

Channel-Type Crystal Packing in the Very Rare Space Group $P4_212$ with $Z' = 3/4$: Crystal Structure of the Complex γ -Cyclodextrin–Methanol– n -Hydrate[†]

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Abstract

The crystal structure of the title compound is discussed with focus on its unusual crystal packing mode. The γ -cyclodextrin molecules stack in columns which have internal channels and additional large channels are formed between the columns. Both types of channels are so wide that more or less free diffusion of water and small guest molecules is possible, preventing characterization of the solvent and guest arrangements. Although the space group $P4_212$ (no. 90) and the unit-cell content $Z' = \frac{3}{4}$ are extremely rare in general, this is the favorite crystal packing arrangement of γ -cyclodextrin inclusion complexes. This space group has not been observed as yet for other purely organic compounds.

1. Introduction

Inclusion complexes of the macrocyclic cyclodextrins (CD's, cyclomaltooligosaccharides) are physically well characterized and many crystal structures have been determined. The CD host molecules are sufficiently flexible to allow their shape to adjust to the shape of a guest, so that in crystal structures of different complexes different host conformations can be observed. The complexes of α - and β -cyclodextrin (α -CD, β -CD; composed of six and seven D-glucoses, respectively) crystallize in a variety of crystal packing modes, which are induced by the nature of the guest molecule (Saenger, 1984, 1985). For γ -CD (composed of eight D-glucoses), the situation is different: only a few crystal structures have been reported as yet and these fall into only two structural categories: γ -CD.16H₂O crystallizes in space group $P2_1$, forming a cage-type structure in which the water-filled molecular cavities are closed on both ends by neighboring γ -CD molecules; in this crystal packing the γ -CD molecules are somewhat distorted with no internal symmetry (X-ray crystal structure: Harata, 1987; neutron crystal structure: Ding, Steiner, Zabel *et al.*, 1991). All other γ -CD complexes crystallized as yet form a channel-type packing in the tetragonal space group $P4_212$, Table 1, with the γ -CD

molecules placed on fourfold axes. For δ -CD (Fujiwara *et al.*, 1990) and ϵ -CD (Ueda *et al.*, 1996; Jacob *et al.*, 1998) only one crystal structure was published, not allowing a comparison of possible different packing modes.

We have crystallized additional inclusion complexes of γ -CD with alcohols and found that they all exhibit very similar unit-cell dimensions to the other published structures in space group $P4_212$. The first impression is that no further crystallographic work is justified, because all these crystal structures must be isostructural. However, we noticed that this particular packing mode possesses rare and peculiar crystallographic characteristics (see below), which have not been in the focus of the earlier studies. Therefore, we present here the crystal structure of the complex γ -CD–methanol– n -hydrate and crystallographic data of other complexes, with the main emphasis on crystal packing.

2. Experimental

Crystals of γ -CD complexed with methanol (MeOH), ethanol (EtOH) and benzyl alcohol (BzOH) were obtained by the slow cooling of corresponding hot saturated aqueous solutions (crystal habitus invariably colorless square bipyramids with truncated apices). Crystals are very sensitive to loss of solvent; contact with the atmosphere leads within seconds to cracking and subsequent disintegration. Therefore, X-ray diffraction experiments were performed on crystals sealed in capillaries together with some mother liquor (Enraf-Nonius Turbo-CAD-4 diffractometer on a FR571 rotating anode generator, Ni-filtered Cu $K\alpha$ radiation with $\lambda = 1.5418$ Å, room temperature). For γ -CD–MeOH– n H₂O a full diffraction data set was collected, Table 2, and for γ -CD–EtOH– m H₂O and γ -CD–BzOH– p H₂O only unit-cell dimensions were determined (from the angular settings of 25 reflections each), see Table 1.

