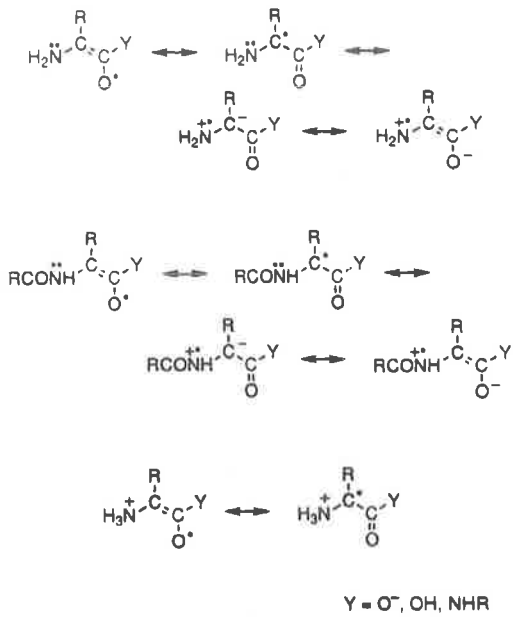


Figure 1. Resonance contributors of α-carbon-centered radicals.

The free radicals that form from amino acids and their derivatives may be divided into three classes: sulfur radicals, aromatic radicals, and aliphatic radicals. Of these, only the aliphatic radicals are characteristic of amino acids and, accordingly, they are the main topic of this review. Reactions involving sulfur radicals, such as those occurring with the thiol and disulfide bonds of cysteine and cystine, respectively, are not included. Material relating to aromatic radicals, such as phenolic coupling, has not been incorporated. Applications of phenolic coupling to the synthesis of peptide secondary metabolites, such as lysobactin and vancomycin, have been discussed recently.[28]

II. α-Carbon-Centered Radicals

The aliphatic radicals which are peculiar to amino acids and their derivatives are α-carbon-centered radicals.[29] When the amino group is present in the free-base form or protected as an amide, there is extensive delocalization of the unpaired spin density in a radical of this type (Figure 1), through the action of the electron-releasing amino or amido substituent and the electron-withdrawing carboxy group. These radicals belong to the class of captodative radicals. The captodative effect was postulated by Viehe *et al.*[30,31] as the combined resonance effect of electron-withdrawing (capto) and electron-donating (dative) substituents on a radical center, leading to enhanced stabilization of the radical. The theoretical basis of this concept was originally formulated by Dewar, in 1952.[32] Analogous concepts of "push–pull" stabilized radicals and merostabilization were independently developed by Balaban[33] and by Katritzky *et al.*,[34–36] respectively.

Much of the interest in this area has been aimed to determine the extent to which the combined stabilization provided by the substituents is synergistic.[37–45] The determination has not been straightforward, as it has been difficult to delineate the effects of radical stabilization from steric and polar effects, and other factors affecting radical formation. Nevertheless, it now seems clear that there is synergistic stabilization of amino carboxy substituted radicals[39,41,42,44–47] and additive, but not synergistic, stabilization of amido carboxy substituted radicals.[47] In any event, the extent of electron delocalization by the substituents is substantial, and the complementary electron-donating and electron-withdrawing effects of the substituents, to delocalize charge and unpaired spin density that develop in reaction transition states facilitate radical formation.[48] By comparison, when the amino group is protonated or quaternized, dative stabilization of a radical centered on the α-carbon does not occur (Figure 1).[46,49] Consequently these radicals are much less stable and much less easily formed. Not surprisingly, therefore, a recent study[50] on the aqueous solution thermochemistry of the radicals of glycine indicated that the α-carbon-centered radicals **2** and **3** are the most stable.

2 **3**

Given their relative instability, it is only as expected that reports of α-carbon-centered amino acid radicals having the amino group protonated or quaternized are rare. There has been a limited number of reports of radicals substituted with free amino groups, but the most common are those involving amido-substituted analogues. Presumably this latter observation is not a reflection of the relative stability of the amino- and amido-substituted radicals, as delocalization of the nitrogen electrons over the carbonyl group would be expected to decrease the extent of dative radical stabilization provided by an amido group. Instead it seems more likely that the predominance of examples of amido-substituted radicals reflects the compatibility of this moiety with the reagents, solvents, and reaction conditions used typically for free-radical transformations. By comparison, the basic conditions required to maintain an amino group in the nonprotonated form are incompatible with free-radical reactions such as halogenation, they limit the range of potential substrates to those that are base-stable, and they lead to competing electron-transfer reactions of amines, which result in deamination.

III. Hydrogen-Transfer Reactions

As mentioned above, free-radical reactions offer particular advantages where they afford products different from those obtained in ionic reactions of the same substrates, or where it is not possible to accomplish the same transformations in ionic processes. One reaction class for which this is particularly pertinent is that of hydrogen atom-transfer reactions. These provide the facility either to introduce a functional group or to form a carbon–carbon bond, by directly substituting for hydrogen at a position which need not be activated by adjacent

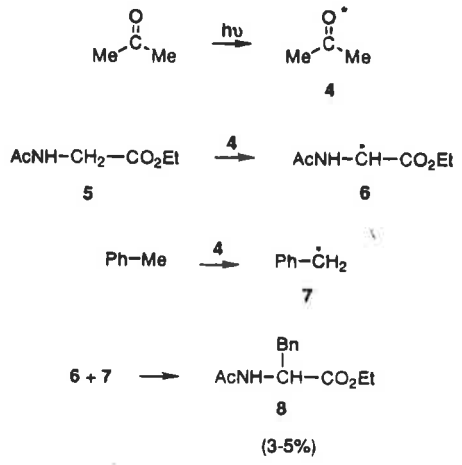
functional groups. The anionic counterparts of these processes involve quite strong bases, and the regioselectivity of proton transfer is typically quite different to that of hydrogen atom transfer, with aliphatic carbanions generally forming most easily at least-substituted positions, while the radicals form more readily at the most-substituted centers.

A. Intermolecular To Give α-Carbon-Centered Radicals

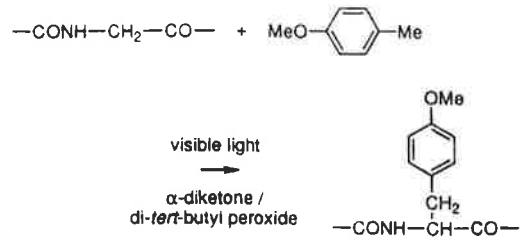
Most intermolecular hydrogen atom-transfer reactions of amino acid derivatives afford mainly α-carbon-centered radicals, presumably as a result of the particular stability of these species, as outlined above. Many examples of these involve hydrogen transfer from derivatives of glycine, the simplest amino acid. They often involve the introduction of an amino acid side chain, with formation of a carbon−carbon bond.

Pioneering work in this area was reported by Elad *et al.*[51−53] This group established that irradiation of a mixture of *N*-acetylglycine ethyl ester (**5**), toluene, and acetone, with ultraviolet light, resulted in the formation of *N*-acetylphenylalanine ethyl ester (**8**), albeit in low yield.[51] A logical mechanism for this reaction is shown in Scheme 1. In the later work,[52,53] it was shown that the reactions could be carried out using visible light instead of ultraviolet light, if an α-diketone, such as biacetyl or camphorquinone, and di-*tert*-butyl peroxide were used in place of acetone. With this combination of reagents, the α-diketone acts as the light-absorbing system, to induce photolysis of the peroxide, and the resultant *tert*-butoxy radicals (and/or methyl radicals produced by β-scission of the *tert*-butoxy radicals) act as the hydrogen atom-abstracting species. Using visible light substantially increased the scope of the procedure, to allow both the reaction and production of amino acid derivatives sensitive to ultraviolet light. Accordingly, reaction with 4-methoxytoluene, in place of toluene, resulted in the conversion of glycine derivatives to the corresponding tyrosine derivatives (Scheme 2). In other variations of this procedure, replacing toluene with 4-fluorotoluene, or acetic acid or acetic anhydride, resulted in the conversion of glycine derivatives to the 4-fluorophenylalanine and aspartic

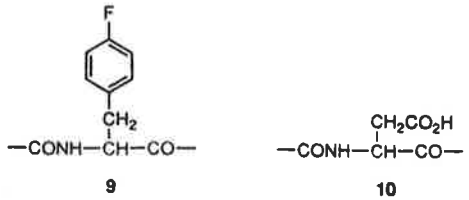
Scheme 1



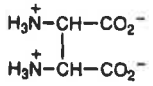
Scheme 2



acid analogues **9** and **10**, respectively.[52,53] In each of these reactions it was necessary to use a large excess of the alkylating agent, in order to obtain the necessary balance between hydrogen atom transfer from that agent and the glycine derivative.



Processes competing with the cross-coupling reactions to give the alkylated glycine derivatives are dimerization of the glycinyl radicals and of the radicals derived from the alkylating species. For example, in the reactions of glycine containing peptides with toluene, biphenyl and 1,2-diaminosuccinic acid (**11**) were identified as components of the products of hydrolysis of the reaction mixtures.[54] These dimers provide good evidence of the radical nature of the reactions. Presumably they are formed only in small quantities because the competing cross-coupling reaction is favored by the different electronegativities of the reacting species.



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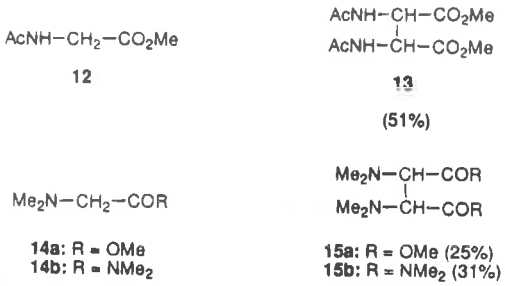
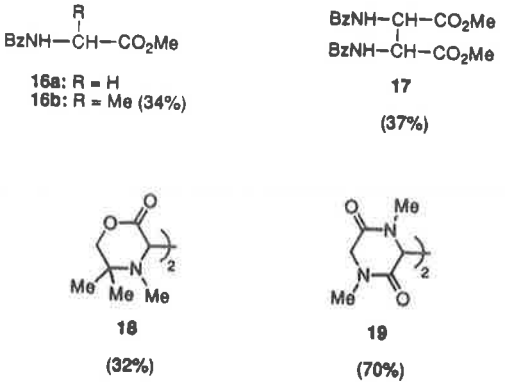
In the absence of an alkylating agent, dimer formation becomes the major reaction pathway, affording cross-linked amino acid derivatives which are of interest in the synthesis of conformationally constrained peptides. Irradiation of a mixture of *N*-acetylglycine methyl ester (**12**) and di-*tert*-butyl peroxide in benzene gave a 1:1 mixture of the diastereomers of the dimer **13**.[55] The reactions can be initiated thermally as well as photochemically, and they proceed when the amino group is present either as a free base or protected as an amide. Accordingly, the glycine derivatives **14a** and **14b** reacted with di-*tert*-butyl peroxide, at 160 °C, to give the corresponding dimers **15a** and **15b**.[30]

As noted above, in reactions with di-*tert*-butyl peroxide, *tert*-butoxy radicals, and/or methyl radicals may be the hydrogen atom-abstracting agents. Methyl radicals are prone to react with the glycinyl radicals, as seen in the photochemical reaction of *N*-benzoylglycine methyl ester (**16a**) to give the corresponding alanine derivative **16b** and a 1:1

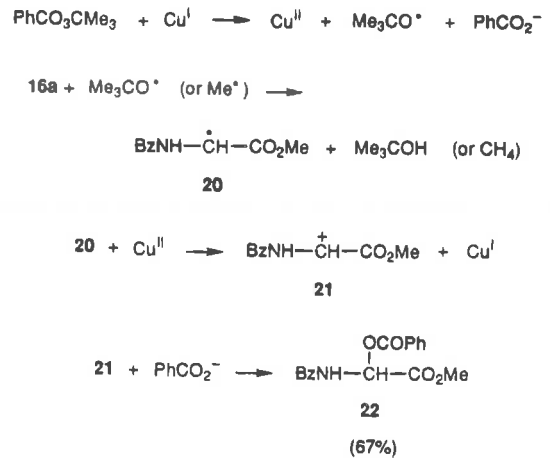


mixture of the diastereomers of the dimer **17**, in approximately equal ratio.[56] Apparently, this process does not detract seriously from the synthetic utility of the dimerization reaction, however, and more recently the method has been used to prepare the dimers **18**[57] and **19**.[47]

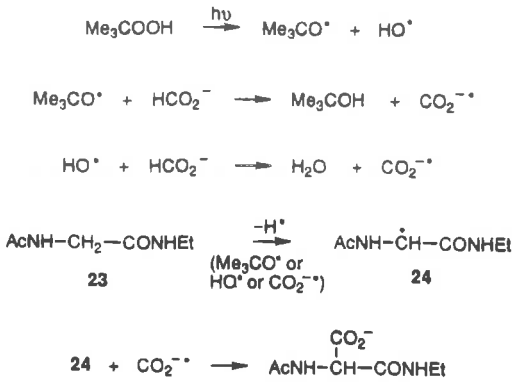


Hydrogen atom-transfer reactions can also be used for the direct introduction of a functional group in place of hydrogen at the α-carbon of a glycine derivative. For example, the copper-catalyzed reaction of *N*-benzoylglycine methyl ester (**16a**) with *tert*-butyl perbenzoate gave the benzoate **22**.[58] This compound has been used in the synthesis of α-substituted and cross-linked amino acid derivatives.[59,60] The probable mechanism[61] of production of the benzoate **22** is outlined in Scheme 3. The electron-transfer reaction of the radical **20** indicates the ease of formation of the carbocation **21**. Oxidations of this type are also apparent in a number of other reactions of glycinyl radicals which are discussed in more detail below.

Scheme 3

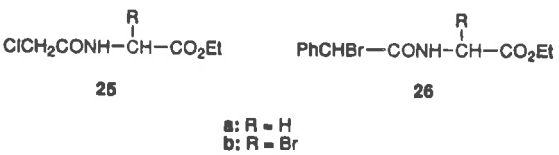


Scheme 4



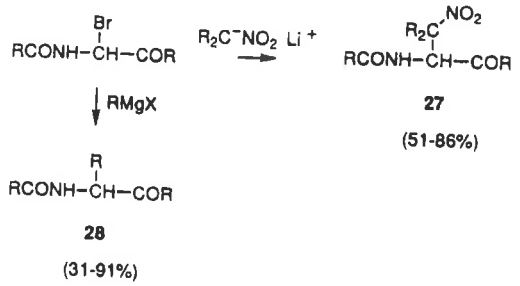
Several alternative procedures for functionalization of glycine derivatives through hydrogen-transfer reactions have been reported. On irradiation with *tert*-butyl hydroperoxide in the presence of formate, glycine derivatives give the corresponding α-carboxy-substituted products, from coupling of the intermediate α-carbon-centered radicals with carbon dioxide radical anion, as illustrated in Scheme 4 for the glycine derivative **23**.[62] This mechanism is more probable than reaction of the amino acid radicals with carbon dioxide, where normally the reverse process of decarboxylation is thermodynamically preferred. This procedure may constitute a biomimetic synthesis of α-carboxyglycine derivatives and indicates that the occurrence of such residues in proteins may be a result of their oxidative degradation.[63]

A far more common approach to the synthesis of α-functionalized glycine derivatives involves free-radical bromination, either with bromine or *N*-bromosuccinimide. In the original report in this area, Lidert and Gronowitz[64] described reactions of the glycine derivatives **25a** and **26a** with the succinimide, to give the corresponding bromides **25b** and **26b**.

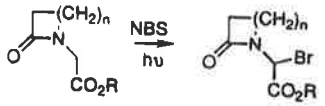


α-Halo amino acids of this type tend to be unstable and for that reason they are isolated only rarely. Nevertheless compounds prepared via halides of this type are usually obtained in high yield, indicating that the bromination is quite practical and efficient. α-Bromoglycine derivatives obtained in this manner have been used extensively in synthesis.[64−76] For example, reactions with Grignard reagents afforded the α-substituted amino acid derivatives **28**,[67] while reactions with lithium alkyl nitronates gave the corresponding β-nitro amino acid derivatives **27**[68,75] (Scheme 5). Reactions with higher order cuprates, trimethylsilyl enol ethers, and β-dicarbonyl compounds,[69] and arylation of bromoglycine derivatives,[72] have also been reported.

Scheme 5



Scheme 6



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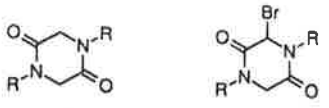
a: n = 1
b: n = 2

The exocyclic functionalization of *N*-(alkoxycarbonyl)methyl-substituted β- and γ-lactams (Scheme 6)[77] is a variation of the bromination procedure. It provides an attractive alternative to the glyoxalate route for the synthesis of *N*-(α-haloalkyl)-substituted lactams,[78,79] which have been used widely in the synthesis of β-lactam antibiotics. In the absence of the alkoxycarbonyl substituent, reaction at the exocyclic carbon adjacent to the lactam nitrogen is no longer favored and endocyclic reaction occurs.[80]

Glycine residues in diketopiperazines have also been converted to the corresponding bromides. The original procedure reported by Trown[81] involved heating the substrate with bromine in *o*-dichlorobenzene at 150 °C. Under these vigorous conditions, it is likely that the transformation could occur via either a radical or an ionic mechanism. More recently, conditions typical of free-radical reactions have been used to promote the same conversions. For example, the diketopiperazine **30a** gave the dibromide **32** in virtually quantitative yield, on treatment with *N*-bromosuccinimide and benzoyl peroxide, at reflux in carbon tetrachloride.[82] The lack of competing reactions of the exocyclic methylene groups is worthy of note, as it demonstrates the relative ease of formation of the radicals **33** and **34**. The brominated diketopiperazines have also attracted interest in synthesis.[82-84]

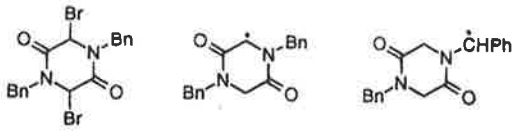
Contrary to initial indications,[85] it is possible to selectively brominate one glycine residue in a symmetric diketopiperazine, without complications from subsequent reactions.[86,87] The diketopiperazines **30a–c** are each approximately seven times more reactive than the corresponding bromides **31a–c** in reactions with *N*-bromosuccinimide. With a limiting amount of that reagent the monosubstituted species **31a–c** were produced and converted to the corresponding α-methoxyglycine derivatives, in overall yields ranging from 41–61%.[87] The monobromides **31a–c** have particular potential for the asymmetric synthesis of diketopiperazine derivatives.[85,86,88]

The potential to exploit bromoglycine derivatives in synthesis has prompted the use of chiral auxiliaries in order to obtain stereocontrol. Accordingly, the glycine derivatives **35a–41a** gave the corresponding bromides **35b–41b**, each in high yield, on treatment with *N*-bromosuccinimide,[74,89-96] and these bromides **35b–41b** have been used in a variety of asymmetric syntheses.[74,89-106] The regioselectivity of reaction of the glycine derivative **35a** again illustrates the ease of formation of α-carbon-centered amino acid radicals, given that there has been no indication of competing reaction at either of the benzylic positions in this molecule.[89] The bromides **35b–41b** were obtained as various mixtures of diastereomers. It seems likely that the ratios of isomers reflect the thermodynamic equilibria attained through reaction via the corresponding imines or iminium ions, rather than the stereochemistry of bromine incorporation in the reactions of the intermediate radicals. In any event, the stereochemistry of the bromides **35b–41b** is not particularly important as most reactions of these compounds involve intermediates which are planar at the α-carbon. In the case of the bromination of the 8-phenylmenthol derivative **38a**, experiments with deuteriated analogues established a high degree of stereoselectivity in the hydrogen atom transfer to give the intermediate glycinyl radical.[92]



30 **31**

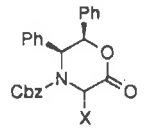
a: R = Bn
b: R = Me
c: R = CH_2Ph-*p*-OMe



32 **33** **34**

The reactions described above involve glycine derivatives which have the amino and carboxyl groups protected in a variety of different forms. However, the effect of these substituents on reactivity toward hydrogen atom transfer can only be delineated where direct comparisons have been made, or where more than one glycine residue is present, for example in a peptide derivative, where there is the possibility of selective reaction. The carboxyl group may be present as either a free acid, a carboxylate anion, an ester, or as is the case with most amino acid residues in peptides and proteins, an amide (or aminocarbonyl group). The relative effects of the methyl ester and *N*-methylamide groups were examined through comparison of reactions of the glycine derivatives **16a** and **42a** on photolysis with di-*tert*-butyl peroxide.[107] The amide **42a** reacted to give the corresponding dimer **43** and the alanine derivative **42b**, in an analogous manner to the reaction of the ester **16a** described above, and in competitive experiments the amide **42a** reacted 2.3 times faster than the ester **16a**.

At first sight, it appears that this activation by the aminocarbonyl group compared to the ester is reflected in the reaction of *N*-benzoylglycylglycine



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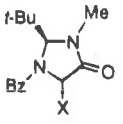

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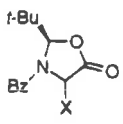

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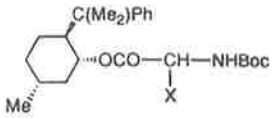

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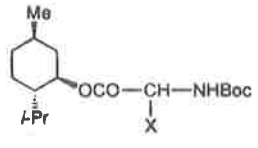

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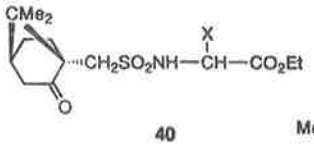

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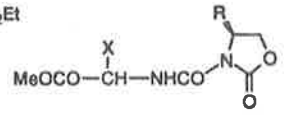
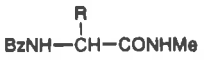


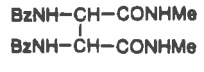
R = *i*-Pr, Bn, *i*-Bu or *t*-Bu

41

a: X = H
b: X = Br



42a: R = H
42b: R = Me (20%)

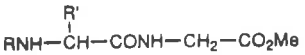


43

(21%)

methyl ester (**44a**) carried out under similar conditions.[107] The derivatives of alanylglycine **44b** and glycylalanine **45b** were produced in a 10:1 ratio, presumably as a result of the relative ease of formation of the radicals **46a** and **47a**. Likewise, reaction of the dipeptide derivative **44a** with *N*-bromosuccinimide gave the bromide **44c**, and none of the regioisomer **45c** was detected.[108] However, the factors contributing to regioselectivity in reactions of peptide derivatives are more complex. Irradiation of a mixture of *N*-acetylglycylglycine methyl ester (**44d**), toluene, and acetone gave the phenylalanine derivatives **44e** and **45e** in the ratio 52:48, indicating little difference between the relative ease of formation of the radicals **46b** and **47b** in that case.[109,110]

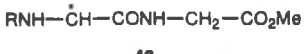
The nature of substitution of the amino group in an amino acid derivative also affects the reactivity toward hydrogen transfer. Reaction of *N*-(trifluoroacetyl)glycylglycine methyl ester (**44f**), as described above for the nonfluorinated analogue **44d**, gave the corresponding phenylalanine derivatives **44g** and **45g** in the ratio 43:57.[109,110] Presumably, the different product ratios obtained in the reactions of the acetamide **44d** and the trifluoroacetamide **44f** reflect the relative ease of formation of the radicals **46b** and **47b**, and **46c** and **47c**. In turn, this can be attributed to the decreased dative stabilization of the radical **46c** by the trifluoroacetamido substituent, compared to the effect of the acetamido group on the radical **46b**. Again the situation is more complicated than



44

45

a: R = Bz, R' = H
b: R = Bz, R' = Me
c: R = Bz, R' = Br
d: R = Ac, R' = H
e: R = Ac, R' = Bn
f: R = CF_3CO, R' = H
g: R = CF_3CO, R' = Bn
h: R = CF_3CO, R' = CH_2Ph-*p*-OMe
i: R = CF_3CO, R' = CH_2CO_2H



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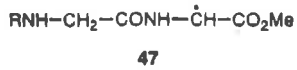


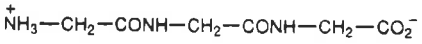
47

a: R = Bz
b: R = Ac
c: R = CF_3CO

this simple interpretation would indicate; however, as the reaction of *N*-(trifluoroacetyl)glycylglycine methyl ester (**44f**) carried out using visible light, biacetyl, and di-*tert*-butyl peroxide, in place of ultraviolet light and acetone, gave a 1:1 mixture of the phenylalanine derivatives **44g** and **45g**.[52] The obvious difference between these reactions is the nature of the hydrogen atom-abstracting species, but it is not clear why that leads to a change in the ratio of products. Despite their stability, captodative radicals still undergo radical coupling reactions at rates which are diffusion controlled.[50,111] Under these conditions the nature of the alkylating agent should not affect the ratio of products of reactions of the dipeptide derivative **44f**. As expected, therefore, when using visible light, biacetyl, and di-*tert*-butyl peroxide, with *p*-methoxytoluene and acetic acid or acetic anhydride, the derivatives of tyrosine **44h** and **45h** and aspartic acid **44i** and **45i** were each obtained in equal ratios.[52]

The substantially greater activating effect of an amido substituent compared to a protonated amino group on formation of a radical on the adjacent carbon is clearly illustrated in the reaction of triglycine **48** with di-*tert*-butyl peroxide.[112] The dimers **49** and **50** were formed in approximately equal quantities, each as a 1:1 mixture of diastereomers, and glycylglycylalanine (**51**) and glycylalanylglycine (**52**) were formed in a 5:1 ratio. There was no evidence of formation of other dimeric species or of alanylglycylglycine (**53**), indicating that hydrogen atom transfer from triglycine **48** affords the radicals **54** and **55**, in preference to the radical **56**. It is also apparent from these results that the radical **54** forms in preference to the regioisomer **55**.

Whereas the reaction of *N*-benzoylglycylglycine methyl ester (**44a**) with *N*-bromosuccinimide gave only the bromide **44c** from reaction of the *N*-terminal glycine residue, the analogous reaction of *N*-phthaloylglycylglycine methyl ester (**57a**) gave only the bromide **57b** from reaction of the *C*-terminal amino acid residue.[108] The regioselectivity of the latter reaction indicates that the α-position of an *N*-phtha-



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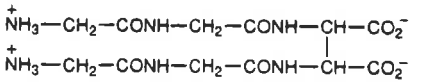

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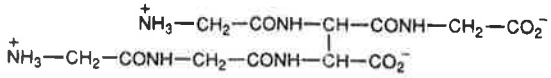

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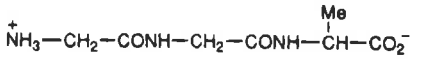

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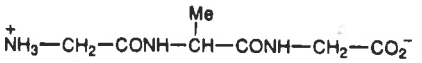

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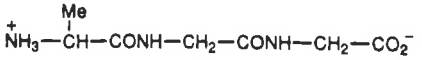

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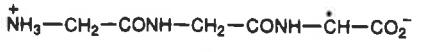

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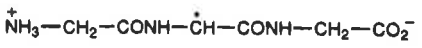

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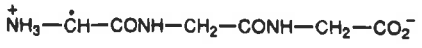
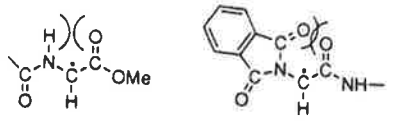


56

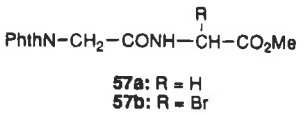
loyl-substituted amino acid derivative is less reactive than that of an *N*-acylamino acid derivative toward hydrogen atom transfer. This may be attributed to the relative stability and ease of formation of the corresponding α-carbon-centered radicals **58** and **59**. Whereas the acylamino-substituted radical **58** can adopt a planar conformation, in which there is good overlap of the π-orbitals of the amido substituent with the semioccupied p-orbital of the radical, steric interactions distort the radical **59** from planarity and limit the extent of orbital overlap in that case (Figure 2). In addition, the π-electrons of the imido substituent are less available to stabilize the radical **59** through resonance. The phthaloyl substituent is also likely to hinder approach of bromine atom to the *N*-terminal glycine residue in the dipeptide derivative **57**.

The relative effects of amido and imido substituents on radical formation are also illustrated in reactions of the diketopiperazines **30b**, **60a**, and **60b**.[113] In competitive experiments, the *N*,*N*-dimethyl-substituted compound **30b** reacted with *N*-bromosuccinimide to the exclusion of the *N*,*N*-diacetyl derivative **60a**. In the case of the asymmetric pip-

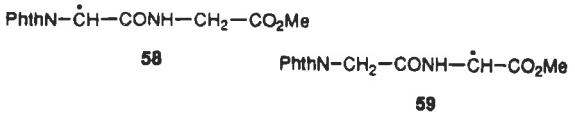


58 59

Figure 2. Nonbonding interactions associated with planar conformations of the radicals **58** and **59**.

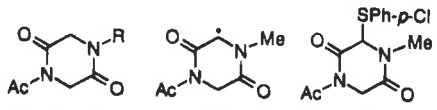


57a: R = H
57b: R = Br



58 59

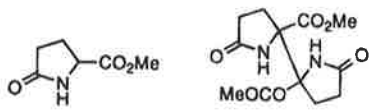
erazinedione **60b**, a strong preference was observed for reaction via the radical **61**, and a reaction with 1 mol equiv of *N*-bromosuccinimide, followed by treatment with *p*-chlorothiophenol, gave only the product **62**.



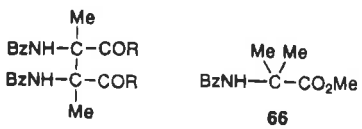
60a: R = Ac
60b: R = Me

61 62 (74%)

In each of the reactions described above, the α-carbon-centered amino acid radical was derived by hydrogen atom transfer from a derivative of glycine. Derivatives of many other amino acids also form α-carbon-centered radicals in a similar manner and in some cases these react in an identical way to the corresponding glycinyl radicals. For example, the irradiation-induced reaction of methyl pyroglutamate (**63**) with di-*tert*-butyl peroxide afforded a 1:1 mixture of the diastereomers of the dimer **64**,[55] in a reaction directly analogous to that of the glycine derivative **16a** already discussed. Likewise, reactions of the alanine derivatives **16b** and **42b** with di-*tert*-butyl peroxide gave the corresponding dimers **65a** and **65b**, in a procedure analogous to that for reaction of the glycine derivatives **16a** and **42a**.[107,114] The reactions



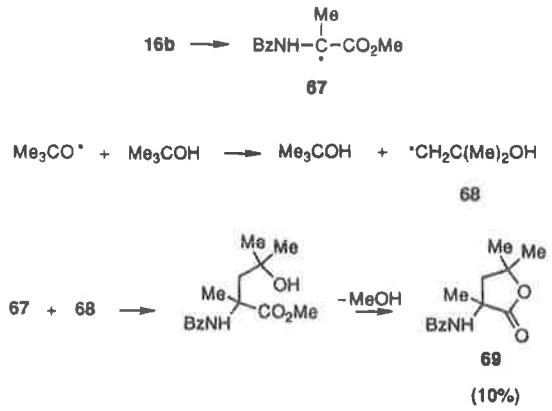
63 64 (64%)



65a: R = OMe (20%)
65b: R = NHMe

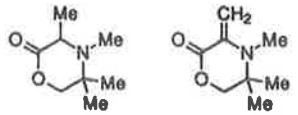
66 (10%)

Scheme 7



of the alanine derivatives **16b** and **42b** were relatively inefficient, however, and competing reactions were more prevalent. The alaninate **16b** gave more substantial quantities of the α-methyl derivative **66** and the lactone **69** was also produced. A mechanism of formation of the lactone **69** is shown in Scheme 7.

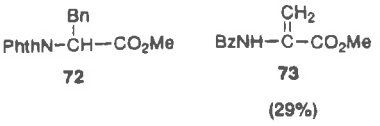
In other cases the presence of the amino acid side chain has a more significant effect on the course of reaction. An abstractable hydrogen at the β-position can lead to the formation of an α,β-dehydro amino acid derivative from an α-carbon-centered amino acid radical. Treatment of the alanine derivative **70** with di-*tert*-butyl peroxide gave the dehydroalanine derivative **71**.[57] While nickel peroxide often causes



70 **71**

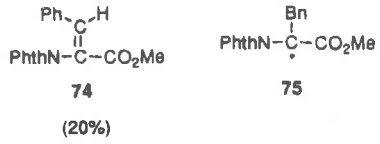
cleavage of α-carbon–nitrogen bonds in amino acid derivatives,[115] the compounds **16b**, **72**, **76a**, and **76b** reacted to give the corresponding unsaturated derivatives **73**, **74**, **77a**, and **77b**, presumably via the radicals **67**, **75**, **78a**, and **78b**, respectively.[116] The regioselective reaction of the *C*-terminal amino acid residue in each of the dipeptide derivatives **76a** and **76b** may reflect the effect of the phthalimido protecting group, described above. Alternatively, the nickel peroxide may selectively complex aspartate residues.

The oxidation of the oxazolines **79** to the respective oxazoles **80**, using either *N*-bromosuccinimide or *tert*-butyl perbenzoate with cuprous bromide, may involve an analogous process of hydrogen atom transfer from the corresponding intermediate radicals **81**. Alternatively, the radicals **81** may be reacting to give the corresponding bromides **82a** and benzoates **82b**, which subsequently undergo elimination to give the oxazoles **80**.[117,118] In any event, incorporation of a functional group at the α-position, in place of hydrogen, is a common mode of reaction for derivatives of other amino acids, as it is for derivatives of glycine. This occurs in the autoxidation of amino acid derivatives, as illustrated by the reactions of the cyclic



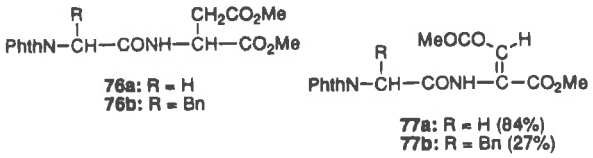
72 **73**

(29%)



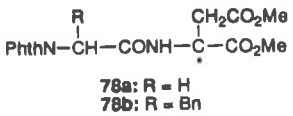
74 **75**

(20%)

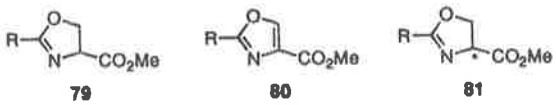


76a: R = H
76b: R = Bn

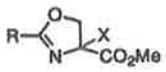
77a: R = H (84%)
77b: R = Bn (27%)



78a: R = H
78b: R = Bn

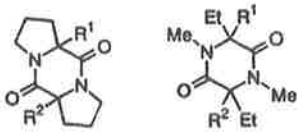


79 **80** **81**



82a: X = Br
82b: X = OBz

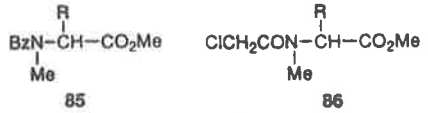
dipeptides **83a** and **84a** to give the corresponding hydroperoxides **83b**, **83c**, **84b**, and **84c**.[119,120]



83 **84**

a: $R^1 = R^2 = H$
b: R^1 = OOH, $R^2 = H$
c: $R^1 = R^2$ = OOH

Free radical reactions with molecular bromine or *N*-bromosuccinimide result in α-bromination, as illustrated in the reactions of the sarcosine derivatives **85a** and **86a**, to give the halides **85b** and **86b**, respectively.[64,70,121] In these examples, further reac-

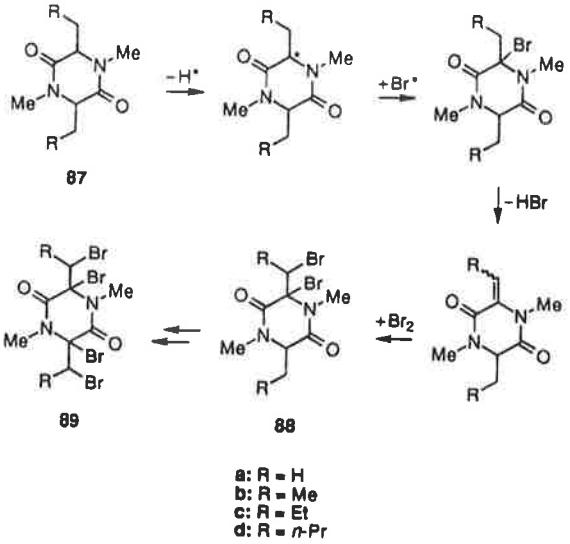


85 **86**

a: R = H
b: R = Br

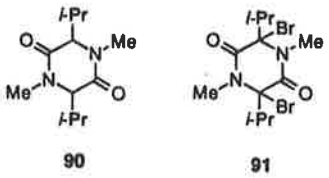
tion through loss of hydrogen bromide is not possible, but where there is an amino acid side chain with a β-hydrogen, the ionic elimination process often occurs

Scheme 8



a: R = H
b: R = Me
c: R = Et
d: R = *n*-Pr

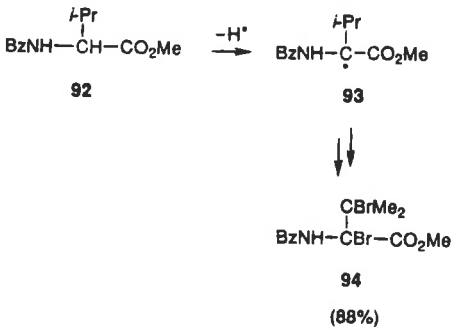
subsequent to the radical bromination, to give dehydro amino acid derivatives which may react by bromine addition. Accordingly, the diketopiperazines **87a–d** gave the corresponding dibromides **88a–d** and tetrabromides **89a–d**, from reaction with 2 and 4 equiv of *N*-bromosuccinimide, respectively,[122] presumably via the reaction sequence shown in Scheme 8. Evidence in support of this sequence is provided from the reactions of related compounds. The valylvaline derivative **90** reacted with 2 equiv of *N*-bromosuccinimide to give the dibromide **91**.[122] In



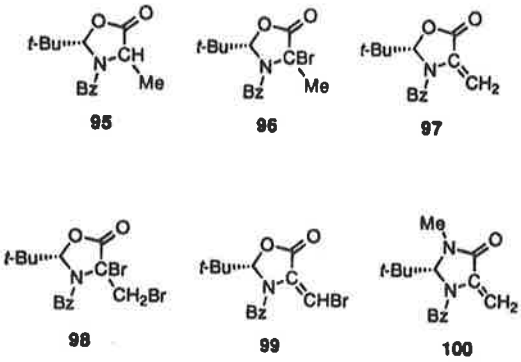
this case the reaction stops at this stage, probably because the elimination of hydrogen bromide is inhibited by steric constraints. The valine derivative **92** afforded the dibromide **94** in a reaction which displayed a deuterium isotope effect of 3.7 for cleavage of the α-carbon–hydrogen bond, indicating reaction via the corresponding α-carbon-centered radical **93**[121,123,124] (Scheme 9).

Often elimination/addition reaction sequences of the type shown in Scheme 8 complicate reactions of

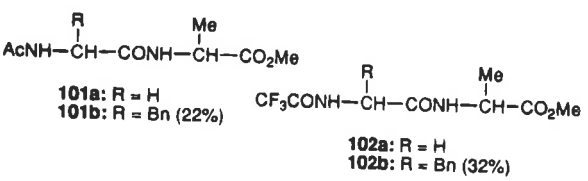
Scheme 9



alanine derivatives with *N*-bromosuccinimide.[64,121] Small changes in reaction conditions affect the relative efficiency of the initial radical reaction and the subsequent ionic processes. As a result, the outcome of reactions of this type tends to be quite variable. Zimmermann and Seebach[94] reported that treatment of the alanine derivative **95** with 1 equiv of *N*-bromosuccinimide afforded the bromide **96**, which underwent base-induced elimination to give the dehydroalanine derivative **97**. Other workers[125] found that elimination/addition reactions of the bromide **96** complicated the preparation of this compound, and found it to be preferable to use 2 equiv of *N*-bromosuccinimide, to extend the reaction to the formation of the dibromide **98**, from which the dehydroalanine derivative **97** was prepared by treatment with sodium iodide in acetone. Even so, the dibromide **98** reacted further to give the bromoalkene **99**,[126,127] unless the radical bromination was particularly efficient and the reaction time was kept short to limit the extent of the subsequent ionic reactions.[128] A similar approach was used to prepare the lactam **100**.[125] These dehydroalanine derivatives **97** and **100** have attracted considerable interest in the asymmetric synthesis of amino acids, using cycloaddition and ionic and free-radical reactions.[94,125–135] The latter are discussed in more detail below.



Where derivatives of different amino acids are present in a system the possibility of selective reaction exists. Under these circumstances glycine residues show particular reactivity in hydrogen atom transfer reactions to give the corresponding α-carbon-centered radicals. This is apparent from the work of Elad *et al.*[52–54,109,110,136–138] In early reports they noted that alkylation of the glycylalanine derivatives **101a** and **102a**, by irradiation in the presence of toluene and acetone, resulted in the selective reaction of the glycine residue in each case, to give the corresponding phenylalanine derivatives **101b** and **102b**.[109,136] Reactions of this type occur without



racemization of other amino acid residues, which can therefore act as chiral auxiliaries in the production

of the new chiral center at the α-carbon of the glycine residue.[54,109,137] Accordingly, synthetic polypeptides consisting of glycine and (*S*)-alanine in a 1:2 ratio showed a preferential reactivity of glycine over alanine of 30:1, and the production of (*S*)- and (*R*)-phenylalanine residues in the ratio 70:30, while peptides containing (*S*)-proline and glycine in a 2:1 ratio formed (*S*)- and (*R*)-phenylalanine in the ratio 38:62.[54,137] Selective reaction of glycine residues in small peptides which also contained leucine, valine, phenylalanine and *O*-methyltyrosine was also reported.[52,110] The degree of selectivity for reaction of glycine residues and the extent of asymmetric induction in the reactions were found to be dependent on the location of the glycine residues in the peptides and to increase as the molecular weight of the peptides increased.[137,138] Selective reaction of glycine residues was also observed in reactions of lysozyme, collagen, gelatin, and ribonuclease.[53] In the case of lysozyme, analysis of the amino acids obtained from hydrolysis of the product of a reaction carried out using ultraviolet radiation indicated that lysine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, alanine, valine, methionine, isoleucine, and leucine were little affected under the conditions required for reaction of glycine, but histidine, cysteine, tyrosine, phenylalanine and tryptophan decomposed. It is likely that the decomposition of the aromatic amino acid residues is at least partly due to the use of ultraviolet radiation and that this could be avoided using the alternative system involving visible light, although results for reaction under these conditions were not reported. In a more recent example of the selective reaction of glycine residues in free-radical reactions of proteins, Koch *et al.*[62] applied the procedure for the carboxylation of glycine derivatives using *tert*-butyl hydroperoxide and formate to the generation of α-carboxyglycine residues in gelatin.

The selective reaction of glycine derivatives to give α-carbon-centered radicals is contrary to the expectation that tertiary radicals are more stable, and should form more easily, than secondary radicals. Studies of reactions of the amino acid derivatives **16a**, **16b**, and **92** with *N*-bromosuccinimide, through formation of the corresponding radicals **20**, **67**, and **93**, have provided an explanation for this anomaly.[124,139] The rate of reaction of the glycine derivative **16a** to give the secondary radical **20** is faster than the rate of reaction of the corresponding alanine derivative **16b** to give the tertiary radical **67**, which is in turn faster than the rate at which the valine derivative **92** reacts to give the radical **93**. The relative ease of formation of the radicals **20**, **67**, and **93** can be attributed to the relative stability of these species. Stabilization of the radicals **20**, **67**, and **93** will result from overlap of their semioccupied p-orbitals with the π-orbitals of the amido and methoxycarbonyl substituents. There will be maximum overlap of these orbitals in planar conformations of the radicals **20**, **67**, and **93** (Figure 3). The alaninyl radical **67** will be destabilized compared to the glycinyl radical **20** due to nonbonding interactions associated with planar conformations, and the valinyl radical **93** will be even less stable due to more severe nonbonding interactions. Consistent with this explanation, the relative rates of reaction of the derivatives of alanine **67** and sarcosine **85a** are nearly identical, since the extent of nonbonding interactions associated with planar conformations of the radicals **67** and **103** is very similar. Methyl pyroglutamate (**63**) reacts faster than the glycine derivative **16a**, because the radical **104** can adopt planar conformations which are relatively free of nonbonding interactions and because formation of the radical **104** is favored by the relief of ring strain and by the release of steric interactions between the methoxycarbonyl substituent and the β-hydrogens.[140-143]

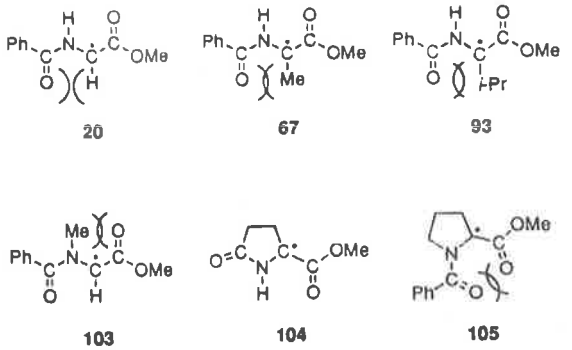
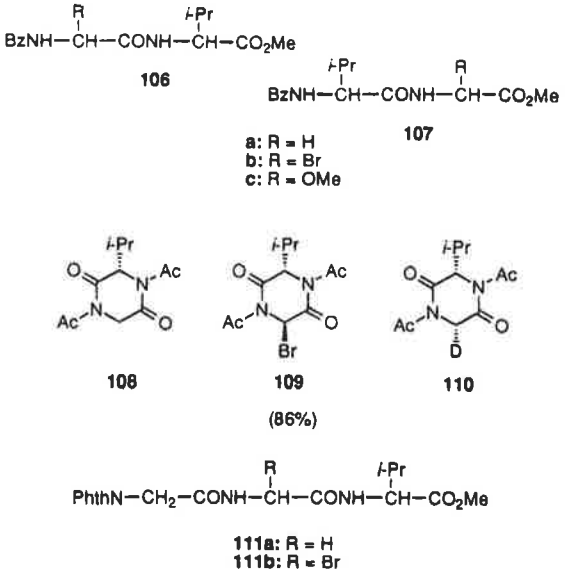


Figure 3. Nonbonding interactions associated with planar conformations of the radicals **20**, **67**, **93**, and **103**–**105**.

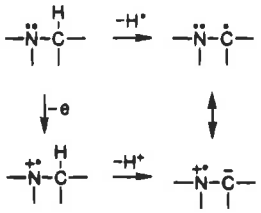
The selectivity for hydrogen atom transfer from glycine residues on treatment of peptides with *N*-bromosuccinimide is illustrated in the reactions of the glycylvaline and valylglycine derivatives **106a** and **107a** to give the corresponding bromides **106b** and **107b**, from which the methoxides **106c** and **107c** were obtained in overall yields of 73% and 65%, respectively.[70,124] Compounds of this type have considerable potential for the asymmetric synthesis of amino acid derivatives, through their use to generate the corresponding reactive *N*-acylimines and electrophilic and radical glycine equivalents.[70,124,144] This use of another amino acid in the peptide as the chiral auxiliary offers several advantages. Normally both enantiomers of the auxiliary are cheap and readily available, and they are easily recovered after reaction, through hydrolysis of the product peptide, for use in subsequent reactions. Reactions of cyclic dipeptide derivatives are of particular interest in this area, due to the relatively rigid spatial arrangement of the chiral and prochiral center. The diketopiperazine **108** gave the bromide **109** from reaction with *N*-bromosuccinimide, due to selective reaction of the glycine residue, and this material was reduced with deuterium over palladium chloride to give the deuteride **110** in 90% enantiomeric excess.[144] Other effects can be exploited in conjunction with the selectivity for reaction of glycine residues, to achieve regioselective functionalization of peptides. On treatment with *N*-bromosuccinimide, the tripeptide derivative **111a** gave only the bromide **111b**, as a result of the effect of the phthaloyl protecting group outlined above.[108]

As an alternative to hydrogen atom transfer, amines and their derivatives also react by electron



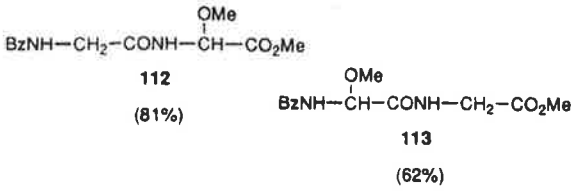
transfer followed by proton loss (Scheme 10). It is possible to form an α-carbon-centered amino acid

Scheme 10

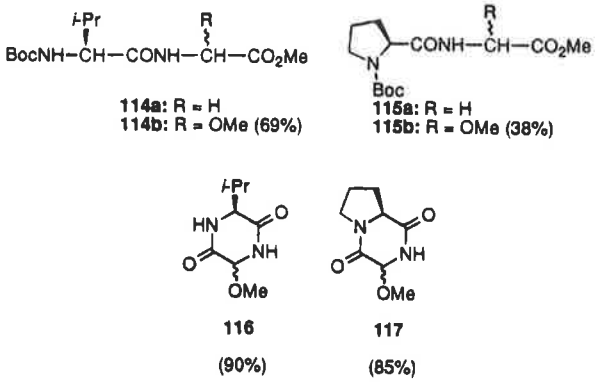


radical by either method, and in some cases there may be ambiguity about which mechanism is involved. The electron-transfer process may be accomplished either using chemical reagents or electrochemically, and a variety of *N*-protected amino acid derivatives react in this manner to give the corresponding imines.[145-151] Depending on the reaction conditions, these may react *in situ* to give α-methoxy[145,147-150] and α-hydroxy[149] amino acid derivatives. The products have the potential to react in similar ways to those described above for other α-functionalized amino acid derivatives.

With dipeptide derivatives, the regioselectivity of reaction depends on the amino acid constituents and the protecting groups. For example, anodic oxidation of *N*-benzoylglycylglycine methyl ester (**44a**) in methanol gave the methoxide **112**, from selective reaction of the *C*-terminal amino acid residue, while reactions of *N*-[(2-nitrophenyl)sulfenyl]-protected dipeptides occurred mainly at the *N*-terminal positions.[152] The regioselectivity of the electrochemical reaction of the dipeptide **44a** is complementary to that of the bromination of the same compound, discussed above. The dipeptide **44a** reacted with *N*-bromosuccinimide and then methanol to give the methoxide **113**,[108] which is isomeric to the oxidation product **112**. Oxidation of the valyl- and prolylglycine derivatives **114a** and **115a** gave the methoxides **114b** and **115b**, respectively.[152,153] Presumably the regioselectivity of these reactions reflects the relative ease of electron



transfer from amides and carbamates. On hydrolysis with formic acid the methoxides **114b** and **115b** gave the corresponding diketopiperazines **116** and **117**, which are of interest in the asymmetric synthesis of amino acid derivatives.

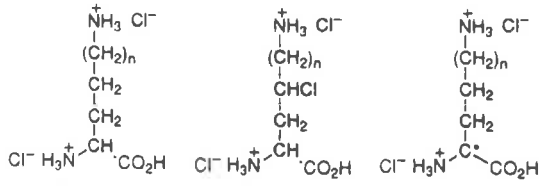


B. Intermolecular To Give Side-Chain Radicals

The tendency for hydrogen atom-transfer reactions of amino acid derivatives to give mainly α-carbon-centered radicals is a direct consequence of the stability of these radicals. In order for reaction to occur on the side chain of an amino acid derivative, in a controlled manner, either the side chain radical must be the more stable or other factors must determine the outcome of the radical process. Reactions on amino acid side chains are of particular interest because the chirality of the starting materials can then be exploited in asymmetric synthesis.

Side-chain chlorination of the amino acid derivatives **118**, **121**, **124a,b**, and **128** occurred on photolysis of solutions with chlorine in sulfuric acid.[154-157] In these cases the regioselectivity of reaction is determined by the inductive electron-withdrawing effect of the carboxy and protonated amino groups and the inability of the latter to stabilize the corresponding α-carbon-centered radicals **120**, **123**, **126a,b**, and **130** through resonance delocalization of the unpaired spin density. In the transition state for hydrogen atom transfer in a free-radical halogenation reaction, an electron-deficient center is formed at the site of hydrogen abstraction, with the result that reactions of the amino acid derivatives **118**, **121**, **124a,b**, and **128** occur remote from the inductively electron-withdrawing substituents, to give the corresponding chlorides **119**, **122**, **125a,b**, and **129**.[154,156,157] The inductive effect of the substituents is highlighted in the reaction of the isoleucine derivative **128** to give the chloride **129**, via the δ-centered primary radical **131**, instead of the tertiary β- and secondary γ-centered radicals **132** and **133**.[156]

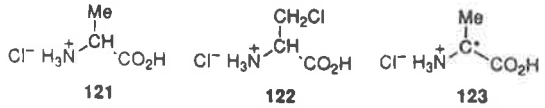
The inductive effect of substituents is also illustrated in the regioselectivity of hydrogen atom-



118a: n = 1
118b: n = 2

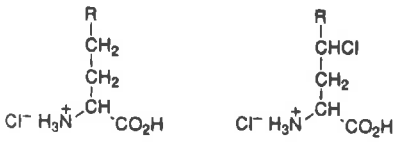
119a: n = 1
119b: n = 2 (74%)

120a: n = 1
120b: n = 2



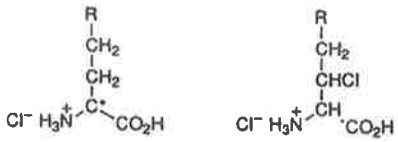
121 122 123

(78%)



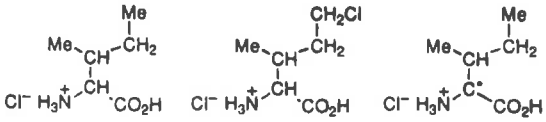
124a: R = H
124b: R = CO_2H

125a: R = H (40%)
125b: R = CO_2H (25%)



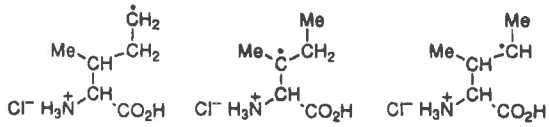
126a: R = H
126b: R = CO_2H

127a: R = H
127b: R = CO2H



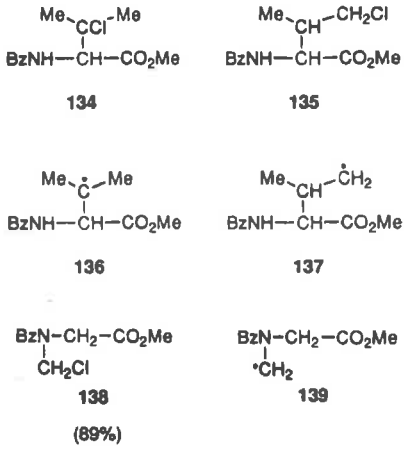
128 129 130

(33%)



131 132 133

transfer reactions of *N*-benzoylvaline methyl ester (**92**). As indicated above, the valine derivative **92** reacted with *N*-bromosuccinimide via the α-carbon-centered radical **93**. By contrast, radical reactions with sulfuryl chloride afforded the chlorides **134** and **135**, via the radicals **136** and **137**, respectively.[123,158,159] With little carbon–hydrogen bond homolysis in the transition state for hydrogen transfer in the chlorination, the regioselectivity in this case is controlled by the inductive electron-withdrawing effect of the amido and carboxy groups, acting to retard attack at the α-position by electrophilic radicals involved in the hydrogen abstraction. The reaction with *N*-bromosuccinimide is more sensitive to radical-stability effects since there is a greater degree of bond homolysis in the transition state. Further studies indicated that the valine derivative **92** reacted by hydrogen atom transfer to *tert*-butoxy radical to give a mixture of the radicals **93** and **136**.[121] The extent of carbon–hydrogen bond homolysis in the transition state for hydrogen transfer to *tert*-butoxy radical is intermediate between that for chlorination and bromination, with the result that there is a balance between the resonance and inductive effects of the substituents in this case. The contrast in the regioselectivity of the reactions of the valine derivative **92** is reflected in reactions of the sarcosine derivative **85a**.[121] Whereas reaction with *N*-bromosuccinimide gave the α-bromide **85b** via the radical **103**, chlorination afforded the (halomethyl)glycine derivative **138** via the radical **139**. Again, the difference can be attributed to the balance between the resonance and inductive effects of the methoxycarbonyl group.



134 135

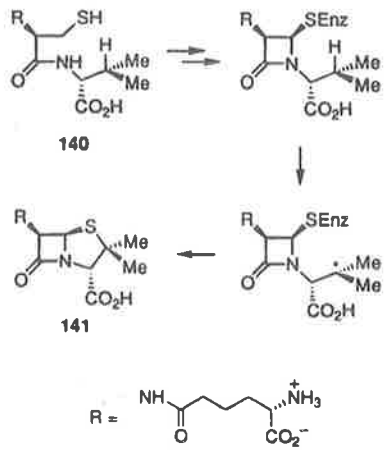
136 137

138 139

(89%)

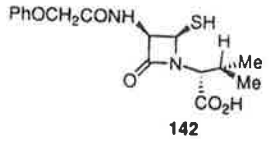
The reactions of the valine derivative **92** indicate that the regioselectivity of hydrogen atom transfer from the valine residue during the biosynthesis of isopenicillin N (**141**) from Arnstein's tripeptide **140** (Scheme 11) can be attributed to polar effects,[158] and the isopenicillin N synthetase enzyme is not essential for regiocontrol. Accordingly, treatment of the β-lactam **142** with Udenfried's reagent [iron(II) sulfate, ascorbic acid, and ethylenediaminetetraacetic acid] in the presence of oxygen gave the penicillin **143**, in the absence of the enzyme.[16] Further evidence that the enzyme does not control the regioselectivity is

Scheme 11

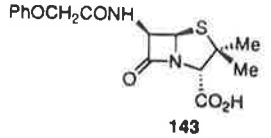


140

141



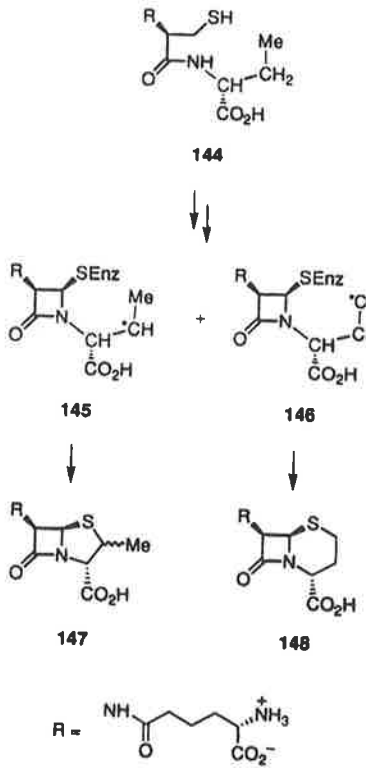
142



143

provided in reactions of modified substrates with the enzyme.[14,160] The α-aminobutyrate derivative **144** gave a mixture of the penam (**147**) and the cepham (**148**), indicating that the radicals **145** and **146** were both produced (Scheme 12).[160] With the modified

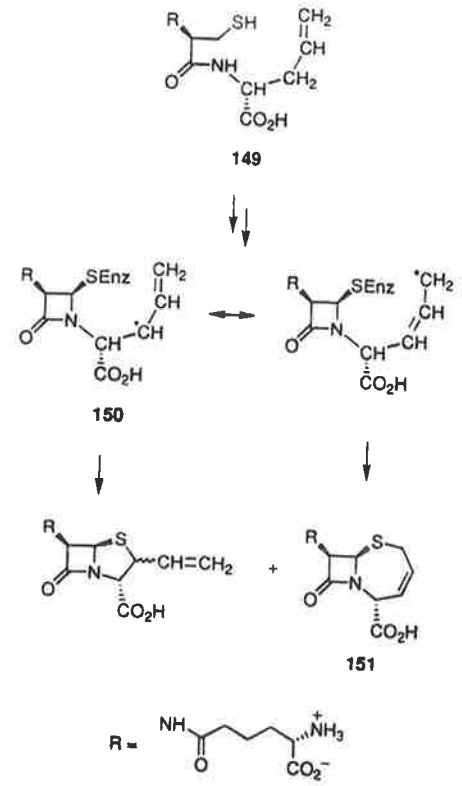
Scheme 12



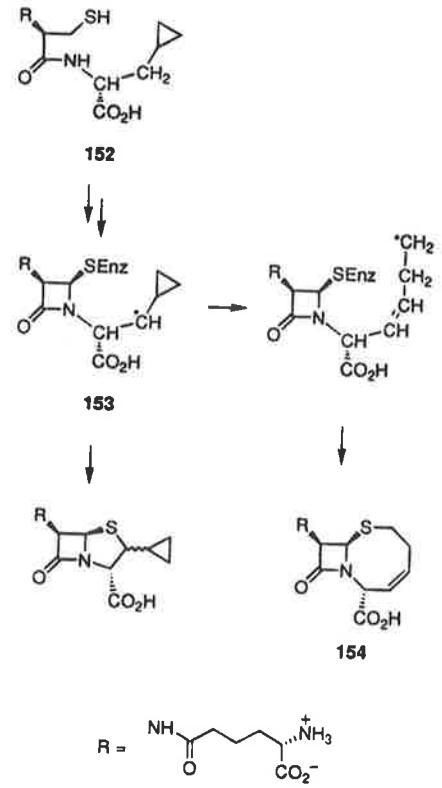
substrates, the balance between the reaction pathways to give penams and cephams appears to be determined primarily by the relative stability of the intermediate side chain radicals.[14,160] The radical nature of the enzyme-catalyzed processes was confirmed through reactions of unsaturated substrate analogues[15,18,161,162] and cyclopropylamino acid derivatives.[23,25,26,163] For example, the allylglycine derivative **149** and the cyclopropylalanine derivative **152** afforded the products **151** and **154**, respectively, from allylic rearrangement and ring opening through the corresponding intermediate radicals **150** and **153** (Schemes 13 and 14).

In addition to the polar effects outlined above, steric effects can lead to reactions occurring on the side chains of amino acid derivatives. Accordingly, the proline derivative **155** reacted to give the radical **156**, instead of by hydrogen transfer from the α-carbon, presumably as a result of the severe nonbonding interactions associated with planar conformations of the radical **105** (Figure 3), distorting that species from planarity and limiting resonance delocalization of the unpaired spin density.[139] The steric and

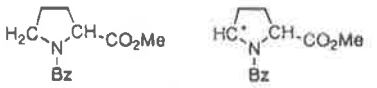
Scheme 13



Scheme 14

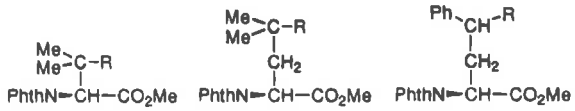


electronic effects of the phthalimido group, illustrated in the reactions of the peptide derivatives **57a** and **111a** described above, also lead to side chain reac-



155 156

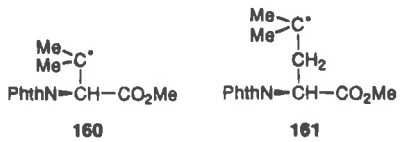
tions of *N*-phthaloyl-protected amino acid derivatives.[108] This is exemplified in the reactions of the amino acid derivatives **157a−159a** and **165a** to give the corresponding bromides **157b−159b** and **165d**, through reaction with *N*-bromosuccinimide. The reactions occur via the most stable side chain radicals **160−163**, and the chiral integrity of the amino acid derivatives **157a−159a** and **165a** at the α-position is maintained in the bromides **157b−159b** and **165d**. This approach to the side chain functionalization of amino acid derivatives has been used in the stereocontrolled synthesis of dehydro,[164] cyclopropyl,[165] and hydroxy[28,166−169] amino acids.



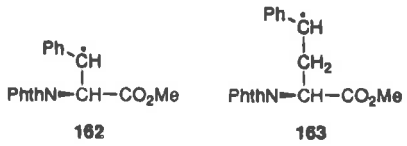
157a: R = H
157b: R = Br (87%)

158a: R = H
158b: R = Br (82%)

159a: R = H
159b: R = Br (69%)

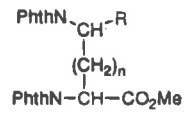


160 161



162 163

While the deactivating effect of the phthalimido group is apparent at the α-position of amino acid derivatives, where the carboxyl group also places steric and electronic constraints on reactions,[48] alone and where the steric constraints are less severe, a phthalimido substituent activates the adjacent carbon toward hydrogen atom transfer. This is indicated in the regioselective side chain bromination of the amino acid derivatives **164a** and **164b**.[48,170] The product bromides **164c** and **164d** are masked imines/aldehydes, and the reaction may therefore have some potential for the oxidative regioselective side chain deamination of diamino acid derivatives.



164a: n = 2, R = H
164b: n = 3, R = H
164c: n = 2, R = Br (74%)
164d: n = 3, R = Br (85%)

Side chain bromination of *N*-phthaloylamino acid derivatives can be accomplished with the carboxyl group present either as the free acid or protected as an amide or ester. In the reactions of the phenylalanine derivatives **165a−c** and **166a−c** to give the corresponding bromides **165d−f** and **166d−f**, the amides **166a−c** reacted approximately five times faster than the corresponding esters **165a−c**.[171] The

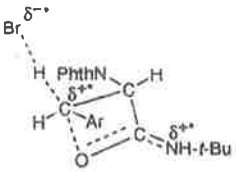
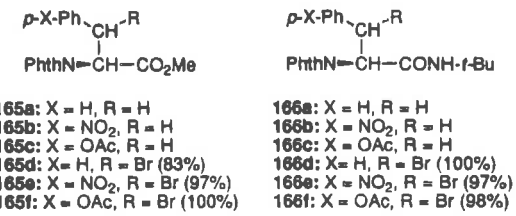


Figure 4. Neighboring group participation in hydrogen atom transfer from the phenylalanine derivatives **166a−c**.



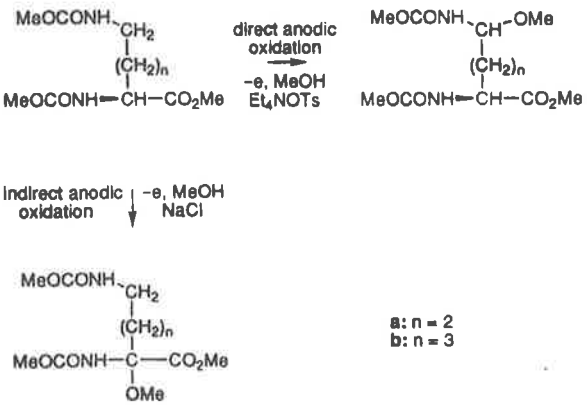
165a: X = H, R = H
165b: X = NO_2, R = H
165c: X = OAc, R = H
165d: X = H, R = Br (83%)
165e: X = NO_2, R = Br (97%)
165f: X = OAc, R = Br (100%)

166a: X = H, R = H
166b: X = NO_2, R = H
166c: X = OAc, R = H
166d: X = H, R = Br (100%)
166e: X = NO_2, R = Br (97%)
166f: X = OAc, R = Br (98%)

effect of the aromatic ring substituents indicates that the hydrogen atom transfer occurs through an electron-deficient transition state and the effect of the carboxyl group can be attributed to stabilization of the electron-deficient center through an unusual mode of neighboring group participation (Figure 4).

Electron-transfer reactions of amino acid derivatives can also lead to side-chain functionalization, although the regioselectivity is restricted to reaction at or near an electron-donating group. With derivatives of diamino acids such as ornithine and lysine, oxidation can occur either at the α-position or on the side chain, depending on the conditions used (Scheme 15).[145,172−174] Cyclizations of the side chain-substituted derivatives have been used for the synthesis of optically active piperidine and pyrrolidine alkaloids.[172,173,175,176] In principle, electron transfer from proline derivatives, followed by proton loss, and then addition of methanol to the resultant imines, could afford products methoxylated at either the 2- or 5-position. In practice, the 5-methoxy derivatives are obtained.[177−181] Interest in these compounds in

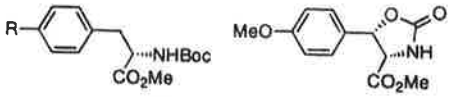
Scheme 15



a: n = 2
b: n = 3

synthesis[181-189] stems from the optical activity of the proline derivatives which is retained in the products.

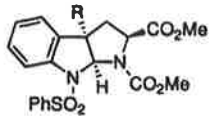
Oxidation of the tyrosine derivative **167a** with potassium persulfate in the presence of cupric sulfate gave the cyclic carbamate **168**, as a result of reaction at the benzylic position, and it seems likely that this reaction involves electron transfer from the aromatic ring since the corresponding phenylalanine derivative **167b** was unreactive.[190] Benzylic bromination of the



167a: R = OMe
167b: R = H

168
(55%)

tryptophan derivative **169a** gave the bromide **169b**, although it is interesting to note that the reaction was stopped at approximately 90% conversion because attempts to drive the reaction to completion resulted in further reaction of the bromide **169b** at the amino acid α-carbon.[191,192] The amino acid derivative **169a** also underwent benzylic oxidation, to give the alcohol **169c**, on treatment with ceric ammonium nitrate.[191,192] The demethylation of *N*-methylated diketopiperazines on treatment with ceric ammonium nitrate[86] and the *N*-methylation of amino acid carbamates through their copper-catalyzed reactions with *tert*-butyl perbenzoate[68] are also likely to involve electron-transfer processes.



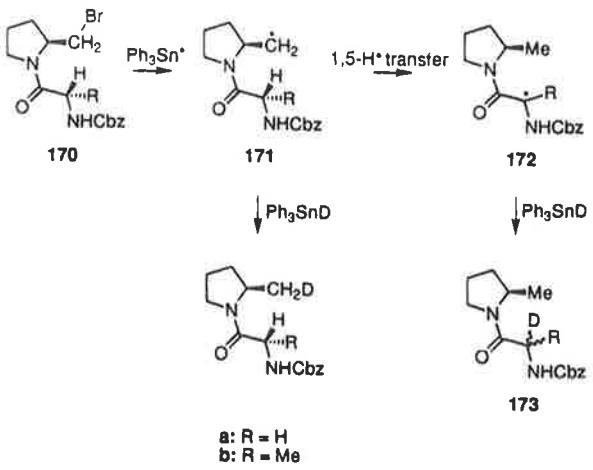
169a: R = H
169b: R = Br (72%)
169c: R = OH (65%)

C. Intramolecular

The reactions described above involve intermolecular hydrogen transfer to give amino acid radicals. Analogous intramolecular processes have also been reported, and while these offer particular opportunities for regiocontrolled synthesis, the reactions are affected by many of the same factors that affect their intermolecular counterparts. Thus, the stability of the product radicals has a major effect on the outome of reactions, and α-carbon-centered radicals are readily formed.

