Hartree−Fock and Density Functional Theory Study of α-Cyclodextrin Conformers

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Herein, we report the geometry optimization of four conformers of α-cyclodextrin (α-CD) by means of PM3, HF/STO-3G, HF/3-21G, HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) calculations. The analysis of several geometrical parameters indicates that all conformers possess bond lengths, angles, and dihedrals that agree fairly well with the crystalline structure of α-CD. However, only three of them (**1**−**3**) resemble the polar character of CDs and show intramolecular hydrogen-bonding patterns that agree with experimental NMR data. Among them, conformer **3** appears to be the most stable species both in the gas phase and in solution; therefore, it is expected to be the most suitable representative structure for α-CD conformation. The purpose of selecting such a species is to identify an appropriate structure to be employed as a starting point for reliable computational studies on complexation phenomena. Our results indicate that the choice of a particular α-CD conformer should affect the results of ab initio computational studies on the inclusion complexation with this cyclodextrin since both the direction and the magnitude of the dipole moment depend strongly on the conformation of α-CD.

Introduction

Cyclodextrins (CDs) are cyclic oligomers of α-D-glucose formed by the action of certain enzymes on starch. These compounds form a hydrophobic cavity and are able to embed a large variety of organic and inorganic molecules of the appropriate size. Cyclodextrins have been the subject of extensive experimental and theoretical research due to their ability to form inclusion complexes. The most employed and widely known CDs are those composed by six, seven, and eight glucopyranose residues, known as α-, *β*-, and *γ*-cyclodextrin, respectively.[1−4] Among them, α-CD has received major attention due to its capability to form inclusion complexes with the most common organic compounds (Figure 1).[5,6]

In the past two decades, computational methods have provided useful tools for the understanding and rationalization of CD chemistry.[7] Indeed, extensive progress has been made in the use of molecular mechanics (MM) and molecular dynamics (MD) techniques in the study of CDs and their inclusion complexes.[7−10] Although these methods have the advantage of being less resource demanding, they lack a representation of electron density, missing many chemically important quantum based effects.[11,12] In recent years, quantum chemical calculations at the semiempirical level have become affordable for the study of CDs and their inclusion complexes.[13] Semiempirical methods employ approximations that accelerate the solution of the Roothan−Hall equations; thus, they are quantum mechanical in nature and improve the description of quantum phenomena over MM techniques.[14] However, the precision of semiempirical methods is limited in nature since they are parametrized to reproduce experimental observables for a large number of molecules and can fail when treating systems that were not considered in the initial parametrization procedure. Diverse semiempirical methods, such as CNDO,[15] AM1,[16] and PM3,[17] have been employed in the study of CDs and their inclusion compounds. Chujo et al.[18] were pioneers in the application of CNDO method to CD chemistry, finding large dipole moments for α-CD and *β*-CD and proposing that the antiparallel orientation of host and guest dipoles is responsible for the stabilization of inclusion complexes. Since 1995, several authors have employed AM1 and PM3 techniques to the study of CDs. From the work of Bodor and Buchwald,[19] Avakyan et al.,[20] and in particular from the contributions of Liu et al.,[21−24] it has been stated that PM3 has a better performance in the CD geometry optimization since it can deal with intramolecular hydrogen bonds better than AM1, reproducing rather superior CD crystalline structures.

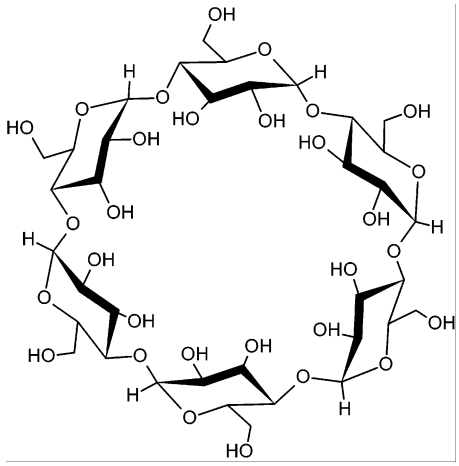

Figure 1. α-Cyclodextrin structure.

Because of the large size and conformational freedom of CDs, the use of ab initio methods is quite problematic, even when symmetry conditions are imposed.[7] Moreover, ab initio computational calculations are often performed in the gas phase, neglecting the effect of aqueous media where almost all complexation processes take place. Despite these restrictions, recently reported approaches have dealt with the use of ab initio methods in the study of CDs and their inclusion compounds.

