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Crystal form III of β-cyclodextrin–ethanol inclusion complex: layer-type structure with dimeric motif

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ABSTRACT

The crystal form **III** of the β-cyclodextrin (β-CD)–ethanol inclusion complex [2($C_6H_{10}O_5$)$_7$·1.5-C_2H_5OH·19H_2O] belongs to the triclinic space group *P*1 with unit cell constants: *a* = 15.430(1), *b* = 15.455(1), *c* = 17.996(1) Å, α = 99.30(1)°, β = 113.18(1)°, γ = 103.04(1)°. β-CD forms dimers comprising two identical monomers that adopt a 'round' conformation stabilized by intramolecular, interglucose O-3(*n*)···O-2(*n* + 1) hydrogen bonds. The two β-CD monomers of form **III** are isostructural to that of form **I** in the monoclinic space group *P*2$_1$ [Steiner, T.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1991**, *113*, 5676–5687], but exhibit a striking difference from that of form **II** in the monoclinic space group *C*2 [Aree, T.; Chaichit, N. *Carbohydr. Res.* **2003**, *338*, 1581–1589]. The small guest EtOH molecule orients differently in the large β-CD cavity. In form **III**, two disordered EtOH molecules are embedded in the β-CD-dimer cavity. A half occupied EtOH molecule (#1) is located above the O-4 plane of β-CD #1, whereas another doubly disordered EtOH molecule (#2, #3) is situated at about the middle of the β-CD-dimer cavity. The three EtOH sites are maintained in positions by making van der Waals contacts to each other and to the surrounding water sites and β-CD O-3–H group. The EtOH molecules disordered (occupancy 0.3) above the β-CD O-4 plane in form **I** and fully occupied beneath the O-4 plane in form **II** are strongly held in positions by hydrogen bonding with the surrounding water site and β-CD O-6–H, O-3–H groups. Occurrence of the β-CD dimer as a structural motif of channel-type packing (form **II**) and layer-type packing (form **III**) is attributed to the higher tendency for self aggregation under the moderate acidic conditions. At weak acidic conditions, β-CD prefers a herringbone mode (form **I**).

1. Introduction

β-Cyclodextrin (β-CD) is a member of cyclic oligosaccharide family comprising seven D-glucose units linked by α-(1→4) glycosidic bonds.[1] It adopts the shape of a hollow, truncated cone and is amphiphilic with hydrophobic cavity coated by C–H groups and O-4, O-5 atoms and hydrophilic rims lined with O-6–H groups on the narrower side and O-2–H, O-3–H groups on the wider side.

CDs can form inclusion complexes[2] with a large variety of guest molecules fitting partially or entirely into the host CD cavity as shown by many crystal structures.[3] In preparation of CD inclusion complexes in solution, a solvent mixture of ethanol–water is usually used to enhance aqueous solubility of the complexes, particularly to reach saturated conditions for crystallization. It has been frequently observed that ethanol co-crystallizes to form quaternary inclusion complexes of CD–guest–ethanol–hydrate.[3] However, the guest molecule is occasionally not found included in the CD cavity because the guest molecule is not sufficiently bound to CD and/or the crystallization conditions are not optimal, that is too acidic or basic.

Two crystal forms of the β-CD–ethanol–hydrate inclusion complexes have been previously investigated using both X-ray and neutron diffraction analyses.[4–7] Since 1980, Saenger and co-workers have disclosed the crystal form **I** (β-CD–ethanol-octahydrate) in the monoclinic space group *P*2$_1$ by X-ray diffraction analysis at 295 K.[4] The ethanol molecule found in the β-CD cavity is twofold disordered that is similar to the neutron structure at 295 K.[6] Three β-CD O-6–H groups are doubly disordered and β-CDs are packed in a herringbone feature.[4] About 10 years later, Saenger and co-workers have scrutinized the crystal form **I** using both neutron and X-ray radiations.[5,6] The neutron diffraction study at 295 K[5] and 15 K[6] reveals the detailed structures and the dynamics of hydrogen bonding networks. At 15 K, homodromic arrangements of hydrogen bonds dominate and suggest a strong influence of the cooperative effect.[6] The doubly disordered ethanol, two β-CD O-6–H groups, and some water sites found at 295 K[5] become well ordered at 15 K.[6] The X-ray and neutron structures of the β-CD–ethanol

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complex at 295 K[5] are similar, except for the ethanol molecule that is well ordered in the former. Recently, we have reported the crystal form **II** (β-CD–0.3ethanol-dodecahydrate) in the monoclinic space group *C*2 by X-ray diffraction analysis at 298 K.[7] The β-CD dimers form endless channels accommodating the severely disordered ethanol and water molecules; five β-CD O-6–H groups are twofold disordered.[7]

In the present work, we report the crystal form **III** (2β-CD–1.5ethanol-nonadecahydrate) in the triclinic space group *P*1 by X-ray diffraction analysis at 298 K and quantitatively compare it with the crystal forms **I**[5] and **II**[7] with respect to β-CD molecular structure, EtOH inclusion geometry, and crystal packing. The β-CD dimers form layers similar to bricks in a wall. The two ethanol and two water molecules are disordered in the β-CD-dimer cavity; the other water molecules are in interstices between β-CD dimers. For the crystal form **I**,[5] we consider only the most recent and more accurately determined X-ray structure for comparison.

