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Note

Crystal structure of a cyclomaltoheptaose–4-hydroxybiphenyl inclusion complex

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Abstract—The crystal structure of the inclusion complex of cyclomaltoheptaose (β-cyclodextrin) with 4-hydroxybiphenyl was determined by single-crystal X-ray diffraction at 150 K. The complex contains two cyclomaltoheptaose molecules, two 4-hydroxybiphenyl molecules, one ethanol molecule and fifteen water molecules in the asymmetric unit, and could be formulated as $[2(C_{42}H_{70}O_{35})\cdot 2(C_{12}H_{10}O)\cdot(C_2H_6O)\cdot 15(H_2O)]$. It crystallized in the triclinic space group $P1$ with unit cell constants $a = 15.257(3)$, $b = 15.564(3)$, $c = 15.592(2)$ Å, $\alpha = 104.485(15)°$, $\beta = 101.066(14)°$, $\gamma = 104.330(17)°$, $V = 3343.6(10)$ Å^3. In the crystal lattice, two β-cyclodextrins form a head-to-head dimer jointed through hydrogen bonds. Two 4-hydroxybiphenyls were included in the dimer cavity with their hydroxyl groups protruding from two primary hydroxyl sides of the cyclodextrin molecules. The guest 4-hydroxybiphenyl molecules linked into a chain via a combination of an O–H···O hydrogen bond and face-to-face π–π stacking of the phenyl rings. The crystal structure supports the calculation results indicating that the 2:2 inclusion complex formed by β-cyclodextrin and 4-hydroxybiphenyl is the energetically favored structure.

Keywords: β-Cyclodextrin; 4-Hydroxybiphenyl; Inclusion complex; X-ray crystal structure

Cyclomaltoheptaose (β-cyclodextrin, β-CD) is a macrocyclic oligosaccharide consisting of seven α-(1→4)-linked D-glucose units. It has a hydrophobic central cavity that preferentially contains hydrophobic guest molecules of suitable size and forms inclusion complexes.[1–4] Such beneficial properties of β-CD has made it among the most widely used host molecules of supramolecular chemistry, and it has been applied in many fields, including synthetic chemistry,[5,6] analytical chemistry,[7,8] foods,[9] and pharmaceuticals,[3,9] among others.

4-Hydroxybiphenyl has been shown to form inclusion complexes with α-CD, β-CD, and γ-CD.[10] The structural, spectroscopic, and photophysical properties of the inclusion complexes were studied theoretically and experimentally.[10] The induced circular dichroism spectra indicated that the 1:1 complex was dominant in the solution of 4-hydroxybiphenyl and β-CD. Nevertheless, computation using a dynamic Monte Carlo procedure showed that both 1:2 and 2:2 complexes were energetically favored. The detailed structure of the inclusion complex is not yet reported. As a part of our systematic investigation into the detailed host–guest interaction between β-CD and its included molecules using single-crystal X-ray diffraction,[11] we wish to report the crystal structure of β-CD complexed with 4-hydroxybiphenyl, which reveals that a 2:2 complex was formed together with one ethanol and fifteen water molecules.

The β-CD–4-hydroxybiphenyl complex, which crystallized as a head-to-head β-CD dimer (β-CD-A and β-CD-B, Fig. 1a), included two 4-hydroxybiphenyls, one ethanol and fifteen water molecules. Each glucose residue of the dimer adopts the usual $^4C_1$ chair conformation, and the overall β-CD molecule has an approximate 7-fold-axis of symmetry. The geometric parameters for the β-CD molecules are listed in Table 1. The O4*n* atoms are almost coplanar, with the largest displacement from the average plane observed for β-CD-A being

