430 μs). The value of k_{solv} should decrease on changing from H_2O to D_2O, due to lowering of the solvent stretching frequency used for vibrational coupling with the $^2T_{1g}$ excited state. Since the $^2T_{1g}$ lifetime for *trans*-Cr(tet a)F_2^+ in room-temperature solution is, to a good approximation, given by $1/k_{nr}$ (where $k_{nr} = k_{intra} + k_{solv}$), then a longer lifetime is anticipated in D_2O.

Finally, the marked contrast in photobehavior between *trans*-Cr(tet a)F_2^+ (photoinert, long-lived emission) and its nonmacrocyclic counterpart *trans*-Cr(en)$_2F_2^+$ (photolabile, short-lived emission) requires comment. We feel these differences are most consistent with the short $^2T_{1g}$ lifetime of *trans*-Cr(en)$_2F_2^+$ in solution being associated with *direct* reaction out of the $^2T_{1g}$ level. This interpretation also rationalizes the much longer lifetime and substantial deuterium isotope effect observed for *trans*-Cr(en)$_2F_2^+$ when photoreaction is suppressed, such as in frozen glasses (77 K) and in the solid state (Table II). Alternatively, it may be argued that $^2T_{1g} \rightsquigarrow {}^4T_{2g}$ back-ISC is primarily responsible for the short $^2T_{1g}$ lifetime of *trans*-Cr(en)$_2F_2^+$ in room-temperature solution, while the $^2T_{1g}$ level is assumed inert toward direct chemical reaction. Since *trans*-Cr(tet a)F_2^+ is photoinert, the quantum yield for $^4T_{2g} \rightsquigarrow {}^2T_{1g}$ ISC (ϕ_{ISC}) may be close to unity and the effective rate constant for back-ISC relatively small in room-temperature solution.[29] However, one might then also anticipate the observation of delayed $^4T_{2g} \rightarrow {}^4A_{2g}$ (O_h) fluorescence for *trans*-Cr(tet a)F_2^+ (since the $^4T_{2g}$ level is now photoinert). We have looked carefully (without success) for evidence of a broad fluorescence signal in room-temperature solution and the solid state, using the high-resolution capabilities of the Jarrell-Ash laser Raman instrument (514.5-nm excitation). A *direct* photochemical role for the $^2T_{1g}$ level for *trans*-Cr(en)$_2F_2^+$ is also supported by the observation by Waltz and co-workers from pulsed-laser conductivity studies[27] that 100% of the photoreaction is associated with the doublet level.

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Registry No. *cis*-[Cr(cyclam)F_2]ClO_4, 105140-76-9; *trans*-[Cr(tet a)F_2]ClO_4, 88415-77-4; *trans*-[Cr(py)$_4F_2$]ClO_4, 27731-45-9; D_2, 7782-39-0.

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Mechanism of Chiral Recognition of Octahedral Metal Complexes Effected by Bis(μ-*d*-tartrato)diantimonate(III) Anion in Solution. 2. Cage Complexes of the Type $[Co(N)_6]^{3+}$

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Some hexaamine cage complexes such as $[Co(sep)]^{3+}$ (sep = 1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]eicosane) and [Co(diNOsar)]$^{3+}$ (diNOsar = 1,8-dinitro-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane) were subjected to ion-exchange chromatography with the bis(μ-*d*-tartrato)diantimonate(III) anion, $[Sb_2(d\text{-tart})_2]^{2-}$, employed as a chiral eluent. It was found that the Λ enantiomers are eluted always first and that the more bulky the alkyl cap that each cage complex has, the better the degree of optical resolution of the complex attained. These experimental results were interpreted reasonably on the basis of the C_2 association model in which two NH protons directed along the (pseudo) C_2 axis of the complex are hydrogen-bonded to two oxygen atoms of the $[Sb_2(d\text{-tart})_2]^{2-}$ ion. It was concluded that chiral recognition of the cage complex is effected through the steric repulsion expected stereoselectively between the alkyl cap of the Δ enantiomer and the distal carboxylate group of the chiral anion.

