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ORIGINAL ARTICLE

Hydrolysis of glutaric anhydride to glutaric acid in the presence of β-cyclodextrin. Crystallographic and NMR study

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Abstract Crystallization of glutaric anhydride in the presence of β-cyclodextrin (βCD) from aqueous solution resulted in crystals of the glutaric acid/βCD inclusion complex. The result was verified by NMR spectroscopic experiments, which moreover showed that βCD does not protect glutaric anhydride from hydrolysis. The structure determination by X-ray crystallography revealed a host:-guest ratio of 1:1 and crystal packing identical to that of natural βCD, i.e., herring bone packing, as is common for guest molecules of small size. Glutaric acid has partial occupancy in the complex and it is disordered in three positions and conformations inside the cavity. All three conformations are stabilised by: (a) Interactions among its carboxyl groups and the host's primary side hydroxyls pointing towards the cavity, thus justifying the conformations of the latter and (b) by two water molecules located on either side of the cavity, as well as hydroxyl groups of neighbouring hosts. In all conformations the guest is not extended, oxygen atoms between the two carboxyl groups being within H-bond distance.

Keywords Cyclomaltoheptaose · Glutaric acid · Glutaric anhydride · Hydrolysis · Dicarboxylic acid · Crystal structure

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Introduction

Cyclodextrins (CDs) are widely used molecular hosts for a variety of guest molecules. Their torus-shaped cavity is sufficiently apolar to induce the inclusion of the hydrophobic moieties of molecules in aqueous environment and thus they have found practical application as solubilisers and carriers [1–4]. However, the CD cavity can also host polar molecules, such as water and alcohols [5]. The structure of hydrated β-cyclodextrin (βCD) has been studied extensively [6], however only few structures of native βCD inclusion complexes with hydrophilic guests have been determined, mainly small aliphatic alcohols [7–11]. All the above complexes are monomeric, "cage type", isostructural to the natural βCD hydrated crystals. The small dicarboxylic acid, succinic acid forms also a 1:1 monomeric complex with βCD, as reported recently [12]. In contrast, inclusion complexes of βCD with longer aliphatic mono and dicarboxylic acids (9–16 carbon atoms) form dimers [13–16]. For both groups, the host:guest ratio is 2:1 for acids with more than 10–12 carbon atoms, whereas 2:2 for the monocarboxylic acid with nine carbon atoms [17]. Aliphatic monocarboxylic acids with 12–16 carbon atoms align almost on the top of each other forming channels, inside which the entrapped carboxylic groups are stabilized by self-association to carboxylic acid dimers [13]. On the other hand, in the long aliphatic diacids the carboxylic groups emerging from the two primary faces of the βCD dimer favor H-bonding with water molecules thus favoring the breaking of the channel. The same packing is exhibited by the complex of the shorter monocarboxylic acid, nonanoic acid with βCD, which induces the packing of a dicarboxylic acid. As mentioned above, two guests are accommodated in each dimer, with their carboxylic groups emerging from the primary faces as in the diacids [17].

In the present study we deal with glutaric acid (GLA, Fig. 1), a dicarboxylic acid longer than succinic acid, whose length fits the length of one CD cavity. Interestingly, the above inclusion complex has been prepared from βCD and glutaric anhydride. The anhydride was chosen, because it has been reported that in the βCD/succinic acid complex [12], the guest was derived during the crystallization process by hydrolysis of the initially used succinic anhydride. It is claimed that βCD catalyses the hydrolysis at ambient temperature, in contrast to the hydrolysis in the absence of βCD that takes place at 60°C. Thus the present study intends to (a) test if the less strained glutaric anhydride is hydrolysed to glutaric acid at room temperature in the presence of βCD; (b) understand the modes of stabilization of dicarboxylic acids, whose extended length spans the height of βCD, in its cavity; (c) further, determine if the functional groups of the guest have any influence to the crystal packing of the host.

