Contribution from the Department of Chemistry, Faculty of Science,
Hiroshima University, Hiroshima 730, Japan

Chiral Recognition of Bis(oxalato)(1,10-phenanthroline)chromate(III) Effected by Cinchona Alkaloid Cations and Their Derivatives in Water

KATSUHIKO MIYOSHI, NAOKO DOHMOTO, and HAYAMI YONEDA*

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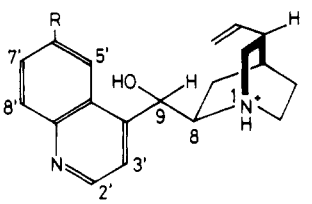
The Pfeiffer effect of $[Cr(ox)_2(phen)]^-$ and $[Cr(ox)_2(bpy)]^-$ (ox = oxalate dianion, phen = 1,10-phenanthroline, and bpy = 2,2′-bipyridine) was examined with the monohydrochloride salts of cinchonine, cinchonidine, quinidine (=6′-methoxycinchonine), quinine (=6′-methoxycinchonidine), and their *N*(1)-methyl and 9-acetoxy derivatives used as chiral environment substances in water. The following observations were noted: (1) The direction of the equilibrium shift induced in these initially racemic complexes depends primarily on the configuration around the C-8 and/or C-9 atoms of the chiral alkaloids. (2) Introduction of a methoxy group to the 6′-position on the quinoline ring of each alkaloid leads to a substantial enhancement of the Pfeiffer effect. (3) N(1)-Methylation diminishes the Pfeiffer effect, while acetylation of the OH group at the C-9 atom shifts the chiral equilibrium greatly in the opposite direction. These observations were successfully interpreted in terms of two concomitant interaction modes involved; a particular alkaloid cation favors one enantiomer of the complex in one mode but favors its antipode in the other mode, and one of the two modes is precluded upon acetylation of the OH group. The nature of the discriminating interactions and the kinetic behavior of the above systems were examined in detail, and an attempt was made to resolve inert $[Co(ox)_2(phen)]^-$ by ion-exchange chromatography with these chiral alkaloid cations as eluting agents.

Introduction

When a certain chiral compound (called an environment substance hereafter) is added to a racemic mixture of a labile metal complex in solution, a chiral equilibrium between the two enantiomers of the complex is sometimes shifted. This phenomenon referred to as the Pfeiffer effect[1] comes from the fact that the environment substance interacts differently with the two enantiomers. For example, Davies and Dwyer[2] found that the inversion rate is a little bit more lowered for Λ-$[Ni(phen)_3]^{2+}$ (phen = 1,10-phenanthroline) than for its antipode upon the addition of ammonium *d*-3-bromocamphor-9-sulfonate in water, the Λ enantiomer being thereby slightly in excess at equilibrium. A similar preferentially retarded inversion has been reported for Δ-$[Ni(phen)_3]^{2+}$ and Λ-$[Cr(ox)_3]^{3-}$ (ox = oxalate dianion) in an aqueous solution of (3*R*,4*S*,8*R*,9*S*)-cinchoninium ion.[2,3] In these systems, however, the inversion is depressed for both enantiomers only to a slightly different extent, so that the enantiomeric excess (ee) attained at equilibrium is relatively low (2–3%)[4] and the chiral equilibrium is shifted with a rate slower than the racemization rate in pure water.



R = H
d-(8R,9S)-cinchoninium ion
l-(8S,9R)-cinchonidinium ion
R = OMe
d-(8R,9S)-quinidinium ion
l-(8S,9R)-quininium ion

In our previous communications,[4] it was reported that a substantial equilibrium shift is attained for a mixed-chelate complex, $[Cr(ox)_2(phen)]^-$, in aqueous solutions of (3*R*,4*S*,8*R*,9*S*)-quinidinium and (3*R*,4*S*,8*S*,9*R*)-quininium ions, which are 6′-methoxycinchoninium and -cinchonidinium ions, respectively. The ee actually attained amounts to more than 10%. However, the parent alkaloids, cinchoninium and cinchonidinium ions, do not serve as an effective environment substance, suggesting some important functions provided by the methoxy group in the stereoselective interaction with the complex. Furthermore, the rate of the equilibrium shift observed in these systems was somewhat higher than the racemization rate of the complex in pure water. This explicitly means that the inversion is accelerated for either or both of the two enentiomers upon the addition of these chiral alkaloid cations. These interesting and unique observations stimulated us to examine the kinetic and stereochemical aspects of the above Pfeiffer-active systems in detail.

Experimental Section

Preparation of Complexes. $K[Cr(ox)_2(phen)]\cdot 4H_2O$ and $[Cr(ox)(phen)_2]Cl\cdot 4H_2O$ were prepared and resolved by the procedures described in the literature.[5,6] $[Co(ox)(phen)_2][Co(ox)_2(phen)]\cdot 3H_2O$, prepared by the literature method,[6] was treated with aqueous KI at room temperature to liberate $[Co(ox)_2(phen)]^-$, which was then precipitated as the barium salt. The potassium salt, derived by treatment with aqueous K_2SO_4, was resolved with chiral $[Co(ox)(en)_2]^+$ by the method employed for the resolution of the corresponding Cr(III) complex.[5] The cobalt(III) complex was so sensitive to light that it was handled in the dark. The Δε value was +4.93 at 582 nm for Λ-$K[Co(ox)_2(phen)]\cdot 4H_2O$. For comparative studies, the following mixed-chelate complexes were prepared as racemates by the literature methods: $K[Cr(ox)_2(bpy)]\cdot 3H_2O$,[5] $[Cr(ox)(bpy)_2]Cl\cdot 4H_2O$,[6] and $K[Cr(ox)_2(en)]\cdot 2H_2O$ (bpy = 2,2′-bipyridine and en = ethylenediamine).

Preparation of Cinchona Alkaloid Derivatives.[7] ***N*(1)-Methyl Derivatives.** Commercially available cinchona alkaloids as free bases were allowed to react with CH_3I in methanol overnight. Products precipitated upon addition of ether were purified as described by Major and Finkelstein.[8] The iodide salts thus obtained were converted to the chloride salts by treatment with freshly prepared AgCl.

9-Acetoxy Derivatives. Acetylation of the OH group at the C-9 atom of each alkaloid was performed according to the procedures described by Pettit and Gupta[9] using pyridine as solvent in place of Me_2SO. Products were obtained as free bases by neutralizing with NH_3 for quinidine and quinine, while for cinchonine and cinchonidine, they were precipitated as monohydriodide salts by adding KI and then were converted to the more soluble monohydrochloride salts as above.

***N*(1)-Methyl-9-Acetoxyquininium Chloride.** 9-Acetoxyquinine prepared as above was allowed to react with CH_3I in ether overnight. The iodide salt recrystallized from hot water was converted to the chloride salt with AgCl.

The purity of these derivatives was confirmed to be satisfactory by elemental analyses and ^1H NMR measurements. When the alkaloids were obtained as free bases, they were converted to the monohydro-

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Table I. Enantiomeric Excess Attained by the Pfeiffer Effect[a]

environment substance (chloride salt)	config at C-8	config at C-9	ee, % $[Cr(ox)_2(phen)]^-$	ee, % $[Cr(ox)_2(bpy)]^-$
cinchoninium	R	S	1.1 (Δ)[b]	0.7 (Λ)[b]
cinchonidinium	S	R	4.3 (Λ)	0.8 (Λ)
quinidinium	R	S	13[c] (Δ)	10[c] (Δ)
quininium	S	R	16.4 (Λ)	10.2 (Λ)
N(1)-methylcinchoninium	R	S	3.3 (Λ)	3.6 (Λ)
N(1)-methylcinchonidinium	S	R	2.7 (Λ)	0.3 (Δ)
N(1)-methylquinidinium	R	S	5.0 (Δ)	... (Δ)
N(1)-methylquininium	S	R	9.0 (Λ)	... (Λ)
9-acetoxycinchoninium	R	S	21.6 (Λ)	16.2 (Λ)
9-acetoxycinchonidinium	S	R	18.3 (Δ)	15.2 (Δ)
9-acetoxyquinidinium	R	S	37.8 (Λ)	33.6 (Λ)
9-acetoxyquininium	S	R	33.6 (Δ)	28.3 (Δ)
N(1)-methyl-9-acetoxyquininium	S	R	29.2 (Δ)	24.8 (Δ)

[a] [Complex] = 3 mM and [alkaloid] = 30 mM. [b] Absolute configuration of an enriched enantiomer. [c] Estimated from the values obtained at lower concentrations.

chloride salts with HCl to prepare their aqueous stock solutions, which were practically neutral in acidity.

