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DFT と ab initio FMO 法によるシクロデキストリンと胆汁酸の包接錯体の相互作用に関する理論研究

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Theoretical Study on Intermolecular Interactions in Complexes of Cyclodextrins with Bile Acids: DFT and ab initio Fragment Molecular Orbital Calculations

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Introduction Cyclodextrins (α-, β-, and γ-CD), which are cyclic oligosaccharides consisting of six, seven and eight α-(1,4)-linked D-glucose units (Fig.1), are good host molecules to accommodate hydrophobic guest molecules inside their cavity. It is reported that CDs form 1:1 inclusion complexes with bile salts such as cholate and deoxycholate, and the binding mode is proposed from the NMR experiments.[1] In the present study, the intermolecular interactions have been investigated for 1:1 complexes of CDs with cholic acid (CA, Fig. 2), deoxycholic acid (DCA), and their anions in the gas phase and in aqueous solution by DFT and ab initio MO calculations in order to clarify causative factors for stabilization of the complexes.

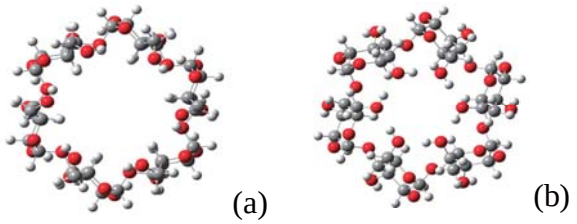

Fig. 1. α-CD in open (a) and closed (b) conformations.

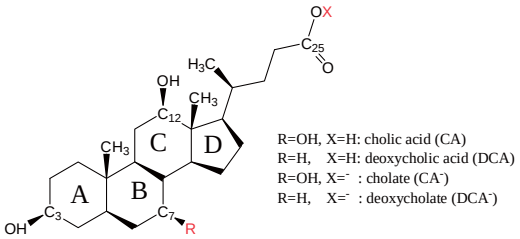

Fig. 2. Structural formulas of guest molecules.

Computational Methods Eight stable structures (Fig. 3) were obtained in our previous study by the B97-D/6-31G(d) calculation.[2] In the present study, geometries were optimized both in gas phase and in aqueous phase by DFT (B97-D, M06-2X, and B3LYP functionals) with the 6-31G(d) basis set. IEF-PCM was employed for aqueous phase. Association energies were computed with correction for basis set superposition error. Single-point energy calculations by the fragment molecular orbital (FMO)-MP2[3]/6-31G(d) method were carried out for the geometries optimized in aqueous phase with B97-D.

Results and Discussion 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[1] whereas they were rather different from that with B3LYP, which is likely because B97-D and M06-2X are known to exhibit better performance than 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. The numbers of intermolecular H-bonds were examined for the β-CD complexes with different guests or orientations in aqueous phase. In the case of β-CD/CA, the open/top1 and closed/mid1 configurations involve six intermolecular H-bonds whereas the open/mid2 involves only three. The β-CD/DCA complex in the open/top1 configuration 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.

Dispersion interaction may be another important driving force in the CD/bile acids complexes. Pair interaction energy decomposition analyses with FMO-MP2 method revealed that both the electrostatic (E_{es}) and dispersion (E_{disp}) terms significantly contribute to the total interaction energies (E_{total}) as shown in Fig. 4. 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. In summary, both the intermolecular H-bonds and dispersion interactions have significant contribution to the stabilization of the CD/bile acid complexes.

In the poster, results of preliminary MD simulation of the complexes in aqueous solution with explicit water molecules will be also presented.

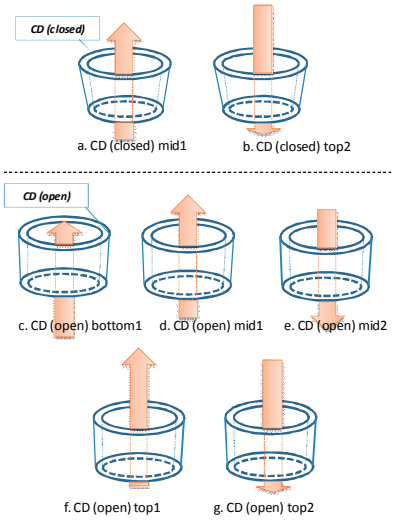

Fig. 3. Schematic drawings of eight stable structures of CD/CA complexes.

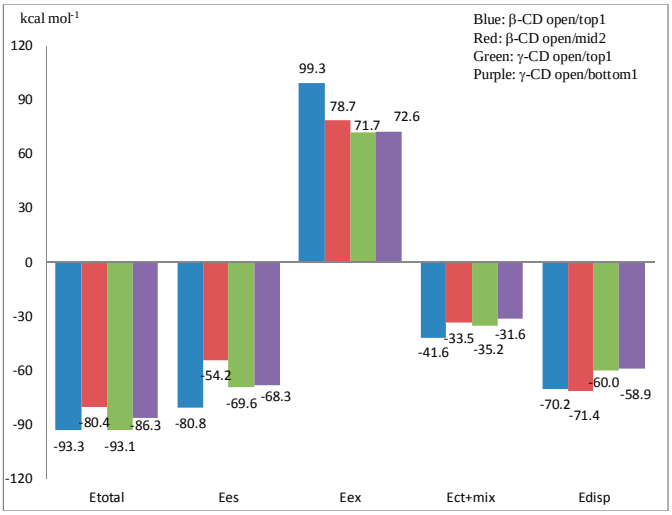

Fig. 4. Interaction energies for β-CD/CA and γ-CD/CA at the B97-D-optimized geometry.

1. P. R. Cabrer *et al. Langmuir* **1999**, *15*, 5489. 2. L. Yao *et al.* 第 6 回分子科学討論会 (2012, 4P101). 3. D. G. Fedorov *et al. J. Chem. Phys.* **2004**, *120*, 6832; D. G. Fedorov *et al. J. Chem. Phys.* **2004,** *121*, 2483.