Chromatographic Study of Optical Resolution. XII. Optical Resolution of Bis(oxalato)(1,10-phenanthroline)cobaltate(III) and Its Related Anion Complexes with Cinchona Alkaloid Cations as Eluent

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Ion-exchange chromatography was applied to the optical resolution of three anion complexes, $[Co(ox)_2(phen)]^-$, $[Co(ox)_2(bpy)]^-$, and $[Co(ox)_2(en)]^-$ (ox=oxalate anion, phen=1,10-phenanthroline, bpy=2,2′-bipyridine, and en=ethylenediamine) using as a chiral eluent aqueous solutions of various cinchona alkaloid cations, *i.e.*, cinchoninium, cinchonidinium, quinidinium, and quininium ions, and their 9-acetoxy and N^1-methyl derivatives. Fairly good resolution was achieved for the first two complexes with the 9-acetoxy derivatives as eluent, but no practical resolution was attained for $[Co(ox)_2(en)]^-$. Retention volumes V_R determined and separation factors α estimated from V_R revealed that both of the HO-C(9) and H-N(1)$^+$ groups of each alkaloid participate in the interaction with the complex, and that the α value is increased upon acetylation of the OH group with the elution order reversed. These observations were interpreted in terms of two concomitant interaction modes in which the HO-C(9) and H-N(1)$^+$ groups are hydrogen-bonded to the ox ligand(s) and the quinoline ring is stacked with the phen or bpy ligand of the anion complex.

Many examples of successful optical resolution by chromatography have been reported for cationic metal complexes, and the mechanism by which chiral discrimination is effected there have been discussed in detail.[1,2] On the other hand, only few anionic metal complexes have been subjected to chromatographic resolution simply because suitable cationic resolving agents are not available. Cinchona alkaloids, *i.e.*, (8*R*,9*S*)-cinchonine, (8*S*,9*R*)-cinchonidine, (8*R*,9*S*)-quinidine, and (8*S*,9*R*)-quinine, have long been used as resolving agents in optical resolution of several anionic complexes *via* diastereomer formation. Thus, these chiral alkaloid cations may potentially serve as eluent in chromatographic resolution of anionic complexes. In fact, Yamazaki[3] succeeded in complete resolution of $[Co(edta)]^-$ and *cis*-$[Co(ida)_2]^-$ (edta and ida=ethylenediaminetetraacetate and iminodiacetate anions, respectively) using quininium ion as an ion-pairing reagent in reversed-phase chromatography, and Izumoto *et al.*[4] extended this technique to the optical resolution of several anion complexes of the type *cis*-$[Co(O)_4(N)_2]^-$. However, these anion complexes are not easily resolved by normal-phase ion-exchange chromatography even with cinchona alkaloid cations used as eluent. This is probably because these alkaloids exhibit no strong tendency to associate with common anionic complexes unless they are introduced into some special environment, *e.g.*, hydrophobic environment as in reversed-phase chromatography.

In our previous paper,[5] it was reported that monoprotonated species of cinchona alkaloids bear a strong ability to displace the chiral equilibrium between two enantiomers of a labile metal complex, $[Cr(ox)_2(phen)]^-$ (ox=oxalate anion and phen=1,10-phenanthroline) in aqueous solution. This observation suggests that cinchona alkaloid cations associate appreciably with $[Cr(ox)_2(phen)]^-$ and impose their spacial demands on the two enantiomers differently. Therefore, the corresponding inert cobalt(III) complex is expected to be resolved by usual ion-exchange chromatography if these alkaloids are used as eluent. With this expectation in mind, an attempt was made to resolve the three anion complexes, $[Co(ox)_2(phen)]^-$, $[Co(ox)_2(bpy)]^-$, and $[Co(ox)_2(en)]^-$, (bpy=bipyridine and en=ethylenediamine) with various cinchona alkaloid cations employed as a chiral eluent, and their stereoselective interactions are discussed in detail.

