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^{1}H-NMR Investigation of the Binding of 2-Methylnaphthalene to α-Cyclodextrin in D_2O Solutions

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Abstract. As α-cyclodextrin (α-CD) was added to D_2O solutions of 2-methylnaphthalene, its proton signals shifted to lower fields at low concentrations of α-CD. At 2.0×10^{-2} mol dm^{-3} of α-CD, however, a reverse, higher-field shift was observed for the H-8 signal, indicating the formation of 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes. Intrinsic chemical shift differences of all the protons in 2-methylnaphthalene have been evaluated for both the 1 : 1 and the 2 : 1 α-CD–2-methylnaphthalene inclusion complexes. These intrinsic chemical shift differences suggest that the first α-CD molecule has no selectivity in accommodating one end of uncomplexed 2-methylnaphthalene; α-CD binds to a methyl group, as well as a naphthalene ring-end having no methyl group, to form the 1 : 1 inclusion complex, resulting in the formation of two kinds of 1 : 1 complexes.

Key words: α-cyclodextrin, 2-methylnaphthalene, inclusion complexes, ^{1}H-NMR.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven, and eight glucose units, which are designated as α-, β-, and γ-CD, respectively. Since CDs are shaped like a truncated cone with a relatively hydrophobic cavity, guest molecules of an appropriate size can be incorporated into their cavities to form inclusion complexes [1, 2].

In the formation of a CD inclusion complex, there is a problem regarding the binding site in a guest molecule. In 1 : 1 inclusion complexes of β-CD with phenol, *m-tert*-butylphenol, and *p-tert*-butylphenol, a hydroxyl group of phenol or *tert* butylphenol protrudes from the β-CD cavity or is located near the secondary hydroxyl side of β-CD [3]. For other phenol derivatives, *m*-cyano, *p*-cyano, nitro,

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and carboxyl substituents are also preferentially bound into the α-CD cavity [4–6]. A conformation in which a nitro group selectively enters the α-CD cavity has been described for *m*- and *p*-nitrophenylacetate inclusion complexes with α-CD [7]. 2-Naphthalenecarboxylate is axially included into the β-CD cavity, with an orientation in which a carboxylate group is located on the primary hydroxyl side of the β-CD cavity [8].

Recently, α-CD has been revealed to form a 2 : 1 α-CD–naphthalene derivative inclusion complex in aqueous solutions [9–14]. Since, unlike the β-CD cavity, the α-CD cavity is not large enough to include an entire naphthalene ring, a question arises as to the binding site of an α-CD molecule in α-CD–naphthalene derivative inclusion complexes. 6-Bromo-2-naphthol is bound to the α-CD cavity first from a bromine atom on a naphthalene ring to form a 1 : 1 inclusion complex [11]. The second α-CD molecule accommodates the other end (hydroxyl-group side) of the naphthalene ring, resulting in the formation of a 2 : 1 α-CD–guest inclusion complex. For 2-methylnaphthalene, however, the binding site of α-CD in a 1 : 1 inclusion complex has not been investigated so far [12].

In the course of studies on 2 : 1 α-CD–naphthalene derivative inclusion complexes in aqueous solutions, we thus aimed to examine the binding site of 2-methylnaphthalene in forming a 1 : 1 α-CD–2-methylnaphthalene inclusion complex. In this paper, we report two binding modes of 2-methylnaphthalene in the 1 : 1 complexation with α-CD; 2-methylnaphthalene enters into the α-CD cavity from a methyl group as well as a naphthalene ring-end carrying no methyl group.

2. Experimental

α-Cyclodextrin (α-CD) was purchased from Nacalai Tesque, Inc., and was used as received. 2-Methylnaphthalene obtained from Tokyo Kasei Kogyo Co., Ltd. was purified employing silica-gel column chromatography.

^{1}H-NMR and ^{1}H-^{1}H COSY spectra were run on a Varian VXR-500S or a Varian Unity Plus 400 spectrometer, operating at 500 or 400 MHz, respectively. About 500 transients were collected for each ^{1}H-NMR spectrum. Chemical shifts were expressed in parts per million (ppm) relative to methyl protons (2.00 ppm) of acetonitrile, which was used as an internal reference [15, 16]. Measurements of ^{1}H-NMR spectra were performed at 25 $\pm$ 0.2 °C.

