research papers

Structure of the inclusion complex of β-cyclodextrin with 1,12-dodecanedioic acid using synchrotron radiation data; a detailed dimeric β-cyclodextrin structure

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A detailed crystal structure study of the dimeric inclusion complex of β-cyclodextrin (βCD) with 1,12-dodecanedioic acid is presented [IUPAC name: β-cyclodextrin–1,12-dodecanedioic acid (2/1)]. The structure was solved with synchrotron high-resolution data (0.65 Å) at 100 K [crystal data: $P1$, $Z = 1$, $a = 18.153$ (7), $b = 15.456$ (8), $c = 15.251$ (4) Å, $\alpha = 102.81$ (2), $\beta = 113.13$ (2), $\gamma = 99.90$ (3)$^\circ$, $V = 3673$ (3) Å^3, $R = 0.0474$ for 25 134 unique reflections with $I > 2\sigma(I)$]. Moreover, the room-temperature structure is used for comparison [crystal data: $P1$, $Z = 1$, $a = 18.220$ (3), $b = 15.488$ (3), $c = 15.409$ (3) Å, $\alpha = 102.903$ (6), $\beta = 113.122$ (5), $\gamma = 99.708$ (5)$^\circ$, $V = 3735.2$ (12) Å^3, $R = 0.0828$ for 8235 unique reflections with $I > 2\sigma(I)$]. Combining the high-resolution data and the low-temperature made possible the location of the disordered guest molecule, 1,12-dodecanedioic acid, inside the wide cavity of the macrocycle formed by two βCD monomers. Moreover, almost all the H atoms of the βCD macrocycle and many of the water molecules have been located in the low-temperature structure. Thus, for the first time, it has been possible to show in detail, up to now only given by neutron diffraction data, that two βCD monomers self-assemble through O3···O3 intermolecular hydrogen bonds to form the βCD dimer, as well as describe the hydrogen-bonding scheme between the dimer's hydroxyl groups among themselves and with water molecules in the lattice. The long guest threads through two host molecules forming a [3]pseudo-rotaxane. Its polar carboxyl groups, fully hydrated at the primary faces of the βCD dimers, influence their packing so that those faces are exposed to the solvent. This is in contrast to the packing of the β-cyclodextrin complexes of the corresponding aliphatic monoacids, where the dimeric complexes form channels in order to isolate the terminal methyl group from the water environment of the lattice.

1. Introduction

β-Cyclodextrin (βCD), a macrocycle consisting of seven glucose units linked by $\alpha(1–4)$ bonds in a cyclic fashion, has the ability to encapsulate a plethora of compounds to form inclusion complexes (Harata, 1998), the majority of which are dimeric in the crystalline state. The βCD dimer, formed by self-association of the monomers through hydrogen bonding, exhibits sevenfold symmetry (Mentzafos et al., 1991), its shape resembling that of a hollow cylinder. The elongated cavity is hydrophobic, including the intradimer space where the two monomers meet to form hydrogen bonds between their secondary hydroxyl groups. Thus, the βCD dimeric complex composed of two βCD monomers and one or more guest

Table 1
Experimental details.

	Low temperature	Room temperature
Crystal data		
Chemical formula	$2(C_{42}H_{70}O_{35})\cdot C_{12}H_{22}O_4\cdot$ $1.16(C_2H_6O)\cdot 27.46(H_2O)$	$2(C_{42}H_{70}O_{35})\cdot C_{12}H_{22}O_4\cdot$ $0.51(C_2H_6O)\cdot 22.18(H_2O)$
Chemical formula weight	3048.57	2923.49
Cell setting	Triclinic	Triclinic
Space group	$P1$	$P1$
a (Å)	18.153 (7)	18.220 (3)
b (Å)	15.456 (8)	15.488 (3)
c (Å)	15.251 (4)	15.409 (3)
α (°)	102.81 (2)	102.903 (6)
β (°)	113.130 (19)	113.122 (5)
γ (°)	99.90 (3)	99.708 (5)
V (Å^3)	3673 (3)	3735.2 (12)
Z	1	1
D_x (Mg m^{-3})	1.378	1.300
Radiation type	Synchrotron	Cu $K\alpha$
Wavelength (Å)	0.6500	1.54180
μ (mm^{-1})	0.125	1.024
Temperature (K)	100 (2)	293 (2)
Crystal form	Diamond shaped	Diamond shaped
Crystal size (mm)	$0.6 \times 0.4 \times 0.2$	$0.5 \times 0.5 \times 0.3$
Crystal color	Colorless	Colorless
Data collection		
Diffractometer	MAR image plate	Syntex
Data collection method	None	θ–2θ scans
Scan speed (° min^{-1})	–	4.5
Absorption correction	None	Applied
No. of measured reflections	25 720	9805
No. of independent reflections	25 720	9795
No. of observed reflections	25 134	8235
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.041	0.0534
θ_{max} (°)	30.00	55.02
Range of h, k, l	$0 \rightarrow h \rightarrow 27$ $-23 \rightarrow k \rightarrow 23$ $-20 \rightarrow l \rightarrow 20$	$-19 \rightarrow h \rightarrow 17$ $-16 \rightarrow k \rightarrow 16$ $0 \rightarrow l \rightarrow 16$
No. of standard reflections	–	3
Frequency of standard reflections	–	Every 97 reflections
Completeness (%)	91.8	99.6
Refinement		
Refinement on	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0474	0.0828
$wR(F^2)$	0.1376	0.2478
S	1.043	1.041
No. of reflections used in refinement	25 720	9795
No. of parameters	2748	1365
No. of restraints	124	69
H-atom treatment	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0948P)^2$ $+ 0.9466P]$, where P $= (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.1852P)^2$ $+ 2.7569P]$, where P $= (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	4.788	0.562
$\Delta\rho_{max}$ (e Å^{-3})	1.046	0.543
$\Delta\rho_{min}$ (e Å^{-3})	−0.750	−0.413
Extinction method	None	None
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs		
Data collection	*DENZO* (Otwinowski & Minor, 1997)	*CRYSTAL LOGIC* (Strause, unpublished)
Cell refinement	*DENZO* (Otwinowski & Minor, 1997)	*CRYSTAL LOGIC* (Strause, unpublished)
Data reduction	*SCALEPACK* (Otwinowski & Minor, 1997)	*CRYSTAL LOGIC* (Strause, unpublished)
Structure solution	Isomorphous molecular replacement	Isomorphous molecular replacement
Structure refinement	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)
Preparation of material for publication	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)

Table 2
β-Cyclodextrin macrocycle characteristics for the low temperature structure.

