

Substituent Effects on the Driving Force for Inclusion Complexation of α - and β -Cyclodextrin with Monosubstituted Benzene Derivatives

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Abstract. The association constant values, K_a , for the inclusion of α - and β -CD with monosubstituted benzene derivatives were determined by means of UV-vis and fluorescence spectroscopy. The stability of the complexes is influenced by the properties of the substituents of the guest compounds. Regression analysis was used to create a set of inclusion models with the experimental association constant $\ln K_a$ and the corresponding substituent molar refraction R_m , hydrophobic constant π and Hammett σ constant of the benzene derivatives. The $\ln K_a$ value mainly correlated with R_m for α -CD and with both R_m and π for β -CD complexes. The association constants predicted by the models are in good agreement with the experimentally determined data. This suggests that the inclusion complexation of benzene derivatives with α -CD is predominantly driven by van der Waals force and with β -CD mainly by van der Waals force and hydrophobic interactions.

Key words: Cyclodextrin, driving force, inclusion complexation, substituent effect.

1. Introduction

It is well known that cyclodextrins (CDs) can form inclusion complexes with a variety of organic molecules [1–3]. Owing to this property, they have attracted widespread interest in separation science and technology [4, 5], pharmaceutical applications [2, 6, 7], and especially in enzyme-mimetic chemistry [8–13]. Enzymes usually have a hydrophobic pocket or cleft which provides a strong recognition site to bind a substrate, inhibitor, activator, or other species through hydrophobic interaction. As an enzyme model, CDs have a well defined apolar cavity which can recognize and bind guest compounds in a way similar to enzyme–substrate interaction.

Information from model studies on the complexation of CDs has afforded a reasonable picture of the nature of molecular recognition; it is significant in understanding enzyme–substrate interaction. Several driving forces have been postulated for the inclusion complexation of CD with guest compounds [1, 14]: (1) van der Waals forces; (2) hydrophobic interactions; (3) hydrogen bonding; (4) release of

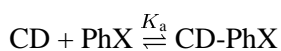
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distortional energy of cyclodextrin by binding guest; and (5) extrusion of 'high energy water' from the cavity of CD upon inclusion complex formation. Tabushi and coworkers [10] proposed a thermodynamic model for the process of cyclodextrin inclusion complex formation. Based on the thermodynamic parameters calculated for the inclusion of benzene, *p*-iodoaniline, and methyl orange by α -CD, they concluded that the van der Waals interaction, the conformation energy, and breaking of the water cluster around the apolar guest compound mainly dominate the driving force for inclusion complex formation.

Recently, correlation analysis was applied to the study of the inclusion complexation of cyclodextrins [15, 16]. The logarithm of the association constant of aqueous host-guest complexes of CDs and benzene derivatives showed a correlation coefficient of 0.935 for α -CD with the Hammett σ -values and molar refractivities of substituents [15]. The linear solvation energy relationship (LSER) was also applied to analyze the driving force of inclusion complexes between β -CD and a number of organic solutes [17]. In a previous paper [18] we reported that in the inclusion complexation of β -CD with sodium alkyl sulfates, the driving force ($-\Delta G^0$) is proportional to the carbon numbers of the alkyl groups. Plotting ($-\Delta G^0$) against carbon number (n), a straight line was obtained with a correlation coefficient of 0.99. In our laboratory, an artificial neural network (ANN) was also used to study the inclusion complexation of α - and β -CD with substituted benzenes. The association constants (K_a) computed by ANN are close to those determined experimentally [19a, 19b].

Although significant efforts have been devoted to describing the mechanism of CD inclusion complex formation, the nature of the driving forces still remains controversial [1, 2, 14a, 15].

In a preliminary communication [19c], we briefly described the application of the regression method to the prediction of driving forces for the inclusion of α - and β -CD with benzene derivatives. Here we wish to report the regression study on the relationship between the driving force of inclusion complexation of α - and β -CD with monosubstituted benzene derivatives (PhX) and the properties of the substituent of the guest compounds. The regression equations were established for the inclusion of α - and β -CD, respectively. The association constant is influenced mainly by the molar refraction for α -CD and by both the molar refraction and the hydrophobic constant of the substituent of the guest compounds for β -CD.



2. Experimental

2.1. INSTRUMENTS

The fluorescence and absorption spectra were measured with a Hitachi MF 850 spectrofluorimeter and Hitachi 557 UV-vis spectrophotometer, respectively.

