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UTILIZATION OF THE PFEIFFER EFFECT AND OUTER-SPHERE COMPLEXATION FOR THE PREDICTION OF ABSOLUTE CONFIGURATIONS OF OPTICALLY ACTIVE METAL COMPLEXES

STANLEY KIRSCHNER and IMAD BAKKAR

Department of Chemistry, Wayne State University, Detroit, Michigan 48202 (U.S.A.)

CONTENTS

A. INTRODUCTION

The Pfeiffer effect [1] is the change in optical rotation of an optically active system (usually a solution of one enantiomer of an optically active compound, called the "environment substance"), upon the addition of a racemic mixture of a dissymmetric, optically labile coordination compound. A considerable amount of work has been done on this effect by Brasted, Yoneda, Brittain, Kirschner and others [2–11], and several proposed mechanisms to explain it have been described in an excellent review by Schipper [12].

The Pfeiffer effect has been utilized for the study of the resolution and racemization of optically active coordination compounds [13], and for studies of the optical properties of complexes which are extremely labile and which racemize very rapidly [14]. Recent work [15,16] has also been done on applying the Pfeiffer effect to the determination of absolute configurations of optically active complexes which are also optically liable and organic compounds and on explaining the nature of the "equilibrium displacement"

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mechanism proposed for the effect. In this paper further work is described on the application of the Pfeiffer effect and of outer-sphere complexation to the prediction of absolute configurations of both optically labile and optically stable dissymmetric coordination compounds.

B. THE EQUILIBRIUM DISPLACEMENT MECHANISM FOR THE PFEIFFER EFFECT

It has been proposed by Dwyer et al. [2] that an equilibrium exists between the enantiomers of a racemic mixture of an optically labile, dissymmetric complex in solution, with the equilibrium constant being equal to unity. However, in the presence of an appropriate optically active environment substance (one which will cause the Pfeiffer effect to occur and which will not displace a coordinated ligand during the time required for the appearance of the Pfeiffer effect), this equilibrium is shifted toward one of the enantiomers, with the equilibrium constant then becoming greater or less than 1, depending on the direction of the shift.

If such a shift occurs, then it should be possible to identify the enantiomer produced in excess by means of techniques such as optical rotatory dispersion and circular dichroism, as well as by a "time" experiment (see below). For example, Fig. 1 shows the circular dichroism spectrum of $(+)_D[Cr(ox)_3]^{3-}$ in water along with the Pfeiffer circular dichroism spectrum of D,L-$[Cr(ox)_3]^{3-}$ in water containing *d*-cinchonine hydrochloride as the environment substance (ox = oxalate anion). It can be seen that the two

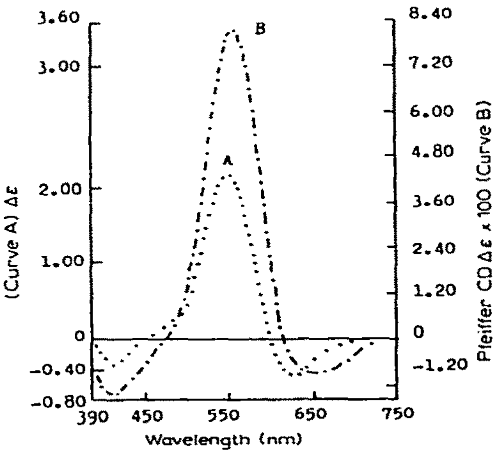

Fig. 1. (A) Circular dichroism spectrum of $(+)_D[Cr(ox)_3]^{3-}$ in H_2O. (B) Pfeiffer circular dichroism spectrum of D,L-$[Cr(ox)_3]^{3-}$ in water containing *d*-cinchonine hydrochloride (all measurements at 23°C).

spectra are essentially the same, with the difference in intensity between them being due to the different concentrations of the optically active complex ion in solution in the two cases.

