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Structure of the complex of β-cyclodextrin with β-naphthyloxyacetic acid in the solid state and in aqueous solution☆

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Abstract

The structure of the complex of β-cyclodextrin (cyclomaltoheptaose) with β-naphthyloxyacetic acid was studied in solid state by X-ray diffraction and in aqueous solution by ^{1}H NMR spectroscopy. The complex crystallizes in the channel mode, space group *C*2, with a stoichiometry of 2:1; two β-cyclodextrin molecules related by a twofold crystal axis form dimers, in the cavity of which one guest molecule is found on average. The above stoichiometry indicates one guest per β-CD dimer statistically oriented over two positions or two guest molecules in π–π interactions in half of the β-CD dimers and the rest of the β-CD dimers empty. In addition, occupancy of 0.5 for the guest per every β-CD dimer is in accord with the occupancy of the two disordered primary hydroxyls. These two hydroxyl groups, to which the carboxylic oxygen atoms of the guest are hydrogen bonded, point towards the interior of the β-CD cavity. In aqueous solution, the ^{1}H NMR spectroscopic study indicated that there is a mixture of complexes with host–guest stoichiometries both 1:1 and 2:1. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Crystal structures; ^{1}H NMR spectroscopy; β-Cyclodextrin; β-Naphthyloxyacetic acid; Channel packing; Inclusion compound

1. Introduction

β-Naphthyloxyacetic acid (NOA) is a synthetic compound, exhibiting physiological action similar to that of the naturally occurring auxins. It is widely used in agriculture as a pesticide to control fruit diseases and in tissue culture applications as plant growth regulator to prevent the premature falling of fruits.[2] Cyclodextrins (CDs) can be applied in plant cell biotechnology acting as solubilizers of relatively insoluble precursors for bioconversions by plant cells or enzymes and they probably protect agents and reactant carriers.[3] Inclusion compounds of naphthalene or naphthalene derivatives in CDs have received sufficient attention.[2,4–8] Although no crystal structure of inclusion complexes between natural β-CD and naphthalene or a naphthalene derivative has been reported up to now, some structures of complexes of modified CDs with naphthalene derivatives have been reported: the 2-naphthoic acid/heptakis(2,6-di-*O*-methyl)-β-CD complex,[9] the (*S*)-naproxen/heptakis-

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(2,3,6-tri-*O*-methyl)-β-CD complex[10] and the self inclusion complex of 6-deoxy-6-*N*-(*N*′-(5-dimethyl-amino-1-naphthalenesulfonyl)diaminomethane)β-CD.[11] Having a continuous interest in inclusion compounds of plant growth regulators in CDs, we studied the complex of NOA with β-CD, in the crystalline state, by X-ray diffraction, and in aqueous solution by ^{1}H NMR spectroscopy. Preliminary experiments concerning the effect of β-CD/NOA complex to *Apium nodiflorum* showed enhanced rooting; the complete results will be presented elsewhere.

2. Experimental

Crystallization.—An ethyl alcohol solution of NOA obtained from Sigma was added to an aq solution of β-CD (purchased from Cyclolab) at a host–guest molar ratio 1:1. The resulting precipitate was redissolved in water at 65 °C and was let to cool to rt over a period of 7 days at the end of which colorless crystals suitable for data collection had been formed.

X-ray data collection.—Data collection was performed on a crystal, sealed in a Linderman glass capillary to prevent water loss, on a Syntex P2$_1$ diffractometer upgraded by Crystal Logic. Ni-filtered Cu Kα radiation was used, the scan mode was $\theta - 2\theta$, at a scan rate of 3°/min and scan width 2.7° (2θ) plus α_1–α_2 divergence. Three standard reflections monitored every 97 reflections, showed an intensity fluctuation less than 3%. Lorenz, polarization and absorption (by the Psi-scan) corrections were applied to the intensity data. Preliminary oscillation and Weissenberg photographs had indicated a space group $P\bar{1}$ with three axes nearly equal (15.666, 15.651 and 15.975 Å, angles: 101.41, 101.52 and 103.72°). Consequently, one half of the sphere was collected giving 6885 reflections with $2\theta_{\max} < 95°$.

Structure solution and refinement.—The structure was solved by isomorphous replacement using the skeleton atom coordinates of the β-CD molecules in the β-CD/3,5-dimethylbenzoic acid complex.[12] Sequential difference electron density ($\Delta\rho$) maps revealed the positions of the remaining non-hydrogen atoms of the host molecule, some water molecules and the guest atoms. The progress of the refinement and the examination of the electron density maps showed that the β-CD monomers and the guest molecules of each dimer were related by an exact twofold symmetry axis. In β-CD dimeric complexes crystallized in space group $P\bar{1}$ (packing type: channel CH), the two β-CD molecules of the same dimer are related by a pseudo twofold axis. By applying the transformation $a' = a - b$, $b' = b - a$ and $c' = c$, a C centered unit cell results and the pseudo twofold axis is transformed into a true twofold crystal axis.[13,14] As the difference electron density corresponding to the guest molecule was quite symmetric, we decided to restart the refinement in the space group *C*2 after the appropriate conversion of the original data and using the coordinates of the skeleton atoms of the β-CD molecule of the β-CD/(Z)-9-dodecen-1-ol complex.[15] Notice that when the guest(s) inside the β-CD dimer does not possess an exact twofold symmetry,[16] the above transformation is not true and the lattice is pseudo-*C* centered.

