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Molecular Mechanics Study of the Inclusion of Trimethylbenzene Isomers in α-Cyclodextrin

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Abstract. Molecular mechanics calculations were employed to study the inclusion of triethylbenzene isomers in α-cyclodextrin and their solvation energy in aqueous solution. Trimethylbenzene penetrates partially into the cavity of α-cyclodextrin to form 1 : 1 or 2 : 1 host–guest complexes. The interaction energy between host and guest is dominated by van der Waals energy. The inclusion complexes have higher solvation energies than free α-cyclodextrin.

Key words: molecular mechanics calculation, inclusion, solvation energy, α-cyclodextrin, trimethylbenzene.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaacharides consisting of six, seven or eight glucopyranose units, called α-, β- or γ- cyclodextrins, respectively. With central cavities of corresponding sizes, cyclodextrins have unique properties. A variety of molecular species are held in an aqueous medium as guests inside the cavity. Cyclodextrins themselves are rather hydrophilic and moderately soluble in water with saturation concentrations of 0.149(α-CD), 0.0163(β-CD), and 0.179 M (γ-CD) at 25 °C [1]. In the presence of particular organic substances, however, the solubility decreases depending on the nature of the substances used [2, 3]. This decrease in the solubility is mainly due to the formation of a CD inclusion complex with the guest substance of low solubility in water. In addition, the concentration of CDs in aqueous solution, the annular size of the CDs (α-CD, β-CD, γ-CD) as well as the CDs-guest combination have important effects on the precipitation.

A vapor-circulation method to prepare CD precipitates with various volatile substances has been reported [2, 4]. It was found that each of three trimethylbenzene (TMB) isomers was precipitated with β- and γ-CDs, while 1,3,5-TMB was not precipitated with α-CD even at a CD concentration near to saturation in water [5]. This observation suggests a possibility that the 1,2,3- or 1,2,4-TMB may

be selectively precipitated with α-CD from water in the presence of 1,3,5-TMB. Considering the following precipitation reaction,

$$\alpha\text{-CD} + n\ \text{TMB} = \alpha\text{-CD}:\text{TMB}_n(\text{s})$$

the solubility product (K_{sp}) is expressed as follows:

$$K_{\text{sp}} = [\alpha - \text{CD}][\text{TMB}]^n.$$

The experimental values of K_{sp} and n are $7.6 \times 10^{-4}(K_{\text{sp}})$ and $0.4(n)$ for 1,2,3-TMB and $4.0 \times 10^{-4}(K_{\text{sp}})$ and $0.38(n)$ for l,2,4-TMB [6]. This means that a 2 : 1 complex of α-CD : TMB was formed in precipitates. The association constant of the inclusion complexes was reported as 13 M^{-1} (1 : 1 α-CD–1,2,3–TMB), 46 M^{-1} (1 : 1 α-CD–1,2,4–TMB), 61 M^{-1} (α-CD–1,3,5–TMB), and 470 M^{-1} (2 : 1 α-CD_2–1,2,3–TMB) [7]. These data do not allow the solubility differences of α-CD–TMB isomer complexes to be explained.

Up to now, molecular mechanics (MM) and molecular dynamics (MD) simulations have led to the proposal of several driving forces for the inclusion of cyclodextrin with substrates [8, 9]: van der Waals force, hydrophobic interactions, hydrogen bonding, the release of the distortional energy of cyclodextrin by binding a guest compound, and extrusion of "high energy water" from the cavity of cyclodextrin upon formation of the inclusion complex. It was suggested that van der Waals interaction and/or conformation energy mainly dominate the driving force for the inclusion complexation of α-CD [10]. However, the effect of solvent [11, 12] must be considered for the stabilization of inclusion complexes, especially for their solubility in aqueous solution.

In this paper, molecular mechanics calculations were employed to study the inclusion of α-CD with TMB isomers, using the CFF91 force field. The conformations of inclusion complexes were determined and the interaction energies were calculated. Furthermore, we have calculated and compared the solvation energy of α-CD–TMB complexes in aqueous solution.