The "time" experiment referred to above is described in Fig. 2. In this figure it can be seen that the optical rotation of *levo*-malic acid does not change over time. However, when D,L-$[Ni(o\text{-phen})_3]^{2+}$ is added to the solution (at time = 0), it can be seen that the Pfeiffer effect develops, with its maximum being attained at about 100 h (*o*-phen = *ortho*-phenanthroline). If, at that time, exactly the same concentration of *d*-malic acid is added to the system, then this has the effect of eliminating or "optically neutralizing" the optically active environment, with the result being that the excess of the *levo* enantiomer of the complex undergoes racemization until the optical rotation of the substance disappears. Note however that the nickel–*ortho*-phenanthroline complex retains its integrity throughout the Pfeiffer effect experiment, as evidenced by the fact that there is no change in the UV–visible spectrum of the complex throughout the entire "time" experiment. All of this provides considerable support for the mechanism which proposes that one enantiomer of the complex is produced in excess during the appearance of the Pfeiffer effect.

It should be noted that, in Fig. 2, if the *d*-malic acid had not been added, then curve B would continue parallel to the horizontal axis until decomposition begins. This permits the study of many optical properties of extremely labile complexes which heretofore could not be studied because the racemi-

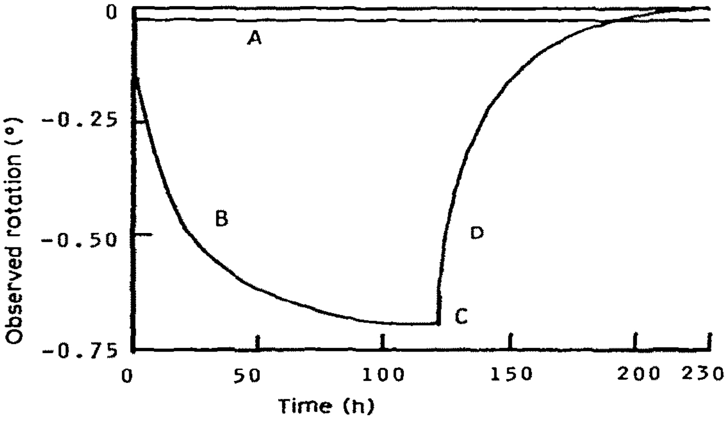

Fig. 2. The "time" experiment. The Pfeiffer effect and subsequent racemization in water of D,L-$[Ni(o\text{-phen})_3]Cl_2$ with *levo*-malic acid as the environment substance. (A) *Levo*-malic acid in water; (B) *levo*-malic acid + D,L-$[Ni(o\text{-phen})_3]Cl_2$; (C) the system in (B) + added *dextro*-malic acid after 123 h; (D) racemization of the system in (C) (excess L-$[Ni(o\text{-phen})_3]Cl_2$ produced via the Pfeiffer effect).

zation rate is so rapid that any resolved compounds would racemize too quickly to be studied. With the displaced equilibrium mentioned above continuing for some time, the excess of one enantiomer can be studied with regard to racemization rate, optical rotatory dispersion, circular dichroism, etc. This has already been achieved with certain manganese complexes [14].

A proposed explanation for the displacement of the equilibrium between the complex enantiomers, which is postulated to occur during the Pfeiffer effect, is that hydrogen bonding occurs preferentially between electronegative atoms of an environment substance of a given absolute configuration and the π-electron clouds of the ligands of one enantiomer of the complex [15]. Such hydrogen bonding interactions to π-electron clouds of aromatic and unsaturated systems are known to occur with organic molecules [17,18].

This proposal is a most attractive one from several standpoints. First of all it provides an explanation for the chiral discrimination which is observed to occur for the Pfeiffer effect, since molecular models of the proposed system indicate that S-malic acid, for example, fits quite well into the Δ_{c_3} propeller system of the $[Ni(o\text{-phen})_3]^{2+}$ enantiomer with no strong non-bonded hydrogen interactions, whereas the R enantiomer of malic acid in the same propeller system shows two strong non-bonded hydrogen interactions. Consequently, the Δ_{c_3} system is stabilized by S-malic acid, resulting in an equilibrium shift in favor of the Δ_{c_3} enantiomer, which is observed.

