Dipotassium Complex of Per-3,6-anhydro-β-cyclodextrin

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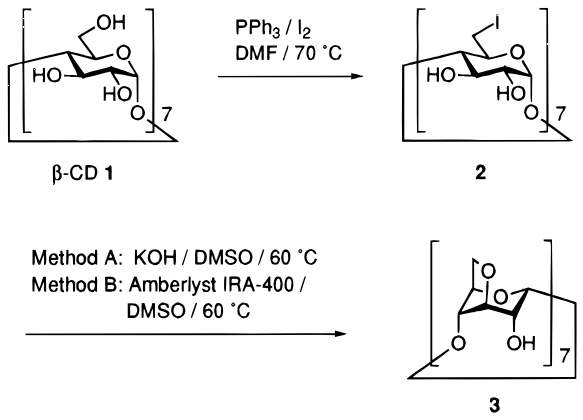
Cyclodextrins (CDs) have been studied widely on account of their abilities to form inclusion complexes with a wide variety of different substrates.[1] In an effort to change and extend their binding capabilities, many chemical modifications have been performed on the CD tori.[2] However, the majority of these chemically-modified CDs have structures which differ only slightly from those of their parent compounds. One way to affect significantly their geometries and, consequently, their binding capabilities is to alter dramatically the conformation of the CDs' carbohydrate residues. Two approaches to these substantially modified CDs have emerged: they are (i) the total synthesis of CD analogues[3−5] containing carbohydrate residues other than glucose—from linear oligosaccharides,[3] by cyclooligomerization of disaccharide monomers[4] or by using a semisynthetic approach[5]—and (ii) the major modifications that can accompany and follow anhydration of the 2,3- or 3,6-hydroxyl groups of the D-glucopyranose residues in the CDs.[6−10] The anhydration approach destroys the $^4C_1$ chair conformation of the α-(1,4)-linked D-glucopyranose residues. 2,3-Epoxidation[6,7] results in the conformation of the pyranose ring being changed from a chair to a half-chair. This change in the conformation of the pyranose rings has a profound effect on the CD geometry. In fact, the configuration of these monosaccharide residues no longer corresponds to that of D-glucose, as a result of nucleophilic substitution with inversion of configuration at one of the chiral centers.[6] The 2,3-anhydration has not only been performed on a single D-glucopyranose residue in CDs but the syntheses of per-2,3-anhydro-CDs have also been reported.[7] 3,6-Anhydration can be employed to achieve even greater distortions of the CD tori as a result of transforming the conformations of the D-glucopyranose rings from the $^4C_1$ to the $^1C_4$ form. Among others,[8] Fujita and co-workers[9] have reported the synthesis and isolation of a number of unsymmetrically-substituted CD derivatives in which this modification has been achieved. More recently, the syntheses of the symmetrically-modified per-3,6-anhydro-CDs have been reported.[10] The prediction that these structures differ markedly from those of their naturally-occurring precursors has been confirmed very recently by the publication[11] of the X-ray crystal structure of the per-3,6-anhydro-γ-CD. The inversion of all the D-glucopyranose rings results in a dramatic change in their binding properties: mass spectrometric experiments performed on the per-3,6-anhydro-CDs have suggested that these new compounds become capable of binding strongly with metal cations.[11,12] A correlation has been noted between the CD cavity dimensions, the size of the metal cation, and the corresponding binding affinities of the CDs. Thus, per-3,6-anhydro-γ-CD prefers to bind large cations, whereas per-3,6-anhydro-α-CD prefers to bind small ones. In this Note, we report the solid state structure of per-3,6-anhydro-β-CD (**3**), which, like its γ-analogue, exhibits a substantial alteration with respect to the original shape of the β-CD cavity.

Scheme 1



Results and Discussion

The synthesis of the per-3,6-anhydro-β-CD (**3**) was achieved (Scheme 1) by reacting the heptaiodide **2** with

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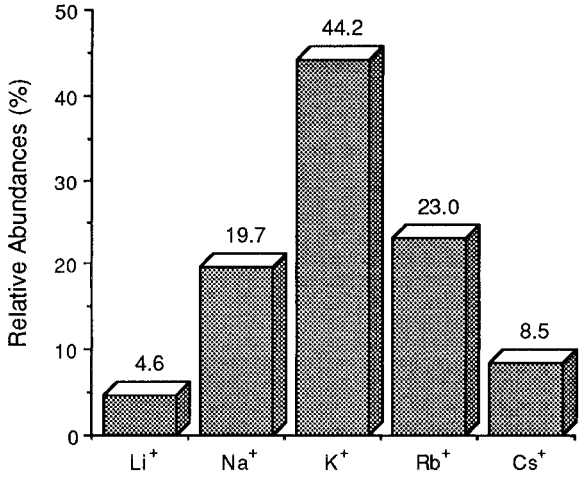