Sequential $\Delta\rho$ maps revealed again the positions of the remaining non-H atoms of the host molecule, the water molecules and the guest atoms. The refinement, based on F^2, proceeded by using the SHELXL-97 program.[17] Calculated positions of hydrogen atoms linked to carbon atoms of the β-CD molecule were used with a C–H distance of 0.97 Å for the secondary and 0.98 Å for the tertiary hydrogen atoms, while their thermal parameters were set at $1.2 \times U_{\text{iso}}$ of the isotropic thermal parameter of the corresponding C-atom. The relatively small number of observations (reflections/parameters ratio = 7.6, Table 1) did not allow an anisotropic refinement for all the non-H atoms. Thus, only the non-disordered oxygen atoms, the C-6*n* atoms linked to non-disordered O-6*n* atoms of the β-CD molecule and some water molecules were refined anisotropically.

The guest molecule geometry was optimized by fitting the atomic positions into the $\Delta\rho$ map, using the molecular graphics program ‘*O*’,[18] on an O$_2$ Silicon Graphics workstation. After optimization, the positions of the atoms of the guest were kept constant, but their thermal parameters were refined. The thermal parameters of the guest atoms O-1, C-9, O-2 and O-3 refined to very high values. Alternatively, a refinement of the occupancy factor (k) of the whole guest molecule, while the temperature factors of the guest atoms were kept constant, resulted in $k = 0.5$. In order to confirm that k is less than one, two cycles of refinement were carried out by varying the thermal parameters of the guest atoms and keeping k at constant values between 1.00 and 0.00 (Table 2). It was observed that the contribution of the guest to the R factors is small; their values being nearly invariable for a k ranging between 0.60 and 0.25. Therefore for $k = 0.5$, the result of the previous refinement, can be considered as an optimum, since it yields reasonable thermal parameters and it is the occupancy factor of the disordered hydroxyl groups to which the guest is H-bonded (vide infra). Accordingly it was set to that value, but a k value close to 0.75 that corresponds to the ratio of host–guest as determined by NMR cannot be excluded.

Table 1
Crystal data and structure refinement for β-CD/NOA complex

Empirical formula	$C_{42}H_{70}O_{35}\cdot(C_{12}H_{10}O_3)_{0.5}\cdot(H_2O)_{11.79}$
Formula weight	1448.22
Temperature (K)	295(2)
Wavelength (Å)	1.5418
Crystal system, space group	monoclinic, $C2$
Unit cell dimensions	
a (Å)	19.341(2)
b (Å)	24.632(2)
c (Å)	15.975(2)
β (°)	108.770(10)
V (Å^3)	7205.9(13)
Z, D_{calcd} (Mg/m^3)	4, 1.335
Absorption coefficient (mm^{-1})	1.051
$F(000)$	2868
θ Range for data collection (°)	2.92–47.51
Limiting indices	$-14 \leq h \leq 18$, $-23 \leq k \leq 14$, $-15 \leq l \leq 14$
Reflections collected/unique/observed [$I > 2\sigma(I)$]	6859/4821/4493
R_{int}	0.0457
Refinement method	full-matrix least-squares on F^2
Data/parameters	4821/636
Goodness-of-fit on F^2	1.246
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0868$, $wR_2 = 0.2414$
R indices (all data)	$R_1 = 0.0916$, $wR_2 = 0.2524$
Absolute structure parameter	0.2(4)
Extinction coefficient	0.0019(4)
Largest difference peak and hole (e Å^{-3})	0.597 and -0.331
Weighting scheme	$1/[\sigma^2(F_o^2) + (0.2P)^2]$ where $P = [\max(F_o^2) + 2(F_c^2)]/3$

Table 2
R factors of refinement of the β-CD/NOA complex with guest–host ratios varying between 1.0 and 0.0 and the corresponding isotropic displacement parameters (Å$^2 \times 10^3$) of some guest atoms

k	R_{obs}	R_{all}	O-1	C-9	O-2	O-3
1.00	0.0918	0.0976	0.71	0.81	1.04	0.63
0.95	0.0911	0.0961	0.70	0.79	1.01	0.61
0.90	0.0903	0.0951	0.69	0.78	0.97	0.60
0.85	0.0896	0.0944	0.69	0.76	0.92	0.58
0.80	0.0890	0.0937	0.68	0.75	0.88	0.56
0.75	0.0884	0.0931	0.67	0.74	0.83	0.55
0.70	0.0878	0.0926	0.67	0.73	0.77	0.54
0.65	0.0874	0.0922	0.66	0.72	0.68	0.53
0.60	0.0871	0.0919	0.62	0.64	0.63	0.52
0.55	0.0869	0.0917	0.57	0.55	0.58	0.50
0.50	0.0868	0.0916	0.55	0.51	0.52	0.48
0.45	0.0867	0.0916	0.51	0.44	0.47	0.45
0.40	0.0868	0.0917	0.48	0.38	0.44	0.41
0.35	0.0866	0.0915	0.49	0.38	0.46	0.41
0.30	0.0867	0.0916	0.45	0.31	0.43	0.37
0.25	0.0871	0.0921	0.38	0.21	0.36	0.29
0.20	0.0896	0.0948	0.27	0.03	0.22	0.15
0.15	0.0926	0.0981	0.26	0.03	0.04	0.03
0.10	0.0910	0.0963	0.07	0.03	0.04	0.03
0.05	0.0911	0.0963	0.00	0.04	0.06	0.02
0.00	0.0945	0.0977				

