6-*S*-Hydroxyethylated 6-Thiocyclodextrins: Expandable Host Molecules

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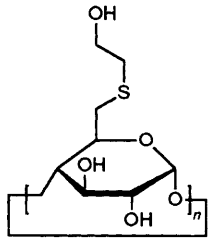
6-*S*-Hydroxyethylated 6-thiocyclodextrins have been synthesised as a new class of host molecule in which the multiple side chains may adopt conformations which increase the cavity size; spectroscopic evidence is presented that implies that the γ-cyclodextrin derivative behaves in this way when complexing with anthraquinone-2-sulfonate.

The α-, β- and γ-cyclodextrins (CDs), cyclomaltohexaose, cyclomaltoheptaose and cyclomaltooctaose, respectively, are well known for their ability to include and transport a wide variety of organic molecules.[1] In general, it is considered that the cavity size of α-CD is suitable for complexation of derivatives of benzene, while the cavity sizes of β-CD and γ-CD are also suitable for derivatives of naphthalene and anthracene, respectively. Although they have different cavity diameters, the heights of the cavities are about the same, 7.9 Å, and the maximum volume is fixed in each case.

To our knowledge, no attempt has been made to synthesise derivatives of cyclodextrin capable of varying the size of their hydrophobic cavity. Rigid capping of β-cyclodextrin by aryl bridges,[2] by pH-controlled nucleic acid base pairs,[3] or with photochemical control,[4] has been demonstrated as an approach to extending the cavity by a fixed volume; while flexible capping with multiple 6-*N*-methyl or -ethyl groups creates a shallower cavity.[5] We are interested in hosts with variable cavities for two purposes: either they could vary their cavity size to suit complexation of guests of different size; or they could complex more than one molecule by enlarging the cavity volume, so increasing the effectiveness of transport or bimolecular guest interactions. With this motivation compounds **1–3** have been prepared.



1; *n* = 6
2; *n* = 7
3; *n* = 8

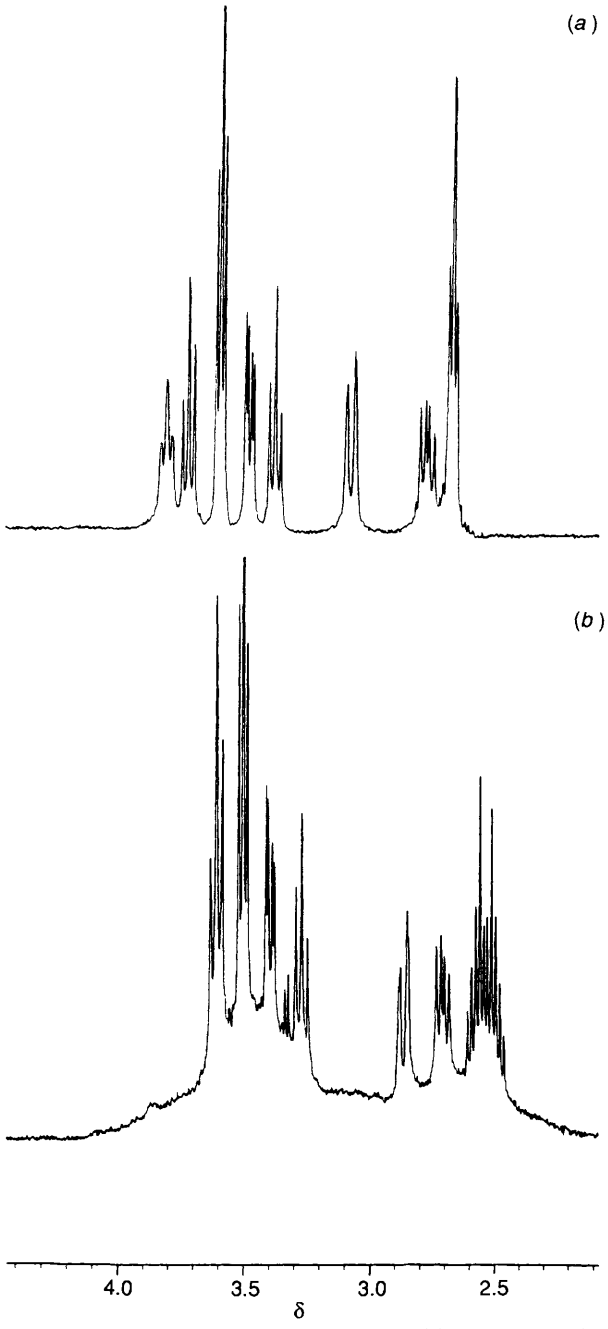


Fig. 1 Partial 400 MHz ^1H NMR spectrum of: (*a*) compound **3** (1.5 mmol dm^{-3}) and (*b*) compound **3** (1.5 mmol dm^{-3}) + sodium anthraquinone-2-sulfonate (3.0 mmol dm^{-3}), in D_2O at 25 °C

