Chiral Recognition of Helical Metal Complexes by Modified Cyclodextrins

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Abstract: Chirality of metal complexes $M(phen)_3{}^{n+}$ (M = Ru(II), Rh(III), Fe(II), Co(II), and Zn(II), and phen = 1,10-phenanthroline) is recognized by heptakis(6-carboxymethylthio-6-deoxy)-β-cyclodextrin heptaanion (per-$CO_2{}^-$-β-CD) and hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMe-α-CD) in D_2O. The binding constant (K) for the Δ-$Ru(phen)_3{}^{2+}$ complex of per-$CO_2{}^-$-β-CD ($K = 1250$ M^{-1}) in 0.067 M phosphate buffer at pD 7.0 is ~2 times larger than that for the Λ-isomer (590 M^{-1}). Definite effects of inorganic salts on stability of the complexes indicate a large contribution of Coulomb interactions to complexation. The fact that hydrophilic $Ru(bpy)_3{}^{2+}$ (bpy = 2,2′-bipyridine) does not form a complex with per-$CO_2{}^-$-β-CD suggests the importance of inclusion of the guest molecule into the host cavity for forming a stable ion-association complex. The positive entropy change for complexation of $Ru(phen)_3{}^{2+}$ with per-$CO_2{}^-$-β-CD shows that dehydration from both the host and the guest occurs upon complexation. Similar results were obtained with trivalent $Rh(phen)_3{}^{3+}$ cation. Pfeiffer effects were observed in complexation of racemic $Fe(phen)_3{}^{2+}$, $Co(phen)_3{}^{2+}$, and $Zn(phen)_3{}^{2+}$ with per-$CO_2{}^-$-β-CD with enriched Δ-isomers. Native cyclodextrins such as α-, β-, and γ-cyclodextrins as well as heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin do not interact with $Ru(bpy)_3{}^{2+}$. However, hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TMe-α-CD) interacts with $Ru(phen)_3{}^{2+}$ and $Ru(bpy)_3{}^{2+}$ and discriminates between the enantiomers of these metal complexes. The K values for the Δ- and Λ-$Ru(phen)_3{}^{2+}$ ions are 54 and 108 M^{-1}, respectively. Complexation of the Δ- and Λ-isomers of $Ru(phen)_3{}^{2+}$ with TMe-α-CD is accompanied by negative entropy changes, suggesting that cationic $Ru(phen)_3{}^{2+}$ is shallowly included into the cavity of the neutral host through van der Waals interactions. The Δ-enantiomer, having a right-handed helix configuration, fits the primary OH group side of per-$CO_2{}^-$-β-CD ($SCH_2CO_2{}^-$ side) well, while the Λ-enantiomer, having a left-handed helix configuration, is preferably bound to the secondary OH group side of TMe-α-CD. The asymmetrically twisted shape of a host cavity seems to be the origin of chiral recognition by cyclodextrin.

Introduction

Cyclodextrin (CD) is one of the receptors which discriminate between enantiomers of various guest compounds. The first example of chiral recognition by CD was reported by Cramer and Dietsche, who found partial optical resolution of mandelic acid derivatives by β-CD.[1] Numerous studies have since been carried out to examine the ability of CDs to recognize chirality.[2] From previous investigations, it has been realized generally that native CDs such as α-, β-, and γ-CDs show weak ability to recognize central chirality of guests such as α-amino acids,[3] phosphinate compounds,[4] sulfinyl compounds,[5] α-pinene,[6] mandelic acid,[3a,7] 1-phenylethanol,[8] and their related compounds. Recently, however, it was found that β- and γ-CDs recognize the helicity of a tetrahelicene dicarboxylate, 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylate (HDC), well with binding constants for the (*M*)- and (*P*)-HDC-β-CD complexes of 18 700 and 2200 M^{-1}, respectively, at 25 °C.[9] As a similar phenomenon, β- and γ-CDs are known to induce conformational enantiomerism of bilirubin.[10,11] The bilirubin dianion is achiral in water, but upon binding with β-CD, bilirubin becomes optically active by preferentially taking an (*M*)-helix conformation. The binding site of both HDC and bilirubin is the secondary OH group side of β-CD. Conformational enantiomerism was also observed with pamoic acid (4,4′-methylenebis(3-hydroxy-2-naphthalenecarboxylic acid)) bound to γ-CD.[12] Pamoic acid included in the primary OH group side of γ-CD preferentially

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takes a (*P*)-helix conformation. In addition, a major conformational isomer of the pyrene dimer formed at the secondary OH group side of γ-CD cavity has (*M*)-helicity.[13] These results demonstrate that native CDs are good hosts to recognize asymmetrically helical shapes and that the primary and secondary OH group sides of CD prefer the right- and left-handed helix configurations, respectively. Is this nature of CDs observable for modified CDs?

Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMe-β-CD) is the modified CD where all OH groups of β-CD are substituted by OCH_3 groups. In native β-CD, intramolecular hydrogen bonding between the OH groups at the 2-positions of the glucopyranose units and at the 3-positions of the adjacent glucopyranose units provides a relatively rigid cyclic structure.[14] In contrast, TMe-β-CD has a more flexible structure because of the absence of intramolecular hydrogen bonding. Several studies have been carried out with chiral recognition of guests having central chirality by per-*O*-methylated CDs.[3d,3f,6,8,15] However, no examples which show highly enantioselective complexation of compounds with central chirality have been reported, although other types of chirality can be discriminated by CDs. A noteworthy example of chiral recognition by TMe-α-CD is optical resolution of (±)-1,7-dioxaspiro[5.5]undecane having planar chirality.[16] Precipitates from a mixture of this (±)-dioxaspiro compound and TMe-α-CD contain almost optically pure (*R*)-enantiomer of the guest. We found that TMe-β-CD is a good host that recognizes axial chirality of binaphthyl derivatives such as 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate and 1,1′-binaphthyl-2,2′-dicarboxylic acid.[17] Similar to the case of native CDs, per-*O*-methylated CDs also recognize asymmetrically twisted structures of the guests well, though they are poor receptors for recognizing central chirality of the guests. Because permethylated CDs scarcely interact with ionic compounds, the range of guest numbers that can be examined is strictly limited.

When chiral guest molecules are ionic species, cationic or anionic CDs can be utilized to form host−guest complexes. For example, protonated heptakis(6-amino-6-deoxy)-β-cyclodextrin (per-NH_3^+-β-CD) recognizes the central chirality of *N*-acetylated Trp (AcTrp) with *K* values for (*S*)- and (*R*)-AcTrps of 2310 and 1420 M^{-1}, respectively.[18] Anionic heptakis[6-carboxymethylthio-6-deoxy]-β-cyclodextrin (per-CO_2^--β-CD) also shows low enantioselectivity for the methyl esters of α-amino acids[18b] and dipeptides in their protonated forms.[19] Per-NH_3^+-β-CD induces the conformational enantiomerism of the bilirubin dianion with the bound bilirubin dianion preferentially adopting (*P*)-helicity.[20] The enantioselectivity of per-NH_3^+-β-CD is opposite to that of β-CD itself. The recognition site of per-NH_3^+-β-CD is the primary OH group side of the CD while that of β-CD is the secondary OH group side.

On the basis of all results cited herein, it may be concluded that native CDs as well as modified CDs can discriminate between right-handed and left-handed helix structures of guests; the secondary OH group side prefers left-handed helix configurations, and the primary OH group side prefers right-handed helix configurations. In other words, *CD has an asymmetrically twisted cavity in which a guest having a helix configuration is well fit*. This is our hypothetical mechanism for chiral recognition by CD. The aim of the present study is to extend such a hypothesis to a more general conclusion.

In the present study, we chose tris(1,10-phenanthroline) metal complexes ($M(phen)_3^{n+}$, M = Ru(II), Rh(III), Fe(II), Co(II), and Zn(II)) as chiral guests having helix configurations to study asymmetrically twisted shape of CD. Right- and left-handed helix configurations of metal complexes are referred Δ- and Λ-enantiomers, respectively.[21] Interconversion between the Δ- and Λ-enantiomers of $Ru(phen)_3^{2+}$ is very slow, and these enantiomers can be isolated.[22] If the hypothesis mentioned above is correct, the Δ- and Λ-enantiomers of $Ru(phen)_3^{2+}$ should be discriminated by CD. We used polyanionic per-CO_2^--β-CD as a chirality-recognizable host because $Ru(phen)_3^{2+}$ scarcely interacts with most CDs without charge (vide infra). Interestingly, only TMe-α-CD having a small cavity size meaningfully interacts with $Ru(phen)_3^{2+}$. These two types of CDs may provide the information about recognition modes of primary and secondary OH group sides of CD. Our preliminary results were reported as a short communication.[23]

Results

Capillary Zone Electrophoresis. Capillary zone electrophoresis (CZE)[24] is a convenient and effective method to predict the system that is appropriate to study enantioselective host−guest complexation. Figure 1 shows the examples of electropherograms that were measured for (±)-$Ru(phen)_3(ClO_4)_2$ (1×10^{-4} M) using β-CD and per-CO_2^--β-CD (1×10^{-3} M) as chiral selectors in 0.067 M phosphate buffer at pH 7.0. Baseline separation of the enantiomers of $Ru(phen)_3^{2+}$ was realized in CZE using per-CO_2^--β-CD, while no separation was achieved in the case of β-CD. Because a detector was placed at a negative electrode side, the Δ-enantiomer, showing a longer retention time, seems to be bound to per-CO_2^--β-CD more strongly than the Λ-enantiomer. The results of CZE for $Ru(phen)_3^{2+}$, $Rh(phen)_3^{3+}$, $Fe(phen)_3^{2+}$, and $Ru(bpy)_3^{2+}$ (bpy = 2,2′-bipyridine) are summarized in Table 1. Usually, the separation factor (α) is defined as

$$\alpha = (t_2 - t_0)/(t_1 - t_0) \qquad (1)$$

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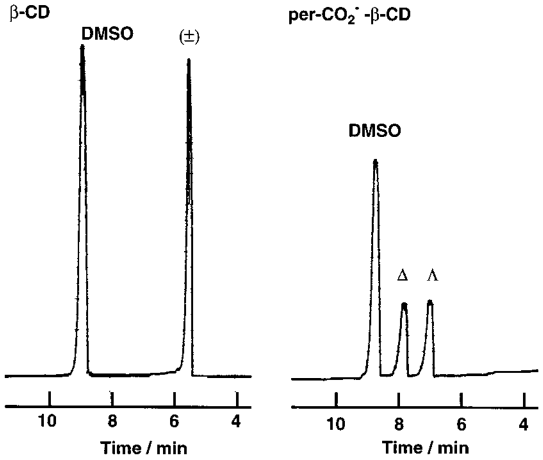

Figure 1. Electropherograms of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ (1×10^{-4} M) using β-CD and per-CO$_2^-$-β-CD (1×10^{-3} M) as chiral selectors at ambient temperature: buffer solution, 0.067 M phosphate buffer at pH 7.0; applied voltage, 6.1 kV; current, 23 μA for β-CD and 24−25 μA for per-CO$_2^-$-β-CD.