Detection of the Pfeiffer Effect. Aqueous mixtures of racemic K-$[Cr(ox)_2(phen)]$ (3 mM) with each of the hydrochloride or chloride salts of various cinchona alkaloids (30 mM) were kept standing at room temperature in the dark until a chiral equilibrium was completely established (2 days). CD spectra of these solutions were recorded on a Jasco J-40CS spectropolarimeter. The direction of the equilibrium shift and the enantiomeric excess (ee) attained at equilibrium were determined by comparing the sign and intensity of the CD spectrum thus recorded with those of optically pure $[Cr(ox)_2(phen)]^-$ ($\Delta\epsilon = +3.10$ at 526 nm for the Λ-$(+)_{546}$ isomer[10]). The same procedures were applied to other racemic complexes, $[Cr(ox)_2(bpy)]^-$, $[Cr(ox)(phen)_2]^+$, $[Cr(ox)(bpy)_2]^+$, and $[Cr(ox)_2(en)]^-$. The $\Delta\epsilon$ values adopted here for the Λ enantiomers were +2.22 at 513 nm,[11] +2.43 at 499 nm,[12] +1.40 at 486 nm,[13] and +2.00 at 515 nm,[11] respectively. When a weak CD intensity attributable to the racemic complex (called induced CD) was detected instantaneously after it was mixed with the environment substance, the contribution due to the induced CD was taken into account in estimating the ee.

Racemization and Antiracemization. Racemization was followed polarimetrically for aqueous solutions of optically pure Λ- and Δ-$[Cr(ox)_2(phen)]^-$ (2 mM) containing varying amounts of each of various alkaloid salts (5–30 mM) at 25 °C. An appropriate amount of KCl was added to each solution to maintain a constant ionic strength ($\mu = 0.052$). Δ-$[Cr(ox)(phen)_2]^+$ (1 mM) was also subjected to racemization in mixtures of water with acetone (30 wt %) and with methanol (40 wt %) and in an aqueous tetra-*n*-butylammonium bromide (100 mM) solution at 25 °C.

The rate of the equilibrium shift (antiracemization rate) of $[Cr(ox)_2(phen)]^-$ was determined at 25 °C by detecting the CD intensity that developed at 526 nm after the racemate (3 mM) was mixed with quininium chloride or 9-acetoxyquininium chloride (30 mM) in water. Antiracemization of $[Cr(ox)(phen)_2]^+$ (3 mM) was also followed at 499 nm in an aqueous 9-acetoxyquininium chloride solution (30 mM) at 25 °C.

^{1}H NMR Spectra. ^{1}H NMR spectra were recorded on a Hitachi R-90H spectrometer at room temperature for D_2O solutions of chlorides or hydrochlorides of various alkaloids (30 mM) in the absence and presence of Λ- and Δ-$K[Co(ox)_2(phen)]$ (3 mM). Solubility limitation did not allow us to measure at higher concentrations, so that the data were acquired 64 times for each. Methanol was added as an internal reference.

Chromatography. Racemic $K[Co(ox)_2(phen)]$ was loaded on a QAE-Sephadex column (diameter 12 mm) and was eluted at a rate of 0.8 mL/min with aqueous solutions of chlorides or hydrochlorides of various alkaloids (20 mM). The column was covered with an aluminum foil to avoid photodecomposition of the complex during elution. CD spectra were recorded for the effluents to determine the elution order.

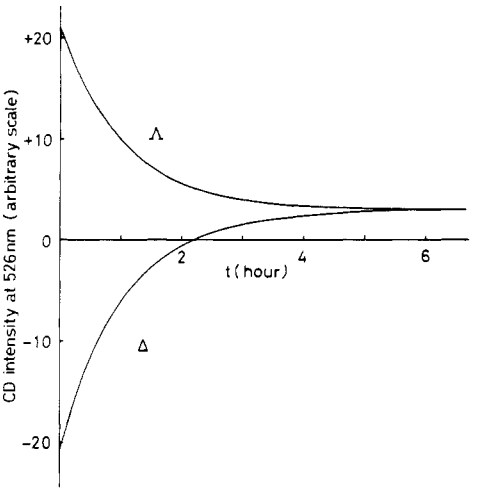

Figure 1. Racemization of Λ- and Δ-$[Cr(ox)_2(phen)]^-$ in the presence of quininium chloride in water at 25 °C.

Results

Pfeiffer Effect. In Table I are listed the enantiomeric excess (ee) and the direction of the equilibrium shift (i.e., absolute configuration of the enriched enantiomer) attained by the Pfeiffer effect of $[Cr(ox)_2(phen)]^-$ and $[Cr(ox)_2(bpy)]^-$ with hydrochloride or chloride salts of various cinchona alkaloids and their derivatives as environment substances in water. Six observations are noted here: (1) With one exception, the ee is higher for the phen complex than for the bpy complex regardless of which alkaloid is used. (2) The direction of the equilibrium shift induced with these alkaloid cations is governed primarily by the configuration around the C-8 and/or C-9 atoms of each alkaloid. With the first eight cations listed, the 8*R*,9*S* configuration generally enriches the Δ isomer (three exceptions) and the 8*S*,9*R* configuration enriches the Λ isomer (one exception). The four exceptions are underlined in Table I. (3) The Pfeiffer effect is diminished or sometimes reversed upon N(1)-methylation of each alkaloid. (4) Acetylation of the OH group leads to a large Pfeiffer effect up to an ee of 30%, and the direction of the equilibrium shift is the reverse of that noted with the first eight cations. (5) For the alkaloids of similar type, quinidinium and quininium species are more effective environment substances than cinchoninium and cinchonidinium species, indicating that the MeO group on the 6′-position of the quinoline ring plays a very important role in their interaction with the complexes. (6) For the first eight cations, alkaloids with an 8*S*,9*R* configuration attain higher ee's than those with an 8*R*,9*S* configuration, whereas the reverse holds with the 9-AcO derivatives.

Though both quinidinium and quininium ions are found to serve as very effective environment substances, the former easily forms a precipitate with the complex. As a result, we focus our attention in the following to the systems involving the quininium ion and its derivatives.

Racemization and Antiracemization. Figure 1 shows how the CD intensity decays with time for Λ- and Δ-$[Cr(ox)_2(phen)]^-$ (2 mM) in aqueous quininium chloride solution (30 mM) at 25 °C. It is evident that the Δ enantiomer racemizes more rapidly than its antipode and that an appeciable CD intensity due to the Λ enantiomer survives at equilibrium regardless of which enantiomer is allowed to racemize. From the CD intensity at equilibrium, the ee is estimated to be ca. 14%, which is by far higher than those usually attained (2–3%).[4]

In order to estimate the inversion rate constants k_Λ and k_Δ of the Λ and Δ enantiomers in the presence of the environment substance, the plots shown in Figure 1 were analyzed by using the relations

$$\ln [(CD_\infty - CD_0)/(CD_\infty - CD_t)] = (k_\Lambda + k_\Delta)t \qquad (1)$$
$$K_{eq} = C_\Lambda/C_\Delta = k_\Delta/k_\Lambda$$

(10) The $\Delta\epsilon$ value has been reported to be >+2.45 at 526 nm in ref 11, which is smaller than +3.10 obtained in this work.
(11) Kaizaki, S.; Hidaka, J.; Shimura, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 988.
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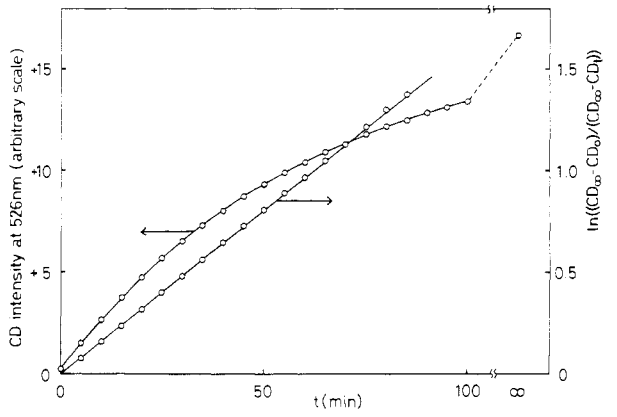

Figure 2. Antiracemization of $[Cr(ox)_2(phen)]^-$ in aqueous quininium chloride solution at 25 °C.

where CD_0, CD_t, and CD_∞ refer to the CD intensities at $t = 0$, $t = t$, and equilibrium, respectively, and C_Λ and C_Δ, to the concentrations of the Λ and Δ enantiomers at equilibrium. The plot of the left-hand side of eq 1 vs. t, however, did not give a straight line for either enantiomer. This is probably because the apparent inversion rate constants k_Λ and k_Δ vary gradually as the racemization proceeds. Thus, antiracemization of $[Cr(ox)_2(phen)]^-$ was followed in an aqueous solution of quininium chloride to determine the k_Λ and k_Δ values.

