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The Dimeric Complex of Beta-Cyclodextrin with 1,13-tridecanedioic acid

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The structure of the complex of beta cyclodextrin (βCD) with 1,13-tridecanedioic acid has been determined at low temperature. The compound crystallizes in *P*1, $a = 18.207(6)$, $b = 15.510(5)$, $c = 15.280(6)$ Å, $\alpha = 103.02(3)$, $\beta = 113.13(3)$, $\gamma = 99.79(3)°$ and $D_c = 1.339\,g cm^{-3}$ for $Z = 1$. Refinement based on 13134 observed MoKα reflections led to a final $R = 0.076$. The diacid molecules thread through two βCD arranged in dimers thus, forming [3]pseudorotaxanes. The aliphatic chain of the guest has a few weak, non-bonded interactions with the host inside the long hydrophobic cavity. However, the end carboxyl groups form several strong H-bonds with the solvent in a fashion similar to other βCD/carboxylic acid complexes that have similar building blocks as the present one: βCD dimers and carboxylic groups of the guest emerging from their two primary faces. Conversely, in the corresponding complexes with aliphatic monocarboxylic acids the carboxyl groups form carboxylic dimers because they are isolated from the environment inside hydrophobic channels.

Keywords: Beta-cyclodextrin, 1,13-tridecanedioic acid, dimer, inclusion complex, [3]pseudorotaxane

INTRODUCTION

The title system exhibits the threading of a long aliphatic dicarboxylic acid, 1,13-tridecanedioic acid, through two β-cyclodextrin (βCD) macrocycles associated *via* H-bonds to form a [3]pseudorotaxane. Rotaxanes [1] belong to a class of supramolecular compounds in which a dumbbell-shaped molecule has been threaded through a macrocycle with bulky stopper groups added to the thread's extremities to prevent its unthreading, while pseudorotaxanes differ in that they lack the stopper groups. Cyclodextrins (CDs) [2], cyclic oligosaccharides consisting of six or more α-1,4 linked D-glucopyranose units are obvious and readily available starting materials to be used as macrocycles in the assembly of the above class of compounds [3], because they possess a hydrophobic cavity that can enclose a plethora of guest compounds. The presence of the stopper groups in rotaxanes provides a stable association *via* a so-called mechanical bond, while in pseudorotaxanes unthreading is possible [1]. However, [3]pseudorotaxanes of α

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and βCD with long aliphatic compounds, like the present one, have been detected in aqueous environment by NMR [4], a fact indicating that they are quite stable in water solutions. The stabilization is due to numerous non-bonding interactions of the guest's aliphatic part in the elongated cavity formed by the two βCD macrocycles, supplemented by possible H-bonds between the guest's polar end groups and the host's primary hydroxyl groups and/or the water environment.

The present investigation is one in a series of studies of inclusion complexes of βCD dimers with long aliphatic mono and diacids in order to determine how the nature of the guest influences the crystal packing. Association of two βCD monomers to form a dimer is very common among βCD inclusion complexes [5]. The dimer's overall shape resembles a barrel with two open faces lined by the primary hydroxyl groups of the βCD monomers (primary faces). The βCD dimer is an entity that keeps its integrity irrespective of the nature of the guest. Thus, it forms a long cavity that is hydrophobic even in the region where the two monomers meet (intradimer region) and its exterior forms a semi-invariant network of H-bonds, which connect it to other neighboring dimers either directly or through water molecules. The result is formation of infinite 2-D layers [6] of the same overall geometry for all dimeric βCD inclusion complexes determined so far. The influence of the guest on the surface of the dimer is limited only to the primary faces. Therefore, the class of dimeric βCD complexes is a suitable system to study crystal engineering because it is easy to introduce small changes at a specific surface of the building block, namely the primary faces of the βCD dimer, by simply changing the guest included inside the cavity.

RESULTS AND DISCUSSION

The inclusion complex of 1,13-tridecanedioic acid in β-cyclodextrin forms a [3]pseudorotaxane composed of a dimer of βCD through which a molecule of the long acid, disordered over two sites, has been threaded. Crystallographic data are summarized in Table I. Final atomic coordinates and thermal parameters of the non-hydrogen atoms are available from the author. The numbering scheme for the host and guest molecules is given in Figure 1; C(A or B) *mn* and O(A or B) *mn* denote the *m*th atom within the *n*th glucosidic residue (G*n*) of the crystallographically independent βCD molecules A and B. The dimer's 7-fold axis forms an angle of 20° with the **a** axis (Fig. 2) therefore, the dimers do not stack on top of each other to form channels. The packing belongs to the intermediate packing mode [5] of βCD dimeric complexes with the centers of consecutive dimers laterally shifted by 6.2 Å. Consequently, the carboxylic groups of the guest are displaced about 7.5 Å and do not interact directly.