Experimental

Materials. $Na[Co(ox)_2(en)]\cdot H_2O$[6] and $K[Co(ox)_2(bpy)]\cdot 3H_2O$[7] were prepared as described in the literature. $K[Co(ox)_2(phen)]\cdot 4H_2O$ was derived from $[Co(ox)(phen)_2]\cdot[Co(ox)_2(phen)]\cdot 3H_2O$[7] at room temperature according to the procedures applied to the corresponding bpy complex.[7,8] Absolute configurations of these complexes were assigned previously. 9-Acetoxy and N^1-methyl derivatives of various cinchona alkaloids used as eluent were obtained as monohydrochlorides and monochlorides, respectively, according to the procedures presented earlier.[4,8] They were found to be satisfactorily pure by elemental analysis. Unmodified cinchona alkaloids commercially available were also converted to monohydrochlorides to prepare their aqueous solutions. The anion-exchange resin used was IEX-520 QAE-SIL (Toyo Soda Manufacturing Co. Ltd.), which carries quaternary ammonium groups covalently bonded to the surface of silica gel.

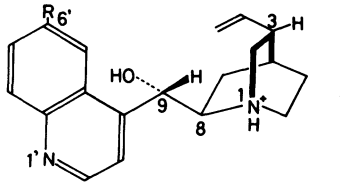
Chromatography. Columns (4×150 mm) were packed with IEX-520 QAE-SIL and each was equilibrated with an aqueous eluent containing one of various cinchona alkaloids as monohydrochloride or monochloride salt at a concentration of 0.01 mol/dm^3. Each eluent with pH adjusted to 4.0 with acetic acid, was degassed by an

aspirator before use. An aqueous solution (20 μl) of a racemic complex (0.1 mol/dm³) containing bis(ethylenediamine)copper(II) chloride (0.05 mol/dm³) as a marker for void volume measurement, was injected by a syringe on the top of the column and was eluted at an elution rate of 1.0 cm³/min. The eluate was guided to a flow cell to detect the complex at 535 nm with a Shimadzu UV-140 spectrophotometer. The adjusted retention volumes V_R of both enantiomers were estimated from the elution curves thus recorded and were found to be reproducible to within at least ±0.2 cm³ for $[Co(ox)_2(phen)]^-$ and $[Co(ox)_2(bpy)]^-$ and ±0.1 cm³ for $[Co(ox)_2(en)]^-$. The elution order was determined by the CD spectra of fractionally collected eluates. Each complex was also eluted with an aqueous NaCl solution (0.01 mol/dm³) to estimate its intrinsic affinity for the resin. The chromatographic apparatus used in this study was the same as in our previous works[9] except that a Jasco BIP-1 pump for HPLC was newly employed. The CD spectra were recorded on a Jasco J-40CS spectropolarimeter at ambient temperature.

Results and Discussion

Elution Curves. Figure 1 shows the structures of the cinchona alkaloids used as eluents in the present study. In addition to these naturally occurring alkaloids, their 9-acetoxy (9-AcO) and N^1-methyl (N^1-Me) derivatives were used. The three racemic complexes $[Co(ox)_2(phen)]^-$, $[Co(ox)_2(bpy)]^-$, and $[Co(ox)_2(en)]^-$ were at first eluted with a neutral eluent in which each alkaloid exists predominantly as a monoprotonated species. The adjusted retention volumes V_R, however, showed no satisfactory reproducibility. This implies that protonation and deprotonation take place on the N(1) and N(1′) atoms of the alkaloid as well as on the incompletely alkylated amine groups present in the resin. On the other hand, the separation factor α, the ratio of V_R for the late-eluted enantiomer to V_R for the other, was found to be higher than that obtained with a slightly acidified eluent (pH=4.0 with acetic acid) used in the later runs. For example, α values of 1.10 and 1.05 were derived for the phen and bpy complexes, respectively, with a neutral (8*S*,9*R*)-9-acetoxycinchonidinium (9-AcO-CD) chloride solution, whereas 1.08 and 1.03 were obtained respectively with an acidified 9-AcO-CD chloride solution. The present study was undertaken to elucidate the mechanisms of chromatographic resolution of the anion complexes rather than to search for the optimum conditions for the resolution. Accordingly, acidified eluents were used throughout the following chromatographic runs at the expense of discrimination efficiency. Under these conditions, each alkaloid exists predominantly as a diprotonated species, and protonation is complete on the incompletely alkylated amine groups partly present in the resin.