D = distances between atoms O4n···O4(n + 1).; φ = angles between atoms O4(n − 1)···O4n···O4(n + 1); d = deviations (Å) from the least-squares optimum plane of the seven O4n atoms; α = dihedral angle between the O4n plane and optimum planes through O4(n − 1), C1n, C4n and O4n. D_3 = intramolecular distances between atoms O3n···O2(n + 1).

Residue	D (Å)	φ (°)	d (Å)	α (°)	D_3 (H···O) (Å)	D_3 (O···O) (Å)	O—H···O (°)	Torsion angle (°) O5n—C5n—C6n—O6n
Molecule A								
G1	4.314 (2)	127.86 (5)	−0.011 (1)	5.48 (6)	2.09 (5)	2.782 (3)	155 (5)	−53.5 (2)
G2	4.349 (3)	124.29 (5)	0.018 (1)	7.23 (6)	2.10 (6)	2.800 (3)	166 (6)	64.0 (2)
G3	4.499 (3)	133.14 (5)	−0.031 (1)	7.08 (9)	2.1 (1)	2.795 (3)	172 (14)	−65.2 (2)
G4	4.253 (2)	128.54 (5)	0.043 (1)	12.80 (7)	2.14 (4)	2.820 (3)	161 (4)	−66.2 (2)
G5	4.395 (2)	125.61 (5)	−0.042 (1)	6.73 (6)	2.12 (7)	2.763 (3)	154 (8)	−66.1 (2)
G6	4.330 (3)	129.40 (5)	0.023 (1)	10.51 (12)	2.04 (4)	2.797 (3)	164 (4)	−78.6 (3)
								63.4 (4)
G7	4.455 (3)	131.03 (5)	−0.001 (1)	7.06 (11)	1.6 (1)	2.701 (3)	140 (8)	−64.3 (2)
Molecule B								
G1	4.403 (3)	130.89 (5)	−0.029 (1)	7.87 (8)	1.91 (4)	2.793 (3)	165 (4)	−58.1 (2)
G2	4.279 (2)	125.95 (5)	0.000 (1)	9.06 (8)	2.09 (6)	2.802 (2)	161 (6)	−62.4 (2)
G3	4.423 (3)	129.00 (5)	0.049 (1)	8.41 (5)	–	2.779 (3)	–	−67.0 (2)
G4	4.309 (3)	129.68 (5)	−0.057 (1)	11.00 (9)	2.03 (4)	2.786 (3)	171 (4)	−67.5 (2)
G5	4.383 (2)	128.32 (5)	0.020 (1)	6.04 (11)	–	2.785 (3)	–	−65.0 (2)
G6	4.300 (3)	128.13 (5)	0.006 (1)	12.94 (11)	–	2.732 (3)	–	63.7 (4)
G7	4.406 (3)	127.93 (5)	0.011 (1)	5.26 (6)	1.98 (5)	2.746 (3)	159 (5)	−66.2 (2)

molecules enclosed in the cavity is a supermolecule assembled *via* hydrogen bonding and van der Waals interactions.

It has been observed in the dimeric βCD complexes studied so far that the secondary hydroxylic groups are not influenced by the guest, but they participate in an invariant network of hydrogen bonds connecting neighboring dimers directly or through water molecules (Le Bas & Tsoucaris, 1994). Primary hydroxyl groups, at the top and bottom of the cylinder, also form a network of hydrogen bonds connecting dimers. However, primary faces are influenced by the presence of the guest, if the latter emerges from those faces. Therefore, overall the dimers associate through a semi-invariant network of hydrogen bonds, either directly or *via* water molecules, and form infinite two-dimensional layers of C-centered geometry with two orthogonal axes of dimensions close to 19 and 24 Å. The layers pack by interaction of the primary faces of the βCD dimers and thus the parts of the guests emerging from the primary faces play a crucial role in determining how the two-dimensional layers pack to form the crystal lattice. Such a system is appropriate for crystal engineering studies, since its building blocks keep their integrity upon complexation, while a limited surface on them is possible to change by careful selection of the enclosed guest.

Up to now only four packing patterns (modes) of βCD dimeric complexes have been observed:

(*a*) channel (CH),
(*b*) screw-channel (SC),
(*c*) chessboard (CB) and
(*d*) intermediate (IM) (Mentzafos *et al.*, 1991).

Complexes belonging to the same mode are isomorphic, a very important regularity that allows the determination of the crystal packing just by the knowledge of the unit cell. The crystals are all built by linking together the previously described, practically invariant, two-dimensional dimeric

layers by hydrogen bonds involving primary hydroxylic groups, water and/or the guest molecule(s). The two extreme cases are the CH and CB modes. In the CH mode the two-dimensional layers are placed in such a way that dimers align almost on top of each other to form channels. These are hydrophobic and the guests inside them are shielded from the water environment. The lateral displacement between two consecutive βCD dimers along the channel is only 2.7 Å. On the contrary, in the CB mode each dimer is isolated. The lateral distance between two dimers of successive layers is 8.9 Å. The primary faces and therefore the guest are exposed to water molecules and hydroxylic groups of neighboring macrocycles. The IM packing mode is a case in-between the CH and CB modes. The dimer's sevenfold axis forms an angle of ∼20° with the stacking axis and consequently adjacent layers are far from exactly aligned. The lateral displacement of dimers in consecutive layers is 6 Å (the inner diameter of the primary face of βCD), thus the dimer's cavity entrance is partially closed by the βCD atoms of adjacent layers and parts of the guests are left free to interact with hydroxylic groups of neighboring host and water molecules.

The present investigation is one in a series of studies of inclusion complexes of βCD dimers with long aliphatic monocarboxylic and α,ω-dicarboxylic acids in order to determine how the nature of the guest influences the crystal packing (Makedonopoulou *et al.*, 1998; Makedonopoulou *et al.*, 2000). Aliphatic monoacids with 12–16 C atoms induce CH packing of the βCD dimeric complexes, while in the case of aliphatic diacids with 10–16 C atoms the packing mode is IM. In both cases the inclusion complexes have a host:guest ratio of 2:1, thus two monomers of βCD are threaded by one molecule of the long guest. We believe that in the case of the aliphatic monoacids the hydrophobic end of the amphiphilic guests influences the packing towards the channel mode in

order to protect that part of the guest from the polar aqueous environment that surrounds the dimers. The carboxyl groups, found entrapped in the hydrophobic channel, self-associate forming carboxylic dimers and thus stabilizing the whole system. In contrast, in the case of the diacids the two polar ends of the guest are free to interact with the solvent environment.

