Crystal structure of a new cyclomaltoheptaose hydrate: β-cyclodextrin·7.5H$_2$O

Jian-Ye Li, Dao-Feng Sun, Ai-You Hao *, Hong-Yuan Sun, Jian Shen

School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, PR China

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ABSTRACT

The crystallographic study of a partially hydrated form of cyclomaltoheptaose (β-cyclodextrin, βCD) is reported. $C_{42}H_{70}O_{35}\cdot7.5H_2O$; space group $P2_1$ with unit cell constants $a = 15.1667(5)$, $b = 10.1850(3)$, $c = 20.9694(7)$ Å, $\beta = 110.993(2)°$; final discrepancy index $R = 0.0760$ for the 6181 observed reflections and 784 refined parameters. One water molecule is included in the cavity and distributed over two partially occupied positions, the other 6.5 waters distributed over eight positions are located as space-filler between the macrocycles. The crystal structure belongs to the cage-type, like that observed in Form I (βCD·12H$_2$O; Lindner, K; Saenger, W. *Carbohydr. Res.* **1982**, *99*, 103–115) and Form II (βCD·11H$_2$O; Betzel, C., et al. *J. Am. Chem. Soc.*, **1984**, *106*, 7545–7567).

1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are a series of doughnut-shaped cyclic oligosaccharides, mostly composed of 6, 7, and 8 glucose units named α, β, and γCD, respectively. They are amphiphilic with a hydrophobic cavity and hydrophilic rims. The particular structure of CDs allows various guest molecules to be included to form inclusion complexes, and this beneficial property has been applied in many industries, for example, foods, pharmaceutics, and agriculture.[1,2] The increasing interest in CDs' complexes stimulates more and more research with different techniques. In particular, the crystallographic study can be helpful to clarify inclusion phenomena, this approach being able to give a clear picture of non-covalent interactions between CDs and guest molecules because of its high resolution (<1 Å).[3,4]

Two isomorphous crystalline modifications of 'empty' cyclomaltoheptaose (βCD) hydrate, that is, the species occurring in an aqueous solution without added guest molecule, Form I (βCD·12H$_2$O)[5] and Form II (βCD·11H$_2$O),[6] have already been described. In Form I, 6.5 water molecules are distributed statistically over eight sites in the cavity, the remaining 5.5 water molecules occupying eight sites between symmetry-related βCD molecules. In Form II, the 11 water molecules are distributed over 16 positions, 8 in the cavity of βCD (6.13 water molecules) and 8 in interstices (4.88 water molecules), cavity water molecules form only 2 hydrogen bonds to enclosing βCD and 6 contacts to neighboring βCD. For cyclodextrins, different crystal forms of the same complex are sometimes obtained under different crystallization conditions.[7]

We tested different solvents trying to obtain different βCD crystal forms and to explain the effect of the solvents with the inclusion behaviors of βCD. During this study, a new crystal modification of βCD (βCD·7.5H$_2$O) was obtained from a mineral water, and named Form III. In this new CD hydrate, one water molecule is included in the cavity and distributed over two partially occupied positions, the other 6.5 water molecules, distributed over eight positions, are located as space-filler between the macrocycles.

2. Experimental

2.1. Crystallization and X-ray diffraction

βCD was purchased from Guangdong Yunan Chemical Reagent Co. Ltd, China, recrystallized twice from distilled water and dried at 100 °C in vacuum for 12 h. Mineral water (composition, mg/L: Na$^+$, 11.0; K$^+$, 1.5; HCO$_3^-$, 175, Li$^+$, 1.32; Sr^{2+}, 2.69; Zn^{2+}, 0.41; Br$^-$, 1.6; I$^-$, 0.33; HSiO$_3^-$, 28.6; Se, 0.027; As, 0.018; F$^-$, 1.60; NO$_3^-$, 39.0) was purchased from Yinxinyuan Co. Ltd, China. The dried βCD (0.2 mmol) was directly dissolved in mineral water (4 mL) at 60 °C and was stirred for 1 h, then cooled down slowly. The resulting suspension was filtered and the white powder was air dried. Recrystallization of the white powder in mineral water afforded colorless prismatic crystals within 1 week.

