

Homodromic hydrogen bonds in low-energy conformations of single molecule cyclodextrins

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Abstract Low-energy conformations of β -cyclodextrin under anhydrous conditions in the gas phase were investigated by DFT calculations. In these conformations, two homodromic hydrogen bond rings are formed with very short hydrogen bonds at the narrow side of the cyclodextrin ring and a second one at the wider side. These hypothetical conformations are not comparable to those conformations, which have been studied experimentally, forming inclusion complexes with small and medium-sized guest molecules, but their energy is significantly lower than the open conformations ($\Delta E = 10$ kcal/mol).

Keywords Cyclodextrin · ab initio · Density functional calculations · Homodromic hydrogen bonds

Introduction

Hydrogen bonding is very important for the structure of cyclodextrin and cyclodextrin complexes. Particularly, crystal structures of β -CD exhibit a number of O-H \cdots O hydrogen bonds between the three different hydroxyl groups and water molecules, which were investigated by X-ray crystallography and by neutron diffraction [1–6].

In addition to intermolecular hydrogen bonds, intramolecular hydrogen bonds are formed between the secondary hydroxyl groups of the glucose units to the adjacent units. These intramolecular hydrogen bonds stabilize the macrocyclic conformation of β -CD, increase the rigidity of the molecule and lead in this special case to a reduced solubility of the compound in comparison to other CDs, with a smaller or larger number of glucose units, and also to substituted derivatives.

The application of ab initio and DFT calculations was limited in the past by the size of the molecular system. Numerous theoretical studies were performed on the structure of CDs and CD complexes, based on semiempirical quantum chemical methods [7]. Accurate molecular calculations were performed only for smaller systems like glucose dimers [8–11]. For the structure of CDs only a few papers were published, comparing empirical, semiempirical and low-level ab initio methods (HF/3-21G), concluding that Molecular Mechanics is the most convenient method to describe structural features of CDs, followed by the ab initio method [12]. Some recent investigations were performed using DFT methods [13].

In the present paper, we describe the gas phase structures of β -CD as obtained from ab initio (HF/3-21G and HF/6-31G(d,p)) as well as DFT (B3LYP/6-31G(d,p)) calculations, in order to get some insight into the intramolecular hydrogen bond network of this molecule.

Methods of calculation

C7 symmetry was forced by building up the Z-matrix starting from the oxygen-oxygen distances at the more

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narrow rim of the β -CD moiety. HF/3-21G and HF/6-31G(d,p), as well as B3LYP/6-31G(d,p) were used for full geometry optimisation. The calculations were performed, using the program package GAUSSIAN03 [14] on the Schrödinger III cluster of the University of Vienna. Scanning of the oxygen-oxygen distance was done in order to obtain the structures of minimum energies.

Results and discussion

X-ray crystals of CDs and CD complexes are grown from aqueous solution and also most of the equilibrium constants and the related thermodynamic parameters were obtained from solution of pure water or water co-solvent mixtures. Only a very few examples are known for CD-guest complexation in non-aqueous conditions [15, 16].

In order to investigate the conformational behaviour of CDs, we have analysed the gas phase conformations of β -CD under symmetric conditions (C7) by a systematic scan of the oxygen-oxygen distance of the O6 hydroxyl groups. Three conformational minima were found.

The energies of the minimum conformations are given in Table 1, together with selected structural parameters.

The lowest energy minimum (HF/3-21G and B3LYP/6-31G(d,p)) was found for a rather short O6-O6 distance, a second less pronounced at a slightly elongated distance, a third minimum at a distance around 6.5 Å, which is similar to the experimentally (X-ray crystallographic) determined structure.

Although all methods used describe a very similar geometry, the energy differences between the obtained minima vary drastically. Even the energy ranking is described differently by HF/6-31G(d,p), whereas HF/3-21G and B3LYP/6-31G(d,p) calculations lead to the same ranking. The reason for these discrepancies is that hydrogen bonding superimposed by quite subtle steric interactions determines the geometry of the molecule. A higher-level DFT method is therefore necessary to describe the geometries sufficiently well, and this method will be used for further considerations.