The reported system has an intrinsic interest besides the crystal engineering interest. The threading of an elongated molecule through a macrocycle held together by non-covalent interactions is called pseudorotaxane (Ashton *et al.*, 1991). It is
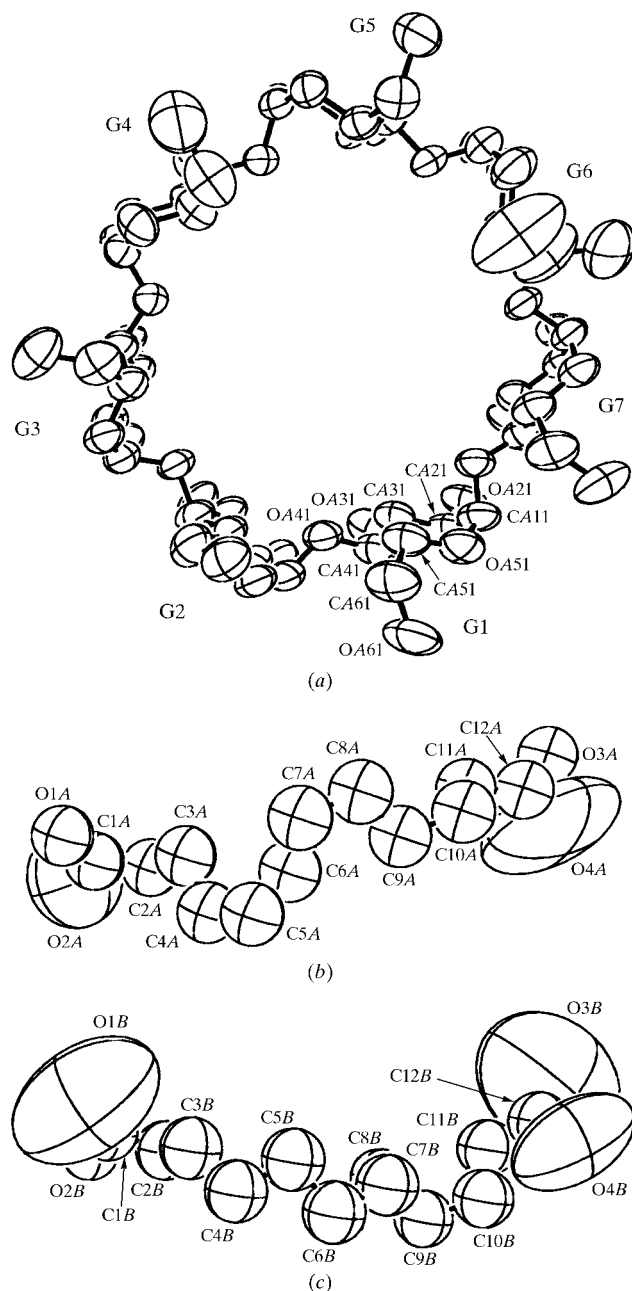
Table 3
Hydrogen bonds of the βCD-1,12 dodecanedioic acid complex at low temperature.

(*a*) Intermolecular hydrogen bonds within the dimer

H—D	A	H···A (Å)	D···A (Å)	D—H···A (°)
OA31—HO31	OB37	1.93 (4)	2.787 (2)	156 (3)
OA32—HO32	OB36	2.20 (8)	2.892 (3)	154 (8)
OB35—HO35	OA33	2.2 (1)	2.720 (2)	116 (7)
OA34—HO34	OB34	1.83 (9)	2.777 (2)	166 (8)
OB33	OA35	–	2.765 (2)	–
OA36—HO36	OB32	1.96 (8)	2.788 (3)	149 (8)
OB31—HO31	OA37	1.64 (8)	2.754 (2)	169 (7)

(*b*) Direct hydrogen bonds between dimers

H—D	A	H···A (Å)	D···A (Å)	D—H···A (°)
OB25—HO25	OA27[i]	1.90 (6)	2.769 (2)	171 (4)
OB27—HO27	OA25[ii]	2.03 (4)	2.770 (3)	171 (4)
OA67	OA63[iii]	–	2.732 (3)	–
OB67—HO67	OB63[ii]	2.02 (4)	2.745 (2)	167 (4)
OA62—HO62	OB62[iv]	1.82 (8)	2.700 (3)	171 (8)
OA65—HO65	OA61[v]	2.09 (5)	2.844 (3)	164 (5)
OB65—HO65	OB61[i]	1.99 (4)	2.838 (3)	166 (3)

Symmetry codes: (i) $x, y, z - 1$; (ii) $x, y - 1, z$; (iii) $x, y, z + 1$; (iv) $x + 1, y + 1, z + 1$; (v) $x, y + 1, z$.

Figure 1
*ORTEP*II (Johnson, 1976) diagram showing the atom-numbering scheme of (*a*) βCD molecule *A*, (*b*) 1,12-dodecanedioic acid molecules *a* and (*c*) *b*, respectively, of the low-temperature structure. Displacement ellipsoids are plotted at the 25% level.

to be discriminated from the rotaxane, the supramolecular compound formed in the same way but with bulky stopper groups added to the thread's extremities to prevent unthreading (Nepogodiev & Stoddart, 1998). The reported inclusion complex is a [3]pseudorotaxane, where the [3] refers to the number of individual molecules associated. [3]Pseudo-rotaxanes are found not only in the crystalline state but in aqueous solution as well, since their presence, in equilibrium with [2]pseudorotaxanes, has been detected by NMR spectroscopy in the case of long aliphatic molecules and α-cyclo-dextrin (Eliadou *et al.*, 1999). Therefore, it is important that the interactions between the three molecules forming βCD [3]pseudorotaxanes are studied in detail, which has been accomplished for the first time in the reported structure. This is because the high resolution of the data collection permitted the location of almost all H atoms of the host macrocycle and many of the water molecules, thus an accurate picture of the hydrogen bonding within the βCD monomers and their association is presented. Moreover, the interactions between the host, guest and the water molecules are determined.

2. Experimental

The complex was precipitated by the addition of 38 μmol of 1,12-dodecanedioic acid in a solution of 56 μmol of β-cyclo-dextrin in 1 ml of H_2O. It was redissolved by adding 1 ml of H_2O and 0.2 ml of ethanol and heating to 343 K. Subsequently, it was allowed to cool slowly over a period of 5 d. The crystals obtained had the form of colorless diamond-shaped thin plates glued together in multiple layers. The multiple plates were separated and a single crystal was used for data collection. A few crystals were isolated, washed by cool *n*-hexane and

dissolved in N,N'-dimethylsulfoxide-d_6. The ^{1}H NMR spectrum indicated a host:guest:ethanol ratio of 1.8:1:1.1.

