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Chiral Recognition of Phenylacetic Acid Derivatives by Aminated Cyclodextrins

TAKASHI KITAE, HIROSHI TAKASHIMA and KOJI KANO*
Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-03, Japan.

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Abstract. Chiral recognition of mandelic acid (**1**), acetylmandelic acid (**2**), 1-methoxyphenylacetic acid (**3**), phenylsuccinic acid (**4**), 2-phenylpropanoic acid (**5**) and ibuprofen (**6**) in their anionic forms by protonated 6^A-amino-6^A-deoxy-β-cyclodextrin (mono-NH_3^+-β-CD) and 6^A,6^D-diamino-6^A,6^D-dideoxy-β-cyclodextrin (di-NH_3^+-β-CD) has been studied by means of capillary zone electrophoresis (CZE) and ^{1}H NMR spectroscopy. Both methods show the preferable guests for mono-NH_3^+-β-CD to be the (*R*)-enantiomers of **1**, **3** and **5** and the (*S*)-enantiomers of **2**, **4** and **6**. Cooperative work of Coulomb interactions and inclusion is essential for chiral recognition of these anionic guests.

Key words: chiral recognition, phenylacetic acid derivatives, aminated cyclodextrins, capillary zone electrophoresis, ^{1}H NMR.

1. Introduction

Native cyclodextrins (CDs) having toroidal shapes with a C_n symmetric nature have been assumed to show low ability to recognize chirality of guests having an asymmetric carbon [1]. Cooper and MacNicol [2] determined the binding constants (K) for complexation of the enantiomers of phenylalanine (Phe), 1-phenylethylamine, mandelic acid (**1**), α-trifluoromethylbenzyl alcohol and amphetamine with α-CD. The K values for these guests having charges are less than 60 dm^3 mol^{-1} and the differences in free-energy changes for complexation between the enantiomers ($\Delta\Delta G$) are 0–0.65 kJ mol^{-1}. Other papers also report poor ability of native CDs to include ionic guests and to recognize the central chirality of these guests [3]. Improvement of the binding ability of the CDs for ionic guests can be achieved by introducing opposite charge(s) to the native CDs. For example, the K values for complexation of (*R*)- and (*S*)-2-phenylpropanoates (**5**) with protonated 6^A-amino -6^A-deoxy-β-cyclodextrin (mono-NH_3^+-β-CD) are 150 and 110 dm^3 mol^{-1}, respectively, while those with β-CD are 63 and 52 dm^3 mol^{-1} for (*R*)-**5** and (*S*)-**5**, respectively [4]. Although the K values increase to some extent, the enantioselectivity is still poor ($\Delta\Delta G$ = 0.7 kJ mol^{-1}) even if Coulomb interactions are used for complexation [4]. Recently, we found that the chirality of *N*-acetylated α-amino

* Author for correspondence.

acids in the dissociated forms is recognized by heptakis(6-amino-6-deoxy)-β-CD in the protonated form (per-NH_3^+-β-CD), while native CDs such as α- and β-CDs do not discriminate at all between the enantiomers of these anionic amino acids as well as amino acids in zwitterionic forms [5]. This is a remarkable effect of Coulomb interactions because chiral recognition occurs only in the cases where point charge–point charge interactions between host and guest work in complexation, though the enantioselectivity is also still poor. Prior to concluding that CDs show poor ability to discriminate between enantiomers of guests having a central chirality, we need to accumulate experimental data dealing with the mechanisms for chiral recognition.

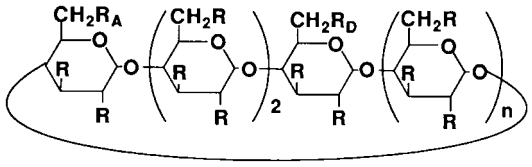
In this study, we applied capillary zone electrophoresis (CZE) and ^{1}H NMR spectroscopy for studying the chiral recognition of mandelic acid and its related compounds in anionic forms by protonated mono-NH_3^+-β-CD and 6^A,6^D-diamino-6^A,6^D-dideoxy-β-cyclodextrin (di-NH_3^+-β-CD). CZE is an excellent method for revealing systems where chiral recognition occurs [6]. Even if ordinary methods such as absorption, emission, ^{1}H NMR and mass spectroscopic techniques do no show any evidence for chiral recognition, CZE can detect extremely low enantioselectivity in certain cases [7]. In addition, since retention times can be correlated with relative K values for complexation of guest enantiomers with CD, CZE is a very convenient tool for studying chiral recognition. From an analytical point of view, the CZE studies on chiral recognition of mandelic acid and its related compounds by aminated CDs have been carried out [8]. Most CZE studies, however, do not involve the detailed spectroscopic examination to correlate the CZE data with the mechanisms for chiral recognition. In the present study we used two independent methods, CZE and ^{1}H NMR, to study the chiral recognition.