Table 1. Chiral Separation of Ru(phen)$_3^{2+}$, Rh(phen)$_3^{3+}$, Fe(phen)$_3^{2+}$, and Ru(bpy)$_3^{2+}$ by CZE Using Host−Guest Complexation with CDs at pH 7.0 and Ambient Temperature[a]

guest	host	current (μA)	t_1 (min)[b]	t_2 (min)[b]	α
Ru(phen)$_3^{2+}$	β-CD	23	5.50	5.50	1.00
	TMe-α-CD	20−21	7.60	7.60	1.00
	TMe-α-CD[c]	21−22	13.7	14.3	1.05
	mono-CO$_2^-$-β-CD	21	6.40	6.40	1.00
	per-CO$_2^-$-α-CD	26−27	8.22	8.22	1.00
	per-CO$_2^-$-β-CD	24−25	6.64	7.44	1.83
	per-CO$_2^-$-γ-CD	28−29	7.00	7.62	1.66
Rh(phen)$_3^{3+}$	β-CD	22	7.44	7.44	1.00
	mono-CO$_2^-$-β-CD	25	6.98	6.98	1.00
	per-CO$_2^-$-α-CD	26−27	9.00	9.20	1.02
	per-CO$_2^-$-β-CD	22	13.0	14.5	1.14
	per-CO$_2^-$-γ-CD	27−28	9.00	10.4	1.35
Fe(phen)$_3^{2+}$	β-CD	22−23	5.58	5.58	1.00
	mono-CO$_2^-$-β-CD	19−20	9.24	9.24	1.00
	per-CO$_2^-$-α-CD	22	9.70	9.70	1.00
	per-CO$_2^-$-β-CD	21	9.84	11.6	1.98
	per-CO$_2^-$-γ-CD	25	8.10	8.54	1.23
Ru(bpy)$_3^{2+}$	β-CD	20	6.50	6.50	1.00
	TMe-α-CD	21	7.00	7.00	1.00
	TMe-α-CD[c]	21−22	11.1	11.4	1.02
	mono-CO$_2^-$-β-CD	21	6.24	6.24	1.00
	per-CO$_2^-$-α-CD	24	8.90	8.90	1.00
	per-CO$_2^-$-β-CD	21	7.48	7.48	1.00
	per-CO$_2^-$-γ-CD	25−26	7.04	7.04	1.00
	per-CO$_2^-$-β-CD[d]	27−28	10.1	10.1	1.00
	per-CO$_2^-$-γ-CD[d]	26−27	8.76	8.96	1.37

[a] Separation conditions: capillary, 300 mm (effective length) × 50 μm i.d.; buffer, 0.067 M phosphate buffer at pH 7.0 containing 1×10^{-3} M CD; applied voltage, 6.1 kV; sample, 1×10^{-4} M metal complex in 0.067 M phosphate buffer at pH 7.0; sample injection, electrokinetic method (6.1 kV, 10 s). [b] Except for the systems of TMe-α-CD, the Λ- and Δ-enantiomers of the guests show the shorter (t_1) and longer (t_2) retention times, respectively, when enantiomer separation is realized. In the cases of TMe-α-CD, the opposite enantioselectivity was observed. [c] The concentration of CD was 2×10^{-2} M. [d] The concentration of CD was 5×10^{-3} M.

where t_1 and t_2 are the retention times of the first and second peaks, respectively, and t_0 is the retention time of a coexisting compound that does not interact with CD. In the present system, we used DMSO as a standard material showing t_0. Because the retention times of the samples are shorter than that of DMSO because of a fast electrophoretic mobility of the cationic guests, we defined α as eq 2 in the present study:

$$\alpha = (t_0 - t_1)/(t_0 - t_2) \qquad (2)$$

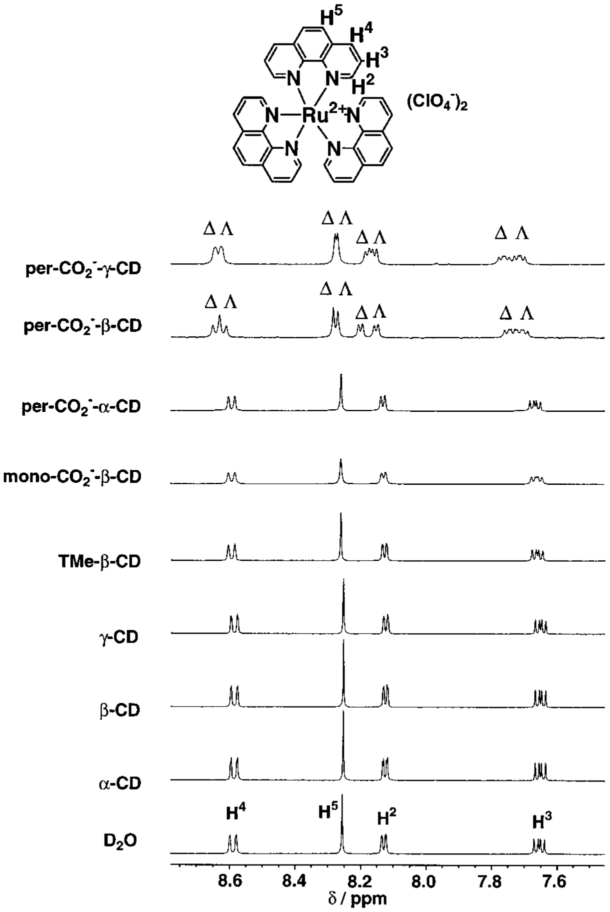

Figure 2. ^{1}H NMR spectra of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ (1×10^{-3} M) in D$_2$O at pD 7.0 (Na$_2$CO$_3$) and 25 °C in the absence and the presence of various CDs (8×10^{-3} M) under argon atmosphere.

Neutral CDs such as α-CD, β-CD, γ-CD, TMe-α-CD, and TMe-β-CD do not act as the chiral selectors for all guest compounds when 1×10^{-3} M CD solutions are used as the background solutions. Per-CO$_2^-$-β-CD and per-CO$_2^-$-γ-CD act as the chiral selectors for the M(phen)$_3^{n+}$ ions. In all cases, the retention times of the Δ-enantiomers of the metal complexes are longer than those of the Λ-enantiomers. Only per-CO$_2^-$-γ-CD acts as the chiral selector for Ru(bpy)$_3^{2+}$ among anionic CDs.

When highly concentrated TMe-α-CD (1×10^{-2} M) was used, slight enantiomer separation was achieved with Ru(phen)$_3^{2+}$ and Ru(bpy)$_3^{2+}$. No separation was measured in the cases of TMe-β-CD and β-CD under the same conditions. On the basis of these CZE results, the following assumptions can be made:

(1) The enantiomers of the M(phen)$_3^{n+}$ cations are discriminated by per-CO$_2^-$-β- and -γ-CDs. These anionic CDs preferentially interact with the Δ-enantiomers of the metal complexes.

(2) Neutral CDs such as α-, β-, and γ-CDs and TMe-β-CD scarcely interact with the cationic metal complexes. Only TMe-α-CD has a possibility to recognize chirality of Ru(phen)$_3^{2+}$ and Ru(bpy)$_3^{2+}$.

^{1}H NMR Spectroscopic Study for Ru(phen)$_3^{2+}$ System. Figure 2 shows the ^{1}H NMR spectra of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ in D$_2$O at pD 7.0 (Na$_2$CO$_3$) in the absence and the presence of various CDs. Native CDs such as α-, β-, and γ-CDs do not

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Table 2. Complexation of $Ru(phen)_3(ClO_4)_2$ and $Rh(phen)_3(ClO_4)_3$ with Per-CO_2^--β- and -γ-CDs in 0.067 M Phosphate Buffer at pD 7.0 (D_2O) and 25 °C[a]

guest	host	K (M^{-1})	K_Δ/K_Λ	$\Delta\Delta G°$ (kJ mol^{-1})
Δ-$Ru(phen)_3^{2+}$	per-CO_2^--β-CD	1250 ± 50		
Λ-$Ru(phen)_3^{2+}$	per-CO_2^--β-CD	590 ± 40	2.12	1.86
Δ-$Ru(phen)_3^{2+}$	per-CO_2^--γ-CD	1140 ± 50		
Λ-$Ru(phen)_3^{2+}$	per-CO_2^--γ-CD	890 ± 40	1.28	0.61
Δ-$Rh(phen)_3^{3+}$	per-CO_2^--β-CD	1500 ± 60		
Λ-$Rh(phen)_3^{3+}$	per-CO_2^--β-CD	1050 ± 40	1.43	0.88
Δ-$Rh(phen)_3^{3+}$	per-CO_2^--γ-CD	1560 ± 40		
Λ-$Rh(phen)_3^{3+}$	per-CO_2^--γ-CD	1380 ± 40	1.13	0.31

[a] Details on determination of K values were shown in the Experimental Section.

