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Neutron Diffraction Structure of α-Cyclodextrin Cyclopentanone Hydrate at 20 K: Host–Guest Interactive Disorder

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Abstract

$0.5(C_{36}H_{60}O_{30}.C_5H_8O).2.3(H_2O)$, $M_r = 1098$, hexagonal, $P6$, $a = 23.725$ (1), $c = 7.935$ (1) Å, $V = 3868$ Å^3, $Z = 6$, neutron mean $\lambda = 1.3177$ Å, $\mu_{calc} = 2.93$ cm^{-1}, $F(000) = 570$ fm, $T = 20$ K, $R = 0.086$ for all 2053 observed reflections, $R = 0.078$ for 1905 reflections with $F \geq 4\sigma(F)$. Although the low-temperature crystal structure displays static disorder, the structure analysis reveals features not yet found in other cyclodextrin structures. There are two non-crystallographically related complexes in the crystal. In each of them, the host conformation is modified by the guest interaction but to a different extent. In addition, an interactive disorder, associated with different orientations of the guest molecules, is observed in both complexes, giving other additional 'frozen pictures' of the host–guest interaction. α-Cyclodextrin flexibility is clearly shown by the formation of alternative intramolecular hydrogen bonds involving solvent molecules. Alternative hydrogen-bonded networks in the whole crystal are described and partial chiral discrimination is discussed.

Introduction

Hydrogen bonding is an important factor of specificity in biological interactions. Water molecules may influence molecular recognition betweeen macromolecules and substrates in competing for hydrogen bonds. Structure analysis of hydrated cyclodextrin clathrates provides detailed atomic information (more easily than larger molecular systems) and furnishes a reliable model for studying molecular association and hydrogen bonding. Sometimes this information is impaired by disorder resulting from weak binding forces.

In the case of α-cyclodextrin clathrate, a symmetry-controlled disorder may also appear: the molecular symmetry of α-cyclodextrin (composed of six glucose residues) is compatible with crystallographic symmetry. Unlike, for example, β-cyclodextrin (composed of seven glucose residues), the α-cyclodextrin molecule has potentially twofold, threefold and sixfold symmetries, which may coincide with crystallographic axes. In such a case, if the guest molecule does not have the same symmetry, the crystal symmetry axis will generate several equivalent orientations of the guest.

An exceptional case of host–guest interactive disorder involving hydrogen bonds is provided by the complex of α-cyclodextrin and cyclopentanone. Cyclopentanone, a conformationally labile molecule, complexed with α-cyclodextrin in aqueous solution exhibits optical activity. In order to see whether the cyclodextrin shows a definite preference for one chiral conformer of cyclopentanone, we have examined the crystal structure of this complex.

The crystal structure determined first at room temperature by X-ray diffraction is highly symmetrical with space group $P6$ (Le Bas, 1985). There are two non-crystallographically related host molecules in the asymmetric unit, one on the sixfold axis, the other on the threefold axis.

Only a few of the H atoms were located in the X-ray diffraction work. Further, as the site occupancy factor (s.o.f.) of some atoms was very low, < 0.3, it was highly desirable to have an independent experimental confirmation. It was also interesting to determine whether the disorder would persist at low temperature; this question is especially relevant in the case of dynamical phenomena. For these reasons, a neutron diffraction experiment at low temperature was undertaken. In spite of much static disorder, the positions of most H atoms have been located.

In this article we discuss the crystal packing and the hydrogen-bonding network which maintains the crystal edifice and the stereospecificity of the host–guest interaction. Unless otherwise stated, bond lengths, bond angles *etc.* refer to the neutron work, since that model is more complete and is considered to be more accurate.

Data collection

Crystals of the α-cyclodextrin cyclopentanone complex (1:1) were obtained by slow cooling of a saturated aqueous solution of α-cyclodextrin with a twofold excess of cyclopentanone. The hexagonal prisms were found by X-rays to have the unit-cell constants $a = 23.85$, $c = 8.00$ Å, space group $P6$, $Z = 6$, $V = 3941$ Å^3, at room temperature. The structure was determined using Cu $K\alpha$ X-rays and refined to a final R of 0.08 (using 1713 observed reflections out of a total of 1940 reflections to $\theta = 60°$) with isotropic temperature factors (Le Bas, 1985).

