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A Systematic Quantum Chemistry Study on Cyclodextrins

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Summary. AM1 and PM3 modeling of β-hydroxyethyl ether and α-(1→4)-glucobiose indicated that PM3 is advantageous to AM1 in cyclodextrin (*CD)* chemistry. The conclusion was supported by direct structure optimization of α- and β-*CD* with AM1 and PM3, in which AM1 gave badly distorted geometries due to unreasonable hydrogen bonding, whereas PM3 reproduced the crystalline structures rather well. *Ab initio* calculation was for the first time performed on *CD*, demonstrating the feasibility of this method for future studies concerning *CD* chemistry. The results also provided valuable insights into the driving forces in *CD* molecular recognition.

Keywords. *Ab initio* calculations; Cyclodextrins; Density functional calculations; Molecular modeling; Semiempirical calculations.

Introduction

Cyclodextrins (*CD*), cyclic oligomers of α-*D*-glucose [1], can form inclusion complexes with many compounds [2]. *CD* chemistry offers valuable insights into non-covalent interactions and hence causes much interest [3]. The industrial applications of *CD* are promising [1], and *CD* represents an important model mimicking enzyme-substrate interactions [4].

Molecular modeling has become popular in *CD* chemistry [5]; molecular mechanics (MM) [6] and dynamics (MD) methods [7] have often been used. Quantum mechanical (QM) study of *CD* remains difficult [5], but its future is optimistic if we should improve our present understanding. Moreover, QM is desirable for certain *CD* systems containing radicals or excited species, because these systems are difficult to handle with the empirical stick-and-ball methods [8–10].

To date, QM studies on *CD* have employed CNDO [11] and AM1 [12–15] protocols. Recently, detailed studies of CD with AM1 have been reported [16–18]. Interestingly, compared with a QM-optimized one, the MM-optimized *CD* was found far from stable. However, the AM1-optimized *CD* also turned out to be badly distorted, obviously caused by the poor ability of AM1 to model hydrogen bonding

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[19]. Nevertheless, AM1 has become a frequently chosen method in *CD* chemistry [21–21].

Very recently, PM3 studies on *CD* complexation have been reported [8–10, 22, 23]. As PM3 is superior to AM1 in dealing with hydrogen bonding, it seemed necessary to conduct a systematic study to compare PM3 with AM1 in modeling *CD*.

Methods

All calculations were performed with GAUSSIAN 98 [24]. α- and β-*CD* were constructed from the crystalline structures reported in the literature [25, 26]. Full geometry optimizations of α- and β-*CD* without any symmetry constraint were performed with AM1 and PM3. Frequency calculations using AM1 and PM3 were conducted to confirm the completeness of optimization. *Ab initio* methods including HF/STO-3G, HF/3-21G*, and HF/6-31G* as well as density functional theory (DFT) methods including B3LYP/3-21G* and B3LYP/6-31G* were used in the single point calculations on the crystalline and PM3-optimized α- and β-*CD*, respectively.

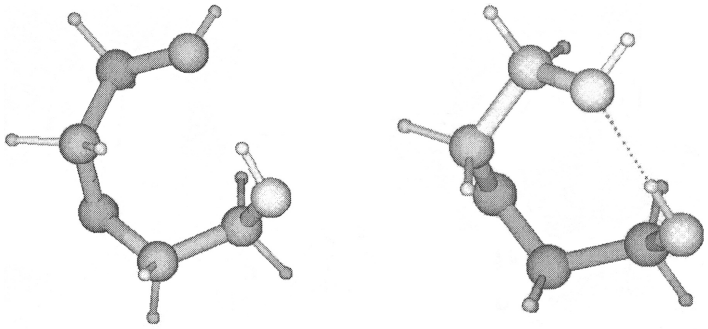
Results and Discussion

Study on the model compound

Though AM1 and PM3 belong to the same family of MNDO, the quality of their results depends on the nature of the system under investigation and on the chemical properties that are the target of the study. In dealing with hydrogen bonding, AM1 tends to give questionable interaction geometries [19] with overestimated inter- [27] and intramolecular [28] interaction distances. In contrast, PM3 can offer good structures and energies in modeling hydrogen bonding [19, 29, 30].

