Conformational, calorimetric and NMR spectroscopic studies on inclusion complexes of cyclodextrins with substituted phenyl and adamantane derivatives

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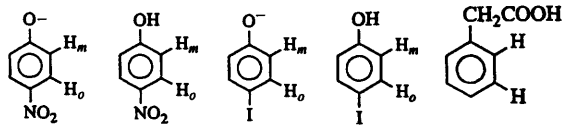
Inclusion modes in complexes with α- and β-cyclodextrins in water have been investigated by NMR spectroscopy at 400 or 500 MHz, and compared with structures obtained by computer-aided molecular modelling and with calorimetric data. The NOEs observed on *o*- and *m*-aryl protons upon irradiation of either H3 or H5 inside the CD cavity indicate for all phenols an inclusion mode with the hydroxy group at the wide cavity end, and an increasingly deep immersion for phenol or phenolate with iodine compared with this nitro group, as *para*-substituent. This is found to be in line with the complexation-induced NMR shifts. Adamantane-1-carboxylate is indicated by distinct NOEs to be fully immersed into the β-CD cavity; the corresponding complex with α-CD shows contact only at the wider rim and a tilted conformation which allows formation of a hydrogen bond between the guest COO^- and the 2-OH group of the CD. The same conformation is found by CHARMm calculations, including simulations in a water box. The results, together with some ΔG° values derived from NMR titrations, are in line with data from calorimetric studies. These show for complexes with tight fit (in α-CD) large enthalpies of up to 43 kJ mol^{-1} as the predominating driving force against sizeable entropy disadvantages ($T\Delta S^\circ \leqslant -24$ kJ mol^{-1}), particularly for guest molecules of higher electron density and/or polarizibility. These observations point to predominating dispersive interactions. In contrast, inclusion in the wider β-CD cavity suffers less from entropy disadvantage ($T\Delta S^\circ \leqslant -11$ kJ mol^{-1}); the binding, however, is still dominated by ΔH°, pointing to predominant cohesive and not entropic hydrophobic forces.

Introduction

Supramolecular complexes of cycloamyloses have received much attention in recent years due to their significance for the understanding of non-covalent forces for the development of enzyme analogues, as well as for their industrial importance, particularly with respect to drug encapsulation and targeting.[2-4] The different cavity widths of α- and β-CDs in combination with substrates of different size, polarity and polarizibility offer a unique opportunity to study the change in binding mechanisms in aqueous solutions, presenting geometrically well defined models for many biologically important complexes. A tight fit, *e.g.* with α-CD and phenyl compounds or with β-CD and adamantyl structures, is expected to lead to predominating van der Waals interactions, *e.g.* of a dispersive type, and should increase with substrate polarizibility, as expected with phenolates compared with electroneutral phenols. At the same time one expects the equilibria to be driven mostly by enthalpic contributions. In contrast, the classical hydrophobic effect, which is more likely with loosely bound substrates such as with phenyl derivatives and β-CD, should be seen as entropy gain. Calorimetric measurements[5] therefore provide an essential basis for the distinction between different binding mechanisms in cyclodextrins.[6]

In most studies, either calorimetric or spectroscopic methods (UV–VIS NMR, fluorescence *etc.*) have been used. We believe that further progress can be expected if the methods are combined in such a way that both the energetics and the geometries of the complexes are elucidated. NMR spectroscopy has played a major role both in the determination of complex stabilities as well as in structural elucidation in solution. The application of NMR techniques as the most promising method for structural data in solution is of particular importance as recent studies have shown that cyclodextrin associations are often not formed by the usually expected intracavity inclusion mode.[7,8] Several of the calorimetrically studied cyclodextrin complexes, in particular those with acyclic alcohols, may actually associate outside the cavity.[7b]



1 2 3 4 5

The substrates chosen (compounds **1**–**6**) were those used in earlier studies or substituted phenols,[2a,9] which fit perfectly in α-CD and allow us to apply less frequently used NMR techniques such as the shift induced by the CD host on the guest molecule, as well as spin lock-NOE (ROESY[10,11]) measurements. *p*-Iodo-phenol and -phenolate were chosen as the highly polarizable iodine might contribute significantly to dispersive, as opposed to solvophobic, binding mechanisms. Adamantane-1-carboxylic acid and adamantane-1-carboxylate (**6**) were studied as we believed that the extensive calorimetric studies by Eftink *et al.*[6c] deserve elucidation of the underlying structures by NMR spectroscopy, complemented by computer-aided molecular modelling.[12]

Experimental

All compounds were commercially available. The cyclodextrins were dried prior to use in a drying pistol over phosphorus pentoxide at 90 °C overnight.