In Figs. 2 and 3 are shown typical elution curves of the three anion complexes recorded with (8*R*,9*S*)-quinidinium (QD) chloride and (8*R*,9*S*)-9-acetoxyquinidinium (9-AcO-QD) chloride as eluent, respectively. Fairly good resolution is achieved for $[Co(ox)_2(phen)]^-$ with QD (separation factor α=1.09) and for $[Co(ox)_2(bpy)]^-$ and $[Co(ox)_2(phen)]^-$ with 9-AcO-QD (α=1.10 and 1.16, respectively), but no practical resolution is accomplished for $[Co(ox)_2$-



R=H
(8R,9S)-Cinchoninium(CN)
(8S,9R)-Cinchonidinium(CD)
R=MeO
(8R,9S)-Quinidinium(QD)
(8S,9R)-Quininium(QN)

Fig. 1. Structures of cinchona alkaloids used as an eluent.

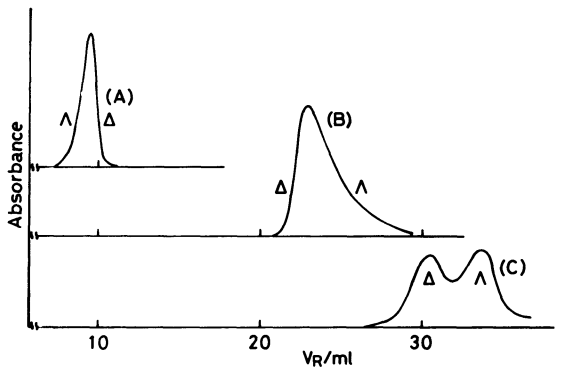


Fig. 2. Elution curves of $[Co(ox)_2(en)]^-$ (A), $[Co(ox)_2(bpy)]^-$ (B), and $[Co(ox)_2(phen)]^-$ (C) obtained with (8*R*,9*S*)-quinidinium (QD) chloride as an eluent.

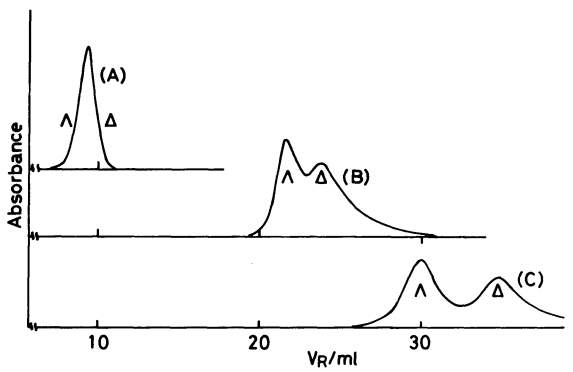


Fig. 3. Elution curves of $[Co(ox)_2(en)]^-$ (A), $[Co(ox)_2(bpy)]^-$ (B), and $[Co(ox)_2(phen)]^-$ (C) obtained with (8*R*,9*S*)-9-acetoxyquinidinium (9-AcO-QD) chloride as an eluent.

(en)]$^-$ with any of the two eluents, as seen in Figs. 2 and 3. It is also notable that the elution order is reversed for the phen and bpy complexes when the HO-C(9) group of QD is acetylated. The reversal in the elution order is also observed for the two complexes with other alkaloids, as seen later (Table 1).

