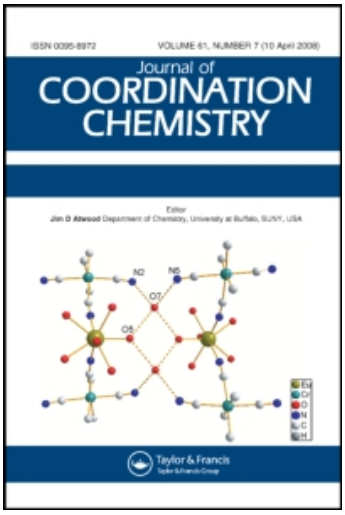

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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To cite this Article Jun, Moo-Jin , Yoon, Nung Min and Liu, Chui Fan(1983) 'ASYMMETRIC SYNTHESIS OF PROLINE USING COBALT(III)-TETRAAMINE COMPLEXES', Journal of Coordination Chemistry, 12: 4, 279 — 285
To link to this Article: DOI: 10.1080/00958978308073858
URL: http://dx.doi.org/10.1080/00958978308073858

J. Coord. Chem., 1983, Vol. 12, pp. 279–286
0095-8972/83/1204-0279 $18.50/0

ASYMMETRIC SYNTHESIS OF PROLINE USING COBALT(III)-TETRAAMINE COMPLEXES

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(Received March 29, 1982; in final form July 9, 1982)

The decarboxylation reaction of Λ-*cis*-β-[Co(L_1)(pdH)]$^{2+}$ complex yielded Λ-*cis*-β-[Co(L_1)(*R*-pro)]$^{2+}$, while the Δ-*cis*-β-[Co(L_2)(*S*-pro)]$^{2+}$ was obtained from the reaction of Δ-*cis*-β-[Co(L_2)(pdH)]$^{2+}$, where L_1 is (3*R*)3-methyl-1, 6-bis[(2*S*)-pyrrolidin-2-yl]-2, 5-diazahexane, L_2 is (3*S*) 3-methyl-1, 6-bis-[(2*S*)-pyrrolidin-2-yl]-2, 5-diazahexane, and pdH is the pyrrolidine-2, 2-dicarboxylate ion. The asymmetrically synthesized prolines were isolated *via* the decomposition of the decarboxylated complexes. The proline isolated from Λ-*cis*-β-[Co(L_1)(*R*-pro)]$^{2+}$ showed a specific rotation of +12.0, representing a 24% excess of *R*-proline over *S*-proline, while the proline isolated from Δ-*cis*-β-[(Co(L_2)-(*S*-pro)]$^{2+}$ showed a specific rotation of −10.0, indicating a 20% excess of *S*-proline over *R*-proline.

INTRODUCTION

An asymmetric synthesis of alanine has been accomplished using a dissymmetric cobalt (III) complex of α-amino-α-methylmalonate which was the precursor of the alanine.[2] The ligand, *S, S*-2, 9-dimethyltriethylenetetraamine, has been shown to be stereoselective and the cobalt(III) complex of the ligand has been able to induce a stereoselective decarboxylation of the precursor of alanine. Such an asymmetric synthetic process is important in view of the fact that while naturally occuring amino acids are optically active, those synthesized *in vitro* are usually obtained as racemic mixtures.

The ligands, (3*R*) 3-methyl-1, 6-bis[(2*S*)-pyrrolidin-2-yl]-2, 5-diazahexane (L_1) and (3*S*) 3-methyl-1, 6-bis[(2*S*)-pyrrolidin-2-yl]-2, 5-diazahexane (L_2) have been shown to be highly stereoselective[3] and yield, respectively, Λ-*cis*-β- and Δ-*cis*-β- isomers in the case of dichloro-*cis*-cobalt(III) complexes. These complexes were considered as ideal starting materials for the asymmetric synthesis of amino acids, and in the present work an asymmetric synthesis of proline was undertaken using the cobalt(III) complexes of L_1 and L_2 using diethylpyrrolidine-2, 2-dicarboxylate as the precursor.