In Figure 2 is plotted vs. t the CD intensity that developed at 526 nm after racemic $K[Cr(ox)_2(phen)]$ (3 mM) was mixed with quininium chloride (30 mM) in water at 25 °C. The plot of ln $[(CD_\infty - CD_0)/(CD_\infty - CD_t)]$ vs. t, which is also shown in Figure 2, gave a good straight line, indicating that k_Λ and k_Δ are almost constant. This is probably because relative concentrations of the two enantiomers are not drastically changed in the course of antiracemization. From the slope of the plot, the antiracemization rate constant k_{anti} ($=k_\Lambda + k_\Delta$) was estimated to be 2.67×10^{-4}/s, which is somewhat greater than the racemization rate constant k°_{rac} of 2.32×10^{-4}/s in pure water at 25 °C.[14] The ee (13.4%) attained at equilibrium afforded an equilibrium constant K_{eq} of 1.31, from which 1.16 and 1.51×10^{-4}/s were assigned to k_Λ and k_Δ, respectively.

Since the k_Λ value thus derived is accidentally equal to the inversion rate constant k_i in pure water (1.16×10^{-4}/s), a substantial enrichment of the Λ enantiomer accomplished in this system is apparently ascribed to the preferentially accelerated inversion of the Δ enantiomer in the presence of quininium ion. A similar experiment on the $[Cr(ox)_2(phen)]^-$–9-acetoxyquininium ion system revealed that the Δ enantiomer is enriched with a rate slightly slower than the usual racemization rate and that k_Λ is greater but k_Δ is smaller than k_i. That is, the greatest equilibrium shift attained in this system is attributed not only to an accelerated inversion of the Λ enantiomer but also to a retarded inversion of the Δ enantiomer in the presence of 9-acetoxyquininium ion.

Antiracemization could not be followed for those systems in which the ee was not so high. However, the k_Λ and k_Δ values can be determined by following racemization of each of the two enantiomers in the presence of an environment substance.

In Figure 3 is plotted ln (CD_0/CD_t) vs. t for the earlier stage of racemization of Λ- and Δ-$[Cr(ox)_2(phen)]^-$ (2 mM) in aqueous quininium chloride (30 mM) solution at 25 °C. Since k_Λ and k_Δ are unequal, the plot shown in Figure 3 gives a curved line for both enantiomers, as expected.[2] However, it can be regarded as linear up to about 13% loss in CD intensity, where the concentration of the antipode that forms is negligibly low. The k_Λ and k_Δ values obtained from the initial slopes in other systems as well are given in Table II together with the ee's estimated from the ratios k_Δ/k_Λ. It is confirmed here that the ee's (as well as the directions of the equilibrium shift) estimated from these kinetic measurements are all in qualitative agreement with those obtained by the Pfeiffer effect (Table I).

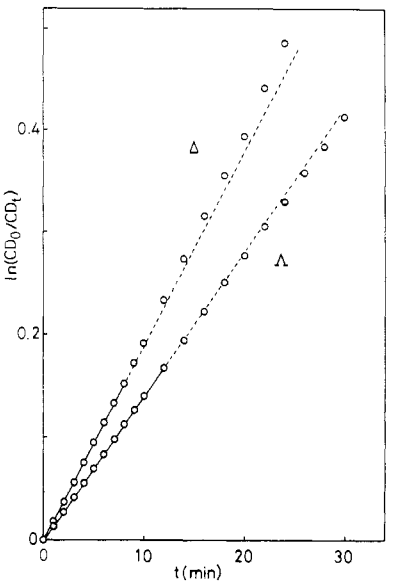

Figure 3. Plots of ln (CD_0/CD_t) vs. t for the earlier stages of racemization of Λ- and Δ-$[Cr(ox)_2(phen)]^-$ in aqueous quininium chloride at 25 °C.

Table II. Inversion Rate Constants k_Λ and k_Δ of $[Cr(ox)_2(phen)]^-$ Determined by Racemization at 25 °C[a]

environment substance (chloride salt)	$10^4 k_\Lambda$, s^{-1}	$10^4 k_\Delta$, s^{-1}	ee, %
(8*R*,9*S*)-cinchoninium	1.24	1.21	1.2 (Δ)
(8*S*,9*R*)-cinchonidinium	1.23	1.28	2.0 (Λ)
(8*R*,9*S*)-quinidinium	1.57	ppt[b]	... (Δ)
(8*S*,9*R*)-quininium	1.17	1.58	14.9 (Λ)
(8*R*,9*S*)-*N*(*1*)-methylcinchoninium	1.10	1.19	3.8 (Λ)
(8*S*,9*R*)-*N*(*1*)-methylcinchonidinium	1.13	1.21	3.4 (Λ)
(8*S*,9*R*)-*N*(*1*)-methylquininium	1.03	1.23	8.7 (Λ)
(8*R*,9*S*)-9-acetoxycinchoninium	0.89	1.23	16.0 (Λ)
(8*S*,9*R*)-9-acetoxycinchonidinium	1.23	0.91	14.9 (Δ)
(8*R*,9*S*)-9-acetoxyquinidinium	0.80	1.43	28.3 (Λ)
(8*S*,9*R*)-9-acetoxyquininium	1.42	0.81	27.4 (Δ)
(8*S*,9*R*)-*N*(*1*)-methyl-9-acetoxyquininium	1.09	0.67	23.8 (Δ)

[a] [Complex] = 2 mM and [alkaloid] = 30 mM. [b] Precipitate formed.

Noteworthy in Table II is the fact that the 9-AcO derivatives accelerate the inversion for one enantiomer, but they retard it for the antipode, a substantial equilibrium shift being thereby accomplished with them. Since the antiracemization rate constant k_{anti} is the sum of k_Λ and k_Δ, kinetic data in Table II suggest that the equilibrium is shifted with a rate slower than the racemization rate when the 9-AcO derivatives including the *N*(*1*)-methyl-9-acetoxyquininium ion are employed as an environment substance. On the other hand, k_{anti} is greater than k°_{rac} for intact and N-(1)-methylated alkaloids. Another notable finding is that all the *N*(*1*)-Me and 9-AcO derivatives have still an ability to accelerate the inversion for either enantiomer, but the *N*(*1*)-methyl-9-acetoxyquininium ion gives rise to only a retarded inversion for both enantiomers. Thus, both of the N(1)–H^+ and C(9)–OH groups of each alkaloid seem responsible for the accelerated inversion of the complex, and the hydrogen-bonding interaction of these electrophilic groups with the ox part of the complex is fairly plausible, since the complex has been assigned to racemize through a one-ended dissociation of one of the ox ligands, which may be promoted by electrophilic attacks of these groups.[15,16]

In Figure 4 are plotted k_Δ and k_Λ of $[Cr(ox)_2(phen)]^-$ against the concentration C_E of quininium or 9-acetoxyquininium chloride.

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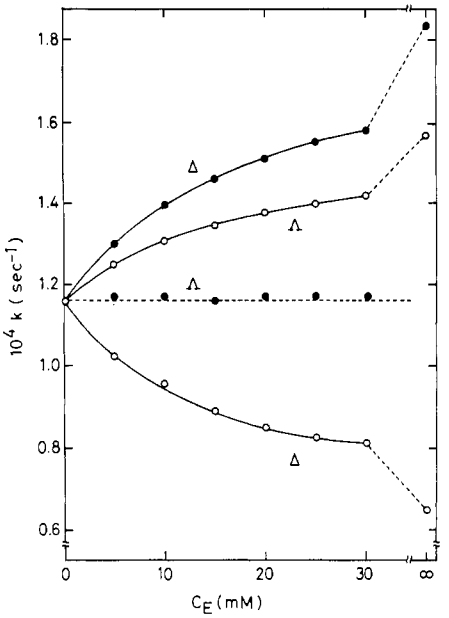

Figure 4. Dependence of inversion rate constants k_Λ and k_Δ of Λ- and Δ-$[Cr(ox)_2(phen)]^-$ on the concentration C_E of quininium chloride (filled circles) and 9-acetoxyquininium chloride (open circles).

Table III. Inversion Rate Constants k^a, Association Constants K_A, and Equilibrium Constants K_{eq} for $[Cr(ox)_2(phen)]^-$ at 25 °C[a]

enantiomer	environment substance	$10^4 k^a$, s^{-1}	K_A, M^{-1}	K_{eq}[b]	ee, %
Λ	quininium	1.16_0	>57	1.58	22.5 (Λ)
Δ		1.83_5	$57._0$		
Λ	9-acetoxy-	1.57_1	$59._6$	0.414	41.4 (Δ)
Δ	quininium	0.65_0	$80._5$		

[a] Ionic strength $\mu = 0.052$ (KCl). [b] $k^a{}_\Delta/k^a{}_\Lambda$.

