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Binding Forces in Complexation of *p*-Alkylphenols with β-Cyclodextrin and Methylated β-Cyclodextrins

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Abstract. Fluorescence spectroscopy has been used to determine the binding constants (K) for inclusion complexes of six kinds of *p*-alkylphenols with β-cyclodextrin (β-CDx), heptakis(2,6-di-*O*-methyl)-β-CDx (DMe-β-CDx), and heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx). The stability of the inclusion complex of each cyclodextrin increases with increasing alkyl chain length of the *p*-alkylphenol. The K values decrease in the order of DMe-β-CDx, β-CDx, and TMe-β-CDx for each guest. In complexation of 3-(*p*-hydroxyphenyl)-1-propanol (**3**) with β-CDx as well as with DMe-β-CDx, negative enthalpy (ΔH) and positive entropy changes (ΔS) have been obtained, suggesting both van der Waals and hydrophobic interactions as binding forces. The inclusion of **3** by TMe-β-CDx, however, is an enthalpically favorable but entropically unfavorable process. The van der Waals interactions may be the main binding forces for complexing **3** with TMe-β-CDx.

Key words. *p*-Alkylphenols, β-cyclodextrin, methylated β-cyclodextrins, thermodynamic parameters, binding forces.

1. Introduction

Several forces have been postulated for the formation of inclusion complexes of cyclodextrins (CDx) [1]; (1) van der Waals interactions, (2) dipole interactions, (3) hydrophobic interactions, (4) hydrogen-bonding interactions, (5) release of distortional energy of CDx by the including guest, and (6) extrusion of 'high-energy water' from the CDx cavity by the including guest. In the first case, Tabushi and co-workers [2] calculated the thermodynamic parameters for the inclusion of benzene, *p*-iodoaniline, and methyl orange by α-CDx and concluded that the van der Waals stabilization, the strain release, and breaking of the water clusters around an apolar guest mainly dominate the stabilization of the inclusion complexes. The van der Waals interactions have been widely demonstrated to be the main binding forces in a variety of host–guest systems [3]. Recent molecular mechanics calculations for complexation of a cyanine dye with β- and γ-CDxs reveal an importance of the van der Waals stabilization energy [4]. The electrochemically generated anion radicals of 1,2- and 1,4-dicyanobenzenes form inclusion complexes with CDxs that are more stable in comparison with their uncharged parent dicyanobenzenes [5]. The results have been explained in terms of the participation of dipole-induced dipole interaction in such complexation. In general, the formation of inclusion complexes of CDxs is enthalpically favorable but entropically unfavorable [6].

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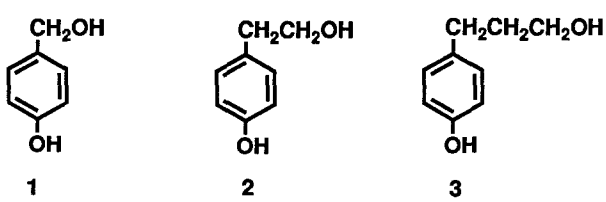
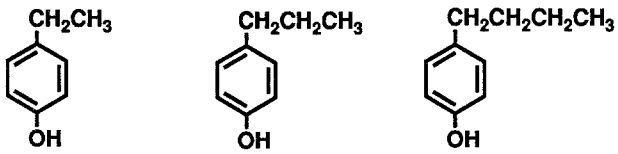
However, a detailed study of the thermodynamics of association of alkanols with α- and β-CDxs indicates a cooperative contribution of hydrophobic and van der Waals interactions [7]. The association of 1-alkanols, such as 1-butanol, 1-pentanol, and 1-hexanol, with β-CDx is endothermic ($\Delta H > 0$) and is promoted by an entropy term ($\Delta S > 0$). Increase of the alkyl chain length of 1-alkanol causes a decrease of ΔH and an increase of ΔS. The association becomes exothermic for the bulky alcohol–β-CDx systems, while ΔS values are still positive. These results can be summarized by stating that the hydrophobic interaction plays a primary role in complexation and the contribution of van der Waals interactions increases with increasing alkyl chain length and/or bulkiness of the alcohol. Hydrogen bonding has scarcely been reported as a main binding interaction for forming inclusion complexes. A reliable example is the hydrogen bonded complex of bilirubin with β-CDx [8]. Bilirubin bound to β-CDx shows a bisignate circular dichroism Cotton effect, suggesting that a conformational enantiomerism of bilirubin occurs upon complexation with β-CDx [9]. The facts that no circular dichroism signal of bilirubin is observed when methylated β-CDxs are used, and that noncyclic oligosaccharides also induce the bisignate Cotton effect, are suggestive of hydrogen bonding interactions between bilirubin and β-CDx [8].

