

drolisis as compared to those of bis(ethylenediamine) and tetraammine analogs can be understood in terms of the thermodynamic nephelauxetic effect of these various amine ligands on the central cobalt(III) ion. It has been discussed and successfully tested in a few systems¹²⁻¹⁴ that the central cobalt(III) ion in cyclam complexes would very much prefer negatively charged ligands, such as Cl⁻ and OH⁻, to neutral molecules, such as NH₃ and OH₂, than the corresponding bis(ethylenediamine) and tetraammine complexes. The relative stability of *trans*-Co(am)₄NH₃OH₂³⁺ with respect to *trans*-Co(am)₄OH₂Cl²⁺ and the latter with respect to *trans*-Co(am)₄Cl₂⁺ would, therefore, be expected to decrease with (am)₄ as follows: (NH₃)₄ > (en)₂ > cyclam. Thus, although the Co-NH₃ bond in bis(ethylenediamine) and tetraammine complexes is very stable that it is never broken under normal kinetic conditions, it is weakened enough in the cyclam complex that its dissociation is observed here. This also explains satisfactorily the much smaller chloride aquation equilibrium constant of this complex as compared to those of other lower charged Co^{III}-cyclam complexes, e.g., $K = 7.0 \times 10^{-3} M$ at 70.4° for *trans*-Co(cyclam)Cl₂⁺.¹⁵

When the rapid preequilibrium of eq 3 was disturbed and shifted completely to the right either by removing the chloride with Hg²⁺ or by converting the amminequo species into its conjugate base with hydroxide ion (base hydrolysis) or into the isothiocyanatoammine complex with thiocyanate, release of ammonia was not observed and the system appeared normal.

Assuming an SN1cb mechanism^{3,13,16} for the base hydrolysis of cobalt(III)-amine complexes, the present investigation appears to give some indication on the nature of the amido conjugate base. It is controversial whether a *cis*- or a *trans*-conjugate base relative to the leaving group is responsible for the hydrolysis reaction whenever both types of

amines are present in the complexes.^{3,13,16-19} In the present investigation, the base hydrolysis of *trans*-Co(cyclam)NH₃Cl²⁺ with ammonia release would probably occur *via* a *cis* conjugate base formed from one of the cyclam secondary nitrogens. Otherwise, the observed base-catalyzed path for the release of the coordinated ammonia would involve the breakage of Co=NH₂, which is rather unlikely.

The entropy of activation for the ammonia aquation ($\Delta S^\ddagger = 20$ eu) was very much higher than those of stereoretentive chloride and bromide aquation ($\Delta S^\ddagger \leq 0$) of other Co^{III}-cyclam complexes.¹³ It is quite probable that the coordinated ammonia, by virtue of its acidic protons, is strongly solvated in the ground state. The lengthening of the Co-NH₃ bond in the transition state would seriously break down the structure of the solvating water molecules and would, therefore, be accompanied by a big increase in the entropy.

The facts, as shown in Table IV, that the chloride aquation rate constants of analogous *trans*-Co(am)₄NH₃Cl²⁺ complexes decrease and that the base hydrolysis rate constants increase along the above series of (am)₄ further support the earlier proposal¹²⁻¹⁴ concerning the influence of the kinetic nephelauxetic effect of these amine ligands on the central cobalt(III) ion.

Registry No. *trans*-[Co(cyclam)NH₃Cl]Cl₂, 34424-18-5; *trans*-[Co(cyclam)Cl₂]Cl, 15220-74-3; *trans*-[Co(cyclam)NCS]ClO₄, 34424-17-4; *trans*-[Co(cyclam)NH₃Cl](NO₃)₂, 40685-47-0; *trans*-[Co(cyclam)Cl₂]⁺, 19973-61-6; *trans*-[Co(cyclam)NH₃NCS](ClO₄)₂, 40685-49-2; *trans*-[Co(cyclam)NH₃OH]²⁺, 40685-50-5; *trans*-[Co(cyclam)NH₃OH₂]³⁺, 40685-51-6; chlorine, 7782-50-5; thiocyanate, 302-04-5; hydroxide, 14280-30-9.

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Stereospecificity in the [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ and [Co(en)₂((*S*)-pro)]²⁺ Ions

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Both Λ -(+)_{s89}- (82%) and Δ -(-)_{s89}-[Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ (18 ± 2%) ions result on treating *trans*-[Co(en)₂X₂]X (X = Cl, Br) with *N*-methyl-(*S*)-alanine in alkaline methanol solutions; a similar isomer distribution, 80 ± 2% Λ -(+)_{s89}- and 20 ± 2% Δ -(-)_{s89}-, is obtained by mutarotation on carbon and on cobalt. The analogous reaction with (*S*)-proline results in both Δ -(-)_{s89}- (74 ± 1%) and Λ -(+)_{s89}- (26 ± 1%) [Co(en)₂((*S*)-pro)]²⁺ being formed; equilibration on activated charcoal gives a 77 ± 1% Δ -(-)_{s89}-(*S*) and 23 ± 1% Λ -(+)_{s89}-(*S*) isomer distribution.

