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Crystal structure of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin dihydrate: a water molecule in an apolar cavity[☆],[☆☆]

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Abstract

Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin crystallized from water at 18 °C as dihydrate (DIMEB·2 H_2O) in the monoclinic space group $P2_1$ with unit cell dimensions $a = 15.2415(5)$, $b = 10.6391(4)$, $c = 23.3239$ (8) Å, $\beta = 101.798(1)°$. X-ray analysis reveals a torus-like macrocycle stabilized by systematic hydrogen bonds O-3–H··O-2′ and C-6–H··O-5′ between adjacent glucose residues. The O-6–CH_3 methoxy groups of three glucose units are directed toward but do not close the cavity. Both ends of the cavity are closed by adjacent molecules which are related by the characteristics of 'cage type' crystal packing. One water molecule is included in the apolar cavity of the torus and has very high anisotropic thermal displacement factor due to lack of hydrogen bonding interactions to DIMEB, while the other one is located in an intermolecular void and forms hydrogen bonds to O-3 and O-6 oxygen atoms. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: β-Cyclodextrin; Dimethylated β-cyclodextrin; Inclusion complexes; Hydrogen bonding

1. Introduction

β-Cyclodextrin (β-CD) is a cyclic molecule consisting of seven D-(+)-glucopyranose units linked by α-(1→4) glycosidic bonds. It forms a torus-like macrocycle with the primary O-6–H hydroxy groups at the narrow side and the secondary O-2–H and O-3–H hydroxy groups at the wide side. Upon methylation of the 2 and 6 or 2, 3, and 6 hydroxyl groups, β-CD exhibits a negative solubility coefficient, i.e., dimethylated β-CD is more soluble in cold water (> 60 g/100 mL at 20 °C) than in hot water (< 5 g/100 mL at 60 °C) [1].

Since cyclodextrins as well as their methylated derivatives form inclusion complexes, they play an important role as pharmaceutical carrier molecules for drugs which are unstable at ambient conditions or poorly water-soluble [2,3]. So far, only few structures of methylated cyclodextrins crystallized from pure water without addition of guest molecules have been elucidated: anhydrous hexakis(2,6-di-*O*-me-

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[☆] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center and may be obtained, on request, from the director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2, IEZ, UK, quoting CCDC 116999.

[☆☆] Topography of cyclodextrin inclusion complexes, part 44. For part 43, see T. Steiner, W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 37 (1998) 3404–3407.

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thyl)-α-cyclodextrin (DIMEA) [4,5], DIMEA monohydrate [4], anhydrous hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TRIMEA) [6], anhydrous heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) [7], and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) monohydrate [8]. In addition, preliminary X-ray studies of different hydrates of DIMEB have been reported [9].

In crystals of TRIMEB monohydrate grown at 50 °C, the water molecule is located outside the cavity and the macrocycle shows a harshly deformed geometry as one of the permethylated glucose residues adopts the unusual $^1C_4$ conformation. This contrasts with anhydrous DIMEA, DIMEB, and DIMEA monohydrate crystals grown at 60 or 90 °C and room temperature, respectively, in which the molecules maintain the commonly observed 'round' shape with all glucoses in the preferred $^4C_1$ form; and in DIMEA monohydrate, the water is included inside the cavity. A characteristic structural feature of all methylated cyclodextrins crystallized thus far from aqueous solution is the rotation of two or three of the O-6–CH_3 groups toward the cavity to close it on one side. Thus, the overall appearance of these molecules resembles rather a bowl than an open torus. Here we report the crystal structure of DIMEB dihydrate crystallized at 18 °C, which is the first methylated CD observed in the form of an open torus with one water molecule included.