Experimental

Materials and methods

Glutaric anhydride and βCD were obtained from Fluka and Jansen, respectively. All solvents were reagent grade. Water was purified by the Purelab Plus (ELGA LABWATER) system.

X-ray crystallography

The complex was prepared by mixing an aqueous solution of βCD (20 mM) with an ethanol solution of glutaric anhydride (10 mM), while stirring at RT for approximately 6 h. The clear solution was covered with paraffin film and left for slow evaporation. Diamond shaped, colourless crystals of moderate quality were obtained after a period of 10 days.

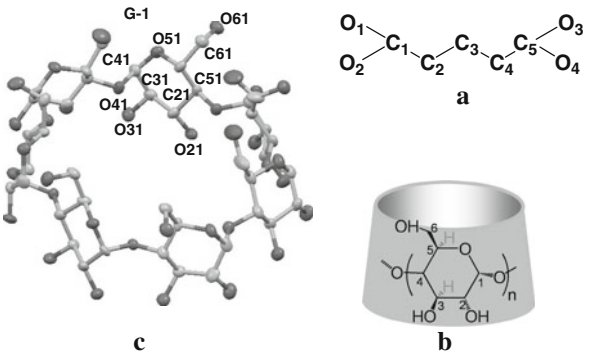

Fig. 1 **a** Diagrammatic illustration and numbering of glutaric acid; **b** schematic diagram of βCD; **c** ORTEP diagram [18] and numbering scheme in the GLA/βCD complex, Cmn, Omn denoting the mth atom within the *n*th glucosidic residue (G-n) of βCD

X-ray data were collected on a single crystal (of dimensions 0.3 × 0.2 × 0.1 mm) enclosed in a capillary in order to prevent water loss, at RT by a four-circle diffractometer (Cyntex) equipped with a Rigaku rotating anode and a graphite monochromator using the θ–2θ scanning mode. The data were corrected for Lorentz and polarization effects. Crystal data are given in Table 1. The structure was solved by molecular replacement using as model the βCD skeleton of the ethylene glycol/βCD [9]. The coordinates of the remaining non-H atoms and the solvent atoms were determined by consecutive difference Fourier maps. The refinement by full-matrix least-squares based on F^2 was carried out with the program SHELXL97 [19]. The occupation factors of the solvent atoms were first refined by keeping the temperature factors constant (U at 0.05 A^2) and subsequently were kept constant, while the temperature factors were refined. The cyclodextrin non-hydrogen atoms and solvent atoms were treated isotropically up to $R = 15.02\%$ and then anisotropically. Hydrogen atoms were placed at idealized positions on the host carbon atoms and refined by the riding model ($U_H = 1.25\ U_C$). For the host's CH_2 group bearing the disordered hydroxyl group O67 (O67A and O67B) only the H-atoms of the major orientation (O67A) were used. Guest atom positions were revealed at R-factor around 11%. In order to

Table 1 Crystal data and structure refinement parameters

Molecular formula	C42 H70 O35·0.6(C5 H8 O4)·4.2(H2 O)
Formula weight	1289.92
Temperature	293(2) K
Radiation/wavelength	1.54180 Å
Space group	$P2_1$
a, α	15.15(2), 90°
b, β	10.343(15), 109.69(4)
c, γ	20.93(3), 90
Volume/Z	3088(8) $Å^3$/2
Density (calculated)	1.369 Mg/m^3
2θ range for data collection	2.24°–50.00°
Index ranges	$0 \le h \le 15$, $0 \le k \le 10$, $-20 \le l \le 19$
Reflections collected/observed [$F_o > 4\sigma(F_o)$]	3381/2148
Solution method	Isomorphous replacement
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3381/159/789
Goodness-of-fit on F^2	1.109
Final R indices [$F_o > 4\sigma(F_o)$]	$R_1 = 0.0966$, $wR_2 = 0.2339$
R indices (all data)	$R_1 = 0.1423$, $wR_2 = 0.2825$
Largest diff. peak and hole	0.40 and −0.31

account for all the difference-Fourier peaks inside the cavity the guest had to be modeled as disordered over three positions. The refinement continued after placing H-atoms on the guest carbon atoms at idealized positions. For the guest molecules, the refinement was isotropic and distances and angles were restrained to the values of the uncomplexed molecule. The guest atoms were not refined at the last stage of the refinement.

