

## Physical Chemistry

### Structure of guest-host complexes of $\beta$ -cyclodextrin with arenes: a quantum-chemical study

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The structure of  $\beta$ -cyclodextrin ( $\beta$ -CD), as well as the structure and energetics of  $\beta$ -CD—naphthalene,  $\beta$ -CD—fluorene,  $\beta$ -CD—phenanthrene,  $\beta$ -CD—cyclohexane (1 : 1), and  $\beta$ -CD—naphthalene (2 : 2) inclusion complexes was studied by the semiempirical MNDO/PM3 method. Calculations of a  $\beta$ -CD—naphthalene—cyclohexane (1 : 1 : 1) complex were also performed. The minimum heat of formation was found for the symmetric  $\beta$ -CD conformation with  $C_7$  symmetry axis. The structure is stabilized by the ring of interunit H-bonds formed by the protons of the 2-OH groups and the O atoms of the 3'-OH groups of the glucose units. Preferableness of this orientation of interunit H-bonds was confirmed by *ab initio* calculations of the molecule of  $\alpha$ -(1-4)-glucobiose (maltose) in the MP2/6-31G(d,p)//6-31G(d,p) approximation. The formation of any inclusion compounds of  $\beta$ -CD with arenes is energetically favorable: the complexation energy varies in the range  $-9$  to  $-12$  kcal mol<sup>-1</sup>. Among complexes with naphthalene, that of composition 2 : 2 is the most energetically favorable, which is in agreement with experimental data. In this complex,  $\beta$ -CD exists as a dimer of the "head-to-head" type, in which both partners are linked by a system of H-bonds. The structure of the "head-to-head" dimer of  $\beta$ -CD was simulated by *ab initio* calculations of the H-bonded dimer of  $\alpha$ -D-glucose in the RHF/6-31G(d,p) approximation. In the dimer, both components are linked by a pair of H-bonds formed by the protons of the 3-OH groups and the O atoms of the 2-OH groups. The dimerization energies obtained from *ab initio* and semiempirical MNDO/PM3 and AM1 calculations differ by about 2.5 times (8.6 vs. 3.2 and 3.8 kcal mol<sup>-1</sup>, respectively).

**Key words:**  $\beta$ -cyclodextrin, dimer of  $\beta$ -cyclodextrin molecule, inclusion complexes of  $\beta$ -cyclodextrin with naphthalene, fluorene, phenanthrene, and cyclohexane,  $\beta$ -cyclodextrin--naphthalene--cyclohexane complex, H-bonds in  $\beta$ -cyclodextrin molecule, *ab initio* quantum-chemical calculations of maltose molecule and glucose dimer, semiempirical MNDO/PM3 method.

Cyclo- $\alpha$ -(1-4)-glucoheptaoside ( $\beta$ -cyclodextrin,  $\beta$ -CD) is a cyclic polysaccharide comprising seven  $\alpha$ -D-glucose units in <sup>4</sup>C<sub>1</sub> conformation linked by glyco-

sidic 1-4'-bonds<sup>1</sup> (Fig. 1). The macrocycle of the  $\beta$ -CD molecule resembles a basket. The cavity of the  $\beta$ -CD molecule with an average diameter of 7.8 Å has a hydro-

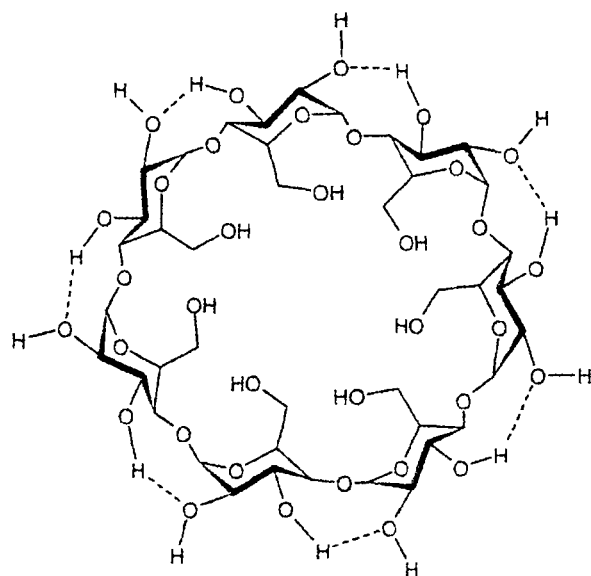


Fig. 1. Schematic representation of  $\beta$ -CD molecule (top view). H-bonds between 3'-OH and 2-OH groups of glucose units forming the wider rim of the  $\beta$ -CD cavity are shown on the outside. Primary OH groups forming the narrower rim of the  $\beta$ -CD cavity are shown on the inside.

phobic character and readily traps molecules of appropriate size from the environment (mostly, from aqueous solutions) to form various "guest—host" inclusion complexes of different composition and structure.<sup>2–4</sup>

Of particular interest for photochemistry are complexes of CD with arenes, since their formation is accompanied by appreciable changes in the luminescence properties of substrates<sup>5,6</sup>: the quantum yield and lifetime of fluorescence increase, excimer<sup>2,3</sup> and exiplex<sup>7</sup> fluorescence appear, and room temperature phosphorescence (RTP) is observed.<sup>5,8–10</sup> The appearance of different types of luminescence is closely related to different composition of the complexes. Thus, addition of trace amounts of cyclohexane to aqueous solution of  $\beta$ -CD—naphthalene complex, resulting in the formation of triple 1 : 1 : 1 complexes, is accompanied by the appearance of long-lived (up to 17.6 s for deuterated naphthalene<sup>10</sup>) high quantum yield RTP even in undegassed solutions, *i.e.*, in the presence of dioxygen.<sup>5,9</sup> It is likely that under these conditions the naphthalene molecule in the CD cavity is to a great extent protected from contact with dioxygen (an active quencher of triplet states) dissolved in water, which favors the appearance of RTP. At the same time, binary 1 : 2 or 2 : 2 complexes of CD with naphthalene exhibit excimer fluorescence,<sup>2,3,11,12</sup> which precludes the appearance of RTP because of competition between the emission and intercombination conversion.

To understand the reasons for photophysical phenomena reflected in the luminescence spectra of arenes,<sup>10,11</sup> it is necessary to establish the structure of

$\beta$ -CD complexes with these compounds (in particular, with naphthalene, phenanthrene, and fluorine) and to elucidate the role of cyclohexane as the third component, the addition of which in trace amounts gives rise to RTP. However, X-ray studies are rather time-consuming. To date, only three complexes of  $\beta$ -CD with *unsubstituted* arenes have been studied by X-ray analysis, namely, a "molecular necklace"<sup>13</sup> with participation of a benzene molecule,  $\beta$ -CD—pyrene—octanol, and  $\beta$ -CD—pyrene—tricyclohexanol triple complexes.<sup>14</sup> Therefore the necessity appeared of using computational methods.

Usually, conformations of CD and the structure of inclusion complexes are studied using molecular mechanics (MM) methods (see review<sup>15</sup>). Quantum-chemical methods, in particular, AM1 and MNDO/PM3<sup>16</sup> (hereafter PM3) and AM1<sup>17–19</sup> are much more rarely used. For instance, the structures of free CD molecules and several 1 : 1 inclusion complexes have been calculated by MM methods. The calculations showed that cyclodextrins (including  $\beta$ -CD) have flexible structures.<sup>15</sup> The symmetric conformation with  $C_7$  symmetry axis, which could be expected since the  $\beta$ -CD molecule comprises seven equivalent glucose units, is not the most stable conformation. According to MM data,<sup>20</sup> the asymmetric form in which three glucose units are characterized by larger tilt angles compared to four other units is 5.5 kcal mol<sup>–1</sup> more energetically favorable. As a result, these units are to a greater extent drawn into the cycle, thus favoring the decrease in the intracycle energy of nonvalence interactions.

This result contradicts the opinion that the actual shape of a  $\beta$ -CD molecule is very close to a symmetric one<sup>21</sup> (though no estimates of the degree of similarity were made). In our opinion, the reason for obtaining an asymmetric shape by the MM method is inadequate consideration of the energy of H-bonds in the parametrization, because hydrogen bonds that make the structure more rigid might favor the "strengthening" of symmetric shape of the  $\beta$ -CD molecule. In addition,  $\beta$ -CD and its associates form complex systems with intra- and intermolecular H-bonds,<sup>21</sup> which should be correctly taken into account in hope that calculating the structures of inclusion complexes other than 1 : 1 be a success.

Semiempirical AM1 and PM3 quantum-chemical calculations performed to estimate the hydration energy of the  $\beta$ -CD cavity<sup>16</sup> showed that it is comparable with the association energy of neat water. Optimization of the geometry of a free  $\beta$ -CD molecule has led to a symmetric structure stabilized by interunit hydrogen bonds (3'-OH...O(2)H) (the prime indicates that the OH group belongs to the adjacent unit). The symmetry of the structure was characterized by the value of the O—O—O angle between the O(4) atoms of the seven-membered pseudocycle of the  $\beta$ -CD molecule. However, these data are insufficient to estimate the degree of symmetry of the calculated conformation of the  $\beta$ -CD molecule, since information on the tilt angles of glucose units is also required.

