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ORIGINAL ARTICLE

Crystal and molecular structure of β-cyclodextrin inclusion complex with succinic acid

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Abstract The crystal complex of β-cyclodextrin with succinic acid, intermediate product of hydrolysis reaction of succinic anhydride in the presence of β-cyclodextrin, was isolated and studied by X-ray analysis (monoclinic, space group $P2_1$, $a = 15.1977(7)$ Å, $b = 10.1763(5)$ Å, $c = 20.6943(6)$ Å, $\beta = 109.239(4)°$, $V = 3021.8(2)$ Å^3, $Z = 2$, $R_1 = 0.0359$, w$R_2 = 0.0947$). It was proved that β-cyclodextrin and succinic acid form an inclusion complex, which exists in crystal state as a heptahydrate. The molecule of succinic acid is fully included in the β-cyclodextrin cavity with its carboxyl groups accessible for water molecules. Water molecules located at borders of cavity rims and in interstices between molecules of β-cyclodextrin participate in formation of intermolecular hydrogen bonds. The overall structure does not contain disordered fragments. The crystal conformation of succinic acid corresponds to one of possible conformers of the molecule in vacuo and is almost not disturbed by intermolecular interactions in crystal. Based on the analysis of structural features of the crystal conformation of succinic acid and character of its location in the β-cyclodextrin cavity, it was suggested that hydrolysis of succinic anhydride via ring opening and formation of succinic acid is mediated by cyclodextrin microenvironment and it likely occurs near the narrow rim of the macrocycle cavity.

Keywords β-Cyclodextrin inclusion complex · Conformational analysis · Crystal structure · Hydrogen bonding · Mediator of reaction · Succinic acid · Succinic anhydride · X-ray analysis

Introduction

Supramolecular control of catalysis and reactivity is a fundamental function of supramolecular systems. β-Cyclodextrin (β-CD) is a representative of cyclic polysaccharides, macrocycles with hydrophilic external and hydrophobic internal surface. β-CD is known by its ability to form supramolecular inclusion complexes with other molecules and such inclusion usually changes properties of these guest molecules (e.g. it enhances solubility of barely water-soluble substances) [1–4]. Additionally, β-CD is widely used as an artificial enzyme [5] or a mediator [6–8], which accelerates various reactions and modifies reaction paths. As a mediator, β-CD does not form a covalent bond with a reactant but the hydrophobic cavity of β-CD provides the reactant with a new reaction environment, so-called an ''extra reaction field'', which changes rate or selectivity of the reaction [6].

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Succinic anhydride is one of the most widely used acylation agents in supramolecular chemistry for focused modification of biological macromolecules (including proteins, polynucleotides and polysaccharides) [9–11]. The reaction of acylation of a nucleophile by succinic anhydride via ring opening and formation of succinic acid [12] is shown in Fig. 1. However, high stability of succinic anhydride in normal conditions to hydrolytic cleavage essentially restricts its potential use [13] and stimulates a search to enhance its reactivity.

We hypothesized that due to good fit of the succinic anhydride molecule to a size of the β-CD cavity the reactivity of succinic anhydride is enhanced by formation of its inclusion complex with β-CD. This hypothesis was confirmed by successful hydrolysis of succinic anhydride with formation of succinic acid, which was carried out at ambient temperature. In contrast to regular hydrolysis of succinic anhydride [12] this reaction did not require heating and was about 20 times faster than one without β-CD that serves as indirect indication of formation of the β-CD inclusion complex with succinic anhydride in solution. The intermediate product of hydrolysis of the succinic anhydride inclusion complex of β-CD with succinic acid was isolated in crystal state from the reaction medium. To understand better the mechanism of the reaction mediated by β-CD microenvironment the crystal and molecular structure of this complex was studied by means of X-ray diffractometry and molecular mechanics calculations. The crystal conformation of succinic acid molecule was compared with its possible conformers in vacuo at the final stage of this investigation.

Experimental

Preparation of inclusion complex of β-CD with succinic acid

Succinic anhydride (Fluka, USA) and β-CD (Cyclodex, USA) were used in all experiments. To obtain the inclusion complex 88 mg of previously ground succinic anhydride were added to 50 ml of 2% water solution of β-CD at molar ratio 1:1. The solution was stirred at room temperature during 10–12 min until complete dissolution of succinic anhydride. After that the solution was cooled down to +2 °C. Crystal precipitate of succinic acid (m.p. = 183.0 °C) was observed and confirmed by X-ray analysis. Supernatant liquid was stored at room temperature during 24 h until precipitation of rhomb shaped crystals (m.p. = 295.0 °C with decomposition). Yield of the complex was 34.2% (relative to initial content of β-CD).