EXPERIMENTAL

Instruments Used.

A Perkin-Elmer model 337 spectrophotometer (for i.r.), a Hewlett-Packard 8450A UV/VIS spectrophotometer (for electronic absorption spectra), a Varian A-60 spectrometer (for pmr), and a Jasco ORD/CD-5 spectrophotometer (for ORD and CD). Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Diethylpyrrolidine-2, 2-dicarboxylate Hydrochloride (pdH.HCl).

This was prepared by the known method.[4] *Anal.* Calcd. for $C_{10}H_{17}NO_4.HCl$: C, 47.42; H, 7.21; N, 5.56%. Found: C, 47.68; H, 7.20; N, 5.51%.

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Λ-cis-β-[Co(L$_1$)(pdH)]Cl$_2$.H$_2$O and Δ-cis-β-[Co(L$_2$)(pdH)]Cl$_2$.H$_2$O.

0.742 g of Λ-*cis*-β-[Co(L$_1$) Cl$_2$]ClO$_4$[3] was dissolved in 20 cm^3 of water and heated on a steam bath for 30 min; after cooling, 0.395 g of pdH.HCl was added. The pH was adjusted to 5.0 with 2 M NaOH and heating was continued for 30 min. The solution was cooled to room temperature and evaporated under moving air until the volume reached 10 cm^3. The reaction mixture was stored in a refrigerator overnight. The precipitate was filtered, washed with acetone, and recrystallized from hot water. *Yield:* 0.550 g (65%). *Anal.* Calcd. for $CoC_{19}H_{37}N_5O_4Cl_2.H_2O$: C, 41.69; H, 7.18; N, 12.91%. Found: C, 41.65; H, 7.19; N, 12.88%. Δ-*cis*-β-[Co(L$_2$) (pdH)] Cl$_2$.H$_2$O was also prepared by the same method using 0.825 g of Δ-*cis*-β-[Co(L$_2$)Cl$_2$].ClO$_4$.[4] *Yield:* 0.557 g (58%). *Anal.* Found: C, 51.66; H, 7.20; N, 12.93%.

Λ-cis-β-[Co(L$_1$)(pro)]Cl$_2$.H$_2$O and Δ-cis-β-[Co(L$_2$)(pro)]Cl$_2$.H$_2$O.

0.78 g of Λ-*cis*-β-[Co(L$_1$) (pdH)] Cl$_2$.H$_2$O was dissoved in 30 cm^3 of water and the pH was adjusted to 8.0 using dilute LiOH. The solution was boiled for 15 min, and then evaporated to dryness under moving air. The product was washed with methanol three times and recrystallized from hot water and ethanol. *Yield:* 0.572 g (80%). *Anal.* Calcd. for $CoC_{18}H_{36}N_5O_2Cl_2.H_2O$: C, 43.03; H, 7.62, N, 13.94; Cl, 14.11%. Found: C, 43.09; H, 7.59; N, 13.88; Cl, 14.10%. Δ-*cis*-β-[Co(L$_2$) (pro)] Cl$_2$.H$_2$O was prepared by the same method using 0.82 g of Δ-*cis*-β-[Co(L$_2$) (pdH)] Cl$_2$.H$_2$). *Yield:* 0.64 g (85%). *Anal.* Found: C, 42.98; H, 7.75; N, 13.95; Cl, 14.13%.

Isolation of Proline from Λ-cis-β-[Co(L$_1$)(pro)]Cl$_2$.H$_2$O.

