Entropy-Dominating Strong Binding of Carboxylate Anions to Protonated Aminocyclodextrin

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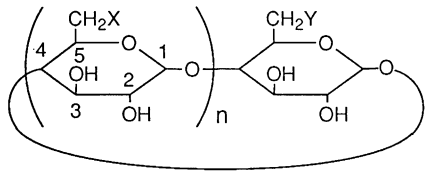
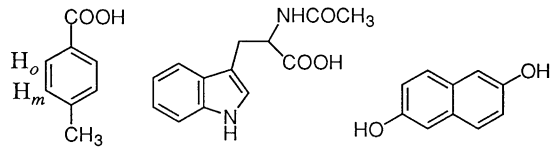
Protonated heptakis(6-amino-6-deoxy)-β-cyclodextrin complexes with *p*-methylbenzoate and *N*-acetyltryptophan anions more strongly than a monoamino-β-cyclodextrin cation. Such a strong association is dominated by large and positive entropy changes for complexation which might be due to extensive dehydration from both host and guest upon complexation.

Three-point attachment model[1] is generally accepted for the mechanism of chiral recognition in host-guest chemistry. This model implies that a chiral host molecule needs to interact with a guest enantiomer at three points to discriminate from another guest-enantiomer. Although hydrogen bonding can be used as an attractive point-interaction for achieving chiral recognition in organic solvents,[2] this interaction is hardly utilized in water because of strong hydration to the hydrogen-bonding sites of both host and guest. In place of hydrogen bonding, Coulomb interaction is promising as a point interaction which is available even in water. Point charge-point charge attractive interaction is useful when ions form a contact ion-pair in water. Table 1 lists a part of aminated cyclodextrins so far reported as the hosts for molecular recognition. These cyclodextrins in their protonated forms are interesting cations for studying Coulomb interaction in host-guest chemistry.[3] Brown et al.[4] reported that the binding constants (K) for complexation of undissociated benzoic acid, *p*-methylbenzoic acid, and 2-phenylpropanoic acid with MA-β-CDx are much larger than those of the complexes of the corresponding carboxylate anions. This suggests that the Coulomb interaction of the univalent cationic cyclodextrin with carboxylate anions is unexpectedly weak. Hamelin et al.[5] demonstrated that the dissociating power of water is so strong that an association constant for complexation of low-valent ions with opposite charges is small while highly charged ions form a stable association complex. Polyaminated cyclodextrins such as PBA-β-CDx, PA-α-CDx, PA-β-CDx, and PA-γ-CDx are known to associate with inorganic anions through Coulomb interaction.[6,7] $Fe(CN)_6^{4-}$ are bound to polyaminated cyclodextrins more strongly than $Fe(CN)_6^{3-}$.[7] PMA-β-CDx forms a very stable inclusion complex with 5'-AMP through both inclusion and Coulomb interactions (K = 1.26 x 10^5 dm^3 mol^{-1}).[8] We are interested in the mechanism for such a strong Coulomb interaction of multivalent ions. In the present study, we carried out thermodynamic study on complexation of β-CDx, MA-β-CDx, and PA-β-CDx with the dissociated *p*-methylbenzoic acid (**1**) and *N*-acetyltryptophan (**2**) and found that the strong association of PA-β-CDx with these carboxylate anions is dominated by the large and positive entropy changes.

Table 1. Structures of cyclodextrins and their abbreviations



X	Y	n	Abbreviation
OH	OH	6	β-CDx
OH	NH_3^+	6	MA-β-CDx
NH_3^+	NH_3^+	5	PA-α-CDx
NH_3^+	NH_3^+	6	PA-β-CDx
NH_3^+	NH_3^+	7	PA-γ-CDx
$NH_2CH_3^+$	$NH_2CH_3^+$	6	PMA-β-CDx
$NH_2C_3H_7^+$	$NH_2C_3H_7^+$	6	PBA-β-CDx



1 **2** **3**

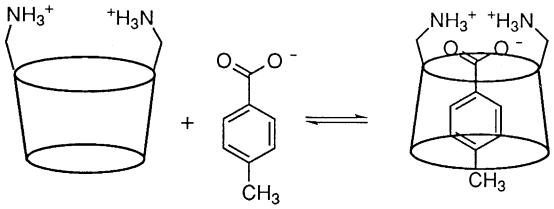
Table 2 shows the K values for complexation of **1**, **2**, and 2,6-dihydroxynaphthalene (**3**), which is a control guest without charge. The K values were determined from ^1H NMR titrations in D_2O at pD 6.0 where MA-β-CDx and PA-β-CDx have one and seven positive charges, respectively,[9] and the CO_2H groups of both **1** and **2** are dissociated. The **1** anion is included weakly into the β-CDx and MA-β-CDx cavities. ROESY spectrum of the **1**-β-CDx system clearly shows the correlations between H_o and H5, H_m and H3, and the CH_3 protons and H3, where H3 and H5 represent the protons of β-CDx at the 3- and 5-positions, respectively. This indicates that the **1** anion is included into the CDx cavity where the CO_2^- group of **1** is located at the primary OH group side of β-CDx. Such an orientation has also been

