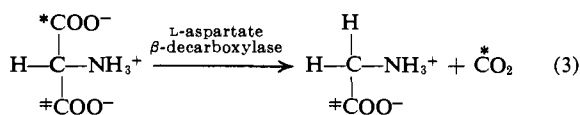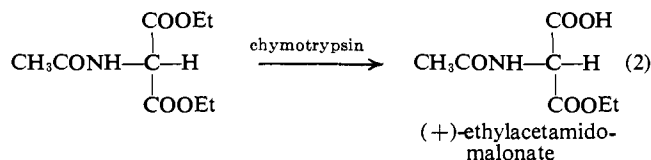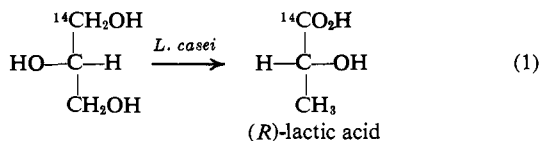# Chiral Recognition of Prochiral Centers. The (2S,9S)-2,9-Diamino-4,7-diazadecanecobalt(III) Mediated Decarboxylation of Aminoalkylmalonic Acids

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Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. Received April 30, 1973

Abstract: The reaction of $\Lambda(-)_{436}$-α-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III) dichloride]$^+$ with α,α-aminomethylmalonate to yield $\Lambda(-)_{436}$-β_2-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III) (R)-aminomethylmalonate]$^+$ **(3)** (which was shown to contain the N–O bound malonate moiety exclusively in the R configuration) represents the first instance of absolute chiral recognition of a prochiral center (Caabd) by a small molecule (a characteristic common to enzymic reactions). The complexes $\Lambda(-)_{436}$-α-[N$_4$Co(III)UV]$^{n+}$ and $\Lambda(-)_{436}$-β_2-[N$_4$Co(III)XY]$^{n+}$ where N$_4$ = (2S,9S)-2,9-diamino-4,7-diazadecane with UV = (NO$_2$)$_2$ **(6)** and Cl$_2$ **(7)** and XY = glycinate **(9)**, (S)-alaninate **(5$_S$)**, (R)-alaninate **(5$_R$)**, (S)-valinate **(12$_S$)**, (R)-valinate **(12$_R$)**, and α,α-aminoisopropylmalonate **(11)** and where N$_4$ = (3S,10S)-3,10-diamino-5,8-diaza-2,11-dimethyldodecane with UV = (NO$_2$)$_2$ **(13)** and Cl$_2$ **(14)** and XY = (S)-alaninate **(16$_S$)**, (R)-alaninate **(16$_R$)**, and α,α-aminomethylmalonate **(15)** were prepared and characterized by elemental analysis, ir, nmr, ORD, and CD. Considerable asymmetric induction by the dissymmetric cobalt center was observed upon decarboxylation of **3** in acidic solution to yield the (S)-alanine complex **(5$_S$)** in 30% excess over the (R)-alanine complex **(5$_R$)**. Decarboxylation of **11** and **15** showed similar degrees of asymmetric induction. To establish ORD–structure relationships (+)$_{578}$-trans-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III) dichloride]$^+$ and $\Delta(+)_{436}$-β-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III) XY]$^+$ where XY represents (NO$_2$)$_2$ and (ONO)-(NO$_2$) were also prepared and characterized.

Chiral recognition of prochiral molecules of the general structure Caabc is a most important biochemical phenomena, one that has elicited much interest and debate. The aconitase mediated conversion of citric acid to α-ketoglutaric acid[2] and the stereospecific transfer of a hydride ion (or equivalent) from 1,4-dihydronicotinamides serve as the two most noteworthy examples.[3] This feature is now recognized as being common to enzymic reactions.[4] Examples are provided in eq 1,[5] 2,[6] and 3.[7] The reaction of eq 2 is

$$\overset{^{14}CH_2OH}{\underset{CH_2OH}{HO-\overset{|}{\underset{|}{C}}-H}} \xrightarrow{\text{L. casei}} \overset{^{14}CO_2H}{\underset{CH_3}{H-\overset{|}{\underset{|}{C}}-OH}} \quad (1)$$

