ELSEVIER

www.elsevier.nl/locate/carres

Carbohydrate Research 328 (2000) 399–407

CARBOHYDRATE
RESEARCH

Crystal structure of octakis(2,3,6-tri-*O*-methyl)-γ-cyclodextrin·4.5 H_2O: evidence for conformational flexibility of permethylated cyclodextrins☆

Thammarat Aree [a], Helga Hoier [a], Burkhard Schulz [b], Günter Reck [b], Wolfram Saenger [a,]*

[a] *Institut für Kristallographie, Freie Universität Berlin, Takustraße 6, D-14195 Berlin, Germany*
[b] *Bundesanstalt für Materialforschung und -prüfung, Rudower Chaussee 5, D-12489 Berlin, Germany*

Received 10 December 1999; accepted 15 March 2000

Abstract

Octakis(2,3,6-tri-*O*-methyl)-γ-CD (TRIMEG) cocrystallized at 18 °C with 4.5 water molecules in the orthorhombic space group $P2_12_12_1$, unit cell dimensions $a = 10.7879(3)$, $b = 29.0580(9)$, $c = 32.2909(11)$ Å. The TRIMEG macrocycle is in a 'round' form with all glucose units oriented *syn*, and one O-6–CH_3 methoxy group points 'toward' the molecular cavity. The TRIMEG·4.5 H_2O molecules are stacked to form infinite cylinders with the central cavities aligned into channels filled for each TRIMEG by 4.5 water molecules distributed over 15 partially occupied sites. This structure differs from the two known structures of TRIMEG in which two diametrically opposed glucoses are oriented *anti* to yield an 'elliptical' form, and their O-6–CH_3 groups are directed 'toward' the cavity and close it at this side to form a bowl-shaped molecule. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: γ-Cyclodextrin; Octakis(2,3,6-tri-*O*-methyl)-γ-CD; Inclusion complexes; Hydrogen bonding; Conformational flexibility

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of 6, 7 or 8 α-(1→4)-linked D-glucose units generally known as α-, β- and γ-CDs [1]. Their structures resemble hollow, truncated cones with hydrophobic central cavities coated with C-3–H and C-5–H hydrogen atoms and ether-like O-4, O-5 oxygen atoms, and hydrophilic rims lined with primary O-6–H hydroxyl groups at the narrow side and secondary O-2–H, O-3–H hydroxyl groups at the wide side. The latter form systematic intramolecular, interglucose O-2(n)···O-3($n-1$) hydrogen bonds stabilizing the *syn* orientation of adjacent glucose units in the CD macrocycles. The most remarkable property of CDs is the formation of inclusion complexes with guest molecules of suitable sizes to fit into the host CD cavity [2].

In water, the CDs show a *positive* solubility coefficient as is usually observed for organic molecules. However, if they are methylated at O-2–H and O-6–H or at O-2–H, O-3–H and O-6–H hydroxyl groups, their solubility coeffi-

---

☆ Topography of cyclodextrin inclusion complexes, Part 48. For Part 47, see: [T. Aree et al., *Angew. Chem., Int. Ed. Engl.*, in press].

* Corresponding author. Tel.: +49-30-8383412; fax: +49-30-8386702.

E-mail address: saenger@chemie.fu-berlin.de (W. Saenger).

PII: S0008-6215(00)00100-2

cient in water is *negative*, i.e., they are well soluble in cold water and poorly soluble in hot water [3]. When a concentrated aqueous solution of methylated CD is heated above 50 °C, crystals are formed and redissolve when this suspension is cooled. (Hereafter we use abbreviations for methylated CDs, e.g., DIMEA and TRIMEG to denote hexakis(2,6-di-*O*-methyl)-α-CD and octakis(2,3,6-tri-*O*-methyl)-γ-CD, respectively.) X-ray crystallographic analyses showed that the methylated CDs crystallize from *hot* water as anhydrate: DIMEA [4,5], TRIMEA [6], DIMEB [7]; monohydrate: TRIMEB·H_2O [8]; dihydrate: TRIMEG·2 H_2O [9]. The absence or the small number of water molecules in these crystals correlates with the poor solubility of methylated CDs in water at high temperature. By contrast, DIMEB·15 H_2O [10] and (4TRIMEG)·19.3 H_2O [11] crystallized from *cold* water are well hydrated which may reflect their high solubility under these conditions.

In the two crystal structures reported so far, TRIMEG adopts an 'elliptical' shape with pseudo-twofold rotational symmetry, Fig. 1(a,b). The glucoses are oriented *syn* (O-2 and O-3 of adjacent glucoses are on the same side of the macrocycle) except for two diametrically opposed glucoses (#1 and #5), which are flipped by ≈180° (*anti*). In TRIMEG·2 H_2O [9] crystallized at 80 °C, the central cavity is occupied by the O-6–CH_3 groups of the two glucoses in *anti* orientation, Fig. 1(a) and the two water molecules are distributed over four positions in intermolecular voids between TRIMEG molecules. In contrast, in (4TRIMEG)·19.3 H_2O [11] crystallized from cold water at 18 °C, the asymmetric unit contains four independent TRIMEG molecules hydrated with a total of 19.3 water molecules. The four TRIMEG molecules adopt comparable 'elliptical' shapes as in TRIMEG·2 H_2O, and one water molecule is located right on the pseudo-twofold rotation axis at the center of each of the four macrocycles, forming hydrogen bonds to O-6 atoms of the two O-6–CH_3 groups rotated toward the central cavities, Fig. 1(b). The other water molecules are included in the cavities or close to the O-2, O-3, O-6 oxygen atoms of the four TRIMEG molecules, with no common pattern.

