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Association of Benzene and Alkylbenzenes with Cyclodextrins in Aqueous Medium

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Formation constants of the following aromatic hydrocarbons with α-,β-, and γ-cyclodextrin(CyD) were determined in aqueous medium at 25 °C in the presence of excess CyD: benzene, toluene, ethylbenzene, propylbenzene, isopropylbenzene, (*o*-, *m*-, and *p*-)xylene, and (1,2,3-, 1,2,4-, and 1,3,5-)trimethylbenzene. The technique used to study association between host(CyD) and guest (hydrocarbon) is based on the facts that the guest molecules can be driven out to gaseous phase by introducing an inert gas at a constant flow rate into the aqueous solution and that the volatilization rate of guest decreases with increasing association with the host in the aqueous solution. The 1 : 1 and 2 : 1 (host : guest) formation constants were evaluated. As a measure of hydrophobicity of guest molecules, the free energy change of dehydration derived from Henry's law constant was used. Based on hydrophobicity and a host-guest spatial-fitting model, the formation constants have been discussed.

α-, β-, and γ-Cyclodextrins(CyD) are cyclic oligosaccharides consisting of six, seven, and eight D-glucopyranose units linked by α(1—4) bonds with a central cavity. The cavity is thought to be hydrophobic and a wide variety of inorganic and organic compounds is held if they suitably fit in the space, making CyD act as a host. Aromatic hydrocarbons, which are generally hydrophobic, have been extensively studied, but most of the hydrocarbons so far examined have hydrophilic substituent groups in order to increase solubility. There have been two reports concerning the benzene-CyD association system,[1,2] and there appears no data on alkylbenzene-CyD system. The scarcity of examination of these substances may be partially attributed to low aqueous solubility of these nonelectrolytes and partially to their high volatility; both reasons make it difficult to estimate accurately the amount of CyD-associated species formed in the aqueous medium.

In our preveous papers,[3,4] a method was presented which estimates 1 : 1 association constants between volatile and nonvolatile solutes in aqueous medium. The method is based on volatility of nonelectrolyte solute in aqueous solution. Volatile molecules are driven out to gaseous phase by introducing an inert gas at a constant flow rate into the aqueous solution. The volatilization rate was measured with and without addition of nonvolatile solute which associates with the volatile solute and decreased with the degree of association between the solutes. The method is simple, versatile, and applicable to such systems where (a) one of the solutes is volatile, (b) the concentration of nonvolatile solute is sufficiently high in comparison with that of volatile solute, and (c) the rate of association is rapid compared with the volatilization rate.

The method seems to be particularly suitable for studying association where solutes such as benzene and alkylbenzenes are concerned, because these solutes are highly volatile and scarecely soluble in water. The present study was undertaken to demonstrate the volatilization method and to interpret formation constants by a host-guest spatial-fitting model and hydrophobicity of guest molecule. A series of alkylbenzene have been chosen for this purpose: straight-chain series and some isomers (propylbenzenes, xylenes, and trimethylbenzenes).

Experimental

Materials and Preparation of Sample Solutions. Distilled deionized water was used throughout the experiments. Aromatic hydrocarbons used for guest are of analytical reagent grade (the purity is listed in Table 1). Cyclodextrins (α-, β-, and γ-CyD) used for host were of guaranteed grade from Nakarai Chemicals Co. Both guest and host reagents were used without further purification. An aqueous solution of each guest was prepared using a technique previously described.[5] The solute vapor in equilibrium with the liquid solute was introduced into water at 25 °C and circulated in a closed system. An aqueous solution saturated with guest liquid hydrocarbon can be prepared within 5 min by this technique. A portion of the saturated guest solution was transferred into a separatory funnel and the concentration of guest was determined by solvent extraction with chloroform, and another portion was transferred into a 2.5φ×25 cm cylindrical glass tube. A suitable amount of CyD, which had been dried over phosphorus pentaoxide under vacuum, was weighed and dissolved into the guest solution. The solution

Table 1. Experimental Conditions

Guest substance	Purity	λ[a]	N_2 flow rate
	%	nm	$cm^3 min^{-1}$
Benzene	99.5	254.4	15.8
Toluene	99.0	261.4	18.0
Ethylbenzene	98	261.0	20.0
o-Xylene	96	263.0	20.2
m-Xylene	98	264.0	20.9
p-Xylene	99	267.2	20.9
Propylbenzene	97.0	260.6	19.9
Isopropylbenzene	98.0	259.6	22.2
1,2,3-Trimethylbenzene	97	262.0	30.0
1,2,4-Trimethylbenzene	98	267.4	29.0
1,3,5-Trimethylbenzene	97.0	264.8	28.0

a) The wavelength for determining the concentration of guest molecules after $CHCl_3$ extraction.

was then diluted to 100 cm^3 with water. Ranges of concentration of guest and host are given in Table 3.

Amberlite XAD-2 resin (Rohm and Hass) as an adsorbent of guest vapor was ground in an agate mortar, a 150—200 mesh portion was collected and washed with ethanol by decantation until the supernatant became clear.