A single crystal of βCD hydrate with dimensions 0.2 × 0.2 × 0.15 mm^3 was mounted in a glass capillary sealed at both ends with a trace of mother liquor. X-ray data collection was performed at room temperature using a SMART CCD diffractometer (Bruker) with Mo Kα radiation ($\lambda = 0.71073$ Å) operating at 50 kV, 30 mA. A total of 23,984 reflections were measured in θ range of 1.04–26.49° (0.7 Å resolution). Data were corrected for Lorentz polarization, and absorption effects and merged by

* Corresponding author. Tel.: +86 053188363306.
E-mail address: haoay@sdu.edu.cn (A.-Y. Hao).

SHELXL-97[8] to yield 11,532 unique reflections. The crystal belongs to the monoclinic space group $P2_1$ (for more details, see Table 1).

2.2. Structure determination and refinement

The crystal structure was determined by direct methods with the program SHELXS-97,[8] developed by difference Fourier techniques, and refined by full-matrix least-squares on F^2.[9] After the 784 atomic parameters (atomic coordinates and anisotropic temperature factors) were refined against 11,532 data with $I > 2\sigma(I)$, the R factor converged at 0.0760. U_{eq} was defined as one third of the trace of the orthogonalized U_{ij} tensor. All atoms show normal thermal motion with U_{eq} in the range 0.04–0.15 Å^2, except for most water molecules that have higher U_{eq}, 0.10–0.66 Å^2. One water molecule occupying two sites is included in the cavity, the remaining 6.5 molecules are distributed over eight positions and located as space-filler between the macrocycles with an extensive hydrogen bonded network between themselves as well as with the hydroxyl oxygen atoms of βCD.

3. Results and discussion

3.1. General

A summary of crystallographic data and final fractional atomic coordinates and equivalent isotropic displacement parameters are given in Table 1 and Supplementary data, respectively. The geometrical parameters were calculated using SHELXS-97. The atomic numbering scheme is that used conventionally for carbohydrates, that is, the first number denotes the position in the glucose residue and the second number the glucose residue number in the CD macrocycle; for instance C-46 denotes C-4 of glucose residue 6 (Fig. 1).

The calculated density $D_{calcd} = 1.395$ g/cm^3 is appreciably lower than Form I (1.453 g/cm^3)[5] and Form II (1.462 g/cm^3).[6]

Table 1
Crystallographic data

|	
Empirical formula	$C_{42}H_{85}O_{42}$
Formula weight	1315.14
Crystal form, color	Block, colorless
Crystal size (mm^3)	0.2 × 0.2 × 0.15
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2(1)$
a (Å)	15.1667(5)
b (Å)	10.1850(3)
c (Å)	20.9694 (7)
β (°)	110.993(2)
Volume (Å^3)	3024.20(17)
Z	2
D_{calcd} (g/cm^{-3})	1.395
Absorption coefficient (mm^{-1})	0.132
$F(0\,0\,0)$	1404.0
θ range for data collection (°)	1.04–26.49
Index ranges	$-18 < h < 14$, $-12 < k < 12$, $-26 < l < 26$
Reflections collected	23,984
Independent reflections	11,532[R(int) = 0.0427]
Reflections observed (>2σ)	6181
Data/restraints/parameters	11,532/1/784
Data completeness (θ = 26.49)	0.993
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.967
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0760$, $wR_2 = 0.1870$
R (all data)	$R_1 = 0.1438$, $wR_2 = 0.2335$
Absolute structure parameter	0.7(15)
Largest diff. peak and hole (e Å^{-3})	0.881 and −0.496
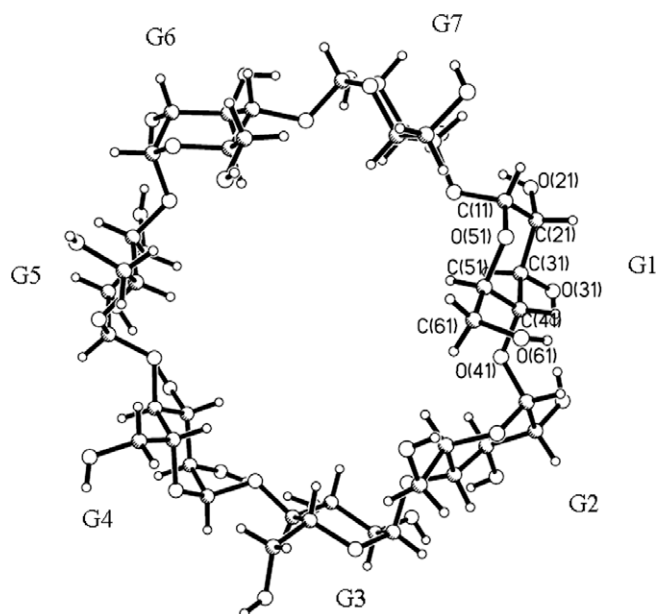
Figure 1. Structure and numbering of the βCD molecule in projection on the O-4 least-squares plane.

