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Interplay between Molecular Recognition and Redox Properties: A Theoretical Study of the Inclusion Complexation of β-Cyclodextrin with Phenothiazine and its Radical Cation

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Abstract. The PM3 molecular orbital method was employed in the conformational analysis of the inclusion complexation of β-cyclodextrin with phenothiazine and its radical cation from a complete and unrestricted geometry optimization. *Ab initio* calculations at the level of HF/3-21G(d) and B3LYP/3-21G(d) were utilized to determine the electronic structures of the host, guest and their complexes. The results indicated that the complexation of β-cyclodextrin with the phenothiazine radical cation was significantly more favorable than that with the neutral one, in good agreement with the experimental observation. The charge-transfer interaction was proposed as a physical reason for such behavior. It is suggested that caution should be given when extrapolating one oxidation state behavior to the supramolecular systems in their other oxidation states.

Key words: cyclodextrin, inclusion, phenothiazine, radical cation, theoretical study.

1. Introduction

α-, β- and γ-Cyclodextrins (CDs) are cyclic oligomers of six, seven and eight α-*D*-glucose units connected through glycosidic α-1,4 bonds [1]. These compounds, usually characterized as a doughnut or wreath-shaped truncated cones, have a hydrophobic cavity of appropriate dimensions and hence can form inclusion complexes with a variety of organic compounds in aqueous solution [2].

Model studies on the inclusion complexation of CD with various substrates offer important insights into molecular recognition and enzyme-substrate interactions [3]. Theoretical calculations [4] help illustrate the driving forces for the complexation [5] and the inclusion regioselectivity in CD-catalyzed reactions [6]. Due to its large size, most studies on CD chose molecular mechanics (MM) calculation [7] and molecular dynamics (MD) simulation [8] based on various empirical

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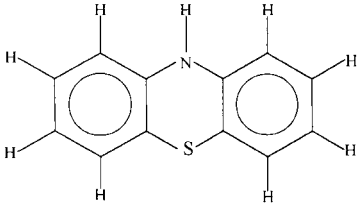
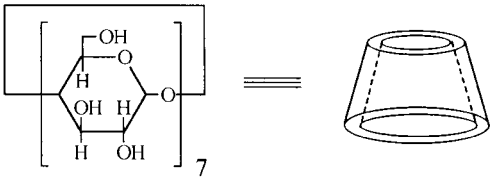
force fields. To obtain the electrostatic properties of CD explicitly, Kitagawa *et al.* presented the first quantum mechanics (QM) studies on CD with semiempirical CNDO methods [9–10]. Their calculations were based on fixed geometry. Recently, the AM1 method was found to be useful for studies of CD complexation [11]. Huang *et al.* performed a series of AM1 calculations for CD complexation with substituted phenols and benzoic acids [12–13]. However, the optimum positions of complexation were determined by trying several starting points rather than by a global search. Recently, the AM1 method was applied to the complexation between CD and organic dye [14]. Furthermore, the host–guest interaction in CD complexes was also investigated by the *ab initio* calculation of certain model compounds [15].

Computations on CD inclusion complexation have selected a variety of stable guest compounds [4], such as phenol, aniline, benzoic acid, adamantane and their derivatives. However, the interesting interplay between molecular recognition of CD and redox properties has not been a subject of a theoretical study. This theme is especially important for the enzymatic process involving redox-active substrates, e.g., in the metabolism of life [16]. The enzymes are in fact intricate and efficient molecular devices that utilize molecular recognition to control redox events. Lessons from these enzymes and their model systems can also provide valuable insights into the design of artificial molecular devices [17].

Phenothiazines represent an important class of bioactive molecules [18], whose applications to dyestuffs, antioxidants, sedative drugs, cationic initiators of polymerization, and solar energy storage materials, have attracted considerable attention. The molecular recognition between CD and the phenothiazines has been extensively studied by various experimental approaches [19] for possible pharmaceutical and industrial applications. The effect of inclusion complexation on the redox reactions of phenothiazines was also investigated [20–21], and it was found, surprisingly, that the association constant for the 10-methylphenothiazine radical cation with β-CD is significantly larger than that measured for the neutral form [22]. Dipole-induced dipole interaction and the conformation change were proposed as possible reasons, although no further theoretical investigation was carried out. Here, we report a study of the energy and geometry of β-CD complexation with the neutral phenothiazine and its radical cation. The advanced semiempirical molecular orbital PM3 method [23], which has been recently proved powerful in the conformational study of supramolecular systems [24] as well as cyclodextrin inclusion complexes [25], was employed in the geometry optimization and conformational analysis. *Ab initio* calculations at the level of Hartree-Fock (HF) and Density Functional Theory (DFT), which have not been applied in CD chemistry [4], were also performed to obtain the electronic structures of the complexes.