On treatment of the bromides **170a** and **170b** with triphenyltin deuteride, the corresponding deuteriated products **173a** and **173b** were obtained. This indicates that the radicals **171a** and **171b** formed by bromine transfer from the substrates **170a** and **170b**, respectively, each underwent 1,5-hydrogen atom transfer, to give the corresponding α-carbon-centered radicals **172a** and **172b** (Scheme 16).[193] The reactions of the radicals **171a** and **171b** were studied as a model for reactions catalyzed by the enzyme pyruvate formate-lyase.[193] The photochemically induced cyclization of the *N*-(benzoylethyl)glycine derivatives **174** occurred diastereoselectively, in this case via 1,6-

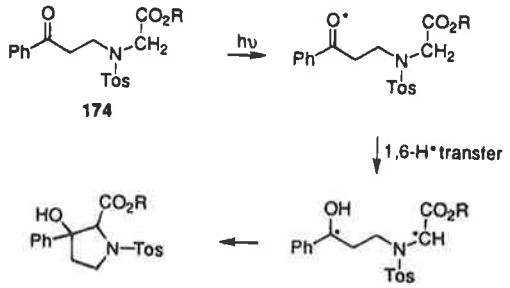
Scheme 16



170 **171** **172** **173**

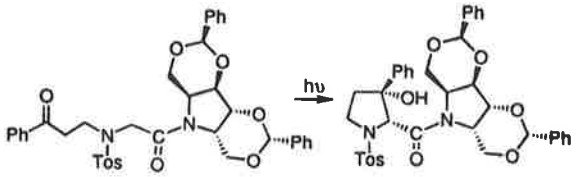
a: R = H
b: R = Me

Scheme 17



174

Scheme 18

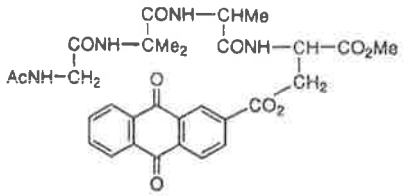


175 **176**
(70%)

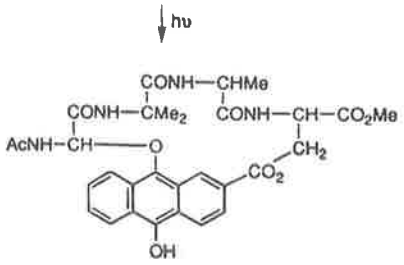
hydrogen atom transfer (Scheme 17).[194,195] Similar products were obtained from reactions of derivatives of alanine and phenylglycine.[194] More recently, reactions of analogous C_2-symmetric pyrrolidine derivatives have been found to occur with a high degree of stereocontrol, as illustrated in the reaction of the glycinamide **175** to give only the stereoisomer **176** (Scheme 18).[196]

While 1,5- and 1,6-hydrogen atom transfer reactions are not unusual, the efficiency of intramolecular hydrogen abstraction tends to decrease as the distance between the origin and terminus of hydrogen migration increases. In this regard the photochemical reactions of oligopeptide-linked anthraquinones, reported by Maruyama *et al.*[197,198] are of special interest. In examples typical of the work, photolysis of solutions of the anthraquinone derivatives **177** and **179**, in acetonitrile, afforded the corresponding cyclized products **178** and **180** (Schemes 19 and 20). These reactions involve 1,19- and 1,21-hydrogen atom-transfer reactions, and they are each highly regioselective for coupling the α-carbon of the glycine

Scheme 19



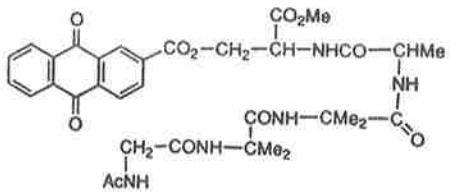
177



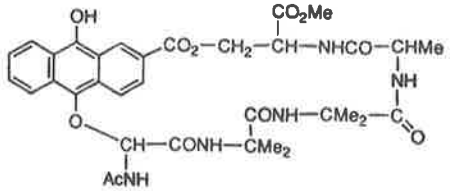
178

(58%)

Scheme 20



179

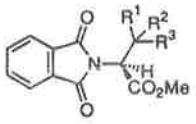


180

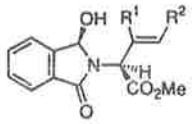
(57%)

residue to a specific carbonyl group of the anthraquinone moiety. In part this must be attributable to the rigid structure of the anthraquinone, but it seems likely that the reactions are also facilitated by the particular stability of α-carbon-centered amino acid radicals.

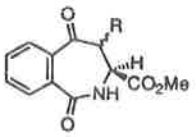
In some cases, geometrical constraints prevent intramolecular hydrogen transfer reactions to give α-carbon-centered radicals, and under these circumstances, side chain radicals are formed. This is the situation with the photolysis of *N*-phthaloylamino acid derivatives,[199,200] where intramolecular reaction of the photochemically excited phthalimide to give an α-centered radical would involve an unusual 1,4-hydrogen atom transfer. In typical photochemical reactions of *N*-phthaloylamino acid derivatives, the esters **157a** and **181a–d** underwent a variety of reactions to give the unsaturated amino acid derivatives **182a–d**, the ring-expanded products **183a** and **183b**, and the tricyclic amino acid derivative **184**.[199,200]



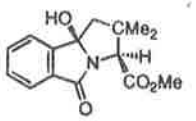
181a: R^1 = Me, R^2 = R^3 = H
181b: R^1 = Et, R^2 = R^3 = H
181c: R^1 = Me, R^2 = Et, R^3 = H
181d: R^1 = R^2 = R^3 = Me



182a: R^1 = R^2 = H (20%)
182b: R^1 = Me, R^2 = H (85%)
182c: R^1 = H, R^2 = Me (15%)
182d: R^1 = Et, R^2 = H (75%)



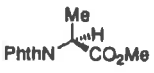
183a: R = H (60%)
183b: R = Me (60%)



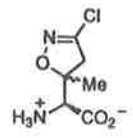
184

(90%)

In each case reaction occurred with retention of stereochemical integrity at the α-position and with high diastereoselectivity. The products **182a–d**, **183a,b**, and **184** can be attributed to reaction of the first singlet excited state phthalimido group, by 1,6-hydrogen atom transfer. The product diradicals then react by further hydrogen atom transfer to give the alkenes **182a–d**, by rearrangement to give the bicyclic products **183a** and **183b**, or by coupling to give the tricyclic species **184**. It is interesting to note that the alanine and phenylalanine analogues **185** and **165a** of the amino acid derivatives **157** and **181a–d** did not react on photolysis, indicating that 1,5-hydrogen transfer to the excited state phthalimide does not occur.[199,200] The route outlined above for the preparation of the β,γ-dehydrovaline derivative **182b** has been exploited in the asymmetric synthesis of the amino acid derivative **186**.[201]



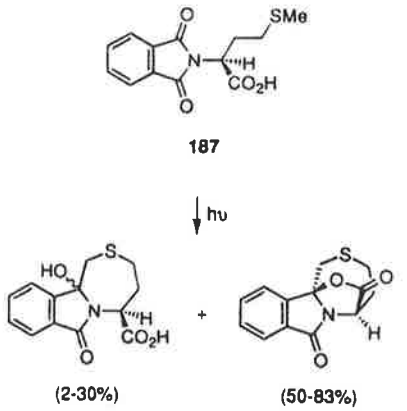
185



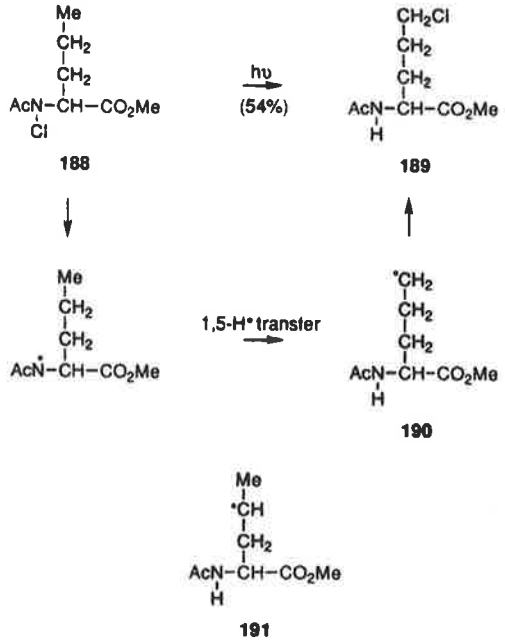
186

For the photochemically initiated hydrogen transfer reactions of *N*-phthaloylamino acid derivatives, the carboxyl group must be protected, otherwise decarboxylation is the predominant reaction.[202,203] Alternatively, electron-transfer reactions sometimes compete effectively with the hydrogen abstraction and decarboxylation processes.[200,203–208] This accounts for the reactions of the methionine derivative **187** (Scheme 21) and analogous reactions of the corresponding methyl ester.[200,203,205] Evidence strongly supporting the electron-transfer mechanism of these reactions comes from the fact that the sulfoxide and sulfone analogues of the sulfide **187** reacted solely by decarboxylation.[209] While the *N*-phthaloylphen-

Scheme 21



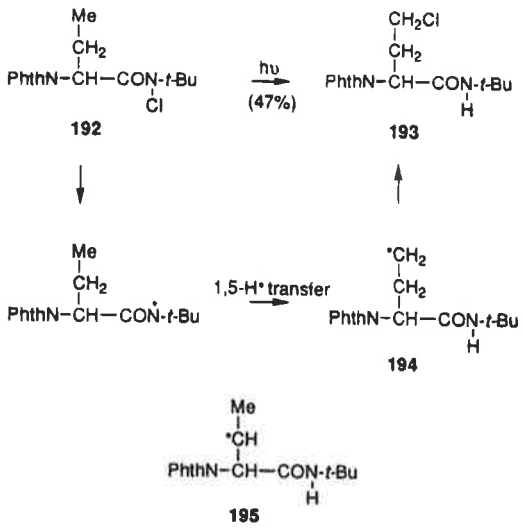
Scheme 22



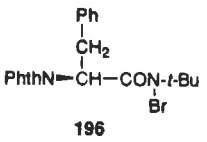
ylalanine derivative **165a** is photochemically inert,[199,200] analogues bearing electron-donating substituents attached to the aromatic ring undergo photocyclization,[210-212] irrespective of protection of the carboxyl group. Again this is consistent with an electron-transfer mechanism.

Amidyl radicals generated by photolysis of *N*-halo amino acid derivatives also react via intramolecular hydrogen atom-transfer to give side-chain radicals. Accordingly the α-amido pentanoate derivative **188** afforded the chloride **189**, while photolysis of the butyramide **192** gave the chloride **193** (Schemes 22 and 23).[213] Presumably, each reaction involves a 1,5-hydrogen atom transfer. Formation of the primary radicals **190** and **194**, in preference to the secondary radicals **191** and **195**, respectively, reflects the relative ease of 1,5-hydrogen transfer compared to the corresponding 1,4-processes. Nevertheless, it appears that the phenylalanine derivative **196** affords a mixture of diastereomers of the bromide **166d**

Scheme 23



through intramolecular 1,4-hydrogen atom transfer.[171]

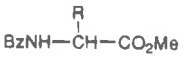


IV. Functional Group Transformations

While free-radical reactions may be used to introduce a functional group or to form a carbon–carbon bond, by substituting for hydrogen, they can also be used to remove or manipulate a functional group and, in a limited number of cases, for the cleavage of a carbon–carbon bond. In the simplest examples, functional groups may be replaced with hydrogen through reaction with tributyl- and triphenyltin hydride. Although the synthetic utility of these reductions is limited, the examples that have been reported show the types of functional groups that may be modified selectively and others that remain unaffected.

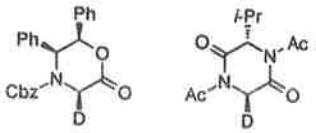
Reactions of this type occur easily at the α-position of amino acid derivatives, due to the stability of the intermediate amino acid radicals. α-Haloglycine derivatives react readily with tributyltin hydride,[70,124] as illustrated by the conversion of the bromide **197a** and the chloride **197b** to the glycine derivative **16a**. The high reactivity of the halides **197a** and **197b** is apparent from the observation that the reductions proceed efficiently, even in potentially reactive halogenated solvents, such as dichloromethane, chloroform, and carbon tetrachloride. The methoxide **197c** and the benzoate **22** were also reduced with tributyltin hydride, in yields of 91 and 92%, respectively.[59] Reactions of the glycine derivatives **22** and **197a–c** with hexabutylditin in place of tributyltin hydride gave the dimer **17**,[56,59] providing strong evidence for the radical nature of these processes. Reductions of α-alkylthio-substituted glycine derivatives have also been reported.[60,214]

Tributyltin deuteride may be used as an alternative to tributyltin hydride; then the products are



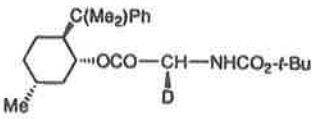
197a: R = Br
197b: R = Cl
197c: R = OMe

chiral α-deuteriated glycine derivatives. In cases where the glycine derivative has been bonded to a chiral auxiliary, generally the diastereoselectivity of deuterium transfer to the intermediate glycinyl radical has been found to be only modest.[95,102,144] The bromides **35a** and **109** gave the corresponding deuterides **198** and **199**, in 60 and 33% diastereomeric excess, respectively.[102,144] The stereoselectivity of these processes is much less than that of the reactions of the bromides **35a** and **109** with deuterium over palladium chloride. Increased stereoselectivity was observed in the reaction of the 8-phenylmenthol derivative **38a** with tributyltin deuteride, which afforded the deuteride **200** in up to 90% diastereomeric excess.[91,92]



198 **199**

(55%)



200

(70%)

The dihalovaline derivatives **94** and **201** each reacted with 1 mol equiv of tributyltin hydride, to give only the corresponding β-halovaline derivatives **202** and **134**.[121,123,124] The regioselectivity of these reactions and the lack of subsequent reactions of the product halides **202** and **134** indicates the relative stability and ease of formation of the α-carbon-centered radicals **203a** and **203b**, compared with the β-carbon-centered radicals **204a**, **204b**, and **136**. In competitive experiments with limiting quantities of the stannane, the haloglycine derivatives **197a** and **197b** reacted to the exclusion of the corresponding dihalovaline derivatives **94** and **201**, indicating the comparative ease of formation of the radicals **20**, **203a**, and **203b**.[121,124] These examples of selective halogen atom transfer from glycine derivatives are analogous to those observed in hydrogen-transfer reactions discussed above, and they can be rationalized in a similar fashion.

While reductions with tin hydrides and deuterides occur most easily at the α-position of amino acid derivatives, efficient reactions also occur on amino acid side chains. The β-chlorovaline derivative **134** reacted with triphenyltin deuteride to give the β-deuteriated valine derivative **205**.[215] Since the chloride **134** was prepared from the valine derivative **92**, and the chlorination and the reduction can be accomplished with optically pure material and without loss

201 **202**

(51%)

203a: X = Br
203b: X = Cl

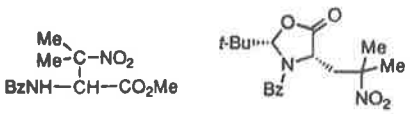
204a: X = Br
204b: X = Cl

of stereochemical integrity, the procedure is applicable to the stereocontrolled synthesis of β-deuteriated valine. The diastereomers of the bromophenylalanine derivative **165d** each reacted with tributyltin deuteride, to give a 3:1 mixture of the diastereomers of the deuteride **206**.[216] The low stereoselectivity observed in these reactions compares with complete retention of configuration in the reactions of the diastereomers of the bromide **165d** with deuterium over palladium on carbon.[217] Tributyltin deuteride has been used to reduce bromocyclopropyl amino acid derivatives to obtain labeled compounds for studies of the mechanism of penicillin biosynthesis.[25,26]

205 **206**

(78%) (89%)

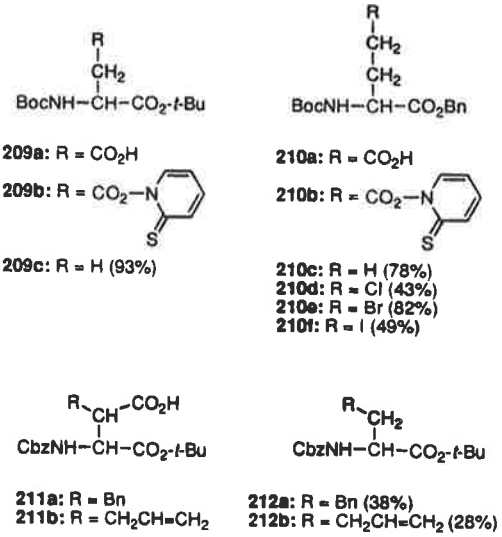
Often free-radical reductions with tributyltin hydride are used to remove a functional group that has been incorporated in an amino acid derivative as part of an overall synthetic strategy. Accordingly, reactions of the derivatives of nitrovaline **207** and nitroleucine **208** were used to substitute the nitro group for hydrogen, in syntheses of amino acid derivatives using alkyl nitronates.[68,129] Xanthate transfer cyclizations and addition reactions have been used in the synthesis of amino acid derivatives, as discussed in more detail below, and reductive cleavage of the product xanthates has been exploited to increase the utility of these processes.[218,219] Iodides have been reduced with tributyltin hydride, as part of syntheses of constrained hydroxy amino acid derivatives,[220-222] while tris(trimethylsilyl)silane has been exploited in a similar manner for the synthesis of bicyclic amino acid derivatives.[223]



207 **208**

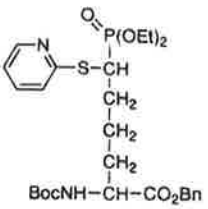
Barton esters of aspartate and glutamate derivatives have been used to remove side-chain carboxyl groups.[224-226] This free-radical methodology is particularly useful, given the lack of ionic alternatives. As examples, the amino acid derivatives **209a** and **210a** were treated with isobutyl chlorocarbonate, then *N*-hydroxypyridine-2-thione to give the corresponding esters **209b** and **210b**. Irradiation of the

esters **209b** and **210b** in the presence of *tert*-butyl mercaptan, as a hydrogen atom source, gave the corresponding derivatives of alanine **209c** and α-aminobutyrate **210c**.[224,225] The method has been applied to the decarboxylation of a glutamate residue in a dipeptide derivative.[225] Side-chain decarboxylation of amino acid derivatives is less facile than loss of the α-carboxyl group, as would be expected from the relative stabilities of the product radicals. In a variation of the decarboxylation procedure, developed for the reactions of α-disubstituted carboxylic acids,[227] the aspartate derivatives **211a** and **211b** were treated with 1-oxa-2-oxo-3-thiaindolizinium chloride, and the products were irradiated in the presence of *tert*-butyl mercaptan, to give the derivatives of homophenylalanine **212a** and butenylglycine **212b**, respectively.[228] Tributyltin hydride has been used to reduce

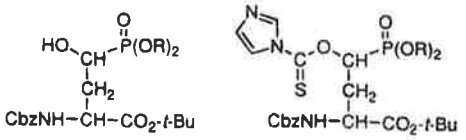


thio- and selenopyridines, such as the phosphonate **213**, as part of synthetic sequences discussed below which involve using Barton esters of amino acid derivatives.[229–231] In a related procedure, radical dehydroxylation of the amino acid derivatives **214a** and **214b** was accomplished by treatment with 1,1-thiocarbonyldiimidazole and then reaction of the products **215a** and **215b** with tributyltin hydride.[232]

By altering the reagents and reactions conditions, many of the free-radical procedures described above for replacing functional groups with hydrogen can be used to interconvert functional groups. In general terms, this involves avoiding hydrogen atom transfer to the intermediate amino acid radicals, by removing the hydrogen source, and providing alternative reaction pathways for these species. In the absence of *tert*-butylmercaptan or another hydrogen atom donor, *N*-hydroxy-2-thio- and 2-selenopyridinone esters of carboxylic acids undergo decarboxylative rearrangement,[233–235] as illustrated in Scheme 24 for the glutamate derivative **216**.[233] Oxidative elimination of the selenopyridine **218** has been used in the synthesis of vinylglycine.[233] Barton esters undergo decarboxylative halogenation when the reactions are conducted in the presence of halogen atom donors, to trap the intermediate amino acid radicals.[224,225,233,235–238] Accordingly, the glutamate de-



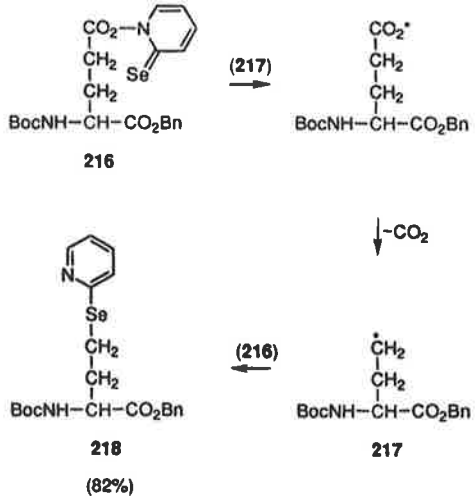
213



214a: R = Me
214b: R = Et

215a: R = Me
215b: R = Et

Scheme 24



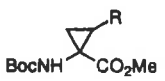
216

218

217

(82%)

rivative **210a** was converted to the corresponding chloride **210d**, bromide **210e**, and iodide **210f**, when the ester **210b** was irradiated in carbon tetrachloride, bromoform and iodoform, respectively.[225] In this manner it was possible to prepare the bromocyclopropane **219b** from the methanoaspartate derivative **219a** without ring opening.[237] Diselenides and di-

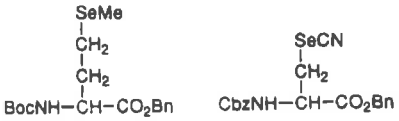


219a: R = CO_2H
219b: R = Br (52%)

cyano triselenide **220** have also been used to trap the intermediate amino acid radicals.[235] For example, the esters **210b** and **221** gave the corresponding methyl selenide **222** and the selenocyanate **223**, when the reactions were carried out in the presence of diphenyl diselenide and the triselenide **220**, respectively. Reactions of this type are of interest in the synthesis of selenomethionine and selenocysteine derivatives.

Functional group interconversions can also be accomplished at the α-position of amino acid deriva-

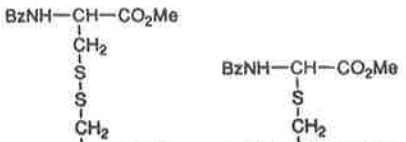
220 221



222 223

(78%) (73%)

tives. The bromide **197a**, the methoxide **197c**, and the benzoate **22** were each treated with hexabutylditin and dialkyl disulfides, to give α-alkylthio-substituted glycine derivatives, through homolytic substitution reactions of the intermediate glycinyl radical **20**.[59,60] When the cystine derivative **224** was used as the disulfide, the cross-linked amino acid derivative **225** was produced. Bromoglycine deriva-

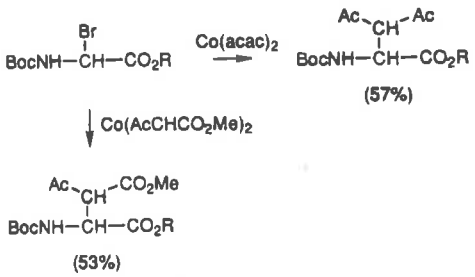


224 225

(73%)

tives have also been used in reactions with cobalt(II) bis(pentane-2,4-dioate) and cobalt(II) bis-(methyl acetoacetate) (Scheme 25).[74] In cases where

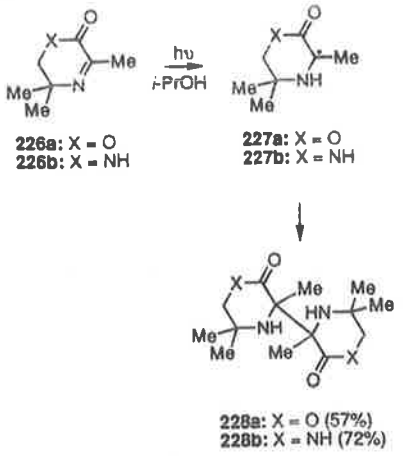
Scheme 25



the glycine carboxyl group was protected as the menthol ester, modest diastereoselectivity was observed.

Photochemical reduction of the imines **226a** and **226b** has been used to produce the dimers **228a** and **228b**, respectively, through coupling of the corresponding α-carbon-centered amino acid radicals **227a** and **227b** (Scheme 26).[38,239,240] The coupling reaction is reversible, and in solution at room temperature, the dimers **228a** and **228b** exist in equilibrium with the corresponding radicals **227a** and **227b**. Through spontaneous carbon−carbon bond homolysis the diastereomers of the dimers **228a** and **228b** interconvert, they undergo oxidation in air to revert to the

Scheme 26

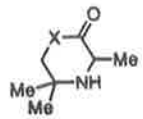


226a: X = O
226b: X = NH

227a: X = O
227b: X = NH

228a: X = O (57%)
228b: X = NH (72%)

imines **226a** and **226b**, and they give mixtures of the imines **226a** and **226b** and the reduced analogues **229a** and **229b** as a result of disproportionation of the corresponding radicals **227a** and **227b**.[240−242]

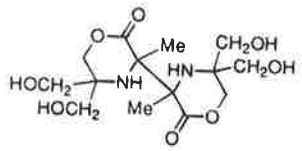


229a: X = O
229b: X = NH

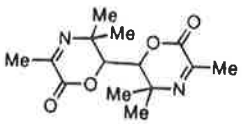
For the diastereomers of the dimer **228a**, the dissociation enthalpy is 11 kcal mol^{-1} in ethanol and 22 kcal mol^{-1} in chloroform.[241] The apparent ease of homolysis of these diastereomers and those of the other dimer **228b** is consistent with the stability of the product radicals **227a** and **227b** although it could result from steric interactions between the monomer units. Elongation of the central bond in the crystal structure of the racemic isomer of the dimer **228a** is consistent with either interpretation.[243] The solvent dependence may reflect the polar nature of α-carbon-centered amino acid radicals (Figure 1) and their stabilization in polar solvents, or it may reflect the disruption of intramolecular hydrogen bonding when the dimers **228a** and **228b** are dissolved in the more polar solvent.

A range of dimers has been obtained,[244] including the diol **230** which has been designed to be soluble in water.[245,246] In a variation of the dimerization procedure, the bis(oxazinone) **231** was used to make macrocycles with coronand structure.[247] The radicals formed by bond homolysis of the dimers act as one electron reducing agents, reflecting the ease of electron transfer from α-carbon-centered amino acid radicals, referred to above. Reductions by the dimers of compounds such as adriamycin and daunomycin have been studied in detail, as models for the *in vivo* manipulation of quinone antitumor drugs.[240,245,246,248−258]

As a final example of the production of amino acid radicals through functional group transformations, photolysis of the pyrazolines **232a−c** gave the corresponding cyclopropylamino acid derivatives **234a−**



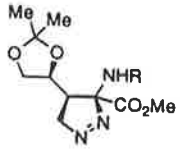
230



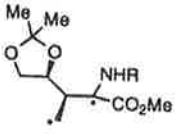
231

(50-66%)

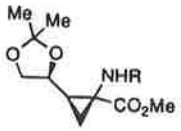
c, presumably through homolytic cleavage followed by coupling of the intermediate diradicals **233a–c**.[259]



232a: R = Cbz
232b: R = Boc
232c: R = Ac



233a: R = Cbz
233b: R = Boc
233c: R = Ac



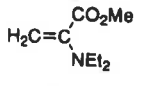
234a: R = Cbz (100%)
234b: R = Boc (100%)
234c: R = Ac (100%)

V. Addition Reactions

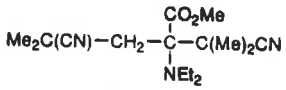
The hydrogen atom-transfer reactions and functional group transformations referred to above involve a diverse range of amino acid radicals, and they illustrate the range of processes available to produce these species. Similar radicals are also formed in addition reactions of unsaturated amino acid derivatives, and the amino acid radicals themselves undergo addition and allyl group transfer reactions. These processes are of particular interest in synthesis as they provide a range of opportunities for building the carbon framework of target species.[6]

A. Intermolecular

Addition reactions of radicals to α,β-unsaturated amino acid derivatives have been the subject of several investigations. For example, reaction of the dehydroalanine derivative **235** with azobisisobutyronitrile gave the bisadduct **236**.[30] It is reasonable to assume that the mechanism of this process involves radical addition at the β-position of the alkene **235** to give the corresponding α-carbon-centered radical **237**, although the product **236** could have formed through the alternate regioselectivity. In the

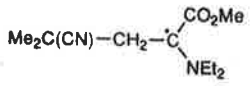


235



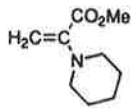
236

(37%)

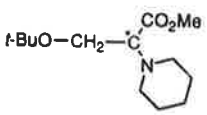


237

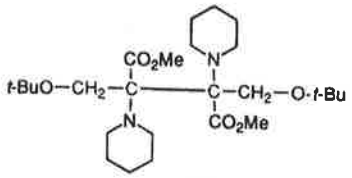
reaction of the dehydroalanine derivative **238** with di-*tert*-butyl peroxide, the mechanism is less ambiguous, and formation of the product **240** can be attributed to dimerization of the radical **239**.[260] This regioselectivity can be attributed mainly to steric effects, with radical addition at the less hindered end of the alkene **238**.[261] Stabilization of the adduct radicals has little effect on reactions of this type, although radical additions to alkenes are favored due to polar effects when the alkenes are substituted with electron-withdrawing groups.[6,261] On this basis, it is as expected that vitamin B_{12}-photoelectrocatalyzed addition reactions to *N*-acetyldehydroalanine methyl ester gave similar yields of products to those obtained from the analogous reactions of methyl acrylate,[262] indicating that the acetamido substituent has little effect in this case.



238



239

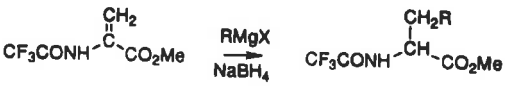


240

(30%)

The *N*-(trifluoroacetyl)dehydroalanine derivative **241** reacted with primary, secondary, and tertiary alkyl radicals, generated by the treatment of alkylmercury halides with sodium borohydride (Scheme 27),[6] but did not react with phenyl radicals.[263] Simi-

Scheme 27

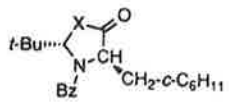


241

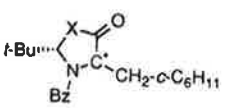
(30-85%)

lar products could not be obtained using tributyltin hydride and alkyl bromides and chlorides, due to competing hydrostannylation of the alkene **241**. In an extension of the work, addition reactions of dehydroalanine residues in di- and tripeptide derivatives were examined.[264] Modest yields of adducts were obtained but the reactions occurred with only poor diastereoselectivity.

Greater diastereoselectivity was achieved in reactions of the cyclic dehydroalanine derivatives **97** and **100**, with either cyclohexylmercury chloride and sodium borohydride or alkyl iodides and tributyltin hydride. Using either method, the adducts **242a** and **242b** were each obtained in at least 60% diastereomeric excess.[125] The diastereoselectivity of these reactions is anomalous as hydrogen atom is apparently delivered to the respective intermediate radicals **243a** and **243b** *syn* to the *tert*-butyl group. In later

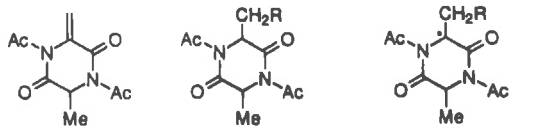


242a: X = O (68%, 73%)
242b: X = NMe (44%, 25%)

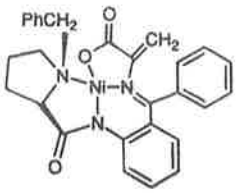


243a: X = O
243b: X = NMe

work, the diastereoselectivity of reactions of analogues of the alkene **97** was found to depend on the nature of the nitrogen protecting group, indicating that it is the steric effect of this substituent which determines the stereochemical outcome.[133] From reactions of the unsaturated piperazine-2,5-dione **244** with isopropyl- and cyclohexylmercury chloride in the presence of sodium borohydride, only the *cis*-isomers of the corresponding disubstituted diketopiperazines **245a** and **245b** were isolated.[265] This indicates that hydrogen atom transfer to the intermediate radicals **246a** and **246b** occurs *anti* to the methyl substituent. Diastereoselective radical addition to the chiral Schiff base derivative of dehydroalanine **247** has also been reported.[266]



244 **245a:** R = *i*-Pr (46%) **245b:** R = *c*-C_6H_{11} (49%) **246a:** R = *i*-Pr **246b:** R = *c*-C_6H_{11}

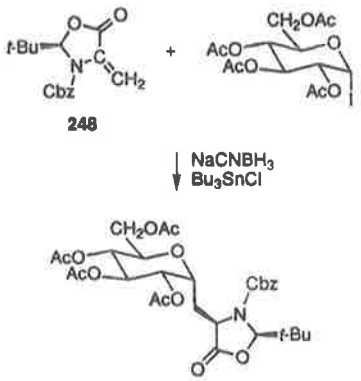


247

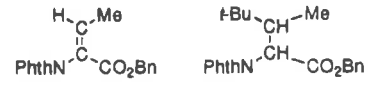
C-Glycopeptides have been obtained through the radical addition of glycosyl halides to dehydroalanine derivatives, using sodium cyanoborohydride and tributyltin chloride.[133,267] In all cases studied the reactions displayed high stereoselectivity for the formation of α-*C*-glycosides. The degree of stereocontrol of bond formation at the α-carbon of the alanine moiety depended on the substrate, however, ranging from very low in reactions of dehydroalanine residues in small peptides[267] to diastereospecific in reactions of the alkene **248** (Scheme 28).[133]

The addition reactions described above each involve dehydroalanine residues, where the lack of a β-substituent is likely to favor reaction on steric grounds.[6,261] There has been only one report of radical addition to a β-substituted α,β-dehydroamino acid derivative.[268] The phthalimide **249** reacted with *tert*-butyl iodide and tributyltin hydride to give a 2.3:1 mixture of the diastereomers of the adduct **250**. Radical addition

Scheme 28



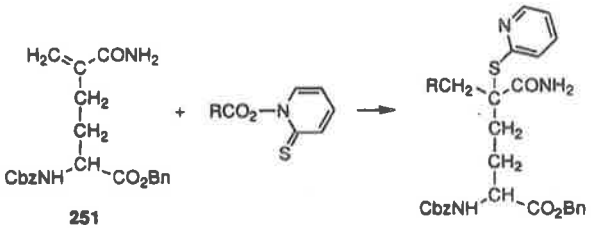
248 (88%)



249 **250** (41%)

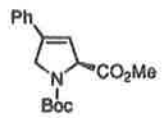
to the less hindered end of the double bond of the δ,ϵ-dehydro amino acid derivative **251** has also been reported (Scheme 29).[230] This is one of several

Scheme 29



251

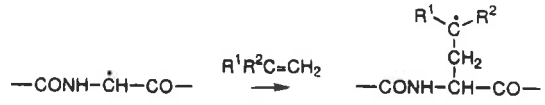
examples of reactions of dehydro amino acid derivatives which proceed via side chain radicals. Others involve reactions of hydrogen bromide, and sulfuryl and phosphoryl radicals, with vinyl- and allylglycine derivatives,[165,269-272] and manganese(III) acetate-catalyzed addition of monomethyl malonate to the proline derivative **252**.[273]



252

The observation that addition reactions of dehydro amino acid derivatives occur irrespective of whether the adduct is an α-carbon-centered radical or a side-chain radical is consistent with the understanding that the stability of the product radical has little effect on the efficiency of these processes.[261] It is also known that the stability of the radical which adds to the alkene has little effect on the ease of addition,[261] explaining why α-carbon-centered amino acid radicals also add to alkenes, despite their stability. The synthetic utility of the photoalkylation procedures developed by Elad *et al.* (Schemes 1 and 2) is significantly enhanced by the ease with which the intermediate glycinyl radicals **253** react with terminal alkenes such as but-1-ene, 2-methylpropene, hex-1-ene, and oct-1-ene (Scheme 30).[51,53,54,109,110,136-138,274,275] Subsequent reactions of the adduct radicals **254** to produce the telomers **255** occurred to only a small extent.[109,110,138,275] By exploiting alkenes in the photoalkylation processes, glycine residues in peptides were selectively elaborated to produce a range of α-substituted amino acid derivatives, with

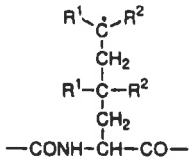
Scheme 30



253 254

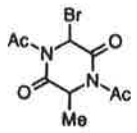
a: R^1 = Et, R^2 = H
b: R^1 = Me, R^2 = Me
c: R^1 = Bu, R^2 = H
d: R^1 = n-C_6H_{13}, R^2 = H

a small degree of diastereoselectivity in some cases.[53,109,137,138,275] Glycinyl radicals generated from

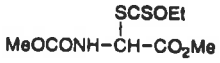


255

the bromide **256**[88] and the xanthate **257**,[219] using tributyltin hydride and di-*tert*-butyl peroxide, respectively, also reacted by addition to alkenes. In the latter case, 1,2-disubstituted alkenes were used as well as terminal alkenes.

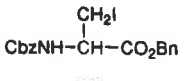


256

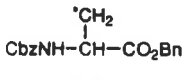


257

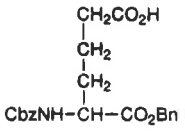
Amino acid side-chain radicals have also been exploited in addition reactions with alkenes. Treatment of the iodide **258** with tributyltin hydride in the presence of acrylic acid afforded the adducts **260** and **261**, from sequential addition reactions of the alaninyl radical **259**.[276] A similar reaction of the bromide **169b** with tributyltin hydride and methyl vinyl ketone has also been reported.[192] Radicals obtained by decarboxylation of aspartate and glutamate derivatives, via the *N*-hydroxypyridine-2-thione esters, have also been used in addition reactions with alkenes.[229-231,234] When the decarboxylations were performed using the corresponding pyridine-2-selenone derivatives, there was no addition to activated



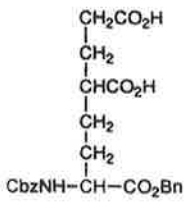
258



259



260 (30%)



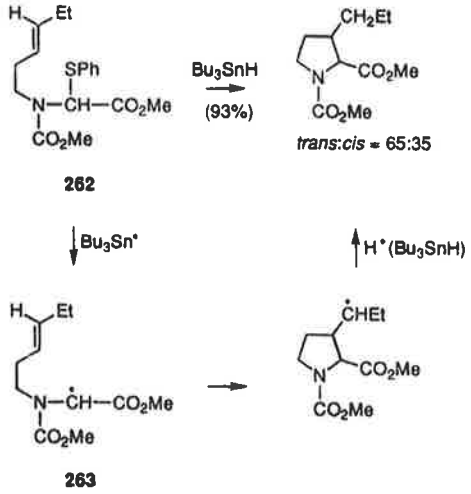
261 (6%)

olefins, however, and only rearranged products were obtained.[233]

B. Intramolecular

Intramolecular addition reactions of amino acid radicals provide access to cyclized derivatives. The advantage of free radicals in this area is that their characteristic cyclization modes[5,277] are distinct from those of their ionic counterparts. In particular, radicals typically react in the *exo*-mode, as illustrated in Scheme 31 for reaction of the α-(phenylthio)glycine

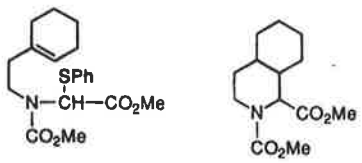
Scheme 31



262

263

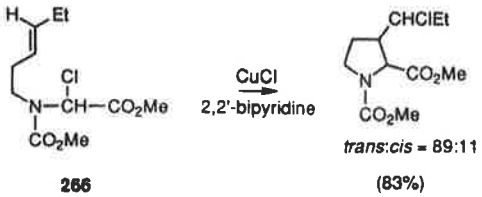
derivative **262** on treatment with tributyltin hydride.[278-280] Subtle geometrical constraints can affect the balance between the *exo*- and *endo*-cyclizations; however, particularly in reactions to give bicyclic compounds, and the cyclohexene derivative **264** reacted in the *endo* mode, to give mainly the ring-fused species **265**.[278,280]



264 265 (61%)

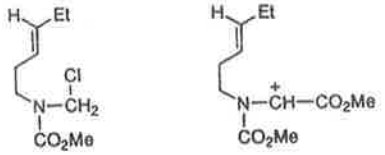
In a variation of the cyclization procedure, treatment of α-chlorinated glycine derivatives with cuprous chloride in the presence of 2,2′-bipyridine resulted in radical ring closure (Scheme 32).[279,281-283] The advantage of this method is that it avoids the

Scheme 32



266 (83%)

reductive termination of the tin hydride process, leaving a functional group in the product for further manipulation. The decarboxylated analogue **267** of the chloroglycine derivative **266** underwent cyclization in the *endo*-mode, presumably in a cationic reaction.[282] The change in mechanism can be attributed to the effect of the methoxycarbonyl group to stabilize the radical **263** and destabilize the corresponding carbocation **268**. Xanthate transfer reactions have also been used to accomplish cyclizations of glycinyl radicals without reductive termination.[218] Using this method, 1,5- and 1,6-*exo*-cyclizations occurred, whereas the copper-catalyzed reaction of chloroglycine derivatives failed in the latter case.



267 **268**

Glycinyl radical cyclizations have been used in the synthesis of fused bicyclic β-lactams.[284-286] The strain imposed by the preexisting azetidinone ring generally outweighs the normal tendency for reaction in the *exo*-mode, as illustrated in Scheme 33 for reaction of the chloroglycine derivative **269**.[284] *exo*-Cyclization only occurred to a significant extent with the analogues **270** (Scheme 34),[284] where the substituents retard *endo*-cyclization, due to steric effects, and may favor the *exo*-process by stabilizing the cyclized radicals. Prior functionalization of the glycine residue is not essential for reaction, and the β-lactam **271** reacted directly with a catalytic amount of tributyltin hydride to give the carbacephem (**272**, Scheme 35).[287] Presumably, the glycinyl radical **273** is generated in this chain process through hydrogen atom transfer to the bicyclic radical **274**.

Scheme 33

269 (47%)

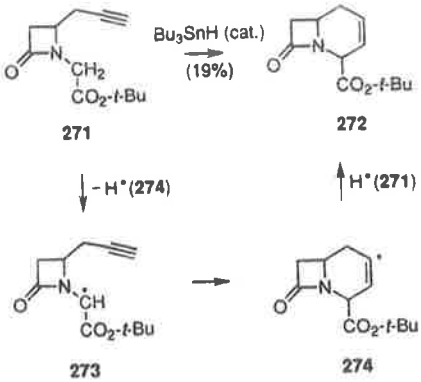
Scheme 34

270

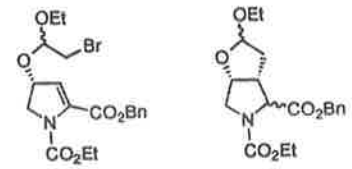
a: R = CO_2Me (68%)
b: R = Ph (68%)

The bromide **275** reacted with tributyltin hydride to give the cyclized derivative **276**,[288] and analogous reactions have been used to produce a range of fused bicyclic species.[289,290] Again this illustrates the preference for 1,5-*exo*-cyclization. By contrast 1,5-*endo*-cyclization is favored over the 1,4-*exo*-process, due to the ring strain associated with the latter. Accordingly, the chlorides **277a–d** reacted with tributyltin hydride to give the pyrrolidinones **278a–d**, respectively,[291,292] while cyclization of the imine **279** gave the α-carbon-centered radical **280** (Scheme 36).[293]

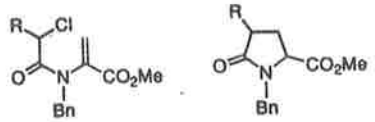
Scheme 35



271 **272** **273** **274**



275 **276** (100%)

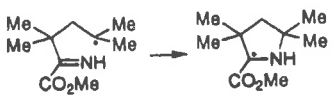


277a: R = H
277b: R = Me
277c: R = Ph
277d: R = Bn

278a: R = H (70%)
278b: R = Me (47%)
278c: R = Ph (56%)
278d: R = Bn (33%)

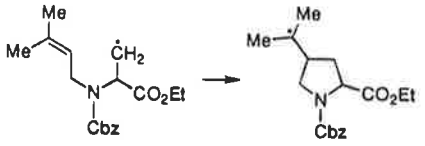
In addition to cyclization reactions of α-carbon-centered amino acid radicals, and reactions to give those species, intramolecular addition reactions involving only side chain radicals have also been reported. In representative examples, the *N*-allyl-substituted β-alaninyl radical **281** reacted by 1,5-*exo*-cyclization to give the proline derivative **282** (Scheme 37),[294-298] whereas reaction of the aztidinyl radical **282** occurred in the 1,6-*endo*-mode (Scheme 38),[299-301] presumably due to the strain associated with the bicyclic system. Thiyl radical additions such as those illustrated in Scheme 39 have been used in the construction of the penam and cepham carbon skeletons, through 1,5-*exo*- and 1,6-*endo*-cyclizations, respectively,[302-308] and thiopyroglutamates and thiopiperidinones have been generated by *exo*-cyclizations of the type shown in Scheme 40.[309] The radicals **283a**

Scheme 36



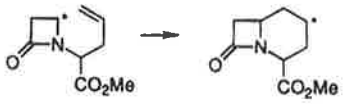
279 **280**

Scheme 37



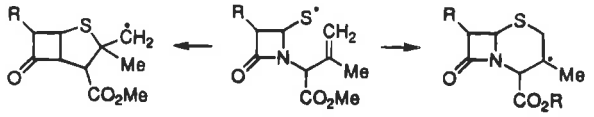
281 **282**

Scheme 38

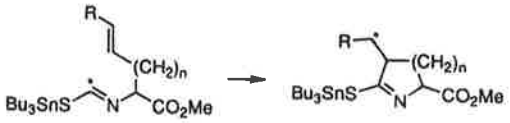


283

Scheme 39



Scheme 40

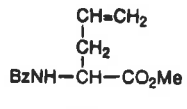


284a: R = Me, n = 2
284b: R = Ph, n = 1,2

and **283b** were produced through addition of tributyltin radical to isothiocyanates, derived from α-amino acids. Analogous thiol-mediated cyclizations of isocyanides have also been reported.[310,311]

C. Allylations and Rearrangements

Allyl group transfer reactions have provided another procedure for the elaboration of amino acid derivatives using free-radical methodology. α-Carbon-centered amino acid radicals readily undergo reactions of this type, as demonstrated by reaction of the bromide **197a** with allylstannanes to produce the corresponding allylglycine derivative **285**.[70,312] The

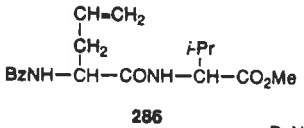


285

(62%, 65%)

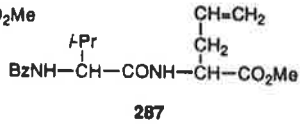
process is not restricted to reactions of bromides, and the alkoxide **197c** and the benzoate **22** also reacted to give the same product **285**.[59] 2-Chloro-, 2-cyano-, and 2-ethoxycarbonyl-substituted allylstannanes reacted in a similar manner, to give the corresponding γ-functionalized allylglycine derivatives.[312] Normally reactions of 1- and 3-alkyl-substituted allylstannanes are complicated by competing elimination reactions,[6,313-315] but difficulties of this type were not encountered in reactions of the bromide **197a**.[316]

The allylation procedure has been used for the elaboration of glycine residues in peptides, as an extension of the selective bromination of those residues.[70] Reactions of the bromides **106b** and **107b** afforded the corresponding products **286** and **287**, as 1:1 and 3:1 mixtures of the diastereomers, respectively. More substantial asymmetric induction was observed in reactions of cyclic dipeptides, and the bromide **109** afforded only the *trans*-diketopiperazine **288**.[144] The bromoglycine derivative **38b** also reacted with allyltributylstannanes with a high degree of asymmetric induction.[104,105] The same substrate **38b** was treated with allenyl- and alkynyl-stannanes but the products obtained in those cases were consistent with an ionic rather than a radical mechanism, involving the glycinyl cation instead of the corresponding radical.[104,105] In the reaction of the bromide **289** with allyltributylstannane, zinc chloride was found to act as a radical initiator and to increase the diastereoselectivity of allyl transfer.[93]



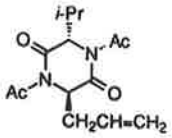
286

(35%)



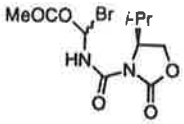
287

(33%)



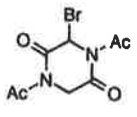
288

(60%)

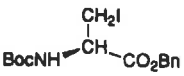


289

In other examples of the allylation procedure which involve α-carbon-centered amino acid radicals, reactions of the bromides **29**[317] and **290**,[88] and an alkylthio-substituted glycine residue in a peptide,[214] with allyltributylstannane have also been reported. In examples which involve side chain radicals, the bromotryptophan derivative **169b**[192] and the iodoalanine derivatives **258** and **291**[315,318] underwent allyl transfer reactions with stannanes. Treatment of



290



291

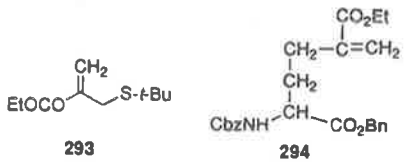
haloalanine derivatives with triphenylprop-2-ynylstannane (**292**) afforded allenyl amino acids, as illustrated in Scheme 41 for the iodide **258**.[319]

Allyl sulfides can be used as alternatives to allylstannanes, in cases where thiyl radicals can propagate the radical chain processes. Accordingly the

Scheme 41

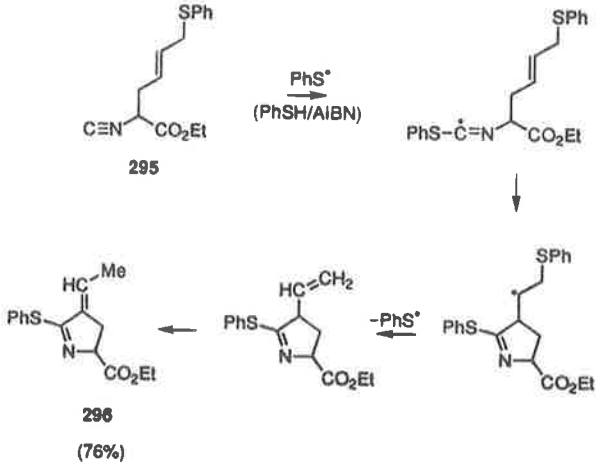
258 **292** (60%)

Barton ester **221** reacted with the sulfide **293** to give the amino acid derivative **294**.[234] In an intramolecu-



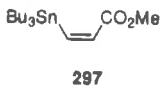
lar variation of this type of reaction involving a sulfide, the isocyanide **295** reacted with catalytic amounts of thiophenol and azobisisobutyronitrile to give the pyrroline **296** (Scheme 42).[310]

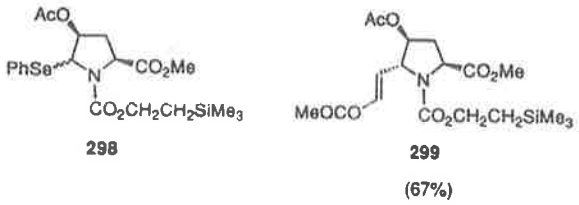
Scheme 42

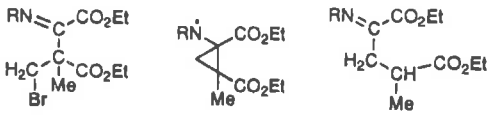


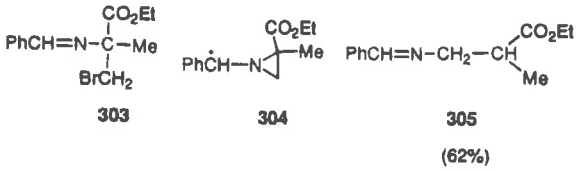
Methyl β-(tributylstannyl)acrylate (**297**) was developed as another reagent for alkylation through an addition–elimination radical chain sequence.[320,321] It has been exploited in the reaction of the proline derivative **298** to give the corresponding acrylate **299**.[184] Another type of radical addition–elimination reaction sequence of amino acid derivatives which has attracted attention has involved reactions of the bromoimines **300a**, **300b**, and **303**.[322–326] On treatment with tributyltin hydride, these react by intramolecular addition, with formation of the corresponding cyclopropyl radicals **301a**, **301b**, and **304**, and then β-scission to give the rearranged products **302a**, **302b**, and **305**, respectively. Reactions of this type have been studied as models of biochemical systems involving catalysis by vitamin B_{12}.[327] The rearrangement of the bromo imine **300b** is also catalyzed by vitamin B_{12} *in vitro*,[324] and analogous reactions have been reported using vitamin B_{12} analogues,[328–332] but it is not clear if these processes involve radical or ionic intermediates.

An intramolecular radical addition is also involved in the reaction of the proline derivative **306** with tributyltin hydride (Scheme 43).[333] The cyclization is preceded by an intramolecular 1,5-radical translocation.[334,335] Processes of this type significantly expand the utility of radicals in synthesis because they provide new opportunities for regioselective radical formation.

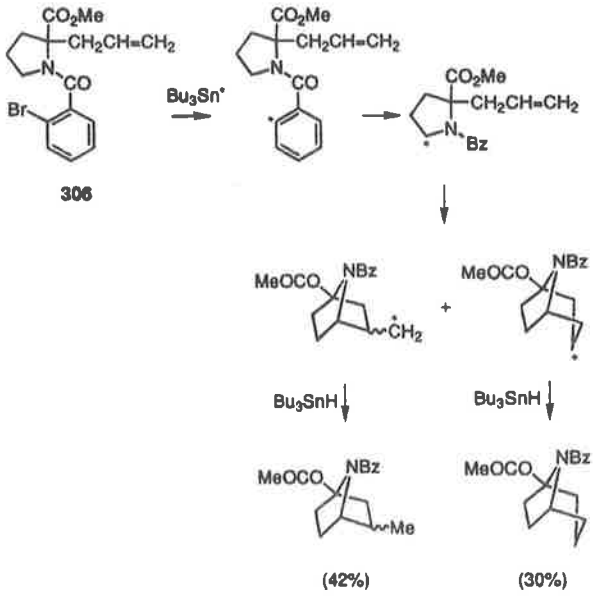








Scheme 43



VI. Conclusion

The chemistry summarized in this review indicates the extent to which free-radical chemistry has been developed for, and applied to, the synthesis of amino acids and their derivatives. Unique transformations have been accomplished and, in many cases, good product yields have been obtained. Procedures for addition and cyclization reactions, and for the introduction and manipulation of functional groups, have been discussed. These indicate the level of regio- and stereocontrol that can be achieved and highlight the potential utility of radical reactions in this area. The

examples reported to date clearly demonstrate the key role that radical reactions can be expected to play in the continuing search for methods to access these important compounds.

VII. Acknowledgments

This review was partially compiled while the author was on leave in the Department of Chemistry at the University of Otago. The generous support of the Department is gratefully acknowledged. The author's continuing interest in this area has been stimulated by an enthusiastic group of co-workers whose professional contributions and social interactions are greatly appreciated.

Note Added in Proof

While this review was in press, an article by Renaud and Giraud was published,[336] in which they reviewed aspects of the chemistry of amino- and amidoalkyl radicals.

VIII. References

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Free-radical reactions for the stereoselective synthesis of amino acid derivatives

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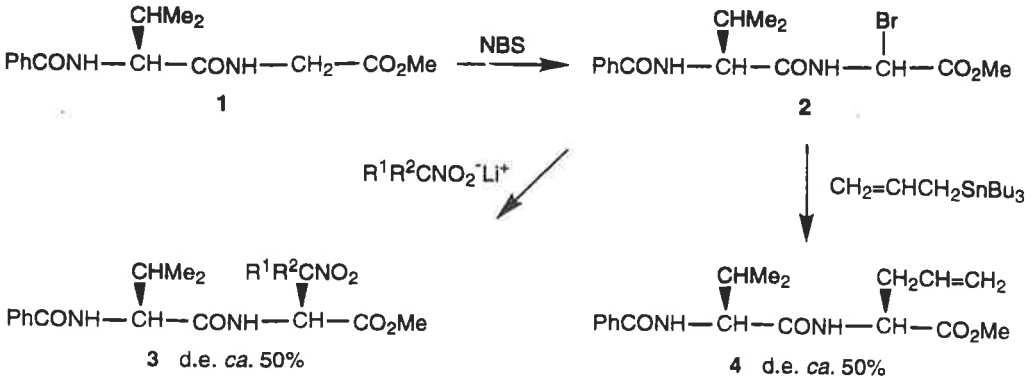
Abstract: By exploiting the selective hydrogen atom transfer reactions of glycine residues in small peptides, it is possible to utilise other amino acid residues as chiral auxiliaries in stereoselective synthesis. Alternatively, radical side-chain functionalisation of *N*-phthaloyl-substituted amino acid derivatives occurs without racemisation. The synthetic utility of the latter procedure is enhanced by the ability to use the phthaloyl group in subsequent reactions to remember the chirality of the amino acids.

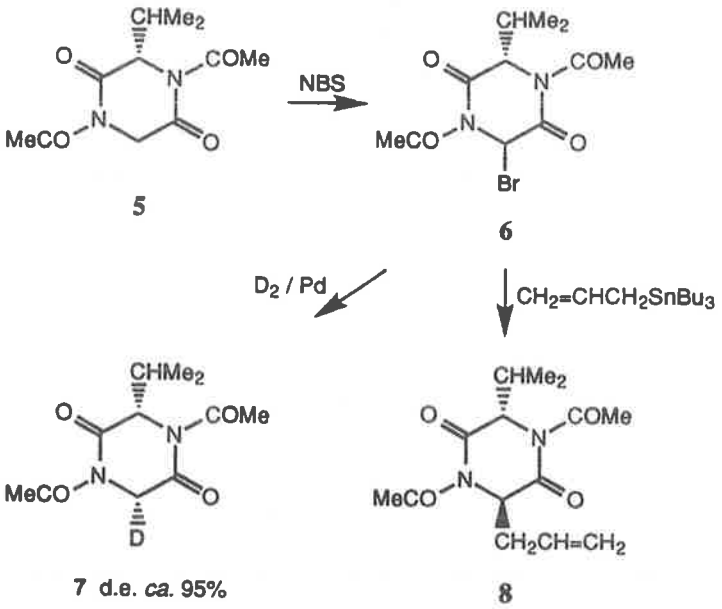
The proteinogenic α-amino acids constitute an important pool of optically active starting materials for asymmetric synthesis. Ionic reactions of these compounds have been extensively exploited but less attention has been given to using free radical chemistry in this area. In part this must be attributed to the tendency for amino acid derivatives to form α-carbon-centred radicals (ref. 1), with consequent loss of optical purity. Now it has been recognised that there are several ways to either exploit or avoid formation of these species, in order that radical reactions of amino acid derivatives can be accomplished efficiently and in good yield, with a high degree of regio- and stereo-control.

Hydrogen atom transfer reactions of amino acid derivatives are known to be selective for formation of glycinyl radicals (ref. 2-4). For example, treatment of the valylglycine derivative **1** with *N*-bromosuccinimide gave only the bromide **2** (ref. 4), presumably through bromine incorporation at the site of hydrogen atom abstraction. Bromoglycine derivatives of this type are suitable for further elaboration, as illustrated in the synthesis of the allylglycine derivative **4** and the β-nitroamino acid derivatives **3**, through reaction of the bromide **2** with allyltributylstannane (ref. 4-6) and alkyl nitronates (ref. 7), respectively. In these reactions the valine residue in the dipeptide derivative **1** is acting as a chiral auxiliary. Given that either enantiomer of the auxiliary is cheap and readily avaliable, and that the auxiliary can be recovered through product hydrolysis and recycled, the limitation to this approach to the asymmetric synthesis of amino acid derivatives is the modest degree of diastereoselectivity.



1 **2**

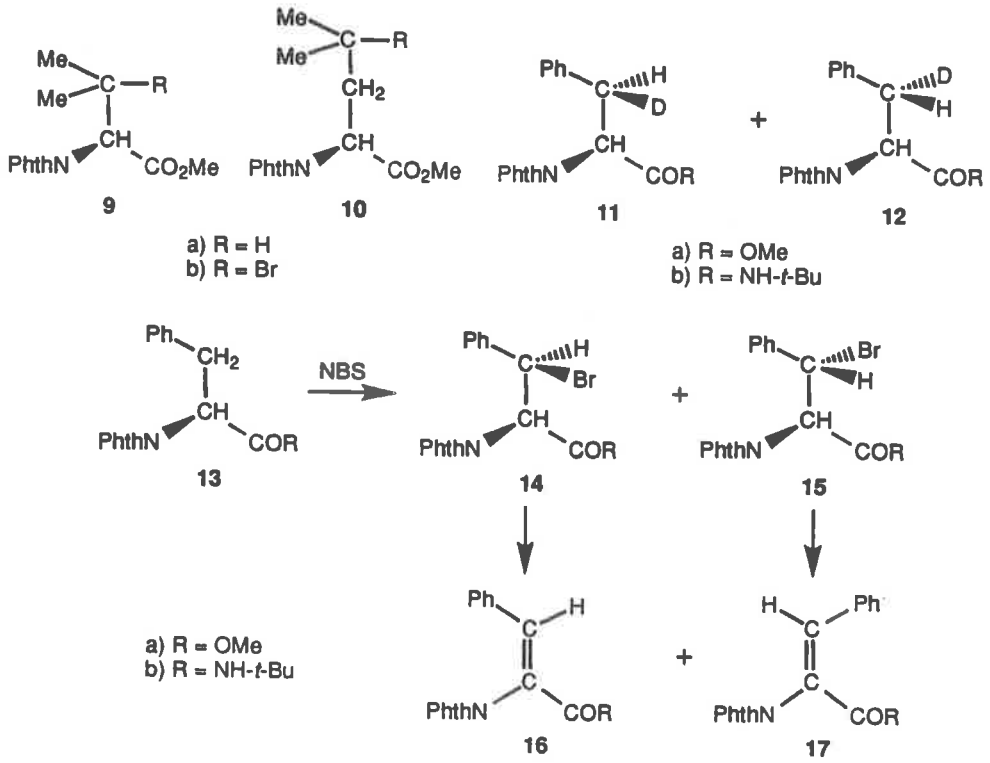
3 d.e. *ca.* 50% **4** d.e. *ca.* 50%



5 6

7 d.e. *ca.* 95% 8

This limitation may be overcome through the use of more highly constrained systems, in which the relative geometry of the chiral and prochiral centres is more rigidly defined (ref. 8). Accordingly, bromination of the glycine residue in the cyclic dipeptide derivative **5** gave the bromide **6**. Reaction of the bromide **6** with allyltributylstannane gave only the diastereomer **8**, from incorporation of the allyl group *anti* to the side chain of the valine residue. Deuteriolysis of the bromide **6** gave the labelled product **7** and this reaction also occurred with a high degree of diastereoselectivity. The reactions of the diketopiperazine **5** illustrate an approach for the asymmetric synthesis of amino acid derivatives which is complementary to the Schöllkopf procedure for the elaboration of bislactim ethers (ref. 9).



9 10 11 12

a) R = H
b) R = Br

a) R = OMe
b) R = NH-*t*-Bu

13 14 15

a) R = OMe
b) R = NH-*t*-Bu

16 17

An alternative way to exploit radical reactions in asymmetric synthesis is to use optically active amino acid derivatives as starting materials, and to carry out reactions on the amino acid side chains, while avoiding formation of the α-carbon-centred radicals. This can be accomplished through the use of *N*-phthaloyl-protected amino acid derivatives (ref. 10). The amino acid derivatives **9a** and **10a** reacted with *N*-bromosuccinimide, without racemisation, to give the bromides **9b** and **10b**, respectively. In the case of the phenylalanine derivatives **13a,b**, 1:1 mixtures of the corresponding bromides **14a,b** and **15a,b** were obtained. The diastereomeric pairs were separated by chromatography and fractional crystallisation, and in this way each of the bromides **14a,b** and **15a,b** was obtained as a single stereoisomer.

18 **19**

a) R = OMe
b) R = NH-*t*-Bu

The bromides **14a,b** and **15a,b** are suitable for elaboration in stereocontrolled syntheses, and they gave the corresponding dehydrophenylalanine derivatives **16a,b** and **17a,b** in reactions with potassium fluoride (ref. 11). Their reactions with deuterium over palladium on carbon resulted in the stereospecific production of the deuterides **11a,b** and **12a,b**, respectively (ref. 12). Treatment of a 1:1 mixture of the bromide diastereomers **14a** and **15a** with silver nitrate in aqueous acetone afforded a 5:1 mixture of the corresponding alcohols **18a** and **19a**, while a mixture of the bromoamides **14b** and **15b** gave only the hydroxyamide **18b** (ref. 13). The stereoconvergent nature of these transformations negates the need for separation of the bromide diastereomers **14a,b** and **15a,b** prior to reaction. The diastereoselectivity of reaction of the bromophenylalaninamides **14b** and **15b** was significantly greater than that of the reactions of the corresponding esters **14a** and **15a**, as a result of neighbouring group participation by the amido group, to effectively block one face of the intermediate carbocation (Fig. 1).

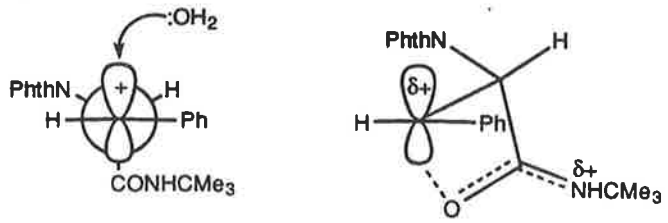
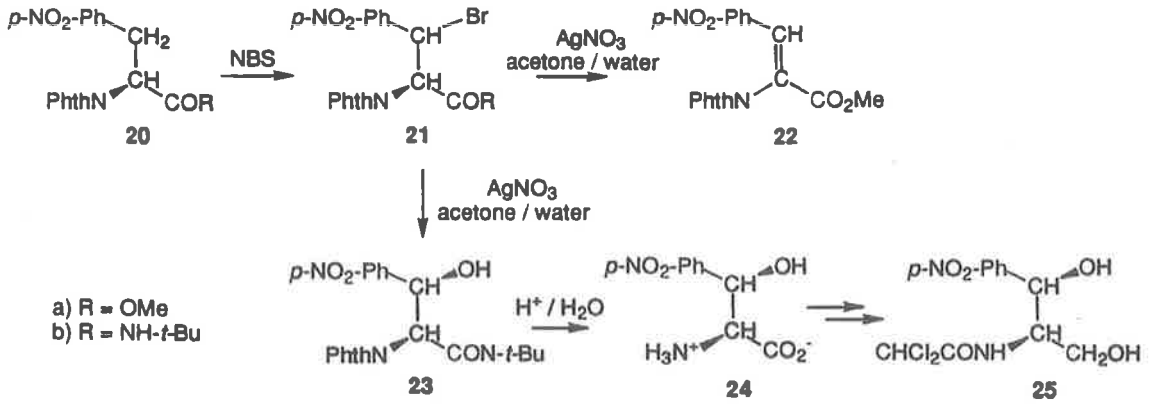


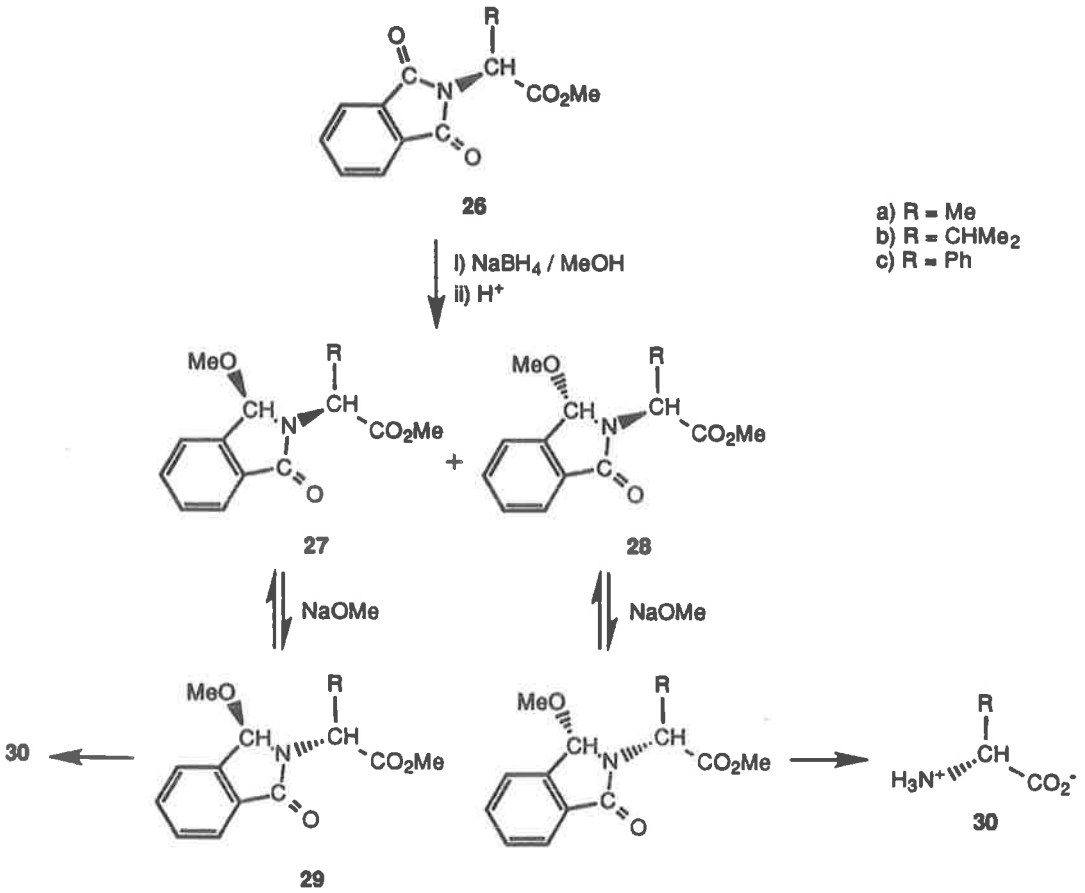
Fig. 1 Neighbouring group participation in reaction of the bromides **14b** and **15b**

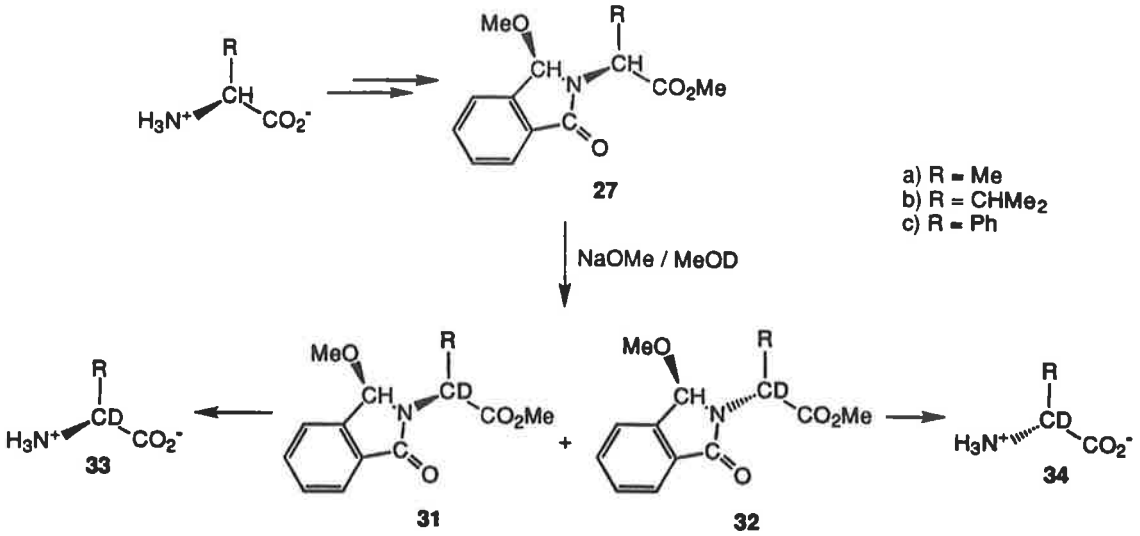
This neighbouring group effect of the carboxyl substituent affects the mechanism of reaction as well as the stereochemical outcome (ref. 14). The nitrophenylalanine derivatives **20a** and **20b** gave the corresponding bromides **21a** and **21b**, each as a 1:1 mixture of the diastereomers, through reaction with *N*-bromosuccinimide. On treatment with silver nitrate in aqueous acetone, the bromoester **21a** gave the dehydrophenylalanine derivative **22**, while the bromoamide **21b** afforded the alcohol **23**. Presumably the amide **21b** reacts by substitution, where formation of the intermediate carbocation is facilitated by the amido group, whereas the ester **21a** reacts by elimination because the extent of neighbouring group participation is reduced in that case and, therefore, the corresponding benzylic cation does not form.

