A Good Linear Relationship between the Logarithms of Formation Constants and the Stabilization Energies of α- and β-Cyclodextrin Complexes of Several Phenol and Benzoic Derivatives

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Semiempirical PM3 calculations in vacuo were performed on the inclusion complexation of α- and β-cyclodextrin (CD) with several phenol and benzoic acid derivatives. Those inclusion complexes with a higher negative value of stabilization energy (ΔE_s) in vacuo should lead to a larger positive value of formation constant (K_f) in aqueous solution. A proposed mathematical expression was firstly given to assess the negative linear relationship between log K_f and ΔE_s.

Cyclodextrins (CDs) are frequently characterized as doughnut-shaped truncated cones.[1] Inclusion phenomena of CD with various kinds of guest molecules have been the subject of numerous experimental and theoretical studies for many years.[2,3] A great majority of these works have focused on the driving forces of inclusion process of CD with guest, as well as on the conformations and stabilities of CD–guest complexes.[4–6] In view of the relatively large molecular size of CDs and their inclusion complexes, most of these theoretical studies were done using molecular dynamics, molecular mechanics, or semiempirical quantum mechanics method.[6]

It is very important to make direct comparisons of the stability of CD–guest inclusion complexes between theoretical calculations and experimental observations. The results of the present study firstly gave a proposed mathematical expression of the negative linear relationship between the logarithms of the formation constants (K_f) of the inclusion complexes of a series of phenol and benzoic acid derivatives acted as guests in aqueous solution and the stabilization energies (ΔE_s) of these complexes in vacuo. In this work, α- and β-CD were selected as hosts. The structures of the guest molecules used in the present study were shown in Figure 1.

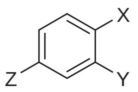
PM3 method implemented in the GAUSSIAN 98[7] software package was chosen to investigate the stability of host–guest inclusion complexes in vacuo. The initial geometries of CDs were fully optimized without any restrictions. All guest molecules were also fully optimized.

The glycosidic oxygen atoms of α- or β-CD were placed onto the *xy*-plane, and the center of the CD cavity was designated as the origin of the Cartesian coordinate system. The longer dimension of a guest molecule was initially placed along *z* axis. The inclusion process was simulated by putting a guest in one end of CD and then letting it pass through the CD cavity by steps. Two different starting geometries of the inclusion complexes were considered.[5]

The ΔE_s values of the supramolecular complexes were the difference between the energy of the complex and the sum of the heats formation of the guest and CD in their respective optimized equilibrium geometry.[8] Theoretically speaking, if the value of ΔE_s of an inclusion complex was more negative, the complex should be more thermodynamically stable.

Deformation energy (ΔE_f) is the difference between the energy of partners of the complex at their respective equilibrium geometry and their energy at complex geometry. Interaction energy (ΔE_t) is the difference between the energy of the complex and the sum of the energies of both partners at their complex geometry.

As ΔE_s values strongly depend on the starting geometries, only the lowest ΔE_s values of the different starting geometries are listed in Table 1. A highly positive correlation between the values of K_f based on different references and the absolute values of ΔE_s obtained from this work could be easily seen



1, X = OH, Y = H, Z = H
2, X = OH, Y = H, Z = NO_2
3, X = OH, Y = H, Z = COOH
4, X = OH, Y = OCH_3, Z = H
5, X = OH, Y = OCH_3, Z = $CH_2CH{=}CH_2$
6, X = OH, Y = H, Z = OCH_3
7, X = OH, Y = NO_2, Z = H
8, X = H, Y = H, Z = COOH
9, X = NH_2, Y = H, Z = COOH
10, X = NO_2, Y = H, Z = COOH
11, X = CH_3, Y = H, Z = COOH

Figure 1. Structures of guest molecules.

Table 1. Formation constants (K_f, $mol^{-1}\cdot dm^3$), stabilization energies (ΔE_s), deformation energies (ΔE_f), and interaction energies (ΔE_t) in $kJ\cdot mol^{-1}$ of the host–guest inclusion complexes

Complexes	K_f	Refs	ΔE_s[a]	Dev	ΔE_f^{H}[a]	ΔE_f^{G}[a]	ΔE_t
α-CD–**1**	4.07×10^1	9	−13.4	−0.062	2.1	1.6	−9.7
α-CD–**2**	2.04×10^2	10	−19.3	0.103	1.8	0.6	−16.9
α-CD–**3**	1.43×10^3	11	−39.4	−0.049	−2.7	0.5	−41.6
α-CD–**4**	1.47×10^5	12	−65.9	0.042	−7.9	−2.7	−76.5
α-CD–**5**	4.95×10^4	13	−62.1	−0.004	−2.2	0.4	−63.9
α-CD–**6**	6.31×10^1	11	−20.7	−0.186	2.4	3.6	−14.7
α-CD–**7**	6.31×10^4	14	−65.5	−0.025	0.9	−5.4	−70.0
α-CD–**8**	8.11×10^2	5	−33.5	−0.014	2.7	1.5	−29.4
α-CD–**9**	5.01×10^2	14	−26.8	0.061	2.6	0.9	−23.3
α-CD–**10**	2.14×10^2	15	−25.2	−0.045	3.5	−6.3	−28.0
α-CD–**11**	8.13×10^2	16	−35.4	−0.053	−2.8	0.5	−37.7
β-CD–**1**	9.33×10^1	9	−20.5	−0.090	0.9	0.9	−18.7
β-CD–**2**	1.91×10^2	17	−17.7	0.135	1.0	2.0	−14.8
β-CD–**3**	5.21×10^2	18	−26.3	0.078	2.0	2.3	−22.0
β-CD–**4**	1.53×10^4	12	−52.8	0.011	2.6	0.9	−49.3
β-CD–**5**	3.96×10^5	13	−78.9	−0.027	6.1	3.4	−69.4
β-CD–**8**	5.49×10^2	19	−32.2	−0.047	2.6	1.6	−28.1
β-CD–**9**	5.00×10^2	18	−30.2	−0.017	2.3	3.8	−26.4