Extinction correction was applied and 20 reflections, either negative or exhibiting poor agreement, were given zero weight during the final refinement cycles. The refinement converged to $R_1 = 0.0868$ and 0.0916 (Table 1) for observed and all reflections, respectively. The numbering scheme of the host and guest molecules is given in Fig. 1, C-*mn* and O-*mn* denoting the *m*th atom within the *n*th glucosidic residue.

NMR studies.—NOA (Aldrich) was recrystallized from water. ^{1}H NMR spectra were acquired at 250 and at 500 MHz. Titration experiments were not feasible owing to the very small solubility of NOA in the aq solution, which could be maximized after sonication for 45 min to only 4.44 mM. Continuous variation (Job) plots were constructed by mixing equimolar (4.44 mM each) solutions of β-CD and of NOA in unbuffered and buffered D_2O (pH ~ 7, NaH_2PO_4–K_2HPO_4) at different ratios, to a constant total volume. Measurements of the chemical shift displacements of β-CD and NOA signals were aided by series of 2D COSY spectra, especially at the ambient temperature experiments. On the other hand, crystals from a crystallization batch were selected and washed with THF and then redissolved in Me_2SO-d_6. Integration of the host and guest signals yielded a stoichiometry of 1:0.75 host–guest, for the crystalline complex. The excess (over 1:0.5) NOA measured by integration is not surprising since in the aq solution NOA recrystallizes under the same conditions in which the crystal of the inclusion complex is formed. The 2D ROESY spectra were acquired at 300 K, 500 MHz and neutral pH, using solvent presaturation, 350 ms mixing (spinlock) time, and 256 scans/FID.

3. Results and discussion

Crystalline state

Molecular geometry and conformation of the β-CD.—Two primary hydroxyl groups of the β-CD molecule, O-64 and O-65, are disordered over two sites, the occupancies of their major sites, B, being, respectively, 0.58 and 0.51. As indicated in Table 3 by the values of their torsion angles, their minor sites, A, exhibit a *gauche–gauche* orientation pointing outside the β-CD cavity, while their major ones, B, have a *gauche–trans* orientation and point towards the interior of the cavity. This is an unusual characteristic as the major sites generally point outwards. However it is explained by the fact that both form H-bonds

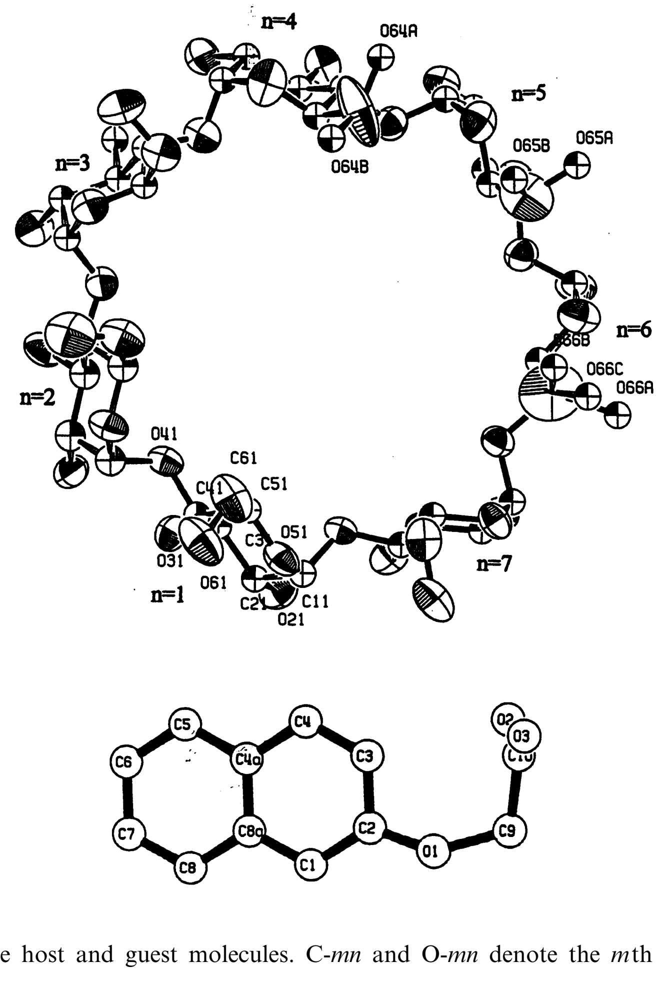


Fig. 1. Numbering scheme of the host and guest molecules. C-*mn* and O-*mn* denote the *m*th atom within the *n*th glucosidic residue.