Geometry of the Host

The pyranose rings have the $^4C_1$ conformation with the gauche–gauche orientation for the primary hydroxyl groups as shown in Table II, except for residue G2 and G6 (disordered site OC66) of the βCD molecule A and G6 of the βCD molecule B. The same table also shows that βCD molecules possess near seven-fold symmetry. The values of the angle between the glucosidic oxygen atoms O4*n* do not differ significantly from 128.57°, the angle of the regular heptagon, and the deviations of the O4*n* atoms from their optimum plane are very close to zero, while the glucose units tilt very regularly towards the 7-fold axis. The conformation of each βCD macrocycle, as in all βCD dimeric complexes [5], is stabilized through intramolecular hydrogen bonds connecting the O3*n* and O2(*n* + 1) atoms of neighboring glucosidic units (average O3*n* ... O2(*n* + 1) distances 2.78 Å, range 2.72–2.83 Å) and the angles C3*n*-O3*n* ... O2(*n* + 1) (average 116.8°, range 112.7–121.4°) and O3*n* ... O2(*n* + 1)–C2(*n* + 1) (average 119.2°

TABLE I Crystal data and structure refinement

Molecular formula	$(C_{42}H_{70}O_{35})_2 \cdot C_{13}H_{24}O_2 \cdot (H_2O)_{24.5} \cdot (C_2H_6O)_2$
Formula weight	3015.84
Temperature	173 K
Radiation/Wavelength	0.71069 Å
Space group	P1
a, α	$a = 18.207(6)$ Å, $\alpha = 103.02(3)°$
b, β	$b = 15.510(5)$ Å, $\beta = 113.13(3)°$
c, γ	$c = 15.280(6)$ Å, $\gamma = 99.79(3)°$.
Volume/Z	3701(2)Å^3/1
Density (calculated)	1.339 Mg/m^3
2θ range for data collection	0°–52°
Index ranges	$-22 \le h \le 22$, $-19 \le k \le 0$, $-18 \le l \le 18$
Reflections collected/sindependent	13163/13134
Solution method	Isomorphous molecular replacement [10]
Refinement method	Full matrix least squares on F^2
Data/restraints/parameters	13134/68/1891
Goodness of fit on F^2	1.023
Final R indices $[I > 2\sigma(I)]$	$R1 = 0.076$, $wR_2 = 0.204$
R indices (all data)	$R1 = 0.094$, $wR_2 = 0.226$
Largest diff. peak and hole	0.61 and −0.41 e Å^{-3}