Introduction

Investigations into the stereospecific coordination of *N*-substituted amino acids in asymmetric cobalt(III) complexes have provided some information on the kinetic and thermodynamic relationships between diastereoisomers containing adjacent asymmetric centers, one of which is a metal atom.

The initial studies on the [Co(en)₂(sar)]²⁺¹ and β_2 -[Co(trien)(sar)]²⁺² ions (sar = *N*-methylglycinate anion) established that the configuration about the N center of sarcosine was

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controlled by the configuration about the metal with only Δ -*S* and Λ -*R* diastereoisomers being formed both preparatively and under equilibrium controlled conditions. An X-ray study³ confirmed the Λ -*R* configuration in the bis(ethylene-diamine) system. The coordination of (*S*)-proline was also proposed to be stereospecific with only the Δ -(*S*)-[Co(en)₂-((*S*)-pro)]²⁺,^{4,5} and Δ - β_2 -(*RRS*)-[Co(trien)((*S*)-pro)]²⁺,^{6,7} ions being observed, but subsequent studies demonstrated that reaction of β -[Co(trien)(OH)(H₂O)]²⁺ with (*S*)-proline was kinetically controlled with approximately equal amounts of Δ - β_2 -(*RRS*)- and Λ - β_2 -(*SSS*)-[Co(trien)((*S*)-pro)]²⁺ being formed.⁸ It was not possible to measure the relative stabilities of the Δ - β_2 -(*RRS*)-[Co(trien)((*S*)-pro)]²⁺ and Δ - β_2 -(*RRR*)-[Co(trien)((*R*)-pro)]²⁺ ions since base-catalyzed dissociation of the amino acid preceded mutarotation, but equilibration in the Co(II) state on activated charcoal gave a free energy difference of 1.3 kcal mol⁻¹ in favor of the Δ - β_2 -*RRS*(*S*) isomer.⁹ This result was in good agreement with calculations based on structures of minimum energy (1.6 kcal mol⁻¹).⁸ The difficulty of mutarotation in the Co(III) state was avoided in the β_2 -[Co(trien)(*N*-Me-(*S*)-ala)]²⁺ ion [*N*-Me-(*S*)-ala = *N*-methyl-(*S*)-alaninate anion] and the two distinct equilibria observed at pH \sim 6.5 and \sim 12 were attributed to mutarotation at the "planar" N center of the trien moiety and the C center of the amino acid, respectively;¹⁰ the alternative possibility of mutarotation about the N atom of the amino acid at pH 6.5 was considered unlikely, although no direct evidence to support this claim was obtained.

In the [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ ion, where this difficulty in interpretation is avoided, it has been proposed that Λ -(*R*)-[Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ is formed stereospecifically and that mutarotation does not occur at either the N or C centers of the amino acid in alkaline solution.⁴ While the absence of mutarotation about the N center supported the interpretation given for the [Co(trien)(*N*-Me-(*S*)-ala)]²⁺ results, the absence of mutarotation at carbon was somewhat unexpected in view of its presence in the trien complex and raised serious doubts in our minds as to the similarity of the two systems and the merit in making comparisons between them. For this reason we decided to reexamine the [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ chemistry and report here the results obtained. Also, since the [Co(en)₂((*S*)-pro)]²⁺ ion provides a closely related system, and since we have results which differ from those reported previously,^{4,5} we record these as well.

Experimental Section

Analytical reagents were used for all purposes without further purification. *N*-Methyl-(*S*)-alanine was synthesized by the method of Quitt, Hellerbach, and Vogler¹¹ and (*S*)-proline was obtained from SAS Scientific Chemical Limited. *trans*-[Co(en)₂Br₂]Br was prepared as follows. [Co(en)₂CO₃]Br (58 g) was added over 2 hr to 47% HBr (200 ml) at 70°. Heating was continued for 4 hr at 70° and the solution allowed to cool. The product was collected and washed with

ethanol until the washings, and an aqueous solution of the green complex, were neutral to litmus.

Rotatory dispersion (RD) spectra were measured in 1-dm cells on a Perkin-Elmer P22 spectropolarimeter, and pmr spectra obtained on a Joel JNM 100-MHz minimar instrument. Cobalt estimations were on a Techtron AA4 atomic absorption spectrometer and visible spectra were obtained using a Cary 14 instrument. Bio-Rad analytical grade Dowex 50 WX2 (200-400 mesh, H⁺ form) or CM Sephadex C25 (Na⁺ form) cation exchange resins were used for separation of reaction products and for diastereoisomer separation. NaOD solutions were made up by carefully adding Na metal to D₂O. Norite A animal charcoal was used for isomer equilibration experiments.

[Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ Preparative Mixture. *trans*-[Co(en)₂-Br₂]Br (4.2 g) or *trans*-[Co(en)₂Cl₂]Cl (2.8 g) was suspended in methanol (30 ml) containing *N*-methyl-(*S*)-alanine (1.1 g) and LiOH · H₂O was (0.43 g) added. The mixture was heated under reflux for 20-30 min. In one preparation the methanol was then removed on a rotary evaporator, the contents were dissolved in warm water, and Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)](ClO₄)₂ was crystallized by adding NaClO₄. In other preparations the methanol solution was diluted with water (1 l) and the products were sorbed on and eluted from (1 M HCl) cation exchange resin. The three major products were estimated spectrophotometrically, polarimetrically, and by atomic absorption spectroscopy for Co. The orange band containing [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ was reduced to dryness on a rotary evaporator, the residue taken up in a small volume of water (3 ml), and methanol added. On standing Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · 5H₂O crystallized; addition of more methanol and cooling resulted in further product. Recrystallization from aqueous methanol did not alter the optical purity and no evidence for crystallization of the Δ -*S* diastereoisomer was obtained. The methanol-soluble fractions were combined and sorbed on and eluted (1 M HCl) from a column of cation exchange resin (50 × 1 cm); the first fractions contained the optically pure Δ -*S* diastereoisomer.

Alternatively, the total [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ product was sorbed on cation exchange resin and eluted with 0.5 M NaH₂PO₄-0.5 M Na₂HPO₄ solution (pH 6.8). The two orange bands containing the Δ -*S* and Λ -*S* diastereoisomers separated overnight and were eluted with either 1 M NaClO₄, 1 M HCl, or with the phosphate buffer and separately sorbed on and eluted from Dowex 50 WX2 resin using 1 M HCl. The solutions were estimated photometrically, polarimetrically, and by atomic absorption spectroscopy for Co. The complexes were recovered as their chloride salts by evaporation to dryness of the HCl eluates and crystallized from aqueous methanol. The less soluble iodide salts were obtained from aqueous solution by adding NaI. Recrystallization was effected from hot water by cooling. *Anal.* Calcd for [Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · H₂O: C, 25.89; H, 7.33; N, 18.87. Calcd for [Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · 0.5H₂O: C, 26.52; H, 7.23; N, 19.33. Found (Δ -*S* isomer): C, 25.85; H, 7.17; N, 18.66. Found (Λ -*S* isomer): C, 26.46; H, 7.32; N, 19.28. Calcd for [Co(en)₂(*N*-Me-(*S*)-ala)]I₂: C, 17.96; H, 4.52; N, 13.09. Found (Δ -*S* isomer): C, 18.04; H, 4.41; N, 13.16. Found (Λ -*S* isomer): C, 18.1; H, 4.5; N, 13.0.

The optically pure Δ -*S* and Λ -*S* iodides were equilibrated on active charcoal as follows. The complex (0.2 g) in water (50 ml) was treated with charcoal (0.3 g) and the mixture shaken at 25°. At various times a sample was removed and filtered, and its visible spectrum and rotation were measured. When no further change was observed (53 hr) the solution was chromatographed on cation exchange resin (1 M NaClO₄) and the visible spectrum and rotation of the [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ fraction were obtained.

Preparation and Resolution of [Co(en)₂((*S*)-pro)]²⁺. To a slurry of *trans*-[Co(en)₂Br₂]Br (20.9 g) and (*S*)-proline (5.75 g) in methanol (800 ml) at 60° was added LiOH · H₂O (2.09 g) in methanol (200 ml). The solution was refluxed for 45 min, diluted with water (3 l), and sorbed onto H⁺ from Dowex 50 WX2 exchange resin. Elution with 1 M HCl resulted in the separation of three major bands, [Co(en)₂Br(MeOH)]²⁺, [Co(en)₂((*S*)-pro)]²⁺, and [Co(en)₂]³⁺, in order of elution. The [Co(en)₂((*S*)-pro)]²⁺ product (60-70%) was reduced to dryness on a rotary evaporator and dissolved in water and the solution neutralized (pH \sim 5) with 0.5 M LiOH solution. Addition of NaI and cooling resulted in the crystallization of Δ -[Co(en)₂((*S*)-pro)]I₂. This material was recrystallized from warm water, and all fractions had similar rotations: [α]₅₈₉, -279°; [α]₅₄₆, -471° in water at 25° from a 0.1% solution. *Anal.* Calcd for [Co(en)₂((*S*)-pro)]I₂ · H₂O: C, 19.13; H, 4.64; N, 12.40. Found: C, 19.1; H, 4.7; N, 12.1. The filtrate and washings were diluted with water and the remaining [Co(en)₂((*S*)-pro)]²⁺ was sorbed onto and eluted from a cation exchange resin (1 M HCl). The eluate containing the complex was reduced to dryness, dissolved in water (100 ml), and adjusted to pH 5