2. Experimental

The CDs and the guests used in this study are listed in Tables I and II, respectively. α- and β-CDs (Nacalai) were purchased and recrystallized from water after an antioxidant contained in these compounds was removed by extraction with THF using a Soxhlet extractor. Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMe-β-CD, Nacalai, commercially obtained) was used without further purification. Mono-NH_3^+-α-CD, mono-NH_3^+-β-CD [9], di-NH_3^+-β-CD [10] and mono-NH_3^+-Me-β-CD [11] were prepared according to the procedures described in the literature. These aminated CDs were purified by ion-exchange column chromatography (Sephadex CM-25, an NH_4^+ form). Compounds **1** (Nacalai), **2**, **3**, **5**, **6** (Aldrich) and **4** (ACROS) were used as received. Water was distilled using a Yamato Auto Still Glass Model WAG220 and further purified by a Yamato MILLIPORE WQ500 Auto Pure.

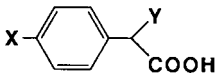
^{1}H NMR spectra were measured on a JEOL JNM-400 FT-NMR spectrometer (400 MHz) in D_2O (CEA). Sodium 3-(trimethylsilyl)propanoate-d_4 (Aldrich) was used as an external standard. The CZE measurements were carried out using a JASCO capillary electrophoresis system CE-800 with a 300 mm (effective length)

Table I. Structures and abbreviations of the cyclodextrins used in this study



abbrebiation	n	R	R_A	R_D
α-CD	2	OH	OH	OH
β-CD	3	OH	OH	OH
TMe-α-CD	2	OCH_3	OCH_3	OCH_3
TMe-β-CD	3	OCH_3	OCH_3	OCH_3
mono-NH_3^+-α-CD	2	OH	NH_3^+	OH
mono-NH_3^+-β-CD	3	OH	NH_3^+	OH
mono-NH_3^+-Me-β-CD	3	OCH_3	NH_3^+	OCH_3
di-NH_3^+-β-CD	3	OH	NH_3^+	NH_3^+

Table II. Structures of the guest acids used in this study



compound	X	Y
1	H	OH
2	H	$OCOCH_3$
3	H	OCH_3
4	H	CH_2COOH
5	H	CH_3
6	$CH_2CH(CH_3)_2$	CH_3

$\times$ 50 μm (diameter) fused silica capillary cartridge (non-coated). A UV detector JASCO 875-CE UV was set at the negative electrode side of the capillary.

The molecular mechanics-molecular dynamics (MM-MD) calculations were performed by the use of an AMBER program system (Version 4 presented by P. Kollman, University of California at San Francisco) on a COMTEC 4D RPC XS24Z R4000 workstation at 250–300 K for 12 ps (time step 0.001 ps). The effects of water molecules as solvent were involved. The data on charges were collected using a MOPAC program (Version 6 developed by J. J. P. Stewart, US Airforce Academy, USA).

3. Results and Discussion

3.1. CZE USING CDS AS CHIRAL SELECTORS

Table III summarizes the results of CZE of racemic **1**, **2**, **3** and **4** in the anionic forms. Native β-CD without charge does not show any effect as a chiral selector for **1**, **2** and **3**. For a dicarboxylate **4**, β-CD acts as a weak chiral selector. TMe-β-CD does not discriminate between the enantiomers of all guests examined herein. Meanwhile, mono-NH_3^+-β-CD having a positive charge is a good chiral selector toward all guests, but mono-NH_3^+-Me-β-CD is not. According to the theory of CZE [12], an anionic guest having a shorter retention time (t_1) has a larger K value compared with another anionic guest having a longer retention time (t_2) in complexation with mono-NH_3^+-β-CD. This theory can be applied for CZE separation of different guests coexisting in the same solution. The results predict that the mono-NH_3^+-β-CD complexes of the (*R*)-enantiomers of **1** and **3** and of the (*S*)-enantiomers of **2** and **4** are more stable than those of the corresponding antipodes. However, it is difficult to discuss relative stability of two complexes whose hosts are different from each other by comparing the retention times measured in alternate CZE. For example, there is a problem in the systems of cationic CDs which arises from adsorption of the cationic CDs on the anionic silica surface of the capillary. The cationic selector molecules seem to move to a negative electrode by a repeat adsorption–desorption process. Such a process causes the delay in the retention time of the sample which is bound to the cationic selector. In spite of the fact that the K values for the mono-NH_3^+-β-CD complexes of the anionic guests are larger than those for the corresponding β-CD complexes (*vide infra*), the retention times of **1**, **2** and **3** in CZE using mono-NH_3^+-β-CD are longer than the retention times of the corresponding guests in CZE using β-CD. This might be due to the adsorption of the cationic selector on the silica surface. Adsorption of polycationic species on the silica surface should be stronger than that of the monocationic one. Absence of the peaks of **1**, **2** and **3** in CZE using di-NH_3^+-β-CD and heptakis(6-amino-6-deoxy)-β-CD (per-NH_3^+-β-CD) might be ascribed to such an interaction.