Compounds **1–3** were synthesised in excellent yield (>95%) by substitution reaction of the corresponding per-6-bromo-6-deoxy-CDs[6] with potassium 2-hydroxyethylthiolate. Persubstitution is confirmed by elemental analysis and by the simple high-resolution ^1H and ^{13}C NMR spectra. The synthetic hosts possess the same numbers of hydroxy groups as the corresponding natural cyclodextrins, and so are structually similar to these. However, the primary-hydroxy chains are elongated by insertion of the hydrophobic, mobile fragments $-S-CH_2-CH_2-$. We hoped that these flexible groups might organise themselves to form a flexible hydrophobic region which would adapt itself to the size of the included guest molecule.

The γ-CD derivative **3** is the most interesting, as it has the highest solubility in water (0.9 g 100 ml^{-1}), while compounds **1** and **2** are only slightly soluble in water. We used compound **3** to study inclusion of sodium anthraquinone-2-sulfonate **4**, which has been proposed by Perly *et al.*[7] as a shift reagent for

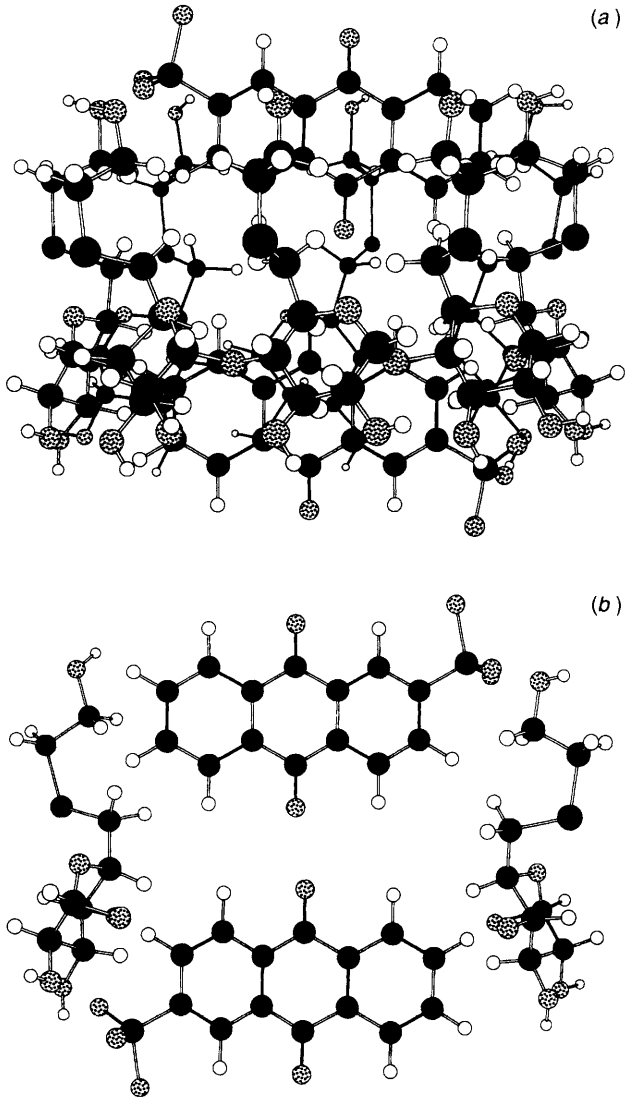


Fig. 2 Molecular model of 1:2 inclusion; (*a*) complete model, (*b*) profile. A unique orientation of guests is not implied

