CYCLODEXTRINS: MOLECULAR WHEELS FOR SUPRAMOLECULAR CHEMISTRY

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Declaration

I declare that the work presented within this thesis is original work that I carried out at the University of Adelaide and, to the best of my knowledge, contains no material previously published or written by another person, except where due reference is given. Part of the work described in Chapter 2 was carried out during my honours year, but accepting this no material contained herein has previously been submitted for the award of any other degree at this university or elsewhere.

I give consent to a copy of my thesis, when deposited in the University of Adelaide Library, being available for loan and photocopying.

Julia Lock

July, 2004

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Abstract

This work describes the construction and characterisation of a variety of supramolecular architectures based on cyclodextrins.

The trinorbornylmethyl-, cubyl-, dimethylcubyl- and adamantyl-substituted cyclodextrins **35**, **36**, **37** and **38** were prepared by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** by the 4-nitrophenyl esters **25**, **26**, **27** and **28**, respectively. 2D ^{1}H ROESY NMR spectra are consistent with the trinorbornylmethyl, cubyl and dimethylcubyl substituents of the cyclodextrins **35-37** being self-included in D_2O to give **35'-37'**, but with the adamantyl substituent of **38** being too large to be self-included. The mechanism for the acylations involves reaction of the 4-nitrophenyl esters with the aminohexylamine substituent of **34** outside of the cyclodextrin; subsequent inclusion of the substituents of **35-37** in aqueous solution produces **35'-37'**.

The azacoronand-substituted cyclodextrins **43-46** were prepared by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** by either of the 4-nitrophenyl esters **41** or **42**. 2D ^{1}H ROESY NMR spectra are consistent with the substituents of the modified β-cyclodextrins **45** and **46** being self-included to give **45'** and **46'** in D_2O at pD 9, but with the substituents of the modified α-cyclodextrins **43** and **44** not being self-included in aqueous solution. In D_2O at pD 9, the substituents of **43** and **44** include in the annulus of β-cyclodextrin to form the [2]-pseudorotaxanes βCD.**43** and βCD.**44**. β-Cyclodextrin includes the central section of the hexyl chain of **43** or **44**. Metal-locking of the azacoronand moiety of **45/45'** was investigated, and pK_a values of 5.84 and 8.49 and metal complex stability constants (log(K) values) of <2 ([**45/45'**.Ca]$^{2+}$), 6.34 ([**45/45'**.Zn]$^{2+}$) and 5.38 ([**45/45'**.La]$^{3+}$) were determined for this system.

The water-soluble axles **50** and **51** were prepared and shown by 2D ^{1}H ROESY NMR experiments to form the [2]-pseudorotaxanes βCD.**50**, αCD.**51** and βCD.**51** in aqueous solution. The cobalt(III)-blocked α-cyclodextrin and β-cyclodextrin [2]-rotaxanes **57**, **58** and **59** were prepared in good yields, by the reaction of the terminal tetramine groups of the axle in each of the corresponding [2]-pseudorotaxanes with sodium triscarbonatocobalt(III). 2D ^{1}H ROESY NMR experiments provided evidence for the structures of the [2]-rotaxanes. The

β-cyclodextrin [2]-rotaxanes **57** and **59** were obtained as almost pure products directly from the reaction mixtures. Each of the [2]-rotaxanes was further purified as the chloro complex analogue. The [2]-rotaxane **57** can also be formed by a slippage mechanism, while the [2]-rotaxane **59** forms very slowly by slippage and the α-cyclodextrin [2]-rotaxane **58** does not form by such a mechanism. Work towards the synthesis of a [2]-rotaxane containing the urea-linked β-cyclodextrin dimer *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** was carried out, but was hindered by the low water-solubility of the corresponding [2]-pseudorotaxane.

Photo-controlled molecular devices were constructed utilising the urea-linked cyclodextrin dimers *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** and *N*-(6^A-deoxy-α-cyclodextrin-6^A-yl)-*N'*-(6^A-deoxy-β-cyclodextrin-6^A-yl)urea **77** and the stilbenes *trans*/*cis*-4-*t*-butyl-4'-oxystilbene **78**$^-$/**80**$^-$ and *trans*/*cis*-4-*t*-butyl-4'-carboxystilbene **79**$^-$/**81**$^-$. In these molecular devices, one annulus of the cyclodextrin dimer is occupied by the *t*-butylphenyl end of the stilbene, while the other annulus is alternately occupied and vacated by the phenoxy or benzenecarboxy end of the stilbene, as the stilbene is isomerised between the *trans* and *cis* configurations. 4-Methylbenzoate **94**, 4-methylphenolate **95** and 4-methylbenzenesulfonate **96** were utilised as second guests which are alternately included and excluded from one annulus of the cyclodextrin dimer during the stilbene isomerisation reactions to give rise to three-component molecular devices. The switching of the devices was followed by 2D ^{1}H ROESY NMR and UV/Vis experiments. Examination of the inclusion of the *trans* stilbenes **78**$^-$ and **80**$^-$ inside native α-cyclodextrin and β-cyclodextrin revealed a significant influence of the annulus size on the nature of the inclusion complex. Each β-cyclodextrin.stilbene complex exists either with β-cyclodextrin in a single orientation, or as two inclusion isomers in fast equilibrium, while each α-cyclodextrin.stilbene complex exists as two inclusion isomers in slow equilibrium at room temperature. Rate constants and activation parameters for exchange between the two isomeric αCD.**78**$^-$ inclusion complexes are k_1(298 K) = 12.3 ± 0.6 s^{-1}, k_2(298 K) = 10.7 ± 0.5 s^{-1}, $\Delta H^{\ddagger}_1$ = 94.3 ± 4.7 kJ mol^{-1}, $\Delta H^{\ddagger}_2$ = 93.1 ± 4.7 kJ mol^{-1}, $\Delta S^{\ddagger}_1$ = 92.0 ± 5.0 J K^{-1} mol^{-1} and $\Delta S^{\ddagger}_2$ = 87.3 ± 5.0 J K^{-1} mol^{-1} (where the subscripts 1 and 2 refer to the less and more populated states, respectively). The ground state parameters for exchange between the two isomeric αCD.**79**$^-$ inclusion complexes are ΔG^0 = -910 ± 160 J mol^{-1}, ΔH^0 = 12.6 ± 1.5 kJ mol^{-1} and ΔS^0 = 46 ± 3 J K^{-1} mol^{-1} (in the direction from the less populated to more populated state).

Abbreviations

The following abbreviations have been used within this thesis:

Å	angström (10^{-10} m)
aq	aqueous
Ar	aryl
bp	boiling point (°C)
calc.	calculated
CD	cyclodextrin
conc.	concentrated
δ	chemical shift
dec.	decomposed
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
$\Delta G^{\ddagger}$	free energy of activation
ΔG^{o}	standard free energy of reaction
$\Delta H^{\ddagger}$	enthalpy of activation
ΔH^{o}	standard enthalpy of reaction
$\Delta S^{\ddagger}$	entropy of activation
ΔS^{o}	standard entropy of reaction
ES	electrospray
equiv.	equivalents
et al.	*et alia*
FAB	fast atom bombardment
K	stability constant
K_a	acid dissociation constant
IR	infrared
Hz	Hertz
J	coupling constant (Hz)
lit.	literature
M^+	molecular ion (in mass spectra)

MALDI-TOF	matrix-assisted laser desorption-ionisation time-of-flight
Me	methyl
mp	melting point (°C)
MS	mass spectrometry
m/z	mass/charge ratio
mmol	millimole
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
Ph	phenyl
pK_a	-log(K_a)
pH	-log[H^+]
ppm	parts per million
R_f	retention factor (for TLC)
ROESY	rotating frame Overhauser spectroscopy
t	tertiary
T	temperature (K)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
tren	tris(2-aminoethylamine)
trien	triethylenetetramine
UV/Vis	ultraviolet/visible

Chapter 1. Introduction

1.1 Cyclodextrins: Their Properties and Applications

Cyclodextrins are naturally occurring cyclic sugars, formed by the action of the amylase of *Bacillus macerans* on starch [1]. The molecules are homochiral, being composed of α-1,4-linked D-glucopyranose units. The three most common cyclodextrins comprise 6, 7 or 8 glucose units and are named α-cyclodextrin **1** (cyclohexamylose), β-cyclodextrin **2** (cycloheptamylose) and γ-cyclodextrin **3** (cyclooctamylose), respectively [1, 2].

Cyclodextrins are annular molecules, with a hydrophobic interior lined by methine units and glycosidic oxygens, and hydrophilic rims, of which one lined is with primary hydroxyl groups and the other is lined with secondary hydroxyl groups [3]. The primary hydroxyl rim has a slightly smaller diameter than the secondary hydroxyl rim, such that the molecule is commonly depicted as a shallow, truncated cone (Figure 1.1) [3]. Cyclodextrins may be considered to be 'wheel-like' and this structure makes them convenient tools for supramolecular chemistry [4], which encompasses the principles of molecular recognition and self-assembly.

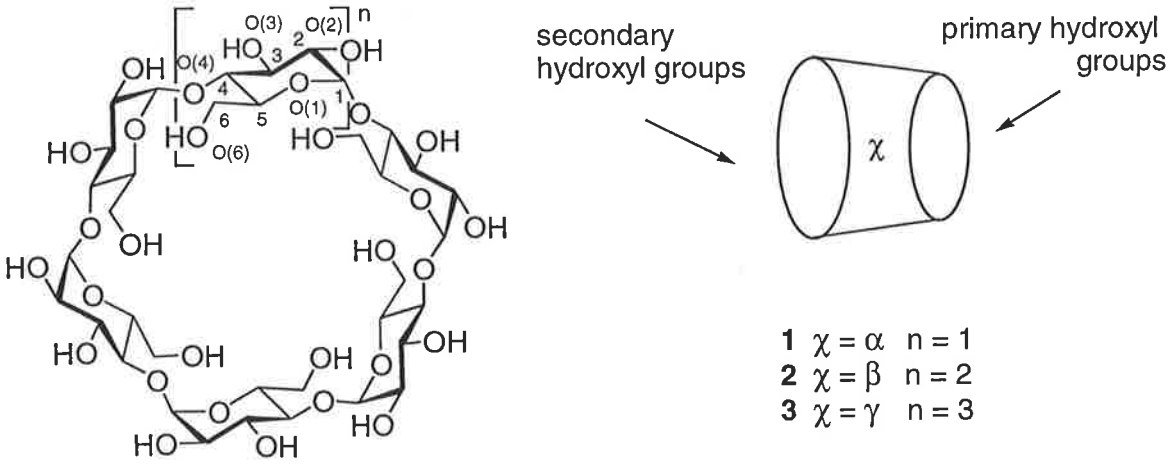
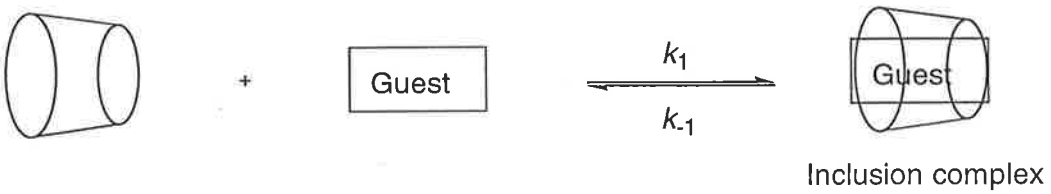


Figure 1.1 Schematic representation of α-, β- and γ-cyclodextrin, showing the numbering system referred to in the text.

Interest in cyclodextrins has primarily arisen from their formation of inclusion complexes with a variety of guest molecules in aqueous solution [2, 3]. The hydroxyl groups on the outside of cyclodextrins give the molecules water-solubility, but when a cyclodextrin is dissolved in aqueous solution, the hydrophobic groups on the inside of the cyclodextrin experience unfavourable interactions with water molecules. A hydrophobic molecule in aqueous solution experiences similar unfavourable intermolecular interactions. The cyclodextrin annulus provides a suitable environment for hydrophobic molecules in aqueous solution, and inclusion of a guest inside a cyclodextrin is often attributed to this fact, termed 'the hydrophobic effect'. Inclusion complex formation, or host-guest complex formation, is shown in Scheme 1.1.



$$K = \frac{[\text{Inclusion complex}]}{[\text{Cyclodextrin}][\text{Guest}]} = \frac{k_1}{k_{-1}}$$

Scheme 1.1 Schematic representation of inclusion complex formation between a cyclodextrin and a guest.

Although the hydrophobic effect is generally accepted to be the major driving force for cyclodextrin complex formation, other factors are also believed to contribute to this, and cyclodextrin complexes have been observed in mediums other than water. Alternative hypotheses that have been proposed are: (1) release of 'high-energy' water molecules from the cyclodextrin annulus, (2) relief of conformational strain energy possessed by the free cyclodextrin, (3) electrostatic interactions, mostly dipole-dipole and hydrogen-bonding and (4) induction forces and dispersion forces [3]. Hypothesis (2), however, now lacks support [3].

The structure of a cyclodextrin, being a 'cycle of cycles', gives rise to some degree of rigidity in the molecule. Formation of a ring of hydrogen bonds between the hydroxyl groups in the 2 and 3 positions helps to stabilise the cyclic structure [3]. However, the early view of cyclodextrins as being conformationally very rigid has undergone review. Molecular dynamics simulations of α-cyclodextrin have indicated considerable flexibility, suggesting that α-cyclodextrin might, to a limited extent, be able to adopt its shape to suit a guest

molecule [5]. Molecular modelling studies have predicted that α-cyclodextrin and β-cyclodextrin are more flexible than γ-cyclodextrin [6].

Cyclodextrin inclusion complexes have potential and current applications in a number of industries; cyclodextrins have been used as food additives, binding sites of enzyme models, solubilisers of water insoluble substances (such as pharmaceuticals) and molecular capsules for stabilising chemicals [2, 7-10]. The stabilisation of azo dyes is particularly well-known [9, 11, 12]. Due to their homochirality, cyclodextrins formdiastereomeric inclusion complexes with enantiomers. These complexes are usually of different stability, leading to enantioselectivity of guest inclusion. Commercial cyclodextrin-based chromatography columns have been developed for the separation of enantiomers, based on this principle [8]. Recently, the large η-cyclodextrin that comprises 12 glucose units, has been utilised to solubilise carbon nanotubes and to separate them to some extent, based on their sizes [13].

1.2 Appropriate Guests for Cyclodextrin Inclusion Complexes and Evidence for Guest-Inclusion

Aromatic compounds have most commonly been employed as guests in cyclodextrin inclusion complexes [3], but the inclusion of guests containing polymethylene chains or alicyclic moieties is also well-known. Stable complexes have been formed when the guest consists of a polymethylene chain (of n CH_2 units) terminating in either bulky or charged groups [14-19]. In general, the stability of such a complex has been found to increase with n.

The size of the cyclodextrin annulus limits the size of the guests that can be included [6]. Table 1.1 contains the dimensions of α-, β- and γ-cyclodextrin. The diameter of the annulus decreases from the secondary end to the primary end, such that the diameter values given are averages.

Table 1.1 Annular dimensions of α-, β- and γ-cyclodextrin.

Cyclodextrin	Cavity Diameter/Å	Length/Å
1	5.2	8
2	6.6	8
3	8.4	8

Guest molecules can be completely or partially included inside the cyclodextrin annulus [3], with strong inclusion being attributed to a close match in sizes of the guest and the cyclodextrin annulus. Studies of the inclusion of substituted adamantanes and other alicyclics in cyclodextrins are particularly interesting as these guests are rigid molecules, very non-polar and close to spherical [20, 21]. It has been found that 1-adamantanecarboxylate includes very strongly inside β-cyclodextrin, consistent with a close match between the annulus and guest diameters. The association constant for this complex is of the order of 10^4 dm^3 mol^{-1}; this is comparable with the stability of protein-ligand systems [20].

Strong guest-inclusion is often observed when the guest is a hydrophobic substituent of a modified cyclodextrin. There are many examples of the self-inclusion of aromatic substituents of cyclodextrins, and there have been some recent studies of the self-inclusion of alicyclic substituents [2, 22, 23]. Such intramolecular inclusion has an entropic advantage over intermolecular inclusion.

The stoichiometries of cyclodextrin inclusion complexes vary, encompassing the most common 1:1 stoichiometry, to 1:2, 2:1 and 2:2 where the first and second numbers refer to cyclodextrin and guest, respectively [3]. In the presence of two different guests, a 1:1:1 stoichiometry may result, as exemplified by the 1:1:1 β-cyclodextrin:pyrene:1-pentanol complex [24].

^{1}H NMR methods have become very useful in the study of the kinetics and structure of cyclodextrin inclusion complexes. Guest-inclusion gives rise to changes in the chemical shifts of the H3 and H5 annular protons, the magnitude of the change being proportional to the strength of the interaction between these protons and those of the guest (or the proximity of the annular protons to the guest protons) [25]. The Nuclear Overhauser Enhancement Spectroscopy (NOESY) experiment cannot be used for cyclodextrin derivatives. This is because the sign of a nuclear Overhauser enhancement (nOe) changes depending on molecular correlation time, and for the magnitude of molecular weights of cyclodextrins the nOe is close to zero and the cross peaks often disappear [26]. Instead, Rotating frame Overhauser Enhancement Spectroscopy (ROESY) experiments, for which an nOe is always positive, are carried out to determine whether a guest or substituent is included in the cyclodextrin annulus [2, 25]. An nOe cross-peak between the resonance of a proton of the

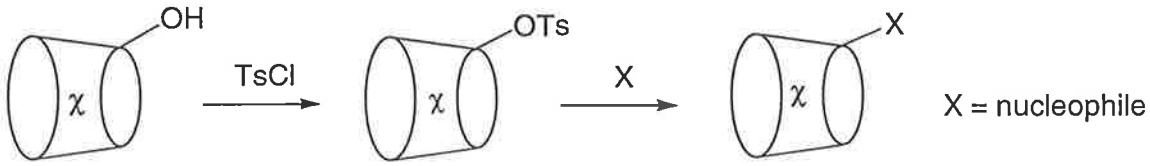
cyclodextrin annulus and that of a proton of the guest will be observed if the protons are closer than 4Å, which infers that the guest is included in the annulus [25].

1.3 Modified Cyclodextrins

The naturally occurring cyclodextrins are limited in terms of their shape, size and available functional groups [27]. It is possible to introduce functionality by selectively modifying the hydroxyl groups that line the rims of the molecule [27]. By modifying cyclodextrins, they can be altered to suit the requirements of a particular guest [3]. Cyclodextrins may also be modified to improve their solubility in a particular solvent. For example, hydroxyl groups have been randomly sulfonylated to make highly water-soluble cyclodextrins, which have applications in drug formulation [28]. Functional groups, which act as catalysts, have been introduced at the 6-position to produce cyclodextrin-based artificial enzymes [29].

All modifications of cyclodextrins occur at the hydroxyl groups. Hydroxyl groups are nucleophilic, so modifications involve electrophilic attack at a hydroxyl group as the first step. Cyclodextrins have three types of hydroxyl groups, which compete for reagents, making selective modifications challenging [27]. The primary hydroxyl groups in the 6-position are the most basic (and usually the most nucleophilic), the secondary hydroxyl groups in the 2-position are the most acidic and the secondary hydroxyl groups in the 3-position are the most inaccessible [27]. The hydrophobic annulus of a cyclodextrin often includes reagents and this may direct the reaction [30]. Electrophilic attack preferentially occurs at the 6-position under neutral conditions.

Mono-substitution of a cyclodextrin can also present a challenge [27]. For example, β-cyclodextrin has seven hydroxyl groups of each type, so electrophilic attack may result in multiple substitutions. Purification is then required to obtain the mono-substituted compound. Mono-6-tosylated cyclodextrins are often prepared as precursors to modified cyclodextrins (Scheme 1.2) [27].



χ = α	**1**	**4**	**6**
χ = β	**2**	**5**	**7**

Scheme 1.2 Cyclodextrins are often tosylated in the 6-position as the first step in synthesising modified cyclodextrins.

Cyclodextrins have been joined through a variety of linkers to create dimers [2, 31-33]. The linkers that have been employed range from the short and rigid disulphide linker [34, 35] to long and floppy ether linkers [36]. The cyclodextrins are generally linked at the primary faces, although there are examples of dimers linked at the C2 and C3 positions [33, 36]. In general, cyclodextrin dimer inclusion complexes of long guests are very stable, as the guest is included at two sites in the dimer. Also, cooperativity [2] often enhances the stability of such complexes (the stability constant of a complex formed between a cyclodextrin dimer and a long guest is often much greater than simply double that of the corresponding native cyclodextrin complex). The length and flexibility of the linker partially controls how the cyclodextrin annuli of the dimer orient themselves, relative to each other, to cooperatively bind a single guest [37].

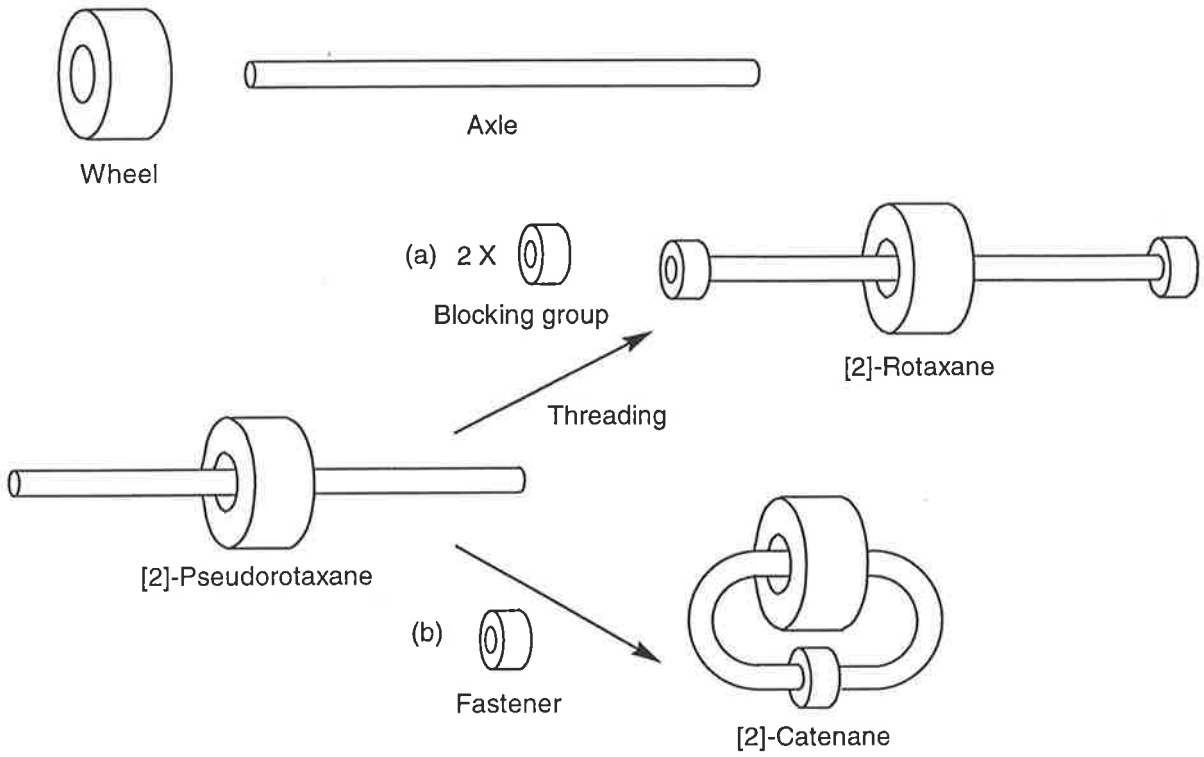
Recently, cyclodextrin trimers have been reported [38]. The trimers act as receptors for a long ester and a catalyst to give rise to enhanced hydrolytic activity.

1.4 Mechanically Restrained Molecular Systems

The inclusion of a guest molecule in a wheel-shaped host molecule produces the possibility of permanently trapping the guest inside the wheel, by either attaching suitably large blocking groups to the ends of the guest, or linking the ends of the guest together to form a second wheel. The resulting structures are referred to as a [2]-rotaxane and a [2]-catenane (where [2] refers to the total number of components), respectively, and such systems are of great interest because they are held together by mechanical forces rather than covalent bonds [39]. A [2]-rotaxane can be pictured as a molecular 'wheel-on-axle', while a [2]-catenane consists of two interpenetrating wheels resembling the links of a chain (Scheme 1.3)

[2, 3]. The precursor to these systems is a [2]-pseudorotaxane, in which the 'axle' is missing one or both blocking groups in a [2]-rotaxane, or a 'fastener' in a [2]-catenane. Often, there is a portion of the axle over which the wheel tends to reside due to favourable intermolecular forces. The axle used in the synthesis of a [2]-catenane needs to be sufficiently long for the ends to both reach a common fastener.

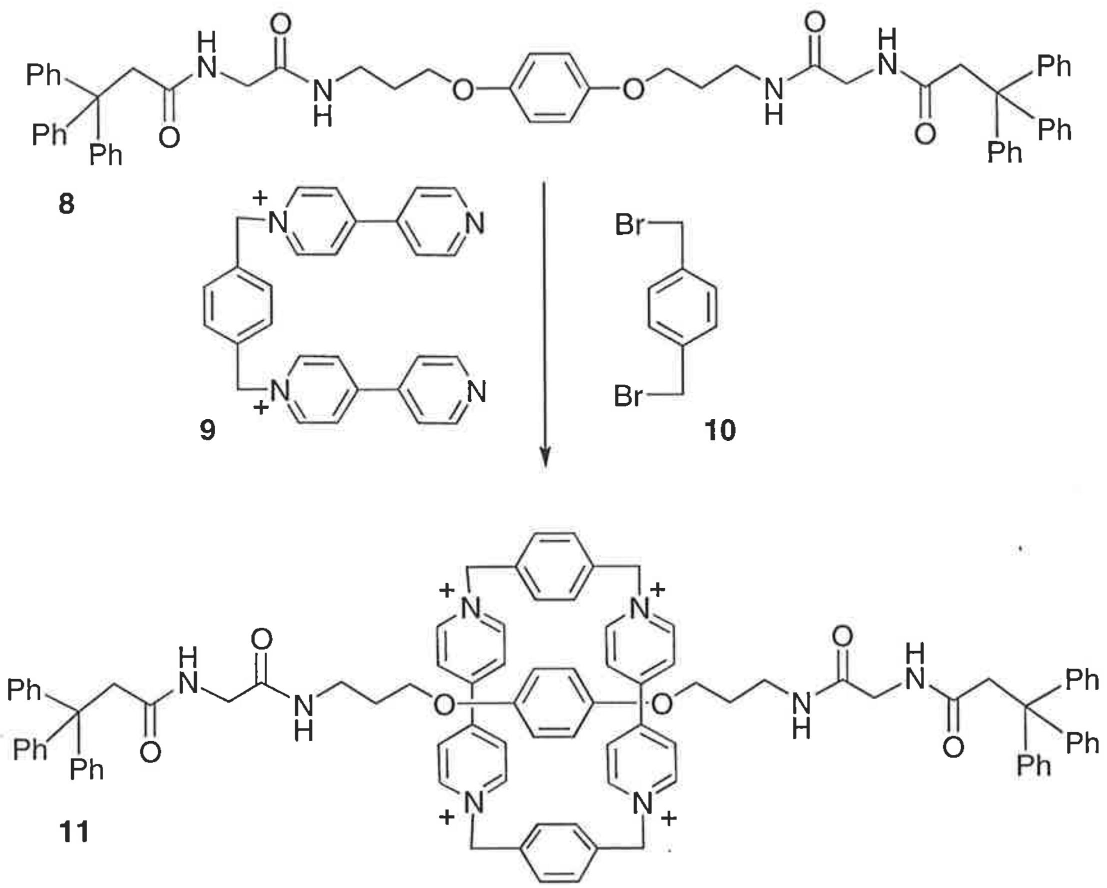
Scheme 1.3(a) shows the most common method of [2]-rotaxane assembly, which is referred to as 'threading' [40]. [2]-Rotaxanes can be synthesised by two other methods, both of which involve attachment of the blocking groups before the axle is included inside the wheel. 'Slippage' is the slow inclusion of a pre-blocked axle inside a wheel, usually with the aid of heat. Once the wheel is on the axle, a combination of favourable interactions with the axle and the mechanical restraint of the blocking groups create a large thermodynamic barrier to the wheel leaving the axle [41]. In 'clipping' the wheel is constructed from smaller, acyclic components around the pre-blocked axle. The synthesis of a [2]-catenane, although similar to the threading method for [2]-rotaxane synthesis, is also akin to clipping, as the axle component becomes a wheel (Scheme 1.3(b)) [40].



Scheme 1.3 The attachment to the ends of a [2]-pseudorotaxane of (a) blocking groups to form a [2]-rotaxane or (b) a fastener to form a [2]-catenane.

Although challenging to prepare, there are now many reports in the literature of rotaxanes [11, 12, 42-46] and catenanes [47-50]. Often, directed or templated syntheses of these systems are employed to improve the yields. Metal-binding or favourable intermolecular bonding, such as hydrogen-bonding, π-π electron-donor/electron-acceptor and hydrophobic interactions direct the assembly of the components [51-53].

Electron-donor/electron acceptor interactions have been employed to synthesise [2]-rotaxanes and [2]-catenanes, using a clipping approach. An example of the synthesis of a [2]-rotaxane by such a method is shown in Scheme 1.4 [54]. Interactions between the electron-rich hydroquinone unit of the axle **8** and the electron-deficient bipyridyl units of the component **9** direct the [2]-rotaxane synthesis.

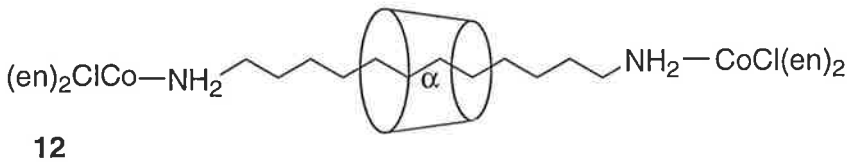


Scheme 1.4 Templated synthesis of a [2]-rotaxane using a clipping approach.

A cyclodextrin [2]-pseudorotaxane is simply an inclusion complex in which the guest is very long compared with the cyclodextrin. The principles behind [2]-pseudorotaxane self-

assembly are identical to those previously discussed for inclusion complex formation [3, 40], the hydrophobic effect being the major driving force in most examples. Several [2]-rotaxanes [40, 46, 55] and some examples of [2]-catenanes [56, 57] containing cyclodextrins have now been reported. The yields of these systems have generally been low, but there are some recent examples of cyclodextrin [2]-rotaxanes that have been obtained in yields of over 70 % [46, 55].

The self-assembly of a [2]-rotaxane incorporating a cyclodextrin as the wheel component was first carried out by using transition metal blocking groups to cap the ends of the axles [58, 59]. α,ω-Diaminoalkanes axles were included inside α- or β-cyclodextrin, and the reaction of the terminal amines with cis-$[CoCl_2(en)_2]Cl$ (en denotes 1,2-diaminoethane) produced blocking groups, thus forming [2]-rotaxanes. Reactions were carried out in DMSO, rather than water, due to the low water-solubility of the axles. Low yields resulted, the best (19 %) being obtained when α-cyclodextrin and 1,12-diaminododecane were used (compound **12**). Attachment of metal blocking groups to axles terminating in bipyridyl units has also produced [2]-rotaxanes [60-62]. Stable α-cyclodextrin [2]-rotaxanes such as **13** were prepared from the reaction of $[Fe(CN)_5OH_2]^{3-}$ with axles terminating in 1,1''-(α,ω-alkanediyl)bis(4,4'-bipyridinium) dicationic ligands $(bpy(CH_2)_nbpy^{2+}$ n = 8-12).



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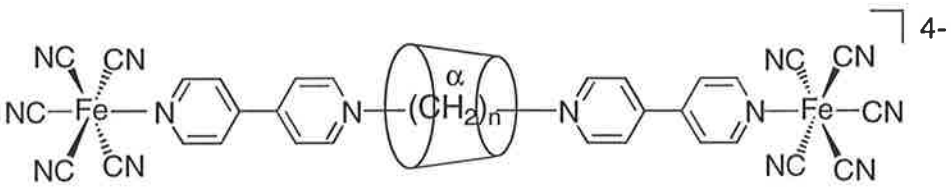
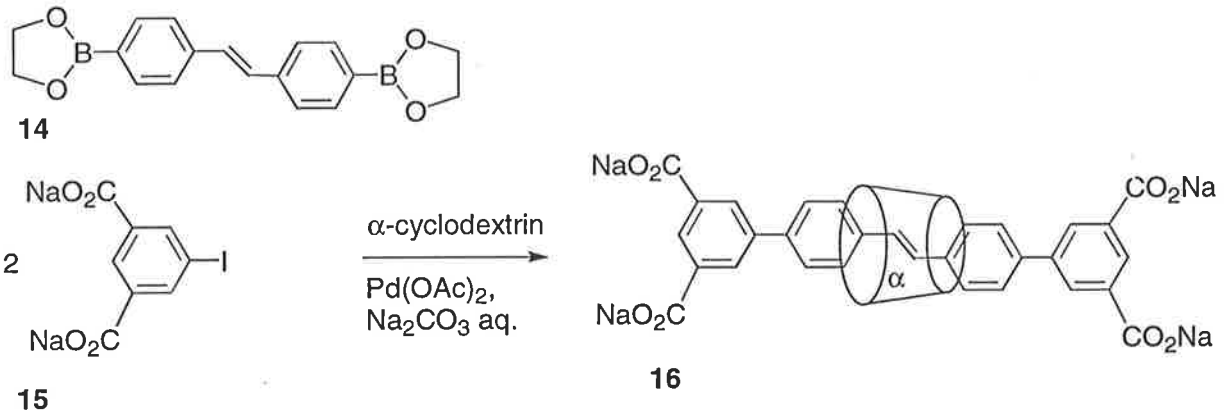


13 n = 8 - 12

There are few examples of cyclodextrin-based [2]-rotaxanes incorporating axles with covalently attached blocking groups. Such systems are considerably challenging to synthesise, as the covalent attachment of blocking groups to the [2]-pseudorotaxane must be carried out in aqueous solution to ensure that a large percentage of axle components are included inside cyclodextrin annuli [40]. Sodium 2,4,6-trinitrobenzenesulfonate has been

used to cap axles terminating in amine groups in water [55, 63]. Suzuki coupling (reaction of an aryl iodide blocking group with a diboronic acid axle) has produced both α- and β-cyclodextrin [2]-rotaxanes in yields of up to 73 % (Scheme 1.5) [46].



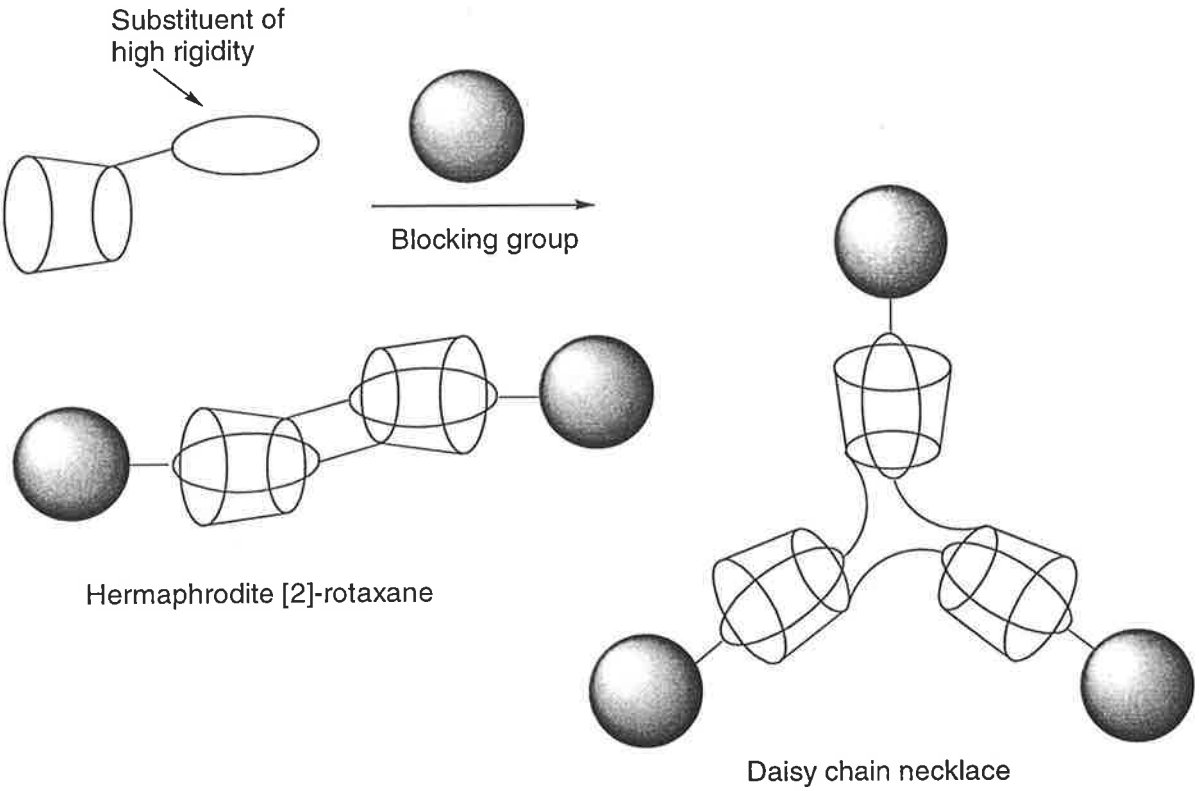
Scheme 1.5 One of a series of cyclodextrin [2]-rotaxanes with organic stoppers synthesised by Suzuki coupling.

Several examples of cyclodextrin polyrotaxanes, which are polymers incorporating multiple cyclodextrin molecules, have been reported [2, 4, 43, 64]. In recent work, threads that consist of conjugated π-systems have been encapsulated by multiple cyclodextrins to form 'insulated molecular wires' in which the luminescence efficiency and chemical stability of the thread is enhanced [65].

Synthesis of a catenane incorporating a cyclodextrin was first attempted in 1958 [66]. A series of paraphenylene and biphenyl derivatives with two flexible side chains ending in thiol groups were prepared, and a cyclodextrin was expected to include the aromatic part of these compounds. It was proposed that a disulphide bond would form upon oxidation and achieve macrocyclisation, but no cyclic products were obtained. The efficient self-assembly of a β-cyclodextrin [2]-catenane with non-covalent fasteners has recently been described [57], but cyclodextrin catenanes with covalent fasteners have been synthesised only in very low yields [56].

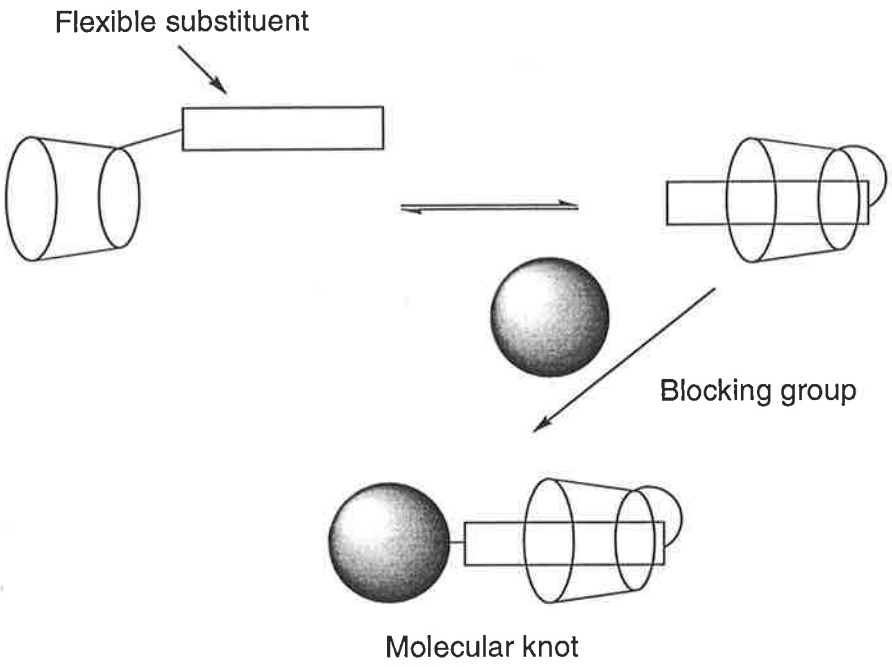
Cyclodextrins have been utilised in the construction of elaborate structures such as 'Hermaphrodite' [2]-rotaxanes and daisy chain necklaces [67, 68]. These systems are constructed by the self-assembly of modified cyclodextrins, followed by blocking group attachment (Scheme 1.6). The hydrophobic substituent of the cyclodextrin is generally of

high rigidity to prevent self-inclusion. A daisy chain (linear version of a daisy chain necklace) is another potential product in these syntheses. Although there are examples of modified cyclodextrins that have a 'pseudo-daisy chain' structure [69, 70], mechanically restrained species have not been reported in the literature.



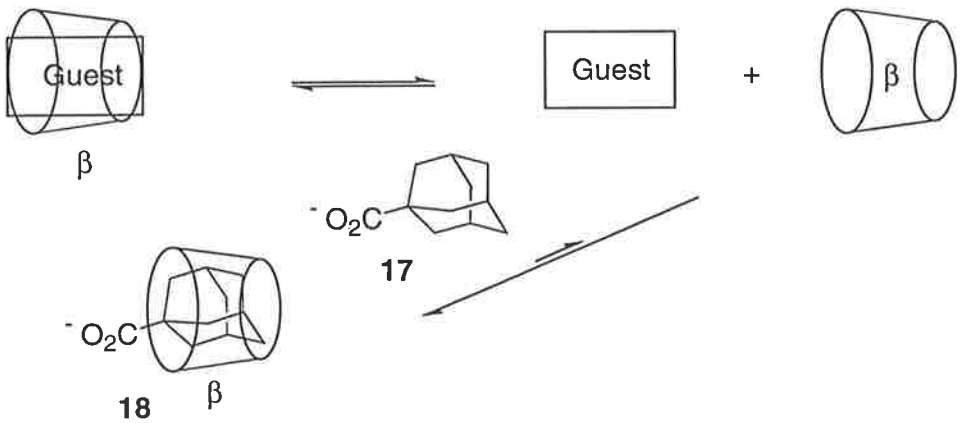
Scheme 1.6 Mechanically restrained structures which have been formed from modified cyclodextrins.

There has been interest in the construction of cyclodextrin molecular knots [23], which are mechanically restrained, self-included species, as yet theoretical structures only (Scheme 1.7). Molecular knot construction requires that a modified cyclodextrin must contain a substituent of sufficient length and flexibility to be self-included. If the self-included substituent has a reactive terminal group, there is the possibility of reacting this group with a molecule which is too large to pass through the annulus [23]. The species formed would then effectively be held in a knot. Recently, work towards synthesising a molecular knot utilising various alicyclic blocking groups has been reported [23, 71].



Scheme 1.7 A molecular knot, synthesised from a modified cyclodextrin containing a flexible substituent.

The high stability of the complex **18** formed by β-cyclodextrin and 1-adamantanecarboxylate **17** results in **17** competing strongly with other guests for inclusion in β-cyclodextrin (Scheme 1.8). Thus, testing for the displacement of a guest by 1-adamantanecarboxylate **17** may be used for assessing the thermodynamic stability of a β-cyclodextrin complex and for evidence of mechanical restraint preventing displacement of a guest [23].



Scheme 1.8 1-Adamantanecarboxylate competitively displaces a guest from the β-cyclodextrin annulus.

1.5 Molecular Devices

Nanotechnology encompasses the construction and control of the function of molecular or 'nanoscale' devices [51, 72-80]. Interest in nanotechnology has arisen from the realisation that miniaturizing technologies by the 'top-down' approach of creating continuously smaller versions of current systems is reaching its limits and the 'bottom-up' approach of starting with the smallest possible components: molecules, and building them into devices has been postulated [81]. A range of sophisticated systems, which are essentially molecular-sized versions of the components of machinery in the human world, has been developed. Current work involves the synthesis of molecular components and the self-assembly by favourable intermolecular forces (e.g. hydrophobic interactions, hydrogen-bonding) of these components into devices [51, 78]. In response to a chemical, electrochemical or photochemical stimulus, selected fragments of a multi-component system are set in motion while the rest of the system remains stationary to create molecular switches, shuttles and even artificial muscles [72, 74, 82-84]. The ultimate goal is the construction of molecular systems capable of information processing and storing for the smallest possible computers [81, 85-87].

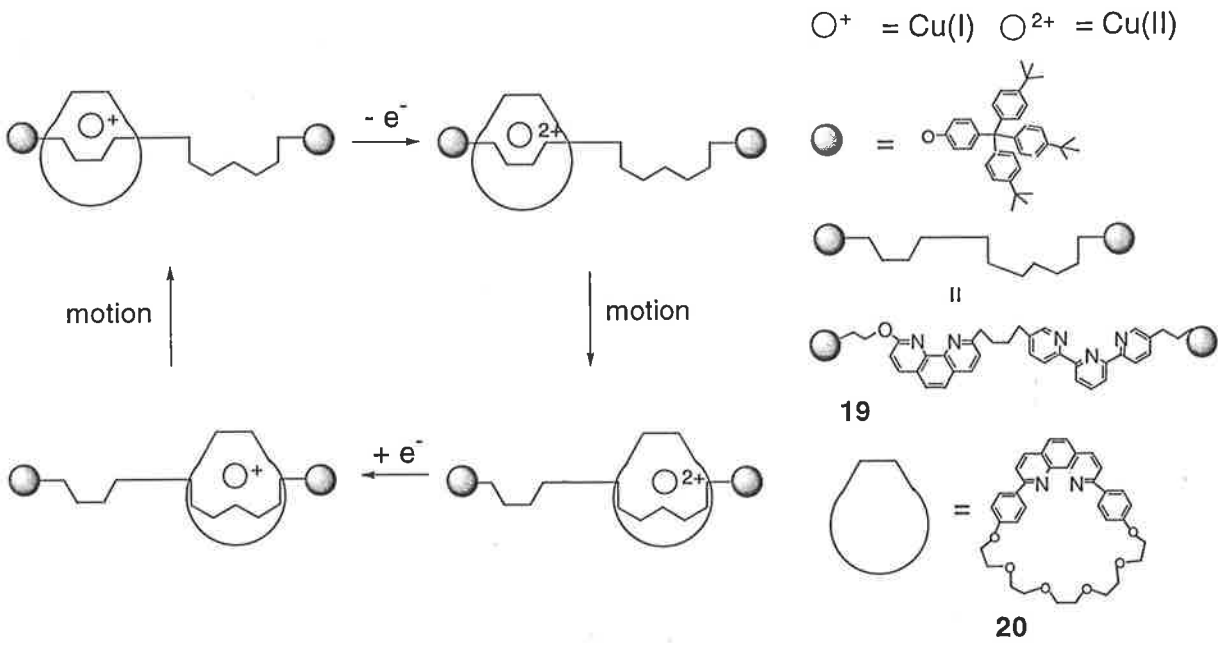
Thermal motion within molecular devices requires that the motion must also occur in the reverse direction. However, when energy is supplied to a selected part of the system, unidirectional motion can be induced [88]. It is also desirable that repetition of the motion is possible [82]. A 'molecular brake' has been reported, which is an example of chemically driven (and therefore thermodynamically allowed) unidirectional motion [89].

Pseudorotaxanes, rotaxanes and catenanes incorporating different 'stations' on one component have been constructed, in which movement of a wheel between the stations is controlled by a variety of stimuli [54, 72, 87, 90-99]. The motion possible within a [2]-rotaxane has been compared with that of natural molecular devices such as ATP synthase, which couples the movement of an axle in a wheel to the production of ATP, the source of chemical energy in biological systems [78].

There are examples of [2]-pseudorotaxanes in which inclusion and exclusion of the axle component can be controlled. The photochemical/thermal isomerisation of an azobenzene axle has been utilised to initiate the assembly and disassembly of a [2]-

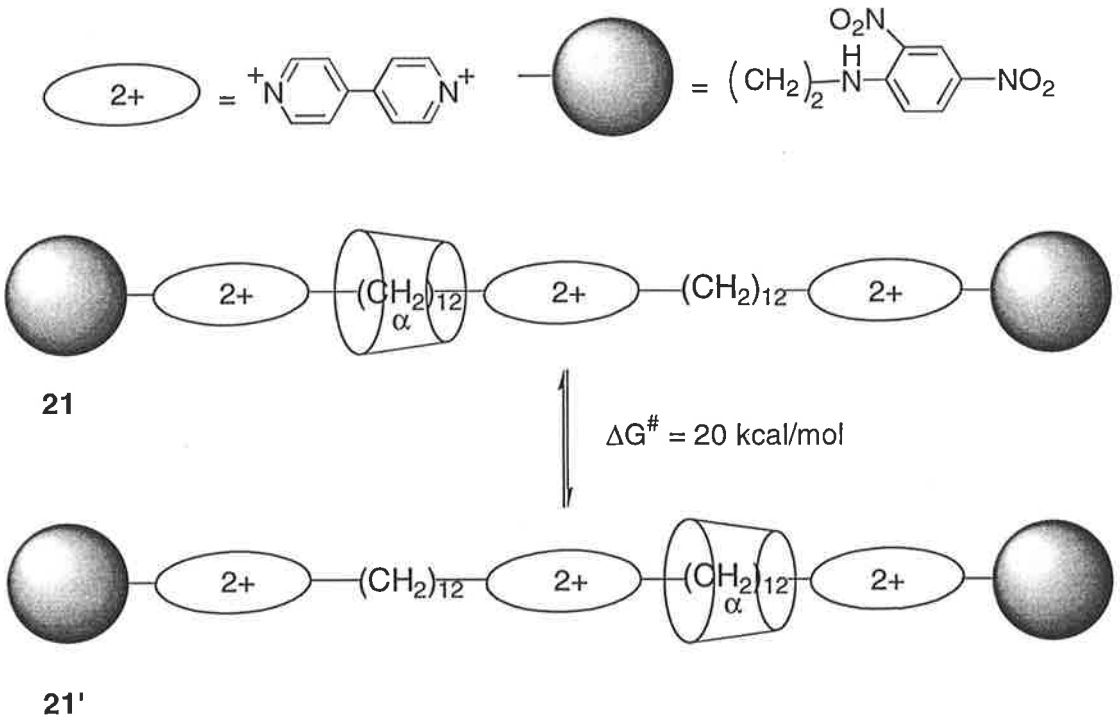
pseudorotaxane [100]. In another system, the selective inclusion of one of two axles in a single wheel has been controlled. The wheel component is 1,5-dinaphtho-38-crown-10 and the axles are 1,1'-dibenzyl-4,4'-bipyridinium (DBV^{2+}) and 2,7-dibenzyldiazapyrenium (DAP^{2+}) dications. The addition of different chemicals (amine and acid) controls which axle enters the wheel [99].

Electrochemical stimulus drives motion in a [2]-rotaxane containing the units **19**, **20** and Cu(I)/(II) (Scheme 1.9) [101]. In this system, the axle **19** contains two stations consisting of bidentate (a phenanthroline derivative) and terdentate (2,2',6',2"-terpyridine) coordinating units, and the wheel component **20** is a 30-membered ring containing a bidentate coordinating unit. The different coordination preferences of Cu(I) (4-coordinate) and Cu(II) (5 or 6 coordinate) provide the driving force for motion in this system. Oxidation/reduction of Cu(I)/Cu(II) causes movement of the metal and the wheel along the axle between the bidentate and terdentate coordinating units. A [2]-catenane incorporating Cu(I)/(II) has also been described. The two wheel components both contain bidentate and terdentate coordinating units and can be rotated with respect to each other upon oxidation/reduction [72].



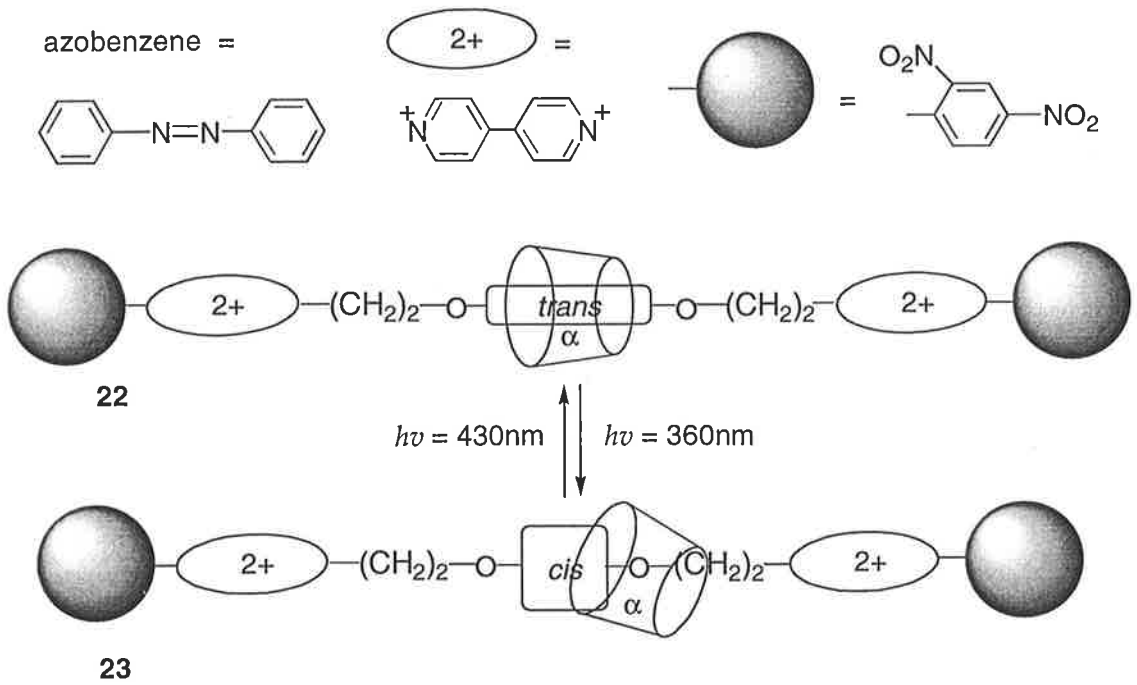
Scheme 1.9 Electrochemically induced motions in a [2]-rotaxane containing Cu(I)/Cu(II).

Cyclodextrins are considered to have great potential as wheel components for the construction of molecular devices due to their ability to include very long molecular axles and slide along an axle or rotate around it [77]. An example of a cyclodextrin-containing molecular shuttle, **21/21'**, is shown in Scheme 1.10 [102]. The movement of α-cyclodextrin between the stations of the axle is sensitive to both temperature and solvent; it is jointly controlled by the favourable hydrophobic interactions between the cyclodextrin and stations, and the repulsive interactions between the cyclodextrin and bipyridinium units. A very similar system, which is controlled by pH, has also been reported [98].



Scheme 1.10 A molecular shuttle containing α-cyclodextrin.

An α-cyclodextrin [2]-rotaxane which acts as a photochemically-controlled shuttle is shown in Scheme 1.11 [103]. The α-cyclodextrin molecule includes the central section of the *trans*-azobenzene moiety, but it slides away from this section of the axle when the azobenzene moiety is converted to the *cis* isomer by irradiation of light (360 nm). The movement is reversed when the azobenzene moiety is converted back to the *trans* isomer by irradiation at 430 nm. Similar photochemically-controlled motion has been observed in a cyclodextrin [2]-rotaxane which contains a stilbene moiety in the axle [104].



Scheme 1.11 A photochemically-controlled molecular shuttle containing α-cyclodextrin.

Systems which exist in two different stable states, due to the controllable movement of a component, can be thought of as containing '1' and '0' (ON and OFF) digital states. There are examples of redox-active rotaxanes and catenanes which have been assembled in monolayers between electrodes, with switching between '1' and '0' states being controllable by applying a voltage [87, 105, 106]. Molecular logic gates, which convert a combination of input signals into specific output signals, are now being developed [79, 80]. A three-state molecular device, which responds to one chemical and two photochemical inputs to produce two photochemical outputs, has been described. The selected inputs and corresponding outputs represent AND, OR and NOT logic gates [79].

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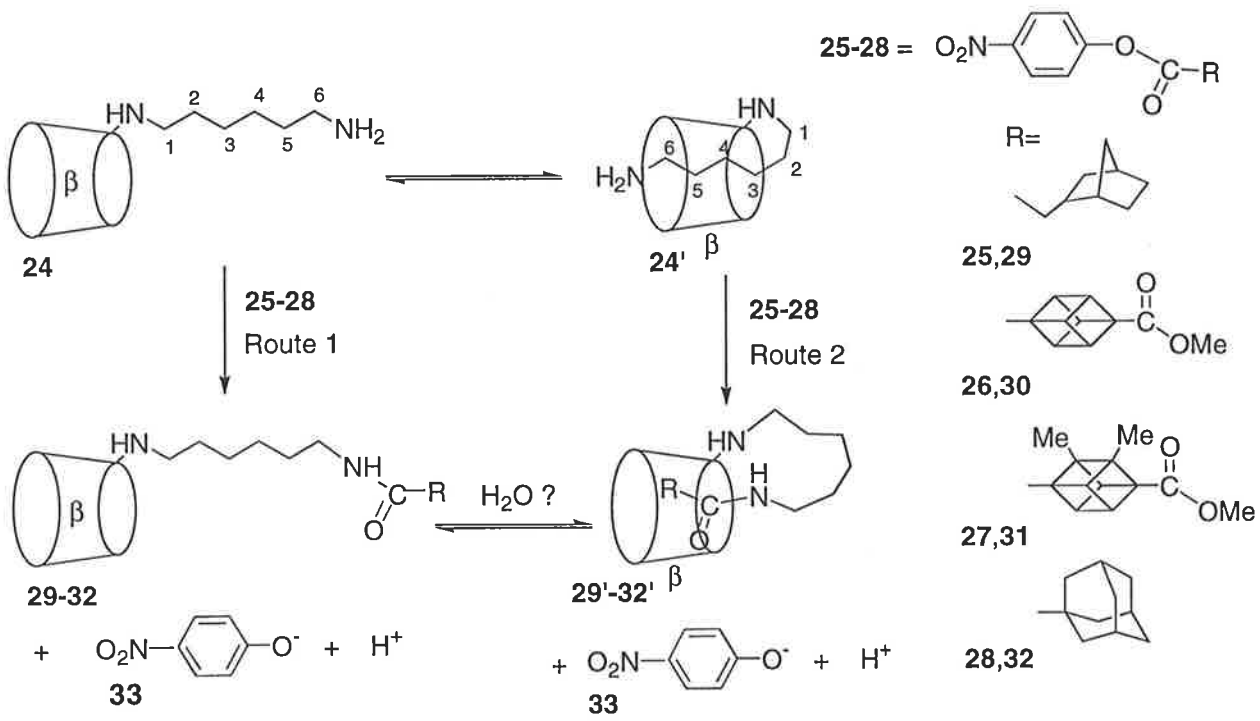
Chapter 2. Size Discrimination in Modified Cyclodextrins

2.1 Alicyclic-substituted Cyclodextrins

2.1.1 Introduction

The self-inclusion of the substituents of modified cyclodextrins in aqueous solution is well-known and has given rise to some interesting molecular architectures [1]. There is the possibility of controlling the in and out motion of the substituent with respect to the cyclodextrin annulus, or alternatively a blocking group may be attached to the substituent to permanently trap it inside the cyclodextrin and produce a molecular knot. In previous work, the modified β-cyclodextrins **29-32** with trinorbornylmethyl, cubyl, dimethylcubyl, and adamantyl substituents, respectively, were synthesised and each was shown to exhibit self-inclusion of the substituent to form the species **29'-32'** in basic aqueous solution [2]. The substituent of **32'** is not displaced by 1-adamantanecarboxylate **17**, but at the time that this work was carried out it was not resolved whether **32'** could be classified as a molecular knot, as the mechanism by which the self-included cyclodextrins **29'-32'** are formed was not clarified (Scheme 2.1.1). It was considered that the modified cyclodextrins **29'-32'** may be formed either directly by attack at the intramolecularly included substituent of **24'** by the 4-nitrophenyl esters **25-28** (Route 2), or indirectly by Route 1, which involves attack by **25-28** at the non-included substituent of **24**, followed by equilibration from **29-32** to **29'-32'** after work-up in water. The products of these two routes cannot be distinguished unless the substituent is too large to pass through the cyclodextrin annulus.



Scheme 2.1.1 Preparation of the modified β-cyclodextrins **29'-32'** by two possible routes, showing the numbering scheme of the hexyl chain in **24/24'**. The same numbering scheme is applied to all modified cyclodextrins containing this unit in Chapter 2.

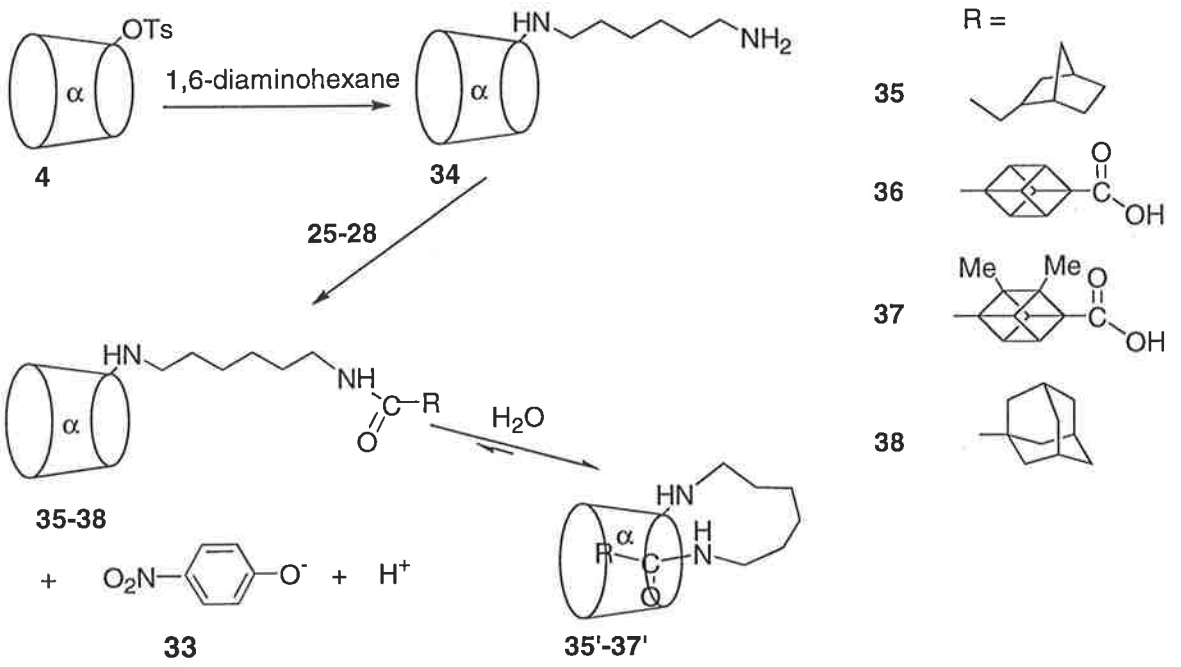
To resolve the mechanism of these syntheses, it was decided to prepare the α-cyclodextrin analogues of the modified β-cyclodextrins **29/29'-32/32'**. As the 1-adamantyl moiety is too large to fit completely inside the α-cyclodextrin annulus [3], it was envisaged that the α-cyclodextrin analogue of **32'**, if it is formed, would be a molecular knot, and verify the reaction in Scheme 2.1.1 occurring via Route 2. Alternatively, if no intramolecularly-included product is formed during the reaction, evidence for Route 1 would be obtained. This study also offered the opportunity to calibrate the size of the α-cyclodextrin annulus. Although alicyclic molecules have been found to be included very strongly in the annuli of cyclodextrins, they have low water-solubility. Substitution of such species onto cyclodextrins enhances their water solubility and allows for size discrimination studies by 2D ^{1}H ROESY NMR spectroscopy. This may lead to applications for these guests as components of rotaxanes and other supramolecular architectures.

2.1.2 Results and Discussion

Synthesis

The trinorbornylmethyl-, cubyl-, dimethylcubyl- and adamantyl-substituted α-cyclodextrins **35**, **36**, **37** and **38** were prepared by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** by the 4-nitrophenyl esters **25-28**, respectively (Scheme 2.1.2) [2].

6^A-*O*-(4-Methylbenzenesulfonyl)-α-cyclodextrin **4** was prepared from α-cyclodextrin **1** and a large excess of 4-methylbenzenesulfonyl chloride. The monotosylate **4** was obtained as a white powder in 29 % yield after some modifications to literature procedures [4, 5]. This was converted to 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** by reaction with 1,6-diaminohexane, the product being obtained in 44 % yield as a pale brown powder [6]. The modified cyclodextrins **35-38** were obtained as white powders in yields of 22, 17, 19 and 38 %, respectively, and their structures were verified by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and microanalysis. The methyl esters of **36** and **37**, which were the initial reaction products, were found to have partially hydrolysed during the work up procedure. To obtain a single product, the methyl esters of **36** and **37** were heated in water and water made basic with one drop of triethylamine, respectively, at 80 °C for 24 hours, to obtain the carboxylic acids **36** and **37**.



Scheme 2.1.2 Synthesis of the modified cyclodextrins **35-38** and **35'-37'**.

Molecular modelling

To enable visualisation of the sizes of the trinorbornylmethyl, cubyl, dimethylcubyl and adamantyl moieties compared to the α-cyclodextrin annulus size, models of the cyclodextrins **35'-38'** were studied. The models were deliberately constructed with the alicyclic moieties protruding from the secondary rim of the α-cyclodextrin annulus such that their sizes relative to the α-cyclodextrin annulus size can be seen clearly. Each model was constructed and minimised (MM2) in Chem3D and is displayed in the space-filling representation (Figure 2.1.1).

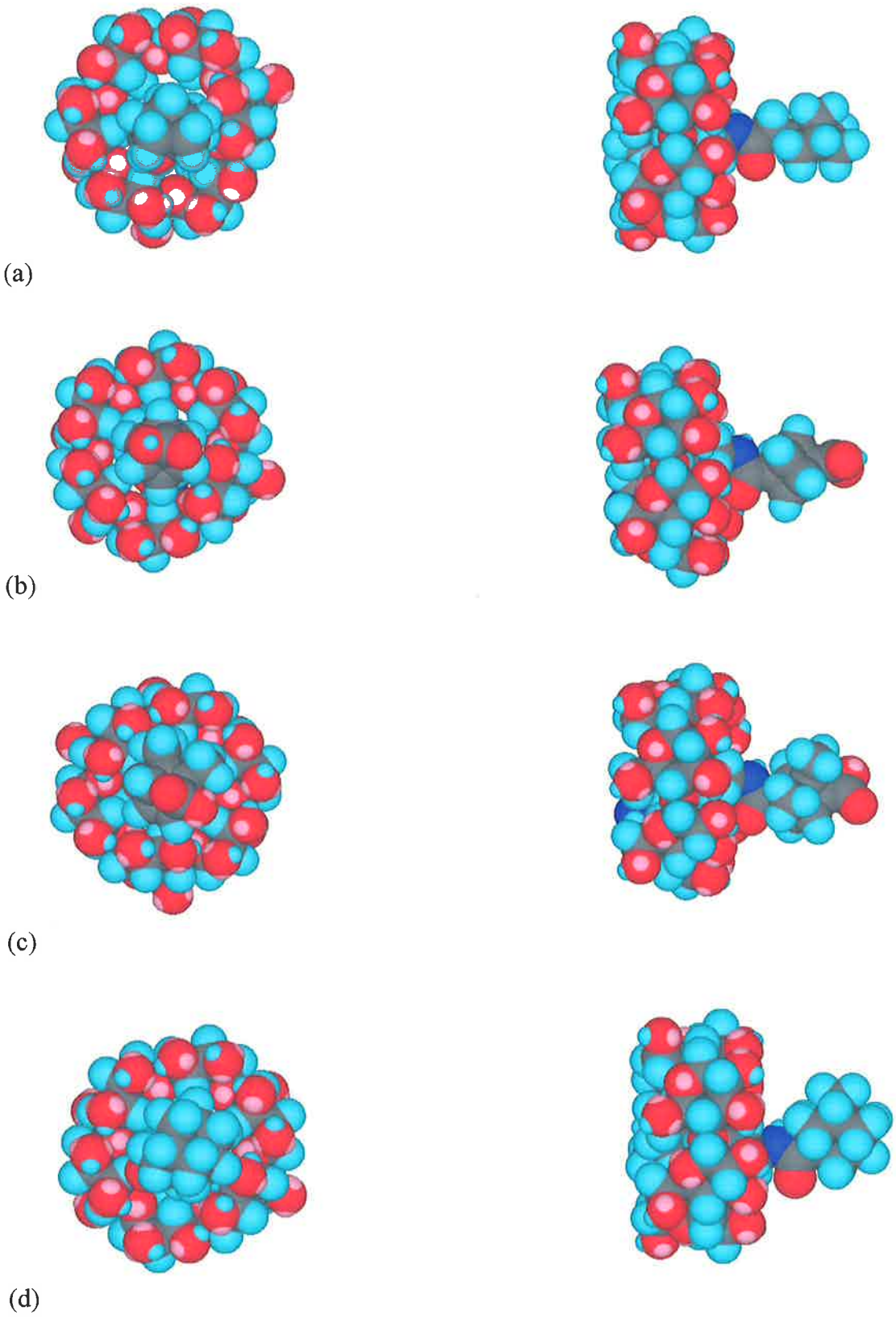


Figure 2.1.1 Space-filling representations of the modified α-cyclodextrins (a) **35'**, (b) **36'**, (c) **37'** and (d) **38'**, displayed from the secondary annulus and from the side, C = grey, H = light blue, O = red, N = dark blue.

From inspection of the models, the trinorbornylmethyl and cubyl moieties of **35'** and **36'**, respectively, both appear to be small enough to include in the α-cyclodextrin annulus. The dimethylcubyl moiety of **37'** appears to be of comparable size to the α-cyclodextrin annulus size, making it difficult to predict whether this moiety can be included inside α-cyclodextrin. It does appear that the 1-adamantyl moiety of **38'** is too large to be fully included in the α-cyclodextrin annulus, in agreement with earlier work.

2D ^{1}H ROESY NMR spectroscopy

The 2D ^{1}H ROESY NMR spectrum of the aminohexylamine substitued α-cyclodextrin **34** in basic D_2O contains strong cross peaks between the resonances arising from the hexyl chain protons and those arising from the α-cyclodextrin annular protons, which is indicative of significant self-inclusion of the substituent. The substituents of the trinorbornylmethyl-, cubyl-, and dimethylcubyl-substituted α-cyclodextrins **35**, **36** and **37**, respectively, were shown to be self-included to give **35'-37'** in D_2O, by examination of 2D ^{1}H ROESY NMR spectra (Figures 2.1.2-2.1.4). However, the adamantyl substituent of **38** is not self-included to give **38'** (Figure 2.1.5). To obtain the 2D ^{1}H ROESY NMR spectra of the cyclodextrins, basic D_2O solutions of **35/35'** and **38** were used such that protonation of the amine would not inhibit self-inclusion of the substituent, but neutral D_2O solutions of **36/36'** and **37/37'** were used to prevent complete deprotonation of the carboxyl group, which may also inhibit self-inclusion.

The 2D ^{1}H ROESY NMR spectrum of the trinorbornylmethyl-substituted α-cyclodextrin **35'** contains strong cross peaks due to nOe interactions between the trinorbornylmethyl moiety protons and the α-cyclodextrin annular protons, indicating that the trinorbornylmethyl moeity is included in the α-cyclodextrin annulus. Due to considerable overlap of the resonances arising from the trinorbornylmethyl protons with those arising from the hexyl chain, it cannot be ruled out that the hexyl chain is also partially included in the α-cyclodextrin annulus.

Considerable overlap of the resonances of the α-cyclodextrin annular protons and the resonances of the cubyl protons in the spectra of the cubyl- and dimethylcubyl-substituted cyclodextrins **36'** and **37'**, respectively, makes it impossible to conclusively discuss the nature of the self-inclusion of these cyclodextrins. The resonances arising from the cubyl protons of

the modified cyclodextrin **36'** are distinctive from, but are in close proximity to, the α-cyclodextrin H3, H5 and H6 proton resonances. There are strong cross peaks between the resonances of the cubyl protons and the resonances of the α-cyclodextrin annular protons, but because the cross peaks are so close to those due to nOe interactions between the cyclodextrin H2, H3, H4, H5 and H6 protons, it cannot be determined whether these are 'true' cross peaks.

The resonances arising from the cubyl protons of the dimethylcubyl-substituted cylodextrin **37'** cannot be distinguished at all from those arising from the α-cyclodextrin protons. However, cross peaks can clearly be seen due to nOe interactions between the methyl group protons of the dimethylcubyl moiety and the α-cyclodextrin annular protons. For both modified cyclodextrins **36'** and **37'**, the 2D ^{1}H ROESY NMR spectra contain no cross peaks due to nOe interactions between the protons of the hexyl chain and the α-cyclodextrin annular protons. The structural implication is that the cubyl entity, not the hexyl chain, is included in the α-cyclodextrin annulus in each case, though it may be only partial inclusion in the case of the larger dimethylcubyl moiety of **37'**.

The 2D ^{1}H ROESY NMR spectrum of the adamantyl-substituted cyclodextrin **38** does not contain cross peaks due to nOe interactions between the protons of the adamantyl entity and the α-cyclodextrin annular protons. Nor are there cross peaks due to nOe interactions between the protons of the hexyl chain and the α-cyclodextrin annular protons. This is consistent with the adamantyl entity being too large to pass through the α-cyclodextrin annulus, and the hexyl chain being too short to enter the annulus when it is attached to a large substituent.

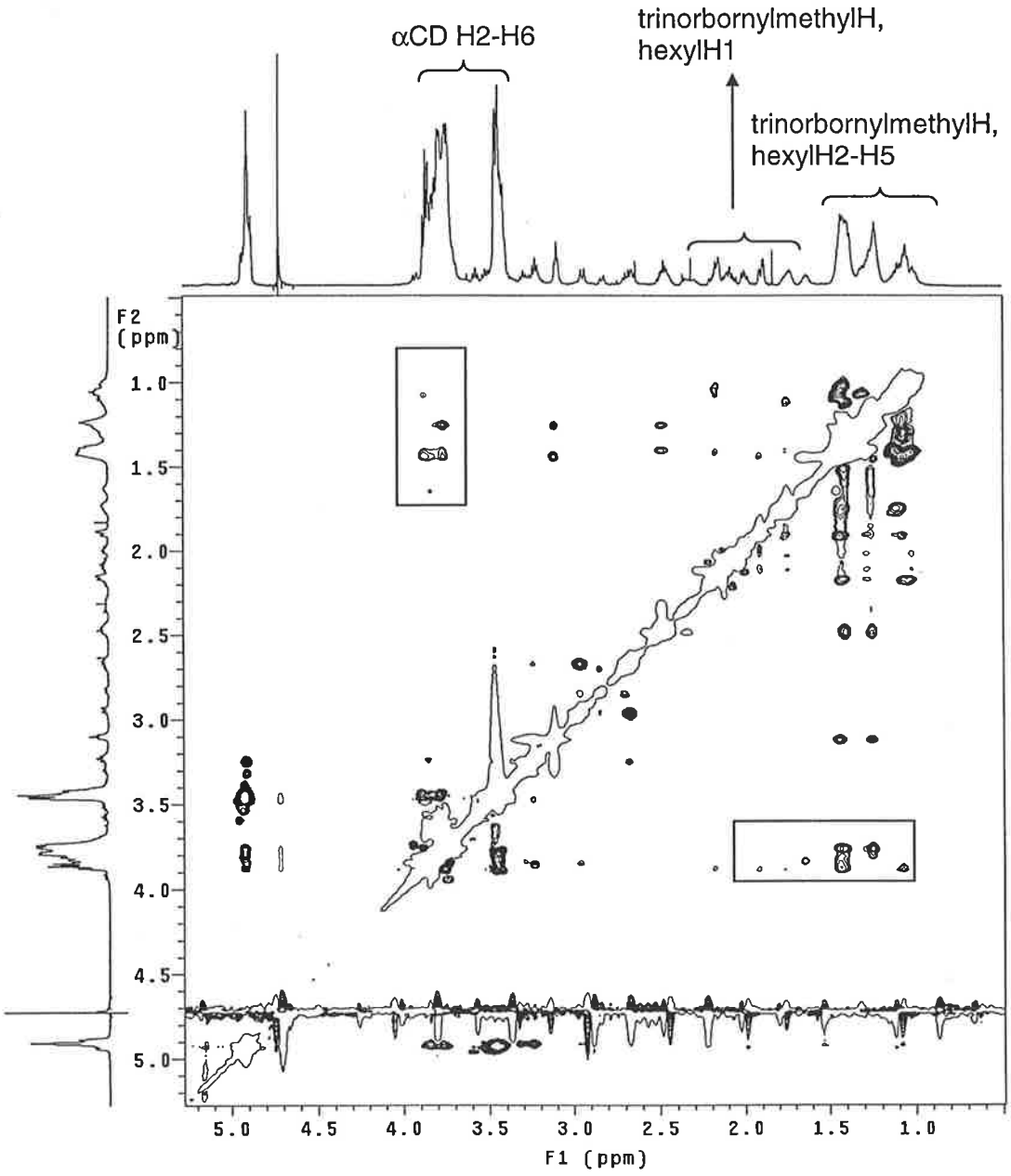


Figure 2.1.2 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 3 sec mixing time, 298 K) of 0.040 mol dm^{-3} modified α-cyclodextrin **35/35'** in D_2O, containing cross peaks (boxed) due to nOe interactions between the trinorbornylmethyl moiety protons and the α-cyclodextrin annular protons.

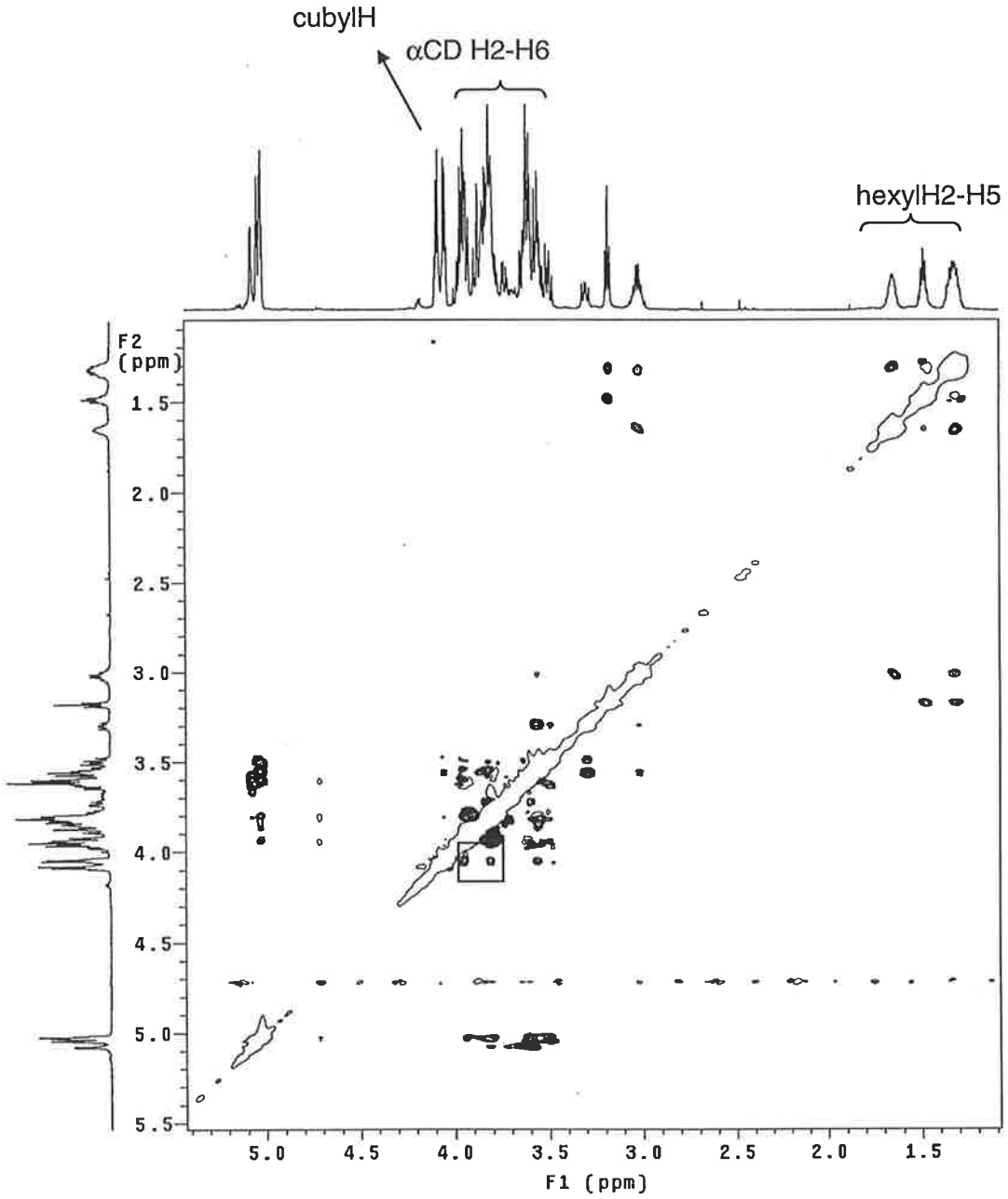


Figure 2.1.3 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 7, 3 sec mixing time, 298 K) of 0.031 mol dm^{-3} modified α-cyclodextrin **36/36'** in D_2O, containing cross peaks (boxed) due to nOe interactions between the cubyl moiety protons and the α-cyclodextrin annular protons.

