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SUBSTANTIAL EQUILIBRIUM SHIFT IN RACEMIC $[Cr(ox)_2(phen)]^-$ ATTAINED BY THE PFEIFFER EFFECT WITH QUININE OR QUINIDINE HYDROCHLORIDE AS AN ENVIRONMENT SUBSTANCE IN WATER

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The chiral equilibrium of $[Cr(ox)_2(phen)]^-$ was found to be displaced greatly (ca. 18% O.Y.) in water toward its $(+)_{546}$- or $(-)_{546}$-enantiomer upon the addition of ℓ-(8S,9R)-quinine or d-(8R,9S)-quinidine hydrochloride, respectively, which was attributed to the combined action of electrostatic and hydrophobic (or π-π) interactions between the complex and ℓ-quininium or d-quinidinium cation.

The Pfeiffer effect is an anomalous change in optical activity observed when a racemic mixture of a labile metal complex is mixed with an optically active compound (called an environment substance) in solution.[1)] Partial resolution of some metal complexes achieved by means of the Pfeiffer effect[2,3)] established that the origin of the Pfeiffer effect lies in a shift of the chiral equilibrium of an initially racemic metal complex in the presence of the environment substance, and therefore this phenomenon is a prototype of so-called first order asymmetric transformations. However, the degree of the equilibrium shift, i.e., the optical yield (O.Y.) attained by the Pfeiffer effect is extremely low. In Table I are listed the optical yields attained so far with d-(8R,9S)-cinchoninium cation (d-cinchoH$^+$) and ℓ-(S)-malic acid as an environment substance in water. The low optical yield has been ascribed mainly to relatively weak interaction of the metal complex with the environment substance.[4)]

Table I. Optical Yield Attained by the Pfeiffer Effect

racemic complex	concn mol/dm^3	environment substance	concn mol/dm^3	optical yield(%)	enriched isomer	Ref.
$[Cr(ox)_3]^{3-}$	(0.05)	d-cinchoHCl	(0.15)	2.6	Λ	1a
$[Co(ox)_3]^{3-}$	(0.05)	d-cinchoHCl	(0.15)	1.4	Λ	1a
$[Ni(phen)_3]^{2+}$	(0.02)	d-cinchoHCl	(0.02)	3*	Δ	4a
$[Ni(phen)_3]^{2+}$	(0.03)	d-cinchoH1/2SO$_4$	(0.03)	3.0**	Δ	$
$[Ni(phen)_3]^{2+}$	(0.05)	ℓ-malic acid	(0.20)	2.8	Δ	2
$[Ni(bpy)_3]^{2+}$	(0.05)	ℓ-malic acid	(0.20)	1.5	Δ	2
$[Co(phen)_3]^{2+}$	(0.04)	ℓ-malic acid	(0.30)	2-3	Δ	3

$)K. Miyoshi, Y. Kuroda, H. Okazaki, and H. Yoneda, Bull. Chem. Soc. Jpn., 50, 1476 (1977). *) 0.5 mol/dm^3 NaCl added. **) 0.4 mol/dm^3 Na_2SO_4 added.

In our previous paper on the Pfeiffer effect,[5)] it was proposed that $[Cr(ox)_3]^{3-}$ attacks d-cinchoH$^+$ through the electrostatic interaction with the positively charged

N(1) atom, while $[Co(phen)_3]^{2+}$ associates with d-cinchoH$^+$ through the hydrophobic interaction with the quinolyl group, the equilibrium shift being thereby induced for both complexes. Then, if the two interactions work cooperatively to reinforce the interaction of the labile complex with the environment substance, an appreciably great equilibrium shift is expected. With this expectation in mind, we examined the Pfeiffer effect of a mixed-chelate complex, $[Cr(ox)_2(phen)]^-$ using ℓ-(8S,9R)-quinine and d-(8R,9S)-quinidine hydrochlorides as a chiral environment substance in water.