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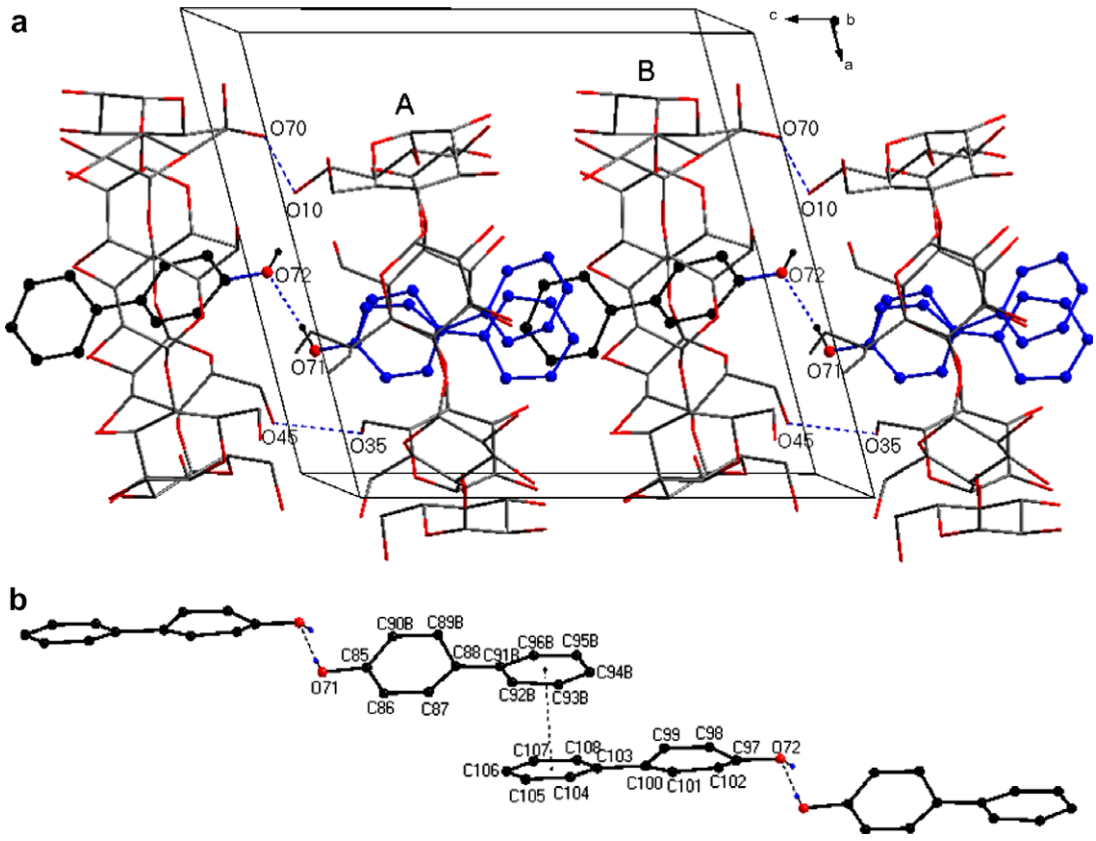

Figure 1. (a) The packing arrangement along the *c*-axis showing the channel formed by the β-CD molecules and the included guest molecules. The hydrogen bonds formed between the β-CD molecules, and between the guest molecules, are shown as dashed lines. (b) Hydrogen bonds and face-to-face π–π stacking interaction between the included guest 4-hydroxylbiphenyl molecules. Only one of the two sites of the disordered guest molecule is shown.

Table 1. Geometrical parameters for the β-CD molecule (distance in Å and angles in °)

		Residue						
		1	2	3	4	5	6	7
φ	A	127.1(1)	126.8(6)	133.2(0)	126.7(8)	124.6(6)	133.0(2)	128.2(0)
	B	126.7(9)	131.5(7)	128.8(9)	125.7(5)	129.5(3)	130.8(5)	126.3(4)
D	A	4.385(1)	4.342(1)	4.330(3)	4.530(0)	4.259(8)	4.438(8)	4.395(3)
	B	4.323(8)	4.394(6)	4.402(2)	4.430(7)	4.318(8)	4.450(5)	4.394(7)
Tilt angle	A	10.6	8.8	2.6	11.3	15.9	7.2	10.1
	B	7.8	10.3	10.3	6.4	3.5	7.1	11.1
d	A	0.0062	0.0768	−0.0722	−0.0171	0.0582	−0.0016	−0.0502
	B	−0.0892	0.0838	0.0228	−0.0641	−0.0185	0.0857	−0.0204
O3*n*–O2(*n*+1)	A	2.799(2)	2.799(0)	2.713(3)	2.944(8)	2.915(4)	2.774(9)	2.828(8)
	B	2.823(3)	2.733(7)	2.771(6)	2.791(1)	2.723(2)	2.790(4)	2.806(1)
Torsion angle	A	−63.4	60.7	−63.5	−70.2, 51.9	−56.8	−63.0	−70.4
	B	−65.9	−66.1	−57.0	−56.9	−65.5	−59.7	68.7