Firstly, data at room temperature were collected (Table 1) on a crystal of dimensions $0.5 \times 0.5 \times 0.3$ mm^3, sealed in a glass capillary in the presence of the mother liquor with Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) and θ–2θ scanning mode. A Syntex P2$_1$ diffractometer was used, equipped with a fine-focus sealed tube and graphite monochromator. The data were corrected for Lorentz and polarization effects, and absorption. The structure was solved by the isomorphous molecular replacement method using the coordinates of the glucosidic skeleton atoms of the isomorphous structure of β-cyclodextrin with 1,13-tridecanodioic acid (Makedonopoulou *et al.*, 1999). The structure was refined using the program *SHELXL*97 (Sheldrick, 1997). There were 22.2 water molecules located, distributed over 30 sites, and 0.5 ethanol molecules. Nine reflections of low resolution were rejected, taking into account the ΔF^2/e.s.d. parameter. It was possible to identify two disordered orientations of the guest molecule, but the exact location of the individual atoms was ambiguous.

Low-temperature data were collected using the synchrotron radiation light source at the EMBL BW7A beamline at the DORIS storage ring, DESY, Hamburg (Table 1). The crystal used was from a different batch prepared under the same conditions as the previous one. A crystal of dimensions $0.6 \times 0.4 \times 0.2$ mm^3, covered with oil and mounted on a hair fiber loop, was frozen to 100 K. Two sets of data were collected:

(*a*) a high-resolution set (0.65 Å) of 91 frames of rotation $\delta\varphi = 2°$ with an image plate detector MAR 30 cm and

(*b*) a low-resolution set (1.75 Å) of 46 frames of rotation $\delta\varphi = 4°$ with an image plate detector MAR 18 cm.

The complete data set was processed and scaled using the programs *DENZO* and *SCALEPACK*, respectively (Otwi-

nowski & Minor, 1997). The completeness of the data collection was 91.8% and the R_{merge} was 4.1%. The estimated errors of the unit-cell dimensions were calculated by the least-squares method from the cell dimensions of the high-resolution frames. The structure was solved by isomorphous molecular replacement of the βCD glucosidic skeleton atoms of the same complex at room temperature. The rest of the cyclodextrin atoms as well as 27.5 water molecules distributed over 54 sites and 1.2 ethanol molecules distributed over three sites were located from the difference-Fourier electron density maps. The presence of ethanol molecules in the crystals was justified by the ^{1}H NMR spectra and the peaks attributed to them were selected from their relative distances and angles. The refinement was performed using the program *SHELXL*97 (Sheldrick, 1997). Almost all the H atoms of the macrocycle and some of the high occupancy water molecules have been identified. The carboxyl O atoms of the guest, although disordered, were distinguishable but the rest of the aliphatic chain was difficult to follow because of the disorder. A model of the guest was first built from a difference Fourier map and it was subsequently improved by fitting into the difference electron density corresponding to the guest using the graphics program '*O*' (Jones & Kjeldgaad, 1993). Two positions of the guest were found each with occupancy of 50%. The refinement continued anisotropically for all the host atoms, the water and the ethanol molecules and the guest's carboxyl groups. Calculated H atoms were added to the guest's aliphatic chain with the thermal parameter $U' = 125\% U$ of the corresponding non-H atom. The aliphatic chain of the guest was refined as a rigid body. The refinement converged to $R_1 = 0.0474$ for the $F_o \geq 4\sigma(F_o)$ reflections.

The same disordered model of the guest was used for the completion of the refinement of the room-temperature structure. Owing to the limited amount of data, it was not possible to anisotropically refine all the atoms. Thus, only the hydroxyl O atoms and the C6n atoms of the host plus the O atoms of most of the water molecules were refined anisotropically. Calculated H atoms were used with $U' = 125\% U$ of the corresponding non-H atom. The R_1 for the $F_o \geq 4\sigma(F_o)$ reflections converged to 0.0828 (Table 1).

3. Results and discussion

The crystal structure of the inclusion complex of βCD with 1,12-dodecanedioic acid is examined in detail with data collected at 0.65 Å resolution at low temperature. Although the structure has also been solved at room temperature, results related to this are discussed
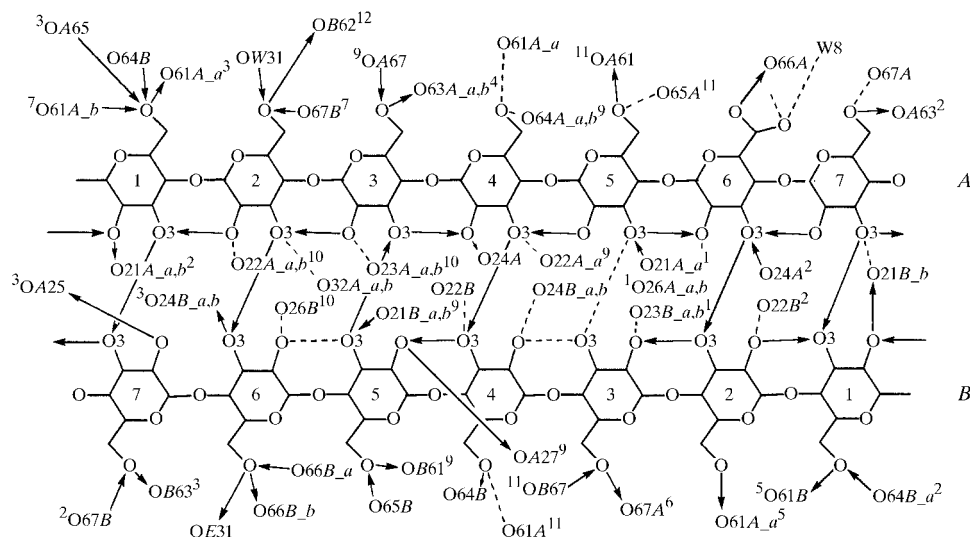

Figure 2
Schematic diagram showing the hydrogen bonding of each dimer. Arrows indicate the H-atom donors. The scheme also shows the hydrogen bonds of the hydroxyl groups [$OA(B)mn$] with water molecules [$OmnA(B)\_a(b)$, *a* and *b* being disordered positions of the same water molecules] on which the superscript indicates the translational symmetry. Symmetry codes: (i) $x, y+1, z+1$; (ii) $x, y, z+1$; (iii) $x, y-1, z$; (iv) $x, y+1, z-1$; (v) $x+1, y, z+1$; (vi) $x+1, y+1, z$; (vii) $x-1, y, z$; (viii) $x-1, y, z-1$; (ix) $x, y, z-1$; (x) $x, y-1, z-1$; (xi) $x, y+1, z$; (xii) $x-1, y-1, z-1$.

