Experimental and Theoretical Studies on the Inclusion Complexation of Syringic Acid with α-, β-, γ- and Heptakis(2,6-di-*O*-methyl)-β-cyclodextrin

Le Xin SONG,*[,a] Hai Ming WANG,[a] Peng XU,[a] Yan YANG,[b] and Zi Qiang ZHANG[a]

[a] *Department of Chemistry, University of Science and Technology of China; Hefei 230026, China: and* [b] *Department of Chemical Engineering, Anhui University of Science and Technology; Huainan 232001, China.*

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Intermolecular interactions of α-, β-, γ- and heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (CD) with syringic acid (Syr) in aqueous solution are investigated by fluorescence spectroscopy. The fluorescence intensity of Syr gradually increases with the addition of the CDs. The formation constants (*K*) of the host–guest inclusion complexes are determined using a nonlinear analysis. The association abilities of Syr with the CDs decrease in the order γ-CD > β-CD > α-CD ≈ DMβ-CD. Both the intrinsic binding abilities of the CDs and the structural effect of Syr are taken into consideration when comparing the *K* values. Based on the results of NMR experimental and theoretical PM3 calculations both *in vacuo* and in water, it is found that Syr stays near the wider rim of α-CD cavity. Both the number of substituted groups (*NSG*) in a guest and the molar volume ratio of the guest to host cavity (*MVR*) play an important role in forming the CD supramolecular complexes of a homologous series of phenol derivatives, such as 2-methoxylphenol (2-Mop), eugenol (Eug) and Syr, *i.e.*, an appropriate *NSG* or *MVR* in an inclusion system, such as in 2-Mop–α-CD, Eug–β-CD and Syr–γ-CD systems, can maximize the intermolecular interaction between host and guest.

Key words cyclodextrin; inclusion complex; syringic acid; formation constant; parameterized model 3

Cyclodextrins (CDs, Fig. 1) are cyclic oligosaccharides consisting of glucose subunits connected through glycosidic α-1,4 bond, forming a structure as a hollow truncate with one ring wider than the other.[1)] The most common CDs are α-, β- and γ-CD, composed of six, seven and eight glucose units, respectively. Heptakis(2,6-di-*O*-methyl)-β-CD (DMβ-CD) is a simple derivative of β-CD, in which all 2- and 6-OH groups of the seven glucose units are substituted by $-OCH_3$ groups. Many papers have been published concerning the formation and spectral properties of guest–CD complexes in aqueous solution using various analytical methods.[2—6)]

In solution, phenol and its simple analogs can be partly or wholly included into a CD cavity.[7)] There have been a few structural studies on the inclusion complexes of CDs with phenol and substituted phenols based on experimental measurements or theoretical calculations.[8—11)] Huang and his coworkers performed a detailed investigation on the conformation and stabilization energies of CD inclusion complexes of several substituted phenols, including 2-methylphenol, 2-ethylphenol and 2-isopropylphenol, using semiempirical molecular orbital method.[8)] These authors pointed out that one of the principal driving forces for the formation of the inclusion complexes should be attributed to van der Waals interaction.

Previous experimental studies showed that there were no enough strong interactions between a parent CD and phenol or its simple derivatives such as nitrophenol, methylphenol, aminophenol, halogenphenol and hydroxydiphenyl.[12—14)] However, it is found that eugenol (Eug), a phenol derivative with three substituents on benzene ring, while being accommodated into CD cavity, is able to form considerably stable inclusion complexes with three common parent CDs.[9)] These results urge us to estimate the effects of the number of substituted groups (*NSG*) in guest and the molar volume ratio (*MVR*) of guest to the cavity of CD on the formation and stability of CD supramolecular complexes of phenol derivatives.

Syringic acid (Syr) is usually used as sedative and local anaesthetic. 2-Methoxylphenol (2-Mop), with antitussive and expectorant effects, is widely used as a medicine for bronchitis. Eugenol is known to be an effective snake repellent. The three molecules are the important derivatives of phenol. Their structure features and molar volumes are displayed in Fig. 2.

CDs are known to form inclusion complexes with a variety of organic guests.[3,6)] Introduction of CD into the pharmaceutical process can alter the solubility and stability of included medicines so as to be applied as drug carriers in some chemotherapy. In the present work, α-, β- and γ-CD are selected as hosts to assess the influence of different sizes of CD cavities on the stability of the CD supramolecular complexes of Syr. In addition, in order to estimate the effects of *NSG* and *MVR* on the binding abilities of CDs in aqueous solution,

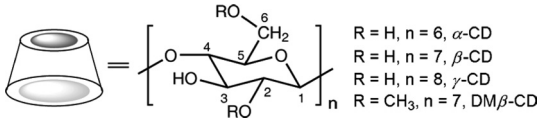

Fig. 1. Molecular Structure and Atom Numbering Scheme for CDs

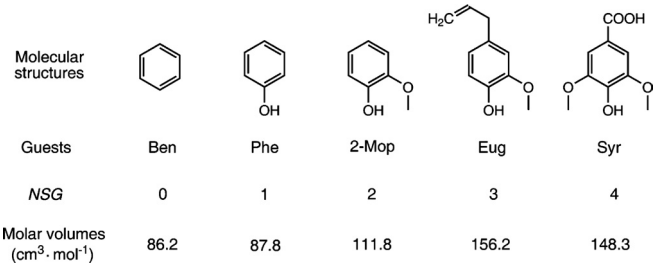

Fig. 2. Chemical Structures, Numbers of Substituted Groups and Molar Volumes of a Homologous Series of Benzene Derivatives