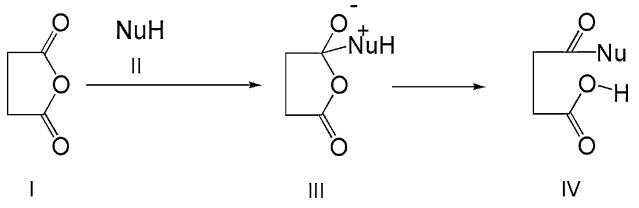

Fig. 1 Hydrolytic cleavage of succinic anhydride via ring opening and formation of succinic acid: I—succinic anhydride; II—nucleophile, NuH = –NH_2, –OH, –SH; III—intermediate; IV—succinic acid (Nu=OH)

Crystal structure determination and refinement

The X-ray diffraction experiment was carried out using ''X-Calibur-3'' automated diffractometer (Oxford Diffraction Ltd.) equipped with ''Sapphire-3'' CCD detector (MoKα radiation, λ= 0.71073 Å graphite monochromator) at room temperature. The structure was solved by direct method (SIR-97 program [14]) and refined with Shelx-97 program package [15] on F^2(hkl). Hydrogen atoms in CH_2 groups were placed in idealized positions and refined using the riding model [15]. The rest of hydrogen atoms was located in a difference map and refined isotropically. Crystal data and final agreement factors are summarized in Table 1.

Conformation analysis of succinic acid in vacuo

Calculations were performed using the molecular modeling package HyperChem® with molecular mechanics force field MM^+ [16]. Electrostatic interactions were estimated in monopole-monopole approximation (ε = 1.5). Atomic charges were calculated using AM-1 method [17]. Conformational space of an isolated molecule of succinic acid was investigated using random search method [18]. Starting conformations of the molecule were generated by random variations of 5 torsion angles, $\varphi_1 - \varphi_5$ (Fig. 2), with subsequent optimization of the structure. Starting structures were selected by means of directed scheme [19]. Structure optimization was performed by Polak-Ribiere method until energy root-mean-square (RMS) gradient of < 0.01 kcal/(Å mol). After rejection of degenerated structures, the set of optimized conformations was further optimized until RMS gradient of < 0.001 kcal/(Å mol). The ranges of the torsion angle ϕ of $0° < \varphi < 120°$, $-120° < \varphi < 0°$ and of $120° < \varphi < -120°$ were classified as gauche clockwise, gauche counterclockwise and trans, respectively. They were defined as G, G′ and T for C–C–C–C torsions (φ_3), and similarly, as g, g′ and t for the C–C–C–O torsions (φ_2 and φ_4). Trans and cis arrangements for C–C–O–H torsions (φ_1 and φ_5)

Table 1 Crystallographic data for inclusion complex of β-CD with succinic acid

Empirical formula	$C_{46}\ H_{90}\ O_{46}$
Formula weight	1379.18
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2_1
Unit cell dimensions	a = 15.1977(7) Å, b = 10.1763(5) Å, c = 20.6943(6), β = 109.239(4) Å,
Volume	3021.8(2) $Å^3$
Z, Calculated density	2, 1.516 mg m^{-3}
Absorption coefficient (MoKα)	0.138 mm^{-1}
F(000)	1468
Crystal size	0.2 × 0.2 × 0.2 mm
θ range for data collection	2.92° to 34.84°
Index ranges	$-24 \le h \le 23$, $-16 \le k \le 16$, $-32 \le l \le 32$
Reflections collected/unique	120472/23622 [R_{int} = 0.038]
Completeness to 2θ = 34.84°	93.1%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	23622/1/981
Goodness-of-fit on F^2	0.939
Final R indices [$I > 2\sigma$ (I)]	R_1 = 0.0359, wR_2 = 0.0947
R indices (all data)	R_1 = 0.0380, wR_2 = 0.0972
Absolute structure parameter	0.3(2)
Largest diff. peak and hole	0.519 and –0.388 e $Å^{-3}$

were defined as t and c, respectively. Type of conformers obtained is determined by the sequence of these designations beginning from φ_1 (Fig. 2). For example, the all-trans conformer shown in Fig. 2 is defined as ttTtt. For all conformers the relative energies, ΔE, were calculated with respect to the global minimum. The solvent accessible surfaces [20] were built using the molecular modeling package Chem 3D® [21]. The adopted radius for the solvent (water) probe was 1.4 Å.

Results and discussion

Structure of β-CD inclusion complex with succinic acid

Crystal data and final agreement factors for inclusion complex of β-CD with succinic acid existing as a heptahydrate in a crystal state are shown in Table 1. Atom numbering scheme and thermal ellipsoids for the complex are presented in Fig. 3.