To a solution of 1.14 g of Λ-*cis*-β-[Co(L$_1$) (pro)] Cl$_2$.H$_2$O in 30 cm^3 of water an excess amount of sodium sulfide was added and the solution was warmed at 50° in an oil bath for 30 min. The color of the solution was rapidly turned dark-brown. A saturated solution of 0.55 g of $CoCl_2.6H_2O$ was slowly added to the solution with stirring. The precipitate formed was separated, the solution was acidified with HCl, and air was bubbled through the solution for 30 min. The solution was passed through a column containing Dowex 3 ion-exchange resin in the chloride form, which was then washed with 1.5 dm^3 of water. 2 M HCl was used to elute the proline. Upon evaporation to dryness the proline was isolated and recrystallized from hot water and acetone. *Yield:* 0.14 g (38%). *Anal.* Calcd. for $C_5H_9NO_2$.HCl: C, 44.05; H, 6.16; N, 8.56; Cl, 21.67%. Found: C, 44.02; H, 6.18; N, 8.50; Cl, 21.61%. The structure of the proline was confirmed by pmr and ir spectra. The optical rotation of the proline measured in 1 M HCl was $\alpha_{obsd,D}$ + 0.116; $[\alpha]_D^{22}$ = + 12.0. $[\alpha]_D^{22}$ = + 50.2 for pure *R*-proline measured in 1 M HCl.

Isolation of Proline from Δ-cis-β-[Co(L$_2$)(pro)]Cl$_2$.H$_2$O.

Proline was isolated by the method described above using 1.02 g of Δ-*cis*-β-[Co(L$_2$)-(pro)] Cl$_2$.H$_2$O. *Yield:* 0.10 g (30%). *Anal.* Calcd. for $C_5H_9NO_2$.HCl: C, 44.05; H, 6.16; N, 8.56; Cl, 21.67%. Found: C, 44.00; H, 6.11; N, 8.55; Cl, 21.70%. The optical rotation of the proline measured in 1 M HCl was $\alpha_{obsd,D}$ −0.09; $[\alpha]_D^{22}$ = −10.0. $[\alpha]_D^{22}$ = − 50.2 for pure S-proline measured in 1 M HCl.

Λ-cis-β-[Co(L$_1$)(R-pro)]Cl$_2$.H$_2$O.

0.738 g of Λ-*cis*-β-[Co(L$_1$)Cl$_2$] C10$_4$ was dissolved in 20 cm^3 of water and warmed for 30 min on a steam bath. 0.25 g of *R*-proline was added and the pH of the solution was

adjusted to 8.0 with dilute LiOH. The solution was gently warmed on a steam bath for 1 hr. After cooling to room temperature it was evaporated to dryness under moving air. The product was washed with acetone, and recrystallized from hot water and ethanol. *Yield:* 0.512 g (65%). *Anal.* Calcd. for $CoC_{18}H_{36}N_5O_2Cl_2.H_2O$: C, 43.03; H, 7.62; N, 13.94%. Found: C, 42.99; H, 7.62; N, 13.90%.

Λ-cis-β-[Co(L$_1$)(S-pro)]Cl$_2$.H$_2$O.

This was prepared by the method described above using *S*-proline in place of *R*-proline. *Yield:* 60%. *Anal.* Calcd. for $CoC_{18}H_{36}N_5O_2Cl_2.H_2O$: C, 43.03; H, 7.62; N, 13.94%. Found: C, 43.05; H, 7.58; N, 13.97%.

Δ-cis-β-[Co(L$_2$)(R-pro)]Cl$_2$.H$_2$O.

This was prepared by the same method as that used for Λ-*cis*-β-[Co(L$_1$)(*R*-pro)]Cl$_2$.H$_2$O using 0.85 g of Δ-*cis*-β-[Co(L$_2$)Cl$_2$]Cl0$_4$.0.5H$_2$O. *Yield:* 0.52 g (58%). *Anal.* Calcd. for $CoC_{18}H_{36}N_5O_2Cl_2.H_2O$: C, 43.03; H, 7.62; N, 13.94%. Found: C, 42.96; H, 7.65; N, 13.95%.

Δ-cis-β-[Co(L$_2$)(S-pro)]Cl$_2$.H$_2$O.

This was prepared by the same method as that used for Δ-*cis*-β-[Co(L$_1$)(*R*-pro)]Cl$_2$.H$_2$O using *S*-proline and Δ-*cis*-β-[Co(L$_2$)Cl$_2$]Cl0$_4$.0.5H$_2$O. *Yield:* 52%. *Anal.* Calcd. for $CoC_{18}H_{36}N_5O_2Cl_2.H_2O$: C, 43.03; H, 7.62; N, 13.94%. Found: C, 43.06; H, 7.60; N, 13.87%.

