Bull. Chem. Soc. Jpn., 71, 2323—2329 (1998) 2323

Molecular Recognition in Ternary Complexes of γ-Cyclodextrin with Naphthalenedicarboxylate Ions and a Space-Regulator Ion

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(Received April 16, 1998)

Complexation of γ-cyclodextrin (γ-CD) with the 2,6-naphthalenedicarboxylate ion (2,6-NDC) in alkaline D_2O was greatly enhanced by the addition of 2,6-bis(1-pyridiniomethyl)naphthalene dibromide (2,6-PMN) as a space-regulator. Formation of a ternary 1 : 1 : 1 complex between γ-CD, 2,6-NDC, and 2,6-PMN was confirmed by means of ^{1}H NMR spectroscopy, together with the measurements of induced circular dichroism spectra and UV absorption spectra. Changes in chemical shifts (δ) of the γ-CD protons in the presence of an excess amount of 2,6-PMN with the addition of NDC regioisomers were analyzed by a curve-fitting procedure to give binding constants (K_6) for complexation of NDC's with a γ-CD–2,6-PMN binary complex. The K_6 values increased in the order of 1,5-NDC < 1,4-NDC < 1,8-NDC < 1,3-NDC < 1,6-NDC < 2,3-NDC < 2,7-NDC < 2,6-NDC, indicating that a binary complex of γ-CD with 2,6-PMN is able to recognize the molecular structures of NDC's. The open space between the γ-CD cavity and 2,6-PMN will be favorable for the accommodation of a slender molecule such as 2,6-NDC, but unfavorable for the accommodation of a bulky molecule such as 1,5-NDC.

Cyclodextrin (CD) is a cyclic oligomer composed of six (α-CD), seven (β-CD), eight (γ-CD), or more α-D-glucopyranose units. The doughnut-shaped CD molecule has an interior cavity with the diameter of 0.47—0.57 nm (α-CD), 0.60—0.64 nm (β-CD), or 0.75—0.83 nm (γ-CD).[1] The cavity is hydrophobic and accommodates a variety of organic molecules and ions to form inclusion complexes. Recently, we have found that β-CD is able to recognize the molecular structures of naphthalenedicarboxylic acid regioisomers (NDC).[2] The binding constants (K_a) for β-CD complexes with NDC's increased in the order of 1,4-NDC $\approx$ 1,5-NDC < 1,3-NDC < 1,6-NDC < 2,3-NDC < 2,7-NDC $\leqq$ 2,6-NDC. On the other hand, interactions of α- and γ-CD's with NDC's were very weak and nonspecific to NDC's. The cavity of α-CD will be too small to include NDC, and that of γ-CD, too large to attain close van der Waals contact with NDC. According to Ueno et al.,[3] two molecules of a naphthalene derivative, 1-naphthylacetate, are accommodated within a γ-CD cavity to form a ternary complex. They also found that 1-naphthyloxyacetic acid loosely and weakly included in the γ-CD cavity is strongly bound to γ-CD by the addition of cyclohexanol.[4] Cyclohexanol acts as a space-regulator which narrows the cavity of γ-CD to allow the inclusion of the acid.

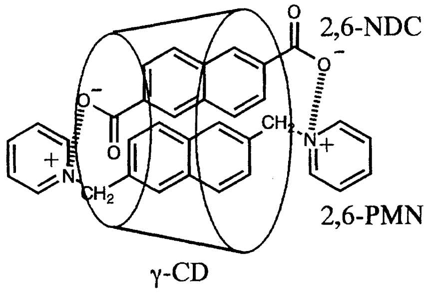

Fig. 1. Expected molecular structure of a 1 : 1 : 1 ternary complex between γ-CD, 2,6-NDC, and 2,6-PMN.

The present study deals with an effect of 2,6-bis(1-pyridiniomethyl)naphthalene dibromide (2,6-PMN) as a space-regulator on the molecular recognition of NDC regioisomers by γ-CD (Fig. 1). The 2,6-PMN bears two positive charges far apart from each other in a molecule, whereas 2,6-NDC in an alkaline solution has two negative charges apart similarly to those in 2,6-PMN. Thus, electrostatic interactions of 2,6-PMN with 2,6-NDC will be more advantageous than those with other NDC regioisomers. It is also anticipated that 2,6-PMN acts as a space-regulator for the inclusion of 2,6-NDC in the γ-CD cavity. The γ-CD cavity is so hydrophobic that electrostatic interactions between 2,6-PMN and 2,6-NDC will be enhanced. Moreover, steric factors arising from the γ-CD cavity will play a part of molecular recognition in the formation of ternary complexes. The open space between the γ-CD cavity and 2,6-PMN will be favorable for the accommodation of a slender molecule such as 2,6-NDC, but unfavorable for the accommodation of a bulky molecule such as 1,5-NDC. Only a few reports[5—7] have been published on molecular recognition in CD ternary complexes, though a number of examples have been reported for molecular recognition in CD binary complexes.