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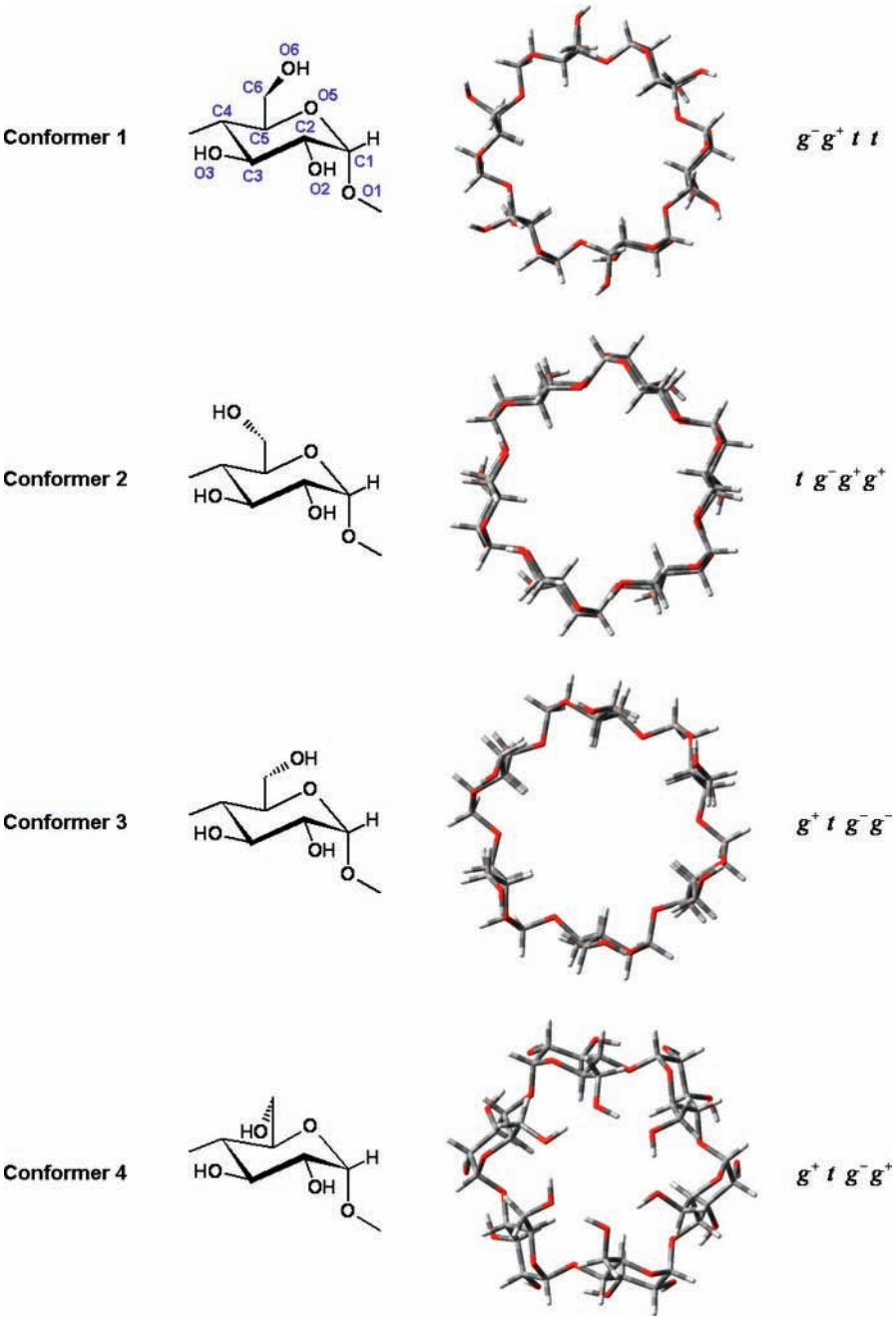

Figure 2. Minimum energy conformers of α-cyclodextrin, obtained at the B3LYP/6-31G(d) level.

The first systematic ab initio study on CDs was performed by Liu et al.[25] in 2000, who employed single point calculations on crystalline and PM3 optimized structures of α-CD and *β*-CD. Using a number of HF and DFT techniques, they found that PM3 structures have lower energies than the crystalline structures and that all CDs have large dipole moments. In 2004, De Almeida et al.[26] reported theoretical studies on α-CD hexahydrate and α-CD dimer employing the B3LYP/6-31G(d,p)//PM3 calculations. In addition, Dos Santos et al.[27] reported a comparative study among molecular mechanics MM2, semiempirical PM3, and ab initio HF/3-21G(d) methods to analyze the optimized geometries of α-CD and *β*-CD. Recently, Pinjari et al.[28] have reported electrostatic potentials and the geometry optimization of α-CD, *β*-CD, and *γ*-CD at the B3LYP/6-31G(d) level. Thus far, ab initio studies on CDs have been based on the study of single structures, and no further information has been attained to describe the effect of the conformation over electronic and electrostatic properties of CDs. In addition, no information has been provided about the reliability of optimized geometries of CDs to employ them as starting points for further computational modeling of CDs and their inclusion complexes.

The large conformational freedom of CDs makes it difficult to identify one single structure that provides a realistic view about CDs' conformations. As part of our systematic computational study of CDs, herein we propose to take into account both theoretical and experimental information to select representative structures for α-CD among its most stable conformations both in gas and in solution phases. The geometry optimization of α-CD lead to four minimum energy conformers at the PM3, HF/STO-3G, HF/3-21G, HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels. These structures were employed in solution-phase calculations with the PCM method at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of theory.