Similar to all published isostructural crystal structures, the diffraction quality has been moderate, in particular, in the high-angle region. Only to a resolution of $\lambda/2\sin\theta = 1.1$ Å are over 50% of the measured reflections actually 'observed' [$I > 2\sigma(I)$]. In the resolution shell 1.1–1.0 Å only 41.1% of the measured

[†] *Topography of Cyclodextrin Inclusion Complexes*, Part 41. For Part 40, see Steiner *et al.* (1996).

Table 1. Unit-cell dimensions of γ -CD inclusion complexes crystallizing in the space group $P4_212$

All complexes contain molecules of crystal water, only part of which have been located; therefore, exact crystal compositions cannot be given.

Guest molecule	$a = b$ (Å)	c (Å)	V (Å ³)	R value	Reference
1-Propanol, study 1†	23.759 (7)	23.069 (7)	13 022 (7)	0.14	Lindner & Saenger (1980)
1-Propanol, study 2, crystal 1	23.840 (5)	23.227 (5)	13 201 (5)	0.067	Ding, Steiner & Saenger (1991)
1-Propanol, study 2, crystal 2	23.8093 (5)	23.2069 (5)	13 155.6 (5)	0.082	Ding, Steiner & Saenger (1991)
12-Crown-4	23.808 (2)	23.175 (2)	13 136 (2)	0.154	Kamitori <i>et al.</i> (1986)
12-Crown-4-LiSCN (3:1)	23.75 (2)	22.92 (3)	12 928 (20)	0.16	Kamitori <i>et al.</i> (1987)
12-Crown-4-KCl (3:1)	23.842 (2)	23.123 (2)	13 144 (2)	0.15	Kamitori <i>et al.</i> (1987)
12-Crown-4-NaCl (3:1)	23.816 (3)	23.072 (3)	13 086 (3)	0.168	Kamitori <i>et al.</i> (1988)
MeOH	23.808 (4)	23.140 (3)	13 116 (4)	0.086	This work
EtOH	23.823 (9)	23.189 (8)	13 160 (8)		This work
Benzylalcohol	23.805 (2)	23.196 (7)	13 094 (4)		This work

† In the original publication erroneously refined in space group $P4$.

reflections are observed and in the shell 1.0–0.9 Å this fraction falls to 19.4%. This is typical behavior for crystal structures containing large amounts of disordered water and/or solvent. The authors of the very interesting inclusion complexes with 12-crown-4 and 12-crown-4-complexes, which represent ‘molecular anions’, suffered similar or even more severe problems, Table 1 (Kamitori *et al.*, 1987, 1988; also see the foregoing work of Vögtle & Müller, 1979).

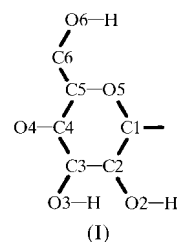
Atomic coordinates of the γ -CD molecules (except the primary hydroxyl groups) in the isostructural complex γ -CD–1-propanol (Ding, Steiner & Saenger, 1991) were used for initial phasing. Anisotropic refinement on F^2 was performed with standard methods (Sheldrick, 1993), Table 2.† 17 water molecule sites were located, only four of which are fully occupied; the sum of water occupancies is 10.1 per asymmetric unit, corresponding to 13.5 H₂O’s per γ -CD molecule. Owing to extensive disorder (see below) no distinct atomic sites could be found in large parts of the channel regions. No electron density could be unambiguously interpreted as MeOH. This parallels the crystal structure of γ -CD–1-propanol– n H₂O, where, because of disorder, the guest molecule could not be identified either. Four of the six symmetry-independent glucoses exhibit twofold disorder of the primary hydroxyl groups O(6); the alternative sites were restrained in refinement to have the occupancy sum 1.0. Since not all water and no MeOH molecules could be located, it is not reasonable to give numerical values for n (H₂O), m (MeOH), FW , μ and D_{calc} . Refinement converged with $R = 0.086$ (for observed reflections), which is not atypical for structures of this kind (Table 1). The largest remaining difference electron density peak $\Delta\rho = 0.30 \text{ e } \text{Å}^{-3}$ is not indicative of appreciably populated atomic sites which might have been missed.