Apparatus and Procedures. The cylindrical glass tube containing guest and host at each desired concentration was immersed in a bath thermostated at 25.0±0.1 °C. A gas-inlet-type adaptor was mounted on the tube and N_2 was blown in the solution through Teflon tube of 1 mm i.d. at a constant flow rate controlled by a Stec Type Sec 400 mass-flow controller in the range of 15.8 to 30.0 $cm^3 min^{-1}$ (Table 1) depending on the volatility of guest and its association with host in aqueous solution. The N_2 flow rate was kept same irrespective of the presence of host. The N_2 leaving the sample solution was passed through a 0.5ϕ×12 cm glass column filled with XAD-2 resin beads of 8 cm in length. The exit and the bed top of column was plugged and covered with glass wool. After a fixed time, N_2 stream was interrupted, the XAD column was replaced by a fresh one and N_2 flow was resumed. This operation was repeated at regular time intervals. The guest hydrocarbon adsorbed on the resin was completely eluted out with $CHCl_3$ of 3 or 4 cm^3. The amount of hydrocarbon expelled from the sample solution during a fixed time, ΔQ, i.e., the amount of guest collected on a single XAD column, was determined by UV spectroscopy at the optimum wavelength for each guest hydrocarbon (Table 1) with reference to a calibration curve prepared for each guest-$CHCl_3$ solution. The XAD column can be used repeatedly by washing with $CHCl_3$ and drying in hot air.

Results

Derivation of Equation Estimating 1:1 and 2:1 (Host:Guest) Formation Constants. As for the CyD-benzene systems, the possible host:guest stoichiometric ratios are 1:1, 2:1, and 1:2.[2] The last one is, however, excluded under the present experimental condition that host molecules are always excess over guest molecules. Then, the reactions that should be taken into account are:

$$\mathrm{CyD}+\phi \rightleftharpoons \mathrm{CyD}\cdot\phi, (K_1) \quad (1)$$

$$\mathrm{CyD}\cdot\phi+\mathrm{CyD} \rightleftharpoons \mathrm{CyD_2}\cdot\phi, (K_2), \quad (2)$$

$$\phi\,(\mathrm{aq})\rightarrow\phi\,(\mathrm{gas}), (k), \quad (3)$$

where ϕ refers to a hydrocarbon molecule, K_1 and K_2 are the corresponding stepwise formation constants, and k is the rate constant for transfer of guest molecules from aqueous to gaseous phase.

The guest molecules expelled into the gaseous phase are collected successively by the adsorbent, and the total amount, Q_ϕ, which is the summation of ΔQ_ϕ, is measured as a function of aeration time, t. Here, we assume that the releasing of guest molecules at a constant N_2 flow rate is of first-order with respect to the concentration of free species in the solution as follows:

$$dQ_\phi V^{-1}/dt = k[\phi], \quad (4)$$

where V is the volume of the aqueous solution. The mass-balance equations are:

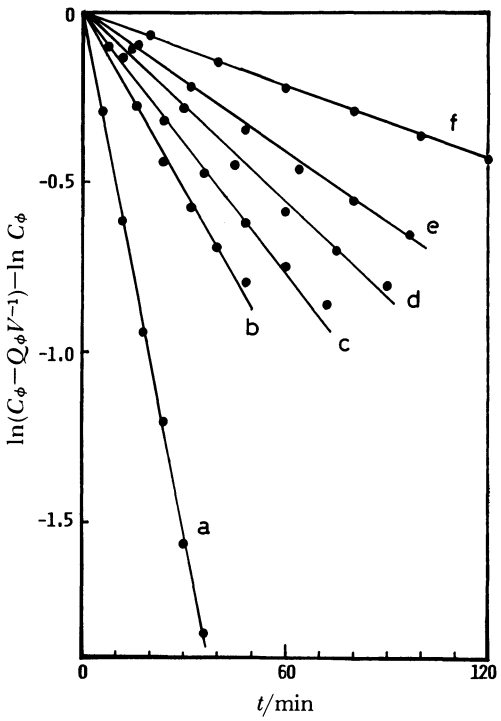

Fig. 1. Propylbenzene-α-CyD system. The plots of $\ln(C_\phi - Q_\phi V^{-1}) - \ln C_\phi$ vs. t in the absence and presence of cyclodextrin. N_2 gas flow rate 19.9 $cm^3 min^{-1}$; $C_{CyD}/10^{-3}$ M; (a) 0, (b) 2.52, (c) 5.04, (d) 7.56, (e) 10.1, (f) 20.2; $C_\phi/10^{-4}$ M: (a) 4.46, (b) 2.42, (c) 2.61, (d) 3.91, (e) 3.91, (f) 3.63.

Table 2. The Rate Constant for Transfer of Propylbenzene from Aqueous to Gaseous Phase with and without α-, β-, and γ-Cyclodextrin

k or k'[a]	C_ϕ[b]	Total concentration of		
		α-CyD	β-CyD	γ-CyD
$10^{-2} min^{-1}$	10^{-4} M	10^{-3} M	10^{-3} M	10^{-3} M
5.40	4.44			
5.14	4.46			
5.30	3.35			
5.16	3.14			
5.26	3.14			
1.72	2.42	2.52		
1.28	2.61	5.04		
0.932	3.91	7.56		
0.694	3.91	10.1		
0.361	3.63	20.2		
3.04	1.04		1.42	
2.53	1.04		2.13	
2.01	2.08		2.85	
1.09	1.97		4.19	
4.51	2.04			4.78
3.27	2.08			7.97
2.94	2.08			15.9

a) $k'=k/(1+K_1C_{CyD}+K_1K_2C_{CyD}^2)$, where C_{CyD} is the total concentration of cyclodextrin. b) The initial concentration of propylbenzene.