φ = angle between atoms O4(*n*−1)–O4*n*–O4(*n*+1).
D = distance between atoms O4(*n*−1)···O4*n*.
Tilt angle is the angles between the O4 plane and the planes defined by O4(*n*−1), C1*n*, C4*n*, and O4*n*.
d = deviation of O4*n* atom from the least-squares optimum plane formed by the seven O4*n* atoms.
Torsion angle: O5*n*–C5*n*–C6*n*–O6*n*.

the O11 and O16 atoms (0.0768 Å and −0.0722 Å, respectively), and for β-CD-B being the O66 and O41 atoms (0.0857 Å and −0.0892 Å, respectively). The O4*n*···O4(*n*+1) distances vary between 4.259(8) and 4.530(0) Å. The distances from the center of seven O4 atoms to each individual O4 atom are in the range of 4.852(1)–5.217(0) Å for β-CD-A and in the range of 4.898(2)–5.171(6) Å for β-CD-B. The O4(*n*−1)···O4*n*···O4(*n*+1) angles, varying from 124.6(6)° to 133.0(2)° for β-CD-A and 125.7(5)° to 131.5(7)° for β-CD-B, are

within 4.45° from the regular heptagon of 128.57°. The annular shape of β-CD is stabilized by interglucose O2(n+1)–H···O3n hydrogen bonds with O···O distances 2.713(3)–2.944(8) Å for β-CD-A, 2.723(2)–2.823(3) Å for β-CD-B. Overall, the geometrical parameters indicate that upon complex formation, the guest molecule has slightly distorted the macrocyclic conformation of the β-CD. The orientation of the C6n–O6n bond is generally described by the torsion angles of O5n–C5n–C6n–O6n. For β-CD-A, five of the seven primary hydroxyl groups exhibit the (−)-*gauche* orientation pointing outwards from the β-CD cavity, as shown by the torsion angle of O5n–C5n–C6n–O6n in the range of −56.8° to −70.4°. One of them (O10–H) has a (+)-*gauche* orientation pointing inwards, as indicated by the corresponding torsion angles of 60.7°. The last one is disordered at two sites, among which one points outwards from the β-CD cavity, and the other one points inwards with the occupation of 0.686 (O20A) and 0.314 (O20B), respectively. For β-CD-B, six primary hydroxyl groups point away from the β-CD cavity, and one (O70–H) points inwards. The two (+)-*gauche* hydroxyl groups form a hydrogen bond O10–H···O70 that contributes to the interlinkage between adjacent dimers (Fig. 1a, Table 2).

The included 4-hydroxylbiphenyl molecules display twisted conformations favorable for forming the π–π stacking and hydrogen-bonding interactions, as shown in Figure 1b, which is different from that observed in the native crystal structure in which the 4-hydroxybiphenyl molecules were essentially coplanar.[12] Similar observation was made in the β-CD inclusion complexes formed with *p*-amino-*p*′-nitrobiphenyl[13] and biphenyl,[14] which were essentially planar in the native solid state, but adopted a twisted conformation in both the gas phase and their crystalline β-CD inclusion complexes. The two guest molecules reside within the dimer cavity in similar manner with their hydroxyl groups protruding from the primary ends of β-CDs. Their axes are inclined about 24° with respect to the normal of the O-4 plane. The *para*-carbon atoms (C88 and C100) of the hydroxyl groups are approximately in the O-4 plane with a deviation of less than 0.53 Å, and are 0.5–0.8 Å away from the O4-plane center. In the β-CD dimer, two 4-hydroxylbiphenyl molecules also form a dimer by face-to-face π–π stacking with about 0.37 Å of centroids (Fig. 1b). Furthermore, the dimers of the guest molecules are linked to generate a chain via a O71–H71A···O72 hydrogen bond with the O···O distance of 2.80 Å. One of the guest molecules in the dimer is disordered at two sites (blue ball-and-stick plot in Fig. 1a).