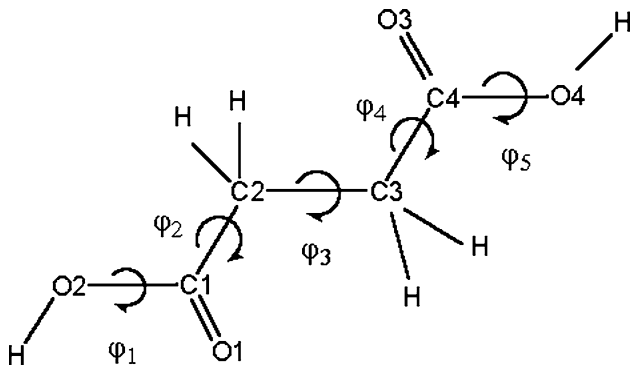

Fig. 2 A molecule of succinic acid. Arows show torsion degrees of freedom $\varphi_1 - \varphi_5$

The β-CD molecule adopts a slightly elliptically distorted from an ideal torus shape of a macrocycle. The molecule of succinic acid (with φ_3 torsion in G conformation) is fully included in its cavity (Fig. 4). Methylene groups of succinic acid are located near the plane of glycosidic oxygens of β-CD and a center of mass of the acid molecule is shifted from this plane to the narrow rim by about 1 Å. First carboxyl group C(01)O(01)O(02)H(02) (in the cis form) and carbonyl oxygen O(03) of second carboxyl group (in the trans form) face primarily hydroxyls of β-CD whereas hydroxyl group O(04)H(04) faces the wide rim of the macrocycle cavity. Water molecules are disposed outside the cavity at borders of toroid rims (molecules O06 and O05) and in interstices between β-CD molecules. Four water molecules (O07, O05, O08 and O09) are situated near primarily hydroxyls and other three (O06, O10 and O11) are disposed in the vicinity of secondary hydroxyls. The entire structure does not contain disordered fragments.

The position of guest succinic acid inside the cavity of host β-CD allows for its carboxyl groups to be accessible to water molecules (see Fig. 5 and Table 2) that agrees well with conclusions of Hallén et al. [22] and Rekharsky and Inoue [23] regarding the location of hydrophilic carboxyl groups of guest molecules when cyclodextrin inclusion complexes are formed in aqueous solutions. Aversa et al. [24] observed this trend for aliphatic dicarboxylic acids (including

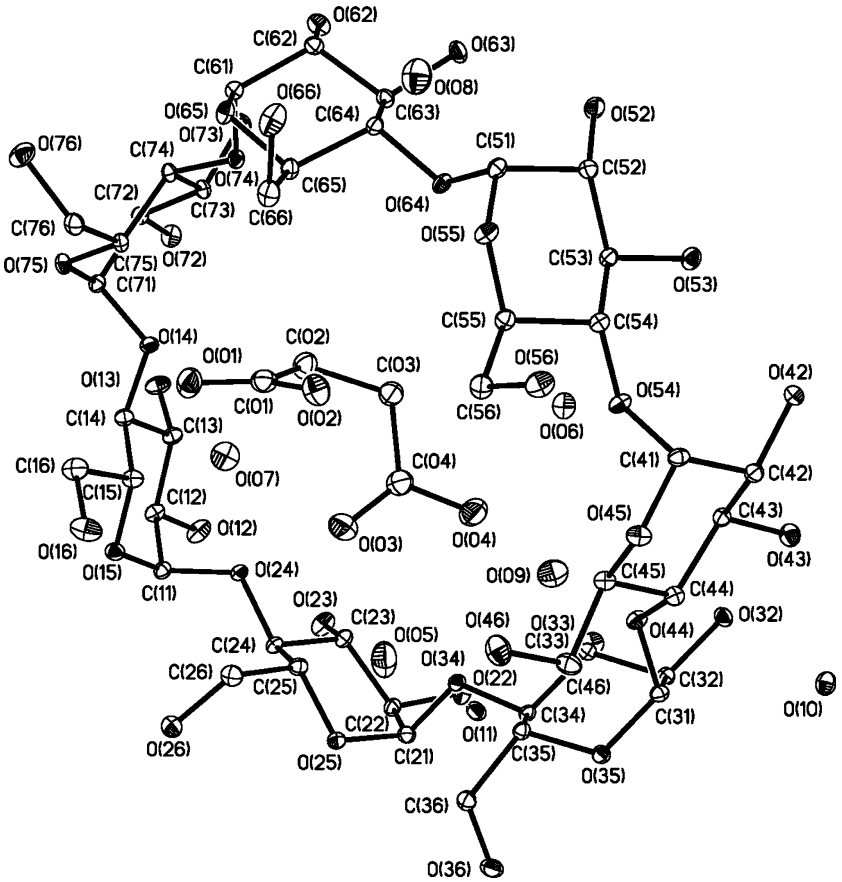

Fig. 3 Atom numbering scheme and thermal ellipsoids for hydrated complex of β-CD with succinic acid (view from the narrow rim of the macrocycle). Hydrogen atoms are not shown for clarity. Oxygen atoms O(05)–O(11) belong to seven water molecules which are designated in the text as O05–O11, respectively

succinic acid) in inclusion complexes with α-CD. Interestingly, in the crystal inclusion complex of 3-iodopropionic acid with α-CD carboxyl group is similarly located at the primary hydroxyl side of α-CD [25].

In the crystal complex studied in this work, the β-CD molecules form a herringbone cage type structure [26] in which the cavity of one β-CD molecule is blocked off on both sides by adjacent β-CD's (Fig. 5). The guest molecules do not contact each other in isolated in such a way β-CD cavities and the crystal structure has no continuous channels for diffusion of included molecules (in opposite to those found in channel-type packing arrangements [26, 27]).

