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Density functional calculations on cyclodextrins

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Abstract Conformations of α-, β-, and γ-*CD*s under anhydrous conditions in the gas phase were investigated by a density functional method, *B3LYP*/6-31G(d,p). These calculations resulted in several symmetric conformations with different energies. The lowest energy conformations contain two rings of homodromic hydrogen bonds and are referred to "*one-gate-closed*" conformations. Different orientations of hydrogen bonds lead to four minima. Other conformational minima were found for "*open*" conformations which correspond to some extent to experimentally determined structures.

Keywords Hydrogen bonding; Conformation; Molecular modeling; Homodromic.

Introduction

Cyclodextrins (*CD*s) are indispensable recipients not only in pharmacy and pharmaceutical technology, but also in many other scientific disciplines, like environmental, technical and analytical chemistry, for stereo-specific separations of diastereomers and optical isomers, extraction of natural products, protection and stabilization of light-, temperature-, or oxidation-sensitive compounds. The reason for this broad field of applications of *CD*s is their ability to form inclusion complexes with small or even medium-sized organic or inorganic compounds. Such an inclusion influences the physico-chemical behavior of the guest molecules, like the reactivity or the solubility significantly. Emulsification of highly apolar compounds, change of the catalytic activities, support in organic syntheses, masking of odor or taste, increase of bioavailability and subsequently higher efficiency of the active substance as a consequence of solubility enhancement, and the permission of controlled release are topics of actual *CD* research.

Steric as well as electronic parameters of both the *CD*s and the guest molecules determine the driving forces of the complexation and the geometries of the inclusion complexes. Also the use of various *CD*s and *CD* derivatives enhances the variability of applications tremendously. Many review articles have been published, which give excellent overviews about a large number of applications and detailed descriptions of molecular properties of *CD*s and *CD* complexes [1–4]. Particularly, as a consequence of the high importance of *CD*s in pharmaceutical applications many extensive reviews have been published [5–13]. Finally, a review emphasizing historical development perspectives of pharmaceutical applications has been presented quite recently [14].

Native *CD*s are obtained by the degradation of starch [$\alpha(1\rightarrow4)$ linked polyglucose] by α-1,4-glucan-glycosyltransferases. Depending on the respective transferase, different types of *CD*s result, consisting of 6 (α-*CD*), 7 (β-*CD*), or 8 (γ-*CD*)

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$\alpha(1\rightarrow4)$ linked glucose units. There also exist larger *CD*s, as δ-, ε-, and ι-*CD*s with 9, 10, and 14 glucose residues. *CD*s with higher degrees of polymerization up to several hundred glycosyl units produced by a number of α-4-glucotransferase have been also described briefly [15–18]. Because of the high ring flexibility and the consequently distorted interior, the importance of these *CD*s is rather low. Modified *CD*s have been synthesized to change their inclusion properties and also to induce biomimetic functions. Random mono- and dimethylation as well as permethylation have been applied widely, leading to an increase of the solubility and to changes of the thermodynamic parameters of host guest association [19]. Other modified *CD* derivatives result from the hydroxypropyl substitution at the positions O6 and O2 [20]. Monosubstitution of *CD*s offers the entrance into a broad field of applications as supramolecular capsules. Entities grafting on one of the *CD* faces are so called ''caps'', whereas caps attached to only one glucose unit are called ''flexible caps'' and in the case of ''rigid caps'' an organic fragment forms a bridge by linking two glucose units at one end of the *CD*. These caps induce significant cavity distortions and therefore have been believed to provide better complementarity between host and guests leading to higher binding constants or higher catalytic reaction rates [21]. The use of *CD*s in nanoparticles for controlled drug release is also of high interest [22–24].

The special structures of *CD*s have been investigated widely, mainly by X-ray crystallography [25–30] and by neutron diffraction [31–34]. In most of these experimentally determined structures water molecules are included, as a consequence of strong hydrogen bonds, which are formed between the hydroxyl groups of the *CD*s rims and the solvent. A few experimental data are available about the structure of *CD*s obtained from more or less anhydrous conditions [35–38].

