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A new crystal form of β-cyclodextrin–ethanol inclusion complex: channel-type structure without long guest molecules

Thammarat Aree,[a,*] Narongsak Chaichit[b]

[a] *Department of Chemistry, Faculty of Science, Chulalongkorn University, Phyathai Rd., Pathumwan, Bangkok 10330, Thailand*
[b] *Department of Physics, Faculty of Science and Technology, Thammasat University, Rangsit, Pathum Thani 12121, Thailand*

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Abstract

A new crystal form of β-cyclodextrin (β-CD)–ethanol–dodecahydrate inclusion complex [$(C_6H_{10}O_5)_7 \cdot 0.3C_2H_5OH \cdot 12H_2O$] belongs to monoclinic space group $C2$ (form **II**) with unit cell constants $a = 19.292(1)$, $b = 24.691(1)$, $c = 15.884(1)$ Å, $\beta = 109.35(1)°$. The β-CD macrocycle is more circular than that of the complex in space group $P2_1$ [form **I**: J. Am. Chem. Soc. 113 (1991) 5676]. In form **II**, a disordered ethanol molecule (occupancy 0.3) is placed in the upper part of β-CD cavity (above the O-4 plane) and is sustained by hydrogen bonding to water site W-2. In form **I**, an ethanol molecule located below the O-4-plane is well ordered because it hydrogen bonds to surrounding O-3–H, O-6–H groups of the symmetry-related β-CD molecules. In the crystal lattice of form **I**, β-CD macrocycles are stacked in a typical herringbone cage structure. By contrast, the packing structure of form **II** is a head-to-head channel that is stabilized at both O-2/O-3 and O-6 sides of each β-CD by direct $O_{CD} \cdots O_{CD}$ and indirect $O_{CD} \cdots O_W \cdots (O_W) \cdots O_{CD}$ hydrogen bonds. The 12 water molecules are disordered in 18 positions both inside the channel-like cavity of β-CD dimer (W-1–W-6) and in the interstices between the β-CD macrocycles (W-7–W-18). The latter forms a cluster that is hydrogen bonded together and to the neighboring β-CD O–H groups.

Keywords: β-Cyclodextrin; Ethanol inclusion complexes; Crystal structures; X-ray analysis; Hydrogen bond

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1. Introduction

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

CDs are well known for their ability to form inclusion complexes[2] with a variety of guest molecules fitting partially or completely into the host CD cavity as shown by crystallographic results.[3] In preparation of CD inclusion complexes, ethanol is a common solvent used together with water. Because ethanol has low affinity to the CD, it can be readily displaced by guest molecule and be easily removed by evaporation. However, it is infrequently observed that ethanol cocrystallized to form quaternary complexes of CD-guest-ethanol-hydrate.[3]

Crystal structure of β-CD–ethanol–octahydrate complex in the monoclinic space group $P2_1$ has been investigated unequivocally using both X-ray and neutron radiations.[4–6] For neutron structure at room temperature,[5] one ethanol molecule occupying two sites, three water molecules occupying four sites are found enclosed in the β-CD cavity, and two O-6–H groups are doubly disordered, whereas at 15 K[4] the ethanol, six water molecules (two found in the β-CD cavity), and all O–H groups are well ordered; the other two ones are doubly disordered. The neutron studies at both temperatures of the β-CD–ethanol complex show that the disorder at room temperature is of dynamic nature. The X-ray and neutron structures of β-CD–ethanol complex at room temperature[5] are similar, except for the ethanol in the former is fully occupied. In the original X-ray

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* Corresponding author. Tel.: +66-2-2187584; fax: +66-2-2541309.
E-mail address: mam@atc.atccu.chula.ac.th (T. Aree).

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structure of β-CD–ethanol complex,[6] twofold disorder of the enclosed ethanol molecule was observed; this is similar to the neutron structure at room temperature.[5] One of the three water molecules included in the β-CD cavity, two of five water molecules in the interstices between β-CD macrocycles, and three O-6–H groups are twofold disordered.[6]

In this work, we report a new crystal form of β-CD–ethanol–dodecahydrate complex with higher symmetry in space group $C2$ (form **II**) and compare it with the X-ray structure of the complex in space group $P2_1$ (form **I**, $R = 7.0\%$).[5] Because the original X-ray analysis of β-CD–ethanol complex is less accurate ($R = 11.5\%$),[6] the crystal structure is not used for comparison.

2. Experimental

2.1. Crystallization and X-ray diffraction

β-CD purchased from Cyclolab (Budapest, Hungary), phenol and abs EtOH from Merck were used without further purification. β-CD 0.12 mmol and phenol 0.12 mmol were dissolved in 5 mL of 50% aq EtOH at 60 °C. The values of initial pH of the solution were 3.36 at 60 °C and 3.30 at room temperature (rt). The CD solution cooled down slowly, stayed at rt for many days and its pH was monitored daily. It was found that the pH of CD solution changed slightly after slow solvent evaporation and the rodlike, colorless single crystals grew in 2 weeks. However, the crystals are not of β-CD–phenol complex as expected, but only solvent molecules were found cocrystallized with β-CD. The sample preparation in the present study is similar to those in the studies of Steiner and coworkers[5] and of Tokuoka and coworkers.[6] Exceptions are the use of deuterated samples and higher temperature (70 °C),[5] and the use of higher solvent concentration (65% aq EtOH).[6]

A single crystal was mounted in a glass capillary sealed at both ends by a drop of mother liquor. X-ray diffraction experiment was carried out at rt using a SMART CCD (Bruker) with Mo K_α radiation ($\lambda = 0.71073$ Å) operating at 50 kV, 30 mA. A total of 26,002 reflections were measured in the θ-range 1.36–30.58° (0.7 Å resolution). Data were corrected for Lorentz, polarization, and absorption effects and merged by SADABS[7] and SHELXTL[8] to yield 7197 unique reflections. The crystal belongs to monoclinic space group $C2$ (further details, see Table 1).