NMR spectroscopy

NMR measurements were carried out as described earlier[8] at 400 or 500 MHz, respectively. Established NMR titration methods[13] were used to determine the complexation-induced

Table 1 NOE (ROESY) effects[a] upon irradiation of H3 and H5 of α-cyclodextrin in complexes with compounds **1–5**

	1		2		3		4		5	
H_{obs}	*o*	*m*	*o*	*m*	*o*	*m*	*o*	*m*	aryl	CH_2
{H_3}	+	+	+	+	++	++	+	++	+	−
{H_5}	−	+	−	+	−	++	−	++	−	−

[a] ++: strong; +: medium; −: no cross peaks.

Table 2 Relative intensity (I)[a] of ROESY cross-peaks between CyD and adamantane-1-carboxylate **6** signals

CyD	H1	H2	H3
α/H3[b]	2.1	3.4	1.9
β/H3 + H5[c]	4.3	6.3	5.9

[a] Solution: [β-CyD] = [AC] = 4.49 × 10^{-3} M, D_2O, ambient temp., pD = 9.8. [b] H3 and H5 overlapping. [c] No cross-peaks of **6** signals with other CD signals were observed except for a weak (I < 1) peak between H6 (CD) and H2, 3 (**6**).

shifts (CIS) values. The association K or ΔG° values were taken either from titration calorimetry[5] or from literature values.[2a,9] NOEs (Table 1) and CIS values (Table 2) were measured[10,11] with concentrations at which 68–80% complexation has occurred usually with [CD] = 0.005 M and [guest] < 0.01 M; the CIS values were then corrected for 100% complexation with the help of the known K values.

Computer-aided molecular modelling

Molecular modelling was performed with the CHARMm22 force field,[14] using an effective relative permittivity of 3 for the electrostatics. The structures were energy minimized until 0.001 kcal mol^{-1} (1 cal = 4.184 J), with the major aim only to control the possible complex geometries. In the case of the α-CD complex with adamantyl-1-carboxylate, the structure (Fig. 1) was also subject to the simulation in a water box (diameter 30 Å, containing 1370 water molecules); the complex retained the same geometry obtained from 'gas-phase' structure opimization.

Calorimetric measurements

Calorimetric measurements are described in detail elsewhere.[5]

Results

Nuclear Overhauser effects (NOE) have been used for the study of cyclodextrin complexes in solution since the pioneering studies of Bergeron and Rowan.[15] The advent of high magnetic fields have greatly enhanced the attainable spectral dispersion; at the same time, however, the unfavourable correlation times of complexes with molecular weights around 10^3 lead to a drop of the observed NOEs, *e.g.* from 34% at 90 MHz to 9% at 250 MHz. The present investigation was carried out on a 400 or 500 MHz spectrometer, which required the application of spin-lock techniques such as ROESY[10,11] for obtaining sizeable NOEs. Technical problems, such as decoupling field instabilities and the absence of cross peak integration software in the 2D spectra allowed us to assign only relative values + + for strong, + for medium and − for no cross peaks in the ROESY matrix (Table 1). Only for the adamantane complexes could quantitative ROEs be obtained on a new suitable 500 MHz system (Table 2).

Fig. 2 describes different inclusion modes for the cyclodextrin complexes; it also illustrates our strategy to distinguish between inclusion modes I, II or III. Intermolecular NOEs on the substrates are only observed upon irradiation of the protons H3 and H5 inside the cyclodextrin cavity. For mode I with no or little immersion of the phenyl ring into the cavity one expects only very small ROEs, and only at a few phenyl protons. For

