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# A PM3 Molecular Orbital Study on the Conformational Equilibrium of Cyclohexane upon $\alpha$ -Cyclodextrin Inclusion Complexation

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**Abstract** The effect of  $\alpha$ -cyclodextrin ( $\alpha$ -CD) inclusion complexation on the conformational equilibrium of cyclohexane was studied with the semiempirical PM3 molecular orbital calculations. The calculation results indicated that the chair form of cyclohexane is 18.5 kJ·mol<sup>-1</sup> lower than that of boat one in energy, however, the  $\alpha$ -cyclodextrin inclusion complex of boat cyclohexane is 4.4 kJ·mol<sup>-1</sup> more stable than the complex of chair form. It demonstrated that the conformational equilibrium of cyclohexane was influenced by the  $\alpha$ -CD inclusion complexation. Hence, caution should be given when extrapolating the conformational behaviors of the guest compounds in the supramolecular systems to their free forms, since the interactions between the host and guest significantly affect the conformation of the guest compounds.

**Key words**  $\alpha$ -Cyclodextrin , Cyclohexane , Conformational equilibrium , PM3

## 1 Introduction

Cyclodextrins (CD), a group of cone-shaped macrocyclic oligomers of  $\alpha$ -D-glucose, can form inclusion complexes with many organic compounds in aqueous solution<sup>[1]</sup>. The molecular recognition of CD has attracted much interest since it offers valuable insights into the non-covalent interactions in supramolecular science and biochemistry<sup>[2]</sup>. Meanwhile, CD can mediate a number of organic reactions<sup>[3]</sup>, and these reactions are regarded as nice models mimicking the enzyme systems<sup>[4]</sup>.

Computation studies on CD illustrate the driving forces and regioselectivity in the molecular recognition, and hence attract considerable attentions<sup>[5]</sup>. For the large size of the cyclodextrin complexes, most computational studies on CD chose molecular mechanics (MM)<sup>[6]</sup> or molecular dynamics (MD)<sup>[7]</sup> methods based on various empirical forcefields. However, quantum mechanics (QM) study on CD has also gained much attention recently since it could provide more detailed information.

To date, QM studies on CD are restricted in the semi-empirical molecular orbital methods including CNDO<sup>[8]</sup> and AMI<sup>[9-13]</sup>. Most of them were fixed-geometry computation, or partial optimization under certain symmetry constraints. Recently, full geometry optimization of CD complexes using AM1 was reported<sup>[10,12]</sup>. It has been applied to the complexation between CD

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and organic dyes<sup>[13]</sup>. Furthermore, the host-guest interaction in CD complexes was also investigated by the ab initio calculation on certain model compounds<sup>[14]</sup>.

Recently, we studied the molecular recognition of cyclodextrin by QM method and obtained interesting results<sup>[15,16]</sup>. In the present study, the conformational equilibrium of cyclohexane in  $\alpha$ -CD-cyclohexane complex was studied. The advanced semiempirical molecular orbital method PM3<sup>[17]</sup> was employed and a complete unrestricted geometry optimization was performed.

## 2 Method

All the calculations were performed using a GAUSSIAN 94 software package<sup>[18]</sup>.  $\alpha$ -CD was optimized by PM3 from the experimental structure<sup>[19]</sup>. The chair and boat conformers of cyclohexane was constructed by means of MOLGEN and optimized with PM3<sup>[15,16]</sup>. The inclusion complex was constructed by the PM3-optimized  $\alpha$ -CD and cyclohexane. Two complexation conformers, chair and boat cyclohexane, were considered. For each complex, several starting points were tried. The optimum geometry with the minimum energy was shown in Fig. 1 and 2, and the key features of the complexes were summarized in table 1.

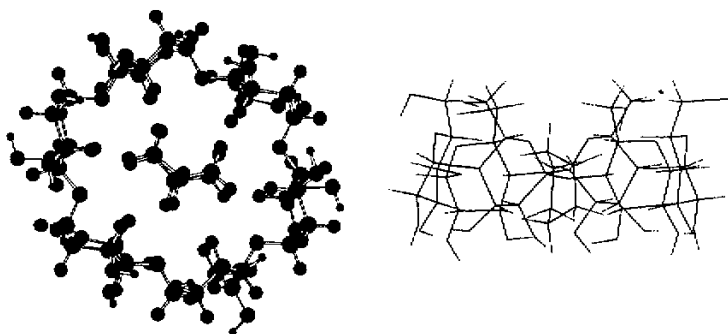


Fig. 1 Structures of the energy minimum obtained by the PM3 calculations for the  $\alpha$ -CD-boat cyclohexane complex  
Seen from the end of the secondary hydroxyls of the  $\alpha$ -CD (a) and from the side of the  $\alpha$ -CD wall (b)

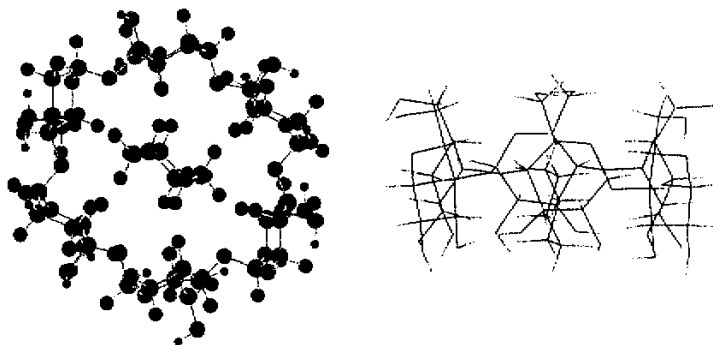


Fig. 2 Structures of the energy minimum obtained by the PM3 calculations for the  $\alpha$ -CD-chair cyclohexane complex  
Seen from the end of the secondary hydroxyls of the  $\alpha$ -CD (a) and from the side of the  $\alpha$ -CD wall (b)

