Binding Forces Contributing to the Association of Cyclodextrin with Alcohol in an Aqueous Solution

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The association constants and thermodynamic parameters were determined for complexes of α- and β-cyclodextrins (CD) with a variety of alcohols (ROH) by the spectrophotometric examination of the inhibitory effect of ROH on the association of CD with azo dyes, and they were analyzed in connection with the partition coefficients of ROH in a diethyl ether–water solvent system in order to elucidate the binding forces contributing to the association of CD with an organic substrate. Hydrophobic and van der Waals interactions were of primary importance in the complexation. Among them, the latter was preferential in α-CD–1-alkanol adducts, while the former, in β-CD–1-alkanol adducts. As the bulkiness of ROH increased, the stability of the α-CD adduct was lowered owing to van der Waals repulsion between ROH and the relatively small α-CD cavity, whereas that of the β-CD adduct was enhanced by the attainment of the close van der Waals contact of ROH with the relatively large β-CD cavity.

Cyclodextrin (CD) is a doughnut-shaped molecule and includes a variety of substrates within the hole of the doughnut.[1–4] The stability of the CD adducts varies markedly either with the size of the CD cavity or with the structure of a substrate. In order to understand the mechanism from which the substrate specificity arises, it is necessary to clarify binding forces contributing to the inclusion process. Hydrogen bonding,[5–8] van der Waals interactions,[8–13] and/or hydrophobic interactions[2,12–17] have been proposed to explain the inclusion phenomena. Among them, hydrophobic interactions have been regarded as especially significant on the basis of the fact that the inclusion phenomena of CD exclusively occur in an aqueous solution.[2] However, a number of thermodynamic parameters determined for the inclusion equilibria indicated that the process is governed by a negative enthalpy change. The entropy term was always negative and contributed unfavorably to the complexation, despite hydrophobic interactions being normally caused by a favorable positive entropy change.[18–19]

Bender *et al.*[2,10] and Bergeron *et al.*[11,20] explained the thermodynamic parameters in terms of the relief of high energy water from the CD cavity. According to them, the water molecules associated with the cavity are enthalpy rich, because they can not have a full complement of hydrogen bonds owing to interference from the glucopyranose rings of CD. The inclusion of a substrate results in the expulsion of these high energy water molecules into bulk water. Another binding force was proposed by Saenger *et al.*,[21–24] who systematically examined the molecular structures of α-CD adducts by means of X-ray crystallography. They found that the macrocycle of α-CD bears an unstrained hexagonal geometry in most of α-CD adducts except for a α-CD–water adduct, in which the macrocyclic conformation of α-CD is unsymmetrically distorted and energetically unstable. The relief of conformational strain energy in the α-CD–water adduct upon substrate inclusion was regarded as the main binding force of complexation. However, Tabushi *et al.*[13] recently showed that the strain relief as well as the relief of high energy water molecules is not major driving force of inclusion, but van der Waals interactions and the breaking of water clusters around an apolar guest molecule are of primary importance in the stabilization of an inclusion complex.

The present study was undertaken to estimate the extent of the contribution of these binding forces to the inclusion process on the basis of the association constants (K_a) and the thermodynamic parameters for the complexation of α- and β-CD with a variety of alcohols (ROH). The observed K_a values were analyzed in connection with the partition coefficients (P_e) of ROH's which are a reasonable measure of hydrophobicity and is often successfully applied to biological structure-activity relationship studies.[25–31] ROH's are well suited for substrates, since they are the simplest organic analogs of water which plays an important role in the inclusion process.

Experimental

Materials. The α- and β-CD were prepared by the method of Lane and Pirt.[32] These substances were separated and purified according to the directions of Cramer and Henglein.[33] Unless otherwise noted, ROH's of reagent grade were used after distillation. 3-Methyl-2-butanol and 3,3-dimethyl-2-butanol were prepared by the reduction of the corresponding 2-butanones with $LiAlH_4$: bp 112.8—113.2 °C (lit,[34] bp 113—114 °C) for the former and bp 120.5—122.2 °C (lit,[34] bp 120—121 °C) for the latter. 2-Methyl-2-pentanol and 2-methyl-2-hexanol were prepared by the reaction of acetone with propyl- and butylmagnesium bromides respectively: bp 52—56 °C/45 mmHg (1 mmHg=133.322 Pa) (lit,[34] bp 122.5—123.5 °C/762 mmHg) for the former and bp 64—67 °C/30 mmHg (lit,[34] bp 141—142 °C/755 mmHg) for the latter. 3-Methyl-3-pentanol and 3-ethyl-3-pentanol were prepared by the reaction of ethylmagnesium bromide with 2-butanone and 3-pentanone respectively: bp 121—123 °C (lit,[34] bp 122.5 °C/758 mmHg) for the former and bp 56—58 °C/33 mmHg (lit,[34] bp 142 °C/764 mmHg) for the latter. 2-Methyl-1-butanol, 2-pentanol, 2-hexanol, 4-methyl-2-pentanol, cyclobutanol, cyclopentanol, cycloheptanol, and cyclooctanol of reagent grade were used without further purification. An azo dye, sodium 4-(4-hydroxy-1-naphthylazo)-1-naphthalenesulfonate (**1**), was prepared and purified as has been described previously.[35] Methyl Orange (**2**) of reagent grade was used without further purification.