Crystallographic investigations reveal that the structures of *CD*s seem to be rather rigid, which can be also assumed from the fact that relatively rigid glucose units are joined in a cyclic arrangement. Nevertheless, some flexibility has been postulated for *CD*s as well as for their complexes [39, 40].

The interior of *CD*s is postulated to be hydrophobic to some extent. The inclusion of some compounds with a proton transfer equilibrium by β-*CD* shifts the equilibrium in the same direction as the addition of dioxane to 24% (v/v) [41]. The possibility to form hydrogen bonds is another important driving force for complexation of *CD*s. Hydrogen bonding determines the geometries of *CD*s and their physicochemical properties. Intramolecular hydrogen bonds make the molecules more rigid, and in solution there is a competition between inter- and intramolecular hydrogen bond networks, which is reflected in extraordinary physico-chemical properties. For example, the solubilities of the parent compounds in water are influenced so far that β-*CD* is less soluble than α- and γ-*CD* [42–44], and surprisingly methyl-substituted derivatives. Negative solvation enthalpies result from the competition of intramolecular hydrogen bonds with hydrogen bonds to the solvent [45, 46].

Also the thermodynamical parameters of the complexation reaction depend on the type of *CD*. An example of significant differences is the inclusion reaction of triflumizole to β-*CD* and dimethyl-β-*CD*. Although the complexation constants are similar for both cases, completely different reaction enthalpies are observed [47]. Enthalpy-entropy compensation occurs for β-*CD*, whereas the reaction is mainly entropy-controlled for dimethyl-β-*CD*.

Prediction models for the free energy of complexation of *CD*s reveal that for β-*CD* mainly hydrophobic interactions contribute to the driving forces for the complexation; hydrogen bond dependent descriptors are suggested to play a minor role. For the other *CDs* (α- and γ-*CD*) hydrogen bond donor as well as acceptor properties determine significantly the prediction correlation [48].

As already mentioned, hydrogen bonding in *CD*s has been investigated intensively by various experimental and theoretical methods. Most of the experimentally available structures of *CD*s contain solvent molecules, mainly water; they are therefore unsymmetric and show also intermolecular hydrogen bonds. Not many examples are known for structures of *CD*s under anhydrous conditions. Comparatively few molecular calculations have been performed based on semiempirical [49–51] and more accurate ab initio and density functional theory (DFT) methods [52–54]. In this paper, we describe in continuation of our studies on intramolecular hydrogen bonds in *CD*s [55, 56] a systematic investigation on the structures of α-, β-, and γ-*CD* by a DFT method, *B3LYP*, using 6-31G(d,p) basis set, in order to get more detailed information about the conformational minima and the energy differences between them.

Results and discussion

Homodromic hydrogen bonds

Under symmetric conditions several conformational minima can be found for α-, β-, and γ-*CD* by varying the distances of the oxygen atoms of the primary hydroxyl groups. The resulting energy profiles are given in Fig. 1.

The global minima, the lowest energy conformations (A) are detected at rather close O6–O6′ distances. Two homodromic hydrogen bond rings are formed in these conformations, one very short at the primary hydroxyl groups and another intramolecular hydrogen bond ring include the secondary hydroxyl groups of *CDs*. This "*one-gate-closed*" conformation (A) shows a basket-like shape. The geometry of these conformations of α-, β-, and γ-*CD*s is shown in Fig. 2, where both hydrogen bond rings are given as *van der Waals* balls in gray (primary hydroxyl groups) and black (secondary hydroxyl groups).

The second important conformational minima occur at larger O6–O6′ distances and describe open conformations, which correspond to some extent to structures, which are found experimentally. These open conformations exhibit significantly higher energies than the low-energy conformations A, as a consequence of the missing hydrogen bonds at the primary hydroxyl groups. In these conformations only one hydrogen bond rim built from the secondary hydroxyl groups exists. The conformational minima B (Fig. 2) are rather flat and will not be considered in detail here.

