^{1}H NMR Response of Mono[6-(1-pyridinio)-6-deoxy]-α-cyclodextrin to Inorganic Anions

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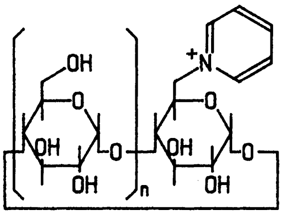
The chemical shifts (δ) of some ^{1}H NMR signals given by mono[6-(1-pyridinio)-6-deoxy]-α-cyclodextrin (**1**) in D_2O were significantly changed by the addition of alkali salts of chaotropic anions such as Br^-, I^-, SCN^-, N_3^-, NO_3^-, and ClO_4^-. However, only small changes in δ were brought about by the addition of alkali salts of antichaotropic anions such as F^-, Cl^-, SO_4^{2-}, $H_2PO_4^-$, and HPO_4^{2-}. The addition of the chaotropic anions caused a marked downfield shift in the signal of a C(5)–H located in the interior of the cavity of **1**, and a marked upfield shift in the signal of one of the C(6)–H's involved in the unsubstituted glucopyranose rings of **1**. These facts indicate that the anions are included within the cavity and attract the pyridinio group of **1** close to the C(6)–H. The signal of the α-H's in the pyridinio group showed a significant downfield shift with the addition of the alkali salts of Br^-, I^-, and SCN^-, which form charge-transfer complexes with **1**.

In sharp contrast to the extensively studied cation complexation with host compounds, such as crown ethers and cryptands, anion complexation with hosts has received little attention,[1] in spite of its chemical and biological significance.[2] Cyclodextrins (CD's) are known to form 1 : 1 inclusion complexes with chaotropic inorganic anions,[3] such as Br^-, I^-, SCN^-, and ClO_4^-, though the binding constants (K_a) are small in aqueous solutions. We recently found that the substitution of pyridinio group(s) for the 6-hydroxyl group(s) of α-CD results in a significant increase in the K_a values for 1 : 1 complexes with I^-.[4] UV spectrophotometry has shown that I^- forms charge-transfer (CT) complexes with the pyridinio derivatives of CD to give the characteristic absorption spectra.[5] In the present study, the complexation of mono[6-(1-pyridinio)-6-deoxy]-α-CD (**1**) and its β-CD (**2**) and γ-CD (**3**) analogs with several inorganic anions was examined by ^{1}H NMR spectrometry in order to elucidate the molecular structures of the complexes in solution (Chart 1).

Experimental

Parent α-, β-, and γ-CD's were kindly supplied by Nihon Shokuhin Kako Co., Ltd. and Ensuiko Seito Co., Ltd. They were dried overnight in vacuo at 110 °C. Reagent-grade pyridine was dried over CaH_2 and distilled in the presence of CaH_2. The methyl α-D-glucopyranoside and inorganic salts used were of reagent grade and commercially available.



1 ($n = 5$)
2 ($n = 6$)
3 ($n = 7$)

Chart 1. **1** (n=5), **2** (n=6), **3** (n=7).

The HCO_3^- salts of **1**—**3** were prepared by refluxing solutions of the corresponding 6-O-arylsulfonylated CD's in dry pyridine, followed by elution of the products from a column of CM-cellulose (50×550 mm, Serva) with aqueous NH_4HCO_3, as described previously.[5,6] The 6-(1-pyridinio)-6-deoxy derivative (**4**) of methyl α-D-glucopyranoside was also prepared in a similar manner. Some well-resolved ^{1}H NMR signals of these host compounds (9—11 mmol dm^{-3}) in D_2O (Merck, 99.75%) are given in Table 1. The ^{1}H NMR spectra were recorded using a JEOL Model JNM-GX270 FT NMR spectrometer (270 MHz) at 25 °C. Acetonitrile (δ=2.00[7]) was used as an internal reference.[8]

Results and Discussion

^{1}H NMR of 1 and Its Analogs. The ^{1}H NMR spectrum of **1** (9.0 mmol dm^{-3}) in D_2O at 25 °C is illustrated in Fig. 1. The α-, β-, and γ-H's of the pyridinio group gave clear signals of a doublet or triplet in the low-field region of δ=8.0—8.9. The H's of the glucopyranose moieties (GP) gave complex signals in the high-field region of δ=2.6—5.2. Among them, the following signals were relatively distinct: A doublet at δ=5.21 due to the gauche C(6)–H [C(6)–H(A, g)] of the substituted GP ring [GP(A)]; doublets at δ=4.9—5.1 due to anomeric C(1)–H's; a probable triplet signal at δ=4.17 due to one of C(5)–H's; a probable doublet signal at δ=2.86; and a double doublet (dd) signal at δ=2.57. The last two signals were due to the geminal gauche and trans C(6)–H's [C(6)–H(B, g) and C(6)–H(B, t), respectively] of the unsubstituted GP [GP(B)] adjacent to GP(A).[6] The significant upfield shift of the signals is due to shielding by the ring current of the adjacent pyridinio group.[6] Similar ^{1}H NMR spectra were obtained for **2**—**4** (Table 1). The standard deviations of the chemical shifts for **1** (n=10) were less than 0.005 ppm.

