

An Approach to Resolution of DL-2, 2'-Bipiperidine

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Abstract

The reaction of $(\pm)$ -*trans*-dichlorobis(2,2'-bipiperidine)cobalt(III) ion with ammonium oxalate under acidic conditions has been shown to yield only one dl pair of *oxalatobis*(2,2'-bipiperidine)cobalt(III) complex ions. The oxalato complex isolated has been characterized by elemental analysis, absorption spectrum and ^{13}C -NMR spectrum. Partial resolution of the oxalato complex has been observed on cation exchange resin (SP-Sephadex C-25).

Introduction

Optical resolution of racemic compounds, which has many empirical aspects, is an important area of chemistry. On the other hand, the stereochemistry of octahedral metal complexes containing *N*-alkyl group substituted optically active polyamines has been of recent interest. Because the alkyl groups substituted in polyamines affect significantly the configuration of metal complexes, they are expected to be capable of asymmetric reactions in these systems (AJIOKA *et al.*, 1981). Although the diamines containing aliphatic heterocyclic rings belong to the class of *N*-alkylated polyamines; for example, 2,2'-bipiperidine (abbr. 2,2'-bpp), there is very limited information concerning their stereochemical behaviors to transition metal ions (YAMAGUCHI *et al.*, 1980).

Racemic 2,2'-bipiperidine, which has two six-membered heterocyclic rings, was first separated from the meso form in our recent work. Several attempts to resolve this racemic compound were performed, but no tendency to resolve into optical isomers was observed. However, we succeeded in optical resolution of the racemic diamine through its *trans*-dinitrobis(diamine)cobalt(III) complex, by using the resolving agent ammonium *d*-3-bromocomphor-9-sulfonate (abbr. HN_4 *d*-BCS). Namely, the repeated fractional recrystallization from its aqueous solution gave pure $(-)$ ₅₅₉-form complex. The absolute configuration of $(-)$ ₅₅₉-2,2'-bipiperidine, moreover, was determined as

R, R around the asymmetric carbon atoms by our recent X-ray structure study of $(-)_{{}_{546}}\text{-trans-[Co(NO}_2)_2((-)_{{}_{559}}\text{-2,2'-bpp)}_2] (d\text{-BCS)} \cdot 4\text{H}_2\text{O}$ (SATO *et al.*, 1982).

Although the previous method of optical resolution was available and not complicated, the final yield of optically active 2,2'-bipiperidine was not good (merely ca. 3%) and $(+)_{{}_{559}}\text{-2,2'-bipiperidine}$ could be hardly recovered. Those results will be reported elsewhere. We have investigated the stereoselective synthesis of a *cis-bis* (2,2'-bipiperidine)cobalt(III) complex and studied the optical resolution of the complex on the cation exchange resin (SP-Sepadex C-25) in hopes that this would give us the opportunity to obtain both $(+)$ and $(-)$ -bipiperidine. We report here our preliminary results from this work.

Experimental Section

Measurements: In this work the following instruments were used: a Shimadzu UV-210 spectrophotometer for absorption spectra (AB), a Jasco J-40 recording spectropolarimeter for circular dichroism measurements (CD). The ^{13}C -NMR spectra were obtained in D_2O or CD_3OD , with tetramethylsilane (TMS) as an external standard. The spectra were obtained in methanol for the *trans-dichloro* complex and in water for the other complexes. These measurements were performed on the instruments at the University of Tokyo. 2,2'-Bipiperidine was prepared by the method of KRUMHOLZ (1953) with slight modification.

The preparation of $(\pm)\text{-trans-[Co(NO}_2)_2(2,2'\text{-bpp)}_2] \text{NO}_2$ and $(\pm)\text{-trans-[CoCl}_2(2,2'\text{-bpp)}_2]\text{Cl}$ used in this study will be reported elsewhere.

Preparation of $(\pm)\text{-[Co(ox)(2,2'\text{-bpp)}_2]\text{ClO}_4 \cdot \text{H}_2\text{O}$

To an acidic solution of 1.0 g of $(\pm)\text{-trans-[CoCl}_2(2,2'\text{-bpp)}_2]\text{Cl}$ (pH=1.9 with hydrochloric acid, 40 ml) 0.3 g of ammonium oxalate monohydrate was added with stirring. The mixture was heated on a steam bath for 1 h at 55°C. The original green solution quickly turned reddish blue, and then colored reddish violet. After cooling, the solution was filtered and diluted with a small portion of water. A saturated aqueous solution of sodium perchlorate was useful to precipitate the product. Anal. Calcd for $\text{C}_{22}\text{H}_{42}\text{N}_4\text{O}_9\text{CoCl}$: C, 43.97; H, 7.04; N, 9.32. Found: C, 43.67; H, 6.75; N, 9.37.