A crystal of size 1.1 × 1.5 × 1.8 mm, suitable for neutron diffraction, was supported at one end by quartz wool in a sealed quartz capillary containing some mother liquor. The usual artifice of growing crystals from the deuterated mother liquor (in order to reduce incoherent neutron scattering by H atoms) was not employed, as a test of the possibility of resolving disordered solvent atoms in native non-deuterated crystals. A limited neutron data set was measured at room temperature to check that the crystal structure was similar to that found in the earlier X-ray work. The crystal was then cooled over some hours to 20 K using a Displex cryorefrigerator, while carefully monitoring the diffraction pattern: there were no dramatic changes. All neutron diffraction measurements were made on the Institut Laue-Langevin four-circle diffractometer D19 with a 4 × 64° position-sensitive detector. Bragg intensities at 20 K were measured in equatorial geometry for low Bragg angles ($2\theta \leq 30°$) and in normal-beam geometry for higher shells up to $2\theta = 96°$. The Bragg peaks were integrated in three dimensions by the procedure of Wilkinson, Khamis, Stansfield & McIntyre (1988).

The final data set, after elimination of unsatisfactory observations such as reflections falling on the detector edges, included 5973 reflections with a statistical R factor $[\sum\sigma(F^2)/\sum F^2]$ of 0.041. R.m.s. deviations from predicted positions for the 3646 non-weak reflections were 0.03° in ω, 0.05° in γ and 0.05° in ν, where γ and ν are along the horizontal and vertical directions in the detector plane. Absorption corrections were applied with $\mu_{calc} = 2.93$ cm^{-1}, before averaging in space group $P6$ to give 2053 unique reflections, including 1866 of the 1868 possible reflections with 2θ less than 91° and a further 185 reflections up to 96°.

Structure refinement

Initial neutron difference Fourier maps were based on the positions of the C and O atoms of α-cyclodextrin determined in the X-ray study and using the preliminary set of neutron structure amplitudes measured at room temperature. The positions of most ring H atoms and some of the solvent atoms were then confirmed by several cycles of least-squares refinement.*

The 20 K structure was then refined by alternating series of difference Fourier syntheses with full-matrix least-squares refinement cycles using the program *SHELX* (Sheldrick, 1976). The neutron coherent scattering lengths (H = −3.7409, C = 6.6484, O = 5.805 fm) were from Sears (1984). Fourier calculations permitted the location of all the individual atomic positions except those of the guest molecule in the sixfold site. The negative sign relative to the other atoms of the hydrogen scattering density was particularly useful in the interpretation of the solvent density, where the atomic centres were often in close proximity but not superposed. Constraints were used for the guest molecules, disordered primary hydroxyl groups and for disordered water molecules. *SHELX* allows the user to impose the desired geometry on disordered molecular fragments. These molecular fragments with the idealized geometry were used as rigid blocks. Fourier difference and omit maps were calculated using the Cambridge Crystallography Subroutine Library (Matthewman, Thompson & Brown, 1982). An Evans and Sutherland PS300 vector graphics system and the program *FRODO* (Jones, 1978) were used to obtain the best match between the disordered guest molecules and the neutron scattering density.

The atomic s.o.f.'s for disordered atoms were first determined from difference maps and refined by least-squares and in the final stages fixed to those of the other atoms in the same molecular fragment. A unique isotropic thermal factor was attributed to all the atoms of one fragment. The final isotropic refinement using all 2053 observed structure amplitudes and 309 variable parameters gives an R value of 0.086. If we exclude the 148 structure amplitudes with $F < 4\sigma(F)$, the R value becomes 0.078.† If the C and O atoms of the two disordered glucopyranose rings $G1$ and $G3$ are refined anisotropically, all other atoms having isotropic thermal parameters, the R value using 397 variable parameters and 2053 amplitudes is 0.076. This latter refinement was useful in confirming our interpretation of certain difficult regions of the structure, but is not considered further: all geometrical data in this paper refer to the isotropic refinement. In the final difference maps, the absolute value of the highest residual peak is about one-tenth of the height of an ordered C atom.

* The origin, on the c-axis, was chosen close to the plane of the primary hydroxyl of the sixfold α-cyclodextrin molecule.

† R is defined as $\sum||F_o| - |F_c||/\sum|F_o|$. Unit weights were used throughout the refinement.

Results and discussion

Final coordinates and thermal parameters are given for the isotropic refinement in the supplementary material deposited.* Tables 1 and 2 contain geometric data. The atom numbering in the glucose residues is shown in Fig. 1. Figures are drawn using *Ball & Stick* software (Muller & Falk, 1986).

(*a*) *Crystal symmetry and packing*

There are three molecules of α-cyclodextrin in the unit cell, two on the threefold axes and one on the sixfold axis. The molecules on the threefold axes are related by the twofold axis and the molecule on the sixfold axis is crystallographically independent. The asymmetric unit consists of one glucose residue *G*1 from the sixfold molecule denoted by (1) and two, *G*2 and *G*3, from the threefold molecule denoted by (2) (Fig. 2). The host molecules (1) and (2) pack in antiparallel columns running along the *c*-axis direction. Therefore, the column of molecules (1), along the sixfold axis, 'runs up' and the two columns of molecules (2), on the threefold axes, 'run down' (Fig. 3). We have thus a 'perfect channel' inclusion compound, formed by cyclodextrin molecules in a head-to-tail mode.

