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Crystal structure of anhydrous heptakis-(2,6-di-*O*-methyl)cyclomaltoheptaose (dimethyl-β-cyclodextrin) ☆

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Abstract

An X-ray diffraction study was carried out on dimethyl-β-cyclodextrin which crystallized from aqueous solution at 60°C without water of hydration. The molecule adopts a round shape which is stabilized by systematic intramolecular O-3–H · · · O-2 hydrogen bonds between neighboring glucose units. The O-6–C-8 groups of three glucoses are oriented towards the molecular axis so that the cyclodextrin cavity is closed at one end. The remaining volume of the bowl-shaped cavity is occupied by part of the C-6–O-6–C-8 rim of a neighboring molecule (self-inclusion).

Keywords: Crystal structure; Dimethyl-β-cyclodextrin; β-Cyclodextrin; Hydrogen bonding

1. Introduction

Compared with unsubstituted ("native") cyclodextrins (cyclomalto-oligosaccharides, CDs), the methylated cyclodextrins have very different physical and complexation properties. A particularly peculiar property is the negative temperature coefficient of their aqueous solubilities: if a cold concentrated solution is heated, crystals appear, and if it is cooled again, the crystals re-dissolve. This effect is most pronounced for β-cyclodextrin methylated at all O-2 and O-6 positions [heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin, dimethyl-β-cyclodextrin, DIMEB]. For this compound, the solubility in

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water at room temperature is about 60 g/100 mL, and for increasing temperature it gradually reduces and falls to values < 1 g/100 mL for temperature > 70°C [1]. Crystallization and subsequent re-dissolving in a cyclic heating–cooling process shows a hysteresis effect of about 10°C [2]. These properties are not yet understood. Crystal structures were published for numerous complexes of DIMEB [3], whereas for the pure or hydrated compound itself, a structure solution was attempted [4] but never finished.

Recently, the structure was determined for 2,3,6-*O*-trimethylated β-cyclodextrin, TRIMEB, with crystals grown from a hot aqueous solution [5]. The TRIMEB molecule was found in a highly distorted geometry with one glucose residue showing ring inversion from the normal $^4C_1$ to $^1C_4$ chair conformation. The tilt angles of the glucoses with respect to the equatorial plane covered the extremely wide range from -4.6 to $+72.9$°. One glucose residue was tilted inwards so much that the cavity is closed at the O-6 side. One water molecule per TRIMEB was found co-crystallized between the macrocycles, whereas no water was found in the TRIMEB cavities. To see whether similar distortions occur in other methylated cyclodextrins crystallized from hot water, we determined the crystal structure of DIMEB crystallized at 60°C, and find a rather regularly shaped molecule.

2. Experimental

Crystallization.—Dilute aqueous solutions of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin (purchased from Aldrich) were prepared at room temperature, and heated to 60°C. The initial concentrations were so low that this did not yet lead to crystallization. As the water slowly evaporated, opaque, white, rod shape, crystals appeared. Since the crystals would dissolve again if the solution was cooled, the sample was kept at 60°C until all the water had evaporated. The crystals obtained this way are stable at room temperature in an atmosphere of moderate humidity [2]. At temperatures of 70 and 80°C, crystals grow of the same kind, but of lower quality.

X-ray diffraction experiments.—In the X-ray beam, crystals always showed diffuse and broad Bragg-reflections and poor intensities at high diffraction angles, indicating high mosaicity (this is not surprising for crystals grown at elevated temperatures). Several crystals had to be tested until one was found which showed diffraction quality suitable for structure determination. Diffraction data were collected on a $0.9 \times 0.2 \times 0.2$ mm^3 specimen cut out of a longer rod (Enraf–Nonius Turbo-CAD4 diffractometer on a FR571 rotating anode generator, Ni-filtered Cu-K_α radiation with $\lambda = 1.542$ Å). The space group is orthorhombic $P2_12_12_1$ with $a = 13.821(2)$, $b = 17.424(6)$, $c = 29.610(7)$ Å, Vol. = 7131 (3) Å^3 (determined from the diffraction angles of 25 reflections), $Z = 4$, MW = 1331, $D_x = 1.24$ g/cm^3. Intensities of 5881 unique reflections were measured to a nominal resolution of $\lambda/2 \sin \theta_{max} = 0.89$ Å ($2\theta_{max} = 120$°, $\omega - \theta$ scan mode).