Also, the initially unexpected behavior of Pfeiffer-active systems with pH changes is explained well by this proposal. One might expect that with increasing pH, Pfeiffer activity would increase, since chiral recognition by an optically active complex cation of an anionic environment substance (e.g., *levo*-malate ion) would be expected to be greater than that for the same complex cation and a neutral environment substance (e.g., *levo*-malic acid). In fact, the opposite behavior is observed, with the Pfeiffer activity undergoing a marked decrease with an increase in pH. This can be explained by the hydrogen bonding proposal, since an increase in pH will result in removal of the carboxylic hydrogens, thus diminishing the ability of the proposed hydrogen bonding to occur [15].

C. THE PREDICTION OF ABSOLUTE CONFIGURATIONS OF OPTICALLY LABILE, DISSYMMETRIC METAL COMPLEXES

It has been found [15] that the Pfeiffer effect on D,L-$[Co(o\text{-phen})_3]^{2+}$ in the presence of *levo*-malic acid, *levo*-tartaric acid, and *dextro*-aspartic acid all produce enrichment of the same enantiomer of the metal complex. Since all three of these environment substances have "S" absolute configurations, it is proposed that those Pfeiffer-active metal complexes undergoing the Pfeiffer effect will shift their equilibrium in the same direction (i.e., all in favor of the

TABLE I

Absolute configurations of dissymmetric complexes predicted by the Pfeiffer effect

Environment substance	Enriched complex enantiomer	Absolute configuration	
		Predicted	Observed
$S(-)_D$ malic acid	$(-)_D[Ni(o\text{-phen})_3]^{2+}$	Δ_{C_3}	Δ_{C_3}
$S(+)_D$ aspartic acid	$(-)_D[Ni(o\text{-phen})_3]^{2+}$	Δ_{C_3}	Δ_{C_3}
$S(-)_D$ malic acid	$(+)_D[Fe(o\text{-phen})_3]^{2+}$	Δ_{C_3}	Δ_{C_3}
$S(+)_D$ aspartic acid	$(+)_D[Fe(o\text{-phen})_3]^{2+}$	Δ_{C_3}	Δ_{C_3}
$R(+)_D$ malic acid	$(+)_D[Ni(o\text{-phen})_3]^{2+}$	Λ_{C_3}	Λ_{C_3}
$R(+)_D$ malic acid	$(-)_D[Fe(o\text{-phen})_3]^{2+}$	Λ_{C_3}	Λ_{C_3}

enantiomer having the same absolute configuration) in the presence of environment substances having the same absolute configuration. Table I illustrates this phenomenon.

It should be noted, in particular, that, in the presence of $S(-)_D$malic acid, the equilibrium between the enantiomers of D,L-$[Fe(o\text{-phen})_3]^{2+}$ shifts in favor of $(+)_D$ enantiomer. Therefore, it must be postulated that this enantiomer has the Δ_{C_3} absolute configuration. This has been confirmed by X-ray studies carried out by Scouloudi and Carlisle [19]. Thus, it can be seen that the Pfeiffer effect has utility in the prediction of absolute configurations of metal complexes which are both dissymmetric and optically labile.

D. PREDICTION OF THE ABSOLUTE CONFIGURATIONS OF OPTICALLY STABLE DISSYMMETRIC METAL COMPLEXES

In 1965 Norman and Mason [20] noted that a strong circular dichroism appears for $[Co(NH_3)_6]^{3+}$ in the presence of a 400-fold excess of diethyl-*d*-tartrate in the visible region. Normally this complex would not exhibit a circular dichroism spectrum because it is optically inactive, nor would the environment substance exhibit a circular dichroism in the visible region, since it is colorless. It has been postulated [15] that, in this instance, strong hydrogen bonding occurs between the oxygens of the tartrate and the nitrogens of the ligand, resulting in the conversion of an optically inactive chromophore into an optically active one.

A study [15] of D,L-$[Co(en)_3]^{3+}$ in the presence of a 400-fold excess of the *dextro-* and *levo-*enantiomers of tartaric acid (and malic acid) shows a strong circular dichroism in the visible region. The signs of the Cotton effects of these circular dichroism spectra are in the same direction when the enantiomers of the tartaric and malic acids have the same absolute configuration. In these cases there would not be expected to be any circular dichroism spectra. even if strong hydrogen bonding occurs between the environment substance and the optically stable complex enantiomers, because the complex is present in racemic form. However, a circular dichroism spectrum would be expected to occur (and does occur) in the visible region, if the hydrogen bonding interactions between the environment substance and the *dextro-* and *levo*-enantiomers of the complex are not equally strong.