### 3.2. Structural description of βCD macrocycles

Figure 1 shows a perspective view of the final crystallographic model of the structure. All glucose residues are in the $^4C_1$ chair conformation. When comparing average values of bond lengths and angles with average values stated for Form I,[5] Form II,[6] and αCD,[10] no significant differences between glucose units are found. The overall mean C–C and C–O distances in Form III (1.524, 1.420 Å) are especially in agreement with Form I (1.523, 1.426 Å), while in Form II (1,517, 1.417 Å) these distances are slightly shorter than Form I and Form III. The C-5-O-5 mean bond lengths of 1.440(8) Å are larger than the overall mean C-O distance of 1.424 Å, each of the mean C-1-O-4 and C-1-O-5 bonds is approximately 0.013 Å shorter than the above-mentioned mean value. These differences are similar to those found in other diffraction studies involving glucopyranose rings. As in the other cyclodextrin structures, the C–C and C–O bond lengths are specifically dependent upon the chemical nature of the atoms involved.[10] The possible exception is the glucosidic angle C-3$_n$–C-4$_n$–C-5$_n$ (111.4 ± 1.6°), C-4$_n$–O-4$_n$–C-1$_{n-1}$ (113.2 ± 4.3°), which appears to be slightly smaller than for the average Form I structure (110.7 ± 1.3°, 117.7 ± 1.0°).

Torsion angles, as stated in Table 2, are by no means unusual if compared to the values found for Form I structures. Five C-6-O-6 bonds point 'away' from the center of the ring with torsion angles O-5$_n$-C-5$_n$-C-6$_n$-O-6$_n$ corresponding to (−)gauche, while one is twofold disordered over (−)gauche and (+)gauche. θ torsion angles (θ = O-4$_n$···C-1$_n$-O-4$_{n+1}$–C-4$_{n+1}$) in Form I and Form III are similar (168.9 ± 6.0 and 168.7 ± 1.9°, respectively), but ψ torsion angle (ψ = C-1$_n$–O-4$_{n+1}$-C-4$_{n+1}$···O-4$_{n+2}$) average −171.1 ± 8.4° in Form I belonging to glucose residues 2 of Form III is 174.6° (Fig. 2), this value has not been reported previously in hydrated CDs.

The O-4$_n$ atoms are almost co-planar, with the largest displacement from the average plane observed for O-44 and O-54 atoms (−0.2699 and 0.1998 Å, respectively). The mean distance of O-4$_n$···O-4$_{n+1}$, O-4$_n$···O-4$_{n+2}$, O-4$_n$···O-4$_{n+3}$ is 4.373 ± 0.110, 7.871 ± 0.228, 9.807 ± 0.296 Å, respectively. The O-4$_{n-1}$···O-4$_n$···O-4$_{n+1}$ angles range from 124.22° to 133.64° (128.34 ± 3.50 Å), corresponding to 128.57° for an ideal heptagon. Overall, the geometrical parameters indicate that there is no significant deviation of the βCD molecule compared to Form I.