Apparatus. Absorption spectra were recorded using a Hitachi Model 124 spectrophotometer. The cells (1.0 cm) were maintained at a constant temperature by means of a jacket through which water was circulated from a constant-temperature bath. The pH of an aqueous solution was measured by means of an Orion Model 801A digital pH/mV meter. A Hitachi Model 063 gas chromatograph with a FID detector and 2% DEGS columns was used for the quantitative determination of ROH in diethyl ether and in water.

Spectrophotometric Determination of Equilibrium Constants for the Association of α- and β-CD with ROH. The association constant (K_a) for a CD–ROH system was determined by the spectrophotometric examination of the inhibitory effect of the ROH on the association of the CD with a dye. In order to obtain the K_a values in a satisfactory accuracy by this method, it is necessary to choose such a dye as to exhibit a large absorbance change upon the addition of a small amount of CD. If the concentration of CD is high, a large amount of ROH must be added to a CD–dye solution for the sufficient observation of the inhibitory effect of ROH on the association of CD with the dye. However, the addition of a large amount of ROH is undesirable owing either to low solubility in some ROH's or to alteration in solvent composition. In the present study, azo dyes, **2** and **1**, were used for α- and β-CD systems respectively. In 0.10 mol/dm^3 H_2SO_4 containing Na_2SO_4 for the adjustment of the ionic strength (I_c) to be 0.50 mol/dm^3, **2** gave an absorption maximum at 507 nm, the absorbance of which was markedly lowered by the addition of a small amount of α-CD (Fig. 1). Similarly, the addition of β-CD to a solution of **1** in a citrate–phosphate buffer (pH 6.4, $I_c=0.05$ mol/dm^3, and 25 °C) markedly lowered the absorbance at λ_{max} of 485 nm.[35] Each azo dye forms a 1 : 1 complex with CD at a CD concentration below 2 mmol/dm^3.[35] Although such experimental conditions as pH and I_c were different between α- and β-CD systems, these may little affect the K_a values since both of CD and ROH are neutral molecules.

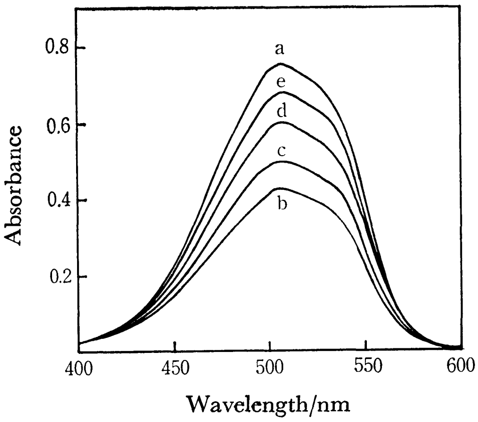

Fig. 1. Effect of α-CD and 1-butanol on the spectrum of **2** in 0.10 mol/dm^3 H_2SO_4 ($I_c=0.50$ mol/dm^3) at 25 °C.
a) 1.86×10^{-5} mol/dm^3 **2**; b) a+1.01 mmol/dm^3 α-CD; c) b+6.07 mmol/dm^3 1-butanol; d) b+24.3 mmol/dm^3 1-butanol; e) b+70.7 mmol/dm^3 1-butanol.

