

Association Involving Optically Active Ions. III. Pfeiffer Effect in Tris(phenanthroline)-zinc(II) or -nickel(II) -Alkaloid Systems

Kazuko OGINO* and Tokue KUMAGAI**

Department of Chemistry, Faculty of Science, Tohoku University, Aoba, Aramaki, Sendai 980

(Received October 11, 1973)

Pfeiffer effect was studied in aqueous solutions containing tris(phenanthroline)metal(II) (metal=zinc or nickel) complexes and various alkaloids. The results were interpreted quantitatively from the viewpoint of stereoselective association and the resulting equilibrium shift. The contribution of π - π interaction between the complex and the alkaloid conjugate systems to the stereoselective association is suggested. NMR data were found to be consistent with the π - π interaction. Relation between the sign of the Pfeiffer rotation and the absolute configuration of the complex is presumed.

The induction of new optical activity by the addition of some resolvable complexes to a solution containing optically active substances is known as Pfeiffer effect.¹⁾ It has been interpreted from the viewpoint of equilibrium shift,¹⁻⁶⁾ configurational activity,³⁾ differential association,²⁾ hydrophobic bonding,⁶⁾ etc. However, few quantitative analyses based on the mechanisms listed above have been reported. In this paper, Pfeiffer rotation was measured in solutions containing various alkaloids, and a quantitative analysis of Pfeiffer rotation from the viewpoint of differential association and the resulting equilibrium shift was attempted.

Experimental

Optical rotatory dispersion curves were obtained with a Jasco UV/ORD 5 spectrophotometer equipped with a constant temperature cell compartment. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. The complexes $[\text{Zn}(\text{phen})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ and $[\text{Ni}(\text{phen})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ were obtained by mixing the corresponding metal chloride with stoichiometric amount of phenanthroline and recrystallized from water. Alkaloid hydrochlorides were obtained by neutralizing the free base with an equivalent amount of hydrochloric acid. All other chemicals were of guaranteed reagent grade.

Results and Discussion

Optical rotatory dispersion curves were recorded from 350 to 650 nm in aqueous solutions containing phenanthroline complexes, alkaloid monohydrochloride and some electrolyte in a 1 cm cell. Fig. 1 shows the curves in a solution containing 0.02 M $[\text{Ni}(\text{phen})_3]^{2+}$, 0.02 M cinchonine hydrochloride and 0.5 M NaCl. An instantaneous change in rotation takes place after mixing the solution. Rotation at this stage is denoted by α_i . A further change in rotation proceeds gradually and after *ca.* 70 hours a final value, α_∞ is reached. This slow change is considered to be due to the inversion of configuration of the complex. The rotatory dispersion curve of cinchonine hydrochloride (denoted by α_x) is also given in Fig. 1. In the case of zinc complex, the inversion of configuration is so rapid

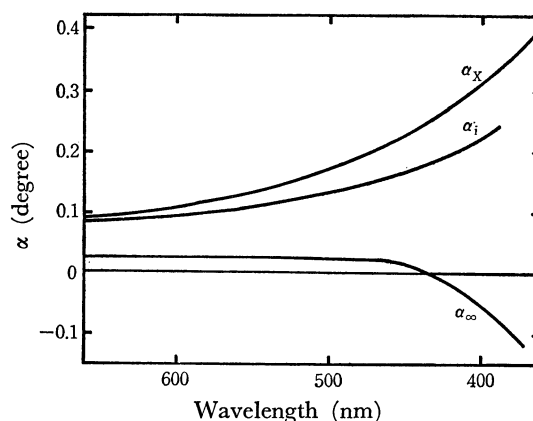
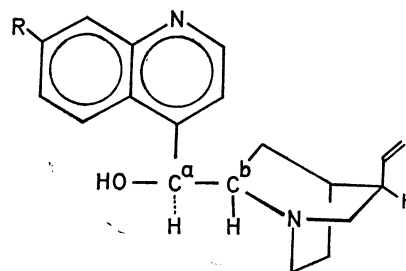


