Stereochemical Aspects of the Optical Resolution of *cis*(N)-$[Co(N)_2(O)_4]^-$ Complexes by Reversed-phase Ion-pair Chromatography with Cinchona Alkaloid Cations as the Ion-pairing Reagents[1)]

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The reversed-phase ion-pair chromatography with cinchona alkaloid cations as the ion-pairing reagents has been used to resolve optically several anionic complexes of the type *cis*(N)-$[Co(N)_2(O)_4]^-$. Complete optical resolution has been achieved for $[Co(edta)]^-$, *cis*-$[Co(ida)_2]^-$, $[Co(cydta)]^-$, $[Co(ox)_2(en)]^-$, and *cis*-*α*-$[Co(ox)(edda)]^-$ by quinine, quinidine, and cinchonidine but not by cinchonine, where edta=ethylenediaminetetraacetate, ida=iminodiacetate, cydta=*trans*-1,2-cyclohexanediaminetetraacetate, ox=oxalate, en=ethylenediamine, and edda=*N*,*N*′-ethylenediaminediacetate. The adjusted retention volumes have been measured for the enantiomers. From comparison of the retention volumes and separation factors obtained for the alkaloids and their derivatives, the mode of chiral discrimination has been proposed.

Cinchona alkaloids, *e.g.*, cinchonine, quinine, quinidine, and cinchonidine, are well-known resolving agents for the optical resolution of anionic metal complexes. The cations of these alkaloids are soluble in water, yet bear a hydrophobic character, which suggests these cations to be likely candidates for good ion-pairing reagents in the reversed-phase ion-pair chromatography.[2)] Recently, Yamazaki[3)] has exploited this technique for the optical resolution of several anionic complexes. Using the cation of quinine as the ion-pairing reagent, complete optical resolution has been achieved for $[Co(edta)]^-$, *cis*-$[Co(ida)_2]^-$, $[Co(ox)_2(en)]^{-1}$, and *cis*-*α*-$[Co(Cl)_2(edda)]^-$, where edta=ethylenediaminetetraacetate, ida=iminodiacetate, ox=oxalate, en=ethylenediamine, and edda=*N*,*N*′-ethylenediaminediacetate. The mechanism of optical resolution has been explained by assuming that both dynamic ion-exchange and ion-pairing are important. The stereochemical aspects has not, however, been considered.

In this work, we have applied the reversed-phase ion-pair chromatography with several cinchona alkaloids as the ion-pairing reagents to the optical resolution of anionic complexes of the type *cis*(N)-$[Co(N)_2(O)_4]^-$. Figure 1 shows the schematic illustration of the structure of the complexes examined in this work. The structure of the cinchona alkaloids used here is depicted in Fig. 2, where the atom numbering scheme is also indicated. The adjusted retention volume has been measured for each enantiomer over a range of pH values. From comparison of these retention volumes obtained for these alkaloids and their derivatives, the stereochemical aspects of the mechanism of optical resolution have been discussed.

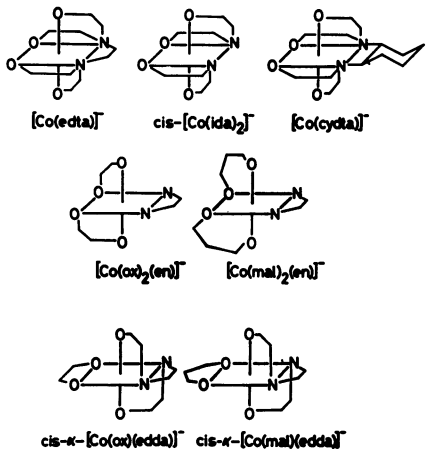

Fig. 1. The structure of the complexes investigated in this work. The figure is drawn for the *Λ* absolute configuration.

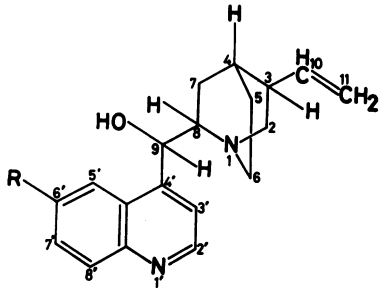

Fig. 2. The structure of the alkaloids used in this work. Cinchonine ((8*R*, 9*S*), R=H); cinchonidine ((8*S*, 9*R*), R=H); quinine ((8*S*, 9*R*), R=OCH_3); quinidine ((8*R*, 9*S*), R=OCH_3). 1-Methylquininium chloride and 9-acetoxyquinine were also employed.