(R)-lactic acid

$$\overset{COOEt}{\underset{COOEt}{CH_3CONH-\overset{|}{\underset{|}{C}}-H}} \xrightarrow{\text{chymotrypsin}} \overset{COOH}{\underset{COOEt}{CH_3CONH-\overset{|}{\underset{|}{C}}-H}} \quad (2)$$

(+)-ethylacetamido-malonate

$$\overset{^*COO^-}{\underset{^\ddagger COO^-}{H-\overset{|}{\underset{|}{C}}-NH_3^+}} \xrightarrow[\beta\text{-decarboxylase}]{\text{L-aspartate}} \overset{H}{\underset{^\ddagger COO^-}{H-\overset{|}{\underset{|}{C}}-NH_3^+}} + {}^*CO_2 \quad (3)$$

one of many and is of particular interest since it represents the chiral handling of a molecule that is not a natural substrate for chymotrypsin.

Hirschman[8] pointed out that molecules of structure Caa'bc possess a degree of dissymmetry if viewed along the bonds connecting a to C (I and II) and coined the term meso carbon. Like meso compounds, the meso
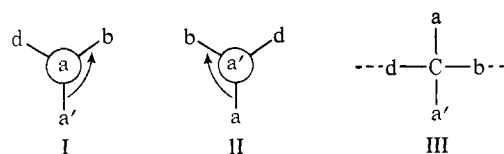
carbon has a plane of symmetry (III). In theory, if an asymmetric reagent, such as an enzyme composed of all (S)-amino acids, reacts at either a or C kinetic or kinetic and thermodynamic recognition is possible.[9] The term meso carbon has given way to prochiral[10] which includes compounds of type Caa'bc and bcC=a.

Nonenzymatic reactions establishing chiral recognition of prochiral centers are few. In the reaction of (S)-menthol with β-phenylglutaric anhydride[11] a total yield of 95.9% monoester (IV and V) was obtained which upon fractionation yielded two diastereomeric monoesters in 54 and 46% of recovered product. Aminolysis of the diastereomeric monoesters with lithium pyrrolidide provided two enantiomeric monoamides.

(1) Postdoctoral Fellow, University of California.

(2) P. E. Wilcox, *Nature (London)*, **164**, 757 (1949); P. E. Wilcox, C. Heidelberger, and U. K. Potter, *J. Amer. Chem. Soc.*, **72**, 5019 (1950); C. Martius and G. Schorre, *Justus Liebigs Ann. Chem.*, **570**, 140, 143 (1950).

(3) H. R. Levy, P. Talalay, and B. Vennesland, *Progr. Stereochem.*, **3**, 299 (1962).

(4) C. H. Werkman and H. G. Wood, *Advan. Enzymol.*, **2**, 135 (1942); H. A. Krebs, *ibid.*, **3**, 191 (1943); E. A. Evans, Jr., and L. Slotin, *J. Biol. Chem.*, **141**, 439 (1941); S. Weinhouse, G. Medes, N. F. Floyd, and L. Noda, *ibid.*, **161**, 745 (1945); J. M. Buchanan, W. Sakami, S. Guriu, and D. W. Wilson, *ibid.*, **159**, 695 (1945).

(5) R. W. Swick and A. N. Kao, *J. Biol. Chem.*, **206**, 883 (1954).

(6) S. G. Cohen and L. Altschul, *Nature (London)*, **183**, 1678 (1959). See also S. G. Cohen and L. H. Klee, *J. Amer. Chem. Soc.*, **82**, 6038 (1960); S. G. Cohen and E. Khedouri, *ibid.*, **83**, 1093 (1961); S. G.

Cohen, Y. Sprinzak, and E. Khedouri, *ibid.*, **83**, 4225 (1961); S. G. Cohen and E. Khedouri, *ibid.*, **83**, 4228 (1961).

