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Supplementary Material Available: Medium effects on quenching rate constants, and H_2 yields as a function of sensitizer, solvent, donor, etc. (8 pages). Ordering information is given on any current masthead page.

Metal Ion Promoted Elimination Reactions. Conversion of β-Hydroxy α-Amino Acids to α-Imino Acids

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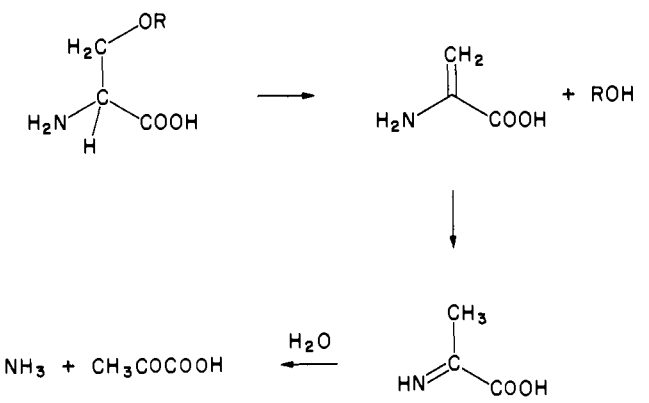
Abstract: Base-catalyzed elimination reactions of *O*-acetyl- and *O*-sulfonylserine coordinated to cobalt(III) give rise to chelated 2-iminopropanoate. The reaction rates are first order in [OH^-] and independent of buffer base concentration and are equal in magnitude to the methine proton exchange rates. Comparison with the rate of elimination for the free ligand, *O*-sulfonylserine, in base shows that coordination results in $\sim 10^7$-fold increase in reactivity. For N,O-coordinated (*S*)-methylcysteine, elimination of methanethiol is similarly facilitated, though in this complex the rate of methine proton exchange exceeds that of elimination by a factor of ~ 25. Reaction mechanisms are discussed. The methyl group in chelated 2-iminopropanoate is deprotonated readily in base and the carbanion so generated reacts rapidly with electrophiles such as aldehydes.

Subtle control of the reaction pathways available to an organic substrate is one of the well-known consequences of complex formation with a metal ion. Recognition of the formal charge donation and acceptance involved in complexation leads to the anticipation that ligand nucleophilicity should be reduced while electrophilicity is enhanced[1,2] and, in gross terms, metal ion catalysis can often be assessed in this way. However, detailed investigations of mechanism attest to the superficiality of this view,[3] so that it is necessary in as many instances as possible to probe beyond the mere metal ion dependence of a process. One convenient means of so doing is to examine metal ion promoted reactions (occurring at a substitutionally inert metal ion center) where the ligand remains bound to the metal ion for the lifetime of the organic reaction.

Hydroxy amino acids and their derivatives have numerous biological and synthetic uses.[4-6] Elimination processes are apparently involved in the enzymic conversion of, in particular, serine and its derivatives to other β-functionalized amino acids.[7-9] The immediate product, dehydroalanine, is either captured by a nucleophile to give a new amino acid or it rearranges to the iminopyruvate (2-iminopropanoate), which then decays further to ammonia and pyruvic acid (Scheme I).

Some of these processes involve pyridoxal to trigger the elimination, others do not. One such pyridoxal free system has been described by Tudball et al. for the elimination of sulfate ion from *O*-sulfonylserine to produce iminopyruvate and hence ammonia and pyruvate ion.[9] The question which arises for these latter systems is what triggers the elimination process. This paper examines the possibility of metal ions activating the elimination since it is well-known that the methine proton of α-amino acids becomes more acidic on chelation of the amine and carboxylate groups to some metal ions.[5] Certainly, simple metal ion pyridoxal catalyzed elimination reactions of serine and threonine (and their derivatives) have been observed, though often only in conditions where the anticipated immediate reaction products were not detected.[10]

Scheme I



The facile β-elimination of the nitro group in chelated nitroalanine to give a stable Co(III)–pyruvate–imine chelate[11] implied

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some value in the investigation of related reactions for the preparation of synthetically useful α-iminocarboxylato chelates. As readily available materials, the diastereoisomers of $Co(en)_2((S)\text{-ser})^{2+}$ ((S)-ser = anion of (S)-serine) were first examined. The present work describes the kinetics of the pH-dependent β-elimination reactions of both acetyl and sulfonyl derivatives of coordinated serine. Some preliminary studies of methanethiol elimination from N,O-coordinated S-methylcysteine are reported and finally reactions of chelated iminopropanoate with formaldehyde and 3-hydroxybenzaldehyde are described also.

Experimental Section

Analytical reagents were used for all purposes without further purification. Commercial CF_3SO_3H (3M Co.) was distilled before use. CF_3SO_3Li was prepared from Li_2CO_3 and CF_3SO_3H. *trans*-$[Co(en)_2Cl_2]Cl$ and *trans*-$[Co(en)_2(OH)(OH_2)](ClO_4)_2$ were synthesized by using standard procedures.[12,14] Both Sephadex SP C25 and Dowex 50W-X2 (200–400 mesh) cation-exchange resins were used for the separation of the complexes studied. All evaporations were carried out with Büchi rotatory evaporators at ≃15 mmHg pressure; the temperature of the solutions did not exceed 30 °C (external heating bath 40–50 °C). Spectrophotometric measurements were made with Cary 16K and 118C instruments. Kinetic studies employed a thermostated, hand-operated, stopped-flow mixer which could be fitted to the cell compartment of either instrument. Circular dichroism (CD) spectra were obtained on a Jasco UV/5 instrument fitted with a Sproul Scientific SS20 CD modification and rotatory dispersion (RD) spectra on an Perkin-Elmer P22 spectropolarimeter. Molar absorptivities ($(\lambda, \epsilon)_{max}$ nm, M^{-1} cm^{-1}) and molar rotations at 25 °C ([M] deg M^{-1} m^{-1}) are given where relevant. pH measurements were made under nitrogen by using a Radiometer Model 26 meter, with G202B glass electrodes standardized with phosphate (pH 6.86, 25 °C) and borate (pH 9.18, 25 °C) buffers. For μ = 1.0 media at 25 °C, pK_w was taken as 13.77 and $[H^+]$ computed using $\gamma_\pm$ 0.67.[13] ^1H NMR spectra were recorded on a JEOL Minimar 100-MHz instrument using sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) as internal reference. ^{13}C NMR spectra were recorded at 15.04 MHz on a JEOL FX-60 instrument. 1,4-Dioxane was the internal reference (taken to be at δ 67.4). Cobalt was determined by atomic absorption using a Techtron AA4 spectrometer.

Δ,Λ-[Co(en)$_2$((S)-ser)]Cl$_2$. Finely ground (S)-serine (10.5 g) was added to a solution of *trans*-$[(Co(en)_2)(OH_2)OH](ClO_4)_2$ (41 g) in dimethyl sulfoxide (200 mL). The mixture was stirred at 80 °C for 45 min (efficient stirring is essential to ensure that all the amino acid dissolves). The final orange-brown solution was cooled to room temperature and diluted with water (1 L) before being absorbed on Dowex 50W-X2 cation-exchange resin (H^+ form, 45 cm × 10 cm column). Elution with 1 M HCl removed two minor pink bands ($Co(en)((S)\text{-ser})_2^+$ species) and then a major orange component. The major fraction eluate was taken to dryness under vacuum, and the mixture of diastereoisomers in the residue crystallized by dissolution in boiling methanol followed by slow cooling (30 g, 86%). Anal. Calcd for $CoC_7H_{22}N_5O_3Cl_2$: Co, 16.64; C, 23.87; H, 6.26; N, 19.78; Cl, 20.02. Found: Co, 16.7; C, 23.9; H, 6.3; N, 19.5; Cl, 20.1. Spectroscopic characterization is given below for the separated diastereoisomers.

Separation of Diastereoisomers of [((S)-Serinato)bis(ethylenediamine)cobalt(III)] Chloride. Λ,Δ-$[Co(en)_2((S)\text{-ser})]Cl_2$ (20 g) was sorbed on Dowex cation-exchange resin (Na^+ form, 40 cm × 10 cm wet resin). On elution with phosphate buffer (0.25 M, pH 7) the two diastereoisomers separated as approximately equal-intensity orange bands. The Λ-isomer which eluted first was collected and, after dilution with water (fivefold), was resorbed on Dowex (H^+ form). On elution with HCl (2 M) and evaporation to dryness, the residue was taken up in 3 M HCl, and diluted with an equal volume of methanol. Acetone was then added slowly to crystallize the complex as a chloride salt (7 g). Anal. Calcd for $[CoC_7H_{22}N_5O_3]Cl_2$: Co, 16.64; C, 23.74; H, 6.26; N, 19.78; Cl, 20.02. Found (Λ): Co, 16.7; C, 23.9; H, 6.3; N, 19.9; Cl, 20.1. Visible spectrum $(\lambda, \epsilon)_{max}$ (H_2O): (345, 105), (484, 93). ^1H NMR spectrum: δ 2.80 (4(>CH_2), en, br), 3.84 (>CH–, m), 3.97 (>CH_2, d), ~4.3 (–NH_2, br), ~4.8 (–NH_2, br), ~5.2 (2(–NH_2), br), ~5.9 (NH_2, br) in 10^{-2} M DCl. ^{13}C NMR spectrum: δ 44.3, 45.6, 45.8, 46.5 (4(>CH_2), en), 60.1 (>CH–), 62.2 (>CH_2), 185.4 (Co–OCO) in 10^{-2} M DCl. $[M]_{589}$ = +1500; $[M]_{472}^{min}$ = −5350; $[M]_{542}^{max}$ = +3150 and $\Delta\epsilon_{505}^{max}$ = +1.88 (H_2O). Values of [M] and Δε are for the $S_2O_6^{2-}$ salt.

