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The role of intra- and intermolecular hydrogen bonds in the formation of β-cyclodextrin head-to-head and head-to-tail dimers. The results of *ab initio* and semiempirical quantum-chemical calculations

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The conformation of a free β-cyclodextrin molecule optimized by the MNDO/PM3 quantum-chemical calculations has C_7 symmetry. The "right" orientation of the interglucose hydrogen bonds in β-cyclodextrin, in which the 2-OH groups act as the proton donors and the O atoms of the nearby 3′-OH groups function as the proton acceptors, is advantageous for thermodynamic reasons. The ring of seven H bonds thus formed stabilizes the symmetrical form of β-cyclodextrin. The β-cyclodextrin head-to-head dimer has D_7 symmetry and consists of molecules whose 2-OH groups partcipate as proton donors in the formation of fourteen complementary intermolecular hydrogen bonds. The energy of H bonds in the β-cyclodextrin monomer and dimer was estimated to be 1.0—1.4 kcal mol^{-1}. Of the two possible β-cyclodextrin dimers, the "head-to-tail" dimer is more thermodynamically stable. The thermodynamic preference of the right orientation of the inter-glucose H bonds in β-cyclodextrin was confirmed by the MP2/6-31G(d,p)//6-31G(d,p) *ab initio* calculations for maltose (α-glucodioside). The maltose molecule with inter-glucose H bonds of the type 2-OH→O(3′)-H is more stable than the structure with the H-(2)O←H-O(3′) orientation of H bonds with a difference of ~2.7 kcal mol^{-1}. According to the MNDO/PM3 method, the maltose structure with the right H bond orientation is more stable by ~3.1 kcal mol^{-1}.

Key words: β-cyclodextrin, maltose, quantum-chemical calculations, hydrogen bonds.

The β-cyclodextrin (β-CD) molecule, which resembles in shape a basket, consists of seven α-D-glucopyranose units linked by (1-4) glucoside bonds.[1] The rigidity of the β-CD structure is due to seven interglucose H bonds connecting the secondary (2)OH and (3′)OH groups of adjacent glucose residues, which occupy close positions in space.[2] In ordered β-CD structures, the system of seven intramolecular interglucose H bonds can be oriented in two fashions. In one case, the ring of H bonds is formed by the H atoms of the (2)OH groups and the O atoms of the (3′)O—H groups ((2)OH→O(3′)H), while in the second case, it is formed by the H atoms of the (3′)O—H groups and the O atoms of the (2)O—H groups (H(2)O←H—O(3′)). Examination of the wider part of the β-CD basket shows that in the former case, the system of ring H bonds is arranged clockwise. This orientation will be conventionally called right orientation and designated by a "plus" sign, while the counterclockwise arrangement will be called left and designated by a "minus" sign. These two structures are shown in Scheme 1; they are assumed to have different energies because glucose is an asymmetric molecule.

The structural data on CD available from the Cambridge Structural Data Bank[3] (CSD) do not allow one to decide unambiguously which orientation is energetically preferred because most structures have been solved by X-ray diffraction analysis, which normally does not locate the H atoms. Only two structures of deuterated β-CD were studied by neutron diffraction. In the crystal of natural β-CD dodecahydrate, five left and two right H bonds were detected,[4,5] whereas the octahydrate of the β-CD · deuterioethanol inclusion complex was found to contain three left and four right H bonds.[6] The structure of γ-CD consisting of eight glucose units has four left and four right H bonds.[7]

The β-CD containing a "guest" molecule often crystallize as head-to-head dimers, which resemble a barrel in shape and in which the dimers are connected to each other by the wider rims of the cavity; as a consequence, the free volume of the cavity doubles.[2] In such a dimer, both CD are fixed by complementary intermolecular H bonds whose maximum number in regular structures is 14. In the case of right orientation of the H bonds (**A**) in the monomeric β-CD, the partners in the dimer are

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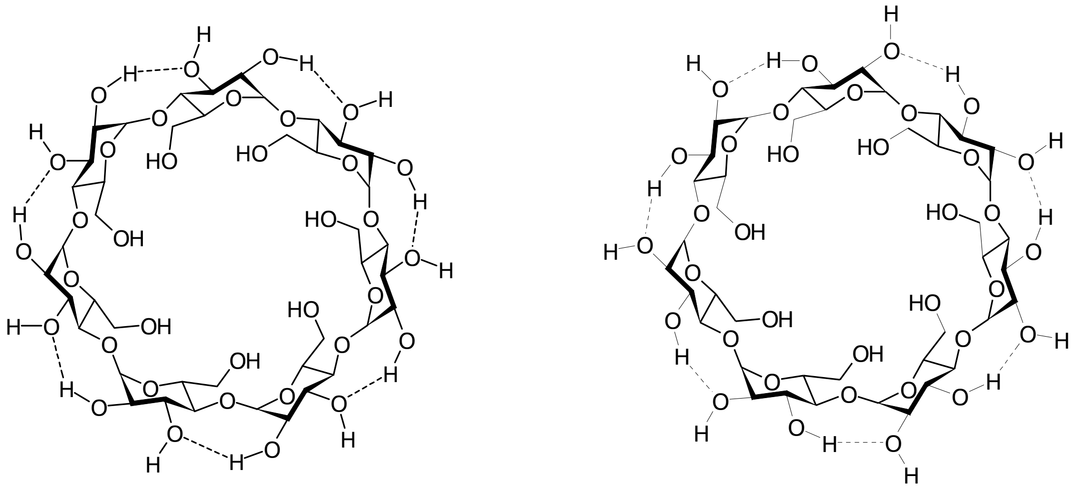
Scheme 1



(+) (−)

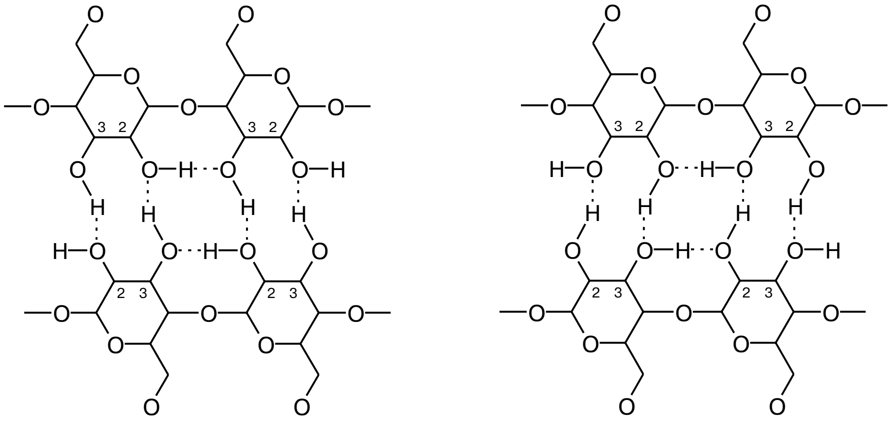
linked through the secondary (3)OH groups; in the case of left orientation (**B**), they are linked by the (2)OH groups (this is represented in Scheme 2); the energies of these H bonds appear to be different.