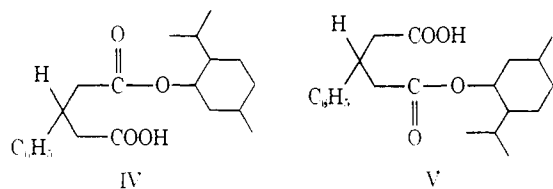(7) A. G. Palekar, S. S. Tate, and A. Meister, *Biochemistry*, **10**, 2180 (1971).

(8) H. Hirschman, *J. Biol. Chem.*, **235**, 2762 (1960).

(9) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter IV.

(10) As employed by Eliel and Mislow; see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 6.

(11) R. Altschul, P. Bernstein, and S. G. Cohen, *J. Amer. Chem. Soc.*, **78**, 5091 (1956); see also P. J. Scheuer and S. G. Cohen, *ibid.*, **80**, 4933 (1958).

IV   V

The abundance of one ester over the other was not great; nevertheless this difference was greater than the 4.5% of product not recovered. However, esterification is an equilibrium process and the preferred formation of one ester over the other may have been due to thermodynamic dissimilarity of the products. A clearer example is found in the reaction of the same anhydride with (R)-(−)-α-methylbenzylamine[12] for which case a 95% total yield of half-amides was obtained composed of a 60:40 ratio of diastereomeric amides. For this example, the ratio of amides based on a 100% yield falls between 1:1.32 and 1:1.63.

Since dissymmetric amine complexes of Co[III] exhibit slow rates of ligand exchange, it is possible to employ complexes of the general structure $[N_4CoCaa'bd]^{n+}$ to investigate the influence of the dissymmetric nature of the N_4Co^{III} moiety upon the chiral behavior of the prochiral Caa'bd moiety. Dissymmetric transformation of a molecule Caa'bd proceeding through a chiral complex of Co[III] can be due to: (1) the dissimilar standard free energy of formation of diastereomeric complexes involving a and a' as ligating atoms (eq 4);

$$\text{(4)}$$
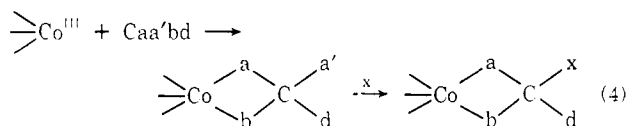
or (2) asymmetric induction by the dissymmetric Co[III] moiety controlling the chirality of the product arising from an intermediate (eq 5 and 6). An example for


$$\text{(5)}$$

$$\text{(6)}$$
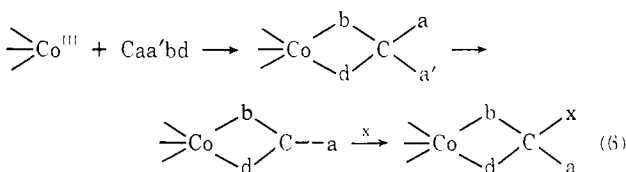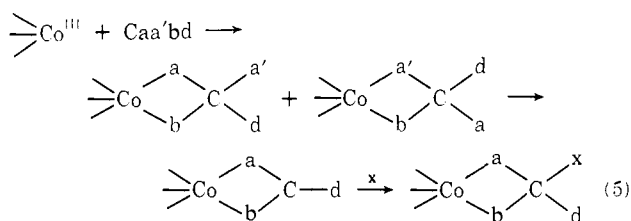
eq 6 has been explored in the asymmetric condensation of (−)-glycinatobis(ethylenediamine)cobalt(III) iodide with acetaldehyde which was found to yield, after hydrolysis and precipitation of cobalt sulfide, in part optically active threonine. In this instance one of the two protons at the prochiral carbon is replaced in a condensation reaction under the influence of the dissymmetric environment of the complex.[13] As an ex-

(12) P. S. Schwartz and H. E. Carter, Proc. Nat. Acad. Sci. U. S., 40, 499 (1954).