Introduction

In the preceding paper,[1] we proposed two association models called as the C_3 and C_2 models, which account for how bis(μ-*d*-tartrato)diantiomonate(III) anion, $[Sb_2(d\text{-tart})_2]^{2-}$ ion, recognizes the chirality of some octahedral complexes of the type $[Co(N)_6]^{3+}$ in solution. In the C_3 association model where two or three NH protons directed along the (pseudo) C_3 axis of the compex are hydrogen-bonded to the oxygen atoms of $[Sb_2(d\text{-tart})_2]^{2-}$ ion, the Λ enantiomer forms a more favorable ion pair with the chiral anion than does the Δ enantiomer. In the C_2 association model, on the other hand, two NH protons directed along the (pseudo) C_2 axis participate in the hydrogen bonding to the chiral anion, and the Δ enantiomer associates more smoothly with the chiral anion than does the Λ enantiomer.

Recently, Sargeson and coworkers[2,3] have prepared some hexaamine cage complexes with alkyl caps along the C_3 axis, e.g., $[Co(sep)]^{3+}$, $[Co(diNOsar)]^{3+}$, $[Co(azaMEsar)]^{3+}$, and $[Co(MENOsar)]^{3+}$, starting with $[Co(en)_3]^{3+}$ or $[Co(sen)]^{3+}$,[4] and some of them have been resolved by ion-exchange chromatography using $[Sb_2(d\text{-tart})_2]^{2-}$ ion as an eluent, with the Λ enantiomers eluted first.[2,5] Since these cage complexes have alkyl caps that block the access of $[Sb_2(d\text{-tart})_2]^{2-}$ ion along the C_3 axis, the chiral anion probably approaches each complex along the (pseudo) C_2 axis. Then, the formal application of our C_2 association model leads us to expect that the Δ enantiomers of these cage complexes interact more smoothly with $[Sb_2(d\text{-tart})_2]^{2-}$ ion than do the antipodes. Nevertheless, the Λ enantiomers are actually eluted first by $[Sb_2(d\text{-tart})_2]^{2-}$ ion in ion-exchange chromatography, which stimulated us to elucidate the mechanism by which

(1) Miyoshi, K.; Izumoto, S.; Yoneda, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3475-3482.
(2) Creaser, I. I.; Geue, R. J.; Harrowfield, J. M.; Herlt, A. J.; Sargeson, A. M.; Snow, M. R.; Springborg, J. *J. Am. Chem. Soc.* **1982**, *104*, 6016-6025.
(3) Geue, R. J.; Hambley, T. W.; Harrowfield, J. M.; Sargeson, A. M.; Snow, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 5478-5488.
(4) Abbreviations; en = ethylenediamine, sen = 1,1,1-tris(((2-aminoethyl)amino)methyl)ethane, sep = 1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]eicosane, diNOsar = 1,8-dinitro-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane, azaMEsar = 8-methyl-1,3,6,10,13,16,19-heptaazabicyclo[6.6.6]eicosane, MENOsar = 1-methyl-8-nitro-3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane, AMsartacn = 9-amino-1,4,7,11,14,19-hexaazatricyclo[7.7.4.2^{4,14}]docosane, NOsartacn = 9-nitro-1,4,7,11,14,19-hexaazatricyclo[7.7.4.2^{4,14}]docosane, and azasartacn = 1,4,7,9,11,14,19-heptaazatricyclo[7.7.4.2^{4,14}]docosane.
(5) Hammershøi, A.; Sargeson, A. M. *Inorg. Chem.* **1983**, *22*, 3554-3561.

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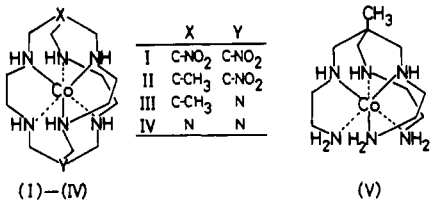

	X	Y
I	C-NO_2	C-NO_2
II	C-CH_3	C-NO_2
III	C-CH_3	N
IV	N	N

Figure 1. Schematic structures of Δ cage complexes: Δ-[Co(diNOsar)]$^{3+}$ (I); Δ-[Co(MENOsar)]$^{3+}$ (II); Δ-[Co(azaMEsar)]$^{3+}$ (III); Δ-[Co(sep)]$^{3+}$ (IV); Δ-[Co(sen)]$^{3+}$ (V).