Guest molecules are sequestered in the cavity formed by two translated cyclodextrin molecules along the two types of columns. The carbonyl extremity is included in one cyclodextrin at the level of the primary hydroxyl groups, the two opposite C atoms of the cyclopentanone ring in the other cyclodextrin being near the secondary hydroxyl atoms. The guest in column 1 is, by crystal symmetry, statistically distributed over six orientations; for the column 2 guest, in spite of being surrounded by the nearly hexagonal host, the experimental results, room-temperature X-rays and low-temperture neutrons clearly show that the distribution is threefold, in accordance with the crystal symmetry.

* Lists of structure factors, isotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI0167). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

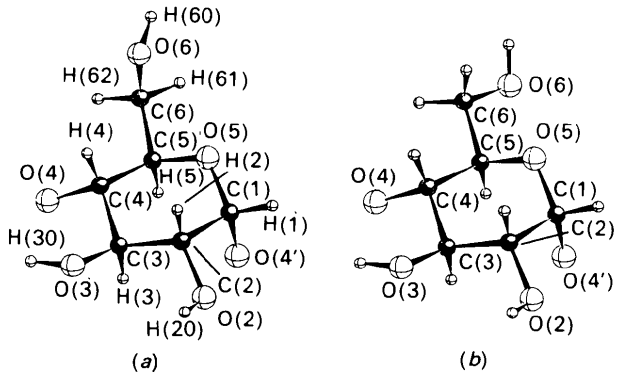

Fig. 1. A perspective view of a glucopyranose residue (with atomic numbering scheme) in the two different conformations, (*a*) 'away' from the cavity and (*b*) 'inwards' to the cavity.

Table 1. *Geometrical features* (Å, °) *of the cyclodextrin rings*

Atoms marked with a single prime belong to the next glucose unit and those marked with a double prime belong to the following glucose unit. In each glucose unit, the primary hydroxyl groups are disordered: C(61)O(61) is one position, C(62)O(62) is the other.

	*G*1	*G*2	*G*3
O(4)···O(4′)	4.26 (1)	4.23 (1)	4.26 (1)
O(3)···O(2′)	2.82 (2)	2.94 (1)	2.79 (2)
C(1)—O(4′)—C(4′)	119.5 (6)	120.3 (7)	116.9 (6)
φ: O(4)···C(1)—O(4′)—C(4′)	165.8 (9)	169.5 (9)	161.2 (8)
ψ: C(1)—O(4′)—C(4′)···O(4″)	−170.3 (7)	−170.8 (7)	−170.0 (7)
O(5)—C(5)—C(61)—O(61)	−55.1 (1.1)	−68.6 (1.1)	−57.6 (1.1)
O(5)—C(5)—C(62)—O(62)	70.2 (1.9)	−67.9 (2.1)	60.2 (1.6)

Table 2. *Distances* (Å) *and angles* (°) *for the hydrogen bonds*

The standard deviations of distances between non-H atoms are 0.008–0.02 and 0.02–0.05 Å otherwise. For angles not involving H atoms, the e.s.d.'s are 0.5–0.9 and 0.8–2° otherwise. The geometry of water molecules has been constrained.

