Association of Cycloalkanes with Cyclodextrins in Aqueous Medium

Tomonori Osajima, Toshio Deguchi, and Isao Sanemasa*
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami 2-39-1,Kumamoto 860

(Received April 15, 1991)

The complex formation of α-, β-, and γ-cyclodextrins (CyDs, hosts) with five cycloalkanes (guests), cyclo(pentane, hexane, heptane, octane, and decane), has been studied in aqueous media at 25 °C by making use of the volatilization rate of guest molecules from the aqueous into gas phase. In the excess of the host, α-CyD forms both 1 : 1 and 2 : 1 (host : guest) complexes, while β- and γ-CyDs form 1 : 1 complexes with an exception that β-CyD forms a 2 : 1 complex with cylodecane. The 2 : 1 complex formation constants of α-CyD with cyclo(hexane, heptane, octane, and decane), particularly with cyclooctane, are extremely large compared with their 1 : 1 formation constants. The host–guest spatial fitting models are proposed.

We studied host–guest associations using α-, β-, and γ-cyclodextrins (CyDs) as hosts and C_5—C_9 normal alkanes as guests.[1)] The results are summarized as follows.

With an increase in the chain length of alkane, both 1 : 1 and 2 : 1 (host–guest) formation constants for three CyDs increase; in the case of α-CyD, the 1 : 1 formation constant is saturated at C_8. The cross section diameter of an alkane molecule being close to that of α-CyD cavity (5 Å), the guest molecule is assumed to be included in α-CyD along the fully extended alkyl chain. Relatively large formation constants of β-CyD indicate that the cavity diameter of β-CyD (6.9 Å) is sufficiently large to allow a conformational change of the guest alkyl chain so that the guest molecule contacts favorable with the cavity wall. In view of the large cavity diameter (8.5 Å), γ-CyD might form much weaker complexes with alkanes. Contrary to this expectation, however, the formation constants with shorter-chain alkanes are comparable to α-CyD complexations and those with longer-chain alkanes are comparable to β-CyD complexations. In order to rationalize these observations, we made two hypotheses: (1) a flexible conformation of alkyl chain to get contact as widely as possible with the γ-CyD cavity wall and (2) γ-CyD accepts a guest molecule without releasing water molecules originally present in the cavity.

In the present work, cycloalkanes of C_5 to C_8 and C_{10} have been used as guests. These guest molecules, compared to normal alkanes, are more bulky and more rigid. The cavity of α-CyD is too small to include even a cyclopentane molecule as a whole, while, if the guest takes a suitable puckered ring conformation, β-, and γ-CyDs can accept a cycloalkane molecule of fairly large ring. The object of this study is to elucidate the relationship between the guest size and the stability of CyD complexes.

In analytical chemistry, CyDs have been recently used to modify the partition of hydrophobic solutes between organic and aqueous phase.[2)] In the field of organic syntheses, water-insoluble CyD derivatives are used in organic solvents.[3)] Since cycloalkanes are of common choise as organic solvents, the knowledge of their associations with CyDs is required. There are, nevertheless, few data available concerning the host–guest systems. Cyclohexane–α-, and -β-CyD systems have been so far studied by solubility measurements.[4)] The method used in this work to determine the association constant is the same as that employed in our previous works.[1,5)]

Experimental

Deionized distilled water was used throughout the experiments. An appropriate amount of α-, β-, and γ-CyDs of guaranteed grade (Nacalai Chemical Co.), dried over phosphorus pentoxide under vacuum, was weighed and dissolved in water to prepare CyD stock solutions of desired concentrations. Five guest substances were used as received; cyclopentane (Nacalai Chemical Co., 98%), cyclohexane (Wako Pure Chemical Co., 99.5%), cycloheptane (Tokyo Kasei Kogyo Co., 98%), cyclooctane (Nacalai Chemical Co., 99%), and cyclodecane (Aldrich, the purity is not specified).

The same device described in the previous paper,[1)] was used to prepare aqueous solutions saturated with cycloalkane and to vaporize the guest with a nitrogen gas stream. Depending on the volatility of the guest, the N_2 gas flow rate was adjusted constant at 20 (cyclopentane) to 100 $cm^3\ min^{-1}$ (cyclodecane). As was described previously,[1)] the vaporized guest was collected with Tenax GC resin, determined by gas chromatography, and the ammount of guest vaporized during a definite time, ΔQ_ϕ, was calculated.