Retention Volumes V_R *and Separation Factors* α. In Table 1 are summarized the fast-eluted enantiomers (Λ or Δ), average retention volumes V_R, and separation factors α obtained for the three complexes with various cinchona alkaloid cations as eluents. Several important observations are noted here. (1) Better resolution is attained for the phen complex with a particular eluent than for the bpy complex, while no practical resolution is possible for $[Co(ox)_2(en)]^-$ with any of the eluents examined. (2) Except for $[Co(ox)_2(en)]^-$, the Δ enantiomer is generally eluted faster with the unmodified and N^1-methylated alkaloids having an (8*R*,9*S*) configuration, and the Λ enantiomer is eluted faster with those having an (8*S*,9*R*) configuration. The elution order is completely reversed upon acetylation of the HO-C(9) group on each alkaloid. (3) The elution ability of each alkaloid is diminished upon acetylation of the HO-C(9) group and N^1-methylation for all three complexes, while the former modification leads not only to the reversal in the elution order but also to the increased separation factor α for the phen and bpy complexes. (4) The alkaloids with an (8*R*,9*S*) configuration bear a stronger elution ability for each complex than those with an (8*S*,9*R*) configuration. (5) For the unmodified and N^1-methylated alkaloids, the (8*S*,9*R*) isomers afford higher α values than the (8*R*,9*S*) isomers, whereas higher α values are obtained with the (8*R*,9*S*) isomers for the 9-AcO derivatives. It is not obvious from the data in Table 1 whether α values of the en complex also depend on the configurations of the C(8) and C(9) atoms of the eluent alkaloids. (6) The alkaloids carrying a methoxy (MeO) group at the 6′ position on the quinoline ring, *i.e.*, quinidine (QD) and quinine (QN) and their derivatives afford lower V_R values for each complex, *i.e.*, they bear a greater elution ability for it, than cinchonine (CN) and cinchonidine (CD) and their derivatives, respectively. This does not hold for the en complex.

The first observation suggests that the aromatic phen or bpy ligand plays an essential role in the interaction with the eluent cation. In fact, the pmr measurements reported previously[8] indicate that the quinoline ring of QN or 9-AcO-QN is stacked with the phen ligand of $[Co(ox)_2(phen)]^-$ in D_2O. Since the stacking is expected to be more extensive with the phen ligand, observation (1) is consistent with the pmr measurements. If the MeO group on the quinoline ring works to strengthen the stacking between the two aromatic rings, for example by its π electron-releasing effect,[10] observation (6) also supports the view that the stacking leads to an appreciable association between the eluent cation and the phen or bpy complex in water. For the en complex, no such stacking is possible, so that no practical resolution is achieved with any of the cinchona alkaloids and the presence of the MeO group should have no effect on the elution ability of any alkaloid for this complex, as is actually the case.

Observation (3) is interpreted to mean that both of

Table 1. Fast-eluted enantiomers, averaged retention volumes V_R, and separation factors α