3. Results and Discussion

Figure 1 shows partial ^{1}H-NMR spectra of 2-methylnaphthalene in D_2O containing varying concentrations of α-CD. Assignments of proton signals were made based on both a ^{1}H-^{1}H COSY spectrum of 2-methylnaphthalene in D_2O containing 1.0×10^{-2} mol dm^{-3} α-CD (Figure 2) and the assignments in $CDCl_3$ reported by Emsley *et al.* [17] and Ernst and Schulz [18]. In the absence of α-CD, doublet signals of H-4 and H-8 of 2-methylnaphthalene overlap at 7.80–7.82 ppm. When

α-CD is added to a D_2O solution of 2-methylnaphthalene, all the proton signals of 2-methylnaphthalene are shifted to lower fields. At an α-CD concentration of 2.0×10^{-2} mol dm^{-3}, chemical shift differences for H-3, H-5, and H-7 are considerably greater than those for H-1, H-4, H-6, and H-8. In addition, the proton signals of H-4 and H-8, which coalesce in the absence of α-CD, are separated at α-CD concentrations higher than approximately 5.0×10^{-3} mol dm^{-3}. On the basis of a ^{1}H-^{1}H COSY spectrum of 2-methylnaphthalene solution containing 1.0×10^{-2} mol dm^{-3} α-CD (Figure 2), we tentatively assign the proton signals for H-4 and H-8 as shown in Figure 1. Of the proton signals, the H-8 doublet signals alone are reversely shifted to higher fields as the α-CD concentration is raised from 1.0×10^{-2} to 2.0×10^{-2} mol dm^{-3}, indicating the existence of at least two kinds of inclusion complexes. From analyses of electronic absorption and emission spectra, it has been concluded that 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes are present in aqueous α-CD solutions [12]. Therefore, the result obtained from ^{1}H-NMR spectra is consistent with the conclusion obtained from the results based on absorption and fluorescence spectroscopy. The equilibria in aqueous α-CD solutions of 2-methylnaphthalene are represented as follows:

$$\alpha\text{-CD} + 2\text{MN} \overset{K_1}{\rightleftharpoons} \alpha\text{-CD} \cdot 2\text{MN}. \tag{1}$$

$$\alpha\text{-CD} \cdot 2\text{MN} + \alpha\text{-CD} \overset{K_2}{\rightleftharpoons} (\alpha\text{-CD})_2 \cdot 2\text{MN}. \tag{2}$$

Here, 2MN, α-CD·2MN, and $(\alpha\text{-CD})_2$·2MN stand for uncomplexed 2-methylnaphthalene, the 1 : 1 α-CD–2-methylnaphthalene inclusion complex, and the 2 : 1 α-CD–2-methylnaphthalene inclusion complex, respectively, and K_1 and K_2 are the equilibrium constants for the formation of the 1 : 1 and the 2 : 1 inclusion complexes, respectively.

Observed chemical shift differences, $\Delta\delta_{obs}$, are expressed as the sum of a contribution from the product of the intrinsic chemical shift difference, $\Delta\delta_0$, and the concentration of each species:

$$\begin{aligned}\Delta\delta_{obs} = {} & (\Delta\delta_0(\alpha\text{-CD} \cdot 2\text{MN})[\alpha\text{-CD} \cdot 2\text{MN}] \\ & + \Delta\delta_0((\alpha\text{-CD})_2 \cdot 2\text{MN})[(\alpha\text{-CD})_2 \cdot 2\text{MN}]/[2\text{MN}]_0\end{aligned} \tag{3}$$

where a subscript 0 with respect to the concentration represents the initial concentration. The concentrations of the 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes at a given α-CD concentration are respectively estimated using the known K_1 (44.6 mol^{-1} dm^3) and K_2 (376 mol^{-1} dm^3) values [12]:

$$[\alpha\text{-CD} \cdot 2\text{MN}] = K_1[2\text{MN}]_0[\alpha\text{-CD}]_0/(1 + K_1[\alpha\text{-CD}]_0 + K_1K_2[\alpha\text{-CD}]_0^2) \tag{4}$$