Yet another type of association of β-CD molecules arises during the self-assembly of nanotubes, for example, in the case where the solution contains hydrophobic polymers.[8] The cyclodextrin rings are stacked along a polymer chains to give so-called molecular necklaces. In this cases, the CD molecules are arranged according to the head-to-tail pattern; thus the wider part of the cavity of one molecule is connected to the narrower part in the other molecule. Scheme 3 shows the formation of this dimer from β-CD molecules with right- (**C**) and left-oriented (**D**) H bonds. In both cases, the secondary OH groups are proton donors and the O atoms of the primary OH groups at the narrower edge of the cavity act as proton acceptors.

Despite the fact that structural data for twenty two natural head-to-head dimers of β-CD have been obtained to date, none of the dimeric structures have been studied by neutron diffraction; therefore, positions of the H atoms in them were not established. The orientation of the H bonds in monomeric β-CD and the probable type of H bonding in β-CD dimers can, in principle, be found by calculations.

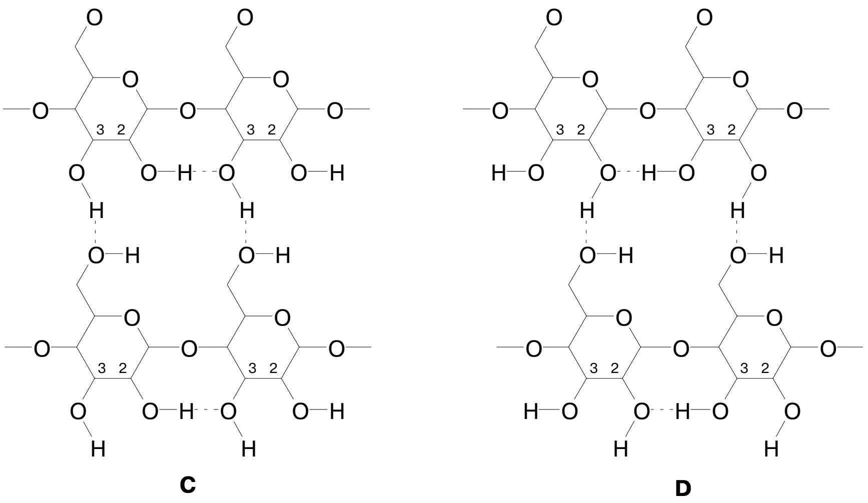
In calculating the conformations of β-CD and inclusion compounds, molecular mechanics (MM) techniques are used most often.[9] Since the β-CD molecule consists of seven equivalent glucose residues, a symmetrical structure with a C_7 axis is expected to be thermodynamically the most stable. However, MM calculations showed that free β-CD molecules have flexible structures; the symmetric form of β-CD proved to be 5.5 kcal mol^{-1} less stable than the asymmetric one, in which the bending angles of three glucose rings are greater than those of the

Scheme 2



A **B**

Scheme 3



C **D**

other four rings.[10] Apparently, in the MM2 parametrization,[10] the possibility of the formation of H bonds is underestimated, although these bonds could make the structure more rigid and contribute to stabilization of the symmetric form of β-CD.

Semiempirical quantum chemical methods such as MNDO/AM1 and MNDO/PM3 (below referred to as AM1 and PM3) have been used much more rarely, in particular, to estimate the energy of hydration of the internal cavity of β-CD [11] whose H bonds has the left orientation. In the β-CD structure thus determined, the ϕ(O—O—O) angle in the O_7 heptagon formed by the seven bridging O atoms of β-CD is equal to 128.3±2.4°, while the τ(O—O—O—O) dihedral angle is 0.2±7.9°. Although these values are close to those expected for a completely symmetric structure ($\phi = 128.57°$ and $\tau = 0°$), the relatively large standard deviations of the ϕ and τ angles implies an irregular shape of the O_7 heptagon and a nonplanar configuration of bonds in it. Thus the conformation found for β-CD cannot be regarded strictly symmetrical.

The energies of formation of the inclusion compounds between β-CD and benzoic acid derivatives were estimated by AM1 calculations[12,13]; however, the structure of β-CD taken from the CSDB had not been optimized. The same approach was used to perform calculations for the hydrolysis of phenyl acetate catalyzed by β-CD with the left orientation of H bonds.[14] Recently, the energy of formation of the α-CD inclusion compound with acetophenone was found by PM3 calculations.[15]

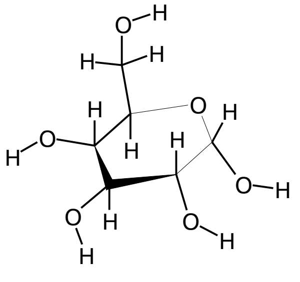
Previously, we carried out PM3 calculations for β-CD,[16] which demonstrated that a much more symmetric form of β-CD can be attained if the optimization has started from a structure having equal bending angles for all seven glucose residues. The heat of formation of the form thus obtained is 8.7 kcal mol^{-1} lower than that determined previously,[11] while the angles $\phi = 128.5\pm0.6°$ and $\tau = 0.0\pm4.9°$ are closer to the values expected for a fully symmetric conformation. The fact that the energy of the molecule decreases as ϕ approaches 128.57° and τ approaches 0° suggests that, within the framework of the PM3 method, the global minimum exactly corresponds to the β-CD molecule with C_7 symmetry.

In this work, we carried out a PM3 quantum chemical calculation aimed at elucidating whether the symmetric structure of free β-CD is energetically the most favorable. We tried to establish the optimum orientation of the interglucose H bonds in the wider part of the β-CD cavity and to determine the thermodynamically most stable type of β-CD dimers. To evaluate the reliability of the results, we also performed *ab initio* and PM3 calculations for maltose disaccharide in which two glucose units are linked by the same bond as in CD.