Eluent (chloride salt)	$[Co(ox)_2(phen)]^-$			$[Co(ox)_2(bpy)]^-$			$[Co(ox)_2(en)]^-$		
		V_R/ml	α		V_R/ml	α		V_R/ml	α
(8*R*, 9*S*)-CN	Δ	40.3[a]	—[c]	Λ[e]	23.5	—[c]	Λ	9.5	—[c]
(8*S*, 9*R*)-CD	Λ	40.1	1.05	Λ	24.6	—	Δ	9.6	—
(8*R*, 9*S*)-QD	Δ	32.0	1.09	Δ	22.8	—	Λ	9.4	—
(8*S*, 9*R*)-QN	Λ	36.2	1.11	Λ	23.4	—	Δ	9.6	—
(8*R*, 9*S*)-N^1-Me-CN	Λ[e]	41.4[b]	—[c]	Λ[e]	25.1	—[c]	—[d]	10.1	1.00
(8*S*, 9*R*)-N^1-Me-CD	Λ	45.3	1.03	Λ	26.1	—	—	10.4	1.00
(8R, 9*S*)-N^1-Me-QD	Δ	36.2	1.07	Δ	23.9	—	—	9.4	1.00
(8*S*, 9*R*)-N^1-Me-QN	Λ	40.8	1.10	Λ	25.3	—	—	10.6	1.00
(8*R*, 9*S*)-9-AcO-CN	Λ	41.1	1.11	Λ	26.1	1.04	Λ	10.6	—[c]
(8*S*, 9*R*)-9-AcO-CD	Δ	44.6	1.08	Δ	27.8	1.03	Δ	11.2	—
(8*R*, 9*S*)-9-AcO-QD	Λ	32.3	1.16	Λ	22.8	1.10	Λ	9.3	—
(8*S*, 9*R*)-9-AcO-QN	Δ	38.4	1.14	Δ	25.7	1.06	Δ	10.4	—
(8*R*, 9*S*)-9-AcO-N^1-Me-CN	Λ	42.4	1.13	Λ	26.6	1.07	—[d]	10.8	1.00
(8*S*, 9*R*)-9-AcO-N^1-Me-QN	Δ	45.8	1.18	Δ	30.3	1.08	—	12.5	1.00
NaCl	—[d]	90.6	1.00	—[d]	46.3	1.00	—[d]	16.8	1.00

a) V_R for the late-eluted enantiomer. b) V_R for the fast-eluted enantiomer. c) Partial resolution. d) No practical resolution. e) Type 2 mode predominates over the type 1 mode (see the text).

the HO-C(9) and H-N(1)$^+$ groups of each alkaloid participate in the interaction with the anion complexes. These acidic groups are likely to form hydrogen bonds to the basic ox ligand(s) of the complex. Then, acetylation and N^1-methylation of each alkaloid naturally prohibit these hydrogen-bonding interaction, its elution ability being thereby lowered. It is also probable from observation (3) that acetylation of each alkaloid leads to a drastic change in the interaction mode with the phen and bpy complexes. On the other hand, N^1-methylation leads only to diminished elution ability of each alkaloid for the respective complexes. The elution ability is similarly lowered for the 9-AcO derivatives upon N^1-methylation with the elution order unaltered.

Observation (4) implies that each complex interacts with the eluents by responding differently to their (8*R*,9*S*) and (8*S*,9*R*) isomers. Since these isomers are not enantiomeric owing to the presence of other two asymmetric carbon atoms (3*R*,4*S*) in common, the vinyl group at the C(3) atom must have some influence on the interaction with the complex.

Association Models. All the implications drawn from the experimental data given in Table 1 are interpreted reasonably within the framework of the association models advanced previously to account for the stereochemical aspects of the Pfeiffer effect of [Cr(ox)$_2$(phen)]$^-$.[8] The model called the type 1 is reproduced in Figs. 4 and 5 for the phen complex with (8*S*,9*R*)-QN and (8*R*,9*S*)-QD, respectively. In this model, two interaction modes are involved; the stacking between the phen and quinoline rings, and the hydrogen bonds of the H-N(1)$^+$ and HO-C(9) groups to the ox ligand(s). The simultaneous hydrogen bonds of the two groups to the complex are possible only when the complex approaches the alkaloid from above, as seen in Figs. 4 and 5. That is, type 1 model is valid only for the alkaloids having the OH group available for the hydrogen-bonding interaction.

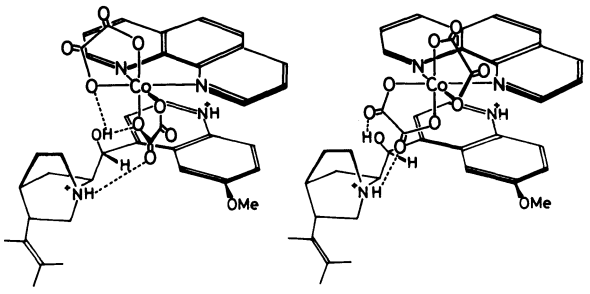


Fig. 4. Type 1 association models for (8*S*,9*R*)-quininium (QN) ion with Λ-[Co(ox)$_2$(phen)]$^-$ (left) and with Δ-[Co(ox)$_2$(phen)]$^-$ (right).