Figure 1. Relative abundance of the peaks for the complexes M^+:**3** ions in LSIMS. Abundances are shown as the relative intensity of the corresponding peak to the sum of the intensities of $[\mathbf{3} + M]^+$ peaks in the spectrum. The intensities for K^+ and Rb^+ were calculated as (intensity of $[\mathbf{3} + {}^{39}K]^+$) × 1.07 and (intensity of $[\mathbf{3} + {}^{85}Rb]^+$) × 1.39, respectively.

base, following a modification of Defaye's method,[10b] using either (i) KOH as the base or (ii) employing a basic ion-exchange resin in DMSO to perform the final peranhydration. The crude products of these reactions were crystallized from a minimum volume of DMF to yield, in both cases, the pure compound **3**. Although some product is lost during the crystallization, this bulk method avoids the use of reverse-phase HPLC, which was employed[10b] previously in the isolation of the per-3,6-anhydro-β-CD (**3**).

In order to determine the cation binding selectivity of **3**, a solution of **3** (10^{-2} M) and Li^+, Na^+, K^+, Rb^+, and Cs^+ (2.3×10^{-2} M for each cation) in MeOH was subjected to liquid secondary ion mass spectrometry[13] (LSIMS) analysis. The data from this experiment (Figure 1) showed a preferential binding for K^+ ions, in contrast with the data reported by Yamamura *et al.*,[12] where Rb^+ ions were found to be bound preferentially.

A single crystal, suitable for X-ray crystallographic analysis, was obtained by vapor diffusion of Me_2CO into an aqueous solution of a particular sample of **3**, which had been prepared using the KOH method (*vide supra*). The solid state structure reveals (Figure 2) a highly folded conformation for **3** with the seven glycosidic oxygen atoms defining (Figure 3) a severely puckered array. This folded conformation facilitates the binding[14] of two potassium ions (separated by 4.25 Å) within the cavity of **3**. These cations, which are 10- and 11-coordinate, bind to

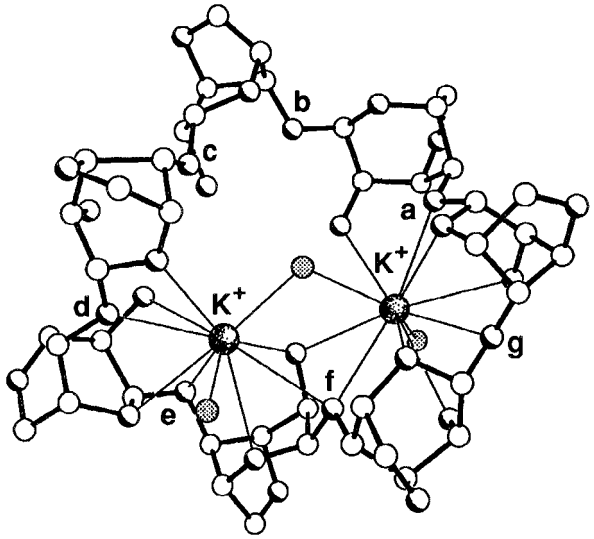

Figure 2. Solid state structure of the dipotassium complex of **3**. The coordinated HO^-/H_2O oxygen atoms are speckled.

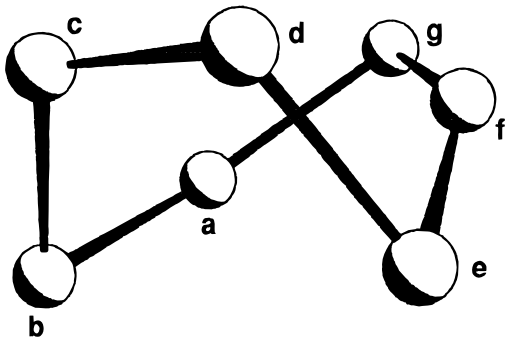

Figure 3. Puckered array formed by the seven glycosidic oxygen atoms **a**−**g** identified in Figure 2.

oxygen atoms,[15] other than the anhydro ring oxygen atoms, in six (two only partially) of the seven 3,6-anhydro-D-glucopyranose residues. Included H_2O molecules and/or HO^- ions serve to satisfy the remaining coordination sites. Inspection of the packing of these dipotassium complexes of **3** reveals (Figure 4) C_3 symmetric "clover leaf" aggregates, each comprising three back-to-back-to-back ionophoric entities, the Me_2CO molecule of solvation (not shown) being trapped in the center of that aggregate.

Summary

Mass spectrometric evidence that per-3,6-anhydro-β-cyclodextrin (**3**) binds preferentially with potassium ions has been presented. Significantly, X-ray crystallographic analysis of crystals isolated from a synthesis employing KOH reveals that, in the solid state, the cyclodextrin derivative **3** assumes a highly distorted conformation and that it binds two potassium ions within its cavity. The 2:1 complexes assemble to form trimeric "clover leaf" aggregates.

