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Original Article

Use of Quantum Chemical Methods to Study Cyclodextrin Chemistry

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Abstract

Studies of cyclodextrin chemistry by quantum chemical methods are briefly surveyed. Emphases are put on what types of quantum chemical methods can be used for cyclodextrin chemistry, how to use quantum chemical methods to find the global minimum, to study the structures, binding energies, driving forces for cyclodextrin complexes, as well as chemical reactions occurring inside cyclodextrin cavities. Problems associated with the application of quantum chemical methods in cyclodextrin chemistry are also discussed.

Introduction

Cyclodextrins are macrocyclic oligomers of α-D-glucose [1]. They are shaped like truncated cones with primary and secondary hydroxyl groups crowning the narrower rim and wider rim, respectively. Three species of CDs are the most widely used [2]. They have rings comprising from 6 to 8 glucose units: α-CD (6 units), β-CD (7 units), and γ-CD (8 units) (Figure 1). Because CDs have a hydrophilic exterior and a hydrophobic cavity of appropriate dimension, they can bind with various guest molecules to form inclusion complexes in aqueous solution [3]. This property has enabled CDs to be widely used in pharmaceutical science [4], catalysis [5], separation technology [6] and other areas [7]. Furthermore, the CD inclusion complexation has been considered an ideal model mimicking the enzyme–substrate interactions [8].

Because of the diverse applications of CDs, during the past several decades considerable efforts have been devoted to CD chemistry. Many experimental methods such as UV, IR, fluorescence, circular dichroism, calorimetry, and NMR have been developed to study the complexation behaviors of native and functionalized CDs [9]. In order to get a better understanding of the binding events, a lot of theoretical methods [10] including molecular mechanics (MM) [11], molecular dynamics [12], and more recently, quantum mechanics (QM) methods, have also been used to study the CD complexes. All these experimental and theoretical methods, when properly utilized in combination with each other, have proven to be extremely powerful in solving the structural, energetic, and dynamic problems associated with CD complexes.

The focus of the present paper is to survey the progress that has been made in the use of QM methods to study CD chemistry. We will show, on the basis of the recent research results obtained by many others and ourselves, how the QM methods can be used to study CD complexes, what have been achieved so far in this field, and what remain to be done in the future. Before the survey, it is worthwhile to give a few remarks about the choice of QM or MM methods in the study of CD chemistry. (1) MM method is much less resource-demanding than QM method. However, we should keep developing and trying QM methods in the study of supramolecular chemistry because it is our ultimate goal to fully understand supramolecular chemistry on the basis of first principles. (2) MM method has difficulty in solving problems associated with the open-shell systems (i.e., radicals, excited states), reaction transition states, and transition metal ions. In comparison, QM method can provide the electronic structure of the system and it does not, in principle, have any problem with any exotic chemical system.

Use of different quantum chemistry methods in CD chemistry

CNDO

The CNDO method is the first semiempirical QM method that went beyond just π electrons [13]. This method uses a minimal valence basis set of Slater-type orbitals, in which each atom has the usual number of valence atomic orbitals. It is the lowest-level QM method that can be applied to the whole CD system.

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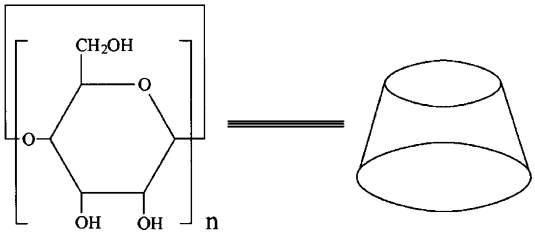


Figure 1. Structure of cyclodextrin ($n = 6$(α-CD), $n = 7$(β-CD), $n = 8$(γ-CD)).