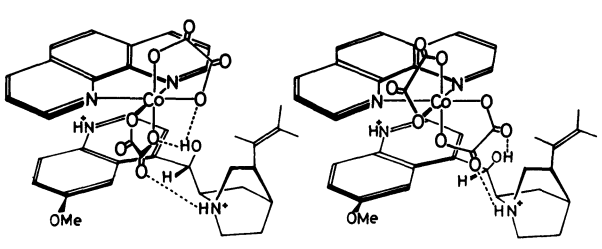


Fig. 5. Type 1 association models for (8*R*,9*S*)-quinidinium (QD) ion with Δ-[Co(ox)$_2$(phen)]$^-$ (left) and with Λ-[Co(ox)$_2$(phen)]$^-$ (right).

When the complex has a Λ configuration, the HO-C(9) group of (8*S*,9*R*)-QN can be nicely located to form hydrogen bonds to both ox ligands, and the H-N(1)$^+$ group is also hydrogen-bonded to the carbonyl group on one of the ox ligands (left model in Fig. 4). On the other hand, when the complex has a Δ configuration, only one ox ligand can participate in the hydrogen-bonding interaction with (8*S*,9*R*)-QN (right model in Fig. 4). In this way, chiral discrimination between the two enantiomers is effected for [Co(ox)$_2$(phen)]$^-$, and [Co(ox)$_2$(bpy)]$^-$ is similarly discriminated, though to a lesser extent owing to the reduced aromaticity of the ligand.

With (8*R*,9*S*)-QD, the Δ complex can interact more favorably, as seen in Fig. 5, in keeping with the elution orders listed in Table 1. When a comparison is made between (8*S*,9*R*)-QN and (8*R*,9*S*)-QD with respect to type 1 interaction, they behave evidently in an enantiomeric fashion; no definite difference is discernible between them. Then, it follows that the dependence of V_R and α on the configurations around the C(8) and C(9) atoms is not accounted for by the type 1 model alone. Further discussions are needed to interpret observations (4) and (5) reasonably (see later).

If the H-N(1)$^+$ group of each alkaloid is methylated, it ceases to hydrogen bond to the C=O group on the ox ligand. Then, it is natural for the elution ability to be lowered upon N^1-methylation in the type 1 model. Since the elution ability is similarly lowered for the en complex, the hydrogen-bonding interaction of the H-N(1)$^+$ group certainly prevails also for the en complex.

The chromatographic behavior exhibited by the 9-AcO derivatives is now examined in detail. It is evident that the 9-AcO-derivatives cannot adopt the type 1 mode in which the hydrogen-bonding interaction of the HO-C(9) group is indispensable. Then, an alternative association model (called type 2) is proposed in which the complex approaches the alkaloid from below to gain the stacking between the phen and quinoline rings as before (Figs. 6 and 7). In this model, the AcO group is not involved in the interaction with the complex, but it blocks access of the complex from above. Hence, the Δ complex can associate more favorably through dual hydrogen bonds with (8*S*,9*R*)-9-AcO-QN (left model in Fig. 6), the parent alkaloid of which (*i.e.*, (8*S*,9*R*)-QN) favors

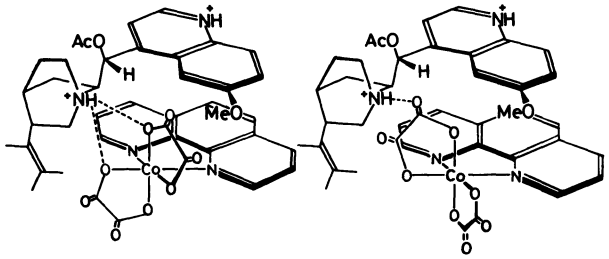


Fig. 6. Type 2 association models for (8*S*,9*R*)-9-acetoxyquininium (9-AcO-QN) ion with *Λ*-$[Co(ox)_2(phen)]^-$ (left) and with *Δ*-$[Co(ox)_2(phen)]^-$ (right).