Effect of KI on ^{1}H NMR of 1—4. Table 2 shows changes in the chemical shifts of some well-resolved signals of **1**—**4** upon the addition of KI to a D_2O solution at 25 °C. It was estimated on the basis

Table 1. Chemical Shifts of Some Well-Resolved ^{1}H NMR Signals of Compounds **1**—**4** in D_2O at 25 °C

Proton		**1**	**2**	**3**	**4**
α-H	(2H, d[a])	8.85 (6[b])	8.84 (6)	8.84 (6)	8.84 (7)
β-H	(2H, t)	8.06 (7)	8.08 (7)	8.08 (7)	8.04 (7)
γ-H	(1H, t)	8.59 (8)	8.60 (8)	8.60 (8)	8.56 (8)
C(1)–H(L[c])	(1H, d)	5.10 (4)	5.12 (4)	5.16 (4)	—[d]
C(1)–H(H[c])	(1H, d)	4.90 (4)	4.93 (4)	4.96 (4)	—[d]
C(5)–H(L[c])	(1H, t)	4.17 (9)	4.23 (9)	4.26 (8)	3.94 (10)
C(6)–H(A, g)	(1H, d)	5.21 (13)	5.18 (12)	5.14 (11)	4.99 (13)
C(6)–H(B, g)	(1H, d)	2.86 (11)	2.88 (13)	2.85 (12)	—
C(6)–H(B, t)	(1H, dd)	2.57 (13,4)	2.60 (13,4)	2.68 (11,3)	—

a) Number of protons and multiplicity. b) J value in Hz. c) Signals observed at the lowest (L) and highest (H) sides of magnetic field among the protons concerned. d) Overlapped on the HDO signal (δ=4.65—4.76).

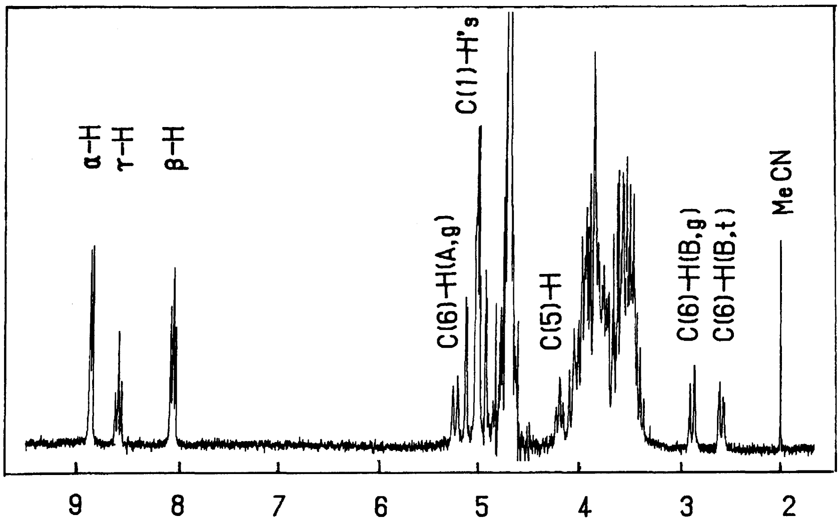


Fig. 1. ^{1}H NMR spectrum of **1** (10 mmol dm^{-3}) in D_2O at 25 °C, δ/ppm.