Conversion of Perchlorate Salts to Chloride Salts

For ^{13}C -NMR measurements, slightly soluble perchlorate salts were converted to more soluble chloride salts by passing the perchlorate salts through a column of an anion exchange resin (Dowex 1-X8, 100–200 mesh) in the Cl^- form. The solutions were then evaporated on a rotary evaporator to the desired solids.

Separation of isomers of monooxalatobis(2,2'-bpp)cobalt(III) complex: Optical Resolution

A column chromatographic procedure was carried out as follows. The reaction mixture of $(\pm)\text{-trans-[CoCl}_2(2,2'\text{-bpp)}_2]\text{Cl}$ with ammonium oxalate was loaded onto a column (3 cm $\times$ 60 cm) of cation exchange resin (SP-Sephadex C-25, 40–120 micro-

meter mesh, Na^+ form). The volume of the reaction mixture used was 30 ml (1/3 of total). After flushing with 500 ml of water, the reddish violet complex ion adsorbed on the top of exchange resin was eluted by 0.01 M d-tartaric acid aqueous solution ($\text{pH}=\text{ca. } 2.5$). The flow rate was 20 ml/h.

Results and Discussion

Preparation of the complex. Under acidic conditions ($\text{pH}=1.9$), the mono-oxalato complex ion $(\pm)\text{-}[\text{Co}(\text{ox})(2,2'\text{-bip})_2]^+$ was synthesized by the reaction of the *trans*-dichloro complex with ammonium oxalate, and the distinct color change described above was then observed. The method described WERNER *et al.* (1899) was applied with modifications. Since the oxalato complex is very soluble in dilute hydrochloric acid, it can be crystallized by the addition of a saturated solution of sodium perchlorate with a sufficient yield. Therefore, the ^{13}C -NMR spectrum of the complex, which was treated with sodium perchlorate, was obtained after anion exchange by using the anion exchange resin (Dowex 1-X8, Cl^- form) in D_2O . The elemental analysis of this compound was confirmed as a monohydrate salt (*vide supra*).

Structures of the diacido complexes. The absorption spectrum of the dinitro complex is given in Fig. 1. The absorption spectra of *bisdiamine* complexes of Co(III) do not vary significantly with changes in the diamine. It is recognized that dinitro complexes of Co(III) show λ_{max} at ~ 330 nm for the *cis* isomers and ~ 350 nm for the *trans* isomers. The dinitro complex of racemic 2,2'-bipiperidine shows λ_{max} at 344 nm. This indicates that the present complex has the *trans* configuration with respect to the two nitro groups. The absorption spectrum of the dichloro complex is also shown in Fig. 1. The dichloro complex is green, which is characteristic of the *trans*- $[\text{CoCl}_2\text{N}_4]^+$ type of complex. The absorption spectrum of the complex is very similar to that of the *trans*- $[\text{CoCl}_2(\text{en})_2]^+$ complex, where en represents the simplest bidentate ligand ethylenediamine (LINHARD *et al.*, 1952). Moreover these spectra of the dinitro and the dichloro complexes are comparable with those of the respective

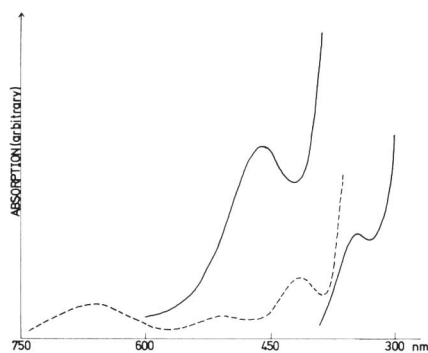


Fig. 1. The absorption spectra of $(\pm)\text{-trans-}[\text{Co}(\text{NO}_2)_2(2,2'\text{-bip})_2]^+$ in H_2O and $(\pm)\text{-trans-}[\text{CoCl}_2(2,2'\text{-bip})_2]^+$ in CH_3OH . The broken line indicates the latter complex ion.