Experimental

Materials. The anionic complexes used in this work were K[Co(edta)],[4)] *cis*-K[Co(ida)$_2$],[5)] K[Co(cydta)](cydta=*trans*-1,2-cyclohexanediaminetetraacetate),[6)] Na[Co(ox)$_2$(en)],[7)] Na[Co(mal)$_2$(en)] (mal=malonate),[8)] *cis*-*α*-K[Co(ox)(edda)],[9)] *cis*-*α*-K[Co(mal)(edda)].[10)] All these complexes were prepared by the literature methods. The absolute configurations of the enantiomers of these complexes were assigned previously.

The following cinchona alkaloids were used as the ion-pairing reagents; (+)-(8*R*, 9*S*)-cinchonine, (−)-(8*S*, 9*R*)-cinchonidine, (−)-(8*S*, 9*R*)-quinine, (+)-(8*R*, 9*S*)-quinidine, 1-methylquininium chloride, and 9-acetoxyquinine. The last two alkaloids were prepared by the literature methods[11,12)] and identified by ^{1}H NMR and chemical analysis. The other alkaloids were obtained from Wako Pure Chemical Industries, Ltd. and used without further purification.

The column packing used in this work was LS-410.ODS.SIL. (Toyo Soda Manufacturing Co., Ltd.), which carries linear

long-chain alkyl groups (octadecyl groups) covalently bonded to the surface of silica gel.

Chromatographic Experiments. A column (4×300 mm) packed with LS-410.ODS.SIL. was equilibrated with an eluent, which was a 0.2 mol dm^{-3} sodium acetate/acetic acid buffered solution containing 0.01 mol dm^{-3} ion-pairing reagent. An aqueous solution of a racemic complex (0.1 mol dm^{-3}) and bis(ethylenediamine)copper(II) chloride (0.1 mol dm^{-3}), which was used as a marker for void volume measurements, was injected by a syringe on top of the column and eluted at an elution rate of 0.50 cm^3/min. The eluate containing an optically resolved anionic complex was fractionally collected and the circular dichroism (CD) spectra were measured to assign the absolute configuration of the resolved complex anion. Interference in the CD spectra due to chiral ion-pairing reagents, an effect called induced CD,[13] was not observed. The pH of the buffered solution was changed from 4.28 to 6.12.

The chromatographic apparatus used here was the same as in previous studies.[3,14] The CD spectra were obtained on a JASCO J-40CS recording spectropolarimeter.

Results and Discussion

Figure 3 shows the elution curves of [Co(edta)]$^-$, [Co(ox)$_2$(en)]$^-$, and *cis*-*α*-[Co(ox)(edda)]$^-$, all obtained with quinine at pH 4.28. The [Co(edta)]$^-$ and [Co(ox)$_2$(en)]$^-$ ions are completely resolved with separation factors of 1.14 and 1.10, respectively. As a rough measure of complete resolution, we may use the separation factor greater than about 1.07 in our experiments. Tables 1 to 4 summarize the results obtained for quinine, quinidine, cinchonidine, and cinchonine, respectively, in terms of the later-eluted enantiomers, their retention volumes, and the separation factors. From these tables, the following points are noted. (i) [Co(edta)]$^-$, *cis*-[Co(ida)$_2$]$^-$, [Co(cydta)]$^-$, and [Co(ox)$_2$(en)]$^-$ are completely resolved by any one of quinine, quinidine, and cinchonidine. (ii) [Co(mal)$_2$(en)]$^-$ and *cis*-*α*-[Co(mal)(edda)]$^-$ can not be resolved completely by any alkaloids. (iii) *cis*-*α*-[Co(ox)(edda)]$^-$ can be resolved completely only by quinidine or cinchonidine. (iv) Cinchonine is ineffective in resolving all the complexes and the retention volumes with this alkaloid are much smaller than those with the other alkaloids for all the complexes.

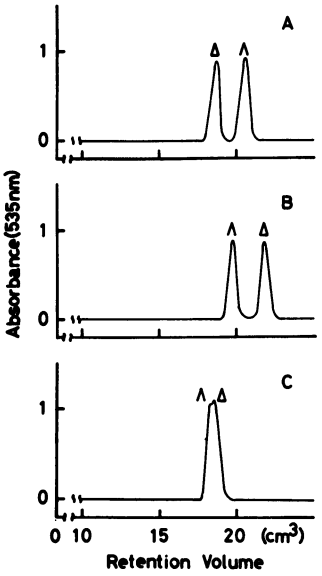

Fig. 3. The elution curves of (A) [Co(edta)]$^-$, (B)[Co(ox)$_2$(en)]$^-$, and (C) *cis*-*α*-[Co(ox)(edda)]$^-$, obtained with quinine at pH 4.28.