Fig. 1. Optical rotatory dispersion curves of 0.02 M cinchonine hydrochloride (α_x) and a solution containing 0.02 M cinchonine hydrochloride, 0.02 M $[\text{Ni}(\text{phen})_3]\text{Cl}_2$ and 0.5 M NaCl (α_i and α_∞). The α_i curve was measured immediately after mixing and the α_∞ curve at equilibrium. Cell length, 1 cm; temperature, 30 °C.

that only the α_∞ value is measured. The overall rotational change is defined as the Pfeiffer rotation in this paper:

$$\alpha_p = \alpha_\infty - \alpha_x$$

Nature of Alkaloids. The Pfeiffer rotations with various alkaloids are tabulated in Table 1. The α_p values were obtained most accurately at 400 nm, and data at this wavelength are given. The magnitude of Pfeiffer rotation decreases in the order, cinchonine and cinchonidine > strychnine and brucine ≥ quinine and quinidine for both zinc(II) and nickel(II) complexes. The same order was observed at other wave-



- I. R=H: cinchonine
II. R=OCH₃: quinidine

* Present address: College of Medical Sciences, Tohoku University, Seiryomachi, Sendai.

** Present address: Research Institute for Catalysis, Hokkaido University, Sapporo.

TABLE 1. PFEIFFER ROTATION AT 400 nm IN SOLUTIONS CONTAINING 0.02 M ALKALOID HYDROCHLORIDE AND 0.02 M $[\text{Zn}(\text{phen})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ OR $[\text{Ni}(\text{phen})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, 30°C

Alkaloid	$[\text{Zn}(\text{phen})_3]^{2+}$			$[\text{Ni}(\text{phen})_3]^{2+}$				
	α_x	α_∞	α_p	α_i	α_∞	$\alpha_i - \alpha_x$	$\alpha_\infty - \alpha_i$	α_p
Cinchonine	0.308°	0.028°	-0.280°	0.263°	0.130°	-0.045°	-0.133°	-0.178°
Cinchonidine	-0.248°	-0.043°	0.205°	-0.178°	-0.069°	0.070°	0.109°	0.179°
Quinine	-0.405°	-0.324°	0.081°	-0.334°	-0.305°	0.071°	0.029°	0.100°
Quinidine	0.505°	0.420°	-0.085°	0.425°	0.418°	-0.080°	-0.007°	-0.087°
Strychnine	-0.075°	-0.175°	-0.100°	-0.083°	-0.180°	-0.008°	-0.097°	-0.105°
Brucine	-0.110°	-0.195°	-0.085°	-0.105°	-0.214°	-0.005°	-0.109°	-0.104°

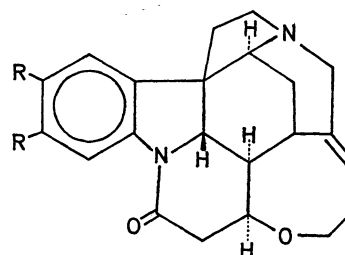
TABLE 2. 60 MHz NMR DATA. The chemical shifts are against external TMS* standard (Hz)

Solution	Cinchonine		Phenanthroline ^b			
	Quinolyl ^a	-CH=CH ₂	2, 9	3, 8	4, 7	5, 6
0.05 M Cinchonine hydrochloride	542	372, 326				
0.05 M Cinchonine hydrochloride + 0.01 M $[\text{Zn}(\text{phen})_3]^{2+}$	534	366, 321	501	469	527	493
0.01 M $[\text{Zn}(\text{phen})_3]^{2+}$			504	472	531	497

a) The chemical shift is for the proton on the carbon atom adjacent to the quinolyl nitrogen atom. b) The assignment is after J. D. Miller and R. M. Prince, *J. Chem. Soc.*, **1965**, 3185.

