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シクロデキストリンと 胆汁酸・胆汁塩の複合体についての理論的研究

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Theoretical study on complexes of cyclodextrins with bile acids and bile salts

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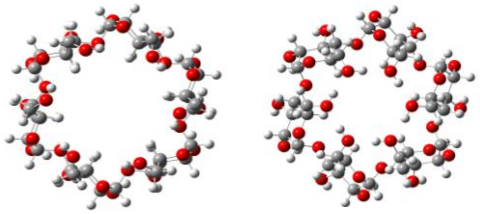
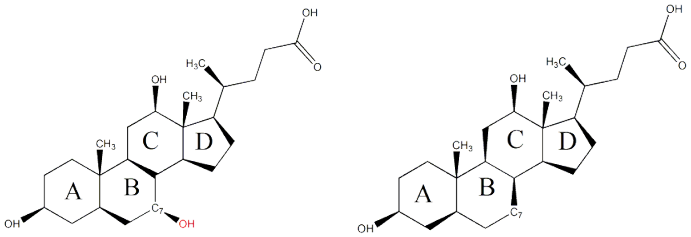
Introduction

Cyclodextrins (α-CD, β-CD, and γ-CD) are cyclic oligosaccharides consisting of six, seven and eight α-(1,4)-linked D-glucose units, and they are good host molecules to accommodate hydrophobic guest molecules inside their cavity. According to the previous calculation in the gas phase, the lowest energy conformation is the closed conformation (Fig. 1a), while another energy minimum is the open conformation, which resembles the structures observed in the solid state (Fig. 1b).[1] It is reported that CDs form 1:1 inclusion complexes with bile salts such as cholate (CA^-) and deoxycholate (DCA^-) in aqueous solution. In this study, the intermolecular interactions have been investigated for 1:1 complexes of CDs with cholic acid (CA, Fig. 2a), deoxycholic acid (DCA, Fig. 2b) and their anions (CA^-, DCA^-) in the gas phase and in aqueous solution by means of the DFT calculations.



(a)　　(b)

Fig. 1. Top and side views of α-CD in the open (a) and closed (b) conformations.



(a) CA　　(b) DCA

Fig. 2. The structural formulas of cholic acid (CA) and deoxycholic acid (DCA)

Computational methods

The geometries of the CD/CA inclusion complexes were optimized by the DFT-D (B97-D) and DFT (M06-2X) methods with the standard 6-31G(d) basis set. The strengths of interactions were quantified by the basis set superposition error (BSSE)-corrected binding energies ($E_{binding}$) both in the gas phase and in aqueous solution. The polarizable continuum model (PCM) was applied for the aqueous solution. The strain energy (E_{strain}) was also evaluated. The intermolecular hydrogen bonds and van der Waals interactions between CA and CD were investigated by inspection of the optimized geometries

Results and Discussion

According to the results of the calculations by the B97-D and M06-2X methods, the open/top1 and the open/mid2 are energetically favored configurations for the β-CD/CA complex in the gas phase, while open/bottom1 and open/top1 are favorable for the γ-CD/CA complex. The structures are schematically shown in Fig.3, in which the arrow indicates the direction from the carboxylic group toward the A-ring of CA (defined as direction 1, otherwise is direction 2). The diameter of α-CD (d_{up} =7.13Å, d_{down} = 6.71 Å in the open conformation) prohibits the steroid skeleton of the bile acid or bile salt (width = 6.20 Å for CA) from entering into the cavity of α-CD, and only the side chain can enter into it. Such geometrical features are in good agreement with those suggested by the experimental study.[2]

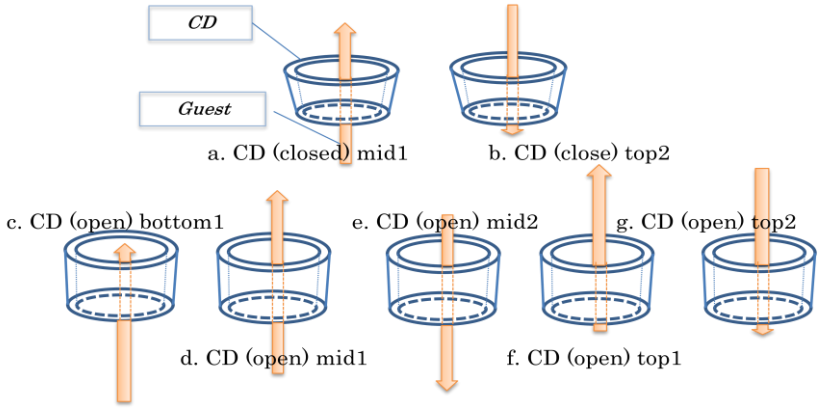


Fig. 3. Schematic drawings of the stable configurations of the CD/CA complexes.
(Top, mid, and bottom are defined by the complexed position of the main part of guest molecule.)

Three hydrogen bonds are seen between β-CD and CA, suggesting that the H-bonds and van der Waals interactions play a decisive role in the complexation in the gas phase.

The BSSE-corrected binding enthalpies were calculated by the M06-2X/6-31G(d) method for the β-CD complexes in aqueous solution (Table 1). The present calculations overestimate the absolute values of $H_{binding}$, but the difference between CA^- and DCA^- is quite small, which agrees with the experimental observation. Such small difference between CA^- and DCA^- suggests that the hydroxyl group at C7 only slightly affects the complexation with β-CD.

Table 1. BSSE-corrected binding energies and binding enthalpies /kcal mol^{-1} in aqueous solution

Guest	$E_{binding}$	$H_{binding}$	Experimental $H_{binding}$[2]
CA	-22.5	-19.8	-----
CA^-	-25.0	-22.9	-5.5
DCA	-22.9	-21.1	-----
DCA^-	-25.0	-22.5	-6.2

1. Karpfen *et al*. *Monatsh. Chem*. **2008**, *139*, 363.
2. Liu Y *et al*. *J. Org. Chem*. **2007,** *72*, 8227.