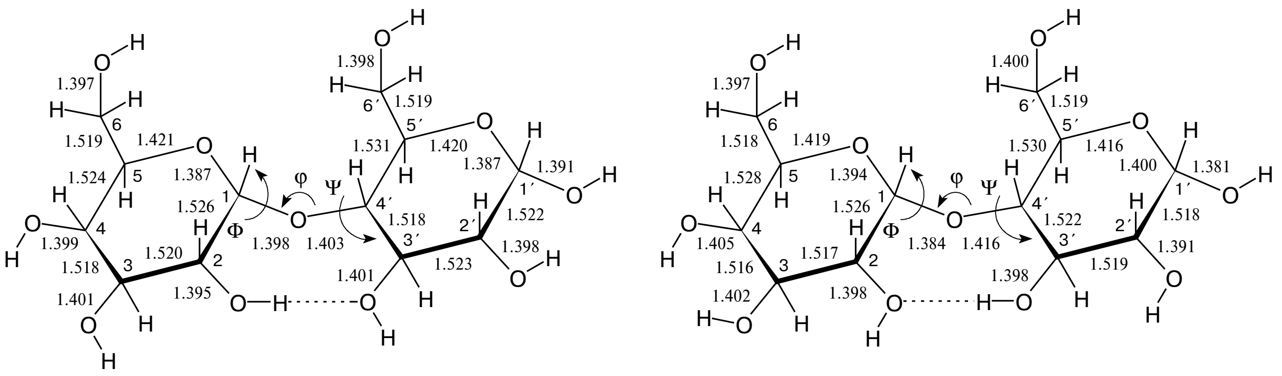
Calculation Procedure

The quantum chemical calculations for β-CD monomers and dimers were performed with full optimization of all geometric parameters. After the minimum had been attained, the vibration frequencies for each of the three monomeric structures were calculated in the harmonic approximation. The absence of imaginary frequencies indicated that the local energy minima were attained for all the structures. The semiempirical PM3 method with a standard set of parameters was used.[17] The calculations were performed using the GAMESS program package[18] (version 1999). The graphical interface of the HyperChem program was employed to prepare the input files and to visualize the results of calculations.

Model calculations. The maltose ((1-4)α-glucobiose) molecule consists of two α-D-glucopyranose units linked by a (1-4)-glycoside bond.



Scheme 4



Maltose(+) Maltose(−)

Since the hydroxy groups at C(1)—C(4) in the most stable *GG* conformer of glucose are oriented counter-clockwise,[19] the maltose molecule formed by these conformers has the right orientation of the interglucose H bonds (maltose(+), see Scheme 4). The left orientation (maltose (−)) can be attained by the appropriate rotation of the secondary hydroxy groups (Scheme 4).

The maltose molecules with the right and left orientations of the interglucose H bonds were calculated by the *ab initio* method with the MP2/6-31G(d,p)//6-31G(d,p) basis sets. Comparison of the results obtained with the results of calculations[19] of the α-D-glucose molecule using the MP2/6-31G(d) and 6-31G(d) basis sets demonstrated that the geometric parameters of the glucose components obtained in the two calculations are close (see Scheme 4), whereas the parameters of the interglucose bonds in the maltose forms with right- and left-oriented bonds are different

Maltose molecule	E^a /a.u.	ΔE^a	ΔH_f^b	ΔE^b
		kcal mol^{-1}		
(+)	−1294.363764	0	−479.3	0
(−)	−1294.359537	2.7	−476.3	3.1

[a] MP2/6-31G(d, p)//6-31G(d,p). [b] PM3.

The calculations showed that the maltose with the right orientation of H bonds is thermodynamically more stable than the structure with the left orientation. The PM3 method also confirmed that the right orientation is preferred. This confirms the applicability of the PM3 method for determination of the structure and orientation of hydrogen bonds in molecules formed by glucose units.

Results and Discussion

Characteristic features of the interglucose binding in maltose molecules with right and left orientations of H bonds. Maltose molecules with the right and left orientations of H bonds are known. In the crystal of β-maltose, 4-O-(α-D-glucopyranosyl)-β-D-glucopuranose, an intramolecular H bond of the (2)OH→O(3′)H type is formed,[20] while in the crystal of α-maltose, 4-O-(α-D-glucopyranosyl)-α-D-glucopyranose, the glucose units are linked by the H(2)O←H—O(3′) H bonds.[21] The parameters of H bonds and the interglucose angles Φ, Ψ, and φ for the two maltose anomers are compared in Tables 1 and 2. In both crystal structures, maltose molecules are incorporated in networks of intermolecular hydrogen bonds. These bonds extends through the whole structure and influence the geometry of separate glucose units; therefore, the native structural parameters differ markedly from the values calculated for free molecules.

Subsequently we will compare only the calculated structural characteristics of maltose assuming that the *ab initio* calculation most adequately reproduces the structures of both forms of free molecule. Comparison of these structures (see Tables 1 and 2) shows that both angles (Φ and Ψ) in the (+) form are greater than in the

Table 1. Structural parameters characterizing the mutual orientation of the two glucose residues in maltose and β-CD with the right orientation of H bonds

Parameter	Neutron diffraction	*Ab initio*	PM3	PM3 (β-CD(+))
Φ/deg	121.7	116.5	136.7	117.6
Ψ/deg	132.7	137.7	131.9	119.3
φ/deg	117.9	120.5	116.6	115.9
ω(O—H...O)/deg	165.5	163.3	169.0	156.1
R(OH...O)/Å	1.836	2.053	1.814	1.812
D(O...O)/Å	2.789	2.975	2.761	2.718

Table 2. Structural parameters characterizing the mutual orientation of the two glucose residues in maltose and β-CD with the left orientation of H bonds

Parameter	X-Ray diffraction analysis	*Ab initio*	PM3	PM3 (β-CD(−))
Φ/deg	116.1	108.4	112.6	115.7
Ψ/deg	122.2	114.4	116.3	119.0
φ/deg	120.1	120.5	115.3	115.7
ω(O—H...O)/deg	169.4	164.0	167.8	166.7
R(OH...O)/Å	2.058	1.988	1.815	1.810
D(O...O)/Å	2.770	2.912	2.758	2.752

(−) form. The H bond is somewhat longer in the former structure than in the latter. The calculation of the maltose(−) model with the Φ and Ψ angles taken from maltose(+) showed that an increase in Φ and Ψ results in a noticeable elongation of the H bond and in a greater deviation of the ω(O—H...O) angle from 180°.