The addition of ROH to each CD–azo dye system resulted in an increase in absorbance (Fig. 1), indicating that a part of the added ROH is included by CD to expel the complexed azo dye to a bulk solution. Upon an assumption that each ROH also forms a 1 : 1 inclusion complex with CD, a relation between the absorbance and the concentration of the added ROH was analyzed by the application of the law of mass action and Lambert-Beer's law to the following two chemical equilibria:

$$\mathrm{CD + AZO \rightleftarrows CDAZO} \qquad (1)$$

$$\mathrm{CD + ROH \rightleftarrows CDROH} \qquad (2)$$

where AZO represents an azo dye, and CDAZO and CDROH, corresponding CD complexes. The initial and equilibrium concentrations were designated by a_0 and a for AZO, b_0 and b for ROH, and c_0 and c for CD respectively. Since CD, ROH, and CDROH are spectrophotometrically transparent in a visible region, the change (ΔA) in absorbance of an azo dye with the addition of CD and ROH is related to the equilibrium concentration (a_0-a) of CDAZO by Eq. 3:

$$a_0 - a = \frac{\Delta A}{\Delta\varepsilon}, \qquad (3)$$

where $\Delta\varepsilon$ is the difference in molar absorbance between AZO and CDAZO. Similarly, a is given by

$$a = \frac{(\Delta A_\infty - \Delta A)}{\Delta\varepsilon}, \qquad (4)$$

where ΔA_∞ is the difference in absorbance between AZO and CDAZO ($\Delta A_\infty = \Delta\varepsilon \cdot a_0$). The dissociation constant (K_d) for CDAZO is represented by $K_d = c\cdot a/(a_0-a)$, so that the equilibrium concentration of CD is given by

$$c = \frac{K_d(a_0-a)}{a}. \qquad (5)$$

On the other hand, the association constant (K_a) for CDROH is represented by

$$K_a = \frac{c_0 - c - (a_0-a)}{c[b_0 - c_0 + c + (a_0-a)]}. \qquad (6)$$

Since the value of a_0-a is very small compared with either c_0-c or b_0-c_0+c under the experimental condition of $a_0 \ll b_0$, c_0, Eq. 6 is simplified as Eq. 7:

$$K_a = \frac{c_0-c}{c(b_0-c_0+c)}. \qquad (7)$$

The values of K_d and $\Delta\varepsilon$ are easily determined by the Hildebrand-Benesi plot[36] (Table 1). By indroducing these values and the observed ΔA value into Eqs. 3, 4, and 5, we obtain the value of c, which is in turn introduced into Eq. 7 to give the K_a value. Actually, absorption spectra were measured at five or more different concentrations of ROH for each CD–ROH system. The calculated values of log K_a were in good agreement with one another wihin the standard error of ±0.04.

Table 1. The K_d and $\Delta\varepsilon$ values for CD–azo dye inclusion complexes at various temperatures

$\frac{T}{\mathrm{K}}$	$\frac{K_d}{\mathrm{mmol/dm^3}}$	$\frac{\Delta\varepsilon\times10^{-4}}{(\mathrm{mmol/dm^3})^{-1}\,\mathrm{cm^{-1}}}$
	α-CD–**2** system[a]	
283	0.762	3.95
288	0.917	3.93
293	1.08	3.90
298	1.25	3.88
	β-CD–**1** system[b]	
288	0.320	0.773
293	0.360	0.763
298	0.397	0.740
303	0.457	0.723
308	0.491	0.684

a) pH 1.2, $I_c=0.50$ mol/dm^3, and $\lambda=507$ nm.
b) pH 6.4, $I_c=0.05$ mol/dm^3, and $\lambda=485$ nm.

Determination of Thermodynamic Parameters for the Association of CD with ROH. The K_a values were determined at 10, 15, 20, and 25 °C for α-CD–ROH systems and at 15, 20, 25, 30, and 35 °C for β-CD–ROH systems. The method of least squares was applied to the relationship between log K_a and $1/T$. The values of ΔH and ΔS were calculated from the slope and the intercept respectively of the straight line obtained. The values of K_d and $\Delta\varepsilon$ at temperatures used for the determination of K_a are shown in Table 1.

Determination of Partition Coefficient of ROH in a Diethyl Ether–Water System. A proper amount of ROH was added to a mixture of diethyl ether (5 cm^3) and water (5 cm^3). The resulting mixture was vigorously shaken in a constant-temperature bath at 25 °C for *ca.* 1—2 min and was then allowed to stand in the bath. The aliquots of diethyl ether and aqueous solutions were analyzed by gas chromatography to determine the concentrations of ROH in diethyl ether (c_e) and in water (c_w). The partition coefficient (P_e) of ROH was evaluated as the mean of the values of c_e/c_w determined at five or more different amounts of the added ROH. The standard errors of log P_e were less than 0.04 except for the case of methanol, where it was 0.08.