complexes involving optically active $(-)-_{5S9}$ -2,2'-bipiperidine (SATO *et al.*, 1982). Thus, it is clear that the dinitro and the dichloro complexes are *trans* with respect to the anionic substituents. The ^{13}C -NMR spectra of the dinitro and the dichloro complexes, which contain 20 carbon atoms as their components in each complex ion, are given in Fig. 2. For both complexes, five signals were observed under irradiating all of the hydrogen nuclei. These results require that both complexes have at least double twofold symmetry, respectively.

The probable structures of *trans*-*diacido* complex of racemic 2,2'-bipiperidine are shown in Fig. 3. The enantiomeric isomers must necessarily occur in equal

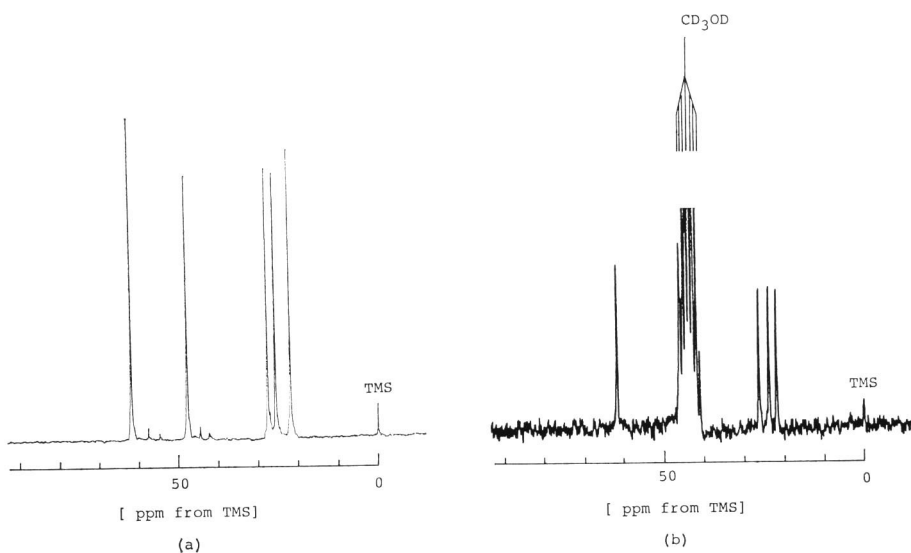


Fig. 2. The ^{13}C -NMR spectra; (a) $(\pm)$ -*trans*- $[\text{Co}(\text{NO}_2)_2(2,2'\text{-bpp})_2]^+$ in D_2O , (b) $(\pm)$ -*trans*- $[\text{CoCl}_2(2,2'\text{-bpp})_2]^+$ in CD_3OD .

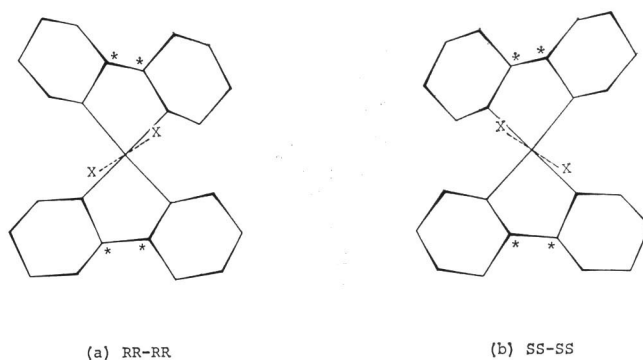


Fig. 3. The probable structures of the *trans*-*diacido* complexes. The relation between the two molecules is an enantiomeric isomer each other. X indicates the *nitro* or the *chloro* group.

amounts. Because the nonbonded interactions between the N-methylene groups of the other biperidine significantly influence the structure of complexes, remarkable distortions from the ideal octahedron were observed even in the complex $(-)\text{546-}trans\text{-}[Co(NO_2)_2((-)\text{559-}2,2'\text{-bip})_2](d\text{-BCS})\cdot 4H_2O$ (Fig. 3 (a), $X=NO_2$), whose structure was established by an X-ray structure determination. In addition, a remarkable result of our recent conformational analysis, which compares the stability of the racemic form with that of the meso form, can support the stereoselective formation of the complexes. Consequently, the meso isomer, which is shown in Fig. 4, should be excluded owing to its unstable structure. This result agrees with the present structural assignment.