2. Experimental

2.1. Crystallization and X-ray diffraction

β-CD purchased from Cyclolab (Budapest/Hungary), benzoic acid, and EtOH from Merck were used as received. We intended to reproduce crystallization of the inclusion complex between β-CD and benzoic acid by slow solvent evaporation of a saturated solution of 1:2 host–guest molar ratio in the 50% aqueous ethanol as previously reported by our research group[8] for detailed structural analysis of hydrogen bonding in the β-CD dimer using neutron diffraction. However, several crystallization attempts by dissolving the different host–guest molar ratios ranging from 1:1, 1:2, 1:3 to 1:4 in a solvent mixture of EtOH–water (50% v/v) did not provide the desired β-CD–benzoic acid inclusion complex, but gave the β-CD–EtOH inclusion complex form **III** (for host–guest molar ratios 1:1, 1:2, 1:3) and form **II** (for 1:4). pH measurements showed that the saturated benzoic acid-containing solutions were moderately acidic (pH ~3.5) that was comparable to the saturated phenol-containing solution (pH ~3.3) used for the crystallization of form **II**.[7]

A single crystal of the β-CD–EtOH inclusion complex (form **III**) with dimensions $0.3 \times 0.3 \times 0.5\ mm^3$ was mounted in a thin-walled glass capillary sealed at both ends with a drop of mother liquor. X-ray diffraction experiment was performed at 298 K using a Bruker X8 APEX2 Kappa CCD area-detector diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å) operating at 50 kV, 30 mA and software suite APEX2.[9] A total of 14175 reflections were measured in the θ range of 8.18–22.45°. Data were integrated, reduced by SAINT+,[10] corrected for Lorentz, polarization and absorption effects, and scaled by SADABS[11] to yield 10907 independent reflections. The crystal belongs to the triclinic space group *P*1. For more details, see Table 1.

Table 1
Summary of crystallographic data for $2\beta\text{-CD}\cdot1.5C_2H_5OH\cdot19H_2O$

Chemical formula	$2(C_6H_{10}O_5)_7\cdot1.5\ C_2H_5OH\cdot19H_2O$
Formula weight	2681.39
Crystal habit, color	Rod, colorless
Crystal size (mm^3)	$0.3 \times 0.3 \times 0.5$
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	
a, *b*, *c* (Å)	15.430(1), 15.455(1), 17.996(1)
α, β, γ (°)	99.30(1), 113.18(1), 103.04(1)
Volume ($Å^3$)	3690.0(4)
Z	1
D_x ($g\ cm^{-3}$)	1.199
μ (mm^{-1})	0.11
F(000)	1398
Diffractometer	APEX2 CCD (Bruker)
Wavelength, Mo Kα (Å)	0.71073
Temperature (°C)	25
θ Range for data collection (°)	8.18–22.45
Measured reflections	14175
Unique reflections	10907
R_{int}	0.032
Index ranges	$-15 \leqslant h \leqslant 16$, $-13 \leqslant k \leqslant 8$, $-18 \leqslant l \leqslant 19$
Unique reflections $[F^2 > 2\sigma(F^2)]$	8766
Structure solution	Molecular replacement (PATSEE)
Refinement method	Block-matrix least-squares on F^2
Weighting scheme	$w = [S^2(F_o^2) + (0.1364P)^2 + 0.8496P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$
Data/parameters	14175/1695
R $[F^2 > 2\sigma(F^2)]$	$R^a = 0.065$, $wR^b = 0.170$
R (all data)	$R^a = 0.085$, $wR^b = 0.189$
Goodness of fit	1.023
Highest peak/deepest hole (e $Å^{-3}$)	0.47/−0.25

[a] $R = \sum ||F_o| - |F_c|| / \sum |F_o|$.
[b] $wR = \sum\{w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2\}^{1/2}$.

2.2. Structure solution and refinement

The crystal structure was solved by molecular replacement with PATSEE[12] using the β-CD–benzoic acid inclusion complex[8] as a search model. Only the atomic coordinates of β-CD-dimer skeleton, excluding O-6 atoms were used for the calculation. The β-CD O6 atoms, EtOH, and water oxygen atoms were subsequently located by difference Fourier electron density maps assisted by the graphic program XTALVIEW.[13] All hydrogen atoms of β-CD and EtOH molecules were placed at theoretical positions according to the 'riding model'.[14] Hydrogen atoms of freely rotating β-CD OH groups were included in the structure model solely for the correct estimates of the unit-cell content and crystal density. Hydrogen atoms of water molecules could not be determined. The structure was anisotropically refined by block-matrix least-squares on F^2 with SHELXL-97,[14] to converge at an *R*-factor of 0.064 for 8766 data with $F_o^2 > 2\sigma(F_o^2)$. Exceptions are the disordered EtOH, water sites W-1, W-2 located in the β-CD-dimer cavity, W-3–W-8 in the interfaces between β-CD-dimers, and W-11–W-13, W-17, W-18, W-23, W-24 in the intermolecular spaces between β-CD macrocycles that were refined isotropically.

A summary of crystallographic data is given in Table 1. β-CD geometrical parameters including glucose puckering parameters and interatomic, intermolecular contacts calculated with PARST[15] and PLATON[16] are listed in Table 2 and depicted in Figure 3a and b. The final fractional atomic coordinates and equivalent isotropic thermal displacement factors are given as Supplementary data.