Table 3
Selected torsion angles and tilt angles (°) formed between the O-4*n* mean plane and the individual O-4($n+1$)···C-1*n*···C-4*n*···O-4*n* mean planes for the β-CD/NOA complex [a]

Residue	Site	$n=1$	$n=2$	$n=3$	$n=4$	$n=5$	$n=6$	$n=7$
Torsion angles (°)								
C-4*n*–C-5*n*–C-6*n*–O-6*n*	A	64.8(1.1)	54.3(1.3)	62.9(9)	44.8(1.9)	60.6(1.5)	57.6(1.7)	51.3(1.0)
O-5*n*–C-5*n*–C-6*n*–O-6*n*	A	−59.3(1.0)	−66.5(1.1)	−59(1)	−70.4(1.5)	−59.3(1.3)	−62.0(1.7)	−68.(1.0)
C-4*n*–C-5*n*–C-6*n*–O-6*n*	B				−178.2(1.8)	167(2)	169(5)	
O-5*n*–C-5*n*–C-6*n*–O-6*n*	B				66(2)	47(3)	49(5)	
C-4*n*–C-5*n*–C-6*n*–O-6*n*	C						84(5)	
O-5*n*–C-5*n*–C-6*n*–O-6*n*	C						−36(5)	
Tilt angles (°)		11.66(15)	13.79(15)	8.97(12)	15.2(2)	12.9(3)	11.8(4)	8.18(19)

[a] Standard deviations in parentheses.

with the guest (vide infra). A third hydroxyl group, O-66, is disordered over three sites, A, B and C, with occupancies 0.50, 0.15 and 0.35, respectively. The minor site B with an occupancy 0.15 points inwards having a *gauche–trans* orientation, while the two others have a *gauche–gauche* orientation pointing to the outside of the β-CD cavity. The macrocyclic ring has the usual truncated-cone shape with a pseudo-sevenfold axis. The glycosidic O-4*n* atoms lie in a plane within 0.024 (4) Å, the O-4*n*···O-4($n+1$) distances vary between 4.27 and 4.50 Å and the O-4($n-1$)···O-4*n*···O-4($n+1$) angles range from 125.7 to 131.0°. This gives the cavity a slightly elliptical shape that could be related to the shape of the guest molecule. The tilt angles of glucopyranose residues, defined as the angles between the O-4*n* atoms best plane and the individual O-4($n-1$)···C-1*n*···C-4*n*···O-4*n* planes, range between 8.18(19) and 15.2(2)° (Table 3), indicating tilt of all glucose residues towards the interior of the cavity at the primary face. Two β-CD molecules, related by the twofold rotation axis parallel *b*, form dimers in a head-to-head fashion and, as in all the β-CD dimeric inclusion complexes crystallizing in space group *C*2, the dimers pack in the Channel Packing Mode (Fig. 2).[13] Water molecules (11.79) distributed over 17 sites form the usual network of hydrogen bonds[13,19] with the hydroxyl groups of the β-CD molecule and among themselves. Some of them are located on or near the twofold crystal axis.

The host–guest stoichiometry.—The host–guest stoichiometry of 0.5 indicates that one guest molecule corresponds to each β-CD dimer (Fig. 3). This could mean that one cyclodextrin cavity of the dimer is filled, while the other is empty. This is an unexpected fact, as the dimeric cavity is wide enough for two NOA molecules to be accommodated with the two naphthyl groups almost parallel (8.9°) and the least distance of 3.48 Å between the planes suggesting a π–π interaction (Fig. 2). On the other hand, this latter interaction is not excluded at the observed 2:1 host–guest ratio, meaning that half of the β-CD dimers host two guests and half are empty.

The side chain of the guest is positioned in the primary side of β-CD. The whole NOA molecule is found inside the cavity, the naphthyl group forming an angle of 63.2° with the glycosidic O-4*n* plane. The C-2 and C-3 atoms are found at small distances from the O-4*n* plane, the C-4*a* and C-8*a* are nearly in the height of the O-2*n* and O-3*n* atoms, while the extreme naphthyl group atoms, C-6 and C-7, are located in the intra-dimeric hydrophobic interface (Fig. 3). The carboxyl group is out of the naphthalene plane, its mean plane forming an angle of 54.8° with it and 43.7° with the C-6*n* mean plane. The thermal parameters of all the atoms of the naphthyl group are small enough (i.e., 0.220 Å^2 for C-2), comparable to those of the oxygen atoms of the water molecules (i.e., 0.205 Å^2 for O-W3), and the disordered O-6*n* atoms of the host (i.e., 0.191

