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Carbohydrate Research 333 (2001) 251–256

CARBOHYDRATE RESEARCH

X-ray structure of β-cyclodextrin-2,7-dihydroxy-naphthalene·4.6 H_2O: an unusually distorted macrocycle

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Received 4 January 2001; accepted 10 May 2001

Abstract

The inclusion complex β-cyclodextrin·2,7-dihydroxynaphthalene·4.6 H_2O crystallized in the monoclinic space group $P2_1$, with $a = 14.082(3)$, $b = 19.079(4)$, $c = 12.417(3)$ Å, $\beta = 109.28(3)°$, $V = 3149.0(11)$ Å^3, and $Z = 2$. An X-ray study performed at room temperature shows that the crystal packing is of the herringbone type with one 2,7-dihydroxynaphthalene included completely in the β-CD cavity, its long axis being oriented along the β-CD molecular axis, and 4.6 water molecules are placed in the interstitial space. The β-CD macrocycle is elliptically distorted, and the guest molecule is held in the hydrophobic β-CD cavity by C–H···O and C–H···π interactions.

Keywords: β-Cyclodextrin; 2,7-Dihydroxynaphthalene; X-ray structure; Inclusion complex

1. Introduction

Cyclodextrins (CDs) produced by enzymatic degradation of amylose are cyclic oligosaccharides consisting of six, seven or eight, α-(1→4)-linked D-glucose units well-known as α-, β-, and γ-CDs, respectively.[1–3] The D-glucose units adopt the common and most stable $^4C_1$ chair conformation. CDs are shaped like truncated cones with central cavities. The narrow and wide rims of the cones are occupied by primary and secondary hydroxyl groups, respectively, so that the CDs are hydrophilic at the periphery and hydrophobic in the central cavity which is able to accommodate guest molecules of suitable size. In these inclusion complexes, the guest molecules are not covalently bonded to the host, but stabilized by weak interactions (van der Waals forces, hydrogen bonds, dipole–dipole interactions, and the hydrophobic effect).

In β-CD, a belt of seven hydrogen bonds formed between O-2···O-3′ hydroxyl groups of adjacent glucose units gives rise to a relatively rigid, round structure. The overall shape and packing of the β-CD macrocyle in crystal lattices is affected by the size and character of the respective guest molecule. Inclusion complexes of β-CD with guest molecules like water or small alcohols usually crystallize in $P2_1$ herringbone packing mode with a slightly deformed macrocycle, whereas inclusion com-

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0008-6215/01/$ - see front matter
PII: S0008-6215(01)00131-8

plexes with larger guests often crystallize in the triclinic $P\bar{1}$[4] or orthorhombic $C222_1$ [Ref. 5 and references therein] space groups. In these latter crystal forms the macrocycles form dimers which stack like coins in a roll to produce channels.

From a structural point of view, the most suitable guest molecules for β-CD should have a hydrophobic body and hydrophilic 'ends' which can form hydrogen bonds to the hydroxyl groups on both sides of the host molecule to stabilize the inclusion complex. In this study, such a guest molecule, 2,7-dihydroxynaphthalene (DHN), has been cocrystallized with β-CD to investigate interactions occurring between host and guest molecule.

Table 1
Crystallographic data: data collection, structure determination and refinement

	β-CD·DHN·4.6 H_2O
Chemical formula	$C_{52}H_{78}O_{37}$·4.6 H_2O
Formula weight	1384
Crystal size (mm^3)	$0.2 \times 0.3 \times 0.2$
Crystal system	$P2_1$
Unit cell dimensions	
a (Å)	14.082(3)
b (Å)	19.079(4)
c (Å)	12.417(3)
β (°)	109.28(3)
V ($Å^3$)	3149.0(11)
Z	2
D_{calcd} (g cm^{-3})	1.442
μ (mm^{-1})	1.101
$F(000)$	1444
Diffractometer	Turbo CAD4 (Enraf–Nonius)
Wavelength (Å)	Cu K_α 1.5418
Temperature	room temperature
Unique reflections	
All data	4830
$>2\sigma F$	3052
Max resolution (Å)	0.89
Structure solution	ab initio method (SHELXD)
Refinement method	SHELXL97
Parameters	824
$wR[F_o > 2\sigma(F_o)]$ [a]	0.175
$R[F_o > 2\sigma(F_o)]$ [b]	0.082
Goodness-of-fit	0.991