Table 1
Summary of crystallographic data for DIMEB·2 H_2O

Chemical formula	$C_{56}H_{98}O_{35}\cdot 2\ H_2O$
Formula weight	1363.36
Crystal habit, color	Rod, colorless
Crystal size (mm^3)	$0.2\times 0.5\times 1.5$
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	15.2415(5)
b (Å)	10.6391(4)
c (Å)	23.3239(8)
β (°)	101.798(1)
Volume (Å^3)	3702.2(2)
Z	2
D_x (g cm^{-3})	1.22
μ (mm^{-1})	0.10
F(000)	1460
Diffractometer	Siemens, CCD
Wavelength (Å)	MoKα; 0.71073
Temperature (°C)	Room temperature
θ range for data collection (°)	0.89 to 23.31
Resolution (Å)	0.9
Index ranges	$-15<h<16$, $-11<k<11$, $-25<l<23$
Measured reflections	16750
Unique reflections	5606
Structure solution	direct methods (SIR92)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5606/5/944
R (F^2)	$R=0.078$
Goodness of fit	1.121
Highest peak and deepest hole (e Å^{-3})	0.64 and −0.42

2. Experimental

Crystallization.—Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) purchased from Aldrich (Steinheim, Germany) was used without further purification. A saturated aqueous solution of DIMEB was prepared at −5 °C and transferred to 18 °C. After 2 months, rod-shaped colorless crystals, up to 1.5 mm in length, had grown by slow solvent evaporation.

X-ray diffraction experiments.—A crystal, $0.2\times 0.5\times 1.5$ mm^3 in dimensions, was mounted in a quartz capillary. Graphite-monochromatized MoKα radiation ($\lambda=0.71073$ Å) was produced by a Siemens generator operating at 50 kV and 30 mA. A total of 16,750 X-ray diffraction data were collected at room temperature with a Siemens CCD camera; the swing angle Θ was 23.3° and step size $\omega=0.2°$. Data reduction was carried out with the program SAINT (Siemens software), including semiempirical absorption correction ($\mu=0.1$ mm^{-1}) with SADABS (Siemens software); symmetry-equivalent reflections were merged to yield 5606 unique data.

The crystal belongs to the monoclinic space group $P2_1$ with unit cell dimensions $a=15.2415(5)$, $b=10.6391(4)$, $c=23.3239$ (8) Å, $\beta=101.798(1)°$. The formula per asymmetric unit is $C_{56}H_{98}O_{35}\cdot 2\ H_2O$, $V=3702.2(2)$ Å^3, $Z=2$, MW = 1363.36, $D_x=1.22$ g cm^{-3} and $F(000)=1460$.

Table 2
Fractional atomic coordinates and equivalent isotropic thermal displacement factors of DIMEB·2 H_2O

