



# 6A-Amino-Cyclodextrins: Their Preparation, Reactions and Host-guest Chemistry

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## Abstract

This thesis describes the preparation and characterisation of a series of 6<sup>A</sup>-amino-substituted  $\beta$ -cyclodextrins. The reactions of 6<sup>A</sup>-*O*-(4-methylbenzenesulfonyl)- $\beta$ -cyclodextrin **32** with a range of primary and secondary amines in 1-methyl-pyrrolidin-2-one at 70 °C produce thirteen amino-substituted  $\beta$ -cyclodextrins in yields of 30-50%. The product cyclodextrins have been fully characterised by NMR, electrospray-ms and elemental analysis.

Potentiometric titration was used to determine the  $pK_a$  values of the protonated amines and the formation constants of the complexes formed by them with benzoate, 4-methylbenzoate and (*R*)- and (*S*)-2-phenylpropionate. The formation constants of these complexes were much greater than those found for the complexes formed with  $\beta$ -cyclodextrin. In particular, the complexes formed with cyclodextrins bearing a cyclic polyamine substituent were extremely stable, with formation constants in the range 9650-44000 dm<sup>3</sup> mol<sup>-1</sup> for the complexes formed between the cyclodextrins bearing a 1,5,9-triazacyclododecanyl or a 1,4,7,10-tetraazacyclododecanyl substituent and these carboxylates. NMR studies suggest that the high stability of these complexes may be due to the capping of the primary face of the cyclodextrin by the cyclic substituent.

The solution structures of the complexes formed between the carboxylates and some of the modified cyclodextrins were examined by 2D-ROESY NMR spectroscopy. Hydrophobic linear substituents are included within the annulus at high pH, when the substituent is non-protonated. The spectra of the complexes formed between 6<sup>A</sup>-(6-aminohexyl)amino-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin and the carboxylates indicate that the 6-aminohexyl substituent is included simultaneously with the carboxylate.

The Zn(II) complexes of 6<sup>A</sup>-(1,5,9-triazacyclododecan-1-yl)- and 6<sup>A</sup>-(1,4,7,10-tetraazacyclododecan-1-yl)-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin were examined as mimics of esterases. The reactions of 6<sup>A</sup>-(1,5,9-triazacyclododecan-1-yl)-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin with 4-

nitrophenyl acetate are inhibited by the presence of Zn(II). The reactions of 6<sup>A</sup>-(1,4,7,10-tetraazacyclododecan-1-yl)-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin with 4-nitrophenyl acetate were marginally enhanced by the presence of Zn(II) at pH  $\leq$  7.5 but were inhibited by the presence of Zn(II) at higher pH.

The reactions of  $\omega$ -aminoalkylamino-substituted  $\beta$ -cyclodextrins with 4-nitrophenyl acetate involve the nucleophilic attack of the primary nitrogen on the carbonyl of the ester to give the acetamides. The major reactive species is the non-protonated species as shown by the pH dependence of the reaction of 6<sup>A</sup>-(6-aminohexyl)amino-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin with 4-nitrophenyl acetate. The reaction of this ester with the  $\omega$ -aminoalkylamino-substituted  $\beta$ -cyclodextrins involves the inclusion of the ester within the annulus as shown by the inhibition of the reaction in the presence of adamantane-1-carboxylate. The inhibition is not quantitative, some of the reaction between the ester and the cyclodextrins occurs by a normal S<sub>N</sub>2 pathway. The solution structure of the complex formed between adamantane-1-carboxylate and 6<sup>A</sup>-(6-aminohexyl)amino-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin was examined by 2D-ROESY NMR spectroscopy. The adamantyl group is deeply included within the annulus while the 6-aminohexylamino substituent forms a rigid structure within the primary face of the cyclodextrin.

The effect of the hydrophobicity of the substituent on the inclusion chemistry of modified cyclodextrins was examined by 2D-ROESY NMR spectroscopy. A 12-aminododecyl substituent is much more strongly included within the annulus than is 6-aminohexyl substituent, preventing the inclusion of 4-methylbenzoate within the annulus of 6<sup>A</sup>-(12-aminododecyl)amino-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin. Adamantane-1-carboxylate is able to displace most of the alkyl chain of the 12-aminododecyl substituent from the annulus but is itself only partially included within the annulus.

The reactions of 6<sup>A</sup>-(6-aminohexyl)amino-6<sup>A</sup>-deoxy- $\beta$ -cyclodextrin with the 4-nitrophenyl esters of 1-methoxycarbonyl-cubane-4-carboxylic acid, 2,3-dimethyl-1-methoxycarbonyl-cubane-4-carboxylic acid and adamantane-1-carboxylic acid lead to the formation of the corresponding 6-amidohexylamino-substituted cyclodextrins. The substituents of each of these derivatives is included within the annulus. Addition of adamantane-1-carboxylate to solutions of these modified cyclodextrins causes the cubanyl substituents to be

excluded from the annulus as the adamantane-1-carboxylate is included. The adamantyl substituent of 6<sup>A</sup>-(6-*N*-(adamantan-1-oyl)aminohexyl)amino-6<sup>A</sup>-deoxy-β-cyclodextrin is not excluded from the annulus by adamantane-1-carboxylate under these conditions and no inclusion of the added adamantane-1-carboxylate occurs. 6<sup>A</sup>-(6-*N*-(adamantan-1-oyl)aminohexyl)amino-6<sup>A</sup>-deoxy-β-cyclodextrin may be a molecular knot.

The reaction of 1,4-bis(4-nitrophenoxycarbonyl)-cubane with 6<sup>A</sup>-(6-aminohexyl)amino-6<sup>A</sup>-deoxy-β-cyclodextrin gives a cyclodextrin dimer. The cubanyl group is included within the annulus of one of the cyclodextrin moieties leading to a product which is asymmetric on the NMR time-scale. Addition of two equivalents of adamantane-1-carboxylate to the dimer generates a symmetric 1:2 host-guest complex where the cubanyl group has been displaced from the annulus and each cyclodextrin moiety has included a molecule of adamantane-1-carboxylate.