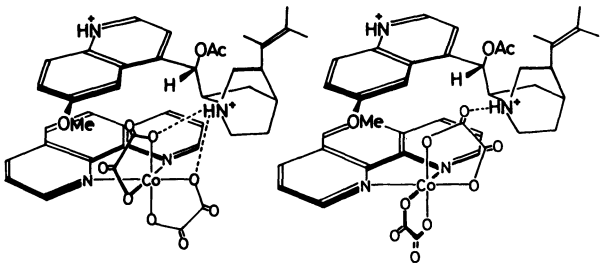


Fig. 7. Type 2 association models for (8*R*,9*S*)-9-acetoxyquinidinium (9-AcO-QD) ion with *Λ*-$[Co(ox)_2(phen)]^-$ (left) and with *Δ*-$[Co(ox)_2(phen)]^-$ (right).

the opposite enantiomer in the type 1 model (Fig. 4). By contrast, the *Λ* complex interacts with (8*S*,9*R*)-9-AcO-QN only through a single hydrogen bond (right model in Fig. 6). The reversal in the elution order upon acetylation is rationalized in this way. Furthermore, it is to be expected from a consideration of Figs. 6 and 7 that the elution ability of each alkaloid will be lowered upon acetylation, because only the H–N(1)$^+$ group is involved in the hydrogen bond to the complex in the type 2 mode, and that N^1-methylation of the 9-AcO derivatives will lead to their further diminished elution ability.

Figure 7 shows how (8*R*,9*S*)-9-AcO-QD interacts more favorably with the *Λ* complex than with the *Δ* complex *via* the type 2 mode, in accordance with the elution orders of the phen and bpy complexes. However, a close comparison between (8*R*,9*S*)-9-AcO-QD and (8*S*,9*R*)-9-AcO-QN with respect to the type 2 interaction reveals that steric hindrance is anticipated between the vinyl group at the C(3) atom and one ox ligand when the interacting alkaloid has an (8*S*,9*R*) configuration like QN and CD (Fig. 6). On the contrary, the vinyl group is far from any part of the complex when the alkaloid has an (8*R*,9*S*) configuration like QD and CN (Fig. 7). In other words, the type 2 model predicts that (8*R*,9*S*)-CN and (8*R*,9*S*)-QD associate with the complex more smoothly than (8*S*,9*R*)-CD and (8*S*,9*R*)-QN, respectively, in the type 2 mode. This prediction is fulfilled by the V_R and α values obtained with their 9-AcO derivatives which adopt the type 2 mode exclusively; (8*R*,9*S*)-9-AcO-CN and (8*R*,9*S*)-9-AcO-QD afford smaller V_R values and higher α values than (8*S*,9*R*)-9-AcO-CD and (8*S*,9*R*)-9-AcO-QN, respectively, for both phen and bpy complexes.