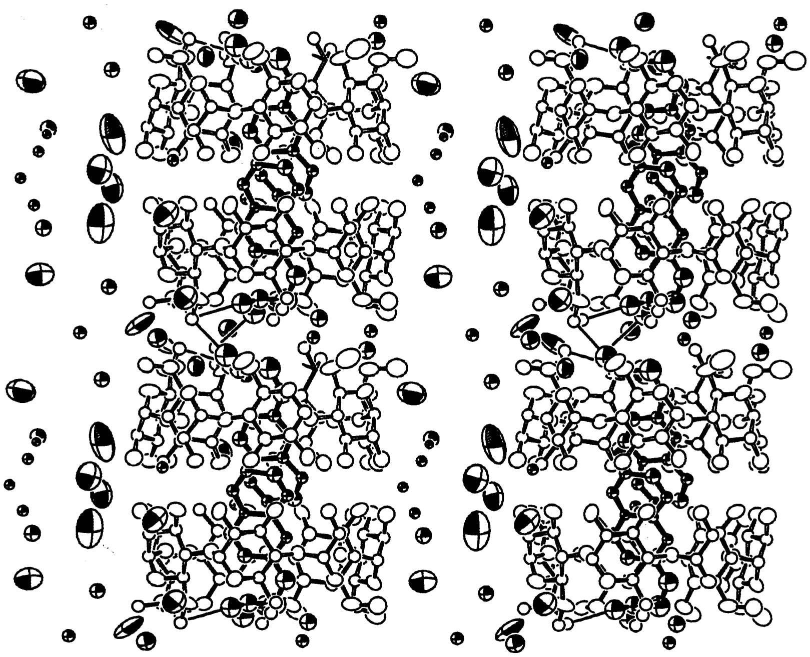


Fig. 2. A stereo diagram of the channel of the dimeric complex.

Å^2 for O-65B), while those of the atoms of the oxyacetic acid chain are larger (i.e., 0.510 Å^2 for C-9). The two oxygen atoms of the carboxyl group lie almost on the C-6*n* mean plane and they are hydrogen-bonded to the inward pointing major sites of the disordered hydroxyl groups of the host (Table 4): O-64B (O-64B···O-2 = 2.77 Å), belonging to the guest molecule of the same asymmetric unit and O-65B (O-65B···O-3 = 2.68 Å) of the next dimer in the channel both pointing towards the interior of the cavity (Fig. 3). Due to these two hydrogen bonds, two adjacent dimers, related by the *b* crystal axis, approach sufficiently to form channels. Many van der Waals contacts between non H-atoms of the host and guest molecules of the dimer are observed, ranging from 3.21 to 3.95 Å (Table 4).

Comparing the mode of inclusion of the naphthyl derivatives in the cyclodextrin cavity, we observe that in the 2-naphthoic acid/heptakis(2,6-di-*O*-methyl)-β-CD complex[9] the naphthyl group is found in the vicinity of the

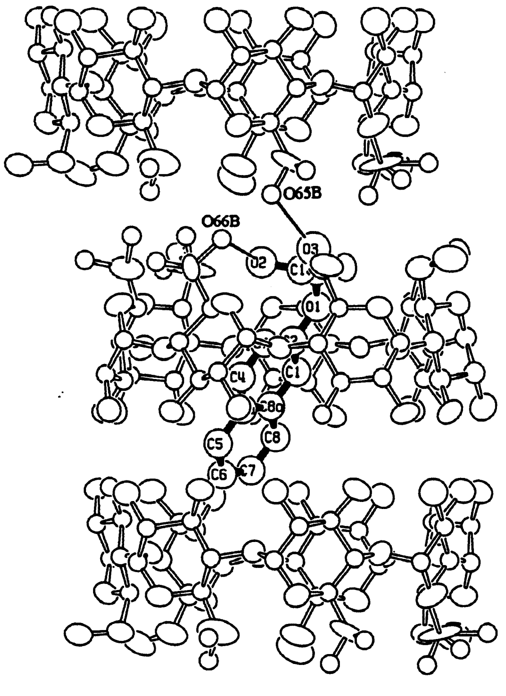


Fig. 3. A diagram indicating the accommodation of the NOA molecule in the dimeric cavity and the hydrogen bonds of the O-2 and O-3 guest atoms. Distances are given in Table 4.

Table 4
Hydrogen bonds and van der Waals contacts of the guest molecule in the β-CD/NOA complex [a]

Distances (Å) and angles (°) of the hydrogen bonds between host and guest atoms					
O-64B···O-2	2.77	C-64–O-64B···O-2	102.2	O-64B···O-2–C-10	116.9
O-65B···O-3	2.68	C-65–O-65B···O-3	108.3	O-65B···O-3–C-10	125.4
Distances between host and guest atoms less than 4.00 Å					
C-1···O-44(i)	3.50	C-1···C-35(i)	3.94	C-4···O-46(i)	3.94
C-4···C-37(i)	3.90	C-4···O-47(i)	3.61	C-8···C-35(i)	3.88
C-8···O-35(i)	3.93	C-7···C-32(ii)	3.65	C-7···O-32(ii)	3.81
C-7···O-42(ii)	3.77	C-7···C-33(ii)	3.95	C-6···O-41(ii)	3.83
C-6···C-32(ii)	3.53	C-6···O-32(ii)	3.90	C-5···C-37(i)	3.71
C-5···O-37(i)	3.91	O-1···C-51(i)	3.65	O-1···C-61(i)	3.95
C-9···C-66B(ii)	3.21	C-10···O-64B(i)	3.60	C-10···O-65B(ii)	3.52
C-10···O-66B(ii)	3.62	O-2···C-54(i)	3.56	O-2···C-64(i)	3.37
O-2···C-65B(ii)	3.30	O-3···C-62(i)	3.65	O-3···C-53(i)	3.44
O-3···C-63(i)	3.30	O-3···O-64B(i)	3.38	O-3···C-65(ii)	3.29
O-3···O-65A(i)	3.70	O-3···O-66B(ii)	3.25		

