

Formation, Structure, and Stability of α - and β -Cyclodextrin Inclusion Complexes of Phenol and Benzoic Acid Derivatives in Vacuo and in Water

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Inclusion complexations of α - and β -cyclodextrin (CD) with a series of phenol and benzoic acid derivatives both in vacuo and in water were investigated by semiempirical PM3 method. The inclusion systems with a higher negative value of complexation energy or interaction energy were found to have also a larger value of formation constant (K_f) in aqueous solution. The stability of β -CD inclusion complexes depended on the size/shape-fit between host and guest. A good size fitting between the volume of a guest molecule and the free space size of CD cavity effectively improved the stability of CD inclusion complex of the guest. Even though there was no appropriate molar volume ratio (MVR) of a guest to β -CD cavity, a good structural matching between the shape of a guest molecule and the arrangement of β -CD cavity should also obviously improve the stability of β -CD inclusion complex of the guest. Moreover, the CD cavity size exerted a big influence on the stability of these supramolecular complexes. There was an energetic advantage of larger than 45 kJ mol⁻¹ in favor of the intermolecular complexations between α -CD and mono-ortho-substituted phenol derivatives relative to phenol or mono-para-substituted phenol derivatives.

Cyclodextrins (CDs, Fig. 1) are cyclic oligosaccharides connected by α -1,4 linkages, frequently characterized as a doughnut-shaped truncated cone.^{1,2} The primary hydroxy groups (OHs) of glucose units are located on the narrower rim of the cone, and the secondary OHs are on the wider one. The diameters of the free space of α -CD cavity are approximately 0.54 nm at the wider rim and 0.47 nm at the narrower rim, whereas for β -CD cavity, the diameters were 0.65 and 0.60 nm, respectively.¹ Thus, the central region of CDs can be considered to be a frontier dividing the cavity into two different regions, one close to the primary OH rim and the other close to the secondary OH rim.³ The free space sizes of α - and β -CD cavity are 104 and 157 cm³ mol⁻¹, respectively.¹

Inclusion complexations between various guest molecules and CDs in aqueous solution have been the subject of numerous experimental studies for many years.^{1,4,5} Intensive theoretical works have also been performed over the past few years on inclusion complexations between CDs and guests.^{6,7} In view of the relatively large molecular size of CDs and their complexes, most of these theoretical studies were done using molecular dynamics (MD), molecular mechanics (MM),^{8,9} and semiempirical quantum mechanics (MNDO, AM1, and PM3) methods.^{10,11} Higher levels of theoretical methods, such as ab initio and density functional theory, generally give a better level of agreement with experimental data. However, the use of semiempirical MO methods rests on the fact that this method is significantly faster than either the ab initio method or the density functional theory. The PM3 method, which permits the modeling of large systems beyond the capacity of ab initio method, has been shown to be a powerful tool for the

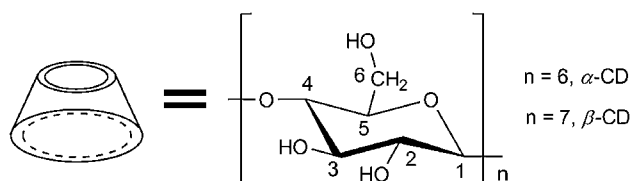


Fig. 1. Chemical structures of α - and β -CD.

theoretical study of supramolecular systems.^{12,13} Theoretical calculations of CD–guest complexations are very useful, and they may provide a valuable insight into the nature of intermolecular interactions between CD and guest.^{14,15} A great majority of these works have focused on the driving forces of inclusion processes of CDs with guests, as well as on the arrangement and stability of CD–guest inclusion complexes.^{14,15}

However, only very few theoretical investigations have been performed to evaluate the influence of CD cavity size and molar volume of guest molecule on the stability of inclusion complexes, though many reports on inclusion phenomena in solution have indicated that size/shape-fit plays an important role in CD–guest inclusion complexations.^{3,16,17}

In the present work, α - and β -CD were selected as hosts, and a homologous series of phenol and benzoic acid derivatives were chosen as guests. The chemical structures and molar volumes of these guest molecules were all in Fig. 2.

The semiempirical PM3 method was used to investigate the inclusion complexation behaviors between CDs and the guests both in vacuo and in water, to determine the complexation differences of the two parent CDs possessing different internal

Guest	Molar volume (/cm ³ ·mol ⁻¹)
1, X = OH, Y = H, Z = H	87.8
2, X = OH, Y = H, Z = NO ₂	99.7
3, X = OH, Y = H, Z = COOH	100.3
4, X = OH, Y = OCH ₃ , Z = H	111.8
5, X = OH, Y = OCH ₃ , Z = CH ₂ CH=CH ₂	156.2
6, X = OH, Y = H, Z = OCH ₃	118.0
7, X = OH, Y = NO ₂ , Z = H	99.7
8, X = COOH, Y = H, Z = H	101.9
9, X = CH(CH ₃)COOH, Y = H, Z = CH ₂ C(CH ₃) ₃	218.5
10, X = COOH, Y = H, Z = NH ₂	104.2
11, X = COOH, Y = H, Z = NO ₂	113.8
12, X = COOH, Y = H, Z = CH ₃	118.2

Fig. 2. Chemical structures and molar volumes of the selected organic guests. The center of the benzene ring was designated as the center of a guest molecule.

diameters and to evaluate the effects of molar volume ratio (MVR) of guest to CD cavity or/and structure matching between the shape of guest and the free space size of CD cavity on the stability of the host–guest complexes.

Method

The inclusion complexations between α - and β -CD, and the twelve guest molecules, illustrated in Fig. 2, both in vacuo and in water were investigated using PM3 method¹⁸ in the present work. All theoretical calculations were performed using the Gaussian 98 software package.¹⁹ The initial geometries of α - and β -CD were built based on their respective crystal structures^{20,21} and then fully optimized by PM3 method without any symmetrical restrictions. All guest molecules were also fully optimized. Harmonic frequency analyses were then performed to make sure that the stationary point was a true minimum.

The glycosidic oxygen atoms of α - or β -CD were placed onto the *xy* plane, and the center of the hexagon or heptagon composed of six or seven glycosidic oxygen atoms was designated as the origin of the Cartesian coordinate system. The secondary OH rim of CD was placed pointing toward the positive *z*-axis. The longer dimension of a guest molecule was initially placed along *z*-axis, and the center of benzene ring of a guest was designated as the center of the guest molecule. The calculated energy values of CD inclusion complexes depended on the starting geometries of host and guest.²² Many published researches on the inclusion complexation between CDs and benzoic acid or phenol analogs in solution have shown that most of the CD inclusion complexes of these guests adopted one of the two different orientations: “head-first” and “tail-first” positions.^{11,12,22} In connection with the fact that the diameter of CD cavity was comparable with the widths of benzoic acid and phenol molecules, two starting geometries were tried in this work, i.e., taking into account the penetration of a guest molecule into the inner cavity both from the primary OH rim and from the secondary OH rim of CD. It should be noted that, for some of the guest molecules calculated in this study, one of the two starting geometries as starting guesses could be in good agreement with the reported experimental results.^{9,11} Figure 3 is a representative schematic sketch illustrating the relative positions of CD and guest molecules. As shown in Fig. 3, the host–guest complexation process was simulated by making a guest molecule penetrate into the cavity of CD from either the wider rim (Fig. 3A) or the narrower rim (Fig. 3B), then letting it pass through the cavity in steps. In

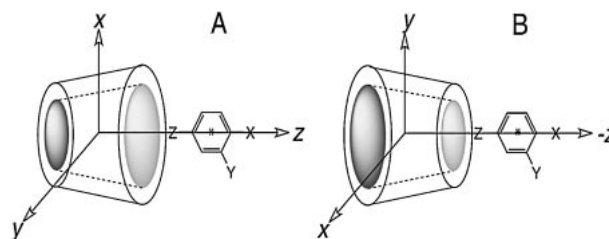


Fig. 3. Schematic sketches illustrating the relative positions between host and guest molecules.

every step, the geometry of host–guest inclusion complex was completely optimized by PM3 without any restrictions. The value of *Z*, which is the distance between host and guest in a complex, was determined along the *z*-coordinate between the center of benzene ring of a guest molecule and the origin of the Cartesian coordinate system.