† Lists of atomic coordinates, anisotropic displacement parameters and structure factors have been deposited with the IUCr (Reference: KA0038). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

3. Results and discussion

3.1. Molecular conformation

In the crystal structure there are three independent γ -CD molecules A , B and C . They are placed on the crystallographic fourfold axis and have, therefore, fourfold internal symmetry. Consequently, the number of symmetry-independent glucose residues is six, amounting to $\frac{3}{4}$ of a γ -CD molecule. The conformations of the three independent molecules are very similar, so that only one needs to be shown in Fig. 1; the atomic numbering scheme of the glucose units is given in (I). Selected numerical data are given in Table 3.



The round shapes of the macrocycles are stabilized by systematic intramolecular hydrogen bonds $O(2)n \cdots O(3)n + 1$, with $O \cdots O$ separations in the narrow range 2.77–2.92 Å. Since the hydroxyl H atoms could not be located, the orientation of these hydrogen bonds is not determined. In addition, there are much weaker, but equally systematic, $C-H \cdots O$ interactions $C(6)n-H \cdots O(5)n - 1$ (Steiner & Saenger, 1992; Steiner, 1997). Molecules A and B exhibit twofold disorder of the primary hydroxyl groups O(6), which may rotate around the C(5)–C(6) bond. This is a very common phenomenon in cyclodextrin crystal structures and has been observed in all the isostructural crystals given in Table 1. Molecule C has well ordered primary hydroxyl groups.

3.2. Crystal packing in space group $P4_212$ with $Z' = \frac{3}{4}$

With some delay after publishing the previous crystal structure (Ding, Steiner & Saenger, 1991) we noticed

Table 2. *Experimental details*

Crystal data	
Chemical formula	C ₄₈ H ₈₀ O ₄₀ · <i>n</i> CH ₄ O· <i>m</i> H ₂ O
Chemical formula weight	Uncertain, as <i>m</i> and <i>n</i> unknown
Cell setting	Tetragonal
Space group	<i>P</i> 4 ₂ 1 ₂
<i>a</i> (Å)	23.808 (4)
<i>b</i> (Å)	23.808 (4)
<i>c</i> (Å)	23.140 (3)
<i>V</i> (Å ³)	13 116 (4)
<i>Z</i>	6
<i>Z'</i>	3/4
<i>D_x</i> (Mg m ⁻³)	Not determined
Radiation type	Cu <i>K</i> α
Wavelength (Å)	1.54176
No. of reflections for cell parameters	25
θ range (°)	1.91–59.83
μ (mm ⁻¹)	0.994
Temperature (K)	293 (2)
Crystal form	Square bipyramid
Crystal size (mm)	0.5 × 0.2 × 0.2
Crystal color	Colorless
Data collection	
Diffractometer	Enraf–Nonius CAD-4
Data collection method	ω -2 θ scans
Absorption correction	None
No. of measured reflections	6681
No. of independent reflections	5389
No. of observed reflections	3860
Criterion for observed reflections	<i>I</i> > 2 σ (<i>I</i>)
<i>R</i> _{int}	0.043
Range of <i>h, k, l</i>	0 → <i>h</i> → 18 0 → <i>k</i> → 25 0 → <i>l</i> → 25
No. of standard reflections	3
Frequency of standard reflections (min)	60
Intensity decay (%)	4.2
Refinement	
Refinement on	<i>F</i> ²
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)]	0.0860
<i>wR</i> (<i>F</i> ²)	0.262
<i>S</i>	1.009
No. of reflections used in refinement	5376
No. of parameters used	773
H-atom treatment	H-atom parameters not refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1241P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
(Δ/σ) _{max}	-0.001
$\Delta\rho$ _{max} (e Å ⁻³)	0.30
$\Delta\rho$ _{min} (e Å ⁻³)	-0.26
Extinction method	None
Source of atomic scattering factors	Flack (1983)
Computer programs	
Data collection	CAD-4 software (Enraf–Nonius, 1989)
Cell refinement	CAD-4 software (Enraf–Nonius, 1989)
Data reduction	CAD-4 software (Enraf–Nonius, 1989)
Structure solution	Isomorphous structure (Ding, Steiner & Saenger, 1991)
Structure refinement	SHELXL93 (Sheldrick, 1993)