3. Results and discussion

3.1. General

β-CD did not form a ternary inclusion complex with benzoic acid and ethanol as expected but co-crystallized with ethanol as $2\beta\text{-CD}\cdot1.5\text{EtOH}\cdot19H_2O$ in the triclinic space group *P*1 with unit cell dimensions: $a = 15.430(1)$ Å, $b = 15.455(1)$ Å, $c = 17.996(1)$ Å, $\alpha = 99.30(1)°$, $\beta = 113.18(1)°$, $\gamma = 103.04(1)°$. The asymmetric unit is composed of two β-CD, 1.5EtOH, and 19 water molecules that are distributed over 32 positions (average occupancy = 0.59): water sites W-1, W-2 are located in the β-CD-dimer cavity; W-3–W-8 in the interfaces between β-CD dimers; and W-9–W-32 in the interstices between β-CD macrocycles. The β-CD dimeric structure exhibits normal thermal motion with equivalent isotropic temperature factors (U_{eq}) of 0.029(2)–0.113(6) $Å^2$ for the β-CD

Table 2
Geometrical parameters of β-CD dimer in 2β-CD·1.5C_2H_5OH·19H_2O inclusion complex (distance in Å and angle in °)

Residue	1	2	3	4	5	6	7
Puckering							
Q[a], θ[b]	0.59(1), 6.4(8)	0.56(1), 5.2(9)	0.55(1), 7.0(9)	0.58(1), 2.4(8)	0.55(1), 6.3(9)	0.55(1), 2.5(9)	0.57(1), 5.7(8)
	0.56(1), **3.1(9)**[j]	**0.55(1)**, **1.5(9)**	**0.55(1)**, **7.7(9)**	**0.56(1)**, **3.3(9)**	**0.57(1)**, **0.9(8)**	**0.56(1)**, **4.4(9)**	**0.59(1)**, **5.4(8)**
Angle							
ϕ[c], ψ[c]	114.9(6)	112.4(6)	115.3(7)	109.3(7)	113.3(6)	114.5(6)	118.6(7)
	128.9(6)	124.2(7)	131.9(6)	122.6(6)	127.0(7)	123.7(7)	125.6(6)
	116.4(6)	**111.5(8)**	**115.5(6)**	**112.6(5)**	**116.2(8)**	**112.9(6)**	**116.6(6)**
	129.0(7)	**125.8(6)**	**130.2(6)**	**125.6(7)**	**127.4(6)**	**124.8(5)**	**123.3(6)**
τ[d]	9.6(2)	6.4(1)	10.4(3)	6.5(3)	8.8(3)	4.9(1)	6.4(1)
	6.0(2)	**8.1(1)**	**6.3(2)**	**10.5(1)**	**7.9(2)**	**9.5(4)**	**5.9(3)**
ω[e]	126.3(2)	129.1(2)	129.7(1)	127.9(2)	128.1(2)	129.0(2)	130.0(1)
	130.7(2)	**129.4(2)**	**127.1(2)**	**127.8(1)**	**130.4(2)**	**129.4(2)**	**125.2(2)**
γ[f]	−65.7(11)	−64.5(8)	−69.2(10)	−67.7(9)	−65.1(11)	−67.4(8)	−63.1(8)
	−54.5(10)[i]	**−67.6(9)**	**−67.8(8)**	**−64.7(8)**	**−72.6(11)**[i]	**−65.2(9)**	**−56.4(8)**
	45.7(13)[i]				**67.4(19)**[i]		
Distance							
η[g]	2.80(1)	2.82(1)	2.77(1)	2.80(1)	2.76(1)	2.75(1)	2.80(1)
	2.83(1)	**2.81(1)**	**2.80(1)**	**2.80(1)**	**2.81(1)**	**2.74(1)**	**2.79(1)**
δ[h]	0.00(0)	0.02(1)	−0.02(1)	0.01(1)	0.00(0)	0.00(0)	−0.01(1)
	−0.01(1)	**0.01(1)**	**−0.02(1)**	**0.03(1)**	**−0.03(1)**	**0.00(0)**	**0.01(1)**

[a] Cremer–Pople puckering amplitude.[17]
[b] Ideal chair conformation has $\theta = 0$.
[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.
[d] Tilt angle, defined as the angle between the O4 plane and the planes through C-1(n), C-4(n), O-4(n) and O-4($n-1$).
[e] Angle at each glycosidic O-4: O-4($n+1$)–O-4(n)–O-4($n-1$).
[f] Torsion angle O-5–C-5–C-6–O-6.
[g] Distance O-3(n)···O-2($n+1$).
[h] Deviation of O-4 atoms from the least-squares plane through the seven O-4 atoms.
[i] Values for sites A, B of the twofold disordered O-61, O-65 with the occupancy factors 0.6, 0.4; 0.6, 0.4, respectively (β-CD #2).
[j] Bold numbers are the values of the β-CD #2.

backbones, 0.061(2)–0.160(13) $Å^2$ for the β-CD O-6 atoms, whereas the disordered EtOH molecules and water sites show higher thermal motion with U_{eq} two times larger (see ORTEP plots in Fig. 1).