Transformation of the trans-dichloro complex to oxalato one. The absorption spectrum of $(\pm)\text{-}[Co(ox)(2,2'\text{-bip})_2]^+$, which was obtained by the reaction of the *trans*-dichloro complex with ammonium oxalate, was shown in Fig. 5. This spectrum is very similar to that of *cis*- $[Co(ox)(en)_2]^+$ and gives the typical *cis*- $[CoN_4O_2]^+$ absorption (MATSUOKA *et al.*, 1967). The $^{13}C\text{-NMR}$ spectrum of this complex (Fig. 6) has nine signals at 169.8, 69.1, 66.0, 50.7, 48.6, 19.6, 19.1, 26.8, 23.5 ppm. The single

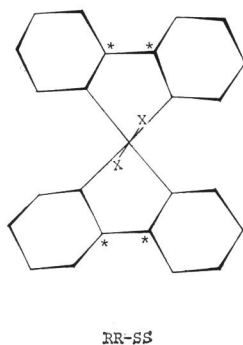


Fig. 4. The meso structure of the *trans*-diacido complexes. X shows the *nitro* or the *chloro* group.

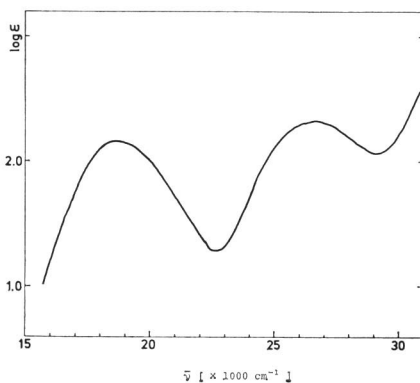


Fig. 5. The absorption spectrum of the complex ion $(\pm)\text{-}[Co(ox)(2,2'\text{-bip})_2]^+$ in H_2O .

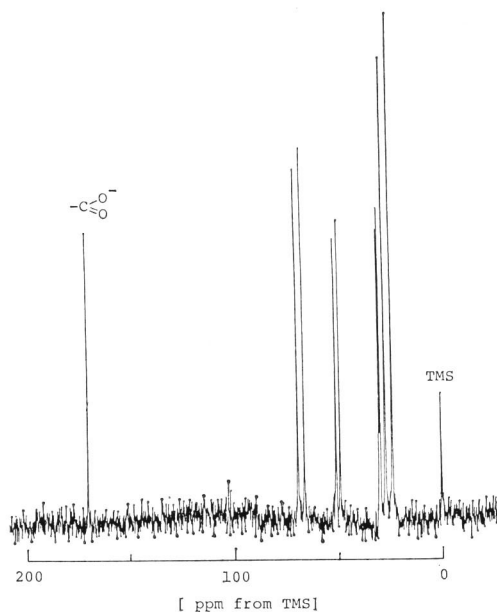


Fig. 6. The ^{13}C -NMR spectrum of the complex ion $(\pm)\text{-}[\text{Co}(\text{ox})(2,2'\text{-bpp})_2]^+$ in D_2O .