$$[(\alpha\text{-CD})_2 \cdot 2\text{MN}] = K_1K_2[2\text{MN}]_0[\alpha\text{-CD}]_0^2/$$

$$(1 + K_1[\alpha\text{-CD}]_0 + K_1K_2[\alpha\text{-CD}]_0^2). \tag{5}$$

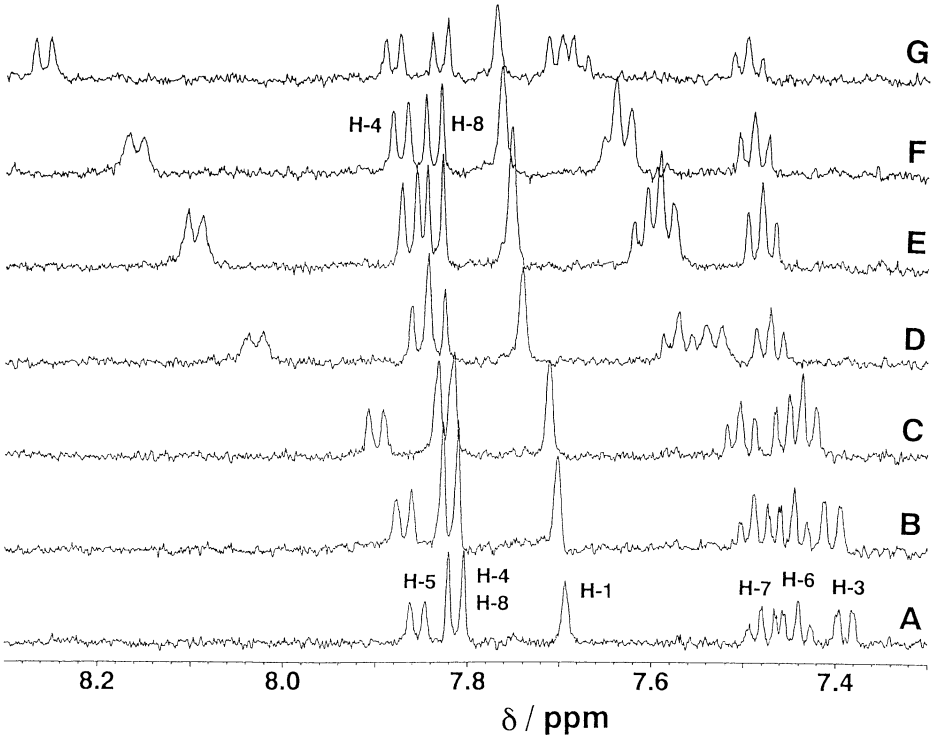

Figure 1. Partial ^{1}H-NMR spectra of 2-methylnaphthalene in D_2O solutions containing various concentrations of α-CD. The 2-methylnaphthalene concentrations were about 2×10^{-4} mol dm^{-3}. Concentration of α-CD: (A) 0, (B) 1.0×10^{-3}, (C) 2.0×10^{-3}, (D) 5.0×10^{-3}, (E) 7.0×10^{-3}, (F) 1.0×10^{-2}, and (G) 2.0×10^{-2} mol dm^{-3}.

Consequently, we simulated chemical shift differences for all the protons of 2-methylnaphthalene as a function of α-CD concentration. Figure 3 illustrates the best fit curves for H-1 and H-8, in which $\Delta\delta_0$ values of H-1 for the 1 : 1 and 2 : 1 inclusion complexes are assumed to be 0.212 and 0.0706 ppm, respectively, and those of H-8 are assumed to be 0.160 and 0.00249 ppm, respectively. The values of $\Delta\delta_0$ for other protons of 2-methylnaphthalene were similarly evaluated from the simulation procedures. Figure 4 depicts the $\Delta\delta_0$ values for all the protons with respect to the 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes. The $\Delta\delta_0$ values, of the 1 : 1 inclusion complex, for H-3, H-7, and methyl protons are nearly the same as those of the inclusion complex. In addition, the $\Delta\delta_0$ values of H-4, H-5, and H-6 are not too different between the 1 : 1 and 2 : 1 inclusion complexes. These findings suggest that a 2-methylnaphthalene molecule is bound to the α-CD cavity from a methyl group as well as a naphthalene ring-end carrying no methyl group to form a 1 : 1 inclusion complex; there are two kinds of 1 : 1 α-CD–2-methylnaphthalene inclusion complexes in aqueous α-CD solutions. In one complex (Complex 1), an α-CD molecule encapsulates a methyl group of