It is seen that k_Δ increases with C_E and k_Λ remains constant when the environment substance used is the quininium ion, whereas k_Δ decreases but k_Λ increases with C_E when it is the 9-acetoxyquininium ion. If 1:1 association with these alkaloid cations is assumed, the observed inversion rate constant k is expressed as[17]

$$k = [k_i + k^a K_A(C_E - x)]/[1 + K_A(C_E - x)]$$
$$K_A = x/(C_M - x)(C_E - x) \quad (2)$$

where k_i (=1.16×10^{-4}/s) and k^a refer to the inversion rate constants for "free" and "associated" complexes, respectively, K_A refers to the association constant, and C_M (=2 mM), C_E, and x refer to the total concentrations of the complex, the environment substance, and their associated species, respectively. The kinetic data shown in Figure 4 are analyzed in a usual manner according to eq 2, and the K_A and k^a values thus derived are given in Table III. The kinetic behavior of the Λ enantiomer in aqueous quininium chloride is rationalized if $k^a = k_i$ or $K_A = 0$. The latter situation is not realistic, because the Λ enantiomer is eluted slightly faster than the antipode when inert $[Co(ox)_2(phen)]^-$ is chromatographed on an ion-exchange column with aqueous quininium chloride as an eluent (see later). This observation implies that the Λ enantiomer has a greater K_A value than the Δ enantiomer.

Table III clearly demonstrates that the quininium and 9-acetoxyquininium ions exert highly stereoselective influences on the inversion of $[Cr(ox)_2(phen)]^-$; the former accelerates the inversion preferentially for the Δ enantiomer, while the latter accelerates and retards it for the Λ and Δ enantiomers, respectively. These observations suggest that the two enantiomers interact in a kinetically different manner with these alkaloids. In fact, the equilibrium constant K_{eq} defined as $C_\Lambda/C_\Delta = k_\Delta{}^a/k_\Lambda{}^a$ amounts to 1.57 and 0.414 for the quininium and 9-acetoxyquininium ions, respectively, which correspond to the free energy differences $\delta\Delta G$ of 1.13 and 2.19 kJ/mol at 25 °C, and the ee amounts of 22.5 and 41.4%, respectively, when the 1:1 association with the environment substance is complete for both enantiomers. These figures are much greater than those reported for $[Ni(phen)_3]^{2+}$ in neat *l*-2,3-butanediol[18] and neat diethyl (*R,R*)-tartrate[19] (K_{eq} = 0.942, ee = 3.0%, $\delta\Delta G$ = 148 J/mol and K_{eq} = 1.09, ee = 4.3%, $\delta\Delta G$ = 213 J/mol, respectively, at 25 °C). The highest ee has been attained for $Rb_3[Cr(ox)_3]$ in neat diethyl (*R,R*)-tartrate in which K_{eq} = 4.88, ee = 66.0%, and $\delta\Delta G$ = 3.99 kJ/mol at 30 °C.[19]

Also seen in Table III is that the association constants K_A are much greater than are expected for usual 1:1 electrolytes in water. Thus, it is presumed that hydrophobic stacking interaction between phen and quinoline rings contributes appreciably to the overall interaction of the complex with those alkaloid cations, as proposed previously.[4,20] This presumption is supported by the observations that a higher ee is attained for the phen complex than for the bpy complex and that upfield shifts are induced in the ^1H NMR spectrum of the quinoline ring of each alkaloid cation upon the addition of $[Co(ox)_2(phen)]^-$ (see below).

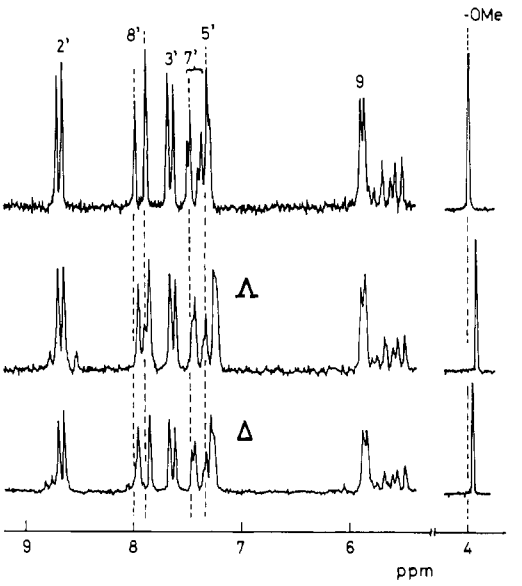

Figure 5. Upfield shifts in the ^1H NMR spectrum of the quininium ion induced upon addition of Λ- and Δ-$[Co(ox)_2(phen)]^-$ in D_2O.

^1H NMR Spectra. In order to get some information on the interaction with $[Cr(ox)_2(phen)]^-$, ^1H NMR spectra of the quininium ion and its various derivatives (30 mM) were measured in D_2O solutions containing a small amount of diamagnetic and inert Λ- or Δ-$[Co(ox)_2(phen)]^-$ (3 mM), which should closely resemble the corresponding Cr(III) complex with respect to the outer-sphere interaction in solution. Since the amount of the added complex was so small that the signals due to the complex scarcely appeared in the spectra. The spectra of the quinoline part are depicted in Figure 5 for the quininium ion and in Figure 6 for the 9-acetoxyquininium ion. Spectral features observed for the *N*(*1*)-methylquininium and *N*(1)-methyl-9-acetoxyquininium ions are qualitatively similar to those for the quininium and 9-acetoxyquininium ions, respectively.

It is evident that upfield shifts are definitely induced for the quininium ion in the spectra of the 5′-, 7′-, and 8′-protons and of the MeO protons at the 6′-position upon the addition of Λ- and Δ-$[Co(ox)_2(phen)]^-$. The signal positions are not changed

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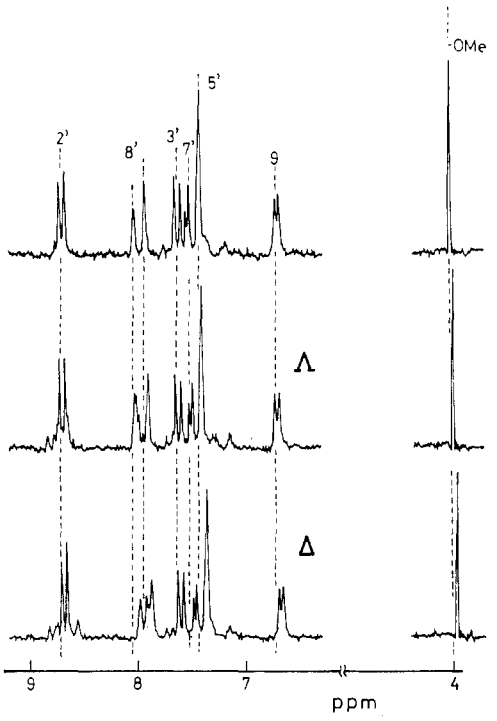

Figure 6. Upfield shifts in the ^1H NMR spectrum of the 9-acetoxyquininium ion induced upon addition of Λ- and Δ-$[Co(ox)_2(phen)]^-$ in D_2O.

practically for other protons. These shifts are interpreted to mean that the quininium ion associates with the complex in such a fashion that its quinoline ring is partially stacked[21] with the phen part of the complex. The stacking of the two aromatic groups has been actually found in the crystal structure of the quinidinium salt of Δ-$[Cr(ox)_2(phen)]\cdot H_2O$.[20]

For the 9-acetoxyquininium ion, similar shifts are experienced by all the protons on the quinoline ring including the MeO protons as well as by the proton on the C-9 atom. Thus, the quinoline ring of the 9-acetoxyquininium ion is stacked more extensively with the phen ligand than that of the quininium ion. This observation tempts us to suppose that quininium and 9-acetoxyquininium ions interact differently with $[Co(ox)_2(phen)]^-$. In fact, they enrich opposite enantiomers of $[Cr(ox)_2(phen)]^-$ (Table I).

A close inspection of Figures 5 and 6 reveals two further noteworthy characteristics. One is that the upfield shift of the MeO protons is greater for the quininium ion than for the 9-acetoxyquininium ion, though the K_A values with the complex are greater for the latter (Table III). This indicates that, though the MeO group is situated above or below the phen ligand for both quininium and 9-acetoxyquininium ions, the former experiences so-called ring current effect[22] on its MeO group more seriously. The other is that Δ-$[Co(ox)_2(phen)]^-$ exerts greater upfield shifts to the 9-acetoxyquininium ion than does its antipode, in keeping with the K_A values of Λ- and Δ-$[Cr(ox)_2(phen)]^-$ with the 9-acetoxyquininium ion (Table III). By contrast, the two enantiomers of $[Co(ox)_2(phen)]^-$ give rise to almost similar upfield shifts in the spectrum of the quininium ion except for the MeO signal, which is shifted to a slightly greater extent by the Λ enantiomer.