$$C_{CyD}=[\mathrm{CyD}]+[\mathrm{CyD}\cdot\phi]+2[\mathrm{CyD_2}\cdot\phi], \quad (5)$$

$$C_\phi = [\phi]+[\mathrm{CyD}\cdot\phi]+[\mathrm{CyD_2}\cdot\phi]+Q_\phi V^{-1}$$
$$= [\phi]+K_1[\mathrm{CyD}][\phi]+K_1K_2[\mathrm{CyD}][\phi]+Q_\phi V^{-1}, \quad (6)$$

where C_{CyD} and C_ϕ denote the total concentration of CyD and the total concentration of guest, respectively. Substituting Eq. 6 by Eq. 4 we obtain

$$dQ_\phi V^{-1}/dt = k(C_\phi - Q_\phi V^{-1})/(1+K_1[CyD]+K_1K_2[CyD]^2), \quad (7)$$

which becomes, on integration and with $Q_\phi=0$ at $t=0$,

$$\ln(C_\phi - Q_\phi V^{-1}) = -kt/(1+K_1[CyD]+K_1K_2[CyD]^2) + \ln C_\phi = -k't + \ln C_\phi, \quad (8)$$

where

$$k' = k/(1+K_1[CyD]+K_1K_2[CyD]^2). \quad (9)$$

Plots of $\{\ln (C_\phi - Q_\phi V^{-1}) - \ln C_\phi\}$ vs. t will give a straight line with a slope which corresponds to $-k'$ in the presence of CyD or to $-k$ in the absence of CyD. Under the condition that the total concentration of CyD is sufficiently higher than that of the associated complexes formed, that is, $C_{CyD} \gg [CyD\cdot\phi]+[CyD_2\cdot\phi]$, [CyD] in Eq. 9 is equal to C_{CyD}. Rearrangement of Eq. 9 gives the equation:

$$1/k' = K_1K_2C_{CyD}^2/k + K_1C_{CyD}/k + 1/k, \quad (10)$$

from which we can estimate K_1 and K_2 by plotting $1/k'$ against C_{CyD}.

Preliminary experiments show that the rate constant k is a function of gas flow rate and that the constant k' is proportional to k at a constant CyD concentration. We assume from the latter observation that the reaction (3) is the rate-determining step.

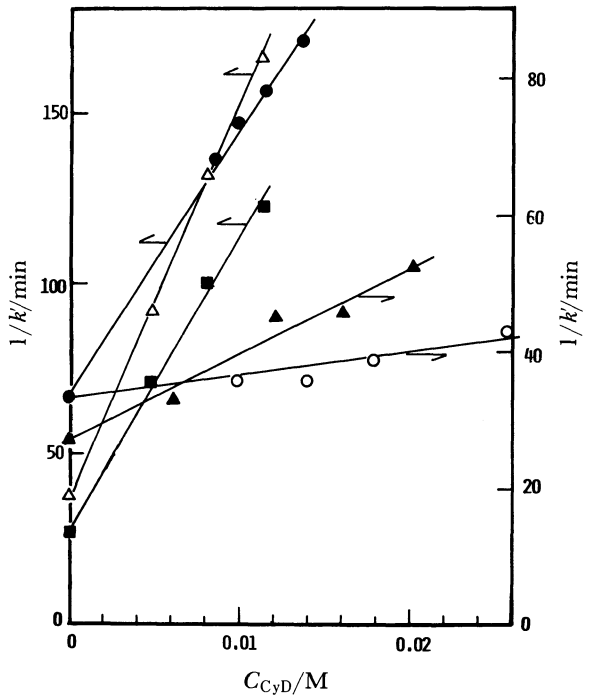

Fig. 2. The plots of $1/k'$ vs. C_{CyD}. Examples of straight line. Benzene-β-CyD(●), benzene-γ-CyD (○), 1,2,4-trimethylbenzene-α-CyD(▲), o-xylene-β-CyD(△), ethylbenzene-β-CyD(■).

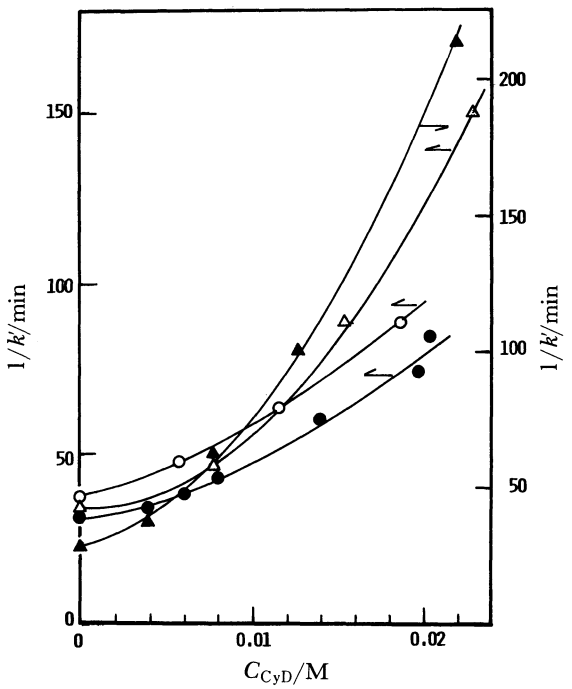

Fig. 3. The plots of $1/k'$ vs. C_{CyD}. Examples of parabolic curve. Benzene-α-CyD(●), o-xylene-γ-CyD(○), p-xylene-α-CyD(▲), 1,2,3-trimethylbenzene-α-CyD(△).