lengths in 350~700 nm region. Cinchonidine is a stereoisomer of cinchonine(I)⁷⁾ with reversed configurations of the two carbon atoms C^a and C^b. The magnitude of Pfeiffer rotation caused by these alkaloids are similar to each other except the sign. Quinine and quinidine(II) are methoxyl derivatives of cinchonidine and cinchonine respectively. The magnitudes of Pfeiffer rotations by these alkaloids are much smaller than those by cinchonine and cinchonidine. These differences should be related to the presence of a methoxyl group on the quinolyl part in quinine or quinidine. This fact suggests that there is π - π interaction between the conjugate system of phenanthroline rings of the complex and the quinolyl group of cinchonine or cinchonidine, and that stereoselectivity in such an interaction is responsible for Pfeiffer rotation. The presence of methoxyl group at the quinolyl part of quinine or quinidine would make π - π interaction less favorable sterically than in cinchonine or cinchonidine. As will be mentioned later, such stereoselectivity is related more directly to $(\alpha_\infty - \alpha_i)$ values than to α_p values (see Eq. 11). It is seen in Table 1 that $\alpha_\infty - \alpha_i$ values for cinchonine or cinchonidine are much larger than those for quinine or quinidine for nickel(II) complexes. The π - π interaction mentioned above has hydrophobic nature. Brasted *et al.*⁶⁾ reported that the effects of solvent and urea on the Pfeiffer effect in $[\text{Zn}(\text{phen})_3]^{2+}$ -alkaloid(cinchonine hydrochloride or strychnine hydrosulfate) systems and in other systems indicate hydrophobic bonding between the complex and the optically active substance.

The magnitudes of the Pfeiffer rotations of strychnine(III)⁸⁾ hydrochloride and brucine(IV) hydrochloride are of the same order to each other and much smaller than those of cinchonine or cinchonidine hydrochloride. This fact shows that the methoxyl groups in brucine do not exert significant influence on Pfeiffer effect. The π - π interaction between the phenanthrol-



III. R=H; strychnine

IV. R=OCH₃; brucine

ine rings of the complex and the phenyl group of strychnine may be smaller than that between the complex and the quinolyl group of cinchonine or contribution of other interactions may be larger.

NMR Data. Table 2 gives NMR data of cinchonine hydrochloride and $[\text{Zn}(\text{phen})_3]^{2+}$. Chemical shifts were given in cps from sodium trimethylsilyl sulfonate(TMS*) used as external standard.⁹⁾ The data in the table indicate that the quinolyl protons of cinchonine are shifted toward higher field by 8 or 9 cps by the addition of 0.01 M $[\text{Zn}(\text{phen})_3]^{2+}$. Other protons in cinchonine are shifted by only 5 to 6 cps. The phenanthroline protons of the complex are also affected by the addition of cinchonine hydrochloride: 2, 9 and 3, 8 protons are shifted by 2 or 3 cps and 4, 7 and 5, 6 protons by *ca.* 4 cps toward higher field. These shifts can be due to the effect of the ring current of the phenanthroline or the quinolyl group. These results are not inconsistent with the π - π interaction mentioned above.

Influence of Indifferent Electrolyte. Both the complex ion and the monoprotinated alkaloid ion are positively charged. Association between these cations by hydrophobic bonding or π - π interaction should overwhelm the electrostatic repulsion between them.

TABLE 3. EFFECT OF ELECTROLYTE ON PFEIFFER ROTATION AT 400 nm IN $[\text{Zn}(\text{phen})_3]^{2+}$ -CINCHONIDINE HYDROCHLORIDE SYSTEM
Cell length, 1 cm; temperature, 30 °C

$[\text{Zn}(\text{phen})_3]\text{Cl}_2$, M	Cinchonidine, M	Electrolyte	α_P
0.02	0.02	None	0.205°
0.02	0.02	0.02 M NaCl	0.314°
0.02	0.02	0.02 M CaCl_2	0.403°
0.02	0.02	0.5 M NaCl	0.52°
0.01	0.02	0.03 M CaCl_2	0.248°
0.01	0.02	0.5 M NaCl	0.294°