Chromatographic Resolution. In Table IV are given the distances from the top of the resin to the band(s) developed when racemic and inert $[Co(ox)_2(phen)]^-$ is eluted through an anion-exchange column with 200 mL of aqueous solutions of various alkaloid cations (20 mM). When complete resolution is attained, two figures are given for each. It is safely accepted that the longer the distance, the greater the affinity that the alkaloid has for the complex.

Table IV. Chromatographic Resolution of $[Co(ox)_2(phen)]^-$

eluent (chloride salt)	dist,[a] cm	enantiomer eluted faster
(8*R*,9*S*)-cinchoninium	3.1	Δ
(8*S*,9*R*)-cinchonidinium	1.9	Λ
(8*S*,9*R*)-quininium	4.0	Λ
(8*R*,9*S*)-*N*(1)-methylcinchoninium	2.9	Λ
(8*S*,9*R*)-*N*(1)-methylquininium	3.4	Λ
(8*R*,9*S*)-9-acetoxycinchoninium	3.4	Λ
(8*S*,9*R*)-9-acetoxycinchonidinium	2.2	Δ
(8*R*,9*S*)-9-acetoxyquinidinium	5.3, 9.1[b]	Λ
(8*S*,9*R*)-9-acetoxyquininium	4.9, 8.9[b]	Δ

[a] Distance by which the complex moved when eluted with 200 mL of aqueous solution of each eluent (20 mM). [b] Complete resolution attained.

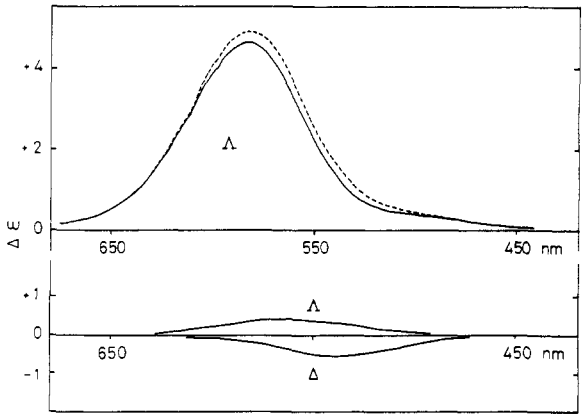

Figure 7. CD and DCD spectra of Λ- and Δ-$[Co(ox)_2(phen)]^-$ (3 mM) with and without added 9-acetoxyquininium chloride (30 mM) in H_2O.

Four observations are noted in Table IV: (1) The cinchoninium ion has a greater eluting ability than the cinchonidinium ion, though the latter attains a higher ee in labile $[Cr(ox)_2(phen)]^-$ (Table I). (2) N(1)-Methylation of each alkaloid diminishes its eluting ability, whereas acetylation of the OH group enhances it. This is consistent with our earlier observation that the Pfeiffer effect is diminished and enhanced by N(1)-methylation and acetylation, respectively, of each alkaloid (Table I). (3) Complete resolution is accomplished with the 9-acetoxyquininium or 9-acetoxyquinidinium ion, both of which attain the greatest ee in $[Cr(ox)_2(phen)]^-$. If the elution is carried out by more than 300 mL of each eluent, complete resolution is attainable even with the 9-acetoxycinchoninium or 9-acetoxycinchonidinium ion, which serves also as an effective environment substance to $[Cr(ox)_2(phen)]^-$. (4) The enantiomer of $[Co(ox)_2(phen)]^-$, eluted faster with a particular alkaloid cation, has the same absolute configuration as that of $[Cr(ox)_2(phen)]^-$ enriched by the Pfeiffer effect with the same alkaloid as an environment substance. This correlation holds for every alkaloid cation examined here (Table IV). Therefore, it follows that a particular alkaloid enriches the enantiomer of $[Cr(ox)_2(phen)]^-$ for which the alkaloid has a greater affinity.

Differential CD Spectra. CD spectra of Λ- and Δ-$[Co(ox)_2(phen)]^-$ were recorded in the absence and presence of quininium or 9-acetoxyquininium chloride in water. In Figure 7 is shown how the CD spectrum of the Λ isomer in the d–d transition region is affected by the addition of the 9-acetoxyquininium ion. The change in the spectrum (i.e., the difference between the dotted and solid curves) is also depicted here for both isomers. The differential CD (DCD) spectra differ certainly in shape and intensity between the two isomers, and similar DCD spectra are obtained for quininium chloride. This observation indicates that the two isomers associate with these alkaloids differentially. However, it is not possible at present to deduce any stereochemical information on the interaction of the complex with these alkaloid

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(22) Fischer, B. E.; Sigel, H. *J. Am. Chem. Soc.* **1980**, *102*, 2998. Mitchell, P. R. *J. Chem. Soc., Dalton Trans.* **1979**, 771. Ohkawa, H.; Ueda, K.; Kida, S. *Inorg. Chem.* **1982**, *21*, 1594 and references cited therein.

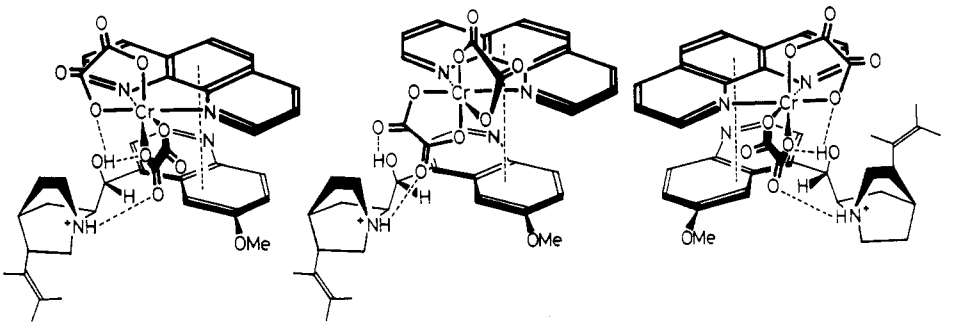

Figure 8. Type 1 association models for the (8*S*,9*R*)-quininium ion with Λ-$[Cr(ox)_2(phen)]^-$ (left) and with Δ-$[Cr(ox)_2(phen)]^-$ (middle) and for the (8*R*,9*S*)-quinidinium ion with Δ-$[Cr(ox)_2(phen)]^-$ (right).

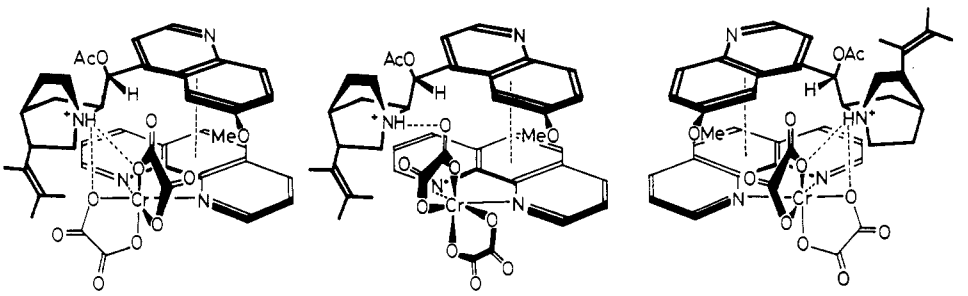

Figure 9. Type 2 association models for the (8*S*,9*R*)-9-acetoxyquininium ion with Δ-$[Cr(ox)_2(phen)]^-$ (left) and with Λ-$[Cr(ox)_2(phen)]^-$ (middle) and for the (8*R*,9*S*)-9-acetoxyquinidinium ion with Λ-$[Cr(ox)_2(phen)]^-$ (right).

cations from these DCD spectra.[23,24]

Discussion

Association Model: Type 1. Now, we propose here a model of stereoselective association of $[Cr(ox)_2(phen)]^-$ with the alkaloid cation, on the basis of which the experimental data given in Tables I and II may be rationally interpreted. A plausible model (called a type 1 model) is depicted in Figure 8 for quininium and quinidinium ions whose three-dimensional structures adopted here are the same as those established by X-ray analyses.[7,20] In this model are satisfied the two requisites: the phen ligand of the complex is stacked with the quinoline ring of the alkaloid, and the ox ligand or ligands participate in the hydrogen-bonding interaction with both of the N(1)–H^+ and C(9)–OH groups. The first requisite is satisfied if the complex approaches the alkaloid from either above or below to achieve an appreciable stacking between the two aromatic rings. However, the hydrogen-bonding interaction with the OH group is possible only when the complex approaches the alkaloid from above, as seen in the models shown in Figure 8.