	Donor	Acceptor	O—H	O···O	O—H···O	H···O
*G*1	O(2)H(20)	*W*2 O^{i}	0.97	2.76	170.3	1.79
		*W*4 O^{i}		2.66	157.4	1.73
	O(3)H(30)	*G*1 O(2^{iii})	0.99	2.82	171.0	1.84
		*G*1 O(4^{i})		2.82	107.4	2.36
	O(61)H(06)	*G*1 O(3^{iii})	0.96	2.73	163.4	1.80
	O(62)H(60)	*G*1 O(3^{iii})	0.93	2.83	171.9	1.90
*G*2	O(2)H(21)	*G*3 O(3^{iv})	0.96	2.79	157.9	1.87
		*G*3 O(4^{iv})		2.74	102.9	2.37
	O(2)H(20)	*W*3 O^{ii}	0.91	2.58	169.8	1.68
	O(3)H(30)	*G*3 O(2^{i})	0.99	2.94	170.7	1.96
		*G*2 O(4^{i})		2.85	106.7	2.40
	O(61)H(60)	*G*1 O(61^{v})	0.87	2.78	155.0	1.96
	O(62)H(06)	*G*2 O(3^{iii})	0.92	2.79	174.7	1.87
*G*3	O(2)H(20)	*W*1 O^{vi}	0.98	2.72	174.3	1.74
		*W*5 O^{vi}		2.79	168.5	1.82
	O(3)H(30)	*G*2 O(2^{viii})	0.98	2.79	164.7	1.83
		*G*3 O(4^{i})		2.87	112.1	2.36
	O(3)H(31)	*G* O(3^{viii})	0.94	2.80	179.2	1.86
	O(61)H(60)	*W*1 O^{i}	1.05	2.83	161.7	1.81
	O(62)H(06)	*G*3 O(2^{iii})	0.96	3.22	175.0	2.36
		*G*3 O(3^{iii})		3.22	113.9	2.75
*W*1	OH(010)	*G*2 O(2^{ix})	0.96	2.86	151.1	1.98
	OH(01)	*W*2 O^{i}		2.83	165.1	1.89
*W*2	OH(020)	*G*2 O(61^{i})		2.81	168.8	1.86
	OH(02)	*G*1 O(5^{iii})		3.02	138.3	2.24
*W*3	OH(030)	*G*2 O(5^{ii})		2.89	146.0	2.04
		*G*2 O(62^{iii})		3.00	130.6	2.33
	OH(03)	*W*5 O^{i}		2.75	155.5	1.84
		*W*4 O^{i}		3.17	118.6	2.60
*W*4	OH(04)	*G*2 O(62^{i})		2.81	174.3	1.85
	OH(040)	*G*1 O(5^{iii})		2.81	161.1	1.88
*W*5	OH(050)	*G*3 O(5^{i})		2.81	156.3	1.90
		*W*4 O^{i}		3.02	108.2	2.60
	OH(05)	*G*3 O(61^{viii})		2.70	169.4	1.75

Symmetry codes: (i) x, y, z; (ii) $x-y, x, z$; (iii) $x, y, z+1$; (iv) $1-y, x-y, z$; (v) $y, y-x, z+1$; (vi) $x, y, z-1$; (vii) $y-x+1, 1-x, z$; (viii) $1-x, 1-y, z$; (ix) $x-y, x, z+1$.

O(61)H(60) and O(62)H(06) are two different conformations for the disordered primary hydroxyls.

(b) Host–guest interactive disorder

A remarkable feature is that the guest's orientation is correlated with the conformational disorder of the primary hydroxyl group of the host. In molecule (1), this O(6) hydroxyl is statistically distributed between the 'inwards' conformation and the usual conformation 'away' from the cavity. In the inwards conformation, the distance between the O atom of the guest's carbonyl and the O atom of the hydroxyl is that of a hydrogen bond, 2.87 Å, and the s.o.f. of the primary hydroxyl in the inwards conformation is 0.26 ($\sigma = 0.03$) for neutrons and 0.24 for X-rays; these values are slightly higher than s.o.f. = 1/6 of the guest, which is imposed by symmetry. In molecule (2), the primary hydroxyl of residue *G*3 is threefold disordered, one with an inwards conformation and two away. The distance between the O atom of the guest carbonyl and the O atom of the hydroxyl with the inwards conformation is 2.45 Å. The s.o.f. of this hydroxyl, 0.4, is correlated with the symmetry-controlled value of s.o.f. = 1/3 for the guest (2) molecule. For the *G*3 primary hydroxyl with the away conformation, there are two positions, one main position with s.o.f. = 0.5 and a second position with a very low occupancy, s.o.f. = 0.1. The first is compatible with the inwards *G*3 hydroxyl conformation of the twofold symmetry-related cyclodextrin molecule. The location of the second is imposed by the proximity of the same related hydroxyl when it is in the away conformation. In the latter case the interatomic distance is 2.94 Å instead of 1.43 Å. The corresponding s.o.f.'s from the least-squares refinement could thus be explained by the disorder of this region.

We must distinguish the two different inclusion complexes in columns 1 and 2. In column 1, for each position of the cyclopentanone molecule there are two short distances between the carbonyl O and two primary hydroxyl O atoms in the inwards conformation, 2.87 and 2.98 Å, giving two possible host–guest hydrogen bonds. But there is no perceptible hydrogen peak between these O atoms. Instead a low peak was found between the primary hydroxyl O atom and the secondary hydroxyl oxygen O(3) of the translated cyclodextrin molecule along the *c* axis; although this H-atom site is close to the resolution limit, it is intriguing to note that this site forms an intracolumn hydrogen bond with a reasonable geometry. In column 2, the distance between the O atoms of the cyclopentanone carbonyl and the O atom of the primary hydroxyl is very short, 2.45 Å, while the distance between the C atom of the carbonyl and the O atom of the hydroxyl is 2.75 Å.* No peak corresponding to a H atom appears between the two O atoms of the guest carbonyl and the host hydroxyl, respectively. It is worth noting, however, that one site of low occupation (s.o.f. = 0.3) has been found for the hydroxyl H atom, hydrogen bonded to the translated cyclodextrin molecule. Since we have an average image of the structure, we cannot exclude the possibility that the hydroxyl group is in a posi-

* The values of these interatomic distances are in agreement with those found in the X-ray room-temperature structure, respectively, 2.52 and 2.81 Å.