TABLE 1: Average Values and Standard Deviations of Exocyclic Dihedral Angles Calculated at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) Levels for Optimized Conformers of α-CD

		exocyclic dihedral (deg)											
		O6−C6−C5−O5			O6−C6−C5−C4			O6−C6−C5−H5			H6−O6−C6−C5		
conformer		HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP
1	g^-g^+tt	−68.8 (0.0)	−69.1 (0.1)	−69.1 (0.5)	53.8 (0.0)	54.1 (0.1)	54.0 (0.5)	173.2 (0.0)	173.2 (0.2)	173.0 (0.5)	−171.5 (0.0)	−169.6 (0.1)	−168.7 (0.2)
2	$tg^-g^+g^+$	165.8 (0.0)	166.1 (0.1)	166.3 (0.5)	−74.5 (0.0)	−73.8 (0.1)	−73.6 (0.4)	48.6 (0.0)	49.3 (0.1)	49.5 (0.5)	70.9 (0.0)	70.5 (0.1)	70.7 (0.3)
3	$g^+tg^-g^-$	56.9 (0.0)	54.6 (0.1)	54.7 (0.2)	177.2 (0.0)	175.2 (0.0)	175.2 (0.3)	−60.7 (0.0)	−62.0 (0.1)	62.0 (0.2)	−60.8 (0.0)	−55.8 (0.1)	55.7 (0.1)
4	$g^+tg^-g^+$	93.4 (0.0)	95.7 (0.1)	96.3 (0.0)	−146.0 (0.0)	−143.1 (0.1)	−142.5 (0.0)	−24.9 (0.0)	−22.2 (0.1)	21.5 (0.0)	110.6 (0.0)	108.3 (0.1)	107.9 (0.1)

Figure 3. Labels assigned to glucopyranose units in α-cyclodextrin. Ψ and Φ are the glycosidic torsions.

Computational Aspects

The α-CD structure was built from X-ray data and was fully optimized at the PM3 level without any symmetry restriction.[33] The PM3 optimized geometry was employed to perform a conformational search, where the orientation of primary hydroxyl groups was sequentially modified in 12 steps of 30°, allowing us to identify four minimum energy conformers for α-CD. These four minimum energy conformers were fully optimized at the HF/STO-3G, HF/3-21G, HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of theory. In addition, PCM[34] solvation calculations at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels were performed over gas-phase optimized structures to account for solvation effects on the relative stability of the α-CD conformers.

Each conformer was characterized by the relative orientation of the primary hydroxyl groups in glucopyranose units. In addition, several geometrical and energetic parameters were calculated to compare the optimized α-CD conformers with the experimental information available for the α-CD structure. All parameters are reported as average values calculated from those determined in each glucopyranose residue. Also, standard deviations are provided to account for the regularity of the geometric parameters along the macrocycle. All calculations were performed with the Gaussian 94 package of programs.[35]

Results and Discussion

Conformational Analysis of α-CD Optimized Conformers. The conformational search at the PM3 level lead us to four minimum energy α-CD conformers, named **1**−**4**. These structures were reoptimized at the HF/STO-3G, HF/3-21G, HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of theory. Figure 2 shows the optimized structures at the B3LYP/6-31G(d) level. The other methods lead to analogous conformations.

According to Figure 2, all conformers appear to be highly symmetric and preserve an overall circular shape. The differences among them arise mainly from the internal rotation of the primary hydroxyl groups within the glucopyranose residues. These rotamers also differ in the relative orientation of the glucopyranose units with respect to the mean plane described by the anomeric oxygen atoms. As can be seen in Figure 2, the glucopyranose units in conformer **4** are slanted, whereas in conformers **1**−**3**, these monomeric units are almost perpendicular to the O anomeric mean plane.

The relative orientation of the primary hydroxyl groups in each α-CD conformer was characterized by means of several exocyclic torsional angles—customarily employed in carbohy-

TABLE 2: Average Values and Standard Deviations of Glycosidic Torsions (Ψ and Φ), Tilt Angles (τ), Interanomeric Angles (ω), and Interanomeric Dihedrals (Ω) Calculated for Optimized Conformers of α-CD at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) Levels

	conformer **1**			conformer **2**			conformer **3**			conformer **4**		
	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP
ψ	66.7 (0.0)	63.0 (0.0)	63.1 (0.3)	65.5 (0.0)	66.5 (0.0)	66.6 (0.1)	65.9 (0.0)	64.8 (0.0)	65.1 (0.0)	79.0 (0.0)	80.9 (0.0)	80.6 (0.0)
ϕ	126.5 (0.0)	123.5 (0.0)	123.9 (0.5)	122.9 (0.0)	123.2 (0.0)	123.2 (0.1)	124.4 (0.0)	122.5 (0.0)	122.8 (0.1)	133.1 (0.0)	133.7 (0.0)	133.5 (0.1)
τ	83.0 (0.0)	81.5 (0.0)	81.3 (0.0)	84.3 (0.0)	82.3 (0.0)	82.5 (0.0)	83.2 (0.0)	81.3 (0.0)	81.5 (0.0)	74.1 (0.0)	74.0 (0.0)	74.3 (0.0)
ω	120.0 (0.0)	120.0 (0.1)	120.0 (0.2)	120.0 (0.0)	120.0 (0.1)	120.0 (0.2)	120.0 (0.0)	120.0 (0.1)	120.0 (0.0)	120.0 (0.0)	120.0 (0.1)	120.0 (0.0)
Ω	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

drate conformational analysis—that have been measured and reported in Table 1.[36,37] The values of the selected dihedrals shown in Figure 3 (O6−C6−C5−O5, O6−C6−C5−C4, O6−C6−C5−H5, and H6−O6−C6−C5) are related to different designations according to the usual notation:[38] 0−120° (g^+), 120−240° (t), and 240−360° (g^-).