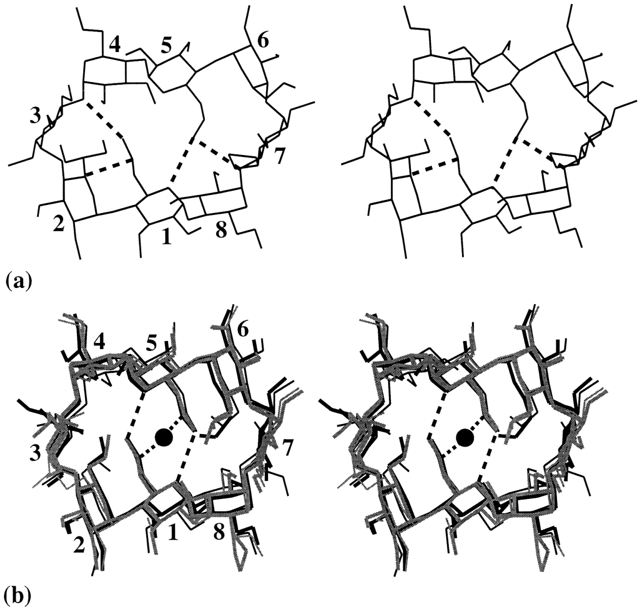

Fig. 1. 'Elliptical' shapes of TRIMEG with pseudo-twofold rotation symmetry; rotation axes are perpendicular to the plane of the paper and pass through the centers of the macrocycles. Glucose residues 1 and 5 are oriented *anti* with respect to the other six glucoses which are *syn*. (a) Stereo plot of TRIMEG·2 H_2O [9]; two water molecules located outside the cavity are not shown, dashed lines indicate C–H···O hydrogen bonds. (b) Stereo plot of overlay of the four TRIMEG molecules in (4TRIMEG)·19.3 H_2O [11], indicated by the thin and thick black and gray lines. The filled circle indicates the common water molecules located on the pseudo-twofold rotation axis of each of the four TRIMEG molecules. Dotted and dashed lines show systematic hydrogen bonds O_w–H···O-61, O_w–H···O-65 and C-91–H···O-55, C-95–H···O-51, respectively.

In this paper, we report a new molecular structure of TRIMEG with a 'round' macrocycle; all eight glucoses are in *syn* orientation and 4.5 water molecules are located in the central cavity.

2. Experimental

Crystallization.—A concentrated solution of TRIMEG (Cyclolab, Budapest/Hungary) in cold water was kept at 0 °C for a month, but no crystals formed. To enforce crystallization, the solution was heated to 80 °C. In contrast to other experiments which afforded crystallization of TRIMEG·2 H_2O [9] under these conditions, the solution became highly viscous. When the solution was cooled to 18 °C after 30 min, it remained viscous and rod-shaped crystals were obtained after 1 week.

Table 1
Summary of crystallographic data for TRIMEG·4.5 H_2O

Chemical formula	$C_{72}H_{128}O_{40}$·4.5 H_2O
Formula weight	1705.74
Crystal habit, color	rod, colorless
Crystal size (mm^3)	0.2 × 0.2 × 0.5
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	10.7879(3)
b (Å)	29.0580(9)
c (Å)	32.2909(11)
Volume (Å^3)	10122.4(5)
Z	4
D_{calcd} (g cm^{-3})	1.119
μ (mm^{-1})	0.093
F(000)	3664
Diffractometer	Bruker, CCD
Wavelength, Mo K_α (Å)	0.71073
Temperature (°C)	25
θ Range for data collection (°)	2.01–20.82 (1.0 Å resolution)
Measured reflections	31,669
Unique reflections	5779
Index ranges	$0<h<10$, $0<k<29$, $0<l<32$
Unique reflections [$F^2>2\sigma(F^2)$]	4311
Structure solution	direct methods (SHELXS-97)
Refinement method	full-matrix least-squares on F^2
R [$F^2>2\sigma(F^2)$]	$R=0.104$
R (all data)	$R=0.134$
Goodness of fit	1.146
Highest peak and deepest hole (e Å^{-3})	0.26 and −0.25

X-ray diffraction experiments.—A crystal was mounted in a quartz capillary for X-ray diffraction experiments performed at rt with a Bruker-AXS CCD area detector using graphite-monochromatized Mo K_α radiation, see Table 1. Semiempirical absorption correction using ψ-scans and data reduction were accomplished with the programs SAINT and SHELXTL (Siemens software) and merged to yield 5779 unique reflections.

Structure solution and refinement.—The crystal structure was determined by direct methods with the program SHELXS-97 [12], developed by difference Fourier techniques, and refined by full-matrix least-squares on F^2 [13]. All hydrogen atoms of TRIMEG were put in the standard geometry according to the 'riding model' [13] — those of the water molecules could not be determined. The TRIMEG methoxy groups and disordered water molecules show excessive thermal parameters. After the 1096 atomic parameters (atomic coordinates and anisotropic temperature factors) were refined against 4311 data with $F_o^2 > 2\sigma(F_o^2)$, the R factor converged at 0.104. The total of 4.5 water molecules located within the central cavity of TRIMEG are distributed over 15 positions (occupancy factors 0.25–0.60, see caption of Fig. 2(a,b)). The relatively high R factor may be due to instability of the crystal, which tended to dry out during data collection resulting in a large number of weak X-ray data at high resolution.