(13) M. Murokami and K. Takahashi, Bull. Chem. Soc. Jap., 32, 308 (1959). [For probable intermediate, see J. P. Aune, P. Maldonado, G. Larcheres, and M. Pierrot, Chem. Commun., 135 (1970).]

ample of eq 4 or 5, Asperger and Liu[14] have reported what they believed to be the stereospecific decarboxylation of α,α-aminomethylmalonic acid coordinated to an asymmetric cobalt tetramine center (1). In essence these workers isolated some complex to which they attributed structure 1, which on decarboxylation at pH 7 underwent a transient color change which they attributed to the intermediate formation of 2a. Following decarboxylation at pH 7 the product was allowed to crystallize at pH 1.0 over a period of 7 days. Decarboxylation would not occur at pH 7.0 but could have occurred during the "crystallization" step. The product of decarboxylation was said to be the (S)-alanine complex 4a, a belief predicated upon the product ORD,

1

2a   4a

$$\text{(7)}$$
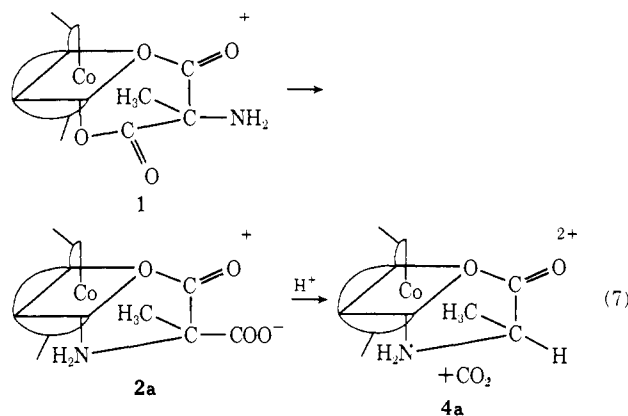
which resembled that for a complex prepared from (S)-alanine. However, their (S)-alanine complex was itself impure.[15]

The concept of employing the tetramine (2S,9S)-2,9-diamino-4,7-diazadecane to restrict the number of possible isomers, for any particular amino acid, from ten to three[16] and the choice of aminomalonic acid decarboxylation as a model system, must be considered ingenious. However, experimental inconsistencies in the work of Asperger and Liu lead us to doubt their conclusion. A few examples suffice: in our hands their synthesis for the pure (S)-alanine complex gave a mixture of isomers, the most prevalent of which was a Λβ complex (5), not 4a as claimed. The nmr spectrum they presented for the pure alanine complex[15] indicates the presence of some impurity in concentration up to 20%. Alanine they recovered from decomposed complex (prepared from pure (S)-alanine) was shown to have only 28% excess of the S antipode. In our hands unracemized (S)-alanine was recovered upon decomposition with Na_2S of a tetramine cobalt (S)-alanine complex.

Even if the experimental work had been reliable, the use of an O–O bound malonate complex (1) as starting point must be considered an unfortunate choice. The intermediate in the decarboxylation reaction could have been a mixture of isomers (2a–c, 3), each of which could exist with malonate in R or S configuration and each of which could decarboxylate to two different products (eq 7 and 8). The structure of 3 has been

(14) R. G. Asperger and C. F. Liu, Inorg. Chem., 6, 796 (1967).

(15) R. G. Asperger and C. F. Liu, J. Amer. Chem. Soc., 89, 708 (1967).

(16) Molecular models indicate that steric hindrance due to the methyl groups of the tetramine will decrease or eliminate certain configurations about the secondary N atoms (see D. A. Buckingham, et al., J. Chem. Soc., Chem. Commun., 57 (1972)).