2.2. MATERIALS

α -Cyclodextrin and β -cyclodextrin were purchased from Tokyo Kasei and were used as received. The substituted benzenes were the best available grade, and doubly distilled water was used.

2.3. METHODS

Solutions of substituted benzenes (2×10^{-5} to 2×10^{-4} mol/L) were prepared containing α -CD (2×10^{-3} to 1.8×10^{-2} mol/L) and β -CD (1.9×10^{-3} to 1.1×10^{-2} mol/L), respectively. After ultrasonification for 10 min at room temperature, the solution was allowed to stand for several hours before measurements. The samples were measured at 25 ± 0.1 °C.

3. Results and Discussion

The absorption or fluorescence intensities of the benzene derivatives in water changed upon addition of CD. The changes of both absorbance (ΔA) and fluorescence intensity (ΔI) were observed as a function of the concentration of cyclodextrin added. The association constant values, K_a , can therefore be evaluated from the Benesi–Hildebrand equation for the 1 : 1 inclusion complexes of CD with benzene derivatives [20–26]. The K_a values for the inclusion complexation of α -CD and β -CD are listed in Table I.

Table I shows that the association constants apparently varied with the properties of the substituents. In the earlier studies on the inclusion of some substituted phenyl acetates, an approximately linear relationship was observed between $\log K_a$ of the cyclodextrin–guest complex and the molar refraction (R_m) of the guest compound [27]. The substituent molar refraction (R_m) can be used as a parameter reflecting the volume and polarizability of the substrate. The greater the R_m value of the substituent, the larger the volume and thus the higher the polarizability of the compound. Plotting $\ln K_a$ against substituent molar refraction values gave a linear relationship (Figure 1), which shows that the association constants increased with increasing R_m values. This finding demonstrated that the substituents of benzene derivatives are located in the narrower rim of the CD cavity. The substituent with a larger R_m value fits more snugly into the cyclodextrin cavity. Furthermore, the higher polarizability of the substituents with larger R_m values favors binding through interaction between permanent dipoles of CDs and induced dipoles of guests.

The strength of interaction is also dependent on the size of the cyclodextrin cavity. As Figure 1 shows, the slope of the straight line for α -CD (0.16) is twice that of β -CD (0.08). This means that the interaction is more sensitive to the size of substituents in the complexation of α -CD than β -CD. The cyclodextrins are truncated, right-cylindrical, cone-shaped molecules, 7.9 Å high with a central cavity. The diameters of the narrower and wider rim of the cavity for α -CD are 5.3 Å and

Table I. Association constants (L/mol) for the inclusion complexation of α - and β -CD with mono substituted benzenes in H₂O at 25 °C.