Hydrolysis of the alcohol **23** gave the corresponding free amino acid **24**, providing a route for the stereocontrolled synthesis of the antibiotic chloramphenicol **25**. In a similar fashion, (2*S*,3*R*)-β-hydroxy-phenylalanine and tyrosine were obtained, and these compounds are of interest in the synthesis of peptide antibiotics such as lysobactin and vancomycin.



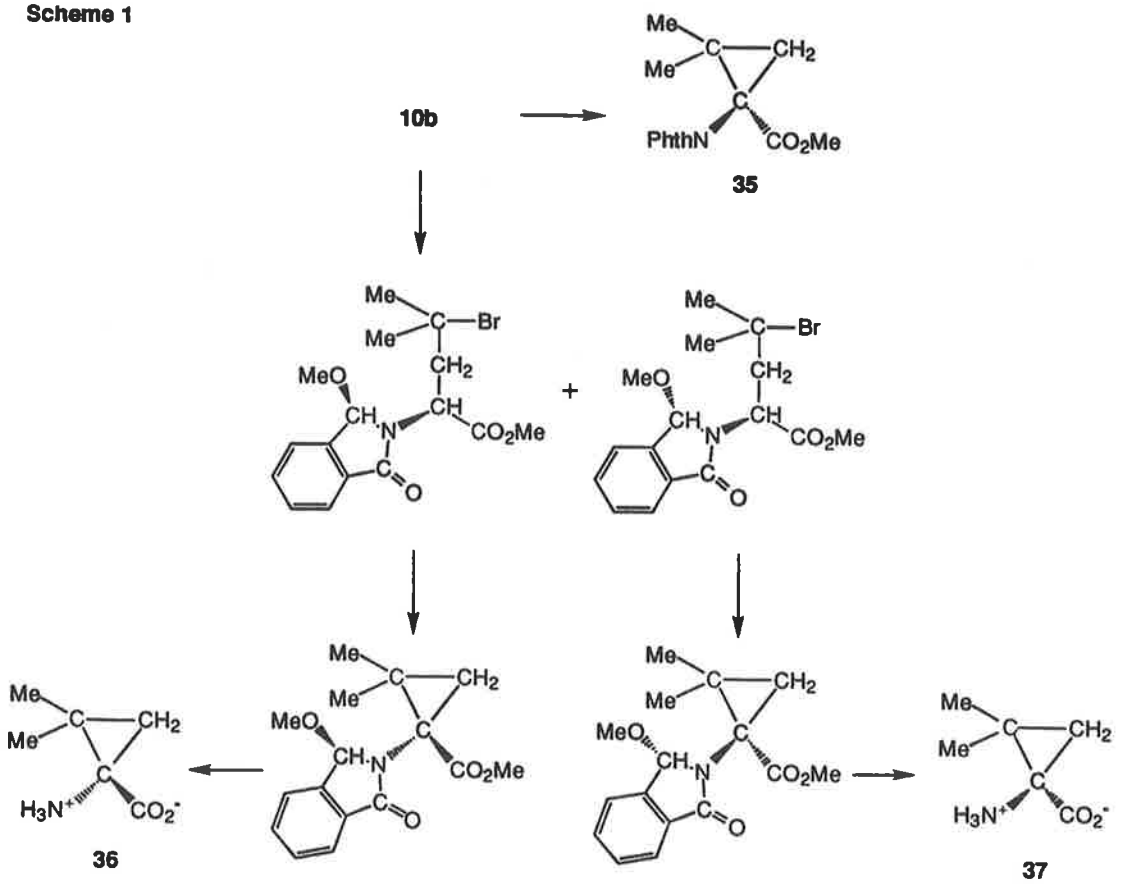
Obviously the phthaloyl protecting group can be removed without racemisation of the amino acid. It is also possible to epimerise the amino acid during the deprotection, by exploiting the phthaloyl group to remember the chirality (ref. 15). The (*S*)-amino acid derivatives **26a-c** reacted with sodium borohydride in methanol, then hydrochloric acid, to give the partially reduced products **27a-c** and **28a-c**. The diastereomers **27a-c** and **28a-c** were separated by using either chromatography or fractional crystallisation. Treatment of the (*S*,*S*)-diastereomers **27a-c** with sodium methoxide in methanol resulted in isomerisation at the α-position. Again the diastereomers **27a-c** and **29a-c** were separated and the new components **29a-c** were hydrolysed to give the (*R*)-amino acids **30a-c**, respectively. The (*R*,*S*)-diastereomers **28a-c** were also used to prepare the corresponding (*R*)-amino acids **30a-c**, in a similar manner.





Using sodium methoxide in deuteriated methanol, the isomerisation of the partially reduced phthalimides **27a-c** is accompanied by deuterium incorporation. Separation of the labelled products **31a-c** and **32a-c**, followed by hydrolysis, affords the (*S*)-α-deuterio amino acids **33a-c** and the (*R*)-isomers **34a-c** in a stereocontrolled fashion.

Scheme 1



This chemistry significantly enhances the utility of the phthaloyl group in the asymmetric synthesis of amino acid derivatives, particularly when it is exploited in conjunction with the use of the phthalimide to achieve side chain functionalisation of amino acid derivatives. For example, it provides a route for the

stereocontrolled synthesis of the methanovaline enantiomers **36** and **37**. As outlined above, halogenation of the leucine derivative **10a** afforded the bromide **10b**. When the bromide **10b** was treated with sodium hydride, cyclisation occurred to give the methanovaline derivative **35** (ref. 16), but the reaction resulted in complete racemisation. This was avoided, however, by using the phthaloyl protecting group to remember the amino acid chirality (Scheme 1).

The author is greatly indebted to an enthusiastic group of co-workers, for their intellectual and practical contributions to this research, as well as for social interactions. Individual contributions are noted in the references.

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A Versatile Synthesis of Linked Cyclodextrins

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Reactions of amino-substituted cyclodextrins with bis(3-nitrophenyl) oxalate, malonate, succinate and glutarate, and with diphenyl carbonate, afford a range of linked cyclodextrins. These include α- and β-cyclodextrin dimers, joined by substitution at either C6 or C3, and asymmetric species with a β-cyclodextrin bonded to an α-cyclodextrin and a C3-substituted cyclodextrin attached to a C6-substituted moiety.

Introduction

The concept that cooperative binding by the hydrophobic cavities of covalently bonded cyclodextrins leads to the formation of particularly stable inclusion complexes with large aromatic guests has been investigated by a number of groups. Diamine,[1] diester,[2–5] disulfide,[4–9] dithioether,[5,8–15] diether[16] and imidazolium[5] linked cyclodextrins have been studied. Several years ago, we reported[17] a procedure for the efficient synthesis of the diamide-linked cyclodextrins (4c–e) and the cooperative binding of 6-(*p*-toluidino)naphthalene-2-sulfonate by these species.[18] More recently, Nolte *et al.*[19,20] reported a related procedure for the synthesis of C3-linked cyclodextrins.

The studies with cyclodextrin dimers have highlighted the way in which a molecular host can be modified to match the geometry of a guest, to form a more stable host–guest inclusion complex. This concept of tailoring a linked cyclodextrin to a guest is exemplified in the work of Sikorski and Petter,[14] where a variety of dithioether-linked cyclodextrins were synthesized, in order to examine the effect of the tether length on the extent of cooperative guest binding. In a similar fashion, Breslow *et al.*[5,8,21] accomplished tight binding of rigid guests in linked cyclodextrins having defined optimal geometry. This group has also developed linked cyclodextrins as catalysts, by controlling the orientation and geometry of host–guest binding to align reactive centres of the guest and host.[11,12,21]

In order to be able to match the cyclodextrin host to a particular guest, it is necessary to have versatile procedures for synthesis of the linked species. Our initial studies[17] were limited to the synthesis of the three cyclodextrin dimers (4c–e), each linked by substitution of a cyclodextrin primary hydroxy group. The procedure has now been extended to the synthesis of a much greater range of linked cyclodextrins, including dimers joined at either end of the cyclodextrin annulus and some asymmetric linked species. These examples are described in the present report, together with full details of our earlier work, to illustrate the scope and general utility of this methodology.

Results and Discussion (See Fig. 1)

The amines (1a,b) and (2) used in the synthesis of the linked cyclodextrins (4a–f), (5a,b), (7) and (8) were obtained as reported previously.[22,23] The diester (3a) was obtained through treatment of oxalyl chloride with 3-nitrophenol,[24] while the diesters (3b–d) were prepared from the corresponding dicarboxylic acids, through reaction with either dicyclohexylcarbodiimide or thionyl chloride, followed by treatment with 3-nitrophenol.[3,25] This choice of starting materials was based on the expectation that 3-nitrophenyl esters would undergo nucleophilic substitution reactions selectively with the amino groups of the modified cyclodextrins (1a,b) and (2). Accordingly, treatment of the diesters (3a–d) with 2 mol. equiv. of the amine (1a), in either pyridine or *N,N*-dimethylformamide, at room temperature for 36 h, afforded the corresponding cyclodextrin dimers (4a–d), in yields ranging from 60 to 78%. In a similar manner, the α-cyclodextrin derivative (1b) reacted with the succinate (3c) to give the dimer (4e) in 94% yield. The analogous reactions of the C3 amino-substituted cyclodextrin derivative (2) with the oxalate (3a) and the succinate (3c) were relatively inefficient, however, giving the diamides (5a) and (5b) only in 29 and 47% yield, respectively. This difference may be attributed to the fact that the amine substituent of the cyclodextrin (2) is located within the annulus, while the amino groups of the C6-substituted derivatives (1a,b) are more exposed and therefore more reactive.

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When the reactions to give the linked cyclodextrins (4a–e) were monitored by thin-layer chromatography, two distinct processes were observed. In each case a primary product formed, during the first 0·5–2 h after the reagents were mixed, and subsequently reacted. In the case of the reaction of the amine (1a) with the succinate (3c), the primary product was isolated and identified as the cyclodextrin derivative (6). The yield of this material was optimized to 95% by repeating the reaction with a fivefold molar excess of the diester (3c) to limit the secondary process. Presumably the reaction to give the monosubstituted product (6) is faster than the subsequent process, due to the effect of the greater steric bulk of the cyclodextrin derivative (6) compared to the diester (3c) on the relative susceptibility of those species towards nucleophilic substitution.

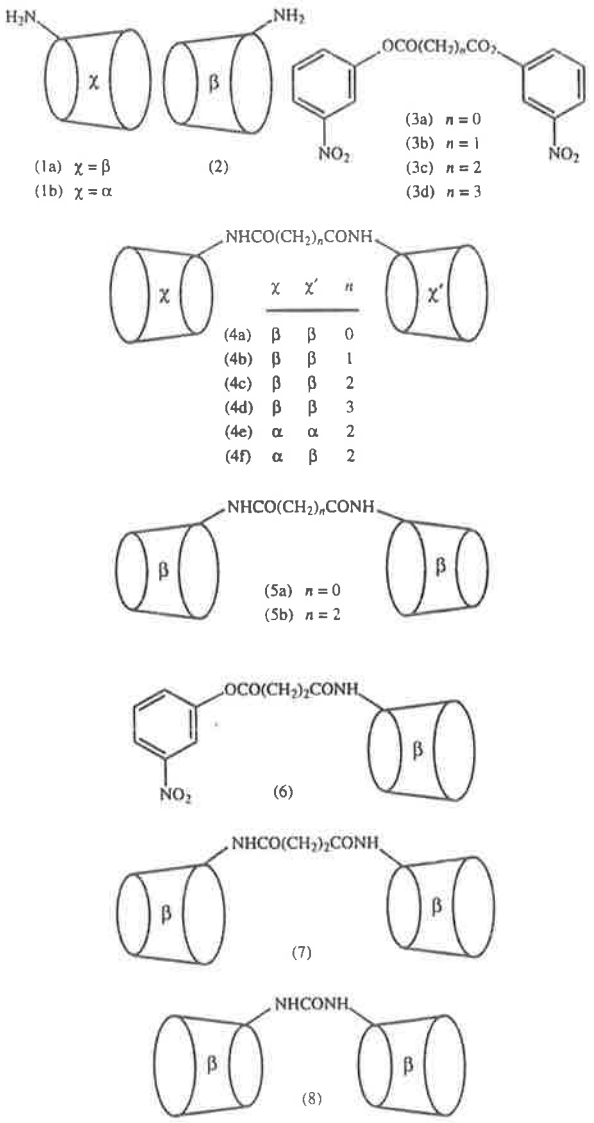

Fig. 1. A truncated cone is commonly used to represent a cyclodextrin. A substituent drawn at the narrow end of the cone indicates that it replaces a primary hydroxy group. In this paper, a substituent drawn at the wide end of the cone indicates that it replaces a C 3 hydroxy group, with inversion of stereochemistry at C 2 and C 3 of the modified D-glucopyranose residue.

With access to the cyclodextrin derivative (6), it was possible to prepare asymmetric linked species. The reaction with the amine (1b) gave a 92% yield of the diamide (4f), in which an α-cyclodextrin is linked to a β-cyclodextrin. Again, the analogous reaction of the amine (2) was relatively inefficient, but the diamide (7) comprising two β-cyclodextrin moieties linked at opposite ends was obtained in 32% yield.

Synthesis of the diamides (4a–f), (5a,b) and (7) shows that a wide variety of linked cyclodextrins can be obtained through reaction of amino-substituted cyclodextrins with diesters. The oxalamide-bridged dimers (4a) and (5a) have the shortest tether between the cyclodextrins, but the bridge can be made even smaller, by using diphenyl carbonate instead of a diester as the linking agent. This is illustrated in the reaction of the amine (1a) to give the urea derivative (8), in 53% yield. This route to the cyclodextrin derivative (8) is complementary to that reported recently by Sallas *et al.*[26] involving reaction of 6^A-azido-6^A-deoxy-β-cyclodextrin with triphenylphosphine and carbon dioxide.

Each of the linked species (4a–f), (5a,b), (7) and (8) was shown to be homogeneous, through t.l.c. and h.p.l.c. analysis. They were dried to constant weight over phosphorus pentoxide before elemental analysis, but they still retained residual water, which is likely to be contained mostly within the cyclodextrin cavities. The most convincing diagnostic evidence for the structures of the cyclodextrins (4a–f), (5a,b), (7) and (8) came from their ^{13}C n.m.r. spectra. In particular, each of the dimers (4a–e), (7) and (8) gave rise to a signal in the range δ 41·0–43·7, for C 6^A of each cyclodextrin moiety, while the diamides (5a) and (5b) which are linked by substitution of a cyclodextrin secondary hydroxy group showed signals for C 3^A at δ 54·0 and 53·0, respectively. The spectrum of the cyclodextrin (7) showed signals at δ 41·9 and 53·0, indicating one C 6^A- and one C 3^A-substituted annulus, while the asymmetry of the diamide (4f) was evident from the presence of two amide carbon signals, at δ 175·7 and 176·9.

In summary, the reactions described above illustrate a general method for the synthesis of a wide range of linked cyclodextrins. The products are chemically stable, to the extent that no degradation has been observed in samples stored at −20° for several years. The yields of the linked cyclodextrins range from modest to good, but they are generally much higher than those obtained by other procedures, and the method is suitable for the synthesis of multigram quantities. Access to these compounds should facilitate a systematic evaluation of cooperative binding by linked cyclodextrins, as indicated by our initial studies in this area.[18,27]

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C n.m.r. spectra were recorded on a Bruker ACP-300 spectrometer, as dilute solutions in D_2O. Fast atom bombardment mass spectra were recorded on a Vacuum Generators ZAB 2HF mass spectrometer. Infrared spectra were recorded as Nujol mulls on a Hitachi 270-30 spectrometer. Elemental analyses were performed by either the Canadian Microanalytical Service Ltd, Vancouver, or the Research School of Chemistry, Australian National University. High-performance liquid chromatography (h.p.l.c.) was carried out by means of a Waters 510 solvent delivery system coupled to a Waters 410 differential refractometer in conjunction with an ICI DP-700 data station. The column used was a Waters 3·9 by 300 mm carbohydrate analysis column, eluting at 1·5 ml min^{-1} with acetonitrile/water (70%, v/v) (the t_r of a cyclodextrin derivative indicates the retention time relative to that of the parent cyclodextrin). Ether refers to diethyl ether. Light petroleum refers to the fraction with b.p. 66–68°. Cyclodextrin derivatives were dried to constant weight over phosphorus pentoxide before analysis or use.

N,N′-*Bis(6^A-deoxy-β-cyclodextrin-6^A-yl)oxalamide (4a)*

Bis(3-nitrophenyl) oxalate (3a)[24] (36 mg, 0·108 mmol) was added to a solution of the amino-substituted cyclodextrin (1a)[22] (250 mg, 0·22 mmol) in *N,N*-dimethylformamide (5 ml), and the mixture was left to stir at room temperature for 36 h, then it was concentrated to 1 ml under reduced pressure. The residue was added dropwise to acetone (20 ml), and the precipitate which formed was collected by vacuum filtration and washed with ether (5 ml). The crude product (269 mg) was dissolved in aqueous ammonia (20%, v/v, 5 ml), and the solution was added dropwise to ice-cooled acetone (30 ml). The precipitate which formed was collected by vacuum filtration and washed with acetone (20 ml) and ether (20 ml), then it was dissolved in water (5 ml). This solution was added to a stirred suspension of BioRex 70 (1·0 g, H^+ form) in water (20 ml), and the mixture was stirred at room temperature for 24 h. The mixture was filtered and the resin was rinsed with water (3×10 ml). The combined filtrates were evaporated under reduced pressure and dried over phosphorus pentoxide to give the oxalamide (4a) (186 mg, 71%) as a colourless *powder* (Found: 42·1; H, 6·1; N, 1·3. $C_{86}H_{140}N_2O_{70}.7H_2O$ requires C, 42·2; H, 6·3; N, 1·1%). H.p.l.c. t_r 3·5. ν_{max} 1662 cm^{-1}. Mass spectrum *m/z* 2322 (M$^+$). ^{1}H n.m.r. δ 3·6, m, 28H; 3·9, m, 54H; 5·05, m, 14H. ^{13}C n.m.r. δ 43·7 (C6^A), 61·7, 71·6, 73·8, 74·6, 75·0, 82·8, 84·4, 103·6, 162·2 (C=O).

N,N′-*Bis(6^A-deoxy-β-cyclodextrin-6^A-yl)malonamide (4b)*

The malonamide (4b) was prepared as colourless *crystals* in 78% yield by treatment of the amino-substituted cyclodextrin (1a) with bis(3-nitrophenyl) malonate (3b),[25] according to the method described above for the synthesis of the oxalamide (4a) (Found: C, 42·6; H, 6·3; N, 1·4. $C_{87}H_{142}N_2O_{70}.7H_2O$ requires C, 42·4; H, 6·4; N, 1·2%). H.p.l.c. t_r 1·6. ν_{max} 1658 cm^{-1}. Mass spectrum *m/z* 2336 (M$^+$). ^{1}H n.m.r. δ 3·5, m, 30H; 3·9. m, 54H; 5·1, m, 14H. ^{13}C n.m.r. δ 42·2 (C6^A), 45·2, 62·2, 72·1, 73·7, 74·0, 74·7, 75·0, 83·0, 85·0, 103·8, 171·3 (C=O).

N,N′-*Bis(6^A-deoxy-β-cyclodextrin-6^A-yl)succinamide (4c)*

The succinamide (4c) was prepared as a colourless powder in 64% yield, by treatment of the amino-substituted cyclodextrin (1a) with bis(3-nitrophenyl) succinate (3c).[3] according to the method described above for the synthesis of the oxalamide (4a) (Found: C, 42·8; H, 6·4; N, 1·1. Calc. for $C_{88}H_{144}N_2O_{70}.6H_2O$: C, 43·0; H, 6·4; N, 1·1%). H.p.l.c. t_r 5·6. ν_{max} 1642 cm^{-1}. Mass spectrum *m/z* 2350 (M$^+$). ^{1}H n.m.r. δ 2·07, s, 4H; 3·6, m, 28H; 3·85, m, 54H; 5·05, m, 14H. ^{13}C n.m.r. δ 31·9, 41·0 (C6^A), 61·2, 71·2, 72·8, 73·0, 74·0, 82·0, 84·0, 102·8, 175·5 (C=O).

N,N′-*Bis(6^A-deoxy-β-cyclodextrin-6^A-yl)glutaramide (4d)*

The glutaramide (4d) was prepared as a colourless powder, in 60% yield, by treatment of the amino-substituted cyclodextrin (1a) with bis(3-nitrophenyl) glutarate (3d), according to the method described above for the synthesis of the oxalamide (4a) (Found: C, 42·3; H, 6·4; N, 1·2. Calc. for $C_{89}H_{146}N_2O_{70}.8H_2O$: C, 42·6; H, 6·5; N, 1·1%). H.p.l.c. t_r 3·4. ν_{max} 1642 cm^{-1}. Mass spectrum *m/z* 2364 (M$^+$). ^{1}H n.m.r. δ 1·75, m, 2H; 2·15, m, 4H; 3·6, m, 28H; 3·85, m, 54H; 5·05, m, 14H. ^{13}C n.m.r. δ 22·7, 35·9, 41·0 (C6^A), 61·0, 61·3, 71·1, 72·6, 73·0, 74·0, 82·0, 84·1, 102·8, 176·7 (C=O).

N,N′-*Bis(6^A-deoxy-α-cyclodextrin-6^A-yl)succinamide (4e)*

The succinamide (4e) was prepared as a colourless powder, in 94% yield, by treatment of the amino-substituted cyclodextrin (1b) with bis(3-nitrophenyl) succinate (3c), according to the method described above for the synthesis of the oxalamide (4a) (Found: C, 42·5; H, 6·6; N, 1·3. Calc. for $C_{74}H_{120}N_2O_{60}.6H_2O$: C, 42·2; H, 6·3; N, 1·3%). H.p.l.c. t_r 3·2. ν_{max} 1658 cm^{-1}. Mass spectrum *m/z* 1998 (M$^+$). ^{1}H n.m.r. δ 2·29, s, 4H; 3·6, m, 24H; 3·85, m, 46H; 5·05, m, 12H. ^{13}C n.m.r. δ 32·2, 41·4 (C6^A), 61·3, 61·6, 71·5, 72·9, 73·2, 74·3, 74·5, 82·4, 84·3, 102·6, 175·9 (C=O).

N,N′-*Bis((2^{A}S,3^{A}S)-3^A-deoxy-β-cyclodextrin-3^A-yl)oxalamide (5a)*

The oxalamide (5a) was prepared as colourless *crystals*, in 29% yield, by treatment of the amino-substituted cyclodextrin (2) with bis(3-nitrophenyl) oxalate (3a), according to the method described above for the synthesis of the oxalamide (4a) (Found: C, 41·4; H, 6·3; N, 1·2. $C_{86}H_{140}N_2O_{70}.10H_2O$ requires C, 41·3; H, 6·5; N, 1·1%). H.p.l.c. t_r 1·9. ν_{max} 1660 cm^{-1}. Mass spectrum *m/z* 2322 (M$^+$). ^{1}H n.m.r. δ 3·6, m, 28H; 3·85, m, 54H; 5·05, m, 14H. ^{13}C n.m.r. δ 54·0 (C3^A), 62·3, 73·5, 73·8, 74·1, 74·5, 75·1, 83·0, 83·1, 103·4, 104·0, 105·2, 162·6 (C=O).

N,N′-*Bis((2^{A}S,3^{A}S)-3^A-deoxy-β-cyclodextrin-3^A-yl)succinamide (5b)*

The succinamide (5b) was prepared as colourless crystals, in 47% yield, by treatment of the amino-substituted cyclodextrin (2) with bis(3-nitrophenyl) succinate (3c), according to the method described above for the synthesis of the oxalamide (4a). ν_{max} 1662 cm^{-1}. Mass spectrum *m/z* 2350 (M$^+$). ^{1}H n.m.r. δ 2·6, s, 4H; 3·6, m, 28H; 3·85, m, 54H; 5·05, m, 14H. ^{13}C n.m.r. δ 32·3, 53·0 (C3^A), 61·7, 62·3, 71·9, 73·3, 73·6, 73·9, 74·1, 74·4, 74·7, 75·0, 75·2, 81·9, 82·7, 82·8, 83·0, 83·1, 103·2, 103·5, 103·8, 103·9, 105·8, 176·9 (C=O). These spectroscopic characteristics are consistent with those reported previously.[17]

6^A-Deoxy-6^A-(3-(3-nitrophenoxycarbonyl)propionamido)-β-cyclodextrin (6)

The amino-substituted cyclodextrin (1a) (300 mg, 0·26 mmol) was added to a solution of bis(3-nitrophenyl) succinate (3c) (500 mg, 1·39 mmol) in *N,N*-dimethylformamide (35 ml), and the mixture was left to stir at room temperature for 2 h, then it was concentrated to *c.* 1 ml under reduced pressure. The residue was added dropwise to acetone (50 ml); the precipitate which formed was collected by vacuum filtration and washed with acetone (3×20 ml), then it was dried under vacuum over phosphorus pentoxide, to give the propionamide (6) as a cream *solid* (340 mg, 95%) (Found: C, 44·2; H, 5·9; N, 2·1. $C_{52}H_{78}N_2O_{39}.3H_2O$ requires C, 44·3; H, 6·0; N, 2·0%). ν_{max} 1770, 1650 cm^{-1}. Mass spectrum *m/z* 1355 (M$^+$). ^{1}H n.m.r. δ 2·50, s, 2H; 2·78, s, 2H; 3·4, m, 14H; 3·6, m, 27H; 4·8, m, 7H; 7·3–8·4, m, 4H. ^{13}C n.m.r. δ 33·2, 33·6, 41·9 (C6^A), 63·9, 73·8, 76·0, 76·4, 77·0, 85·4, 85·6, 87·5, 105·9,

121·2, 124·7, 132·8, 134·7, 152·2, 154·8, 174·8 (C=O), 175·1 (C=O).

N-(6^A-Deoxy-α-cyclodextrin-6^A-yl)-N′-(6^A-deoxy-β-cyclodextrin-6^A-yl)succinamide (4f)

A mixture of the propionamide (6) (270 mg, 0·2 mmol) and the amino-substituted cyclodextrin (1b) (200 mg, 0·21 mmol) in pyridine (5 ml) was stirred at room temperature for 3 days, then it was concentrated to dryness under reduced pressure. The residue was dissolved in water (30 ml), and the resultant solution was concentrated to dryness under reduced pressure. After that process had been repeated twice, the residue was dissolved in water (3 ml), and the resultant solution was added dropwise to acetone (50 ml). The precipitate which formed was collected by vacuum filtration and washed with acetone (2×30 ml). The residue was dissolved in water (10 ml), and the solution was added to a suspension of BioRex 70 (1 g, H^+ form) in water. The suspension was stirred at room temperature for 2 days, after which time it was filtered. The filtrate was concentrated under reduced pressure, to *c.* 3 ml, and the residue was added to acetone (50 ml). The precipitate which formed was collected by vacuum filtration, and washed with acetone (2×30 ml). Then it was dried under reduced pressure over phosphorus pentoxide to give the succinamide (4f) as a colourless *solid* (401 mg, 92%) (Found: C, 44·1; H, 6·7; N, 1·2. $C_{82}H_{134}N_2O_{65}.3H_2O$ requires C, 43·9; H, 6·3; N, 1·3%). H.p.l.c. t_r 3·0. ν_{max} 1645 cm^{-1}. Mass spectrum *m/z* 2188 (M^+). ^{1}H n.m.r. δ 2·60, s, 4H; 3·6, m, 26H; 3·85, m, 50H; 5·0, m, 13H. ^{13}C n.m.r. δ 32·0, 41·2 (C6^A), 61·0, 61·3, 61·4, 71·4, 72·7, 72·9, 73·0, 74·1, 74·3, 82·2, 84·1, 102·4, 102·9, 175·7 (C=O), 176·9 (C=O).

N-((2^{A}S,3^{A}S)-3^A-Deoxy-β-cyclodextrin-3^A-yl)-N′-(6^A-deoxy-β-cyclodextrin-6^A-yl)succinamide (7)

The succinamide (7) was prepared as colourless *crystals*, in 32% yield, by treatment of the amino-substituted cyclodextrin (2) with the propionamide (6), according to the method described above for the synthesis of the succinamide (4f) (Found: C, 41·5; H, 6·7; N, 1·1. $C_{88}H_{144}N_2O_{70}.12H_2O$ requires C, 41·2; H, 6·6; N, 1·1%). H.p.l.c. t_r 2·0. ν_{max} 1650 cm^{-1}. Mass spectrum *m/z* 2350 (M^+). ^{1}H n.m.r. δ 2·60, s, 4H; 3·6, m, 28H; 3·85, m, 54H; 5·0, m, 14H. ^{13}C n.m.r. δ 33·0, 33·1, 41·9 (C6$^{A'}$), 53·0 (C3^A), 61·6, 62·8, 72·0, 72·3, 73·3, 73·5, 73·6, 73·9, 74·1, 74·3, 74·7, 74·8, 75·1, 82·0, 82·7, 82·8, 82·9, 83·1, 85·0, 103·2, 103·4, 103·6, 104·0, 105·9, 176·7 (C=O), 176·9 (C=O).

N,N′-Bis(6^A-deoxy-β-cyclodextrin-6^A-yl)urea (8)

Diphenyl carbonate (30 mg, 0·14 mmol) was added to a solution of the amino-substituted cyclodextrin (1a) (500 mg, 0·44 mmol) in pyridine (6 ml) and water (4 ml); the mixture was heated at 100° for 4 h, then it was concentrated under reduced pressure. The residual solid was dissolved in pyridine (5 ml), and the solution was added dropwise with stirring to ether (30 ml). The precipitate which formed was separated by vacuum filtration and washed with ether (30 ml) and acetone (30 ml), then it was dissolved in a mixture of water (13·5 ml) and methanol (1·5 ml). The solution was passed through a column of Sephadex SP-C 25 cation exchange resin, and the column was eluted with the same solvent mixture. The eluate was concentrated to dryness under reduced pressure, finally over phosphorus pentoxide for 24 h, to give the urea (8) as a colourless *solid* (170 mg, 53%) (Found: C, 42·4; H, 6·4; N, 1·0. $C_{85}H_{140}N_2O_{69}.6H_2O$ requires C, 42·5; H, 6·5; N, 1·2%). H.p.l.c. t_r 1·8. ν_{max} 1658 cm^{-1}. Mass spectrum *m/z* 2294 (M^+). ^{1}H n.m.r. δ 3·5, m, 28H; 3·85, m, 54H; 5·0, m, 14H. ^{13}C n.m.r. δ 42·3 (C6^A), 62·2, 72·6, 73·7, 74·0, 74·7, 75·0, 83·0, 84·6, 103·8, 162·3 (C=O).

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Complexation of Methyl Orange and Tropaeolin 000 No. 2 by β-cyclodextrin dimers

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Spectrophotometric studies of the complexation of Methyl Orange (MO^-) and Tropaeolin 000 No. 2 (TR^-) anions by dimeric *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin)urea $(\beta CD)_2ur$ and its oxalamide and succinamide analogues, $(\beta CD)_2ox$ and $(\beta CD)_2su$, respectively, are consistent with the predominant formation of complexes of the general formulae $(\beta CD)_2x \cdot MO^-$ characterized by stability constants $K_1 = (1.05 \pm 0.04) \times 10^5$, $(1.92 \pm 0.04) \times 10^5$ and $(2.50 \pm 0.02) \times 10^4$ dm^3 mol^{-1} and $(\beta CD)_2x \cdot TR^-$ characterized by $K_1 = (1.39 \pm 0.03) \times 10^4$, $(7.4 \pm 0.1) \times 10^3$ and $(4.60 \pm 0.05) \times 10^3$ dm^3 mol^{-1}, in aqueous phosphate buffer at pH 9.0 and 5.5 and 298.2 K. These values are significantly greater than $K_1 = 2160$ and 710 dm^3 mol^{-1} for the β-cyclodextrin complexes, $\beta CD \cdot MO^-$ and $\beta CD \cdot TR^-$ and are indicative of cooperative binding in $(\beta CD)_2x \cdot MO^-$ and $(\beta CD)_2x \cdot TR^-$. The factors affecting complex stability are discussed and comparisons are made with related systems.

β-Cyclodextrin (βCD) is produced from the enzymatic degradation of starch, and is the cyclic α-1,4-linked heptamer of glucopyranose in which seven primary and fourteen secondary hydroxy groups, respectively, delineate the narrow and wide ends of a macrocyclic annulus whose hydrophobic interior is lined with methine and methylene groups and ether oxygens.[1–3] This hydrophobic interior functions as a recognition site when βCD acts as the host in the formation of $\beta CD \cdot G$ host–guest complexes with a wide range of guests (G), most of which contain an aromatic group which enters the hydrophobic region of the βCD annulus on complexation.[4–6] When two βCD are joined through a linker, x, in a dimer, $(\beta CD)_2x$,[7–9] the stability of the host–guest complex, $(\beta CD)_2x \cdot G$, in which G has two aromatic binding sites, is usually substantially increased over that of $\beta CD \cdot G$.[7,8,10–20] This is attributable to cooperation between the two βCD recognition sites in complexing G in $(\beta CD)_2x \cdot G$. We now seek further insight into this cooperative effect through a study of the influence of the variation of the linker length in the β-cyclodextrin dimers *N,N'*-bis-(6^A-deoxy-6^A-β-cyclodextrin)-urea, $(\beta CD)_2ur$, and its oxalamide [$(\beta CD)_2ox$] and succinamide [$(\beta CD)_2su$] analogues[9] on the binding of the anions of Methyl Orange and Tropaeolin 000 No. 2. Both dyes possess one phenylsulfonate binding site but their second binding sites are phenyl and naphthyl groups, respectively, (Fig. 1) which facilitate an assessment of the effect of guest structural variation on complexation.

Experimental

The dimer β-cyclodextrins, $(\beta CD)_2x$, were prepared by methods similar to those reported in the literature[9] and were shown to be >95% pure by microanalysis, thin layer chromatography (TLC) and ^1H and ^{13}C NMR spectroscopy. The minor impurity was βCD. The $(\beta CD)_2x$ were dried to constant weight and stored over P_2O_5 in vacuum desiccators in the dark prior to use. Methyl Orange (BDH) was used as supplied. Tropaeolin 000 No. 2 (BDH) was purified by salting out from hot water using sodium acetate, after which it was recrystallized three times from water and then twice from ethanol. Deionized water, purified with a MilliQ-Reagent system to produce water with a specific resistance of > 15 MΩ cm, was used in the preparation of all solutions immediately prior to measurement.

Methyl Orange, Tropaeolin 000 No. 2 and $(\beta CD)_2x$ solutions were prepared in aqueous 0.100 mol dm^{-3} Na_2HPO_4 and 0.020 mol dm^{-3} K_2SO_4 adjusted to pH 9.0 and 5.5, respectively, with either NaOH or H_2SO_4, under which conditions both dyes existed in their anionic forms MO^- and TR^-.[21,22] Total $[MO^-]$ was constant at 3.8×10^{-5} mol

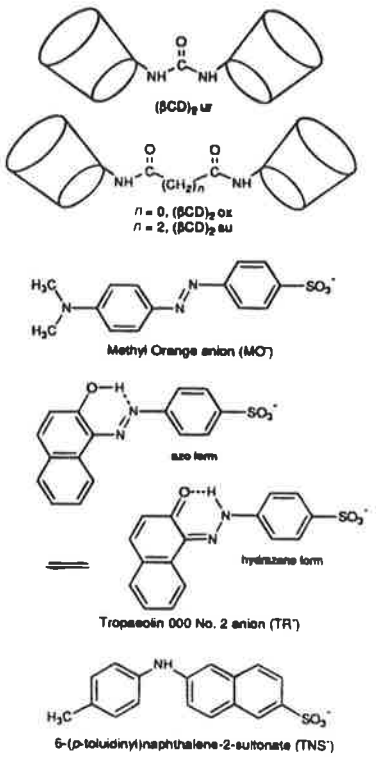

Fig. 1 Schematic illustrations of the β-cyclodextrin dimers, $(\beta CD)_2x$, where the cyclodextrin annulus is represented by a truncated cone in which the narrow end is delineated by six primary hydroxy groups and a secondary amine group, and the wide ends delineated by fourteen secondary hydroxy groups. The structures of Methyl Orange anion MO^-, Tropaeolin 000 No. 2 anion, TR^- and of 6-(*p*-toluidinyl) naphthalene-2-sulfonate, TNS^-, are also shown.

dm^{-3} for the $(\beta CD)_2$ur studies and 4.0×10^{-5} mol dm^{-3} for the $(\beta CD)_2$ox and $(\beta CD)_2$su studies. Total $[(\beta CD)_2ur]$ was varied in the range (1.81×10^{-6})–(2.66×10^{-4}) mol dm^{-3} (21 solutions), $[(\beta CD)_2ox]$ in the range (2.80×10^{-6})–(1.00×10^{-2}) mol dm^{-3} (28 solutions) and $[(\beta CD)_2su]$ in the range (8.12×10^{-6})–(8.01×10^{-3}) mol dm^{-3} (28 solutions) in the spectrophotometric MO^- complexation studies. Total $[TR^-]$ was constant at 4.1×10^{-5}, 3.7×10^{-5} and 4.0×10^{-5} mol dm^{-3} for the $(\beta CD)_2$ur, $(\beta CD)_2$ox and $(\beta CD)_2$su studies, respectively. Total $[(\beta CD)_2ur]$ was varied in the range (3.86×10^{-6})–(3.73×10^{-4}) mol dm^{-3} (29 solutions), $[(\beta CD)_2ox]$ in the range (9.47×10^{-6})–(3.20×10^{-3}) mol dm^{-3} (29 solutions) and $[(\beta CD)_2su]$ in the range (2.38×10^{-5})–(4.93×10^{-3}) mol dm^{-3} (36 solutions) for the TR^- complexation studies.

Stability constants for the MO^- complexes formed with $(\beta CD)_2x$ were determined from data in the range 410–440 and 464–520 nm for $(\beta CD)_2$ur, 404–446 and 464–520 nm for $(\beta CD)_2$ox and 404–444 and 464–520 nm for $(\beta CD)_2$su. Stability constants for the TR^- complexes formed with $(\beta CD)_2x$ were determined from data in the range 450–510 nm for $(\beta CD)_2$ur, 440–492 nm $(\beta CD)_2$ox and 450–510 nm for $(\beta CD)_2$su. All data fitting was carried out on a AcerPower 466d computer using a non-linear least-squares regression analysis program based on Method 5 of Pitha and Jones.[23] Absorbance spectra were run at 298.2 ± 0.1 K in 1 cm pathlength matched quartz cells on a Zeiss DMR 10 spectrophotometer against reference solutions containing all components of the solution of interest except the dye. Spectra were digitized at 2 nm intervals over the range 350–550 nm.

Aggregation of MO^- [24] and TR^- [25,26] is reported to occur in aqueous solution, as evidenced by a decrease from a linear absorption increase as $[MO^-]$ and $[TR^-]$, respectively, increase. No departures from Beer's law were observed up to the $[MO^-]$ and $[TR^-]$ used in this study.

Results

Complexation of MO^- by $(\beta CD)_2x$

The variation of the MO^- absorption spectrum with $[(\beta CD)_2x]$ is exemplified by the montage shown in Fig. 2 for the $MO^-/(\beta CD)_2$su system. Those observed as total $[(\beta CD)_2ur]$, and $[(\beta CD)_2ox]$ are varied, are similar. An isosbestic point is observed at 388 nm for the $MO^-/(\beta CD)_2$su system [compared with 390 nm for both the $MO^-/(\beta CD)_2$ur and $MO^-/(\beta CD)_2$ox systems] and a second, less well defined, isosbestic point is observed at 451–453 nm which compares with 448–454 and 453–457 nm for the $MO^-/(\beta CD)_2$ur and $MO^-/(\beta CD)_2$ox systems. These variations are consistent with the presence of two predominant environments for MO^- [eqn. (1)] where $(\beta CD)_2x \cdot MO^-$ is a host–guest complex. The fitting of the absorbance data for each system to the algorithm for the variation of MO^- absorption with total $[(\beta CD)_2x]$ for the equilibrium shown in eqn. (1), exemplified by the $MO^-/(\beta CD)_2$su system in Fig. 3, yields the K_1 values in Table 1. The small variation in wavelength in the longer-wavelength isosbestic point may arise from experimental error or the presence of a small amount of a second complex which could be $(\beta CD)_2x \cdot (MO)_2^{2-}$ in which the MO^- dimer is complexed as shown in eqn. (2).

$$(\beta CD)_2x + MO^- \overset{K_1}{\rightleftharpoons} (\beta CD)_2x \cdot MO^- \quad (1)$$

$$(\beta CD)_2x \cdot MO^- + MO^- \overset{K_2}{\rightleftharpoons} (\beta CD)_2x \cdot (MO)_2^{2-} \quad (2)$$

The absorption data for all three systems were fitted to the algorithm for the variation of MO^- absorption with total $[(\beta CD)_2x]$ arising from the combined equilibria shown in eqn. (1) and (2), and derived K_1 and K_2 appear in Table 1. The errors in K_2 are large and those in K_1 are greater than those obtained when the data were fitted to the algorithm arising from the equilibrium shown in eqn. (1) alone, but the sum of the squares of the residuals (ssr) for the overall data fits decrease. However, over the ranges of total $[MO^-]$ and $[(\beta CD)_2x]$ studied, the maximum percentages of MO^- existing in the free MO^-, $(\beta CD)_2x \cdot MO^-$ and $(\beta CD)_2x \cdot (MO)_2^{2-}$ environments as $[(\beta CD)_2x]$ is varied are 83.7, 99.6 and 5.7% for the $(\beta CD)_2$su system, 93.5, 100.0 and 0.4% for the $(\beta CD)_2$ox system, and 95.7, 96.8 and 0.6% for the $(\beta CD)_2$ur system, as calculated from the simultaneously fitting of the data to eqn. (1) and (2). Thus, $(\beta CD)_2x \cdot (MO)_2^{2-}$ is not a significant species under the conditions of this study.

The formation of $\beta CD \cdot MO^-$ [eqn. (3)] is characterized by K_1 in the range (2.16×10^3)–(4.88×10^3) dm^3 mol^{-1}, a variation which is attributable to the differing experimental conditions and data treatments employed in the reported studies.[7,27–33] A value of $K_1 = 2.16 \times 10^3$ dm^3 mol^{-1} was determined under identical conditions to this study.[21] Some studies have also detected $\beta CD \cdot (MO)_2^{2-}$ [eqn. (4)] for which values of $K_2 = 606$ and 600 dm^3 mol^{-1} have been determined.[7,25] It is seen from these data that $(\beta CD)_2x \cdot MO^-$ is much more stable than is $\beta CD \cdot MO^-$ consistent with the strength of cooperative binding varying in the sequence $(\beta CD)_2ox \cdot MO^- > (\beta CD)_2ur \cdot MO^- > (\beta CD)_2su \cdot MO^-$.

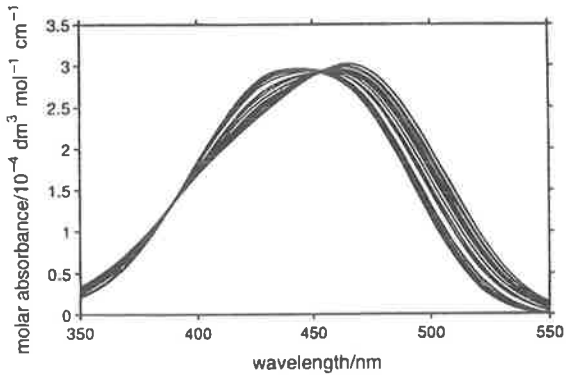

Fig. 2 Absorbance variation of MO^- $(4.0 \times 10^{-5}$ mol $dm^{-3})$ with $[(\beta CD)_2su]$ in the range (8.12×10^{-6})–(8.01×10^{-3}) mol dm^{-3} in aqueous phosphate buffer at pH 9.0 and 298.2 K. The MO^- absorbance decreases with increase in $[(\beta CD)_2su]$ from 350 nm to the first isosbestic point and from the second isosbestic point to 550 nm. Between the isosbestic points MO^- absorbance increases with increase in $[(\beta CD)_2su]$.

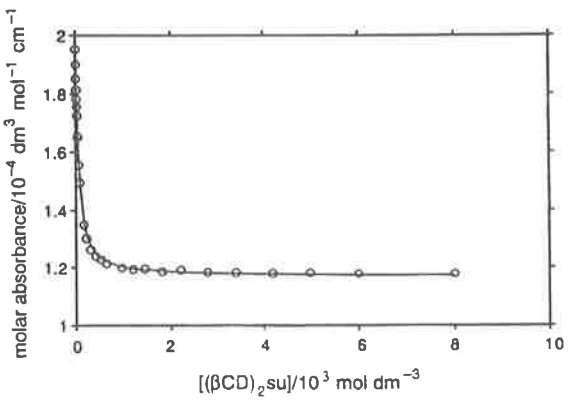

Fig. 3 Absorbance variation of MO^- with $[(\beta CD)_2su]$ at 500 nm under the same conditions as for Fig. 2. The solid curve represents the best fit of the data, collected at 2 nm intervals in the range 404–444 and 464–520 nm, to the algorithm arising from the equilibrium shown in eqn. (1).

Table 1 Stability constants for βCD and $(\beta CD)_2x$ complexes of MO^-, TR^- and TNS^- in aqueous phosphate buffer at pH 9.0, 5.5 and 7.0, respectively, and 298.2 K

host	guest	$K_1/10^{-3}$ dm^3 mol^{-1} [a]	$K_2/10^{-3}$ dm^3 mol^{-1} [a]	10^{-2} ssr[b]
βCD	MO^-	2.16[c]		
$(\beta CD)_2$su	MO^-	25.0 ± 0.2[d]		11.8
$(\beta CD)_2$ox	MO^-	192 ± 4[d]		50.0
$(\beta CD)_2$ur	MO^-	105 ± 4[d]		50.0
$(\beta CD)_2$su	MO^-	46 ± 2[e]	8 ± 2[e]	6.5
$(\beta CD)_2$ox	MO^-	240 ± 30[e]	0.9 ± 3.1[e]	32.5
$(\beta CD)_2$ur	MO^-	150 ± 20[e]	2 ± 5[e]	31.6
βCD	TR^-	0.71 ± 0.07[f]	4000 ± 7000[f]	
$(\beta CD)_2$su	TR^-	4.60 ± 0.05[g]		4.50
$(\beta CD)_2$ox	TR^-	7.4 ± 0.1[g]		1.97
$(\beta CD)_2$ur	TR^-	13.9 ± 0.3[g]		3.17
$(\beta CD)_2$su	TR^-	3.1 ± 0.6[h]	6 ± 2[h]	3.75
$(\beta CD)_2$ox	TR^-	140 ± 20[h]	390 ± 80[h]	1.19
$(\beta CD)_2$ur	TR^-	51 ± 8[h]	160 ± 50[h]	2.68
βCD	TNS^-	3.14 ± 0.02[i]	0.086 ± 0.005[i]	
$(\beta CD)_2$su	TNS^-	16.70 ± 0.02[i]		
$(\beta CD)_2$ox	TNS^-	32.64 ± 0.09[i]		
$(\beta CD)_2$ur	TNS^-	45.23 ± 0.07[i]		

[a] Errors represent one standard deviation. [b] Sum of the squares of the residuals. [c] Ref. 27. [d] From fitting for the equilibrium in eqn. (1). [e] From fitting for the equilibria in eqn. (1) and (2). [f] Ref. 26. [g] From fitting for the equilibrium in eqn. (5). [h] From fitting for the equilibria in eqn. (5) and (6). [i] Ref. 20.

$$\beta CD + MO^- \overset{K_1}{\rightleftharpoons} \beta CD \cdot MO^- \quad (3)$$

$$\beta CD \cdot MO^- + MO^- \overset{K_2}{\rightleftharpoons} \beta CD \cdot (MO)_2^{2-} \quad (4)$$

Complexation of TR^- by $(\beta CD)_2x$

The variations in the TR^- absorption spectrum with total $[(\beta CD)_2x]$ are exemplified by the montage shown in Fig. 4 for the $TR^-/(\beta CD)_2$su system. Those observed as total $[(\beta CD)_2$ur] and $[(\beta CD)_2$ox] are varied, are similar. An isosbestic point is observed at 526 nm [compared with 524 nm for the $TR^-/(\beta CD)_2$ur and 512 nm for $TR^-/(\beta CD)_2$ox systems, respectively.] These variations are consistent with the presence of two predominant environments for TR^- [eqn. (5)] where $(\beta CD)_2x \cdot TR^-$ is a host–guest complex. The fitting of the absorbance data for each system to the algorithm for the variation of TR^- absorption with total $[(\beta CD)_2x]$ for the equilibrium shown in eqn. (5), exemplified by the $TR^-/(\beta CD)_2$su system in Fig. 5, yields the K_1 values in Table 1.

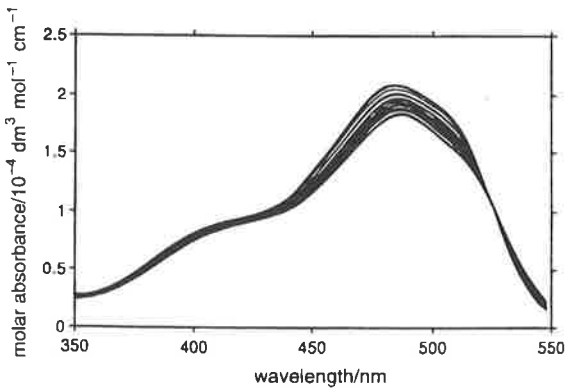

Fig. 4 Absorbance variation of TR^- (4.0×10^{-5} mol dm^{-3}) with $[(\beta CD)_2$su] in the range (2.38×10^{-5})–(4.93×10^{-3}) mol dm^{-3} in aqueous phosphate buffer at pH 5.5 and 298.2 K. The TR^- absorbance decreases with increase in $[(\beta CD)_2$su] from 350 nm to the isosbestic point beyond which it increases.

$$(\beta CD)_2x + TR^- \overset{K_1}{\rightleftharpoons} (\beta CD)_2x \cdot TR^- \quad (5)$$

$$(\beta CD)_2x \cdot TR^- + TR^- \overset{K_2}{\rightleftharpoons} (\beta CD)_2x \cdot (TR)_2^{2-} \quad (6)$$

The absorption data for all three systems were fitted to the algorithm for the variation of TR^- absorption with total $[(\beta CD)_2x]$ arising from the combined equilibria shown in eqn. (5) and (6), and the derived K_1 and K_2 appear in Table 1. The errors in K_1 are greater than those derived when the data were fitted to the single equilibrium of eqn. (5), but the ssr are smaller. Over the total $[TR^-]$ and $[(\beta CD)_2x]$ ranges studied, the maximum percentages of TR^- existing in the free TR^-, $(\beta CD)_2x \cdot TR^-$ and $(\beta CD)_2x \cdot (TR)_2^{2-}$ environments as $[(\beta CD)_2x]$ is varied are 91.5, 91.3 and 2.7% for the $(\beta CD)_2$su system, 53.6, 94.1 and 43.5% for the $(\beta CD)_2$ox system and 84.0, 64.9 and 31.4% for the $(\beta CD)_2$ur system, as calculated from the simultaneously derived K_1 and K_2. On this basis, $(\beta CD)_2$ox$\cdot(TR)_2^{2-}$ and $(\beta CD)_2$ur$\cdot(TR)_2^{2-}$ appear to be significant species. However, the isosbestic points require the three environments for TR^- shown in the equilibria illustrated by eqn. (5) and (6) to produce identical absorbances for each of the three systems studied. This seems unlikely, and the formation of $(\beta CD)_2x \cdot TR^-$ as the greatly predominant species [eqn. (5)] appears the more plausible interpretation of

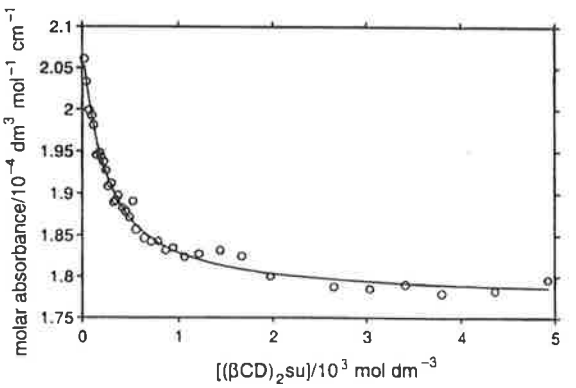

Fig. 5 Absorbance variation of TR^- with $[(\beta CD)_2$su] at 480 nm under the same conditions as for Fig. 4. The solid curve represents the best fit of the data, collected at 2 nm intervals in the range 450–510 nm, to the algorithm arising from the equilibrium shown in eqn. (5).

the variation of the TR^- absorbance variation. Thus, $(\beta CD)_2x \cdot TR^-$ is much more stable than $\beta CD \cdot TR^-$, which is discussed below, and the strength of cooperative binding varies in the sequence $(\beta CD)_2ur \cdot TR^- > (\beta CD)_2ox \cdot TR^- > (\beta CD)_2su \cdot TR^-$.

For the formation of $\beta CD \cdot TR^-$ and $\beta CD \cdot (TR)_2^{2-}$

$$\beta CD + TR^- \overset{K_1}{\rightleftharpoons} \beta CD \cdot TR^- \quad (7)$$

$$\beta CD \cdot TR^- + TR^- \overset{K_2}{\rightleftharpoons} \beta CD \cdot (TR)_2^{2-} \quad (8)$$

$K_1 = (7.1 \pm 0.7) \times 10^2$ dm^3 mol^{-1} and $K_2 = (4 \pm 7) \times 10^6$ dm^3 mol^{-1}, respectively, as shown by temperature-jump spectroscopy under identical conditions to those used in this study.[26] The uncertainty in K_2 is very high, but the values of $K_1 = (4.18 \pm 1.47) \times 10^2$ dm^3 mol^{-1} and $K_2 = (1.68 \pm 0.54) \times 10^6$ dm^3 mol^{-1} for the analogous γCD are better determined and show similar relative orders of magnitude for K_1 and K_2. The relatively high value of K_2, by comparison with K_1, is attributed to the dimerization of TR^- ($K_{dimerization}$ = 910 dm^3 mol^{-1}) being enhanced by γCD complexation.[26]

Discussion

It is seen (Table 1) that K_1 decreases in the sequence $(\beta CD)_2x \cdot MO^- > (\beta CD)_2x \cdot TNS^- > (\beta CD)_2x \cdot TR^-$ for each of the linkers, x, (Fig. 1) where TNS^- is 6-(*p*-toluidinyl) naphthalene-2-sulfonate.[20] [This discussion is confined to the formation of $(\beta CD)_2x \cdot G$ as shown in eqn. (1) and (5) for the reasons given above.] If the βCD moieties in $(\beta CD)_2x$ could act independently, $(\beta CD)_2x \cdot MO^{-1}$ should be twice as stable as $\beta CD \cdot MO^-$ on a statistical basis and the same relationship should exist for the analogous TNS^- and TR^- complexes. However, in all cases, K_1 for the $(\beta CD)_2x$ complex $\gg 2K_1$ for βCD, consistent with cooperative binding of the guest by the linked βCD moieties being the dominant complex stabilizing force. Accordingly, it is probable that variations in $(\beta CD)_2x \cdot G$ complex stability with change in guest largely reflect differences in interaction of the two aromatic binding groups of the guest with the linked βCD, and that changes in complex stability for a given guest with change in $(\beta CD)_2x$ reflect the extent to which the host–guest interactions approach optimization as the length of the linker changes.

The most strongly complexed guest is linear MO^-, whose flexibility is restricted by conjugation through the diazo linkage. This restriction may be a contributing cause of the increase in complex stability in the sequence $(\beta CD)_2su \cdot MO^- < (\beta CD)_2ur \cdot MO^- < (\beta CD)_2ox \cdot MO^{-1}$. Because $(\beta CD)_2ur$ has the shortest and least flexible linker, the two βCD moieties are probably less able to align their annuli to accommodate linear MO^- than is the more flexible $(\beta CD)_2ox$. However, while the longer linker in $(\beta CD)_2su$ leads to greater flexibility, the greater separation of the βCD moieties apparently does not allow them to accommodate both MO^- phenyl groups to maximize binding and complex stability decreases as a result. The second most strongly complexed guest, TNS^-, has a more extended aromatic system because of its naphthyl group and might be expected to interact more extensively with the hydrophobic interior of the βCD annulus. However, the rigidity of the naphthyl group seems to offset the flexibility gained from free rotation about the amine nitrogen of TNS^- so that it is less able to adapt to the steric restraints imposed in $(\beta CD)_2x \cdot TNS^-$ which is consequently less stable than $(\beta CD)_2x \cdot MO^-$. The least strongly complexed guest, TR^-, is also the most rigid and the most angular guest. [In the largely hydrophobic environment of $(\beta CD)_2x \cdot TR^-$, TR^- probably exists predominantly in the azo form shown in Fig. 1].[29,34] It appears that these properties render TR^- less able to adapt to the stereochemical constraints of $(\beta D)_2x$ so that $(\beta CD)_2x \cdot TR^-$ is less stable than its MO^- and TNS^- analogues. Thus, in the most stable complex, $(\beta CD)_2ox \cdot MO^-$, the interaction between the $(\beta CD)_2ox$ recognition sites and the MO^- binding sites is maximized and strain is minimized by comparison with the least stable complex, $(\beta CD)_2su \cdot TR^-$, in which the combination of these characteristics is less effective in stabilizing the complex.

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Exploiting the 1,3-Dithiane of 2-Oxopropanenitrile Oxide to Limit Competing Dimerization in 1,3-Dipolar Cycloaddition Reactions

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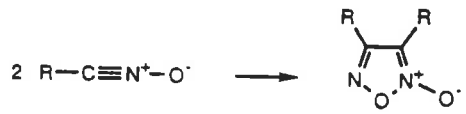
Abstract: The 1,3-dithiane of 2-oxopropanenitrile oxide is less prone to dimerization than the parent compound and, as a consequence, it undergoes more efficient cycloaddition reactions with a range of mono- and 1,1- and 1,2-di-substituted alkenes. © 1997 Elsevier Science Ltd.

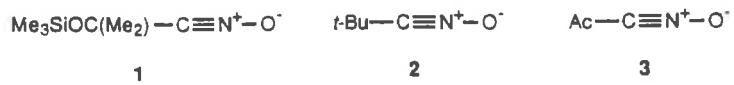
INTRODUCTION

1,3-Dipolar cycloaddition reactions of nitrile oxides with alkenes provide ready access to Δ^2-isoxazolines, which are of interest as precursors of β-amino alcohols, β-hydroxy ketones, 1,3-diols and many other classes of compounds.[1] Nitrile oxides also undergo dimerization to give furoxans (Scheme 1), and the extent to which this competing process limits access to the isoxazolines depends on the degree of substitution of the alkene and the nature of the nitrile oxide.[1,2] Alkylnitrile oxides are more prone to dimerization than the more bulky aryl derivatives. While they give modest yields of cycloadducts in reactions with mono- and 1,1-di-substituted alkenes, generally dimerization of alkylnitrile oxides occurs in preference to reaction with 1,2-disubstituted and more highly substituted alkenes, even when the nitrile oxide is generated *in situ* in the presence of an excess of the dipolarophile.



Scheme 1

Several methods have been developed to circumvent dimerization of alkylnitrile oxides. The furoxans can react as masked nitrile oxides, undergoing cycloaddition with alkenes.[3] Alternatively, some furoxans undergo thermolytic cycloreversion to nitrile oxides.[2,4] Although these methods are not applicable generally, due to the vigorous reaction conditions that usually must be employed, Curran and Fenk[2] have shown that bis(2-((trimethylsilyl)oxy)prop-2-yl)furoxan affords the corresponding nitrile oxide **1**, on heating in benzene at 165 °C, and the nitrile oxide **1** gives good yields of cycloadducts with mono-, di- and tri-substitituted

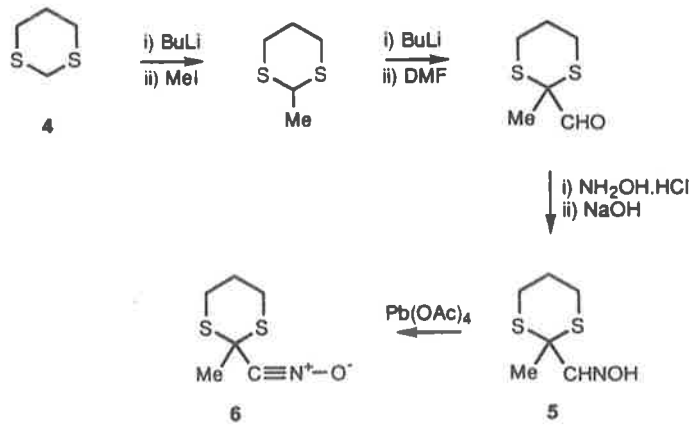


1 2 3

alkenes under these conditions. The nitrile oxide **1** is also accessible from the corresponding nitroalkane,[5] and it reacts with a variety of alkenes without competing dimerization.[5,6] The tendency of the nitrile oxide **1** and the analogous *tert*-butyl derivative **2** to undergo cycloaddition in preference to dimerization can be attributed to the steric bulk of these species.[2,5] With this in mind, we anticipated that an alternative solution to the problem of dimerization of nitrile oxides would be to temporarily introduce bulky substituents or steric auxiliaries, to affect the reactivity of the nitrile oxides and favour the cycloaddition processes. This hypothesis has now been examined using the dithiane **6** as an analogue of the nitrile oxide **3**.

RESULTS AND DISCUSSION

The nitrile oxide **6** was obtained from 1,3-dithiane **4** as shown in Scheme 2. Lead tetraacetate was used for the oxidation of the aldoxime **5**.[7] In order to prevent condensation of the nitrile oxide **6** with the acetic acid formed as a by-product in this reaction, it was necessary to wash the crude reaction mixture with aqueous sodium bicarbonate. The yield of the nitrile oxide **6** was only approximately 40% using this reagent, but the more commonly used method of treatment with *N*-chlorosuccinimide followed by triethylamine[8] resulted in decomposition, presumably as a result of oxidation on sulfur. Reactions of the nitrile oxide **6** were monitored by ^{1}H NMR spectroscopy, using solutions (*ca.* 0.06 M) in deuteriochloroform, containing methyl benzoate as an internal standard. In the absence of a dipolarophile, less than 30% of the nitrile oxide **6** reacted in solutions stored at room temperature for three days. Under the same conditions, the nitrile oxide **6** reacted with each of the alkenes **7-13** (2 mole equivalents), however, to give the corresponding cycloadducts, in yields ranging from 56-85% (Table 1).

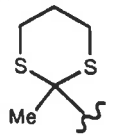
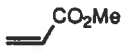
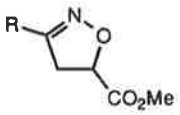
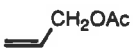
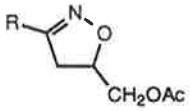
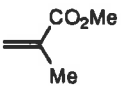
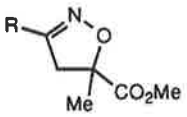
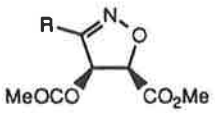
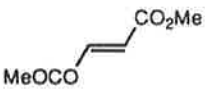
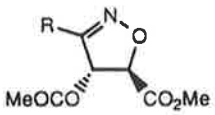
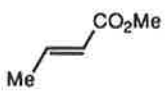
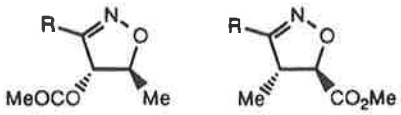
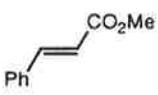
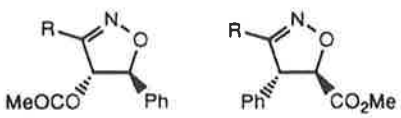


4 6 5

Scheme 2

The nitrile oxide **6** is the 1,3-dithiane of 2-oxopropanenitrile oxide **3**. To examine the effect of the dithiane moiety as a steric auxiliary, reactions of the latter compound were also investigated and compared. The

Table 1. Products and yields of reactions of the nitrile oxides **3** and **6** with the alkenes **7-13**.

Alkene	Cycloadduct[9]	Yield (%)	
		R = Ac	R = 
		3	**6**
 **7**		29	83
 **8**		23	85
 **9**		27	80
 **10**		-	73
 **11**		-	78
 **12**		-	58 (5:1)
 **13**		-	56 (3:1)

nitrile oxide **3** undergoes relatively rapid dimerization, and no starting material remained detectable after 5 minutes in a *ca.* 0.08 M solution prepared in deuteriochloroform. For this reason it was generated *in situ*, by treatment of the corresponding nitrite with *N*-chlorosuccinimide and triethylamine. Otherwise the experimental conditions for the reactions of the nitrile oxide **3** with the alkenes **7-13** were the same as those used for the reactions of the dithiane **6**, although the reactions of the ketone **3** were complete in less than one hour. Under these conditions, 2-oxopropanenitrile oxide **3** gave modest yields of cycloadducts with the monosubstituted alkenes **7** and **8**, and the 1,1-disubstituted alkene **9**, but no cycloadducts were formed from the 1,2-disubstituted alkenes **10-13** (Table 1).

Clearly the results of the experiments with 2-oxopropanenitrile oxide **3** are in marked contrast to those with the dithiane **6** and they show that the protecting group of the dithiane **6** significantly increases the yields of cycloadducts. Presumably this is a result of the dithiane moiety acting as a steric auxiliary to reduce the rate of the competing dimerization reaction by at least three orders of magnitude, as indicated in the preliminary experiments described above. Our present studies have been restricted to a comparison of the reactions of the nitrile oxides **3** and **6**, but it seems likely that steric auxiliaries may provide a general method to ameliorate the problem of dimerization of alkylnitrile oxides, since analogues of the dithiane **6** are readily available and synthetically versatile. Currently we are investigating alternative methods for the preparation of the dithiane **6**, to overcome the limitation of the method due to the modest yield of that compound. We also intend to examine reactions of the corresponding 1,3-dioxane, as a way to avoid complications due to reactions on sulfur.

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9. All new compounds were fully characterized. Stereochemical descriptors show relative stereochemistry only.

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Nitrate esters in the generation of amino acid radicals

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Nitrate esters, prepared by treatment of β-hydroxy-α-amino acid derivatives with nitric acid, react with tributyltin hydride to give the corresponding alkoxyl radicals. These radicals readily undergo β-scission, providing a convenient route for the regiocontrolled production of α-carbon-centred amino acid radicals. By examining the partitioning of the alkoxyl radicals between the β-scission process and the competing hydrogen transfer reaction, it has been possible to evaluate the influence of electronic and steric effects on the β-scission reaction and the formation of the carbon-centred radicals.

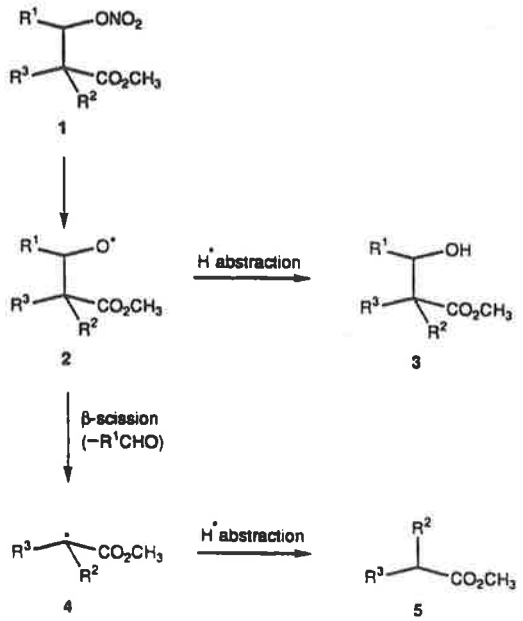
Hydrogen atom transfer reactions of *N*-acyl-α-amino acid derivatives generally favour formation of α-carbon-centred radicals.[1] Reactions of this type occur upon irradiation of proteins[2] and they are involved in the photoalkylation[3] and carboxylation[4] of peptides. Studies of hydrogen atom transfer reactions of amino acid derivatives have shown them to be selective for reaction of glycine residues.[2–6] The reactions are also affected by the nature of the protecting groups applied to the amino and carboxy substituents.[7] and by polar and steric effects.[8] While these effects can be exploited in the regioselective functionalisation of amino acid and peptide derivatives,[3–7] the extent of regiocontrol is limited.

In order to develop the synthetic potential of α-carbon-centred amino acid radicals, halogen[1,6,9] and other functional group[10] transfer reactions have been used as alternative procedures for their generation. In this report we describe a complementary procedure for the synthesis of the amino acid radicals. The conversion of alcohols to nitrate esters is well documented,[11,12] as is the use of reactions of the esters with stannanes to generate radicals.[12,13] Exploiting this methodology and beginning with readily available β-hydroxy-α-amino acid derivatives, reaction with nitric acid affords nitrate esters, which react on treatment with tributyltin hydride and irradiation to give alkoxyl radicals. In turn, the alkoxyl radicals undergo β-scission reactions to give α-carbon-centred radicals.

Alkoxyl radicals also react by hydrogen abstraction to give alcohols. The rate of hydrogen abstraction has been shown to be relatively independent of the nature of the alkoxyl radical.[14,15] For example, the rate constants for hydrogen atom abstraction from benzhydrol (diphenyl methanol) at 27 °C by the primary, secondary and tertiary alkyloxyl radicals, benzyloxyl, cyclohexyloxyl and *tert*-butoxyl, differ by less than a factor of 2.5.[16] Even this variation is likely to be due largely to steric effects, which will be more important with benzhydrol as the hydrogen donor, rather than tributyltin hydride where the hydrogen to be transferred is more exposed. Thus, the ratio of products derived through partitioning of an alkoxyl radical between the β-scission process and hydrogen abstraction from the stannane is a good measure of the efficiency of the former. The β-scission of alkoxyl radicals is dependent upon a number of factors. These include the stability of the product radical,[17,18] the stability of the aldehyde or ketone by-product[13,14] and polar and steric effects[19] which may influence the stability of the reaction transition state. In the present work, a range of amino acid derivatives and related compounds has been studied, in order to evaluate the influence of these effects on the formation of α-carbon-centred amino acid radicals using this approach.