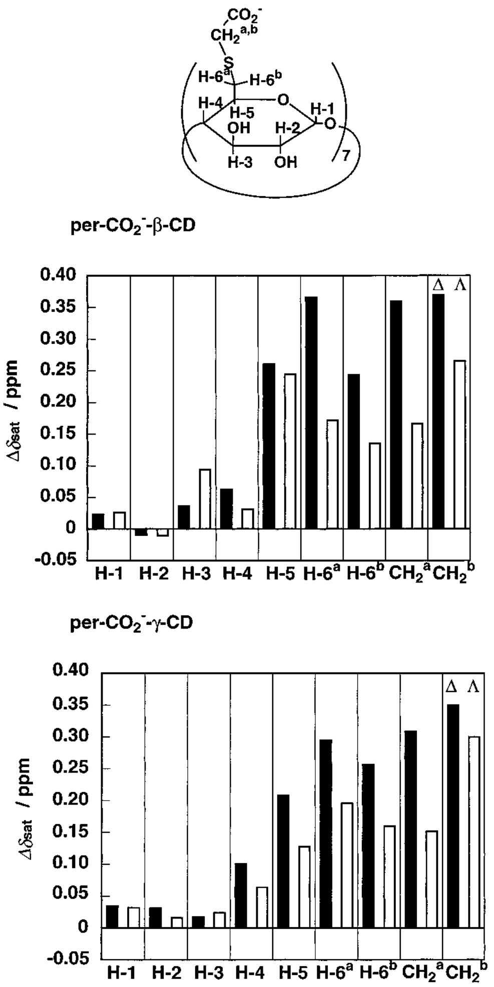

Figure 3. Saturated complexation-induced shifts ($\Delta\delta_{sat}$) of per-CO_2^--β- and -γ-CDs complexed with Δ- and Λ-$Ru(phen)_3(ClO_4)_2$ in 0.067 M phosphate buffer (D_2O) at pD 7.0 and 25 °C under argon atmosphere. The positive and negative values represent upfield and downfield shifts, respectively.

affect the NMR spectrum of $Ru(phen)_3^{2+}$. These neutral CDs do not interact with the divalent cationic guest. Slight broadening was observed upon addition of TMe-β-CD, mono-CO_2^--β-CD, and per-CO_2^--α-CD. These modified CDs weakly interact with $Ru(phen)_3^{2+}$. Meanwhile, per-CO_2^--β-CD causes downfield shifts of all signals of $Ru(phen)_3^{2+}$, and each signal was split into two signals because of the formation of the diastereomeric complexes. Splitting of the signals means there is a difference in binding constants and/or in structures of the complexes between the Δ- and Λ-enantiomers of the guest. In other words, per-CO_2^--β-CD recognizes the chirality of $Ru(phen)_3^{2+}$. Splitting was not remarkable in the case of per-CO_2^--γ-CD.

Binding constants (Ks) for complexation were determined from ^1H NMR titration curves which were analyzed by a nonlinear least-squares method (Supporting Information).[19] The NMR spectral change of $Ru(phen)_3^{2+}$ as a function of CD concentration was measured in 0.067 M phosphate buffer at pD 7.0, because pD gradually increased with increasing the host concentration. The data were well fit with the equation for 1:1 complex formation. The results are listed in Table 2. The K value for the Δ-$Ru(phen)_3^{2+}$-per-CO_2^--β-CD complex is ~2 times larger than that for the Λ-enantiomer complex. The difference in free-energy changes between Λ- and Δ-enantiomers ($\Delta\Delta G° = \Delta G_\Lambda° - \Delta G_\Delta°$) is one of the measures for indicating enantioselectivity. $\Delta\Delta G°$ obtained for the present system is 1.9 kJ mol^{-1}. In recognition of central chirality by CDs, $|\Delta\Delta G°|$ values are usually less than 1 kJ mol^{-1} for the systems showing moderate K values (>100 M^{-1}).[2b] The $\Delta\Delta G°$ value of 1.9 kJ mol^{-1} indicates that the present system is one of the examples where CD recognizes chirality well. As indicated in Table 2, the enantioselectivity of per-CO_2^--γ-CD ($\Delta\Delta G° = 0.61$ kJ mol^{-1}) is lower than that of per-CO_2^--β-CD. Lower enantioselectivity of per-CO_2^--γ-CD is ascribed to the relatively large K value for the Λ-enantiomer complex. This means that the cavity size of per-CO_2^--γ-CD is too large to recognize the difference in the geometric structures of the guest enantiomers.

To know the binding sites, the ^1H NMR spectra of the host CDs were taken in 0.067 M phosphate buffer at pD 7.0 in the absence and the presence of the Δ- and Λ-enantiomers of $Ru(phen)_3^{2+}$. The NMR data were processed by saturated complexation induced shifts ($\Delta\delta_{sat}$) defined as

$$\Delta\delta_{sat} = (\delta_f - \delta_c)/\chi \quad (3)$$

where δ_f and δ_c are the chemical shifts of protons in free and complexed host, respectively, and χ is the mole fraction of complex. Because the χ value can be calculated from K, $\Delta\delta_{sat}$ can be evaluated from eq 3. $\Delta\delta_{sat}$ is defined as the change in chemical shift when all host molecules have formed complexes with guest. The $\Delta\delta_{sat}$ values for the protons of per-CO_2^--β-CD and per-CO_2^--γ-CD complexed with the Δ- and Λ-enantiomers of $Ru(phen)_3^{2+}$ are shown in Figure 3. It can be concluded from the results shown in Figure 3 that the binding site of both guest enantiomers is the $SCH_2CO_2^-$ group side (the primary OH group side), because the protons at the 5- and 6-positions (H-5 and H-6) and at the methylene linkages of the host markedly shift to higher magnetic fields because of the ring current effects of the aromatic ring(s). The secondary OH group side does not participate in complexation. Because the pK_a values of per-CO_2H-β-CD are below 5.6,[25] complexation is mainly promoted by Coulomb interactions between the polyvalent anionic host and the divalent cationic guest. The signals due to the Δ-enantiomer complex shift more largely than those due to the Λ-enantiomer complex. The NMR data may be explained using the cartoons drawn in Figure 4. Per-CO_2^--β-CD or per-CO_2^--γ-CD takes a bucket-type shape because of the electrostatic repulsion between the CO_2^- groups arranged at the rim of the primary OH group side (vide infra). The Δ-$Ru(phen)_3^{2+}$ ion penetrates into the per-CO_2^--β-CD or per-CO_2^--γ-CD cavity including the wall provided by the $SCH_2CO_2^-$ groups, while the Λ-enantiomer is bound to the host more shallowly. No essential difference in the structures of the host–guest com-

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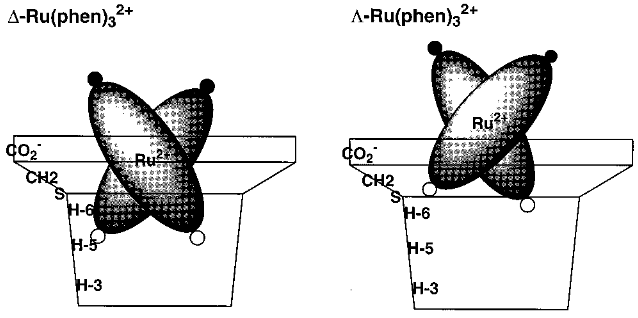

Figure 4. Simple models for the complexes of the Δ- and Λ-Ru(phen)$_3^{2+}$ ions and per-CO$_2^-$-β-CD deduced from the ^{1}H NMR spectral data.

plexes is found between the per-CO$_2^-$-β-CD and per-CO$_2^-$-γ-CD systems.

Rotating frame nuclear Overhauser and exchange spectroscopy (ROESY) is an effective method to estimate the structure of a CD inclusion complex. Figure 5 shows the ROESY spectra of the systems composed of the Δ- and Λ-enantiomers of Ru(phen)$_3^{2+}$ and per-CO$_2^-$-β-CD. In the Δ-Ru(phen)$_3^{2+}$-per-CO$_2^-$-β-CD system, the distinct correlation peaks were observed between H^3 and H^5 of the guest and H-5 of the host. Such a result reveals that, at least, one phenanthroline ring of the Δ-Ru(phen)$_3^{2+}$ ion penetrates into the CD cavity. Any correlations with H-6 of per-CO$_2^-$-β-CD were not observed. This seems to be ascribed to the relatively high fluctuation of this position. Very weak correlations between the protons of the SCH$_2$CO$_2^-$ groups of per-CO$_2^-$-β-CD and the H^2 and H^5 protons of Δ-Ru(phen)$_3^{2+}$ may also be ascribed to the fluctuating nature of the wall provided by the SCH$_2$CO$_2^-$ groups. On the other hand, in the Λ-Ru(phen)$_3^{2+}$-per-CO$_2^-$-β-CD system, all correlation peaks are much weaker than those for the Δ-isomer system, and no correlation peak between H^3 and H-5 was observed. The ROESY spectrum supports the previous assumption that Λ-Ru(phen)$_3^{2+}$ forms the shallow inclusion complex.

The ROESY spectra of the per-CO$_2^-$-γ-CD complexes are shown in Figure 6. Characteristic correlations were observed between all protons of the Δ-guest enantiomer and the protons of the SCH$_2$CO$_2^-$ groups of per-CO$_2^-$-γ-CD together with a strong correlation between H^5 of the Δ-guest enantiomer and H-5 of the host. These results suggest that the SCH$_2$CO$_2^-$ groups approach the Δ-Ru(phen)$_3^{2+}$ molecule to form a relatively tight inclusion complex. The correlation peaks of the protons of the SCH$_2$CO$_2^-$ groups of the host indicate the reduction in fluctuation of these groups. In contrast, no strong correlations were measured between the protons of the Λ-guest enantiomer and the protons of the SCH$_2$CO$_2^-$ groups of the host. The SCH$_2$CO$_2^-$ groups of the Λ-guest complex of per-CO$_2^-$-γ-CD may be more fluctuant than those of the Δ-enantiomer complex. ROESY clearly indicates that the structure of the Δ-Ru(phen)$_3^{2+}$-per-CO$_2^-$-γ-CD complex is significantly different from that of the Λ-enantiomer complex.