AM1 calculations of  $\beta$ -CD complexes with benzoic acid derivatives<sup>18</sup> performed without optimization of the structure of the  $\beta$ -CD molecule have led to complexation energies ( $\Delta E$ ) which, in our opinion, are unjustifiably low. Only three out of 30 calculated inclusion complexes, for which the  $\Delta E$  values were less, comparable, or slightly higher than  $kT$  ( $-0.3$ ,  $-0.7$ , and  $-1.6$  kcal mol<sup>-1</sup>, respectively), could be conditionally considered energetically favorable. The AM1 method was also used for calculating the reaction of phenyl acetate hydrolysis catalyzed by  $\beta$ -CD.<sup>19</sup>

The fact that MM methods are used more often than quantum-chemical ones<sup>15</sup> is due, on the one hand, to the fact that the former explicitly treat intermolecular interactions determining the ability of substrate molecules to penetrate into the CD cavity and that MM calculations require much less computational resources than quantum-chemical calculations of such large systems. On the other hand, the known force fields used in MM methods to describe intermolecular interactions lead to fairly good results only for a limited number of systems. Description of a complex combination of polar and van der Waals interactions between arenes and carbohydrates (including CD) requires specific force fields, which, to our knowledge, have not been developed as yet.

The formation of an inclusion complex in solution is a result of several processes, among which the release of a substrate from the solvate shell and its penetration into the cavity of the CD molecule surrounded by a large number of water molecules, replacement of cavity-bound water by the substrate, *etc.*, are of importance. Simulation of such processes is usually performed by molecular dynamics methods.<sup>22</sup>

At the same time, it was established experimentally<sup>23</sup> that inclusion complexes are also formed simply by grinding  $\beta$ -CD crystals and solid substrates (naphthalene, dyes, *etc.*) entrapped in the cavity of the  $\beta$ -CD molecule. In this case, inclusion complexes are formed as a result of direct local interaction of CD with the substrate. This interaction can well be simulated taking a supramolecular system consisting of isolated "guest" and "host" molecules as an example. In this case quantum-chemical methods can appear to be efficient. Since it is impossible to use *ab initio* methods for calculations of such large systems to obtain reliable estimates of structural and energy parameters, an adequate semiempirical quantum-chemical method should be chosen. In our opinion, it is the PM3 method<sup>24</sup> developed with particular emphasis placed on correct reproduction of the geometry and energetics of H-bonds that could be used in this case.

The aim of this work is to study the structure and energetics of various inclusion complexes of  $\beta$ -CD with naphthalene, fluorene, phenanthrene, and cyclohexane by the quantum-chemical PM3 method. Since no detailed quantum-chemical data on  $\beta$ -CD itself are available in the literature, we first studied its molecular and electronic structure by the same method. Particular em-

phasis was placed on checking for the possibility of obtaining symmetric  $\beta$ -CD structure and establishing the optimum orientation of interunit hydrogen bonds of the wide rim of the  $\beta$ -CD cavity, formed by secondary OH groups, and their participation in the formation of  $\beta$ -CD dimers of the "head-to-head" type. The data of semiempirical calculations are compared with those of *ab initio* (MP2/6-31G(d,p)/6-31G(d,p)) calculations of model systems, namely, an  $\alpha$ -(1-4)-glucobiose (maltose) molecule with two different orientations of interunit H-bonds and a H-bonded glucose dimer (the RHF/6-31G(d,p) method). (Details of *ab initio* calculations will be published elsewhere.)

The study included: 1) search for the lowest-energy conformation of the  $\beta$ -CD molecule; 2) comparison of the data obtained with the theoretical structure of  $\beta$ -CD<sup>16</sup> and experimental structures of native  $\beta$ -CD undecahydrate<sup>25</sup> and the inclusion complex of  $\beta$ -CD with diethanolamine<sup>26</sup>; 3) calculations of  $\beta$ -CD dimers and  $\beta$ -CD—naphthalene,  $\beta$ -CD—phenanthrene,  $\beta$ -CD—fluorene, and  $\beta$ -CD—cyclohexane 1 : 1 inclusion complexes; and 4) calculations of  $\beta$ -CD—naphthalene 2 : 1 and 2 : 2 complexes and the  $\beta$ -CD—naphthalene—cyclohexane 1 : 1 : 1 complex.

Calculations showed that the PM3 and AM1 methods lead to a symmetric (with  $C_7$  symmetry)  $\beta$ -CD conformation with the lowest heat of formation. The structure obtained by the PM3 method is more similar to the native structure than that obtained from AM1 calculations. The formation of any inclusion compounds of  $\beta$ -CD with arenes is energetically favorable and their complexation energies vary from  $-9$  to  $-12$  kcal mol<sup>-1</sup>. Among  $\beta$ -CD complexes with naphthalene, the 2 : 2 complex is the most energetically favorable. In this complex,  $\beta$ -CD molecules are united to form a dimer of the "head-to-head" type, in which both partners are linked by a system of H-bonds. The results of calculations are in agreement with experimental data.

### Procedure for calculations

All semiempirical calculations of  $\beta$ -CD molecules (147 atoms, 378 AOs), its H-bonded dimers (294 atoms, 756 AOs), inclusion compounds with naphthalene, phenanthrene, fluorene,<sup>27</sup> and cyclohexane of compositions 1 : 1, 2 : 1, and 2 : 2 (330 atoms, 852 AOs), as well as the triple  $\beta$ -CD—naphthalene—cyclohexane complex were carried out with full geometry optimization by the PM3 method with standard parameters.<sup>24</sup> The GAMESS 96 and GAMESS 97 program packages and the GAMESS PC version by A. A. Granovskii (Department of Chemistry, M. V. Lomonosov Moscow State University) were also used.

No restrictions on the variation of geometric parameters (including symmetry restrictions) were imposed on the systems. In some instances, to check the structure obtained for correspondence to a local minimum, optimization of the geometry was followed by calculations of frequencies of normal vibrations in the harmonic approximation (Table 1).

**Calculations of symmetric  $\beta$ -CD structure.** The main problem in calculations of the  $\beta$ -CD molecule is due to the large

**Table 1.** Calculated total energies ( $E_{\text{total}}$ ), heats of formation ( $\Delta H_f$ ), energy differences between different conformations of the  $\beta$ -CD molecule (underlined), and complexation energies ( $\Delta E$ )

Calculation procedure	System (symmetry, orientation)	$E_{\text{total}}$ /au	$\Delta H_f$ kcal mol <sup>-1</sup>	$\Delta E$
MM2	$\beta$ -CD-MM	-153.3 <sup>a</sup>	—	—
PM3	$\beta$ -CD ( $C_7$ , OCC, right orientation of H-bonds)	-600.375065	-1467.9	0
PM3	$\beta$ -CD		-1459.7 <sup>16</sup>	<u>8.2</u>
PM3	$\beta$ -CD ( $C_7$ , left orientation of H-bonds)	-600.366579	-1462.5	<u>5.3</u>
AM1	$\beta$ -CD ( $C_7$ )	-645.595648	-1670.7	0
	$\beta$ -CD		-1657.8 <sup>17</sup>	<u>12.9</u>
			-1656.6 <sup>18</sup>	<u>14.1</u>
			-1656.4 <sup>16</sup>	<u>14.3</u>
AM1	$\beta$ -CD ( $C_7$ , left orientation of H-bonds)	-645.584351	-1665.3	<u>5.4</u>
PM3	Dimer $\beta$ -CD ("head-to-head") (right orientation of H-bonds)	-1200.771397	-2949.1	-13.3
PM3	$\beta$ -CD—diethanolamine—3 H <sub>2</sub> O	-687.444684		-9.3
AM1	$\beta$ -CD—diethanolamine—3 H <sub>2</sub> O	-739.638578		-5.3
PM3	$\beta$ -CD—naphthalene	-648.437567		-12.4
PM3	$\beta$ -CD—naphthalene · 10 H <sub>2</sub> O	-767.875105		-6.2
PM3	$\beta$ -CD—phenanthrene	-666.971879		-9.3
PM3	$\beta$ -CD—fluorene	-662.624462		-10.5
PM3	$\beta$ -CD—cyclohexane	-633.363072		-10.7
PM3	$\beta$ -CD—10 H <sub>2</sub> O	-719.822593		-40.9
PM3	$\beta$ -CD—naphthalene—cyclohexane	-681.401783		-5.6
PM3	2- $\beta$ -CD("head-to-head")—naphthalene <sup>b</sup>	-1248.823283		-16.4
PM3	2- $\beta$ -CD("head-to-head")—naphthalene <sup>c</sup>	-1248.79714		-7.1
PM3	2- $\beta$ -CD("head-to-head")—2 naphthalene	-1296.891323		-35.0, -10.2 <sup>d</sup>
PM3	Naphthalene	-48.042704	40.7 (40.7 <sup>24</sup> )	
PM3	Phenanthrene		54.7	
PM3	Fluorene	-62.235254	49.0	
PM3	Cyclohexane	-32.970943	-31.3	
PM3	Diethanolamine	-51.2255027	-100.2	