phenothiazine



β-cyclodextrin

2. Methods

All the calculations were performed with a GAUSSIAN 98 software package [26]. The initial geometries of neutral phenothiazine and its radical cation were constructed with the help of Molden and then optimized by PM3 using the Berny analytical gradient algorithm. The β-CD molecule was built and optimized by PM3 from the crystal structure [27]. The glycosidic oxygen atoms were placed onto the XY plane and their center was defined as the center of the coordination system. The primary hydroxyl groups were placed pointing toward the positive Z axis.

The longer dimension of the guest molecule was initially placed onto the Z axis. The position of the guest was determined by the Z coordinate of the sulfur atom of the neutral phenothiazine as well as its radical cation. The inclusion process was simulated by putting the guest in one end of the β-CD cavity and then letting it pass through the CD cavity by steps. In every step, the geometry of the host-guest complex was completely optimized by PM3 without any restriction.

Ab initio calculations at the level of HF/3-21G(d) and B3LYP/3-216(d) were used to study the electronic structures of the PM3-optimized host, guest, and their complexed molecules. In case of radical cations, the spin-unrestricted approximation (UHF or UB3LYP), where electrons with different spins occupy different sets of orbitals, was employed. The total energy, dipole moment, frontier molecular orbitals, and charge and spin density distributions have been obtained.

3. Results and Discussion

The graphic representation of the energy changes involved in the inclusion process produced two curves for the neutral and radical cation forms, respectively (Figure 1). The optimized host–guest molecular structures of both forms at each energy minimum are shown in Figure 2.

From Figure 2, it can be seen that for both the neutral and the radical cation the phenothiazine is partially included in the β-CD at the energy minimum. One aromatic ring of the phenothiazine is completely inside the CD cavity. This inclusion pattern has also been predicted by the Molecular Dynamics (MD) simulation for

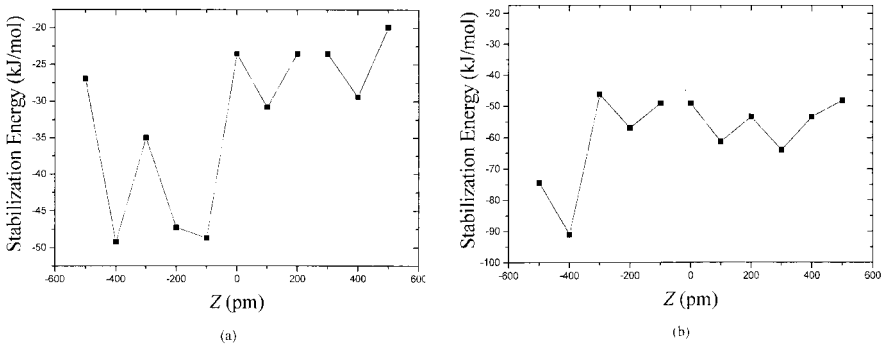


Figure 1. Graphic diagram for the simulation of the inclusion complexation of phenothiazine into β-CD. The position of the guest was determined by the Z coordinate of the nitrogen atom in the phenothiazine ring from the center of the glycosidic oxygens. (a) Neutral phenothiazine. (b) Phenothiazine radical cation.

the neutral substituted phenothiazines [28], and it is in agreement with the observed inclusion structure for the β-CD complex of a similar compound, resorufin [14].

Comparison of the calculation results of different QM methods reveals that the β-CD inclusion complexation with the phenothiazine radical cation is always favorable in energy. However, the prediction by HF/3-21G(d) indicates that the inclusion complexation of β-CD with the neutral phenothiazine is unstable, in contrast with PM3 and B3LYP/3-21G(d). Since it is a matter of experimental fact that β-CD can form a stable inclusion complex with the neutral phenothiazine, it indicates that the medium-sized basis set 3-21G(d) for Hartree-Fock theory is not high enough to well reflect the inclusion property in this special supramolecular system. In comparison, since the experimental molecular properties were used in the parameter optimization of some semiempirical methods, PM3, the precision offered by these methods is comparable to that of *ab initio* with medium-sized basis sets or even better [29, 30]. Here, the agreement between the PM3 and B3LYP/3216(d) calculations confirmed such a viewpoint.