Thermodynamic Parameters for Complexation of Ru(phen)$_3^{2+}$. Thermodynamic parameters for the enantioselective complexation of the Δ- and Λ-Ru(phen)$_3^{2+}$ ions with per-CO$_2^-$-β-CD were determined from the van't Hoff plots (Supporting Information). The results are listed in Table 3. Complexation of the Δ-isomer is an enthalpically dominated process that is assisted by a positive entropy change. Meanwhile, the formation of the Λ-Ru(phen)$_3^{2+}$ complex of per-CO$_2^-$-β-CD is dominated by an entropy term. NMR spectroscopy suggests the penetration of the Δ-Ru(phen)$_3^{2+}$ ion into the per-CO$_2^-$-β-CD cavity. The penetration of the guest into the host cavity seems to be promoted through van der Waals interactions. Such complexation is an exothermic process. By the way, many examples

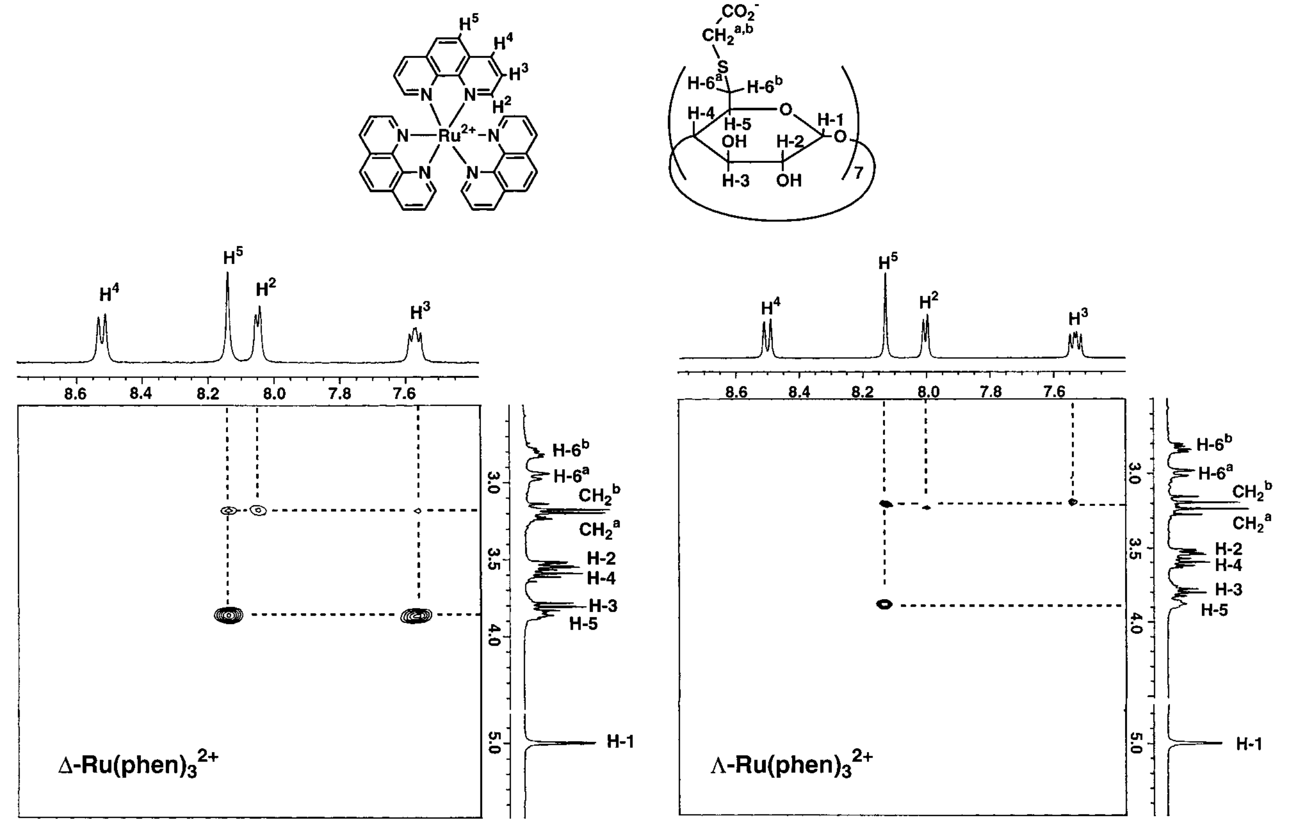

Figure 5. ROESY spectra of the Δ- and Λ-Ru(phen)$_3^{2+}$-per-CO$_2^-$-β-CD complexes in D$_2$O at pD 7 and 25 °C under argon atmosphere. The concentrations of Ru(phen)$_3$(ClO$_4$)$_2$ and per-CO$_2^-$-β-CD were 3 × 10^{-3} and 1.6 × 10^{-2} M, respectively.

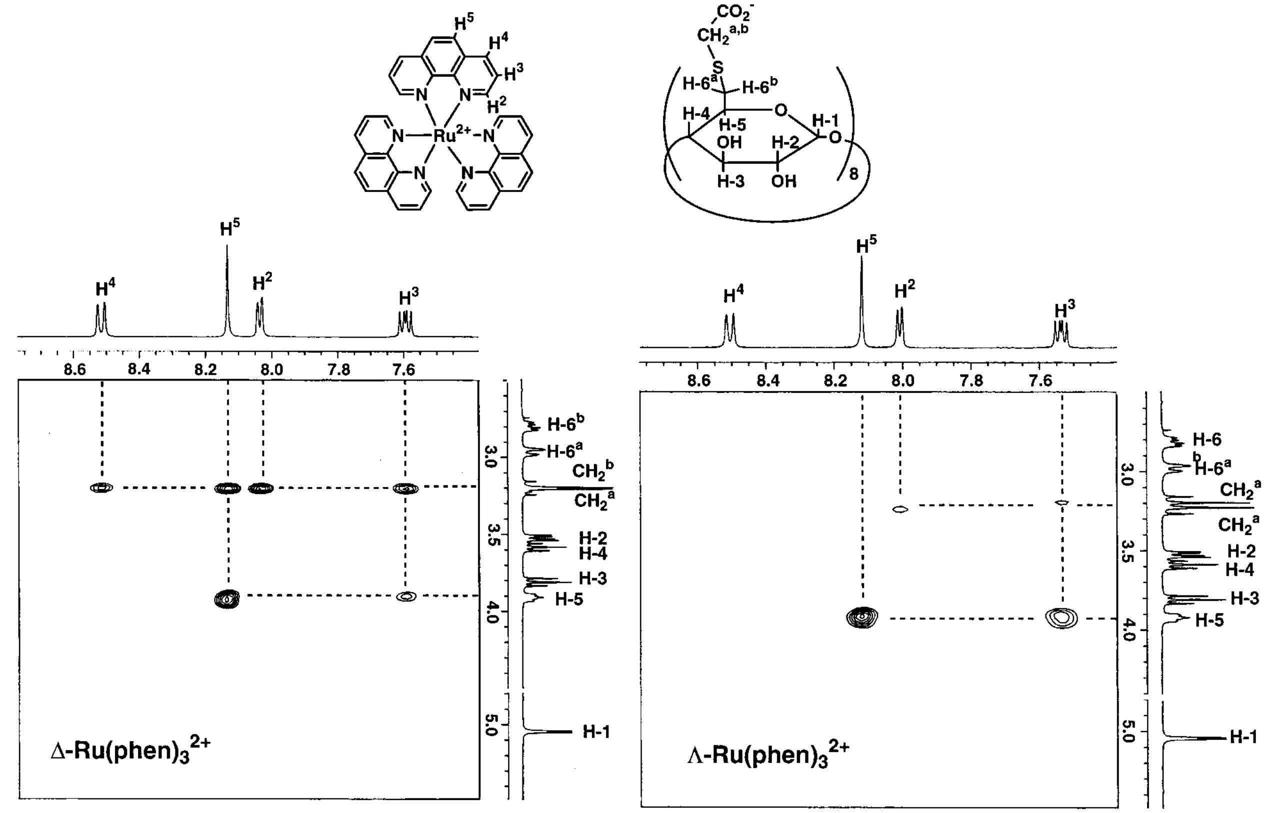

Figure 6. ROESY spectra of the Δ- and Λ-Ru(phen)$_3^{2+}$-per-CO$_2^-$-γ-CD complexes in D$_2$O at pD 7 and 25 °C under argon atmosphere. The concentrations of Ru(phen)$_3$(ClO$_4$)$_2$ and per-CO$_2^-$-γ-CD were 3×10^{-3} and 1.6×10^{-2} M, respectively.

Table 3. Thermodynamic Parameters for Complexation of Ru(phen)$_3$(ClO$_4$)$_2$ and Rh(phen)$_3$(ClO$_4$)$_3$ with Per-CO$_2^-$-β-CD in 0.067 M Phosphate Buffer (D$_2$O) and D$_2$O without Salt at pD 7.0

guest	host	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J mol^{-1}K^{-1})	$T\Delta S°$ (kJ mol^{-1})[a]	$\Delta C_p°$ (kJ K^{-1}mol^{-1})
Δ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-β-CD[b]	−11.4 ± 1.0	22.2 ± 2.2	6.6 ± 0.6	
Λ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-β-CD[b]	−4.4 ± 1.2	39.4 ± 4.3	11.7 ± 1.3	
Δ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-γ-CD[b]	−12.9 ± 0.5	16.9 ± 1.6	5.0 ± 0.5	−1.8 ± 0.1
Λ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-γ-CD[b]	−15.1 ± 0.9	6.7 ± 3.2	2.0 ± 1.0	−1.4 ± 0.3
Δ-Rh(phen)$_3^{3+}$	per-CO$_2^-$-β-CD[b]	−6.1 ± 0.1	40.2 ± 0.5	12.0 ± 0.1	
Λ-Rh(phen)$_3^{3+}$	per-CO$_2^-$-β-CD[b]	−4.4 ± 0.1	43.0 ± 0.4	12.8 ± 1.2	
Δ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-β-CD[c]	−6.7 ± 1.0	61.8 ± 3.3	18.4 ± 1.0	
Λ-Ru(phen)$_3^{2+}$	per-CO$_2^-$-β-CD[c]	−10.0 ± 1.2	47.3 ± 2.5	14.1 ± 0.7	

[a] $T\Delta S°$ values were calculated for 298 K. [b] The experiments were carried out in 0.067 M phosphate buffer. [c] The experiments were carried out in D$_2$O without inorganic salt.

indicate that complexation of strongly polar guests with CDs is accompanied by positive entropy changes.[26,27] We also found previously that ion-association complexes of charged CDs and oppositely charged guests are formed by the cooperative work of Coulomb and van der Waals interactions, where large positive entropy changes due to extensive dehydration from both host and guest promote complexation.[18,28] The thermodynamic parameters measured for the present system can be explained reasonably as follows. The Δ-Ru(phen)$_3^{2+}$ ion is bound to per-CO$_2^-$-β-CD through Coulomb interactions. In this step, dehydration of both the host and guest molecules leads to an entropic gain. A part of the Ru(phen)$_3^{2+}$ molecule further penetrates into the host cavity through van der Waals interactions. Such a process may cause the negative enthalpy and positive entropy changes. On the other hand, shallow inclusion occurs in the case of Λ-Ru(phen)$_3^{2+}$ to yield a more unfavorable enthalpy change, which is compensated by favorable entropy change.