In the study referred to above [15], the unequal hydrogen bonding interactions between one enantiomer of an environment substance and each of the two enantiomers of the optically stable complex can be observed by comparing the circular dichroism spectra of the two enantiomers of the resolved complex in water solution with the spectra of these enantiomers in water solutions which also contain a 400-fold excess of one enantiomer of an environment substance (e.g., R-tartaric acid or S-malic acid). The experimentally observed strong circular dichroism referred to in the previous paragraph can be calculated by graphical techniques when the difference between two differences is plotted. The first of these two differences is obtained by subtracting the CD spectrum of one enantiomer of the complex alone (e.g.. $(+)_D[Co(en)_3]^{3+}$) from the CD spectrum of a solution of this enantiomer of the complex which also contains a 400-fold excess of the environment substance (e.g., $(+)_D[Co(en)_3]^{3+}$ with R-tartaric acid). The second difference is obtained by subtracting the CD spectrum of a solution of the other enantiomer of the complex containing a 400-fold excess of the same enantiomer of the environment substance (e.g., $(-)_D[Co(en)_3]^{3+}$ with R-tartaric acid) from the CD spectrum of that enantiomer of the complex alone (e.g.. $(-)_D[Co(en)_3]^{3+}$).

A plot of the resulting difference between these two differences yields the experimentally observed CD spectrum of a solution of the racemic complex containing a 400-fold excess of that enantiomer of the environment substance. In the case described in the paragraph above, the sign of the observed Cotton effect in the CD spectrum of the racemic complex with a 400-fold excess of the environment substance is negative (see Figs. 3 and 4), which is indicative of a stronger hydrogen bonding interaction between the $(+)_D$ enantiomer of the complex and the R enantiomer of the environment substance than between the $(-)_D$ enantiomer of the complex and the R enantiomer of the environment substance. This is to say that the Λ_{c_3}–R interaction is stronger than the Δ_{c_3}–R interaction.

From the above it is proposed that Δ_{c_3}–S interactions will be stronger than Λ_{c_3}–S interactions during outer-sphere complexation, which has been found to be the case [15], as was demonstrated by a study involving racemic $[Co(en)_3]^{3+}$ and S-malic acid. In this case the sign of the observed Cotton

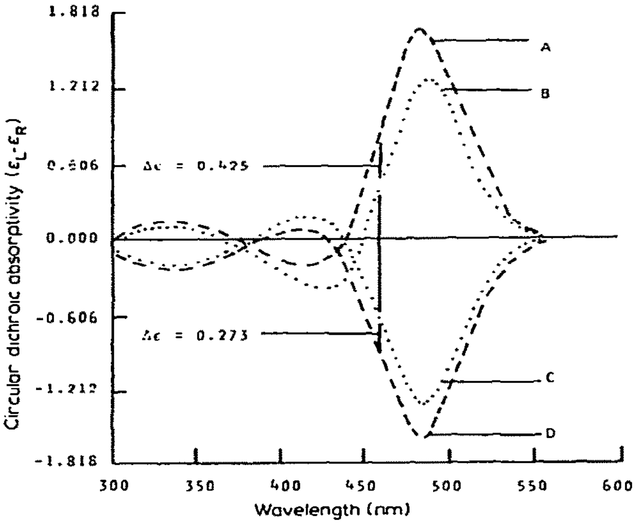

Fig. 3. Interaction of Λ-$[Co(en)_3]I_3$ and Δ-$[Co(en)_3]I_3$ with *d*-tartaric acid. (A) Circular dichroism spectrum of $(+)_D[Co(en)_3]I_3$; (B) circular dichroism spectrum of $(+)_D[Co(en)_3]I_3$ with excess *d*-tartaric acid; (C) circular dichroism spectrum of $(-)_D[Co(en)_3]I_3$ with excess *d*-tartaric acid; (D) circular dichroism spectrum of $(-)_D[Co(en)_3]I_3$.

effect is positive. It should therefore be possible to predict the absolute configuration of an optically stable, dissymmetric complex by observing which of its enantiomers undergoes stronger hydrogen bonding interaction with an environment substance of a known absolute configuration.