The second band, containing the Δ-isomer, was treated in a similar manner and the crystalline chloride salt obtained (10.5 g). Found (Δ): Co, 16.8; C, 23.9; H, 6.3; N, 19.8; Cl, 20.1. Visible spectrum $(\lambda, \epsilon)_{max}$ (H_2O): (346, 105), (484, 98). ^1H NMR spectrum: δ 2.84 (4(>CH_2), en, br), 3.96 (>CH_2, d), 4.0 (>CH–, m), 4.32 (–NH_2, br), ~4.8 (–NH_2, br), ~5.2 (3(–NH_2), br) in 10^{-2} M DCl, DSS reference. ^{13}C NMR spectrum: δ 44.4, 44.9, 46.0, 46.4 (4(>CH_2), en), 59.6 (>CH–), 62.5 (>CH_2), 185.3 (Co–OCO–) in 10^{-2} M DCl. $[M]_{589}$ = 1880, $[M]_{464}^{max}$ = +6120, $[M]_{539}^{min}$ = −4160, and $\Delta\epsilon_{505}^{max}$ = −2.38 (H_2O).

Δ,Λ-[Co(en)$_2$(NH=C(CH$_3$)CO$_2$)]Cl$_2$ was synthesized either by using the serinato complex as starting material (preparation 1) or by using directly the crude reaction mixture from the reaction of *trans*-$[Co(en)_2Cl_2]Cl$ and serine (preparation 2).

(1) A mixture of thoroughly ground Δ,Λ-$[Co(en)_2((S)\text{-ser})]Cl_2$ (40 g) and LiCl (40 g) was added to glacial acetic acid (200 mL) in a round-bottomed flask fitted with a condenser and a $CaCl_2$ drying tube. The stirred suspension was heated at ca. 110 °C until all the solid had dissolved (~20 min). Acetic anhydride (100 mL) was then added and the solution heated at reflux for 90 min, during which time a brown-yellow precipitate formed. After cooling to room temperature, the excess acetic anhydride was hydrolyzed by addition of water (200 mL). From the resultant clear orange-yellow solution the product was crystallized by slow addition of acetone (750 mL) with frequent stirring until the deposition of solid had been initiated (35 g, 92%).

(2) To a mixture of *trans*-$[Co(en)_2Cl_2]Cl$ (28.5 g) and (R,S)-serine (10.5 g) was added methanol (250 mL) and water (250 mL). The suspension was heated with stirring to 60 °C and then a solution of $LiOH\cdot H_2O$ (4.2 g, 0.1 mol) in a mixture of water (40 mL) and methanol (250 mL) was added portionwise. The solution was refluxed for 45 min and then evaporated almost to dryness under vacuum. Acetic acid (200 mL, 17.4 M) and LiCl (40 g) were added to the resulting oil. The suspension was refluxed for 10 min to form a brownish solution which was transferred to a conical flask equipped with a condenser. Acetic anhydride (100 mL) was added, and the solution was refluxed for 1.5 h. After cooling to 30 °C, the excess acetic anhydride was hydrolyzed by addition of water (200 mL). The resulting black-green solution was treated slowly with acetone (1000 mL). Sometimes an oil was formed at this stage. In such instances, addition of a few drops of water always initiated crystallization and these were collected, washed with acetone, and dried in air. This procedure gave 25 g of crude orange chloride salt contaminated with $[Co(en)_3]Cl_3$.

The complex was purified by dissolution in water (135 mL) at 55 °C. The solution, which was never quite clear, was cooled to ~0 °C. Then, with cooling and stirring, 2 M NaOH (70 mL, 20 °C) was added to precipitate the basic imine salt. The resulting thick suspension was filtered as dry as possible and washed thoroughly three times with 80% ethanol (80 mL) followed by 96% ethanol (80 mL) and finally dried on the filter.

Water (35 mL, ~20 °C) was added to the basic imine salt on the filter; some dissolved. The suspension was stirred as 12 M HCl (25 mL, ≃ 20 °C) was added. Practically all the solid dissolved and the solution was rapidly filtered. From the filtrate, orange crystals separated and acetone (115 mL) was slowly added to obtain quantitative precipitation. The crystals were washed with 96% ethanol and dried in the air (13.8 g, 85%).

The complex was analyzed after conversion to orange, needlelike clusters of the perchlorate salt by addition of $HClO_4$ to a concentrated aqueous solution of the chloride. Also, the perchlorate salt of the deprotonated form was readily precipitated from dilute NaOH solution by addition of $NaClO_4$. Anal. Calcd for $CoC_7H_{20}N_5O_{10}Cl_2\cdot H_2O$: Co, 12.22; C, 17.44; H, 4.60; N, 14.53; Cl, 14.71. Found: Co, 12.29; C, 17.88; H, 4.63; N, 14.75; Cl, 14.57. Anal. Calcd for $CoC_7H_{19}N_5O_6Cl$: Co, 16.21; C, 23.12; H, 5.27; N, 19.27; Cl, 9.75. Found (deprotonated complex): Co, 16.33; C, 23.03; H, 5.11; N, 19.11; Cl, 9.69. (Spectroscopic data are given below for the separated enantiomers.)

Resolution of Δ,Λ-[Co(en)$_2$(NH=C(CH$_3$)CO$_2$)]$^{2+}$. To a solution of $[Co(en)_2(NH{=}C(CH_3)CO_2)]Cl_2$ (12.0 g) in water (60 mL, 20 °C) was added ammonium $(+)_{589}$-3-bromocamphor-8-sulfonate, (NH_4·bcs) (5.2 g). Within 15 min, crystallization of Λ-$(+)_{589}$-$[(en)_2Co(NH{=}C(CH_3)CO_2)]$Cl·bcs commenced and after 1 h the crystals were collected, washed three times with 96% ethanol (20 mL), and dried in the air; $[\alpha]^{25}_{589}$ 330°.

The bcs·Cl salt (5.2 g) was converted to the chloride by dissolution in 12 M hydrochloric acid (27 mL) and addition of acetone (525 mL). The oil which formed was dissolved in 1 M HCl (13 mL), and acetone (75 mL) was added. Crystals of Λ-$(+)_{589}$-$[Co(en)_2(NH{=}C(CH_3)CO_2)]Cl_2\cdot H_2O$ separated, which were collected and washed with acetone

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(10 mL) and twice with ethanol (70 mL) (2.8 g), $[M]_{589}$ = 1660.

The purity of the Λ-$(+)_{589}$ salt was checked as follows: 2 g was dissolved in water (30 mL, 20 °C) and recrystallized by addition of acetone (150 mL) (1 g, $[\alpha]_{589}$ 335°). Further addition of acetone (350 mL) gave 0.8 g ($[\alpha]^{25}_{589}$ 341°). The two fractions were transformed into chlorides as described above and showed $[M]_{589}$ = 1670 and 1650, respectively.

The Δ-$(-)_{589}$ isomer was isolated from the initial filtrate by adding 96% ethanol (160 mL). After 15 h at ~20 °C a precipitate of mainly racemic chloride was collected (4.7 g). The filtrate was treated with acetone (450 mL) to crystallize Δ-$(-)_{589}$-$[Co(en)_2(NH{=}C(CH_3)CO_2)]Cl_2$. The precipitate was washed with acetone (20 mL) and twice with ethanol (20 mL) and dried in the air (3.1 g). Recrystallization of the crude salt (1.0 g) from water (10 mL) using acetone (18.5 mL) gave 0.16 g pure Δ-$(-)_{589}$ isomer ($[M]_{589}$ = −1640). Further spectroscopic data are given below.

Λ-$(+)_{589}$-[Co(en)$_2$(NH=C(CH$_3$)CO$_2$)]Cl$_2$·H$_2$O. Λ-$(+)_{589}$-$[Co(en)_2((S)\text{-}serSO_3)]Cl\cdot H_2O$ (0.5 g) was dissolved in $NaHCO_3$–Na_2CO_3 buffer (0.2:0.05 M, pH 9.48, 30 mL) at 25 °C. After 4 h the reaction was quenched with glacial acetic acid and the solution sorbed on Dowex cation-exchange resin (H^+ form). Elution with 1 M HCl provided a single band and the eluate was taken to dryness under vacuum. The residue was crystallized by dissolution in the minimum volume of 3 M HCl, addition of an equal volume of methanol, addition of acetone to the point of turbidity, and standing at room temperature. Recrystallizations did not alter the properties of the orange crystals. Anal. Calcd for $[CoC_7H_{20}N_5O_2]Cl_2\cdot H_2O$: Co, 16.64; C, 23.74; H, 6.26; N, 19.78; Cl, 20.02. Found: Co, 16.4; C, 23.9; H, 6.7; N, 19.9; Cl, 20.5. Visible spectrum (λ, ϵ)$_{max}$ (H_2O): (477, 100). ^{1}H NMR spectrum: δ 2.44 ($-CH_3$, s), 2.80 (4(>CH_2), en, br), 5.0 (4($-NH_2$), br) in 10^{-2} M DCl. ^{13}C NMR spectrum: δ 22.7 ($-CH_3$), 44.7, 45.5, 46.1, 46.8 (4(>CH_2), en), 173.8 (CoN=C<), 186.5 (CoOCO), in 10^{-2} M DCl. $[M]_{589}$ = +1700 in H_2O, $[M]_{533}^{max}$ = +4000, $[M]_{460}^{min}$ = −6140, and $\Delta\epsilon_{500}^{max}$ = +2.39.