1. Analysis of Data. In the reversed-phase ion-pair chromatography, the enantiomer that associates more favorably with the ion-pairing reagent is better adsorbed to the hydrophobic stationary phase and eluted later.[2,3] Since protonation of all the alkaloids except 1-methylquininium chloride has been reported[15] to take place at pH 9.70 to 10.03 on the quinuclidine N(1) nitrogen and at pH 5.07 to 5.85 on the quinoline N(1′) nitrogen, the ion-pairing reagents exist as monopositive or dipositive cations in the pH range studied (pH 4.3 to 6.1). Thus, the ion association of the anionic complex ions with the alkaloid cations will take place mainly *via* electrostatic forces. This reasoning has been substantiated clearly by examining the pH dependence of the retention volumes.

(*a*) *Effect of pH*: For all the complex/alkaloid combinations, the retention volume increases substantially as the pH of the eluent solution is lowered beyond the point where the quinoline N(1′) protonation occurs. This is due to an increase in the concentration of alkaloid dications rather than monocations and hence to an increase in the concentration of ion-pairs. The effect of solution pH on the separation factor is, however, rather small, which indicates that the association of metal complex ions to the protonated N(1) nitrogen is effective in chiral discrimination but that to the quinoline N(1′) nitrogen is not. The only mode of association that is effective for chiral discrimination is, therefore, at the protonated N(1) nitrogen. One peculiar result may be noted in Table 4 for the combinations cinchonine/[Co(edta)]$^-$ and cinchonine/[Co(mal)$_2$(en)]$^-$. For these two combinations, the elution order of enantiomers is inverted by the pH of the eluent. Since these combinations gave only single elution curves and the degree of resolution was very low at any pH, no further investigation on this point was attempted.

(*b*) *Effect of C(8) and C(9) Configurations*: From Tables 1 to 4, it can be seen that the enantiomer eluted faster by the (8*R*,9*S*) alkaloids (cinchonine and quinidine) is eluted later by the (8*S*,9*R*) alkaloids (cinchonidine and quinine). Note here that the latter alkaloids are not the mirror images of the former ones owing to the presence of four asymmetric centers, C(3), C(4), C(8), and C(9).[16] Further, the C(8) and C(9) centers are close to the N(1) nitrogen spatially (see below), this result is considered to be consistent with the inference that the association of complex anions with the protonated N(1) nitrogen is essential in chiral discrimination. Broadly speaking, the (8*S*,9*R*) alkaloids yielded larger separation factors than the (8*R*,9*S*) alkaloids but the reason for this trend is not clear as yet.

(*c*) *Effect of C(6′) Methoxyl Group*: Another point to be noted in Tables 1 to 4 is that the alkaloids with the C(6′) methoxyl group, quinine and quinidine, gave rise to greater retention volumes and separation factors than the alkaloids without the methoxyl group, cinchoni-

Table 1. The absolute configuration of the later-eluted enantiomer, its retention volume (V), and the separation factor (α), obtained with quinine

Complex	pH 4.28			pH 4.93			pH 5.48			pH 6.02		
		V/cm³	α		V/cm³	α		V/cm³	α		V/cm³	α
[Co(edta)]⁻	Λ	21.70	1.14	Λ	13.20	1.10	Λ	9.60	1.10	Λ	8.80	1.09
cis-[Co(ida)$_2$]⁻	Λ	24.80	1.21	Λ	16.10	1.22	Λ	11.60	1.20	Λ	10.20	1.15
[Co(cydta)]⁻	Λ	17.50	1.08	Λ	10.70	1.08	Λ	7.70	1.08	Λ	7.10	1.07
[Co(ox)$_2$(en)]⁻	Δ	22.90	1.10	Δ	13.80	1.14	Δ	10.80	1.09	Δ	9.90	1.09
[Co(mal)$_2$(en)]⁻	Λ	10.10	1.0[a]	b)	6.40	1.0[a]	b)	5.00	1.0[a]	b)	4.80	1.0[a]
cis-α-[Co(ox)(edda)]⁻	Δ	19.60	1.02	Δ	12.40	1.0[a]	Δ	10.10	1.0[a]	Δ	8.80	1.0[a]
cis-α-[Co(mal)(edda)]⁻	Λ	7.40	1.0[a]	b)	4.70	1.0[a]	b)	3.70	1.0[a]	b)	3.50	1.0[a]

a) Single elution curve. b) The absolute configuration of the later-eluted enantiomer could not be determined owing to very low degree of optical resolution.