The formation of the host–guest inclusion complex (HG) of guest (G) and CD (host, H) could be represented by Eq. 1 as follows:



The complexation energy (ΔE_c^v) between guest and CD in vacuo was the difference between the energy of the inclusion complex (ΔE_{HG}^v) and the sum of the energies of guest ($\Delta E_{c,G}^v$) and CD ($\Delta E_{c,H}^v$) at their respective optimized equilibrium geometries in vacuo. Thus, ΔE_c^v could be calculated²³ according to Eq. 2:

$$\Delta E_c^v = \Delta E_{HG}^v - \Delta E_{c,H}^v - \Delta E_{c,G}^v. \quad (2)$$

It is inevitable that the molecular inclusion resulting from the insertion of a guest molecule into CD cavity will be accompanied with deformation behaviors of both CD and guest molecules.²⁴ Accordingly, the deformation energies of CD and guest molecules during complexation processes could not be neglected. The deformation energy ($\Delta E_{f,X}^v$) of a component, X, here X represented host or guest at its optimum position before and after inclusion in vacuo, was calculated²⁵ from Eq. 3 or Eq. 4 as follows:

$$\Delta E_{f,H}^v = \Delta E_{e,H}^v - \Delta E_{c,H}^v, \quad (3)$$

$$\Delta E_{f,G}^v = \Delta E_{c,G}^v - \Delta E_{e,G}^v, \quad (4)$$

where $\Delta E_{f,X}^v$ corresponds to the energy difference between the energy of free X at its optimized equilibrium geometry ($\Delta E_{e,X}^v$) and the energy of complexed X at its optimized complex geometry ($\Delta E_{c,X}^v$) in vacuo. Upon inclusion, the total deformation energy (ΔE_f^v) of host and guest in vacuo was calculated by Eq. 5:

$$\Delta E_f^v = \Delta E_{f,H}^v + \Delta E_{f,G}^v. \quad (5)$$

Interaction energy (ΔE_i^v) between host and guest in vacuo was defined as the difference between the energy of the inclusion complex at its optimized equilibrium geometry and the sum of the energies of both partners (H and G) at their complex geometries.²⁴ Hence, ΔE_i^v could be represented by Eq. 6 as follows:

$$\Delta E_i^v = \Delta E_{HG}^v - \Delta E_{c,H}^v - \Delta E_{c,G}^v. \quad (6)$$

Table 1. The Formation Constants (K_f) of the Host–Guest Complexes in Aqueous Solution, and the Complexation Energies, Deformation Energies, Hydrate Energies, and Interaction Energies of the Inclusion Systems in kJ mol^{-1}

Complex	K_f / $\text{mol}^{-1} \text{dm}^3$	Refs. ^{a)}	MVR	ΔE_c^v	ΔE_c^w	ΔE_f^v	ΔE_f^w	ΔE_h^w	ΔE_i^v	ΔE_i^w	$\Delta \Delta E_i^w$	Z /pm
α -CD-1	4.07×10^1	27	0.844	-13.4	-12.8	3.7	3.3	0.2	-9.7	-9.5	0	200
α -CD-2	2.04×10^2	22	0.959	-19.3	-17.4	2.4	2.4	1.9	-16.9	-15.0	-5.5	300
α -CD-3	1.43×10^3	28	0.964	-39.4	-35.7	-2.2	-1.4	4.5	-41.6	-37.1	-27.6	100
α -CD-4	1.47×10^5	29	1.075	-65.9	-57.1	-10.6	-8.2	11.2	-76.5	-65.3	-55.8	500
α -CD-5	4.95×10^4	5	1.502	-62.1	-59.0	-1.8	-1.5	3.4	-63.9	-60.5	-51.0	200
α -CD-6	6.31×10	28	1.135	-20.7	-17.9	6.0	5.2	2.0	-14.7	-12.7	-3.2	0
α -CD-7	6.31×10^4	30	0.959	-65.5	-62.0	-4.5	-2.0	6.0	-70.0	-64.0	-54.5	400
α -CD-8	8.11×10^2	12	0.980	-33.5	-31.1	4.2	2.8	1.0	-29.3	-28.3	-18.8	-200 ^{b)}
α -CD-10	5.01×10^2	30	1.002	-26.8	-24.3	3.5	3.4	2.4	-23.3	-20.9	-11.4	200
α -CD-11	2.14×10^2	31	0.752	-25.2	-23.0	-2.8	-1.8	3.2	-28.0	-24.8	-15.3	-300 ^{b)}
α -CD-12	8.13×10^2	32	1.137	-35.4	-32.1	-2.3	-2.0	3.6	-37.7	-34.1	-24.6	-300 ^{b)}
β -CD-1	9.33×10^1	27	0.559	-20.5	-19.2	1.8	1.6	1.1	-18.7	-17.6	0	0
β -CD-2	1.91×10^2	33	0.635	-17.7	-18.0	3.0	2.5	-0.8	-14.7	-15.5	2.1	300
β -CD-3	5.21×10^2	34	0.639	-26.3	-24.7	4.3	3.5	0.8	-22.0	-21.2	-3.6	0
β -CD-4	1.53×10^4	29	0.712	-52.8	-48.4	3.5	3.7	4.6	-49.3	-44.7	-27.1	300
β -CD-5	3.96×10^5	5	0.995	-78.9	-72.4	9.5	8.0	5.0	-69.4	-64.4	-46.8	200
β -CD-8	5.49×10^2	35	0.649	-32.2	-29.8	4.2	3.0	1.2	-28.0	-26.8	-9.2	-300 ^{b)}
β -CD-9	1.95×10^5	36	1.392	-67.5	-62.3	7.4	6.0	3.8	-60.1	-56.3	-38.7	0 ^{b)}
β -CD-10	5.00×10^2	34	0.664	-30.2	-28.1	6.1	4.4	0.4	-24.1	-23.7	-6.1	300

a) Refs represents references. b) The Z values obtained based on the starting geometry in Fig. 3B, the others based on the starting geometry in Fig. 3A.