The concentration of cycloalkane in the saturated aqueous solution was not determined in this work; the data were taken from the literature.[6)] The concentrations of hosts and guests employed in the present study are given in Table 1.

Results and Discussion

Association Constants. The 1 : 1 and 2 : 1 (host : guest) association constants, K_1 and K_2, were estimated using an equation derived in the previous paper:[5)]

$$\begin{aligned}\ln(C_\phi - Q_\phi V^{-1}) &= -kt/(1+K_1 C_{\mathrm{CyD}} + K_1 K_2 C^2{}_{\mathrm{CyD}}) + \ln C_\phi \\ &= -k't + \ln C_\phi, \qquad (1)\end{aligned}$$

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

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

Rearrangement of Eq. 2 yields

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

The plots according to Eq. 1 for all the cycloalkane–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. The 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 exhibit upward curvatures for α-CyD complexations with the cycloalkanes studied here and for the β-CyD–cyclodecane system, indicating the formation of both 1 : 1 and 2 : 1 (host–guest) complexes. The plots for the other host–guest systems are linear, supporting the formation of 1 : 1 complexes. The K_1 and K_2 values were determined by the curve-fitting method and are summarized in Table 1.

Wishnia and Lappi reported K_1 of 4.2×10^2 $\mathrm{M^{-1}}$ (1 M=1 mol $\mathrm{dm^{-3}}$) and K of 5.3×10^3 $\mathrm{M^{-1}}$ at 25 °C for cyclohexane–α- and β-CyDs, respectively.[4] The cavity of α-CyD is too small to include completely any cycloalkane molecule studied in this work; even cyclopentane has a diameter of ca. 6 Å. In this view, the literature K_1 value of cyclohexane seems too large. Matsui and Mochida studied associations of various alcohols with α- and β-CyDs.[7] Their 1 : 1 association constants of cyclopentanol, cyclohexanol, cycloheptan-

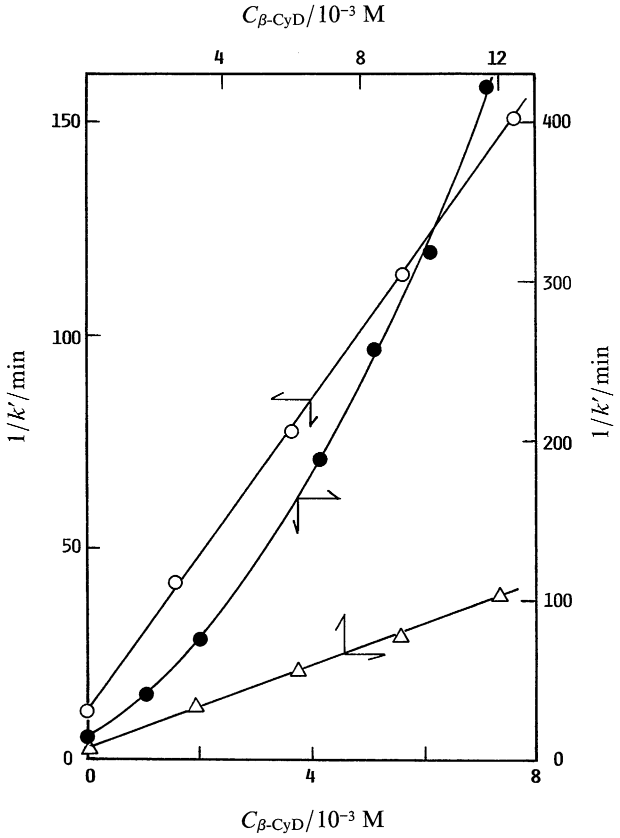

Fig. 2. Plots of $1/k'$ vs. $C_{\beta\text{-CyD}}$. Cycloheptane (△), cyclooctane (○), cyclodecane (●).