In the absence of CD, the dicarboxylic acid **4** moved to the positive electrode by an electrophoretic flow with a rate faster than the electroosmotic flow under

Table III. Retention times (t) and separation factors (α) in CZE of (±)-mandelic acid (**1**), acetylmandelic acid (**2**), 1-methoxyphenylacetic acid (**3**) and phenylsuccinic acid (**4**) using CDs as chiral selectors[a]

guest	host	pH	current / μA	t_1 / min	t_2 / min	α[b]
1	β-CD	6.00	9	25.8 (±)	25.8 (±)	1.00
1	TMe-β-CD	6.00	11	31.6 (±)	31.6 (±)	1.00
1	mono-NH_3^+-β-CD	6.03	9	26.9 (*R*)	32.2 (*S*)	1.20
2	β-CD	6.00	9	21.0 (±)	21.0 (±)	1.00
2	TMe-β-CD	6.00	11	26.9 (±)	26.9 (±)	1.00
2	mono-NH_3^+-β-CD	6.00	11	24.7 (*S*)	26.6 (*R*)	1.08
2	mono-NH_3^+-Me-β-CD	6.00	12	19.3 (±)	19.3 (±)	1.00
3	β-CD	6.00	9	23.5 (±)	23.5 (±)	1.00
3	TMe-β-CD	6.00	12	23.8 (±)	23.8 (±)	1.00
3	mono-NH_3^+-β-CD	5.81	10	24.6 (*R*)	29.2 (*S*)	1.19
4	β-CD	8.00	13	48.9 (*S*)	50.3 (*R*)	1.03
4	TMe-β-CD	8.00	14	43.9 (±)	43.9 (±)	1.00
4	mono-NH_3^+-β-CD	8.00	29	38.6 (*S*)	46.6 (*R*)	1.20
4	di-NH_3^+-β-CD	8.00	21	19.2 (*S*)	31.6 (*R*)	1.65

[a] The capillary was filled with the 0.033 mol dm^{-3} phosphate buffer containing CD (0.01 mol dm^{-3}) and the sample (4×10^{-4} mol dm^{-3}) in the same buffer solution was introduced into the capillary by applying the potential (6.1 kV) for 10 s. The electropherograms were measured by applying the same potential.

[b] The separation factor α is defined as

$$\alpha = (t_2 - t_0)/(t_1 - t_0)$$

where t_1 and t_2 represent the retention times of the samples, respectively, and t_0 is the retention time of the coexisting compound (CH_3OH) which does not interact with selector.

the conditions indicated in Table III. The long retention times in CZE using β-CD and TMe-β-CD suggest that very weak complexes are formed between **4** and these CDs. When mono-NH_3^+-β-CD was used as the selector, two peaks appeared at 38.6 and 46.6 min which correspond to (*S*)-**4** and (*R*)-**4**, respectively. The retention times were markedly shortened and the separation factor α became large when dicationic CD, di-NH_3^+-β-CD, was used as a selector, the retention times being 19.2 and 31.6 min for the (*S*)- and (*R*)-**4** enantiomers, respectively. Such a result is inconsistent with those of CZE for **1**, **2** and **3** using a buffer solution at pH 6.0

Table IV. Retention times (t) and separation factors (α) in CZE of (±)-2-phenylpropionic acid (**5**) and ibuprofen (**6**) using CDs as chiral selectors[a]

guest	host	pH	current / μA	t_1 / min	t_2 / min	α
5	β-CD	6.00	9	20.2 (±)	20.2 (±)	1.00
5	TMe-β-CD	6.00	11	27.1 (±)	27.1 (±)	1.00
5	mono-NH_3^+-β-CD	9.00	10	12.0 (±)	12.0 (±)	1.00
5	mono-NH_3^+-β-CD	8.04	14	14.4 (±)	14.4 (±)	1.00
5	mono-NH_3^+-β-CD	7.21	12	14.6 (*R*)	14.8 (*S*)	1.01
5	mono-NH_3^+-β-CD	6.39	10	15.0 (*R*)	15.2 (*S*)	1.01
5	mono-NH_3^+-β-CD	6.00	10	15.2 (*R*)	15.4 (*S*)	1.01
5	mono-NH_3^+-β-CD	5.35	10	15.6 (*R*)	15.9 (*S*)	1.02
5	mono-NH_3^+-β-CD	5.15	9	16.0 (*R*)	16.4 (*S*)	1.03
6	β-CD	6.00	9	22.9 (±)	22.9 (±)	1.00
6	TMe-β-CD	6.00	11	15.3 (±)	15.3 (±)	1.00
6	mono-NH_3^+-β-CD	9.00	10	7.6 (±)	7.6 (±)	1.00
6	mono-NH_3^+-β-CD	6.86	12	10.0(±)	10.0 (±)	1.00
6	mono-NH_3^+-β-CD	6.39	10	10.2 (*S*)	10.4 (*R*)	1.03
6	mono-NH_3^+-β-CD	5.50	10	10.5 (*S*)	10.8 (*R*)	1.03
6	mono-NH_3^+-β-CD	4.68	10	10.8 (*S*)	11.2 (*R*)	1.04