It is easily accepted that the unmodified and N^1-methylated alkaloids having the HO–C(9) group can also adopt the type 2 mode in which the OH group is not involved. Then, it follows that the (8*R*,9*S*)-alkaloids, for example, favor the *Λ* complex in the type 1 mode, but they favor the *Λ* complex in the type 2 mode. The overall elution order is of course governed by the type 1 mode, since the type 1 mode predominates over the type 2 mode (with three exceptions, see below.) owing to the presence of the hydrogen-bonding interaction of the HO–C(9) group in the former mode. Then, lower α values are naturally obtained with the unmodified and N^1-methylated alkaloids which adopt the two modes simultaneously than with their 9-AcO derivatives which are forced to adopt the type 2 mode only. Furthermore, the unmodified and N^1-methylated alkaloids with an (8*R*,9*S*) configuration should exhibit much lower α values and stronger elution ability, since they interact with the complex more intimately in the type 2 mode than do those with an (8*S*,9*R*) configuration. In this way, the dependence of V_R and α values on the configurations around the C(8) and C(9) atoms is explained for these unmodified and N^1-methylated alkaloids in terms of the two concomitant interaction modes (type 1 and type 2) which favor opposite enantiomers of each complex with a particular alkaloid.

It is evident from Table 1 that (8*R*,9*S*)-CN and (8*R*,9*S*)-N^1-Me-CN afford very low α values, as expected, while α values obtained with (8*R*,9*S*)-QD and (8*R*,9*S*)-N^1-Me-QD carrying a MeO group are not so low as compared with those obtained with (8*S*,9*R*)-QN and (8*S*,9*R*)-N^1-Me-QN. This suggests that the MeO group works to strengthen the stacking in the type 1 mode to a greater extent than in the type 2 mode. In fact, if the (8*R*,9*S*)-alkaloids having no MeO group like CN and N^1-Me-CN are used as eluent, the resulting elution order is reverse to that predicted by the type 1 model. Thus, it is fairly likely that the type 2 mode predominates over the type 1 mode for these alkaloids. In this way, the three exceptional elution orders are rationalized. The above discussions lead us to conclude that the 9-AcO derivatives, particularly those with an (8*R*,9*S*) configuration, are effective as eluents in the chromatographic resolution of $[Co(ox)_2(phen)]^-$ and $[Co(ox)_2(bpy)]^-$, since these eluents adopt the type 2 mode exclusively and interact with the complex smoothly in the type 2 mode. N^1-Methylation of these 9-AcO derivatives tends to give rise to further improved discrimination efficiency.

Resolution of $[Co(ox)_2(en)]^-$. The above discussions apply to the phen and bpy complexes only. For the en complex, no practical resolution is achieved by usual ion-exchange chromatography with any alkaloids as eluent probably owing to the absence of the stacking interaction mentioned earlier. Izumoto *et al.*,[4] on the other hand, resolved this complex successfully by reversed-phase chromatography using (8*S*,9*R*)-QN as an ion-pairing reagent (α=1.14 at pH=4.9), and they proposed a mode of chiral discrimination in which the hydrogen bond of the H–N(1)$^+$ group to the ox ligands served as a dominant interaction, but the HO–C(9) group was not involved at all. The discrimination mechanism they proposed, however, fails to accommodate our present experimental results that V_R of the en complex also depends on the configurations around the C(8) and C(9) atoms of the eluent alkaloid and it is increased upon acetylation. As judged from the elution orders of the en complex obtained in the present study, this complex is likely to interact with each alkaloid dominantly *via* the type 2 mode. If the type 1 and 2 modes are compared from the electrostatic point of view, the negative charge on the ox ligands is more effectively neutralized in the latter mode by the positively charged H–N(1)$^+$ group. Since the en complex has no aromatic ligand leading to an appreciable association with the eluent alkaloid, electrostatic and hydrogen-bonding interactions are expected to serve as the main driving forces for the en complex to interact with the eluent. As a result, it is not unreasonable to suppose that the en complex adopts the type 2 mode predominantly in which the electrostatic interaction prevails to a greater extent than in the type 1 mode. Then, it is exactly what is predicted in the type 2 mode that the (8*R*,9*S*)-alkaloids elute this complex faster than the (8*S*,9*R*)-alkaloids. In addition, the elution order of the en complex is naturally unaltered upon acetylation. The contribution of the type 1 mode is, of course, not ruled out, since the lowered elution ability for this complex upon acetylation of each eluent could not otherwise be explained.

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