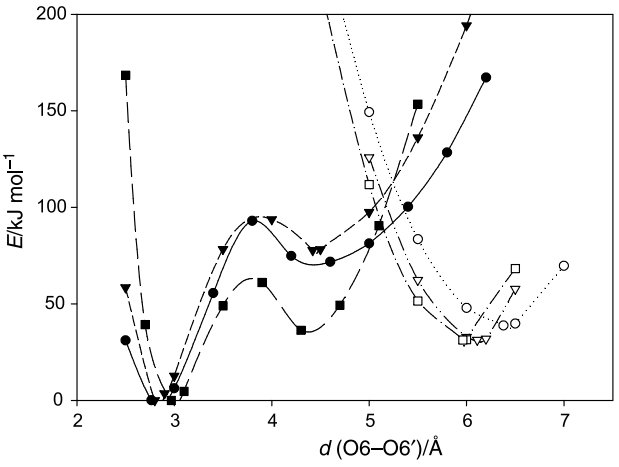

Fig. 1. Energy profiles of the various conformations of α (circle)-, β (triangle)-, and γ (rectangle)-*CD* by varying the distances of the oxygen atoms of the primary hydroxyl groups. Filled and unfilled symbols represent structures according to A and C, respectively

Four orientations of the homodromic hydrogen bond rings are possible, which differ in energy: both hydrogen bond rims orientated counterclockwise (cccc) or clockwise (cwcw) and the primary rim clockwise and the secondary rim counterclockwise (cwcc) and *vice versa* (cccw). For the orientations cccw and cccc the conformational minima B do not exist.

In Table 1, the distances of the heavy atoms of the hydrogen bridges are given for the minima A and C and also possible orientations of the homodromic hydrogen bonds together with some characteristic parameters describing the shape of the *CD*s. Moreover, the relative energies calculated by DFT/6-31G(d,p) are included in the table. The energy of the lower energy conformation is set to zero. For all *CD*s, the conformations A exhibit short distances of the oxygen atoms of the primary hydroxyl groups indicating short and strong hydrogen bonds. A slight increase only of these distances can be observed going from α- to γ-*CD*. No significant differences are found for the various orientations of the hydrogen bonds. In the open conformations C no hydrogen bonds are observable at the primary hydroxyl groups, the distances O6–O6′ depend on the orientation of the hydroxyl groups at these positions. cw orientation is connected with slightly smaller distances throughout. The hydrogen bonds at the second rim, built by the secondary hydroxyl groups, do not show any remarkable changes for all conformations and *CD*s. Somewhat smaller distances can be found for O2–O3′ between conformations A and C.

Comparison with experimental parameters

The comparison to related structural parameters obtained experimentally is given in Table 2a and b.

Three randomly selected crystallographic geometries were considered [34, 57, 58]. As water molecules are included in the crystallographic data and intermolecular hydrogen bonds are formed, the resulting structures are unsymmetric with quite large deviations for the oxygen-oxygen distances. Nevertheless, the mean values of these distances are in relatively good agreement with the calculated structural data of the conformations C (open conformations).