[a] $wR = \Sigma\{w(F_o - F_c)^2/\Sigma_w(F_o)^2\}^{1/2}$.
[b] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.

2. Methods

Crystallization, data collection, structure determination and refinement.—Lightbrown crystals of β-CD·DHN·4.6 H_2O were obtained at 18 °C by slow evaporation of a saturated solution of (1:2 molar ratio) β-CD–DHN in water. X-ray diffraction data were collected from a crystal mounted in a glass capillary together with some mother liquor using a CAD4 Diffractometer with Ni-filtered Cu K_α-radiation (see Table 1). All attempts failed to determine the crystal structure by conventional direct-methods[6] and by molecular replacement using a 'round' β-CD model taken from published structures. The reasons for failure were not analyzed; they might be associated with space group $P2_1$ and size of the structure (94 non-H atoms), and with the distortion of the β-CD macrocycle (see below), respectively. The crystal structure was finally obtained by a novel 'ab initio' real/reciprocal space recycling procedure[7] implemented in SHELXD which revealed the positions of nearly all non-hydrogen atoms. The remaining atoms and the cocrystallized water molecules were located by inspection of difference Fourier maps using the graphic program XTALVIEW.[8] In the refinement procedure based on F with full-matrix least-squares (SHELXL97),[9] all non-hydrogen atoms were treated anisotropically, and hydrogen atoms were placed at idealized positions (C–H = 0.97 Å) according to a 'riding model'. The refinement converged at a final $R = 0.082$ for 3052 reflections with $F_o > 2\sigma$ (0.17 for all 4830 reflections).

All the atoms of β-CD and the guest molecule 2,7-dihydroxynaphthalene (DHN) are in well-defined positions, and all atom sites are fully occupied except for two water molecules W-1 and W-5, each with occupation factors of about 0.8.

3. Results and discussion

The numbering scheme adopted for the inclusion complex is given in Fig. 1. C-$m(n)$ or O-$m(n)$ denotes the mth C or O atom within the nth glucosidic residue Gn. The β-CD macrocycle is elliptically distorted (see Fig. 2).