Estimation of K_1 and K_2. Plots according to Eq. 8 for propylbenzene-α-CyD system are shown in Fig. 1. The plots give straight lines up to ca. 70% release of the guest hydrocarbon from the solution. This linearity verifies the validity of the assumption that the volatilization of guest molecules follows a first-order reaction at a constant gas flow rate. The slopes of resulting straight lines, k and k', were evaluated using the least-squares method; the results for propylbenzene are shown in Table 2. Figures 2 and 3 show some typical results plotted by a curve-fitting method with the aid of Eq. 10. The $1/k'$ vs. C_{CyD} plots appear to be linear (Fig. 2) or parabolic (Fig. 3) depending on the host-guest combination. All the data were first treated by quadratic equations and when coefficients of the C_{CyD}^2 term were slightly negative, the plots were taken to be linear. The K_1 (and K_2) values thus determined are summarized in Table 3.

Discussion

Comparison of Results with Those in the Literature. In a previous paper,[4] which concerns with 1 : 1 associations of molecular iodine with α-, β-, and γ-CyD, we reported that the method making use of the difference in I_2 volatility rate with and without CyD provides formation constants in reasonable agreement with the literature values and that the method can be used to study association with a small formation constant in the order of 10. The present work is based on the same technique. In order to discuss whether we

Table 3. Concentration Ranges of Host and Guest and the Formation Constants, K_1 (1:1) and K_2 (2:1) of (Host:Guest) Complexes at 25.0 °C

	Concentration		Formation constant	
	C_ϕ [a]	C_{CyD} [b]	K_1	K_2 [c]
	10^{-4} M	10^{-3} M	M^{-1}	M^{-1}
Benzene				
α-CyD	6.20—17.5	10.5 —51.0	17±2	17±3
β-CyD	7.17—10.4	8.54—13.7	(1.2±0.1)×10²	—
γ-CyD	6.78—10.4	9.93—25.8	12±2	—
Toluene				
α-CyD	3.99—5.14	6.07—60.7	33±3	11±5
β-CyD	4.83—5.11	7.30—10.5	(1.4±0.1)×10²	—
γ-CyD	4.72—5.31	5.83—19.4	20±1	—
Ethylbenzene				
α-CyD	3.23—3.79	7.95—23.8	(1.1±0.1)×10²	21±9
β-CyD	3.13—3.76	4.87—11.3	(3.3±0.1)×10²	—
γ-CyD	3.25—3.76	5.83—19.4	36±6	—
o-Xylene				
α-CyD	2.86—3.50	7.57—22.7	22±8	—
β-CyD	3.03—3.38	4.87—11.4	(3.0±0.1)×10²	—
γ-CyD	3.13—3.44	5.80—18.7	34±1	61±2
m-Xylene				
α-CyD	3.41—3.59	7.94—23.8	40±1	37±5
β-CyD	2.29—3.59	4.82—11.2	(1.6±0.1)×10²	—
γ-CyD	3.37—3.59	12.2 —20.3	27±2	—
p-Xylene				
α-CyD	2.28—2.83	3.90—22.0	72±7	(1.4±0.4)×10²
β-CyD	2.79—2.90	4.87—11.4	(2.4±0.1)×10²	13±3
γ-CyD	2.78—2.81	5.93—19.5	7.9±0.1	32±1
Propylbenzene				
α-CyD	2.42—4.46	2.52—20.2	(5.9±0.1)×10²	6.6±2.5
β-CyD	1.04—4.46	1.42—4.19	46±9	(4.3±0.9)×10³
γ-CyD	2.04—4.46	4.78—15.9	52±14	—
Isopropylbenzene				
α-CyD	2.21—2.47	7.83—22.5	72±11	—
β-CyD	1.76—2.46	2.61—7.80	(1.2±0.1)×10³	—
γ-CyD	2.21—2.51	4.59—15.3	94 [d]	—
1,2,3-Trimethylbenzene				
α-CyD	2.50—2.76	7.63—23.0	13±1	(4.7±0.2)×10²
β-CyD	2.19—2.76	2.98—7.45	(1.8±0.1)×10²	74 [d]
γ-CyD	1.65—2.76	3.94—13.1	(2.9±0.1)×10²	—
1,2,4-Trimethylbenzene				
α-CyD	1.59—2.32	6.05—20.2	46±5	—
β-CyD	1.65—2.32	2.92—8.69	(8.7±0.5)×10²	—
γ-CyD	1.98—2.31	3.91—13.0	53±3	15 [d]
1,3,5-Trimethylbenzene				
α-CyD	1.94—2.12	5.05—20.2	61±5	—
β-CyD	1.60—1.94	3.05—6.87	60±4	—
γ-CyD	1.83—1.94	3.44—13.7	24±4	—

a) The initial concentration of guest substance. b) The total concentration of cyclodextrin. c) The dash-sign indicates that K_2 was not evaluated, because $1/k'$ vs. C_{CyD} plots by Eq. 10 gave nearly straight line only. d) The mean of two determinations.

can apply the method in the cases of aromatic hydrocarbons as guest molecules, the estimated formation constants are to be compared with those in the literature. Of the guest substances studied in this work, however, the literature data are only available for benzene. Then, we applied the method to naphthalene-β-CyD to find the formation constant K_1 to be 680 M^{-1} (M=mol dm^{-3}) at 25 °C.[6] Our estimation was in reasonable agreement with the literature value of 630 M^{-1} at 25 °C.[7]

Hoshino et al. measured fluorescence enhancement of benzene by forming inclusion complex with β-CyD, and reported K_1 for benzene-β-CyD at 28 °C to be 196 M^{-1}.[1] Tucker and Christian measured vapor pressure of benzene with and without CyD in aqueous solutions at various temperatures.[2] Their K values at 25 °C are as follows; for α-CyD K_1=31.6 M^{-1}, K_1K_2= 325 M^{-2}, for β-CyD K_1=169 M^{-1}, and for γ-CyD K_1= 9.1 M^{-1}.