The atomic numbering scheme is that used conventionally for carbohydrates, which is regularly used in our previous works. The first number denotes the position in the glucose unit, the second number the glucose number in the CD macrocycle and the third number the β-CD #1, #2 in the dimer. Letters A and B indicate twofold disorder. For example, O-61A_2 stands for the disordered O-6 of glucose residue 1 of β-CD #2. Ethanol is labeled with E.

3.2. Structural similarity of β-CD macrocycles

The β-CD macrocycles of the three crystal forms of β-CD–EtOH inclusion complex are very similar and superimposable (Fig. 2). The two β-CD monomers of form **III** are nearly identical and isostructural to that of form **II**,[7] as shown by the small rms deviations of superposition of 0.07, 0.12, and 0.15 Å. By contrast, β-CD of form **I**[5] shows a striking difference from those of forms **II** and **III** with the corresponding values of 0.39, 0.44, and 0.43 Å. Only the atomic coordinates of β-CD skeleton are used for the calculations.

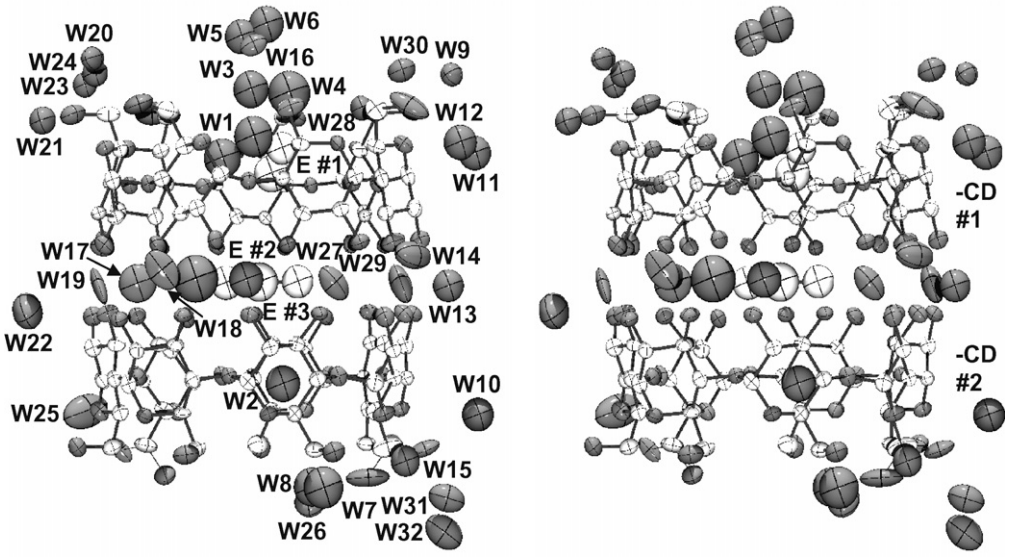

Figure 1. Stereo ORTEP plot (50% probability level) of 2β-CD·1.5ethanol·19H_2O; C in white, O gray, H not shown. Drawn with GRETEP2[27] and rendered with POV-RAY.[28]

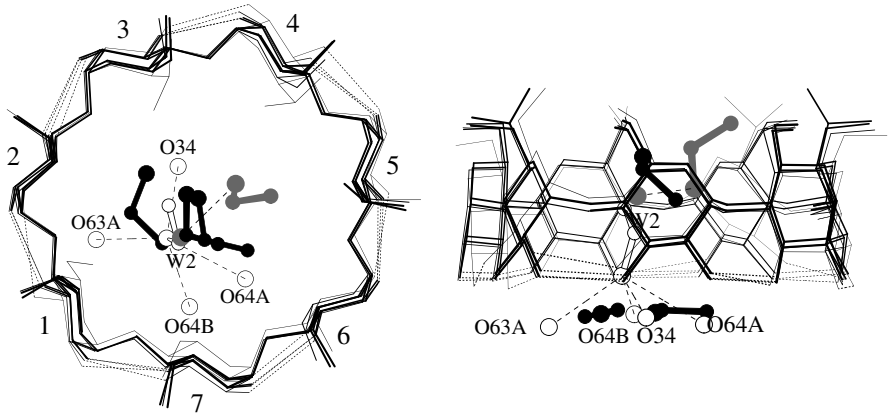

Figure 2. Overlay of β-CD–ethanol-hydrate structures (form **III** (triclinic *P*1): thick line–black ball-and-stick; form **II** (monoclinic *C*2): moderately thick line–gray ball-and-stick; form **I** (monoclinic $P2_1$): thin line–white ball-and-stick); small balls are C and bigger O. Annular conformation of β-CDs is stabilized by intramolecular, interglucose O-3(n)···O-2($n+1$) hydrogen bonds (dotted lines). Ethanol molecule is maintained in the β-CD cavity by hydrogen bonding to the symmetry-related β-CD O-3-H, O-6-H groups (white balls; form **I**), by hydrogen bonding to water site W-2 (gray ball; form **II**), and by making van der Waals contacts to another ethanol molecule (form **III**). For clarity, hydrogen atoms are not shown. Dashed lines indicate hydrogen bonds with O···O separation within 3.5 Å. Drawn with MOLSCRIPT.[29]