[a] The conditions of CZE are shown in the footnote of Table III.

where no peaks were detected in CZE using di-NH_3^+-β-CD. A faster electroosmotic flow and a partial dissociation of the protonated diamino CD at higher pH (pH 8.0) seem to bring the **4**-di-NH_3^+-β-CD complexes to the negative electrode. On the basis of these results, it can be concluded that only cationic CDs act as good chiral selectors for separating the enantiomers of the chiral phenylacetic acids by CZE.

The guest molecules **1**, **2**, **3** and **4** have the substituents involving an electronegative oxygen atom at the α-position of α-phenylacetic acid. Meanwhile, the guests **5** and **6** are α-phenylpropanoic acid and its derivative, respectively. Table IV shows the results of CZE of **5** and **6**. Very small α values were obtained for these guests, suggesting that mono-NH_3^+-β-CD has a very weak ability to discriminate between the enantiomers of **5** or **6**.

3.2. ^{1}H NMR SPECTROSCOPY

It is known that the CDs can act as chiral solvating agents in ^{1}H NMR spectroscopy [13]. Figure 1 shows the effects of various CDs on the ^{1}H NMR spectra of **2** in D_2O at pD 6. TMe-β-CD does not affect the spectrum of **2** at all, indicating that hydrophobic TMe-β-CD scarcely interacts with anionic **2**. Upon addition of mono-NH_3^+-Me-β-CD, the signals due to the phenyl ring protons of **2** are not affected while that of the methine proton is broadened. An external ion-association complex seems to be formed. A part of the signals due to the phenyl ring protons as well as the methine proton signal shifts to higher magnetic fields in the presence of β-CD, suggesting inclusion of **2** into the β-CD cavity. However, β-CD does not act as the chiral solvating agent. Broadening and slight upfield-shifts of the ^{1}H NMR signals reveal the formation of the inclusion complexes of **2** with α-CD and mono-NH_3^+-α-CD. However, we cannot know from these NMR data whether the chiral recognition of **2** by these α-CDs is achieved or not. Only in the case of mono-NH_3^+-β-CD is the methine proton signal split into two peaks. The peaks at lower and higher magnetic fields are assigned to the signals due to the (*R*)- and (*S*)-enantiomer complexes of **2**, respectively. Comparing the NMR data with the CZE data, we can conclude that the chirality of **2** can be recognized only by mono-NH_3^+-β-CD. The split signals of the methine proton and the broad singlet signal of the phenyl ring protons of **2** suggest that the **2** molecule anchors at the NH_3^+ group position of mono-NH_3^+-β-CD using Coulombic binding while the phenyl group of **2** fluctuates at the inside of the CD cavity. Figure 2 exhibits the changes in the chemical shifts ($\Delta\delta$) of mono-NH_3^+-β-CD upon addition of **2**. The signals of the H-5′, H-6 and H-6′ protons as well as that of the H-3 proton shift remarkably to higher magnetic fields. This suggests deep penetration of **2** into the CD cavity due to Coulomb interaction.

The ^{1}H NMR spectra of (±)-**4** in the absence and the presence of the β-CD derivatives are shown in Figure 3. In the presence of native β-CD, the signals due to the phenyl ring protons are markedly broadened and the signals due to the methylene protons shift and are slightly split. These results suggest that the **4** molecule is included into the β-CD cavity and the environment where the methylene group of **4** is located is slightly different between the guest enantiomers. In the case of mono-NH_3^+-β-CD, the methylene proton signals of **4** are clearly split due to the chiral recognition in NMR spectroscopic meaning. In both cases of β-CD and mono-NH_3^+-β-CD, no splitting was observed with the signal due to the phenyl ring protons upon complexation. Meanwhile, the signals due to the phenyl ring protons are slightly split upon complexation with di-NH_3^+-β-CD. Relatively large difference between the enantiomers is expected in the structures of the complexes of **4** and di-NH_3^+-β-CD.

