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A quantum-chemical study on the molecular recognition of β-cyclodextrin with ground and excited xanthones

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Abstract

PM3 and density function theory B3LYP/3-21G(d) calculations in vacuo and in water were performed on the inclusion complexation of β-cyclodextrin (CD) with the ground singlet and excited triplet xanthones. It revealed that the complex of β-CD with the singlet xanthone was significantly more stable than that with the triplet one, which agreed with the experimental observation. Calculations on the model system at the level of B3LYP/6-311G(p, d) supported the above result, which indicated that the repulsion between the oxygens of xanthone and the oxygens of the secondary hydroxyls of β-CD constituted the origin for the above behavior. Hence, caution should be given when extrapolating excited state behavior to the supramolecular systems in their ground state.

Keywords: Cyclodextrin; Xanthone; Triplet state; PM3; Density function theory

1. Introduction

α-, β-, γ-Cyclodextrins (CD) 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 the aqueous solution [2].

Model studies on CD complexation offer valuable insights into molecular recognition and enzyme–substrate interactions [3]. In addition to experimental approaches, theoretical calculations [4] can illustrate the driving forces of the complexation [5] and the inclusion regioselectivity in CD-catalyzed reactions [6]. Due to the large size, most calculations on CD chose the molecular mechanic (MM) method based on various empirical force fields [7–10]. However, as MM has difficulty in modeling the molecules in their excited states, quantum mechanic (QM) methods must also be developed to study the CD chemistry. [11–13].

Recently, the molecular recognition of CD with the substrates in their excited states has drawn much attention [14–22], in which the xanthone–CD system is a representative one [23–29]. Interestingly, the binding constant of the complexation of β-CD (or Hp-β-CD and γ-CD) with excited triplet xanthone was found 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 remained unclear. Herein, semiempirical PM3 and DFT calculations were performed to investigate the problem.

2. Methods

All calculations were performed with GAUSSIAN 98 [30]. β-CD was built and optimized with PM3 from the crystal structure [31]. The glycosidic oxygens were placed onto the *XY* plane and their center was defined as the center of the coordination system. The primary OH groups were placed pointing toward the positive *Z*-axis. The inclusion complex was constructed from the PM3-optimized β-CD and xanthone. The longer dimension of the substrate was initially placed onto the *Z*-axis. Its position was defined by the *Z*-coordinate of the carbon atom of the carbonyl group of xanthone (Fig. 1). The inclusion complexation was emulated by entering xanthone from one end of β-CD and then letting it pass through β-CD by steps. In each step, the geometry of the complex was completely optimized with PM3 without any restriction. In case of the excited state, the spin-unrestricted approximation was employed, where electrons with different spins occupy different sets of orbitals.

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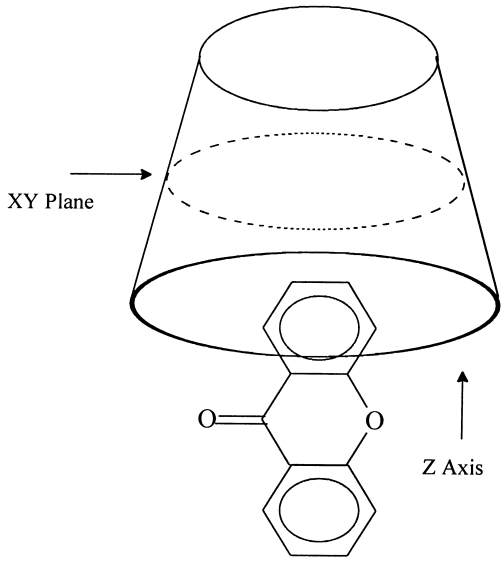

Fig. 1. The relative position of xanthone to β-CD.

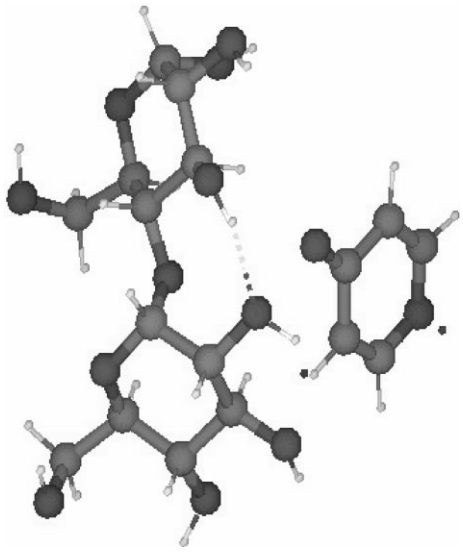

Fig. 2. The complex of α-1,4-di-glucose with 1,4-pyrone.

