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Polymorphism in β-cyclodextrin–benzoic acid inclusion complex: a kinetically controlled crystal growth according to the Ostwald's rule

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ABSTRACT

Crystal form **II** of the β-cyclodextrin–benzoic acid (β-CD–BA) inclusion complex was obtained from the 1.5-year stored aqueous EtOH solution of β-CD and BA as 2β-CD·1.5BA·0.7EtOH·21H_2O in the monoclinic space group *C*2 with unit cell constants: $a = 19.413(3)$, $b = 24.306(4)$, $c = 32.975(1)$ Å, $\beta = 104.41(1)°$. By contrast, the desired crystal form **I** in the triclinic space group *P*1 that ever grew up from the fresh solution as 2β-CD·2BA·0.7EtOH·20.65H_2O was not reproducible any more [Aree, T.; Chaichit, N. *Carbohydr. Res.* **2003**, *338*, 439–446]. In the two crystal forms, β-CDs are isostructural with a 'round' conformation stabilized by intramolecular O-3(n)···O-2($n + 1$) hydrogen bonds. The BA inclusion geometries are similar with a preferred orientation, that is, BAs are situated above the O-4 plane, point their COOH groups to the β-CD O-6 side, incline 52° with respect to the O-4 plane and are mainly maintained in positions by hydrogen bonding with the surrounding water molecules. β-CDs form dimers as structural motif of different packing modes: the screw-channel type in form **II** and the average of intermediate and tetrad types in form **I**. Polymorphism in the β-CD–BA inclusion complex is a kinetically controlled crystal growth following the Ostwald's rule: the less stable crystal form **I** grew up first within one week from the fresh solution, whereas the more stable crystal form **II** appeared after 1.5-year storage.

1. Introduction

β-Cyclodextrin (β-CD), a member of cyclic oligosaccharide family, comprises seven D-glucose units linked by α-(1→4) glycosidic bonds. It resembles 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.[1]

Polymorphism[2] is a phenomenon in which a compound exists in more than one crystal form while a similar term, pseudopolymorphism,[2,3] is used to express a compound crystallized with different amounts or types of solvent molecules. Various crystal forms do not crystallize concurrently but the least stable form appears first followed by the more stable forms as stated by the Ostwald's rule.[4] (Pseudo)polymorphism in CDs having different properties plays a crucial role in pharmaceutical utilization because CDs are used as drug carriers and solubilizers to enhance the bioavailability of poorly water soluble drugs.[5] (Pseudo)polymorphism is commonly observed in the uncomplexed native and methylated CDs co-crystallized with different solvents (predominated by water, MeOH, EtOH, and their mixtures).[6] However, only a few examples of polymorphism are found in the CD inclusion complexes: β-CD with methyl-4-hydroxybenzoate[7] and barbital.[8]

Recently, we have reported the detailed structure of the β-CD–benzoic acid(BA) inclusion complex (form **I**) by means of single crystal X-ray diffraction.[9] β-CD dimer accommodates two BA molecules forming a 2:2 inclusion complex. Each BA is situated above the β-CD O-4-plane, inclined by 52° against the plane and points its COOH group to the O-6–H side. The crystallographic result gives better insight into the β-CD–BA inclusion complex than do the others previously reported.[10–14] For example, the results obtained in solution by NMR,[10] by potentiometric titration;[11] in the gas phase by FAB mass spectrometry,[12] by theoretical calculations[13] have shown that the host–guest stoichiometry is 1:1, the BA aromatic ring is parallel to the CD molecular axis and the COOH group points toward the narrower rim of the cone. In the solid state, thermal analyses and X-ray powder diffraction have revealed significant interactions between β-CD and BA in both physical and kneaded mixtures with a 1:1 host–guest molar ratio.[14] In the present work, we report crystal form **II** and compare it with form **I**. Polymorphism in the β-CD–BA inclusion complex obtained by kinetically controlled crystal growth follows the Ostwald's rule.

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2. Experimental

2.1. Crystallization and X-ray diffraction

β-CD purchased from Cyclolab (Budapest/Hungary), benzoic acid and EtOH from Merck were used without further purification. Our intention was to reproduce the crystal form **I** of the β-CD–BA inclusion complex[9] for detailed structure elucidation of the hydrogen bonding networks in the β-CD dimer by neutron diffraction. Briefly, β-CD 57 mg (0.05 mmol) and BA 12 mg (0.10 mmol) were dissolved in a small vial containing 2 mL of 50% v/v EtOH–H_2O at 333 K for 1 h.[9] After a week of slow solvent evaporation at 303 K, many colorless, rod-like single crystals grew up. However, several attempts were fruitless; the crystals were not of form **I** of the β-CD–BA complex[9] but belonged to form **III** of the β-CD–EtOH complex.[15] The crystals in mother liquor kept at 298 K in an air-conditioned room for 1.5 years remained clear and colorless. Several indistinguishable, rod-like single crystals were selected for the determination of unit cell constants. Unexpectedly, some crystals were of form **II** of the β-CD–BA complex (monoclinic, *C*2) and some crystals were of form **II** of the β-CD–EtOH complex (monoclinic, *C*2).[16] Crystal form **III** of the β-CD–EtOH complex (triclinic, *P*1)[15] ever obtained from the fresh solution was disappeared. Polymorphic variation in the β-CD–BA and β-CD–EtOH complexes is summarized in Table 1.

A single crystal of the β-CD–BA complex with dimensions 0.2 × 0.4 × 0.5 mm^3 was mounted in a thin-walled glass capillary and used for X-ray diffraction data collection at 298 K by a Bruker SMART CCD diffractometer with MoKα radiation (λ = 0.71073 Å) operating at 50 kV, 30 mA. A total of 40,506 reflections were collected to 0.75 Å resolution (θ = 28.56°). Data were integrated by SAINT,[17] corrected for Lorentz, polarization, absorption effects and scaled by SADABS.[18] For more details, see Table 2.