$K[Cr(ox)_2(phen)]\cdot 4H_2O$ was prepared according to the method described in the literature and was identified by its absorption (AB) spectrum.6) Other chemicals used were of reagent grade. An aqueous mixture of the racemic complex and ℓ-quinine or d-quinidine hydrochloride (ℓ-quinineHCl or d-quinidineHCl) was kept standing overnight in the dark to attain the chiral equilibrium (the half-life of racemization is reported to be ca. 50 min for $[Cr(ox)_2(phen)]^-$ in water at 25°C7)), and then it was passed through a cation-exchange column. The AB and CD spectra of the effluent were recorded on a Shimadzu UV-200 spectrometer and a Jasco J-40CS spectropolarimeter, respectively. The optical yield was estimated by comparing the CD intensity thus obtained with that of resolved $[Cr(ox)_2(phen)]^-$ ($\Delta\varepsilon$ = +2.46 at 526 nm for the $(+)_{546}$-isomer6c)). The rate of appearance of the Pfeiffer effect (antiracemization rate) was also measured at 25°C in the same manner as described previously.5)

In Fig. 1 is plotted the CD intensity developed at 526 nm as a function of time elapsed after racemic $K[Cr(ox)_2(phen)]$ (2.9×10^{-3} mol/dm^3) was mixed with ℓ-quinineHCl (1.5×10^{-2} mol/dm^3) in water at 25°C. It is evident that the chiral equilibrium is gradually displaced in favor of its $(+)_{546}$-isomer, since it has a positive main CD component at 526 nm.6c) A standard analysis of the plot5) shown in Fig. 1 gave the antiracemization rate constant of 2.7×10^{-4}/sec, which is almost comparable to the racemization rate constant reported previously (2.32×10^{-4}/sec7)) in water at 25°C.

In Fig. 2 are shown the CD spectra obtained after equilibration for the $[Cr(ox)_2(phen)]^-$(6.66×10^{-3} mol/dm^3)-ℓ-quinineHCl(0.04 mol/dm^3) and -d-quinidineHCl (0.04 mol/dm^3) systems in water. It is confirmed that the chiral equilibrium of initially racemic $[Cr(ox)_2(phen)]^-$ is shifted toward its Λ-$(+)_{546}$- and Δ-$(-)_{546}$-isomers6c) in the presence of ℓ-(8S,9R)-quinineH$^+$ and d-(8R,9S)-quinidineH$^+$, respectively, and the optical yield is estimated to be 18.3 and 17.5 %, respectively, both of which are by far greater than those listed in Table I. If the conformation of d-quinidineH$^+$

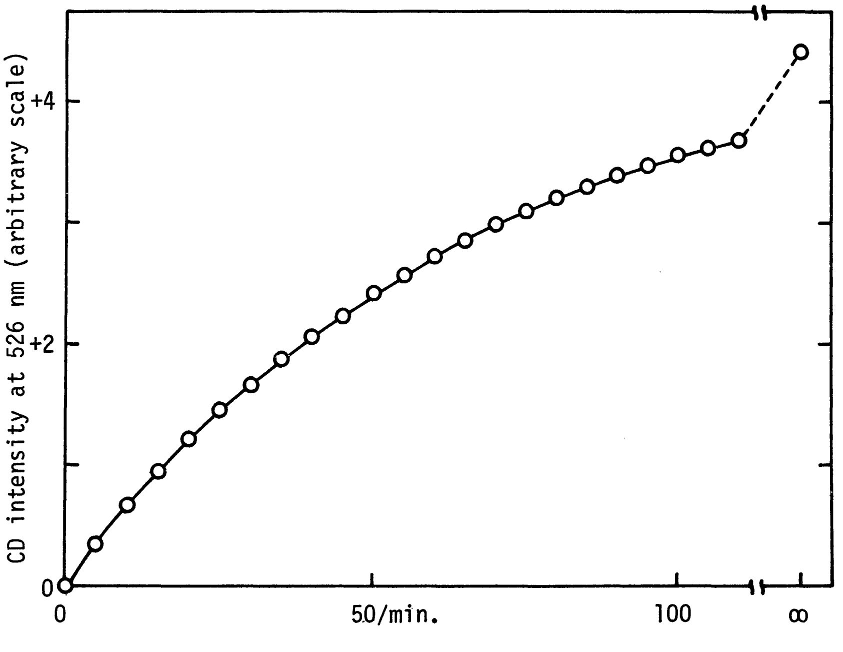

Fig. 1. Plot of the CD intensity of $[Cr(ox)_2(phen)]^-$ developed at 526 nm as a function of time.