The calculated average values and standard deviations of the selected exocyclic torsions (Table 1) reveal that conformers **1**−**3** possess analogous structures to the most stable conformations of isolated glucopyranose.[38] In conformers **1** and **3**, primary hydroxyls are gauche with respect to the O5 in the glucopyranosilic ring (g^- and g^+, respectively), whereas in conformer **2**, the hydroxyl groups adopt a trans configuration with respect to O5. On the other hand, the corresponding exocyclic torsions of conformer **4** do not match with any minimum energy conformer of isolated glucopyranose.[38] Just as in conformer **3**, the primary hydroxyl groups in conformer **4** are g^+ with respect to O5, t with respect to C4, and g^- with respect to H5. However, the dihedral O6−C6−C5−H5 is close to −25°, describing a nearly eclipsed conformation, which is not expected to be stable for isolated glucopyranose. In addition, O6−C6−C5−O5 defines a dihedral angle close to +90°.

On the other hand, the relative orientation of the glucopyranose residues in the macrocycle has been described by calculating the average glycosidic torsions (Ψ and Φ) and tilt angles (τ) for each optimized conformer of α-CD (Table 2). Ψ and Φ define the mutual orientation of adjacent glucopyranose units in CDs as shown in Figure 3. The calculated average values of Ψ and Φ show that conformers **1**−**3** possess cylinder-like structures, whereas conformer **4** has a cone-like shape, possessing a narrower end in its primary side. In addition, the tilt angle τ reflects the orientation of the mean plane of glucopyranosilic rings with respect to the plane formed by the anomeric oxygen atoms. The calculated τ values are consistent with the cylinder-like shape for conformers **1**−**3** since their tilt angles are close to 90°. On the other hand, conformer **4** shows larger deviations of τ from 90°, which is in agreement with its cone-like shape. Experimental reports on the structure of crystalline α-CD do not provide unequivocal values for the corresponding glycosidic torsions (Ψ and Φ) and tilt angles (τ) since the crystalline form shows significant deviations in the mutual orientation of glucopyranose units along the macrocyclic structure. Therefore, we have not compared the calculated values of Ψ, Φ, and τ with those reported from X-ray data.

To account for the symmetry and circular shape of the optimized α-CD conformers, the relative position of the anomeric oxygen atoms in the macrocycle was analyzed by means of calculating the average angles (ω) and dihedrals (Ω) formed by three and four adjacent anomeric oxygen atoms in the α-CD structure, respectively. In a totally symmetric α-CD structure, the angles formed by three adjacent anomeric oxygen atoms (ω) should be 120°. The closer ω is to this referential value, the higher the symmetry of the optimized α-CD will be. In addition, symmetric conformations of α-CD are characterized by the coplanarity of the anomeric oxygen atoms. This property can be easily verified by measuring the average dihedral angle formed by four adjacent anomeric O atoms (Ω) in a determined α-CD conformation. Table 2 contains the calculated average values of ω and Ω for the optimized conformers of α-CD at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels. These results show that all α-CD conformers possess highly symmetric structures, with coplanar anomeric oxygen atoms describing regular polygons and negligible standard deviations.

Table 3 contains the average bond lengths, bond angles, and endocyclic dihedrals calculated for the optimized α-CD conformers at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels. These parameters were compared with the X-ray reported information for the crystal structure of α-CD, to identify the most representative conformer for the α-CD structure.[33] Calculated parameters (Table 3) suggest that all conformers agree fairly well with the experimentally determined geometry of α-CD. In addition, all conformers are characterized by negligible variations in bond lengths, bond angles, and endocyclic dihedrals when comparing different glucopyranose residues within each corresponding conformer. This property is reflected by the small standard deviations obtained for all geometrical properties in α-CD optimized conformers. Moreover, no significant differences were observed when comparing the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) optimized structures of the α-CD conformers. These results indicate that the sole measure of bond lengths, bond angles, and endocyclic dihedrals cannot be employed as a valid criterion for the selection of the most representative conformer of α-CD among the optimized structures. Therefore, other molecular properties must be employed to better account for the differences among the optimized conformers of α-CD and to identify the conformation that provides the most realistic and representative view of this molecule's structure.