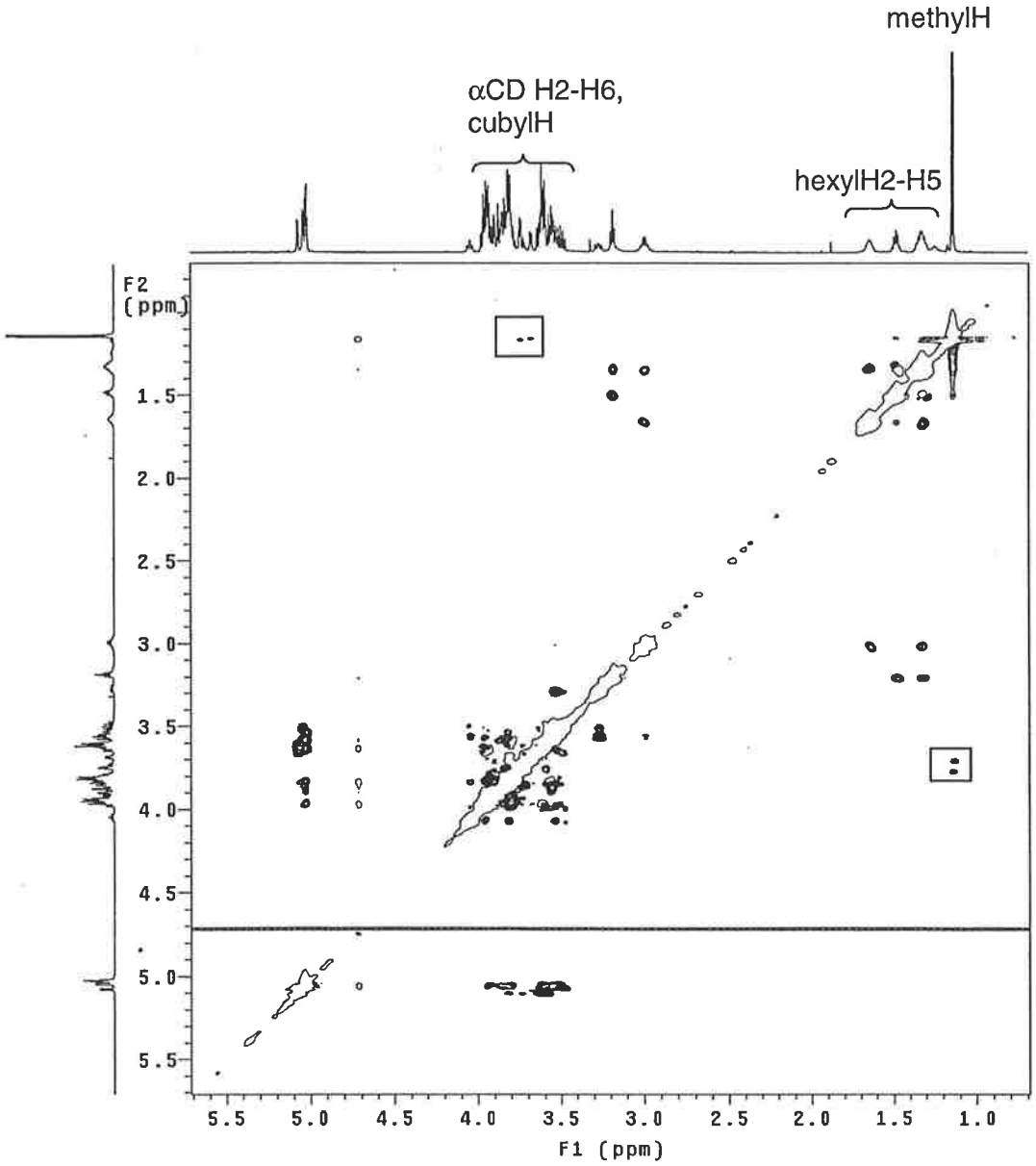


Figure 2.1.4 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 7, 3 sec mixing time, 298 K) of 0.035 mol dm^{-3} modified α-cyclodextrin **37/37'** in D_2O, containing cross peaks (boxed) due to nOe interactions between the methyl group protons and the α-cyclodextrin annular protons.

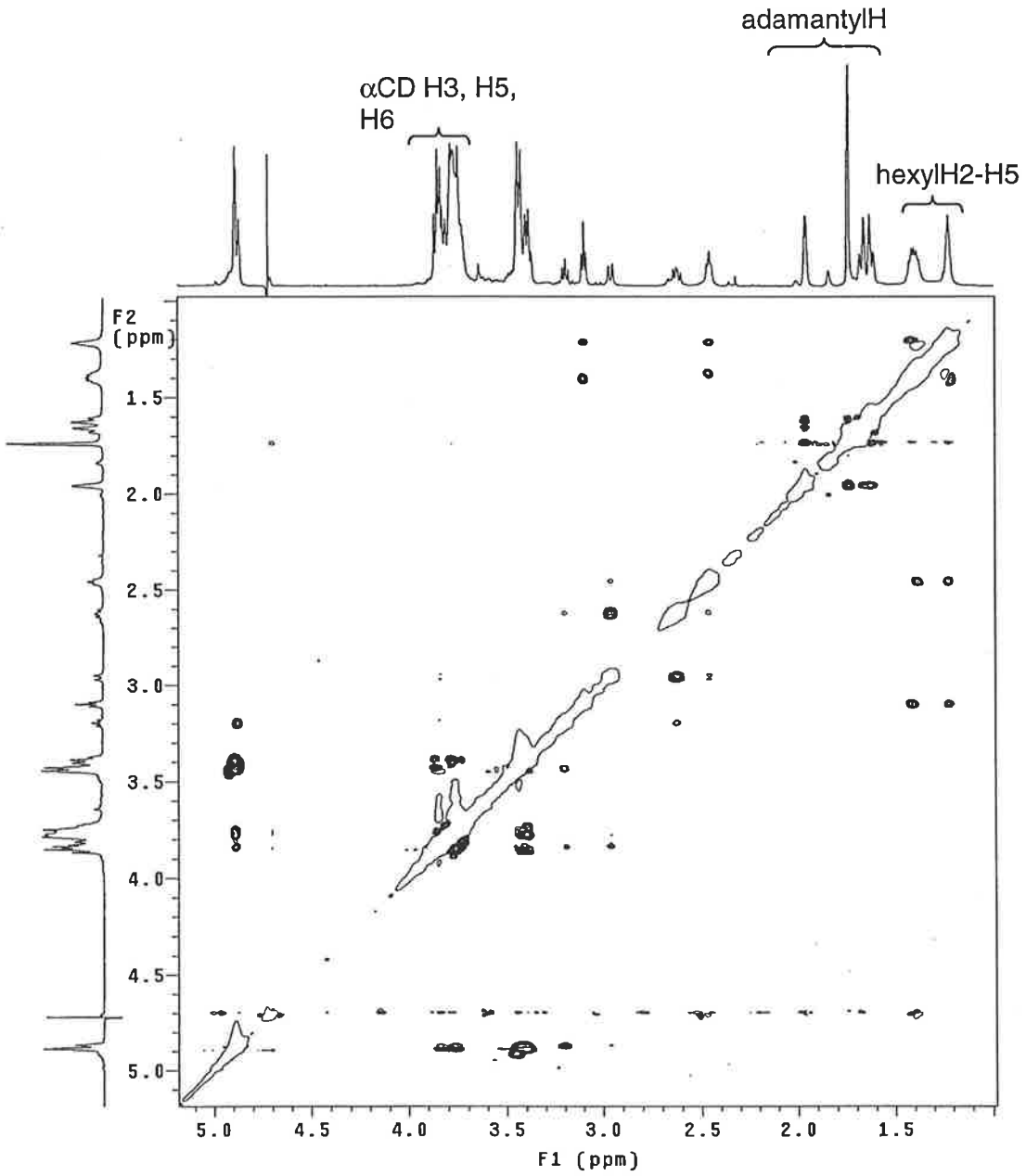


Figure 2.1.5 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 3 sec mixing time, 298 K) of 0.040 mol dm^{-3} modified α-cyclodextrin **38** in D_2O, containing no cross peaks due to nOe interactions between the adamantyl moiety protons and the α-cyclodextrin annular protons.

From the formation of the cyclodextrins **35/35'**, **36/36'**, **37/37'** and **38**, but not **38'**, the mechanistic uncertainty raised earlier has been solved. It is evident that the mechanism for the reaction involves electrophilic attack by **25-28** on the non-included aminohexylamine substituent of **34** to give **35-38**, followed by self-inclusion of the smaller substituents of **35-37** to give **35'-37'** in water, while the adamantyl moiety of **38** is too large to enter the α-cyclodextrin annulus and form **38'** (Scheme 2.1.2). It is assumed that the earlier reactions which formed the β-cyclodextrin analogues would have proceeded via the same mechanism (Scheme 2.1.1, Route 1), and that the self-included species **32'** was simply entropically favoured rather than mechanically restrained.

The reactions of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** and the β-cyclodextrin analogue **24** with **25-28** were carried out in DMF. Carrying out the reactions in a basic aqueous solution, a medium in which self-inclusion would be favoured through the hydrophobic effect, has problems associated with it in that the 4-nitrophenyl esters **25-28** react faster with water than with the modified cyclodextrins **24** and **34** [7].

It should be noted that the substituent of 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** is self-included in d_7-DMF. Although the hydrophobic effect is absent in DMF, other favourable intermolecular forces such as dipole-dipole and instantaneous dipole forces lead to inclusion of the aminohexylamine substituent. The 2D ^{1}H ROESY NMR spectrum of **24/24'** in d_7-DMF contains strong cross peaks between the resonances of the protons of the hexyl chain and the resonances of the cyclodextrin annular protons, which is indicative of considerable self-inclusion of the substituent. It is likely that a non-included substituent of **24** or **34** is substantially less hindered than a self-included substituent of **24'** or **34'** and this may lead to greater reactivity of the non-included species.

2.1.3 Conclusion

The substituents of the trinorbornylmethyl-, cubyl-, and dimethylcubyl-substituted α-cyclodextrins **35**, **36** and **37**, respectively, are self-included to give **35'-37'** in D_2O while the adamantyl moiety of **38** is too large to be self-included to give **38'**. These findings have provided evidence for the formation of **35'-37'** via the mechanism displayed in Scheme 2.1.2, involving reaction of the non-included species **34** with the 4-nitrophenyl esters **25-28** to give

35-38, followed by an aqueous work-up to give **35'-37'**, but not **38'**. It follows that the β-cyclodextrin analogues **29'-32'** were formed via Route 1 in Scheme 2.1.1, and that **32'** is simply a very stable self-included cyclodextrin, rather than a molecular knot.

2.1.4 References

1. C. J. Easton and S. F. Lincoln, *Modified Cyclodextrins: Scafffolds and Templates for Supramolecular Chemistry*, 1999, Imperial College Press, London.
2. B. L. May, P. Clements, J. Tsanaktsidis, C. J. Easton and S. F. Lincoln, *J. Chem. Soc., Perkin Trans. 1*, 2000, 463.
3. M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Perlmutter and D. S. Kristol, *J. Am. Chem. Soc.*, 1989, **111**, 6765.
4. L. D. Melton and K. N. Slessor, *Carbohydr. Res.*, 1971, 29.
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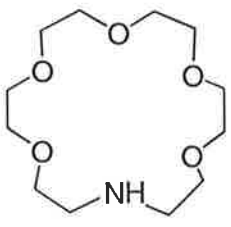
2.2 Azacoronand-Substituted Cyclodextrins

2.2.1 Introduction

The reactions of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** with the 4-nitrophenyl esters **25-28**, discussed in section 2.1, did not produce molecular knots. The necessity of carrying out the attachment of the 'blocking groups' to **34/34'** in organic solution, rather than in water, resulted in a small percentage of the cyclodextrin molecules existing as the self-included species **34'**. Considerable hindrance to attack at the included substituent of **34'** is also envisaged. A molecular knot cannot be prepared directly from a modified cyclodextrin such as **34'** by the reaction of a blocking group with the terminal group on the substituent under the conditions employed.

An alternative method for preparing molecular knots was investigated. If a modified cyclodextrin containing a flexible ligand, which is attached through a sufficiently long tether, is prepared in organic solution, the ligand may subsequently slip through the cyclodextrin annulus in aqueous solution. Expansion of the ligand when it is bound to a metal ion could then produce a blocking group, thus forming a molecular knot. Molecular modelling showed the azacoronands 1,4,7,10-tetraoxa-13-azacyclopentadecane **39** and 1,4,7,10,13-pentaoxa-16-azacyclooctadecane **40** to have a similar size to the β-cyclodextrin annulus size. Due to the considerable flexibility of the azacoronands, it was envisaged that the passage of these ligands through both α- and β-cyclodextrin annuli could occur.

39

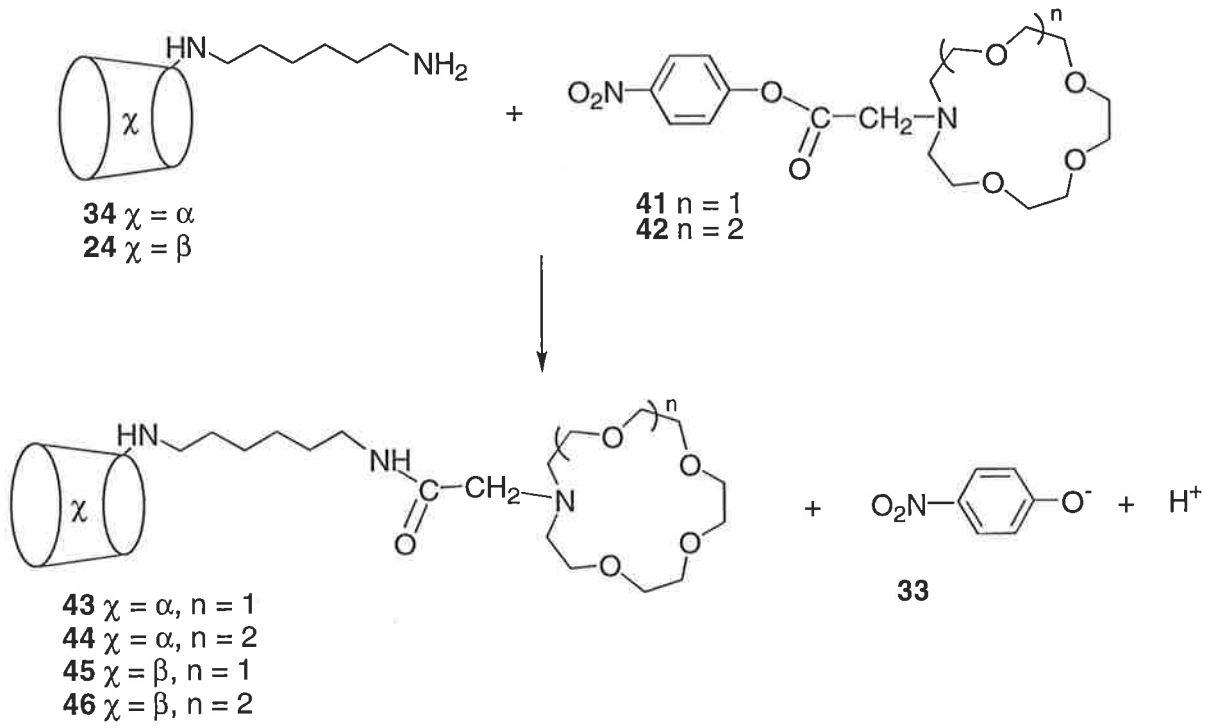


40

2.2.2 Results and Discussion

Synthesis

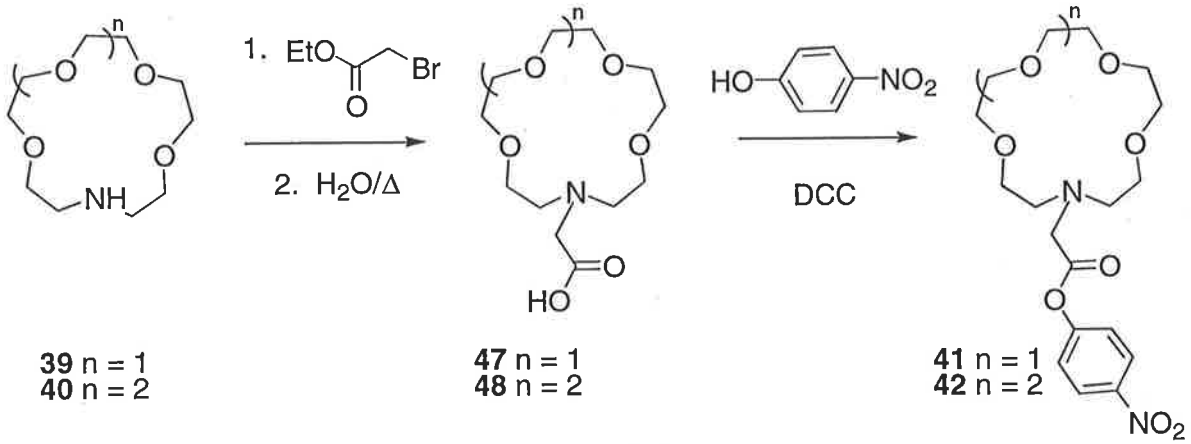
The azacoronand-substituted α- and β-cyclodextrins **43-46** were synthesized by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** by either of the 4-nitrophenyl esters **41** or **42** (Scheme 2.2.1). 6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** was prepared as described in section 2.1 and 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** was prepared in a similar manner from 6^A-*O*-(4-methylbenzenesulfonyl)-β-cyclodextrin **5** [1].



Scheme 2.2.1 Synthesis of the azacoronand-substituted cyclodextrins **43-46**.

The precursors to the 4-nitrophenyl esters **41** and **42**, 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetic acid **47** and 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetic acid **48**, were prepared in a similar manner to literature procedures (Scheme 2.2.2) [2-4]. The ethyl esters of **47** and **48** were prepared from the reactions of 1,4,7,10-tetraoxa-13-azacyclopentadecane **39** or 1,4,7,10,13-pentaoxa-16-azacyclooctadecane **40**, respectively, with ethyl bromoacetate in the presence of sodium carbonate. Hydrolysis of the esters by heating at reflux in water for two days gave the corresponding carboxylic acids **47**

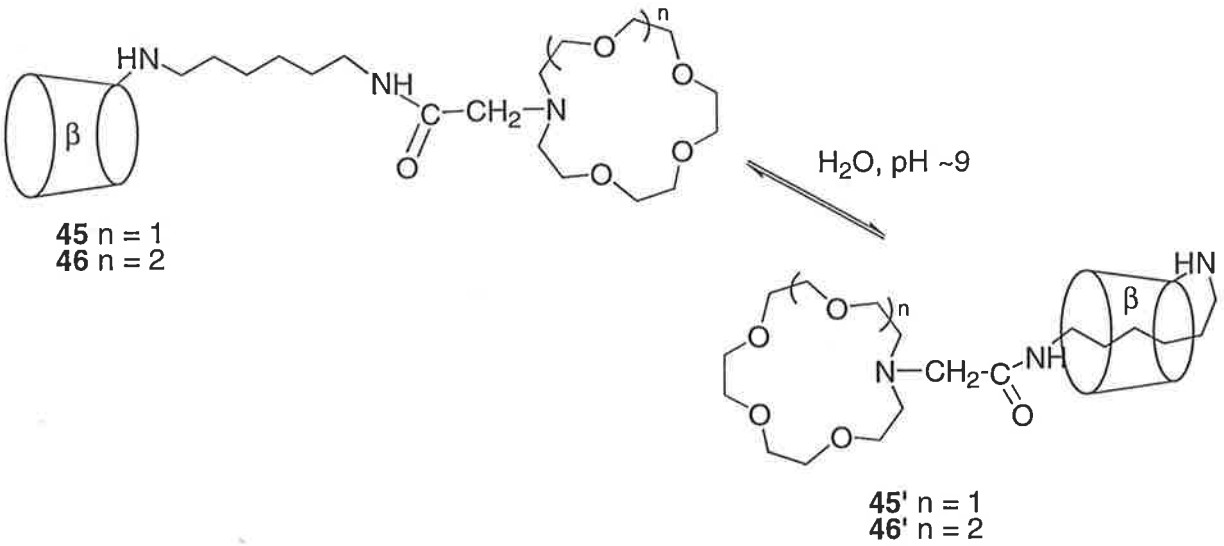
and **48**. The reactions of **47** or **48** with 4-nitrophenol in the presence of dicyclohexylcarbodiimide (DCC) produced the 4-nitrophenyl esters **41** and **42**, respectively.



Scheme 2.2.2 Synthesis of the 4-nitrophenyl esters **41** and **42**.

2D ^{1}H ROESY NMR spectroscopy

In D_2O at pD ~ 9 (the pD of 0.02-0.03 mol dm^{-3} solutions of **43-46**), the hexyl chains of the modified β-cyclodextrins **45** and **46** are self-included to form **45'** and **46'**, while the substituents of the modified α-cyclodextrins **43** and **44** are not self-included (Scheme 2.2.3). Cross peaks due to nOe interactions between the β-cyclodextrin annular protons and the hexyl H2-H5 protons in the 2D ^{1}H ROESY NMR spectra of **45/45'** (Figure 2.2.1) and **46/46'** (Figure 2.2.2) are indicative of the inclusion of the central part of the hexyl chain in the β-cyclodextrin annulus in each case. (The cross peaks due to interactions between the cyclodextrin annular protons and the hexyl H2 and H5 protons are comparatively weak due to these hexyl protons being positioned towards the ends of the cyclodextrin annulus. At the intensity of some ROESY spectra in this section, these cross peaks are absent on the F2 axis.) No such cross peaks are present in the 2D ^{1}H ROESY NMR spectra of the modified α-cyclodextrins **43** and **44** (Figures 2.2.3 and 2.2.4). The overlap of the resonances of the azacoronand protons with those of the cyclodextrin H2 and H4 protons renders it impossible to determine whether the azacoronand moieties of **43** and **44** are self-included, although it is unlikely that the azacoronands would be included in preference to the more hydrophobic hexyl chain. The primary end of the α-cyclodextrin annulus is too small to allow the azacoronands to slip through, despite their flexibility.



Scheme 2.2.3 Self-inclusion of the substituents of the modified β-cyclodextrins **45** and **46** to give **45'**and **46'**.

The ^{1}H NMR spectra of **45/45'** and **46/46'** display broadening of the resonances arising from the hexyl chain protons, indicative of there being restricted motion in these systems. The equilibria between **45** and **45'** and **46** and **46'** are slow on the NMR timescale, due to the close match in the sizes of the azacoronands and that of the β-cyclodextrin annulus. The ^{1}H NMR spectra of the modified α-cyclodextrins **43** and **44** do not display broadened resonances, in agreement with the 2D ^{1}H ROESY data; there is no evidence for the formation of **43'** and **44'**.

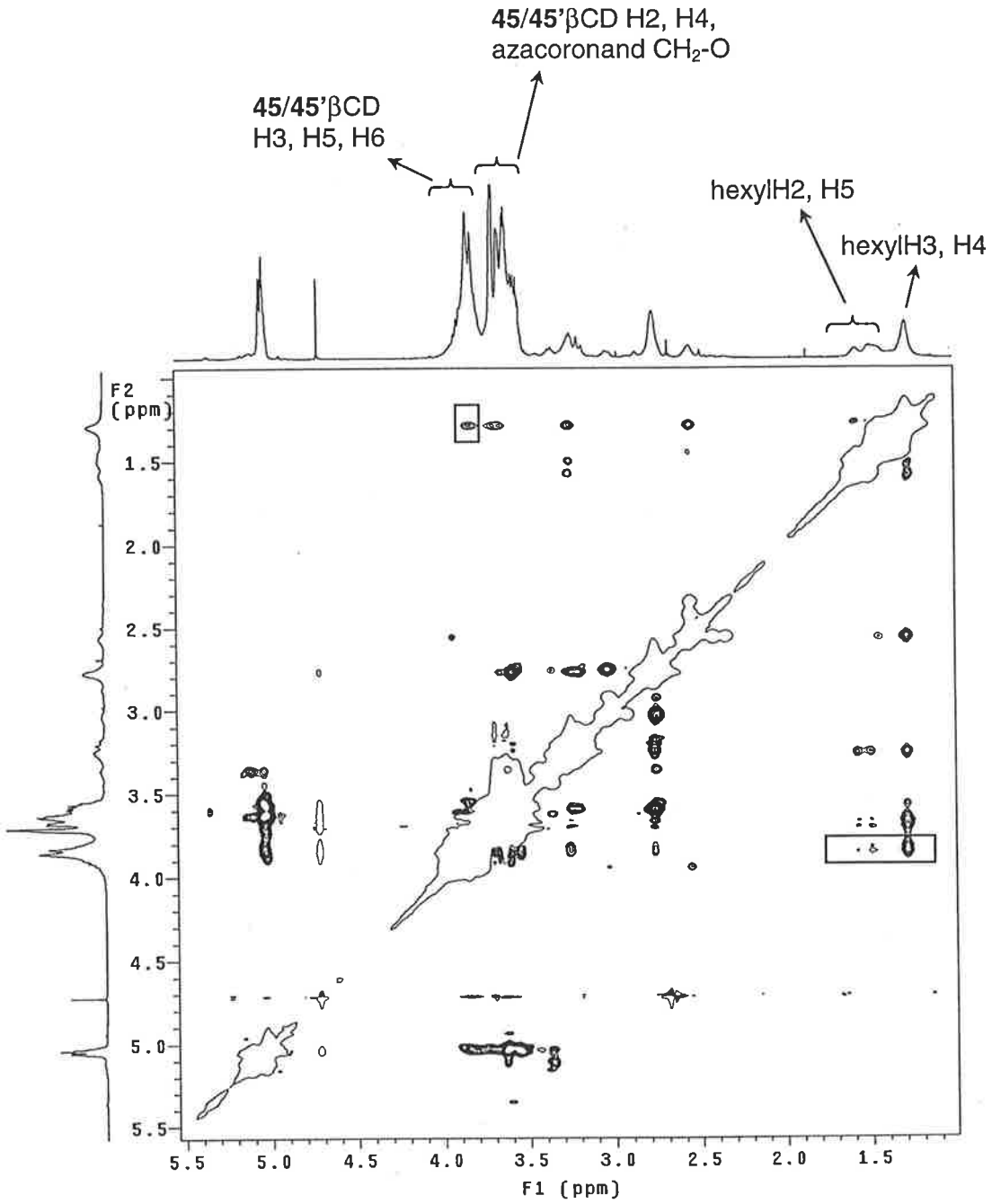


Figure 2.2.1 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.025 mol dm^{-3} modified β-cyclodextrin **45/45'** in D_2O, containing cross peaks (boxed) due to nOe interactions between the hexyl chain protons and the β-cyclodextrin annular protons.

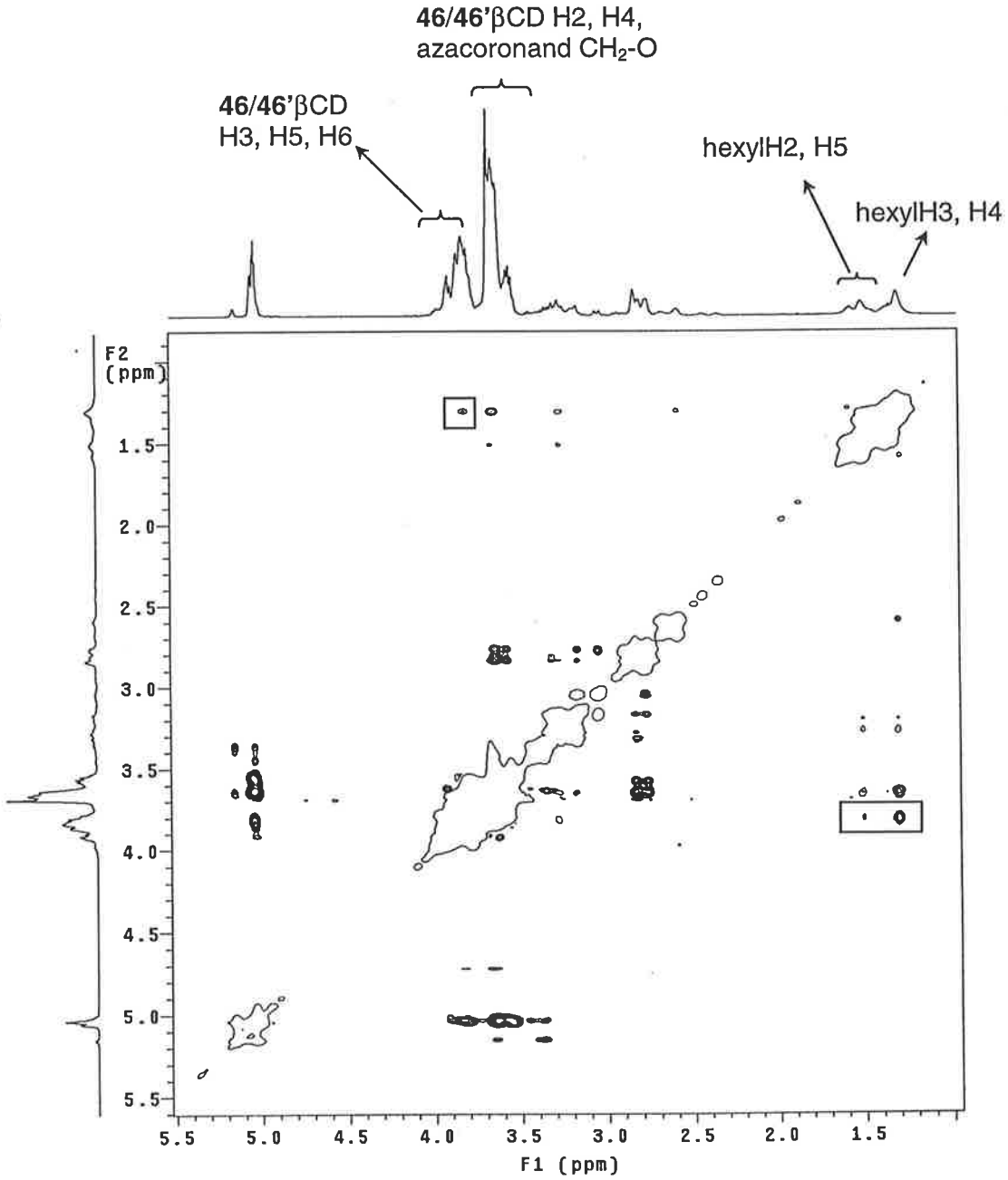


Figure 2.2.2 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.025 mol dm^{-3} modified β-cyclodextrin **46/46'** in D_2O, containing cross peaks (boxed) due to nOe interactions between the hexyl chain protons and the β-cyclodextrin annular protons.

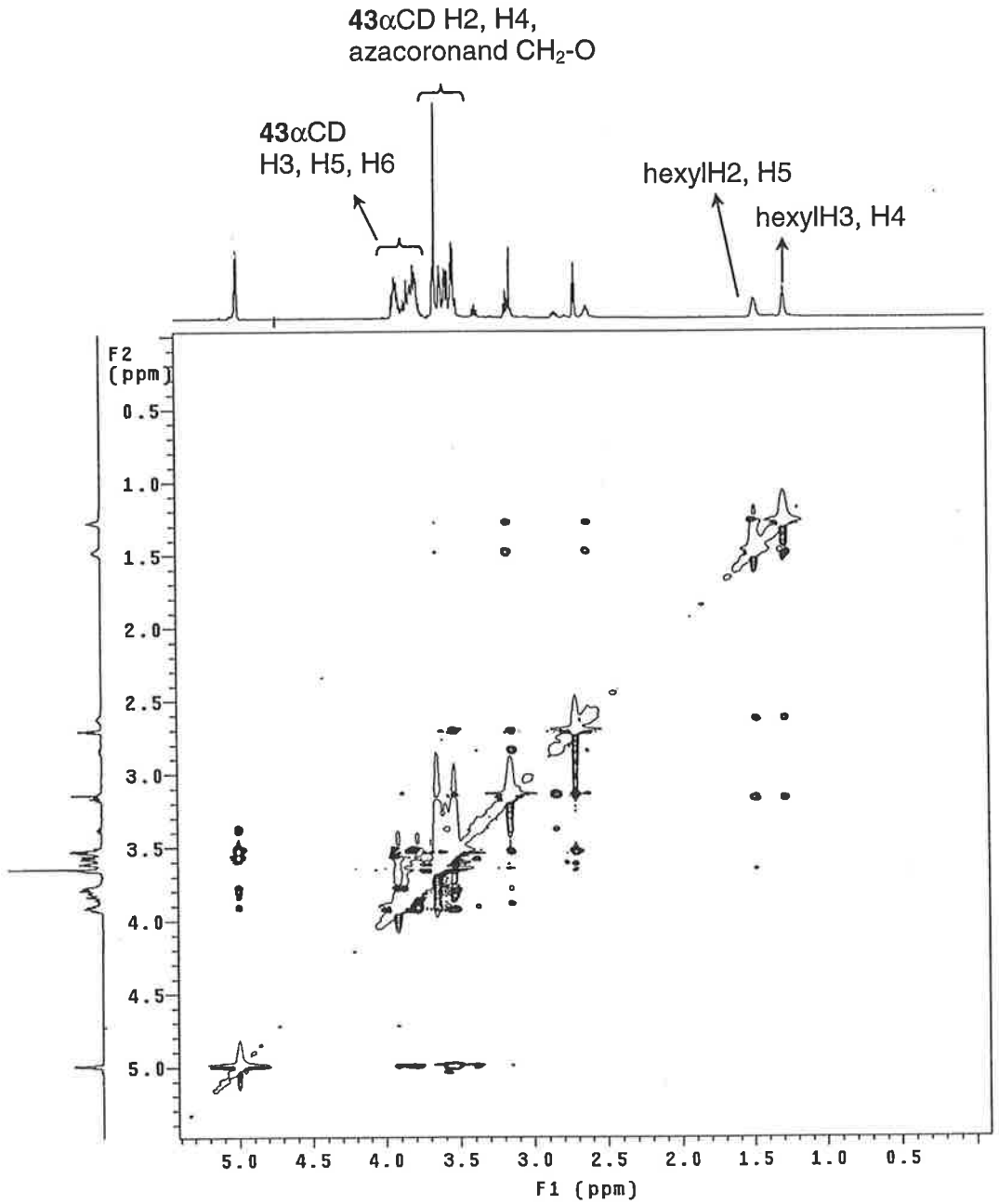


Figure 2.2.3 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.023 mol dm^{-3} modified α-cyclodextrin **43** in D_2O, containing no cross peaks due to nOe interactions between the hexyl chain protons and the α-cyclodextrin annular protons.

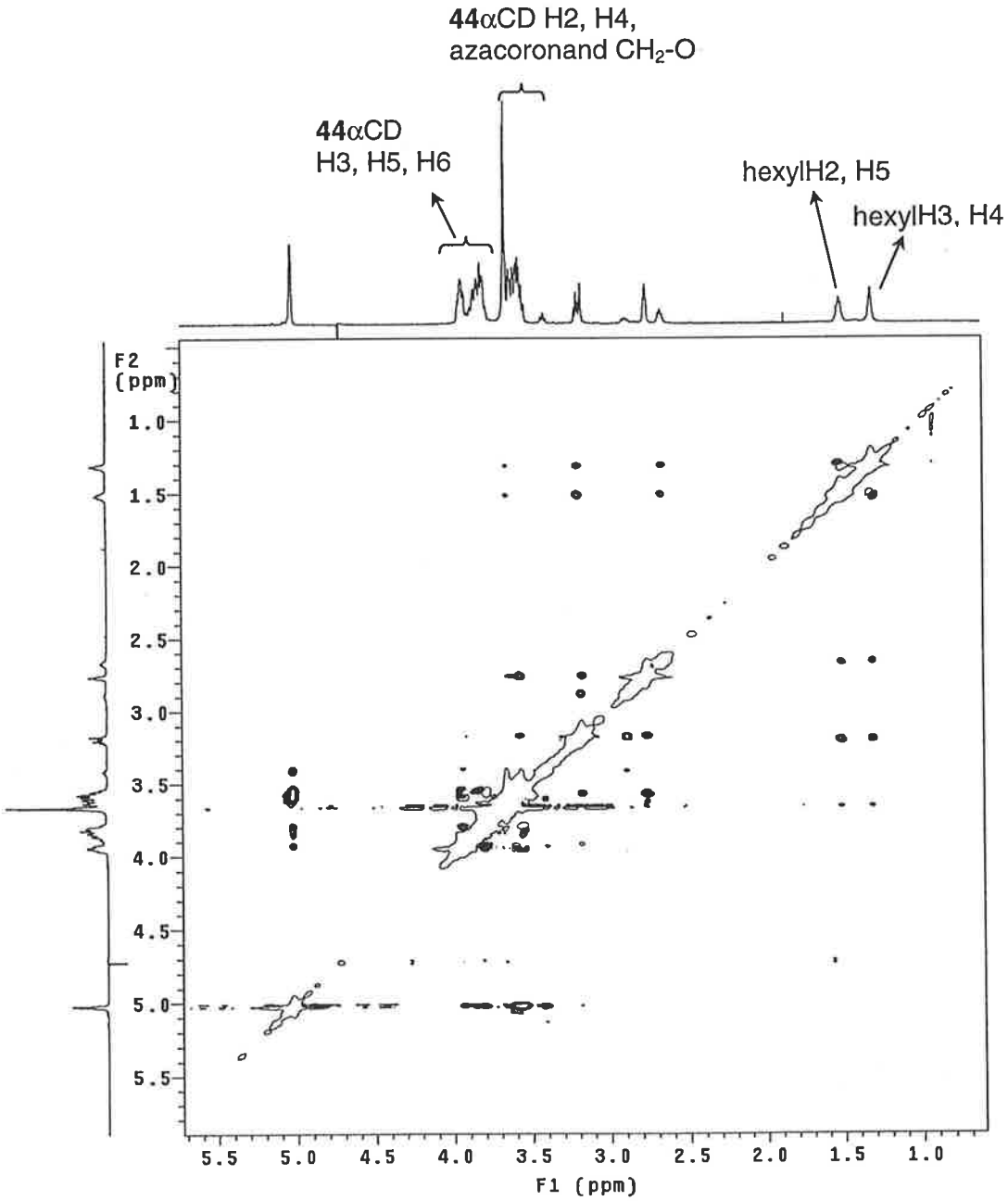
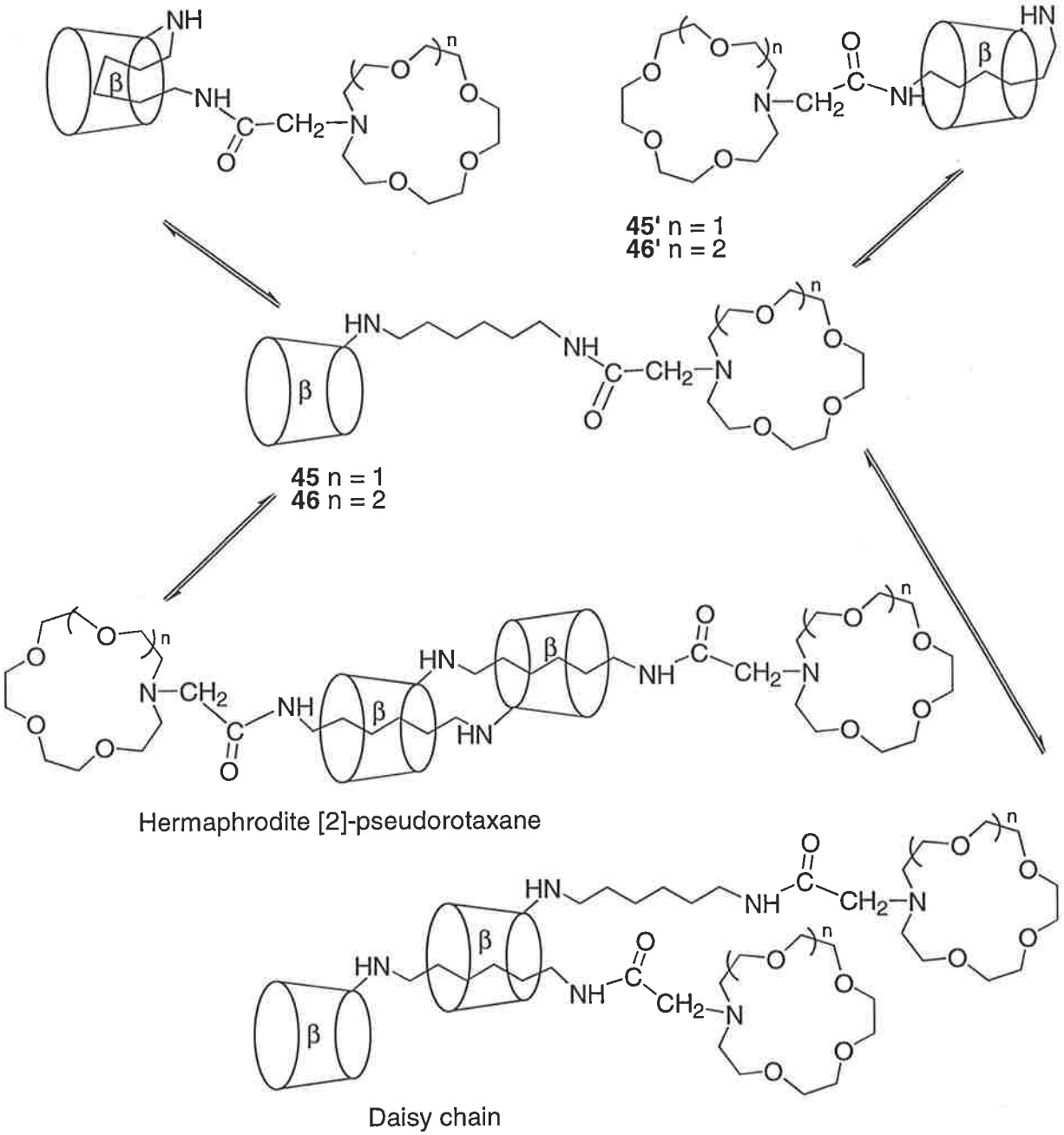


Figure 2.2.4 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.014 mol dm^{-3} modified α-cyclodextrin **44** in D_2O, containing no cross peaks due to nOe interactions between the hexyl chain protons and the α-cyclodextrin annular protons.

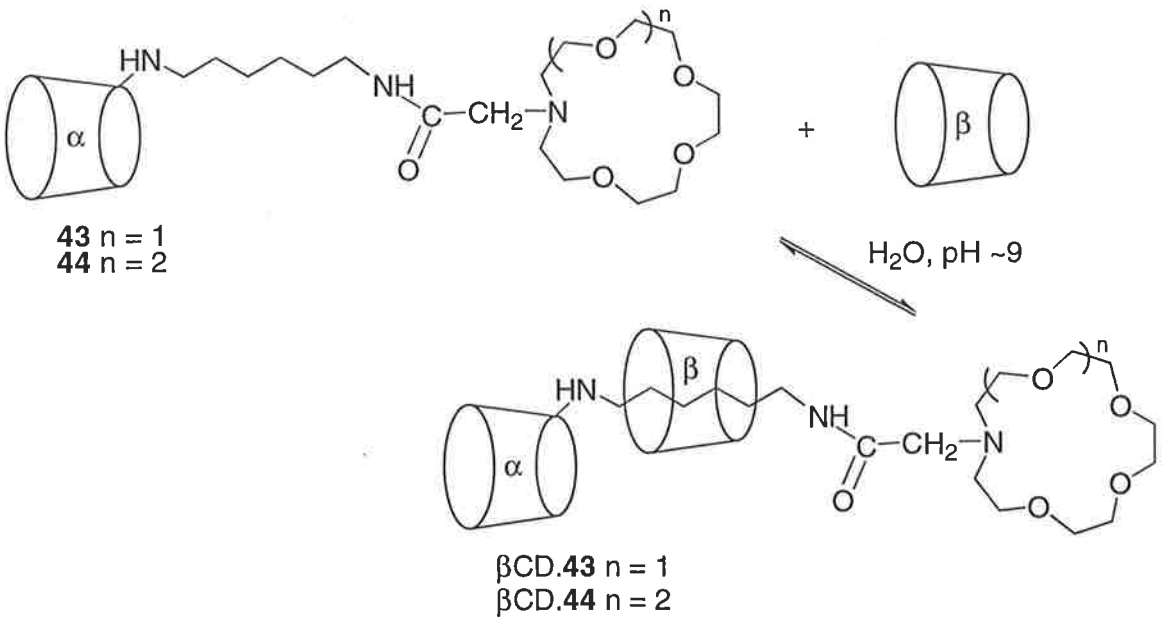
The representations of **45'** and **46'** in Scheme 2.2.3 are not the only architectures that could give rise to the cross peaks which are present in the 2D ^{1}H ROESY NMR spectra. In theory, equilibria between all of the species depicted in Scheme 2.2.4 could exist. Entropic arguments support self-inclusion of the hexyl chain rather than formation of a daisy chain or an Hermaphrodite [2]-pseudorotaxane, structures which are generally formed when the substituent of the cyclodextrin is rigid [5], and it is believed that the hexyl chain is too short to curl back into the β-cyclodextrin annulus. In previous work, a 2,4,6-trinitrophenyl moiety, which is too large to be included in a β-cyclodextrin annulus, was tethered to β-cyclodextrin by a hexyl chain [6]. It was found that the hexyl chain was not self-included when tethered to a group that is too large to enter β-cyclodextrin. This is also evident in the spectra of the α-cyclodextrins **43** and **44**.



Scheme 2.2.4 Possible intramolecular and intermolecular inclusion complexes in equilibrium with the modified cyclodextrins **45** and **46** in D_2O at pD 9.

Evidence for the azacoronand moieties being small and flexible enough to slip through a β-cyclodextrin annulus was obtained from the 1D ^1H and 2D ^1H ROESY NMR spectra of D_2O solutions containing either **43** or **44** and β-cyclodextrin. Cross peaks due to nOe interactions between the β-cyclodextrin annular protons and the hexyl H2-H5 protons of **43** or **44** are present in the 2D ^1H ROESY NMR spectra of D_2O solutions of the components

(Figures 2.2.5 and 2.2.6), and the ^{1}H 1D NMR spectra of **43** or **44** in the presence of β-cyclodextrin display considerably broadened resonances compared with those in the spectra of **43** or **44** alone. This supports the formation of the intermolecular inclusion complexes βCD.**43** and βCD.**44** in which the hexyl chain of **43** or **44** is included in a β-cyclodextrin annulus (Scheme 2.2.5). The intermolecular inclusion complexes βCD.**43** and βCD.**44** are unusual examples of [2]-pseudorotaxanes, in that the wheel component and a blocking group at one end of the axle are both cyclodextrins. Similar [2]-pseudorotaxanes probably form in competition with **45'** and **46'** if β-cyclodextrin is added to an aqueous solution of either of the modified β-cyclodextrins, but due to the overlap of the resonances of the cyclodextrin protons that would result, this was not studied in detail.



Scheme 2.2.5 The substituents of the modified α-cyclodextrins **43** and **44** include in β-cyclodextrin to form the [2]-pseudorotaxanes βCD.**43** and βCD.**44**.

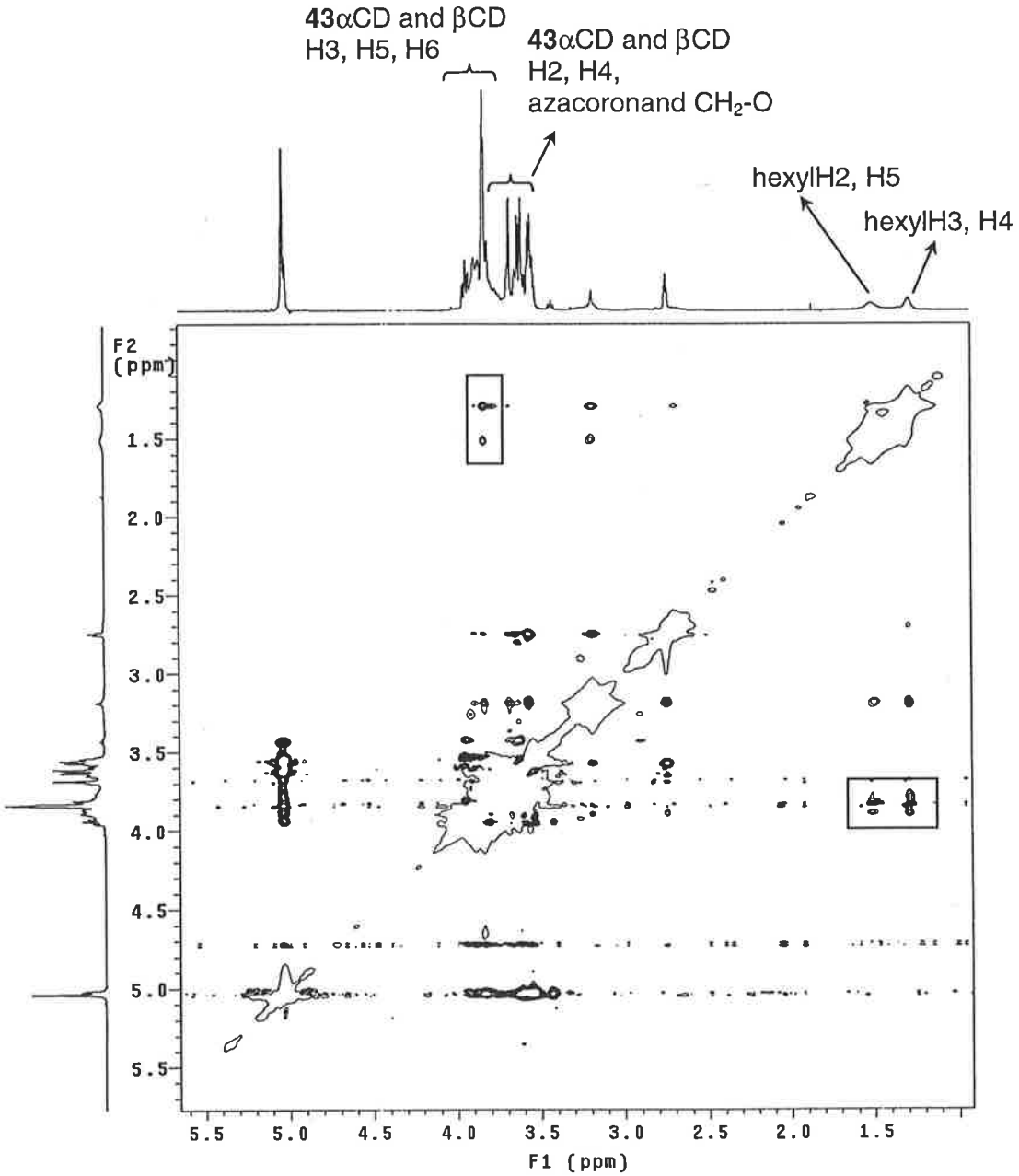


Figure 2.2.5 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.023 mol dm^{-3} modified α-cyclodextrin **43** and 0.030 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the hexyl chain protons of **43** and the β-cyclodextrin annular protons.

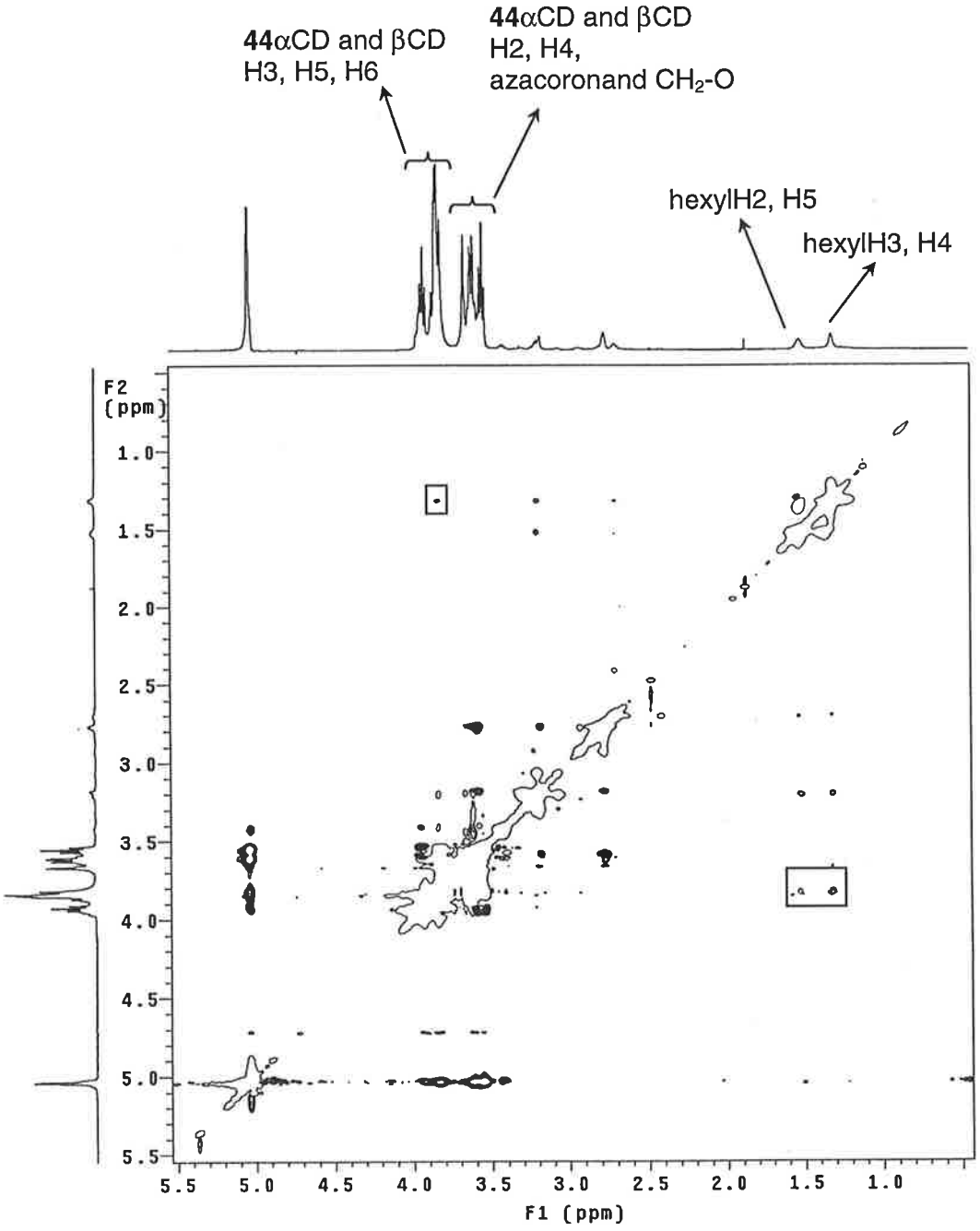
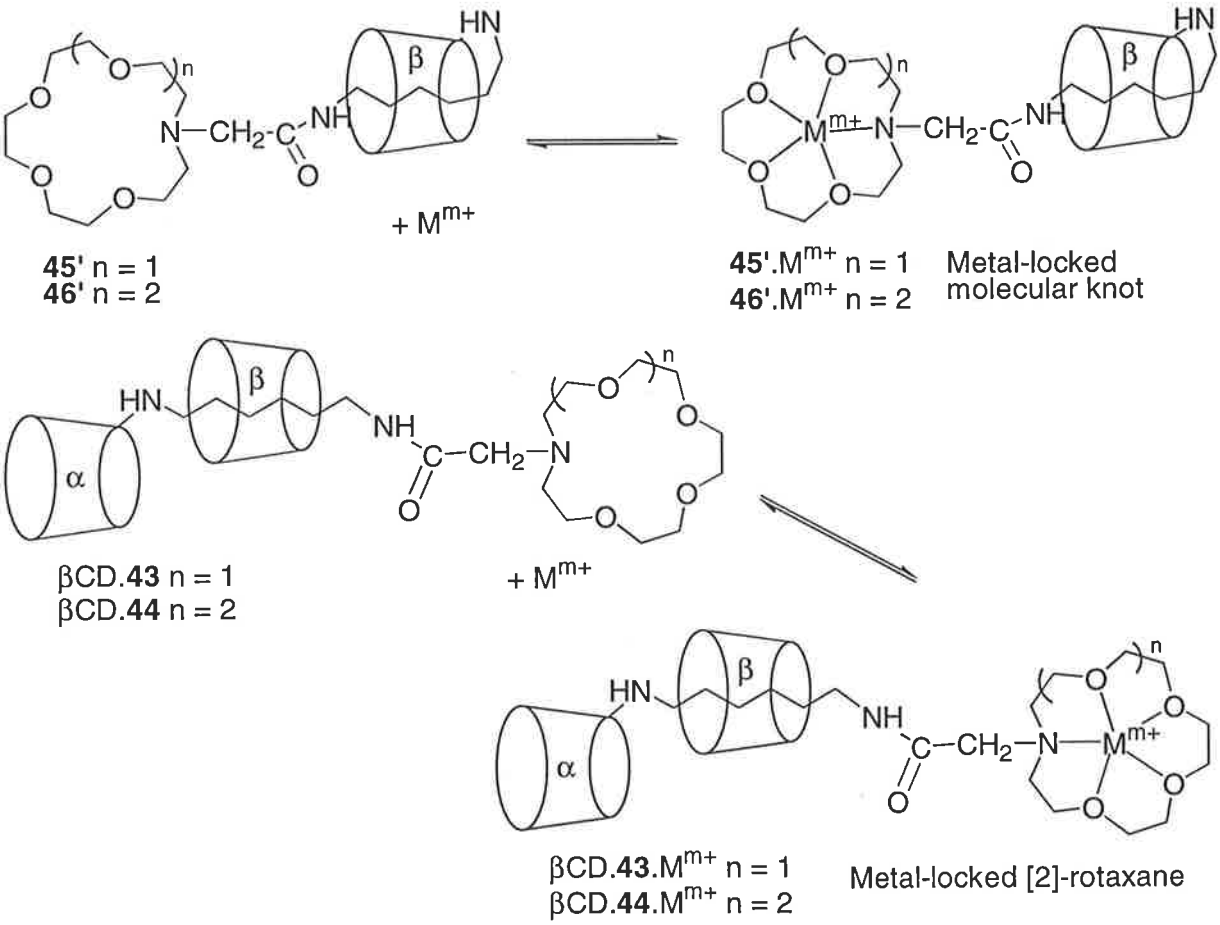


Figure 2.2.6 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 9, 0.3 sec mixing time, 298 K) of 0.014 mol dm^{-3} modified α-cyclodextrin **44** and 0.022 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the hexyl chain protons of **44** and the β-cyclodextrin annular protons.

Metal binding studies

The binding of an appropriate metal by the azacoronand moieties of **45'** and **46'** was expected to expand these ligands and make them more rigid such that their passage back through the β-cyclodextrin annulus is not possible. The resulting architectures would be 'metal-locked' molecular knots and it was expected that similar metal attachment to the [2]-pseudorotaxanes βCD.**43** and βCD.**44** would produce [2]-rotaxanes (Scheme 2.2.6).



Scheme 2.2.6 Metal-locking of the azacoronand moiety of the modified β-cyclodextrins **45'** and **46'** to form molecular knots, and metal-locking of the azacoronand moiety of the modified α-cyclodextrins **43** and **44** inside β-cyclodextrin to form [2]-rotaxanes.

From inspection of the 2D ^{1}H ROESY NMR spectrum of the modified cyclodextrin **45/45'** at pD 7, it is evident that only a small percentage of the self-included species **45'** is present in solution, as the cross peaks due to nOe interactions between the hexyl chain protons and the cyclodextrin annular protons are very weak. The substituent of the modified β-cyclodextrin **46** is not self-included at pD 7 and the [2]-pseudorotaxanes βCD.**43** and βCD.**44**

do not form at pD 7. Most metal hydroxides have negligible solubility above pH 7, thus only **45/45'** was selected for metal binding studies. Potentiometric titrations were carried out and the titration curves were fitted using the program SUPERQUAD [7] to obtain the pK_as of $[\mathbf{45/45'}.2H]^{2+}$ (Table 2.2.1). The titration of **45/45'** was repeated in the presence of calcium(II), zinc(II) or lanthanum(III) to determine the stability constants (log(K) values) of the metal complexes of **45/45'** and $[\mathbf{45/45'}.H]^{+}$ (Table 2.2.2).

Table 2.2.1 Acid dissociation constants (pK_as) of the cyclodextrin $[\mathbf{45/45'}.2H]^{2+}$, determined by the titration of a solution containing 0.001 mol dm^{-3} **45/45'**, 0.0032 mol dm^{-3} $HClO_4$ and 0.1 mol dm^{-3} NEt_4ClO_4 with 0.0975 mol dm^{-3} NEt_4OH at 298 K.

Equation	pK_a
(1) $[\mathbf{45/45'}.2H]^{2+} \rightleftharpoons [\mathbf{45/45'}.H]^{+} + H^{+}$	5.84 ± 0.03
(2) $[\mathbf{45/45'}.H]^{+} \rightleftharpoons \mathbf{45/45'} + H^{+}$	8.49 ± 0.04

Table 2.2.2 Stability constants (K) of the metal complexes of the cyclodextrin **45/45'** determined by the titration of solutions containing 0.001 mol dm^{-3} **45/45'**, 0.0032 mol dm^{-3} $HClO_4$, 0.1 mol dm^{-3} NEt_4ClO_4 and either 0.002 mol dm^{-3} $Ca(ClO_4)_2$, 0.002 mol dm^{-3} $La(CF_3SO_3)_3$ or 0.002 mol dm^{-3} $Zn(ClO_4)_2$ with 0.0975 mol dm^{-3} NEt_4OH at 298 K.

Equation	log(K/dm^3 mol^{-1})
(5) $\mathbf{45/45'} + Ca^{2+} \rightleftharpoons [\mathbf{45/45'}.Ca]^{2+}$	<2
(6) $[\mathbf{45/45'}.H]^{+} + Zn^{2+} \rightleftharpoons [\mathbf{45/45'}.H.Zn]^{3+}$	3.93 ± 0.07
(7) $\mathbf{45/45'} + Zn^{2+} \rightleftharpoons [\mathbf{45/45'}.Zn]^{2+}$	6.34 ± 0.06
(8) $[\mathbf{45/45'}.H]^{+} + La^{3+} \rightleftharpoons [\mathbf{45/45'}.H.La]^{4+}$	3.06 ± 0.07
(9) $\mathbf{45/45'} + La^{3+} \rightleftharpoons [\mathbf{45/45'}.La]^{3+}$	5.44 ± 0.05

The pK_as of 5.84 and 8.49 determined for $[\mathbf{45/45'}.2H]^{2+}$ are assigned to the amine of the azacoronand and the amine directly attached to the β-cyclodextrin, respectively, by comparison with previous work [8]. In D_2O at pD 7, the amine of the azacoronand is less than 10 % protonated, but the amine attached to the β-cyclodextrin is close to completely

protonated. Protonation of the amine attached to the β-cyclodextrin in **45** makes the primary end of the annulus too hydrophilic for the substituent to slip through. It is envisaged that similar protonation of the amine attached to the cyclodextrin in **43**, **44** and **46** hinders formation of the species $[\beta CD.\mathbf{43}.H]^+$, $[\beta CD.\mathbf{44}.H]^+$ and $[\mathbf{46'}.H]^+$ at pD 7. Under these conditions, the protonated amine attached to the α-cyclodextrin in $[\mathbf{43}.H]^+$ and $[\mathbf{44}.H]^+$ is too closely situated to the β-cyclodextrin annulus in $[\beta CD.\mathbf{43}.H]^+$ and $[\beta CD.\mathbf{44}.H]^+$ for these [2]-pseudorotaxanes to form. The cyclodextrin $[\mathbf{45'}.H]^+$ has an entropic advantage over $[\beta CD.\mathbf{43}.H]^+$, such that a small amount of $[\mathbf{45'}.H]^+$ forms in D_2O at pD 7.

The strongest metal binding of **45/45'** that was observed was by zinc(II), while lanthanum(III) exhibited weaker binding and in the case of calcium(II), the binding was so weak that the data could not be fitted reliably using SUPERQUAD. Only the data at a pH lower than ~7 for lanthanum(III) and lower than ~6 for zinc(II) were used to fit the titration curves due to precipitation of the corresponding metal hydroxides above pH ~8 and pH ~7, respectively. The stability of the complex formed is partially dependent on the comparative sizes of the metal ion and azacoronand. This implies that the azacoronand of **45/45'** is of appropriate size to bind zinc(II), but too small to strongly bind lanthanum(III) and calcium(II) (zinc(II) has a smaller ionic radius than calcium(II) and lanthanum(III) which have very similar ionic radii [9]). The higher charge of lanthanum(III) compared to that of calcium(II) may partly account for the stronger binding of lanthanum(III) by the azacoronand. A study on the bond dissociation energies of gas-phase M^+-coronand complexes (M = Na, K, Rb, Cs) has shown the charge density of the metal to have a significant impact on the affinity of the coronand for the metal [10].

The weak cross peaks that are present in the 2D ^1H ROESY NMR spectrum of $[\mathbf{45/45'}.H]^+$ in D_2O at pD 7 are absent in the spectrum of the solution at pD ~6.5 after the addition of ~2 equivalents of zinc(II) perchlorate. The major species present in solution before the addition of zinc(II) is $[\mathbf{45}.H]^+$, not $[\mathbf{45'}.H]^+$, thus a negligible percentage of zinc(II) ions are bound by the azacoronand moiety of the modified cyclodextrin while the substituent is self-included. Despite the demonstration of strong binding of zinc(II) ions by **45/45'**, a molecular knot cannot be formed under these conditions.

2.2.3 Conclusion

The substituents of the azacoronand-substituted β-cyclodextrins **45** and **46** are self-included to form **45'** and **46'** in D_2O at pD 9, while the substituents of the corresponding modified α-cyclodextrins are not self-included due to the α-cyclodextrin annulus being too small. The unusual [2]-pseudorotaxanes βCD.**43** and βCD.**44**, in which both the wheel component and one blocking group are cyclodextrins, form in D_2O at pD 9. Protonation of the amine directly attached to the cyclodextrin in **43-46** in D_2O at pD 7 makes the formation of the self-included species $[\mathbf{45'}.H]^+$ and $[\mathbf{46'}.H]^+$ and the [2]-pseudorotaxanes $[\beta CD.\mathbf{43}.H]^+$ and $[\beta CD.\mathbf{44}.H]^+$ unfavourable.

The azacoronand of **45/45'** was found to bind zinc(II) and lanthanum(III) strongly, but conditions could not be found for which an included azacoronand moiety of **45'** could be reacted with a soluble metal ion. Further work may involve the synthesis of modified cyclodextrins with an amide group, rather than an amine, directly attached to the cyclodextrin to remove the possibility of protonation at this point. This may remove the pH-dependence of the self-inclusion of the substituent and allow molecular knot formation by metal-locking to be investigated. In addition, utilisation of axles terminating in either 1,4,7,10-tetraoxa-13-azacyclopentadecane **39** or 1,4,7,10,13-pentaoxa-16-azacyclooctadecane **40** may provide a route to β-cyclodextrin [2]-rotaxanes in a manner akin to the 'slippage' mechanism, in which the axle slowly slips inside the cyclodextrin annulus and is locked in place by a metal ion.

2.2.4 References

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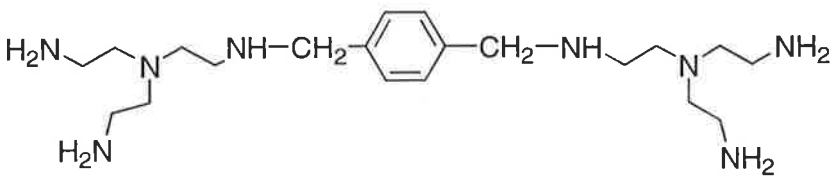
Chapter 3. Cobalt(III)-Blocked Cyclodextrin [2]-Rotaxanes

3.1 Introduction

A [2]-rotaxane is a two-component system consisting of a molecular 'wheel' threaded onto a long molecular 'axle' that is capped by blocking groups large enough to mechanically prevent the separation of the components. The most common method for constructing a [2]-rotaxane is 'threading', which involves the attachment of stable blocking groups to the ends of the axle once it is included inside the wheel component. This is a challenging task in aqueous solution, which is the preferred medium for cyclodextrin [2]-rotaxane syntheses. The binding of amines to cobalt(III) to form inert complexes (in which at least four amines bind cobalt(III)) is well-known [1-5], making cobalt(III) tetramine complexes attractive alternatives to covalent blocking groups. Previously, cobalt(III) 1,2-diaminoethane complexes have been exploited as blocking groups for cyclodextrin [2]-rotaxanes. In these examples the blocking group attachments were carried out in DMSO due to the low water solubility of the axles used [6-8]. In DMSO the hydrophobic effect is absent, which led to low yields of the [2]-rotaxanes. The research discussed herein was based on the belief that substituting the axles used in earlier work with a water-soluble axle would produce a considerable advantage over earlier systems, as the hydrophobic effect would drive the inclusion of the axle inside a cyclodextrin annulus.

The axle **49** was designed with 'tren' (tris(2-aminoethyl)amine) groups at the ends of the axle to give it water-solubility and to provide four amine groups for the formation of a stable cobalt(III) complex. The inclusion of aromatic guests inside cyclodextrins in aqueous solution is well-known [9], thus an aromatic centre was incorporated into the axle design.



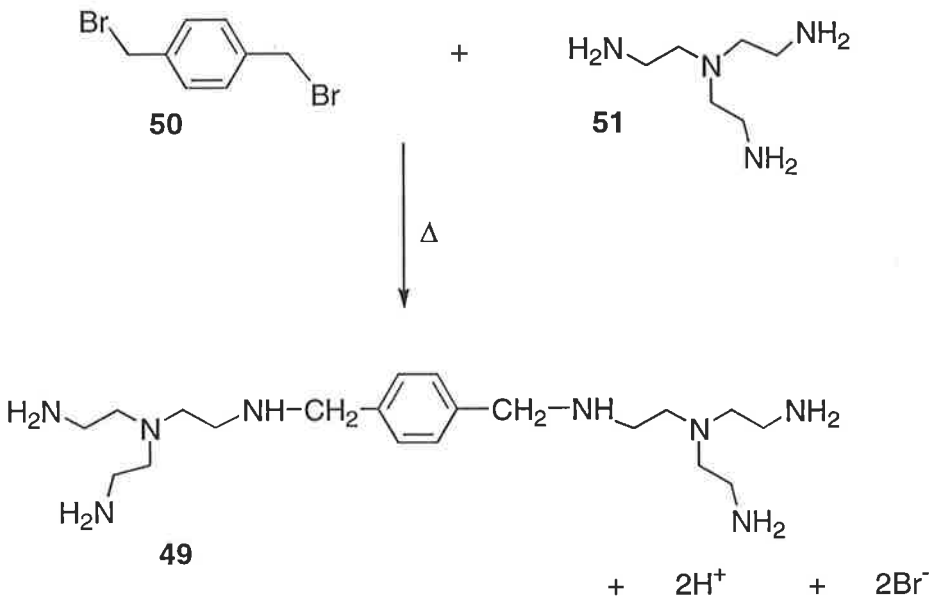
49

It was envisaged that if the axle **49** is included inside a cyclodextrin, the binding of cobalt(III) to the tren end groups of the axle would expand these groups, increase their rigidity and make them highly charged to form blocking groups.

3.2 Results and Discussion

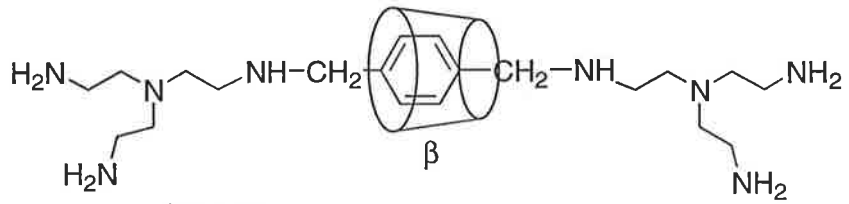
Preparation of a [2]-pseudorotaxane

The axle **49** was prepared by a literature procedure, from the corresponding dibromide **50** (Scheme 3.1) [10, 11]. To avoid the formation of polymers, the dibromide **50** was added slowly to a large excess of tren **51**.



Scheme 3.1 Synthesis of the axle **49**.

Attempts to purify the axle **49** by reverse phase HPLC (as by the literature procedure) and cation exchange chromatography proved to be tedious and not very successful. However, **49** was easily separated from impurities as a β-cyclodextrin [2]-pseudorotaxane. After stirring **49** with an excess of β-cyclodextrin in water, the mixture was passed down a Sephadex G10 size exclusion column. The axle **49** was obtained as the β-cyclodextrin [2]-pseudorotaxane βCD.**49** (with some excess β-cyclodextrin) in 34 % yield (lit. 33 %) and was shown to be > 95 % pure by ^{1}H and ^{13}C NMR spectroscopy.



βCD.**49**

The axle **49** is included in β-cyclodextrin, but not α-cyclodextrin, in basic D_2O solution (pD ≥ 12). Cross peaks due to nOe interactions between the aromatic protons and alkyl protons of the axle **49** and the annular protons of β-cyclodextrin are present in the 2D ^{1}H ROESY NMR spectrum of a mixture of the two components in D_2O (Figure 3.1). As the resonances arising from the benzyl protons of **49** overlap with those of the tren group protons, it is not possible to determine from the spectrum which protons are included most strongly inside β-cyclodextrin. However, substantial inclusion of the benzyl protons of **49** inside β-cyclodextrin is expected, considering that the aromatic protons are strongly included, and the central part of **49** is more hydrophobic than the tren end groups. Separate resonances for the protons of the included and free axle are not present in the 1D ^{1}H NMR spectrum, which indicates that there is either complete inclusion of **49** or a fast exchange process on the NMR timescale. After allowing a D_2O mixture of **49** and α-cyclodextrin to stand for several days at room temperature, or heating the mixture at 70 °C for 24 hours, no cross peaks indicative of inclusion of **49** in the α-cyclodextrin annulus were observed in the 2D ^{1}H ROESY NMR spectrum of the mixture. It was concluded that the tren end groups of **49** are too large to pass through the α-cyclodextrin annulus.

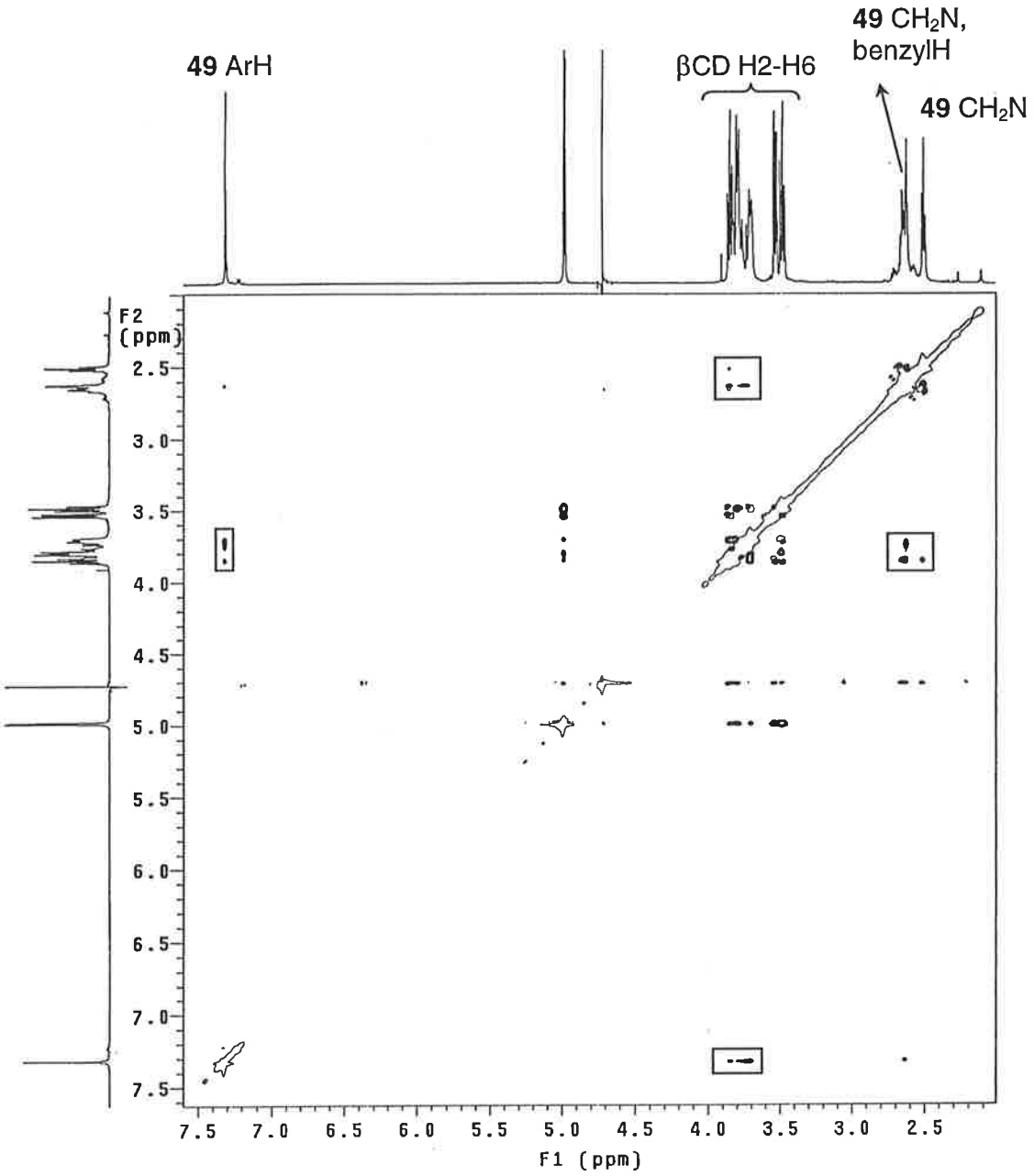


Figure 3.1 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.027 mol dm^{-3} axle **49** and 0.030 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic protons and alkyl protons of **49** and the β-cyclodextrin annular protons.

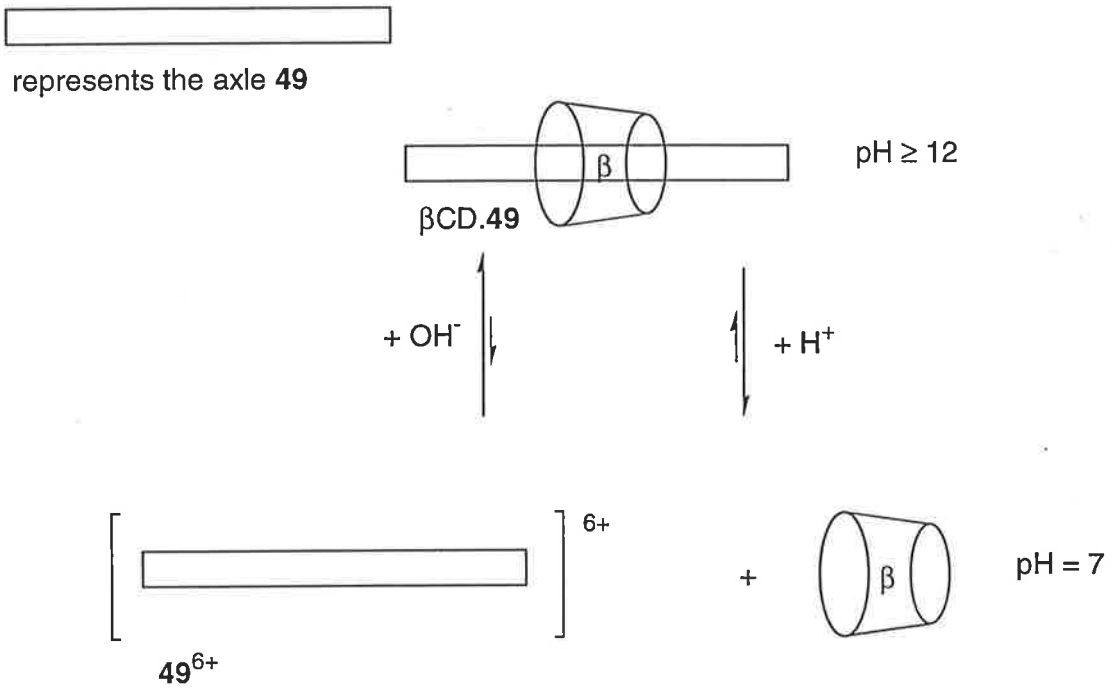
Although the axle **49** is included in β-cyclodextrin at high pH (pH ≥ 9), there is not significant inclusion of the axle at pH 7. It was previously found that **49** binds six protons at pH 7, making it 6+ charged [11]. Protonation probably expands the ends of **49** due to repulsion between the charged $-CH_2CH_2NH_3^+$ arms, such that the tren groups become too big to pass through the β-cyclodextrin annulus.

The absence of the [2]-pseudorotaxane βCD.**49** in aqueous solution at pH 7 hindered [2]-rotaxane synthesis by metal attachment. When a mixture of the axle **49**, β-cyclodextrin and $[Co(NH_3)_5H_2O](NO_3)_3$ in aqueous sodium hydroxide solution (pH 10) was stirred at room temperature, cobalt(II) oxides formed in under 24 hours. A similar result was observed for a solution of the complex $[Co(NH_3)_5H_2O](NO_3)_3$ in aqueous sodium hydroxide solution, in the absence of cyclodextrin and **49**, providing evidence for the complex being unstable in basic aqueous solution. Generally cobalt(III) complexes with four or more amine ligands are stable, but if these amines exchange with aqua ligands in aqueous solution the resulting $cobalt(III)_{aq}$ complex is reduced by water to $cobalt(II)_{aq}$. The redox reaction produces H^+ ions, so is favoured in basic solution [12]. It was not possible to obtain evidence for [2]-rotaxane formation by NMR spectroscopy, as cobalt(II) is paramagnetic and a 1D ^1H NMR spectrum of the mixture could not be produced.

An alternative method for synthesising cobalt(III) amine complexes is the acid-catalysed hydrolysis of carbonato complexes of cobalt(III) in the presence of amines. However, this method is carried out at low pH, rendering it unsuitable for the synthesis of a [2]-rotaxane from the [2]-pseudorotaxane βCD.**49** which forms at high pH only [13].

The pH-driven assembly/disassembly process of the [2]-pseudorotaxane βCD.**49** is interesting in itself and can be thought of as a switch-like mechanism (Scheme 3.2). Host-guest complexes in which the assembly/disassembly process of the components can be controlled are considered to have potential as molecular switches if the motion can be repeated [14-16]. However, the [2]-pseudorotaxane βCD.**49** is in equilibrium with the free axle and cyclodextrin components at high pH, which is not a well-defined 'state'. Also, pH change, when compared with electrochemical and photochemical stimuli, is a relatively slow stimulus for inducing switching between different states of the system, as time is needed for

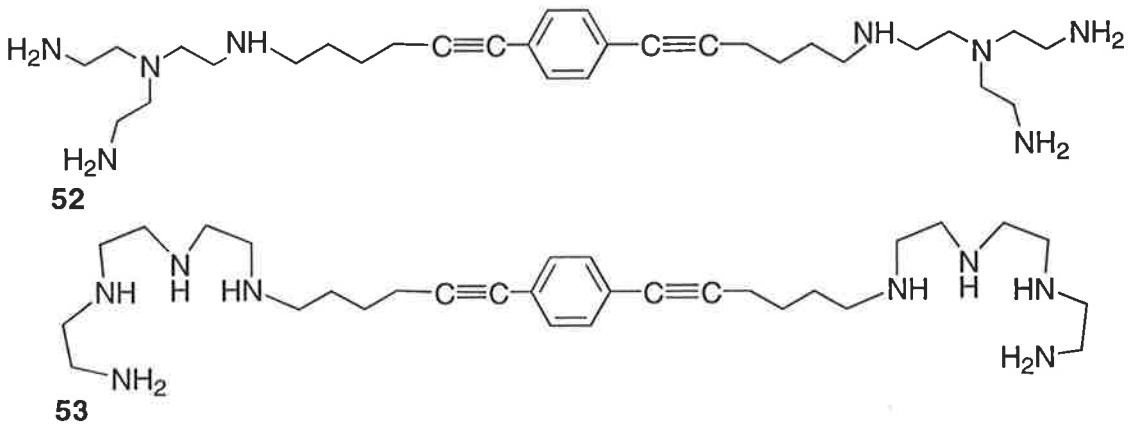
equilibration. A system in which there is instantaneous switching between states is more suitable for a molecular switch.