A summary of crystallographic data and final fractional atomic coordinates and equivalent isotropic thermal displacement factors are given in Tables 1 and 2, respectively. The geometrical parameters listed in Table 3 were calculated using PARST-96 [14].

In the atomic labeling used, the letter denotes the atom type, the first number the position in the glucose and the second number the glucose number in the macrocycle; for instance C-46 denotes C-4 of glucose residue 6. Methyl carbon atoms connected to O-2, O-3, and O-6 are designed C-7, C-8 and C-9, respectively, see Fig. 2(a).

3. Results and discussion

Molecular conformation of TRIMEG.—The eight glucose units of TRIMEG are all oriented *syn* and in the regular $^4C_1$ chair conformation as indicated by the Cremer–Pople parameters, Q and θ [15], Table 3. The narrow variation of O-4(n)···O-4($n-1$) distances and the moderate deviation of the glycosidic oxygen O-4 atoms from their common least-squares plane indicate that the TRIMEG macrocycle adopts a 'round' shape, but individual glucoses are tilted considerably as shown by their tilt angles (8.0–57.9°) and by the distribution of torsion angles around glycosidic O-4 atoms, ϕ and ψ [16] in the ranges 76.8–126.1 and 87.2–157.1°, respectively, Fig. 2(a,b), and Table 3. This contrasts the known structures, TRIMEG·2 H_2O [9] and (4TRIMEG)·19.3 H_2O [11] where the macrocycles adopt ‘elliptical’ shapes because diametrically opposed glucoses are flipped by ≈ 180° (*anti*), Fig. 1(a,b). The systematic interglucose C-6–H(n)···O-5($n+1$) hydrogen bonds, which usually contribute to the stability of the CD structures exist in only six contacts because

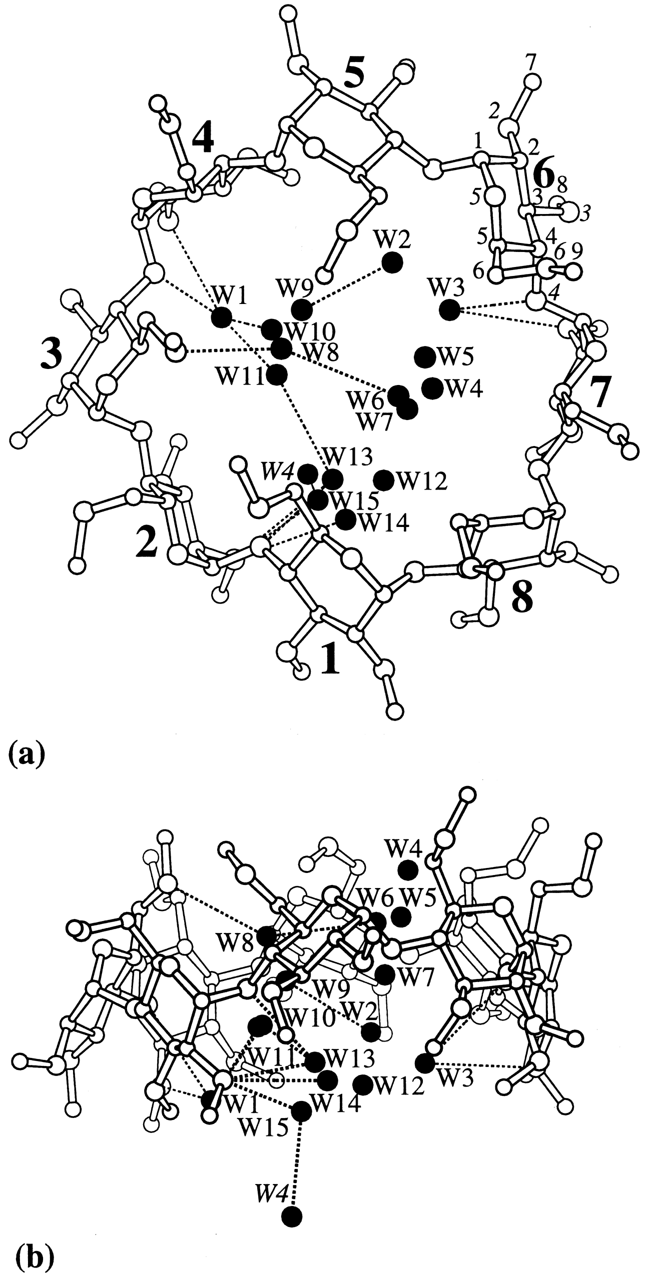

Fig. 2. Molecular structure of TRIMEG·4.5 H_2O, (a) top and (b) side views. Filled circles are water molecules. Dashed lines indicate possible hydrogen bonds within 3.50 Å distance. Italic lettered water site W-4, which is hydrogen bonded to water site W-15 is located in an adjacent asymmetric unit. Water sites are occupied as follows: W-1, 0.50; W-2, 0.40; W-3, 0.60; all others 0.25. Atomic numbering of TRIMEG shown in 2(a) for glucose residue 6, carbon atoms with normal numbers and oxygen atoms with italics.