Intramolecular Hydrogen-Bonding Patterns. One characteristic feature concerning the CD structure is the existence of intramolecular hydrogen bonds, formed by the interaction between adjacent glucopyranose units in the macrocyclic structure. From NMR data, it has been stated that secondary hydroxyls are involved in an intramolecular array of hydrogen bonds, where the O2 acts as proton acceptor from the O3 located in the adjacent monomeric glucose unit.[39]

Herein, we analyzed the consistency between experimentally determined hydrogen-bonding patterns and those observed in the optimized structures of α-CD. Our results indicate that all optimized conformations possess intramolecular hydrogen-bonding arrays but that they differ in the position of the hydroxyls involved in the interactions. Conformers **1**−**3** possess an intramolecular hydrogen-bonding network along their secondary face, in agreement with experimental observations. On the other hand, the hydrogen-bonding arrangement found in conformer **4** involves the interaction between primary hydroxyls, in discrepancy with the experimental evidence. According to

TABLE 3: Average Values and Standard Deviations of Bond Distances, Bond Angles, and Dihedral Angles Calculated at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) Levels for Optimized Conformers of α-CD

	conformer **1**			conformer **2**			conformer **3**			conformer **4**			
	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	crystalline av value
							Bond lengths (Å)						
C1−C2	1.522 (0.000)	1.532 (0.000)	1.531 (0.000)	1.519 (0.000)	1.529 (0.000)	1.528 (0.000)	1.522 (0.000)	1.532 (0.000)	1.531 (0.000)	1.523 (0.000)	1.534 (0.000)	1.533 (0.000)	1.532 (0.009)
C2−C3	1.517 (0.000)	1.523 (0.000)	1.522 (0.000)	1.515 (0.000)	1.521 (0.000)	1.520 (0.000)	1.517 (0.000)	1.524 (0.000)	1.522 (0.000)	1.517 (0.000)	1.524 (0.000)	1.522 (0.000)	1.511 (0.008)
C3−C4	1.521 (0.000)	1.527 (0.000)	1.526 (0.000)	1.525 (0.000)	1.531 (0.000)	1.530 (0.000)	1.524 (0.000)	1.532 (0.000)	1.531 (0.000)	1.524 (0.000)	1.532 (0.000)	1.531 (0.000)	1.521 (0.010)
C4−C5	1.532 (0.000)	1.540 (0.000)	1.539 (0.000)	1.537 (0.000)	1.542 (0.000)	1.541 (0.000)	1.532 (0.000)	1.538 (0.000)	1.536 (0.000)	1.530 (0.000)	1.538 (0.000)	1.536 (0.000)	1.534 (0.008)
C5−C6	1.516 (0.000)	1.521 (0.000)	1.520 (0.000)	1.530 (0.000)	1.538 (0.000)	1.537 (0.000)	1.520 (0.000)	1.527 (0.000)	1.526 (0.000)	1.527 (0.000)	1.534 (0.000)	1.533 (0.000)	1.518 (0.013)
O5−C1	1.390 (0.000)	1.413 (0.000)	1.412 (0.000)	1.392 (0.000)	1.420 (0.000)	1.418 (0.000)	1.389 (0.000)	1.414 (0.000)	1.412 (0.000)	1.388 (0.000)	1.414 (0.000)	1.413 (0.000)	1.417 (0.007)
C1−O1	1.388 (0.000)	1.409 (0.000)	1.408 (0.000)	1.385 (0.000)	1.402 (0.000)	1.401 (0.000)	1.386 (0.000)	1.406 (0.000)	1.404 (0.000)	1.383 (0.000)	1.403 (0.000)	1.401 (0.000)	1.417 (0.012)
C2−O2	1.403 (0.000)	1.428 (0.000)	1.426 (0.000)	1.401 (0.000)	1.426 (0.000)	1.425 (0.000)	1.402 (0.000)	1.427 (0.000)	1.425 (0.000)	1.401 (0.000)	1.424 (0.000)	1.423 (0.000)	1.431 (0.012)
C3−O3	1.398 (0.000)	1.417 (0.000)	1.415 (0.000)	1.397 (0.000)	1.416 (0.000)	1.414 (0.000)	1.397 (0.000)	1.416 (0.000)	1.414 (0.000)	1.398 (0.000)	1.418 (0.000)	1.416 (0.000)	1.440 (0.004)
							Bond angles (deg)						
C1−C2−C3	110.4 (0.0)	110.2 (0.0)	110.1 (0.1)	110.4 (0.0)	110.0 (0.0)	110.0 (0.1)	110.5 (0.0)	110.4 (0.0)	110.3 (0.0)	110.3 (0.0)	110.0 (0.0)	109.9 (0.0)	110.2 (0.6)
C2−C3−C4	110.5 (0.0)	110.5 (0.0)	110.4 (0.2)	111.3 (0.0)	111.3 (0.0)	111.3 (0.1)	111.1 (0.0)	111.5 (0.0)	111.5 (0.0)	111.4 (0.0)	111.6 (0.0)	111.5 (0.0)	111.0 (0.8)
C3−C4−C5	111.1 (0.0)	111.6 (0.0)	111.5 (0.1)	111.5 (0.0)	111.9 (0.0)	111.9 (0.1)	111.1 (0.0)	110.9 (0.0)	110.8 (0.0)	110.3 (0.0)	110.4 (0.0)	110.4 (0.0)	112.0 (0.4)
C4−C5−C6	112.7 (0.0)	112.3 (0.0)	112.2 (0.0)	115.0 (0.0)	115.1 (0.0)	115.1 (0.1)	113.3 (0.0)	114.9 (0.0)	114.9 (0.0)	115.4 (0.0)	116.1 (0.0)	116.1 (0.0)	113.2 (0.1)
O6−C6−C5	109.5 (0.0)	109.3 (0.0)	109.2 (0.0)	113.6 (0.0)	113.6 (0.0)	113.6 (0.0)	111.6 (0.0)	111.0 (0.0)	111.0 (0.0)	111.3 (0.0)	111.9 (0.0)	111.9 (0.0)	109.3 (0.2)
O5−C1−*C*2	108.7 (0.0)	109.0 (0.0)	109.0 (0.0)	107.9 (0.0)	108.6 (0.0)	108.6 (0.0)	108.0 (0.0)	108.1 (0.0)	108.2 (0.0)	109.1 (0.0)	109.9 (0.0)	109.9 (0.0)	112.0 (0.8)
O2−C2−C3	110.9 (0.0)	110.4 (0.0)	110.3 (0.0)	110.8 (0.0)	110.6 (0.0)	110.6 (0.0)	110.8 (0.0)	110.4 (0.0)	110.4 (0.0)	111.5 (0.0)	111.6 (0.0)	111.5 (0.0)	110.6 (1.0)
O3−C3−C4	112.2 (0.0)	113.0 (0.0)	113.1 (0.0)	112.3 (0.0)	112.8 (0.0)	112.9 (0.0)	112.3 (0.0)	113.0 (0.0)	113.0 (0.0)	111.7 (0.0)	111.9 (0.0)	112.0 (0.0)	108.8 (1.0)
							Dihedral angles (deg)						
C1−C2−C3−C4	−54.0 (0.0)	−54.5 (0.1)	54.7 (0.4)	−53.3 (0.0)	−53.5 (0.1)	53.5 (0.1)	−52.9 (0.0)	−52.6 (0.0)	52.6 (0.1)	−51.4 (0.0)	51.0 (0.1)	51.2 (0.1)	−52.6 (1.4)
C2−C3−C4−C5	49.6 (0.0)	49.2 (0.1)	49.6 (0.4)	48.9 (0.0)	49.7 (0.1)	49.7 (0.2)	48.9 (0.0)	49.4 (0.0)	49.5 (0.1)	51.5 (0.0)	51.9 (0.1)	52.2 (0.1)	50.3 (1.3)
C3−C4−C5−O5	−49.4 (0.0)	48.8 (0.1)	49.3 0.3)	−48.7 (0.0)	−49.9 (0.1)	50.0 (0.3)	−49.7 (0.0)	−51.6 (0.1)	51.8 (0.1)	−53.9 (0.0)	−55.4 (0.0)	55.6 (0.1)	−51.9 (1.4)
C4−C5−O5−C1	57.7 (0.0)	56.6 (0.1)	57.0 (0.2)	58.9 (0.0)	58.9 (0.0)	59.0 (0.2)	59.8 (0.0)	61.7 (0.0)	61.7 (0.1)	62.7 (0.0)	63.2 (0.0)	63.3 (0.1)	59.8 (1.1)
C5−O5−C1−C2	−61.5 (0.0)	−61.5 (0.1)	61.7 (0.1)	−63.3 (0.0)	−63.5 (0.0)	63.6 (0.1)	−63.3 (0.0)	−64.6 (0.0)	64.5 (0.0)	−63.1 (0.0)	−63.4 (0.0)	63.6 (0.1)	−63.1 (1.7)
O5−C1−C2−C3	58.0 (0.0)	59.5 (0.0)	59.6 (0.2)	57.8 (0.0)	58.8 (0.0)	58.8 (0.2)	57.7 (0.0)	58.3 (0.1)	58.2 (0.1)	54.8 (0.0)	55.2 (0.0)	55.4 (0.1)	57.9 (1.0)

