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Regression Analysis for the Host–Guest Interaction of β-Cyclodextrin with Mono- and 1,4-Disubstituted Benzenes

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Abstract. A multiple regression model was generated, which can satisfactorily estimate the association constants (K_a) for the inclusion complexation of β-cyclodextrin with mono- and 1,4-disubstituted benzenes. It was found that $\ln K_a$ was correlated with the substituent molar refraction (R_m), hydrophobic constant (π) and Hammett constant (σ) of the guest compounds with a correlation coefficient of 0.95. The main driving forces for β-cyclodextrin complexation was concluded to consist of van der Waals forces and hydrophobic interactions, while the influence of electronic effects was small.

Key words: benzene derivatives, β-cyclodextrin, driving force, inclusion, regression analysis.

1. Introduction

α-, β- and γ-cyclodextrin (α-, β- and γ-CD), cyclic oligosaccharides of 6, 7 and 8 D-glucose units, can form inclusion complexes with a variety of molecules through a process called molecular recognition. This property enables CD to be applied to many important areas such as analytical chemistry, pharmaceutical chemistry, catalysis, and separation technology [1]. CD inclusion complexes are also the most valuable models for understanding noncovalent interactions of organic compounds in aqueous solution. Furthermore, CDs are excellent models for mimicking the enzyme-substrate interaction [2]. Great efforts have been devoted to understanding the driving forces of CD inclusion complexation. To date, several driving forces have been postulated in the host-guest interaction: (1) van der Waals forces, (2) hydrophobic interactions, (3) electronic effects, (4) hydrogen bonding, (5) steric effects, etc. However, there still remains no clear agreement on the mechanism for the CD inclusion complexation [1, 3], the relative contributions and even the nature of the different driving forces are not well known.

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Recently, quantitative studies on the CD inclusion complexation have attracted much attention. Methods including quantum and molecular mechanics computation [4], linear regression [5] and artificial neural networks (ANN) [6] have been used. Many studies have demonstrated that there exists a quantitative relation between CD association constants and the substituent properties of the guest molecules. Although good results have been generated for α-CD complexes [3, 5], less work has been performed on β-CD complexation systems. Some authors [5a] have attempted to generalize the binding mechanism for β-CD with 1,4-disubstituted benzenes. They took the electronic effects and the van der Waals forces into consideration, but a correlation coefficient of only 0.723 could be reached for a rather small sample of 16 complexes [5a].

In the present paper, we wish to report a multiple linear regression (MLR) analysis of the driving forces, especially in the composition of the driving forces for the inclusion complexation of β-CD with a number of substituted benzenes. The effects of the substituent properties of the guest compounds on the driving forces have been studied.

2. Regression Analysis

The association constants (K_a) of β-CD binding with benzene derivatives were taken from our previous studies [7] and the literature (see Table I) [8–17]. *X* refers to the substituent located in the β-CD cavity and *Y* outside the cavity in the host-guest complex. It is well known that the determination of the orientation of the guest molecule in the CD cavity is rather complicated and controversial not only theoretically [5], but also experimentally [3]. In our present study, the orientation of the benzene derivatives in the complexes was postulated as follows:

1. For mono-substituted benzenes, since the substituent groups generally are far larger than hydrogen, which in consequence fit more snugly in the β-CD cavity via van der Waals forces, the substituent groups are proposed to be located near the narrower rim of the β-CD cavity [7].

2. For *p*-substituted phenols and *p*-substituted anilines, the OH and NH_2 are proposed to stay outside since OH and NH_2 are highly hydrophilic.

3. For *p*-nitrobenzoic acid, the carboxyl group was proposed to stay in the β-CD cavity since COOH is larger than NO_2 in volume.