Rearranging Eqs. 2, 3, and 4 gave the expressions of ΔE_{HG}^v , $\Delta E_{\text{c,H}}^v$, and $\Delta E_{\text{c,G}}^v$, respectively. Then, substituting them into Eq. 6 afforded Eq. 7 as follows:

$$\Delta E_i^v = \Delta E_c^v + \Delta E_{\text{c,H}}^v + \Delta E_{\text{c,G}}^v - (\Delta E_{\text{c,H}}^v - \Delta E_{\text{f,H}}^v) - (\Delta E_{\text{c,G}}^v - \Delta E_{\text{f,G}}^v). \quad (7)$$

Accordingly, ΔE_i^v could also be calculated as the sum of their complexation energy and their total deformation energy (see Eq. 8).

$$\Delta E_i^v = \Delta E_c^v + \Delta E_f^v. \quad (8)$$

Furthermore, the intermolecular interactions of CDs and guests with solvent molecules during CD–guest complexation process is inevitable. Therefore, solvent effects on the formation of an inclusion complex in solution must be taken into account throughout all calculations.¹⁴ Calculations of the solvation energy, i.e., hydration energy, in the present work, were carried out using PM3 method. The solvation model for calculating hydration energies of a variety of organic solutes in water was the Conductor-like Screening Model (COSMO).²⁶ The COSMO algorithm was invoked using the keyword NSPA = 60, 1SCF EPS = 78.4, PM3 CHARGE = 0.

$$\Delta E_c^w = \Delta E_{\text{HG}}^w - \Delta E_{\text{c,H}}^w - \Delta E_{\text{c,G}}^w, \quad (9)$$

$$\Delta E_f^w = \Delta E_{\text{f,H}}^w + \Delta E_{\text{f,G}}^w, \quad (10)$$

$$\Delta E_i^w = \Delta E_c^w + \Delta E_f^w. \quad (11)$$

Accordingly, by applying COSMO-based methods the values of the complexation energy (ΔE_c^w), total deformation energy (ΔE_f^w), and interaction energy (ΔE_i^w) in water could be represented by Eqs. 9, 10, and 11, respectively. Thus, the hydration energies (ΔE_h^w) in the inclusion process between CD and a guest molecule could be expressed by Eq. 12:

$$\Delta E_h^w = \Delta E_i^w - \Delta E_i^v. \quad (12)$$

Results and Discussion

Complexation Energy and Interaction Energy. The lowest values of ΔE_c^v , ΔE_c^w , ΔE_i^v , and ΔE_i^w of each inclusion system were listed in Table 1. The values of $\Delta \Delta E_i^w$ represented the energetic advantages of α - and β -CD complexes in comparison with α -CD-1 and β -CD-1 in water, respectively. According to Eq. 1, the formation constants (K_f) of the host–guest inclusion complexes in aqueous solution could be represented by Eq. 13 as follows:

$$K_f = [\text{HG}] \cdot ([\text{H}] \cdot [\text{G}])^{-1}, \quad (13)$$

where [H], [G], and [HG] represent the equilibrium concentrations of CD, guest, and CD–guest inclusion complex, respectively. The measured values of K_f and the calculated values of ΔE_f^v , ΔE_f^w , ΔE_h^w , MVR, and Z are summarized in Table 1.

The values of ΔE_i^v and ΔE_i^w should directly reflect the stabilities of CD supramolecular complexes in vacuo and in water, respectively. As shown in Table 1, the sufficiently large negative values of ΔE_i^w clearly demonstrated that the formation of the inclusion complexes in water was energetically very favorable. Theoretically speaking, if the calculated ΔE_i^w value of an inclusion system is more negative, the obtained inclusion complex should be more thermodynamically stable in water.

The calculated values of complexation energies and interaction energies of the nineteen inclusion systems in vacuo and in water are plotted as bar-graphs in Figs. 4A and 4B, respectively. The bar graphs depicting two kinds of energies were found not only to have the same trends from left to right both in vacuo and in water, but also to be quite similar to each other, except for some slight differences in the heights of the bars.

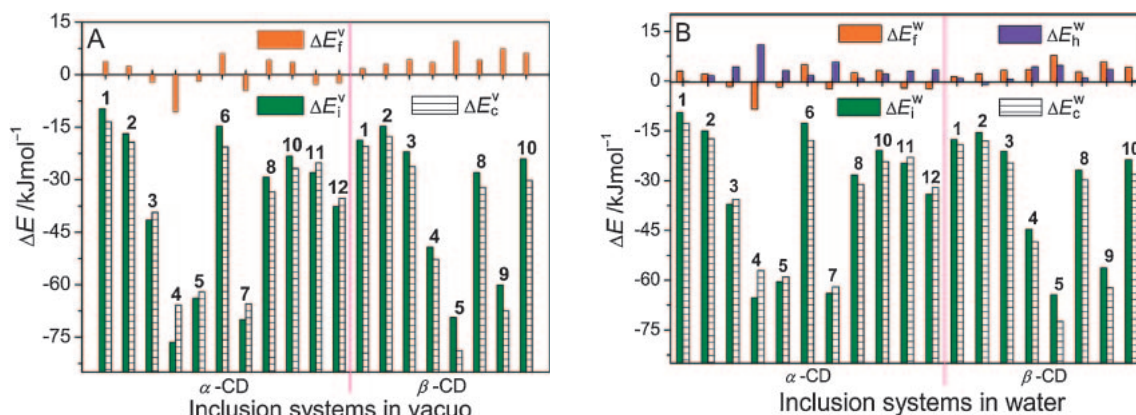


Fig. 4. Calculated energy values of nineteen inclusion systems (A) ΔE_c^v , ΔE_f^v , and ΔE_i^v in vacuo and (B) ΔE_c^w , ΔE_f^w , ΔE_i^w , and ΔE_h^w in water.

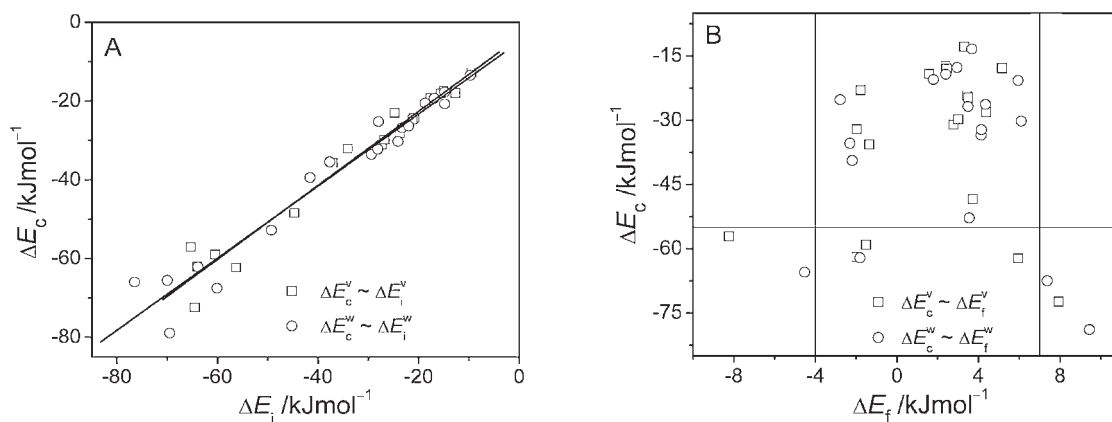


Fig. 5. (A) Linear relationships between ΔE_i and ΔE_c of the nineteen inclusion systems of CDs; (B) plots of the distribution of ΔE_c values of the CD–guest inclusion systems with different ΔE_f values.

For example, the inclusion complex β -CD–5 had the most negative ΔE_c^v value ($-78.9 \text{ kJ mol}^{-1}$) among the nineteen inclusion systems, but it did not have the lowest ΔE_i^v value among these inclusion systems.

The linear correlation coefficient (r) of the regression line for the data set of ΔE_i^v and ΔE_c^v was 0.976. For the data set of ΔE_i^w and ΔE_c^w , the r value was 0.981. Since the two beelines in Fig. 5A appeared to be a near superposition, ΔE_i^v and ΔE_c^v of the inclusion systems could to a great extent be regarded as their respective ΔE_i^w and ΔE_c^w . In other words, the contribution from the sum of both deformation energy and hydration energy of the inclusion systems to ΔE_i in vacuo and in water should be approximately equivalent.