2.2. Structure solution and refinement

The crystal structure was solved by molecular replacement with PATSEE[19] using the β-CD–1,2-bis(4-aminophenyl)ethane inclusion complex[20] as a search model. Only the atomic coordinates of the β-CD-dimer skeleton, excluding O-6 atoms were used for the calculation. The missing β-CD O-6 atoms, BA molecules, and water O atoms were subsequently located from difference Fourier electron density maps assisted by the graphic program XTALVIEW.[21] All H-atom positions of β-CD (CH, CH_2, OH), BA (aromatic CH, COOH), and EtOH were calculated theoretically according the riding model,[22] except for those of the half occupied BA (#2). Water H-atoms could not be determined. All non-H atoms of the β-CD dimer, the fully occupied BA (#1) and some water sites (W-2–W-5, W-8, W-9, W-12, W-14–W-19, W-21, W-22, W-25–W-27) were refined anisotropically. The remaining water sites, the disordered EtOH and the half occupied BA (#2) were refined isotropically. The refinement of 1776 atomic parameters against 6106 diffraction data with $F_o^2 > 2\sigma(F_o^2)$ converged at *R* = 0.080. The low data/parameter ratio (3.44) could be attributed to the relatively poor crystal quality.

Table 2
Summary of crystallographic data for 2β-CD·1.5BA·0.7EtOH·21H_2O (see also Table 1)

Diffractometer	SMART CCD (Bruker)
Wavelength, MoKα (Å)	0.71073
Temperature (K)	298
θ Range for data collection (°)	8.18–28.56
Resolution (Å)	0.75
Measured reflections	40,506
Unique reflections	15,650
R_{int}	0.114
Index ranges	$0 \leqslant h \leqslant 26$, $-24 \leqslant k \leqslant 32$, $0 \leqslant l \leqslant 44$
Unique reflections [$F^2 > 2\sigma(F^2)$]	6106
Structure solution	Molecular replacement (PATSEE)
Refinement method	Block-matrix least-squares on F^2
Weighting scheme	$w = [S^2(F_o^2) + (0.0902P)^2 + 2.5380P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$
Data/parameters	15,650/1776
R [$F^2 > 2\sigma(F^2)$]	R^a = 0.080, wR^b = 0.165
R (all data)	R^a = 0.214, wR^b = 0.228
Goodness of fit	0.971
Highest peak/ Deepest hole (e Å^{-3})	0.35/−0.25

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

Table 1
Polymorphism in the β-CD–BA and β-CD–EtOH inclusion complexes[a]

	β-CD–BA form **II**[b]	β-CD–BA form **I**[c]	β-CD–EtOH form **III**[d]	β-CD–EtOH form **II**[e]
Chemical formula	2β-CD·1.5BA·0.7EtOH·21H_2O	2β-CD·2BA·0.7EtOH·20.65H_2O	2β-CD·1.5EtOH·19H_2O	β-CD·0.3EtOH·12H_2O
Crystal habit, color	Rod, colorless	Rod, colorless	Rod, colorless	Rod, colorless
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	*C*2	*P*1	*P*1	*C*2
Unit cell				
a (Å)	19.413(3)	15.210(1)	15.430(1)	19.292(1)
b (Å)	24.306(4)	15.678(1)	15.455(1)	24.691(1)
c (Å)	32.975(1)	15.687(1)	17.996(1)	15.884(1)
α (°)	90	89.13(1)	99.30(1)	90
β (°)	104.41(1)	74.64(1)	113.18(1)	109.35(1)
γ (°)	90	76.40(1)	103.04(1)	90
Vol. (Å^3)	15070.1(3)	3501.4(1)	3690.0(4)	7139.1(2)
Z	2	1	1	4
D_x (g cm^{-3})	1.236	1.364	1.199	1.218
Crystal packing	Screw-channel type built from β-CD dimers	Average of intermediate and tetrad types built from β-CD dimers	Layer type built from β-CD dimers	Channel type built from twofold symmetry related β-CD dimers
Crystal growth	1.5-year storage at 298 K	7-day storage at 298 K	7-day storage at 298 K	1.5-year storage at 298 K
Crystal stability	Most stable; reproducible	Least stable; irreproducible	Less stable; reproducible	Stable; reproducible

[a] Crystals were obtained from the solution of β-CD and BA (1:2 molar ratio) in 50% aqueous EtOH at different storage time.
[b] This work.
[c] Ref. 9.
[d] Ref. 15.
[e] Crystals could also be obtained from the moderate acidic solution of β-CD and phenol (1:2 molar ratio) in 50% aqueous EtOH.[16]

Table 3
Geometrical parameters of β-CD dimer in the 2β-CD·1.5BA·0.7EtOH·21H_2O inclusion complex (distance in Å and angle in °)