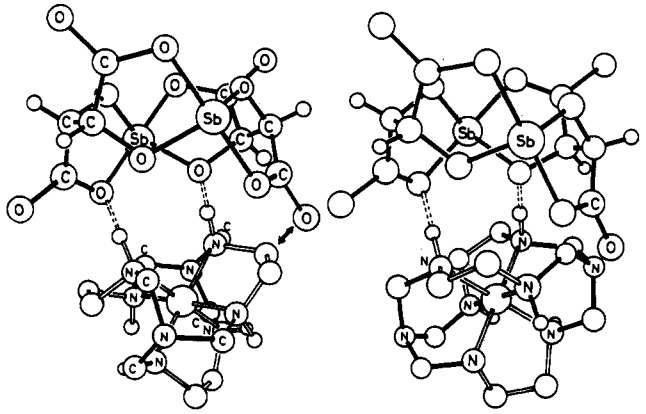

Figure 2. C_2 association models for Λ-[Co(sep)]$^{3+}$–[Sb_2(*d*-tart)$_2$]$^{2-}$ (left) and Δ-[Co(sep)]$^{3+}$–[Sb_2(*d*-tart)$_2$]$^{2-}$ (right).

[Sb_2(*d*-tart)$_2$]$^{2-}$ ion recognizes the chirality of these cage complexes in solution.

Experimental Section

Preparation of Complexes. All the complexes used in the present study, [Co(en)$_3$]$^{3+}$, [Co(sen)]$^{3+}$, [Co(sep)]$^{3+}$, [Co(diNOsar)]$^{3+}$, [Co(MENOsar)]$^{3+}$, and [Co(azaMEsar)]$^{3+}$[4] were prepared as chloride salts by the procedures described earlier,[2,3,6-8] and their purity was checked by absorption and/or circular dichroism (CD) spectra and by ion-exchange chromatography.

Chromatography. A stainless-steel column (7.5 mm × 75 mm) packed with the TSK gel SP-2SW (cation exchanger) was equilibrated with an aqueous eluent containing Na_2[Sb_2(*d*-tart)$_2$]·5H_2O in 0.075 mol/dm^3. An aqueous solution (20 μL) of a racemic complex (0.1 mol/dm^3) containing K[Co(edta)]·2H_2O (0.05 mol/dm^3) as a marker, was injected by a syringe on the top of the column, and was eluted at an elution rate of 1.0 mL/min. Retention volumes V_R and elution orders were determined as described previously with a Jasco BIP 1 pump for HPLC and a Jasco J-40CS spectropolarimeter.[9]

Results and Discussion

C_2 Association of Cage Complexes. Schematic structures of the cage complexes (Δ enantiomer) examined here are shown in Figure 1. In addition to these complexes, [Co(en)$_3$]$^{3+}$ and [Co(sen)]$^{3+}$ were also chromatographed for comparison. Since these cage complexes have alkyl caps along both sides of the C_3 axis, the access of [Sb_2(*d*-tart)$_2$]$^{2-}$ ion to them is allowed only along the (pseudo) C_2 axis. In fact, the addition of the chiral anion to [Co(sep)]$^{3+}$ in solution enhances the rotational strength of its E_a component, which is polarized perpendicular to the C_3 axis.[6] Thus, it is highly plausible that [Sb_2(*d*-tart)$_2$]$^{2-}$ ion approaches [Co(sep)]$^{3+}$ predominantly along the C_2 axis to recognize its chirality in solution. If our C_2 association model[1] is formally applied to [Co(sep)]$^{3+}$, its Δ enantiomer should be eluted first by the chiral eluent anion in ion-exchange chromatography. In practice, however, Λ-[Co(sep)]$^{3+}$ associates more favorably with the chiral anion in aqueous solution than does Δ-[Co(sep)]$^{3+}$.[6,10] Then, our C_2 hydrogen-bonding-association model is constructed as in Figure 2, taking [Co(sep)]$^{3+}$ as an example.

In Figure 2, two oxygen atoms coordinated to the same Sb atom in [Sb_2(*d*-tart)$_2$]$^{2-}$ ion, viz. the alcoholic oxygen atom of one *d*-tartrate moiety and the carboxylic oxygen atom of the other *d*-tartrate moiety, are hydrogen bonded to two NH protons directed along the C_2 axis of the complex. When the complex has a Λ configuration (left-hand model), the distal carboxylate group of [Sb_2(*d*-tart)$_2$]$^{2-}$ ion, particularly its C=O group, experiences a steric hindrance from one "ethylenediamine" (en) chelate ring, as indicated by an arrow. The steric hindrance is the same in nature as that expected in the C_2 association with Λ-[Co(en)$_3$]$^{3+}$ or Λ-*cis*-[Co(X)$_2$(en)$_2$]$^+$ (X = anionic ligand).[1] By contrast, the newly introduced alkyl caps are so far from any part of the [Sb_2(*d*-tart)$_2$]$^{2-}$ ion that they exert no steric influence on the chiral anion.