Δ-$(-)_{589}$-[Co(en)$_2$(NH=C(CH$_3$)CO$_2$)]Cl$_2$·H$_2$O. Starting with Δ-$(-)_{589}$-$[Co(en)_2((S)\text{-}(serSO_3)]Cl$, the procedure above was repeated. Δ-$CoC_7H_{20}N_5O_2Cl_2\cdot H_2O$: $[M]_{589}$ = −1800, $[M]_{460}^{max}$ = +6440, $[M]_{533}^{min}$ = −4320, and $\Delta\epsilon_{500}^{max}$ = −2.53.

Λ-$(+)_{589}$-[Co(en)$_2$((S)-serSO$_3$)]Cl·H$_2$O and Δ-$(-)_{589}$-[Co(en)$_2$((S)-serSO$_3$)]Cl·H$_2$O. Λ-$(+)_{589}$-$[Co(en)_2((S)\text{-}ser)]Cl_2$ (2.0 g) was dissolved in concentrated H_2SO_4 (15 mL). After the evolution of the HCl gas had ceased, SO_2Cl_2 (3 mL) was added. The mixture was then stirred vigorously for 30 min (SO_2Cl_2 is not miscible with concentrated H_2SO_4). The less dense unreacted SO_2Cl_2 was separated from the H_2SO_4 complex phase, and the latter was added dropwise to a vigorously stirred mixture of cold ethanol (50 mL) and ether (100 mL). The flocculent orange precipitate, which occluded a considerable volume of solvent, was collected and immediately redissolved in a minimum volume of 3 M HCl. Methanol (2 volumes) was added followed by slow addition of acetone until turbidity. On standing, the complex chloride crystallized. It was collected, washed with ethanol, and recrystallized by dissolution in a minimum of HCl (3 M), followed by addition of methanol and gradual addition of acetone. The orange-red crystals were collected and washed with ethanol and ether and dried over P_2O_5 in vacuo. Anal. Calcd for $[CoC_7H_{21}N_5O_6S]Cl\cdot H_2O$: Co, 14.17; C, 20.22; H, 5.58; N, 16.85; Cl, 8.53. Found (Λ): Co, 14.3; C, 20.4; H, 5.4; N, 16.6; Cl, 8.8. Visible spectrum (λ, ϵ)$_{max}$ (H_2O): (345, 110), (486, 100). ^{1}H NMR spectrum: δ 2.80 (4(>CH_2), en, br), 3.96 (>CH–, m), 4.42 (>CH_2, d), ~4.5 ($-NH_2$, br), ~5.2 (2($-NH_2$), br), 5.4 ($-NH_2$, br), 6.0 ($-NH_2$, br) in D_2O. ^{13}C NMR spectrum: δ 44.0, 45.5, 46.0 (4(>CH_2), en), 57.9 (>CH–), 68.8 (>CH_2), 183.1 (Co–OCO) in D_2O. $[M]_{589}$ = +1400, $[M]_{542}^{max}$ = +3200, $[M]_{472}^{min}$ = −6900, and $\Delta\epsilon_{507}^{max}$ = +2.27 (H_2O).

The Δ-$(-)_{589}$-$[Co(en)_2((S)\text{-}serSO_3)]Cl\cdot H_2O$ diastereoisomer was synthesized in a similar manner starting with Δ-$(-)_{589}$-$[Co(en)_2((S)\text{-}ser)]Cl_2$. Anal. Calcd for $[CoC_7H_{21}N_5O_6S]Cl\cdot H_2O$: Co, 14.17; C, 20.22; H, 5.58; N, 16.85; Cl, 8.53. Found (Δ): Co, 14.1; C, 20.3; H, 5.6; N, 16.6; Cl, 8.9. Visible spectrum (λ, ϵ)$_{max}$ (H_2O): (345, 110), (485, 103). ^{1}H NMR spectrum: δ 2.90 (4(>CH_2), en, br), 4.10 (>CH–, m), 4.43 (>CH_2, d), ~4.3 (NH_2, br), ~4.9 (NH_2, br), ~5.4 (3($-NH_2$), br) in D_2O. ^{13}C NMR spectrum: δ 44.4, 45.6 (4(>CH_2), en): 57.3 (>CH–); 68.8 (>CH_2), 183.1 (Co–OCO) in D_2O. $[M]_{589}$ = −1680, $[M]_{470}^{max}$ = +5480, $[M]_{543}^{min}$ = −3580, and $\Delta\epsilon_{507}^{max}$ = −2.17 (H_2O).

Λ-$(+)_{589}$-[Co(en)$_2$((S)-serCOCH$_3$)](CF$_3$SO$_3$)$_2$. Λ-$(+)_{589}$-$[Co(en)_2((S)\text{-}ser)]Cl_2$ (1.0 g) in water (10 mL) was mixed with $Ag(O_3S\cdot CF_3)$ (1.8 g) in water (10 mL) and the precipitated AgCl removed. The filtrate was evaporated to dryness under vacuum and the residue redissolved in acetone and filtered to remove traces of residual AgCl. The complex was then precipitated by the addition of ether. Dissolution in acetic anhydride (25 mL) and standing for 60 min at 20 °C gave fine orange needles. These were calculated and the remaining complex in the filtrate was precipitated with ether. ^{1}H NMR spectra of both fractions were identical and consistent with the chelated serine–acetate complex. They were recombined and dissolved in water, filtered, and recrystallized by addition of $Na(O_3S\cdot CF_3)$. The crystals were collected, washed with ethanol and ether, and air-dried in vacuo over P_2O_5 (0.9 g). Anal. Calcd for $[CoC_9H_{24}N_5O_3](CF_3SO_3)_2$: Co, 9.45; C, 21.19; H, 3.88; N, 11.23. Found (Λ): Co, 9.5; C, 21.3; H, 3.9; N, 10.9. Visible spectrum (λ, ϵ)$_{max}$ (H_2O): (347, 111), (487, 101). ^{1}H NMR spectrum: δ 2.15 ($-CH_3$, s), 2.8 (4(>CH_2), en, br), 3.95 (>CH–, m), 4.40 (>CH_2, d), ~4.8 (3($-NH_2$), br), ~5.6 ($-NH_2$), ~6.0 ($-NH_2$) in 10^{-2} M DCl. ^{13}C NMR spectrum: δ 44.2, 45.5, 46.0 (4(>CH_2), en), 57.3 (>CH–), 65.7 (>CH_2), 174.0 (–OCO–), 183.1 (Co–OCO–) in 10^{-2} M DCl. $[M]_{589}$ = +940, $[M]_{542}^{max}$ = +2240, $[M]_{472}^{min}$ = −4800 and $\Delta\epsilon_{508}^{max}$ = +1.53 (H_2O).

***p*- and *t*-[Co(tren)(*S*)-ser)]$^{2+}$.** The synthesis closely followed that described for the *p*- and *t*-Co(tren)(glycinate)$^{2+}$ analogues.[14] (Isomers with O trans to a primary or tertiary amine center are described as *p* or *t*, respectively.) To $[Co(tren)(OH)(OH_2)](ClO_4)_2$[14] (4.4 g, 0.010 mol) in H_2O (50 mL) was added a moderate excess of fresh serine ethyl ester (2.0 g, 0015 mol) (obtained from ester hydrochloride as described for the glycine species). The deep red-violet solution became red-orange on heating (80 °C, 45 min). The cooled product mixture was diluted to 500 mL (H_2O) and sorbed on, washed and eluted (1.5 M Na^+, phosphate buffer pH ~7) from Dowex 50W-X2 (Na^+ form, 200–400 mesh). A clean separation of the two major bands was obtained; the faster running (yellow-orange) proved to be the *p*-Co(tren)(*S*)-ser^{2+} ion, the slower band (orange-red) the *t*-isomer. The phosphate was removed by separate sorption and re-elution (2 M HCl) from H^+ form Dowex resin. Following removal of solvent by evaporation, the separate isomers were crystallized readily from concentrated aqueous solutions using $Li_2S_2O_6$ or $ZnCl_2$/HCl. Methanol was added (slowly) as appropriate to increase the recoveries. The *p*-isomer was obtained as the $S_2O_6^{2-}$ salt, the *t*-isomer as both $ZnCl_4^{2-}$ and $S_2O_6^{2-}$ salts. The overall yield was ~85%, approximately $^2/_3$ being the *t*-isomer. Some *p*-isomer was synthesized from $[Co(tren)(Me_2SO)_2](ClO_4)_3$ and (*S*)-serine in Me_2SO containing "Tris" or triethylamine, and also from $[Co(tren)(OH)(OH_2)](ClO_4)_2$ and (*S*)-serine in H_2O, as well as via the BH_4^- reduction[14] of *p*-$[Co(tren)(NH_2CH(CHO)CO_2)]^{2+}$. These reductions gave the *p*-isomer exclusively, identical in all properties with that obtained above. The UV/vis spectra of the *p*- and *t*-serinato complexes closely parallel those for the glycinato and threoninato analogues. The ^{13}C NMR spectra confirmed the structural assignments; the resonances attributable to the tren ligand are diagnostic[14] of the *p*- or *t*-geometry, while the chelated serinate ligand absorptions were very similar to those given earlier for the two Co(en)$_2$((*S*)-ser)$^{2+}$ diastereoisomers. The ^{13}C NMR spectra also established isomeric purity. *p*-isomer: 184.5 ($-CO_2$), 62.7, 62.5, 60.2, 46.4, 45.6 (tren CH_2), 62.6 (CH_2OH), 60.1 (CH–, ser). *t*-isomer: 183.1 ($-CO_2$), 61.6, 61.4, 59.3, 42.6, 42.6, 41.8 (tren-CH_2), 62.9 (CH_2OH), 58.9 (CH–, ser). The diastereotopic splittings of the resonances attributable to the tren carbon skeleton (six carbons) are consistent with the presence of the chiral C center of chelated (*S*)-serinate ion; each complex has strictly C_1 symmetry.