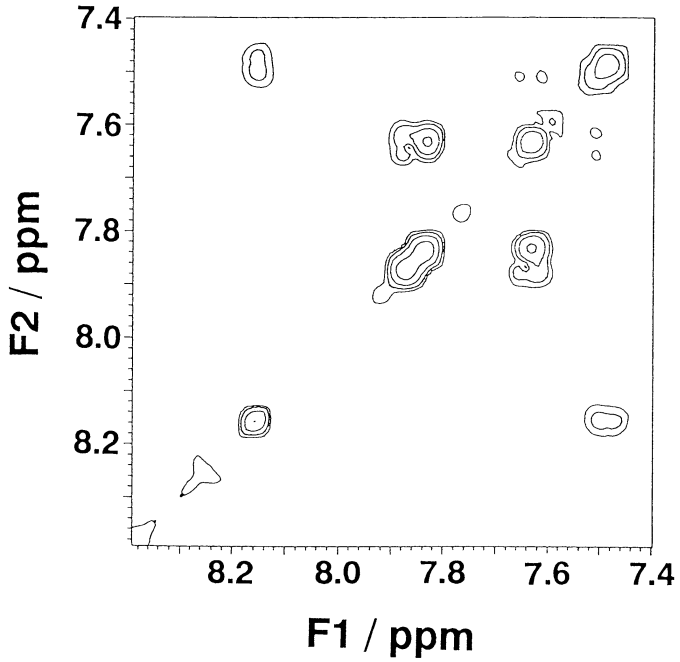

Figure 2. ^{1}H-^{1}H COSY spectrum of 2-methylnaphthalene in D_2O solution containing 1.0×10^{-2} mol dm^{-3} of α-CD.

2-methylnaphthalene, and in the other complex (Complex 2), an α-CD molecule encapsulates the other end of 2-methylnaphthalene carrying no methyl group. As seen in Figure 4, a plot of $\Delta\delta_0$ for the 1 : 1 inclusion complex against proton position follows a pattern analogous to that for the 2 : 1 α-CD–2-methylnaphthalene inclusion complex, although the $\Delta\delta_0$ values of the 1 : 1 inclusion complex for H-1, H-4, H-6, and H-8 are greater than those of the 2 : 1 inclusion complex. The $\Delta\delta_0$ value, of methyl protons, for the 1 : 1 inclusion complex is slightly greater than that for the 2 : 1 inclusion complex, whereas $\Delta\delta_0$, of H-5, for the 1 : 1 inclusion complex is smaller than that for the 2 : 1 inclusion complex. This finding may imply that the inclusion of 2-methylnaphthalene by α-CD somewhat prefers the naphthalene-ring side possessing the methyl group; that is, the concentration of Complex 1 may be slightly higher than that of Complex 2.

From analyses of induced circular dichroism spectra of aqueous CD solutions of 2-methylnaphthalene, it is suggested that in 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes, symmetry axes of α-CD molecules are tilted by about 30° from the longitudinal axis of 2-methylnaphthalene [13]. Consequently, the H-6 signal of 2-methylnaphthalene is not too much affected by the α-CD cavity since the H-6 is not in close contact with the wall of the α-CD cavity. This deduction is consistent with the result obtained from $\Delta\delta_0$ as shown in Figure 4. The $\Delta\delta_0$ value of H-6 for the 1 : 1 inclusion complex is considerably less than those of H-5 and