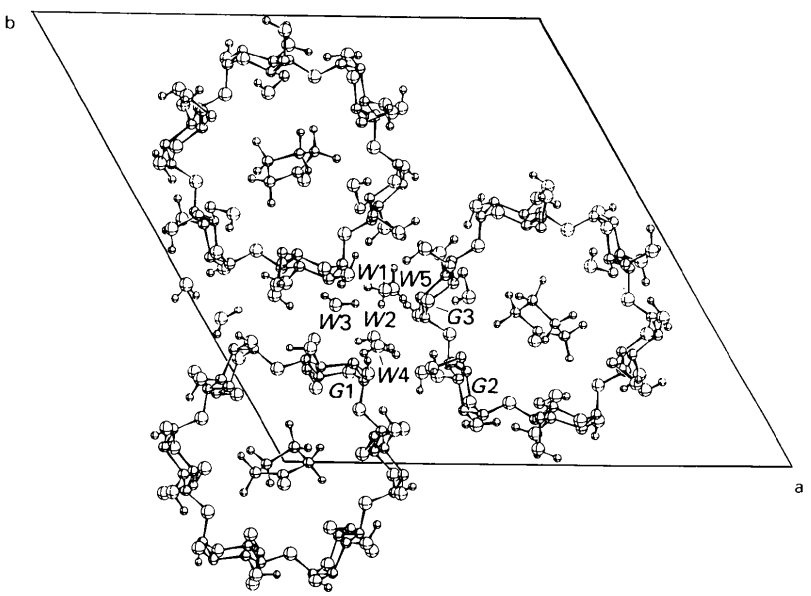

Fig. 2. Projection of the unit cell on the *ab* plane. For cyclodextrin molecules, only H atoms involved in hydrogen bonds are shown. The naming scheme is shown for the independent residues of the asymmetric unit, as well as for the water molecules.

tion 'away' from the cavity, when the carbonyl group is close to the glucose residue. However, if the hydroxyl group is 'inwards' to the cavity, the short distances suggest that the weakly nucleophilic O atom of the primary hydroxyl involved in the hydrogen-bonded network approaches the electrophilic C atoms of the carbonyl (Burgi, Dunitz & Shefter, 1974); the O···C distance is significantly less than the sum of the van der Waals radii. The observed position of the hydroxyl H atoms would favour the nucleophilic approach of the lone pair of the hydroxyl O atom to the carbonyl C atom. The two molecules would then be close enough to react with each other. The detailed geometrical pattern of this intermolecular interaction is not exactly the same as that described by the authors cited above; this can be explained by the disorder of the present structure and the perturbing effects of crystal-packing forces.

(*c*) *Cyclodextrin rings and intramolecular hydrogen bonds*

In the sixfold site, if we neglect the disorder of the primary hydroxyl, the cyclodextrin molecule has a perfect 'round' shape, compared with the tense state of the hydrated 'empty' α-cyclodextrin molecule form (I) with one tilted glucose (McMullan, Saenger, Fayos & Mootz, 1973), or compared with the elliptically distorted conformation resulting, for example, from the inclusion of a benzene ring as in the *p*-nitrophenol adduct (Harata, 1977). The six O(4) atoms form an undistorted hexagonal prism. The mean distance is close to that in the α-cyclodextrin form (III) (Chacko & Saenger, 1981), as are the other main geometrical features (Table 1). However, the O(2)···O(3) distance in a glucopyranose residue is slightly lower than the corresponding distance in hydrated α-cyclodextrin form III (2.98 Å), indicating that the shape of the molecule is more cylindrical.

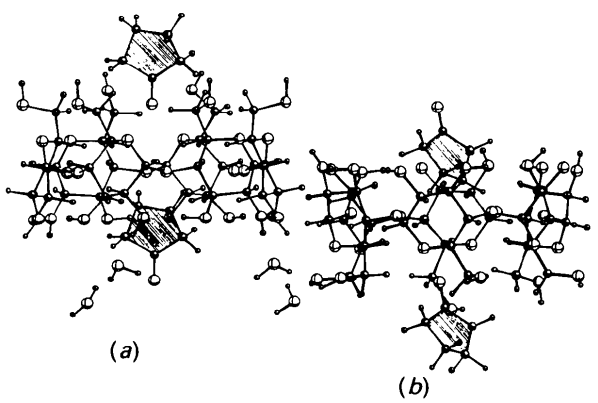

Fig. 3. A view of the structure approximately along the *a*-axis showing (*a*) cyclodextrin molecule (1) and (*b*) molecule (2). For each molecule two *c*-translated guest cyclopentanone molecules are shown (shaded).