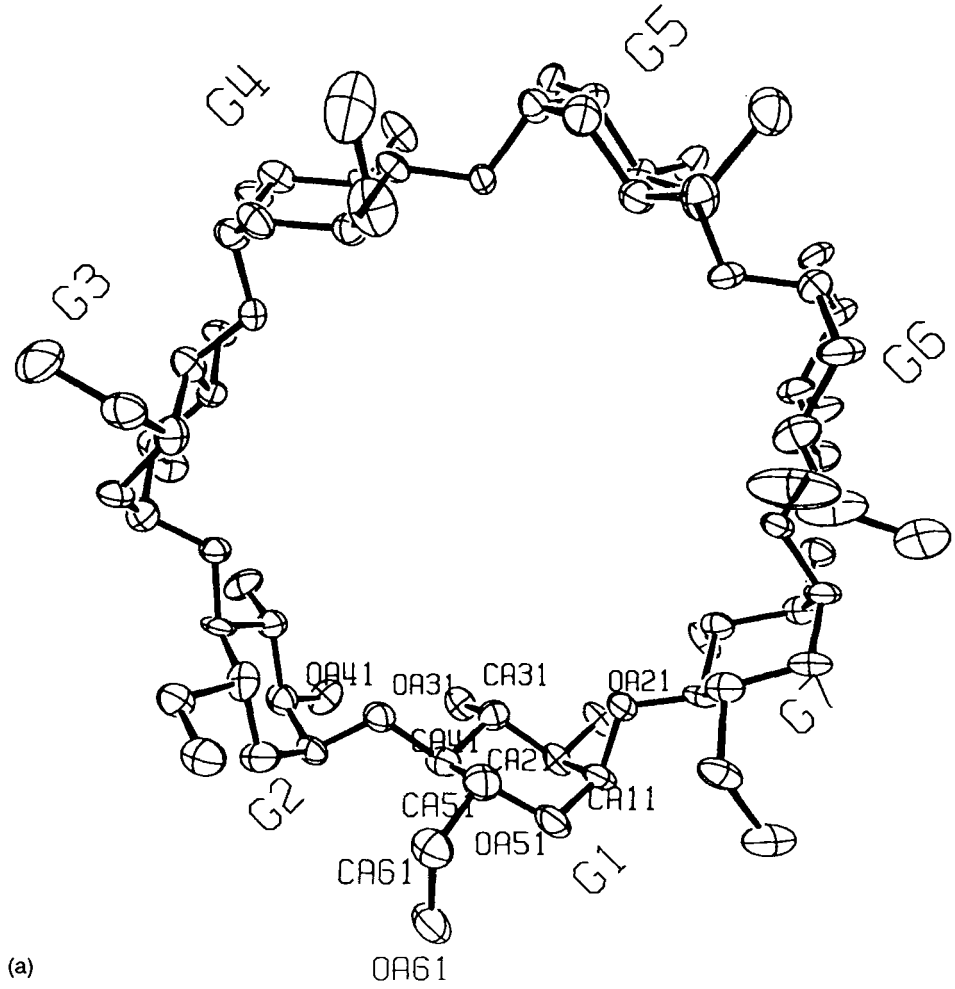

FIGURE 1 Atom numbering scheme (a) for host and (b) for guest atoms. Displacement ellipsoids (a) are plotted at the 4% level.

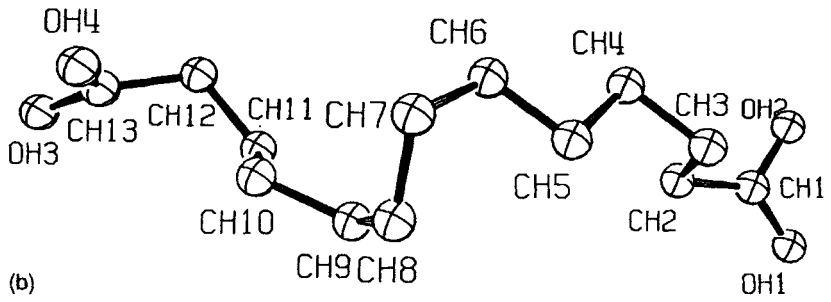

FIGURE 1 (Continued).