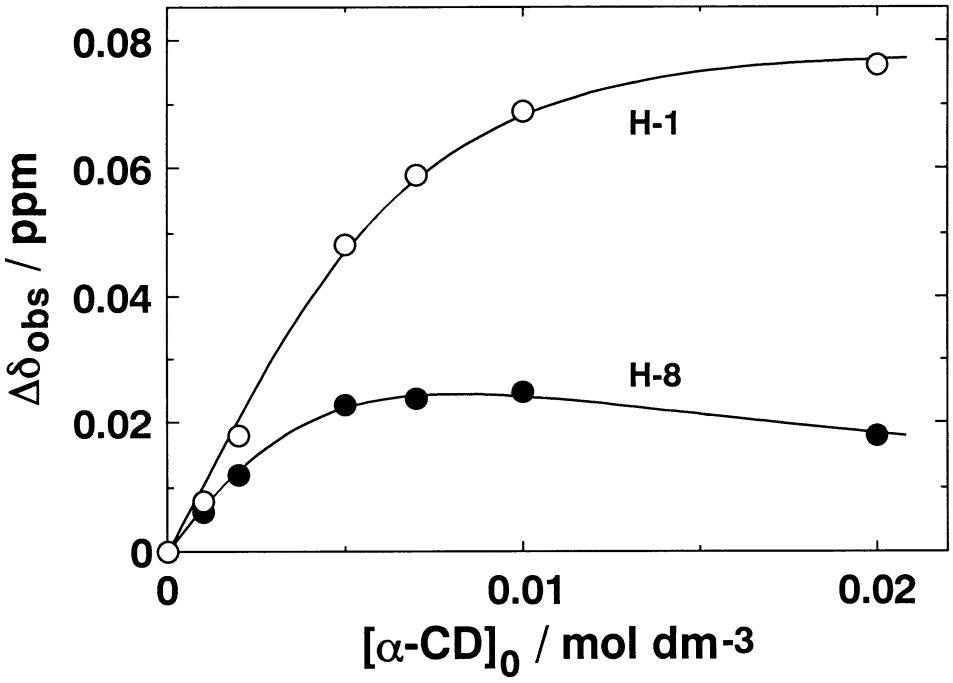

Figure 3. Best fit curves for the observed chemical shift differences of H-1 and H-8 of 2-methylnaphthalene in D_2O solutions. The best fit curves were calculated, assuming that values of $\Delta\delta_0$(α-CD·2MN) and $\Delta\delta_0$((α-CD)$_2$·2MN) for H-1 are 0.212 and 0.0706 ppm, respectively, and that those for H-8 are 0.160 and 0.00249 pm, respectively.

H-7 which are adjacent to H-6. The same is true for the 2 : 1 inclusion complex. In aqueous β-CD solutions of azulene, an azulene molecule is axially included by a β-CD molecule to form a 1 : 1 β-CD–azulene inclusion complex [19]. The chemical shift differences for H-2 and H-6 of azulene are remarkably less than those of the other protons. The smaller $\Delta\delta_0$ value for H-6 of 2-methylnaphthalene is consistent with the results concerning those for H-2 and H-6 of azulene. Protons near the center of the cavity end are affected to a lesser extent by the cavity wall, resulting in the significantly small chemical shift differences.

In a 1 : 1 α-CD–6-bromo-2-naphthol inclusion complex, a bromine atom on a naphthalene ring is preferentially bound into the α-CD cavity [5]. A bromine atom is more hydrophobic than a methyl substituent, so that the selective accommodation of a bromine atom by the first α-CD molecule occurs in the 1 : 1 α-CD–6-bromo-2-naphthol inclusion complex. The hydroxyl-group side of 6-bromo-2-naphthol within the 1 : 1 inclusion complex progressively enters another empty α-CD cavity, leading to a 2 : 1 α-CD–6-bromo-2-naphthol inclusion complex [20]. Similarly, the encapsulation of a chlorine atom in 2-chloronaphthalene is preferred by the first α-CD molecule to form a 1 : 1 inclusion complex [14]. The second α-CD molecule successively binds to the other naphthalene-ring end carrying no chlorine atom,