Experimental

Materials. The α-CD was supplied by Nihon Shokuhin Kako Co., Ltd. The β- and γ-CD's were supplied by Ensuiko Seito Co., Ltd. They were dried overnight in vacuo at 110 °C. The $CDCl_3$ (Isotec) and D_2O (Isotec) which we used contained 99.8 atm% D. The 1,4-, 2,3-, and 2,6-NDC's were of reagent grade and commercially available. The 1,3-, 1,5-, 1,6-, 1,8-, and 2,7-NDC's were prepared and identified as described in a previous paper.[2)] The 2,6-PMN was prepared by refluxing 2,6-bis(bromomethyl)-naphthalene (2,6-BrMN) in pyridine for 8 h. After removing pyridine by evaporation, a residual crude product was recrystallized from aqueous ethanol. ^{1}H NMR (0.10 mol dm^{-3} $NaHCO_3$ in D_2O) δ = 8.96 (dd, J = 1.4, 6.8 Hz, 4H), 8.56 (tt, J = 1.4, 7.8 Hz, 2H), 8.08 (t, J = 7.6 Hz, 4H), 8.04 (d, J = 1.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H), 7.58 (dd, J = 1.5, 8.5 Hz, 2H), and 6.00 (s, 4H). The 2,6-BrMN was prepared by a reaction of commercially available 2,6-dimethylnaphthalene with *N*-bromosuccinimide in CCl_4 containing a small amount of 2,2′-azobisisobutyronitrile.[8)] ^{1}H NMR ($CDCl_3$) δ = 7.82 (s, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.52 (dd, J = 1.5, 8.3 Hz, 2H), and 4.65 (s, 4H).

Apparatus. ^{1}H NMR spectra were recorded using a JEOL Model JNM-A400 FT NMR spectrometer (400 MHz) with a sample tube of 5.0 mm diameter at 25.0±0.1 °C. Sample solutions were composed of NDC, 2,6-PMN, and/or CD in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$. Methanol (0.4 mmol dm^{-3}) was used as an internal reference (δ = 3.343) for ^{1}H NMR.[9)] The phase-sensitive ROESY spectrum of a γ-CD inclusion complex with 2,6-NDC and 2,6-PMN was acquired with a mixing time of 250 ms, 512 points for t_2, and 256 points for t_1, followed by zero-filling. The induced circular dichroism (ICD) spectra of 2,6-NDC and 2,6-PMN in the presence of γ-CD were recorded using a JASCO Model J-720 spectrometer at 25 °C.

Results and Discussion

Formation of a Ternary Complex. Figure 2 illustrates changes in ^{1}H NMR spectra of 10.0 mmol dm^{-3} γ-CD in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ with the separate and combined addition of 10.0 mmol dm^{-3} 2,6-NDC and 10.0 mmol dm^{-3} 2,6-PMN. The pD value of 0.10 mol dm^{-3} $NaHCO_3$ in D_2O is 8.97, at which 2,6-NDC completely dissociates into the dicarboxylate anion.[2)] In the absence of 2,6-NDC and 2,6-PMN, γ-CD gave ^{1}H NMR signals at δ = 5.108 (d, J = 3.9 Hz) for C(1)–H, 3.651 (dd, J = 3.9, 10.0 Hz) for C(2)–H, 3.933 (t, J = 9.5 Hz) for C(3)–H, 3.588 (t, J = 9.4 Hz) for C(4)–H, 3.860 (m) for C(5)–H, and 3.870 (m) for C(6)–H (Fig. 2a). The separate addition of 2,6-NDC and 2,6-PMN caused slight upfield shifts in all the signals of γ-CD (Figs. 2b and 2c). 2,6-NDC is weakly bound to γ-CD to form a 1 : 1 inclusion complex, the binding constant (K_a) of which is 8 mol^{-1} dm^3.[2)] 2,6-PMN is also bound to γ-CD (K_a = 3 mol^{-1} dm^3), as will be mentioned below. On the other hand, the combined addition of 2,6-NDC and 2,6-PMN caused remarkable upfield shifts (Fig. 2d), especially in C(3)–H and C(5)–H located at the interior cavity of γ-CD, indicating that a pair of 2,6-NDC and 2,6-PMN is cooperatively bound to the γ-CD cavity to form a stable 1 : 1 : 1 ternary complex.

Figure 3 illustrates the effects of α-, β-, and γ-CD on the ^{1}H NMR spectrum of a solution containing equimolar 2,6-NDC and 2,6-PMN. Based on 2D COSY spectra, the peaks in the spectra were assigned as shown in the illustration, where the letters N and P in parentheses refer to 2,6-NDC and 2,6-PMN, respectively; the figures 1, 3, and 4, to the positions of protons in the naphthalene moiety; the Greek letters α, β, and γ, to the positions of protons in the pyridinio moiety; and the letter M, to the methylene proton of 2,6-PMN. The addition