* To whom correspondence should be addressed. e-mail: solexin@ustc.edu.cn

direct comparisons among association abilities of CDs with a homologous series of benzene derivatives, including benzene (Ben), phenol (Phe), 2-Mop, Eug and Syr, have been also made, based on the formation constants (K) of the inclusion complexes in aqueous solution. It should be noted the guests not only all possess a basic skeleton of benzene, but also respectively contain zero, one, two, three and four substituted groups on benzene ring (see Fig. 2).

Experimental

Materials α-CD was purchased from Nihon Toshin Chemical Company. β-CD was purchased from Shanghai Chemical Reagent Company and recrystallized twice from deionized distilled water. γ-CD and DMβ-CD were kindly donated by Harata. 2-Mop and Syr were obtained from Shanghai Chemical Reagent Company and used without further purification. All other chemicals are of general purpose reagent grade unless otherwise stated.

Preparation of the Aqueous Solutions for Fluorescence Spectroscopy Measurements Stock solutions of 2-Mop or Syr were prepared by dissolving the commercial product in deionized distilled water. In fluorescence spectroscopy measurements, the aqueous solutions used to detect were freshly prepared by dilution of concentrated stocks with deionized distilled water. The concentration of 2-Mop or Syr in sample solutions is kept constant at 1.00×10^{-5} mol·dm^{-3}, and the concentration of α-, β-, γ- or DMβ-CD varies from 0 to 5.00×10^{-3} mol·dm^{-3} in order to determine the formation constants of the inclusion complexes. Continuous variation method was employed to establish the host–guest stoichiometry in these supermolecules with the total concentration of host and guest at 5.00×10^{-4} mol·dm^{-3}.

It is worthy of note that all samples were prepared by mixing a host with a guest in aqueous solution before use, and kept for 30 min under a fierce vibration at 298.2 K.

Instrumentation and Measurement Fluorescence spectra of 2-Mop and Syr, with and without α-, β-, γ- and DMβ-CD were recorded in a Shimadzu RF-5301PC spectrophotometer using quartz cells of 10.0 mm path with excitation and emission slits of 6 nm width at 298.2 K.

^{1}H- and ^{13}C-NMR spectra of free α-CD, Syr and their inclusion complex in D_2O were recorded at 298.2 K using a Bruker NMR spectrometer operating at 300 and 75 MHz, respectively. 2,2-Dimethyl-2-silapentane-5-sulfonate sodium salt (DSS) was used as internal reference in all cases.

Molecular Modeling PM3 method[15] was chosen to investigate the inclusion complexation between CD and guest both *in vacuo* and in water. All the calculations in the present work were performed with the MOPAC[16] software package. The initial geometries of α-, β-, γ-, and DMβ-CD are constructed based on the available crystallographic data determined by X-ray crystal structure method[17—20] and then fully optimized by parameterized model 3 (PM3) without any symmetrical restrictions. Two guest molecules, 2-Mop and Syr, are also fully optimized. The harmonic frequency analyses are then performed to make sure that a unique stationary point is a true minimum.

The glycosidic oxygen atoms of CD are placed onto x–y plane, and the center of its cavity is designated as the origin of the Cartesian coordinate system. The secondary OHs rim of CD is placed pointing toward the positive z-axis. The longer dimension of a guest molecule is initially placed along z-axis,[8] and the center of benzene ring in a guest is designated as the center of the guest molecule.

The complexation energies (ΔE_c) of the supramolecular complexes locating the energy minimum upon inclusion between CD and guest are calculated according to Eq. 1[21]:

$$\Delta E_c = \Delta E_{HG} - \Delta E_{e,H} - \Delta E_{e,G} \quad (1)$$

where $\Delta E_{e,H}$, $\Delta E_{e,G}$ and ΔE_{HG} are the energies of free CD, guest and their inclusion complex in their respective optimized equilibrium geometries.

The deformation energy ($\Delta E_{f,X}$) of host or guest (X) before and after inclusion can be calculated from Eq. 2 as follows:

$$\Delta E_{f,X} = \Delta E_{e,X} - \Delta E_{c,X} \quad (2)$$

where $\Delta E_{f,X}$ corresponds to the energy difference between the energy of X at its equilibrium geometry ($\Delta E_{e,X}$) and the energy of X at its complex geometry ($\Delta E_{c,X}$). Upon inclusion, the total deformation energy (ΔE_f) is the sum of $\Delta E_{f,H}$ and $\Delta E_{f,G}$.

The interaction energy (ΔE_i) is defined as the difference between the energy of the inclusion complex of H with G and the sum of the energies of both partners (H and G) at their respective complex geometries. Hence, according to Eqs. 1 and 2, ΔE_i can also be calculated using Eq. 3 as follows:

$$\Delta E_i = \Delta E_c + \Delta E_{f,H} + \Delta E_{f,G} \quad (3)$$

Clearly, ΔE_i should be a reflection of the stability of a supramolecular complex. A negative value of ΔE_i means that the formation of an inclusion complex is energetically favorable. Theoretically speaking, if the ΔE_i value of an inclusion complex is more negative, the complex will be more thermodynamically stable.