X	α -CD		β -CD	
	This work	Lit. (ref.)	This work	Lit. (ref.)
H	$2.86(\pm 0.14) \times 10$	31.6(20)	$1.94(\pm 0.09) \times 10^2$	120 \pm 10(21) 169 \pm 11(20) 196 \pm 10(22)
CH ₃	$3.65(\pm 0.27) \times 10$	33 \pm 3(21)	$2.14(\pm 0.12) \times 10^2$	140 \pm 10(21)
C ₂ H ₅	$1.04(\pm 0.07) \times 10^2$	110 \pm 10(21)	$3.89(\pm 0.15) \times 10^2$	330 \pm 10(21)
C \equiv CH	$8.65(\pm 4.30) \times 10$		$2.30(\pm 0.13) \times 10^2$	
OH	$4.03(\pm 0.19) \times 10$	37 \pm 4(23)	$9.46(\pm 0.42) \times 10$	40 \pm 2.0(22)
OCH ₃	$1.41(\pm 0.07) \times 10^2$		$2.09(\pm 0.10) \times 10^2$	
OC ₂ H ₅	$1.71(\pm 0.08) \times 10^2$		$3.08(\pm 0.15) \times 10^2$	286 \pm 15(22)
CH ₂ OH	$9.65(\pm 0.43) \times 10$		$1.43(\pm 0.06) \times 10^2$	
CH ₂ Cl	$2.04(\pm 0.11) \times 10^2$		$2.80(\pm 0.10) \times 10^2$	
CHO	$1.02(\pm 0.04) \times 10^2$		$1.50(\pm 0.07) \times 10^2$	
COCH ₃	$1.40(\pm 0.06) \times 10^2$		$1.88(\pm 0.08) \times 10^2$	
COOCH ₃	$2.13(\pm 0.10) \times 10^2$		$3.17(\pm 0.11) \times 10^2$	
COOC ₂ H ₅	$3.61(\pm 0.13) \times 10^2$		$5.39(\pm 0.16) \times 10^2$	
CN	$7.81(\pm 0.38) \times 10$		$1.70(\pm 0.08) \times 10^2$	
NH ₂	$1.46(\pm 0.11) \times 10$	8.8 \pm 0.12(24)	$8.56(\pm 0.25) \times 10$	50 \pm 3(22)
NHCH ₃	$8.32(\pm 0.25) \times 10$		$1.31(\pm 0.03) \times 10^2$	47.6 \pm 2.4 (22) 52.6 \pm 2.6(22)
NHC ₂ H ₅	$1.28(\pm 0.05) \times 10^2$		$2.17(\pm 0.09) \times 10^2$	
N(CH ₃) ₂	$1.72(\pm 0.08) \times 10^2$		$2.52(\pm 0.10) \times 10^2$	230 \pm 10(22) 217 \pm 10(22)
NHCOCH ₃	$1.03(\pm 0.04) \times 10^2$		$1.57(\pm 0.06) \times 10^2$	
NO ₂	$8.94(\pm 0.48) \times 10$	49 \pm 10(25)	$2.79(\pm 0.12) \times 10^2$	
F	$3.97(\pm 0.16) \times 10$	34 \pm 1(26)	$9.09(\pm 2.00) \times 10$	70 \pm 30(26)
Cl	$1.12(\pm 0.10) \times 10^2$	100 \pm 10(26)	$1.86(\pm 0.12) \times 10^2$	160 \pm 10(26)
Br	$5.40(\pm 0.17) \times 10^2$	510 \pm 10(26)	$3.22(\pm 0.15) \times 10^2$	310 \pm 10(26)
I	$1.20(\pm 0.02) \times 10^3$	1100 \pm 10(26)	$8.46(\pm 0.20) \times 10^2$	800 \pm 10(26)

4.7 Å, respectively, and for β -CD 6.5 Å and 6.0 Å, respectively [28]. It is well known that the van der Waals force including the dipole–induced dipole interaction [29] and London dispersion [30] are proportional to the reciprocal of the 6th power of the distance between the guest and the wall of the CD cavity and to the polarizabilities of the two components. It is thus a short range interaction. The substituent may therefore, interact strongly with α -CD but, in contrast, the benzene derivatives can be embedded deeper by β -CD than by α -CD. The phenyl moiety may achieve a maximum contact area [16] with the internal surface of the cavity of the β -CD, hence, the interaction of the phenyl ring with β -CD would play an important role. Thus for the same substituted benzene, the association constant with β -CD is greater than with α -CD, except for bromobenzene and iodobenzene (Table I).

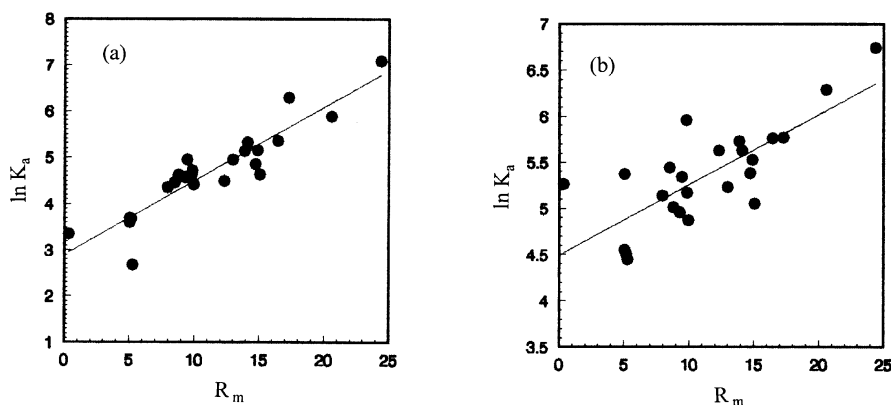


Figure 1. Plots of $\ln K_a$ vs. substituent molar refraction (R_m) for the inclusion of α -CD (a) and β -CD (b) with substituted benzenes. The linear relationships fit the following equations with correlation coefficients of 0.92 (a) and 0.76 (b), respectively.