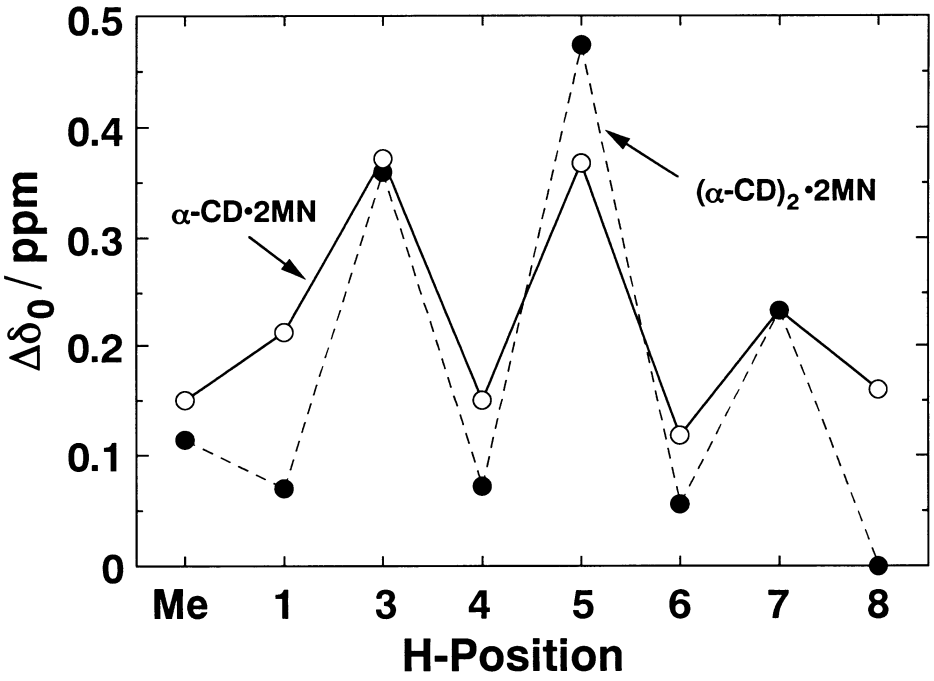

Figure 4. Intrinsic chemical shift differences of protons for 2-methylnaphthalene in the inclusion complexes with α-CD.

resulting in the formation of a 2 : 1 α-CD–2-chloronaphthalene inclusion complex. For 2-methylnaphthalene, the hydrophobicity of the methyl group seems to be not too different from that of the naphthalene ring-end bearing no methyl group. Consequently, it is possible that the first α-CD molecule binds to a methyl group of 2-methylnaphthalene as well as a naphthalene ring-end carrying no methyl group. The fact that the K_2 value is an order of magnitude greater than the K_1 value seems to indicate that the two α-CD molecules are hydrogen-bonded with each other in the 2 : 1 α-CD–2-methylnaphthalene inclusion complex.

As in the case of 6-bromo-2-naphthol, the $\Delta\delta_0$ values for some protons of 2-methylnaphthalene in the 1 : 1 inclusion complex are rather smaller than those in the 2 : 1 α-CD–2-methylnaphthalene inclusion complex. This finding suggests that the molecular disposition of 2-methylnaphthalene in the 2 : 1 inclusion complex relative to α-CD molecules is slightly different from that in the 1 : 1 inclusion complex.

4. Conclusions

As the α-CD concentration is increased in the low α-CD concentration range, ^{1}H-NMR signals of 2-methylnaphthalene are shifted to lower fields. At 2.0×10^{-2} mol dm^{-3} of α-CD, the H-8 signal is reverse shifted to higher fields, indicating