As in most cyclodextrin clathrates, a crown of intramolecular hydrogen bonds is found between the secondary hydroxyl groups of the molecule (Klar, Hingerty & Saenger, 1980). For the unique glucose residue of the asymmetric unit in the sixfold site, the hydroxyl O(3)H is a donor and the O(2)H an acceptor (Fig. 2).

In the threefold site, the two residues *G*2 and *G*3 are different. The difference between the values of the φ torsion angle is significant (Table 1). The primary hydroxyl of the *G*2 glucose is slightly disordered. It is always in the away conformation, but a small modification occurs in the conformation when the position of the H atom changes; this atom is alternatively involved in two different hydrogen bonds (Table 2).

The *G*3 residue is a special case. The two conformations of the primary hydroxyl away and inwards with respect to the cavity are well defined; the primary hydroxyl C atom occupies a different position for each of them. The inwards hydroxyl protrudes into the cavity. The glucopyranose ring position is obviously modified by such a conformation of the primary hydroxyl and tilted towards the cavity, as occurs in the case of the α-cyclodextrin form (I). Indeed, the difference maps display slight disorder for all atomic positions of the *G*3 glucopyranose ring corresponding to two close positions. In this study, only the mean positions were determined; however, the tilt is manifested by the value of the mean torsion angle (161°) which is lower than the corresponding value of the glucose *G*2 (169°), but greater than 147° found for the tilted glucose of hydrated α-cyclodextrin form (I). This flexibility is associated with alternative intramolecular hydrogen bonds (involving secondary hydroxyls), as discussed below.

For the cyclodextrin molecule in the threefold site, the intramolecular hydrogen-bonding scheme is more complex than for the sixfold site. The secondary hydroxyl O(3)H of *G*2 is a donor and secondary O(2)H of G3 an acceptor. However, O(3)H of *G*3 and O(2)H of *G*2 become alternatively donor and acceptor. This implies that the H atom of each of these two secondary hydroxyl groups occupies two positions, with s.o.f. = 0.5. This phenomenon has been described in the β-cyclodextrin structure (Zabel, Saenger & Mason, 1986), However, in the present case, it could be simply statistical disorder and not a dynamic effect as in β-cyclodextrin. In the alternative position of O(2)H, the H atom of *G*2 points towards a water molecule site *W*3, which is partially occupied. The alternative position of the O(3)H hydrogen atom of *G*3 points towards the O(3)H O atom of the symmetry-related *G*3 residue in another cyclodextrin molecule. It is likely, as

indicated in Fig. 4, that when the *G*3 primary hydroxyl is in the inwards conformation, the hydroxyl O(2)H is donor in the intramolecular hydrogen bond and O(3)H is donor in an intermolecular hydrogen bond (Table 2).

It should be noted that the nearest O(4) atom is involved in all these intramolecular hydrogen bonds, which are consequently three-centred (Steiner & Saenger, 1992).

(*d*) *Intracolumn and intercolumn hydrogen bonds*

In the sixfold column, whatever the primary hydroxyl conformation, an intracolumn hydrogen bond has been observed, giving strong cohesion to the column. The primary hydroxyl O(6)H (donor) forms a hydrogen bond with the secondary hydroxyl O(3)H (acceptor) of the translated molecule along *c*.

By contrast with the sixfold site, the cohesion of the threefold column is not mainly assured by intracolumn hydrogen bonds. For the *G*2 residue, one partially occupied position (s.o.f. = 0.3) of the H atom has been located along the column. The alternative position of this H atom participates in an intercolumn hydrogen bond (see below).

In the case of the *G*3 residue, when the primary hydroxyl group is in the inwards conformation, one position of the H atom exhibited by difference maps