NMR spectroscopy

The hydrolysis of GLA anhydride was followed by recording two series of ^{1}H NMR spectra at 500 MHz (Bruker Avance) at 298 K: of (a) a solution of deuterium oxide (1 mL) + absolute ethanol (0.3 mL) + GLA anhydride (0.0017 g) and (b) a solution of deuterium oxide (1 mL) + absolute ethanol (0.3 mL) + GLA anhydride (0.0017 g) + βCD (0.0300 g). The concentrations and the constitution of the βCD containing solution was exactly the same as the one used for crystallization. The ratio [GLA anhydride]/[GLA] was obtained by integration of the respective central methylene peaks (on C3) at 1.882 ppm (GLA anhydride) and 1.753 ppm (GLA) and plotted as a function of time (Fig. 2).

Results and discussion

The structure determination showed that the guest of the crystallized inclusion complex is glutaric acid (Fig. 1a). This result was confirmed by NMR spectroscopy: no glutaric anhydride was detected in a solution, in which crystals obtained for the crystal structure determination were dissolved. Moreover, the hydrolysis of glutaric anhydride was monitored in water/ethanol solutions in the presence and absence of βCD by ^{1}H NMR spectroscopy. The results (Fig. 2) show that a first order exponential decay seems to

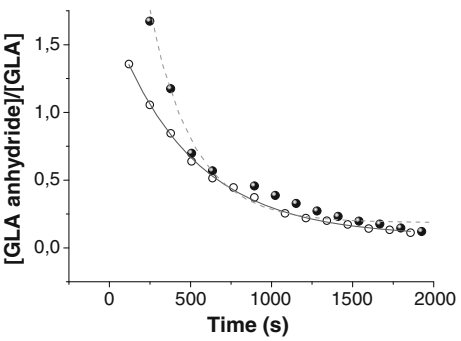

Fig. 2 GLA anhydride hydrolysis to GLA in a 23% ethanolic D_2O solution monitored by ^{1}H NMR spectroscopy at 298 K and fitting to a first order exponential decay: *filled circle* GLA anhydride alone; *open circle* GLA anhydride + βCD

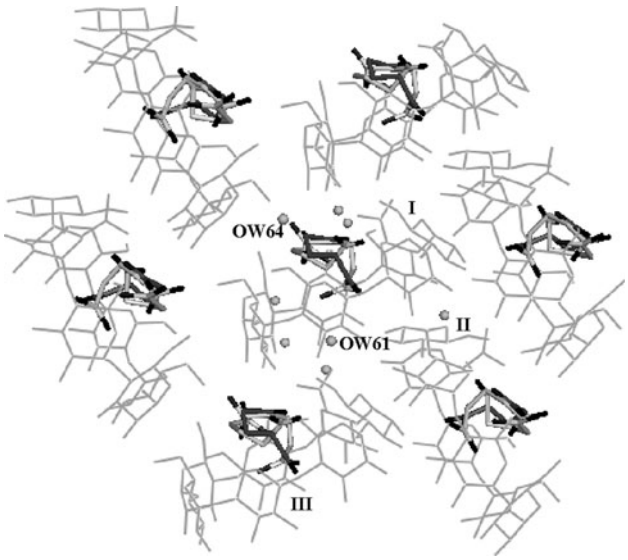

Fig. 3 Packing of the GLA/βCD complex [20]. The host molecules are stacked in "herring-bone" packing. The guest, disordered in three positions (in different *shades of gray*), is inside the cavity of the host and interacting with the water molecules OW61 and OW64