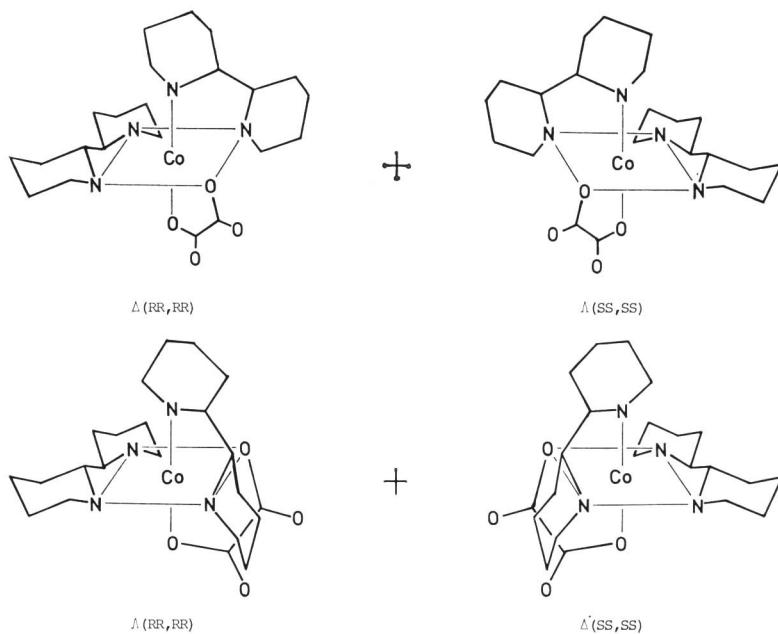


Fig. 7. The probable structures of the enantiomeric pairs of the resulting $(\pm)\text{-}[\text{Co}(\text{ox})(2,2'\text{-bpp})_2]^+$ ion.

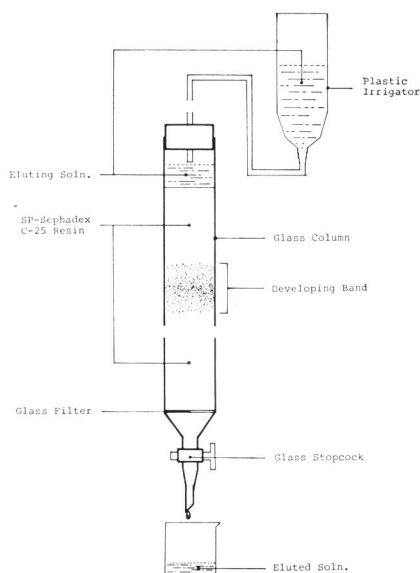


Fig. 8. The brief illustration of the column-chromatographic apparatus.

resonance at 169.8 ppm is due to the carboxyl carbon atoms, which belong to the coordinated oxalato anion. This indicates that the precipitated oxalato complex, which is almost all of the resulting product, has C_2 symmetry and is composed of the single species, though the enantiomeric isomers must necessarily be present in equal amounts. This result suggests that the each enantiomer of the oxalato complex derives from the corresponding enantiomer of the *trans-dichloro* complex without mixing of (+) and (–)-2,2'-bipiperidine, and the transformation of the *trans-dichloro* complex occurs stereoselectively. Thus, the oxalato complex obtained may be an equivalent mixture of enantiomeric pairs, either $\Delta(RR, RR)$ and $\Delta(SS, SS)$, or $\Lambda(RR, RR)$ and $\Lambda(SS, SS)$ (ref. Fig. 7), though the corresponding enantiomer of the *trans-dichloro* complex (Fig. 3 (a) or (b), $X=Cl$) has not yet been established. Consequently, the conversion of the *trans-dichloro* complex to the oxalato one gives rise to a possible route to optically resolve 2,2'-bipiperidine through its *cis-oxalato* Co(III) complexes.

Column chromatographic procedure and optical resolution. In several cases, complete resolutions of racemic *cis*-type Co(III) complexes have been performed by column chromatographic procedures utilizing SP- or SE-Sephadex ion-exchange resins (FUJITA *et al.*, 1974). Most of them are trivalent complexes, whereas the present oxalato complex is a monovalent one. The racemic oxalato complex, which was obtained by the reaction of the *trans-dichloro* complex with ammonium oxalate, was first attempt to resolve it into its optical isomers using a similar procedure. The chromatographic apparatus is briefly illustrated in Fig. 8. The developing band, which contains a reddish violet Co(III) complex ion, is also shown by the crowded dots in

the Figure. The separation of the eluted band, which was first expected to be resolved into two groups, was not observed. However, the eluted solution of the head line and the end line indicated a negative and positive *Cotton* effect respectively, in the first absorption region of the oxalato complex ion (Fig. 5.), though their intensities were weak. This suggests that partial resolution of the oxalato complex was attained using the resolving agent d-tartaric acid.

Conclusion

The monooxalato complex of racemic 2,2'-bipiperidine was prepared by the reaction of the racemic *trans*-dichloro Co(III) complex with ammonium oxalate. The transformation of the *trans*-dichloro complex occurs stereoselectively allowing the possibility of optical resolution of 2,2'-bipiperidine through its *cis*-oxalato Co(III) complex. An attempt at column chromatographic separation provided partial resolution using SP-Sephadex ion-exchange resin and d-tartaric acid.

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