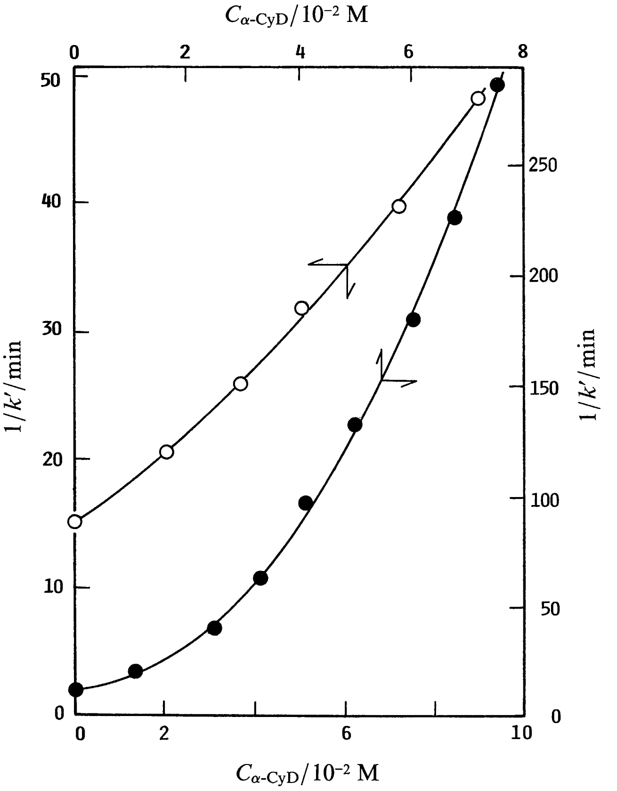

Fig. 1. Plots of $1/k'$ vs. $C_{\alpha\text{-CyD}}$. Cyclopentane (○), cyclohexane (●).

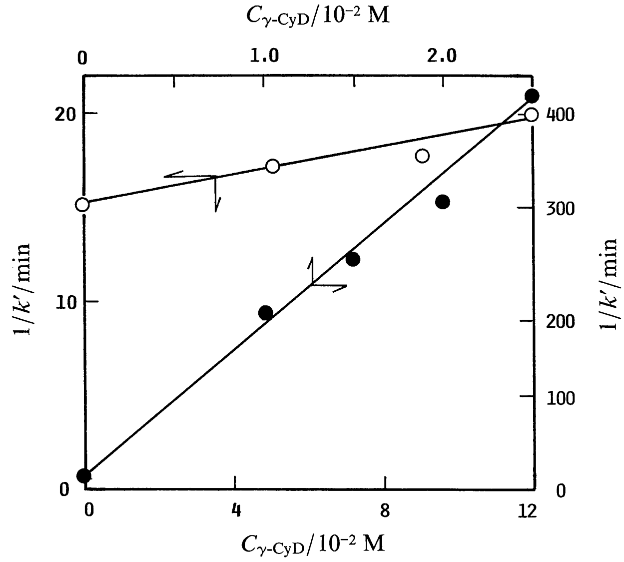

Fig. 3. Plots of $1/k'$ vs. $C_{\gamma\text{-CyD}}$. Cyclopentane (○), cyclodecane (●).

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

	$C_{\mathrm{CyD}}$$^{a)}$	Formation constant	
		K_1	$K_2$$^{b)}$
	10^{-2} M	M^{-1}	M^{-1}
Cyclopentane: $C_\phi$$^{c)}$$=2.80\times10^{-5}$ M			
α-CyD	2.01 —9.01	18±1	4±2
β-CyD	0.405—1.41	90±20	—
γ-CyD	5.01 —12.0	3±1	—
Cyclohexane: $C_\phi$$^{c)}$$=4.13\times10^{-5}$ M			
α-CyD	1.05 —7.51	9±3	$(6.0\pm2.0)\times10^2$
β-CyD	0.623—1.41	156±8	—
γ-CyD	4.01 —9.90	11±3	—
Cycloheptane: $C_\phi$$^{c)}$$=3.86\times10^{-5}$ M			
α-CyD	0.502—4.01	20±8	$(9.0\pm5.0)\times10^2$
β-CyD	0.310—1.20	$(7.4\pm0.3)\times10^2$	—
γ-CyD	2.50 —7.49	16±2	—
Cyclooctane: $C_\phi$$^{c)}$$=3.54\times10^{-5}$ M			
α-CyD	0.506—2.00	0.6±0.2	$(7.0\pm2.0)\times10^4$
β-CyD	0.154—0.758	$(1.7\pm0.1)\times10^3$	—
γ-CyD	1.01 —5.01	70±20	—
Cyclodecane: $C_\phi$$^{c)}$$=3.54\times10^{-5}$ M			
α-CyD	0.514—2.51	$(1.8\pm0.4)\times10^2$	$(3.1\pm0.8)\times10^2$
β-CyD	0.102—0.717	$(1.62\pm0.07)\times10^3$	$(2.1\pm0.3)\times10^2$
γ-CyD	1.01 —2.50	$(1.1\pm0.1)\times10^3$	—