Table 2
Selected torsion angles

Torsion angle (°)	D-Glucosyl residue								
	1	2	3	4	5	6	7	Mean	σ
$C\text{-}1_n\text{–}C\text{-}2_n\text{–}C\text{-}3_n\text{–}C\text{-}4_n$	−49.6	−53.5	−54.0	−54.4	−55.8	−53.0	−52.6	−53.3	1.9
$C\text{-}2_n\text{–}C\text{-}3_n\text{–}C\text{-}4_n\text{–}C\text{-}5_n$	54.1	51.9	51.0	58.1	56.9	50.3	53.4	53.7	2.9
$C\text{-}3_n\text{–}C\text{-}4_n\text{–}C\text{-}5_n\text{–}O\text{-}5_n$	−61.0	−53.1	−50.3	−60.3	−56.7	−49.6	−56.8	−55.4	4.5
$C\text{-}4_n\text{–}C\text{-}5_n\text{–}O\text{-}5_n\text{–}C\text{-}1_n$	64.7	57.4	56.6	61.9	60.4	54.3	63.7	59.8	3.9
$C\text{-}5_n\text{–}O\text{-}5_n\text{–}C\text{-}1_n\text{–}C\text{-}2_n$	−60.4	−60.6	−61.2	−58.4	−61.0	−59.7	−63.0	−60.6	1.4
$O\text{-}5_n\text{–}C\text{-}1_n\text{–}C\text{-}2_n\text{–}C\text{-}3_n$	51.5	57.4	58.4	55.0	56.9	57.8	56.1	56.2	2.3
$O\text{-}5_n\text{–}C\text{-}5_n\text{–}C\text{-}6_n\text{–}O\text{-}6_n$	−66.6	−64.7	61.9	70.2	−60.8	−61.5	80.9	−	−
$O\text{-}2_n\text{–}C\text{-}2_n\text{–}C\text{-}3_n\text{–}O\text{-}3_n$	64.0	65.3	61.2	58.1	62.9	60.8	66.3	62.6	2.8
$C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}\text{–}C\text{-}3_{n+1}$	139.0	113.6	130.1	130.0	128.0	118.2	134.8	127.7	8.9
$O\text{-}5_n\text{–}C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}$	115.7	103.0	117.5	112.2	107.8	103.2	108.0	109.6	5.7
$C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}\text{–}C\text{-}5_{n+1}$	−99.3	−122.5	−110.6	−108.9	−108.6	−121.4	−105.7	−111.0	8.3
$C\text{-}2_n\text{–}C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}$	−121.3	−135.8	−122.4	−125.8	−132.5	−135.1	−132.2	−129.3	6.0
$O\text{-}4_n\cdots C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}$ (θ)	175.8	162.5	176.0	172.3	166.0	162.4	166.0	168.7	1.9
$C\text{-}1_n\text{–}O\text{-}4_{n+1}\text{–}C\text{-}4_{n+1}\cdots O\text{-}4_{n+2}$ (ψ)	−160.2	174.6	−169.1	−169.3	−170.5	−179.6	−162.7	−	−
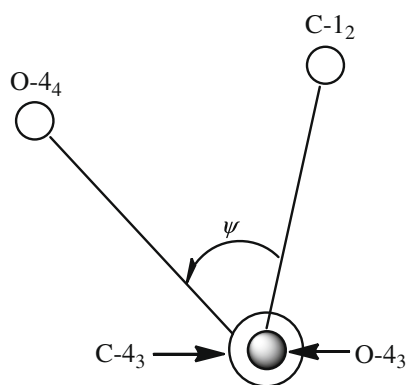
Figure 2. The schematic diagram of ψ torsion angle.

3.3. Hydrogen bonding

The geometrical details of hydrogen bonds are given in Table 3. Criteria to define D–H⋯A interactions are according to the literature.[11–13] The O-2 and O-3 atoms of all neighboring glucoses are within hydrogen bonding distance: this indicates a ring of $O\text{-}2_n\text{–}H\cdots O\text{-}3_{n+1}$ hydrogen bonds stabilizing the molecular conformation. The involved O-2⋯O-3 intramolecular distances are in the range 2.752–3.027 Å. There are six intramolecular O-3–H⋯O-2 and five O-2–H⋯O-3 hydrogen bonds associated with a minor bonding interaction to the O-4 atom, with H⋯O-4 separations around 2.27–2.52 Å. It is assumed that these O-3–H⋯O-2 hydrogen bonds are also of the three-center type with a minor component accepted by O-4.[13]

In addition, there are much weaker systematic intramolecular C–H⋯O contacts, $C\text{-}6_n\text{–}H\cdots O\text{-}5_{n-1}$, $C\text{-}5_n\text{–}H\cdots O\text{-}4_{n+1}$, $C\text{-}4_n\text{–}H\cdots O\text{-}5_n$, with H⋯O around 2.41–2.59 Å, which is in the range of the weak C–H⋯O hydrogen bonds.[13,14] These contacts have also significant stabilizing function.