[a] Symmetry code: (i) = x, y, z; (ii) = $-x, y, -z$.

primary region while the carboxyl group is completely out of the cavity. Furthermore, the complex is stabilized only by van der Waals contacts and the plane of the naphthyl group forms an angle of 60° with the glycosidic O-4*n* plane. This is the only resemblance to the host–guest geometry with the title complex. In the (*S*)-naproxen/heptakis(2,3,6-tri-*O*-methyl)-β-CD complex,[10] the guest, as opposed to the present structure, enters the cavity through the secondary rim and it is hydrogen-bonded to the oxygen atom of the methoxy group of a symmetry related host molecule. Finally, in the 6-deoxy-6-*N*-(*N*′-(5-dimethylamino-1-naphthalenesulfonyl) diaminomethane)-β-CD[11] the naphthyl group, which is covalently bound to the primary side of the β-CD, is entirely buried in the cavity entering from the primary side and nearly perpendicular to the mean squares plane of the glycosidic O-4*n* atoms, forming an angle of 79.6° with it, greater than found in the title complex. A remarkable distortion of the host cavity from the heptagonal symmetry is observed, as opposed to the present case.

^{1}H NMR studies in aqueous solution.—Previous complexation studies in solution of various naphthalene derivatives with β-CD showed either a 1:1 or a 2:1 host–guest stoichiometry, depending on the derivative.[20] For the particular β-CD/NOA complex, UV and fluorescence spectroscopy[2] or temperature dependent circular dichroism[4] studies in solution have proposed a stoichiometry of 1:1, and a model[2] where the naphthyl group is found in the cavity along the sevenfold axis, with the oxyacetic acid group protruding from the secondary rim of β-CD. These results are opposite to our present findings in the crystalline state. We therefore decided to reexamine the process of complexation in aq solution (in D_2O) using ^{1}H NMR spectroscopy. Inclusion of NOA in the β-CD cavity was immediately evident in the ^{1}H NMR spectra, as the cavity protons H-3 and especially H-5 were strongly shielded (Fig. 4) upon increasing the proportion of NOA relative to β-CD in the aq solution. The spectral lines of NOA in the presence of the host underwent significant

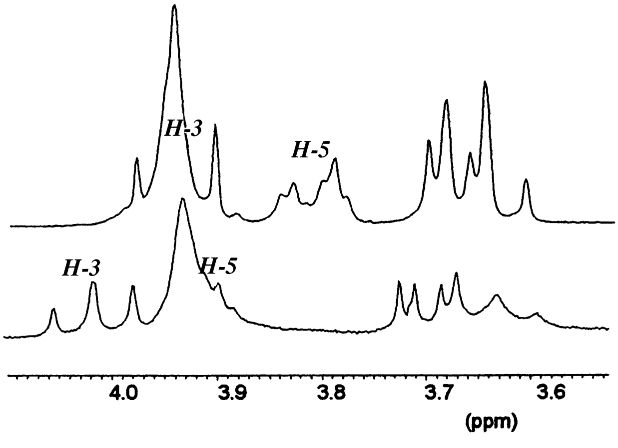


Fig. 4. Partial ^{1}H NMR spectrum (250 MHz) of β-CD at 298 K (bottom) and of [β-CD]/[NOA] 3:7 (top). The shielding of the cavity protons H-5 and H-3 is prominent.

broadening at 250 and at even more at 500 MHz, as the result of an exchange process taking place in the solution (Fig. 5(a)). At the higher field, the signals of β-CD had also become broad (Fig. 5(b)), and especially those of the cavity protons H-3 and H-5. Well resolved spectra in both guest and host regions were obtained when the samples were heated up to 318–320 K where the dynamic process had evidently reverted from an intermediate to a fast exchange rate regime. There was a significant influence of the pH on the chemical shifts of the guest in the unbuffered solutions, i.e., the pH increased from 2.7 to 5.2 with increasing NOA concentration, from 1.8 to 4.44 mM and that was accompanied by sizeable and irregular changes of the guest's chemical shifts. In the buffered solutions, at neutral pH, where all guest is ionized (pK_a ~ 2.5^2), there was a moderate but uniform shielding of all protons on increasing the NOA concentration, more pronounced for the CH_2 group. In the presence of β-CD, the aromatic proton signals were shielded in an unequal manner except for H-3, which was deshielded. Continuous variation plots were constructed at ambient and high temperatures and are shown in Figs. 6 and 7, respectively. The maxima of the diagrams corresponding to the β-CD protons at both temperatures indicate that a 1:1 complex is formed. However, in the diagram of the NOA protons at 300 K, the deflection point is close to 0.4, which would indicate a β-CD/NOA ratio of 2:1, whereas at 320 K that point shifts to 0.5, i.e., ratio of 1:1.