Solvent effects were also taken into consideration during theoretical calculations. The calculations of solvation energy, *i.e.*, hydration energy in the present work were carried out using PM3 method. The solvation model is the Conductor-like Screening Model (COSMO).[22] The COSMO algorithm is invoked using the keywords NSPA=60 1SCF EPS=78.4 (water has a dielectric constant of 78.4 at 298.2 K) PM3 CHARGE=0.

Results and Discussion

Stoichiometries and Formation Constants of the CD Inclusion Complexes of Syr in Aqueous Solution CDs are able to influence the fluorescence property of a guest molecule upon complexation between CDs and the guest.[23] Typical fluorescence emission spectra of Syr and 2-Mop, with and without β-CD, in aqueous solution at 298.2 K are shown in Figs. 3A and B, respectively.

The concentrations of Syr are kept at 1.00×10^{-5} mol·dm^{-3} and the concentration of CDs varies from 0 to 5.00×10^{-3} mol·dm^{-3}. As shown in Fig. 3A, the emission spectra of Syr in water are characterized using a broad band with the maximum spectral intensity at 356 nm. The fluorescence intensity of Syr gradually increases with the addition of β-CD, indicating that there is a change of chemical circumstances around Syr. It should be reasonable that the intermolecular interaction between β-CD and Syr in aqueous solution results in this phenomenon, because the interaction allows benzene ring of Syr to penetrate partly or wholly into the hydrophobic cavity of β-CD from a highly polar medium of water.[24]

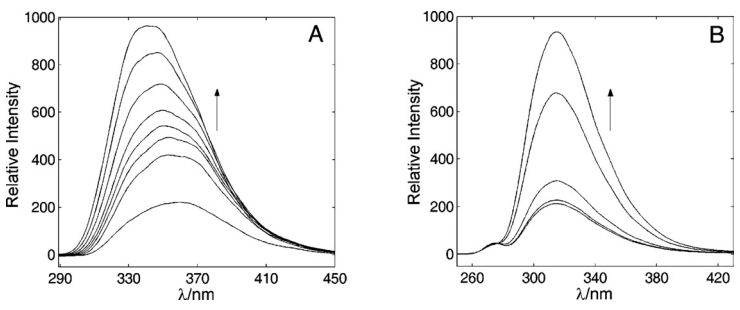

Fig. 3. Fluorescence Spectral Changes of Syr (A, 1.00×10^{-5} mol·dm^{-3}) and 2-Mop (B, 1.00×10^{-5} mol·dm^{-3}) upon Addition of β-CD

Excitation wavelengths of Syr and 2-Mop are 280 and 288 nm, respectively. The concentration of β-CD is in the range from 0 to 5.00×10^{-3} mol·dm^{-3}.

In the case of 2-Mop with β-CD, the spectrum of 2-Mop exhibits a broad band centred near 315 nm (see Fig. 3B). The fluorescence intensity of the complexed 2-Mop increases nonlinearly with increasing concentration of β-CD in solution. This phenomenon can also be attributed to the intermolecular interaction between β-CD and 2-Mop. The fluorescence intensity of the complexed 2-Mop increases nonlinearly with increasing concentration of β-CD in solution, unlike that of the complexed Syr that gradually increases with the addition of β-CD. We propose that different guest specificities of two phenol families: Mop and Syr, are responsible for the difference in fluorescence spectra. The different structures of the two guests lead to the different stabilities of two complexes, 2-Mop–β-CD and Syr–β-CD, due to their structural difference. The observation suggests that there exists a difference in the manner of complexation between the two guests and β-CD, which is described in the following section of the paper, based on the different equilibrium distance between the centers of gravity of the two guest molecules and β-CD.

The chemical stoichiometries of the inclusion complexes are determined using the continuous variation method.[25] Eleven samples of a mixed solution of β-CD and Syr are measured, in which the total concentration of host and guest is kept constant at 5.00×10^{-4} mol·dm^{-3}. A representative Job's plot describing the inclusion system of Syr and β-CD is displayed in Fig. 4A. The position of the maximum difference (ΔF) in fluorescence intensity at a mole fraction of 0.5 clearly indicates a 1 : 1 stoichiometry of host to guest in the inclusion complex, Syr–β-CD.

The stability of CD inclusion complexes can be evaluated by analyzing the sequential changes in fluorescence intensity of guest molecules, which will occur with changing host's concentration, as shown in Fig. 4B. The obtained data are described by the curve fitting equation, *i.e.*, Eq. 4 as follows, and a nonlinear regression analysis according to this equation can yield the value of K.[26]

$$F = \frac{F_o + F_\infty K[\mathrm{H}]}{1 + K[\mathrm{H}]} \tag{4}$$

where [H] refers to the equilibrium concentration of CD, F_o is the fluorescence intensity of guest molecules in the absence of CD, F_∞ is the fluorescence intensity when all guest molecules are bound in the cavities of CDs, F is the measured fluorescence intensity at each CD concentration.