2. Methods

The calculations were performed with the Discover program package 95.0/3.00 using the CFF91 force field [13]. This force field is a second-generation (Class II) force field. It was parameterized against a wide range of experimental observables and has been shown to be more accurate than Class I such as CVFF and AMBER. The CFF91 force field approximates the conformational energy of a molecule as the sum of terms for bond stretching, angle bending, torsion, out-of-plane coordinate and cross terms up through third order, and van der Waals electrostatic interactions.

Molecular structures of α-CD and three TMB isomers were built using Biosym software. All structures were optimized by MM and MD until the root mean square (RMS) gradient reached less than 0.01 kcal mol^{-1} $Å^{-1}$.

The inclusion with α-CD as host and TMB isomers as guests was obtained using the docking method [14, 15]. The objective of a docking calculation is to evaluate the interaction energies of many orientations of one molecule relative to the other, while searching for the orientations that results in low interaction energies. In docking, the interaction energy is computed by summing the energy contributions between all atoms of the two molecules. The contribution between atoms interacting with other atoms in the same molecule is ignored. For example, for CFF91:

$$E_{\text{interaction}} = \sum_i \sum_j \left(\frac{A_{ij}}{R_{ij}^9} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon r_{ij}} \right).$$

Here $E_{\text{interaction}}$ is the nonbond interaction energies, term 1 and term 2 represent the van der Waals interactions, and term 3 is the Coulombic interaction between the atomic charges. The model with strongest interaction between host and guest was selected to be as the initial structure. A docking operation was carried out through calculating over 1000 cycles by molecular mechanics and dynamics separately. Three conformations with energy difference $\Delta E = 30$ kcal mol^{-1} were obtained. The model with lowest interaction energy was minimized by molecular mechanics. The dielectric constant ϵ was chosen to be 1. The nonbonded cutoff distances were 15 Å for van der Waals and electrostatic interaction. Over 800 cycles including steepest descendant and conjugate gradient process were used until the RMS was less than 0.1 kcal mol^{-1} Å^{-1}. For 2 : 1 host–guest complexes, another α-CD was selected as host, and the corresponding 1 : 1 complexes were selected as guest for the docking operation.

Finally the solvation energies of all complexes were computed by the solvation model of the DelPhi program. The DelPhi-based solvation model [16], which we have selected, calculates a total solvation energy comprising two main components: the electrostatic energy and the non-polar energy which is assumed to be proportional to the solvent accessible surface area of the solute. The parameter sets of CFF91 were used.

The free energy transfer of a molecule from vacuum to water is called its solvation free energy ΔG_{sol}. Most discussions break ΔG_{sol} into three components:

$$\Delta G_{\text{sol}} = \Delta G_{\text{vdw}} + \Delta G_{\text{cav}} + \Delta G_E = \Delta G_N + \Delta G_E.$$

where ΔG_{vdw} is the energy of the van der Waals interactions between solvent and solute; ΔG_{cav} is a term which is composed of the entropy penalty for reorganizing the solvent molecules around a solute and the work done against solvent pressure to create a cavity in the solvent to immerse a solute molecule (ΔG_{cav} is positive) [17]. ΔG_N is the sum of the last two terms and is called the nonpolar solvation energy. ΔG_E is the change in the electrostatic energy of transfer of the solute from vacuum to solvent, which is water here. The dielectric constant of water, ϵ, is set to 80.0, ϵ of the solute is set to l.0 (as in vacuum).

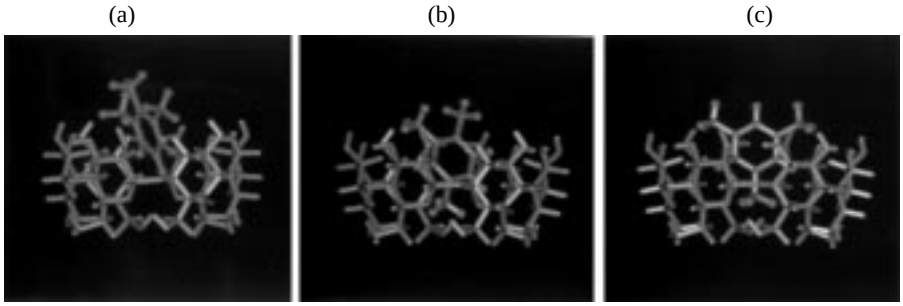

Figure 1. The structures of the 1 : 1 α-CD: TMBs inclusion complexes. (a) α-CD–1,2,3–TMB, (b) α-CD–1,2,4–TMB, (c) α-CD–1,3, 5–TMB.