Table 4
Hydrogen bonds (range 240–310 Å) between βCD dimers and water or ethanol molecules of the low-temperature structure, unless otherwise indicated (RT = room temperature).

H−D	A	H···A (Å)	D···A (Å)	D···A (Å) (RT)	D−H···A (°)	H−D	A	H···A (Å)	D···A (Å)	D···A (Å) (RT)	D−H···A (°)
OA21	O21A_a	1.92 (6)	2.670 (3)	2.67 (2)	166 (6)	OB21	O21B_a	1.78 (4)	2.651 (3)	2.68 (2)	175 (4)
	O21A_b	2.05 (6)	2.754 (3)	–	152 (6)		O21B_b	1.90 (4)	2.750 (8)	–	163 (4)
O22A_a	OA22	–	2.82 (1)	2.73 (3)	–	O22B	OB22	–	2.82 (2)	2.70 (3)	–
O22A_b		–	2.98 (4)	–	–						
O23A_b	OA23	–	2.759 (7)	–	–	O23B_b	OB23	–	2.504 (6)	2.76 (4)	–
O23A_a		–	2.95 (1)	2.89 (3)	–	O23B_a			2.832 (4)	–	116 (7)
OA24	O24A	1.95 (4)	2.717 (3)	2.77 (2)	153 (4)	O24B_b	OB24	–	2.700 (5)	2.76 (4)	–
						O24B_a		–	2.86 (2)	–	–
OA26	O26A_a	–	2.692 (4)	2.70 (4)	–	O26B	OB26	–	2.758 (4)	2.84 (2)	–
	O26A_b	–	2.76 (1)	–	–	O21B_a		–	3.00 (4)	–	–
O32A_b	OA32	–	3.19 (8)	–	–						
O32A_a		–	3.02 (2)	–	–						
O22A_a	OA34	–	2.65 (1)	2.84 (3)	–	O22B	OB34	–	2.69 (1)	2.84 (2)	–
O24B_b		–	3.110 (6)	–	–						
O21A_a	OA35	2.00 (7)	2.952 (4)	2.87 (2)	167 (6)	O21B_b	OB35	–	2.814 (8)	–	–
						O21B_a		2.15 (6)	2.933 (3)	2.90 (2)	149 (5)
O24A	OA36	1.9 (1)	2.716 (4)	2.83 (2)	158 (11)	OB36	O24B_b	1.99 (4)	2.769 (5)	2.91 (2)	130 (3)
							O24B_a	2.03 (5)	2.94 (3)	–	147 (3)
O21B_b	OA37	–	2.539 (8)	3.10 (2)	–	O23B_b	OB37	–	3.054 (6)	–	–
OA61	O61A_a	2.4 (2)	2.667 (3)	2.70 (1)	148 (21)	OB61	O61B	1.6 (1)	2.711 (3)	2.79 (2)	170 (9)
	OW3_b	–	2.91								
O61A_a	OA61	2.3 (2)	2.668 (3)	–	138 (1)	O64B_a	OB61	2.0 (6)	2.751 (4)	2.74 (1)	171 (6)
O64B_b		–	2.61 (2)	–	–						
O61A_b		1.7 (1)	2.729 (6)	–	156 (5)						
O67B	OA62	1.9 (1)	2.754 (3)	2.78 (2)	174 (10)	OB62	O61A_a	1.84 (7)	2.716 (3)	2.74 (1)	173 (7)
OW31		–	2.81	–	–						
OA63	O63A_a	1.97 (7)	2.692 (4)	2.70 (2)	176 (8)	OB63	O67A	1.92 (4)	2.751 (2)	2.79 (1)	168 (4)
	O63A_b	2.03 (7)	2.734 (5)	–	166 (7)						
OA64	O64A_a	–	2.680 (5)	2.71 (3)	–	OB64	O64B_a	1.95 (4)	2.768 (3)	2.76 (1)	153 (4)
	O61A_a	–	2.699 (3)	2.73 (3)	–						
	O64A_b	–	2.85 (2)	–	–						
						O64B_b	OB64	–	2.45 (3)	–	–
						OE11		–	2.94	–	–
O65A	OA65	–	2.737 (4)	2.72 (2)	–	O65B	OB65	2.36 (6)	2.710 (3)	2.71 (2)	146 (8)
OA66_a	O63A_a	–	2.710 (5)	2.82 (3)	–	OB66	OE31	1.9 (1)	2.64 (1)	–	102 (8)
	O66A_a	–	2.727 (9)	–	–		O66B_b	1.9 (1)	2.773 (9)	2.91	108 (8)
	O66A_c	–	3.01 (3)	–	–						
	O64A_b	–	3.02 (2)	–	–						
OA66_b	O66A_g	–	3.07 (6)	–	–	O66B_a	OB66	–	2.69 (1)	2.73	–
	OW8	–	2.79 (3)	–	–	O66A_g		–	3.08	–	–
	O66A_e	–	2.80 (1)	2.8 (1)	–						
	O66A_d	–	2.84 (4)	–	–						
	O66A_b	–	2.92 (1)	3.02 (5)	–						
O67A	OA67	–	2.726 (3)	2.73 (1)	–	O67B	OB67	1.86 (7)	2.729 (3)	2.72 (1)	161 (6)

only whenever they are different. The asymmetric unit consists of two molecules of βCD, labeled as A and B, forming a head-to-head dimer through which one molecule of 1,12-dodecanedioic acid threads. The crystallographic data of low- and room-temperature data sets are summarized in Table 1. Final atomic coordinates, thermal parameters of the non-H atoms and structure factors of the structures at low and at room temperature are provided in CIF format.[1] The numbering scheme for the host and guest molecules is given in Fig. 1; C(A or B)mn and O(A or B)mn denote the mth atom within the nth glucosidic residue (Gn) of the crystallographically independent βCD molecules A and B.

3.1. Macrocyclic conformation

The glucose units have the usual $^4C_1$ chair conformation. The orientation of the majority of the primary hydroxyl groups of both low- and room-temperature structures have the (−)-gauche orientation pointing outwards. Exceptions are

(a) in the low-temperature structure atoms OA62 and OB66 that point inwards [(+)-gauche orientation], as well as OA66_b, the minor component of the only disordered hydroxyl group OA66;

(b) for the room-temperature structures atoms OA62, OA66_b and OB66_b, the last two being the minor components of the disordered atoms OA66 and OB66, pointing inwards.