The calculated K values of the inclusion complexes of Syr with α-, β-, γ- and DMβ-CD, as well as those of the inclusion complexes of 2-Mop with α-, β-, γ- and DMβ-CD, are listed in Table 1. Moreover, the published K values of the CD inclusion complexes of Ben, Phe and Eug are also cited in

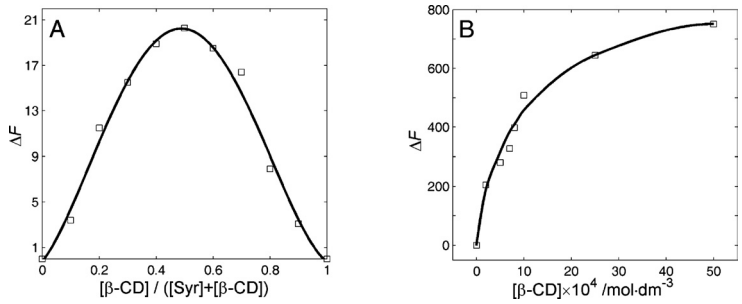

Fig. 4. (A) Job's Plot for Syr–β-CD Inclusion System with [Syr]+[β-CD]$=5.00\times10^{-4}$ mol·dm^{-3}
The excitation and emission slit widths are set at 5.0 and 5.5 nm, respectively.
(B) Fluorescence Spectral Changes of Syr (1.00×10^{-5} mol·dm^{-3}) upon Addition of β-CD (0—5.00×10^{-3} mol·dm^{-3})
The excitation wavelength of Syr is 280 nm.

Table 1. Formation Constants (K) of the Inclusion Complexes of a Homologous Series of Benzene Derivatives with α-, β-, γ- or DMβ-CD at 298.2 K in Aqueous Solution

Host	Guest	*MVR*	*NSG*	K/mol^{-1}·dm^3	Method[a]	Ref.[b]
α-CD	Ben	0.829	0	$3.16\pm0.10\times10^{1}$	vap	28
α-CD	Phe	0.844	1	$4.07\pm0.11\times10^{1}$	cal	12
α-CD	2-Mop	1.075	2	$1.74\pm0.36\times10^{5}$	fl	This work
α-CD	Eug	1.502	3	$4.95\pm0.23\times10^{4}$	uv	9
α-CD	Syr	1.425	4	$1.88\pm0.28\times10^{3}$	fl	This work
β-CD	Ben	0.549	0	$1.69\pm0.01\times10^{2}$	vap	28
β-CD	Phe	0.559	1	$9.33\pm0.10\times10^{1}$	cal	12
β-CD	2-Mop	0.712	2	$8.90\pm0.23\times10^{3}$	fl	This work
β-CD	Eug	0.995	3	$3.96\pm0.52\times10^{5}$	uv	9
β-CD	Syr	0.945	4	$1.66\pm0.05\times10^{4}$	fl	This work
γ-CD	Ben	0.337	0	$9.12\pm1.02\times10^{0}$	vap	28
γ-CD	2-Mop	0.436	2	$1.67\pm0.31\times10^{5}$	fl	This work
γ-CD	Eug	0.610	3	$1.47\pm0.07\times10^{5}$	uv	9
γ-CD	Syr	0.579	4	$7.35\pm0.13\times10^{4}$	fl	This work
DMβ-CD	2-Mop	0.828	2	$5.19\pm0.08\times10^{4}$	fl	This work
DMβ-CD	Eug	1.157	3	$9.33\pm0.74\times10^{4}$	uv	9
DMβ-CD	Syr	1.098	4	$1.73\pm0.11\times10^{3}$	fl	This work

a) Method employed: cal, calorimetry; fl, fluorimetry; uv, UV–Vis spectrophotometry; vap, vapor pressure measurement. *b*) Ref. is an abbreviation for reference.

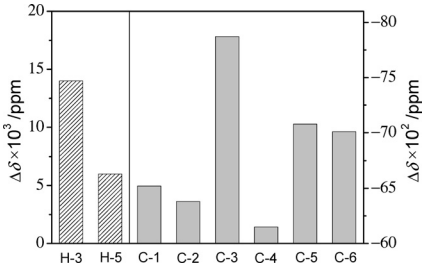

Fig. 5. Chemical Shift Changes of the Selected NMR Signals in α-CD before and after Inclusion with Syr

Table 1 in order to make possible a direct comparison of binding abilities of CDs to a homologous series of substituted benzenes, including Ben, Phe, 2-Mop, Eug and Syr. The pH value of a typical sample solution of Syr (10^{-5} mol^1·dm^{-3}) with and without β-CD (3×10^{-3} mol·dm^{-3}) is both 5.37. Accordingly, Syr in the mixed solution exists as the monoanionic form (>90%) according to the concentration calculation of species in terms of ionization constant and pH at constant concentration. The calculated binding constant (K) of β-CD to Syr should, theoretically, represent the stability of the inclusion complex of β-CD with the mono-ionized Syr. However, no significant differences in the K values between the β-CD inclusion complexes of the mono-ionized Syr and the neutral molecular Syr are found by other authors.[27)]

NMR Analysis of the Inclusion Complex of Syr with α-CD NMR techniques have been widely used to gain important information about the location of a guest molecule in its complex of CD by determining the chemical shift changes ($\Delta\delta$) of some protons of CD and the guest in solution.[29)] The chemical shifts (δ) of both the interior protons (H-3 close to the wider rim and H-5 close to the narrower rim) of CD cavity and the guest protons are usually used to provide information concerning inclusion mode and binding affinity between CD and guest. The $\Delta\delta$ values of the selected NMR signals of α-CD before and after inclusion are displayed in Fig. 5.