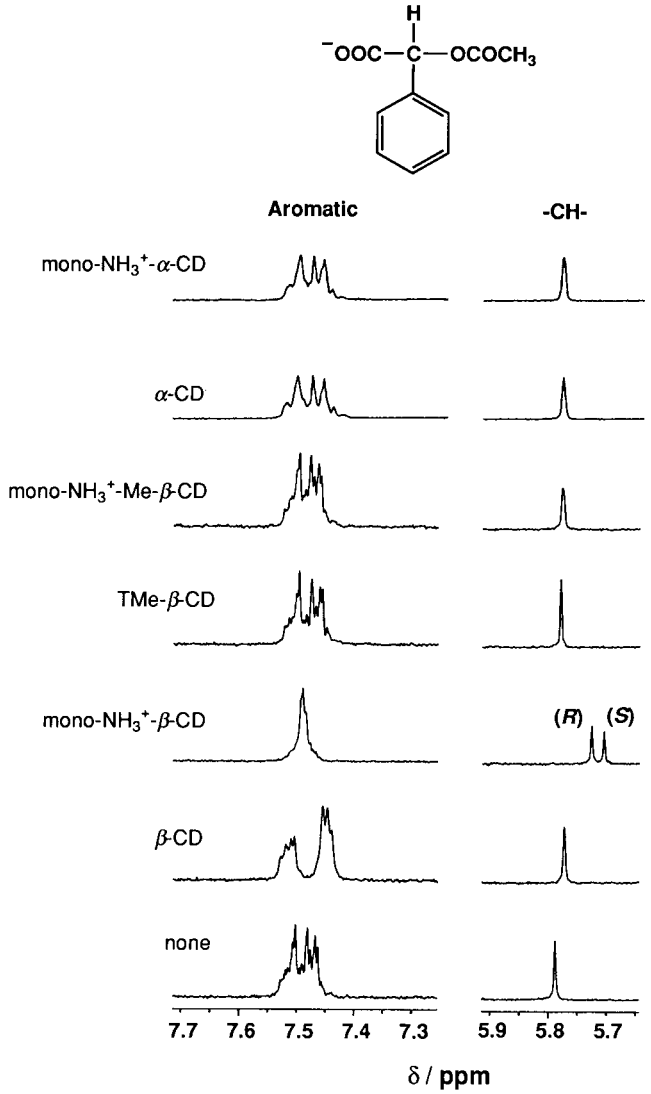


Figure 1. ^{1}H NMR spectra of **2** (2×10^{-3} mol dm^{-3}) in D_2O in the absence and the presence of CDs (1.6×10^{-2} mol dm^{-3}) at pD 6.0 and 25 °C.

3.3. BINDING CONSTANTS

A continuous variation method applied to the change in the chemical shift ($\Delta\delta$) of the methine proton upon complexation clearly reveals the formation of the 1 : 1 complex of **2** and mono-NH_3^+-β-CD. The K value was then determined from the ^{1}H NMR titration curve, which was analyzed by a nonlinear least-squares method. The results are listed in Table V, which shows that the relative K values for the enantiomers is predictable from the CZE data. Namely, the determined K

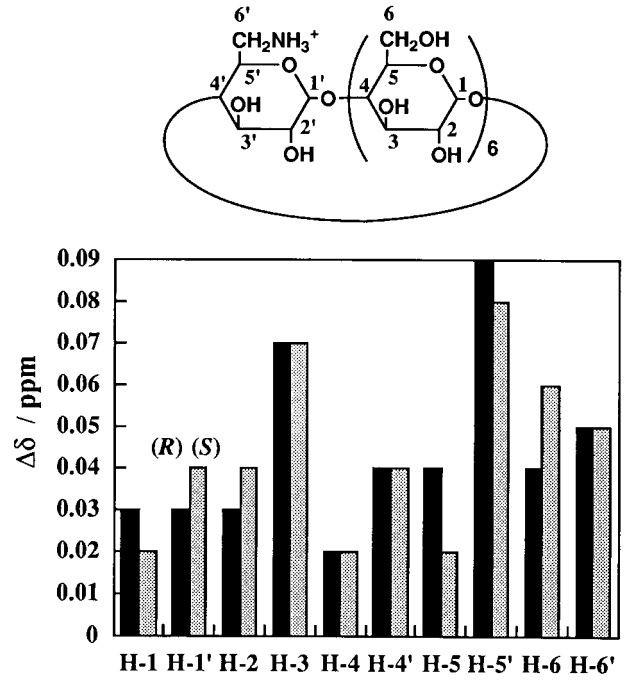


Figure 2. Changes in the proton chemical shifts ($\Delta\delta$) of mono-NH_3^+-β-CD (2×10^{-3} mol dm^{-3}) upon addition of (*R*)- and (*S*)-enantiomers of **2** at pD 6.0 and 25 °C.

values indicate that mono-NH_3^+-β-CD prefers (*R*)-**1**, (*S*)-**2**, (*R*)-**3** and (*S*)-**4** as the guests and native β-CD does not discriminate between the enantiomers of these carboxylate anions. Such a conclusion corresponds with that derived from the CZE measurements. Insufficient separation of the enantiomers of **4** in CZE using β-CD (α = 1.03) was not reflected in the *K* values.