Experimental Section

General. All chemicals were purchased from Aldrich and used as received. Cyclodextrins were dried before use over P_4O_{10}

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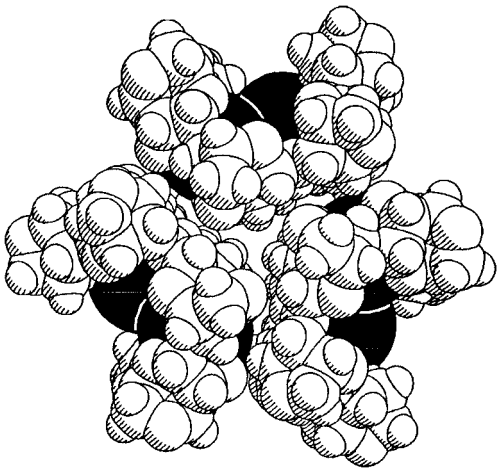

Figure 4. Space-filling representation of the back-to-back-to-back aggregation of complexes of **3** to form a C_3 symmetric "clover leaf" array. The three pairs of coordinated potassium ions are blackened.

at 90 °C for 24 h. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel. The plates were inspected under UV light and developed with H_2SO_4 (5%) in EtOH. ^{1}H-NMR spectra were recorded at 300.1 MHz. ^{13}C-NMR spectra were recorded at 75.5 MHz. Liquid secondary ion mass spectrometry (LSIMS) was performed by employing a cesium ion beam with *m*-nitrobenzyl alcohol as matrix.

Per-3,6-anhydro-β-cyclodextrin[10a−d] **(3). Method A.** Per-6-iodo-β-CD[10b] (**2**) (0.302 g, 0.16 mmol, prepared from β-CD (**1**) by following Defaye's method) was dissolved in DMSO (10 mL), and KOH (0.75 g, 1.6 mmol) was added to the solution. The reaction was stirred at 60 °C for 17 h. The DMSO solution was then concentrated under reduced pressure to give a clear glass, which was dissolved in H_2O (15 mL) and washed with CH_2Cl_2 (2 × 40 mL), before being concentrated to dryness under reduced pressure, giving a white solid. This solid was redissolved in the minimum volume of DMF and allowed to stand for 18 h, during which time a precipitate formed. This precipitate was filtered off, washed thoroughly with Me_2CO, and dried under high vacuum. Successive recrystallyzations from DMF afforded a potassium-free sample of **3** (0.048 g, 30%). The spectroscopic data are in agreement with those reported[10a−d] previously: mp 224−225 °C (lit.[10] mp 226−227 °C); ^{1}H NMR (300 MHz, D_2O) δ 3.93−4.05 (m, 14H), 4.26 (d, $J_{6a,6b}$ = 11 Hz, 7H), 4.32−4.37 (m, 7H), 4.43 (dd, $J_{2,3} = J_{3,4}$ = 4.5 Hz, 7H), 4.61 (m, 7H), 5.26 (d, $J_{1,2}$ = 3 Hz, 7H); ^{13}C NMR (75.5 MHz, D_2O) δ 70.5, 71.4, 73.9, 76.7, 79.3, 100.5.

Method B. Per-6-iodo-β-CD[10b] (**2**) (0.302 g, 0.16 mmol, prepared from β-CD (**1**) by following Defaye's method) was dissolved in DMSO (10 mL), and Amberlyst IRA-400 resin (2.30 g, HO^- form) was added to the solution. The reaction was stirred at 60 °C for 17 h. The ion-exchange resin was then filtered off and washed with H_2O. The DMSO and H_2O washings were combined, and the aqueous solution was then concentrated under reduced pressure to give a clear glass, which was dissolved in H_2O (15 mL) and washed with CH_2Cl_2 (2 × 40 mL), before being concentrated to dryness under reduced pressure, giving a white solid. This solid was redissolved in the minimum volume of DMF and allowed to stand for 18 h, during which time a precipitate formed. This precipitate was filtered off, washed thoroughly with Me_2CO, and dried under high vacuum. The compound was identified as **3** (0.040 g, 26%). The spectroscopic data are in agreement with those reported above.

X-ray Crystallography. Crystal data for the dipotassium complex of **3**: $C_{42}H_{56}O_{28}K_2 \cdot 2[OH] \cdot 3^1/_2H_2O \cdot {}^1/_3Me_2CO$, M = 1203.5, hexagonal, a = 26.477(4), b = 26.477(4), and c = 20.167(4) Å, V = 12244(4) Å^3, space group $P6_3$, Z = 6, ρ_{calcd} = 0.98 g cm^{-3}, μ(Cu Kα) = 16.2 cm^{-1}. A total of 6307 independent measured reflections [$2\theta \leq 120°$] of which 2716 were considered to be observed [$|F_o| > 4\sigma|F_o|$]. Data were measured on a Siemens P4/PC diffractometer, with Cu Kα radiation (graphite monochromated) using ω scans. The structure was solved by direct methods, and the non-hydrogen atoms of **3** and the two potassium ions were refined anisotropically (based on F^2) to give R_1 = 0.153, wR_2 = 0.416. The absolute stereochemistry was confirmed by the Flack parameter which refined to −0.02(7). Computation were carried out using the SHELXTL program system version 5.03. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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