4. For *p*-chloronitrobenzene, the NO_2 group was proposed to stay outside because Cl is more hydrophobic than NO_2.

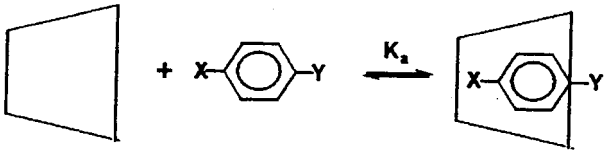

Table I. The $\ln K_a$ values calculated by the MLR and the experimental data for the inclusion complexation of β-CD with mono- and 1,4-disubstituted benzenes

No.	X	Y	$\ln K_a$ (obs)	Ref.	$\ln K_a$ (calc)	R_{mX}	π_X	σ_X	R_{mY}	π_Y	σ_Y
1	H	H	5.13	8	4.80	0.34	0.00	0.00	0.34	0.00	0.00
2	CH_3	H	5.37	7	5.30	5.07	0.56	−0.17	0.34	0.00	0.00
3	Et	H	5.96	7	5.79	9.77	1.02	−0.15	0.34	0.00	0.00
4	CCH	H	5.44	7	5.49	8.52	0.40	0.23	0.34	0.00	0.00
5	OH	H	4.55	7	4.58	5.05	−0.67	−0.37	0.34	0.00	0.00
6	OCH_3	H	5.34	7	5.16	9.44	−0.02	−0.32	0.34	0.00	0.00
7	OEt	H	5.73	7	5.65	13.86	0.44	−0.24	0.34	0.00	0.00
8	CH_2OH	H	4.96	7	4.72	9.31	−1.03	0.08	0.34	0.00	0.00
9	CH_2Cl	H	5.63	7	5.63	14.11	0.17	0.18	0.34	0.00	0.00
10	CHO	H	5.01	7	4.93	8.78	−0.65	0.22	0.34	0.00	0.00
11	COMe	H	5.23	7	5.27	13.00	−0.55	0.50	0.34	0.00	0.00
12	CO_2Me	H	5.76	7	5.71	16.42	−0.01	0.39	0.34	0.00	0.00
13	CO_2Et	H	6.29	7	6.18	20.59	0.45	0.45	0.34	0.00	0.00
14	CN	H	5.14	7	5.05	7.79	−0.57	0.66	0.34	0.00	0.00
15	$NHCH_3$	H	4.87	7	4.86	9.96	−0.36	−0.84	0.34	0.00	0.00
16	NHEt	H	5.38	7	5.43	14.69	0.13	−0.61	0.34	0.00	0.00
17	$N(CH_3)_2$	H	5.44	7	5.38	14.48	0.18	−0.83	0.34	0.00	0.00
18	NHCOMe	H	5.06	7	5.02	15.04	−0.97	0.00	0.34	0.00	0.00
19	NO_2	H	5.63	7	5.46	12.29	−0.28	0.78	0.34	0.00	0.00
20	F	H	4.51	7	5.18	5.17	0.14	0.06	0.34	0.00	0.00
21	Br	H	5.76	7	6.19	17.25	0.86	0.27	0.34	0.00	0.00
22	I	H	6.74	7	6.69	24.38	1.12	0.30	0.34	0.00	0.00
23	NH_2	H	3.91	9	4.21	5.25	−1.23	−0.66	0.34	0.00	0.00
24	CH_3	CH_3	5.48	10	5.70	5.07	0.56	−0.17	5.07	0.56	−0.17
25	Br	Br	6.85	11	6.65	17.25	0.86	0.27	17.25	0.86	0.27
26	I	I	7.31	11	7.37	24.38	1.12	0.30	24.38	1.12	0.30
27	CH_2OH	OH	4.98	12	4.81	9.31	−1.03	0.08	5.05	−0.67	−0.37
28	Et	OH	6.20	12	5.88	9.77	1.02	−0.15	5.05	−0.67	−0.37
29	NO_2	OH	5.50	13	5.58	12.29	−0.28	0.78	5.05	−0.67	−0.37
30	COOH	OH	5.06	13	5.51	13.07	−0.28	0.45	5.05	−0.67	−0.37
31	NO_2	NH_2	5.72	13	5.55	12.29	−0.28	0.78	5.25	−1.23	−0.66
32	I	OH	6.86	14	6.79	24.38	1.12	0.30	5.05	−0.67	−0.37
33	CH_3CO	OH	5.02	15	5.37	13.00	−0.55	0.50	5.05	−0.67	−0.37
34	Br	OH	6.10	15	6.28	17.25	0.86	0.27	5.05	−0.67	−0.37
35	CH_3O	OH	5.09	15	5.26	9.44	−0.02	−0.32	5.05	−0.67	−0.37
36	OH	OH	4.73	16	4.67	5.05	−0.67	−0.37	5.05	−0.67	−0.37
37	Cl	OH	6.02	16	5.84	9.83	0.71	0.30	5.05	−0.67	−0.37
38	CH_3	OH	5.52	16	5.39	5.07	0.56	−0.17	5.05	−0.67	−0.37
39	COOH	NO_2	5.39	16	5.05	13.07	−0.28	0.45	12.29	−0.28	0.78
40	Cl	NO_2	4.95	17	5.38	9.83	0.71	0.30	12.29	−0.28	0.78

