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# Interactions with Charged Cyclodextrins and Chiral Recognition

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**Abstract**

Anionic *N*-acetylated $\alpha$-amino acids ($AcTrp^-$, $AcPhe^-$, $AcLeu^-$ and $AcVal^-$) are bound to protonated heptakis(6-amino-6-deoxy)-$\beta$-cyclodextrin (per-$NH_3^+$-$\beta$-CD) by a cooperative work of inclusion and Coulomb interactions. Such complexation occurs enantioselectively ((*S*)-selective) and is accompanied by positive entropy changes. Similar (*S*)-selective complexation occurs in the oppositely charged system. Namely, cationic $\alpha$-amino acid methyl esters are enantioselectively bound to dissociated heptakis(6-carboxymethylthio-6-deoxy)-$\beta$-cyclodextrin (per-$COO^-$-$\beta$-CD). In order to obtain the general mechanism for complexation of a charged host with an oppositely charged guest, we examined the $^1$H NMR spectra on complexation of simple carboxylate anions such as *p*-methylbenzoate anion and alkanoate anions with per-$NH_3^+$-$\beta$-CD. Both Coulomb interactions and inclusion are essential to form stable complexes of these carboxylate anions. In all cases, positive entropy changes promote the complexation between the carboxylate anions and per-$NH_3^+$-$\beta$-CD. Dehydration from both charged host and guest is the origin of entropic gains. The mechanism for complexation of a charged host with an oppositely charged guest involving the cooperative work of inclusion and Coulomb interactions and positive entropy change due to dehydration upon complexation is generally applied for related systems such as enantioselective complexation of $Ru(phen)_3^{2+}$ with per-$COO^-$-$\beta$-CD and of $Ru(phen)_3^{2+}$ with DNA.

## Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides having appropriate cavities for including various lipophilic organic compounds. Proposed driving forces for forming inclusion complexes of CDs are (1) van der Waals interaction, (2) hydrophobic interaction, (3) dipole-dipole interaction, (4) hydrogen-bonding interaction, (5) release of distortional energy upon complexation, and (6) extrusion of high-energy water molecules from the CD cavity upon complexation. The most common force is the van der Waals interaction. Therefore, size fitting between the host cavity and guest molecule is the most important factor to form a stable inclusion complex. Classical hydrophobic interaction accompanied by a positive entropy change has been assumed to participate in complexation of guests having relatively smaller sizes compared with the CD cavity size [1]. It is expected that CD does not include strongly polar guests such as anions and cations because of the hydrophobicity of the CD cavity. However, it has been known that $\alpha$-CD can include inorganic anions such as $ClO_4^-$, $SCN^-$, $I^-$, $Br^-$, $NO_3^-$ and $IO_3^-$ [2]. The binding constants ($K$s) for complexation of $I^-$ and $SCN^-$ with $\alpha$-CD are 18.8 and 33.5 $M^{-1}$, respectively. The enthalpy ($\Delta H$) and entropy changes ($\Delta S$) are $-24.7$ kJ $mol^{-1}$ and $-57.3$ J $mol^{-1}$ $K^{-1}$, respectively, for $I^-$ and $-28.5$ kJ $mol^{-1}$ and $-66.5$ J $mol^{-1}$ $K^{-1}$, respectively, for $SCN^-$. Ion-dipole interactions may participate in complexation of the anions. The anion binding to mono[6-(1-pyridinio)-6-deoxy]-$\alpha$-cyclodextrin has also been studied and it was found that chaotropic anions such as $Br^-$, $I^-$ ($K$ = 199 $M^{-1}$), $SCN^-$, $N_3^-$, $NO_3^-$, and $ClO_4^-$ are well bound to the CD, but antichaotropic anions such as $F^-$, $Cl^-$, $SO_4^-$, $H_2PO_4^{2-}$ and $HPO_4^-$ are not. NMR spectroscopy suggests that the inorganic anions are located at the inside of the CD cavity [3]. Polyvalent cationic heptakis(6-butylamino)-6-deoxy)-$\beta$-cyclodextrin shows the ability to bind $SCN^-$ ($K$ = 93 $M^{-1}$) and $SO_4^{2-}$ (470 $M^{-1}$) [4]. Meanwhile, there have been several studies on interactions of organic anions with native CDs. For example, Inoue *et al*. carried out calorimetric studies on the interactions of the naphthalene sulfonates with $\alpha$- and $\beta$-CDs [5]. They discussed the $\Delta H$–$\Delta S$ compensation relationship and demonstrated the contribution of dehydration upon complexation to get entropic gains observed in some anionic guest-neutral host systems. The anion binding accompanied by positive entropy changes has been found in similar systems [6]. The stability of complexes of organic anions depends upon size matching between the lipophilic part of the guest and the cavity of the host. In general, the stability of the CD complexes of organic anions whose lipophilic parts are phenyl or groups having the sizes smaller than benzene is considerably small (Table 1).

