1246 © *1990 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn., 63, 1246—1248 (1990)* [Vol. 63, No. 4

Association of Halobenzenes 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 November 27, 1989)

Synopsis. The complex formation of cyclodextrin (CyD) with fluoro-, chloro-, bromo-, and iodobenzene has been studied in aqueous medium at 25 °C. It was found that van der Waals force is the main factor to stabilize the complex. Formation constsnts for α- and β-CyDs increase with the size of halogen atom, while those for γ-CyD are almost independent of the size.

We have proposed a method which can determine the association constants in the aqueous medium between volatile and nonvolatile solutes.[1] The method is based on the fact that the rate of transfer of the volatile solute from aqueous into gaseous phase decreases with its increasing association with nonvolatile solutes present in the aqueous medium. In this work, halobenzenes have been chosen as volatile guests and α-, β-, and γ-cyclodextrins (CyDs) are used as nonvolatile hosts.

Although the complex formation of α-CyD with *p*-dihalobenzenes has been reported,[2] there are no literature data published on halobenzenes. The halogen atoms have some regularity in their physicochemical properties such as the van der Waals radius, electronegativity, and affinity for solvent water. It is interesting to examine how the CyD complex formation changes with different halogenated benzenes and what physicochemical property of the guest molecule is the major factor governing the association with a given CyD.

Experimental

Materials and Preparation of Sample Solutions. Distilled deionized water was used throughout the experiments. Cyclodextrins (α-, β-, and γ-CyD), fluorobenzene (Nakarai Chemicals Co.), chlorobenzene, bromobenzene (Wako Pure Chemicals Co.), and iodobenzene (Tokyo Kasei Co.) were all of analytical reagent grade and used as received. An aqueous stock solution of each guest was prepared by adding an excess of each halobenzene to water and stirring for at least 24 h in the dark. After standing the mixture 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. Each guest concentration of the saturated aqueous solution at 25 °C in mol dm^{-3} (M), 1.55×10^{-2} (fluorobenzene), 4.22×10^{-3} (chlorobenzene), 2.69×10^{-3} (bromobenzene), and 1.01×10^{-3} (iodobenzene), was in good agreement with the literature value.[3]

A suitable portion of the saturated guest solution was transferred into a $2.5\phi\times25$ 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 was then diluted to 80 cm^3 with water. 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 the previous paper.[1] Nitrogen gas was blown into the aqueous guest solution with or without CyD placed in the cylindrical glass tube immersed in a bath thermostated at 25.0±0.1 °C, at the following constant flow rate (in parentheses, $\times$cm^3 min^{-1}) suitable for each guest volatility: fluoro- and chlorobenzene (30), bromobenzene (50), and iodobenzene (200). The N_2 gas leaving the sample solution was passed through a glass column of $0.5\phi\times23$ cm filled with XAD-2 resin beads (80—150 mesh) of 8 cm in length. The guest adsorbed on the resin within a fixed time was eluted out with cyclohexane of 4 cm^3, and the amount of guest, ΔQ_ϕ, was determined by UV absorption measurements at the following wavelength (nm): fluorobenzene (266.5), chloro- and bromobenzene (264), and iodobenzene (257).

Results

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

$$\begin{aligned}\ln(C_\phi - Q_\phi V^{-1}) &= -kt/(1+K_1C_{\mathrm{CyD}}+K_1K_2C^2_{\mathrm{CyD}})+\ln C_\phi\\ &= -k't+\ln C_\phi,\end{aligned} \tag{1}$$

where C_{CyD} and C_ϕ refer to the total concentration of host and that of guest, respectively, V is the volume of the aqueous solution, k is the rate constant for transfer of guest molecules from aqueous to gaseous phase, and

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

Rearrangement of Eq. 2 yields:

$$1/k' = K_1K_2C^2_{\mathrm{CyD}}/k + K_1C_{\mathrm{CyD}}/k + 1/k. \tag{3}$$

The plots according to Eq. 1 for all the haloben-

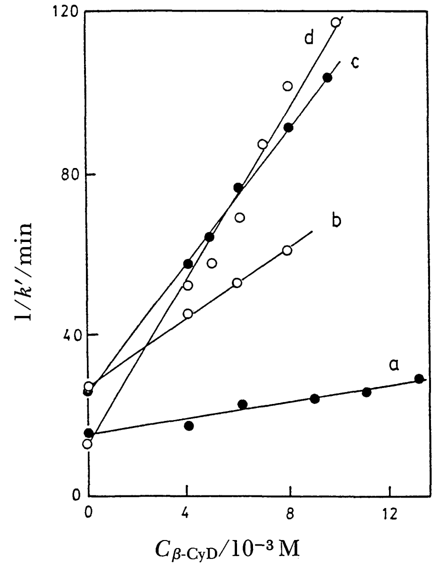

Fig. 1. The plots of $1/k'$ vs. C_{CyD}. β-CyD-fluorobenzene (a), -chlorobenzene (b), -bromobenzene (c), -iodobenzene (d).

