2814 © *1990 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, *63*, *2814—2819 (1990)* [Vol. 63, No. 10

Association of C_5—C_9 Normal Alkanes with Cyclodextrins in Aqueous Medium

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(Received May 7, 1990)

The complex formation of cyclodextrin (CyD, host) with C_5 to C_9 normal alkanes (guests) has been studied in aqueous medium at 25 °C by making use of the volatilization rate of alkane molecules from aqueous into gaseous phase. In the excess of the host, β- and γ-CyDs form 1 : 1 complexes, while α-CyD forms 1 : 1 and 2 : 1 (host : guest) complexes. With an increase in the chain length of alkane, association constants for three CyDs increased; in the case of α-CyD, the 1 : 1 association constant for C_9 was identical to that for C_8, while the 2 : 1 association constant continued to increase. The cavity size of CyD, the alkane chain length, and hydrophobicity and surface area of alkane molecules were taken into account to discuss the host-guest inclusion mechanism.

α-, β-, and γ-cyclodextrins(CyDs) are cyclic oligosaccharides consisting of six, seven, and eight glucopyranose units, respectively, with a central cavity of 7 Å deep, almost irrespectively of the type of CyD. While the outside of CyD molecule is hydrophilic, the cavity inside forms a hydrophobic environment, and a variety of molecular species are held as guests in aqueous medium if they suitably fit in the space, making CyD act as a host. Another factor which governs the host-guest association is the guest hydrophobicity: more hydrophobic guest molecules form more stable inclusion complexes with CyDs.

Owing to their amphiphilic character, anionic surfactants with long alkyl chains are suitable guests to study how the polar head and the alkyl tail behave in complexation with CyD. Association constants have been measured mainly by a conductivity technique for surfactants such as alkyl sulfates,[1-4] alkanesulfonates,[3-6] and alkyl carboxylates[7,8] with different alkyl chain lengths. Systematic studies have been also made on aliphatic alcohols to examine the relationship between the chain length and the CyD cavity depth or to elucidate the order of association constants based on thermodynamic parameters.[9-12]

The presence of hydrophilic functional groups in such guests, i.e., polar heads of surfactants and hydroxyl group of alcohols, however, makes it difficult to appreciate unambiguously the contribution of alkyl chain to the host-guest association. These functional groups have 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 at its outside. The hydration cosphere of the hydrophilic functional group of guest molecule may also play a fundamental role in the association with CyDs.

From this point of view, the use of normal alkanes themselves as guests is desirable. Such substances are only sparingly soluble in water and, moreover, volatile. Additionaly, they have neither absorption peaks in the ordinarily accessible ultraviolet region, nor fluorescence. This characteristic of alkanes limits their uses as guests. To our knowledge, there is only one paper dealing with heptane-α- and β-CyD systems.[13] To have better knowledge of the basic relationship between the alkyl chain length and the CyD cavity, systematic studies using a homologous series of alkane are needed.

We have recently proposed a method which can determine the association constants of volatile-nonvolatile solutes in aqueous medium. 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. This technique has been applied to study associations of CyDs with various volatile guests of low aqueous solubility, such as benzene and alkylbenzene,[14] naphthalene and its methyl derivatives,[15] some polynuclear aromatic hydrocarbons,[16] CCl_4, $CHCl_3$, and CH_2Cl_2,[17] and monohalobenzenes.[18]

In this work, we will apply this technique to the study of associations between alkanes of C_5 to C_9 and α-, β-, and γ-CyDs. We are not concerned here with the guests of the C number(n) smaller than 4 and those larger than 10, because the former groups present as gaseous state are difficult to deal with and the latter groups exhibit low solubility in water so that the amount volatilized during a definite aeration time cannot be determined accurately by a GC detector (FID).

Experimental

Deionized distilled water was used throughout the experiments. α-, β-, and γ-CyDs of guaranteed grade and C_5—C_9 alkanes of analytical reagent grade were used as received; CyDs, heptane, and octane were purchased from Nakarai Chemicals Co., pentane and hexane from Wako Pure Chemicals Co., and nonane from Tokyo Kasei Co. A suitable amount of CyD, dried over phosphorus pentaoxide under vacuum, was weighed and dissolved in water to prepare CyD solutions of desired concentrations.