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*Table 1.* Binding constants for complexation of various guests with native CDs

| Guest[a] | CD | $K$, $M^{-1}$ | Ref. |
|---|---|---|---|
| Ph-COOH | $\beta$-CD | 590 | b |
| Ph-$COO^-$ | $\beta$-CD | 60 | b |
| $p$-$CH_3$-Ph-COOH | $\beta$-CD | 1680 | b |
| $p$-$CH_3$-Ph-$COO^-$ | $\beta$-CD | 110 | b |
| ($R$)-Ph-CH($CH_3$)-COOH | $\beta$-CD | 1090 | b |
| ($S$)-Ph-CH($CH_3$)-COOH | $\beta$-CD | 1010 | b |
| ($R$)-Ph-CH($CH_3$)-$COO^-$ | $\beta$-CD | 63 | b |
| ($S$)-Ph-CH($CH_3$)-$COO^-$ | $\beta$-CD | 52 | b |
| Ph-OH | $\beta$-CD | 129 | c |
| Ph-$O^-$ | $\beta$-CD | 15 | c |
| $o$-$NO_2$-Ph-OH | $\beta$-CD | 145 | c |
| $o$-$NO_2$-Ph-$O^-$ | $\beta$-CD | 100 | c |
| $m$-$NO_2$-Ph-OH | $\beta$-CD | 130 | c |
| $m$-$NO_2$-Ph-$O^-$ | $\beta$-CD | 75 | c |
| $p$-$NO_2$-Ph-OH | $\beta$-CD | 130 | c |
| $p$-$NO_2$-Ph-$O^-$ | $\beta$-CD | 410 | c |
| Ph-$NH_2$ | $\beta$-CD | 56 | c |
| Ph-$NH_3^+$ | $\beta$-CD | 2 | c |
| $p$-$NO_2$-Ph-$NH_2$ | $\beta$-CD | 300 | c |
| $p$-$NO_2$-Ph-$NH_3^+$ | $\beta$-CD | 100 | c |
| C3-COOH | $\alpha$-CD | 135 | d |
| C3-$COO^-$ | $\alpha$-CD | 15 | d |
| C5-COOH | $\alpha$-CD | 809 | d |
| C5-$COO^-$ | $\alpha$-CD | 210 | d |

[a] Ph-COOH: benzoic acid, Ph-CH($CH_3$)-COOH: 2-phenylpropanoic acid, Ph-OH: phenol, $o$-$NO_2$-Ph-OH: $o$-nitrophenol, Ph-$NH_2$: aniline, $p$-$NO_2$-Ph-$NH_2$: $p$-nitroaniline, C3-COOH: propanoic acid, C5-COOH: hexanoic acid.
[b] S. E. Brown, J. H. Coates, P. A. Duckworth, S. F. Lincoln, C. J. Easton, and B. L. May: *J. Chem. Soc. Faraday Trans.* **89**, 1035 (1993).
[c] A. Buvári and L. Barcza: *J. Chem. Soc., Perkin Trans. 2*, 543 (1988).
[d] R. I. Gelb and L. M. Schwartz: *J. Incl. Phenom. Mol. Recognit.* **7**, 465 (1989).

## Chiral recognition of amino acids by charged CDs

The weak ability of native CDs to bind ionic guests limits studies on chiral recognition by $\alpha$-, $\beta$- and $\gamma$-CDs. $\alpha$-Amino acids are typical targets to study. Cooper and MacNicol reported the binding constants ($K$) for complexation of anionic phenylalanine (Phe$^-$) with $\alpha$-CD, the $K$ values for the ($R$)- and ($S$)-enantiomers of Phe$^-$ being 21 and 16 $M^{-1}$, respectively [7]. The $K$ values are too small to discuss chiral recognition by CD. Tabushi and his coworkers prepared theoretically well-designed CDs (**1**, **2** and **3**) and determined the $K$ values (Table 2) [8]. Although slight improvement of the binding ability of CD is achieved, enantioselectivity is low. Use of Coulomb interactions for molecular recognizing host-guest complexation has been attempted [9]. Lincoln, Easton and their coworkers studied chiral recognition of 2-phenylpropanoic acid by $6^A$-amino-$6^A$-deoxy-$\beta$-cyclodextrin (mono-$NH_2$-$\beta$-CD) [10]. Their results are shown in Table 3. Comparing the results in Table 1 with those in Table 3, it can be found that introduction of a hydrophilic group, $NH_3^+$, reduces the ability of $\beta$-CD to bind benzoic acid (Ph-COOH) and

*Table 2.* Binding constants for complexation of ($R$)- and ($S$)-Trps with zwitter ionic hosts **1**, **2** and **3**[a]

| Host | Guest | $K$, $M^{-1}$ |
|---|---|---|
| **1** | ($R$)-Trp | $45.5 \pm 8.2$ |
| **1** | ($S$)-Trp | $34.5 \pm 5.7$ |
| **2** | ($R$)-Trp | $54.0 \pm 7.6$ |
| **2** | ($S$)-Trp | $42.5 \pm 7.3$ |
| **3** | ($R$)-Trp | $15 \pm 10$ |
| $\beta$-CD | ($R$)-Trp | $13 \pm 8$ |

[a] I. Tabushi, Y. Kuroda and T. Mizutani: *J. Am. Chem. Soc.* **108**, 4514 (1986).