Structure solution and refinement.—The structure was solved by Patterson search methods (program PATSEE [6]) using the published atomic coordinates of the DIMEB molecule in the complex DIMEB–*p*-iodophenol-dihydrate [7]. In the starting model, the O-6 and the methyl-C atoms were omitted. During anisotropic refinement after empirical absorption correction [8], these missing sites could be picked from difference Fourier

maps (program SHELX76 [9] aided by the computer graphics program FRODO [10], the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized with $w = 1.0$). Refinement of the O-2–C-7 and C-6–O-6–C-8 groups was troublesome due to their conformational flexibility and resulting high displacement factors. The O-6–C-8 group of residue 5 is disordered over at least two alternative positions, and for residue 1, similar disorder became apparent but could not be resolved. No H-atom positions could be located. H-atoms bonded to C were tentatively included in their ideal positions, but since this did not significantly improve the *R*-factor, they were not used in the final refinement cycles. No water site could be located, neither in the cavity nor in interstices between the molecules. Refinement converged with $R = 0.101$ for the 4143 reflections with $F_o > 2\sigma(F_o)$. The highest residual electron density peak corresponds to 0.27 Å^3. The final *R*-factor is high compared to typical crystal structures of native β-cyclodextrin, but is in the normal range for methylated cyclodextrins.

3. Results and discussion

General.—Fractional atomic coordinates and equivalent isotropic temperature factors are listed in Table 1. Atom labeling is as in our previous contributions ([11] and references therein), e.g. C-2^3 means atom C-2 of glucose residue 3 of the oligosaccharide. The methyl C-atoms attached to O-2^n and O-6^n are labeled C-7^n and C-8^n, respectively.

Molecular conformation.—The DIMEB molecule is shown in Fig. 1 in a projection on the equatorial plane. The molecule is in a round shape, and the O-2 and O-3 atoms of all neighboring glucoses are within hydrogen bonding distance, Table 2. This indicates a ring of O-3^n–H $\cdots$ O-2^{n-1} hydrogen bonds stabilizing the molecular conformation. In native β-cyclodextrin, the systematic intramolecular O-3–H $\cdots$ O-2 or O-2–H $\cdots$ O-3 hydrogen bonds are always associated with a minor bonding interaction to the O-4 atom, with H $\cdots$ O-4 separations typically in the range 2.4 ± 0.2 Å [12]. Since the steric situation around O-4 is identical in native and substituted cyclodextrins, it is assumed that the O-3–H $\cdots$ O-2 hydrogen bonds in DIMEB are also of the three-center type [13] with a minor component accepted by O-4.

In addition, there are systematic intramolecular C–H $\cdots$ O contacts from C-6^n–H to O-5^{n-1}, with H $\cdots$ O-5 around 2.4–2.6 Å, Table 3 (for theoretical H-positions), which is in the range of the weak C–H $\cdots$ O hydrogen bonds [14]. These contacts occur in native cyclodextrins with similar geometries [15]. In TRIMEB-monohydrate, C-6–H $\cdots$ O-5 interactions were also reported as having significant stabilizing function [5]. Therefore, the regular pattern of intramolecular hydrogen bonds between adjacent glucoses is presumably as shown in **1** (Scheme 1). Without question, the dominant interaction in this motif is the O-3–H $\cdots$ O-2 hydrogen bond.

Despite the round shape and the regular inter-residue interactions of the molecule, there are variations in the conformation of the individual glucoses. The tilt angles with respect to the least-squares plane through the O-4 atoms vary between -5.9 and $+30.5°$, Table 2. The ring puckering parameters [16], Table 2, show a significant distortion from an ideal chair conformation for residue **6**, which also has the largest tilt

Table 1
Fractional atomic coordinates and equivalent isotropic temperature factors U_{eq}