The two identical β-CD monomers of form **III** adopt an 'annular' conformation sustained by intramolecular, interglucose O-3(n)···O-2($n+1$) hydrogen bonds with O···O distances (η) of 2.74(1)–2.83(1) Å (Table 2, Fig. 2). The β-CD 'round' conformation is also evidenced from the small fluctuations of the geometrical parameters involving the seven glycosidic O-4 atoms (Table 2). For example, (i) the parameters defining the glucose inclination with respect to the β-CD O-4 plane are torsion angles ϕ, ψ; tilt angle τ and (ii) the parameters describing the well-defined heptagon formed by the seven O-4 atoms are angle ω (~128.6°) and distance δ (~0 Å). The values of torsion angles ϕ, ψ, tilt angle τ, angle ω, and distance δ are 109.3(7)–118.6(7)°, 122.6(6)–131.9(6)°, 4.9(1)–10.5(1)°, 125.2(2)–130.7(2)°, and −0.03 to 0.03 Å, respectively. The seven glucose units constituting each β-CD monomer are in a regular $^4C_1$ chair form with puckering parameters Q and θ[17] of 0.55(1)–0.59(1) Å and 0.9(8)–7.7(9)° (Table 2, Fig. 2). All C-6–O-6 groups are directed 'away' from the β-CD cavity with torsion angle O-5–C-5–C-6–O-6 (γ) ranging from −54.5(10)° to −72.6(11)°. Exceptions are the C-61–O-61B and C-65–O-65B groups of β-CD #2 that point 'toward' the β-CD cavity with the corresponding torsion angles 45.7(13)° and 67.4(19)° (Table 2, Fig. 2).

3.3. Structure of β-CD dimer

The two identical β-CD monomers form a perfect dimer that has parallel O-4 planes with interplanar angle 0.83(1)° and the distance between the two O-4 centers is 7.08(1) Å (Fig. 1). The β-CD dimeric structure is possibly maintained by 28 intermolecular O-2(n)_1/O-3(n)_1···O-2(m)_2/O-3(m)_2 hydrogen bonds with O···O distances 2.73(1)–3.21(1) Å. The CD dimeric structures with head-to-head arrangement as observed in this work are energetically most favorable among the three possible orientations: head-to-head, head-to-tail, tail-to-tail, as theoretically investigated in vacuum by molecular mechanics and molecular dynamics simulations.[18,19] However, a recent high resolution (0.65 Å) synchrotron diffraction study at 100 K of the β-CD–1,12-dodecanedioic acid inclusion complex[20] reveals that only the β-CD O-3–H groups are engaged in intermolecular hydrogen bonds although not all H-atom positions of β-CD and water molecules are reliably determined. For insight into the hydrogen bonding patterns and disorder nature in the CD dimeric structure, neutron diffraction at low and room temperatures, which provides an accurate determination of H atoms is worthy of further investigation.

3.4. Inclusion geometry of disordered EtOH

In form **III**, the two disordered EtOH molecules are embedded in the β-CD-dimer cavity. A half occupied EtOH molecule (#1) is located above the O-4 plane of β-CD #1 (Figs. 1, 2, 4). Its C–O bond points to the β-CD O-6 side and the C–C–O plane is inclined by 41.4° with respect to the β-CD O-4 plane. EtOH #1 does not hydrogen bond to water sites W-1–W-3 because the O···O distances 1.49–2.31 Å are too short. Another doubly disordered EtOH molecule (#2, #3; 1.43 Å far apart) is situated at about the middle of the β-CD-dimer cavity. The C–C–O planes of EtOH #2, #3 are almost co-planar with the β-CD O-4 planes; the interplanar angles are 10.8° and 6.3° (Figs. 1, 2, 4). The three EtOH sites are maintained in positions by making van der Waals contacts to each other and to the surrounding water sites and β-CD O-3–H group: W-5, W-6 for EtOH #1 and W-2, O-34–H group of β-CD #1 for EtOH #2, #3 (Fig. 3a).

The guest EtOH molecule is small when compared with the host β-CD cavity. It is indeed a variation in the EtOH inclusion geometries is perceivable from the other two crystal forms. In form **II**,[7] the disordered EtOH (occupancy 0.3) located above the β-CD O-4 plane is stabilized by hydrogen bonding with water site W-2. In form **I**,[5] the fully occupied EtOH situated beneath the O-4 plane is sustained by hydrogen bonding with symmetry-related β-CD O-6–H and O3–H groups (Fig. 2).

3.5. Hydrogen bonding network

The hydrogen bonding network in the crystal form **III** is complicated because of the severe disorder of the 19 water molecules distributing over 32 positions. Water sites have different occupancies: 0.25 (W-3, W-4, W-7, W-11, W-23, W-24); 0.3 (W-5); 0.4 (W-6, W-8, W-12, W-32); 0.5 (W-1, W-2, W-10, W-13, W-17–W-19, W-25); 0.6 (W-14, W-30, W-31); 0.8 (W-16); and 1.0 (W-9, W-15, W-20–W-22, W-26–W-29). Three water clusters form an extensive network of hydrogen bonds stabilizing the entire crystal structure. Water cluster 1 consisting of five water sites (W-1 and W-3–W-6) is located in the interfaces of β-CD dimers and hydrogen bonds with the doubly disordered O-65–H group and O-55 atom of the symmetry-related β-CD #2 (Fig. 3a). It links with cluster 2 at water site W-15 and with cluster 3 at water site W-25 that are located in the interstices between β-CD macrocycles. Water cluster 2 has a long hydrogen bond chain of 17 water sites (W-9, W-11–W-16,