Methylated β-CDxs, heptakis(2,6-di-*O*-methyl)-β-CDx (DMe-β-CDx) and heptakis(2,3,6-tri-*O*-methyl)-β-CDx (TMe-β-CDx), have been widely used for a variety of purposes. A unique property of TMe-β-CDx is its ability to recognize the chiralities of binaphthyl derivatives [10]. For example, an (*S*)-enantiomer of 1,1′-bi-2-naphthol is more preferably included in TMe-β-CDx than an (*R*)-enantiomer. In order to clarify the mechanism for chiral recognition by TMe-β-CDx, the binding forces should be elucidated. It is especially important to know whether hydrogen bonds are formed between the hydroxyl group(s) of binaphthol and the ether oxygen(s) of TMe-β-CDx. Unfortunately, little has been reported about the mechanism for complexation of methylated CDxs. Harata *et al.* [11] have determined the thermodynamic parameters of TMe-α-CDx complexes with monosubstituted benzenes and found negative values of ΔH and ΔS. Such complexation, dominated by the enthalpy term, has been explained in terms of the van der Waals interactions mainly promoting the formation of inclusion complexes.

In the present study we have evaluated binding constants (K) of inclusion complexes of *p*-alkylphenols, **1**–**6**, with β-, DMe-β-, and TMe-β-CDxs. The phenols **1**, **2**, and **3** have two terminal hydroxyl groups. These phenols have the capability of interacting with CDxs through hydrogen bonding at two points, while only one-point attachment by hydrogen bonding can occur in the cases of the phenols **4**, **5**, and **6**. If hydrogen bonding participates in complexation, the difference between one- and two-point attachments may be reflected in the K values. In



1 **2** **3**



4 5 6

addition, we expected that the difference in the binding mechanism between β-CDx and methylated β-CDxs is derived from the results of association of a certain guest with β-, DMe-β-, and TMe-β-CDxs.

2. Experimental

β-CDx (Nacalai) was purchased and an antioxidant containing this material was extracted with THF. DMe-β-CDx, TMe-β-CDx (Nacalai), compounds **1**, **2**, **3**, **5** (Aldrich), **4** (Nacalai), and **6** (Tokyo Kasei) were obtained commercially and used without further purification.

Although we tried to purify DMe-β-CDx and TMe-β-CDx, the amounts of fluorescent impurities increased during procedures. Since the K values were determined by means of fluorescence spectroscopy, we omitted the purification procedures for these methylated β-CDxs. No resonance peaks due to impurities were observed in the ^{1}H-NMR spectra of commercially obtained DMe-β-CDx and TMe-β-CDx in D_2O. Trace amounts of the fluorescent impurities included in these methylated β-CDxs did not prevent the determination of the K values.

The absorption and fluorescence spectra were measured on a Shimadzu UV-2100 spectrophotometer and a Hitachi 650-60 spectrofluorometer, respectively.

