CHROMATOGRAPHIC STUDY OF OPTICAL RESOLUTION

V*. RESOLUTION OF cis-DIAZIDOBIS(ETHYLENEDIAMINE) AND cis-α-DIAZIDO(TRIETHYLENETETRAMINE) COBALT(III) COMPLEXES BY ANTIMONY d-TARTRATE

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(First received March 16th, 1979; revised manuscript received May 14th, 1979)

SUMMARY

Among several cis-[CoX$_2$(en)$_2$]$^+$ and cis-α-[CoX$_2$trien]$^+$ (X = NCS$^-$, NO$_2^-$ and N$_3^-$) complexes, only cis-diazido complexes were found to be well resolved into enantiomers by ion-exchange chromatography using K$_2$(Sb d-tart)$_2$ aqueous solution as eluent, and a mechanism involving the ion (Sb d-tart)$_2^{2-}$ is proposed. Study of the chromatographic behaviour of cis- and trans-[Co(N$_3$)$_2$(en)$_2$]$^+$ has revealed that whereas the separation factor of geometric isomers decreases with increasing concentration of the resolving agent, the separation factor of optical isomers increases.

INTRODUCTION

Many examples of complete resolution by ion-exchange chromatography of tervalent cobalt(III) complexes, such as [Co(en)$_3$]$^{3+}$ and its related luteo-type complexes have been reported[1-7]. In contrast, there has been only one example[8] of complete resolution of a univalent complex cation, namely cis(O)trans(N)cis(NH$_3$)[Co(gly)$_2$(NH$_3$)$_2$]$^+$, and no complete resolution of univalent bis(ethylenediamine)cobalt(III) complexes has been reported. This seems to be quite strange. The electrostatic interaction between the complex cation and the counter anion (resolving agent) should be weaker in the univalent complex than in the tervalent complex. Therefore, chiral discrimination should be more favoured in the univalent complex than in the tervalent complex. However, the problem must not be considered from this kind of abstract viewpoint. Because optical resolution is concerned with specific stereochemical interaction, we should pay attention to the molecular structures of the individual interacting species. Here we should notice that there are limitations to the kinds of resolving agents that are available for chromatographic separation: d-tartrate and antimony d-tartrate have been the only two available in practice. Accordingly, the possibility

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of optical resolution should be considered based on the structures of these resolving agents. That is, we have to examine whether these resolving agents make a good fit to one of the enantiomers of the complex to be resolved.

As to the mechanism of optical resolution by d-tartrate anion (abbreviated as d-tart^{2-}), the close contact association model between the complex and d-tart^{2-} has been established[9–11]. According to this model, the d-tart^{2-} ion approaches the Λ-[Co(en)$_3$]$^{3+}$ ion along its three-fold axis and makes a face-to-face close contact with the complex through the three N–H$\cdots$O hydrogen bonds. Combination of d-tart^{2-} and Δ-[Co(en)$_3$]$^{3+}$ does not produce such a good fit. For such a close contact, the triangular facet made of three NH$_2$ groups is necessary. Complexes having such a triangular facet can be resolved by d-tart. However, cis-[CoX$_2$(en)$_2$]$^+$ type complexes have no such facet. They are not expected to be resolved by d-tart^{2-} in chromatography.

A mechanism for chromatographic optical resolution by antimony d-tartrate anion [abbreviated as (Sb d-tart)$_2$$^{2-}$] has also been proposed recently[12], whereby the anion fits the special L-shaped channel formed by chelate rings of the enantiomer of the complex. Such a channel also exists in cis-[CoX$_2$(en)$_2$]$^+$. Therefore, we can expect optical resolution of some cis-[CoX$_2$(en)$_2$]$^+$ complexes using antimony d-tartrate solution as eluent. Our attempts to find an example of complete resolution of cis-[CoX$_2$(en)$_2$]$^+$ by ion-exchange chromatography eventually led to a fairly successful separation of the enantiomers of diazido complexes.