Table 2. Binding constants (K) for complexation of **1**, **2**, and **3** with cyclodextrins in D_2O at pD 6.0 and 25°C

Guest	Host	K / dm^3 mol^{-1}
1	β-CDx	250±20 (200±22)[a]
1	MA-β-CDx	660±37 (520±20)
1	PA-β-CDx	15000±1800 (9180±480)
(*S*)-**2**	MA-β-CDx	99±4
(*R*)-**2**	MA-β-CDx	64±6
(*S*)-**2**	PA-β-CDx	2670±100
(*R*)-**2**	PA-β-CDx	1930±90
3	β-CDx	810±53
3	MA-β-CDx	360±27
3	PA-β-CDx	68±7

[a] The values in the parentheses are the K values in the presence of 0.02 mol dm^{-3} NaCl.

observed for the benzoate anion-α-CDx system.[10] Essentially the same ROESY spectrum was obtained for the **1**-PA-β-CDx system of which the *K* value was extremely large. The orientation of the guest anion in the PA-β-CDx cavity is the same as that of the **1**-β-CDx complex. A remarkable difference between the β-CDx, MA-β-CDx, and PA-β-CDx complexes is found in the *K* values. Introduction of an NH_3^+ group into β-CDx causes the significant increase in the *K* value which can be understood by the Coulomb interaction between the host and the guest. Drastic increase in the *K* value was measured for the **1**-PA-β-CDx complex. Similar binding behavior was also observed in the complexation of (*R*)-**2** and (*S*)-**2** with aminated cyclodextrins (see Table 2). The *K* values of the **2**-PA-β-CDx complexes are much larger than those of the **2**-MA-β-CDx. Meaningful but humble chiral-recognition of **2** by aminated cyclodextrins occurs in this case. For comparison, the ability of aminated cyclodextrins to include a guest without charge was examined by using **3**. As shown in Table 2, the binding ability decreases in the order of β-, MA-β-, and PA-β-CDxs for **3**. Increase in the number of charges of the host cation causes the decrease in the binding ability. Such a trend is opposite to the binding of the carboxylate anions, indicating the participation of the Coulomb interaction in the complexation of the cationic cyclodextrins with the anionic guests. Easton et al.[11] claimed that the NH_3^+ group attached to cyclodextrin significantly destroys the hydrophobic nature of the cyclodextrin cavity. This must be the reason for the small *K* values of the MA-β-CDx and PA-β-CDx complexes of **3**. It is clear that the van der Waals and/or hydrophobic interactions in complexation of PA-β-CDx are much weaker than those of β-CDx and MA-β-CDx. The problem is the reason(s) for the anomalously large *K* values for binding of the anions to the multivalent cation compared with those to the univalent cation. Table 3 shows the thermodynamic parameters for complexation of **1** and (*S*)-**2** with cyclodextrins. The complexation of **1** with PA-β-CDx shows a small and positive enthalpy change (ΔH) and a large and positive entropy change (ΔS) while that with β-CDx and MA-β-CDx is mainly dominated by negative and large ΔHs. The entropically dominated complexation also occurs in the (*S*)-**2**-PA-β-CDx system. The large *K* values of the carboxylate anion-PA-β-CDx complexes are ascribed to the large and positive ΔSs. Since hydrophobic interaction cannot be considered in the present system, dehydration from the host and the guest upon complexation might be a cause for such large and positive ΔS values. Insertion of the CO_2^- group of the guest into the hydrophobic cyclodextrin cavity causes the dehydration from the guest. The Coulomb interaction between the CO_2^- group of the anionic guest and the NH_3^+ groups situated at a rim of the microscopically hydrophobic host cavity seems to cause the extensive dehydration from PA-β-CDx. The molecular mechanics-molecular dynamics calculations[12] exhibit that the protonated amino group side of PA-β-CDx in water is expanded because of the strong electrostatic repulsion between the NH_3^+ groups. The expanded rim of this cyclodextrin becomes narrow upon complexation with an anionic guest included in the host



cavity through Coulomb interaction. Such a process might be endothermic to yield the positive ΔH in the case of **1** and the negative but very small ΔH in the case of (*S*)-**2**.

Table 3. Thermodynamic parameters for complexation of **1** and (*S*)-**2** with cyclodextrins in D_2O at pD 6.0[a]

Guest	Host	ΔH / kJ mol^{-1}	ΔS / J mol^{-1} K^{-1}
1	β-CDx	-8.56±0.02	15.3±0.67
1	MA-β-CDx	-10.40±1.82	18.1±6.03
1	PA-β-CDx	3.76±0.68	88.6±2.17
(*S*)-**2**	PA-β-CDx	-0.19±1.84	65.5±5.90

[a] The thermodynamic parameters for complexation of **1** were determined in D_2O in the presence of 0.02 mol dm^{-3} NaCl.

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