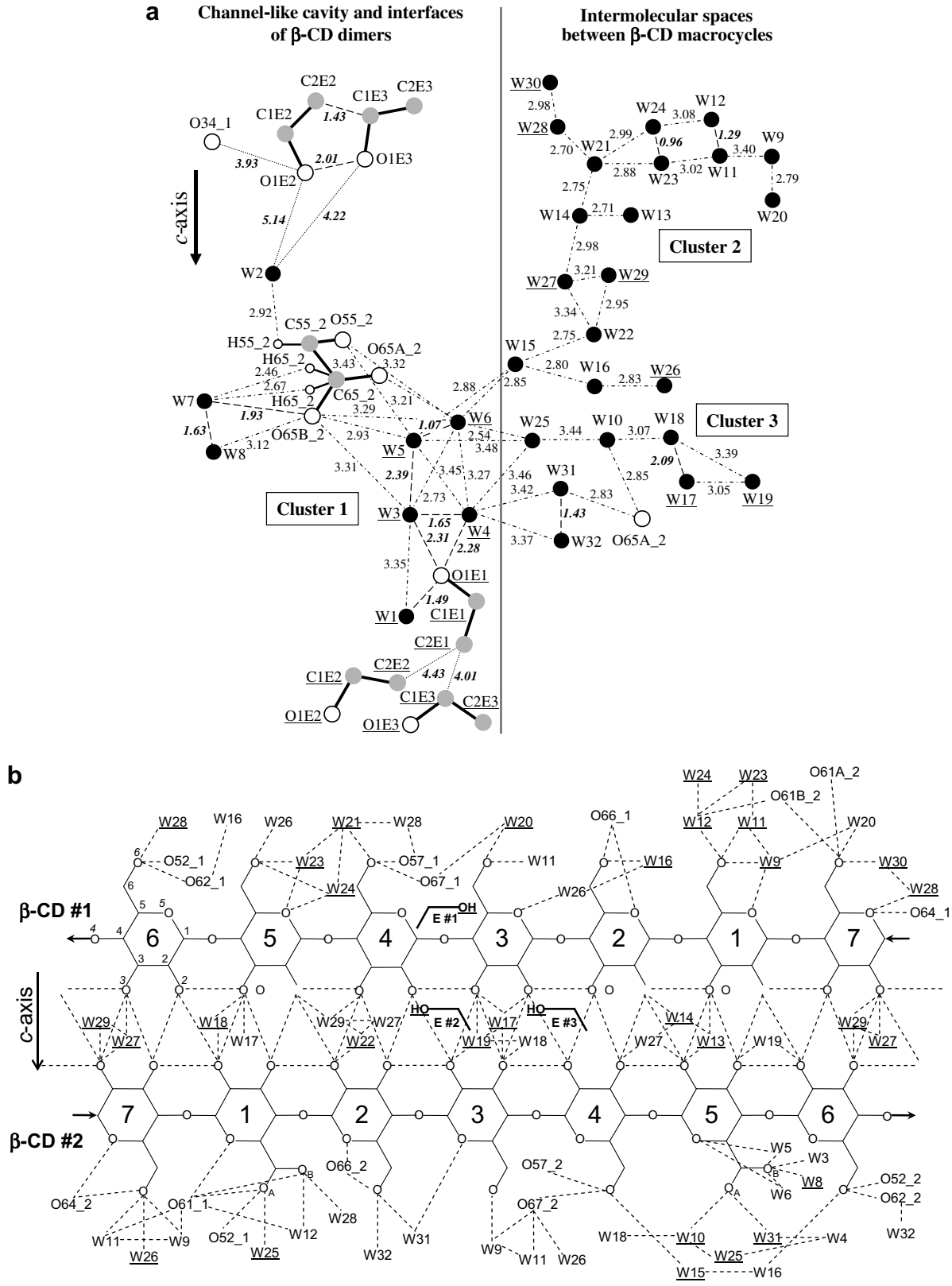

Figure 3. O–H···O hydrogen bonds network involving (a) the three water clusters, (b) the β-CD dimer with O···O distance within 3.5 Å. In (a), water cluster 1 is in the channel-like cavity and interfaces of β-CD dimers, whereas clusters 2, 3 are in the intermolecular spaces between the β-CD macrocycles. Dashed-dotted lines indicate the hydrogen bonds with given O···O distances in Å. Dotted lines indicate van der Waals interactions stabilizing ethanol #2, #3 located in middle of the channel-like cavity of β-CD dimer and dashed lines show the too short O···O distances in Å (*italics*). Water O atoms, CD O-3, O-5, O-6, ethanol O atoms, and CD C-5, C-6, ethanol C atoms, are represented as filled, unfilled, and gray circles, respectively. In (b), dashed lines indicate O–H···O hydrogen bonds. Arrows show connection of glucose units in β-CD. Atomic numbering of the β-CD is given for the glucose residue 6 of β-CD #1. In (a) and (b), underlined atomic names indicate atoms in the general position *x*, *y*, *z*; the others are in symmetry-related positions.