Residue	1	2	3	4	5	6	7
Puckering							
Q[a], θ[b]	0.55(1)	0.56(1)	0.56(1)	0.55(1)	0.55(1)	0.57(1)	0.55(1)
	0.58(1)[j]	**0.58(1)**	**0.54(1)**	**0.58(1)**	**0.56(1)**	**0.57(1)**	**0.56(1)**
	5.8(8)	1.3(8)	4.9(9)	3.7(9)	3.1(9)	2.8(9)	4.2(8)
	4.5(9)	**2(1)**	**2(1)**	**2(1)**	**5.3(8)**	**4.2(8)**	**1.9(9)**
Angle							
ϕ[c], ψ[c]	114.2(6)	114.8(6)	112.6(7)	113.2(7)	111.7(7)	114.6(7)	116.2(7)
	110.0(8)	**112.6(7)**	**109.3(7)**	**107.4(7)**	**109.2(7)**	**114.3(7)**	**111.4(7)**
	121.2(6)	131.4(6)	125.0(7)	129.5(7)	124.1(7)	127.2(7)	125.4(7)
	124.0(7)	**135.2(7)**	**126.4(7)**	**128.1(7)**	**124.3(7)**	**130.7(6)**	**128.4(7)**
τ[d]	3.3(1)	9.6(2)	8.7(2)	10.2(1)	7.6(2)	8.6(3)	8.7(2)
	7.2(4)	**13.1(2)**	**12.2(2)**	**11.3(2)**	**7.2(1)**	**12.0(3)**	**12.5(5)**
γ[e]	−60.6(8)	67.5(9)	−68(1)[h] 67(1)[h]	−71(1)	−64.4(9)	−66(1)	−64(1)
	−67.1(9)	**−68(2)**[i] **61(2)**[i]	**−61(1)**	**−67(1)**	**−66.1(8)**	**69(1)**	**−65(1)**
Distance							
η[f]	2.82(1)	2.77(1)	2.82(1)	2.77(1)	2.82(1)	2.79(1)	2.76(1)
	2.88(1)	**2.83(1)**	**2.83(1)**	**2.81(1)**	**2.80(1)**	**2.84(1)**	**2.81(1)**
δ[g]	0.04(1)	−0.02(1)	−0.01(1)	0.02(1)	0.01(1)	−0.03(1)	−0.01(1)
	−0.04(1)	**0.03(1)**	**0.01(1)**	**−0.04(1)**	**0.01(1)**	**0.02(1)**	**0.00(1)**

[a] Cremer–Pople puckering amplitude.[25]
[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] Torsion angle O-5–C-5–C-6–O-6.
[f] Distance O-3(n)···O-2($n+1$).
[g] Deviation of O-4 atoms from the least–squares plane through the seven O-4 atoms.
[h] Values for sites A, B of the twofold disordered O-63 with the occupancy factors 0.45, 0.55 of β-CD #1, respectively.
[i] Values for sites A, B of the twofold disordered O-62 with the occupancy factors 0.7, 0.3 of β-CD #2, respectively.
[j] Bold numbers are the values of the β-CD #2.

A summary of crystallographic data is given in Table 2. Geometrical parameters of the β-CD dimer including the glucose puckering parameters and the interatomic, intermolecular contacts calculated with PLATON[23] and PARST[24] are listed in Tables 3 and 4, respectively. The final fractional atomic coordinates and equivalent isotropic thermal displacement factors are given as Supplementary data.

3. Results and discussion

3.1. General

The asymmetric unit comprises two β-CD, 1.5 BA, 0.7 EtOH and 21 water molecules. Two O-6–H groups of the glucose units 3 (β-CD #1) and 2 (β-CD #2) are twofold disordered. BA #1 is fully occupied the cavity of β-CD #1 while BA #2 is half occupied the cavity of β-CD #2. The solvents in the crystal are moderately disordered. The disordered EtOH (0.7) is located in interstices between β-CD dimers, whereas the 21 water molecules are spread over 28 positions mostly outside the β-CD cavity (average occupancy = 0.75). Exception is the water site W-1 that is half occupied the cavity of β-CD #2. Water sites W-2 and W-17 are situated in the intermolecular space of the tail-to-tail β-CD heterodimer (i.e., the space between the approaching O-6–H groups of β-CD #1 and #2) while water site W-28 is located in the intermolecular space of the head-to-head β-CD homodimer (i.e., the space between the approaching O-2–H/O-3–H groups of the twofold symmetry related β-CD #1). Two water sites W-13 and W-28 are placed at the special positions. The β-CD dimer exhibits normal thermal motion with U_{eq}: 0.041(2)–0.113(5) Å^2 (β-CD skeleton) and 0.076(2)–0.188(5) Å^2 (β-CD O-6). BA, EtOH, and water molecules show higher thermal motion with U_{eq} 2–3 times larger (Fig. 1).

The atomic numbering scheme is that conventionally used for carbohydrates. For the present β-CD dimeric structure, each atom of β-CD is labeled with three numbers. The first number indicates the position in the glucose unit, the second number the glucose in the β-CD macrocycle and the third number the monomer in the β-CD dimer. Additional letters A and B show the doubly disordered O-6–H group. For example, O-63A_1 denotes site A of the disordered O-6 of glucose residue 3 of β-CD #1 (Scheme 1). For the guest and solvent molecules, similar atomic numbering is adopted and the letters Z, E, and W indicate BA, EtOH, and water molecules, respectively. For example, O-2Z_1 stands for O-2 of BA #1 (Scheme 1).

3.2. Isostructure of the β-CD macrocycles

Four β-CD macrocycles in the crystal forms **I** and **II** of the β-CD–BA inclusion complex are round and isostructural with relatively small rms deviations of superposition: 0.10–0.13 Å (within form **I**/**II**) and 0.16–0.22 Å (between forms **I** and **II**). Only the atomic coordinates of the β-CD skeletons are used for the calculations. The structural overlay is depicted in Figure 2. The rigid conformation of the β-CD macrocycles generally observed in the crystalline state is due to the intramolecular, interglucose O-3(n)···O-2($n+1$) hydrogen bonds maintained by the water and crystal-lattice effects (Fig. 2). The O···O distances involved are 2.76(1)–2.88(1) Å (Table 3). Other geometrical parameters indicating the β-CD 'round' conformation are torsion angles around O-4 atoms (ϕ,ψ); glucose tilt angle (τ) and deviation of O-4 atoms from their mean plane (δ). The corresponding values are 107.4(7)–116.2(7)°, 121.2(6)–135.2(7)°; 3.3(1)–13.1(1)° and −0.04(1) to 0.04(1) Å (Table 3). Also accumulated in Table 3 are the puckering parameters (Q,θ)[25] defining the glucose conformation and the torsion angle O-5–C-5–C-6–O-6 (γ) describing the orientation of the C-6–O-6 groups. All 14 glucose units of the two β-CDs are in a regular $^4C_1$ chair conformation with Q and θ values of 0.54(1)–0.58(1) Å and 1.9(9)–5.8(8)°. All C-6–O-6 groups point 'toward' the β-CD cavity with torsion angle γ ranging from −60.6(8)° to −71(1)°. Exceptions are the C-62–O-62, C-63–O-63B groups of β-CD #1 and the C-62–O-62B, C-66–O-66 groups of β-CD #2 that point 'away' from the β-CD cavity with