The van't Hoff plots ($R \ln K$ vs T^{-1}) for the per-CO$_2^-$-γ-CD system are not linear, and temperature-dependent $\Delta H°$ has to be considered. Temperature dependency of $\Delta H°$ is expressed by heat capacity change ($\Delta C_p° = \partial H°/\partial T$). Sometimes, the $\Delta C_p°$ term is important in host−guest complexation.[26,29] Assuming that $\Delta C_p°$ is constant at the present temperature range, $\Delta H°$, $\Delta S°$, and $\Delta C_p°$ can be evaluated from the van't Hoff plot by

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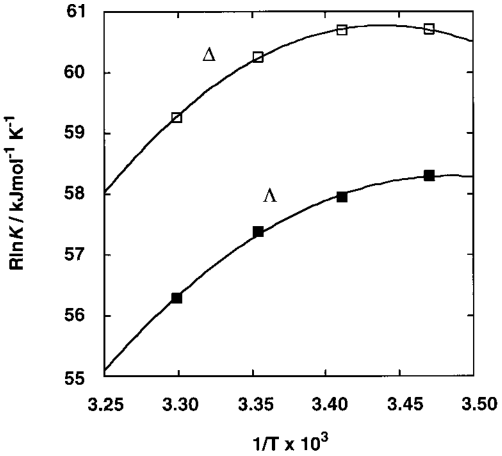

Figure 7. Van't Hoff plots for complexation of Δ- and Λ-Ru(phen)$_3$(ClO$_4$)$_2$ with per-CO$_2^-$-β-CD in 0.067 M phosphate buffer at pD 7.0.

fitting experimental data with the following equation:[30]

$$R \ln K(T) = -(\Delta H°(T)/T) + \Delta S°(T) = -[\Delta H°(T_0) + (T - T_0)\Delta C_p°]/T + \Delta C_p° \ln(T/T_0) + \Delta S°(T_0) \quad (4)$$

where $K(T)$, $\Delta H°(T)$, and $\Delta S°(T)$ are temperature-dependent parameters and $\Delta H°(T_0)$ and $\Delta S°(T_0)$ are constant with $T = T_0$. The van't Hoff plots for the Δ- and Λ-Ru(phen)$_3^{2+}$ systems are shown in Figure 7. Curve fitting using a nonlinear least-squares method provided $\Delta H°$, $\Delta S°$, and $\Delta C_p°$. The results are exhibited in Table 3. The $\Delta H°$ values for the per-CO$_2^-$-γ-CD systems are smaller than those for the per-CO$_2^-$-β-CD systems. The large cavity of per-CO$_2^-$-γ-CD may make it possible to include the guest more deeply, leading to an increase in the contribution of van der Waals interactions. Degrees of hydration to the polar groups of both the host and the guest and of the inclusion complex at low temperature are higher than those at high temperature. The degrees of hydration are, of course, different between the monomers and the inclusion complex. Temperature dependency of enthalpy for the initial state (monomer state) should be different from that for the final state (complex state). Such a difference in temperature dependency of enthalpies between the initial and final states is a plausible origin of temperature-dependent $\Delta H°$. We could not explain the reason(s) why nonlinear van't Hoff plots were observed only in the case of per-CO$_2^-$-γ-CD.

Complexation of Rh(phen)$_3$(ClO$_4$)$_3$. The ^{1}H NMR spectra of (±)-Rh(phen)$_3$(ClO$_4$)$_3$ in D$_2$O at pD 7.0 in the absence and the presence of various CDs are essentially the same as those of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ (Supporting Information). Slight splitting of the signals due to H^2 and H^3 of Rh(phen)$_3^{3+}$ was observed in the presence of per-CO$_2^-$-α-CD. Each proton signal except for H^4 of the guest was definitely split in the presence of per-CO$_2^-$-β- and -γ-CDs.

The K value obtained for the enantiomer of Rh(phen)$_3^{3+}$ is meaningfully larger than that for the corresponding enantiomer of Ru(phen)$_3^{2+}$. This should be ascribed to stronger Coulomb interactions of the trivalent cationic Rh complex with the polyvalent anionic host as compared with the divalent Ru complex. Enantioselectivity of both per-CO$_2^-$-β- and -γ-CDs for Rh(phen)$_3^{3+}$ is lower than that for Ru(phen)$_3^{2+}$. Strong Coulomb interactions without directivity in binding between the Rh^{3+} complex and per-CO$_2^-$-β-CD seem to lower the enantioselectivity.

Table 4. Salt Effects on Chiral Recognition of Ru(phen)$_3^{2+}$ by Per-CO$_2^-$-β-CD in D$_2$O at 25 °C

bulk phase	NaX ([NaX] (M))	configuration	K (M^{-1})	K_Δ/K_Λ
phosphate buffer[a]		Δ	1250 ± 50	
phosphate buffer[a]		Λ	590 ± 40	2.1
phosphate buffer[a]	NaCl (0.02)	Δ	790 ± 30	
phosphate buffer[a]	NaCl (0.02)	Λ	490 ± 30	1.6
phosphate buffer[a]	NaCl (0.05)	Δ	580 ± 30	
phosphate buffer[a]	NaCl (0.05)	Λ	400 ± 20	1.4
D$_2$O		Δ	20 100 ± 1500	
D$_2$O		Λ	12 700 ± 1100	1.6
D$_2$O	NaCl (0.05)	Δ	1710 ± 40	
D$_2$O	NaCl (0.05)	Λ	1120 ± 40	1.5
D$_2$O	NaCl (0.075)	Δ	960 ± 30	
D$_2$O	NaCl (0.075)	Λ	890 ± 60	1.1
D$_2$O	NaI (0.05)	Δ	1130 ± 30	
D$_2$O	NaI (0.05)	Λ	760 ± 20	1.5
D$_2$O	NaClO$_4$ (0.05)	Δ	1160 ± 20	
D$_2$O	NaClO$_4$ (0.05)	Λ	530 ± 30	2.2
D$_2$O	KCl (0.05)	Δ	2260 ± 50	
D$_2$O	KCl (0.05)	Λ	1290 ± 50	1.7

[a] 0.067 M phosphate buffer (D$_2$O) at pD 7.0.

Thermodynamic parameters for complexation of Rh(phen)$_3^{3+}$ with per-CO$_2^-$-β-CD are shown in Table 3. The $\Delta S°$ value for complexation of Δ-Rh(phen)$_3^{3+}$ with per-CO$_2^-$-β-CD is much larger than that for the Δ-Ru(phen)$_3^{2+}$ system. In the complexation of the trivalent Rh(phen)$_3^{3+}$ system, dehydration may occur more extensively than in the case of divalent Ru(phen)$_3^{2+}$. Both the $\Delta H°$ and $\Delta S°$ values for the Δ-Rh(phen)$_3^{3+}$ system are close to those for the Λ-enantiomer system.

Salt Effects on Chiral Recognition of Ru(phen)$_3^{2+}$. Salt effects were studied to optimize the chiral recognition of Ru(phen)$_3^{2+}$ by per-CO$_2^-$-β-CD. The results are summarized in Table 4. The K values for complexation in D$_2$O without salt are much larger than those in the 0.067 M phosphate buffer, though the enantioselectivity is lowered. The K value decreases with increasing NaCl concentration, suggesting a strong contribution of Coulomb interactions in water in the absence of inorganic salt. Enantioselectivity could not be improved by inorganic salt under the present conditions. It has been expected that enantioselectivity is raised by adding an appropriate amount of salt because of the enhanced contribution of van der Waals interactions to the complexation of Ru(phen)$_3^{2+}$ with per-CO$_2^-$-β-CD. However, we could not observe such improvement by controlling salt concentration in the present study.

The thermodynamic parameters for complexation of Ru(phen)$_3^{2+}$ with per-CO$_2^-$-β-CD in D$_2$O without inorganic salt are shown in Table 3. The $\Delta S°$ value (61.8 ± 3.3 J mol^{-1}K^{-1}) for complexation of Δ-Ru(phen)$_3^{2+}$ in D$_2$O without salt is much larger than that in 0.067 M phosphate buffer (22.2 ± 2.2 J mol^{-1}K^{-1}) and is largely responsible for the increased K value in the absence of salt. Meanwhile, the $\Delta H°$ value for complexation of Λ-Ru(phen)$_3^{2+}$ in D$_2$O is negative and larger than that in the phosphate buffer. The entropic gain in complexation of the Δ-enantiomer and the enthalpic gain in complexation of the Λ-enantiomer cause lower enantioselectivity in D$_2$O in the absence of salt.

Pfeiffer Effects by Per-CO$_2^-$-β-CD. Pfeiffer and Quehl observed a change in optical rotation of (±)-Zn(phen)$_3^{2+}$ when it is bound to an optically active camphor derivative.[31] The Zn(II),[32] Ni(II),[33] and Co(II)[34] complexes of 1,10-phenanthroline are known to show induced enantiomerism upon complexation

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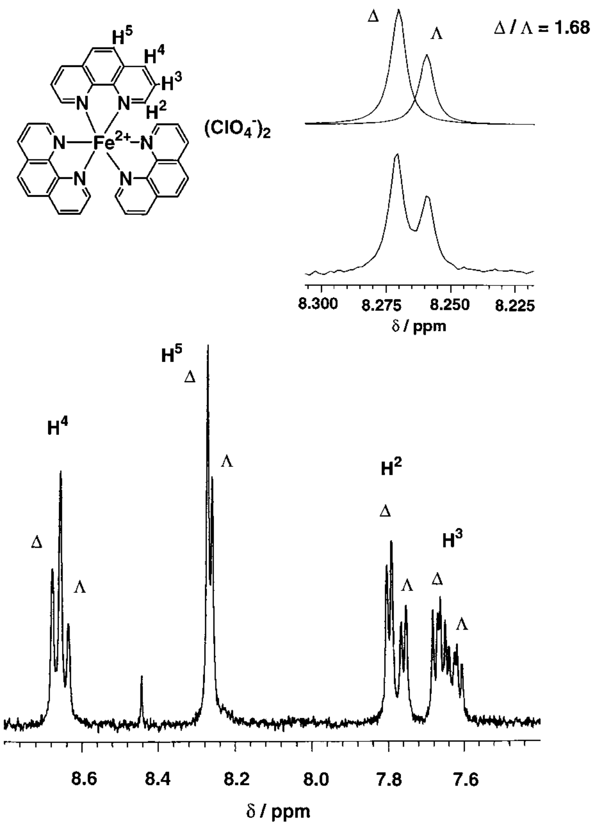

Figure 8. ^{1}H NMR spectrum of (±)-Fe(phen)$_3$(ClO$_4$)$_2$ (1×10^{-3} M) in 0.067 M phosphate buffer (D$_2$O) at pD 7.0 and 25 °C in the presence of per-CO$_2^-$-β-CD (1.2×10^{-2} M).

with chiral compounds. In the present study, we found that per-CO$_2^-$-β-CD also shows Pfeiffer effects toward Fe(II), Co(II), and Zn(II) complexes of 1,10-phenanthroline.