be followed during hydrolysis both in the solution of GLA anhydride alone ($k_{hydrol} \cong 3.6 \times 10^{-3}$ s^{-1}, $R^2 = 0.99006$) as well as in the solution of GLA anhydride with βCD ($k_{hydrol} \cong 2 \times 10^{-3}$ s^{-1}, $R^2 = 0.99886$). Each case proceeds with a different hydrolysis rate as βCD seems to slow the process; however both show almost complete hydrolysis within 35 min. Therefore, protection of GLA anhydride from hydrolysis offered by βCD during the lengthy crystallization process is not justified by the above data, thus the crystallographic results are verified.

The inclusion complex is a 1:1 host:guest complex isomorphous to the natural βCD [6], as is commonly observed in complexes with small guest molecules that can be completely enclosed in the host cavity. The numbering scheme of the βCD is given in Fig. 1b, c, Cmn and Omn(A or B) denoting the mth atom within the nth glucosidic residue (G-n), whereas A and B refer to different orientations of disordered O-atoms. The crystal packing of the monomeric complex is shown in Fig. 3: **I** is the asymmetric unit comprising one βCD host and one guest molecule (occupation 0.6) disordered over three positions inside the cavity of the host, as well as 4.2 water molecules in eight partially occupied positions.

The conformation of the βCD macrocycle has similar distortions as that of natural βCD [6], but more than the monomers in βCD dimeric complexes [13, 21] (Table 2). The glucopyranose residues adopt the regular $^4C_1$ chair conformation. The range in the angles of the glucosidic oxygen atoms O4*n* is similar to these of the macrocycles of βCD dimers (125.2–132.0°), whereas the tilting of the glucose units with respect to the O4*n* atoms plane is greater

Table 2 Inclusion complex βCD/glutaric acid. Conformation of the macrocycle (esds in parentheses)

Glucose unit	D[a] (Å)	Φ[b] (°)	D[c] (Å)	D_5^d (Å)	Tilt angles[e] (°)	O-5*n*–C-5*n*–C-6*n*–O-6*n* (°)[f]
G1	4.29(2)	127.1(3)	0.10(1)	2.93(2)	23(1)	64(2)
G2	4.45(2)	125.9(3)	−0.23(1)	2.92(2)	11(1)	−64(2)
G3	4.45(2)	132.2(3)	−0.03(1)	2.80(2)	6.9(0.6)	−62(2)
G4	4.25(2)	127.9(4)	0.28(1)	2.76(2)	11(1)	−69(2)
G5	4.34(2)	125.4(4)	−0.12(1)	2.89(2)	21(1)	64(2)
G6	4.50(2)	130.6(3)	−0.21(1)	2.88(2)	2(1)	−64(2)
G7	4.41(2)	129.0(3)	0.21(1)	2.93(2)	16(1)	A 64(3)
						B −70(3)

[a] O-4*n*···O-4(n + 1); [b] O-4(n-1)···O-4*n*···O-4(n + 1) angles; [c]deviations (Å) from the least-squares optimum plane of O-4*n* atoms; [d] intramolecular H-bonds between O-3*n*···O-2(n + 1); [e]Tilt angles between the optimum O-4*n* plane and the mean planes through atoms O-4(n-1), C-1*n*, C-4*n*, O-4*n*; [f]A, B, indicate the various orientations of the C-6*n*–O-6*n* bond

(tilt angles 2.0–23.2°) than in βCD dimers (tilt angles 5.0–13.0°). The βCD adopts a rather 'round' shape stabilized by intramolecular hydrogen bonds connecting the O-3*n* and O-2(n + 1) atoms of neighboring glucopyranose units with O-3*n*···O-2(n + 1), distances as in native βCD (range 2.76–2.93 Å and average 2.87 Å) longer than in the βCD dimers (range 2.79–2.81 Å). At the primary side, four hydroxyl groups exhibit the (−)-gauche conformation pointing outward, two hydroxyl groups (O61 and O65) have the (+)-gauche conformation and point inward, whereas hydroxyl O67 is disordered in two orientations with major occupancy, O67A, [(+)-*gauche*] 54%.