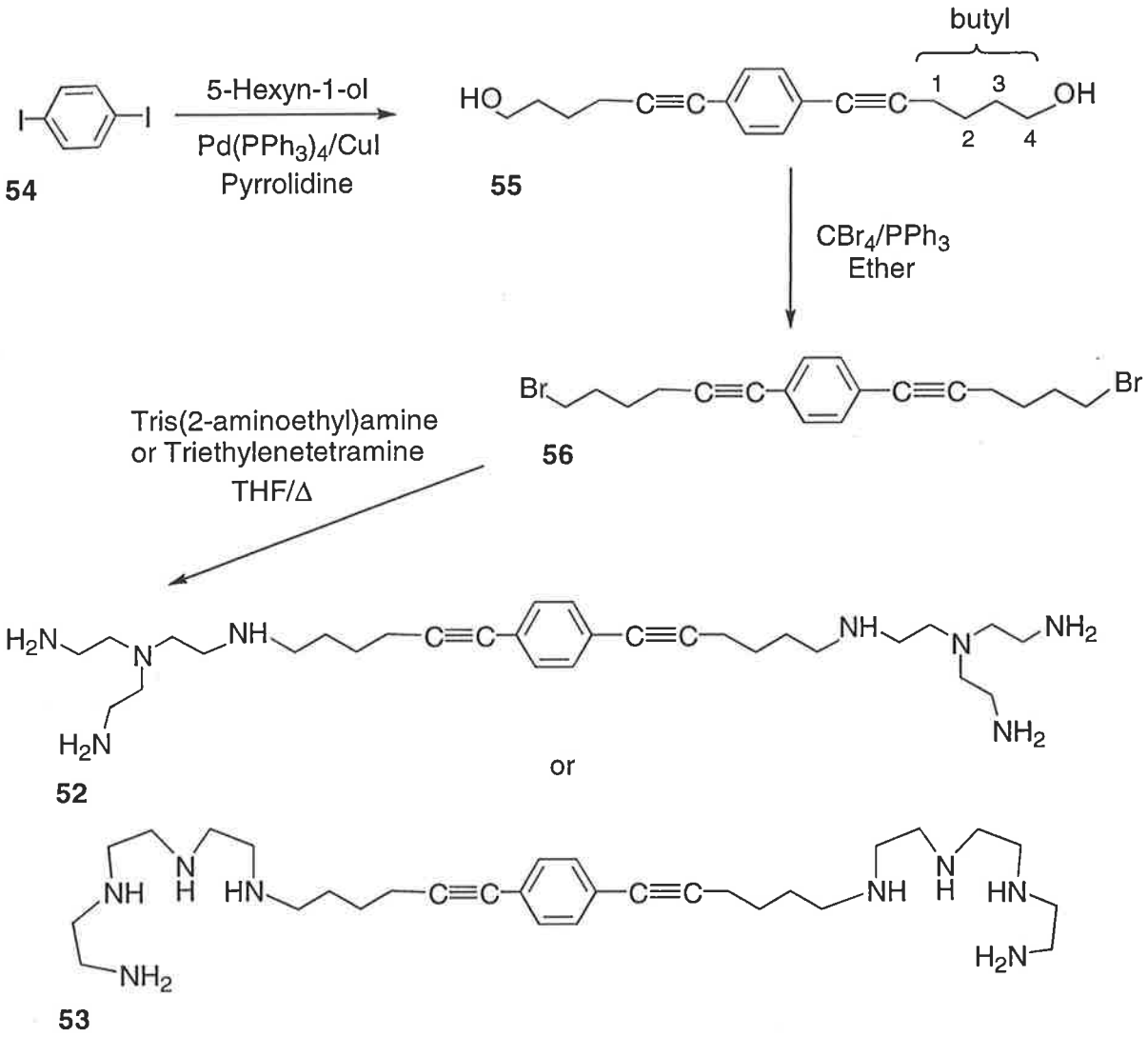
Scheme 3.2 The pH-dependent switch-like assembly/disassembly of the [2]-pseudorotaxane βCD.**49**.

Improvement of [2]-pseudorotaxane stability: synthesis of longer axles

New axles were designed with the aim of forming [2]-pseudorotaxanes that are stable at pH 7. The axles **52** and **53** were designed with a larger central hydrophobic section than **49** in order to drive the inclusion of these axles in β-cyclodextrin.



Both tren and 'trien' (triethylenetetramine) were utilised as end groups in the extended axles. Trien end groups were utilised in the axle **53** to allow the inclusion of this axle in the smaller α-cyclodextrin as well as β-cyclodextrin. The amine groups of **52** and **53** are far-removed from the aromatic region of the axle, such that protonation/deprotonation of the amine groups was not expected to have a significant effect on the inclusion of the axle. The syntheses of the axles are outlined below (Scheme 3.3).

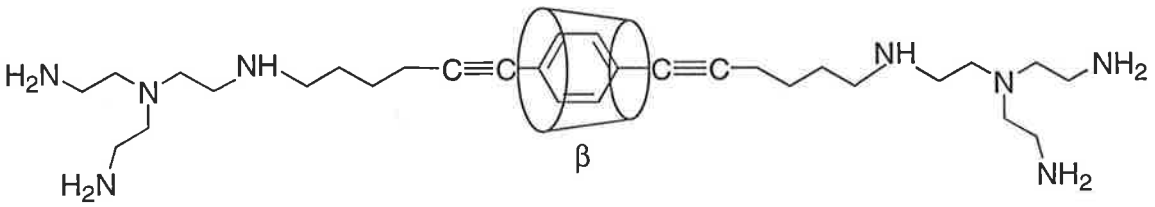


Scheme 3.3 Synthesis of the axles **52** and **53**. The numbering scheme on the butyl chain of **55** is applied to all compounds that contain this fragment throughout Chapter 3.

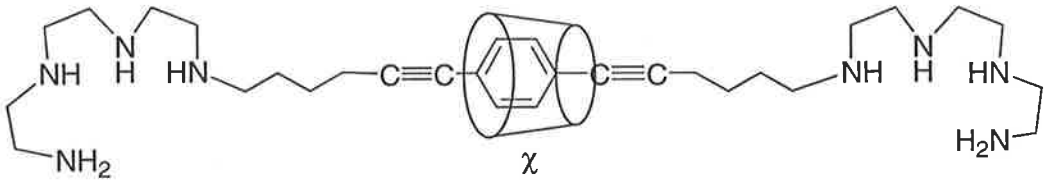
The diol **55** was readily synthesised by a palladium coupling of the diiodide **54** and 5-hexyn-1-ol and was obtained in 84 % yield after recrystallisation. This was converted to the dibromide **56**, which was purified by flash column chromatography and was isolated in 87 %

yield. Substitution reactions of the appropriate amines with the dibromide **56** produced the axles **52** and **53**. It was possible to purify the axles **52** and **53** as [2]-pseudorotaxanes by size-exclusion column chromatography, in a similar manner to that used for the axle **49**. Later, a superior method was found which did not require the use of β-cyclodextrin, and allowed the axles to be isolated. An aqueous solution of the crude axle was loaded onto a Diaion HP-20 column, and impurities were washed off the column with water. The axle **52** or **53** was eluted with 0.05 % TFA in 15-25 % methanol/water. After removal of the solvent, the axles **52** and **53** were obtained as sticky, pale yellow solids in 54 % and 53 % yields, respectively, and were characterised by ^{1}H and ^{13}C NMR spectroscopy and accurate mass spectrometry.

1D and 2D NMR spectra provided evidence for the inclusion or lack of inclusion of the axles **52** and **53** in α-cyclodextrin and β-cyclodextrin. The 1D ^{1}H NMR spectrum of a mixture of **52** and β-cyclodextrin in D_2O at pD 7 displays splitting of the aromatic proton resonance into an AB quartet, while the spectrum of **52** alone contains a singlet in the aromatic region, as the aromatic protons of free **52** are equivalent by symmetry in the molecule. This implies that the central section of **52** is included in the β-cyclodextrin annulus to give the [2]-pseudorotaxane βCD.**52**. The axle within the [2]-pseudorotaxane βCD.**52** contains two pairs of aromatic protons in different magnetic environments, as the primary and secondary ends of β-cyclodextrin are non-equivalent. The ^{1}H NMR spectrum of the mixture also displays shifting of some of the cyclodextrin annular proton resonances compared with those of native β-cyclodextrin. The ^{13}C NMR spectrum of the mixture contains four resonances in the aromatic region and four resonances in the acetylene region, while the spectrum of **52** alone contains two resonances in each region. Shifting of the β-cyclodextrin ^{13}C resonances, compared with those of native β-cyclodextrin, was also observed. The 2D ^{1}H ROESY NMR spectrum (Figure 3.2) of the mixture contains cross peaks due to nOe interactions between the aromatic protons of **52** and the β-cyclodextrin annular protons, confirming that **52** is included in the β-cyclodextrin annulus. Similar characteristics are visible in the corresponding 1D and 2D ^{1}H ROESY NMR spectra (Figure 3.3) of a D_2O solution of the axle **53** and β-cyclodextrin at pD 7, providing evidence for the existence of the [2]-pseudorotaxane βCD.**53**.



βCD.**52**



χCD.**53**
χ = α or β

The 1D ^{1}H NMR spectra of D_2O solutions of either of the axles **52** or **53**, β-cyclodextrin and 1-adamantanecarboxylate **17** (1.2 equivalents) each contain a singlet arising from the axle aromatic protons, and the proton resonances of **17** are split in the characteristic manner of the β-cyclodextrin complex **18**. The 2D ^{1}H ROESY NMR spectra contain cross peaks due to nOe interactions between the protons of **17** and the β-cyclodextrin annular protons, and no cross peaks due to interactions between the protons of **52** or **53** and the annular protons (Figure 3.4 displays the spectrum of a D_2O mixture of **52**, β-cyclodextrin and **17**). This indicates that **17** displaces both **52** and **53** from the β-cyclodextrin annulus (Scheme 3.4).

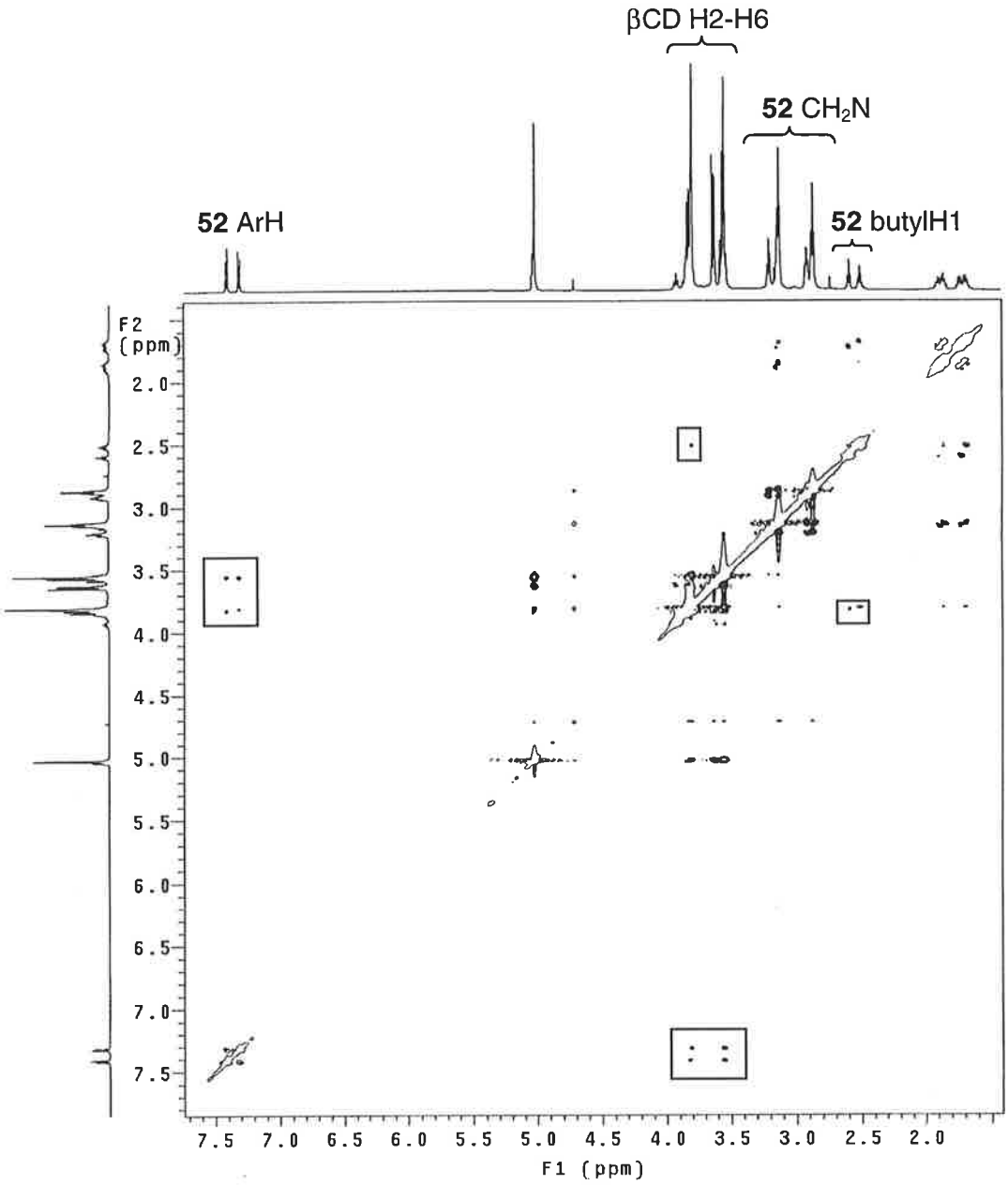


Figure 3.2 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.026 mol dm^{-3} axle **52** and 0.028 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl H1 protons of **52** and the β-cyclodextrin annular protons.

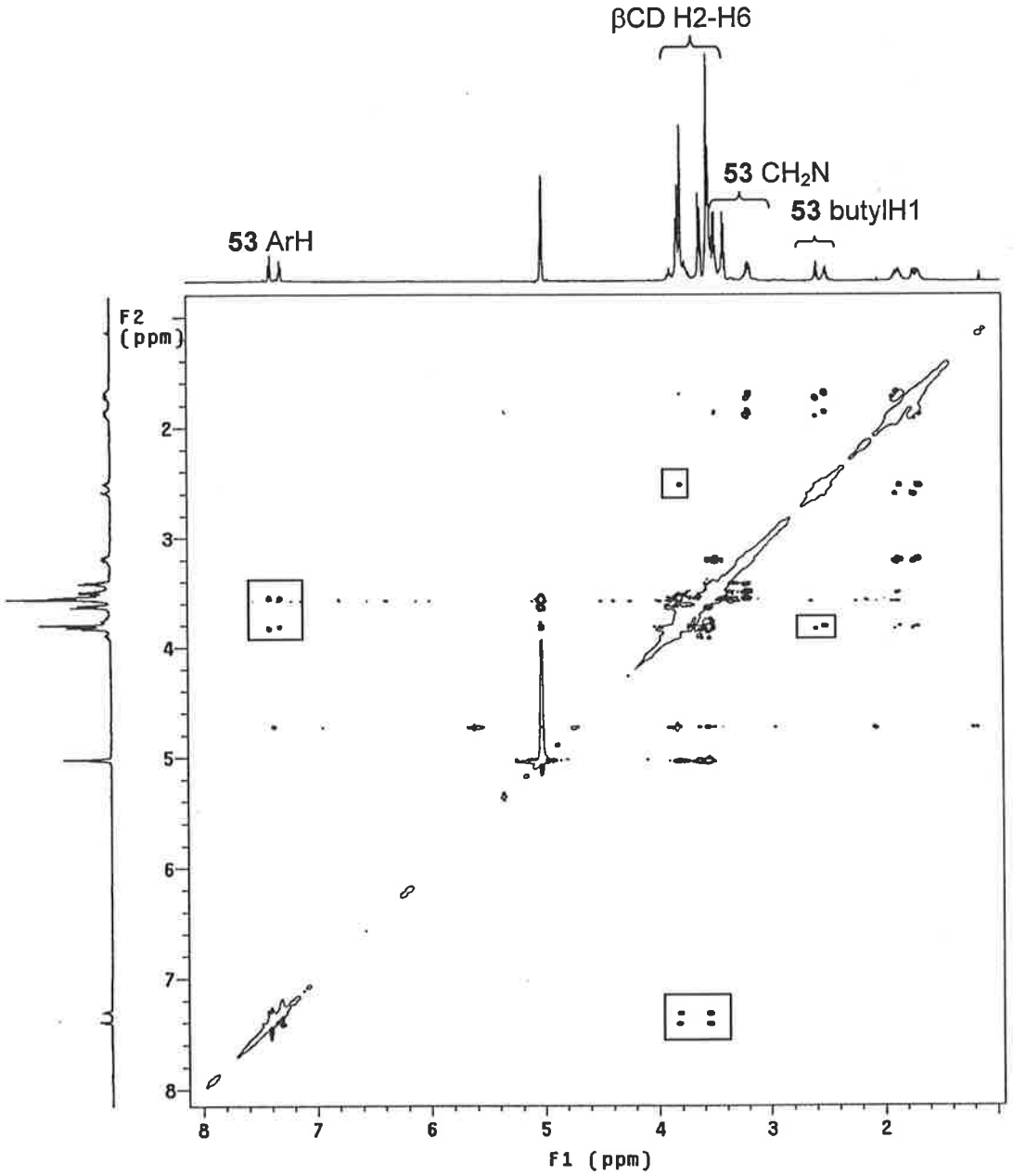


Figure 3.3 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.024 mol dm^{-3} axle **53** and 0.028 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl H1 protons of **53** and the β-cyclodextrin annular protons.

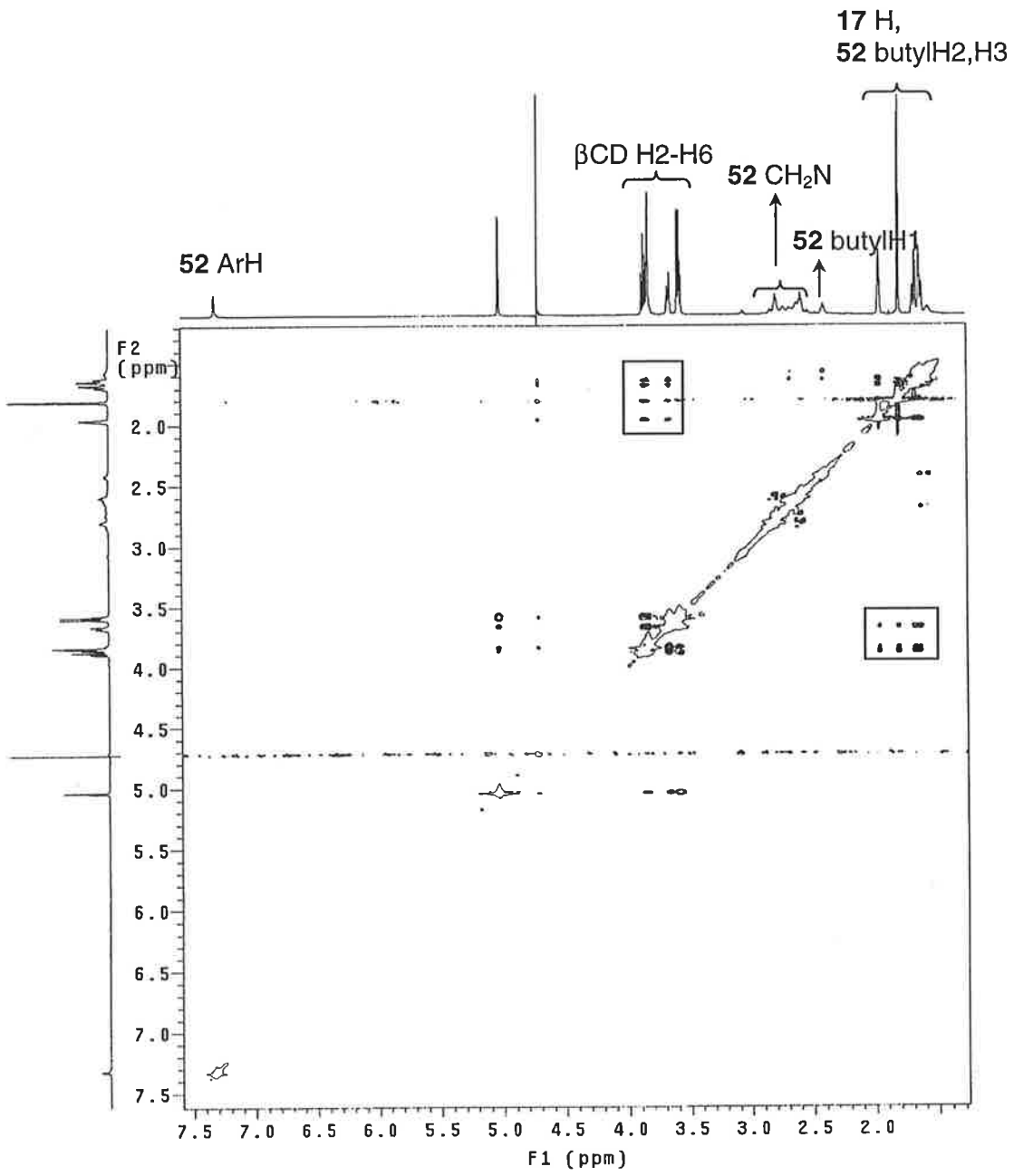
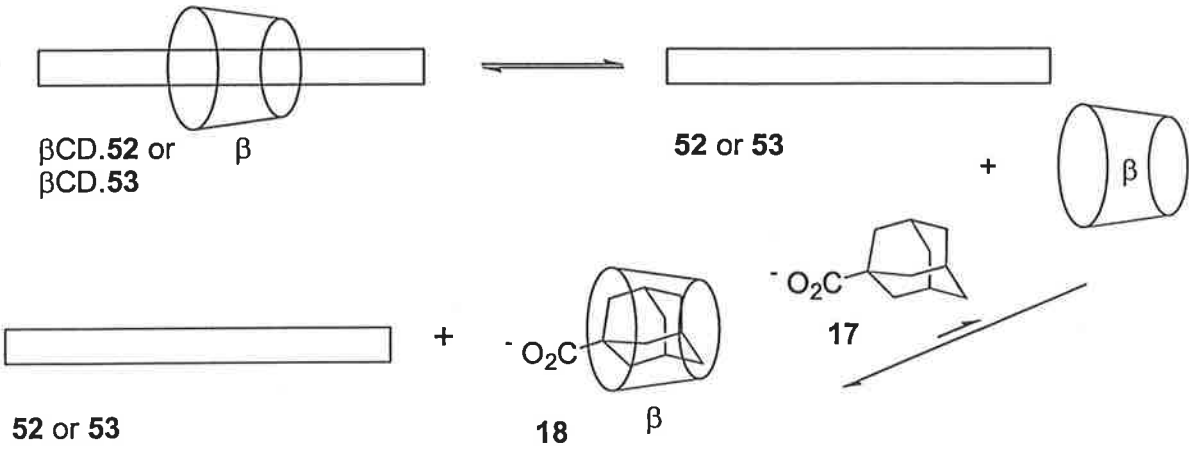


Figure 3.4 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 8, 0.3 sec mixing time, 298 K) of 0.028 mol dm^{-3} axle **52**, 0.030 mol dm^{-3} β-cyclodextrin and 0.033 mol dm^{-3} 1-adamantanecarboxylate **17** in D_2O, containing cross peaks (boxed) due to nOe interactions between the protons of **17** and the β-cyclodextrin annular protons.



Scheme 3.4 Displacement of the axle **52** or **53** from the β-cyclodextrin annulus by 1-adamantanecarboxylate **17**.

No inclusion of the axle **52** in the annulus of α-cyclodextrin occurs in D_2O at pD 7 even after heating (80 °C) a mixture of the components. The axle **52** is not included in the α-cyclodextrin annulus at pD ≥ 12 at room temperature and when a solution of **52** and α-cyclodextrin, or **52** alone, in D_2O at pD ≥ 12 was heated, **52** partially decomposed.

The 1D ^{1}H NMR spectrum of a D_2O solution of the axle **53** and α-cyclodextrin is very complicated, particularly in the aromatic region. The 2D ^{1}H ROESY NMR spectrum of the mixture contains cross peaks between three aromatic resonances and the resonances arising from the α-cyclodextrin annular protons (Figure 3.5), indicative of the inclusion of **53** in α-cyclodextrin to give the [2]-pseudorotaxane αCD.**53**. Strong cross peaks are also present due to nOe interactions between the annular protons of α-cyclodextrin and the butyl protons of **53**. Additional small multiplets that do not show cross peaks to the cyclodextrin annular proton resonances are visible in the aromatic region of the 1D ^{1}H NMR spectrum, and a singlet (~25 % of total aromatic resonances) at approximately 7.4 ppm that possibly arises from free **53** is also present. The ^{13}C NMR spectrum of αCD.**53** is complicated and contains several resonances in the aromatic and acetylene regions. The appearances of the 1D and 2D ^{1}H ROESY NMR spectra imply that the α-cyclodextrin molecule slides along and includes different parts of **53** and, due to the tighter fit of **53** in α-cyclodextrin than in β-cyclodextrin, the movement is slow on the NMR timescale, making the NMR spectra of αCD.**53** more complicated than those of βCD.**53**.

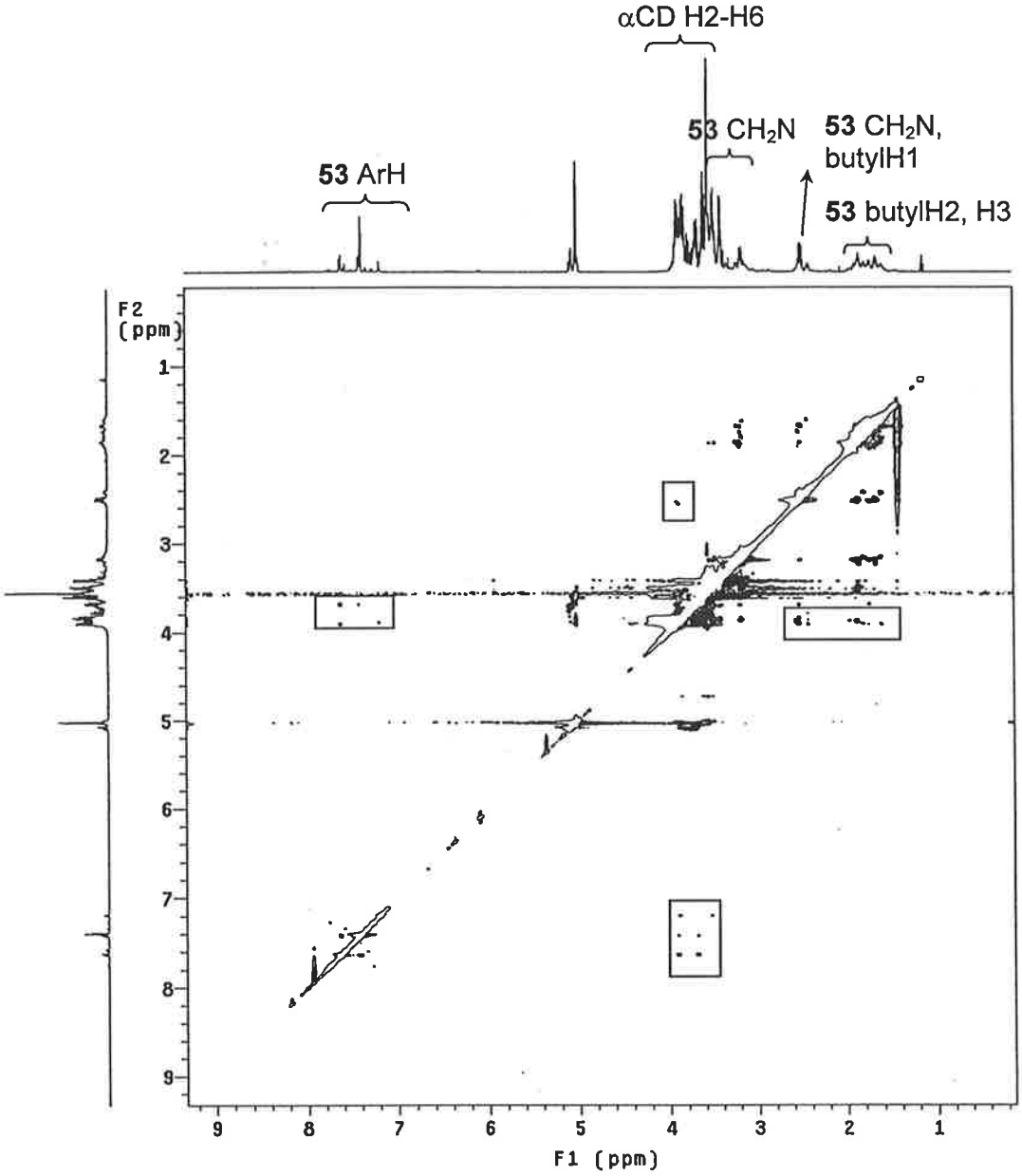
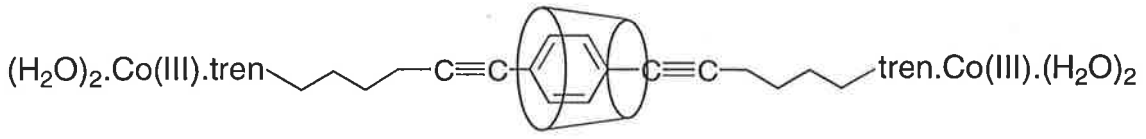


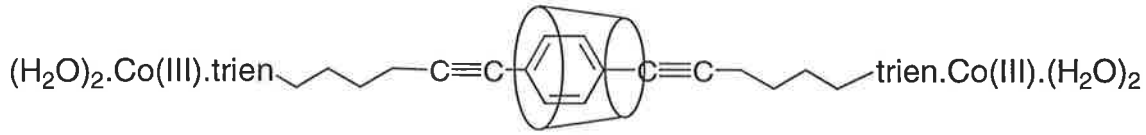
Figure 3.5 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.024 mol dm^{-3} axle **53** and 0.027 mol dm^{-3} α-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of **53** and the α-cyclodextrin annular protons.

Cobalt(III)-blocked cyclodextrin [2]-rotaxanes

The terminal amine groups of the axles in the [2]-pseudorotaxanes βCD.**52**, αCD.**53** and βCD.**53** were built into blocking groups through the attachment of cobalt(III), to give the [2]-rotaxanes **57**, **58** and **59**. The tren and trien end groups of the axles **52** and **53** form three and seven isomeric cobalt(III) complexes (including enantiomers), respectively, but will be represented by the abbreviations tren.Co(III).$(H_2O)_2$ and trien.Co(III).$(H_2O)_2$ throughout this chapter for simplicity.

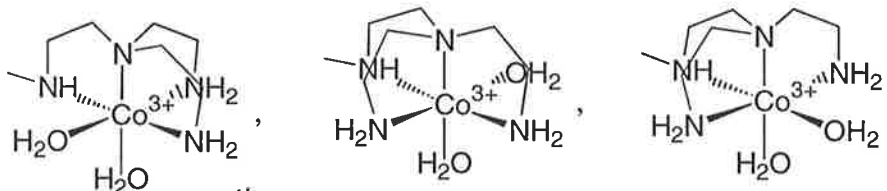


57



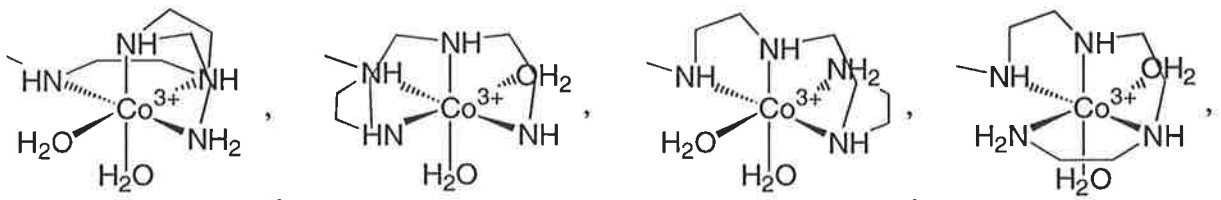
58 χ = α
59 χ = β

tren.Co(III).$(H_2O)_2$ represents one of

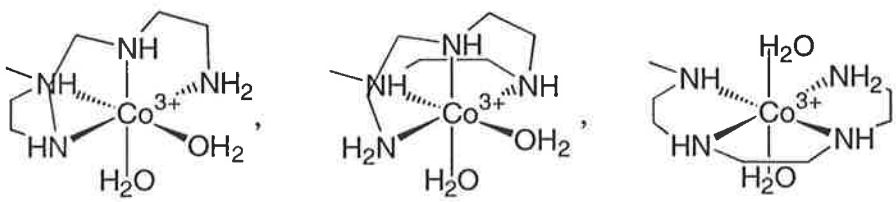


enantiomers

trien.Co(III).$(H_2O)_2$ represents one of

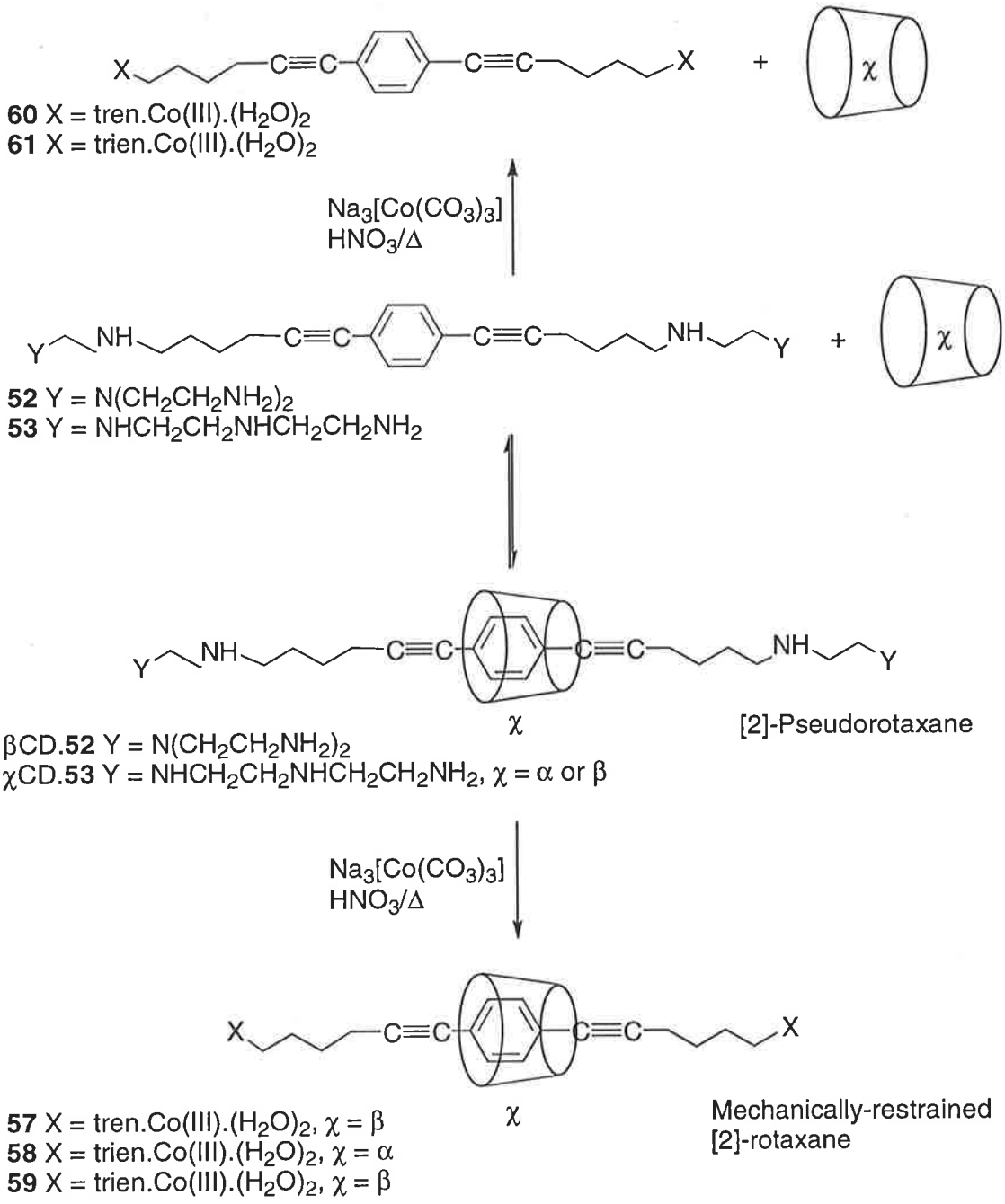


enantiomers



enantiomers

The axle **52** or **53** and α-cyclodextrin (utilised with axle **53** only) or β-cyclodextrin (~1.1 equivalents) were stirred with sodium triscarbonatocobalt(III) in dilute nitric acid with gentle warming [13]. Nitric acid was specifically selected because of the poor metal-coordinating ability of nitrate ions. After the effervescence ceased there was a rapid colour change from the dark green colour of the carbonato complex to the characteristic red/pink colour of cobalt(III) tetramine complexes. Scheme 3.5 displays the synthesis of the [2]-rotaxanes and other possible products.



Scheme 3.5 Synthesis of the [2]-rotaxanes **57**, **58** and **59**.

The possible impurities in the crude [2]-rotaxanes were sodium nitrate (a by-product in the syntheses), cyclodextrin and free axle (as the cobalt(III) complexes **60** and **61**). Attempts to purify the [2]-rotaxane **57** on a variety of resins did not improve the purity of the product. Purification on a column of CM Sephadex C-25 cation exchange resin has previously been employed for similar systems, but when **57** was subjected to this method it was necessary to use a highly concentrated sodium chloride solution (1 mol dm^{-3}) to wash the material off the column. Removal of the sodium chloride from the eluted material was tedious, much product was lost and there were no significant differences between the 1D ^{1}H NMR spectra of the material obtained after purification and that obtained directly from the reaction mixture. One broad band formed when the material was purified on CM Sephadex C-25 cation exchange resin, indicative of there being one major product, or of by-products not separating efficiently. Similarly, when the crude [2]-rotaxane was loaded onto a column of Sephadex G10 size exclusion resin, only one band formed and purification by this method had little effect on the 1D ^{1}H NMR spectrum of the product.

It was judged from the appearance of the ^{1}H and ^{13}C NMR spectra of the [2]-rotaxanes **57** and **59** and from the results of 2D ^{1}H ROESY NMR experiments (discussed below) that the materials contained very little excess cyclodextrin and free axle complex, while it was not determined whether significant amounts of such impurities were present in the α-cyclodextrin [2]-rotaxane **58**, due to the complicated nature of the spectra of this compound. There is a broad singlet in the aromatic region of the spectrum of **58**, the chemical shift of which is similar to that arising from the aromatic protons of the free axle. When the synthesis of **58** was repeated using a large excess of α-cyclodextrin (3 equivalents), the area of this resonance did not decrease, so it may arise from an inclusion isomer in which α-cyclodextrin includes the butyl chain. It was considered that the major impurity present in the crude [2]-rotaxanes was sodium nitrate, and its removal was attempted by repeatedly dissolving the materials in water and precipitating them from acetone (no further steps were carried out to remove sodium nitrate from cobalt(III) amine complexes prepared similarly in earlier work [13]). The products **57**, **58** and **59** were obtained in 83 %, 74 % and 76 % yields, respectively, as red or red/pink sticky solids (UV/Vis λ_{max} = 503 nm (**57**), 508 nm (**58**) and 511 nm (**59**)). Samples of the [2]-rotaxanes were subsequently synthesised as the corresponding chloro complexes in order to obtain good microanalyses.

The 1D ^{1}H NMR spectra of **57**, **58** and **59** are very similar to those of the respective [2]-pseudorotaxanes, but the resonances in the CH_2-N region are more complicated in the spectra of the [2]-rotaxanes. These spectra support the structures of the [2]-rotaxanes as it is expected that the [2]-rotaxanes would have spectra similar to those of the [2]-pseudorotaxanes, but that the possible isomeric cobalt(III) complexes that may exist at each end of the axle in the [2]-rotaxanes would give rise to several resonances in the CH_2-N region. In addition, the ^{13}C NMR spectra of **57**, **58** and **59** are similar to those of the corresponding [2]-pseudorotaxanes, but the isomeric cobalt(III) complex end groups give rise to a greater number of resonances in the CH_2-N region in the spectra of the [2]-rotaxanes.

The 2D ^{1}H ROESY NMR spectra of **57**, **58** and **59** in D_2O (Figures 3.6, 3.7 and 3.8) contain cross peaks due to nOe interactions between the axle aromatic protons (and axle butyl protons in the case of **58**) and the cyclodextrin annular protons, which confirms the structures of the [2]-rotaxanes. At the intensity of the spectrum of **58** in Figure 3.7, there are cross peaks between the resonances of the α-cyclodextrin annular protons and only one multiplet in the aromatic region. At higher intensity, additional weak cross peaks between the resonances of the α-cyclodextrin annular protons and other aromatic resonances can be seen, similar to those in the spectrum of the corresponding [2]-pseudorotaxane.

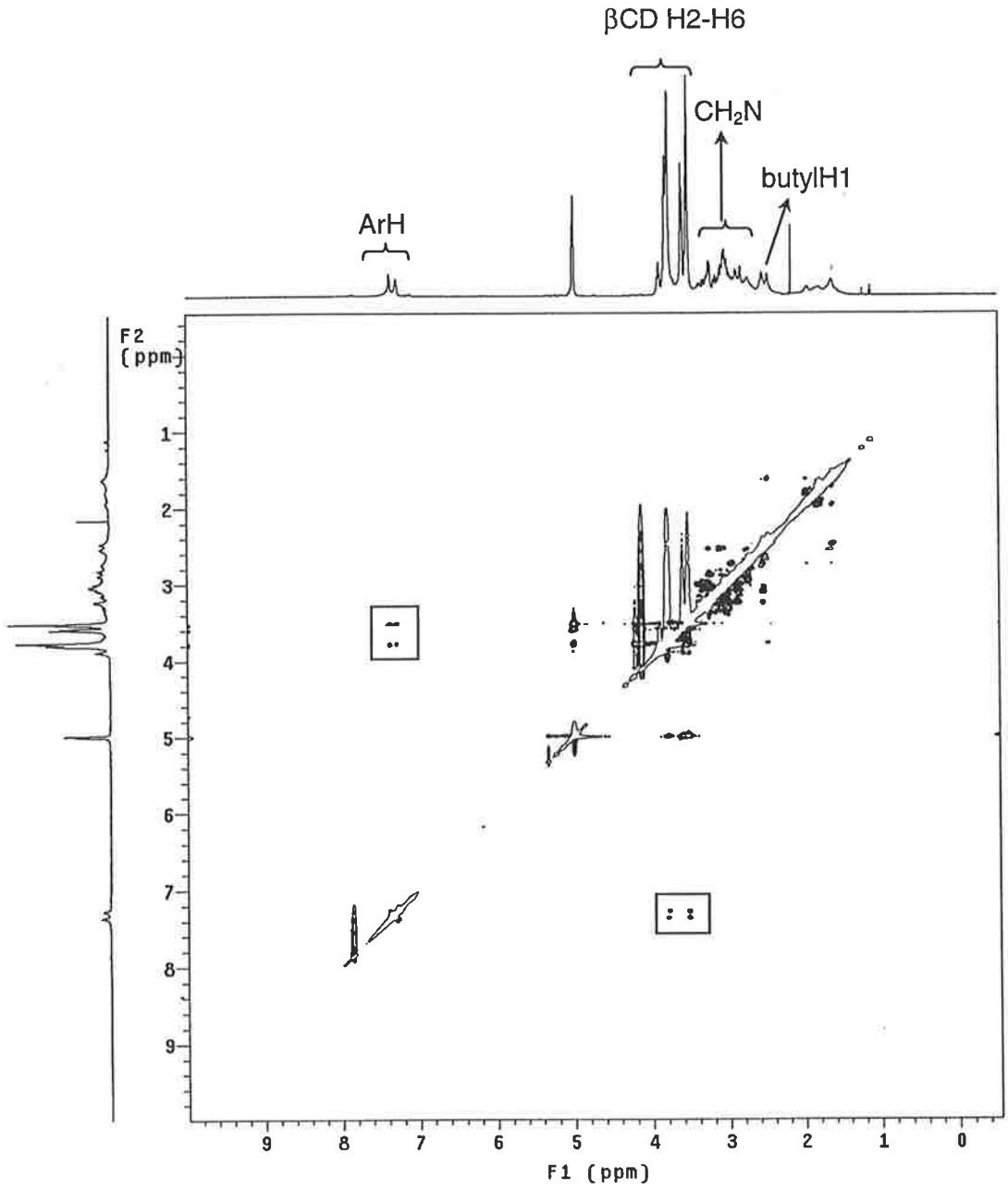


Figure 3.6 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.022 mol dm^{-3} [2]-rotaxane **57** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic protons of the axle and the β-cyclodextrin annular protons.

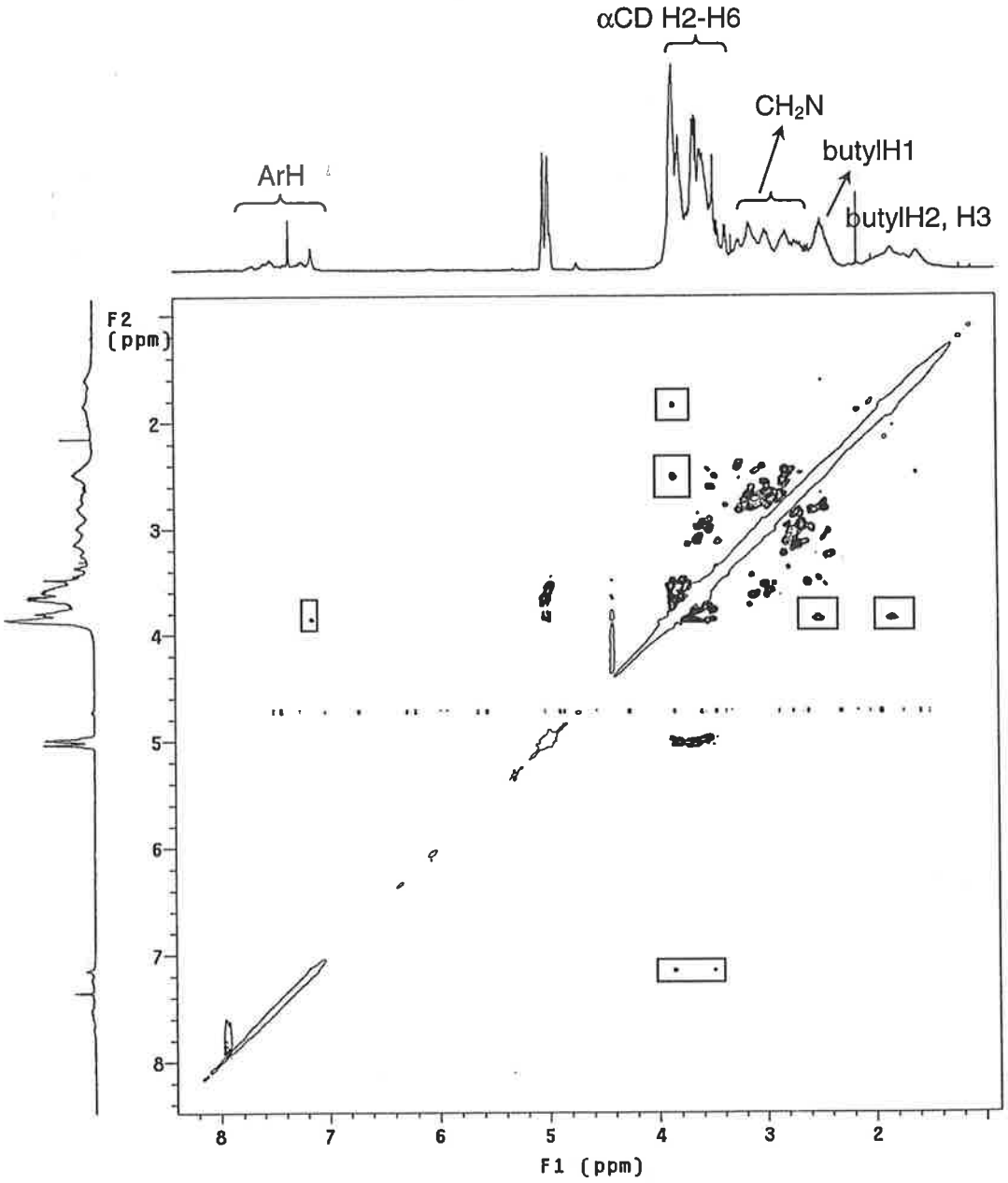


Figure 3.7 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.020 mol dm^{-3} [2]-rotaxane **58** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of the axle and the α-cyclodextrin annular protons.

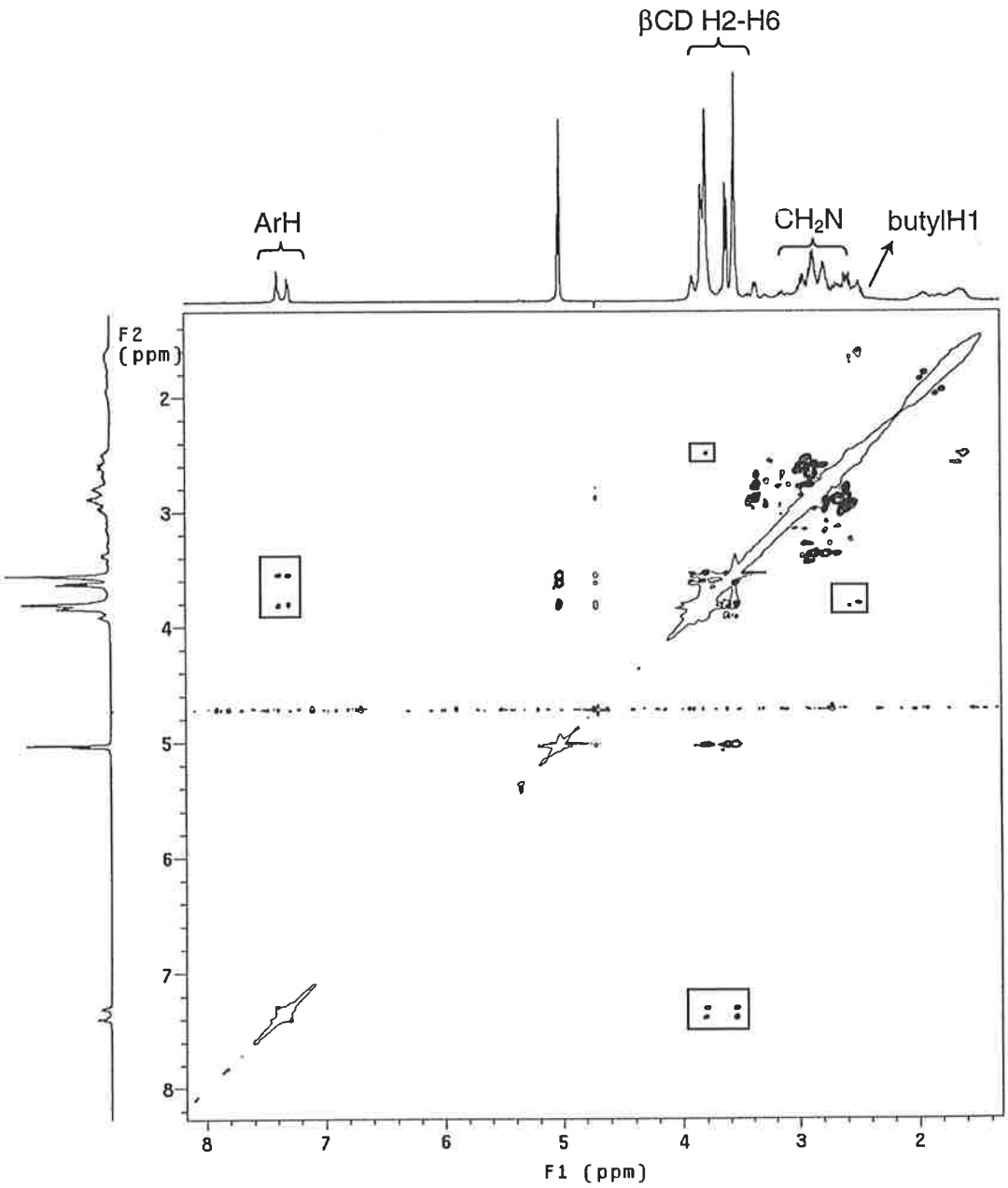
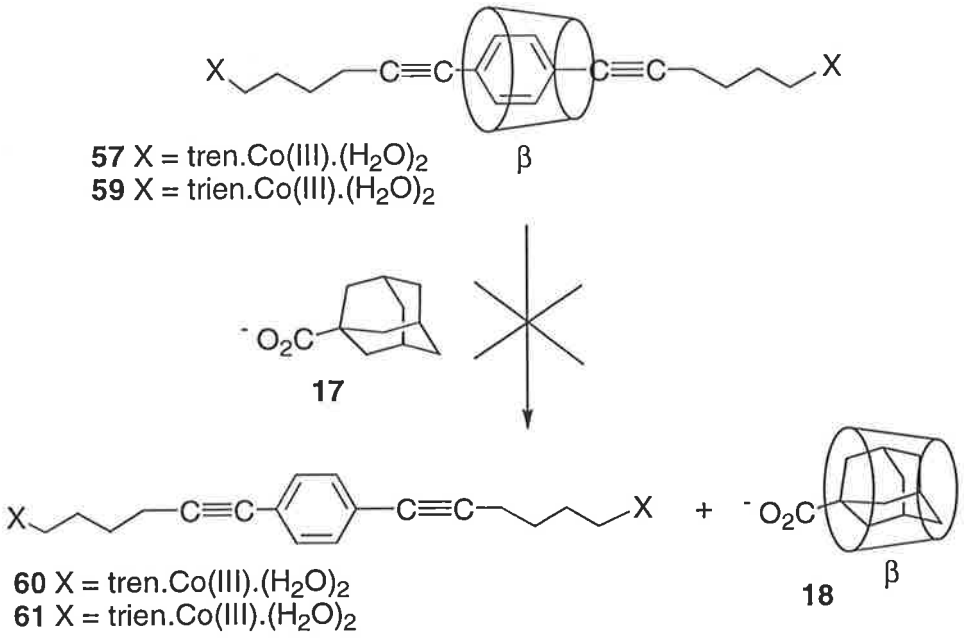


Figure 3.8 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.019 mol dm^{-3} [2]-rotaxane **59** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of the axle and the β-cyclodextrin annular protons.

The 2D ^{1}H ROESY NMR spectra of mixtures of either of the β-cyclodextrin [2]-rotaxanes **57** or **59** and 1-adamantanecarboxylate **17** (1.5 equivalents) in D_2O contain cross peaks due to nOe interactions between the aromatic protons of the axle and the annular protons of β-cyclodextrin. No cross peaks indicative of the inclusion of 1-adamantanecarboxylate **17** in β-cyclodextrin are present (Figure 3.9 displays the spectrum of a D_2O mixture of **57** and **17**). It is evident that mechanical restraint exists in the systems, as 1-adamantanecarboxylate **17** does not displace either axle from the β-cyclodextrin annulus when the terminal groups are bound to cobalt(III) (Scheme 3.6). The isolated materials contained very little free β-cyclodextrin, as the inclusion of **17** would have given rise to cross peaks in the 2D ^{1}H ROESY NMR spectra. It follows that little of the free cobalt(III)-blocked axle complexes **60** and **61** contaminated the [2]-rotaxanes as the syntheses were carried out using approximately equimolar solutions of the axle and the cyclodextrin.



Scheme 3.6 1-Adamantanecarboxylate **17** does not displace an axle with cobalt(III) blocking groups from β-cyclodextrin in the [2]-rotaxanes **57** and **59**.

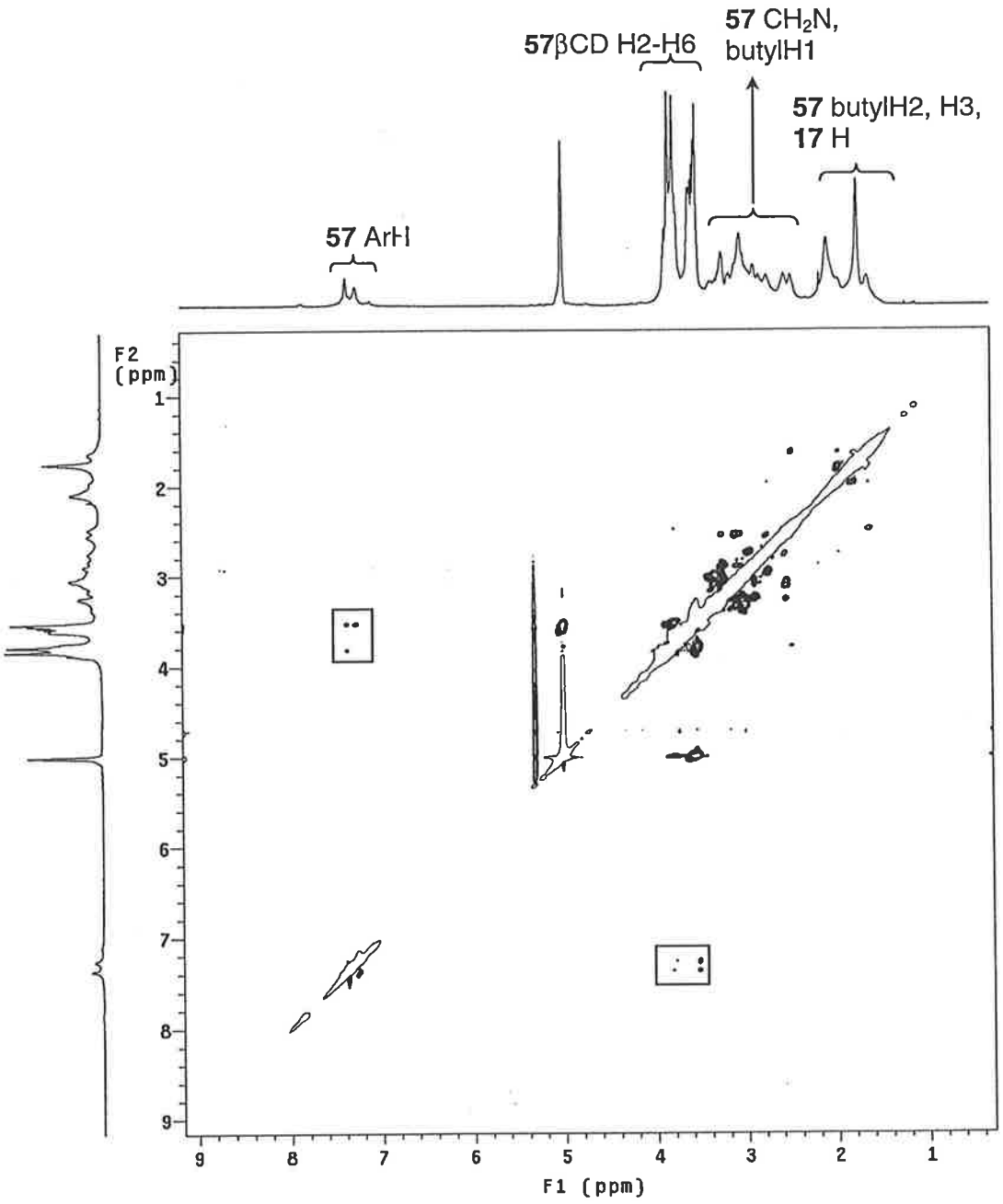
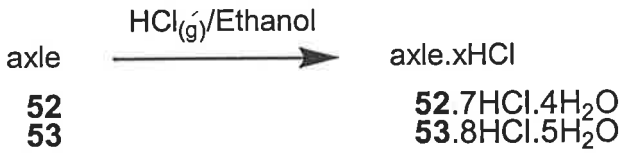


Figure 3.9 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ~ 8, 0.3 sec mixing time, 298 K) of 0.022 mol dm^{-3} [2]-rotaxane **57** and 0.026 mol dm^{-3} **17** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic protons of the axle and the β-cyclodextrin annular protons.

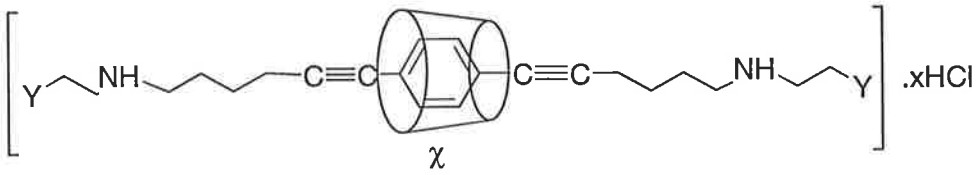
Purification of the [2]-rotaxanes as chloro complexes

The axles **52** and **53** were obtained as sticky solids and could only be manipulated in solution. To further purify these compounds, and obtain easily transferable samples for microanalyses, the hydrochloride salts of the axles were synthesised. Each of the hydrochloride salts was synthesised by bubbling hydrogen chloride gas into a solution of the axle **52** or **53** in ethanol (Scheme 3.7). From the analytical data, each axle hydrochloride salt was shown to contain 7-8 molar equivalents of HCl.

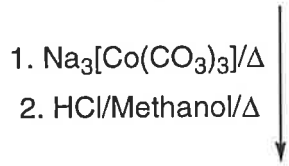


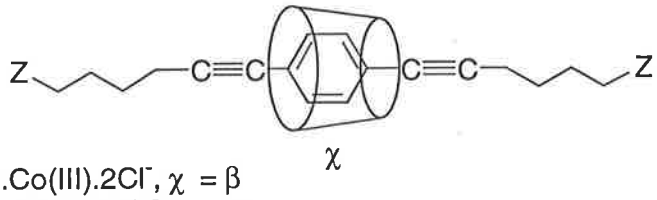
Scheme 3.7 Synthesis of the hydrochloride salts of the axles **52** and **53**.

The analytically pure hydrochloride salts of **52** and **53** were utilised to prepare samples of the [2]-rotaxanes as chloro complexes, by a similar method to that used before. The reactions were carried out in water rather than nitric acid solution as the hydrochloride salts acid-catalysed the hydrolysis of the carbonato ligands. To ensure complete hydrolysis of the carbonato ligands, the complexes were suspended in ~1.5 % hydrochloric acid/methanol and warmed gently, which yielded the purple chloro complexes (Scheme 3.8). Precipitation of the products from acetone and methanol, followed by repeated washing with methanol allowed removal of most of the sodium chloride (6 equivalents of sodium chloride are produced).



52.βCD.7HCl Y = $N(CH_2CH_2NH_2)_2$, χ = β
53.χCD.8HCl Y = $NHCH_2CH_2NHCH_2CH_2NH_2$, χ = α or β





62 Z = tren.Co(III).2Cl$^-$, χ = β
63 Z = trien.Co(III).2Cl$^-$, χ = α
64 Z = trien.Co(III).2Cl$^-$, χ = β

Scheme 3.8 Synthesis of the chloro analogues of the [2]-rotaxanes **57**, **58** and **59**. All the isomers of the aqua complexes shown earlier are also possible for the chloro complex analogues **62**, **63** and **64**.

The 1D ^{1}H NMR spectra of the [2]-rotaxanes are very similar to those of the corresponding aqua complexes, as the NMR samples were dissolved in D_2O in which the chloro ligands of the cobalt(III) complexes exchange with D_2O. The UV/Vis spectra of the complexes were obtained using a 1 mol dm^{-3} sodium chloride solution, in which an equilibrium mixture of dichloro, chloro and diaqua existed. Absorption maxima are present at 530, 514 and 514 nm in the UV/Vis spectra of solutions of the [2]-rotaxanes **62**, **63** and **64**, respectively.

Rotaxane synthesis by 'slippage'

To study the possibility of forming the [2]-rotaxanes **57**, **58** and **59** by a slippage mechanism, the cobalt(III)-blocked axle complexes **60** and **61** were synthesised. These complexes were synthesised by a similar method to that used in the blocking group attachment reaction displayed in Scheme 3.5, in the absence of cyclodextrin. The complexes **60** and **61** were obtained as red and red/pink sticky solids (UV/Vis λ_{max} = 502 nm and 510 nm for **60** and **61**, respectively), and could also be isolated as the chloro complex analogues **65**

and **66** in a similar manner to that discussed for the [2]-rotaxanes **62-64** (UV/Vis λ_{max} = 531 nm and 513 nm for **65** and **66**, respectively).

65 Z = tren.Co(III).2Cl$^-$
66 Z = trien.Co(III).2Cl$^-$

The 1D ^{1}H NMR spectrum of the complex **60** contains a singlet in the aromatic region (Figure 3.10(a)), consistent with near equivalence of the aromatic protons. The resonance is slightly broadened due to the existence of one of two possible $[Co(tren)(H_2O)_2]^{3+}$ isomers at each end of the axle, but the isomers are far removed from the aromatic protons and thus have little influence on the magnetic environments of these protons. The ^{13}C spectrum of **60** contains two resonances in the aromatic region and two resonances in the acetylene region of the spectrum, consistent with the equivalence argument discussed above. The CH_2-N regions of both the ^{1}H and ^{13}C NMR spectra are complicated due to the overlap of resonances arising from $[Co(tren)(H_2O)_2]^{3+}$ isomers.

The ^{1}H and ^{13}C NMR spectra of the complex **61** are very similar to the corresponding spectra of **60**, indicating that the near equivalence argument discussed for **60** is also applicable to **61**. Due to the different $[Co(trien)(H_2O)_2]^{3+}$ isomers possible, there are several resonances in the CH_2-N region of the ^{13}C spectrum of **61**, but seven resonances are of significantly higher intensity than the others, indicating that there is one major $[Co(trien)(H_2O)_2]^{3+}$ isomer present.

Initially, when β-cyclodextrin was added to a D_2O solution of the complex **60**, there was no change in the aromatic region of the 1D ^{1}H NMR spectrum. However, within 30 minutes, additional resonances in the 1D ^{1}H NMR spectrum of the mixture were observed. The singlet arising from the aromatic protons of free **60** slowly disappeared and was replaced by a multiplet, similar to that observed in the aromatic region of the spectrum of the [2]-rotaxane **57** (Figure 3.10).

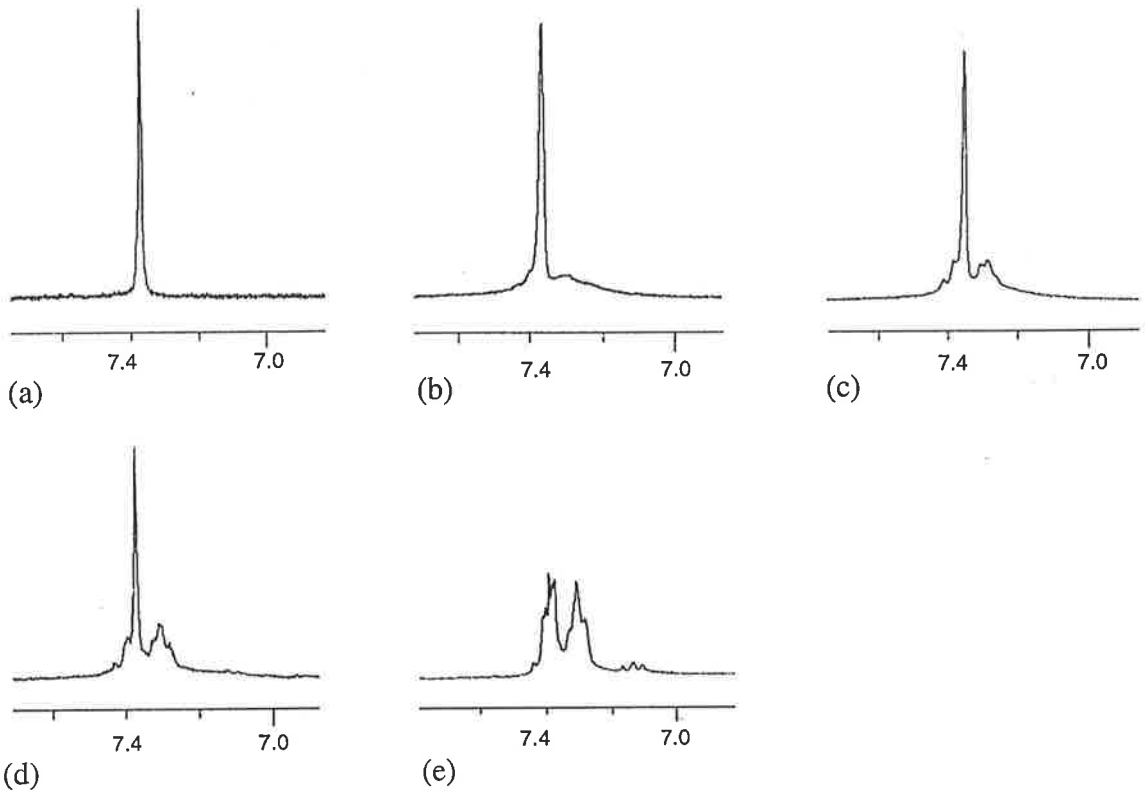
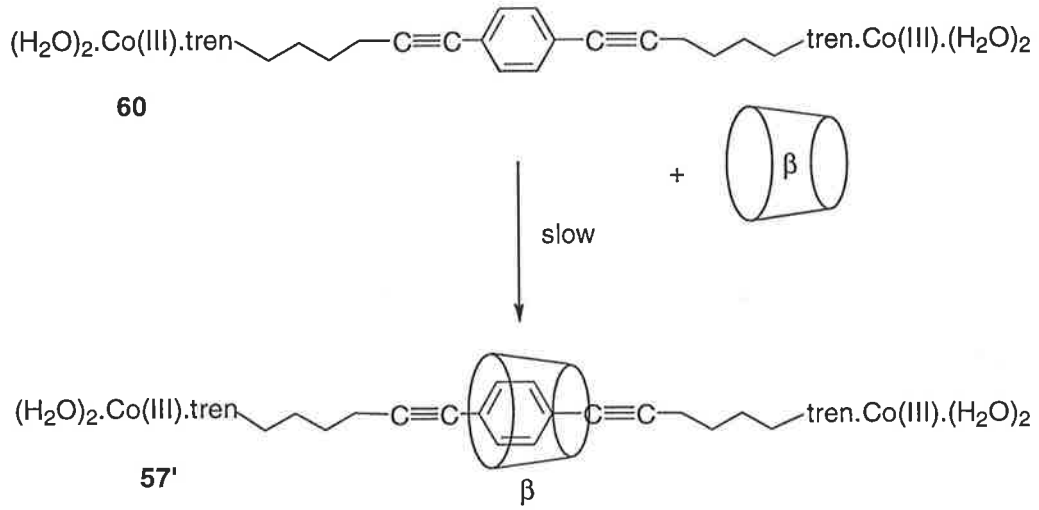


Figure 3.10 (a) The aromatic region of the 1D ^{1}H NMR spectrum of 0.020 mol dm^{-3} complex **60** in D_2O and (b)-(e) the changing spectrum of a D_2O mixture of 0.020 mol dm^{-3} **60** and 0.026 mol dm^{-3} β-cyclodextrin due to slow [2]-rotaxane formation by slippage, (b) 30 minutes, (c) 5 hours, (d) 3 days, (e) 24 days.

The changes in the 1D ^{1}H NMR spectrum of a solution of the complex **60** and β-cyclodextrin that occurred are indicative of β-cyclodextrin being large enough to slowly slip over the $[Co(tren)(H_2O)_2]^{3+}$ blocking groups of **60** (Scheme 3.9). After allowing the mixture to stand at room temperature for several days, a 2D ^{1}H ROESY NMR spectrum of the solution was obtained. Cross peaks due to nOe interactions between the aromatic protons of the axle and the cyclodextrin annular protons were observed in the spectrum of the mixture, confirming that the axle had become included in the cyclodextrin annulus.



Scheme 3.9 Synthesis of the [2]-rotaxane **57'** by slippage.

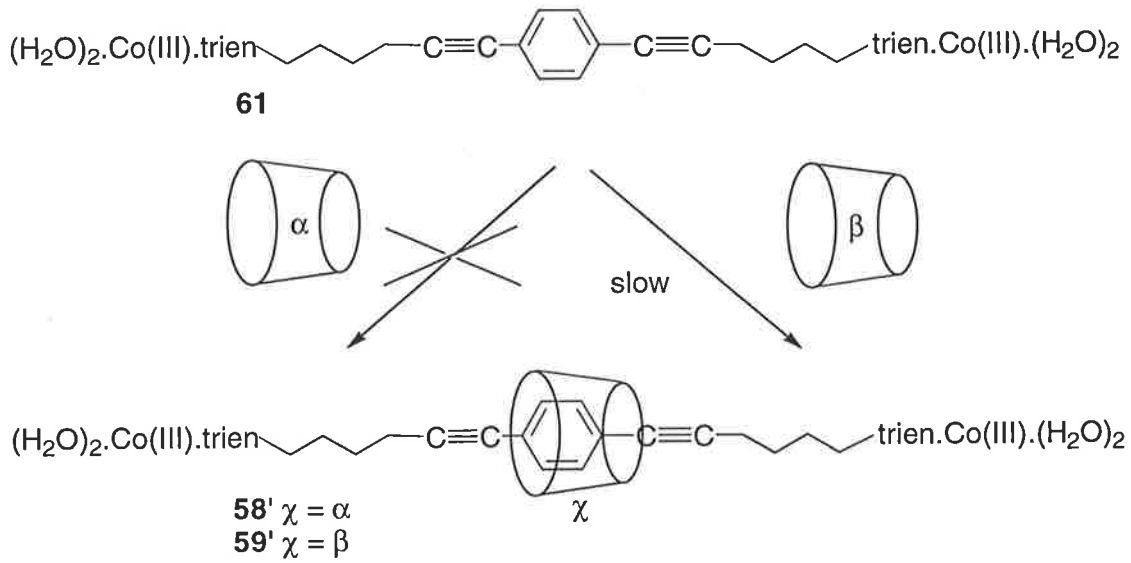
The progress of the slippage reaction in a solution containing the complex **60** and β-cyclodextrin was followed by 1D ^{1}H NMR spectroscopy at regular intervals. After a period of 8 hours, approximately 50 % of the area of the singlet arising from the aromatic protons of free **60** had been replaced by a multiplet, which implied that the half-life of the slippage reaction is in the order of 8 hours. However, a further 24 hours was required for the area of the singlet to halve again to 25 % of the total area of the aromatic resonances. This suggests that the slippage reaction occurs by a two-step process, or that more than one separate slippage processes occur.

It is likely that the mechanism by which the [2]-rotaxane **57'** forms involves a simultaneous distortion of β-cyclodextrin and the ligands around cobalt(III) such that the cyclodextrin can slowly slip over a blocking group of **60**. As the only stable coordination geometry for cobalt(III) is 6-coordinate, it is implausible that a tren end group or an aqua ligand of the complex **60** dissociates to allow threading by β-cyclodextrin. The different isomers possible for the $[Co(tren)(H_2O)_2]^{3+}$ blocking groups of **60** are of slightly different sizes and shapes and the relative tendencies of the tren and aqua ligands to distort may influence the sizes to which the isomers can contract. It is likely that that β-cyclodextrin slips over the isomeric blocking groups at different rates.

The slippage reaction reached a state of completion (< 5 % free complex **60**) after approximately 24 days at room temperature. The 1D ^{1}H NMR spectrum of the [2]-rotaxane **57'** synthesised by slippage is very similar to that of **57**, which was synthesised directly by

threading. There is a minor multiplet (< 5 % of total aromatic resonances) at 7.0-7.2 ppm in the spectrum of **57'**. A similar minor resonance also appears in the spectrum of **57** if a D_2O solution of the [2]-rotaxane is allowed to stand at room temperature for a period of over 1-2 weeks. This may arise from an impurity due to partial decomposition of the axle after a prolonged period in aqueous solution.

α-Cyclodextrin does not slip over the $[Co(trien)(H_2O)_2]^{3+}$ blocking groups of the complex **61**, which was expected from consideration of the relative sizes of the $[Co(trien)(H_2O)_2]^{3+}$ complexes and the smaller end of the α-cyclodextrin annulus. β-Cyclodextrin is large enough to slip over the $[Co(trien)(H_2O)_2]^{3+}$ blocking groups of **61** (Scheme 3.10), but does so much more slowly than was observed for the $[Co(tren)(H_2O)_2]^{3+}$ blocking groups of **60**. After allowing a D_2O mixture of **61** and β-cyclodextrin to stand at room temperature for four days, no evidence of included product was observed in the 1D ^1H NMR and 2D ^1H ROESY NMR spectra of the mixture. However, changes in the 1D ^1H NMR spectrum were observed over a period of several weeks; a multiplet similar to that seen for the [2]-rotaxane **59** slowly appeared. After a month at room temperature, the area of the singlet arising from the aromatic protons of the free complex **61** decreased to approximately 60 % of the total area of the aromatic resonances. However, after such a prolonged period in aqueous solution, it is possible that the components partially decomposed.



Scheme 3.10 β-Cyclodextrin is large enough to slowly slip over a cobalt(III) blocking group of the complex **61**, while α-cyclodextrin is too small.

It is uncertain why the slippage mechanism occurs so much more slowly for the complex **61** than for the complex **60**, as molecular models of the possible isomers of the $[Co(trien)(H_2O)_2]^{3+}$ and $[Co(tren)(H_2O)_2]^{3+}$ blocking groups (without considering enantiomers) show the trien complexes and tren complexes to be of similar sizes (Figure 3.11). Each model was constructed and minimised (MM2) in Chem3D and is shown in the space-filling representation. The models are displayed from the opposite side of the complex to the point of attachment of the axle butyl chain, which would be the necessary direction of approach of a β-cyclodextrin molecule if it were to slip over a blocking group. The isomers of $[Co(trien)(H_2O)_2]^{3+}$ and other cobalt(III) trien complexes have previously been studied in detail and the models in Figure 3.11 are labelled with the names of the isomers to which they correspond [4, 5]. The complex $[Co(tren)(H_2O)_2]^{3+}$ does not have isomeric forms, however in **60** the substitution of one of the primary amine groups gives rise to isomers.

The only model which displays a significant difference in shape to the others is the $[Co(trien)(H_2O)_2]^{3+}$ model (f) (which has aqua ligands in a *trans* geometry), but based on previously determined relative stabilities of $[Co(trien)(H_2O)_2]^{3+}$ isomers, little of this particular isomer is likely to exist [5]. By far the most stable $[Co(trien)(H_2O)_2]^{3+}$ isomer is that with the *cis*-β geometry, followed by that with the *cis*-α geometry (the ratio of species at equilibrium is 85:15 *cis*-β:*cis*-α, the isomers are distinguishable in that only in the *cis*-β geometry do three adjacent amines lie in a plane) and generally only trace amounts of the *trans* isomer can be detected [5]. However, this order of stability varies for other cobalt(III) trien complexes, upon substitution at either a carbon or a nitrogen of the trien ligand and is also dependent on the solvent [5, 17, 18].

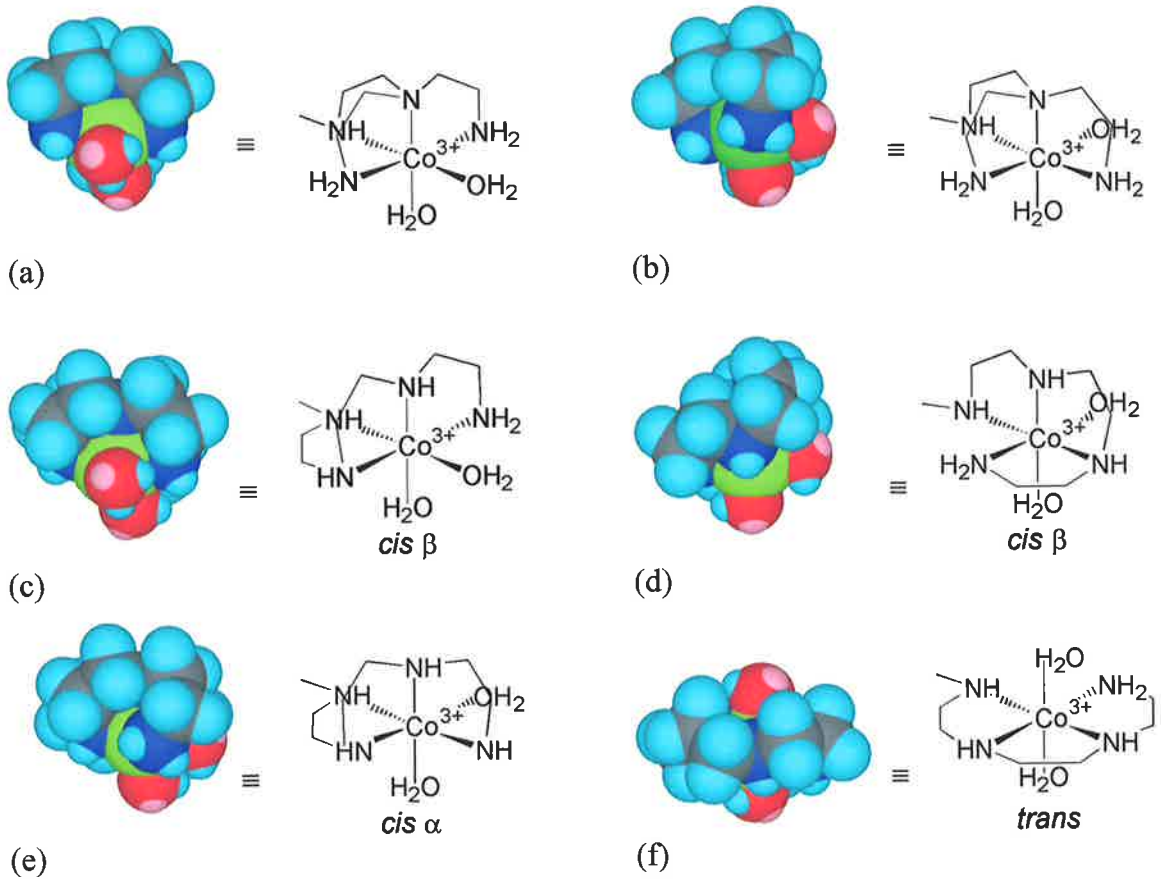


Figure 3.11 Models of the aqua cobalt(III) complexes of the tren and trien end groups of the axles, viewed from the direction of approach of β-cyclodextrin, (a) and (b) $[Co(tren)(H_2O)_2]^{3+}$ isomers, (c) $[Co(trien)(H_2O)_2]^{3+}$ *cis* β, (d) $[Co(trien)(H_2O)_2]^{3+}$ *cis* β, (e) $[Co(trien)(H_2O)_2]^{3+}$ *cis* α, (f) $[Co(trien)(H_2O)_2]^{3+}$ *trans*; C = grey, H = light blue, O = red, N = dark blue, Co = green.