Table 2
Fractional atomic coordinates and equivalent isotropic thermal displacement factors of TRIMEG·4.5 H_2O

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
C-11	0.2835(13)	0.1943(4)	0.8977(4)	0.079(4)
C-21	0.1829(13)	0.2246(4)	0.8827(4)	0.078(4)
C-31	0.0762(12)	0.1979(4)	0.8628(3)	0.063(3)
C-41	0.1275(11)	0.1642(4)	0.8311(3)	0.065(3)
C-51	0.2303(12)	0.1351(5)	0.8490(4)	0.081(4)
C-61	0.2930(19)	0.1017(7)	0.8200(6)	0.143(7)
C-71	0.1786(7)	0.2971(2)	0.9162(7)	0.194(11)
C-81	−0.1170(14)	0.2367(6)	0.8681(5)	0.118(6)
C-91	0.402(2)	0.0878(11)	0.7593(8)	0.282(16)
O-21	0.1299(10)	0.2526(2)	0.9131(3)	0.109(4)
O-31	−0.0112(10)	0.2274(3)	0.8437(2)	0.085(3)
O-41	0.0326(8)	0.1325(2)	0.8182(2)	0.073(2)
O-51	0.3253(8)	0.1656(3)	0.8652(3)	0.089(3)
O-61	0.3332(13)	0.1223(7)	0.7840(5)	0.196(7)
C-12	−0.0460(14)	0.1471(5)	0.7838(4)	0.090(5)
C-22	−0.1657(14)	0.1201(5)	0.7836(5)	0.099(5)
C-32	−0.1448(13)	0.0705(4)	0.7718(4)	0.076(4)
C-42	−0.0708(11)	0.0679(4)	0.7333(4)	0.067(3)
C-52	0.0479(13)	0.0949(4)	0.7354(4)	0.081(4)
C-62	0.1258(14)	0.0990(4)	0.6969(4)	0.089(4)
C-72	−0.3385(16)	0.1475(8)	0.8230(8)	0.199(11)
C-82	−0.2778(16)	0.0088(6)	0.7834(6)	0.144(7)
C-92	0.027(3)	0.1581(5)	0.6567(5)	0.178(11)
O-22	−0.2207(10)	0.1236(4)	0.8232(3)	0.120(4)
O-32	−0.2640(9)	0.0516(4)	0.7661(3)	0.108(3)
O-42	−0.0461(7)	0.0204(2)	0.7248(2)	0.069(2)
O-52	0.0186(10)	0.1423(3)	0.7467(2)	0.087(3)
O-62	0.0544(12)	0.1093(3)	0.6612(3)	0.123(4)
C-13	−0.0218(11)	0.0062(4)	0.6837(4)	0.068(3)
C-23	−0.1127(11)	−0.0308(4)	0.6708(4)	0.066(3)
C-33	−0.0915(11)	−0.0749(4)	0.6958(4)	0.065(3)
C-43	0.0433(12)	−0.0874(4)	0.6971(4)	0.073(4)
C-53	0.1248(10)	−0.0465(4)	0.7066(4)	0.075(4)
C-63	0.2613(14)	−0.0590(5)	0.6977(6)	0.111(5)
C-73	−0.2787(15)	0.0141(4)	0.6426(5)	0.116(6)
C-83	−0.2786(14)	−0.1191(6)	0.6957(6)	0.142(7)
C-93	0.448(2)	−0.0236(10)	0.7000(9)	0.236(13)
O-23	−0.2390(8)	−0.0179(3)	0.6730(3)	0.099(3)
O-33	−0.1573(8)	−0.1128(3)	0.6789(3)	0.084(3)
O-43	0.0598(7)	−0.1222(2)	0.7286(2)	0.066(2)
O-53	0.0975(8)	−0.0101(3)	0.6796(2)	0.077(2)
O-63	0.3302(12)	−0.0245(5)	0.7152(4)	0.152(5)
C-14	0.0703(11)	−0.1695(3)	0.7165(4)	0.063(3)
C-24	0.0163(13)	−0.2004(4)	0.7487(4)	0.079(4)
C-34	0.1044(12)	−0.2022(4)	0.7861(4)	0.070(3)
C-44	0.2350(12)	−0.2139(4)	0.7721(3)	0.070(4)
C-54	0.2755(10)	−0.1806(4)	0.7416(3)	0.061(3)
C-64	0.4025(12)	−0.1897(4)	0.7215(4)	0.077(4)
C-74	−0.1889(16)	−0.2225(6)	0.7620(6)	0.149(7)
C-84	0.0320(18)	−0.2217(6)	0.8551(4)	0.133(6)
C-94	0.5167(13)	−0.2440(5)	0.6850(5)	0.121(6)
O-24	−0.1025(8)	−0.1870(3)	0.7606(3)	0.091(3)
O-34	0.0554(9)	−0.2361(3)	0.8147(3)	0.099(3)
O-44	0.3076(8)	−0.2123(3)	0.8100(2)	0.088(3)
O-54	0.1926(7)	−0.1807(3)	0.7061(2)	0.069(2)

Table 2 (*Continued*)