The guest molecule, disordered in three positions and conformations (**a**, **b**, **c** with occupancies *ca.* 17, 20 and 23%, respectively), is located close to the primary side of the macrocycle (Fig. 4), where it is stabilised by formation of H-bonds with the primary hydroxyls: There are close contacts between the guest's carboxylic oxygen atoms with the inward pointing hydroxyls O61 and O65 and O67A of the host, which justify the inward conformations of the hydroxyl groups. Water molecules OW64 and OW61 located close to the primary and secondary rims of the host (Figs. 3 and 5) exhibit also close contacts with the carboxylic groups of some guest positions (Table 3a) contributing to the further stabilisation of the guest. In all conformations, the guest does not exhibit an extended structure, carboxylic oxygen atoms O2 and O4 being within H-bond distance. This was observed also in the structure of the βCD/succinic acid complex, but in this case the experimentally determined carboxylic H-atom was not pointing towards the neighbouring O-atom in order to form intramolecular H-bond [12].

The width of the host cavity is actually sufficient to accommodate guest **a** horizontally, possibly as glutaric anhydride would have been positioned. Close contacts [21] (Table 3a) suggest that two carboxylic oxygen atoms interact with hydroxyls O61, O65 and O67A, while one with water molecule OW64 (occupancy 51%). Guests **b**

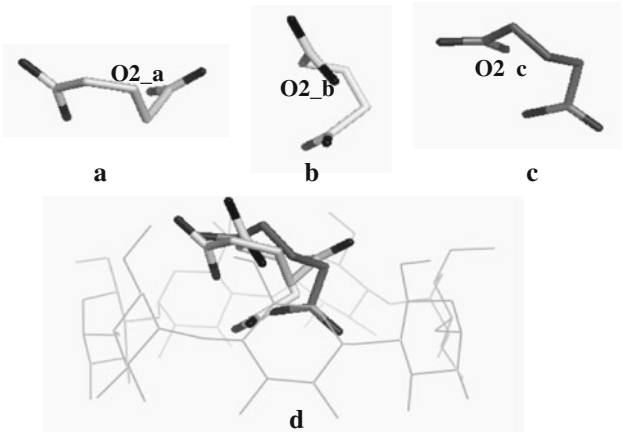

Fig. 4 The three conformations of the guest (**a**, **b**, **c**) shown in stick type and their positions inside the host cavity (**d**) [20]. *Color code*: carbon atoms in *dark*, *medium* and *light grey*, for guests **c**, **a**, **b**, respectively, oxygen atoms in *black*

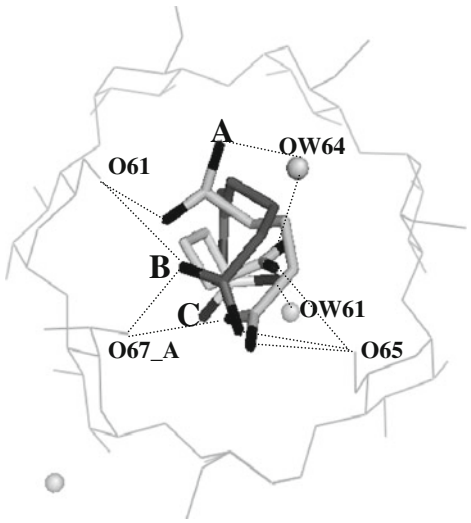

Fig. 5 The most important interactions between host and guest molecules (colour code as in Fig. 4)

Table 3 Selected intermolecular distances (Å) and angles (°) in the GLA/βCD complex