Table 2. The absolute configuration of the later-eluted enantiomer, its retention volume (V), and the separation factor (α), obtained with quinidine

Complex	pH 4.30			pH 4.97			pH 5.53			pH 6.02		
		V/cm³	α		V/cm³	α		V/cm³	α		V/cm³	α
[Co(edta)]⁻	Δ	22.90	1.07	Δ	14.30	1.07	Δ	10.80	1.07	Δ	9.40	1.06
cis-[Co(ida)$_2$]⁻	Δ	29.30	1.21	Δ	19.30	1.21	Δ	14.50	1.21	Δ	12.30	1.22
[Co(cydta)]⁻	Δ	19.90	1.05	Δ	12.10	1.05	Δ	9.10	1.05	Δ	7.90	1.04
[Co(ox)$_2$(en)]⁻	Λ	23.10	1.13	Λ	15.60	1.15	Λ	11.40	1.11	Λ	9.80	1.10
[Co(mal)$_2$(en)]⁻	Δ	10.60	1.0[a]	Δ	6.70	1.0[a]	Δ	4.90	1.0[a]	Δ	4.60	1.0[a]
cis-α-[Co(ox)(edda)]⁻	Λ	18.60	1.09	Λ	13.40	1.12	Λ	9.65	1.11	Λ	8.70	1.12
cis-α-[Co (mal) (edda)]⁻	Δ	9.80	1.0[a]	b)	6.10	1.0[a]	b)	5.10	1.0[a]	b)	4.40	1.0[a]

a) Single elution curve. b) The absolute configuration of the later-eluted enantiomer could not be determined owing to very low degree of optical resolution.

Table 3. The absolute configuration of the later-eluted enantiomer, its retention volume (V), and the separation factor (α), obtained with cinchonidine

Complex	pH 4.28			pH 4.93			pH 5.30			pH 6.02		
		V/cm³	α		V/cm³	α		V/cm³	α		V/cm³	α
[Co(edta)]⁻	Λ	20.70	1.08	Λ	13.60	1.10	Λ	9.50	1.07	Λ	8.65	1.06
cis-[Co(ida)$_2$]⁻	Λ	25.60	1.15	Λ	18.50	1.15	Λ	11.35	1.12	Λ	10.45	1.12
[Co(cydta)]⁻	Λ	17.55	1.06	Λ	11.10	1.06	Λ	7.90	1.06	Λ	7.15	1.05
[Co(ox)$_2$(en)]⁻	Δ	16.90	1.07	Δ	10.65	1.06	Δ	7.95	1.05	Δ	7.10	1.05
[Co(mal)$_2$(en)]⁻	Λ	9.80	1.0[a]	Λ	6.25	1.0[a]	Λ	4.70	1.0[a]	Λ	4.40	1.0[a]
cis-α-[Co(ox)(edda)]⁻	Δ	16.85	1.07	Δ	10.95	1.06	Δ	8.00	1.06	Δ	7.30	1.06
cis-α-[Co(mal)(edda)]⁻	b)	7.55	1.0[a]	b)	5.10	1.0[a]	b)	3.90	1.0[a]	b)	3.55	1.0[a]

a) Single elution curve. b) The absolute configuration of the later-eluted enantiomer could not be determined owing to very low degree of optical resolution.

Table 4. The absolute configuration of the later-eluted enantiomer, its retention volume (V), and the separation factor (α), obtained with cinchonine