Cooper and MacNicol [2] reported the *K* values for the α-CD complexes of (*R*)-**1** and (*S*)-**1** to be 7.9 and 8.3 dm^3 mol^{-1}, respectively. Harata et al. [14] measured the crystal structures of the TMe-α-CD complexes of (*R*)-**1** and (*S*)-**1** and found that (*R*)-**1** penetrates into the CD cavity more deeply than (*S*)-**1**. In the present study, we did not determine the *K* values for the complexes of **1** and TMe-α-CD. We measured CZE of (±)-**1** using TMe-α-CD. The enantiomers of **1** could be separated from each other under very constricted conditions. The retention times of (*R*)-**1** and (*S*)-**1** are 9.5 and 10.0 min (α = 1.05) in pH 4.66 phosphate buffer (0.006 mol dm^{-3}) at 29.1 kV. CZE of **1** is very sensitive to the pH of the buffer as well as applied voltage. We had to seek the CZE conditions very carefully. The results of CZE suggest that the *K* values of the complexes of (*R*)-**1** and (*S*)-**1** with TMe-α-CD are almost the same. The enantiomer separation of **1** could not be achieved when α-CD was used as a selector, predicting that α-CD shows the same *K* values in complexation with (*R*)-**1** and (*S*)-**1**. Such a result of CZE well corresponds with that of the *K*-value determination [2]. Meanwhile, the *K* value

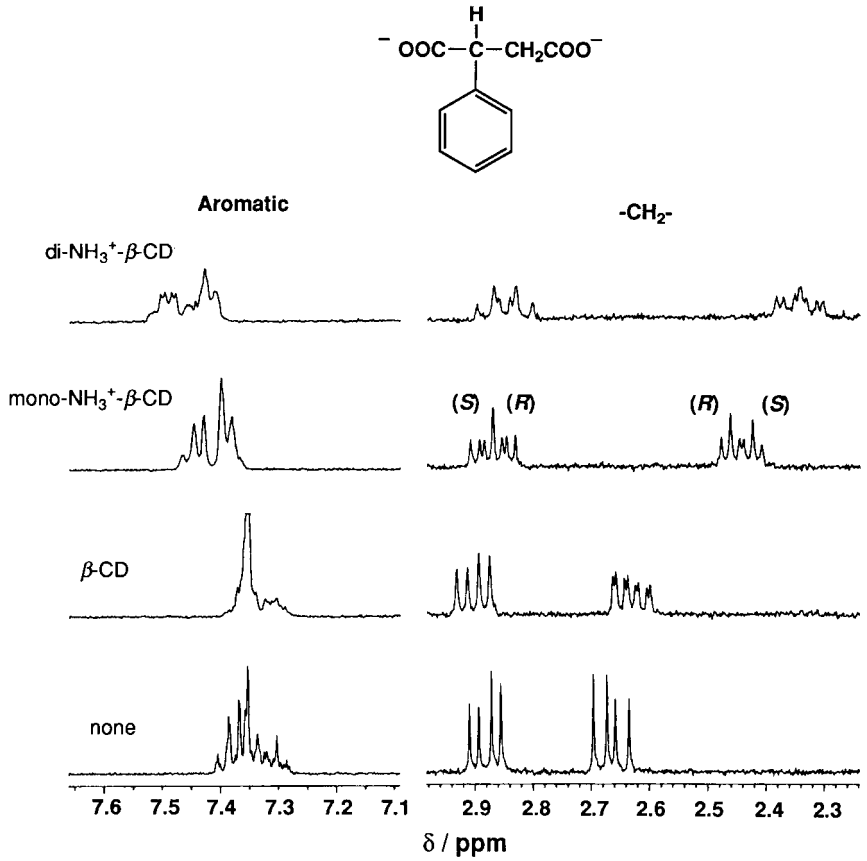


Figure 3. ^{1}H NMR spectra of **4** (2×10^{-3} mol dm^{-3}) in D_2O in the absence and the presence of CDs (1.6×10^{-2} mol dm^{-3}) at pD 6.0 and 25 °C.

for the (*R*)-**1**-mono-NH_3^+-β-CD complex is larger than that of the (*S*)-**1** complex, $\Delta\Delta G$ being -1.02 kJ mol^{-1} where $\Delta\Delta G = \Delta G_R - \Delta G_S$. The *K* values for the **1**–β-CD complexes are too small to be determined accurately. All results obtained for **1** clearly reveal the importance of Coulomb interactions in the chiral recognition of the anionic guests examined here.

Regarding the guests **2** and **4**, a very small difference between the enantiomers was observed in the *K* values for complexation with mono-NH_3^+-β-CD. Usually, such a small difference is counted to be within the region of experimental error. However, CZE suggests that the difference in the *K* values between the (*R*)- and (*S*)-enantiomer complexes of **2** and of **4** shown in Table V is meaningful. The *K* values also indicate the poor ability of native β-CD to discriminate between the enantiomers of these guests. The enantioselectivity as well as the *K* values for **4** increased markedly when di-NH_3^+-β-CD was used. The large α value in CZE