$$(a) \ln K_a = 0.16(0.01) R_m + 2.95(0.18)$$

$$(b) \ln K_a = 0.08(0.01) R_m + 4.52(0.17).$$

The binding of halobenzenes (PhX, X = F, Cl, Br, I) with α -CD is more dependent on the R_m values than with β -CD. Figure 2 shows the relationship between $\ln K_a$ and the R_m values of halogen atoms for the inclusion of halobenzenes with α - and β -CD. Interestingly, K_a values for the inclusion complexes of β -CD with PhF and PhCl are larger than those of the corresponding α -CD complexes, whereas the $\ln K_a$ values for β -CD-PhBr and β -CD-PhI are smaller than those of the corresponding α -CD complexes. This can be rationalized in view of the van der Waals interaction. The effective van der Waals radii of F, Cl, Br and I in halobenzenes are 1.47, 1.77, 1.92, and 2.06 Å, respectively [31]. Since the substituent locates near the narrower rim of the CD cavity, the $\ln K_a$ values are proportional to the radii of the halogen atoms. The difference in slope in Figure 2 for α - and β -CD complexes indicates that the interactions of halogen atoms, especially Br and I with α -CD, are much stronger because the interaction components approximate to the van der Waals contact; with β -CD they are somewhat weak, since the halogen atoms are far from the internal surface of the CD cavity in the inclusion complexes. Iodobenzene, as well as bromobenzene, matches α -CD better than β -CD.

The inclusion of cyclodextrins with guest compounds is also affected by hydrophobic interactions [32]. The stability of binding by hydrophobic interaction is partly the result of van der Waals force but is mainly due to the effects of entropy produced on the water molecules [33]. In aqueous solution, a hydrophobic guest compound is restricted by the water shell formed by the hydrogen bonding network [34]. It has a strong tendency to break down the water cluster and penetrate the apolar cavity of CD. This process is exothermic due to entropic gain [10, 33, 34]. The association constants for the inclusion of α - and β -CD with benzene derivatives were observed to be proportional to the substituent hydrophobic constant of the

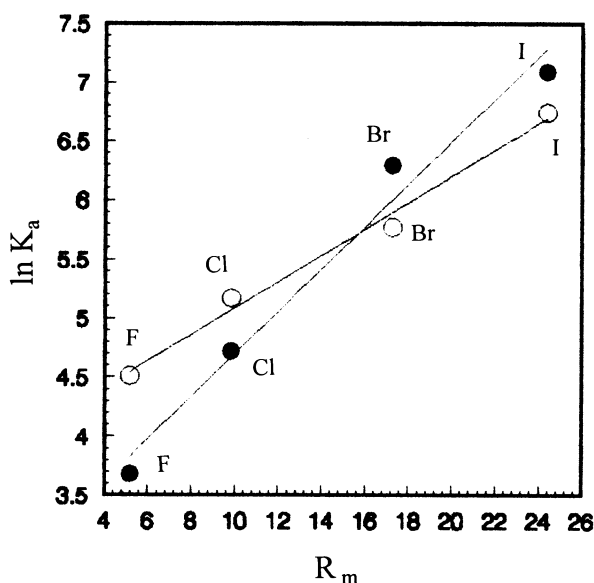


Figure 2. Plots of $\ln K_a$ vs. molar refraction (R_m) of halogen atoms for the inclusion of α -CD (●) and β -CD (○) with halobenzenes. The linear relationships fit the following equations with excellent correlation (0.99) for both α -CD and β -CD.

$$\text{For } \alpha\text{-CD, } \ln K_a = 0.18(0.02)R_m + 2.90(0.29)$$

$$\text{For } \beta\text{-CD, } \ln K_a = 0.11(0.01)R_m + 4.00(0.13).$$

guest. A plot of $\ln K_a$ against the substituent hydrophobic constant, π , showed an approximately linear relationship (Figure 3). The π value is a reasonable measure of hydrophobicity and is highly correlated with various types of biological activities, e.g. many beneficial effects of drugs, toxicity, pesticidal activity [35–42]. The change in hydrophobicity of benzene derivatives is caused only by the substituents. The substituent with greater π value showed a higher tendency of the corresponding guest compound to be driven into the hydrophobic cavity of cyclodextrin in aqueous solution [43].

The complexation of CD with guest compounds can be affected by electronic effects [1, 15]. It was reported that the association constants increased with increasing Hammett σ values which reflect the electronic effect. Since CDs have a permanent dipole [44–46], the primary hydroxyl end is positive and the secondary hydroxyl end is negative in the glucose units of CDs. The substituents with larger positive σ values are electron withdrawing and this favors binding to CD by dipole–dipole interaction. However, a simple regression analysis showed that the correlation of $\ln K_a$ with the σ constant was very poor for the inclusion of α - and β -CD with benzene derivatives; the correlation coefficient is only 0.30 for α -CD and 0.35 for β -CD ($n = 24$). Compared with the contributions of the variables R_m and π to the response of $\ln K_a$, σ is not important for the inclusion of cyclodextrins with monosubstituted benzenes used in this work.