Complex	pH 3.63			pH 4.46			pH 5.76			pH 6.12		
		V/cm³	α		V/cm³	α		V/cm³	α		V/cm³	α
[Co(edta)]⁻	Δ	5.55	1.0[a]	b)	4.40	1.0[a]	Λ	4.10	1.0[a]	Λ	4.10	1.0[a]
cis-[Co(ida)$_2$]⁻	Δ	5.95	1.04	Δ	4.75	1.03	Δ	4.50	1.0[a]	Δ	4.50	1.0[a]
[Co(cydta)]⁻	Δ	4.40	1.0[a]	Δ	3.40	1.0[a]	Δ	3.10	1.0[a]	Δ	3.10	1.0[a]
[Co(ox)$_2$(en)]⁻	Λ	4.75	1.0[a]	Λ	3.80	1.0[a]	Λ	3.60	1.0[a]	Λ	3.60	1.0[a]
[Co(mal)$_2$(en)]⁻	Δ	4.10	1.0[a]	Δ	3.20	1.0[a]	Λ	2.95	1.0[a]	Λ	2.95	1.0[a]
cis-α-[Co(ox)(edda)]⁻	Λ	4.20	1.0[a]	Λ	3.50	1.0[a]	Λ	3.70	1.0[a]	Λ	3.70	1.0[a]
cis-α-[Co(mal)(edda)]⁻	b)	2.40	1.0[a]	b)	2.40	1.0[a]	b)	2.10	1.0[a]	b)	2.10	1.0[a]

a) Single elution curve. b) The absolute configuration of the later-eluted enantiomer could not be determined owing to very low degree of optical resolution.

Table 5. The absolute configuration of the later-eluted enantiomer, its retention volume (V/cm^3), and the separation factor(α), obtained with 1-methylquininium chloride (1-MeQ) and 9-*O*-acetylquinine (9-*O*-acetylQ)

Complex	1-MeQ (pH 4.78)			9-*O*-AcetylQ (pH 4.90)		
		V/cm^3	α		V/cm^3	α
$[Co(edta)]^-$	Λ	13.10	1.03	Λ	10.10	1.10
cis-$[Coi(da)_2]^-$	Λ	12.50	1.05	Λ	11.50	1.28
$[Co(cydta)]^-$	Λ	10.60	1.01	Λ	8.10	1.08
$[Co(ox)_2(en)]^-$	Δ	8.80	1.0[a]	Δ	16.40	1.24
$[Co(mal)_2(en)]^-$	Λ	6.10	1.0[a]	Λ	5.30	1.0[a]
cis-α-$[Co(ox)(edda)]^-$	Δ	10.70	1.10	Δ	11.60	1.15
cis-α-$[Co(mal)(edda)]^-$	Λ	4.50	1.0[a]	Λ	3.90	1.0[a]

a) Single elution curve.

dine and cinchonine (see also Fig. 2). This result indicates that the association with complex anions and also the chiral discrimination are enhanced by the presence of the methoxyl group, which is in turn consistent with the postulated N(1) association, because the C(6′) methoxyl group is spatially in rather close proximity to the N(1) center (see below).

(d) Effect of N(1)-Methylation of Quinine: Now that the association to the protonated N(1) center is seen to play a key role in chiral discrimination, it would be expected that the methylation at this nitrogen reduces the degree of ion association and also the degree of chiral discrimination. Thus, 1-methylquininium cation was employed to measure the retention volumes and separation factors. The results are given in Table 5. The separation factors for all but *cis*-α-$[Co(ox)(edda)]^-$ are in fact reduced greatly compared with those obtained with quinine, as expected. The exceptional behavior of *cis*-α-$[Co(ox)(edda)]^-$ has not been properly explained.

(e) Effect of C(9)-OH Acetylation: The C(9)-OH group is spatially close to the N(1) center (see below), and might be thought to take part in chiral discrimination through, *e.g.*, hydrogen bonding to an oxygen atom of complex anions. This possibility may be tested by measuring retention volumes or separation factors using an acetylated (at C(9)-OH) alkaloid. Thus, 9-*O*-acetylquinine was prepared and measurements were made similarly. The results are given in Table 5. The separation factors with 9-*O*-acetylquinine will be seen to be better somewhat than those with quinine itself. Though this result does not support nor deny that the postulated hydrogen bond with C(9)-OH group takes part in chiral discrimination, this result suggests that the C(9)-OH group is indeed involved in chiral discrimination in some ways.

2. Mode of Chiral Discrimination. Taken all the above experimental results together, we may envisage the mode of association which is effective for chiral discrimination. Before the presentation of the association model, it will be pertinent to see the structure of the alkaloids. The structures of quinidine,[17] quinidinium monocation,[18] cinchonine,[19] and cinchoninium dication[20] have been determined previously by three-

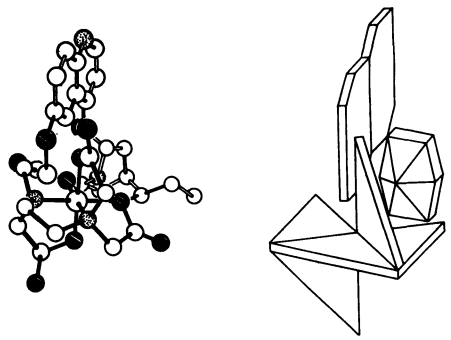

Fig. 4. (a) Proposed mode of chiral discrimination between the quininium cation and Λ-$[Co(edta)]^-$. The dotted and hatched circles represent nitrogen and oxygen atoms, respectively. (b) Simplified version of (a).