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
C-1^1	0.5517 (12)	0.6906 (7)	0.4325 (5)	0.13 (1)
C-2^1	0.4742 (11)	0.6562 (8)	0.4066 (5)	0.13 (1)
C-3^1	0.5009 (9)	0.5845 (7)	0.3827 (4)	0.10 (1)
C-4^1	0.5781 (12)	0.6051 (7)	0.3503 (5)	0.14 (1)
C-5^1	0.6672 (11)	0.6386 (8)	0.3752 (5)	0.13 (1)
C-6^1	0.7555 (16)	0.6679 (11)	0.3432 (6)	0.22 (2)
C-7^1	0.3017 (10)	0.6535 (10)	0.4243 (6)	0.16 (2)
C-8^1	0.7030 (24)	0.7870 (12)	0.2939 (9)	0.32 (2)
O-2^1	0.3927 (10)	0.6408 (5)	0.4400 (3)	0.16 (1)
O-3^1	0.4205 (7)	0.5583 (5)	0.3548 (3)	0.14 (1)
O-4^1	0.6148 (6)	0.5291 (5)	0.3336 (2)	0.120 (9)
O-5^1	0.6309 (9)	0.7062 (5)	0.3990 (3)	0.16 (1)
O-6^1	0.6985 (14)	0.7127 (10)	0.3048 (4)	0.31 (2)
C-1^2	0.6710 (13)	0.6269 (8)	0.6004 (5)	0.14 (1)
C-2^2	0.5665 (15)	0.6567 (9)	0.5883 (5)	0.16 (2)
C-3^2	0.5410 (13)	0.6340 (8)	0.5394 (4)	0.14 (1)
C-4^2	0.6235 (13)	0.6642 (9)	0.5073 (5)	0.14 (1)
C-5^2	0.7202 (13)	0.6264 (9)	0.5196 (4)	0.14 (1)
C-6^2	0.8053 (10)	0.6554 (10)	0.4901 (6)	0.16 (2)
C-7^2	0.4244 (18)	0.6747 (13)	0.6330 (7)	0.31 (2)
C-8^2	0.9643 (21)	0.6155 (16)	0.4686 (10)	0.32 (2)
O-2^2	0.5034 (9)	0.6248 (7)	0.6198 (3)	0.19 (1)
O-3^2	0.4539 (8)	0.6705 (6)	0.5301 (3)	0.17 (1)
O-4^2	0.5918 (7)	0.6351 (4)	0.4632 (3)	0.13 (1)
O-5^2	0.7374 (9)	0.6502 (5)	0.5665 (3)	0.16 (1)
O-6^2	0.8803 (11)	0.6039 (11)	0.4982 (5)	0.26 (2)
C-1^3	0.7704 (12)	0.3708 (6)	0.6827 (4)	0.13 (1)
C-2^3	0.6655 (9)	0.4011 (7)	0.6933 (5)	0.11 (1)
C-3^3	0.6365 (9)	0.4432 (8)	0.6510 (4)	0.12 (1)
C-4^3	0.7078 (11)	0.5074 (8)	0.6409 (4)	0.12 (1)
C-5^3	0.8055 (10)	0.4739 (7)	0.6315 (4)	0.12 (1)
C-6^3	0.8842 (11)	0.5315 (7)	0.6224 (4)	0.13 (1)
C-7^3	0.5507 (12)	0.3425 (9)	0.7422 (4)	0.17 (1)
C-8^3	0.9506 (12)	0.6509 (7)	0.6480 (5)	0.15 (1)
O-2^3	0.6111 (7)	0.3352 (5)	0.7019 (3)	0.14 (1)
O-3^3	0.5380 (7)	0.4770 (5)	0.6606 (3)	0.15 (1)
O-4^3	0.6693 (6)	0.5452 (4)	0.6004 (3)	0.12 (1)
O-5^3	0.8324 (6)	0.4319 (5)	0.6718 (2)	0.110 (9)
O-6^3	0.8750 (7)	0.5915 (5)	0.6558 (3)	0.13 (1)
C-1^4	0.8651 (8)	0.1091 (8)	0.6008 (4)	0.11 (1)
C-2^4	0.7925 (10)	0.1052 (7)	0.6358 (4)	0.12 (1)
C-3^4	0.7363 (10)	0.1840 (7)	0.6396 (4)	0.12 (1)
C-4^4	0.8206 (10)	0.2462 (7)	0.6488 (4)	0.12 (1)
C-5^4	0.8959 (9)	0.2472 (8)	0.6109 (4)	0.11 (1)
C-6^4	0.9745 (10)	0.2995 (10)	0.6231 (5)	0.16 (1)
C-7^4	0.6655 (12)	0.0106 (9)	0.6533 (5)	0.17 (2)
C-8^4	1.0254 (21)	0.3668 (12)	0.5604 (7)	0.27 (2)
O-2^4	0.7159 (7)	0.0512 (5)	0.6180 (3)	0.14 (1)
O-3^4	0.6731 (6)	0.1823 (5)	0.6779 (3)	0.125 (9)