Results

Table 2 shows the values of log K_a for each CD–ROH system, log P_e for ROH in a diethyl ether–water system, and a few related parameters for each ROH. The number of ROH examined is thirty-four, involving twenty-seven saturated aliphatic ROH's, five alicyclic ROH's, and two aromatic ROH's. Among the saturated aliphatic ROH's, twelve are primary, nine, secondary, and six, tertiary. All the structural isomers are involved among them with regard to saturated aliphatic monofunctional ROH's containing less than five carbon atoms in a molecule. Table 3 shows the thermodynamic parameters determined for the association of several ROH's with CD.

Discussion

Three characteristic relationships were recognized between the structure and log K_a for the examined

Table 2. The values of log K_a, log P_e, log P_o, E_s, and ν (25 °C)

No.	ROH	log K_a		log P_e	log P_o[a]	E_s[b]	ν[c]
		α-CD	β-CD				
1	Methanol	−0.03	−0.49	−1.15	−0.82	0.00	0.52
2	Ethanol	0.75	−0.03	−0.50	−0.32	−0.07	0.56
3	1-Propanol	1.37	0.57	−0.02	0.34	−0.36	0.68
4	2-Propanol	0.69	0.58	−0.18	0.06	−0.47	0.76
5	1-Butanol	1.95	1.22	0.61	0.88	−0.39	0.68
6	2-Methyl-1-propanol	1.44	1.62	0.65	0.83	−0.93	0.98
7	2-Butanol	1.42	1.19	0.41	0.61	−1.13	1.02
8	2-Methyl-2-propanol	0.64	1.68	0.09	0.37	−1.54	1.24
9	1-Pentanol	2.51	1.80	1.20	1.40	−0.40	0.68
10	2-Methyl-1-butanol	2.04	2.08	1.13			1.00
11	3-Methyl-1-butanol	1.87	2.25	1.19	1.16	−0.35	0.68
12	2,2-Dimethyl-1-propanol	1.47	2.76	1.21	1.36	−1.74	1.34
13	2-Pentanol	2.13	1.49	0.89	1.34		
14	3-Pentanol	1.94	1.35	0.96	1.37		
15	3-Methyl-2-butanol	1.27	1.92	0.94			
16	2-Methyl-2-butanol	1.53	1.91	0.64	0.89		
17	1-Hexanol	2.95	2.34	1.80	2.03		0.73
18	2-Hexanol	2.55	1.98	1.58			
19	4-Methyl-2-pentanol	1.72	2.04	1.47			
20	3,3-Dimethyl-2-butanol	1.30	2.75	1.56			
21	2-Methyl-2-pentanol		1.99	1.16			
22	3-Methyl-3-pentanol		2.15	1.10			
23	1-Heptanol	3.36	2.85	2.40	2.41		0.73
24	2-Methyl-2-hexanol		2.33	1.79			
25	3-Ethyl-3-pentanol		2.28	1.63			
26	1-Octanol	3.80	3.17	2.91	3.15	−0.33	0.68
27	2-Octanol	3.15	3.13	2.87			
28	Cyclobutanol	1.59	1.18	0.18		−0.06	
29	Cyclopentanol	1.66	2.08	0.74		−0.51	
30	Cyclohexanol	1.81	2.70	0.95	1.23	−0.79	0.87
31	Cycloheptanol	1.90	3.23	1.22		−1.10	
32	Cyclooctanol	2.25	3.30	1.70			
33	Benzyl alcohol	1.33	1.70	0.96	1.10	−0.38	0.70
34	2-Phenylethanol		2.15	1.18	1.30	−0.38	0.70

a) Ref. 27. b) Ref. 38. c) Ref. 39.

Table 3. Thermodynamic parameters for the association of CD with ROH in an aqueous solution at 25 °C

ROH	α-CD			β-CD		
	$\frac{\Delta G}{\text{kJ mol}^{-1}}$	$\frac{\Delta H}{\text{kJ mol}^{-1}}$	$\frac{\Delta S}{\text{J mol}^{-1}\text{K}^{-1}}$	$\frac{\Delta G}{\text{kJ mol}^{-1}}$	$\frac{\Delta H}{\text{kJ mol}^{-1}}$	$\frac{\Delta S}{\text{J mol}^{-1}\text{K}^{-1}}$
1-Butanol	−11.1	−12	−2	−7.0	2.9	33
1-Pentanol	−14.3	−16	−5	−10.3	4.6	50
1-Hexanol	−16.8	−19	−8	−13.3	0.4	46
2,2-Dimethyl-1-propanol	−8.4	−12	−12	−15.5	−8.8	21
Cyclohexanol	−10.3	−14	−14	−15.3	−10.0	17

ROH's by a direct comparison of the data in Table 2 with one another.