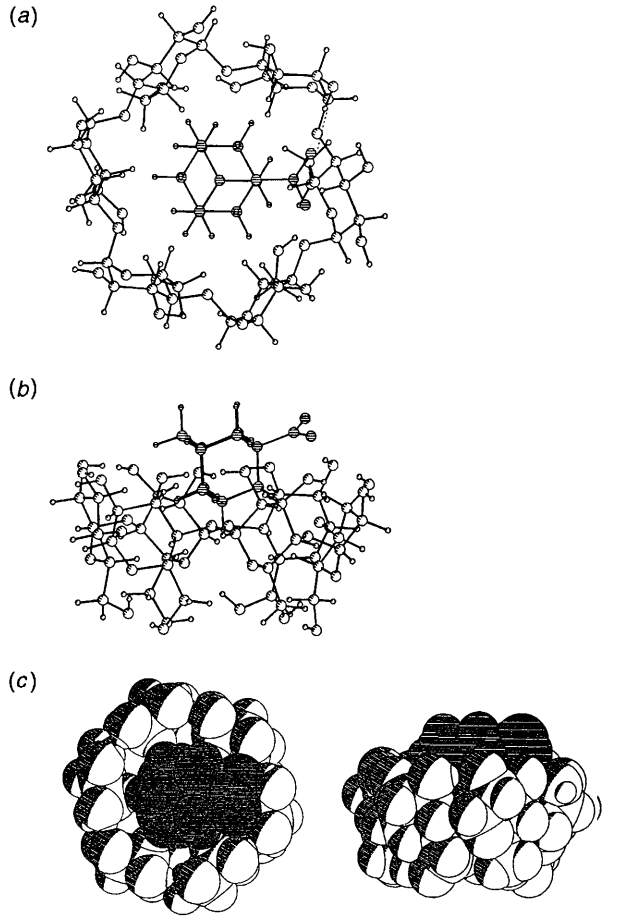


Fig. 1 α-CD with adamantane-1-carboxylate (**6**) (*a*) top view; the hydrogen bond between CD-2-OH and COO^- is shown with ····; $d_{H\cdots O}$ = 2.02 Å, $d_{O\cdots O}$ = 3.01 Å; almost linear O–H–O bridge (angle O–H–O = 166°); (*b*) side view; (*c*) space filling model, top view; force field (CHARMm) energy minimized structures

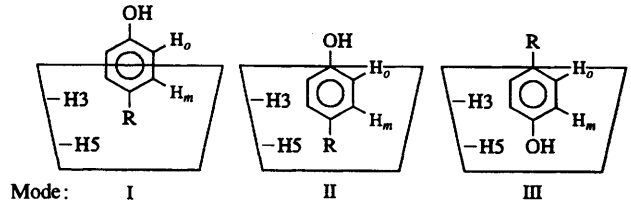


Fig. 2 Complexation modes of phenyl-derivatives with cyclodextrin

mode II irradiation at H3 should lead to ROE of both *o*- and *m*-proton signals, at H5 only of the *m*-proton. In contrast, one expects no effect on the *ortho* signal upon saturation of H5 for mode III. As in some related studies we find for all investigated phenol derivatives mode II with the most solvated hydroxy or phenolate group at the rim of the wider cavity end where no or little desolvation is needed upon complexation. Both iodo-derivatives (**3** and **4**) show remarkably similar and exceptionally large ROEs with the phenyl *m*-protons (Table 1), which indicates that the iodine compounds are more deeply immersed into the cavity than the other phenyl compounds.

The same picture emerges from the complexation-induced shifts on the cyclodextrin protons H1 to H6 (Table 3). As expected, protons H1, H2, H4 and H6, being remote from the complexation site, show almost negligible CIS. Only proton H3 shows substantial shielding effects of up to −0.35 ppm, which not only proves intracavity inclusion, but is in full accord with mode II or III. In both cases only H3 rests on the centre of the benzene ring which has been estimated by Komiyama and Bender[3a] to lie 0.7 Å above the H3 plane. Recent calculations[16]

Table 3 Complexation-induced ^{1}H NMR shifts (CIS) on α-CD protons[a] (ppm) and $\Delta G°$ values

Proton	1	2	3	4	5
1	−0.04	−0.03	−0.02	−0.01	−0.03
2	−0.08	−0.04	−0.05	−0.03	−0.06
3	−0.25	−0.35	−0.25	−0.26	−0.13
4	0.00	0.01	0.00	0.01	−0.01
5	0.02	−0.05	0.35	0.36	0.14
6	0.00	0.00	0.03	0.03	0.01
$\Delta G°$[b]/kJ mol^{-1}	13.6	19.3	20.5	19.2	9.5

[a] All shift CIS values are determined by NMR titration except for compounds **3** and **4**; these are calculated with the *K* value determined by calorimetry and a single NMR experiment. [b] With $\Delta G°$ taken from the literature[9] to obtain the CIS value at 100% complexation.