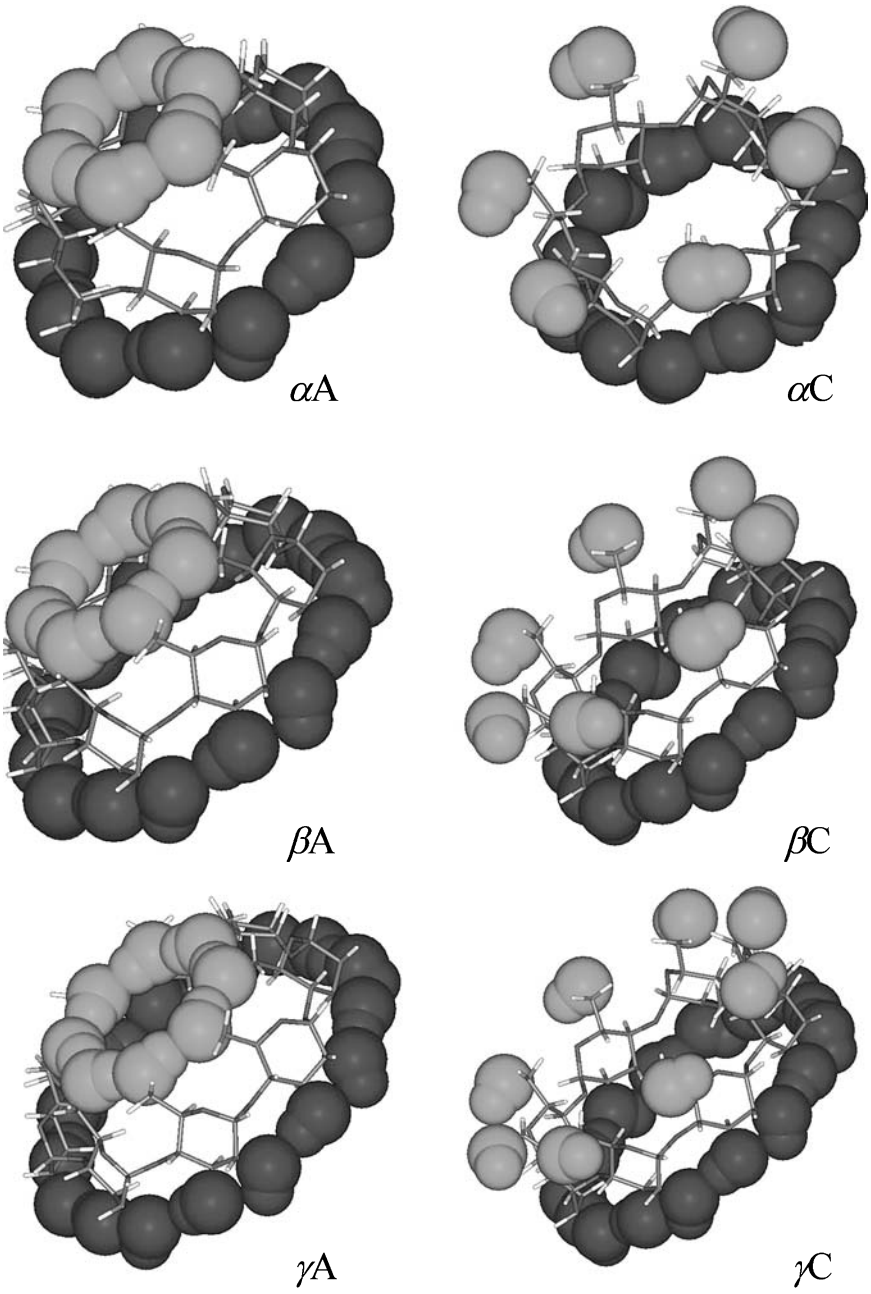

Fig. 2. "*One-gate-closed*" and "*open*" conformations of α-, β-, and γ-*CD*

Connections between the glucose units of CDs

The dependence of the dihedral angles O5–C1–O4′–C4′ on the distances of the oxygen atoms of the primary hydroxyl groups (O6–O6′) is depicted in Fig. 3.

Moreover, the dihedral angles describing the connections between the glucose units of *CD*s (O5–C1–O4′–C4′, O6-C6-C5-C4) are given in Table 3a, b and c. There are evidently differences of these angles between conformations A and C. The torsional angles O5–C1–O4′–C4′ are somewhat larger in conformations C, the torsional angles C1–O4′–C4′–C3′ are here slightly decreased. There is almost no significant influence of the orientation of the homodromic hydrogen bonds on both dihedral angles in conformations A, some influence of the orientation at the rim built from the secondary hydroxyl groups on O5–C1–O4′–C4′ can be observed.