1) The values of K_a for CD–ROH adducts change with a change in the structure of ROH to a great extent (from −0.03 to 3.80 and from −0.49 to 3.30 for α- and β-CD systems respectively). This fact suggests that neither hydrogen bonding nor the relief of conformational strain energy of CD is of primary importance in stabilizing an inclusion complex between CD and ROH, since these binding forces have been regarded as either weak[2)] or virtually constant,[21–24)] independent of the structure of a guest molecule, in an aqueous solution.

2) A considerably high positive correlation exists between the observed log K_a and log P_e values. Thus, for α-CD systems;

$$\log K_a = 0.83 \log P_e + 1.00, \quad (8)$$
$$n=29,\ r=0.895,\ \text{and}\ s=0.381,$$

and for β-CD systems;

$$\log K_a = 0.90 \log P_e + 0.98, \quad (9)$$
$$n=34,\ r=0.871,\ \text{and}\ s=0.441,$$

where n, r, and s are the number of data, a correlation coefficient, and the standard deviation of residuals respectively. These observations indicate that hydrophobic interactions play a significantly important role in the complexation.

3) Virtually half of the examined ROH's associate with α-CD more strongly than with β-CD, while the others are reverse. The log K_a values for α-CD complexes with the following ROH's are larger, by 0.5 or more, than those for the corresponding β-CD complexes: Ethanol, 1-propanol, 1-butanol, 1-, 2-, and 3-pentanols, 1- and 2-hexanols, 1-heptanol, and 1-octanol. All of these ROH's contain a straight-chain alkyl group. On the other hand, the following ROH's associate with β-CD more strongly than with α-CD by 0.5 or more in log K_a: 2-Methyl-2-propanol, 2,2-dimethyl-1-propanol, 3-methyl-2-butanol, 3,3-dimethyl-2-butanol, cyclohexanol, cycloheptanol, and cyclooctanol. All of these ROH's contain a bulky alkyl group. It is interesting to compare data for the structural isomers of 1-pentanol and 2,2-dimethyl-1-propanol with each other. The log P_e values for the isomers are 1.20 and 1.21, being virtually equal to each other. Nevertheless, the log K_a value for a α-CD–1-pentanol adduct (2.51) is larger than that for a α-CD–2,2-dimethyl-1-propanol adduct (1.47) by more than unity, whereas the log K_a value for a β-CD–1-pentanol adduct (1.80) is smaller than that for a β-CD–2,2-dimethyl-1-propanol adduct (2.76) by nearly unity. These observations indicate that not only hydrophobic interactions but also the bulkiness of a guest molecule relative to the size of the CD cavity affects on the stability of a CD–ROH adduct. It seems that straight-chain alkanols with rod-like structure are closely fitted to the relatively small α-CD cavity, whereas they are too small in size to be in close contact with the relatively large cavity of β-CD. On the other hand, bulky or globular molecules, such as multi-branched alkanols and cycloalkanols, may be too large in size to be included deeply within the α-CD cavity, while they may be closely fitted to the β-CD cavity. In this connection, it is interesting that the log K_a value for a β-CD–3-ethyl-3-pentanol adduct (2.28) is significantly smaller than that for the corresponding straight-chain isomer (1-heptanol) system (2.85). In this case, the guest molecule is so large in size that it may be difficult even for β-CD to include deeply the guest within the cavity. The above presumptions were substantiated by an examination with the Corey-Pauling-Koltum molecular models, too. Thus, ROH's in α-CD–1-pentanol and β-CD–2,2-dimethyl-1-propanol adducts are readily inserted into the bottom of the corresponding CD cavity to come into close contact with the C-5 hydrogens which locate at the bottom-half of the CD cavity. On the other hand, ROH's in α-CD–2,2-dimethyl-1-propanol and β-CD–3-ethyl-3-pentanol adducts are only able to be inserted into the top-half of the corresponding CD cavity not or hardly to come into contact with the C-5 hydrogens. Taking into account the fact that the CPK models are constructed on the basis of van der Waals radii of atoms, we may say that van der Waals interactions also significantly contribute to the complexation of CD with ROH.