Table 1
Summary of crystallographic data for β-CD·$0.3C_2H_5OH \cdot 12H_2O$

Chemical formula	$(C_6H_{10}O_5)_7 \cdot 0.3C_2H_5OH \cdot 12H_2O$
Formula weight	1365
Temperature (°C)	20
Wavelength, Mo K_α (Å)	0.71073
Crystal habit, color	rod, colorless
Crystal size (mm^3)	$0.5 \times 0.5 \times 0.8$
Crystal system	monoclinic
Space group	$C2$
Unit cell dimensions	
a (Å)	19.292(1)
b (Å)	24.691(1)
c (Å)	15.884(1)
β (°)	109.35(1)
V (Å^3)	7139.1(2)
Z	4
D_x (g cm^{-3})	1.218
μ (mm^{-1})	0.11
F(000)	2759
Diffractometer	SMART CCD (Bruker)
θ range for data collection (°)	1.36–30.58
Resolution (Å)	0.70
Measured reflections	26,002
Unique reflections	7197 ($R_{int} = 0.055$)
Index ranges	$0 \le h \le 24$, $-30 \le k \le 29$, $0 \le l \le 19$
Unique reflections [$F^2 > 2\sigma(F^2)$]	4352
Structure solution	direct methods (SHELXS-97)
Refinement method	full matrix least-squares on F^2
Weighting scheme	$w = [S^2(F_o^2) + (0.1184P)^2 + 2.6441P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$
R [$F^2 > 2\sigma(F^2)$]	R [a] $= 0.073$, wR [b] $= 0.127$
R (all data)	R [a] $= 0.178$, wR [b] $= 0.214$
Goodness of fit	1.037
Highest peak/deepest hole (e Å^{-3})	0.34/−0.22

[a] $R = \Sigma \lVert F_o \rvert - \lvert F_c \rVert / \Sigma \lvert F_o \rvert$.
[b] $wR = \Sigma \{ w(F_o^2 - F_c^2)^2 / \Sigma\, w(F_o^2)^2 \}^{1/2}$.

2.2. Structure determination and refinement

The crystal structure was determined by direct methods with program SHELXS-97,[9] providing all β-CD non-H atoms which were used as initial phases for refinement. Water oxygen atoms, and most of CH, CH_2 H-atoms of β-CD could be located by difference Fourier electron density maps guided by the graphic program XTALVIEW.[10] The remaining H atoms were placed at theoretical positions according to the 'riding model'.[11] Difference Fourier electron density maps revealed the absence of the phenol molecule in the β-CD cavity, but a disordered EtOH (occupancy 0.3) was found instead. The structures was refined by full-matrix least-squares on F^2 with program SHELXL-97.[11] Anisotropic refinement of 1008 atomic parameters against 4352 X-ray diffraction data with $F_o^2 > 2\sigma(F_o^2)$ converged at $R =$

0.073 (except for EtOH molecule, some water sites that were refined isotropically). The severely disordered β-CD O-6–H groups and water molecules made refinement difficult. All O-6–H groups are doubly disordered, except for those of glucose residues 2, 5 that are fully occupied. The 12 water molecules are distributed over 18 positions (average occupancy 0.67) both inside and outside the β-CD cavity. Some water sites were found located on the special positions along the twofold rotation axes (e.g., W-5, W-6, W-7, W-11, W-15, particularly W-7 was placed at the center of unit cell) (Table 2). The β-CD structure exhibits normal thermal motion with U_{eq} in the ranges 0.05–0.17 (β-CD skeleton), 0.08–0.22 Å^2 (β-CD O-6), whereas water sites and EtOH show slightly higher thermal motion with U_{eq} 0.10–0.32 and 0.10–0.21 Å^2, respectively (Table 2, Fig. 1(a and b)).

A summary of crystallographic data, list of final fractional atomic coordinates and equivalent isotropic thermal displacement factors, and list of geometrical parameters are given in Tables 1–3, respectively. The atomic numbering scheme is that used conventionally for carbohydrates (i.e., the first number denotes the position in the glucose and the second number the glucose number in the CD macrocycle). Letters A, B indicate disordered atoms. For example, O-63A denotes site A of the disordered O-6 of glucose unit 3. In addition, letter E shows EtOH molecule. For comparison, the glucose units of β-CD in form **I** are relabeled, whereas the labeling of water and EtOH is the same.

3. Results and discussion

3.1. Structural comparison of β-CD macrocycles

The β-CD molecules in forms **II** and **I** are similar as shown with moderate rms deviation of superposition 0.39 Å (all β-CD O-6, H atoms are excluded from the calculations) (Fig. 2). The former is more circular than the latter as indicated by short spans of Cremer–Pople puckering parameters Q, θ,[12] tilt angles, and O-4($n+1$)···O-4(n)···O-4($n-1$) angles in the ranges 0.55–0.58 Å, 1–4°, 4.7–10.5°, and 126.6–130.1°, respectively (Table 3). The corresponding values of form **I** are 0.52–0.58 Å, 1–9°, 3.6–26.2°, 124.5–130.6°, respectively.[5] In addition, an annular conformation of β-CD is also evidenced by torsion angles ϕ, ψ about glycosidic O-4, deviation of O-4 atoms from their common least-squares plane, and O-3(n)···O-2($n+1$) distances representing the intramolecular O-3(n)···O-2($n+1$) hydrogen bonds, which are 107.9–116.6°, 122.7–130.4°, <0.06 Å, 2.79–2.90 Å for form **II** (Figs. 1 and 2, Table 3), and 103.2–118.6°, 114.0–136.5°, <0.27 Å, 2.75–2.96 Å for form **I**.[5]

Table 2
Fractional atomic coordinates and equivalent isotropic thermal displacement factors of β-CD·$0.3C_2H_5OH\cdot 12H_2O$