Table 1. Geometry parameters of conformations A and C of α-, β-, and γ-*CD* with various orientations of the hydrogen bond rings. The hydrogen containing heavy atoms distances are given together with the radii of the primary and the secondary hydroxyl groups. τ is the tilt angle, σ is the angle between the plane through equivalent oxygen and the plane through the heavy atoms of the glucose unit (distances/Å, angles/°)

CD	E_{min}	Orientation	O6–O6′	O2–O3	O2–O3′	O3–O3′	rO6	rO3	Δ (rO6–rO3)	τ	σ	E/kJ mol^{-1}
α	A	cccw	2.77	2.86	3.12	5.61	3.19	6.47	0.87	58.5	73.8	0.6
		cccc	2.76	2.89	3.15	5.59	3.19	6.45	0.86	58.4	76.8	0.1
		cwcw	2.78	2.86	3.16	5.65	3.21	6.52	0.87	58.0	72.8	0.1
		cwcc	2.78	2.89	3.18	5.62	3.21	6.49	0.87	58.7	72.5	0.0
	C	cccw	6.38	2.78	2.86	5.22	7.37	6.03	0.81	105.1	85.3	48.4
		cccc	6.37	2.83	2.87	5.14	7.35	5.94	0.80	106.0	85.0	51.0
		cwcw	5.50	2.84	2.99	5.45	6.35	6.29	0.84	90.7	78.5	106.0
		cwcc	5.47	2.89	3.01	5.41	6.30	6.23	0.07	90.8	77.5	110.0
β	A	cccw	2.80	2.86	3.08	5.65	3.23	6.45	3.23	57.3	70.7	0.0
		cccc	2.80	2.89	3.09	5.60	3.23	6.45	3.23	57.2	70.4	0.0
		cwcw	2.82	2.86	3.11	5.68	3.25	6.55	3.30	57.3	69.7	8.8
		cwcc	2.82	2.89	3.12	5.63	3.25	6.49	3.24	57.7	69.7	9.4
	C	cccw	6.11	2.77	2.84	5.25	7.04	6.05	−0.99	101.1	83.5	43.8
		cccc	6.11	2.82	2.85	5.17	7.04	5.96	−1.08	105.8	83.5	44.1
		cwcw	5.33	2.83	2.96	5.48	6.14	6.32	0.17	88.0	76.2	88.7
		cwcc	5.34	2.87	2.96	5.41	6.15	6.23	0.08	89.1	76.2	90.9
γ	A	cccw	2.85	2.87	3.06	5.70	3.73	7.45	1.75	51.4	66.6	0.0
		cccc	2.85	2.9	3.07	5.64	3.73	7.37	1.73	51.9	66.7	0.7
		cwcw	2.88	2.87	3.08	5.72	3.76	7.47	1.75	52.4	66.2	18.4
		cwcc	2.88	2.89	3.09	5.66	3.76	7.40	1.74	52.9	66.4	20.0
	C	cccw	5.96	2.76	2.82	5.26	7.79	6.87	1.61	100.2	82.7	31.3
		cccc	5.97	2.8	2.83	5.16	7.80	6.74	1.58	101.9	82.6	28.4
		cwcw	5.26	2.82	2.91	5.47	6.87	7.14	1.68	87.0	75.2	64.8

Table 2a. Oxygen-oxygen distances of three examples of crystal structures for α-, β-, and γ-*CD*. The related calculated parameters are given (distances/Å, angles/°)