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with LiOH. Treatment with NaAsO-(*R*)-tartrate (12 g) resulted in the separation of Δ -[Co(en)₂((*S*)-pro)](NaAsO-(*R*)-tart)₂ · H₂O, and this was collected. Three more fractions were collected after standing at 20°. The combined diastereoisomer was recrystallized from hot water and air-dried: [α]₅₈₉, -204°; [α]₅₄₆, -350° from a 0.1% solution in water. *Anal.* Calcd: C, 25.87; H, 4.34; N, 8.87. Found: C, 25.6; H, 4.4; N, 8.9. On reducing the volume of the filtrate and treating with further NaAsO-(*R*)-tartrate (5 g), a series of Δ -*R* and Δ -*R* fractions separated. Those of similar rotation were combined and recrystallized to constant rotation; Λ -[Co(en)₂((*S*)-pro)](NaAsO-(*R*)-tart)₂ · H₂O crystallized from the more soluble fractions: [α]₅₈₉, +233°; [α]₅₄₆, +526° from 0.1% solution in water. *Anal.* Found: C, 25.9; H, 4.4; N, 8.7. Both diastereoisomers were converted to iodide salts by titration with NaI and the complexes recrystallized to constant rotation: for Δ -[Co(en)₂((*S*)-pro)]I₂ · H₂O [α]₅₈₉, -278°; [α]₅₄₆, -470° (*Anal.* Found: C, 19.1; H, 4.7; N, 12.6); for Λ -[Co(en)₂((*S*)-pro)]I₂ · H₂O [α]₅₈₉, +321°; [α]₅₄₆, +732° (*Anal.* Found: C, 19.0; H, 4.4; N, 12.2). Rotations were measured for 0.1% solutions in water.

Several smaller scale preparations were carried out as above using *trans*-[Co(en)₂Br₂]Br (4.2 g) or *trans*-[Co(en)₂Cl₂]Cl (2.8 g) in methanol or dimethyl sulfoxide (30 ml) and LiOH · H₂O (0.43 g). The resulting solution was diluted to ca. 300 ml with water, sorbed on cation exchange resin (H⁺ form), and eluted with 1 *M* and then 2 *M* HCl. The [Co(en)₂((*S*)-pro)]²⁺ product was collected and its optical activity and visible spectrum were recorded; it was reduced to dryness at ~30° and the measurements were repeated in water. In all experiments addition of NaI or NaClO₄ resulted in crystallization of optically pure Δ -[Co(en)₂((*S*)-pro)]I₂ · (ClO₄)₂; no evidence was obtained for racemic or Λ -*S* products in these isolated complexes.

The optically pure Δ -*S* and Λ -*S* iodides were equilibrated on Norit A animal charcoal as follows. The complex (0.1–0.2 g) in water (50 ml) was treated with charcoal (0.1 g) and the solution shaken at 25°. Samples were removed at various times (30 min–4 days) and filtered, and their rotations and visible spectra were recorded. For the longer times (>90 min) the complexes were sorbed on and eluted from Dowex resin, and the [Co(en)₂((*S*)-pro)]²⁺ band was collected and its properties were measured. Six experiments were carried out; in two cases (Δ -*S* and Λ -*S*) the equilibrated mixture (60 min) was chromatographed using the 0.2 *M* phosphate buffer (*vide supra*) and the properties of the separated diastereoisomers were recorded.

Separation of Δ - and Λ -[Co(en)₂((*S*)-pro)]²⁺ from Preparative Mixture. About 0.2 g of [Co(en)₂((*S*)-pro)]Cl₂ obtained chromatographically from the preparative mixture was sorbed on 50 WX2 cation exchange resin (Na⁺ form) and eluted with NaH₂PO₄ (0.2 *M*)–Na₂HPO₄ (0.2 *M*) buffer (pH ~6.2). Two orange bands separated overnight and these were eluted using 2 *M* HCl. The solutions were reduced to dryness by rotary evaporation and made up to 100 ml with water, and their absorption spectra and rotations were recorded.

The separated diastereoisomers from a larger scale chromatographic experiment (2 g) were treated with NaI and the resulting iodide complexes recrystallized from the minimum volume of hot water. The properties of the salts, Δ -(-)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O ([α]₅₈₉, -281°; [α]₅₄₆, -478°) and Λ -(+)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ ([α]₅₈₉, 319°; [α]₅₄₆, 728°), agree with those obtained by direct resolution.

Results and Discussion

[Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ System. The present experiments confirm that optically pure Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)] · (ClO₄)₂ ([α]₅₈₉, 260°) may be crystallized from the solution resulting from treating *trans*-[Co(en)₂Cl₂]Cl with *N*-methyl-(*S*)-alanine and LiOH (1 equiv) in refluxing methanol.⁴ The properties of the material obtained in the present study (visible, rotatory dispersion and pmr spectra) are the same or similar to those reported previously.⁴ Cation exchange chromatography was used to examine the total reaction products; the above method gave 14% of a red 2+ band, probably [Co(en)₂Cl(MeOH)]²⁺ [it contained no *N*-methylalanine (pmr)], 58% [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ ([M]₅₈₉, 678° in 1 *M* HCl), and 28% Co(en)₃³⁺. The similar reaction using *trans*-[Co(en)₂Br₂]Br occurred more rapidly and gave a similar product distribution, [Co(en)₂(*N*-Me-(*S*)-ala)]²⁺ (60–62%; [M]₅₈₉, 678, 789° in 1 *M* HCl (duplicate experiments)), [Co(en)₂Br(MeOH)]²⁺ (14%), and Co(en)₃³⁺ (26%). Optically pure Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · 5H₂O ([α]₅₈₉

348°) was obtained as the least soluble salt by recrystallizing the total [Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ product from aqueous methanol. The properties of this material (rotatory dispersion, pmr spectra) are identical with those of the perchlorate salt. Crystallization of this material as Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂ ([α]₅₈₉, 232°) did not change the optical purity.