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
C-11	0.7060(4)	0.5004(3)	0.6795(4)	0.0700(16)
C-21	0.6758(4)	0.5340(2)	0.5956(4)	0.0667(15)
C-31	0.7285(4)	0.5791(2)	0.5942(4)	0.0607(14)
C-41	0.7451(4)	0.6125(2)	0.6793(4)	0.0575(14)
C-51	0.7719(4)	0.5765(3)	0.7612(4)	0.0751(18)
C-61	0.7798(8)	0.6071(4)	0.8485(5)	0.136(4)
O-21	0.6589(3)	0.50119(18)	0.5170(3)	0.0841(13)
O-31	0.6978(3)	0.61310(17)	0.5179(3)	0.0782(12)
O-41	0.8009(2)	0.65058(14)	0.6814(2)	0.0565(9)
O-51	0.7204(3)	0.53251(18)	0.7562(3)	0.0828(13)
O-61A [a]	0.7124(11)	0.6319(9)	0.8430(10)	0.217(11)
O-61B [a]	0.8053(16)	0.5721(8)	0.9221(11)	0.210(9)
C-12	0.7879(4)	0.7074(2)	0.6879(4)	0.0569(14)
C-22	0.8046(3)	0.7366(2)	0.6134(3)	0.0570(13)
C-32	0.8841(3)	0.7293(2)	0.6240(3)	0.0535(12)
C-42	0.9308(3)	0.7502(3)	0.7162(3)	0.0551(13)
C-52	0.9090(3)	0.7230(3)	0.7903(4)	0.0611(14)
C-62	0.9448(5)	0.7480(3)	0.8812(4)	0.0763(18)
O-22	0.7575(2)	0.71768(15)	0.5279(2)	0.0661(10)
O-32	0.9009(3)	0.75872(19)	0.5563(3)	0.0779(12)
O-42	1.0069(2)	0.73641(14)	0.7295(2)	0.0573(9)
O-52	0.8304(2)	0.72828(16)	0.7725(2)	0.0626(10)
O-62	0.9321(3)	0.8050(2)	0.8808(3)	0.0918(14)
C-13	1.0605(3)	0.7784(3)	0.7571(4)	0.0630(15)
C-23	1.0987(3)	0.7838(2)	0.6868(4)	0.0596(14)
C-33	1.1423(3)	0.7330(2)	0.6858(3)	0.0549(13)
C-43	1.1961(3)	0.7227(2)	0.7786(4)	0.0574(13)
C-53	1.1549(4)	0.7184(3)	0.8451(4)	0.0735(17)
C-63	1.2043(6)	0.7123(4)	0.9422(5)	0.129(4)
O-23	1.0457(2)	0.79452(17)	0.6021(3)	0.0756(11)
O-33	1.1812(2)	0.73900(17)	0.6245(3)	0.0685(10)
O-43	1.2330(2)	0.67242(14)	0.7764(2)	0.0593(9)
O-53	1.1117(2)	0.76761(17)	0.8417(3)	0.0715(11)
O-63A [a]	1.2508(5)	0.7567(5)	0.9699(5)	0.126(4)
O-63B [a]	1.1839(14)	0.7214(9)	1.0174(10)	0.160(9)
C-14	1.3101(4)	0.6712(3)	0.8123(4)	0.0654(15)
C-24	1.3397(4)	0.6487(2)	0.7408(4)	0.0669(15)
C-34	1.3154(4)	0.5897(2)	0.7215(4)	0.0593(14)
C-44	1.3386(3)	0.5570(2)	0.8059(4)	0.0559(13)
C-54	1.3099(5)	0.5832(3)	0.8751(4)	0.0672(16)
C-64	1.3338(6)	0.5546(3)	0.9636(5)	0.111(3)
O-24	1.3176(2)	0.68223(16)	0.6637(3)	0.0728(11)
O-34	1.3466(3)	0.56774(16)	0.6582(3)	0.0778(12)
O-44	1.3083(2)	0.50394(14)	0.7851(2)	0.0551(9)
O-54	1.3345(2)	0.63828(16)	0.8896(3)	0.0700(11)
O-64A [a]	1.4092(5)	0.5539(3)	1.0020(4)	0.105(3)
O-64B [a]	1.3317(19)	0.5737(10)	1.0457(12)	0.160(10)
C-15	1.3560(3)	0.4577(2)	0.8079(3)	0.0518(12)
C-25	1.3371(4)	0.4226(3)	0.7245(4)	0.0577(14)
C-35	1.2600(3)	0.4016(2)	0.7006(3)	0.0524(12)
C-45	1.2507(3)	0.3725(2)	0.7804(3)	0.0486(12)
C-55	1.2740(3)	0.4076(2)	0.8629(3)	0.0539(12)
C-65	1.2761(4)	0.3792(3)	0.9479(4)	0.0661(16)
O-25	1.3509(2)	0.45055(16)	0.6539(3)	0.0675(10)
O-35	1.2442(2)	0.36492(15)	0.6271(2)	0.0663(10)

Table 2 (*Continued*)