Results and discussion

The nitrate esters **1a–e**, **6a–c** and **11a–c** reacted with tributyltin hydride to give the alcohols **3a–c**, **3e**, **8a–c** and **13a–c**, through hydrogen transfer from the stannane to the corresponding alkoxyl radicals **2a–c**, **2e**, **7a–c** and **12a–c**. In addition, the amino acid derivatives **5a** and **5d**, and the products **10a** and **15** were formed, through β-scission of the alkoxyl radicals **2a**, **2d**, **7a** and **12b,c**, followed by hydrogen transfer to the carbon-centred radicals **4a**, **4d**, **9a** and **14** (Schemes 1–3).



a R^1 = H, R^2 = H, R^3 = NHCOPh
b R^1 = Me, R^2 = H, R^3 = NHCOPh
c R^1 = Ph, R^2 = H, R^3 = NHCOPh
d R^1 = H, R^2 = Me, R^3 = NHCOPh
e R^1 = H, R^2 = H, R^3 = PhthN

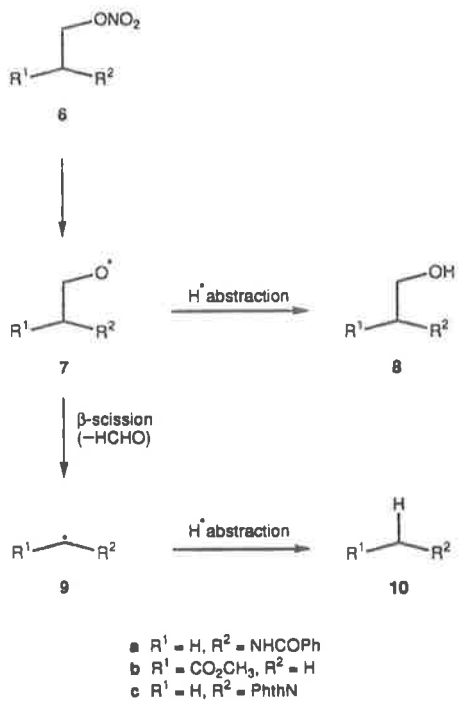
Scheme 1

The ratios of reaction products depended on the reaction conditions. In order to use these ratios to compare the ease of β-scission of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c**, each of

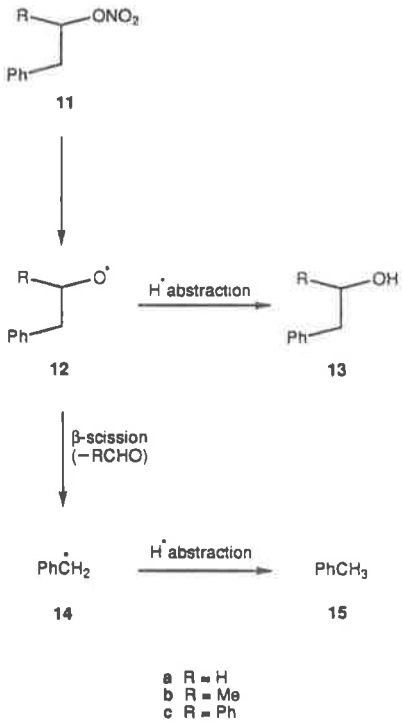
Table 1 Results of irradiation of the nitrate esters **1a–e**, **6a–c** and **11a–c** with tributyltin hydride

Nitrate ester	Alkoxyl radical	β-Scission product[a] Compound	Yield[b] (%)	H-abstraction product Compound	Yield[b] (%)	Ratio of β-scission to H-abstraction
1a	**2a**	**5a**	17 (17)	**3a**	51 (51)	1:3
1b	**2b**	**5b**	31 (48)	**3b**	14 (22)	2:1
1c	**2c**	**5c**	73 (73)	**3c**	12 (12)	6:1
1d	**2d**	**5d**	88 (88)	**3d**	—	>20:1
1e	**2e**	**5e**	—	**3e**	44 (91)	<1:20
6a	**7a**	**10a**	8 (10)	**8a**	61 (78)	1:8
6b	**7b**	**10b**	—	**8b**	100 (100)	<1:20
6c	**7c**	**10c**	—	**8c**	100 (100)	<1:20
11a	**12a**	**15**	—	**13a**	82 (92)	<1:20
11b	**12b**	**15**	12 (20)	**13b**	18 (30)	2:3
11c	**12c**	**15**	48 (74)	**13c**	17 (26)	3:1

[a] The reactions afford either formaldehyde, acetaldehyde or benzaldehyde as a by-product of the β-scission process. Analysis of the formation of acetaldehyde and benzaldehyde in the reactions of the nitrate esters **1b** and **11c**, respectively, gave yields identical to those of the alternative β-scission products **5b** and **15**. [b] Yields in parentheses are adjusted for unreacted starting materials.



Scheme 2



Scheme 3

the nitrate esters **1a–e**, **6a–c** and **11a–c** (0.2 mmol) was treated with tributyltin hydride (1.0 mmol) in [$^2H_6$]benzene (0.3 ml) under argon, in a sealed quartz ^1H NMR tube. The mixtures were irradiated, to initiate reaction, at 40 °C for 2 h. The reaction mixtures were analysed directly using ^1H NMR spectroscopy, and product yields were calculated through the use of ethylbenzene (0.2 mmol) as an internal standard. The rate constant for hydrogen transfer to *tert*-butoxyl radical from tributyltin hydride, of 2×10^8 dm^3 mol^{-1} s^{-1} at 22 °C,[20] is almost two orders of magnitude higher than that for the reaction of the alkoxyl radical with ethylbenzene, of 1.05×10^6 dm^3 mol^{-1} s^{-1} at 22 °C.[21] On the basis of this comparison it is reasonable to assume that the extent of reaction of ethylbenzene by hydrogen atom transfer is negligible in the present work, particularly given the excess of tributyltin hydride employed. Products were identified through spectroscopic and chromatographic comparisons with authentic samples. The yields and ratios of the products **3a–c**, **3e**, **5a**, **5d**, **8a–c**, **10a**, **13a–c** and **15** obtained in these experiments are shown in Table 1.

The combined yields of the products **3a–c**, **3e**, **5a**, **5d**, **8a–c**, **10a**, **13a–c** and **15**, corrected for the unreacted starting materials **1a–e**, **6a–c** and **11a–c**, indicate that the β-scission and hydrogen abstraction reactions of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c** represent the major reaction pathways. The use of a five molar excess of tributyltin hydride ensures that the concentration of the stannane does not change substantially during the course of the reactions. Under these conditions, the partitioning of the alkoxyl radicals **2a–e**, **7a–c** and **12a–c** between the β-scission and hydrogen abstraction processes will vary little as a function of the extent of reaction. Then, irrespective of the extent of reaction, the ratios of products formed through β-scission and hydrogen abstraction indicate the relative efficiency of the β-scission processes.

Each of the alkoxyl radicals **2a–c** undergoes β-scission to give the glycyl radical **4a**. This process is slower for the threonine derivative **2b** than for the β-phenylserine derivative **2c**, and even slower for the serine derivative **2a**. These relative reaction rates can be attributed to the release of steric strain accompanying carbon–carbon bond cleavage.[13,14,17–19] The methyl and phenyl

substituents of the radicals **2b** and **2c**, respectively, increase steric interactions that are relieved during the course of the reaction. In addition, β-scission of the radical **2c** is favoured by conjugation[13,14] of the phenyl substituent with the incipient carbonyl group of the reaction by-product, benzaldehyde. The effect of the methyl and phenyl substituents of the radicals **2b** and **2c** is mirrored in the reactions of the radicals **12a–c**, formed from the corresponding nitrate esters **11a–c**, where β-scission is slower for the propoxyl radical **12b** than for the 2-phenylethoxyl radical **12c**, and even slower for the ethoxyl radical **12a**.

The effect of steric strain is also apparent from a comparison of the reactions of the derivatives of serine **1a** and α-methylserine **1d**. β-Scission of the corresponding alkoxyl radicals **2a** and **2d** is much faster for the latter, presumably as a result of the additional methyl group. Apparently, this effect outweighs the normal tendency for more stable radicals to be produced at a faster rate,[17,18] since there is strong evidence[5] that the alanyl radical **4d**, formed through reaction of the alkoxyl radical **1d**, is less stable than the glycyl radical **4a**, which results from β-scission of the radical **1a**.

The reactions of the nitrate esters **1a**, **6a** and **6b** indicate that the alkoxyl radicals **7a** and **7b** undergo β-scission less readily than the serine derivative **2a**. Again this can be attributed to steric effects, since the alkoxyl radicals **7a** and **7b**, respectively, lack the methoxycarbonyl and benzamido substituents of the radical **2a**. It is likely that there is also an additional electronic effect reflected in these reactions, since both the methoxycarbonyl and benzamido substituents would be expected to contribute to the stability and ease of formation of the glycyl radical **4a**.[22]

Each of the benzamides **2a** and **7a** underwent β-scission, at least to some extent, whereas there was no evidence of the analogous reaction for either of the phthalimides **2e** or **7c**, despite the greater bulk of the phthalimido group. These results correlate with the comparative ability of benzamido and phthalimido (PhthN) substituents to stabilise radicals,[7] and they highlight the relationship between the ease of β-scission of an alkoxyl radical and the stability of the product radical.[17,18]

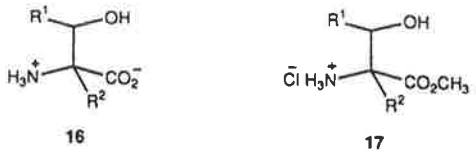
In summary, the reactions described above illustrate a new approach to the generation of amino acid radicals. While alternative procedures[5] are avaliable to access the α-carbon-centred amino acid radicals **4a** and **4d** involved in this work, it seems likely that the new method will be useful for the generation of radicals in peptides where the other procedures would lack regiospecificity. For example, a serine residue in a peptide should serve as a convenient glycyl radical precursor.

Experimental

General

Melting points were determined on a Kofler hot stage melting point apparatus under a Reichert microscope and are uncorrected. Microanalyses were carried out by the Chemistry Department at the University of Otago, Dunedin, New Zealand, and by the Research School of Chemistry at the Australian National University, Canberra, Australia. IR spectra were recorded on a Hitachi 270–30 IR spectrometer and data processor. Samples were prepared either as Nujol mulls or neat liquids, between NaCl plates. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on either a Bruker ACP-300 or a GEMINI 300 spectrometer and refer to deuteriochloroform solutions with chloroform as the internal standard measured at δ_H 7.26 ppm and δ_C 77.04 ppm. Coupling constant values J between protons are given in Hertz. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on an AEI MS-30 spectrometer operating at 70 eV. Accurate mass determinations were carried out by the Chemistry Department at the University of Melbourne, Victoria, Australia, using a JEOL AX505H mass spectrometer. Preparative column chromatography was carried out as either dry flash column chromatography or positive pressure flash chromatography using Merck Kieselgel 60 PF_{254} and Merck Kieselgel 60 (230–400 mesh ASTM). Analytical TLC was performed using Merck Kieselgel 60 F_{254} silica on aluminium backed plates. Detection was *via* either visualisation with ultraviolet light or development with a solution of phosphomolybdic acid in ethanol. R_f values are indicated for those products purified by preparative chromatography and refer to the chromatographic eluent indicated. All solvents and reagents used were purified using standard methods and all organic extracts were dried over $MgSO_4$.

Serine **16a**, threonine **16b** and α-methylserine **16d** were



16 **17**

a R^1 = H, R^2 = H
b R^1 = Me, R^2 = H
c R^1 = Ph, R^2 = H
d R^1 = H, R^2 = Me

purchased as racemates from Sigma Chemical Co. and all derivatives of these compounds were assumed to be racemic. (2*SR*,3*SR*)-β-Phenylserine **16c** was purchased from Aldrich Chemical Co. In subsequent derivatisations no interconversion between diastereomers was observed, indicating no loss of stereochemical integrity. *N*-(2-Hydroxyethyl)phthalimide **8c**, 2-phenylethanol **13a**, 1-phenylpropan-2-ol **13b**, *N*-methylbenzamide **10a**, methyl acetate **10b**, 2-aminoethanol, β-propiolactone and deoxybenzoin were purchased from Aldrich Chemical Co. Samples of *N*-phthaloylserine methyl ester **3e**, *N*-benzoylglycine methyl ester **5a**, *N*-benzoylalanine methyl ester **5d** and *N*-phthaloylglycine methyl ester **5e** were available.[23,24]

General procedure for reaction of the nitrate esters 1a–e, 6a–c and 11a–c with tributyltin hydride

A mixture of nitrate ester (0.2 mmol), tributyltin hydride (0.27 ml, 1.0 mmol) and ethylbenzene (0.2 mmol) in [$^2H_6$]benzene (0.3 ml) in a quartz ^{1}H NMR spectroscopy tube under argon was irradiated with ultraviolet light (300 nm) at 40 °C in a Rayonette Photochemical Reactor for 2 h. The reaction mixture was analysed before and after irradiation using ^{1}H NMR spectroscopy and TLC, by comparison with authentic product samples.

General procedure for the synthesis of the alcohols 3a–d

Thionyl chloride (2.0 equiv.) was added dropwise to a solution of the amino acid **16a–d** in dry methanol (50 ml) at 0 °C under argon. The resulting solution was stirred at room temp. overnight. Removal of solvent under reduced pressure afforded the methyl ester hydrochloride **17a–d** as a white solid. To a solution of this solid and benzoyl chloride (1.1 equiv.) in ethyl acetate (50 ml) was added a solution of sodium hydrogencarbonate (3.0 equiv.) in water (50 ml). The resulting mixture was stirred at room temp. for 4 h. Extraction with ethyl acetate followed by drying and evaporation of solvent under reduced pressure afforded the product **3a–d**, which was purified by either recrystallisation or flash column chromatography.

***N*-Benzoylserine methyl ester 3a.** Serine **16a** (9.62 g, 91.6 mmol) afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **3a** as a colourless, viscous oil (16.50 g, 81%). R_f 0.4 (Found: M$^+$, 223.0846. Calc. for $C_{11}H_{13}NO_4$: M, 223.0845); ν_{max}/cm^{-1} 3374, 2954, 1747, 1648, 1579, 1528, 1489, 1349, 1225, 1074 and 712; δ_H 3.55 (1 H, br s, OH), 3.77 (3 H, s, CH_3), 4.00 (1 H, dd, J 11.4 and 3.6, β-CH), 4.06 (1 H, dd, J 11.4 and 3.6, β-CH′), 4.84 (1 H, dt, J 7.3 and 3.6, α-CH), 7.22 (1 H, br d, J 7.3, NH), 7.34–7.52 (3 H, m, ArH) and 7.80 (2 H, d, J

7.3, ArH); δ_C 52.51, 55.00, 62.69, 127.08, 128.48, 131.73, 133.30, 167.78 and 171.02; *m/z* (EI) 223 (M^+, 16%), 206 (17), 192 (13), 164 (13), 160 (10), 146 (14), 122 (12), 106 (14), 105 (100), 77 (43) and 50 (16).

***N*-Benzoylthreonine methyl ester 3b.** Threonine **16b** (3.10 g, 26.1 mmol) afforded the product **3b** as a colourless crystalline solid (5.68 g, 92%), mp 114–117 °C (from CH_2Cl_2–hexane) (Found: MH^+, 238.1064. Calc. for $C_{12}H_{15}NO_4$: MH, 238.1079); δ_H 1.29 (3 H, d, *J* 6.4, CCH_3), 2.60 (1 H, br s, OH), 3.80 (3 H, s, CO_2CH_3), 4.47 (1 H, dq, *J* 2.4 and 6.4, β-CH), 4.84 (1 H, dd, *J* 2.4 and 8.8, α-CH), 6.99 (1 H, br d, *J* 8.8, NH), 7.42–7.56 (3 H, m, ArH) and 7.84–7.87 (2 H, m, ArH); δ_C 20.00, 52.62, 57.69, 68.21, 127.20, 128.57, 131.88, 133.65, 168.00 and 171.62; *m/z* (EI) 238 (M + H^+, 100%), 221 (24), 220 (85), 206 (4), 193 (18), 178 (5), 161 (17), 160 (10), 133 (6), 105 (9), 104 (72) and 76 (20).

(2*SR*,3*SR*)-*N*-Benzoyl-β-phenylserine methyl ester 3c. (2*SR*,3*SR*)-β-Phenylserine **16c** (2.67 g, 14.8 mmol) afforded the product **3c** as a colourless solid (3.10 g, 70%), mp 92–94 °C (from CH_2Cl_2–hexane); δ_H 2.95 (1 H, br s, OH), 3.77 (3 H, s, CH_3), 5.08 (1 H, dd, *J* 8.7 and 3.2, α-CH), 5.40 (1 H, d, *J* 3.2, β-CH), 6.98 (1 H, d, *J* 8.7, NH), 7.26–7.71 (8 H, br m, ArH) and 7.68 (2 H, m, ArH); δ_C 52.58, 58.58, 73.42, 125.68, 127.03, 127.92, 128.29, 128.41, 131.69, 133.45, 139.71, 167.79 and 170.93; *m/z* (EI) 300 (M + H^+, 2%), 268 (2), 240 (10), 193 (77), 161 (72), 133 (32), 105 (100) and 77 (78).

***N*-Benzoyl-α-methylserine methyl ester 3d.** α-Methylserine **16d** (1.50 g, 12.6 mmol) afforded the product **3d** as a colourless, viscous oil (0.94 g, 31%), δ_H 1.66 (3 H, s, CCH_3), 3.83 (3 H, s, CO_2CH_3), 3.90 (1 H, br s, OH), 3.93 (1 H, d, *J* 11.4, β-CH), 4.22 (1 H, d, *J* 11.4, β-CH′), 7.18 (1 H, br s, NH), 7.42–7.56 (3 H, m, ArH) and 7.80 (2 H, d, *J* 8.2, ArH); δ_C 20.14, 53.18, 62.48, 66.60, 127.07, 128.67, 131.93, 134.05, 167.54 and 173.92; *m/z* (EI) 238 (M + H^+, 8%), 220 (7), 219 (15), 207 (23), 206 (26), 178 (33), 175 (15), 160 (14), 122 (36), 105 (31), 104 (94), 101 (26), 78 (13), 77 (100), 76 (9), 51 (35) and 42 (43).

2-Benzamidoethanol 8a

To a solution of 2-aminoethanol (3.00 g, 49.2 mmol) and benzoyl chloride (7.51 g, 53.5 mmol) in ethyl acetate (50 ml) was added a solution of sodium hydrogencarbonate (10.0 g, 66.8 mmol) in water (50 ml). The resulting mixture was stirred at room temp. for 4 h. Extraction with ethyl acetate followed by drying and evaporation under reduced pressure afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **8a** as a colourless solid (5.10 g, 63%), R_f 0.3, mp 52–56 °C (Found: MH^+, 166.0863. Calc. for $C_9H_{12}NO_2$: MH, 166.0868); δ_H 3.07 (1 H, br s, OH), 3.59 (2 H, dt, *J* 4.8 and 4.8, CH_2N), 3.80 (2 H, t, *J* 4.8, CH_2O), 6.94, (1 H, br t, *J* 4.8, NH), 7.37–7.51 (3 H, m, ArH) and 7.76 (2 H, d, *J* 8.3, ArH); δ_C 43.31, 62.00, 127.53, 128.92, 132.01, 134.59 and 169.31; *m/z* (CI) 166 (M + H^+, 96%), 148 (100), 134 (7), 122 (15), 105 (99), 77 (60) and 51 (39).

3-Hydroxypropionic acid methyl ester 8b

A solution of β-propiolactone (1.10 g, 15.3 mmol) and a catalytic amount of toluene-*p*-sulfonic acid in dry methanol (10 ml) was heated at reflux under nitrogen for 4 h and then poured into a sodium hydrogencarbonate solution (1 M, 20 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded, after chromatography [(95:5) CH_2Cl_2–MeOH], the product **8b** as a colourless oil (0.38 g, 24%), R_f 0.35, bp 175–184 °C (lit.,[25] 177–184 °C); ν_{max}/cm^{-1} 3700–2500 (br), 2952, 2892, 1738, 1440, 1366 and 1046; δ_H 2.50 (1 H, br s, OH), 2.59 (2 H, t, *J* 5.6, CH_2O), 3.72 (3 H, s, CH_3) and 3.88 (2 H, t, *J* 5.6, CH_2CO_2); δ_C 36.58, 51.71, 58.18 and 173.23.

1,2-Diphenylethanol 13c

To a solution of deoxybenzoin (5.00 g, 25.5 mmol) in anhydrous EtOH (80 ml) was slowly added sodium borohydride (1.13 g, 30.2 mmol). The resulting clear solution was stirred for 1.5 h and then it was poured cautiously into dilute HCl (200 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded the product **13c** as a colourless solid (5.04 g, 100%), mp 67 °C (lit.,[26] 67 °C).

General procedure for the synthesis of the nitrate esters 1a–e, 6a–c and 11a–c

To a solution of the alcohol **3a–e**, **8a–c** and **13a–c** in acetic anhydride (20 ml) at 0 °C was added a freshly prepared solution of fuming nitric acid (1.1 equiv.) in acetic anhydride (5 ml). The resulting clear solution was stirred for 5 min and then it was poured into an ice-cold saturated sodium hydrogencarbonate solution (100 ml). Extraction with CH_2Cl_2 followed by drying and evaporation under reduced pressure afforded the products **1a–e**, **6a–c** and **11a–c** which were purified by either recrystallisation or flash column chromatography.

***N*-Benzoyl-*O*^{β}-nitroserine methyl ester 1a.** *N*-Benzoylserine methyl ester **3a** (3.80 g, 17.0 mmol) afforded the product **1a** as a colourless solid (3.63 g, 79%), mp 94–95 °C (from EtOH–H_2O) (Found: C, 49.42; H, 4.40; N, 10.21. $C_{11}H_{12}N_2O_6$ requires C, 49.26; H, 4.51; N, 10.44%); δ_H 3.84 (3 H, s, CH_3), 4.91 (1 H, dd, *J* 3.5 and 11.3, β-CH), 4.98 (1 H, dd, *J* 3.5 and 11.3, β-CH′), 5.15 (1 H, dt, *J* 7.0 and 3.5, α-CH), 6.93 (1 H, d, *J* 7.0, NH), 7.26–7.56 (3 H, m, ArH) and 7.83 (2 H, d, *J* 6.9, ArH); δ_C 51.01, 53.42, 71.31, 127.16, 128.76, 132.30, 132.93, 167.18 and 168.95; *m/z* (EI) 269 (M + H^+, 36%), 268 (M^+, 5), 224 (14), 207 (23), 206 (83), 192 (5), 147 (13), 146 (82), 118 (40), 104 (100), 90 (48), 76 (19) and 50 (9).

***N*-Benzoyl-*O*^{β}-nitrothreonine methyl ester 1b.** *N*-Benzoylthreonine methyl ester **3b** (1.00 g, 4.2 mmol) afforded the product **1b** as a colourless solid (1.13 g, 95%), mp 82–84 °C (Found: C, 51.34; H, 4.93; N, 9.85. $C_{12}H_{14}N_2O_6$ requires C, 51.06; H, 5.00; N, 9.92%); ν_{max}/cm^{-1} 3308, 1740, 1650, 1632, 1534, 1462, 1282, 1244, 738 and 722; δ_H 1.48 (3 H, d, *J* 6.5, CCH_3), 3.82 (3 H, s, CO_2CH_3), 5.21 (1 H, dd, *J* 2.6 and 8.8, α-CH), 5.73 (1H dq, *J* 2.6 and 6.5, β-CH), 6.73 (1 H, br d, *J* 8.8, NH), 7.46–7.60 (3 H, m, ArH) and 7.86 (2 H, d, *J* 5.8, ArH); δ_C 15.85, 53.24, 54.62, 79.72, 127.22, 128.77, 132.31, 133.05, 167.72 and 169.33; *m/z* (EI) 283 (M + H^+, 51%), 220 (17), 193 (10), 192 (29), 161 (9), 106 (34), 105 (100) and 77 (61).

(2*SR*,3*SR*)-*N*-Benzoyl-*O*^{β}-nitro-β-phenylserine methyl ester 1c. (2*SR*,3*SR*)-*N*-Benzoyl-β-phenylserine methyl ester **3c** (2.00 g, 6.7 mmol) afforded the product **1c** as a colourless solid (1.50 g, 65%), mp 128–130 °C (from CH_2Cl_2–hexane) (Found: C, 59.46; H, 4.35; N, 8.15. $C_{17}H_{16}N_2O_6$ requires C, 59.28; H, 4.69; N, 8.14%); ν_{max}/cm^{-1} 3372, 1746, 1648, 1640, 1520, 1464, 1292, 714 and 700; δ_H 3.79 (3 H, s, CH_3), 5.42 (1 H, dd, *J* 9.0 and 4.0, α-CH), 6.44 (1 H, d, *J* 4.0, β-CH), 6.87 (1 H, br d, *J* 9.0, NH), 7.32–7.51 (8 H, br m, ArH) and 7.69 (2 H, m, ArH); δ_C 53.25, 55.41, 82.91, 126.17, 127.11, 128.71, 128.90, 129.50, 130.68, 132.15, 133.68, 167.15 and 168.94; *m/z* (EI) 345 (M + H^+, 27%), 298 (8), 283 (36), 282 (100), 264 (25), 105 (6), 104 (59) and 76 (17).

***N*-Benzoyl-*O*^{β}-nitro-α-methylserine methyl ester 1d.** *N*-Benzoyl-α-methylserine methyl ester **3d** (0.91 g, 3.8 mmol) afforded the product **1d** as a colourless solid (0.78 g, 72%), mp 79–83 °C (from CH_2Cl_2–hexane) (Found: C, 51.46; H, 4.80; N, 9.76. $C_{12}H_{14}N_2O_6$ requires C, 51.06; H, 5.00; N, 9.92%); ν_{max}/cm^{-1} 3268, 1752, 1632, 1536, 1494, 1366, 1330, 1282, 1254, 1134, 982 and 862; δ_H 1.76 (3 H, s, CCH_3), 3.87 (3 H, s, CO_2CH_3), 4.97 (1 H, d, *J* 11.1, β-CH), 5.35 (1 H, d, *J* 11.1, β-CH′), 6.94 (1 H, br s, NH), 7.44–7.54 (3 H, m, ArH) and 7.78 (2 H, d, *J* 7.9, ArH); δ_C 20.62, 53.52, 58.76, 72.13, 126.99, 128.69, 132.07, 133.61, 166.96 and 171.89; *m/z* (CI) 283 (M + H^+, 10%), 236 (35), 220 (17), 208 (60), 160 (20), 148 (26), 105 (100) and 77 (16).

***N*-Phthaloyl-*O*^{β}-nitroserine methyl ester 1e.** *N*-Phthaloylserine methyl ester **3e** (0.58 g, 2.5 mmol) afforded, after chrom-

atography [(70:30) hexane–ethyl acetate], the product **1e** as a colourless solid (0.36 g, 49%), mp 62–64 °C (Found: $M^+ - NO_3$, 232.0599. Calc. for $C_{12}H_{10}NO_4$: $M - NO_3$, 232.0609); δ_H 3.79 (3 H, s, CH_3), 4.60 (1 H, dd, *J* 9.9 and 11.7, β-CH), 4.92 (1 H, dd, *J* 4.3 and 11.7, β-CH′); 5.18 (1 H, dd, *J* 4.3 and 9.9, α-CH) and 7.76–7.91 (4 H, m, ArH); δ_C 50.65, 52.98, 60.84, 123.66, 131.62, 134.32, 167.18 and 170.42; *m/z* (EI) 294 (M^+, 10%), 293 (43), 292 (100), 250 (19), 233 (37), 232 (96), 219 (23), 200 (17), 190 (50), 187 (48), 172 (26), 133 (15), 132 (17) and 104 (15).

***O*-Nitro-2-benzamidoethanol 6a.** 2-Benzamidoethanol **8a** (2.00 g, 12.1 mmol) afforded the product **6a** as a colourless solid (1.45 g, 57%), mp 117–119 °C (from CH_2Cl_2–hexane) (Found: C, 51.47; H, 4.52; N, 13.08. $C_9H_{10}N_2O_4$ requires C, 51.43; H, 4.80; N, 13.33%); δ_H 3.77 (2 H, apparent q, *J* 5.41, CH_2N), 4.62 (2 H, t, *J* 5.41, CH_2O), 6.87 (1 H, br t, *J* 5.41, NH), 7.38 (2 H, t, *J* 7.14, ArH), 7.49 (1 H, t, *J* 7.14, ArH) and 7.76 (2 H, d, *J* 7.14, ArH); δ_C 37.13, 71.49, 126.85, 128.30, 131.55, 133.40 and 168.20; *m/z* (CI) 211 ($M + H^+$, 7%), 166 (100), 148 (90), 136 (20), 117 (55) and 105 (75).

***O*$^\beta$-Nitro-3-hydroxypropionic acid methyl ester 6b.** 3-Hydroxypropionic acid methyl ester **8b** (0.50 g, 4.8 mmol) afforded, after chromatography [(50:50) CH_2Cl_2–hexane] the product **6b** as a colourless oil (0.49 g, 69%), R_f 0.45 (Found: C, 32.22; H, 4.51; N, 9.66. $C_4H_7NO_5$ requires C, 32.22; H, 4.73; N, 9.39%); ν_{max}/cm^{-1} 2952, 2934, 1746, 1644, 1440, 1372, 1080 and 1018; δ_H 2.73 (2 H, t, *J* 6.25, CH_2CO_2), 3.72 (3 H, s, CH_3) and 4.72 (2 H, t, *J* 6.25, CH_2O); δ_C 31.60, 52.09, 67.85 and 169.74; *m/z* (EI) 149 (M^+, 20%), 118 (70), 105 (14), 83 (12), 76 (65), 71 (100) and 59 (80).

***O*-Nitro-2-phthalimidoethanol 6c.** *N*-(2-Hydroxyethyl)phthalimide **8c** (2.43 g, 12.7 mmol) afforded the product **6c** as a colourless solid (1.95 g, 65%), mp 85–87 °C (from CH_2Cl_2–hexane) (Found: C, 50.70; H, 3.20; N, 11.56. $C_{10}H_8N_2O_5$ requires C, 50.85; H, 3.41; N, 11.86%); ν_{max}/cm^{-1} 1773, 1708, 1608, 1289, 982, 870 and 721; δ_H 4.06 (2 H, t, *J* 5.34, NCH_2), 4.68 (2 H, t, *J* 5.34, CH_2O), 7.70–7.78 (2 H, m, ArH) and 7.81–7.90 (2 H, m, ArH); δ_C 35.07, 69.47, 123.41, 131.57, 134.15 and 167.68; *m/z* (CI) 254 ($M + NH_4^+$, 75%), 237 ($M + H^+$, 20), 192 (80), 174 (22), 160 (100), 133 (25) and 104 (27).

***O*-Nitro-2-phenylethanol 11a.** 2-Phenylethanol **13a** (5.00 g, 41.0 mmol) afforded, after chromatography (CH_2Cl_2), the product **11a** as a pale-yellow oil (6.45 g, 94%), R_f 0.9 (Found: C, 57.62; H, 5.23; N, 8.58. $C_8H_9NO_3$ requires C, 57.48; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3065–2936 (br), 1625, 1455, 1277, 876, 749 and 701; δ_H 3.01 (2 H, t, *J* 7.11, CH_2Ph), 4.63 (2 H, t, *J* 7.11, CH_2O) and 7.27–7.41 (5 H, m, ArH); δ_C 33.19, 73.31, 127.03, 128.71, 128.80 and 135.96; *m/z* (EI) 167 (M^+, 15%), 105 (21), 91 (100), 77 (8) and 65 (12).

***O*-Nitro-1-phenylpropan-2-ol 11b.** 1-Phenylpropan-2-ol **13b** (5.00 g, 36.7 mmol) afforded, after chromatography (CH_2Cl_2), the product **11b** as a pale-yellow oil (5.80 g, 87%), R_f 0.8 (Found: C, 59.90; H, 5.99; N, 7.95. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.73%); ν_{max}/cm^{-1} 3089–2898 (br), 1628, 1498, 1455, 1279, 981, 878 and 700; δ_H 1.36 (3 H, d, *J* 6.57, CH_3), 2.82 (1 H, dd, *J* 6.84 and 13.80, CHPh), 3.04 (1 H, dd, *J* 6.27 and 13.80, CH′Ph), 5.29 (1 H, apparant sextet, *J* 6.4, CH) and 7.27–7.41 (5 H, m, ArH); δ_C 23.65, 46.27, 87.24, 132.81, 134.43, 135.20 and 141.75; *m/z* (EI) 181 (M^+, 3%), 149 (3), 119 (5), 91 (100) and 65 (15).

***O*-Nitro-1,2-diphenylethanol 11c.** 1,2-Diphenylethanol **13c** (2.00 g, 10.1 mmol) afforded, after chromatography (CH_2Cl_2), the product **11c** as a pale-yellow oil (2.21 g, 90%) R_f 0.95 (Found: C, 69.47; H, 5.15; N, 5.79. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76%); δ_H 3.08 (1 H, dd, *J* 6.12 and 14.13, CHPh), 3.27 (1 H, dd, *J* 8.10 and 14.13, CH′Ph), 5.92 (1 H, dd, *J* 6.12 and 8.10, CH) and 7.09–7.36 (10 H, m, ArH); δ_C 40.94, 86.01, 126.49, 126.97, 128.43, 128.60, 128.88, 129.33, 135.50 and 137.25; *m/z* (EI) 243 (M^+, 1%), 197 (15), 181 (32), 165 (15), 105 (35) and 91 (100).

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Glycine-selective α-Carbon-Nitrogen Bond Cleavage of Dipeptides by Nickel Peroxide

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Abstract: Nickel peroxide selectively cleaves the α-carbon-nitrogen bond of glycine residues in dipeptide derivatives to give the corresponding amides. The glycine selectivity is attributable to preferential complexation of the reactant residue to nickel peroxide and subsequent reaction *via* a stable α-centred glycyl radical. The oxidation process serves as a chemical model for peptidylglycine α-amidating monooxygenase (PAM) and, in addition, may have potential for the synthesis of α,β-didehydro amino acid residues within peptides. © 1997 Elsevier Science Ltd.

Nickel peroxide, obtained by the action of alkaline hypochlorite on a nickel (II) salt,[1] is a black, high valency, non-stoichiometric oxide of nickel which is useful as an oxidant of a variety of organic substrates in both aqueous and organic solvents.[2] The free radical nature of oxidations with nickel peroxide has been established in deuterium isotope experiments and electron spin resonance (esr) studies with radical spin traps,[3,4] and the mechanism of reaction is in general considered to involve both hydrogen atom abstraction and hydroxyl radical donation by nickel peroxide.[2,5]

We have investigated nickel peroxide oxidation of amino acid derivatives as a chemical model for peptidylglycine α-amidating monooxygenase (PAM). In the preliminary report[6] of our work in this area it was demonstrated that the *N*-benzoyl amino acid derivatives **1a – c** reacted by oxidative cleavage of the α-carbon-nitrogen bond to give benzamide (**2**) in each case (*Scheme 1*). The reactions were selective for cleavage of the glycine derivative **1a**, such that in competitive experiments using mixtures of the alanine derivative **1b** with either the glycine derivative **1a** or the valine derivative **1c**, each at 0.025 mol dm^{-3} in benzene at 80 °C, the glycine derivative **1a** reacted with nickel peroxide 10.4 ± 2.5 times faster than the alanine derivative **1b**, which in turn reacted 7.0 ± 1.5 times faster than the valine derivative **1c**.

1 **2**

a: R = H
b: R = Me
c: R = CHMe$_2$

Scheme 1

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In probing the basis of the glycine selectivity, we have now examined reactions of the dipeptide derivatives **3a – c** and **5a – d** with nickel peroxide. In the particular cases of the dipeptide derivatives **5c** and **5d**, reaction with nickel peroxide provides convenient access to α,β-didehydro amino acid derivatives. Reactions of the deuterated glycine derivative **11** and the sarcosine derivative **12** have also been investigated, and the outcome of these reactions, along with the reactions of the dipeptide derivatives **3a – c** and **5a – d** has aided elucidation of the reaction mechanism.

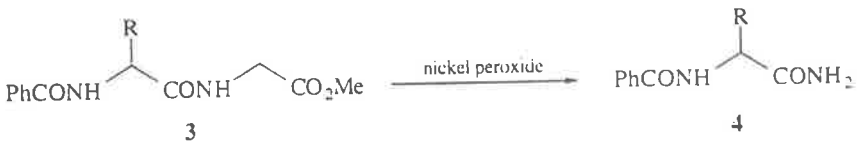
RESULTS AND DISCUSSION

The glycine-containing dipeptide derivatives **3a – c** and **5a,b** reacted upon treatment with nickel peroxide in refluxing benzene to give the corresponding amides **4a – c** and **8a,b** (*Table 1*). No amide bond cleavage was observed in these reactions and the product amides **4a – c** and **8a,b** arise as a result of oxidative cleavage of the α-carbon-nitrogen bond of the *C*-terminal glycine residue in each case (*Schemes 2 and 3*). The aspartic acid containing dipeptide derivatives **5c** and **5d**, however, reacted with nickel peroxide to afford the didehydroaspartate derivatives **10c** and **10d**, as well as the amide **8c**, in the case of **5c** (*Table 1*). The assignment of *Z*-stereochemistry to the dehydropeptides **10c** and **10d** was made on the basis of the tendency of dehydro amino acid derivatives to favour this configuration.[7]

Table 1. Reactions of the dipeptide derivatives **3a – c** and **5a – d** with nickel peroxide.

Substrate	Product	Yield†	Corrected Yield††
3a	**4a**	23%	74%
3b	**4b**	27%	68%
3c	**4c**	37%	46%
5a	**8a**	54%	79%
5b	**8b**	41%	55%
5c	**8c**	21%	33%
	10c	17%	27%
5d	**10d**	54%	86%

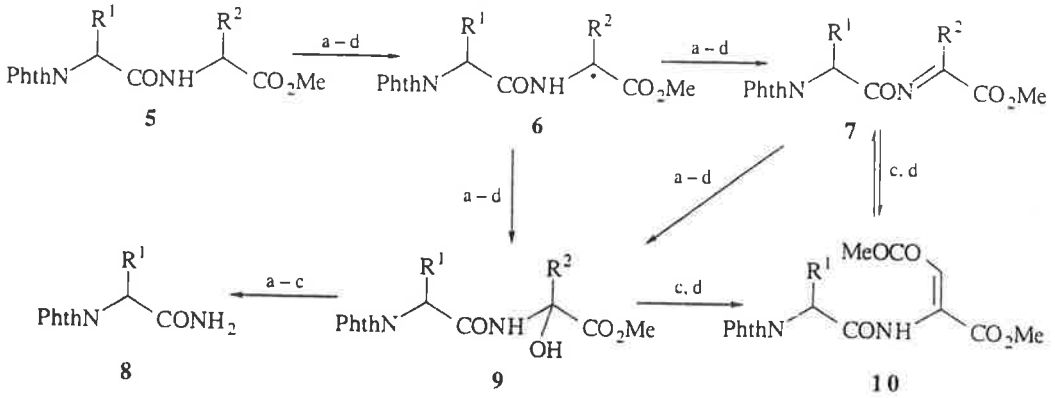
† yields not optimised †† based on recovered starting material



3 **4**

a: R = Me
b: R = $CHMe_2$
c: R = CH_2CHMe_2

Scheme 2

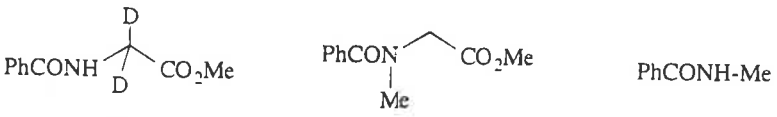


5 6 7 8 9 10

a: R^1 = $CHMe_2$, R^2 = H
b: R^1 = CH_2CHMe_2, R^2 = H
c: R^1 = CH_2Ph, R^2 = CH_2CO_2Me
d: R^1 = H, R^2 = CH_2CO_2Me

Scheme 3

Production of the amides **4a – c** and **8a – c** from the glycyl dipeptides **3a – c** and **5a – c**, and of the didehydroaspartate derivatives **10c** and **10d** from the aspartyl dipeptides **5c** and **5d** may be rationalised as outlined in *Scheme 3*, for the case of the dipeptides **5a – d**. Following complexation to nickel, hydrogen atom transfer from the substrates **5a – d** affords the corresponding α-carbon-centred radicals **6a – d**, which combine with hydroxyl radical from nickel peroxide to give the corresponding α-hydroxy amino acid derivatives **9a – d**. Alternatively, the α-centred radicals **6a – d** may form the corresponding *N*-acylimines **7a – d**, *via* a second hydrogen atom transfer, followed by addition of water to give the corresponding α-hydroxy amino acid derivatives **9a – d**. Subsequent hydrolysis of the α-hydroxy amino acid derivatives **9a – c** then affords the respective amides **8a – c**. Formation of the dehydroaspartate derivatives **10c** and **10d** from the dipeptides **5c** and **5d** is attributable to either the elimination of water from the alcohols **9c** and **9d** or tautomerisation of the intermediate *N*-acylimines **7c** and **7d** (*Scheme 3*). This process is presumably favoured for aspartate residues due to extended conjugation in the products.



11 **12** **13**

Supporting evidence for the mechanism described above is provided by reactions of nickel peroxide with the dideuteroglycine derivative **11** and the *N*-benzoylsarcosine derivative **12**. The deuterated glycine derivative **11** reacted upon treatment with nickel peroxide to give benzamide (**2**) and recovered starting material **11**, for which the isotopic ratio was little changed. This indicates that the deuterium label is not exchanged under the reaction conditions and further, that the reaction with nickel peroxide is irreversible. In a competitive experiment using an equimolar mixture of substrates, the glycine derivative **1a** reacted 2.9 ± 0.5 times faster than its deuterated analogue **11**, representing a deuterium isotope effect consistent with that reported for

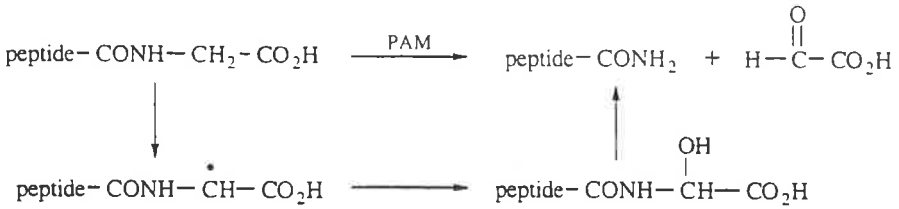
α-hydrogen atom transfer from amino acid derivatives under free radical conditions.[8] This, in turn, indicates that α-carbon-hydrogen bond homolysis is an irreversible rate-determining step in reactions of the dipeptide derivatives **3a – c** and **5a – d** with nickel peroxide.

The *N*-benzoylsarcosine derivative **12** reacted with nickel peroxide to give *N*-methylbenzamide (**13**) and benzamide (**2**). In a separate experiment, the nickel peroxide oxidation of *N*-methylbenzamide (**13**) gave benzamide (**2**), consistent with the amide **13** being the initial oxidation product of the sarcosine derivative **12**. As imine formation is not possible in the oxidation of the sarcosine derivative **12**, this establishes that oxidative α-carbon-nitrogen bond cleavage of amino acid derivatives by nickel peroxide can occur *via* direct hydroxylation of intermediate α-centred amino acid radicals, and need not involve imine intermediates.

Selective reaction at the *C*-terminal residues in the dipetides **5c** and **5d** is presumably due to the deactivating effect of the *N*-phthaloyl substituent[9] toward hydrogen atom abstraction at the adjacent carbon. When a single diastereomer of the dipeptide **5c** was treated with nickel peroxide, both **10c** and **8c** were produced without racemisation of the *N*-terminal phenylalanine residue. This example serves to illustrate the utility of the nickel peroxide oxidation procedure as methodology for *in situ* synthesis of α,β-didehydroamino acid residues within peptides.

The reactions of the dipeptide derivatives **3a – c** and **5a,b** to give the respective amides **4a – c** and **8a,b** each demonstrate selective cleavage by nickel peroxide of glycine residues. Whereas reaction at the *C*-terminal glycine residue in each of the phthaloyl substituted dipeptide derivatives **5a** and **5b** may simply reflect the deactivating effect of the *N*-phthaloyl substituent toward hydrogen atom abstraction from the adjacent carbon,[9] cleavage of the *C*-terminal residue in the reaction of each of the benzoyl substituted dipeptide derivatives **3a – c** clearly demonstrates a selectivity for reaction of glycine residues, as radical reactions of dipeptide derivatives of this type are normally selective for reaction of the *N*-terminal amino acid residue.[10] In contrast to reaction of the amino acid derivatives **1a – c**, wherein the selectivity for reaction of the glycine derivative **1a** may be affected by the relative solubilities of the reactant substrates in the reaction medium, insofar as this affects their relative ease of complexation to nickel peroxide,[6] the selectivity for reaction of the glycine residues in the dipeptides **3a – c** and **5a,b** is not affected by the individual solubilities of the dipeptides. Consequently, the selectivity for reaction of the glycine residues in the dipeptides **3a – c** and **5a,b** must be attributed to preferential complexation of the reactant residue to the nickel peroxide surface and subsequent reaction once bound. It is presumable that complexation of metal ions to amino acid derivatives with large α-substituents will be disfavoured by steric interactions, and evidence for preferential complexation of glycine residues by copper ions has been reported in earlier work.[11] In addition, the relative ease of formation of α-centred glycine radicals *via* hydrogen atom abstraction[8] presumably contributes to the selectivity for reaction of glycine residues in the dipeptides **3a – c** and **5a,b**.

Nickel peroxide provides methodology for selective oxidative cleavage of glycine residues in dipeptides, which is analogous to the process catalysed in biology by peptidylglycine α-amidating monooxygenase (PAM).[12,13] This enzyme complex[13] is responsible for posttranslational activation of many peptide hormones and neuropeptides, through reaction of glycine-extended precursors to give *C*-terminal amides (*Scheme 4*). Both the nickel peroxide reaction and the enzyme catalysed process involve α-hydrogen atom transfer from the reactive centre[14] and proceed *via* formation of an α-hydroxy amino acid intermediate.[15] The glycine selectivity displayed by nickel peroxide mirrors that of PAM[16] and the factors that contribute to this selectivity may similarly contribute to the substrate selectivity displayed by PAM. It is likely that the natural substrates of PAM are synthesised with a *C*-terminal glycine residue because that residue is so easily removed by oxidative cleavage, and this process presumably provides the most efficient route available in biology for the synthesis of



Scheme 4

peptidyl amides. Nickel peroxide serves as a chemical model for PAM, and this model has potential applicability in the development of enzyme inhibitors for the control of metabolic disorders associated with overproduction of peptide hormones.

EXPERIMENTAL

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Jasco IRA-1 spectrophotometer as nujol mulls between sodium chloride plates, or as solutions as indicated. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on either a Bruker ACP 300 or CXP 300 spectrometer as dilute solutions in deuterochloroform, using tetramethylsilane as internal standard. Electron impact mass spectra and high resolution mass spectra were recorded on an AEI MS-3010 spectrometer, using an ionising voltage of 70 eV. Elemental analyses were performed by Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada. Preparative thin layer chromatographies were carried out on a Chromatotron 7924T (Harrison Research, Palo Alto / TC Research, Norwich) using Merck silica gel 60_{PF-254} (Art. 7749). All organic extracts were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction with b.p. 66 – 69 °C.

Nickel peroxide was prepared according to the method of Nakagawa *et al.*,[1] and its available oxygen content was determined as 2.9×10^{-3} mol g^{-1}. α,α-Dideuteroglycine was prepared by treatment of glycine with acetic anhydride / D_2O.[17] The amino acid and dipeptide derivatives **1a**, **3a – c**, **5a – d**, **11** and **12** used in this work were prepared from the corresponding amino acids using standard procedures. Of these compounds **1a**, **3a – c**, **5a.b.d**, **11** and **12** had spectroscopic properties and physical constants in agreement with those previously reported,[8,10,16,18–22] whereas **5c** was fully characterised, as described below.

General Procedure for Nickel Peroxide Oxidations of Amino Acid and Dipeptide Derivatives. Typically a solution of the amino acid or dipeptide derivative (100 - 200 mg) in benzene (20 ml) was treated with nickel peroxide (2 – 4 mole equiv.) at reflux under nitrogen for 2 – 4 hr. The heterogeneous reaction mixture was filtered on diatomaceous earth whilst hot, to remove nickel salts, and the filtrate was concentrated under reduced pressure. The products of reaction were isolated *via* preparative thin layer chromatography of the residue, eluting with a mixture of light petroleum and ethyl acetate (*Tables 1 and 2*). The products of these reactions, **4a – c**, **8a – c** and **10c.d**, were either fully characterised, as described below, or had spectroscopic properties and physical constants in agreement with those previously reported.[9,23–26]

Table 2. Reaction of *N*-benzoylsarcosine methyl ester (**12**) and *N*-methylbenzamide (**13**) with nickel peroxide.

Substrate	Product	Yield	Corrected Yield†
12	**13**	25%	35%
	2	7%	10%
13	**2**	22%	50%

† based on recovered starting material.

N-Phthaloyl-(S)-phenylalanyl-(R,S)-aspartic Acid Dimethyl Ester (5c). *N*-Phthaloyl-(*S*)-phenylalanine,[26] prepared in a melt reaction[27] between phthalic anhydride and (*S*)-phenylalanine, was coupled with (*R,S*)-aspartic acid dimethyl ester hydrochloride *via* the mixed anhydride formed upon treatment with ethyl chloroformate. Chromatography of the crude product gave *N*-phthaloyl-(*S*)-phenylalanyl-(*R,S*)-aspartic acid dimethyl ester (**5c**) as a colourless oil, the diastereomers of which were separated by fractional crystallisation from methanol.

N-Phthaloyl-(*S*)-phenylalanyl-(*R,S*)-aspartic acid dimethyl ester (**5c**), first diastereomer: m.p. 110 – 115 °C; IR (nujol) 3525, 3370, 3028, 2950, 1780, 1710, 1620, 1524, 1443, 1386, 1220, 1100, 1000, 918, 880, 800, 720, 700 cm^{-1}; ^1H NMR δ 2.92 (1H, dd, *J* 17.2, 4.4 Hz), 2.98 (1H, dd, *J* 17.2, 4.4 Hz), 3.58 (2H, m), 3.68 (3H, s), 3.71 (3H, s), 4.85 (1H, dt, *J* 9.2, 4.4 Hz), 5.14 (1H, dd, *J* 9.3, 7.3 Hz), 7.09 (1H, broad d, *J* 9.2 Hz), 7.16 (5H, m), 7.55 (2H, m), 7.80 (2H, m); ^{13}C NMR δ 171.36, 170.79, 168.30, 167.76, 136.59, 134.24, 131.34, 128.89, 126.84, 128.57, 123.45, 55.07, 52.83, 52.04, 48.89, 35.77, 34.58; MS *m/z* (relative intensity) 438 (M^+, 19), 437 (4), 436 (2), 370 (1), 292(5), 291 (7), 278 (8), 277 (11), 251 (31), 250 (100), 249 (57), 233 (12), 232 (76), 160 (40), 132 (15), 131(76), 130(12); HRMS calcd for $C_{23}H_{22}N_2O_7$ *m/z* 438.1427 (M^+), found 438.1441; Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 63.11; H, 5.08; N, 6.45.

N-Phthaloyl-(*S*)-phenylalanyl-(*R,S*)-aspartic acid dimethyl ester (**5c**), second diastereomer: m.p. 94 – 97 °C; IR (nujol) 3525, 3370, 3028, 2950, 1780, 1710, 1620, 1524, 1443, 1386, 1220, 1100, 1000, 918, 880, 800, 720, 700 cm^{-1}; ^1H NMR δ 2.94 (1H, dd, *J* 17.3, 4.4 Hz), 2.99 (2H, dd, *J* 17.3, 4.4 Hz), 3.49 (2H, m), 3.63 (3H, s), 3.73 (3H, s), 4.88 (1H, dt, *J* 9.2, 4.4 Hz), 5.15 (1H, dd, *J* 10.6, 5.8 Hz), 7.09 (1H, broad d, J 9.2 Hz), 7.13 (5H, m), 7.69 (2H, m), 7.77 (2H, m); ^{13}C NMR δ 171.47, 170.78, 168.07, 167.79, 136.50, 134.27, 131.37, 128.93, 128.59, 126.94, 123.48, 55.21, 52.92, 52.00, 48.84, 35.68, 34.69; MS *m/z* (relative intensity) 438 (M^+, 19), 437 (4), 436 (2), 370 (1), 292 (5), 291 (7), 278 (8), 277 (11), 251 (31), 250 (100), 249 (57), 233 (12), 232 (76), 160 (40), 132 (15), 131(76), 130 (12); HRMS calcd for $C_{23}H_{22}N_2O_7$ *m/z* 438.1427 (M^+), found 438.1441; Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.64; H, 5.14; N, 6.34.

Reaction of N-Phthaloyl-(S)-phenylalanyl-(R,S)-aspartic Acid Dimethyl Ester (5c) with Nickel Peroxide. *N*-Phthaloyl-(*S*)-phenylalanyl-(*R,S*)-aspartic acid dimethyl ester (**5c**) (30 mg, 0.07 mmol) in benzene (5 ml) was treated with nickel peroxide (4 mole equiv.) at reflux under nitrogen overnight. Workup and chromatography of the reaction mixture afforded the didehydroaspartate **10c**, the amide **8c** and unreacted starting material **5c** (11 mg, 37%).

N-Phthaloyl-(*S*)-phenylalanyl-α,β-didehydroaspartic acid dimethyl ester (**10c**), as an oil (5 mg, 17%): IR ($CDCl_3$) 3320, 3288, 3028, 2952, 1800, 1740, 1710, 1660, 1500, 1480, 1438, 1400, 1396, 1310, 1240,

1200, 1145, 1115, 1100, 1040, 980, cm^{-1}; ^1H NMR δ 3.61 (2H, m), 3.63 (3H, s), 3.86 (3H, s), 5.26 (1H, t, *J* 8.3 Hz), 5.58 (1H, s), 7.19 (5H, s), 7.70 (2H, m), 7.78 (2H, m), 10.75 (1H, broad s); ^{13}C NMR δ 167.96, 167.40, 166.77, 163.78, 142.84, 136.02, 134.3, 131.32, 128.86, 128.61, 127.03, 123.60, 103.29, 55.00, 53.16, 51.99, 33.96; MS *m/z* (relative intensity) 436 (M^+, 4), 406 (1), 405 (2), 404 (1), 378 (5), 377 (14), 345 (2), 317 (1), 287 (4), 251 (21), 250 (100), 249 (67), 232 (28), 230 (8), 229 (12), 174 (6), 160 (4), 147 (6); HRMS calcd for $C_{23}H_{20}N_2O_7$ *m/z* 436.1270 (M^+), found 436.1276.

N-Phthaloyl-(*S*)-phenylalaninamide (**8c**), recrystallised from ethanol as colourless crystals (4 mg, 21%): m.p. 228 – 230 °C (lit.[26] 229 – 230 °C); ^1H NMR δ 3.56 (2H, m), 5.13 (1H, dd, *J* 9.1, 7.7 Hz), 5.50 (1H, broad s), 6.12 (1H, broad s), 7.19 (5H, m), 7.71 (2H, m), 7.79 (2H, m); MS *m/z* (relative intensity) 294 (M^+, 39), 292 (4), 278 (7), 277 (15), 251 (22), 250 (100), 249 (72), 233 (17), 232 (78), 160 (33), 147 (78); HRMS calcd for $C_{17}H_{14}N_2O_3$ *m/z* 294.1004 (M^+), found 294.1018.

Reaction of N-*Phthaloylglycyl-(*R,S*)-aspartic Acid Dimethyl Ester (**5d**) with Nickel Peroxide.* *N*-Phthaloylglycyl-(*R,S*)-aspartic acid dimethyl ester (**5d**)[9,21] (30 mg, 0.09 mmol) in benzene (5 ml) was treated with nickel peroxide (4 mole equiv.) at reflux under nitrogen overnight. Workup and chromatography of the reaction mixture afforded the didehydroaspartate **10d** and unreacted starting material **5d** (11 mg, 37%).

N-Phthaloylglycyl-α,β-didehydroaspartic acid dimethyl ester (**10d**), recrystallised from ethyl acetate / light petroleum as colourless needles (16 mg, 54%): m.p. 179 – 181 °C (lit.[9] 175 – 176 °C); IR ($CHCl_3$) 3288, 2952, 1788, 1728, 1694, 1640, 1438, 1420, 1396, 1290, cm^{-1}; ^1H NMR δ 3.76 (3H, s), 3.82 (3H, s), 4.53 (2H, s), 5.60 (1H, s), 7.76 (2H, m), 7.90 (2H, m), 10.54 (1H, broad s); ^{13}C NMR δ 168.18, 167.33, 164.40, 163.62, 142.78, 134.35, 131.94, 123.77, 102.97, 53.15, 52.10, 40.71; MS *m/z* (relative intensity) 346 (M^+, 5), 315 (9), 288 (72), 256 (5), 186 (24), 161 (39), 160 (100); HRMS calcd for $C_{16}H_{14}N_2O_7$ *m/z* 346.0801 (M^+), found 346.0791.

Reaction of N-*Benzoyl-α,α-dideuteroglycine Methyl Ester (**11**) with Nickel Peroxide.* *N*-Benzoyl-α,α-dideuteroglycine methyl ester (**11**)[8] (80% $^2H_2$, 18% $^2H_1$ by mass spectrometry, 50 mg, 0.26 mmol) in benzene (10 ml), was treated with nickel peroxide (2.6 mole equiv.) at reflux under nitrogen for 1 hr. Workup and chromatography of the reaction mixture afforded benzamide (**2**) (6 mg, 19%) and unreacted starting material **11** (82% $^2H_2$, 13% $^2H_1$, 35 mg, 70%).

Relative Rate of Reaction of N-*Benzoylglycine Methyl Ester (**1a**) and* N-*Benzoyl-α,α-dideuteroglycine Methyl Ester (**11**), with Nickel Peroxide.* A mixture of **1a**[18] (50 mg, 0.26 mmol) and **11** (50 mg, 0.26 mmol) with *N-tert*-butylbenzamide (25 mg, 0.15 mmol) as internal standard, in benzene (10 ml), was treated with nickel peroxide (2.6 mole equiv.) at reflux, under nitrogen. Aliquots were removed at intervals and analysed by ^1H NMR spectroscopy following filtration and solvent removal. The initial and final relative ratios of the amino acid derivatives **1a** and **11** were determined by peak integration. The relative rate of reaction of **1a** to **11** was calculated using *Equation 1*[8,28] as 2.9 ± 0.5. The error limits quoted represent the sample standard deviation for experiments carried out in triplicate and analyses performed in triplicate.

$$k_X/k_Y = \ln([X]_{t=1}/[X]_{t=0})/\ln([Y]_{t=1}/[Y]_{t=0}) \qquad \textit{Equation 1}$$

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Cyclodextrins and modified forms in chemistry and industry

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Natural cyclodextrins

Cyclodextrins[1] are naturally occurring cyclic sugars which are obtained through the enzymic degradation of starch. Interest in these compounds stems from their ability to act as molecular hosts in the formation of host–guest or inclusion complexes with a wide range of guests (Fig. 1). Many of the industrial applications involve hydrophobic guests, where the solubility of the cyclodextrins in aqueous solution confers solubility on the host–guest complexes. Thus it is possible to prepare aqueous solutions of hydrophobic molecules.

APPLICATIONS IN THE FOOD AND PHARMACEUTICAL INDUSTRIES

In parts of the world the natural cyclodextrins have been approved for use as food additives to reduce the odour of garlic, for example by complexing the components and limiting their volatility in the dry state. In this and other applications involving cyclodextrins, the guests remain accessible in solution through the equilibrium shown in Fig. 1.

Many potential applications of cyclodextrin host–guest complexes in the pharmaceutical industry still await regulatory approval, but there is a great deal of interest in this area.[2] Cyclodextrin host–guest complexes may be regarded as drug capsules, with the encapsulation occurring at the molecular level. One advantage of these complexes is that they can be used to prepare aqueous formulations of hydrophobic pharmaceuticals, for oral, intravenous, ocular and other forms of administration. With oral administration, complexation of the drug may reduce degradation in the acidic environment of the stomach, reduce irritation of the gastro-intestinal tract, and increase bioavailability of the drug through these effects and by improving absorption in the small intestine.

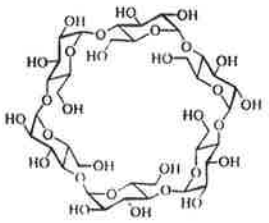
Sustained release drug formulations can also be expected, according to the equilibrium shown in Fig. 1, where the guest is a drug. The rate of drug absorption through the intestinal wall depends on the concentration of the drug in the free state, which is determined by the position of the equilibrium between the free drug and the cyclodextrin and the host–guest complex (the two latter components are not absorbed significantly). This equilibrium is maintained while absorption proceeds, and makes the drug available in a controlled and sustained manner.

CHEMICAL APPLICATIONS

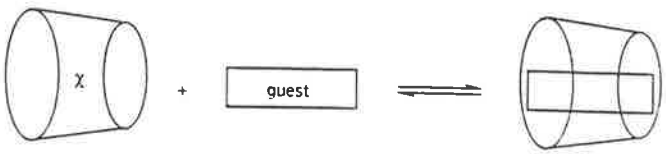
There are also many chemical applications of cyclodextrin host–guest complexes. Often similar molecules will form quite distinct host–guest complexes which aid their separation. This is particularly the case with racemic guests, which form diastereomeric host-guest complexes, since the cyclodextrins are homochiral.[3] Probably the most notable contribution in this area is that of Armstrong and co-workers, who have developed commercial cyclodextrin-based chromatography columns for the analytical resolution of enantiomers. The enantioselectivity displayed by cyclodextrins in forming complexes with racemic guests is reflected in the stereoselectivity of reactions of included guest molecules, and the use of cyclodextrins in asymmetric synthesis is another topical area of research.

In the broader context, cyclodextrins are capable of affecting the rate and regio- and stereo-selectivity of

A truncated cone is often used to represent a cyclodextrin. A substituent drawn at the narrow end of the cone indicates that it replaces a primary hydroxy group in the cyclodextrin while a substituent drawn at the wide end of the cone indicates that it replaces a secondary hydroxy group.



α-Cyclodextrin (shown) has six α-D-glucopyranose units, whereas β- and γ-cyclodextrins have seven and eight respectively.



χ = α, α-cyclodextrin
χ = β, β-cyclodextrin
χ = γ, γ-cyclodextrin

host–guest complex

Figure 1. Structure of the cyclodextrins and the equilibrium for the formation of host–guest complexes.

chemical reactions by changing the microenvironment for those reactions through complexation and by preassembly of the reagents for multicomponent reactions. This ability of cyclodextrins to bind guest molecules and facilitate reactions of the bound species is akin to the catalytic activity displayed by enzymes and, for this reason, cyclodextrins have been studied intensively as enzyme mimics. The cyclodextrin hydroxy groups have been shown to participate in hydrolysis and esterification reactions which are similar to those catalysed by the serine esterases and proteases.[4]

Alternatively, cyclodextrins can be used in conjunction with enzymes to improve the efficiency of enzyme-catalysed processes. Selective complexation by a cyclodextrin of either a product or a reagent of an enzyme-catalysed reaction can alter the equilibrium position, or the rate at which equilibrium is attained, by reducing product inhibition or through other allosteric effects. For example, the catalysis of the conversion of (S)-phenylalanine to *trans*-cinnamate by the enzyme phenylalanine ammonia lyase is inhibited by the product, but that inhibition can be reduced and the efficiency of the reaction increased through the addition of a cyclodextrin to selectively sequester the product as it forms.[5]

Modified cyclodextrins

Most of our recent work in Canberra and Adelaide, and a large portion of the current international research effort relating to cyclodextrins, has involved modified forms. The naturally occurring cyclodextrins are relatively inert molecular hosts, as they contain only hydroxy functional groups. As a consequence the range of host–guest interactions available to them is restricted. However, through modification, the natural cyclodextrins become effective templates for the generation of an extraordinary range of new molecular hosts, which opens up a vast range of chemistry not available with the natural cyclodextrins.

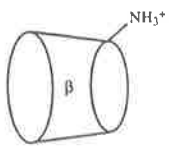
ENHANCED COMPLEXATION

By using modified cyclodextrins it is possible to tailor a cyclodextrin host to a particular guest, to meet specific requirements in the host–guest complex. Modifications to a cyclodextrin may involve altering its cavity size, shape, charge and/or polarity. As an example, at neutral pH the β-cyclodextrin derivatives (1) and (2) form host–guest complexes with deprotonated carboxylic acids and protonated amines, respectively, where the extent of complex formation (or thermodynamic stability of the complex) is increased over that observed with the natural β-cyclodextrin, due to the ionic host-guest interactions which are only made possible through the cyclodextrin modifications.[2] In addition, the cyclodextrin derivatives (1) and (2) are each approximately forty times more soluble than β-cyclodextrin, so substantially more concentrated solutions of these compounds and their complexes can be obtained.

Covalently linked cyclodextrin dimers allow the possibility of cooperative guest binding by the cyclodextrin annuli, and the thermodynamic stability of the complex of Methyl Orange (3) with the β-cyclodextrin dimer (4) is almost two orders of magnitude higher than that of the complex with the parent cyclodextrin.[6] Recent work of Breslow and Zhang,[7] on the particularly effective complexation of cholesterol by an alternative cyclodextrin dimer, indicates that compounds of this type may find application as dietary supplements to reduce cholesterol absorption. A similar usage has already been proposed for the natural cyclodextrins.[8]

APPLICATIONS IN CHEMICAL SEPARATION

The ability to use modified cyclodextrins to tailor host–guest complexes to meet specific requirements and to increase the extent of host–guest interactions in the complexes provides improved procedures for chemical separation, including chiral discrimination.[3] The thermodynamic stability of the diastereomeric complexes formed between the enantiomers of tryptophan anion and the nickel(II) complex of the 6^{A}-aminopropylamino-6^{A}-deoxy-—cyclodextrin (5) differ by an order of magnitude, whereas neither β-cyclodextrin nor the apometallocyclodextrin (5) display enantioselectivity for complexation of that guest.[3] The cyclodextrin ester (6) of the non-steroidal anti-inflammatory agent Ibuprofen is produced as a 5:1 mixture of the diastereomers through reaction of β-cyclodextrin with an excess of the acid chloride of Ibuprofen, and a complementary selectivity of 10:1 occurs in the hydrolysis



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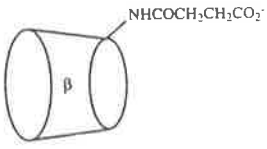

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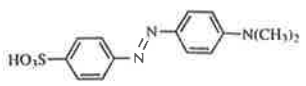

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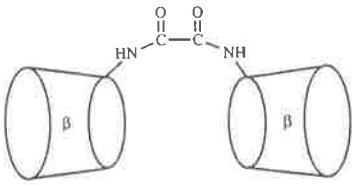

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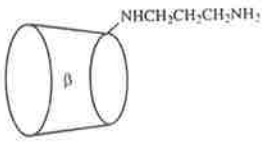

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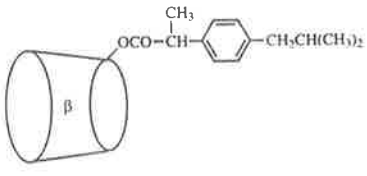

(6)

of the diastereomers, with the preferentially formed isomer hydrolysing the fastest.[3] The marked stereoselectivity displayed by modified cyclodextrins, and illustrated by these examples, can be attributed to increased host–guest interactions resulting from metal complexation and covalent attachment of the host to the guest, respectively.

CHEMICAL SYNTHESIS, CATALYSIS AND PHOTOCHEMISTRY

The option to introduce diverse functional groups through modifications to the natural cyclodextrins dramatically expands the utility of cyclodextrins in chemical synthesis and catalysis. Now, no longer limited to hydroxy functional groups, modified cyclodextrins present a much greater range of possibilities to mimic the entire span of enzymic activity. This is exemplified by the bifunctional catalysis of the hydrolysis of 4-*tert*-butylcatechol cyclic phosphate by a bisimidazole – cyclodextrin (Fig. 2).[9]

Modifications to the cyclodextrins also lead to a wide range of photochemistry of cyclodextrin complexes, through which enhancement of guest reactivity occurs, and light harvesting molecular devices and frequency switches may be constructed. A particularly interesting example in this area is illustrated in Fig. 3.[10]

Summary

In the space available it has only been possible to give a very brief overview of cyclodextrin chemistry and its applications. The current level of activity in this area is enormous, as indicated by the frequency of journal articles and the level of patent activity in the field, and there is every reason to expect that exciting research in this area will continue to lead to impressive new developments and applications.

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Stephen Lincoln holds a personal chair at the University of Adelaide. He is a graduate of UMIST and the University of Adelaide, and he received a D.Sc. from the University of Manchester in 1984. He held a postdoctoral position at Washington State University before joining the staff at Adelaide. His research interests include inorganic and bioinorganic reaction mechanisms and molecular recognition chemistry.

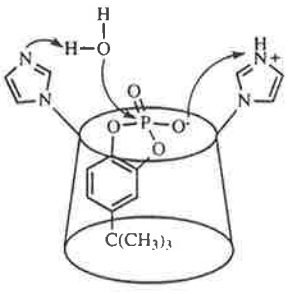

Figure 2. Bifunctional catalysis by a modified cyclodextrin.

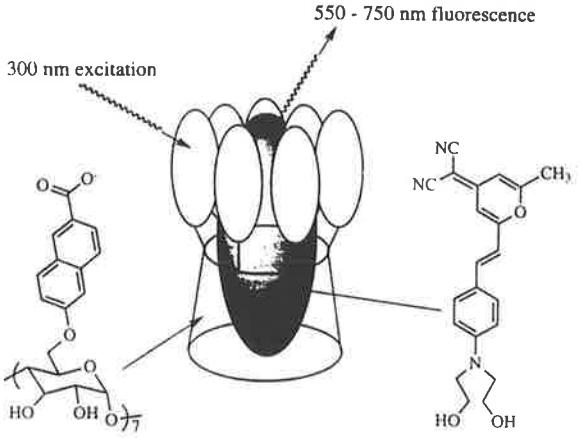

Figure 3. Photochemical frequency switching in the host–guest complex of a modified cyclodextrin.

Aust. J. Chem., 1997, **50**, 447–450

Complexes of Naproxen and Ibuprofen with 6^A-Amino-6^A-deoxy-β-cyclodextrin

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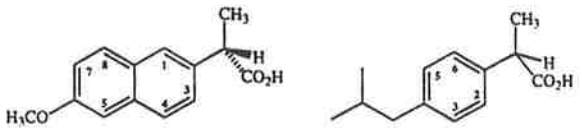
At pD 6·80 in D_2O containing 0·10 mol dm^{-3} phosphate buffer, the association constants of the complexes of Naproxen and Ibuprofen with 6^A-amino-6^A-deoxy-β-cyclodextrin are 810±200 and 8900±2100 mol^{-1} dm^3, respectively, while those of the corresponding complexes with β-cyclodextrin are 940±170 and 8800±1800 mol^{-1} dm^3, respectively. A 2D-ROESY experiment shows that Naproxen includes lengthwise in the substituted cyclodextrin, with the reverse orientation to that of the complex with β-cyclodextrin. The orientation in the host–guest complex of the substituted cyclodextrin results in the alignment of the host amino substituent and the guest carboxy group, which at this pD are predominantly protonated and deprotonated, respectively. The similarity in the association constants of the complexes of Naproxen indicates that any stabilization provided by interactions between the ionic groups in the complex of the substituted cyclodextrin is offset by other factors, such as the extent of desolvation of the host and guest.

Introduction

Naproxen* (1) and Ibuprofen† (2) are systematic non-steroidal antiinflammatory and analgesic agents which are used widely in the relief of the symptoms of various forms of arthritis.[1–4] Such drugs have deleterious effects on the epithelium of the gastrointestinal tract and it has been proposed that their administration as inclusion complexes within cyclodextrins will result in reduced concentrations of the free drugs available to cause such damage.[5,6] Consequently the formation of host–guest complexes of Naproxen (1) and Ibuprofen (2) with the naturally occurring cyclodextrins has been studied.[7,8] The most stable complexes are formed with β-cyclodextrin, such results indicating that it has the optimal cavity size for binding these guests.