Cation exchange chromatography of the total [Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ fraction obtained from the *trans*-[Co(en)₂-Br₂]Br reaction using NaH₂PO₄ (0.5 *M*)–Na₂HPO₄ (0.5 *M*) as eluent resulted in the rapid separation of two distinct orange bands; removal of the complexes and spectrophotometric analysis (visible spectra and atomic absorption for Co) gave 16 and 84%, respectively, in order of elution. A duplicate experiment gave 20 and 80%, and from *trans*-[Co(en)₂Cl₂]Cl, 16 and 84%. The complexes were recovered and crystallized as Δ -(-)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · H₂O ([α]₅₈₉, -632°) and Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · 0.5H₂O ([α]₅₈₉, 348°), respectively, and the pmr (D₂O) and rotary dispersion curves (1 *M* HCl) for these isolated complexes, Figures 1 and 2, were identical with those for the total products obtained by ion exchange separation. The less abundant Δ -*S* complex was also obtained from the methanol-soluble fractions on fractionation of the total [Co(en)₂(*N*-Me-(*S*)-ala)] · Cl₂ product and removal of the less soluble Λ -*S* isomer. Chromatography using 1 *M* HCl resulted in the isolation of Δ -(-)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂ · H₂O ([α]₅₈₉, -622° in H₂O) from the initial eluate fractions. Addition of NaI gave Δ -(-)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂ (ε₄₉₂, 116; ε₃₅₂, 117; [α]₅₈₉, -408; [α]₅₄₆, -684° in H₂O); this material remained unchanged on recrystallization and moved as one band on chromatography using NaH₂PO₄–Na₂HPO₄ eluent. The Λ -(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂ salt was also obtained ([α]₅₈₉, 232°; [α]₅₄₆, 489°; ε₄₉₀, 108; ε₃₄₈, 114).

The pmr spectrum of the Δ -*S* complex in D₂O, Figure 1B, shows doublets centered at 2.56 and 1.44 ppm (100 MHz). These can be attributed to the N and C methyl groups, respectively. The former collapses to a singlet at pH ~7 (N–H exchange) and two singlets of unequal intensity (1.48 and 1.44 ppm) slowly grow out of the C-methyl doublet in 0.01 *M* NaOD, Figure 1E. The *N*-methyl doublet in the Λ -*S* isomer occurs at the same frequency as in the Δ -*S* complex, but the C-methyl doublet is found at a slightly higher field, 1.48 ppm. Under conditions where N–H exchange is rapid (pH ~7, 5τ_{1,2} < 2 min) the N-CH₃ singlet in the Δ -*S* complex remained unaltered over 3 days; likewise at pH 6.49 the rotatory dispersion curve (600–320 nm) remained unchanged over 4 days. These results are consistent with the stereospecific coordination of the N-CH₃ group. Mutarotation at coordinated asymmetric N centers in similar Co(III) complexes occurs under such conditions and has been shown to involve significant changes in optical rotation in the visible region.¹² The possibility of the same equilibrium mixture of *RS* (*cis*-methyls) and *SS* (*trans*-methyls) in the chloride and iodide salts is unlikely, and the pmr result would require coincidence of their N-CH₃ absorptions.

Although no evidence for mutarotation was obtained at pH ~7, in 0.10 and 0.04 *M* NaOH mutarotation was observed both polarimetrically and by pmr spectroscopy. The polarimetric change was large in the case of the Δ -*S* isomer ([M]₅₈₉, -2183 to -1440°) but it is clear that the configuration about the metal is preserved. Plots of log (α_t - α_∞) vs.

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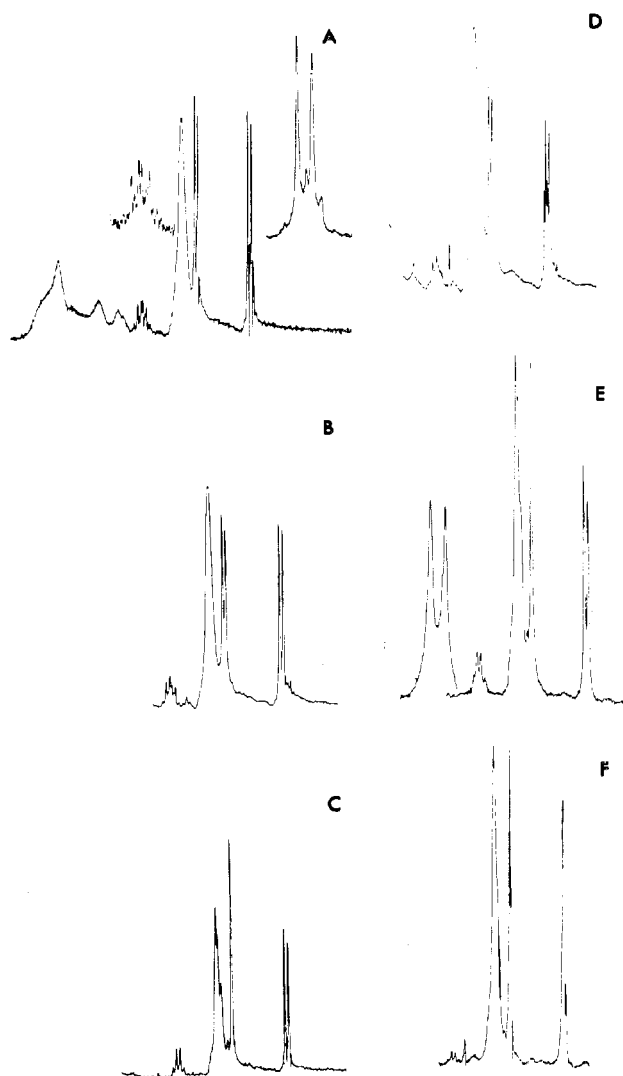