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
O-1W-1	−0.0080(9)	−0.4777(17)	0.65121(16)	0.0543(11)
C-11	0.6833(3)	0.0128(6)	0.6308(2)	0.0572(12)
C-21	0.6449(4)	0.1439(6)	0.6199(2)	0.0628(13)
C-31	0.5458(3)	0.1429(5)	0.6213(2)	0.0559(12)
C-41	0.4978(3)	0.0442(5)	0.5799(2)	0.0512(11)
C-51	0.5425(3)	−0.0825(5)	0.5911(2)	0.0543(11)
C-61	0.5049(4)	−0.1789(6)	0.5448(2)	0.0722(15)
C-71	0.7151(7)	0.3424(9)	0.6429(5)	0.145(4)
C-81	0.4982(7)	−0.3695(9)	0.5947(5)	0.127(3)
O-21	0.6944(3)	0.2254(4)	0.66238(18)	0.0805(12)
O-31	0.5104(3)	0.2651(4)	0.60697(19)	0.0774(11)
O-41	0.4077(2)	0.0394(4)	0.58835(12)	0.0537(8)
O-51	0.6360(2)	−0.0718(4)	0.58938(13)	0.0606(9)
O-61	0.5407(3)	−0.3013(5)	0.5581(2)	0.0844(12)
C-12	0.3364(3)	0.0581(6)	0.5398(2)	0.0582(13)
C-22	0.2733(3)	0.1553(6)	0.5561(2)	0.0610(13)
C-32	0.2254(3)	0.1064(6)	0.6021(2)	0.0614(13)
C-42	0.1851(3)	−0.0199(6)	0.5858(2)	0.0567(12)
C-52	0.2516(3)	−0.1129(6)	0.5680(2)	0.0583(12)
C-62	0.2117(4)	−0.2358(7)	0.5454(3)	0.0776(16)
C-72	0.2819(7)	0.3826(8)	0.5587(5)	0.124(3)
C-82	0.0988(10)	−0.3330(10)	0.4767(6)	0.181(6)
O-22	0.3238(3)	0.2653(4)	0.5747(2)	0.0828(12)
O-32	0.1596(3)	0.1949(5)	0.6094(2)	0.0839(12)
O-42	0.1558(2)	−0.0662(4)	0.63646(13)	0.0596(9)
O-52	0.2900(2)	−0.0563(4)	0.52282(14)	0.0642(9)
O-62	0.1405(3)	−0.2189(5)	0.4983(2)	0.1005(15)
C-13	0.0635(3)	−0.0939(8)	0.6325(3)	0.0779(18)
C-23	0.0345(4)	−0.0320(7)	0.6847(3)	0.0758(17)
C-33	0.0818(3)	−0.0930(6)	0.7407(2)	0.0612(13)
C-43	0.0693(3)	−0.2331(6)	0.7379(2)	0.0626(13)
C-53	0.0949(5)	−0.2872(6)	0.6827(2)	0.0699(14)
C-63	0.0751(8)	−0.4211(9)	0.6750(3)	0.142(4)
C-73	−0.0029(7)	0.1797(9)	0.7106(5)	0.136(4)
C-83A[a]	0.0232(12)	−0.5571(11)	0.5971(8)	0.158(7)
C-83B[a]	−0.051(3)	−0.515(5)	0.6089(12)	0.29(4)
O-23	0.0505(3)	0.0991(5)	0.6826(2)	0.0951(15)
O-33	0.0498(3)	−0.0438(5)	0.78967(17)	0.0766(10)
O-43	0.1255(2)	−0.2811(4)	0.79001(14)	0.0572(8)
O-53	0.0488(3)	−0.2223(5)	0.63249(16)	0.0834(13)
O-63A[a]	0.0834(7)	−0.4603(8)	0.6200(3)	0.137(3)
O-63B[a]	−0.0080(9)	−0.4777(17)	0.6657(7)	0.111(6)
C-14	0.0890(3)	−0.3691(6)	0.8241(2)	0.0609(13)
C-24	0.1136(4)	−0.3301(6)	0.8880(2)	0.0599(12)
C-34	0.2128(4)	−0.3429(5)	0.9125(2)	0.0567(11)
C-44	0.2418(3)	−0.4745(6)	0.9003(2)	0.0610(12)
C-54	0.2161(4)	−0.5034(6)	0.8359(3)	0.0711(14)
C-64	0.2389(7)	−0.6339(8)	0.8201(4)	0.112(3)
C-74	0.0569(4)	−0.1746(7)	0.9458(2)	0.0733(15)
C-84	0.2752(13)	−0.748(3)	0.7451(9)	0.289(14)
O-24	0.0810(2)	−0.2055(4)	0.89174(15)	0.0659(9)
O-34	0.2315(3)	−0.3152(5)	0.97308(17)	0.0790(12)
O-44	0.3374(2)	−0.4783(4)	0.92111(16)	0.0626(9)
O-54	0.1206(3)	−0.4903(4)	0.81736(17)	0.0720(10)
O-64	0.2352(7)	−0.6419(8)	0.7605(3)	0.168(3)
C-15	0.3740(4)	−0.5829(6)	0.9545(3)	0.0676(14)
C-25	0.4278(4)	−0.5385(7)	1.0124(3)	0.0709(14)
C-35	0.5141(4)	−0.4721(6)	1.0046(2)	0.0656(13)
C-45	0.5635(3)	−0.5477(5)	0.9666(2)	0.0644(13)
C-55	0.5005(4)	−0.5867(6)	0.9095(3)	0.0687(14)
C-65	0.5420(5)	−0.6722(8)	0.8717(4)	0.093(2)
C-75	0.3682(6)	−0.4880(8)	1.0964(3)	0.103(2)
C-85	0.5306(10)	−0.727(2)	0.7736(6)	0.210(8)
O-25	0.3754(3)	−0.4563(6)	1.03941(18)	0.0940(14)
O-35	0.5681(3)	−0.4504(5)	1.05989(17)	0.0840(12)
O-45	0.6333(2)	−0.4675(4)	0.95395(16)	0.0612(8)
O-55	0.4262(3)	−0.6545(4)	0.9240(2)	0.0781(11)
O-65	0.4985(6)	−0.6555(10)	0.8128(3)	0.173(4)
C-16	0.7232(3)	−0.5080(6)	0.9689(2)	0.0614(13)
C-26	0.7784(4)	−0.3973(6)	0.9973(2)	0.0631(13)
C-36	0.7724(4)	−0.2903(5)	0.9537(2)	0.0550(11)
C-46	0.7986(3)	−0.3368(5)	0.8980(2)	0.0507(11)
C-56	0.7480(3)	−0.4562(5)	0.8740(2)	0.0537(11)
C-66	0.7816(3)	−0.5157(6)	0.8244(2)	0.0626(12)
C-76	0.7903(6)	−0.4260(8)	1.1003(3)	0.099(2)
C-86	0.9071(5)	−0.5959(7)	0.7943(3)	0.090(2)
O-26	0.7507(3)	−0.3573(4)	1.04852(16)	0.0765(11)
O-36	0.8276(3)	−0.1897(4)	0.97885(16)	0.0712(10)
O-46	0.77881(18)	−0.2370(4)	0.85614(13)	0.0494(7)
O-56	0.7548(2)	−0.5489(4)	0.91920(15)	0.0586(8)
O-66	0.8745(2)	−0.5368(4)	0.83951(17)	0.0722(10)
C-17	0.8486(3)	−0.1914(5)	0.83089(19)	0.0496(10)
C-27	0.8444(3)	−0.0487(5)	0.82940(19)	0.0515(11)
C-37	0.7625(3)	−0.0017(5)	0.78521(19)	0.0472(10)
C-47	0.7601(3)	−0.0650(5)	0.72705(18)	0.0472(10)
C-57	0.7622(3)	−0.2071(5)	0.7336(2)	0.0524(11)
C-67	0.7615(4)	−0.2762(6)	0.6772(2)	0.0685(14)
C-77	0.8840(5)	0.1120(7)	0.9040(3)	0.0847(18)
C-87	0.8240(6)	−0.2799(13)	0.5945(3)	0.137(4)
O-27	0.8452(2)	−0.0087(4)	0.88758(14)	0.0617(9)
O-37	0.7675(3)	0.1308(4)	0.78111(16)	0.0686(9)
O-47	0.67918(18)	−0.0235(4)	0.68846(12)	0.0508(7)
O-57	0.8428(2)	−0.2404(4)	0.77409(13)	0.0549(8)
O-67	0.8294(3)	−0.2308(6)	0.65121(16)	0.0905(14)
O-1W-1	0.406(2)	−0.222(5)	0.767(3)	0.72(5)
O-1W-2	1.0010(6)	−0.5535(11)	0.9500(4)	0.179(3)