The aromatic proton signals of Syr show a downfield shift of 0.029 ppm after it has interacted with α-CD in solution. A downfield shift of 0.050 ppm, which belongs to the protons of methoxy groups of Syr upon inclusion, is also observed. The chemical shift value of H-3 in free α-CD is 3.956 ppm, after inclusion, it changes to 3.970 ppm. For H-5 protons of α-CD, it shows a downfield shift of 0.006 ppm (from 3.820 to 3.826 ppm) upon complexation between α-CD and Syr. Hence, the chemical shift change of H-3 located in large end side of the cavity of α-CD is comparatively bigger than that of H-5 located in small end side of the cavity (see Fig. 5).

These observations suggest that there should be the expected van der Waals interactions between the C–H protons within the α-CD cavity, in particular, the protons of C-3 located in large end side of the cavity, and the protons of benzene ring of Syr. In consideration of the size, shape and symmetry of Syr, hence, it can be concluded that the phenyl ring of Syr is located closely to the wider rim of the α-CD cavity and the phenolic hydroxyl is likely to project outward α-CD cavity. The large downfield shift of the protons of methoxy groups of Syr in the inclusion mode can be explained by the hydrogen bonding interactions between some of primary OH groups of α-CD and the methoxy groups of Syr.

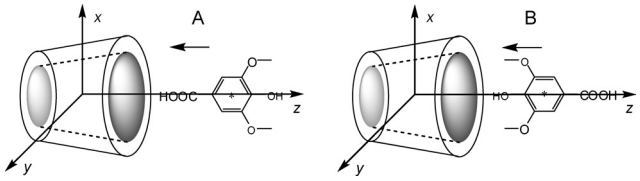

Fig. 6. Schematic Drawings of the Relative Positions of CD and Syr

As ^{13}C-NMR chemical shifts can extend to a much larger scale than ^{1}H-NMR, it is usually used to characterize the formation of CD inclusion complexes.[29)] As can be found in Fig. 5, upon inclusion, all the signals of carbon atoms of α-CD show obviously upfield shifts. The chemical shift change of C-3 ($\Delta\delta$, −0.787 ppm, from 74.210 to 73.423 ppm) is bigger than that of C-5 ($\Delta\delta$, −0.708 ppm, from 72.910 to 72.202 ppm) in the α-CD complex of Syr. For C-1, C-2, C-4 and C-6, before and after complexation, their chemical shift changes are −0.652, −0.638, −0.615 and −0.701 ppm, respectively, all of which are indeed smaller than the $\Delta\delta$ values of C-3 and C-5 especially that of C-3. These data not only provide a direct evidence of the intermolecular interaction between α-CD and Syr, but also demonstrate that such an interaction likely occurs in the wider rim of α-CD cavity. In order to further examine the details of the complexation process between CDs and Syr, theoretical PM3 calculations *in vacuo* and in water are carried out in the present work.

Inclusion Complexation between CDs and Syr *in Vacuo* and in Water Figure 6 is a representative schematic illustration describing the relative positions of CDs and Syr. Two different starting geometries, *i.e.*, the COOH-inserting mode and the OH-inserting mode are treated in Figs. 6A and B, respectively.[8,21)] The host–guest complexation process is simulated by making Syr penetrate into the CD cavity from the larger end side and letting it pass through the cavity by steps. In every step, the geometry of the host–guest inclusion complex is completely optimized by PM3 without any restrictions.

The values of ΔE_c, ΔE_f and ΔE_i of CD inclusion complexes of Syr are calculated and listed in Table 2. Although two different starting geometries are considered, only the lowest energy value of an inclusion complex is given in Table 2. The optimum position of Syr inside the cavity of CD at the same starting geometry is determined according to the lowest value of complexation energy. The most stable structure of an inclusion complex is established through comparing the ΔE_c values between two different starting geometries. The detailed results of the inclusion processes of Syr with α-CD and the most stable structure of Syr–α-CD are depicted in Fig. 7.