Figure 1. Pmr spectra (100 MHz) for various *N*-methyl-(*S*)-alaninate complexes and mixtures: (A) preparative sample $[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{Cl}_2$ (0.1 *M* DCl); (B) minor component $\Delta(-)_{589}\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{Cl}_2$ in D_2O ; (C) minor component $\Delta(-)_{589}\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{Cl}_2$ deuterated at N; (D) isolated minor isomer (Δ -*S*) plus smaller amount of isolated major isomer (Λ -*S*) in D_2O ; (E) major isomer (deuterated at N) $\Lambda(+)_589\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{Cl}_2$ in D_2O ; (F) minor isomer $\Delta(-)_{589}\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{Cl}_2$ after mutarotation at C in NaOD.

time were linear for $4t_{1/2}$ with $k_{\text{obsd}} = 1.72 \times 10^{-3}$ (0.1 *M* NaOH) and $0.70 \times 10^{-3} \text{ sec}^{-1}$ (0.04 *M* NaOH) at 25° . These data fit the rate law $k_{\text{obsd}} = k[\text{OH}^-]$, with $k = 1.7 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$ at 25° ; $\mu = 1.0$ (NaClO_4). This second-order rate constant is similar to that found for mutarotation at carbon in the similar complexes of α -alanine ($1.78 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$) and valine ($2.81 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$).¹³ Also, the pmr spectrum in 0.1 *M* NaOD showed the appearance of a new *C*-methyl singlet at 1.48 ppm. Clearly, mutarotation under these conditions involves establishing the Δ -*S* \rightleftharpoons Δ -*R* equilibrium and from the integrated intensities of the two methyl singlets an equilibrium constant of about 4 was obtained. A more accurate value was found by quenching the final solution to pH \sim 4, separating the total $[\text{Co}(\text{en})_2(\text{N-Me-ala})]^{2+}$ product chromatographically (1 *M* NaClO_4), and estimating it spectrophotometrically (visible and atomic absorption for Co) and polarimetrically (at equilibrium $[\text{M}]_{589} = 1430^\circ$ from

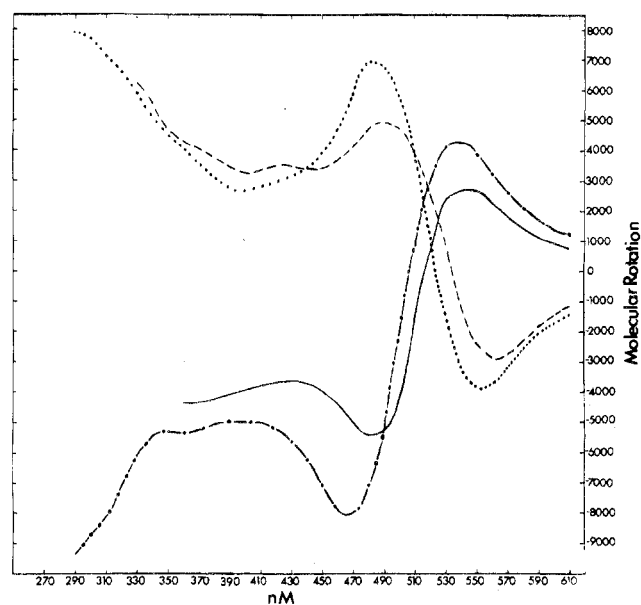


Figure 2. Rotatory dispersion spectra for $\Delta(-)_{589}\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{I}_2$ ($\cdots\cdots$), $\Lambda(+)_589\text{-}[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]\text{I}_2$ (—), $\Delta(-)_{589}\text{-}[\text{Co}(\text{en})_2((S)\text{-pro})]\text{I}_2 \cdot \text{H}_2\text{O}$ (---), and $\Lambda(+)_589\text{-}[\text{Co}(\text{en})_2((S)\text{-pro})]\text{I}_2 \cdot \text{H}_2\text{O}$ ($\cdot\cdot\cdot\cdot$). Units of molecular rotation $\text{deg M}^{-1} \text{ m}^{-1}$.