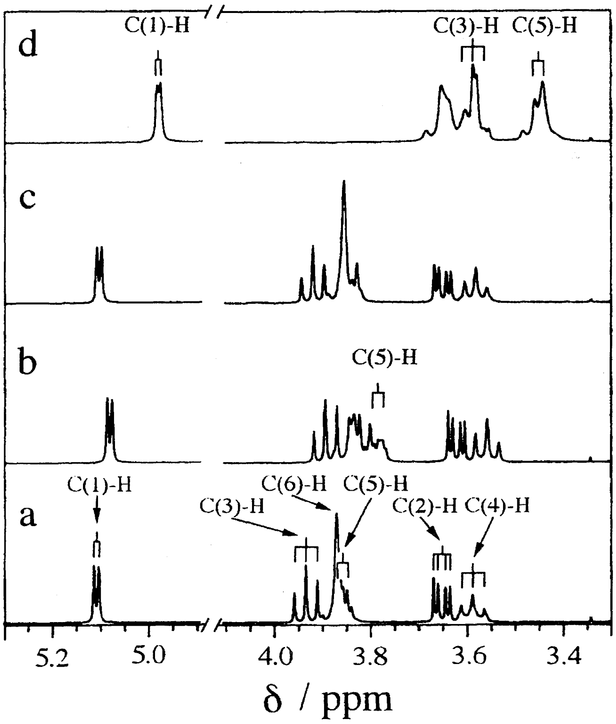

Fig. 2. The ^{1}H NMR spectra of 10.0 mmol dm^{-3} γ-CD in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C, in the absence (a) and in the presence of 10.0 mmol dm^{-3} 2,6-NDC (b), 10.0 mmol dm^{-3} 2,6-PMN (c), and 10.0 mmol dm^{-3} 2,6-NDC and 10.0 mmol dm^{-3} 2,6-PMN (d).

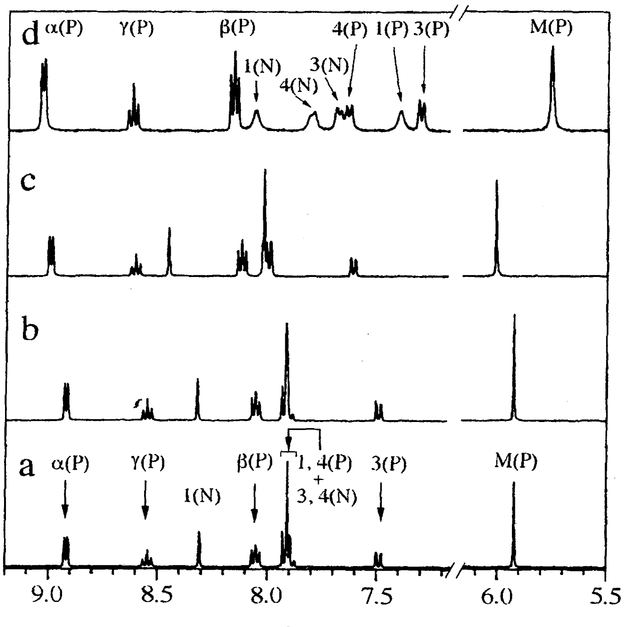

Fig. 3. The ^{1}H NMR spectra of equimolar (3.0 mmol dm^{-3}) solutions of 2,6-NDC and 2,6-PMN in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C in the absence (a) and in the presence of 10.0 mmol dm^{-3} α-CD (b), 10.0 mmol dm^{-3} β-CD (c), and 10.0 mmol dm^{-3} γ-CD (d).

of α-CD had virtually no effect on the spectrum, indicating that α-CD does not interact with 2,6-NDC and 2,6-PMN. The addition of β-CD caused significant downfield shifts in peaks due to 2,6-NDC and 2,6-PMN. β-CD and 2,6-NDC forms a 1 : 1 inclusion complex (K_a = 537 mol^{-1} dm^3).[2] We have also found that β-CD forms a 1 : 1 inclusion complex with 2,6-PMN (K_a = 102 mol^{-1} dm^3). Hence, the downfield shifts of the peaks are attributable to the formation of 1 : 1 complexes of β-CD with 2,6-NDC and with 2,6-PMN. The β-CD cavity is too small to accommodate both 2,6-NDC and 2,6-PMN. On the other hand, the addition of γ-CD gave rise to a large and characteristic change in the spectrum of an equimolar 2,6-NDC and 2,6-PMN solution: The peaks due to the pyridinio protons showed downfield shifts, whereas the peaks due to the naphthalene protons and methylene proton shifted to an upfield direction. Furthermore, significant peak broadening was observed in most of peaks due to the naphthalene protons. In general, the line width is inversely proportional to the life time of a nucleus magnetically excited to a higher energy state. The life time will be shortened by the acceleration of spin–spin and/or chemical exchange relaxation upon complexation of 2,6-NDC with γ-CD and 2,6-PMN.

Figure 4 shows a 2D ROESY spectrum of an equimolar (10.0 mmol dm^{-3}) solution of γ-CD, 2,6-NDC, and 2,6-PMN in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$. We found clear cross-peaks connecting the C(3)- and C(5)-H′s of γ-CD to the H(3) and H(4) of 2,6-PMN and to the H(1) and H(3) of 2,6-NDC, together with small cross-peaks connecting the C(3)–H′s to γ-CD to the H(1) of 2,6-PMN and the H(4) of 2,6-NDC. In general, a cross-peak appears when two protons lie close to each other. The C(3)- and C(5)-H′s are located at the interior cavity of γ-CD. Thus, the observed cross-peaks indicate that both of 2,6-NDC and 2,6-PMN are accommodated within the γ-CD cavity to form a 1 : 1 : 1 ternary complex.

