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^{1}H-NMR Study on Inclusion Modes of 2-Chloronaphthalene and α-Cyclodextrin in D_2O

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With a 1:1 and a 2:1 host-guest stoichiometry, α-cyclodextrin (α-CD) forms inclusion complexes with 2-chloronaphthalene. From simulations concerning observed chemical-shift differences ($\Delta\delta_{obs}$) of proton signals of 2-chloronaphthalene, intrinsic Δδ values are estimated for all the guest protons in the 1:1 and 2:1 inclusion complexes. The intrinsic Δδ values indicate that α-CD first binds to a part of a naphthalene ring bearing a Cl atom to form the 1:1 inclusion complex. In the 1:1 and 2:1 inclusion complexes, the symmetry axes of α-CD are tilted approximately 30° relative to a naphthalene longitudinal axis. In the 2:1 inclusion complex, the association through hydrogen bonding most likely occurs between two α-CD molecules whose symmetry axes are laterally shifted.

Keywords: ^{1}H-NMR, α-cyclodextrin, 2-chloronaphthalene, inclusion complexes

INTRODUCTION

Cyclodextrins (CDs), which are shaped like a truncated cone having a cavity in center, are cyclic oligomers of D-glucose. Since the CD cavity is hydrophobic, hydrophobic organic compounds of appropriate dimensions are incorporated into the CD cavity to form an inclusion complex in aqueous solution. Usually, an inclusion complex with a 1:1 host-guest stoichiometry is formed between CD and a guest molecule. It is widely believed that a benzene ring snugly fits to the α-CD cavity while a naphthalene ring best fits to the β-CD cavity. It has also been recognized that α-CD is too small to thoroughly encapsulate a naphthalene ring. Consequently, interactions between α-CD and the naphthalene ring have not fully been investigated so far.

Recently, however, α-CD has been found to form 1:1 and 2:1 host-guest inclusion complexes with 2-naphthol, 6-bromo-2-naphthol, 2-methylnaphthalene, and 2-chloronaphthalene [1-4]. For these 1:1 inclusion complexes, a question arises concerning a position of binding of a naphthalene ring by an α-CD molecule, although a more hydrophobic part of the guest is expected to be first accommodated into the α-CD cavity. In the case of 2-naphthol, the C-5-C-8 portion of a naphthalene ring is likely to be first encapsulated by α-CD [1]. From ^{1}H-NMR spectroscopic studies on 6-bromo-2-naphthol inclusion complexes, the

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first α-CD molecule has been found to bind to a portion of the naphthalene ring bearing a Br atom [2b]. Consequently, the second α-CD molecule binds to a hydroxyl-group side, thereby forming a 2:1 inclusion complex. Since these guests examined have a hydrophilic hydroxyl group, the preference of the α-CD binding position may be affected by the presence of a hydroxyl group to some extent.

Thus, we selected a guest molecule possessing no hydroxyl group, 2-chloronaphthalene which has been found to form a 1:1 inclusion complex followed by a 2:1 inclusion complex with α-CD [4], and investigated the binding mode of α-CD by means of ^{1}H-NMR spectroscopy. In this article, we report the binding of the first α-CD molecule to a Cl atom substituted on a naphthalene ring, and the formation of a non-coaxial α-CD dimer, in a 2:1 inclusion complex, through hydrogen bonding.

RESULTS AND DISCUSSION

^{1}H-NMR Spectra of 2-Chloronaphthalene

Figure 1 shows ^{1}H-NMR spectra of 2-chloronaphthalene in D_2O containing varying concentrations of α-CD. Proton signals of 2-chloronaphthalene were assigned on the basis of the proton-signal assignment of 2-chloronaphthalene in $CDCl_3$ (not shown) and several ^{1}H – ^{1}H correlation spectroscopy (COSY) spectra (*e.g.*, Fig. 2) for D_2O solutions containing different α-CD concentrations. In the absence of α-CD, signals of H-6 and H-7 shown in Figure 1 are partially overlapped each other. The signals of H-4 and H-5 are also partially overlapped. Upon adding α-CD to a 2-chloronaphthalene solution, all the proton signals of 2-chloronaphthalene are shifted to lower fields, indicating the formation of an inclusion complex between α-CD and 2-chloronaphthalene. However, the extents of shift are different from each other. For the H-1 and H-4 signals, the reverse shift (higher-field shift) is seen at high α-CD concentrations. Such reverse shifts of proton signals have been observed for the α-CD – 6-bromo – 2-naphthol and β-CD – 1-propanol – azulene systems [2b, 5].

