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Hartree-Fock and Density Functional Theory Studies on the Molecular Recognition of the Cyclodextrin

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Abstract: This study involves initial Hartree-Fock and Density Functional theory calculations on the molecular recognition of the cyclodextrins. The α-cyclodextrin-acetophenone complexation system was investigated with PM3, HF/3-21G* and B3LYP/3-21G* methods. The results indicated that the inclusion orientation in which the acetyl group of the acetophenone points towards the secondary hydroxyls of the α-cyclodextrin was preferable in energy. The steric effect was supposed as the physical reason of such a behavior. Hence, the simple rule the anti-parallel arrangement of the dipoles of the host and guest molecules in the cyclodextrin complexation is not generally applicable.

Keywords: *ab initio*, acetophenone, cyclodextrin, density functional theory, molecular recognition

Cyclodextrins (CD), cyclic oligomers of α-D-glucose connected through glycosidic α-1,4 bonds, are seductive molecules appealing to researchers in pure academic fields and applied technologies[1]. Model studies on CD inclusion complexation offer important insights into enzyme-substrate interactions[2] and hence attract great attention. Although many experimental approaches are available, molecular modeling provides an important alternative way in studying the CD chemistry[3].

Due to their large size, most theoretical studies on CD chose molecular mechanics or molecular dynamics methods[4]. However, quantum mechanics study on CD is necessary since it can provide more detailed information[5]. To date, quantum mechanics studies on CD are restricted in the semiempirical molecular orbital methods including CNDO[6] and AM1[7]. No *ab initio* calculation using Hartree-Fock (HF) or Density Functional Theory (DFT) has been reported yet[3]. However, for a more reliable calculation and for a deeper understanding of the molecular recognition, such methods are still needed.

The present study represents an initial attempt in applying the HF and DFT methods to the molecular recognition of CD. The interesting inclusion complexation of α-CD with acetophenone was studied. The HF energy, stabilization energy upon complexation, dipole moment, and frontier molecular orbitals were obtained. The calculation results well explain the abnormal experimental observations.

Methods

All the calculations were performed with GAUSSIAN 98 software package on a PIII 450 personal computer[8]. The acetophenone, constructed with the help of MOLDEN, was

optimized by the standard PM3 semiempirical molecular orbital method[9]. The α-CD was built and optimized by PM3 from the crystal structure[10]. The inclusion complex was constructed with the PM3-optimized α-CD and acetophenone. Two possible orientations in the complexation were considered, respectively. The orientation in which the acetyl group points toward the primary hydroxyls of the α-CD was called acetyl up, while the other in which acetyl group points toward the secondary hydroxyls of the α-CD was named acetyl down. The inclusion complexation was emulated by entering the guest molecule from one end of the α-CD molecule and then letting it pass through the host molecule by steps. Each step is fully optimized by the PM3 method[5]. The final structure of the complex is determined as that with the minimum energy.

The standard HF and B3LYP (Becke's Three Parameter Hybrid Functional Using the LYP Correlation Functional) methods[11] were employed to calculate the electronic structure of the PM3-optimized host, guest, and their complex. The standard 3-21G* basis set was used.

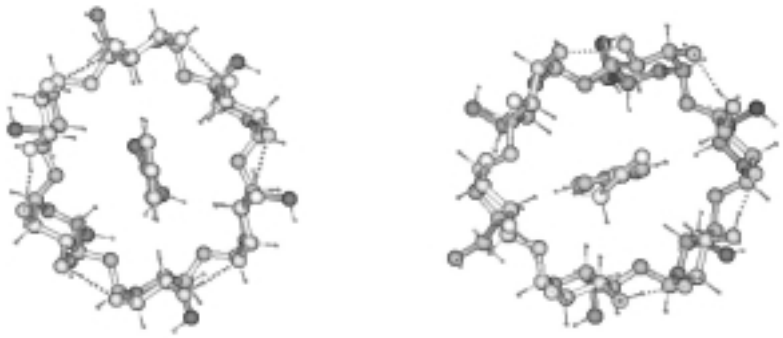
Results and Discussion

Table 1. The HF energies, stabilization energies upon complexation, the energy levels of the frontier molecular orbitals, and dipole moments of the α-CD-acetophenone complex