Table 1 (continued)

Atom	x / a	y / b	z / c	U_{eq} (Å^2)
O-4^4	0.7664 (6)	0.3186 (4)	0.6450 (2)	0.112 (9)
O-5^4	0.9360 (6)	0.1669 (6)	0.6117 (2)	0.119 (9)
O-6^4	1.0376 (10)	0.3069 (8)	0.5836 (6)	0.25 (2)
C-1^5	0.8680 (9)	0.0520 (7)	0.4236 (5)	0.11 (1)
C-2^5	0.8016 (9)	0.0066 (7)	0.4541 (4)	0.12 (1)
C-3^5	0.7698 (10)	0.0541 (8)	0.4947 (4)	0.12 (1)
C-4^5	0.8613 (8)	0.0717 (7)	0.5205 (4)	0.10 (1)
C-5^5	0.9360 (9)	0.1192 (7)	0.4905 (4)	0.11 (1)
C-6^5	1.0252 (8)	0.1347 (8)	0.5131 (4)	0.11 (1)
C-7^5	0.6712 (13)	−0.0826 (9)	0.4326 (7)	0.21 (2)
C-8^{5}a [a]	1.1552 (11)	0.0852 (12)	0.5561 (7)	0.16 (2)
C-8^{5}b [a]	1.1862 (39)	0.1365 (44)	0.5057 (26)	0.18 (1)
O-2^5	0.7116 (8)	−0.0102 (6)	0.4255 (3)	0.16 (1)
O-3^5	0.7029 (6)	0.0101 (5)	0.5236 (3)	0.13 (1)
O-4^5	0.8307 (5)	0.1219 (4)	0.5572 (3)	0.102 (8)
O-5^5	0.9510 (6)	0.0713 (5)	0.4511(3)	0.110 (9)
O-6^{5}a [a]	1.0672 (8)	0.0692 (6)	0.5322 (4)	0.13 (1)
O-6^{5}b [a]	1.0998 (22)	0.1664 (21)	0.4855 (11)	0.123 (9)
C-1^6	0.8116 (9)	0.2545 (8)	0.2916 (4)	0.12 (1)
C-2^6	0.7724 (13)	0.1701 (8)	0.2915 (5)	0.16 (1)
C-3^6	0.7438 (12)	0.1419 (7)	0.3409 (4)	0.14 (1)
C-4^6	0.8465 (9)	0.1477 (8)	0.3659 (4)	0.11 (1)
C-5^6	0.8677 (8)	0.2345 (7)	0.3690 (4)	0.10 (1)
C-6^6	0.9702 (10)	0.2481 (9)	0.3926 (5)	0.15 (1)
C-7^6	0.6832 (15)	0.1707 (12)	0.2218 (5)	0.22 (2)
C-8^6	0.9999 (15)	0.3587 (13)	0.4378 (7)	0.24 (2)
O-2^6	0.6751 (9)	0.1710 (6)	0.2684 (3)	0.19 (1)
O-3^6	0.7232 (9)	0.0604 (6)	0.3364 (3)	0.20 (1)
O-4^6	0.8243 (5)	0.1213 (4)	0.4109 (2)	0.102 (8)
O-5^6	0.8859 (6)	0.2565 (5)	0.3213 (3)	0.119 (9)
O-6^6	0.9705 (13)	0.3262 (10)	0.4060 (6)	0.30 (2)
C-1^7	0.6372 (10)	0.5224 (8)	0.2863 (4)	0.12 (1)
C-2^7	0.5728 (11)	0.4570 (8)	0.2680 (4)	0.13 (1)
C-3^7	0.6038 (9)	0.3802 (8)	0.2901 (4)	0.12 (1)
C-4^7	0.7119 (10)	0.3724 (8)	0.2870 (4)	0.13 (1)
C-5^7	0.7731 (10)	0.4371 (7)	0.3070 (4)	0.12 (1)
C-6^7	0.8757 (9)	0.4377 (10)	0.3021 (5)	0.15 (1)
C-7^7	0.4158 (12)	0.4873 (11)	0.2357 (5)	0.20 (2)
C-8^7	1.0064 (10)	0.4105 (14)	0.2493 (6)	0.22 (1)
O-2^7	0.4756 (7)	0.4735 (6)	0.2758 (3)	0.14 (1)
O-3^7	0.5523 (7)	0.3187 (5)	0.2663 (3)	0.15 (1)
O-4^7	0.7338 (6)	0.3015 (5)	0.3103 (2)	0.122 (9)
O-5^7	0.7374 (7)	0.5061 (5)	0.2830 (3)	0.125 (9)
O-6^7	0.8999 (9)	0.4159 (7)	0.2558 (3)	0.19 (1)