DFT single-point calculation at the level of B3LYP/3-21G(d) was performed on all the PM3-optimized species, both in vacuo and in water solution by using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method.

In addition, a simpler system was also examined which had two components, i.e. α-1,4-di-glucose and 1,4-pyrone. These two components were obviously similar to β-CD and xanthone in the above CD complexes in their physicochemical properties. Initially, they were both optimized with DFT B3LYP/6-311G(p, d) method. Then the optimized α-1,4-di-glucose and 1,4-pyrone were placed together to form a complex, in which the relative orientation of and the distance between the two components were the same as the corresponding values in the above CD complexes (Fig. 2). The energy of the complex was evaluated by a single point calculation at the level of B3LYP/6-311G(p, d).

3. Results and discussion

The graphic representation of the energy changes involved in the inclusion complexation produces two curves for the ground singlet and excited triplet state, respectively (Fig. 3). The structures of the PM3-optimized complexes at their energy minimums are shown in Fig. 4, whose energies are summarized in Table 1. It should be pointed out that although the rotation of the substrate within the CD cavity prior to energy minimization was not performed in the present study due to its very high CPU cost, it has been shown in a previous study that the minimization process can find the best rotational orientation of the substrate automatically [32]. Moreover, to test the performance of the PM3 optimization, a simple molecular dynamic (MD) simulation was performed using DISCOVER3 program with the consistent valence force field (CVFF) at 300 K. In the

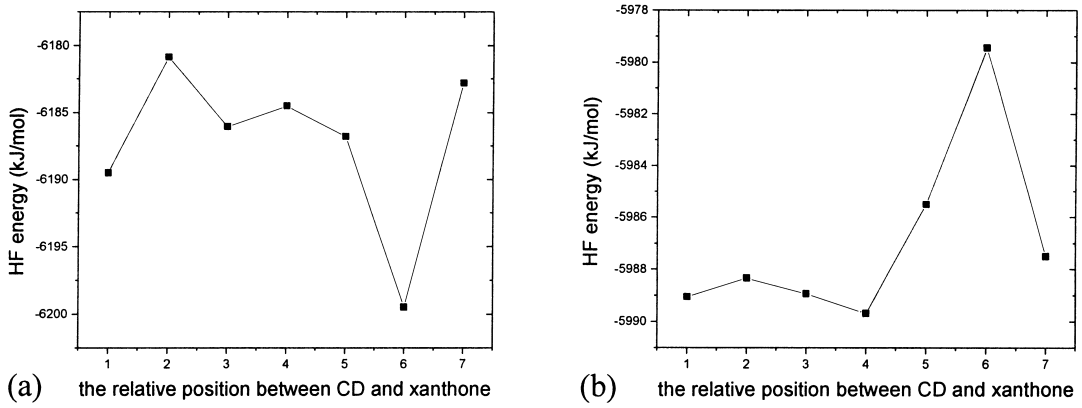

Fig. 3. Graphics for the emulation of the inclusion complexation of xanthone into β-CD cavity: (a) singlet state; (b) triplet state.