RESULTS AND DISCUSSION

The asymmetric synthesis of proline was accomplished as depicted in Figure 1. The infrared spectrum of each of Λ-*cis*-β-[Co(L$_1$)(pdH)]Cl$_2$.H$_2$O and Δ-*cis*-β-[Co(L$_2$)(pdH)]Cl$_2$.H$_2$O showed single carboxyl peak at 1650 cm^{-1}, which indicated that both carboxyl groups were coordinated to the cobalt(III) ion in the complexes.

The ORD spectra of the standard cobalt(III) complexes of optically active proline are shown in Figure 2, while those of the complexes obtained from the decarboxylation reaction are indicated in Figure 3. The ORD spectrum of Λ-*cis*-β-[Co(L$_1$)(pro)]$^{2+}$ obtained from the decarboxylation of Λ-*cis*-β-[Co(L$_1$)(pdH)]$^{2+}$ is almost same as that of

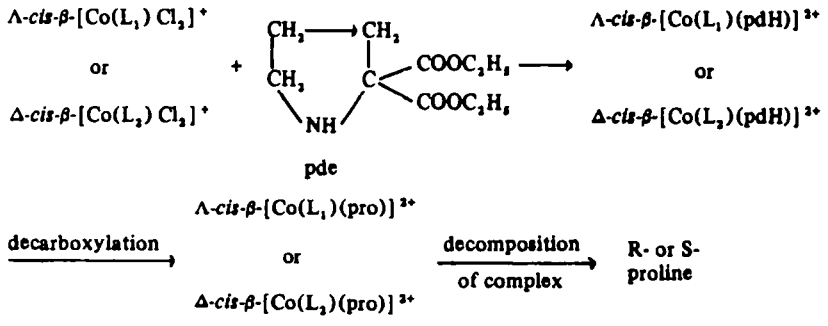


FIGURE 1 Asymmetric synthetic route to proline.