Herein, the intramolecular hydrogen bonding of β-hydroxyethyl ether was studied, a model compound containing the methylene, hydroxyl, and ethereal oxygen groups of *CD*. Its intramolecular hydrogen bond leads to an eight-membered ring similar to the intramolecular hydrogen bonding between the 2-OH and 3-OH groups of adjacent glucoses in *CD*. Several initial structures of β-hydroxyethyl ether were constructed and fully optimized with AM1, PM3, HF/3-21G*, and B3LYP/6-311G** methods. The structures with the lowest energies according to AM1 and PM3 are shown in Fig. 1. The O$\cdots$H distance of the hydrogen bond in the PM3-optimized structure was 1.815 Å, similar to those calculated by HF/3-21G* (1.746 Å) and by B3LYP/6-311G** (1.876 Å). However, AM1 gave a highly overestimated O$\cdots$H distance of 2.148 Å. B3LYP/6-311G** calculation gave an energy of -384.1889 a.u. for the PM3-optimized structure and an energy of -384.1843 a.u. for the AM1-optimized one. Obviously, the former structure was much better than the latter with a significant energy gap of 12.1 kJ/mol. Interestingly, this energy gap approached to the energy of a usual hydrogen bond.

A larger and obviously better model compound for cyclodextrins is α-(1$\rightarrow$4)-glucobiose (maltose). Geometry optimization of this molecule with AM1, PM3, HF/3-21G*, and B3LYP/6-311G** methods were performed. The PM3-optimized structure is shown in Fig. 2. As can be seen, a hydrogen bond is formed between the H atom of the 2-OH group of one glucose unit and the O atom of the 3′-OH



(a) (b)

Fig. 1. AM1- (a) and PM3-optimized (b) β-hydroxyethyl ether

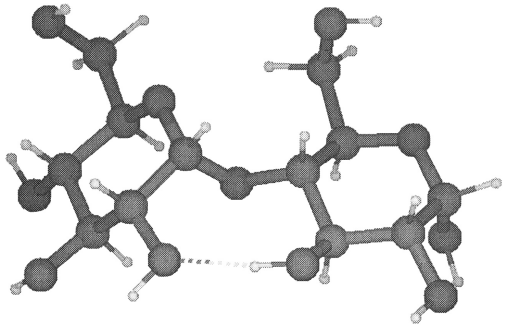


Fig. 2. PM3-optimized α-(1→4)-glucobiose

group of the other glucose unit similar to the situation in cyclodextrins. PM3 predicted that the length of this intramolecular hydrogen bond was 1.814 Å, in accordance with HF/3-21G* (1.777 Å) and B3LYP/6-311G** (1.850 Å) methods. However, as before AM1 gave a highly overestimated O· · ·H distance of 2.194 Å, again demonstrating that PM3 works better than AM1 in dealing with the intramolecular hydrogen bonding responsible for the conformations of β-hydroxyethyl ether, α-(1→4)-glucobiose, and cyclodextrins.

In brief, calculations on model compounds indicated that PM3 was superior to AM1 in modeling intramolecular hydrogen bonding. As *CD* is stabilized *via* intramolecular hydrogen bonds [31], PM3 should represent a better QM method than AM1 in modeling *CD*.

AM1- and PM3-optimized CD

α- and β-*CD* were optimized with AM1 and PM3, respectively. Tables 1 and 2 summarize the corresponding structural features. As all structures were found to be non-symmetrical, only the average bond lengths, bond angles, dihedral angles, and their average deviations are listed.

All average structural values in Tables 1 and 2 well reproduced those found in crystals. Thus, AM1 and PM3 are both applicable in modeling *CD*. However,

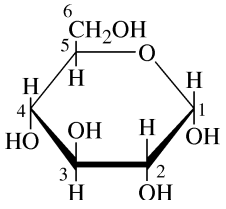


Table 1. Bond lengths/Å, bond angles/deg, and dihedral angles/deg of crystalline, AM1-optimized, and PM3-optimized α-*CD*