As shown in Fig. 7A, the inclusion complex, Syr–α-CD, with the starting geometry displayed in Fig. 6A, has the most negative ΔE_c value near the secondary hydroxyl rim (Z= 200 pm, $\Delta E_c = -48.0$ kJ·mol^{-1}). Figure 7B indicates that the other structural form of the inclusion complex with starting geometry exhibited in Fig. 6B can get the most negative ΔE_c value near the secondary hydroxyl rim of α-CD cavity (Z=300 pm, $\Delta E_c = -25.3$ kJ·mol^{-1}). Clearly, the supramolecular structure of the inclusion complex of Syr with α-CD, as presented in Fig. 7A, has a relatively lower complexation en-

Table 2. Complexation Energies (ΔE_c), Deformation Energies ($\Delta E_{f,H}$, $\Delta E_{f,G}$) and Interaction Energies (ΔE_i) in kJ·mol^{-1} of the Host–Guest Complexes

Complexes	ΔE_c		$\Delta E_{f,H}$		$\Delta E_{f,G}$		ΔE_f		ΔE_i		$Z^{a)}$/pm
	VA[b)]	WA[b)]	VA	WA	VA	WA	VA	WA	VA	WA	
2-Mop–α-CD[c)]	−65.9	−57.1	−7.91	−5.73	−2.73	−2.51	−10.64	−8.24	−76.5	−65.3	500
2-Mop–β-CD[c)]	−52.8	−48.4	2.61	2.49	0.93	1.25	3.54	3.74	−49.3	−44.7	300
2-Mop–γ-CD	−60.5	−51.2	6.59	6.72	2.79	2.81	9.38	9.53	−54.9	−41.7	200
2-Mop–DMβ-CD	−58.3	−50.7	2.21	2.29	2.45	2.81	4.66	5.10	−53.6	−45.6	300
Syr–α-CD	−48.0	−40.2	2.26	2.44	3.77	3.91	6.03	6.35	−42.0	−33.9	200
Syr–β-CD	−70.6	−61.4	6.12	6.43	3.47	3.62	9.59	10.05	−61.0	−51.4	100
Syr–γ-CD	−68.2	−53.7	6.42	7.01	2.94	3.21	9.36	10.22	−58.8	−43.5	0
Syr–DMβ-CD	−65.7	−52.3	6.23	6.54	3.54	3.82	9.77	10.36	−55.9	−41.9	200

a) *Z* is the distance between the center of CD cavity and the center of benzene ring in a guest molecule when the ΔE_c value of an inclusion system was the lowest. *b*) VA and WA stand for *in vacuo* and in water, respectively. *c*) The calculated values of 2-Mop–α-CD and 2-Mop–β-CD are taken from ref. 21.

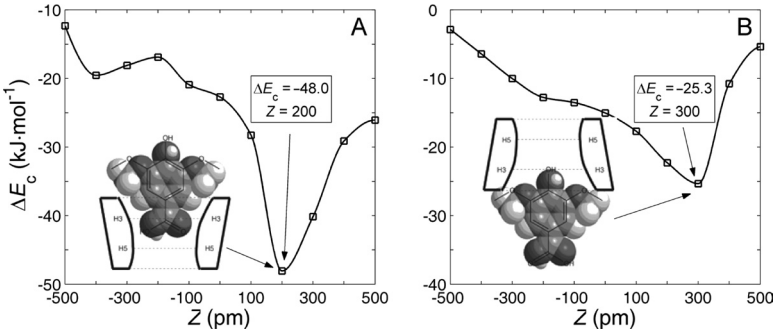

Fig. 7. PM3 Complexation Energy (ΔE_c, kJ·mol^{-1}) Curves of the Host–Guest Inclusion Complexations during the Migrations of Syr into α-CD Cavity with (A) Entry Mode of COOH Side Group and (B) Entry Mode of OH Side Group

ergy ($\Delta\Delta E_c = -22.7$ kJ·mol^{-1}). Furthermore, for either the two structural forms of the complex, when the guest, Syr, is much far away from the region (*Z*, 100—350 pm) from the center to the wider rim of the α-CD cavity, the inclusion system will become obviously instable, which is in good agreement with the results of NMR studies.

Besides Syr–α-CD, as for the inclusion complexes of 2-Mop and Syr with the CDs, the calculated energy values and their respective optimum positions (*Z*) for the guest molecules into the cavities of CDs are also listed in Table 2. It is interesting that for the inclusion systems of γ-CD, the two guest molecules prefer to be deeply included in the γ-CD cavity ($Z=200$ pm for 2-Mop–γ-CD; $Z=0$ pm for Syr–γ-CD), which is different from the inclusion modes of the guests with the other three hosts, especially α-CD. This inclusion phenomenon should be attributed to the large cavity size of γ-CD.

It is found that the interaction energies of the inclusion complexes in water are obviously higher than those of the complexes *in vacuo*. And the ΔE_i value of 2-Mop–α-CD is the lowest in the eight inclusion complexes no matter when it is calculated *in vacuo* or in water. 2-Mop prefers to be stabilized outside of α-CD cavity ($Z=500$ pm>the half-height of the cavity=395 pm), therefore, this inclusion phenomenon implies that the hydrogen bond interaction between 2-Mop and α-CD should be quite significant. In addition, although the *Z* value of Syr–γ-CD is 0 pm, it is worth stressing that the interaction energy between Syr and γ-CD is not the lowest in the inclusion systems. Furthermore, we have also discovered that the guests in the other six inclusion complexes are always situated near the wider rim within the cavities of CDs, *i.e.*, the *Z* values in the complexes are in the range of 100—300 pm.