<sup>a</sup> Strain energy/kcal mol<sup>-1</sup>.<sup>b</sup> Naphthalene molecule is located at the center of the cavity formed by two  $\beta$ -CD molecules.<sup>c</sup> The whole naphthalene molecule is located inside the cavity of one of the  $\beta$ -CD molecules.<sup>d</sup> The first value is the energy of decomposition into individual components and the second value is the energy of decomposition into two 1 : 1 complexes.

number of atoms; optimization of geometric parameters leads, as a rule, to a structure corresponding to a local energy minimum. Optimization affects mostly the  $\Phi$  and  $\Psi$  torsion angles that determine mutual orientation of glucose units in the  $\beta$ -CD molecule and the C(1)—O—C(4') ( $\varphi$ ) glycosidic angle, whereas the structural parameters of glucose units change only slightly.<sup>28</sup> For this reason, optimization of the  $\beta$ -CD geometry beginning with different initial conformations will *a priori* lead to structures with different orientation of glucose units, thus deteriorating the reproducibility of results.

At the same time, to obtain reliable structural and energy characteristics of inclusion complexes of different composition and structure, we needed such a  $\beta$ -CD structure that either corresponded to a global minimum (which, in our opinion, is hard to prove) or to a reproducible local energy minimum. We will call the desired  $\beta$ -CD structure a basic reference structure (BRS). By comparing the energies of different complexes with that of the BRS we could determine the complexation energies and their dependence on the substrate nature, the composition, and structure of the complex. Since the  $\beta$ -CD molecule is a cycle comprising seven equivalent glucose units, special

emphasis in the search for a BRS was placed on obtaining a structure with  $C_7$  symmetry axis, which was assumed to be the most energetically favorable.

The calculations were carried out as follows. First, using five  $\alpha$ -D-glucose molecules with the same structure extracted from the database of saccharide structures incorporated into the ChemPlus program package<sup>30</sup> (this structure was optimized by the MM method with AMBER parametrization<sup>29</sup>), we constructed the molecule of a model five-membered analog of cyclodextrin, *cyclo*- $\alpha$ -(1-4)-glucopentaoside (5-CD), and optimized it by the PM3 method. As previously (calculations by the MM method<sup>31</sup>), PM3 calculations also led to a symmetric structure of 5-CD with  $C_5$  symmetry. Then, the calculated values of the  $\Phi$ ,  $\Psi$ , and  $\varphi$  angles were used as starting values in the optimization of the geometry of the  $\beta$ -CD molecule. The intermediate structure obtained ( $\beta$ -CD-*i*) was asymmetric and had a lower heat of formation as compared with that of the initial structure. Two glucose units out of seven were considerably different from the remaining five units in the  $\Phi$  (101.7° and 102.7°) and  $\Psi$  (127.2° and 126.4°) angles and in the values of the parameters of interunit H-bonds (Table 2). The  $\beta$ -CD-*i*

**Table 2.** Main geometric parameters of native and calculated structures of  $\beta$ -cyclodextrin molecule

Structure	$\Phi$	$\Psi$	$\phi$	$l(\text{O}\cdots\text{O})$	$D(\text{O}\cdots\text{O})$	$\omega(\text{O}\cdots\text{O})$	$R(\text{O}\cdots\text{O})$	$\kappa(\text{H}\cdots\text{O})$	$\omega(\text{OH}\cdots\text{O})$
$\beta$ -CD ( $C_7$ , BRS)	117.2	118.8	115.8	4.736	9.794	128.5	2.718	1.813	156.0
	117.2	118.5	115.9	4.357	9.848	128.4	2.716	1.812	155.8
	118.6	120.1	116.1	4.374	9.857	129.4	2.720	1.810	157.1
	111.6	114.9	115.9	4.376	9.824	127.5	2.740	1.830	157.1
	122.1	124.3	116.9	4.335	9.799	128.8	2.732	1.811	159.6
	111.7	115.4	115.9	4.401	9.791	128.7	2.740	1.831	157.2
	119.9	122.5	116.3	4.355	9.771	128.4	2.723	1.811	157.4
	<u>116.9<math>\pm</math>3.4</u>	<u>119.2<math>\pm</math>3.4</u>	<u>116.1<math>\pm</math>0.4</u>	<u>4.419<math>\pm</math>0.14</u>	<u>9.812<math>\pm</math>0.03</u>	<u>128.5<math>\pm</math>0.6</u>	<u>2.727<math>\pm</math>0.01</u>	<u>1.817<math>\pm</math>0.01</u>	<u>157.2<math>\pm</math>1.2</u>
	$\beta$ -CD-native	107.4	129.8	117.9	4.430	10.231	129.3	2.991	2.022-
117.5		143.1	117.8	4.474	10.169	129.8	2.935	2.011+	158.3
100.9		115.0	119.0	4.200	9.882	128.1	2.770	1.841-	155.4
116.6		129.7	118.9	4.348	9.493	126.1	2.753	1.811-	159.0
108.2		125.6	118.3	4.562	9.287	131.8	2.966	2.005-	176.4
108.2		134.1	118.5	4.309	9.603	127.1	2.913	1.955-	165.2
100.8		120.0	117.7	4.324	10.012	126.9	2.959	2.027+	158.8
<u>108.5<math>\pm</math>6.7</u>		<u>128.2<math>\pm</math>9.2</u>	<u>118.3<math>\pm</math>0.5</u>	<u>4.378<math>\pm</math>0.12</u>	<u>9.811<math>\pm</math>0.36</u>	<u>128.4<math>\pm</math>2.0</u>	<u>2.898<math>\pm</math>0.1</u>	<u>2.084<math>\pm</math>0.38</u>	<u>163.7<math>\pm</math>7.9</u>
$\beta$ -CD- <i>i</i>		123.35	126.21	116.22	4.358	9.826	128.1	2.734	1.815
	116.33	118.02	115.89	4.399	9.850	127.8	2.719	1.814	155.8
	115.92	116.22	115.82	4.375	9.832	128.6	2.712	1.811	155.2
	120.86	122.74	116.31	4.369	9.817	128.3	2.724	1.811	157.9
	101.73	114.87	115.89	4.358	9.813	128.8	3.120	2.458	126.6
	126.35	127.35	116.59	4.382	9.822	128.5	2.739	1.812	161.4
	102.70	117.16	115.80	4.404	9.813	127.9	3.108	2.428	128.3
	<u>115.3<math>\pm</math>9.7</u>	<u>120.4<math>\pm</math>5.0</u>	<u>116.1<math>\pm</math>0.3</u>	<u>4.378<math>\pm</math>0.018</u>	<u>9.824<math>\pm</math>0.013</u>	<u>128.3<math>\pm</math>0.4</u>	<u>2.837<math>\pm</math>0.19</u>	<u>1.993<math>\pm</math>0.31</u>	<u>149.2<math>\pm</math>15.0</u>
	$\beta$ -CD-AM1	105.8 $\pm$ 0.6	128.4 $\pm$ 1.2	116.1 $\pm$ 0	4.404 $\pm$ 0.01	9.896 $\pm$ 0.04	128.5 $\pm$ 0.5	2.984 $\pm$ 0.02	2.157 $\pm$ 0.003
$\beta$ -CD-MM	115.7 $\pm$ 28.4	128.4 $\pm$ 25.8	116.0 $\pm$ 2.2	4.354 $\pm$ 0.1	9.808 $\pm$ 0.32	128.4 $\pm$ 7.6	3.015 $\pm$ 0.28	2.103 $\pm$ 0.27	160.8 $\pm$ 4.2

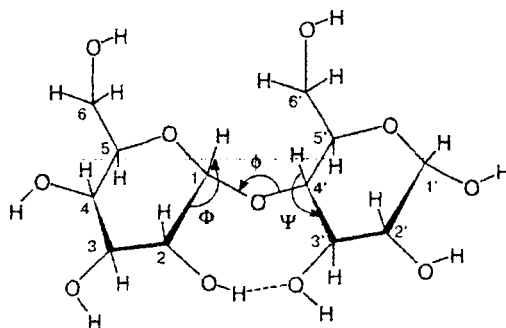
Note. Designations of  $\Phi$ ,  $\Psi$ , and  $\phi$  angles are given in Fig. 2. The  $\Phi$ ,  $\Psi$ ,  $\phi$ , and  $\omega$  angles are given in degrees and the bond lengths are given in Å;  $l(\text{O}\cdots\text{O})$  is the O—O bond length and  $D(\text{O}\cdots\text{O})$  is the O(*i*)...O(*i*+3) distance in the pseudocycle built of O(4) atoms of the  $\beta$ -CD molecule;  $R(\text{O}\cdots\text{O})$ ,  $\kappa(\text{H}\cdots\text{O})$ , and the  $\omega(\text{OH}\cdots\text{O})$  angle are parameters of interunit H-bonds. BRS is the basic reference structure. Average values are underlined. The "+" and "-" signs respectively denote right and left orientations of H-bonds.