dimensional X-ray analysis. Except for the quinidinium salt of (−)-1′,3-dimethyl-1-ferrocenecarboxylic acid, where the conformation about the C(8)-C(9) bond is constrained severely by strong hydrogen bonds between the two carboxyl oxygens and N(1) and C(9)-OH hydrogens,[18] the conformations about C(8)-C(9) and C(9)-C(16) assume surprisingly the same ones (to within $\pm 3.5°$) in all these crystals. This result, as well as considerations using molecular models, suggests strongly that the conformation about these bonds in solution should be rather similar to that in the solid state. Thus, we assume that all the alkaloid cations used in this work have the same conformation in solution (but, of course, not the same absolute configuration); the dihedral angles defined by C(4′)-C(9)-C(8)-N(1) and O-C(9)-C(4′)-C(3′) bonds are about 163° and 22°, respectively.

(a) $[Co(edta)]^-$, cis-$[Co(ida)_2]^-$, and $[Co(cydta)]^-$: The mode of chiral discrimination between the quininium cation and Λ-$[Co(edta)]^-$, as inferred from the results described above, is shown in Fig. 4(a), where hydrogen atoms are omitted for clarity. In Fig. 4(b) is illustrated the mode of fitting of both ions in a very simplified form. It will be seen that the Λ-$[Co(edta)]^-$ ion can fit very nicely with the cation. The Δ-$[Co(edta)]^-$ ion can not fit nicely because the sense of handedness of two R rings is now reversed to that depicted in Fig. 4 and severe steric hindrance with the quinoline ring (including the C(6′) methoxyl group) is anticipated. Thus, in the combination of the quininium cation/$[Co(edta)]^-$, one R ring may be considered as serving as a chiral discriminator. In Fig. 4, the C(6′) methoxyl group may be seen to be useful in chiral discrimination. This mode of association is consistent with the observation that the complexes $[Co(edta)]^-$, *cis*-$[Co(ida)_2]^-$, and $[Co(cydta)]^-$ exhibited the same elution order of enantiomers with similar separation factors, because in this model the substituents ($-CH_2-CH_2-$, H–, and cyclohexane ring) at coordinated nitrogen atoms of complexes are farthest apart from the alkaloid cation.

In the combination with the (8*R*,9*S*) epimers (quinidine and cinchonine) instead of the (8*S*,9*R*) epimers like equinine and cinchonidine, the Δ enantiomers of $[Co(edta)]^-$, *cis*-$[Co(ida)_2]^-$, and $[Co(cydta)]^-$ are

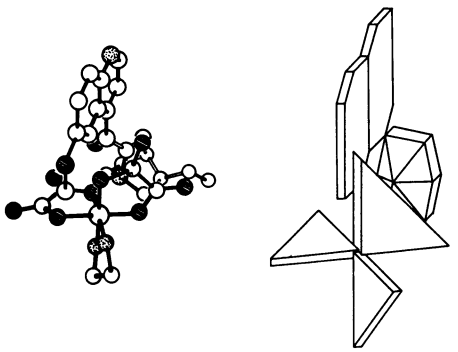

Fig. 5. (a) Proposed mode of chiral discrimination between the quininium cation and Λ-[Co(ox)$_2$(en)]$^-$. The dotted and hatched circles represent nitrogen and oxygen atoms, respectively. (b) Simplified version of (a).

preferred, as opposed to the Λ enantiomer depicted in Fig. 4. If we note that the immediate environment about the N(1) center of these (8*R*,9*S*) epimers is rather similar to the mirror image of the respective (8*S*,9*R*) epimers, this preference is easily understood.

(b) [Co(ox)$_2$(en)]$^-$ and [Co(mal)$_2$(en)]$^-$: Figure 5 illustrates the proposed mode of chiral discrimination between the quininium cation and Λ-[Co(ox)$_2$(en)]$^-$ which is preferred by the cation. The N(1) positive center of the alkaloid cation approaches the complex anion from the side of three anionic oxygen atoms. It will be seen that both ions fit very well from both electrostatic and spatial points of view. If the opposite enantiomer is combined with the cation, a severe steric repulsion is clearly expected. Thus, in the combination of quininium cation/[Co(ox)$_2$(en)]$^-$, the interleaving chelate ring appears to play the role of chiral discriminator.