[a] Occupancy factors of disordered O-63–C-83 are 0.7 and 0.3 for sites A and B, respectively.

Structure solution and refinement.—The crystal structure was solved by direct methods [10], developed by Fourier synthesis [11] and refined by full-matrix least-squares techniques [11]. All non-hydrogen atoms were refined anisotropically. For crystal structures as complex as the present one, location of hydrogen atoms by room temperature X-ray data is usually not possible. In fact, difference Fourier maps of DIMEB·2 H_2O did not permit the positions of the hydrogen atoms of the methyl and hydroxyl groups and of the water molecules to be determined, but it was possible to verify the positions of some O-3–H and C–H hydrogen atoms of the β-CD skeleton. Since all hydrogen atoms of hydroxyl and methyl groups could not be located, they were not considered in the refinement, but all C–H hydrogen atoms of the glucoses were calculated into idealized positions and, during refinement, restrained according to the 'riding model' [11]. The high thermal displacement factors of the methoxy groups made refinement difficult. Two-fold disorder was observed for O-6–C-8 of glucose residue 3. Water W-1 is included in the cavity and has a very high thermal displacement factor ($U_{eq} = 0.72(5)$ Å^2) due to lack of interactions with DIMEB, while W-2 is located in interstices between DIMEB molecules and hydrogen-bonded to O-3 and O-6 atoms ($U_{eq} = 0.176(3)$ Å^2). The refinement of 944 parameters (C–O bond distances in the disordered methoxy group C-63–O-63A–C-83A and C-63–O-63B–C-83B restrained to the normal range, 1.35–1.42 Å) converged at a final $R(F^2) = 0.0780$ for all 5606 data.