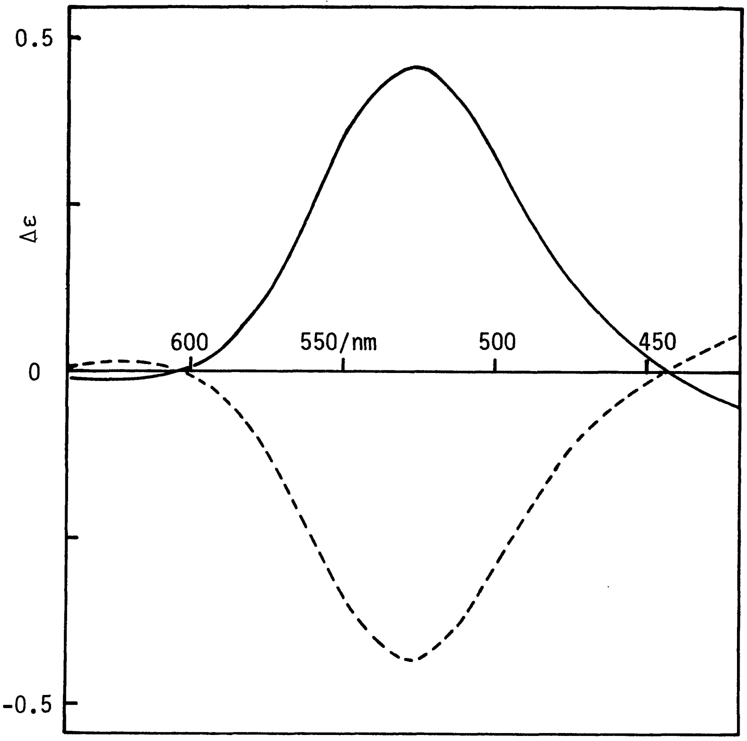

Fig. 2. CD spectra obtained for the $[Cr(ox)_2(phen)]^-$-ℓ-quinineH$^+$(——) and -d-quinidineH$^+$(---) systems.

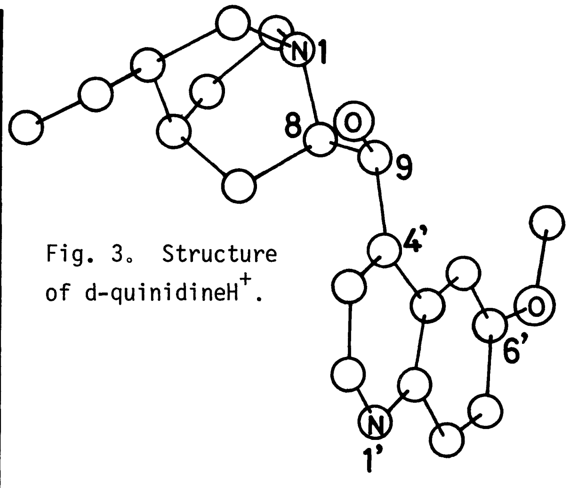

Fig. 3. Structure of d-quinidineH$^+$.

assumed in solid state[8)] (shown in Fig. 3) remains unaltered in solution, a molecular model consideration indicates that d-quinidineH$^+$ can associate preferably with Δ-$[Cr(ox)_2(phen)]^-$ with its positively charged N(1) atom located between the two anionic ox^{2-} chelate rings and the planar quinolyl group stacked with the phen ring. In other words, a surprisingly great equilibrium shift induced here is, we propose, attributed to the combined action of the electrostatic and hydrophobic (or π-π[4a)]) interactions between d-quinidineH$^+$ or ℓ-quinineH$^+$ and $[Cr(ox)_2(phen)]^-$. On the other hand, if the phen ring of Λ-$[Cr(ox)_2(phen)]^-$ is stacked with the quinolyl group of d-quinidineH$^+$, one ox^{2-} chelate ring will suffer a steric hindrance from the N(1) atom, the chiral discrimination being thereby effected.