The present result for benzene-β-CyD (K_1=120 M^{-1})

is smaller than each literature value. Compared with Tucker-Christian's results for benzene-α-CyD, the present K_1 (17 M^{-1}) seems considerably small. Since their K_1K_2 product (325 M^{-1}) is in reasonable agreement with our corresponding value (289 M^{-2}), our K_2 is larger than their K_2. Because of lack of data available in the literature, it is difficult at present to judge which is more reliable and to know if the agreement observed for benzene-γ-CyD is meaningful.

The vapor pressure method employed by Tucker and Christian makes use of the fact that the volatility of substrate is depressed by forming inclusion complexes with CyD and it resembles our method in this respect: the former may be called "static" and the latter "dynamic" technique. Their method seems, however, to be only applicable to a high volatile guest like benzene, because it is the total vapor pressure that can be measured. Accurate measurement of vapor pressure for low volatile solute is difficult due to the vapor pressure of water. Our present technique seems advantageous in this respect. The present method, however, accompanies large deviation of formation constants. This may arise from uncertainty in determining the amount of released guest. The overall error in Q_ϕ becomes large due to the accumulation of error in ΔQ_ϕ. Moreover, it should be noted that the present method cannot be applied for determining formation constants of guest-rich complexes. This is an unavoidable disadvantage. Tucker and Christian succeeded in determining the 1 : 2 (host : guest) formation constant for benzene-α-CyD.

Henry's Law Constant as a Measure of Hydrophobicity of Guest. Hydrogen bonding, van der Waals forces, and hydrophobic interaction are generally accepted to be the binding forces between CyD and guest molecules. The first one is excluded in the present case because the guests used have no ability to form hydrogen-bond with CyDs. It is considered that the host-guest spatial fitting plays a dominant part in van der Waals forces. On the other hand, it is generally difficult to evaluate the contribution of hydrophobic interaction. Some physico-chemical parameters such as aqueous solubility and partition coefficient of 1-octanol-water or chloroform-water systems have been used as a measure of hydrophobicity: Their logarithmic values plotted against log K gave fairly good linear relationships for some guest substances.[8,9]

Tabushi et al. have calculated the free-energy change caused by hydrophobic interaction of three model guests including benzene.[10] Their theory is reasonably based on the idea that the hydrophobic interaction arises from dehydration process, that is, a guest molecule is transferred from a hydrated state to an ideal gas state leaving behind a cavity (water cluster) which is collapsed and redistributed. A suitable parameter for describing hydrophobicity of nonelectrolyte guests like those employed in this work is Henry's law constant, K_H, a measure of free-energy

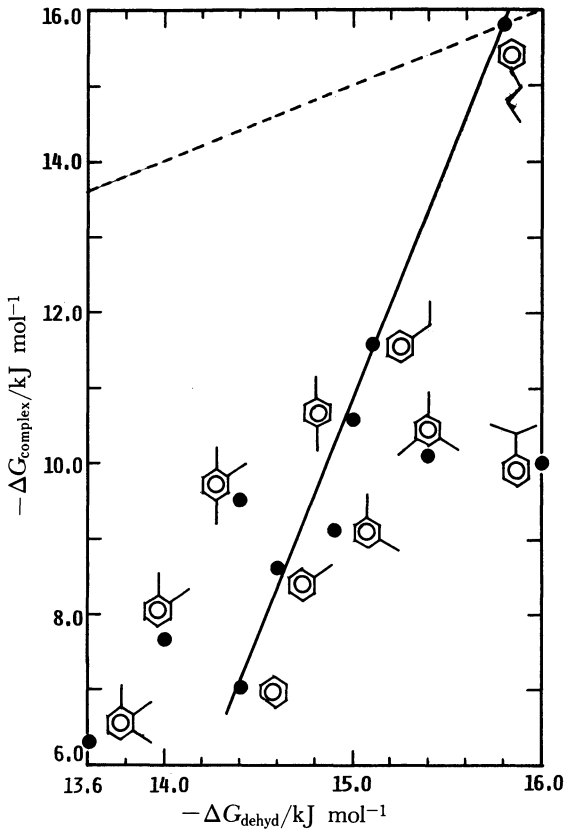

Fig. 4. The plots of $-\Delta G_{complex}$ vs. $-\Delta G_{dehyd}$. α-Cyclodextrin. The dotted lines in Figs. 4—6 indicate $-\Delta G_{complex}=-\Delta G_{dehyd}$.

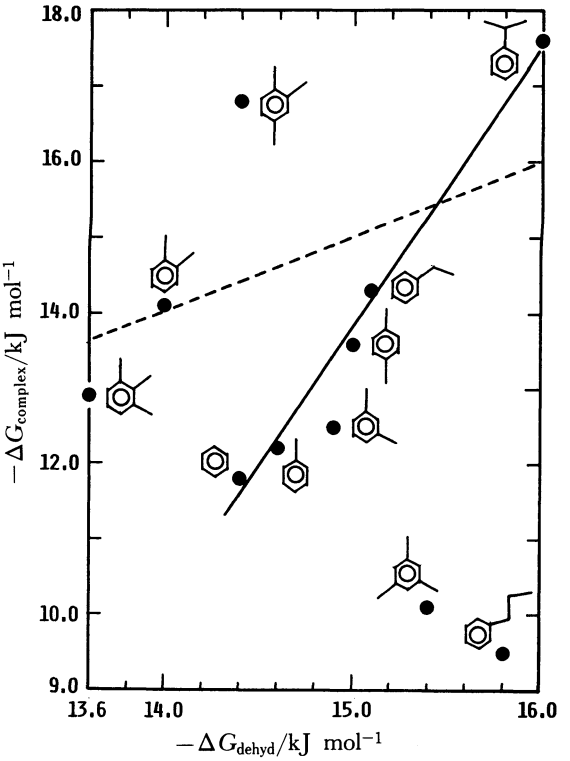

Fig. 5. The plots of $-\Delta G_{complex}$ vs. $-\Delta G_{dehyd}$. β-Cyclodextrin.

