Radical Functionalisation of Amino Acid Derivatives

A Thesis

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ABSTRACT

Carbamate derivatives of glycine, alanine and serine have been shown to react by *N*-methylation, without racemisation, on treatment with *tert*-butyl perbenzoate in the presence of cupric octanoate. The selective reaction of *N*-*tert*-butoxycarbonylglycine methyl ester, in preference to the corresponding alanine and valine derivatives, indicates that the relative reactivity of these substrates is determined by the comparative ease of their complexation to the copper. *N*-Methylation is thought to proceed either through electron transfer from the substrate to cupric ion, followed by combination with methyl radical, or through complexation between the substrate and a methyl-copper(III) species.

The relative reactivity of *N*-protected glycine methyl esters exhibited in hydrogen transfer reactions involving *tert*-butyl perbenzoate, nickel peroxide and *N*-bromosuccinimide has been shown to be markedly affected by the electronic nature of the amine protecting group. Relative rate constants obtained from competitive reactions between *N*-protected glycine methyl esters and *N*-bromosuccinimide indicate a direct correlation between the relative rates of reaction and the pK_a values for the carboxylic acids corresponding to the *N*-acyl substituents of the glycine derivatives. The relative reactivity of the glycine derivatives was attributed to the ability of the *N*-acyl substituents to donate electrons towards the stabilisation of an electron deficient site, developed in the transition state, at the site of hydrogen abstraction. This relative reactivity was reflected in reactions of hippuric acid and *N*-pentafluorobenzoylglycine with peptidylglycine α–amidating monooxygenase (PAM), and gave a preliminary indication that the *N*-acyl substituent of *N*-pentafluorobenzoylglycine has an inhibitory effect on the reaction catalysed by this enzyme.

Relative rates of reaction of modified substrates of *(S)*-phenylalanine ammonia-lyase (PAL) were found not to reflect the relative acidities of the corresponding β–protons. This suggests that β–hydrogen abstraction is not the rate determining step in the reaction catalysed by PAL.

The *(2R,3S)* and *(2R,3R)* stereoisomers of 2,3-dideuteriophenylalanine have been prepared and reacted with PAL. Both gave the product *trans*-cinnamic acid with no deuterium content at the 2-position and approximately 25% deuterium content at the 3-position. Treatment of unlabelled *(R)*-phenylalanine with PAL in deuteriated buffer gave *trans*-cinnamic acid with approximately 25% deuterium content at the 2-position and 50% deuterium content at the 3-position. These results indicate that a minor pathway for reaction of *(R)*-phenylalanine with the enzyme may be attributed, at least in part, to proton exchange. It was therefore not possible to obtain accurate data to distinguish between isomerisation to *(S)*-phenylalanine, before elimination, and synperiplanar elimination as the minor reaction pathway for *(R)*-phenylalanine, both previously suggested.