One limitation to using β-cyclodextrin in the preparation of aqueous drug formulations is its low solubility in water, restricted to 18·5 g dm^{-3} at 298·2 K.[9] Modified cyclodextrins which are more soluble provide the opportunity to prepare more concentrated solutions of host–guest complexes, and the modifications also provide additional sites for host–guest interactions, which may affect the thermodynamic stability of the complexes. The solubility of the hydrochloride salt of 6^A-amino-6^A-deoxy-β-cyclodextrin (3)‡ in water at 298·2 K is 705 g dm^{-3}.[10] In solutions near neutral pH the amine is predominantly in the protonated form,



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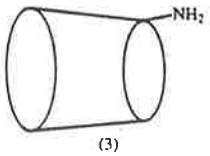

(3)

* (*S*)-2-(6-Methoxy-2-naphthyl)propanoic acid.
† 2-[4-(2-Methylpropyl)phenyl]propanoic acid.
‡ Cyclodextrins are commonly represented as truncated cones with the narrow and wide ends representing the circles delineated by the primary and secondary hydroxy groups respectively. The protons located within the cyclodextrin annulus, ordered from the primary end, are those attached to C6, C5 and C3.

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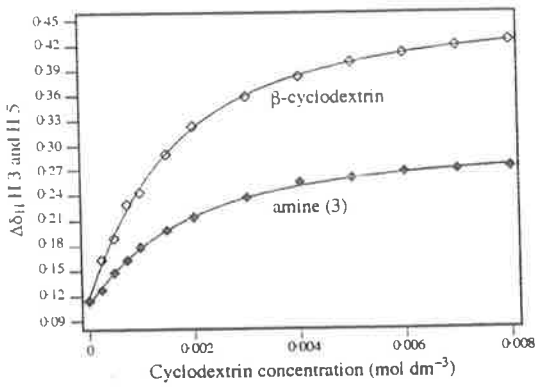

Fig. 1. Differences between chemical shifts of the resonances of H3 and H5 in the ^{1}H n.m.r. spectrum of Naproxen (1) in the presence of varying concentrations of β-cyclodextrin or 6^A-amino-6^A-deoxy-β-cyclodextrin (3) at pD 6·80 in D_2O containing 0·10 mol dm^{-3} phosphate at 298·2 K.

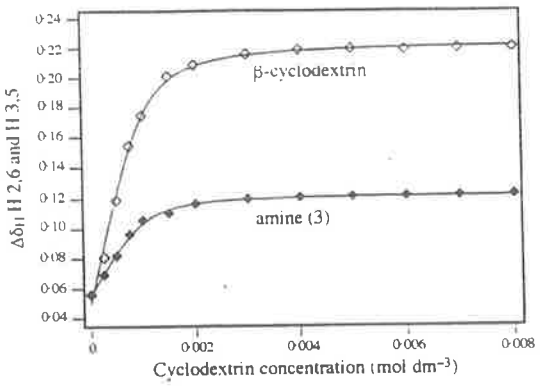

Fig. 2. Differences between chemical shifts of the resonances of H2,6 and H3,5 in the ^{1}H n.m.r. spectrum of Ibuprofen (2) in the presence of varying concentrations of β-cyclodextrin or 6^A-amino-6^A-deoxy-β-cyclodextrin (3) at pD 6·80 in D_2O containing 0·10 mol dm^{-3} phosphate at 298·2 K.

since its pK_b is 8·7.[10] and Naproxen (1) and Ibuprofen (2) are each predominantly in the deprotonated form, with pK_a values of 4·2[11] and 4·4.[11] respectively. We have now studied the complexation of the drugs (1) and (2) by the amine (3), to examine the ability of the modified cyclodextrin (3) to include the guests (1) and (2), and to investigate the possible effects of ionic host–guest interactions on the inclusion complexes.

Results and Discussion

Inclusion of a guest within the cavity of a cyclodextrin changes the physical and spectroscopic properties of the host and guest, and the complexation can be characterized by monitoring the change in one of these properties as a function of increasing cyclodextrin concentration.[12–17] In the present work, the ^{1}H n.m.r. spectra were recorded of solutions of the drugs (1) and (2) ($1·00\times10^{-3}$ mol dm^{-3}) and the cyclodextrin (3) (0–8 mol. equiv.) in D_2O containing 0·10 mol dm^{-3} phosphate buffer, at pD 6·80. For comparison, analogous experiments were performed with α- and β-cyclodextrin, and 6^A-amino-6^A-deoxy-α-cyclodextrin. The chemical shifts of the resonances of the aromatic protons of Naproxen (1) and Ibuprofen (2) varied with changing cyclodextrin concentration. This indicates that the free and complexed guests are in fast exchange on the n.m.r. time scale, and the signals represent environmental averages for the free and complexed species. The effects of 0–8 mol. equiv. of α-cyclodextrin and 6^A-amino-6^A-deoxy-α-cyclodextrin on the ^{1}H n.m.r. spectra of the drugs (1) and (2) were much less than those caused by the same quantities of β-cyclodextrin and the amine (3). Substantial changes were observed when larger excesses of the former cyclodextrins were employed, however, indicating that the association constants of the complexes of these hosts are much lower.

The observed changes in the differences between the chemical shifts of the resonances of H3 and H5 of Naproxen (1), and H2,6 and H3,5 of Ibuprofen (2), induced by β-cyclodextrin and the amine (3), are shown in Figs 1 and 2. The H3 and H5 signals of Naproxen were used because they are shifted the most downfield and upfield, respectively, by the cyclodextrins. By fitting these data according to equations *(1)* and *(2)*, which apply when the free and complexed species are in fast exchange on the n.m.r. time scale and environmentally averaged signals are observed,[17] the association constants (K) of the complexes of Naproxen (1) and Ibuprofen (2) with the amine (3) were calculated to be 810±200 and 8900±2100 mol^{-1} dm^3, respectively, while those of the corresponding complexes with β-cyclodextrin were found to be 940±170 and 8800±1800 mol^{-1} dm^3, respectively. The similarity between the association constants of the complexes of the amine (3) and β-cyclodextrin shows that the introduction of the amino group, protonated at pD 6·80, has little effect on the thermodynamic stability of the complexes of deprotonated Naproxen (1) and Ibuprofen (2).

$$K = \frac{[\text{complex}]}{[\text{host}][\text{guest}]} \qquad (1)$$

$$\delta_{\text{observed}} = \frac{\delta_{\text{free}}[\text{guest}] + \delta_{\text{complexed}}[\text{complex}]}{[\text{guest}] + [\text{complex}]} \qquad (2)$$

From molecular modelling studies,[8] the orientation of Naproxen (1) included within β-cyclodextrin has been proposed. The guest was found to include lengthwise in the cavity, as is typical of 2-substituted naphthalene complexes,[18] with the carboxylate group adjacent to the secondary hydroxy groups of the host (Fig. 3*a*). To determine the alignment of Naproxen (1) in the annulus of the amine (3), a two-dimensional rotating frame ^{1}H–^{1}H nuclear Overhauser effect (2D-ROESY) experiment was conducted on a 1:8 mixture of Naproxen (1) and the amine (3). The resulting spectrum is

shown in Fig. 4. Resonances at *c.* δ 3·7, 3·8 and 3·9 can be assigned to the $C6^{B-G}$, $C5^{A-G}$ and $C3^{A-G}$ protons of the host (3), respectively.[19] The 2D-ROESY experiment shows through-space interactions between H5 of Naproxen (1) (*c.* δ 7·2) and H3 of the host (3), and between H5 and H6 of the host (3) and H1 of the guest (1) (*c.* δ 7·65). These interactions show that the orientation of the guest (1) is such that its carboxylate group is adjacent to the primary hydroxy groups and the protonated amino substituent of the cyclodextrin (3) (Fig. 3*b*), an orientation which is the reverse of that indicated by the molecular modelling studies[8] for the same guest complexed in β-cyclodextrin (Fig. 3*a*).

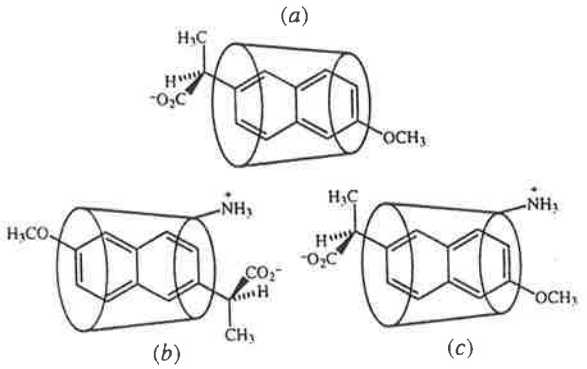

Fig. 3. Complexes of Naproxen (1) in β-cyclodextrin and 6^A-amino-6^A-deoxy-β-cyclodextrin (3).

It appears that the protonated amino substituent alters the orientation of Naproxen (1) in the annuli of β-cyclodextrin and the amine (3), as a result of the ionic interaction between the guest and the modified host (3). This does not lead to an increase in the thermodynamic stability of the inclusion complex, however, indicating that other factors offset the ionic interaction. The extent of desolvation of the host and guest on inclusion complex formation is an important component of the free energy change accompanying complexation.[20,21] It seems likely that this is greater for complexation by β-cyclodextrin than by the amine (3), with the result that the complex of Naproxen (1) with the amine (3) having the orientation shown in Fig. 3*c* is less stable than the analogous complex with β-cyclodextrin (Fig. 3*a*). The reverse orientation of Naproxen in the amine (3) (Fig. 3*b*) is therefore preferred, where ionic host–guest interactions stabilize the complex.

Experimental

α-Cyclodextrin and β-cyclodextrin were the generous gifts of Nihon Shokuhin Kako Co. 6^A-Amino-6^A-deoxy-β-cyclodextrin

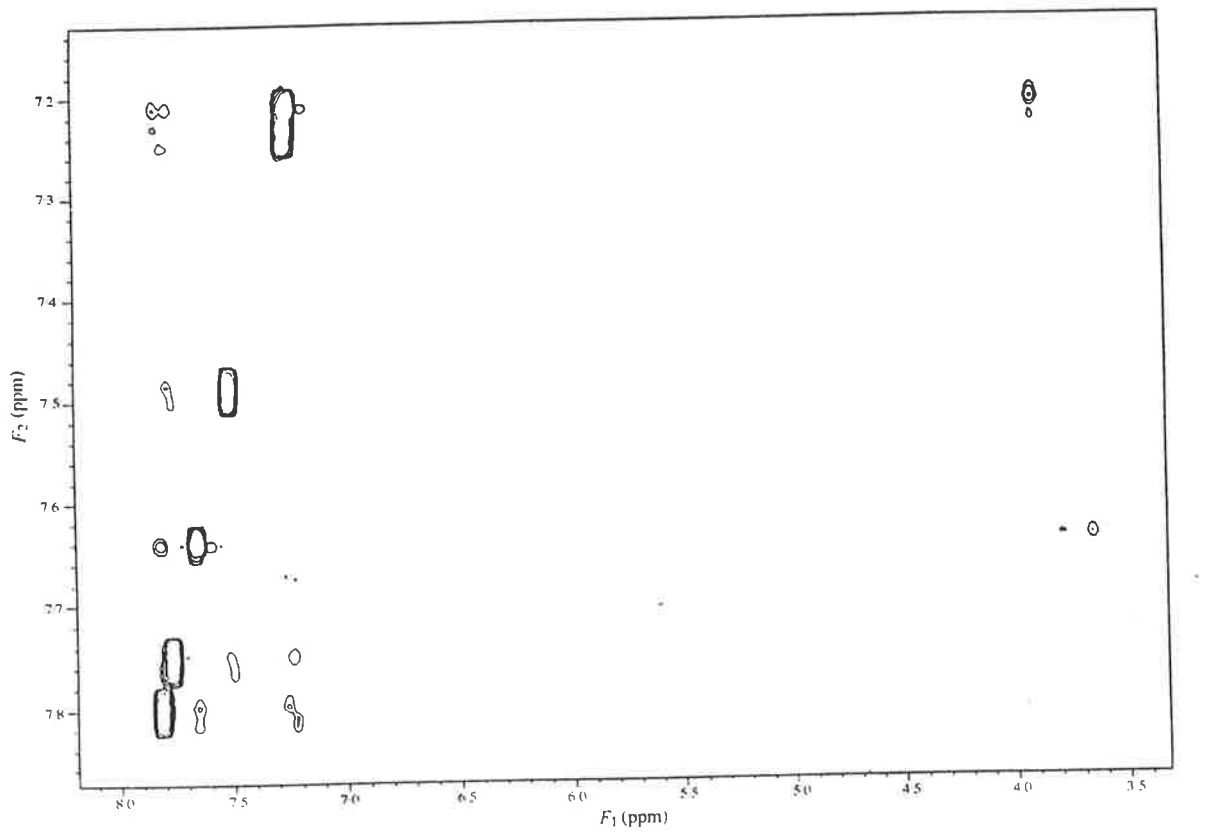

Fig. 4. 2D-ROESY experiment on a solution of Naproxen (1) ($1{\cdot}00\times10^{-3}$ mol dm^{-3}) and 6^A-amino-6^A-deoxy-β-cyclodextrin (3) ($8{\cdot}00\times10^{-3}$ mol dm^{-3}) at pD 6·80 in D_2O containing 0·10 mol dm^{-3} phosphate at 298·2 K.

(3) and 6^A-amino-6^A-deoxy-α-cyclodextrin were obtained as reported previously.[10] All cyclodextrins were dried to constant weight under vacuum over phosphorus pentoxide prior to use. Naproxen (1) and Ibuprofen (2) were purchased from Aldrich Chemical Company Inc.

For all pD measurements, BDH Standard Buffer reference solutions at pH 4·00, 7·00 and 10·00 were used with an Orion 520A pH meter and a Ross 81-56 pH electrode.

^{1}H n.m.r. spectroscopy was carried out on a Gemini BB spectrometer for the one-dimensional experiments and on a 500 Unity INOVA spectrometer for the two-dimensional experiment.

Preparation of 0·10 mol dm^{-3} pD 6·80 Phosphate Buffer

Sodium hydroxide (0·100 g, $2{\cdot}50\times10^{-3}$ mol) was dissolved in D_2O, and the volume was made up to 25·0 cm^3 with D_2O. To 11·2 cm^3 of this solution was added potassium dihydrogen phosphate (0·340 g, $2{\cdot}50\times10^{-3}$ mol), and the volume was made up to 50·0 cm^3 with D_2O. The pD was checked and found to be as required.

Preparation of Naproxen (1) and Ibuprofen (2) Stock Solutions

Naproxen (1) ($11{\cdot}5\times10^{-3}$ g, $5{\cdot}00\times10^{-5}$ mol) was dissolved in 0·10 mol dm^{-3} pD 6·80 phosphate buffer, and the volume was made up to 25·0 cm^3 with the buffer. Ibuprofen (2) ($10{\cdot}3\times10^{-3}$ g, $5{\cdot}00\times10^{-5}$ mol) was dissolved in 0·10 mol dm^{-3} pD 6·80 phosphate buffer, and the volume was made up to 25·0 cm^3 with the buffer.

Preparation of Solutions for N.M.R. Experiments

Aliquots of the Naproxen (1) solution (1·00 cm^3) were added to series of 2·00 cm^3 volumetric flasks containing weighed amounts of either α- or β-cyclodextrin, or 6^A-amino-6^A-deoxy-α-cyclodextrin or 6^A-amino-6^A-deoxy-β-cyclodextrin (3). The amount of the cyclodextrin was varied to give from 0 to 8 mol. equiv. of the host relative to the guest. The volume of each solution was made up to 2·00 cm^3 with 0·10 mol dm^{-3} pD 6·80 phosphate buffer. The ^{1}H n.m.r. spectrum of each solution was recorded. In the absence of any cyclodextrin host Naproxen (1) showed: δ 7·252, dd, J 2·5, 8·5 Hz, 1H, H7; 7·401, d, J 2·5 Hz, 1H, H5; 7·512, dd, J 1·5, 8·5 Hz, 1H, H3; 7·791, d, J 1·5 Hz, 1H, H1; 7·860, d, J 8·5 Hz, 1H, H4; 7·884, d, J 8·5 Hz, 1H, H8. The assignments are based on literature values.[22]

The experiments were repeated with Ibuprofen (2). In the absence of any cyclodextrin host Ibuprofen (2) showed: δ 7·143, d, J 8 Hz, 2H, H2,6; 7·200, d, J 8 Hz, 2H, H3,5.

In addition, the sample containing 8 mol. equiv. of the cyclodextrin (3) relative to the guest (1) was deoxygenated by repeatedly purging with nitrogen, and a 2D-ROESY experiment was performed.

Calculation of Complex Association Constants

The difference between the observed chemical shifts of the resonances of H3 and H5 of Naproxen (1) was plotted against the concentration of the host (Fig. 1) and curves were fitted to the data according to equations *(1)* and *(2)* by using MacCurvefit v1.2. This gave values for the association constants of the complexes of Naproxen (1) with β-cyclodextrin and the modified cyclodextrin (3) of 940±170 and 810±200 mol^{-1} dm^3, respectively. This was repeated for the difference between the observed chemical shifts of the resonances of H2,6 and H3,5 of Ibuprofen (2) (Fig. 2) to give association constants for the complexes with β-cyclodextrin and the modified cyclodextrin (3) of 8800±1800 and 8900±2100 mol^{-1} dm^3, respectively.

Acknowledgments

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Inclusion Complexes of the Cyclodextrins

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Contents

I. Introduction

Cyclodextrins (CDs) are naturally occurring homochiral cyclic oligosaccharides, composed of from 6 to 13 α-1,4-linked D-glucopyranose units. They are produced, together with some linear oligosaccharides, through the degradation of starch by the enzyme CD glycosyl transferase. Those composed of 6, 7, and 8 glucopyranose units are referred to as α-, β-, and γ-CD (Figure 1), respectively, and are the most plentifully produced and extensively studied [1-7]. They possess annular structures whose wide and narrow hydrophilic ends are delineated by O(2)H and O(3)H secondary and O(6)H primary hydroxy groups, respectively, while their hydrophobic annular interiors are lined with methine and methylene groups and ether oxygens. Crystallographic X-ray studies show that each glucose unit possesses a rigid $^4C_1$ chair conformation. Usually the C(6)-O(6) bonds are directed away from the center of the CD annulus, such that the torsion angle O(5)-C(5)-C(6)-O(6) is (-)-*gauche*, although hydrogen bonding between a guest molecule in the annulus and the O(6)H group may turn the C(6)-O(6) bonds towards the center of the annulus, such that the torsion angle O(5)-C(5)-C(6)-O(6) becomes (+)-*gauche* [2,3,8]. Neutron diffraction studies show that the CD structure is stabilized in the solid state by intramolecular hydrogen bonding between the secondary hydroxy groups of adjacent glucose units [9]. The size of the CD annulus increases with the number of linked glucopyranose units (Figure 1).

Figure 1 here

Interest in CDs stems from their ability to partially or completely include a wide range of guest species within their annuli to form inclusion complexes, also referred to as host-guest complexes [1-7]. The bonding between the CD and guest is solely secondary in nature, nevertheless the inclusion complexes can exhibit considerable thermodynamic stability. The homochirality and variation in size of the α-, β- and γ-CD annuli provide opportunities for both chiral [7,10] and size [1-6] discrimination in this inclusion process, as indicated by differences in complex stability as the identity of either the guest or the CD is varied. Quite a wide range of neutral and ionic species, exemplified by inorganic anions [11-13], various cations [14], noble

gases [15], aliphatic species [16,17] and fullerenes [18-20] are included, but the most stable inclusion complexes are usually formed with guests possessing some aromatic character. Generally, in the absence of steric hindrance, hydrophobic guests bind more strongly than hydrophilic ones [6].

In the absence of other guests, CDs are obtained in the hydrated state and βCD may contain as many as 12 water molecules in its crystal structure, but the average is 6.5 [21,22]. The extent to which expulsion of either some or all water molecules from the annulus by a guest species represents a significant component of the free energy change accompanying the formation of an inclusion complex has been the subject of debate [23-25]. The ΔH^o and ΔS^o of formation of a very large number of CD inclusion complexes have been determined and vary over a wide range. It is found that for a given CD a plot of ΔH^o against ΔS^o is linear for all guests so far studied and the slope of this plot is a temperature, referred to as the 'compensating' or 'isoequilibrium' temperature [5]. When $T\Delta S^o$ is plotted against ΔH^o for the formation of 191 α-, β-, and γ-CD inclusion complexes with a wide range of different guest molecules, a linear relationship, with a correlation coefficient of 0.88, a slope (α) = 0.90, and an intercept $T\Delta S_0^o$ = 3.1, is obtained [24]. In broad terms this linear relationship (equation (2)) indicates that the dominant factors stabilizing all of these inclusion complexes are the same and that a change in $T\Delta S^o$ is compensated for by a change in ΔH^o as indicated by equation (3). Equation (2) shows that the overall entropy change is made up of a term ($T\Delta S^o$) proportional to the enthalpy change and a term independent of it ($T\Delta S_0^o$). Equation (5) follows from equations (3) and (4) and shows that α represents the entropic contribution decreasing the enthalpic stabilization of the inclusion complex such that only a (1 - α) portion of $\Delta(\Delta H^o)$ contributes to increasing the inclusion complex stability. It appears that α and $T\Delta S_0^o$ arise from conformational change and the extent of desolvation occurring on inclusion complex formation, respectively, which are the dominant effects determining stability. An α value close to unity (0.90) indicates substantial conformational change which may arise from reorganization of the extensive hydrogen bonding in CDs on complex formation, and $T\Delta S_0^o$ = 3.1 is consistent with the occurrence of substantial desolvation.

$$\Delta G^o = \Delta H^o - T\Delta S^o \qquad (1)$$

$$T\Delta S^{o} = \alpha\Delta H^{o} + T\Delta S_{o}^{o} \quad (2)$$

$$T\Delta(\Delta S^{o}) = \alpha\Delta(\Delta H^{o}) \quad (3)$$

$$\Delta(\Delta G^{o}) = \Delta(\Delta H^{o}) - T\Delta(\Delta S^{o}) \quad (4)$$

$$\Delta(\Delta G^{o}) = (1 - \alpha)\Delta(\Delta H^{o}) \quad (5)$$

Alternatively, it has been proposed for the formation of αCD inclusion complexes that the $\Delta H^{o}/\Delta S^{o}$ linear relationship may be explained solely in terms of polar interactions between the CD and the guest, to provide the driving force for complexation, which results in conformational changes in the CD and the entropy change accompanying complexation, and desolvation of αCD or the guest does not occur [23]. The latter part of this proposal seems untenable as X-ray crystallographic [26-28] and NMR solution [25,29-31] studies of CD inclusion complexes show guests penetrating into the CD annulus, which requires some desolvation of both the CD and the guest.

The inclusion chemistry of CDs has been extensively exploited in diverse areas, including chromatography [32,33], asymmetric synthesis [34], capillary electrophoresis [7] and other areas of analytical chemistry [6]. Work in each of these fields began with the natural CDs but more recent developments have involved modified forms, prepared through a wide range of substitutions of one or more of either the primary or secondary CD hydroxy groups. Often the CD derivatives have been tailored to have specifically altered complexation characteristics and three design strategies to achieve this goal are discussed below. These approaches are indicative of current trends in CD research and they involve:

i) CDs substituted through the introduction of functional groups, in order to affect complex stability, provide additional sites for molecular recognition and to produce enzyme mimics,

ii) dimeric and linked CDs, where the additional binding site affects complexation, and

iii) metalloCDs, where coordination to the metal center affects thermodynamic discrimination of guest binding and reactions of bound species.

Within the space available it is not possible to review the literature exhaustively, but it is hoped that by combining the citation of studies largely arising in the last decade with some of the seminal earlier literature we have achieved a reasonable coverage of this exciting area of

chemistry and have provided a basis for readers to probe more deeply into specific areas of interest.

II. Modified Cyclodextrins

The naturally occurring CDs display enantioselectivity in the formation of inclusion complexes with racemic hosts [10]. This area continues to attract attention as improved techniques are employed to quantify the enantioselectivity and characterize the diastereomeric complexes. The thermodynamic discrimination displayed by α-, β- and γ-CD in aqueous solution is quite modest [35,36] but marked spectroscopic discrimination has been observed. Substantial differences between diastereomeric complexes have also been observed in the solid state [26]. X-ray crystallographic determination of the structures of the complexes of (*R*)- and (*S*)-Fenoprofen with βCD has shown that in each case βCD is present as a head-to-head dimer, as a result of extensive intermolecular hydrogen bonding between secondary hydroxyl groups, with one molecule of Fenoprofen present in each CD annulus. The (*R*)-Fenoprofen guests adopt an antiparallel arrangement in the CD dimer, whereas the (*S*)-enantiomers are arranged in parallel.

With α-, β- and γ-CD there is often little interaction between chiral centers of the CDs and those of the guests. The stereoselectivity of guest complexation is often greater with modified CDs where, through the modification, the degree of asymmetry of the CD may be increased and there are additional interactions between chiral centers of the CDs and those of the guests [37]. The formation constants of the complexes of (*R*)- and (*S*)-2-phenylpropanoate anion with βCD, K_{11} = 63 and 52 $dm^3\ mol^{-1}$, respectively, while those of the analogous complexes of protonated 6^A-amino-6^A-deoxy-βCD and 3^A-amino-3^A-deoxy-(2^AS,3^AS)-βCD are 36 and 13, and 51 and 32 $dm^3\ mol^{-1}$ [38,39]. (In this chapter K_{11} is the formation constant for a 1:1 mole ratio CD:guest complex and K_{21} and K_{12} are the step-wise formation constants for $(CD)_2$:guest and CD:$(guest)_2$ complexes, respectively.) This indicates that unfavorable interactions between substituents of the modified hosts and the racemic guests destabilize the complexes and lead to greater enantioselectivity. Enhanced spectroscopic discrimination with modified CDs has also been reported [40,41]. NMR studies and complementary molecular modelling calculations of the enantioselective complexation of (*R*)- and (*S*)-atenolol with

perphenylcarbamate βCD show that the aromatic moiety of the (*S*)-enantiomer is included within the CD annulus, with the chiral center outside the toroidal cavity, while the opposite is the case with the (*R*)-isomer (Figure 2) [41].

Figure 2 here

An alternative approach to designing modified CDs in order to enhance enantioselectivity is to introduce chiral substituents. Takahashi *et al.* [42,43] prepared the diastereomeric C(6)-phenylalanine substituted βCDs **1** and **2** and examined their interaction, and that of βCD, with (*R*)- and (*S*)-*N*-dansylphenylalanine. The K_{11} for the complexes of βCD and the modified hosts **1** and **2** with the (*R*)- and (*S*)-isomers of the guest were found to be 197 and 153, 160 and 83, and 139 and 231 $dm^3\ mol^{-1}$, respectively. Clearly the enantioselectivity displayed by the modified CDs **1** and **2** is greater than that displayed by the parent. The chiral discrimination by the CDs **1** and **2** is approximately equal in magnitude, although reversed in terms of absolute stereochemistry. On this basis it appears that the annuli of the modified CDs **1** and **2** serve mainly to bind the guests and contribute little towards the enantioselectivity. Instead, stereoselectivity probably results from interactions between the chiral substituents of the modified CDs **1** and **2** and those of the guests. In the absence of other guests, the substituents of the modified CDs **1** and **2** are included within the CD annuli, from where they are displaced by the enantiomers of *N*-dansylphenylalanine. The enantiomers of *N*-formylphenylalanine do not induce this substituent movement, presumably because their interactions with the CD annuli are less favorable. In support of this hypothesis, K_{11} for the complexes of βCD with the (*R*)- and (*S*)-enantiomers of *N*-formylphenylalanine are 41 and 35 $dm^3\ mol^{-1}$, respectively, which are much less than those cited above for the complexation of *N*-dansylphenylalanine. The ease of displacement of a CD substituent also depends on the thermodynamic stability of the intramolecular or self-included complex. Borneol, menthol and 5-methoxypsoralen have been shown to replace the substituent of a tryptophanyl modified βCD but they do not affect the analogous tyrosinyl βCD, where the intramolecular complex is more stable [44].

Structures 1 and 2 here

Several other examples of guest-induced substituent displacement have been reported [45-48] and these offer particular advantages for molecular recognition and guest discrimination. 6^A-(4-(Dimethylamino)benzamido)-6^A-deoxy-substituted α-, β- and γ-CDs have been prepared and exploited as sensors of complex formation [45]. The fluorescence of the substituent included in the CD annulus decreases markedly on displacement outside to an aqueous environment, and thereby indicates inclusion of a guest through the equilibria shown in Figure 3. The 6^A-(4-(dimethylamino)-benzamido)-6^A-deoxy-β-cyclodextrin inclusion complexes are exemplified by those formed with cyclohexanol, cyclooctanol, cyclododecanol, 1-adamantanol, and 1-adamantanecarboxylic acid for which K_{11} = 2 x 10^3, 5 x 10^4, 2.8 x 10^4, 1.28 x 10^5, and 2.2 x 10^5 dm^3 mol^{-1} in water at 298.2 K, which illustrate the effect of change in substrate size on complex stability, and by K_{11} = 1.0 x 10^4 and 1.8 x 10^4 dm^3 mol^{-1} for *d*- and *l*-menthol, respectively, which illustrate chiral discrimination. The extent of intramolecular complexation is dependent on the length of the link between the substituent and the CD [49], and the temperature. The latter effect is clearly shown with 3^A-*O*-(naphth-2-ylmethyl)-β-cyclodextrin (Figure 4) [50].

Figures 3 and 4 here

The change in fluorescence of substituents bound to CDs and of guests upon inclusion has been widely used to monitor inclusion processes as is evident from the examples referred to throughout this discussion. Observation of fluorescence may also be used to monitor energy transfer processes within CD inclusion complexes, as is illustrated by the particularly innovative example discussed below. The antennae chromophores of photosynthetic units absorb photons whose energy is then transferred to other components in the photosynthetic process. This process has been modelled using 6^{A-G}-heptanaphthoate-β-cyclodextrin (NAβCD) where naphthoate antennae are attached to βCD (Figure 5) as one component of an energy transfer system, and which is an example of a range of similarly modified βCDs [51-54]. When

NAβCD complexes the dye 4-(dicyanomethylene)-2-methyl-6-(*p*-(bis(hydroxyethyl)styryl-4*H*-pyran (DCM-OH) and the complex NAβCD·DCM-OH is irradiated at 300 nm, the NAβCD emission band (λ_{max} = 355) overlaps the absorption band of DCM-OH which in turn fluoresces in the range 550-750 nm. This energy transfer from NAβCD to DCM-OH has an efficiency close to unity. The high K_{11} of 1.2 x 10^5 dm^3 mol^{-1} for NAβCD·DCM-OH is attributed to the increased hydrophobicity of NAβCD over βCD arising from the naphthalene rings of the attached chromophores.

Figure 5 here

III. Natural and Modified Cyclodextrins in Catalysis

Another aspect of CD inclusion complexes which continues to be studied intensively is their use as models for covalent catalysis by enzymes [22,55-59]. For example, the hydrolysis of *m*-nitrophenyl acetate by αCD involves formation of a host-guest complex, then transesterification between host and guest, followed by hydrolysis of the acylated CD. More recent studies have shown that the mode and extent of complex formation depends on the nature of the ester and the CD, and should not be generalized or assumed [60-63]. The CDs exhibit enantioselectivity in their reactions with chiral esters [64-75]. In this area the highest enantioselectivity so far reported is that for the hydrolysis of the esters **3** and **4** by βCD, where a 62-fold difference between the rates of reaction of the included species was observed [72]. Force field based molecular modelling of the inclusion of these ferrocenylacrylate esters by βCD, the tetrahedral intermediate for the acylation of βCD, and the resulting acyl-βCD have provided considerable insight into the overall hydrolysis mechanism [76,77]. As with enzymes, stereoselectivity in the hydrolysis of esters by CDs may arise either from chiral discrimination in the formation of the CD-substrate inclusion complex, or in the reactions of the bound species, or from a combination of these processes. Generally, the greatest stereoselectivity occurs in the reactions of the bound species, however, as indicated in the reactions of the enantiomers of the phenylpropionate **5** with βCD, where the enantioselectivities of complexation (K_R/K_S) and reaction of the complexed species (k_R/k_S) are 1.2 and 15.5,

respectively [69]. If the chiral portion of the ester is transferred to the CD as part of the hydrolysis, there is also the possibility of stereoselectivity in the hydrolysis of the acylated CD. This is illustrated by the 10-fold diastereoselectivity in the hydrolysis of the ester **6** [74]. Since the ester is obtained as a 5:1 mixture of diastereomers, through reaction of the corresponding acid chloride with βCD, and reaction of the (*R*)-isomer of the carboxylate moiety is favored in both the acylation and deacylation of the CD, the overall stereoselectivity for the two step process is approximately 50:1 [75].

Structures 3-6 here

Reactions of the natural CDs as models for enzyme catalysis are limited because they can only involve the CD hydroxyl groups. This restriction has been overcome with modified CDs, through the introduction of a variety of reactive functional groups [22,78-87]. In some cases the substituent functions in a way analogous to that of an enzyme cofactor. A variety of pyridoxamine derivatives of CDs has been synthesized and studied as models of pyridoxal-phosphate dependent enzymes [79-82]. For example, Tabushi *et al.* [79,82] studied reactions of the disubstituted βCD derivative **7** (where the substitution is on the adjacent A and B glucopyranose units) with ketoacids, showing that reactions occurred smoothly in water under mild reaction conditions to give the (*S*)-enantiomers of phenylalanine, tryptophan and phenylglycine, each in at least 90% enantiomeric excess. FlavoCDs such as the βCD derivative **8** have also been synthesized and used for the catalytic oxidation of thiols [83].

Structures 7 and 8 here

Disubstituted CDs provide particular opportunities for catalysis [22,78,84,85,88]. The regioselective hydrolysis of 4-*tert*-butylcatechol cyclic phosphate **9** by the bisimidazole βCD **10a** occurs through a bifunctional catalytic mechanism in which one imidazole acts as a base, while the other is protonated and acts as an acid (Figure 6) [22,78,88]. Through studies of related reactions it has been shown that the efficiency of substrate binding and reaction, and the regioselectivity of ring opening, is dependent on the substrate and the CD. Bisimidazole CD

derivatives have also been used in the catalytic enolization of ketones. For example, the CD derivative **10a** increased the rate of isomerization of 4-*tert*-butylacetophenone, but the $6^A,6^D$-disubstituted host analogue **10b** was a more effective catalyst of this reaction [84]. Of the modified CDs **10a** and **10b**, the former exhibited greater regiocontrol in catalysing the aldol condensation of the dialdehyde **11**, however, showing a 97% preference for production of the cyclized product **12** over the regioisomer **13** [85]. The analogous reaction catalysed by imidazole buffer in the absence of a CD displayed little regioselectivity.

Structures 9-13 and Figure 6 here

The examples discussed above illustrate design aspects of the use of substituted CDs in catalysis, where modifications to the host can be tailored to meet specific requirements for guest binding and molecular recognition, and to introduce reactive groups for catalytic activity. Further examples are discussed in the following sections. Another option to develop more efficient catalytic systems is to use CDs to enhance the utility of enzymes. Thus, α- and β-CD have been shown to increase the efficiency of the conversion of (*S*)-phenylalanine to *trans*-cinnamate catalyzed by (*S*)-phenylalanine ammonia lyase [89]. In this system the CDs are thought to reduce product inhibition of the enzyme by selectively sequestering the cinnamate from solution. It has been reported that βCD enhances the rate and enantioselectivity of hydrolysis of arylpropionic esters by bovine serum albumin [90], although the origin of these effects is unclear. There are also reports of the use of βCD to alter the regiochemistry of nitrile oxide cycloaddition reactions [91-93], but these appear to be in error. Any effect in these systems is most likely due to product complexation by the CD, limiting extraction into the organic solvent during work-up of the reactions, rather than the CD affecting the ratio of formation of cycloadducts [94]. Another use of βCD with enzymes has been to complex detergents used to denature the proteins, to allow refolding [95].

IV. Dimerization of Cyclodextrins

While there is little evidence for the aggregation of natural CDs in water, dimerization may occur if a guest molecule is simultaneously included by two CDs, and modified CDs may

dimerize if they either possess substantial opposite charges or are substituted by groups which include in another CD (in this context a dimer refers to any combination of two cyclodextrins). The first effect is seen in the inclusion of *o*-, *p*- and α-fluoro-*trans*-cinnamate and *o*,*p*- and α,*p*-difluoro-*trans*-cinnamate by αCD where both 1:1 and 2:1 inclusion complexes form:

$$\alpha\text{CD} + \text{cinnamate} \overset{K_{11}}{\rightleftharpoons} \alpha\text{CD}\cdot\text{cinnamate} \qquad (6)$$

$$\alpha\text{CD} + \alpha\text{CD}\cdot\text{cinnamate} \overset{K_{21}}{\rightleftharpoons} (\alpha\text{CD})_2\cdot\text{cinnamate} \qquad (7)$$

as indicated by a biphasic variation of the ^{19}F NMR chemical shift of the cinnamate with increase in αCD concentration [96]. For *p*-fluoro-*trans*-cinnamate, K_{11} and K_{21} = 109 and 35 $dm^3\ mol^{-1}$, respectively, in aqueous 0.1 mol dm^{-3} NaCl at 294.0 K.

The formation of dimer complexes can be of importance in catalysis as observed in a study of *p*-nitrotrifluoroacetanilide (PNTA) and *p*-nitroacetanilide (PNA) in the presence of CDs [97]. Thus, while the hydrolysis of PNTA is accelerated by αCD and that of PNTA and PNA is accelerated by βCD, that of trifluoroacetanilide is slowed by βCD. Both βCD·PNTA and βCD·PNA and $(\beta\text{CD})_2$·PNTA and $(\beta\text{CD})_2$·PNA complexes are formed and both types of complex accelerate hydrolysis, but through different mechanisms. The first promotes acylation of βCD by the amide in βCD·PNTA and βCD·PNA (as is also the case for αCD in αCD·PNTA) and in the second, which predominates at pH 7, the combined effect of the two βCDs in $(\beta\text{CD})_2$·PNTA and $(\beta\text{CD})_2$·PNA stabilizes the transition state for water addition.

An interesting example of a modified CD forming a dimer through the inclusion of a guest is provided by heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DMβCD) which forms very stable 1:1 and 2:1 complexes with tetraaminoporphyrin and its Fe^{3+} heme analogue, as shown in Figure 7 [98]. These are analogues of heme containing proteins and exhibit some of their characteristics. When more than one potential guest is available not only does the possibility of forming two different complexes with a single CD host arise, but also the possibility of forming dimers including either two of the same guest or one of each arises. This is exemplified by the G_1-βCD·DMABN complex of 6^A-*O*-α-D-glucosyl-β-cyclodextrin (G_1-βCD) with 4-(dimethylamino)benzonitrile (DMABN) which exists in equilibrium with a homodimer of composition $(G_1\text{-}\beta\text{CD})_2\cdot(\text{DMABN})_2$ as shown by changes in the fluorescence of DMABN with

changes in solution composition. This homodimer is probably stabilized by interactions between the DMABN guests, and simultaneous interactions of each DMABN with both G_1-βCD annuli [99]. Addition of other guests such as benzene, anisole, and benzonitrile to solutions of the homodimer results in the formation of dimers of composition $(G_1\text{-}\beta CD)_2\cdot(DMABN)(benzene)$ and so on.

Figure 7 here

The effect of charge on CD dimerization is demonstrated by βCD when it is substituted at all seven C-6 sites by either $-NH_2$ ($\beta CD(NH_2)_7$) or $-SCH_2CO_2H$ ($\beta CD(SCH_2CO_2^-)_7(H^+)_7$). This results in 7 positively and 7 negatively charged species, respectively, at low and high pH, so that a solution of both modified βCDs contains a range of opposite and highly charged species at intermediate pH values [100]. The formation of at least five electrostatically bound heterodimers, $[\beta CD(NH_2)_7\cdot\beta CD(SCH_2CO_2^-)_7(H^+)_{14-n}]^{(7-n)+}$ where n ranges from 5 to 9, occurs in the equilibrium:

$$[\beta CD(NH_2)_7(H^+)_{14-i-n}]^{(14-i-n)+} + [\beta CD(SCH_2CO_2^-)_7(H^+)_i]^{(7-i)-} \overset{P_n}{\rightleftharpoons} [\beta CD(NH_2)_7\cdot\beta CD(SCH_2CO_2^-)_7(H^+)_{14-n}]^{(7-n)+} \quad (8)$$

where for the heterodimers the number of protons varies in integers (i) from 7 to 14 and the corresponding variation in charge ranges from 0 to 7, P_n is the phenomenological formation constant, and $\log P_n = 7.7$, 8.35, 10.25, 8.6, and 6.6 when n increases from 5 to 9.

Homodimers are formed between the photochemically generated radical cations of 6^A-deoxy-6^A-(1'-hexyl-4,4'-bipyridin-1-yl)-β-cyclodextrin ($\beta CDC_nV^{\cdot+}$) and their heptyl and octyl analogues as shown in Figure 8 [101]. The homodimer formation results from the inclusion of the alkyl tails of adjacent $\beta CDC_nV^{\cdot+}$ which is disrupted by either βCD competing for inclusion of the tail or by an amphiphile such as *n*-octyl sulfate including in the $\beta CDC_nV^{\cdot+}$ annulus. The dimer formation constants in aqueous 0.1 mol dm^{-3} NaCl solutions at 298.2 K are 1.0×10^2, 4.0×10^4, 8.9×10^5, and 6.8×10^6 dm^3 mol^{-1}, when the alkyl tail is methyl, hexyl, heptyl, and octyl, respectively, and demonstrate the systematic variation of complex stability with tail length.

Figure 8 here

In the solid state the proximity of one CD to another is inevitably close, nevertheless it is interesting to note that X-ray crystallography shows that the tail of each 6^A-(6-aminohexyl)–amino-6^A-deoxy-β-cyclodextrin molecule enters the secondary end of the annulus of an adjacent CD molecule and protrudes from the primary end to form polymeric like columns [102]. Similarly head to tail arrangements of 6^A-azido-6^A-deoxy-α-cyclodextrin and of 2^A-allyl-2^A-deoxy-α-cyclodextrin form helical columns where the azido and allyl tails, respectively, enter the annuli of adjacent molecules [103].

V. Covalently Linked Cyclodextrin Dimers

The observation of the formation of CD dimers, as described in the preceeding section, and the expectation that the covalent linking of two CDs together should result in enhanced guest binding as a consequence of cooperativity between the CD moieties has resulted in the production of a wide range of linked cyclodextrins. Thus, disulfide [87,104-112], dithioether [87,104-106,108,109,112-117], diether [118], diamine [110,119], diester [104,107,110,112,120], diamide [115,121-124], imidazole [87,112], porphyrin [114,115] and urea [125,126] linked cyclodextrins have been synthesized and their complexing properties studied. This linking may occur by substituting either a primary hydroxy group on each CD, or a secondary hydroxy group on each CD, or a primary hydroxy group on one CD and a secondary hydroxy group on the other CD. In some cases two hydroxy groups are substituted on each CD or different combinations of α-, β- and γ-CD may be joined.

On a statistical basis the stability of the inclusion complex formed by a linked CD dimer with a given guest should be twice that of the analogous CD inclusion complex because two opportunities arise for complexation in the linked CD dimer. If the two CD moieties of the linked dimer simultaneously complex the guest this may increase the formation constant to a magnitude substantially greater than that expected from the statistical effect, under which cicumstances a cooperative effect is in operation. This is frequently observed, as is exemplified by the complexation of the fluorescent dye 6-(*p*-toluidinyl)naphthalene-2-sulfonate (TNS^-) (**14**)

by the βCD dimers **15**, **16a-d**, and **17a,b**. While TNS^- fluoresces weakly in water, it fluoresces strongly when included in the hydrophobic cavity of a cyclodextrin, and the complex formation constants were determined from this change in fluorescence. In aqueous 0.10 mol dm^{-3} phosphate buffer at pH 7.0 and 298.2 K K_{11} for the complexes formed with **15** and **16a-d** are 4.5 x 10^4, 3.3 x 10^4, 1.1 x 10^4, 1.7 x 10^4, and 1.3 x 10^4 dm^3 mol^{-1}, respectively [127], and with **17a** and **17b** are 1.05 x 10^4 and 6.7 x 10^3 dm^3 mol^{-1}, respectively [121]. In this series stability generally increases as the linker length decreases, consistent with optimization of the hydrophobic interaction between both TNS^- aromatic moieties and the two βCD annuli. (The drop in the stability of the **16b**·TNS^- complex may indicate a secondary effect of geometric constraint on stability, however, the similar stabilities of **16b**·TNS^- and **17a**·TNS^- show that the change in βCD orientation in these complexes has little effect on stability.) The inclusion of TNS^- by βCD has been much investigated and under the conditions of the above studies may be fitted to a model where βCD.TNS^- (K_{11} = 1.85 x 10^3 dm^3 mol^{-1}) alone forms or a model where both βCD.TNS^- and $(\beta CD)_2$.TNS^- are formed (K_{11} = 3.14 x 10^3 dm^3 mol^{-1} and K_{21} = 86 dm^3 mol^{-1}) [127]. It is seen from comparison with these data that there is substantial cooperativity in the complexation of TNS^- by **15**, **16a-d**, and **17a,b**, and that the lengthening of the linker in **17b** substantially decreases the cooperativity. (It is possible that some of the decrease in stability of the **17b** complex is because the linker itself partially includes, as has been reported to be the case for an analogue of **17b** in which one of the βCD moieties is replaced by an αCD [122], and competes with TNS^- for inclusion.) Similar cooperativities are found for the inclusion of methyl orange and tropaeolin by **15**, **16a**, and **16c** [128]. A variation on **16a** in which one of the βCDs is replaced by αCD shows cooperative and site-specific binding of isoamyl *p*-dimethylaminobenzoate, where the isoamyl group includes in the βCD annulus and the *p*-dimethylaminobenzoate moiety partially includes in the αCD annulus [123].

Structures 14-17 here

A series of 1:1 complexes of 6-(4-*t*-butylanilino)-naphthalene-2-sulfonate (BNS^-) (which has the same structure as TNS^- except that the methyl group is replaced by a *t*-butyl

group) with the βCD dimers **18a-f**, linked by substitution of a primary hydroxy group by a sulfur of -S$(CH_2)_n$S-, shows a smooth decrease in stability as the linker lengthens from n = 2 to n = 6, such that K_{11} decreases from 8.2 x 10^6 to 1.5 x 10^4 dm^3 mol^{-1} [109]. However, when n = 0, K_{11} drops to 7.9 x 10^3 dm^3 mol^{-1} because of a destabilizing decrease in the geometric match of the hydrophobic areas of the host and guest. When the nature of the aromatic guest is varied K_{11} for the inclusion complexes formed with **18a** varies over a range < 3 x 10^3 - 10^8 dm^3 mol^{-1} in water at 298.2 K [107]. Under the same conditions, the hydrophobic nature of cholesterol causes it to form a strong complex with **18a**, for which K_{11} = 5.54 x 10^6 dm^3 mol^{-1}, although it contains no aromatic moiety [129].

When the size of the CD is varied substantial changes in the stability and stoichiometry of the inclusion complexes are found. Thus, **18a** respectively binds methyl orange and ethyl orange 196 and 224 times more strongly in 1:1 complexes than when both annuli are αCDs [110]. Both linked CDs bind these dyes much more strongly than α- and β-CD and neither detectably bind two dye molecules simultaneously. In contrast, when both annuli are γCDs the larger annular size results in the dominant complex having two dye molecules included, with β_{12} ($K_{11}.K_{12}$) = 1.06 x 10^{11} and 3.60 x 10^{10} dm^6 mol^{-2} for methyl orange and ethyl orange, respectively, at pH 10.6 and 298.2 K [111]. These values compare with 6.67 x 10^6 and 4.36 x 10^7 dm^6 mol^{-2} for the analogous γCD.$(dye)_2$ complexes in which two dye molecules are included. A head-to-tail isomer of **18a** where the βCDs are linked one through C(3) and the other through C(6) has been prepared [130] but no studies of the effect of this linkage variation on complexation have been reported.

The geometric aspects of formation of inclusion complexes have been cleverly studied through the double linking of βCD in an occlusive or 'clamshell' structure **19** and an aversive or 'loveseat' structure **20** [87,108]. The occlusive isomer can close on a ditopic guest like a clamshell, leading to strong complexation, while in the aversive isomer the two βCD annuli are directed away from each other and show no cooperative binding of ditopic guests. Thus, in water at 298.2 K BNS^- binding by **20** is characterized by K_{11} = 2 x 10^5 dm^3 mol^{-1} which is only slightly greater than that for binding by βCD, while K_{11} = 4 x 10^6 dm^3 mol^{-1} for binding by **19** as a result of cooperative binding. Ditopic guests of more appropriate lengths are bound

much more strongly by **19** as illustrated by $K_{11} = 4 \times 10^8$ and 10^{10} dm^3 mol^{-1}, respectively, for the binding of **21** and **22**.

Structures 18-22 here

Table 1. Inclusion complex association constants and thermodynamic parameters for guest binding to βCD and linked βCDs in aqueous 0.020 mol dm^{-3} HEPES buffer solution at 298.2 K.

host	guest	K_{11}[a] or K_{12}[b] dm^3 mol^{-1}	ΔG^o kJ mol^{-1}	ΔH^o kJ mol^{-1}	$T\Delta S^o$ kJ mol^{-1}
βCD[a]	**23**	3.95×10^4	-26.2	-21.8	4.44
βCD[a]	**24**	2.26×10^5	-30.5	-29.3	1.26
βCD[b]	**24**	4.39×10^3	-20.8	-16.1	4.73
18a[a]	**24**	1.79×10^7	-41.4	-67.6	-26.2
25[a]	**24**	1.13×10^7	-38.7	-60.5	-20.2
26[a]	**24**	2.14×10^6	-36.1	-62.3	-26.2
βCD[a]	BNS$^-$	5.57×10^4	-27.1	-25.3	1.76
18a[a]	BNS$^-$	3.67×10^6	-37.4	-65.5	-28.1
βCD[a]	**21**	8.05×10^4	-28.0	-18.5	9.50
βCD[b]	**21**	2.34×10^3	-19.2	-16.2	3.01
25[a]	**21**	3.50×10^7	-43.1	-89.5	-46.48

[a]Binding of first guest. [b]Binding of second guest.

A calorimetric study shows that the inclusion of the guests BNS$^-$, **21**, **23**, and **24** by βCD is dominantly enthalpy driven and the cooperativity between the two linked βCD moieties in **18a**, **25**, and **26** in complexing BNS$^-$, **21**, and **24** is due to a much greater ΔH^o than observed for the complexing of these guests by βCD (Table 1) [105]. This contrasts with the observation that hydrophobic interactions [131] and the formation of chelated metal complexes tend to be entropy driven [132]. A linear relationship exists between $T\Delta S^o$ and ΔH^o from

Table 1, consistent with an enthalpy/entropy compensation which probably arises largely through solvation changes accompanying complexation [105]. The decreases in heat capacity, ΔC_p^o, resulting from the complexation of **23** by βCD and **24** by **18a** are -400 and -657 J mol^{-1} K^{-1}, respectively, and typify hydrophobic binding interactions [131,133,134].

Structures 23-26 here

The bipyridyl moiety in the linker of **25** readily chelates metal ions, thereby providing an opportunity for a metal bound hydroxide group to make a nucleophilic attack on a guest [86,87,135,136]. Thus, while the hydrolysis of the esters **27** and **28** is characterized in each case by an uncatalyzed rate constant k_{uncat} (310.2 K) = 3 x 10^{-8} s^{-1} at pH 7.0, the Cu^{2+} metallocyclodextrin formed by **25** catalyzes the hydrolysis of these esters by several orders of magnitude under the same conditions, as shown by the respective rate constants, k_{cat} (310.2 K) = 5.5 x 10^{-4} and 6.8 x 10^{-3} s^{-1} [113]. The catalysis proceeds through a nucleophilic attack by a coordinated hydroxide (the pK_a of its conjugate acid coordinated water is 7.15) on the carbonyl carbon as shown schematically in Figure 9. With an excess concentration of the ester **28** at least 50 turnovers were observed for the hydrolysis. The linked CD **25** is also the basis for an impressive catalyst for cleavage of the phosphate esters **29a** and **29b** in the presence of La^{3+} and H_2O_2 [86,137]. The cleavage of **29a** to produce one mole of phosphate and two of *p*-nitrophenol is considered to proceed through an intermediate similar to that shown in Figure 10, and a similar mechanism is proposed for the production of one mole of methyl phosphate and two of *p*-nitrophenol from **29b**.

Structures 27-29 and Figures 9 and 10 here

Linked CDs offer the opportunity to tailor both the separation of the two CDs and the position of a catalytic group on the link to produce selectivity in catalyzing reaction of a guest. This has been explored in the catalysis of the hydrolysis of the *p*-nitrophenyl alkanoates (**30a-d**) by the linked βCD **31** where the histidine moiety is the catalytic group [138]. The catalysis follows Michaelis-Menten kinetics and shows a substantial dependence on the alkyl chain length

as seen from Table 2. The positioning of the guests **30a-d** within the complex has a major influence on the magnitudes of k_{cat} and K_M, and the ratio k_{cat}/k_{uncat}. While, in terms of the ratio k_{cat}/k_{uncat}, **31** is not as effective a catalyst as **32**, it does show a greater catalytic discrimination between guests.

Table 2. Parameters for hydrolysis of the *p*-nitrophenyl alkanoates **30a-d** by **31** and **32** in aqueous phosphate buffer at pH 7.8 and 298.2 K

cyclodextrin	substrate	k_{cat} x 10^{-6} s^{-1}	K_M x 10^{-6} $dm^3\ mol^{-1}$	k_{cat}/K_M $dm^3\ mol^{-1}\ s^{-1}$	k_{cat}/k_{uncat}
31	**30a**	2690	3700	0.726	134
31	**30b**	2830	3170	0.893	191
31	**30c**	191	6.73	28.4	10.7
31	**30d**	86.2	12.5	6.90	12.2
32	**30a**	4700	6730	0.698	234
32	**30b**	4220	5080	0.830	285
32	**30c**	1630	1970	0.827	91.9

Structures 30-32 here

The porphyrins have attracted attention either as guest species in linked CD dimer inclusion complexes, or as the linker itself, substantially because of an interest in better understanding the role of the porphyrin moiety in photosynthesis and in heme proteins. The inclusion of the porphyrins **33a** and **33b** by βCD is characterized by K_{11} = 1.4 x 10^3 and 1.7 x 10^3 $dm^3\ mol^{-1}$ at pH 7.0 and 298.2 K. For complexation by the linked CD **17a** the corresponding K_{11} = 8 x 10^5 and 1.9 x 10^6 $dm^3\ mol^{-1}$, for **17b** K_{11} = 4 x 10^5 and 9 x 10^5 $dm^3\ mol^{-1}$, and for **33b** with **34** K_{11} > 5 x 10^7 $dm^3\ mol^{-1}$, which demonstrates strong cooperativity between the two βCD moieties in the linked CDs [139]. The complex formed between **17a** and **33a** has a *syn* stereochemistry where the two βCD annuli include adjacent

aromatic groups while the complex formed between **17b** and **33a** exists both as the *syn* isomer and the *anti* isomer where the two βCD annuli include alternate aromatic groups. The complex formed between the more rigid **34** and **33a** appears to exist only as the *syn* isomer, however, complexes in which two molecules of **34** simultaneously complex a single **33a** and two molecules of **34** complex two molecules of **33a** are also formed. Metalloporphyrins are able to coordinate to metal binding sites in the linker as demonstrated by the inclusion of the porphyrin **35a** and the metalloporphyrins **35b-d** by the linked βCD dimer **36** [117]. Thus, K_{11} = 2.5 x 10^4, 3.4 x 10^6, 7.6 x 10^6, and 1.7 x 10^8 dm^3 mol^{-1} for the complexation of **35a-d**, respectively, by the linked βCD dimer **36** at 298.2 K and pH 7.0, and the increased binding of the metalloporphyrins is attributed to coordination of the pyridine nitrogen of the host by the metal center. This is supported by the observation that the closely related linked βCD dimer **37**, which lacks a nitrogen in the linker, shows no enhanced binding of the metalloporphyrins as indicated by K_{11} = 1.7 x 10^4, 1.9 x 10^4, 1.0 x 10^4, and 1.3 x 10^4 dm^3 mol^{-1}, respectively, for the complexation of **35a-d**. A range of other metal complexes are included by **36** and **37** as are dyes [116]. A novel extension of linked cyclodextrin chemistry is the βCD tetramer **38** where each βCD linkage occurs at C(3) [140]. Both tetraarylporphyrins and metalloporphyrins are bound in 1:1 complexes with K_{11} values up to 10^8 dm^3 mol^{-1}, but the number of porphyrin aryl substituents simultaneously bound in the complex is unclear.

Structures 33-38 here

The porphyrin-linked βCD dimer **39** forms inclusion complexes with the guests **40-42** (Figure 11) with K_{11} = 7.4 x 10^3, 2.2 x 10^4, and > 5.x 10^5 dm^3 mol^{-1}, respectively, at pH 9.0 and 296.2 K. The rate of electron transfer from the porphyrin linker to the guests **40-42**, k_{et} = 2 x 10^9, 10^9, and 10^9 s^{-1}, respectively, as measured from the quenching of the porphyrin fluorescence in the presence of the guests **40-42** [114]. Other porphyrin-linked βCD dimers which show potential for similar electron transfer studies have also been reported [115].

Structures 39-42 in Figure 11 here

A logical extension of linked CD dimers is to increase the number of linkages to produce polymers but this has not been as extensively studied as have the linked CD dimers. Such polymers are exemplified by polyacryloyl-βCD and poly-*N*-acryloyl-6-aminocaproyl-βCD where the βCD moieties are attached to the polymer by single linkers [141-143]. The acryloyl polymer catalyses the hydrolysis of *p*-nitrophenyl acetate and *p*-nitrophenyl *p*-nitrobenzoate through a mechanism which appears to involve cooperative binding of these molecules by adjacent βCDs attached to the polymer. The same polymer also binds TNS^- (**14**) through simultaneous inclusion by adjacent βCDs. The reaction of βCD with epichlorohydrin produces a polymer where βCDs are linked through their C(6) sites and are part of the polymer backbone [144]. These polymers bind pyrene more strongly than does βCD, through cooperative binding by adjacent βCDs in the polymer chain. This stronger binding by epichlorohydrin-generated polymers of α-, β-, and γ-CD, by comparison with that of the parent CDs, has been found for several guest molecules and is mainly attributed to cooperative binding of the guests by adjacent CD moieties in the polymer [145,146].

Another interesting extension of the linking of CDs is the linking of other strong binding groups to CDs as exemplified by the linking of calix[4]arenes through different linkers to the C(6) and C(2) sites of βCDs [147] and modified βCDs [148], and mono and bis linking of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane through one and two C(6) sites of βCD, respectively [149,150]. This approach is used extensively in the metallocyclodextrin chemistry discussed in the next section.

VI. Metallocyclodextrins

Natural cyclodextrins may bind metal ions to form metallocyclodextrins but this complexation is generally weak and involves the formation of hydroxy species in alkaline solution [151-153]. The majority of metallocyclodextrin studies concern the coordination of a metal ion by a functionalized cyclodextrin to produce a binary metallocyclodextrin. Subsequently, a guest may both include in the cyclodextrin annulus and coordinate the metal center to give a ternary

metallocyclodextrin as shown in Figure 12. This presents an opportunity to study the effects of metal center and cyclodextrin interactions on metallocyclodextrin stability and guest binding as is exemplified by the binary metallo-6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrins ($[M(\beta CDpn)]^{2+}$) and metallo-6^A-(2-(bis(2-aminoethyl)amino)ethylamino)-6^A-deoxy-β-cyclodextrins ($[M(\beta CDtren)]^{2+}$) and their complexation of tryptophan anion (Trp^-) to form the ternary metallocyclodextrins ($[M(\beta CDpn)Trp]^+$ and $[M(\beta CDtren)Trp]^+$) [154-156]. The substitution of a βCD primary hydroxyl group by $-NH(CH_2)_3NH_2$, and $-NH(CH_2)_2N((CH_2)_2NH_2)_2$ results in strong M^{2+} binding in the binary cyclodextrins (Table 3) which, nevertheless, is not as strong as that in $[M(pn)]^{2+}$ and $[M(tren)]^{2+}$ where pn is 1,3-diaminopropane and tren is tris(2-aminoethyl)amine [157]. This probably reflects a difference in the electron donating powers of the secondary amine groups in βCDpn and βCDtren and primary amine groups in pn and tren, and the greater steric hindrance to M^{2+} binding caused by βCDpn and βCDtren. The stabilities of $[M(\beta CDtren)]^{2+}$ are much greater than those of $[M(\beta CDpn)]^{2+}$ because of the tetradentate nature of βCDtren, and the stability variations for both binary metallocyclodextrins with the nature of M^{2+} arise through a combination of M^{2+} size and ligand field variations.

Figure 12 and Table 3 here

The binding of (*R*)-Trp^- and (*S*)-Trp^- by $[Ni(\beta CDpn)]^{2+}$ exhibits a tenfold chiral discrimination in favor of $[Ni(\beta CDpn)(S)\text{-}Trp]^+$ over $[Ni(\beta CDpn)(R)\text{-}Trp]^+$ while the Co^{2+} and Cu^{2+} analogues show lesser discrimination, and the Zn^{2+} analogue shows none [154,155]. This influence of M^{2+} on chiral discrimination coincides with the variation in the ionic radii of six-coordinate Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}, which are 0.745, 0.69, 0.73 and 0.74 Å, respectively, and the geometric constraints arising from ligand field effects in Co^{2+}, Ni^{2+} and Cu^{2+}. It is particularly interesting that $[Zn(\beta CDpn)(R)\text{-}Trp]^+$ and $[Zn(\beta CDpn)(S)\text{-}Trp]^+$ are of the same stability, while the analogous diastereomeric complexes for the other three metal ions differ in stability. This suggests that the absence of ligand field generated stereochemical constraints on d^{10} Zn^{2+} allows more flexibility in the structures of $[Zn(\beta CDpn)(R)\text{-}Trp]^+$ and $[Zn(\beta CDpn)(S)\text{-}Trp]^+$ and as a result enantioselectivity is negligible. In contrast, the d^9

electronic configuration for similar sized Cu^{2+} imposes a tetragonally distorted octahedral stereochemistry which may place greater constraints on the interaction of the chiral centres of (*R*)-Trp$^-$ and (*S*)-Trp$^-$ with the βCDpn moiety and decrease the stability of [Cu(βCDpn)(*R*)-Trp]$^+$ by comparison with that of [Cu(βCDpn)(*S*)-Trp]$^+$. Similar arguments apply in the cases of d^7 Co^{2+} and d^8 Ni^{2+} whose six-coordinate geometries more closely approach regular octahedra. The greater enantioselectivity caused by Ni^{2+} may indicate that the size of the metal center is important, and that a difference of 0.04 Å can result in a substantial change in the degree of enantioselectivity. The crucial influence of M^{2+} in chiral discrimination in these systems is demonstrated by the lack of chiral discrimination in the βCDpn·(*S*)-Trp$^-$ and βCDpn·(*R*)-Trp$^-$ complexes. A similar variation in chiral discrimination is seen in the analogous phenylalanine anion metallocyclodextrins [158].

The major factors contributing to the stability of a ternary metallocyclodextrin appear to be: i) the hydrophobic interaction between the βCD annulus interior and the guest, ii) the coordination of the guest to the metal center, and iii) the interaction of the guest's chiral center with those of βCD. Significant thermodynamic chiral discrimination only occurs when the latter factor makes a significant and different contribution to the stabilities of diastereomeric ternary metallocyclodextrins. This is illustrated by the absence of chiral discrimination in [M(βCDtren)(*R*)-Trp]$^+$ and [M(βCDtren)(*S*)-Trp]$^+$ where factors i) and ii) appear to dominate despite a considerable increase in stability over that of [M(βCDpn)(*R*)-Trp]$^+$ and [M(βCDpn)(*S*)-Trp]$^+$. The effect of the degree of protonation of the guest is shown by [M(βCDtren)(*R*)-TrpH]$^{2+}$ where the monodentate tryptophan (TrpH) does not coordinate as strongly as bidentate Trp$^-$ in the more stable [M(βCDtren)(*R*)-Trp]$^+$. The [M(βCDpn)(*R*)-TrpH]$^{2+}$ species was not detected probably because it has a lower stability, reflecting the lesser stability of [M(βCDpn)]$^{2+}$ by comparison with that [M(βCDtren)]$^{2+}$ in which the tetradentate tren substituent binds M^{2+} much more strongly than does the bidentate pn substituent.

The stabilities of βCDtren·(*R*)-Trp$^-$ and βCDtren·(*S*)-Trp$^-$ are *ca.* 10^3 times greater than those for βCDpn·(*R*)-Trp$^-$ and βCDpn·(*S*)-Trp$^-$ which are *ca.* 10 times greater than those for βCD·(*R*)-Trp$^-$ and βCD·(*S*)-Trp$^-$ (Table 3). This variation is attributable to the interaction of the Trp$^-$ amino and carboxylate groups with the narrow end of the cyclodextrin annulus such that

Trp^- egress is hindered more than ingress with the substitution of a polyamine. The stabilities of [M(βCDtren)(*R*)-Trp]$^+$ and [M(βCDtren)(*S*)-Trp]$^+$ are greater than those of the analogous $MTrp^+$ and βCDtren·Trp^-, consistent with the coordination of Trp^- by M^{2+} and the interaction of Trp^- with the βCD annulus reinforcing each other to stabilize [M(βCDtren)(*R*)-Trp]$^+$ and [M(βCDtren)(*S*)-Trp]$^+$. However, while the stabilities of [M(βCDpn)(*R*)-Trp]$^+$ and [M(βCDpn)(*S*)-Trp]$^+$ are greater than those of βCDpn·Trp^-, indicating the stabilizing effect of coordination of Trp^- by M^{2+}, they more closely approach those of $MTrp^+$ which is consistent with significant competition between the Trp^- binding effects of the βCD annulus and M^{2+} in these ternary metallocyclodextrins [156].

The above systems illustrate aspects of two major areas in which metallocyclodextrins are presently the subject of study. The first is their use in chiral resolution, and the second, their use as catalysts and metalloenzyme mimics, arises from the close proximity of the metal center to a hydrophobic cavity capable of including a guest; a structural characteristic found in metalloenzymes.

Chiral discrimination is very dependent on the nature of the metal ion and the coordinating group as we have seen above. It is also critically dependent on the nature of the chiral guest. Some of these aspects are illustrated by the complexation of amino acids by 6^A-[2-(4-imidazolyl)ethylamino]-6^A-deoxy-β-cyclodextrincopper(II), [Cu(βCDhm)]$^{2+}$ [159], and its use as a chiral discriminating agent added to the mobile phase in HPLC studies [160,161]. Thus, the elution of the (*R*)-enantiomers of tyrosine, phenylalanine and tryptophan ahead of the (*S*)-enantiomers (the ratio of their elution rates, α = 1.10, 1.12, and 1.23, respectively) was attributed to the (*R*)-enantiomers forming more stable ternary metallocyclodextrins in which the aromatic moieties of the guest (*R*)-amino acid anions include in the βCD annulus (**43**), as is observed in the crystalline state [162], while such inclusion does not occur for the (*S*)-amino acid anions (**44**). The amino acid anions participate in a partitioning equilibrium between the mobile aqueous phase and the non-aqueous stationary phase, while the binary and ternary metallocyclodextrins are insoluble in the latter phase. The enantiomers which form the most stable ternary metallocyclodextrins spend less time in contact with the HPLC column and elute first. The enantiomers of the aliphatic amino acids alanine,

proline, and leucine were not separated by this HPLC method. This indicates the importance of the presence of an aromatic moiety in the guest in engendering enantioselectivity. Potentiometric titrations yield the $\log(\beta/dm^6\ mol^{-2})$ values shown in parentheses for the (*S*)- and (*R*)-amino acid anions, respectively: alanine (15.53 and 15.51), leucine (14.89 and 14.96), norvaline (14.80 and 14.87), phenylalanine (15.68 and 15.85), tyrosine (14.82 and 15.22), tryptophan (16.12 and 16.47), and histidine (16.78 and 16.70), where $\beta = [Cu(\beta CDhm)(guest)^+][Cu^{2+}]^{-1}[\beta CDhm]^{-1}[guest^-]^{-1}$ [161]. Thus, more substantial enantioselectivity for the (*R*)-enantiomer over the (*S*)-isomer occurs for the aromatic amino acid anions than for the aliphatic amino acid anions.

Structures 43-46 here

In contrast to $[Cu(\beta CDhm)]^{2+}$, 6^A-[4-(2-aminoethyl)imidazol-1-yl]-6^A-deoxy-β-cyclodextrincopper(II), $[Cu(\beta CDmh)]^{2+}$, causes (*S*)-Trp^- to elute before (*R*)-Trp^- in HPLC studies with an $\alpha = 2.4$ [163]. This reversal of discrimination is attributed to the higher stability of the (*S*)-Trp^- ternary metallocyclodextrin which is thought to include the aromatic moiety of the guest inside the βCD annulus (**45**), whereas that of its less stable (*R*)-Trp^- analogue **46** does not. The greater enantioselectivity of $[Cu(\beta CDhm)]^{2+}$ is attributed to **45** and **46** being more rigid than **43** and **44**. 6^A-(2-Aminoethylamino)-6^A-deoxy-β-cyclodextrincopper(II), $[Cu(\beta CDen)]^{2+}$, shows no thermodynamic enantioselectivity for alanine, phenylalanine, and trytophan anions, but does give a partial HPLC separation of tryptophan anion with the (*S*)-enantiomer eluting first [164]. This is consistent with amplification of a very small enantioselectivity by chromatography.

As in many metalloenzymes, binary metallocyclodextrins incorporate a metal center in close proximity to a hydrophobic cavity capable of including a guest to form a ternary metallocyclodextrin which resembles a Michaelis metalloenzyme complex, and might therefore be expected to act as a metalloenzyme mimic [59,86,135]. It should be noted, however, that metalloenzymes have optimized their active site-substrate geometry over eons, and it is expected that substantial misalignments will occur in many metallocyclodextrins and that their catalytic activities and selectivities will often be relatively low as a consequence. The first reported [165]

catalysis by a metallocyclodextrin appears to be that of the hydrolysis of *p*-nitrophenyl acetate included in the annulus of the nickel(II) metallo-α-cyclodextrin **47**. Reaction is accelerated by $> 10^3$ over the uncatalyzed rate, and proceeds through acylation of the pyridinecarboxaldoxime ligand followed by deacylation of the resulting acetate. However, the catalysis by **47** is only four-fold more effective than that caused by the pyridinecarboxaldoximenickel(II) complex. It appears that while the αCD annulus of **47** assists in the catalysis by retaining the included *p*-nitrophenyl acetate in close proximity to the attacking pyridinecarboxaldoxime oxygen, either significant freedom of movement exists for *p*-nitrophenyl acetate in the annulus or the geometry of binding is not optimal for catalysis, so the extent of the catalytic effect is small.

The importance of the orientation of both the metal center and the included guest in the ternary metallocyclodextrin is demonstrated by the 1000-fold rate acceleration of the hydrolysis of *p*-nitrophenyl acetate over the uncatalyzed rate caused by 6^A-deoxy-6^A-(1,4,7,10-tetraazadodec-1-yl)-β-cyclodextrincobalt(III) (**48**), and the lesser catalysis caused by 3^A-deoxy-3^A-(1,4,7,10-tetraazadodec-1-yl)-β-cyclodextrincobalt(III) (**49**) at pH 7 [166,167]. It appears that the probability of nucleophilic attack on included *p*-nitrophenyl acetate by a hydroxo ligand bound to the Co^{3+} substituent in **49** is diminished by steric hindrance. The $[Co(cyclen)(OH)(H_2O)]^{2+}$ complex alone (where cyclen is 1,4,7,10-tetraazacyclododecane) has no catalytic effect, but 6^A-deoxy-6^A-(1,4,7,10-tetraazadodec-1-yl)-β-cyclodextrin causes an 8.6-fold hydrolysis rate acceleration under the same conditions. In contrast to **48**, its Ni^{2+}, Cu^{2+}, and Zn^{2+} analogues cause only 16-, 14-, and 12-fold accelerations of hydrolysis of *p*-nitrophenyl-acetate and indicate the lesser effectiveness of these metal centers in this catalysis [168].