Table 4
O–H···O hydrogen bonds in 2β-CD·1.5BA·0.7EtOH·21H_2O with O···O separation ⩽3.2 Å

Interaction	Dist. (Å)	Symmetry	Interaction	Dist. (Å)	Symmetry
β-CD–β-CD[a]			*β-CD–*H_2O		
O-61_1···O-65_1	2.85(1)	$x-0.5, y+0.5, z$	O-62A_2···W-23	2.60(3)	x, y, z
O-62_1···O-67_2	2.74(1)	x, y, z	O-62A_2···W-24	3.15(5)	x, y, z
O-63A_1···O-62A_2	3.13(3)	$x-0.5, y-0.5, z$	O-62A_2···W-9	2.78(3)	$x+0.5, y+0.5, z$
O-63A_1···O-67_1	3.14(3)	$x-0.5, y-0.5, z$	O-62B_2···W-2	2.68(3)	x, y, z
O-63B_1···O-57_2	3.11(2)	x, y, z	O-62B_2···W-10	2.93(3)	$x+0.5, y+0.5, z$
O-63B_1···O-67_2	2.54(2)	x, y, z	O-62B_2···W-11	2.69(3)	$x+0.5, y+0.5, z$
O-25_1···O-27_1	2.75(1)	$-x+0.5, y-0.5, -z+1$	O-33_2···W-16	2.84(2)	$x+0.5, y+0.5, z$
O-61_2···O-65_2	2.80(1)	$x-0.5, y+0.5, z$	O-53_2···W-24	2.95(4)	x, y, z
O-23_2···O-25_2	2.73(1)	$-x+0.5, y+0.5, -z$	O-63_2···W-24	3.18(5)	x, y, z
BA–H_2O[b]			O-63_2···W-26	2.83(2)	x, y, z
O-1Z_1···W-17	2.75(2)	x, y, z	O-24_2···W-16	3.20(1)	$x+0.5, y+0.5, z$
O-2Z_1···W-2	2.59(3)	x, y, z	O-24_2···W-20	3.15(4)	$-x, y, -z$
O-1Z_2···W-17	2.75(3)	x, y, z	O-24_2···W-27	2.98(4)	x, y, z
O-2Z_2···W-2	2.66(4)	x, y, z	O-24_2···W-27	3.11(4)	$-x+1, y, -z$
EtOH–β-CD/H_2O[c]			O-34_2···W-25	2.93(1)	$x+0.5, y-0.5, z$
O-1E···O-21_1	2.72(2)	x, y, z	O-64_2···W-21	2.73(2)	$x+0.5, y-0.5, z$
O-1E···O-35_1	2.97(2)	$x-0.5, y+0.5, z$	O-65_2···W-5	2.75(1)	$x+0.5, y-0.5, z$
O-1E···O-26_1	3.19(2)	$x-0.5, y+0.5, z$	O-26_2···W-16	2.68(1)	x, y, z
O-1E···O-37_1	3.16(2)	$-x, y, -z+1$	O-66_2···W-17	2.66(2)	x, y, z
O-1E···W-13	2.95(3)	$x-0.5, y+0.5, z$	O-66_2···W-3	2.75(1)	$x+0.5, y-0.5, z$
O-1E···W-13	2.95(3)	$-x+0.5, y+0.5, -z+1$	O-27_2···W-19	2.71(2)	x, y, z
β-CD–H_2O[d]			O-37_2···W-20	3.01(4)	x, y, z
O-61_1···W-3	2.72(1)	x, y, z	O-57_2···W-23	3.18(3)	$x-0.5, y-0.5, z$
O-61_1···W-4	2.95(2)	x, y, z	H_2O–H_2O		
O-22_1···W-6	2.75(3)	x, y, z	W-1···W-17	2.82(3)	x, y, z
O-62_1···W-5	2.77(1)	x, y, z	W-3···W-5	2.84(1)	x, y, z
O-63A_1···W-9	2.60(3)	x, y, z	W-4···W-14	2.72(2)	x, y, z
O-63A_1···W-10	2.88(3)	x, y, z	W-4···W-18	2.74(2)	$x-0.5, y+0.5, z$
O-63B_1···W-8	2.68(3)	x, y, z	W-4···W-21	2.83(2)	x, y, z
O-63B_1···W-23	3.18(3)	$x-0.5, y-0.5, z$	W-5···W-26	2.87(1)	$x-1, y, z$
O-24_1···W-7	2.76(2)	x, y, z	W-8···W-9	3.08(3)	x, y, z
O-34_1···W-6	2.86(2)	$x+0.5, y-0.5, z$	W-8···W-15	3.08(5)	$x-0.5, y-0.5, z$
O-34_1···W-7	3.17(2)	$-x, y, -z+1$	W-9···W-21	2.70(2)	$x-0.5, y-0.5, z$
O-64_1···W-3	2.77(1)	$x+0.5, y-0.5, z$	W-10···W-23	3.15(4)	$x-0.5, y-0.5, z$
O-65_1···W-12	2.71(2)	x, y, z	W-10···W-24	3.10(5)	$x-0.5, y-0.5, z$
O-26_1···W-13	3.17(1)	x, y, z	W-12···W-14	2.76(3)	$x+0.5, y-0.5, z$
O-36_1···W-6	3.16(2)	$-x, y, -z+1$	W-14···W-15	2.80(4)	x, y, z
O-36_1···W-7	2.98(2)	$x+0.5, y+0.5, z$	W-16···W-16	3.22(2)	$-x, y, -z$
O-66_1···W-10	2.80(2)	$x+0.5, y+0.5, z$	W-16···W-22	2.95(2)	$-x-0.5, y-0.5, -z$
O-66_1···W-11	2.99(3)	$x+0.5, y+0.5, z$	W-16···W-27	2.95(4)	$x-0.5, y-0.5, z$
O-57_1···W-11	2.93(3)	$x+0.5, y+0.5, z$	W-16···W-27	2.97(4)	$-x+0.5, y-0.5, -z$
O-67_1···W-14	2.77(2)	x, y, z	W-17···W-18	2.82(3)	x, y, z
O-67_1···W-9	2.91(2)	$x+0.5, y+0.5, z$	W-19···W-25	2.61(4)	$-x-0.5, y-0.5, -z$
O-21_2···W-22	2.83(2)	x, y, z	W-20···W-27	2.92(4)	$x-1, y, z$
O-61_2···W-21	2.70(1)	x, y, z	W-20···W-27	2.35(5)	$-x, y, -z$
O-22_2···W-25	2.81(1)	x, y, z	W-22···W-26	2.80(3)	$x-1, y, z$
O-32_2···W-19	2.90(2)	$x+0.5, y+0.5, z$	W-22···W-27	2.79(3)	$-x, y, -z$
O-52_2···W-9	3.17(2)	$x+0.5, y+0.5, z$	W-25···W-25	2.99(2)	$-x, y, -z$