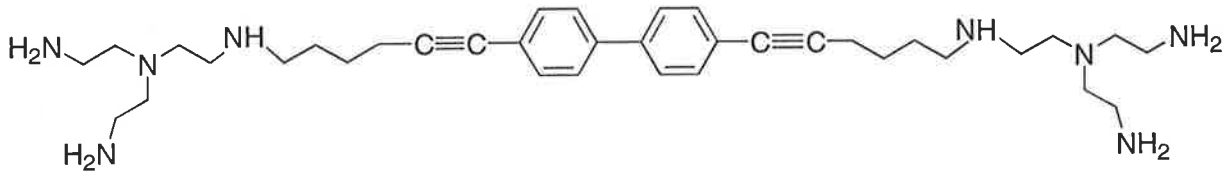
Of the possible $[Co(trien)(H_2O)_2]^{3+}$ isomers at the ends of the complex **61**, those depicted by the models (c) and (d) have the *cis*-β type geometry, so may be presumed to be the most stable. The presence of the axle will have some bearing on the relative stabilities of the isomers, but in previous work it was found that a trien ligand with methyl groups substituted at some of the nitrogens was still most stable in the *cis*-β geometry [17]. It is uncertain whether the geometry depicted by model (c) or (d) is more stable, but these isomers are of similar sizes and shapes to the possible isomers of $[Co(tren)(H_2O)_2]^{3+}$.

The restraints of the tren and trien ligands causes some amount of distortion from an octahedral geometry in all of the models, but in particular for the $[Co(tren)(H_2O)_2]^{3+}$ models, and it can be envisaged that the branched tren ligand would form 'tighter' complexes than the linear trien ligand. The difference in rates of the slippage processes for the complexes **60** and

61 is likely to be a result of the relative ease with which the tren and trien complexes distort to allow their passage through β-cyclodextrin. It is interesting that the unbranched nature of the free trien ligand makes it effectively smaller than the branched tren ligand, but when the ligands bind cobalt(III), the trien complex produced is a larger blocking group than the corresponding tren complex.

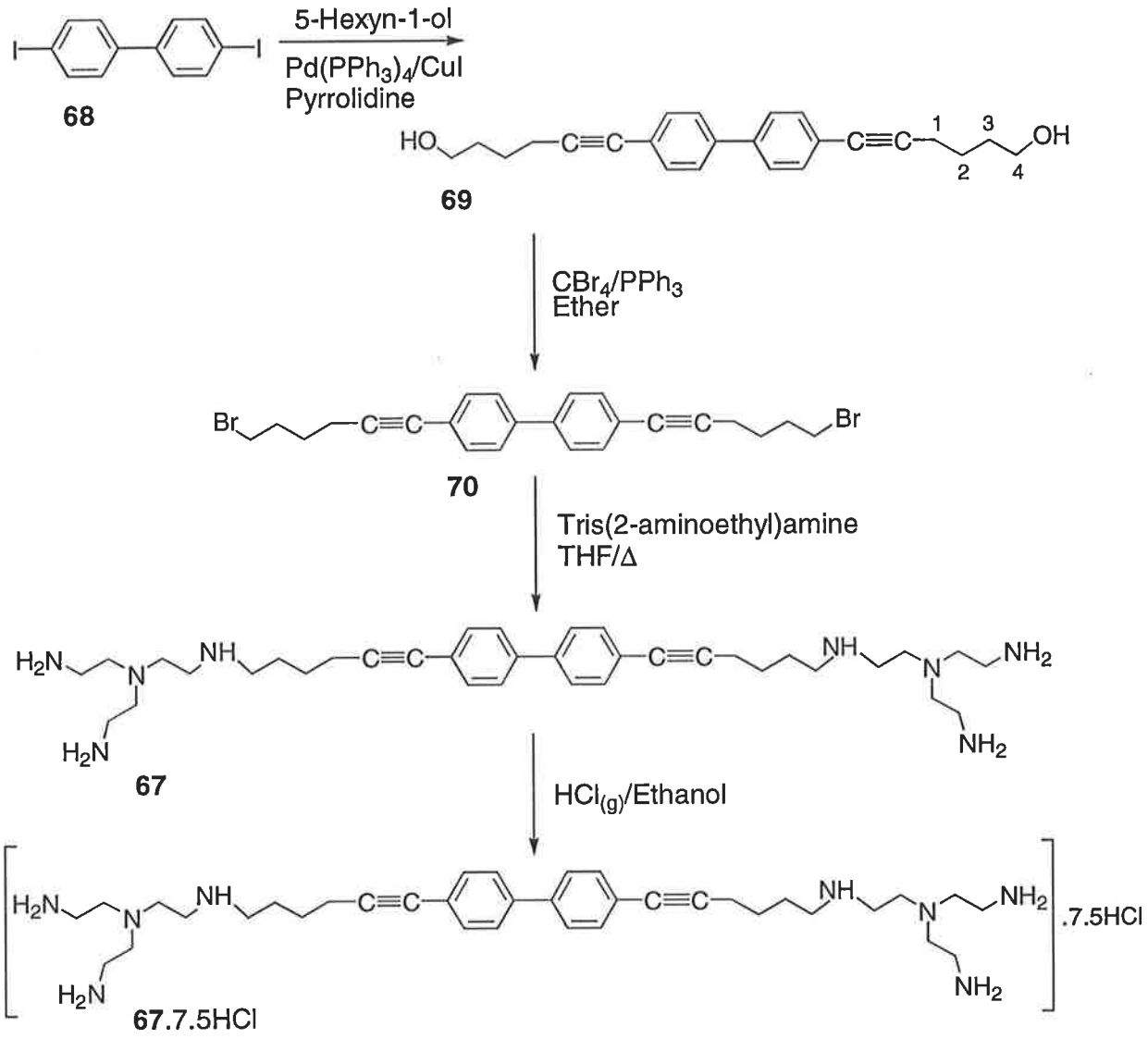
A β-cyclodextrin dimer [2]-rotaxane

The axle **67** was designed with an extended aromatic core to make it long enough to be included in a cyclodextrin dimer. It was expected that a [2]-pseudorotaxane in which the guest is included inside the host at two sites would be considerably stable and lead to a high yield of the [2]-rotaxane.

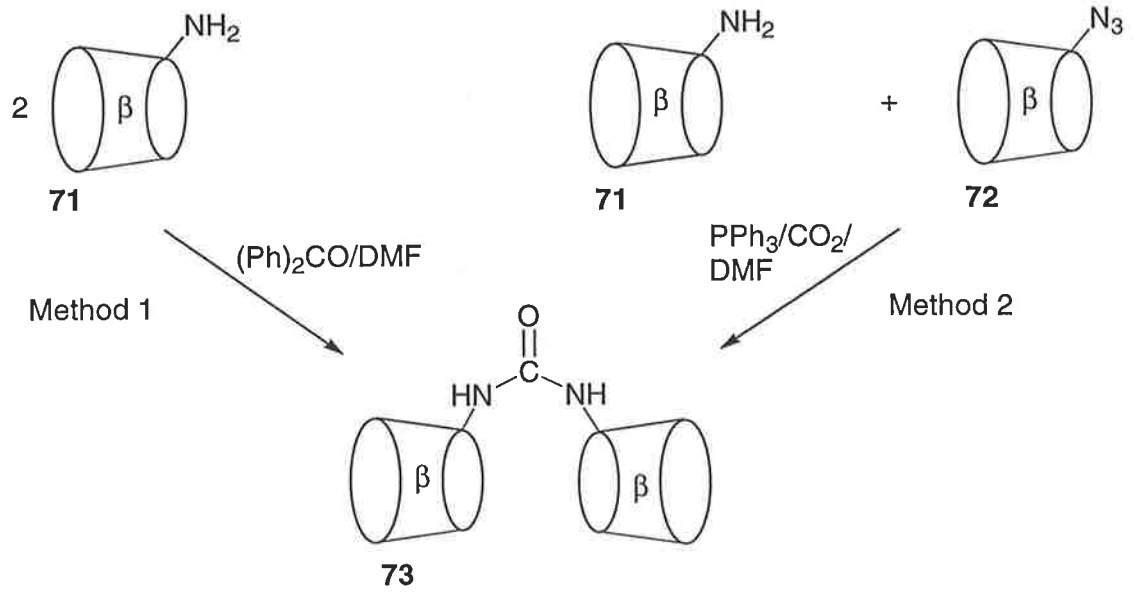


67

The axle **67** was synthesised and could be purified as a hydrochloride salt in a similar manner to the axles **52** and **53**, and was obtained in 47 % yield (Scheme 3.11). Two methods for the synthesis of the urea-linked cyclodextrin dimer **73** are reported in the literature and both methods were examined (Scheme 3.12). The first method [19] gave pure **73** after some extension of the reported purification procedure, but in poor yield (~25 %). A slight modification of the second method [20] gave a much better yield (~ 80 %) of the pure product.



Scheme 3.11 Synthesis of the axle **67**.



Scheme 3.12 Synthesis of the urea-linked cyclodextrin dimer **73** by two methods.

The 2D ^{1}H ROESY NMR spectrum (Figure 3.12) of a D_2O solution of the axle **67** and the dimer **73** contains cross peaks due to nOe interactions between the aromatic protons of **67** and the β-cyclodextrin annular protons of **73**, as well as weaker cross peaks due to interactions between the butyl H1-H3 protons of **67** and the β-cyclodextrin annular protons of **73** (some of which are not visible on the F2 axis at the intensity of Figure 3.12), indicative of substantial inclusion of **67** in the β-cyclodextrin annuli of **73**. The aromatic region of the 1D ^{1}H NMR spectrum contains an AB quartet, similar to that present in the spectrum of the free axle, which implies that the aromatic protons of **67** that are equivalent by symmetry in the molecule remain equivalent in the [2]-pseudorotaxane **73.67**. The dimer **73** must be predominantly located over the central section of **67** in order to maintain the level of symmetry of **67** in the [2]-pseudorotaxane **73.67** (Scheme 3.13). There are some minor resonances in the aromatic region of the spectrum, which may arise from inclusion isomers in which a different section of the axle **67** is included in **73** or **67** is included in only one β-cyclodextrin annulus of **73**.

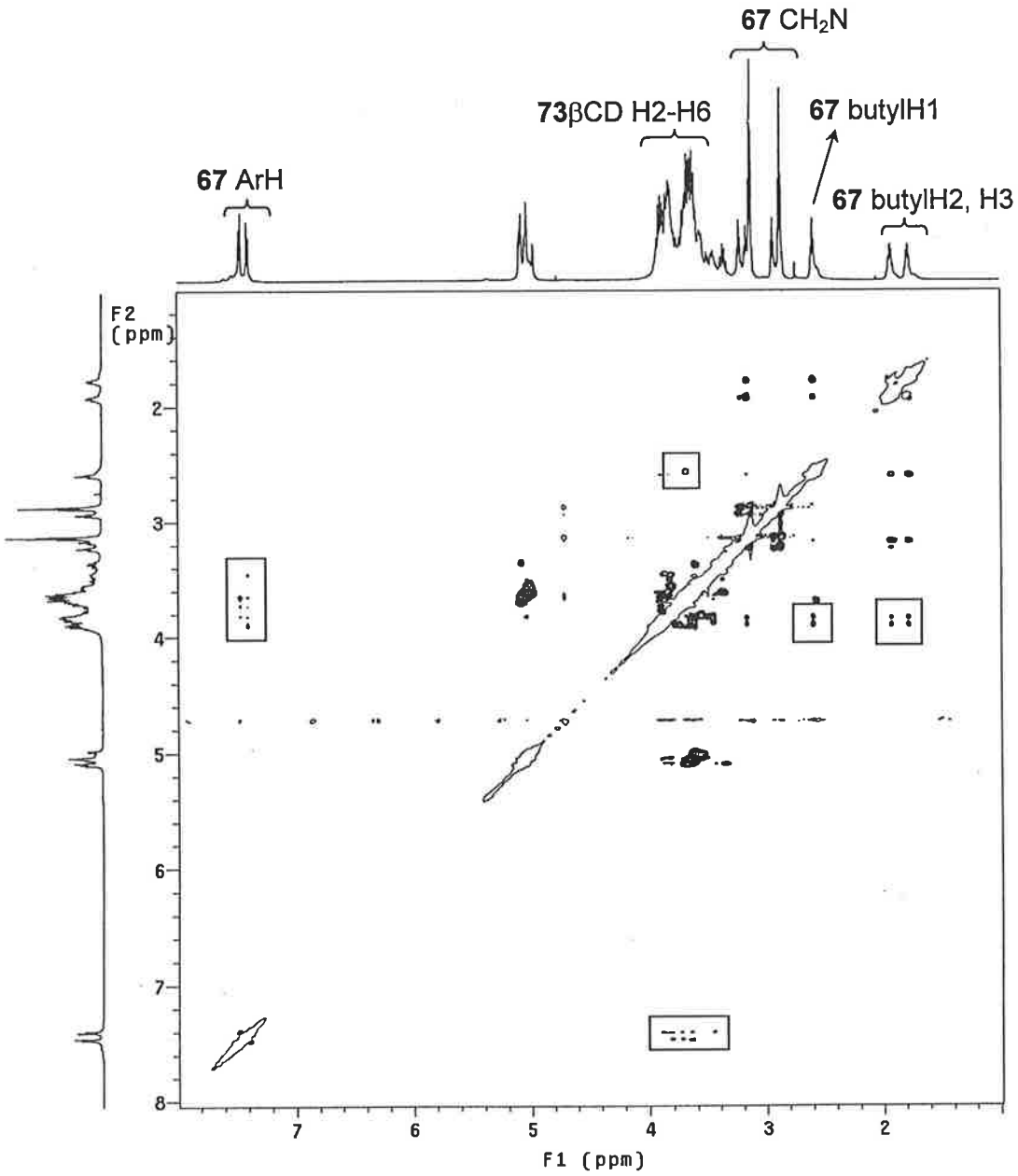
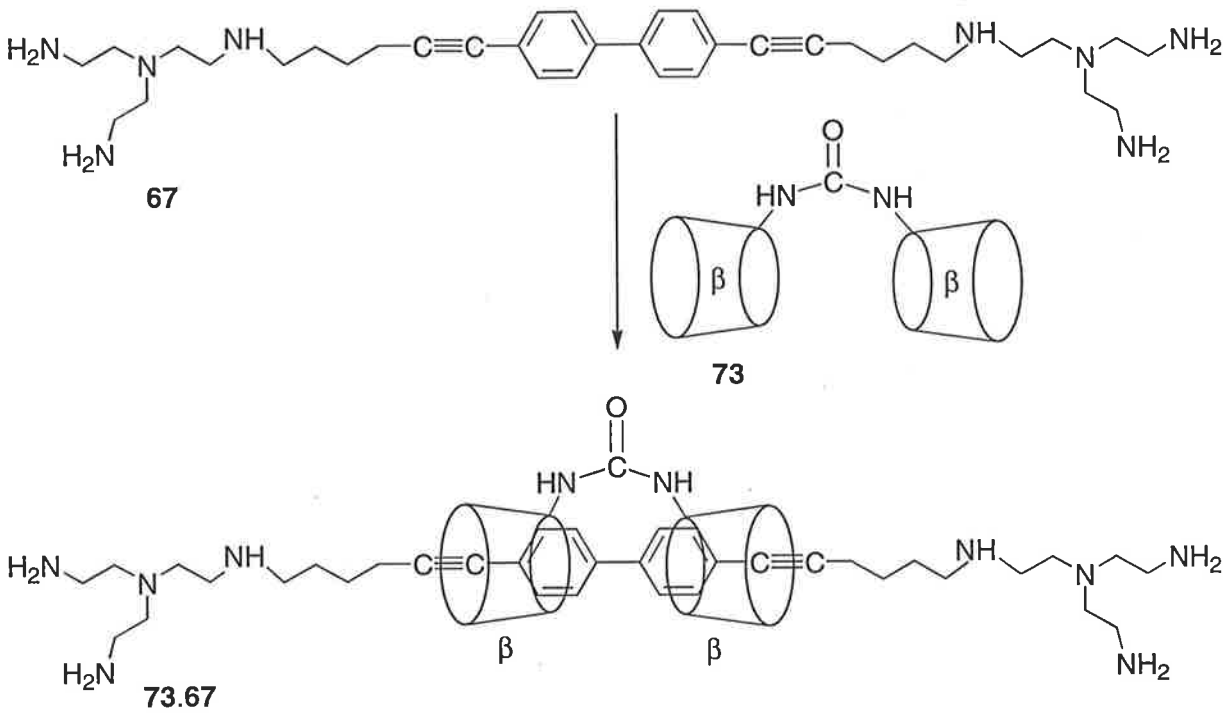


Figure 3.12 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.013 mol dm^{-3} axle **67** and 0.014 mol dm^{-3} dimer **73** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of **67** and the β-cyclodextrin annular protons of **73**.



Scheme 3.13 Formation of the [2]-pseudorotaxane **73.67**. The cyclodextrin dimer is located at a central position of the axle.

The 2D ^{1}H ROESY NMR spectrum (Figure 3.13) of a D_2O solution of the axle **67**, the dimer **73** and ~1 equivalent of 1-adamantanecarboxylate **17** contains strong cross peaks due to nOe interactions between the β-cyclodextrin annular protons of **73** and both the protons of **67** and the protons of **17**. The aromatic region of the 1D ^{1}H spectrum is complicated; it contains an AB quartet identical to that in the spectrum of the [2]-pseudorotaxane **73.67** alone, as well as other overlapping multiplets. The presence of several sets of resonances in the aromatic region indicates that the solution contains multiple species, which most likely include the complexes **73.67**, **73**.2(**17**) and **73.67.17**. It is implied that the dimer **73** can simultaneously include both **67** and **17**, one in each annulus.

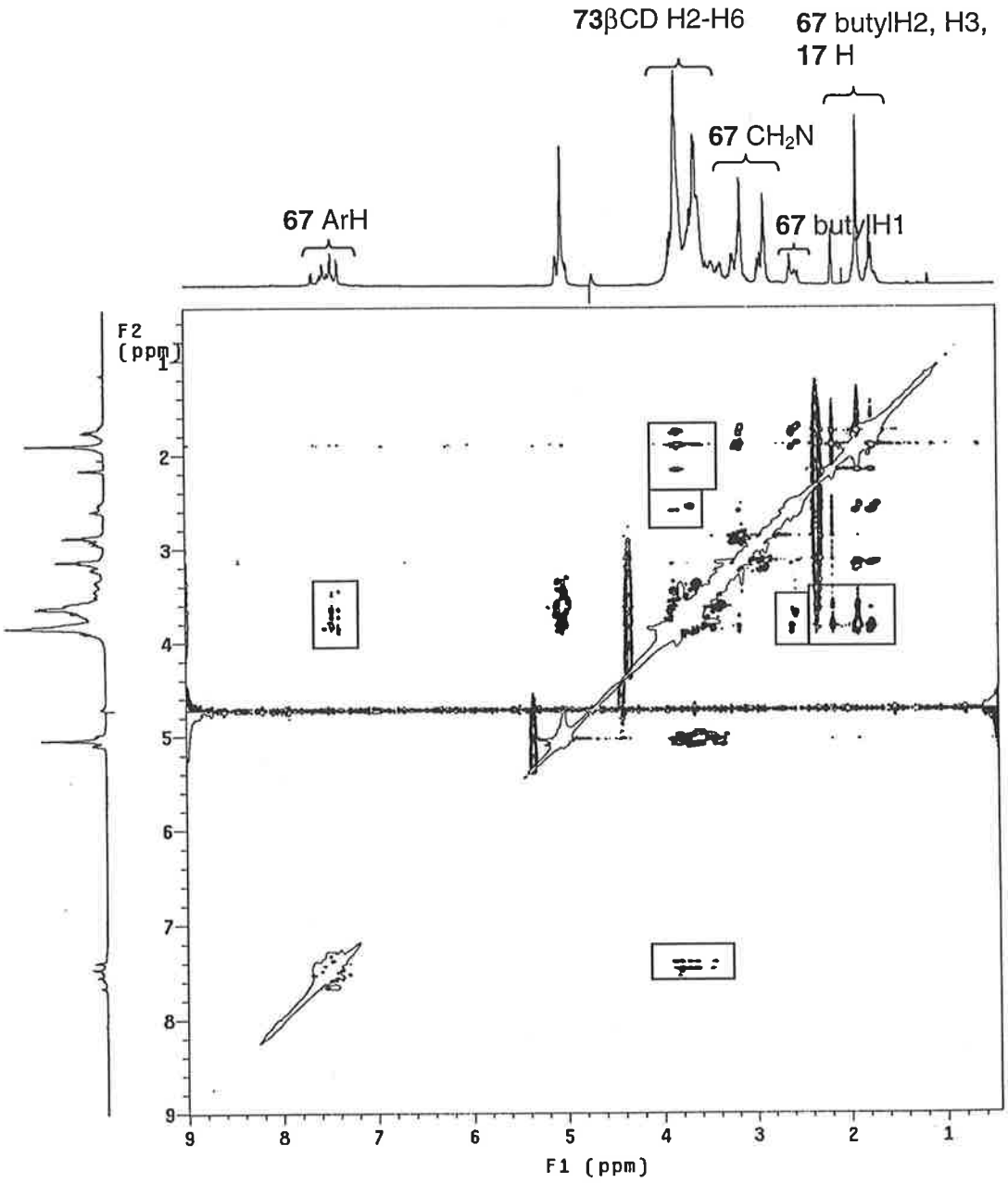


Figure 3.13 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.013 mol dm^{-3} axle **67**, 0.014 mol dm^{-3} dimer **73** and 0.014 mol dm^{-3} 1-admantanecarboxylate **17** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of **67** and the β-cyclodextrin annular protons of **73** and cross peaks (boxed) due to nOe interactions between the protons of **17** and the β-cyclodextrin annular protons of **73**.

The 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the axle **67**, the β-cyclodextrin dimer **73** and ~2.5 equivalents of 1-adamantanecarboxylate **17** contains strong cross peaks due to nOe interactions between the protons of **17** and the β-cyclodextrin annular protons of **73**. Cross peaks due to nOe interactions between the aromatic protons of **67** and the β-cyclodextrin annular protons of **73** are also present, but are so weak as to be considered insignificant. This is consistent with the major complex present in solution being the 1:2 **73/17** complex **73**.2(**17**).

The inclusion of the axle **67** in native β-cyclodextrin was also examined. The 2D ^{1}H ROESY NMR spectrum of a mixture of the axle **67** and ~2.5 equivalents of β-cyclodextrin in D_2O contains strong cross peaks due to nOe interactions between the aromatic protons of **67** and the β-cyclodextrin annular protons. However, the aromatic proton resonances in the 1D ^{1}H NMR spectrum of the mixture are very complicated, which is most likely due to the possible inclusion modes of **67** in β-cyclodextrin giving rise to a mixture of [2]- and [3]-pseudorotaxanes (Figure 3.14). It was decided not to attempt to synthesise a rotaxane from this system. A complex mixture of [2]- and [3]-rotaxanes would probably be obtained.

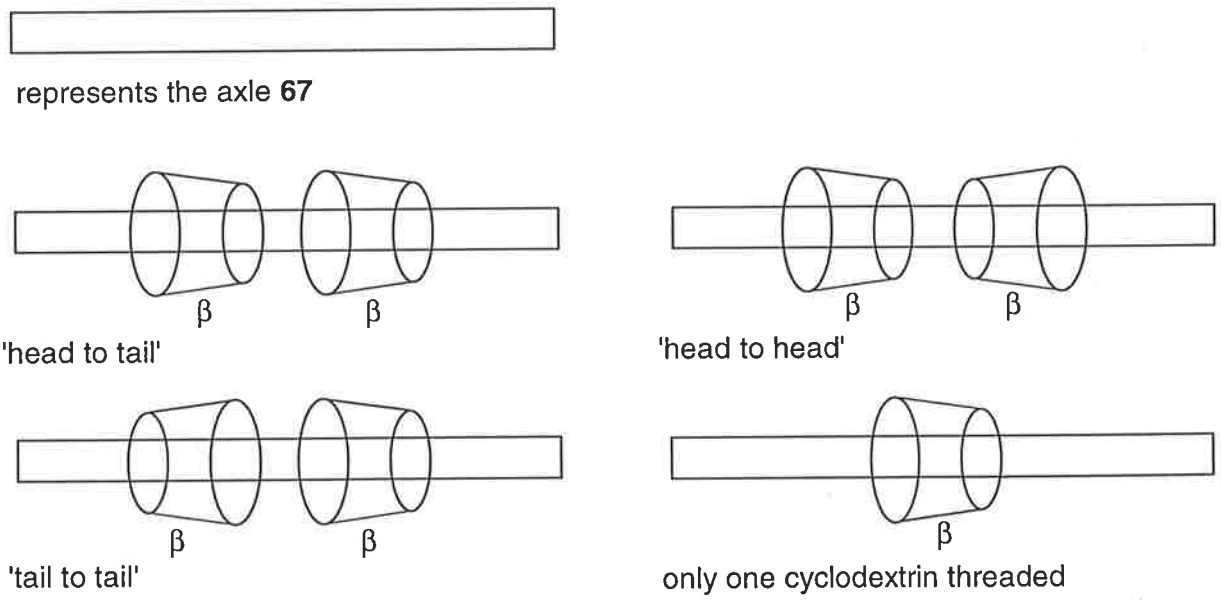
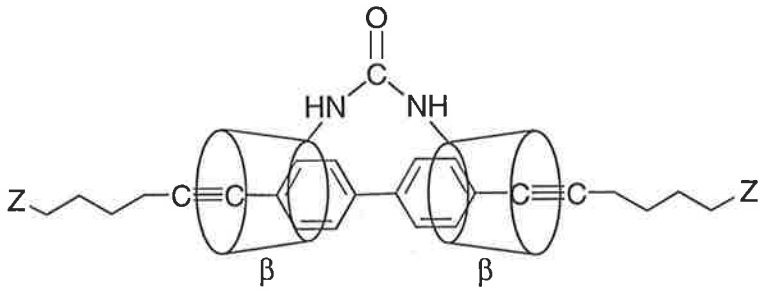


Figure 3.14 The [2]- and [3]-pseudorotaxanes that may be formed from a mixture of the axle **67** and β-cyclodextrin.

The [2]-rotaxane **74** was synthesised by a similar method to that used to synthesise the [2]-rotaxanes **57**, **58** and **59**, but at a higher dilution (~3×) due to the low water solubility of

the [2]-pseudorotaxane **73.67**. A red/brown sticky solid was isolated (UV/Vis λ_{max} = 508 nm), and the 1D ^{1}H NMR spectrum of the material contains resonances which are considerably broadened. Both the red/brown colour of the product and appearance of the 1D ^{1}H NMR spectrum obtained are indicative of some percentage of the cobalt(III) having been reduced to cobalt(II) during the [2]-rotaxane synthesis. After several attempts at the synthesis, this could not be improved upon. A hypothesis as to why cobalt(III) was reduced more readily during the synthesis of **74** than in the other [2]-rotaxane syntheses, is that this reaction was carried out at a lower concentration. As cobalt(III)$_{aq}$ is not stable, a decrease in the rate of attachment of cobalt(III) to the axle would lead to reduction of cobalt(III) to cobalt(II). Also, the axle **67** contains an extended π-system, which is an electron rich region and may attract cobalt(III), such that the reaction of cobalt(III) with the terminal tren groups is hindered. A sample of the [2]-rotaxane was also prepared as the chloro complex analogue **75** (UV/Vis λ_{max} = 535 nm), but the ^{1}H NMR spectrum of this complex is very similar in appearance to that of **74**.



74 Z = tren.Co(III).2H_2O
75 Z = tren.Co(III).2Cl^-

In an attempt to synthesise the cobalt(III) complex of **67**, the reaction of **67** with sodium triscarbonatocobalt(III) was repeated in the absence of the dimer **73**, but the product isolated was brown in appearance and a ^{1}H NMR spectrum of this material could not be obtained, possibly because too much cobalt(II) was present. The inclusion of **67** inside **73** during the synthesis of **74** may have protected the biphenyl region of **67**, such that more cobalt(III) was bound by the tren end groups and a spectrum of **74** could be obtained.

The [2]-rotaxane **74** is of low water-solubility and it was necessary to use a very dilute D_2O solution of the compound to obtain a ^{1}H NMR spectrum; obtaining a ^{13}C spectrum with a reasonable signal/noise ratio was not possible. Cross peaks in the 2D ^{1}H ROESY NMR spectrum of **74** in D_2O (Figure 3.15) are present due to nOe interactions between the aromatic

and butyl H1-H3 protons of the axle and the β-cyclodextrin annular protons of the dimer (cross peaks to the butyl H2 and H3 proton resonances are not visible on the F2 axis at this level of intensity). The cross peaks are very weak, but are indicative of some [2]-rotaxane **74** having formed. Addition of 1-adamantanecarboxylate **17** to the D_2O solution led to partial precipitation of **74**. As a result, the mixture of **17** and **74** on which a 2D ^1H ROESY NMR spectrum was run contained such low concentrations of the components that no cross peaks could be seen due to nOe interactions between the β-cyclodextrin annular protons and the protons of the axle or the protons of **17**. This made it impossible to determine what percentage of the axle was included inside the dimer.

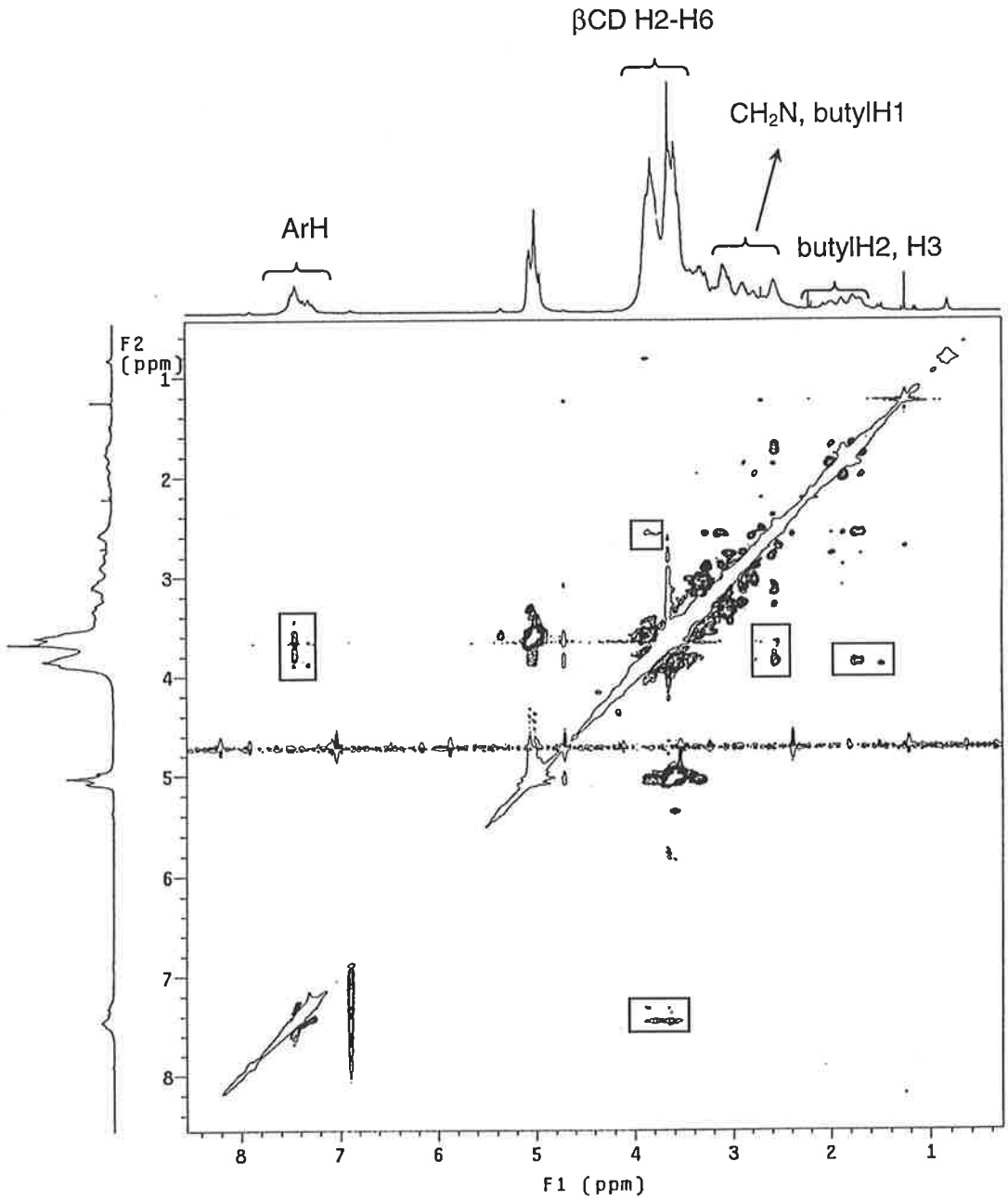


Figure 3.15 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD 7, 0.3 sec mixing time, 298 K) of 0.010 mol dm^{-3} [2]-rotaxane **74** in D_2O, containing weak cross peaks (boxed) due to nOe interactions between the aromatic and butyl protons of the axle and the β-cyclodextrin annular protons.

3.3 Conclusion

The design and synthesis of the water-soluble axles **52** and **53** enabled stable cyclodextrin [2]-pseudorotaxanes to be formed in aqueous solution. The series of cobalt(III)-blocked [2]-rotaxanes **57**, **58** and **59** was constructed by the threading method, in which the reaction of sodium triscarbonatocobalt(III) with the terminal amine groups of the axle in the corresponding [2]-pseudorotaxane expanded these groups and made them highly charged to form blocking groups. The [2]-rotaxanes were synthesised in good yields and the β-cyclodextrin [2]-rotaxanes **57** and **59** were obtained as almost pure products directly from the reaction mixtures, as shown by the inspection of 1D ^{1}H NMR and 2D ^{1}H ROESY NMR spectra. As the NMR spectra of the α-cyclodextrin [2]-rotaxane **58** are complicated, the purity of **58** could not be verified in this manner, and this [2]-rotaxane may contain some free axle complex **61**. It is concluded that β-cyclodextrin is a more appropriate 'wheel' than α-cyclodextrin for constructing [2]-rotaxanes by the method employed, without the need for extensive purification. Further purification of the [2]-rotaxanes as the chloro complex analogues allowed good microanalyses to be obtained.

The [2]-rotaxane **57** was also synthesised by a slippage mechanism; the reaction was followed to completion by 1D ^{1}H NMR spectroscopy. The [2]-rotaxane **59** formed very slowly by a slippage mechanism, while the α-cyclodextrin [2]-rotaxane **58** did not form by such a mechanism.

Work towards synthesising the cyclodextrin dimer [2]-rotaxane **74** was carried out, but was hindered by the low water solubility of the corresponding [2]-pseudorotaxane.

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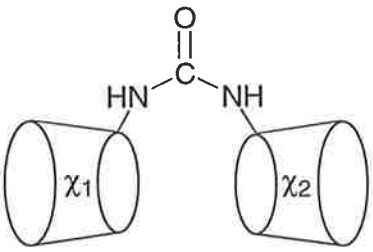
Chapter 4. Photochemically-Driven Molecular Devices

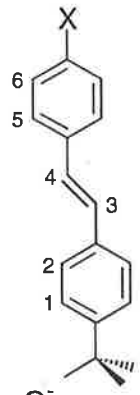
4.1 Introduction

The 'bottom-up' approach to creating miniature computational components has recently seen the development of a multitude of molecular devices, which are rapidly becoming more sophisticated. There has been great interest in pseudorotaxane, rotaxane and catenane based devices in which motion of the components can be controlled to give well-defined states for the system. The motion is generally accompanied by an observable change in the NMR, UV/Vis absorption or fluorescence spectrum to give ON/OFF switching. These systems carry out translational motion, either a shuttling of one component relative to the other or an in-out motion similar to that of a piston, rotational motion and in some examples a motion that resembles the stretching and contracting of muscles [1-5]. A variety of stimuli, chemical, electrochemical and photochemical in nature, have been utilised to create motion in molecular devices, but there is a growing preference for the stimulus to be photochemical [6-9], and there has been a recent review of photochemically-powered systems [10]. Photochemical stimulus is considered to be 'clean', because there is no need for chemical input, which causes waste build-up, and it is also compatible with most compounds and solvents [9, 11].

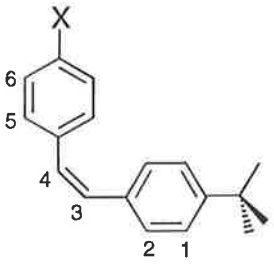
The urea-linked cyclodextrin dimers **73**, **76** and **77**, having two separate sites for guest-inclusion, are convenient hosts for host-guest shuttle-type systems. A guest may be included in either one or both of the cyclodextrin annuli, and the host may accommodate two separate guests simultaneously. Strictly, the urea-linked cyclodextrin **77** is not a dimer, because the two cyclodextrins it contains are of different sizes; this compound shall be referred to as a 'mixed dimer'.



76 $\chi_1 = \chi_2 = \alpha$
73 $\chi_1 = \chi_2 = \beta$
77 $\chi_1 = \alpha, \chi_2 = \beta$



78$^-$ X = O^-
79$^-$ X = CO_2^-



80$^-$ X = O^-
81$^-$ X = CO_2^-

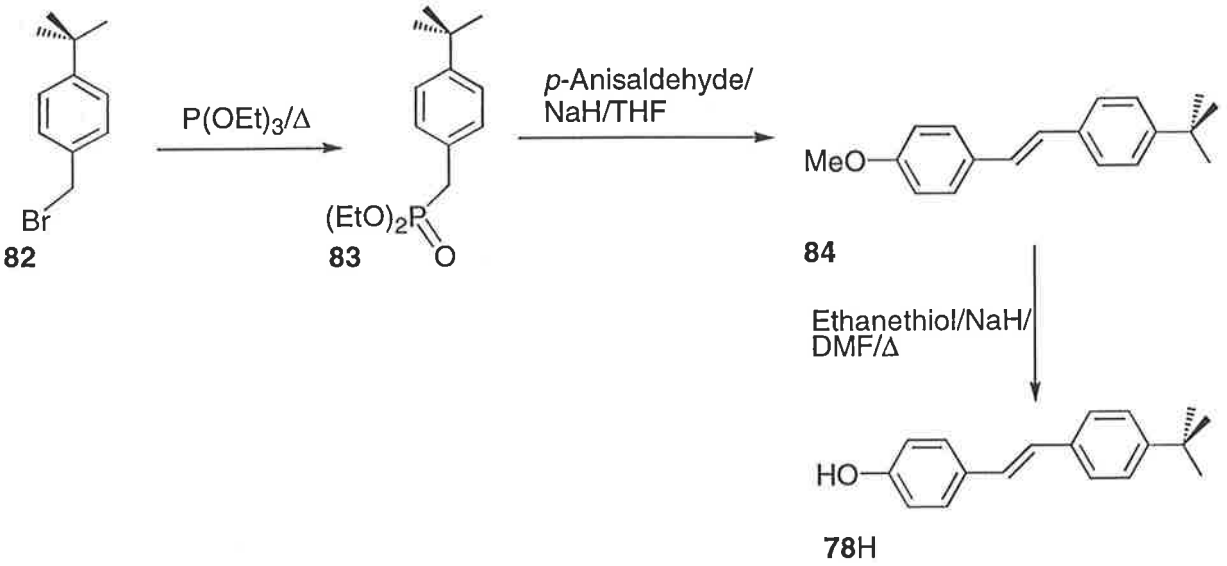
Stilbenes are appropriate guests to utilise with urea-linked cyclodextrin dimers, as they contain two suitably separated aromatic rings for inclusion in the annuli of the dimer. The derivatised *trans*/*cis* stilbenes **78**$^-$/**80**$^-$ and **79**$^-$/**81**$^-$ were designed with a *t*-butyl group at one end, as a high stability constant (1.8×10^4 dm^3 mol^{-1}) for the complex βCD.4-*t*-butylbenzoate has been determined previously [12]. Strong inclusion of the *t*-butylphenyl end of the stilbenes inside the dimers that contain a β-cyclodextrin unit, **73** and **77**, was expected. An acidic hydroxy group or carboxylic acid group was introduced at the other end of the stilbenes to enhance their water solubility, particularly at high pH.

The property of *cis*/*trans* isomerisation of stilbenes at different wavelengths of light is well-known [13-16]. It was envisaged that in the complexes formed by the cyclodextrin dimers **73** and **77** and the stilbenes **78**$^-$-**81**$^-$, a change in shape of the stilbene guest during isomerisation from the *trans* isomer **78**$^-$ or **79**$^-$ to the *cis* isomer **80**$^-$ or **81**$^-$ would require either a change in conformation of the host, or sliding of the host and guest relative to each other, giving rise to a molecular device.

4.2 Results and Discussion

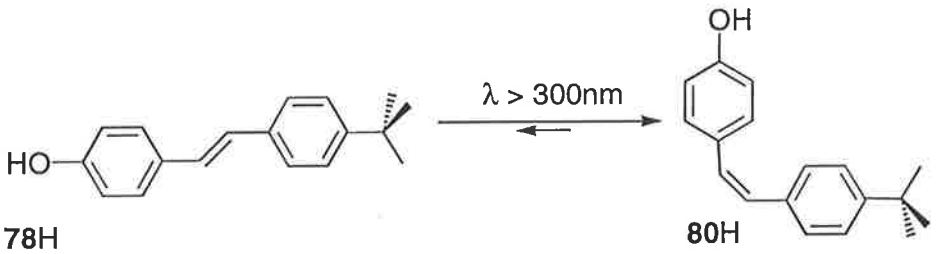
Synthesis

The *trans* methoxystilbene **84** was synthesised in 70 % yield by a Wadsworth-Emmons-Hörner modification of the Wittig reaction, this method being known to give predominantly *trans* product and to produce a water-soluble by-product that is easily removed [17]. Demethylation gave the *trans* hydroxystilbene **78**H in 85 % yield (Scheme 4.1).



Scheme 4.1 Synthesis of the *trans* hydroxystilbene **78H**.

The *cis* stilbene **80H** was prepared by exposing a solution of the *trans* stilbene **78H** in methanol to sunlight (Scheme 4.2). Methanol was chosen as the solvent because polar solvents increase the rate of isomerisation of stilbenes due to stabilisation of the polar transition state [18]. The solvent was deoxygenated before use to prevent oxidation of the phenol. Under these conditions, the *cis* isomer was the major species, and was separated from the residual *trans* isomer on a column of neutral alumina (54 % yield). The stilbenes were characterised by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and microanalysis.



Scheme 4.2 Isomerisation of the *trans* hydroxystilbene **78H** to the *cis* hydroxystilbene **80H** in sunlight (λ > 300 nm).

The isomerisation reaction in Scheme 4.2 was carried out in a pyrex flask through which only light with a wavelength greater than approximately 300 nm is transmitted. Inspection of the UV/Vis absorption spectra of the *cis* and *trans* stilbenes **78H** and **80H** in methanol revealed that the *trans* isomer **78H** absorbs light above a wavelength of 300 nm

much more strongly than the *cis* isomer **80**H (Figure 4.1), such that the reaction in Scheme 4.2 lies to the right.

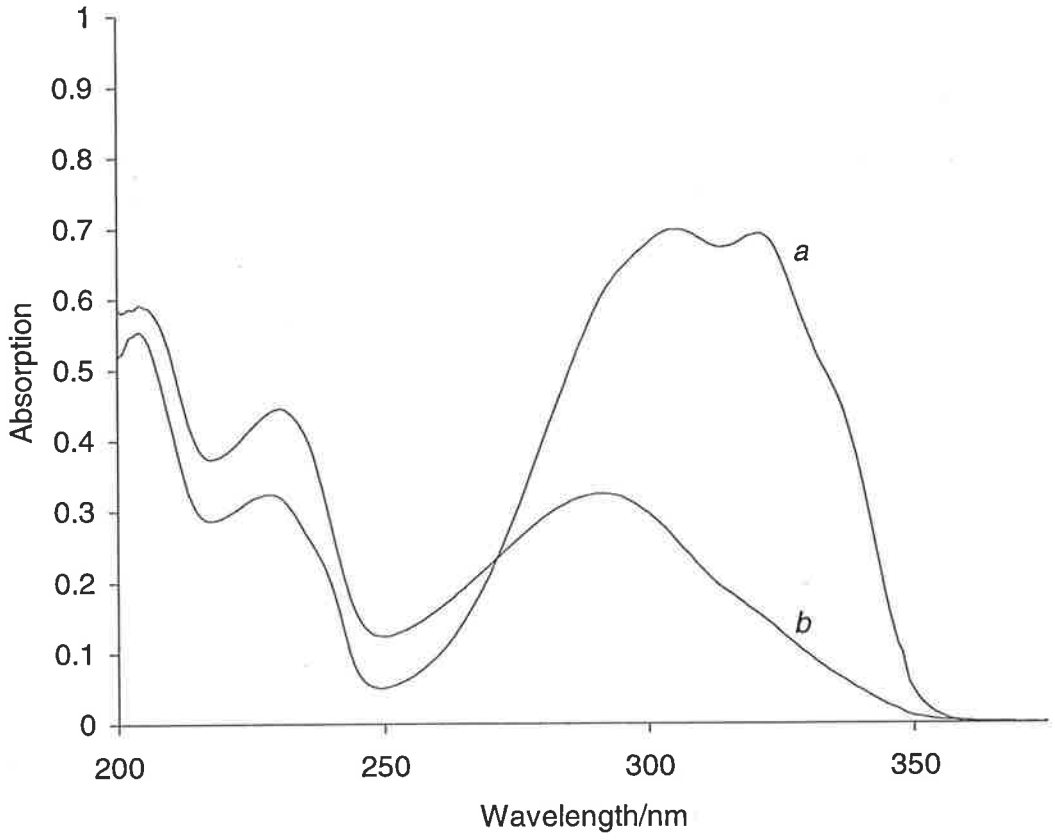
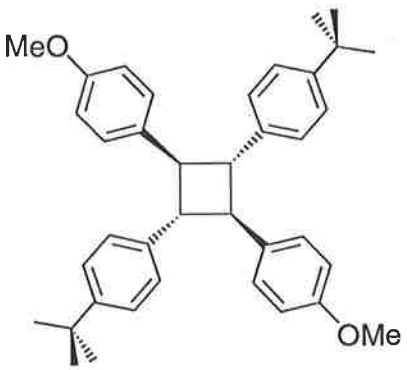


Figure 4.1 Absorption spectra of solutions containing (a) 2.5×10^{-5} mol dm^{-3} *trans* hydroxystilbene **78**H in methanol, (b) 2.5×10^{-5} mol dm^{-3} *cis* hydroxystilbene **80**H in methanol.

The isomerisation of **78**H to **80**H was carried out at a low concentration of the stilbene in order to limit the formation of the [2 + 2] cycloaddition products **85** – **88**, which form due to aggregation of the stilbene molecules in polar solvents such as methanol and particularly water [19].



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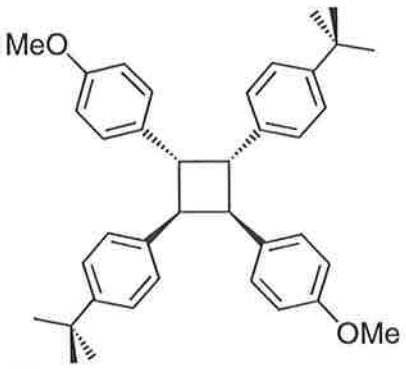

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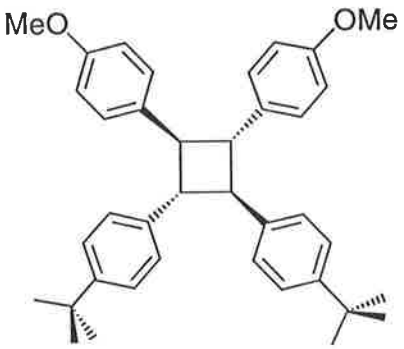

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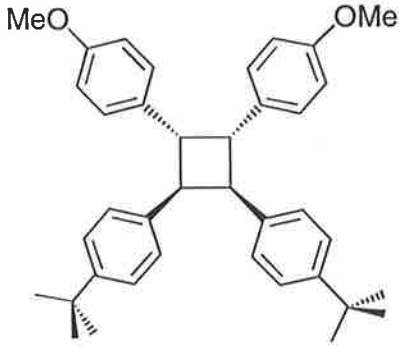

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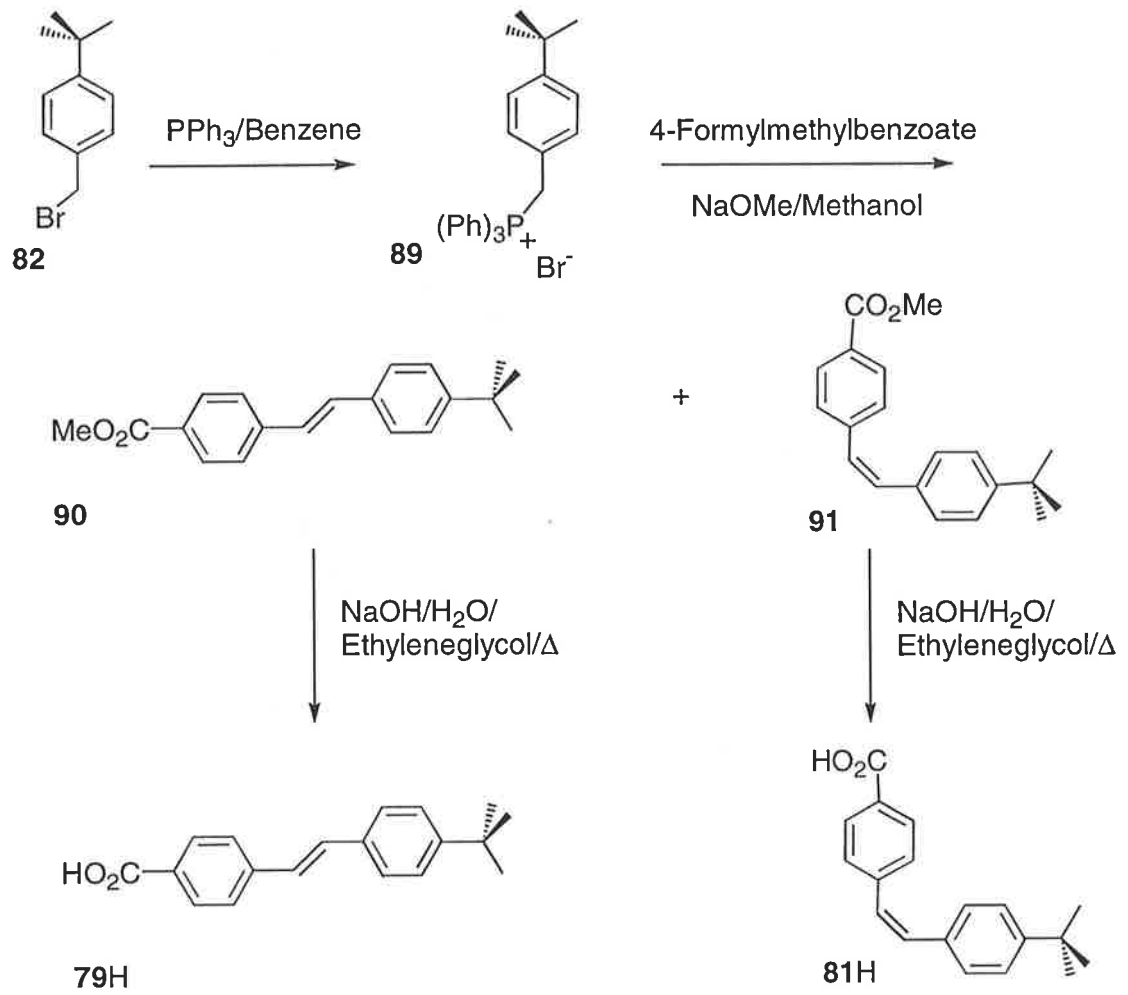
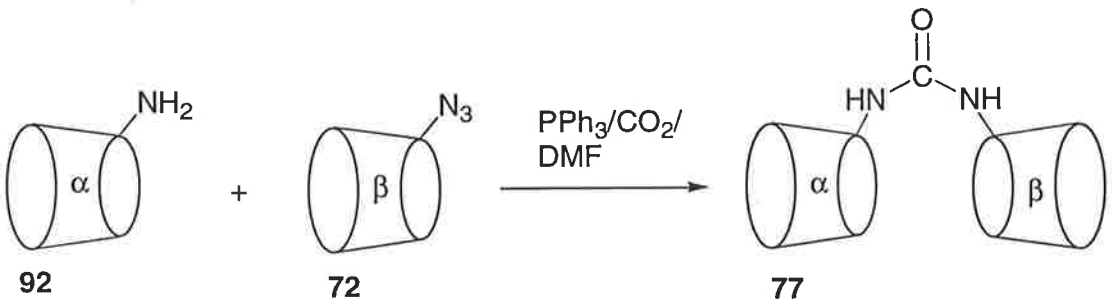
The methylcarboxystilbene **90** was initially prepared from the phosphonate **83** and 4-formylmethylbenzoate in a similar manner to the methoxystilbene **84**. The desired stilbene **90** was isolated in poor yield (18 %) from a complex mixture of products. A much better yield was obtained when **90** was prepared by a Wittig reaction from the phosphonium salt **89**. The *trans* and *cis* isomers, **90** and **91**, were produced in 43 % and 19 % yields, respectively, and were readily separated by flash column chromatography. The methoxystilbenes **90** and **91** were hydrolysed to give the corresponding carboxylic acids **79**H and **81**H in 80 % and 65 % yields, respectively (Scheme 4.3). The stilbenes **79**H and **81**H were each characterised by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and microanalysis.



Scheme 4.3 Synthesis of the the *trans* and *cis* stilbenecarboxylic acids **79H** and **81H**.

Two methods for the synthesis of the dimer **73** have been discussed in Chapter 3. The second method given in Scheme 3.12 was used to prepare **73** and also the mixed dimer **77**, which can only be prepared by this method (Scheme 4.4).



Scheme 4.4 Synthesis of the mixed dimer **77**.

Cyclodextrin dimer.stilbene inclusion complexes

Solutions containing 1:1 mixtures of the cyclodextrin dimer **73** or **77** and one of the stilbenes **78**$^-$-**81**$^-$ in D_2O were prepared for 2D ^{1}H ROESY NMR experiments. Strong cross peaks in the 2D ^{1}H ROESY NMR spectra of the mixtures provide evidence for the formation of inclusion complexes between each dimer and stilbene. The stilbenes **78**$^-$-**81**$^-$ have very low water-solubility, but are solubilized as their cyclodextrin dimer complexes, which indicates that close to 100 % of the stilbene molecules are included in each case. A sodium hydroxide concentration of 0.15 mol dm^{-3} (pD ≥ 12) is required to dissolve the stilbene complexes at a suitable concentration for NMR. It is considered that partial deprotonation of the cyclodextrin hydroxy groups increases the solubility of the complexes formed by the dimers and the stilbenes.

The 2D ^{1}H ROESY NMR spectra of solutions of the mixed dimer **77** and one of the *trans* stilbenes **78**$^-$ or **79**$^-$ in D_2O contain cross peaks due to nOe interactions between all the aromatic protons and *t*-butyl protons of **78**$^-$ or **79**$^-$ and the cyclodextrin annular protons of **77**. This indicates that in the complexes **77**.**78**$^-$ and **77**.**79**$^-$, the stilbene component is included in both the α-cyclodextrin and β-cyclodextrin annuli of **77**. (Figure 4.2 displays the 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the *trans* oxystilbene **78**$^-$ and the mixed dimer **77**. At the level of intensity of this spectrum, cross peaks to the *t*-butyl group resonance cannot be seen clearly on the F2 axis due to the level of the noise, and this is also true in some other spectra in this chapter.) It is assumed that each stilbene is oriented such that the *t*-butylphenyl end is included in the β-cyclodextrin annulus of **77**, as β-cyclodextrin is known to form a very stable complex with *t*-butylbenzoate [12]. The 2D ^{1}H ROESY NMR spectra of the individual α-cyclodextrin and β-cyclodextrin complexes of **78**$^-$ and **79**$^-$, αCD.**78**$^-$, αCD.**79**$^-$, βCD.**78**$^-$ and βCD.**79**$^-$, also support this. β-Cyclodextrin preferentially includes the *t*-butyl group and aromatic H1 and H2 protons of **78**$^-$ or **79**$^-$, while α-cyclodextrin includes the central section of each stilbene and shows either no or very weak inclusion of the *t*-butyl group in the complexes αCD.**78**$^-$ and αCD.**79**$^-$. This will be discussed in more detail later.

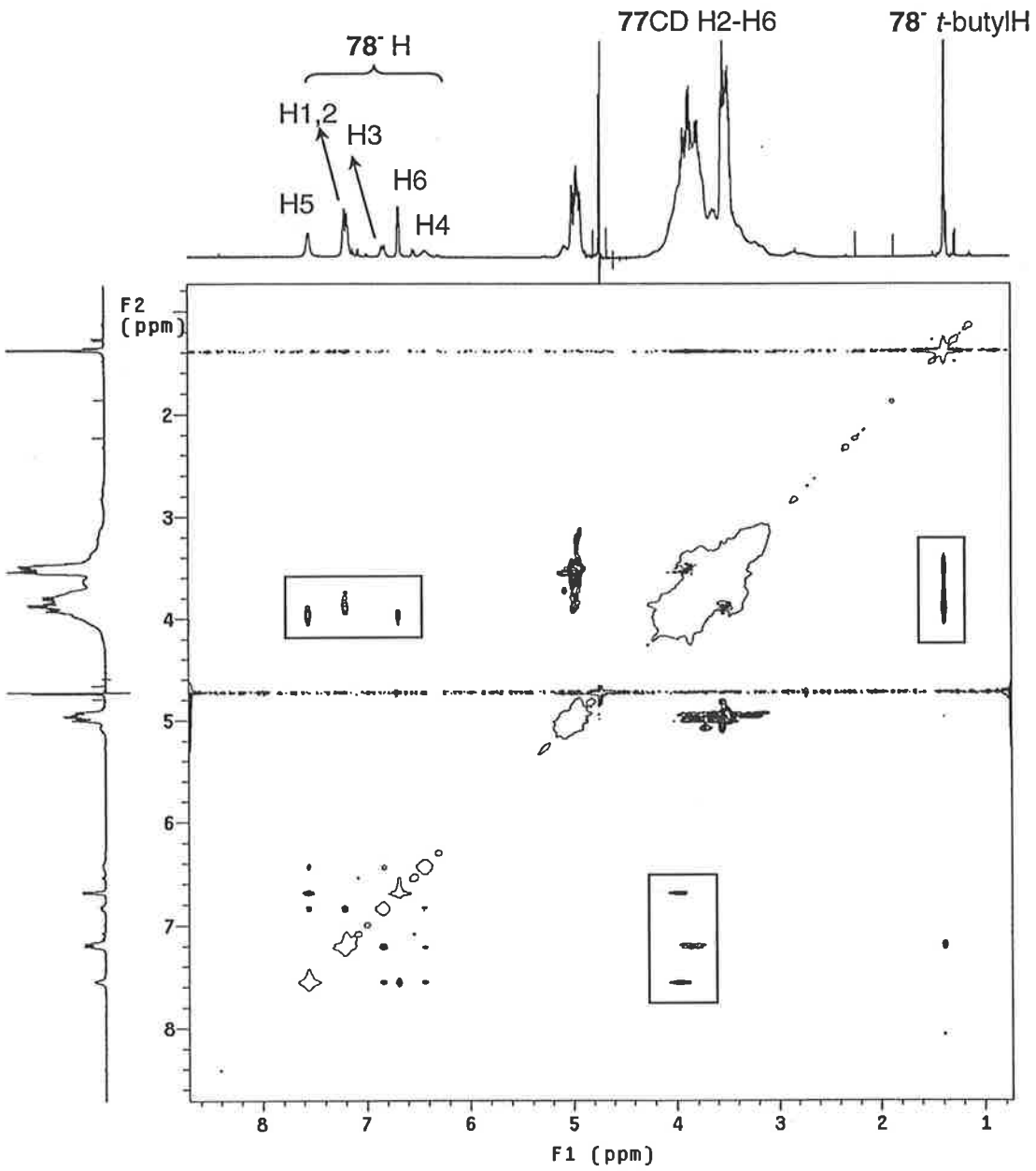
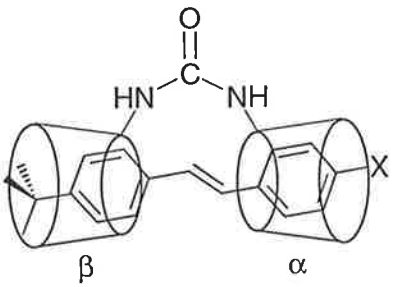
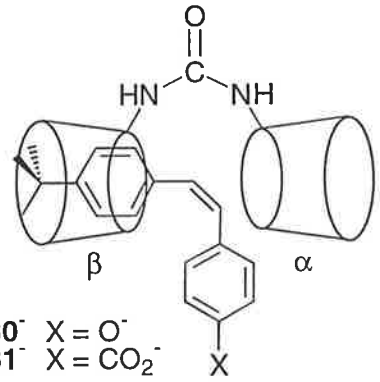


Figure 4.2 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* oxystilbene **78**$^{-}$ and 0.016 mol dm^{-3} mixed dimer **77** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic protons of **78**$^{-}$ and the cyclodextrin annular protons of **77**.

The 2D ^{1}H ROESY NMR spectra of solutions of the mixed dimer **77** and one of the *cis* stilbenes **80**$^-$ or **81**$^-$ in D_2O both contain cross peaks due to nOe interactions between the *t*-butyl group protons and the aromatic H1 and H2 protons of **80**$^-$ or **81**$^-$ and the annular protons of **77**. No cross peaks due to nOe interactions between the protons of the phenolate end of **80**$^-$ or the benzenecarboxylate end of **81**$^-$ and the cyclodextrin annular protons are present (Figure 4.3 displays the 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the mixed dimer **77** and the *cis* oxystilbene **80**$^-$). When either of the stilbenes is in the *cis* configuration, the mixed dimer **77** cannot distort enough to allow the simultaneous inclusion of both of the aromatic rings, such that only the more hydrophobic *t*-butylphenyl end of **80**$^-$ or **81**$^-$ is included in the β-cyclodextrin annulus of **77**. The *cis* stilbenes **80**$^-$ and **81**$^-$ are only 'half-included' in the annuli of **77**, such that the more water-soluble phenolate or benzenecarboxylate end of the stilbene enters the aqueous solution. The architectures of the *trans* stilbene complexes **77.78**$^-$ and **77.79**$^-$ and those of the *cis* stilbene complexes **77.80**$^-$ and **77.81**$^-$ are shown below.



77.78$^-$ X = O^-
77.79$^-$ X = CO_2^-



77.80$^-$ X = O^-
77.81$^-$ X = CO_2^-

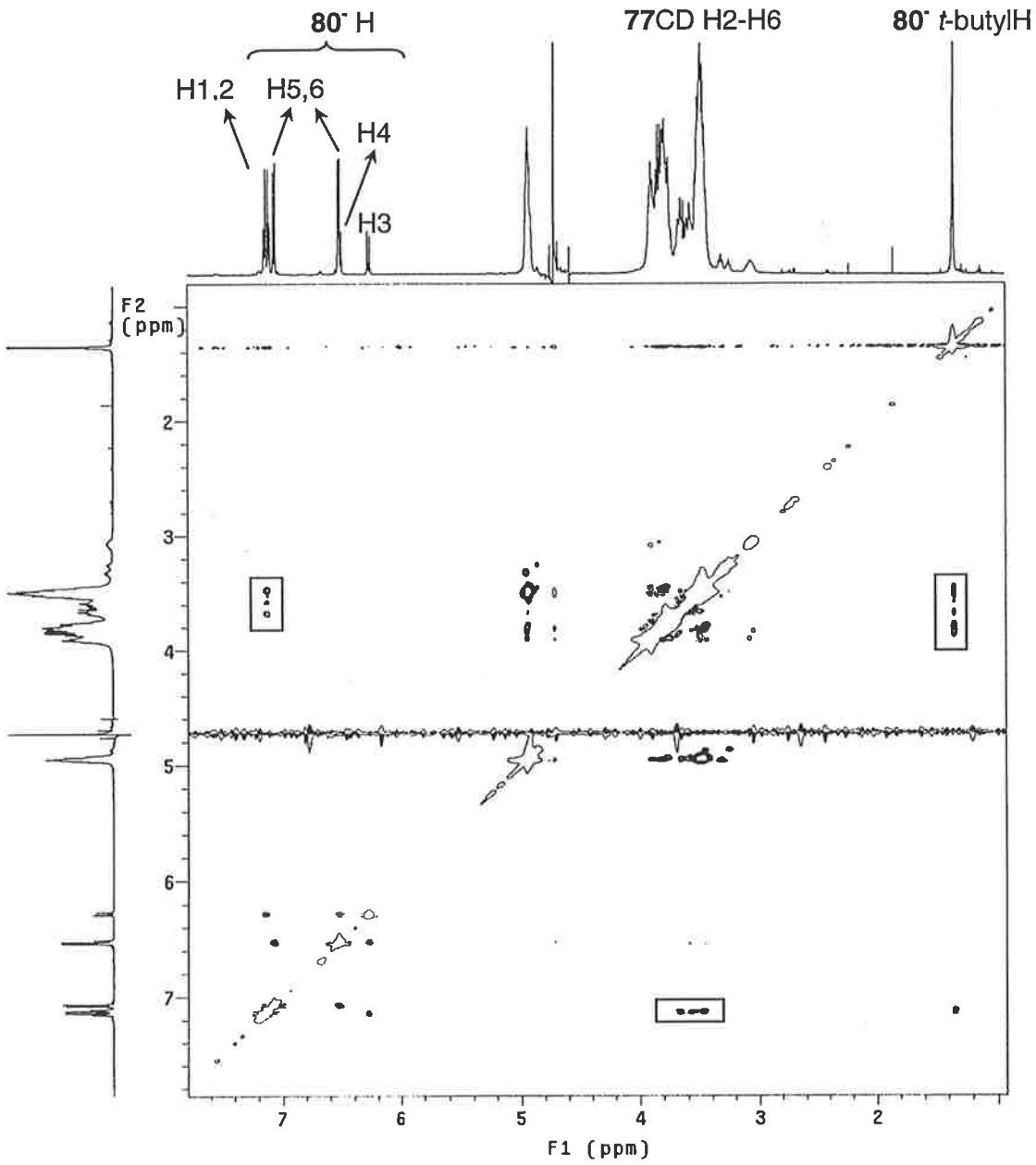


Figure 4.3 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *cis* oxystilbene **80⁻** and 0.016 mol dm^{-3} mixed dimer **77** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group protons and aromatic H1 and H2 protons of **80⁻** and the cyclodextrin annular protons of **77**.

The inclusion complexes formed by the dimer **73** and the *trans* stilbenes **78**$^-$ and **79**$^-$ have very similar architectures to those of the corresponding complexes formed by the mixed dimer **77**. The 2D ^{1}H ROESY NMR spectra of D_2O solutions of **73** and either **78**$^-$ or **79**$^-$ both contain cross peaks due to nOe interactions between all the aromatic protons and *t*-butyl group protons of **78**$^-$ or **79**$^-$ and the β-cyclodextrin annular protons of **73** (Figures 4.4 and 4.5), which implies that each *trans* stilbene is included in both β-cyclodextrin annuli of **73**. The *cis* stilbene complexes **73.80**$^-$ and **73.81**$^-$ have differing architectures. Cross peaks due to nOe interactions between all the aromatic protons and *t*-butyl group protons of the *cis* oxystilbene **80**$^-$ and the β-cyclodextrin annular protons of **73** are present in the 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the components (Figure 4.6). Strong cross peaks due to nOe interactions between the *t*-butyl group protons and only the aromatic H1 and H2 protons of the *cis* carboxystilbene **81**$^-$ and the β-cyclodextrin annular protons of **73** are present in the 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the components (Figure 4.7). This implies that both aromatic rings of **80**$^-$ are included in the annuli of **73**, but only the *t*-butylphenyl end of **81**$^-$ is included. It is considered that the carboxylate group of **81**$^-$, being a bulkier charged group than the oxy group of **80**$^-$, would ideally sit further out of the secondary rim of **73**. The carboxylate group of **81**$^-$ cannot fully protrude into solution while both aromatic rings are included in the β-cyclodextrin annuli of **73**, and a half-included complex forms instead. The smaller oxy group of **80**$^-$ would experience weaker repulsive interactions at the secondary end of a β-cyclodextrin annulus such that both aromatic rings of **80**$^-$ are simultaneously included in the annuli of **73**. The cross peaks due to interactions between the protons of the phenoxy end of **80**$^-$ and the β-cyclodextrin annular protons are relatively weak, and it is believed that two possible forms of the complex **73.80**$^-$ exist in equilibrium. (In the 2D ^{1}H ROESY NMR spectrum of the complex **73.81**$^-$, there are very weak cross peaks due to nOe interactions between the benzenecarboxylate end of **81**$^-$ and the β-cyclodextrin annular protons of **73**, which indicate that some percentage of **81**$^-$ is simultaneously included in both β-cyclodextrin annuli, but in this case the cross peaks are so weak as to be insignificant.) Scheme 4.5 depicts the nature of the complexes formed by the stilbenes **78**$^-$-**81**$^-$ and the dimer **73**.

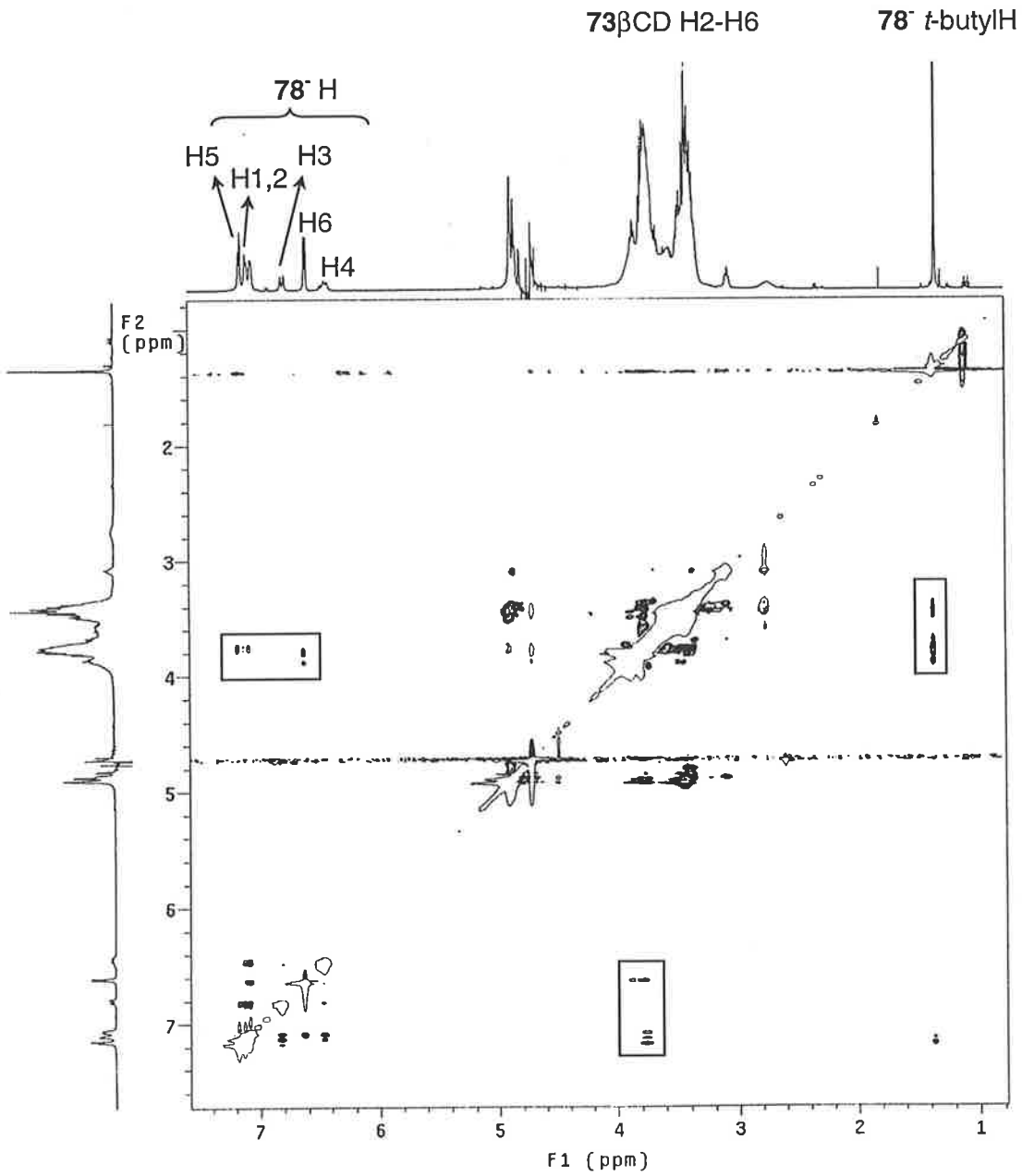


Figure 4.4 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* oxystilbene **78**$^{-}$ and 0.016 mol dm^{-3} dimer **73** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic protons of **78**$^{-}$ and the β-cyclodextrin annular protons of **73**.

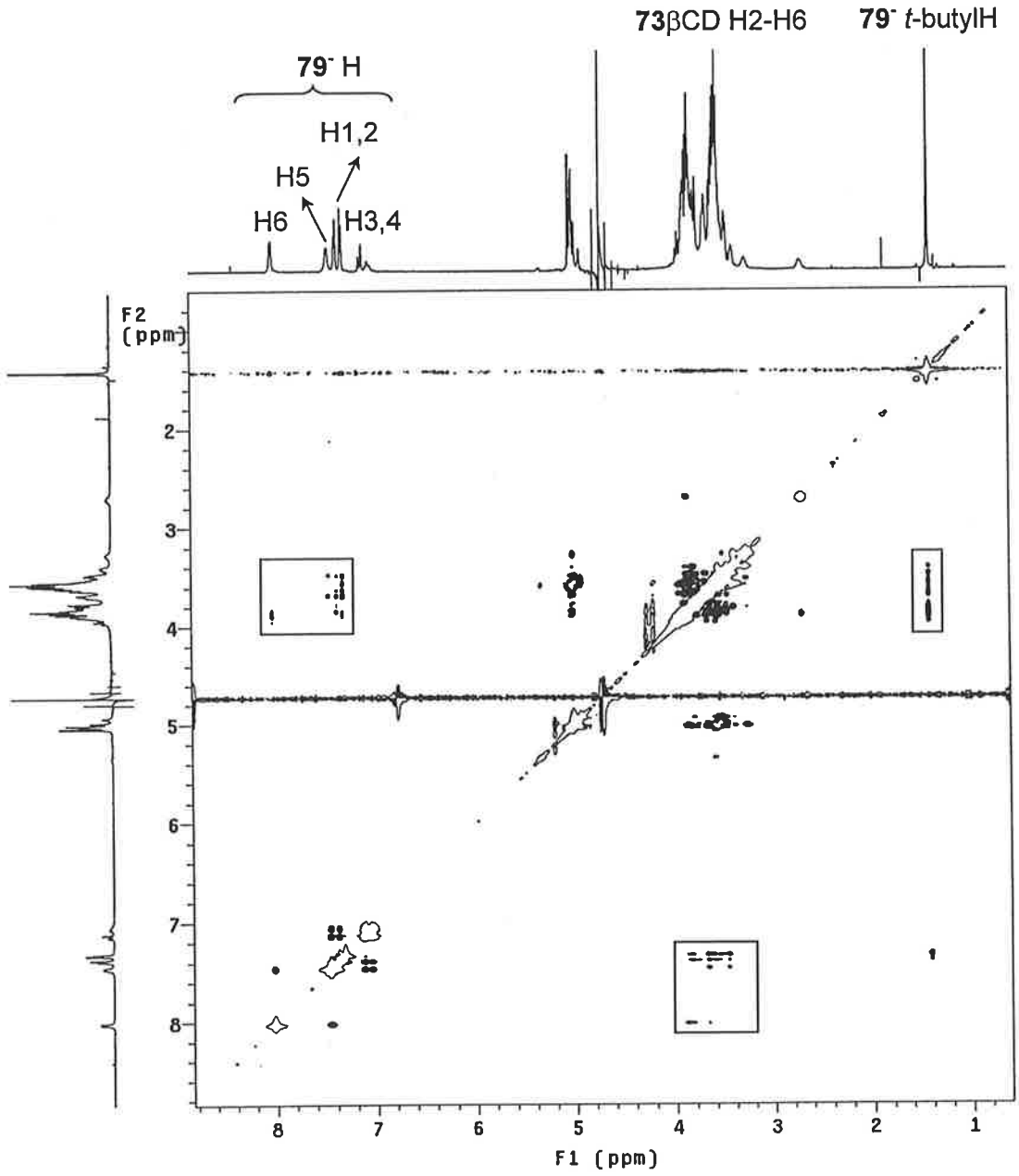


Figure 4.5 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* carboxystilbene **79**$^{-}$ and 0.016 mol dm^{-3} dimer **73** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic protons of **79**$^{-}$ and the β-cyclodextrin annular protons of **73**.

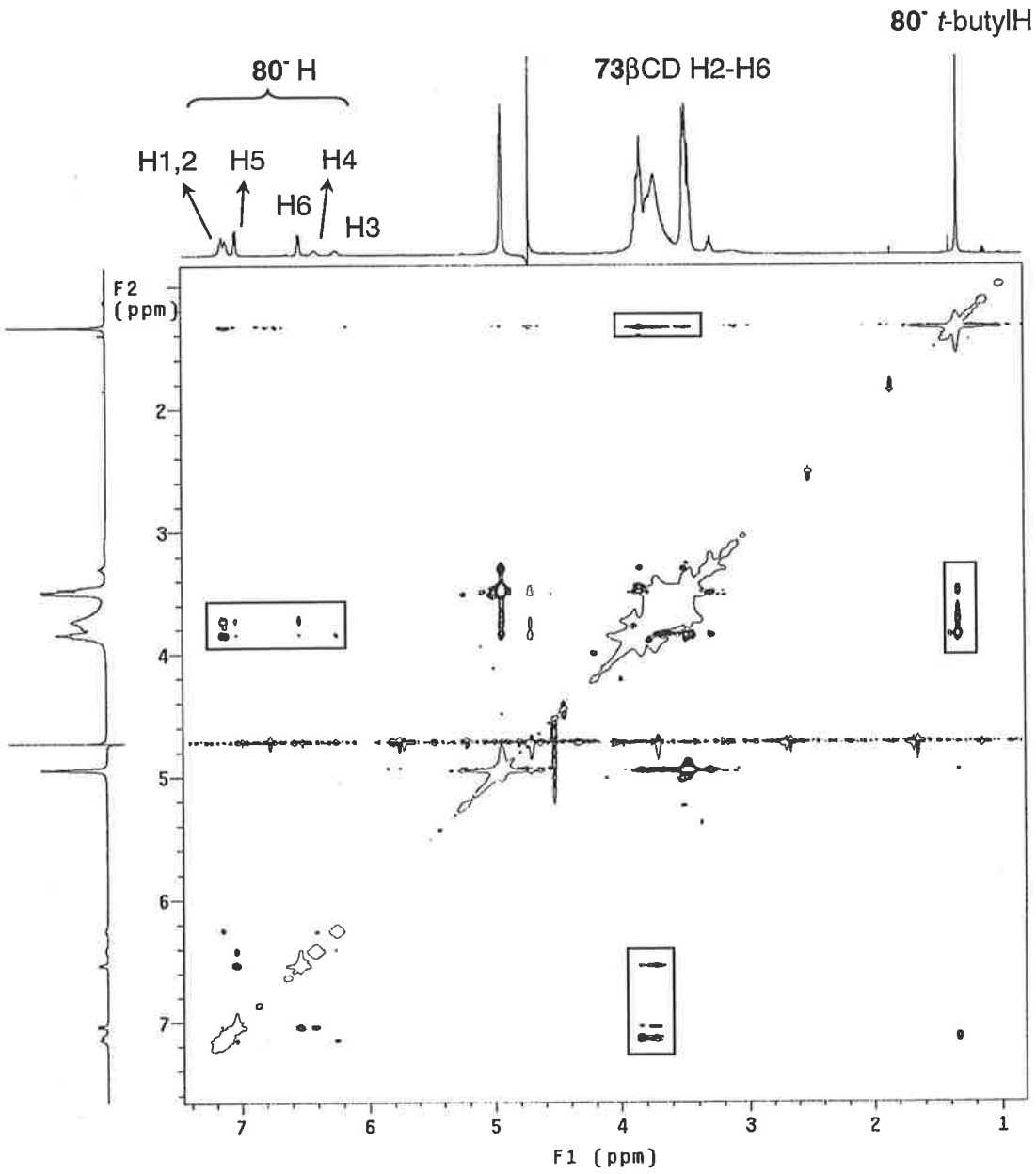


Figure 4.6 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *cis* oxystilbene **80⁻** and 0.016 mol dm^{-3} dimer **73** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic protons of **80⁻** and the β-cyclodextrin annular protons of **73**.