TABLE 4: Relative Energies (kJ/mol) and Dipole Moments (D) for α-Cyclodextrin Conformers in Gas Phase and Solution, Calculated at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) Levels[a]

	dipole moment (D) (z-component)						relative energy (kJ/mol)					
	gas phase			solution			gas phase			solution		
conformer	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP	HF	B3LYP	X3LYP
1	8.2	8.1	8.0	10.5	10.6	10.5	79.0	131.9	139.2	17.7	59.8	62.5
2	−7.9	−7.5	−7.5	−10.7	−10.8	−10.7	71.2	74.0	76.6	52.2	40.1	36.7
3	−7.2	−7.0	−7.1	−9.1	−9.2	−9.2	46.3	78.4	84.8	0.0	29.2	30.8
4	−2.7	−3.0	−2.9	−3.7	−4.3	−4.3	0.0	0.0	0.0	27.3	0.0	0.0

[a] Calculations in solution were performed with the PCM solvation method at both levels of theory.

these results, conformers **1**−**3** appear as equally representative structures for α-CD, whereas conformer **4** can be discarded as a representative structure for α-CD since it does not agree with the experimental hydrogen-bonding pattern.

Furthermore, it is worth noting that the intramolecular hydrogen bonds found in conformer **4** can be helpful in understanding this species' stabilization since these interactions may allow conformer **4** to overcome the intrinsic destabilization that arises from the nearly eclipsed conformation found in each glucopyranose residue within this species.