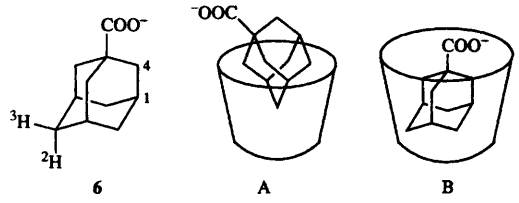


Fig. 3 Adamantane-1-carboxylate and its inclusion complexes with α- (A) and β-cyclodextrin (B)

with realistic geometries obtained from computer-aided molecular modelling and independently verified ring current models[17] show that linear electric field effects must be taken into account for more rigorous approaches. Preliminary calculations[16] again support the general inclusion mode II or III for such arene–cyclodextrin complexes. Exceptionally high deshielding is observed only with the iodides **3** and **4** at H5 where the iodine substituent can lead to an electrical field-induced deviation. In line with the ROEs this suggests that the iodides, in contrast to the other guest molecules, contain the *para*-substituent close to the bottom of the cavity.

Computer-aided molecular modelling agrees with these conclusions: the α-CD ring allows full immersion of *para*-substituted phenols in particular for R = I where the contact of the highly polarizable iodine with the lipophilic 'bottom' allows even some deformation of the electron cloud, whereas the anisotropic nitro-substituent in **1** and **2** pushes the phenyl ring slightly (0.2 Å) out of the cavity towards mode I.

The NMR investigation of adamantane complexes was restricted to a ROESY study (Table 2), as the shifts induced by the aliphatic guest molecule on the CD are too weak. The much larger ROEs observed with β-cyclodextrin, where unfortunately H3 and H5 shifts were too close in the complex for a separate NOE evaluation, clearly indicate the deep immersion mode indicated in Fig. 3 (structure B). The smaller cavity in α-cyclodextrin leads to smaller NOEs with distinctly larger values only at the unresolved protons, H2 and H3, suggesting a partial immersion with the symmetry axis tilted towards the CD axis as visualized in Fig. 3 (structure A).

These conclusions are fully supported by computer-aided molecular modelling which shows that, (*a*), even in the β-CD–adamantane complex there is no room for water molecules inside the cavity (Fig. 2), (*b*) that β-CD allows an optimal contact between the CH bonds of host and guest [Fig. 4(*b*)], whereas the complex with α-CD forms only at the upper rim and (*c*) allows for an additional stabilization by hydrogen bonding between the CD-2-OH group and the COO- group (Fig. 1), leading to the tilted conformation, exactly as established experimentally by the observed NOEs. The force field calculated geometries (Figs. 1 and 4) indicate a strong hydrogen bond with an O–H–O angle of 166°, and short distances for the acceptor–donor combinations (d_{O-H} = 2.08 Å; d_{O-O} = 3.01 Å). Noticeably, the tilted geometry as well as the

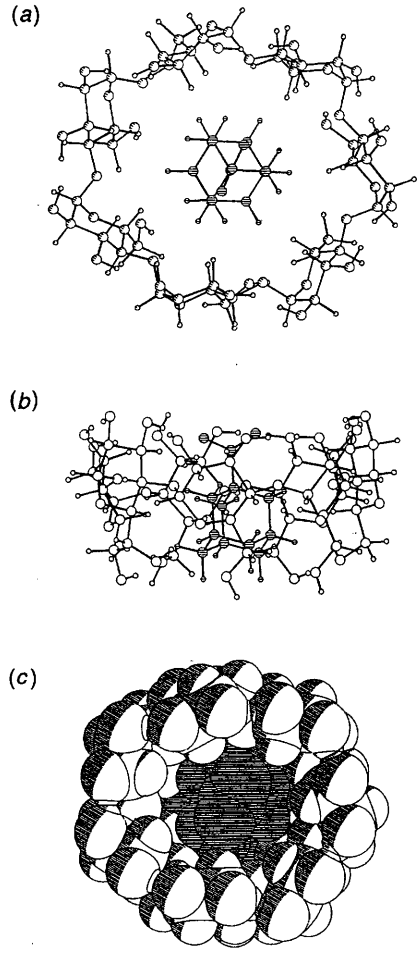


Fig. 4 β-CD with adamantane-1-carboxylate (**6**): (*a*) top view; (*b*) side view; (*c*) space filling model, side view

specific hydrogen bonds are retained in several energy minimizations from quite different starting geometries, as well as in simulations with a water box.