When the complex has a Λ configuration, the C(9)–OH group of the quininium ion can be located between the two coordinating O atoms of the ox ligands, so that it is hydrogen bonded to both of the two ox ligands, and the N(1)—H^+ group is associated with the free C=O group on one of the ox ligands through both hydrogen-bonding and electrostatic interactions (left model). Thus, a one-ended dissociation of the ox ligand may be facilitated by these interactions. However, the inversion of the complex may be depressed since these hydrogen bonds will limit the ligand rearrangement leading to the inverted configuration. Similar favorable association is possible between Δ-$[Cr(ox)_2(phen)]^-$ and the quinidinium ion (right model). If we remember that the inversion rate of Λ-$[Cr(ox)_2(phen)]^-$ is not affected by the addition of the quininium ion (Figure 4), the interpretation presented above does not meet our observation. This discrepancy will be resolved later.

On the other hand, if the complex has a Δ configuration, only one of its ox ligands is hydrogen bonded to the N(1)–H^+ and C(9)–OH groups of the quininium ion (middle model); the other ox ligand is not involved at all in the interaction with these groups. Thus, somewhat weak interaction with the alkaloid is expected for Δ-$[Cr(ox)_2(phen)]^-$, and an accelerated inversion is anticipated for it, since at least one of its ox ligands is allowed to rearrange freely. These expectations are fulfilled experimentally (Tables II and III).

If the N(1)—H^+ group is methylated, its hydrogen-bonding interaction with the C=O group will disappear. Then, we expect that the overall interaction of the alkaloid with the complex will be weakened, and thus, both its eluting ability and the ee attained with it will be diminished upon N(1)-methylation, which is exactly what is found (Tables I, II, and IV). The hydrogen-bonding interaction with the positively charged N(1)–H^+ group seems mainly responsible for the accelerated inversion of the complex, since the *N(1)*-Me derivatives do not markedly accelerate the inversion (Table II).

In all of the association models shown in Figure 8, the phen ligand is stacked with the quinoline ring, which explains the relatively great K_A values for 1:1 electrolytes in water (Table III). In these models, it is possible to locate the MeO group nicely below one of the py (=pyridine) rings of the phen ligand if the stacking is made partial. In fact, the partial stacking is evidenced by the ^1H NMR spectrum of the quininium ion, and a greater upfield shift is detected in the ^1H NMR spectrum of the MeO group for the quininium ion than for the 9-acetoxyquininium ion, which does not adopt the type 1 interaction mode (see later). If the interaction of the MeO group with the phen ligand is attractive in nature as has been recently claimed by Sigel et al.,[22,25] it is natural that the alkaloids having a MeO group elute $[Co(ox)_2(phen)]^-$ faster and attain a higher ee in $[Cr(ox)_2(phen)]^-$ (Tables I and IV).

Brittain[26] has recently demonstrated that quinine and quinidine induce a greater optical activity in a tris(β-diketonato)europium(III) complex than cinchonidine and cinchonine in chloroform. He interpreted the function of the MeO group in terms of its electronic effect on the quinoline ring. His interpretation may apply to our case, if its electronic effect works to strengthen the interaction between the two aromatic rings.

Association Model: Type 2. It is evident that the above association model does not accommodate the experimental results

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(24) Sakaguchi, U.; Tsuge, A.; Yoneda, H. *Inorg. Chem.* **1983**, *22*, 1630, 3745.
(25) Sigel, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 389.
(26) Brittain, H. G. *J. Chem. Soc., Dalton Trans.* **1980**, 2369.

obtained when the 9-AcO derivatives are used. In particular, the hydrogen-bonding interaction of the C(9)–OH group, which is indispensable in the type 1 model, is prohibited for the 9-AcO derivatives. Moreover, the direction of the equilibrium shift in $[Cr(ox)_2(phen)]^-$ and the elution order of $[Co(ox)_2(phen)]^-$ are inverted upon acetylation of each alkaloid (Tables I and IV). An alternative association model proposed is shown in Figure 9 for 9-acetoxyquininium and 9-acetoxyquinidinium ions. In this model (type 2), the complex approaches the alkaloid from below, so that the phen ligand is stacked with the quinoline ring as in the type 1 model. The MeO group is situated near one of the py rings as before, which explains the higher ee's and the faster elution attained with the 9-AcO derivatives having a MeO group. The AcO group does not participate in any interactions, but it blocks the access of the complex from above. A molecular model consideration reveals that more wide-range stacking is possible in this model than in the previous one, if the attactive interaction between the MeO group and the py ring is reduced. This is consistent with the observation that upfield shifts are experienced by all the protons on the quinoline ring of the 9-acetoxyquininium ion in its ^1H NMR spectrum and that the upfield shift of the MeO protons is smaller for the 9-acetoxyquininium ion than for the quininium ion (Figures 5 and 6).

When the complex has a Δ configuration, the N(1)–H^+ group of the 9-acetoxyquininium ion can form hydrogen bonds to both of the two ox ligands (left model). Then, the retarded inversion of the complex upon association with the 9-acetoxyquininium ion is explained on the basis of the same reasoning as discussed above. Furthermore, the positively charged N(1)–H^+ group is situated between the two ox ligands to neutralize their negative charge so nicely that a greater K_A value is expected with the 9-acetoxyquininium ion than with the quininium ion, the N(1)–H^+ group of which can interact with only one ox ligand for both enantiomers in the type 1 mode (Figure 8). In accord with this expectation, the eluting ability of each alkaloid is increased upon acetylation (Table IV). For the 9-acetoxyquinidinium ion, similar favorable association is possible with the Λ isomer (right model).

When the complex has a Λ configuration, only one of its ox ligands can participate in the hydrogen-bonding interaction with the N(1)–H^+ group of the 9-acetoxyquininium ion, though the two aromatic rings are stacked extensively with each other as before (middle model). Then, the accelerated inversion is expected for the Λ isomer. If the association models for the two enantiomers are compared from the electrostatic point of view, the negative charge on the ox ligands is neutralized by the N(1)–H^+ group more effectively for the Δ isomer. Thus, a greater difference in the K_A values between the two isomers is anticipated in the present model than in the previous one (type 1) where the N(1)–H^+ group interacts with only one ox ligand for both isomers. As a matter of fact, complete resolution of $[Co(ox)_2(phen)]^-$ is accomplished by ion-exchange chromatography when any of the 9-AcO derivatives is used as an eluting agent.

If the N(1)-H^+ group of the 9-AcO derivatives is methylated, its hydrogen-bonding interaction with the ox ligand(s) will disappear. Then, the alkaloid will cease to accelerate the inversion of the complex, since the interaction with the N(1)–H^+ group is thought to be mainly responsible for the accelerated inversion. In fact, the *N*(1)-methyl-9-acetoxyquininium ion retards the inversion for both isomers (Table II). In accord with the above observation, addition of the NH_4^+ ion accelerates the inversion of $[Cr(ox)_2(phen)]^-$ and $[Cr(ox)_3]^{3-}$, both of which are known to racemize via a one-ended dissociation of one ox ligand,[16] whereas addition of R_4N^+ ions having no hydrogen-bonding ability retards it.[3,27,28]

Comparison between 8*R*,9*S* and 8*S*,9*R* Alkaloids. The type 2 association models shown in Figure 9 indicate that the vinyl group on the C(3) atom of the alkaloid is expected to exert a steric hindrance to one of the ox ligands, particularly for the Δ isomer when the alkaloid has an 8*S*,9*R* configuration like that of the 9-acetoxyquininium ion. On the contrary, if the alkaloid has an 8*R*,9*S* configuration like that of the 9-acetoxyquinidinium ion, its vinyl group is situated far from any part of the complex (right model). Thus, our model predicts that the 8*R*,9*S* alkaloids associate with the complex more intimately than their 8*S*,9*R* diastereomers in the type 2 mode. This prediction is in complete agreement with the observation that the 9-AcO 8*R*,9*S* isomers attain higher ee's in $[Cr(ox)_2(phen)]^-$ and elute $[Co(ox)_2(phen)]^-$ faster than the 9-AcO 8*S*,9*R* isomers (Tables I and IV).