We also attempted to confirm the formation of a ternary complex between γ-CD, 2,6-NDC, and 2,6-PMN by the spectral measurements of induced circular dichroism (ICD), UV absorption, and fluorescence. Figure 5 illustrates the ICD spectra of 1.0 mmol dm^{-3} 2,6-NDC, 1.0 mmol dm^{-3} 2,6-PMN, and their equimolar mixture in the presence of 10.0 mmol dm^{-3} γ-CD in 0.10 mol dm^{-3} $NaHCO_3$. A γ-CD–2,6-PMN system gave virtually no peak. A γ-CD–2,6-NDC system gave weak negative peaks at λ = 340 and 329 nm. On the other hand, a γ-CD–2, 6-NDC–2,6-PMN system gave a strong negative peak at λ = 308 nm, together with shoulders at λ = 340 and 330 nm. This fact clearly indicates the formation of a ternary complex between γ-CD, 2,6-NDC, and 2,6-PMN. Needless to say, a solution of equimolar 2,6-NDC and 2,6-PMN gave no ICD peak in the absence of γ-CD. UV absorption spectra also supported the formation of a ternary complex: The addition of 10.0 mmol dm^{-3} γ-CD to a solution of either 2,6-NDC or 2,6-PMN (1.0 mmol dm^{-3}) caused virtually no change in UV spectra. However, absorption maxima at 339 and 323 nm for an equimolar 2,6-NDC and 2,6-PMN solution are shifted to 341 and 325 nm, respectively, by the addition of 10 mmol dm^{-3} γ-CD. This bathochromic shift will be due to the formation of a ternary complex. In fluorescence spectra, the concentration of 2,6-NDC suitable for measurement was too low to observe the formation of a ternary complex.

Determination of Binding Constants for 1 : 1 Binary Complexes. We assumed that chemical equilibria in a solution containing γ-CD, NDC's, and 2,6-PMN can be

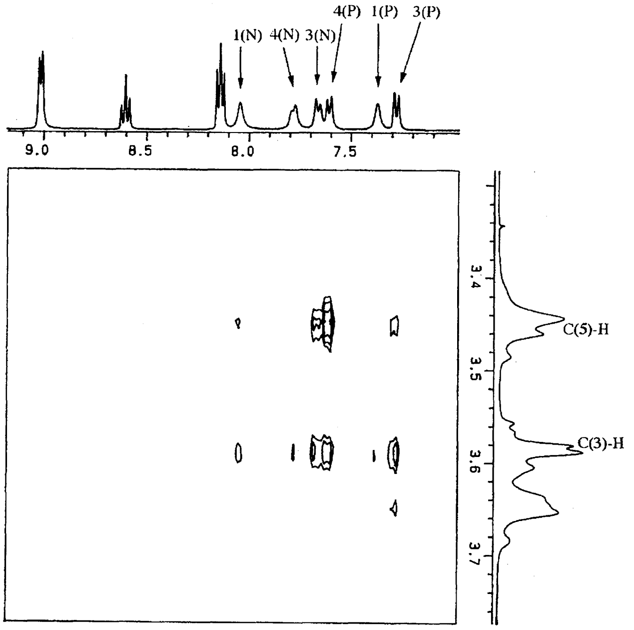

Fig. 4. The ROESY spectrum of a mixture of 10.0 mmol dm^{-3} γ-CD with 10.0 mmol dm^{-3} 2,6-NDC and 10.0 mmol dm^{-3} 2,6-PMN in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C.

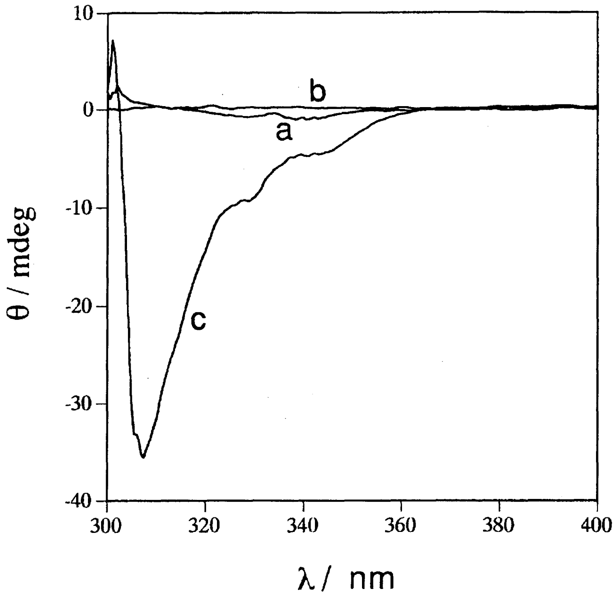

Fig. 5. The ICD spectra of 1.0 mmol dm^{-3} 2,6-NDC (a), 1.0 mmol dm^{-3} 2,6-PMN (b), and 1.0 mmol dm^{-3} 2,6-NDC and 1.0 mmol dm^{-3} 2,6-PMN (c) in the presence 10.0 mmol dm^{-3} of γ-CD in 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C.