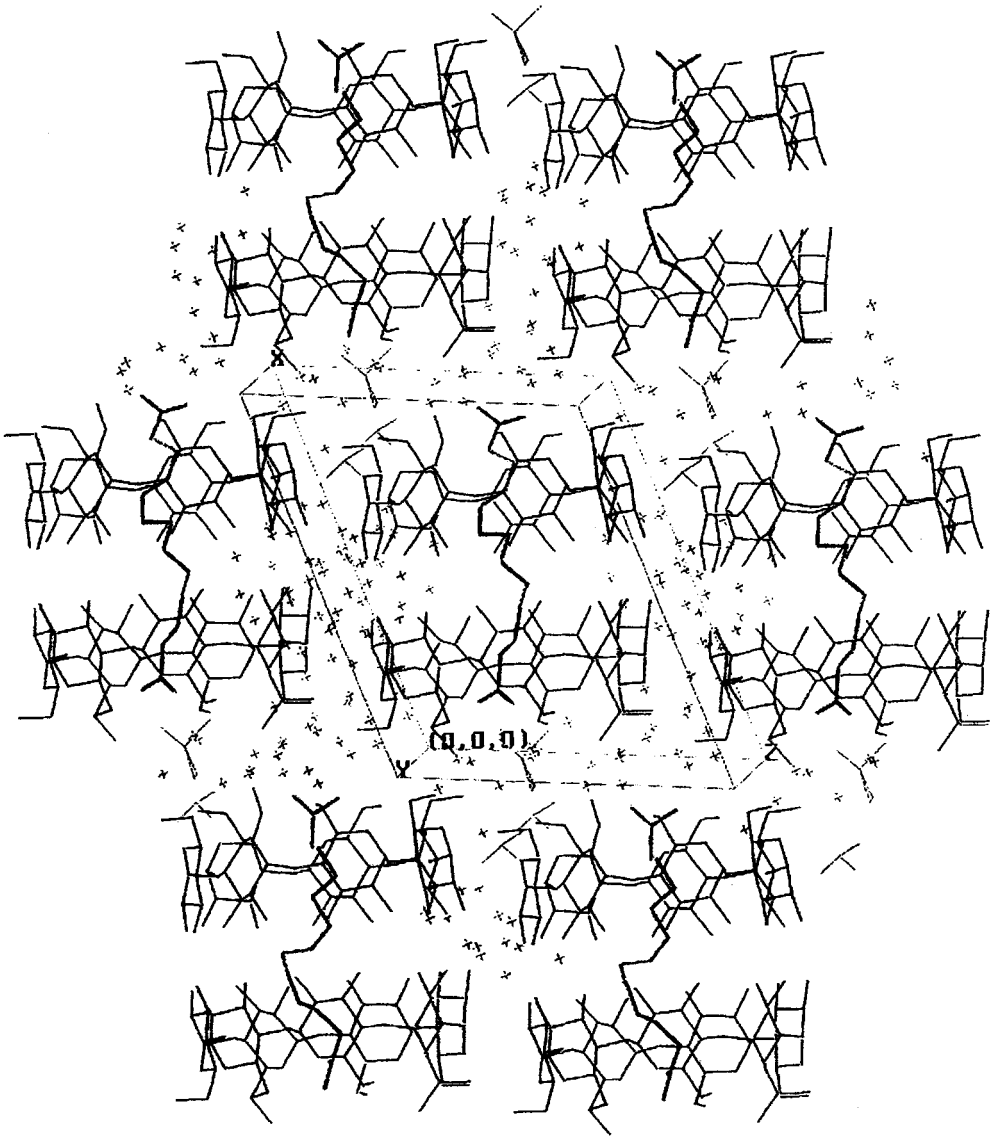

FIGURE 2 The packing of the dimeric complex molecules. Diacids shown bold.

TABLE II β-Cyclodextrin macrocycle characteristics

Residue	D[a] (Å)	φ[b] (°)	d[c] (Å)	α[d] (°)	D_3[e] (Å)	Torsion angle(°) C4n–C5n–C6n–O6n
Molecule A						
G1	4.36	124.5	−0.010(4)	85.5(2)	2.78	66.0(9)
G2	4.51	132.8	0.016(4)	84.0(2)	2.81	−175.2(9)
G3	4.26	129.1	−0.030(4)	85.8(2)	2.79	54.9(9)
G4	4.38	125.1	0.045(4)	79.7(2)	2.83	54.1(9)
G5	4.35	129.7	−0.045(4)	85.5(2)	2.77	56.4(8)
G6	4.47	131.2	0.025(4)	82.7(2)	2.80	40.6(13) −174.7(11)
G7	4.31	127.6	−0.002(4)	85.7(2)	2.72	56.0(9)
Molecule B						
G1	4.42	127.3	−0.022(4)	84.9(2)	2.80	62.4(9)
G2	4.41	131.3	0.004(4)	83.1(2)	2.82	57.5(9)
G3	4.29	126.1	0.028(4)	84.7(2)	2.78	54.2(8)
G4	4.42	128.6	−0.043(4)	82.6(2)	2.79	54.1(9)
G5	4.32	129.6	0.029(4)	85.7(2)	2.79	57.1(9)
G6	4.38	128.9	−0.013(4)	80.4(2)	2.75	−176.9(9)
G7	4.31	128.1	0.016(4)	86.4(2)	2.76	55.2(9)

[a] Distances between atoms O4n...O4(n+1).
[b] Angles between atoms O4(n−1)...O4n... O4(n+1).
[c] Deviations (Å) from the least-squares optimum plane of the seven O4n atoms.
[d] Dihedral angle between the O4n plane and optimum planes through C2n, C3n, C5n and O5n.
[e] Intramolecular hydrogen-bond distances between atoms O3n...O2(n+1).

range 115.4–123.4°) lie within the normal values for H-bonds. The βCD dimer is formed *via* OA3n...OB3(8−n) H-bonds with an average distance 2.79 Å (range 2.72–2.88 Å). The angles CA3n–OA3n...OB3(8−n) and OA3n...OB3(8−n)–CB3(8−n) have mean values 117.7° (range 115.6–120.8°) and 118.8° (range 115.2–121.1°), respectively.