An aqueous solution saturated with each alkane was prepared at 25 °C by a vapor-circulation technique previously described.[19] Since the alkane dissolved in water is highly volatile, we used a device shown in Fig. 1 to prevent

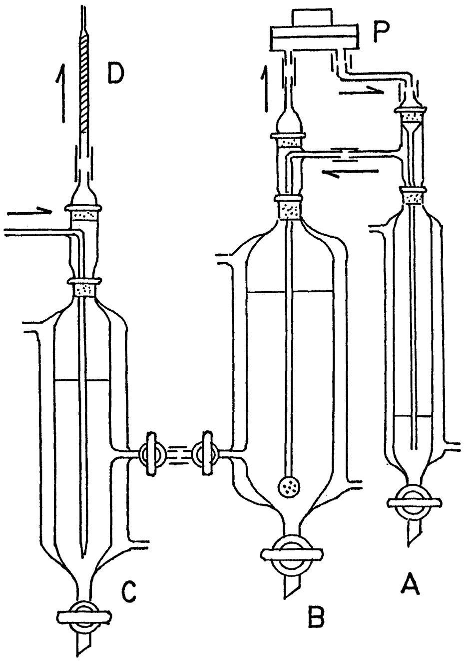

Fig. 1. The device used to prepare aqueous solutions saturated with guest and to volatilize the dissolved guest from aqueous to gaseous phase by nitrogen gas stream.

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

		Formation constant	
	C_{CyD}[a)]	K_1	K_2[b)]
	10^{-2} M	M^{-1}	M^{-1}
Pentane: C_{ϕ}[c)]$=3.36\times10^{-5}$ M			
α-CyD	3.01—12.0	8±1	6±3
β-CyD	0.600—1.39	50±10	—
γ-CyD	7.92—15.8	6.0±0.3	—
Hexane: C_{ϕ}[c)]$=2.20\times10^{-5}$ M			
α-CyD	1.93—9.46	18±3	30±10
β-CyD	0.319—1.19	60±20	—
γ-CyD	3.92—9.46	11±3	—
Heptane: C_{ϕ}[c)]$=1.48\times10^{-5}$ M			
α-CyD	2.21—6.21	37±2	$(1.8\pm0.1)\times10^2$
β-CyD	0.211—0.783	69±4	—
γ-CyD	1.01—6.93	30±9	—
Octane: C_{ϕ}[c)]$=0.958\times10^{-6}$ M			
α-CyD	0.507—3.93	80±10	$(2.2\pm0.5)\times10^2$
β-CyD	0.311—0.996	76±7	—
γ-CyD	0.986—4.89	62±5	—
Nonane: C_{ϕ}[c)]$=0.855\times10^{-6}$ M			
α-CyD	0.500—1.99	80±20	$(5.0\pm1.0)\times10^2$
β-CyD	0.158—0.760	90±20	—
γ-CyD	0.990—2.98	$(1.0\pm0.2)\times10^2$	—

a) The total concentration of cyclodextrin. b) The dash sign indicates that K_2 was not evaluated, because $1/k'$ vs. C_{CyD} plots gave a nearly straight line. c) The initial concentration of guest after mixed with CyD aqueous solution; the guest concentration before mixing was estimated from the aqueous solubility of each guest (Refs. 20, 21).

the loss of alkane during the transfer of the saturated aqueous solution. The alkane vapor in equilibrium with the liquid alkane (placed in A) was introduced into water (in B) and circulated in a closed system using a Viton diaphragm airpump (P). The aqueous phase can thus be saturated with alkane within 1 h without any need to separate the excess solute in the liquid state. A suitable portion of the saturated aqueous solution was transferred into a graduated cylinder (C) through a connecting tube by opening stopcocks. A suitable volume of water or CyD solution was then poured in the cylinder; the total volume was set at 80 cm^3 in most cases.