represented by the following equations:

$$\mathrm{N+P=NP}, \quad (1)$$

$$\mathrm{C+N=CN}, \quad (2)$$

$$\mathrm{C+P=CP}, \quad (3)$$

$$\mathrm{C+NP=CNP}, \quad (4)$$

$$\mathrm{CN+P=CNP}, \quad (5)$$

$$\mathrm{CP+N=CNP}, \quad (6)$$

where, C, N, and P refer to γ-CD, NDC, and 2,6-PMN, respectively; NP, CN and CP, to their binary complexes; and CNP, to a ternary complex. Prior to the determination of binding constants for a 1 : 1 : 1 ternary complex of γ-CD with NDC's and 2,6-PMN, we evaluated binding constants for 1 :1 binary complexes composed of γ-CD, NDC's, and/or 2,6-PMN. Figure 6 illustrates changes in the ^{1}H NMR spectra of 3.0 mmol dm^{-3} 2,6-NDC with the addition of 2,6-PMN in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$. In the absence of 2,6-PMN, 2,6-NDC gave three signals at $\delta = 8.44$ (d, $J = 1.5$ Hz) for H(1, 5), 8.07 (d, $J = 8.5$ Hz) for H(4, 8), and 7.98 (dd, $J = 1.5$ and 8.5 Hz) for H(3, 7). The addition of 2,6-PMN caused an upfield shift in these signals, indicating that 2,6-NDC interacts with 2,6-PMN. The signals of H(3, 7) and H(4, 8) gradually approached each other, coalesced to give a single signal at [2,6-PMN] = 4.0 mmol dm^{-3}, and separated at higher 2,6-PMN concentrations. This change is explained in terms of the AB system of the Pople notation.[2] Figure 7 shows changes ($\Delta\delta$) in ^{1}H NMR chemical shifts of 2,6-NDC protons with the addition of 2,6-PMN. Based on the assumption that 2,6-NDC forms a 1 : 1 complex with 2,6-PMN, the binding constant (K_1) for the complex was determined by a nonlinear least-squares curve-fitting analysis of changes in $\Delta\delta$ with 2,6-PMN concentration. The thus-calculated curves (solid lines) were well-fitted to the observed data, indicating that the assumption of 1 : 1 complexation was valid. The mean K_1 value obtained was 90±1 mol^{-1} dm^3. We also examined changes in ^{1}H NMR chemical shifts of 2,6-PMN protons with the addition of 2,6-NDC. The signals of 2,6-PMN shifted to an upfield direction with the addition of 2,6-NDC. The curve-fitting analysis of the changes in $\Delta\delta$ gave the mean K_1 value of 89±5 mol^{-1} dm^3, which well agreed with that obtained by the analysis of 2,6-NDC protons. By using the same method, we determined the K_1 values for 1 : 1 complexes of NDC regioisomers with 2,6-PMN (Table 1). The K_1 value was the largest in 2,6- and 2,7-NDC's and the smallest in 1,8-NDC among NDC's examined. Two negative charges of 2,6- and 2,7-NDC's locate far apart from each other, similarly to two positive charges of 2,6-PMN. Thus, interactions of 2,6-PMN with 2,6- and 2,7-NDC's will be electrostatically enhanced. On the other hand, two negative charges of 1,8-NDC lie so close to each other that electrostatic interactions between 1,8-PMN with 2,6-NDC will be less advantageous. It is interesting that such a simple cation as 2,6-PMN recognizes the distances between two negative charges of counterpart NDC anions.

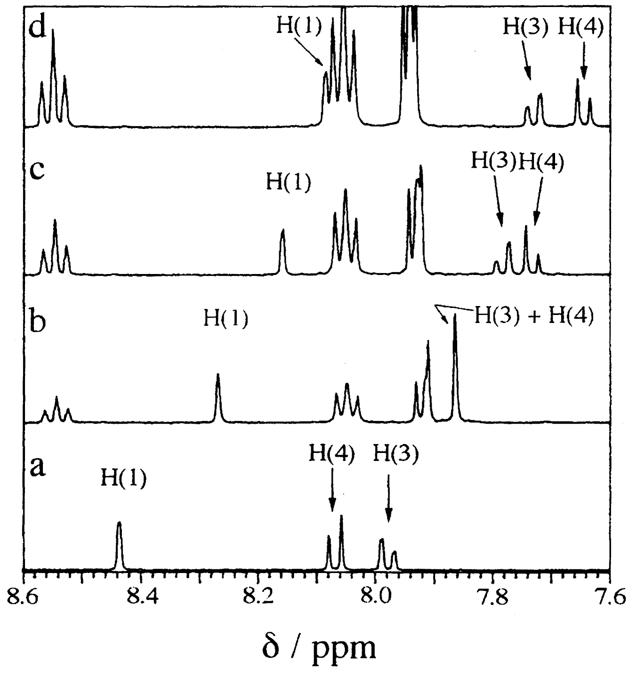

Fig. 6. Effect of the addition of 2,6-PMN on the ^{1}H NMR spectra of 3.0 mmol dm^{-3} 2,6-NDC in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C.
[2,6-PMN] = 0 (a), 4.0 (b), 8.0 (c), and 12.0 (d) mmol dm^{-3}.