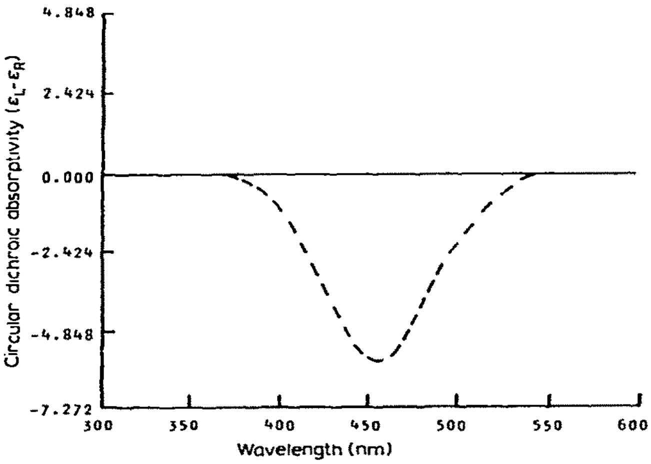

Fig. 4. Circular dichroism of Δ, Λ-$[Co(en)_3]I_3$ in the presence of a 400-fold excess of *d*-tartaric acid.

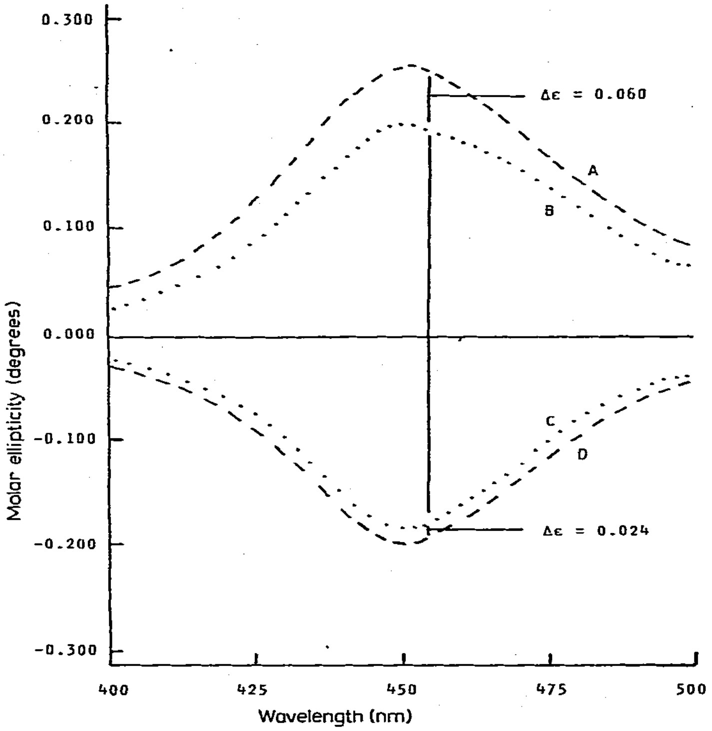

Fig. 5. Interaction of Λ-$[Cr(en)_3]^{3+}$ and Δ-$[Cr(en)_3]^{3+}$ with R(+)tartaric acid. (A) $(+)_D[Cr(en)_3]^{3+}$ circular dichroism spectrum; (B) circular dichroism spectrum of $(+)_D[Cr(en)_3]^{3+}$ with excess $R(+)_D$tartaric acid; (C) circular dichroism spectrum of $(-)_D[Cr(en)_3]^{3+}$ with excess $R(+)_D$tartaric acid; (D) circular dichroism spectrum of $(-)_D[Cr(en)_3]^{3+}$.