Multiple hydrogen bonds are observed in the investigated crystal structure (Table 2). Intramolecular hydrogen bonds between secondary hydroxyls of adjacent glucose units of β-CD form a heterodromic ring of seven H-bonds, which stabilize the macrocycle structure [28]. Donor hydrogen atoms H12, H13, H42 and H62 of secondary hydroxyls form bifurcated H-bonds to stabilize additionally the structure of the macrocycle by H-bonds with corresponding glycosidic oxygens, namely O24, O14, O54 and O74 (Fig. 6). Secondary 2-hydroxyls of second and third glucose units are hydrogen bonded with water molecules O11 and O10, respectively. Oxygen atoms O46 and O56 of primarily hydroxyls are connected by H-bond through the bridging water molecule O09 (Fig. 6).

Five intermolecular H-bonds connect molecules of neighboring β-CD's directly. Two of them connect secondary hydroxyls O23–H23···O73#2 and O72–H72···O33#2 (see the list of symmetry elements in the footnote to Table 2), two H-bonds are formed between primarily and secondary hydroxyls, O26–H26···O32#1 and O53–H53···O16#4, and one H-bond (bifurcated) connects primarily hydroxyl O66–H66 with glycosidic oxygen O35#6 and primarily hydroxyl O36#6 (Fig. 6). Molecules of neighboring β-CD are also bound by H-bonds through water bridges in which all water molecules are involved. The bridges are formed by both single water molecules (O05–O11) and pairs of water molecules O07···O08 and O09···O10 (Fig. 6, 7). Water molecules O10 and O11 connect three and four β-CD molecules, respectively. Two bifurcated intermolecular H-bonds are observed: hydrogens H07B and H11A as donors and oxygens O55#9, O08#9 and O75#8, O76#8 as acceptors are involved in their formation (Fig. 6, 7).

Host-guest hydrogen bonding plays a crucial role in determining the orientation of a guest molecule in the

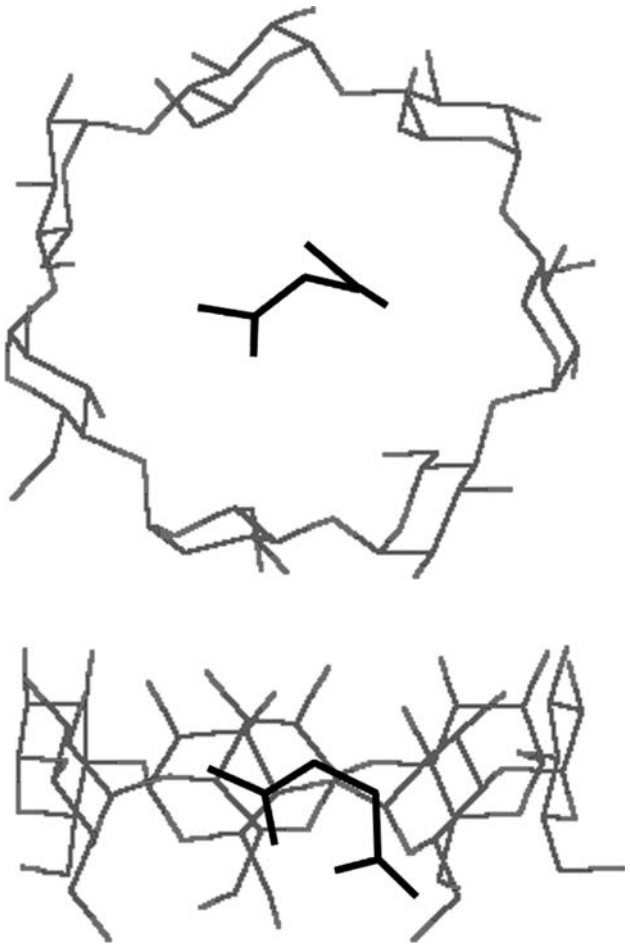

Fig. 4 The structure of the β-CD inclusion complex with succinic acid in two projections (hydrogen atoms are omitted)

cavity [27]. In our case, molecule of succinic acid forms no direct H-bonds with β-CD host. It is hydrogen bonded with neighboring β-CD (O01···[H52–O52]#1), similarly to 3-iodopropionic acid in the crystal inclusion complex with α-CD [25]. In addition, succinic acid is hydrogen bonded with three water molecules O07, O06 and O05: O02–H02···O07, O04–H04···O06 and O03···O05–H05A (Fig. 7). Particularly, succinic acid is bound indirectly through water bridges formed by these water molecules with five β-CD molecules (including the host molecule) by seven hydrogen bonds. Two of them (including H-bond with primarily hydroxyl O46–H46 of host β-CD) involve water molecule O05, three H-bonds involve O06 and two H-bonds involve O07 water molecule (Fig. 7, Table 2). It should be noted that according to the H-bond definitions based on geometric criteria (distance (D···A) < R_D + R_A and angle D–H···A > 110°, where R_D and R_A are van der Waal's radii of donor and acceptor atoms, respectively [29]), H-bonds formed by succinic acid with water molecules O07 and O06 as well as by the water molecule O06 with O26 of primarily hydroxyl of neighboring β-CD are the strongest among H-bonds observed in the overall structure (Table 2).