Deformation Energy and Hydration Energy. The bar-graphs depicting the values of ΔE_f^v and ΔE_f^w of the nineteen CD–guest inclusion systems are drawn in Figs. 4A and 4B, respectively. The highest and lowest points of these orange bars appeared for β -CD–5 and α -CD–4, respectively.

The distribution of ΔE_c values of the nineteen CD–guest inclusion systems with different ΔE_f values is shown in Fig. 5B. It should be noted that a great majority of the nineteen host–guest inclusion systems both in vacuo and in water appeared in the area with a horizontal and vertical dimension of -4 to 7 kJ mol^{-1} and -53 to -15 kJ mol^{-1} , respectively. The maximum and minimum ΔE_f^v values of the eleven α -CD inclusion

systems were 6.0 and $-10.6 \text{ kJ mol}^{-1}$, respectively. However, for the eight β -CD inclusion systems, these values became 9.5 and 1.8 kJ mol^{-1} , respectively. Accordingly, for all the CD inclusion systems, the energy contribution from deformation energy to interaction energy in vacuo was insignificant, though it could not be completely neglected (see Fig. 4A). Moreover, the maximum and minimum values of ΔE_f^w were 5.2 (α -CD–6) and -8.2 (α -CD–4) kJ mol^{-1} for the eleven α -CD inclusion systems, whereas for the eight inclusion systems of β -CD, these values were all higher than zero (see Fig. 4B), and the maximum and minimum ΔE_f^w values were 8.0 (β -CD–5) and 1.6 (β -CD–1) kJ mol^{-1} , respectively.

The results revealed that there was no significant difference between the two calculated ΔE_f values both in vacuo and in water as described before. In addition, the energy differences in the $\Delta E_{f,X}$ values of the host and guest molecules in an inclusion complex, such as α -CD–1, between in vacuo and in water were only 0.02 kJ mol^{-1} for α -CD and 0.35 kJ mol^{-1} for guest 1.²⁰ The weak deformation behaviors of host and guest upon complexation could be attributed to the rather rigid skeleton of α - and β -CD,⁹ and to the structural rigidity of the benzene ring on the substituted phenols and benzoic acids.

Intermolecular interactions of water, used as reaction medium, with CD and guest molecules is important for making a CD–guest inclusion complex in aqueous solution. This is

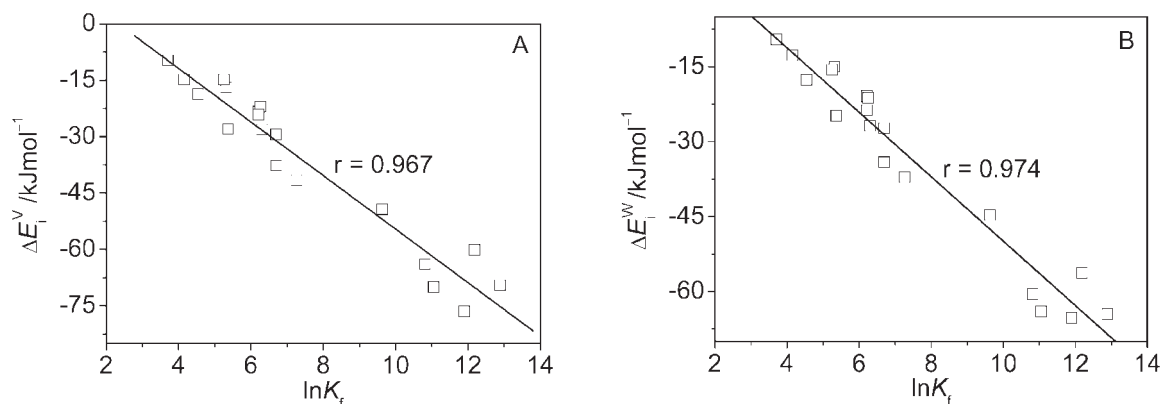


Fig. 6. Linear relationships between $\ln K_f$ and (A) ΔE_i^v or (B) ΔE_i^w of the nineteen inclusion systems of CDs.

because the water environment around CDs and guests would surely influence the CD–guest complexation process.¹⁴ As can be seen in Table 1 and Fig. 4B, when solvent effects were taken into consideration during calculation, the values of ΔE_c^w and ΔE_i^w became obviously less negative relative to the values of ΔE_c^v and ΔE_i^v .

Furthermore, $\Delta\Delta E_i^w$ represented the energetic advantages of α - and β -CD complexes in comparison with α -CD-1 and β -CD-1 in water, respectively. Based on the data summarized in Table 1, it was easily seen that the $\Delta\Delta E_i^w$ values were higher than the values of $\Delta\Delta E_i^v$. For example, as for α - and β -CD inclusion systems, the minimum values of $\Delta\Delta E_i^v$ were -66.8 and -50.7 kJ mol⁻¹, respectively. However, the minimum $\Delta\Delta E_i^w$ values of the two inclusion systems had increased to -55.8 and -46.8 kJ mol⁻¹, respectively. The energy increase in the inclusion system in water clearly reflected that the intermolecular complexations between host and guest were impeded, at least to a certain extent, by water molecules around the host and guest molecules. These findings indicate that water molecules weaken the intermolecular interactions between CDs and the substituted benzenes.

The maximum and minimum hydration energy (ΔE_h^w) values of the α -CD inclusion systems listed in Table 1 were 11.2 and 0.2 kJ mol⁻¹, respectively. The values of β -CD inclusion systems were 4.6 and -0.8 kJ mol⁻¹, respectively. The sum values of ΔE_f and ΔE_h^w were all above zero, which are unfavorable for the formation of the CD inclusion complexes. It was also found that, although α -CD-4 and β -CD-5 did not possess the lowest sum value of ΔE_f and ΔE_h^w , they were the most stable complexes in the α -CD inclusion systems and β -CD inclusion systems respectively. Therefore, it gave us a strong impression that the contribution from the structure matching between the shape/size of a guest molecule and the cavity size of CD was dominant to stabilize the inclusion complexes, though the energy contribution of ΔE_f and ΔE_h^w could not be neglected.

Linear Relationships between the Interaction Energy and the Natural Logarithm of K_f . As can be seen in Table 1, strikingly, if an inclusion complex possessed a higher negative value of the interaction energy whether in vacuo or in water, by and large, it would have a larger value of K_f measured in aqueous solution. In Fig. 6, the two nearly linear relationships between the natural logarithms of K_f and the interaction energies calculated both in vacuo and in water were appar-

ent in Fig. 6A with the r value of 0.967 and in Fig. 6B with the r value of 0.974 , respectively. Two suitable mathematical representations describing the linear relationships are given in Eqs. 14 and 15 as follows:

$$\Delta E_i^v = -7.12 \ln K_f + 16.6, \quad (14)$$

$$\Delta E_i^w = -6.45 \ln K_f + 14.6. \quad (15)$$

Two plots of these data were well fit by straight lines, both with similar slopes and intercepts, and two equations exhibited a similar tendency. Since both formation constant and interaction energy could reflect the stability of a supramolecular inclusion complex, accordingly, a good linear relationships between $\ln K_f$ and ΔE_i^v or ΔE_i^w of the nineteen inclusion systems seemed to be reasonable.²⁴

The data in Table 1 shows that the order of the absolute values of ΔE_i as well as ΔE_c is in approximate agreement with that of the K_f values. In addition, the linear relationship in Fig. 6 suggests that the values of ΔE_i linearly decrease with an increase in $\ln K_f$ values in these inclusion systems. Hence, the linear equations as shown in Eq. 14 especially in Eq. 15, should reflect the intrinsic correlations between the inclusion energies and the formation abilities of the CD supramolecular complexes of the substituted benzenes. Clearly, this observation in the present work will help us to further understand the nature of intermolecular interaction between CD and guest and to predict the formation and stability of novel CD inclusion complexes in solution, only using theoretical studies.