H-Bonding Network and Solvent Molecules

There are 7 direct H-bonds among hydroxyl groups of adjacent host dimers (Tab. IIIa), of which six bind hydroxyl groups in the 2-D layer semiinvariant for all packing modes of dimeric complexes: three along the **c** axis, OA63...OA67, OB61...OB65 and OA27...OB25 and three along the **b** axis, OA65...OA61, OB63...OB67 and OA25...OB27. Only one direct H-bond is formed between different layers OA62...OB62.

There are 24.5 water molecules in the asymmetric unit distributed over 42 sites around the βCD dimer and 35 of them are within H-bonding distance from oxygen atoms of the hydroxy groups as shown in Table IIIb. The water sites have been labeled by the number of the closest oxygen atom to which they H-bond. It is assumed that distances 2.50–3.14 Å and angles C—O...O(water) of 90–139° indicate H-bonding. The angle range, although quite wide, is justifiable because of the usual disorder accompanying water molecules and the inability to locate their H-atoms. It has been suggested [5, 6] that there exist separate, segregated water networks linking the primary or secondary hydroxy groups in the crystals of dimeric βCD inclusion complexes. In general, this is true for the water molecules of the present structure, although some deviations are observed *i.e.*, water molecules W22A, W23A$_1$, W23A$_2$, W32A attributed to secondary hydroxy groups are also H-bonded to water molecules associated with primary hydroxy groups.

Two ethanol molecules, disordered over two orientations each, are also found in the crystal lattice. One is located in the primary region and is taking part in H-bonding the guests (Tab. IIIb).

TABLE III Hydrogen bonds of the βCD-1,13-tridecanedioic acid complex

a. Direct Hydrogen-bonds between dimers

Omn...Om'n'	Distance (Å) Omn...Omn'	Angle (°) Cmn–Omn...Omn'	Angle (°) Omn...Omn'–Cmn'
OA27...OB25	2.78	113	109
OA63...OA67	2.77	127	108
OB61...OB65	2.84	128	110
OA25...OB27	2.79	115	102
OB63...OB67	2.77	128	109
OA65...OA61	2.85	104	129
OA62...OB62	2.70	106	121

b. Hydrogen-bonds between βCD dimers and water or ethanol molecules

Molecule A	Distance (Å)	Angle (°)	Molecule B	Distance (Å)	Angle (°)
OA21...W21A_1	2.68	107	OB21...W21B_1	2.67	109
...W21A_2	2.87	91	...W21B_2	2.95	108
OA22...W22A	2.79	105	OB22...W22B	2.84	109
OA23...W23A_1	2.74	115	OB23...W23B_1	2.46	107
...W23A_2	2.92	113	...W23B_2	2.83	109
...W21B_2	3.09	115			
OA24...W24A	2.74	101	OB24...W24B	2.67	98
OA26...W26A_1	2.70	104	OB26...W26B	2.69	99
...W26A_2	2.78	97	...W21B_1	3.13	129
OA32...W32A_1	2.96	116			
...W32A_2	3.02	139			
OA34...W22A	2.68	118	OB34...W22B	2.72	124
OA35...W21A_1	2.92	118	OB35...W21B_2	2.62	126
			...W21B_1	2.89	122
OA36...W24A	2.69	117	OB36...W24B	2.82	118
			OB37...W23B_1	3.12	117
OA61...W61A_1	2.68	113	OB61...W61B	2.76	101
...W61A_2	2.73	100	...W64B	2.76	118
OA62...W67B	2.76	107	OB62...W61A_1	2.73	99
OA63...W63A_1	2.71	118	OB63...W67A	2.77	105
...W63A_2	2.82	107			
OA64...W64A_1	2.69	114	OB64...W64B	2.75	106
...W64A_2	2.90	121	...W61A_2	3.08	97
...W61A_1	2.71	107	...OA1	2.91	128
OA65...W65A	2.74	123	OB65...W65B	2.71	122
OA66...W66A_1	2.81	127	OB66...W66B	2.68	123
...W66A_2	3.08	127	...OB2	2.84	98
...W63A_1	2.72	114			
OC66...W66A_3	2.82				
...W66A_4	2.93				
...W66A_5	3.14				
...W66B	3.02				
OA67...W67A	2.74	120	OB67...W67B	2.71	123

c. Hydrogen bonds between guest's carboxylic groups and water or ethanol molecules