[a] Occupancies of sites O-6^{5}a, C-8^{5}a are 0.80, and of O-6^{5}b, C-8^{5}b are 0.20.

angle. This is associated with the longest O-2 $\cdots$ O-3^{n+1} separation in the molecule, indicating the weakest O-2 $\cdots$ H–O-3^{n+1} hydrogen bond for residue **6**.

The O-2–C-7 groups of all residues are oriented away from the molecular axis, Fig.

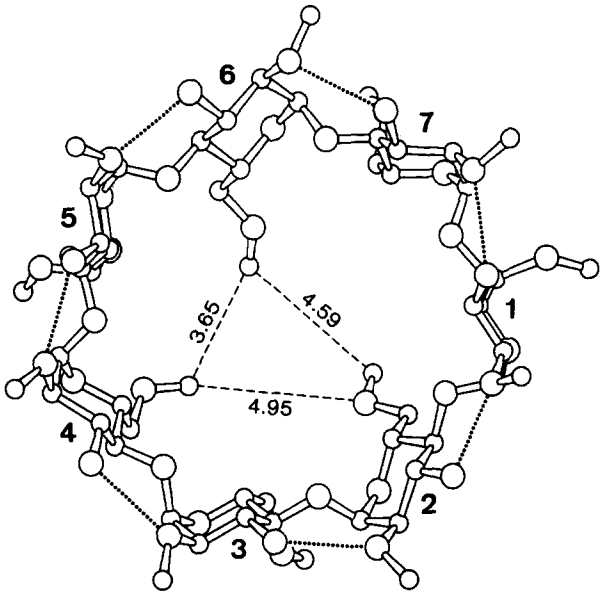


Fig. 1. The heptakis-(2,6-di-*O*-methyl)cyclomaltoheptaose (DIMEB) molecule in projection on the O-4 least-squares plane. Dotted lines show O · · · O distances indicative of hydrogen bonds, dashed lines show van der Waals contacts between the O-6–C-8 groups.

Table 2
Geometric parameters of the per-*O*-2,6-methyl-β-cyclodextrin molecule

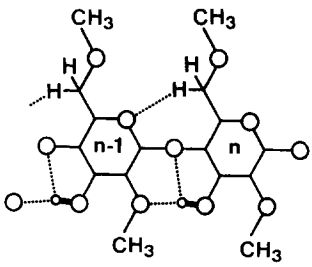
Residue/parameter	1	2	3	4	5	6	7
O-3^n · · · O-2^{n-1} (Å)	2.87 (1)	2.85 (1)	2.89 (2)	2.89 (1)	2.89 (1)	2.92 (1)	3.08 (1)
Tilt angle [a] (deg)	−5.9	19.6	9.7	13.6	5.4	30.5	12.8
QT [b] (Å)	0.60 (2)	0.60 (2)	0.62 (1)	0.64 (1)	0.62 (1)	0.69 (1)	0.56 (1)
θ_2 [c] (deg)	2 (1)	8 (2)	3 (1)	3 (1)	4 (1)	13 (1)	3 (2)

[a] Deviation of the least-squares plane through C1–C2–C3–C4–C5–O5 from being perpendicular to the least-squares plane through the O-4 atoms; positive and negative signs denote tilt of the O-6 side towards and away from the molecular axis, respectively.
[b] Puckering amplitude [16].
[c] θ_2 measures the deviation from ideal chair conformation [16] (ideal value: $\theta_2 = 0°$).