CZE results predict that per-CO$_2^-$-β-CD discriminates between the enantiomers of Fe(phen)$_3^{2+}$. Figure 8 shows the ^{1}H NMR spectrum of (±)-Fe(phen)$_3$(ClO$_4$)$_2$ in 0.067 M phosphate buffer at pD 7.0 in the presence of per-CO$_2^-$-β-CD. The signals of H^2, H^3, H^4, and H^5 of the guest are split because of formation of the diastereomeric complexes of per-CO$_2^-$-β-CD. The peak area of the proton signal of H^5 at lower magnetic field is ~1.7 times wider than that at higher magnetic field. The pattern of the Cotton effects in the circular dichroism spectrum (Figure 9) clearly indicates that per-CO$_2^-$-β-CD enriches the Δ-enantiomer of Fe(phen)$_3^{2+}$.[35] It has been known that the interconversion between the Δ- and Λ-enantiomers of Fe(phen)$_3^{2+}$ occurs easily and the Δ-isomer is enriched upon complexation of (±)-Fe(phen)$_3^{2+}$ with DNA having a right-handed helix configuration.[36] The effect of per-CO$_2^-$-β-CD is similar to that of DNA. The NMR spectral changes of (±)-Fe(phen)$_3^{2+}$ (1×10^{-3} M) as a function of temperature (Supporting Information) show a coalescence temperature of 75 °C in the 0.067 M phosphate buffer at pD 7.0 in the presence of per-CO$_2^-$-β-CD (1.2×10^{-2} M).

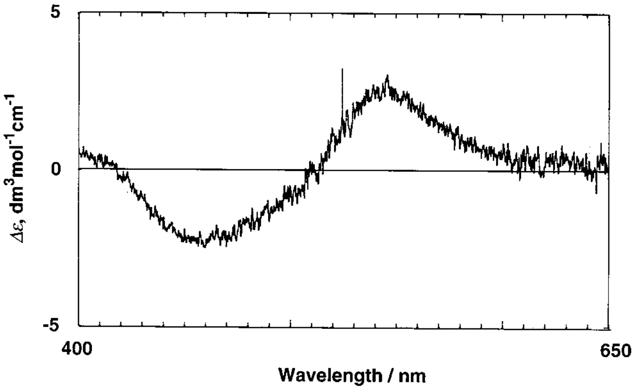

Figure 9. Circular dichroism spectrum of Fe(phen)$_3$(ClO$_4$)$_2$ (1×10^{-4} M) in 0.067 M phosphate buffer at pH 7.0 and 25 °C in the presence of per-CO$_2^-$-β-CD (4×10^{-3} M).

Table 5. Enantiomerism of Tris(1,10-phenanthroline)metal Complexes Induced by Per-CO$_2^-$-β-CD in 0.067 M Phosphate Buffer at pD 7.0 and 25 °C[a]

M(phen)$_3$(ClO$_4$)$_2$	I_Δ/I_Λ[b]	T_c (°C)[c]
Fe(II)	1.67	75
Co(II)	2.13	65
Zn(II)	3.45	45

[a] The ^{1}H NMR spectra were measured with 1×10^{-3} M (±)-M(phen)$_3$(ClO$_4$)$_2$ in 0.067 M phosphate buffer at pD 7.0 in the presence of 1.2×10^{-2} M per-CO$_2^-$-β-CD. [b] The ratios of peak areas of the signals due to the H^5 protons of the Δ- and Λ-enantiomers of the guests were determined from the computer-resolved signals in ^{1}H NMR spectra. [c] The coalescence temperatures were determined from the NMR spectra of (±)-M(phen)$_3^{2+}$, measured by changing the temperature from 15 to 85 °C (10 °C interval).

Similar Pfeiffer effects were observed with Zn(phen)$_3^{2+}$ and Co(phen)$_3^{2+}$, and the results are shown in Table 5. Without regard to metal ion, per-CO$_2^-$-β-CD enriches the Δ-enantiomers of the tris(1,10-phenanthroline)metal complexes.

Chiral Recognition of Ru(phen)$_3^{2+}$ by TMe-α-CD. Although it is very important to compare the results obtained for charged CDs with those for neutral CDs, most neutral CDs such as α-, β-, and γ-CDs and TMe-β-CD show slight or no interactions with positively charged M(phen)$_3^{n+}$. Only TMe-α-CD, however, interacts with Ru(phen)$_3^{2+}$ and Ru(bpy)$_3^{2+}$ and discriminates between the enantiomers of these metal complexes.

Figure 10 shows the effects of TMe-α- and -β-CDs on the ^{1}H NMR spectrum of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ in D$_2$O without inorganic salt. Each proton signal of the guest is split into two signals upon addition of TMe-α-CD, while no effect is found with TMe-β-CD. The NMR spectrum of the Λ-enantiomer is affected more remarkably than that of the Δ-enantiomer by TMe-α-CD. In accord with this, the retention time of the Λ-enantiomer in CZE using TMe-α-CD as the chiral selector is longer than that of the Δ-enantiomer (Table 1). These results are opposite to those for the per-CO$_2^-$-β-CD system. In the case of (±)-Ru(bpy)$_3^{2+}$, similar but weaker effects of TMe-α-CD on the ^{1}H NMR spectrum were observed (Supporting Information).

The K value for the TMe-α-CD complex is much smaller than that for the corresponding per-CO$_2^-$-β-CD complex (Table 6). This should be due to the absence of Coulomb interactions. In contrast with the case of per-CO$_2^-$-β-CD, Λ-Ru(phen)$_3^{2+}$ is the preferable guest for TMe-α-CD. Weak Λ-selectivity of TMe-α-CD was also observed with Ru(bpy)$_3^{2+}$.

The $\Delta\delta_{sat}$ values for the signals due to TMe-α-CD are shown in Figure 11 for the complexes of Ru(phen)$_3^{2+}$ and Ru(bpy)$_3^{2+}$. The signals due to the OCH$_3$ groups at the 3-positions of TMe-

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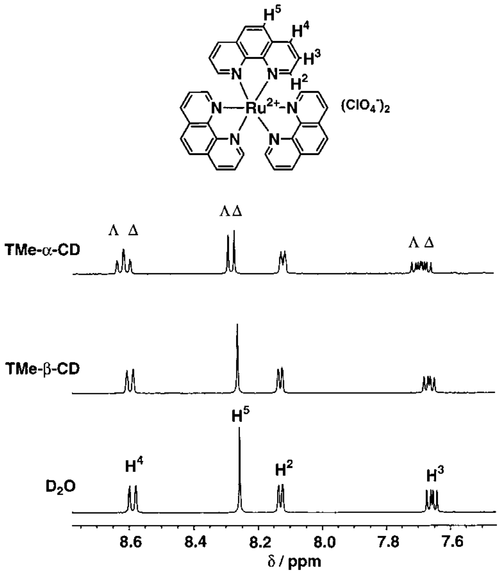

Figure 10. ^{1}H NMR spectra of (±)-Ru(phen)$_3$(ClO$_4$)$_2$ (1×10^{-3} M) in D$_2$O at pD 7.0 and 25 °C in the absence and the presence of TMe-α- and -*β*-CDs.

Table 6. Complexation of of Ru(phen)$_3$(ClO$_4$)$_2$ and Ru(bpy)$_3$(ClO$_4$)$_2$ with TMe-α-CD in D$_2$O at pD 7.0 and 25 °C

guest	*K* (M^{-1})	K_Δ/K_Λ	$\Delta\Delta G°$ (kJ mol^{-1})
Δ-Ru(phen)$_3^{2+}$	54 ± 4		
Λ-Ru(phen)$_3^{2+}$	108 ± 4	2.0	−1.7
Δ-Ru(bpy)$_3^{2+}$	59 ± 4		
Λ-Ru(bpy)$_3^{2+}$	77 ± 4	1.3	−0.7

α-CD shift most remarkably upon complexation with Δ- or Λ-Ru(phen)$_3^{2+}$, indicating the secondary OH group side of the CD as the binding side. In the ROESY spectrum (Supporting Information), strong correlation peaks were observed between H^2, H^3, H^4, and H^5 of Λ-Ru(phen)$_3^{2+}$ and the protons of the OCH$_3$ groups at the 3-positions of the host (3-OCH$_3$), while only H^2 and H^3 of Δ-Ru(phen)$_3^{2+}$ strongly correlate with 3-OCH$_3$. ROESY suggests the formation of a shallow inclusion complex of the Δ-enantiomer and a deeper inclusion complex of the Λ-enantiomer.

In contrast with the case of per-CO$_2^-$-*β*-CD, complex formation of TMe-α-CD with positively charged guests is an enthalpically favorable but entropically unfavorable process (Table 7). The thermodynamic parameters indicate that the guest cation is bound to TMe-α-CD through van der Waals interactions and no positive contribution of the entropy term due to dehydration participates.