Comparison with calorimetric data and conclusions

The conformational results with the α-CD complexes and the phenols support earlier conclusions by Connors and co-workers[4b,18] who concluded that the 4-substituent R is the predominating site of complexation. This is as expected most pronounced for the iodo compounds which by CIS and NOE values shows the deepest immersion mode II. For the same reason the complexation Gibbs' energies $\Delta G°$ between acid and base differ less for R = I than for all other substituents.[4b,18] The new NMR data, in line with the computer-aided structure simulations, show the closest possible contact between cavity and substrate also for the nitrophenol complexes. As pointed out by several authors the exceptionally large $\Delta G°$ difference between nitrophenol and its anion agrees with the unique increase of van der Waals contributions due to the large charge delocalization in the anion. In contrast, this difference almost disappears with the β-CD complexes, indicating predominantly solvophobic interactions with the too wide cavity.

Thermodynamic data (summarized in Table 4) show consistently the complexes with tight fit (phenols **1**–**4** with α-CD; adamantanes with β-CD) to be dominated by $\Delta H°$, with opposing entropy contributions $T\Delta S°$. These observations again point to dominating dispersive interactions; this agrees also with the distinct $\Delta H°$ increase with the better polarizable and more electron-rich phenolates **1** and **3**. The presence of iodine in **3** and **4** does not lead to enhanced $\Delta H°$, which is in line

Table 4 Calorimetric results[a]

Compound	α-CD			β-CD		
	$-\Delta G$/kJ mol^{-1}	$-\Delta H$/kJ mol^{-1}	$T\Delta S$/kJ mol^{-1}	ΔG/kJ mol^{-1}	ΔH/kJ mol^{-1}	$T\Delta S$/kJ mol^{-1}
1	18.7[b]	42.8	−24.1	15.0[c]	16.1	−1.1
2	11.5[d]	23.0	−11.5	14.2	10.2	3.9
3	19.1	36.5	−17.3	17.1	12.7	4.5
4	16.8	26.3	−9.5	17.0	16.1	0.9
6	11.6	14.3	−2.7	24.5	21.6	2.9
7[e]	—	—	—	32.4	42.1	−9.7

[a] All values in kJ mol^{-1}; *cf.* earlier measurements. [b] Ref. 6*a* $-\Delta G°$ 19.0; $-\Delta H°$ 41.0; $T\Delta S°$ −22.0: ref. 6*c* $-\Delta G°$ 18.0; $-\Delta H°$; 39.0; $T\Delta S°$ −21.0. [c] Ref. 6*a* $-\Delta G°$ 15.0; $-\Delta H°$ 15.0; $T\Delta S°$ 0.0: ref. 6*c* $-\Delta G°$ 9.5; $-\Delta H°$ 12.0; $T\Delta S°$ −2.5.0. [d] Ref. 6*a* $-\Delta G°$ 14.0; $-\Delta H°$ 26.0; $T\Delta S°$ −12.0. [e] Adamantane-1-carboxylic acid.

with NMR results, showing the phenyl part, and to a lesser degree the iodine, to be in contact with the CD cavity. The complexes with the larger cavity of β-CD show entropy effects to be close to zero within the error limits; the diminished binding constants thus are therefore the result of smaller $\Delta H°$ values, which is understandable in view of the necessarily smaller simultaneous contact between host and guest surfaces. For some other calorimetric studies on cyclodextrin complexes[6a,e,v] even positive $T\Delta S°$ contributions have been reported.

The dominating $\Delta H°$ contributions also with the larger β-CD cavity obviously rule out the entropically driven 'classical'[19] hydrophobic binding mechanism. Cohesive interactions, which also are exceptionally high in water as a consequence of its extremely low polarizibility, will also show up as $\Delta H°$ effects, and therefore must be the major driving force for the β-CD complexes. These interactions, which have been identified by Diederich *et al.*[20] also for some cyclophane complexes, can be the result of 'high energy' water inside the CD cavity: these molecules show much weaker hydrogen bonds compared with bulk water.

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