TABLE 2

Absolute configurations of dissymmetric, optically stable complexes predicted by outer-sphere complexation

Environment substance	Enantiomer exhibiting stronger outer-sphere interaction	Absolute configuration	
		Predicted	Observed
$R(+)_D$ tartaric acid	$(+)_D[Co(en)_3]^{3+}$	Λ_{C_3}	Λ_{C_3}
$R(+)_D$ tartaric acid	$(+)_D[Cr(en)_3]^{3+}$	Λ_{C_3}	Λ_{C_3}
$S(-)_D$ malic acid	$(-)_D[Co(en)_3]^{3+}$	Δ_{C_3}	Δ_{C_3}
$S(-)_D$ malic acid	$(-)_D[Cr(en)_3]^{3+}$	Δ_{C_3}	Δ_{C_3}

This has been shown to occur with the enantiomers of $[Cr(en)_3]^{3+}$, as can be seen from Fig. 5, which indicates that a stronger interaction occurs between the $(+)_D$ enantiomer of the complex (positive CD) and R-tartaric acid than between the $(-)_D$ enantiomer of the complex and R-tartaric acid. Consequently, the $(+)_D$ enantiomer of the complex is predicted to have the Λ_{c_3} absolute configuration and the $(-)_D$ enantiomer is proposed to be Δ_{c_3}, which is actually the case, as determined by X-ray studies [21]. A summary of these results is given in Table 2.

E. EXPERIMENTAL

All CD spectra were determined with a Cary-60 spectropolarimeter with a CD attachment. Optical rotations at single wavelengths were determined with a Perkin Elmer Model 141 photoelectric polarimeter. The designations "R" and "S" refer to absolute configurations of organic compounds using the system developed by Cahn, Ingold and Prelog, [22,23]. The optically active organic compounds used as environment substances were purchased in their purest available forms, and their optical rotations were checked against the values given in the literature. The ethylenediamine complex of cobalt(III) and the oxalate complex of chromium(III) were synthesized and resolved according to well-known procedures which appear in "Inorganic Syntheses". The $[Cr(en)_3]^{3+}$ complex was prepared by the method of Gillard and Mitchell [24] and resolved using the technique of Galsbol [25].

The Pfeiffer effect studies were carried out in aqueous solutions in which the concentrations of the complexes and the environment substances were 0.02 M and 0.04 M, respectively. The $[Ni(o\text{-phen})_3]^{2+}$ complex was synthesized by the method of Harkins et al. [26] and resolved by the method of Dwyer and Gyarfas [27]. The outer-sphere complexation studies were carried out in aqueous solutions in which the concentrations of the complexes and environment substances were 5×10^{-3} M and 2 M, respectively.

F. CONCLUSIONS

The Pfeiffer effect may be used to predict the absolute configurations of optically labile, dissymmetric coordination compounds by utilizing environment substances of known absolute configurations. For tris(bidentate) metal complexes and analogous complexes, the enantiomer which is enriched during the Pfeiffer effect experiment is predicted to have a Δ_{c_3} absolute configuration when the environment substance (usually one enantiomer of an optically active organic acid or salt capable of undergoing hydrogen bonding to π-electron clouds of unsaturated systems) has an "S" absolute configuration. The Pfeiffer effect is proposed to occur via a mechanism involving an equilibrium displacement of the enantiomers of the complex, as a result of hydrogen bonding between electronegative atoms on the environment substance and the π-electron clouds of the ligands of the complex.

Outer-sphere coordination may be used to predict the absolute configurations of optically stable, dissymmetric tris(bidentate) and analogous coordination compounds by observing the sign of the Cotton effect of the CD spectrum of a solution of a racemic mixture of the complex containing a 400-fold excess of an optically active environment substance of known absolute configuration. If a negative Cotton effect is observed using the racemic complex and an environment substance of "R" absolute configuration, then the absolute configuration of the complex enantiomer having a positive Cotton effect (i.e. the enantiomer interacting more strongly with that environment substance) is predicted to be Λ_{c_3}. This outer-sphere complexation is proposed to occur through hydrogen bonding interactions between the evironment substance and the donor atoms of the ligands of the complex.

G. DEDICATION TO PROFESSOR LUIGI SACCONI

This paper is dedicated to Professor Luigi Sacconi of Florence, Italy on the occasion of his retirement, and was presented at a symposium in his honor entitled "Achievements and Perspectives in Coordination Chemistry", which was held in Florence, Italy from April 21–24, 1981. Professor Sacconi is one of the "giants" in coordination chemistry, and both his work and the students he has trained are testimony to his achievements and contributions to the field. Further, he has been a friend and counsellor to many scientists in the field, and his influence on coordination chemistry will continue to be felt long after his retirement.

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