In the type 1 mode shown in Figure 8, on the other hand, the vinyl group is far from the complex for both 8*R*,9*S* and 8*S*,9*R* alkaloids; no definite difference in the interaction with the complex is discernible between these diastereomers. However, this mode is not adopted by the 9-AcO derivatives, since the approach of the complex from above is prohibited by the AcO group on the C(9) atom. It is true that the affinity of each alkaloid for the complex is enhanced upon acetylation (Table IV), but fairly high ee's in $[Cr(ox)_2(phen)]^-$ and complete chromatographic resolution of $[Co(ox)_2(phen)]^-$ attained with the 9-AcO derivatives are not accounted for by their enhanced total affinity for the complex alone. For example, the 9-acetoxycinchoninium ion attains an almost 20 times higher ee than the cinchoninium ion, and complete resolution of $[Co(ox)_2(phen)]^-$ is attainable even with the 9-acetoxycinchoninium ion. The greatly increased efficiency of chiral discrimination by acetylation is rationalized on the basis that the 9-AcO derivatives adopt the type 2 mode exclusively (see below).

On the other hand, there is no stereochemical reason to deny that the intact and N(1)-methylated alkaloids can adopt both of the two association modes simultaneously; a particular alkaloid may favor one enantiomer of $[Cr(ox)_2(phen)]^-$ in one mode but favor its antipode in the other mode. If we take the (8*S*,9*R*)-quininium ion as an example, the Λ enantiomer is enriched in the type 1 mode, but its antipode is enriched in the type 2 mode. As a result, the ee (Λ) attained in the type 1 mode is diminished by the other concomitant mode (type 2) in which the Δ enantiomer is favored; the type 1 mode predominates over the type 2 mode, and thus, the net ee attained is very low.

The same interpretation applies to the results obtained with the quinidinium ion. Since this alkaloid has an 8*R*,9*S* configuration, it is expected to interact with the complex more favorably in the type 2 mode than does the (8*S*,9*R*)-quininium ion. Therefore, the ee attained in the type 1 mode is diminished by the type 2 mode to a greater extent for the (8*R*,9*S*)-quinidinium ion than for the (8*S*,9*R*)-quininium ion, since the type 2 mode is stronger for the former alkaloid. In this way, our models afford a reasonable explanation for the observation that the intact and N(1)-methylated 8*R*,9*S* alkaloids attain lower ee's than their 8*S*,9*R* diastereomers. Furthermore, since no difference in the interaction with the complex is expected between these diastereomers in the type 1 mode, the total affinity of the (8*R*,9*S*)-quinidinium ion for the complex should be stronger than that of the (8*S*,9*R*)-quininium ion. Unfortunately, this could not be ascertained by chromatography because of the precipitation of the complex with the quinidinium ion. The same explanation applies to the observation that the (8*R*,9*S*)-cinchoninium ion attains a lower ee than the (8*S*,9*R*)-cinchonidinium ion, though the former elutes $[Co(ox)_2(phen)]^-$ faster.

The kinetic anomaly left unresolved for Λ-$[Cr(ox)_2(phen)]^-$ in the presence of the quininium ion is now interpreted similarly on the basis of the two concomitant interaction modes. That is, the inversion of Λ-$[Cr(ox)_2(phen)]^-$ is retarded upon association with the quininium ion in the type 1 mode, while it is accelerated in the type 2 mode. Consequently, the observed inversion rate, which is accidentally equal to the inversion rate in pure water, should be regarded as an average of retarded and accelerated inversion rates by the quininium ion in the type 1 and 2 modes, respectively. If the inversion rate of the Δ enantiomer is analyzed similarly, its rate constant expected solely in the type 1 mode must be much greater than is actually estimated.

The higher ee's and the faster elution attained with quininium and quinidinium ions than with cinchonidinium and cinchoninium ions are attributed, for the most part, to the attractive interaction

(27) Yoneda, H.; et al., unpublished data.
(28) Miyoshi, K.; Matsumoto, Y.; Yoneda, H. *Inorg. Chem.* **1981**, *20*, 1057.

Table V. Pfeiffer Effect of $[Cr(ox)(phen)_2]^+$ and $[Cr(ox)(bpy)_2]^+$ [a]

environment substance (chloride salt)	ee, % $[Cr(ox)(phen)_2]^+$	ee, % $[Cr(ox)(bpy)_2]^+$
(8*R*,9*S*)-9-acetoxycinchoninium	6.4 (Λ)[b]	3.8 (Λ)[b]
(8*S*,9*R*)-9-acetoxycinchonidinium	4.4 (Δ)	2.5 (Δ)
(8*R*,9*S*)-9-acetoxyquinidinium	13.0 (Λ)	8.5 (Λ)
(8*S*,9*R*)-9-acetoxyquininium	12.6 (Δ)	8.1 (Δ)
(8*S*,9*R*)-*N*(*1*)-methyl-9-acetoxyquininium	9.5 (Δ)	... (Δ)

[a] [Complex] = 3 mM and [alkaloid] = 30 mM. [b] Absolute configuration of an enriched enantiomer.

of the MeO group with the py ring of the phen ligand, as discussed earlier. However, as judged from the eluting abilities of these alkaloids, much higher ee's attained with quinidinium and quininium ions having the MeO group are not rationalized by their stronger total affinity for the complex alone. As pointed out in the ^1H NMR spectra, the MeO group interacts with the phen ligand more intimately for the quininium ion, which adopts mainly the type 1 mode, than for the 9-acetoxyquininium ion, which adopts the type 2 mode exclusively. That is, the attractive interaction contributes to the type 1 mode to a greater extent than to the type 2 mode. Then, it follows that the type 1 mode prevails over the type 2 mode to a greater extent for quininium and quinidinium ions having the MeO group than for cinchonidinium and cinchoninium ions. Thus, much higher ee's should be attained with the former alkaloids than are expected from their total affinities for the complex (Tables I and IV).

Cinchoninium ion attains the lowest ee. This is because the type 1 mode barely predominates over the type 2 mode for this alkaloid; it has no MeO group leading to an enhanced interaction in the type 1 mode, and it has an 8*R*,9*S* configuration fitting well with the type 2 mode. Instead, if it is forced to adopt the type 2 mode exclusively by acetylation, the chiral equilibrium should be shifted greatly in the opposite direction and the complete resolution should be attained (Tables I and IV).

Finally, let us examine the anomalous behavior exhibited by the four exceptional cases underlined in Table I. Three of them involve (8*R*,9*S*)-cinchoninium species having no MeO group. Thus, the contribution of the type 1 mode to their overall interaction with the complex is comparatively small. Therefore, it is fairly plausible that the type 2 mode predominates over the type 1 mode when the phen ligand is replaced by the bpy ligand and/or when the N(1)-H^+ group is methylated. In fact, a moderate ee of 3.6% is attained for the $[Cr(ox)_2(bpy)]^-$–(8*R*,9*S*)-*N*(*1*)-methylcinchoninium ion system where both of the above two modifications are made. That is, both the decreased size of the aromatic ligand and the N(1)-methylation cause damage to the type 1 mode to a greater extent; the type 2 mode is not easily amenable to the effect of the two modifications since more extensive stacking and stronger electrostatic interaction are possible in the type 2 mode, as discussed earlier. The type 2 mode seems to predominate over the type 1 mode even when the methylated alkaloid has an 8*S*,9*R* configuration, provided that it has no MeO group and the phen ligand is replaced by the bpy ligand (the fourth exception).

The ee is considerably diminished for other intact alkaloids also when they are methylated. This is, thus, attributed not only to their weakened total affinity for the complex but also to the preferentially damaged type 1 mode, which eventually governs the direction of the equilibrium shifts. In fact, for the 9-acetoxyquininium ion, which does not adopt the type 1 mode, the N(1)-methylation does not appreciably diminish the ee (33.6 to 29.2%). In this way, all the experimental results obtained here are interpreted reasonably within the framework of our proposed association models.

Pfeiffer Effect in Other Systems. The Pfeiffer effect of the positively charged complexes $[Cr(ox)(phen)_2]^+$ and $[Cr(ox)(bpy)_2]^+$ was examined similarly, with various cinchona alkaloid cations used as environment substances. In Table V are given the results obtained with the 9-AcO derivatives in water. Broadly speaking, it is one ox and one phen (or bpy) ligands that play a key role in the interaction of $[Cr(ox)_2(phen)]^-$ (or $[Cr(ox)_2(bpy)]^-$) with the alkaloids, as seen in Figures 8 and 9. Thus, both $[Cr(ox)(phen)_2]^+$ and $[Cr(ox)(bpy)_2]^+$, which have also one ox ligand and one phen or bpy ligand, are expected to adopt the interaction modes similar to those shown in Figures 8 and 9. In accord with this expectation, the chiral equilibrium in these complexes is shifted in the same direction as observed in $[Cr(ox)_2(phen)]^-$ and $[Cr(ox)_2(bpy)]^-$ for most alkaloids (including intact and N(1)-methylated ones), though the ee's are very low, probably owing to the electrostatic repulsion between the alkaloid cations and the cationic complexes. Nevertheless, moderately high ee's are attained with the 9-AcO derivatives (Table V). This is mainly because they are restricted to adopt the type 2 mode only. It is notable in Table V that the ee's are higher for the phen complex, for the alkaloids having the MeO group, and for those having an 8*R*,9*S* configuration.