3. Results and Discussion

In all host–guest pairs, the absorption spectra of p-alkylphenols in water were changed upon addition of CDxs. The changes in absorbances, however, were so small that the K values could not be determined accurately by means of absorption spectroscopy. Each p-alkylphenol emits a fluorescence whose intensity is enhanced upon addition of CDxs. The K values can therefore be evaluated from Benesi–Hildebrand plots [12] of fluorescence intensity changes.

The excitation wavelengths for measuring fluorescence spectra were chosen so that nil or very small changes in absorbances were observed at the wavelengths when CDxs were added. In all cases, linear plots were obtained between ΔI^{-1} and $[\mathrm{CDx}]^{-1}$, where ΔI denotes the difference in the fluorescence intensities in the absence and the presence of CDx. The linear Benesi–Hildebrand plots indicate the formation of the 1:1 complexes of p-alkylphenols and CDxs. The K values obtained at 25°C and the fluorescence maxima of p-alkylphenols are summarized in Table I. The experiments were repeated at least three times in the determination of each K value.

For each CDx, the K value of the ω-(p-hydroxyphenyl)alkyl alcohol is smaller than that of the corresponding 1-(p-hydroxyphenyl)alkane. An increase in the hydrophobicity of the guest seems to cause stabilization of the inclusion complex.

Table I. Fluorescence maxima (λ_{max}) of *p*-alkylphenols and binding constants (K) for inclusion complexes of *p*-alkylphenols with β-, DMe-β-, and TMe-β-CDxs in water at 25°C

Guest	λ_{max}(nm)	K(L mol^{-1})		
		β-CDx	DMe-β-CDx	TMe-β-CDx
1	306	146 ± 3	244 ± 20	65 ± 4
2	307	330 ± 19	246 ± 21	65 ± 1
3	306	964 ± 36	1359 ± 10	107 ± 3
4	308	492 ± 18	920 ± 10	136 ± 5
5	308	2652 ± 196	3418 ± 232	358 ± 20
6	308	4041 ± 200	–	1019 ± 36

If the two-point attachment through hydrogen bonding interactions contributes greatly to the stabilization of the inclusion complex, the K value of ω-(*p*-hydroxyphenyl)alkyl alcohols should be larger than that of the corresponding 1-(*p*-hydroxyhenyl)alkane. A Corey–Pauling–Koltun (CPK) molecular model suggests that the two hydroxyl groups of ω-(*p*-hydroxyphenyl)alkyl alcohol can spatially interact with the primary and secondary hydroxyl groups of β-CDx or the ether oxygens located at both sides of the methylated β-CDx cavities if the guest forms an axial inclusion complex. It is probable that the hydrogen bonding interactions at two points scarcely participate in stabilization of the inclusion complexes of ω-(*p*-hydroxyphenyl)alkyl alcohols. For each guest, except for **3**, the stabilities of the complexes decrease in the order of DMe-β-CDx, β-CDx, and TMe-β-CDx. It is known that the inclusion complexes of dicyanobenzenes and their anion radicals with DMe-β-CDx are more stable than those with β-CDx [5]. The authors of this paper simply mentioned that the more hydrophobic nature of DMe-β-CDx can account for the formation of more stable complexes of this CDx.

Table II shows the K values of the inclusion complexes of **3** with β-, DMe-β-, and TMe-β-CDxs at various temperatures. ΔH and ΔS for complexation were determined from van 't Hoff plots of the data shown in Table II. The results are exhibited in Table III. In the case of the **3**–β-CDx system, negative ΔH and fairly

Table II. Binding constants (K) for complexation of **3** with β-, DMe-β-, and TMe-β-CDxs in water at various temperatures

Temperature (K)	K(L mol^{-1})		
	β-CDx	DMe-β-CDx	TMe-β-CDx
283		1535	159
288	1169	1434	139
291			126
293	1043	1378	
298	964	1359	107
303	955	1275	86
308	885		

Table III. Thermodynamic parameters for complexation of **3** with β-, DMe-β-, and TMe-β-CDxs in water