EXPERIMENTAL

Sample solution

All complexes except cis-α-[Co(N$_3$)$_2$trien]$^+$ salt were prepared by the method given in the Inorganic Synthesis. cis-α-[Co(N$_3$)$_2$trien]$^+$ salt was prepared by modifying the method for the corresponding ethylenediamine complex. Optical resolution of cis-[Co(N$_3$)$_2$(en)$_2$]$^+$ was done according to the literature[16]. The compounds were identified by their ultraviolet (UV), proton magnetic resonance and circular dichroism (CD) spectra. Sample solutions were prepared by dissolving 5–10 mg of complexes in the same solution as the eluents.

Eluent

Reagent grade potassium antimony tartrate was purchased from Hayashi (Osaka, Japan). Sodium antimony tartrate was prepared from the potassium salt and sodium perchlorate. The saturated solution of the potassium salt was *ca.* 0.12 M and that of the sodium salt *ca.* 0.5 M.

Chromatography

SP-Sephadex C-25 (Pharmacia, Uppsala, Sweden) was used as a packing material in potassium form. The columns were 98 $\times$ 1.1 cm I.D., and 18 $\times$ 0.65 cm I.D. The flow of the eluent was effected by gravity and was controlled by hydrostatic pressure, using a Mariottes flask. The effluent was collected in fractions by means of a balance fraction collector. The amount of a solute in the fractions was determined by measurement of the intensity of the first absorption band of each complex. Blue Dextran 2000 was used as a marker for the void volume of the column.

To calculate the separation factor of azido complexes, a small column (packed sodium form resin) was used. Optically active azido complexes were injected individually into the column through a septam kit by a syringe, with 20 μl being typical. This flow-rate was controlled by a peristaltic pump at 0.2 ml/min. The effluent was introduced into the micro flow cell (10 μl) by capillary tubing. The detector was operated at 535 nm.

RESULTS AND DISCUSSION

Although the discrimination mechanism in diastereomeric crystals containing (Sb d-tart)$_2^{2-}$ has not been elucidated yet, cis-[Co(NCS)$_2$(en)$_2$]$^+$, cis-[Co(NO$_2$)$_2$(en)$_2$]$^+$ and cis-[Co(N$_3$)$_2$(en)$_2$]$^+$ are well known to be resolved into enantiomers by way of the diastereomeric crystals of (Sb d-tart)$_2^{2-}$ (refs. 13–16). Unlike cis-[CoCl$_2$(en)$_2$]$^+$ and cis-[Co(CH$_3$CO$_2$)$_2$(en)$_2$]$^+$, these three complexes are all fairly inert and do not show aquation during the elution. This was confirmed by their UV spectra which did not change over 24 h in an aqueous solution of Na$_2$ (Sb d-tart)$_2$. Thus, it seems to be natural to start the study of chromatographic resolution by using antimony d-tartrate aqueous solution as eluent for these three complexes. Fig. 1 shows the elution curves of these three complexes eluted with 0.05 M K$_2$(Sb d-tart)$_2$ aqueous solution. The elution curves of the dirhodanato and dinitro complexes consis tof a single peak. The fractions of the front and the rear of the peak showed almost no CD peak. (However, with 0.075 M K$_2$(Sb d-tart)$_2$, the front fraction of the peak showed the CD spectrum of the Δ enantiomer and the rear fraction showed the CD spectrum of the Λ enantiomer in both complexes. This will be discussed later.) This indicates that optical resolution
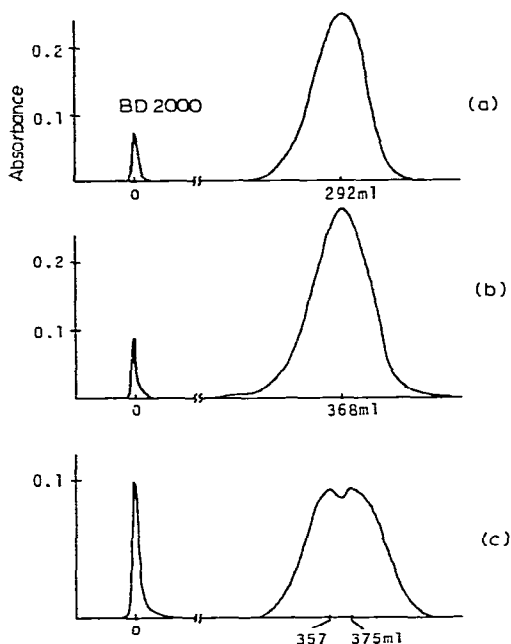