Nitrogen gas was immediately blown into aqueous guest solution with or without CyD placed in the graduated cylinder thermostated at 25.0±0.1 °C at the following constant flow rate (in parentheses, $\mathrm{cm}^3\,\mathrm{min}^{-1}$) suitable for each guest volatility: pentane (10), hexane, heptane, and octane (20), and nonane (30). The N_2 gas leaving the sample solution was passed through a collector (D) packed with Tenax GC resin beads for a fixed time and the collector was connected with a furnace to analyse by the same way as previously described;[17)] the column temperature was set at 100 °C in this work. The amount of guest collected at definite time intervals, ΔQ_{ϕ}, and that collected during a sufficiently long time to expel almost all guest molecules from sample solutions, Q_{ϕ}, were determined with reference to the chromatogram peak areas.

The concentration of each alkane in the saturated aqueous solution was not determined in this work; the data were taken from the literatures.[20,21)] The concentrations of host and guest employed in the present runs are given in Table 1.

Results and Discussion

Host(α-, β-, and γ-CyDs)-Guest(Alkanes) Association Constants. The equation derived in the previous papers[14,15)] 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 host-guest systems studied in this work gave straight lines over the whole aeration time, during which ca. 70% of the guest molecules present initially in the sample solutions were expelled. 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. 2 and 3. The plots appeared to be linear for β- and γ-CyDs, supporting the formation of 1 : 1 complexes, whereas those for α-CyD curved

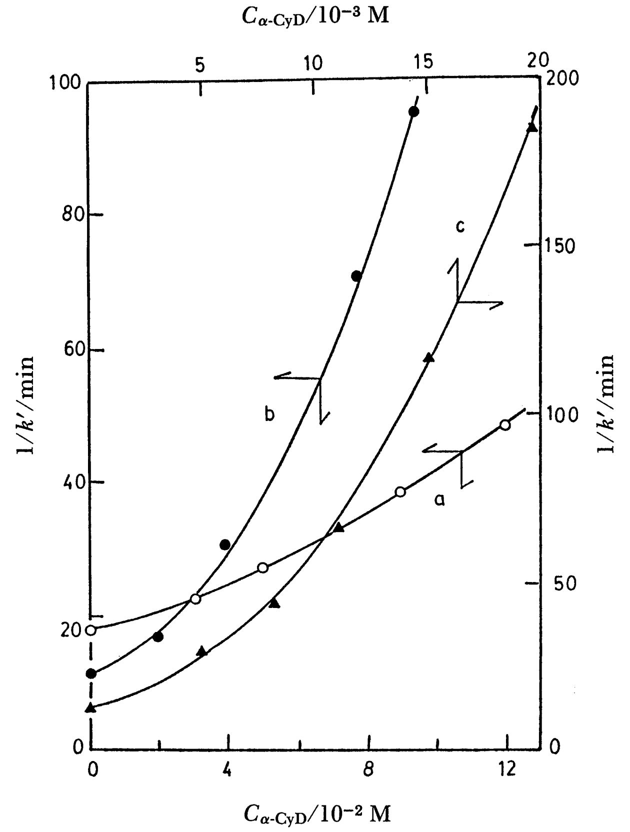

Fig. 2. The plots of $1/k'$ vs. C_{CyD}. α-pentane(a), -hexane(b), -nonane(c).