Molecule A side	Distance (Å)	Angle (°)	Molecule B side	Distance (Å)	Angle (°)
OH1...W4	2.76	116	OH3...W61B	2.78	128
...W66A_3	2.36[a]	147	...W66A_4	2.96	130
			...W66A_5	2.33[a]	131
OH2...W64A_1	2.98	153	OH4...OB3	2.55	117
OG1...W5	2.80	112	OG3...W61B	2.70	122
...W4	2.80	112	...OB3	3.09	120
OG2...W64A_1	2.72	125	OG4...W66A_5	2.20[a]	152
			...W66A_6	2.67	156

[a] Since the occupancies of guests G or H, W66A_3 and W66A_5 are 50%, the molecules might not coexist.

Guest Geometry and Interactions with Its Environment

Both orientations of the guest have a bent in the middle of the aliphatic chain (Fig. 2). This is due to the width of the βCD cavity, particularly in the interdimer region, since in analogous inclusion complexes of α-cyclodextrin [7] the aliphatic chain is not disordered and it has a regular zig-zag shape. Because of the bend, some very weak CH...O interactions (C...O distances in the range of 3.6 – 4.0 Å) are observed between the methylene H-atoms and the glucosidic oxygen atoms.

The end carboxy groups of the guest form multiple H-bonds (Tab. IIIc). The disordered carboxy groups G and H of two consecutive guest molecules are connected by H-bond networks as shown in Figure 3. It is noteworthy that the only disordered primary hydroxyl group, OC66, with the orientation toward the interior of