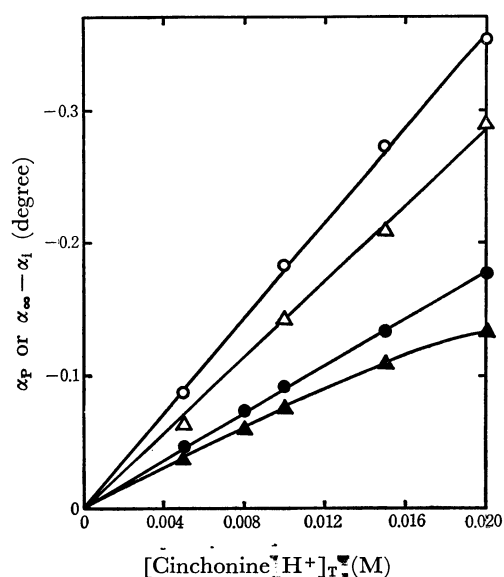


Fig. 2. Dependence of α_P (O, ●) and $\alpha_\infty - \alpha_i$ (Δ, ▲) values on cinchonine hydrochloride concentration in solutions with (O, Δ) and without (●, ▲) 0.5 M NaCl. Cell length, 1 cm; temperature, 30 °C; $[\text{Ni}(\text{phen})_3]\text{Cl}_2$, 0.02 M.

Addition of electrolyte would diminish such a repulsion. Table 3 and Fig. 2 give Pfeiffer rotations in the presence and in the absence of electrolytes. It is seen that both sodium chloride and calcium chloride have considerable enhancing effect on Pfeiffer rotation. The enhancing effect seems to be more than that to be understood from simple electrostatic consideration.

Concentrations of Alkaloids and the Complex. The dependencies of Pfeiffer rotation on concentrations of the complexes and alkaloids were studied (Figs. 2 to 4). In these solutions 0.5 M NaCl was added in order to maintain ionic strength of the solution constant. The concentration ranges of the complexes and alkaloids were restricted because of the limited solubility. In the following, concentration dependence is analyzed quantitatively in terms of stereoselective association between the complex and the alkaloid cations. As is mentioned later, 1:1 association seems to be predominant under the experimental condition and only 1:1 association was taken into consideration in the following treatment. The association of the optically active alkaloid with one enantiomer of the complex

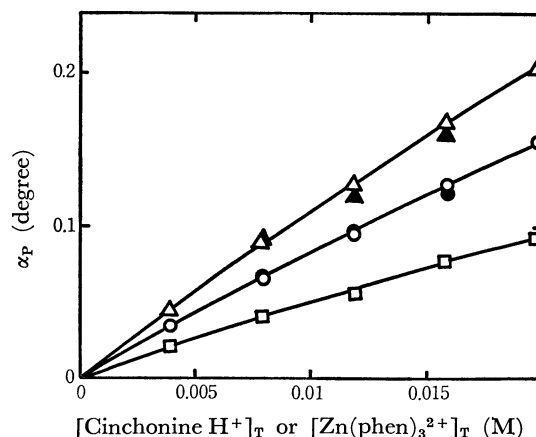


Fig. 3. Dependence of Pfeiffer rotation on cinchonine hydrochloride concentration in solutions containing 0.0049 M $[\text{Zn}(\text{phen})_3]\text{Cl}_2$ and 0.5 M NaCl at 380 (Δ), 400 (O) and 450 (□) nm. Dependence on $[\text{Zn}(\text{phen})_3]^{2+}$ concentration in solutions containing 0.0049 M cinchonine hydrochloride and 0.5 M NaCl at 380 (▲) and 400 (●) nm is also shown. Cell length, 1 cm; temperature, 30 °C.