Table 1 Calculated energies of three symmetric β -CD conformations, relative to the energy of conformation A

	Energy values (kcal mol ⁻¹)		
	HF/3-21G	HF/6-31G(d,p)	B3LYP/6-31G(d,p)
A	0.0	0.0	0.0
B	43.4	10.6	18.6
C	24.1	-0.6	10.5

The geometries of the three symmetric conformations are depicted in Fig. 1. The top view shows that the lowest energy minimum (A), which is 10 kcal/mol more stable than the second one (C), possesses a very narrow rim at the upper side of the β -CD ring. Both other conformations are somewhat more open, and differ in the arrangement of the glucose units. Some selected structural parameters are given in Table 2 including the numbering of the atoms for one glucose unit in the adjacent scheme. Scheme 1

Table 2 is divided into four groups of structural parameters. In the first three rows, the distances between oxygen atoms are reported, which are involved in hydrogen bonding contacts at least in one conformation. Strong hydrogen bonds exist in conformation A within the ring built up from oxygens 6 (O6). This distance is very close to those found for hydrogen bond networks in open chains and cyclic polymers of water and alcohols [17]. Also the valence angle of the hydrogen bond is rather close to the optimal value of 180°. A second hydrogen bond system occurs between oxygens O2 and O3. These interactions are somewhat weaker, as the heavy atom distance is longer and also the valence angle is less favourable. The shortest distance exhibits conformation C. The third distance

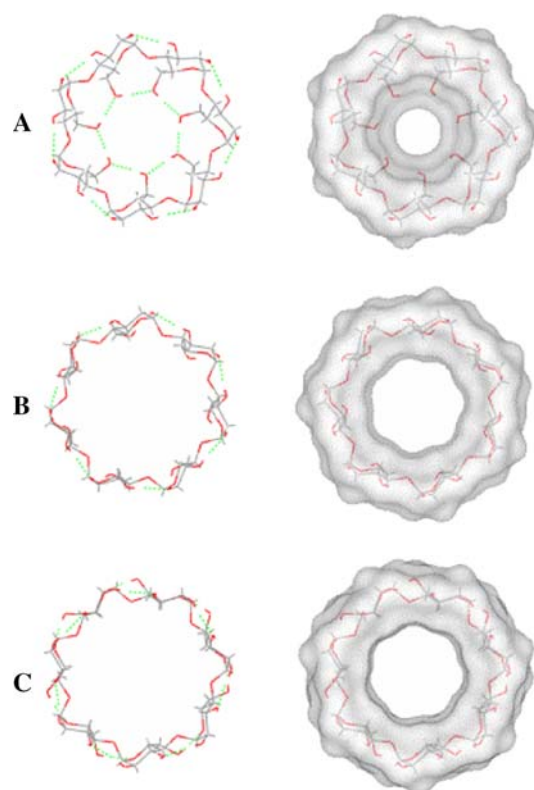
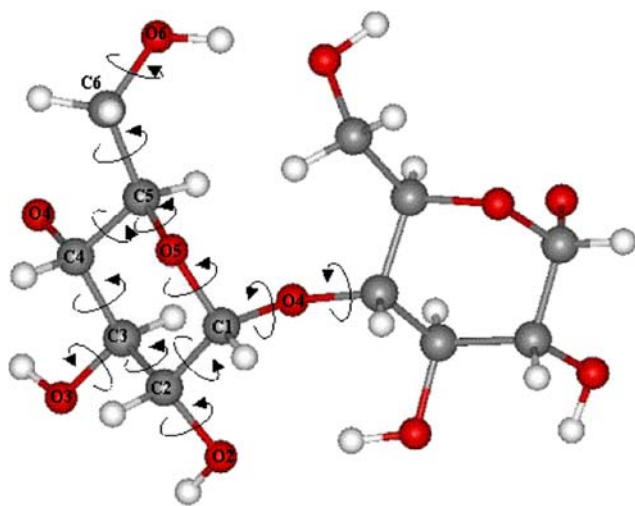