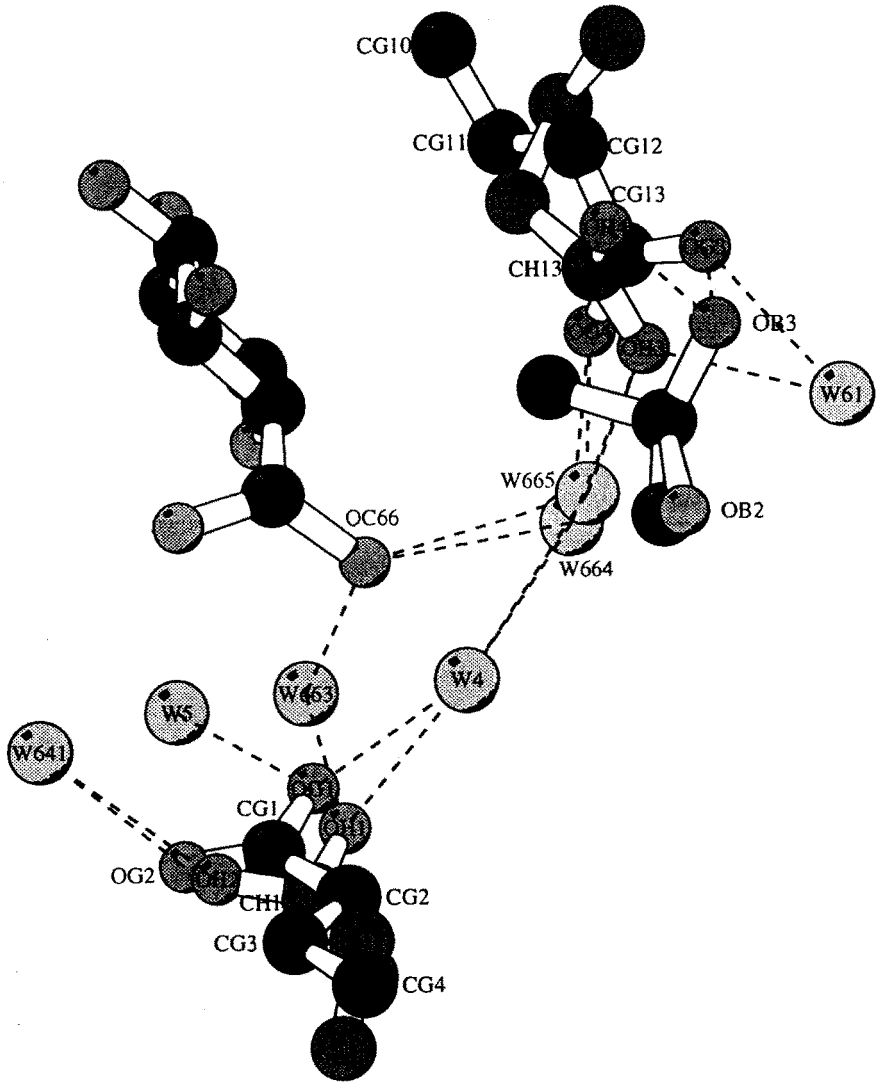

FIGURE 3 Detail of the hydrogen-bonding around the carboxyl groups in the interface of two layers of dimers. OC66 is the position of the only disordered primary hydroxyl group of βCD.

the cavity, is participating in the above networks, thus justifying the disorder.

The end carboxy groups far apart, fully solvated associate indirectly through water molecules with each other. This is in contrast to corresponding βCD inclusion complexes of long aliphatic monoacids [8] with 12–16 carbon atoms. Crystal structures of the latter show that βCD dimers enclosing one molecule of the guest also form [3]pseudorotaxanes, that pack one on top of the other and form infinite hydrophobic channels, inside of which the carboxylic ends, having no opportunity to get hydrated, form carboxylic dimers. The driving force of the channel formation is not the tendency of the carboxy group to form dimers but the hydrophobic terminal methyl groups that require a hydrophobic environment [8]. On the other hand, carboxylic acids of shorter length, like nonanoic acid [9] or 4-*tert*-butylbenzoic acid [10], form βCD complexes with a host:guest ratio of 2:2 in which the carboxyl groups emerge from the primary faces of the dimer. Having building blocks of the same overall shape as the present structure, they consequently have the same packing and form isomorphous crystals.

MATERIALS AND METHODS

Preparation and Crystallization of the Complex

The complex was prepared by adding 1,13-tridecanedioic acid to an aqueous solution of βCD, to a host/guest ratio 1 : 1. The precipitate was redissolved in a mixture of water and ethanol at 70°C and was allowed to return to room temperature over a period of 7 days at the end of which colorless crystals were formed.

X-ray Structural Analysis

The crystals were colorless plates exhibiting twinning but it was possible to obtain a single crystal by separating the plates into thinner ones. A single crystal of dimensions 0.6 × 0.3 × 0.1 mm covered with oil (Exxon's Paratone *N*) was mounted on a thin glass fiber and instantly frozen at 173 K. Data were collected at that temperature from a Rigaku four-circle diffractometer using Mo-Ka radiation ($\lambda = 0.71069$ Å). The cell dimensions were obtained by least-squares analysis of 20 reflections in the range of $8° < 2\theta < 20°$. A hemisphere of data was collected by a $2\theta-\omega$ scan technique to $2\theta \approx 52°$ with a speed of 4.0°/min. Three standard reflections, monitored every 150 reflections, showed no decay in intensity during data collection.

The structure was solved using the coordinates of the isomorphous inclusion complex of βCD with 4-*tert*-butylbenzoic acid [10]. The starting coordinates were those of the glucosidic skeleton. The remainder of the host atoms, followed by the solvent molecules were found by consecutive difference Fourier calculations. The structure refined isotropically by full-matrix least-squares (SHELX97) [11] to an *R*-factor 13.1%. One oxygen atom from the primary side of the βCD cavity was found to be disordered. At this point, a difference Fourier map revealed the guest atoms. Four distinct lobes appeared to be the positions of the carboxylic oxygen atoms in each side of the cyclodextrin cavity indicating a disordered guest molecule. Chain atoms were also found but the resulting geometries were distorted because some atoms in the two models of the guest were located very close. Thus, geometries were optimized by fitting in the difference Fourier map using the graphics program O [12]. All host atoms were assigned anisotropic thermal parameters and calculated hydrogen atoms with temperature factors 1.2 of the corresponding βCD atoms to which they were bonded. Then a full matrix least-squares refinement followed to a final *R* factor of 0.0764. Toward the end, the coordinates of the guest were subjected to constrained refinement, where all guest atoms were left isotropic and calculated hydrogen atoms were added to the carbon atoms as before, while one peak located 1.0 Å away from a carboxyl oxygen atom was considered as a hydrogen atom. The occupancy

factors of guest molecules G and H were refined to 52% and 48%, respectively.

Acknowledgments

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