For comparison, the antiracemization was examined for $[Cr(ox)(phen)_2]^+$ (3 mM) in the presence of 9-acetoxyquininium chloride (30 mM) in water at 25 °C. The rate constant derived was 3.94×10^{-5}/s, from which k_Λ and k_Δ were estimated to be 2.22 and 1.72×10^{-5}/s, respectively. Since both of them are greater than k_i of 1.32×10^{-5}/s in pure water (cf. 1.4×10^{-5}/s in 0.05 M HCl at 25 °C[16]), the equilibrium shift induced in $[Cr(ox)(phen)_2]^+$ is attributed to the differentially accelerated inversion of the two enantiomers in the presence of the 9-acetoxyquininium ion. This complex has been assigned to racemize by a twist mechanism[16] like $[Fe(phen)_3]^{2+}$,[29,30] racemization of which is known to be accelerated drastically upon addition of common polar organic solvents such as acetone and methanol[31,32] and of R_4N^+ [33] and RSO_3^- [34] ions. The rate-accelerating effect of these "solvents" on $[Fe(phen)_3]^{2+}$ has been elegantly interpreted in terms of stabilization of the complex by solvation in the transition state,[32] in which the phen ligands are exposed to solvent to a greater extent than in the ground state. Then, the rates of racemization were measured for Δ-$[Cr(ox)(phen)_2]^+$ (1 mM) in mixtures of water with acetone (30 wt %) and with methanol (40 wt %) and in an aqueous solution of $(n\text{-}Bu)_4NBr$ (100 mM) at 25 °C. The inversion rate constants estimated were 4.03, 5.09, and 1.60×10^{-5}/s, respectively, all of which are greater than k_i (1.32×10^{-5}/s). These observations lead us to suppose that the quinolyl group "solvates" the phen ligand by stacking to promote the inversion. The interaction of the N(1)–H^+ group with the ox ligand may also accelerate the inversion. If so, the more accelerated inversion would be anticipated for the Δ isomer, since it interacts with the 9-acetoxyquininium ion more favorably than its antipode. However, the stacking of the quinoline ring is also expected to oppose the rearrangement of the phen ligand(s), particularly because it carries a bulky quinuclidinyl group, which serves as an obstacle to the ligand motion. This "obstacle" effect is stronger again for the Δ isomer. If the "solvation" effect dominates over the "obstacle" effect, the differentially accelerated inversion of the two enantiomers may be rationalized.

For comparison, the Pfeiffer effect of $[Cr(ox)_2(en)]^-$ (en = ethylenediamine) was also examined, with various cinchona alkaloids used as environment substances in water. The ee attained was found much less than 1%, and the equilibrium shift was opposite in direction to that induced in $[Cr(ox)_2(phen)]^-$. In addition, the direction of the equilibrium shift was not inverted upon acetylation of each alkaloid. These findings indicate that the interaction mode of $[Cr(ox)_2(en)]^-$ with these alkaloids is entirely different from those adopted by $[Cr(ox)_2(phen)]^-$. In other words, it is the phen (or bpy) ligand and, thus, its stacking with the quinoline ring that play a crucial role in the discriminating

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interaction of $[Cr(ox)_2(phen)]^-$ or $[Cr(ox)_2(bpy)]^-$ with the cinchona alkaloid cations.

Registry No. $[Cr(ox)_2(phen)]^-$, 21748-33-4; $[Cr(ox)_2(bpy)]^-$, 21748-32-3; $[Cr(ox)(phen)_2]^+$, 32626-76-9; $[Cr(ox)(bpy)_2]^+$, 32629-19-9; $[Cr(ox)_2(en)]^-$, 21827-84-9; cinchoninium chloride, 5949-11-1; cinchonidinium chloride, 524-57-2; quinidinium chloride, 1668-99-1; quininium chloride, 130-89-2; *N*(*1*)-methylcinchoninium chloride, 93862-43-2; *N*(*1*)-methylcinchonidinium chloride, 77452-64-3; *N*(*1*)-methylquinidinium chloride, 93862-44-3; *N*(*1*)-methylquininium chloride, 64868-38-8; 9-acetoxycinchoninium chloride, 93862-45-4; 9-acetoxycinchonidinium chloride, 93862-46-5; 9-acetoxyquinidinium chloride, 93862-47-6; 9-acetoxyquininium chloride, 93862-48-7; *N*(*1*)-methyl-9-acetoxyquininium chloride, 93862-49-8.

Contribution from the Laboratoire de Chimie du Solide et Inorganique Moléculaire, LA 254, Université de Rennes I, 35042 Rennes Cedex, France, Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1, and Ecole Nationale Supérieure de Chimie, 75231 Paris Cedex 05, France

Molecular Orbital Study of Heterometallic M_3C_2 Organo-Transition-Metal Clusters: Orientation of the Alkyne Moiety

JEAN-FRANÇOIS HALET,† JEAN-YVES SAILLARD,*† ROLAND LISSILLOUR,† MICHAEL J. McGLINCHEY,‡ and GÉRARD JAOUEN§

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EHMO calculations are reported for a series of trimetal-alkyne five-vertex clusters, $M_3C_2R_2$, where M = $Fe(CO)_3$, $Co(CO)_3$, CpFe, CpNi, $CpMo(CO)_2$. The preferred orientation of the alkyne moiety relative to the trimetallic fragments is rationalized on the basis of the donor and acceptor properties of the R_2C_2 and M_3 fragments, respectively. These predictions correlate very well with the known structures of M_3C_2 clusters. H edge-bridging clusters are also investigated.

In recent years a large number of five-vertex organo-transition-metal clusters have been synthesized and structurally characterized. These clusters, given in Table I, are well typified by the trimetallic systems in which an alkyne moiety furnishes the remaining two vertices.[1-19] These clusters are found in two quite distinct geometries: those possessing seven skeletal electron pairs adopt a square-based-pyramidal geometry while the molecules with only six skeletal electron pairs have the trigonal-bipyramidal structure. In terms of the polyhedral skeletal electron pair (PSEP) theory[20] (which, in effect, takes advantage of the isolobal nature of a BH moiety and a variety of organo-transition-metal fragments),[21] one may classify the former geometry as being derivable from an octahedron with a vacant vertex (as in Figure 1) and as such analogous to the *nido*-borane B_5H_9. In contrast, the latter molecules closely resemble the *closo*-carboranes $R_2C_2B_3H_3$.[22] These two geometries are distinguished by the orientation of the acetylenic moiety with respect to the metal triangle. The acetylene can be positioned parallel to a metal-metal vector, η^2-||,[23] as in the nido configuration, or perpendicular, η^2-$\perp$, as in the closo arrangement (Figure 1).

A molecular orbital analysis of both closo and nido $Fe_3(CO)_9C_2H_2$ will serve as a model for a general introduction to the bonding modes of heterometallic clusters. This model has already been the subject of a detailed study by Schilling and Hoffmann,[24] but we think it useful to briefly reiterate the important points. Figure 2 gives an orbital energy level diagram for the two geometries.

Frontier Orbitals of the $Fe_3(CO)_9$ Fragment (26)

In accordance with the C_s symmetry of both the nido and closo complexes, the orbitals are classified as being *s* (symmetric) or *a* (antisymmetric) with respect to the molecular mirror plane. The construction of the $Fe_3(CO)_9$ entity, **26**,[24] from three $Fe(CO)_3$ fragments[25] is known and leads to six frontier orbitals; three of these (*1s*, *2s*, *1a*) are donor orbitals while the remaining three (*2a*, *3s*, *4s*) are situated at higher energy and can function as acceptor orbitals (see Figure 2). Of these six orbitals *1s*, *2s*, *1a*, and *4s* are metal-metal bonding while *3s* and *2a* are metal-metal antibonding. For our purposes, the acetylenic ligand will be considered formally as $(C_2H_2)^{2-}$ in all the nido complexes and as C_2H_2 in all the closo systems studied here.

The Nido Case: $[Fe_3(CO)_9C_2H_2]^{2-}$ (27)

The *1s* frontier orbital, which possesses pronounced d_{z^2} character, is only slightly perturbed by complexation with the acetylene. The *2s* orbital, which is principally composed of $d_{x^2-y^2}$ combina-

† Université de Rennes I.
‡ McMaster University.
§ Ecole Nationale Supérieure de Chimie.

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