Sakurai *et al.* pioneered the application of CNDO method to CD chemistry [14]. They used the CNDO method to study the dipole moments of α-CD and its complexes with aromatic guest molecules. They found that α-CD has a remarkably large dipole moment which amounts to 13.5 and this dipole moment is directed from the secondary hydroxyl side of α-CD towards the primary hydroxyl side of α-CD. The dipole moments of the guest molecules, benzene derivatives, run antiparallel to that of α-CD in the complexes (see Figure 2). The CNDO total energies of the α-CD-aromatic guest systems show that these antiparallel orientations are energetically more favorable than the reversed ones. These results are in excellent agreement with the results from the X-ray diffraction studies on the complexes in the crystalline state and the results from the NMR studies on the complexes in the solution. It was concluded that the electrostatic interaction, mainly dipole–dipole interaction, between α-CD and guest plays an essential role for the inclusion complex formation.

Sakurai's later studies using the CNDO method showed that the dipole moments of different CDs increase in the order α-CD < β-CD < γ-CD [15]. They demonstrated that the dipole–dipole interaction is also important for the orientation of the guest molecules in the cavities of other CDs.

MNDO, AM1, and PM3

MNDO is a modified the neglect of diatomic differential overlap (NDDO) method [16]. It uses a minimal valence basis set of Slater-type orbitals and the one-center core integrals. AM1 (Austin method 1) is an improved version of MNDO in which the main change is that the core–core repulsion is modified to overcome the tendency of MNDO to overestimate repulsions between atoms separated by about their van der Waals distances [17]. PM3 is a variation of AM1, differing mainly in how the parameterization is done [18]. Comparing AM1 and PM3 methods, Anh *et al.* have shown that PM3 tends to give more reliable structures whereas AM1 tends to provide better energetics [19].

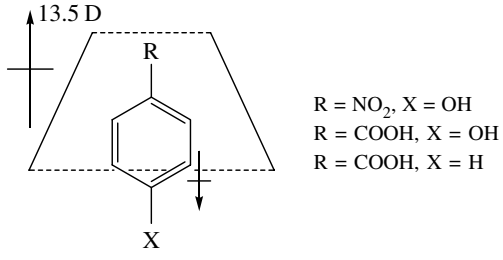


Figure 2. Orientation of aromatic compounds in α-CD cavity.

Since 1995 [20, 21] a number of groups have used the AM1 and PM3 method to study CDs and their complexes. Among them, three groups have studied in detail about the performances of AM1 and PM3 methods on CD systems. In 1995, Bodor *et al.* studied the performance of the AM1 method on natural and alkylated α-and β-CDs [20b]. Three geometries were considered: (1) Molecular mechanics optimized geometry; (2) AM1 fully optimized geometry; (3) X-ray structures based on the experimental coordinates for heavy atoms with positions of hydrogen atoms optimized by AM1. Large differences between the three geometries were found. Nevertheless, the difference between the second and the third geometry is relatively small and could be attributed to crystal packing forces.

In 1999, Avakyan *et al.* performed detailed studies on the performance of PM3 method on CDs [22]. They found that the minimum energy structure of β-CD should have C_7 symmetry. They proposed that the symmetry was caused by the ring of interunit hydrogen bonds formed by the protons of the 2-OH groups and the oxygen atoms of the 3′-OH groups of the glucose units. Preferableness of this orientation of interunit hydrogen bonds was confirmed by *ab initio* calculations on maltose at MP2/6-31G(d,p) level. Therefore, the PM3-optimized structure for β-CD was believed to be reliable. In comparison, the geometry for β-CD was predicted to be asymmetric by the MM method. Avakyan *et al.* suggested that the asymmetric shape of β-CD should be incorrect and should be caused by the inadequacy of the MM methods in dealing with hydrogen bonds.