Details of the crystallographic data are given in Table 1; fractional atomic coordinates and thermal displacement factors are listed in Table 2. Geometrical parameters were analyzed by PARST96 [12], and the thermal ellipsoid plot was drawn by ORTEPIII [13].

3. Results and discussion

General.—The atomic labeling is as in the former work [14], e.g., C-21 denotes carbon atom 2 (C-2) of glucose residue 1, and the methoxy C atoms bonded to O-2 and O-6 of each glucose are assigned C-7 and C-8, respectively; disordered atoms are named A and B. Atoms belonging to an adjacent glucose are primed (′).

Structure of DIMEB·2 H_2O.—The 7 glucose residues in DIMEB adopt the $^4C_1$ conformation with slight deviations from the theoretical chair form (see ring puckering parameters Q and θ [15] in Table 3). The orientations of glucoses which are described by torsion angles ϕ and ψ [16] are in the normal range 101–113° and 120–136°, respectively, because hydrogen bonds O-3–H··O-2′ between neighboring glucose residues (2.79–3.02 Å; Table 3) stabilize and maintain the 'round' geometry of DIMEB as observed in the parent β-cyclodextrin. The regular structure of the DIMEB macrocycle is indicated by the small variance in O-4··O-4′ distances (4.27–4.51 Å) and the very small deviation (< 0.24 Å) of O-4 atoms from the common least-squares plane.

Other interglucose interactions which contribute to the stabilization of the macrocyclic geometry are the weak intramolecular, interglucose hydrogen bonds C-6–H-6··O-5′. The contact distances H-6··O-5′ and the angles at H-6 atoms are in the range 2.44–2.82 Å and 128–157°, respectively (Table 3). These data are in good agreement with those observed in unsubstituted cyclodextrins [17].

All O-2–C-7 methoxy groups point 'away' from the cavity with torsion angles C-1–C-2–O-2–C-7 at + gauche to trans (in range 85–155°). Three O-5–C-5–C-6–O-6 torsion angles belonging to glucose residues 1, 4 and 5 are in the + gauche range (66, 76 and 88°, respectively) and direct the O-6–C-8 groups toward the cavity, while the others are − gauche. O-63–C-83 is two-fold disordered (O-63A, C-83A at 70% and O-63B, C-83B at 30%) giving rise to + gauche and − gauche conformations (see Fig. 1). A similar disorder was also observed in anhydrous DIMEB [7]. The cavity of DIMEB is not closed by 'inward' rotation of three O-6–C-8 groups as observed in anhydrous DIMEB [7].

While W-1 is located within the macrocyclic cavity, W-2 is found in a void between DIMEB molecules. The nearest interatomic distances between W-1 and C-5–H atoms of glucoses 2, 3, 4 and C-8–H of glucose 1 of the enclosing DIMEB are > 3.7 Å (Fig. 2), too long to be of van der Waals or hydrogen bond type. The location of this polar water molecule in an apolar cavity is associated with a very high thermal motion. W-2 can form hydrogen bonds to O-66 and O-36, and reveals close contacts to endocyclic O-5 oxygen atoms (O-56, O-54) of two adjacent DIMEB molecules, as well as weak interactions to C-2–H and C-7–H of glucose residue 4 (Fig. 2).

Table 3
Geometrical parameters of the DIMEB·2 H_2O macrocycle (distances in Å and angles in °)