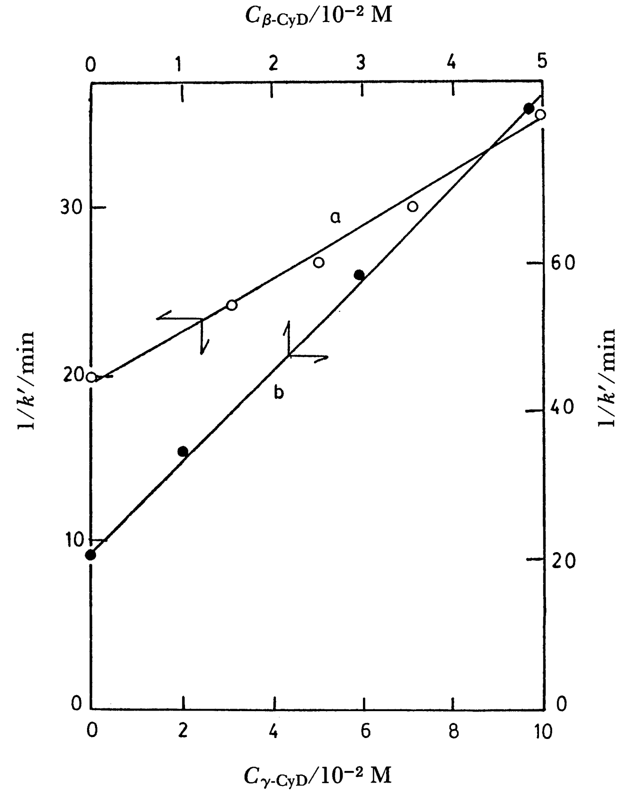

Fig. 3. The plots of $1/k'$ vs. C_{CyD}. Octane-β(a), -γ(b).

upward. This indicates that, two α-CyD molecules associate with one guest molecule under the present experimental conditions that host molecules are always excess over guest molecules.

The K_1 and K_2 values were determined by the curve-fitting method using Eq. 3 and are summarized in Table 1.

The association constants determined in this work are considerably lower than those reported by Wishin and Lappi,[13] who gave K_1 of 5.6×10^3 M^{-1} (1 M=1 mol dm^{-3}) and K of 2.6×10^3 M^{-1} at 25 °C for heptane-α- and β-CyDs, respectively, based on solubility measurements. We have no criterion at the present stage to claim that their values are too large.

The Association Model. In evaluating association constants of surfactants and alcohols with CyDs, some workers have delt with their data on the basis of 1 : 1 stoichiometry irrespective of the type of CyD. On the other hand, there have been reported some experimental evidence indicating that surfactants with varying length of alkyl chain form 1 : 1 complexes with β- and γ-CyDs and that with α-CyD they form 2 : 1 (host : guest) complexes.[2,3,8] The 2 : 1 complex formation for α-CyD is explained by assuming that the polar group of surfactants (sulfate or sulfonate) is accommodated most efficiently by α-CyD to encapsulate the surfactant monomer at both ends with two CyD molecules.[8] This hypothesis seems unreasonable after the present results, because α-CyD forms 2 : 1 complexes with alkanes themselves. Wishnia and Lappi also reported formation of 2 : 1 complex for α-CyD-hexane;[13] their opinion is that the 2 : 1 complexation occurs by the overall process rather than the successive one.

Our present work indicates that K_2 value for the α-CyD complexes increases steeply with increasing alkane chain length. Though we did not examine the guests of n smaller than 4, judging from the decreasing tendency of K_2, we assume that for such short chain guests there is hardly any 2 : 1 complexes with α-CyD. Incidentally, ratios of the ternary to the binary species in an equilibrium at the α-CyD total concentration of 4×10^{-2} mol dm^{-3} are 20, 1.2, and 0.25 for nonane, hexane, and pentane, respectively.

It seems to be reasonable from this study to conclude that the formation of 1 : 1 or 2 : 1 complexes of CyDs with long alkyl-chain guests depends solely on the chain length of alkyl group compared with the CyD cavity depth. In order to show molecular sizes in the relative scale, an alkane molecule with a fully extended chain is depicted in Fig. 4 together with the dimension of each CyD.

The cross section diameter of an alkane molecule (4.5 Å) being close to that of α-CyD cavity (5 Å), we assume that the guest molecule is included in the CyD cavity along the fully extended alkyl chain. The van der Waals radius of C atom, 1.7 Å, being considered, the cavity depth of α-CyD is slightly insufficient to