***p*- and *t*-[Co(tren)(NH=C(CH$_3$)CO$_2$)].** To a stirred mixture of CF_3COOH (50 mL) and $(CF_3CO)_2O$ (20 mL) was added *p*- or *t*-$[Co(tren)((S)\text{-}ser)]S_2O_6$ (0.75 g); this dissolved and reacted over 36 h at ~20 °C. The product mixture was diluted to 500 mL with ice–water and sorbed on and eluted (2 M HCl) from Dowex 50W-X2 (H^+ form) resin. A single band was observed in each case. Synthetic mixtures showed that the imine product elutes in front of and well separated from the corresponding serinato reactant. Also, *p*- and *t*-isomers separate. The products were crystallized by removal of solvent from the column eluates, dissolution in a small volume of water, and addition of an equal volume of methanol followed by careful dilution with acetone. Yields of the yellow *p*- and orange *t*-isomers were essentially quantitative. They reversibly deprotonate in 0.01 M NaOH to give deep orange (*p*-) and deep red (*t*-) species. The $S_2O_6^{2-}$ salts of both protonated and deprotonated complexes were crystallized by using $Li_2S_2O_6$ and LiOH as appropriate. Anal. Calcd for $[Co(C_6H_{18}N_4)(C_3H_4NO_2)]Cl_2$: Co, 15.50; C, 28.43; H, 6.36; N, 18.43; Cl, 18.65. Found (*p*-): Co, 15.5; C, 28.7, H, 6.3; N, 18.0; Cl, 19.2. Calcd for $[Co(C_6H_{18}N_4)(C_3H_4NO_2)]S_2O_6$: Co, 13.06; C, 23.95; H, 4.9; N, 15.52; Cl, 13.06. Found (*p*-): Co, 13.0; C, 24.0; H, 5.1; N, 15.1; Cl, 13.0. ^{13}C NMR spectrum (10^{-3} M DCl) *p*-isomer: δ 187.4 (Co—OCO), 172.9 (Co—N=C), 6275 (2 C), 60.02, 46.26 (2 C), 45.59 (tren CH_2), 22.79 (CH_3). *t*-isomer: δ 186.4 (Co—OCO), 174.1 (Co—N=C), 63.74 (2 C), 62.5, 44.9 (2 C), 44.3 (tren CH_2), 22.6 (CH_3). ^{1}H NMR spectrum (D_2O): *p*-isomer δ 2.84–3.86 (m, 12 H; tren CH_2), 2.53 (s, 3 H, CH_3).

Reaction of *p*-*N*,*O*-[Co(tren)((*R*-)-cys-SCH$_3$)]Cl$_2$ in Aqueous Carbonate Buffer. The title complex (5.0 g) was reacted for 14 h at 34 °C in $NaHCO_3/Na_2CO_3$ buffer (50 mL, pH 10.4). Dilution, sorption, and elution (2 M HCl) from Dowex 50W-X2 (H^{2-} form) resin yielded *p*-

$Co(tren)(NH{=}C(CH_3)CO_2)^{2+}$ followed by starting material. The solvent was removed by evaporation and the Cl^- salts crystallized as described above. The ^1H and ^{13}C NMR spectra were identical with those of authentic specimens. Concurrently with the ^1H NMR studies about to be described, a similar experiment was performed in $NaDCO_3/Na_2CO_3$ buffer (0.5 mL, pD 10.83) using 0.05 g reactant.

Potassium (*S*)-Serine-*O*-sulfonate, $K(NH_2CH(CH_2OSO_3)CO_2$. The compound was prepared by the method of Tudball[15] and characterized through its ^1H NMR spectrum (δ 3.57 (CH, t), 4.19 (CH_2, d)) in 1 M NaOD.

Bis(ethylenediamine)(2-imino-3-(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) Chloride Hydrate. $[Co(en)_2(NH{=}C(CH_3)CO_2)](ClO_4)_2\cdot H_2O$ (2.0 g, 0.0035 mol) was dissolved in a suspension of water (125 mL) and Li_2CO_3 (4.0 g) and then 36 w/w % formaldehyde in water (50 mL, 0.67 mol) was added to the stirred solution. After 2 min at room temperature (27 °C) the mixture was rapidly filtered (≤10 s) into glacial acetic acid (10 mL). The solution was diluted with H_2O (1 L), sorbed on Sephadex SP C-25 (6 × 20 cm) and eluted with 0.05 M trisodium citrate. Two red and one brown front-running bands were discharged. The main band (orange) separated finally into a major leading band and a much smaller trailing band. The first was sorbed on Dowex 50W-X2 (H^+ form) and eluted with 3 M HCl. The eluate was evaporated to ~3 mL and then 50% *v*/*v* ethanol in acetone (12 mL) was slowly added. Orange crystals precipitated which were washed with 96% ethanol and diethyl ether and dried in the air (0.40 g, 28%). Anal. Calcd for $[Co(C_4N_4H_{16})(C_5NH_8O_4)]Cl_2\cdot H_2O$: Co, 14.22; C, 26.09; N, 16.91; H, 6.32; Cl, 17.12. Found: Co, 13.60; C, 25.95; N, 16.60; H, 6.02; Cl, 17.73. ^1H NMR spectrum: δ 2.0 (4(>CH_2), en, br), 3.5 (>CH−, m), 3.9 (2(CH_2O), m) in 1 M DCl; N-deuterated complex. ^{13}C NMR spectrum: δ 42.2, 42.9, 43.4, 43.8 (4(>CH_2), en), 47.7 (>CH), 57.0, 58.7 (2(CH_2O)), 170.0 (OCO), 184.7 (N=C) in D_2O.

Bis(ethylenediamine)(2-imino-3,3-bis(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) Chloride Hydrate. $[Co(en)_2(NH{=}C(CH_3)CO_2)](ClO_4)_2\cdot H_2O$ (2.0 g) was reacted with formaldehyde exactly as described in the preparation above, but with a 20-min reaction time. The product solution was separated by using Sephadex SP C-25 as before. Two orange bands separated. The leading major band eluate was sorbed on Dowex 50W-X2 (H^+ form) and then eluted with 3 M HCl. The eluate was evaporated to dryness, dissolved in ~20 mL of water and then precipitated by addition of 96% ethanol (40 mL), followed by slow addition of acetone (200 mL). The precipitate was washed with 96% ethanol and diethyl ether and dried in the air (yield, 0.39 g, 25%). Anal. Calcd for $[Co(C_4N_4H_{16})(C_6NH_{10}O_5)]Cl_2\cdot H_2O$: C, 27.03; N, 15.77; H, 6.35; Cl, 15.96. Found: C, 27.22; N, 15.32; H, 6.23; Cl, 16.10. ^1H NMR spectrum (1 M DCl, N-deuterated complex): δ 2.9 (4(>CH_2), en, br), 4.2 (3(CH_2O), s). ^{13}C NMR spectrum (D_2O): δ 42.2, 43.0, 43.4, 43.7 (4(>CH_2), en), 55.1 (−C), 58.7 (3(CH_2O)), 185.6 (OCO), 169.1 (N=C) in D_2O.

Bis(ethylenediamine)(2-imino-4-(3-hydroxyphenyl)-3-butenoato)cobalt(III) Chloride Hydrate. $[Co(en)_2(NH{=}C(CH_3)CO_2)](ClO_4)_2\cdot H_2O$ (4.7 g, 0.0082 mol) and *m*-hydroxybenzaldehyde (3.0 g, 0.0246 mol) were dissolved in 1.0 M NaOH (50 mL). After 5 h at 25 °C the solution was added to a mixture of water (200 mL) and glacial acetic acid (25 mL). After cooling for 1 h a brownish precipitate was removed. The filtrate was diluted with water (2 L) and sorbed on Sephadex SP C-25 (Na^+ form, 7 cm × 35 cm). Elution with 0.05 M trisodium citrate gave four bands. The last two (minor) bands were not identified. The eluates for the first two bands were sorbed on Dowex 50W-X2 (H^+ form) and eluted with 3 M HCl.