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
O-45	1.17411(19)	0.35790(15)	0.7582(2)	0.0564(9)
O-55	1.3469(2)	0.42854(14)	0.8800(2)	0.0568(9)
O-65	1.3268(3)	0.33456(18)	0.9667(3)	0.0829(13)
C-16	1.1563(4)	0.3044(3)	0.7707(4)	0.0646(14)
C-26	1.1018(3)	0.2831(3)	0.6820(4)	0.0643(14)
C-36	1.0305(3)	0.3147(3)	0.6587(3)	0.0599(14)
C-46	0.9990(3)	0.3109(3)	0.7332(3)	0.0619(14)
C-56	1.0567(4)	0.3307(4)	0.8208(4)	0.082(2)
C-66	1.0303(5)	0.3238(7)	0.9015(5)	0.171(7)
O-26	1.1347(2)	0.28497(18)	0.6155(2)	0.0687(10)
O-36	0.9779(2)	0.2931(2)	0.5783(2)	0.0737(12)
O-46	0.9349(2)	0.34487(16)	0.7119(3)	0.0658(10)
O-56	1.1233(2)	0.3008(2)	0.8392(2)	0.0866(14)
O-66A [a]	1.0014(8)	0.2744(7)	0.9092(7)	0.143(6)
O-66B [a]	1.0903(6)	0.3165(7)	0.9821(6)	0.143(5)
C-17	0.8678(3)	0.3210(3)	0.7136(4)	0.0591(14)
C-27	0.8100(4)	0.3315(2)	0.6253(4)	0.0598(14)
C-37	0.7949(3)	0.3923(2)	0.6112(3)	0.0579(13)
C-47	0.7745(3)	0.4154(2)	0.6882(3)	0.0571(13)
C-57	0.8334(4)	0.4011(3)	0.7773(4)	0.0697(16)
C-67	0.8082(5)	0.4138(4)	0.8582(4)	0.098(2)
O-27	0.8278(2)	0.30790(16)	0.5533(2)	0.0673(10)
O-37	0.7361(2)	0.40189(17)	0.5301(3)	0.0720(11)
O-47	0.7703(2)	0.47296(15)	0.6779(3)	0.0656(10)
O-57	0.8469(2)	0.34354(18)	0.7843(2)	0.0689(11)
O-67A [a]	0.7441(6)	0.3822(5)	0.8509(6)	0.119(3)
O-67B [a]	0.8688(8)	0.4151(8)	0.9401(7)	0.126(5)
C-1E [b]	1.0955(15)	0.5078(12)	0.8776(17)	0.104(8)
C-2E [b]	1.159(2)	0.477(2)	0.943(3)	0.185(18)
O-1E [b]	1.112(2)	0.5220(16)	0.7973(18)	0.205(13)
W-1 [c]	1.020(3)	0.5810(19)	0.767(3)	0.272(17)
W-2 [c]	0.969(3)	0.525(2)	0.751(3)	0.241(18)
W-3 [c]	0.863(3)	0.612(2)	0.466(4)	0.30(2)
W-4 [c]	0.822(3)	0.504(2)	0.461(4)	0.294(18)
W-5 [c]	1.0000	0.5310(14)	0.5000	0.307(12)
W-6 [c]	1.0000	0.655(2)	0.5000	0.32(2)
W-7 [c]	0.5000	0.5000	0.5000	0.249(13)
W-8 [c]	0.6040(5)	0.4259(4)	0.7996(6)	0.167(3)
W-9 [c]	1.0434(3)	0.8806(2)	0.9159(4)	0.1003(15)
W-10 [c]	1.3764(10)	0.6956(9)	1.0687(17)	0.237(11)
W-11 [c]	1.5000	0.6504(13)	1.0000	0.258(18)
W-12 [c]	1.4375(10)	0.6842(6)	0.6083(19)	0.236(10)
W-13 [c]	1.4836(10)	0.5476(15)	0.614(3)	0.31(2)
W-14 [c]	1.4234(12)	0.5368(5)	1.1794(8)	0.201(7)
W-15 [c]	1.5000	0.4689(3)	1.0000	0.115(2)
W-16 [c]	1.4098(4)	0.3783(4)	0.4745(7)	0.146(4)
W-17 [c]	1.4854(9)	0.4168(11)	0.6491(11)	0.229(11)
W-18 [c]	1.0862(7)	0.1852(5)	0.5364(12)	0.207(6)

[a] Twofold disordered O-61, O-63, O-64, O-66, O-67 with the occupancy factors 0.5, 0.5; 0.65, 0.35; 0.7, 0.3; 0.5, 0.5; 0.6, 0.4 for sites A, B, respectively.

[b] Occupancy factor of ethanol is 0.3.

[c] Occupancy factors of water sites are 0.4(W-1), 0.3(W-2), 0.4(W-3), 0.4(W-4), 1.0(W-5), 0.6(W-6), 0.6(W-7), 1.0(W-8), 1.0(W-9), 0.6(W-10), 0.6(W-11), 0.7(W-12), 0.5(W-13), 0.7(W-14), 1.0(W-15), 0.8(W-16), 0.6(W-17), 0.8(W-18).

A striking difference is observed for the disorder and orientation of O-6–H groups. In form **I**, the β-CD has two doubly disordered O-63, O-64 groups, whereas in form **II**, it has five twofold disordered O-61, O-63, O-64, O-66, O-67 groups. In form **II**, all C-6–O-6 groups point 'away' from the β-CD cavity as shown by the torsion angles O-5–C-5–C-6–O-6 in the range −58.8 to −73.7°. Exceptions are the disordered O–61B, O–63B, O–64B, O–66B, O–67B that point 'inward' to the β-CD cavity with the corresponding angles in the range 30.1–76.7° (Figs. 1 and 2, Table 3). This contrasts to the orientation of O-6–H groups in form **I** as only the disordered O–63B, O–64B that point 'inward' to the β-CD cavity (Fig. 2).

3.2. Inclusion geometry of ethanol in the β-CD cavity

Due to a small size of ethanol molecule and a large volume of β-CD cavity, it is plausible that ethanol is placed and oriented differently in the β-CD cavity to yield a stable inclusion complex with adequate host–guest interactions (Fig. 2). In form **I**, a fully occupied ethanol located below the O-4 plane points its C–O bond to the O-2/O-3 side of the β-CD cavity. It is maintained in position by hydrogen bonding to the surrounding O–H groups (e.g., O-63A, O-34, O-64A, O-64B) with O···O distances 2.76–3.40 Å. Upper part of β-CD cavity is occupied by water sites W-6, W-8, W-9 with occupancies 0.95, 0.73, 0.80. By contrast, in form **II**, a disordered ethanol (occupancy 0.3) is placed above the O-4 plane with its O atom is almost situated on this plane. It is sustained by hydrogen bonding to water site W-2 (occupancy 0.3) and by van der Waals interactions to atoms O-44, C-54 with O···O, O···C distances 2.60, 3.89, 3.91 Å, respectively. The ethanol–W-2 and water site W-1 (occupancy 0.3) are mutually exclusive, i.e., water site W-1 cannot be occupied simultaneously with ethanol and water site W-2. Because the O-1E···W-1, W-2···W-1 distances are rather short 2.22, 1.67 Å that cannot be accounted for hydrogen bonds (Fig. 3(a)). The occupancies of ethanol, water sites W-1, and W-2 add up to one. Regarding the environment of ethanol in the β-CD cavity, ethanol in form **II** with fewer numbers of hydrogen bond interactions to β-CD O–H groups is less energetically stable than in form **I** (Fig. 2).