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq} (Å^2)
O-64	0.4075(9)	−0.2346(3)	0.7074(3)	0.099(3)
C-15	0.4191(12)	−0.2378(5)	0.8097(4)	0.078(4)
C-25	0.4136(14)	−0.2758(4)	0.8429(4)	0.079(4)
C-35	0.3973(13)	−0.2558(4)	0.8847(3)	0.072(4)
C-45	0.4928(14)	−0.2215(5)	0.8955(4)	0.087(4)
C-55	0.5039(12)	−0.1860(4)	0.8609(4)	0.078(4)
C-65	0.614(2)	−0.1566(2)	0.8661(4)	0.174(9)
C-75	0.3547(8)	−0.3496(2)	0.8204(7)	0.252(14)
C-85	0.299(2)	−0.3082(7)	0.9295(6)	0.176(9)
C-95	0.5365(4)	−0.0854(4)	0.8249(17)	0.89(9)
O-25	0.3185(10)	−0.3051(3)	0.8318(3)	0.112(3)
O-35	0.4103(11)	−0.2923(3)	0.9143(3)	0.106(3)
O-45	0.4579(8)	−0.1980(3)	0.9327(3)	0.084(3)
O-55	0.5193(9)	−0.2082(4)	0.8212(3)	0.103(3)
O-65	0.6224(17)	−0.1215(5)	0.8366(5)	0.300(11)
C-16	0.5403(13)	−0.2020(5)	0.9660(5)	0.098(5)
C-26	0.4694(19)	−0.2091(6)	1.0074(5)	0.117(6)
C-36	0.4038(16)	−0.1672(4)	1.0200(4)	0.100(5)
C-46	0.4797(14)	−0.1248(5)	1.0203(4)	0.097(5)
C-56	0.5513(4)	−0.1198(3)	0.9768(5)	0.107(5)
C-66	0.6439(5)	−0.0837(4)	0.9646(2)	0.44(3)
C-76	0.443(3)	−0.2872(6)	1.0241(7)	0.226(14)
C-86	0.240(3)	−0.1892(8)	1.0652(7)	0.253(15)
C-96	0.8297(3)	−0.0739(7)	1.0114(13)	0.62(6)
O-26	0.3926(15)	−0.2464(4)	1.0075(3)	0.148(5)
O-36	0.3617(14)	−0.1716(3)	1.0616(3)	0.131(5)
O-46	0.4039(8)	−0.0829(3)	1.0257(2)	0.075(2)
O-56	0.6138(9)	−0.1612(3)	0.9685(3)	0.111(3)
O-66	0.7027(11)	−0.0869(6)	1.0024(3)	0.462(17)
C-17	0.4176(12)	−0.0631(4)	1.0645(4)	0.071(4)
C-27	0.2977(13)	−0.0438(5)	1.0788(4)	0.085(4)
C-37	0.2646(12)	0.0014(5)	1.0579(4)	0.080(4)
C-47	0.3687(11)	0.0348(4)	1.0561(4)	0.068(4)
C-57	0.4796(12)	0.0100(4)	1.0382(4)	0.069(4)
C-67	0.5959(14)	0.0381(4)	1.0331(4)	0.088(4)
C-77	0.1264(17)	−0.0833(7)	1.1115(6)	0.168(9)
C-87	0.0547(16)	0.0347(6)	1.0590(7)	0.158(8)
C-97	0.7366(15)	0.0869(5)	1.0667(5)	0.119(6)
O-27	0.1991(9)	−0.0759(4)	1.0761(3)	0.111(3)
O-37	0.1618(9)	0.0205(4)	1.0808(3)	0.117(4)
O-47	0.3312(8)	0.0727(3)	1.0319(2)	0.074(2)
O-57	0.5100(7)	−0.0279(3)	1.0647(2)	0.070(2)
O-67	0.6238(9)	0.0608(3)	1.0695(3)	0.093(3)
C-18	0.3779(14)	0.1160(5)	1.0412(4)	0.082(4)
C-28	0.2706(13)	0.1514(4)	1.0440(3)	0.075(4)
C-38	0.2097(13)	0.1583(5)	1.0016(4)	0.082(4)
C-48	0.3046(13)	0.1685(4)	0.9682(4)	0.076(4)
C-58	0.4093(13)	0.1339(4)	0.9708(4)	0.076(4)
C-68	0.5139(16)	0.1432(5)	0.9400(5)	0.119(6)
C-78	0.1688(19)	0.1552(4)	1.1099(3)	0.236(14)
C-88	0.0041(16)	0.1906(7)	0.9949(6)	0.151(8)
C-98	0.6821(3)	0.2030(6)	0.9521(8)	0.248(14)
O-28	0.1819(12)	0.1370(4)	1.0714(3)	0.122(4)
O-38	0.1265(11)	0.1967(3)	1.0071(3)	0.112(3)
O-48	0.2383(8)	0.1676(3)	0.9307(3)	0.075(2)
O-58	0.4630(9)	0.1314(3)	1.0112(3)	0.093(3)
O-68	0.5548(6)	0.1892(4)	0.9449(6)	0.186(7)
W-1 [a]	−0.148(6)	−0.1015(9)	0.8100(9)	0.28(3)
W-2 [a]	0.185(7)	−0.132(3)	0.9247(14)	0.38(4)
W-3 [a]	0.127(4)	−0.0945(14)	0.9805(17)	0.36(3)
W-4 [a]	0.545(7)	0.018(2)	0.916(2)	0.21(3)
W-5 [a]	0.442(11)	−0.020(4)	0.922(3)	0.30(4)
W-6 [a]	0.386(8)	0.013(3)	0.904(2)	0.21(3)
W-7 [a]	0.258(10)	0.014(3)	0.926(3)	0.27(4)
W-8 [a]	0.286(11)	−0.036(4)	0.813(3)	0.32(5)
W-9 [a]	0.214(9)	−0.080(3)	0.840(3)	0.26(4)
W-10 [a]	0.067(10)	−0.073(3)	0.830(3)	0.26(4)
W-11 [a]	0.051(8)	−0.032(3)	0.835(3)	0.24(3)
W-12 [a]	−0.072(6)	0.055(2)	0.9401(19)	0.18(2)
W-13 [a]	−0.056(6)	0.057(2)	0.8934(19)	0.17(2)
W-14 [a]	−0.112(5)	0.0902(18)	0.9103(16)	0.142(16)
W-15 [a]	−0.200(7)	0.065(2)	0.896(2)	0.20(3)