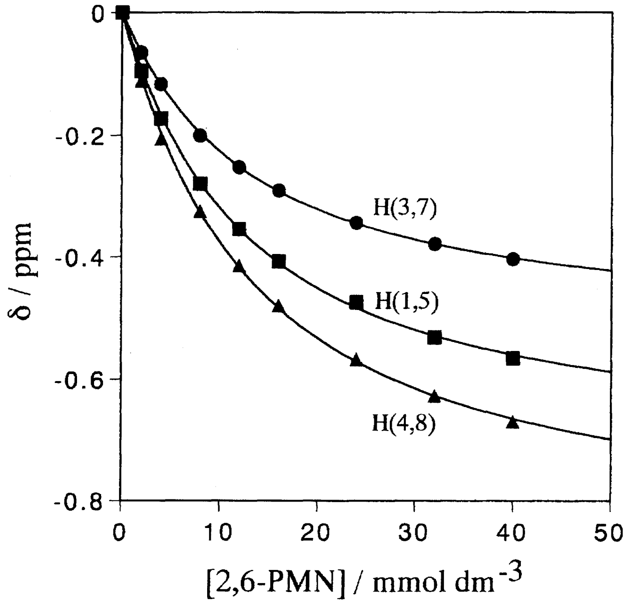

Fig. 7. Changes ($\Delta\delta$) in ^{1}H NMR chemical shifts for the H(1,5) (■), H(3,7) (●), and H(4,8) (▲) signals of 3.0 mmol dm^{-3} 2,6-NDC upon the addition of 2,6-PMN in D_2O containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C.

As shown in Fig. 2, ^{1}H NMR peaks due to γ-CD protons slightly shifted to a upfield direction with the separate addition of NDC's and 2,6-PMN. The binding constants (K_2) for complexes of γ-CD with NDC regioisomers were determined by a curve-fitting analysis of changes in $\Delta\delta$ of γ-CD protons with the concentration of NDC's in a similar manner to that described in a previous paper.[2] The binding constant

Table 1. Binding Constants (K_1) for 1 : 1 Complexes of NDC Regioisomers with 2,6-PMN in D_2O Containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C

NDC	K_1/mol^{-1} dm^3
1,3-NDC	46±1
1,4-NDC	31±1
1,5-NDC	30±2
1,6-NDC	53±3
1,8-NDC	17±1
2,3-NDC	29±1
2,6-NDC	90±1
2,7-NDC	89±5

(K_3) for a complex of γ-CD with 2,6-PMN was also determined in a similar manner. The obtained K_2 and K_3 values were small and similar to one another (Table 2). The γ-CD cavity will be too large to attain close van der Waals contact with these guest molecules.

Determination of Binding Constants for 1 : 1 : 1 Ternary Complexes. Figure 8 illustrates an effect of 2,6-NDC on the ^{1}H NMR spectrum of a 3.0 mmol dm^{-3} γ-CD solution containing a large excess (108 mmol dm^{-3}) of 2,6-PMN in 0.10 mol dm^{-3} $NaHCO_3$. In the absence of 2,6-NDC, 25% of total γ-CD was bound to 2,6-PMN (calculated from K_3), and the C(5)–H signal of γ-CD overlapped with the C(2)–H. The addition of 2,6-NDC caused significant upfield shifts in the signals of γ-CD protons. At 4.0 mmol dm^{-3} 2,6-NDC, the C(5)–H signal overlapped with the C(4) signal to give a seemingly simple doublet signal of the AB type. The C(3)–H signal also overlapped with the C(2) signal. At the maximum concentration (10.0 mmol dm^{-3}) of 2,6-NDC, the C(5)- and C(3)-H's appeared at more upfield than the C(4)- and C(2)–H's, respectively. At the concentration of 2,6-NDC, only 7%, at most, of γ-CD was consumed for the formation of a binary complex CN with 2,6-NDC (calculated from K_2), so that the contribution of CN to γ-CD signals was negligible. Thus, the large upfield shifts in the γ-CD protons were attributable to the formation of a ternary complex of γ-CD with 2,6-NDC and 2,6-PMN.

Table 2. Binding Constants for 1 : 1 Complexes of γ-CD with NDC's (K_2) and 2,6-PMN (K_3) in D_2O Containing 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C

Guest	K_2 or K_3/mol^{-1} dm^3
1,3-NDC	6±1
1,4-NDC	5±1
1,5-NDC	9±2
1,6-NDC	17±4
1,8-NDC	6±1
2,3-NDC	3[a]
2,6-NDC	8±1[a]
2,7-NDC	6±1[a]
2,6-PMN	3±1

a) Ref. 2.

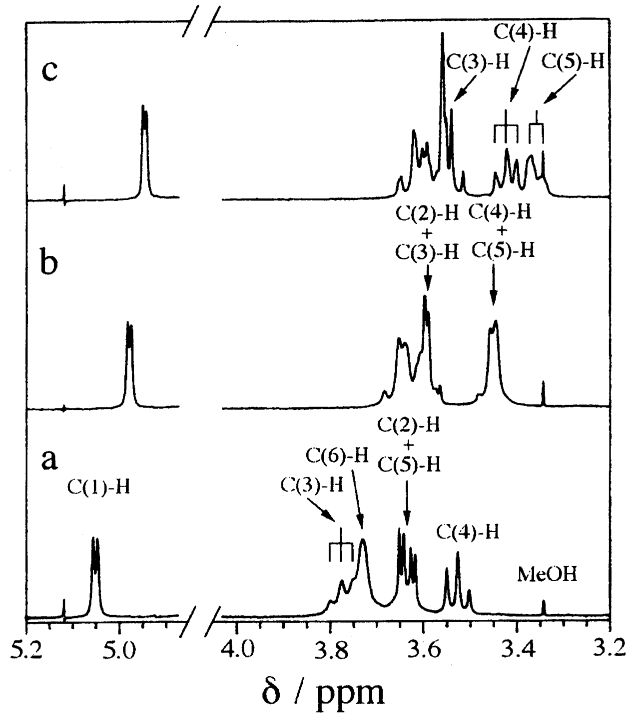

Fig. 8. The ^{1}H NMR spectra of 3.0 mmol dm^{-3} γ-CD in D_2O containing 108 mmol dm^{-3} 2,6-PMN and 0.10 mol dm^{-3} $NaHCO_3$ at 25 °C in the absence (a) and in the presence of 4.0 mmol dm^{-3} (b) and 10.0 mmol dm^{-3} 2,6-NDC (c).