[a] Disordered O-6-H with occupancy factors: 0.55, 0.45 (O-63A/B_1); 0.7, 0.3 (O-62A/B_2).

[b,c] Disordered BA #2 and EtOH with occupancy factors 0.5 and 0.7.

[d] Water sites with occupancy factors: 1.0 (W-3, W-5, W-9, W-12, W-17, W-18, W-21, W-25, W-28); 0.8 (W-4, W-8, W-13, W-15, W-16, W-19); 0.7 (W-14, W-22, W-26); 0.6 (W-20, W-23); 0.5 (W-1, W-2, W-6, W-7, W-10, W-11, W-27) and 0.4 (W-24); water sites W-13 and W-28 are at the special positions.

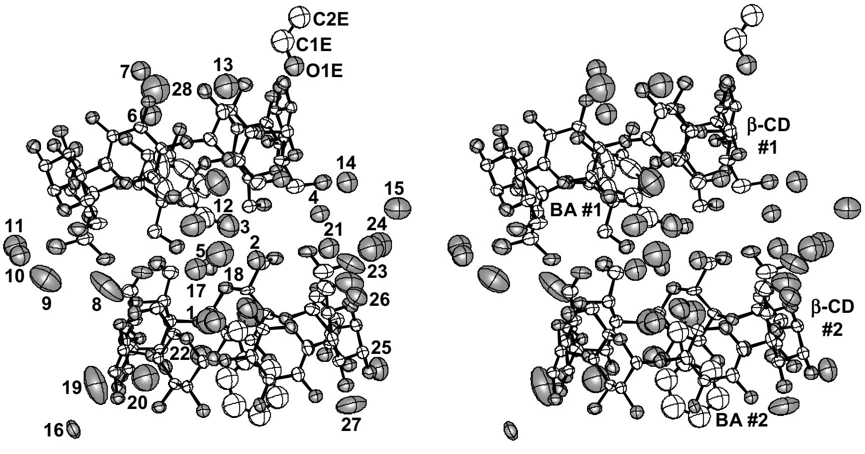
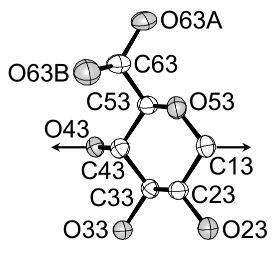


Figure 1. Stereo ORTEP plot (40% probability level) of 2β-CD·1.5BA·0.7EtOH·21H_2O; C in white, O gray, H not shown. Numbers 1–28 indicate water sites. Drawn with GRETEP2.[33]



Scheme 1. Atomic numbering of β-cyclodextrin (β-CD) and benzoic acid (BA). Shown here are the ORTEP plots of the glucose residue 3 of β-CD #1 and BA #1 (30% probability level); C in white, O gray, H not shown. Arrows indicate the connection of glucose unit 3 with the adjacent units 2 and 4. Drawn with GRETEP2.[33]

torsion angle γ of 61(2)–69(1)° (Table 3). The two orientations of the C-6–O-6 groups are sustained by hydrogen bonding with the embedded water/guest molecules in the β-CD cavity and the water molecules located around the O-6 side, outside the β-CD cavity (see Section 3.4 below).

3.3. Inclusion geometry of BA molecules

Although the β-CD macrocycles in both crystal forms are isostructural, the BA inclusion geometries in form **II** are both similar to and different from those in form **I**. In form **I**, the two fully occupied BAs are situated at $\sim$1.0 Å above the β-CD O-4-plane, point their COOH groups toward the β-CD O-6–H-side and incline 52° against the O-4 plane. In form **II**, the fully occupied BA #1 is enclosed in the cavity of β-CD #1 similarly to form **I** while the half occupied BA #2 is located at 2.68 Å beneath the O-4 plane of β-CD #2 and incline 67° against the O-4 plane (Fig. 2). The preferred orientation of BA with the COOH group directing toward the β-CD O-6 side observed in the crystal forms **I** and **II** is consistent with the results obtained in solution by NMR spectroscopy[10] and potentiometric titration[11] as well as in the gas phase by FAB mass spectrometry[12] and theoretical calculations.[13]

The two BAs are maintained in positions by hydrogen bonding with two bridging water sites W-17 (1.0) and W-2 (0.5): O-1Z_1···W-17···O-1Z_2 and O-2Z_1···W-2···O-2Z_2 (Fig. 3). Water sites W-17 and W-2 also hydrogen bond with the O-6–H groups of β-CD #2: W-17···O-66_2 and W-2···O-62B_2 (Fig. 3). The O···O distances involved are 2.59(3)–2.75(3) Å (Table 4). Note that the half occupied BA #2 and water site W-1 do not exist simultaneously because the distance O-1Z···W-1 of 1.00(3) Å is too short to be accounted for hydrogen bonding. Disordered EtOH (0.7) in form **I** is found included in the β-CD-dimer cavity, whereas in form **II** it is located in the intermolecular spaces between β-CD macrocycles and hydrogen bonds with the O-21–H, O-35–H, O-26–H, O-37–H groups of β-CD #1 and water site W-13 (Figs. 3 and 4).