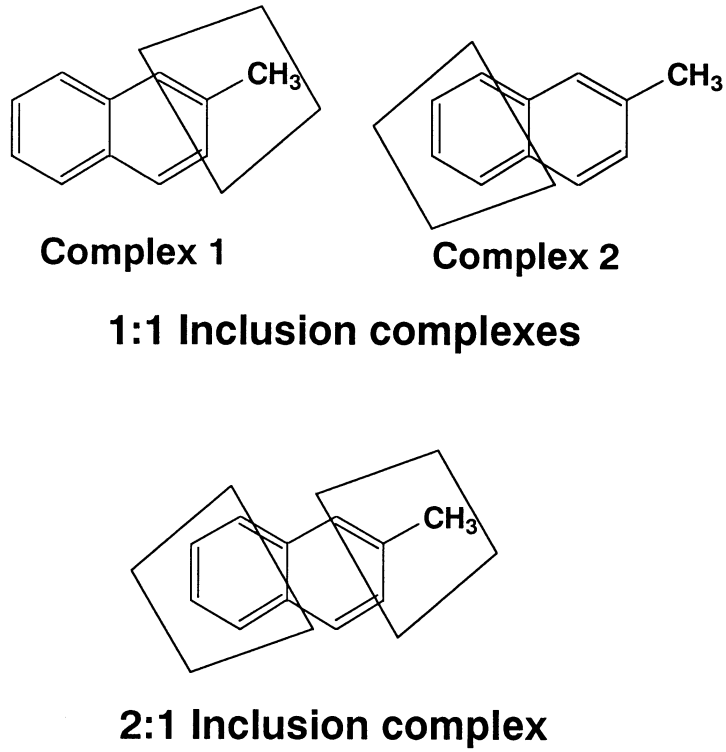

Figure 5. Possible structures of α-CD–2-methylnaphthalene inclusion complexes. Trapezoids represent α-CD molecules.

the formation of the two kinds of inclusion complexes; taking into account the small cavity size of α-CD, it is most reasonable that the 1 : 1 and 2 : 1 α-CD–2-methylnaphthalene inclusion complexes are present in D_2O containing α-CD. The intrinsic chemical shift differences, of protons in 2-methylnaphthalene, estimated from a simulation method, suggest that the selectivity of α-CD towards the binding site is nearly the same with respect to a methyl group end and a naphthalene ring-end carrying no methyl group. This finding implies the existence of two kinds of 1 : 1 inclusion complexes, in which the binding site of α-CD is different from one another.

References

1. D. W. Griffiths and M. L. Bender: *Adv. CataIysis* **23**, 209 (1973).
2. S. Hamai: *Bull. Chem. Soc. Jpn.* **55**, 2721 (1982); S. Hamai: *J. Phys. Chem.* **93**, 6527 (1989).
3. M. Komiyama and H. Hirai: *Chem. Lett.* 1467 (1980)
4. 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).
5. Y. Inoue, H. Hoshi, M. Sakurai, and R. Chujo: *J. Am. Chem. Soc.* **107**, 2319 (1985).
6. Y. Inoue, M. Kitagawa, H. Hoshi, M. Sakurai, and R. Chujo: *J. Incl. Phenom.* **5**, 55 (1987).

7. M. Komiyama and H. Hirai: *Chem. Lett.* 1471 (1980).
8. H. Hirai, Y. Shiraishi, H. Mihori, and T. Kawamura: *Polymer J.* **27**, 1064 (1995).
9. H. Park, B. Mayer, P. Wolschann, and G. Köhler: *J. Phys. Chem.* **98**, 6158 (1994).
10. S. Hamai: *J. Chem. Soc., Chem. Commun.* 2243 (1994).
11. S. Hamai: *J. Phys. Chem.* **99**, 12109 (1995).
12. S. Hamai: *J. Incl. Phenom.* **27**, 57 (1997).
13. S. Hamai: *J. Phys. Chem. B* **101**, 1707 (1997).
14. S. Hamai and K. Hori: submitted.
15. A. J. Gordon and R. A. Ford: *The Chemist's Companion*, J. Wiley & Sons, New York, p. 249 (1972).
16. Y. Matsui, E. Tanemura, and T. Nonomura: *Bull. Chem. Soc. Jpn.* **66**, 2827 (1993).
17. J. W. Emsley, S. R. Salman, and R. A. Storey: *J. Chem. Soc. (B)* 1513 (1970).
18. L. Ernst and P. Schulz: *Magn. Reson. Chem.* **30**, 73 (1992).
19. S. Hamai, T. Ikeda, A. Nakamura, H. Ikeda, A. Ueno, and F. Toda: *J. Am. Chem. Soc.* **114**, 6012 (1992).
20. The fact that the solubilities of bromonaphthalenes in water are significantly lower than those of methylnaphthalenes indicates the more hydrophobic nature of a bromine substituent than a methyl substitutent.