a)Total concentration of cyclodextrin. b) Dash sign indicates that K_2 was not evaluated, because $1/k'$ vs. C_{CyD} plots gave a nearly straight line. c) Initial concentration of guest after being mixed with CyD aqueous solution.

ol, and cyclooctanol are 45.7, 64.6, 79.4, and 178 M^{-1} with α-CyD, 120, 501, 1700, and 2000 M^{-1} with β-CyD, respectively. The literature values of cycloalkanols are considerably larger than the present cycloalkane–α-CyD data, but well comparable to the cycloalkane–β-CyD data. The hydroxyl group of alcohols has a potential ability to bind through hydrogen bonding with primary or secondary OH groups on the rims of CyD molecule or with glycosidic oxygens that constitute the cavity.

Association Model. It is difficult to explain our extraordinarily large K_1 value observed for the cyclodecane–α-CyD system. A plausible explanation is that the high flexibility of the large ring allows the molecule to take such a conformation that a part of the ring, which can be inserted more deeply into the α-CyD cavity, is formed more easily. While the K_1 values of cyclohexane, cycloheptane, and cyclooctane are small, their K_2 values are extremely large. Cromwell et al. suggested that if K_2 is larger than K_1, the cross-section of secondary hydroxyl group sides of two CyDs are situated parallel to each other in a suitable distance to form hydrogen bond.[8] Taking cyclohexane as an example, the 2 : 1 (host : guest) association model is depicted in Fig. 4(A). Two α-CyDs, including in their cavities a part of the cycloalkane ring, ($-CH_2-CH_2-$), attach to the guest molecule from the oposite side. The magnitude of K_2 depends on the distance between the two CyDs to cooperate with each other to form hydrogen bonds; the distance may be too short for cyclopentane and may be a little long for cyclodecane (the K_2 of cyclodecane is larger than its K_1, but smaller than the K_2 of cyclooctane, cycloheptane, or cyclohexane). It is noteworthy that