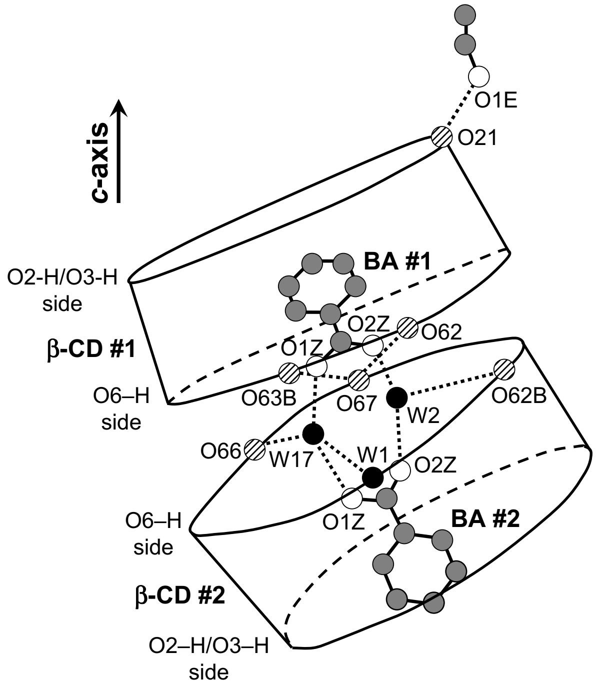


Figure 3. Schematic presentation of the BA inclusion geometry in the β-CD cavity. The two BA molecules pointing their COOH groups to the β-CD O-6–H side make indirect hydrogen bonds to each other via the bridging water sites W-2 and W-17. The β-CD heterodimer (#1, #2) is stabilized by hydrogen bonding between the adjacent O-6–H groups: O-63B_1···O-67_2···O-62_1. Dotted lines indicate hydrogen bonds with O···O separation $\leqslant$3.2 Å. Atoms are shown with circles: gray, white (C, O atoms of BA, EtOH); hatched (O atoms of β-CD OH); and black (O atoms of water).

3.4. Hydrogen bonding network

Water molecules (21) are distributed over 28 positions, forming two clusters filled the spaces between the screw-channel-oriented

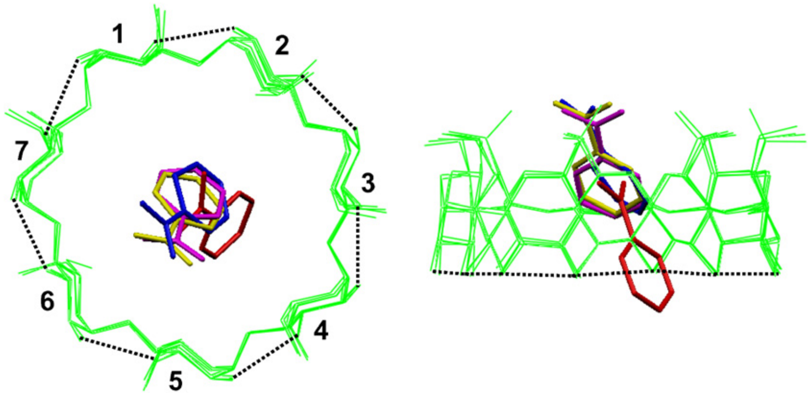


Figure 2. Structural overlay of the four β-CDs and BAs in the two crystal forms of the β-CD–BA inclusion complex: **I** (triclinic, *P*1) and **II** (monoclinic, *C*2). Similarity of the four β-CDs is shown with green lines. Distinction in inclusion geometry of the four BAs is indicated with stick models: yellow (BA #1), magenta (BA #2) of **I** and blue (BA #1), red (BA #2) of **II**. Annular conformation of β-CDs is stabilized by interglucose O-3(n)···O-2($n+1$) hydrogen bonds (dotted lines). Drawn with MERCURY.[34]