On the other hand, when the complex has a Δ configuration (right-hand model), the distal carboxylate group is disposed nicely between two "en" chelate rings of the complex. This is the main reason why [Sb_2(*d*-tart)$_2$]$^{2-}$ ion elutes the Δ enantiomer first in ion-exchange chromatography for *cis*-[Co(X)$_2$(en)$_2$]$^+$-type complexes, which adopt the C_2 association mode predominantly.[1] However, as clearly seen in the right-hand model shown in Figure 2, one of the two aza caps of Δ-[Co(sep)]$^{3+}$ is situated in the vicinity of the distal carboxylate group of [Sb_2(*d*-tart)$_2$]$^{2-}$ ion to impose a severe steric repulsion on the C=O group. Therefore, if the steric repulsion due to the aza cap of Δ-[Co(sep)]$^{3+}$ is severer than that due to one "en" chelate ring of Λ-[Co(sep)]$^{3+}$, the chiral anion forms a more stable ion pair with Λ-[Co(sep)]$^{3+}$ in the C_2 association than with Δ-[Co(sep)]$^{3+}$.

In this way, we propose here that the chiral recognition of the cage complexes is effected by the steric repulsion due to the newly introduced alkyl caps rather than the preexisting "en" chelate rings. Consequently, it is naturally expected that the more bulky the alkyl cap that a cage complex has, the severer the steric repulsion and thus the better the recognition efficiency of the complex attained by the [Sb_2(*d*-tart)$_2$]$^{2-}$ ion. Then, several cage complexes with different alkyl caps were subjected to ion-exchange chromatography using [Sb_2(*d*-tart)$_2$]$^{2-}$ ion as an eluent, and their retention volumes V_R and separation factors α are given in Table I.

Table I. Retention Volumes V_R and Separation Factors α of Cage Complexes Obtained by HPLC[a]

complex	$V_{R(\Lambda)}$/mL	$V_{R(\Delta)}$/mL	α
[Co(en)$_3$]$^{3+}$	62.0	81.6	1.32
[Co(sen)]$^{3+}$ (V)	60.0	83.2	1.39
[Co(sep)]$^{3+}$ (IV)	65.2	85.6	1.31
[Co(azaMEsar)]$^{3+}$ (III)	62.6	86.0	1.37
[Co(MENOsar)]$^{3+}$ (II)	58.6	102.6	1.75
[Co(diNOsar)]$^{3+}$ (I)	40.2	73.6	1.83

[a] $V_{R(\Lambda)}$ and $V_{R(\Delta)}$ refer to retention volumes for Λ and Δ enantiomers, respectively.

It is evident in Table I that the Λ enantiomer is eluted always first, as expected, for all four cage complexes as well as for [Co(sen)]$^{3+}$ and [Co(en)$_3$]$^{3+}$. In addition, small retention volumes are obtained for those cage complexes that have an electron-withdrawing nitro group on the cap. In ion-exchange chromatography, a small retention volume of a complex means its stronger interaction with the eluent and/or its weaker affinity for the stationary phase (ion-exchange resin). Since the resin used is a silica-based one and both the concentration and the electric charge of the eluent anion are relatively high, the present chromatography is elution-controlled rather than adsorption-controlled. As a result, the above finding is interpreted to mean that the NO_2 group increases the acidity of the NH protons,[8] thereby promoting the hydrogen-bonding interaction with [Sb_2(*d*-tart)$_2$]$^{2-}$ ion.

(6) Sakaguchi, U.; Tsuge, A.; Yoneda, H. *Inorg. Chem.* **1983**, *22*, 1630–1634, 3745–3749.
(7) Tomioka, K.; Sakaguchi, U.; Yoneda, H. *Inorg. Chem.* **1984**, *23*, 2863–2867.
(8) Sakaguchi, U.; Tamaki, S.; Tomioka, K.; Yoneda, H. *Inorg. Chem.* **1985**, *24*, 1624–1627.
(9) Miyoshi, K.; Natsubori, M.; Dohmoto, N.; Izumoto, S.; Yoneda, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1529–1534.