Table V. Binding constants for complexation of mandelic acid (**1**), *O*-acetylmandelic acid (**2**), 1-methoxyphenylacetic acid (**3**) and phenylsuccinic acid (**4**) with CDs at 25 °C and pD 6.0

guest	host	K / dm^3 mol^{-1}	$\Delta\Delta G$ / kJ mol^{-1}
(*R*)-**1**	mono-NH_3^+-β-CD	89±6	
(*S*)-**1**	mono-NH_3^+-β-CD	59±4	-1.02
(*R*)-**2**	β-CD	23±9	
(*S*)-**2**	β-CD	23±9	0.00
(*R*)-**2**	mono-NH_3^+-β-CD	52±3	
(*S*)-**2**	mono-NH_3^+-β-CD	56±4	+0.18
(*R*)-**3**	mono-NH_3^+-β-CD	83±4	
(*S*)-**3**	mono-NH_3^+-β-CD	54±5	-1.07
(*R*)-**4**	β-CD	36±5	
(*S*)-**4**	β-CD	34±6	-0.08
(*R*)-**4**	mono-NH_3^+-β-CD	124±7	
(*S*)-**4**	mono-NH_3^+-β-CD	130±6	+0.13
(*R*)-**4**	di-NH_3^+-β-CD	268±15	
(*S*)-**4**	di-NH_3^+-β-CD	328±22	+0.50

(α = 1.65) for the **4**-di-NH_3^+-β-CD system reflects the large K values and high enantioselectivity in this system.

The K values for the β-CD and mono-NH_3^+-β-CD complexes of **5** have been determined by Brown et al. [4], who reported the K values to be 63 and 52 dm^3 mol^{-1} for the β-CD complexes of (*R*)-**5** and (*S*)-**5**, respectively. Since the enantiomers of **5** could not be separated in CZE using β-CD, such a small difference in the K values might be within the region of experimental error. The reported K values for the (*R*)- and (*S*)-**5** complexes of mono-NH_3^+-β-CD are 150 and 110 dm^3 mol^{-1} [4], which can explain our CZE data.

Although the ability of aminated CDs to recognize the central chirality of anionic guests is very low, it is noteworthy that only aminated CDs in the protonated forms discriminate between the enantiomers of these anionic acids.

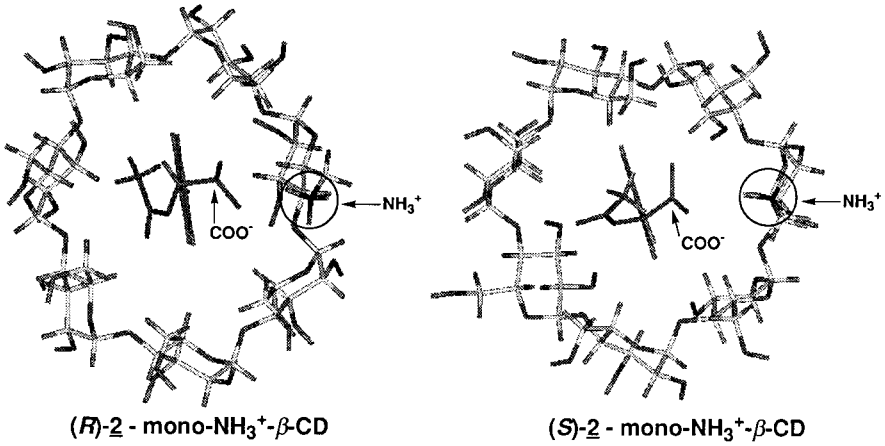


Figure 4. Calculated structures of the mono-NH_3^+-β-CD complexes of (*R*)-**2** and (*S*)-**2**. In each case, the CO_2^- and $OCOCH_3$ groups of **2** are situated at right- and left-hand sides, respectively.

3.4. STRUCTURES OF COMPLEXES AND MECHANISM OF CHIRAL RECOGNITION

In order to discuss the mechanism of chiral recognition by CD, we need to know the structure of the complex of each guest enantiomer. ^{1}H NMR spectroscopy as well as CZE indicates that the anionic guest molecule is included into the cavity of mono-NH_3^+-β-CD and electrostatic interaction exists between anionic guest and cationic host. Measurement of the ROESY spectrum is one of the best ways to gain more detailed knowledge of the structure of an inclusion complex. However, this method is not suitable for the present system because the stoichiometry of the ion-association complex changes at higher guest concentration. We therefore tried to apply MM-MD calculations to get the possible structures of the inclusion complexes. Recent studies demonstrate the validity of the MM-MD calculations in CD chemistry [15, 16].

The calculated structures of the mono-NH_3^+-β-CD complexes of (*R*)-**2** and (*S*)-**2** are shown in Figure 4. The (*S*)-**2**, a preferable enantiomer, is located at the center of the cavity of mono-NH_3^+-β-CD to minimize the steric repulsion. No distinct difference in the calculated structures is observed between the (*S*)- and (*R*)-**2** complexes, corresponding to the small difference in the *K* values.