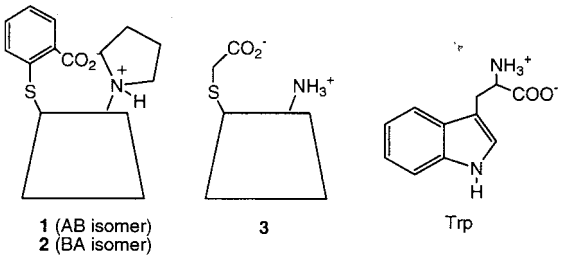



*Table 3.* Binding constants for complexation of carboxylic acids and carboxylates with mono-$NH_2$-$\beta$-CD and mono-$NH_3^+$-$\beta$-CD[a]

| Host | Guest[b] | $K$, $M^{-1}$ |
|---|---|---|
| mono-$NH_2$-$\beta$-CD | Ph-$COO^-$ | 50 |
| mono-$NH_2$-$\beta$-CD | $p$-$CH_3$-Ph-$COO^-$ | 100 |
| mono-$NH_2$-$\beta$-CD | ($R$)-Ph-CH($CH_3$)-$COO^-$ | 36 |
| mono-$NH_2$-$\beta$-CD | ($S$)-Ph-CH($CH_3$)-$COO^-$ | 13 |
| mono-$NH_3^+$-$\beta$-CD | Ph-COOH | 340 |
| mono-$NH_3^+$-$\beta$-CD | Ph-$COO^-$ | 120 |
| mono-$NH_3^+$-$\beta$-CD | $p$-$CH_3$-Ph-COOH | 910 |
| mono-$NH_3^+$-$\beta$-CD | $p$-$CH_3$-Ph-$COO^-$ | 330 |
| mono-$NH_3^+$-$\beta$-CD | ($R$)-Ph-CH($CH_3$)-COOH | 580 |
| mono-$NH_3^+$-$\beta$-CD | ($S$)-Ph-CH($CH_3$)-COOH | 480 |
| mono-$NH_3^+$-$\beta$-CD | ($R$)-Ph-CH($CH_3$)-$COO^-$ | 150 |
| mono-$NH_3^+$-$\beta$-CD | ($S$)-Ph-CH($CH_3$)-$COO^-$ | 110 |

[a] S. E. Brown, J. H. Coates, P. A. Duckworth, S. F. Lincoln, C. J. Easton and B. L. May: *J. Chem. Soc., Faraday Trans.* **89**, 1035 (1993).
[b] The abbreviations of the guests are shown in the footnote of Table 1.

$p$-methylbenzoic acid ($p$-$CH_3$-Ph-COOH). The $K$ values for complexation of the carboxylate anions with protonated monoamino $\beta$-CD (mono-$NH_3^+$-$\beta$-CD) are ca. 2–3 times larger than those of the carboxylate anions with unprotonated per-$NH_2$-$\beta$-CD. Coulomb interactions, however, do not improve the enantioselectivity of CD for 2-phenylpropanoate anion.

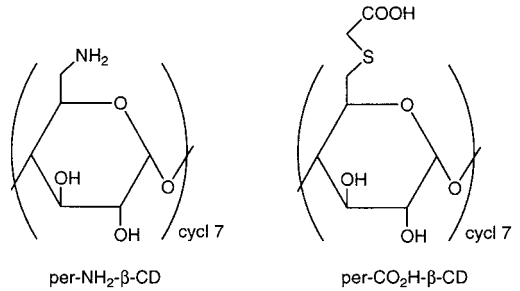


*Table 4.* Chiral recognition of *N*-acetylated $\alpha$-amino acids in the anionic forms by aminated $\beta$-cyclodextrins in the cationic forms[a,b]

| Host | Guest | $K$, $M^{-1}$ | $K_S/K_R$ |
|---|---|---|---|
| mono-$NH_3^+$-$\beta$-CD | (*S*)-AcTrp$^-$ | 99 ± 4 | |
| mono-$NH_3^+$-$\beta$-CD | (*R*)-AcTrp$^-$ | 64 ± 6 | 1.5 |
| mono-$NH_3^+$-$\beta$-CD | (*S*)-AcPhe$^-$ | 67 ± 8 | |
| mono-$NH_3^+$-$\beta$-CD | (*R*)-AcPhe$^-$ | 55 ± 7 | 1.2 |
| mono-$NH_3^+$-$\beta$-CD | (*S*)-AcLeu$^-$ | 58 ± 4 | |
| mono-$NH_3^+$-$\beta$-CD | (*R*)-AcLeu$^-$ | 50 ± 3 | 1.2 |
| per-$NH_3^+$-$\beta$-CD | (*S*)-AcTrp$^-$ | 2310 ± 90 | |
| per-$NH_3^+$-$\beta$-CD | (*R*)-AcTrp$^-$ | 1420 ± 50 | 1.6 |
| per-$NH_3^+$-$\beta$-CD | (*S*)-AcPhe$^-$ | 2180 ± 130 | |
| per-$NH_3^+$-$\beta$-CD | (*R*)-AcPhe$^-$ | 2000 ± 130 | 1.1 |
| per-$NH_3^+$-$\beta$-CD | (*S*)-AcLeu$^-$ | 2480 ± 110 | |
| per-$NH_3^+$-$\beta$-CD | (*R*)-AcLeu$^-$ | 2380 ± 110 | 1.0 |
| per-$NH_3^+$-$\beta$-CD | (*S*)-AcVal$^-$ | 2090 ± 160 | |
| per-$NH_3^+$-$\beta$-CD | (*R*)-AcVal$^-$ | 1310 ± 80 | 1.6 |

[a] T. Kitae, T. Nakayama and K. Kano: *J. Chem. Soc., Perkin Trans. 2*, 207 (1998).
[b] The $K$ values were determined by $^1$H NMR spectroscopy in $D_2O$ at pD 6.0 and 25 °C.