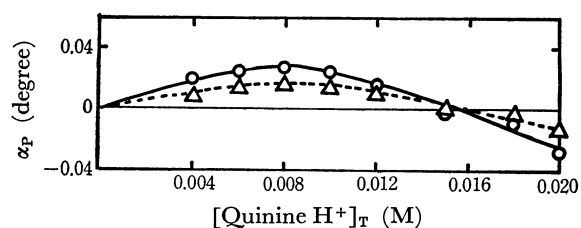
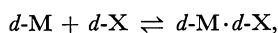
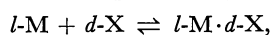


Fig. 4. Pfeiffer rotation at 400 (O) and 450 (Δ) nm in solutions containing 0.01 M $[\text{Zn}(\text{phen})_3]\text{Cl}_2$, 0.5 M NaCl and various amount of quinine hydrochloride. Cell length, 1 cm; temperature, 30 °C.

can be different from that with the other enantiomer:



$$K_{da} = [d\text{-M} \cdot d\text{-X}] / ([d\text{-M}][d\text{-M}][d\text{-X}]) \quad (1)$$



$$K_{la} = [l\text{-M} \cdot d\text{-X}] / ([l\text{-M}][d\text{-X}]) \quad (2)$$

where $d\text{-M}$ and $d\text{-X}$ denote one enantiomer of the complex and the optically active substance (e.g. alkaloid cation), respectively and $l\text{-M}$ and $l\text{-X}$ their antipodes. A stereoselective association has been reported between some trivalent complex ions and tartrate ions.^{10,11)}

The optical rotation of the solution containing a racemic salt of the complex and alkaloid in a cell of unit cell length is given by

$$\alpha = \theta_x[d\text{-X}] + \theta_a([d\text{-M}] - [l\text{-M}]) + \theta_{da}[d\text{-M} \cdot d\text{-X}] + \theta_{la}[l\text{-M} \cdot d\text{-X}] \quad (3)$$

where θ_x , θ_a , θ_{da} and θ_{la} denote molecular rotations of $d\text{-X}$, $d\text{-M}$, $d\text{-M} \cdot d\text{-X}$ and $l\text{-M} \cdot d\text{-X}$, respectively. Until inversion of the complex takes place, the concentrations of the two enantiomers of the complex should be equal:

$$[d\text{-M}]_i + [d\text{-M} \cdot d\text{-X}]_i = [l\text{-M}]_i + [l\text{-M} \cdot d\text{-X}]_i = [M]_T/2 \quad (4)$$

where the suffix i denotes the time immediately after

mixing before any inversion takes place. It follows from Eqs. (1) to (4) that a new optical activity is induced even when no inversion occurs unless $K_{da} = K_{la}$ and $\theta_{da} = -\theta_{la}$. It was shown previously that θ_{da} is considerably different from θ_{la} in some Co(III) complex-tartrate systems.¹¹⁾ In the case of the nickel complex, the rate of inversion is slow and the α_1 values in Table 1 are considered to correspond to the optical rotations given by Eqs. (3) and (4).

When K_{da} is not equal to K_{la} , associations represented by Eqs. (1) and (2) cause differences in concentrations of free d -M and l -M, and inversion of the complex will take place to make them equal:

$$[d-M]_{\infty} = [l-M]_{\infty} \quad (5)$$

where the parenthesis with suffix ∞ denotes the concentration at equilibrium. The optical rotation of the equilibrated solution, α_{∞} , is given by

$$\alpha = \theta_X[d-X]_{\infty} + (\theta_{da}K_{da} + \theta_{la}K_{la})[d-M]_{\infty}[d-X]_{\infty} \quad (6)$$

If the extent of association is small, the equation

$$[d-X]_T \approx [d-X]_{\infty} \quad (7)$$

holds, where $[d-X]_T$ is the total concentration of the alkaloid salt, and the Pfeiffer rotation is expressed as

$$\alpha_P = a[d-M]_{\infty}[d-X]_{\infty} \quad (8)$$

where

$$\alpha = \theta_{da}K_{da} + \theta_{la}K_{la} \quad (9)$$

Eq. (8) is transformed to

$$[d-X]_{\infty}/\alpha_P = 2(1 + K_{app}[d-X]_{\infty})/(a[M]_T) \quad (9)$$

where

$$K_{app} = (K_{da} + K_{la})/2 \quad (10)$$

The plot of the left-hand side of Eq. (9) vs. $[d-X]_{\infty}$ should be a straight line, and the ratio of slope to intercept is equal to K_{app} .