Correlation between log K_a and log P_e. In order to learn the implication of the results in Table 2 more closely, the correlation between log K_a and log P_e was examined either graphically or by regression analysis. The partition coefficient of an organic compound in an apolar solvent–water system is a practical and reasonable index of the hydrophobicity of the compound.[25–31)] Although 1-octanol is ordinarily used as an apolar solvent,[27,30)] diethyl ether was used in the present study, since a number of ethereal oxygens are aligned within the CD cavity to give an ether-like atmospher.[10)] However, it was found that a good linear correlationship exists between the observed P_e and the partition coefficient (P_0) in a 1-octanol–water system for twenty ROH's thus far reported.

$$\log P_e = (1.03\pm0.03)\log P_0 - (0.26\pm0.04), \quad (10)$$
$$n=20,\ r=0.993,\ \text{and}\ s=0.115.$$

A similar equation has been reported by Leo *et al.*[27] for a variety of organic compounds including ROH's:

$$\log P_e = (1.13\pm0.04)\log P_0 - (0.17\pm0.05), \quad (11)$$
$$n=71,\ r=0.988,\ \text{and}\ s=0.186.$$

Accordingly, no difference may arise in conclusion whether log P_e or log P_0 is used as an index of the hydrophobicity of ROH.

Regression analysis of log P_e for twenty-seven acyclic alkanols examined showed that the following equation holds for with a very high multiple correlation coefficient:

$$\log P_e = -1.72 + 0.58N - 0.22S - 0.61T, \quad (12)$$
$$n=27,\ r=0.998,\ \text{and}\ s=0.061,$$

where N is the number of carbon atoms contained in ROH, S and T, indicator variables which are equal to zero or unity. If the ROH is primary, $S=T=0$; if secondary, $S=1$ and $T=0$; if tertiary, $S=0$ and $T=1$. Equation 12 indicates that log P_e of ROH is virtually defined only by the number of carbon atoms in ROH and the class of the ROH.

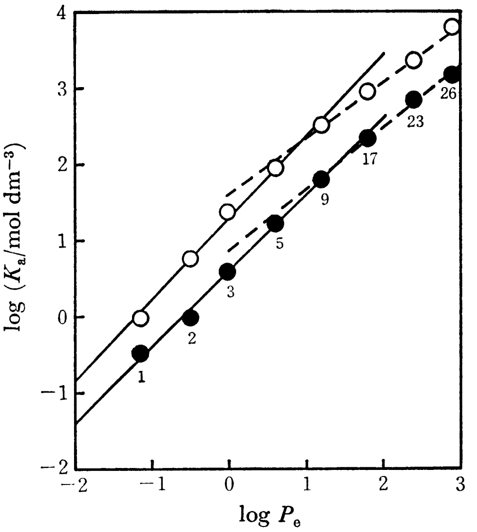

Fig. 2. Plots of log K_a *vs.* log P_e for $CH_3(CH_2)_nOH$ (n=0—7).
○: α-CD system; ●: β-CD system.
The solid and dashed lines were obtained by the application of the least squares method to the set of data for n=0—4 and n=4—7 respectively. Numbers shown refer to the numbers in the first column of Table 2.

Figure 2 shows the plot of log K_a *vs.* log P_e for CD–1-alkanol systems. Both the plots for α- and β-CD systems gave approximately straight lines with a slope of *ca.* unity. For the α-CD system,

$$\log K_a = 0.92\log P_e + 1.25, \quad (13)$$
$$n=8,\ r=0.994,\ \text{and}\ s=0.153,$$

and for the β-CD system,

$$\log K_a = 0.94\log P_e + 0.58, \quad (14)$$
$$n=8,\ r=0.998,\ \text{and}\ s=0.099.$$

However, it was recognized in each system that a refractive point does exist around the point corresponding to 1-pentanol and the plots for the higher alkanols tend to locate below a straight line drawn through the plots for the lower alkanols. The solid and dashed lines in Fig. 2 were obtained by the application of the least squares method to the sets of data from methanol to 1-pentanol and from 1-pentanol to 1-octanol respectively. Taking into account the depth of the CD cavity (*ca.* 7 Å[2]) together with the mean length of an aliphatic C–C bond (1.537 Å[37]), we can presume that the whole molecule of 1-butanol or even 1-pentanol is completely included within the CD cavity, while a part of the molecule of 1-hexanol or higher alkanols is protruded from the CD cavity to a bulk solution. In the case of the latter, interactions between CD and ROH may be lowered either by the incomplete liberation of iceberg water[18] or water cluster[19] around the apolar alkyl chain of ROH upon inclusion or by the incomplete van der Waals contact of the alkyl group with the CD cavity.