In 2000 we also performed some studies about the performances of AM1 and PM3 methods on CD systems [23]. On the basis of AM1 and PM3 calculation results for some model compounds including β-hydroxyethyl ether and α-(1 → 4)-glucobiose, we suggested that PM3 should be advantageous to AM1 in CD chemistry because PM3 can deal with the O—H···O hydrogen bonds better than AM1. This proposal 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 *and DFT methods*

Compared to the semiempirical methods, *ab initio* and density function theory (DFT) methods are extremely CPU-demanding for the CD systems which contain over 60 non-hydrogen atoms. Currently it is still too hard to use any *ab initio* or DFT method to optimize the

Table 1. Total electronic energy (10^6 kJ/mol) and dipole moments (D) of α- and β-CDs

State	Method	α-CD		β-CD	
		Electronic energy	Dipole moment	Electronic energy	Dipole moment
Crystalline	HF/3-21G	−9.5046	9.32	−11.0870	13.12
	HF/6-31G(d)	−9.5571	8.60	−11.1486	12.04
	B3LYP/3-21G	−9.5585	8.54	−11.1499	11.66
	B3LYP/6-31G(d)	−9.6112	8.35	−11.2116	11.01
PM3-optimized	HF/3-21G	−9.5048	5.10	−11.0888	3.50
	HF/6-31G(d)	−9.5576	4.67	−11.1504	2.97
	B3LYP/3-21G	−9.5588	5.21	−11.1517	3.73
	B3LYP/6-31G(d)	−9.6116	4.87	−11.2134	3.07

structure of a CD or CD complex. Nevertheless, we have demonstrated recently that it is possible to carry out single point energy calculations on the CD complexes using fairly high-level *ab initio* and DFT methods [23, 24].

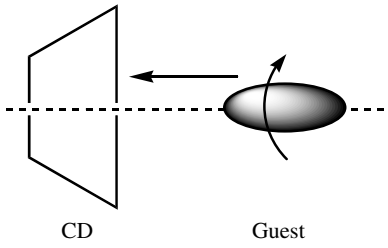
Using a number of *ab initio* and DFT methods, we have calculated the total electronic energies and dipole moments of α- and β-CDs in their crystalline or PM3-optimized structures (see Table 1) [23]. As seen from Table 1, all the theoretical methods suggest that the PM3-optimized structures have low energies than the crystalline structure. Therefore, the structures of free CD molecules should be closer to the PM3-optimized structures than to the crystalline ones. Interestingly, in the crystals both α- and β-CDs have fairly large dipole moments. However, in the PM3-optimized structures both α- and β-CD have relatively low dipole moments. The considerable change in dipole moment is in agreement with the structure flexibility of CD molecules. It is also understandable that CDs in the crystal tend to have large dipole moments in order to maximize the electrostatic interaction to each other, while free CD molecules tend to have small dipole moments in order to minimize the polarization of the whole molecule.

Use of quantum chemistry method to study the structures of CD complexes

Search for global minimum

In Sakurai's early work [14, 15] the authors could not carry out any geometry optimization due to the resource limitation at that time. Thus they only performed single point energy calculations of the CD complexes using the crystalline structures. This single point energy approach is clearly not sufficient when we need to use the quantum chemistry method to predict the structures of CD complexes. Therefore, geometry optimization on the CD complexes is necessary.

Unfortunately, others and we have found that geometry optimization of CD complexes is a multiple minimum problem. The whole potential energy surface is fairly complicated and there are a lot of local minima.



Scheme 1.

Strictly we need to utilize the statistical sampling method to describe the observable thermodynamic parameters for this kind of potential surface. Nonetheless, others and we have found that the global minimum is usually located fairly deeply compared to the other local minima on the potential energy surface. Therefore, for many cases it would be sufficient to use the energy of the global minimum to describe the whole complex system.

A simple and fast method has been developed for the search of global minimum on the potential energy surface of a CD complex. When using this method, the first step is to use the glycosidic oxygen atoms of CD to define the XY plane and to use the center of the plane as the center of the coordination system. Then the guest molecule was placed along the Z axis of the coordination system, where a few different orientations of the guest molecule relative to CD must be taken into consideration if the CD complex has several different binding modes. In the third step, the guest molecule is allowed to enter and then pass through the CD molecule by steps. At each step the geometry of the complex is fully optimized by a certain theoretical method (see Scheme 1). Sometimes, in order to improve the accuracy we should rotate the guest molecule to find the optimal angle at each step. In this way the whole potential energy surface can be scanned and the global minimum can be identified.