CD	Struct. param.	1	2	3	4	5	6	7	8
α	O6–O6′	4.67	6.01	5.35	5.74	4.96	6.06	–	–
	O2–O3	2.94	2.88	2.92	2.88	2.91	2.86	–	–
	O2–O3′	2.95	3.01	2.82	3.37	4.21	3.02	–	–
	O3–O3′	5.50	5.60	5.20	6.02	6.16	5.59	–	–
	τ	122.00	92.90	89.80	89.50	125.10	74.10	–	–
	σ	112.12	98.59	99.14	104.53	132.52	99.35	–	–
β	O6–O6′	3.82	5.20	6.26	4.67	5.80	5.85	6.09	–
	O2–O3	2.92	2.91	2.90	2.87	2.86	2.92	2.89	–
	O2–O3′	2.96	2.96	2.86	2.77	2.78	2.90	2.88	–
	O3–O3′	5.42	5.30	5.58	5.62	5.69	5.75	5.70	–
	τ	113.97	109.04	77.41	114.88	92.26	75.63	78.14	–
	σ	111.00	106.20	85.00	102.00	103.00	97.50	95.00	–
	σ lit	112.30	106.50	85.30	103.60	103.50	92.20	94.90	–
γ	O6–O6′	5.11	5.55	5.89	6.01	4.06	5.31	6.09	3.93
	O2–O3	2.92	2.91	2.85	2.92	2.84	2.89	2.90	2.86
	O2–O3′	2.91	2.78	2.77	2.83	2.81	2.84	2.77	2.88
	O3–O3′	5.50	5.57	5.04	5.58	5.31	5.47	5.45	5.47
	τ	116.50	74.90	91.00	86.10	115.50	90.80	80.20	113.90
	σ	108.31	90.69	111.62	95.56	107.56	103.94	101.13	112.53

Table 2b. Mean values of three examples of crystal structures for α-, β-, and γ-*CD* of oxygen-oxygen distances have been determined and compared to the values of the symmetric conformations (distances/Å, angles/°)

CD	Structural parameters	Mean value	sym A (cccw)	sym C (cccw)
α	O6-O6′	5.47	2.77	6.38
	O2-O3	2.90	2.86	2.78
	O2-O3′	3.23	2.86	2.86
	O3-O3′	5.68	5.61	5.22
	τ	98.90	121.50	74.94
	σ	107.72	106.19	94.75
β	O6-O6′	5.38	2.80	6.11
	O2-O3	2.90	2.86	2.77
	O2-O3′	2.87	3.08	2.84
	O3-O3′	5.58	5.60	5.25
	τ	86.98	122.81	78.83
	σ	99.67	109.28	96.53
	σ lit	99.76		
γ	O6-O6′	5.24	2.85	5.96
	O2-O3	2.89	2.87	2.76
	O2-O3′	2.82	3.06	2.82
	O3-O3′	5.42	3.73	5.26
	τ	96.11	128.57	79.79
	σ	103.92	113.45	97.30

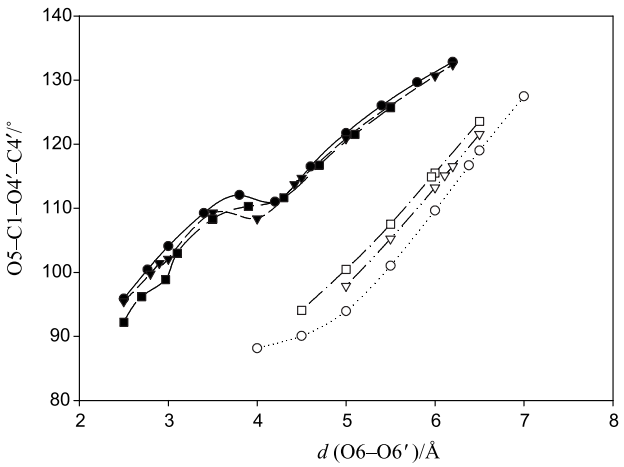

Fig. 3. Dependence of the dihedral angle O5-C1-O4′-C4′ on the O6–O6′ distance for various conformations of α (circle)-, β (triangle)-, and γ (rectangle)-*CD*. Filled and unfilled symbols represent minima A and C

A graphical presentation of the dihedral angles of the bonds connecting the glucose units is given in Fig. 4, together with averaged values from some selected crystal structures.