[a] ΔE_f^{H}, deformation energies of CDs; ΔE_f^{G}, deformation energies of guest molecules. ΔE_s values of α-CD–**3** and β-CD–**8** were taken from References 5 and 16, respectively.

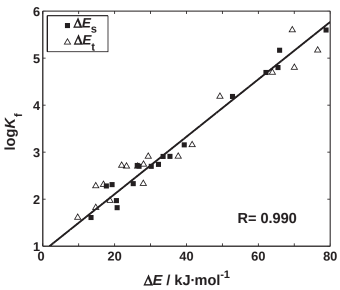


Figure 2. A good linear relationship between log K_f and ΔE_s of the inclusion complexes of α- and β-CD.

for those CD–guest complexes in Table 1. The inclusion complex possessing a high negative value of ΔE_s would have a larger positive value of K_f. In other words, the order of ΔE_s values of the eighteen inclusion systems calculated in vacuo was in good accordance with that of the known experimental values of K_f in aqueous solution. Therefore, it might allow us to establish a quantitative relationship between the formation constants obtained from measurements and the stabilization energies calculated by PM3 method.

Figure 2 showed a plot of the logarithms of K_f as a function of the ΔE_s values of the CD–guest inclusion complexes. The regression line and the data points for the 18 studies were depicted in Figure 2. The correlation coefficient (R) was 0.990, with a slope of -0.0610 and intercept of 0.886. These data indicated a good linear correlation between log K_f and ΔE_s of these inclusion complexes.

A suitable mathematical representation (eq 1) between log K_f and ΔE_s of the eighteen CD–guest inclusion complexes was made in terms of the data in Table 1.

$$\log K_f = -0.0610(\Delta E_s) + 0.886 \tag{1}$$

The relative deviation (Dev) between the measured and fitted value of K_f was calculated according to eq 2,

$$\mathrm{Dev} = (\log K_f - \log K_f') \cdot (\log K_f)^{-1} \tag{2}$$

where log K_f and log K_f' were the logarithms of the measured and fitted values of K_f, respectively. These values of Dev for the supramolecular complexes were also listed in Table 1. The absolute values of the maximal and minimal of Dev for these complexes were 0.186 and 0.004, respectively. They were so negligible that eq 1 was much likely to well reflect the intrinsic relationship between log K_f and ΔE_s of the CD inclusion complexes of these phenol and benzoic acid derivatives. The energy contribution of deformation energy to interaction energy was shown to be small but non neglectable. A similar significant linear relationship, not perfect, but still pretty good ($R = 0.973$), between log K_f and ΔE_t was also found.

It is worth stressing that the mathematical representation of eq 1 was made based on the results of the same inclusion system under different reaction conditions: K_f measured in aqueous solution and ΔE_s calculated in vacuo. Since both log K_f and ΔE_s could reflect the stability of a supramolecular complex, hence the exposal of their intrinsic correlation might be able to help us to further comprehend the CD–guest inclusion phenomena in solution, only using theoretical studies. When solvent effects were taken into consideration, the values of ΔE_s became somewhat different. However, for an inclusion system studied in this work, there was no significant difference between two calculated ΔE_s values in vacuo and in water. For example, only an energy difference of 2.5 kJ·mol^{-1} between two calculated ΔE_s values of β-CD–**5** was found.

A preliminary evaluation was made of the applicability of eq 1. Representative examples are as follows: Ibuprofen, a benzoic acid derivative, was found to form an inclusion complex with β-CD in aqueous solution. The values of log K_f, log K_f', and Dev for the complex are 5.29,[20] 5.05, and 0.045, respectively.

The values of log K_f, log K_f' and Dev for the inclusion complex of α-CD with benzaldehyde, a simple substituted benzene, were 3.39,[21] 3.33, and 0.018, respectively.

The above results showed that the equation might be valuable in prediction of the formation constants of the inclusion complexes of α- and β-CD with phenol or benzoic acid analogs in solution since solvent effect plays a minor role for such processes.

PM3 method was satisfactorily used to examine the eighteen inclusion systems of α- and β-CD with a series of substituted phenol and benzoic acid. Experimental data for equilibrium constants were available for these molecules allowing us to establish a linear relationship between experimental data and calculated inclusion energies. However, the approach was only tested on a limited number of complexes. Therefore, in order to determined if the relationship given in the eq 1 has a broad applicability in the complexation of CDs with guests, the generality of this approach and its applicability to other phenols and benzoic acid derivatives as well as to other kinds of guests remains to be established, and the validation set including a large number of guest molecules is being considered.

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