The [Co(mal)$_2$(en)]$^-$ ion could be resolved very little by any ion-pairing reagents, which makes a sharp contrast to the case of [Co(ox)$_2$(en)]$^-$, where complete optical resolution was attained for all the alkaloids except cinchonine. (Cinchonine was ineffective in the optical resolution of all the complexes investigated, as noted above). Further, the elution order of enantiomers of [Co(mal)$_2$(en)]$^-$ is opposite to that of [Co(ox)$_2$(en)]$^-$ for any alkaloids and at any pH (see, Tables 1 to 5). Two possibilities could be considered as the reason for [Co(mal)$_2$(en)]$^-$ being not resolved. One is that since the malonate chelate ring is more bulky than the oxalate ring and flexible to such an extent that the chelate ring is interconverting rapidly among several conformers,[21] [Co(mal)$_2$(en)]$^-$ can not make a so close contact or can not make a so compact fit to the alkaloids as [Co(ox)$_2$(en)]$^-$ does. The other possibility is that the [Co(mal)$_2$(en)]$^-$ ion is hydrated to a greater degree than [Co(ox)$_2$(en)]$^-$ and its association with hydrophobic alkaloid cations is proportionately weaker. The latter possibility gains some support from the the fact that the retention volume of [Co(mal)$_2$(en)]$^-$ is substantially smaller than that of [Co(ox)$_2$(en)]$^-$ at any pH and for all the alkaloids. A result pointing to greater hydration of [Co(mal)$_2$(en)]$^-$ than [Co(ox)$_2$(en)]$^-$ has been found recently in ion-exchange chromatographic experiments.[14] Further, *cis*-*α*-[Co(ox)(edda)]$^-$ and *cis*-*α*-[Co(mal)(edda)]$^-$ exhibited a similar trend in retention volumes (see Tables 1 to 5), which seems to favor the view that the cobalt(III)-malonate ring is more hydrophilic and hydrated more extensively than the cobalt(III)-oxalate counterpart.

(c) cis-α-[Co(ox)(edda)]$^-$ and cis-α-[Co(mal)(edda)]$^-$: The *cis*-*α*-[Co(ox)(edda)]$^-$ ion could be resolved completely by quinidine and to a lesser extent by cinchonidine but not by quinine and cinchonine. The separation factors of this ion are generally smaller than those of [Co(edta)]$^-$, *cis*-[Co(ida)$_2$]$^-$, [Co(cydta)]$^-$, and [Co(ox)$_2$(en)]$^-$ for any alkaloids and at any pH. This lower degree of chiral discrimination of *cis*-*α*-[Co(ox)(edda)]$^-$ seems to preclude the proposal of any plausible mode of chiral discrimination for this ion. The distinctive behavior between *cis*-*α*-[Co(ox)(edda)]$^-$ and *cis*-*α*-[Co(mal)(edda)]$^-$ is noted above. As for [Co(ox)$_2$(en)]$^-$ and [Co(mal)$_2$(en)]$^-$, *cis*-*α*-[Co(ox)(edda)]$^-$ and *cis*-*α*-[Co(mal)(edda)]$^-$ appear to show opposite elution orders of enantiomers.

Finally, it will be interesting to compare the present results with the results of the Pfeiffer effect observed[22] for [Cr(ox)$_3$]$^{3-}$, [Cr(ox)$_2$(phen)]$^-$, and [Cr(ox)$_2$(bpy)]$^-$ with the monocations of the cinchona alkaloids as the environment substances, where phen=1,10-phenanthroline and bpy=2,2′-bipyridine. As for the present complexes, the [Cr(ox)$_3$]$^{3-}$ ion was assumed to approach the N(1) positive center of the alkaloids *via* electrostatic forces. For [Cr(ox)$_2$(phen)]$^-$, both electristatic forces (between the oxalate ligands and the N(1) center) and hydrophobic attractive forces (between the phen ligand and the quinolyl ring) were invoked. The mode of chiral discrimination of [Cr(ox)$_2$(phen)]$^-$ was thus utterly different from any of the chiral discrimination modes proposed here.[23]

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References

1) Part X of "Chromatographic Study of Optical Resolution." Part IX: S. Yamazaki and H. Yoneda, *J. Chromatogr.*, **235**, 289 (1982).