The deformation behavior of host and guest should be discussed, when they close with each other and formed a host–guest complex *in vacuo* or in water. As shown in Table 2, there are not many differences when the deformation energies of host and guest are calculated *in vacuo* or in water. All of the deformation energies of host and guest are in the range from 8 to −8 kJ·mol^{-1}. Unlike α- and β-CD, γ-CD is relatively more flexible.[1)] Accordingly, the deformation energy of γ-CD during the complexation process, both *in vacuo* and in water, is slightly larger than that of α- or β-CD. It is important that the molecular deformation behaviors resulted from CDs and the two guests weaken the interaction between host and guest (see Table 2), with the exception of 2-Mop–α-CD system (with the largest *Z* value of 500 pm). It should also be mentioned that Syr–γ-CD system, in which the value of *Z* was 0 pm, has the largest positive value of $\Delta E_{f,H}$ both *in vacuo* and in water, suggesting that the complete penetration of Syr into the cavity of γ-CD leads to the largest deformation of γ-CD.

As the value of ΔE_c or ΔE_i is a reflection of the stability of supramolecular complexes, the sufficiently large negative values of ΔE_c (<−40.2 kJ·mol^{-1}) and ΔE_i (<−33.9 kJ·mol^{-1}) shown in Table 2 both *in vacuo* and in water clearly demonstrate that the two guests, 2-Mop and Syr, can form stable supramolecular complexes with α-, β-, γ- and DMβ-CD, which are in good accordance with the results ($K>1.73\times10^3$ mol^{-1}·dm^3) obtained by fluorescence spectroscopy.

Furthermore, it is necessary that the intermolecular interactions of water molecules with CDs and guest molecules are

evaluated for forming an inclusion complex in aqueous solution.[30] As shown in Table 2, when solvent effects are taken into consideration, the values of ΔE_i become obviously less negative in comparison with their respective values of ΔE_c, clearly indicating that the intermolecular complexations between CDs and 2-Mop or between CDs and Syr are impeded, to a certain extent, by water molecules as solvent. Moreover, in this study, the deformation behaviors of both host and guest molecule are not very much affected by the water environment around them (see Table 2).

Intermolecular Binding Abilities of CDs in Aqueous Solution The size of free space (α-CD, 104 $cm^3 \cdot mol^{-1}$; β-CD, 157 $cm^3 \cdot mol^{-1}$; γ-CD, 256 $cm^3 \cdot mol^{-1}$) inside three common parent CD cavities available for guests decreases in the order: γ->β->α-CD.[1] Based on the size/shape-fit concept between host and guest, it might allow us to presume that, to some extent, α-CD would have relatively larger binding abilities to small guest molecules. Likewise, those guests with larger molecular volumes should form more stable complexes with β-CD especially γ-CD having more free space within its cavity.[4]

The logarithms of formation constants ($\log K$) of the inclusion complexes are listed in Table 1 while Fig. 8 exhibits a more direct impression of the formation constants among different inclusion systems. The binding abilities of the four different CDs to 2-Mop and Syr decrease in the order α-≈γ->DMβ->β-CD and γ->β->α-≈DMβ-CD, respectively. Furthermore, among the K values of the inclusion complexes of Syr with the CDs, as expected, the K value of Syr–γ-CD is the biggest, which should be related to a large cavity diameter (8.3 Å, the wider rim) in γ-CD and a big *NSG* value of 4 in Syr.

In addition, it can be found in Table 1 and Fig. 8 that, as for α-CD inclusion systems, with increasing the *MVR* and *NSG* values of a guest, structurally, the guest, such as Eug and Syr, should only be partially included into the cavity of α-CD, because the values of *MVR* and *NSG* are 1.502 and 3 for Eug, 1.425 and 4 for Syr, respectively. However, 2-Mop (*MVR* of 1.075), with two small substituents, is so well embedded in the small cavity of α-CD that it could be rather difficult for 2-Mop to pass through the cavity of α-CD freely, when compared with Ben (*MVR*, 0.829) and Phe (*MVR*, 0.844). Hence, according to the size/shape-fit concept, this result, that 2-Mop–α-CD has the biggest value of K among the inclusion complexes of 2-Mop with the CDs, should be very reasonable, reflecting that a guest molecule, which possesses a suitable value of *MVR* or *NSG*, can better fit into the cavity of α-CD.

The cavity diameter of β-CD is about 6.5 Å (the wider rim), which is just a bit larger than the maximum breadth (6.4 Å) of Eug molecule, suggesting that the Eug–β-CD inclusion mode should be a very good size-fitted combination of β-CD cavity and Eug (*MVR*, 0.995). Consequently, as shown in Fig. 8, it could be easily seen that the inclusion complex, Eug–β-CD, had the highest value of K among all the inclusion complexes. However, Syr–β-CD (*MVR*, 0.945) was nearly 20 times weaker than Eug–β-CD. Clearly, it should be caused by the difference in structure between the two guests, such as *NSG*.

Although the order of binding abilities of γ-CD to the three polysubstituted phenols, 2-Mop, Eug and Syr, is the same as that of binding abilities of α-CD to them, the differences in binding abilities of γ-CD to these guests are much smaller than those in binding abilities of α-CD to them, as shown in Fig. 8A. Furthermore, the binding abilities of γ-CD to 2-Mop, Syr and Eug are all rather strong ($K>7\times10^4$ $mol^{-1} \cdot dm^3$) and quite close (K in the narrow range of 7—17×10^4 $mol^{-1} \cdot dm^3$). It should be noted that the molecular volumes of the polysubstituted phenols are all very small (*MVR*<0.620) in comparison with the big cavity size of γ-CD. Therefore, the results suggest that the γ-CD cavity shows a considerably poor structure or shape sensitivity to the polysubstituted phenols. Contrarily, α-CD has a structural or shape sensitivity to them.