We used polyvalent cationic and anionic CDs for chiral recognition of $\alpha$-amino acids [11] and dipeptides. Per-$NH_2$-$\beta$-CD and per-COOH-$\beta$-CD can be prepared by the methods described by Guillo *et al.* [12]. The p$K_{a1}$-p$K_{a7}$ values of the conjugate acid of per-$NH_2$-$\beta$-CD exist between 6.9 and 8.5. The p$K_a$ values of per-COOH-$\beta$-CD are below 5.6 [13]. The electronic work ($W_{el}$) between charged compounds is represented by the following equation,

$$W_{el} = (Ne^2\nu\lambda)/d\epsilon, \quad (1)$$

where $W_{el}$ is the electric work to be gained per mole for ion association, $N$ is the Avogadro's number, $e$ is the electronic charge, $d$ is the distance between oppositely charged ions, $\epsilon$ is the dielectric constant, and $\nu$ and $\lambda$ are the numbers of positive and negative charges, respectively [14]. Therefore, Coulomb interactions are expected to be strengthened when polyvalent hosts and/or guests are used. The results of the complexation of *N*-acetylated $\alpha$-amino acids in the anionic forms with aminated CDs in the cationic forms in $D_2O$ are shown in Table 4. As can be expected, the $K$ values for the complexes of per-$NH_3^+$-$\beta$-CD are much larger than those of mono-$NH_3^+$-$\beta$-CD. Both aminated CDs prefer the (*S*)-enantiomers of the guests. The absolute values of the differences in the $\Delta G$ values between the enantiomers ($|\Delta\Delta G|$) of *N*-acetylated Trp anion (AcTrp$^-$) are 1.21 and 1.08 kJ mol$^{-1}$ for per-$NH_3^+$-$\beta$-CD and mono-$NH_3^+$-$\beta$-CD, respectively. The thermodynamic parameters for complexation of AcTrp$^-$ (Table 5) indicate that complexation of AcTrp$^-$ is an entropically dominated process. The large $K$ values for the per-$NH_3^+$-$\beta$-CD complexes are ascribed to the large entropic gains. Coulomb interaction is an enthalpic process. What is the origin of such a large entropic gain?

Rotating frame nuclear Overhauser and relaxation spectroscopy (ROESY) is an excellent method to observe nuclear Overhauser effects (NOE) of samples having molecular weights of 800–1000. ROESY spectra clearly indicate that

*Table 5.* Thermodynamic parameters for complexation of AcTrp$^-$ with per-$NH_3^+$-$\beta$-CD[a]

| Guest | $\Delta H$, kJ mol$^{-1}$ | $\Delta S$, J mol$^{-1}$ K$^{-1}$ |
|---|---|---|
| (*S*)-AcTrp$^-$ | −0.56 ± 1.88 | 63.1 ± 5.9 |
| (*R*)-AcTrp$^-$ | 0.07 ± 0.65 | 60.5 ± 2.2 |

[a] T. Kitae, T. Nakayama, and K. Kano: *J. Chem. Soc., Perkin Trans. 2*, 207 (1998).

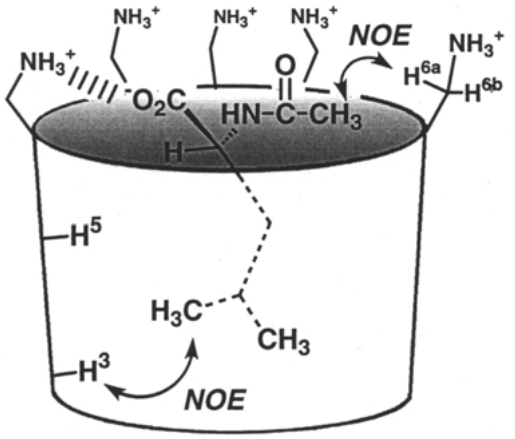



*Figure 1.* Structure of the (*S*)-AcLeu$^-$-per-$NH_3^+$-$\beta$-CD complex estimated from the ROESY spectrum.

the anionic $\alpha$-amino acid molecule is included into the cavity of per-$NH_3^+$-$\beta$-CD and the $CO_2^-$ group of the guest electrostatically interacts with the $NH_3^+$ groups of the host (Figure 1). Complexation-induced shifts in chemical shifts (CIS) of the host also show that the anionic guest is electrostatically bound to the cationic host and is included wholly into the host cavity. No external complex is suggested.

Similar chiral recognition of the methyl esters of $\alpha$-amino acids and dipeptides (Ala-Ala-OMe$^+$, Ala-Leu-OMe$^+$ and Ala-Trp-OMe$^+$) in the cationic forms occurs when per-COO$^-$-$\beta$-CD is used as an anionic host [15]. For example, the $K$ values for the (*R*,*R*)- and (*S*,*S*)-Ala-Trp-OMes are 460 and 250 $M^{-1}$ ($|\Delta\Delta G|$ = 1.5 kJ mol$^{-1}$), respectively.

## Entropically favorable complexation of organic anions

Many thermodynamic studies have been carried out to clarify the mechanisms for inclusion of guests into CD cavities [16]. However, no data have been presented with complexation of ionic guests with oppositely charged hosts. In order to know the reason(s) for the positive entropy changes observed in the complexation of AcTrp$^-$ with per-$NH_3^+$-$\beta$-CD, we investigated the thermodynamics of complexation of simple carboxylate anions with per-$NH_3^+$-$\beta$-CD [17].