$O_G\cdots OH_{host}$ or O_w	Distance (Å)	$C_G–O_G\cdots OH_{host}$ or O_w (°) *$C1_G–O2_G\cdots O4_G$ (°)	$O_G\cdots OH_{host}–CH_{host}$ (°) * $O_G\cdots C_G–O_G$ (°)
a. Close contacts involving the guest			
Guest A			
$O1\__a\cdots OW64$	3.18(2)	101(2)	
$O2\__a\cdots O61$	2.47(4)	108(1)	90(1)
$O2\__a\cdots O4\__a$	3.14(2)	90(1)*	104(1)*
$O3\__a\cdots O65$	2.75(3)	88(1)	94(1)
$\cdots O25^1$	2.62(2)	107(1)	127(1)
Guest B			
$O1\__b \ldots O31^3$	2.99(2)	109(1)	123(1)
$\ldots O46^1$	3.14(2)	143(1)	112(1), 126(1)
$O2\__b\cdots OW61$	2.58(3)	98(3)	
$O2\__b\cdots O4\__b$	2.26(2)	97(1)*	121(1)*
$O3\__b\cdots O65$	2.98(2)	121(1)	128(1)
$\cdots O25^1$	2.31(2)	107(1)	121(1)
$\cdots O34^1$	3.11(2)	87(1)	149(1)
$O3\__b\cdots OW64$	2.51(2)	86(2)	
$O4\__b\cdots OW64$	2.91(2)	121(3)	
Guest C			
$O1\__c\cdots O21^3$	2.62(2)	128(1)	111(1)
$\cdots O42$	3.15(2)	132(1)	104(1), 134(1)
$O2\__c\cdots O4\__c$	2.51(2)	96(1)*	95(1)*
$O3\__c\cdots O25^1$	2.89(2)	79(1)	138(1)
$\cdots O67\_A^a$	2.95(5)	75(3)	140(3)
$\cdots O65$	3.17(2)	120(1)	91(1)
$O4\__c\cdots O67\_A^a$	2.54(4)	91(3)	95(3)
$O4\__c\cdots O61$	3.21(2)	115(1)	130(1)
$OH_{host}\cdots OH_{host}$	Distance (Å)	Cmn–Omn···Om′n′ (°)	Onm···Om′n′–Cm′n′ (°)
b. Direct hydrogen-bond distances (Å) between host molecules			
$O61\cdots O34^1$	2.99(2)	146(1)	89(1)
$O22\cdots O36^2$	2.75(2)	97(1)	122(1)
$O63\cdots O66^4$	2.81(3)	101(1)	125(1)
$O35\cdots O67\_A^{a5}$	2.50(5)	104(2)	130(2)
$O26\cdots O67\_B^{a5}$	2.90(4)	123(2)	114(2)
$OH_{host}\cdots Ow$	Distance/Å	Cmn–Omn…Ow (°)	
c. Close contacts involving the guest host hydroxyls and water molecules			
$O61\cdots OW61^1$	2.79(4)	114(2)	
$O62\cdots OW23^2$	3.06(2)	113(2)	
$O62\cdots OW26^6$	2.87(2)	97(2)	
$O63\cdots OW63^4$	2.75(3)	129(2)	
$O64\cdots OW64^7$	2.73(3)	110(2)	
$O64\cdots OW66^8$	2.62(3)	121(2)	
$O65\cdots OW65^9$	2.28(3)	137(2)	
$O65\cdots OW66^8$	3.05(3)	111(2)	
$O66\cdots OW66\_A^a$	2.85(3)	116(2)	
$O66\cdots OW66\_B^a$	2.80(5)	136(2)	
$O67\_B\cdots OW61^1$	2.78(5)	109(2)	