This procedure was applied to the data in Fig. 3. A correction was made for Eq. (7) by stepwise approximation. The values of K_{app} thus obtained are listed in Table 4. Values obtained from data at different wavelengths are in agreement with one another. It is in accord with the assumption of the absence of the higher order association.¹¹⁾ Theoretical curves calculated by use of Eq. (8) and K_{app} values in Table 4 are given in Fig. 3 by solid lines. They are in agreement with experimental plots. From the

TABLE 4. ASSOCIATION CONSTANTS BETWEEN $[Zn(phen)_3]^{2+}$ AND MONOPROTONATED ALKALOID CATIONS IN SOLUTIONS CONTAINING 0.5 M NaCl OBTAINED BY USE OF Eq. (9)

Alkaloid	Temp.	K_{app}^a
Cinchonine	30°	8.3 (380 nm) 8.3 (400 nm)
		8.4 (450 nm)
	35°	7.7 (400 nm)
	25°	8.9 (400 nm)
Cinchonidine	30°	7.3 (400 nm) 7.0 (420 nm)
		9.5 (450 nm)

a) Because of the uncertainty in the measurement in optical rotation the precision of K_{app} values is ± 1.5 . The values in parentheses are wavelengths at which measurement was made.

temperature dependence of Pfeiffer rotation and that of K_{app} value, the ΔH° for the association between $[Zn(phen)_3]^{2+}$ and cinchonine hydrochloride was calculated to be -3 kcal/mol. This value is comparable with those reported for some systems where hydrophobic bonding is concerned.¹²⁾

Figure 4 shows concentration dependence of Pfeiffer rotation in $[Zn(phen)_3]^{2+}$ -quinine hydrochloride system. The magnitude is much smaller than those observed in cinchonine or cinchonidine hydrochloride systems, and the sign of α_P changes with change in quinine concentration, positive for $[X] < 0.015$ M and negative for $[X] > 0.015$ M at 400 nm. It may be because of the presence of higher order association to a considerable extent.

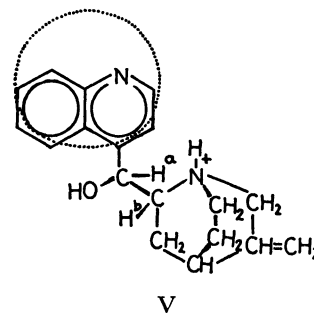
As is seen in Fig. 2, α_P is proportional to the alkaloid concentration within experimental error in $[Ni(phen)_3]^{2+}$ -cinchonine hydrochloride system. Though K_{app} value could not be obtained in this system, an upper limit is given: $K_{app} \leq 8$. From a comparison of Eqs. (3) and (6), it follows that the value $\alpha_{\infty} - \alpha_1$ can be approximated as

$$\alpha_{\infty} - \alpha_1 \approx \theta_d([d-M]_i - [l-M]_i) \approx \theta_d([l-M]_{T,\infty} - [d-M]_{T,\infty}) \quad (11)$$

within $\pm 10\%$ if $K_{app} \leq 8$, $0.5 < K_{da}/K_{la} < 2$ and $0.5 < |\theta_{da}/\theta_{la}| < 2$. From data in Fig. 2 and optical rotation of pure $(-)_D-[Ni(phen)_3](ClO_4)_2$, it is calculated that when a solution containing 0.02 M $[Ni(phen)_3]Cl_2$, 0.02 M cinchonine hydrochloride and 0.5 M NaCl is equilibrated, the total amount of l -rotatory complex is more than that of the d -rotatory complex by about 3 %. Taking $K_{app} < 8$ for this system into account, it follows that K_{la} is considerably larger than K_{da} for the association between $[Ni(phen)_3]^{2+}$ and cinchonine hydrochloride.