Fig. 1. Chromatograms of cis-[Co(X)$_2$(en)$_2$]$^+$. (a) X = NCS$^-$; (b) X = NO$_2^-$; (c) X = N$_3^-$. Packing, SP-Sephadex C-25; flow-rate, 0.5–0.7 ml/min: column, 98 × 1.1 cm glass bore; eluent, 0.05 M K$_2$(Sb d-tart)$_2$ aqueous solution.

is not achieved practically for dirhodanato and dinitro complexes. However, the elution peak of the diazido complex shows a slight splitting (Fig. 1c), and the fractions corresponding to these split peaks showed CD spectra of opposite signs (Fig. 2). Therefore, it can be said that optical resolution is achieved to a considerable extent for cis-[Co(N$_3$)$_2$(en)$_2$]$^+$.

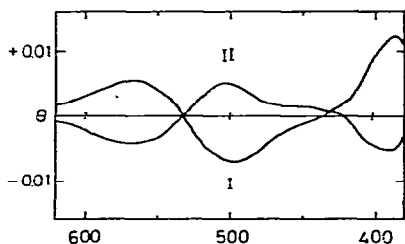Fig. 2. CD spectra of the first eluate (I) and the second eluate (II) of cis-[Co(N$_3$)$_2$(en)$_2$]$^+$.

Here it is necessary to decide whether the first eluted isomer is Λ or Δ. As to the assignment of the absolute configuration of cis-[Co(N$_3$)$_2$(en)$_2$]$^+$ there is confusion. Yamasaki et al.[16] assigned the enantiomer whose major CD peak (500 nm, $\Delta\varepsilon = 1.17$) is positive (curve II in Fig. 2) to be Λ. Kindred and House[17] gave the opposite assignment[17]. Our assignment agrees with that of Kindred and House on the basis of the Pfeiffer effect[18]. Thus, we will assign the first eluted isomer to be Λ, in agreement with the discrimination mechanism proposed in the second paper of this series[4], in which the (Sb d-tart)$_2$$^{2-}$ anion fits the L-shaped channel of the Λ enantiomer and associates more with the Λ than with the Δ and elutes the former faster.

Here it must be explained why the diazido complex is resolved but the dirhodanato and dinitro complexes are not. If we assume that the discrimination of Λ and Δ by (Sb d-tart)$_2$$^{2-}$ is due to its fitting into the L-shaped channel of the Λ, (Sb d-tart)$_2$$^{2-}$ should approach the complex in the directions indicated by thin arrows in Fig. 3a. However, the L-shaped channel in cis-[CoX$_2$(en)$_2$]$^+$ is adjacent to the anionic ligand X$^-$, so that the coming (Sb d-tart)$_2$$^{2-}$ anion will feel electrostatic repulsion from X$^-$, which makes the possibility of approach from this direction very small. Thus, it is understandable that most of cis-[CoX$_2$(en)$_2$]$^+$ can not be resolved by ion-exchange chromatography. However, since cis-[Co(N$_3$)$_2$(en)$_2$]$^+$ is fairly well resolved by (Sb d-tart)$_2$$^{2-}$, ion association using the L-shaped channel should occur to a considerable extent, as shown by the broader arrows in Fig. 3c. This may be possible because the negative charge of N$_3$$^-$ is diluted on two terminal nitrogen atoms, as suggested in the following resonance scheme, so that the electrostatic repulsion against the approaching (Sb d-tart)$_2$$^{2-}$ is lowered.