Furthermore, this finding should be very important especially for some unique CD–guest complexations that are difficult to examine in aqueous solution. For example, these guest molecules could be those possessing some minor structural units of CD, such as glucose, maltose, and some other saccharides, those that are light, air or moisture sensitive, such as many transition-metal organic compounds, and those that are either rather difficult to be prepared or quite expensive.

However, the approach was only tested on a limited number of CD inclusion systems of substituted benzenes. Therefore, the broad applicability of the linear relationship presented in Eq. 15 remains to be established by applying a validation set including a large number of guest molecules.

Effects of the Values of MVR on the Stability of CD Complexes. Figure 7 displayed clearly a significant interaction energy difference, $\Delta\Delta E_i^w$, between CD-1 and all other CD–guest inclusion systems.

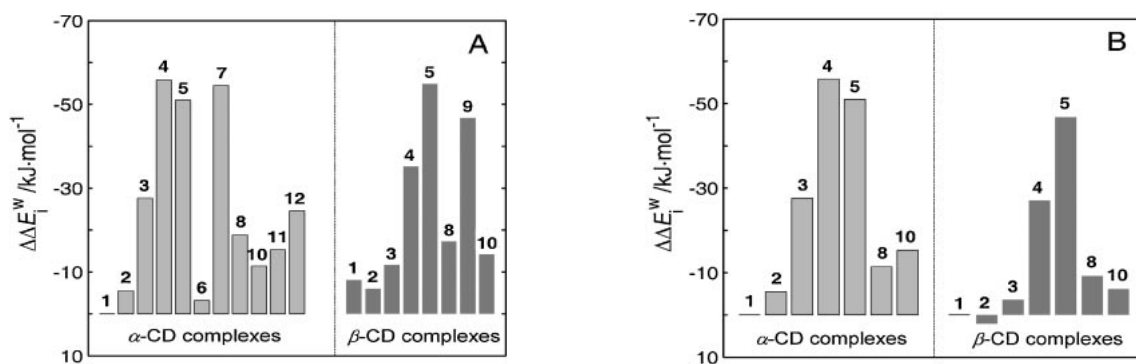


Fig. 7. Interaction energy difference ($\Delta\Delta E_i^w$, kJ mol^{-1}) of two inclusion systems, (A) between α -CD-1 and all other CD-guest complexes, (B) between the same CD complexes of guest 1 and guest 2, 3, 4, 5, 8, or 10.

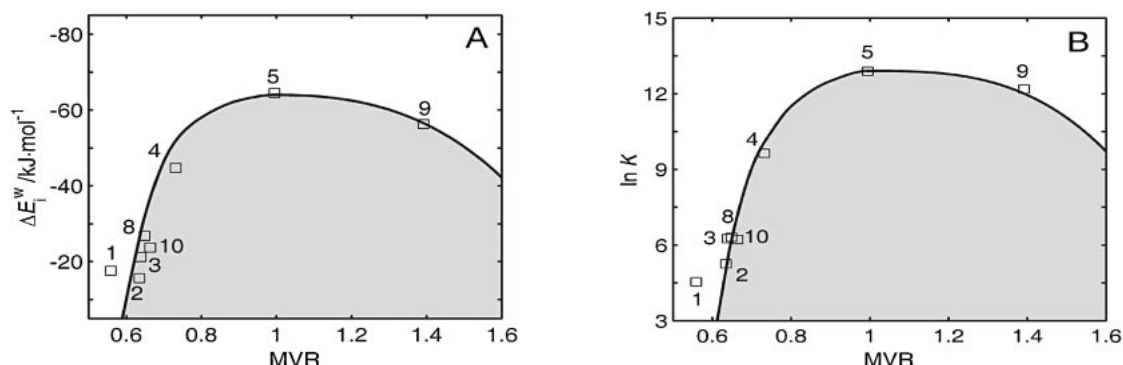


Fig. 8. The ΔE_i^w values of the inclusion systems of β -CD (A) as a function of MVR, and $\ln K_f$ of β -CD inclusion complexes as a function of MVR (B).

As can be seen in Fig. 7A, the inclusion complexes of guests 4, 5, and 7 with α -CD, and guests 5 and 9 with β -CD, in which ΔE_i^w was lower than -55 kJ mol^{-1} and K_f was larger than $10^4 \text{ mol}^{-1} \text{ dm}^3$, were much more stable than the complexes of all other guests with the same CD, in which ΔE_i^w was higher than -45 kJ mol^{-1} and K_f was smaller than $2 \times 10^3 \text{ mol}^{-1} \text{ dm}^3$. The inclusion complexes of α -CD with guest 1, 2, or 6, in which ΔE_i^w was higher than -20 kJ mol^{-1} and K_f was smaller than $2.5 \times 10^2 \text{ mol}^{-1} \text{ dm}^3$, and β -CD with guest 1, 2, or 3, in which ΔE_i^w was higher than -25 kJ mol^{-1} and K_f was smaller than $2 \times 10^2 \text{ mol}^{-1} \text{ dm}^3$, were much less stable than all other complexes of the same CD.

Figure 7B illustrated that the α -CD complexes of 2, 3, 4, 5, 8, and 10 had more than a 5.5 kJ mol^{-1} energetic advantage, i.e., $\Delta\Delta E_i^w$, when compared with α -CD-1 in water. And the energy advantages between β -CD complexes of the guests such as 3, 4, 5, 8, and 10 and β -CD-1 were all 3.6 kJ mol^{-1} above.

The bar diagrams on the left and right side in Fig. 7A or 7B, respectively corresponding to α -CD and β -CD complexes, looked somewhat alike in their profiles, indicating that there existed, as a whole, similar inclusion behaviors between the same guest and the two parent CDs. However, the guests in those complexes located at the vertex and nadir in each group were completely different for different CD. The guests in α -CD complexes were 1 (the lowest) and 4 (the highest), and those in β -CD complexes were 2 (the lowest) and 5 (the highest), respectively.

These results suggested that the CDs cavity size might exert

a big influence on the stability of these inclusion complexes.^{37,38} That is to say, the effects of the values of MVR on the stabilities of CD complexes of the phenol and benzoic acid derivatives should be important.

The ΔE_i^w values of the inclusion systems of β -CD as a function of the values of MVR are plotted in Fig. 8. As can be seen in Fig. 8A, the absolute values of ΔE_i^w of the β -CD inclusion systems nonlinearly increased with an increase in the MVR value within the range from 0.635 to 0.995, and then gradually decreased. The curve is shaped like an asymmetric arch. Its profile seemed to be similar to that of the arch-shaped curve resulting from the K_f values listed in Table 1 as a function of MVR (see Fig. 8B).