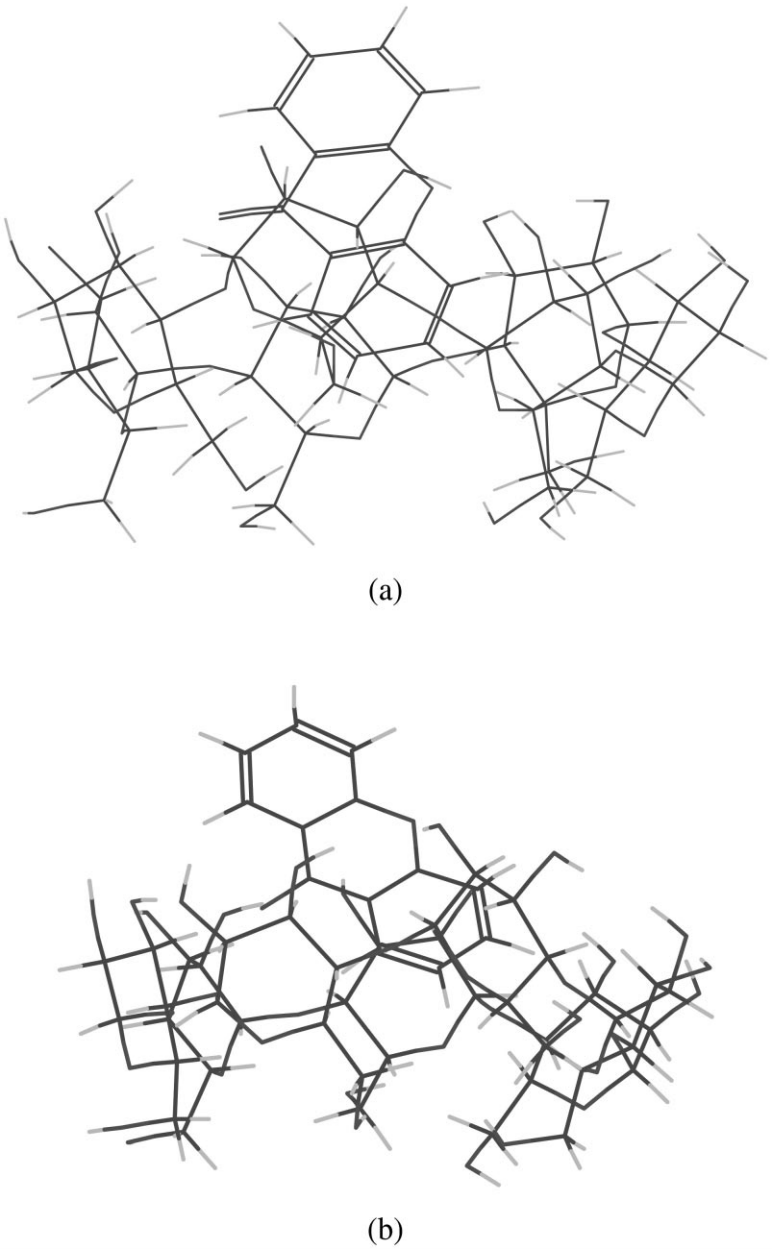

Fig. 4. Structures of the energy minimum obtained by PM3 for the β-CD complex with: (a) singlet xanthone; (b) triplet xanthone.

simulation, an integration step of 1 fs was chosen and the coordinates were recorded every 10 step. After a period of 20 ps, the average structure of the complex was obtained based on the trajectory analysis using ANALYSIS module of INSIGHT2. As seen from Fig. 5, the MD average structure is indeed very similar to the PM3-optimized one, indicating the reliability of the scf minimization procedure.

From Fig. 4, it can be seen that both the singlet and triplet xanthone are partially included in β-CD at the energy minimum. One ring of xanthone is completed inside the CD cavity, and the oxygens of xanthone are very near to the secondary hydroxyl groups of β-CD. This inclusion pattern is in agreement with the MM calculation results [28].

The negative enthalpy changes upon complexation clearly demonstrate that β-CD can form stable complex with both the ground singlet and excited triplet xanthone, which is observed in the experiments. Notably, the stabilization energies upon complexation calculated with PM3 are close to those with B3LYP/3-21G(d). Thus, PM3 is a good feasible theoretical tool at a level of quantum mechanics in the study of CD complexation [33,34].

Interestingly, the complexation of β-CD with triplet xanthone is significantly less favorable than that with the singlet one by an energy difference of 16.53 kJ/mol according to PM3 calculations. The same result is also obtained with the B3LYP/3-21G(d) calculation in vacuo, in which the energy

Table 1
The energies in the inclusion complexation of β-CD with xanthone

Species	Xanthone (singlet)	Xanthone (triplet)	β-CD	β-CD–xanthone (singlet)	β-CD–xanthone (triplet)
PM3					
E (kJ/mol)[a]	−67.89	125.38	−6082.82	−6199.48	−5989.68
ΔE (kJ/mol)[b]	–	–	–	−48.77	−32.24
B3LYP/3-21G(d) (in vacuo)					
E (kJ/mol)	−1697283.54	−1696949.07	−11151691.54	−12849033.96	−12848678.21
ΔE (kJ/mol)	–	–	–	−58.88	−37.60
B3LYP/3-21G(d) (in water)					
E (kJ/mol)	−1697300.65	−1696947.76	−11151692.68	−12849046.56	−12848683.65
ΔE (kJ/mol)	–	–	–	−53.23	−43.21

[a] E is the heat of formation.
[b] ΔE is the stabilization energy upon complexation.

difference becomes 21.28 kJ/mol. When the solvation effect is taken into consideration, the energy difference becomes a little smaller (10.02 kJ/mol) from the B3LYP/3-21G(d) SCRF calculation in water. Thus, the calculation results agree with the experimental observations, i.e. the complexation of β-CD with singlet xanthone is more stable than that with the triplet one. Nevertheless, it should be mentioned that herein the solvent effect is only taken into account on the basis of a continuum solvation model, which considers the solvent as a continuous dielectric with a cavity accurately modeled for the solute. In the model, the solvent reacts against the solute charge distribution, generating a reaction field, and the electrostatic interaction between the solute and the solvent is introduced as a perturbation operator in the solute hamiltonian. Apparently, the solvent reorganization involved in the solvation is not considered in the model. Therefore, the calculation results in solution are only indicative.