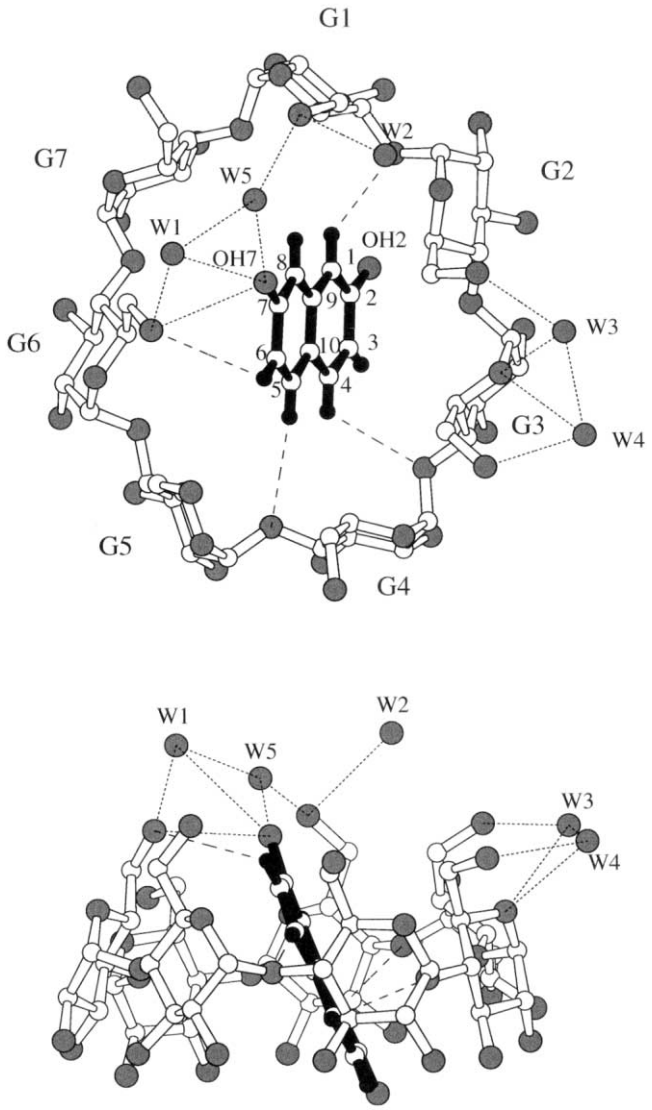

Fig. 1. The structure and numbering scheme of the inclusion complex β-CD·DHN·4.6 H_2O, viewed from the top and after rotation by 90° about the horizontal, from the side. The carbon atoms are shown in white, oxygen atoms in gray and C–H hydrogen atoms of DHN in black. Dotted fine lines are possible O–H···O hydrogen bonds and the dashed thick lines represent possible C–H···O interactions. Figures drawn with MOLSCRIPT.[21]

This is reflected in the O-4(n)–O-4($n-1$) (4.07–4.74 Å) distances and in the O-4(n)–O-4($n+1$)–O-4($n+2$) (119.5–139.1°) angles (Table 2, D_4 and A_4), which differ significantly from the respective values found in β-CD·11 H_2O with values of 4.27–4.5 Å and 125.2–132.5°[10] (Table 2 shows average values). In addition, the large differences between the O-4(n)···O-4($n+2$) values (7.38–8.37 Å) reflect the elliptical distortion (Table 2, D_3).The distortion of the macrocycle does not significantly affect the intramolecular O-2(n)–O-3($n-1$) hydrogen bond lengths, which are in the range 2.79–3.09 Å (β-CD·11 H_2O: 2.80–2.98 Å[10]).

The torsion angles ϕ and ψ describe the relative orientation of adjacent glucose units with respect to their glycosidic link.[11] The conformational space of torsion angles ϕ and ψ is limited due to the intramolecular O-2–O-3′ hydrogen bonds, which stabilize the macrocyclic conformation and the orientation of each glucose unit relative to its adjacent neighbors. The values for these angles ($\phi = 100.1$–$117.9°$, $\psi = 102.8$–$138.3°$, average $\phi = 109.2°$, $\Psi = 127.6°$) of the complex do not deviate significantly from the average values given in Table 2 for β-CD·11 H_2O. Similarly, the individual glucose residues show nearly ideal chair geometry according to Cremer and Pople,[12] only glucose G-2 shows significant distortion of the θ value. This may be related with the relatively large tilt angle T of this glucose unit, which is defined as the angle between the mean O-4-plane and the plane through C-1(n), C-4(n), O-4(n), and O-4($n+1$) atoms of each glucose. The large positive tilt angles found for glucoses G-2 (30.19°) and G-6 (20.05°) indicate that these residues are rotated with their O-6 side towards the center of the cavity.

The hydrophobic cavity of β-CD includes only the DHN molecule; all cocrystallized water molecules are located at the narrow end of the CD-cavity (on the O-6-side). The DHN molecule is completely enclosed in the β-CD cavity, its long axis being oriented in the direction of the molecular axis of β-CD. The hydroxyl group OH-7 is close to the O-6 side of the macrocycle and forms a hydrogen bond to the O-6 atom of glucose G-6 (O–H···O = 3.23 Å). For this interaction to take place, glucose unit G-6 must incline by 20.05° toward the cavity (Table 2). The aromatic guest molecule is engaged in four $C–H_{(guest)}\cdots O_{(host)}$ hydrogen bond interactions,[13,14] three with O-$4_{(host)}$ atoms and one with O-$6(6)_{(host)}$ (Fig. 1, Table 3).

