Association of Symmetrical *p*-Dihalobenzenes with Cyclodextrins in Aqueous Medium

Tatsuyoshi TAKUMA, Toshio DEGUCHI, and Isao SANEMASA*
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1, Kumamoto 860
(Received October 3, 1990)

The complex formation of cyclodextrin (CyD, host) with symmetrical *p*-difluoro-, dichloro-, dibromo-, and diiodobenzenes (guests) has been studied in aqueous medium at 25 °C by making use of the volatilization rate of guest molecules from the aqueous into gaseous phase. In the excess of the host, α- and β-CyDs form 1 : 1 and 2 : 1 (host : guest) complexes, while γ-CyD forms 1 : 1 complexes. The association constants, especially for α- and β-CyDs, increased with an increase in the size of the halogen atom. A linear relationship between the logarithm of the 1 : 1 association constant and the total surface area of guest molecule was found for CyD–monohalobenzenes and CyD–*p*-dihalobenzenes. The van der Waals force seems to be the main factor in stabilizing the associated complexes. The validity of the concept of microscopic binding constant is discussed.

We studied host-guest associations using α-, β-, and γ-cyclodextrins (CyDs) as hosts and four monohalobenzenes as guests.[1] The present work is concerned with symmetrical *p*-dihalobenzenes as analogous guests. Although complex formations of α-CyD with *p*-dichloro-, dibromo-, and diiodobenzenes have been reported,[2] there are no literature data published on other CyDs and *p*-difluorobenzene. The object of this study is to compare the association constants of monohalobenzenes with those of *p*-dihalobenzenes and to discuss the mechanism of CyD-halobenzene complexations.

Several methods are available to approach CyD-guest complexations. Of these, UV absorption and fluorescence spectroscopies are generally used; the former is based on the shift of absorption spectrum by association, and the latter on the enhancement of guest fluorescence intensity in the presence of host. These methods, however, cannot be satisfactorily applied to guests of high volatility and low aqueous solubility, because in aqueous medium it is difficult to prepare CyD-guest associated species in an appreciable amount and to maintain its concentration constant during measurements. To such guests the solubility method can be applied, which makes use of an increase in the guest solubility in water as a consequence of association with CyD. This method is usually based on a "shake-flask technique:" an excess quantity of a guest substance is added to water containing CyD of known concentration, the mixture is mechanically shaken, and then the excess guest, which may be present in water as a liquid or solid phase, is separated. The solubility method is simple and versatile, but there are some essential problems. It is difficult to separate the excess guest phase while maintaining the temperature of the aqueous solution constant. The presence of an excess guest phase is particularly troublesome: CyD (host) molecules will be adsorbed on the surface of the liquid or solid guest phase or, in an extreme case, can penetrate into the guest phase to cause modification of its physicochemical properties and consequently its aqueous solubility.

The method used in this work to determine the association constant is the same as that employed in our previous works.[3,4] This method is based on the volatility of guest in aqueous solutions. Volatile guest molecules are driven out to the gas phase by introducing an inert gas at a constant flow rate into the aqueous solution. The volatilization rate is measured with and without addition of CyD; the rate decreases as a result of the association with CyD. The method is applicable to host-guest association systems where (a) the guest molecule is volatile, (b) the concentration of host is sufficiently high in comparison with that of guest, and (c) the rate of association is rapid compared with the volatilization rate. This method has been applied to CyD associations with such guests as iodine,[5] benzene and alkyldenzenes,[3] naphthalene and its methyl derivatives,[6] polynuclear aromatic hydrocarbons,[4] carbon tetrachloride, chloroform, and dichoromethane,[7] monohalobenzenes,[1] and normal alkanes,[8] and proved to give satisfactory association constants in reasonable agreement with the literature data.

Experimental

Materials and Preparation of Sample Solutions. Deionized distilled water was used throughout the experiments. An appropriate amount of α-, β-, and γ-CyD of guaranteed grade (Nakarai Chemical Co.), dried over phosphorus pentoxide under vacuum, was weighed and dissolved in water to prepare CyD stock solutions of desired concentrations. Four guest substances, *p*-difluoro-, *p*-dichloro-, *p*-dibromo-, and *p*-diiodobenzene, were used as received; the minimum purities are 95, 98, 99, and 98%, respectively, as claimed by the manufacturers (Tokyo Kasei Kogyo Co. for the first three and Kanto Kagaku Co. for the last one). An aqueous stock solution of each guest was prepared by adding an excess of each *p*-dihalobenzene to water and stirring for at least 24 h in the dark. After leaving the mixture standing for at least 24 h, a portion of the saturated guest solution was transferred to a separatory funnel and the absorbance of its cyclohexane extract was measured to determine the guest

concentration at the following wavelengths: *p*-difluoro- at 272.4, *p*-dichloro- at 273, *p*-dibromo- at 273, and *p*-diiodobenzene at 241 nm.