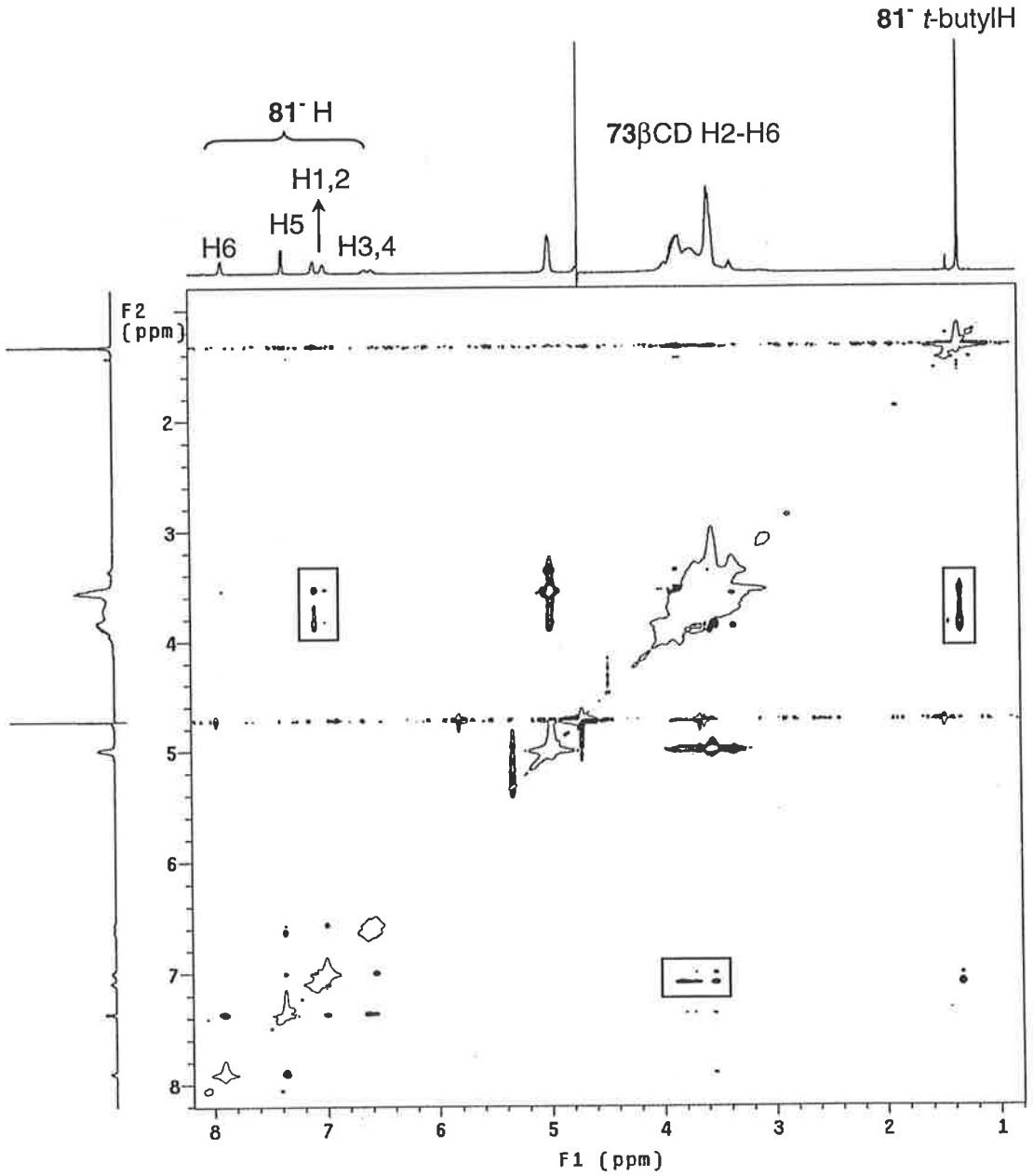
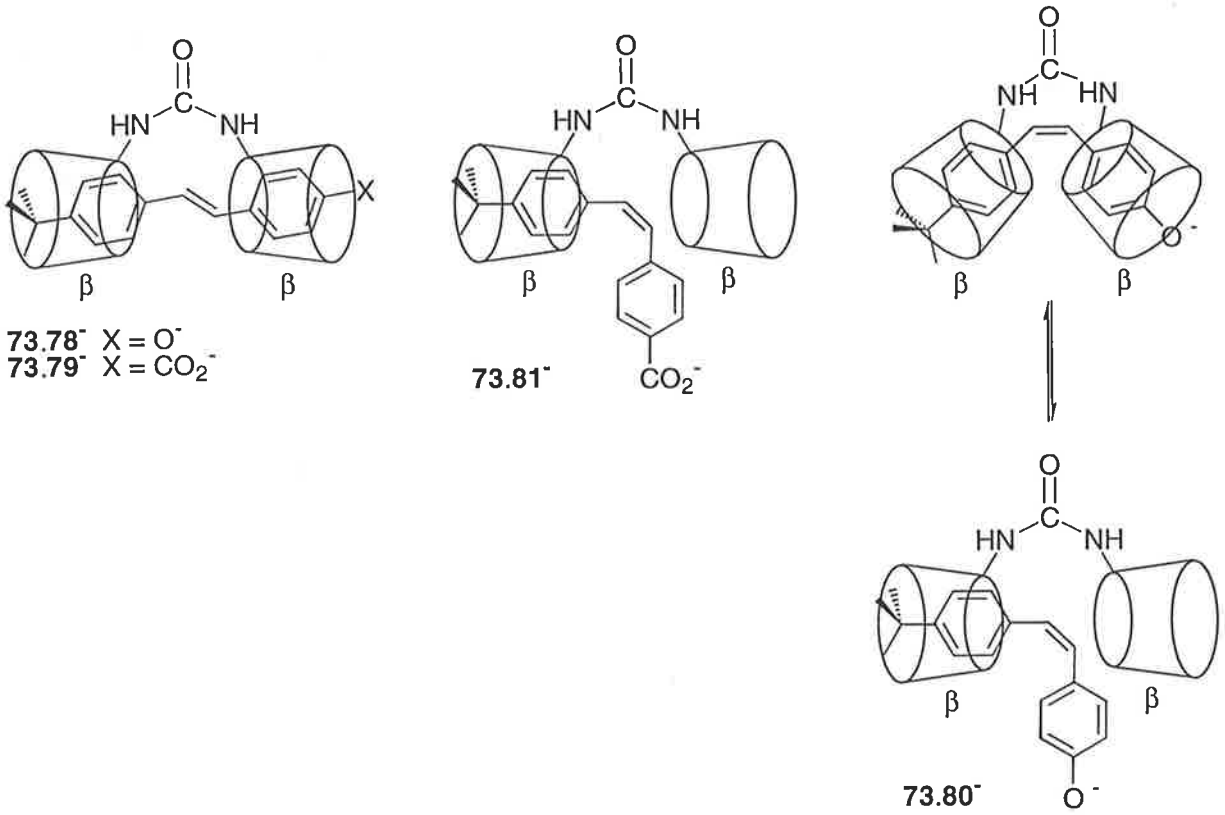


Figure 4.7 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *cis* carboxystilbene **81**$^{-}$ and 0.016 mol dm^{-3} dimer **73** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group protons and aromatic H1 and H2 protons of **81**$^{-}$ and the cyclodextrin annular protons of **73**.

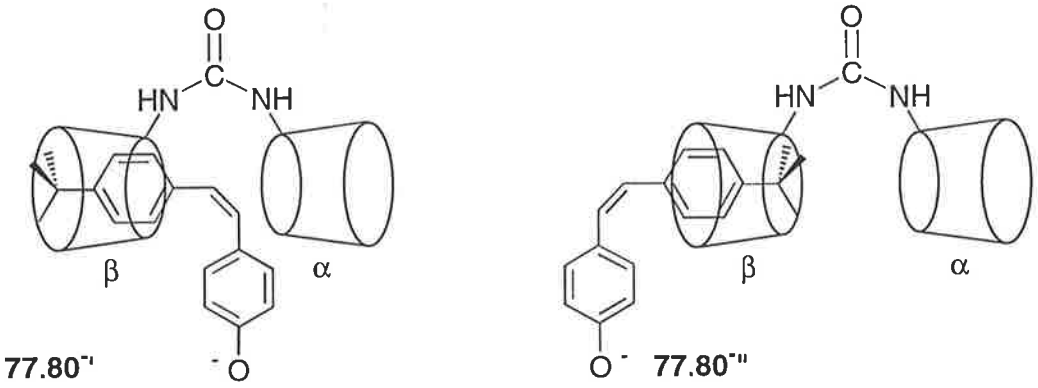


Scheme 4.5 The architectures of the inclusion complexes formed by the dimer **73** and the *trans* stilbenes **78**⁻ and **79**⁻ and the *cis* stilbenes **80**⁻ and **81**⁻.

The smaller size of the α-cyclodextrin annulus compared with that of the β-cyclodextrin annulus gives rise to a significant difference in the architectures of the complexes formed by the *cis* oxystilbene **80**⁻ and the dimers **77** and **73**. The comparatively 'loose' fit of the stilbene **80**⁻ in the β-cyclodextrin annuli of **73** allows the dimer to simultaneously accommodate both aromatic rings of **80**⁻. The small α-cyclodextrin annulus of **77** imparts a tight fit on the stilbene, such that both aromatic rings of **80**⁻ are not simultaneously included in **77**.

Evidence for the tight fit imparted by the mixed dimer **77** on the *trans* stilbenes **78**⁻ and **79**⁻ is given by the considerable broadening of the peaks arising from the aromatic protons in the 1D ^{1}H NMR spectra of the complexes **77.78**⁻ and **77.79**⁻. Significant broadening of the stilbene aromatic proton resonances is not observed in the spectra of the complexes **73.78**⁻ and **73.79**⁻. This suggests that some kind of restricted motion takes place in the complexes **77.78**⁻ and **77.79**⁻, either shuttling or rotating of each *trans* stilbene, **78**⁻ or **79**⁻, within **77**, at a rate that is intermediate on the NMR timescale.

It should be noted that there are two possible architectures that each of the *cis* stilbene complexes **77.80**$^-$, **77.81**$^-$ and **73.81**$^-$ may adopt, which will only be discussed for the complex **77.80**$^-$ as the same argument applies to all three complexes. The two possible architectures of **77.80**$^-$ are denoted **77.80**$^{-\prime}$, in which the excluded aromatic group protrudes from the primary end of the β-cyclodextrin annulus, and **77.80**$^{-\prime\prime}$, in which the excluded aromatic group protrudes from the secondary end of the β-cyclodextrin annulus.



The simpler case is the formation of the complex **77.80**$^{-\prime}$ as it would result from the phenolate end of the stilbene slipping out of the β-cyclodextrin annulus of the mixed dimer **77** during isomerisation from the *trans* stilbene **78**$^-$ to the *cis* stilbene **80**$^-$ (each of the *cis* stilbene complexes can be obtained by standing a basic D_2O solution of the corresponding *trans* stilbene complex in sunlight). Formation of the second complex **77.80**$^{-\prime\prime}$ would involve the stilbene becoming completely excluded from **77** during or after the isomerisation of **78**$^-$ to **80**$^-$ and then being included again, but facing the opposite direction with respect to **77**. The stilbenes **78**$^-$-**81**$^-$ are almost completely insoluble in water when they are not included inside a cyclodextrin host, rendering it unlikely that **80**$^-$ becomes completely excluded from **77** to give rise to **77.80**$^{-\prime\prime}$. Therefore, the architectures of **77.80**$^-$, **77.81**$^-$ and **73.81**$^-$ that have been depicted earlier are the most likely representations.

Photochemical and thermal stimuli in molecular devices

The *trans* oxystilbene **78**$^-$ within the complex **77.78**$^-$ was isomerised to produce predominantly the *cis* oxystilbene complex **77.80**$^-$ (> 90 % by ^{1}H NMR) by standing a basic aqueous solution of **77.78**$^-$ in a pyrex flask in sunlight for ~2 hours. The UV/Vis spectra of aqueous solutions containing **77** and either **78**$^-$ or **80**$^-$ display a large difference in the intensity of absorption of the complexes **77.78**$^-$ and **77.80**$^-$ above 300 nm, with **77.78**$^-$ absorbing much

more strongly in this region (Figure 4.8). This explains why the photostationary state in sunlight (in pyrex) of the system **77.78⁻/80⁻** lies towards the *cis* stilbene complex **77.80⁻**. The formation of cycloaddition products was not observed, even though the isomerisation was carried out in water. It has previously been found that the percentage of cycloaddition products formed during the irradiation of stilbenes in aqueous solution is greatly reduced when the stilbene molecules are included in either α-cyclodextrin or β-cyclodextrin [20]. The stilbene molecules cannot form aggregates while they are included in α- or β-cyclodextrin annuli so do not dimerise. (In the presence of γ-cyclodextrin the percent formation of cycloaddition products is increased as two stilbene molecules can include simultaneously in the larger annulus [21].)

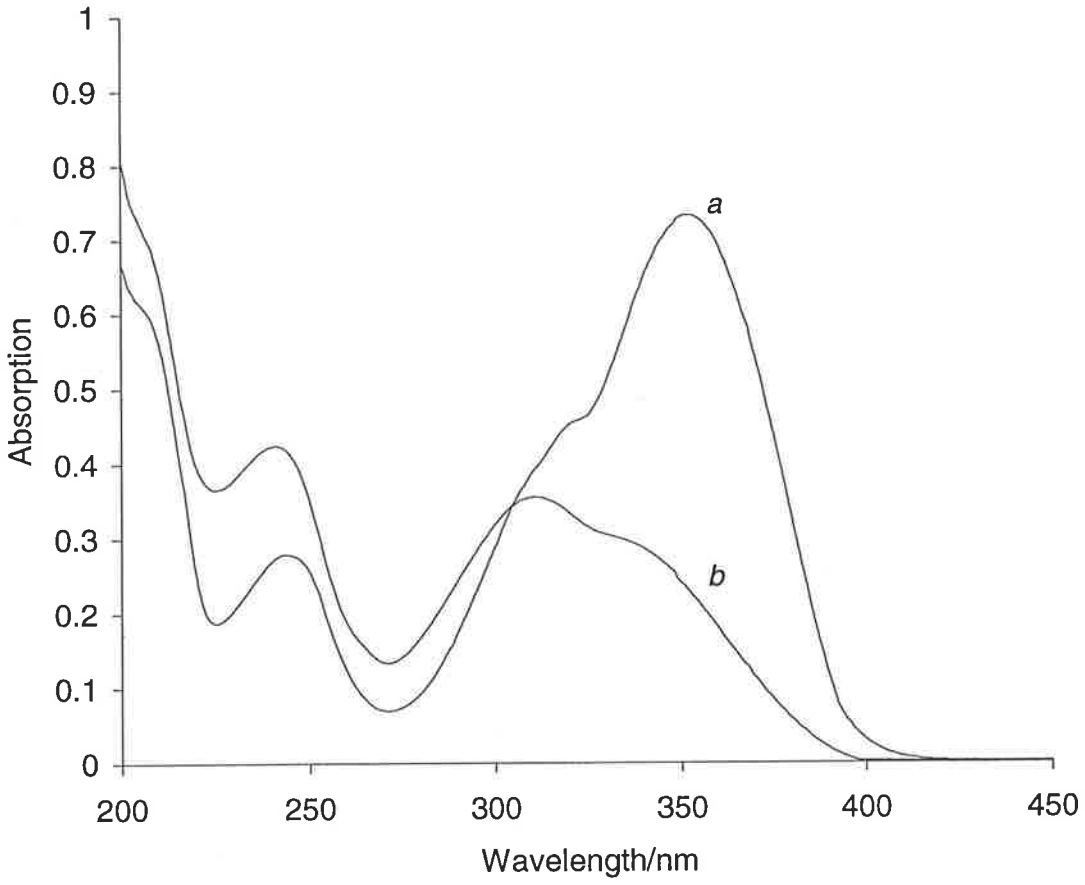
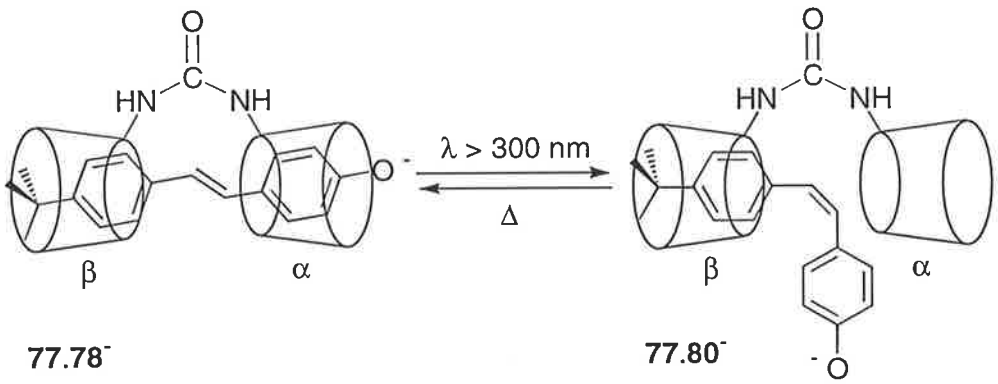


Figure 4.8 Absorption spectra of solutions containing (a) 2.4×10^{-5} mol dm^{-3} *trans* oxystilbene **78⁻** and 2.6×10^{-5} mol dm^{-3} mixed dimer **77** in 5 % methanol/ water, pH 10, (b) 2.4×10^{-5} mol dm^{-3} *cis* oxystilbene **80⁻** and 2.6×10^{-5} mol dm^{-3} mixed dimer **77** in 5 % methanol/ water, pH 10.

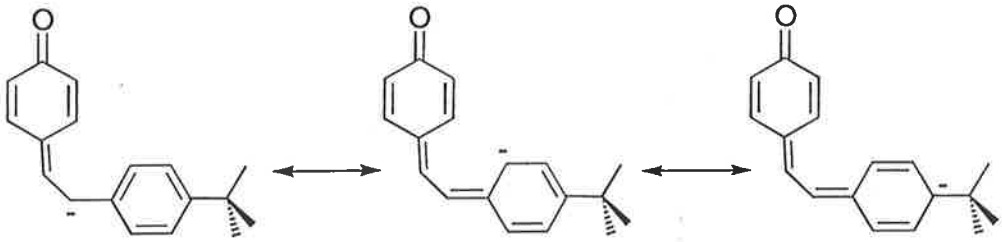
Warming a solution of the complex **77.80**$^-$ at ~70 °C in the dark for 12 hours resulted in the isomerisation of the stilbene component to predominantly the *trans* oxystilbene **78**$^-$, with no *cis* oxystilbene **80**$^-$ being visible by ^{1}H NMR spectroscopy. Therefore, by using sunlight and heat as stimuli, the isomerisation of the oxystilbenes within **77.78**$^-$ and **77.80**$^-$ can be controlled, without the addition of any chemical impurities, and with no evidence of decomposition after 1 full cycle. It is uncertain whether the mixed dimer **77** is flexible enough to allow the stilbene to isomerize while remaining fully included, or if the stilbene must become partially excluded before the isomerisation can take place. Regardless, the isomerisation between **78**$^-$ and **80**$^-$ causes a movement of the guest relative to the host, which represents a two-state molecular device, photochemically-powered in one direction and thermally-powered in the other direction (Scheme 4.6).



Scheme 4.6 In-out movement of the phenolate end of the oxystilbene **78**$^-$/**80**$^-$ from the β-cyclodextrin annlus of the mixed dimer **77** as a result of *cis*/*trans* isomerisation between **78**$^-$ and **80**$^-$.

Although exposure of a basic D_2O solution of either of the *trans* carboxystilbene complexes **77.79**$^-$ or **73.79**$^-$ to sunlight caused partial isomerisation of the stilbene component to give the complexes **77.81**$^-$ or **73.81**$^-$, respectively (~70 % in each case), these systems could not be thermally reverted under the same conditions as those applied to **77.80**$^-$. Heating the complexes of the *cis* carboxystilbene **81**$^-$ for several days at a higher temperature (90 °C) also caused no thermal reversion of the stilbene to the *trans* isomer that could be detected by ^{1}H NMR spectroscopy. The thermal *cis* → *trans* isomerisation of alkenes involves the conversion of the double bond into a diradical, which has a very large energy requirement. The presence of the *p*-phenoxy group in the *cis* oxystilbene **80**$^-$ gives the central bond some degree of single bond character, as seen in the resonance contributors of **80**$^-$ shown below,

which lowers the barrier to rotation around this bond and allows the thermal *cis* → *trans* isomerisation to be carried out under mild conditions.



The stilbene component in each of the systems **77.78⁻/80⁻**, **77.79⁻/81⁻** and **73.79⁻/81⁻** can be induced to isomerise back and forth solely using photochemical stimuli, by controlling the wavelength of light at which the complexes are irradiated, giving rise to photo-controlled molecular devices. This was followed by UV/Vis spectroscopy. A dilute aqueous mixture of the *trans* oxystilbene **78⁻** and the mixed dimer **77** was alternately irradiated at $\lambda = 355$ nm and $\lambda = 300$ nm (10 nm bandwidth), to give rise to photostationary states in which **77.80⁻** and **77.78⁻** predominated, respectively. The photostationary states were reached in 2 hours (irradiation for a further 24 hours caused no observable changes in the UV/Vis spectrum). Figure 4.9 shows the UV/Vis spectra of solutions of **77.78⁻** and **77.80⁻** in basic aqueous solution, and the photostationary states after irradiation of a solution of **77.78⁻** at $\lambda = 355$ nm and $\lambda = 300$ nm.

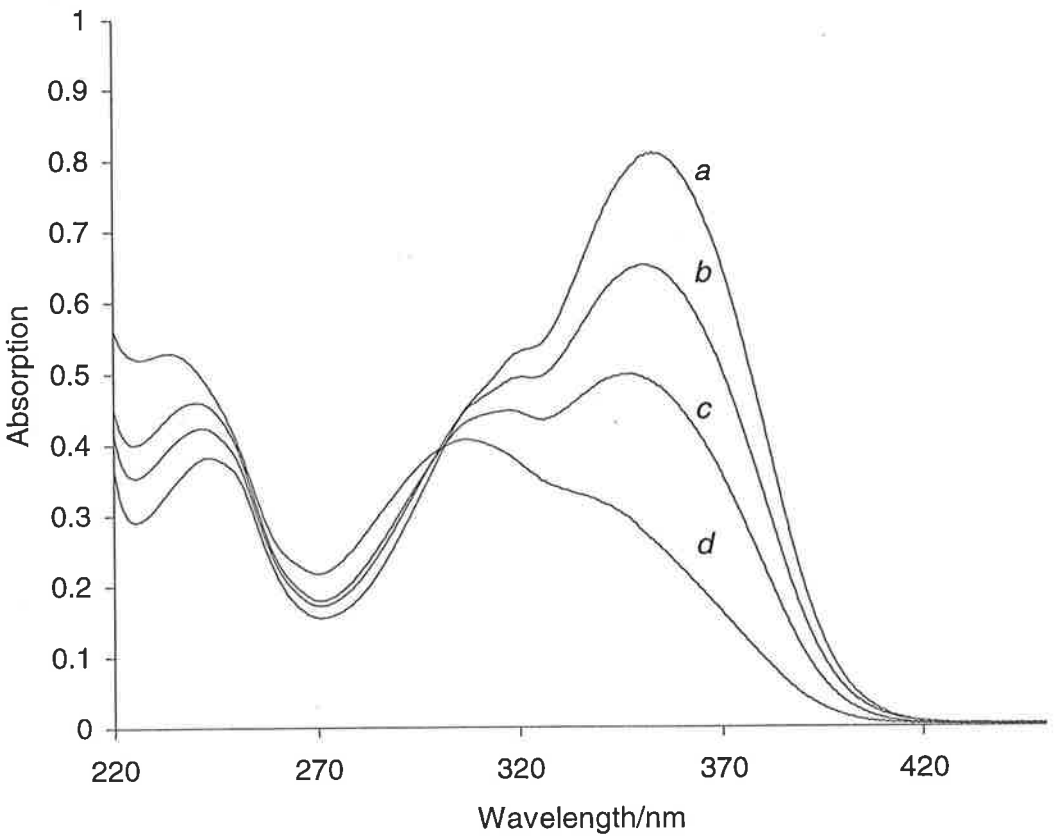


Figure 4.9 Absorption spectra of (a) a solution containing 2.6×10^{-5} mol dm^{-3} *trans* oxystilbene **78**$^-$ and 2.8×10^{-5} mol dm^{-3} mixed dimer **77** in aqueous sodium hydroxide solution, pH 10, (b) the photostationary state after irradiation of (a) at λ = 300 nm, (c) the photostationary state after irradiation of (a) at λ = 355 nm, (d) the photostationary state after exposure of (a) to sunlight for 2 hours (> 90 % *cis* oxystilbene **80**$^-$).

In a similar manner, dilute aqueous solutions of the *trans* carboxystilbene **79**$^-$ and either **73** or **77** were alternately irradiated at λ = 340 nm and either λ = 275 nm for the system **77.79**$^-$**/81**$^-$ or λ = 270 nm for the system **73.79**$^-$**/81**$^-$ (the isosbestic point is shifted to a slightly lower wavelength for the system **73.79**$^-$**/81**$^-$), to give rise to photostationary states in which the *cis* stilbene complexes and *trans* stilbene complexes predominated, respectively. The photostationary states were reached in 3.5 hours. Figures 4.10 and 4.11 display the UV/vis spectra of the complexes **77.79**$^-$ and **77.81**$^-$, **73.79**$^-$ and **73.81**$^-$ and the respective photostationary states of the systems after irradiation at the specified wavelengths.

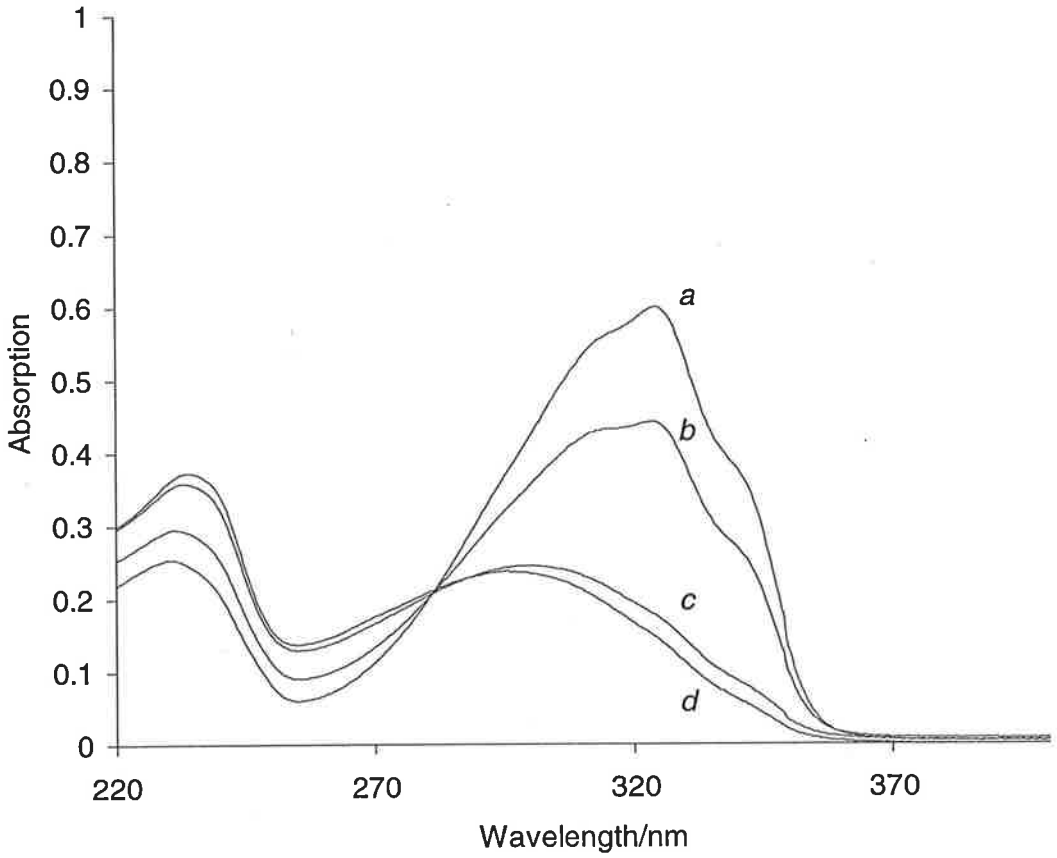


Figure 4.10 Absorption spectra of (a) a solution containing 1.8×10^{-5} mol dm^{-3} *trans* carboxystilbene **79**$^{-}$ and 2.3×10^{-5} mol dm^{-3} mixed dimer **77** in 2.5 % methanol/water, pH 10, (b) the photostationary state after irradiation of (a) at $\lambda = 275$ nm, (c) the photostationary state after irradiation of (a) at $\lambda = 340$ nm, (d) a solution containing 1.8×10^{-5} mol dm^{-3} *cis* carboxystilbene **81**$^{-}$ and 2.3×10^{-5} mol dm^{-3} mixed dimer **77** in 2.5 % methanol/water, pH 10.

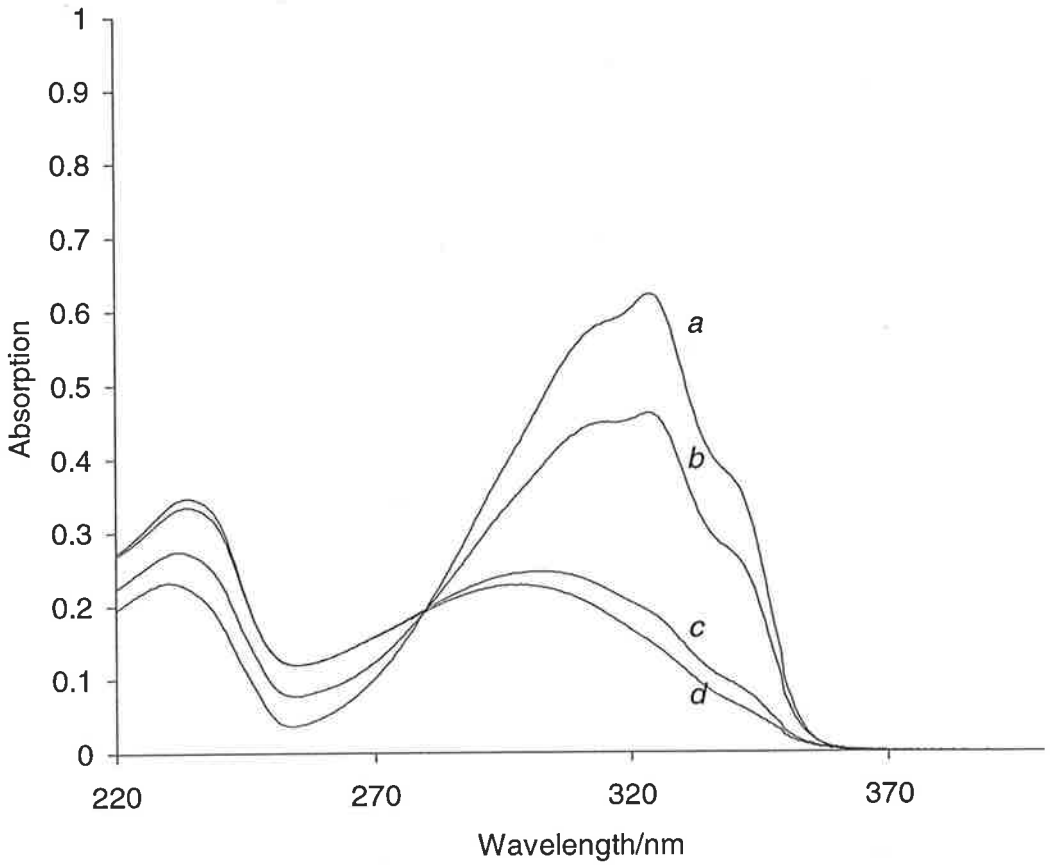
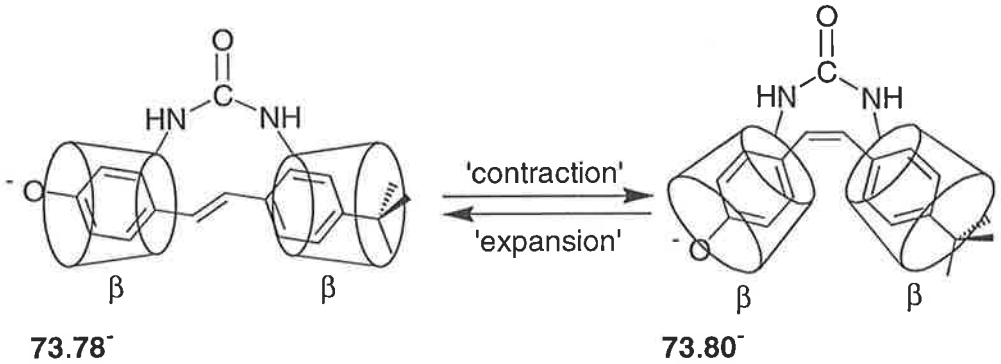


Figure 4.11 Absorption spectra of (a) a solution containing 1.8×10^{-5} mol dm^{-3} *trans* carboxystilbene **79**$^-$ and 2.3×10^{-5} mol dm^{-3} dimer **73** in 2.5 % methanol/water, pH 10, (b) the photostationary state after irradiation of (a) at $\lambda = 270$ nm, (c) the photostationary state after irradiation of (a) at $\lambda = 340$ nm, (d) a solution containing 1.8×10^{-5} mol dm^{-3} *cis* carboxystilbene **81**$^-$ and 2.3×10^{-5} mol dm^{-3} dimer **73** in 2.5 % methanol/water, pH 10.

The *trans* and *cis* oxystilbenes, **78**$^-$ and **80**$^-$, are each included in both annuli of the dimer **73**. Due to the different 'shapes' of the *trans* (relatively straight) and *cis* (bent) stilbene isomers, the β-cyclodextrin rings of **73** must adopt different conformations to include the two isomers. The urea linker or 'hinge' of **73** is reasonably flexible, and *cis/trans* isomerisation of **78**$^-$**/80**$^-$ causes a bending in and out of the β-cyclodextrin rings of **73**. This could be considered as a contracting and expanding of the host to accommodate the guest (Scheme 4.7).



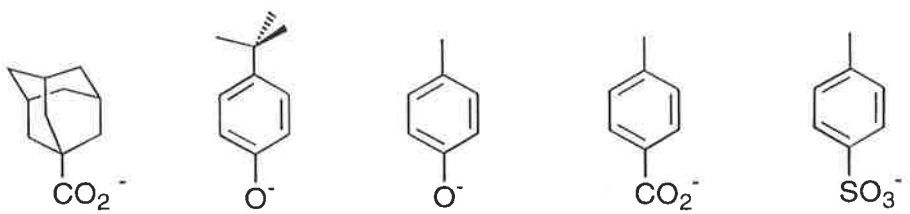
73.78$^-$ **73.80**$^-$

Scheme 4.7 The dimer **73** adopts different conformations in the complexes **73.78**$^-$ and **73.80**$^-$.

Controlled movement in this system would loosely constitute the action of a molecular device, because movement in the form of 'bending' of one component (the guest) causes movement in the other component (the host). However, the magnitude of the movement is small and the complex **73.80**$^-$ is likely to exist as two equilibrating forms as shown in Scheme 4.5. This system was not pursued.

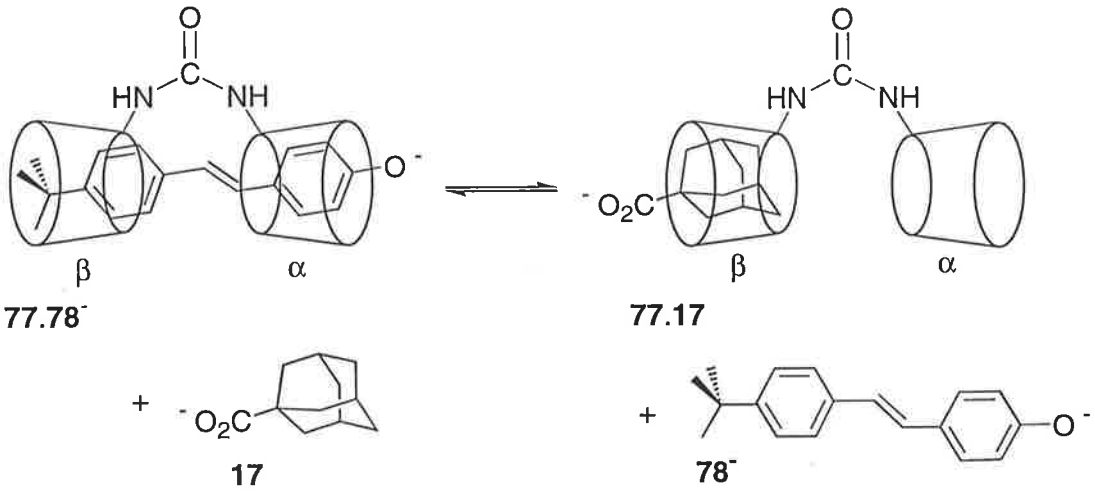
Construction of three-component molecular devices

The nature of the complexes **77.80**$^-$, **77.81**$^-$ and **73.81**$^-$, having an α-cyclodextrin or β-cyclodextrin annulus empty, is attractive in that it gives rise to the possibility of introducing a second guest to be included in this available cyclodextrin annulus to form three-component host-guest complexes. The second guest would be displaced from **77** or **73** when the *cis* stilbene **80**$^-$ or **81**$^-$ is isomerised to the corresponding *trans* stilbene **78**$^-$ or **79**$^-$ if the second guest forms a complex with the cyclodextrin of lower stability than that of the *trans* stilbene complex. This would give rise to a piston-like motion. A series of guest molecules were combined with the system **77.78**$^-$**/80**$^-$ in order to find one or more guests suitable for producing a three-component device. The guests that were examined are 1-adamantanecarboxylate **17**, 4-*t*-butylphenolate **93**, 4-methylphenolate **94**, 4-methylbenzoate **95** and 4-methylbenzenesulfonate **96**.



17 **93** **94** **95** **96**

1-Adamantanecarboxylate **17** is strongly included in the available β-cyclodextrin annulus of the complex **77.80**$^-$ to form the complex **77.80**$^-$**.17** (evident by 2D ^{1}H ROESY NMR). However, **17** also competes with the *trans* oxystilbene **78**$^-$ for inclusion in the β-cyclodextrin annulus of the mixed dimer **77**. Cross peaks in the 2D ^{1}H ROESY NMR spectrum of a D_2O mixture of **78**$^-$, **77** and **17** are present due to nOe interactions between the β-cyclodextrin annular protons of **77** and the protons of **17**. There are also cross peaks present due to nOe interactions between the *t*-butyl group protons and aromatic protons of **78**$^-$ and the cyclodextrin annular protons of **77**, but they are weak compared with when **17** is absent. It is likely that the binary complexes **77.78**$^-$ and **77.17** exist in equilibrium (Scheme 4.8). Significant competition between **17** and the *t*-butylphenyl end of **78**$^-$ for inclusion in the β-cyclodextrin end of **77** is envisaged, as comparable stability constants for the β-cyclodextrin complexes of *t*-butylbenzoate and **17** have been determined previously [12, 22]. Both *t*-butylbenzoate and **17** have been found to include very weakly inside α-cyclodextrin, rendering it unlikely that the ternary complex **77.78**$^-$**.17** forms. 1-Adamantanecarboxylate **17** could not be used to form a device as it includes strongly in the β-cyclodextrin annulus of **77** in the presence of either **78**$^-$ or **80**$^-$, rather than slipping in and out as desired.



Scheme 4.8 The complexes **77.78**$^-$ and **77.17** exist in equilibrium.

The 2D ^{1}H ROESY NMR spectra of D_2O solutions containing the mixed dimer **77**, either the *trans* oxystilbene **78**$^-$ or the *cis* oxystilbene **80**$^-$ and 4-*t*-butylphenolate **93** are difficult to interpret due to overlap of resonances in the aromatic region, especially when the *cis* stilbene **80**$^-$ is present. The resonance arising from the *t*-butyl group protons of **93** is clearly distinguishable from other resonances, and strong cross peaks between this resonance

and the resonances of the cyclodextrin annular protons of **77** are observed in the spectra of the solutions containing either **78**$^-$ or **80**$^-$. When **78**$^-$ is present, the 2D ^{1}H ROESY NMR spectrum of the mixture contains cross peaks due to nOe interactions between all of the aromatic protons of **78**$^-$ and the cyclodextrin annular protons of **77**, and although there is some overlap of resonances, there are no cross peaks due to interactions between the aromatic protons of **93** and the cyclodextrin annular protons. This implies that either **78**$^-$ remains fully included in the cyclodextrin annuli of **77**, but shares the β-cyclodextrin annulus with the *t*-butyl group of **93**, or the binary complexes **77.78**$^-$ and **77.93** exist in equilibrium. In the 2D ^{1}H ROESY NMR spectrum of the solution in which **80**$^-$ is present in place of **78**$^-$, it is not possible to determine whether there are cross peaks due to nOe interactions between the aromatic protons of **93** and the cyclodextrin annular protons of **77**, because the overlap of resonances in the aromatic region is too great. It is not clear whether there is a change in the position of **93** with respect to the host when the stilbene is isomerised from **78**$^-$ to **80**$^-$. It was decided not to pursue this system, as **93** partially includes in **77** in the presence of **78**$^-$, which was not desired. Also, the architectures of each of the three-component host-guest systems are somewhat uncertain.

The tolyl guests 4-methylphenolate **94**, 4-methylbenzoate **95** and 4-methylbenzenesulfonate **96** were found to interact with the system **77.78**$^-$**/80**$^-$ in the desired manner. The 2D ^{1}H ROESY NMR spectra of solutions containing the *trans* oxystilbene **78**$^-$, the mixed dimer **77** and approximately 2 equivalents of one of the tolyl guests **94**, **95** or **96** in D_2O contain no cross peaks due to nOe interactions between the aromatic or methyl group protons of the tolyl guest and the annular protons of **77**. The spectra contain cross peaks between all the aromatic protons and *t*-butyl group protons of **78**$^-$ and the cyclodextrin annular protons of **77**, corresponding to those seen in the 2D ^{1}H ROESY NMR spectrum of **77.78**$^-$ alone. Therefore, the tolyl guests **94-96** do not interact with the complex **77.78**$^-$, and **78**$^-$ remains completely included in the annuli of **77** (Figure 4.12 displays the 2D ^{1}H ROESY NMR spectrum of a D_2O solution containing **77**, **78**$^-$ and **95**). When **80**$^-$ is present in the solutions in place of **78**$^-$, weak cross peaks in the 2D ^{1}H ROESY NMR spectra are present due to nOe interactions between the methyl group protons (and in some cases the protons of one end of the aromatic ring) of the tolyl guest and the annular protons of **77**. There are also cross peaks due to nOe interactions between the *t*-butyl group protons and aromatic H1 and H2 protons of **80**$^-$ and the cyclodextrin annular protons of **77**, corresponding to those seen in the

spectrum of the complex **77.80**$^-$ alone. This implies that each of the tolyl guests **94-96** include in the α-cyclodextrin annulus of **77**, while the *t*-butylphenyl end of **80**$^-$ remains included in the β-cyclodextrin annulus (Figure 4.13 displays the 2D ^{1}H ROESY NMR spectrum of a D_2O solution containing **77**, **80**$^-$ and **95**).

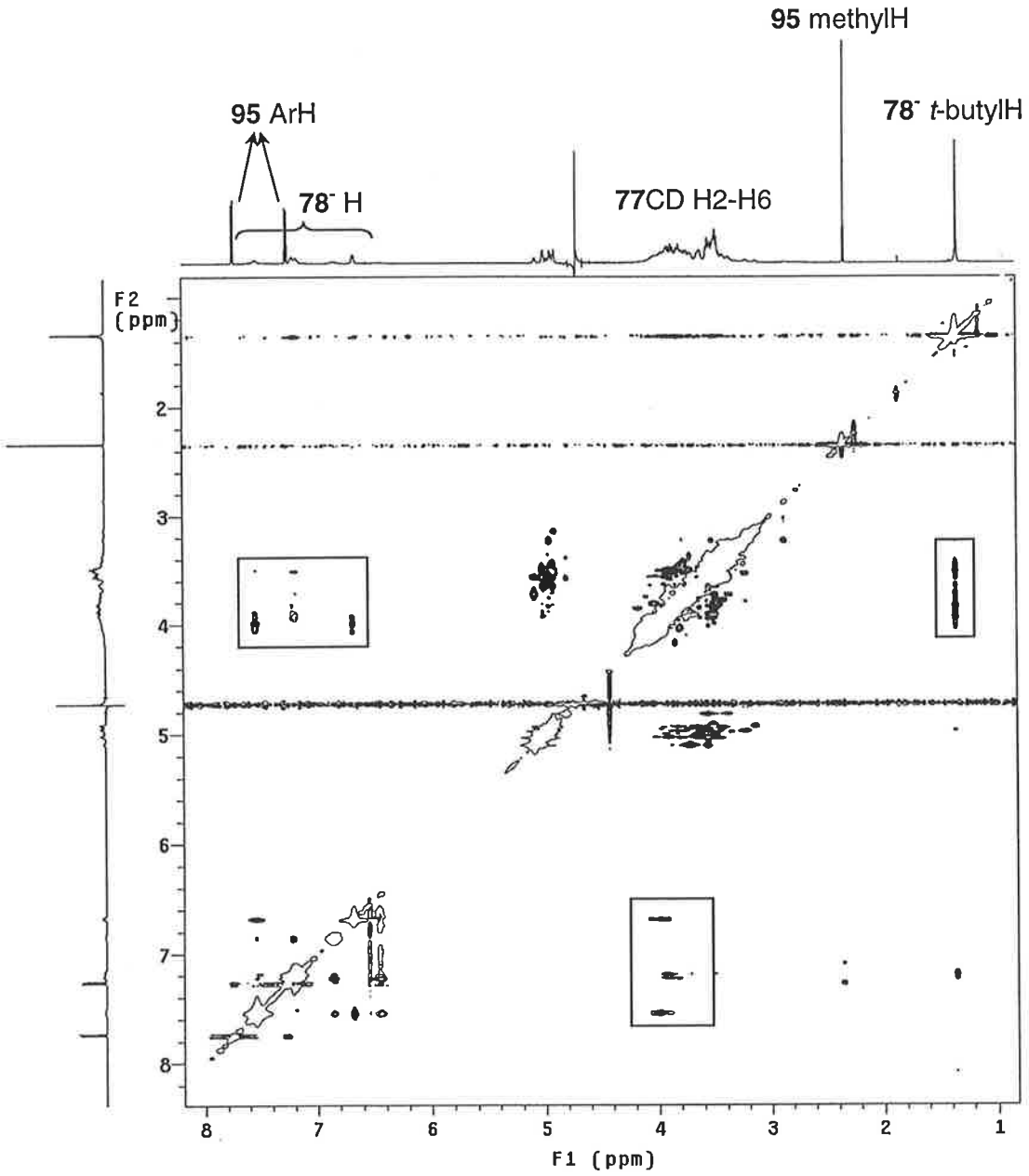


Figure 4.12 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* oxystilbene **78**$^{-}$, 0.016 mol dm^{-3} mixed dimer **77** and 0.022 mol dm^{-3} 4-methylbenzoate **95** in D_2O containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic protons of **78**$^{-}$ and the cyclodextrin annular protons of **77**.

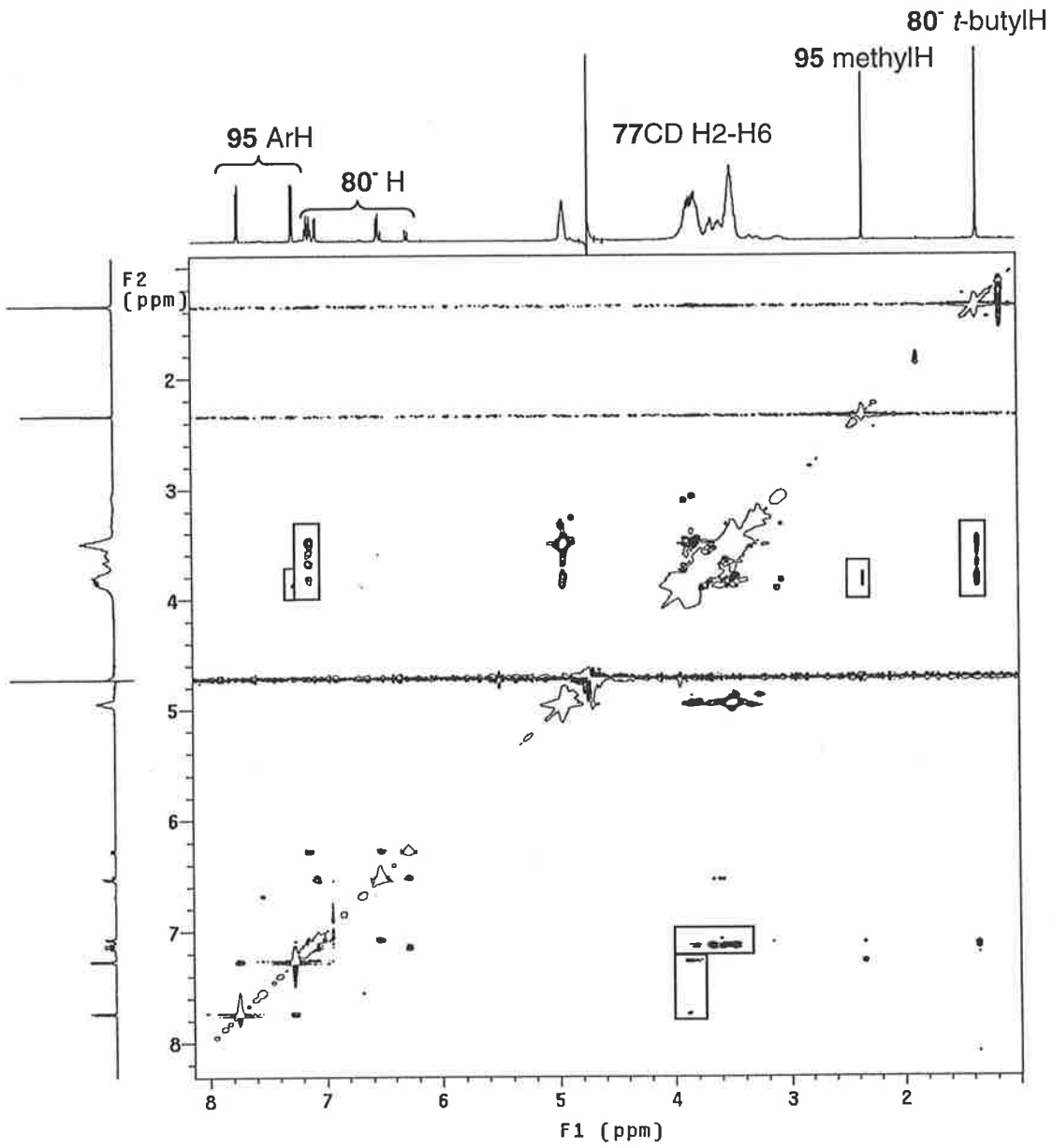


Figure 4.13 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *cis* oxystilbene **80**$^{-}$, 0.016 mol dm^{-3} mixed dimer **77** and 0.022 mol dm^{-3} 4-methylbenzoate **95** in D_2O, containing cross peaks (boxed) due to nOe interactions between the *t*-butyl group and aromatic H1 and H2 protons of **80**$^{-}$ and the cyclodextrin annular protons of **77**, as well as cross peaks (boxed) due to nOe interactions between the methyl group and aromatic protons of **95** and the cyclodextrin annular protons of **77**.

The tolyl guests **94**, **95** and **96** were utilised with the systems **77.79⁻/81⁻** and **73.79⁻/81⁻** to construct three-component molecular devices in a similar manner to that described above. Analysis of the 2D ^{1}H ROESY NMR spectra of D_2O solutions containing a dimer, **73** or **77**, the *trans* or *cis* carboxystilbene, **79⁻** or **81⁻**, and one of **94**, **95** and **96** provided evidence for the nature of the complexes. When the *trans* carboxystilbene **79⁻** is present, the stilbene is fully included in the annuli of **73** or **77** and the tolyl guest is excluded. When the *cis* carboxystilbene **81⁻** is present, only the *t*-butylphenyl end of the stilbene is included in a β-cyclodextrin annulus of **73** or **77** and the tolyl guest is partially included in the other annulus (either α-cyclodextrin or β-cyclodextrin). The 2D ^{1}H ROESY NMR spectra of D_2O solutions containing **73**, either **79⁻** or **81⁻** and **94** are shown in Figures 4.14 and 4.15.

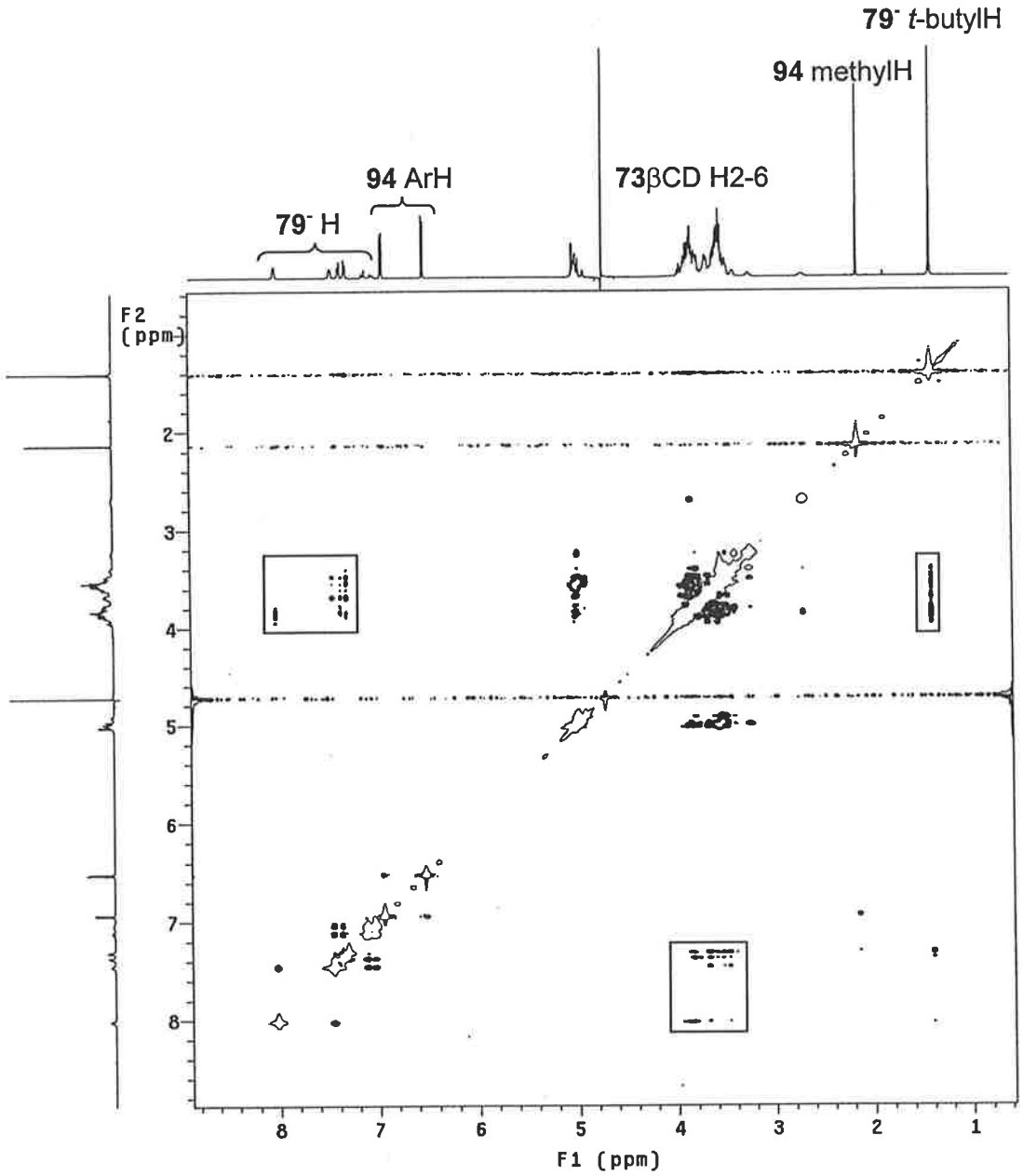


Figure 4.14 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* carboxystilbene **79**$^{-}$, 0.016 mol dm^{-3} dimer **73** and 0.024 mol dm^{-3} 4-methylphenolate **94** in D_2O containing cross peaks (boxed) due to nOe interactions between the aromatic and *t*-butyl group protons of **79**$^{-}$ and the cyclodextrin annular protons of **73**.

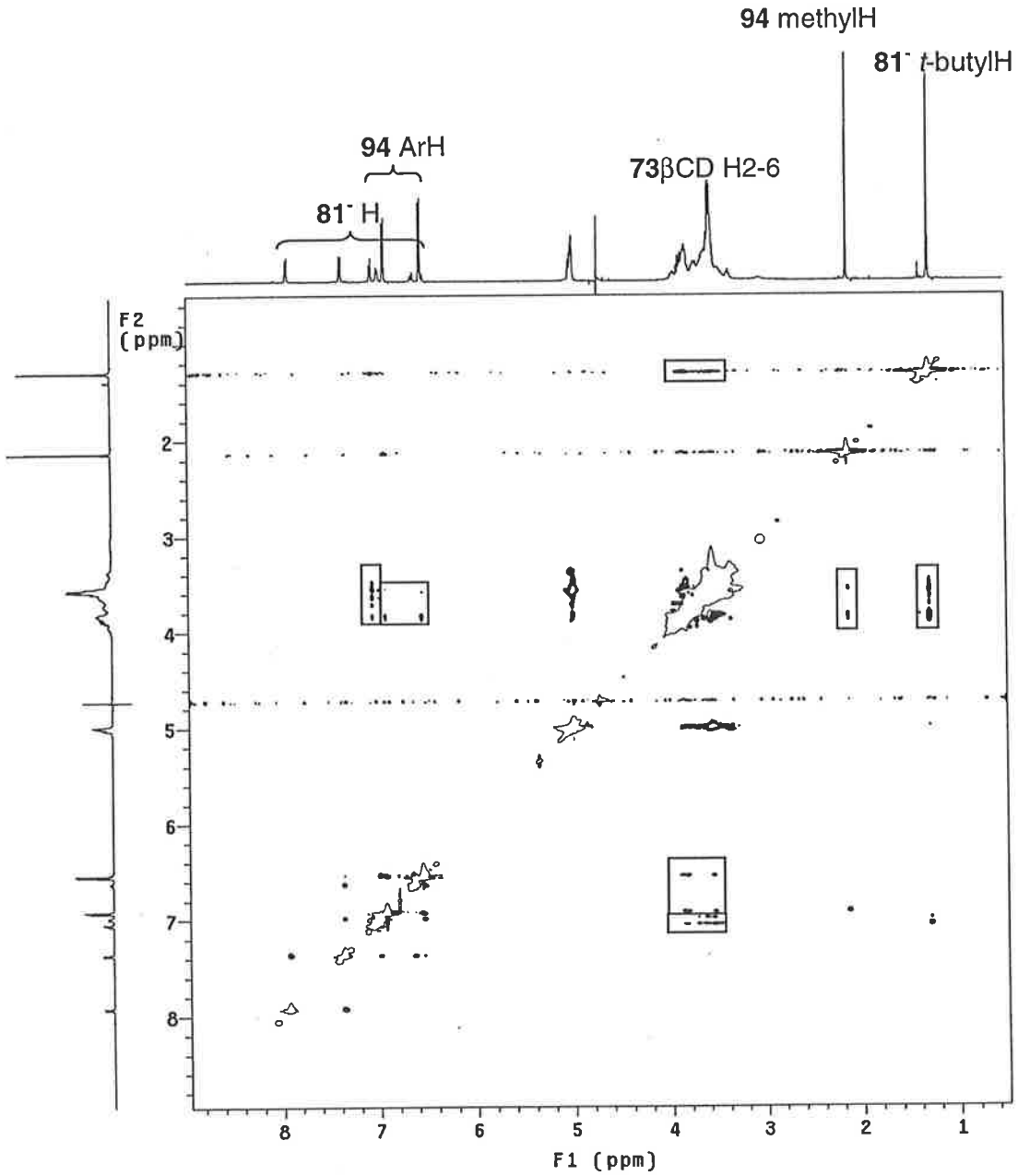


Figure 4.15 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *cis* carboxystilbene **81**$^{-}$, 0.016 mol dm^{-3} dimer **73** and 0.024 mol dm^{-3} 4-methylphenolate **94** in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic H1 and H2 and *t*-butyl group protons of **81**$^{-}$ and the cyclodextrin annular protons of **73**, as well as cross peaks (boxed) due to nOe interactions between the methyl group and aromatic protons of **94** and the cyclodextrin annular protons of **73**.

The three-component molecular devices can be switched in the same manner as the two component systems discussed earlier. The devices that consist of **77.78⁻/80⁻** and either **94**, **95** or **96** can be switched using sunlight and heat as stimuli, as described for the system in the absence of a tolyl guest, and the switching was followed by 2D ^{1}H ROESY NMR. Each of the three-component devices can be switched using only photochemical stimuli. Alternately irradiating an aqueous solution containing a stilbene, **78⁻** or **79⁻** initially, either **73** or **77**, and 2 equivalents of one of **94**, **95** or **96** at 355 nm and 300 nm, 340 nm and 275 nm or 340 nm and 270 nm for the systems **77.78⁻/80⁻**, **77.79⁻/81⁻** and **73.79⁻/81⁻**, respectively, produced UV/Vis spectra similar to those shown in Figures 4.9, 4.10 and 4.11. The photochemical switching of the system **73.79⁻/81⁻** in the presence of **95** is shown in Figure 4.16 as an example. Scheme 4.9 displays a summary of the three-component molecular devices.

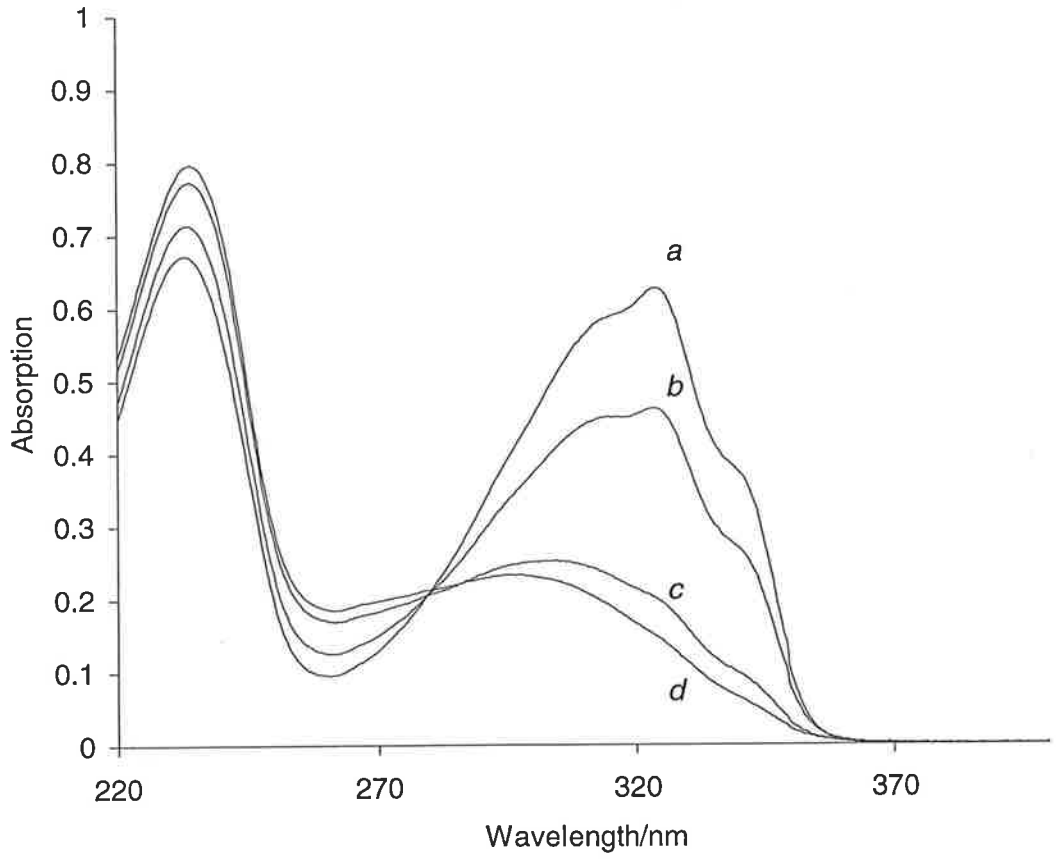
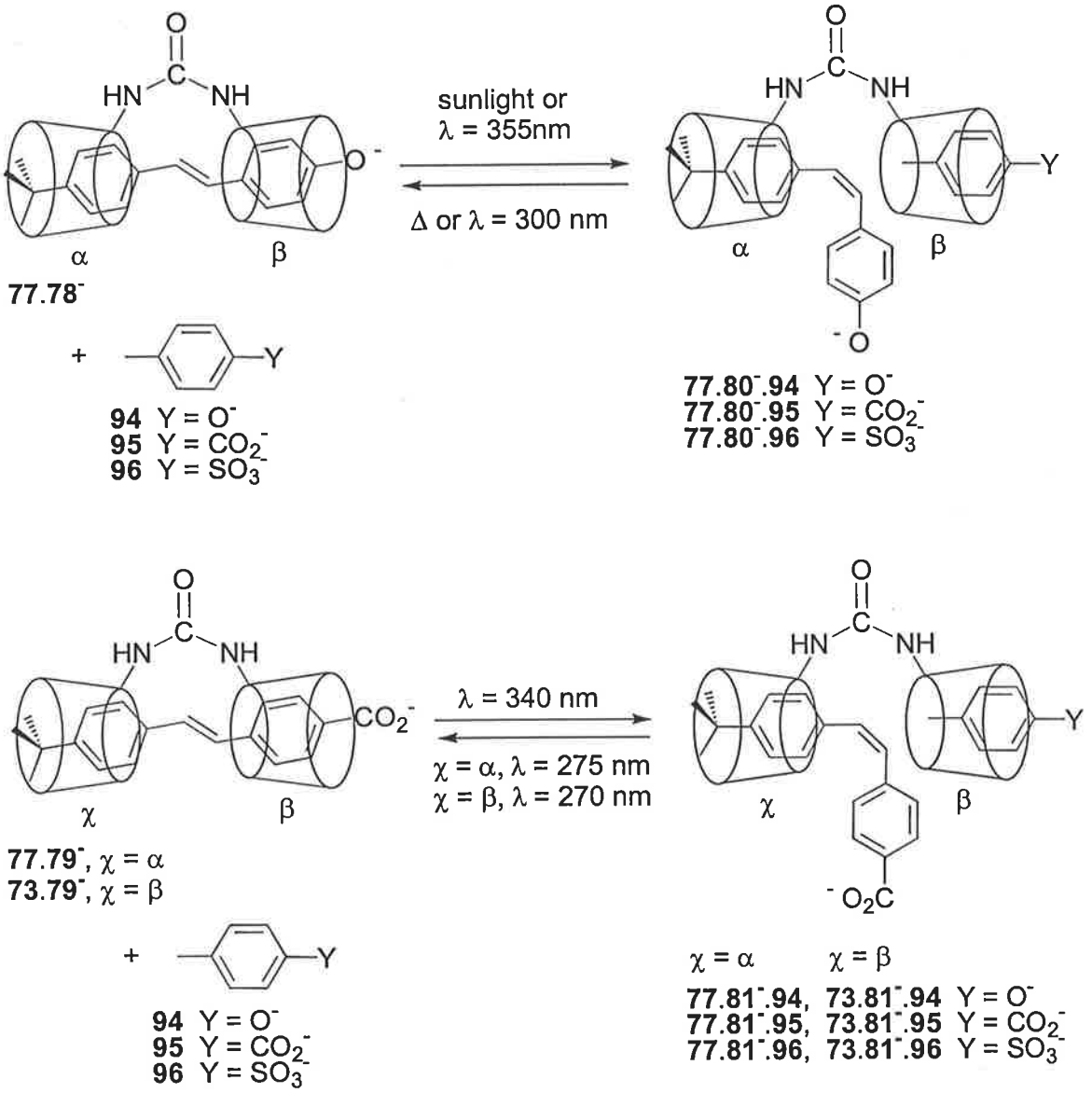


Figure 4.16 Absorption spectra of (a) a solution containing 1.8×10^{-5} mol dm^{-3} *trans* carboxystilbene **79⁻**, 2.3×10^{-5} mol dm^{-3} dimer **73** and 3.4×10^{-5} mol dm^{-3} 4-methylbenzoate **95** in 2.5 % methanol/water, pH 10, (b) the photostationary state after irradiation of (a) at 270 nm, (c) the photostationary state after irradiation of (a) at 340 nm, (d) a solution containing 1.8×10^{-5} mol dm^{-3} *cis* carboxystilbene **81⁻**, 2.3×10^{-5} mol dm^{-3} dimer **73** and 3.4×10^{-5} mol dm^{-3} 4-methylbenzoate **95** in 2.5 % methanol/water, pH 10.

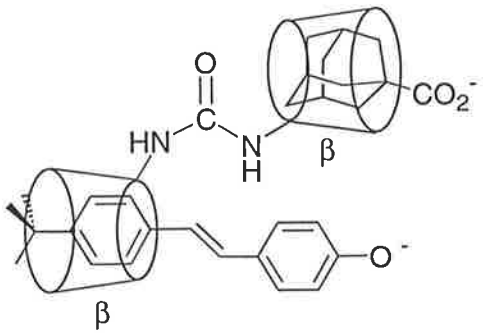


Scheme 4.9 Switching of the three-component molecular devices utilising photochemical and thermal stimuli.

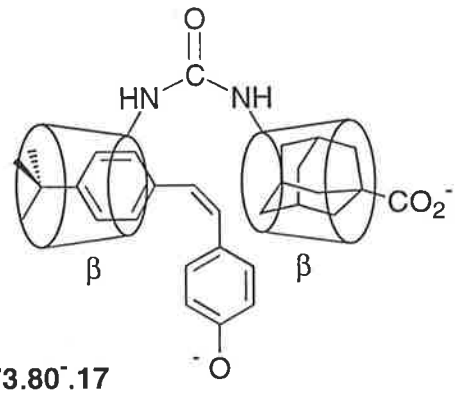
It was considered that if the *trans* and *cis* oxystilbenes, **78**⁻ and **80**⁻, form inclusion complexes with the dimer **73** which are of significantly different stability, an appropriate second guest may be capable of displacing a single end of **80**⁻, but not **78**⁻, from **73**. This would give rise to a shuttling of the second guest in and out of **73** in a similar manner to that in the systems shown in Scheme 4.9. The stability constants of the complexes **73**.**78**⁻/**80**⁻ were not measured due to the considerable light sensitivity of the *cis* and *trans* stilbenes. In a mixture of **73** and either **78**⁻ or **80**⁻ in basic aqueous solution, or in a solution of either **78**H or **80**H in methanol, the stilbene was found to very quickly form an equilibrium mixture of the *cis* and *trans* isomers in sunlight, or even in light from fluorescent tubes. It was considered

that using UV/Vis measurements to determine the stability constants of the complexes **73.78**$^-$ and **73.80**$^-$ would give rise to invalid results.

1-Adamantanecarboxylate **17** was utilised as a second guest with the system **73.78**$^-$**/80**$^-$ in a trial to build a molecular device. The cross peaks in the 2D ^{1}H ROESY NMR spectrum of a D_2O solution of the *cis* oxystilbene **80**$^-$, the dimer **73** and 1-adamantanecarboxylate **17** are consistent with the phenolate end of **80**$^-$ being completely displaced from one β-cyclodextrin annulus of **73**, and the ternary complex **73.80**$^-$**.17** being the major species in solution. However, **17** also partially displaces the *trans* oxystilbene **78**$^-$ from the dimer **73**. When **78**$^-$ is present in the solution in place of **80**$^-$, the 2D ^{1}H ROESY NMR spectrum of the mixture contains weak cross peaks due to nOe interactions between the *t*-butyl group protons and all the aromatic protons of **78**$^-$ and the β-cyclodextrin annular protons of **73**, as well as strong cross peaks due to nOe interactions between the protons of **17** and the annular protons of **73**. It is likely that binary complexes, similar to those formed in a solution containing **78**$^-$, **77** and **17** (Scheme 4.8), exist in equilibrium. The presence of some amount of the ternary complex **73.78**$^-$**.17** is also possible.



73.78$^-$**.17**



73.80$^-$**.17**

The interaction of 4-methylbenzoate **95** with the system **73.78**$^-$**/80**$^-$ was also investigated. The cross peaks which are present in the 2D ^{1}H ROESY NMR spectrum of the complex **73.78**$^-$ alone are also visible in the spectrum of a mixture of **73.78**$^-$ and **95**, consistent with **95** not competing with the *trans* oxystilbene **78**$^-$ for inclusion in the dimer **73**. When the *cis* oxystilbene **80**$^-$ is present in place of **78**$^-$, the 2D ^{1}H ROESY NMR spectrum of the solution contains cross peaks due to nOe interactions between the annular protons of **73** and the methyl group and aromatic protons of **95**, consistent with the inclusion of **95** in **73**. However, there are weak cross peaks due to interactions between the annular protons of **73**

and the protons at the phenolate end as well as those at the *t*-butylphenyl end of **80**$^-$. This is consistent with a competition existing between the complexes **73.80**$^-$ and **73.80**$^-$**.95**.

Movement of the trans stilbenes 78$^-$ *and 79*$^-$ *inside cyclodextrin dimer hosts*

As briefly discussed earlier, the 1D ^{1}H NMR spectra of the complexes formed by the *trans* stilbenes **78**$^-$ and **79**$^-$ and the mixed dimer **77**, **77.78**$^-$ and **77.79**$^-$, obtained at room temperature show significant broadening of the resonances in the aromatic region and, to some extent, broadening of the resonance arising from the *t*-butyl group protons. This is not displayed in the spectra of the corresponding *cis* stilbene complexes **77.80**$^-$ and **77.81**$^-$, or in the spectra of the complexes of **73**, **73.78**$^-$ and **73.79**$^-$. The aromatic regions of the 1D ^{1}H NMR spectra of the complexes **77.78**$^-$, **77.80**$^-$ and **73.78**$^-$ are compared in Figure 4.17 (those for the corresponding complexes of **79**$^-$**/81**$^-$ display similar features).

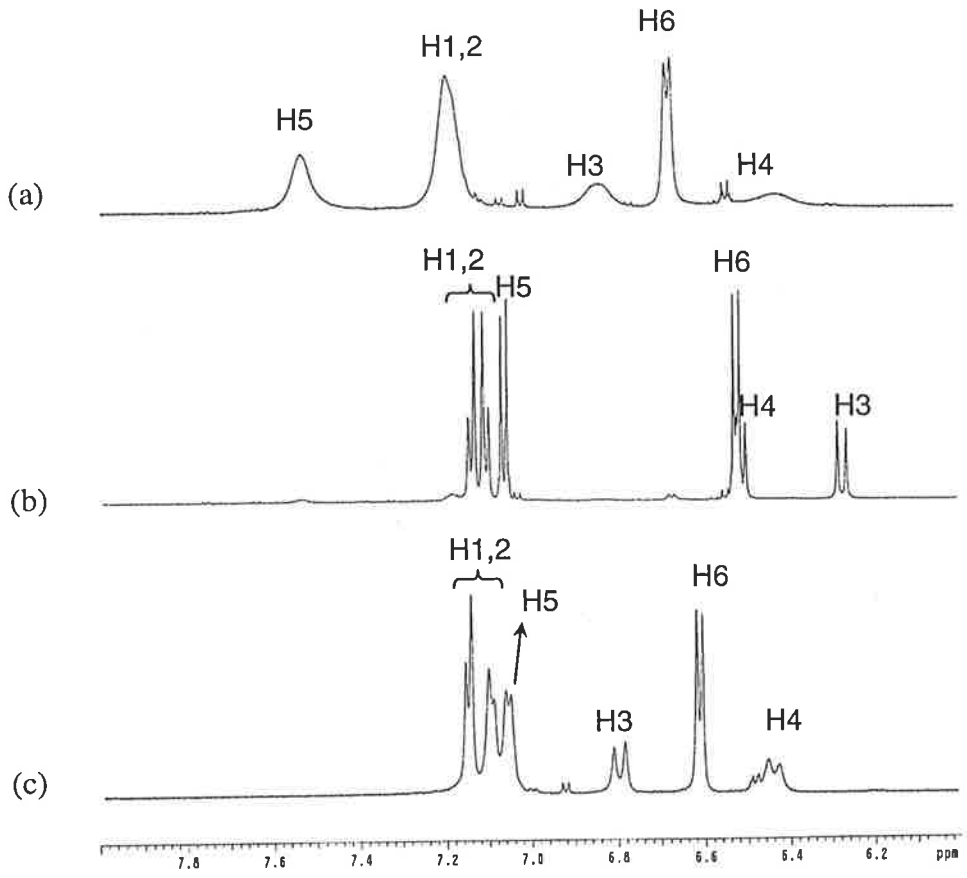


Figure 4.17 The aromatic region of the 1D ^{1}H NMR spectra of the complexes (a) **77.78**$^-$, (b) **77.80**$^-$ and (c) **73.78**$^-$ in D_2O at 298 K, showing the comparative broadness of the resonances in the spectrum of the complex **77.78**$^-$. Each solution was made up at approximate concentrations of 0.015 mol dm^{-3} stilbene and 0.016 mol dm^{-3} cyclodextrin dimer.

It is implied that there is restricted movement of the *trans* stilbenes **78**$^-$ and **79**$^-$ in the annuli of **77**. Increasing the temperature of a D_2O solution of the complex **77.78**$^-$ causes the resonances in the aromatic region of the spectrum to sharpen considerably, as shown in Figure 4.18, which provides evidence for a kinetic process. Even at low temperature (383 K) separate resonances arising from individual inclusion isomers are not distinguishable, so it was not possible to determine the rate constants for motion at the various temperatures. It was considered that the same would be true of the complex **77.79**$^-$.

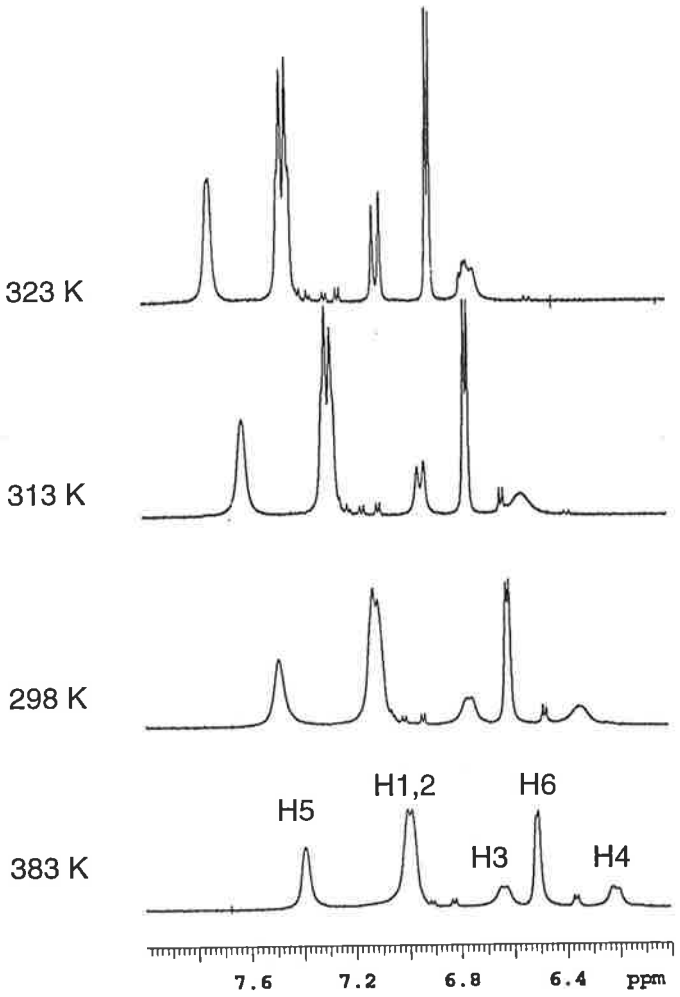


Figure 4.18 The aromatic region of the 1D ^1H NMR spectra of a D_2O solution containing 0.015 mol dm^{-3} *trans* stilbene **78**$^-$ and 0.016 mol dm^{-3} mixed dimer **77**, showing a set of broad resonances at low temperature which sharpen with increasing temperature.

Native cyclodextrin.trans stilbene inclusion complexes

The α-cyclodextrin and β-cyclodextrin complexes of the *trans* stilbenes **78**$^-$ and **79**$^-$ were examined to further investigate the influence of annulus size on the nature of the

inclusion complex formed. Cross peaks in the 2D ^{1}H ROESY NMR spectra of solutions of either **78**$^-$ or **79**$^-$ and either α-cyclodextrin or β-cyclodextrin in basic D_2O provide evidence for the formation of the complexes αCD.**78**$^-$, βCD.**78**$^-$, αCD.**79**$^-$ and βCD.**79**$^-$ (Figures 4.19-4.22; expansions of the aromatic regions of the spectra of αCD.**78**$^-$ and αCD.**79**$^-$ are provided due to the complicated nature of the 1D spectra). In the spectra of βCD.**78**$^-$ and βCD.**79**$^-$, there are strong cross peaks due to nOe interactions between the β-cyclodextrin annular protons and the *t*-butyl group protons and aromatic H1 and H2 protons of the stilbene. There are no cross peaks due to interactions between the β-cyclodextrin annular protons and the aromatic H3-H6 protons (although there is some overlap of the aromatic H1, H2 and H5 resonances in the spectrum of βCD.**78**$^-$). This implies that only the *t*-butylphenyl end of **78**$^-$ or **79**$^-$ is included in β-cyclodextrin. In the spectra of αCD.**78**$^-$ and αCD.**79**$^-$, there are cross peaks due to nOe interactions between most of the aromatic protons of the stilbene and the α-cyclodextrin annular protons but either no or very weak cross peaks due to nOe interactions between the *t*-butyl group protons of the stilbene and the annular protons of α-cyclodextrin. There is preferential inclusion of the aromatic rings of the stilbenes **78**$^-$ and **79**$^-$ in α-cyclodextrin, which is most likely too small to fully include the *t*-butyl group.

