Synthesis of Modified Cyclodextrins and Studies of Their Inclusion Complexes

John Papageorgiou

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Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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ABSTRACT

The stability constants of the inclusion complexes of the conjugate bases of *para*-fluorobenzoic acid and the corresponding *ortho*-isomer, and the methyl esters of those acids, with β-cyclodextrin and the conjugate acids of 6^A-amino-6^A-deoxy-β-cyclodextrin and 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin, in pH 6.0 phosphate buffer, have been determined through the application of ^{19}F nuclear magnetic resonance spectroscopy. In addition the ^{19}F chemical shifts of the fluoro substitutents of the guests in their fully complexed states have been derived. The stability constant of the inclusion complex of β-cyclodextrin with the *ortho*-substituted anion is 19 ± 3 mol^{-1} dm^3, with the *para*-substituted anion is 50 ± 2 mol^{-1} dm^3, with the *ortho*-substituted ester is 253 ± 11 mol^{-1} dm^3 and with the *para*-substituted ester is 228 ± 7 mol^{-1} dm^3. The stability constant of the inclusion complex of the conjugate acid of 6^A-amino-6^A-deoxy-β-cyclodextrin with the *ortho*-substituted anion is 65 ± 2 mol^{-1} dm^3, with the *para*-substituted anion is 69 ± 4 mol^{-1} dm^3, with the *ortho*-substituted ester is 152 ± 7 mol^{-1} dm^3 and with the *para*-substituted ester is 128 ± 7 mol^{-1} dm^3. The stability constant of the inclusion complex of the conjugate acid of 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin with the *ortho*-substituted anion is 32 ± 3 mol^{-1} dm^3, with the *para*-substituted anion is 19 ± 5 mol^{-1} dm^3, with the *ortho*-substituted ester is 69 ± 2 mol^{-1} dm^3, and with the *para*-substituted ester is 59 ± 2 mol^{-1} dm^3.

The results of this study show that the factors affecting complexation include the charge and extent of hydration of the hosts and guests, the antiparallel alignment of the dipole moments of the hosts and guests in the inclusion complexes, and ionic interactions between the hosts and guests. Complexes of the conjugate acid of 6^A-amino-6^A-deoxy-β-cyclodextrin with the esters are less stable than those of β-cyclodextrin. This is probably a reflection of the decreased hydrophobicity of the annulus of the modified cyclodextrin, resulting from the

effect of hydration of the protonated amino substituent to impinge on the character of the cyclodextrin cavity. The stability constants of complexes of the esters with the conjugate acid of 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin are even lower. The synthesis of 3^A-amino-3^A-deoxy-(2^AS,3^AS)-β-cyclodextrin occurs with inversion of stereochemistry at C-2 and C-3 of the modified glucopyranose unit,[79] with the result that the amino substituent intrudes into the cavity of the cyclodextrin. The consequent hydration of the protonated substituent will decrease the hydrophobicity of the cyclodextrin annulus, to an even greater extent than for the conjugate acid of 6^A-amino-6^A-deoxy-β-cyclodextrin.

C-3 and C-6 substituted cyclodextrin derivatives of 2-phenylpropanoic acid and the non-steroidal antiinflammatory drug Ibuprofen have been prepared *via* reactions of *meta*-nitrophenyl esters. In addition, C-6 cyclodextrin derivatives of the above acids have been prepared by the hydrolysis and subsequent decarboxylation of malonate substituted cyclodextrin derivatives. The diastereoselectivity of these reactions was determined by nuclear magnetic resonance spectroscopic analysis of the products. A modest diastereoselectivity of 2:1 was typically seen in these reactions.

Stability constants of the 1:1 inclusion complexes of C-3-C-3, C-3-C-6 and C-6-C-6 substituted diamide linked β-cyclodextrins with the biaromatic species, 6-(*para*-toluidino)-2-naphthalenesulfonic acid in aqueous buffer at pH 6.9 have been determined through the application of fluorescence spectroscopy. The stability constants of the C-3-C-3 succinamide and oxalamide linked cyclodextrin inclusion complexes are 8,800 and 5,500 mol^{-1} dm^3 respectively, and the stability constant of the analogous C-3-C-6 substituted succinamide linked cyclodextrin complex is 11,050 mol^{-1} dm^3. The stability constant of the C-6-C-6 substituted malonamide linked cyclodextrin complex is 12,000 mol^{-1} dm^3, and the stability constant of the analogous C-6-C-6 substituted urea linked cyclodextrin complex is 55,000 mol^{-1} dm^3. These compare with a stability constant of the corresponding β-cyclodextrin complex of 2,800 mol^{-1} dm^3.

The results of this work indicate that the extent of cooperative binding by the cyclodextrin annuli of the C-3-C-3 and C-6-C-3 diamide linked β-cyclodextrins is only modest, and the extent of cooperative binding shown is lower than that exhibited by the corresponding C-6-C-6 diamide linked cyclodextrins. The extent of cooperative binding by the cyclodextrin annuli of the C-3-C-3 substituted linked β-cyclodextrins decreases as the length of the bridge connecting the annuli is shortened. However the extent of cooperative binding by the cyclodextrin annuli of the C-6-C-6 substituted diamide linked cyclodextrins increases as the length of the tether is shortened. Presumably the inclusion complex conformations of the C-3-C-3 and C-3-C-6 substituted diamide linked β-cyclodextrins are more strained than those of the corresponding C-6-C-6 substituted diamide linked cyclodextrins especially when the tether joining the annuli of these dimers is shortened. The strain may be attributed to the stereochemistry of the cyclodextrin substitution, where the substituents of the C-3 modified cyclodextrins point toward the interior of the cyclodextrin annuli, analogous to the stereochemistry of the amino group of their precursor, 3^{A}-amino-3^{A}-deoxy-($2^{A}S$,$3^{A}S$)-β-cyclodextrin. In direct contrast, the substituents of C-6-C-6 substituted diamide linked cyclodextrins are attached to sterically non-hindered methylene carbons which are free to point away from the cyclodextrin cavity, resulting in less strained systems.