It is evident that these changes can induce weakening of the H bond. Since the parameters of the H bonds in the maltose(−) and maltose(+) equilibrium structures are similar, the bond energies are expected to be close. Hence, the fact that maltose(−) is energetically less favorable is due to the greater torsion strain caused by smaller Φ and Ψ angles. To verify the assumption of the higher strain in the maltose(−) molecule, calculations with the MMX, MM3, and MMFF94 force fields were carried out using the PCMODEL V.7 program package.[22] All three sets of force field predict that maltose(+) should be energetically more favorable; this actually means that the maltose(−) molecule is more strained.

It follows from comparison of the results of *ab initio* and PM3 calculations that the latter always give shorter H bonds. Thus, it can be expected that the β-CD structure predicted by PM3 optimization would be somewhat more compressed than the native forms due to shorter H bonds in the wider rim of the cavity.

Obtaining a symmetrical structure of β-*CD.* In all the calculations for β-CD, a conformation of the *GG* type was chosen for the primary OH groups because, according to neutron diffraction data,[4,5] in this conformation, the primary OH groups are linked by H bonds to the ring O atom. A symmetric structure of β-CD was obtained in two ways. The initial β-CD parameters used in one method[16] were the interglucose angles Φ, Ψ, and φ found by the PM3 optimization of a highly symmetric structure of cyclo-α(1-4)-glucopentaoside (cyclodextrin, 5-CD), consisting of five glucose units and having a rigid structure. Previously,[23] MM calculations for 5-CD have resulted in a symmetric structure with a C_5 axis. Preliminary optimization of the β-CD geometry by the PM3 procedure results in a conformation in which the bending angles of two glucose units differ from those of the five other units. After correction, a symmetric structure of β-CD(+) was obtained. The heat of formation and the average values of parameters are listed in Tables 3—5.

The second procedure giving rise to symmetrical β-CD is based on the use of the geometry of the natural molecule. The bis(β-cyclodextrin)ethylcinnamate hydrate structure (its CSD Refcode is BIDMOQ) was extracted from the CSD[7] as a graphical file. In this structure, β-CD exists as a head-to-head dimer. The hydration water and substrate molecules were removed, and the H atoms absent from the hydroxy groups were added in the required orientation. Two β-CD dimers were prepared in this way for the subsequent optimization. In one dimer (see Scheme 2, **A**), the (3)OH groups of one partner are involved in the formation of fourteen H bonds as proton donors, the O(2) atoms of the other partner being proton acceptors. In the second dimer (see Scheme 2, **B**), the (2)OH groups are the proton donors and the O(3) atoms are the proton acceptors. The type of bonding in the dimer depends entirely on the H bond orientation in the monomeric β-CD, namely, dimer **A** is formed by β-CD(+) and dimer **B** consists of β-CD(−).

Table 3. Heats of formation (ΔH_f) and differences between the energy of formation and the energy of dimerization of β-CD (ΔE)

Molecule, symmetry	ΔH_f	ΔE	ΔI^a
	kcal mol^{-1}		
		MNDO/PM3	
β-CD(+), C_7	−1468.4	0	$8.7 \cdot 10^{-4}$
β-CD(−), C_7	−1462.6	5.8	$1 \cdot 10^{-3}$
β-CD−hb[b]	−1460.4	8.0	$3.8 \cdot 10^{-4}$
β-CD(+), C_7[c]	−1467.9	0.5	$1.1 \cdot 10^{-2}$
β-CD(−), C_7[c]	−1462.5	5.9	—
β-CD[d]	−1459.6	8.7	—
(β-CD(+)*hh*)$_2$, D_7	−2945.4	0 (8.7)[f]	$4.7 \cdot 10^{-4}$
(β-CD(−)*hh*)$_2$, D_7	−2936.7	8.7 (11.5)	$3.5 \cdot 10^{-4}$
(β-CD(+)*hh*)$_2$, D_7[e]	−2950.3	0 (13.6)	
(β-CD(−)*hh*)$_2$, D_7[e]	−2944.7	5.6 (19.5)	
(β-CD(+)*ht*)$_2$, C_7	−2959.2	0 (22.4)	$5.8 \cdot 10^{-5}$
(β-CD(−)*ht*)$_2$, C_7	−2938.4	20.8 (13.2)	
		MNDO/AM1	
β-CD(+), C_7[c]	−1670.7	0	
β-CD(−), C_7[c]	−1665.3	5.4	
β-CD[d]	−1656.4	13.3	

Note. (β-CD(±)*hh*)$_2$, two dimers of the head-to-head type, (β-CD(±)*ht*)$_2$, head-to-tail.

[a] $\Delta I = |I_{xx} - I_{yy}|/I_{xx}$, where I_{xx}, I_{yy} are the principal moments of inertia of the molecule relative to the x and y axes, respectively.

[b] The structure of β-CD "without H bonds".

[c] Literature data.[16]

[d] Literature data.[11]

[e] Dimers with a short H bonds.

[f] The value in parentheses is the dimerization energy.

Full PM3 optimization of the geometry without any symmetry limitations gave two highly symmetric head-to-head dimers corresponding to the D_7 group of symmetry. Then one component in each dimer was removed and the geometry of monomeric β-CD with right and left orientations of H bonds was fully optimized. The heat of formation was found to be 5.8 kcal mol^{-1} lower for β-CD(+) than for β-CD(−); both structures corresponded to C_7 symmetry (Fig. 1). The difference in energies points to a greater thermodynamic stability of the isomer with the right orientation of H bonds.

The heats of formation of β-CD(+) and β-CD(−) are lower than the ΔH_f value found previously for β-CD with the left orientation of H bonds[11] by 8.7 and 2.9 kcal mol^{-1}, respectively. The heats of formation of β-CD(+) and β-CD(−) determined in this study are 0.5 and 0.1 kcal mol^{-1} lower than the values we found previously.[16] This indicates that the structures obtained here are closer to the sought-for global minimum of the potential energy.