The complex in the first band was identified (1.00 g) by its ^1H NMR spectrum as starting material. The eluate containing the second band was evaporated almost to dryness and the 96% ethanol was added. The crystals so obtained were washed with 96% ethanol and dried in the air (1.2 g, 32%). Anal. Calcd for $[CoC_{14}N_5H_{24}O_2]Cl_2\cdot H_2O$: Co, 12.86; C, 36.69; N, 15.29; H, 5.72; Cl, 15.47. Found: Co, 12.18; C, 36.74; N, 15.14; H, 5.39; Cl, 15.48. ^1H NMR spectrum: δ 2.4, 3.0 (4(>CH_2), br), 6.5–7.7 (4(ArH) and CH=CH, br) in 1 M DCl.

Kinetic Studies. Proton exchange and some hydrolysis/elimination reactions were monitored by ^1H NMR spectroscopy using $NaDCO_3/Na_2CO_3$ buffers or NaOD and DCl solutions. Where the reactions were slow, the reaction mixtures were kept in an external, thermostat bath and spectra recorded intermittently. Faster reactions were monitored continuously at the normal probe temperature (33 °C).

Precise rate measurements were made by constant wavelength spectrophotometry at 25.00 ± 0.05 °C in aqueous buffers, μ = 1.0 M ($NaNO_3$), prepared from diethylamine, diethanolamine or "Tris", and CO_2-free water. Where necessary, a simple stopped-flow device with a mixing time ≤1 s was employed to initiate reactions.

(15) Tudball, N. *Biochem. J.* **1962**, *85*, 456–460.

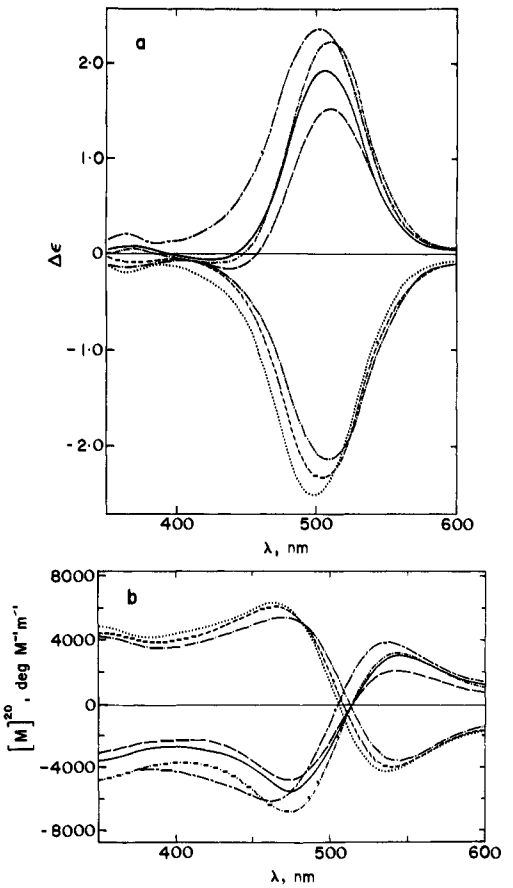


Figure 1. Circular dichroism (CD) ($\Delta\epsilon$) and rotatory dispersion (RD) ($[M]^{20}$) curves for Λ- (−·−·−) and Δ-$[Co(en)_2((S)\text{-serOSO}_3)]^{2+}$ (−·−·−); Λ-(—) and Δ-$[Co(en)_2((S)\text{-ser})]^{2+}$ (− − −); Λ-(−·−·−) and Δ-$[Co(en)_2(NH{=}C(CH_3)OCO)]^{2+}$ (···); and Λ-$[Co(en)_2((S)\text{-serOAc})]^{2+}$ (− − −) in H_2O, 20 °C.

For determination of reaction stoichiometry, reaction mixtures were analyzed by ^1H NMR spectroscopy and ion-exchange chromatography on Na^+ or H^+ forms of Dowex 50W-X2, 200–400 mesh resin. Ion-exchange eluates were taken to dryness under reduced pressure and the residual solids characterized spectroscopically (where the original eluate contained Na^+, it was first reabsorbed on H^+ form resin and the complex re-eluted using HCl).

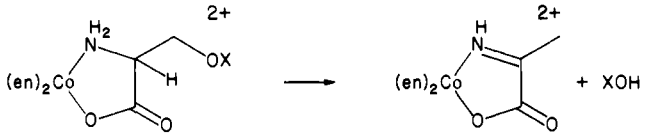
Results and Discussion

1. Complex Ion Synthesis and Stereochemistry. (Amino acidato)bis(ethylenediamine)–cobalt(III) complexes have been widely investigated and a variety of methods employed in their synthesis.[16] The "obvious" procedure of reacting a $Co(en)_2(unidentate)_2^{n+}$ species with the amino acid anion is usually complicated by disproportionation,[17] necessitating sometimes tedious separations of product mixtures. The product distribution does, however, apparently depend on the solvent and the preparation of $Co(en)_2((S)\text{-ser})^{2+}$ in dimethyl sulfoxide proceeds in high yield provided the amino acid is finely ground and the reaction mixture well agitated to achieve optimal dissolution of this least soluble component. The preparative procedure presently described leads to essentially equal amounts of the two diastereoisomers Δ- and Λ-$Co(en)_2((S)\text{-ser})^{2+}$. Racemization of the amino acid under the preparative conditions was not appreciable, as the diastereoisomeric materials obtained by Na_2HPO_4/NaH_2PO_4 elution from Dowex 50W-X2 were homogeneous to chromatography on SP Sephadex

(16) For some discussion of preparative procedures and problems in this area, see: (a) Warner, B. D.; Legg, J. I. *Inorg. Chem.* **1981**, *20*, 1625–1627; **1979**, *18*, 1839–1842 and references therein. (b) Freeman, H. C.; Moore, C. J.; Jackson, W. G.; Sargeson, A. M. *Inorg. Chem.* **1978**, *17*, 3513–3521. (c) Buckingham, D. A.; Dekkers, J.; Sargeson, A. M.; Wein, M. *Inorg. Chem.* **1973**, *12*, 2019–2023.

(17) Buckingham, D. A.; Dwyer, F. P.; Sargeson, A. M. *Aust. J. Chem.* **1963**, *16*, 921–925.

with $Na[Sb_2(tartrate)_2]$ elution, a treatment which was shown independently to resolve Λ-$Co(en)_2((S)\text{-ser})^{2+}$/$\Delta$-$Co(en)_2((R)\text{-ser})^{2+}$ (and Λ-$Co(en)_2((R)\text{-ser})^{2+}$/$\Delta$-$Co(en)_2((S)\text{-ser})^{2+}$). Identification of the Δ and Λ forms of $Co(en)_2((S)\text{-ser})^{2+}$ was based on their RD and CD spectra, so that the isomer showing dominant positive rotatory strength associated with the first ligand field band was assigned the Λ configuration.[18] As was anticipated, the CD and rotatory dispersion spectra of the $Co(en)_2(serX)^{n+}$ complexes (X = CH_3CO, SO_3) (**1**) differed little from their parent species (Figure 1).



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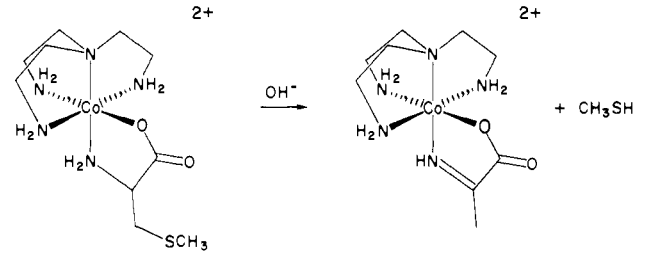
Under the particular preparative conditions described (see Experimental Section), $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ (**2**) was the only isolable product from the reactions of $Co(en)_2(serX)^{n+}$ in both acidic and basic media. The reaction in aqueous base is especially efficient and rapid but the convenience of a "one pot" preparation from $Co(en)_2(ser)^{2+}$ and $CH_3CO_2H/(CH_3CO)_2O$ renders reaction in this particular acidic medium synthetically useful (it is, however, perhaps inappropriate to consider this a simple acidic medium in that the elimination is very much faster than for $Co(en)_2(serSO_3)^+$ in concentrated H_2SO_4 and the reactions of $Co(en)_2(serX)^{n+}$ in dilute aqueous acid lead to $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ in only very low yield (see below)). That the preparative reaction product was the α-iminocarboxylato complex, $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ (**2**), was readily established from the close similarities in its properties to those of its well-characterized tetraammine analogue.[6,13] Thus, the ^1H NMR spectrum shows resonances at δ 2.44 (3 H) and 12.2 (1 H) in Me_2SO-d_6, as expected for $CH_3C{=}$ and $=NH$ groups, while the ^{13}C spectrum shows C=N and CH_3 resonances at δ 173.8 and 22.7 (relative to external tetramethylsilane), respectively. The complex also ionizes in aqueous solutions of pH $\geq$10 to give an intensely colored, nucleophilically active base form.[19] The identity of the complex, of course, established that the reaction leading to its formation was an elimination process, although the simplest possible intermediate (enamine) was never observed nor trapped.

Separation of the $Co(en)_2((S)\text{-ser})^{2+}$ diastereoisomers afforded a simple means of obtaining the resolved $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ complex. Circular dichroism spectra (Figure 1) show that there is no change of configuration about Co(III) during the conversion reaction. Independent resolution (fractionation of chloride/3-bromocamphor-8-sulfonate salts) of Δ,Λ-$Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ confirmed that the same species obtained from the separated $Co(en)_2((S)\text{-ser})^{2+}$ diastereoisomers were fully resolved and thereby demonstrated the absence of amino acid methine center racemization during the preparative procedures for the $Co(en)_2((S)\text{-ser})^{2+}$ isomers.