(10) It must be remembered that the interactions of Δ enantiomers of several $[Co(N)_6]^{3+}$-type complexes with [Sb_2(*l*-tart)$_2$]$^{2-}$ ion and [Sb_2(*d*-tart)$_2$]$^{2-}$ ions are discussed in ref 6.

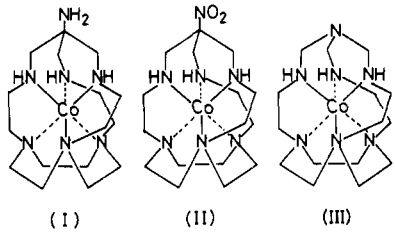

Figure 3. Schematic structures of $[Co(AMsartacn)]^{3+}$ (I), $[Co(NO$-sartacn$)]^{3+}$ (II), and $[Co(azasartacn)]^{3+}$ (III).

It is also evident in Table I that the separation factor α increases with the bulkiness of the substituent X or Y on the alkyl cap, as our model predicts. A somewhat small difference in the α value between $[Co(azaMEsar)]^{3+}$ and $[Co(sep)]^{3+}$ implies that Δ-$[Co(azaMEsar)]^{3+}$ associates with $[Sb_2(d\text{-tart})_2]^{2-}$ ion such that the distal carboxylate group of the chiral anion suffers a steric repulsion from the aza cap rather than the more bulky methyl cap. In fact, the two complexes have comparable V_R values. On the other hand, considerably high α values are derived for the two nitro-capped complexes, $[Co(diNOsar)]^{3+}$ and $[Co(MENOsar)]^{3+}$, which have bulky substituents X and Y on the alkyl caps. A detailed examination of their V_R values suggests that the NO_2 group enhances the association of both of the Λ and Δ enantiomers with $[Sb_2(d\text{-tart})_2]^{2-}$ ion through its electron-withdrawing effect, but the chiral anion suffers a severe steric repulsion stereoselectively from the NO_2 or CH_3 group of the Δ enantiomer, the high α values being thereby derived. Hammershøi and Sargeson[5] have found that $[Co(AMsartacn)]^{3+}$ and $[Co(NOsartacn)]^{3+}$ are resolved much more effectively than $[Co(azasartacn)]^{3+}$[4] by ion-exchange chromatography with the Λ enantiomers eluted first, using $[Sb_2(d\text{-tart})_2]^{2-}$ ion as an eluent (Figure 3). The high recognition efficiency attained for the former two complexes may be also attributed to the severe steric repulsion imposed by their bulky terminal NH_2 or NO_2 group on the chiral anion, though double hydrogen bonding is impossible for these tacn complexes.[11]

Association of $[Co(sen)]^{3+}$. $[Co(sen)]^{3+}$ has a methyl cap along one side of the C_3 axis, but the other side is available for C_3 hydrogen-bonding association with the $[Sb_2(d\text{-tart})_2]^{2-}$ ion (Figure 1). Thus, this complex can adopt, in principle, both of the C_3 and C_2 association modes like $[Co(en)_3]^{3+}$.

It is well-known that the addition of the $[Sb_2(d\text{-tart})_2]^{2-}$ ion to Λ- and Δ-$[Co(en)_3]^{3+}$ in solution leads to an enhancement of the CD intensity of the A_2 component at the first d-d transition region.[6,10] Since the A_2 transition is polarized along the C_3 axis of the complex, this CD change is taken as evidence that the $[Sb_2(d\text{-tart})_2]^{2-}$ ion approaches the complex predominantly along the C_3 axis for both the Λ and Δ enantiomers, though the access of the chiral anion along the C_2 axis is also sterically allowed. Similar CD-spectral studies[6,10] have established that both Λ- and Δ-$[Co(sep)]^{3+}$ adopt the C_2 association mode exclusively, while both Λ- and Δ-$[Co(chxn)_3]^{3+}$ (chxn = *trans*-1,2-cyclohexanediamine) adopt the C_3 mode predominantly. Then, CD spectra of aqueous Λ- and Δ-$[Co(sen)]^{3+}$ are measured in the presence of the $[Sb_2(d\text{-tart})_2]^{2-}$ ion, to infer the access direction of the chiral anion to this complex.