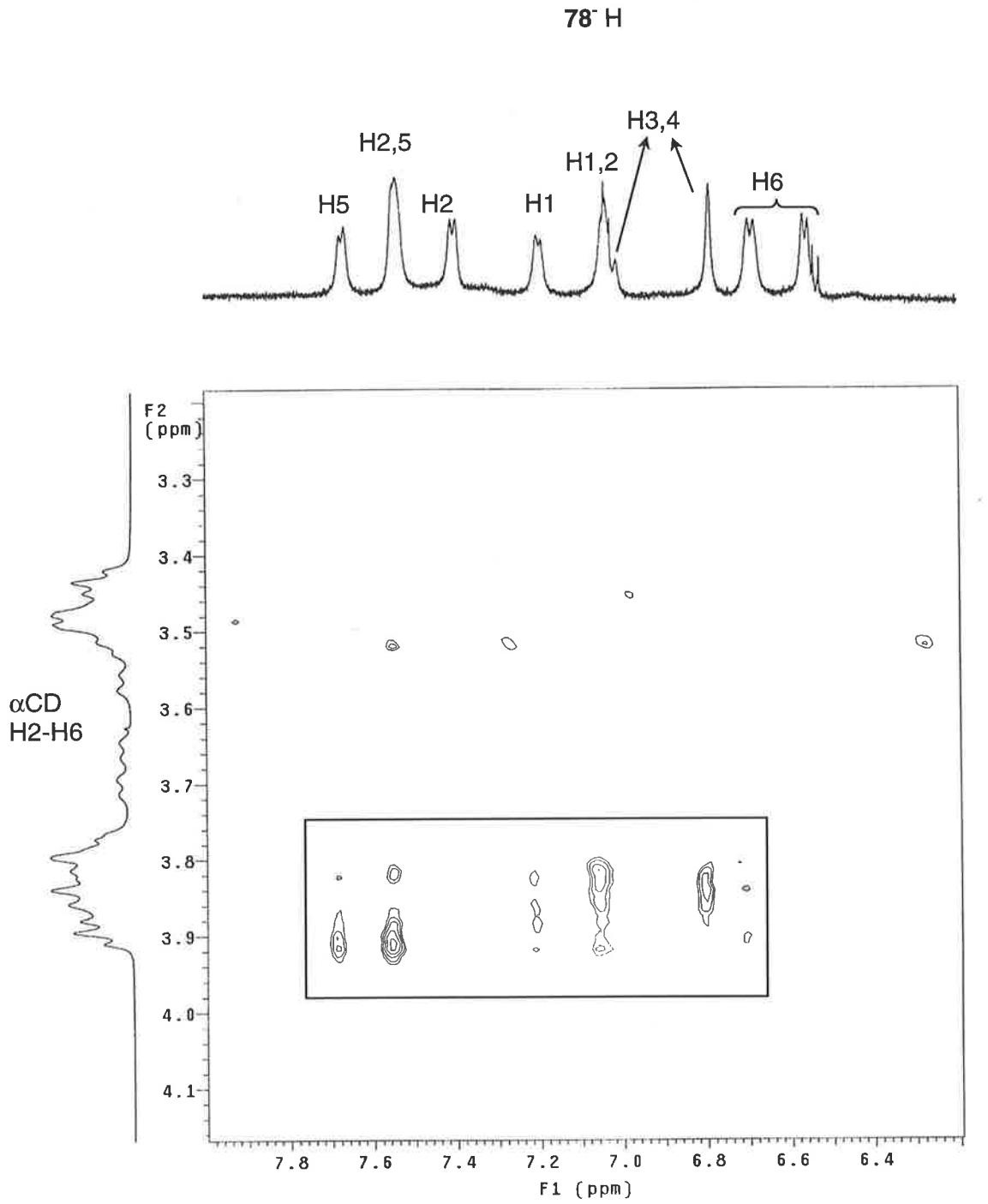


Figure 4.19 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.0034 mol dm^{-3} *trans* oxystilbene **78**$^{-}$ and 0.010 mol dm^{-3} α-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic protons of **78**$^{-}$ and the α-cyclodextrin annular protons.

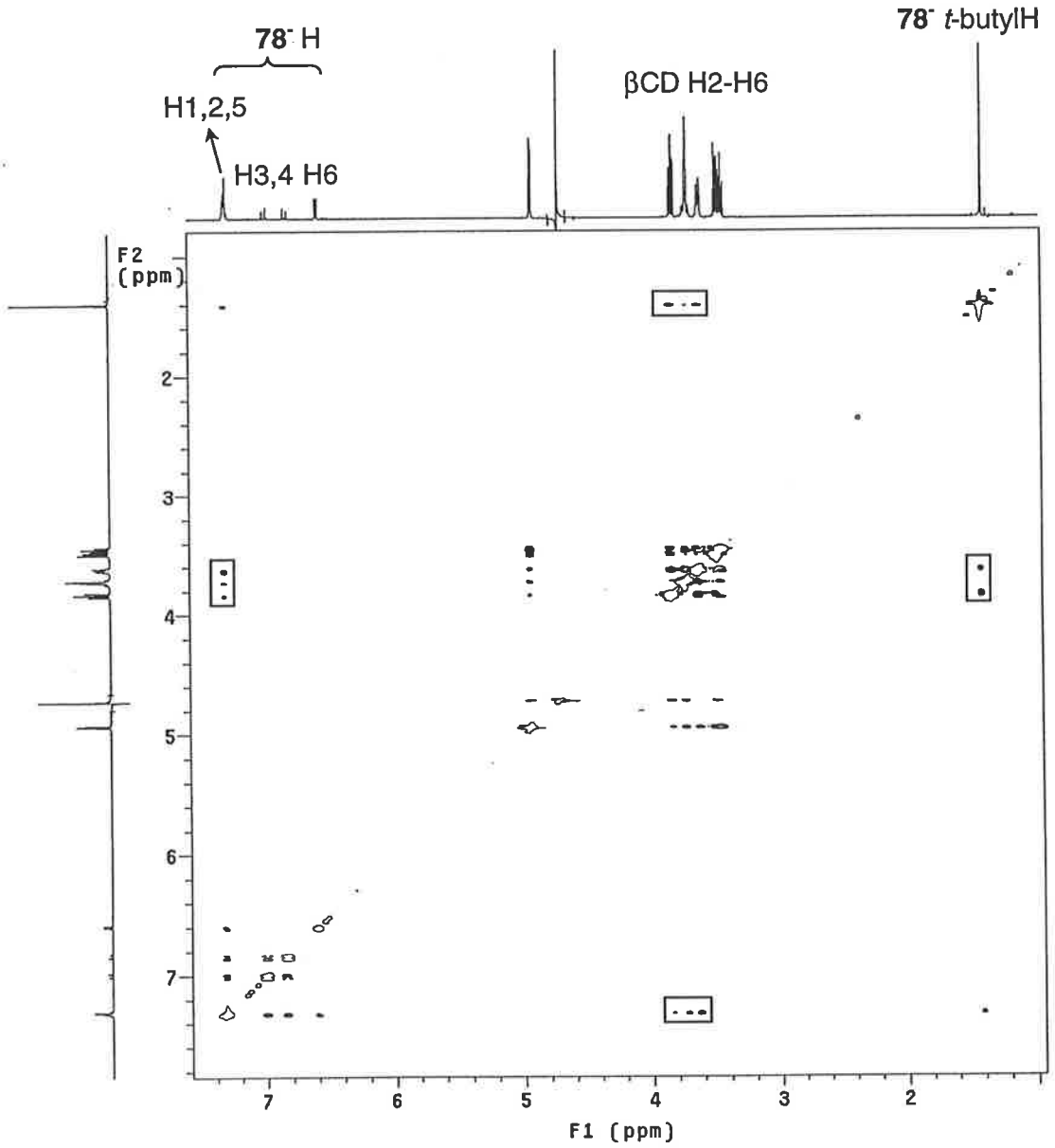


Figure 4.20 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* oxystilbene **78**$^{-}$ and 0.016 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic and *t*-butyl group protons of **78**$^{-}$ and the β-cyclodextrin annular protons.

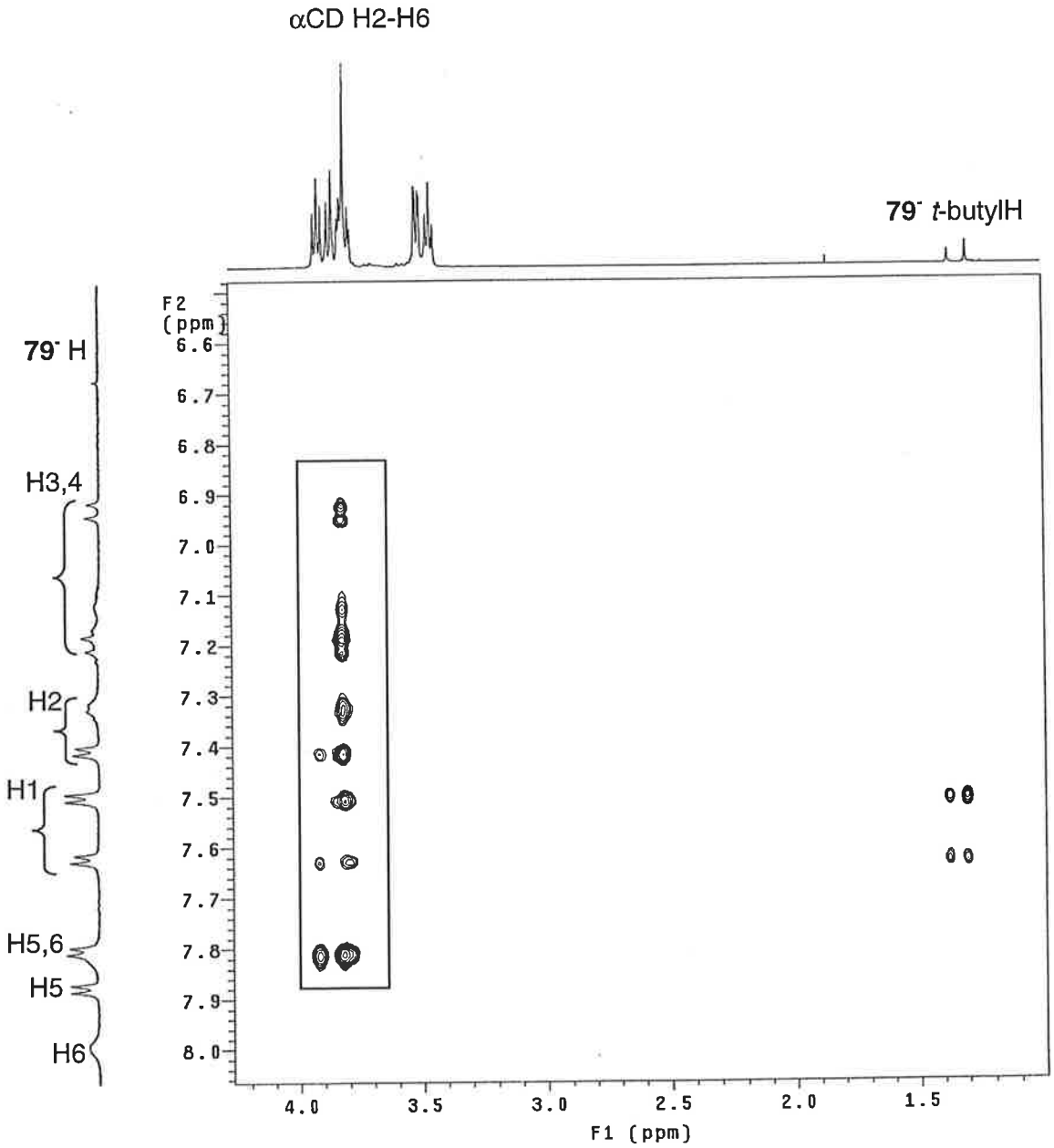


Figure 4.21 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.0034 mol dm^{-3} *trans* carboxystilbene **79⁻** and 0.010 mol dm^{-3} α-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic protons of **79⁻** and the α-cyclodextrin annular protons.

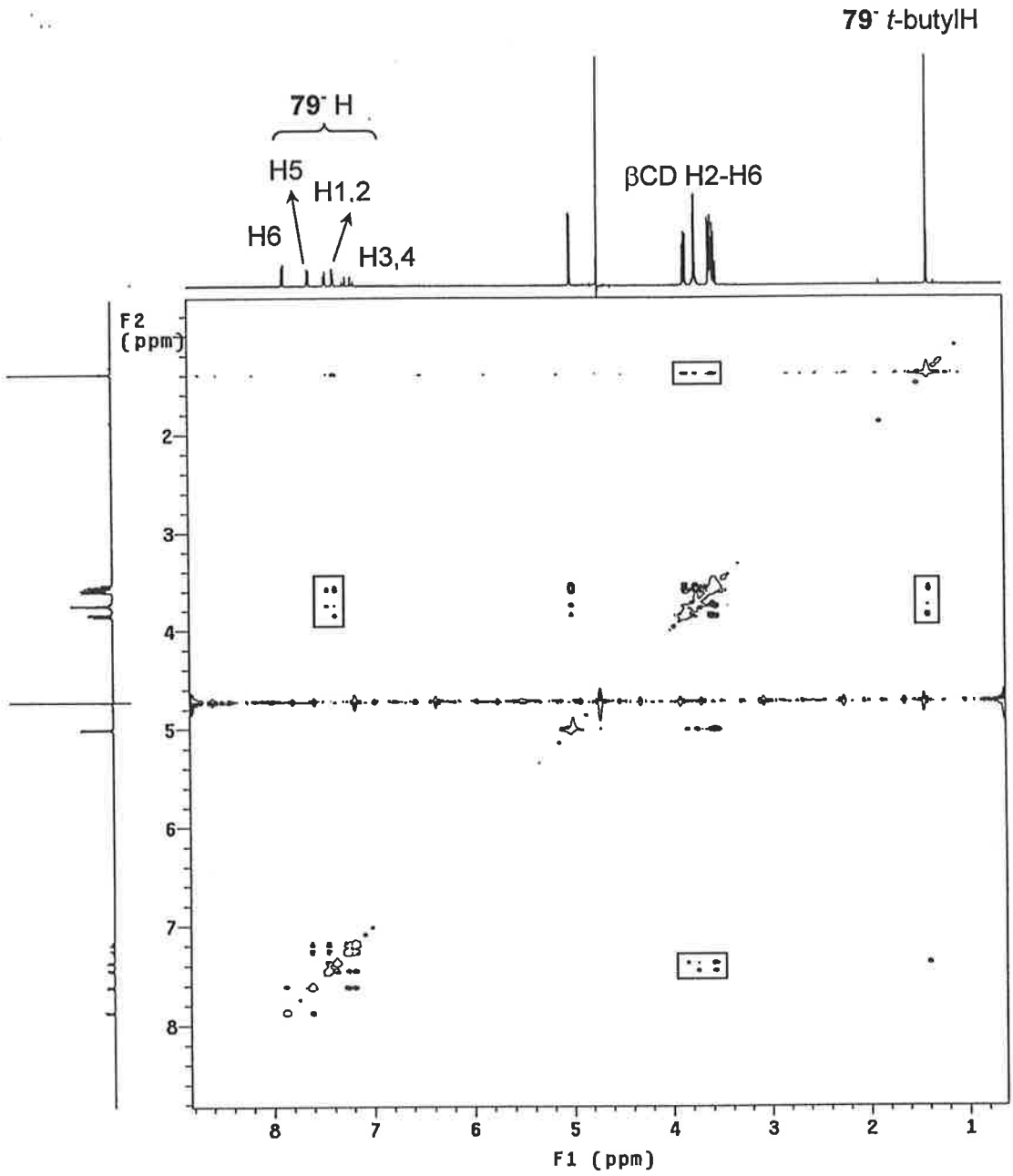


Figure 4.22 2D ^{1}H(600 MHz) ROESY NMR spectrum (pD ≥ 12, 0.3 sec mixing time, 298 K) of 0.015 mol dm^{-3} *trans* carboxystilbene **79**$^{-}$ and 0.016 mol dm^{-3} β-cyclodextrin in D_2O, containing cross peaks (boxed) due to nOe interactions between the aromatic H1 and H2 and *t*-butyl group protons of **79**$^{-}$ and the β-cyclodextrin annular protons.

There are substantial differences between the 1D ^{1}H NMR spectra of the α-cyclodextrin and β-cyclodextrin complexes of the *trans* stilbenes **78**$^-$ and **79**$^-$ (Figure 4.23 displays expansions of the aromatic regions of the spectra of αCD.**78**$^-$ and βCD.**78**$^-$). The spectra of the complexes βCD.**78**$^-$ and βCD.**79**$^-$ each contain one set of sharp resonances in the aromatic region, which implies that there is unrestricted motion of each stilbene within the β-cyclodextrin annulus, and that one inclusion complex exists or there is a fast exchange between co-existing complexes in each case. However, the spectra of the complexes αCD.**78**$^-$ and αCD.**79**$^-$ each contain two overlapping sets of broadened resonances in the aromatic region. There are also two broadened singlets in the region of the *t*-butyl group protons in each spectrum, compared with just one sharp resonance arising from the *t*-butyl group protons in the spectra of the β-cyclodextrin complexes.

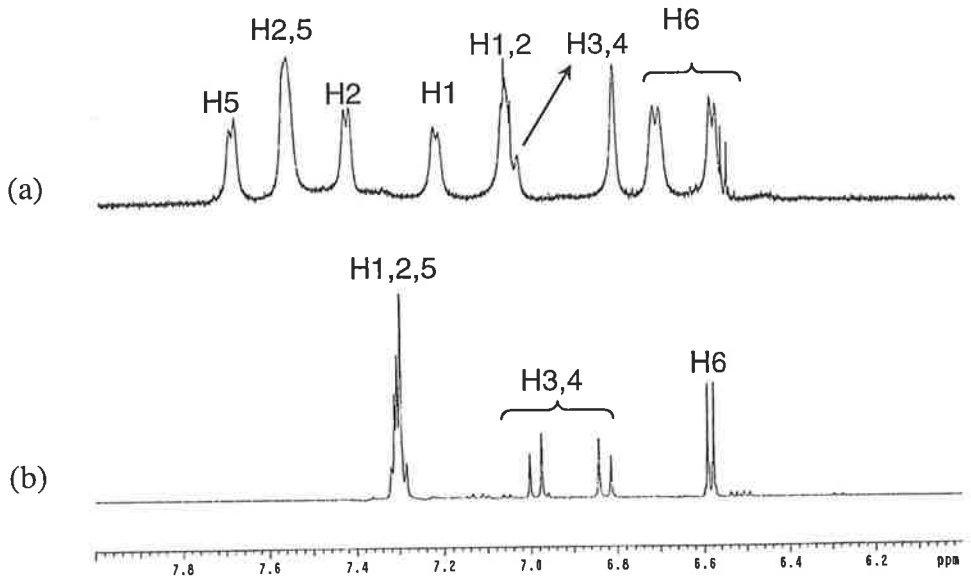


Figure 4.23 The aromatic regions of the 1D ^{1}H NMR spectra of (a) αCD.**78**$^-$ and (b) βCD.**78**$^-$ in D_2O at 298 K, showing the complicated nature and broadness of the resonances in the spectrum of αCD.**78**$^-$ compared with those in the spectrum of βCD.**78**$^-$. The solutions were made up at approximate concentrations of (a) 0.0034 mol dm^{-3} *trans* oxystilbene **78**$^-$ and 0.010 mol dm^{-3} α-cyclodextrin and (b) 0.015 mol dm^{-3} *trans* oxystilbene **78**$^-$ and 0.016 mol dm^{-3} βCD.

It was found that the sets of resonances in both the *t*-butyl group region and the aromatic region of the 1D ^{1}H NMR spectrum of αCD.**78**$^-$ each converge into one set of resonances upon warming of the mixture (Figures 4.24 and 4.25). This is consistent with the existence of two isomeric αCD.**78**$^-$ complexes (inclusion isomers), which exchange slowly on

the NMR time-scale at room temperature, with the rate of exchange speeding up with increasing temperature.

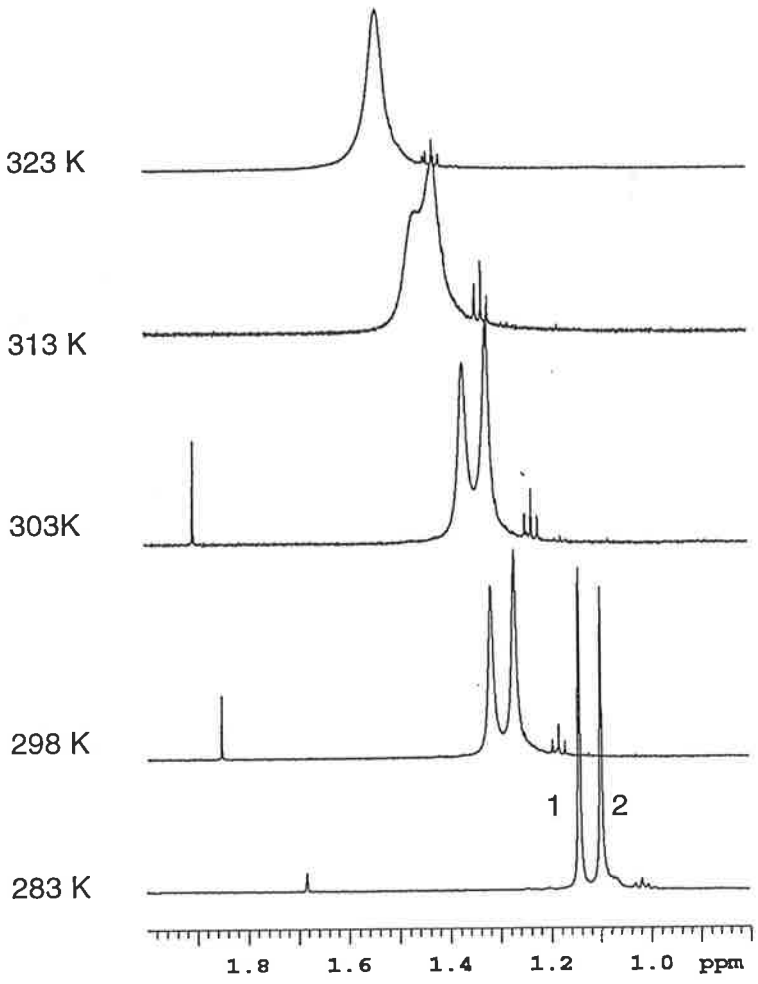


Figure 4.24 The *t*-butyl region of the 1D ^{1}H NMR spectra of a D_2O solution containing two exchanging αCD.**78**$^-$ inclusion isomers, showing two resonances at low temperature and the convergence of the resonances with increasing temperature. The solution was made up at approximate concentrations of 0.0034 mol dm^{-3} *trans* oxystilbene **78**$^-$ and 0.010 mol dm^{-3} α-cyclodextrin.

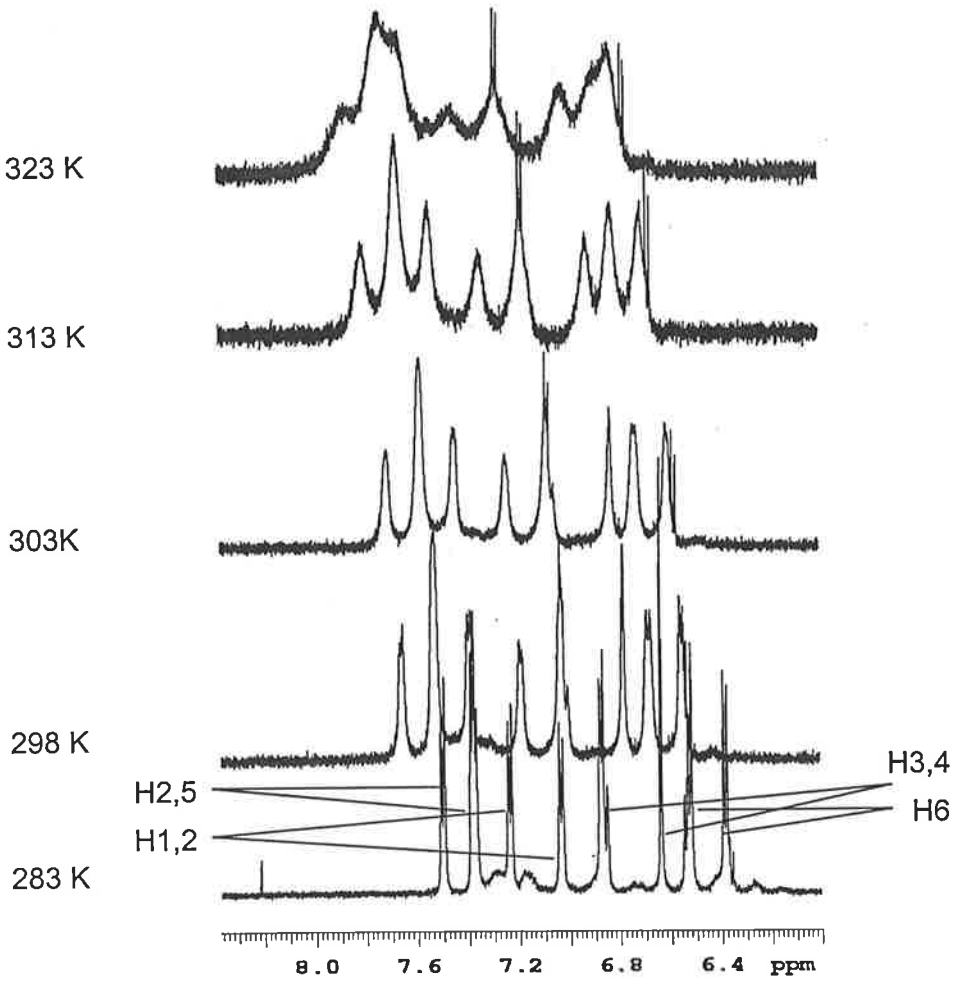
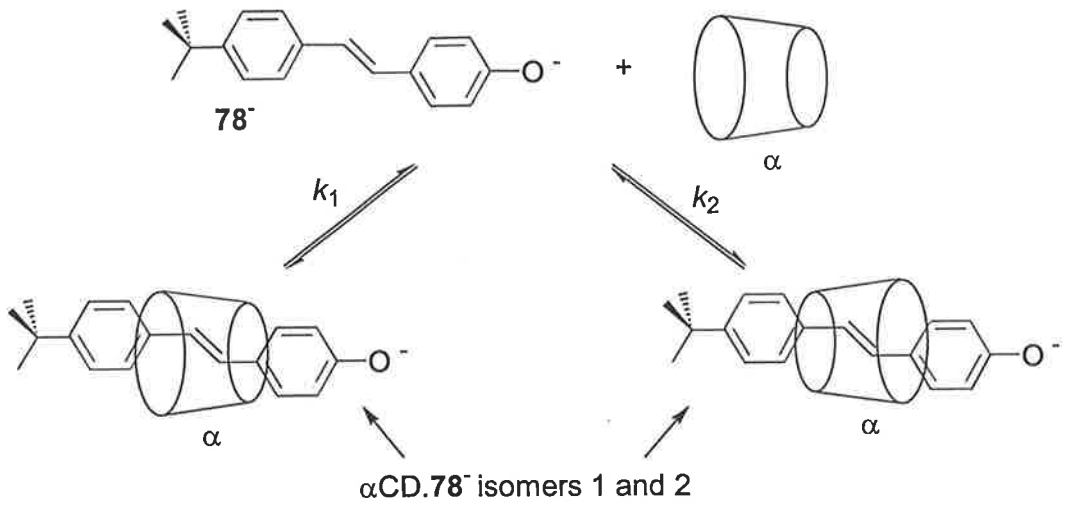


Figure 4.25 The aromatic region of the 1D ^{1}H NMR spectra of a D_2O solution containing two exchanging αCD.**78**$^-$ inclusion isomers, showing two sets of overlapping resonances at low temperature and the convergence of the resonances with increasing temperature. The solution was made up at approximate concentrations of 0.0034 mol dm^{-3} *trans* oxystilbene **78**$^-$ and 0.010 mol dm^{-3} α-cyclodextrin.

The two inclusion isomers are 1:1 αCD/**78**$^-$ complexes in which the orientation of the stilbene **78**$^-$ with respect to the α-cyclodextrin annulus differs, as depicted in Scheme 4.10. Although there is excess α-cyclodextrin in the solution (this was necessary to dissolve a sufficient amount of the complex for 2D ^{1}H ROESY NMR spectroscopy), it is considered unlikely that 2:1 αCD/**78**$^-$ complexes are present. The *t*-butyl group of the stilbene is not included in the α-cyclodextrin annulus, and a 2:1 complex without such inclusion cannot be rationalised.



Scheme 4.10 Exchange between two possible αCD.**78**⁻ inclusion isomers, in which the primary end of the α-cyclodextrin annulus is oriented towards either the phenolate end or the *t*-butylphenyl end of **78**⁻. It is not known which of the isomers is more abundant, k_1 and k_2 are assigned arbitrarily.

Kinetic data for the exchange between the two αCD.**78**⁻ inclusion isomers was obtained using an in-house program, DAVNMR [23]. The peak-width at half-height of a resonance at the slow exchange limit (at which each species exhibits its own distinct resonance) is related to the lifetime of that inclusion isomer. The lifetime of the inclusion isomer at other temperatures is calculated by comparing the peak-width at half-height values measured at that temperature and at the slow exchange limit. The rate constant for exchange (k_1 or k_2) is the inverse of the lifetime of the associated inclusion isomer.

The resonances in the *t*-butyl region, rather than those in the aromatic region, of the spectra of αCD.**78**⁻ were fitted as they are clearly separated at low temperature and do not overlap with other proton resonances. The resonances in the spectrum obtained at 298 K were considered to have broadened significantly compared with those in the spectrum obtained at the slow exchange limit (283 K), and the temperature at the probe could be controlled most reliably at temperatures of up to 323 K. Therefore, fitting was carried out using the spectra obtained in the temperature range 298-323 K. In this range the population ratio for the two inclusion isomers remains essentially unchanged and is approximately 1:8.5 isomer2/isomer1, (where the isomers 1 and 2 give rise to the assigned resonances in Figure 4.24). It is not known which of the orientations of α-cyclodextrin in the αCD.**78**⁻ inclusion isomers is

favoured, k_1 and k_2 are assigned arbitrarily in Scheme 4.10. The rate constants for exchange between the two inclusion isomers are given in Table 4.1.

Table 4.1 The rate constants for exchange between two αCD.**78**$^-$ inclusion isomers in which the orientation of α-cyclodextrin differs.

Temperature/K	k_1/s^{-1}	k_2/s^{-1}
298	12.3 ± 0.6	10.7 ± 0.5
303	23.8 ± 1.2	20.7 ± 1.0
308	45.3 ± 2.3	38.1 ± 1.9
313	76.7 ± 3.8	64.7 ± 3.2
318	146 ± 7.3	123 ± 6.2
323	256 ± 13	216 ± 11

Equation (4.1) describes the relationship between the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and the rate constant k at various temperatures. The equation can be manipulated to give another form, equation (4.2), which allows $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to be determined from a graph of ln(k/T) vs 1/T,

$$k = \frac{k_B T}{h} e^{\frac{-\Delta H^{\ddagger}}{RT}} e^{\frac{\Delta S^{\ddagger}}{R}} \qquad (4.1)$$

$$\ln\frac{k}{T} = \ln\frac{k_B}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} \qquad (4.2)$$

where k = rate constant (s^{-1}), T = temperature (K), $\Delta H^{\ddagger}$ = enthalpy of activation (J mol^{-1}), $\Delta S^{\ddagger}$ = entropy of activation (J mol^{-1}), k_B = Boltzmann constant, h = Planck's constant, R = gas constant.

The transition state parameters $\Delta H^{\ddagger}_1$, $\Delta H^{\ddagger}_2$, $\Delta S^{\ddagger}_1$ and $\Delta S^{\ddagger}_2$ for exchange between the αCD.**78**$^-$ inclusion isomers are 94.3 ± 4.7 kJ mol^{-1}, 93.1 ± 4.7 kJ mol^{-1}, 92.0 ± 5.0 J mol^{-1} and 87.3 ± 5.0 J mol^{-1}, respectively. The ground state parameters ΔG^0, ΔH^0 and ΔS^0 (in the direction 1 → 2) are –201 ± 10 J mol^{-1}, 1.20 ± 0.06 kJ mol^{-1} and 4.70 ± 0.25 J K^{-1} mol^{-1}, respectively.

Similar changes to those observed in the 1D ^{1}H NMR spectrum of αCD.**78**$^-$ are seen in the aromatic and *t*-butyl group regions of the spectrum of αCD.**79**$^-$ with an increase in temperature (Figures 4.26 and 4.27), but the resonances in the spectrum of αCD.**79**$^-$ do not broaden significantly at temperatures lower than ~313 K. The spectra of αCD.**79**$^-$ were not fitted using DAVNMR, as it was considered that insufficient data points would be collected to obtain reliable values for the activation parameters. The population ratio of the two αCD.**79**$^-$ inclusion isomers does change considerably with increasing temperature, with the inclusion isomer that gives rise to resonance 2 becoming considerably more abundant than the inclusion isomer that gives rise to resonance 1. Equation (4.3) describes the relationship between the ground state parameters ΔH^0 and ΔS^0 and the equilibrium constant K and can be manipulated to give the more convenient representation, equation (4.4),

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \qquad (4.3)$$

$$\Delta G^\circ = -RT \ln K \qquad (4.4)$$

where k = rate constant (s^{-1}), K = equilibrium constant, T = temperature (K), ΔH° = standard enthalpy of reaction (J mol^{-1}), ΔS° = standard entropy of reaction (J mol^{-1}), R = gas constant.

By calculating the population ratio of the exchanging inclusion isomers at each of the various temperatures, and considering that the ratio is equivalent to K at each temperature, the ground state parameters (in the direction 1 → 2) were determined to be ΔG^0 = -910 ± 160 J mol^{-1}, ΔH^0 = 12.6 ± 1.5 kJ mol^{-1} and ΔS^0 = 46 ± 3 J mol^{-1}. The errors in the parameters are large, due to the crudeness of the method from which they were obtained.

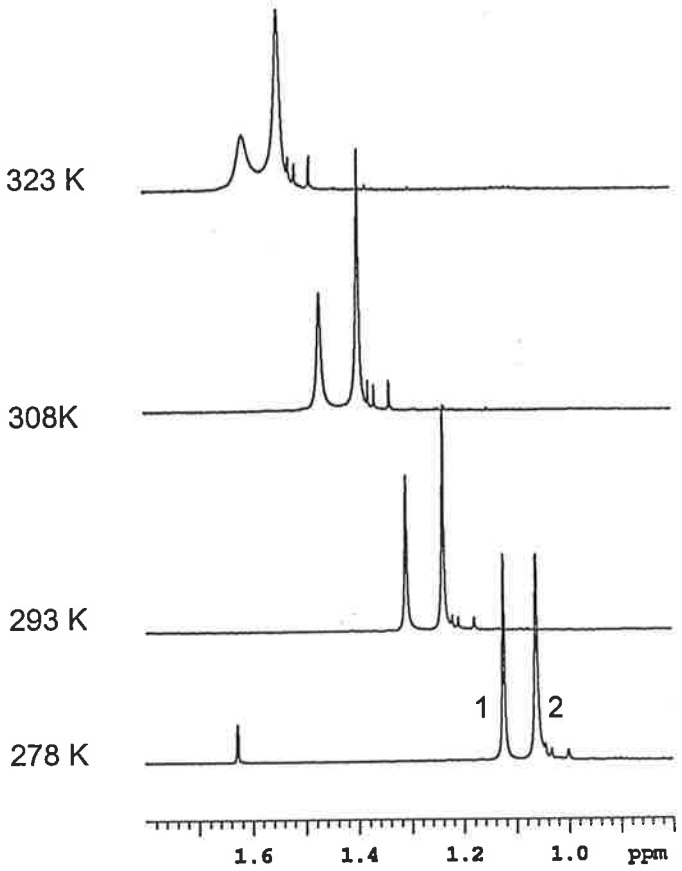


Figure 4.26 The *t*-butyl region of the 1D ^{1}H NMR spectra of a D_2O solution containing two exchanging αCD.**79**$^-$ inclusion isomers, showing two resonances which broaden and begin to converge with increasing temperature. The population ratio of the inclusion isomers changes substantially over the temperature range 278-323 K. The solution was made up at approximate concentrations of 0.0034 mol dm^{-3} *trans* carboxystilbene **79**$^-$ and 0.010 mol dm^{-3} α-cyclodextrin.

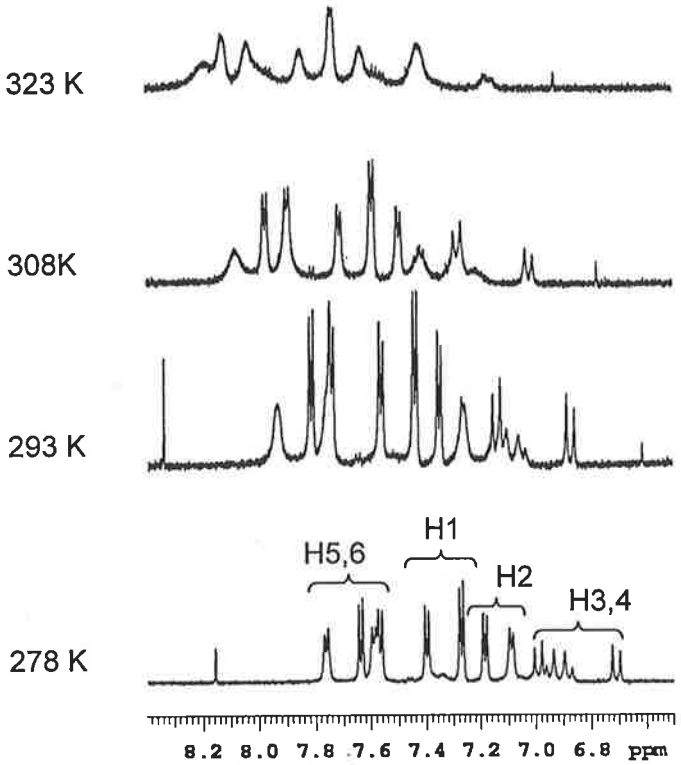


Figure 4.27 The aromatic region of the 1D ^{1}H NMR spectra of a D_2O solution containing two exchanging αCD.**79**$^-$ inclusion isomers, showing two sets of overlapping resonances which broaden and begin to converge with increasing temperature. The solution was made up at approximate concentrations of 0.0034 mol dm^{-3} *trans* carboxystilbene **79**$^-$ and 0.010 mol dm^{-3} α-cyclodextrin.

4.3 Conclusion

The change in shape of a stilbene during isomerisation between the *cis* and *trans* configurations has been exploited to create a series of molecular devices. The cyclodextrin dimer.stilbene inclusion complex systems **77.78**$^-$**/80**$^-$, **77.79**$^-$**/81**$^-$ and **73.79**$^-$**/81**$^-$ each represent a two-state molecular device in which one end of the stilbene component is alternately included and excluded from a cyclodextrin annulus, and the switching between the two states is controlled using thermal (for **77.78**$^-$**/80**$^-$ only) and photochemical stimuli. A molecular device was not constructed from the components **73** and **78**$^-$**/80**$^-$ due to **73** being large enough to fully include both **78**$^-$ and **80**$^-$. This demonstrates the importance of selecting components of appropriate relative sizes in molecular device construction.

The introduction of a tolyl guest, **94**, **95** or **96**, as a third component into the systems **77.78**$^{-}$**/80**$^{-}$, **77.79**$^{-}$**/81**$^{-}$ and **73.79**$^{-}$**/81**$^{-}$ allowed the construction of three-component molecular devices in which the tolyl guest is alternately included and excluded from a cyclodextrin annulus as the annulus is vacated and occupied by one end of the stilbene.

Examination of the individual α-cyclodextrin and β-cyclodextrin complexes of the *trans* stilbenes **78**$^{-}$ and **79**$^{-}$ provided insight into the influence of annulus size on the nature of the complex formed. The stilbenes **78**$^{-}$ and **79**$^{-}$ form relatively loose complexes with β-cyclodextrin in which the *t*-butyl group is most strongly included, and each stilbene forms either one major inclusion complex, or two inclusion isomers which are in fast exchange. α-Cyclodextrin imparts a much tighter fit on **78**$^{-}$ and **79**$^{-}$ and includes the central section of each stilbene most strongly. Each of the stilbenes **78**$^{-}$ and **79**$^{-}$ form two inclusion isomers with α-cyclodextrin that are in slow exchange on the NMR timescale at room temperature, but exchange more quickly with increasing temperature.

4.4 References

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Conclusion

Two series of modified cyclodextrins with alicyclic and azacoronand substituents have been prepared and approaches to the synthesis of a cyclodextrin molecular knot have been examined. Calibration studies of the relative sizes of the α- and β-cyclodextrin annuli were facilitated by this work. The trinorbornylmethyl-, cubyl-, dimethylcubyl- and adamantyl-substituted α-cyclodextrins **35**, **36**, **37** and **38** were prepared by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** by the 4-nitrophenyl esters **25-28**, respectively. The trinorbornylmethyl, cubyl, and dimethylcubyl substituents of the modified α-cyclodextrins **35**, **36** and **37**, respectively, are self-included to give **35'-37'** in D_2O, but the adamantyl substituent of **38** is too large to be self-included to give **38'**. From the formation of **35/35'**, **36/36'**, **37/37'** and **38**, but not **38'**, the mechanism for the formation of the self-included species has been determined. It is evident that the acylations involve nucleophilic attack by the appropriate 4-nitrophenyl ester at the non-included aminohexylamine substituent of **34** to give **35-38**. The self-inclusion of the smaller substituents of **35-37** produces **35'-37'** in water, while the adamantyl entity of **38** is too large to enter the α-cyclodextrin annulus and form **38'**. It is assumed that the reactions to form the β-cyclodextrin analogues, which were prepared previously, would have proceeded via the same mechanism.

The azacoronand-substituted cyclodextrins **43-46** were prepared by the acylation of 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** by either of the 4-nitrophenyl esters **41** or **42**. The substituents of the modified β-cyclodextrins **45** and **46** are self-included to form **45'** and **46'** in D_2O at pD 9, while the substituents of the corresponding modified α-cyclodextrins are not self-included due to the α-cyclodextrin annulus being too small. In D_2O at pD 9, the unusual [2]-pseudorotaxanes βCD.**43** and βCD.**44** form, in which both the wheel component and one blocking group are cyclodextrins. Protonation of the amine directly attached to the cyclodextrin in **43-46** in D_2O at pD 7 prevents significant formation of the self-included species $[\mathbf{45'}.H]^+$ and $[\mathbf{46'}.H]^+$ and the [2]-pseudorotaxanes $[\beta CD.\mathbf{43}.H]^+$ and $[\beta CD.\mathbf{44}.H]^+$. High stability constants were determined for the zinc(II) and lanthanum(III) complexes of **45/45'** by potentiometric titrations. However, metal-locking of the azacoronand of **45'** to give a molecular knot was not possible due to the low water-solubility of the hydroxides of zinc(II)

and lanthanum(III) at pH 9. Modifications to remove the basic amine attached to the cyclodextrin in **43-46** and replace it with a group that does not protonate may give rise to self-included cyclodextrins and [2]-pseudorotaxanes that exist at a significant concentration at pH 7, and allow metal-locked species to be investigated.

The design and synthesis of the water-soluble axles **52** and **53** allowed a series of cobalt(III)-blocked α-cyclodextrin and β-cyclodextrin [2]-rotaxanes, **57**, **58** and **59**, to be constructed in aqueous solution in good yield. The [2]-rotaxanes **57** and **59** were obtained as almost pure products directly from the reaction mixtures as shown by 1D ^{1}H NMR and 2D ^{1}H ROESY NMR experiments. The complicated nature of the NMR spectra of the α-cyclodextrin [2]-rotaxane **58** rendered it impossible to verify the purity of **58** by NMR experiments, such that the use of β-cyclodextrin was found to be more convenient in these syntheses. An alternative synthesis of the [2]-rotaxane **57** is the slow slippage of β-cyclodextrin over a blocking group of the complex **60**. The [2]-rotaxane **59** forms very slowly by a slippage mechanism, while the α-cyclodextrin [2]-rotaxane **58** does not form by such a mechanism. Further purification of the [2]-rotaxanes as the chloro complex analogues allowed microanalyses to be obtained. Work towards synthesising the cyclodextrin dimer [2]-rotaxane **74** was carried out, but was hindered by the low water-solubility of the corresponding [2]-pseudorotaxane.

A series of three two-component molecular devices was constructed from cyclodextrin dimer and stilbene components. Movement of the guest relative to the host was controlled in complexes comprised of the cyclodextrin dimers **73** and **77** and the *trans* and *cis* oxystilbenes and carboxystilbenes **78**$^{-}$-**81**$^{-}$. One annulus of the cyclodextrin dimer is alternately occupied and vacated as the stilbene is isomerised between the *trans* and *cis* isomers, respectively. Either a combination of thermal energy and sunlight, or specific irradiation wavelengths were used to switch the device **77.78**$^{-}$/**79**$^{-}$. Switching of the systems **77.80**$^{-}$/**81**$^{-}$ and **73.80**$^{-}$/**81**$^{-}$ was controlled using specific irradiation wavelengths only. A molecular device could not be constructed from the system **73.78**$^{-}$/**79**$^{-}$, demonstrating the significance of selecting components of appropriate relative sizes. Each of the two-component molecular devices was built into a series of three-component molecular devices by combining tolyl guests with the original components of the device. 4-Methylbenzoate **94**, 4-methylphenolate **95** or 4-methylbenzenesulfonate **96** are included in the available cyclodextrin annulus of the *cis*

stilbene complexes **77.79**$^-$, **77.81**$^-$ and **73.81**$^-$, but are excluded from the cyclodextrin annulus in the corresponding *trans* stilbene complexes.

The cyclodextrin annulus size was found to significantly influence the nature of the complexes formed by the *trans* stilbenes **78**$^-$ and **79**$^-$ and native α-cyclodextrin and β-cyclodextrin. Each β-cyclodextrin.stilbene complex exists either with β-cyclodextrin in a single orientation, or as two inclusion isomers in fast equilibrium, while each α-cyclodextrin.stilbene complex exists as two inclusion isomers in slow equilibrium at room temperature. The rate constants and activation parameters for exchange between the two αCD.**78**$^-$ inclusion isomers were obtained by variable temperature NMR experiments.

Experimental

E.1 General

Melting points were measured using a Kofler hot-stage apparatus under a Reichert microscope and are uncorrected. As cyclodextrin derivatives decompose without melting above 180 °C, melting points were not determined for such compounds.

Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. As cyclodextrin derivatives, hydrochloride salts of amines and some stilbene derivatives have water molecules associated with them, they were characterised by adding whole numbers of water molecules to the molecular formula to give the best fit to the microanalytical data.

^{1}H and ^{13}C NMR spectra were recorded using a Varian Gemini ACP-300 spectrometer operating at 300.145 MHz (^{1}H) or 75.4 MHz (^{13}C), unless otherwise stated. A Varian Gemini 200 spectrometer operating at 199.953 MHz (^{1}H) and 50.4 MHz (^{13}C) was also used. The abbreviations singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m) refer to the multiplicity of the NMR signals. Compounds were dissolved in $CDCl_3$, d_6-DMSO or D_2O, and resonances were referenced against tetramethylsilane in $CDCl_3$, the residual solvent multiplet (δ_H = 2.49, δ_C = 39.5) in d_6-DMSO or an external standard, aqueous trimethylsilylpropiosulfonic acid, in D_2O. The 2D ^{1}H ROESY NMR spectra of modified cyclodextrins, cyclodextrin complexes and [2]-rotaxanes were recorded on a Varian Inova 600 Spectrometer operating at 599.957 MHz, using a standard sequence with a mixing time of 0.3 seconds. Compounds were dissolved in D_2O to give approximate concentrations of 0.02-0.03 mol dm^{-3} modified cyclodextrin, [2]-pseudorotaxane or [2]-rotaxane, and approximate concentrations of 0.016 mol dm^{-3} cyclodextrin, 0.015 mol dm^{-3} stilbene and 0.1 mol dm^{-3} NaOD for cyclodextrin.stilbene complexes. Resonances were referenced against the HOD resonance (δ = 4.72). The lineshape analysis of the coalescence of the *t*-butyl resonances of the αCD.**78**$^{-}$ inclusion isomers was carried out using the program DAVNMR [1].

Infrared spectra were recorded on an ATI Mattson Genesis FT-IR. The abbreviations strong (s), medium (m), weak (w) and broad (b) are used for reporting the intensity of the

bands observed. UV/Visible spectra were recorded on a Cary 300 Bio spectrophotometer (scanning rate 2 nm s^{-1}). Cobalt(III)-blocked [2]-rotaxanes and cobalt(III) axle complexes were dissolved in water (or 1.0 mol dm^{-3} sodium chloride solution for the chloro analogues) to give approximate concentrations of 1.0×10^{-3} mol dm^{-3}. The UV/Visible spectra obtained for photochemical switching experiments were recorded using aqueous solutions that were approximately 2.5-3.0 $\times$ 10^{-5} mol dm^{-3} in cyclodextrin dimer, 2.0-2.5 $\times$ 10^{-5} mol dm^{-3} in stilbene, 4×10^{-5} mol dm^{-3} in tolyl guest (when present) and 1.0×10^{-3} mol dm^{-3} in sodium hydroxide. Irradiation of solutions of stilbene complexes was carried out in a quartz cuvette in a Perkin Elmer LS50B fluorimeter.

MALDI-TOF mass spectrometry was carried out at the Research School of Chemistry at the Australian National University, Canberra, ACT. Electrospray mass spectrometry (ES-MS) and fast atom bombardment mass spectrometry (FAB-MS) were carried out at the University of Adelaide. Samples for ES-MS were dissolved in water for injection. Accurate mass spectrometry was carried out at the University of Tasmania, Hobart, Tasmania.

Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} on aluminium-backed sheets. For analysis of cyclodextrin derivatives, plates were developed with 7:7:5:4 v/v ethyl acetate/propan-2-ol/ammonium hydroxide/water and the compounds were visualised by drying the plate then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat gun. To visualise amino bearing compounds, plates were dried then dipped into a 0.5% ninhydrin in ethanol solution and heated with a heat-gun, prior to being dipped in the acid solution. The value R_c represents the R_f of a modified cyclodextrin relative to the R_f of the parent cyclodextrin.

Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh ASTM) silica. Squat column chromatography was carried out using Merck Kieselgel 60 F_{254} thin layer chromatography silica.

Potentiometric titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer and an Orion 81-03 combination electrode that was filled with 0.10 mol dm^{-3} tetraethylammonium perchlorate (TEAP) solution. The electrode was soaked in 0.10 mol dm^{-3} TEAP solution for at least three days prior to use. Titrations were performed

in a water-jacketed 2 cm^3 titration vessel held at 298 ± 0.1 K. A gentle stream of nitrogen was passed through the titration solutions, which were magnetically stirred. The titration solutions were allowed to stand in the titration vessel for 15 minutes before the titration was begun to allow the solution to equilibrate to 298 K and become saturated with nitrogen. In titrations of **45/45'**, 0.0975 mol dm^{-3} tetraethylammonium hydroxide (TEAOH) was titrated against a solution that was 1.0×10^{-3} mol dm^{-3} in **45/45'**, 3.2×10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in TEAP ($I = 0.1$). The TEAOH solution was standardised by titrating it against a 0.010 mol dm^{-3} potassium hydrogenphthalate solution. All titrations that were performed in the presence of metal ions were carried out using ~2 equivalents of the metal ion. The electrode was calibrated every 24 hours by titration of a solution that was 3.2×10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in TEAP. Values of pK_a (acid dissociation constant) and K (metal complex stability constant) were determined using the program SUPERQUAD [2]. For each system, the titration was performed at least three times and at least two of the runs were averaged. Only runs for which χ^2 was < 12.6 at the 95 % confidence interval were selected for averaging.

All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. β-Cyclodextrin was donated by Nihon Shokuhin Kako Co. Both α- and β-cyclodextrin were dried by heating at 100 °C under reduced pressure for 18 hours. 6^A-*O*-(4-Methylbenzenesulfonyl)-β-cyclodextrin **5** [3], 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** [4], 6^A-amino-6^A-deoxy-β-cyclodextrin **71** [5], 6^A-amino-6^A-deoxy-α-cyclodextrin **92** [5] and 6^A-azido-6^A-deoxy-β-cyclodextrin **72** [6] were prepared by literature methods. 6^A-*O*-(4-Methylbenzenesulfonyl)-α-cyclodextrin **4** was prepared by a modification of previous procedures [5, 6]. The 4-nitrophenol esters **25-28** were prepared by reaction of the corresponding carboxylic acids with 4-nitrophenol in the presence of DCC [7]. 1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triazaoct-8-yl)benzene **49** [8] and the carboxylic acids 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetic acid **47** and 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetic acid **48** [9-11] were prepared in a similar manner to literature procedures. *N,N'*-Bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** [12] and *N*-(6^A-deoxy-α-cyclodextrin-6^A-yl)-*N'*-(6^A-deoxy-β-cyclodextrin-6^A-yl)urea [13] were prepared by modified literature procedures. Ethanethiol was dried by distillation from calcium chloride. Pyridine and *N*-methylpyrrolidin-2-one (NMP) were dried by distillation from calcium hydride. Ether,

tetrahydrofuran (THF) and dichloromethane were dried by distillation from sodium wire. *N*,*N*-Dimethylformamide (DMF) and methanol were dried over molecular sieves.

The drying of products was carried out under reduced pressure (approximately 0.1 torr) over phosphorus pentoxide at room temperature for 16 hours unless otherwise stated.

E.2 Preparation of compounds described in Chapter 2

6^A-*O*-(4-Methylbenzenesulfonyl)-α-cyclodextrin **4** [5, 6]

α-Cyclodextrin **1** (6.91 g, 7.10 mmol) was dissolved in dry pyridine (1 dm^3) with gentle warming and shaking. 4-Methylbenzenesulfonyl chloride (21.0 g, 111 mmol) was added in one portion. The solution was stirred at room temperature for 45 minutes and quenched with water (40 cm^3). Pyridine was removed under reduced pressure and the residue was triturated with 1:1 v/v ether/acetone (3 × 500 cm^3). The crude solid (~10 g) was dissolved in water (40 cm^3) and loaded onto a Diaion HP-20 column (5 × 20 cm). The column was washed with water (1 dm^3) to remove α-cyclodextrin (1.5 g), and monotosylated α-cyclodextrin was eluted with 30-40% aqueous methanol (3 dm^3). Polytosylated material was eluted with 80-100% aqueous methanol. Fractions containing monotosylated α-cyclodextrin were combined and solvent was removed under reduced pressure. The residue was dried to give the product **4** as a white solid (1.65 g, 21 %); $\delta_H(D_2O)$ 7.74 (d, J = 8.4 Hz, 2H, ArH); 7.43 (d, J = 8.4 Hz, 2H, ArH); 4.90-4.94 (m, 6H, H1); 4.82-4.84 (m, 2H); 4.37 (d, J = 10.8 Hz, 1H); 4.21-4.29 (m, 1H); 3.61-3.92 (m, 22H, H3, H5, H6); 3.41-3.46 (m, 12H, H2, H4); 3.36 (d, J = 9.3 Hz, 1H); 2.37 (s, 3H, CH_3).

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34**

A mixture of 6^A-*O*-(4-methylbenzenesulfonyl)-α-cyclodextrin **4** (0.495 g, 0.440 mmol) and 1,6-diaminohexane (0.201 g, 1.73 mmol) in dry NMP (2 cm^3) were stirred in a lightly stoppered flask at 70 °C for 18 hours. Ethanol (50 cm^3) was added and the pale orange precipitate was collected by suction filtration and washed with ethanol (50 cm^3) and ether (30 cm^3). The solid was dissolved in water (5 cm^3) and loaded onto a BioRex 70 (H^+ form) cation exchange column (4.5 × 4.5 cm). The column was washed with water and the product was eluted with 0.5 mol dm^{-3} aqueous ammonia solution. Water was removed under reduced pressure and the residue was redissolved in water (10 cm^3) and concentrated under reduced

pressure to remove ammonia (3 ×). The residue was freeze-dried to give the product **34** as a white solid (0.213 g, 44 %), R_c = 0.60; MALDI-TOF-MS *m/z* 1072 ($[M + H]^+$); [Found: C, 43.83; H, 7.14; N, 2.33 %. Calc. for **34**.4H_2O ($C_{42}H_{82}N_2O_{33}$) C, 44.13; H, 7.23; N, 2.45 %]; δ_H(D_2O/NaOD, pD ≥ 12) 5.04 (s, 6H, H1); 3.82-3.97 (m, 22H, H3, H5, H6); 3.58-3.66 (m, 11H, H2, H4); 3.45 (t, J = 9.0 Hz, 1H, H_4^A); 3.05 (d, J = 12.0 Hz, 1H, H_6^A); 2.75-2.91 (m, 3H, $H_6^{A'}$, hexylH6); 2.50-2.61 (m, 2H, hexylH1); 1.44-1.67 (m, 4H, hexylH2, hexylH5); 1.31-1.44 (m, 4H, hexylH3, hexylH4); δ_C(D_2O/NaOD, pD ≥ 12) 104.15, 103.98 (C1); 84.47 ($C4^A$); 83.99, 83.84 (C4); 75.98, 74.75, 74.37 (C2, C3, C5); 73.30 ($C5^A$); 63.02 (C6); 52.29, 51.77, 42.68 ($C6^A$, hexylC1, hexylC6); 31.27, 29.19, 28.95, 28.77 (hexylC2-C5).

General procedure for the preparation of the modified cyclodextrins 35-38

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (~ 0.19 mmol) was added to a solution of the appropriate 4-nitrophenyl ester (1.2 equivelants, ~0.23 mmol) in DMF (3 cm^3) and the mixture was stirred at room temperature for 12-18 hours. The reaction mixture was added drop-wise to cold acetone (50 cm^3) and the precipitate that formed was collected by suction filtration and washed with acetone (30 cm^3) and 1:1 acetone/ether (30 cm^3). The precipitate was dissolved in water (3 cm^3) and the solution was acidified with concentrated hydrochloric acid to pH 1 and washed with dichloromethane (3 × 5 cm^3). Dichloromethane (in the partially emulsified aqueous phase) was removed under reduced pressure and the solution was loaded onto an AG-4X4 (free base form) anion exchange column (4.5 × 4.5 cm). The modified cyclodextrin was eluted with water (100 cm^3). Water was removed under reduced pressure and the residue was redissolved in water (3 cm^3) and loaded onto a BioRex 70 (NH_4^+ form) cation exchange column (4.5 × 4.5 cm). The modified cyclodextrin was eluted with water (200 cm^3). Fractions containing the product were combined and water was removed under reduced pressure. The residue was freeze-dried and dried over phosphorous pentoxide to yield the modified cyclodextrin as a white solid.

6^A-Deoxy-(6-(trinorbornan-2-ylacetamido)hexylamino)-α-cyclodextrin 35

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.205 g, 0.191 mmol) was added to a solution of 4-nitrophenyl trinorbornane-2-acetate **25** (0.0547 g, 0.199 mmol) in DMF (3 cm^3) and the mixture was stirred at room temperature for 12 hours. After the general work-up and purification procedure, the modified cyclodextrin **35** was obtained as a white solid (0.51 g, 22 %), R_c = 1.2; Accurate mass spectrum *m/z* 1207.528, Calc. 1207.534

([M + H]$^+$); [Found: C, 44.12; H, 7.00; N, 2.29 %. Calc. for **35**.9H_2O ($C_{50}H_{102}N_2O_{39}$) C, 44.13; H, 7.59; N, 2.07 %]; δ_H(D_2O/NaOD, pD ≥ 12) 4.88-4.93 (m, 6H, H1); 3.73-3.93 (m, 22H, H3, H5, H6); 3.21-3.62 (m, 12H, H2, H4); 3.10 (t, J = 6.6 Hz, 1H, hexylH6); 2.94 (d, J = 12.6 Hz, 1H, H6^A); 2.29-2.82 (m, 4H, hexylH1, H6$^{A'}$, trinorbornylmethylH); 1.83-2.20 (m, 4H, trinorbornylmethylH); 1.71-1.78 (m, 1H, hexylH6); 1.01-1.63 (m, 16H, hexylH2-H5, trinorbornylmethylH); δ_C(D_2O/NaOD, pD ≥ 12) 178.79 C=O; 105.04 (C1); 87.04 (C4^A); 84.39 (C4); 76.86, 76.75, 75.29, 74.86 (C2, C3, C5); 72.92 (C5^A); 63.27 (C6); 52.05, 51.23 (C6^A, hexylC); 45.44, 43.36, 41.90, 39.65, 39.27, 37.45 (trinorbornylmethylC); 33.58, 32.21, 30.95, 28.72, 28.57 (hexylC).

6^A-(6-(8-Carboxycuban-1-ylcarbonylamino)hexylamino)-6^A-deoxy-α-cyclodextrin 36

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.208 g, 0.194 mmol) was added to a solution of 1-methoxycarbonyl-8-(4-nitrophenoxycarbonyl)cubane **26** (0.083 g, 0.25 mmol) in DMF (3 cm^3) and the mixture was stirred at room temperature for 16 hours. Analysis by TLC of the residue after the general work-up and purification procedure revealed two products (R_c = 1.5, 1.6). After stirring the residue in water (20 cm^3) at 80 °C for 24 hours, analysis by TLC revealed a single product (R_c = 1.5). Water was removed under reduced pressure and the residue was freeze-dried to give the modified cyclodextrin **36** as a white solid (0.041 g, 17 %), ES-MS spectrum *m/z* 1245.5 ([M + H]$^+$); [Found: C, 44.05; H, 6.52; N, 1.88 %. Calc. for **36**.9H_2O ($C_{52}H_{98}N_2O_{41}$) C, 44.36; H, 7.02; N, 1.99 %]; δ_H(D_2O, pD ~7) 5.01-5.09 (m, 6H, H1); 4.08-4.10 (m, 3H, cubylH); 4.03-4.07 (m, 3H, cubylH); 3.67-3.99 (m, 22H, H3, H5, H6); 3.54-3.65 (m, 11H, H2, H4); 3.47-3.52 (m, 2H, H4^A, H6^A); 3.28-3.31 (m, 1H, H6$^{A'}$); 3.18 (t, J = 5.8 Hz, 2H, hexylH6); 2.99-3.04 (m, 2H, hexylH1); 1.46-1.69 (m, 4H, hexylH2, hexylH5); 1.29-1.36 (m, 4H, hexylH3, hexylH4); δ_C(D_2O, pD ~7) 181.96 (C=O); 175.49 (C=O); 102.34, 101.67, 101.31 (C1); 83.35 (C4^A); 81.76, 81.51, 81.45, 81.38 (C4); 73.65, 73.60, 73.53, 73.36, 73.31, 72.84, 72.55, 72.39, 72.34, 72.23 (C2, C3, C5); 68.17 (C5^A); 61.05, 60.75 (C6); 59.14, 57.86, 48.56, 48.40, 47.17, 47.03, 46.63, 46.58, 46.41, 39.16, 39.16 (C6^A, cubylC, hexylC1, hexylC6); 28.44, 25.68, 25.64, 25.50 (hexylC2-C5).

6^A-(6-(8-Carboxy-2,3-dimethylcuban-1-ylcarbonylamino)hexylamino)-6^A-deoxy-α-cyclodextrin 37

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.223 g, 0.208 mmol) was added to a solution of 2,3-dimethyl-1-methoxycarbonyl-8-(4-nitrophenoxycarbonyl)cubane **27** (0.080 g, 0.22 mmol) in DMF (3 cm^3) and the mixture was stirred at room temperature for 18 hours. After the general work-up and purification procedure, the product was stirred in water (20 cm^3) with 1 drop of triethylamine (24 hours). Analysis by TLC revealed one product (R_c = 1.0). The solution was concentrated under reduced pressure and the residue was freeze-dried to give the product **37** as a white solid (0.049 g, 19 %), Accurate mass spectrum *m/z* 1273.507, Calc. 1273.508 ($[M + H]^+$); [Found: C, 45.46; H, 7.04; N, 1.89 %. Calc. for **37**.9H_2O ($C_{54}H_{102}N_2O_{41}$) C, 45.19; H, 7.16; N, 1.95 %]; δ_H(D_2O, pD ~7) 5.02-5.08 (m, 6H, H1); 4.04 (t, *J* = 10.7 Hz, 1H, $H3^A$); 3.68-3.98 (m, 27H, H3, H5, H6, cubylH); 3.47-3.65 (m, 13H, H2, H4, $H6^A$); 3.25-3.31 (m, 1H, $H6^{A'}$); 3.18 (t, *J* = 6.6 Hz, 2H, hexylH6); 2.95-3.05 (m, 2H, hexylH1); 1.62-1.68 (m, 2H, hexylH2); 1.46-1.50 (m, 2H, hexylH5); 1.29-1.36 (m, 4H, hexylH3, hexylH4); 1.34 (s, 1H, Me); 1.44 (s, 1H, Me); δ_C(D_2O, pD ~7) 183.40 (C=O); 176.89 (C=O); 104.15, 103.79 (C1); 85.87 ($C4^A$); 85.86, 84.22, 83.98, 83.93, 83.66 (C4); 76.13, 76.08, 76.01, 75.84, 75.80, 75.33, 75.02, 74.87, 74.71, 74.37, 74.16 (C2, C3, C5); 70.78 ($C5^A$); 63.52, 63.24 (C6); 60.97, 59.75, 58.78, 58.03, 51.07, 50.95, 50.48, 49.51, 46.80, 45.67, 41.54 (cubylC, $C6^A$, hexylC1, hexylC6); 31.16, 28.22, 28.16 (hexylC2-C5).

6^A-(6-(1-Adamantylcarbonylamino)hexylamino)-6^A-deoxy-α-cyclodextrin 38

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.193 g, 0.180 mmol) was added to a solution of 1-(4-nitrophenoxycarbonyl)adamantane **28** (0.0694 g, 0.230 mmol) in DMF (3 cm^3) and the mixture was stirred at room temperature for 12 hours. After the general work-up and purification procedure, the modified cyclodextrin **38** was obtained as a white solid (0.840 g, 38 %), R_c = 1.7; MALDI-TOF-MS *m/z* 1234 (M^+); [Found: C, 47.64; H, 6.92; N, 2.14 %. Calc. for **38**.6H_2O ($C_{53}H_{100}N_2O_{36}$) C, 47.46; H, 7.41; N, 2.09 %]; δ_H(D_2O/NaOD, pD ≥ 12) 4.98 (s, 6H, H1); 3.76-3.92 (m, 22H, H3, H5, H6); 3.39-3.49 (m, 11H, H2, H4); 3.23 (t, *J* = 8.7 Hz, 1H, $H4^A$); 3.13 (t, *J* = 5.8 Hz, 2H, hexylH6); 3.01 (d, *J* = 11.6 Hz, 1H, $H6^A$); 2.61-2.69 (m, 1H, $H6^{A'}$); 2.47-2.52 (m, 2H, hexylH1); 1.62-2.00 (m, 15H, adamantylH); 1.41-1.49 (m, 4H, hexylH2, hexylH5); 1.25-1.31 (m, 4H, hexylH3, hexylH4); δ_C(D_2O/NaOD, pD ≥ 12) 184.22 (C=O); 105.13, 104.94, 104.78, 104.69 (C1); 87.13 ($C4^A$); 84.38, 84.27 (C4); 76.89, 75.34, 74.97, 74.85 (C2, C3, C5); 73.11 ($C5^A$); 63.36 (C6); 52.51,

51.35, 43.28, 41.85 ($C6^A$, hexylC); 41.34, 38.69 (adamantylC); 31.06 (hexylC); 30.51 (adamantylC); 28.83, 28.49 (hexylC).

2-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)acetic acid 47 [9-11]

(a) Preparation of ethyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate:

1,4,7,10-Tetraoxa-13-azacyclopentadecane **39** (0.449 g, 2.26 mmol) was dissolved in dry acetonitrile (10 cm^3). Sodium carbonate (0.275 g, 2.59 mmol) and ethyl bromoacetate (0.420 g, 2.51 mmol) were added successively and the mixture was stirred at reflux under nitrogen for 24 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the product as a yellow oil (quantitative yield), δ_H(200 MHz, $CDCl_3$) 4.21 (q, J = 7.2 Hz, 2H, CH_3-C<u>H_2</u>); 3.68-3.75 (m, 12H, azacoronandO-CH_2); 3.57 (t, J = 4.8 Hz, 4H, azacoronandO-CH_2); 3.51 (s, 2H, O=C-CH_2-N); 2.83 (t, J = 4.8 Hz, 4H, azacoronandN-CH_2); 1.28 (t, J = 7.2 Hz, 3H, C<u>H_3</u>-CH_2); δ_C(50.4 MHz, $CDCl_3$) 172.33 (C=O); 68.06, 67.96, 67.44, 66.23, 60.55 (CH_3-<u>C</u>H_2, azacoronandC-O); 55.82 (O=C-<u>C</u>H_2-N); 54.26 (azacoronandC-N); 13.22 (CH_3); ν_{max} (Thin film)/cm^{-1} 1730s (C=O).

(b) Hydrolysis:

The ester was hydrolysed, without prior purification, by heating a solution of the material obtained in water (10 cm^3) at reflux under nitrogen for 48 hours. Water was removed under reduced pressure and the residue was dried to give the product **47** (sodium bromide salt) as a viscous yellow oil (0.812 g, 94%), δ_H(200 MHz, D_2O) 3.87 (broad s, 6H); 3.69-3.73 (m, 12H); 3.56-3.59 (m, 4H); δ_C(50.4 MHz, D_2O) 172.65 (C=O); 72.51, 72.02, 71.63, 66.03 (azacoronandC-O); 59.00 (O=C-<u>C</u>H_2-N); 57.21 (azacoronandC-N); ν_{max} (Thin film)/cm^{-1} 2600-3000b (OH), 1715m (C=O).

2-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)acetic acid 48

(a) Preparation of ethyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate:

1,4,7,10,13-Pentaoxa-16-azacyclohexadodecane **40** (0.483 g, 1.90 mmol) was dissolved in dry acetonitrile (10 cm^3). Sodium carbonate (0.230 g, 2.15 mmol) and ethyl bromoacetate (0.343 g, 2.05 mmol) were added successively and the mixture was stirred at reflux under nitrogen for 24 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a pale orange oil. The crude material was distilled (155-160 °C/ 0.20 torr) to yield the product as a pale yellow oil (0.514g, 77%); δ_H(200 MHz, $CDCl_3$) 4.15 (q, J = 7.2 Hz, 2H, CH_3-C<u>H_2</u>); 3.61-3.69 (m, 20H,

azacoronandO-CH_2); 3.52 (s, 2H, O=C-CH_2-N); 2.96 (t, J = 5.6 Hz, 4H, azacoronandN-CH_2); 1.26 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$-CH_2); δ_C(50.4 MHz, $CDCl_3$) 172.73 (C=O); 67.65, 67.46, 67.31, 67.18, 65.58, 60.18 (CH_3-$\underline{C}H_2$, azacoronandC-O); 55.05, 53.41 (O=C-$\underline{C}H_2$-N, azacoronandC-N); 12.62 (CH_3); ν_{max} (Thin film)/cm^{-1} 1736s (C=O).

(b) Hydrolysis:

The ester was suspended in water (10 cm^3) and heated at reflux under nitrogen for 48 hours. Water was removed under reduced pressure and the residue was dried to give the product **48** as a viscous colourless oil (0.423 g, 88 %), δ_H(200 MHz, D_2O) 3.75-3.81 (m, 6H); 3.63-3.67 (m, 20H); δ_C(50.4 MHz, D_2O) 172.59 (C=O); 72.48, 72.39, 72.18, 66.49 (azacoronandC-O); 56.95, 54.63 (O=C-$\underline{C}H_2$-N, azacoronandC-N); ν_{max} (Thin film)/cm^{-1} 2400-2800b (OH), 1726m (C=O).

4-Nitrophenyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate 41

2-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)acetic acid **47** (0.151 g, 0.403 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.058 g, 0.42 mmol) and DCC (0.086 g, 0.42 mmol) were added and the mixture was stirred under nitrogen for 2 hours. The solution was filtered through celite and solvent was removed under reduced pressure to give the ester **41** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (Thin film)/cm^{-1} 1764m (C=O), 855m (Ar).

4-Nitrophenyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate 42

2-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)acetic acid **48** (0.116 g, 0.372 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.057 g, 0.41 mmol) and DCC (0.086 g, 0.42 mmol) were added and the mixture was stirred at room temperature for 4 hours, then heated at reflux under nitrogen for 24 hours. After cooling the reaction mixture to room temperature, the mixture was filtered through celite and solvent was removed under reduced pressure to give the ester **42** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (Thin film)/cm^{-1} 1767m (C=O), 856m (Ar).

General procedure for the preparation of the azacoronand-substituted cyclodextrins 43-46

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** (~0.30 mmol) was added to a solution of the appropriate

nitrophenyl ester, **41** or **42** (~1.5 molar equivalents, ~0.45 mmol), in dry DMF (5 cm^3) and the mixture was stirred for 18-48 hours in a lightly stoppered flask at room temperature. A 1:1 v/v ethanol/ether solution (100 cm^3) was added to precipitate out the product. The pale yellow precipitate was collected and washed with 1:1 v/v ethanol/ether (60 cm^3) followed by ether (60 cm^3). The precipitate was dissolved in water (10 cm^3) and loaded onto an AG-4X4 (free base form) anion exchange column (4.5 × 4.5 cm). The modified cyclodextrin was eluted with water (100 cm^3). Water was removed under reduced pressure and the residue was redissolved in water (10 cm^3) and loaded on to a BioRex 70 (NH_4^+ form) column (4.5 × 4.5 cm) and the product was eluted with water (250 cm^3) followed by 0.05 mol dm^{-3} ammonium bicarbonate solution (250 cm^3). Fractions containing the product were combined and water was removed under reduced pressure. The residue was redissolved in water and evaporated to dryness under reduced pressure (3×). The residue was freeze-dried, then dried over phosphorus pentoxide to give the product as a white or pale yellow solid.

6^A-Deoxy-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin 43

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.286 g, 0.267 mmol) was added to a solution of 4-nitrophenyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate **41** (0.240 g, 0.478 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **43** was obtained as a white solid (0.086 g, 24 %), R_c = 1.3; ES-MS *m/z* 1331 (M^+); [Found: C, 44.50; H, 7.20; N, 2.77 %. Calc. for **43**.7H_2O ($C_{54}H_{109}N_3O_{41}$) C, 44.53; H, 7.54; N, 2.89 %]; δ_H(D_2O, pD ~ 9) 4.97-5.00 (m, 6H, H1); 3.76-3.93 (m, 22H, H3, H5, H6); 3.50-3.66 (m, 27H, H2, H4, azacoronandO-CH_2); 3.39 (t, J = 9Hz, 1H, $H4^A$); 3.13-3.17 (m, 5H, hexylH6, $H6^A$, N-CH_2-C=O); 2.82-2.85 (m, 1H, $H6^{A'}$); 2.70 (t, J = 4.8 Hz, 4H, azacoronandN-CH_2); 2.62 (t, J = 7.2 Hz, 2H, hexylH1); 1.43-1.48 (m, 4H, hexylH2, hexylH5); 1.25-1.29 (m, 4H, hexylH3, hexylH4); δ_C(D_2O, pD ~ 9) 177.30 (C=O); 104.17, 104.07, 103.83 (C1); 86.37 ($C4^A$); 83.94, 83.90, 83.80 (C4); 76.43, 76.08, 76.02, 75.90, 75.76, 74.77, 74.36 (C2, C3, C5); 72.68 ($C5^A$); 72.43, 72.12, 71.64, 71.42 (azacoronandC-O); 63.14 (C6); 61.38, 56.92, 51.96, 51.49, 41.80 ($C6^A$, hexylC1, hexylC6, N-C-C=O, azacoronandC-N); 31.20, 30.34, 28.69 (hexylC2-C5).

6^A-Deoxy-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin 44

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **34** (0.192 g, 0.179 mmol) was added to a solution of 4-nitrophenyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate **42** (0.159 g, 0.359 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **44** was obtained as a white solid (0.082 g, 45 %), R_c = 1.6; MALDI-TOF-MS *m/z* 1375.5 ($[M + H]^+$); [Found: C, 45.04; H, 7.26; N, 2.90%. Calc. for **44**.$6H_2O$ ($C_{56}H_{111}N_3O_{41}$) C, 45.33; H, 7.55; N, 2.83 %]; δ_H(D_2O, pD ~ 9) 5.02 (s, 6H, H1); 3.79-3.96 (m, 22H, H3, H5, H6); 3.53-3.66 (m, 31H, H2, H4, azacoronandO-CH_2); 3.41 (t, *J* = 8.4 Hz, 1H, $H4^A$); 3.17-3.21 (m, 5H, hexylH6, N-CH_2-C=O, $H6^A$); 2.87-2.91 (m, 1H, $H6^{A'}$); 2.76 (t, *J* = 4.8 Hz, 4H, azacoronandN-CH_2); 2.66 (t, *J* = 6.6 Hz, 2H, hexylH1); 1.47-1.52 (m, 4H, hexylH2, hexylH5); 1.26-1.33 (m, 4H, hexylH3, hexylH4). δ_C(D_2O, pD ~ 9) 174.29 (C=O); 102.71, 102.50, 102.30 (C1); 84.72 ($C4^A$); 81.98, 81.85 (C4); 74.49, 72.94, 72.49, 72.40 (C2, C3, C5); 70.79 ($C5^A$); 69.58, 69.49, 67.99 (azacoronandC-O); 60.96 (C6); 57.58, 55.28, 50.16, 49.08, 39.46 ($C6^A$, hexylC1, hexylC6, N-C-C=O, azacoronandC-N); 28.78, 28.69, 26.49, 26.36 (hexylC2-C5).

6^A-Deoxy-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-β-cyclodextrin 45

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** (0.483 g, 0.392 mmol) was added to a solution of 4-nitrophenyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate **41** (0.275 g, 0.549 mmol) in dry DMF (5 cm^3) and the mixture was stirred at room temperature for 18 hours. After the general work-up and purification procedure, the product **45** was obtained as a pale yellow solid (0.287 g, 49 %), R_c = 1.4; MALDI-TOF-MS *m/z* 1493 ($[M + H]^+$); [Found: C, 43.50; H, 7.59; N, 2.54 %. Calc. for **45**.$9H_2O$ ($C_{60}H_{123}N_3O_{48}$) C, 43.55; H, 7.49; N, 2.61 %]; δ_H(D_2O, pD ~ 9) 5.00-5.03 (m, 7H, H1); 3.70-3.90 (m, 26H, H3, H5, H6); 3.56-3.70 (m, 29H, H2, H4, azacoronandO-CH_2); 3.18-3.39 (m, 5H, $H4^A$, hexylH6, N-CH_2-C=O); 3.03-3.08 (m, 1H, $H6^A$); 2.70-2.81 (m, 5H, $H6^{A'}$, azacoronandN-CH_2); 2.52-2.57 (m, 2H, hexylH1); 1.41-1.60 (m, 4H, hexylH2, hexylH5); 1.24-1.31 (m, 4H, hexylH3, hexylH4); δ_C(D_2O, pD ~ 9) 174.10 (C=O); 103.54, 103.39, 103.33, 103.26, 103.17 (C1); 84.76 ($C4^A$); 82.22, 82.08 (C4); 74.47, 74.32, 74.21, 73.53, 72.32 (C2, C3, C5); 69.23, 68.94,

68.90, 68.72, 68.35, 67.95, 67.72 (azacoronandC-O, C6); 60.69, 58.99, 55.57, 55.22, 39.50 ($C6^A$, hexylC1, hexylC6, N-C-C=O, azacoronandC-N); 28.72, 26.36 (hexylC).

6^A-Deoxy-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-β-cyclodextrin 46

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **24** (0.404 g, 0.328 mmol) was added to a solution of 4-nitrophenyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate **42** (0.210 g, 0.450 mmol) in dry DMF (5 cm^3) and the mixture was stirred at room temperature for 18 hours. After the general work-up and purification procedure, the product **46** was obtained as a white solid (0.249 g, 50 %), R_c = 1.3; ES-MS *m/z* 1537 (M^+); [Found: C, 43.58; H, 6.70; N, 2.38 %. Calc. for **46**.9H_2O ($C_{62}H_{127}N_3O_{49}$) C, 43.84; H, 7.54; N, 2.47 %]; δ_H(D_2O, pD ~ 9) 5.02-5.05 (m, 7H, H1); 3.73-3.99 (m, 26H, H3, H5, H6); 3.53-3.69 (m, 31H, H2, H4, azacoronandO-CH_2, N-CH_2-C=O); 3.22-3.24 (m, 3H, $H4^A$, hexylH6); 3.04 (d, *J* = 14.4 Hz, 1H, $H6^A$); 2.76-2.84 (m, 5H, $H6^{A'}$, azacoronandN-CH_2); 2.59-2.61 (m, 2H, hexylH1); 1.42-1.57 (m, 4H, hexylH2, hexylH5); 1.25-1.38 (m, 4H, hexylH3, hexylH4); δ_C(D_2O, pD ~ 9) 176.90 (C=O); 104.96, 104.60, 102.61 (C1); 85.15 ($C4^A$); 84.14, 83.86 (C4); 77.02, 76.07, 75.53, 74.78, 74.67, 73.95 (C2, C3, C5); 72.63, 72.47, 72.34, 71.43 (azacoronandC-O); 62.85 (C6); 60.30, 57.46, 48.40, 46.61, 41.53 ($C6^A$, hexylC1, hexylC6, N-C-C=O, azacoronandC-N); 31.41, 29.80, 28.67, 28.26 (hexylC2-C5).

E.3 Preparation of compounds described in Chapter 3

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triazaoct-8-yl)benzene 49 [8]

α,α'-Dibromoxylene **50** (0.949 g, 3.60 mmol) in THF (50 cm^3) was added to a refluxing solution of tris(2-aminoethyl)amine **51** (11.2 g, 76.2 mmol) in THF (250 cm^3) over 2.5 hours. The solution was cooled to room temperature and filtered. Solvent was removed under reduced pressure and excess tris(2-aminoethyl)amine was partially distilled (70 °C/ 0.5 torr) from the mixture to leave a viscous brown oil. The residue was dissolved in water (50 cm^3) and β-cyclodextrin (0.150 g, 0.132 mmol) was added to 5 % of the solution. The mixture was stirred for 2 hours, loaded onto a Sephadex G10 column and the product was eluted with water. Water was removed under reduced pressure to give the product **49** as a sticky pale yellow solid (1:1.5 mixture with β-cyclodextrin), (0.751 g, 34 %), ES-MS *m/z* 395.6 ($[M + H]^+$); δ_H(D_2O, 200 MHz) 7.53 (s, 4H, ArH); 4.27 (s, 4H, benzylH); 3.15 (t,

J = 6.9 Hz, 4H, CH_2-N); 3.05 (t, J = 6.3 Hz, 8H, N-CH_2); 2.86 (t, J = 6.9 Hz, 4H, N-CH_2); 2.80 (t, J = 6.3 Hz, 8H, N-CH_2); δ_C(D_2O, pD ~7) 132.33, 131.16 (ArC); 51.23, 50.21, 48.97, 44.31, 36.86 (C-N).