At first, interactions of the *p*-methylbenzoate anion (*p*-$CH_3$-Ph-COO$^-$) with native $\alpha$- and $\beta$-CDs were examined. *p*-$CH_3$-Ph-COO$^-$ was chosen because of its simplicity in the NMR spectrum. The results are shown in Table 6. $\beta$-CD is capable of including the anionic guest while $\alpha$-CD shows a very weak ability to interact with the guest. Interest-

*Table 6.* Complexation of *p*-methylbenzoate anion with native $\alpha$- and $\beta$-CDs[a]

| Host | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|
| $\alpha$-CD | $41 \pm 2$ | $-22.0 \pm 1.9$ | $-42.1 \pm 5.5$ |
| $\beta$-CD | $200 \pm 20$ | $-8.6 \pm 0.1$ | $31.2 \pm 2.6$ |

[a] K. Kano, T. Kitae, Y. Shimofuri, N. Tanaka and Y. Mineta: *Chem. Eur. J.* **6**, 2705 (2000).
[b] The $K$ values were determined in $D_2O$ at pD 6.0 and 25 °C.

ingly, thermodynamic behavior in the formation of the $\alpha$-CD complex is quite different from that of the $\beta$-CD one. Formation of the $\alpha$-CD complex is enthalpically favorable, but entropically unfavorable. This is the common behavior of a system where van der Waals interactions mainly participate in complexation. The ROESY spectrum of the *p*-$CH_3$-Ph-$COO^-$-$\alpha$-CD system suggests the formation of an inclusion complex where the phenyl group penetrates into the cavity from the secondary OH group side of the host and the carboxylate group protrudes from the cavity to place it in the aqueous bulk phase (Figure 2). Meanwhile, complexation of *p*-$CH_3$-Ph-$COO^-$ with $\beta$-CD shows a positive and large entropy change. The $\Delta H$–$\Delta S$ compensation effect provides a negative and small enthalpy change. The ROESY spectrum suggests the structure of this complex is as shown in Figure 2. The *p*-$CH_3$-Ph-$COO^-$ anion is wholly included into the $\beta$-CD cavity where the carboxylate anion group is located at the primary OH group side of $\beta$-CD. Such a novel structure of the *p*-$CH_3$-Ph-$COO^-$-$\beta$-CD complex can be explained by the thermodynamic parameters. Namely, penetration of a hydrophilic carboxylate group into the hydrophobic CD cavity is promoted by the large entropic gain. Since no hydrophobic interaction participates in this complexation, dehydration from both the host and the guest upon complexation is the most plausible origin of the entropic gain. It might be concluded that the entropic gain due to dehydration causes the penetration of the anion into the hydrophobic CD cavity. Penetration of an anion into the CD cavity has been proven from the study on the interactions of an anionic porphyrin with CDs [18].

The *p*-$CH_3$-Ph-$COO^-$ anion penetrates into the cavities of the aminated CDs where the $CO_2^-$ group is placed at the $NH_3^+$ group sides of the CDs. The structures of the complexes estimated from the ROESY spectroscopy are shown in Figure 2. The molecular mechanics–molecular dynamics (MM–MD) calculations suggest the bucket-type shape of per-$NH_3^+$-$\beta$-CD. Such a shape is ascribed to strong electrostatic repulsion between the $NH_3^+$ groups. The $K$ values as well as the thermodynamic parameters for the aminated CD-*p*-$CH_3$-Ph-$COO^-$ systems are listed in Table 7. Coulomb interactions between per-$NH_3^+$-$\alpha$-CD and *p*-$CH_3$-Ph-$COO^-$ are strong leading to an inverted orientation of the guest anion compared with the case of native $\alpha$-CD. The thermodynamic parameters for the per-$NH_3^+$-$\alpha$-CD system are quite different from those for the $\alpha$-CD one. Namely, the positive and large entropy change stabilizes the complex of per-$NH_3^+$-$\alpha$-CD and *p*-$CH_3$-Ph-$COO^-$. The $K$ values for the complexes of mono-$NH_3^+$-$\beta$-CD and $6^A$,$6^D$-diamino-$6^A$,$6^D$-

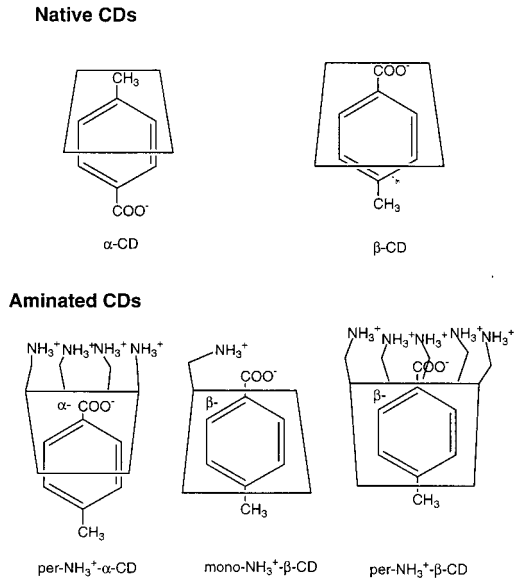



*Figure 2.* Structures of the complexes of *p*-$CH_3$-Ph-$COO^-$ and various CDs estimated from the ROESY spectra.