Table 3 continued

OH_{host}···Ow	Distance/Å	Cmn–Omn…Ow (°)
O31···OW61[2]	2.89(4)	132(2)
O32···OW23[4]	2.81(2)	113(2)
O23···OW23[3]	2.76(3)	121(2)
O33···OW26[4]	2.95(3)	115(2)
O24···OW66[10]	2.91(5)	101(2)
O34···OW64[5]	2.93(3)	119(2)
O25···OW63[8]	2.84(2)	113(2)
O26···OW26	2.70(3)	111(2)
O26···OW65	3.11(6)	87(2)
O27···OW23	2.80(2)	118(2)

[a] A or B denote the two orientations of the host's disordered OH groups

[1] $x, y + 1, z$; [2] $-x + 1, y + 1/2, -z$; [3] $-x + 1, y-1/2, -z$; [4] $x + 1, y, z$; [5] $x, y - 1, z$; [6] $x + 1, y + 1, z$; [7] $-x + 2, y - 1/2, -z + 1$; [8] $-x + 1, y - 1/2, -z + 1$; [9] $-x + 1, y + 1/2, -z + 1$; [10] $x + 1, y - 1, z$

and **c** extend more towards the secondary side of the host (Fig. 4) and they are also stabilised by similar interactions. Thus O1_b and O2_b of guest **b**, which extends most into the cavity, interact with the secondary hydroxyl O31 of the neighbouring host below and water OW61, respectively, and the O3_b and O4_b, positioned in the primary side, with O65 and OW64, respectively. The O1_c atom of guest **c** forms a strong H-bond with the secondary O21 hydroxyl of the host below (**II**) (Fig. 3) and O3_c and O4_c with the primary hydroxyls O65 and O67_A of the hosting βCD, respectively. Thus the multifunctional host and the crystal packing permit stabilisation of this small and flexible guest molecule in more than one conformations and positions. The three guest positions may present snapshots of its movement from the horizontal position near the primary side further inside the cavity. In the present structure, glutaric acid is completely enclosed in the cavity but exposed to the solvent from both sides of it. The fact that inclusion does not prevent hydrolysis of glutaric anhydride suggests that the same must be true for this guest too.

In this packing mode [6], glucose residue G-1 of host **II** (Fig. 3) is located at the secondary entrance of molecule **I**, at the level of the hydroxyls of the latter, so that the set of secondary hydroxyls of residue-1, O21 and O31 are placed at the middle of the secondary circle of **I** and establish close contacts with guests **b** and **c** (Table 3a). On the same side of **I**, the primary side of host **III** comes also close to **I** forming H-bonds with the secondary hydroxyls of the latter (O61(**III**)···O34(**I**) and O67A(**III**)···O26(**I**), (Table 3b). The above features have as a consequence the blocking of the cavity of **I** from the secondary side. Water molecules interacting with the exposed hydroxyls form a network connecting the hosts in the lattice (Table 3c). Water molecules OW61 and OW64 have the additional function to stabilise the guest molecule.

Conclusion

In summary, inclusion of glutaric anhydride in βCD does not protect it from hydrolysis into glutaric acid. The latter forms a 1:1 inclusion complex with βCD and is enclosed entirely inside its cavity by acquiring a bent conformation. The end-functional groups of glutaric acid do not influence the crystal packing of βCD, since they are stabilized by close contacts with hydroxyls of the enclosing and neighboring hosts, as well as water molecules. A major influence of the packing would be if two GLA molecules would acquire the extended conformation and associate by their carboxylic groups forming a long system that would be accommodated inside a βCD dimer (2:2 complex). However, this would require a strong driving force, as in the case of the long mono-carboxylic acids, in which the end-methyl group, requiring to be isolated from the water environment, forces the βCD hosts to pack in channels, in the hydrophobic environment of which the carboxylic groups associate into dimers [13]. The guest exhibits three distinct conformations and positions (of partial occupation), probably due to multiple of ways of stabilisations through H-bonding of its carboxylic groups with the hydroxyls of the enclosing and neighbouring hosts and water molecules at both the primary and secondary sides of βCD.

Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC 765236.

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