NMR analysis of cyclodextrins. Fig. 1 shows the results of inclusion. In D_2O each proton of the host molecule [spectrum (*a*)] is well resolved with δ H-5 at 3.82, H-3 at 3.73, H-6 at 3.08, and H-6′ at 2.78; the four methylene protons of the SCH_2CH_2O side chain appear as two sets, each with apparent magnetic equivalence, CH_2O as a triplet at δ 3.61 and SCH_2 as another triplet at δ 2.68. On addition of two mol equiv. of the shift reagent **4**, proton H-3 shifts to δ 3.60 [spectrum (*b*)], and H-5 shifts to δ ~ 3.6 (overlapping the other signals), indicating that the molecule **4** is included in the cavity of cyclodextrin. However, there is also striking evidence for interaction with the side chains. The SCH_2 methylene, for which there is a clear triplet when no guest molecule is present, resonates as a complex multiplet, and the CH_2O triplet shifts upfield to δ 3.50. Analysis of the signals indicates that they relate to a $-CH_aH_bCH_2-$ system, in which H_a and H_b couple to each other ($J_{Ha,Hb}$ 13.0 Hz), and also couple to another pair of magnetically equivalent protons to give two quintuplet patterns ($J_{Ha,H} = J_{Hb,H}$ = 6.5 Hz). While this clearly demonstrates interaction between the side chains and guest molecule, underlying broad signals also appear and it is possible that a mixture of isomeric 1:1 complexes as well as a 1:2 complex (containing two molecules of anthraquinonesulfonate) is present.

The chemical shift changes are compared in Table 1 with those for γ-cyclodextrin under the same conditions.[7] This shows that in the modified γ-cyclodextrin **3**, while large shift

Table 1 Chemical-shift changes $\Delta\delta$ (ppm) induced in NMR spectra of CDs (1.5 mmol dm^{-3}) by sodium anthraquinone-2-sulfonate (3.0 mmol dm^{-3}) in D_2O at 25 °C

	H-3	H-5	H-6,6′	SCH_aH_b	CH_2O
γ-CD	−0.19	−0.22	−0.09, −0.1		
3	−0.13	−0.22	−0.2, −0.06	−0.1, −0.17	−0.11

changes occur in the SCH_2CH_2OH side chain, those for H-3 and H-5 are not reduced, and there is a significant increase in $\Delta\delta$ for the H-6 protons compared with the natural cyclodextrin. From these results, we consider that at a high concentration of **3**, the guest molecules are mainly included in the cyclodextrin cavity, but as the concentration of **4** is increased, the guest molecules are included in the cavity of cyclodextrin and also in the hydrophobic volume formed by the side chains.

Molecular modelling[8] demonstrates that the side chains of the host molecule can organise themselves to form a hydrophobic zone with sufficient depth to include a second molecule of **4** (Fig. 2). The splitting of the two SCH_aH_b protons can be explained as follows: when there is no hydrophobic guest molecule, rotation around each bond of the side chain is totally free, and the protons show no magnetic inequivalence; as soon as an excess of hydrophobic molecules is present in solution, the eight side chains organise themselves to form a relatively apolar zone which can be occupied by a guest molecule to maintain the system in a state of minimum energy. Molecular modelling shows (Fig. 2) that since polarity of this zone is efficiently controlled by rotation of the three bonds C_5–C_6, C_6–S, and S–C_{HaHb}, they are practically 'frozen' in position so that the polarity of the zone can reach a minimum. Consequently, the two SC_{HaHb} protons become magnetically inequivalent. However, rotation around the bond C_{HaHb}–CH_2 and CH_2–OH does not affect as much the structure or polarity of the apolar zone formed, so that the two CH_2O protons retain apparent magnetic equivalence on complexation.

We tried to measure association constants K_{11} and K_{12} by NMR titration. However, varying the concentration of compound **4** in D_2O showed that this compound forms aggregates (as shown by changes in the NMR spectrum), when the concentration exceeds $\sim 6.5 \times 10^{-3}$ mol dm^{-3}. In order to avoid this phenomenon, we adopted the technique of UV titration so that the concentration of **4** could be maintained at a very low level ($< 5 \times 10^{-4}$ mol dm^{-3}). In contrast to the results for γ-cyclodextrin,[7] the data did not fit a 1:1 stoichiometry. However, using the method of non-linear regression analysis described by Connors[9] and treating the system as an equilibrium between 1:1 and 1:2 complexes, the association constants K_{11} and K_{12} were estimated as 5.9×10^3 dm^3 mol^{-1} and 7.3×10^2 dm^6 mol^{-2}, respectively. The K_{11} for γ-cyclodextrin–anthraquinonesulfonate has been reported as 5×10^2 dm^3 mol^{-1} (40 °C).[7]

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