Two β-CDs form a head-to-head dimer in which the two O-4 planes are almost parallel with an angle of 1.2°. The dimers are stacked in a channel mode, along the *c*-axis, as frequently observed in the β-CD complexes. The axes of the two adjacent dimers running parallel to each other have a lateral translation of 3.0 Å and an incline of 11.1° with respect to the crystallographic *c*-axis. Two β-CD monomers assemble through O3–H···O3 intermolecular hydrogen bonds to form the β-CD dimer.[15] The dimers are held together by hydrogen bonds between the primary hydroxy groups of adjacent dimers and between the guest molecules (Fig. 1a). One water molecule was observed as a hydrogen-bond bridge contributing to the interlinkage between channels. A summary of intermolecular hydrogen bonds that are crucial for packing is given in Table 2, excluding the hydrogen bonds in which water molecules are donors.

The crystal structure data of some inclusion complexes with similar guest molecules are summarized in Table 3. They all form head-to-head β-CD dimers. Among them, inclusion complexes formed by *p*-amino-*p*′-nitrobipheny1[13] and benzidine,[16] which are 4,4′-disubstituted derivatives of biphenyl, crystallized and

Table 2. Intermolecular hydrogen bonds (distance in Å and angles in °)

D–H	*d*(H···A)	∠DHA	*d*(D···A)	A
Between dimers				
O10–H10C	2.011	150.33	2.753	O70 [x, y, $z+1$]
O45–H45A	2.009	158.68	2.789	O35 [x, y, $z-1$]
Between channels				
O20A–H20A_a	2.434	145.56	3.145	O40 [x, $y+1$, $z+1$]
O30–H30	2.136	154.44	2.898	O65 [$x+1$, y, $z+1$]
O30–H30	2.608	134.40	3.235	O64 [$x+1$, y, $z+1$]
O40–H40A	2.026	147.78	2.755	O20B_b [x, $y-1$, $z-1$]
O40–H40A	2.366	112.18	2.781	O19 [x, $y-1$, $z-1$]
O40–H40A	2.417	148.29	3.145	O20A_a [x, $y-1$, $z-1$]
O65–H65A	2.413	142.17	3.102	O50 [$x-1$, y, z]
A water molecule as hydrogen bond bridge				
O35–H35A	1.893	169.28	2.703	O78_b [$x+1$, y, z]
O65–H65A	2.294	137.76	2.953	O78_b [x, y, $z-1$]
Between guest molecules				
O71–H71A	1.958	170.83	2.771	O72_a [x, y, $z+1$]

Table 3. Crystal data for β-CD inclusion complexes with substituted biphenyls

Guest molecule	Substituent mode	Space group	*a* (Å) α (°)	*b* (Å) β (°)	*c* (Å) γ (°)	*Z*	Type of packing[21]	Ref.
Benzidine	4,4′-Two groups	$P2_1$	15.394(7)	31.995(12) 103.74(1)	15.621(7)	2	Screw channel	16
p-Amino-*p*′-nitrobiphenyl	4,4′-Two groups	$P2_1$	15.454	31.693 102.92	15.255	2	Screw channel	13
S-Flurbiprofen	4,2-Two groups	*P*1	15.446(2) 113.52(1)	15.513(2) 99.32(1)	18.107(2) 102.39(1)	1	Intermediate	17
rac-Flurbiprofen	4,2-Two groups	*P*1	15.420(2) 113.63(1)	15.490(2) 99.36(1)	18.033(2) 103.05(1)	1	Intermediate	18
4-Hydroxybiphenyl	4-One group	*P*1	15.2570 104.4848	15.5636 101.0658	15.5921 104.3298	1	Channel	
Biphenyl	None	*C*2	19.34	24.49 109.8	15.8	2	Channel	14
2,2-Dipyridine		*C*2	19.427(6)	24.100(8) 103.783	33.457(11)	4		19
4,4-Dipyridine		*P*1	15.364(3) 99.463(4)	15.497(3) 113.195(3)	18.115(3) 103.022(3)	1	Intermediate	19
Tolidine	3,4,3′,4′-Four groups	$C222_1$	19.347(5)	24.266(6)	32.806(6)	8	Chessboard	20