3.4. Water of hydration and crystal packing

The number of water molecules contained in the crystals of cyclodextrin hydrates increases with the ring size,[6] so that chemical compositions αCD·6H₂O,[14,15] αCD·7.57H₂O,[10] αCD·11H₂O,[16] βCD·11H₂O,[6] βCD·12H₂O,[5] and γCD·13.3H₂O[3] are observed. In the present work, there are 7.5 water molecules contained in Form III. It could be found, from the full difference electron density maps (Fig. 3) of the crystals, that only one water molecule (O-W-9, O-W-9′, occupancy factor, 0.60 and 0.40, respectively) is included in the

Table 3
Hydrogen-bonding geometry

Donor⋯H⋯Acceptor	D⋯A (Å)	H⋯A (Å)	D–H⋯A (°)	Symmetry code
O-27–H⋯O-13	3.013(8)	2.20	169	
O-27–H⋯O-14	2.762(6)	2.32	114	
O-24–H⋯O-35	2.839(8)	2.03	167	
O-24–H⋯O-55	2.788(7)	2.36	113	
O-62–H⋯O-51	2.778(8)	2.38	111	
O-35–H⋯O-24	2.839(8)	2.02	172	
O-35–H⋯O-54	2.834(7)	2.43	111	
O-31–H⋯O-27	3.013(8)	2.20	174	
O-31–H⋯O-41	2.807(8)	2.40	112	
O-43–H⋯O-32	2.805(8)	1.99	170	
O-43–H⋯O-44	2.826(7)	2.43	111	
O-32–H⋯O-43	2.805(8)	2.00	168	
O-32–H⋯O-43	2.817(7)	2.40	112	
O-61–H⋯O-W-1	2.860(15)	2.04	176	x, 1+y, z
O-63–H⋯O-W-7	3.07(2)	2.30	156	
O-33–H⋯O-22	2.856(7)	2.04	178	
O-33–H⋯O-34	2.862(7)	2.54	105	
O-62–H⋯O-65	2.898(9)	2.10	164	x, 1+y, z
O-65–H⋯O-W-5	2.761(9)	2.01	153	−1+x, y, z
O-25–H⋯O-W-6	2.710(7)	1.90	170	x, −1+y, z
O-64–H⋯O-W-2	2.825(9)	2.02	166	1−x, −1/2+y, −z
O-21–H⋯O-W-6	2.835(7)	2.03	166	1−x, −1/2+y, 1−z
O-37–H⋯O-W-1	2.796(10)	2.04	153	1−x, 1/2+y, 1−z
O-66–H⋯O-W-3	2.792(8)	2.00	162	−1+x, −1+y, z
O-22–H⋯O-W-3	2.711(9)	1.89	173	x, −1+y, z
O-36–H⋯O-32	2.756(6)	1.96	163	1−x, 1/2+y, 1−z
O-32--H⋯O-36	2.756(6)	1.95	166	1−x, −1/2+y, 1−z
O-26–H⋯O-W-6	2.834(7)	2.02	175	−x, −1/2+y, 1−z
C-67–H⋯O-56	3.410(13)	2.57	131	
C-51–H⋯O-42	2.824(9)	2.41	105	
C-34–H⋯O-67	3.169(18)	2.57	119	x, −1+y, z
C-66–H⋯O-24	3.402(9)	2.53	150	x, 1+y, z
C-66–H⋯O-35	3.302(8)	2.49	141	x, 1+y, z
C-66–H⋯O-55	3.420(9)	2.59	143	
C-42–H⋯O-62	2.889(9)	2.49	104	
C-42–H⋯O-55	3.502(8)	2.55	164	1+x, y, z
C-54–H⋯O-45	2.851(8)	2.51	100	
C-15–H⋯O-21	3.513(8)	2.54	172	−1+x, y, z
C-46–H⋯O-56	2.932(8)	2.53	104	