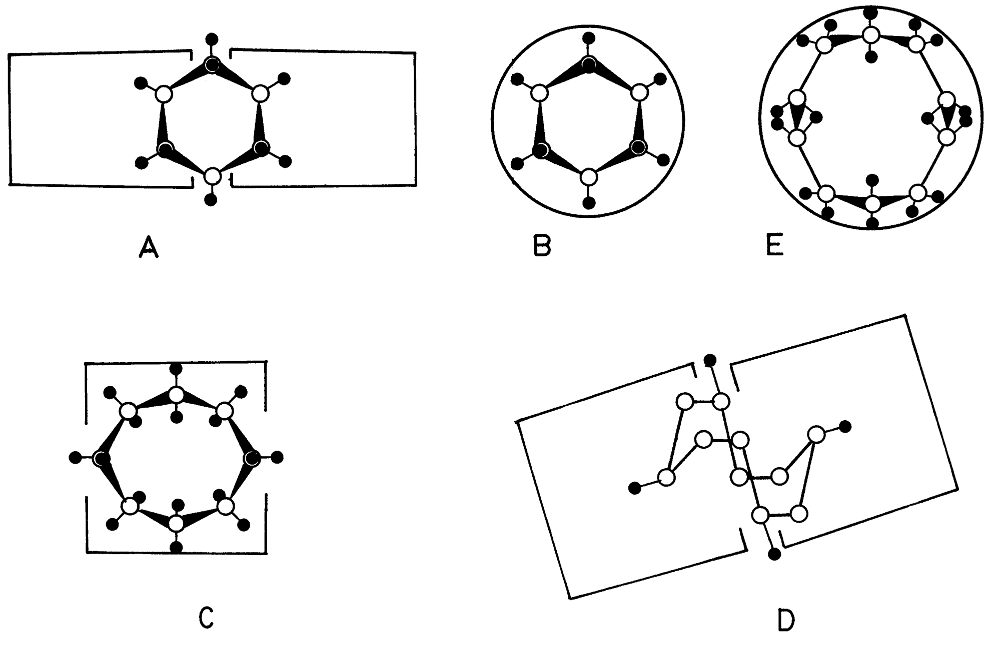

Fig. 4. Inclusion model. A: α-Cyclohexane; B: β-cyclohexane (cross section); C: β-cyclooctane; D: β-cyclodecane; E: γ-cyclodecane (cross section).

the K_2 of cyclooctane is larger by about two orders of magnitude than that of C_6, C_7, or C_{10} cycloalkane; the distance between the two α-CyDs sandwiching a cyclooctane molecule may be most suitable among the cycloalkanes studied to form hydrogen bonds.

Wishnia and Lappi presented a model of association of chair cyclohexane, which has a diameter of 7.0 Å and a thickness of 4.7 Å, with β-CyD.[4] Their model is shown in Fig. 4(B); the guest is best fitted by its periphery with the inner wall of the host cavity. This association mode, however, cannot be applied to the guests of ring size larger than cyclohexane. For these guests, we speculate that the guest enters the host cavity with the ring-planes of both host and guest perpendicular to each other. The association model considered to be reasonable for cyclooctane is shown in Fig. 4(C). The oblate ellipsoid of this guest has a diameter of 7.3 and 8 Å. The diameter of 7.3 Å is a little larger than that of β-CyD cavity employed in this study, but the cavity size itself is still uncertain; ranging from 4.5 to 6.0 Å (α-CyD), from 6.0 to 8.0 Å (β-CyD), and from 8.0 to 10.0 Å (γ-CyD).[9] Cyclodecane has a diameter of 7.6 (the minor axis) and 8.3 Å (the major axis), that is a little larger than the corresponding value of cyclooctane. Cyclodecane can also enter fully the β-CyD cavity, if we employ the larger cavity size, along the longer axis of the guest molecule. It is noteworthy that cyclodecane forms a 2:1 complex. This observation cannot be explained by a simple consideration that the length of the longer axis of cyclodecane exceeds the cavity depth (the cavity is 7 Å deep irrespectively of the type of CyD), because this is also the case for cyclooctane. We speculate, therefore, that the diameter of the shorter axis of cyclodecane is a littile larger than that of β-CyD so that a complete inclusion by the host is inhibited. The 2:1 (β-CyD : cyclodecane) association model is depicted in Fig. 4(D).

The cavity diameter of γ-CyD is sufficiently large to accept any cycloalkane studied in this work. If we adopt 8.5 Å for the host diameter, a cyclodecane molecule is snugly fitted in the host cavity with the ring-planes of both host and guest parallel to each other, as illustrated in Fig. 4(E).

The Volume of Guest and the Association Constant. In preceding studies on associations of CyDs with polynuclear aromatic hydrocarbons,[10] halogenated benzenes,[11] normal alkanes,[1] we pointed out that there is a linear relationship between the total surface area of guest and log K_1. In the case of cycloalkane, the volume of a guest molecule is a better parameter to judge the host–guest fitness, because the part inside the ring of the guest molecule does not take part in the contact with the host cavity wall. Taking the molar volume of cycloalkane from the literature,[12] the plots are shown in Fig. 5. There is no linear relationship for α-CyD, indicating that a cycloalkane molecule is not included as a whole in this host cavity. For β- and γ-CyDs, on the other hand, good linear relationships are observed. In the case of β-CyD, the inclusion is saturated at cyclooctane. The volume inside the host cavity is 150 (α), 270 (β), and 400 Å³ (γ).[8] In this view, the saturation phenomenon should occur at cyclodecane. Cyclodecane, however, due to the steric hindrance, does not seem to be fully included in the cavity of β-CyD; this is a reasonable explanation why the cylodecane–β-CyD system forms a 2:1 complex. In Fig. 5 are also plotted association constants of cycloalkanol–β-CyD systems taken from the literature,[7] against the molar volume of cycloalkane on the assumption that β-CyD includes only the ring part of a cycloalkanol molecule. It is noteworthy that the plot is almost paralell to that of the cycloalkane –β-CyD system. A slight stabilization observed for cycloalkanols is probably due to their hydrogen bonding with the periphery of β-CyD.