Δ -*S*; 1410° from Λ -*S*), giving 82% Δ -*R* and 18% Δ -*S*. This value was essentially confirmed for the Δ -*S* complex by separating the two diastereoisomers chromatographically using the NaH_2PO_4 - NaHPO_4 eluent and separately measuring their concentrations (21% Δ -*S*; 79% Δ -*R*). Equilibration of the optically pure Δ -*S* and Λ -*S* isomers on active charcoal led to the same result ($[\text{M}]_{546} 1294^\circ$ from Δ -*S*; 1302° from Λ -*S*), 79% Λ -*S* and 21% Δ -*S*, giving an average value of $K = \Delta\text{S}/\Lambda\text{S} = \Delta\text{R}/\Delta\text{S} = 4$. For these complexes mutarotation at the cobalt center was much slower (50 hr) than for the $[\text{Co}(\text{en})_2((S)\text{-pro})]^{2+}$ isomers (45 min), and more disproportionation (\sim 50%) occurred. However, it is clear that the isomer distribution obtained by mutarotation at C and Co agrees and that the preparative mixture is close to the thermodynamic distribution of the isomers.

Comparisons between the $[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]^{2+}$ and $\beta_2\text{-}[\text{Co}(\text{trien})(\text{N-Me-}(S)\text{-ala})]^{2+}$ ions demonstrate their close similarity. Both favor the Λ configuration about the metal, $0.79 \text{ kcal mol}^{-1}$ in the case of $[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]^{2+}$ and $0.65 \text{ kcal mol}^{-1}$ for $\beta_2\text{-}[\text{Co}(\text{trien})(\text{N-Me-}(S)\text{-ala})]^{2+}$ at 25° and pH \sim 12. Furthermore, the absence of mutarotation at the *N*-methyl center in $[\text{Co}(\text{en})_2(\text{N-Me-}(S)\text{-ala})]^{2+}$ at pH \sim 7 supports the interpretation favoring mutarotation of the N center of the triethylenetetramine moiety in the $\beta_2\text{-}[\text{Co}(\text{trien})(\text{N-Me-}(S)\text{-ala})]^{2+}$ ion. However, the question concerning the configuration about the *N*-methyl center in both complexes still remains. In the Λ -*S* complex it is likely that the *trans* arrangement obtains with the *N*-methyl group directed between the two ethylenediamine chelate rings¹ (*R* configuration). Considerations based on structures of minimum energy support this arrangement in $\Lambda\text{-}\beta_2\text{-}(\text{RRR})\text{-}[\text{Co}(\text{trien})(\text{N-Me-}(S)\text{-ala})]^{2+}$.⁸ In the Λ -*R* isomer a clear decision is not so apparent; the *N*-methyl group may either adopt the *R* configuration at the expense of steric interactions with the adjacent *cis*-methyl group or it may avoid these in the *S* configuration (*trans*-methyls) but with more significant interactions with one of the ethylenediamine rings. A comparison with the $\Lambda\text{-}[\text{Co}(\text{en})_2((S)\text{-pro})]^{2+}$ ion (*vide infra*) where the amino acid substituents are *cis*, and where the observed energy difference is similar ($0.72 \text{ kcal mol}^{-1}$ in favor of the Λ -*R* isomer), tends to support the *cis* configuration in the Λ -

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N-methyl-(*R*)-alanine complex. However, an X-ray study and structural and energy minimization calculations are presently being carried out to answer this question.

[Co(en)₂((*S*)-pro)]²⁺ System. The preparation of [Co(en)₂((*S*)-pro)]²⁺ from *trans*-[Co(en)₂Br₂]Br or *trans*-[Co(en)₂Cl₂]Cl results in the formation of both the Δ-*S* and Λ-*S* diastereoisomers. Previously only Δ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ had been isolated⁵ and it was proposed that the reaction was stereospecific.^{4,5} The diastereoisomers have been separated on cation exchange resin using NaH₂PO₄-NaHPO₄ as eluent and atomic absorption spectroscopy for Co gives a product distribution of 74 ± 2% Δ-[Co(en)₂((*S*)-pro)]²⁺ and 26 ± 2% Λ-[Co(en)₂((*S*)-pro)]²⁺. The complexes have been isolated as Δ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O (ε₄₉₀ 103; [α]₅₈₉ −281°; [α]₅₄₆ −478°) and Λ-(+)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O (ε₄₉₀ 118; [α]₅₈₉ +321°; [α]₅₄₆ +732°). Visible and pmr spectra and rotatory dispersion curves are given in Figures 2-4. Based on this data the preparative mixture ([M]₅₈₉ −635, −644°; [M]₅₄₆ −785, −801° (duplicate experiments) in water at 25°) contains 74 ± 1% Δ- and 26 ± 1% Λ-[Co(en)₂((*S*)-pro)]²⁺; the same result was obtained with *trans*-[Co(en)₂Cl₂]Cl and *trans*-[Co(en)₂Br₂]Br in methanol and in dimethyl sulfoxide.