A portion of the saturated guest solution was transferred into a 2.5ϕ×25 cm cylindrical glass tube for *p*-difluoro- and dichlorobenzenes, or into a round-bottom flask of 500 cm^3 capacity for the other two guests. An appropriate fraction of the CyD stock solution was then added, and the solution was diluted with water to 100 cm^3 for the former two guests or to 500 cm^3 for the latter two guests. The concentration ranges of host and guest are given in Table 1.

Apparatus and Procedures. The apparatus and the experimental procedure were the same as those described in a previous paper.[1] Nitrogen gas was bubbled into the aqueous guest solution with or without CyD placed in the cylindrical glass tube, or in the round-bottom flask immersed in a bath thermostated at 25.0±0.1 °C, at a constant flow rate suitable for each guest volatility: *p*-difluoro- at 30, *p*-dichloro- at 50, *p*-dibromo- at 400, and *p*-diiodobenzene at 400 cm^3 min^{-1}. The N_2 gas leaving the sample solution was passed through a glass column of 0.5ϕ×23 cm filled by 8 cm in length with XAD-2 resin beads (80—150 mesh). The guest adsorbed on the resin within a fixed time was eluted out with 4 cm^3 of cyclohexane, and the amount of guest, ΔQ_ϕ, was determined by UV absorption measurements.

Results

The equation derived in previous papers[3,4] was used to estimate the 1 : 1 and 2 : 1 (host : guest) association constants, K_1 and K_2:

$$\ln(C_\phi - Q_\phi V^{-1}) = -kt/(1 + K_1C_{CyD} + K_1K_2C^2_{CyD}) + \ln C_\phi = -k't + \ln C_\phi, \quad (1)$$

where C_{CyD} and C_ϕ refer to the total concentration of host and that of guest, respectively, Q_ϕ is the sum of ΔQ_ϕ from time 0 to t, V is the volume of the aqueous solution, k is the rate constant for transfer of guest molecules from the aqueous to gas phase, and

$$k' = k/(1 + K_1C_{CyD} + K_1K_2C^2_{CyD}). \quad (2)$$

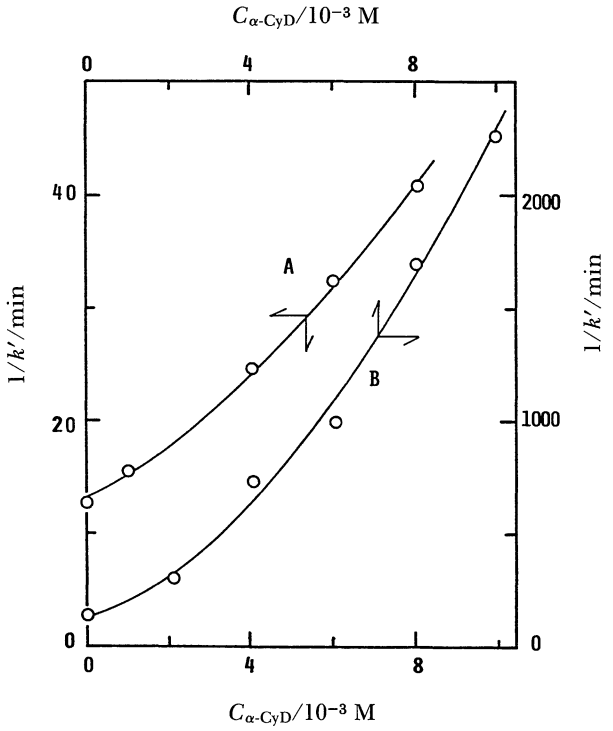


Fig. 1. Plots of $1/k'$ vs. C_{CyD}. α-CyD-*p*-difluorobenzene(A), -*p*-diiodobenzene (B).