that the occurrence of space group *P*4₂1₂ and the parameter $Z' = \frac{3}{4}$ (Z' = formula units per asymmetric crystal unit) are very rare events and are of interest in themselves. In a statistical study of Padmaja *et al.* (1990) on organic and organometallic crystal structures the space group *P*4₂1₂ appears to be very exceptional: it was assigned to only 3 out of 51 611 crystal structures published at that time. In inorganic crystal structures

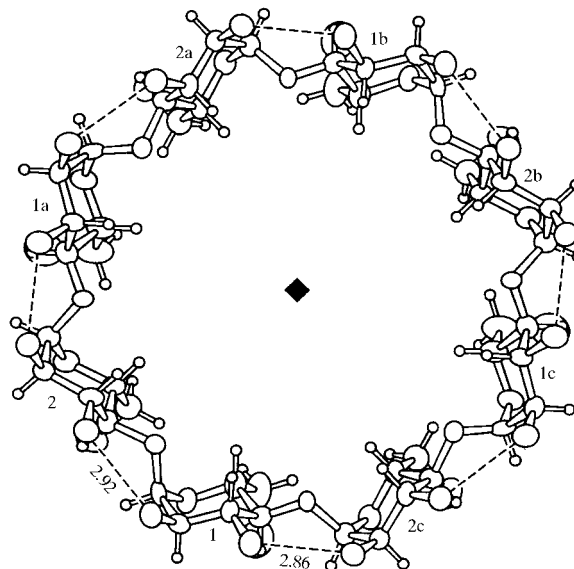


Fig. 1. Molecular structure and atomic numbering scheme of molecule *C* with well ordered O(6) hydroxyl groups. Intramolecular hydrogen bonds are indicated by dashed lines (A). Displacement ellipsoids are drawn at the 30% probability level.

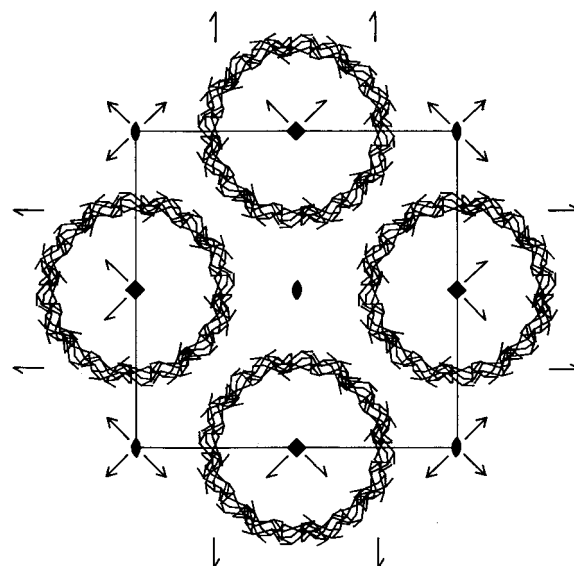


Fig. 2. Crystal packing shown in a projection on the *x, y* plane. Crystallographic symmetry elements of the space group *P*4₂1₂ are indicated.

Table 3. Selected geometrical parameters (\AA , $^\circ$) of the γ -CD molecules

For definition of the symmetry-equivalent fragments *a*, *b* and *c*, see Fig. 1.