3.3. Disordered water molecules

In form **II**, the 12 water molecules are distributed over 18 positions (average occupancy 0.67) with only water sites W-8, W-9, W-15 that are well ordered, whereas the rest are disordered with occupancies 0.3–0.8 (Fig. 1, Table 2). Water sites W-1, W-2 are located in the β-CD cavity, water sites W-3–W-6 in the channel-like cavity of β-CD dimer, and the others in the intermolecular space between β-CD macrocycles (Fig. 1(a and b), Fig. 3(a)).

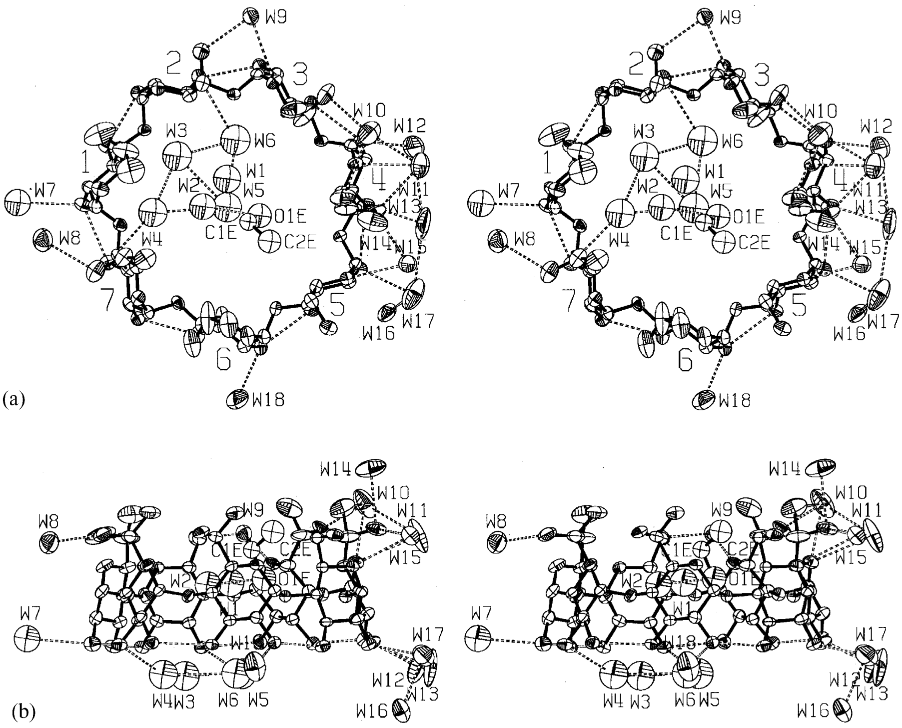

Fig. 1. ORTEP-III[24] stereo plots in: (a) top; and (b) side views of the β-CD·0.3C_2H_5OH·12 H_2O inclusion complex drawn with thermal ellipsoid (30%) representation. Ellipsoids with and without octant shading are O and C atoms, respectively. Dashed lines indicate possible O–H···O hydrogen bonds with O···O separation within 3.5 Å.

Five water sites (e.g., W-5, W-6, W-7, W-11, W-15) are placed on the special positions along the twofold rotation axes, especially water site W-7 that is at 0.5, 0.5, 0.5 (Fig. 4, Table 2). By contrast, the 7.56 water molecules in form **I** are much well ordered as they are occupied in 9 positions (average occupancy 0.84) and

Table 3
Geometrical parameters of β-CD macrocycle in the ethanol inclusion complex (distances in Å and angles in °)

Residue	1	2	3	4	5	6	7
Q [a], *θ* [b]	0.56, 2	0.57, 4	0.57, 2	0.57, 1	0.55, 3	0.58, 2	0.56, 2
ϕ [c], *ψ* [c]	111.5(5)	110.0(6)	116.6(5)	113.4(5)	107.9(5)	113.9(5)	113.0(5)
	127.7(5)	122.7(5)	129.3(5)	130.4(5)	125.4(5)	128.8(5)	126.2(5)
Tilt angle [d]	9.7(2)	4.7(1)	10.4(1)	13.6(1)	8.1(1)	10.5(1)	10.0(2)
O-4 angle [e]	126.6(1)	130.1(1)	129.4(1)	126.8(1)	128.7(1)	129.7(1)	128.7(1)
Distance							
O-4 deviation [f]	−0.06	0.02	0.04	−0.04	−0.01	0.03	0.01
O-3(*n*)···O-2(*n*+1)	2.81(1)	2.79(1)	2.86(1)	2.90(1)	2.85(1)	2.81(1)	2.84(1)
Torsion angle							
O-5–C-5–C-6–O-6	−65.7(13) [g]	−66.5(7)	−60.5(8) [g]	−61.6(8) [g]	−62.8(6)	−73.7(10) [g]	−58.8(8) [g]
	59.0(17) [g]		41.1(17) [g]	42.2(22) [g]		30.1(15) [g]	76.7(11) [g]

[a] Cremer–Pople puckering amplitude.[12]

[b] Indicates the deviation from the theoretical chair conformation (ideal value: $\theta = 0$).

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

[e] Angle at each glycosidic O-4: O-4($n+1$)–O-4(n)–O-4($n-1$).

[f] Deviation of O-4 atoms from the least-squares plane through the seven O-4 atoms.

[g] Values for sites A, B of the twofold disordered O-61, O-63, O-64, O-66, O-67 with the occupancy factors 0.5, 0.5; 0.65, 0.35; 0.7, 0.3; 0.5, 0.5; 0.6, 0.4, respectively.