The tilting of the glucose units, as shown in Table 2, is small and within the normal values of the dimeric βCD inclusion complexes. The angles between the glucosidic O atoms do not

Table 5
Hydrogen bonds formed by carboxyl groups of the guest molecules.

LT = low temperature; RT = room temperature.

Guest molecule A	LT O···Ow (Å)	RT O···Ow (Å)	C—O···Ow (°)
O1_a ···OW31	2.571 (6)	–	121 (2)
O2_a···O61B	2.785 (4)	2.98 (3)	139.3 (1)
O3_a···OW5_a	2.51 (1)	–	112.5 (4)
O3_a··· O64A_a	2.743 (6)	2.54 (4)	125.8 (2)
O3_a··· OW5_c	2.55 (6)	–	106 (2)
O3_a···O64A_b	2.96 (2)	–	135.1 (3)
O3_a···OW5_b	3.05 (5)	2.37 (4)	132 (1)
O4_a··· OW5_c	2.35 (9)	–	114 (1)
O4_a···OW4	2.81 (1)	–	121.4 (3)
O4_a···OW5_a	2.49 (1)	–	107.5 (4)
O4_a···OA66_b	3.03	–	137.1

Guest molecule B	LT O···Ow (Å)	RT O···Ow (Å)	C—O···Ow (°)
O1_b···OW7	2.45 (3)	–	104.9 (7)
O1_b···O66A_b	2.67 (1)	2.78 (4)	159.3 (3)
O2_b···O61B	2.687 (4)	2.64 (3)	116.5 (1)
O3_b···O66A_f	2.72 (2)	–	101.0 (8)
O3_b···OW5_a	2.81 (1)	–	119.7 (2)
O3_b···OW5_c	2.87 (7)	–	112 (1)
O4_b···O64A_a	2.715 (5)	2.82 (5)	138.6 (1)

differ significantly from 128.6°, the angle of the regular heptagon, denoting that the cavity is not becoming distorted due to inclusion. The deviations from planarity of the glucosidic O atoms of the βCD molecules are very small, as listed in Table 2. The planes formed by the glucosidic O atoms are almost parallel for monomers A and B. The macrocycle remains undistorted because of the intramolecular hydrogen bonds O3n···O2(n + 1).
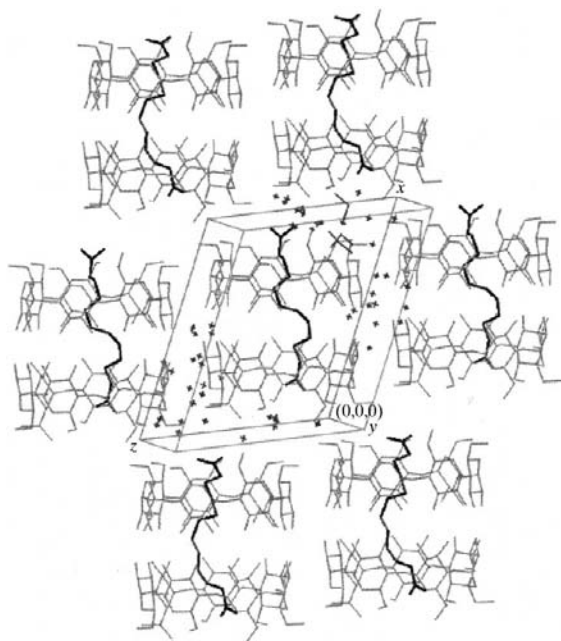

Figure 3
Crystal packing of the dimeric inclusion complex. The guest molecule is disordered over two positions bending in opposite directions. The carboxyl groups interact through water molecules. For clarity reasons, only water molecules around the central complex are shown.

Owing to the accuracy of the low-temperature structure, it has been possible to identify both the donors and acceptors of the H atoms in the hydroxyl groups and some of the water molecules. The detailed hydrogen bonding in the dimer is shown schematically in Fig. 2, where the hydrogen donors are indicated by arrows. Wherever a H atom has not been located, a dotted line indicates the hydrogen bonding based on the geometry of the O atoms. There are three hydrogen bonds of the type O3n—H3n···O2(n + 1) in monomer A, in agreement with the neutron diffraction data of the βCD–ethanol–octahydrate structure (Steiner *et al.*, 1990), where the O3 hydroxyl O atom is a H-atom donor three times. In monomer B it has been found that three O3 atoms are also H-atom donors, but we do not know if they are the only ones, because three H atoms (those of atoms OB24, OB26 and OB33) have not been located. Moreover, residues G6 and G7 are not connected by hydrogen bonds, although it is geometrically favorable. Atom OB27 is a H-atom donor to a direct hydrogen bond between dimers in the dimeric layer (OB27—HO27···OA25). Alternatively, atom OB36 could have been a H-atom donor between G6 and G7, but it gives its H atom to the neighboring water molecule O24B. If the same happens between residues G3–G4 and G5–G6 of monomer B, we do not know. Certainly the hydrogen-bonding scheme in this monomer is not as regular as in A (Table 2), probably because it acts as an H-atom donor with neighboring molecules, as discussed above. The intramolecular hydrogen bonds in the monomers have an average distance between O2···O3 of 2.78 Å (range 2.73–2.82 Å) and angle O···H···O of 154° (range 136–173°).

The O3n atoms, which are not H-atom donors in the intramolecular hydrogen-bonding process, are donors in the intermolecular hydrogen bonds between the OA3n···OB3(8 − n) hydroxyl O atoms which connect monomers A and B in order to form the dimers. These intermolecular hydrogen bonds have an average O3···O3 distance of 2.78 Å (range 2.72–2.89 Å) and angle O3···H···O3 of 154° (range 112–170°; see Table 3a). Therefore, the secondary hydroxyl O atoms O2 and O3, which are H-atom donors and acceptors in the intramolecular and intermolecular hydrogen bonds within each dimer, are complementary (Fig. 2). This is the first time that the accuracy of the structure of the dimeric βCD inclusion complex permits the description of the hydrogen bonding in the βCD dimer. It is proven that the head-to-head dimers are held by the hydrogen bonds only through the O3 atoms. The O2 atoms, although sufficiently close, do not take part in the hydrogen bonding between monomers. In previous structures, this fact has been postulated on the basis of the angles CA3n—OA3n···OB3(8 − n) and OA2n···OB3(8 − n)—CB3(8 − n) (Mavridis *et al.*, 1991; Mavridis & Hadjoudis, 1992).