Residue	1	2	3	4	5	6	7
Q[a]	0.56	0.54	0.55	0.57	0.55	0.56	0.57
θ[b]	2	5	2	3	6	5	4
ϕ[c]	112.5(4)	108.2(5)	107.2(5)	105.6(5)	112.9(5)	103.9(5)	101.4(4)
ψ[c]	135.5(4)	123.8(5)	119.7(5)	132.0(4)	134.7(5)	123.1(5)	123.5(4)
Tilt angle[d]	19.5(3)	16.6(3)	6.9(2)	10.3(3)	24.3(3)	16.4(2)	3.6(2)
O-4 deviation[e]	−0.21	0.00	0.24	−0.14	−0.18	0.24	0.05
Distances							
O-4··O-4′[f]	4.37	4.36	4.35	4.49	4.42	4.27	4.51
O-3··O-2′	2.79(1)	2.81(1)	2.90(1)	2.84(1)	3.02(1)	2.92(1)	2.94(1)
C-6··O-5′	3.46(1)	3.52(1)	3.33(1)	3.35(1)	3.46(1)	3.36(1)	3.31(1)
H-6··O-5′	2.61(1)	2.82(1)	2.51(1)	2.44(1)	2.55(1)	2.67(1)	2.59(1)
C-6–H-6··O-5′ angle	146.7(4)	129.9(4)	142.8(4)	155.9(6)	157.4(5)	128.1(4)	131.0(4)
O-3··O-4[g]				2.77–2.85			
C-6··O-4[g]				3.00–3.06			
C-7··O-3[g,h]				3.01–3.35			

[a] Puckering amplitude [15].

[b] Indicates the deviation from theoretical chair conformation (ideal value: $\theta = 0$; [15]).

[c] Torsion angles ϕ and ψ at glycosidic O-4, defined as O-5–C-1–O-4′–C-4′ and C-1–O-4′–C-4′–C-3′, respectively [16].

[d] Tilt angles, defined as the angles between the O-4 plane and the planes through C-1, C-4, O-4 and O-4′.

[e] Deviation of O-4 atoms from the least-squares plane through the seven O-4 atoms.

[f] Primed atoms (′) belong to the following glucose residue.

[g] Systematic O-3–H··O-4, C-6–H··O-4, and C-7–H··O-3 interactions, given values are in range of O··O and C··O distances, respectively.

[h] Except for the glucose residue 6 because the C··O distance is too long (3.91 Å).

Crystal packing.—Fig. 3 shows that DIMEB dihydrate packs in ‘herring bone’ fashion with molecules arranged along the 2_1 screw-axis parallel to the *b*-axis and slanted about 40° against the *a*–*c* plane. Both sides of each macrocycle cavity are blocked by glucose residues of neighboring molecules leading to a typical cage structure. No self-inclusion occurs in contrast to anhydrous DIMEB [7] or other complexes of DIMEB crystals [18–22]. This may be due to differences in space groups which are orthorhombic ($P2_12_12_1$) for anhydrous DIMEB [7] but monoclinic ($P2_1$) for DIMEB dihydrate; the latter displays the characteristic packing motif as in β-cyclodextrin dodecahydrate [23], DIMEA monohydrate [4,5], and the complex between DIMEA and 1-propanol [24,25].

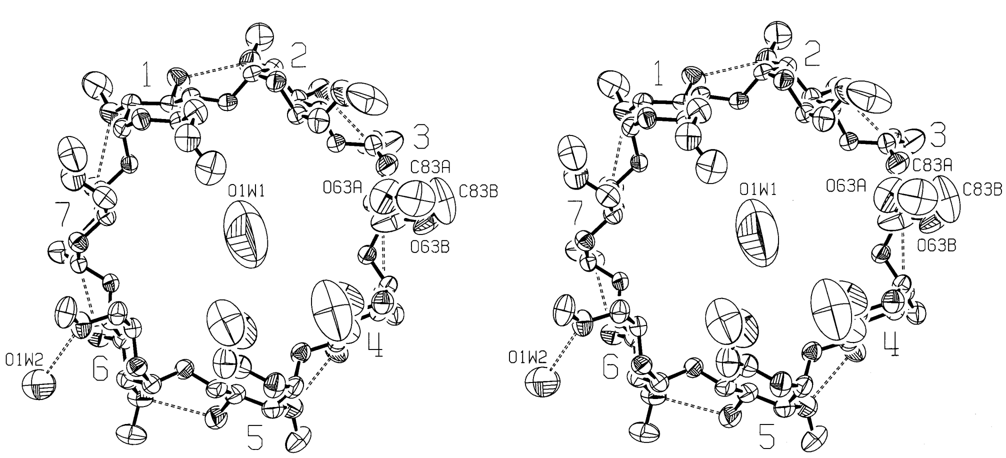

Fig. 1. Stereo plot of DIMEB·$2H_2O$ drawn with thermal ellipsoid (50%) representation.