Conformational analysis of succinic acid molecule in vacuo

To estimate an extent of possible effect of intermolecular interactions in crystal on a conformation of a guest molecule and to compare the crystal conformation of succinic acid with its possible conformers in vacuo we carried out conformational analysis of an isolated molecule of succinic acid. There were 4,185 starting structures initially generated and optimized. After rejecting all conformational isomers, 21 unique conformations of the succinic acid molecule were revealed (Table 3).

The structures obtained were divided into three groups depending on values of torsion angle C–C–O–H (i.e. trans or cis arrangements with respect to C–C bond). In carboxylic acids, trans position of hydroxyl is known to be more energetically favorable than cis position [30]. Our calculations with MM^+ force field show that this difference is about 7.5 kcal/mol (e.g. conformers 16, 9 and 1 in Table 3). Conformers of first group are identified by trans orientation of both

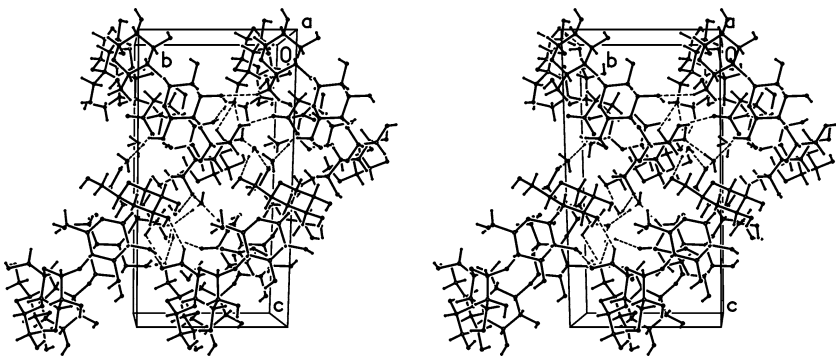

Fig. 5 Stereoview of molecular packing in the unit cell

Table 2 Hydrogen bonding in the structure of hydrated complex of β-CD with succinic acid (D—donor atom, A—acceptor atom, H—hydrogen atom)

D–H	A	H···A distance (Å)	D···A distance (Å)	DHA angle (°)	D–H	A	H···A distance (Å)	D···A distance (Å)	DHA angle (°)
O12–H12	O23	2.163	2.919	156.91	O66–H66	O35#6	2.613	3.080	116.35
O12–H12	O24	2.354	2.793	115.32	O72–H72	O33#2	1.945	2.741	164.40
O13–H13	O72	2.055	2.857	170.00	O73–H73	O11#6	2.020	2.830	162.90
O13–H13	O14	2.437	2.845	112.31	O76–H76	O10#7	2.019	2.837	167.41
O16–H16	O06#1	1.982	2.789	175.50	O02–H02	O07	1.634	2.626	176.21
O22–H22	O11	2.079	2.863	165.61	O04–H04	O06	1.658	2.647	177.26
O23–H23	O73#2	2.084	3.005	177.77	O05–H05A	O03	2.152	2.865	140.92
O26–H26	O32#1	1.947	2.791	167.09	O05–H05B	O42#1	1.923	2.799	152.78
O32–H32	O10	1.891	2.672	170.00	O06–H06A	O26#4	1.769	2.648	173.93
O33–H33	O22	2.179	2.934	166.49	O06–H06B	O13#8	1.924	2.774	152.96
O36–H36	O09#3	2.085	2.855	174.11	O07–H07A	O53#1	1.945	2.802	175.12
O42–H42	O53	2.108	2.776	165.80	O07–H07B	O08#9	1.996	2.749	153.09
O42–H42	O54	2.466	2.810	113.44	O07–H07B	O55#9	2.621	3.090	118.04
O43–H43	O32	2.203	2.959	178.34	O08–H08A	O42#9	2.124	2.851	154.17
O46–H46	O05	2.018	2.763	159.97	O08–H08B	O66	1.891	2.778	170.35
O52–H52	O01#4	2.110	2.849	168.87	O09–H09A	O46	2.051	2.838	169.04
O53–H53	O16#4	1.922	2.710	155.12	O09–H09B	O56	2.025	2.827	157.56
O56–H56	O07#5	1.957	2.790	178.43	O10–H10A	O63#10	2.033	2.782	168.83
O62–H62	O73	2.230	2.927	158.74	O10–H10B	O09#3	1.804	2.732	173.50
O62–H62	O74	2.354	2.765	116.85	O11–H11A	O75#8	2.174	2.918	150.81
O63–H63	O52	2.092	2.762	153.41	O11–H11A	O76#8	2.532	3.172	135.71
O66–H66	O36#6	1.960	2.781	165.41	O11–H11B	O62#2	2.005	2.754	172.04