Studies about the structures of CD complexes

Using the above method for the search of global minimum, others and we have been able to investigate the structures of a number of CD complexes [25–38].

However, since in most of these studies the solvent effects have not been taken into consideration, the results may only be relevant to the binding events occurring in the gas phase or in the crystalline state. Therefore, in the following we will not discuss in detail about these studies. Instead, we briefly summarize in Table 2 all the studies that have been reported.

Nevertheless, a few studies have taken the solvent effects into consideration. In 2000, Dos Santos *et al.* studied the complexation of α-CD with methyl mercury chloride using the PM3 method [38]. The solvation effect of water was included by explicitly adding three to six water molecules to the system. The calculation results suggested that the structure of the complex should have CH_3HgCl situated perpendicular to the α-CD ring but not parallel. The results also suggested that in the complex the methyl group of CH_3HgCl should stay close to the primary hydroxyl side of α-CD. Furthermore, the experimentally observed Raman shift for the Hg–Cl stretching mode after the complexation was used in conjunction with the respective PM3 calculated vibrational frequencies for the determination of the preferred structure for the inclusion complexes.

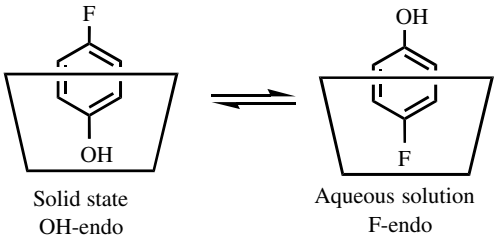
Also in 2000, we used the PM3 method to study the structure of the complex between α-CD and 4-fluorophenol [39]. This is quite an interesting case, because X-ray studies on the solid complex of α-CD with 4-fluorophenol revealed that the OH group of phenol was hidden inside the CD cavity (OH-endo) [40] while NMR experiments indicated that the F remained inside and OH outside the CD cavity in aqueous solution (F-endo) [41] (see Scheme 2).

From PM3 calculations we found that the gas-phase binding energy for the OH-endo structure is −35.6 kJ/mol while the binding energy for the F-endo structure is −31.6 kJ/mol. Therefore, the OH-endo structure should the favored one in the solid state. This result is in good agreement with the experimental finding. Further analyses indicated that in the OH-endo structure there is an O—H···O hydrogen bond between the phenol and cyclodextrin (see Figure 3). This hydrogen bond is absent in the F-endo structure.

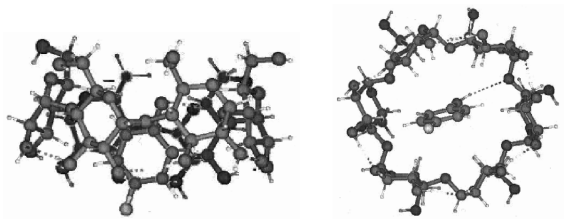
Thus, the fact that F-endo is favored in the aqueous solution must be caused by the solvent effect. For 4-fluorophenol we proposed that this solvent effect stems mainly from different hydrogen bonding either between F and water or between OH and water. For the OH-endo structure, only F can form hydrogen bond with water. The energy of this F···H—OH hydrogen bond is calculated to be −11.3 kJ/mol. For the F-endo structure, only OH can form hydrogen bond with water. The energy of this $OH\cdots OH_2$ hydrogen bond is calculated to