Importance of C–H··O interactions.—As shown in Table 3, a number of systematic O–H··O and C–H··O interactions stabilize the ‘round’ shape of the DIMEB macrocycle. Three-center hydrogen bonds are donated by O-3–H with major O-3–H··O-2′ and minor O-3–H··O-4 components determining the macrocyclic geometry of DIMEB. The intramolecular weak interactions of C-7–H··O-3′, C-6–H··O-4, and C-6–H··O-5′ contribute to the stabilization of the orientation of the O-2–C-7 methoxyls and of the C-6–O-6–C-8 groups.

DIMEB·2 H_2O is the first crystal structure of a water inclusion complex of the methylated β-CD.—Except for DIMEB·2 H_2O and DIMEA·H_2O [4], all other 2,6 or 2,3,6 methylated CDs were crystallized from hot water > 50 °C. They do not occur in the common doughnut shape with both sides of the cavity open but rather adopt a bowl shape [4–8] with the primary O-6-sides closed by ‘inside’ rotation of two or three O-6–CH_3 groups which touch each other in van der Waals contacts. This largely reduces the volume of the cavity, which is partially occupied by an O–CH_3 group of an adjacent molecule. In contrast, DIMEB·2 H_2O crystallizes from cold water (18 °C), includes one water molecule in the cavity and adopts an ‘open’ cylinder-like form which probably reflects the structure of DIMEB in cold aqueous solution. There is no obvious stabilizing interaction between the included water molecule and the enclosing host cavity. Since the hydrogen bonding potential of this water is not satisfied, we envisage that it tries to escape if the aqueous solution of DIMEB is heated up, followed by the collapse of DIMEB to a bowl-shaped conformation which is found in the anhydrous crystal form (obtained from aqueous solution at > 50 °C). Conversely, if any small, hydrophobic guest molecule is added to an aqueous solution of DIMEB, it should easily displace W-1 from the cavity, yielding high affinity. In this respect, methylated cyclodextrins will be better-suited hosts for such guest molecules than their unsubstituted analogues [26].

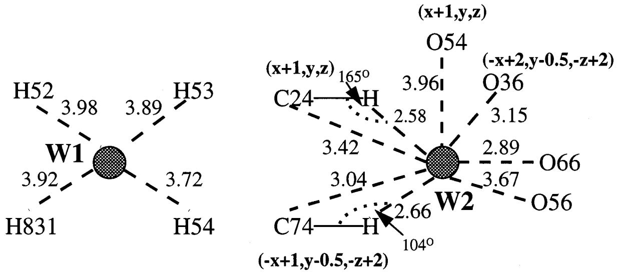

Fig. 2. Environment of the two water molecules. Atoms from symmetry-related molecules are indicated with their symmetry operators (distances in Å and angles in degree).

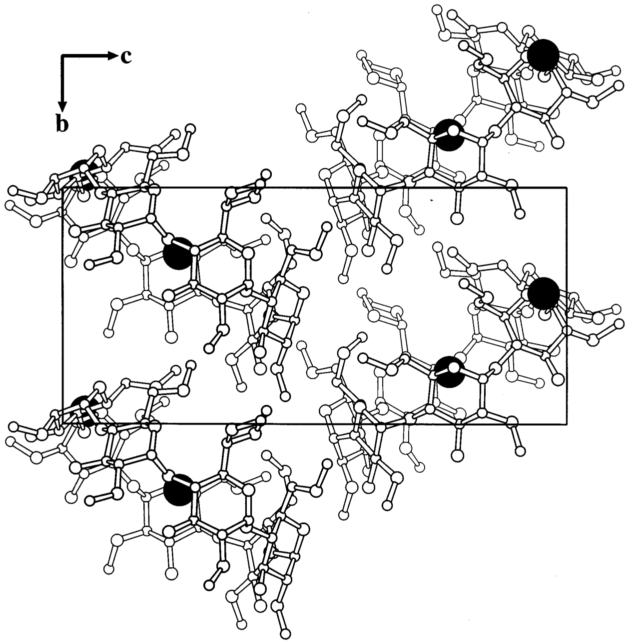

Fig. 3. Plot of crystal packing; water molecules are drawn with filled spheres.

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