The cavity size of β-CD is somewhat larger than that of DMβ-CD (free space, 135 $cm^3 \cdot mol^{-1}$) according to our calculated results. Consequently, DMβ-CD can only afford less free space to accommodate a guest molecule in contrast with β-CD. As shown in Tables 1 and 2, a notable difference in the values of K or ΔE_i has been observed between the inclusion complexes of DMβ- and β-CD with the same polysubstituted phenol. The binding abilities of the two CDs to the same guest decrease in the orders: DMβ->β-CD for 2-Mop and β->DMβ-CD for Eug and Syr. Therefore, the introduction of fourteen methoxy groups onto the two end sides of β-CD cavity has an important effect on its binding abilities to the guest molecules.

There is very limited data reported so far on the smaller K values for DMβ-CD complexes compared to those for parent β-CD complexes. Similar orders of the binding abilities determined by UV–Vis method of the two CDs to the same guest were also found by Yang. In her master thesis,[31] the K_{uv} for the DMβ-CD complexes of 2-Mop, Eug and Syr are determined to be $6.81\pm0.34\times10^4$, $9.33\pm0.74\times10^4$ and $1.53\pm0.08\times10^3$ $mol^{-1} \cdot dm^3$, respectively, based on UV–Vis spectrophotometry, which are in approximate agreement with

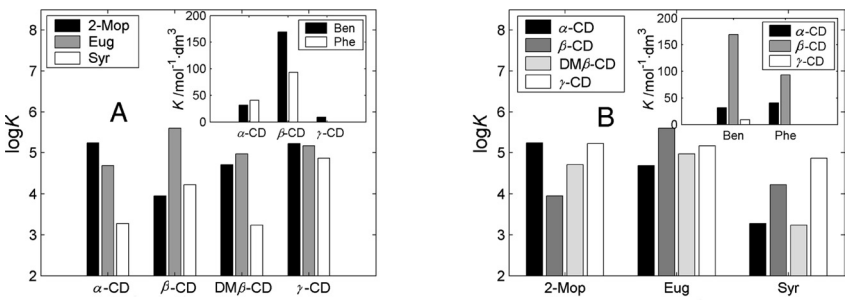

Fig. 8. Plots of the $\log K$ Values of the Host–Guest Inclusion Complexes Listed in Table 1 *versus* Four Hosts (A) and Three Guests (B)

Plots of the K values of the inclusion complexes of Ben and Phe with α-, β-, DMβ- and γ-CD *versus* hosts and guests are included in the insets.

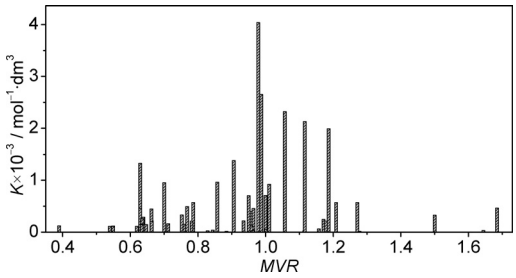

Fig. 9. Plots of the Reported K Values of α-, β- and γ-CD Inclusion Complexes of 71 Substituted Phenols

the present results from spectrofluorimetry. Therefore, comparisons between different CDs and between different methods confirm the smaller K values of present DMβ-CD systems.

It was worth stressing that since Ben or Phe has a smaller molecular volume than the polysubstituted phenols, the interaction between the two guests and CD becomes comparatively weak as can be seen in Table 1 and Fig. 8. There is a slight difference between the K values of the inclusion complexes of Ben and Phe with the same CD. However, the K values of the CD inclusion complexes of the three polysubstituted phenol are significantly larger than those of the CD inclusion complexes of Ben and Phe. In other words, all the inclusion systems of Ben and Phe with these CDs produced only very small values of K, possibly due to uncomfortable *MVR* values.

The K values of 71 inclusion complexes of CDs with various kinds of substituted phenols in solution, described in previous papers by other authors,[4,6,10] are summarized in Fig. 9 to further evaluate the effect of *MVR* values on the stability of CD supramolecular complexes. As shown in Fig. 9, the best size-matched combination of CD cavity and guest molecule, *i.e.*, while *MVR* has a value of approximately 1.0, results in the highest value of K among all these inclusion systems. On the contrary, a poorly size-fitted host–guest pair (too big or too small *MVR* values) leads to a small value of K. For example, the inclusion complex, 4-iodophenol–α-CD,[10] with the *MVR* value of 1.06, was found to have the largest value of K among the inclusion complexes of α-CD. For β-CD inclusion systems, the *MVR* value of the most stable inclusion complex, 4-*n*-butylphenol–β-CD,[6] is found to be 0.98. Nevertheless, if a guest molecule was too large to be able to fully penetrate into the cavity of CD, or too small to be effectively embedded within the CD cavity, the guest would form a less stable inclusion complex of α- or β-CD.

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