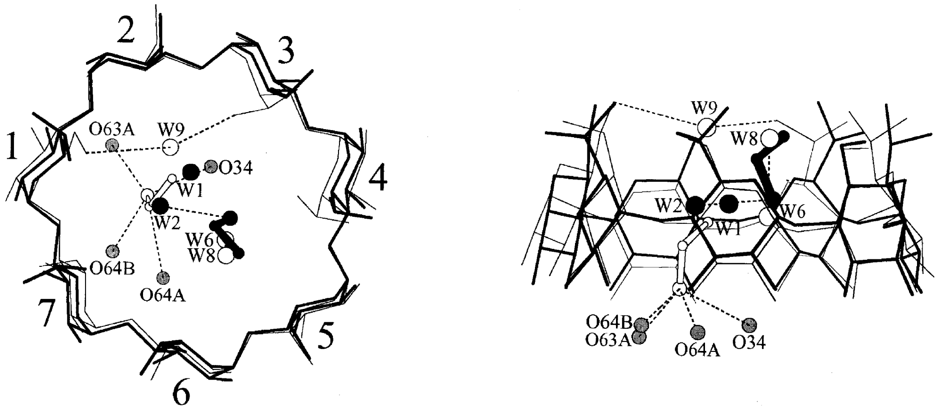

Fig. 2. Superposition of β-CD–ethanol-hydrate structures ($C2$ (form **II**): thick line–black ball-and-stick; $P2_1$ (form **I**): thin line–white ball-and-stick); small balls are C and bigger O. Gray balls are O-3–H, O-6–H groups that are hydrogen bonded to ethanol of form **I**. For clarity, hydrogen atoms not shown. Dashed lines indicate hydrogen bonds with O···O separation within 3.5 Å. Drawn with MOLSCRIPT.[25]

the water sites W-6, W-8, W-9 are enclosed in the β-CD cavity (Fig. 2).

3.4. Hydrogen bonding network

Two water clusters construct a complicate hydrogen bonds network. Water cluster 1 consisting of water sites W-3–W-6 is enclosed in the channel-like cavity of β-CD dimer and hydrogen bonds to O-32–H, O-37–H, O-33–H with O···O distances 3.40–3.48 Å (Fig. 3(a)). Water cluster 2 comprising water sites W-7–W-9, W-12–W-18 is located in the interstices between β-CD macrocycles. It links to cluster 1 via a hydrogen bonds chain W-6···O-32···W-16, and can be divided into three parts (Fig. 3(a)). A main part (W-7, W-16, W-17, W-13) has the feature of a distorted square planar (similar to cluster 1) and is connected to another two parts (i.e., water chains W-12···W18, W-14···W-8···W-9···W-15). Water cluster 2 hydrogen bonds to many surrounding O–H groups of β-CDs with O···O distances 2.73–3.45 Å. In addition, the O-64A–H group bridges the water cluster 2 to the water chain W-10···W-11. Water molecules play an important role as hydrogen bonding mediator in stabilizing the crystal structure. The β-CD O-2–H groups are systematically hydrated by water sites W-7/W-13/W-16, W-18, W-16/W-17, W-12, W-4/W-17, W-18, W-12 (listed sequentially from glucose units 1–7) with O···O distances 2.68–3.49 Å (Fig. 3(b)). Exception is the O-27···W-12 distance that is too long, 3.65 Å. Similar hydration pattern is also found for the β-CD O-3–H, O-6–H groups. In the case of O-3–H groups, the water sites are W-12/W-18, W-6/W-16, W-3, W-13, W-4, W-12/W-18, W-4/W-16 with O···O distances 2.85–3.48 Å, except for the O-35···W-4 distance 3.78 Å (Fig. 3(b)). For O-6-H groups, the water sites are W-10/W-14, W-9, W-10, W-10/W-11/W-14/W-15, W-9, W-10/W-11, W-8 with O···O distances 2.74–3.45 Å (Fig. 3(b)).

3.5. Crystal packing

Packing of β-CD–ethanol complex is not exclusive in a herringbone cage type[13] as observed in space group $P2_1$ (form **I**),[5] but when the complex crystallizes in space group $C2$ (form **II**), the packing structure is a head-to-head channel[13] (Fig. 4 viewed along c-axis). At O-2/O-3 and O-6 sides of each β-CD are stabilized by direct O-2/O-3···O-2/O-3 and O-6···O-6 hydrogen bonds (thick lines in Fig. 3(b)) and by indirect O-2/O-3···W···(W)···O-2/O-3 and O-6···W···(W)···O-6 hydrogen bonds (dashed lines). One or two water molecules link some O-2/O-3···O-2/O-3, O-6···O-6 intermolecular distances that are greater than 3.5 Å. The hydrogen bonding scheme of the present structure is similar to those of the other β-CD complexes that also crystallize in space group $C2$ (e.g., potassium hepta-iodide,[14] *trans*-cinnamic acid,[15] naphthyloxyacetic acid[16]). This contrasts to the β-CD complexes in space group $P1$ (e.g., 4-*t*-butylbenzoic acid,[17] *p*-hydroxylbenzabenzaldehyde,[18] benzoic acid[19]) as all direct O-2/O-3···O-2/O-3 hydrogen bonds may exist because the O···O separations do not exceed 3.5 Å. Note that although there are no long guest molecules embedded in the channel-like cavity of the host molecules inducing a channel type packing, the present β-CD–ethanol complex exhibits a channel structure. This is probably due to β-CD itself tends to arrange in a thermodynamically stable dimer (a motif of channel-type structure) where the intermolecular O–H···O hydrogen bonds can be formed, as evidenced by many CD crystal structures[3] and by recent molecular dynamics studies in aqueous solution[20] and in a vacuum.[21]