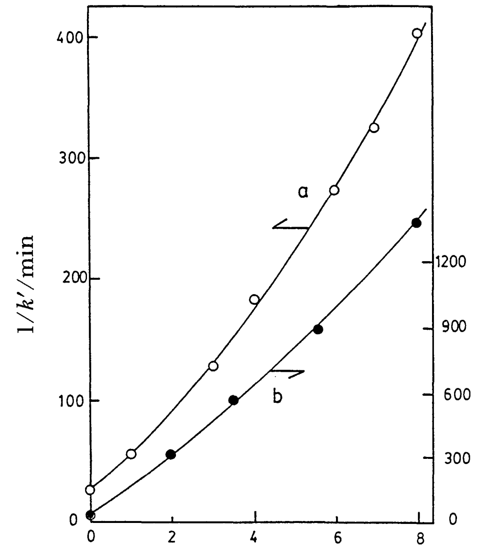

Fig. 2. The plots of $1/k'$ vs. C_{CyD}. α-CyD-chlorobenzene (a), -bromobenzene (b).

zene-CyD systems examined gave straight lines over the whole aeration time. Slopes of the resulting straight lines, k'(and k), were evaluated by using the least squares method. Typical $1/k'$ vs. C_{CyD} plots are shown in Figs. 1 and 2. The plots appeared to be linear for β- and γ-complexes, whereas those for α-complexes curved upward. The K_1 and K_2 values were determined by the curve-fitting method and are summarized in Table 1.

Upon addition of γ-CyD to guest aqueous solutions, both in relatively high concentrations, the aqueous phase became turbid due to the deposition of CyD. Except for the fluorobenzene system, where the turbidity was not observed, the guest and γ-CyD concentrations were set relatively low.

Discussion

The hydrogen bonding, van der Waals forces, and hydrophobic interaction are generally accepted to be responsible for bonding of guest molecules to CyD cavity. Of these, the first does not seem to play an important role in the present host-guest systems, because fluorobenzene, which contains the most electronegative fluorine atom among the halogens, forms the least stable complexes with three different CyDs, compared with other guests. In general, the guest molecule with an electronegative atom or group is likely to associate with CyD by hydrogen bonding to one of the hydroxyl groups of the CyD periphery.

The hydrophobicity of the guest is an important factor in estimating the contribution of hydrophobic interaction. We have proposed in the preceding papers,[1] that the most suitable parameter of hydrophobicity for volatile solutes is the Henry's law constant, K_{H}, which is defined as $K_{\mathrm{H}}=p/X$, where p is the partial vapor pressure of the solute and X is the mole fraction solubility of the solute in water. The K_{H} value is a measure how easily the solute is transferred from aqueous to gaseous phase; a solute with larger K_{H} is more hydrophobic. The K_{H} values at 25 °C are estimated to be 3.62, 2.11, 1.13, and 0.72×10^7 Pa for fluoro-, chloro-, bromo-, and iodobenzene, respectively. The free-energy change derived from Henry's law constant, $\Delta G_{\mathrm{dehyd}}$ ($=-RT\ln K_{\mathrm{H}}$), involves the energy change during a guest molecule is transferred from the aqueous environment to CyD cavity, accompanied by redistribution of the water molecules surrounding the guest. The energy change of this process is usually difficult to estimate accurately by

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	
	C_{ϕ}[a)]	C_{CyD}[b)]	K_1	K_2[c)]
	10^{-4} M	10^{-2} M	M^{-1}	M^{-1}
Fluorobenzene:				
α-CyD	2.67—2.83	4.00 —9.98	34±1	1.7±0.4
β-CyD	2.60	0.402—1.31	70±30	—
γ-CyD	2.49—2.76	1.00 —5.01	14±6	—
Chlorobenzene:				
α-CyD	11.0	1.00 —8.03	$(1.0\pm0.1)\times10^2$	8±4
β-CyD	11.0	0.402—0.801	$(1.6\pm0.1)\times10^2$	—
γ-CyD	8.14—8.54	0.501—0.796	33±2	—
Bromobenzene:				
α-CyD	9.80—13.3	2.00 —8.00	$(5.1\pm0.1)\times10^2$	3.1±0.2
β-CyD	10.2	0.401—0.957	$(3.1\pm0.2)\times10^2$	—
γ-CyD	3.47	0.603—0.798	39±8	—
Iodobenzene;				
α-CyD	1.82—2.78	2.00 —9.97	$(1.1\pm0.1)\times10^3$	1±5
β-CyD	1.82—2.80	0.401—1.00	$(8.0\pm1.0)\times10^2$	—
γ-CyD	1.82—2.84	0.403—1.00	30±10	—

a) The total 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 gave a nearly straight line.