*Table 7.* Complexation of *p*-methylbenzoate anion with aminated CDs in the cationic forms[a]

| Host | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|
| per-$NH_3^+$-$\alpha$-CD | $2040 \pm 100$ | $-9.6 \pm 0.8$ | $31.2 \pm 2.6$ |
| mono-$NH_3^+$-$\beta$-CD | $520 \pm 20$ | $-10.4 \pm 1.8$ | $18.1 \pm 0.6$ |
| di-$NH_3^+$-$\beta$-CD | $750 \pm 40$ | $-8.1 \pm 0.6$ | $27.8 \pm 2.2$ |
| per-$NH_3^+$-$\beta$-CD | $9180 \pm 480$ | $3.8 \pm 0.7$ | $88.6 \pm 2.2$ |

[a] K. Kano, T. Kitae, Y. Shimofuri, N. Tanaka and Y. Mineta: *Chem. Eur. J.* **6**, 2705 (2000).
[b] The K values were determined in $D_2O$ at pD 6.0 and 25 °C.

dideoxy-$\beta$-cyclodextrin (di-$NH_3^+$-$\beta$-CD) are considerably larger than that of $\beta$-CD, suggesting that Coulomb interactions participate in stabilization of the complexes of these mono- and divalent cationic hosts. The *p*-$CH_3$-Ph-$COO^-$ complex is greatly stabilized by seven $NH_3^+$ groups of per-$NH_3^+$-$\beta$-CD. Both the $\Delta H$ and $\Delta S$ values increase linearly with increasing the number of the $NH_3^+$ groups. Such a result suggests that hydrogen-bonding interaction between the $NH_3^+$ and $CO_2^-$ groups does not participate in the present complexation [19]. Although the number of the data are not enough, a linear relationship is observed between $\Delta H$ and $\Delta S$ for complexation of *p*-$CH_3$-Ph-$COO^-$ with aminated $\beta$-CDs ($T\Delta S = 1.49\Delta H + 20.7$ (in kJ $mol^{-1}$, $R^2 = 0.999$)). The large slope and the large intercept in the $\Delta H$ vs. $-\Delta S$ linear relationship suggests a large conformational change of the host and extended dehydration, respectively, upon complexation [5a, 16].

Per-$NH_3^+$-$\alpha$- and -$\beta$-CDs include alkanoate anions such as butanoate ($C_3COO^-$) and hexanoate ($C_5COO^-$), but not acetate ($C1COO^-$). Table 8 exhibits the data on complexation of $CnCOO^-$ with per-$NH_3^+$-$\alpha$- and -$\beta$-CDs. The acetate anion might be too hydrophilic to be included. The $K$ value increases with increasing hydrophobicity of the alkanoate anion. The complexation of the hexanoate anion with per-$NH_3^+$-$\beta$-CD is endothermic and is dominated by the entropy

*Table 8.* Complexation of alkanoate anions with peraminated CDs in the cationic forms[a]

| Host | Guest | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|---|
| per-$NH_3^+$-$\alpha$-CD | C5$COO^-$ | $5750 \pm 380$ | $-6.0 \pm 0.3$ | $51.8 \pm 1.1$ |
| per-$NH_3^+$-$\beta$-CD | C1$COO^-$ | very small | nd[c] | nd[c] |
| per-$NH_3^+$-$\beta$-CD | C3$COO^-$ | $370 \pm 20$ | nd[c] | nd[c] |
| per-$NH_3^+$-$\beta$-CD | C5$COO^-$ | $2230 \pm 20$ | $8.4 \pm 1.1$ | $91.9 \pm 3.8$ |

[a]K. Kano, T. Kitae, Y. Shimofuri, N. Tanaka and Y. Mineta: *Chem. Eur. J.* **6**, 2705 (2000).
[b]The $K$ values were determined in $D_2O$ at pD 6.0 and 25 °C.
[c]These values were not determined.

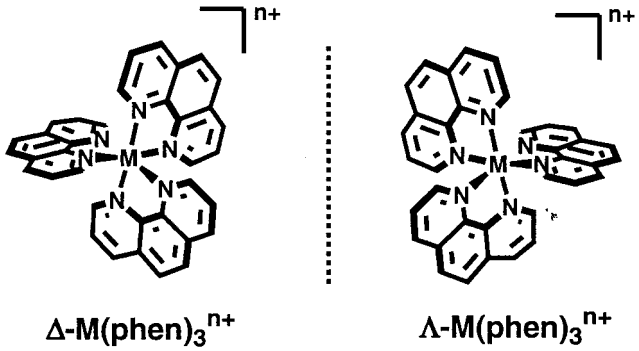
term. Matsui and Mochida studied the thermodynamics of inclusion of 1-alkanols into the $\beta$-CD cavity. The $K$ value increases with increasing the alkyl chain length of the alkanol [1]. The positive and small enthalpy changes and the positive and large entropy changes are shown in the complexation of butanol ($\Delta H$ = 2.9 kJ $mol^{-1}$, $\Delta S$ = 33 J $mol^{-1}$ $K^{-1}$), pentanol (4.6 kJ $mol^{-1}$, 50 J $mol^{-1}$ $K^{-1}$) and hexanol (0.4 kJ $mol^{-1}$, 46 J $mol^{-1}$ $K^{-1}$). They discussed that hydrophobic interaction is the primary force and the contribution of van der Waals interactions increases with increasing the alkyl chain length of the alkanol. Van der Waals interactions in the C5$COO^-$-per-$NH_3^+$-$\alpha$-CD system should be stronger than those in the C5$COO^-$-per-$NH_3^+$-$\beta$-CD system because of more extended van der Waals contacts leading to the enthalpic gain in the per-$NH_3^+$-$\alpha$-CD system. The positive entropy changes in complex formation of peraminated CDs cannot be ascribed to hydrophobic interaction. Release of bound water molecules is considered to be the origin of the positive entropy changes.