The MVR value of guest 5 to β -CD was 0.995, indicating an appropriate fit between the cavity size of β -CD and the molecular volume of the guest, 4-allyl-2-methoxyphenol. Consequently, as shown in Table 1, Figs. 8A and 8B, it can be easily seen that inclusion complex β -CD-5 had the highest stability among all these inclusion complexes whether measured (K_f , $3.96 \times 10^5 \text{ mol}^{-1} \text{ dm}^3$) in aqueous solution or calculated both in vacuo (ΔE_i^v , $-69.4 \text{ kJ mol}^{-1}$) and in water (ΔE_i^w , $-64.4 \text{ kJ mol}^{-1}$). The molecule volume of guest 9 was quite larger than free space size of the cavity of β -CD. Hence, as shown in Fig. 8B, the absolute value of ΔE_i^w (56.3 kJ mol^{-1}) in β -CD-9 is obviously lower than the absolute value of ΔE_i^w (64.4 kJ mol^{-1}) in β -CD-5. That is to say, if a guest molecule is too large, for example, β -CD-9 with a MVR value of 1.392, to fully penetrate into the cavity, or too small, for example, β -CD-1 with a MVR value of 0.559, to be effectively embedded

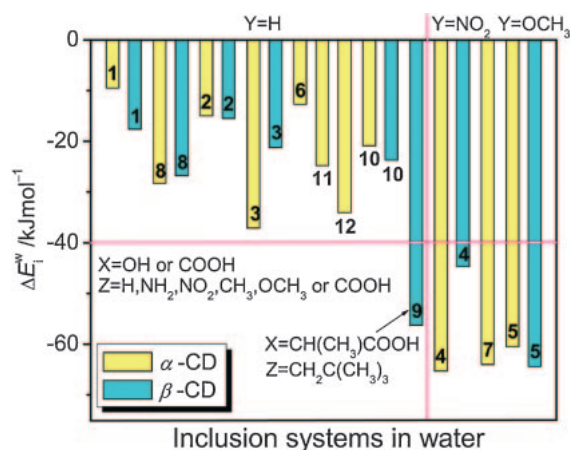


Fig. 9. Plots of the Y-position of the guests vs. the ΔE_i^w values of the nineteen CD–guest inclusion systems in water.

within the cavity, the guest will form a less-stable inclusion complex with β -CD. These results showed that a good size fitting between the molecular volume of a guest molecule and the free space size of β -CD cavity would effectively improve the stability of β -CD–guest inclusion complex.^{2,39}

However, the relative sensitivity of the α - and β -CD cavity to the molecular volumes of the guests could not be established only based on the limited data listed in Table 1. This is because the stabilities of the inclusion complexes might be influenced by the polarity, hydrophobicity, and position of the substituted groups in the guest molecules as well as molecular volumes of the guests. The effects of the substitution position, especially, the Y-position of the guests in Fig. 2 on the stabilities of CD complexes were evaluated in the present work.

Effects of the Substitution Position of the Guests on the Stabilities of CD Complexes. On the basis of the calculated values, it was found that the stabilities of the inclusion complexes were obviously influenced by the substitution positions of the guests.

The stabilities of α -CD inclusion complexes of the mono-ortho-substituted phenol derivatives ($Y \neq H$ in Fig. 2) was markedly higher than those of the complexes of α -CD with phenol or the mono-para-substituted derivatives of phenol ($Y = H$ in Fig. 2). For example, guests **2** and **7** had the same molar volumes but differed in the position of the NO_2 group on the benzene ring. As can be seen in Fig. 9, the stability of the inclusion complex of the mono-ortho-substituted guest **7** (ΔE_i^w , $-64.0 \text{ kJ mol}^{-1}$) with α -CD was significantly higher than that of the inclusion complex of α -CD with the mono-para-substituted guest **2** (ΔE_i^w , $-15.0 \text{ kJ mol}^{-1}$). A significant difference was also observed between the stabilities of the α -CD inclusion complexes of the mono-ortho-substituted guest **4** (ΔE_i^w , $-65.3 \text{ kJ mol}^{-1}$) and mono-para-substituted guest **6** (ΔE_i^w , $-12.7 \text{ kJ mol}^{-1}$).

There was an energy advantage of larger than 45 kJ mol^{-1} in favor of the intermolecular complexations between the mono-ortho-substituted phenol derivatives and α -CD. For example, the difference in ΔE_i^w between α -CD–**4** and α -CD–**6** was 52.6 kJ mol^{-1} , and the energy difference between α -CD–**7** and α -CD–**2** was 49.0 kJ mol^{-1} according to the data shown in Fig. 9 and Table 1. These results suggest that in the complexes

of the guests **4** and **7**, the NO_2 or OCH_3 groups in Y-position of the guests should be located in the hydrophobic cavity of α -CD, but not in Z-position of the guests **6** and **2**.

Furthermore, due to the existence of some polar and bulky substituents, such as $-\text{OCH}_3$ and $-\text{NO}_2$, at the Y-position on the guests **4**, **5**, and **7**, the five inclusion complexes of CDs with these guests showed rather larger negative values of ΔE_i^w ($< -40 \text{ kJ mol}^{-1}$, see Fig. 9). The inclusion complexes of CDs with phenol, benzoic acid, and their mono-para-substituted derivatives, such as guests **1**, **2**, **3**, **6**, **8**, **10**, **11**, and **12**, all of which has a proton H at Y-position, were less stable ($\Delta E_i^w > -40 \text{ kJ mol}^{-1}$). In addition, no significant difference in the values of ΔE_i^w values between the inclusion complexes of α - and β -CD with guests **2**, **5**, **8**, and **10** was found.

It should be noted that the guest **9** bearing two extremely bulky substituents, i.e., $-\text{CH}(\text{CH}_3)\text{COOH}$ group and $-\text{CH}_2\text{C}(\text{CH}_3)_3$ group at the X- and Z-position on the benzene ring, respectively, formed a more stable inclusion complex, β -CD–**9**, ($\Delta E_i^w < -40 \text{ kJ mol}^{-1}$, see Fig. 9) than any other mono-para-substituted guests. This phenomenon could be attributed to the structure matching between CD cavity and the guest.

Structures of the CD–Guest Inclusion Complexes. The optimum position of a guest in CD cavity was determined according to relative values of ΔE_i^w between two starting geometries described above. Although the two starting geometries could produce their respective lowest values of the interaction energy between host and guest, only the starting geometry with a lower calculated value of ΔE_i^w (see Table 1) was considered to be present for the formation of a stable CD–guest complex. The Z values of the nineteen inclusion systems in water corresponding to their respective lowest values of ΔE_i^w are listed in Table 1. Two representative pictures, which illustrate the relationships between Z and ΔE_i^v or ΔE_i^w , are depicted in Fig. 10.

As can be seen in Fig. 10, fifteen of the nineteen inclusion systems formed their respective inclusion complexes in the range from cavity center ($Z = 0 \text{ pm}$) to the exterior near the secondary OH rim of the cavity ($Z = 500 \text{ pm}$) both in vacuo and in water. These results are in accordance with those published recently.^{10–12} Among the inclusion systems calculated in vacuo, ten of the nineteen CD–guest inclusion complexes appeared in the central area with a horizontal and vertical dimension of 0 to 300 pm and -15 to -60 kJ mol^{-1} , respectively (see Fig. 10A). In water, the systems in the central area, with a horizontal and vertical dimension of 0 to 300 pm and -12 to -57 kJ mol^{-1} , respectively, were still the 10 inclusion systems (see Fig. 10B).