Host	ΔH(kJ mol^{-1})	ΔS(J mol^{-1} K^{-1})
β-CDx	-9.6 ± 1.4	25.4 ± 4.8
DMe-β-CDx	-6.1 ± 0.7	40.0 ± 2.5
TMe-β-CDx	-21.2 ± 1.5	-33.2 ± 5.2

large, positive ΔS were obtained. The negative ΔH may be due to the contribution of the van der Waals interactions between the host and the guest to the complex formation. Water clusters should be constructed around the apolar solute **3** in water. The water clusters are broken upon association of **3** with β-CDx, leading to positive ΔS. Therefore, it seems that both van der Waals and hydrophobic interactions participate in the formation of the complex of **3** and β-CDx. Release of water molecules bound to both host and guest upon complexation also accounts for positive values of ΔS. This factor may be included in the ΔS values shown in Table III. ΔH increases slightly and ΔS increases significantly when β-CDx is replaced by DMe-β-CDx. Since DMe-β-CDx is more hydrophobic than β-CDx [13], the entropy gain due to breaking of the water clusters around the host may be larger in the complexation with DMe-β-CDx than in that with β-CDx. Therefore, the higher stability of the **3**–DMe-β-CDx complex can be attributed to the stronger hydrophobic interaction. The complexation of **3** with TMe-β-CDx, however, is an enthalpically favorable but entropically unfavorable process. The small K value for the **3**–TMe-β-CDx complex is due to negative and large ΔS. Permethylation of β-CDx deepens the cavity and reduces the diameters of both rings of the toroid. The guest **3** seems to be included more tightly in the TMe-β-CDx cavity than in β- and DMe-β-CDx cavities. The negative and large ΔH for the **3**–TMe-β-CDx, therefore, can be ascribed to the stronger van der Waals interactions. Meanwhile, the decrease in the entropy can be interpreted in terms of the strict reduction in rotational freedom of the methyl groups of TMe-β-CDx and the hydroxypropyl group of **3** upon complexation. The rotational entropy of TMe-β-CDx is much larger than that of β-CDx because of the presence of 21 methyl groups. The restriction of the rotation upon complexation, therefore, should be much more remarkable in TMe-β-CDx than in β-CDx. The decrease in the entropy due to the loss of the translational and rotational freedoms upon complexation of **3** with TMe-β-CDx seems to overcome the entropy gain obtained by breaking of the water clusters.

4. Conclusion

The energy of a hydrogen bond in water is ca. 4–8 kJ mol^{-1} [14]. A stable hydrogen bonded complex, therefore, can be formed if the hydrogen bonds are formed at least at two points. Recently, it has been pointed out that a new vibrational freedom appears when a hydrogen bond is formed [15]. The new vibrations cause an increase in entropy leading to a decrease of free energy change for complexation. In addition, the release of bound water molecules from solute

molecules upon complexation yields an increase of entropy. A negative factor in hydrogen bond formation is the reduction in rotational and translational freedoms. This factor, however, cannot explain the reason why hydrogen bonding hardly occurs in water. It is evident that a hydrogen bonding site of a solute molecule in water is hydrated. Hydrated solute can be regarded as a hydrogen bonded complex. The following equilibria should therefore be considered:

$$A + mH_2O \rightleftharpoons A \cdot mH_2O \quad (1)$$

$$B + nH_2O \rightleftharpoons B \cdot nH_2O \quad (2)$$

$$A \cdot mH_2O + B \cdot nH_2O \rightleftharpoons AB \cdot xH_2O + yH_2O \quad (3)$$

where AB is the intermolecular, hydrogen bonded complex of solutes A and B. In water, the equilibria lie towards the $A \cdot mH_2O$ and $B \cdot nH_2O$ forms because of the very high concentration of H_2O. This is the reason why a hydrogen bonded complex is hardly formed in water. In order to obtain AB in water, a microenvironment where water molecules are excluded should be used. The CDx cavity is expected to act as A, which provides a hydrophobic microenvironment in water. Contrary to our expectation, no evidence for hydrogen bonding was obtained in complex formation between *p*-alkylphenols and CDxs. Probably, an unfavorable geometric relation between the hydrogen bonding sites of the host and the guest and/or unsatisfactory exclusion of water molecules from CDxs make it difficult to form the hydrogen bonded complex.