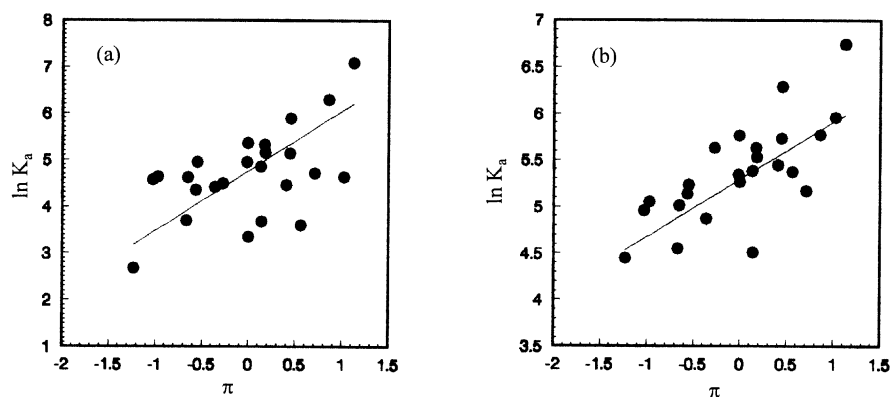


Figure 3. Plots of $\ln K_a$ vs. substituent hydrophobic constant (π) for the inclusion of α -CD (a) and β -CD (b) with benzene derivatives. The linear relationships fit the following equations with correlation coefficients of 0.72 (a) and 0.73(b), respectively.

$$\text{For } \ln K_a = 0.79(0.26)\pi + 4.71(0.17)$$

$$\text{For } \ln K_a = 0.60(0.12)\pi + 5.37(0.08)$$

Actually, a few factors play roles simultaneously in the inclusion complexation of CD with guests. In order to clarify the factors which played a major role in the complexation, a regression analysis was performed. Using the substituent molar refraction (R_m), hydrophobic constant (π) and Hammett σ constant and the corresponding observed association constant (K_a), a set of linear regression equations is given as follows:

For α -CD complexes,

$$\ln K_a = 3.13(0.17) + 0.14(0.01)R_m + 0.32(0.06)\pi + 0.22(0.16)\sigma \quad (1)$$

$$n = 24 \quad R = 0.94 \quad \text{sd} = 0.33 \quad \Psi = 0.35 \quad F = 56.12 \quad (P = 0.0001)$$

For β -CD complexes,

$$\ln K_a = 4.78(0.13) + 0.05(0.01)R_m + 0.42(0.08)\pi + 0.20(0.12)\sigma \quad (2)$$

$$n = 24 \quad R = 0.91 \quad \text{sd} = 0.24 \quad \Psi = 0.44 \quad F = 30.48 \quad (P = 0.0001)$$

In the linear regression models (Equations 1 and 2) the multiple correlation coefficient (R), standard deviation (sd), Ψ factor and F -test are all satisfactory, despite the limited number of available points ($n = 24$). The prominence tests of the coefficients of the regression equations have also been calculated. The F -value, prominence level (P), partial correlation coefficient (r_{y,x_1}) and relative independent contribution (q_i) [47] of each term in Equations 1 and 2 are summarized in Table II.

From Table II it is worth noting that for α -CD both the partial correlation coefficient (0.91) and the relative independent contribution (1.75) of the R_m term

Table II. Prominence tests of the regression coefficients in Equations 1 and 2.

		Constant	R_m	π	σ
α -CD	F	335.20	99.97	7.94	2.02
	P	0.0001	0.0001	0.01	0.17
	r_{y,x_1}		0.91	0.53	0.30
	q_i		1.75	0.14	0.01
β -CD	F	1408.64	25.30	23.89	2.84
	P	0.0001	0.0001	0.0001	0.11
	r_{y,x_1}		0.75	0.74	0.35
	q_i		0.83	0.78	0.09