When β-CD was added to a D_2O solution of azulene, higher-field shifts of all the proton signals of azulene were observed owing to the formation of a 1:1 inclusion complex between β-CD and azulene [5]. Further addition of 1-propanol to the azulene solution containing β-CD

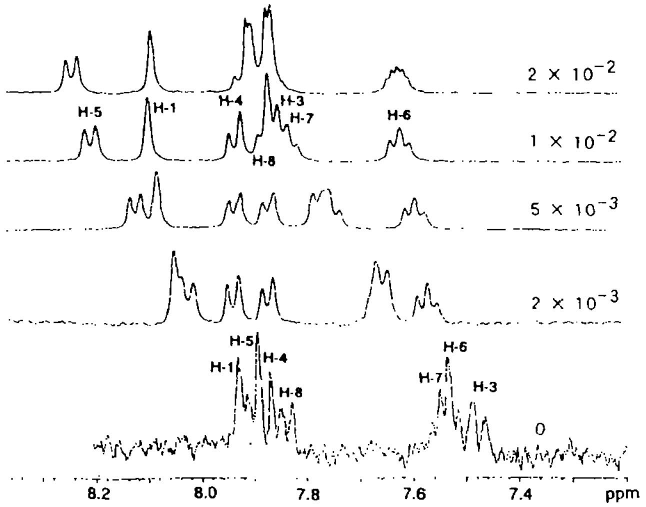

FIGURE 1 ^{1}H-NMR spectra of 2-chloronaphthalene in D_2O containing varying concentrations of α-CD. The concentration of α-CD is shown at the right-hand side of each spectrum.

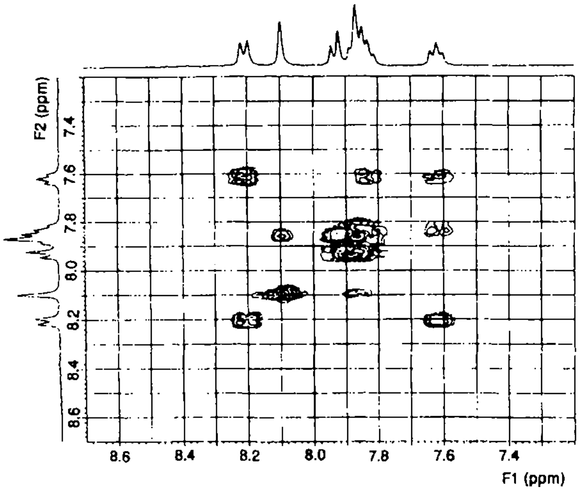

FIGURE 2 ^{1}H-^{1}H COSY spectrum of 2-chloronaphthalene in D_2O containing α-CD (1×10^{-2} mol dm^{-3}).

resulted in the reverse shifts (lower-field shifts) except for the H-4 and H-8 signals. The reverse shifts are due to the formation of a 2:2:1 β-CD – 1-propanol – azulene inclusion complex in which azulene is located within the cavities of two associating β-CD molecules. Each 1-propanol molecule is incorporated into an open mouth of the β-CD molecule which associates with the other β-CD molecule. As evidenced by the α-CD – 6-bromo-2-naphthol and β-CD – 1-propanol – azulene systems, the formation of a multi-component inclusion complex causes reverse chemical shifts of some proton signals of a guest, in contrast to monotonous chemical shifts for a 1:1 inclusion complex.