It is clear also here that the preparative isomer distribution is close to the thermodynamically controlled isomer distribution. Treatment of the Δ-*S* and Λ-*S* complexes with charcoal resulted in rapid equilibration about the Co center (45 min) and gave solutions of similar optical activity ([M]₅₈₉ −820, −800° (Δ-*S*); −822, −797, −851° (Λ-*S*). Disproportionation to give detectable amounts (>5%) of [Co(en)₃]³⁺ and [Co(en)₂(H₂O)₂]³⁺ was a slower process (5 hr, ~23°) as was mutarotation of the proline ligand ([M]₅₈₉ −391° (2 days, 23°); −357° (4 hr, 86°)). In two experiments the Λ-*S* and Δ-*S* diastereoisomers were separated chromatographically using the phosphate eluent and the results of spectrophotometric and polarimetric analysis of the separated diastereoisomers (Λ-*S* 22, 23%; Δ-*S* 78, 77%) agree well with those for the mutarotated mixtures. The energy difference between the diastereoisomers is therefore not substantial (Δ*G* = 0.72 kcal mol^{−1}) although the isomer with the N proton, rather than the pyrrolidine ring, poised over the ethylenediamine chelate is stabilized as required by the arguments in ref 1. In the corresponding β₂-[Co(trien)((*S*)-pro)]²⁺ system strain energy minimization calculations give an energy difference of 1.6 kcal mol^{−1} in favor of the Δ-β₂-(*RRS*)-[Co(trien)((*S*)-pro)]²⁺ isomer with the largest contribution coming from valence angle deformations.⁸ The crystal structures of the two diastereoisomers^{14,15} support the energy minimization results and demonstrate that the nonbonded interactions between the pyrrolidine ring and the apical chelate of triethylenetetramine are reduced by distortion in the vicinity of the pyrrolidine ring (CoNC: Δ-*RRS*, 120.7°; Λ-*SSS*, 122.2°) and opening up of the N-Co-N angle subtended by an ethylenediamine NH₂ and proline N (Δ-*RRS*, 92.4°; Λ-*SSS*, 98.9°).^{8,14,15} It is likely that a similar situation occurs in

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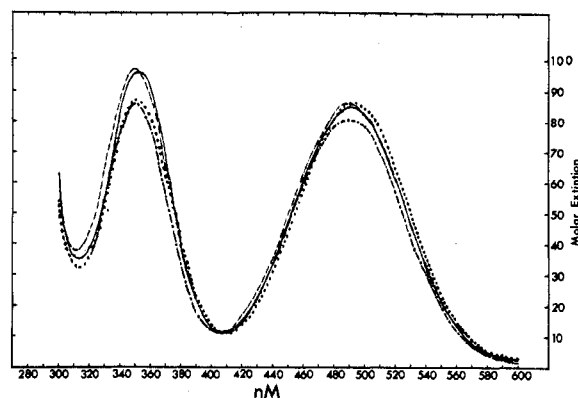


Figure 3. Visible spectra for Δ-(−)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂ (⋯⋯), Λ-(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂ (− · − · −), Δ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O (− − − −), and Λ-(+)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O (—). Units of molar extinction M^{−1} cm^{−1}.

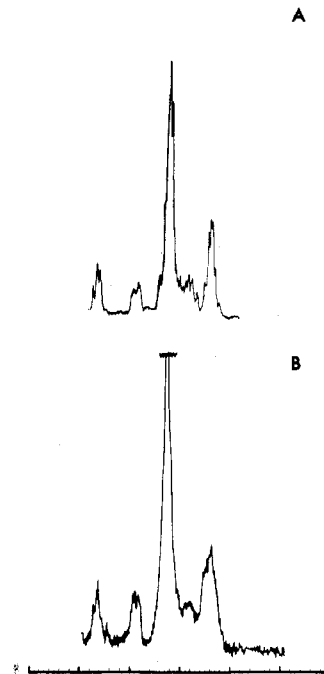


Figure 4. PMR spectra (100 MHz) for (A) Δ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ · H₂O and (B) Λ-(+)₅₈₉-[Co(en)₂((*S*)-pro)]I₂ in D₂O (deuterated at N).

the [Co(en)₂((*S*)-pro)]²⁺ diastereoisomers, and calculations are in progress to investigate this aspect.

Registry No. *trans*-[Co(en)₂Br₂]Br, 15005-14-8; *trans*-[Co(en)₂Cl₂]Cl, 14040-33-6; Δ-(−)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂, 40603-61-0; Λ-(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]Cl₂, 40629-29-6; Δ-(−)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂, 40603-62-1; Λ-(+)₅₈₉-[Co(en)₂(*N*-Me-(*S*)-ala)]I₂, 23348-04-1; Δ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂, 20594-20-1; Λ-(−)₅₈₉-[Co(en)₂((*S*)-pro)]I₂, 20594-19-8; Δ-[Co(en)₂((*S*)-pro)](AsO-(*R*)-tart)₂, 39291-55-9; Λ-[Co(en)₂((*S*)-pro)](AsO-(*R*)-tart)₂, 39291-54-8.

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