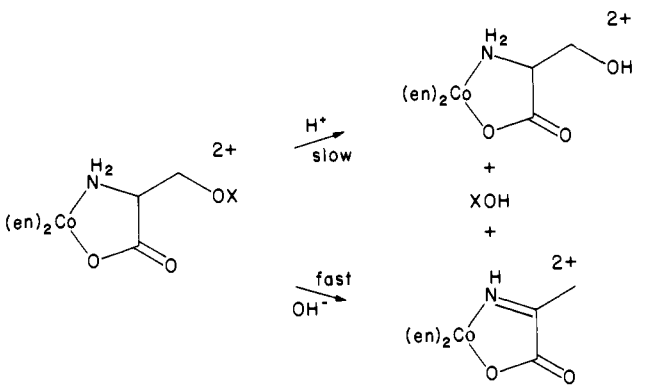
Detailed studies were not made of the reactions of *p*-N,O-Co(tren)(cys–SCH_3)$^{2+}$ (**3**) in base, as several processes appeared



3 4

(18) Saito, Y. In "Topics in Stereochemistry"; Eliel, E. L., Allinger, N., Eds.; Wiley: New York, 1978; Vol. 10, p 95.
(19) Harrowfield, J. MacB.; Sargeson, A. M. *J. Am. Chem. Soc.* **1974**, *96*, 2634–2635.

Scheme II



to follow the initial elimination. Acid quenching of reaction mixtures after consumption of ca. 50% of the reactant showed, however, only unchanged reactant and material identified from its ^1H and ^{13}C NMR spectra as *p*-$Co(tren)(NH{=}C(CH_3)CO_2)^{24}$ (**4**). This was confirmed by an independent synthesis of this imine complex (see Experimental Section). Hence, the reaction observed under these conditions can be identified as **3** → **4**.

2. Reaction Pathways. (a) Hydrolysis and Elimination. For reaction media where precise rate measurements could readily be made, both ^1H NMR spectroscopy and ion-exchange chromatography were used to establish reaction pathways. In acidic aqueous solutions, ^1H NMR spectroscopy was especially convenient to apply in that nonexchanging proton resonances of the reactant and product species were well resolved and readily detected. Thus, in 3 M DCl at 70 °C, for example, the slow reactions of Δ-$Co(en)_2((S)\text{-ser}SO_3)^+$ were readily monitored by observing the disappearance of the CH_2OSO_3 proton resonance at δ 4.43 and the concomitant appearances of CH_2OH (hydrolysis pathway) and $=CCH_3$ (elimination pathway) resonances at δ 3.96 and 2.44, respectively. The low intensity of the δ 2.44 imine chelate methyl resonance and its proximity to strong 1,2-ethanediamine CH_2 resonances made precise integration difficult, but the yield of this species was thereby estimated as only 7% ± 3%.

As the basicity of aqueous reaction media increased, the yield of $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$ did also, until above pH 8 this complex was the only detectable reaction product. This was shown by ion-exchange chromatography (Na_2HPO_4/NaH_2PO_4 eluant on Dowex 50W-X2) of the reaction mixture after approximately 10 half-lives. A single band, containing only $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$, was observed, under conditions which allowed for the efficient separation of artificial mixtures of $Co(en)_2(NH{=}C(CH_3)CO_2)^{2+}$, Δ-$Co(en)_2((S)\text{-ser})^{2+}$, and Λ-$Co(en)_2((S)\text{-ser})^{2+}$. Thus, the aqueous solution reactions of $Co(en)_2(serX)^{n+}$ have been interpreted in terms of the overall reaction (Scheme II).

(b) Proton Exchange. A process necessarily involved in the base-dependent elimination is the loss of the methine proton of the original amino acid. In simple amino acid chelates, the enhanced acidity of this proton is well-known and the ionization rate has been frequently studied by monitoring the exchange with D^+.[5,20] For elimination reactions in general, this proton loss may be faster than the overall reaction (E1CB mechanism) or may have the same rate (E1 and E2 mechanisms),[21] so that direct determination of the proton exchange rate for comparison with

(20) Recent references on this topic include the following: (a) McClarin, J. A.; Dressel, L. A.; Legg, J. I. *J. Am. Chem. Soc.* **1976**, *98*, 4150–4154. (b) Yoneda, H.; Miyanaga, A.; Sakaguchi, V.; Morimoto, Y.; Kushi, Y. *Inorg. Chem.* **1982**, *21*, 1387–1391. (c) Hine, J.; Hahn, S. *J. Org. Chem.* **1982**, *47*, 1738–1741.
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(22) Thomas, J. H.; Dodgson, K. S.; Tudball, N. *Biochem. J.* **1968**, *110*, 687–692.
(23) Martell, A. E. *J. Chem. Soc., Chem. Commun.* **1977**, 342–344.
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Table I. Rate Constants for Reactions of Serine (and Cysteine) Derivatives in Aqueous Solutions

reactant	medium	process	k_{obsd},[a] s^{-1}	$k = k_{obsd}{}^{b}$-[OH^-], M^{-1} s^{-1}
Λ-$CO(en)_2(serSO_3)^+$	Tris buffer (0.1 M), μ = 1.0, pH 8.23, 25 °C	elimination	9.2×10^{-5} [c]	22
	Tris buffer (0.1 M), μ = 1.0, pH 8.23, 25 °C	elimination	9.2×10^{-5} [c]	22
	Tris buffer (0.2 M), μ = 1.0, pH 8.23, 25 °C	elimination	1.1×10^{-4} [c]	25
	Tris buffer (0.2 M), μ = 1.0, pH 8.23, 25 °C	elimination	1.1×10^{-4} [c]	25
	diethanolamine buffer (0.1 M), μ = 1.0, pH 9.09, 25 °C	elimination	6.3×10^{-4} [c]	20
	diethanolamine buffer (0.1 M), μ = 1.0, pH 9.08, 25 °C	elimination	6.3×10^{-4} [c]	21
	diethanolamine buffer (0.2 M), μ = 1.0, pH 9.09, 25 °C	elimination	6.4×10^{-4} [c]	21
	diethanolamine buffer (0.02 M), μ = 1.0, pH 9.10, 25 °C	elimination	7.0×10^{-4} [c]	22
	diethylamine buffer (0.1 M), μ = 1.0, pH 11.12, 25 °C	elimination	7.1×10^{-2} [c]	22
	diethylamine buffer (0.1 M), μ = 1.0, pH 11.12 25 °C	elimination	6.9×10^{-2} [c]	21
	diethylamine buffer (0.2 M), μ = 1.0, pH 11.12, 25 °C	elimination	6.9×10^{-2} [c]	21
	diethylamine buffer (0.2 M), μ = 1.0, pH 11.12 25 °C	elimination	7.1×10^{-2} [c]	22
	0.01 M NaOH, μ = 1.0, pH 11.75, 25 °C	elimination	2.1×10^{-4} [c]	22
		elimination	2.1×10^{-4} [c]	22
	Tris buffer (0.1 M), μ = 1.0, pH 8.27, 25 °C	elimination	8.7×10^{-5} [c]	19
Λ-$Co(en)_2(serCOCH_3)^{2+}$	diethanolamine buffer (0.1 M), μ = 1.0, pH 9.16, 25 °C	elimination	5.5×10^{-4} [c]	15
	diethylamine buffer (0.1 M), μ = 1.0, pH 11.18, 25 °C	elimination	5.3×10^{-2} [c]	14
	0.01 M NaOH, μ = 1.0, pH 11.78, 25 °C	elimination	1.5×10^{-1} [c]	16
$H_2NCH(CO_2)CH_2OSO_3^{2-}$	NaOD, 1.0 M, 25 °C	elimination	$2.5(\pm 0.1) \times 10^{-6}$ [d]	
Λ-$Co(en)_2(serSO_3)^+$	D_2O/carbonate buffer, pD 10.83, $NaDCO_3$, 0.2 M–Na_2CO_3, 0.05 M	elimination	$1.7(\pm 0.1) \times 10^{-3}$ [c]	
	3 M DCl, 70 °C	hydrolysis/elimination	$(1.7 \pm 0.1) \times 10^{-4}$ [d,e] $(1.5 \pm 0.1) \times 10^{-5}$ [d,f]	
p-N,O-$Co(tren)(cys\text{-}SCH_3)^{2+}$	D_2O/carbonate buffer, μ = 0.35, pD = 10.83, 34 °C	methine H-exchange elimination	$(3.4 \pm 0.1) \times 10^{-4}$ [d]	
			$\sim 1.4 \times 10^{-5}$ [g]	

[a] Averageof triplicate determinations. [b] [OH^-] calculated from measured pH values, using pK_w = 13.77, $\gamma_{\pm}$ = 0.68. [c] Spectrophotometric monitoring, λ = 350 nm. [d] Monitored by ^1H NMR. [e] Rate constant for loss of reactant. [f] Rate constant for formation of Δ-$Co(en)_2(ser)^{2+}$. [g] Estimated from amounts of product and recovered reactant in ion-exchange experiments (~50% reaction in 14 h).

the rate of elimination is of mechanistic significance. The pathway was readily monitored in the present complex ion systems by ^1H NMR spectroscopy.