The energetic description of molecules often involves a comparison between different conformations. The total solvated conformational energy of the solute is defined as

$$G^{\text{conf}} = \Delta G_{\text{sol}} + G_{FF}.$$

Here, G_{FF} is the force field intramolecular energy which is calculated using the Discover program and includes the Coulombic term.

All computations were performed on a Silicon Graphics workstation 4d310 and the images of molecules were visualized with help of the Insight II.

3. Results and Discussion

3.1. CONFORMATIONS OF COMPLEXES OF α-CD WITH TMB ISOMERS

The conformations of the three 1 : 1 complexes with α-CD–TMB are shown in Figure 1. It can be seen that for 1,2,3-TMB, only the benzene ring inserts partially into the cavity of CD, and its molecular plane is not parallel to the central axis of the annulus; three methyl groups lie outside the CD cavity. For 1,2,4-TMB or 1,3,5-TMB, the benzene ring with one methyl group inserts deeply into the cavity of CD, and the other two methyl groups in *meta*-positions or *meta*- and *para*-positions are outside the CD cavity.

These 1 : 1 inclusion complexes can include with a second α-CD molecule to form 2 : 1 host–guest complexes, with TMB in the center of two opposed CD cavities. In Figure 2 we find an obvious change in conformation of the 2 : 1 inclusion complex for 1,2,3-TMB. The 1- and 3-methyl-groups of 1,2,3-TMB penetrate in two CD cavities separately, while the benzene ring with 2-methyl-groups is not in any cavity of two CDs, but is in the intermediate zone between them. For the 2 : 1 host–guest inclusion complexes of 1,2,4- and 1,3,5-TMB, the second CD cavity partially includes the remaining parts of TMBs outside the first α-CD cavity.

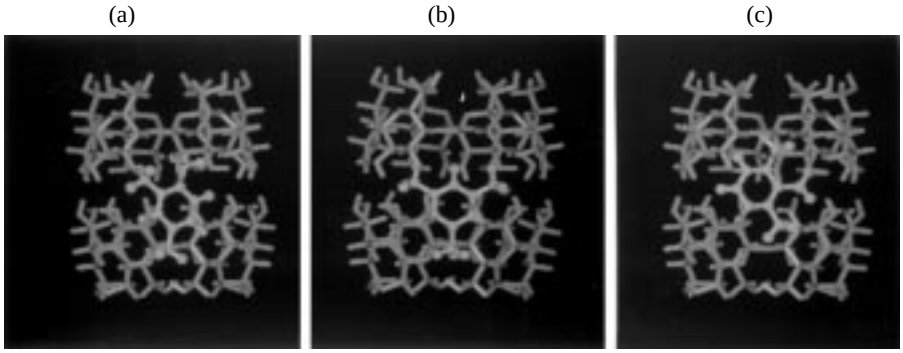

Figure 2. The structures of the 2 : 1 α-CD : TMBs inclusion complexes. (a) α-CD_2–1,2,3–TMB, (b) α-CD_2–1,2,4–TMB, (c) α-CD_2–1,3,5–TMB.

3.2. INTERACTION ENERGIES OF α-CD-TMB COMPLEXES

The interaction energies of the various complexes are listed in Table I. It can be seen that the interaction energies between host and guest in α-CD–TMB complexes mainly come from the van der Waals energy. The order of interaction energies for 1 : 1 complexes is 1,2,4-TMB > 1,3,5-TMB > 1,2,3-TMB. The deeper the TMB molecule inserts into the CD cavity, the stronger the van der Waals attraction between host and guest. All the 2 : 1 α-CD-TMB complexes have stronger van der Waals interactions, but also greater electrostatic energies. This results from the electrostatic repulsion among the hydroxyl groups on the rim of the CD cavity between two opposed CD cavities, which reduces the total interaction between hosts and guest in 2 : 1 α-CD–TMB complexes. The 2 : 1 complex for 1,2,3-TMB is much more stable than its 1 : 1 complex because of a greater van der Waals attraction from including the 2- and 3-methyl groups by two CD cavities separately. The interaction energy of the 2 : 1 complex for 1,2,4-TMB almost equals that of the 1 : 1 complex. For 1,3,5-TMB the interaction energy of the 2 : 1 complex is lower than that of the 1 : 1 complex, which is unfavorable for forming a double inclusion complex. The other two TMB isomers have a greater tendency to form 2 : 1 host–guest complexes with α-CD.