$$\overset{-}{\text{Co-N}}\text{-}\overset{+}{\text{N}} \equiv \text{N} \longleftrightarrow \text{Co-N} = \overset{+}{\text{N}} = \overset{-}{\text{N}}$$
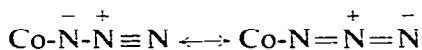
If this interpretation is valid, more efficient optical resolution should be achieved for cis-α-[Co(N$_3$)$_2$trien]$^+$ in which the bridging ethylene group between two en prevents the approach of (Sb d-tart)$_2$$^{2-}$ in this direction (a thin arrow in Fig. 3d) and forces the anion to associate with the complex using the L-shaped channel, as

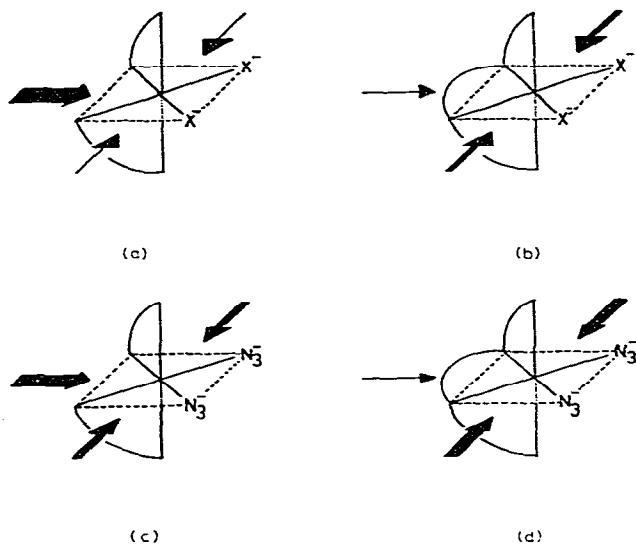(a)   (b)

(c)   (d)

Fig. 3. Access of $[Sb_2(d\text{-tart})_2]^{2-}$ to $cis\text{-}[Co(X)_2(N)_4]^+$: (a) $cis\text{-}[Co(X)_2(en)_2]^+$; (b) $cis\text{-}\alpha\text{-}[Co(X)_2\text{-}trien]^+$ (X = NCS and NO_2); (c) $cis\text{-}[Co(N_3)_2(en)_2]^+$; (d) $cis\text{-}\alpha\text{-}[Co(N_3)_2trien]^+$.

shown with broad arrows in Fig. 3d. This expectation was fulfilled. The splitting of the elution peak became more marked for $cis\text{-}\alpha\text{-}[Co(N_3)_2trien]^+$ as shown Fig. 4c. The situation should be similar for $cis\text{-}\alpha\text{-}[Co(NO_2)_2trien]^+$ and $cis\text{-}\alpha\text{-}[Co(NCS)_2trien]^+$. In these complexes, although the elution curves still remained as a single peak, the front and the rear of the peak showed CD spectra of opposite signs. Thus, partial resolution is definitely achieved in these two cases. It must be noted that the CD spectrum of the first eluted enantiomer is that of the $\varLambda$ for all these three complexes.