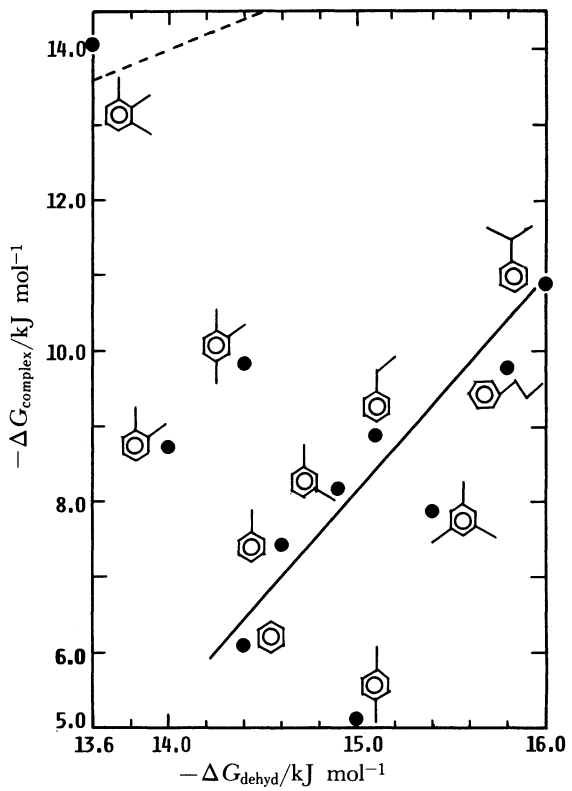

Fig. 6. The plots of $-\Delta G_{complex}$ vs. $-\Delta G_{dehyd}$. γ-Cyclodextrin.

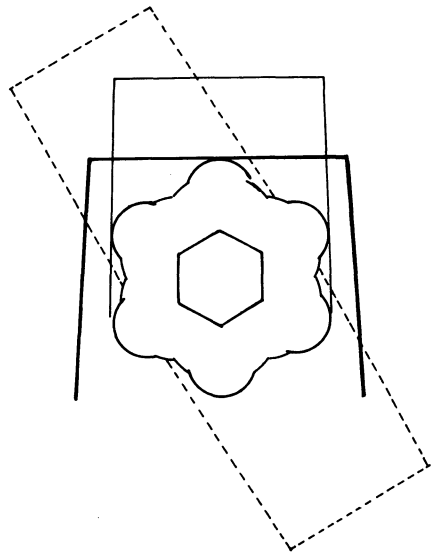

Fig. 7. Benzene-CyD inclusion model. α-, β-, and γ-cyclodextrin cavities in Figs. 7—9 are drawn by dotted, thin solid, and thick solid lines, respectively.

necessary to bring a nonelectrolyte from aqueous medium to vapor phase. The free-energy change associated with dehydration of a guest, ΔG_{dehyd}, can be evaluated by $\Delta G_{dehyd}=-RT \ln K_H$. The ΔG_{dehyd} values for all the guests examined were already reported in a previous paper.[5] The free-energy change in the 1 : 1 complex formation, $\Delta G_{complex}$ ($=-RT \ln K_1$) is plotted against ΔG_{dehyd} in Figs. 4 to 6; a dotted line indicates

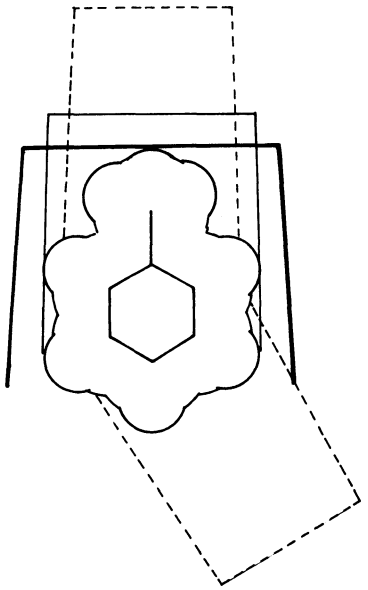

Fig. 8. Toluene-CyD inclusion model.

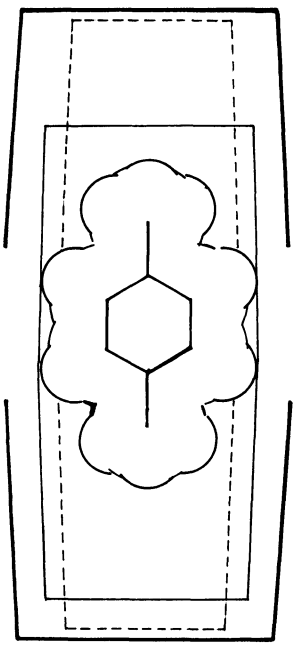

Fig. 9. *p*-Xylene-CyD inclusion model.

$\Delta G_{dehyd}=\Delta G_{complex}$.