Table 1. Concentration Ranges of Host and Guest and the Formation Constants, K_1 (1 : 1) and K_2 (2 : 1) of (Host : Guest) Complexes at 25 °C

	Concentration		Formation constant (Literature value)[a]			
	C_ϕ[b]	C_{CyD}[c]	K_1		K_2	
	10^{-5} M	10^{-2} M	M^{-1}		M^{-1}	
p-Difluorobenzene:						
α-CyD	13.2—16.4	0.974—8.03	19.6±0.3		4.9±0.8	
β-CyD	11.0—14.8	0.401—1.20	40±10		110±80	
γ-CyD	11.6—15.7	1.00—3.00	28±9		—[d]	
p-Dichlorobenzene:						
α-CyD	21.7—27.7	1.00—5.00	225±8	(232±16)	42±3	(90±12)
β-CyD	25.2—27.7	0.201—0.703	320±20		90±30	
γ-CyD	21.3—27.7	1.00—3.00	43±1		—[d]	
p-Dibromobensene:						
α-CyD	4.61—5.86	0.100—0.500	1020±60	(913±22)	100±40	(397±14)
β-CyD	5.34—6.50	0.0604—0.230	940±20		100±20	
γ-CyD	5.34—6.40	0.500—2.00	48±8		—[d]	
p-Diiodobenzene:						
α-CyD	0.132—0.295	0.0204—0.100	4200±900	(5060±940)	2000±1000	(6255±1270)
β-CyD	0.132—0.239	0.0203—0.0807	1500±200		1500±400	
γ-CyD	0.132—0.414	0.362—1.50	81±8		—[d]	

a) Literature values given in the parentheses are from Ref. 2. b) Total concentration of guest. c) Total concentration of cyclodextrin. d) K_2 was not evaluated because $1/k'$ vs. C_{CyD} plots gave a nearly straight line.

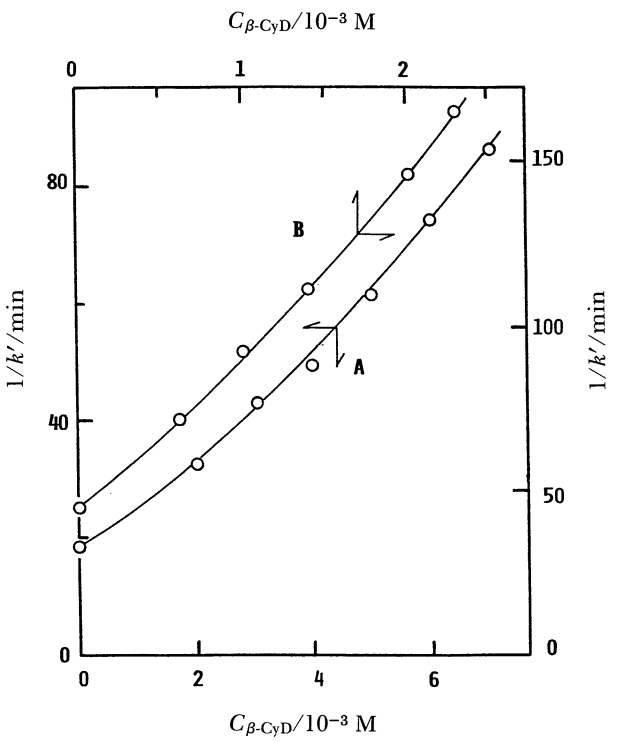


Fig. 2. Plots of $1/k'$ vs. C_{CyD}. β-CyD-*p*-dichlorobenzene (A), -*p*-dibromobenzene (B).