Table 3
Geometry of the intramolecular C-6^n–H · · · O-5^{n-1} contacts (for ideal H-positions with C–H = 1.09 Å)

Residue	1	2	3	4	5	6	7
C-6 · · · O-5^{n-1} (Å)	3.34 (2)	3.72 (2)	3.34 (2)	3.36 (2)	3.22 (2)	3.54 (2)	3.21 (2)
H-6 · · · O-5^{n-1} (Å)	2.54	2.84	2.61	2.36	2.38 [a]	2.61	2.47
Angle at H-6 (deg)	130	138	123	151	133 [a]	144	124

[a] Values for the minor site O-6^{5}b–C-8^{5}b (occupancy = 0.20): H-6^5 · · · O-5^4 = 2.36 Å; angle at H = 134°.



1

Scheme 1.

Table 4
Selection of torsion angles (deg)

Residue	1	2	3	4	5	6	7
O-5–C-5–C-6–O-6	−73 (1)	79 (2)	−73 (1)	76 (1)	−66 (1) [a]	87 (1)	−74 (1)
C-4–C-5–C-6–O-6	44 (2)	−167 (1)	44.5 (2)	−172 (1)	51 (1) [a]	−163 (2)	43 (2)
C-5–C-6–O-6–C-8	118 (2)	172 (2)	−179 (1)	100 (2)	−178 (1) [a]	142 (2)	−176 (1)
C-1–C-2–O-2–C-7	142 (1)	144 (1)	134 (1)	151 (1)	143 (1)	81 (1)	114 (1)
C-3–C-4–O-4–C-1′	140 (1)	106 (1)	137 (1)	124 (1)	135 (1)	114 (1)	143 (1)
C-4–O-4–C-1′–O-5′	118 (1)	103 (1)	113 (1)	104 (1)	106 (1)	100 (1)	112 (1)

[a] Values for site O-6^{5}b–C-8^{5}b with occupancy 0.20: O-5–C-5–C-6–O-6 = 54 (2)°, C-4–C-5–C-6–O-6 = 171 (2)°, C-5–C-6–O-6–C-8 = −148 (3)°.

1. For the very flexible C-6–O-6–C-8 groups, however, there are considerable variations, Fig. 1 and Table 4. For residues **1**, **3**, **5** and **7**, these groups point away from the molecular axis, whereas for residues **2**, **4** and **6**, they point "inward". The latter three glucoses are those with the largest tilt angles, Table 2. This way, by combination of large tilt angles and the "inward" orientation of C-6–O-6–C-8 of three glucoses, the O-6 side of the cyclodextrin cavity is closed; note that the the relevant terminal groups are within van der Waals distance, Fig. 1. The appearance of the molecule is therefore not "torus"- but "bowl"-shaped, and the volume of the cavity is significantly reduced compared to the "normal" conformation in which the O-6–C-8 groups would be turned to the outside.

Crystal packing.—In the crystal lattice, the DIMEB molecules are stacked in columns along the 2_1 screw-axis parallel *a*, Fig. 2. These columns, however, are not like a roll of coins (which are a more typical motif of cyclodextrin packing [17]). The O-4–centroids of adjacent molecules are laterally shifted by 4.36 Å with respect to each other, and the O-4 least-squares planes of adjacent molecules form dihedral angles of 39.6°. In the direction of the column axis, the stacking squence is only 6.91 Å. This is significantly shorter than the height of the molecules, ~ 10 Å (native β-cyclodextrin: ~ 8 Å), because a part of the O-6–C-8 rim of one molecule is inserted into the cavity of the next molecule by self-inclusion. In particular, C-6^5–O-6^5–C-8^5 intrudes deeply into the neighboring cavity, where it experiences little steric restrictions, and O-6^5–C-8^5 is