It is also evident from Fig. 2 that each 1-alkanol associates with α-CD more strongly by a factor of 6—7 than with β-CD. Although pH and I_c of solutions used are different between α- and β-CD systems for the sake of experimental convenience (*cf.* Experimental), such difference may have no or little effect on the value of log K_a, since both of CD and ROH are neutral molecules. The difference in log K_a between α- and β-CD systems might be attributed to the difference either in size or, if any, in hydrophobicity between the α- and β-CD cavities. However, no evidence has ever been offered for a postulate that the hydrophobicity of the α-CD cavity is greater than that of the β-CD cavity. The solubility of α-CD in water is rather 8 times that of β-CD.[1] Thus, it is unlikely that the α-CD cavity is more hydrophobic than the β-CD cavity to cause the difference in log K_a between α- and β-CD systems. It is much reasonable to consider that α-CD includes 1-alkanol in closer contact with each other than β-CD does. According to Bergeron and Meely,[20] the relief of high-energy water molecules in the inclusion process of CD is substantiated by the fact that a number of organic molecules associate with β-CD more strongly than with α-CD. However, the reverse is true for the present CD–1-alkanol systems, indicating that the basis given by them is not always general.

Figures 3 and 4 show the plots of log K_a *vs.* log P_e for branched or cyclic ROH–CD systems. Both of the plots for the α- and β-CD systems showed considerable scatter in contrast to the plots for 1-alkanol systems. However, a remarkable trend was found by comparing both plots with each other. Most of the plots for a α-CD system (Fig. 3) locate below the straight line obtained by the regression analysis of the data for a α-CD–1-alkanol system (Eq. 13), while those for a β-CD system (Fig. 4) locate above the straight line given by Eq. 14. This observation shows that it is general for a bulky ROH to associate with α-CD less strongly and with β-CD more strongly than a rod-like 1-alkanol if the log P_e values are the same.

An interesting indication is afforded by the plots of log K_e *vs.* log P_e for cycloalkanols shown by solid circles

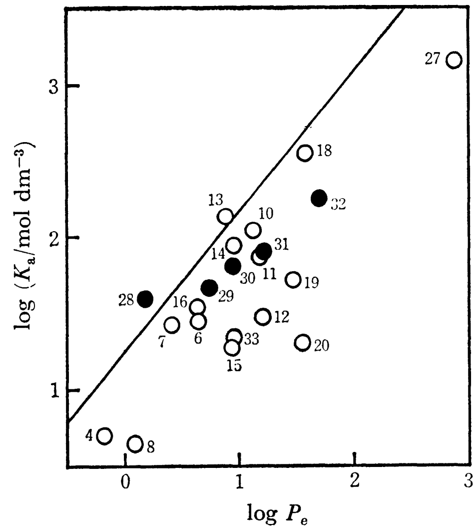

Fig. 3. Plots of log K_a *vs.* log P_e for complexes of α-CD with branched ROH's (○) and cycloalkanols (●). The solid line was given by the plots for a α-CD–1-alkanol system. Numbers shown refer to the numbers in the first column of Table 2.

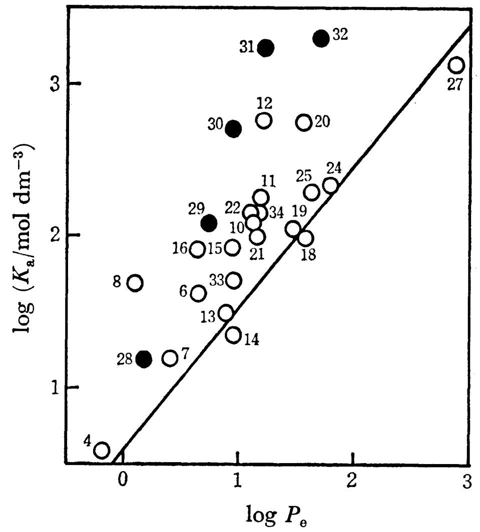

Fig. 4. Plots of log K_a *vs.* log P_e for complexes of β-CD with branched ROH's (○) and cycloalkanols (●). The solid line was given by the plots for a β-CD–1-alkanol system. Numbers shown refer to the numbers in the first column of Table 2.

in Figs. 3 and 4. In the case of a α-CD system, a plot for cyclobutanol locates slightly above the straight line for a 1-alkanol system. As the size of the cycloalkanol ring increases, the plot comes to locate below the line and the difference between them increases. On the other hand, each plot for a β-CD–cycloalkanol system locate above the straight line for 1-alkanols. The difference between them increases with increasing size of the cycloalkanol ring. The maximum difference is attained at the plot for cycloheptanol and the difference for cyclooctanol is significantly smaller than that for cycloheptanol. These results suggest that the α- and β-CD cavities are large in size enough to come into the closest contact with cyclobutanol and cycloheptanol respectively.