Parameter	Molecule A	Molecule B	Molecule C
Macrocycle conformation			
C(4)1—O(4)1—C(1)2c	116.0 (9)	116.3 (8)	116.4 (8)
C(4)2—O(4)2—C(1)1	115.8 (9)	117.0 (8)	114.3 (8)
O(4)1···O(4)1b	8.33 (1)	8.30 (1)	8.33 (1)
O(4)2···O(4)2b	8.33 (1)	8.27 (1)	8.26 (1)
Tilt angle \dagger residue 1	13.2 (3)	14.0 (3)	17.0 (3)
Tilt angle \dagger residue 2	12.2 (3)	13.0 (3)	15.4 (3)
Intramolecular O···O hydrogen-bond contacts			
O(2)1···O(3)2	2.77 (1)	2.84 (1)	2.92 (1)
O(2)2···O(3)1a	2.77 (1)	2.85 (1)	2.86 (1)
Intramolecular C—H···O interactions			
C(6)1···O(5)2c	3.40 (2)	3.27 (2)	3.37 (2)
C(6)2···O(5)1	3.42 (2)	3.30 (2)	3.29 (1)
H(6)2···O(5)2c	2.76/2.47 \ddagger	2.39/2.81 \ddagger	2.55
H(6)1···O(5)1	2.83/2.46 \ddagger	2.48/2.38 \ddagger	2.45

\dagger Tilt angle of the least-squares plane through atoms C(1), C(2), C(3), C(4), C(5) and O(5) with respect to the molecular axis. \ddagger For partially occupied O(6) sites (*a*) and (*b*), respectively.

this space group is similarly rare (5 out of 34 692 structures analyzed by Baur & Kassner, 1992). Notably, it is not as rare for proteins (2 out of 208 structures; Padmaja *et al.*, 1990), which pack more frequently in high-symmetry space groups than organic molecules.

Since the statistical analyses given above are somewhat dated now, the Cambridge Structural Database, CSD (Allen & Kennard, 1993), Spring 1997 update with 160 091 entries, was searched again for organic and organometallic crystal structures with space group no. 90. This yielded nine hits, *i.e.* 0.006% of all structures. Of these nine hits six are from γ -CD inclusion complexes (Table 1; the first entry of the table is not contained) and the other three are from organometallic compounds (Schlemper, 1977; Collins *et al.*, 1978; Elschenbroich *et al.*, 1992). No purely organic compound other than a γ -CD inclusion complex was ever found to crystallize in space group $P4_21_2$.

The unit-cell content with $\frac{3}{4}$ formula units per asymmetric unit is also very uncommon: we find it for only 30 crystal structures archived in the Spring 1997 update of the CSD (14 organic, 16 organometallic; 20 in monoclinic, 3 in orthorhombic and 7 in tetragonal space groups).

Since γ -CD complexes crystallize so persistently (Table 1) in such a rare crystal symmetry, the packing mode is shown below in detail and in a different presentation than in the previous papers. In the crystal lattice γ -CD molecules stack in columns parallel to the tetragonal *c* axis. These columns exhibit internal channels of $\sim 8 \text{ \AA}$ van der Waals diameter, which extend through the whole crystal. The columns are not arranged in a hexagonal or quasi-hexagonal pattern, which would be typical for effective close-packing (Saenger, 1985), but in a square pattern containing large channels between the columns (Fig. 2). The interstitial channels have a van der Waals diameter of $\sim 7 \text{ \AA}$. The internal

channels of the γ -CD columns and the interstitial channels are filled with water and MeOH molecules. Both types of channels are so wide that more or less free diffusion of small molecules is possible. Therefore, the solvent arrangement and the MeOH/H₂O ratio cannot be described satisfactorily with diffraction methods. These wide channels explain the observed sensitivity against loss of solvent: the microstructure of the crystal determines the macroscopic properties.