A reverse charged system has been studied by using per-$COO^-$-$\beta$-CD. The results are summarized in Table 9. When the guest is $p$-methylbenzylammonium cation ($p$-$CH_3$-Ph-$CH_2NH_3^+$), a positive $\Delta S$ greatly assists the complexation with per-$COO^-$-$\beta$-CD, though the formation of the complexes of neutral guests such as 2,6-dihydroxynaphthalene (2,6-diOH-Naph) and $p$-methylphenol ($p$-$CH_3$-Ph-OH) is entropically unfavorable. Differing from the system of per-$NH_3^+$-$\beta$-CD, the complexation of $p$-$CH_3$-Ph-$CH_2NH_3^+$ with per-$COO^-$-$\beta$-CD shows a negative and considerably large $\Delta H$. This might be ascribed to relatively strong van der Waals interactions due to the hydrophobic arms of per-$COO^-$-$\beta$-CD. The $SCH_2COO^-$ groups may provide an elongated CD cavity to strengthen the hydrophobicity of this host. A similar effect has been discussed elsewhere [20].

On the basis of these results, we can obtain a general conclusion that *complexation of a polyvalent ionic cyclodextrin with an oppositely charged guest where cooperative work of inclusion and electrostatic interactions participates is assisted or promoted by a large entropic gain due to dehydration from both host and guest.*

## Chiral recognition of tris(1,10-phenanthroline)ruthenium complex by anionic CD

In order to generalize the above conclusion, chiral recognition of $M(phen)_3^{n+}$ (M = Ru(II) and Rh(III) and phen = 1,10-phenanthroline) by per-$COO^-$-$\beta$-CD has been carried out [21]. Since $M(phen)_3^{n+}$ is a cationic guest and per-$COO^-$-$\beta$-CD is an anionic host, the above conclusion is expected to be applied. The results are summarized in Table 10. Although $Ru(phen)_3^{2+}$ does not interact with native CDs such as $\alpha$- and $\beta$-CDs, it is bound to anionic per-$COO^-$-$\beta$-CD at the $COO^-$ group side of this CD through Coulomb interactions. Since $Ru(bpy)_3^{2+}$ (bpy = 2,2′-dipyridine) does not form a complex with per-$COO^-$-$\beta$-CD, inclusion of a part of the metal complex is essential to form the host-guest complex. In other words, the cooperative work of inclusion and electrostatic interactions needs to form the host-guest complex of the ion pairs. Right- and left-handed helix configurations of metal complexes are referred to as the $\Delta$- and $\Lambda$-enantiomers, respectively. The anionic host, per-$COO^-$-$\beta$-CD, prefers the $\Delta$-enantiomer of $Ru(phen)_3^{2+}$, the $|\Delta\Delta G|$ value being 1.86 kJ $mol^{-1}$. The enantioselectivity of per-$COO^-$-$\beta$-CD ($|\Delta\Delta G|$ = 0.88 kJ $mol^{-1}$) is lower than that of per-$COO^-$-$\gamma$-CD. Several data suggest that chiral recognition of CDs occurs at the rims of CDs and no or weak enantioselectivity is observed when the size of a CD cavity is enough to place a guest molecule in it [22]. Penetration of the $Ru(phen)_3^{2+}$ ion into the per-$COO^-$-$\gamma$-CD cavity seems to be too deep to be recognized by its chirality. On the other hand, no complexation occurs in the case of per-$COO^-$-$\alpha$-CD, whose cavity size might be too small to include the guest ion. The enantioselectivity of per-$COO^-$-$\beta$-CD for $Rh(phen)_3^{3+}$ is lower than that for $Ru(phen)_3^{2+}$. Electrostatic interactions between the trivalent Rh complex and the polyvalent anionic host is stronger than those between the divalent Ru complex and the same host. Strong electrostatic interactions should lower the ability of per-$COO^-$-$\beta$-CD to recognize the chirality of a guest.




In all cases shown in Table 10, the complexation is accompanied by positive entropy changes. The $\Delta S$ values for the per-$COO^-$-$\gamma$-CD complexes are smaller than those for the per-$COO^-$-$\beta$-CD complexes. Instead, the complexation of per-$COO^-$-$\gamma$-CD is enthalpically more favorable than that of per-$COO^-$-$\beta$-CD. This might be ascribed to the deeper penetration of the $Ru(phen)_3^{2+}$ ion into the per-

*Table 9.* Complexation of $\beta$-CD and per-$CO_2^-$-$\beta$-CD[a]

| Host | Guest | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|---|
| per-$CO_2^-$-$\beta$-CD | $p$-$CH_3$-Ph-$CH_2NH_3^+$ | 6840 ± 510 | −14.3 ± 0.9 | 25.1 ± 2.9 |
| per-$CO_2^-$-$\beta$-CD | 2,6-diOH-Naph | 2100 ± 170 | −22.7 ± 0.6 | −12.7 ± 2.2 |
| per-$CO_2^-$-$\beta$-CD | $p$-$CH_3$-Ph-OH | 550 ± 60 | −18.1 ± 0.2 | −8.2 ± 0.8 |
| $\beta$-CD | $p$-$CH_3$-Ph-$CH_2NH_3^+$ | 33 ± 12 | nd[c] | nd[c] |
| $\beta$-CD | 2,6-diOH-Naph | 73 ± 8 | nd[c] | nd[c] |

[a] K. Kano, T. Kitae, Y. Shimofuri, N. Tanaka and Y. Mineta: *Chem. Eur. J.* **6**, 2705 (2000).
[b] The $K$ values were determined in $D_2O$ at pD 7.0 and 25 °C.
[c] These values were not determined.