[a] Occupancy factors of water sites W-1, W-2, W-3 and W-4–W-15 are 0.50, 0.40, 0.60 and 0.25, respectively.

for glucose residues 1 and 6 C-6(n)···O-5($n+1$) distances are too long and C-6–H(n)···O-5($n+1$) angles are too small to indicate such interactions (see Table 3).

The orientations of methoxy groups, O-2–CH_3, O-3–CH_3 and O-6–CH_3 are described by torsion angles in Table 3. All O-2–CH_3, and O-3–CH_3 methoxy groups point 'away' from the TRIMEG cavity (Fig. 2(a,b)) as indicated by the torsion angles C-1–C-2–O-2–C-7 and C-2–C-3–O-3–C-8. The torsion angles O-5–C-5–C-6–O-6 of the glucose units 3 and 5 are +*gauche*, whereas the others are −*gauche*, and all torsion angles C-5–C-6–O-6–C-9 are *trans* except for glucose units 2 and 5 which are +*gauche* (82.8 and 55.4°). Only O-6–CH_3 of glucose residue 5 is directed 'toward' the cavity so that the geometry of TRIMEG is an open cylinder as shown by the space-filling model in Fig. 3. This agrees with previous structures of methylated CD crystals grown from cold water, DIMEA·H_2O [4] and DIMEB·2 H_2O [17]. By contrast, in crystals obtained from hot water [4–9] methylated CDs exhibit a bowl-shaped conformation because two or three O-6–CH_3 groups are rotated 'inward' and close the cavity from this side.

The 4.5 water molecules are included in the TRIMEG cavity.—A total of 4.5 water molecules are distributed over 15 positions of which none is fully occupied (occupancy fac-

Table 3
Geometrical parameters of the TRIMEG·4.5 H_2O macrocycle (distances in Å and angles in °)

Residue	1	2	3	4	5	6	7	8
Q [a]	0.55	0.53	0.54	0.56	0.56	0.53	0.56	0.56
θ [b]	5	2	8	4	6	4	12	6
ϕ [c]	113.2(12)	76.8(12)	115.2(10)	85.2(12)	126.1(11)	100.4(13)	94.0(11)	108.7(11)
ψ [c]	152.7(10)	87.2(11)	155.2(10)	100.5(11)	157.1(10)	119.8(12)	107.9(12)	148.2(11)
Tilt angle [d]	57.9(3)	8.0(8)	29.6(4)	10.9(4)	41.3(6)	22.7(8)	12.3(6)	28.1(5)
O-4 deviation [e]	0.01	0.30	0.29	−0.43	−0.37	0.59	0.33	−0.73
Distances								
O-4(n)···O-4($n-1$)	4.38(1)	4.52(1)	4.30(1)	4.57(1)	4.30(1)	4.54(1)	4.59(1)	4.39(1)
C-6(n)···O-5($n+1$)	3.97(2) [f]	3.23(1)	3.63(2)	3.50(2)	3.31(2)	3.90(1) [f]	3.15(2)	3.22(2)
∠C-6–H(n)···O-5($n+1$)	99.5(8) [f]	132.5(8)	137.3(9)	138.1(8)	143.5(7)	98.5(8) [f]	129.0(8)	140.3(10)
Torsion angles								
C-1–C-2–O-2–C-7	95.0(13)	115.5(14)	71.3(14)	133.0(14)	113.5(14)	95.2(18)	127.9(15)	104.6(14)
C-2–C-3–O-3–C-8	−98.2(13)	−136.4(13)	−91.3(13)	−124.2(13)	−101.5(15)	−92.3(20)	−128.9(14)	−127.9(14)
O-5–C-5–C-6–O-6	−70.1(17)	−76.3(13)	74.4(15)	−70.2(12)	63.7(15)	−83.1(13)	−71.0(12)	−71.9(14)
C-5–C-6–O-6–C-9	175.6(15)	82.8(16)	−162.4(18)	174.1(11)	55.4(33)	157.4(19)	178.0(11)	126.3(21)

[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(n)–C-1(n)–O-4($n-1$)–C-4($n-1$) and C-1(n)–O-4($n-1$)–C-4($n-1$)–C-3($n-1$), respectively [16].