Species and method	HF energy (kJ/mol)	Stabilization energy upon complexation (kJ/mol)	HOMO (eV)	LUMO (eV)	HOMO-LUMO gap (eV)	Dipole (Debye)
α-CD (PM3)	-5212.4	-	-10.82	1.41	12.23	-
α-CD (HF)	-9504854.7	-	-10.87	5.17	16.04	5.10
α-CD (B3LYP)	-9558750.8	-	-6.34	0.95	7.29	5.37
Acetophenone (PM3)	-75.5	-	-9.99	-0.44	9.55	-
Acetophenone (HF)	-997605.0	-	-9.47	2.36	11.83	3.24
Acetophenone (B3LYP)	-1004011.4	-	-6.57	-1.40	5.17	2.75
Acetyl up complex (PM3)	-5331.0	-43.1	-10.12	-0.60	9.52	-
Acetyl up complex (HF)	-10502401.1	58.6	-9.74	2.05	11.79	7.74
Acetyl up complex (B3LYP)	-10562749.1	13.1	-6.21	-1.57	4.70	7.49
Acetyl down complex (PM3)	-5338.3	-50.4	-10.06	-0.53	9.53	-
Acetyl down complex (HF)	-10502433.4	26.3	-9.66	2.21	11.87	3.80
Acetyl down complex (B3LYP)	-10562776.0	-13.8	-6.41	-1.45	4.96	4.30

The structures of the acetyl up and acetyl down complexes optimized by the PM3 method were shown in **Figure 1**. The HF energies, stabilization energies upon complexation, the energy levels of the frontier molecular orbitals, and dipole moments calculated by the PM3, HF/3-21G*, and B3LYP/3-21G* methods were summarized in **Table 1**.

Figure 1. Structures of the PM3-optimized α-CD-acetophenone complex seen from the end of the secondary hydroxyls of the CD. (a) Acetyl up, and (b) acetyl down orientations.



(a) (b)

From **Table 1**, it can be seen that there is some difference between the calculation results by the PM3, HF/3-21G*, and B3LYP/3-21G* methods. The difference in HF energy is due to the specific definition of the PM3 method and hence not comparable. However, the observation that B3LYP/3-21G* always provides significant lower energy for a certain species than HF/3-21G* is obvious.

The difference in the stabilization energy is comparable. From **Table 1**, it can be seen that PM3 indicates that the complexation under both orientations is favorable in energy. However, HF/3-21G* suggests that the two kinds of complexation orientations are both highly unstable. In contrast, B3LYP/3-21G* indicates that the acetyl down orientation is favorable while the acetyl up one is unstable. Herein, it is worthwhile to point out the positive energy in the HF and DFT calculations does not necessarily mean that the complexation is unfavorable, for the large complexed system is optimized at the level of PM3 but not HF/3-21G* and B3LYP/3-21G*. The latter two methods are now too CPU-costing to be practical.

Interestingly, the present results by PM3, HF/3-21G*, as well as B3LYP/3-21G* all indicate that the acetyl down orientation is more favorable than the acetyl up orientation with a significant energy difference. This seems in controversy with the conventional viewpoint that the anti-parallel arrangement of the dipoles of the host and guest molecules is preferable in the CD complexation[6], since the $COCH_3$ group is obviously electron withdrawing. However, the present results corroborate recent experimental observations, which also suggested that the acetyl down orientation might be preferred in α-CD-acetophenone system[12]. Herein, the three smallest distances separating the hydrogens of the $COCH_3$ group and those of the α-CD molecule in the PM3-optimized complex are measured to be 174 pm, 176 pm and 221 pm for the acetyl up orientation.

These values are considerably less than the sum of the van der Waals radii of two hydrogens which should be 240 pm. This is caused by the structure of the $COCH_3$ group, whose approximation to the narrower rim of the α-CD is greatly unfavorable in energy due to the van der Waals repulsion. Although herein the van der Waals repulsion is not too large to destroy the complex, it obviously overweighs the dipole-dipole interactions in determining the orientation of host-guest complexation.

The dipole moments of the host, guest, and their complex are interesting. From **Table 1** it can be seen that the acetophenone and α-CD molecules both possess large dipole moments. Although the acetyl down orientation will arrange the dipoles of the host and guest in parallel, the dipole moment of the complex is actually smaller than that of the free α-CD. This finding is important. It indicates that the conformational change plays a document role in determining the dipole of the CD and their complexes. Hence, the simple rule that the anti-parallel arrangement of the dipoles of the host and guest molecules is preferable in the CD complexation is in fact not soundly founded. Interestingly, the dipole moment of the acetyl up complex, in which the dipoles of host and guest are arranged in anti-parallel, is significantly larger than that of the free α-CD. This again proves that the conformation change is important to the dipole of the CD. It also explains why the acetyl down orientation is more favorable in energy.

Comparing the energy levels of the frontier molecular orbitals calculated by PM3, HF/3-21G*, and B3LYP/3-21G* indicate that the frontier molecular orbitals of the complex are similar with those of acetophenone. Hence, the spectroscopic and chemical properties of the complex should also be similar with those of acetophenone. This result is obvious, since the chemical reactivity of acetophenone is surely active than that of the α-CD.

Conclusions

Ab initio calculations at the level of Hartree-Fock theory and Density Functional Theory have been applied to the inclusion complexation of α-CD with acetophenone for the first time. The results indicate that the acetyl down orientation is preferable in energy than the acetyl up one, which is in accordance with experimental observations.

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