(c) Reactions of the Free Ligands. The reactions of "free" acetyl and sulfonyl serine (and some related compounds) in aqueous media have been studied and several pathways, including hydrolysis, elimination, retro-aldolization, and acyl transfer, have been identified.[10,22-24] Perhaps most relevant to the present work are the observations that the inefficient formation of serine from *O*-acetylserine (O to N acetyl transfer is the dominant reaction)[24] is inhibited by base and that in strongly basic solutions *O*-sulfonylserine reacts with 100% C–OSO_3 bond cleavage to give pyruvate, ammonia, and sulfate.[22] This elimination pathway for *O*-sulfonylserine was also revealed in the present ^1H NMR observations where only reactant resonances of slowly decreasing magnitude could be observed in 1 M NaOD. Whereas pyruvate ion undergoes rapid methyl group proton exchange in base, serine methylene resonances are preserved.

3. Reaction Kinetics. All reactions studied were found to conform to first-order (or pseudo-first-order) kinetics, plots of log (integrated reactant peak height) or log $(A_\infty - A_t)$ (A = absorbance) vs. time being linear over at least $4t_{1/2}$. For reactions in alkaline buffer media, no dependence on the nature or concentration of the buffer was found. The base dependent reactions therefore appeared to be subject to specific catalysis by OH^-. Rate data are given in Table I.

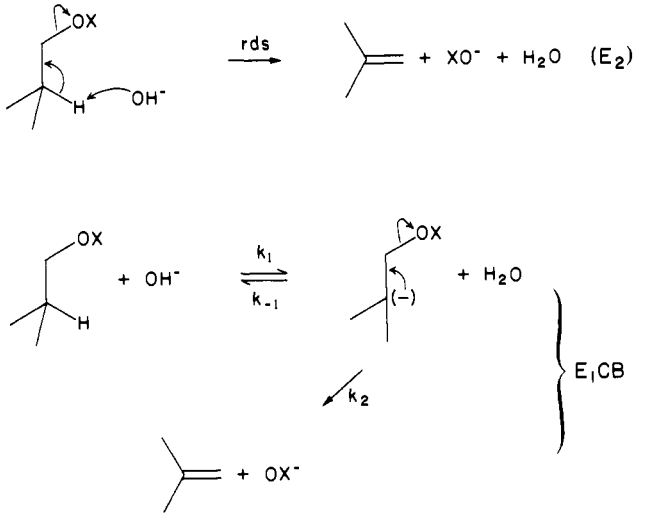
The apparent first-order rate constants for both $Co(en)_2(serSO_3)^+$ and $Co(en)_2(serCOCH_3)^{2+}$ show a linear dependence on [OH^-], indicating that the reaction rate law is

$$R = k[Co(en)_2(serX)^{n+}][OH^-]$$

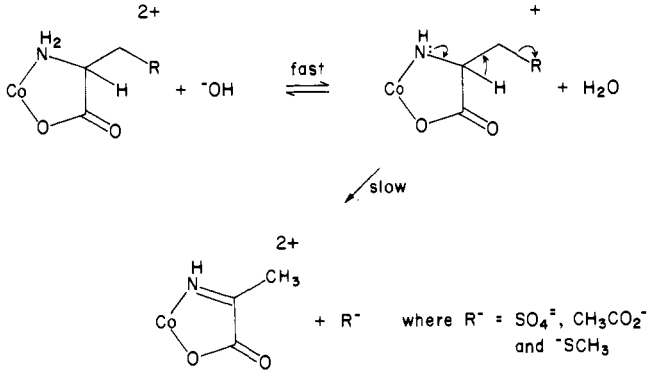
with mean values for the second-order rate constant k at 25 °C, μ = 1.0 M ($NaNO_3$), being 22 ± 1 M^{-1} s^{-1} (X = SO_3) and 16 ± 2 M^{-1} s^{-1} (X = CH_3CO). Within experimental error, the reactant diastereoisomers showed no difference in reactivity and hence these k values were averaged without regard to configuration. Given the preparative result that the chiral center at carbon (in serine) does not greatly discriminate between Δ and Λ centers at Co(III), it is perhaps not surprising that reaction rates for Δ- and Λ-$Co(en)_2(serX)^{n+}$ are so similar.

The difference between sulfate and acetate as leaving groups, though genuine, is so small as to be attributable to a variety of minor factors, upon which it would seem pointless to speculate. Perhaps more worthy of comment is the difference between the oxygen and the sulfur, CH_3S^-, leaving groups. Ion-exchange separation of the components of the reaction mixture from *p*-N,O-$Co(tren)(cys\text{-}SCH_3)^{2+}$ in the same medium as used for proton exchange measurements (see Table I) showed equal amounts of reactant and imine product to be present after approximately 14 h. Assuming pseudo-first-order kinetics, this showed the rate constant to be only ~120-fold smaller than that for elimination in $Co(en)_2(serSO_3)^+$ in the same medium (Table I). This limited range of reactivity for quite different leaving groups possibly reflects the high stability of the product α-iminocarboxylate chelate. However, it must also be noted that the proton exchange measurements reveal a rather significant difference between the serine and cysteine derivatives. Attempts to monitor methine proton exchange in $Co(en)_2(serX)^{n+}$ by quenching D_2O reaction mixtures with acid, isolating unreacted $Co(en)_2(serX)^{n+}$, and determining its ^1H NMR spectrum showed only that appreciable exchange had *not* occurred, i.e., that elimination and proton ex-

Scheme III



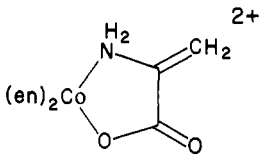
Scheme IV



change were occurring at essentially the same rate. However, with *p*-N,O-Co(tren)(cys-SCH_3)$^{2+}$, methine proton exchange was at least 25-fold faster than elimination.

4. Reaction Mechanisms. A term first order in [OH^-] in the rate law for elimination in Co(en)$_2$(serX)$^{n+}$ shows that of the conventional elimination mechanisms of organic chemistry, only the E2 and E1CB categories[21] are applicable (Scheme III). Where proton exchange is faster than the overall reaction (k_1, $k_{-1} > k_2$), the two mechanisms are easily distinguished but where proton exchange is rate determining ($k_2 > k_1 > k_{-1}$), an experimental distinction is difficult to make (if indeed it is of practical significance). However, the simplest rationalization of all the present results would be to suggest that the E1CB mechanism obtains in all instances, with methine proton removal being the rate-determining step in the Co(en)$_2$(serX)$^{n+}$ reactions but not in the *p*-N,O-Co(tren)(cys-SCH_3)$^{2+}$ reaction. Such an analysis is consistent, qualitatively, with the leaving group expectations.

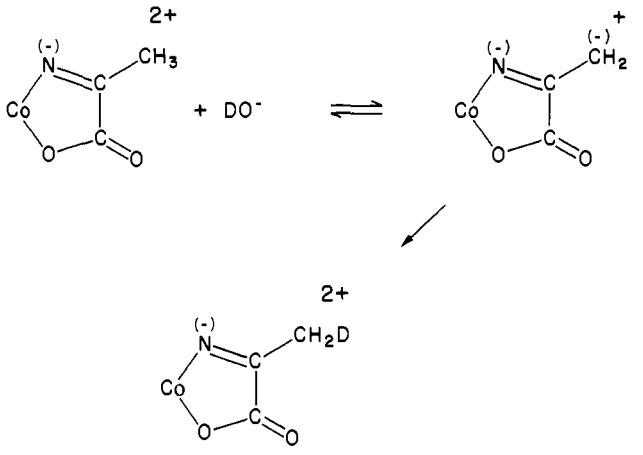
Regardless of this choice of mechanism the immediate product shown in Scheme III in both cases corresponds to the enamine chelate (**5**). Undoubtedly, such a species could tautomerize



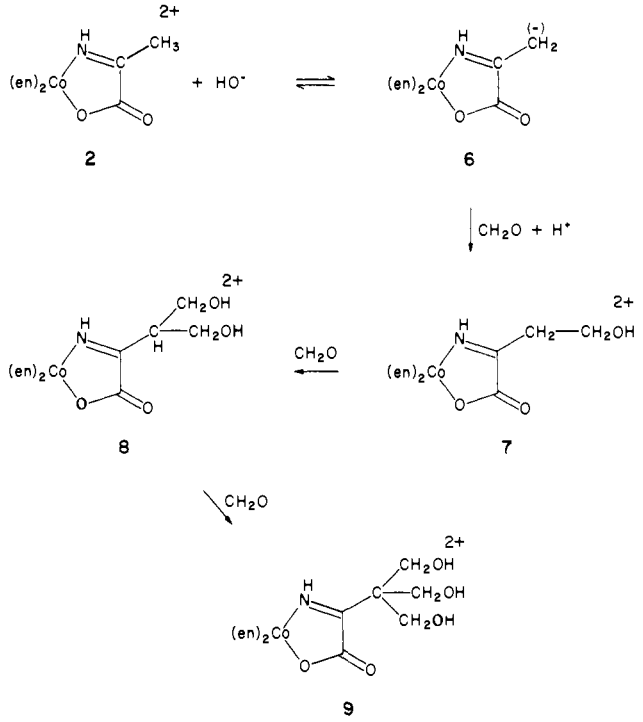
5

rapidly to the observed imine product under the reaction conditions and structural data for Co(III) complexes do show Co—N= bonds to be shorter, hence presumably stronger, than Co—NH_2,[25]

Scheme V



Scheme VI



which implies that the rearrangement is thermodynamically favored. However, no spectroscopic or chemical evidence (trapping with nucleophiles) for the intermediacy of an enamine species could be obtained in the present systems and its involvement is therefore only a plausibility. Indeed, were the rate law to be interpreted in terms of deprotonation at N (the preliminary step in the S_N1CB process for base-catalyzed substitution at Co(III)),[26] an enamine intermediate (**5**) need not be postulated. Thus, the [OH^-] dependence could be accommodated by Scheme IV. Such a scheme, however, would require the methine proton exchange rate in *p*-N,O[Co(tren)cysSCH_3]$^{2+}$ to be independent of that for CH_3S^- elimination. On the whole, therefore, the results are rationalized more cogently as an E_1CB process.