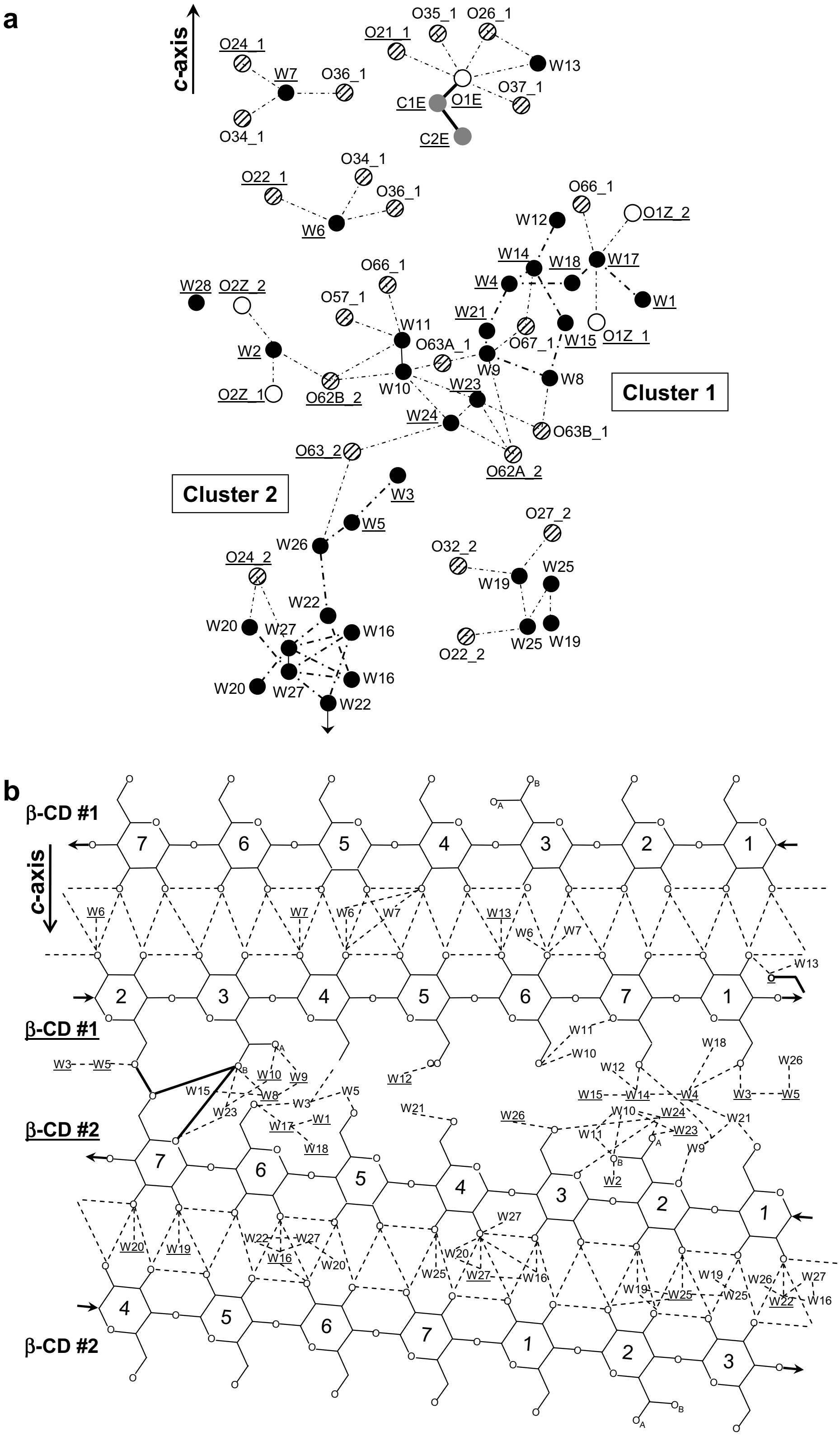


Figure 4. O-H···O hydrogen bonding networks involving (a) the two water clusters and (b) the β-CD dimers with O···O distance ⩽3.2 Å. In (a), water clusters 1 and 2 are in interstices between the screw-channel-oriented β-CD dimers. Dashed-dotted lines indicate the hydrogen bonds with O···O distances in Å given in Table 3; thicker lines emphasize the two water clusters. Arrow at water site W-22 shows the hydrogen bond with W-26. Atoms are represented with different circles: black (water O); hatched (β-CD O-2, O-3, O-6); white (EtOH O); and gray (EtOH C). In (b), dashed lines indicate O-H···O hydrogen bonds; thicker solid lines emphasize the hydrogen bonds stabilizing the β-CD heterodimer (#1 and #2). Arrows show the connection of glucose units in β-CD. In (a) and (b), the underlined atomic names indicate atoms in the general position *x*, *y*, *z*; the others are in symmetry related positions.

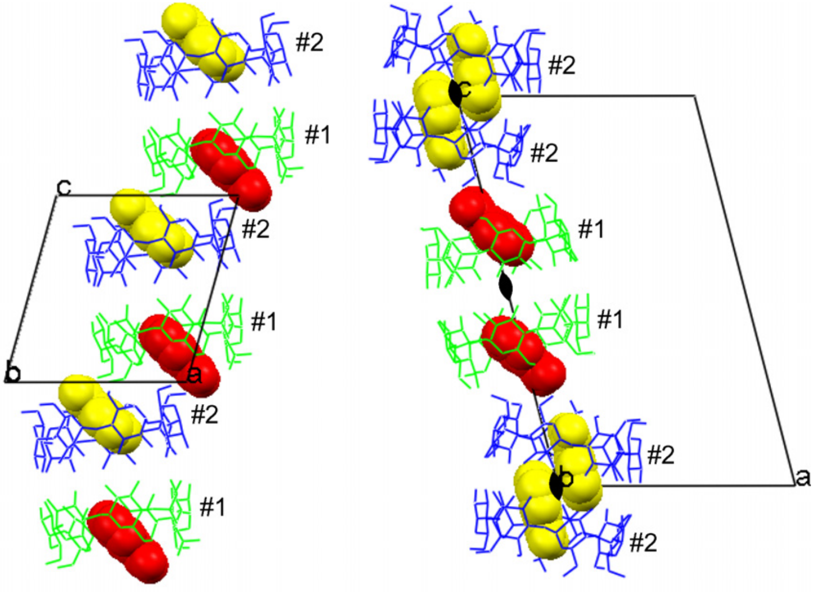
β-CD dimers along the *c*-axis. Water cluster 1 comprises 10 water sites of a distorted hydrogen bond hexagon (W-4···W-14···W-15···W-8···W-9···W-21···W-4) and two short hydrogen bond chains (W-4···W-18···W-17···W-1 and W-14···W-12) (Fig. 4a, Table 4). Water cluster 2 consists of twofold symmetry related 14 water sites: W-3···W-5···W-26···W-22···W-16···W-27···W-20. Some water sites form short hydrogen bond chains: W-19···W-25···W-25···W-19 and W-10···W-23···W24. The remaining water sites (W-2, W-6, W-7, W-11, W-13) are isolated from the others but hydrogen bond to the surrounding β-CD OH groups, except for water site W-28 that is situated at the special position (Fig. 4a, Table 4).