Typical pictures of two representative complexes, β -CD–**1** and β -CD–**9**, given in Figs. 11A and 11B respectively, could to a certain extent reflect the effect of size fitting or structure matching between CD and guest on the formation and stability of CD–guest inclusion complexes. As shown in Fig. 11A, guest **1**, a tortoise-shaped guest with a maximum breadth of 0.433 nm, which is obviously shorter than the diameter of the free space within β -CD cavity, should be able to pass through this cavity freely. At the same time, the two inclusion complexes of guest **1**, β -CD–**1**, and α -CD–**1**, were found to be significantly less stable (see Table 1) when compared with the other complexes. Figure 11B shows a schematic picture

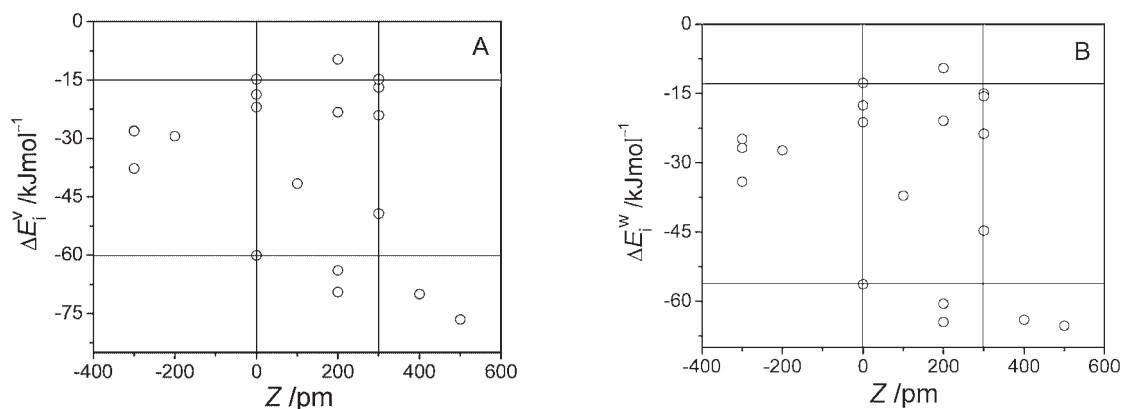


Fig. 10. Plots of the Z values vs. the ΔE_i values of the nineteen CD-guest inclusion systems in vacuo (A) and in water (B).

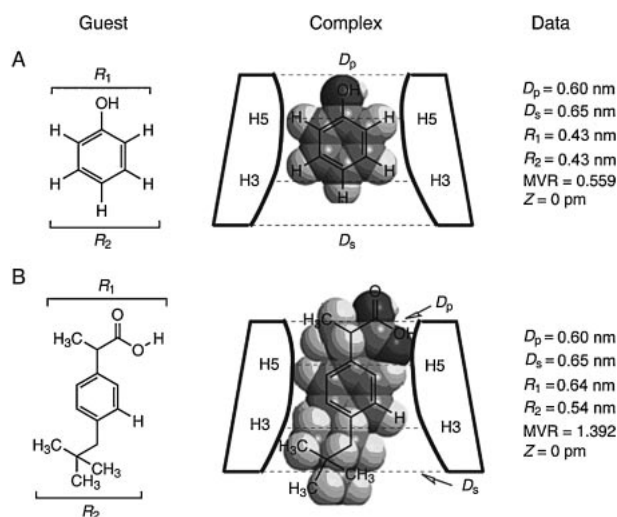


Fig. 11. Structural sketches of two inclusion complexes, (A) β -CD-1 and (B) β -CD-9. D_p and D_s are the diameters of the narrower and wider rims of the free space in the inner cavity of β -CD, respectively. R_1 and R_2 are widths of the upper and lower portions of guest molecules, respectively.

of β -CD-9, where with an upper width R_1 of 0.644 nm and a lower width R_2 of 0.540 nm, guest 9 looked like a special-shaped column structure. The column-like structure makes it possible to fill the free space within the β -CD cavity.^{16,17}

Figure 12 illustrated the complexation processes between guest 9 and β -CD in two different starting geometries. As can be seen in Figs. 12A and 12B, the difference in interaction energy of guest 9 and β -CD between two different arrangements was 8.7 kJ mol⁻¹. Based on the lowest energy principle, guest 9 should enter into β -CD cavity from the primary OHs rim (see Fig. 12A). Although the lowest ΔE_i^w values of two arrangements were different from each other, their corresponding values of Z were the same, i.e., upon inclusion, their Z values were equal to 0 pm. This result indicates that there is an optimal superposition between the designated centers of β -CD and 9 in the complex, β -CD-9. After inclusion, whether the Z value decreased or increased, the absolute value of ΔE_i^w for β -CD-9 should decrease swiftly and sharply as displayed in Fig. 12. Therefore, guest 9 cannot form a stable complex possessing a ΔE_i^w value of lower than -40 kJ mol⁻¹, unless it penetrates fully into the cavity of β -CD. Structurally, upon inclusion the guest molecule could be adequately locked within this cavity as shown in Fig. 11B and Fig. 12A.

The stability of β -CD-9 was only less than that of β -CD-5, but greater than those of all other complexes listed in Table 1. It should be noted that the molecular volume of guest 9 was

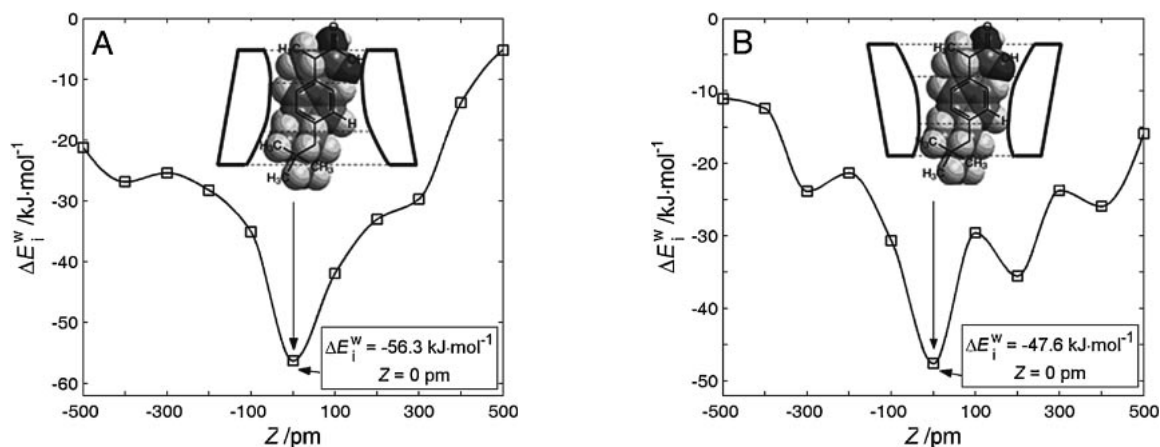


Fig. 12. Schematic drawings depicting complexation process between guest 9 and β -CD in two different arrangements, (A) migration of guest 9 into β -CD cavity from the primary OH rim and (B) from the secondary OH rim.