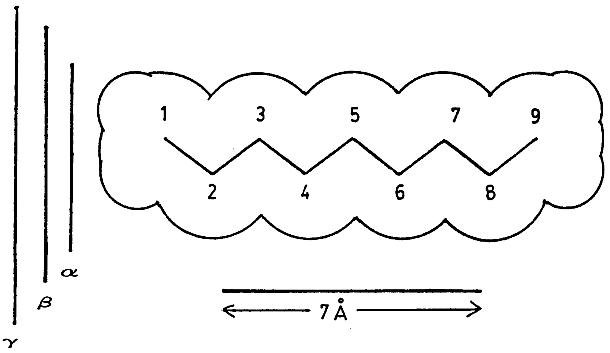

Fig. 4. The relative size of host and guest (octane). Cavity depth: 7 Å (α, β, γ); cavity diameter: 5(α), 6.9(β), 8.5 Å (γ).

include a C_5 molecule as a whole. With increasing n over 6, the part of the guest molecule extruding outside the host cavity becomes larger. From this point of view, the K_1 value for α-CyD will be expected to be saturated at C_5. In reality, the saturation phenomenon for alkanes occurs at C_8. This inconsistency cannot be fully explained. A plausible interpretation is that a margin to some extent may be necessary for the saturation phenomenon to occur. If the depth of α-CyD cavity is considered, nearly midpoints of C_1—C_2 and C_7—C_8 bonds are situated at the both ends of the cavity.

Saturation phenomena of α-CyD complexations were also observed for 1-alkanesulfonates[5] and for fatty acid salts;[7] the former occurs at C_{10} and the latter, consistent with our present work, at C_8. By taking into account of hydration shell of a CyD molecule, Satake et al. explained why the saturation phenomena occur for surfactants at which the guest molecule is sufficiently long compared to the depth of the host cavity.[6]

It is interesting to note that K_1 value is saturated at C_8, but K_2 is not. This may indicate that an alkane molecule is included centering around the midpoint of its chain in the CyD cavity to form the binary complex, while the coexisting ternary complex is formed through sharing equal chain of one guest molecule with two host molecules. It has been suggested that, if 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.[22] This model may be the case for the present 2 : 1 complexes with α-CyD.

It can be seen from Fig. 4 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 favorably with the cavity wall. This idea was presented by Ono et al.,[7] who studied α- and β-CyD complexations for alkyl carboxylates and found that the association constant of α-CyD is saturated at C_8, while that of β-CyD at C_{12}. They explained this difference, based on the host-guest association model and also on thermodynamic data, by assumption of a trans to gauche conformational change of alkyl chain in the β-CyD cavity. This assumption can be plausibly applied to our present host-guest systems.

We expected that γ-CyD forms much weaker complexes with alkanes, because its cavity diameter (8.5 Å) is too large to accept an alkane molecule suitably. Contrary to the expectation, the association constant of γ-CyD was found to be almost comparable to that of α-CyD for the corresponding alkane. We will propose two hypothetical explanations. One is to postulate a flexible conformation of alkyl chain to get contact as widely as possible with the cavity wall; guests of short chain length (e.g., pentane) orient themselves in the cavity almost perpendicular to the cavity wall. Another postulation is that γ-CyD accepts a guest molecule without releasing water molecules which are present originally in the cavity. The water molecules are released in the inclusion process of the guest molecule of a suitable size.

Inclusion Mechanism. 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, hydrogen bonding is ignored in the present case.

Okubo et al. evaluated thermodynamic parameters of the α-CyD-sodium dodecyl sulfate system. They have concluded from negative ΔH and positive ΔS that the driving forces of the inclusion process are van der Waals and hydrophobic interaction between the alkyl chain of the surfactant and the inner wall of the CyD cavity.[4] On the other hand, Satake et al. have drawn a conclusion that hydrophobic interaction governs associations of $C_nH_{2n+1}SO_3^-$ with α-CyD, by taking into account of increments of ΔH and ΔS as a function of n.[6] As for the aliphatic alcohol-α-CyD system, Barone et al. observed negative ΔH and positive ΔS, from which they concluded that hydrophobic interaction does not always play the major role in these associations.[11] Negative ΔH and positive ΔS were also observed in the heptane-α-CyD system, though this is not the case for the corresponding β-CyD system.[13]

It should be noted here that positive ΔS does not necessarily mean hydrophobic interaction. A definite number of water molecules replaced by a guest molecule are to be released from the CyD cavity to bulk water, which gives rise to positive ΔS.[12]