Clearly, we were observing more than one equilibrium in solution, taking also into ac-

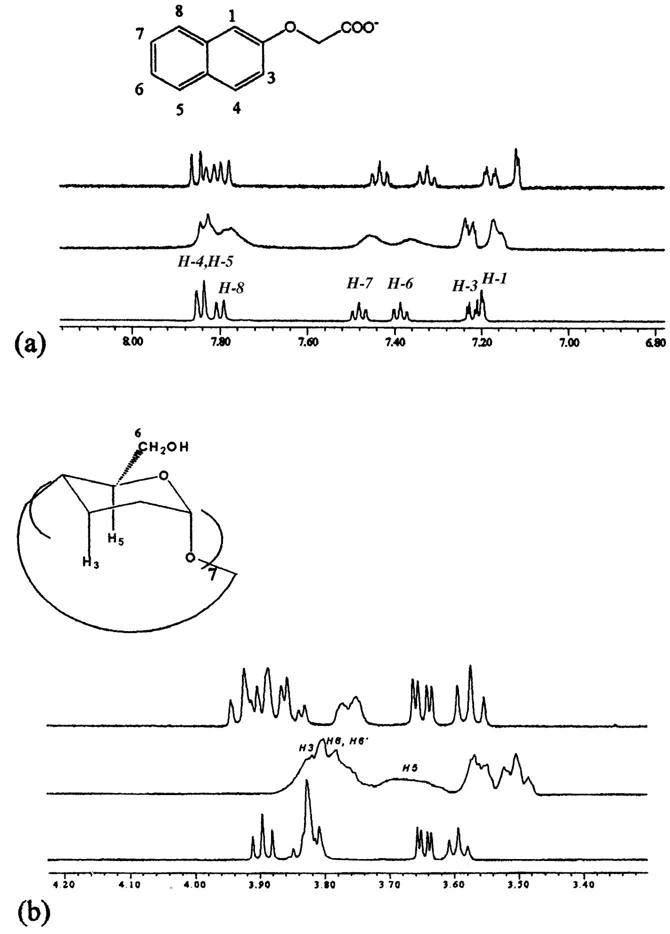
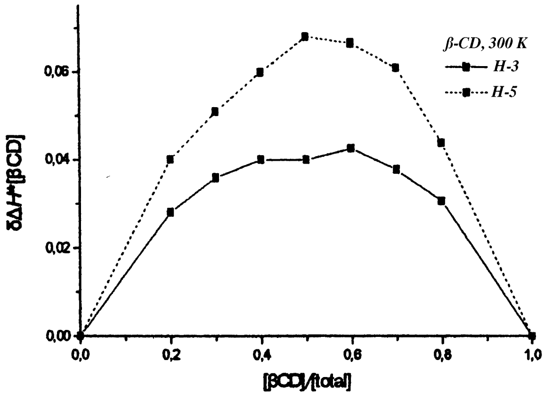


Fig. 5. Partial ^1H NMR (D_2O, pH ~ 7, 500 MHz) spectrum of (a) NOA, 300 K (bottom); [β-CD]/[NOA] 6:4, 300 K (middle); [β-CD]/[NOA] 6:4 at 320 K (top). (b) β-CD, 300 K (bottom); [β-CD]/[NOA] 6:4, 300 K (middle); [β-CD]/[NOA] 6:4 at 320 K (top).



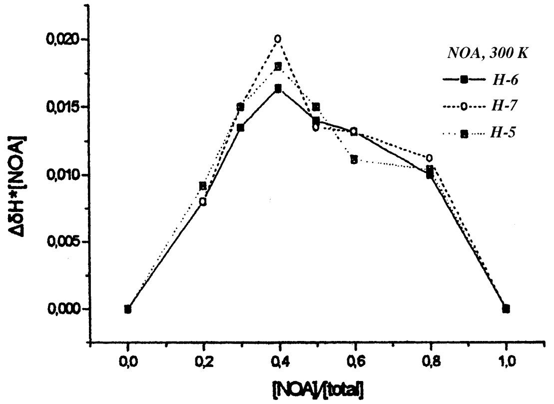
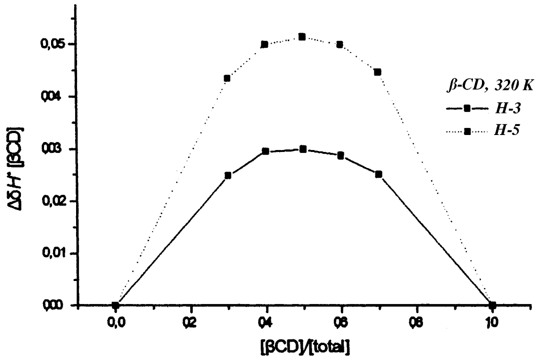