Table 4. Average values of the parameters (and standard deviations) of the O_7 heptagons constructed on the bridging oxygen atoms in calculated and natural β-CD

Molecule, symmetry	ω(O—O—O)	τ(O—O—O—O)	$R(O_n—O_{n+1})$	$D(O_n...O_{n+3})$	ε
	deg		Å		
β-CD(+), C_7	128.57(3)	0.00(4)	4.372(1)^h	9.825(3)	1.0007
β-CD(+), $C_7{}^a$	128.5(6)	0.0(49)^h	4.42(14)	9.812(30)	1.009
β-CD(−), C_7	128.57(5)	0.004(39)	4.374(1)	9.829(4)	1.001
β-CD−hb^b	128.5(7)	0.0	4.412(1)	9.914(1)	1.002
β-CD^c	128.3(24)	0.2(79)	—	—	1.085
β-CD^d	128.2(41)	0.3(92)	—	—	—
(β-CD(+))$_2$, D_7	128.57(12)	0.01(13)	4.372(4)	9.824(8)	1.002
(β-CD(−))$_2$, D_7	128.57(6)	0.00(7)	4.374(2)	9.829(4)	1.001
(β-CD)$_2{}^e$	128(4)	0.54(38)	4.437(13)	9.84(19)	1.043^f 1.059
(β-CD)$_2{}^g$ BIDMOQ	128.6(22)	0.0(10)	4.372(69)	9.82(18)	1.043^f 1.059
(β-CD)$_2{}^g$ YOVVIO	128.6(14)	0.0(17)	4.392(79)	9.88(12)	1.032^f 1.029
(β-CD)$_2{}^g$ DIFHOP	128.6(24)	0.0(15)	4.355(68)	9.78(20)	1.060^f 1.054
(β-CD)$_2{}^g$ KUTJUE	128.56(71)	0.0(16)	4.391(65)	9.86(48)	1.016^f 1.011
(β-CD)$_2{}^g$ Tejhar	128.6(18)	0.2(14)	4.370(62)	9.82(15)	1.032^f 1.049
(β-CD)$_2{}^g$ GETPEA	128.6(44)	0.0(30)	4.372(107)	9.17(23)	1.008^f 1.120

[a] Literature data.[16]

[b] The structure of β-CD "without H bonds".

[c] Literature data.[11]

[d] Literature data.[4,5]

[e] Literature data.[7]

[f] For cyclodextrin molecules in the natural dimer, the ellipticities are different.

[g] The CSD Refcodes.[3]

[h] The average values of parameters are followed by their standard deviations given in parentheses, *e.g.*,: $R(O_n—O_{n+1})$ 4.372(1) Å implies 4.372±0.001 Å, and τ 0.0(49)° means 0.0±4.9°.

Estimation of the symmetry of the calculated structures. Structures having a threefold or higher rotation axis are symmetric tops; the β-CD molecule is an oblate symmetric top. For the exact C_7 symmetry, the relation $I_C > I_A = I_B$ should hold for the principal moments of inertia. The β-CD dimers are prolate symmetrical tops. For the exact D_7 symmetry, the relation $I_A < I_B = I_C$ should hold for the principal moments of inertia. The degree of proximity of the calculated structure to a strictly symmetric one can be estimated from the deviation from zero of the $\Delta I = |I_A - I_B|/I_{av}$ value (for the monomer) and $\Delta I = |I_C - I_B|/I_{av}$ value (for the dimer). The ΔI values that we calculated are presented in Table 3.

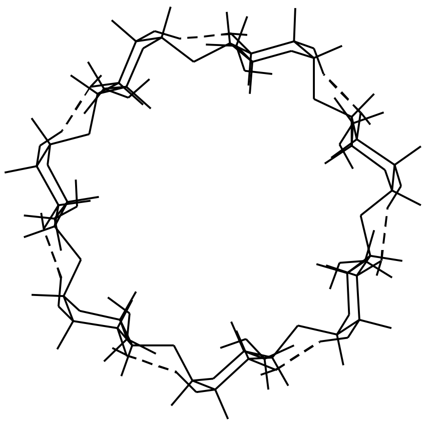


Fig. 1. Structure of the symmetric (C_7) β-CD(+). The interglucose right-oriented H bonds ((2)OH→O(3′)—H) are shown by the dashed line.

The monomeric and dimeric β-CD molecules have a C_7 symmetry axis. The symmetric β-CD structure contains groups of seven equivalent bond lengths and angles. In addition, in the regular heptagon, corresponding to the symmetric molecule and formed by the bridging O atoms linking the neighboring glucose units, all the ϕ angles should equal 128.57°; the figure should be strictly planar, *i.e.*, all seven τ(O—O—O—O) dihedral angles should be equal to zero and the closed curve circumscribed around the heptagon should be a circle.

Then the calculated structure can be characterized by average values of equivalent bond lengths and angles and by the ellipticity ε of the circle circumscribed around the O_7 pseudo-ring ($\varepsilon = R_{max}/R_{min}$, where R is the circum-

Table 5. Average values (and standard deviations) of the interglucose parameters in the calculated and natural β-CD

Compound, symmetry	Φ	Ψ	φ	ω(O—H...O)	*R*(OH...O)	*D*(O...O)
		deg			Å	
β-CD(+), C_7	117.61(5)	119.32(6)	115.92(1)	156.14(2)	1.812(0)	2.718(0)
β-CD(+), C_7[a]	116.9(34)	119.2(34)	116.1(4)	157.2(12)	1.817(10)	2.727(10)
β-CD(−), C_7	115.65(7)	119.0(1)	115.7(0)	166.7(1)	1.810(0)	2.752(0)
β-CD−hb[b]	109.2(1)	126.2(1)	115.8(1)	124.9	2.429	3.074
β-CD* (290 K)[c]	109.8(59)	126.3(118)	118.7(8)	164.0(61)	1.974(77)	2.885(64)
β-CD* (120 K)[c]	108.5(67)	128.2(92)	118.3(5)	163.5(78)	1.953 (90)	2.898 (96)
β-CD · C_2D_5OD*[d]	110.5(66)	126.9(123)	118.2(12)	164.8(72)	1.896(102)	2.812(32)
β-CD*[e]	111.9(68)	127.6(80)	117.7(26)	—	—	—
(β-CD(+)*hh*)$_2$, D_7[f]	117.10(14)	119.20(22)	115.82(4)	157.34(24)	1.807(0)	2.718(1)
				140.14(21)	2.512(5)	3.298(7)
(β-CD(−)*hh*)$_2$, D_7	115.61(4)	118.96(8)	115.72(3)	167.37(16)	1.804(0)	2.748(1)
				140.78(33)	2.534(4)	3.326(6)
(β-CD(+)*hh*)$_2$, D_7[g]				141.90(3)	1.8300(1)	2.6520(2)
(β-CD(−)*hh*)$_2$, D_7[g]				140.30(2)	1.827(1)	2.6390(2)
(β-CD(+)*ht*)$_2$, C_7				170.2(2)	1.813(1)	2.764(2)
(β-CD(−)*ht*)$_2$, C_7				166.9(16); 174.0(5)	1.812(7); 1.800(3)	2.754(2)
				151.1(40)	1.828(1)	
(β-CD)$_2$*[d]	112.85(97)	126.11(84)	117.76(77)	—	—	2.802(7)
						3.115(80)
(β-CD)$_2$*[h]	114.6(23)	128.4(31)	117.0(14)	—	—	2.802(44)
BIDMOQ						3.091(69)
(β-CD)$_2$*[h]	109.1(41)	128.7(42)	117.88(89)	—	—	2.857(38)
YOVVIO						3.186(76)
(β-CD)$_2$*[h]	117.7(49)	126.8(31)	116.5(15)	—	—	2.767(32)
DIFHOP						3.095(75)
(β-CD)$_2$*[h]	113.1(27)	126.1(27)	119.0(16)	—	—	2.804(27)
KUTJUE						3.098(72)
(β-CD)$_2$*[h]	113.1(29)	127.6(26)	117.98(81)	—	—	2.788(34)
TEJHAR						3.124(80)
(β-CD)$_2$*[h]	113.9(54)	126.2(49)	118.5(26)	—	—	2.781(68)
GETPEA						3.081(79)