As the basis set of the above calculation is moderate, it is interesting to see if a higher-level calculation can also give the same results. However, as the CPU cost for such a calculation will be extremely high, a simpler model system [35] of the β-CD–xanthone complex has to be used instead, in which α-1,4-di-glucose and 1,4-pyrone are selected to model β-CD and xanthone, respectively. Herein, the relative orientation of the distance between α-1,4-di-glucose and 1,4-pyrone are chosen to be the same as the corresponding values in the β-CD–xanthone complexes. The energies (see Table 2) of the system in the singlet and triplet state are evaluated with B3LYP/6-311G(p, d) calculations. From Table 2, it can be seen that the stabilization energy upon complexation is more negative for the singlet complex than for the triplet one. Thus, a higher-level calculation also reveals that the singlet complex is more stable.

The above behavior may be caused by the orientation of the complex. As shown in a recent study, the complexation of α-CD with triplet quinone is more favorable than that with singlet quinone [13]. In the complex, the major axis of quinone parallels with that of α-CD so that the oxygens of quinone are modestly far away from the hydroxyls of

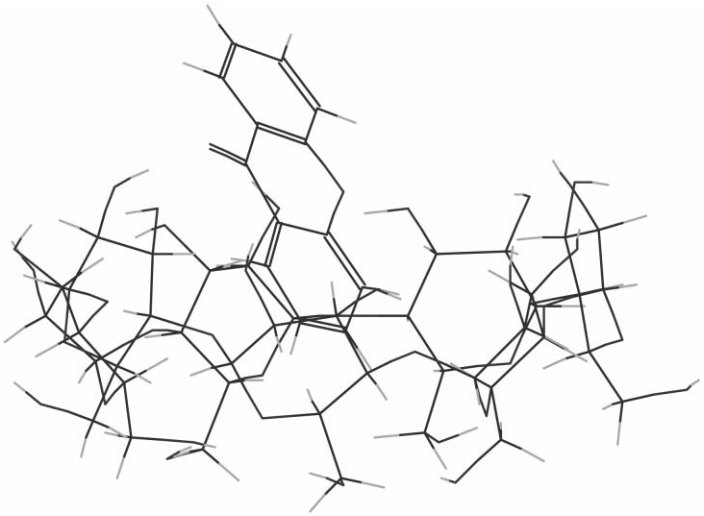

Fig. 5. The average structure of the β-CD complex with singlet xanthone obtained from a MD simulation.

Table 2
The interaction energy between α-1,4-di-glucose and singlet and triplet 1,4-pyrone calculated with B3LYP/6-311G(p, d)

Species	E (kJ/mol)[a]	ΔE (kJ/mol)[b]
1,4-Pyrone (singlet)	−900850	–
1,4-Pyrone (triplet)	−900533	–
α-1,4-Di-glucose	−3405449	–
Complex (singlet)	−4306040	−259
Complex (triplet)	−4305788	−194

[a] E is the heat of formation.
[b] ΔE is the stabilization energy upon complexation.

the cyclodextrin. Apparently, any significant interaction between the oxygens of quinone and the hydroxyls of α-CD is unlikely to occur. However, in the complex of β-CD with xanthone, the oxygens of xanthone are very near to the secondary hydroxyls of the cyclodextrin. In the triplet state, one electron of the oxygen of xanthone is excited ($n \rightarrow n^*$) and becomes farther away from the core of the oxygen atom. As this electron will be nearer to the non-paired electrons of the oxygens of the secondary hydroxyls of β-CD, the repulsion between the two types of oxygens is expected to be larger. Presumably, this larger repulsion is the reason for which the complex of β-CD with singlet xanthone is more stable than that with the triplet one. In fact, in the PM3-optimized complexes the nearest distance between the xanthone oxygen and the oxygens of the secondary hydroxyls of CD is 3.38 Å for the singlet substrate and 3.48 Å for the triplet one, which clearly indicates that the repulsion between xanthone oxygen and cyclodextrin hydroxyl oxygens is larger when the substrate is in a triplet state.

4. Conclusions

PM3 and B3LYP/3-21G(d) calculations in vacuum and in water were performed on the complexation of β-CD with xanthone in the ground singlet and excited triplet state, respectively. The results suggested that the complexation of β-CD with the singlet xanthone was much more favorable than that with the triplet one. The repulsion between the oxygens of the xanthone and the oxygens of the secondary hydroxyls of β-CD was proposed as the physical origin of such a behavior. It indicated that caution should be given in extrapolating excited state behavior to the supramolecular systems in their ground state.

Acknowledgements

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