structure was corrected by replacing the values of the  $\Phi$  and  $\Psi$  angles by the values averaged over five calculated close-lying angles (120.6° and 117.8°, respectively) and then the final geometry optimization was performed. As a result, we obtained the BRS of  $\beta$ -CD, which had a lower heat of formation (−1467.9 kcal mol<sup>−1</sup>) than the structure calculated earlier (−1459.65 kcal mol<sup>−1</sup>).<sup>16</sup>

The symmetry of this and other calculated structures was assessed as follows. For each set of seven equivalent atoms in the  $\beta$ -CD structure we calculated the length of the radius vector  $\mathbf{R}_i$  connecting the center of mass of the molecule and a given *i*th atom, the average  $\mathbf{R}_{\text{av}}$  value, and corresponding root-mean-square deviation  $\sigma_i$ . All structures for which the ratio  $r_i = \sigma_i/\mathbf{R}_{\text{av}}$  did not exceed 5% were considered approximately symmetric. The maximum  $r_i$  value for the obtained "symmetric" form of  $\beta$ -CD was 2.5%. Calculations of harmonic frequencies of vibrations showed that this structure corresponds to a local energy minimum ( $\Delta H_f = -1467.9$  kcal mol<sup>−1</sup>) and we then used it as the BRS (see Table 1).

It is noteworthy that an attempt to use new (averaged) values of the  $\Phi$ ,  $\Psi$ , and  $\phi$  parameters (see Table 2) for a further optimization did not lead to a structure with lower energy. This is in agreement with the data of AM1 calculations,<sup>19</sup> according to which a global energy minimum for  $\beta$ -CD most likely does not correspond to a highly symmetric shape of the  $\beta$ -CD molecule, which could be obtained by imposing symmetry restrictions in the course of optimization.

In Table 2, the values characterizing the shape of the "basket" for several calculated structures of the  $\beta$ -CD molecule are compared: the tilt angles  $\Phi$  of glucose cycles (the O(5)—C(1)—O(1)—C(4') torsion angle),  $\Psi$  (the C(1)—O(1)—C(4')—C(3') torsion angle), and  $\phi$  (the C—O—C glycosidic angle)<sup>28</sup> (Fig. 2), the "basket" conicity ( $\gamma$ ) and ellipticity ( $\epsilon$ ), and the parameters of interunit hydrogen bonds.



**Fig. 2.** Designations of the tilt angles of glucose units in the  $\beta$ -CD molecule:  $\Phi$  (torsion angle O(5)—C(1)—O(1)—C(4')),  $\Psi$  (the C(1)—O(1)—C(4')—C(3') torsion angle), and  $\phi$  (the C—O—C glycosidic angle).

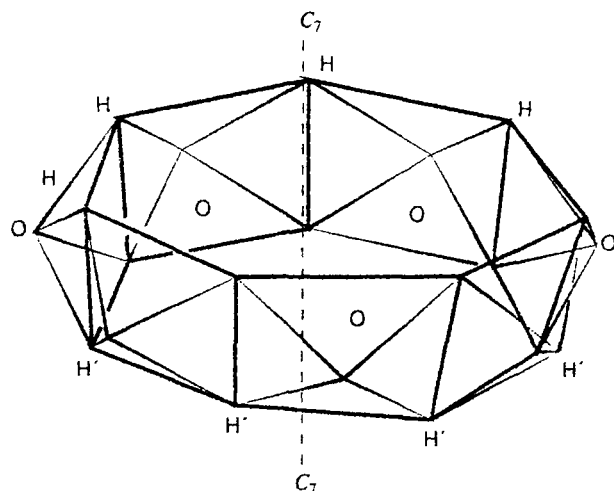


Fig. 3. Schematic representation of the interior of the  $\beta$ -CD cavity, confined by the rims composed of H(3) atoms, interunit O atoms, and H(5) atoms.

The polyhedron built of the atoms that confine the interior of the  $\beta$ -CD molecule, which is usually considered as a truncated cone, is shown in Fig. 3. The upper edge of the cavity is formed by the rim of H(3) atoms of seven glucose units, the medium part of the cavity is confined by the interunit O(4) atoms, and the lower edge of the cavity is confined by the rim of H(5) atoms of glucose units. Since the diameter of the circle circumscribed about the O atoms is larger than those of the circles circumscribed about the H atoms, it can be seen that it is the H atoms that limit the cavity size. Considering this, conicity  $g$  was calculated as the tilt angle of the generatrix  $h$  of the cone with respect to its vertical axis  $C_7$ ,  $g = 2\arcsin((D - d)/2h)^\circ$ , where  $D$  is the average diameter of the upper circle circumscribed about the H(3) atoms,  $d$  is the average diameter of the lower circle circumscribed about the H(5) atoms, and  $h$  is the distance between the H(3) and H(5) atoms averaged over the seven glucose units (see Fig. 3). Ellipticity  $e$  of the  $\beta$ -CD "basket" is the ratio of

the largest diameter of the pseudocycle formed by the interunit O atoms to its smallest diameter.

**Orientation of interunit H-bonds.** A rim of interunit H-bonds formed by secondary OH groups is an important characteristic feature of the structure of the  $\beta$ -CD molecule. These H-bonds are formed owing to the spatial proximity of secondary OH groups in positions 2 and 3 in adjacent  $\alpha$ -D-glucose units. The orientation of bonds formed by 2-OH and 3-OH groups in a glucose unit is such<sup>32</sup> that constructing the  $\beta$ -CD molecule by successive linking of glucose units gives an  $\alpha$ -(1-4)-glucobiose in which the interunit H-bonds between the H atoms of the 2-OH group of *preceding* units and the O atom of the 3'-OH group of *succeeding* units are formed due to the spatial proximity of the above-mentioned groups. This is illustrated in Fig. 4 taking  $\alpha$ -(1-4)-glucobiose (maltose) calculated by the MP2/6-31G(d,p)//6-31G(d,p) method as an example. The structure of the glucose unit is analogous to that obtained from *ab initio* calculations.<sup>32</sup> Then, a belt of clockwise oriented interunit H-bonds (we called this orientation *right*) is formed in the  $\beta$ -CD molecule as a result of the closure of the seven-membered cycle composed of  $\alpha$ -D-glucose molecules. However, it is believed<sup>19</sup> that the structure with the opposite orientation of H-bonds (we called this orientation *left*), in which the interunit H-bonds are formed by the H atom of the 3'-OH group of the *succeeding* unit and the O atom of the 2-OH group of the *preceding* unit (see Fig. 1), better fits the experimental data.<sup>33</sup>

Experimental solution of the problem of orientation of the interunit H-bonds is complicated by the fact that often it is impossible to directly locate the H atoms by X-ray analysis, which is widely used for studying the structure of CD and inclusion complexes. Only the distances between O atoms of adjacent OH groups are determined,<sup>34</sup> which admits both the right and left orientation of H-bonds (the so-called "flip-flop H-bonds").<sup>35</sup> Neutron diffraction (in those few cases when it was used) gives a rather complex pattern of H-bonding, which is to a great extent due to the presence of crystallization water.<sup>25,35,36</sup> For instance, the distances between the O atoms of adjacent OH groups in crystal hydrates of  $\beta$ -CD at 295 K admit both the right and left orientation<sup>32</sup> with  $R$ -factors of 4.3 and 6.4%, respectively. At 120 K, five out of seven H-bonds in the structure of  $\beta$ -CD undecahydrate are left-oriented while the remaining two H-bonds are right-oriented. Four out of seven H-bonds in the structure of perdeuterioethanol octahydrate in  $\beta$ -CD have the left orientation and three H-bonds have the