3.3. SOLVATION ENERGIES OF α-CD–TMB COMPLEXES

When α-CD forms an inclusion complex with TMB, the solubility can be changed. The solvation energies of all α-CD–TMB complexes in aqueous solution were calculated, and the results are presented in Table II.

The solvation energies of free α-CD and its inclusion complexes with TMB isomer are dominated by the electrostatic energy. The nonpolar solvation energy makes a minor contribution to the total solvation energies of these complexes. According to the experimental results, a 2 : 1 host–guest stoichiometry was found in the precipitates of α-CD with 1,2,3- as well as 1,2,4-TMB. Since solvation energy

Table I. Interactive energies of α-CD–TMB complexes after docking (kcal mol^{-1})

Complex		E_{total}	E_{vdw}	E_{ele}
1 : 1	α-CD–1,2,3–TMB	−14.30	−14.97	0.68
	α-CD–1,2,4–TMB	−19.67	−19.61	−0.06
	α-CD–1,3,5–TMB	−18.48	−18.95	0.64
1 : 2	α-CD$_2$–1,2,3–TMB	−22.73	−36.36	13.63
	α-CD$_2$–1,2,4–TMB	−20.18	−32.60	12.42
	α-CD$_2$–1,3,5–TMB	−17.68	−31.13	13.45

Table II. The solvation energies of α-CD–TMB complexes (kcal/mol)

Complex	Solvation energy			G_{conf}
	ΔG_{sol}	ΔG_N	ΔG_E	
α-CD	−80.16	7.52	−87.67	−14.35
α-CD–1,2,3–TMB	−60.22	7.53	−67.75	−22.77
α-CD–1,2,4–TMB	−60.97	7.33	−68.30	−38.40
α-CD–1,3,5–TMB	−59.84	7.31	−67.15	−48.57
α-CD$_2$–1,2,3–TMB	−123.86	10.39	−134.25	−69.27
α-CD$_2$–1,2,4–TMB	−122.53	10.45	−132.97	−79.22
α-CD$_2$–1,3,5–TMB	−123.68	10.42	−134.10	−89.28

is proportional to the solvent accessible surface area of the solute [16, 17], it is sensible to compare the solvation energies of 2 : 1 α-CD–TMB with that of two α-CDs, which is $2 \times (-80.16) = -160.32$ kcal mol^{-1}. By including with 1,2,3-TMB or 1,2,4-TMB, the solvation energy of α-CDs increased by about 36.46 kcal mol^{-1}, which should be responsible for the decrease of the solubility of 2 : 1 α-CD–TMB complexes. The structural difference of guests has no important influence on the solvation energy of α-CD–TMB isomer complexes, but affects the conformational solvation energies. The order of the conformational solvation energies of 2 : 1 α-CD–TMB is 1,2,3-TMB $<$ 1,2,4-TMB. The lower the conformational solvation energies, the more stable the complex is in aqueous solution; in other words, the greater their solubility. The results calculated above are in agreement with the experimental data [6].

By forming a 1 : 1 α-CD–1,3,5–TMB complex the solvation energy of α-CD increased by 20.32 kcal/mol over free α-CD, which is less than that of the 2 : 1 complexes; from this it is not difficult to explain why the solubility of the 1 : 1 α-

CD–1,3,5–TMB complex is lower than free α-CD, but higher than that of the 2 : 1 complexes. One of the reasons that no precipitation of α-CD with l,3,5-TMB was found in aqueous solution may be the size of this 1 : 1 complex, which is too small.

The compensation of solvation energies of inclusion complexes are mainly from the electrostatic energy between host–guest complexes and solvent. This is because trimethylbenzene penetrates partially into the hydrophobic cavity of α-CD, it hinders the hydrogen bond interaction of hydroxyl groups on the rim of CD cavity with waters and reduces the solvation.

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