In Figure 4 are shown CD spectra of aqueous Λ- and Δ-$[Co(sen)]^{3+}$ in the absence and presence of $K_2[Sb_2(d\text{-tart})_2]\cdot 3H_2O$. It is surprising that the CD change is quite different between the two enantiomers; the A_2 component is enhanced for the Λ enantiomer, while the E_a component is enhanced for the Δ enantiomer. This novel finding thus leads to a very interesting conclusion that the $[Sb_2(d\text{-tart})_2]^{2-}$ ion approaches Λ- and Δ-$[Co(sen)]^{3+}$ predominantly along the C_3 and C_2 axes, respectively.[12]

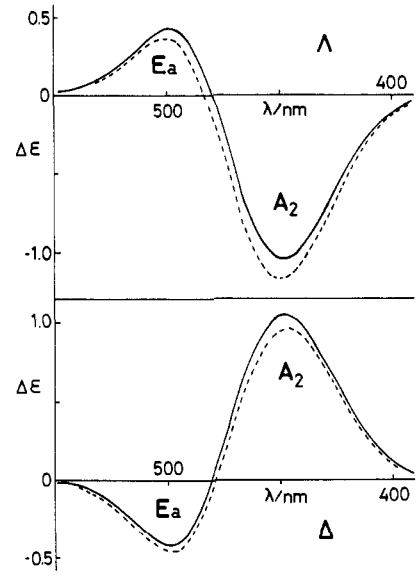

Figure 4. CD spectra of aqueous Λ- and Δ-$[Co(sen)]^{3+}$ in the presence (- - -) and absence (—) of the $[Sb_2(d\text{-tart})_2]^{2-}$ ion.

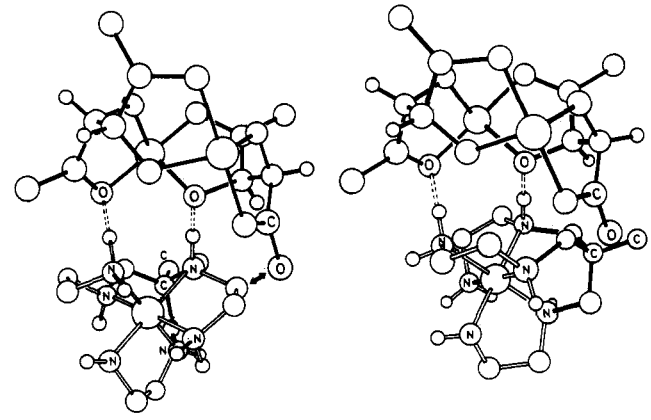

Figure 5. C_2 association models for Λ-$[Co(sen)]^{3+}$–$[Sb_2(d\text{-tart})_2]^{2-}$ (left) and Δ-$[Co(sen)]^{3+}$–$[Sb_2(d\text{-tart})_2]^{2-}$ (right).

Whether such differential interactions are actually probable is examined in the following section on the basis of our C_3 and C_2 association models.

In the C_3 association model, Λ-$[Co(sen)]^{3+}$ forms a favorable ion pair with the $[Sb_2(d\text{-tart})_2]^{2-}$ ion like Λ-$[Co(en)_3]^{3+}$ does.[1] In the C_2 association model, by contrast, Λ-$[Co(sen)]^{3+}$ imposes a steric repulsion on the chiral anion like Λ-$[Co(en)_3]^{3+}$ and Λ-$[Co(sep)]^{3+}$, as shown in the left-hand model of Figure 5. As a result, it is likely that Λ-$[Co(sen)]^{3+}$ prefers to adopt the C_3 association mode predominantly in the interaction with the $[Sb_2(d\text{-tart})_2]^{2-}$ ion.