2) For this chromatographic technique, see, *e.g.*; a) B. A. Bidlingmeyer, *J. Chromatogr. Sci.*, **18**, 525 (1980); b) W. R. Melander, K. Kalghatgi, and C. Horvath, *J. Chromatogr.*, **201**, 201 (1980); c) W. R. Melander and C. Horvath, *ibid.*, **201**, 211 (1980); d) C. Peterson and G. Schill, *ibid.*, **204**, 179 (1981), and references cited therein.

3) S. Yamazaki, Ph. D. Thesis, Hiroshima Univ., 1982.

4) a) Synthesis; F. P. Dwyer, E. Gyarfas, and D. Meller, *J. Phys. Chem.*, **59**, 296 (1955); b) CD; C. W. Van Saun and B. E. Douglas, *Inorg. Chem.*, **8**, 1145 (1969).

5) a) Synthesis; J. Hidaka, Y. Shimura, and R. Tsuchida, *Bull. Chem. Soc. Jpn.*, **35**, 567 (1962); b) CD; Ref. 4(b).

6) a) Synthesis; F. P. Dwyer and F. L. Garvan, *J. Am. Chem. Soc.*, **83**, 2610 (1961); b) CD; B. J. Brennan, K. Igi, and B. E. Douglas, *J. Coord. Chem.*, **4**, 19 (1974).

7) a) Synthesis; F. P. Dwyer, I. K. Reid, and F. L. Garvan, *J. Am. Chem. Soc.*, **83**, 1285 (1961); b) CD; B. E. Douglas, R. A. Harnes, and J. B. Brushmiller, *Inorg. Chem.*, **2**, 1194 (1963).

8) a) Synthesis; Ref. 7a; b) CD; Ref. 7b.
9) a) Synthesis; C. W. Van Saun and B. E. Douglas, *Inorg. Chem.*, **8**, 115 (1969); b) CD; C. W. Maricondi and B. E. Douglas, *Inorg. Chem.*, **11**, 688 (1972).
10) a) Synthesis; Ref. 9a; b) CD; W. T. Jordan and J. I. Legg, *Inorg. Chem.*, **13**, 955 (1974).
11) R. T. Major and J. Finkelstein, *J. Am. Chem. Soc.*, **63**, 1368 (1941).
12) G. R. Pettit and S. K. Gupta, *J. Chem. Soc.*, **C**, **1968**, 1208.
13) See, *e.g.*; U, Sakaguchi, H. Nakazawa, K. Sakai, and H. Yoneda, *Bull. Chem. Soc. Jpn.*, **55**, 1862 (1982), and references therein.
14) a) U. Sakaguchi, I. Yamamoto, S. Izumoto, and H. Yoneda, *Bull. Chem. Soc. Jpn.*, **56**, 153 (1983); b) *ibid.*, in press.
15) The protonation occurs at the following pH; 5.85 and 9.92 for cinchonine, 5.80 and 10.03 for cinchonidine, 5.07 and 9.70 for quinine, and 5.40 and 10.00 for quinidine.
16) All the alkaloids used here have the common (3*R*, 4*S*) absolute configuration.
17) R. Doherty, W. R. Benson, M. Maienthal, and J. McD. Stewart, *J. Pharm. Sci.*, **67**, 1698 (1978).
18) O. L. Carter, A. T. McPhail, G. A. Sim, *J. Chem. Soc.*, **A**, **1967**, 365.
19) B. Oleksyn, L. Lebioda, M. Ciechanowicz-Rutkowska, *Acta Crystallogr., Sect. B*, **35**, 440 (1979).
20) B. J. Oleksyn, K. M. Stadnicka, and S. A. Hodorowicz, *Acta Crystallogr., Sect. B*, **34**, 811 (1978).
21) U. Sakaguchi, K. Morito, and H. Yoneda, *Bull. Chem. Soc. Jpn.*, **53**, 2821 (1980), and references cited therein.
22) a) K. Miyoshi, Y. Matsumoto, and H. Yoneda, *Chem. Lett.*, **1980**, 1319; b) H. Ohbo, H. Okazaki, K. Miyoshi, and H. Yoneda, submitted.
23) Additionally, we found that the *cis*-*a*-$[Co(NO_2)_2(edda)]^-$ ion can be resolved completely by cinchonidine and partially by quinine and quinidine but not by cinchonine. Since this ion does not belong to the *cis*(N)-$[Co(N)_2(O)_4]^-$ type, the data for this ion were not included in this paper.