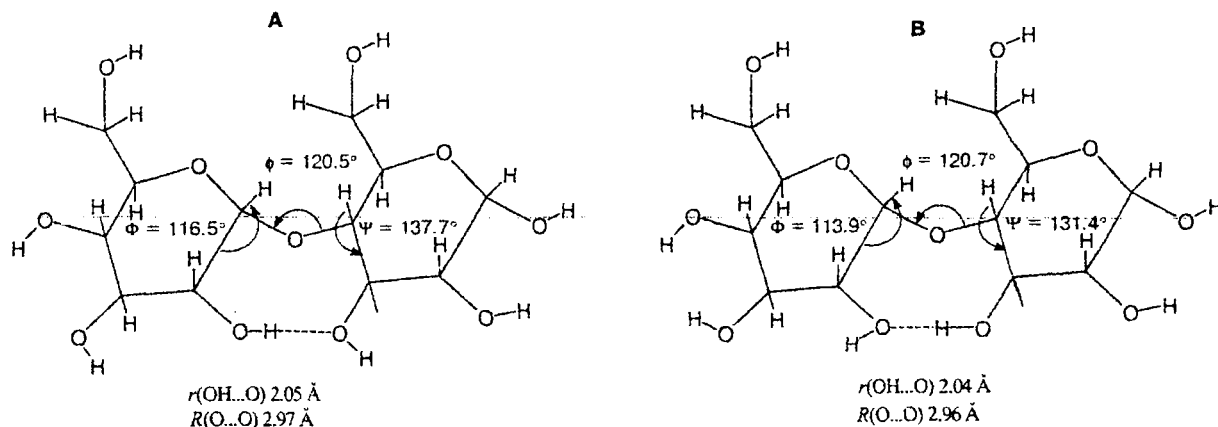


Fig. 4. The structures of  $\alpha$ -(1-4)-glucobiose (maltose) molecules with right (A) and left (B) orientation of H-bonds calculated by the MP2/6-31G(d,p)//6-31G(d,p) method. Structure A is more energetically favorable than structure B (the energy difference is 2.65 kcal mol<sup>-1</sup>).

right orientation<sup>36</sup> (the data were obtained from the Cambridge Structural Database, CSD).

In addition, the left orientation of interunit H-bonds in the native structures of inclusion complexes of  $\beta$ -CD is also not the only possibility. For instance, in  $\beta$ -CD dimers of the "head-to-head" type, many of which exist in the crystal state,<sup>21</sup> both partners are linked by a system of H-bonds formed between 3-OH groups of the two  $\beta$ -CD molecules (see below). Such structures can exist only if interunit H-bonds are right-oriented. Therefore, to determine the most energetically favorable orientation of H-bonds, we calculated the structures of  $\beta$ -CD molecules with both right and left orientations. Previously,<sup>16,19</sup> only structures of  $\beta$ -CD molecules with left orientation of H-bonds were considered.

**Calculations of inclusion complexes of  $\beta$ -CD** in which the substrate molecules were included in the cavity of the BRS of  $\beta$ -CD were performed with full optimization of geometric parameters. The complexation energy ( $\Delta E$ ) was calculated as the difference

$$\Delta E = \Delta H_f(c) - \Delta H_f(\text{BRS}) - \Delta H_f(s),$$

where (c) and (s) respectively denote the complex and substrate.

To check for the applicability of the PM3 method to predicting the geometry of inclusion complexes of  $\beta$ -CD with substrates, we calculated the  $\beta$ -CD—diethanolamine— $3\text{H}_2\text{O}$  complex,<sup>26</sup> whose structure was extracted from CSD. The lacking H atoms were added to the structure so that the H atoms of secondary OH groups were counterclockwise oriented (similar to the left orientation of most of the OH groups in  $\beta$ -CD undecahydrate) and full geometry optimization was performed. According to calculations, the found structure is analogous to the native one and the complexation energy is  $-9.3 \text{ kcal mol}^{-1}$ . Thus, the formation of  $\beta$ -CD—diethanolamine— $3\text{H}_2\text{O}$  inclusion compound in the gas phase is also energetically favorable.

**Model calculations.** Predictive power of the PM3 method was tested by comparing the results of *ab initio* (MP2/6-31G(d,p)//6-31G(d,p)) and semiempirical (AM1 and PM3) calculations of the  $\alpha$ -(1-4)-glucobiose (maltose) molecule (see Fig. 4) with right and left orientation of interunit H-bonds. Preliminary data of *ab initio* and PM3 calculations show that the maltose molecule with right orientation of H-bonds is, respectively, by  $2.7 \text{ kcal mol}^{-1}$  and  $3.1 \text{ kcal mol}^{-1}$  more energetically favorable than an analogous molecule with their left orientation. Thus, both methods predict nearly equal preferableness of the right orientation of interunit H-bonds in the maltose molecule.

The values of structural parameters of interunit H-bonds obtained from *ab initio* (PM3) calculations are  $r(\text{OH}\cdots\text{O}) = 1.96 \text{ \AA}$  ( $1.82 \text{ \AA}$ ) and  $R(\text{O}\cdots\text{O}) = 2.91 \text{ \AA}$  ( $2.77 \text{ \AA}$ ). According to the results of a neutron diffraction study, the weighted average experimental  $r(\text{OD}\cdots\text{O})$  values for deuterated  $\beta$ -CD are  $1.98$  and  $1.87 \text{ \AA}$  at  $295$  and  $120 \text{ K}$ , respectively.<sup>36</sup>

For  $\beta$ -CD—naphthalene 1 : 2 and 2 : 2 inclusion complexes it was necessary to test the ability of the PM3 method to predict the configuration and energy of intermolecular H-bonds responsible for the "head-to-head" type association of two  $\beta$ -CD molecules. To this end, an H-bonded glucose dimer was studied by the RHF/6-31G(d,p), PM3, and AM1 methods. The calculated dimerization energies appeared to be equal to  $8.6$ ,  $3.2$ , and  $3.8 \text{ kcal mol}^{-1}$ , respectively, with very similar relative orientation of partners in the dimer. This means that semiempirical calculations underestimate the dimerization energy of  $\beta$ -CD, though structural characteristics appear to be fairly close.

## Results and Discussion

**Structure of  $\beta$ -cyclodextrin molecule.** According to PM3 calculations, the BRS of the  $\beta$ -CD molecule is symmetric and has an  $r_f$  of 2.5% (Fig. 5). Comparison of the  $\Phi$ ,  $\Psi$ , and  $\phi$  angles in the BRS ( $116.9 \pm 3.4^\circ$ ,  $119.2 \pm 3.4^\circ$ , and  $116.1 \pm 0.4^\circ$ , respectively) and in the native  $\beta$ -CD structure ( $108.5 \pm 6.7^\circ$ ,  $128.2 \pm 9.2^\circ$ , and  $118.3 \pm 0.5^\circ$ , respectively) shows that the calculated average values of the  $\Psi$  and  $\phi$  angles are smaller while those of the  $\Phi$  angle are larger than the average values of these parameters in the native structure, though the scatter in the latter case is appreciably larger. The calculated values of the  $\Phi$ ,  $\Psi$ , and  $\phi$  angles for the BRS fall in the confidence intervals for these angles ( $111.9 \pm 6.8^\circ$ ,  $127.6 \pm 8.0^\circ$ , and  $117.7 \pm 2.6^\circ$ , respectively) obtained on statistical processing<sup>28</sup> of all  $\beta$ -CD structures deposited in the CSD.

The parameters of the heptagon formed by the interunit O(4) atoms in the calculated and native  $\beta$ -CD

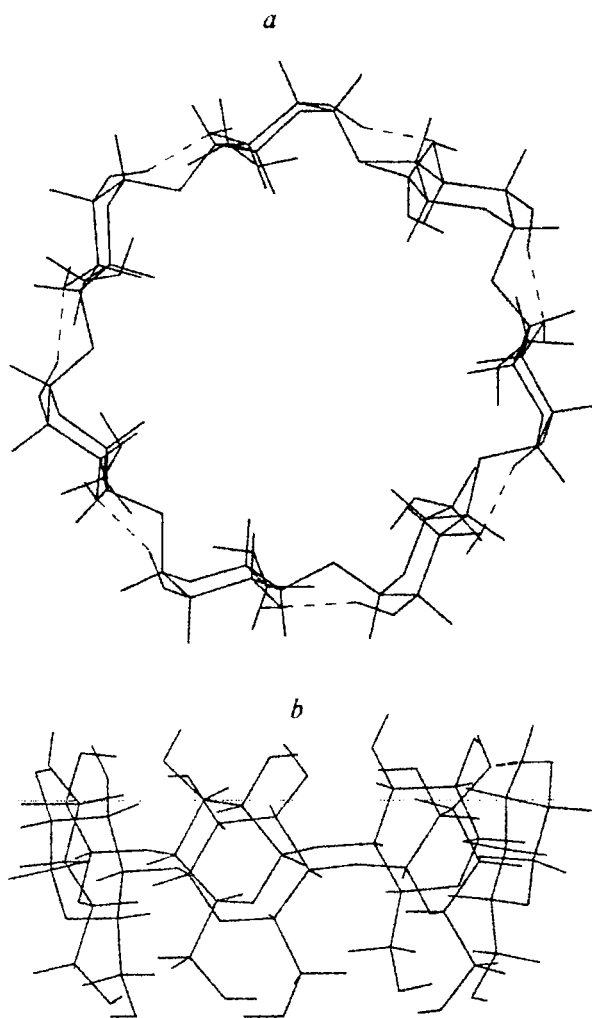


Fig. 5. Structure of  $\beta$ -CD molecule calculated by the PM3 method: a, top view; b, side view.

molecules, viz., the side lengths  $l(\text{O}\cdots\text{O})$  ( $4.419\pm 0.14$  Å and  $4.378\pm 0.12$  Å, respectively), the O—O—O angles ( $128.5\pm 0.6^\circ$  and  $128.4\pm 2.0^\circ$ , respectively), and the average diameter  $D(\text{O}\cdots\text{O})$  ( $9.812\pm 0.03$  Å and  $9.811\pm 0.36$  Å, respectively) are in good agreement with each other, whereas the  $l(\text{O}\cdots\text{O})$  and  $D(\text{O}\cdots\text{O})$  values averaged over all structures extracted from the CSD are  $4.64\pm 0.34$  Å and  $9.83\pm 0.24$  Å, respectively.<sup>28</sup> Since the O—O—O angle in the equilateral heptagon is  $128.6^\circ$ , it can be seen that the macrocycles in the BRS and in the native form are nearly regular heptagons. The only difference is that the parameters of the native structure are characterized by somewhat larger deviations from the average values than those of the BRS.