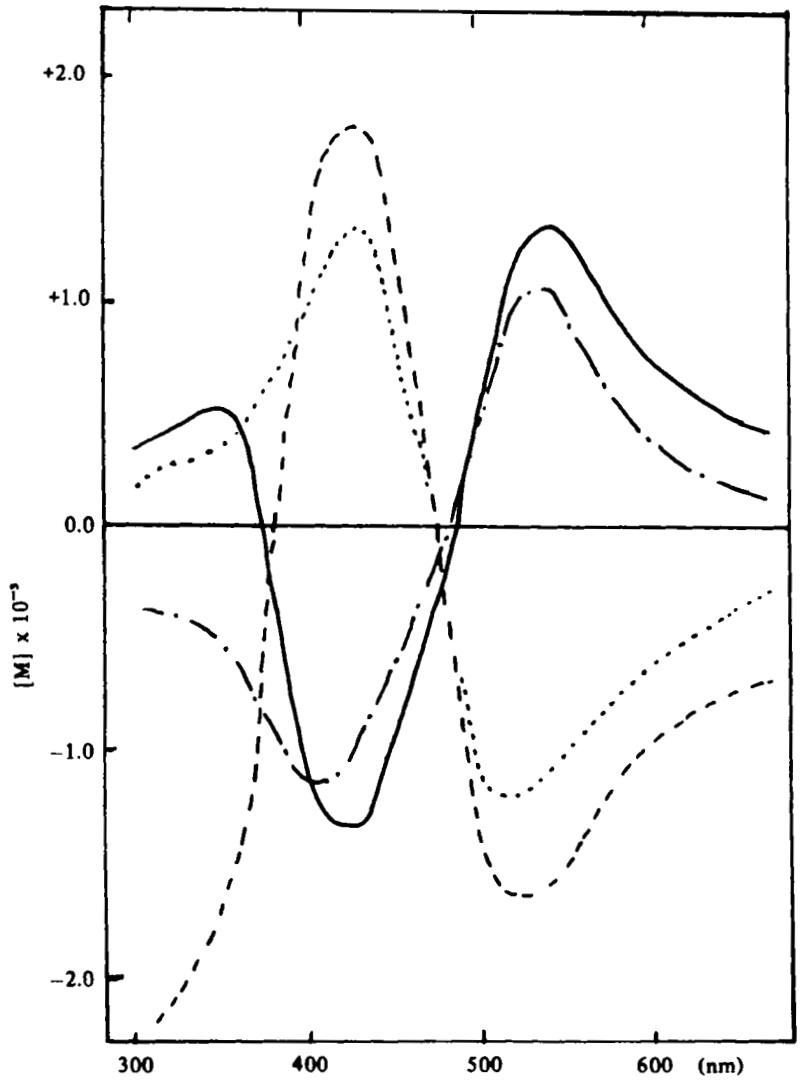


FIGURE 2 RD curves for the standard complexes: Λ-*cis*-β-[Co(L$_1$) (R-pro)]$^{2+}$ (———), Λ-*cis*-β-[Co(L$_1$) (S-pro)]$^{2+}$ (— . — . —), Λ-*cis*-β-[Co(L$_2$) (R-pro)]$^{2+}$ (. . . . . .), and Δ-*cis*-β-[Co(L$_2$) (S-pro)]$^{2+}$ (– – – – – –).

the standard Λ-*cis*-β-[Co(L$_1$) (*R*-pro)]$^{2+}$ complex, which indicates that the precursor of proline has been stereoselectively decarboxylated to *R*-proline. Calculations based on the optical rotation at the peak wavelengths in the long-wavelength region implied that the stereoselectivity in the decarboxylation step was more than 95%. The proline isolated from the decarboxylated complex, however, showed a specific rotation of only +12.0, representing a 24% excess of *R*-proline over *S*-proline. The decarboxylation of Δ-*cis*-β-[Co(L$_2$) (pdH)]$^{2+}$ complex, on the other hand, yielded *S*-proline stereoselectively in the resultant Δ-*cis*-β-[Co(L$_2$) (pro)]$^{2+}$ ion. The specific rotation of proline isolated from this complex was −10.0, showing a 20% excess of the *S*-proline over the *R*-antipode. The relatively low specific rotation of proline isolated from the decarboxylated complex must