Figure 5 shows the calculated structures of the di-NH_3^+-β-CD complexes of (*R*)-**4** and (*S*)-**4**. In the case of (*S*)-**4**, which is the preferable enantiomer, the guest molecule are located at the center of the cavity where the steric hindrance is minimized. The (*R*)-**4** complex is calculated as a shallower inclusion complex where several parts of the guest molecule are close to the wall of the CD cavity. The difference in the structures of the complexes between the guest enantiomers is more remarkable for **4** than for **2**.

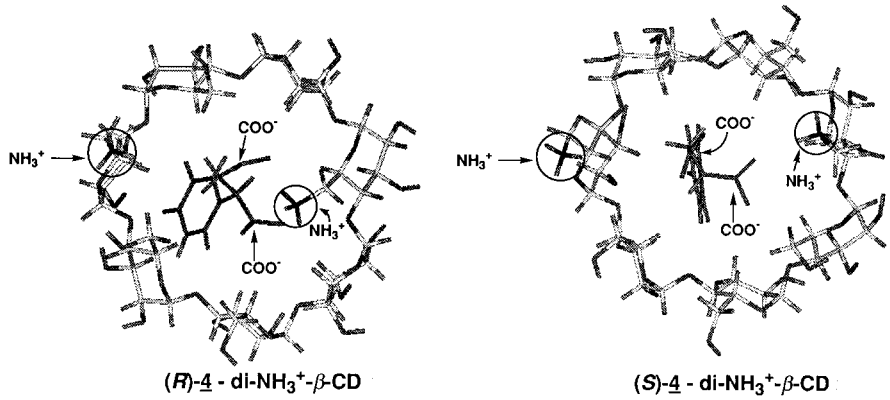


Figure 5. Calculated structures of the di-NH_3^+-β-CD complexes of (*R*)-**4** and (*S*)-**4**.

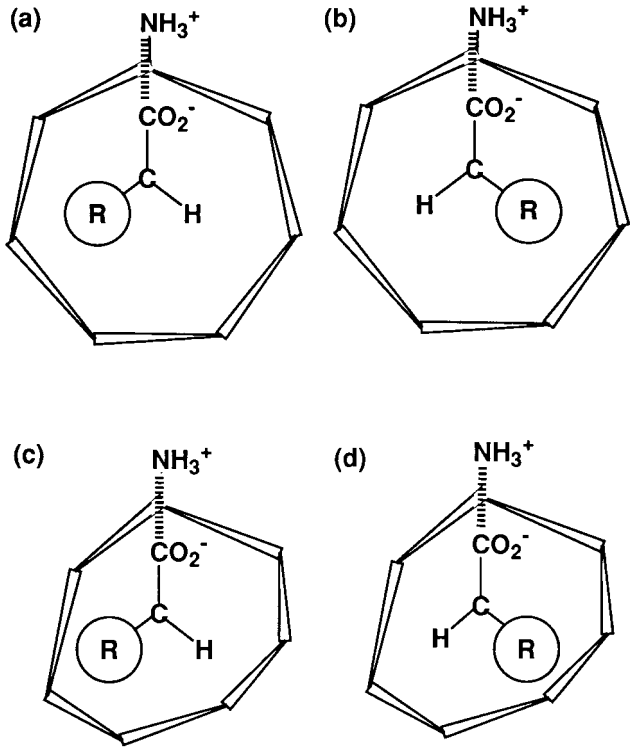


Figure 6. Models for the non-distorted (top) and distorted mono-NH_3^+-β-CD complexes (bottom) of (*R*)- and (*S*)-carboxylic acids in the dissociated forms.

Figure 6 shows the models of ion-association complexes of chiral guest acid and mono-NH_3^+-β-CD. A triangle in the CD structure denotes a glucopyranose unit. Such a monosubstituted CD involving α(1–4) glucoside linkages belongs to the C_1 point group, similar to a guest with an asymmetric carbon. Diastereomers are formed when mono-NH_3^+-β-CD complexes with racemic guest. Essentially, the nature of one diastereomer is different from that of another diastereomer. However, it might be difficult to recognize that the structure of the diastereomer shown in Figure 6a is quite different from that of the other one shown in Figure 6b especially when R is a substituent such as CH_3. This is due to the symmetrical toroidal shape of the CD shown in Figures 6a and 6b. In order to enhance the ability of CD to recognize the chirality, it needs to strengthen the C_1 symmetric nature of the CD by distorting the shape of the toroid (see Figures 6c and 6d). As the MM-MD calculations suggests, mono-NH_3^+-β-CD can change its shape by including a guest. Such an induced-fit-type inclusion has been known in CD chemistry [14, 17]. Of course, the stability of the complex shown in Figure 6c is different from that in Figure 6d. If the complex shown in Figure 6d is more unstable than that in Figure 6c, the CD complex alters its shape to another one to minimize the energy. This might be the mechanism for chiral recognition of anionic guest having an asymmetric carbon by protonated monoamino-CD.

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