Undoubtedly the hydrophobicity of a guest is the most important factor in estimating the contribution of hydrophobic interaction. We have proposed in the preceding papers,[16,18] that the most suitable parameter of hydrophobicity for volatile solutes is the Henry's law constant, K_H, which is defined as $K_H=p/X$, where p is the partial vapor pressure of the solute and X is the mole fraction solubility of the solute in water. The free energy change of the dehydration

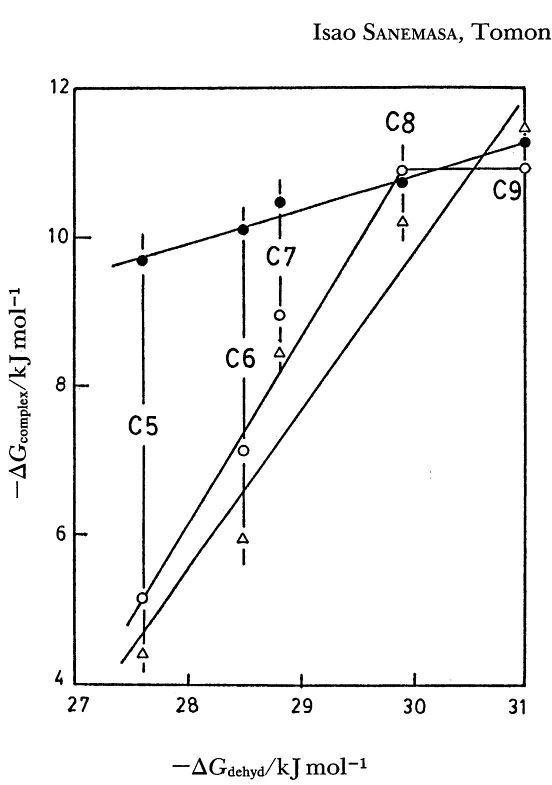

Fig. 5. The plots of the free energy change of CyD-guest complexation, $\Delta G_{\mathrm{complex}}$ (=$-RT \ln K$), vs. that of dehydration, $\Delta G_{\mathrm{dehyd}}$ (=$-RT \ln K_{\mathrm{H}}$), of guest. Host: α (○), β (●), γ (△).

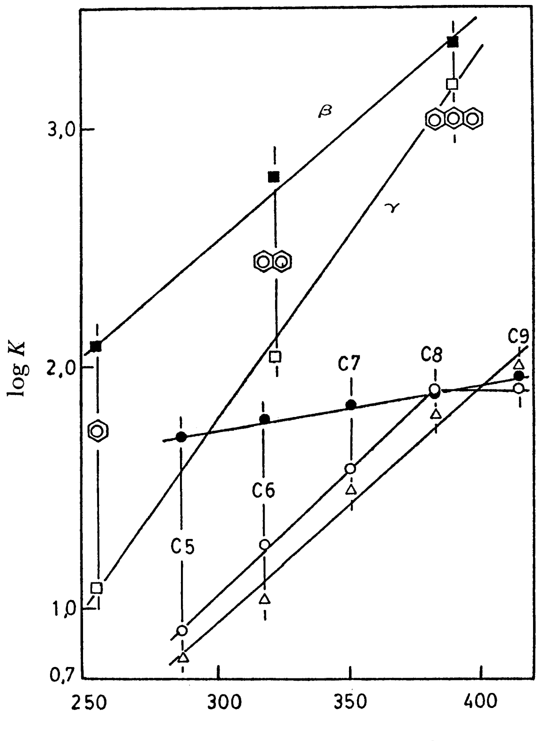

Fig. 6. The dependence of association constant on the surface area of guest molecule. Benzene, naphthalene, and anthracene are indicated by the structural formulae. The symbols of CyDs for alkanes are the same as those shown in Fig. 5.

process is expressed as $\Delta G_{\mathrm{dehyd}}$ (=$-RT \ln K_{\mathrm{H}}$); the larger the $-\Delta G_{\mathrm{dehyd}}$ value, the more hydrophobic the solute. The $\Delta G_{\mathrm{dehyd}}$ data of alkanes are available from the literature;[23,24] hydrophobicity increases with the chain length.