of the K_a values (as described below) that at the KI concentrations examined most of the hosts were bound to I^- (93% of **1**, 87% of **2**, and 85% of **3**). The addition of KI caused significant changes in the chemical shifts of **1**, especially in those of α-H, C(5)–H,[9] and C(6)–H(B, t). Similar changes, though to a less extent, were observed for **2** and **3**. On the other hand, the addition of 500 mmol dm^{-3} KI caused only slight changes in the chemical shifts of **4**, which has no cavity into which I^- is incorporated. The incorporation of I^- into the cavities of **1**—**3** was substantiated by the remarkable downfield shift of C(5)–H upon the addition of KI. The C(5)–H is located in the interior of the cavities. The cavity size increases in the order **1**<**2**<**3**. The close fitness of I^- to the smallest cavity of **1** may be related to the greatest changes in the chemical shifts. The significant downfield shift of the α-H of the pyridinio group indicates that I^- also interacts with the pyridinio group, probably through the CT and/or electrostatic interactions.[5] These attractive interactions may bring the pyridinio group closer to the C(6)–H(B, t), thus enhancing the magnetic shielding due to the ring current of the pyridinio group and causing a significant upfield shift of C(6)–H(B, t). It is known that the chemical shifts of C(1)–H's are sensitive to any conformational change in the macrocycle of CD.[10] The chemical shifts of the C(1)–H's of **1**, **2**, and **3** showed slight, but definitive, changes upon the addition of KI, indicating that the conformations of the host macrocycles are slightly changed by the inclusion of I^-. The β- and γ-H's of the pyridinio groups, as well as C(6)–H(A, g) and C(6)–H(B, g) of the hosts, were not very sensitive to the addition of KI as to be worth noting.

The chemical shifts of the α-H's of **1**—**3** increased and approached constant values with increasing KI concentration (Fig. 2). Based on an assumption that these hosts form 1 : 1 complexes with I^-, the data were analyzed by a curve-fitting method with a microcomputer. The thus-calculated curves (solid lines) were well-fitted to the observed data, indicating that the assumption of 1 : 1 complexation is valid. Similar results were also obtained for C(5)–H and C(6)–H(B, t). The binding constants (K_a) determined for these 1 : 1 complexes are summarized in Table 3. The K_a values were in

Table 2. Changes[a)] in Chemical Shifts of Some Well-Resolved ^{1}H NMR Signals given by **1**—**4** in D_2O at 25 °C with the Addition of KI

Proton	**1**[b)]	**2**[c)]	**3**[d)]	**4**[e)]
α-H	0.174	0.104	0.061	0.008
β-H	0.000	0.021	0.032	0.015
γ-H	−0.007	0.004	0.000	0.006
C(1)–H(L)[f)]	−0.003	0.005	0.021	—
C(1)–H(H)[f)]	−0.033	−0.031	0.020	—
C(5)–H(H)[f)]	0.341[g)]	0.176	0.135	0.014
C(6)–H(A, g)	0.041	0.033	−0.010	0.005
C(6)–H(B, g)	−0.021	−0.020	0.000	—
C(6)–H(B, t)	−0.194	−0.105	−0.066	—

a) Positive and negative values indicate downfield and upfield shifts, respectively. b) [**1**] = 11 mmol dm^{-3}, [KI] = 80 mmol dm^{-3}. c) [**2**] = 9 mmol dm^{-3}, [KI] = 200 mmol dm^{-3}. d) [**3**] = 10 mmol dm^{-3}, [KI] = 300 mmol dm^{-3}. e) [**4**] = 10 mmol dm^{-3}, [KI] = 500 mmol dm^{-3}. f) Letters in parentheses represent the same meaning as those in Table 1. g) A value at [KI] = 15 mmol dm^{-3}.

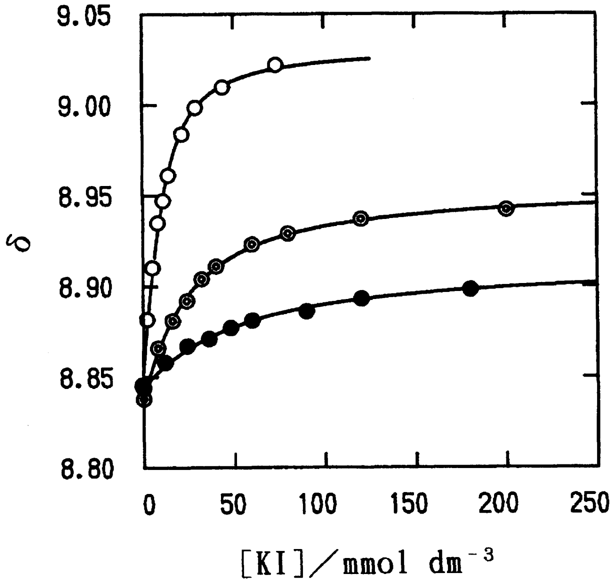


Fig. 2. Changes in the chemical shifts (δ) of the α-H's of **1** (○), **2** (◎), and **3** (●) upon the addition of KI. The concentrations of **1**, **2**, and **3** were 11, 9, and 10 mmol dm^{-3}, respectively.