We refer to the total concentrations of 2,6-NDC, 2,6-PMN, and γ-CD as a_0, b_0, and c_0, respectively, and the equilibrium concentrations of them as a, b, and c. We also refer to the equilibrium concentrations of binary complexes NP, CP, and a ternary complex CNP as x, y, and z, respectively. Material balance leads to the following equations:

$$a_0 = a + x + z, \tag{7}$$

$$b_0 = b + x + y + z, \tag{8}$$

and

$$c_0 = c + y + z, \tag{9}$$

where the contribution of a binary complex CN to a_0 and c_0 is neglected. Since $b_0 \gg a_0$ and c_0, $b \fallingdotseq b_0$ under the present experimental conditions. Equilibrium constants for Eqs. 1, 2, and 6 are represented by $K_1 = x/ab$, $K_2 = y/bc$, and $K_6 = z/ay$, respectively. By introducing these equations to Eqs. 7 and 9, we obtain

$$c_0 = c[1 + K_2 b_0 + K_2 K_6 a_0 b_0/(1 + K_1 b_0 + K_2 K_3 b_0 c)]. \tag{10}$$

By solving this equation for c, we obtain

$$c = [-q + (q^2 + 4pr)^{1/2}]/2p, \tag{11}$$

where $p = K_2 K_6 (1 + K_2 b_0)$, $q = (1 + K_1 b_0)(1 + K_2 b_0) + K_2 K_6 b_0 (a_0 - c_0)$, and $r = (1 + K_1 b_0) c_0$. Since K_1 and K_2 have been determined as described above, we can calculate c for any a_0, b_0, and c_0, if K_6 is known. Then, a can be calculated by $a = a_0/(1 + K_1 b_0 + K_2 K_6 b_0 c)$. On the other hand, the chemical shift (δ) of a γ-CD proton at any concentration of 2,6-NDC is represented by

$$\delta = (c/c_0)\delta_c + (y/c_0)\delta_y + (z/c_0)\delta_z, \tag{12}$$

where δ_c, δ_y, and δ_z are chemical shifts for protons of free γ-CD, a binary complex CP, and a ternary complex CNP, respectively. At $a_0 = 0$, no ternary complex forms, and the chemical shift (δ') is represented by

$$\delta' = (c'/c_0)\delta_c + (y'/c_o)\delta_y, \tag{13}$$

where $c' = c_0/(1+K_2b_0)$ and $y' = K_2b_0c'$. By combining Eqs. 12 and 13, we obtain

$$\delta = c(\delta'/c' + K_2K_6ab_0\delta_z/c_0). \tag{14}$$

On the basis of this equation, the values of K_6 and δ_z were estimated by the least-squares curve-fitting analysis of a change in δ with a_0. Figure 9 illustrates changes in δ for a few protons of γ-CD with the addition of 2,6-NDC. The calculated solid lines were in excellent agreement with the observed data. The obtained K_6 value was 27000±3000 $\mathrm{mol^{-1}\,dm^3}$, which was extremely large compared with 8±1 $\mathrm{mol^{-1}\,dm^3}$ for a binary complex of γ-CD with 2,6-NDC. The K_6 value corresponds to the inclusion of 2,6-NDC within the cavity of a γ-CD–2,6-PMN binary complex (Eq. 2). Thus, it is apparent that 2,6-PMN acts as an effective space-regulator.

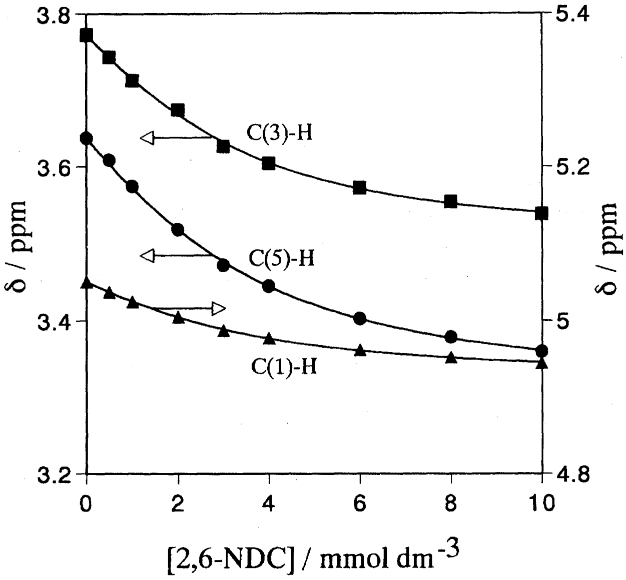

Fig. 9. Changes in ^{1}H NMR chemical shifts (δ) for the C(3)–H (■), C(5)–H (●), and C(1)–H (▲) signals of 3.0 $\mathrm{mmol\,dm^{-3}}$ γ-CD upon the addition of 2,6-NDC in D_2O containing 108 $\mathrm{mmol\,dm^{-3}}$ 2,6-PMN and 0.10 $\mathrm{mol\,dm^{-3}}$ $NaHCO_3$ at 25 °C.