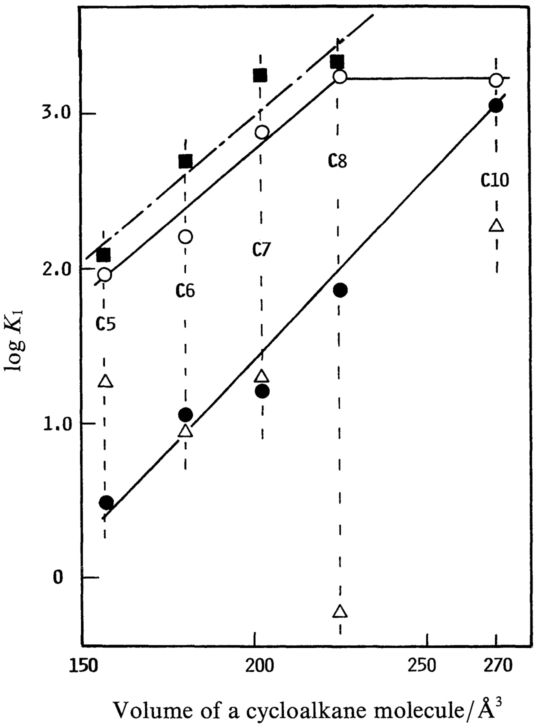

Fig. 5. Dependence of association constant on the volume of a cycloalkane molecule. Cycloalkane–α-CyD (△), –β-CyD (○), –γ-CyD (●), Cycloalkanol–β-CyD (■) (Ref. 7).

Normal and Cycloalkanes. It is interesting to note that, in the complex formation with γ-CyD, the K of a cycloalkane is almost comparable to that of a normal alkane of the same carbon number. This supports one of the hypotheses proposed in our preceding paper.[1] Namely, an alkyl chain takes a herix-coil conformation in the cavity of γ-CyD to get contact as widely as possible with the cavity wall; the cross section of the helix-coil conformation resembles a cycloalkane molecule., With the present study, we reject another hypothesis that takes into account the presence of water in the host cavity. As for β-CyD, the space inside the cavity is not so large as to allow for an alkyl chain to take a cycloalkane-like arrangement.

References

1) I. Sanemasa, T. Osajima, and T. Deguchi, *Bull. Chem. Soc. Jpn.,* **63**, 2814 (1990).

2) K. Matsunaga, M. Imanaka, T. Ishida, and T. Oda, *Anal. Chem.,* **56**, 1980 (1984); L. A. Blyshak, T. M. Rossi, G. Patonay, and I. M. Warner, *ibid.,* **60**, 2127 (1988).

3) M. Komiyama, H. Yamamoto, and H. Hirai, *Chem. Lett.,* **1984**, 1081.

4) A. Wishnia and S. J. Lappi, *J. Mol. Biol.,* **82**, 77 (1974).

5) I. Sanemasa and Y. Akamine, *Bull. Chem. Soc. Jpn.,* **60**, 2059 (1987).

6) A. S. Kertes, "IUPAC Solubility Data Series," ed by D. G. Shaw, Pergamon, Oxford (1989), Vols. 37 and 38.

7) Y. Matsui and K. Mochida, *Bull. Chem. Soc. Jpn.,* **52**, 2808 (1979).

8) W. C. Cromwell, K. Byström, and M. R. Eftink, *J. Phys. Chem.,* **89**, 326 (1985).

9) G. Nelson, G. Patonay, and I. M. Warner, *Anal. Chem.,* **60**, 274 (1988).

10) I. Sanemasa, T. Takuma, and T. Deguchi, *Bull. Chem. Soc. Jpn.,* **62**, 3098 (1989).

11) T. Takuma, T. Deguchi, and I. Sanemasa, *Bull. Chem. Soc. Jpn.,* **63**, 1246 (1990); *ibid.,* **64**, 480 (1991).

12) C. McAuliffe, *J. Phys. Chem.,* **70**, 1267 (1966).