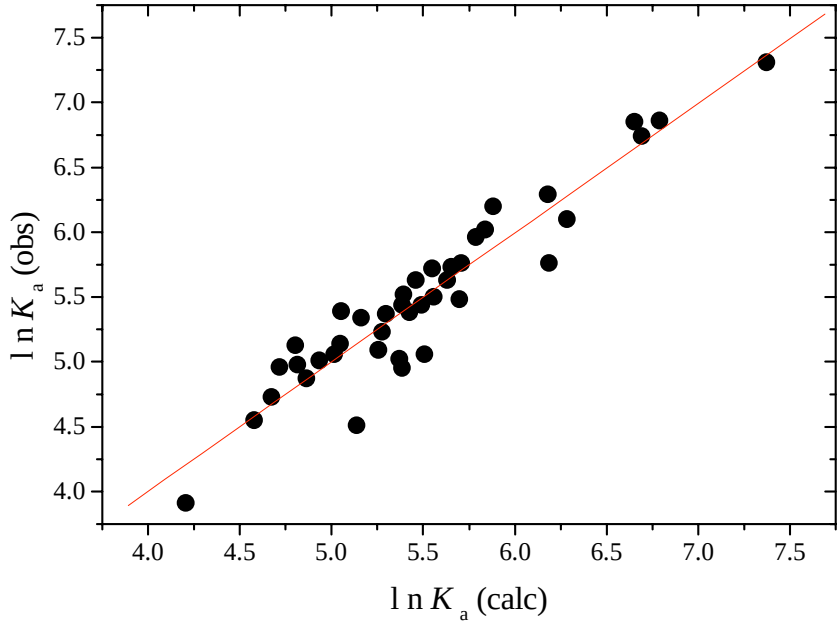

Figure 1. The $\ln K_a$ values calculated by the MLR vs. those determined experimentally.

3. Discussion

Despite the empirical nature of the above postulations, the good estimation by the MLR analysis gives further confidence in them.

The MLR analysis is implemented for the 40 inclusion complexes with the molar refractivity R_m, hydrophobic constant π and Hammett constant σ as input descriptors, respectively reflecting the volume and the polarizibility, the hydrophobicity and the electronic properties of the guest molecules. The MLR equation is generated as follows:

$$\begin{aligned} \ln K_a \;=\; & 4.78(0.11) + 0.05(0.01)R_{mX} + 0.54(0.07)\pi_X + 0.27(0.10)\sigma_X \\ & +0.02(0.01)R_{mY} + 0.35(0.12)\pi_Y - 0.64(0.18)\sigma_Y \\ & (r = 0.95, sd = 0.24, n = 40) \end{aligned} \tag{1}$$

The calculation results, together with the input parameters, are summarized in Table I. Plotting the $\ln K_a$ values calculated by Equation (1) vs. those determined experimentally gives a straight line as shown in Figure 1. Obviously, this result is much better than that reported in the literature previously.