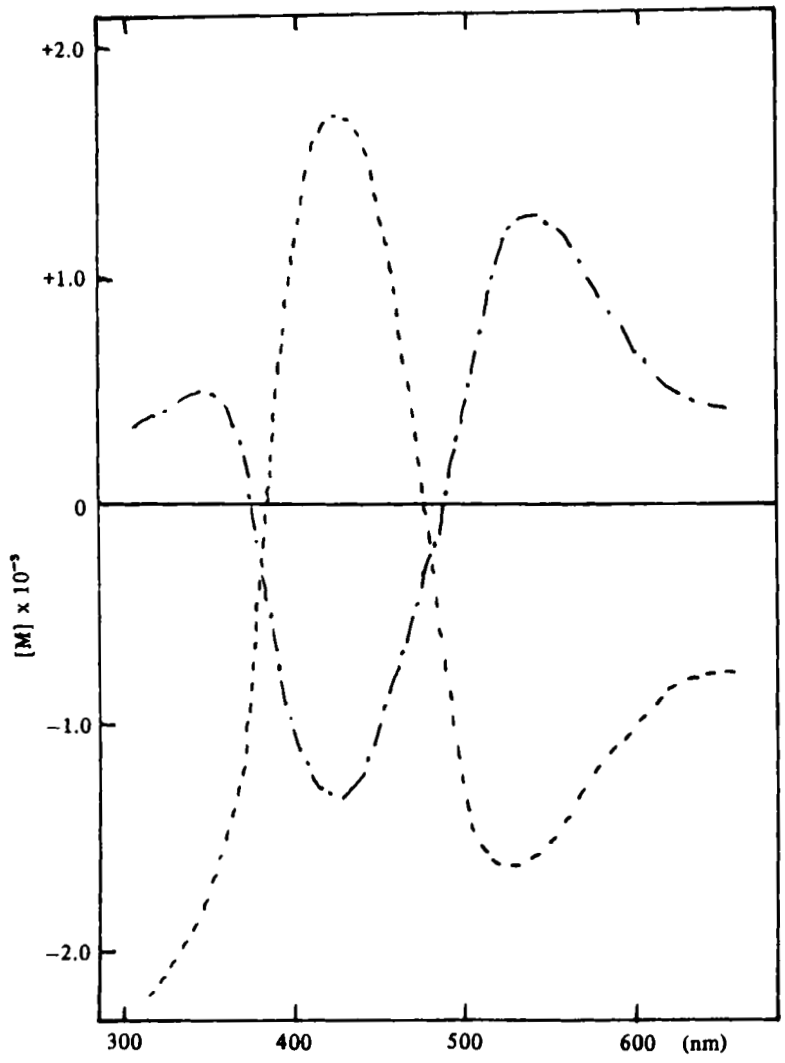


FIGURE 3 RD curves for Λ-*cis*-β-[Co(L$_1$)/(R-pro)]$^{2+}$ (— . — . —) and Δ-*cis*-β-(Co(L$_2$) (S-pro)]$^{2+}$ (– – – – –) obtained from the decarboxylation reaction.

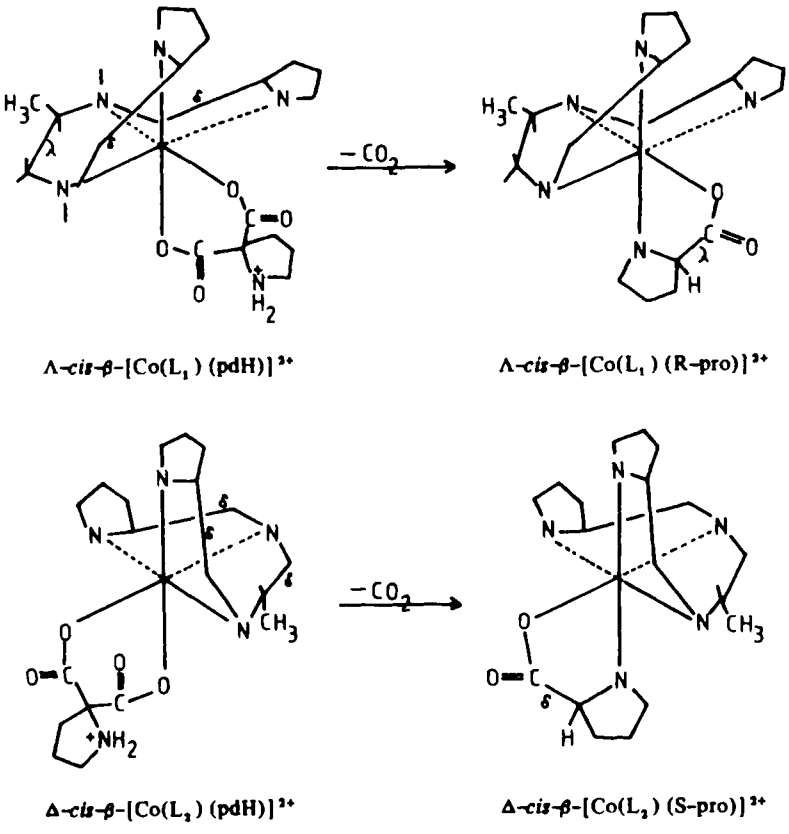
be due to racemization during the isolation process. The racemization of proline has been readily observed by other investigators when optically active proline is brought to boiling in a glacial acetic acid solution.[5]

It is interesting to observe that during the decarboxylation step the Λ-cis-β-isomer yielded *R*-proline, while the Δ-cis-β-isomer gave *S*-proline. Such stereoselectivity could be due to the directing power of the dissymmetric cobalt(III) complexes of pdH, which is in turn due to the strong conformational preferences of the stereoselective tetraamine ligand.[6–8] The directing power of the complex is also enhanced by the presence of pyrrolidine rings located on the outside chelate rings of the tetraamine ligand.