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

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

[f] C-6(n)···O-5($n+1$) distance too long and C-6–H(n)···O-5($n+1$) angle too small so that the systematic intramolecular, interglucose C-6–H(n)···O-5($n+1$) hydrogen bond probably not formed.

tors 0.25–0.60). These water sites are located in the cavity of TRIMEG, Fig. 2(a,b), none is found in interstices between TRIMEG molecules (Fig. 4(a,b)). The water sites are not evenly distributed in the TRIMEG cavity, but form three distinct clusters consisting of four sites each: W-4–W-7; W-8–W-11; W-12–W-15. In these clusters, the distances between water sites, 1.23–1.77 Å, are so short that they cannot be occupied simultaneously and the occupancies are so low (0.25) that they add up to one water molecule for each cluster. The other distances between water sites indicated by dotted lines in Fig. 2(a,b) are 2.54–3.43 Å. Three of the water sites are hydrogen bonded to O-4 and O-2 of adjacent glucoses (2.92–3.50 Å), viz. W-1···O-43/O-24, W-3···O-46/O-27 and W-13···O-41/O-22. Hydrogen bonds to glycosidic O-4 atoms are rare in CDs and formed here probably because the O–CH_3 groups are weaker hydrogen bond acceptors than O-4. The inclusion of water molecules in the TRIMEG cavity appears to stabilize the 'round' structure, but glucose residues 1 and 5 are more tilted than the others (57.9 and 41.3°, Table 2), suggesting that they could easily flip into the *anti* conformations found in the other two TRIMEG structures [9,11].

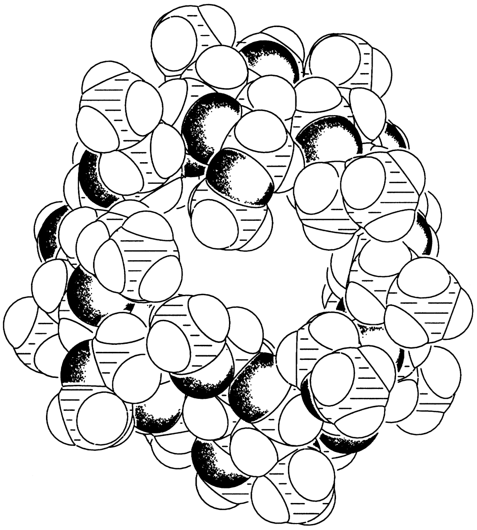

Fig. 3. Space-filling model illustrating that the overall structural feature of TRIMEG·4.5 H_2O is an open cylinder because only one O-6–CH_3 methoxy group is directed 'toward' the molecular cavity; water molecules in the central cavity not shown. Oxygen atoms indicated darker. Carbon hatched, hydrogen white. Drawn with program PLUTON [19].

Crystal packing.—TRIMEG molecules are stacked head-to-tail and inclined about 20° against the *c*-axis. The central cavities form an infinite channel filled by water molecules, Fig. 4(a,b). This molecular arrangement is similar to the pattern typical for native CDs in complex with long molecular or ionic guests where the channels are stabilized by intermolecular

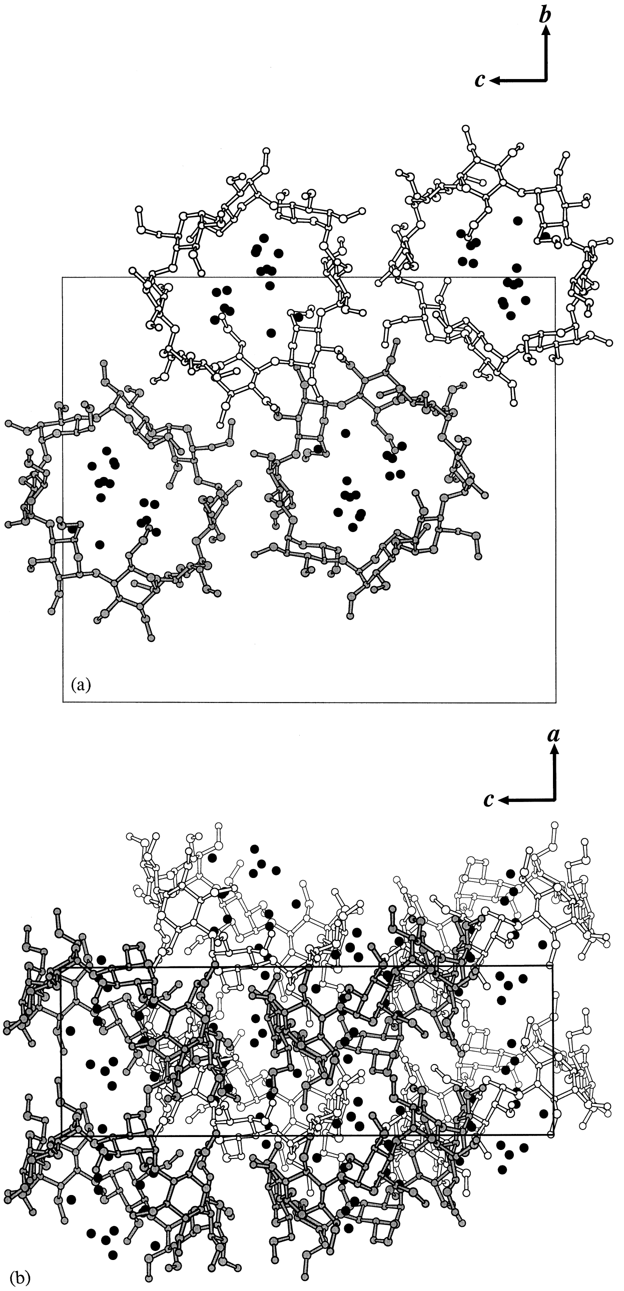

Fig. 4. Crystal packing of TRIMEG·4.5 H_2O in 'head-to-tail' channel pattern, (a) *b*–*c* and (b) *a*–*c* planes. Molecules related by the twofold screw operation along the *b*-axis are shaded gray, filled circles are water molecules. Note that in (b), water molecules form an infinite channel parallel to the *a*-axis and that all water sites are located within the channels; none is between TRIMEG molecules.

hydrogen bonds between O-2–H/O-3–H and O-6–H [18]. For the present crystal structure however, such interactions cannot occur and the crystal lattice is stabilized by van der Waals contacts and C–H···O hydrogen bonds, the shortest being 3.50 Å between C-93 (x, y, z) and O-23 ($x+1, y, z$).