Calculations of the structure of the  $\beta$ -CD molecule with left orientation of H-bonds showed that it also has an approximate  $C_7$  symmetry ( $r_i \leq 1\%$ ); however, its energy is  $5.3 \text{ kcal mol}^{-1}$  higher than that of the BRS. Therefore, reorientation of interunit H-bonds according to the direction of most H-bonds in the native  $\beta$ -CD leads to an energetically less favorable conformation of the free  $\beta$ -CD molecule. Most likely, the formation of the structure with left orientation of H-bonds is caused by the effect of crystallization water, whose molecules are concentrated at that edge of the  $\beta$ -CD molecule in the crystal of  $\beta$ -CD undecahydrate which is formed by the rim of left-oriented H-bonds.

To compare the possibilities of the AM1 and PM3 methods, the BRS conformation was used as the starting geometry for optimization by the AM1 method. The calculated structure appeared to be 14.1 and  $14.3 \text{ kcal mol}^{-1}$  more energetically favorable than the previously calculated structures<sup>18,16</sup> and also had  $C_7$  symmetry ( $r_i \leq 1\%$ ). The parameters of right-oriented H-bonds of the wide rim of the cone of the  $\beta$ -CD molecule appreciably differ from those calculated by the PM3 method as well as from the experimental parameters<sup>25</sup> (see below). In addition, unlike the results obtained by the PM3 method, AM1 calculations have led to the formation of an additional rim of H-bonds formed between primary hydroxyl groups of the lower edge of  $\beta$ -CD molecule. Previously, such a structure, called the closed form (since the rim of H-bonds could preclude the penetration of substrate into the cavity through a narrower lower rim of the cone), was obtained by the MM2 method.<sup>20</sup> Its energy is  $5.6 \text{ kcal mol}^{-1}$  lower than that of the open form. Thus, there are discrepancies between the results of quantum-chemical calculations and data of MM calculations.

We also performed AM1 calculations of the structure of the  $\beta$ -CD molecule with a left-oriented belt of H-bonds of the upper edge of the cone (Fig. 6). The obtained structure also had two belts of H-bonds, with left orientation in the upper part of the cavity and with right orientation in the lower part of the cavity (the closed form). Despite the assumed double stabilization of the structure by H-bonds, it appeared to be  $5.4 \text{ kcal mol}^{-1}$  less energetically favorable than the structure of the  $\beta$ -CD

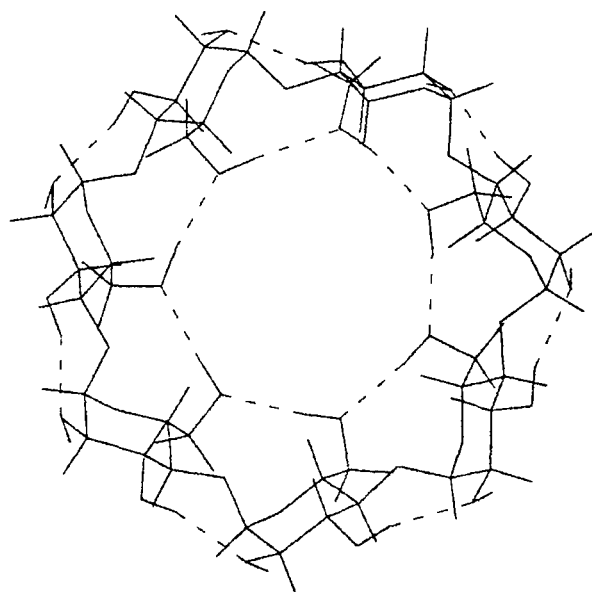


Fig. 6. Structure of  $\beta$ -CD molecule calculated by the AM1 method; top view.

molecule with right-oriented H-bonds calculated by the same method. Thus, it can be said with certainty that in the framework of the AM1 and PM3 methods the right orientation of the rim of H-bonds formed by the H atom of the 2-OH group of a preceding glucose unit with the O atom of the 3'-OH group of a succeeding unit in the  $\beta$ -CD molecule is more energetically favorable. The difference between the results of semiempirical methods is that H-bonds calculated by the method PM3 are shorter ( $r(\text{OH}\cdots\text{O}) = 1.82$  Å,  $R(\text{O}\cdots\text{O}) = 2.73$  Å), whereas those calculated by the AM1 method are longer ( $r(\text{OH}\cdots\text{O}) = 2.16$  Å,  $R(\text{O}\cdots\text{O}) = 3.114$  Å) than the interunit H-bonds in the model maltose molecule obtained from *ab initio* calculations ( $r(\text{OH}\cdots\text{O}) = 1.96$  Å,  $R(\text{O}\cdots\text{O}) = 2.91$  Å). At 120 K, the length of the H-bond between the glucose units in  $\beta$ -CD is 1.84 Å.<sup>36</sup> According to preliminary data, preferableness of right orientation ( $\Delta E = 2.65 \text{ kcal mol}^{-1}$ ) is also confirmed by *ab initio* calculations of the maltose molecule.

To compare the results of quantum-chemical and MM calculations, the BRS configuration was used as the starting point when optimizing the structure of the  $\beta$ -CD molecule by the MM method with the parameters of the MM2 force field. As a result, the  $\beta$ -CD-MM structure with a strain energy of  $-153.3 \text{ kcal mol}^{-1}$  and randomly distributed  $\Phi$  and  $\Psi$  angles (the range of changes was from  $96$  to  $152^\circ$ , see Table 2) was obtained, in which two glucose units were tilted inward toward the macrocycle and two glucose units were tilted outward away from the macrocycle. Optimization of  $\beta$ -CD-MM by the PM3 method led to a  $\beta$ -CD conformation corresponding to a local minimum whose energy was  $2.9 \text{ kcal mol}^{-1}$  higher than that of the BRS. The structure obtained was similar



**Table 3.** Conicity ( $\gamma$ ) and ellipticity ( $\epsilon$ ) of  $\beta$ -cyclodextrins

Molecule (symmetry)	Method	Number and orientation of interunit H-bonds <sup>a</sup>	$\gamma$ <sup>b</sup>	$\epsilon$ <sup>c</sup>
$\beta$ -CD ( $C_7$ )	PM3	7+	14.2	1.009
$\beta$ -CD ( $C_7$ )	PM3	7-	17	1.015
$\beta$ -CD ( $C_7$ )	AM1	7+	34.6	1.007
$\beta$ -CD ( $C_7$ )	AM1	7-	35.6	1.01
$\beta$ -CD-11H <sub>2</sub> O-native	ND <sup>17</sup> <sup>d</sup>	2+, 5-	22.6	1.085
$\beta$ -CD-MM	MM2	5+	?	1.027
$\beta$ -CD-DEA <sup>e</sup> -native	X-ray <sup>18</sup>	?	22	1.06

<sup>a</sup> The "+" and "-" signs respectively denote right and left orientations of H-bonds.

<sup>b</sup>  $\gamma/\text{deg} = 2\arcsin((D - d)/2h)$ , where  $D$  is the diameter of the circle circumscribed about H(3) atoms,  $d$  is the diameter of the circle circumscribed about H(5) atoms, and  $h$  is the distance between H(3) and H(5) atoms averaged over seven glucose units.

<sup>c</sup>  $\epsilon$  is the ratio of the largest diameter of the pseudocycle formed by the interunit O atoms to its smallest diameter.

<sup>d</sup> ND is neutron diffraction study.

<sup>e</sup> DEA is diethanolamine.

to the initial  $\beta$ -CD-MM structure and also had a random distribution of  $\Phi$  and  $\Psi$  angles and different tilt angles of glucose units. Thus, in the framework of PM3 and AM1 quantum-chemical methods the optimum structure of the free  $\beta$ -CD molecule is symmetric and the right orientation of interunit H-bonds formed by secondary OH groups is the most energetically favorable.