Besides the intermolecular H_2O–H_2O hydrogen bonding networks mentioned above, some intermolecular β-CD–H_2O hydrogen bonding networks should be noted. The water sites hydrogen bonding with the β-CD OH groups are listed sequentially for glucose #1–7. The O-6–H groups are systematically hydrated: W-3/W-4, W-5, W-8–W-10/W-23, W-3, W-12, W-10/W-11, W-9/W-14 for β-CD #1 and W-21, W-2/W-10/W-12/W-23/W-24, W-24/W-26, W-21, W-5, W-3/W-17,– for β-CD #2 (Fig. 4b, Table 4). The O-3–H groups of β-CD #2 are also hydrated: W-22, W-25, –, W-27, –, W-16, W-19. Because the present X-ray diffraction analysis does not give the hydrogen atoms of β-CD OH groups and water molecules, structural details of hydrogen bonds cannot be obtained. By contrast, neutron diffraction permits accurate determination of the H-atom positions, providing the CD hydrates an excellent model system for detailed study of hydrogen bonding in biological structures.[26]

3.5. β-CD dimer and crystal packing

The asymmetric unit consists of a β-CD heterodimer (#1, #2) stabilized by intermolecular O-62_1···O-67_2···O-63B_1···O-57_2 hydrogen bond chain with O···O distances 2.54(2)–3.11(2) Å (Figs. 3, 4b, Table 4). The O-4 planes of β-CD #1, #2 are inclined by 10.7(1)°, −10.0(1)° with respect to the *a*–*b* plane and by 20.7(1)° with respect to each other. The β-CD heterodimer is replicated by twofold rotation symmetry, giving rise to repeating units of the homodimers of β-CD #1 and #2 and ultimately a screw-channel-type packing (Fig. 5). The two twofold symmetry related β-CD homodimers with head-to-head arrangement are sustained along the *c*-axis by intermolecular O-2(*n*)_1/O-3(*n*)_1···O-2(*m*)_1/O-3(*m*)_1($-x$, y, $-z+1$) and O-2(*n*)_2/O-3(*n*)_2···O-2(*m*)_2/O-3(*m*)_2($-x$, y, $-z$) hydrogen bonds with O···O distances 2.79(1)–3.18(1) Å and 2.76(1)–3.20(1) Å, respectively. Regarding the O···O separation $\leqslant$3.2 Å, the 28 intermolecular O–H···O hydrogen bonds may form in each β-CD homodimer. The CD dimeric structures with head-to-head arrangement 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.[27,28] However, a recent high resolution (0.65 Å) synchrotron diffraction study at 100 K of the β-CD–1,12-dedecanedioic acid inclusion complex[29] discloses that only the β-CD O-3–H groups are engaged in the 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 deserves further investigation.

A glimpse at the crystal packing of form **I** (triclinic, *P*1)[9] and form **II** (monoclinic, *C*2) of the β-CD–BA inclusion complex with a structural motif of the β-CD dimer gives a pseudo mirror-image relation. However, a closer look reveals structural discrepancy, particularly the BA orientation in the β-CD cavity. In form **I**, there is no interaction between the embedded BAs while in form **II**, there are π–π interactions between the twofold symmetry related BAs included in the cavity of β-CD homodimer #2; the interplanar distance is 3.56(1) Å (Fig. 5). The packing of β-CD dimer has been categorized by Mentzafos and co-workers using the different lateral displacements of the adjacent β-CD dimeric layers into four modes: channel, intermediate, screw-channel and chessboard.[30] Tetrad named from a series of interdimer hydrogen bonds between four O-6–H groups has been reported later by Stezowski and co-workers[31] and further discussed by



(a) Form **I**: triclinic, *P*1 (b) Form **II**: monoclinic, *C*2

Figure 5. Distinction of crystal packing in the β-CD–BA inclusion complexes: (a) form **I** (triclinic, *P*1; intermediate–tetrad type) and (b) form **II** (monoclinic, *C*2; screw-channel type). The β-CD dimer and embedded BAs are shown with wireframe and space-filling models: green–red (#1) and blue–yellow (#2). The twofold rotation axes (⧫) parallel to *b*-axis at *c* = 0, 0.5 build the screw-channel-type packing of form **II**. Water, EtOH molecules and H atoms are omitted for clarity. View down along *b*-axes. Drawn with MERCURY.[34]

Mentzafos and co-workers.[32] Two crystal forms of the β-CD–BA inclusion complexes with different dimeric lateral-displacements of 6.49 Å for form **I** and 2.55 Å for form **II** can be classified into the average of intermediate and tetrad types and screw-channel type, respectively.

4. Summary

Two polymorphs of the β-cyclodextrin–benzoic acid (β-CD–BA) inclusion complex are obtained from saturated solution of β-CD and BA in the 50% aqueous EtOH within a week for form **I**[9] (triclinic, *P*1) and after 1.5 years for form **II** (monoclinic, *C*2).

- The β-CD molecular structures are isostructural with 'round' conformation stabilized by intramolecular O-3(n)···O-2($n+1$) hydrogen bonds. The BA inclusion geometries are similar with a preferred orientation, that is, BAs are situated above the O-4 plane, point their COOH groups to the β-CD O-6 side, incline 52° with respect to the O-4 plane and are mainly maintained in positions by hydrogen bonding with the surrounding water molecules.
- In the crystal lattice, β-CDs form dimers as structural motif of packing: the screw-channel type (form **II**) and the average of intermediate and tetrad types (form **I**). The lateral displacement of the neighboring dimeric layers of form **II** is longer than form **I**: 6.49 Å versus 2.55 Å.
- Polymorphism in the β-CD–BA complex manifests a kinetically controlled crystal growth following the Ostwald's rule:[4] the more stable, higher symmetric form (monoclinic, *C*2) requires a much longer time (slower kinetics) for assembly in the crystal lattice than does the less stable, lower symmetric form (triclinic, *P*1).

5. Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 680567. 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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