4. Conclusions

The present study shows that TRIMEG does not exclusively occur in the 'elliptical' form found in TRIMEG·2 H_2O [9] and (4TRIMEG)·19.3 H_2O [11], but it can also adopt the 'round' form with all glucose residues oriented *syn*. This is the conformation found for native α-, β-, γ-CDs and for their methylated derivatives and even for TRIMEB·H_2O [8], in which one of the glucose residues is 'inverted' to a $^1C_4$ chair. In both TRIMEG forms, the glucose residues are in a seemingly unstrained $^4C_1$ conformation (as indicated by the Cremer–Pople parameters) so that 'elliptical' and 'round' TRIMEG are energetically similar. This implies that in solution, both forms could coexist in equilibrium because the macrocycle is wide enough to permit rotation of individual glucose residues by ≈180° with little or no steric constraints, contrasting with the smaller native and methylated CDs in which all glucoses are oriented *syn*. Out of a variety of possible conformers of TRIMEG, the 'elliptical' form appears to be energetically preferred, probably because it is stabilized by favorable intramolecular C–H···O interactions involving glucose residues 1 and 5 in *anti* orientation (see dashed lines in Fig. 1(a,b)).

The hydration numbers per TRIMEG are comparable in both forms crystallized from cold water: TRIMEG·4.8 H_2O for (4TRIMEG)·19.3 H_2O [11] and TRIMEG·4.5 H_2O. In both, water molecules are located mostly within, or close to, the TRIMEG cavities, while in TRIMEG·2 H_2O [9] crystallized from hot water the disordered water molecules are located close to, but not within, the TRIMEG cavity. This suggests that at low temperature the methylated CDs are heavily hydrated so that they are well soluble in cold water. When the temperature increases, the water molecules become more mobile, leading to the disruption of hydration shells and finally, the hydrophobic, methylated CDs aggregate and crystallize above 50 °C with none, one or two water of hydration molecules [4–8].

5. Supplementary material

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 118818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2, IEZ, UK, (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

T. Aree is supported by a scholarship under the Development and Promotion of Science and Technology Talents Project (DPST) by the Royal Thai Government Agencies and the Institute for the Promotion of Teaching Science and Technology (IPST). In addition, these studies were financed in part by Deutsche Forschungsgemeinschaft and by Fonds der Chemischen Industrie.

References

[1] (a) M.L. Bender, M. Komiyama, *Cyclodextrin Chemistry*, Springer, Berlin, 1978. (b) W. Saenger, *Angew. Chem., Int. Ed. Engl.* 19 (1980) 344–362. (c) W. Saenger, in J.L. Atwood, J.E.D. Davies, D.D. MacNicol (Eds.), *Inclusion Compounds*, Vol. 2, Academic Press, London, 1984, pp. 231–259.

[2] J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.

[3] K. Uekama, T. Irie, in D. Duchêne (Ed.), *Cyclodextrins and their Industrial Uses*, Editions de Santé, Paris, 1987, pp. 395–439.

[4] K. Harata, *Supramol. Chem.*, 5 (1995) 231–236.

[5] T. Steiner, W. Saenger, *Carbohydr. Res.*, 282 (1996) 53–63.

[6] T. Steiner, K. Hirayama, W. Saenger, *Carbohydr. Res.*, 296 (1996) 69–82.

[7] T. Steiner, W. Saenger, *Carbohydr. Res.*, 275 (1995) 73–82.

[8] M.R. Caira, V.J. Griffith, L.R. Nassimbeni, B. van Oudtshoorn, *J. Chem. Soc., Perkin Trans. 2*, (1994) 2071–2072.

[9] T. Steiner, W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 37 (1998) 3404–3407.

[10] T. Aree, H. Hoier, B. Schulz, G. Reck, W. Saenger, *Angew. Chem., Int. Ed. Engl.*, in press.

[11] T. Aree, I. Usón, B. Schulz, G. Reck, H. Hoier, G.M. Sheldrick, W. Saenger, *J. Am. Chem. Soc.*, 121 (1999) 3321–3327.

[12] G.M. Sheldrick, SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Germany, 1997.

[13] G.M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.

[14] M. Nardelli, *J. Appl. Crystallogr.*, 28 (1995) 659.

[15] D. Cremer, J.A. Pople, *J. Am. Chem. Soc.*, 97 (1975) 1354–1358.

[16] IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) Symbols for specifying the conformation of polysaccharide chains, Recommendations 1981, *Eur. J. Biochem.*, 131 (1983) 5–7.

[17] T. Aree, W. Saenger, P. Leibnitz, H. Hoier, *Carbohydr. Res.*, 315 (1999) 199–205.

[18] W. Saenger, *Isr. J. Chem.*, 25 (1985) 43–50.

[19] A.L. Spek, *Acta. Crystallogr., Sect. A*, 46 (1990) C34.