1,4-Di(1-hydroxy-5-hexyn-6-yl)benzene 55

Pyrrolidine (5 cm^3) was deoxygenated by bubbling nitrogen through the liquid for 5 minutes. 1,4-Diiodobenzene **54** (1.09 g, 3.30 mmol) and palladium tetrakis(triphenylphosphine) (0.100 g) were added with stirring, followed by 5-hexyn-1-ol (0.995 g, 10.2 mmol) and copper(I) iodide (0.030 g) at 0 °C. The mixture was slowly warmed up to room temperature and stirred under nitrogen for 3 hours. Saturated ammonium chloride solution (20 cm^3) was added to the reaction mixture. The solution was extracted with ethyl acetate (2 × 20 cm^3), and the combined organic layers were washed with 3 mol dm^{-3} hydrochloric acid (25 cm^3), 10 % sodium bicarbonate solution (25 cm^3) and brine (2 × 20 cm^3), and dried (sodium sulfate). Solvent was removed under reduced pressure and the residue was recrystallised from ethyl acetate/hexane to give the product **55** as pale yellow crystals (0.727 g, 84 %), mp 82-83°C; FAB-MS *m/z* 270 (M^+); [Found: C, 79.83; H, 8.20 %. Calc. C, 79.96; H, 8.20 %]; δ_H($CDCl_3$) 7.29 (s, 4H, ArH); 3.71 (m, 4H, butylH4); 2.46 (t, J = 6.9 Hz, 4H, butylH1); 1.70-1.77 (m, 8H, butylH2, butylH3); 1.34 (broad s, 2H, OH); δ_C($CDCl_3$) 131.27, 123.03 (ArC); 91.40, 80.66 (C≡C); 62.20 (butylC4); 31.76, 24.90, 19.17 (butylC1-C3); ν_{max} (Nujol)/cm^{-1} 3250-3490b (OH), 1506m (Ar), 835s (Ar).

1,4-Di(1-bromo-5-hexyn-6-yl)benzene 56

A mixture of carbon tetrabromide (0.509 g, 1.53 mmol) and triphenylphosphine (0.398 g, 1.52 mmol) in ether (2 cm^3) was stirred under nitrogen for 5 minutes, and 1,4-di(1-hydroxy-5-hexyn-6-yl)benzene **55** (0.197 g, 0.730 mmol) was added. The mixture was stirred at room temperature (12 hours), then filtered through celite and concentrated under reduced pressure. The material was purified by flash column chromatography (5 % ethyl acetate/hexane). Appropriate fractions were combined and the solvent was removed under reduced pressure to give the product **56** as a colourless oil, which solidified upon cooling (0.260 g, 87 %); Accurate mass spectrum *m/z* 393.993 (M^+), Calc. 393.993; [Found: C, 54.31; H, 4.99 %. Calc. C, 54.57; H, 5.09 %]; δ_H($CDCl_3$) 7.30 (s, 4H, ArH); 3.46 (t, J = 6.6 Hz, 4H, butylH4); 2.46 (t, J = 8.8 Hz, 4H, butylH1); 1.71-2.07 (m, 8H, butylH2, butylH3); δ_C($CDCl_3$)

131.32, 123.02 (ArC); 90.78, 80.95 (C≡C); 33.10, 31.73, 27.02, 18.62 (butylC1-C4); ν_{max} (Nujol)/cm^{-1} 1605m (Ar), 835m (Ar).

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene 52

1,4-Di(1-bromo-5-hexyn-6-yl)benzene **56** (0.328 g, 0.829 mmol) in THF (10 cm^3) was added drop-wise over 3 hours to a refluxing solution of tris(2-aminoethyl)amine **51** (2.50 cm^3, 17.5 mmol) in THF (60 cm^3) under nitrogen. The mixture was filtered and solvent was removed under reduced pressure. Excess tris(2-aminoethyl)amine was partially removed by Kugelrohr distillation to leave a viscous orange oil. The oil was dissolved in water (10 cm^3) and extracted with hexane (2 × 5 cm^3). The aqueous layer was separated and loaded onto a Diaion HP-20 column (2.5 × 20 cm) and remaining tris(2-aminoethyl)amine and tris(2-aminoethyl)amine bromide were eluted with water followed by 5-15 % aqueous methanol (2 dm^3). The product was eluted with 0.1 % TFA/15-25 % aqueous methanol (2 dm^3). Solvent was removed under reduced pressure, and the mixture was dissolved in water (5 cm^3) and loaded onto an AG-4X4 (free base form) anion exchange column (4.5 × 2 cm). The product was eluted with water (50 cm^3). Water was removed under reduced pressure and the residue was dried to give the product **52** as a sticky pale yellow solid (0.235 g, 54 %); Accurate mass spectrum *m/z* 527.453 ([M + H]$^+$), Calc. 527.455; δ_H(D_2O/DCl, pD 7) 7.32 (s, 4H, ArH); 3.13 (t, J = 6.6 Hz, 4H, N-CH_2); 3.02-3.09 (m, 12H, N-CH_2); 2.79-2.88 (m, 12H, N-CH_2); 2.42 (t, J = 7.5 Hz, 4H, butylH1); 1.54 -1.73 (m, 8H, butylH2, butylH3); δ_C(D_2O/DCl, pD 7) 134.26, 125.70 (ArC); 95.52, 83.36 (C≡C); 57.48, 55.24, 50.86, 48.19, 40.53 (C-N); 30.52, 28.74, 21.57 (butylC1-C3).

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene 53

1,4-Di(1-bromo-5-hexyn-6-yl)benzene **56** (0.298 g, 0.753 mmol) in THF (10 cm^3) was added drop-wise over 3 hours to a refluxing solution of triethylenetetramine (2.40 cm^3, 16.4 mmol) in THF (60 cm^3) under nitrogen. The mixture was filtered and solvent was removed under reduced pressure. Excess triethylenetetramine was partially removed by Kugelrohr distillation to leave a viscous orange oil. The residue was dissolved in water (10 cm^3) and extracted with hexane (2 × 5 cm^3). The aqueous layer was separated and loaded onto a Diaion HP-20 column (2.5 × 20 cm) and remaining triethylenetetramine and triethylenetetramine bromide were eluted with water followed by 15 % methanol/water (2 dm^3). The product was eluted with 0.1 % TFA/15-25 % aqueous methanol (2 dm^3).

Solvent was removed under reduced pressure, and the mixture was dissolved in water and loaded onto an AG-4X4 (free base form) anion exchange column (4.5 × 2 cm). The product was eluted with water (50 cm^3). Water was removed under reduced pressure and the residue was dried to give the product **53** as a sticky solid (0.210 g, 53 %); Accurate mass spectrum *m/z* 527.455, Calc. 527.455 ($[M + H]^+$); $\delta_H(D_2O/DCl$, pD 7) 7.38 (s, 4H, ArH); 2.82-3.20 (m, 28H, N-CH_2); 2.46 (t, J = 6.9 Hz, 4H, butylH1); 1.59-1.90 (m, 8H, butylH2, butylH3); $\delta_C(D_2O/DCl$, pD 7) 134.31, 125.41 (ArC); 94.81, 83.59 (C≡C); 50.19, 49.17, 48.76, 48.35, 47.91, 46.79, 40.10 (C-N); 27.69, 27.56, 20.96 (butylC1-C3).

4,4'-Di(1-hydroxy-5-hexyn-6-yl)biphenyl 69

Pyrrolidine (10 cm^3) was deoxygenated by bubbling nitrogen through the liquid for 10 minutes. 1,4-Diiodobiphenyl **68** (2.04 g, 4.52 mmol) and palladium tetrakis (0.125 g) were added with stirring, followed by 5-hexyn-1-ol (1.24 g, 12.7 mmol) and copper(I) iodide (0.040 g) at 0 °C. The mixture was slowly warmed up to room temperature and stirred under nitrogen for 4 hours. Saturated ammonium chloride solution (20 cm^3) was added to the reaction mixture. The precipitate that formed was collected by suction filtration and washed successively with 3 mol dm^{-3} hydrochloric acid (25 cm^3), water (2 × 20 cm^3), 10 % sodium bicarbonate solution (25 cm^3) and water (20 cm^3). The solid was dissolved in 1:1 acetone/dichloromethane and dried (sodium sulfate). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (40 % ethyl acetate/hexane) to give the product **69** as pale yellow crystals (0.821 g, 52 %), mp = 154-156 °C; FAB-MS *m/z* 347 (M^+); [Found: C, 83.48; H, 7.58 %. Calc. C, 83.20; H, 7.56 %]; $\delta_H(CDCl_3)$ 7.51 (δ_A), 7.48 (δ_B) (AB q, J_{AB} = 6.0 Hz, 8H, ArH); 3.73 (m, 4H, butylH4); 2.44 (t, J = 6.6 Hz, 4H, butylH1); 1.69-1.79 (m, 8H, butylH2, butylH3); 1.34 (broad s, 2H, OH); $\delta_C(CDCl_3)$ 139.56, 131.94, 126.70, 123.12 (ArC); 90.80, 80.79 (C≡C); 62.49 (butylC4); 31.95, 25.04, 19.30 (butylC1-C3); ν_{max} (Nujol)/cm^{-1} 3300-3450b (OH), 1492w (Ar), 821m (Ar).

4,4'-Di(1-bromo-5-hexyn-6-yl)biphenyl 70

A mixture of carbon tetrabromide (1.60 g, 4.83 mmol) and triphenylphosphine (1.26 g, 4.80 mmol) in ether (10 cm^3) was stirred under nitrogen for 5 minutes, and 4,4'-di(1-hydroxy-5-hexyn-6-yl)biphenyl **69** (0.767 g, 2.21 mmol) was added. The mixture was stirred at room temperature (6 hours), then filtered through celite and concentrated under reduced pressure.

The residue was purified by squat column chromatography (4.5 × 5 cm, 5% ethyl acetate/hexane). Appropriate fractions were combined and the solvent was removed under reduced pressure to give the product **70** as a white solid (0.570 g, 55 %), mp 85-87°C; FAB-MS *m/z* 472 (M^+); [Found: C, 60.89; H, 5.22 %. Calc. C, 61.04; H, 5.12 %]; $\delta_H(CDCl_3)$ 7.50 (δ_A), 7.45 (δ_B) (AB q, J_{AB} = 12.0 Hz, 8H, ArH); 3.49 (t, J = 9.6 Hz, 4H, butylH4); 2.49 (t, J = 10.2 Hz, 4H, butylH1); 1.71-2.10 (m, 8H, butylH2, butylH3); $\delta_C(CDCl_3)$ 139.61, 132.00, 126.72, 122.98 (ArC); 90.17, 81.06 (C≡C); 33.20, 31.80, 27.13, 18.70 (butylC1-C4); ν_{max} (Nujol)/cm^{-1} 1488w (Ar), 823m (Ar).

4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl 67

4,4'-Di(1-bromo-5-hexyn-6-yl)biphenyl **70** (0.457 g, 0.968 mmol) in THF (10 cm^3) was added dropwise over 3 hours to a refluxing solution of tris(2-aminoethyl)amine **51** (3.50 cm^3, 23.4 mmol) in THF (80 cm^3) under nitrogen. The reaction mixture was filtered and solvent was removed under reduced pressure. Excess tris(2-aminoethyl)amine was partially removed by Kugelrohr distillation to leave a viscous orange oil. The residue was dissolved in water and loaded onto a Diaion HP-20 column (2.5 × 20 cm) and remaining tris(2-aminoethyl)amine and tris(2-aminoethyl)amine bromide were eluted with water followed by 5-20 % aqueous methanol (2 dm^3). The product was eluted with 0.1 % TFA/ 25-35 % aqueous methanol (2 dm^3). Solvent was removed under reduced pressure, and the mixture was dissolved in water and loaded onto an AG-4X4 (free base form) anion exchange column (4.5 × 2 cm). The product was eluted with water (50 cm^3). Water was removed under reduced pressure and the residue was dried to give the product **67** as a pale yellow sticky solid (0.275 g, 47 %), ES-MS *m/z* 603.5 ($[M + H]^+$); $\delta_H(D_2O/DCl$, pD 7) 7.65 (δ_A), 7.53 (δ_B) (AB q, J_{AB} = 9.0 Hz, 8H, ArH); 3.05-3.18 (m, 16H, N-CH_2); 2.80-2.89 (m, 12H, N-CH_2); 2.50 (t, J = 6.9 Hz, 4H, butylH1); 1.61-1.90 (m, 8H, butylH2, butylH3); $\delta_C(D_2O/DCl$, pD 7) 140.96, 134.86, 128.98, 125.48 (ArC); 94.53, 83.47 (C≡C); 58.73, 55.97, 51.29, 48.46, 40.76 (C-N); 31.34, 29.28, 21.89 (butylC1-C3).

General procedure for the purification of 1,4-di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene 52, 1,4-di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene 53 and 4,4'-di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl 67 as hydrochloride salts

Neat sulfuric acid (12 cm^3) was added dropwise to sodium chloride (5 g) with stirring and the hydrogen chloride generated was bubbled into a solution of the amine (~0.03 mmol) in ethanol (20 cm^3). The solid product was collected by suction filtration, washed with ethanol and ether and dried over phosphorous pentoxide/calcium chloride under reduced pressure.

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene.7HCl 52.7HCl

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene **52** (0.150 g, 0.378 mmol) was dissolved in ethanol (20 cm^3) and treated with hydrogen chloride by the general procedure to give the product **52**.7HCl as a white solid (0.220 g, 91 %), [Found: C, 41.79; H, 8.61; N, 13.53 %. Calc. for **52**.7HCl.4H_2O ($C_{30}H_{61}N_8Cl_7O_4$) C, 42.19; H, 8.14; N, 13.12 %].

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene.8HCl 53.8HCl

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene **53** (0.201 g, 0.506 mmol) was dissolved in ethanol (20 cm^3) and treated with hydrogen chloride by the general procedure to give the product **53**.8HCl as a white solid (quantitative yield), [Found: C, 39.95; H, 7.10; N, 12.31 %. Calc. for **53**.8HCl.5H_2O ($C_{30}H_{61}N_8Cl_7O_4$) C, 39.66; H, 7.99; N, 12.33 %].

4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl.7.5HCl 67.7.5HCl

4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl (0.200 g, 0.0332 mmol) was dissolved in ethanol (20 cm^3) and treated with hydrogen chloride by the general procedure to give the product **67**.7.5HCl as a white solid (0.280 g, 87 %), [Found: C, 49.10; H, 7.44; N, 12.37 %. Calc. for **67**.7.5HCl.0.5H_2O ($C_{36}H_{75.5}N_8Cl_{7.5}O_{0.5}$) C, 48.84; H, 7.57; N, 12.66 %)

***N,N'*-Bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea 73** [12]

6^A-Amino-6^A-deoxy-β-cyclodextrin **71** (0.699 g, 0.616 mmol) and 6^A-azido-6^A-deoxy-β-cyclodextrin **72** (0.651 g, 0.561 mmol) were dissolved in dry DMF (10 cm^3) and dry carbon dioxide (passed through a $CaCl_2$ drying tube) was bubbled into the solution for 45 minutes.

Triphenylphosphine (0.173 g, 0.660 mmol) in dry DMF (8 cm^3) was added over 5 hours while carbon dioxide was continuously bubbled into the solution. The solution was stirred at room temperature for 24 hours, a second portion of triphenylphosphine (0.050 g, 0.18 mmol) was added and the mixture was stirred at room temperature for a further 24 hours with continuous bubbling of carbon dioxide through the solution. The reaction mixture was concentrated under reduced pressure to approximately half the initial volume, and was added drop-wise to cold 2:1 acetone/ether (240 cm^3). The precipitate was collected by suction filtration and washed with acetone. The crude product was dissolved in 2.8 % ammonia solution (10 cm^3) and added drop-wise to cold acetone (200 cm^3). The precipitate was collected by suction filtration, washed with acetone and air-dried. The precipitate was dissolved in water (20 cm^3) and loaded onto a BioRex (H^+ form) cation exchange column (2 × 4.5 cm) and the product was eluted with water (100 cm^3). Water was removed under reduced pressure and the residue was dried to give the product **73** as a white solid (0.921 g, 71 %); $\delta_H(D_2O)$ 5.03 (m, 14H, H1); 3.50-3.71 (m, 84H, H2-H6).

General procedure for the synthesis of the cobalt(III) axle complexes 60 and 61 and the cobalt(III)-blocked [2]-rotaxanes 57, 58, 59 and 74 [14]

60 and **61**: The axle **52**, **53** or **67** (~0.076 mmol) was dissolved in 1.16 mol dm^{-3} nitric acid (~0.7 cm^3) and sodium triscarbonatocobalt(III) (~0.16 mmol) was added in portions. The solution was swirled at room temperature for 5 minutes, then diluted with water (0.5 cm^3) and heated at 65 °C with swirling for 5 minutes. The solution was filtered through cotton wool onto cold acetone (20 cm^3) and a red/pink precipitate formed. After stirring the solution at room temperature for 30 minutes, the solvent was decanted off the precipitate. The residue was dissolved in water and added drop-wise to cold acetone. The solvent was decanted off the precipitate, which was washed repeatedly with acetone and dried to give the product as a dark red solid.

57, **58**, **59** and **74**: The axle **52**, **53** or **67** (~0.076 mmol) and α-cyclodextrin, β-cyclodextrin or the cyclodextrin dimer **73** (~0.085 mmol) were dissolved in water (1 cm^3) and the mixture was allowed to stand for 2 hours. Water was removed under reduced pressure and the mixture was dissolved in 1.16 mol dm^{-3} nitric acid (~0.7 cm^3) and sodium triscarbonatocobalt(III) (~0.16 mmol) was added in portions. The reaction mixture was treated as described above for **60** and **61**.

μ-(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)-bis[diaquacobalt(III)] nitrate (μ[$(Co(H_2O)_2)_2$(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)]$(NO_3)_6$) 60

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene **52** (0.050 g, 0.095 mmol) was dissolved in 1.16 mol dm^{-3} nitric acid (0.88 cm^3) and sodium triscarbonatocobalt(III) (0.076 g, 0.21 mmol) was added in portions. After the general procedure, the product **60** was obtained as a sticky red/pink solid (0.074 g, 72 %), $\delta_H(D_2O$, pD ~7) 7.37 (s, 4H, ArH); 2.44-3.31 (m, 32H, N-CH_2, butylH1); 1.50-1.98 (m, 8H, butylH2, butylH3); $\delta_C(D_2O$, pD ~7) 134.28, 125.36 (ArC); 95.14, 83.42 (C≡C); 65.27, 64.71, 64.40, 64.24, 60.93, 60.05, 56.09, 54.40, 54.24, 54.12, 47.23, 47.02, 46.71, 46.48, 46.12 (C-N); 28.78, 28.54, 28.09, 27.97, 21.06 (butylC1-C3); λ_{max}/nm 503 (ε/dm^3 mol^{-1} cm^{-1} 283).

μ[$(Co(H_2O)_2)_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)]$(NO_3)_6$ 61

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene **53** (0.030 g, 0.057 mmol) was dissolved in 1.16 mol dm^{-3} nitric acid (0.60 cm^3) and sodium triscarbonatocobalt(III) (0.051 g, 0.14 mmol) was added in portions. After the general procedure, the product **61** was obtained as a sticky red/pink solid (0.036 g, 58 %); $\delta_H(D_2O$, pD ~7) 7.37 (s, 4H, ArH); 2.43-3.05 (m, 32H, N-CH_2, butylH1); 1.50-1.90 (m, 8H, butylH2, butylH3); $\delta_C(D_2O$, pD ~7) 134.34, 125.47 (ArC); 95.20, 83.56 (C≡C); 58.54, 58.00, 56.28, 55.28, 54.79, 54.72, 54.40, 53.95, 53.29, 52.92, 52.75, 52.44, 51.59, 49.23, 48.80, 44.24, 43.64 (C-N); 28.76, 28.15, 21.10 (butylC1-C3); λ_{max}/nm 510 (ε/dm^3 mol^{-1} cm^{-1} 275).

[2]-[μ[$(Co(H_2O)_2)_2$(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)]$(NO_3)_6$]-[β-cyclodextrin]-rotaxane 57

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene **52** (0.040 g, 0.077 mmol) and β-cyclodextrin (0.096 g, 0.085 mmol) were dissolved in water (1 cm^3) and the mixture was allowed to stand for 2 hours. Water was removed under reduced pressure and the mixture was dissolved in 1.16 mol dm^{-3} nitric acid (0.67 cm^3) and sodium triscarbonatocobalt(III) (0.0579 g, 0.160 mmol) was added in portions. After the general procedure, the product **57** was obtained as a sticky red solid (0.154 g, 83 %); $\delta_H(D_2O$, pD ~7) 7.27-7.35 (m, 4H, ArH); 4.98-5.01 (m, 7H, H1); 3.43-3.49 (m, 42H, H2-H6); 2.80-3.16 (m, 28H, N-CH_2); 2.47 (m, 4H, butylH1); 1.60-1.85 (m, 8H, butylH2, butylH3); $\delta_C(D_2O$, pD ~7) 133.76, 133.55, 125.87, 125.18 (ArC); 104.58 (C1); 95.20, 94.66 (C≡C); 83.55 (C4); 82.90,

82.65 (C≡C); 76.02, 74.75, 74.63 (C2, C3, C5); 65.32, 64.74, 64.45, 64.28 (C-N); 62.68 (C6); 60.98, 60.09, 56.10, 54.37, 54.28, 52.54, 47.22, 46.73, 46.50, 46.12 (C-N); 28.63, 28.25, 28.14, 21.24, 21.14 (butylC1-C3); λ_{max}/nm 502 (ε/dm^3 mol^{-1} cm^{-1} 247).

[2]-[μ[(Co(H$_2$O)$_2$)$_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)](NO$_3$)$_6$]-[α-cyclodextrin]-rotaxane 58

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene **53** (0.019 g, 0.037 mmol) and β-cyclodextrin (0.041 g, 0.042 mmol) were dissolved in water (1 cm^3) and the mixture was allowed to stand for 2 hours. Water was removed under reduced pressure and the mixture was dissolved in 1.16 mol dm^{-3} nitric acid (0.38 cm^3) and sodium triscarbonatocobalt(III) (0.034 g, 0.093 mmol) was added in portions. After the general procedure, the product **58** was obtained as a sticky red/pink solid (0.061 g, 76 %); δ_H(D$_2$O, pD ~7) 7.19-7.59 (m, 4H, ArH); 5.02-5.05 (m, 6H, H1); 3.59-3.87 (m, 36H, H2-H6); 2.40-3.10 (m, 32H, N-CH$_2$, butylH1); 1.54-1.93 (m, 8H, butylH2, butylH3); δ_C(D$_2$O, pD ~7) 134.63, 134.33, 133.93, 133.70, 125.40, 124.96 (ArC); 104.73 (C1); 95.21, 94.98 (C≡C); 83.69, 83.59 (C4); 83.75, 83.28, 82.95 (C≡C); 76.65, 76.59, 76.48, 74.74, 74.45, 74.30 (C2, C3, C5); 62.66 (C6); 58.13, 56.39, 55.34, 54.79, 54.46, 54.00, 53.33, 52.96, 52.78, 52.44, 49.28, 48.84, 44.04, 43.67 (C-N); 30.35, 28.71, 28.01, 23.14, 22.24, 20.97 (butylC1-C3); λ_{max}/nm 508 (ε/dm^3 mol^{-1} cm^{-1} 287).

[2]-[μ[(Co(H$_2$O)$_2$)$_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)](NO$_3$)$_6$]-[β-cyclodextrin]-rotaxane 59

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene **53** (0.035 g, 0.067 mmol) and β-cyclodextrin (0.090 g, 0.079 mmol) were dissolved in water (1 cm^3) and the mixture was allowed to stand for 2 hours. Water was removed under reduced pressure and the mixture was dissolved in 1.16 mol dm^{-3} nitric acid (0.60 cm^3) and sodium triscarbonatocobalt(III) (0.053 g, 0.14 mmol) was added in portions. After the general procedure, the product **59** was obtained as a sticky red/pink solid (0.116 g, 74 %); δ_H(D$_2$O, pD ~7) 7.29-7.39 (m, 4H, ArH); 5.01-5.04 (m, 7H, H1); 3.54-3.91 (m, 42H, H2-H6); 2.45-3.27 (m, 32H, N-CH$_2$, butylH1); 1.59-1.96 (m, 8H, butylH2, butylH3); δ_C(D$_2$O, pD ~7) 133.82, 133.66, 125.93, 125.35 (ArC); 104.71 (C1); 95.61, 94.16 (C≡C); 83.65 (C4); 83.18, 82.74 (C≡C); 76.12, 74.77, 74.69 (C2, C3, C5); 62.73 (C6); 58.06, 55.33, 54.83, 53.36, 53.16, 52.98, 52.81, 52.50, 51.73, 49.30,

48.86, 44.31, 43.73 (C-N); 28.97, 28.67, 28.47, 28.12, 21.30, 20.92 (butylC1-C3); λ_{max}/nm 511 (ε/dm^3 mol^{-1} cm^{-1} 290).

[2]-[μ[(Co(H$_2$O)$_2$)$_2$(4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl)](NO$_3$)$_6$]-[*N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea]-rotaxane 74

4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl **67** (0.015 g, 0.025 mmol) and *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** (0.060 g, 0.026 mmol) were dissolved in water (1 cm^3) with heating and the mixture was allowed to stand for 2 hours. The solution was concentrated under reduced pressure to approximately half the initial volume and warmed to redissolve the material. A solution of 1.16 mol dm^{-3} nitric acid (0.23 cm^3) was added, followed by sodium triscarbonatocobalt(III) (0.021 g, 0.055 mmol) in portions. After the general procedure, the product **74** was obtained as a sticky red/brown solid (0.052 g); δ_H(D$_2$O, pD ~7) 7.35-7.58 (m, 8H, ArH); 4.90-5.05 (m, 14H, H1); 3.30-3.94 (m, 84H, H2-H6); 3.07-3.19 (m, 16H, N-CH$_2$); 2.81-2.92 (m, 12H, N-CH$_2$); 2.551-2.62 (m, 4H, butylH1); 1.63-1.95 (m, 8H, butylH2, butylH3); λ_{max}/nm 508 (ε/dm^3 mol^{-1} cm^{-1} 235).

General procedure for the synthesis of samples of the cobalt(III) axle complexes as the chloro analogues 65 and 66 and the cobalt(III)-blocked [2]-rotaxanes as the chloro analogues 62, 63, 64 and 75 from the hydrochloride salts of the axles 52.7HCl, 53.8HCl and 67.7.5HCl [14]

65 and **66**: The axle hydrochloride salt **52**.7HCl or **53**.8HCl (~0.034 mmol) was dissolved in water (0.30 cm^3) and sodium triscarbonatocobalt(III) (~0.076 mmol) was added in portions. The solution was swirled at room temperature for 5 minutes, then heated at 65 °C with swirling for 5 minutes. The solution was filtered through cotton wool onto cold acetone (20 cm^3) to give a pink precipitate. After stirring the solution at room temperature for 30 minutes, the solvent was decanted off the precipitate and the precipitate was washed with acetone (20 cm^3). The precipitate was suspended/partially dissolved in methanol (1 cm^3) and treated with concentrated hydrochloric acid (0.060 cm^3). The solution was warmed at 65 °C for 5 minutes and the mixture was added drop-wise to acetone (10 cm^3). Acetone was decanted off the precipitate and the precipitate was washed with acetone (10 cm^3) and methanol (3 × 5 cm^3), dissolved in water and freeze-dried to give the product as a purple solid.

62, **63**, **64** and **75**: The axle hydrochloride salt **52**.7HCl, **53**.8HCl or **67**.7.5HCl (~0.034 mmol) and α-cyclodextrin, β-cyclodextrin or the cyclodextrin dimer **73** (~0.036 mmol) were dissolved in water (0.30 cm^3) and the mixture was allowed to stand for 12 hours. Sodium triscarbonatocobalt(III) (~0.076 mmol) was added in portions and the reaction mixture was treated as described above for **65** and **66**.

The ^1H NMR spectra of the products corresponded closely with those of the cobalt(III) axle complexes and cobalt(III)-blocked [2]-rotaxanes prepared as hydrates, as the chloro ligands of the complexes rapidly exchange with D_2O.

μ-(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)-bis[dichlorocobalt(III)] chloride (μ[$(CoCl_2)_2$(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)]Cl_2) 65

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene.7HCl **52**.7HCl (0.030 g, 0.035 mmol) was dissolved in water (0.30 cm^3) and sodium triscarbonatocobalt(III) (0.028 g, 0.079 mmol) was added in portions. After the general procedure, the product **65** was obtained as a purple solid (0.023 g, 73 %), ES-MS *m/z* 320.2 ($[M\text{-}2Cl^-\text{-}4HCl]^{2+}$); [Found: C, 37.80; H, 6.59; N, 11.87 %. Calc. for **65**.$2H_2O$.NaCl ($C_{30}H_{58}N_8O_2Cl_7Na$) C, 37.85; H, 6.14; N, 11.77 %]; λ_{max} (1 mol dm^{-3} NaCl)/nm 537 (ε/dm^3 mol^{-1} cm^{-1} 268).

μ[$(CoCl_2)_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)]Cl_2 66

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene.8HCl **53**.8HCl (0.030 g, 0.033 mmol) was dissolved in water (0.30 cm^3) and sodium triscarbonatocobalt(III) (0.025 g, 0.073 mmol) was added in portions. After the general procedure, the product **66** was obtained as a purple solid (0.020 g, 63 %), ES-MS *m/z* 320.2 ($[M\text{-}2Cl^-\text{-}4HCl]^{2+}$); [Found: C, 34.73; H, 6.04; N, 10.35 %. Calc. for **66**.$4H_2O$.2NaCl ($C_{30}H_{62}N_8O_4Cl_8Na_2$) C, 34.44; H, 5.97; N, 10.71 %]; λ_{max} (1 mol dm^{-3} NaCl)/nm 514 (ε/dm^3 mol^{-1} cm^{-1} 214).

[2]-[μ[$(CoCl_2)_2$(1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene)]Cl_2]-[β-cyclodextrin]-rotaxane 62

1,4-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)benzene.7HCl **52**.7HCl (0.029 g, 0.034 mmol) and β-cyclodextrin (0.041 g, 0.036 mmol) were dissolved in water (0.30 cm^3) and the mixture was allowed to stand for 12 hours. Sodium triscarbonatocobalt(III) (0.027 g, 0.076 mmol) was added in portions. After the general

procedure, the product **62** was obtained as a purple solid (0.058 g, 76 %), ES-MS *m/z* 887.5 ($[M\text{-}2Cl^{-}\text{-}4HCl]^{2+}$); [Found: C, 36.78; H, 6.19; N, 4.50 %. Calc. for **62**.$13H_2O$.2NaCl ($C_{72}H_{150}N_8O_{48}Cl_8Na_2$) C, 36.90; H, 6.45; N, 4.78 %); λ_{max} (1 mol dm^{-3} NaCl)/nm 540 (ε/dm^3 mol^{-1} cm^{-1} 274).

[2]-[μ[$(CoCl_2)_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)]Cl_2]-[α-cyclodextrin]-rotaxane 63

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene.8HCl **53**.8HCl (0.031 g, 0.034 mmol) and α-cyclodextrin (0.035 g, 0.036 mmol) were dissolved in water (0.30 cm^3) and the mixture was allowed to stand for 12 hours. Sodium triscarbonatocobalt(III) (0.027 g, 0.076 mmol) was added in portions. After the general procedure, the product **63** was obtained as a purple solid (0.049 g, 71 %), ES-MS *m/z* 806.1 ($[M\text{-}2Cl^{-}\text{-}4HCl]^{2+}$); [Found: C, 38.10; H, 6.38; N, 5.13 %. Calc. for **63**.$10H_2O$.NaCl ($C_{66}H_{134}N_8O_{40}Cl_7Na$) C, 38.32; H, 6.53; N, 5.42 %]; λ_{max} (1 mol dm^{-3} NaCl)/nm 514 (ε/dm^3 mol^{-1} cm^{-1} 231).

[2]-[μ[$(CoCl_2)_2$(1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene)]Cl_2]-[β-cyclodextrin]-rotaxane 64

1,4-Di(1,4,7,10-tetraaza-15-hexadecyn-16-yl)benzene.8HCl **53**.8HCl (0.032 g, 0.035 mmol) and β-cyclodextrin (0.042 g, 0.037 mmol) were dissolved in water (0.30 cm^3) and the mixture was allowed to stand for 12 hours. Sodium triscarbonatocobalt(III) (0.027 g, 0.076 mmol) was added in portions. After the general procedure, the product **64** was obtained as a purple solid (0.062 g, 79 %), ES-MS *m/z* 887.5 ($[M\text{-}2Cl^{-}\text{-}4HCl]^{2+}$); [Found: C, 34.75; H, 5.82; N, 4.49 %. Calc. for **64**.$17H_2O$.3NaCl ($C_{72}H_{158}N_8O_{52}Cl_9Na_3$) C, 34.96; H, 6.44; N, 4.53 %]; λ_{max} (1 mol dm^{-3} NaCl)/nm 514 (ε/dm^3 mol^{-1} cm^{-1} 220).

[2]-[μ[$(CoCl_2)_2$(4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl)]Cl_2]-[*N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea]-rotaxane 75

4,4'-Di(*N4*-(2-aminoethyl)-1,4,7-triaza-12-tridecyn-13-yl)biphenyl.7.5HCl **67**.7.5HCl (0.030 g, 0.034 mmol) and *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** (0.085 g, 0.037 mmol) were dissolved in water (1 cm^3) with gentle warming and the mixture was allowed to stand for 12 hours. Sodium triscarbonatocobalt(III) (0.027 g, 0.076 mmol) was added in portions. After the general procedure, the product **75** was obtained as a purple solid (0.068 g, 59 %), ES-MS *m/z* 1505.1 ($[M\text{-}2Cl^{-}\text{-}4HCl]^{2+}$); [Found: C, 39.85; H, 6.16; N, 3.41 %.

Calc. for **75**.17H_2O.2NaCl ($C_{121}H_{232}N_{10}O_{86}Cl_8Na_2$) C, 39.81; H, 6.41; N, 3.84 %]; λ_{max} (1 mol dm^{-3} NaCl)/nm 538 (ε/dm^3 mol^{-1} cm^{-1} 251).

E.4 Preparation of compounds described in Chapter 4

(The preparation of *N,N'*-bis(6^A-deoxy-6^A-β-cyclodextrin-6^A-yl)urea **73** has been described in section E.3)

N-(6^A-Deoxy-α-cyclodextrin-6^A-yl)-*N'*-(6^A-deoxy-β-cyclodextrin-6^A-yl)urea 77 [13]

6^A-Amino-6^A-deoxy-α-cyclodextrin **92** (0.307 g, 0.316 mmol) and 6^A-azido-6^A-deoxy-β-cyclodextrin **72** (0.338 g, 0.291 mmol) were dissolved in dry DMF (5 cm^3) and dry carbon dioxide (passed through a $CaCl_2$ drying tube) was bubbled into the solution for 15 minutes. Triphenylphosphine (0.089 g, 0.430 mmol) in dry DMF (5 cm^3) was added over 5 hours while carbon dioxide was continuously bubbled into the solution. The solution was stirred at room temperature for 24 hours, a second portion of triphenylphosphine (0.030 g, 0.11 mmol) was added and the mixture was stirred at room temperature for a further 24 hours with continuous bubbling of carbon dioxide through the solution. The solution was added drop-wise to cold 2:1 acetone/ether (150 cm^3). After allowing the fine precipitate to settle, most of the solvent was decanted off the precipitate and the precipitate was collected by gentle suction filtration and washed with acetone. The crude product was dissolved in 2.8 % ammonia solution (6 cm^3) and added drop-wise to cold acetone (150 cm^3). The precipitate was collected by suction filtration and washed with acetone. The precipitate was air-dried, dissolved in water (5 cm^3) and loaded onto a BioRex (H^+ form) cation exchange column (2 × 4.5 cm) and the product was eluted with water (100 cm^3). Water was removed under reduced pressure and the residue was dried to give the product **77** as a white solid (0.502 g, 81 %); δ_H(D_2O) 5.06 (m, 13H, H1); 3.50-3.69 (m, 78H, H2-H6).

trans-4-*t*-Butyl-4'-methoxystilbene 84

(a) A mixture of 4-*t*-butylbenzylbromide **82** (0.451 g, 1.99 mmol) and triethyl phosphite (0.5 cm^3) was stirred at 120 °C for 12 hours. Excess triethyl phosphite was removed under reduced pressure to give diethyl (4-*t*-butylbenzyl)phophonate **83** (quantitative yield), δ_H(200MHz, $CDCl_3$) 7.20-7.29 (m, 4H, ArH); 3.94-4.05 (m, 4H, CH_3-C$\underline{H}_2$-O); 3.11 (d, J = 21 Hz, 2H, CH_2-P); 1.30 (s, 9H, $C(CH_3)_3$); 1.24 (t, J = 6.8 Hz, C$\underline{H}_3$-CH_2-O).

(b) Diethyl (4-*t*-butylbenzyl)phophonate **83** (0.508 g, 1.79 mmol) was dissolved in dry THF (20 cm^3) and sodium hydride (0.067 g (60 %), 2.79 mmol) was added at 0 °C. Anisaldehyde (0.220 cm^3, 1.81 mmol) was added and the mixture was allowed to slowly warm up to room temperature. The mixture was stirred for 24 hours, followed by the addition of water (4 cm^3) and 1 mol dm^{-3} hydrochloric acid (5 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 cm^3). The combined organic layers were washed with saturated ammonium bicarbonate (15 cm^3), dried (sodium sulfate), filtered and concentrated. Purification by flash column chromatography (30 % ethyl acetate/hexane) gave the pure product **84** as white crystals (0.287 g, 60 %), mp 179-181°C; FAB-MS *m/z* 266 (M^+); [Found: C, 85.60; H, 8.01 %. Calc. C, 85.67; H, 8.32 %]; $\delta_H(CDCl_3)$ 7.45 (d, J = 9.0 Hz, 2H, ArH5); 7.43 (δ_A), 7.37 (δ_B) (AB q, J_{AB} = 9.0Hz, 4H, ArH1,2); 7.04 (d, J = 16.6 Hz, 1H, C=C-H); 6.96 (d, J = 16.6 Hz, 1H, C=C-H); 6.90 (d, J = 9.0 Hz, 2H, ArH6); 3.83 (s, 3H, O-CH_3); 1.33 (s, 9H, $C(CH_3)_3$); $\delta_C(CDCl_3)$ 150.30, 134.84, 130.33, 127.56 (ArC); 127.41, 126.40 (C=C); 125.94, 125.55, 114.07 (ArC); 55.31 (O-CH_3); 34.57 ($\underline{C}(CH_3)_3$); 31.28 ($C(\underline{C}H_3)_3$); ν_{max} (Nujol)/cm^{-1} 1602m (C=C), 1590w, 1511m (Ar), 969m (H-C=C-H), 833s (Ar).

***trans*-4-*t*-Butyl-4'-hydroxystilbene 78H**

Sodium hydride (0.242 g (60 %), 6.05 mmol) was suspended in dry DMF (10 cm^3) and ethanethiol (0.250 cm^3, 3.01 mmol) was added drop-wise at room temperature, followed by *trans*-4-*t*-butyl-4'-methoxystilbene **84** (0.297 g, 1.11 mmol). The mixture was stirred at 100 °C for 5 hours, cooled to room temperature and quenched with 3 mol dm^{-3} hydrochloric acid. Ether (5 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with more ether (2 × 5 cm^3). The combined organic layers were washed with 5 % sodium hydroxide (3 × 5 cm^3) and brine (5 cm^3), dried (sodium sulfate) and concentrated. The crude material was purified by flash column chromatography (10-25 % ethyl acetate/hexane) to give the product **78H** as a white solid (0.231 g, 83 %), mp 160-162°C; FAB-MS *m/z* 252 (M^+); [Found: C, 83.70; H, 8.15 %. Calc. for 3(**78H**).H_2O ($C_{54}H_{62}O_4$) C, 83.68; H, 8.06 %]; $\delta_H(CDCl_3)$ 7.35-7.44 (m, 6H, ArH1,2,5); 7.02 (d, J = 16.5 Hz, 1H, C=C-H); 6.94 (d, J = 16.5 Hz, 1H, C=C-H); 6.82 (d, J = 8.4Hz, 2H, ArH6); 4.86 (broad s, 1H, OH); 1.33 (s, 9H, $C(CH_3)_3$); $\delta_C(CDCl_3)$ 155.02, 150.36, 134.78, 130.56, 127.78 (ArC); 127.33, 126.49 (C=C); 125.96, 125.56, 115.54 (ArC); 34.57 ($\underline{C}(CH_3)_3$); 31.28 ($C(\underline{C}H_3)_3$);

ν_{max} (Nujol)/cm^{-1} 3150-3250b (OH), 1607m (C=C), 1592w, 1510w (Ar), 1253m (O-H), 971m (H-C=C-H), 835s (Ar).

cis-4- _t_-Butyl 4'-hydroxystilbene 80H

trans-4-_t_-Butyl-4'-hydroxystilbene **78**H (0.200 g, 0.794 mmol) was dissolved in deoxygenated methanol (15 cm^3), placed in a flask with a lightly greased stopper, and was exposed to sunlight for 24 hours. Solvent was removed under reduced pressure and the crude material was loaded onto a column of neutral alumina (15 × 2.5 cm) and eluted with 30 % ethyl acetate/hexane to give the pure *cis* isomer **80**H as a viscous oil which solidified upon cooling (0.110 g, 55 %) (recovered *trans*-isomer (0.047 g, 24 %)); FAB-MS *m/z* 252 (M^+); [Found: C, 84.18; H, 8.58 %. Calc. for 3(**80**H).H_2O ($C_{54}H_{62}O_4$) C, 83.68; H, 8.06 %]; $\delta_H(CDCl_3)$ 7.20-7.27 (m, 4H, ArH1,2); 7.17 (d, J = 8.4 Hz, 2H, ArH5); 6.71 (d, J = 8.4 Hz, 2H, ArH6); 6.47 (broad s, 2H, H-C=C-H); 4.80 (broad s, 1H, OH); 1.29 (s, 9H, $C(CH_3)_3$); $\delta_C(CDCl_3)$ 154.82, 150.28, 134.71, 130.89, 130.61 (ArC); 129.10, 129.33 (C=C); 128.84, 125.42, 115.40 (ArC); 34.81 ($\underline{C}(CH_3)_3$); 31.59 ($C(\underline{C}H_3)_3$).

4-_t_-Butyl-4'-methylcarboxystilbene (_cis_ and _trans_) 90 and 91

(a) 4-_t_-Butylbenzylbromide **82** (0.992 g, 4.37 mmol) and triphenylphosphine (1.34 g, 5.11 mmol) were added to dry benzene (12 cm^3) and the mixture was stirred under nitrogen at room temperature for 72 hours. Toluene was removed under reduced pressure and the material was washed several times with hexane to give 4-_t_-butylbenzyl(triphenyl)phosphonium bromide **89** as white crystals (1.87 g, 87 %), $\delta_H(CDCl_3)$ 7.60-7.78 (m, 15H, PPh_3); 7.14 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 2H, ArH); 7.05 (d, J = 8.4 Hz, 2H, ArH); 5.31 (d, J = 13.8 Hz, 2H, CH_2-P); 1.23 (s, 9H, $C(CH_3)_3$).

(b) A solution of sodium methoxide was prepared by adding sodium (0.115 g, 5.0 mmol) to dry methanol (2.7 cm^3). After dissolution of the sodium, the solution was added drop-wise to a solution of 4-_t_-butylbenzyl(triphenyl)phosphonium bromide **89** (1.03 g, 2.1 mmol) in methanol (5.5 cm^3) at 0 °C. The solution was stirred at 40-45 °C for 40 minutes, then cooled to 0 °C, and a solution of 4-formylmethylbenzoate (0.298 g, 1.82 mmol) in methanol (3.5 cm^3) was added drop-wise. Once the addition was complete, the mixture was heated at reflux for 3.5 hours. The solution was cooled to 0 °C and concentrated hydrochloric acid (0.55 cm^3) was added drop-wise. The resulting precipitate (which was mostly *trans*-4-_t_-butyl-4'-methylcarboxystilbene **90**) was collected by suction filtration, washed with 10 %

sodium bicarbonate solution (10 cm^3), water (2 × 10 cm^3) and methanol (2 × 10 cm^3) and dried to give *trans*-4-*t*-butyl-4'-methylcarboxystilbene **90** as white crystals (0.202 g, 38 %), mp 145-147 °C; FAB-MS *m/z* 294.4 (M^+); [Found: C, 81.59; H, 7.53 %. Calc. C, 81.64; H, 7.54 %]; $\delta_H(CDCl_3)$ 8.16 (d, J = 4.2 Hz, 2H, ArH6); 7.55 (d, J = 4.2 Hz, 2H, ArH5); 7.47 (δ_A), 7.40 (δ_B) (AB q, J = 9.0 Hz, 4H, ArH1,2); 7.21 (d, J = 16.2 Hz, 1H, C=C-H); 7.08 (d, J = 16.2 Hz, 1H, C=C-H); 3.92 (s, 3H, CH_3-O); 1.33 (s, 9H, $C(CH_3)_3$); $\delta_C(CDCl_3)$ 166.87 (C=O); 151.52, 142.09, 134.01 (ArC); 131.10 (C=C); 129.99, 128.74 (ArC); 126.81 (C=C); 126.55, 126.19, 125.70 (ArC); 51.97 (CH_3-O); 34.67 ($\underline{C}(CH_3)_3$); 31.24 ($C(\underline{C}H_3)_3$); ν_{max} (Nujol)/cm^{-1} 1718s (C=O); 1599m (C=C); 1502w (Ar); 849m (Ar).

The filtrate remaining after precipitation of the *trans* stilbene was concentrated and the residue was extracted with toluene (15 cm^3), ethyl acetate (15 cm^3) and chloroform (15 cm^3). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (2.5-5 % ethyl acetate/hexane) to give *cis*-4-*t*-butyl-4'-methylcarboxystilbene **91** as a white sticky solid (0.110 g, 21 %), FAB-MS *m/z* 295.4 ($[M + H]^+$); $\delta_H(CDCl_3)$ 7.91 (d, J = 8.1 Hz, 2H, ArH6); 7.35 (d, J = 8.1 Hz, 2H, ArH5); 7.24 (d, J = 8.4 Hz, 2H, ArH1); 7.16 (d, J = 8.4 Hz, 2H, ArH2); 6.66 (d, J = 12 Hz, 1H, C=C-H); 6.56 (d, J = 12 Hz, 1H, C=C-H); 3.90, (s, 3H, CH_3-O); 1.29 (s, 9H, $C(CH_3)_3$); $\delta_C(CDCl_3)$ 166.94 (C=O); 150.69, 142.48, 133.64 (ArC); 132.05 (C=C); 129.50, 128.80, 128.58 (ArC); 128.51 (C=C); 125.19 (ArC); 51.96 (CH_3-O); 34.56 ($\underline{C}(CH_3)_3$); 31.22 ($C(\underline{C}H_3)_3$).

trans-4-*t*-Butyl-4'-stilbenecarboxylic acid 79H

trans-4-*t*-Butyl-4'-methylcarboxystilbene **90** (0.110 g, 0.374 mmol) was suspended in a mixture of ethylene glycol (3 cm^3) and water (2 cm^3), and sodium hydroxide (0.250 g, 6.25 mmol) was added. The mixture was heated at reflux (16 hours), diluted with water (20 cm^3) and heated at reflux for a further 1 hour. After cooling the mixture to room temperature, it was acidified with concentrated hydrochloric acid to pH 1. The mixture was extracted with ether (6 × 20 cm^3) and the solution was dried (sodium sulfate) and concentrated. The residue was dissolved in THF (1 cm^3) and added drop-wise to hexane (10 cm^3). The precipitate was collected by suction filtration and washed with hexane (2 cm^3) to give the product **79H** as a white powder (0.065 g, 62 %), mp >206 °C (dec.); FAB-MS *m/z* 280.4 (M^+); [Found: C, 81.61; H, 7.11 %. Calc. C, 81.31; H, 7.19 %]; $\delta_H(d_6\text{-DMSO})$ 7.93 (d, J = 8.1 Hz, 2H, ArH6); 7.70 (d, J = 8.1 Hz, 2H, ArH5); 7.57 (d, J = 8.4 Hz, 2H, ArH); 7.42 (d, J = 8.4 Hz, 2H, ArH); 7.39 (d, J = 16.5 Hz, 1H, C=C-H); 7.27 (d, J = 16.5 Hz, 1H,

C=C-H); 1.29 (s, 9H, $C(CH_3)_3$); δ_C(d_6-DMSO) 166.96 (C=O); 150.81, 141.50, 133.81 (ArC); 130.73 (C=C); 129.66, 129.24 (ArC); 126.51 (C=C, ArC); 126.5, 120.44 (ArC); 34.31 ($\underline{C}(CH_3)_3$); 30.95 ($C(\underline{C}H_3)_3$); ν_{max} (Nujol)/cm^{-1} 2500-2900b (OH), 1681s (C=O); 1601m (C=C); 1594w, 1502w (Ar); 850m (Ar).

cis-4-*t*-Butyl-4'-stilbenecarboxylic acid 81H

cis-4-*t*-Butyl-4'-methylcarboxystilbene **91** (0.055 g, 0.186 mmol) was suspended in a mixture of ethylene glycol (1.5 cm^3) and water (0.5 cm^3) and sodium hydroxide (0.100 g, 2.50 mmol) was added. The mixture was stirred at reflux for 5 hours in the dark, diluted with water (2 cm^3) and heated at reflux for a further 1 hour. After cooling the mixture to room temperature, it was acidified with concentrated hydrochloric acid to pH 1. The resulting precipitate was collected by suction filtration, washed with water (2 cm^3) and cold ethanol (1 cm^3) and dried to give the product **81**H as a white solid (0.043 g, 82 %), FAB-MS *m/z* 281.4 ($[M + H]^+$); [Found: C, 79.79; H, 7.11 %. Calc. for 3(**81**H).H_2O ($C_{57}H_{62}O_7$) C, 79.67; H, 7.27 %]; δ_H(d_6-DMSO) 7.83 (d, J = 8.1 Hz, 2H, ArH6); 7.34 (d, J = 8.1 Hz, 2H, ArH5); 7.28 (d, J = 8.4 Hz, 2H, ArH); 7.14 (d, J = 8.4 Hz, 2H, ArH); 6.71 (δ_A), 6.62 (δ_B) (AB q, J_{AB} = 12 Hz, 2H, H-C=C-H); 1.24 (s, 9H, $C(CH_3)_3$); δ_C(d_6-DMSO) 167.08 (C=O); 150.13, 141.49, 133.34 (ArC); 131.43 (C=C); 129.83, 129.33 (ArC); 128.55 (C=C); 128.42, 128.30, 125.08 (ArC); 34.25 ($\underline{C}(CH_3)_3$); 30.96 ($C(\underline{C}H_3)_3$).

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Appendix

Copies of publications

Size discrimination in intramolecular complexation of modified α-cyclodextrins: † a preparative and nuclear magnetic resonance study ‡

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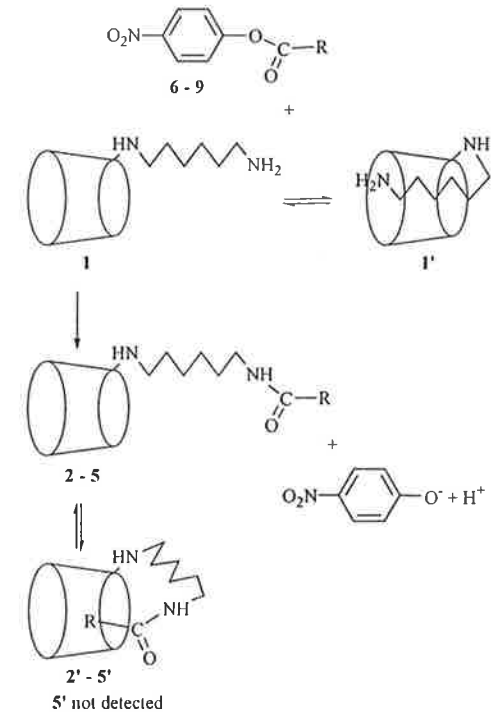
Acylation of the primary amine group of 6^A-(6-aminohexylamino)-6^A-deoxy-α-cyclodextrin **1** by 4-nitrophenyl trinorbornane-2-acetate **6**, 1-methoxycarbonyl-8-(4-nitrophenoxycarbonyl)cubane **7**, 1-methoxycarbonyl-2,3-dimethyl-8-(4-nitrophenoxycarbonyl)cubane **8**, and 1-(4-nitrophenoxycarbonyl)adamantane **9**, respectively, gives 6^A-deoxy-[6-(trinorbornan-2-ylacetylamino)hexylamino]-α-cyclodextrin **2**, 6^A-[6-(8-carboxycuban-1-ylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin **3**, 6^A-[6-(8-carboxy-2,3-dimethylcuban-1-ylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin **4**, and 6^A-[6-(adamantan-1-ylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin **5**, in good yields together with 4-nitrophenolate. In basic D_2O, the substituents of **1**–**4** complex intramolecularly within the α-cyclodextrin annulus, whereas that of **5** does not due to its larger size, as shown by ^{1}H ROESY NMR spectroscopy. This facilitates a mechanistic comparison with the formation of βCD analogues of **2**–**5**.

Introduction

α-Cyclodextrin (αCD), βCD and γCD are composed of six, seven and eight α-1,4 linked glucopyranose residues, respectively, are doughnut shaped, and possess annuli with hydrophobic interiors. In water, they and their modified forms act as hosts in a wide range of inter- and intramolecular host–guest complexes where many of the guests contain aromatic groups which, because of their hydrophobic nature, are usually positioned in the CD annulus in the host–guest complex.[1–3] However, because of their planarity, aromatic guests only occupy a portion of the truncated cone-shaped volume of CD annuli, and most other guests studied do likewise. In reactions where the guest undergoes elaboration after formation of an intermolecular host–guest complex, as in the formation of rotaxanes and catenanes,[4–6] it is desirable that this complex should be as stable as possible. It is anticipated that the closer the fit of the guest to the CD annulus, the greater will be the stability of the host–guest complex, as is supported by the increasingly high stabilities observed for αCD and βCD host–guest complexes as the annular fit of guests derived from bridged cycloalkanes improves.

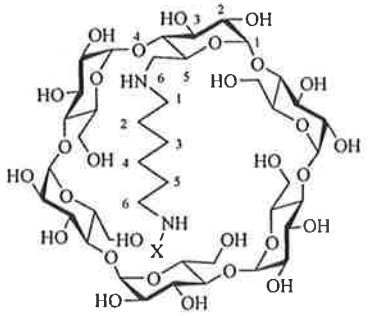
We are particularly interested in guests containing the cubyl entity[7,8] as it is both hydrophobic and appears to closely fit the annulus of αCD which we have used to form rotaxanes and related mechanically restrained species.[6,9] However, poor water solubility of simple cubyl and dimethylcubyl derivatives hampersstudiesoftheirintermolecularcomplexation.Fortunately, both are solubilised when tethered to αCD at C(6), as in structures **3** and **4**, through substitution at the primary amine of **1** as shown in Scheme 1. By comparison with an intermolecular complex, the amidohexylamino tether confers an entropic advantage on the intramolecular complex, and is of sufficient length to allow intramolecular complexation if the sizes of the cubyl, dimethylcubyl, trinorbornylmethyl, and adamantyl entities and the αCD annulus are compatible (Scheme 1). The latter two entities were added to the study because they are smaller and larger than the cubyl and dimethylcubyl entities, respectively, and thereby provide an opportunity to experimentally calibrate the size of the αCD annulus through a ^{1}H ROESY NMR spectroscopic study of NOE interactions



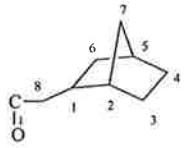
Scheme 1

† α-Cyclodextrin = cyclomaltohexaose.
‡ Electronic supplementary information (ESI) available: ROESY spectra of **4'**, **5**, **1'**, **3** and **1**. See http://www.rsc.org/suppdata/p1/b1/b107324a/

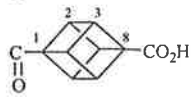
between protons inside the αCD annulus and those of the substituents of **2**–**5**. This also facilitates a mechanistic comparison with analogous βCD systems.[7,8]



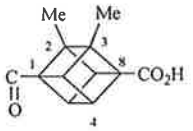
1 and **1'** X = H



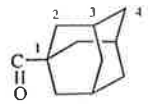
2 and **2'** X =



3 and **3'** X =



4 and **4'** X =



5 X =
5' not detected

Results and discussion

Acylation of the primary amine group of 6^A-(6-aminohexylamino)-6^A-deoxy-α-cyclodextrin, **1** (Scheme 1), by 4-nitrophenyl trinorbornane-2-acetate **6**, 1-methoxycarbonyl-8-(4-nitrophenoxycarbonyl)cubane **7**, 1-methoxycarbonyl-2,3-dimethyl-8-(4-nitrophenoxycarbonyl)cubane **8**, and 1-(4-nitrophenoxycarbonyl)adamantane **9**, respectively, produces 6^A-[6-(trinorbornan-2-ylacetylamino)hexylamino]-6^A-deoxy-α-cyclodextrin **2**, 6^A-deoxy-6^A-[6-(8-carboxycuban-1-ylcarbonylamino)hexylamino]-α-cyclodextrin **3**, 6^A-deoxy-6^A-[6-(8-carboxy-2,3-dimethylcuban-1-ylcarbonylamino)hexylamino]-α-cyclodextrin **4**, and 6^A-[6-(adamantan-1-ylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin, **5**, in good yield. It was found that the methyl ester groups of esters of **3**/**3'** and **4**/**4'** initially produced were partially hydrolysed in water during the work-up procedures. To avoid mixed products this hydrolysis was taken to completion by heating the esters of **3**/**3'** and **4**/**4'** in water and in water made slightly basic with triethylamine, respectively, at 80 °C for 24 h.

In D_2O at pD ≥ 12 where no protonation of the substituent amino group occurs, substituents of **1**–**4** complex within the αCD annulus to form **1'**–**4'** (Scheme 1), whereas that of **5** does not due to its larger size, as is discussed below. The ^{1}H ROESY NMR spectrum of **1**/**1'** shows strong cross-peaks arising from NOE interactions between the hexyl protons and the αCD H3 and H5 protons consistent with the hexyl entity entering the αCD annulus. (The 599.957 MHz ^{1}H NMR ROESY spectra of **1**/**1'**, **3**/**3'**, **4**/**4'**, and **5** appear in the Supplementary Data.) Also observed are cross-peaks arising from interactions between the H1–H6 protons of the hexyl entity and from interactions among the αCD H1, H2, H3, H5 and H6 protons, as is also the case in the other spectra discussed below. The analogous spectrum of **2**/**2'** shows strong cross-peaks between the trinorbornylmethyl protons and the αCD H3 and H5 protons (Fig. 1). Some of the resonances overlap with those of hexyl H2–H5 and it is possible that some of the cross peaks observed in Fig. 1 may arise from dipolar interactions between hexyl H2–H5 and αCD H3 and H5. No cross-peaks between the hexyl protons and the αCD H3 and H5 protons of **3**/**3'** and **4**/**4'** are observed, consistent with the cubyl and dimethycubyl entities complexing more strongly than the hexyl entity in the αCD annulus. The small chemical-shift difference between the resonances of the cubyl protons and those of the H3 and H5 of **3**/**3'** does not allow cross-peaks between them to be unequivocally identified; however, strong cross peaks between the methyl protons and the H3 and H5 protons of **4**/**4'** are clearly seen. No cross-peaks between the adamantyl entity and the H3 and H5 protons of **5** are observed. Neither are cross-peaks between the hexyl protons and the H3 and H5 protons observed, consistent with the adamantyl entity being too big to enter the αCD annulus and with the hexyl entity being too short to enter the αCD annulus while tethering the adamantyl entity. (Intramolecular complexation of aromatic substituents of modified βCDs is well established, particularly in the case of those incorporating the dansyl entity.[10]) The spectra were obtained at pD ≥ 12 under which circumstances some deprotonation may have occurred as the pK_as of OH(2) and OH(3) are 12.33 for native αCD.[3]

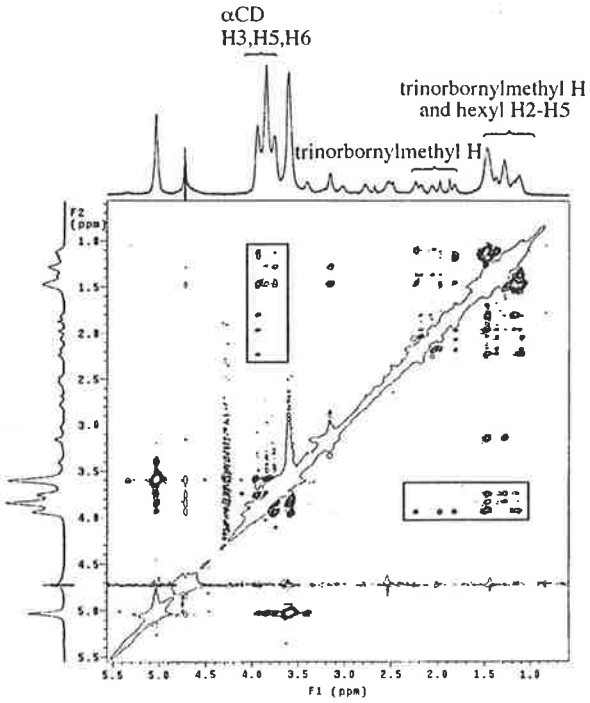


Fig. 1 ^{1}H (599.957 MHz) NMR ROESY spectrum of **2'** in D_2O at pH ≥12. The rectangles enclose the cross-peaks arising from NOE interactions between the trinorbornylmethyl protons and the αCD H3, H5 and H6 protons.

These complexations are similar to those observed for the βCD analogues of **2**–**4** where intramolecular complexation of the trinorbornylmethyl, cubyl and dimethylcubyl entities also occurred.[7,8] However, the βCD analogue of **5** showed strong cross-peaks arising from NOE interactions between the adamantyl protons and the H3 and H5 protons of βCD in its ^{1}H ROESY NMR spectrum, whereas such cross-peaks are not observed for **5**. This is consistent with the primary end of the βCD annulus being sufficiently wide to allow entry of the adamantyl entity, whereas that of αCD is not as a consequence of its smaller diameter resulting from one less glucopyranose unit composing the αCD macrocycle.

These observations resolve a mechanistic quandary associated with the formation of the βCD analogues of **2**–**5**, where in each case intramolecular complexation occurred to form βCD

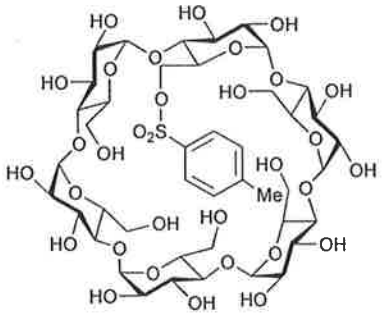
analogues of 2′–5′. Two mechanistic possibilities arise. In the first, intramolecular complexation occurs after attachment of the trinorbornylmethyl, cubyl, dimethylcubyl and adamantyl (only for βCD) entities to the tether as shown in Scheme 1. In the second, the intramolecularly complexed aminohexylamine substituent of **1** makes a nucleophilic attack on the carbonyl carbon of the 4-nitrophenyl ester precursors of the trinorbornylmethyl, cubyl, dimethylcubyl and adamantyl entities through the wide end of either the αCD or βCD annulus to form a molecular knot.§ This is indistinguishable from the intramolecular complex formed through the first mechanism, unless the substituents are too large to pass through the narrow end of the annulus. This was tested in the βCD system by competing the intramolecular formation of **2′–5′** against the intermolecular complexation of adamantane-1-carboxylate by **2–5**.[7,8] Adamantane-1-carboxylate displaced the tethered trinorbornylmethyl, cubyl and dimethycubyl entities from the βCD annulus. However, the tethered adamantyl entity was not displaced from the βCD annulus, consistent with the tethered adamantyl entity either being too large to pass through the narrow end of the annulus, or possessing an entropic advantage in competing with adamantane-1-carboxylate for occupancy of the annulus.[7] The new αCD data showing the formation of **2′–4′**, but not **5′**, is inconsistent with the intramolecularly complexed aminohexylamine substituent of **1** making a nucleophilic attack on the carbonyl carbon of the 4-nitrophenyl ester precursors to form a molecular knot. The inability of adamantane-1-carboxylate to displace the adamantyl entity from the annulus of **5′** in the βCD system is attributable to the entropic advantage gained by being tethered.

Experimental

General

^{1}H (300.145 MHz) and ^{13}C{^{1}H} (75.47 MHz) NMR spectra were recorded using a Varian Gemini 300 NMR spectrometer. ^{1}H (599.957 MHz) 2D-ROESY NMR spectra were recorded on a Varian Inova 600 spectrometer using a standard sequence with a mixing time of 0.3 s.[10] Modified αCD derivatives were dissolved in 0.1 mol dm^{-3} NaOH in D_2O to give concentrations of approximately 0.06 mol dm^{-3} and pH 12. MALDI-TOF mass spectrometry was carried out at the Research School of Chemistry at the Australian National University, Canberra, ACT. ESI mass spectrometric studies were made in positive-ion mode with a Finnigan MAT-ion trap LC-Q mass spectrometer fitted with an electrospray ionisation source. Accurate mass spectrometry was carried out at the University of Tasmania, Hobart. Samples were dissolved in water for injection. Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. As modified αCDs have water molecules associated with them, they were characterised by adding whole numbers of water molecules to the molecular formula to give the best fit to the microanalytical data. Thin layer chromatography (TLC) was carried out on Kieselgel 60 F254 (Merck) on aluminium-backed sheets. Plates were developed with 7 : 7 : 5 : 4 v/v ethyl acetate–propan-2-ol–ammonium hydroxide–water. αCDs were visualised by drying the plate then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat gun. To visualise αCDs bearing amino groups, plates were dried then dipped into a 0.5% ninhydrin in ethanol solution and heated with a heat-gun, prior to being dipped in the acid solution. The value R_c represents the R_f of a modified αCD relative to the R_f of the parent cyclodextrin.

All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. α-CD (Nihon Shokuhin Kako Co.) was dried by heating at 100 °C under vacuum for 18 h. Pyridine and 1-methylpyrrolidin-2-one (NMP) were dried by distillation from calcium hydride. *N,N′*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. The 4-nitrophenol esters **6–9**, were prepared by reaction of the corresponding carboxylic acids with 4-nitrophenol in the presence of dicyclohexylcarbodiimide.[7] 6^A-*O*-(4-Methylphenylsulfonyl)-α-cyclodextrin **10** was prepared by a literature method.[11]



10

6^A-(6-Aminohexylamino)-6^A-deoxy-α-cyclodextrin 1

A solution of **10** (0.495 g, 0.44 mmol) and 1,6-diaminohexane (0.201 g, 1.73 mmol) in dry NMP (2 cm^3) was stirred in a lightly stoppered flask at 70 °C for 18 h. Ethanol (50 cm^3) was added and the pale orange precipitate was collected by vacuum filtration and washed successively with ethanol (50 cm^3) then diethyl ether (30 cm^3). The solid was dissolved in water (5 cm^3) and loaded onto a BioRex 70 (H$^+$-form) cation-exchange column (4.5 cm × 4.5 cm). αCD and **10** were washed off the column with water and **1** was eluted with 1 mol dm^{-3} aq. ammonia. Water was removed under reduced pressure and the residue was dissolved in water (10 cm^3) and concentrated under vacuum to remove ammonia. This process was repeated three times. The product **1** was obtained as an off-white powder after freeze-drying (0.213 g, 44%), R_c = 0.60 [Found: C, 43.83; H, 7.14; N, 2.33. Calc. for **1**·4H_2O ($C_{42}H_{82}N_2O_{33}$): C, 44.13; H, 7.23; N, 2.45%]; δ_H(D_2O–NaOH, pH 12) 5.04 (s, 6H, H1), 3.82–3.97 (m, 22H, H3, H5, H6), 3.58–3.66 (m, 11H, H2, H4), 3.45 (t, J = 9.0 Hz, 1H, H4^A), 3.05 (d, J = 12.0 Hz, 1 H, 6^A), 2.75–2.91 (m, 3H, H6$^{A\prime}$, hexyl H6), 2.50–2.61 (m, 2H, hexyl H1), 1.44–1.67 (m, 4H, hexyl H2, hexyl H5), 1.31–1.44 (m, 4H, hexyl H3, H4); δ_C(D_2O–NaOH, pH 12) 104.15, 103.98 (C1), 84.47 (C4^A), 83.99, 83.84 (C4), 75.98, 74.75, 74.37 (C2, C3, C5), 73.30 (C5^A), 63.02 (C6), 52.29, 51.77 (C6^A, hexyl C6), 42.68, (hexyl C1), 31.27, 29.19, 28.95, 28.77 (hexyl C2–C5); MALDI-TOF mass spectrum *m/z* 1072 (M + H$^+$).

General procedure for synthesis of the modified αCDs 2–5

Typically, a DMF (3 cm^3) solution of **1** (≈0.190 mmol) and the appropriate 4-nitrophenyl ester (≈0.230 mmol) was stirred at room temperature for 12 h. The reaction mixture was then added dropwise to cold acetone (50 cm^3) and the precipitate which formed was collected by suction filtration and washed successively with acetone (30 cm^3) and 1 : 1 acetone–diethyl ether (30 cm^3). The precipitate was dissolved in water (3 cm^3) and acidified to pH 1, then washed with dichloromethane (35 cm^3). Dichloromethane (from the partially emulsified aqueous

§ It should be noted that despite the absence of the hydrophobic driving force for complexation in DMF in which the preparation of **2–5** and of their βCD analogues was carried out, the dipole–dipole, instantaneous dipole and related secondary bonding forces driving intramolecular complexation remain. This results in substantial intramolecular complexation of the 6-aminohexylamino substituent in the CD annulus. This is shown by the ^{1}H NMR ROESY spectrum of 6^A-(6-aminohexylamino)-6^A-deoxy-β-cyclodextrin in [$^2H_7$]DMF where strong cross-peaks between hexyl H2–H5 and βCD H3 and H5 exist consistent with substantial intramolecular complexation as seen in Fig. S5 of the Supplementary Data.)

phase) was removed under reduced pressure and the solution was loaded onto an AG-4X4 (free-base-form)-anion-exchange column (4.5 cm × 4.5 cm). The modified αCD was eluted with water (100 cm^3). Water was removed under reduced pressure to leave a pale yellow solid, which was dissolved in water (3 cm^3) and loaded onto a BioRex 70 (NH_4^+-form) cation-exchange column (4.5 cm × 4.5 cm). Elution with water (≈200 cm^3) removed the modified αCD. Fractions containing the modified αCD were combined and water was removed under vacuum. The residue was freeze-dried to yield the modified αCD as a white solid.

6^A-Deoxy-[6-(trinorbornan-2-ylacetylamino)hexylamino]-α-cyclodextrin 2. A DMF (3 cm^3) solution of **1** (0.205 g, 0.191 mmol) and 1-(4-nitrophenyloxycarbonylmethyl)trinorborane **6** (0.0547 g, 0.199 mmol) was stirred at room temperature for 12 h and **2** was obtained as a white solid after purification (0.051 g, 22%), R_c = 1.2 [Found: C, 44.12; H, 7.00; N, 2.29. Calc. for **2**·9H_2O ($C_{50}H_{102}N_2O_{39}$): C, 44.13; H, 7.59; N, 2.07%]; δ_H(D_2O–NaOH, pH 12) 4.88–4.93 (m, 6H, H1), 3.73–3.93 (m, 22H, H3, H5, H6), 3.21–3.62 (m, 12H, H2, H4), 3.10 (t, J = 6.6 Hz, 1H, hexyl H6), 3.94 (d, J = 6.0 Hz, 1H, $H6^A$), 2.29–3.82 (m, 4H, hexyl H1, $H6^{A'}$, trinorbornylmethyl H), 1.83–2.20 (m, 4H, trinorbornylmethyl H), 1.71–1.78 (m, 1H, hexyl H6), 1.01–1.63 (m, 16H, hexyl H2–hexyl H5, trinorbornylmethyl H); δ_C(D_2O–NaOH, pH 12) 178.79 (C=O), 105.04 (C1), 87.04 ($C4^A$), 84.39 (C4), 76.86, 76.75, 75.29, 74.86 (C2, C3, C5), 72.92 ($C5^A$), 63.27 (C6), 52.20, 51.23 (hexyl C1, $C6^A$), 45.44, 43.36, 41.90, 39.65, 39.27, 37.45 (trinorbornylmethyl C), 33.58, 32.21, 30.95, 28.72, 28.57 (hexyl C). Accurate mass spectrum *m/z* 1207.528. Calc. 1207.534 (M + H^+).

6^A-[6-(8-Carboxycuban-1-ylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin 3. A DMF (3 cm^3) solution of **1** (0.208 g, 0.194 mmol) and 1-(4-nitrophenoxycarbonyl)-8-(methoxycarbonyl)cubane **7** (0.083 g, 0.253 mmol) was stirred at room temperature for 12 h. Analysis by TLC of the residue after the general purification treatment revealed two spots of high R_f (R_c = 1.8, 1.9). After stirring of the residue in water (20 cm^3) at 80 °C for 24 h, analysis by TLC revealed a single spot of high R_f (R_c = 1.5). Water was removed under reduced pressure and the residue was freeze-dried to yield **3** as a white solid (0.041 g, 17%) [Found: C, 44.05; H, 6.52; N, 1.88. Calc. for **3**·9H_2O ($C_{52}H_{98}N_2O_{41}$): C, 44.36; H, 7.02; N, 1.99%]; δ_H(D_2O) 5.01–5.09 (m, 6H, H1), 4.08–4.10 (m, 3H, cubyl H), 4.03–4.07 (m, 3H, cubyl H), 3.67–3.99 (m, 22H, H3, H5, H6), 3.54–3.65 (m, 11H, H2, H4), 3.47–3.52 (m, 2H, $H4^A$, $H6^A$), 3.28–3.31 (m, 1H, $H6^{A'}$), 3.18 (t, J = 5.8 Hz, 2H, hexyl H6), 2.99–3.04 (m, 2H, hexyl H1), 1.46–1.69 (m, 4H, hexyl H2, hexyl H5), 1.29–1.36 (m, 4H, hexyl H3, hexyl H4); δ_C(D_2O) 181.96 (C=O), 175.49 (C=O), 102.34, 101.67, 101.31 (C1), 83.35 ($C4^A$), 81.76, 81.51, 81.45, 81.38 (C4), 73.65, 73.60, 73.53, 73.36, 73.31, 72.84, 72.55, 72.39, 72.34, 72.23 (C2, C3, C5), 68.17 ($C5^A$), 61.05, 60.75 (C6), 59.14, 57.86 ($C6^A$, hexyl C6), 48.56, 48.40, 47.17, 47.03, 46.63, 46.58, 46.41, 39.16 (cubyl C); 39.16 (hexyl C1), 28.44, 25.68, 25.64, 25.50 (hexyl C2, hexyl C3, hexyl C4, hexyl C5). ESMS spectrum *m/z* 1245.5 (M + H^+).

6^A-[6-(8-Carboxy-2,3-dimethylcuban-1-ylcarbonylamino)-hexylamino]-6^A-deoxy-α-cyclodextrin 4. A DMF (3 cm^3) solution of **1** (0.223 g, 0.208 mmol) and 2,3-dimethyl-1-(4-nitrophenoxycarbonyl)-8-(methoxycarbonyl)cubane **8** (0.080 g, 0.224 mmol) was stirred at room temperature for 12 h. After the general purification procedure, the product was stirred in water (20 cm^3) with 1 drop of triethylamine (24 h). Analysis by TLC revealed one product (R_c = 1.0). The product was obtained as a white powder after freeze-drying (0.049 g, 19%) [Found: C, 45.46; H, 7.04; N, 1.89. Calc. for **4**·9H_2O ($C_{54}H_{102}N_2O_{41}$): C, 45.19; H, 7.16; N, 1.95%]; δ_H(D_2O) 5.02–5.08 (m, 6H, H1), 4.04 (t, J = 10.7 Hz, 1H, $H5^A$), 3.68–3.98 (m, 27H, H3, H5, H6, cubyl H), 3.47–3.65 (m, 13H, H2, H4, $H6^A$), 3.25–3.31 (m, 1H, $H6^{A'}$), 3.18 (t, J = 6.6 Hz, 2H, hexyl H6), 2.95–3.05 (m, 2H, hexyl H1), 1.62–1.68 (m, 2H, hexyl H2), 1.46–1.50 (m, 2H, hexyl H5), 1.29–1.36 (m, 4H, hexyl H3, hexyl H4), 1.34 (s, 3H, Me), 1.44 (s, 3H, Me); δ_C(D_2O) 183.40 (C=O), 176.89 (C=O), 104.15, 103.79 (C1), 85.87 ($C4^A$), 85.86, 84.22, 83.98, 83.93, 83.66 (C4), 76.13, 76.08, 76.01, 75.84, 75.80, 75.33, 75.02, 74.87, 74.71, 74.37, 74.16 (C2, C3, C5), 70.78 ($C5^A$), 63.52, 63.24 (C6), 60.97, 59.75 ($C6^A$, hexyl C6), 58.78, 58.03, 51.07, 50.95, 50.48, 49.51, 46.80, 45.67 (cubyl C), 41.54 (hexyl C1), 31.16, 28.22, 28.16 (hexyl C2, hexyl C3, hexyl C4, hexyl C5). Accurate mass spectrum *m/z* 1273.507. Calc. 1273.508 (M + H^+).

6^A-[6-(1-Adamantylcarbonylamino)hexylamino]-6^A-deoxy-α-cyclodextrin 5. A DMF (3 cm^3) solution of **1** (0.193 g, 0.180 mmol) and 1-(4-nitrophenoxycarbonyl)adamantane **9** (0.0694 g, 0.230 mmol) was stirred at room temperature for 12 h. After purification, **5** was collected as a white solid (0.0840 g, 38%), R_c = 1.7 [Found: C, 47.64; H, 6.92; N, 2.14. Calc. for **5**·6H_2O ($C_{53}H_{100}N_2O_{36}$): C, 47.46; H, 7.41; N, 2.09%]; δ_H(D_2O–NaOH, pH 12) 4.98 (s, 6H, H1 + solvent), 3.76–3.92 (m, 22H, H3, H5, H6), 3.39–3.49 (m, 11H, H2, H4), 3.23 (t, J = 8.7 Hz, 1H, $H4^A$), 3.13 (t, J = 5.8 Hz, 2H, hexyl H6), 3.01 (d, J = 11.6 Hz, 1H, $H6^A$), 2.61–2.69 (m, 1H, $H6^{A'}$), 2.47–2.52 (m, 2H, hexyl H1), 1.62–2.00 (m, 15H, adamantyl H), 1.41–1.49 (m, 4H, hexyl H2, hexyl H5), 1.25–1.31 (m, 4H, hexyl H3, hexyl H4). δ_C(D_2O–NaOH, pH 12) 184.22 (C=O), 105.13, 104.94, 104.78, 104.69 (C1), 87.13 ($C4^A$), 84.38, 84.27 (C4), 76.89, 75.34, 74.97, 74.85 (C2, C3, C5), 73.11 ($C5^A$), 63.36 (C6), 52.51, 51.35 ($C6^A$, hexyl C6), 43.28, 41.85 (hexyl C), 41.34, 38.69 (adamantyl C), 31.06, (hexyl C), 30.51 (adamantyl C), 28.83, 28.49 (hexyl C). MALDI-TOF mass spectrum *m/z* 1234.4 (M + H^+).

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Cyclodextrin complexation of a stilbene and the self-assembly of a simple molecular device †

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(*E*)-4-*tert*-Butyl-4′-oxystilbene, **1**$^-$, is thermally stable as the (*E*)-**1**$^-$ isomer but may be photoisomerized to the (*Z*)-**1**$^-$ isomer as shown by UV-vis and ^{1}H NMR studies in aqueous solution. When (*E*)-**1**$^-$ is complexed by αCD two inclusion isomers (includomers) form in which αCD assumes either of the two possible orientations about the axis of (*E*)-**1**$^-$ in αCD·(*E*)-**1**$^-$ for which ^{1}H NMR studies yield the parameters: k_1(298 K) = 12.3 ± 0.6 s^{-1}, $\Delta H_1^{\ddagger}$ = 94.3 ± 4.7 kJ mol^{-1}, $\Delta S_1^{\ddagger}$ = 92.0 ± 5.0 J K^{-1} mol^{-1}, and k_2(298 K) = 10.7 ± 0.5 s^{-1}, $\Delta H_2^{\ddagger}$ = 93.1 ± 4.7 kJ mol^{-1}, $\Delta S_2^{\ddagger}$ = 87.3 ± 5.0 J K^{-1} mol^{-1} for the minor and major includomers, respectively. The βCD·(*E*)-**1**$^-$ complex either forms a single includomer or its includomers interchange at the fast exchange limit of the ^{1}H NMR timescale. Complexation of **1**$^-$ by *N*-(6^A-deoxy-α-cyclodextrin-6^A-yl)-*N*′-(6^A-deoxy-β-cyclodextrin-6^A-yl)urea, **2**, results in the binary complexes **2**·(*E*)-**1**$^-$ in which both CD component annuli are occupied by (*E*)-**1**$^-$ and which exists exclusively in darkness and **2**·(*Z*)-**1**$^-$ in which only one CD component is occupied by (*Z*)-**1**$^-$ and exists exclusively in daylight at $\lambda \geq 300$ nm. Irradiation of solutions of the binary complexes at 300 and 355 nm results in photostationary states dominated by **2**·(*E*)-**1**$^-$ and **2**·(*Z*)-**1**$^-$, respectively. In the presence of 4-methylbenzoate, **4**$^-$, **2**·(*Z*)-**1**$^-$ forms the ternary complex **2**·(*Z*)-**1**$^-$·**4**$^-$ where **4**$^-$ occupies the second CD annulus. Interconversion occurs between **2**·(*Z*)-**1**$^-$·**4**$^-$ and **2**·(*E*)-**1**$^-$ + **4**$^-$ under the same conditions as for the binary complexes alone. Similar interactions occur in the presence of 4-methylphenolate and 4-methylphenylsulfonate. The two isomers of each of these systems represent different states of a molecular device, as do the analogous binary complexes of *N*,*N*-bis(6^A-deoxy-β-cyclodextrin-6^A-yl)urea, **3**, **3**·(*E*)-**1**$^-$ and **3**·(*Z*)-**1**$^-$, where the latter also forms a ternary complex with **4**$^-$.