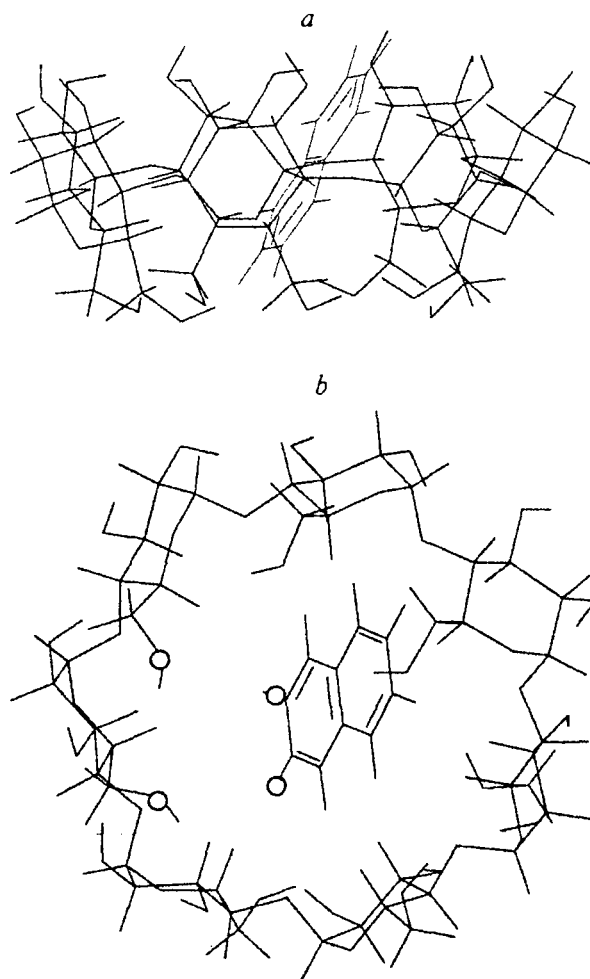
Comparison of the shapes of  $\beta$ -CD cavities calculated by different methods with the data on the native structures extracted from the CSD shows that the PM3 method leads to a somewhat more closed "basket" ( $\gamma = 14.1$  and  $17.0^\circ$ ; for comparison,  $\gamma = 22^\circ$  for  $\beta$ -CD undecahydrate and  $23^\circ$  for the  $\beta$ -CD-diethanolamine complex), whereas AM1 calculations give a much more open "basket" ( $\gamma = 17.8$  and  $17.3^\circ$ ). The latter is explained by the presence of a belt of H-bonds formed by primary OH groups of the lower edge of the  $\beta$ -CD cavity. Nothing can be said of conicity of the structure calculated by the MM method because of the quite irregular shape of the  $\beta$ -CD-MM molecule.

Comparison of ellipticities of calculated and native structures shows that they all slightly differ from one another and are slightly dependent on the method used. The cross-section of the  $\beta$ -CD cavity at the plane of the oxygen macrocycle always is a nearly regular circle, especially in the case of symmetric structures obtained from quantum-chemical calculations.

As can be seen in Fig. 3, the interior of the cavity is confined by rims of H(3) and H(5) and also O(4) atoms. Since the total negative charge of seven O atoms exceeds the total positive charge of fourteen H atoms, the net charge of the cavity is negative.

**$\beta$ -CD-naphthalene complexes.**  $\beta$ -CD-naphthalene 1 : 1, 1 : 2, and 2 : 2 inclusion compounds were calcu-

lated by the PM3 method. In the 1 : 1 complex, whose complexation energy ( $\Delta E$ ) is  $-12.4 \text{ kcal mol}^{-1}$ , the substrate molecule is entirely accommodated inside the cavity and nearly contacts its walls at the top and at the bottom (Fig. 7). The plane of the naphthalene molecule is tilted by  $25^\circ$  with respect to the vertical axis of the  $\beta$ -CD molecule, *i.e.*, the substrate, as if it "hovers" inside the cavity. Symmetry of the naphthalene molecule in the cavity is reduced as compared to that of a free molecule ( $D_{2h}$  vs.  $D_2$ , respectively). Deviations of H atoms in positions 2, 6 and 3, 8 from the plane of the naphthalene molecule accommodated in the cavity are  $6.7$  and  $8.2^\circ$ , respectively. Among other structural peculiarities of the complex, noteworthy are two relatively short contacts ( $2.778$  and  $2.878 \text{ \AA}$ ) between the H atoms of the naphthalene molecule and the O atoms of primary OH groups of the narrow edge of the cavity of the  $\beta$ -CD molecule



**Fig. 7.** The structure of  $\beta$ -CD-naphthalene complex calculated by the PM3 method: *a*, side view; *b*, top view. Indicated are the O atoms of primary OH groups of the  $\beta$ -CD molecule and H atoms of the naphthalene molecule separated by a distance of  $\sim 2.8 \text{ \AA}$ .

(they are indicated by circles in Fig. 7). These contacts can likely be interpreted as weak  $C_{Ar}-H...O$  H-bonds between the "guest" and "host" molecules.

AM1 calculations of the same complex performed for the sake of comparison gave  $\Delta E = -4.6$  kcal mol<sup>-1</sup>. In this case, penetration of the naphthalene molecule into the  $\beta$ -CD cavity appeared to be 1/4 the length of the arene molecule less deep than that calculated by the PM3 method.

Consideration of the  $\beta$ -CD—naphthalene 1 : 1 inclusion complex (see Fig. 7) shows that the volume of the unoccupied part of the cavity remains rather large, which indicates the possibility of inclusion of a cyclohexane molecule in the cavity along with the naphthalene molecule. According to calculations, the formation of a triple  $\beta$ -CD—naphthalene—cyclohexane complex is also energetically favorable, though in this case the energy gain due to inclusion of a cyclohexane molecule is about halved ( $\Delta E = -5.6$  kcal mol<sup>-1</sup>) as compared to that for the binary  $\beta$ -CD—cyclohexane complex ( $\Delta E = -10.7$  kcal mol<sup>-1</sup>).

Since inclusion compounds are mostly formed in aqueous medium, it is of interest to trace the behavior of cavity-bound water in the course of complexation using theoretical methods. To this end, we calculated a complex of  $\beta$ -CD undecahydrate with naphthalene.

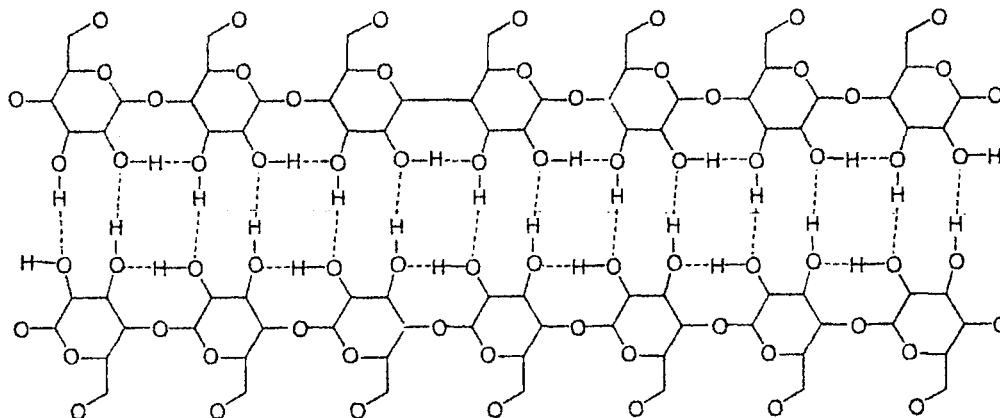
Analysis of the structure of  $\beta$ -CD undecahydrate<sup>25</sup> from CSD data showed that there are ten water molecules in the vicinity of the  $\beta$ -CD molecule. These molecules are bonded with one another and with the  $\beta$ -CD molecule by H-bonds and only three of them are in the cavity, filling a rather small volume. Therefore, the calculations were performed using the  $\beta$ -CD decahydrate structure preliminarily optimized by the PM3 method (see Table 1). In the first stage, the structure of the  $\beta$ -CD decahydrate—naphthalene inclusion compound was calculated without removal of the molecules of cavity-bound water, which likely do not preclude the penetration of a naphthalene

molecule into the cavity at the beginning of the penetration process because of their small size. The energy of naphthalene inclusion into the decahydrate ( $\Delta E = -6.2$  kcal mol<sup>-1</sup>) appeared to be lower than the formation energy of a complex of "hollow"  $\beta$ -CD with naphthalene ( $\Delta E = -12.4$  kcal mol<sup>-1</sup>).