Table 2. Use of QM methods to investigate the structures of CD complexes

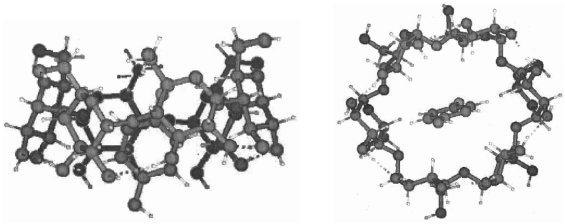
Year	Method	System	Reference
1996	AM1	β-CD-1,7-dioxaspiro[5.5]undecane β-CD-nonanal	[25]
1996	AM1	α-CD-methylated benzoic acid α-CD-phenol β-CD-methylated benzoic acid β-CD-phenol γ-CD-C_{60}	[26]
1996	PM3	β-CD-$PF6^-$	[27]
1997	AM1	β-CD-methylated benzoic acid	[28]
1997	AM1	α-CD-benzoic acid α-CD-phenol β-CD-benzoic acid β-CD-phenol	[29]
1998	AM1	β-CD-aromatic norbornadiene derivatives	[30]
1999	PM3	α-CD-acetophenone	[31]
2000	PM3	α-CD-benzaldehyde α-CD-acetophenone	[32]
2000	PM3	β-CD-salbutamol	[33]
2002	AM1, PM3	β-CD-(3-sulfonatophenyl)(phenyl)-phosphine	[34]
2002	PM3	α-CD-I_3^-	[35]
2002	AM1	β-CD-steroids	[36]
2002	PM3	α-CD-Li^+, α-CD-Na^+ α-CD-F^-, α-CD-Cl^- β-CD-Li^+, β-CD-Na^+ β-CD-F^-, β-CD-Cl^-	[37]



Scheme 2.



(a) OH-endo



(b) F-endo

Figure 3. OH-endo and F-endo structures for the complex between α-CD and 4-fluorophenol.

be −16.2 kJ/mol. The difference in the hydrogen bonding energy is 4.9 kJ/mol favoring the F-endo structure. The difference in the CD binding energy is 4.0 kJ/mol favoring the OH-endo structure. Therefore, in aqueous solution the F-endo structure is the favored one because of the solvent effect.

Use of quantum chemistry method to study the energetics of CD complexes

Radicals and excited states

As mentioned earlier, the MM methods have difficulty in dealing with radicals and excited states. In comparison, the QM methods can relatively easily solve the problems associated with the open-shell species. Therefore, at times it is not only advantageous, but also necessary, to use the QM method to study CD chemistry.

In CD chemistry, although under most conditions the complexes are formed between CDs and the ground-state guest molecules, there are many occasions when we have to face the complexes between CDs and excited-state guest species. Among the many CD complexes of excited-state species, the xanthone-CD system is a representative one [42]. This system is also very intriguing because it has been demonstrated that the binding constant of β-CD (or Hp-β-CD and γ-CD) with excited triplet xanthone is much smaller than that with the ground state one. Caution was advised in extrapolating excited state behavior to the supramolecular systems in their ground state, but the origin of such a behavior had remained unclear for quite a while.

We recently conducted a QM study on the complexation of β-CD with ground-state or excited triplet state xanthone [43]. The PM3 method was used for the geometry optimization and the B3LYP/3-21G method was used for the final energy calculations. We found that the global minimum structure for the ground state β-CD-xanthone complex is very close to that for the excited triplet state β-CD-xanthone complex (see Figure 4). Despite these similar structures, the binding energy for the ground state xanthone was calculated to be −58.9 kJ/mol whereas the binding energy for the excited triplet state xanthone was calculated to be −37.6 kJ/mol. Therefore, the ground state complex is indeed much more stable than the excited triplet state one. This result is in excellent agreement with the experimental findings. A possible reason for the low stability of the triplet state complex is that the oxygen of the triplet xanthone is less negatively charged and therefore, has a weaker interaction with the hydroxyl groups of β-CD.