Analyses of Proton Chemical Shifts for 2-Chloronaphthalene

In addition to the experimental results obtained from absorption and fluorescence spectral analyses [3], the reverse chemical shifts of the guest protons provide evidence for the formation of a 2:1 α-CD – 2-chloronaphthalene inclusion complex:

$$\alpha\text{-CD} + 2\text{CN} \overset{K_1}{\rightleftharpoons} \alpha\text{-CD}\cdot 2\text{CN} \qquad (1)$$

$$\alpha\text{-CD} + \alpha\text{-CD}\cdot 2\text{CN} \overset{K_2}{\rightleftharpoons} (\alpha\text{-CD})_2\cdot 2\text{CN} \qquad (2)$$

Here, 2CN, α-CD·2CN, and $(\alpha\text{-CD})_2\cdot 2\text{CN}$ stand for 2-chloronaphthalene, the 1:1 α-CD – 2-chloronaphthalene inclusion complex, and the 2:1 α-CD – 2-chloronaphthalene inclusion complex, respectively, and K_1 and K_2 are the equilibrium constans for the formation of α-CD·2CN and $(\alpha\text{-CD})_2\cdot 2\text{CN}$, respectively.

The observed chemical-shift difference, $\Delta\delta_{\text{obs}}$, for a proton signal is represented as the sum of a contribution from the 1:1 inclusion complex and that from the 2:1 inclusion complex:

$$\begin{aligned}\Delta\delta_{\text{obs}} = {} & (\Delta\delta(\alpha\text{-CD}\cdot 2\text{CN})[\alpha\text{-CD}\cdot 2\text{CN}] \\ & + \Delta\delta((\alpha\text{-CD})_2\cdot 2\text{CN}) \\ & \times [(\alpha\text{-CD})_2\cdot 2\text{CN}])/[2\text{CN}]_0\end{aligned} \qquad (3)$$

where $\Delta\delta(\alpha\text{-CD}\cdot 2\text{CN})$ and $\Delta\delta((\alpha\text{-CD})_2\cdot 2\text{CN})$ are the intrinsic chemical-shift differences for the 1:1 inclusion complex and the 2:1 inclusion complex, respectively, and $[\alpha\text{-CD}\cdot 2\text{CN}]$, $[(\alpha\text{-CD})_2\cdot 2\text{CN}]$ and $[2\text{CN}]_0$ are the concentrations of α-CD·2CN and $(\alpha\text{-CD})_2\cdot 2\text{CN}$, and the initial concentration of 2CN, respectively. The concentrations of the two inclusion complexes are respectively expressed by

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

and

$$[(\alpha\text{-CD})_2\cdot 2\text{CN}] = K_1K_2[2\text{CN}]_0[\alpha\text{-CD}]_0^2/(1 + K_1[\alpha\text{-CD}]_0 + K_1K_2[\alpha\text{-CD}]_0^2) \qquad (5)$$

Since the K_1 and K_2 values for aqueous solution have already been evaluated to be 486 and 364 mol^{-1} dm^3 from a fluorometric method [3], these values were used for D_2O solutions. Consequently, the $\Delta\delta_{\text{obs}}$ value can be calculated from Eq. (3) by employing $\Delta\delta(\alpha\text{-CD}\cdot 2\text{CN})$ and $\Delta\delta((\alpha\text{-CD})_2\cdot 2\text{CN})$ as parameters. Figure 3 illustrates the

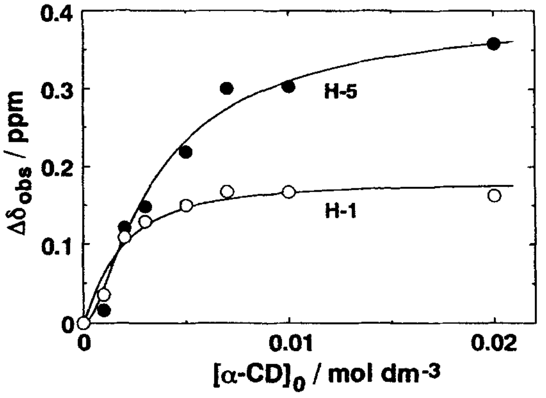

FIGURE 3 Comparison of $\Delta\delta_{obs}$ for H-1 and H-5 with the best fit curves which were calculated with assumed $\Delta\delta$(α-CD·2CN) and $\Delta\delta$((α-D)$_2$·2CN) values. Assumed values: $\Delta\delta$(α-CD·2CN) = 0.141 and $\Delta\delta$((α-CD)$_2$·2CN) = 0.182 ppm for H-1, and $\Delta\delta$(α-CD·2CN) = 0 and $\Delta\delta$((α-CD)$_2$·2CN) = 0.413 ppm for H-5.