Table 3. Binding Constants (K_6) for Complexation of NDC's with a γ-CD–2,6-PMN Binary Complex in D_2O Containing 0.10 $\mathrm{mol\,dm^{-3}}$ $NaHCO_3$ at 25 °C

Guest	K_6/$\mathrm{mol^{-1}\,dm^3}$
1,3-NDC	2000± 200
1,4-NDC	400± 90
1,5-NDC	330± 60
1,6-NDC	3300± 400
1,8-NDC	1100± 100
2,3-NDC	5200± 500
2,6-NDC	27000±3000
2,7-NDC	19000±1000

Molecular Recognition in Ternary Complex Formation. We also examined the effects of NDC regioisomers on the ^{1}H NMR spectra of a solution of 3.0 $\mathrm{mmol\,dm^{-3}}$ γ-CD containing a large excess (100 $\mathrm{mmol\,dm^{-3}}$) of 2,6-PMN in 0.10 $\mathrm{mol\,dm^{-3}}$ $NaHCO_3$ at 25 °C. The addition of each regioisomer caused upfield shifts in δ, more or less, for γ-CD protons. Observed changes in δ were analyzed in a similar manner as in the case of 2,6-NDC to determine K_6 for the regioisomer. The results were summarized in Table 3. The K_6 values varied widely from 330 $\mathrm{mol^{-1}\,dm^3}$ for 1,5-NDC to 27000 $\mathrm{mol^{-1}\,dm^3}$ for 2,6-NDC. The K_6 values for 1,5-NDC, 1,4-NDC, and 1,8-NDC were small compared with the other regioisomers. The carboxylate groups of these NDC's are located only at the α-positions of the naphthalene moieties. Their molecular structures will be too bulky to be deeply accommodated within the opening space of the cavity of a γ-CD–2,6-PMN binary complex. In contrast, the K_6 values for 2,3-, 2,6-, and 2,7-NDC's were very large. These NDC's bear the carboxylate groups only at the β-positions of the naphthalene moieties. Their rod-like molecular structures will be fitted to the opening space composed of γ-CD and 2,6-PMN, as illustrated in Fig. 1. The K_6 values for 1,3- and 1,6-NDC were intermediate. These NDC's contain a carboxylate group at the α-position and another at the β-position of the naphthalene moieties. In order to confirm the formation of 1 : 1 : 1 ternary complexes of γ-CD and 2,6-PMN with these NDC's, we recorded 2D ROESY spectra of ternary mixtures of γ-CD and 2,6-PMN with 1,6-, 2,3-, and 2,7-NDC's. The spectra gave clear cross-peaks connecting the C(3)- and C(5)–H's of γ-CD to protons of NDC's and 2,6-PMN, indicating that the NDC's are accommodated within the γ-CD cavity together with 2,6-PMN. It is interesting that the K_6 value for 2,6-NDC is significantly larger than that for 2,7-NDC. It has been reported that the K_a values for binary complexes of β-CD with 2,6- and 2,7-NDC's are virtually equal to each other.[2)] Thus, an ability to recognize the molecular structures of NDC's is evidently higher in a γ-CD–2,6-PMN system than in a β-CD system. Electrostatic interactions of 2,6-PMN with 2,6-NDC will be more advantageous than those with 2,7-NDC in the hydrophobic cavity of

Table 4. Binding Constants (K_4 and K_5) for 1 : 1 : 1 Ternary Complexes of NDC's in a γ-CD–2,6-PMN System in D_2O Containing 0.10 $\mathrm{mol\,dm^{-3}}$ $NaHCO_3$ at 25 °C

Guest	K_4/$\mathrm{mol^{-1}\,dm^3}$	K_5/$\mathrm{mol^{-1}\,dm^3}$
1,3-NDC	130	1000
1,4-NDC	39	240
1,5-NDC	33	110
1,6-NDC	190	580
1,8-NDC	190	550
2,3-NDC	540	5200
2,6-NDC	900	10000
2,7-NDC	640	9500

γ-CD. Steric factors arising from the γ-CD cavity will also play an important part of the distinct molecular recognition in the ternary complexes. The open space between the γ-CD cavity and 2,6-PMN will be the most favorable for the accommodation of such a slender molecule as 2,6-NDC.

We can calculate the binding constants (K_4) for complexation of γ-CD with binary NDC–2,6-PMN complexes (Eq. 4) and those (K_5) for complexation of 2,6-PMN with binary γ-CD–NDC complexes (Eq. 5), since $K_1K_4 = K_2K_5 = K_3K_6$. The calculated values are summarized in Table 4. The obtained K_4 values were similar in magnitude to those for β-CD complexes with NDC's.[2] The K_5 values for NDC's were significantly different from one another, and that for 2,6-NDC was the largest. This fact indicates that 2,6-NDC is the best space-regulator among examined NDC's for the complexation of γ-CD with 2,6-PMN.

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