Besides the excited-state molecules, another group of unstable guest molecules for CDs are the radicals and radical ions [44]. Recently, we and several other groups found through detailed experimental studies that the binding constant for the phenothiazine radical cation with β-CD is significantly larger than that measured for the neutral phenothiazine [45]. This intriguing behavior cannot be explained by the hydrophobic effect because the phenothiazine radical cation should be more hydrophilic than the neutral phenothiazine. Thus we used the QM method and studied the physical origin of this behavior [46].

The PM3 method was used in the geometry optimization (see Figure 5). The final energy calculation was performed using the B3LYP/3-21G(d) method. It was found that the binding energy for the neutral phenothiazine is −10.9 kJ/mol in the gas phase. The binding energy for the phenothiazine radical cation is −99.6 kJ/mol in the gas phase. Further calculations were performed to include the solvation effect of water using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method [47]. It was found that the hydrophobic effect lowers the difference between the binding energies for neutral phenothiazine and phenothiazine radical cation. Nonetheless, the binding energy for phenothiazine radical cation is still much larger than that for neutral phenothiazine in water. Therefore, both the theoretical and experimental studies suggest that phenothiazine radical cation has a higher binding constant with β-CD than the neutral phenothiazine.

Charge transfer interaction is a driving force for CD complexation

In our recent studies on the complexation of CDs with diverse compounds we noticed a very interesting behavior. That is, the binding constant for the complex

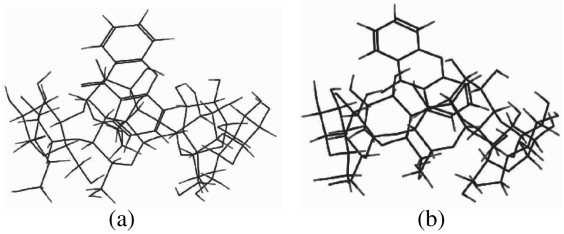


Figure 4. Structures of the energy minimum obtained by PM3 for the β-CD complex with: (a) singlet xanthone. (b) triplet xanthone.

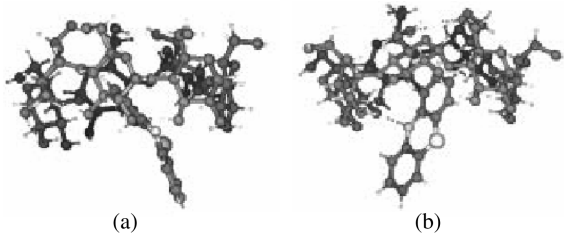


Figure 5. Structures of the energy minimum obtained by PM3 for the β-CD complex with: (a) neutral phenothiazine. (b) phenothiazine radical cation.

between α-CD and 4-nitrophenolate ($K_a \approx 2500\ M^{-1}$) is about ten times larger than that for the complex between α-CD and 4-nitrophenol ($K_a \approx 250\ M^{-1}$). Clearly this behavior cannot be interpreted using the hydrophobic effect because 4-nitrophenolate is more hydrophilic than 4-nitrophenol. The effect cannot be explained either by the hydrogen bonding effect because 4-nitrophenol is a good proton donor but 4-nitrophenolate is not a good proton acceptor. Furthermore, the effect cannot be explained by the dipole–dipole interaction because the dipole moment of 4-nitrophenol is 5.34 D while the dipole moment of 4-nitrophenolate is 0.89 D.

Our own explanation, on the basis of QM calculation results, is that the charge transfer interaction between α-CD and 4-nitrophenolate is larger than that between α-CD and 4-nitrophenol. This explanation is supported by the following reasons [48]: (1) The Mulliken charge of α-CD in α-CD–4-nitrophenol complex is −0.0042e while the Mulliken charge of α-CD in α-CD–4-nitrophenolate complex is −0.0163e. (2) From 4-nitrophenol to α-CD–4-nitrophenol complex, the HOMO energy decreases from −10.16 to −10.28 eV. From 4-nitrophenolate to α-CD–4-nitrophenolate complex, the HOMO energy decreases from −4.24 to −5.12 eV. (3) From 4-nitrophenol to α-CD–4-nitrophenol complex, the LUMO energy decreases from −1.08 to −1.23 eV. From 4-nitrophenolate to α-CD–4-nitrophenolate complex, the HOMO energy decreases from +3.82 to +2.92 eV. All the results are consistent with the proposal that the charge transfer from 4-nitrophenolate to α-CD is larger than that from 4-nitrophenol to α-CD.