All dihedral angles can be found in a rather limited range, as larger deviations lead to an increase of energy caused by steric repulsion. The "*one-gate-closed*" conformations occur somewhat separated at lower values of O5–C1–O4′–C4′. The values for the "*open*" conformations vary according to the orientation of the hydrogen bonds, and they are close to the averaged experimental values throughout.

Table 3a. Dihedral angles of α-, β-, and γ-*CD* describing the connection between the glucose units (angles/°)

CD	Conformational minima	orientation	O5–C1–O4′–C4′	C1–O4′–C4′–C3′
α	A	cccw	100.4	132.7
		cccc	99.8	135.6
		cwcw	99.0	133.8
		cwcc	99.0	136.4
	C	cccw	116.7	123.1
		cccc	115.7	126.0
		cwcw	107.2	127.5
		cwcc	105.8	130.6
β	A	cccw	99.8	131.1
		cccc	100	133.5
		cwcw	98.9	132.0
		cwcc	99.3	134.3
	C	cccw	115.1	124.1
		cccc	114.5	126.7
		cwcw	106.7	127.0
		cwcc	106.5	129.3
γ	A	cccw	98.9	130.1
		cccc	99.3	132.4
		cwcw	98.5	130.7
		cwcc	99.0	133.0
	C	cccw	114.9	124.1
		cccc	114.7	126.7
		cwcw	107.6	125.6
		cwcc	107.2	128.1

Comparison of the glycosidic angles

Due to the structure of the cyclic systems (six-membered glucose units) no pronounced changes of the dihedral angles inside the rings are possible as no inversion of the rings can be performed within the frame of the macrocyclic systems. In Table 3a, the dihedral angles describing the conformations of the glucose units are given.

Surprisingly, there are some significant differences between the values for conformations A and C, particularly for the torsional angles C3–C4–C5–O5 and C4–C5–O5–C1. Moreover, some limited distortions of the glucose units can be found for the different *CD*s. Somewhat smaller changes of these

Table 3b. Dihedral angles of α-, β-, and γ-*CD* describing the orientation of the primary hydroxyl groups substituent (angles/°)

CD	Conformational minima	Orientation	H6–O6–C6–C5	O6–C6–C5–C4	H3–O3–C3–C2	H2–O2–C2–C1
α	A	cccw	−57.0	−127.4	176.9	−167.7
		cccc	−56.7	−128.6	−48.0	−35.9
		cwcw	107.9	−142.6	177.0	−168.0
		cwcc	108.4	−143.2	−47.8	−35.5
	C	cccw	56.4	61.7	174.7	−165.6
		cccc	56.7	61.4	−44.7	−39.1
		cwcw	−93.0	23.8	176.3	−167.6
		cwcc	−95.9	26.1	−47.1	−36.7
β	A	cccw	−61.9	−122.5	174.0	−169.3
		cccc	−61.7	−123	−48.1	−34.4
		cwcw	111.6	−139.2	174.3	−169.6
		cwcc	112.3	−139.6	−48.1	−34.0
	C	cccw	56.6	61.2	170.6	−166.5
		cccc	56.9	60.9	−44.0	−38.3
		cwcw	−95.6	31.0	172.9	−169.0
		cwcc	−97.6	32.0	−46.5	−35.8
γ	A	cccw	−65.2	−119.2	171.8	−170.7
		cccc	−65.0	−119.4	−48.7	−33.0
		cwcw	114.8	−136.6	172.2	−171.1
		cwcc	115.6	−136.9	−48.5	−32.6
	C	cccw	56.7	60.8	167.4	−166.9
		cccc	56.8	60.5	−42.9	−37.9
		cwcw	−96.1	34.0	170.3	−170.0
		cwcc	−98.7	35.6	−46.1	−35.0

Table 3c. Dihedral angles of α-, β-, and γ-*CD* describing the conformation of the glucose subunits (angles/°)