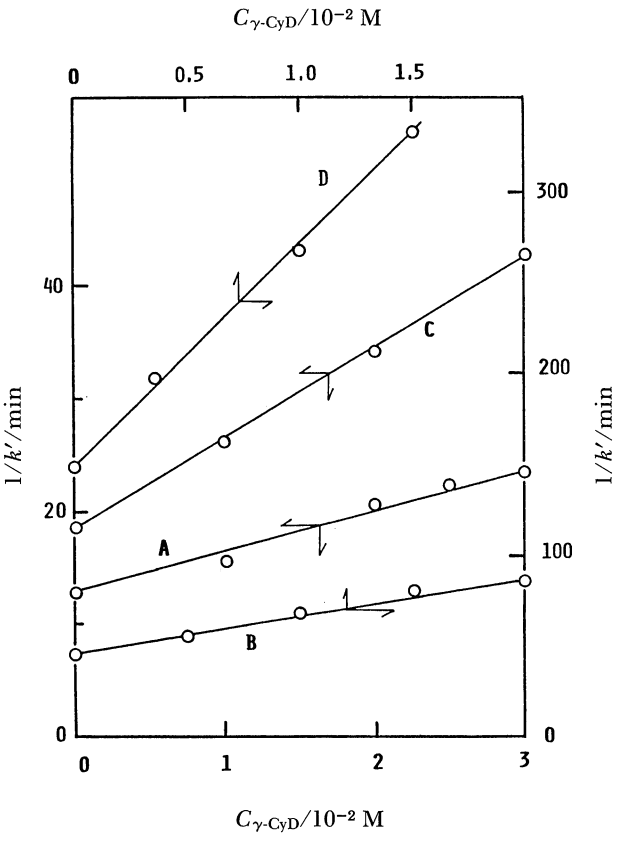


Fig. 3. Plots of $1/k'$ vs. C_{CyD}. γ-CyD-*p*-difluorobenzene (A), -*p*-dichlorobenzene (B), -*p*-dibromobenzene (C), -*p*-diiodobenzene (D).

Rearrangement of Eq. 2 yields

$$1/k' = K_1K_2C^2_{CyD}/k + K_1C_{CyD}/k + 1/k. \quad (3)$$

The plots according to Eq. 1 for all the symmetrical *p*-dihalobenzene-CyD systems examined in this work gave straight lines over the whole aeration time, during which ca. 50 to 70% of the guest molecules present initially in the sample solutions were purged. Slopes of the resulting straight lines, k' (and k), were evaluated by the least-squares method. Typical $1/k'$ vs. C_{CyD} plots are shown in Figs. 1 through 3. The plots display upward curvatures for α- and β-CyDs, indicating the formation of 1 : 1 and 2 : 1 (host : guest) complexes, whereas those for γ-CyD are linear, indicating only 1 : 1 complex formation. The K_1 and K_2 values were determined by the curve-fitting method and are summarized in Table 1, where the data obtained by solubility measurements by Connors and Pendergast[2] are also listed.

The agreement between the present and the literature K_1 values is good, in spite of an essential difference in the methods employed. As for the K_2 value, however, considerable discrepancies are noted; we have no criterion at the present stage to claim that the literature data are overestimated.

Discussion

The concept of microscopic binding constant has been proposed by Connors and Pendergast.[2] They used various kinds of symmetrical *p*-disubstituted benzenes, X-C_6H_4-X, as guests and α-CyD as host, and predicted that the 1 : 1 association constant, K_{11}^{xx}, is just twice the microscopic binding constant, $K_{x'x}$ (the binding site is indicated by a superscript prime). The concept seems reasonable when we consider that a guest molecule with two equivalent binding sites is to be accepted by a host molecule which associates with the guest at a single site (α-CyD, in the present case). There have been reported, however, few data to support directly this idea. An example which seems to support the concept is the α-CyD complex with toluene (K_1=33±3)—*p*-xylene (K_1=72±7 M^{-1})[3] (1 M=1 mol dm^{-3}). It is interesting to compare our previous data on monohalobenzenes with the present data on symmetrical *p*-dihalobenzenes and to examine whether the concept of microscopic binding constant is valid for the halobenzene series. If K_1 of a symmetrical *p*-dihalobenzene is twice that of the corresponding monohalobenzene, the concept is acceptable.

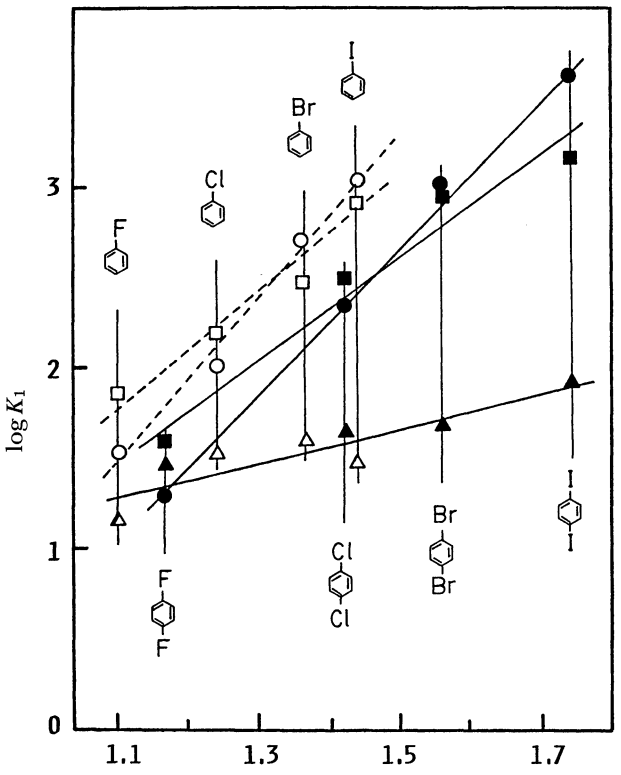
We use the following K_1 in M^{-1} for α-CyD—monohalobenzene: fluorobenzene (34±1), chlorobenzene (100±10), bromobenzene (510±10), and iodobenzene (1100±100).[1] Comparing with the corresponding K_1 value listed in Table 1, the microscopic binding concept seems to hold for chloro- and bromobenzene, but this is not the case for fluoro- and iodobenzene. The K_1 of *p*-difluorobenzene is smaller than that of mono-