Figures 4—6 show that most of the guests have considerably smaller $-\Delta G_{complex}$ than $-\Delta G_{dehyd}$ for three CyDs, especially for α- and γ-CyD. If we postulate that a guest molecule is fully embraced in the cavity of a given CyD and that the environment for the guest is just like a gaseous phase, $-\Delta G_{dehyd}$ for the nonelectrolyte will contribute in full to the $-\Delta G_{complex}$. Such circumstances are, however, hardly realized. Therefore, $-\Delta G_{dehyd}$ from K_H can be taken as an upper limit of the hydrophobic contribution.

Interpretation of Formation Constants. We try to interpret the magnitude of K_1 and K_2 determined for each host-guest combination by an inclusion (or asso-

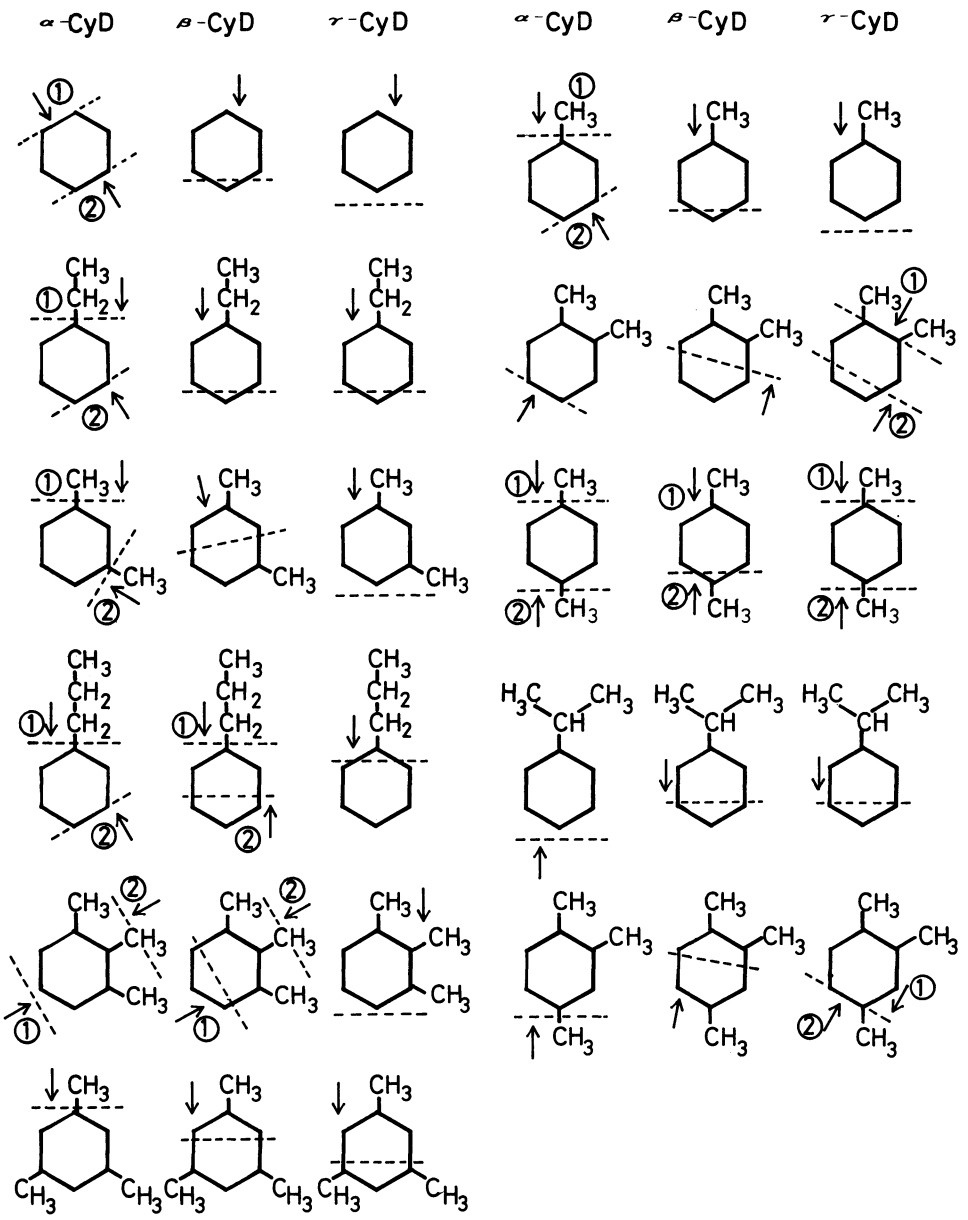

Fig. 10. Host-guest inclusion model. The direction from which the host includes the guest and the extent to which the guest penetrates the host are indicated by an arrow and a dotted line, respectively. The numbers, 1 and 2, in the circle refer to the binding sites corresponding to K_1 and K_2, respectively.

ciation) model and by taking into account the hydrophobicity of guest molecule. The following data in Å unit (1 Å=0.1 nm) are used for guests; bond length: 1.04 for C-C, 1.08 for C-H in benzene ring, 1.54 for C-C, 1.08 for C-H in alkyl group, van der Waals radius:[11] 1.0 for H, 1.7 for C. Concerned with CyDs, the following data in Å reported in the literature are used; the inner diameter of cavity:[12] 4.7—5.2 for α-CyD, 6.0—6.4 for β-CyD, 7.5—8.3 for γ-CyD (the smaller value is for the primary hydroxyl group side and the larger is for the secondary hydroxyl group side), the cavity depth:[13] 6.7 for α-CyD, ≈7 for β- and γ-CyD.