Symmetry transformations used to generate equivalent atoms: #1 x, y + 1, z; #2 –x + 2, y + 1/2, –z + 2; #3 –x + 2, y–1/2, –z + 1; #4 x, y–1, z; #5 –x + 1, y–1/2, –z + 1; #6 x–1, y, z; #7 x–1, y + 1, z; #8 -x + 2, y–1/2, –z + 2; #9 –x + 1, y + 1/2, –z + 1; #10 x + 1, y, z

hydroxyls. This group involves lowest energy structures including the all-trans conformation of succinic acid (Fig. 2), which corresponds to the global minimum on the potential energy surface (PES) of the molecule. Second group is composed from structures with one hydroxyl in trans and the other hydroxyl in cis form. Third group involves high-energy conformers with both hydroxyls in cis position.

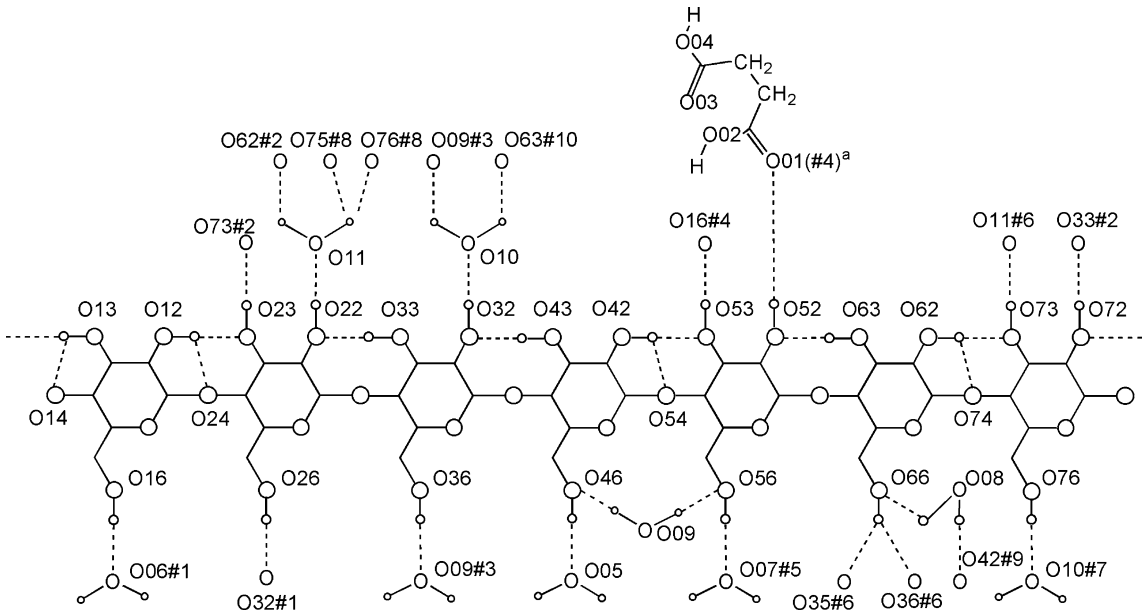

Fig. 6 Schematic representation of the hydrogen-bonding arrangement around the β-CD molecule. [a]Symmetry transformation concerns the whole molecule of succinic acid

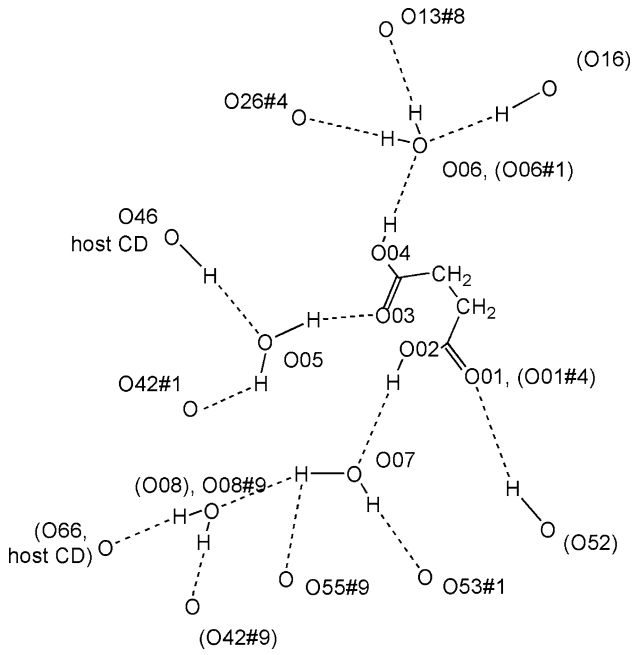

Fig. 7 Schematic representation of the hydrogen-bonding arrangement around the succinic acid molecule

Four structures of succinic acid, namely conformers 8 and 12 (group II) and conformers 15 and 20 (group III), exhibit a presence of an intramolecular hydrogen bond (Fig. 8, Table 4). In the conformer 12, hydroxyl oxygen is an acceptor of H-bond whereas in other conformers carbonyl oxygen becomes an acceptor of H-bond. Comparison of characteristics for intramolecular and intermolecular H-bonding of succinic acid (see Tables 4 and 2) clearly shows that intermolecular hydrogen bonds formed by succinic acid in crystal, especially with the water molecules, are stronger (i.e. shorter and more linear) than intramolecular ones.