3.2. Crystal packing and hydrogen bonding between dimers

As in the complex of βCD with 1,13-tridecanedioic acid (Makedonopoulou *et al.*, 2000), the cyclodextrin macrocycles arranged in head-to-head dimers pack in layers laterally shifted by 6.2 (1) Å, along the **a** axis. The βCD sevenfold axis

forms an angle of 20° with that axis and the packing (Fig. 3) is intermediate (IM; Mentzafos *et al.*, 1991; see above).

Within the same two-dimensional layer, at the secondary hydroxyl level the dimers interact through direct hydrogen bonding of the hydroxyl groups O*B*25—HO25···O*A*27 along the **c** axis and O*B*27—HO27···O*A*25 along the **b** axis (Table 3*b*). At the primary hydroxyl level dimers interact *via* the hydrogen bonding O*A*67···O*A*63 (H atom not located), O*B*65—HO65···O*B*61, along the **c** axis, and O*B*67—HO67···O*B*63, O*A*65—HO65···O*A*61, along the **b** axis. It has been mentioned above that at the primary side the hydrogen bonding of the layers depends on the crystal packing, thus the hydrogen bonds between O*B*65···O*B*61 and O*A*65···O*A*61 do not exist in the βCD complexes of aliphatic monoacids with 13 and 14 C atoms that align in channels (Makedonopoulou *et al.*, 2000). In contrast to the channel packing, the dimer does not form hydrogen bonds with dimers above and below either. However, there are interactions between dimers of adjacent layers diagonally (O*A*62—H*A*62···O*B*62).

3.3. Water networks

In the low-temperature structure, there are 27.5 water molecules per βCD dimer, distributed over 54 sites, only a few of which are fully occupied. The remainder are disordered and it has been difficult to locate their corresponding H atoms. Water molecules, at 41 locations, form direct hydrogen bonds with hydroxyl groups of the macrocycle. Fig. 2 shows the wa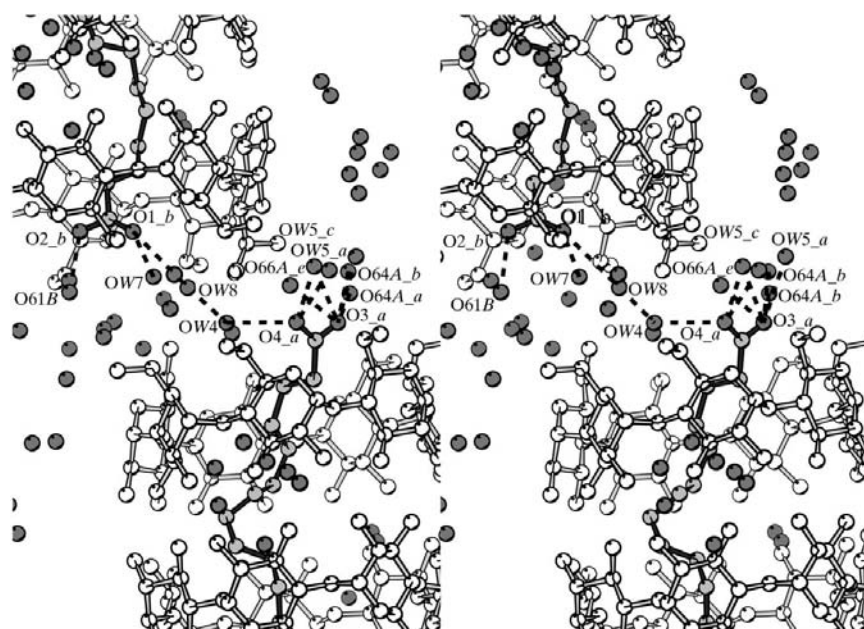ter molecules interacting with the host atoms. The hydrogen bonds of the water molecules with the hydroxyl O atoms of the low-temperature structure appear in Table 4. The number of water sites is much higher than in the room-temperature structure. However, except for the water molecules O*W*9, O*W*10 and O*W*11, all the water molecules found at the room-temperature structure were also present at low temperature, most of them disordered at least over two distinct positions. For comparison reasons, the distances of the corresponding water molecules found in the room-temperature structure are also shown in Table 4. The water sites have been labeled according to the number of the closest hydroxyl O atom to which they are hydrogen bound. It is assumed that distances O···O*w* of 2.40–3.14 Å and angles C—O···O*w* of 95–139° indicate hydrogen bonding. Nearly all water molecules are tetrahedrally coordinated and they form hydrogen-bonding networks which involve, besides the hydroxyl groups, other water molecules, the carboxyl groups of the guest molecules and ethanol molecules. At the secondary hydroxyl side, they act as H-atom donors mostly, since the hydroxyl O atoms donate their H atoms in the hydrogen-bonding scheme within the dimer or between dimers in the lattice.

It has been reported (Le Bas & Tsoucaris, 1994; Mentzafos *et al.*, 1991) that in the dimeric βCD inclusion complexes, examined at room temperature, two separate water networks are formed between the dimers, one connecting the primary and another the secondary hydroxyl groups. In this high-resolution low-temperature study, where more sites are revealed, this separation is not exactly correct. It is true, no hydroxyl O atom of the primary side interacts with a water molecule that binds to a hydroxyl group of the secondary site and *vice versa*. However, close contacts exist between some water molecules of the secondary site network with water molecules of the primary site network with distances: O22*A*_*a* (s.o.f. 0.40)···O66*A*_*c* (s.o.f. 0.26) = 2.95, O23*A*_*b* (s.o.f. 0.45)···O65*A* (s.o.f. 0.82) = 2.69, O23*A*_*a* (s.o.f. 0.55)···O65*A* (s.o.f. 0.82) = 2.86, O32*A*_*a* (s.o.f. 0.32)···O66*A*_*a* (s.o.f. 0.38) = 2.51, O32*A*_*a* (s.o.f. 0.32)···O66*A*_*c* (s.o.f. 0.26) = 2.58, O23*B*_*a* (s.o.f. 0.65)···O65*B* (s.o.f. 0.86) = 2.90 Å.

The thermal parameters of some water molecules of the room-temperature structure have high values, indicating that it is impossible to resolve positional disorder at that temperature. Some of these water molecules at 100 K appear at two distinct positions located very close to each other. However, there are some water molecules even at low temperatures which exhibit large anisotropic displacement parameters. The average structure of the water molecules that exhibit translational disorder and their participation in an extensive network of hydrogen bonds is consistent with results of deuterium magnetic resonance studies on

Figure 4
Details of the interdimer region along the crystallographic **a** axis. Hydrogen bonds of the carboxyl groups of the disordered guest molecules at the one primary face are shown stereoscopically. The carboxyl groups are connected through a bridge of two water molecules: O4_*a*···O*W*4···O*W*8···O1_*b* (distances: 2.80, 2.44 and 3.2 Å, respectively). Some water molecules, not hydrogen-bonded to the guest, have been omitted for clarity. Drawing by *MolScript* (Kraulis, 1991).

powder and single crystals of hydrated cyclodextrins, and two βCD derivatives that indicate rapid exchange averaging between water molecules (Usha & Witlebort, 1992).