The Λ-*cis*-β-[Co(L$_1$)Cl$_2$]$^+$ complex has been shown to take a δλδ chelate ring conformation, while the Δ-*cis*-β-[Co(L$_2$)Cl$_2$]$^+$ complex takes a δδδ chelate ring conformation.[3]

Under such preferred arrangements of chelate rings both the asymmetrically substituted methyl group in the central chelate ring and the asymmetric *C*-methylene group in the central chelate ring and the asymmetric *C*-methylene group of the pyrrolidine ring assume equatorial positions, and the nonbonded interactions between chelate rings as well as between the outside chelate ring and the asymmetric substituent on the central chelate ring are minimized (Figure 4).

When an incoming bidentate chelate take the other two coordination sites in the dichloro-cobalt(III) complexes of L_1 and L_2 (the coordination sites occupied by chlorine ligands), it will adopt a conformation in such a way that nonbonded interactions may be minimized. Three principal sources responsible for such nonbonded interactions[6] may be considered: interactions between chelate rings, interactions between one chelate ring and the substituents on the other chelate ring (methyl groups and axial hydrogen atoms), and interactions between substituents (axial hydrogen atoms on the complexes of the ligands, L_1 and L_2 used in this work, an additional source for such nonbonded interactions could be due to the presence of the pyrrolidine rings which will also impart some rigidity to the molecule. A study using molecular models shows that for an incoming bidentate chelate a chelate ring conformation (δ or λ) will be slightly more favored than the other (λ or δ) owing to such nonbonded interactions. For the Λ-*cis*-β-$[Co(L_1)(pro)]^{2+}$ complex the



Λ-*cis*-β-$[Co(L_1)(pdH)]^{2+}$ Λ-*cis*-β-$[Co(L_1)(R\text{-pro})]^{2+}$

Δ-*cis*-β-$[Co(L_2)(pdH)]^{2+}$ Δ-*cis*-β-$[Co(L_2)(S\text{-pro})]^{2+}$

FIGURE 4 Proposed structures (schematic drawing) for complexes before and after decarboxylation reactions.

favored chelate ring conformation appears to be λ. Since the *R*-proline is ideal for such a conformation owing to the fact that the asymmetric *C*-methylene group of the proline can have an equatorial position in this conformation, it is reasonable to believe that an absolute configuration *R* is imparted when Λ-*cis*-β-$[Co(L_1)(pdH)]^{2+}$ undergoes decarboxylation. In the case of the Λ-*cis*-β-$[Co(L_1)(pro)]^{2+}$ complex, on the other hand, the favored chelate ring conformation appears to be δ, and from a similar reasoning it is appropriate to conclude that an absolute configuration *S* is obtained when the complex is subjected to decarboxylation.

The mechanism of the decarboxylation is not known. A three-point attachment of the precursor of proline in the Cobalt(III) complex of pdH may be possible.[9-11] Initially, the bond between the Cobalt(III) ion and one carboxyl group of the complex may be labilized and broken, and a bond between the Cobalt(III) ion and the secondary amine nitrogen may be formed. If the *N*- and one *O*- atom of the pdH were coordinated, models indicate that it would be easy for the other carboxylate group to hydrogen bond to the proton on a coordinated secondary amine of the tetraamine ligand. Such an attachment of the pdH molecule could lead to selective protonation of the carbanion formed after the loss of CO_2 to give either *R*- or *S*-proline. Studies on the mechanism are continuing.

ACKNOWLEDGEMENTS

Financial support of this work from the Korean Science and Engineering Foundation is gratefully acknowledged. Thanks are also due to the Korean-American Educational Commission for support (to MJJ).

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