The hydrolysis of *p*-nitrophenyl carbonate and *p*-nitrophenyl phosphate is also catalysed by **48**, but much less effectively than is the hydrolysis of *p*-nitrophenyl actetate. It is considered that steric hindrance is the cause of the decreased catalytic activity, and this appears to be supported by the observation that $[Co(cyclen)(OH)(H_2O)]^{2+}$ catalyses the hydrolysis of *p*-nitrophenyl phosphate more effectively than does **48**.

Structures 47-50 here

The hydrolysis of *p*-nitrophenyl diphenyl phosphate in the presence of the Zn^{2+} metallo-β-cyclodextrin **50** shows Michaelis-Menten kinetics (k_{cat} = 3.6 x 10^{-4} s^{-1} and K_M = 1.7 x 10^{-3} mol dm^{-3} at pH 8 in 20% aqueous acetonitrile at 298.2 K) and is accelerated 7-fold by comparison with the catalysis caused by the complex where the modified βCD substituent is replaced by a methyl group in the tetraaza macrocycle [169]. Zinc(II) appears to act as a bifunctional catalytic center through simultaneously providing a nucleophilic hydroxide ligand to attack the phosphate ester, and stabilizing the development of negatively charged phosphate oxygen through coordination. In the ternary metallocyclodextrin, *p*-nitrophenyl diphenyl phosphate is localized adjacent to Zn^{2+} and this causes the increased catalytic effect. While βCD substituted by diethylenetriamine at C(6) is not a catalyst for the hydrolysis of ribonucleoside 2',3'-cyclic phosphates, the corresponding Zn^{2+} metallocyclodextrin is [170]. At pH 9 the rates of hydrolysis of the 2',3'-cyclic monophosphates of adenosine, guanosine, cytosine, and uridine are accelerated 23-, 28-, 3.5-, and 9.6-fold in the presence of 10^{-2} mol dm^{-3} catalyst at 295.2 K. This variation is consistent with the purine residues of the first two 2',3'-cyclic monophosphates aiding the formation of stable ternary metallocyclodextrins more than the pyrimidine residues of the second two, with inclusion of the guest in the metallocyclodextrin cavity being important in the catalytic process. (It is probable that coordination to Zn^{2+} of the ribonucleoside 2',3'-cyclic phosphate guests occurs and increases the stability of the ternary metallocyclodextrin as is the case for the same metallocyclodextrin with a range of different coordinating guests [171].) Smaller accelerations occur for the hydrolysis of ribonucleotide dimers.

The ternary metallocyclodextrin **51** formed when Zn^{2+} is simultaneously coordinated by bis(histamino)-β-cyclodextrin and imidazole resembles the active site of carbonic anhydrase in which Zn^{2+} is bound by three imidazoles at the bottom of a cavity formed by the protein [172]. For CO_2 hydration, **51** is a substantially better catalyst than Zn^{2+} alone, but dehydration of HCO_3^- is not catalyzed by **51**, probably because HCO_3^- coordinates too strongly to Zn^{2+}.

Competition between coordination of the guest by the metal center and binding of the guest in the CD annulus can result in the relative catalytic effectivenesses of the metallocyclodextrin and the modified CD from which it is formed varying substantially with the

nature of the guest. This is illustrated by 3^A-deoxy-3^A-((6-hydroxymethylpyridin-2-yl)methylthio)-β-cyclodextrincopper(II) **52**, where βCD is substituted at C(2) [173]. Thus, **52** accelerates the hydrolysis of the *p*-nitrophenyl esters of picolinic acid, quinaldic acid and its 6-phenyl derivative through the nucleophilic attack of the hydroxy group of the pyridine moiety. However, **52** is less effective than is 2-hydroxymethyl-6-methylthiomethylpyridinecopper(II) which is identical to **52** except that βCD is replaced by a methyl group. This suggests that there is no cooperative catalytic effect of coordination of the guest by Cu^{2+} and its binding in the βCD annulus in **52**.

Sometimes both a binary metallocyclodextrin and its dimer are formed in which the M^{m+}:CD ratios are 1:1 and 1:2 when M^{m+} coordinates one or two modified CDs, respectively. Thus, 6^A-(2-aminoethyl)amino-6^A-deoxy-β-cyclodextrin (βCDen) is reported to form both $[Cu(\beta CDen)]^{2+}$ and $[Cu(\beta CDen)_2]^{2+}$ at pH 10.5, and the latter is found to accelerate the oxidation of furoin to furil 20-fold over the uncatalyzed rate, whereas βCDen does not [174]. Michaelis-Menten kinetics are observed and this is attributed to the inclusion of furoin in the βCD annuli of $[Cu(\beta CDen)_2]^{2+}$ stabilizing the furoin derived enolate anion which may coordinate to the Cu^{2+} center. It appears that Cu^{2+} may be able to act as an oxidant in addition to O_2. In the hydrolysis of *p*-nitrophenyl benzoate $[Cu(\beta CDen)_2]^{2+}$ is a significantly more effective catalyst than βCDen, but the reverse is the case for *p*-nitrophenyl acetate which, being a smaller guest, appears to form a less stable inclusion complex with $[Cu(\beta CDen)_2]^{2+}$ [175].

$6^A,6^C,6^E$-Trideoxy-$6^A,6^C,6^E$-tris(2,3-dihydroxybenzamido)pentadeca-*O*-methyl-α-cyclodextrin **53** has been synthesized to incorporate some characteristics of natural siderophores such as enterobactin, parabactin and agrobactin by coordinating Fe^{3+} and Al^{3+} while binding a guest in the αCD annulus [176]. The coordination of Fe^{3+} by **53** is characterized by the very large $K_{complexation} = 10^{39}$ dm^3 mol^{-1} in aqueous solution, which compares with an even greater value of 10^{52} dm^3 mol^{-1} for enterobactin. ^1H NMR studies indicate that when Al^{3+} is coordinated by **53**, *p*-nitrophenolate binds in the αCD annulus.

The binding of two βCDs to an Fe^{3+} porphyrin produced the sandwiched structure **54**, in which a guest-binding site is positioned above and below the porphyrin plane [177]. In this respect **54** resembles cytochrome P-450 and similar hemoproteins. It is found that the

epoxidation of hydrophobic cyclohexene in aqueous phosphate buffer using iodosylbenzene as the oxygen source and **54** as the catalyst proceeds effectively, while only a trace of cyclohexene oxide was detected when the simple tetrakis(*p*-sulfonatophenyl)porphyrinatoiron(III) was used as the catalyst [178]. The catalytic effect of **54** probably results from either alkene binding, or the stabilization of an oxene in the βCD annuli. The addition of α-, β-, and γ-CD to aqueous solutions of Mn^{2+}, Mn^{3+} and Fe^{3+} tetrakis(4-sulfonatophenyl)porphyrin complexes causes small changes in their uv-visible absorption spectra and increases the rate of water proton spin-lattice relaxation [179]. This is interpreted in terms of the formation of complexes in which the porphyrin complex is sandwiched between two CDs so that its plane is parallel to their annular faces. However, others have concluded that Zn^{2+} and Fe^{3+} tetrakis(4-sulfonatophenyl)porphyrin complexes form strong inclusion complexes with 4 βCDs where each 4-sulfonatophenyl group is included by a βCD [180,181]. A third type of structure is proposed for the inclusion of tetrakis(4-(3-aminopropyloxy)phenyl)porphyrin by two heptakis(2,6-di-*O*-methyl)-β-cyclodextrins where the wide ends of the two cyclodextrins almost touch as they each include almost half each of the porphyrin [182].

Structures 51-54 here

The paramagnetic and luminescent properties of the trivalent lanthanides render them particularly interesting for coordinating to CDs, thereby producing chiral shift reagents and light harvesting assemblies, respectively. Since the trivalent lanthanides are hard acids they have a preference for binding to hard base oxygen donor substituents on CDs. This is exemplified by the substitution of a multidentate oxygen donor ligand on βCD through the reaction of diethylenepentaacetic dianhydride with 6^A-(2-aminoethylamino)-6^A-deoxy-β–cyclodextrin [183]. The subsequent coordination of Dy^{3+} results in the chiral shift reagent **55** which substantially increases ^1H NMR chemical shift differences for the enantiomers of aspartame, tryptophan, propranolol, and 1-anilino-8-naphthalenesulfonate, compared with those observed in the presence of native CDs. The corresponding 2^A-substituted βCD forms a Dy^{3+} metallocyclodextrin which induces a greater chemical shift difference than does **55**. It appears

that in both cases the enantiomeric guests include with a major portion of their aromatic moieties inside the βCD annulus.

The alkali metal ions resemble the trivalent lanthanides in their hard acid character, and also in size in the case of the heavier alkali metal ions. Thus, it is found that the inclusion of the Li^+, Na^+, and K^+ *p*-nitrophenylates by **56** (formed through the 6^A-substitution of βCD by 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane) involves coordination of the alkali metal ions to the diaza crown ether substituent of **56** and the inclusion of *p*-nitrophenylate in its βCD annulus. For the Li^+, Na^+, and K^+ *p*-nitrophenylates K_{11} = 7.5 x 10^3, 2.8 x 10^4, and 9.0 x 10^3 dm^3 mol^{-1}, respectively, in *N,N'*-dimethylformamide, which compare with 1.17 x 10^3, 4.0 x 10^2, and 7.2 x 10^2 dm^3 mol^{-1} for the inclusion of Li^+, Na^+, and K^+ *p*-nitrophenylate in βCD. It appears that the inclusion of *p*-nitrophenylate in the βCD annulus of **56** stabilizes the coordination of the alkali metal ion by the diazacrown ether substituent which in turn provides an electrostatic attraction for *p*-nitrophenylate [149].

Europium(III) is also coordinated by the diazacrown ether of **56**, and also by that of **57** where 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane substitutes through both nitrogens at the 6^A- and 6^D-sites of βCD [184,185]. Generally Eu^{3+} complex ions are characterized by strong red luminescence arising from transitions between the the lowest energy $^5D_0$ excited state to the $^7F_0$ (580 nm), $^7F_1$ (592 nm), $^7F_2$ (616 nm), $^7F_3$ (650 nm), $^7F_4$ (700 nm), $^7F_5$ (750 nm), and $^7F_6$ (810 nm) components of the ground states manifold with the transitions to $^7F_1$, $^7F_2$, and $^7F_4$ accounting for 95% of the emission intensity. Both **57** and the europium analogue of **56** and their parent complex ion, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecaneeuropium(III), exhibit these emissions, and also dominant absorptions at 394 and 470 nm assigned to transitions $^5L_6$ <- $^7F_0$ and $^5D_2$ <- $^7F_0$, respectively. In acetonitrile solution the addition of benzene has little effect on the emission intensity of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecaneeuropium(III), on excitation at the benzene 254 nm absorption frequency, but the Eu^{3+} analogue of **56** showed a substantial increase in emission intensity under the same conditions [184]. This is attributed to absorption-energy transfer-emission (AETE) occurring when benzene includes in the βCD annulus of the Eu^{3+} analogue of **56** and, in its excited state, acts as an energy donor to Eu^{3+} which is in close proximity. The absence of AETE for

1,4,10,13-tetraoxa-7,16-diazacyclooctadecaneeuropium(III) is attributed to its inability to bind benzene so that energy transfer from benzene can only occur through a bimolecular route which is very inefficient because of the short excited state lifetime of benzene.

Structures 55-57 here

In aqueous solution it is found that picolinic and benzoic acid enhance the emission intensity of the Eu^{3+} analogue of **56** to a much greater extent than benzene [185]. This probably arises because picolinate and benzoate both include in the βCD annulus and simultaneouslty coordinate to Eu^{3+} in the ternary metallocyclodextrin, and thereby decrease the distance between the aromatic energy donor and Eu^{3+} to enhance the efficiency of AETE. In contrast, it appears that the 1,4,10,13-tetraoxa-7,16-diazacyclooctadecaneeuropium(III) substituent swings away from the βCD to which it is attached in the ternary metallocyclodextrin formed by benzene and thereby lowers the efficiency of AETE [185]. Addition of benzene to aqueous solutions of **57** where Eu^{3+} is tethered more closely to the βCD annulus causes little increase in Eu^{3+} luminescence. This is because the inclusion of benzene is weak ($K_{11} < 10$ dm^3 mol^{-1}) probably because the close proximity of Eu^{3+} decreases the effective hydrophobicity of the βCD annulus. However, polar pyridine includes in **57** and more strongly in the Eu^{3+} analogue of **56** for which $K_{11} = 3.48 \times 10^2$ and 1.05×10^3 dm^3 mol^{-1}, respectively. In both cases Eu^{3+} luminescence is strongly increased through AETE, the more so for **57**, probably because pyridine and Eu^{3+} are in closer proximity. In a similar way the complex where Tb^{3+} is bound by a diethylenetriamine pentaacetate substituted by its two equivalent nitrogens onto the 6^A- and 6^D-carbons of βCD emits a strong Tb^{3+} luminescence at 544 nm when either naphthalene or 1,2,4,5-tetramethylbenzene included in the βCD annulus is excited at 275 and 278 nm, respectively [186].

It is found that Ce^{4+} in the presence of γCD acts as an effective peptidase for di- and tri-peptides in neutral aqueous solution [187]. Apart from solubilizing Ce^{4+}, the nature of the interaction between Ce^{4+} and γCD is unclear, but presumably some degree of inclusion of the catalytic Ce^{4+}-peptide complex occurs as is the case for the complex ions discussed in the following section.

The inclusion of cyclobutane-1,1-dicarboxyldiamineplatinum(II) by αCD to form a 1:1 complex occurs in water and is characterized by K_{11} = 60 mol^{-1} kg, ΔH^o = -25.3 kJ mol^{-1}, and ΔS^o = -42 J K^{-1} mol^{-1}, determined by microcalorimetry, and ^1H NMR spectroscopic analysis leads to similar results [188]. In the solid state, X-ray crystallography shows the orientation of cyclobutane-1,1-dicarboxyldiamineplatinum(II) to have the cyclobutane ring protruding into, and laying approximately over the center of, the αCD annulus with its plane parallel to the αCD pseudo C_6 axis [189]. The two amine ligands are singly hydrogen bonded to secondary O(3)H groups of adjacent glucose units such that Pt^{2+} is approximately in the plane of the six O(3)Hs. Cycloocta-1,5-dienediaminerhodium(II) and cycloocta-1,5-dieneethane-1,2-diaminerhodium(II) both form 1:1 inclusion complexes with αCD in water with the latter being characterized by K_{11} = 520 mol^{-1} kg, although the X-ray structure of the former shows the inclusion to be shallow in the crystalline state [190]. Thus, the cycloocta-1,5-diene ligand is positioned over the center of the αCD annulus with the two carbons of one of the ethylene groups lying 0.88 and 1.08 Å below the mean plane of the twelve αCD secondary hydroxy groups. Two other ligand carbons are just below the plane of the hydrogens of these hydroxyl groups and the rest of cycloocta-1,5-dienediaminerhodium(II) lies outside the αCD annulus. Electron spin resonance studies are consistent with bis(2-pyridylcarbinolato)copper(II) forming a 1:1 complex with αCD, dimerizing to form a 2:1 complex with γCD, and forming complexes of both stoichiometries with βCD in frozen aqueous solution [191]. Circular dichroic studies at room temperature are consistent with the inclusion of bis(2-pyridylcarbinolato)copper(II) in αCD and γCD at room temperature.

Sometimes direct coordination of CDs to metal complexes occurs. Thus, under basic conditions Δ and Λ diastereomers of (α- and β-cyclodextrinato)bis(1,2-diaminoethane)-cobalt(III), Δ and Λ[Co(αCD and βCD)$(en)_2$]$^+$ and (α- and β-cyclodextrinato)bis(1,4,7,10-tetraazacyclododecane)cobalt(III), [Co(αCD and βCD)(cyclen)]$^+$ are formed where Co^{3+} coordinates to O^-(2) and O^-(3) of a single glucopyranose unit of doubly deprotonated α- or βCD [192]. The coordination of three bidentate ligands by octahedral Co^{3+} results in either Δ or Λ chirality which, combined with the homochirality of the CDs, produces diastereomers as demonstrated by the resulting circular dichroic spectra. Partial resolution of Δ and Λ[$Co(en)_2$(-

$NH_2CH_2CH_2SR]^{3+}$ has been achieved through the inclusion of the side chain, R (which is either $(CH_2)_nBr$ or $(CH_2)_nCH_3$ and n = 7-12) in either αCD or βCD which preferentially interact with the Δ and Λ enantiomers, respectively [193]. This is probably important in the preferential formation of the ΔΔ rotaxane diastereomer discussed below.

An interesting preview of the rotaxanes is provided by a calorimetric and ^1H NMR study of the complexation of the alkyl dimethyl(ferrocenylmethyl)ammonium species **58a-d** [194]. The K_{11} for the inclusion complexes formed by αCD with **58a-d** are 2.1 x 10^2, 1.2 x 10^3, 1.2 x 10^3, and 4.5 x 10^2 dm^3 mol^{-1}, respectively, and K_{11} for the analogous complexes formed with βCD are 2.8 x 10^3, 2.5 x 10^3, 4.8 x 10^3, and 2.5 x 10^3 in aqueous 0.05 mol dm^{-3} NaCl at 298 K. The higher values of K_{11} for the βCD complexes reflect the better fit of the ferrocenyl moiety to the βCD annulus. The smaller αCD only partially includes the ferrocenyl moiety of **58a** and **58d** in its dominant complexes, and threads onto the alkyl tail of **58b** and **58c** when including these guests, and the resulting complexes resemble the rotaxanes discussed below. The differences in the complexing modes of αCD probably result from the ferrocenyl moiety being the only hydrophobic binding site in **58a**, the hydrophobic alkyl tails of **58b** and **58c** providing alternative and more strongly binding sites, and the carboxylate charge on **58d** rendering the tail hydrophilic and an uncompetitive alternative binding site.

Structure 58 here

VII. Cyclodextrin Rotaxanes and Catenanes

To this point the character of the CD inclusion complexes discussed has been largely dominated by the nature of the CD. This is not the case in the CD rotaxanes (from the Latin *rota* meaning wheel and *axis* meaning axle) where one or more CDs are threaded onto a linear chain bearing large end groups which prevent the rotaxane from dissociating, and the CD catenanes (from the Latin *catena* meaning chain) where one or more CDs are threaded onto a cyclic chain. Both types of CD inclusion complex are held together mechanically [195,196].

Inert cobalt(III) complex ions are ideal end groups for the retention of αCD or βCD threaded onto an alkane as exemplified by μ-(diamino-1,12-dodecane)bis(chlorobisethane-1,2-

diamine)cobalt(III) ($[(en)_2ClCo(NH_2(CH_2)_{12})NH_2)CoCl(en)_2]^{4+}$)and its diamino-1,10-decane and diamino-1,14-tetradecane analogues, whose synthesis is outlined in Figure 13 [197,198]. In the racemic starting complex, $[Co(en)_2Cl_2]^+$ may possess either Δ or Λ chirality and this results in the formation of ΔΔ, ΛΛ, ΔΛ, and ΛΔ [2]-rotaxanes. Such diastereomers are shown (**59-62**) for $[(en)_2Co(NH_2(CH_2)_2S(CH_2)_n)S(CH_2)_2NH_2)Co(en)_2]^{6+}$, where n =12 [199,200]. Starting with either Δ or Λ$[Co(NH_2CH_2CH_2S)(en)]^{2+}$, the ΔΔ and ΛΛ diastereomers of this αCD [2]rotaxane and its analogues, where n = 8 and 10, have been isolated and identified by circular dichroic measurements. The yields of the ΔΔ and ΛΛ diastereomers were 3.5 and ~ 0%, 21 and < 7%, and 28 and ~ 14% when n = 8, 10, and 12, respectively, and this was attributed to chiral discrimination exercised by αCD in the step immediately prior to the coordination of the second Co^{3+} center in the rotaxane. A similar chiral discrimination is found in the αCD rotaxanes formed with $[(en)_2CoXCH_2S(CH)_nSCH_2Y)Co(en)_2]^{m+}$ where m = 4 when n = 8, 10, and 12 for X = Y = CO_2^-; and m = 5 when n = 10, X= CO_2^-, and Y = CH_2NH_2 [201].

Structures 59-62 and Figure 13 here

The pentacyanoferrate(II), $[Fe(CN)_5]^{3-}$ moiety has been used as the end group in the rapid self-assembly of the [2]rotaxanes **63-65** in water, and the last two have been the subjects of a comprehensive kinetic and equilibrium study [202,203]. The formation of $[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN)_5]^{4-}$ occurs through the sequential substitution of the labile water ligands of two $[Fe(CN)_5OH_2]^{3-}$ by the end nitrogens of $pyz(CH_2)_npyz^{2+}$ in the $pyz(CH_2)_npyz{\cdot}\alpha CD$ inclusion complex. The rotaxane may also be formed through the reaction of αCD with the $[(NC)_5Fe(pyz(CH_2)_npyz)Fe(CN)_5]^{4-}$ dimer but more slowly than with $[Fe(CN)_5OH_2]^{3-}$ which dissociation of the dimer produces. Thus, depending on the relative concentrations of the reactants the following equilibria feature to a greater or lesser extent in the rotaxane formation, and the formation of $[(NC)_5Fe(bpy(CH_2)_npyz{\cdot}\alpha CD)Fe(CN)_5]^{4-}$ occurs in an analogous manner.

$$pyz(CH_2)_npyz^{2+} + \alpha CD \rightleftharpoons pyz(CH_2)_npyz{\cdot}\alpha CD^{2+} \quad (9)$$

$$pyz(CH_2)_npyz{\cdot}\alpha CD^{2+} + [Fe(CN)_5OH_2]^{3-} \rightleftharpoons$$

$$[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)]^- + H_2O \quad (10)$$

$$[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)]^- + [Fe(CN)_5OH_2]^{3-} \rightleftharpoons$$

$$[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN)_5]^{4-} + H_2O \quad (11)$$

$$pyz(CH_2)_npyz^{2+} + [Fe(CN)_5OH_2]^{3-} \rightleftharpoons [(NC)_5Fe(pyz(CH_2)_npyz)]^- + H_2O \quad (12)$$

$$[(NC)_5Fe(pyz(CH_2)_npyz)]^- + \alpha CD \rightleftharpoons [(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)]^- \quad (13)$$

$$[(NC)_5Fe(pyz(CH_2)_npyz)]^- + [Fe(CN)_5OH_2]^{3-} \rightleftharpoons$$

$$[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN)_5]^{4-} + H_2O \quad (14)$$

Structures 63-65 here

Although metal complex end units have attracted considerable attention, bulky organic end units have also been employed as exemplified by the [2]-rotaxane **66** where αCD is threaded onto a 4,4'-diaminostilbene [204]. When the end units differ the αCD may assume two opposed orientations in the [2]-rotaxane as shown in **67** and **68** for which n = 7 or 11 [205]. An electrostatic interaction between tetraphenyl borate groups and ammonium groups at either end of the axis appears to stabilize the [2]-rotaxane **69** formed with heptakis(2,6-di-*O*-methyl)-β-cyclodextrin, DMβCD [206], and a similar situation arises in a protonated tetraaminoporphyrin complex in which two DMβCDs are bound [182].

Structures 66-69 here

An interesting example of inclusion complex formation by α- and β-CD arises with carbazole-viologen guests where the aliphatic chain threads through the CD annulus and the carbazole function acts as a blocking group as shown in Figure 14 [207]. For the αCD system ΔG^0 = -19, -24, and -27 kJ mol^{-1} in water at 303 K when n = 8, 10, and 12, respectively, and the corresponding $\Delta G^{\ddagger}$ = 75.3, 75.3, and 73.6 kJ mol^{-1}. The large $\Delta G^{\ddagger}$ are attributed to the dehydration of the viologen moiety as it passes through the αCD annulus in the transition state and subsequently rehydrates in the product ground state to form a second blocking group so that the inclusion complex bears some resemblance to the rotaxanes discussed above.

Figure 14 here

The polyrotaxanes, where several CDs are threaded on to a polymer chain, are a logical development of CD inclusion complexes and [2]-rotaxanes and have recently been comprehensively reviewed [208,209]. A well characterized example of a polyrotaxane is one where 12 αCDs are threaded on a monodisperse poly(ethyleneglycol) chain [210], and up to 37 DMβCDs are permanently threaded onto the polymer shown in Figure 15 where x = 25 mol % blocking units and y = 67 mol % αCDs per basic polymer unit.

Figure 15 here

The final extension is to thread a CD onto a second ring to form a catenane. This has proved to be difficult to achieve but the first reported solution and solid state characterization of such catenanes was for the two DMβCD [2]-catananes **70** and **71**, obtained in 3.0 and 0.8% yield, and the two DMβCD [3]-catenanes **72** and **73**, obtained as an isomeric mixture in 1.1% yield [211]. It is to be expected that further catenanes, as well as rotaxanes, will emerge from this area of molecular self assembly [195,196].

Structures 70-73 here

VIII. Conclusion

Two interacting areas emerge from this brief review of CD inclusion complexes . The first is the employment of the natural CDs as hosts for an impressive array of guests, which is likely to be of continuing interest, particularly in the fields of agriculture, drug delivery and food technology as the natural CDs become accepted for medicinal and nutritional use [4,212]. The second area is the modification of natural CDs to interact in very specific ways with included guests, and about which most of this chapter is concerned. While the first area is likely to continue to greatly exceed the second in sheer amount of CD usage, it is the second which is likely to provide the major advances in CD chemistry.

The natural CDs provide a guest size-selective annulus and a quite robust platform onto which can be built specific purpose modifications which promise a vast array of opportunities for exciting chemistry. A daunting aspect of this is the ability to screen each newly modified CD for its complexation characteristics. Fortunately chemistry advances simultaneously on many fronts and the principles of combinatorial chemistry [213,214] have recently been perceptively employed in screening the metallocyclodextrins **74** and **75** for differences in peptide binding which could not have been as rapidly achieved through conventional complexation studies or molecular modelling [215]. Thus, orange colored **74** and **75** were screened against a tripeptide library on hydrophilic poly(ethyleneglycol)polystyrene (TentaGel) beads. The library had the general structure AA3-AA2-AA1-NH$(CH_2)_2$-TentaGel with 29 different amino acids being employed at each site so that it contained maximally 29^3 (24389) different tripeptides. About 1 in 200 of the library beads exhibited the colour of **74** and **75** after equilibration in water at pH 7, indicating inclusion of an amino acid moiety. All of the beads selected by **74** contained the sequence L-Phe-D-Pro or D-Phe-L-Pro, as did most of the beads selected by **75** (Table 4). None of the other possible phenylalanine-containing sequences were selected and neither were the D-Phe-D-Pro and L-Phe-L-Pro sequences. It seems likely that this powerful technique will be applied to a range of other CDs in due course and that this will greatly accelerate the gaining of a better understanding of the factors controlling selectivity in CD inclusion complexes.

Structures 74 and 75 here

In earlier sections the involvement of CDs in catalysis and biomimetic chemistry has been extensively discussed, and it is evident that the CD annulus may to some extent be viewed as a molecular scale chemical reactor in which a reaction may be either accelerated or the reaction product may differ from that obtained in the absence of the CD. This concept is likely to lead to increasing sophisticated CD modifications as exemplified by a study of the photochemical reaction induced in a guest molecule in a CD complex as a result of energy transfer from light-gathering antenna attached to the CD [216]. Thus, when α-(*p*-dimethylaminophenyl)-*N*-phenylnitrone **76** is included in the annulus of NAβCD (instead of DCM-OH as shown in

Figure 5) in aqueous Britton-Robinson buffer at pH 9 (I = 0.1 mol dm^{-3}) and irradiated at 310 nm the product *N*-(*p*-dimethylaminophenyl)formamide **77** is produced at a substantially faster rate than in the buffer alone. This is interpreted in terms of the excitation of NAβCD at 310 nm producing a strong fluorescence in the range 325-500 nm where **76** absorbs strongly (λ_{max} = 380 nm) and which is a much more effective energy transfer process than is the direct irradiation of **76** at 310 nm. As a result **76** isomerises to **77** more rapidly in the NAβCD inclusion complex than in the free state. Further development of such photochemical systems may lead to products being obtained which are not obtained in the absence of the CD reactor.

Structures 76 and 77 here

Most of the CD chemistry discussed in this chapter has been generated from a wide range of chemical endeavour in the past decade. There can be little doubt that the next decade will see impressive extensions of this research.

Table 4. Amino acid sequences selected by the metallocyclodextrins **74** and **75** in the assay of a tripeptide library[a]

AA3	AA2	AA1	Frequency of % occurrence with	
			74	**75**
L-Phe	D-Pro	X	36	46
X	L-Phe	D-Pro	16	8
D-Phe	L-Pro	X	28	31
X	D-Phe	L-Pro	20	0

[a] X, which represents the third amino acid of the tripeptide, was any of: Gly, D-Ala, L-Ala, D-Val, L-Val, D-Leu, L-Leu, D-Ser, L-Ser, D-Thr, L-Thr, D-Asp, L-Asp, D-Glu, L-Glu, D-Asn, L-Asn, D-Gln, L-Gln, D-His, L-His, D-Lys, L-Lys, D-Arg and L-Arg.

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Figure captions

Figure 1. Schematic illustrations of α-, β- and γ-cyclodextrin whose internal diameters measured from the C(5) hydrogens are 4.7, 6.0 and 7.5 Å, respectively, and 5.2, 6.4 and 8.3 Å measured from the C(3) hydrogens, in Corey-Pauling-Koltun models. The depth of each annulus between the primary and secondary hydroxyls is 7.9 - 8.0 Å [2,5]. A truncated cone is often used to represent a natural or modified cyclodextrin. When a substituent is drawn at the narrow end of the cone, it indicates that it replaces one of the C(6) hydroxy groups, while a substituent drawn at the wide end of the cone indicates that it replaces either a C(2) or a C(3) hydroxy group.

Figure 2. Schematic illustration of the inclusion of (*R*)-atenolol (at left) and (*S*)-atenolol (at right) by perphenylcarbamate βCD in which all 7 primary and 14 secondary hydroxy groups are substituted by a phenylcarbamate group.

Figure 3. Schematic illustration of an equilibrium between intra- and inter-molecular inclusion complexes.

Figure 4. Schematic illustration of the temperature dependent intramolecular inclusion equilibrium of 3^{A}-*O*-(naphth-2-ylmethyl)-β-cyclodextrin.

Figure 5. Schematic illustration of the multichromophoric cyclodextrin inclusion complex NAβCD·DCM-OH.

Figure 6. Postulated mechanism for the regioselective hydrolysis of a 4-*tert*-butylcatechol cyclic phosphate by bisimidazole βCD.

Figure 7. The formation of aminoporphyrin complexes with heptakis(2,6-di-*O*-methyl)-β-cyclodextrin where at pH 5.0 and 333.2 K, K_{11} and K_{21} = 7.7 x 10^4 and 5.9 x 10^4 mol dm^{-3},

respectively. When Fe^{3+} binds in the center of the porphyrin ring, the analogous K_{11} and K_{21} = 3.5 x 10^4 and 9.0 x 10^2 mol dm^{-3}, respectively, at pH 3 and 298.2 K.

Figure 8. The formation of dimers by the radical cations of 6^A-deoxy-6^A-(1'-octyl-4,4'-bipyridin-1-yl)-β-cyclodextrin in the presence of βCD and *n*-octyl sulfate.

Figure 9. Postulated intermediate for the nucleophilic attack of a coordinated hydroxide on an ester carbonyl carbon.

Figure 10. Postulated intermediate for the concerted interaction of coordinated La^{3+} and peroxide to produce phosphate ester cleavage.

Figure 11. Schematic illustration of the inclusion of guests by a porphyrin-linked βCD dimer and the electron transfer accompanying quenching of the fluorescence of the porphyrin linker.

Figure 12. The preparation from βCD of the corresponding tosylate and 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrin, βCDpn, and its formation of the inclusion complexes βCDpn·(*R*)-Trp^- and βCDpn·(*S*)-Trp^-, the binary metallocyclodextrins, $[M(\beta CDpn)(H_2O)_4]^{2+}$, and the ternary metallocyclodextrins, $[M(\beta CDpn)(R)\text{-}Trp(H_2O)_2]^+$ and $[M(\beta CDpn)(S)\text{-}Trp(H_2O)_2]^+$. The coordinated water ligands are not shown in the text.

Figure 13. The preparation of the αCD $[(en)_2ClCo(NH_2(CH_2)_{12})NH_2)CoCl(en)_2]^{4+}$ rotaxane.

Figure 14. Schematic illustration of the formation of either αCD or βCD carbazole-viologen inclusion complexes.

Figure 15. Schematic illustration of a DMβCD polyethyleneglycol rotaxane.

Table 3. Formation constants (K) for metallocyclodextrins of 6^A-(3-aminopropylamino)-6^A-deoxy-β-cyclodextrins (βCDpn) and 6^A-(2-(bis(2-aminoethyl)amino)ethylamino)-6^A-deoxy-β-cyclodextrin (βCDtren) and related species in aqueous solution at 298.2 K and I = 0.10 mol dm^{-3} ($NaClO_4$) [154-156].

Equilibrium	$\log(K/dm^3\ mol^{-1})$			
	$M^{2+} = Co^{2+}$	$M^{2+} = Ni^{2+}$	$M^{2+} = Cu^{2+}$	$M^{2+} = Zn^{2+}$
$M^{2+} + pn \rightleftharpoons [M(pn)]^{2+}$		6.31	9.75	
$M^{2+} + tren \rightleftharpoons [M(tren)]^{2+}$	12.7	14.6	18.5	14.5
$M^{2+} + βCDpn \rightleftharpoons [M(βCDpn)]^{2+}$	4.22 ± 0.02	5.2 ± 0.1	7.35 ± 0.04	4.96 ± 0.08
$M^{2+} + βCDtren \rightleftharpoons [M(βCDtren)]^{2+}$		11.65 ± 0.06	17.29 ± 0.05	12.25 ± 0.03
$M^{2+} + βCDpnH^+ \rightleftharpoons [M(βCDpnH)]^{3+}$	2.5 ± 0.2	3.1 ± 0.1	3.09 ± 0.04	3.0 ± 0.1
$M^{2+} + βCDtrenH^+ \rightleftharpoons [M(βCDtrenH)]^{3+}$		8.46 ± 0.06	11.56 ± 0.02	7.92 ± 0.02
$M^{2+} + Trp^- \rightleftharpoons [M(Trp)]^+$	4.41 ± 0.05	5.42 ± 0.03	8.11 ± 0.03	4.90 ± 0.04
$[M(βCDpn)]^{2+} + (R)\text{-}Trp^- \rightleftharpoons [M(βCDpn)(R)\text{-}Trp]^+$	4.04 ± 0.03	4.1 ± 0.2	7.85 ± 0.07	5.3 ± 0.1
$[M(βCDpn)]^{2+} + (S)\text{-}Trp^- \rightleftharpoons [M(βCDpn)(S)\text{-}Trp]^+$	4.32 ± 0.05	5.1 ± 0.2	8.09 ± 0.05	5.3 ± 0.1
$[M(βCDtren)]^{2+} + (R)\text{-}Trp^- \rightleftharpoons [M(βCDtren)(R)\text{-}Trp]^+$		8.2 ± 0.2	9.5 ± 0.3	8.1 ± 0.1
$[M(βCDtren)]^{2+} + (S)\text{-}Trp^- \rightleftharpoons [M(βCDtren)(S)\text{-}Trp]^+$		8.1 ± 0.2	9.4 ± 0.2	8.3 ± 0.1
$[M(βCDtren)]^{2+} + (R)\text{-}TrpH \rightleftharpoons [M(βCDtren)(R)\text{-}TrpH]^{2+}$		4.6 ± 0.2	4.3 ± 0.3	
$[M(βCDtren)]^{2+} + (S)\text{-}TrpH \rightleftharpoons [M(βCDtren)(S)\text{-}TrpH]^{2+}$		4.3 ± 0.2	4.2 ± 0.2	
$[M(βCDtrenH)]^{3+} + (R)\text{-}TrpH \rightleftharpoons [M(βCDtrenH)(R)\text{-}TrpH]^{3+}$		3.56 ± 0.07	4.4 ± 0.2	4.82 ± 0.06
$[M(βCDtrenH)]^{3+} + (S)\text{-}TrpH \rightleftharpoons [M(βCDtrenH)(S)\text{-}TrpH]^{3+}$		3.6 ± 0.3	4.4 ± 0.2	4.96 ± 0.05

Equilibrium not involving M^{2+}	$\log(K/dm^3\ mol^{-1})$
$βCD + (R)\text{-}Trp^- \rightleftharpoons βCD\cdot(R)\text{-}Trp^-$	2.33 ± 0.06
$βCD + (S)\text{-}Trp^- \rightleftharpoons βCD\cdot(S)\text{-}Trp^-$	2.33 ± 0.08
$βCDpn + (R)\text{-}Trp^- \rightleftharpoons βCDpn\cdot(R)\text{-}Trp^-$	3.41 ± 0.02
$βCDpn + (S)\text{-}Trp^- \rightleftharpoons βCDpn\cdot(S)\text{-}Trp^-$	3.40 ± 0.07
$βCDtren + (R)\text{-}Trp^- \rightleftharpoons βCDtren\cdot(R)\text{-}Trp^-$	6.36 ± 0.01
$βCDtren + (S)\text{-}Trp^- \rightleftharpoons βCDtren\cdot(S)\text{-}Trp^-$	6.5 ± 0.1

Figure 1

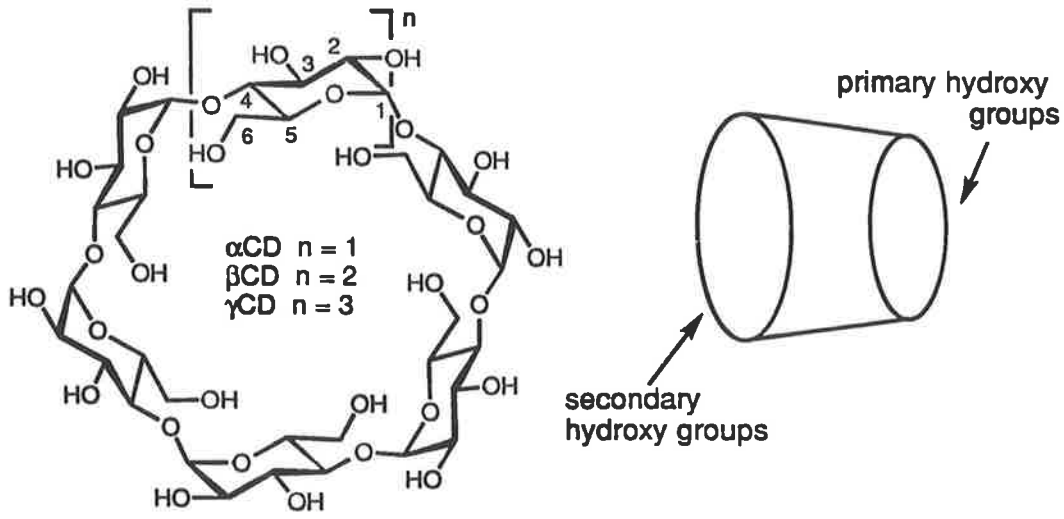
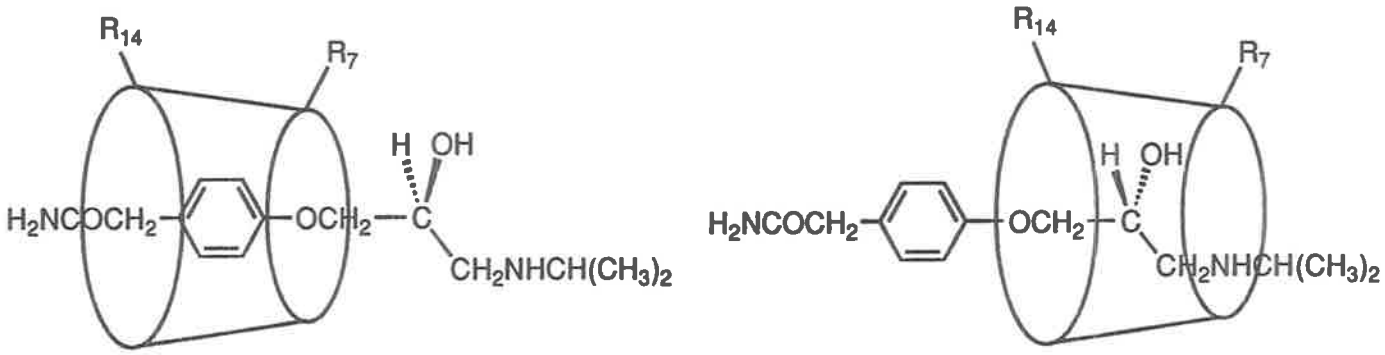

n
αCD n = 1
βCD n = 2
γCD n = 3
primary hydroxy groups
secondary hydroxy groups

Figure 2



R = OCONHPh

Figure 3

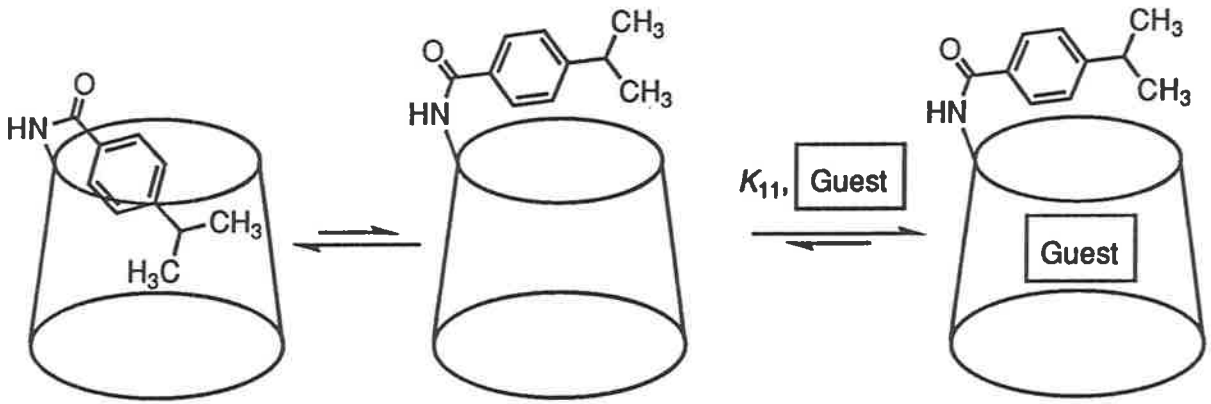


Figure 4

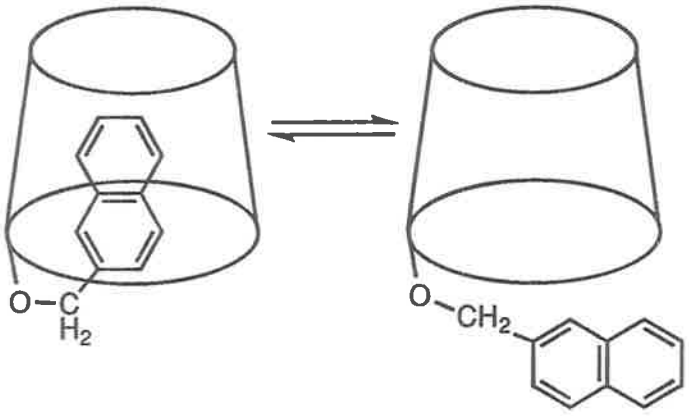


Figure 5

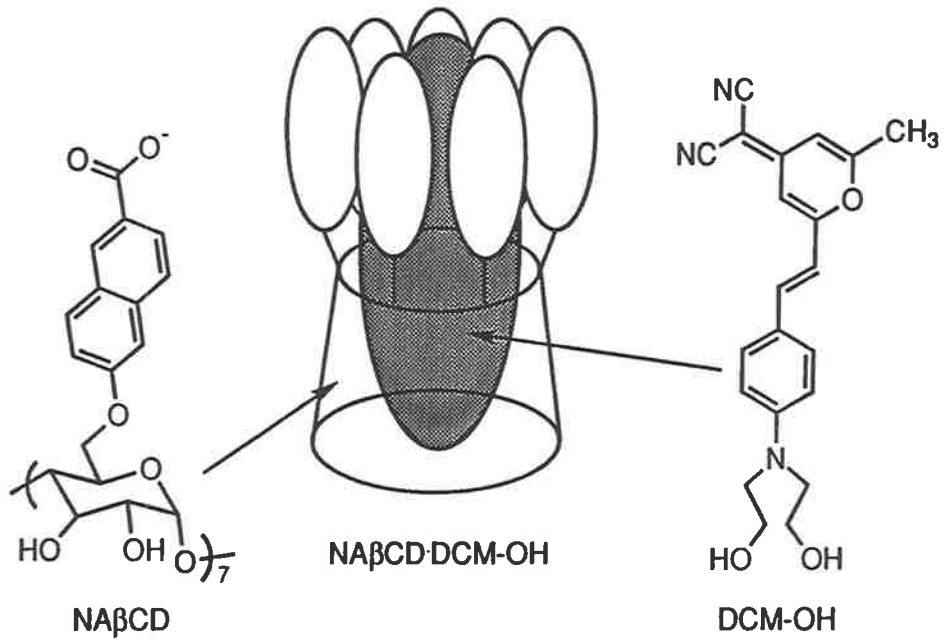


Figure 6

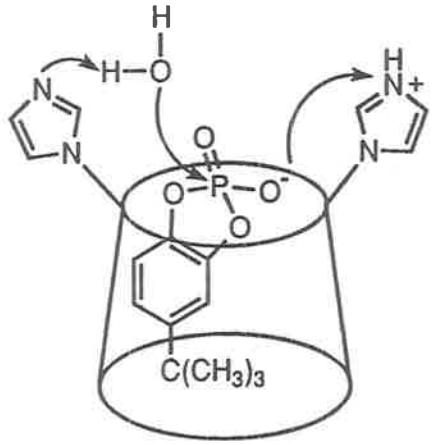


Figure 7

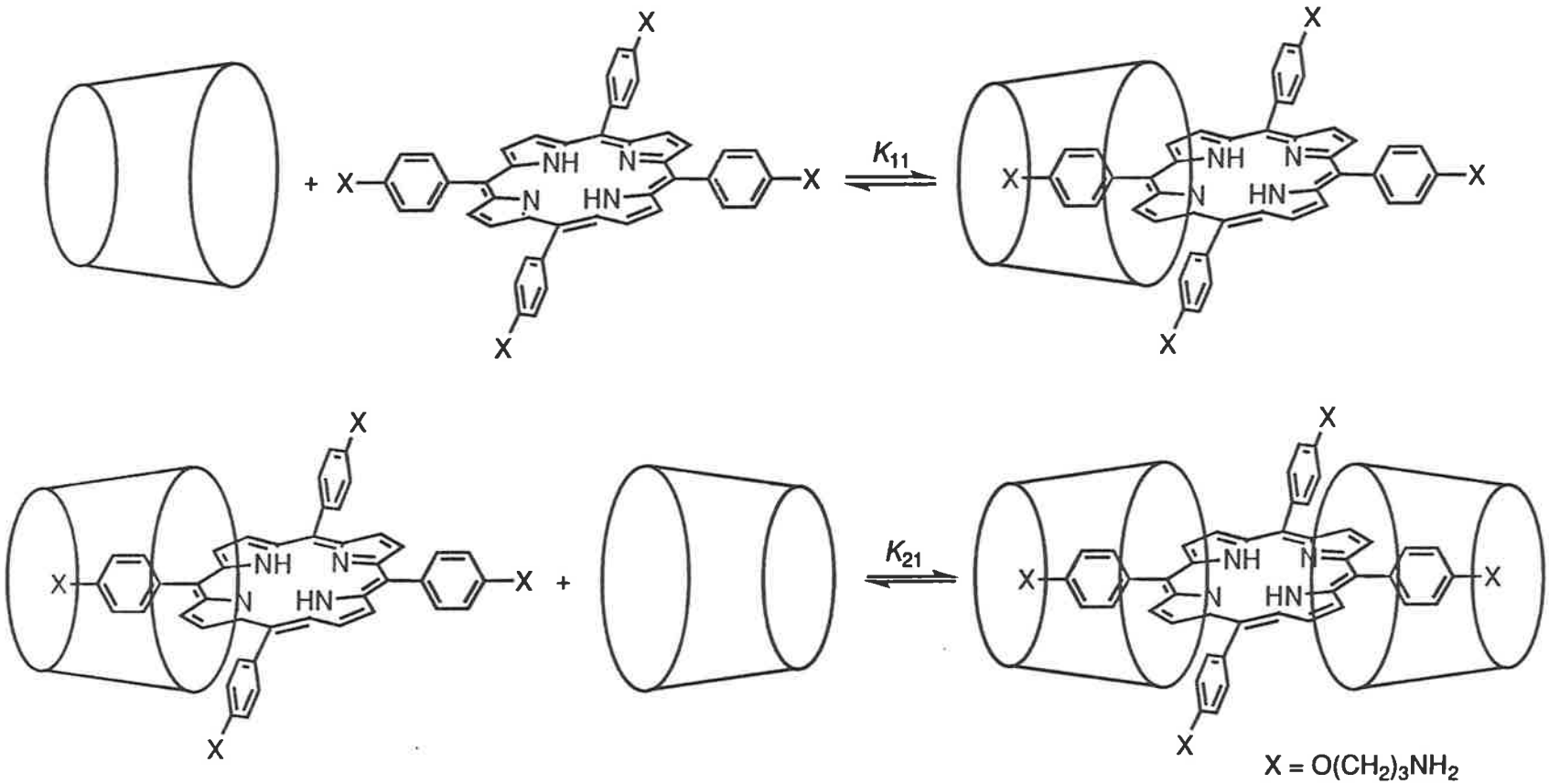


Figure 8

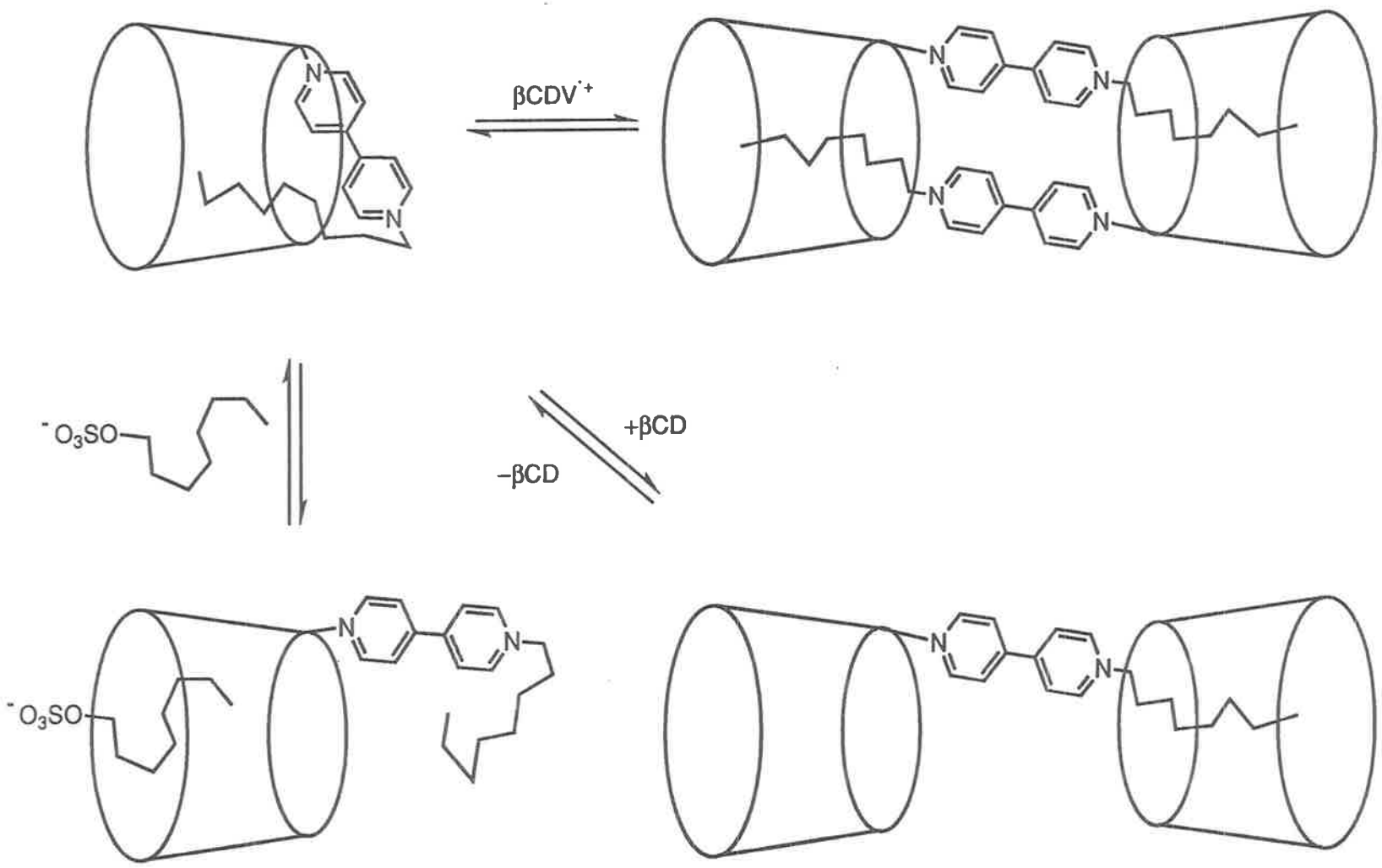


Figure 9

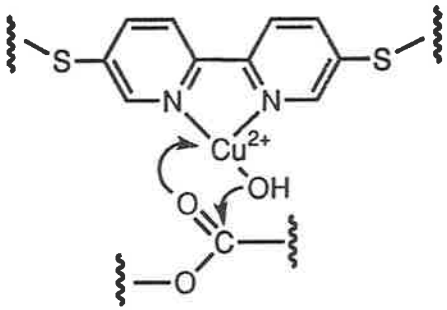


Figure 10

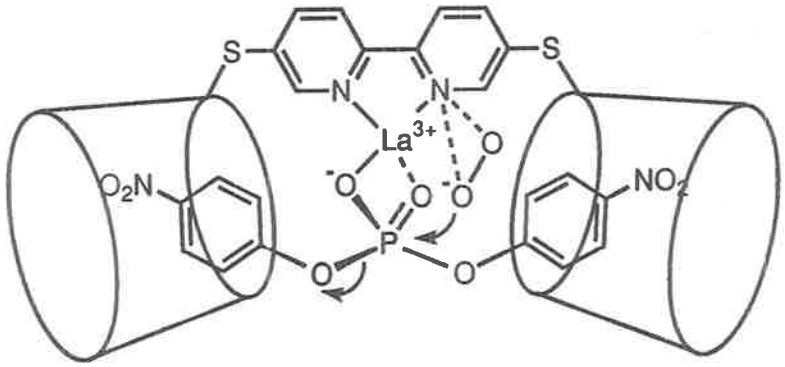
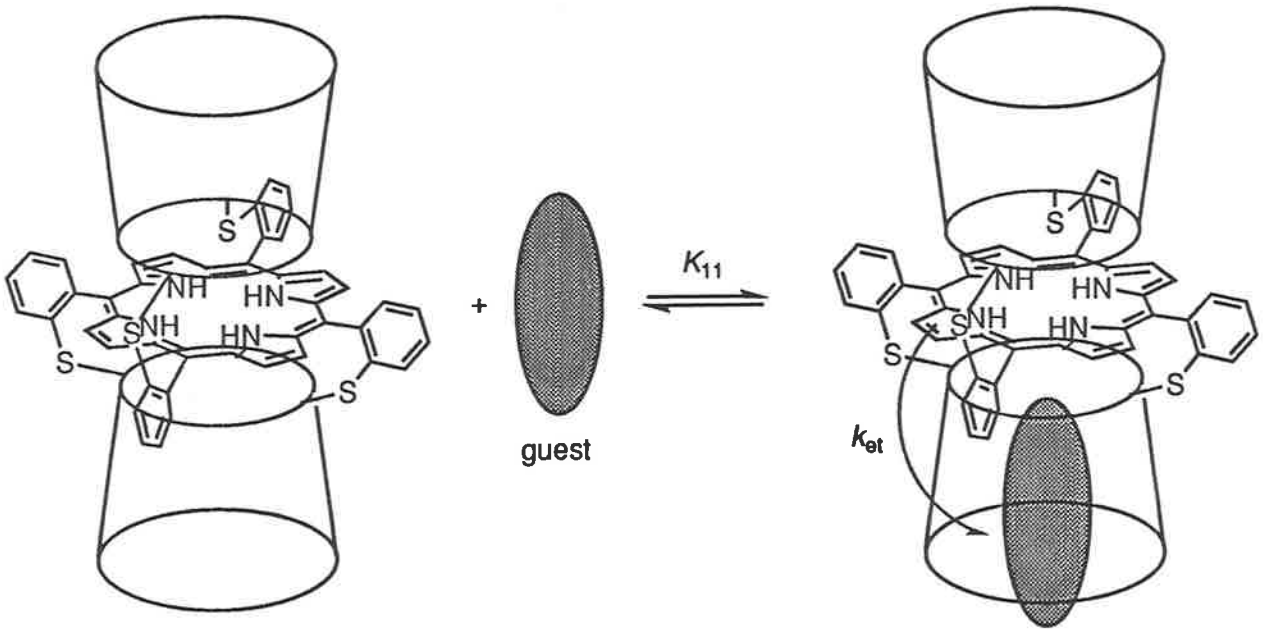
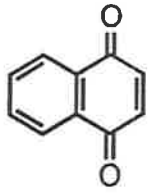


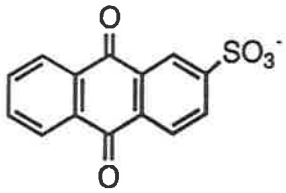
Figure 11

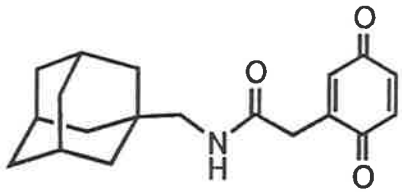


39

guests =







40 **41** **42**

Figure 12

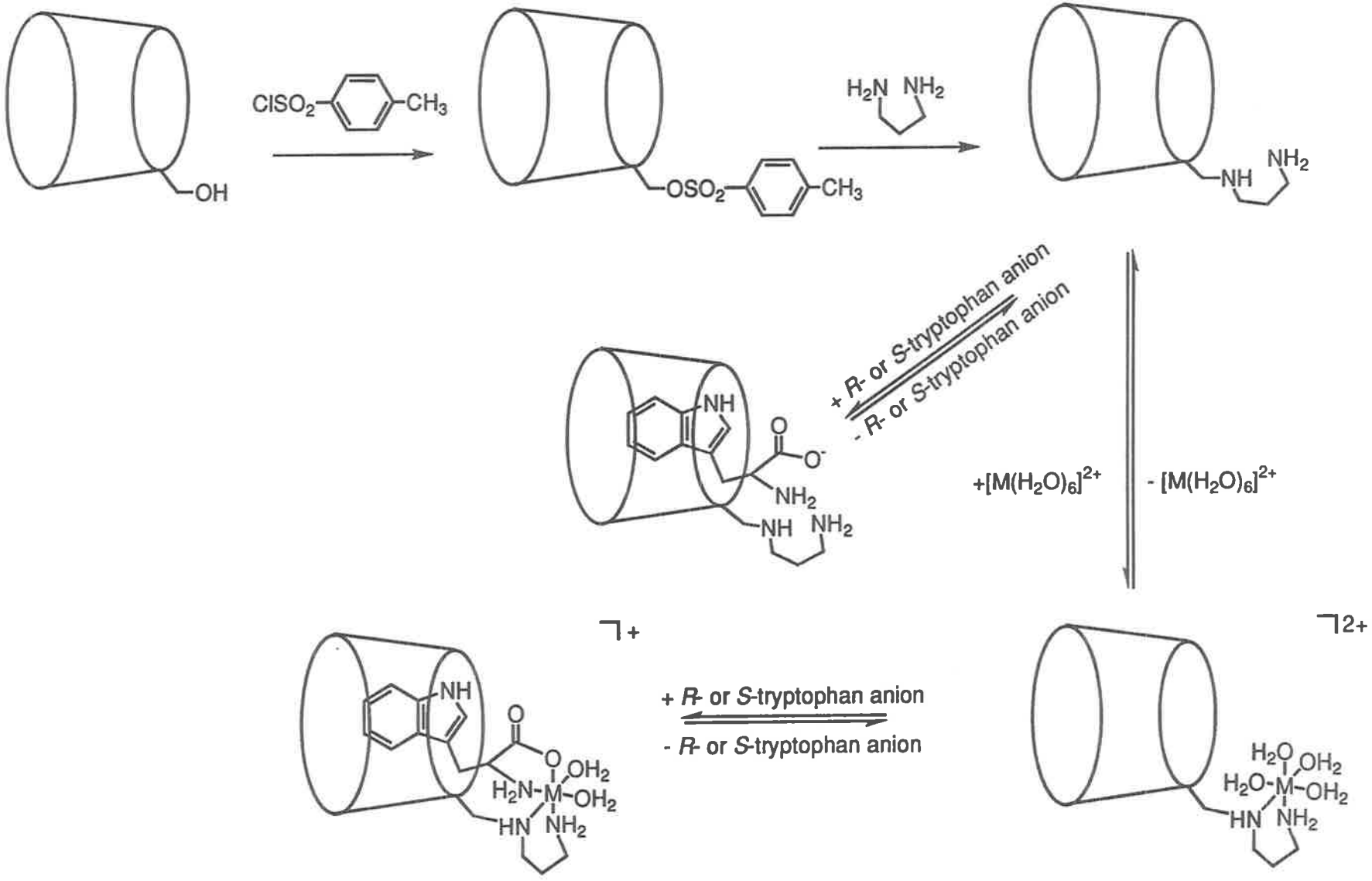

ClSO2
CH3
OH
OSO2
CH3
H2N NH2
NH
NH2
+ R- or S-tryptophan anion
- R- or S-tryptophan anion
+[M(H2O)6]2+
- [M(H2O)6]2+
NH
O
O-
NH2
NH NH2
]+
]2+
+ R- or S-tryptophan anion
- R- or S-tryptophan anion
NH
O
O
OH2
H2N-M-OH2
HN NH2
H2O OH2
H2O-M-OH2
HN NH2

Figure13

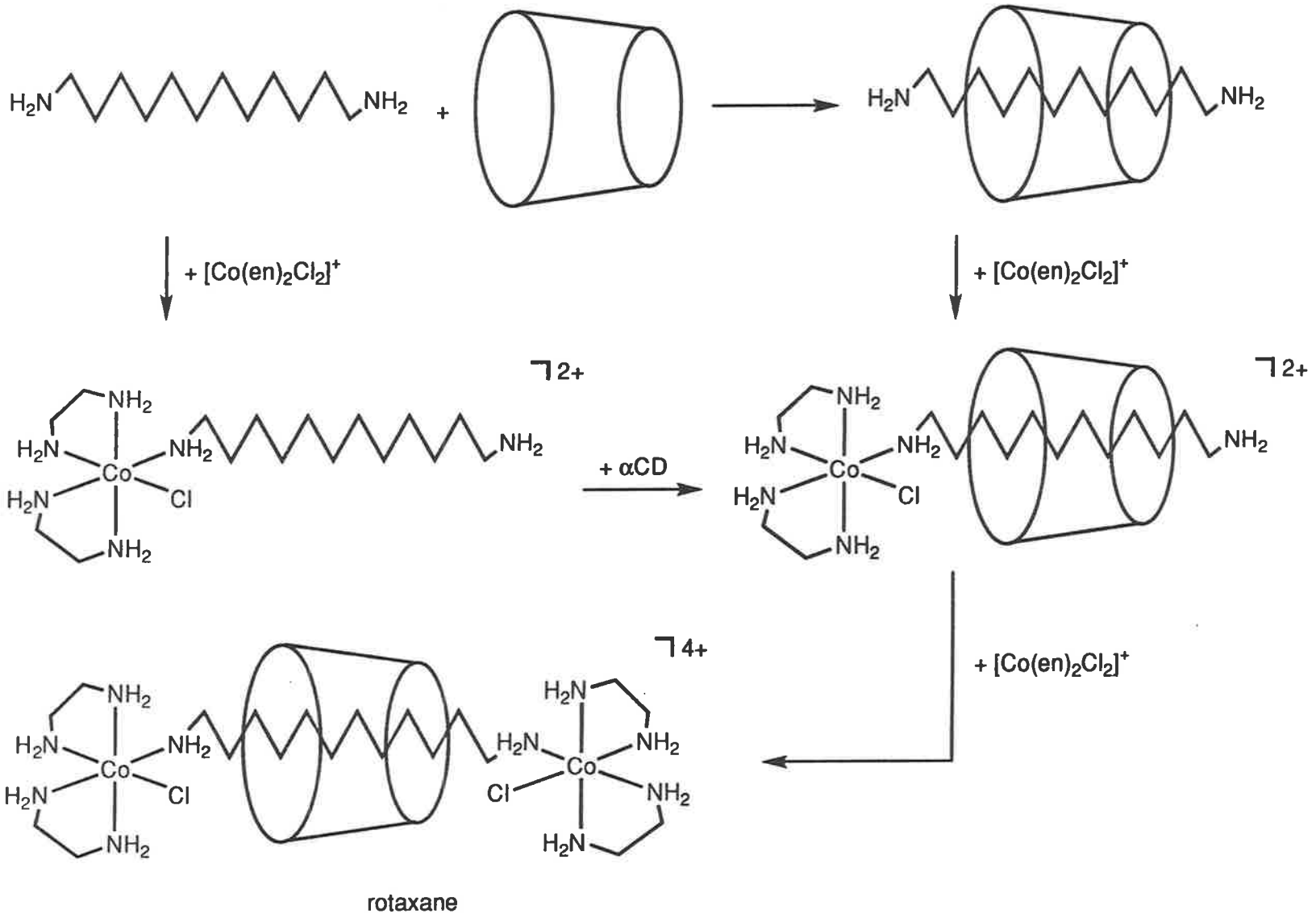
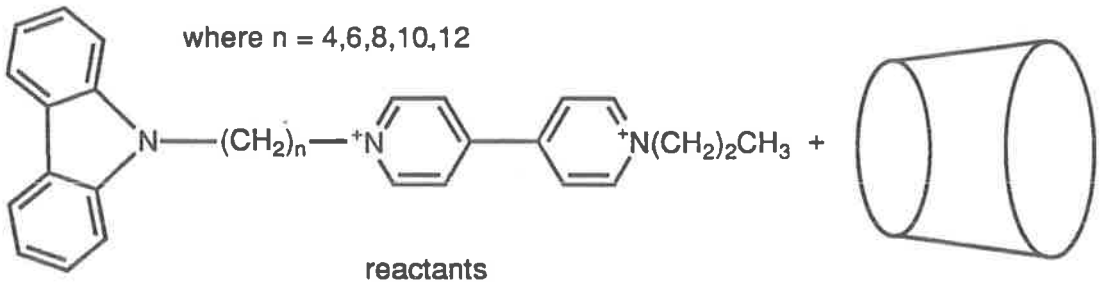
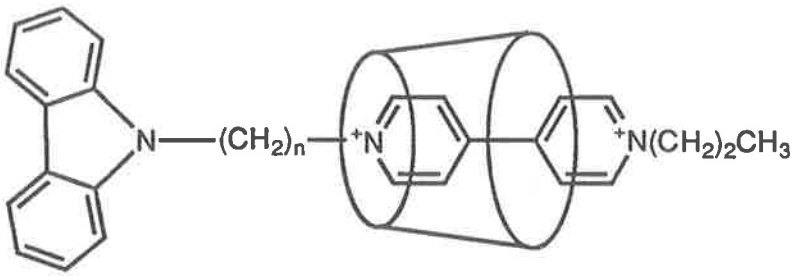

H2N
NH2
+
+ [Co(en)2Cl2]+
+ [Co(en)2Cl2]+
2+
2+
NH2
H2N
Co
Cl
+ αCD
+ [Co(en)2Cl2]+
4+
rotaxane

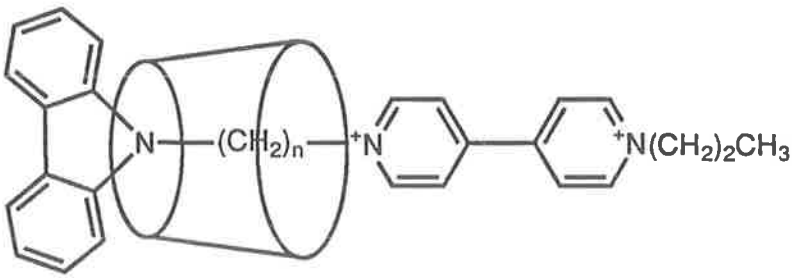
Figure 14



reactants

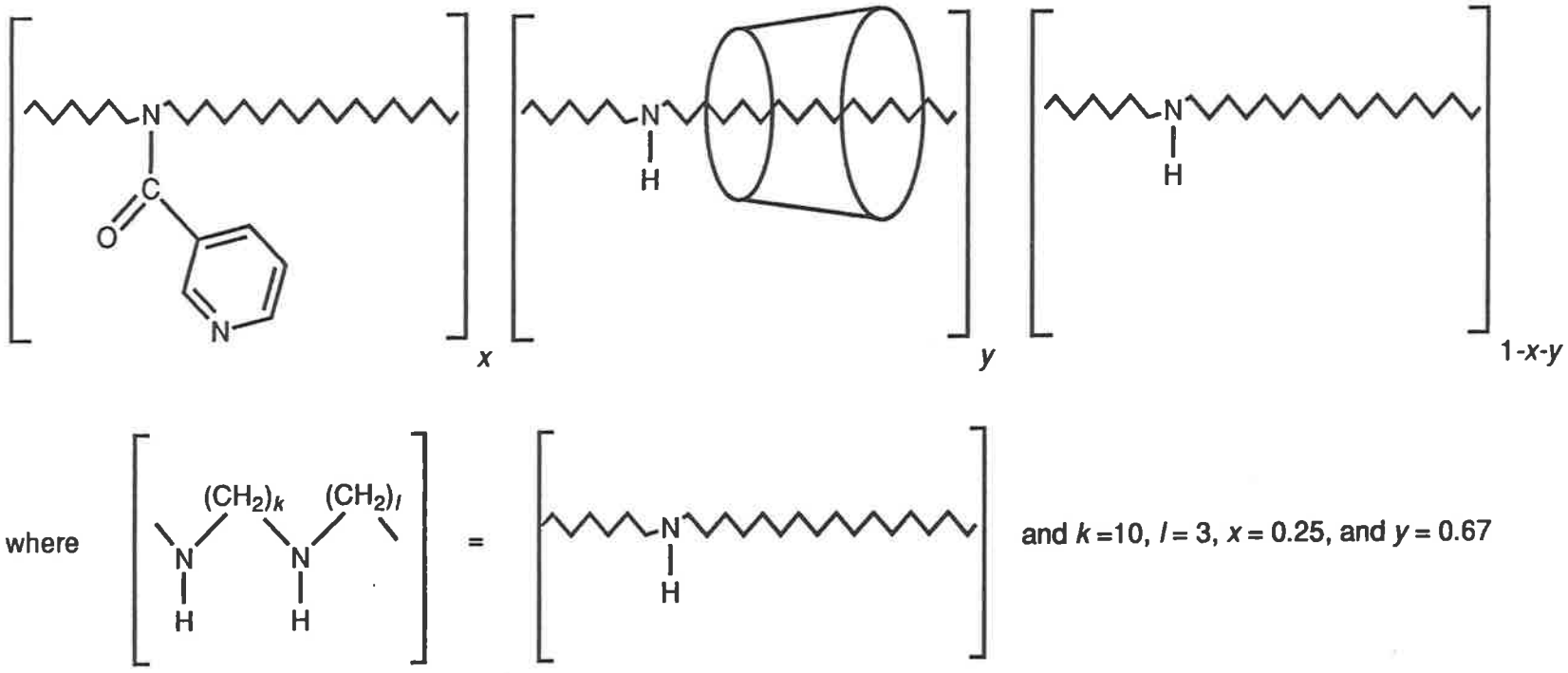


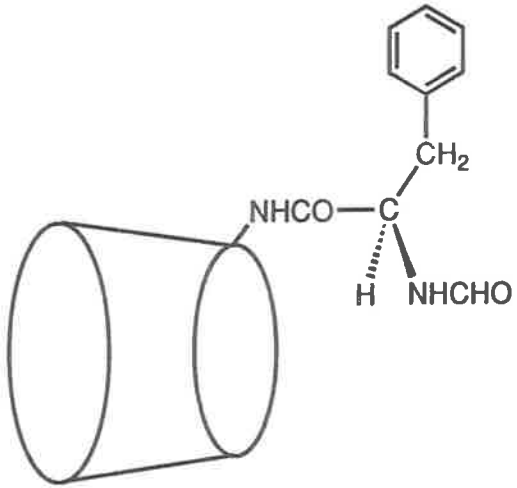
transition state



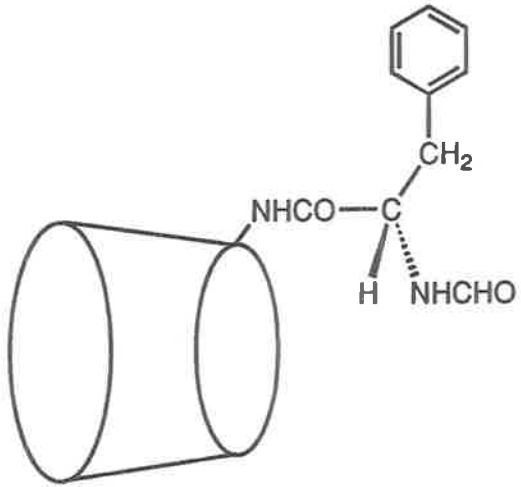
product

Figure 15

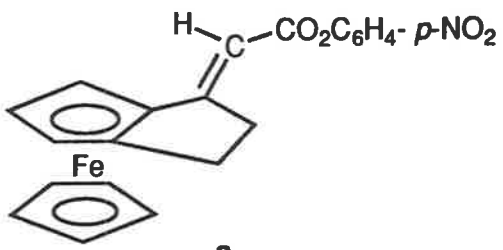

N
C
O
N
x
N
H
y
N
H
1-x-y
where
(CH2)k
(CH2)l
N
H
N
H
=
N
H
and k =10, l = 3, x = 0.25, and y = 0.67