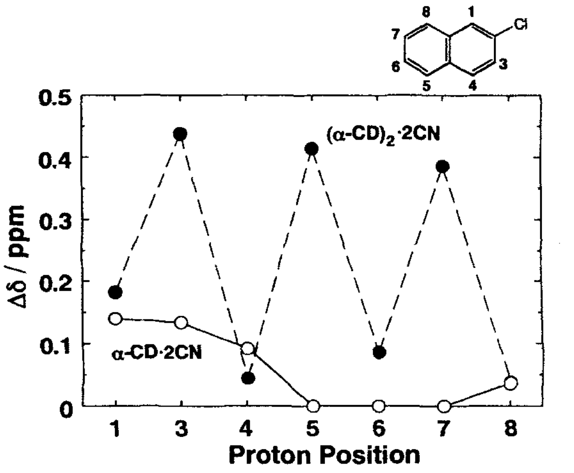

FIGURE 4 Dependence of $\Delta\delta$ for the 1:1 and 2:1 inclusion complexes on the proton position of 2-chloronaphthalene.

best fit curves of $\Delta\delta_{obs}$ calculated for H-1 and H-5 together with observed data points of $\Delta\delta_{obs}$. From the simulation shown in Figure 3, the $\Delta\delta$(α-CD·2CN) and $\Delta\delta$((α-CD)$_2$·2CN) values are estimated to be 0.141 and 0.182 ppm for H-1, and 0 and 0.413 ppm for H-5, respectively. Similarly, the $\Delta\delta$(α-CD·2CN) and $\Delta\delta$((α-CD)$_2$·2CN) values for the other 2-chloronaphthalene protons have been estimated.

All the $\Delta\delta$(α-CD·2CN) and $\Delta\delta$((α-CD)$_2$·2CN) values thus obtained are depicted in Figure 4. As seen in Figure 4, the $\Delta\delta$(α-CD·2CN) values for H-1, H-3, and H-4 are relatively large, and are in the range of 0.1 – 0.14 ppm, whereas those for H-5, H-6 and H-7 are 0 ppm (or nearly 0 ppm). This finding evidently indicates that α-CD first encapsulats 2-chloronaphthalene from a part of a naphthalene ring bearing a Cl atom to form a 1:1 inclusion complex. This is consistent with the fact that a Cl atom is more hydrophobic than a H atom, since CD is anticipated to favorably bind to a more hydrophobic moiety of a guest.

Association Mode of Two α-CD Molecules in the 2:1 Inclusion Complex

In the 2:1 inclusion complex, the $\Delta\delta$((α-CD)$_2$·2CN) values for H-5 and H-7 are 0.413 and 0.386 ppm, respectively, indicating that the C-5 – C-8 portion of 2-chloronaphthalene is accommodated into the second α-CD molecule. However, the $\Delta\delta$((α-CD)$_2$·2CN) value of H-6 is 0.0855 ppm. The much smaller $\Delta\delta$((α-CD)$_2$·2CN) value for H-6 than those for H-5 and H-7 implies that the second α-CD binds to 2-chloronaphthalene, being tilted approximately 30° relative to the longitudinal axis of 2-chloronaphthalene. As a consequence, H-6 is positioned at the open mouth of the α-CD cavity, whose environment resembles a bulk D_2O medium, so that the inclusion by α-CD affects the chemical shift of H-6 to a less degree, compared to H-5 and H-7 which are deeply buried into the cavity. From induced circular dichroism studies on α-CD – 2-chloronaphthalene and β-CD – 2-chloronaphthalene inclusion complexes, it has been concluded that the symmetry axis of an α-CD molecule is tilted approximately 30° with respect to the longitudinal axis of a naphthalene ring [4]. Our conclusion obtained from the ^{1}H-NMR spectra is consistent with that obtained from induced circular dichroism spectra.