	Crystalline		AM1-Optimized		PM3-Optimized	
	Average value	Average deviation	Average value	Average deviation	Average value	Average deviation
			Bond length			
C1-C2	1.532	0.0087	1.542	0.0003	1.558	0.0012
C2-C3	1.511	0.0081	1.534	0.0006	1.548	0.0006
C3-C4	1.521	0.0105	1.540	0.0012	1.557	0.0009
C4-C5	1.534	0.0078	1.537	0.0012	1.554	0.0010
C5-C6	1.518	0.0128	1.534	0.0010	1.547	0.0003
O5-C1	1.417	0.0072	1.412	0.0013	1.400	0.0009
C1-O1	1.417	0.0120	1.415	0.0010	1.411	0.0012
C2-O2	1.431	0.0123	1.414	0.0022	1.412	0.0032
C3-O3	1.440	0.0042	1.417	0.0010	1.412	0.0012
			Bond angle			
C1-C2-C3	110.2	0.6333	109.7	0.1111	109.9	0.1333
C2-C3-C4	111.0	0.7833	110.1	0.4333	109.8	0.2000
C3-C4-C5	112.0	0.4333	111.0	0.7667	112.0	0.2167
C4-C5-C6	113.2	0.1111	112.1	1.0222	112.0	0.2556
O6-C6-C5	109.3	0.2111	111.1	0.6444	112.0	0.1444
O5-C1-C2	112.0	0.8556	112.5	0.7444	114.6	0.3667
O2-C2-C3	110.6	1.0500	111.4	0.4833	113.0	0.3667
O3-C3-C4	108.8	0.9778	110.3	1.1556	111.4	0.2556
			Dihedral angle			
C1-C2-C3-C4	−52.55	1.4333	−53.97	1.5444	−53.38	0.4611
C2-C3-C4-C5	50.32	1.3167	52.02	1.4833	49.22	0.4833
C3-C4-C5-O5	−51.87	1.4000	−51.45	1.7667	−46.63	0.3778
C4-C5-O5-C1	59.83	1.0667	55.78	1.2778	50.90	0.3667
C5-O5-C1-C2	−63.12	1.7167	−58.18	0.7111	−55.77	0.2889
O5-C1-C2-C3	57.92	0.9778	56.22	1.0500	56.45	0.4167
O2-C2-C3-C4	−172.2	1.9500	−173.1	1.0333	−173.9	1.0333
O3-C3-C4-C5	170.3	1.4167	170.0	1.5167	166.9	0.2667

AM1-optimized α- and β-*CD* were significantly distorted from an overall circular shape. The average deviations of bond lengths, bond angles, and dihedral angles were large, indicating that the molecules were badly twisted. Though only five hydrogen bonds were found in the crystalline α-*CD* at the wider rim with the help of the MOLDEN software, additional two were found in the AM1-optimized α-*CD*

Table 2. Bond lengths/Å, bond angles/deg, and dihedral angles/deg of crystalline, AM1-optimized, and PM3-optimized *β-CD*

	Crystalline		AM1-Optimized		PM3-Optimized	
	Average value	Average deviation	Average value	Average deviation	Average value	Average deviation
			Bond length			
C1-C2	1.526	0.0089	1.542	0.0022	1.560	0.0013
C2-C3	1.518	0.0078	1.535	0.0019	1.550	0.0006
C3-C4	1.519	0.0055	1.540	0.0019	1.559	0.0017
C4-C5	1.524	0.0056	1.536	0.0016	1.552	0.0018
C5-C6	1.509	0.0081	1.533	0.0022	1.547	0.0011
O5-C1	1.403	0.0098	1.410	0.0035	1.400	0.0015
C1-O1	1.412	0.0124	1.418	0.0036	1.428	0.0253
C2-O2	1.416	0.0083	1.412	0.0022	1.405	0.0048
C3-O3	1.417	0.0094	1.416	0.0018	1.411	0.0016
			Bond angle			
C1-C2-C3	110.0	0.6735	110.8	0.7469	110.4	0.2776
C2-C3-C4	110.0	0.3837	110.7	1.2653	110.0	0.4816
C3-C4-C5	110.5	0.8776	110.4	1.4204	110.7	0.8531
C4-C5-C6	113.2	0.9265	112.8	1.0531	112.4	0.4204
O6-C6-C5	110.1	0.4041	112.6	0.9020	112.8	0.4531
O5-C1-C2	112.0	1.6408	111.5	0.4694	114.0	0.4612
O2-C2-C3	111.5	0.9592	111.2	0.8000	113.2	0.4449
O3-C3-C4	110.1	1.3551	109.7	1.6367	111.3	0.4408
			Dihedral angle			
C1-C2-C3-C4	−53.83	1.2326	−49.71	2.3020	−51.70	0.6857
C2-C3-C4-C5	53.61	1.3837	52.53	3.3469	52.00	1.6286
C3-C4-C5-O5	−54.77	3.2612	−55.18	4.4082	−52.54	2.8204
C4-C5-O5-C1	59.77	2.7755	58.21	3.9265	54.28	2.6408
C5-O5-C1-C2	−60.57	0.7959	−56.20	2.2000	−54.48	1.2163
O5-C1-C2-C3	56.36	1.8776	50.76	2.3347	52.41	1.5020
O2-C2-C3-C4	−174.4	3.5551	−171.4	1.5837	−175.4	2.1714
O3-C3-C4-C5	174.5	1.3755	172.1	4.2531	170.6	1.9918