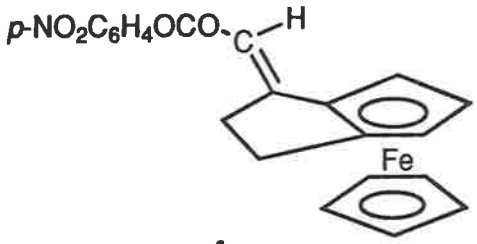
1



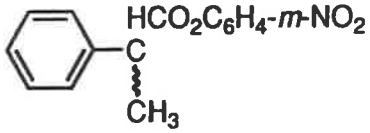
2


H
C
CO2C6H4- p-NO2
Fe

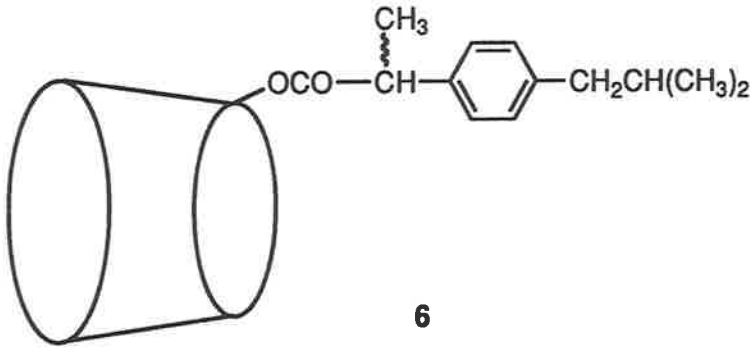
3


p-NO2C6H4OCO
C
H
Fe

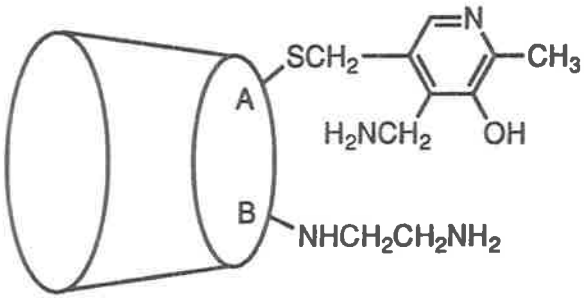
4


HCO2C6H4-m-NO2
C
CH3

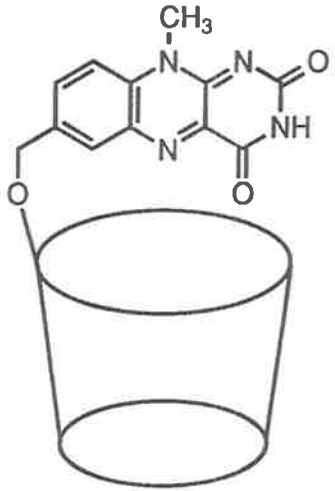
5


CH3
OCO
CH
CH2CH(CH3)2

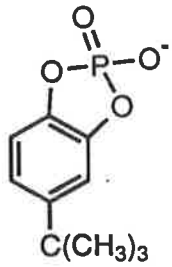
6



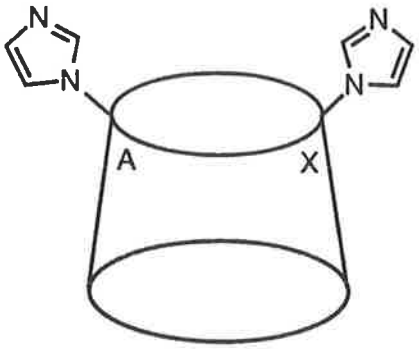
7



8

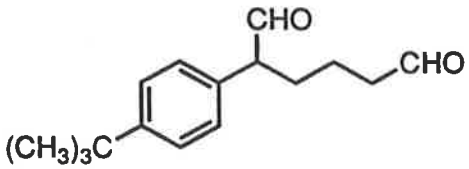


9

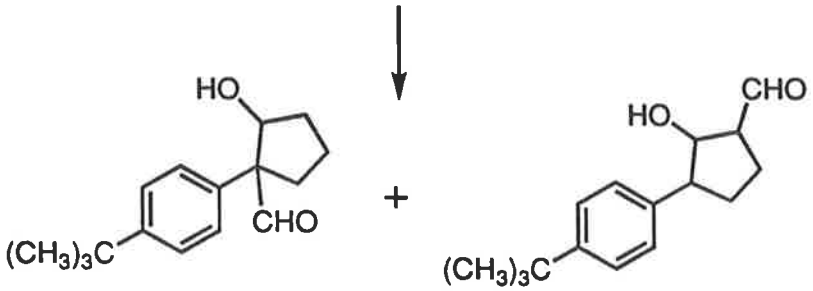


10

a) X = B
b) X = D

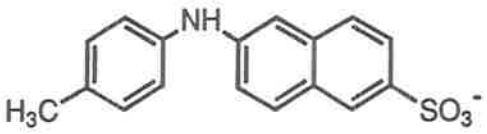


11

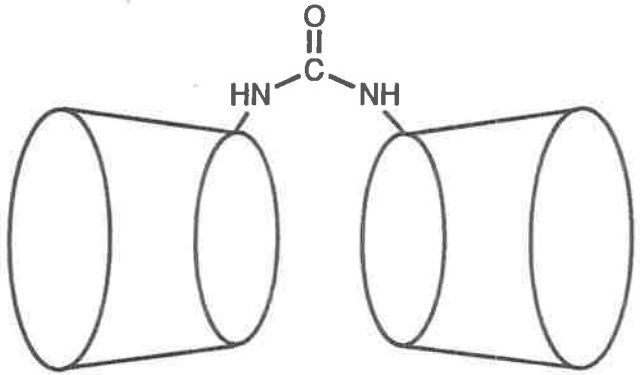


12 (97%)

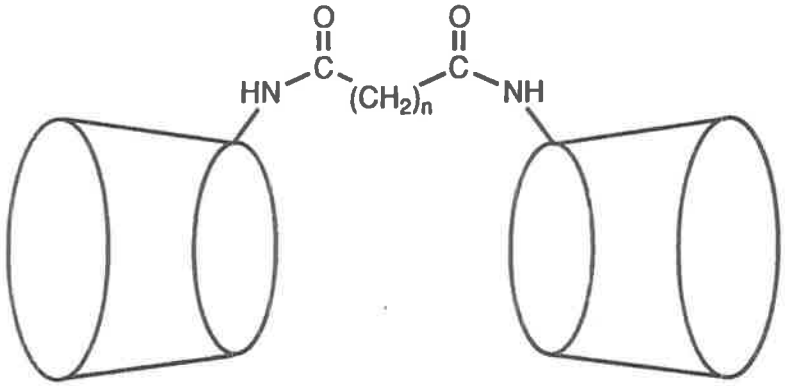
13 (3%)



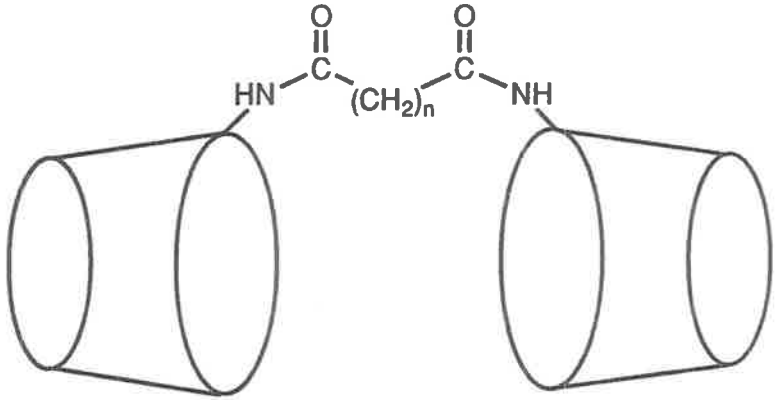
14



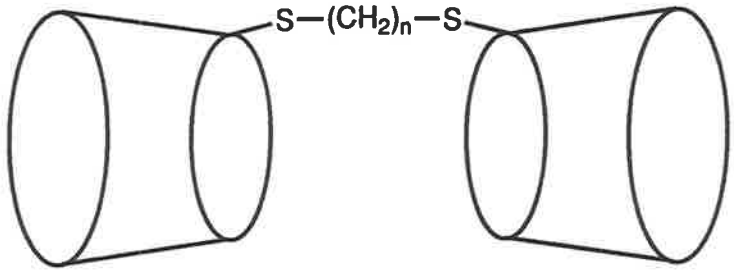
15



16
a) n = 0
b) n = 1
c) n = 2
d) n = 3

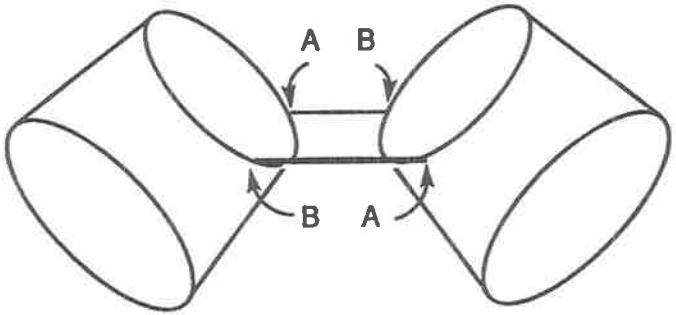


17
a) n = 2
b) n = 8

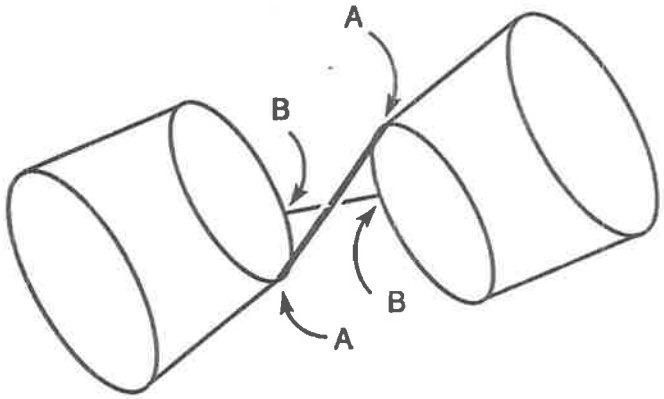


18

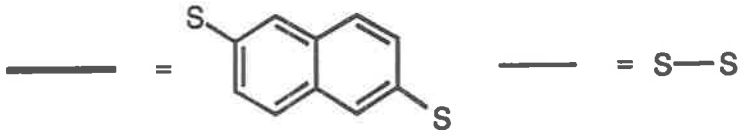
a) n = 0
b) n = 2
c) n = 3
d) n = 4
e) n = 5
f) n = 6



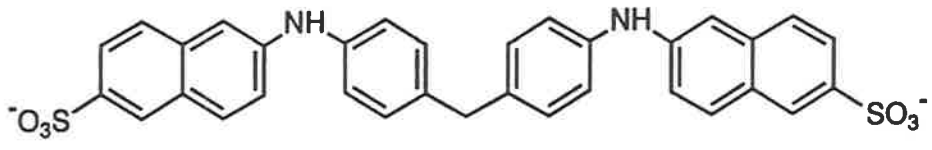
19



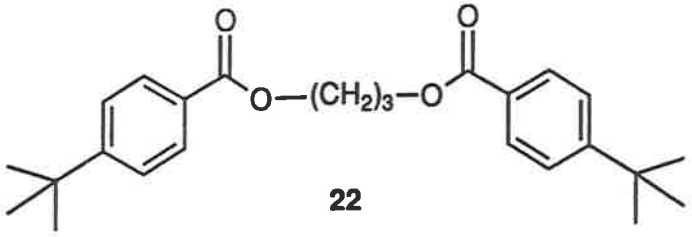
20



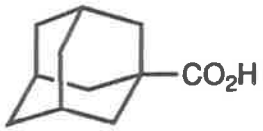
= S—S



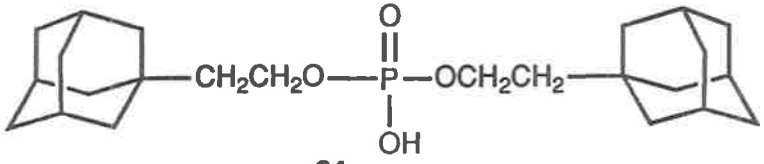
21



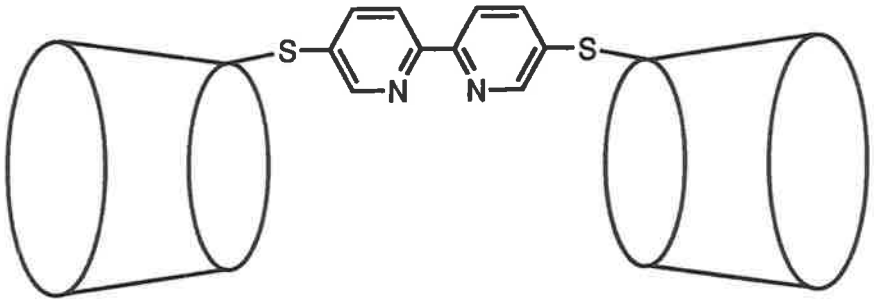
22



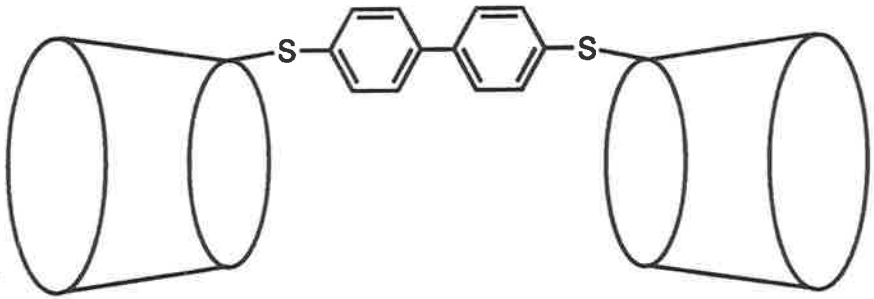
23



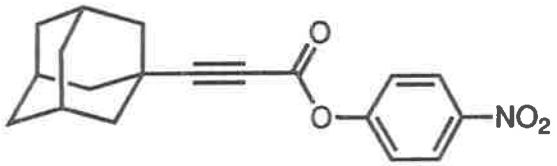
24



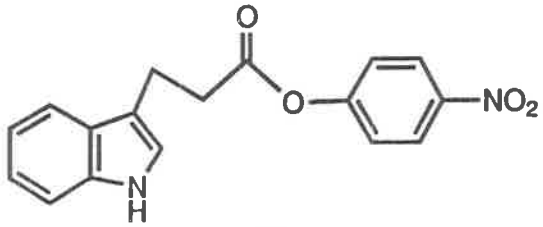
25



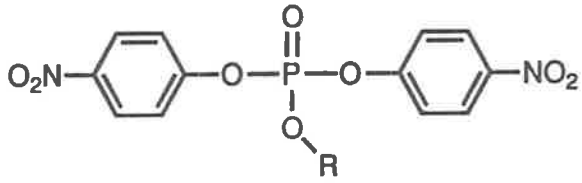
26



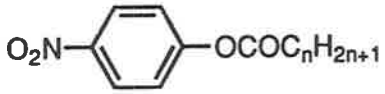
27



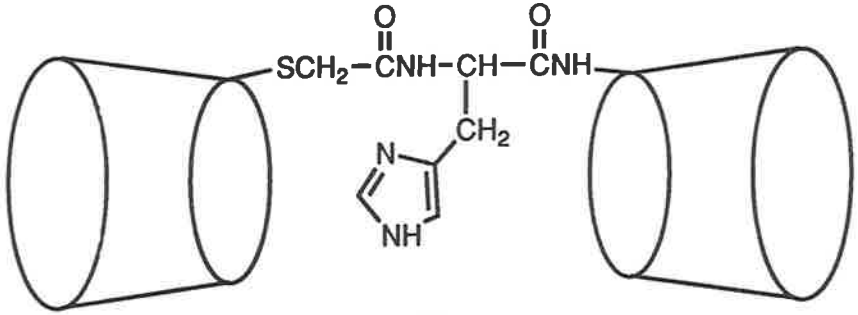
28



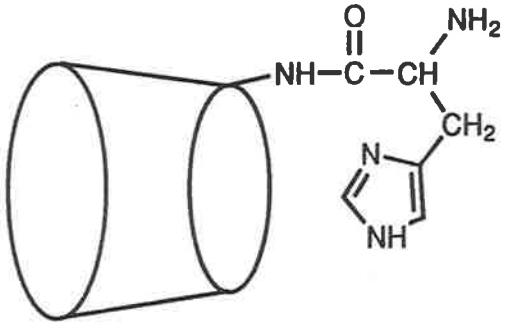
29
a) R = -
b) R = CH3



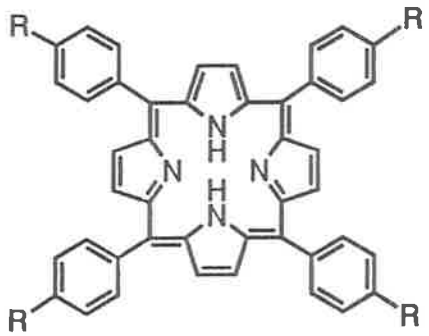
30
a) n = 1
b) n = 2
c) n = 5
d) n = 11



31



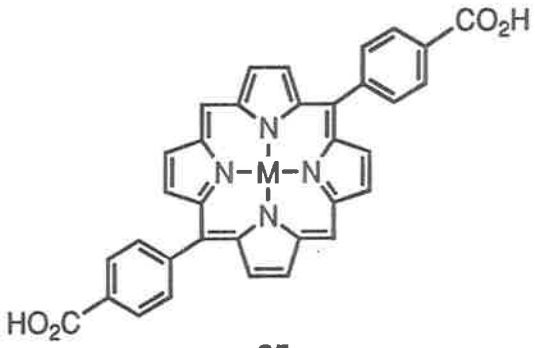
32



33

a) R = SO_3^-

b) R = CO_2^-



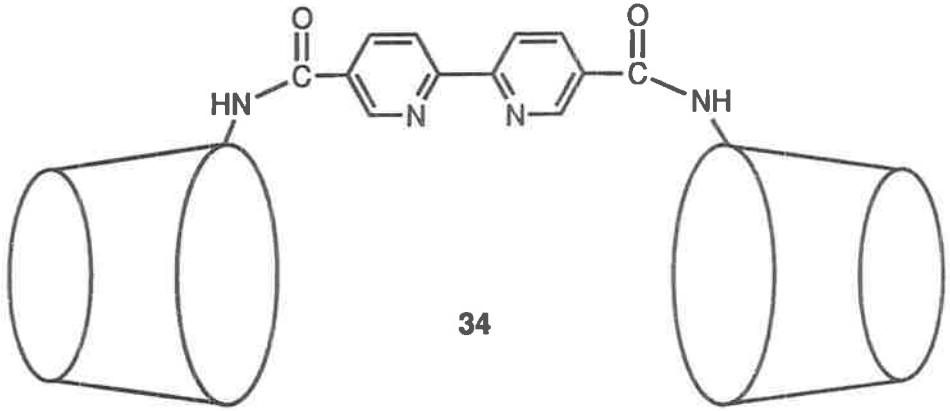
35

a) M = H, H

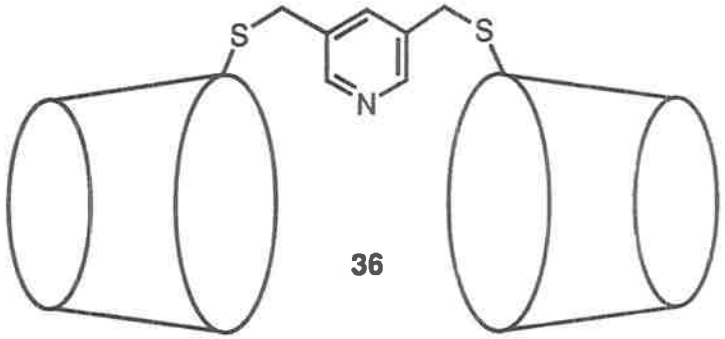
b) M = Zn^{2+}

c) M = Mn^{3+}

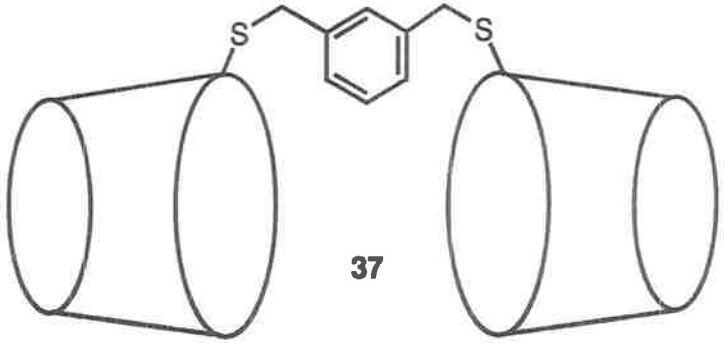
d) M = Co^{3+}



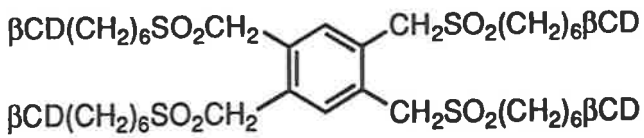
34



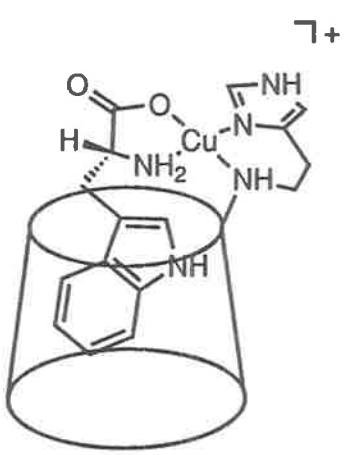
36



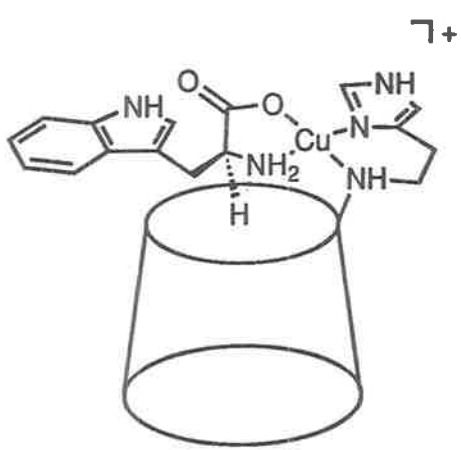
37


βCD(CH2)6SO2CH2
CH2SO2(CH2)6βCD
βCD(CH2)6SO2CH2
CH2SO2(CH2)6βCD

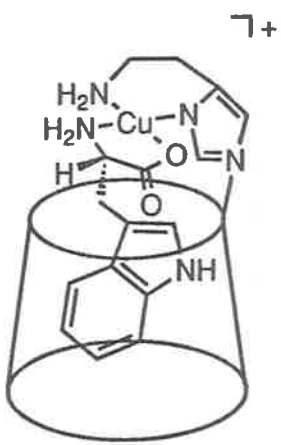
38


O
O
Cu
N
NH
H
NH2
NH
NH
+

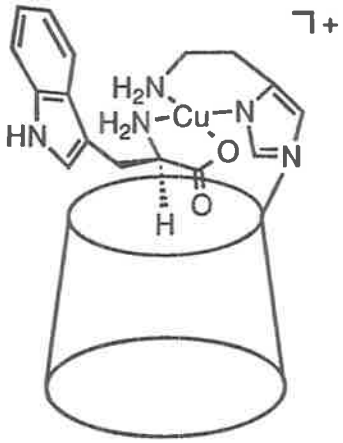
43


NH
O
O
Cu
N
NH
NH2
NH
H
+

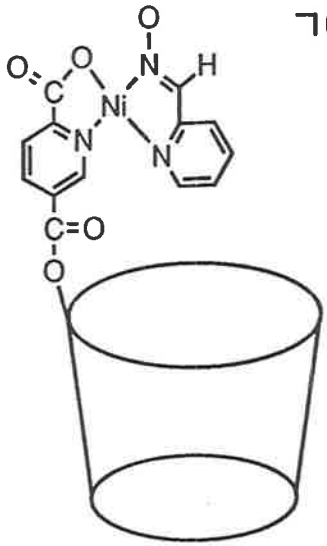
44


H2N
H2N
Cu
N
O
N
H
O
NH
+

45

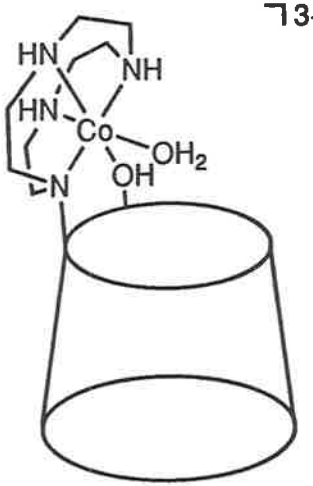

HN
H2N
H2N
Cu
N
O
N
H
O
+

46



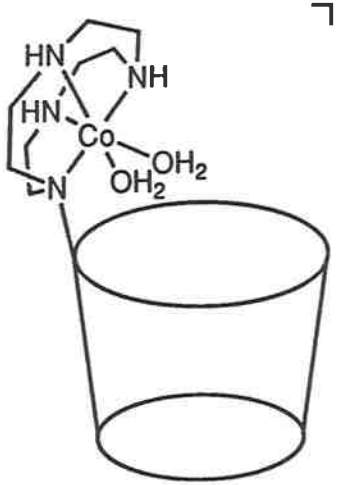
0

47



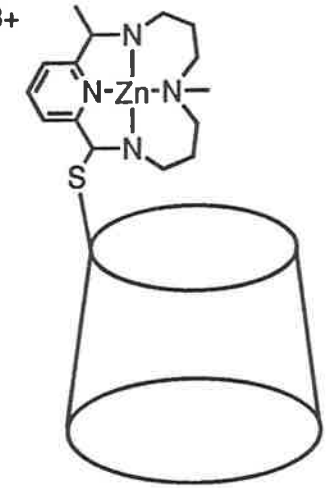
3+

48



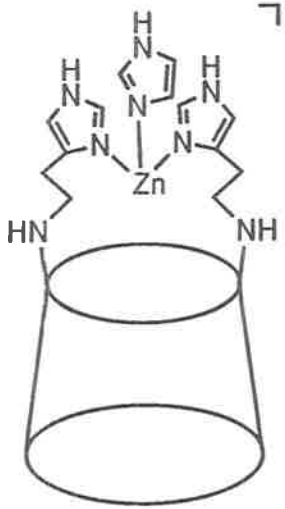
3+

49

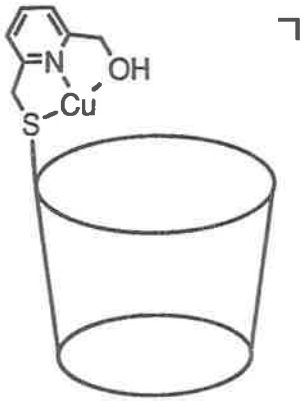


2+

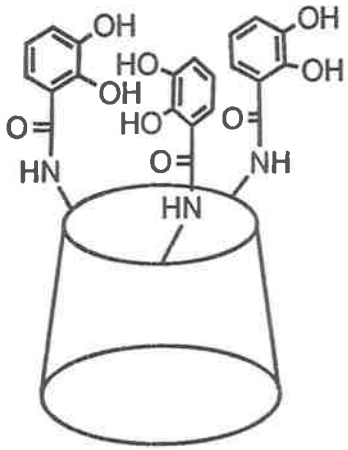
50



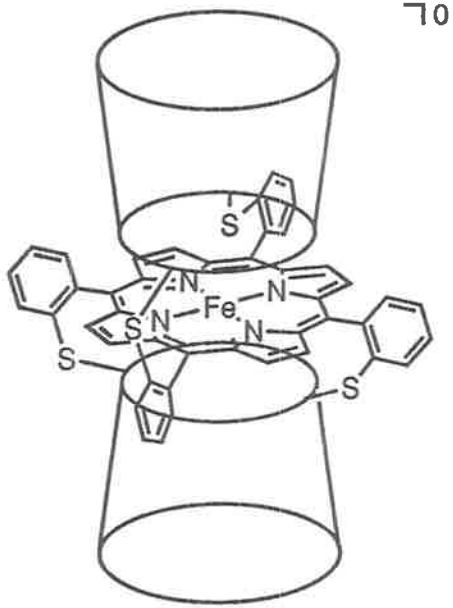
51



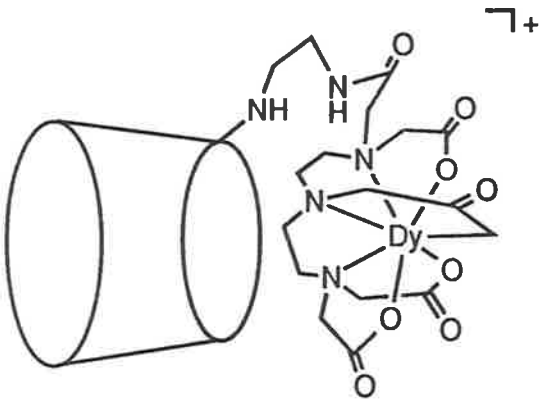
52



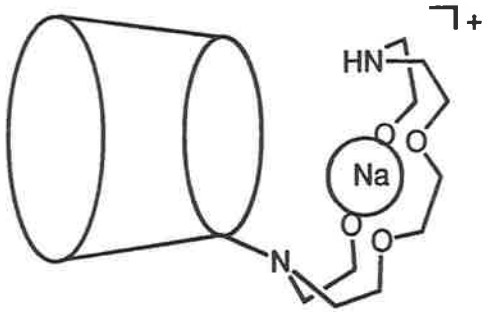
53



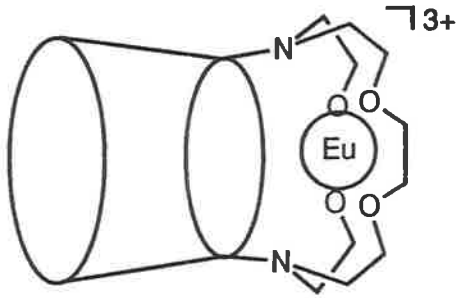
54



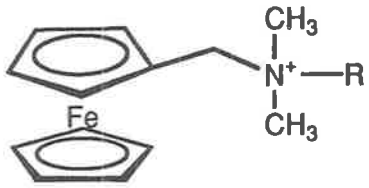
55



56

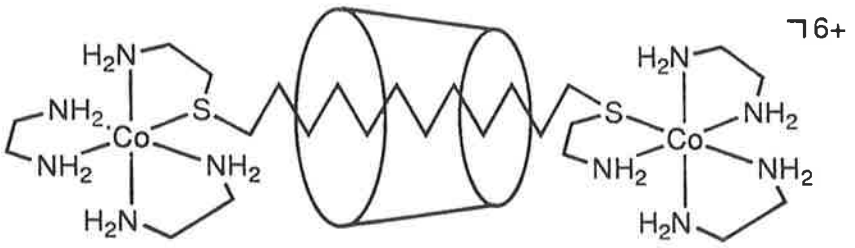


57



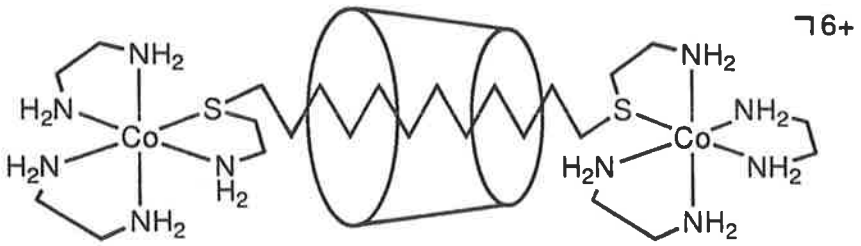
58

a) R = CH_3
b) R = $(CH_2)_6CH_3$
c) R = $(CH_2)_7CO_2H$
d) R = $(CH_2)_7CO_2^-$



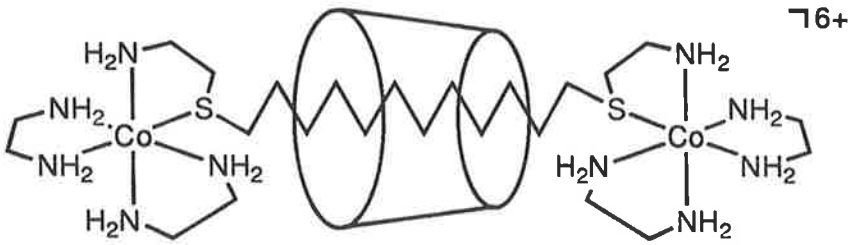
ΔΔ–αCD–rotaxane

59



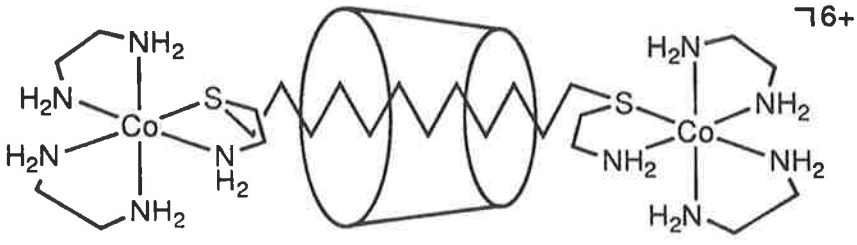
ΛΛ–αCD–rotaxane

60



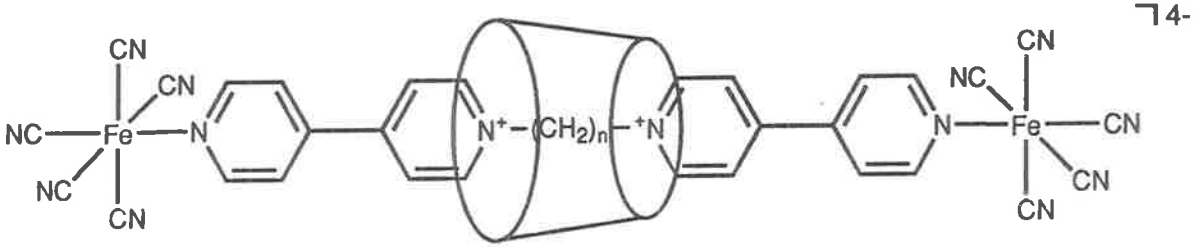
ΔΛ–αCD–rotaxane

61

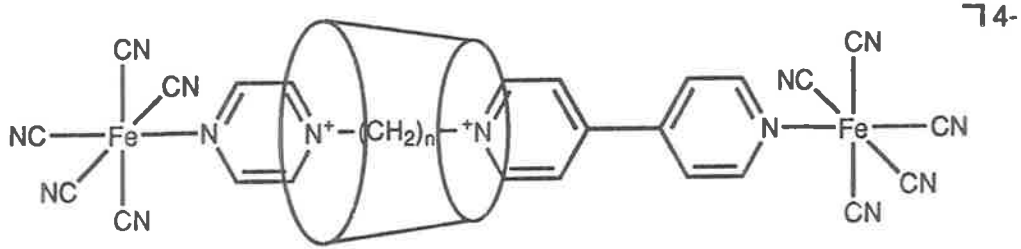


ΛΔ–αCD–rotaxane

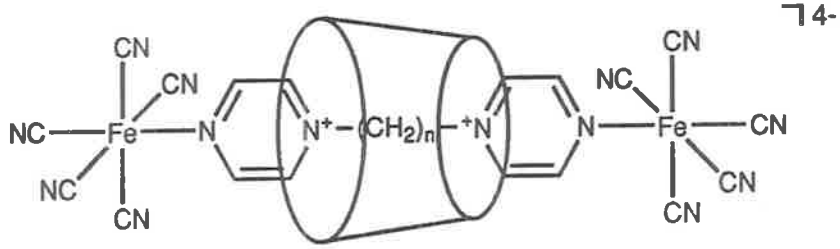
62



63 $[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN_5]^{4-}$

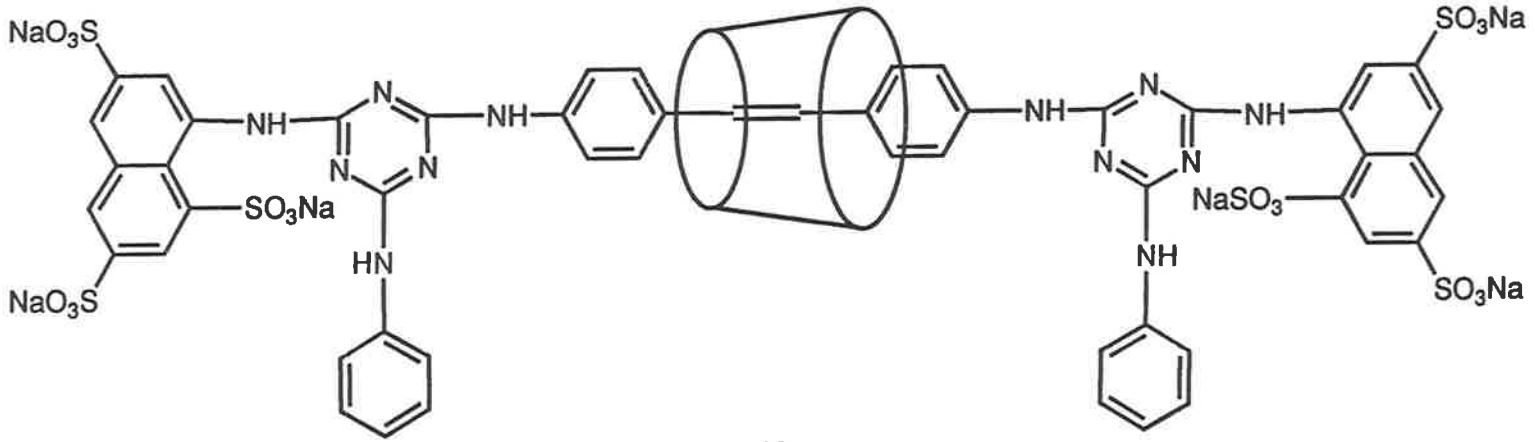


64 $[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN_5]^{4-}$

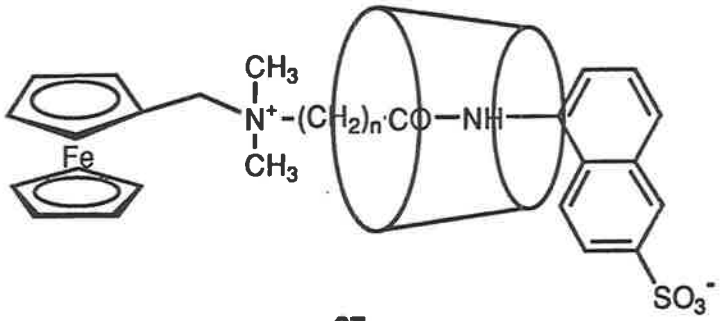


65 $[(NC)_5Fe(pyz(CH_2)_npyz{\cdot}\alpha CD)Fe(CN_5]^{4-}$

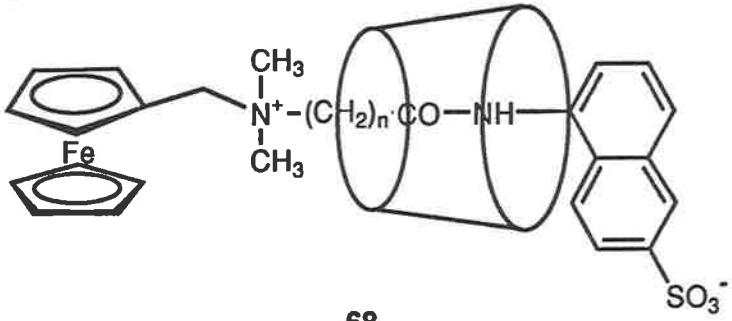
where n = 8 - 12
in all cases


NaO3S
NaO3S
SO3Na
NH
N
N
N
NH
HN
NH
N
N
N
NH
NH
SO3Na
NaSO3
SO3Na

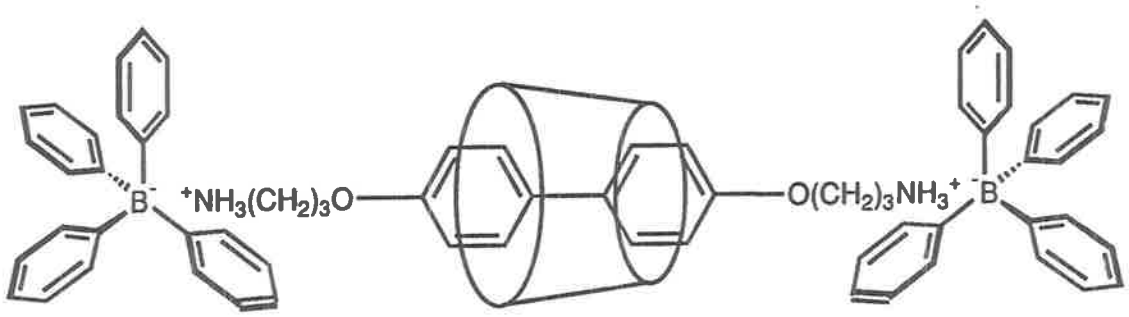
66


CH3
N+
CH3
(CH2)n
CO
NH
Fe
SO3-

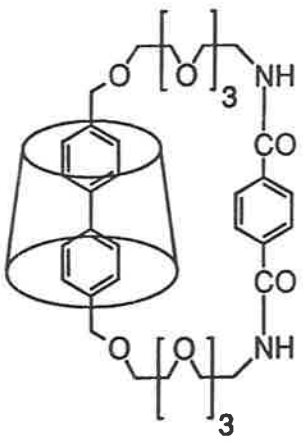
67


CH3
N+
CH3
(CH2)n
CO
NH
Fe
SO3-

68



69



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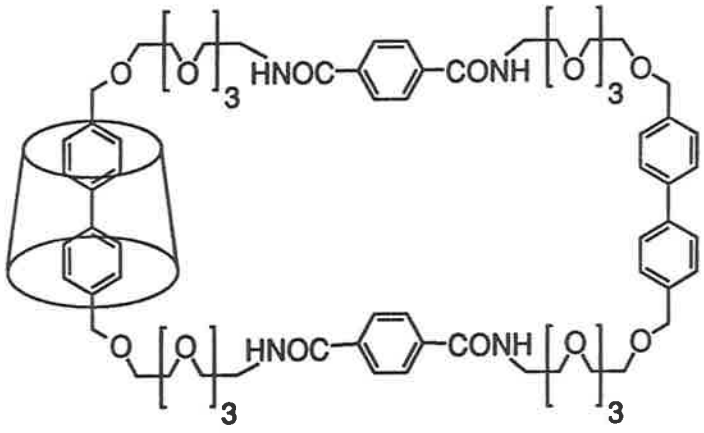

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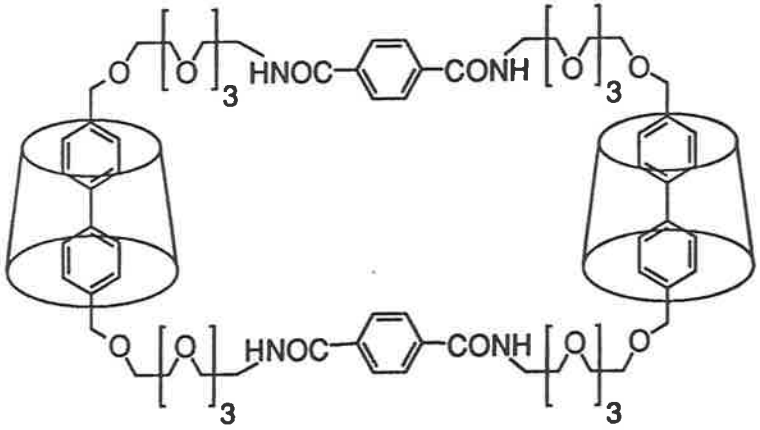

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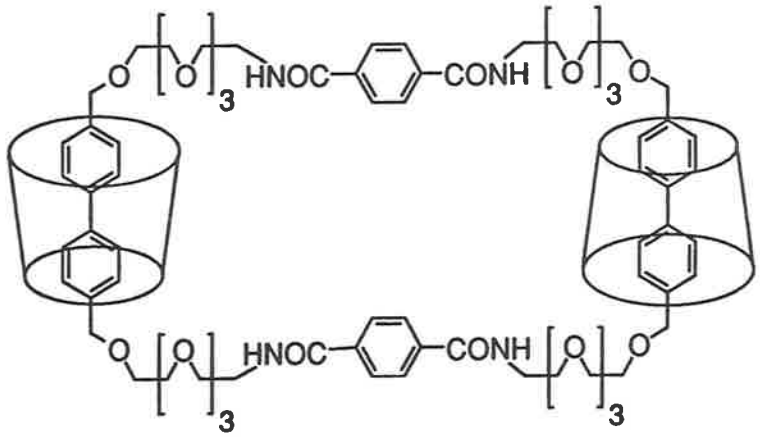

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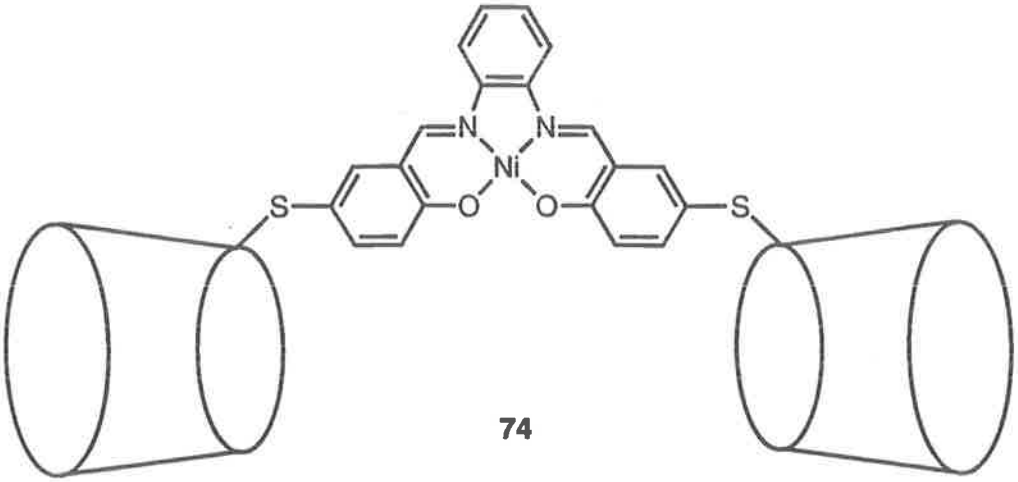

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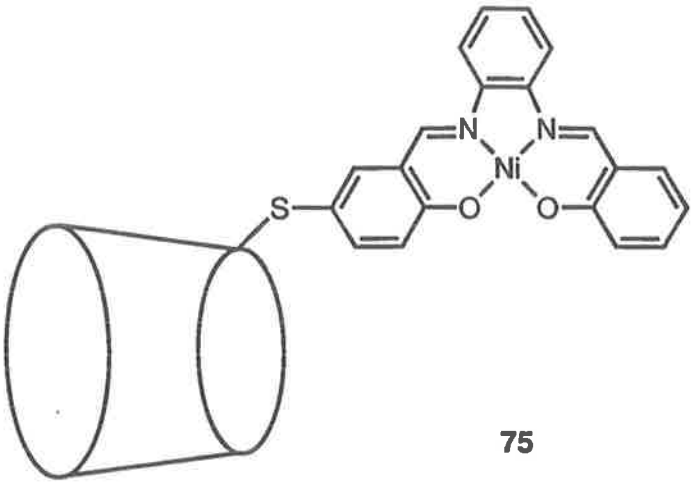

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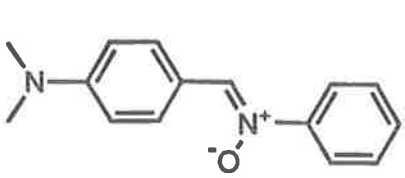

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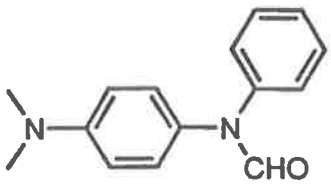

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Reactions of Amino-Substituted Cyclodextrins with 2-Arylpropanoic Acid Derivatives

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Reactions of 6^A-amino-6^A-deoxy-β-cyclodextrin and 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin with the 3-nitrophenyl esters of 2-phenylpropanoic acid and Ibuprofen occur with only low diastereoselectivity, to afford the corresponding arylpropanamido-substituted cyclodextrins. These amides are also formed by decarboxylation of corresponding malonates, again with only low diastereoselectivity. The n.m.r. spectra of the amido-substituted cyclodextrins indicate that the aryl substituent is included within the cyclodextrin annulus at low temperature, but becomes dissociated from the cavity as the temperature is increased.

Introduction

The naturally occurring cyclodextrins each exist as a single enantiomer, and their complexation of a racemic guest gives rise to diastereomeric complexes which may exhibit different thermodynamic and spectroscopic properties.[1,2] This behaviour of the cyclodextrins has been exploited extensively, most notably through the work of Armstrong *et al.*,[3,4] in the development of analytical chromatographic systems for the separation of enantiomers. Usually the thermodynamic chiral discrimination displayed in complexes of the natural cyclodextrins is quite small, but greater diastereoselectivity is often observed in complexes of modified cyclodextrins, where the asymmetry of the cyclodextrin has been increased and/or there is a greater number of interactions between chiral centres of the modified cyclodextrins and those of the guests.[2] The extent of interaction between the host and guest can be increased through metal complexation.[5–7] For example, the association constants of the diastereomeric complexes formed between (*R*)- and (*S*)-tryptophan anion and the nickel(II) complex of 6^A-(3-aminopropyl)amino-6^A-deoxy-β-cyclodextrin differ by a factor of 10, whereas β-cyclodextrin and the aminopropylamino-substituted derivative show no chiral discrimination with these guests.[5,6] Alternatively, reactions involving covalent attachment of the guest to the cyclodextrin can occur with substantial diastereoselectivity, as illustrated in the synthesis and hydrolysis of cyclodextrin esters of 2-arylpropanoic acids.[8,9]

2-Arylpropanoic acids, of which 2-phenylpropanoic acid (3a) is the parent and Ibuprofen (4a) is a typical example, are non-steroidal antiinflammatory agents, and their physiological activity is associated mainly with the (*S*)-enantiomers. Consequently there has been considerable interest in developing methods for the asymmetric synthesis of these compounds.[10,11] Given the importance of these compounds and the promising results obtained with the synthesis of their cyclodextrin esters, we have investigated reactions of the amino-substituted cyclodextrins (1a) and (2a) (Fig. 1) to give the corresponding amides (1b,c) and (2b,c). The amines (1a) and (2a) were selected because they are less symmetric than β-cyclodextrin and might therefore be expected to show greater stereoselectivity in their reactions. In addition, in nucleophilic substitution reactions, selective reaction of the amino substituent of the modified cyclodextrins (1a) and (2a) occurs to give specifically modified cyclodextrins.[12] Amides produced in this manner are more stable than the corresponding esters formed through nucleophilic substitution reactions of the cyclodextrin hydroxy groups.

Results and Discussion

The amino-substituted cyclodextrins (1a) and (2a) were obtained as reported previously.[13–15] Initially reactions with the nitrophenyl esters (3b) and (4b) were investigated. These compounds were prepared as racemates, from 2-phenylpropanoic acid (3a) and Ibuprofen (4a), respectively, by treatment with thionyl chloride, followed by 3-nitrophenol in the presence of

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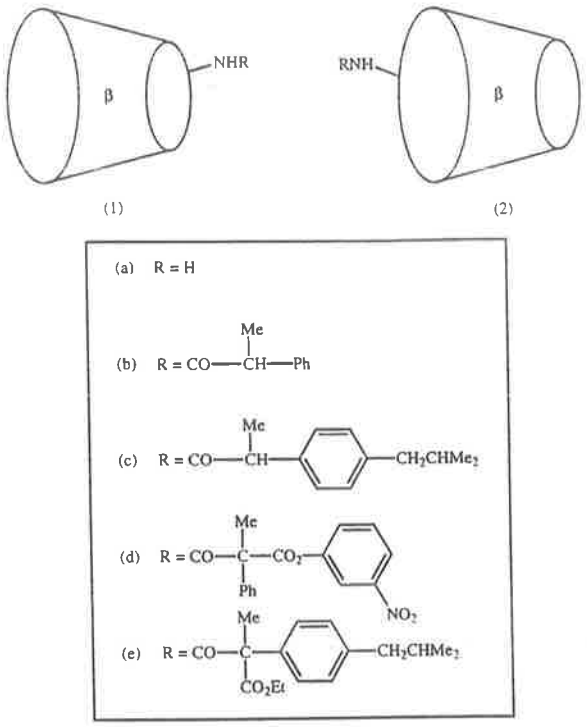
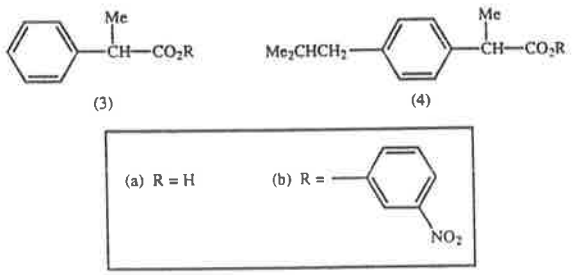


Fig. 1. A truncated cone is commonly used to represent a cyclodextrin. A substituent drawn at the narrow end of the cone indicates that it replaces a C 6 hydroxy group. In this paper, a substituent drawn at the wide end of the cone indicates that it replaces a C 3 hydroxy group, with inversion of stereochemistry at C 2 and C 3 of the modified D-glucopyranose residue.



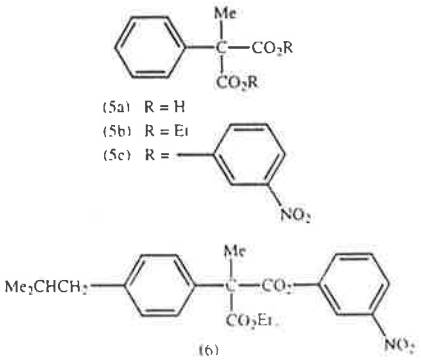
triethylamine. Each of the amino-substituted cyclodextrins (1a) and (2a) was treated with 8 mol. equiv. of the phenylpropanoate ester (3b) in pyridine. The large excess of the ester (3b) was used in order to be able to gauge the diastereoselectivity of these processes. Cyclodextrin-derived products were separated from the reaction mixtures by precipitation with ether, and unreacted amines (1a) and (2a) were removed by ion-exchange chromatography. In this manner, the cyclodextrin amides (1b) and (2b) were obtained as colourless crystalline solids, in yields of 60 and 48%, respectively.

Each of the amides (1b) and (2b) showed a single peak on h.p.l.c. analysis, but each was shown to be a 2 : 1 mixture of diastereomers, from the ^{1}H and ^{13}C n.m.r. spectra. In the ^{13}C n.m.r. spectra, duplicate signals in a ratio of approximately 2 : 1 were observed for the carbamoyl, methyl and benzylic carbon signals. The ^{1}H n.m.r. spectrum of the amide (1b) at 298 K showed doublets at δ 1·30 and 1·24, in a 2 : 1 ratio, for the methyl hydrogens of the diastereomers. The ^{1}H n.m.r. spectrum of the amide (2b) at 298 K was poorly resolved and the methyl hydrogens of both diastereomers gave rise to a broad signal at δ 1·35. When the ^{1}H n.m.r. spectrum was recorded at 343 K, the resolution was greatly improved and two distinct doublets corresponding to the methyl hydrogens of the diastereomers were observed at δ 1·37 and 1·42, in the ratio 2 : 1. The effect of the change in temperature on the resolution of the ^{1}H n.m.r. spectrum can be attributed to the inclusion behaviour of the aryl substituent of the cyclodextrin (2b). It seems likely that at lower temperatures the aryl substituent is complexed within the cyclodextrin annulus, while at higher temperatures the substituent dissociates from the cavity. This temperature-dependent self-inclusion behaviour has been reported previously,[16,17] and with naphthylmethyl cyclodextrin ethers the extent of self-complexation has been shown to be greater with O 2 substituents than with the O 6 isomers. This is consistent with the observation that the temperature required to obtain a well resolved spectrum of the amide (2b) is higher than that needed with the propanamide (1b).

Treatment of the amines (1a) and (2a) with the Ibuprofen ester (4b), as described above for the reactions of the ester (3b), afforded the amides (1c) and (2c) as colourless crystalline solids, in yields of 76 and 52%, respectively. Temperatures of 347 and 377 K were required to obtain well resolved ^{1}H n.m.r. spectra of the amides (1c) and (2c), respectively. These higher temperatures compared to those needed to record well resolved spectra of the amides (1b) and (2b) indicate the preferred complexation of the Ibuprofen moiety relative to that of the phenylpropanoate. This reflects the association constants of the β-cyclodextrin with the anions of the (*R*)- and (*S*)-isomers of the acid (3a),[18] and racemic Ibuprofen (4a),[19] of 63±8, 52±5, and 2900±500 dm^3 mol^{-1}, respectively. As with the amides (1b) and (2b), of the Ibuprofen derivatives (1c) and (2c), the C 3-substituted cyclodextrin derivative (2c) shows a greater tendency for self-inclusion. Diastereomers of each of the amides (1c) and (2c) were evident from the ^{1}H and ^{13}C n.m.r. spectra, although each showed only a single peak on h.p.l.c. analysis. The ^{1}H n.m.r. spectrum of the amide (1c) showed duplicate signals in a 2 : 1 ratio for the benzylic methyl group and the aromatic protons, while that of the amide (2c) showed duplicate signals of equal intensity for the aromatic protons. No spectroscopic discrimination of the diastereomers was observed in the ^{13}C n.m.r. spectrum of the amide (2c), but the C 6-substituted analogue (1c) showed pairs of signals for the carbons of the carbamoyl and α-methyl groups.

In order to assign the stereochemistry of the diastereomers of the amide (1c), the amine (1a) was treated with the (*R*)-enantiomer of the ester (4b), prepared from the (*R*)-enantiomer of Ibuprofen (4a), which had been obtained by resolution of the methyl ester of Ibuprofen (4a) with horse liver acetone powder.[20] The product of this reaction was found to be identical with the major diastereomer of the amide (1c) obtained from the reaction of the racemic ester (4b). Due to the low diastereoselectivity in the reactions to give the amides (1b) and (2b), and the absence of stereoselectivity in the synthesis of the amide (2c), no attempt was made to assign the stereochemistry of the isomers of these compounds.

The amines (1a) and (2a) were also treated with the ester (3b) in aqueous solution instead of pyridine, to examine the effect of solvent. Eighty equivalents of the ester (3b) were used with the amine (1a), at room temperature in sodium borate buffer, pH 9·0, but none of the amide (1b) was detected on analysis of this reaction mixture by h.p.l.c. and n.m.r. spectroscopy. A similar reaction of the amine (2a) with the ester (3b), in aqueous sodium bicarbonate, pH 8·0, afforded a 2:1 mixture of the diastereomers of the amide (2b). The outcome of these reactions can be attributed to complexation of the nitrophenyl moiety of the ester (3b) in the annulus of each of the amines (1a) and (2a) under the aqueous conditions. In each case the orientation in the cyclodextrin cavity is likely to be such that the ester functional group is located at the wide end of the annulus, near the amino substituent of the C3 amine (2a), but distant from that substituent of the C6 amine (1a). This orientation of the nitrophenyl moiety has been established in extensive studies of transesterification reactions involving cyclodextrins,[12,21,22] and it accounts for reaction occurring in the complex of the ester (3b) with the amine (2a), but not in the case of the amine (1a) which constitutes non-productive binding.[12] Presumably the ester (3b) is destroyed in the latter case through hydrolysis in free solution. It is not clear if the reactions of the amines (1a) and (2a) with the ester (3b) in pyridine involve complexation but, in any event, the diastereoselectivity of the processes is low.



(6)

As an alternative synthesis of the amides (1b,c) with the possibility of diastereoselectivity, hydrolysis and decarboxylation reactions of the malonate derivatives (1d,e) were also examined. Diethyl phenylmalonate was methylated with sodium methoxide/methyl iodide[23] to give diethyl methyl(phenyl)malonate (5b). Base hydrolysis of the diester (5b) followed by acidification gave methyl(phenyl)malonic acid (5a), which was converted into the bis(nitrophenyl) ester (5c) by treatment with thionyl chloride, followed by 3-nitrophenol in the presence of triethylamine. The diester (6) was synthesized by alkylation of the dianion of Ibuprofen (4a) with ethyl chloroformate,[24] followed by treatment with thionyl chloride and then 3-nitrophenol in the presence of triethylamine. The malonate derivative (1e) was synthesized in 62% yield by treatment of the amine (1a) with 5 mol. equiv. of the diester (6) in pyridine. The corresponding phenylpropanoate derivative (1d) was prepared in 74% yield, by using a similar procedure and 8 mol. equiv. of the diester (5c). The ^{1}H n.m.r. spectrum of the conjugate (1e) recorded at 343 K showed signals for two diastereomers in the ratio 1:1. The ^{1}H and ^{13}C n.m.r. spectra of the malonate (1d) showed no evidence of isomers, but it seems unlikely that this indicates formation of only a single diastereomer. Instead, it seems more likely that the isomers are not distinguished spectroscopically. Hydrolysis and subsequent decarboxylation of the malonates (1d) and (1e) afforded the amides (1b) and (1c), in 53 and 61% yield, respectively. These samples of the amides (1b,c) were identical to those obtained from reactions of the amine (1a) with the esters (3b) and (4b), even to the extent that each was a 2:1 mixture of the diastereomers.

Experimental

General experimental details have been reported previously.[25] Infrared spectra were recorded on a Hitachi 270-30 spectrometer, either as Nujol mulls or as liquid films between sodium chloride plates. Flash chromatography[26] was performed by using Merck-Kieselgel 60 (230–240 mesh ASTM). Ion-exchange chromatography was carried out by using Pharmacia Sephadex SP-C 25, in the acidic form. High-performance liquid chromatography (h.p.l.c.) was carried out by means of a Waters 510 solvent delivery system coupled to a Waters 410 differential refractometer in conjunction with an ICI DP-700 data station. The column used was a Waters 3·9 by 300 mm carbohydrate analysis column, eluting at 1·5 cm^3 min^{-1} with acetonitrile/water (70%, v/v) (the t_r of a cyclodextrin derivative indicates the retention time relative to that of β-cyclodextrin). Microanalyses were performed by the Microanalytical Laboratory, University of Otago, or by Chemical and Microanalytical Services Pty Ltd, Melbourne. 6^A-Amino-6^A-deoxy-β-cyclodextrin (1a)[13,14] and 3^A-amino-3^A-deoxy-(2^A*S*,3^A*S*)-β-cyclodextrin (2a)[15] were prepared as reported previously.

3-Nitrophenyl 2-Phenylpropanoate (3b)

A mixture of 2-phenylpropanoic acid (3a) (1·0 g, 6·7 mmol) and thionyl chloride (5·0 g, 42 mmol) was stirred at room temperature for 24 h, then it was concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (50 cm^3) and 3-nitrophenol (1·85 g, 13·3 mmol) was added in

one portion, followed by dropwise addition of triethylamine (1·35 g, 13·4 mmol) over 10 min. The resultant mixture was stirred at room temperature for 30 min, then it was concentrated under reduced pressure. Flash chromatography of the residue, eluting with dichloromethane/hexane (9/1, v/v), gave an oil which was distilled to yield the *ester* (3b) (1·31 g, 72%) as a clear light-yellow oil, b.p. 190–193°/0·4 mm (block) (Found: C, 66·2; H, 4·9; N, 5·1. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·1%). ν_{max} (film) 1736 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 1·66, d, J 7·2 Hz, 3H; 4·04, q, J 7·2 Hz, 1H; 7·4–8·2, m, 9H. ^{13}C n.m.r. ($CDCl_3$) δ 18·4, 45·6, 117·2, 120·8, 127·5, 127·7, 127·9, 129·0, 130·0, 139·4, 151·2, 172·5.

3-Nitrophenyl 2-[4-(2-Methylpropyl)phenyl]propanoate (4b)

The *ester* (4b) was prepared in 80% yield, as a clear light-yellow oil, b.p. 185–188°/0·2 mm (block), by treatment of Ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid) (4a) with thionyl chloride, then 3-nitrophenol and triethylamine, as described above for the synthesis of the ester (3b) (Found: C, 69·8; H, 6·6; N, 4·3. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%). ν_{max} (film) 1745 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 0·90, d, J 6·6 Hz, 6H; 1·61, d, J 7·2 Hz, 3H; 1·9, m, 1H; 2·47, d, J 7·2 Hz, 2H; 3·97, q, J 7·2 Hz, 1H; 7·16 and 7·36, ABq, J 7·8 Hz, 4H; 7·3–8·1, m, 4H. ^{13}C n.m.r. ($CDCl_3$) δ 18·4, 22·2, 30·1, 44·7, 45·0, 116·8, 120·6, 126·8, 127·5, 129·0, 129·9, 136·8, 141·1, 148·7, 151·2, 172·5.

The (*R*)-enantiomer of the ester (4b) was prepared in a similar manner from (*R*)-2-[4-(2-methylpropyl)phenyl]propanoic acid.[20]

Diethyl Methyl(phenyl)malonate (5b)

A solution of sodium ethoxide was prepared by adding sodium (2·0 g, 87 mmol) to dry ethanol (200 cm^3). Diethyl phenylmalonate (15·0 g, 64 mmol) was added to this solution in one portion at room temperature and the mixture was stirred at room temperature for 20 min. Methyl iodide (12·5 g, 88 mmol) was then added and the mixture was stirred at room temperature for 1 h, then it was concentrated under reduced pressure. The residue was dissolved in dichloromethane (150 cm^3) and the organic solution was washed with water (2×150 cm^3), dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and the residue was distilled to give the malonate (5b) (11·5 g, 74%) as a clear light-yellow liquid, b.p. 195–198°/28 mm (block) (lit.[27] 156–158°/10 mm). ^1H n.m.r. ($CDCl_3$) δ 1·30, t, J 7·5 Hz, 6H; 2·10, s, 3H; 4·40, q, J 7·5 Hz, 4H; 7·6, m, 5H.

Methyl(phenyl)malonic Acid (5a)

A mixture of aqueous sodium hydroxide (1·2 mol dm^{-3}, 100 cm^3) and diethyl methyl(phenyl)malonate (5b) (10·0 g, 41 mmol) in ethanol (400 cm^3) was stirred at room temperature for 24 h, then it was concentrated under reduced pressure. The residue was dissolved in water (50 cm^3), and the solution was cooled to 0° and acidified to pH 1 with concentrated sulfuric acid, while maintaining the temperature below 10°. The acidified solution was extracted with diethyl ether (3×100 cm^3) and the combined extracts were dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure to give the diacid (5a) (4·0 g, 52%) as a colourless solid, m.p. 154–156° (lit.[27] 156–157°). ^1H n.m.r. ($CDCl_3$) δ 1·75, s, 3H; 7·4, m, 5H.

Bis(3-nitrophenyl) Methyl(phenyl)malonate (5c)

The *malonate* (5c) was prepared in 31% yield, as a clear yellow oil, by treatment of the diacid (5a) with thionyl chloride, then 3-nitrophenol and triethylamine, as described above for the synthesis of the ester (3b) (Found: C, 60·4; H, 3·7; N, 6·2. $C_{22}H_{16}N_2O_8$ requires C, 60·6; H, 3·7; N, 6·4%). ν_{max} (film) 1762 cm^{-1}. Mass spectrum m/z 436 (M^+). ^1H n.m.r. ($CDCl_3$) δ 2·27, s, 3H; 7·5–8·2, m, 13H. ^{13}C n.m.r. ($CDCl_3$) δ 21·8, 59·1, 117·0, 121·4, 127·2, 127·6, 128·8, 128·9, 130·3, 138, 139·9, 150·7, 169·0.