The DHN hydroxyl group OH-2 forms intermolecular hydrogen bonds with symmetry related β-CD-molecules and with water molecule W-2 (Table 3), but not with the enclosing β-CD. The hydrogen bonds formed

by the five water molecules are shown in Table 3 and Fig. 1; additional intermolecular hydrogen bonds stabilize the crystal packing (not shown).

The two midpoints of the aromatic moiety defined as M-1 (resulting from the plane formed by C-1, C-2, C-3, C-4, C-9, and C-10) and M-2 (C-5, C-6, C-7, C-8, C-9, and C-10) were used to investigate possible $C–H_{(host)}\cdots\pi_{(guest)}$ interactions. The contacts given in Table 3 are comparable to weak X–H···π interactions frequently observed for various types of X–H-donors and aromatic π-acceptors[15–17] (for C–H···π,[15] and for stronger donors such as O-H).[16,17]

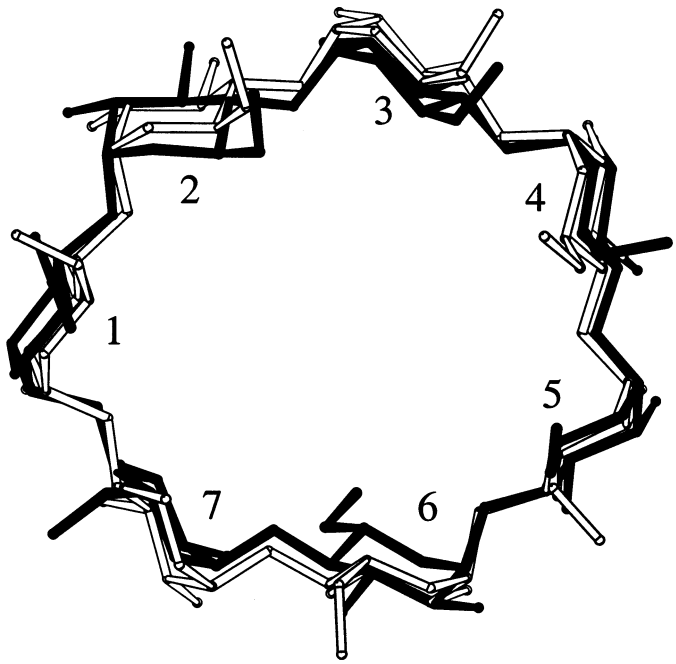

Fig. 2. Comparison of structures of β-CD in complexes with 2,7-dihydroxy-naphthalene (black) and with 11 H_2O (white).[11] The O_4 atoms of the two molecules were superimposed by least-squares fit.

Table 2
Geometrical parameters

	D_2 [a] (Å)	D_4 [b] (Å)	A_4 [c] (°)	D_3 [d] (Å)	ϕ [e] (°)	ψ [e] (°)	QT [f] (Å)	θ [f] (°)	T [g] (°)
G-1	2.82	4.07	137.6	8.37	117.9	138.3	0.58	3.2	8.16
G-2	2.94	4.42	125.6	7.89	100.1	114.4	0.55	12.8	30.19
G-3	3.09	4.57	122.4	7.56	101.4	131.9	0.56	5.3	8.46
G-4	2.79	4.29	128.2	7.87	112.4	125.1	0.56	4.5	1.98
G-5	2.80	4,30	139.1	8.34	114.9	136.2	0.58	3.9	8.53
G-6	2.79	4.43	119.5	7.38	102.9	102.8	0.56	2.6	20.05
G-7	2.91	4.74	124.6	7.52	114.6	131.3	0.53	2.2	8.06
β-CD [h]	2.884	4.385	128.3	7.89	109.8	127.6	0.56	5.2	