cavity, the other 6.5 water molecules are distributed over 8 sites and located as space-filler between the macrocycles, with four oxygen atoms (O-W-1, O-W-2, O-W-3, and O-W-4) fully occupied and the others (O-W-5, O-W-6, O-W-7, and O-W-8) in the range 0.45–0.80. It is known that the number of water molecules in the CD crystals is largely dependent on crystallization and history of the crystals. Since βCD·7.5H₂O was obtained from mineral water, we suggest that ions in mineral water would be involved in crystallization.
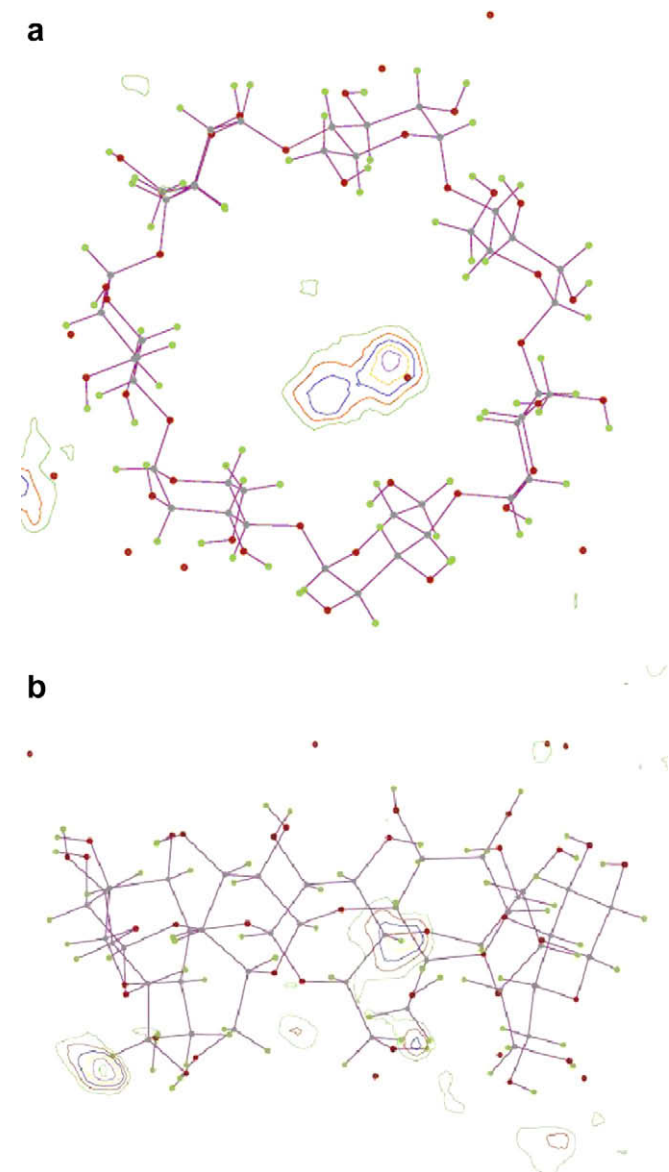
a

b

Figure 3. Difference electron density of the crystals in the βCD cavity ((a) on the O-4 plane; (b) rotated 90° sigma level, 1).
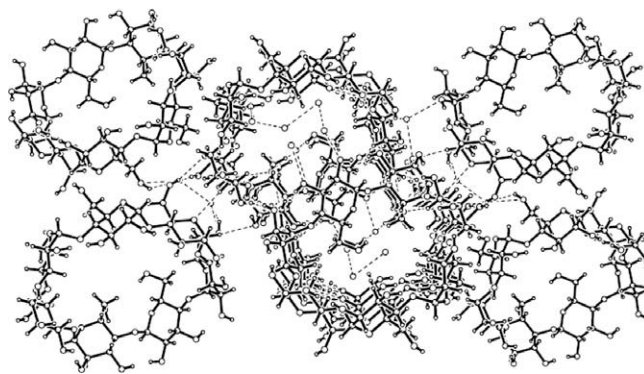

Figure 4. βCD molecular packing projected onto the *ac* plane.

the hydrates carry common features: (i) the crystal structures are isomorphous, belonging to the same group $P2_1$; (ii) the conformation of the βCD macrocycle is stabilized by systematic intramolecular O-2···O-3 hydrogen bonds between neighboring glucose units, existing in an open, round state, with the heptagon formed by seven O-4 atoms being very regular; (iii) in the crystal lattice, the βCD molecules are stacked in a herringbone pattern, different numbers of water molecules are located as space-filler between the macrocycles. In Form III, one water molecule is included in the cavity, and the other 6.5 water molecules are distributed over eight positions and located as space-filler between the macrocycles.

Supplementary data

Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with CCDC No. 703074. 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). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.12.016.

The βCD·7.5H$_2$O arrangement is in cage-type mode, like frequently observed in the other hydrated αCD,[13,14] βCD,[5] and γCD.[3] βCD forms a herringbone pattern along the twofold screw axis, as shown in Figure 4. Both sides of each macrocycle cavity are blocked by glucose residues of neighboring molecules. The intermolecular hydrogen bonds between the adjacent βCD and water molecules, C–H···O bonding significantly contributes to the crystal cohesion in βCD·7.5H$_2$O.

4. Conclusion

This paper reports on the third crystal structure of a native βCD. In both previously described structures,[5,6] and in the present one,

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