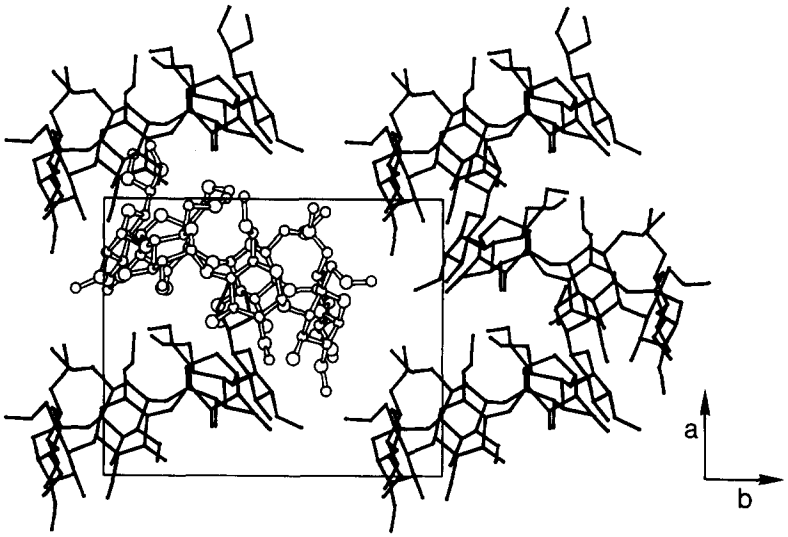


Fig. 2. Crystal packing in a projection on the $a-b$-plane. For clarity, one molecule is drawn with open bonds. Note that C-6^5–O-6^5–C-8^5 is two-fold disordered and intrudes into the cavity of a neighboring molecule.

disordered over at least two alternative sites, Fig. 2. The columns are aligned in a quasi-hexagonal close packing, Fig. 3.

The general packing features are similar to those in some crystalline complexes of DIMEB, such as DIMEB · *p*-iodophenol · $2H_2O$ [7]. There, however, the stacking sequence along the columns is longer, 7.40 Å, and the O-6 side of the DIMEB cavity is not closed by O-6–C-8 groups oriented "inward". In consequence, the cavity volume is larger, and two water molecules are included. The substrate molecule *p*-iodophenol is co-crystallized between the DIMEB-columns, which are separated in the *b*-direction compared to the present structure.

C–H · · · O hydrogen bonds.—The DIMEB molecule carries seven O–H hydrogen bond donors, but 35 O acceptors. This implies that only a fraction of the O acceptor potentials can be fully satisfied, and suggests that numerous C–H · · · O interactions are formed as a result [18]. In fact, all O-2 and O-4 atoms can accept intramolecular hydrogen bonds from O-3–H (**1**), but for none of the other O atoms, there is a potential O–H donor in the vicinity of 3.5 Å. If C–H groups are considered as weak hydrogen bond donors, the O-5 atoms are systematically engaged in intramolecular interactions C-6^n–H · · · O-5^{n-1} (**1**), and a number of O-2, O-3 and O-6 atoms form intermolecular contacts to C–H which are indicative of weak hydrogen bonding, Table 5 (for the methyl donors C-7–H_3 and C–8-H_3, theoretical H-positions cannot be reasonably calculated, so that for these, Table 5 must be restricted to C · · · O separations). Notably, most of these interactions are accepted by the O-3–H groups, which are stronger acceptors than the ether-type O-atoms O-2 and O-6. These observations suggest that, apart from van der Waals interactions, C–H · · · O bonding significantly contributes to the crystal cohesion in anhydrous DIMEB.