W-20–W-24, and W-26–W-30). Water cluster 3 has a short hydrogen bond chain of five water sites (W-10, W-17–W-19, and W-25) and connects with the O-65A–H group of the symmetry-related β-CD #2 (Fig. 3a). Other five water sites (W-2, W-7, W-8, W-31, and W-32) are isolated from the three clusters. Water site W-2 hydrogen bonds with the C-65–H group of β-CD #2 and is in van der Waals contacts with the symmetry-related EtOH #2 and #3. Water sites W-7, W-8 hydrogen bond with the C65–O65B–H group of the symmetry-related β-CD #2. Water sites W-31 and W-32 bridge the water clusters 1, 3 via the O-65A–H group of the symmetry-related β-CD #2 (Fig. 3a). Note the short distances (⩽2.5 Å) involving many doubly disordered water sites: W-3, W-4; W-5, W-6; W-7, W-8; W-11, W-12; W-23, W-24; and W-31, W-32 are not accounted for hydrogen bonds, implying that they are mutually exclusive, and cannot be occupied concurrently.

Some systematic intermolecular O–H···O hydrogen bonds between β-CD and water molecules are worth mentioning (Fig. 3b). The water sites involved are listed sequentially from β-CD glucose #1–7. The β-CD O-6–H groups are heavily hydrated by water sites W-9/W-11/W-12, W-16, W-11/W-20, W-21, W-23/W-24/W-26, W-28 (β-CD #1) and W-12/W-25/W-28, W-31/W-32, W-19, W-15, W-3/W-5/W-6/W-8/W-10/W-31, W-16, W-9/W-11/W-26 (β-CD #2). Most of the O-3–H groups of β-CD #1 and the O-2–H groups of β-CD #2 are also hydrated by water sites W-13, –, W-17/W-19, W-29, W-17/W-18, W-27, – and W-18, W-22, W-19, –, W-13/W-27, W-19, W-27/W-29, respectively.

3.6. Crystal packing

Figure 4 displays the distinct crystal packing of the three forms of the β-CD–EtOH inclusion complex. Clearly, β-CDs are not exclusively packed in a herringbone fashion in form **I** (monoclinic $P2_1$)[4–6] as frequently found when the guest molecule is small, which can be entirely engulfed in the host CD cavity.[21] By contrast, β-CDs form dimers in form **II** (monoclinic $C2$)[7] and form **III** (triclinic $P1$). The β-CD dimers in form **II** are stacked like coins in a roll, giving rise to an infinite channel, whereas β-CD dimers in form **III** are packed in layers like bricks in a wall. The layer-type packing in the present crystal structure is slightly different from that originally reported by Saenger[21] with respect to molecular arrangement and building unit. In the former, β-CD is inclined by 10° against the unit-cell plane and constitutes a dimer, whereas in the latter, β-CD is parallel to the unit-cell plane and acts alone as a building unit. The layer-type packing of the present β-CD dimer has been termed 'intermediate type' by Mentzafos and co-workers.[22] They have categorized the β-CD-dimer crystal packing by different lateral displacements of the adjacent β-CD dimeric layers into four modes: channel, intermediate, screw-channel, and chessboard.[22] Tetrad type has been reported later by Stezowski and co-workers[23] and further discussed by Mentzafos and co-workers.[24]

We envisage that the variation in crystal packing of the β-CD–EtOH inclusion complex is primarily influenced by the distinction in crystallization conditions. The occurrence of β-CD dimer as a building unit of channel-type packing (form **II**) and layer-type packing (form **III**) under moderate acidic solutions containing either phenol (pH ~3.3; form **II**) or benzoic acid (pH ~3.5; form **III**) is consistent with the association in solution of α-, β-, and γ-CDs as dimers or larger aggregates deduced from viscosity[25] and light scattering[26] measurements. The CD crystal packing, that is, primarily influenced by crystallization conditions shows that the β-CD channel-type packing does not require an induction by ionic or long guest molecules, in contradiction to the observation of Saenger.[21]