Molecular Dipole Moments. Even though the experimental dipole moments of CDs are unknown, it is believed that they are quite polar molecules.[18] According to this idea, conformers that possess large dipole moments will be more representative of α-CD's real structure. In addition, they are expected to be more stabilized in aqueous solution, where most complexation phenomena take place.

To discriminate between the optimized conformers of α-CD, we calculated their molecular dipole moments at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of theory (Table 4). Because of the highly symmetric structure of each species, dipole vectors are collinear to the *z*-axis, but they differ both in magnitude and in orientation. The magnitudes of the dipole moments found in conformers **1**−**3** indicate that the CD cavity is highly polarized, in agreement with literature reports.[18] On the other hand, conformer **4** appears as a slightly polar compound with a molecular dipole much smaller than other reported values. This result supports the idea that conformer **4** is not a representative structure for α-CD since it neither possesses the expected molecular polarity nor presents the expected hydrogen-bonding pattern.

According to the magnitude of the molecular dipole moment, conformers **1**−**3** appear to be equally representative of the α-CD structure. A deeper analysis of the dipole vectors shows that they differ in direction, indicating that the charge distribution in each conformer varies as a consequence of the conformation adopted by the molecule. Vector analysis shows that conformer **1** has a positive dipole end on the molecule's primary side, whereas the negative end is located on the secondary side. On the other hand, conformers **2** and **3** possess a negative end on cyclodextrin's primary face. The described differences in molecular dipole orientation are important since both the inclusion mode and the stability of an inclusion complex is affected by the orientation of the dipoles belonging to the interacting species. In this sense, conformers that differ in dipole orientation should result in different minimum energy structures in a computational study on complexation phenomena. This fact forces us to attain a careful selection among conformers **1**−**3**, to select the species that provides the most realistic view about α-CD, allowing us to perform further reliable computational studies on inclusion complexation processes.

Relative Energies in Gas Phase and Aqueous Solution. To select the most appropriate conformer among **1**−**3**, we calculated the gas and solution phase relative energies corresponding to HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31(d) calculations (Table 4).

Gas-phase relative energies (Table 4) indicate that conformer **4** is the most stable species at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of theory. However, this structure has already been discarded as a suitable structure for α-CD since it neither possesses the expected molecular polarity nor presents the expected hydrogen-bonding pattern. Thus, we have to take into account the energetic trends found among conformers **1**−**3**. Among them, conformer **1** appears to be less stable than **2** and **3**. In addition, conformers **2** and **3** show quite similar gas-phase relative energies, suggesting that both species should be equally good representations for the structure of α-CD.

On the other hand, relative energies in the solution phase—obtained with the polarizable continuum method (PCM) of solvation at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) levels of calculation—indicate that conformer **3** undergoes the largest stabilization in solution, becoming the most stable species among **1**−**3**. These results suggest that, among the four conformations explored throughout this study, conformer **3** should be the most appropriate representation of α-CD structure.

Relative Conformation of Glucopyranose Residues. The conformational study herein discussed is centered on the conformers coming from the rotation of hydroxyl groups within each glucopyranose residue. To prove that these conformers represent the most suitable structures for α-CD, we have also analyzed the conformers coming from the rotation of one glucopyranose over the rest of the residues. Even though it has been stated[40] that all glucose units in small CDs (from α-CD to γ-CD) present a syn relative arrangement between them, we intended to explore the energy differences arising from syn, anti, and kink conformations, where neighbor glucoses are in a gauche position.

The set of conformers previously reported (**1**−**4**) correspond exclusively to syn rotamers of α-CD. For each species, we explored the rotation of one glucopyranose unit over the rest of the residues to obtain kink and anti rotamers. However, kink conformations did not lead to stationary energy structures; therefore, their relative energies were not calculated. Figure 4 shows the structures and relative energies of the four syn and anti α-CD conformers obtained at the B3LYP/6-31G(d) level of theory. The other methods herein employed lead to analogous results, as shown in Table 5.

As can be inferred from Figure 4 and Table 5, all anti conformations are highly unstable as compared to the syn species, in particular in the case of conformer **4**. These results suggest that the pass from syn to anti conformations is not easy to achieve; therefore, one should expect that anti arrangements are not of importance in the conformational analysis of α-CD. Our results are in agreement with the work of Ivanov and