*Table 10.* Complexation of $M(phen)_3^{n+}$ with per-$CO_2^-$-$\beta$- and -$\gamma$-CDs in 0.067 M phosphate buffer at pD 7.0[a]

| Host | Guest | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|---|
| per-$CO_2^-$-$\beta$-CD | $\Delta$-$Ru(phen)_3^{2+}$ | 1250 ± 50 | −11.4 ± 1.0 | 22.2 ± 2.2 |
| per-$CO_2^-$-$\beta$-CD | $\Lambda$-$Ru(phen)_3^{2+}$ | 590 ± 40 | −4.4 ± 1.2 | 39.4 ± 4.3 |
| per-$CO_2^-$-$\gamma$-CD | $\Delta$-$Ru(phen)_3^{2+}$ | 1140 ± 50 | −12.9 ± 0.5 | 16.9 ± 1.6 |
| per-$CO_2^-$-$\gamma$-CD | $\Lambda$-$Ru(phen)_3^{2+}$ | 890 ± 40 | −15.1 ± 0.9 | 6.7 ± 3.2 |
| per-$CO_2^-$-$\beta$-CD | $\Delta$-$Rh(phen)_3^{3+}$ | 1500 ± 60 | −6.1 ± 0.1 | 40.2 ± 0.5 |
| per-$CO_2^-$-$\beta$-CD | $\Lambda$-$Rh(phen)_3^{3+}$ | 1050 ± 40 | −4.4 ± 0.1 | 43.0 ± 0.4 |

[a] K. Kano and H. Hasegawa, *J. Am. Chem. Soc.* **123**, 10616 (2001).
[b] The $K$ values were determined by $^1$H NMR in anaerobic 0.067 M phosphate buffer at pD 7.0 and 25 °C.

$COO^-$-$\gamma$-CD cavity. The larger $\Delta S$ values for the trivalent $Rh(phen)_3^{3+}$ complexes suggest that dehydration from the trivalent guest cation occurs more extensively than that from the divalent one.

A neutral host, hexakis(tri-*O*-methyl)-$\alpha$-cyclodextrin (TMe-$\alpha$-CD), also discriminates between the $\Delta$- and $\Lambda$-enantiomers of $Ru(phen)_3^{2+}$ and $Ru(bpy)_3^{2+}$ (Table 11), while no chiral discrimination is achieved by TMe-$\beta$-CD. In these cases, the complexation is dominated by the enthalpy terms, suggesting that van der Waals interaction is the main binding force.

The per-$COO^-$-$\beta$-CD-$Ru(phen)_3^{2+}$ system resembles the DNA-$Ru(phen)_3^{2+}$ system. Many studies have been carried out with the interactions between ruthenium complexes and DNA. Doubly stranded DNA is composed of polyanionic polymer chains and hydrophobic minor and major grooves. Such a character in the structure of DNA is somewhat similar to that of per-$COO^-$-$\beta$-CD. It has been assumed that $Ru(phen)_3^{2+}$ is bound to DNA through electrostatic interactions as the major binding force but contribution of another force cannot be neglected [23]. Our results suggest that another force is van der Waals interaction which is essential to form the complex of $Ru(phen)_3^{2+}$ and DNA. Complexation of $Ru(phen)_3^{2+}$ with DNA is known to be the entropically dominated process ($\Delta H > 0$ kJ $mol^{-1}$) [24]. However, no mechanism has been discussed about the thermodynamics. Binding of $Ru(phen)_3^{2+}$ to DNA by the cooperative work of van der Waals and Coulomb interactions causes extended dehydration from both the phosphate anion groups of DNA and $Ru(phen)_3^{2+}$ which should be the origin of the entropic gain.

*Table 11.* Complexation of $Ru(phen)_3^{2+}$ and $Ru(bpy)_3^{2+}$ with TMe-$\alpha$-CD in $D_2O$

| Guest | $K$, $M^{-1}$ [b] | $\Delta H$, kJ $mol^{-1}$ | $\Delta S$, J $mol^{-1}$ $K^{-1}$ |
|---|---|---|---|
| $\Delta$-$Ru(phen)_3^{2+}$ | 54 ± 4 | −40.5 ± 2.1 | −102 ± 7 |
| $\Lambda$-$Ru(phen)_3^{2+}$ | 108 ± 4 | −34.3 ± 2.3 | −75.0 ± 7.6 |
| $\Delta$-$Ru(bpy)_3^{2+}$ | 59 ± 4 | −46.9 ± 0.4 | −123 ± 1 |
| $\Lambda$-$Ru(bpy)_3^{2+}$ | 77 ± 4 | −36.8 ± 0.6 | −87.2 ± 1.9 |

[a] K. Kano and H. Hasegawa, *J. Am. Chem. Soc.* **123**, 10616 (2001).
[b] The $K$ values were determined by $^1$H NMR spectroscopy in $D_2O$ at 25 °C.

## Conclusion

The present review reports the general mechanism for complexation of ionic guests with oppositely charged ionic cyclodextrin hosts. In order to form a stable ion-association complex, a cooperative work of inclusion of the guest into the host cavity and Coulomb interactions between the ion pair is essential. Complexation is assisted or promoted by a positive entropy change due to dehydration from both host and guest upon complexation. Such a mechanism is generally applied to systems composed of charged CD-charged guest ion pairs. In order to use such a system for chiral recognition, the relative size of a charged guest is very important. Partial inclusion of a guest into a CD cavity might be important to realize chiral recognition.

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