It should be noted that the $\Delta\delta$((α-CD)$_2$·2CN) value for H-3 is significantly increased compared to the $\Delta\delta$(α-CD·2CN) value for H-3. In addition, the $\Delta\delta$((α-CD)$_2$·2CN) value for H-1 is slightly increased, although that for H-4 is conversely decreased. These findings suggest that, in the 2:1 inclusion complex, the C-1 – C-3 portion of 2-chloronaphthalene which is incorporated into the first α-CD molecule is more deeply inserted to the α-CD cavity. Therefore, the two α-CD molecules most likely dimerize in the 2:1 inclusion complex, including a 2-chloronaphthalene molecule within their cavities. The α-CD dimer within the 2:1 inclusion complex seems to be hydrogen bonded with each other, adopting a non-coaxial, face-to-face (probably head-to-head) orientation. That is, two α-CD symmetry axes are laterally shifted in the 2:1 inclusion complex.

For most inclusion complexes in which two CD molecules take a dimeric form, X-ray crystallography has revealed a coaxial (or nearly coaxial), head-to-head orientation of two CD molecules associating in the crystalline state [6 – 9]. The association of the two CD molecules is due to hydrogen bonding between hydroxyl groups attached on the wider rims of the two CD molecules. In crystals of 2:1 α-CD – ferrocene, α-CD-cyclopentadienyl(arene)-Fe(II) complex, and α-CD – metallocenium hexafluorophosphate inclusion complexes, however, the symmetry axes of the two α-CD molecules are not coaxial [10 – 12]. In the ferrocene, cyclopentadienyl (cycloheptatriene)-Fe(II) complex, and cylcopentadienyl(cyclooctatetraene)-Fe(II) complex inclusion complexes, the two α-CD symmetry axes are laterally shifted by 0.12 or 0.13 nm.

In the 2:1 α-CD – 2-chloronaphthalene inclusion complex in solution, the symmetry axes of two α-CD molecules are tilted approximately 30° relative to the longitudinal axis of the naphthalene ring of 2-chloronaphthalene. Using a C—C bond length of 0.1405 nm for a naphthalene ring, a distance between the two non-coaxial, parallel α-CD symmetry axes is calculated to be 0.12 nm which is the same as the corresponding distance determined for an α-CD – cyclopentadienyl(cycloheptatriene)-Fe(II) complex inclusion complex, *etc.*, in which two α-CD molecules in one inclusion complex are hydrogen bonded with each other. Therefore, hydrogen bonding between two α-CD molecules is reasonable for the 2:1 α-CD – 2-chloronaphthalene inclusion complex in D_2O. To form a 2:1 inclusion complex, an additional α-CD molecule has to bind to a less hydrophobic C-5 – C-8 portion of 2-chloronaphthalene, compared to the binding site of a Cl atom in 2-chloronaphthalene, so that the additional α-CD molecule is not expected to favorably encapsulate 2-chloronaphthalene. Nonetheless, the K_2 value ($364\,\mathrm{mol^{-1}\,dm^3}$) for 2-chloronaphthalene is comparable with the K_1 value ($486\,\mathrm{mol^{-1}\,dm^3}$). The comparable K_1 and K_2 values may be interpreted in terms of the association of two α-CD molecules in the 2:1 inclusion complex.

EXPERIMENTAL

Materials

2-Chloronaphthalene purchased from Tokyo Kasei Kogyo, Co. Ltd., is purified by use of silica-gel column chromatography. α-CD obtained from Nacalai Tesque, Inc. was used as received. Concentrations of 2-chloronaphthalene in D_2O were around $4.6 \times 10^{-5}\,\mathrm{mol\,dm^{-3}}$.

Instrumental

^{1}H-NMR spectra were run on a Varian UNITY plus 400 spectrometer, operating at 400 MHz. At least 800 transients were collected for each ^{1}H-NMR spectrum. A trace amount of acetonitrile was used as an internal reference ($\delta = 2.00$ ppm) [13]. Measurements were made at 25 ± 1°C.

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