The conformation of succinic acid in the crystal inclusion complex with β-CD resembles conformer 14 in Table 3. The superposition of the structure of succinic acid derived from our calculations in vacuo and that, which was extracted from its crystal inclusion complex with β-CD is shown in Fig. 9. It can be clearly seen that the crystal conformation is close to the gas phase conformer and is almost undisturbed by intermolecular interactions in crystal: the RMS difference between coordinates of heavy atoms of the molecules is 0.2 Å and the maximum absolute deviation of atomic positions observed for hydrogen atoms of methylene and hydroxyl groups is 0.5 Å.

According to our calculations, conformer 14 of succinic acid and therefore its crystal conformation has high relative energy (Table 3) and it has rather compact than an extended structure. We speculate that this may be a result of a finite space in the β-CD cavity, which permits only limited conformational transformations of succinic acid formed inside the cavity after opening the ring of succinic anhydride. The tight fit between succinic acid and the β-CD cavity can be seen in Fig. 10, where the solvent accessible surfaces for the β-CD and succinic acid molecules involved in and extracted from their inclusion complex as well as for a

Table 3 The set of unique conformers of succinic acid

Group	Number of confor-mation	Type of conformation	Torsion angles, deg					ΔE, kcal/mol
			φ_1	φ_2	φ_3	φ_4	φ_5	
I	1[a]	ttTtt	180.0	180.0	180.0	180.0	180.0	0.00
	2	ttTgt	178.6	178.6	179.2	67.1	180.0	0.83
	3	ttGtt	178.8	–161.4	68.5	–161.4	178.8	1.54
	4	tgTgt	178.3	59.9	177.2	59.8	178.3	1.62
	5	ttGgt	–179.8	–165.7	63.6	29.2	179.8	2.27
	6	tgGgt	179.9	57.6	59.2	57.7	179.9	2.32
	7	tgGg′t	179.5	60.3	65.0	–92.7	178.4	2.41
II	8[b]	ttGg′c	179.6	–168.5	74.1	–77.4	5.8	7.06
	9	ttTtc	–179.9	179.6	179.9	–179.9	–3.3	7.64
	10	ttTgc	–179.7	–174.1	179.4	76.8	0.4	8.51
	11	tgTtc	178.2	70.3	179.5	–179.1	0.3	8.78
	12[b]	tgGg′c	176.2	35.3	68.0	–77.2	4.5	9.01
	13	tgTgc	178.5	63.0	179.9	72.8	–0.1	9.35
	14[c]	tgGtc	–179.3	23.4	65.2	–164.9	1.8	10.56
III	15[b]	ctGg′c	1.3	–168.1	75.0	–78.5	6.1	14.97
	16	ctTtc	0.0	179.9	180.0	179.8	0.1	15.10
	17	cg′Gg′c	5.6	–87.0	66.2	–87.2	5.6	15.81
	18	ctTg′c	–1.2	173.0	178.4	–87.8	–1.5	16.51
	19	cgTg′c	0.0	77.5	179.9	-77.9	0.2	16.76
	20[b]	cgGg′c	0.1	83.3	82.3	-51.3	6.7	17.17
	21	cgTgc	0.1	72.6	175.6	72.6	0.1	18.26

[a] Global minimum
[b] conformation with intramolecular H-bond
[c] analogue of crystal conformation

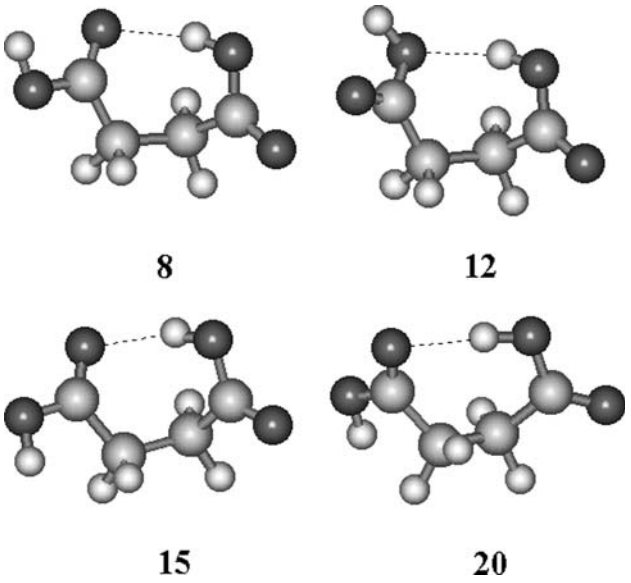

Fig. 8 Four structures of succinic acid with intramolecular H-bonds

Table 4 Intramolecular hydrogen bonding in succinic acid (D—donor atom, A—acceptor atom, H—hydrogen atom)