To see the contribution of the chirality of the Sephadex skeleton to optical resolution, 0.15 M KCl aqueous solution was also used for elution of these six complexes. In these cases, the elution curve appears as a single peak. However, the front of the peak shows the CD spectrum of the $\varLambda$ enantiomer in all these cases. This means that the Sephadex skeleton preferentially adsorbs the $\varDelta$ enantiomer, so that the $\varLambda$ is eluted faster. Thus, it is concluded that the partial resolution was achieved with even achiral eluent. Because $cis\text{-}[Co(NO_2)_2(en)_2]^+$ and $cis\text{-}[Co(NCS)_2(en)_2]^+$ were not resolved with 0.05 M $K_2(Sb\ d\text{-tart})_2$, it should be considered that the preferential adsorption by the Sephadex skeleton of the $\varDelta$ enantiomer cancels the preferential association of $(Sb\ d\text{-tart})_2^{2-}$ with the $\varDelta$ enantiomer, so that not even partial resolution was achieved with 0.05 M $(Sb\ d\text{-tart})_2^{2-}$. Therefore, using a more concentrated solution of $(Sb\ d\text{-tart})_2^{2}$, to make the contribution of the eluent chirality exceed that of the Sephadex, should result in the $\varDelta$ enantiomer being eluted faster. This is, indeed, the case, as shown in Table I. It is worth noting that $(Sb\ d\text{-tart})_2^{2-}$ associates preferentially with the $\varDelta$ enantiomer. This means that $(Sb\ d\text{-tart})_2^{2-}$ can discriminate the $\varDelta$ from the $\varLambda$ through the association along a direction other than the L-shaped channel, in the cases of dinitro and dirhodanato ethylenediamine complexes. Only for $cis\text{-}[Co(N_3)_2(en)_2]^+$ does the association using the L-shaped channel overcome the other type of association, so that the $\varLambda$ enantiomer is always eluted faster than the $\varDelta$.

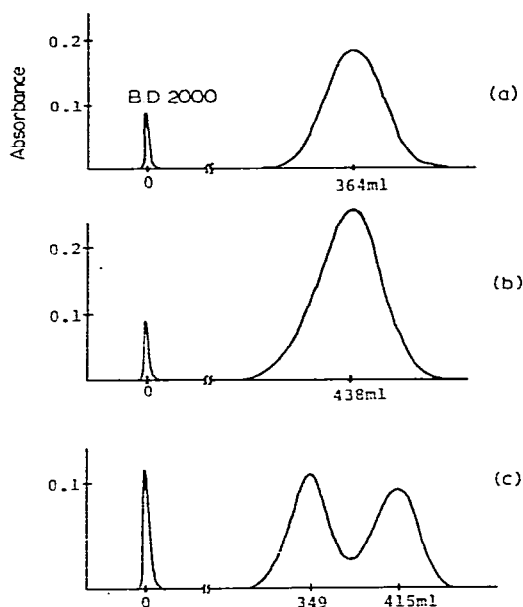Table I shows the absolute configuration of the first eluted enantiomer together

Fig. 4. Chromatograms of cis-α-[Co(X)₂trien]⁺. Conditions for elution as in Fig. 1.

with that of the complex in the less soluble diastereomer of antimony d-tartrate. The two configurations do not always coincide, which means that discrimination by (Sb d-tart)$_2^{2-}$ does not always occur by the same mechanism in chromatography and in crystals.

Next, let us consider how the efficiency of resolution is affected by variation of the conditions of chromatography. Here it is convenient to use the two values, separation factor and resolution factor, as the measure of separation of two samples (Λ and Δ). The separation factor is defined by the ratio of the adjusted retention volumes of two samples. The resolution factor is defined by the difference between two samples divided by the average peak width. The former represents the separation of the two peaks and the latter the sharpness of the peaks. Fig. 5 shows the elution curve at the flow-rate 0.15–0.2 ml/min. The resolution is definitely improved both in

TABLE I

ABSOLUTE CONFIGURATIONS OF THE COMPLEXES

Sample	Eluted faster from column		Formed less soluble (Sb d-tart)₂ ²⁻ diastereomer
	Solution of K₂ (Sb d-tart)₂	Solution of KCl	
[Co(N₃)₂(en)₂]⁺	Λ	Λ	Λ
[Co(NCS)₂(en)₂]⁺	Λ	Λ	Λ
[Co(NO₂)₂(en)₂]⁺	Λ	Λ	Λ
[Co(N₃)₂trien]⁺	Λ	Λ	Λ
[Co(NCS)₂trien]⁺	Λ	Λ	Δ
[Co(NO₂)₂trien]⁺	Λ	Λ	Δ