at the narrower rim. In the case of *β-CD*, though seven hydrogen bonds were found at the wider rim in the crystalline structure with the help of MOLDEN, there were only six in the AM1-optimized *β-CD*. Obviously, the bad reproduction of the structures is a consequence of the poor ability of AM1 to modeling hydrogen bonding.

In contrast, PM3-optimized *α-* and *β-CD* retained the overall circular shape found in the crystals. The average deviations of bond lengths, bond angles, and dihedral angles were much less than in the case of AM1 and close to those in the crystals. The number of hydrogen bonds was six for the PM3-optimized *α-CD* and seven for the PM3-optimized *β-CD* according to MOLDEN. All of them were located at the wider *CD* rims. Obviously, PM3 reproduced the crystalline structures much better than AM1. Interestingly, the PM3-optimized *α-CD* was more circular

Table 3. *Hartree-Fock* energy/10^6kJ/mol and dipole moments/*Debye* of α-*CD* and β-*CD*

		α-*CD*		β-*CD*	
		HF energy	Dipole moment	*HF* energy	Dipole moment
Crystalline	HF/STO-3G	−9.4341	−9.4341	−11.0045	10.08
	HF/3-21G*	−9.5046	−9.5046	−11.0870	13.12
	HF/6-31G*	−9.5571	−9.5571	−11.1486	12.04
	B3LYP/3-21G*	−9.5585	−9.5585	−11.1499	11.66
	B3LYP/6-31G*	−9.6112	−9.6112	−11.2116	11.01
PM3 Optimized	HF/STO-3G	−9.4347	−9.4347	−11.0070	2.95
	HF/3-21G*	−9.5048	−9.5048	−11.0888	3.50
	HF/6-31G*	−9.5576	−9.5576	−11.1504	2.97
	B3LYP/3-21G*	−9.5588	−9.5588	−11.1517	3.73
	B3LYP/6-31G*	−9.6116	−9.6116	−11.2134	3.07

than the crystalline α-*CD* as indicated by the additional hydrogen bond. Presumably, this was caused by lattice packing and hydration waters in the crystal environment, which were not considered in the present modeling.

Ab initio and DFT calculations on CD

Ab initio and DFT calculations on *CD* are still considered as a daunting computational challenge [5]. Herein, it is shown that such calculations are actually feasible now.

Table 3 lists the *Hartree-Fock* energies and dipole moments for α- and β-*CD* obtained from *ab initio* and DFT calculations. Obviously, the *Hartree-Fock* energies of PM3-optimized α- and β-*CD* are lower than in the crystalline state, ones demonstrating that the crystal lattice exerts a nontrivial effect on the equilibrium structure of *CD* by increasing the energy of every *CD* molecule. This energy constitutes a storage of energy in solid *CD* whose relief upon inclusion complexation is a driving force for *CD* molecular recognition [32].

The question of the dipole moment of *CD* remained unsettled so far. No experimental measurements have been performed, although several theoretical results have been reported [2]. Herein, the dipole moments were calculated with *ab initio* and DFT methods. Their magnitudes agreed with the remarkably large values in the literature, indicating that the *CD* cavities are highly polarized. Thus, electrostatic interaction would constitute an important driving force in *CD* complexation [33]. Vector analysis showed that the narrower end of the *CD* cavity was at the positive end of the dipole and its wide end at the negative one. Interestingly, the dipole moment of crystalline *CD* was significantly higher than that of the PM3-optimized one. This behavior is possibly due to the larger deviation from the overall circular shape of crystalline *CD* and indicates that the dipole moments of *CD* are highly susceptible to the influence of chemical environment.

Conclusions

AM1 and PM3 were used in modeling α- and β-*CD*. Based on the comparison with the crystalline structures as well as on the analysis of model systems it was concluded that PM3 is a better QM method than AM1 with respect to *CD* chemistry. *Ab initio* and DFT calculations were for the first time applied to the study of *CD*. They indicated that the relief of conformational strain and electrostatic forces are driving forces for *CD* complexations.

Acknowledgements

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