Note. Natural β-CD are marked by asterisk; (β-CD(±)*hh*)$_2$, two dimers of the head-to-head type, (β-CD(±)*ht*)$_2$, head-to-tail.

[a] Literature data.[19]

[b] The structure of β-CD "without H bonds"; the second line is the averaging over five long and two short bonds.

[c] Literature data.[7]

[d] Literature data.[4—6]

[e] Averaging over the structures of all the β-CD contained in the CSD.[24]

[f] The second lines gives the parameters of the intermolecular H bonds.

[g] Dimers with a short distance between the partners (the global minimum in the PM3 approximation).

[h] The CSD Refcodes.[3]

scribed circle radius). The accuracy of fulfillment of the C_7 symmetry operation and, hence, the optimization quality would be determined by the standard deviations σ from the average bond lengths and angles (the more precise the symmetry of the molecule, the smaller σ) and by the closeness of ε to 1.

The average values of geometric parameters for the structures we calculated are listed in Tables 4 and 5. These values are compared with the structural parameters of the β-CD dimers taken from the CSDB. The abbreviations of names used in the Tables were also taken from the CSDB.

The structures thus obtained are characterized by small ΔI and σ values and by an ellipticity close to 1. The O_7 heptagon formed by bridging O atoms is regular, as indicated by the ϕ and τ angles (see Table 4). These data show that the β-CD structures we obtained are fully symmetric. By comparing the standard deviations of the structural parameters calculated in this study with published data[11,16] (see Table 4), we found that the decrease in σ is parallel to the decrease in the heat of formation. In addition, the fact that the geometric parameters of the β-CD structure we obtained are close to those reported previously[16] means that optimization of structures with different initial parameter results actually in the same final conformation of β-CD(+). Thus, in terms of the PM3 semi-empirical quantum chemical approximation, the structure of free β-CD, having exact C_7 symmetry, corresponds to the global minimum of the potential energy. A similar conclusion can be drawn from consideration of the results of geometry optimization by the AM1 technique.[16]

The native structures of β-CD are irregular[4—6] (see Table 5). They have much higher ΔH_f values than the perfect symmetric conformations. Thus ΔH_f of natural β-CD is equal to −1360.1 kcal mol^{-1}.[11]

By comparing the parameters of interglucose angles, we found that the PM3 method gives Φ angles somewhat higher and Ψ angles somewhat lower than the mean values found in natural structures. In general, the calculated H bond lengths, *R*(OH...O), are shorter than experimental ones, although in the inclusion compound of β-CD with deuteioethanol,[6] whose structure was determined at 120 K, six H bonds have an average length of 1.855(22) Å, which is rather close to the calculated mean *R*(OH...O) values, *viz.*, 1.812(0) Å for β-CD(+) and 1.810(0) Å for β-CD(−).

Parameters of the interglucose binding in the maltose and β-CD molecules with right- and left-oriented H bonds. Comparison of interglucose structural parameters shows that in β-CD(+), the Φ, Ψ, and ω(O—H...O) angles in the H bond are smaller and the *D*(O...O) distances are shorter than those in maltose(+). Hence, the β-CD(+) structure can be considered more strained and the interglucose H bond can be considered more bent than those in maltose(+). This change in the structural parameters upon ring closure accounts for the marked "nonadditivity" of the energy characteristics of β-CD(+) molecule. If the inter-unit geometric parameters of β-CD(+) were identical to those of maltose(+), whose thermodynamic stability is 3.1 kcal mol^{-1} higher than that of maltose(−), the difference between the energies of β-CD(+) and β-CD(−) would reach 21.4 kcal mol^{-1}. In reality, this difference is only 5.8 kcal mol^{-1}. This small difference is due to the greater torsion strain and noticeable deviation of the O—H...O angles from 180° in β-CD.*

Let us compare the interglucose parameters of maltose(−) and β-CD(−). The differences between the Φ and Ψ angles and H-binding parameters of maltose(−) and β-CD(−) are small (see Table 2). Thus, β-CD(−) is less strained than β-CD(+), although the latter is energetically more favorable. Apparently, this implies that the system of (2)OH→O(3′) type H bonds is stronger than the O(2)←H—O(3′) system of bonds, and the seven H bonds of the right orientation make up for the loss of energy due to the torsional strain in β-CD(+). Evidently, due to the higher acidity, the secondary (2)OH groups are better proton donors than the (3)OH groups.

Indeed, the energy of formation of (β-CD(−))$_2$ with participation of the (2)OH groups as proton donors (19.5 kcal mol^{-1}) is greater than the energy of formation of (β-CD(+))$_2$ (13.6 kcal mol^{-1}), in which the secondary (3)OH groups act as proton donors. The conclusion concerning the higher acidity of the (2)OH groups is in line with the results of AM1 quantum chemical calculations[13] and direct measurements of acidity.[25,26]

The energies of H bonds were estimated by calculation of the structure of β-CD (β-CD—hb) in which the orientation of the (2)OH and (3)OH groups minimizes the energy of their interaction due to attainment of the maximum possible distance between the glucose units.

The geometry optimization gave the β-CD—hb structure containing no ring system of H bonds in the wider part of the CD cavity. This is indicated by an elongation of the (2)OH...O(3′)H distances to ~2.43 Å, by an OH...O angle equal to 124.9°, and by an increase in the concity of the CD cavity (γ = 24.2°) calculated by an equation proposed previously[16] with respect to that in β-CD(+). The absence of imaginary vibration frequencies indicates that the structure belongs to a local minimum in the PES.