The driving force behind the formation of the inclusion complex seems to depend on many factors, such as hydrophobicity, polarizability, dipole moment, size matching, and so on. If the size of the guest molecule suits that of the CDx cavity, van der Waals interactions greatly contribute to the complex formation (negative ΔH and ΔS). Matsui and Mochida [7] have found, for example, that both ΔH (4.6 kJ mol^{-1}) and ΔS values (50 J mol^{-1} K^{-1}) for complexing pentanol with β-CDx are positive, but those for complexation with α-CDx are negative ($\Delta H = -16$ kJ mol^{-1}, $\Delta S = -5$ J mol^{-1} K^{-1}). For inclusion of pentanol, the size of the α-CDx cavity is more suitable than that of β-CDx. Good matching causes efficient van der Waals contacts and a marked reduction in rotational freedom of both host and guest, leading to negative ΔH and ΔS. The complexation of **3** with TMe-β-CDx is an example of this case. In the case where size of guest molecule is somewhat smaller than that of the CDx cavity and the guest is so hydrophobic that the water clusters are formed around the guest, hydrophobic interaction may dominate complexation. Such examples are the complexation of **3** with β- and DMe-β-CDxs.

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References

1. M. L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Ch. 3, Springer (1978).
2. I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura: *J. Am. Chem. Soc.* **100**, 916 (1978).

3. (a) F. Cramer: *Angew. Chem.* **68**, 115 (1956). (b) R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender: *J. Am. Chem. Soc.* **89**, 3242 (1967). (c) R. J. Bergeron, M. A. Channing, G. J. Giberly, and D. M. Pillor: *J. Am. Chem. Soc.* **90**, 5146 (1977). (d) E. S. Hall and H. J. Ache: *J. Phys. Chem.* **83**, 1805 (1979).
4. M. Ohashi, K. Kasatani, H. Shinohara, and H. Sato: *J. Am. Chem. Soc.* **112**, 5824 (1990).
5. K. Kano, K. Mori, B. Uno, M. Goto, and T. Kubota: *J. Am. Chem. Soc.* **112**, 8645 (1990).
6. Cf. R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, and D. A. Laufer: *J. Am. Chem. Soc.* **103**, 1750 (1981).
7. Y. Matsui and K. Mochida: *Bull. Chem. Soc. Jpn.* **52**, 2808 (1979).
8. K. Kano, K. Yoshiyasu, and S. Hashimoto, *J. Chem. Soc., Chem. Commun.* 801 (1988).
9. D. A. Lightner, J. K. Gawroński, and K. Gawrońska: *J. Am. Chem. Soc.* **107**, 2456 (1985).
10. K. Kano, K. Yoshiyasu, and S. Hashimoto: *J. Chem. Soc., Chem. Commun.* 1278 (1989).
11. K. Harata, K. Tsuda, K. Uekama, M. Otagiri, and F. Hirayama: *J. Incl. Phenom.* **6**, 135 (1988).
12. H. A. Benesi and J. H. Hildebrand: *J. Am. Chem. Soc.* **71**, 2703 (1949).
13. K. Miyajima, T. Mukai, M. Nakagaki, M. Otagiri, K. Uekama: *Bull. Chem. Soc. Jpn.* **59**, 643 (1986).
14. G. C. Pimentel and A. L. McClellan: *The Hydrogen Bond*, Appendix B, W. H. Freeman and Company (1960).
15. A. J. Doig and D. H. Williams: *J. Am. Chem. Soc.* **114**, 338 (1992).