fluorobenzene itself, while the K_1 of *p*-diiodobenzene is much larger than the doubled K_1 of monoiodobenzene. Although the data available at the present stage are scanty, we conclude that the microscopic binding concept does not necessarily apply to α-CyD complexations with all of symmetrical *p*-disubstituted benzenes. The physicochemical properties of the substituent such as size, polarity, and affinity to water should be taken into consideration.

If the size of the guest relative to the host cavity is considered, the microscopic binding concept seems not to be applicable to β- and γ-CyD associations with mono- and *p*-dihalobenzenes. When we compare these association constants,[1] however, the concept appears to hold for some host-guest association systems. Namely, for β-CyD, the K_1 of chlorobenzene (160±10) is just half that of *p*-dichlorobenzene, and this is also the case for the iodobenzene (K_1=800±100)—*p*-diiodobenzene combination. As for γ-CyD, in view of the range of experimental error, the K_1 of fluorobenzene (14±6), bromobenzene (39±8), and iodobenzene (30±10) are almost half that of the corresponding *p*-dihalobenzenes. These observations rather deteriorate than reinforce the validity of the concept of microscopic binding constant, because γ-CyD forms only 1 : 1 associated complexes with both mono- and *p*-dihalobenzenes.

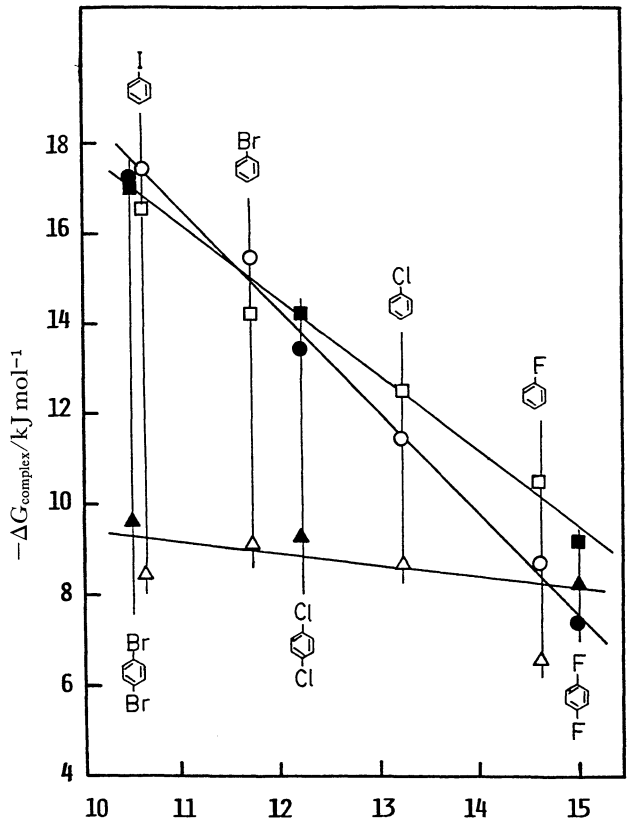
In preceding papers,[1,3] dealing with polyaromatic hydrocarbons and monohalobenzenes as guests, we concluded that the van der Waals interaction of these guests with the CyD inner wall is the main factor to stabilize the CyD complexes. Our conclusion came from the finding that the 1 : 1 complex formation constant K_1 for the homologous guest series decreases with increasing the guest hydrophobicity estimated from the Henry's law constant, and that $\log K_1$ increases almost linearly with the surface area of guest molecule.