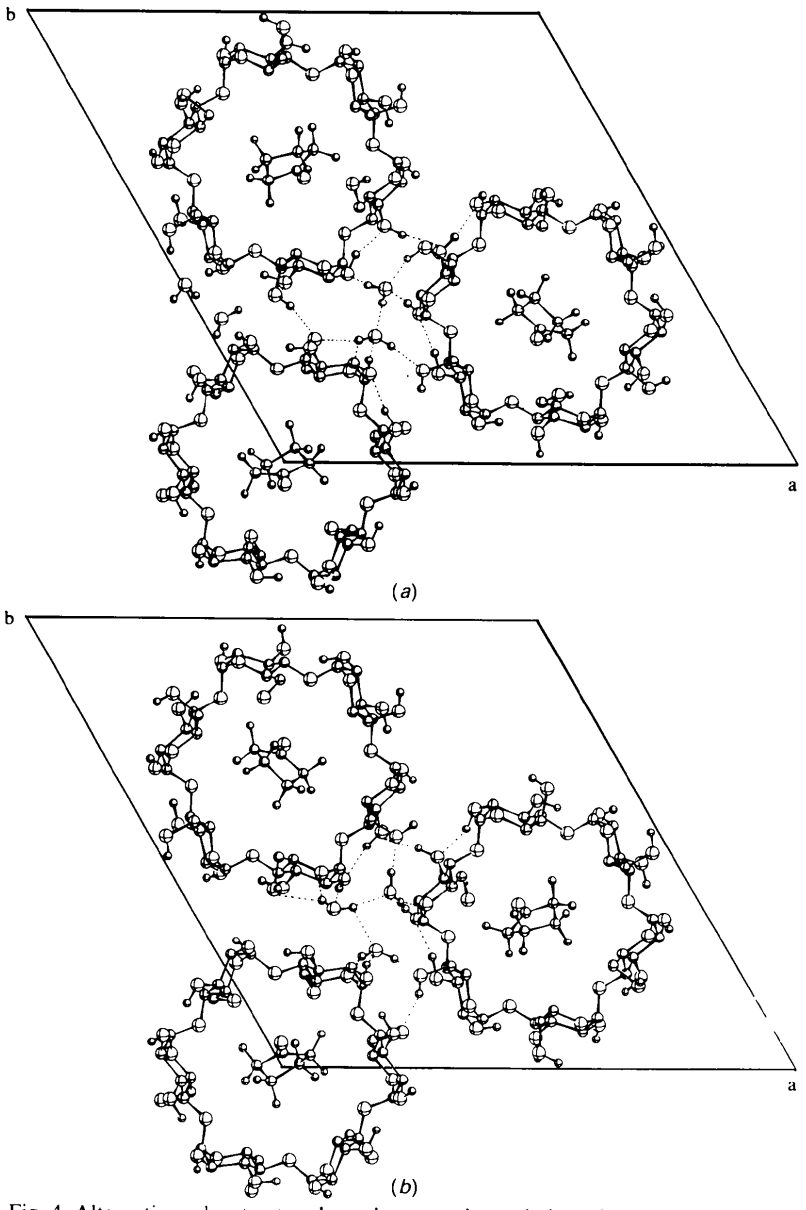

Fig. 4. Alternative solvent networks and proposed correlation with host conformation.

is oriented towards the hydroxyl O atom *G*3 O(2) along the same column. When the primary hydroxyl is in the away conformation, the H atom points towards a water molecule.

There are two direct intercolumn hydrogen bonds (Fig. 4). The sixfold and the threefold columns are joined together by a hydrogen bond between the *G*1 and *G*2 primary hydroxyl groups: *G*1 O(6) is an acceptor and *G*2 O(6)H is a donor, the s.o.f. of *G*1 O(6) and the *G*2 hydroxyl H atom are both 0.7.

Between two adjacent columns having a threefold axis, there is one intermolecular hydrogen bond involving two *G*3 secondary hydroxyl groups. These two secondary hydroxyl O(3) atoms are related by a twofold axis. Both become alternatively donor and acceptor.

(*e*) *Water network*

The water molecules are located in the channels formed outside the cyclodextrin columns. Five positions are found, all partially occupied, for 2.3 water molecules per asymmetric unit and are confined in a narrow layer perpendicualr to the *c*-axis.

*W*2 and *W*4 are two alternative positions for one water molecule, as are *W*1 and *W*5 for a second one. *W*3 has a low occupancy, s.o.f. = 0.3. The atomic sites *W*3 and *G*1 O(6) in the away conformation are excluded from simultaneous occupation as the distance would be only 2.23 Å. It appears more likely that *W*3 is present simultaneously with the primary hydroxyl *G*1 O(6) in the inwards conformation, as indicated respectively by the common value of their s.o.f. (0.3).

As some atomic positions of adjacent solvent molecules exclude one another since they are too close for atoms that are not covalently bonded, alternative positions have been deduced. Consequently, alternative solvent networks appear, as has been extensively detailed for example in the structure of Vitamin B12 coenzyme (Savage, 1986). In Fig. 4, two alternative hydrogen-bonded networks are shown using the partially occupied solvent sites and the alternative positions of the host hydroxyl groups. It has thus been possible to correlate in some detail the two networks with the different orientations of the guest molecules.