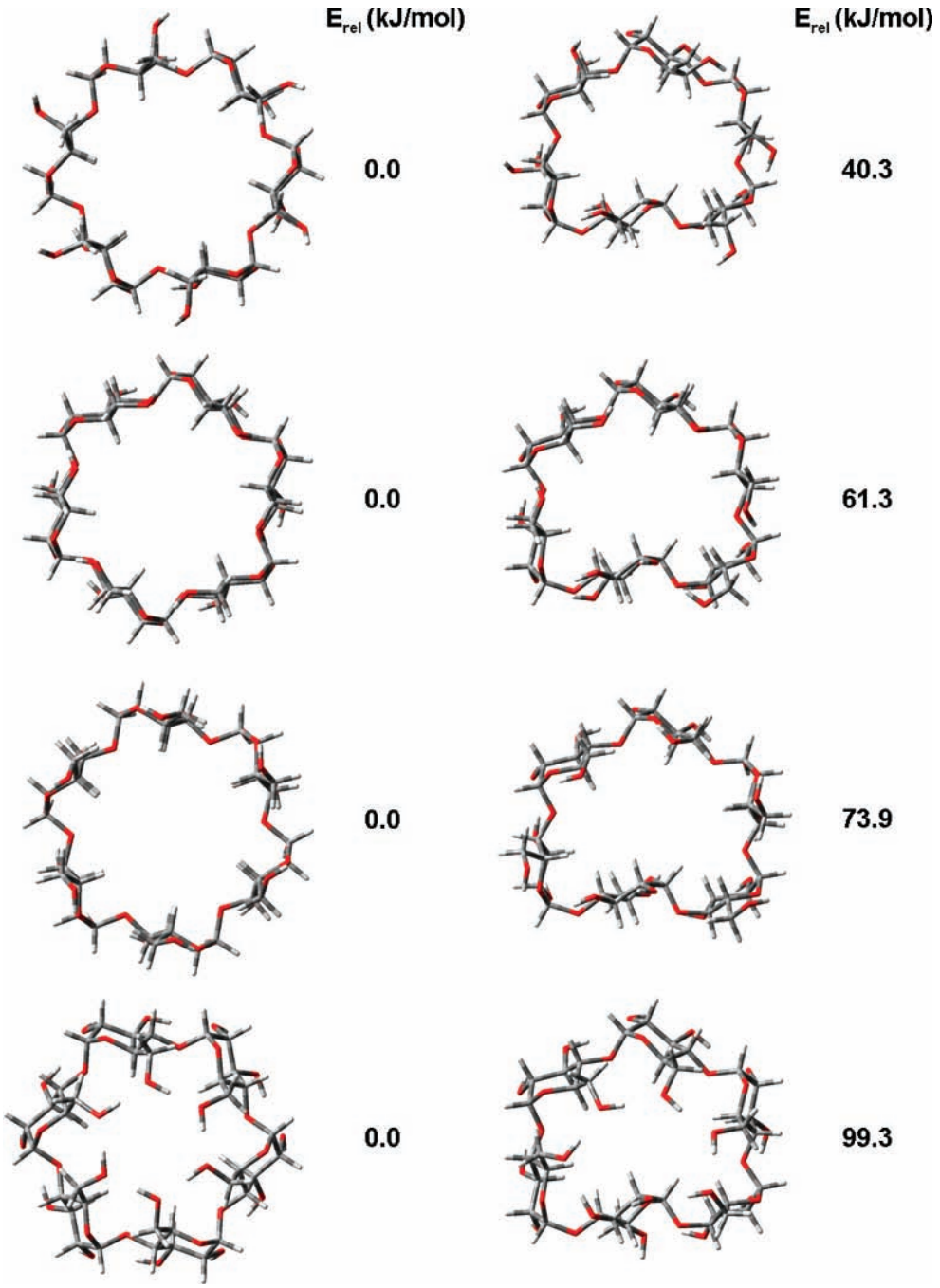

Figure 4. Structure of syn and anti conformers of α-CD and their relative energies E_{rel} (kJ/mol) calculated at the B3LYP/6-31G(d) level. Relative energies are referred to the most stable (syn) conformers.

TABLE 5: Relative Energies (kJ/mol) of syn and anti Conformations of α-CD Conformers Calculated at the HF/6-31G(d), B3LYP/6-31G(d), and X3LYP/6-31G(d) Levels of Theory[a]

	relative energy (kJ/mol)					
	HF		B3LYP		X3LYP	
conformer	syn	anti	syn	anti	syn	anti
1	0.0	49.3	0.0	40.3	0.0	37.8
2	0.0	37.1	0.0	61.3	0.0	61.1
3	0.0	53.6	0.0	73.9	0.0	73.5
4	0.0	96.6	0.0	99.3	0.0	99.3

[a] Relative energies have been calculated with respect to the syn conformers for each α-CD conformer.

Gotsev,[40] who have shown that anti and kink conformations are of importance only in large CDs.

The energy difference between syn and anti conformations is in agreement with the high rigidity of small CDs, which are stabilized by intramolecular hydrogen bonds in the secondary face between neighboring glucopyranose residues. The absence of such hydrogen-bonding interactions should favor the rotation of one or more glucopyranose units leading to anti conformations, as has been observed in the case of per-O-methylated CDs.[41, 42.]

Conclusion

Several geometrical and energetic parameters were analyzed to identify one representative structure for α-CD among four optimized conformers at different levels of theory. According to our results, conformer **3** appears to be the most representative species for α-CD since it has a highly symmetric structure,

shows the experimental hydrogen-bonding pattern, is a highly polar species, and possesses the lowest energy both in gas and in solution phases among the suitable structures for α-CD.

The purpose of selecting such a species is to identify an appropriate structure to be employed as starting point for reliable computational studies on complexation phenomena. Our future efforts are focused on obtaining minimum energy inclusion complex structures employing conformer **3** as the starting point for the host−guest full optimization procedure. Unfinished work has been quite satisfactory since it shows a high resemblance between computationally obtained structures and experimental data available for inclusion complexes between α-CD and several aliphatic and aromatic compounds.

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