Is the structure really anhydrous?—Since the quality of the data is limited, the

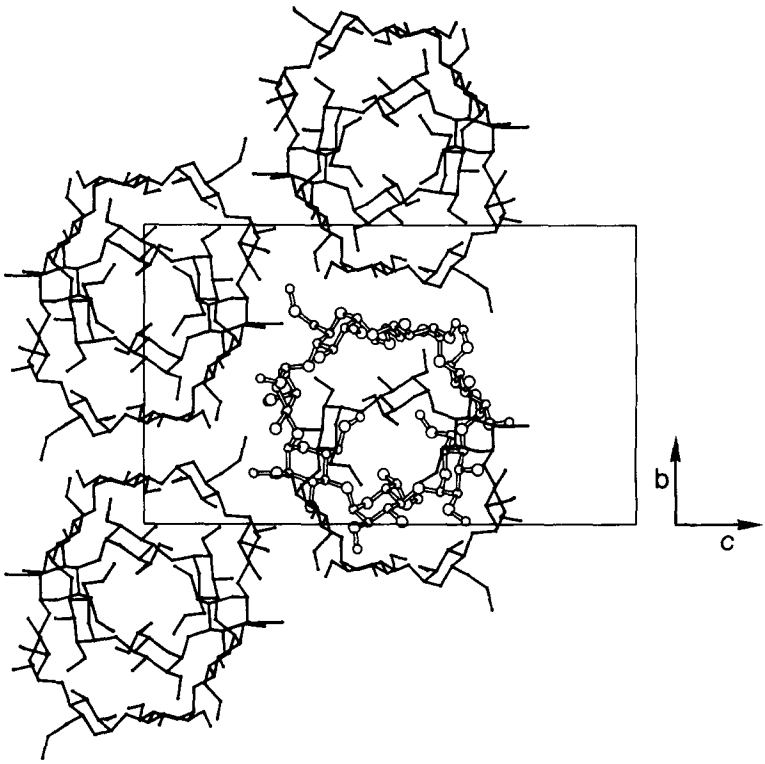


Fig. 3. Crystal packing in a projection on the $b-c$-plane. For clarity, one molecule is drawn with open bonds.

Table 5
Geometry of intermolecular C–H · · · O interactions with H · · · O < 2.8 Å, for calculated H-positions with C–H = 1.09 Å. For methyl donors (C-7 H_3, C-8 H_3), only C · · · O distances < 3.5 Å are given

Contact	H · · · O (Å)	C · · · O (Å)	Angle at H (deg)	Symm.
O-2 acceptors				
C-6^6–H · · · O-2^3	2.69	3.70	154	$x+0.5, 0.5-y, 1-z$
C-7^7 · · · O-2^6		3.44		$1-x, y+0.5, 0.5-z$
O-3 acceptors				
C-1^4–H · · · O-3^1	2.36	3.29	142	$x+0.5, 0.5-y, 1-z$
C-7^6 · · · O-3^1		3.32		$1-x, y-0.5, 0.5-z$
C-2^5–H · · · O-3^2	2.72	3.77	161	$x+0.5, 0.5-y, 1-z$
C-1^5–H · · · O-3^3	2.64	3.46	132	$x+0.5, 0.5-y, 1-z$
C-4^6–H · · · O-3^3	2.47	3.51	160	$x+0.5, 0.5-y, 1-z$
C-8^7 · · · O-3^3		3.34		$1.5-x, 1-y, z-0.5$
C-7^7 · · · O-3^6		3.14		$1-x, y+0.5, 0.5-z$
O-6 acceptors				
C-2^7–H · · · O-6^3	2.44	3.50	165	$1.5-x, 1-y, z-0.5$
C-3^6–H · · · O-6^4	2.71	3.73	156	$x-0.5, 0.5-y, 1-z$
C-3^1–H · · · O-6^5a	2.70	3.79	177	$x-0.5, 0.5-y, 1-z$

question may arise whether the structure is really anhydrous or whether some water sites have just not become apparent in the difference Fourier maps. The maximum residual electron density of 0.27 $Å^3$ is typical for fully refined structures and does not suggest any major omissions of atoms. If there are actually some water sites present in the structure, they can only be spuriously populated or be very "diffuse" in nature.

The high solubility in cold water remains unexplained.—In the present crystal structure, DIMEB is found crystallized as anhydrate from hot water. All hydroxyl groups are engaged in intramolecular hydrogen bonding, so that the intermolecular environment is hydrophobic. The high solubility in cold water and the negative temperature effect of the solubility remain an open question. These fascinating phenomena deserve further investigation.

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