Ethyl 3-Nitrophenyl Methyl[4-(2-methylpropyl)phenyl]malonate (6)

A solution of lithium diisopropylamide in tetrahydrofuran (1·07 mol dm^{-3}, 50 cm^3) was added dropwise over 15 min to a solution of Ibuprofen (4a) (5·0 g, 24·3 mmol) in tetrahydrofuran (250 cm^3), under nitrogen at 0°. The resultant solution was stirred at 0° for 20 min, then ethyl chloroformate (2·8 g, 25·8 mmol) was added and the mixture was allowed to warm to room temperature and stirred for a further 30 min at room temperature. The mixture was then concentrated under reduced pressure and the residue was dissolved in water (100 cm^3). The aqueous solution was acidified with concentrated hydrochloric acid at 0° and the acidified solution was extracted with dichloromethane (3×150 cm^3). The combined organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure to give crude ethyl methyl[4-(2-methylpropyl)phenyl]malonate as a yellow oil. This material was treated with thionyl chloride, then 3-nitrophenol and triethylamine, as described above for the synthesis of the ester (3b), to give the *malonate* (6) (2·2 g, 23%) as a yellow oil (Found: C, 66·1; H, 6·2; N, 3·5. $C_{22}H_{25}NO_6$ requires C, 66·2; H, 6·3; N, 3·5%). ν_{max} (film) 1740, 1765 cm^{-1}. Mass spectrum m/z 400 ($M+H^+$). ^1H n.m.r. ($CDCl_3$) δ 0·90, d, J 6·5 Hz, 6H; 1·33, t, J 7·2 Hz, 3H; 1·6, m, 1H; 2·01, s, 3H; 2·48, d, J 7·2 Hz, 2H; 4·33, q, J 7·2 Hz, 2H; 7·17 and 7·36, ABq, J 8·4 Hz, 4H; 7·4–8·1, m, 4H. ^{13}C n.m.r. ($CDCl_3$) δ 14·1, 21·2, 22·4, 30·1, 45·0, 58·7, 62·2, 117·1, 121, 127·1, 127·8, 129·2, 130·1, 134·4, 141·7, 148·7, 151·1, 169·9, 171·0.

6^A-Deoxy-6^A-[2-(3-nitrophenoxycarbonyl)-2-phenylpropanamido]-β-cyclodextrin (1d)

The amine (1a) (0·7 g, 0·62 mmol) was added in three portions over 1 h to a solution of the malonate (5c) (2·18 g, 5 mmol) in pyridine (8 ml). The mixture was stirred for 3 h at room temperature before it was added to diethyl ether (30 cm^3), dropwise and with vigorous stirring. The resultant precipitate was collected and washed with diethyl ether (50 cm^3), then it was dried under vacuum to give the *amide* (1d) (0·66 g, 74%) as a colourless powder (Found: C, 47·3; H, 6·2; N, 2·0. $C_{58}H_{82}N_2O_{39}.2H_2O$ requires C, 47·5; H, 5·9; N, 1·9%). ν_{max} (Nujol) 1658, 1712 cm^{-1}. Mass spectrum m/z 1432 ($M+H^+$). ^1H n.m.r. (CD_3SOCD_3, 398 K) δ 1·97, s, 3H; 3·2–3·6, 4·4–4·5, 4·8–4·9, 5·6–5·8, m, 70H; 7·3–8·4, m, 9H. ^{13}C n.m.r. (CD_3SOCD_3) δ 22·0, 60·3, 72·6–73·5, 81·8, 102·5, 117·0–151·4, 171·1, 171·8.

6^A-Deoxy-6^A-(2-ethoxycarbonyl-2-[4-(2-methylpropyl)phenyl]propanamido)-β-cyclodextrin (1e)

A mixture of the malonate (6) (1·24 g, 3·1 mmol) and the amine (1a) (0·7 g, 0·62 mmol) in pyridine (7 cm^3) was stirred at room temperature for 3 h, then it was added dropwise to diethyl ether (35 cm^3) with vigorous stirring. The resultant precipitate was collected and washed with diethyl ether (50 cm^3) and acetone (50 cm^3), then it was dissolved in water (15 cm^3) and the solution was applied to an ion-exchange column. Elution with water and concentration of the eluate under reduced pressure gave the *cyclodextrin* derivative (1e) (534 mg, 62%) as a colourless crystalline solid (Found: C, 48·0; H, 7·0; N, 0·9. $C_{58}H_{91}NO_{37}.3H_2O$ requires C, 48·1; H, 6·8; N, 1·0%). H.p.l.c. t_r 0·6. ν_{max} (Nujol) 1656, 1712 cm^{-1}. Mass spectrum m/z 1417 ($M+Na^+$). ^1H n.m.r. (CD_3SOCD_3, 343 K) δ 0·8, m, 6H; 1·21, t, J 7·3 Hz, 3H; 1·72, s, 0·5×3H; 1·75, s, 0·5×3H; 2·0, m, 1H; 2·5, m, 2H; 3·2–3·7, 4·8–5·0, m, 70H; 4·20, q, J 7·3 Hz, 2H; 7·13 and 7·18, ABq, J 7·9

Hz, 0·5×4H: 7·16 and 7·21, ABq, J 8·5 Hz, 0·5×4H. ^{13}C n.m.r. (CD_3SOCD_3) δ 21·4, 22·0, 29·4, 44·0, 58·6, 59·6, 60·8, 71·8–72·9, 81·3, 101·9, 126·7, 128·5, 136·6, 140·2, 171·2 (one diastereomer) and 171·9 (other diastereomer).

6^A-Deoxy-6^A-(2-phenylpropanamido)-β-cyclodextrin (1b)

Method A. A solution of the ester (3b) (1·0 g, 3·69 mmol) and the amine (1a) (0·5 g, 0·44 mmol) in pyridine (7 cm^3) was stirred at room temperature for 6 h, then it was diluted with diethyl ether (40 cm^3) with vigorous stirring. The resultant off-white precipitate was isolated and washed with diethyl ether (50 cm^3) and acetone (50 cm^3), then it was redissolved in water (5 cm^3). The aqueous solution was added dropwise to acetone (30 cm^3) with vigorous stirring and the resultant precipitate was collected and washed with acetone (50 cm^3), then it was dissolved in water (50 cm^3) and the solution was applied to an ion-exchange column. Elution with water and concentration of the eluate under reduced pressure gave the *cyclodextrin* derivative (1b) (355 mg, 60%) as a colourless solid (Found: C, 44·6; H, 6·6; N, 0·9. $C_{51}H_{79}NO_{35}.6H_2O$ requires C, 44·6; H, 6·7; N, 1·1%). H.p.l.c. t_r 0·6. ν_{max} (Nujol) 1652 cm^{-1}. Mass spectrum m/z 1267 (M+H$^+$). ^{1}H n.m.r. (CD_3SOCD_3, 298 K) δ 1·24, d, J 6·6 Hz, 0·33×3H; 1·30, d, J 7·2 Hz, 0·66×3H; 3·2–3·6, 4·5–4·8, 5·6–5·8, m, 70H; 7·2–7·3, m, 5H. ^{13}C n.m.r. ($CDCl_3$) δ 20·3 (minor) and 20·9 (major), 42·6, 47·8 (minor) and 48·2 (major), 62·2, 73·1–75·4, 82·6–85·8, 103·6–104·3, 129·2 129·3 129·5, 130·9, 131·1, 143·9, 144·0, 178·2 (minor) and 178·5 (major).

Method B. A suspension of the cyclodextrin derivative (1d) (0·3 g, 0·21 mmol) in water (8 cm^3) containing concentrated sulfuric acid (0·1 cm^3) was heated at reflux for 8 h, then it was cooled to room temperature and concentrated to approximately 2 cm^3 under reduced pressure. The residue was added dropwise to acetone (10 cm^3) with vigorous stirring and the precipitate which formed was collected by filtration and washed with acetone (10 cm^3) and diethyl ether (10 cm^3), then it was redissolved in water (10 cm^3). The solution was concentrated under reduced pressure to give the cyclodextrin derivative (1b) (144 mg, 53%) as a colourless solid, identical in all respects to the sample obtained as described above.

6^A-Deoxy-6^A-(2-[4-(2-methylpropyl)phenyl]propanamido)-β-cyclodextrin (1c)

Method A. The *cyclodextrin* derivative (1c) was prepared in 76% yield, as a colourless powder, through reaction of the ester (4b) with the amine (1a), as described above for the synthesis of the phenylpropanamide (1b) from the ester (3b) (Found: C, 46·0; H, 7·0; N, 1·0. $C_{55}H_{87}NO_{35}.6H_2O$ requires C, 46·2; H, 6·9; N, 1·0%). H.p.l.c. t_r 0·5. ν_{max} (Nujol) 1650 cm^{-1}. Mass spectrum m/z 1323 (M+H$^+$). ^{1}H n.m.r. (CD_3SOCD_3, 347 K) δ 0·86, d, J 6·6 Hz, 6H; 1·23, d, J 7·2 Hz, 0·33×3H; 1·30, d, J 7·2 Hz, 0·66×3H; 1·8, m, 1H; 2·41, d, J 7·2 Hz, 2H; 3·2–3·7, 4·2–4·8, m, 70H; 7·19 and 7·04, ABq, J 8·2 Hz, 0·66×4H; 7·21 and 7·06, ABq, J 8·0 Hz, 0·33×4H. ^{13}C n.m.r. (CD_3SOCD_3) δ 19·6 (minor) and 19·9 (major), 23·3, 30·8, 45·3, 60·9, 73·2–74·1, 82·6, 103·1, 128·0, 129·6, 133·0, 140·2, 140·3, 140·5, 140·7, 174·9 (minor) and 175·1 (major).

Repeating the reaction with the (*R*)-enantiomer of the ester (4b) gave the major diastereomer of the propanamide (1c).

Method B. Hydrolysis and decarboxylation of the cyclodextrin derivative (1e) as described above for the reaction of the phenylpropanamide (1d) gave a 61% yield of the cyclodextrin derivative (1c) as a colourless powder, identical in all respects to the sample obtained as described above.

3^A-Deoxy-3^A-(2-phenylpropanamido)-(2^{A}S,3^{A}S)-β-cyclodextrin (2b)

Treatment of the amine (2a) with the ester (3b) as described above for the synthesis of the cyclodextrin derivative (1b) from the ester (3b) gave a 48% yield of the *propanamide* (2b) as a colourless solid (Found: C, 44·1; H, 6·8; N, 1·0. $C_{51}H_{79}NO_{35}.7H_2O$ requires C, 44·0; H, 6·7; N, 1·0%). H.p.l.c. t_r 0·8. ν_{max} (Nujol) 1650 cm^{-1}. Mass spectrum m/z 1267 (M+H$^+$). ^{1}H n.m.r. (CD_3SOCD_3, 343 K) δ 1·37, d, J 6·3 Hz, 0·66×3H; 1·42, d, J 7·5 Hz, 0·33×3H; 3·3–4·1, 4·6–4·9, m, 70H; 7·3, m, 5H. ^{13}C n.m.r. (D_2O) δ 18·9 (minor) and 20·4 (major), 48·4 (major) and 49·7 (minor), 52·9 (minor) and 53·2 (major), 62, 77·0–70·4, 83·0–82·2, 102·9–105·2, 129·2, 129·4, 129·8, 131·0, 141·7, 144·7, 179·3 (minor) and 180·4 (major).

3^A-Deoxy-3^A-(2-[4-(2-methylpropyl)phenyl]propanamido)-(2^{A}S,3^{A}S)-β-cyclodextrin (2c)

Treatment of the amine (2a) with the ester (4b) as described above for the synthesis of the phenylpropanamide (1b) from the ester (3b) gave a 52% yield of the *cyclodextrin* derivative (2c) as an off-white powder (Found: C, 48·0; H, 7·4; N, 0·9. $C_{55}H_{87}NO_{35}.3H_2O$ requires C, 48·0; H, 6·8; N, 1·0%). H.p.l.c. t_r 0·8. ν_{max} (Nujol) 1650 cm^{-1}. Mass spectrum m/z 1323 (M+H$^+$). ^{1}H n.m.r. (CD_3SOCD_3, 377 K) δ 0·8, m, 6H; 1·42, d, J 7·2 Hz, 3H; 1·8, m, 1H; 2·44, d, J 6·3 Hz, 2H; 3·2–3·7, 4·6–4·9, m, 70H; 7·04 and 7·21, ABq, J 7·8 Hz, 0·5×4H; 7·08 and 7·25, ABq, J 7·2 Hz, 0·5×4H. ^{13}C n.m.r. (CD_3SOCD_3) δ 18·1, 23·7, 32·7, 47·2, 53·1, 61·9, 70·5–75·7, 83·0–83·3, 104·1–105·5, 129·6, 131·4, 142·5, 142·7, 178·9.

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A cyclodextrin to reverse the regioselectivity of nitrile oxide cycloaddition to a terminal alkene

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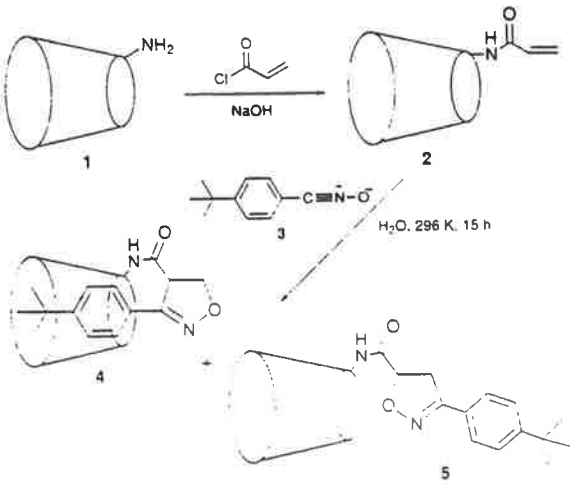
The 1,3-dipolar cycloaddition of 4-*tert*-butylbenzonitrile oxide with 6^A^-acrylamido-6^A^-deoxy-β-cyclodextrin in aqueous solution favours formation of the 4-substituted isoxazoline, in contrast to the normal predominance of the 5-substituted regioisomer from reactions of monosubstituted alkenes.

Nitrile oxide cycloaddition reactions with alkenes afford isoxazolines, which are of interest as versatile precursors of a range of 1,3-bifunctional compounds.[1] With mono- and trisubstituted alkenes the regioselectivity is usually determined by steric effects and the reactions afford almost exclusively 5- and 4,5,5-substituted isoxazolines, respectively. In order to reverse this regioselectivity, we envisaged that inclusion complexes of modified cyclodextrins[2] could be exploited. There have been reports that β-cyclodextrin affects the regioselectivity of nitrile oxide cycloadditions,[3] but it has now been demonstrated that these are in error and the cyclodextrin has no affect on the course of reaction in these examples.[4] Natural cyclodextrins have been used to accelerate Diels–Alder reactions of included guests and affect the distribution of products.[5] This occurs through self-assembly of the reactants within the cyclodextrin annulus, however our aim was to control the orientation of interaction between the reactants.

To develop this strategy, the dipolarophile was tethered to the cyclodextrin as the acrylamide **2** (Scheme 1). 4-*tert*-Butylbenzonitrile oxide **3** was selected as the dipole since alkyl-substituted aromatic compounds of this type are known to form thermodynamically stable inclusion complexes with β-cyclodextrin.[6] It was anticipated that inclusion of the hydrophobic moiety of the dipole **3** within the annulus of the modified cyclodextrin **2** would then establish the alignment for the cycloaddition (Fig. 1).



Scheme 1

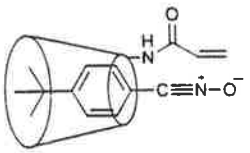
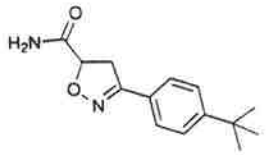


Fig. 1 Alignment of the dipole **3** and the dipolarophile **2** in the host–guest complex

Treatment of the amino-substituted cyclodextrin **1**[7] with acryloyl chloride under basic conditions gave the acrylamide **2**.† 4-*tert*-Butylbenzaldehyde reacted with hydroxylamine, then *N*-chlorosuccinimide,[8] to give the corresponding hydroximinoyl chloride, from which the nitrile oxide **3** was generated *in situ* by reaction with triethylamine. Thus the cycloaddition involved rapidly stirring a mixture of the acrylamide **2** (0.03 mmol) and the hydroximinoyl chloride (0.12 mmol) in water (2.5 ml) at 296 K for 1 h, then adding triethylamine (0.12 mmol) and stirring that mixture for a further 15 h. After work-up, this afforded a quantitative yield of a 2.3 : 1 mixture of the isoxazolines **4** and **5**,† which were separated using HPLC (Scheme 1). The ^{1}H NMR resonances due to the isoxazoline ring protons were assigned with the aid of double quantum filtered COSY experiments. When the cycloaddition reaction was repeated in DMF instead of water, the isoxazolines **4** and **5** were produced in 87% yield, as a 1 : 4 mixture.

The effect of the cyclodextrin annulus of the dipolarophile **2** was established by performing the cycloaddition of the nitrile oxide **3** with acrylamide. As expected, in either water or DMF, this reaction afforded only the 5-substituted isoxazoline **6**.†



6

Therefore, the production of the 4-substituted isoxazoline **4** in the reactions of the cyclodextrin derivative **2** highlights the effect of dipole **3**–dipolarophile **2** host–guest complex formation. As expected, this effect is greater in water than in DMF because the formation of cyclodextrin inclusion complexes is favoured in aqueous solutions.

Footnotes and References

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† *Selected data* for **2**: 79%; ^{1}H NMR (500 MHz; [^{2}H$_6$]DMSO): δ 7.95 (1 H, br s, NH), 6.26 (1 H, dd, *J* 11.0, 17.5), 6.03 (1 H, *J* 17.5), 5.55 (1 H, d, *J* 11.0). For **4**: HPLC (Waters carbohydrate analysis column with 80% MeCN in H_2O): t_R = 25 min; ^{1}H NMR (500 MHz; [^{2}H$_6$]DMSO): δ 7.96 (1 H, br s, NH), 7.46 (2 H, d, *J* 8.0, ArH), 7.37 (2 H, d, *J* 8.0, ArH), 4.63 (1 H, m, isoxazoline C(5)-H), 4.60 (1 H, m, isoxazoline C(5)-H'), 4.37 (1 H, m,

isoxazoline C(4)-H]. For **5**: HPLC (as for **4**): t_R = 20 min; ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.93 (1 H, br s, NH), 7.61 (2 H, d, *J* 8.5, ArH), 7.47 (2 H, d, *J* 8.5, ArH), 5.09 [1 H, m, isoxazoline C(5)-H], 3.62 [1 H, dd, isoxazoline C(4)-H], 3.50 [1 H, dd, *J* 6.5, 17.0, isoxazoline C(4)-H']. For **6**: ^{1}H NMR (500 MHz; [$^2H_6$]DMSO): δ 7.60 (2 H, d, *J* 8.5, ArH), 7.46 (2 H, d, *J* 8.5, ArH), 5.01 [1 H, dd, *J* 6.5, 11.5, isoxazoline C(5)-H], 3.62 [1 H, dd, isoxazoline C(4)-H], 3.50 [1 H, dd, *J* 6.5, 17.0, isoxazoline C(4)-H'].

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Planned 11/97 697 SYNTHESIS 1

Synthesis of Polyunsaturated β-Oxa Fatty Acids via Rhodium Mediated Carbenoid Insertion

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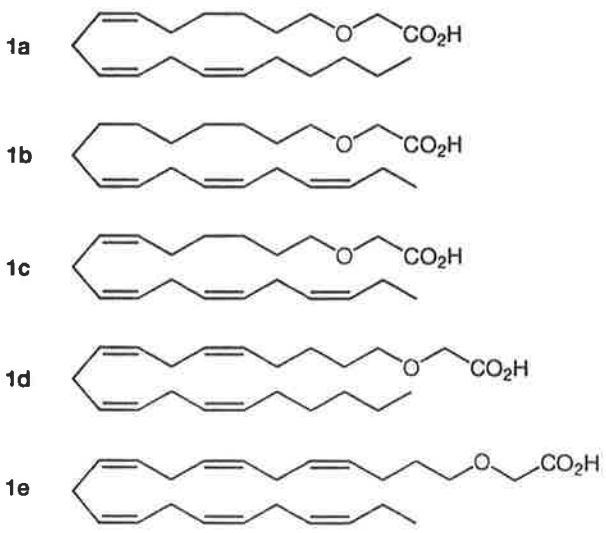
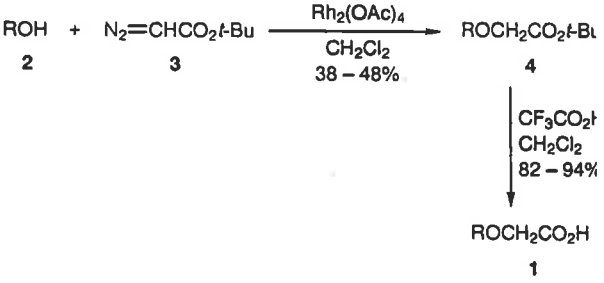
Polyunsaturated β-oxa fatty acids **1** are readily obtained from naturally derived polyunsaturated fatty alcohols **2** via rhodium(II) acetate-catalysed reaction with *tert*-butyl diazoacetate **3**, followed by ester cleavage.

In connection with our interest[1] in analogues of naturally occurring polyunsaturated fatty acids which are resistant to β-oxidation,[2] we sought synthesis of polyunsaturated β-oxa fatty acids, possessing an oxygen in the 3-position. Whilst saturated β-oxa fatty acids may be obtained *via* standard Williamson ether syntheses, such as reaction of an alkoxide with an α-halo acid,[3] polyunsaturated β-oxa fatty acids are inaccessible via this methodology, as both the product ethers and their polyene precursors are unstable to the vigorous conditions required for coupling of the reactant species.

O–H Insertion reactions of metallocarbenoids[4,5] provide efficient methodology for the synthesis of ethers under mild conditions. In particular, Teyssié and co-workers[6,7] have reported that the rhodium(II) acetate-catalysed O–H insertion reactions of unsaturated alcohols such as allyl alcohol[6] and propargyl alcohol[7] with diazoacetates as carbene precursor give very high ratios of O–H bond insertion to alkene or alkyne cycloaddition. Herein, we report application of this methodology in synthesis of the polyunsaturated β-oxa fatty acids **1a–e**, through rhodium(II) acetate-mediated carbenoid insertion reactions between *tert*-butyl diazoacetate (**3**)[8] and the unsaturated fatty alcohols **2a–e**, derived commercially from naturally occurring polyunsaturated fatty acids.



Treatment of dichloromethane solutions of each of the alcohols **2a–e** with in excess of two equivalents of *tert*-butyl diazoacetate (**3**) in the presence of a catalytic amount of rhodium(II) acetate afforded, after chromatography on silica, the β-oxa fatty acid esters **4a–e**, in 38–48 % yield (Scheme). Cleavage of the *tert*-butyl esters **4a–e** with trifluoroacetic acid in dichloromethane solution proceeded at room temperature to give the desired β-oxa fatty acids **1a–e** in 82–94 % yield, after chromatography. In this manner, the polyunsaturated β-oxa fatty acids **1a–e** were obtained in a high degree of purity. No complications arose from competing cyclopropanation or isomerisation of the alkenyl moieties, as was confirmed by comparison of ^1H and ^{13}C NMR spectral data of the product unsaturated fatty acid ethers **1a–e** with those of the respective starting materials **2a–e**.



a: R = (*Z,Z,Z*)-$CH_3(CH_2)_4(CH{=}CHCH_2)_3(CH_2)_4$–
b: R = (*Z,Z,Z*)-$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_7$–
c: R = (*all-Z*)-$CH_3CH_2(CH{=}CHCH_2)_4(CH_2)_5$–
d: R = (*all-Z*)-$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_3$–
e: R = (*all-Z*)-$CH_3CH_2(CH{=}CHCH_2)_6(CH_2)_2$–

Scheme

Gamma linolenyl alcohol (**2a**), linolenyl alcohol (**2b**), arachidonyl alcohol (**2d**) and docosahexaenyl alcohol (**2e**) were obtained from Nu-Chek Prep, Inc. (Elysian, MN, USA). (*all-Z*)-6,9,12,15-Octadecatetraenyl alcohol (**2c**) was prepared by $LiAlH_4$ reduction of methyl (*all-Z*)-6,9,12,15-octadecatetraenoate, obtained from Sigma Chemical Company. Flash column chromatographies were performed under positive N_2 pressure on Merck silica gel 60 (230–400 mesh).

***tert*-Butyl (*Z,Z,Z*)-(Octadeca-6,9,12-trienyloxy)acetate (4a):**
To a stirred solution of gamma linolenyl alcohol (**2a**) (1.16 g, 4.39 mmol) and rhodium(II) acetate dimer (9 mg, 0.5 % mol equiv) in CH_2Cl_2 (15 mL), at r.t. under N_2, was added dropwise a solution of *tert*-butyl diazoacetate (**3**)[8] (1.60 g, 11.2 mmol) in CH_2Cl_2 (5 mL). After the addition was complete, stirring was continued at r.t. for 2 h. The crude mixture was concentrated under a stream of anhyd N_2 and the residue was purified by flash column chromatography, eluting with hexane/Et_2O (9:1), to afford *tert*-butyl (*Z,Z,Z*)-(octadeca-6,9,12-trienyloxy)acetate (**4a**) as a colourless oil; yield: 747 mg (45 %).

IR (film): n = 3004, 2924, 2852, 1750, 1728, 1644, 1460, 1432, 1394, 1368, 1302, 1256, 1222, 1138, 846, 730 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.89 (3 H, t, J = 6.7 Hz, C18′-H_3), 1.35 (10 H, m, C3′-H_2, C4′-H_2, C15′-H_2, C16′-H_2, C17′-H_2), 1.48 (9 H, s, C(CH_3)$_3$), 1.62 (2 H, m, C2′-H_2), 2.07 (4 H, m, C5′-H_2, C14′-H_2), 2.81 (4 H, m, C8′-H_2, C11′-H_2), 3.51 (2 H, t, J = 6.6 Hz, C1′-H_2), 3.94 (2 H, s, C2-H_2), 5.38 (6 H, m, C6′-H, C7′-H, C9′-H, C10′-H, C12′-H, C13′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 169.82, 130.41, 130.10, 128.33, 128.21, 127.87, 127.64, 81.39, 71.72, 68.82, 31.52, 29.57, 29.49, 28.12, 27.18, 25.74, 25.63, 22.56, 14.04.

(*Z,Z,Z*)-(Octadeca-6,9,12-trienyloxy)acetic Acid (1a):
TFA (4 mL) was added to a solution of *tert*-butyl (*Z,Z,Z*)-(octadeca-6,9,12-trienyloxy)acetate **(4a)** (747 mg, 1.97 mmol) in CH_2Cl_2 (10 mL) under N_2, and the solution was stirred at r.t. for 2 h. The crude mixture was concentrated under a stream of anhyd N_2 and the residue was purified by flash chromatography on silica, eluting with hexane/Et_2O/HOAc (40:60:2), affording (*Z,Z,Z*)-(octadeca-6,9,12-trienyloxy)acetic acid **(1a)** as a colourless oil; yield: 595 mg (94%).

IR (film): n = 3008, 2924, 2852, 1730, 1649, 1460, 1434, 1392, 1375, 1344, 1220, 1140, 920, 686 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.89 (3H, t, J = 6.8 Hz, C18′-H_3), 1.33 (10 H, m, C3′-H_2, C4′-H_2, C15′-H_2, C16′-H_2, C17′-H_2), 1.61 (2 H, m, C2′-H_2), 2.05 (4 H, m, C5′-H_2, C14′-H_2), 2.81 (4 H, m, C8′-H_2, C11′-H_2), 3.60 (2 H, t, J = 6.6Hz, C1′-H_2), 4.17 (2 H, s, C2-H_2), 5.37 (6 H, m, C6′-H, C7′-H, C9′-H, C10′-H, C12′-H, C13′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 171.74, 130.45, 129.84, 128.40, 128.20, 128.10, 127.59, 72.13, 67.78, 31.52, 29.70, 29.33, 27.23, 27.09, 25.65, 25.55, 22.57, 14.06.

MS (EI): *m/z* (%) = 322 (M+, 24), 279 (2), 224 (3), 177 (7), 163 (9), 150 (28), 135 (22), 121 (20), 105 (26), 93 (59), 79 (91), 67 (100), 55 (64).

HRMS: *m/z* calc. for $C_{20}H_{34}O_3$ 322.2508, found M+ 322.2510.

$C_{20}H_{34}O_3$	calc.	C 74.49	H 10.63
(322.491)	found	74.46	10.51

tert-Butyl (Z,Z,Z)-(Octadeca-9,12,15-trienyloxy)acetate **(4b)**:
From linolenyl alcohol **(2b)** (1.06 g, 4.01 mmol), using the procedure described above for the preparation of **4a**, *tert*-butyl (*Z,Z,Z*)-(octadeca-9,12,15-trienyloxy)acetate **(4b)** was obtained as a colourless oil; yield: 728 mg (48%).

IR (film): n = 3004, 2924, 2852, 1750, 1720, 1644, 1462, 1432, 1394, 1370, 1306, 1258, 1222, 1138, 848, 724 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.98 (3 H, t, J = 7.5 Hz, C18′-H_3), 1.33 (10 H, m, C3′-H_2, C4′-H_2, C5′-H_2, C6′-H_2, C7′-H_2), 1.48 (9 H, s, C(CH_3)$_3$), 1.59 (2 H, m, C2′-H_2), 2.08 (4 H, m, C8′-H_2, C17′-H_2), 2.81 (4 H, m, C11′-H_2, C14′-H_2), 3.50 (2 H, t, J = 6.6 Hz, C1′-H_2), 3.95 (2 H, s, C2-H_2), 5.37 (6 H, m, C9′-H, C10′-H, C12′-H, C13′-H, C15′-H, C16′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 169.84, 131.94, 130.36, 128.26, 127.66, 127.13, 81.38, 71.83, 68.82, 29.65, 29.45, 29.25, 28.12, 27.24, 26.04, 25.63, 25.54, 20.55, 14.26.

(Z,Z,Z)-(Octadeca-9,12,15-trienyloxy)acetic Acid **(1b)**:
From *tert*-butyl (*Z,Z,Z*)-(octadeca-9,12,15-trienyloxy)acetate **(4b)** (728 mg, 1.92 mmol), using the procedure described above for the preparation of **1a**, (*Z,Z,Z*)-(octadeca-9,12,15-trienyloxy)acetic acid **(1b)** was obtained as a colourless oil; yield: 576 mg (93%).

IR (film): n = 3008, 2924, 2852, 1730, 1650, 1464, 1436, 1400, 1370, 1348, 1260, 1138, 1070, 1024, 866, 798, 694 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.97 (3 H, t, J = 7.5 Hz, C18′-H_3), 1.34 (10 H, m, C3′-H_2, C4′-H_2, C5′-H_2, C6′-H_2, C7′-H_2), 1.57 (2 H, m, C2′-H_2), 2.08 (4 H, m, C8′-H_2, C17′-H_2), 2.81 (4 H, m, C11′-H_2, C14′-H_2), 3.55 (2 H, t, J = 6.5 Hz, C1′-H_2), 4.12 (2 H, s, C2-H_2), 5.37 (6 H, m, C9′-H, C10′-H, C12′-H, C13′-H, C15′-H, C16′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 174.73, 131.92, 130.28, 128.24, 127.67, 127.10, 72.16, 67.70, 29.59, 29.41, 29.19, 27.20, 25.88, 25.60, 25.51, 20.53, 14.23.

MS (EI): *m/z* (%) = 322 (M+, 20), 279 (3), 266 (7), 191 (5), 177 (5), 163 (7), 149 (13), 135 (22), 121 (28), 108 (49), 95 (85), 79 (90), 67 (87), 55 (100).

HRMS: *m/z* calc. for $C_{20}H_{34}O_3$ 322.2508, found M+ 322.2510.

$C_{20}H_{34}O_3$	calc.	C 74.49	H 10.63
(322.491)	found	74.53	10.99

tert-Butyl (all-Z)-(Octadeca-6,9,12,15-tetraenyloxy)acetate **(4c)**:
From (*all-Z*)-octadeca-6,9,12,15-tetraenyl alcohol **(2c)** (29 mg, 111 μmol), using the procedure described above for the preparation of **4a**, *tert*-butyl (*all-Z*)-(octadeca-6,9,12,15-tetraenyloxy)acetate **(4c)** was obtained as a colourless oil; yield: 16 mg (38%).

IR (film): n = 3004, 2976, 2928, 2868, 1750s, 1722, 1644, 1478, 1460, 1394, 1370, 1310, 1258, 1142, 1040, 980, 848 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.98 (3 H, t, J = 7.5 Hz, C18′-H_3), 1.37 (4 H, m, C3′-H_2, C4′-H_2), 1.48 (9 H, s, C(CH_3)$_3$), 1.60 (2 H, m, C2′-H_2), 2.08 (4 H, m, C5′-H_2, C17′-H_2), 2.82 (6 H, m, C8′-H_2, C11′-H_2, C14′-H_2), 3.51 (2 H, t, J = 6.6 Hz, C1′-H_2), 3.95 (2 H, s, C2-H_2), 5.38 (8 H, m, C6′-H, C7′-H, C9′-H, C10′-H, C12′-H, C13′-H, C15′-H, C16′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 169.82, 132.00, 130.15, 128.49, 128.43, 128.01, 127.96, 127.78, 127.05, 81.39, 71.72, 68.81, 29.57, 29.49, 28.12, 27.18, 25.74, 25.63, 25.54, 20.55, 14.25.

(all-Z)-(Octadeca-6,9,12,15-tetraenyloxy)acetic Acid **(1c)**:
From *tert*-butyl (*all-Z*)-(octadeca-6,9,12,15-tetraenyloxy)acetate **(4c)** (16 mg, 42.5 μmol), using the procedure described above for the preparation of **1a**, (*all-Z*)-(octadeca-6,9,12,15-tetraenyloxy)acetic acid **(1c)** was obtained as a colourless oil; yield: 12 mg (88%).

IR (film): n = 3008, 2928, 2856, 1732, 1656, 1464, 1434, 1394, 1350, 1246, 1140, 1070, 1032, 912, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.97 (3 H, t, J = 7.5Hz, C18′-H_3), 1.36 (4 H, m, C3′-H_2, C4′-H_2), 1.61 (2 H, m, C2′-H_2), 2.08 (4 H, m, C5′-H_2, C17′-H_2), 2.82 (6 H, m, C8′-H_2, C11′-H_2, C14′-H_2), 3.56 (2 H, t, J = 6.6 Hz, C1′-H_2), 4.11 (2 H, s, C2-H_2), 5.35 (8 H, m, C6′-H, C7′-H, C9′-H, C10′-H, C12′-H, C13′-H, C15′-H, C16′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 174.90, 131.99, 129.96, 128.48, 128.34, 128.01, 127.89, 127.00, 72.03, 67.70, 29.34, 26.26, 25.59, 25.545, 20.51, 20.53, 14.25.

MS (EI): *m/z* (%) = 320 (M+, 14), 291 (5), 277 (4), 264 (9), 251 (5), 224 (5), 189 (5), 175 (18), 161 (21), 148 (30), 133 (32), 119 (41), 105 (48), 91 (68), 79 (100), 67 (72).

HRMS: *m/z* calc. for $C_{20}H_{32}O_3$ 320.2351, found M+ 320.2352.

$C_{20}H_{32}O_3$	calc.	C 74.96	H 10.06
(320.475)	found	74.79	10.20

tert-Butyl (all-Z)-(Eicosa-5,8,11,14-tetraenyloxy)acetate **(4d)**:
From arachidonyl alcohol **(2d)** (510 mg, 1.76 mmol), using the procedure described above for the preparation of **4a**, *tert*-butyl (*all-Z*)-(eicosa-5,8,11,14-tetraenyloxy)acetate **(4d)** was obtained as a colourless oil; yield: 288 mg (41%).

IR (film): n = 3008, 2924, 2852, 1750, 1730, 1648, 1456, 1432, 1394, 1370, 1298, 1258, 1224, 1138, 846, 728 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.89 (3 H, t, J = 6.7 Hz, C20′-H_3), 1.32 (8 H, m, C3′-H_2, C17′-H_2, C18′-H_2, C19′-H_2), 1.49 (9 H, s, C(CH_3)$_3$), 1.63 (2 H, m, C2′-H_2), 2.08 (4 H, m, C4′-H_2, C16′-H_2), 2.83 (6 H, m, C7′-H_2, C10′-H_2, C13′-H_2), 3.52 (2 H, t, J = 6.6 Hz, C1′-H_2), 3.94 (2 H, s, C2-H_2), 5.39 (8 H, m, C5′-H, C6′-H, C8′-H, C9′-H, C11′-H, C12′-H, C14′-H, C15′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 169.83, 130.48, 129.97, 128.56, 128.42, 128.08, 128.02, 127.96, 127.59, 81.40, 71.63, 68.83, 31.58, 29.29, 29.07, 28.14, 27.23, 27.01, 26.09, 25.66, 22.57, 14.09.

(all-Z)-(Eicosa-5,8,11,14-tetraenyloxy)acetic Acid **(1d)**:
From *tert*-butyl (*all-Z*)-(eicosa-5,8,11,14-tetraenyloxy)acetate **(4d)** (288 mg, 712 μmol), using the procedure described above for the preparation of **1a**, (*all-Z*)-(eicosa-5,8,11,14-tetraenyloxy)acetic acid **(1d)** was obtained as a colourless oil; yield: 223 mg (90%).

IR (film): n = 3008, 2928, 2852, 1734, 1654, 1462, 1434, 1400, 1380, 1348, 1240, 1216, 1136, 950, 684 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) d = 0.89 (3 H, t, J = 6.6 Hz, C20′-H_3), 1.37 (8 H, m, C3′-H_2, C17′-H_2, C18′-H_2, C19′-H_2), 1.64 (2 H, m, C2′-H_2), 2.07 (4 H, m, C4′-H_2, C16′-H_2), 2.82 (6 H, m, C7′-H_2, C10′-H_2, C13′-H_2), 3.58 (2 H, broad t, J = 6.0 Hz, C1′-H_2), 4.08 (2 H, s, C2-H_2), 5.38 (8 H, m, C5′-H, C6′-H, C8′-H, C9′-H, C11′-H, C12′-H, C14′-H, C15′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 173.39, 130.48, 129.66, 128.57, 128.26, 128.15, 128.04, 127.88, 127.54, 71.83, 68.67, 31.51, 29.51, 29.21, 27.22, 26.90, 26.06, 25.64, 22.56, 14.04.

MS (EI): m/z (%) = 348 (M+, 48), 307 (3), 294 (11), 277 (15), 250 (34), 217 (30), 203 (35), 190 (39), 177 (44), 164 (61), 150 (93), 119 (79), 105 (82), 91 (99), 79 (100), 67 (70).

HRMS: m/z calc. for $C_{22}H_{36}O_3$ 348.2664, found M+ 348.2673.

$C_{22}H_{36}O_3$	calc.	C 75.82	H 10.41
(348.529)	found	75.49	10.51

tert-Butyl (all-Z)-(Docosa-4,7,10,13,16,19-hexaenyloxy)acetate **(4e)**:

From docosahexaenyl alcohol **(2e)** (478 mg, 1.52 mmol), using the procedure described above for the preparation of **4a**, *tert*-butyl (*all-Z*)-(docosa-4,7,10,13,16,19-hexaenyloxy)acetate **(4e)** was obtained as a colourless oil; yield: 247 mg (38%).

IR (film): n = 3008, 2964, 2928, 2868, 1750, 1728, 1650, 1456, 1432, 1394, 1368, 1300, 1258, 1224, 1138, 848, 710 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.98 (3 H, t, J = 7.5 Hz, C22′-H_3), 1.48 (9 H, s, $C(CH_3)_3$), 1.67 (2 H, m, C2′-H_2), 2.11 (4 H, m, C3′-H_2, C21′-H_2), 2.83 (10 H, m, C6′-H_2, C9′-H_2, C12′-H_2, C15′-H_2, C18′-H_2), 3.52 (2 H, t, J = 6.6 Hz, C1′-H_2), 3.95 (2 H, s, C2-H_2), 5.37 (12 H, m, C4′-H, C5′-H, C7′-H, C8′-H, C10′-H, C11′-H, C13′-H, C14′-H, C16′-H, C17′-H, C19′-H, C20′-H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 169.77, 132.03, 129.41, 128.57, 128.39, 128.36, 128.24, 128.21, 128.16, 128.12, 128.02, 127.88, 127.02, 81.40, 71.08, 68.83, 29.53, 28.12, 25.63, 25.59, 25.54, 23.72, 20.55, 14.25.

(all-Z)-(Docosa-4,7,10,13,16,19-hexaenyloxy)acetic Acid **(1e)**:

From *tert*-butyl (*all-Z*)-(docosa-4,7,10,13,16,19-hexaenyloxy)acetate **(4e)** (247 mg, 576 μmol), using the procedure described above for the preparation of **1a**, (*all-Z*)-(docosa-4,7,10,13,16,19-hexaenyloxy)acetic acid **(1e)** was obtained as a colourless oil; yield: 176 mg (82%).

IR (film): n = 3008s 2960, 2928, 1730, 1656, 1434, 1392, 1346, 1244, 1140, 1068, 1048, 926m, 696 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): d = 0.97 (3 H, t, J = 7.5 Hz, C22′-H_3), 1.72 (2 H, m, C2′-H_2), 2.11 (4 H, m, C3′-H_2, C21′-H_2), 2.84 (10 H, m, C6′-H_2, C9′-H_2, C12′-H_2, C15′-H_2, C18′-H_2), 3.57 (2 H, t, J = 6.4 Hz, C1′-H_2), 4.12 (2 H, s, C2-H_2), 5.37 (12 H, m, C4′-H, C5′-H, C7′-H, C8′-H, C10′-H, C11′-H, C13′-H, C14′-H, C16′-H, C17′-H, C19′-H, C20′-H), 10.22 (1 H, broad, CO_2H).

^{13}C NMR (50 MHz, $CDCl_3$): d = 172.92, 132.02, 128.96, 128.72, 128.56, 128.46, 128.36, 128.26, 128.20, 128.15, 128.06, 127.84, 126.98, 71.42, 67.76, 29.24, 25.62, 25.56, 25.52, 23.57, 20.53, 14.23.

MS (EI): m/z (%) = 372 (M+, 5), 343 (3), 318 (4), 303 (18), 276 (3), 255 (5), 236 (7), 215 (11), 196 (14), 173 (19), 159 (25), 145 (31), 131 (37), 119 (45), 105 (57), 91 (84), 79 (100), 67 (72).

HRMS: m/z calc. for $C_{24}H_{36}O_3$ 372.2664, found M+ 372.2673.

$C_{24}H_{36}O_3$	calc.	C 77.38	H 9.74
(372.552)	found	77.13	10.03

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Preparation and characterization of 6^A-polyamine-mono-substituted β-cyclodextrins

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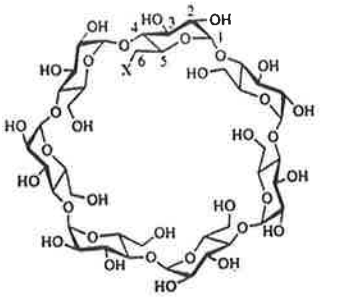
General syntheses for eleven β-cyclodextrins (cyclomaltoheptaoses) mono-substituted at the C6 position by a polyamine are described. The basis of the synthesis is the reaction of 6^A-*O*-(4-methylphenylsulfonyl)-β-cyclodextrin in the presence of KI in 1-methylpyrrolidin-2-one solution. This produces a clean product and obviates the substantial purification procedures which other preparative methods often entail. Systematic studies of the variations of the p*K*$_a$s of the protonated amine groups and the ^{13}C NMR spectra of the modified β-cyclodextrins with pH are reported.

Introduction

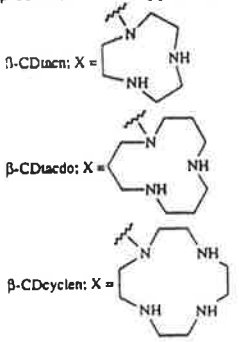
The ability of the naturally occurring cyclodextrins (cyclomaltopolyoses) to form host–guest complexes where a guest molecule enters the annulus of the host cyclodextrin is well established.[1–3] These complexing abilities may be modified by substitution at one or more of the C2, C3 and C6 sites;[1–6] the 6^A-polyamine-substituted β-cyclodextrins (β-CDX) discussed below and shown in Fig. 1 exemplify such substitutions at C6. Some of these β-CDXs have been studied because of their ability to form host–guest complexes,[2,7–10] and also because they coordinate metal ions to form binary metallocyclodextrins which sometimes show enantioselective and biomimetic characteristics in their interaction with guests in ternary metallocyclodextrins.[3,5–19]

We require a range of β-CDXs which can be produced in reasonable yield and high purity for our host–guest complex and metallocyclodextrin studies. Some of these β-CDXs have been reported previously. However, in our hands, the products obtained through these preparations usually required lengthy purification and this provided the impetus for our quest for an improved general synthetic method. Two major routes have been previously reported for the syntheses of the required β-CDXs. For the liquid polyamines, heating either β-cyclodextrin (β-CD),[18] 6^A-*O*-(4-methylphenylsulfonyl)-β-cyclodextrin (β-CDtos)[12] or 6^A-deoxy-6^A-iodo-β-cyclodextrin (β-CDI)[19] in excess polyamine in a sealed tube yields β-CDX which requires purification by lengthy chromatographic separation. For either the more expensive liquid or solid polyamines, reaction of β-CDtos[10–11,16,20] with the polyamine in *N*,*N*-dimethylformamide (DMF) under similar conditions yields β-CDX, but we found it difficult to avoid some formylation of the β-CDX which necessitated tedious separations using this method. We now report a simple general procedure for the synthesis of some reported β-CDXs where X is either the 2-aminoethylamino,[11,18] 3-aminopropylamino,[7–9] 2-(2-aminoethylamino)ethylamino,[12,14,19] 2-[2-(2-aminoethylamino)ethylamino]ethylamino,[12] 2-[bis(2-aminoethyl)amino]ethylamino[10] or 1,4,7,10-tetraazacyclododecan-1-yl[13,15] group bonded through nitrogen to the β-CD C6 carbon which in most cases have not been fully characterised, and some new β-CDXs that yield clean products under mild conditions.

The β-CDX's protonated amine groups exhibit a wide range of p*K*$_a$s which are likely to have a major influence on host–guest complexation and metal ion coordination reactions. Accordingly, a systematic study of p*K*$_a$ variation with the nature of X has been carried out in parallel with a study of the ^{13}C NMR spectral variation of β-CDXs with pH to gain an insight into the factors influencing these characteristics.



β-CDen: X = $NH(CH_2)_2NH_2$
β-CDpn: X = $NH(CH_2)_3NH_2$
β-CDbn: X = $NH(CH_2)_4NH_2$
β-CDhn: X = $NH(CH_2)_6NH_2$
β-CDdien: X = $NH(CH_2)_2NH(CH_2)_2NH_2$
β-CDdipn: X = $NH(CH_2)_3NH(CH_2)_3NH_2$
β-CDtrien: X = $NH(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$
β-CDtren: X = $NH(CH_2)_2N[(CH_2)_2NH_2]_2$



β-CDtacn: X =
β-CDtacdo: X =
β-CDcyclen: X =

Fig. 1 Schematic representations of the β-CDXs prepared. The individual C and H atoms of the polyamino substituent are labelled 1, 2, . . . *n* as distance from the β-CD moiety increases.

Results and discussion

Preparative aspects

The synthesis of 6^A-{2-[bis(2-aminoethyl)amino]ethylamino}-

Table 1 Reaction times, yields and analytical data for the preparation of β-CDXs

β-CDX	Reaction time *t*/h	Yield (%)	Elemental analyses (%)	C	H	N
β-CDen·3H_2O	6	55	Found:	42.70	6.67	2.18
			Calc.:	42.92	6.71	2.27
β-CDpn·3H_2O	4.5	42	Found:	43.65	6.85	2.39
			Calc.:	43.40	6.80	2.24
β-CDbn·2H_2O	4.5	52	Found:	44.88	7.17	2.17
			Calc.:	44.51	6.82	2.25
β-CDhn·3H_2O	5	51	Found:	44.95	7.27	1.88
			Calc.:	44.79	7.04	2.17
β-CDtrien·H_2O	7	40	Found:	44.83	6.89	4.42
			Calc.:	44.99	6.92	4.37
β-CDtren·3H_2O	4	57	Found:	43.84	7.58	4.40
			Calc.:	43.76	7.04	4.25
β-CDdien·H_2O	4.5	54	Found:	44.88	6.75	4.05
			Calc.:	44.62	6.75	3.39
β-CDdipn·2H_2O	6	50	Found:	45.17	6.52	3.12
			Calc.:	44.89	6.98	3.27
β-CDtacn·3H_2O	5	33	Found:	44.59	6.83	3.30
			Calc.:	44.34	6.90	3.23
β-CDtacdo·4H_2O	7	34	Found:	45.28	7.34	3.15
			Calc.:	45.03	7.18	3.08
β-CDcyclen·3H_2O	14	35	Found:	44.76	7.10	4.36
			Calc.:	44.71	7.05	4.17

6^A^-deoxy-β-cyclodextrin (β-CDtren) serves to illustrate preparative aspects which generally apply to the other β-CDX considered. Heating a mixture of β-CDtos and one equivalent of tris(2-aminoethyl)amine in DMF at 70 °C in a loosely stoppered flask for 24 h gave the expected β-CDtren in low yield. This product was contaminated with *N*-formylated material formed by transacylation between primary amino groups and the DMF solvent. Reaction of 6^A^-deoxy-6^A^-iodo-β-cyclodextrin (β-CDI) under the same conditions gave a more rapid conversion to the product but again there was a significant amount of the formylated product formed. When pyridine was used as the solvent in place of DMF, a much cleaner β-CDtren product was obtained, but it was isolated largely as a very stable host–guest complex of pyridine with β-CDtren. Pure β-CDtren was obtained from all three of the above preparative routes, but only after lengthy purification.

NMP is a dipolar aprotic solvent that has been shown to be superior to DMF for nucleophilic substitutions of toluene-*p*-sulfonates[25] but is more stable than DMF under either acid or base conditions.[26] When β-CDtos was heated at 70 °C for 4 h with 3.3 equiv. of tris(2-aminoethyl)amine and 0.1 equiv. of KI (to generate β-CDI *in situ*) in NMP, pure β-CDtren was obtained in 60% yield following a single precipitation with ethanol and product separation through ion exchange chromatography. There was no evidence for reaction between tris(2-aminoethyl)amine or β-CDtren and NMP. The formation of β-CDI in the reaction was shown by TLC of the reaction mixture during the course of the reaction. A series of β-CDXs, having either linear, branched or cyclic polyamine substituents, was prepared under the same conditions (Table 1). All of the β-CDXs prepared by this procedure were shown to be pure by TLC, ^1H and ^{13}C NMR spectroscopy and microanalysis. (A referee has pointed out that the cyclic solvent, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, has been employed in the nucleophilic substitution of a modified cyclodextrin.[27])

pK_a Variations

The two pK_as of β-CDXs increase as X is systematically changed from 1,2-diaminoethane (en) to 1,6-diaminohexane (hn) while the difference between the two pK_as decreases, and a similar trend is seen for the free diamine analogues (Table 2). The latter observation is attributable to increases in charge separation in the diprotonated species, decreasing electrostatic repulsion as the diamine increases in size. The increase in pK_a magnitude coincides with increases in hydrophobicity as the aliphatic chain lengthens and indicates a decrease in the ability of surrounding water to accept a proton from the protonated amine as overall hydration decreases. The two pK_as of β-CDXs are less than those of the analogous free diamine.

Table 2 pK_as[a] for some protonated 6^A^-polyamine-substituted β-cyclodextrins and the corresponding free polyamines in aqueous $NaClO_4$ (I = 0.10 mol dm^{-3}) at 298.2 K

Species	pK_a	Species	pK_a
β-CDenH_2^{3+}	9.42 ± 0.01	enH_2^{2+}	9.97 ± 0.03
	5.70 ± 0.02		7.16 ± 0.02
β-CDpnH_2^{3+}[b]	9.90 ± 0.1	pnH_2^{2+}	10.56 ± 0.02
	7.39 ± 0.04		8.97 ± 0.01
β-CDbnH_2^{3+}	10.26 ± 0.02	bnH_2^{2+}	10.91 ± 0.02
	8.06 ± 0.01		9.49 ± 0.01
β-CDhnH_2^{3+}	10.27 ± 0.03	hnH_2^{2+}	11.01 ± 0.06
	8.72 ± 0.01		10.04 ± 0.03
β-CDdienH_3^{3+}	9.52 ± 0.02	dienH_3^{3+}	9.78 ± 0.01
	7.63 ± 0.03		8.99 ± 0.03
	3.88 ± 0.07		4.32 ± 0.03
β-CDdipnH_3^{3+}	10.06 ± 0.02	dipnH_3^{3+}	10.56 ± 0.05
	8.44 ± 0.03		9.44 ± 0.06
	6.72 ± 0.03		7.54 ± 0.06
β-CDtrienH_4^{4+}	9.33 ± 0.02	trienH_4^{4+}	9.83 ± 0.04
	8.22 ± 0.03		8.93 ± 0.05
	5.61 ± 0.03		5.4 ± 0.05
	3.13 ± 0.07		3.0 ± 0.1
β-CDtrenH_4^{4+}[c]	9.85 ± 0.02	trenH_4^{4+}[d]	10.14
	8.99 ± 0.09		9.43
	6.89 ± 0.05		8.41
	2.6 ± 0.3		
β-CDtacnH_3^{3+}	10.0 ± 0.1	tacnH_3^{3+}	10.69 ± 0.02
	5.89 ± 0.07		7.01 ± 0.01
	2.4 ± 0.2		
β-CDtacdoH_3^{3+}	11.24 ± 0.04	tacdoH_3^{3+}[e]	12.60
	5.85 ± 0.03		7.57
	2.8 ± 0.1		2.41
β-CDcyclenH_4^{4+}	10.40 ± 0.01	cyclenH_4^{4+}[f]	10.6
	8.62 ± 0.02		9.6

[a] Errors represent one standard deviation. [b] Ref. 7. [c] Ref. 10. [d] Ref. 28. [e] Ref. 29. [f] Ref. 30.

The increased acidity of the protonated diamine moiety of β-CDX, by comparison with that of the free diamine analogue (Table 2), may partially arise from either the electronic and steric effects of the substitution of an amine nitrogen by β-CD or the difference in solvation experienced by the protonation sites in β-CDX and the free diamine or a combination of both. In addition, the diamine moiety in β-CDX is bound adjacent to the ring of six primary hydroxy groups delineating the narrow end of the cyclodextrin annulus such that hydrogen bonding between them and the amine nitrogens may decrease the basicity of the latter. This is supported to some extent through the observation that in basic solution more fine structure is seen in the ^{13}C NMR spectra of β-CDX (see Experimental) than is seen in acidic solution, consistent with the unprotonated diamine moiety hydrogen-bonding to the β-CD hydroxy groups more effectively than does its protonated analogue. (This is illustrated by the spectra of β-CDtacdo and β-CDcyclen in Figs. 2 and 3.) A similar interpretation has been presented for β-CDdien (where pK_a magnitude increases in the sequence -NH_3^+ < β-CD-NH_2^+- < -$(CH_2)_2$-NH_2^+-$(CH_2)_2$- as identified by ^{13}C NMR spectroscopy[19]) which together with its β-CDdipn homologue shows similar trends (Table 2) to those discussed above. Generally, similar trends in pK_a magnitudes are observed for the polyamine β-CDX as for their diamine analogues and their origins are probably similar.

^{13}C NMR Spectra

The substituent X on the β-CDX C6 carbon of the A glucopyranose unit renders it and the other six glucopyranoses (often

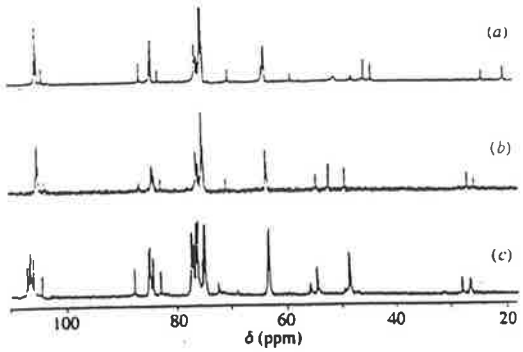


Fig. 2 75.47 MHz ^{13}C NMR spectra of β-CDtacdo in (*a*) 0.1 mol dm^{-3} HCl–D_2O, (*b*) HCl–D_2O, pH ~8.5 and (*c*) 0.1 mol dm^{-3} NaOH–D_2O‡

‡ δ_C(0.1 mol dm^{-3} HCl–D_2O) 104.9, 104.7, 104.6, 103.7 (C1), 86.3 (C4^), 84.3, 84.0, 82.8 (C4), 76.1, 76.0, 75.9, 75.6, 75.2, 75.0, 74.7, 74.6 (C2, C3, C5), 70.0 (C5^), 63.8, 63.3 (C6), 58.6, 50.9 (broad), 47.5, 45.2, 43.9 (C6^, tacdoC1, tacdoC3, tacdoC4), (25.4), 23.7, 19.9 (tacdoC2, tacdoC5); δ_C(HCl–D_2O, pH ~8.5) 104.8, 104.5, 103.4, 103.0 (C1), 86.4 (C4^), 84.1, 83.9, 83.7, 83.6, 82.5 (C4), 76.1, 76.0, 75.9, 75.6, 74.9, 74.7 (C2, C3, C5), 70.5 (C5^), 63.3, 63.2 (C6), 54.3 (C6^), 51.9, 49.0 (tacdoC1, tacdoC3, tadcoC4), 26.6, 25.4 (tacdoC2, tacdoC5); δ_C(0.1 mol dm^{-3} NaOH–D_2O) 106.9, 106.6, 106.4, 106.3, 105.8, 105.7, 104.3 (C1), 87.7 (C4^), 85.2, 85.1, 85.0, 84.9, 84.5, 84.3, 82.9 (C4), 77.4, 77.2, 77.1, 77.0, 76.9, 76.8, 76.7, 76.5, 76.3, 76.1, 75.4, 75.1, 74.9 (C2, C3, C5), 72.5 (C5^), 63.4, 63.1 (C6), 55.9 (C6^), 54.6 (tacdoC1), 48.7, 48.6 (tacdoC3, tacdoC4), 28.0, 26.5 (tacdoC2, tacdoC5).

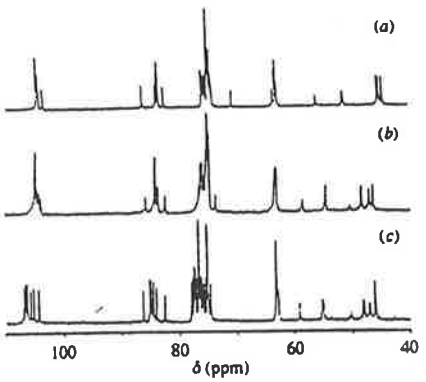


Fig. 3 75.47 MHz ^{13}C NMR spectra of β-CDcyclen in (*a*) 0.1 mol dm^{-3} HCl–D_2O, (*b*) HCl–D_2O, pH ~9 and (*c*) 0.1 mol dm^{-3} NaOH–D_2O§

§ δ_C(0.1 mol dm^{-3} HCl–D_2O) 104.5, 104.4, 104.3, 103.6 (C1), 86.4 (C4^), 84.0, 83.7, 83.6, 82.6 (C4), 75.9, 75.8, 75.6, 75.5, 75.3, 75.2, 74.9, 74.8, 74.7, 74.6, 74.4, 74.3, 74.2 (C2, C3, C5), 70.9 (C5^), 63.6, 63.2, 63.0 (C6), 56.2 (C6^), 51.5 (cyclenC1), 45.7, 45.4, 44.9 (cyclenC2-4); δ_C(HCl–D_2O, pH ~9) 104.9, 104.6, 104.3, 104.2, 103.8 (C1), 85.6 (C4^), 84.1, 83.6, 83.5, 82.2 (C4), 76.4, 76.1, 76.0, 75.8, 75.5, 75.4, 75.2, 75.1, 74.9, 74.6, 74.5, 73.5 (C2, C3, C5), 63.1, 63.0, 62.8 (C6), 58.3 (C6^), 54.3, (50.2), 48.2, 46.9, 46.2 (cyclenC); δ_C(0.1 mol dm^{-3} NaOH–D_2O) 106.9, 106.8, 106.6, 106.4, 105.7, 105.3, 104.4 (C1), 86.35 (C4^), 85.2, 85.0, 84.7, 84.6, 84.0, 82.6 (C4), 77.9, 77.7, 77.5, 77.4, 77.2, 77.1, 76.8, 76.6, 76.4, 76.1, 76.0, 75.8, 75.6, 75.2, 75.1, 74.6 (C2, C3, C5), 63.1, 62.9, 62.8 (C6), 59.0 (C6^), 55.0, (50.2), 48.0, 47.1, 46.1 (cyclenC).

labelled B–G) inequivalent, and as a result they may each exhibit six ^{13}C unique resonances to give a total of 42 resonances when the magnetic inequivalence is sufficiently large. Usually the ^{13}C NMR chemical shift differences between the seven glucopyranose units are insufficient for all 42 ^{13}C resonances to be separately observed. As the polyamine nitrogens of β-CDX protonate as the solution pH decreases, concomitant changes in the β-CDX ^{13}C NMR spectrum occur as has been briefly discussed above and as shown in the Experimental.

The ^{13}C NMR spectra of β-CDtacdo and β-CDcyclen at different pHs appear in Figs. 2 and 3, respectively, and illustrate the substantial spectral changes which occur with change in pH. At pH 1 resolution of the ^{13}C resonances of fully protonated β-CDtacdoH_1^{7+} and β-CDcyclenH_4^{4+} is relatively small consistent with the polyamine substituent swinging out from the β-CD moiety so that it interacts weakly if at all with the primary hydroxy groups and the differentiation of the seven glucopyranose units is minimised. At the highest pH, where β-CDtacdo and β-CDcyclen exist as the deprotonated neutral species, all seven C1 and C4 resonances are observed consistent with the polyamine substituents hydrogen bonding with the primary hydroxy groups of β-CD and maximising the differentiation between the seven glucopyranose units. This interpretation is in agreement with that presented for the similarly pH dependent ^{13}C NMR spectra of β-CDdien.[19]

Experimental

Materials and instrumental methods

The polyamines 1,2-diaminoethane (en), 1,3-diaminopropane (pn), 1,4-diaminobutane (bn), 1,6-diaminohexane (hn), 2-(2-aminoethylamino)ethylamine (dien), 3-(3-aminopropylamino)-propylamine (dipn), tris(2-aminoethyl)amine (tren) and 1,4,7,10-tetraazacyclododecane bis(dihydrogen sulfate) (cyclen·$2H_2SO_4$) were purchased from Aldrich and used without further purification. 2-[2-(2-Aminoethylamino)ethylamino]ethylamine tetrahydrochloride (trien·4HCl, Aldrich) was purified by two recrystallisations from ethanol–water.[21] 1,4,7-Triazacyclononane·3HCl and 1,5,9-triazacyclododecane·3HCl were prepared as in the literature.[22,23] HPLC grade 1-methylpyrrolidin-2-one (NMP, Aldrich) was dried by distillation from CaH_2 at reduced pressure. β-Cyclodextrin was a gift from Nihon Shokhuin Kako Co. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} silica on aluminium sheets and samples were eluted using a mixture of propan-2-ol–ethyl acetate–water–ammonium hydroxide (7:7:5:4). Compounds containing amino groups were detected by dipping the developed plate into a solution of 1% ninhydrin in ethanol and heating the plate. Cyclodextrins were detected by dipping the developed plate into a solution of 1.5% H_2SO_4 in ethanol and heating the plate. R_f values are reported as R_c (retention relative to β-CD).

Titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer, and an Orion 8172 Ross Sureflow combination pH electrode which was filled with 0.10 mol dm^{-3} $NaClO_4$. During all titrations a stream of fine nitrogen bubbles (previously passed through aqueous 0.10 mol dm^{-3} NaOH to remove any last traces of CO_2 and then 0.10 mol dm^{-3} $NaClO_4$ to ensure a constant water vapour pressure) was passed through the titration solution which was magnetically stirred and thermostatted at 298.2 ± 0.1 K in a water-jacketted 20 cm^3 titration vessel which was closed to the atmosphere with the exception of a small exit for the nitrogen stream. Deionised water, purified with a MilliQ-Reagent system to produce water with a specific resistance of >15 MΩ cm, was used in the preparation of all solutions after boiling to remove CO_2. Standardised 0.100 mol dm^{-3} NaOH was titrated against 10.00 cm^3 aliquots of solutions (0.002 mol dm^{-3} in the species of interest, 0.005 mol dm^{-3} in $HClO_4$ and 0.095 mol dm^{-3} in $NaClO_4$ in all titrations). The pK_as were determined using the programme SUPERQUAD[24] on a Digital Venturis 575 computer.

NMR spectra were recorded on a Bruker ACP300 spectrometer operating at 300 (^1H) and 75.47 MHz (^{13}C) for all β-CDXs except for 6^-{2-[bis(2-aminoethyl)amino]-ethylamino}-

6^A-deoxy-β-cyclodextrin (β-CDtren) where a Varian Gemini 200 spectrometer operating at 200 (^{1}H) and 50.29 MHz (^{13}C) was used.

General procedure for preparation of amino-substituted β-cyclodextrins

A solution of β-CDtos[11] (2.0 g, 1.55×10^{-3} mol), KI (0.025 g, 0.15×10^{-3} mol) and the amine (5×10^{-3} mol) in dry NMP (5 cm^3) was stirred at 70 °C in a lightly stoppered flask for 4–8 h. The resultant light yellow solution was cooled to room temperature and diluted with ethanol (100 cm^3). The resulting precipitate was collected by vacuum filtration, washed successively with ethanol (100 cm^3) and diethyl ether (50 cm^3) and dried under vacuum to give the crude product. This material was dissolved in water (10 cm^3) and loaded onto a column (4.5 × 4.5 cm) of H$^+$ form BioRex 70, 100–200 mesh (Biorad). The column was washed with water (400 cm^3) and β-CDX was eluted with 1 mol dm^{-3} NH_4OH. Fractions containing β-CDX were combined and evaporated to dryness under vacuum. The residue was dissolved in water and the solution evaporated under reduced pressure to remove excess ammonia (this procedure was repeated several times). The product was dried under vacuum over P_2O_5 to give β-CDX in yields of 25–60%. Specific preparative descriptions and characterisation data of β-CDtren, previously prepared by other methods,[10] and previously unreported β-CDtacdo are provided below. Similarly detailed preparative and characterisation data for the remaining β-CDXs shown in Fig. 1 is provided as supplementary data.†

6^A-{2-[Bis(2-aminoethyl)amino]ethylamino}-6^A-deoxy-β-cyclodextrin (β-CDtren)

A mixture of β-CDtos (2.048 g, 1.59×10^{-3} mol), tris(2-aminoethyl)amine (0.74 g, 5.07×10^{-3} mol) and KI (0.024 g) in NMP (5 cm^3) was treated according to the general procedure to give β-CDtren as a white powder (1.192 g, 59%). R_f 0.31; Electrospray-MS *m/z* 1263 (M^+) [Found: C, 43.84; H, 7.58; N, 4.40. Calc. for β-CDtren·3H_2O ($C_{48}H_{92}N_4O_{34}$): C, 43.76; H, 7.04; N, 4.25%]; δ_H(D_2O–NaOH, pH ~14) 5.00 (br s, 7H + solvent, H1), 3.5–3.8 (m, 26H, H3, H5, H6), 3.1–3.4 (m, 13H, H2, H4), 3.02 (t, *J* 9.0, 1H, H4^A), 2.85 (d, *J* 12.0, 1H, H6^A), 2.2–2.7 (m, 13H, H6^A', trenH); δ_H(D_2O, pH ~9) 5.05 (br s, 7H, H1), 3.8–4.0 (m, 26H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.41 (t, *J* 9.0, 1H, H4^A), 3.05 (d, *J* 11.4, 1H, H6^A), 2.4–2.9 (m, 13H, H6^A', trenH); δ_H(D_2O–HCl, pH ~1) 5.00 (s, 7H, H1), 4.10 (t, *J* 9.0, 1H, H5^A), 3.6–4.0 (m, 25H, H3, H5, H6), 3.4–3.6 (m, 14H, H2, H4), 2.9–3.4 (m, 14H, H6^A, trenH); δ_C(D_2O–NaOH, pH ~14), 107.0, 106.6, 106.4, 105.2 (C1), 87.6 (C4^A), 85.0, 84.8, 84.5, 83.9 (C4), 77.3, 76.4, 76.3, 75.2, 74.9 (C2, C3, C5), 70.9 (C5^A), 63.0 (C6), 59.8 (trenC3,3'), (56.9), 55.1 (C6^A), 50.5 (trenC2), 46.2 (trenC1), 41.0 (trenC4,4'); δ_C(D_2O, pH ~9) 104.7, 104.3 (C1), 86.4 (C4^A), 84.0, 83.6 (C4), 75.9 (C2), 74.9 (C3), 74.7 (C5), 73.3 (C5^A), 63.1 (C6), 58.7 (trenC3,3'), 55.7 (trenC2), 52.0 (C6^A), 48.7 (trenC1), 40.7 (trenC4,4'); δ_C(D_2O–HCl, pH ~1) 104.5, 103.8 (C1), 85.8 (C4^A), 84.2, 83.8, 83.4 (C4), 75.8, 75.5, 75.0, 74.8, 74.5 (C2, C3, C5), 70.2 (C5^A), 63.6, 63.1 (C6), 52.8 (trenC3,3'), 51.5 (C6^A), 51.3 (trenC2), 47.0 (trenC1), 38.6 (trenC4,4').

6^A-(1,5,9-Triazacyclododecan-1-yl)-6^A-deoxy-β-cyclodextrin (β-CDtacdo)

A mixture of 1,5,9-triazacyclododecane·3HCl[23] (1.451 g, 5.18×10^{-3} mol) and sodium hydroxide (0.625 g, 15.62×10^{-3} mol) in ethanol (30 cm^3) was stirred at room temp. for 90 min. The mixture was filtered and the collected solid was washed with ethanol (10 cm^3). The combined filtrates were evaporated under reduced pressure to give the free amine as a yellow oil. This was dissolved in NMP (5 cm^3) and β-CDtos (2.081 g, 1.61×10^{-3} mol) and KI (0.030 g) were added to the solution. The resultant mixture was treated according to the general procedure to give β-CDtacdo as a white powder (0.709 g, 34%). R_f 0.75; Electrospray-MS *m/z* 1288 (M^+) [Found: C, 45.28; H, 7.34; N, 3.15. Calc. for β-CDtacdo·4H_2O ($C_{51}H_{97}N_3O_{38}$): C, 45.03; H, 7.18; N, 3.08%]; δ_H(D_2O–NaOH, pH ~14) 4.9 (br s, 7H + solvent, H1), 4.14 (t, *J* 6.0, 1H, H5^A), 3.7–4.0 (m, 25H, H3, H5, H6), 3.17 (t, *J* 6.0, 1H, H4^A), 2.88 (d, *J* 15, 1H, H6^A), 2.64 (m, 13H, H6^A', tacdoH1, tacdoH3, tacdoH4), 1.66 (m, 6H, tacdoH2, tacdoH5); δ_H[D_2O–HCl (1:1), pH ~8.5] 5.09 (s, 7H + solvent, H1), 4.26 (t, *J* 9.0, 1H, H5^A), 3.8–4.2 (m, 25H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.39 (t, *J* 9.0, 1H, H4^A), 2.5–3.2 (m, 14H, H6^A, tacdoH1, tacdoH3, tacdoH4), 1.6–2.0 (m, 6H, tacdoH2, tacdoH5); δ_H[D_2O–HCl (1:2), pH ~6.0] (br s, 7H, H1), 4.25 (t, *J* 9.0, 1H, H5^A), 3.8–4.1 (m, 25H, H3, H5, H6), 3.5–3.7 (m, 13H, H2, H4), 3.43 (t, *J* 9.0, 1H, H4^A), 2.7–3.3 (m, 14H, H6^A, tacdoH1, tacdoH3, tacdoH4), 1.7–2.2 (m, 6H, tacdoH2, tacdoH5); δ_H(D_2O–HCl, pH ~1) 5.0 (br s, 7H + solvent, H1), 4.33 (br t, 1H, H5^A), 3.7–4.0 (m, 25H, H3, H5, H6), 3.2–3.6 (m, 27H, H2, H4, H6^A, tacdoH1, tacdoH3, tacdoH4), 2.2 (br, 6H, tacdoH2, tacdoH5).

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