Figure 4 shows the dependence of the optical yield attained on the concentration of the environment substance for the $[Cr(ox)_2(phen)]^-$ (5.83×10^{-3} mol/dm^3)-ℓ-quinineH$^+$ system. It is evident that the optical yield increases with increasing concentration of ℓ-quinineH$^+$, as is usually the case.[1)] The same should hold when d-quinidineH$^+$ is used as an environment substance.

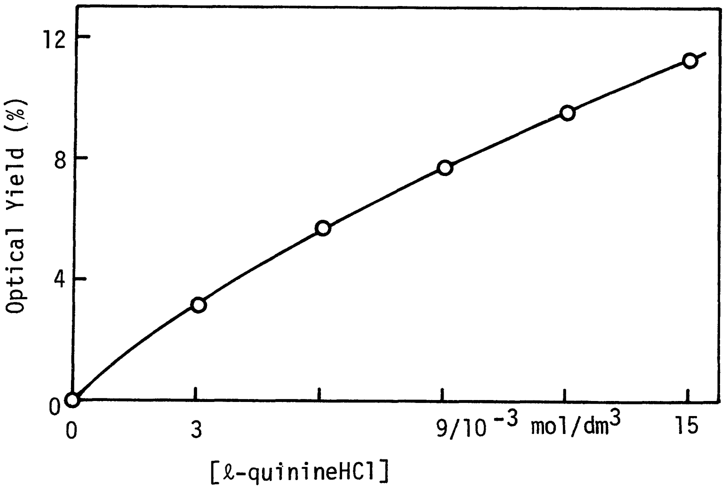

Fig. 4. Dependence of the optical yield attained for the $[Cr(ox)_2(phen)]^-$-ℓ-quinineH$^+$ system on the concentration of the environment substance.

For comparison, d-cinchoninium and ℓ-cinchonidinium cations, the methoxy derivatives of which are d-quinidineH$^+$ and ℓ-quinineH$^+$, respectively, are examined as an environment substance to $[Cr(ox)_2(phen)]^-$ in water. The results

Table II. The Pfeiffer Effect of $[Cr(ox)_2(phen)]^-$ a)

environment substance	concn mol/dm^3	optical yield(%)	enriched isomer b)
d-(8R,9S)-cinchonineHCl	(0.030)	1.1	Δ-$(-)_{546}$
ℓ-(8S,9R)-cinchonidineHCl	(0.030)	4.1	Λ-$(+)_{546}$
d-(8R,9S)-quinidineHCl	(0.015)	10.8	Δ-$(-)_{546}$
ℓ-(8S,9R)-quinineHCl	(0.015)	11.3	Λ-$(+)_{546}$

a) 5.83×10^{-3} mol/dm^3. b) Abs configuration is assigned by the CD spectrum (Ref. 6c).

obtained are summarized in Table II. A noteworthy fact is that d-quinidineH^+ and ℓ-quinineH^+ are much effective in inducing an equilibrium shift of $[Cr(ox)_2(phen)]^-$ than d-cinchonineH^+ and ℓ-cinchonidineH^+. This fact suggests that the methoxy group at the 6' position on the quinolyl group takes an important part in the chiral discrimination effected in the present Pfeiffer systems unlike in the $[M(phen)_3]^{2+}$ systems where the introduction of a methoxy group to the 6' position of the quinolyl group diminishes the Pfeiffer effect to a considerable extent.[4a,5]

A continuous variation method applied to the $[Cr(ox)_2(phen)]^-$-ℓ-quinineH^+ and -d-quinidineH^+ systems revealed that the 1:1 association is responsible for the development of the Pfeiffer effect in both systems. In addition, an increase in the concentration of the complex and/or the environment substance results in a precipitate which is fortunately found to be a diastereomer composed of the enantiomer of $[Cr(ox)_2(phen)]^-$ having the same absolute configuration as the enantiomer enriched by the Pfeiffer effect. Therefore, an X-ray analysis of a pair of the diastereomers of $[Cr(ox)_2(phen)]^-$ with d-quinidineH^+ and d-cinchonineH^+ or with ℓ-quinineH^+ and ℓ-cinchonidineH^+ is now being undertaken in a hope to confirm our proposal mentioned above and to elucidate the detailed part taken by the methoxy group in the present Pfeiffer effect.

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