[a] Hydrogen-bond distances between atoms O-2(n)···O-3($n-1$).
[b] Distances between the atoms O-4(n)···O-4($n-1$).
[c] Angle between the atoms O-4(n)···O-4($n+1$)···O-4($n+2$).
[d] Distance between the atoms O-4(n)···O-4($n+2$).
[e] Torsion angles according to IUPAC rules[10]: ϕ = O-5($n+1$)–C-1($n+1$)–O-4(n)–C-4(n) and ψ = C-1($n+1$)–O-4(n)–C-4(n)–C-3(n).
[f] Glucose puckering parameter according to Cremer and Pople.[12]
[g] Tilt angle, defined as the angle made by the O-4-plane and the plane through (C-1(n), C-4(n), O-4(n), and O-4($n+1$). A positive value indicates that the residue is rotated with its O(6) side towards the inside of the macrocycle.
[h] Average values taken from Ref. 2.

Table 3
Intra- and intermolecular contacts

Contacts	d (Å)	α (°)	Symmetry
β-CD···guest			
O-6(6)···O-7	3.23		
$O_{(host)}$···H-$C_{(guest)}$			
O-4(1)···C-1	3.85		
O-4(1)···H-1	3.16		
O-4(1)···H-1–C-1		133.1	
O-4(3)···C-4	3.62		
O-4(3)···H-4	3.14		
O-4(3)···H-4–C-4		114.2	
O-4(4)···C-5	4.01		
O-4(4)···H-5	3.10		
O-4(4)···H-5–C-5		166.9	
O-6(6)···C-6	3.65		
O-6(6)···H-6	3.16		
O-6(6)···H-6–C-6		134.6	
Water interactions			
W-1···O-6(6)	3.08		
W-1···$O\text{-}7_{(guest)}$	3.51		
W-1···W-5	2.73		
W-2···C-6(1)	3.27		
W-2···$C\text{-}1_{(guest)}$	3.82		
W-3···W-4	2.81		
W-3···O-6(2)	2.74		
W-3···O-5(3)	2.77		
W-4···O-5(3)	3.28		
W-4···O-6(3)	2.77		
W-5···O-6(1)	2.70		
W-5···$O\text{-}7_{(guest)}$	2.68		
$C–H_{(host)}$···$\pi_{(guest)}$			
C-5(2)···M-1	3.86		
C-5(2)···M-2	3.69		
C-6(2)···M-2	3.62		
C-3(3)···M-1	3.65		
C-5(3)···M-1	3.92		
C-5(6)···M-2	3.64		
M-1 = plane defined by C-1, C-2, C-3, C-4, C-9, and C-10			
M-2 = plane defined by C-5, C-6, C-7, C-8, C-9, and C-10			
Intermolecular H···O contacts			
$OH\text{-}2_{(guest)}$···$O\text{-}6(2)_{(host)}$	3.15		$-x-1,\ y-0.5,\ -z$
$OH\text{-}2_{(guest)}$···W-2	2.69		$x-1,\ y-0.5,\ -z$
$OH\text{-}2_{(guest)}$···$O\text{-}5(5)_{(host)}$	3.12		$x,\ y,\ z+1$
$OH\text{-}2_{(guest)}$···$O\text{-}6(5)_{(host)}$	2.80		$x,\ y,\ z+1$

The packing of the CD molecules within the crystal lattice is of the cage type as the cavity of each CD molecule is closed on both sides by adjacent CDs (Fig. 3). The CD molecules are arranged crosswise along *b* (in herringbone fashion), which is the most common packing for β-CD in the monoclinic space group $P2_1$.[5] Compared to similar studies on monoclinic crystals of inclusion complexes of β-CDs, the packing principle is similar, but the cell constants are different.