It is worth mentioning that charge–transfer interaction is in fact a type of van der Waals interaction [49]. However, as in the field of CD chemistry the term van der Waals interaction usually refers to the combination of induction and dispersion forces, it seems necessary to discuss the role of charge–transfer interaction separately. As is known, unlike the induction force in which the electron distribution of a molecule involved in the interaction is distorted within the molecule itself, in charge–transfer interaction the electrons of the higher-lying occupied molecular orbitals of one molecule are transferred into the low-lying unoccupied molecular orbitals of another molecule.

Chiral recognition

Very few groups have used the QM methods to study the chiral recognitions by CDs. In 2002, Zborowski and Zuchowski used the AM1 method to study the interaction between β-CD and alkyl derivatives of 5-ethyl-5-phenyl-2-thiobarbituric acid enantiomers [50]. Both the neutral and anion forms of the guest molecules were considered. The chiral discrimination of enantiomers was analyzed in terms of differences in the calculated interaction energies. The calculated interaction energies between each enantiomer of the investigated 2-thiobarbiturates and β-CD confirmed the ability of β-CD to act as a mobile phase additive in reversed-phase HPLC to separate enantiomers and rationalize their order of elution.

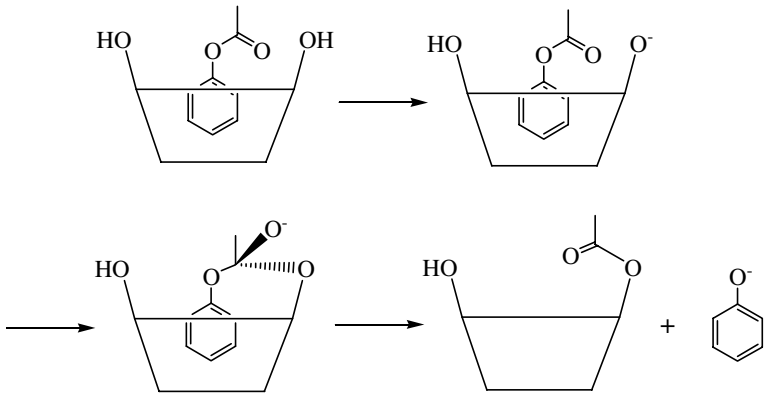
Use of quantum chemistry method to study the reaction of CD complexes

Compared to the MM method, it is more reliable to use the QM method to study the reaction mechanism. The major reason for this is that most force fields are not parameterized for the transition state where some bonds are partially broken or formed. In comparison, the QM method is founded on the first principles and should be able to deal with the transition state without much difficulty. Despite this advantage, so far very few groups have used the QM methods to perform mechanistic studies on the reactions of CD complexes.

In 1995 Luzhov and Venanzi used the AM1 method to study the reaction of phenyl acetate with β-CD (see Figure 3) [51]. It was found that the reaction of the alkoxide ion of cyclodextrin with bound phenyl acetate in the gas phase should have a positive energy of activation. The acylation of the 3′-hydroxyl of cyclodextrin was found to be favored over the 2′-position by about 15 kcal/mol due to less structural reorganization of the macrocycle during hydrolysis at 3′-site. The results also showed that attack of 3′-hydroxyl lowered the activation energy barrier by about 10 kcal/mol compared to attack by hydroxide ion in solution. These theoretical results were in good agreement with the experimental observations (Scheme 3).