Fig. 1 Top-view of the symmetric conformations of β -CD (A, B, and C). On the left side stick presentation, including hydrogen bonds, on the right side the molecular surfaces

Table 2 Structural parameters of three symmetrical conformational minima of β -CD as obtained from B3LYP/6-31G(d,p) calculations. Distances in Å, torsional angles in degrees

Structural parameters			
	A	B	C
Distance O6-O6'	2.80 (173.7)	4.24	6.11
Distance O3-O2'	3.08 (163.5)	2.84 (164.0)	2.84 (164.4)
Distance O2-O3'	2.86 (108.8)	2.78 (111.7)	2.77 (112.0)
Orientation of hydroxyl groups			
H6-O6-C6-C5	-61.9	-56.7	56.6
C4-C3-O3-H3	52.3	52.4	50.1
C3-C2-O2-H2	-46.7	-43.6	-43.6
Outer-ring connections			
O6-C6-C5-C4	-122.5	174.5	61.2
C2-C1-O4-C4'	-138.7	-124.1	-124.1
C1-O4-C4'-C3'	131.1	122.9	124.1
Connections in the glucose units			
C6-C5-C4-C3	180.0	-172.7	-169.0
C5-C4-C3-C2	54.6	52.4	52.4
C4-C3-C2-C1	-50.5	-52.9	-54.9
C3-C2-C1-O5	53.4	56.0	56.8
C2-C1-O5-C5	-62.8	-62.4	-59.2
C1-O5-C5-C4	65.5	62.1	57.2

**Scheme 1**

(O2-O3) describes a very weak hydrogen bond contact for all conformations. The orientation of the hydroxyl groups is identical for all conformations except for the dihedral angle O6-C6-C5-C4 (third group in the table).

Surprisingly small changes occur at the bonds connecting the glucose rings together, only the above-mentioned orientation of the $-\text{CH}_2\text{OH}$ group changes completely. Remarkably, some distortions of the glucose rings can be observed for the different conformations.

Because of the co-operativity of the homodromic hydrogen bonds at the upper and the lower side of the

Table 3 Calculated energies of the conformers derived from conformation A. Conformation A1 is taken as reference

Conformations	Energy values (kcal mol ⁻¹)
A1	0.00
A2	2.15
A3	0.04
A4	2.30

β -CD ring, four conformations of A with different energies are possible as a consequence of the chirality of the glucose rings. For conformation A these energies are given in Table 3.

The top view of the molecule (Fig. 1) indicates, that the strong hydrogen bonds at the smaller rim of β -CD are oriented counter clockwise, whereas the more extended ring is oriented clockwise. This conformation shows the lowest conformational energy (A1, reference in Table 3). Flipping of the orientation of the hydrogen bonds at the larger ring has almost no influence on the energy and enhances the energy value only slightly (conformation A3). Reorientation of the ring of the strong hydrogen bonds leads to a significant increase of the energy (2.15 kcal mol⁻¹ for the clockwise orientation of the larger ring (A2) and 2.30 kcal mol⁻¹) for the counterclockwise one (A4).

Discussion

Three gas phase conformations of β -CD were found with C_7 symmetry, which differ significantly in their energy, obtained from B3LYP/6-31G(d,p) calculations. The lowest-energy conformation is characterized by a surprisingly tight ring at one side of the CDs ring. This shape is not comparable to the structures found experimentally. A ring of homodromic hydrogen bonds was found in this conformation, with hydrogen bonds very close to ideal hydrogen bridge geometries obtained in open chains of cyclic clusters of water or alcohols. The chirality of the glucose units of β -CD induces energy differences between geometries with different orientation of the co-operativity of hydrogen bonds.

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