Table 3. Binding Constants, $K_a/\text{mol}^{-1}\,\text{dm}^3$, Determined by ^{1}H NMR in D_2O and by UV in H_2O at 25 °C for Complexes of **1**—**4** with the Iodide Ion

Host	^{1}H NMR	UV[a)]
1	199±11	136±2
2	36± 6	31±2
3	20± 1	—
4	—	3±0.1

a) Ref. 5.

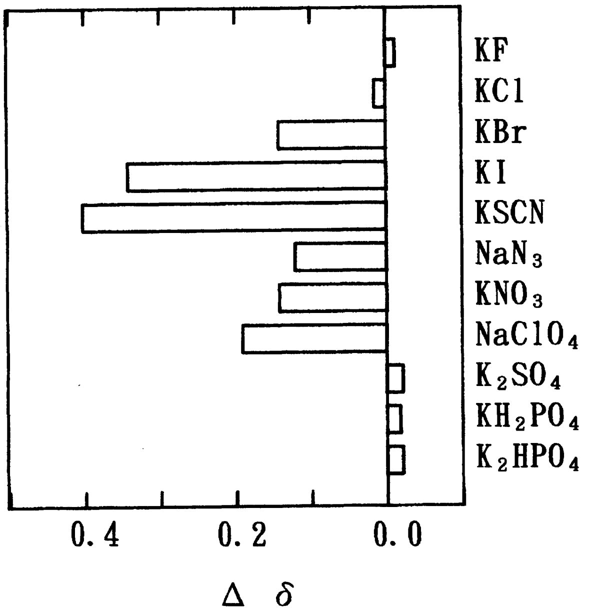


Fig. 3. Changes ($\Delta\delta$) in the chemical shift of the C(5)–H signal of **1** in D_2O at 25 °C upon the addition of inorganic salts. The concentrations of the inorganic salts added were ca. 200 mmol dm^{-3}, except KI (15 mmol dm^{-3}) and KSCN (17 mmol dm^{-3}).

fairly good agreement with those evaluated by the UV method,[5)] and increased with decreasing cavity size of the hosts. A close van der Waals contact between the host and the guest may be responsible for the stabilization of a 1 : 1 complex of **1** with I^-. The addition of NaI in place of KI had virtually no effect on the K_a value for **1**.

Effect of Several Inorganic Anions on the ^{1}H NMR of 1. Figures 3, 4, and 5 show changes in the chemical shifts of the C(5)–H, C(6)–H(B, t), and α-H, respectively, of **1** with the addition of various inorganic salts (ca. 200 mmol dm^{-3}). The C(5)–H showed remarkable downfield shifts with the addition of KBr, KSCN, NaN_3, KNO_3, and $NaClO_4$, similarly to that of KI (Fig. 3). The anions of these salts are known to be chaotropic and to form inclusion complexes with parent α-CD.[3)] The remarkable downfield shifts indicate that these anions are incorporated into the hydrophobic cavity of **1**. The addition of these anions also resulted in considerable "upfield" shifts of C(6)–H(B, t) (Fig. 4), suggesting that the inclusion of these anions within the cavity of **1** brings the pyridinio group closer to C(6)–H(B, t) in a similar manner as in the case of KI. On the other hand, only a slight downfield or upfield shift was observed for the chemical shifts of C(5)–H and C(6)–H(B, t) upon the addition of KF, KCl, K_2SO_4, KH_2PO_4, and K_2HPO_4. The anions of these salts are so antichaotropic that they may form no, or very labile, complexes with **1**. The α-H signal showed significant downfield shifts upon the addition of KBr and KSCN, as well as KI; a significant upfield shift upon the ad-

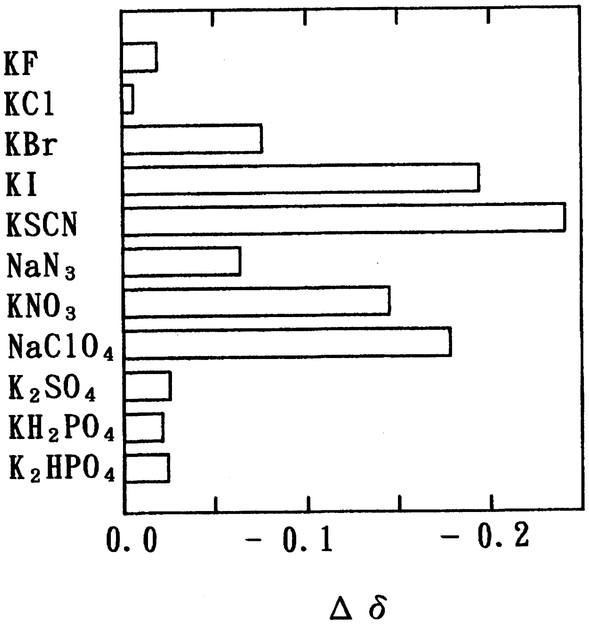


Fig. 4. Changes (Δδ) in the chemical shift of the C(6)–H(B, t) signal of **1** in D_2O at 25 °C upon the addition of inorganic salts. The concentrations of the inorganic salts added were ca. 200 mmol dm^{-3}, except KI (80 mmol dm^{-3}).