Typical inclusion models are depicted for benzene, toluene, and *p*-xylene in Figs. 7—9, and their simplified models are illustrated in Fig. 10. These models were made on the following assumptions. (A) A guest enters into CyD through wider secondary hydroxyl side. (B) Alkyl group is included in CyD cavity preferentially to benzene ring if the cavity entrance radius admits. This assumption is based on the fact that aliphatic series are more hydrophobic than aromatic hydrocarbons.[14] (C) When two hosts share a single guest and K_2 is larger or nearly equal to K_1, the cross-section of secondary hydroxyl group sides of two CyDs are situated in parallel to each other in a suitable distance to form hydrogen bond,[15] and when K_2 is smaller than K_1, the distance between two CyDs is too

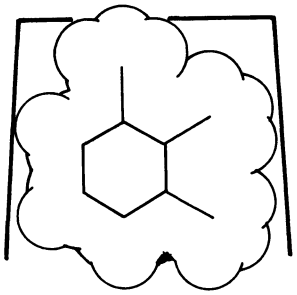

Fig. 11. 1,2,3-Trimethylbenzene-γ-CyD inclusion model.

short or too far to form hydrogen bonding or the axis along the cavity is not coincident with each CyD. (D) Guests come into contact with the wall of host as to increase contact area or to be included by host as deeply as possible. (E) The cavity size of β-CyD is a little small to include two adjacent methyl groups together. (F) The cavity size of γ-CyD is a little small to include adjacent three or alternate two methyl groups together.

For benzene and three straight-chain alkylbenzenes, $-\Delta G_{complex}$ increases almost linearly with $-\Delta G_{dehyd}$ for α-CyD (Fig. 4). The linear relationship is not so good for γ-CyD, but isopropylbenzene-γ-CyD showed a line in Fig. 6. For α-CyD, propylbenzene is far from the straight line as shown in Fig. 5, though the isomer falls on the line. These observations can be explained in terms of the host-guest spatial fitting. α-CyD accepts *n*-propyl group within the cavity, but is incapable of including bulky isopropyl group. Isopropyl group, on the other hand, can be accepted within cavities of β- and γ-CyD, which are large enough to accept the *n*-propyl group, but they are so shallow that only a part of benzene ring of propylbenzene is included; γ-CyD seems to exert less critical effect on isomeric propyl groups than does β-CyD because of its sufficiently large cavity size.

Among three trimethylbenzenes, 1,3,5-isomer exhibits an extremely low K_1 for β-CyD, while 1,2,3-isomer exhibits a large K_1 for γ-CyD. These observations can also be explained by the steric viewpoint. Two bulky methyl groups in 1,3,5-isomer hinder this guest from entering deeply into the cavity of β-CyD; *m*-xylene enters more deeply into β-CyD due to the lack of another methyl group in meta-position. For γ-CyD this steric hindrance of 1,3,5-isomer seems to operate to a less extent. The inclusion model illustrated in Fig. 11 may account for the extremely high *K* value observed for 1,2,3-isomer-γ-CyD; a large van der Waals stabilization works in this case.

The host-guest spatial fitting and the hydrophobicity of guest will be a useful guide to understand formation constants. There are, however, some host-guest combinations difficult to be interpreted. In view of hydrophobicity, *o*-xylene, 1,2,4- and 1,2,3-trimethylbenzene seem to exhibit large K_1 for three CyDs. For γ-CyD, favorable fitting may be responsible as mentioned above, but it is difficult to explain for α- and β-CyD on the same basis. β-CyD as well as α-CyD cannot include two adjacent methyl groups together, then both hosts will come into contact with these guests preferentially on the opposite site of methyl groups. Of the host-guest combinations studied in this work, two are most difficult to interpret. For α-CyD, *m*-xylene complex gave K_1 and K_2, whereas only K_1 was observed for 1,3,5-trimethylbenzene. For γ-CyD, K_1 of *p*-xylene was extraordinarily small.

Spatial fitting will contribute to van der Waals stabilization and hydrophobicity to driving force of complexation, but they don't give satisfactory explanation of the measured formation constants. Other possible energy factors, as Tabushi et al. have pointed out in their theoretical considerations,[10] and motional freedom of host, guest, and water molecules should be taken into account.

References

1) M. Hoshino, M. Imamura, K. Ikehara, and T. Hama, *J. Phys. Chem.*, **85**, 1820 (1981).
2) E. E. Tucker and S. D. Christian, *J. Am. Chem. Soc.*, **106**, 1942 (1984).
3) I. Sanemasa, Y. Nishimoto, A. Tanaka, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **59**, 1459 (1986).
4) I. Sanemasa, Y. Nishimoto, A. Tanaka, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, **59**, 2269 (1986).
5) I. Sanemasa, M. Araki, T. Deguchi, and H. Nagai, *Bull. Chem. Soc. Jpn.*, **55**, 1054 (1982).
6) To be published.
7) S. Hamai, *Bull. Chem. Soc. Jpn.*, **55**, 2721 (1982).
8) K. A. Connors and D. D. Pendergast, *J. Am. Chem. Soc.*, **106**, 7607 (1984).
9) K. Uekama, M. Otagiri, Y. Kanie, S. Tanaka, and K. Ikeda, *Chem. Pharm. Bull.*, **23**, 1421 (1975).
10) I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura, *J. Am. Chem. Soc.*, **100**, 916 (1978).
11) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).
12) W. Saenger, *Angew. Chem., Int. Ed. Engl.*, **19**, 344 (1980).
13) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag, New York (1978).
14) G. Némethy and H. A. Scheraga. *J. Chem. Phys.*, **36**, 3401 (1962).
15) W. C. Cromwell, K. Byström, and M. R. Eftink, *J. Phys. Chem.*, **89**, 326 (1985).