(*f*) *Cyclopentanone chirality*

As a consequence of the intrinsic chirality of the cyclodextrin molecule, the host–guest interaction is asymmetric. The cavity can then prefer one enantiomer of a racemic mixture of a variety of optically active compounds; co-crystallization with cyclodextrin in such a case leads to partial resolution (Szejtli, 1982). In addition, the asymmetric influence of the cavity has been shown to induce a Cotton effect on achiral chromophores (Sensse & Cramer, 1969).

When the guest is a conformationally labile molecule which displays an interconverting pair of enantioconformers, the cyclodextrin cavity is able to choose preferentially one of the chiral conformers. Then, this guest molecule, which is optically inactive in the absence of chiral solicitation, exhibits optical activity in the presence of cyclodextrin. This is the case for bilirubin, 4-helicene *etc.* (Le Bas, 1985).

In aqueous solution, the circular dichroism spectrum of the α-cyclodextrin cyclopentanone complex displays a negative band at $\lambda = 290$ nm, attributed to the n–π^* transition of the carbonyl chromophore. This small but significant Cotton effect could be caused either by preferential complexation of one chiral conformer of the labile cyclopentanone molecule or by chiral perturbation induced by the cyclodextrin cavity on the carbonyl chromophore, or by the combination of the two phenomena (Boisvin, Rassat, Le Bas & Tsoucaris, 1989). One could expect that the crystal structure would provide an answer to that question.

Unfortunately the guest molecule has several orientations and some atomic sites of different guest positions are superposed, even in the threefold site. Assuming that the guest molecule has two intercoverting stable twisted-ring (*C*2 symmetry) conformers (Fig. 5) and that the geometry is not modified on inclusion, we used the geometry given by spectroscopic data (Geise & Mijlhoff, 1971) for the two conformers and we moved these two models in the density map. The third possible non-chiral conformation (*Cs* symmetry) had also been considered, but was quickly excluded because it did not fit the neutron density.

In the threefold site, only the conformer (2) in Fig. 5 could explain all the peaks of the density map. Further, after optimization of the position of conformer (2) the *R* factor was lowered by 0.01 from the value obtained for the conformer (1) in Fig. 5.

In the sixfold site, the disorder is so high that the two models fit the density equally (only the two atoms of the carbonyl group are clearly seen on the density maps). The *R* factor is not appreciably modified by one or other hypothesis. For compari-

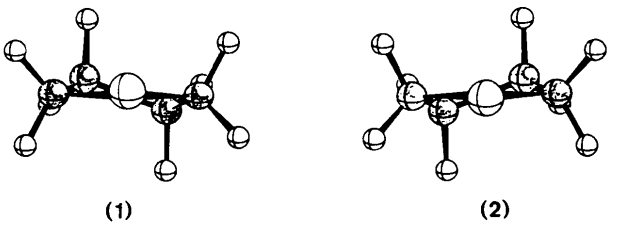

Fig. 5. The two enantioconformers of the cyclopentanone molecule viewed along the carbonyl axis with the O atom in front.

son, we may give other calculations of the R factor. When we calculate the structure factors without the contribution of the cyclopentanone molecule in the threefold site, the value of R is 0.117 instead of 0.086; the structure-factor calculation without the contribution of the guest in the sixfold site gives an R value of 0.095 instead of 0.086.

In conclusion, the best match between the molecular shape and the neutron diffraction density in the threefold site corresponds to the chiral conformer (2), strongly supporting the idea of chiral discrimination. Better discrimination in the threefold site than in the sixfold site may be explained by the greater interaction between host and guest in relation with the shorter intermolecular distances as seen above.

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Crystal Studies of Musk Compounds. XI.* Molecular Structures of Musk Moskene and Two Homologues

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Abstract

The crystal structures of 1,1,3,3,5-pentamethyl-4,6-dinitroindan (1), 1,1,2,3,3,6-hexamethyl-5-nitroindan (2) and 1,1,2,3,3,5-hexamethyl-4,6-dinitroindan (3) have been established by X-ray crystallography. (1) and (3) are strong musks. Some of the structures described show disorder in the cyclopentene ring and/or in the nitro groups. This manifests itself in relatively high displacement parameters and in deviating bond distances and angles. The endocyclic angles of the cyclopentene ring, at the fusion with the aromatic ring, are significantly larger than reported in a study of the geometry of small rings [Allen (1981). *Acta Cryst.* B**37**, 900–906]. The geometry and position on the aromatic ring of the nitro groups is compared with the acylated indan musk compounds and evidence is given that the nitro group in the β-position fulfils the osmophoric function.

Introduction

In part VIII of this series (De Ridder, Čapková, Hatjisymeon, Fraanje & Schenk, 1994), the crystal structures of five homologues of musk phantolid are reported, which all carry an acyl group on the aromatic ring. In this paper, the crystal structures of indan compounds having one or more nitro groups attached

* This work forms part of a thesis by De Ridder (1992).

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