On the other hand, Δ-$[Co(sen)]^{3+}$ cannot interact smoothly with the chiral anion in the C_3 association mode, since the distal carboxylate group of the chiral anion suffers a steric repulsion from one "en" chelate ring of Δ-$[Co(sen)]^{3+}$, like in the C_3 association with Δ-$[Co(en)_3]^{3+}$.[1] Similarly, no smooth C_2 association is possible between Δ-$[Co(sen)]^{3+}$ and the $[Sb_2(d\text{-tart})_2]^{2-}$ ion when the alcoholic and the carboxylic oxygen atoms of the chiral anion are hydrogen bonded, respectively, to the secondary and primary amine protons directed along the pseudo-C_2 axis of the complex (right-hand model in Figure 5), since the methyl cap of the complex lies in the vicinity of the distal carboxylate group and imposes a steric repulsion on it. However, if the two oxygen atoms hydrogen bonded to the complex are interchanged with each other, viz. if the alcoholic and the carboxylic oxygen atoms are hydrogen bonded, respectively, to the primary and secondary amine protons,

(11) The low optical resolution attained for $[Co(azacapten)]^{3+}$ (azacapten = 1-methyl-3,13,16-trithia-6,8,10-19-tetraazabicyclo[6.6.6]eicosane) may be similarly interpreted. By contrast, $[Co(ten)]^{3+}$ (ten = 4,4′,4″-ethylidynetris(3-thiabutan-1-amine)) should be resolved with reasonable efficiency, since the C_3 association is possible for this complex. See: Gahan, L. R.; Hambley, T. W.; Sargeson, A. M.; Snow, M. R. *Inorg. Chem.* **1982**, *21*, 2699–2706.

(12) Mason, S. F., Ed. *Optical Activity and Chiral Discrimination*; D. Reidel: Dordrecht, Holland, 1979; Chapter VII.

the distal carboxylate group is disposed opposite to the methyl cap to escape the steric repulsion from the cap. Consequently, Δ-[Co(sen)]$^{3+}$ forms a relatively stable ion pair with the [Sb_2-(d-tart)$_2$]$^{2-}$ ion in the C_2 association like Δ-[Co(X)$_2$(en)$_2$]$^+$-type complexes. In this way, our C_3 and C_2 association models afford a reasonable interpretation to the novel CD spectral changes of Λ- and Δ-[Co(sen)]$^{3+}$ shown in Figure 4.

Finally, it is noteworthy that the DCD spectrum[6,10,13] of Λ-[Co(sen)]$^{3+}$ is much smaller in magnitude than that of Δ-[Co-(sen)]$^{3+}$ and than those of Λ- and Δ-[Co(sep)]$^{3+}$ and of Λ- and Δ-[Co(chxn)$_3$]$^{3+}$ for which only either the C_2 or the C_3 association is sterically allowed. This is interpreted to mean that Λ-[Co-(sen)]$^{3+}$ adopts not only the C_3 but also the C_2 association mode in the interaction with the [Sb_2(d-tart)$_2$]$^{2-}$ ion, and that the CD change due to the C_3 association is cancelled out by the opposite CD change due to the concomitant C_2 association because of a small energy difference between the A_2 and E_a states for [Co-(N)$_6$]$^{3+}$-type complexes.[14] In fact, the steric repulsion imposed by Λ-[Co(sen)]$^{3+}$ on the chiral anion in the C_2 association is not so severe, since it is the same in nature as that imposed by Λ-[Co(sep)]$^{3+}$, which forms a relatively stable ion pair with the chiral anion in the C_2 association (see the left-hand models in Figures 2 and 5). Thus, it is fairly probable that Λ-[Co(sen)]$^{3+}$ adopts both the C_3 and C_2 modes in the interaction with the [Sb_2(d-tart)$_2$]$^{2-}$ ion. Then, the association constant K_A of Λ-[Co(sen)]$^{3+}$ derived from the usual analysis of the CD changes[6] is artificial and is almost meaningless, since two different association modes are present between Λ-[Co(sen)]$^{3+}$ and the [Sb_2(d-tart)$_2$]$^{2-}$ ion.[15] In fact, the α value of [Co(sen)]$^{3+}$ derived by HPLC is not as high as expected from the apparent K_A values of the two enantiomers.[6]

Similarly, relatively small DCD spectra observed for Λ- and Δ-[Co(en)$_3$]$^{3+}$ [6,10] point to the presence of the concomitant C_2 association even for [Co(en)$_3$]$^{3+}$,[16] though its chirality is recognized mainly by the C_3 association. Then, if [Co(en)$_3$]$^{3+}$ were forced to adopt the C_3 association mode only, its chirality would be recognized more effectively by [Sb_2(d-tart)$_2$]$^{2-}$ ion in solution.