Fig. 5. Chromatograms of (a) cis-[Co(N₃)₂(en)₂]⁺, (b) cis-α-[Co(NCS)₂trien]⁺ and (c) cis-α-[Co(NO₂)₂trien]⁺. Flow-rate, 0.15–0.2 ml/min, other conditions as in Fig. 1.

separation and in sharpness. This is due to decreased turbulence and to the elution being carried out under a better equilibrium between the fixed and moving phases.

Fig. 6 shows the elution curves for cis-[Co(N₃)₂(en)₂]⁺ and for cis-α-[Co(N₃)₂(trien)]⁺ with the more concentrated solution of (Sb d-tart)₂²⁻ (0.075 M). In both cases, the curves show improved separation compared with the curves eluted with 0.05 M (Sb d-tart)₂²⁻. The trien complex shows a complete separation. To see the trend of the separation factor of enantiomers with variation of the concentration of eluent, both enantiomers of cis-[Co(N₃)₂(en)₂]⁺ were prepared and chromatographed
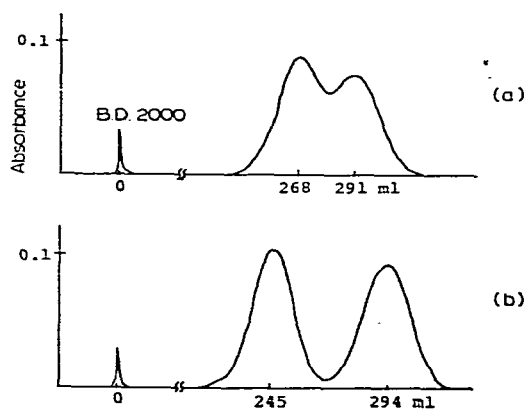
Fig. 6. Chromatogram of (a) cis-[Co(N₃)₂(en)₂]⁺ and (b) cis-α-[Co(N₃)₂trien]⁺. Eluent: 0.075 M K₂ (Sb d-tart)₂ aqueous solution, other conditions as in Fig. 1.

separately with (Sb d-tart)$_2$$^{2-}$ solutions of various concentrations, and the retention volumes were measured. From these retention volumes of the Λ and Δ enantiomers, the separation factors were calculated and plotted along the concentration of (Sb d-tart)$_2$$^{2-}$ (Fig. 7a). As seen in Fig. 7a, the separation factor of enantiomers increases with increasing concentration of the resolving agent. This trend is in marked contrast to that of the geometric isomers, as shown in Fig. 7b. Here, the retention volumes of $trans$-[Co(N$_3$)$_2$(en)$_2$]$^+$ were also measured, and the ratio of these and the average values of the retention volumes of cis-[Co(N$_3$)$_2$(en)$_2$]$^+$ were calculated and plotted against the concentration of (Sb d-tart)$_2$$^{2-}$. The separation factor of geometric isomers decreases with increasing concentration of eluent. As pointed out in a previous paper[19] concerning the elution order of geometric isomers, the separation is determined by the strength of adsorption of samples on the adsorbent, that is, the separation is adsorption-governing. This is because the dielectric constant is smaller in the fixed phase than in the moving phase and, in addition, the concentration of the eluent usually does not exceed that of the functional group in the resin. However, as the concentration of the eluent increases, the electrostatic interaction in the moving phase becomes closer and closer to that in the fixed phase, so that the separation becomes worse, and finally, when the electrostatic interaction becomes the same in both phases, separation does not occur. The decrease in the separation factor with increasing concentration of the eluent can be thus understood.
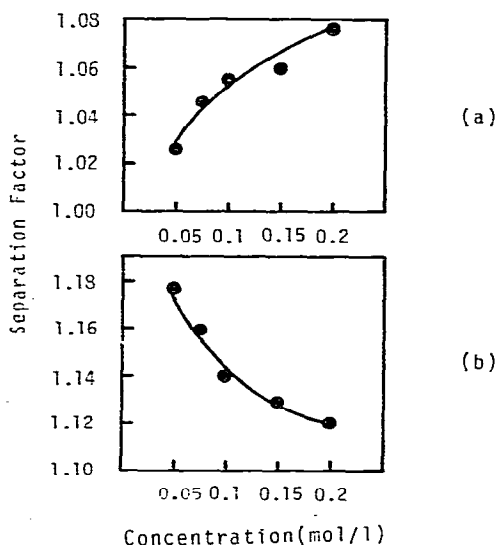