Sign of Pfeiffer Rotation and Absolute Configuration.

The more favorable conformation of cinchonine is presumed to be one in which the two hydrogen atoms on the two carbon atoms adjacent to quinolyl group, H^a and H^b , are *trans* to each other as depicted in V. If π - π interaction between the phenanthroline rings of the complex and the quinolyl group of cinchonine is contributing to the association (see V), cinchonine seems to associate more favorably with *tris*(phenanthroline)complex of Λ configuration than with that of Δ configuration. The absolute configuration of $(+)_D-[Ni(phen)_3]^{2+}$ was determined to be Λ by X ray



V

The dotted circle denotes interaction between the quinolyl group and the phenanthroline rings of the complex.

analysis.¹³⁾ Hence the sign of the Pfeiffer rotation in $[\text{Ni}(\text{phen})_3]^{2+}$ -cinchonine system should be minus. This is in accord with the experimental results. It is concluded that the absolute configuration of phenanthroline complexes can be deduced from the sign of Pfeiffer rotation with certain types of alkaloid. The sign of Pfeiffer rotation in $[\text{Zn}(\text{phen})_3]^{2+}$ -cinchonine system is minus. It follows from above argument that the absolute configuration of $(+)_D$ - $[\text{Zn}(\text{phen})_3]^{2+}$ is *A*.

The prediction of the absolute configuration of Pfeiffer active complexes has also been proposed by Kirschner and Pollock¹⁴⁾ using optically active dibasic acids.

The authors wish to thank Professors Kazuo Saito and Junnosuke Fujita for their helpful discussions.

References

- 1) P. Pfeiffer and K. Quehl, *Ber.*, **64**, 2267 (1931); **65**, 560 (1932); P. Pfeiffer and Y. Nakatsuka, *ibid.*, **66**, 410, 415 (1933).
 - 2) E. E. Turner and M. M. Harris, *Quart. Rev.* (London), **1**, 299 (1947).
 - 3) F. P. Dwyer and E. C. Gyarfas, *Nature*, **168**, 28 (1951).
 - 4) E. C. Gyarfas and F. P. Dwyer, *Rev. Pure Appl. Chem.*, **4**, 73 (1954).
 - 5) S. Kirschner and N. Ahmad, in S. Kirschner ed., "Coordination Chemistry", Plenum Press, New York, 1969, p. 42 and references therein.
 - 6) R. C. Brasted, V. J. Landis, E. J. Kuhajek, P. E. R. Nordquist, and L. Mayer, *ibid.*, p. 64 and references therein.
 - 7) V. P. Prelog and O. Hafliger, *Helv. Chim. Acta* **33**, 2021 (1950).
 - 8) K. Nagarajan, Ch. Weissman, H. Schmid, and P. Karrer, *ibid.*, **46**, 1212 (1963).
 - 9) Proton signals of TMS* is affected by the phenanthroline complex. Presence of 0.025 M $[\text{Zn}(\text{phen})_3]\text{Cl}_2$ makes TMS* signal move by *ca.* 30 cps toward higher field. The phenanthroline signals of the complex were also found to be dependent on its concentration.
 - 10) K. Ogino and U. Saito, *This Bulletin*, **40**, 826 (1967).
 - 11) K. Ogino, *ibid.*, **42**, 447 (1969).
 - 12) P. Molyneur and H. P. Frank, *J. Amer. Chem. Soc.*, **83**, 3169 (1961).
 - 13) K. R. Butler and M. R. Snow, *J. Chem. Soc. A*, **1971**, 565.
 - 14) S. Kirschner and R. J. Pollock, *Proc. XIV ICCG*, Toronto, 1972, p. 545.
-