Two β-CD head-to-head dimers. The PM3 geometry optimization of the β-CD dimers formed from components with the right or left orientation of the interglucose H bonds resulted in each case in two different head-to-head (*hh*) dimers with D_7 symmetry (Fig. 2). In the first pair of dimers, the average distance between the monomers is close to that found in natural structures (*D*(O...O) ≈ 3.3 Å), while in the second pair, it is close to the equilibrium distance predicted by PM3 calculations (*D*(O...O) ≈ 2.7 Å, see Table 5). Binding of the dimer components is shown in Scheme 2. It can be seen that dimerization of both right- and left-oriented β-CD yields a system of complementary H bonds. In the (β-CD(+))$_2$ dimer, the (3)OH groups act as proton donors, while the (2)O atoms are the proton acceptors. Conversely, in (β-CD(−))$_2$, the (2)OH groups serve as proton donors and the (3)O atoms are the proton acceptors.

The energy of dimerization of β-CD(−) forming the (β-CD(−)*hh*)$_2$ dimer of the first type is 2.8 kcal mol^{-1}

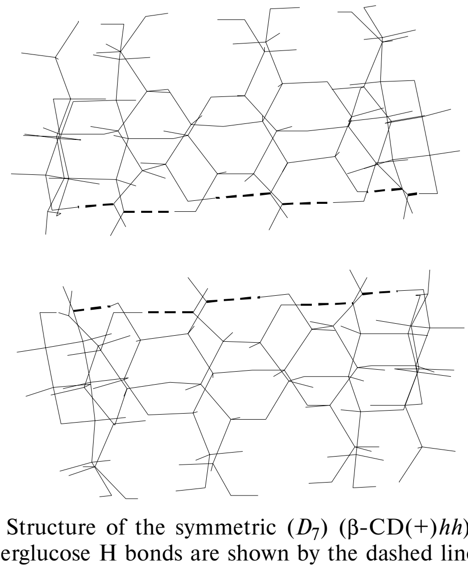


Fig. 2. Structure of the symmetric (D_7) (β-CD(+)*hh*)$_2$ dimer. The interglucose H bonds are shown by the dashed line.

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* Below we demonstrate that for β-CD, the difference between the energies of right- and left-oriented H bonds is only ~0.9 kcal mol^{-1}.

greater than the dimerization energy of β-CD(+) that forms the (β-CD(+)*hh*)$_2$ dimer. The second-type (β-CD(−)*hh*)$_2$ dimer thermodynamically more stable that its analog, (β-CD(+)*hh*)$_2$ with a difference of is 5.9 kcal mol^{-1} (see Table 3).

Comparison of the Φ, Ψ, and φ angles in the monomer and in the β-CD dimer with a similar orientation of the interglucose H bonds shows that these angles virtually do not change upon dimerization. However, the H bonds in the monomer units and those between the two dimer components are substantially different: the interglucose bonds are markedly shorter (1.807 and 1.804 Å) than the inter-component bonds (2.512 and 2.534 Å) (see Table 5). Since the positions of the H atoms in the natural dimer are unknown, we can compare only the distances between the O atoms linked by hydrogen bonds in the natural and theoretical dimers. It follows from Table 5 that the calculated intramolecular distances *D*(O...O) are somewhat shorter (2.718 and 2.748 Å) than their analogs in the natural dimer (2.802 Å). However, the inter-component O...O distances in the theoretical dimer are longer (3.298 and 3.326 Å) than those in the natural dimer (3.115 Å). This means that the native structure of the β-CD dimer is somewhat more compact than that found by PM3 calculations.

In the second-type dimers, the parameters of the intramolecular and intermolecular H bonds are close (see Table 5). In view of the similar geometric parameters of the intramolecular and intermolecular H bonds in head-to-head dimers and assuming that the energy of one H bond of the right orientation is 1.1 kcal mol^{-1}, we find that the energy of formation of the (β-CD(−)*hh*)$_2$ dimer, which has fourteen bonds of this type, should be 15.4 kcal mol^{-1}. Since this value is 4.1 kcal mol^{-1} smaller than that found by direct calculation (19.5 kcal mol^{-1}, see Table 3), the value proposed for the energy of one right-orientated H bond in β-CD should be considered underestimated.

The fact that the optimization of the structure extracted from the CSD (and supplemented by the lacking H atoms) affords symmetric dimers without any limitations on the variation of parameters during optimization indicates that the native structures of the dimers are close to symmetric forms. This is also confirmed by the fact that ε is close to 1 and ϕ is close to 128.57°. However, the native structures are somewhat disordered, which is manifested most clearly as varied conformations of the primary OH groups, due to the low potentials to the internal rotation. Thus, the view that the relatively low solubility of β-CD in water is due to association of its molecules appears to find support because the structures with a regular shape, to which β-CD belongs, attain more easily complementarity of the H bonds between the partners.

We assumed that the reason why the PM3 method detects two types of dimers (with short and long intermolecular H bonds) is related to shortcomings of the parametrization. Our test calculation for the water dimer with different intermolecular distances demonstrated that the dimer with the energy of formation ΔE = 3.5 kcal mol^{-1}, included in the procedure of parameter optimization,[17] is matched by *R*(OH...O) = 1.809 Å and the structure obtained corresponds to a minimum in the potential energy curve (PEC) and is in fairly good agreement with experimental data on ΔE (3.5 kcal mol^{-1}, Ref. 27) and on *R*(OH...O).[28] The second dimer with a distance of 2.374 Å and ΔE = 1.7 kcal mol^{-1} does not correspond to a stationary point in the PEC and has two imaginary vibration frequencies.

In the calculation of the methanol dimer, the global minimum corresponding to ΔE = 2.6 kcal mol^{-1} is detected again at a short distance (1.822 Å). However, at 2.35 Å, a minimum with ΔE = 1.6 kcal mol^{-1} was also found in the PEC; this is a local minimum characterized by 3*N*-6 real vibration frequencies. Thus, the presence of two minima in the potential curve for the H bond in the water and methanol dimers and, hence, in CD dimers, clearly points to a shortcoming of parametrization, despite the fact that the structures of dimers with "long" H bonds are in better agreement with those found in the β-CD crystals. Since the PM3 calculation of the H bond energy in the water dimer gives a value of 3.5 kcal mol^{-1}, which is close to the experimental value, 3.59 kcal mol^{-1}, and the *R*(OH...H) equilibrium distance equal to ~1.8 Å, of the two β-CD(*hh*) dimers with a short and a long intermolecular hydrogen bond, the former should be considered "correct" in terms of the PM3 method.