packed in the same mode. Both the flurbiprofen[17,18] and the 4-hydroxybiphenyl inclusion complexes crystallize in *P*1, but show different unit cells and stacking modes owing to flurbiprofen having an F atom at the 2-site of the biphenyl in addition to a 4-substituent group. Although biphenyl,[14] 2,2′-dipyridine,[19] and 4,4′-dipyridine[19] have very similar frameworks, as they crystallize in different modes that are ascribed to the substitutional nitrogen atoms and their different positions. So far, only one derivative of biphenyl with four substituent groups has been reported.[20]

In summary, the crystal structure reported herein reveals that β-CD and 4-hydroxylbiphenyl form a 2:2 complex, indicating that the 2:2 complex is the energetically favored structure in the solid state, which supports the computational result reported previously.[10]

1. Experimental

1.1. Preparation and crystallization of the inclusion compound

β-CD·12H_2O was recrystallized prior to use. 4-Hydroxylbiphenyl was purchased from E. Merck and used as received. 4-Hydroxylbiphenyl (0.2 mmol) was suspended in 8 mL of an aq solution of β-CD (0.2 mmol) and heated until the solid dissolved. Cooling of the solution produced a saturated aqueous solution of the title inclusion complex. Slow evaporation of the filtered solution at room temperature afforded colorless block-like crystals in one week.

1.2. X-ray crystallography

The crystallographic data are summarized in Table 4. X-ray diffraction data were collected on an Oxford Diffraction Xcalibur Nova with Cu Kα radiation ($\lambda = 1.54178$ Å) at 150 K. The data were processed using CRYSALIS.[22] The structure was solved by isostructural replacement of the β-CD coordinations from an isomorphous structure, the β-CD-(*Z*)-tetradec-7-en-1-al complex.[23] Waters of hydration, as well as the guest and ethanol sites, were located from the difference Fourier

Table 4. Crystallographic data

Chemical formula	2($C_{42}H_{70}O_{35}$)·2($C_{12}H_{10}O$)·(C_2H_6O)·15(H_2O)
Formula weight	2926.67
Temperature (K)	150
Wavelength (Å)	1.54178
Crystal system	Triclinic
Space group	*P*1
a (Å)	15.257(3)
b (Å)	15.564(3)
c (Å)	15.592(2)
α (°)	104.485(15)
β (°)	101.066(14)
γ (°)	104.330(17)
V (Å^3)	3343.6(10)
Z	1
D_{calcd} (Mg/m^3)	1.453
F(000)	1560
Crystal size (mm)	0.43 × 0.35 × 0.28
θ Range (°)	3.04–72.41
Index ranges	$-18 \leqslant h \leqslant 18$; $-18 \leqslant k \leqslant 18$; $-18 \leqslant l \leqslant 19$
Reflections collected	43,414
Independent reflections	20,141 [$R_{int} = 0.0168$]
Reflections observed (>2σ)	18,631
Data completeness	0.986
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	20,141/3/1889
Goodness-of-fit on F^2	1.042
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0662$, $wR_2 = 0.1828$
R indices (all data)	$R_1 = 0.0712$, $wR_2 = 0.1985$
Largest difference in peak and hole (e/Å^3)	1.214 and −0.583

maps. One 4-hydroxylbiphenyl molecule and one of the O-6 atoms of β-CD (O-20) were disordered over two positions. Except for those hydrogen atoms attached to the water molecules, all the other hydrogen atoms were added in ideal positions and refined as riding models. The structure was refined using Full-matrix least-squares based on F^2 with the program SHELXL.[24]

2. Supplementary data

Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 640947. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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