Fig. 6. Job plots of β-CD (top) and NOA protons (bottom), 300 K, 500 MHz, pH ~ 7.

count some contribution of the self-association of the guest. Since these results were inconclusive, we carried out 2D dipolar correlation spectra (ROESY) shown in Fig. 8. We observe strong intermolecular correlation between both cavity protons *H-3* and *H-5* and aromatic protons H-4, H-5, H-8 and H-1, whereas the corresponding interactions of H-3 are weaker. Correlation primarily with the secondary side of the cavity (*H-3*), and less with the primary side (*H-5*) involved H-7 and H-6. Further, the CH_2 group showed correlation with both cavity protons and even with H-6, H-6′.

The above results can be interpreted as follows: the guest molecule could bind from either one of its ends along its long axis, i.e., either from the H-6, H-7 end or from the oxyacetic acid end,[21,22] forming two types of 1:1 complexes, since both ends of the guest molecule show interactions with the cavity. This, however, would most probably result in Job plots corresponding to a clear 1:1 case for both the β-CD and NOA protons, and does not account for the lack of correlation between H-6, H-7 of NOA with H-5, on the primary end of the cavity. The simultaneous existence of a 2:1 complex along with the 1:1 adduct(s) could account for the experimental plots, as well as for the observed slow exchange rate. The engagement of a second host ring onto the 1:1 adduct is expected to be a slow process. This is disfavored at the higher temperature, therefore at 320 K the 1:1 complex predominates, as the diagram in Fig. 7 suggests. The ROESY data can also be arising from such a mixed stoichiometry of the complexes: presence of only 1:1 structures does not justify the very weak correlation of H-6 and H-7 with the interior of the cavity. This last observation as well as the fact that the aliphatic part seems to be extending over to the H-6, H-6′ are in support of the solid state structure (Fig. 3).

We therefore conclude that, from a mixture of 1:1 and 2:1 host–guest complexes in solu-



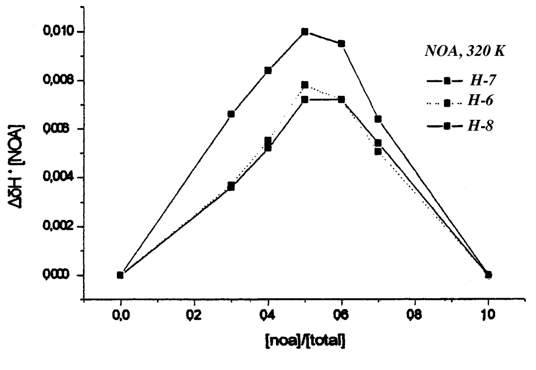


Fig. 7. Job plots of β-CD (top) and NOA protons (bottom) at 320 K, 500 MHz, pH ~ 7.

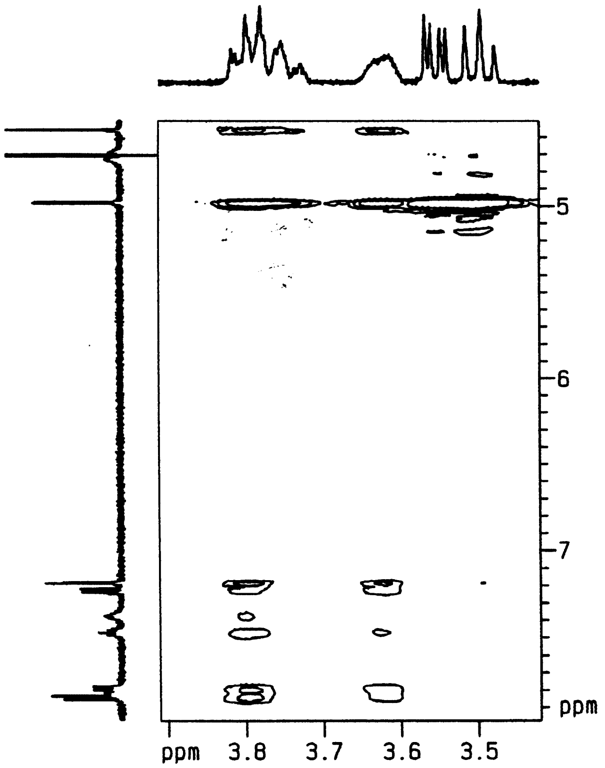


Fig. 8. Partial ROESY correlation map, 300 K, 500 MHz, pH ~ 7, [β-CD]/[NOA] is 2:8.

tion, only the dimeric adduct eventually crystallizes. This has been observed in other cases. We have previously documented that for the case of α-CD with 12-aminododecanoic acid,[21] from a mixture of 1:1 and 2:1 species clearly identified in solution, only the dimeric one crystallized. Complexes of mixed stoichiometry of α-CD with 2-methylnaphthalene[23] and 2-chloronaphthalene[24] have also been reported for the solution state.

4. Supplementary material

Full crystallographic details, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Center, deposition No. CCDC 149241. These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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