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. 5. Since there is a positive correlation between these two energy changes, hydrophobic interaction may be a driving force of CyD complex formation with alkanes. However, we cannot rule out the possibility of van der Waals force. This force is closely related to the associating host-guest contact area, that is, the alkyl chain length of a guest molecule. The plots of log *K* vs. the total surface area of alkane[25] are shown in Fig. 6.

In the cases of polynuclear aromatic hydrocarbons[16] and halobenzenes,[18] there is a negative correlation between their hydrophobicity and surface area, and the *K* values increse with surface area. For such guests, van der Waals force may be taken as the pre-

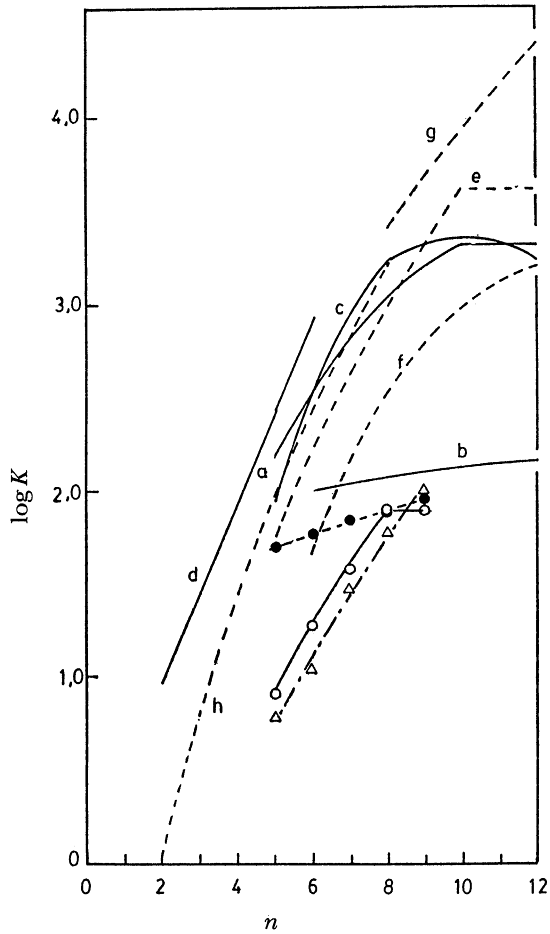

Fig. 7. The plots of log*K* vs. *n* for some 1-alkyl (C_nH_{2n+1}=R) surfactants and alcohols. Solid and dotted lines refer to α and β-complexations, respectively. The symbols of CyD for alkanes are the same as those shown in Fig. 5. R-SO_3^-: a,[5] e,[6] b[4]; R-OSO_3^-: g[3]; R-COO^-: c,[7] f[8]; R-OH: d,[12] h[9].

dominant factor to govern the inclusion complexation. For alkanes, it needs additional data such as temperature dependence of K to get ΔH and ΔS to determine which factor is predominant, van der Waals force or hydrophobic interaction. Even so we wish to say that the former is more responsible for the alkane-CyD complexations. We cannot find any basis on which an essential difference is rationalized in the binding with CyD wall between an aromatic ring and an alkyl chain. It is, therefore, unreasonable to explain one side by van der Waals force and the other by hydrophobic interaction.

In Fig. 7 are shown $\log K$ vs. n for alkyl-homologous series of surfactants and alcohols together with the present results. There are three points to be noted. At first, α-CyD forms more stable complexes than β-CyD. Secondly, the K values of these two CyDs increase monotonously with n and tend to form saturation plateaus. Thirdly, the K values of alkanes are considerably lower than those of surfactants and alcohols. The third point is noteworthy: hydrophilic polar groups work as a stabilizer of the complexes rather than an inhibitor. We speculate that polar groups such as SO_3^-, COO^-, and OH^- interact in a peculiar manner such as hydrogen bonding with a CyD molecule. The micro environment surrounding a CyD molecule may be changed in the presence of such polar guests.

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