

外 国 語 要 旨

学位論文題目 : Theoretical Study on Intermolecular Interactions in Complexes of Cyclodextrins with Bile Acids and Bile Salts

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α -, β -, and γ -Cyclodextrins (CDs), which are cyclic oligosaccharides consisting of six, seven, and eight α -(1,4)-linked D-glucose units, respectively, are good host molecules to accommodate hydrophobic guest molecules inside their cavity. It is reported that CDs form inclusion complexes with bile salts in aqueous solution. In this thesis, the intermolecular interactions have been investigated for 1:1 complexes of CDs with cholic acid (CA), deoxycholic acid (DCA), and their anions in the gas phase and in aqueous solution by density functional theories (DFT), molecular dynamics (MD) simulations, and ab initio fragment molecular orbital (FMO) calculations in order to clarify the structural features and the important factors for stabilization of the CD/bile acid inclusion complexes.

In the present study, geometry optimizations were performed for the stable configurations by the B97-D, M06-2X, and B3LYP functionals with the 6-31G(d) basis set. MD simulations were carried out for aqueous solution of β -CD/CA and γ -CD/CA by using the TIP3P water model. Interaction energies between the host and guest were analyzed by the FMO-MP2/6-31G(d) method for the DFT-optimized structures and several snapshots in the MD trajectories. The exhaustive contents are expressed as below.

In Chapter 1, the background of the host and guest molecules and their 1:1 inclusion complexes are introduced. Chapter 2 mainly expounds the significance and originality of the present research as well as the selection of calculation methods.

In Chapter 3, the DFT studies indicate that the association energies of β -CD/CA and γ -CD/CA are more negative than that of α -CD/CA in the gas phase. The open/top1 configuration was the most stable for β -CD/CA. The structures of β -CD/CA optimized with B97-D and M06-2X in aqueous phase resembled the structure proposed from the NMR experiments in aqueous solution whereas B3LYP gave a rather different structure, which is likely due to insufficient performance of B3LYP on evaluation of dispersion interaction. Formation of intermolecular hydrogen bonds (H-bonds) may be a significant driving force for complexation of a guest by CDs. In the case of β -CD/CA, the most stable configuration, open/top1, involves six H-bonds between β -CD and CA whereas open/mid2 involves only three. The β -CD/DCA complex in open/top1 involves four intermolecular H-bonds. In spite of the difference in the number of H-bonds, the association energies are almost the same for β -CD/CA and β -CD/DCA, suggesting that another factor also contributes to the stabilization.

In Chapter 4, MD simulations were performed for aqueous solution of β -CD/CA or γ -CD/CA by starting from the most stable open/top1 configuration for 5 ns at 298 K, during which the guest molecule, CA, resided in the CD cavity. The position of CA in the cavity fluctuates, resulting the reversible change between open/top1 and open/mid1 in the case of β -CD/CA. The length of CA in γ -CD/CA measured by the O3–C24 distance is similar to that in free CA whereas CA in β -CD/CA adopts a more extended conformation. Intermolecular hydrogen bonds are not always formed between CD and CA, a number of hydrogen bonds between the solute and water are formed instead.

In Chapter 5, pair interaction energy decomposition analyses with FMO-MP2 method revealed that both the electrostatic and dispersion terms significantly contribute to the total interaction energies in the gas phase. The most stable configuration, open/top1, of β -CD/CA exhibits the most negative total and electrostatic interaction energies. The dispersion term in β -CD/CA is more negative than that in γ -CD/CA. On the other hand, the dispersion term has a larger contribution than the electrostatic term in aqueous solution, which is modeled with a hydrate cluster obtained from the snapshots of MD trajectory.

The general overview is summarized in Chapter 6. It is mainly elaborated that dispersion energy plays a more important role than electrostatic energy in aqueous phase in CD/bile acids inclusion complexes.