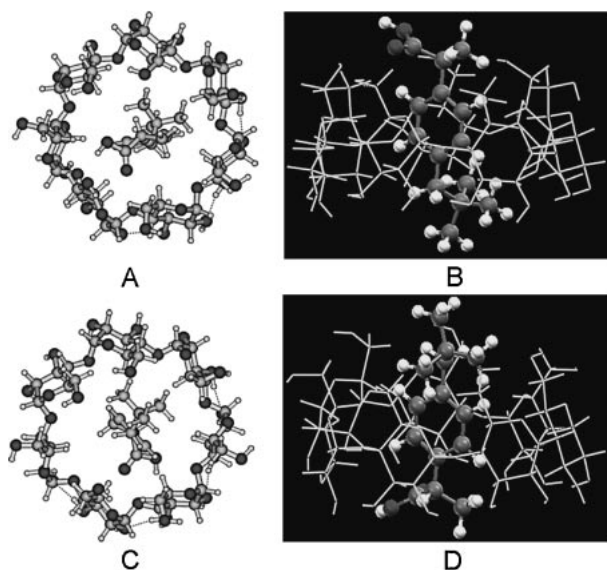


Fig. 13. Structural pictures of guest **9** in the cavity of β -CD: (A) Top view and (B) side view when **9** penetrated into the cavity from the primary OH rim, and (C) top view and (D) side view from the secondary OH rim.

remarkably larger than the cavity size of β -CD. Among the studied α -CD complexes, the molecular volume of guest **10** was rather close to the cavity size of α -CD (MVR, 1.002), but the absolute value of ΔE_1^w was obviously smaller than that of the inclusion complex of α -CD with **4** (MVR, 1.075) or with **7** (MVR, 0.959). Accordingly, these results suggest that, even though there did not exist an appropriate MVR between host and guest, a good structural matching between the shape of a guest molecule and the arrangement of CD cavity could also effectively improve the stability of CD–guest inclusion complexes.² In other words, if a guest molecule with an appropriate shape or spatial structure acclimatize itself to the free space of CD cavity, it could form a comparatively stable CD complex, even though its molecular volume was obviously larger the size of CD cavity.^{37,40,41}

The PM3 optimized structures of two structural forms of β -CD–**9** are illustrated in Fig. 13. As can be seen, with a column-like structure, guest **9** was perfectly accommodated into the cavity of β -CD. However, no intermolecular hydrogen bonds between the hydroxy groups of β -CD and –COOH or –OH in guest **9** were found in the two structures of β -CD–**9**. Accordingly, it seemed to be reasonable to conclude that the driving forces for the formation of the inclusion complex should be mainly from the van der Waals forces between CD and guest molecules and the pairwise hydrophobic interaction between the hydrophobic inner surface of CD cavity and hydrophobic groups of guests.

References

- 1 J. Szejtli, *Chem. Rev.* **1998**, 98, 1743.
- 2 M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, 98, 1875.
- 3 J. Carrazana, A. Jover, F. Mejjide, V. H. Soto, J. V. Tato, *J. Phys. Chem. B* **2005**, 109, 9719.
- 4 K. Harata, L. X. Song, H. Morii, *Supramol. Chem.* **2000**, 11, 217.

- 5 Y. Yang, L. X. Song, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, 53, 27.
- 6 E. A. Castro, D. A. J. Barbiric, *Curr. Org. Chem.* **2006**, 10, 715.
- 7 V. Klepko, S. Ryabov, Y. Kercha, L. Bulavin, R. Bila, V. Slisenko, O. Vasilkevich, V. Krotenko, *J. Mol. Liq.* **2005**, 120, 67.
- 8 I. Bea, M. G. Gotsev, P. M. Ivanov, C. Jaime, P. A. Kollman, *J. Org. Chem.* **2006**, 71, 2056.
- 9 Y. M. Yu, C. Chipot, W. S. Cai, X. G. Shao, *J. Phys. Chem. B* **2006**, 110, 6372.
- 10 C. L. Yan, X. H. Li, Z. L. Xiu, C. Hao, *THEOCHEM* **2006**, 764, 95.
- 11 M. J. Huang, M. Y. Yi, *Int. J. Quantum Chem.* **2004**, 100, 771.
- 12 L. Liu, X. S. Li, K. S. Song, Q. X. Guo, *THEOCHEM* **2000**, 531, 127.
- 13 R. Castro, M. J. Berardi, E. Cordova, M. O. de Olza, A. E. Kaifer, J. D. Evanseck, *J. Am. Chem. Soc.* **1996**, 118, 10257.
- 14 K. B. Lipkowitz, *Chem. Rev.* **1998**, 98, 1829.
- 15 C. Jaime, M. de Federico, *Curr. Org. Chem.* **2006**, 10, 731.
- 16 M. M. Meier, M. T. B. Luiz, P. J. Farmer, B. Szpoganicz, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, 40, 291.
- 17 G. Pistolis, I. Balomenou, *J. Phys. Chem. B* **2006**, 110, 16428.
- 18 J. J. P. Stewart, *J. Comput. Chem.* **1989**, 10, 221.
- 19 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98, Rev. A. 7*, Gaussian, Inc., Pittsburgh PA, **1998**.
- 20 K. K. Chacko, W. Saenger, *J. Am. Chem. Soc.* **1981**, 103, 1708.
- 21 K. Lindner, W. Saenger, *Carbohydr. Res.* **1982**, 99, 103.
- 22 L. Liu, K. S. Song, X. S. Li, Q. X. Guo, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, 40, 35.
- 23 G. Piel, G. Dive, B. Evrard, T. Van Hees, S. H. de Hassonville, L. Delattre, *Eur. J. Pharm. Sci.* **2001**, 13, 271.
- 24 H. M. Wang, L. X. Song, *Chem. Lett.* **2007**, 36, 596.
- 25 N. Chekirou, A. Krallafa, A. Bormann, *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, 53, 89.
- 26 A. Klamt, G. Schuurmann, *J. Chem. Soc., Perkin Trans. 2* **1993**, 799.
- 27 G. L. Bertrand, J. R. Faulkner, Jr., S. M. Han, D. W. Armstrong, *J. Phys. Chem.* **1989**, 93, 6863.
- 28 F. Hirayama, M. Kurihara, K. Uekama, *Int. J. Pharm.* **1987**, 35, 193.
- 29 A. Yoshida, K. Sasaki, S. Morita, *J. Jpn. Soc. Nutr. Food Sci.* **1991**, 38, 294.
- 30 E. A. Lewis, L. D. Hansen, *J. Chem. Soc., Perkin Trans. 2* **1973**, 2081.
- 31 R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, D. A. Laufer, *J. Am. Chem. Soc.* **1981**, 103, 1750.

- 32 K. Kano, T. Ishimura, S. Negi, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, 22, 285.
- 33 K. Harata, *Bioorg. Chem.* **1980**, 9, 530.
- 34 K. Harata, *Bioorg. Chem.* **1981**, 10, 255.
- 35 R. I. Gelb, L. M. Schwartz, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, 7, 465.
- 36 F. A. Menard, M. G. Dedhiya, C. T. Rhodes, *Drug Dev. Ind. Pharm.* **1990**, 16, 91.
- 37 C. Torque, H. Bricout, F. Hapiot, E. Monflier, *Tetrahedron* **2004**, 60, 6487.
- 38 H. Yamamura, M. V. Rekharsky, Y. Ishihara, M. Kawai, Y. Inoue, *J. Am. Chem. Soc.* **2004**, 126, 14224.
- 39 J. S. Lock, B. L. May, P. Clements, J. Tsanaktisidis, C. J. Easton, S. F. Lincoln, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3361.
- 40 Y. Ikeda, F. Hirayama, H. Arima, K. Uekama, Y. Yoshitake, K. Harano, *J. Pharm. Sci.* **2004**, 93, 1659.
- 41 Y. Matsushita, T. Suzuki, T. Ichimura, T. Hikida, *J. Phys. Chem. A* **2004**, 108, 7490.