Then we calculated the structure of  $\beta$ -CD decahydrate—naphthalene complex in which three cavity-bound  $H_2O$  molecules were transferred into the outer sphere to form H-bonds with primary (the nearest) OH groups. Calculations of this model showed a nearly two-fold increase in the complexation energy ( $\Delta E = -11.5$  kcal mol<sup>-1</sup>). The fact that this value is close to the energy of  $\beta$ -CD—naphthalene binary complex ( $-12.4$  kcal mol<sup>-1</sup>) makes it possible to conclude that the 1 : 1 complex contains no cavity-bound water. This is also confirmed by calculations of the energy of interaction between  $\beta$ -CD and cavity-bound water molecules.<sup>16</sup>

Two possible structures of  $\beta$ -CD—naphthalene 2 : 1 complex in which  $\beta$ -CD molecules are united to form a dimer of the "head-to-head" type were calculated. In the first structure the naphthalene molecule is entirely accommodated in the cavity of one of the  $\beta$ -CD molecules, whereas in the second structure it occupies an intermediate position between the "host" molecules. The latter configuration appeared to be more energetically favorable than the former (its energy is 9.3 kcal mol<sup>-1</sup> lower). This is in agreement with the data of X-ray study of  $\beta$ -CD—pyrene 2 : 1 complex in which the substrate molecules also occupy an intermediate position between both  $\beta$ -CD molecules associated into the dimer of the "head-to-head" type.<sup>14</sup> The principle of association of two  $\beta$ -CD molecules in such a dimer is shown in Fig. 8. Numerous inclusion compounds in which  $\beta$ -CD molecules are associated into dimers of the "head-to-head" type to form a cavity of double volume are known.<sup>21</sup>

Of particular interest is the structure of  $\beta$ -CD—naphthalene 2 : 2 complex. This is associated with the



**Fig. 8.** Scheme of the formation of  $\beta$ -CD dimer of the "head-to-head" type. The interunit H-bonds in  $\beta$ -CD molecules are formed by H atoms of the 2-OH groups of preceding glucose units with the O atoms of the 3'-OH groups of succeeding glucose units.  $\beta$ -CD molecules are bonded by intermolecular H-bonds formed by the H atoms of 3-OH groups of one CD molecule with the O atoms of 2-OH groups of the other  $\beta$ -CD molecule.

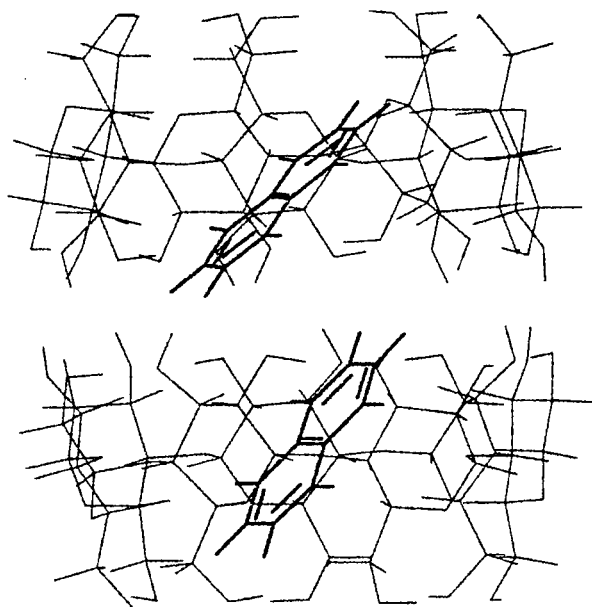


Fig. 9. The structure of  $\beta$ -CD—naphthalene 2 : 2 complex calculated by the PM3 method.

fact that, first, the constant of association of a binary complex into a dimeric 2 : 2 complex is very large ( $4 \cdot 10^3 \text{ L mol}^{-1}$ ),<sup>3</sup> whereas the formation constant of binary  $\beta$ -CD—naphthalene complex is  $685 \text{ L mol}^{-1}$  (see Ref. 3). Second, according to the data of luminescence spectroscopy, it is likely that a similar complex is also formed when obtaining inclusion compounds by grinding solid components.

We calculated a 2 : 2 complex in which the  $\beta$ -CD molecules were associated into a dimer of the "head-to-head" type and the cavity of each  $\beta$ -CD molecule was filled with one naphthalene molecule (Fig. 9). According to calculations, the energy of this complex is extremely high ( $-35 \text{ kcal mol}^{-1}$ ). Subtraction of the energies of two naphthalene molecules from this value shows that their inclusion into the cavity of the dimer "costs"  $-21.7 \text{ kcal mol}^{-1}$ . This is somewhat lower than the doubled formation energy of the  $\beta$ -CD—naphthalene complex ( $-24.8 \text{ kcal mol}^{-1}$ ). Association of two 1 : 1 complexes into a dimeric 2 : 2 complex is estimated at  $-10.2 \text{ kcal mol}^{-1}$ , which is somewhat lower than the dimerization energy of "hollow"  $\beta$ -CD molecules ( $-13.3 \text{ kcal mol}^{-1}$ , see Table 1). Thus, according to calculations, association of binary complexes into a 2 : 2 aggregate is actually very favorable. This is in agreement with the above-mentioned experimental data on complexation constants.

Consideration of the structure of  $\beta$ -CD—naphthalene 2 : 2 complex (see Fig. 9) shows that the naphthalene molecules in the complex are oriented nearly parallel to each other, their planes are tilted by  $35^\circ$  and  $45^\circ$  with respect to the vertical axes of the  $\beta$ -CD molecules, and the distance between their "halves" is rather short

( $\sim 5 \text{ \AA}$ ), so the interaction between them can be responsible for the appearance of excimer fluorescence.<sup>3</sup>

According to PM3 calculations of other inclusion compounds, the formation of  $\beta$ -CD complexes with arenes always is energetically favorable. The complexation energies are close to one another. A complex of  $\beta$ -CD with fluorene is the most energetically favorable ( $\Delta E = -10.5 \text{ kcal mol}^{-1}$ ), while its complex with phenanthrene is somewhat less stable ( $\Delta E = -9.3 \text{ kcal mol}^{-1}$ ). The experimental formation constant of the  $\beta$ -CD—fluorene complex is  $1.2 \cdot 10^3 \text{ L mol}^{-1}$ .<sup>27</sup> All inclusion compounds have similar structures in which the substrate molecules contact the upper and lower H atoms of the interior of the cavity while their planes are tilted by  $\sim 25^\circ$  with respect to the vertical axis of the  $\beta$ -CD molecule. The complexation energies of arenes obtained by semiempirical methods (see Table 1) fall into the range of experimental  $\Delta H$  values (from 1 to  $-12 \text{ kcal mol}^{-1}$ )<sup>1</sup> for inclusion compounds and clearly demonstrate the ability of an isolated  $\beta$ -CD molecule to form "guest—host" compounds.

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Thus, the results of calculations show that naphthalene molecules are capable of replacing cavity-bound water molecules. The energy gain from the formation of  $\beta$ -CD—naphthalene 2 : 2 inclusion complexes is considerable, and that there is space enough to accommodate a cyclohexane molecule in the cavity of a binary  $\beta$ -CD—naphthalene complex. The first fact indicates a low probability of the presence of cavity-bound water molecules in  $\beta$ -CD—naphthalene complexes. The second fact explains the reason for aggregation of 1 : 1 complexes into 2 : 2 complexes in the absence of cyclohexane,<sup>3</sup> and the third fact illustrates the possibility of the formation of a triple  $\beta$ -CD—naphthalene—cyclohexane complex.

Since cyclohexane is less soluble in water than naphthalene, the addition of the former to an aqueous solution of the latter and  $\beta$ -CD results in cyclohexane association with both a free naphthalene and that located in the cavity of a  $\beta$ -CD molecule, as well as to deterioration of the properties of a water—naphthalene—cyclohexane mixture as solvent for  $\beta$ -CD. As a result, fast precipitation of triple 1 : 1 : 1 complexes out of solution is observed. In these complexes the entire free volume of the cavity is occupied by naphthalene and cyclohexane molecules, which virtually blocks the access of dioxygen to the cavity. The formation of the triple complex prevents the formation of other complex (e.g., 2 : 2) associates. Such a character of the action of cyclohexane is likely due to both lower solubility in water compared to naphthalene and rather high energy of its complexation with  $\beta$ -CD and binary  $\beta$ -CD—naphthalene complex. This follows from both the calculated data and the results of studying the effect of the third components on RTP of  $\alpha$ -bromonaphthalene.<sup>37</sup> Cyclohexanol and 2-methylcyclohexanol, the alcohols characterized by much higher solubility in water and

lower (as more hydrophilic substances) constants of complexation with  $\beta$ -CD as compared with those of cyclohexane, were used as the third components. (The constant of  $\beta$ -CD—cyclohexanol association is  $63.1 \text{ L mol}^{-1}$ ).<sup>27</sup> It turned out that the RTP of  $\alpha$ -bromonaphthalene in the presence of cyclohexane is triply as intense as that observed upon addition of five-fold excess of cyclohexanol or 2-methylcyclohexanol.

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