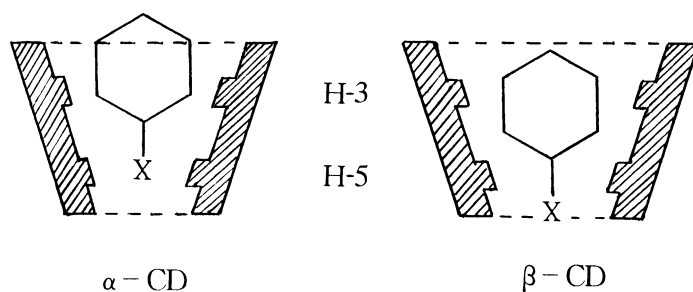


Figure 4. Schematic diagram for the features of orientation and location of the substituted benzene in the cavities of α - and β -CD. The depth of the guest in the inclusion complex refers to the levels of H-3 and H-5 of the glucose units. H-3 and H-5 pointing inside are shown in cross section.

to the response of $\ln K_a$ are very large, but the partial correlation coefficients for the π and σ terms are only 0.53 and 0.30, and the relative independent contributions are small (0.14 for π and 0.01 for σ). These data demonstrate that the volume of the substituent predominantly influences the stability of the inclusion complexes of α -CD with the guest compounds. Whereas, for β -CD, it is seen that the partial correlation coefficients of the terms R_m (0.75) and π (0.74) are almost equal, and the σ term is only 0.35. The relative independent contribution of the R_m term (0.83) is close to that of the π term (0.78), while that of the σ term (0.09) is very small. This indicates that the inclusion complexation of β -CD with substituted benzenes is mainly governed by the volume and hydrophobicity of the substituents in the guests. Obviously, as mentioned above, the difference in the composition of the driving forces for α - and β -CD is caused by the cavity dimensions. The features of the orientation and location of the substituted benzene in the cavities of α - and β -CD are illustrated in Figure 4.

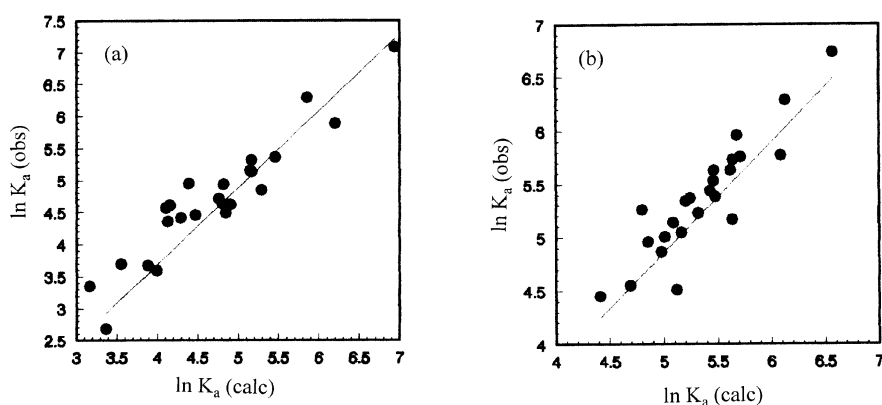


Figure 5. Plots of $\ln K_a(\text{calc})$ calculated by the regression models vs. $\ln K_a(\text{obs})$ determined experimentally for the inclusion of α -CD (a) and β -CD (b) with the benzene derivatives ($n = 24$, $r = 0.94$ (a) and 0.91 (b)).

The $\ln K_a(\text{calc})$ values calculated by Equation 1 and 2 from the R_m , π and σ values of substituents are close to the $\ln K_a(\text{obs})$ values determined experimentally. Plotting $\ln K_a(\text{obs})$ vs. $\ln K_a(\text{calc})$ gives straight lines (Figure 5).

As Figure 5 shows, there is a good linear relationship between $\ln K_a(\text{obs})$ and $\ln K_a(\text{calc})$. This shows that the prediction of driving force by the regression models from the substituent molar refraction (R_m) hydrophobic constant (π) and Hammett constant (σ) is successful. The models can be used to calculate the association constants for the inclusion complexation of α - and β -CD with mono-substituted benzenes,

Based on the regression analysis, we can conclude that the inclusion of substituted benzenes by α -CD is mainly driven by the van der Waals force and with β -CD by both van der Waals force and hydrophobic interactions.

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47. For a multiple regression model as follows:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_m X_m + \epsilon$$

q_i is defined as the relative independent contribution of the variable X_i to the response Y .

$$q_i = m(1 - q'_T/q_T).$$

Where q_T is the total contributions of the variables to Y , and q'_T the sum of the contributions of the variables except X_i , m is the number of variable.