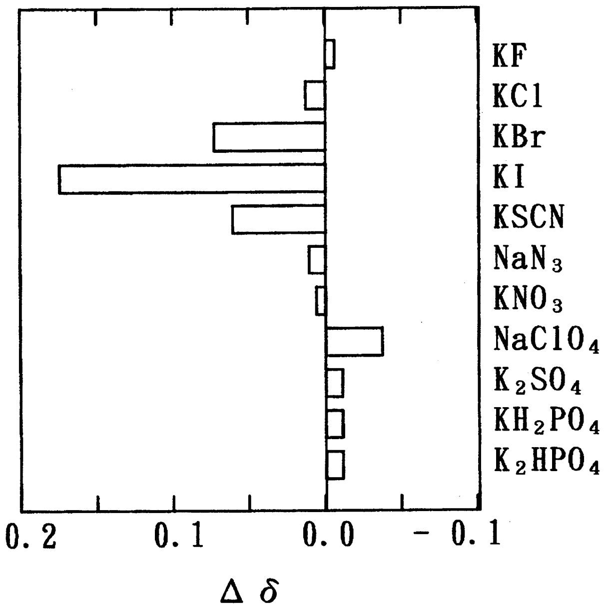


Fig. 5. Changes (Δδ) in the chemical shift of the α-H signal of **1** in D_2O at 25 °C upon the addition of inorganic salts. The concentrations of the inorganic salts added were ca. 200 mmol dm^{-3}, except KI (80 mmol dm^{-3}).

dition of $NaClO_4$; and only a slight downfield or upfield shift upon the addition of KF, KCl, NaN_3, KNO_3, K_2SO_4, KH_2PO_4, and K_2HPO_4 (Fig. 5). The I^-, Br^-, and SCN^- ions form CT complexes with **1** in aqueous solutions.$^{5)}$ The CT interactions between **1** and these anions may be responsible for the downfield shift of the α-H. The ClO_4^- ion forms a stable complex with **1** in an aqueous solution,$^{5)}$ though no CT interaction occurs between them. The reason why the α-H shows an upfield shift with the addition of ClO_4^- is not clear and remains to be solved. The slight changes in the chemical shift of the α-H upon the addition of the other anions are attributed to either labile complexation between the host and the anions or weak effects of complexation, if any, on the chemical shift of the proton.

Table 4. Binding Constants, K_a/mol^{-1} dm^3, Determined by ^{1}H NMR in D_2O at 25 °C for Complexes of **1** with Several Inorganic Anions and Comparison with K_a for Complexes of Parent α-CD

Anion	**1**	α-CD$^{a)}$	Ratio$^{b)}$
Br^-	8.6	0.87	10
I^-	199	19.0	10
SCN^-	395	34.6	11
NO_3^-	20	1.96	10
ClO_4^-	327	45.8	7

a) Ref. 3f. b) Ratio of K_a for **1** to that for α-CD.

The K_a values for 1 : 1 complexes of **1** with some inorganic anions were determined by curve-fitting analysis of any changes in the chemical shifts of C(5)–H, C(6)–H(B, t), and α-H in a similar manner as in the case of I^- (Table 4). The obtained curves were well-fitted to the observed data. Interestingly, the ratios (R) of the K_a's for **1** to those of the parent α-CD were virtually equal to 10, irrespective of the anions. This fact indicates that the substitution of the positively charged pyridinio group for one of the C(6)–OH's is electrostatically favorable for the complexation of the host with the guest anions, whereas the anion selectivity of the host is mainly governed by the chaotropic properties of the anions, and is held virtually constant even after substitution.

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8) Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) is sometimes used as an internal reference in aqueous solution. However, we avoided the use of DSS since we found that the sulfonate anion was strongly bound to **1**.

9) The downfield shift of the C(5)–H signal was very large and the signal was overlapped on the large HDO signal at [KI]>30 mmol dm^{-3}, so that data at [KI]=15 mmol dm^{-3} was shown for this signal.

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