Introduction

The inclusion of hydrophobic guests within the annuli of native and modified cyclodextrins has led to a wide range of complexes among which are enzyme mimics, polymers and rotaxanes.[1,2] The knowledge gained from these cyclodextrin complexes raises the possibility of constructing simple molecular devices, which may be switched between different states as has been done with other types of complexes.[3] Photoisomerization of a stilbene,[4] as occurs with (*E*)- and (*Z*)-4-*tert*-butyl-4′-oxystilbene, (*E*)-**1**$^-$ and (*Z*)-**1**$^-$, is potentially a convenient way of exercising such control. Accordingly, the complexes of thermally stable (*E*)-**1**$^-$ formed with α- and β-cyclodextrin (αCD and βCD), αCD·(*E*)-**1**$^-$ and βCD·(*E*)-**1**$^-$, have been studied in basic aqueous solution to provide insight into the effect of CD annular size on complexation as a prelude to characterizing the (*E*)-**1**$^-$ complexes of the urea linked CDs,[5,6] *N*-(6^A-deoxy-α-cyclodextrin-6^A-yl)-*N*′-(6^A-deoxy-β-cyclodextrin-6^A-yl)urea, **2**, and *N*,*N*-bis(6^A-deoxy-β-cyclodextrin-6^A-yl)-urea, **3** (Scheme 1). The binary complex, **2**·(*E*)-**1**$^-$, is found to isomerize to **2**·(*Z*)-**1**$^-$ photochemically which forms a ternary complex, **2**·(*Z*)-**1**$^-$·**4**$^-$, with 4-methylbenzoate, **4**$^-$, and also with 4-methylphenolate and 4-methylphenylsulfonate, whereas **2**·(*E*)-**1**$^-$ does not. The control of these processes both photochemically and also through a combined photochemical and thermal cycle is examined and reveals the operation of a simple molecular device. The analogous complexes of **3** behave similarly.

† Electronic Supplementary Information (ESI) available: NMR spectra. See http://www.rsc.org/suppdata/ob/b3/b310519a/

Results and discussion

The photoisomerization of 1$^-$

The water solubilities of 4-*tert*-butyl-4′-hydroxystilbene, **1H**, and its conjugate base, **1**$^-$, are extremely low. However, complexation of **1**$^-$ by a CD renders it sufficiently soluble for photochemical and NMR studies to be carried out. The synthetic product (see Experimental section) is (*E*)-**1H** and as a consequence the UV-visible spectrum of a freshly prepared basic aqueous solution of **2** and (*E*)-**1H** represents that of the **2**·(*E*)-**1**$^-$ complex (spectrum *a* in Fig. 1). On exposure of this solution to daylight for 2 h in a Pyrex vessel (which cuts out much of the light of $\lambda \leq 300$ nm) complete isomerization to **2**·(*Z*)-**1**$^-$ occurs (spectrum *d*) as indicated by ^{1}H NMR spectroscopy. Irradiation of this solution at 300 nm in a quartz cuvette for 2 h produces a photostationary equilibrium between **2**·(*E*)-**1**$^-$ and **2**·(*Z*)-**1**$^-$ (spectrum *b*). When this is followed by irradiation at 355 nm for 2 h a new photostationary equilibrium is reached between the two isomers (spectrum *c*). By alternately irradiating at 300 nm and 355 nm, alternation between the photostationary states characterized by spectra *b* and *c* occurs. Complete thermal isomerization of **2**·(*Z*)-**1**$^-$ in solution to **2**·(*E*)-**1**$^-$ occurs on warming at 340 K for 12 h in the dark. Similar spectral changes are observed in the αCD, βCD and **3** complexes, consistent with the isomerization process being little affected by the complexing CDs.

NMR studies of the complexation of (*E*)-1$^-$ by αCD and βCD

Both αCD and βCD greatly increase the solubility of (*E*)-**1**$^-$ in basic aqueous solution consistent with the formation of the

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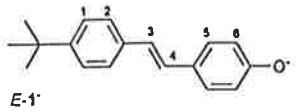
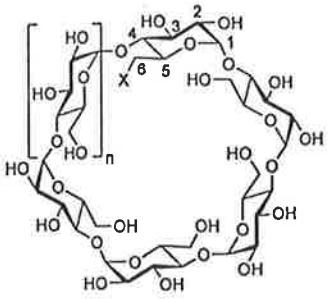
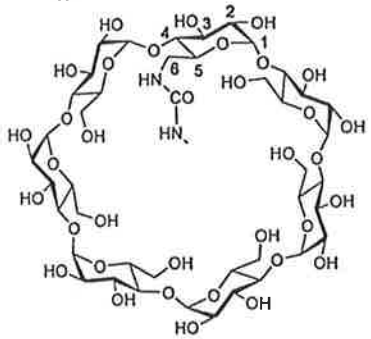


E-**1**$^-$



αCD; X = OH, n = 1
βCD; X = OH, n = 2
2; n = 1
3; n = 2
and for both **2** and **3**,
X =



Scheme 1 The numbering shown for (*E*)-**1**$^-$ is used in the assignment of ^{1}H NMR resonances.

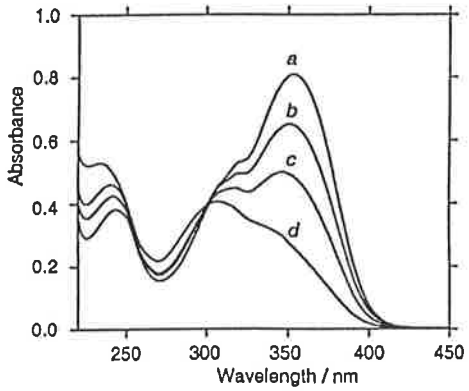


Fig. 1 The UV-visible spectral variation accompanying changes in the position of the equilibrium between (*E*)-**1**$^-$ and (*Z*)-**1**$^-$ for a solution in which total [(*E*)-**1**$^-$ and (*Z*)-**1**$^-$], [2] and [NaOH] = 2.5×10^{-3}, 2.6×10^{-5} and 1.2×10^{-4} mol dm^{-3}, respectively. *a* Initially prepared solution dominated by (*E*)-**1**$^-$; *d* after 2 h exposure to sunlight in a Pyrex vessel (*Z*)-**1**$^-$ dominates; *b* and *c* photostationary equilibria between (*E*)-**1**$^-$ and (*Z*)-**1**$^-$ after irradiation for 2 h at 300 nm and 355 nm, respectively.

complexes αCD·(*E*)-**1**$^-$ and βCD·*E*-**1**$^-$, respectively. To attain the higher concentration required for NMR spectroscopy, [NaOD] = 0.15 mol dm^{-3} is required which may indicate that it is necessary to deprotonate a hydroxy group of αCD·(*E*)-**1**$^-$ and βCD·(*E*)-**1**$^-$ (which is anticipated to have a $pK_a \geq 12$, on the basis that the pK_as of OH(2) and OH(3) are 12.33 for αCD) and thereby increase their solubilities.[7] (Similar NaOD concentrations were employed in studies of the systems of **2** and **3** discussed below.) The ^{1}H ROESY 600 MHz NMR spectrum of a D_2O solution in which $[\alpha CD]_{total}/[(E)\text{-}1^-]_{total} = 3$ (the minimum ratio at which (*E*)-**1**$^-$ was completely solubilized at the concentration required) shows cross-peaks between the broadened doublet resonances of the (*E*)-**1**$^-$ aromatic protons and those of αCD, but no cross-peaks attributable to the *tert*-butyl protons of (*E*)-**1**$^-$ which exhibit two well resolved singlets (Figs. 2 and S1 †). This is consistent with the formation of αCD inclusion complexes of (*E*)-**1**$^-$ where the annulus is positioned over the stilbene double bond and the *tert*-butyl protons of (*E*)-**1**$^-$ are too distant from the aliphatic protons of αCD for sufficiently strong dipolar interactions to generate cross-peaks between them. The simplest explanation of this is the formation of two isomeric αCD·(*E*)-**1**$^-$ inclusion complexes or includomers (Scheme 2). Such includomers produce two magnetic environments for the (*E*)-**1**$^-$ aromatic and vinylic protons through different interactions with the H3, H5 and H6 protons on the interior of the αCD annulus. The differing stereochemical arrangements of the primary and secondary hydroxy groups of αCD affect their interactions with the stilbene *tert*-butyl group of (*E*)-**1**$^-$ and probably its interaction with water and thereby produce two magnetic environments. While these individual interactions are weak their cumulative effects are sufficient to affect the magnetic environment of the *tert*-butyl group to give two resonances under slow includomer interchange conditions at 283 K.‡

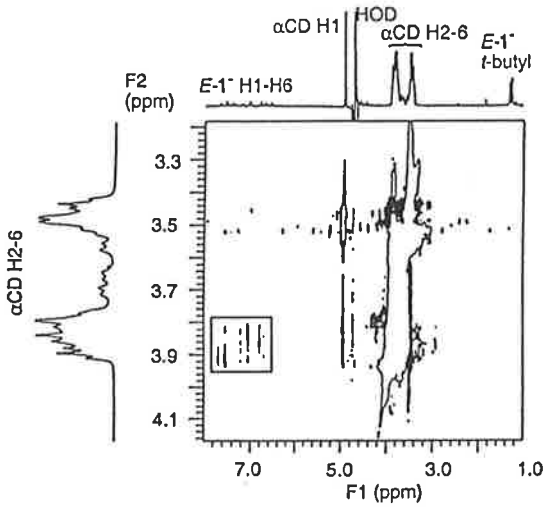
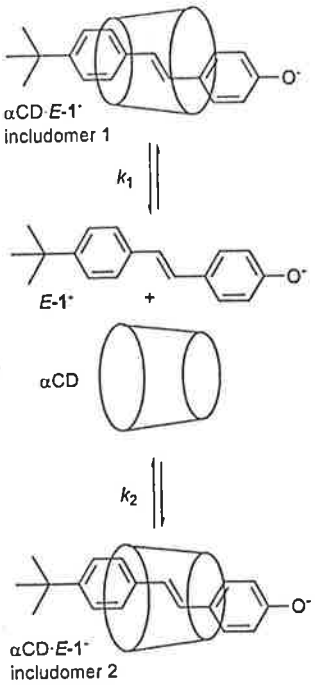


Fig. 2 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [αCD], [(*E*)-**1**$^-$] and [NaOD] = 0.010, 0.0034 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

In contrast, the ^{1}H ROESY NMR spectrum of a D_2O solution in which $[\beta CD]_{total}/[(E)\text{-}1^-]_{total} = 1$ shows cross-peaks between resonances of the aromatic and *tert*-butyl protons of (*E*)-**1**$^-$ and those of βCD consistent with the formation of

‡ An alternative explanation for the complexed (*E*)-**1**$^-$ experiencing different magnetic environments is the formation of an $(\alpha CD)_2\cdot(E)\text{-}1^-$ complex. Such a complex could exist as up to four includomers when the head-to-head, head-to-tail and tail-to-tail arrangements of the αCD pairs are taken into account. Molecular modelling indicates that each $(\alpha CD)_2\cdot(E)\text{-}1^-$ should show ^{1}H ROESY NMR cross-peaks as a consequence of dipolar interactions of some of the H3, H5 and H6 protons on the interior of the αCD annulus with the *tert*-butyl protons of (*E*)-**1**$^-$. Because such cross-peaks are not observed $(\alpha CD)_2\cdot(E)\text{-}1^-$ is not further considered.



Scheme 2

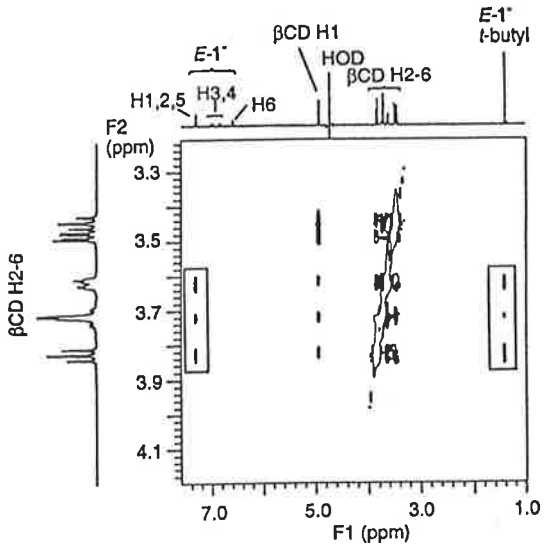


Fig. 3 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [βCD], [(*E*)-**1**$^-$] and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

βCD·(*E*)-**1**$^-$ (Fig. 3). The βCD resonances are also better resolved than those of αCD in αCD·(*E*)-**1**$^-$ (Fig. 2). These differences indicate that the small size of αCD inhibits complexation of the *tert*-butyl end of (*E*)-**1**$^-$ to give two αCD·(*E*)-**1**$^-$ includomers (Scheme 2) and also slows their isomerization. The occurrence of cross-peaks arising from the *tert*-butyl protons and the H1 and H2 protons of (*E*)-**1**$^-$ but not from H3, H4 and H6 (and probably not from H5 although its resonance is too close to those of H1 and H2 to be certain) suggests that a dominant includomer of βCD·(*E*)-**1**$^-$ has the larger βCD annulus positioned over the *tert*-butyl end of (*E*)-**1**$^-$. In principle the two possible orientations of βCD could give two such includomers, but the sharpness of the resonances suggests that either these are in fast exchange or one dominates and is in slow exchange with the minor includomer which is below the level of detection.

Dynamic NMR studies of the αCD·(*E*)-**1**$^-$ complex

At 298 K, the one dimensional 600 MHz ^{1}H NMR spectrum of αCD·(*E*)-**1**$^-$ shows two singlets in a 1.00 : 0.85 area ratio arising from the *tert*-butyl protons of (*E*)-**1**$^-$ and most of the aromatic resonances of (*E*)-**1**$^-$ are split into two doublets. On increasing the temperature these singlets coalesce (Figs 4 and S2†) consistent with (*E*)-**1**$^-$ exchanging between the two magnetic environments of the includomers shown in Scheme 2. Complete lineshape analysis[8,9] yields the exchange parameters: k_1(298 K) = 12.3 ± 0.6 s^{-1}, $\Delta H_1^{\ddagger}$ = 94.3 ± 4.7 kJ mol^{-1}, $\Delta S_1^{\ddagger}$ = 92.0 ± 5.0 J K^{-1} mol^{-1}, k_2(298 K) = 10.7 ± 0.5 s^{-1}, $\Delta H_2^{\ddagger}$ = 93.1 ± 4.7 kJ mol^{-1}, $\Delta S_2^{\ddagger}$ = 87.3 ± 5.0 J K^{-1} mol^{-1}, where the subscripts 1 and 2 refer to the lesser and more populated magnetic environments, respectively. The possibility of the (*E*)-**1**$^-$ coalescence phenomenon arising from exchange between complexed (*E*)-**1**$^-$ and free (*E*)-**1**$^-$ is excluded by the latter being of much too low a solubility to generate either of the *tert*-butyl resonances. Accordingly, the coalescence phenomenon is attributed to interchange of the two includomers of αCD·(*E*)-**1**$^-$ (Scheme 2) although it is not possible to assign the resonances to specific includomers.

As the ^{1}H ROESY NMR data discussed above indicate that αCD has difficulty in encompassing the *tert*-butyl group, dissociation of αCD·(*E*)-**1**$^-$ by passage of αCD over the phenoxy

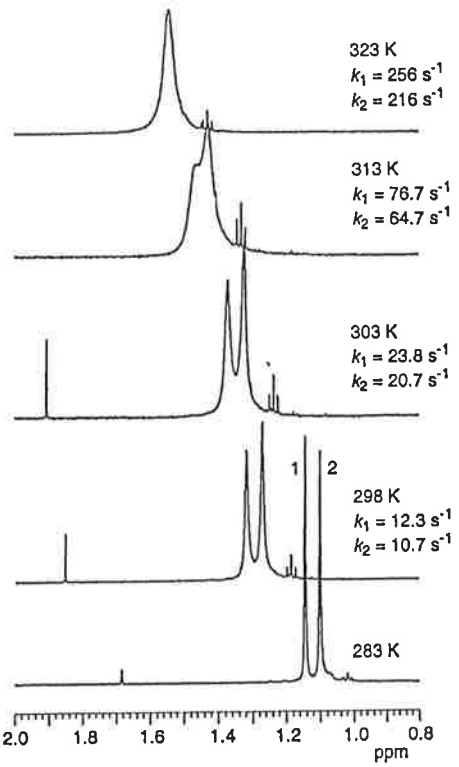


Fig. 4 Representative variable temperature ^{1}H NMR (600 MHz) spectra of the *tert*-butyl protons of (*E*)-**1**$^-$ in αCD·(*E*)-**1**$^-$ showing the derived rate constants k_1 and k_2 (the spectra are not plotted to a constant vertical scale). For the spectra not shown, k_1 = 45.3 s^{-1} and k_2 = 38.1 s^{-1} at 308 K, k_1 = 146 s^{-1} and k_2 = 123 s^{-1} at 318 K. The error in each rate constant is ±5%. The solution was made up in D_2O with total [αCD], [(*E*)-**1**$^-$] and [NaOD] = 0.010, 0.0034 and 0.15 mol dm^{-3}, respectively.

end of (E)-1$^-$ is probably the dominant isomerization mechanism for the includomers. The alternative associative mechanism proceeding *via* a transient $(\alpha CD)_2\cdot(E)$-1$^-$ complex appears less likely because of this steric hindrance. The positive $\Delta S_1^{\ddagger}$ and $\Delta S_2^{\ddagger}$ are consistent with a decrease in order which may indicate a partial dissociation of $\alpha CD\cdot(E)$-1$^-$ into its two components. It has been estimated that if all motions of the CD host and the guest species ceased on going from the free states to the complexed state an entropy change of −209 to −251 J K^{-1} mol^{-1} would result,[10] on which basis the reverse process would be characterised by a positive entropy change of similar magnitude. As it is unlikely that such a complete cessation of motion occurs in $\alpha CD\cdot(E)$-1$^-$, this is an upper limit for the magnitude of $\Delta S_1^{\ddagger}$ and $\Delta S_2^{\ddagger}$ for the includomer interconversion. In addition, hydration changes in both the αCD and (E)-1$^-$ components will occur as the transition state is approached, particularly for the entry of water into the αCD annulus as it is partly or completely vacated by (E)-1$^-$. Some change in hydration of the (E)-1$^-$ phenoxy group may also occur and both hydration changes should make a negative contribution to $\Delta S_1^{\ddagger}$ and $\Delta S_2^{\ddagger}$.

A comparison may be made between the $\alpha CD\cdot(E)$-1$^-$ data and those for the decomplexation of αCD·5$^-$, where 5$^-$ is 4-(4-hydroxy-3,5-dimethylphenylazo)benzenesulfonate which is similar in size and shape to (E)-1$^-$.[11] This decomplexation occurs in two steps for which k(298 K) = 13.3 s^{-1}, $\Delta H^{\ddagger}$ = 44.6 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −73.9 J K^{-1} mol^{-1} and $\Delta V^{\ddagger}$ = −12.6 cm^3 mol^{-1} for the fast decomplexation step and k(298 K) = 0.22 s^{-1}, $\Delta H^{\ddagger}$ = 47.5 kJ mol^{-1}, $\Delta S^{\ddagger}$ = −98.3 J K^{-1} mol^{-1} and $\Delta V^{\ddagger}$ = −16.1 cm^3 mol^{-1} for the slow decomplexation step and analogous data are reported for similar substituted azobenzene guests.[11] The decomplexation of $\alpha CD\cdot(E)$-1$^-$ may also proceed in two steps where the slower step is that characterized by ^{1}H NMR. A comparison with the parameters for the slower decomplexation step for αCD·5$^-$ shows that k(298 K) for $\alpha CD\cdot(E)$-1$^-$ is fifty times greater, $\Delta H^{\ddagger}$ is larger by a factor of 2 and $\Delta S^{\ddagger}$ is of a similar size but opposite in sign. The most obvious differences between the two complexes are that (E)-1$^-$ is very hydrophobic with only a phenoxy group to hydrogen bond with water whereas 5$^-$ incorporates a diazo function, a phenolic hydroxy group and a sulfonate group, all of which are strongly hydrated. Thus, $\Delta S^{\ddagger}$ for αCD·5$^-$ probably incorporates greater negative entropic contributions from hydration changes accompanying decomplexation than does that for $\alpha CD\cdot(E)$-1$^-$ which may explain the different signs of the $\Delta S^{\ddagger}$ characterizing the two systems. A greater participation of water in the approach to the transition state may offset some of the enthalpy required to disrupt secondary bonding between αCD and 5$^-$ in αCD·5$^-$ and thereby lower the overall $\Delta H^{\ddagger}$ by comparison with that for the isomerization of $\alpha CD\cdot(E)$ -1$^-$.

NMR studies of the complexation of (E)-1$^-$ and (Z)-1$^-$ by 2

Evidence for the formation of $2\cdot(E)$-1$^-$ and $2\cdot(Z)$-1$^-$ is provided by ^{1}H ROESY NMR spectroscopy which shows strong cross-peaks arising from dipolar interactions of the *tert*-butyl and the H1, H2, H5 and H6 protons of (E)-1$^-$ with the CD component H3, H5 and H6 protons of 2 as seen in Fig. 5. At 298 K the resonances of (E)-1$^-$ in $2\cdot(E)$-1$^-$ are broadened consistent with the rate of either a rotational or a shuttling motion of (E)-1$^-$ within $2\cdot(E)$-1$^-$ occurring within the intermediate ^{1}H NMR timescale. (As for $\alpha CD\cdot(E)$-1$^-$, resonance coalescence arising from exchange between complexed (E)-1$^-$ and free (E)-1$^-$ is ruled out by the latter being insufficiently soluble in water.) The intermediate rate of the motion of (E)-1$^-$ in $2\cdot(E)$-1$^-$ appears to arise from the close fit of the αCD component annulus of 2 to (E)-1$^-$ and is consistent with no broadening of the (E)-1$^-$ resonances of $3\cdot(E)$-1$^-$ occurring because the two βCD components of 3$^-$ render it more commodious and allow more rapid motion of (E)-1$^-$.

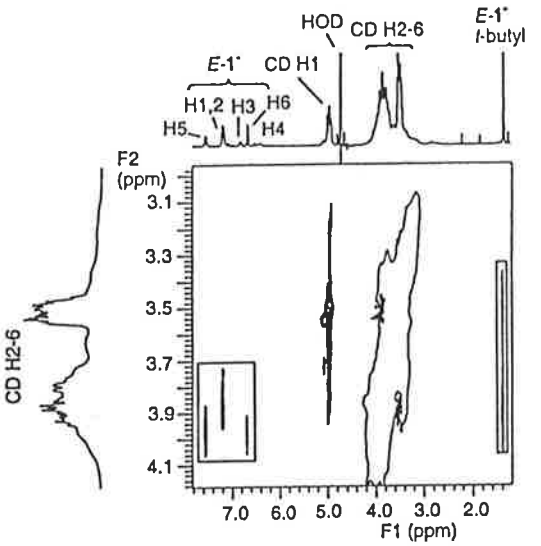


Fig. 5 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [2], $[(E)$-1$^-]$ and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

After exposure of the $2\cdot(E)$-1$^-$ solution to sunlight for 2 h in a Pyrex vessel, during which time changes in its UV-visible spectrum indicated complete isomerization to $2\cdot(Z)$-1$^-$, strong cross-peaks arising from the interaction of the *tert*-butyl and H1 and H2 protons of (Z)-1$^-$ with the CD component protons of 2 were observed in its ^{1}H ROESY NMR spectrum, but cross-peaks attributable to H5 and H6 of (Z)-1$^-$ were absent (Fig. 6). This is consistent with (Z)-1$^-$ occupying only one component annulus in $2\cdot(Z)$-1$^-$. On the basis of the *tert*-butyl cross-peaks observed for both (E)-1$^-$ and (Z)-1$^-$ in $2\cdot(E)$-1$^-$ and 2·Z-1$^-$, in contrast to their absence from the ^{1}H ROESY NMR spectrum of $\alpha CD\cdot(E)$-1$^-$, and their presence in the ^{1}H ROESY NMR spectrum of $\beta CD\cdot(E)$-1$^-$, it appears that the *tert*-butyl groups of (E)-1$^-$ and (Z)-1$^-$ are probably positioned in the βCD component annulus of 2 as shown for $2\cdot(E)$-1$^-$ and $2\cdot(Z)$-1$^-$ in

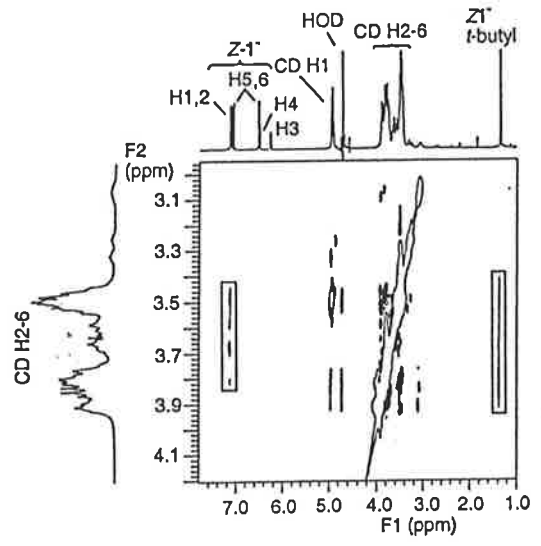
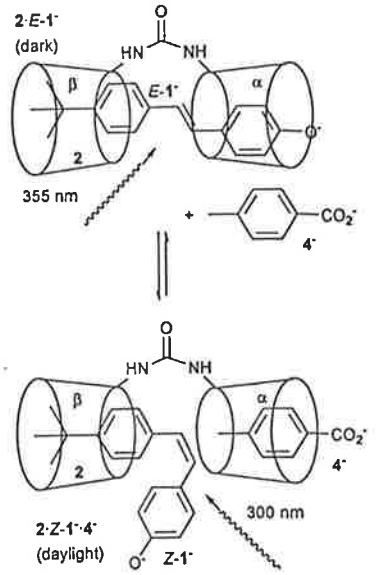


Fig. 6 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [2], $[(Z)$-1$^-]$ and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

Scheme 3. (While subsequent discussion is based on the includomers shown in Scheme 3, the existence of a minor includomer of each complex in which the *tert*-butyl groups of (E)-$\mathbf{1}^-$ and (Z)-$\mathbf{1}^-$ are positioned in the αCD component annulus of **2** cannot be excluded.) The (Z)-$\mathbf{1}^-$ resonances of $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$ are sharper than those of (E)-$\mathbf{1}^-$ in $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ consistent with the motion of (Z)-$\mathbf{1}^-$ in the βCD component annulus being less impeded by comparison with that of (E)-$\mathbf{1}^-$ which is complexed by both CD component annuli in $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$.



Scheme 3 Photoisomerization of $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$, the reverse thermal isomerization in the dark and the single irradiation wavelengths favouring $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$. The vacated αCD component annulus may be occupied by 4-methylbenzoate, $\mathbf{4}^-$, to form $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$.

When 4-methylbenzoate, $\mathbf{4}^-$, is present in solution, the ^{1}H ROESY NMR spectrum of $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ shows no cross-peaks attributable to interactions between the protons of $\mathbf{4}^-$ and **2** (Fig. 7 and expanded in Fig. S3†), whereas in the presence of $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$ a strong cross-peak is observed for the methyl protons

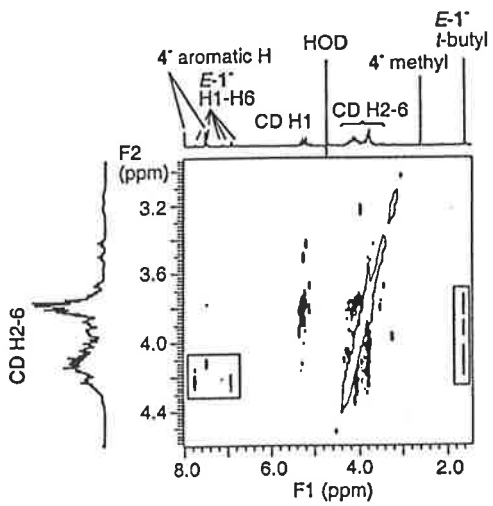


Fig. 7 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [**2**], $[(E)$-$\mathbf{1}^-]$, $[\mathbf{4}^-]$ and [NaOD] = 0.016, 0.015, 0.022 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

of $\mathbf{4}^-$ and a weaker cross-peak for the aromatic protons (Fig. 8 and expanded in Fig. S4†) consistent with the formation of the $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$ ternary complex as shown in Scheme 3. (Analogous cross-peaks are similarly absent and present from the ^{1}H ROESY NMR spectra of $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$, respectively, in the presence of 4-methylphenolate and 4-methylsulfonate.) Thus, it appears that $\mathbf{4}^-$ occupies the αCD component annulus of **2** vacated by the phenoxy end of (Z)-$\mathbf{1}^-$ in $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$. The cross-peak arising from $\mathbf{4}^-$ disappears and the spectrum reverts to that of $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{4}^-$ when $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ reforms through the thermal isomerization path in the dark. The interconversion of these complexes constitute the operation of a molecular device which may be controlled by either alternating photoisomerization of (E)-$\mathbf{1}^-$ and thermal isomerization of (Z)-$\mathbf{1}^-$ or by photoisomerization of (E)-$\mathbf{1}^-$ and (Z)-$\mathbf{1}^-$ alone, although in the latter case this amounts to the attainment of wavelength dependent photostationary states in which the proportions of $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$ and $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{4}^-$ differ. The analogous 4-methylphenolate and 4-methylphenylsulfonate systems behave similarly.

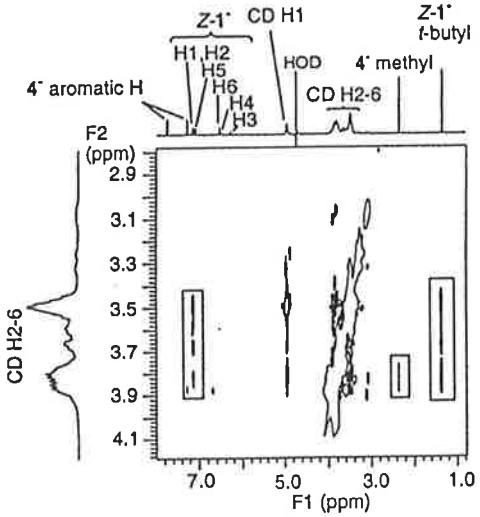


Fig. 8 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of the solution from Fig. 7 after a 2 h exposure to daylight to give $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$, $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-$ and $\mathbf{4}^-$. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

The complexation of $\mathbf{4}^-$ in $\mathbf{2}\cdot(Z)$-$\mathbf{1}^-\cdot\mathbf{4}^-$, but not in $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$, represents a fine balance between the greater complexing abilities of (Z)-$\mathbf{1}^-$ and (E)-$\mathbf{1}^-$ and the lesser complexing ability of $\mathbf{4}^-$. A change in this balance occurs with more strongly complexing adamantane-1-carboxylate, $\mathbf{6}^-$. In contrast to $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{4}^-$, which do not detectably interact in solution, the interaction between **2** and $\mathbf{6}^-$ in a solution where [**2**], $[(E)$-$\mathbf{1}^-]$, $[\mathbf{6}^-]$ and [NaOD] = 0.016, 0.015, 0.022 and 0.15 mol dm^{-3}, respectively, produced strong ^{1}H ROESY NMR cross-peaks and those arising from $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ are decreased in intensity but unchanged in character. This is most simply explained in terms of a competitive equilibrium where the major complexes are $\mathbf{2}\cdot(E)$-$\mathbf{1}^-$ and $\mathbf{2}\cdot\mathbf{6}^-$. Complexation constants $K = 1.8 \times 10^4$ and 1.84×10^4 dm^3 mol^{-1} are reported[12,13] for the complexation of $\mathbf{6}^-$ and 4-*tert*-butylbenzoate, respectively, by βCD on which basis significant competition between $\mathbf{6}^-$ and the *tert*-butyl end of (E)-$\mathbf{1}^-$ for occupancy of the βCD component annulus of **2** is expected. (Complexation of $\mathbf{4}^-$ by αCD is characterized by K = 110 dm^3 mol^{-1} consistent with $\mathbf{4}^-$ not competing with (E)-$\mathbf{1}^-$ for occupancy of the βCD component annulus of **2**.[12]) Because of its large size, $\mathbf{6}^-$ is complexed less strongly by αCD (K = 140 dm^3 mol^{-1})[14] and is therefore less likely to compete with (E)-$\mathbf{1}^-$ and

(*Z*)-**1**$^-$ for occupancy of the αCD component annulus of **2**. The ^{1}H ROESY NMR spectrum of a solution in which [**2**], [(*Z*)-**1**$^-$], [**6**$^-$] and [NaOD] = 0.016, 0.015, 0.022 and 0.15 mol dm^{-3}, respectively, produced strong cross-peaks arising from dipolar interactions between **2** and (*Z*)-**1**$^-$ and between **2** and **6**$^-$ which may also be explained in terms of the competitive formation of **2**·(*Z*)-**1**$^-$ and **2**·**6**$^-$. The possibility of forming the ternary complexes **2**·(*E*)-**1**$^-$·**6**$^-$ and **2**·(*Z*)-**1**$^-$·**6**$^-$ also exists.

NMR studies of the complexation of 1$^-$ by 3

Evidence for the formation of **3**·(*E*)-**1**$^-$ and **3**·(*Z*)-**1**$^-$ is provided by ^{1}H ROESY NMR spectroscopy. For a solution in which total [**3**], [(*E*)-**1**$^-$] and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively, strong cross-peaks arising from dipolar interactions of the *tert*-butyl and the H1, H2, H5 and H6 protons of (*E*)-**1**$^-$ with the H3, H5 and H6 protons of the annuli of the βCD components of **3** in **3**·(*E*)-**1**$^-$ are seen (Fig. 9). This is also the case when (*E*)-**1**$^-$ is isomerized to (*Z*)-**1**$^-$ (Fig. 10) consistent with both of the two βCD components of **3**·(*Z*)-**1**$^-$ being occupied and also with the annuli of the two βCD components together being of sufficient volume to accommodate (*Z*)-**1**$^-$, unlike the situation with **2**·(*Z*)-**1**$^-$.

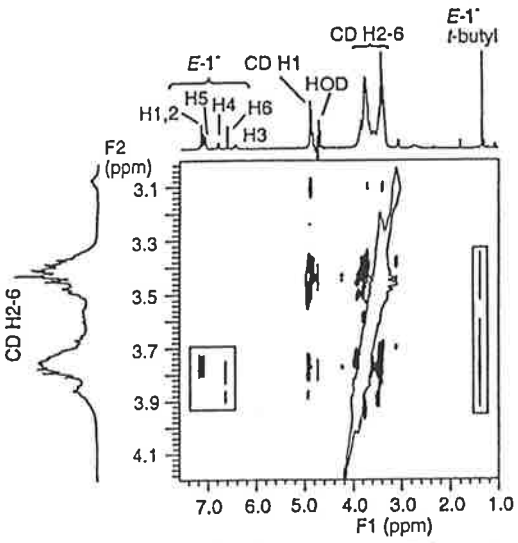


Fig. 9 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [**3**], [(*E*)-**1**$^-$] and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

No cross-peaks arising from the simultaneous complexation of **4**$^-$ in the presence of **3**·(*E*)-**1**$^-$ were observed. However, cross-peaks arising from the interaction of both the aromatic protons of the phenolate end of (*Z*)-**1**$^-$ and **4**$^-$ with a βCD component annulus of **3** were observed for a solution of 0.016, 0.015 and 0.022 mol dm^{-3} in **3**, (*Z*)-**1**$^-$ and **4**$^-$, respectively, in 0.15 mol dm^{-3} NaOD consistent with **3**·(*Z*)-**1**$^-$ existing in an equilibrium between an includomer in which both βCD component annuli are occupied by (*Z*)-**1**$^-$ and one in which only one βCD component annulus is occupied by the *tert*-butyl end of (*Z*)-**1**$^-$ and the other βCD component annulus is empty. It is this vacant annulus which may be occupied by **4**$^-$ to give **3**·*Z*-**1**$^-$·**4**$^-$.

Conclusion

The effect of the smaller αCD annular size on complexation processes is shown by the slowing of the isomerization of αCD·(*E*)-**1**$^-$ to within the NMR kinetic timescale and the exclusion

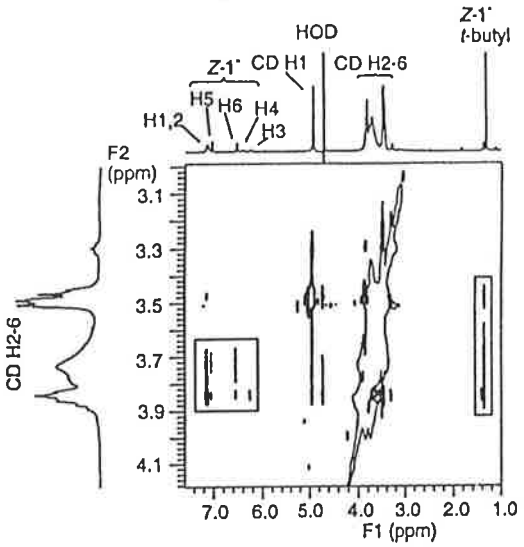


Fig. 10 ^{1}H 600 MHz ROESY NMR spectrum recorded at 298 K of a D_2O solution in which total [**3**], [(*Z*)-**1**$^-$] and [NaOD] = 0.016, 0.015 and 0.15 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangles arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

of the *tert*-butyl group of (*E*)-**1**$^-$ from the αCD annulus. In contrast, βCD·(*E*)-**1**$^-$ allows entry of the *tert*-butyl group of (*E*)-**1**$^-$ into the larger βCD annulus and either a dominant βCD·(*E*)-**1**$^-$ includomer to be formed or isomerization between βCD·(*E*)-**1**$^-$ includomers to occur at a rate in the fast exchange limit of the NMR timescale. The effect of the photoisomerization of (*E*)-**1**$^-$ and (*Z*)-**1**$^-$ is amplified in **2**·(*E*)-**1**$^-$ and **2**·(*Z*)-**1**$^-$ through the occupancy of both the αCD and the βCD component annuli in **2**·(*E*)-**1**$^-$ whereas the vacating of the βCD annulus in **2**·(*Z*)-**1**$^-$ allows 4-methylbenzoate, **4**$^-$, 4-methylphenolate and 4-methylphenylsulfonate to enter it to form a ternary complex exemplified by **2**·(*Z*)-**1**$^-$·**4**$^-$. Thus, **2**·(*E*)-**1**$^-$ and **2**·(*Z*)-**1**$^-$ represent two states of a simple photo-controlled molecular assembly in which the effects of stilbene isomerization is amplified by its environment in **2**. While the **3**·(*E*)-**1**$^-$ and **3**·(*Z*)-**1**$^-$ includomers behave similarly to their **2** analogues, their interactions appear to be more flexible because of the greater combined size of the two βCD component annuli of **3**.

Experimental

General

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were run in $CDCl_3$ on a Varian Gemini 300 spectrometer and were referenced either against internal TMS or the proton impurity ^{13}C multiplet (δ = 39.5 ppm). ^{1}H (600 MHz) NMR spectra were run on an Inova 600 spectrometer. The ^{1}H 2D-ROESY NMR spectra were recorded using a standard pulse sequence with a mixing time of 0.3 seconds. All of the spectra appearing in the Figures were referenced to the HOD resonance at δ = 4.72 ppm. All other spectra were referenced against external trimethylsilylpropiosulfonic acid. The lineshape analysis of the coalescence of the *tert*-butyl resonances of the αCD·(*E*)-**1**$^-$ includomers was carried out using the program DAVNMR.[9] The mole fractions of each includomer and their chemical shift difference showed no significant variation in the slow exchange region over the temperature range 278–298 K and this was assumed to be the case in the range 298–323 K over which lineshape analysis was carried out. The slight narrowing of the includomer resonances occurring in the temperature range 278–288 K was extrapolated into the coalescence temperature range

to give the non-exchange modified T_2 for the lineshape analysis. The best fit of the calculated lineshape to the experimental lineshape was obtained through minimizing the mean of the squares of the residual difference between the two.

MALDI-TOF mass spectrometry was carried out at the Research School of Chemistry at the Australian National University, Canberra, ACT. Electrospray mass spectrometry (ES-MS) and fast atom bombardment mass spectrometry (FAB-MS) were carried out at the University of Adelaide. Samples for ES-MS were dissolved in water for injection. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR. The abbreviations strong (s), medium (m), weak (w) and broad (b) are used for reporting the intensity of the bands observed. UV/vis spectra were recorded on a Cary 300 Bio spectrophotometer. Irradiation of solutions of the (*E*)-**1**$^-$ and (*Z*)-**1**$^-$ complexes were carried out in a quartz cuvette in a LS50B fluorimeter. Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. Thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) on aluminium-backed sheets.

All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. β-Cyclodextrin was donated by Nihon Shokuhin Kako Co. Both αCD and βCD were dried by heating at 100 °C under reduced pressure for 18 hours. The linked CDs **2** and **3** were prepared by a literature procedure.[5] Pyridine and 1-methylpyrrolidin-2-one (NMP) were dried by distillation from calcium hydride. *N*,*N*-Dimethylformamide (DMF) and methanol were dried over molecular sieves.

Preparation of 4-*tert*-butyl-4′-methoxystilbene

(a) 4-*tert*-Butylbenzylbromide (0.451 g, 1.99 mmol) and triethyl phosphite (0.5 cm^3) were stirred at 120 °C for 12 hours. Excess triethyl phosphite was removed at reduced pressure to give diethyl (4-*tert*-butylbenzyl)phosphonate (quantitative yield). δ_H($CDCl_3$) 7.20–7.29 (m, 4H, ArH), 3.94–4.05 (m, 4H, CH_3CH_2O), 3.11 (d, J = 21 Hz, 2H, CH_2–P), 1.30 (s, 9H, $C(CH_3)_3$), 1.24 (t, J = 6.8 Hz, CH_3CH_2O).

(b) Diethyl (4-*tert*-butylbenzyl)phosphonate (0.508 g, 1.79 mmol) was dissolved in dry THF (20 cm^3) and sodium hydride (0.067 g, 2.79 mmol) was added at 0 °C. Anisaldehyde (0.220 cm^3, 1.81 mmol) was added and the mixture was allowed to slowly warm up to room temperature. The mixture was stirred for 24 hours, followed by the addition of water (4 cm^3) and 1 mol dm^{-3} hydrochloric acid (5 cm^3). The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 cm^3). The combined organic layers were washed with saturated ammonium bicarbonate (15 cm^3), dried (sodium sulfate), filtered and concentrated. Purification by flash column chromatography (30% ethyl acetate–hexane) gave the pure product as white crystals (0.287 g, 60 %), mp 179–181 °C; FAB-MS *m/z* 266 (M$^+$) [Found: C, 85.60; H, 8.01%. Calc. for $C_{19}H_{22}O$: C, 85.67; H, 8.32%]; δ_H($CDCl_3$) 7.45 (d, J = 9.0 Hz, 2H, ArH5), 7.43 (δ_A), 7.37 (δ_B) (AB q, J_{AB} = 9.0 Hz, 4H, ArH1,2), 7.04 (d, J = 16.6 Hz, 1H, C=C–H), 6.96 (d, J = 16.5 Hz, 1H, C=C–H), 6.90 (d, J = 9.0 Hz, 2H, ArH6), 3.83 (s, 3H, O–CH_3), 1.33 (s, 9H, $C(CH_3)_3$); δ_C($CDCl_3$) 150.30, 134.84, 130.33, 127.56 (ArC); 127.41, 126.40 (C=C); 127.56, 125.94, 125.55, 114.06 (ArC); 55.31 (O–CH_3); 34.57 ($C(CH_3)_3$); 31.28 ($C(CH_3)_3$); ν_{max} (Nujol/cm^{-1}) 1602m (C=C), 1590w, 1511m (Ar), 969m (H–C=C–H), 833s (Ar).

Preparation of (*E*)-(4-*tert*-butyl-4′-hydroxystilbene), (*E*)-4H

Sodium hydride (0.242 g (60%), 6.05 mmol) was suspended in dry DMF (10 cm^3) and ethanethiol (0.250 cm^3, 3.01 mmol) was added dropwise at room temperature, followed by (*E*)-4-*tert*-butyl-4′-methoxystilbene (0.297 g, 1.11 mmol). The mixture was stirred at 100 °C for 5 hours then cooled to room temperature and quenched with 3 mol dm^{-3} hydrochloric acid. Ether (5 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with more ether (2 × 5 cm^3). The combined organic layers were washed with 5% sodium hydroxide (3 × 5 cm^3) and brine (5 cm^3), dried (sodium sulfate) and concentrated. The crude material was purified by flash column chromatography (10%–25% ethyl acetate–hexane) to give the pure product as a white solid (0.231 g, 83%), mp 160–162 °C; FAB-MS *m/z* 252 (M$^+$) [Found: C, 83.70; H, 8.15%. Calc. for $(C_{18}H_{20}O)_3 \cdot H_2O$: C, 83.68; H, 8.06%]; δ_H($CDCl_3$) 7.35–7.44 (m, 6H, ArH1,2,5), 7.02 (d, J = 16.5 Hz, 1H, C=CH), 6.94 (d, J = 16.5 Hz, 1H, C=CH), 6.82 (d, J = 8.4 Hz, 2H, ArH6), 4.86 (br s, 1H, OH), 1.33 (s, 9H, $C(CH_3)_3$); δ_C($CDCl_3$) 155.02, 150.36, 134.78, 130.56, 127.78 (ArC); 127.33, 126.49 (C=C); 125.96, 125.56, 115.54 (ArC); 34.57 ($C(CH_3)_3$); 31.28 ($C(CH_3)_3$); ν_{max} (Nujol/cm^{-1}) 3150–3250b (O–H), 1607m (C=C), 1592m, 1510m (Ar), 1253m (O–H), 971m (H–C=C–H), 835s (Ar).

Preparation of (*Z*)-(4-*tert*-butyl-4′-hydroxystilbene), (*Z*)-4H

(*E*)-(4-*tert*-Butyl-4′-hydroxystilbene) (0.200 g, 0.794 mmol) was dissolved in deoxygenated methanol (15 cm^3), placed in a flask with a lightly greased stopper, and was exposed to sunlight for 24 hours. Solvent was removed under reduced pressure and the crude material was loaded onto a neutral alumina column and eluted with 30% ethyl acetate–hexane to give the pure (*Z*)-isomer as a viscous oil which solidified upon cooling (0.110 g, 55%), and the (*E*)-isomer was recovered (0.047 g, 24%); FAB-MS *m/z* 252 (M$^+$) [Found: C, 84.18; H, 8.58%. Calc. for $(C_{18}H_{20}O)_3 \cdot H_2O$ C, 83.68; H, 8.06%]; δ_H($CDCl_3$) 7.20–7.27 (m, 4H, ArH1,2), 7.17 (d, J = 8.4 Hz, 2H, ArH5), 6.71 (d, J = 8.4 Hz, 2H, ArH6), 6.47 (br s, 2H, HC=CH), 4.80 (br s, 1H, OH), 1.29 (s, 9H, $C(CH_3)_3$); δ_C($CDCl_3$) 154.82, 150.28, 134.71, 130.89, 130.61 (ArC); 129.10, 129.33 (C=C); 128.84, 125.42, 115.40 (ArC); 34.81 ($C(CH_3)_3$); 31.59 ($C(CH_3)_3$).

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ARTICLE

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Intra- and intermolecular complexation in C(6) monoazacoronand substituted cyclodextrins †

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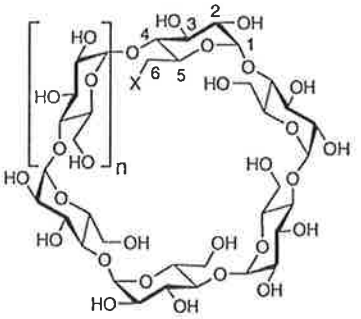
The preparation of 6^A-deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin, **3**, 6^A-deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin, **4**, and their β-cyclodextrin analogues, **5** and **6**, are described. ^{1}H (600 MHz) ROESY NMR spectra of the C(6) substituted β-cyclodextrins, **5** and **6**, are consistent with the intramolecular complexation of their azacyclopentadecanyl- and azacyclooctadecanyl(acetamido)hexylamino substituents in the β-cyclodextrin annulus in D_2O at pD = 8.5 whereas those of their α-cyclodextrin analogues, **3** and **4** are not complexed in the α-cyclodextrin annulus. This is attributed to the monoazacoronand components of the substituents being able to pass through the β-cyclodextrin annulus whereas they are too large to pass through the α-cyclodextrin annulus. However, the substituents of **3** and **4** are intermolecularly complexed by β-cyclodextrin to form pseudo [2]-rotaxanes. Metallocyclodextrins are formed by **5** through complexation by the monoazacoronand substituent component for which log (K/dm^3 mol^{-1}) = <2, 6.34 and 5.38 for Ca^{2+}, Zn^{2+} and La^{3+}, respectively, in aqueous solution at 298.2 K and I = 0.10 mol dm^{-3} (NEt_4ClO_4).

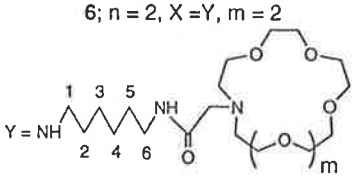
Introduction

A substantial range of modified cyclodextrins (CDs) have been prepared because of their intrinsic interest and their potential and actual use as drug delivery agents, catalysts, chromatographic materials and components of nanodevices.[1–5] Among the latter are rotaxanes and catenanes where the relative size of their components is crucial in achieving the mechanical restraints which hold such assemblies together.

As part of our studies in this area, we have reported substitution at C(6) of both α- and β-cyclodextrin (αCD and βCD) by extended substituents which complex inside the annulus of the CD to which they are attached when the spatial requirements are appropriate.[6] Such intramolecular complexation is entropically favoured over potentially competing intermolecular complexation and provides a method of experimentally calibrating the fit, or otherwise, of components of the extended substituent into the CD annulus. In this study we seek to further explore the utility of this approach in assessing the spatial aspects of intramolecular interactions. Accordingly, we have acylated 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**, and its βCD analogue, **2**, to give 6^A-deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin, **3**, 6^A-deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin, **4**, and their β-cyclodextrin analogues, **5** and **6**, (Scheme 1) through reaction with the 4-nitrophenyl esters, **7** and **8** (Scheme 2). These substituted CDs have either a 15- or 18-membered monoazacoronand attached to the C(6) position by an acetamidohexylamino tether of sufficient flexibility to allow the monoazacoronands to adapt their conformations to enter the CD annulus if it is sufficiently large and possibly pass through it. Both events provide a calibration of CD annular size with respect to the two monoazacoronands. The second event offers the opportunity to stiffen the monoazacoronand conformation in a metal complex with a molecular volume too large to pass through the CD annulus and thereby lock the substituted CD into a molecular knot structure.



αCD; n = 1, X = OH
βCD; n = 2, X = OH
3; n = 1, X =Y, m = 1
4; n = 1, X =Y, m = 2
5; n = 2, X =Y, m = 1
6; n = 2, X =Y, m = 2



Scheme 1

Results and discussion

Intramolecular complexation

The C(6) substituted CDs **3**–**6** were synthesized by the acylation of either 6^A-(6-aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**,

† Electronic supplementary information (ESI) available: ^{1}H 600 MHz 2D ROESY NMR spectra. See http://www.rsc.org/suppdata/ob/b3/b316450k/

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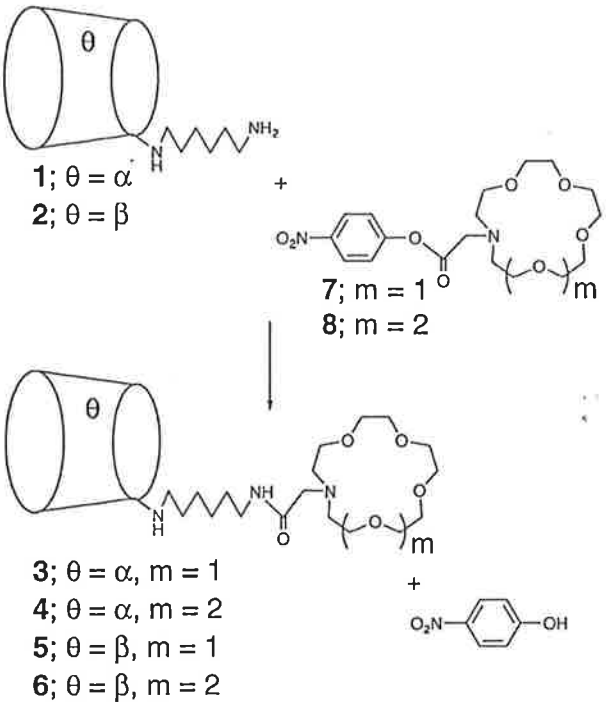


Scheme 2

or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin, **2**, by either of the 4-nitrophenyl esters **7** or **8** (Scheme 2). The secondary and tertiary amine groups of the substituents protonate and are characterised by the potentiometrically determined pK_as for $5H_2^{2+}$ being 5.84 ± 0.03 and 8.49 ± 0.04 at 298.2 K and I = 0.10 mol dm^{-3} (NEt_4ClO_4) in aqueous solution. They are assigned to the amine of the azacoronand and the amine directly attached to β-cyclodextrin, respectively, by comparison with previous work.[7]

Dissolution of **3**–**6** in water results in a mixture of the zero- and monoprotonated species and a solution pH of ~8.5. ^{1}H ROESY NMR (600 MHz) spectra of **3** and **4** in D_2O show no cross-peaks arising from NOE interaction between the substituent at C(6) and protons H3, H5 and H6 of the interior of the CD annulus (Figs S1 and S2)† whereas such cross-peaks are observed for **5** (Fig. 1) and **6** (Fig. 2). This is consistent with the

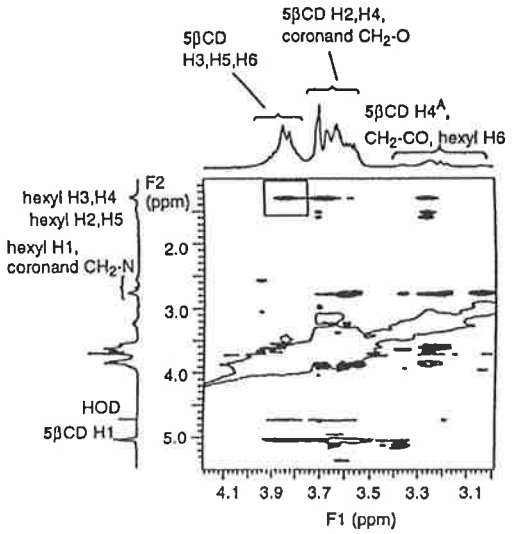


Fig. 1 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[5]_{total}$ is 0.025 mol dm^{-3}. The cross-peak enclosed in the rectangle arises from dipolar interactions between the protons indicated on the F1 and F2 axes.

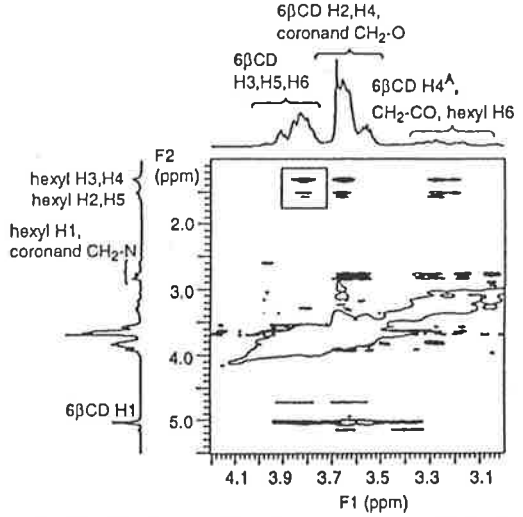
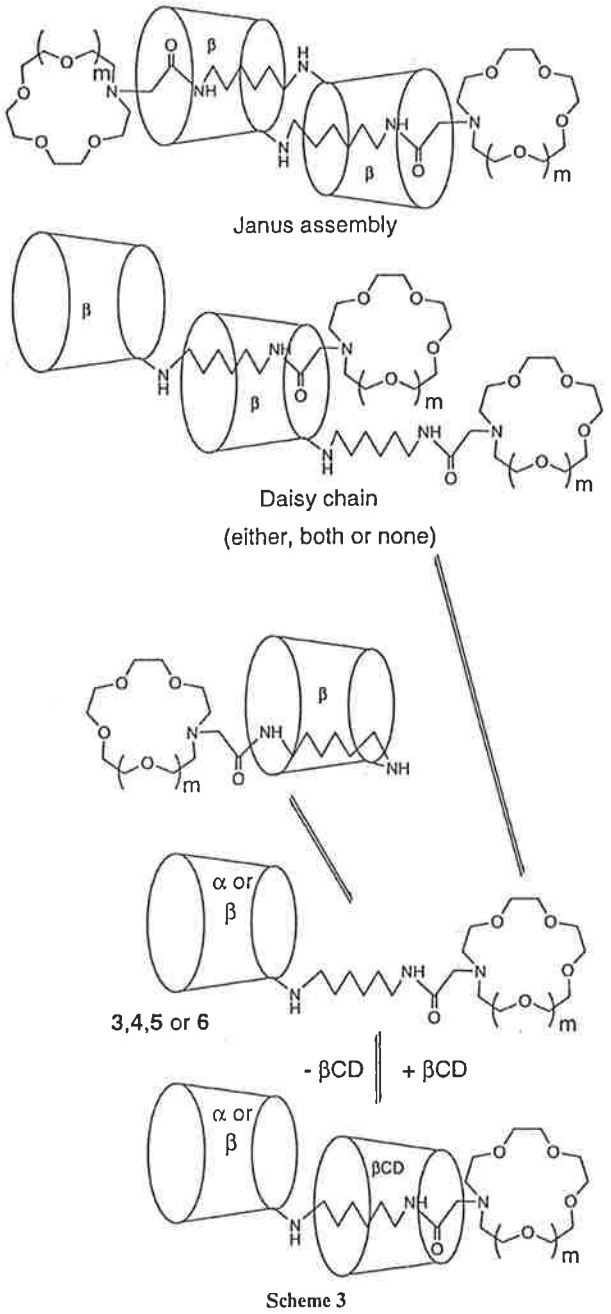


Fig. 2 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[6]_{total}$ is 0.025 mol dm^{-3}. The cross peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

αCD annuli of **3** and **4** being too small to allow the intramolecular complexation of the substituent at C(6) whereas such complexation does occur for **5** and **6**, evidently because of the larger size of the βCD annulus. Strong cross-peaks are observed for NOE interactions in **5** between the hexyl H3 and H4 protons and the H3, H5 and H6 protons in the annulus of the βCD component, similar interactions with the hexyl H2 and H5 protons produce much weaker cross-peaks (which are not visible at the level of spectral presentation of Fig. 1). This is consistent with the substituent azacoronand passing into or through the βCD annulus so that the particularly hydrophobic midsection of the hexyl entity is in the βCD annulus as shown in Scheme 3, and the hexyl H3 and H4 protons are closer to the H3, H5 and H6 annular protons than are the hexyl H2 and H5 protons. (The overlap of the azacoronand resonances with the βCD H2 and H4 resonances renders it impossible to determine whether the azacoronand moieties of **3**–**6** are within the CD annuli, although it is unlikely that they would complex in preference to the hexyl component because of their lesser hydrophobicity. This aspect is further explored under "Intermolecular complexation" below.) In the case of **6** the hexyl H2–H5 protons all produce cross-peaks through NOE interactions with the H3, H5 and H6 annular protons, consistent with the interpretation presented for **5**. This also shows that the size of the azacoronand influences the orientation of the hexyl entity within the annulus as indicated by the differences in the cross-peaks of **5** and **6**.

An alternative explanation that the hexyl component folds into the annulus which the azacoronand does not enter appears to be unlikely as the analogue of both **5** and **6** in which the 1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido- and 1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido entities were replaced by a 1-amino-2,4,6-trinitrophenyl group which is too large to enter βCD through the smaller end of the annulus showed no cross-peaks arising from the substituent protons and the H3, H5 and H6 protons of the annular interior in its ^{1}H ROESY NMR spectrum in D_2O.[8] In contrast, the dodecyl analogue did show cross-peaks arising from NOE interactions between some of the dodecyl protons and the H3, H5 and H6 protons of the βCD annulus interior consistent with the longer alkyl chain being sufficiently long and flexible for part of it to be intramolecularly complexed in the βCD annulus.

The substituent and βCD resonances of **5** and **6** are broadened consistent with constrained motion bringing exchange between two or more magnetic environments into the moderate



Scheme 3

exchange rate region of the NMR timescale. Such exchange is anticipated between the intramolecular and non-complexed forms of **5** and **6**. By comparison, the resonances of **3** and **4** are narrower consistent with no intra- or intermolecular complexation. (The latter could occur through either intermolecular hermaphrodite or daisy chain complexation as observed in other CD systems.[9,10]) When the pD of the solutions of **5** and **6** is decreased to ~7, the ROESY cross-peaks become very weak consistent with protonation of the amine directly attached to βCD in $H5^+$ and $H6^+$ inhibiting intramolecular complexation.

Intermolecular complexation

When substituents are flexible, as in **5** and **6**, intramolecular complexation is entropically favoured over the formation of intermolecular Janus (hermaphrodite) and daisy chain complexes (Scheme 3).[9,10] Generally, the latter two types of complexes form when the substituent is less flexible than those of **5** and **6**. It is also significant that under the conditions of this study **5** and **6** are present as a mixture of zero- and monoprotonated species where the charge of the latter is expected to inhibit intermolecular complexation as it does intramolecular complexation. Intermolecular complexation between either neutral **3** or **4** and βCD to form the pseudo [2]-rotaxanes **3**·βCD and **4**·βCD is more likely as there is no detectable intramolecular substituent complexation (Scheme 3). Evidence for the formation of **3**·βCD and **4**·βCD is afforded by the appearance of cross-peaks from NOE interactions between the substituent H2–H5 protons of the hexyl substituent of **3** and **4** and the H3, H5 and H6 protons of βCD in the ^{1}H ROESY NMR spectra of D_2O solutions of βCD and either **3** or **4** (Figs. 3 and 4). These pseudo [2]-rotaxanes are unusual in possessing αCD as a blocking group on one end of the axle and the complexation and decomplexation of the other end of the axle being slowed by the bulk of the azacoronand as akin to a "slippage" mechanism for rotaxane formation.[11] Evidence for this slowing is adduced from the resonance broadening observed for

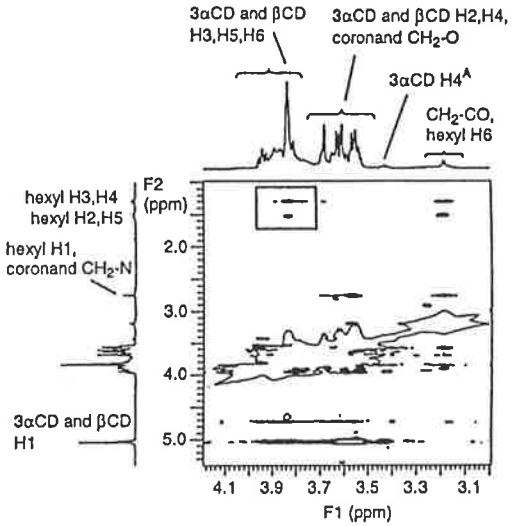


Fig. 3 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[3]_{total}$ and $[\beta CD]_{total}$ are 0.023 mol dm^{-3} and 0.030 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

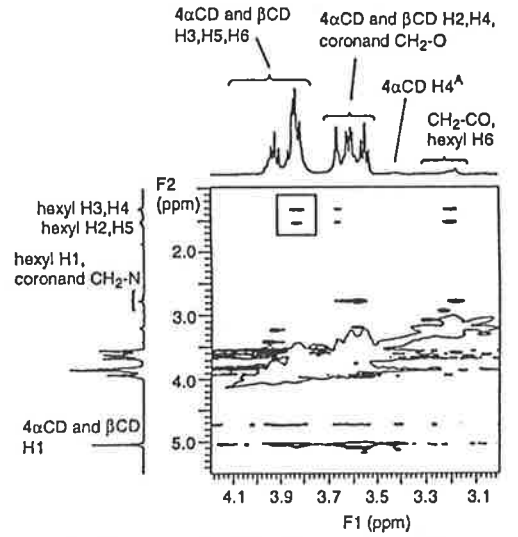


Fig. 4 ^{1}H 600 MHz 2D ROESY NMR spectrum at 298 K of a D_2O solution in which $[4]_{total}$ and $[\beta CD]_{total}$ are 0.014 mol dm^{-3} and 0.020 mol dm^{-3}, respectively. The cross-peaks enclosed in the rectangle arise from dipolar interactions between the protons indicated on the F1 and F2 axes.

the 3·βCD and 4·βCD pseudo [2]-rotaxanes seen in Figs. 3 and 4. It is anticipated that similar 5·βCD and 6·βCD pseudo [2]-rotaxanes should also form in competition with intramolecular complexation, but because of the uncertainty in interpretation of the ROESY spectra resulting from the overlap of the cross-peaks arising from 5, 6 and βCD, these systems were not studied in detail.

The ^{1}H ROESY NMR spectrum of a D_2O solution of 3 and αCD shows no cross-peaks arising from dipolar interactions between the protons of the substituent and the H3, H5 and H6 protons of αCD consistent with the αCD annulus being too small to allow passage of the 15-membered azacoronand through it to form the 3·αCD pseudo [2]-rotaxane (Fig. S3†). This, together with the observations for 5 and 6 and βCD, demonstrates the importance of the relative size of the azacoronand and the CD annulus in intermolecular complexation and reinforces the earlier deductions made concerning intramolecular complexation in 3–6.

Metal ion complexation

In principle, the intramolecular complexes of 5 and 6 could be mechanically restrained to form a molecular knot and the 3·βCD and 4·βCD pseudo [2]-rotaxanes to form [2]-rotaxanes by stiffening the 15- and 18-membered azacoronand components in conformations too large to pass through the βCD annuli as a consequence of complexing metal ions. Potentiometric titrations of 5 in the presence of Ca^{2+}, Zn^{2+} and La^{3+} yield log (K/dm^3 mol^{-1}) = <2, 3.93 ± 0.07, 6.34 ± 0.06, 3.06 ± 0.07 and 5.38 ± 0.05 for Ca^{2+}·5, Zn^{2+}·H5$^+$, Zn^{2+}·5, La^{3+}·H5$^+$ and La^{3+}·5 (where K is the stepwise complexation constant) at 298.2 K and I = 0.10 mol dm^{-3} (NEt_4ClO_4) in aqueous solution.

A combination of the precipitation of the Zn^{2+} and La^{3+} hydroxides above pH 6.5 and 7.5, respectively, and the protonation of 3–6 inhibiting formation of 3·βCD and 4·βCD and the intramolecular complexation of 5 and 6 hindered significant study of [2]-rotaxanes Zn^{2+}·3·βCD and Zn^{2+}·4·βCD and their La^{3+} analogues and the intramolecular complexes Zn^{2+}·3 and Zn^{2+}·4 and their La^{3+} analogues in which it is anticipated that the metal ion complexation induced stiffening of extended azacoronand conformations could cause considerable mechanical restraint. Thus, the weak cross-peaks observed in the ROESY spectrum of 5 at pD = 7 were absent at pD = 6.5 after the addition of 2 equivalents of $Zn(ClO_4)_2$ to the solution consistent with none of Zn^{2+}·5 existing in the molecular knot form.

Conclusion

The preparation of the C(6) mono-substituted αCD and βCD, 3–6, has facilitated an experimental calibration of the αCD and βCD annular sizes relative to those of their 15- and 18-membered azacoronand substituent components. Thus, both azacoronands pass through the βCD annulus whereas they do not pass through the αCD annulus as demonstrated by the formation of intramolecular complexes of 5 and 6 and the formation of 3·βCD and 4·βCD pseudo [2]-rotaxanes. It is also found that monoprotonation of 3–6 inhibits the formation of both the intramolecular complexes and the pseudo [2]-rotaxanes. Metal ion complexation of the azacoronand component of the C(6) substituent of 5 is consistent with the possibility of developing molecular knots and [2]-rotaxanes in which metal ion complexation locks substituent components into mechanically restraining conformations. Several syntheses of cyclodextrin [2]-rotaxanes in water have been reported[12–15] and generally their yields are higher than those obtained in non-aqueous solution[16] probably because of the strong hydrophobic driving force for the formation of precursor pseudo [2]-rotaxanes that exists in water. Accordingly, studies of groups at the ends of the CD substituents of potential molecular knots and of potential rotaxane axles that complex metal ions more strongly than the monoazacoronands are in progress with a view to developing systems in which such groups assume mechanically restraining conformations in molecular knots and [2]-rotaxanes upon metal complexation in water.

Experimental

General

Infrared spectra were recorded on an ATI Mattson Genesis FT-IR. The abbreviations strong (s), medium (m), weak (w) and broad (b) are used for reporting the intensity of the bands observed. ^{1}H and ^{13}C NMR spectra were recorded using a Varian-300 spectrometer operating at 300.145 MHz (^{1}H) or 75.4 MHz (^{13}C), unless otherwise stated. A Varian Gemini 200 spectrometer operating at 199.953 MHz (^{1}H) and 50.4 MHz (^{13}C) was also used. The NMR spectra of cyclodextrin derivatives were recorded at approximate concentrations of 0.02–0.03 mol dm^{-3} in D_2O. Signals were referenced to an external standard, aqueous trimethylsilylpropiosulfonic acid. The 2D-ROESY NMR spectra of cyclodextrin derivatives were recorded on a Varian Inova 600 Spectrometer operating at 599.957 MHz, using a standard sequence with a mixing time of 0.3 seconds. MALDI-TOF mass spectrometry was carried out at the Research School of Chemistry at the Australian National University, Canberra, ACT. Electrospray mass spectrometry (ESMS) was carried out at the University of Adelaide. Samples were dissolved in water for injection.

Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. As cyclodextrin derivatives have water molecules associated with them, they were characterised by adding whole numbers of water molecules to the molecular formula to give the best fit to the microanalytical data.

Potentiometric titrations were carried out using a Metrohm Dosimat E665 titrimator, an Orion SA 720 potentiometer and an Orion 81–03 combination electrode that was filled with 0.10 mol dm^{-3} NEt_4ClO_4. The electrode was soaked in 0.10 mol dm^{-3} NEt_4ClO_4 solution for at least three days prior to use. Titrations were performed in a water-jacketed 2 cm^3 titration vessel held at 298 ± 0.1 K. A gentle stream of nitrogen was passed through the titration solutions which were magnetically stirred. The titration solutions were allowed to stand in the titration vessel for 15 minutes before the titration was begun to allow the solution to equilibrate to 298 K and become saturated with nitrogen. In titrations of 5, 0.0975 mol dm^{-3} NEt_4OH was titrated against a solution that was 1.0 × 10^{-3} mol dm^{-3} in the cyclodextrin derivative, 3.2 × 10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in NEt_4ClO_4 (I = 0.1). The NEt_4OH solution was standardised by titrating against 0.010 mol dm^{-3} potassium hydrogen phthalate. All titrations that were performed in the presence of metal ions were carried out using 2 equivalents of the metal ion. The electrode was calibrated every 24 hours by titration of a solution that was 3.2 × 10^{-3} mol dm^{-3} in $HClO_4$ and 0.10 mol dm^{-3} in NEt_4ClO_4. Values of pK_a (acid dissociation constant) and K (metal complex stability constant) were determined using the program SUPERQUAD. For each system, the titration was performed at least three times and at least two of the runs were averaged. Only runs for which χ^2 was < 12.6 at the 95% confidence interval were selected for averaging.

Thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) on aluminium-backed sheets. Plates were developed with 7 : 7 : 5 : 4 v/v ethyl acetate/propan-2-ol/ammonium hydroxide/water. Cyclodextrin compounds were visualised by drying the plate then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat gun. To visualise amino bearing compounds, plates were dried then dipped into a 0.5% ninhydrin in ethanol solution and heated with a heat-gun, prior to being dipped in the acid solution. The

value R_c represents the R_f of a modified cyclodextrin relative to the R_f of the parent cyclodextrin.

All reagents used were obtained from Aldrich and were not further purified before use, unless otherwise stated. β-Cyclodextrin was donated by Nihon Shokuhin Kako Co. Both α- and β-cyclodextrin were dried by heating at 100 °C under vacuum for 18 hours. 6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin, **1**, and 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin, **2**, were prepared by literature procedures.[6] The precursors to the 4-nitrophenyl esters **7** and **8**, 2-(1,4,7,10-tetraoxa-13-azacyclopentadecanyl)acetic acid and 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecanyl)acetic acid were prepared in a similar manner to literature procedures.[17–19] Pyridine and 1-methylpyrrolidin-2-one (NMP) were dried by distillation from calcium hydride. *N*,*N*′-dimethylformamide (DMF) was dried over molecular sieves.

4-Nitrophenyl 2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetate 7

2-(1,4,7,10-Tetraoxa-13-azacyclopentadecanyl)acetic acid (0.151 g, 0.403 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.0584 g, 0.422 mmol) and dicyclohexylcarbodiimide (0.086 g, 0.42 mmol) were added and the mixture was stirred under nitrogen for 2 hours. The solution was filtered through Celite to remove DCU. Dichloromethane was removed at reduced pressure to leave the ester **7** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (thin film) 1764 cm^{-1} (C=O), 855 cm^{-1} (Ar).

4-Nitrophenyl 2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetate 8

2-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecanyl)acetic acid (0.116 g, 0.372 mmol) was dissolved in dry dichloromethane (5 cm^3). 4-Nitrophenol (0.0570 g, 0.409 mmol) and dicyclohexylcarbodiimide (0.0859 g, 0.417 mmol) were added and the mixture was stirred at room temperature for 4 hours, and then heated at reflux under nitrogen for 24 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and dichloromethane was removed at reduced pressure to leave **8** as a yellow oil, which was used without purification (quantitative yield), ν_{max} (thin film) 1767 cm^{-1} (C=O), 856 cm^{-1} (Ar).

General procedure for the preparation of the monoazacoronand-tethered cyclodextrins 3–6

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** or 6^A-(6-aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.3 mmol) was added to a solution of the nitrophenyl ester **7** or **8** (~1.5 molar equiv.) in dry DMF (5 cm^3) and the mixture was stirred for 18–48 hours in a lightly stoppered flask at room temperature. A 1 : 1 v/v ethanol/ether solution (100 cm^3) was added with stirring to precipitate out the product. The pale yellow precipitate was collected and washed with 1 : 1 v/v ethanol/ether (60 cm^3) followed by ether (60 cm^3). The precipitate was dissolved in water (10 cm^3) and loaded onto an AG-4X4 (4.5 × 3 cm) anion exchange column (free base form). The cyclodextrin product was eluted with water (100 cm^3). The residue was dissolved in water (10 cm^3) and loaded on to a Bio-Rex 70 (NH_4^+ form) column (4.5 × 4.5 cm) and eluted with water (250 cm^3) followed by 0.05 mol dm^{-3} ammonium bicarbonate solution (250 cm^3). Fractions containing the product were combined and water was removed under reduced pressure. The residue was freeze-dried, then dried over phosphorus pentoxide to give the product as a white or pale yellow solid.

6^A-Deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-α-cyclodextrin 3

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** (0.286 g, 0.267 mmol) was added to a solution of the nitrophenyl ester **7** (0.240 g, 0.478 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **3** was obtained as a white solid (0.086 g, 24%), R_c = 1.4; ES-MS *m/z* 1331 (M^+); [Found: C, 44.50; H, 7.20; N, 2.77%. Calc. for **3**·7H_2O ($C_{54}H_{109}N_3O_{41}$) C, 44.53; H, 7.54; N, 2.89%]; δ_H(D_2O, pD ~ 9) 4.97–5.00 (m, 6H, H1), 3.76–3.93 (m, 22H, H3, H5, H6), 3.50–3.66 (m, 27H, H2, H4, coronand CH_2-O), 3.39 (t, J = 9.0 Hz, 1H, H4^A), 3.13–3.17 (m, 5H, hexyl H6, H6^A, N-CH_2-C=O), 2.82–2.85 (m, 1H, H6$^{A'}$), 2.70 (t, J = 4.8 Hz, 4H, coronand N-CH_2), 2.62 (t, J = 7.2 Hz, 2H, hexyl H1), 1.43–1.48 (m, 4H, hexyl H2, hexyl H5), 1.25–1.29 (m, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 177.30 (C=O), 104.17, 104.07, 103.83 (C1), 86.37 (C4^A), 83.94, 83.90, 83.80 (C4), 76.43, 76.08, 76.02, 75.90, 75.76, 74.77, 74.36 (C2, C3, C5), 72.68 (C5^A), 72.43, 72.12, 71.64, 71.42 (coronand C-O), 63.14 (C6), 61.38, 56.92, 51.96, 51.49 (C6^A, hexyl C1, N-C-C=O, coronand C-N), 41.80 (hexyl C6), 31.20, 30.34, 28.69 (hexyl C2–C5).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-α-cyclodextrin 4

6^A-(6-Aminohexyl)amino-6^A-deoxy-α-cyclodextrin **1** (0.192 g, 0.179 mmol) was added to a solution of the nitrophenyl ester **8** (0.159 g, 0.359 mmol) in dry DMF (3 cm^3) and the mixture was stirred at room temperature for 48 hours. After the general work-up and purification procedure, the product **4** was obtained as a white solid (0.082 g, 45%), R_c = 1.6; MALDI-TOF-MS *m/z* 1375.5 (M + H^+); [Found: C, 45.04; H, 7.26; N, 2.90%. Calc. for **4**·6H_2O ($C_{56}H_{111}N_3O_{41}$) C, 45.33; H, 7.55; N, 2.83%]; δ_H(D_2O, pD ~ 9) 5.02 (s, 6H, H1), 3.79–3.96 (m, 22H, H3, H5, H6), 3.53–3.66 (m, 31H, H2, H4, coronand CH_2-O), 3.41 (t, J = 8.4 Hz, 1H, H4^A), 3.17–3.21 (m, 5H, hexyl H6, N-CH_2-C=O, H6^A), 2.87–2.91 (m, 1H, H6$^{A'}$), 2.76 (t, J = 4.8 Hz, 4H, coronand N-CH_2), 2.66 (t, J = 6.6 Hz, 2H, hexyl H1), 1.47–1.52 (m, 4H, hexyl H2, hexyl H5), 1.26–1.33 (m, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 174.29 (C=O), 102.71, 102.50, 102.30 (C1), 84.72 (C4^A), 81.98, 81.85 (C4), 74.49, 72.94, 72.49, 72.40 (C2, C3, C5), 70.79 (C5^A), 69.58, 69.49, 67.99 (coronand C-O), 60.96 (C6), 57.58, 55.28, 50.16, 49.08 (C6^A, hexyl C1, N-*C*-C=O, coronand C-N), 39.46 (hexyl C6), 28.78, 28.69, 26.49, 26.36, (hexyl C2–C5).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamido)hexylamino)-β-cyclodextrin 5

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.483 g, 0.392 mmol) was added to a solution of the nitrophenyl ester **7** (0.275 g, 0.549 mmol) in dry DMF (5 cm^3) and the mixture was stirred for 18 hours in a lightly stoppered flask. After the general work-up and purification procedure, the product **5** was obtained as a pale yellow solid (0.287 g, 49%), R_c = 1.4; MALDI-TOF-MS *m/z* 1493 (M + H^+); [Found: C, 43.50; H, 7.59; N, 2.54%. Calc. for **5**·9H_2O ($C_{60}H_{123}N_3O_{48}$) C, 43.55; H, 7.49; N, 2.61%]; δ_H(D_2O, pD ~ 9) 5.00–5.03 (m, 7H, H1), 3.70–3.90 (m, 26H, H3, H5, H6), 3.56–3.70 (m, 29H, H2, H4, coronand O-CH_2), 3.18–3.39 (m, 5H, H4^A, hexyl H6, N-CH_2-C=O), 3.03–3.08 (m, 1H, H6^A), 2.70–2.81 (m, 5H, H6$^{A'}$, coronand N-CH_2), 2.52–2.57 (m, 2H, hexyl H1), 1.41–1.60 (m, 4H, hexyl H2, hexyl H5), 1.24–1.31 (m, 4H, hexyl H3, hexyl H4); δ_C(D_2O, pD ~ 9) 174.10 (C=O), 103.54, 103.39, 103.33, 103.26, 103.17 (C1), 84.76 (C4^A), 82.22, 82.08 (C4), 74.47, 74.32, 74.21, 73.53, 72.32 (C2, C3, C5), 69.23, 68.94, 68.90, 68.72, 68.35, 67.95, 67.72 (coronand C-O, C6), 60.69, 58.99, 55.57, 55.22 (C6^A, hexyl C1, N-*C*-C=O, coronand C-N), 39.50 (hexyl C6), 28.72, 26.36 (hexyl C).

6^A-Deoxy-6^A-(6-(2-(1,4,7,10,13-pentaoxa-16-azacyclooctadecan-16-yl)acetamido)hexylamino)-β-cyclodextrin 6

6^A-(6-Aminohexyl)amino-6^A-deoxy-β-cyclodextrin **2** (0.404 g, 0.328 mmol) was added to a solution of the nitrophenyl ester **8**

(0.210 g, 0.450 mmol) in dry DMF (5 cm^3) and the mixture was stirred for 18 hours in a lightly stoppered flask. After the general work-up and purification procedure, the product **6** was obtained as a white solid (0.249 g, 50%), R_c = 1.3; ES-MS *m/z* 1537 (M^+); [Found: C, 43.58; H, 6.70; N, 2.38%. Calc. for $6.9H_2O$ ($C_{62}H_{127}N_3O_{49}$) C, 43.84; H, 7.54; N, 2.47%]; $\delta_H(D_2O$, pD ~ 9) 5.02–5.05 (m, 7H, H1), 3.73–3.99 (m, 26H, H3, H5, H6), 3.53–3.69 (m, 31H, H2, H4, coronand O-CH_2, N-CH_2-C=O), 3.22–3.24 (m, 3H, $H4^A$, hexyl H6), 3.04 (d, J = 14.4 Hz, 1H, $H6^A$), 2.76–2.84 (m, 5H, $H6^{A'}$, coronand N-CH_2), 2.59–2.61 (m, 2H, hexyl H1), 1.42–1.57 (m, 4H, hexyl H2, hexyl H5), 1.25–1.38 (m, 4H, hexyl H3, hexyl H4); $\delta_C(D_2O$, pD ~ 9) 176.90, (C=O), 104.96, 104.60, 102.61 (C1), 85.15 ($C4^A$), 84.14, 83.86 (C4), 77.02, 76.07, 75.53, 74.78, 74.67, 73.95 (C2, C3, C5), 72.63, 72.47, 72.34, 71.43 (coronand C-O), 62.85 (C6), 60.30, 57.46, 48.40, 46.61 ($C6^A$, hexyl C1, N-C-C=O, coronand C-N), 41.53 (hexyl C6), 31.41, 29.80, 28.67, 28.26 (hexyl C).

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