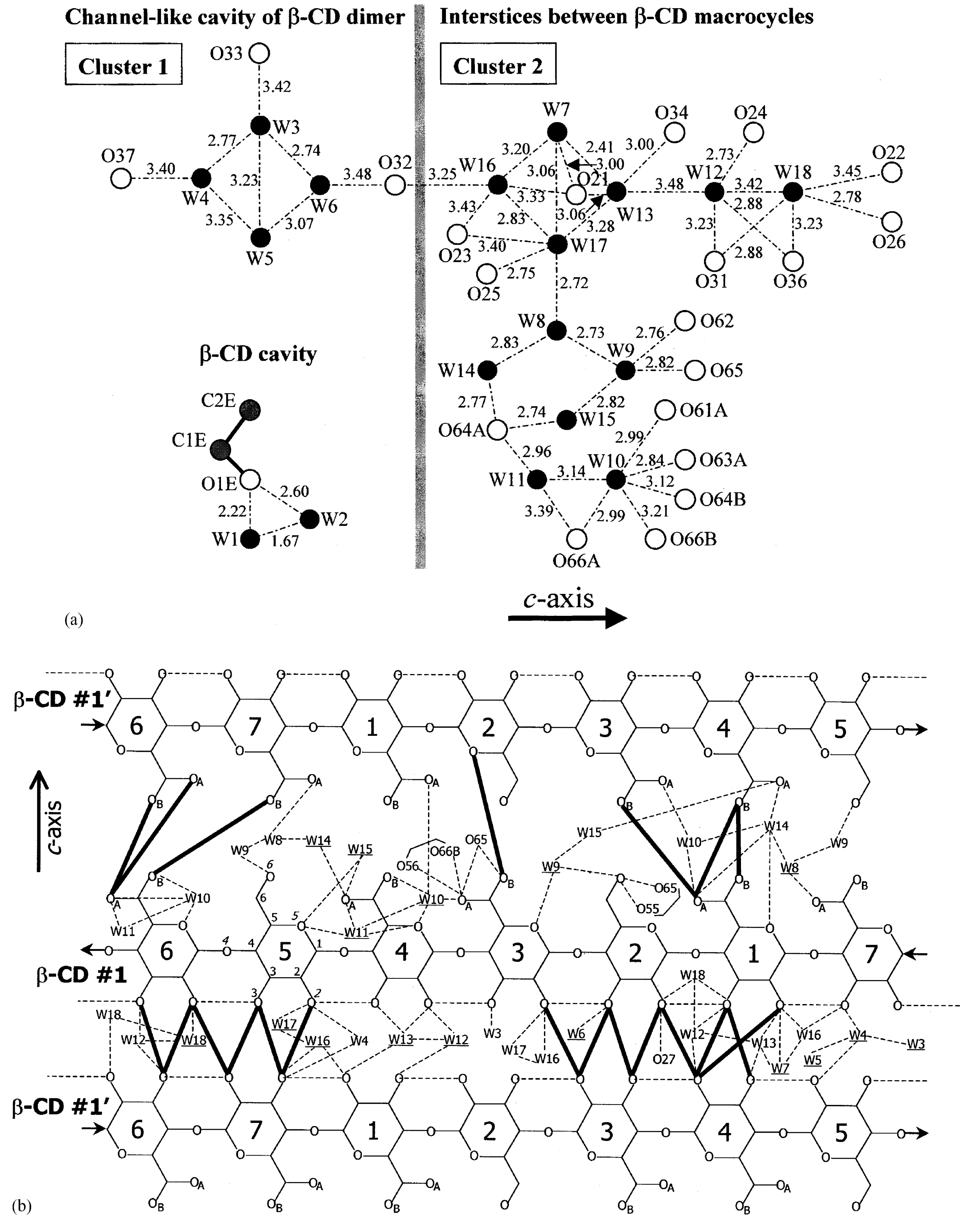

Fig. 3. O–H···O hydrogen bonds network involving: (a) the two water clusters; (b) the head-to-head channel structure of β-CD with O···O distance within 3.5 Å. In (a), water cluster 1 is in the channel-like cavity of β-CD dimer, whereas cluster 2 is in the intermolecular space between the β-CD macrocycles. Dashed–dotted lines indicate the hydrogen bonds with given O···O distances in Å. Exceptions are O-1E···W-1, W-1···W-2 distances that are too short. Water O atoms, CD O-2, O-3, O-6, ethanol O atoms, and ethanol C atom, are represented as filled, unfilled, and gray circles, respectively. In (b), underlined atomic names indicate atoms in the general position x, y, z; the others are in symmetry related positions. Direct (solid lines) and indirect (dashed lines) hydrogen bonds link the β-CD macrocycles, giving rise to an infinite channel. Arrows show connection of glucose units in β-CD. Atomic numbering of the β-CD is given for the glucose residue 5.