Polarizability, molar refraction (MR), Taft's steric substituent constant (E_s),[38] and the ν parameter given by Charton[39] are frequently used for a comparative index of molecular bulkiness in the quantitative study of structure-activity relationship. Among them, the first two were not suitable for the present study, since they vary markedly with a change in the number of carbon atoms in molecule but slightly with a change in structure among isomers. In contrast, the values of E_s and ν for structural isomers are significantly different from one another, so that the possibility is present that either E_s or ν is accessible for the index of molecular bulkiness in the present case. A correlation analysis for ROH's with the known values of E_s and ν (Table 2) gave Eqs. 15—18. For a α-CD system,

$$\log K_a = 0.92 \log P_e + 0.42E_s + 1.24, \tag{15}$$

$$n=17,\ r=0.953,\ \text{and}\ s=0.271,$$

$$\log K_a = 0.95 \log P_e - 0.88\nu + 1.67, \tag{16}$$

$$n=17,\ r=0.968,\ \text{and}\ s=0.269,$$

and for a β-CD system,

$$\log K_a = 0.97 \log P_e - 0.65E_s + 0.60, \tag{17}$$

$$n=18,\ r=0.938,\ \text{and}\ s=0.383,$$

$$\log K_a = 0.91 \log P_e + 1.36\nu - 0.17, \tag{18}$$

$$n=18,\ r=0.962,\ \text{and}\ s=0.296.$$

The results of the F- and t-tests showed that all of Eqs. 15—18 are reliable with a 95% level of confidence, although the values for r and s indicate that ν is somewhat preferred to E_s as an index of molecular bulkiness. In each equation, the dependence of log K_a on log P_e was virtually constant (0.91—0.97) and equal to those for 1-alkanol systems (0.92—0.94, *cf.*, Eqs. 13 and 14). On the other hand, the dependence of log K_a on either E_s or ν was remarkably different between α- and β-CD systems: The coefficient of E_s was positive in sign for a α-CD system and negative for a β-CD system, while the reverse is true for the coefficients of ν. These clear-cut differences in sign between α- and β-CD systems reflect the fact that a bulky ROH is subject to van der Waals repulsion by the α-CD cavity and to van der Waals attraction by the β-CD cavity.

Thermodynamic Parameters for CD–ROH Systems. The above presumptions on the driving forces of inclusion were substantiated by the determination of thermodynamic parameters, ΔH and ΔS, for the association of CD with ROH (Table 3). It is very interesting that both of ΔH and ΔS for β-CD–1-alkanol systems are positive. This fact indicates that the complexation is not governed by enthalpy but by entropy. It has rarely been reported that the inclusion process of CD is accompanied by a positive entropy change. Only a α-CD–1-adamantanecarboxylate system, reported by Komiyama and Bender,[17] falls under this category. Among the binding forces proposed for the inclusion phenomena of CD, only hydrophobic interactions are governed by entropy. Thus, it is obvious that hydrophobic interactions play a primary role in the complexation of β-CD with 1-alkanols.

As the bulkiness of ROH increases, the ΔH term becomes negative and the contribution of ΔS to the binding becomes low even in the case of a β-CD system. Such a change may be attributed to an increase in contribution of van der Waals interactions ($\Delta H<0$, $\Delta S<0$) to the complexation.

On the other hand, both of ΔH and ΔS are negative in the case of α-CD–1-alkanol systems, where it was suggested that the contribution of van der Waals interactions is very large. A decrease in the stability of α-CD–ROH adducts with an increase in bulkiness of ROH is mainly caused by a marked decrease in contribution of the ΔH term to the complexation. Komiyama and Bender[17] have also suggested that the contribution of the ΔH term to complexation is very little compared with that of the ΔS term in the complexation of bulky 1-adamantanecarboxylate with α-CD.

In conclusion, it was shown that hydrophobic and van der Waals interactions are of primary importance in the inclusion process of CD–ROH systems. Among them, the latter is preferential for α-CD–1-alkanol adducts and the former for β-CD–1-alkanol adducts. As the bulkiness of ROH increases, the stability of α-CD adducts decreases owing to van der Waals repulsion, while that of β-CD adducts increases owing to the attainment of the close van der Waals contact of ROH with the β-CD cavity. The present conclusion is very similar to that given by Tabushi *et al.*[13] by means of theoretical calculation.

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