Conformer	D–H	A	H···A distance (Å)	D···A distance (Å)	DHA angle (°)
8	O04–H04	O01	1.990	2.891	153.4
12	O04–H04	O02	2.072	2.985	156.4
15	O02–H02	O03	1.986	2.888	153.5
20	O02–H02	O03	2.084	3.010	159.3

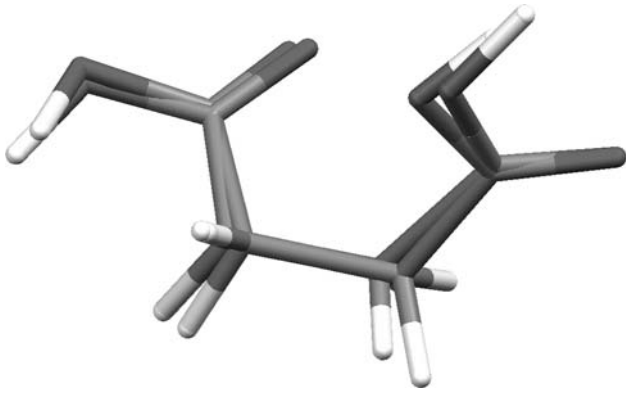

Fig. 9 The superposition of calculated in vacuo (front view) and experimental crystal (rear view) structure of succinic acid

water molecule are shown. The consequence is that the more significant relaxation of the structure to a lower energy minimum on its PES is not allowed and a conformational change occurs only in the vicinity of the nearest local minimum with the relatively high potential energy. Predominance of this conformation of succinic acid in the crystal complex is apparently determined by intermolecular interactions, mainly by hydrogen bond formation (including strong H-bonds with water molecules).

We recall that the center of mass of succinic acid in the crystal complex is shifted to the narrow rim of the β-CD cavity by about 1 Å from the plane of glycosidic oxygens. This position corresponds to the location of the center of mass of the cyclopentadiene molecule (which is very similar in its shape and size to succinic anhydride) in the inclusion complex with β-CD [31]. Unlike the molecules of cyclopentadiene and succinic

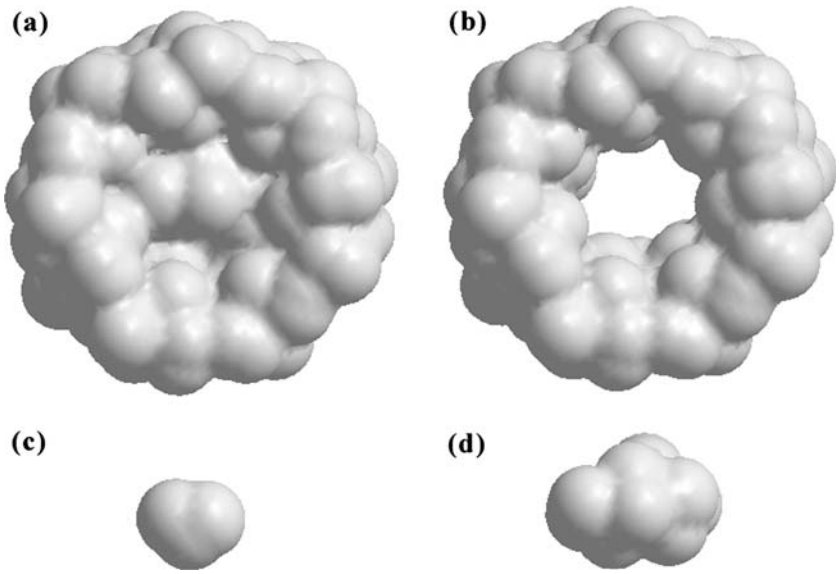

Fig. 10 The solvent accessible surfaces for β-CD and succinic acid molecules: (**a**) involved in and (**b**, **d**) extracted from their inclusion complex. Analogous representation for a water molecule (**c**) is shown for comparison

anhydride, translations and rotations of the larger molecule of succinic acid inside the cavity are essentially restricted (Fig. 10). Three oxygen atoms of succinic acid are located in the region of primarily hydroxyls of β-CD (atoms O1 and O2 of first carboxyl) or in the close proximity to this region (atom O3 of second carboxyl).

Thus, the revealed structural features of the crystal conformation of succinic acid together with its position in the β-CD cavity allow us to conclude that cyclodextrin mediated hydrolysis of succinic anhydride likely occurs near the narrow rim of the macrocycle where the spatial contiguity of an anhydride bond of a guest molecule to highly reactive primarily hydroxyls of a host β-cyclodextrin is provided. Further insights into structural details of hydrolytic cleavage of succinic anhydride in the presence of β-CD can be gained from molecular dynamics simulations of this supramolecular host-guest system in water solution. These computational efforts are currently underway.

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