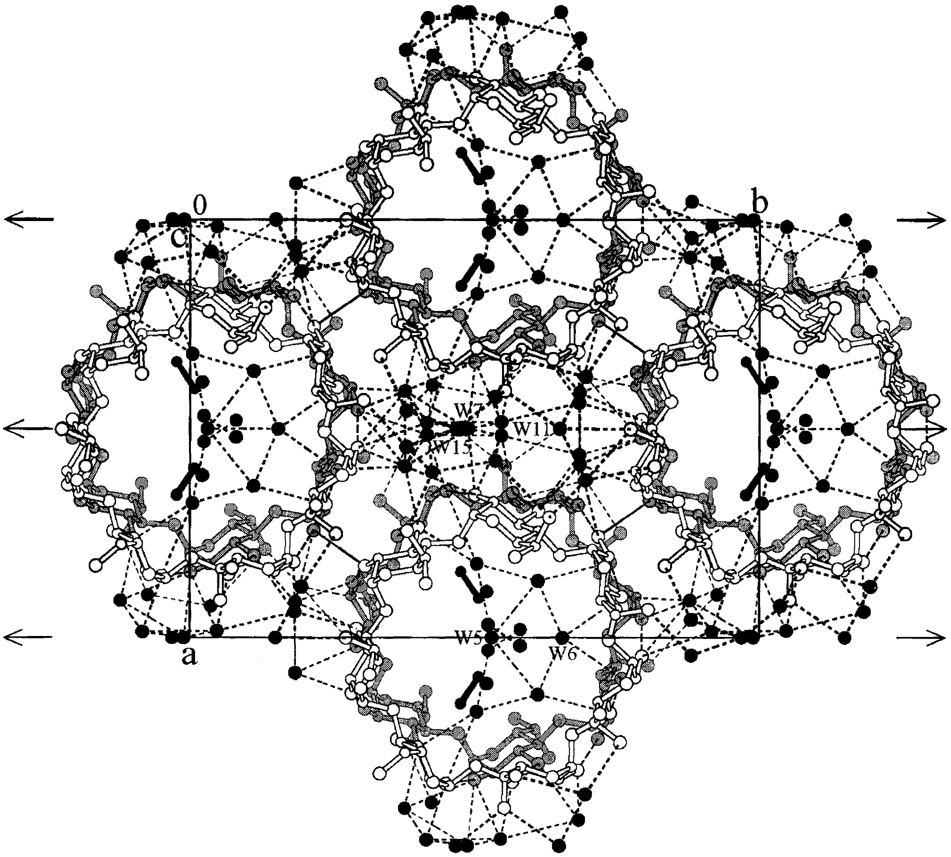

Fig. 4. Crystal packing of β-CD·$0.3C_2H_5OH\cdot 12H_2O$ complex showing a head-to-head channel structure (top view). β-CD molecules are represented in white (upper), gray (lower) ball-and-stick, ethanol in black, and water in black spheres. Arrows indicate the twofold rotation axes parallel to crystallographic *b*-axis. Water sites W-5, W-6, W-7, W-11, W-15 placed on the special positions are labeled. Dashed lines show possible hydrogen bonds with O···O separation within 3.5 Å. Drawn with MOLSCRIPT.[25]

A new crystal form of β-CD–ethanol complex in space group *C*2 (form **II**) was obtained from the crystallization of β-CD and phenol in 50% aqueous ethanol. This suggests the influence of phenol on the crystal formation of β-CD–ethanol complex. The complex between β-CD and phenol is not stable in acidic conditions (pH ~3.3) at high temperature (60 °C) due to deprotonation of the CDs. Consequently, the phenol molecule in the β-CD cavity is replaced by ethanol molecule because the molar ratio of β-CD–ethanol (1:358) is much higher than that of β-CD–phenol (1:1). These reasons are supported by the studies of Kim and coworkers on the α-CD–phenol complex[22] and of Yoshii and coworkers on the complex formation of CDs using anhydrous ethanol as a solvent.[23] The present β-CD–ethanol inclusion complex shows a striking difference from the complex in space group *P*2_1 (form **I**). The β-CD molecular structure of form **II** is more circular when compared to that of form **I**. In addition, the packing structures are different, whereas form **II** prefers a head-to-head channel type, form **I** favors a herringbone cage type.

4. Supplementary material

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CSD-201069. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Tel.: +44-1223-336-408; fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk/conts/retrieving.html).

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References

1. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344–362.
2. Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akademiai Kiado: Budapest, 1982.
3. Cambridge Structural Database, 2002, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK.
4. Steiner, T.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1990**, *112*, 6184–6190.
5. Steiner, T.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1991**, *113*, 5676–5687.
6. Tokuoka, R.; Abe, M.; Fujiwara, T.; Tomita, K.-I.; Saenger, W. *Chem. Lett.* **1980**, 491–494.
7. Sheldrick, G. M. SADABS, Program for Empirical Absorption Correction of Area Dectector Data; University of Göttingen: Germany, 1996.
8. Sheldrick, G. M., SHELXTL, Version 5.0, Siemens Analytical X-ray Instruments Inc., Madison, WI: USA, 1996.
9. Egert, E.; Sheldrick, G. M. *Acta Cryst.* **1985**, *A41*, 262–268.
10. McRee, D. E. *Practical Protein Crystallography*; Academic Press Inc: San Diego, 1993.
11. Sheldrick, G. M.; Schneider, T. R. *Methods Enzymol.* **1997**, *277*, 319–343.
12. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
13. Saenger, W. *Isr. J. Chem.* **1985**, *25*, 43–50.
14. Betzel, C.; Hingerty, B.; Noltemeyer, M.; Weber, G.; Saenger, W.; Hamolton, J. A. *J. Inclusion Phenom. Macrocycl. Chem.* **1983**, *1*, 181–191.
15. Kokkinou, A.; Makedonopoulou, S.; Mentzafod, D. *Carbohydr. Res.* **2000**, *328*, 135–140.
16. Kokkinou, A.; Yannakopoulou, K.; Mavridis, I. M.; Mentzafod, D. *Carbohydr. Res.* **2001**, *332*, 85–94.
17. Makedonopoulou, S.; Tulinsky, A.; Mavridis, I. M. *Supramol. Chem.* **1999**, *11*, 73–81.
18. Braga, S. S.; Aree, T.; Imamura, K.; Vertut, P.; Boal-Palheiros, I.; Saenger, W.; Teixeira-Dias, J. J. C. *J. Inclusion Phenom. Macrocycl. Chem.* **2002**, *43*, 115–125.
19. Aree, T.; Chaichit, N. *Carbohydr. Res.* **2003**, *338*, 439–446.
20. Bonnet, O.; Jaime, C.; Morin-Allory, L. *J. Org. Chem.* **2002**, *67*, 8602–8609.
21. Bonnet, O.; Jaime, C.; Morin-Allory, L. *J. Org. Chem.* **2001**, *66*, 689–692.
22. Kim, H.-J.; Chang, S.-C.; Shim, Y.-B. *Bull. Korean Chem. Soc.* **2002**, *23*, 427–431.
23. Yoshii, H.; Kometani, T.; Furuta, T.; Watanabe, Y.; Linko, Y.-Y.; Linko, P. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2166–2170.
24. Burnett, M. N.; Johnson, C. K. ORTEP-III, Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations; Oak Ridge Natl. Lab., Tennessee: USA, 1996.
25. Kraulis, P. J. *J. Appl. Cryst.* **1991**, *24*, 946–950.