3.4. Guest geometry and interactions with its environment

The guest molecule spans the entire length of the βCD dimer so both terminal carboxyl groups are located at the primary hydroxyl side. The difference electron density corresponding to the guest molecule showed clearly that the guest is disordered, not only at room temperature but also at 100 K. The disorder is possibly due to the wide cavity of βCD, since in dimeric complexes of CD and 1,12-diaminododecane (Rontoyianni & Mavridis, 1999) and 12-aminododecanoic acid (Eliadou *et al.*, 1999) the aliphatic guest is completely ordered in an ideal zigzag geometry. Of the many possible positions of the aliphatic chain inside the βCD cavity, it appears that two predominate at low temperature. The aliphatic skeleton bends and twists inside the cavity so that the carboxyl groups do not extend beyond the primary hydroxyl O atoms (Figs. 4 and 5). Despite the bending, the closest distance between the calculated H atoms of the guest and the glucosidic O atoms are quite long: C2_a—H2_$a\cdots$OA43, C4_a—H4_$a\cdots$OA42, C5_a—H5_$a\cdots$OB35 [distances 2.78 (1), 2.83 (1) and 2.88 (1) Å, and C—H$\cdots$O angles 159 (1), 165 (1) and 160 (1)°, respectively].

Crystalline complexes of βCD with aliphatic diacids with 10–16 C atoms are isomorphous with the present complex, therefore, they pack in the IM mode and they do not form channels as the corresponding monocarboxylic acids. In IM packing the guest is stabilized by hydrogen bonding with host hydroxyl groups and water molecules that intervene between

the dimers (Table 5). The carboxyl groups of adjacent dimers do not interact directly. While in the βCD + 1,13-tridecanedioic acid inclusion complex the two carboxyl groups of both disordered guest positions interact through a bridge of two water molecules (Makedonopoulou *et al.*, 1999), in the present structure a weak association exists only at one of the primary faces of the βCD dimers. A carboxyl group of guest molecule A with a carboxyl group of the adjacent guest molecule B via the water molecules OW4 and OW8 is shown in Fig. 4. At the other primary face (Fig. 5) the carboxyl groups do not form such an interaction. The only strong interaction of the guest molecules with the enclosing host dimer is that of the carboxyl O4_a atom with the inwards pointing, (+)-*gauche*, disordered hydroxylic O atom OA66_b.

4. Conclusions

The high intensity of the synchrotron X-ray source combined with high-resolution data and the low temperature made possible the determination of an accurate structure. Thus, for a class of compounds characterized by poor quality crystals because of disorder, it has been possible to locate H atoms and examine the hydrogen-bonding scheme of a dimeric βCD inclusion complex for the first time and describe the interactions of the host, guest and water molecules. The intermolecular association of the two βCD monomers to form the dimer is only through hydrogen bonding of the secondary O3 hydroxyl O atoms. Moreover, each βCD macrocycle has a rigid geometry because of intramolecular hydrogen bonds between O2 and O3 secondary hydroxyl groups. The H atom donors in the intra- and intermolecular hydrogen bonds are overall complementary in the two monomers. The aforementioned hydrogen bonding determines the additional interactions of the hydroxyl group with hydroxyl groups of adjacent dimers or water molecules.

The guest spans the entire length of the βCD dimer and its carboxyl groups emerge from its primary faces and influence the packing through their association with other dimers and the solvent. Otherwise, the dimers associate by hydrogen bonding directly and through water molecules to form semi-invariant two-dimensional layers common to the all dimeric βCD complexes, irrespective of crystal packing. When the guest is an aliphatic monocarboxylic acid, which is amphiphilic, the dimers form channels inside which the long molecules are isolated from the polar water environment and they associate to form carboxylic dimers. In the present case of the aliphatic dicarboxylic acid inclusion, the presence of two terminal carboxyl groups at the primary faces of the βCD dimer changes the packing from the channel to the intermediate mode. The latter is a more open packing mode that
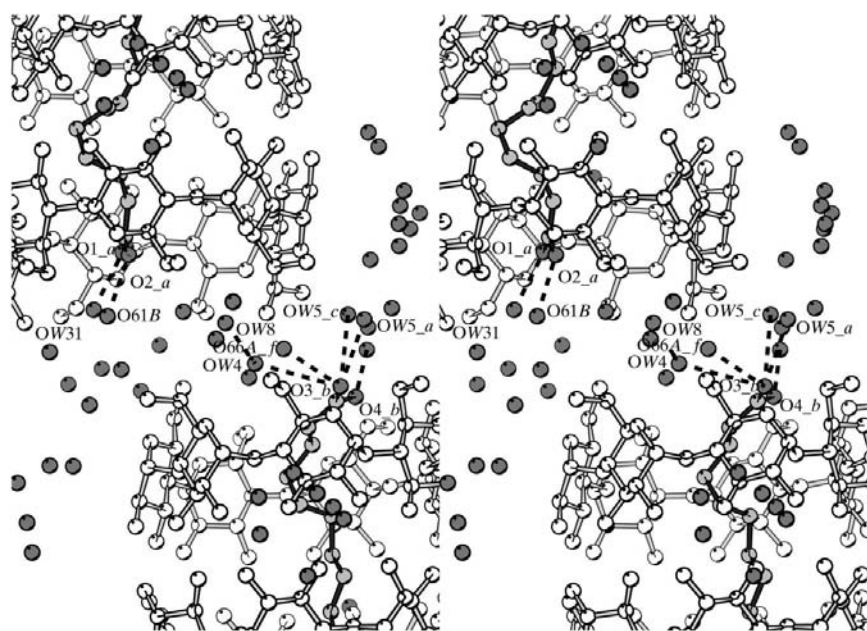

Figure 5
Details of the interdimer region along the crystallographic **a** axis, shown stereoscopically. The carboxyl groups of the disordered guest molecules at the other primary face are not connected by hydrogen bonds through water molecules. Some water molecules, not hydrogen-bonded to the guest, have been omitted for clarity.

permits entrance of water molecules between the primary faces of the dimers and the carboxyl groups are fully hydrated. No direct hydrogen bonds are observed between carboxyl groups of adjacent guests, a weak association existing through water molecules.

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