Interestingly, the present results indicated that the complexation of β-CD with the phenothiazine radical cation was significantly more favorable than that with the neutral phenothiazine in significant energy differences (by PM3, HF/3-21G(d), and B3LYP/3216(d)). The results are in agreement with the recent experimental observation of the inclusion complexation of β-CD with 10-methyphenothiazine [22]. It is instructive, since it means that for the supramolecular system significant change can arise when the guest molecule is oxidized or reduced, even though the backbone of the guest molecule is not changed. Therefore, great caution is warranted when extrapolating one oxidation state behavior to the supramolecular systems in their other oxidation states. This also answers the question why certain enzymes can selectively stabilize specific oxidation states of the substrates or cofactors. Furthermore, it indicates that, by elaborate design, certain supramolecular devices

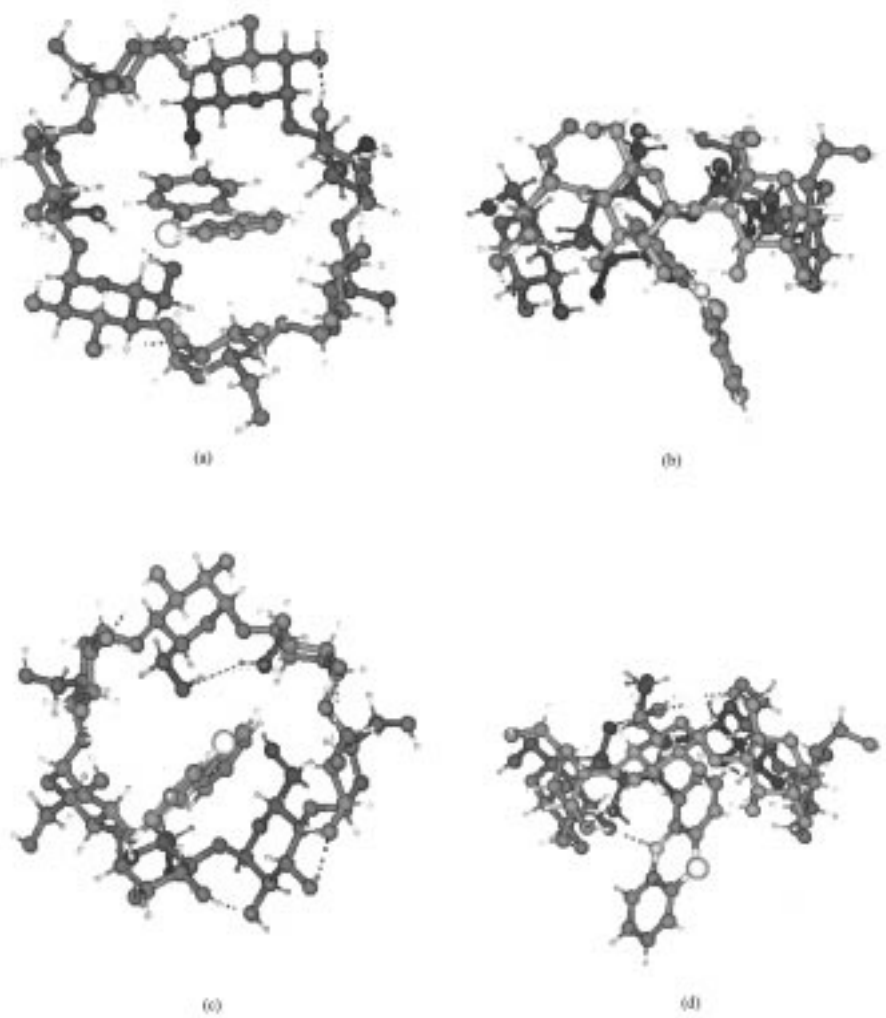


Figure 2. Structures at each energy minimum obtained by the PM3 calculations for the β-CD-phenothiazine complexes. (a) Neutral form seen from the end of the secondary hydroxyls of β-CD. (b) Neutral form seen from the side of β-CD wall. (c) Radical cation form seen from the end of the secondary hydroxyls of β-CD. (d) Radical cation form seen from the side of β-CD wall.

can selectively trigger or control a useful physicochemical process in response to the addition of an oxidizing or reducing agent.