The severe elliptical distortion observed for β-CD in the complex with DHN contrasts the round form of β-CD found in other inclusion complexes with the naphthyl group (Fig. 2). The reason is that the naphthyl ring system in these structures is either unsubstituted or only partially inserted into the β-CD cavity so that steric strain does not occur at all or to a lesser extent. These complexes concern heptakis(2,6-di-*O*-methyl)-β-CD with 2-naphthoic acid[18] and (*S*)-naproxen[19] and the self-inclusion of 6-deoxy-6-*N*-(*N*′-5-dimethylamino-1-naphthalenesulfonyl)di-aminomethane-β-CD.[20]

4. Conclusions

In the inclusion complex with DHN, the β-CD macrocycle is elliptically distorted because two opposite glucose units (G-2 and G-6) incline with their C-6-side towards the cavity to allow for contacts with the guest molecule, in particular an O–H···O hydrogen bond and four C–H···O hydrogen bonds; they hold the guest in a well-defined position. The distortion of β-CD is reflected in unusual O-4(n)–O-4($n-1$) and O-4(n)···O-4($n+2$) distances and angles, and also affects the Cremer and Pople parameter of glucose G-2 which is probably associated with formation of three $C–H_{(host)}\cdots\pi$ interactions with G-2. The size of DHN is 'on the limit' for a guest molecule to fit in the β-CD cavity and provides a good example for the balance between insertion of a guest and deformation of β-CD, associated with intermolecular O–H···O, C–H···O and $C–H\cdots\pi_{guest}$ interactions.

5. Supplementary material

Complete crystallographic data (excluding structure factors) for the reported structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC no. 163106.

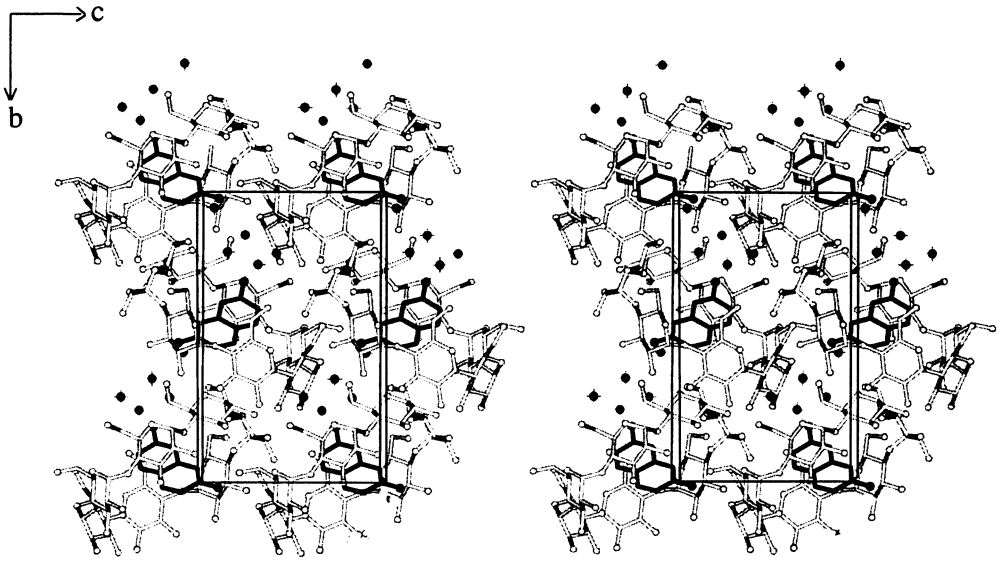

Fig. 3. Stereo view of the crystal packing of β-CD-DHN·4.6 H_2O viewed down the *a*-axis. The β-CD molecules are shown in gray and the DHN molecules in black. The oxygen atoms of the water molecules are indicated as black spheres. Drawn with INSIGHTII.[22]

Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: www.ccdc.cam.ac.uk).

Acknowledgements

These studies were supported by Deutsche Forschungsgemeinschaft Graduiertenkolleg 'Modellstudien an biologischen Makromolekülen' and by Fonds der Chemischen Industrie.

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