According to the signs of the R_m parameters in Equation (1), it can be seen that the larger the R_m value, the more stable is the complex. It is also interesting to note that the coefficient of R_{mX} (0.05) is larger than that of R_{mY} (0.02). Since substituent molar refraction (R_m) well reflects the volume and polarizability of the substrate, it is readily concluded that CD host-guest complexation is affected by van der Waals

forces. The van der Waals forces primarily consist of induction and dispersion forces, which depend on molecular volume and polarizability [18]. The substituent with larger size can be more favorable to bind with the β-CD cavity, therefore, increasing R_m values leads to increasing stability of the β-CD complexes.

Similarly, the signs of the π parameters in Equation (1) also indicate that the more hydrophobic the substituents, the better the binding [7]. Although the hydrophobic interaction partly results from the van der Waals forces, it is mainly due to the effects of entropy produced in the water molecules. Therefore, the hydrophobic interaction is an independent factor influencing the complexation. The substituents with larger π values are more hydrophobic, therefore are strongly driven into the hydrophobic cavity of β-CD from the water cluster. This process is exothermic by entropic gain [19]. It is found that the coefficient of π_X (0.54) is larger than that of π_Y (0.35). This indicates that the substituent located inside the β-CD cavity has a stronger influence on the complexation.

Interestingly, a positive coefficient of σ_X (0.27) and a negative coefficient of σ_Y (-0.64) were obtained in Equation (1). It is well known that cyclodextrin possess large dipole moments. Therefore, the anti-parallel arrangement of the dipoles of the host and the guest favors the binding process [20]. Since the narrower rim of the CD represents the positive end of the CD dipole, the substituent X with positive σ value and thus electron-withdrawing will positively contribute to the complexation, while the substituent Y with positive σ value will negatively contribute to the complexation.

In order to compare the relative importance of the different driving forces, the MLR analysis with each kind of driving force as input parameters was also conducted according to Equations (2)–(4).

$$\begin{aligned} \ln K_a &= 4.41(0.16) + 0.08(0.01)R_{mX} + 0.03(0.01)R_{mY} \\ &\quad (r = 0.79, sd = 0.44, n = 40) \end{aligned} \tag{2}$$

$$\begin{aligned} \ln K_a &= 5.44(0.07) + 0.78(0.11)\pi_X + 0.13(0.16)\pi_Y \\ &\quad (r = 0.78, sd = 0.44, n = 40) \end{aligned} \tag{3}$$

$$\begin{aligned} \ln K_a &= 5.44(0.11) + 0.56(0.25)\sigma_X + 0.02(0.37)\sigma_Y \\ &\quad (r = 0.35, sd = 0.66, n = 40) \end{aligned} \tag{4}$$

From the above equations, it is apparent that van der Waals forces and hydrophobic interactions comprise the major driving forces. Compared to them, the electronic effects play a minor role. Therefore, neglecting the hydrophobic interactions [5a] is not appropriate, as this results in the inability to explain the mechanism for β-CD inclusion complexation. It is worthy of note that a regression equation

(Equation (5)) was obtained with a bad correlation by omitting π_X and π_Y in Equation (1):

$$\begin{aligned} \ln K_a \;=\; & 4.38(0.17) + 0.08(0.01)\,R_{mX} + 0.08(0.18)\sigma_X \\ & +0.04(0.01)\,R_{mY} - 0.33(0.26)\sigma_Y \\ & (r = 0.80,\, sd = 0.44,\, n = 40) \end{aligned} \tag{5}$$

4. Conclusion

The multiple linear regression was carried out for the inclusion complexation of β-CD binding with benzene derivatives from substituent molar refraction R_m, hydrophobic constant π and Hammett constant σ. It was found that van der Waals forces, hydrophobic interactions and electronic effects comprise the driving forces for the binding of β-CD with mono- and 1,4-disubstituent benzenes.

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