Discussion

The present study reveals that the Δ-enantiomer of Ru(phen)$_3^{2+}$ is the preferred guest for per-CO$_2^-$-*β*-CD while its antipode is enantioselectively bound to TMe-α-CD. The binding sites of the guest cation are the primary OH group side of per-CO$_2^-$-*β*-CD and the secondary OH group side of TMe-α-CD. Is there some important meaning in the difference in enantioselectivity between these two CDs? As described in the Introduction, there are several studies on recognition of helicity by CDs, including the investigations on CD-induced conformational enantiomerism.[9−13,37] Table 8 summarizes the reported enantioselectivity of CDs for various guests having helicity.

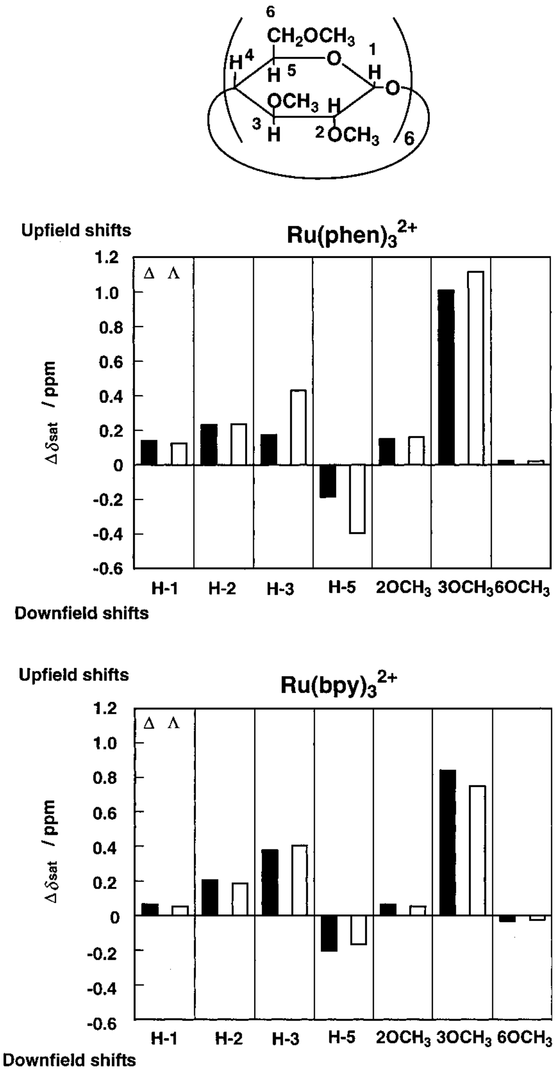

Figure 11. Saturated complexation-induced shifts ($\Delta\delta_{\mathrm{sat}}$) of TMe-α-CD complexed with Δ- and Λ-Ru(phen)$_3$(ClO$_4$)$_2$ and Δ- and Λ-Ru(bpy)$_3$(ClO$_4$)$_2$ in D$_2$O at pD 7.0 and 25 °C. The NMR measurements of the Ru(phen)$_3$(ClO$_4$)$_2$ system were carried out under argon atmosphere. The positive and negative values represent upfield and downfield shifts, respectively.

Table 7. Thermodynamic Parameters for Complexation of Ru(phen)$_3$(ClO$_4$)$_2$ and Ru(bpy)$_3$(ClO$_4$)$_2$ with TMe-α-CD in D$_2$O at pD 7.0

guest	host	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J mol^{-1}K^{-1})	$T\Delta S°$ (kJ mol^{-1})[a]
Δ-Ru(phen)$_3^{2+}$	TMe-α-CD	−40.5 ± 2.1	−102 ± 7	−30.4 ± 2.1
Λ-Ru(phen)$_3^{2+}$	TMe-α-CD	−34.3 ± 2.3	−75.0 ± 7.6	−22.4 ± 2.3
Δ-Ru(bpy)$_3^{2+}$	TMe-α-CD	−46.9 ± 0.4	−123 ± 1	−36.7 ± 0.3
Λ-Ru(bpy)$_3^{2+}$	TMe-α-CD	−36.8 ± 0.6	−87.2 ± 1.9	−26.0 ± 0.6

[a] $T\Delta S°$ values were calculated for 298 K.

Although the number of examples is not enough, it is noteworthy that the primary and secondary OH group sides of CDs prefer the (*P*)- and (*M*)-helix configurations, respectively, without exception. Size matching is the most important factor to form stable inclusion complexes of CDs. Therefore, the *lock and key concept* can be applied in chiral recognition by CDs.[38] On the basis of these findings, it can be concluded that the shape of the primary OH group side of CD fits the guest having a right-handed helix configuration well while the shape of the secondary

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Table 8. Enantioselectivity of CDs toward Guests Having Helicity

binding side	CD	guest	selectivity	ref
secondary OH side	γ-CD	pyrene dimer	*M*	13
secondary OH side(?)	γ-CD	acridine orange dimer	*M*	39
secondary OH side	β-CD	bilirubin	*M*	10,11
primary OH side	γ-CD	pamoic acid	*P*	12
primary OH side	per-NH_3^+-β-CD	bilirubin	*P*	20
secondary OH side	β-CD	HDC[a]	*M*	9
primary OH side	per-CO_2^--β-CD	$Ru(phen)_3^{2+}$	*P* (Δ)	*b*
secondary OH side	TMe-α-CD	$Ru(phen)_3^{2+}$	*M* (Λ)	*b*
primary OH side	per-CO_2^--β-CD	$Zn(phen)_3^{2+}$	*P* (Δ)	*b*
secondary OH side	TMe-α-CD	$Ru(bpy)_3^{2+}$	*M* (Λ)	*b*

[a] 1,12-Dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylic acid. [b] This work.

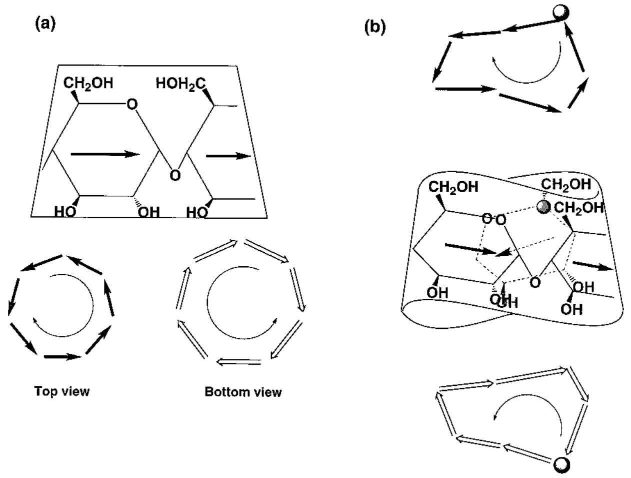

Figure 12. β-Cyclodextrin having C_7 symmetry (a) and twisted β-cyclodextrin (b). The straight and round arrows represent a glucopyranose unit and the direction of helix of a guest, respectively.

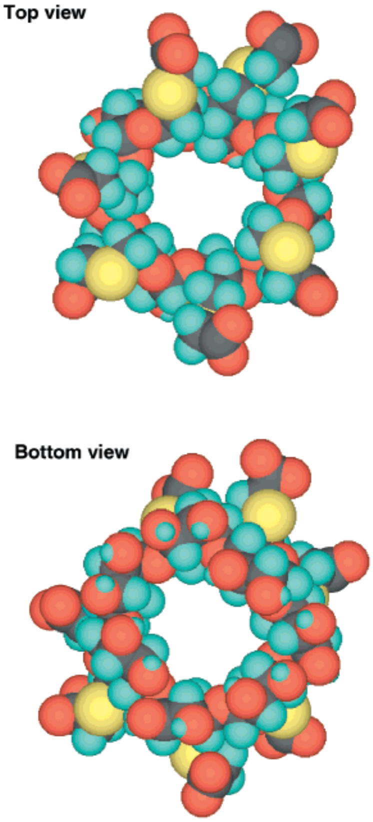

Figure 13. Energy-minimized structure of per-CO_2^--β-CD in aqueous medium calculated by the MD method.

OH group side of CD matches the guest having a left-handed configuration. In other words, CD has an asymmetrically twisted cavity, which is the origin of chiral recognition. A plausible model that can explain chiral recognition by CD is shown in Figure 12. A glucopyranose unit is annotated by an arrow pointing from the 4-position to the 1-position. When β-CD is looked down on from the primary and secondary OH group sides, the arrangement of a series of the arrows in the top view is a mirror image of that in the bottom view. Namely, the rims of the primary and secondary OH group sides of CD are in the enantiomeric relation (Figure 12a). It is reasonable to consider, therefore, that enantioselectivity of the primary OH group side of CD is opposite to that of the secondary OH group side. Judging from the CPK molecular model, however, it is very difficult to understand that CD having C_n symmetry provides largely different environments to the guest enantiomers. Then, we assumed an asymmetrically twisted shape of CD as shown in Figure 12b. Such a twisted CD can provide the strongly different environments for two guest enantiomers. The arrangement of the arrows of the twisted CD predicted from the CPK molecular model are shown in Figure 12b, which can interpret the different modes in binding between two guest enantiomers. The excessive structure of a twisted CD is drawn in Figure 12b. If at least one glucopyranose unit in the CD inclines to the inside of the CD cavity, the CD takes an asymmetrically twisted shape. Such bent structures of α-, β-, and γ-CDs and TMe-α- and -β-CDs including guest molecules such as water, methanol, *p*-nitrophenol, and so forth have been verified from X-ray analyses.[14b,14d,39] The results of X-ray crystallography of native cyclodextrins are summarized in a book by Jeffrey and Saenger.[40] The crystal structures of α-CD·$n$$H_2O$ are affected by hydrogen bonding between the OH groups of α-CD and the water molecule(s) included in the CD cavity. Such intermolecular hydrogen bonding always causes a bent structure of α-CD. Distortion of CD cavities is more remarkable in the cases of alkylated CDs such as TMe-α- and -β-CDs. For example, TMe-α- and -β-CDs take elliptically distorted shapes upon complexation with various kinds of guests.[39c−e] The reported crystal structures of the CDs are similar to that shown in Figure 12b, which also resembles one predicted from molecular dynamics calculations without consideration of solvation (Supporting Information). It may be considered that CD tends to take an asymmetrically twisted shape when intramolecular hydrogen bonds between the secondary OH groups at the 2-positions and the adjacent OH groups at the 3-positions are disrupted by hydration or by substitution of the OH groups by the OCH_3 groups. Figure 13 shows the energy-minimized structure of per-CO_2^--β-CD in the presence of water molecules, which was calculated by the molecular dynamics (MD) method (AMBER 94 force field). The primary OH group side of the CD widens because of electrostatic repulsion between the charged headgroups. The cavity does not show C_7 symmetry, and at least two glucopyranose units incline to the inside of the CD cavity. An asymmetrically twisted CD shape can explain the generally chiral recognition by CDs.