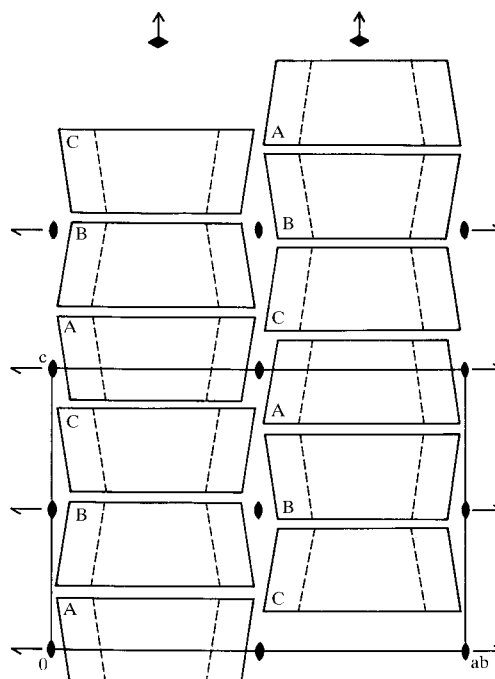


Fig. 3. Stacking sequence within the molecular columns and lateral contacts between the columns shown schematically. Projection is on a diagonal plane of the unit cell (*cf.* Fig. 2).

The stacking sequence of γ -CD molecules within the columns is unusual: in CD columns normally either all molecules are parallel ('head-to-tail arrangement') or neighboring molecules are antiparallel (Saenger, 1984, 1985). In the present structure the crystallographic repeat unit is built of three molecules, two of which are parallel and one is antiparallel (Fig. 3). The columns are then built by translation of these units. The intermolecular contacts involve head-to-tail (molecule pair *A-C*), head-to-head (pair *B-C*) and tail-to-tail (pair *A-B*) contacts. Neighboring molecules are connected by systematic hydrogen-bond patterns that have been described previously (Ding, Steiner & Saenger, 1991). The formation of these hydrogen bonds requires the rotation of the molecules around the molecular axes with respect to each other; the rotation angles are 9.8, 11.2 and -21.0° for the pairs *A-B*, *B-C* and *C-A*, respectively (the sum of the rotation angles must be zero to obtain translation symmetry).

Neighboring columns are symmetry-related and linked by a system of lateral hydrogen-bond interactions (Ding, Steiner & Saenger, 1991), which need not be specified again here. In Fig. 3 the contact geometry is schematically shown, together with the relating symmetry operations.

4. Discussion

The crystal packing mode shown above and the tetragonal space group $P4_21_2$ are extremely rare. For purely organic compounds $P4_21_2$ has not yet been observed in systems other than inclusion complexes of γ -CD. Despite its general rareness, this packing is the preferred one for the γ -CD complexes, which almost exclusively crystallize in this highly exotic way.

In the context of the structural chemistry of cyclodextrins this preference is unfortunate, because in the crystal lattice water and small guest molecules may diffuse within the wide channels, causing severe crystallographic resolution problems and preventing precise description of the solid-state complex. This is the main reason why the γ -CD molecule is still structurally much less well characterized than the lower homologs α -CD and β -CD. Obtaining accurate structural data for γ -CD requires crystallization in a different crystal packing, which might be induced by suitably shaped guest molecules. Our efforts in this direction remained unsuccessful until now.

In the context of crystal packing in general, the present family of complexes provides interesting information: crystallization of γ -CD in the rare space group $P4_21_2$ is not a singular incident which occurs only for a particular guest molecule, but occurs systematically for a wide variety of chemically different guests. On the other hand, it is not an inherent property of γ -CD complexes: the inclusion complex with water crystallizes in a completely different fashion and without internal

molecular symmetry. The circumstance that a compound crystallizes in a rare packing mode possessing unusual values of parameters such as *Z*, *Z'* or the space-group number should, therefore, not be misinterpreted in the way that this packing mode is generally 'unfavorable'. For the example of γ -CD complexes, the packing in space group $P4_21_2$ is clearly favored. Speculating on the reasons for this remarkable behavior is not within the scope of this contribution, in particular, because the structure-determining intermolecular interactions cannot be elucidated in a quantitative manner from X-ray diffraction data of moderate resolution.

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