CD	Conformational minima	Orientation	C2–C3–C4–C5	C3–C4–C5–O5	C4–C5–O5–C1	C5–O5–C1–C2
α	A	cccw	52.1	−55.6	63.4	−64.0
		cccc	53.1	−55.6	62.2	−62.3
		cwcw	52.3	−55.5	63.2	−63.6
		cwcc	53.1	−55.6	62.2	−62.1
	C	cccw	49.2	−48.7	56.8	−61.7
		cccc	51.3	−48.9	55.3	−60.6
		cwcw	51.2	−54.3	62.0	−64.0
		cwcc	52.8	−54.8	61.1	−62.9
β	A	cccw	54.5	−59.6	65.5	−62.8
		cccc	55.9	−59.8	64.4	−61.4
		cwcw	54.7	−59.4	65.2	−62.2
		cwcc	56.0	−59.6	64.1	−60.8
	C	cccw	52.4	−52.0	57.2	−59.2
		cccc	54.6	−52.0	55.5	−58.1
		cwcw	53.8	−57.5	63.0	−62.0
		cwcc	55.6	−57.8	61.8	−61.0
γ	A	cccw	56.3	−62.6	67.0	−61.7
		cccc	57.8	−62.9	65.8	−60.4
		cwcw	56.3	−62.2	66.4	−60.9
		cwcc	57.9	−62.5	65.3	−59.7
	C	cccw	54.7	−53.4	57.0	−57.0
		cccc	57.0	−53.8	55.0	−55.9
		cwcw	55.5	−59.5	63.2	−60.4
		cwcc	57.5	−59.7	61.9	−59.4

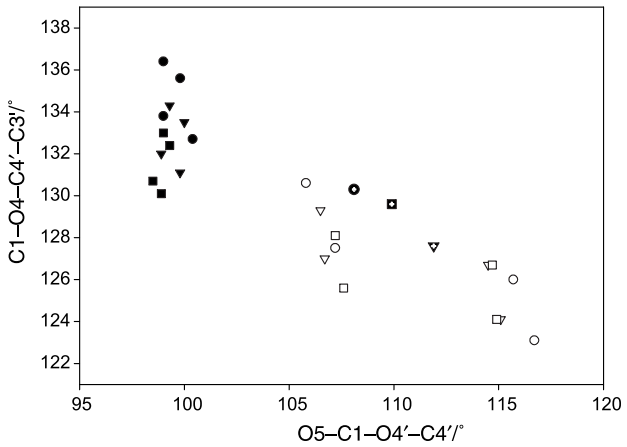

Fig. 4. Plot of the dihedral angle O5–C1–O4′–C4′ against C1–O4′–C4′–C3′ for α (circle)-, β (triangle)-, and γ (rectangle)-*CD*. Filled and unfilled symbols represent minima A and C. Specially marked symbols for the averaged values of the experimental structures

dihedral angles occur for the different orientations for the hydrogen bonds.

Summarizing, *B3LYP*/6-31G(d,p) calculations have been performed on natural α-, β-, and γ-*CD* in the gas phase applying C_n symmetry. Generally, two pronounced energy minimum conformations were detected by varying the oxygen-oxygen distances of the primary hydroxyl groups (O6–O6′). The lowest energy conformations correspond to ''*one-gate-closed*'' structures, characterized by two intramolecular hydrogen bond rings. The hydrogen bond lengths are very close to that found for open chains of water and alcohols. There is no experimental evidence for such conformations, in contrary to the second minima (''*open*'' conformations) of higher energy, which show similarities to geometries of experimentally obtained structures. According to the orientation of the homodromic hydrogen bonds, four different conformations are found for each geometry (see also Table 3b) with different energies as a consequence of the hydrogen bonds and the chirality of the glucose units.

Methods of calculation

Systematic *B3LYP* calculations with 6-31G(d,p) basis set on anhydrous α-, β-, and γ-*CD*s have been applied. Imposing C_n symmetry throughout, the oxygen-oxygen distances were scanned and full geometry optimizations of all remaining geometry parameters were then performed, using the program package Gaussian03 [59]. By subsequent frequency calculations, it was verified that the calculated geometries are indeed minima on the potential energy surface.

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