Fig. 7. Dependence of separation factor on concentration of Na$_2$(Sb d-tart)$_2$ in eluent. (a) Separation factor between cis-Λ- and cis-Λ-[Co(N$_3$)$_2$(en)$_2$]$^+$

$\alpha = V_{cis-\Lambda}/V_{cis-\Lambda}$

(b) Separation factor between cis- and $trans$-[Co(N$_3$)$_2$(en)$_2$]$^-$.

$\alpha = [V_{cis-\Lambda} + V_{cis-\Lambda}] \times 0.5/V_{trans}$

On the other hand, in the separation of optical isomers, the separation is done by the chiral counter-ion in the moving phase. Thus, the separation is always elution-governing. Here, although ion association always takes place owing to the electrostatic

attraction, the chiral discrimination is not electrostatic in nature. Such chiral discrimination may be more effective at high ionic strengths. The increase in the separation factor of enantiomers with increasing concentration of the chiral resolving agent can be thus understood.

REFERENCES

1 Y. Yoshikawa and K. Yamasaki, *Inorg. Nucl. Chem. Lett.*, 6 (1970) 523.
2 Y. Yoshikawa and K. Yamasaki, *Bull. Chem. Soc. Jap.*, 45 (1972) 179.
3 Y. Yoshikawa, K. Fuji and K. Yamasaki, *Bull. Chem. Soc. Jap.*, 45 (1972) 3451.
4 Y. Yoshikawa and K. Yamasaki, *Bull. Chem. Soc. Jap.*, 46 (1973) 3448.
5 M. Kojima, Y. Yoshikawa and K. Yamasaki, *Bull. Chem. Soc. Jap.*, 46 (1973) 1687.
6 H. Ogino and J. Fujita, *Chem. Lett.*, (1973) 517.
7 J. Fujita and H. Ogino, *Chem. Lett.*, (1974) 57.
8 K. Kobayashi and M. Shibata, *Bull. Chem. Soc. Jap.*, 48 (1975) 2561.
9 Y. Kushi, M. Kuramoto and H. Yoneda, *Chem. Lett.*, (1976) 135.
10 Y. Kushi, M. Kuramoto and H. Yoneda, *Chem. Lett.*, (1976) 339.
11 H. Yoneda and T. Taura, *Chem. Lett.*, (1977) 63.
12 H. Nakazawa and H. Yoneda, *J. Chromatogr.*, 160 (1978) 89.
13 D. A. House, *J. Inorg. Nucl. Chem.*, 35 (1973) 3103.
14 F. D. Dwyer and F. L. Garvan, *Inorganic Syntheses*, vol. 13, p. 196.
15 P. J. Staples and M. L. Tobe, *J. Chem. Soc.*, (1960) 4819.
16 K. Yamasaki, J. Hidaka and Y. Shimura, *Bull. Chem. Soc. Jap.*, 49 (1976) 3060.
17 I. J. Kindred and D. A. House, *J. Inorg. Nucl. Chem.*, 37 (1975) 1359.
18 Y. Wada, K. Miyoshi and H. Yoneda, *Chem. Lett.*, (1978) 763.
19 H. Yoneda and S. Yamazaki, *Bull. Chem. Soc. Jap.*, 52 (1979) 1859.