The physical reason for such a behavior cannot be clarified by the previous theory of CD inclusion complexation, which states that the hydrophobic effect is a major contributor to the complexation, and the increase of electron density at the binding site will favor the complexation [31, 32]. Here, the phenothiazine radical cation is obviously more hydrophilic than its neutral form, hence the hydro-

phobic effect actually disfavors the complexation with the former guest. Since the phenothiazine radical cation loses an electron upon oxidation, its electron density at the binding site is also clearly lower than that of the neutral phenothiazine.

However, a quantum mechanical effect, i.e., charge-transfer interaction, seems useful for understanding the above behavior. According to the theory of energy decomposition analysis proposed by Morokuma [33], when a supermolecule is formed, electrons will tend to lose their identity as belonging to one or other component molecule. Therefore, the complete description of the supermolecule should include the contributions from many electronic configurations, i.e., states in which the electrons occupy orbitals other than the lowest-lying ones. In this case, the so-called charge-transfer interaction will come into being, which refers to the contribution from the mixing of the filled orbitals of one component molecule with the vacant orbitals of the other. This kind of interaction is always attractive, and the most important terms in this kind of interaction are contributed from the charge transfer between the HOMO of one component and the LUMO of the other.

Mulliken charge distribution analysis reveals that in the inclusion complex, β-CD as a whole will obtain a nonzero net charge. This means that the charge transfer takes place in CD molecular recognition. When the guest is the neutral phenothiazine, this charge is slightly negative, indicating that β-CD serves as a weak Lewis acid, accepting electrons. However, when the guest is a phenothiazine radical cation, a significant positive charge will be gained by β-CD, and in turn β-CD will serve as a relatively strong Lewis base, donating electrons. This is understandable since calculation demonstrates that the HOMO of the neutral phenothiazine is slightly higher than that of β-CD. In contrast, the HOMO and LUMO of the phenothiazine radical cation are both much lower than those of β-CD. Since the absolute charge gained by β-CD is much larger when the guest is phenothiazine radical cation than that when the guest is the neutral one, it is not strange that the former inclusion complex is much more favorable in energy.

The atomic spin densities are determined with Mulliken population analysis for the phenothiazine radical cations using the UB3LYP/3-21G(d) method. From Table I, the unpaired electron is localized mostly on the guest phenothiazine radical cation. However, a nonzero unpaired electron is also distributed on β-CD. This can be further evidence in support of the occurrence of charge-transfer energy.

The dipole moment found for the neutral phenothiazine and its radical cation are similar. However, the dipole moments of the two complexes are substantially different. The dipole for the β-CD complex of phenothiazine is much larger. This is probably due to the conformational change of β-CD triggered by the charged guest molecule.

4. Conclusions

The PM3, HF/3-21G(d), and B3LYP/3-21G(d) methods were satisfactorily applied to studies of the complexation of β-CD with the neutral phenothiazine and

Table I. The key features in the inclusion complexation of β-CD with phenothiazines

Method	Species	Phenothiazine	Phenothiazine radial cation	β-CD	β-CD-phenothiazine	β-CD-phenothiazine radical cation
PM3	Heats of formation (kJ/mol)	249.79	937.43	−6082.82	−5882.27	−5236.43
	Stabilization energy upon complexation (kJ/mol)	–	–	–	−49.24	−91.04
HF/ 3-21G(d)	Total energy (kJ/mol)	−2378814.18	−2378253.66	−11088818.54	−13467612.27	−13467116.06
	Stabilization energy upon complexation (kJ/mol)	–	–	–	+20.45	−43.86
B3LYP/ 3-21G(d)	Total energy (kJ/mol)	−2389398.00	−2388798.55	−11151691.57	−13541100.49	−13540589.76
	Stabilization energy upon complexation (kJ/mol)	–	–	–	−10.92	−99.64
	HOMO (eV)	−4.87	−9.64 (α) −10.44 (β)	−5.91	−5.33	−8.27 (α) −8.28(α)
	LUMO (eV)	−0.39	−5.14 (α) −7.95 (β)	+0.53	−0.79	−4.20 (α) −6.91 (β)
	The Mulliken charge of β-CD	–	–	0.0000	−0.0195	+0.1804
	The Mulliken spin density of β-CD	–	–	–	–	+0.0022
	Dipole moment (D)	2.143	2.137	3.730	2.732	11.609

its radical cation. The results suggest that the complexation of β-CD with the phenothiazine radical cation is significantly more favorable than that with the neutral one. The different magnitude of the charge-transfer interaction is proposed as a physical reason for such behavior. It indicates that caution should be used when extrapolating one oxidation state behavior to the supramolecular systems in their other oxidation states.

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