Head-to-tail dimers. We calculated the head-to-tail (*ht*) dimers formed by H bonds between the H atoms of the secondary OH groups of one partner and the O atoms of the primary OH groups of the other partner. The regular symmetric structure of each *ht* dimer implies the existence of seven H bonds of this type (Fig. 3)

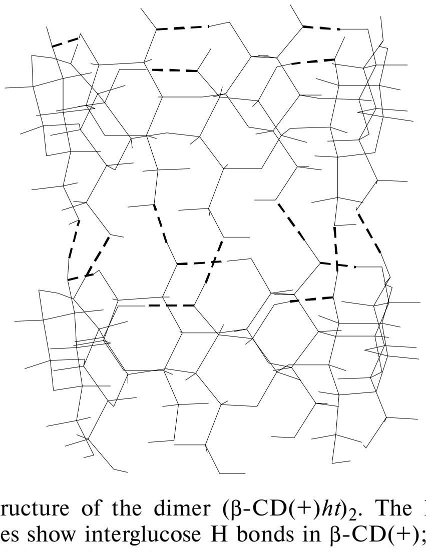

Fig. 3. Structure of the dimer (β-CD(+)*ht*)$_2$. The horizontal dashed lines show interglucose H bonds in β-CD(+); the sloping dashed lines show the inter-component H bonds in the dimer.

formed in accordance with Scheme 3. The calculations showed that the *ht* dimers formed from β-CD molecules with the right orientation of the H bonding system are energetically more favorable than the corresponding *hh* dimers: ΔE = 22.4 kcal mol^{-1} for (β-CD(+)*ht*)$_2$ and ΔE = 13.6 kcal mol^{-1} for (β-CD(+)*hh*)$_2$. The higher stability of the *ht* dimers may be favorable for the self-assembly processes giving rise to nanotubes, which take place in solutions of CD in the presence of hydrophobic substrates.[8]

Apparently, there are two reasons why the *ht* dimers are energetically more favorable than *hh*. Comparison of geometric parameters shows that the ω(O—H...O) angles at the intermolecular H bonds in *hh* dimers are, on average, ~140°, while those in *ht* dimers are ~170°. Since the energy of H bonding is the maximum at 180°, the intermolecular bond in the *ht* dimer is stronger than that in the *hh* dimer. In addition, in the formation of intermolecular H bonds in the *ht* dimer, the O atoms of the primary OH groups, which display a higher proton affinity, act as proton acceptors.[27] In the case of the *GG* conformation of a primary OH group in α-D-glucose (the choice of this conformation for β-CD has been substantiated above), the proton affinity calculated by the HF/6-31G(d) method (193 kcal mol^{-1}) proved to be greater than that of the secondary OH groups (187 kcal mol^{-1}). The calculated values are in agreement with the experimental data on the basicity of these groups in the gas phase (GB). The GB of the primary OH group in the *GG* conformation is estimated to be 184 kcal mol^{-1}, whereas for secondary hydroxy groups, this value is 178 kcal mol^{-1}.[29]

Unlike the pair of dimers (β-CD(+)*hh*)$_2$ and (β-CD(−)*hh*)$_2$, whose energies of formation correlate with the acidities of the (2)OH and (3)OH groups (see above), no correlation of this type is found for (β-CD(+)*ht*)$_2$ and (β-CD(−)*ht*)$_2$. The former dimer is 9.2 kcal mol^{-1} more stable than the latter one; in our opinion, this is due to geometric factors. In (β-CD(+)*ht*)$_2$, the H bond (1.811 Å) is shorter and the O—H...H angle (170.0°) is closer to 180° than those in (β-CD(−)*ht*)$_2$, in which the H bond is longer (1.828 Å) and the O—H...H angle, equal to 151.1°, deviates to a greater extent from 180°. These factors account for a lower energy of formation of (β-CD(−)*ht*)$_2$.

Energies of hydrogen bonds in β-*CD and in dimers.* We estimated the energies of the H bonds of both types by two methods. First, having assumed conventionally that the energies of the elongated H bonds in β-CD−hb are negligibly small and having divided the difference between ΔH_f for β-CD(+) and β-CD−hb, equal to 8 kcal mol^{-1}, into seven, we find that the energy of one H bond with the right orientation is 1.1 kcal mol^{-1}. The energy of the H bond with the left orientation determined in the same way was 0.3 kcal mol^{-1}. These values might be somewhat underestimated due to the fact that the energies of the elongated H bonds in β-CD−hb are not equal to zero. Second, assuming that head-to-head dimerization of β-CD(+) and β-CD(−) occurs only due to the formation of complementary H bonds, we will divide the dimerization energies for (β-CD(+)*hh*)$_2$ and (β-CD(−)*hh*)$_2$ into 14 (according to the number of H bonds in each dimer). For (β-CD(−)*hh*)$_2$, formed by the (2)OH groups, the result is 1.4 kcal mol^{-1}, while for (β-CD(−)*hh*)$_2$, formed by the (3)OH groups, the procedure gives 1.0 kcal mol^{-1}. These values appear more plausible.

* * *

Thus, the equilibrium conformation of a free β-CD molecule has C_7 symmetry and is close to the global minimum. Association of β-CD affords head-to-head dimers with D_7 symmetry and head-to-tail dimers with C_7 symmetry; each dimer is formed through complementary H bonds. In a free regular β-CD molecule, of the two possible orientations of the interglucose H bonds, the bond of the (2)OH→O(3′)H type is the most favorable for thermodynamic reasons. The energy of one H bond was estimated to be 1.1—1.4 kcal mol^{-1}. The preferred formation of H bonds of this type is due to the more acidic character of the (2)OH groups. This conclusion is confirmed by published data and also by the fact that, of the two head-to-head dimers, the (β-CD(−)*hh*)$_2$ dimer in which the (2)OH groups are responsible for the formation of intermolecular H bonds displays the greatest thermodynamic stability. The head-to-tail dimer is energetically more favorable than the head-to-head analog. The high energies of formation of dimers of both types stipulate the high degree of association of β-CD in aqueous solutions and promote fixing of inclusion complexes based on head-to-head dimers of β-CD in the crystalline state.

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