5. Reactions of Co(en)$_2$(NH=C(CH_3)CO_2)$^{2+}$ with Aldehydes. The methyl group of the imine exchanges its protons for D in basic D_2O (Scheme V).

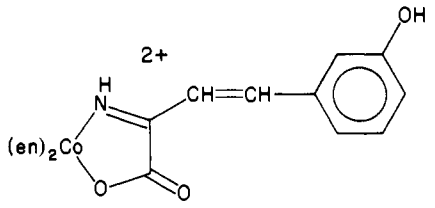
We presume the carbanion so generated is relatively short lived. The kinetics for the exchange process and our inability to deprotonate the methyl group completely indicate that its pK_a is far in excess of 14.

(25) Robertson, G. B.; Whimp, P. O. *Aust. J. Chem.* **1975**, *28*, 2129–2135 and references therein.

(26) Basolo, F.; Pearson, R. G. "Mechanisms of Inorganic Reactions", 2nd ed.; Wiley: New York, 1967; p 182 ff.

The acid properties of the methyl group in the imine complex were further demonstrated by its reaction with aldehydes. At pH 10 the imine complex reacts rapidly at 25 °C with 4 M formaldehyde. The reaction presumably occurs through carbanion species via electrophilic attacks by formaldehyde (Scheme VI). The product formed by the reaction with one formaldehyde (**7**) was not identified and therefore we presume it reacted rapidly with an additional formaldehyde to produce the bis(hydroxymethyl) derivative (**8**) as the first isolable product ($t_{1/2} < 30$ s). Further reaction with formaldehyde gave the tris(hydroxymethyl) derivative (**9**) ($t_{1/2} \sim 300$ s). Their structural assignments have been made on the basis of ^{1}H NMR and ^{13}C NMR spectra in conjunction with the elemental analysis (see Experimental Section).

At pH 14, **4** reacts with 3-hydroxobenzaldehyde (0.5 M) to form the product (**10**). The reaction is much slower than the



10

reaction with formaldehyde, $t_{1/2}$ = 2–3 h at 25 °C. Cation-exchange chromatography showed **10** to be the major product along with minor amounts of two other unidentified products.

The yellow cation (**10**) was isolated as its chloride salt which was sparingly soluble in water. In strong base, the salt dissolved readily and formed an intense red color. The latter process is reversible and on addition of excess hydrochloric acid the yellow chloride salt of **10** reformed. The red solution therefore contains **10** deprotonated, probably both at the imine center and at the phenolic group. Both acidic (3 M HCl) and basic solutions of **10** are stable for hours at 25 °C. The ^{1}H NMR spectrum of deprotonated **10** showed two broad signals around 2.4 and 3.0 ppm. A similar spectrum was observed for deprotonated **4** and these signals are ascribed to the eight carbon hydrogen atoms of ethylenediamine. Furthermore, the spectrum showed complex signals over the range 6.5–7.7 ppm which are ascribed to the four aromatic and the two unsaturated carbon hydrogen atoms. All integrations were in agreement with these assignments. On the basis of the present data it is not possible to establish the configuration around the carbon–carbon double bond.

Conclusions

Metal ion chelation has a dramatic effect on the reactivity of serine-*O*-sulfonate toward elimination. Neglecting possible deuterium isotope effects on the measured rate for the free serine-*O*-sulfonate dianion, a rate enhancement of $\sim 10^7$ results from coordination to Co(III). This activating effect is considerable, though still small relative to that observed under enzymic catalysis and a metal ion could therefore only provide a portion of the basic enzyme activity. The remainder would need to come from an intramolecular enzymic base to remove the methine proton in a facile manner.[27] If methine proton removal is rate determining for elimination in both free and coordinated $serSO_3^{2-}$, then the effect of Co(III) may be simply explained as due to its enhancement of the methine CH acidity, since such an effect could be of the desired magnitude.[28] As noted previously, however, it would be unusual for the effect of a metal ion to be directly related to a single factor and further details of the reaction mechanism remain to be elucidated.

The evidence for metal ion involvement in the Tudball enzyme is not strong so this aspect of the comparison still needs to be validated. However, the enzyme clearly triggers β-elimination in a number of amino acid derivatives including serine esters, cystine, cysteine, and alkylated cysteine, so the parallel with the described chemistry is close.

The elimination reaction of coordinated serine derivatives leads to potentially synthetically useful pyruvate–imine chelates and some properties of such complexes will be reported in subsequent publications. Many β-hydroxy amino acids other than serine are, of course, well-known[4,29] and indeed can be synthesized from metal–glycinate complexes and carbonyl compounds,[4,30] so that preparations may be carried out on a variety of α-iminocarboxylate chelates. Controlled organic syntheses of considerable complexity should be possible by exploitation of the nucleophilic and electrophilic properties of appropriately substituted α-iminocarboxylates.[31]

Acknowledgment. We are grateful to Statens Naturvidenskabelige Forskningsraad, Denmark, for support (J.S.) and to the A.N.U. Microanalytical Service.

Registry No. Λ,Δ-**1**·Cl_2 (X = H), 75441-95-1; Λ-**1**·Cl_2 (X = H), 91237-06-8; Λ-**1**·S_2O_6 (X = H), 95097-98-6; Δ-**1**·Cl_2 (X = H), 91237-05-7; Δ,Λ-**2**·Cl_2, 95098-08-1; Δ,Λ-**2**·$(ClO_4)_2$, 95098-09-2; Λ-$(+)_{589}$-**2**·Cl·bcs, 95189-79-0; Λ-$(+)_{589}$-**2**·Cl_2, 95189-80-3; Δ-$(-)_{589}$-**2**·Cl_2, 95271-94-6; **3**-Cl_2, 66574-20-7; **4**·Cl_2, 95070-01-2; Λ-$(+)_{589}$-[Co(en)$_2$((*S*)-serSO_3)]Cl, 95098-10-5; Δ-$(-)_{589}$-[Co(en)$_2$((*S*)-serSO_3)]Cl, 95189-81-4; Λ-$(+)_{589}$-[Co(en)$_2$((*S*)-serCOCH$_3$)]$(CF_3SO_3)_2$, 95070-03-4; *p*-[Co(tren)((*S*)-ser)]S_2O_6, 84847-59-6; *t*-[Co(tren)((*S*)-ser)]S_2O_6, 95098-11-6; *t*-[Co(tren)((*S*)-ser)]$ZnCl_4$, 95098-12-7; *t*-[Co(tren)(NH=C(CH$_3$)-CO_2)]Cl_2, 95189-82-5; *p*-[Co(tren)(NH=C(CH$_3$)CO_2)]S_2O_6, 95070-05-6; *t*-[Co(tren)(NH=C(CH$_3$)CO_2)]S_2O_6, 95189-23-4; bis(ethylenediamine)(2-imino-3-(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) chloride, 95070-06-7; bis(ethylenediamine)(2-imino-3,3-bis(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) chloride, 95098-13-8; bis(ethylenediamine)(2-imino-4-(3-hydroxyphenyl)-3-butenoato)cobalt(III) chloride, 95070-07-8; bis(ethylenediamine)(2-imino-3-(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) chloride (N deuterated), 95098-15-0; bis(ethylenediamine)(2-imino-3,3-bis(hydroxymethyl)-4-hydroxybutanoato)cobalt(III) chloride (N deuterated), 95098-14-9; *m*-hydroxybenzaldehyde, 100-83-4.

(27) k_{cat} for the enzymic reaction is approximately 40 s^{-1} at 37 °C–Tudball, N.; et al. *Biochem. J.* **1967**, *105*, 467–472; **1969**, *114*, 299–305. Thus, the Co(III) complexes would only give a comparable rate of reaction in ca. 1 M OH^-. This is clearly a rate which an intramolecular enzymic base could readily achieve.

(28) K_a values for such acids are not available, though data for other coordinated acids on Co(III) show that acidity enhancement effects may be as large as 10^{10}. See: Harrowfield, J. MacB.; Norris, V.; Sargeson, A. M. *J. Am. Chem. Soc.* **1976**, *98*, 7282–7289. Note that differences between diastereoisomers would be expected to be small. See: Golding, B. T. *Inorg. Chim. Acta* **1981**, *56*, 95–98.

(29) Several syntheses are described in ref 10.

(30) Pasini, A.; Casella, L. *J. Inorg. Nucl. Chem.* **1971**, *36*, 2133–2144.

(31) Syntheses of benzylisoquinolines from phenylpyruvate imine chelates, for example, have been investigated. Morrison, D. S.; Harrowfield, J. MacB., unpublished work.