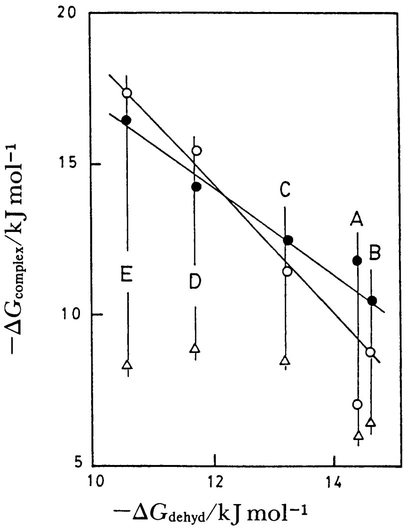

Fig. 3. Free-energy changes of CyD-guest complexation, $\Delta G_{\mathrm{complex}}$ ($=-RT\ln K_1$), and that of dehydration, $\Delta G_{\mathrm{dehyd}}$ ($=-RT\ln K_{\mathrm{H}}$) of guest. Host: α-CyD (○), β-CyD (●), γ-CyD (△), guest: benzene (A), fluorobenzene (B), chlorobenzene (C), bromobenzene (D), iodobenzene (E).

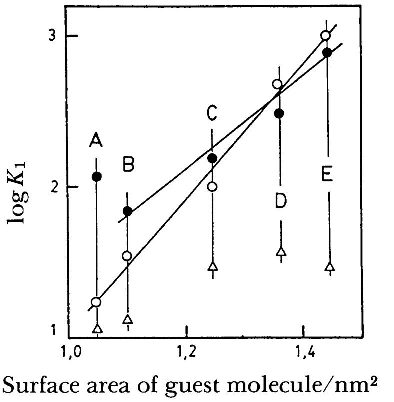

Fig. 4. The dependence of association constant on the surface area of guest molecule. The signs and symbols are the same as those shown in Fig. 3.

theoretical approaches.

The free-energy change in the 1 : 1 complex formation, $\Delta G_{\mathrm{complex}}$ ($=-RT\ln K_1$), is plotted against $\Delta G_{\mathrm{dehyd}}$ in Fig. 3. For the guest substances studied here, hydrophobic interaction as a driving force of CyD complex formation is not significant, because $-\Delta G_{\mathrm{complex}}$ does not increase with $-\Delta G_{\mathrm{dehyd}}$, but the situation is just the reverse. Van der Waals force seems to govern the present host-guest system. The plots of $\log K_1$ vs. the total surface area of associating guest are shown in Fig. 4. Nearly linear relationships can be seen for α- and β-CyD-halobenzene systems. For γ-CyD, on the other hand, the increase in the guest surface area does not considerably contribute to the stabilization, probably because the cavity of this host is too large to suitably accomodate halobenzene molecule.

The α-CyD cavity is too small to accept the guest molecule as a whole, and two α-CyD associate with the halobenzene at different sites. Taking into account that the association constant K_1 varies to a great extent with the kind of halogen atom and K_2 is almost independent of the guest, we assign the site corresponding to K_1 to halogen atom.

References

1) I. Sanemasa and Y. Akamine, *Bull. Chem. Soc. Jpn.*, **60**, 2059 (1987) and I. Sanemasa, T. Takuma, and T. Deguchi, *ibid.*, **62**, 3098 (1989).

2) K. A. Connors and D. D. Pendergast, *J. Am. Chem. Soc.*, **106**, 7607 (1984).

3) A. L. Horvath, "IUPAC Solubility Dats Series, Vol. 20," ed by A. L. Horvath and F. W. Getzen, Pergamon, Oxford (1985), (halogenated hydrocarbons), and R. J. Baker, B. J. Donelan, L. J. Peterson, W. E. Acree Jr., and C.-C. Tsai, *Phys. Chem. Liq.*, **16**, 279 (1987).