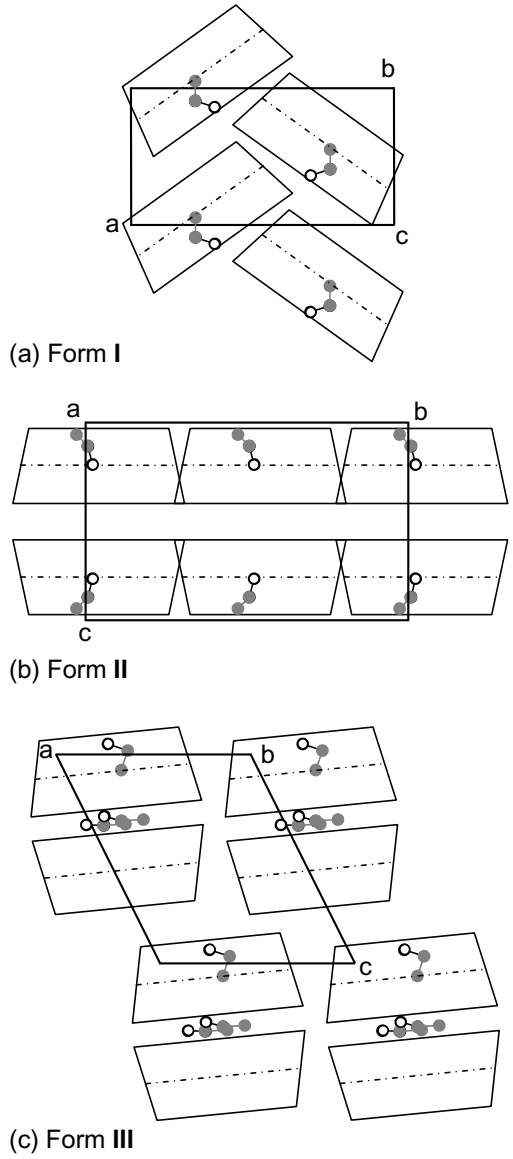

Figure 4. Schematic presentation of crystal packing in the β-CD–ethanol-hydrate inclusion complex: (a) form **I** (monoclinic $P2_1$, β-CD·C_2D_5OD·$8D_2O$, herringbone style); (b) form **II** (monoclinic $C2$, β-CD·$0.3C_2H_5OH$·$12H_2O$, channel mode); (c) form **III** (triclinic $P1$, 2β-CD·$1.5C_2H_5OH$·$19H_2O$, layer type). C atoms are in filled circles and O atoms in open circles; H atoms are not shown. Dashed-dotted lines indicate the position of β-CD molecular plane. View down along *c*-, *a*-, and *b*-axes for forms **I**, **II**, and **III**, respectively.

4. Summary

The existence of a solvated/hydrated complex in various crystalline forms, that is, pseudopolymorphism has been demonstrated for the three crystal forms of the β-CD–EtOH inclusion complex reported thus far (see the summary in Table 3).

- The β-CD macrocycles of the three crystal forms are similar. Crystal form **III** belongs to the triclinic space group $P1$ [$2(C_6H_{10}O_5)_7$·$1.5C_2H_5OH$·$19H_2O$]. β-CD forms dimers comprising two identical monomers that are 'round' and are isostructural to that of form **I** [monoclinic space group $P2_1$; β-CD·C_2D_5OD·$8D_2O$], but are slightly different from that of form **II** [monoclinic space group $C2$; β-CD·$0.3C_2H_5OH$·$12H_2O$].
- The EtOH molecules are buried and stabilized differently in the β-CD cavity of the three crystal forms. In form **III**, two disordered EtOH molecules are embedded in the β-CD-dimer cavity. A half

Table 3
Summary of the crystallization conditions and characteristics of the β-CD–EtOH inclusion complex

	Form I[a]	Form II[b]	Form III[c]
Crystallization			
– Guest	—	Phenol (C_6H_5OH)	Benzoic acid (C_6H_5COOH)
– Host–guest molar ratio	—	1:1	1:1/1:2/1:3
– Solvent; dissolution temp (K)	50% v/v C_2D_5OD–D_2O; 343	50% v/v C_2H_5OH–H_2O; 333	50% v/v C_2H_5OH–H_2O; 333
– pH of solution	~6	3.30	3.50
Data collection temp (K)	295	298	298
Radiation, wavelength (Å)	Cu Kα, 1.54184	Mo Kα, 0.71073	Mo Kα, 0.71073
Crystal system, space group	Monoclinic, $P2_1$	Monoclinic, $C2$	Triclinic, $P1$
Unit cell constants			
– a, b, c (Å)	21.146(4), 10.216(2), 15.185(4)	19.292(1), 24.691(1), 15.884(1)	15.430(1), 15.455(1), 17.996(1)
– α, β, γ (°)	90, 111.64(2), 90	90, 109.35(1), 90	99.30(1), 113.18(1), 103.04(1)
Asymmetric unit	β-CD·C_2D_5OD·$8D_2O$	β-CD·$0.3C_2H_5OH$·$12H_2O$	2β-CD·$1.5C_2H_5OH$·$19H_2O$
EtOH inclusion			
– Location relative to the β-CD O4-center and plane	1.86 Å beneath	2.33 Å above	1.77 Å above; 3.63, 4.45 Å beneath
– Direction of the C–O bond	Toward O-2/O-3 side	Toward O-2/O-3 side	Toward O-6 side
– Angle against the β-CD plane	79.4°	68.6°	41.4°, 10.8°, 6.3°
– Interaction with host/water	H-bonds with the symmetry-related β-CD O-6–H groups	H-bond with a water molecule	Van der Waals contacts with water and β-CD molecules
Crystal packing	Herringbone mode built from β-CD monomers	Channel type built from twofold symmetry-related β-CD dimers	Layer type built from β-CD dimers

[a] Ref. 5.
[b] Ref. 7.
[c] This work.

occupied EtOH molecule (#1) is located above the O-4 plane of β-CD #1, whereas another twofold disordered EtOH molecule (#2, #3) is situated at about the middle of the β-CD-dimer cavity. The three EtOH sites are maintained in positions by making van der Waals contacts to each other and to the surrounding water sites and the β-CD O-3–H group. The EtOH molecules disordered (occupancy 0.3) above the β-CD O-4 plane (form **I**) and fully occupied beneath the O-4 plane (form **II**) are strongly held in positions by hydrogen bonding with the surrounding water site and the β-CD O-3–H, O-6–H groups.

- Pseudopolymorphism in the β-CD–EtOH inclusion complex is attributed to the acidity of the saturated solutions prepared in the crystallization. The β-CD dimer as a structural motif of channel-type packing (form **II**) and layer-type packing (form **III**) suggests the higher tendency for self aggregation due to the β-CD low ionization under the moderate acidic conditions. At weak acidic conditions, β-CD prefers a herringbone mode (form **I**).

5. Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 674965. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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