One naive question arises as to why the C_2 association does not predominate in Δ-[Co(en)$_3$]$^{3+}$, but it does in Δ-[Co(sen)]$^{3+}$. This question is answered in terms of two structural differences between [Co(en)$_3$]$^{3+}$ and [Co(sen)]$^{3+}$. The first is that for the former complex, both sides of the C_3 axis are available for the C_3 hydrogen-bonding association with the [Sb_2(d-tart)$_2$]$^{2-}$ ion, while only one side is available for [Co(sen)]$^{3+}$. Therefore, [Co(en)$_3$]$^{3+}$ tends to adopt the C_3 mode more frequently than [Co(sen)]$^{3+}$. Another difference is that for [Co(sen)]$^{3+}$, a secondary amine proton is involved in the C_2 hydrogen-bonding interaction with the [Sb_2(d-tart)$_2$]$^{2-}$ ion, while it is not involved at all for [Co-(en)$_3$]$^{3+}$. Since a stronger hydrogen bond is formed with a secondary amine proton than with a primary one,[1,8,17] the stronger C_2 association with the [Sb_2(d-tart)$_2$]$^{2-}$ ion is naturally expected for [Co(sen)]$^{3+}$. By contrast, only primary amine protons are involved in the C_3 association for both complexes.

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(13) The difference CD (DCD) spectrum is defined in ref 6 as the CD spectrum of a fully ion-paired complex minus the CD spectrum of a free complex.
(14) Mason, S. F. *Molecular Optical Activity and Chiral Discrimination*; Cambridge University Press: Cambridge, England, 1982.
(15) Nakazawa, H.; Sakaguchi, U.; Yoneda, H. *J. Am. Chem. Soc.* **1982**, *104*, 3885-3891.
(16) Yoneda, H.; Miyoshi, K.; Matsukawa, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1969-1970.
(17) Searle, G. H. *Aust. J. Chem.* **1977**, *30*, 2625-2637.

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Reaction of the Antitumor Drug *cis*-Diamminedichloroplatinum(II) with the Trinucleotide d(GpApG): Identification of the Two Main Products and Kinetic Aspects of Their Formation

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The two main products (total yield over 95%) that are obtained in the reaction of *cis*-diamminedichloroplatinum(II) with the trinucleotide d(GpApG) have been characterized by high-field proton NMR (300 and 500 MHz; using the pH dependence of the chemical shift of the nonexchangeable base proton signals as well as homodecoupling and NOE techniques) and by the analysis of their enzymatically digested products with anion-exchange chromatography (FPLC) and platinum atomic absorption spectroscopy. The results indicate the formation of both *cis*-Pt(NH$_3$)$_2$[d(GpApG)-*N*7(1),*N*7(3)] (yield 80%) and *cis*-Pt(NH$_3$)$_2$[d-(GpApG)-*N*7(2),*N*7(3)] (yield 20%). No influence due to temperature or prior hydrolysis of *cis*-PtCl$_2$(NH$_3$)$_2$ was observed on the product ratio. The reaction of d(GpApG) with the monofunctional platinum compound [PtCl(dien)]Cl, mimicking the first binding step of *cis*-PtCl$_2$(NH$_3$)$_2$, provides more insight into the overall chelate formation. The observation that only an AG chelate but no GA chelate is formed agrees with other studies in which also only the AG chelate is reported. This can be explained by the geometry of the trinucleotide.

Introduction

The working mechanism of the widely applied antitumor drug *cis*-PtCl$_2$(NH$_3$)$_2$ (*cis*-diamminedichloroplatinum(II), abbreviated as *cis*-Pt) and structurally related compounds is only partly understood.[1] Nevertheless, many indications, mainly from biochemical studies, led to an almost general acceptance of the idea that the interaction of *cis*-Pt with cellular DNA is the most important event in the working mechanism of this drug.[1-3] This hypothesis focused many chemical, biochemical, and biophysical studies on the interaction of certain platinum coordination

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(1) Hacker, M. P., Douple, D. P., Krakoff, I. H., Eds. *Platinum Coordination Complexes in Cancer Chemotherapy*; Martinus Nijhoff: Boston, 1984.
(2) Pinto, A. L.; Lippard, S. J. *Biochim. Biophys. Acta* **1985**, *780*, 167.
(3) Roberts, J. J.; Thomson, A. J. *Prog. Nucleic Acid Res. Mol. Biol.* **1979**, *22*, 71.

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