Species	Cyclohexane		$\alpha$ -CD	Complex	
	( Boat )	( Chair )		( Boat )	( Chair )
Heat of formation/ $\text{kJ}\cdot\text{mol}^{-1}$	-111.60	-130.10	-5212.40	-5388.40	-5402.50
Stabilization energy/ $\text{kJ}\cdot\text{mol}^{-1}$	-	-	-	-64.40	-60.00
HOMO /eV	-10.80	-11.28	-10.82	-10.66	-10.78
LUMO /eV	3.51	3.47	1.41	1.40	1.36
LUMO-HOMO energy gap /eV	14.31	14.75	12.23	12.06	12.14
Mulliken charge of the cyclohexane	-	-	-	+0.0153	+0.0137

### 3 Results and Discussion

The negative stabilization energy gained here, its magnitude was in agreement with most molecular mechanic studies on the CD complexation, indicated that  $\alpha$ -CD could form stable complex with cyclohexane. This result was in contrast to the positive stabilization energy obtained by AM1 in the CD complexation<sup>[12]</sup>, which might be due to the better performance of PM3 on hydrogen bonding than AM1<sup>[20]</sup>. Thus, compared to AM1, PM3 seems a better promising tool at the level of quantum mechanics in studying the CD systems.

Interestingly, the results here indicated that the  $\alpha$ -CD inclusion complexation with boat cyclohexane is more favorable than its inclusion complexation with chair cyclohexane by a significant energy difference of  $4.4 \text{ kJ}\cdot\text{mol}^{-1}$ . Hence, although the energy gap between the two free cyclohexane conformers amounts to  $18.5 \text{ kJ}\cdot\text{mol}^{-1}$ , the energy gap between the two complexed conformers decreases to  $14.1 \text{ kJ}\cdot\text{mol}^{-1}$ . This result is interesting, since it indicates that the molecular recognition can exert significant influence on the conformational equilibrium of the guest compound. Since the conformation of the biological substrates often determines their bio-activities, the present result suggests that the enzymes should play important roles in the biochemical reactions by stabilizing certain conformers of the substrates. It also suggests that caution should be given when extrapolating the conformational behaviors of the guest compounds in the supramolecular systems to their free forms.

The energies of HOMO and LUMO of the complex were found to be close to those of the  $\alpha$ -CD. The energy gap between HOMO and LUMO of the complex also approximated that of the  $\alpha$ -CD. This result is reasonable, since the guest compound is a saturated inert hydrocarbon. Hence, the chemical reactivity of whole supramolecular system will be determined by relatively more reactive host  $\alpha$ -CD.

Mulliken charge analysis revealed that in the host-guest complex the cyclohexane molecule as a whole would obtain a nontrivial amount of positive charge. This observation was interesting, since both the host and guest molecules had a full-filled shell of electrons, in which every atom had obtained the octet stability according to the Lewis's octet theory<sup>[21]</sup>. It indicated that the molecular orbitals of the host and guest molecules, which were constituted upon the combination of the atomic orbitals, would further overlap upon the supramolecular complexation. Electrons would then be redistributed among the supramolecular species according to the energy-minimum

rule. And here the electrons flowed from cyclohexane to  $\alpha$ -CD, which means that cyclohexane is an electron donor (a Lewis base) and  $\alpha$ -CD serves as an electron acceptor (a Lewis acid) in the complexation. Therefore, the essential driving force for the molecular recognition is as same as the stabilization effect of the conventional chemical bonding.

## 4 Conclusions

In summary, PM3 was shown to be a promising novel tool for the molecular recognition of CD. Its calculations on the complexation of  $\alpha$ -CD with cyclohexane clearly demonstrated that molecular recognition would exert significant influence on the conformational equilibrium of the guest compound. Hence, caution should be given when extrapolating the conformational behaviors of the guest compounds in the supramolecular systems to their free forms. Quantum chemical analysis indicated that the molecular orbitals of the host and guest compounds would further overlap, which resulted in the electron redistribution among the host and guest molecules upon the complexation.

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## $\alpha$ - 环糊精包合物中环己烷构象平衡的 PM3 研究

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摘 要 : 用 PM3 分子轨道方法研究了  $\alpha$  - 环糊精的包合作用对环己烷构象平衡的影响。发现  $\alpha$  - 环糊精的包合作用可以改变环己烷的构象平衡。计算结果表明 , 虽然环己烷的椅式构象比船式构象稳定  $18.5 \text{ kJ} \cdot \text{mol}^{-1}$  , 但在  $\alpha$  - 环糊精的包合物中 , 船式环己烷包合物比椅式环己烷包合物稳定  $4.4 \text{ kJ} \cdot \text{mol}^{-1}$  。因此 , 超分子体系中客体分子的构象平衡不能简单地从其游离态的构象平衡外推得到 , 而应该考虑在超分子体系中分子间相互作用对构象的影响。

关键词 :  $\alpha$  - 环糊精 ; 环己烷 ; 构象平衡 ; PM3

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