In Fig. 4 are plotted $\log K_1$ vs. the total surface area (TSA) of *p*-dihalobenzenes; the plots for monohalobenzenes are also shown for comparison. Linear positive relationships between $\log K_1$ and TSA are observed for the three CyDs. In analogy with monohalobenzenes, association constants of *p*-dihalobenzenes for α-CyD are most sensitive to the size of halogen atom. For γ-CyD, $\log K_1$ vs. TSA plots of mono- and *p*-dihalobenzenes fall within a single line. This means that the cavity size of γ-CyD is wide enough to allow the guest molecule to orient itself in the cavity to get as



Surface area of guest molecule/nm²

Fig. 4. Dependence of association constant on the total surface area of guest molecule. α-CyD (○, ●), β-CyD (□, ■), γ-CyD (△, ▲). Data of total surface area are from Ref. 9.



$-\Delta G_{dehyd}$/kJ mol^{-1}

Fig. 5. Free energy changes of CyD-guest complexation, $\Delta G_{complex}$ (=$-RT \ln K_1$), and that of dehydration, ΔG_{dehyd} (=$-RT \ln K_H$) of guest. Symbols are the same as in Fig. 4.

large a contact area as possible. On the other hand, for either α- or β-CyD, the linear plot of *p*-dihalobenzenes, compared with that of monohalobenzene, shifts to the lower $\log K_1$ side. This is probably due to a difference in the 1 : 1 CyD-guest association model between mono- and *p*-dihalobenzenes, or to the affinity for water of another halogen atom substituted to monohalobenzene.

In the case of *p*-dihalobenzene, the benzene ring is situated just in the center of the cavity of β-CyD and two halogen atoms extrude equally outside the host cavity to some extent depending on the size of a particular halogen atom, whereas in the case of monohalobenzene the center of the cavity of β-CyD shifts to the halogen atom side. As for α-CyD, its cavity size is too small to include the benzene ring as a whole, but nearly equal to the diameter of the iodine atom. When the 1:1 complex is formed between *p*-dihalobenzene and α-CyD, an unassociated halogen atom might have some influence on the complex formation. That is, iodine, the most hydrophobic among halogen atoms, promotes, whereas fluorine, the most hydrophilic, depresses the association which occurs on the opposite side. This idea is not accepted in general at present, but helps us explain why the microscopic binding concept fails in the two cases mentioned above.

We previously proposed that the most reasonable parameter for the hydrophobicity of volatile solutes is the Henry's law onstant, K_H.[1,3,4] The K_H value is a measure how easily the solute is transferred from the aqueous to gas phase; a solute with the larger K_H is more hydrophobic. The free energy change in the 1 : 1 complex formation, $\Delta G_{complex}$ ($=-RT \ln K_1$), is plotted against ΔG_{dehyd} ($=-RT \ln K_H$) in Fig. 5; because of the lack of the vapor pressure data available for *p*-diiodobenzene, we cannot estimate ΔG_{dehyd} of this guest. In analogy with polyaromatic hydrocarbons,[4] almost linear relationships are observed for the three types of CyD. There are still two points to be noted.

First, as is the case of monohalobenzenes,[1] the hydrophobic interaction as a driving force of CyD complex formation is not significant for *p*-dihalobenzenes, because $-\Delta G_{complex}$ does not increase with $-\Delta G_{dehyd}$ but the situation is just the reverse. The van der Waals force seems to govern the associations of CyD with both mono- and *p*-dihalobenzenes. On an assumption that the positive relationship between $-\Delta G_{complex}$ and $-\Delta G_{dehyd}$ indicates the association being governed by the host-guest hydrophobic interaction, the negative slope of the linear plot may be taken as a measure of nonhydrophobic interaction. Namely, there is some contribution from hydrophobic interaction to γ-CyD complexations, but the least to α-CyD complexations. Secondly, regardless of the type of CyD, the plots for the two different halobenzene homologous series fall on the same linear line. We cannot elucidate this observation at the present stage.

References

1) T. Takuma, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **63**, 1246 (1990).
2) K. A. Connors and D. D. Pendergast, *J. Am. Chem. Soc.*, **106**, 7607 (1984).
3) I. Sanemasa and Y. Akamine, *Bull. Chem. Soc. Jpn.*, **60**, 2059 (1987).
4) I. Sanemasa, T. Takuma, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **62**, 3098 (1989).
5) I. Sanemasa, Y. Nishimoto, A. Tanaka, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **59**, 2269 (1986).
6) M. Fujiki, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **61**, 1163 (1988).
7) M. Nishimura, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.*, **62**, 3718 (1989).
8) I. Sanemasa, T. Osajima, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **63**, 2814 (1990).
9) R. J. Baker, B. J. Donelan, L. J. Peterson, W. W. Acree, Jr., and C.-C. Tsai, *Phys. Chem. Liq.*, **16**, 279 (1987).