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The fact that TMe-α-CD recognizes the helicity of Ru(phen)$_3^{2+}$ but TMe-β-CD does not is very suggestive for the mechanism for chiral recognition by CDs. The cavity size of TMe-α-CD is too narrow to include a phenanthroline moiety completely. Therefore, a very shallow inclusion complex should be formed. We previously reported that the ability of TMe-α-CD to recognize central chirality of 1-arylethanols such as 1-(4-quinolyl)ethanol and 1-(1-pyrenyl)ethanol is much higher than that of TMe-β-CD.[8] The sizes of these 1-arylethanols are too large to be included wholly in the TMe-α-CD cavity. Therefore, shallow inclusion complexes are formed in this system. These findings indicate that chiral recognition by CD occurs at or near the rim of the CD and chiral recognition is not realized if the host has a large enough cavity size to include the guest. We do not deny the previous idea that tight inclusion needs to realize chiral recognition by CDs.[16,41] Shallow inclusion does not mean loose inclusion.

Binding between cationic Ru(phen)$_3^{2+}$ and anionic per-CO$_2^-$-β-CD is promoted by cooperative Coulomb and van der Waals interactions. The fact that hydrophilic Ru(bpy)$_3^{2+}$ is hardly bound to per-CO$_2^-$-β-CD suggests the importance of inclusion of a cationic guest into a cavity of an anionic CD to cause Coulomb interactions between the host and the guest. Such interactions between charged host and oppositely charged guest have been observed in complexation of the carboxylate anions with cationic per-NH$_3^+$-β-CD.[18,28] In binding the Ru complexes to DNA, it was also found that interactions other than Coulombic ones participate and the contribution of other interactions in complexation of a hydrophobic cationic guest is much larger than that of a hydrophilic cationic guest.[42] Complexation between charged guests and oppositely charged polyvalent CD ions is an entropically favorable process whose origin is the extensive dehydration of both host and guest. With no exception, positive entropy changes were observed in complexation of M(phen)$_3^{n+}$ with per-CO$_2^-$-β-CD. Other systems such as the anionic α-amino acid−per-NH$_3^+$-β-CD and carboxylate−per-NH$_3^+$-β-CD systems also show the positive entropy changes without exception. The hydrophobic backbone of an organic ion may be an important driving force to release solvated water molecules upon complexation. Similar entropically favorable binding was observed between DNA and the Ru(II) complexes[43] and between a polyanionic porphyrin having hydrophobic tails and the cationic amino acids.[44] Meanwhile, complexation of charged guests with neutral CDs is not so simple. In such cases, thermodynamic parameters depend on binding modes. *p*-Methylbenzoate anion penetrates into the β-CD cavity from the secondary OH group side of the CD to place the CO$_2^-$ group at the primary OH group side.[28] In this case, a positive $\Delta S°$ assists complex formation. On the other hand, inclusion of *p*-methylbenzoate anion into the α-CD cavity is accompanied by a large and negative $\Delta S°$.[28] The CO$_2^-$ group of *p*-methylbenzoate in the α-CD complex faces the aqueous bulk phase at the secondary OH group side of the CD. Extensive dehydration does not need to form such a complex leading to the enthalpy gain and the entropy loss. Highly enantioselective complexation of a tetrahelicene dicarboxylate (HDC) with β-CD is also the enthalpy-dominated process accompanied by negative and large $\Delta S°$.[9] A hydrophobic part of HDC is included into the β-CD cavity, and the CO$_2^-$ groups are located outside of the CD cavity. The negative $\Delta S°$ values observed in the Ru(phen)$_3^{2+}$−TMe-α-CD and Ru(bpy)$_3^{2+}$−TMe-α-CD systems suggest that a hydrophobic part of the metal complex is included into the TMe-α-CD cavity through van der Waals interactions and the Ru^{2+} ion at a center of the metal complexes is located in the aqueous bulk phase.

Experimental Section

Materials. (±)-Ru(phen)$_3$(ClO$_4$)$_2$,[22] (±)-Ru(bpy)$_3$(ClO$_4$)$_2$,[22] (±)-Rh(phen)$_3$Cl$_3$,[45] (±)-Fe(phen)$_3$(ClO$_4$)$_2$,[46] (±)-Co(phen)$_3$(ClO$_4$)$_2$,[47] and (±)-Zn(phen)$_3$(ClO$_4$)$_2$[32d] were prepared and purified according to the procedures described in the literatures. The Δ- and Λ-enantiomers of Ru(phen)$_3$(ClO$_4$)$_2$[22] and Ru(bpy)$_3$(ClO$_4$)$_2$[22a] and Λ-Rh(phen)$_3$Cl$_3$[48] were resolved from their racemates by the reported methods. The optical purity of the resolved complexes was checked by measuring the optical rotations. Cyclodextrins such as α-, β-, and γ-CDs and TMe-β-CD were used as received (Nacalai). TMe-α-CD was prepared in our laboratory.[49] The purity of these CDs was checked by measuring ^{1}H NMR spectra. Mono-CO$_2$H-β-CD[50] and per-CO$_2$H-α-, -β-, and -γ-CDs[25] were prepared according to the procedures described in the literature. The elemental analysis indicated per-CO$_2$H-β-CD·5H$_2$O. Anal. Calcd for $C_{56}H_{84}O_{42}S_7 \cdot 5H_2O$: C, 38.57; H, 5.43; S, 12.87. Found: C, 38.48; H, 5.14; S, 13.12.

Measurements. The CZE experiments were carried out using a JASCO capillary electrophoresis CE−800 system with a 300 mm (effective length) × 50 μm i.d. fused silica capillary cartridge (noncoated). The capillary was filled with 0.067 M phosphate buffer at pH 7.0 containing appropriate amounts of CD (usually 1×10^{-3} M). The sample solution was prepared by adding 10 μL of the stock solution of the metal complex (5×10^{-3} M) in DMSO into 0.5 mL of the previous buffer solution (final concentrations of metal complex and DMSO were 1×10^{-4} M and 2% (v/v), respectively). The sample was introduced into the capillary by applying the potential for 10 s. The electropherogram was taken at the same potential using a JASCO 875-CE UV−vis detector placed at the negative electrode side.

The ^{1}H NMR spectra were taken on a JEOL JNM-A400 (400 MHz) spectrometer in D$_2$O (CEA, 99.8%) using 3-trimethylsilyl[2,2,3,3-^{2}H$_4$]propionate (TSP, Aldrich) as an external standard. The ROESY spectra were recorded with a spectral width of 3358 Hz. The 90° pulse was 33.3 μs, mixing was 250 ms, delay time was 2.0 s, and 512 × 512 data points were recorded. The pD values were adjusted by Na$_2$CO$_3$ in the nonbuffered system. All samples for NMR measurements were bubbled by nitrogen for 30 s, and then the atmosphere of the sample tubes was replaced by argon. Under aerobic conditions, CDs were decomposed by the action of Ru(phen)$_3^{2+}$ and ambient light, leading to broadening of the NMR signals of CDs.

A typical method for determining *K* values is as follows. The changes in the chemical shifts of the H^2, H^3, H^4, and H^5 protons of Ru(phen)$_3$(ClO$_4$)$_2$ (1×10^{-4} M) in 0.067 M phosphate buffer at pD 7.0 were monitored upon addition of per-CO$_2^-$-β-CD (7.5×10^{-5}−4.8×10^{-3} M) at 25 °C. The NMR titration curves obtained for four different protons of the guest were simultaneously fitted by the following equation, using a nonlinear least-squares method (a damping Gauss−Newton method):

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$$\Delta\delta = \Delta\delta_{sat}\{\beta - (\beta^2 - 4K^2[H]_0[G]_0)^{1/2}\}/2K[G]_0 \qquad (5)$$

where

$$\beta = 1 + K[H]_0 + K[G]_0 \qquad (6)$$

$$\Delta\delta = \delta_f - \delta_{obs} = \chi(\delta_f - \delta_c) = \chi\Delta\delta_{sat} \qquad (7)$$

In eqs 5, 6, and 7, δ_f and δ_{obs} are the chemical shifts of the free guest and the guest complexed with the host, respectively, χ is the mole fraction of the host−guest complex, and $[G]_0$ and $[H]_0$ are the initial concentrations of the guest and the host, respectively. The reliability of each K value was checked by duplicate or triplicate measurements. The errors in the K values indicated in this paper were the standard deviations in the curve fitting. The $\Delta\delta_{sat}$ values for the host protons (Figures 3 and 11) were calculated from eq 7 by using the determined K values.

The circular dichroism spectra were taken on a JASCO J-500A spectropolarimeter with a data processor. The optical rotations were measured by a Horiba SEPA-200 polarimeter.

Molecular Dynamics. The energy-minimized structure of per-CO_2^--β-CD was obtained from the MD calculation using a HyperChem program (Hypercube, Florida), which corresponds to AMBER version 3a. The calculation was carried out by setting the initial and final temperatures of 250 and 298 K, respectively, the heat time of 1 fs, and the run time of 100 ps. Four hundred and two water molecules were placed in a box in which a per-CO_2^--β-CD ion was located.

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Supporting Information Available: ^{1}H NMR titration curves for determining K values, van't Hoff plots for determining $\Delta H°$ and $\Delta S°$, ^{1}H NMR spectra of (±)-Rh(phen)$_3$Cl$_3$ in D_2O containing various CDs, ^{1}H NMR spectrum of (±)-Fe(phen)$_3$-(ClO$_4$)$_2$ in D_2O containing per-CO_2^--β-CD, ^{1}H NMR spectra of Ru(bpy)$_3$(ClO$_4$)$_2$ in D_2O containing TMe-α- and -β-CDs, ROESY spectra of the Δ- and Λ-Ru(phen)$_3$(ClO$_4$)$_2$ complexes of TMe-α-CD, and the structures of β-CD provided by molecular dynamics calculations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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