In 2000, Eto *et al*. used the PM3 method to study the pericyclic reaction of cinnamyl xanthates in β-CD cavities [52]. It was found that the phenyl ring of the guest molecules were included from the larger rim of the β-CD host molecules and the transition state structure was stabilized by a hydrogen bond with one of the hydroxyl groups of β-CD. Therefore, the rate enhancement of the retro-ene type reaction of cinnamyl xanthates in β-CD was successfully explained. Nevertheless, it was found that the ee yield of the reaction was only moderate because the [1,3]oxathiane ring was out of the β-CD cavity.

Very recently, Castro *et al*. studied the effect of β-CD on the hydrolysis of *N*-phenylphtalamide (Ph) and *N*-adamantylphtalamide (Ad) by the PM3 method [53]. Complexes of β-CD with both the reactants and all the reaction intermediates were fully optimized and their energies were calculated. It was found that all the β-CD/Ad complexes are more stable than the β-CD/Ph complexes. Therefore, there should be a stronger driving force towards complexation when the Ad-reactive was involved than when the Ph-reactive was. This prediction is in agreement with the experimental observations.



Scheme 3.

Remaining problems

Local minimum

Despite the efforts that have been devoted to solve the local minimum problem, there is still no method to guarantee the finding of the global minimum for any CD complex. Therefore, a lot of conclusions from the QM (and MM) studies on CD complexes should be considered qualitative and not absolute. Further studies on the local minimum problem are needed.

Solvation and hydrophobic effect

An important driving force for the CD complex formation in aqueous solution is the hydrophobic effect [49]. However, most QM (and MM) studies on CD complexes have not taken this important driving force into consideration. In principle there are two ways to model the solvation effect. In the first method one needs to add a sufficient number of solvent molecules into the system. This method is advantageous in that the results are easy to visualize. However, using this method one often ends up with an extremely large system, which is too hard to handle by any theoretical method. In the second method, the solvent is considered as a continuum medium with certain dielectric constant. Using this method one can easily obtain the solvation free energies and it has been shown that under many circumstances the calculated solvation free energies are quite reliable [54]. So far few people have studied how to use the continuum solvation method to describe the solvent effects involved in CD complexation. It also remains to know whether we can combine the first and second solvation methods together to treat the CD complexes more effectively.

Ab initio *molecular dynamics*

Because of the multiple minimum nature of the CD complexes, a better way to describe the CD systems is to use the molecular dynamics methodology. Molecular dynamics methods based on the force fields have a number of serious limitations because they usually do not include the electronic polarization effects and they suffer from an inability to describe chemical bond breaking and forming events. Therefore, we may need to consider the *ab initio* molecular dynamics (AIMD) methods [55]. So far the AIMD methods have never been tested in the CD chemistry, but we believe that this is going to be an important subject.

QM/MM methods

The QM methods usually have difficulty in dealing with large systems while the MM methods have less trouble with them. On the other hand, the MM methods have difficulty in dealing with unusual species such as open-shell systems and transition states while the QM methods do not have much difficulty with them. Thus it is ideal to partition a large system into a QM region and a MM region, such that only a small part of the system is treated explicated by the QM methods, but still retains the effects of the surrounding environment. This hybrid method is called QM/MM [56]. In CD chemistry, under many circumstances the CD only provides an environment effect and we are more interested in the chemistry of the guest molecules in the CD environment. Therefore, it appears a promising field to use the QM/MM method to study CD chemistry. However, this has never been done before.

Conclusion

In the present paper we surveyed the application of quantum chemical methods in studies of cyclodextrin chemistry. Some suitable methods in quantum chemistry were recommended to be employed in finding the global minimum, determining the structures of the complexes, understanding the binding energies and driving forces for the cyclodextrin complexation, and studying the chemical reactions occurred inside cyclodextrin cavities.

Furthermore, the problems which should be solved in future were discussed. These include the local minimum problem, the solvent effect, the use of the *ab initio* molecular dynamics and the QM/MM methods. We wish that our survey would interest more chemists to pay attention to this important field.

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