2b

4b

1 →

2c

+ CO₂ (8)

3   5
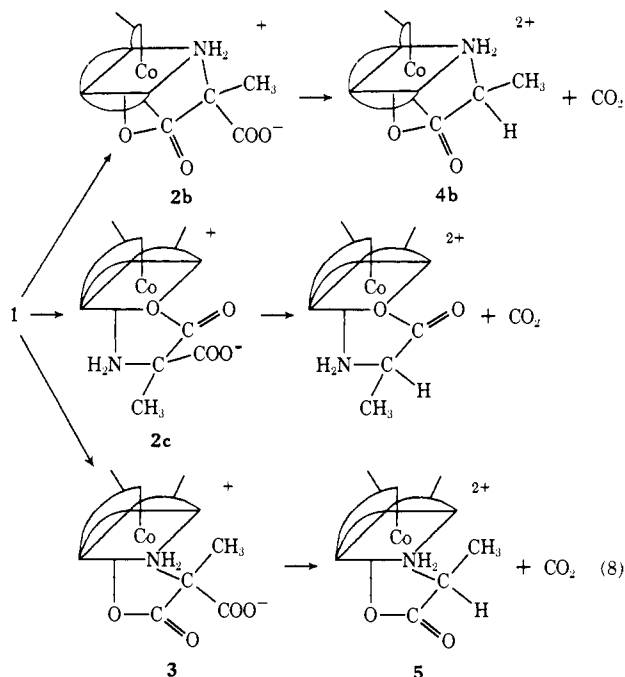
determined by X-ray crystallography in the laboratory of Dr. Jenny Glusker at the Institute for Cancer Research, Philadelphia, Pa., and will be reported in detail in a future publication.

We believe greater insight into chiral induction at the malonate α carbon should arise from study of the properties of the pure N–O bound complexes (2a–c, 3). This would greatly simplify product analysis since the decarboxylation product would be limited to a mixture of two complexes instead of a possible eight. We chose to investigate the synthesis of and study the most readily synthesized N–O bound tetraminecobaltmalonate complex (3) in hopes that this would give us the opportunity to observe what changes affect the stereoselectivity of the decarboxylation. Accordingly, this paper reports the stereospecific synthesis of $\Lambda(-)_{436}$-β_2-[(2S,9S)-2,9-diamino-4,7-diazadecane](α,α-aminomethylmalonate)cobalt(III) perchlorate (3) and its stereoselective decarboxylation.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian T-60 nmr spectrometer with sodium 2,2-dimethyl-2-silapentane-5 sulfonate as internal reference. Optical rotations were obtained on a Perkin-Elmer Model 141 polarimeter. Visible spectra were taken on a Cary Model 15 spectrophotometer. Infrared spectra were obtained on a Perkin Elmer Model 137 sodium chloride spectrophotometer. Optical rotatory dispersion and circular dichroism curves were obtained on a Perkin-Elmer Model 60. Mathematical manipulations were carried out on a Hewlett-Packard 9820 desk calculator with plotter attachment.

(R)-Alanine, (R)-valine, and (S)-valine were purchased from Nutritional Biochemicals, Cleveland, Ohio; (S)-alanine was purchased from Aldrich Chemical Co., Milwaukee, Wis. Diethylformamidomalonate was purchased from Sigma Chemical Co., St. Louis, Mo. AG-50WX2 cation exchange resin was purchased from Bio-Rad Laboratories, Richmond, Calif.

α,α-Aminomethylmalonic acid and α,α-aminoisopropylmalonic acid were prepared from diethylformamidomalonate by the method of Thanassi and Fruton.[17]

The following represents an improved synthesis of (2S,9S)-2,9-diamino-4,7-diazadecane[18] (dimethyltrien). (S)-Alanine (180 g, 2.02 mol) was treated with phthallic anhydride (300 g, 2.03 mol) in

(17) J. Thanassi and J. S. Fruton, *Biochemistry*, 1, 975 (1962).
(18) R. G. Asperger and C. F. Liu, *Inorg. Chem.*, 4, 1395 (1965).

600 ml of refluxing toluene. Water (43 ml) was collected in a Dean-Stark water trap. Thionyl chloride (256 g, 2.15 mol) was added to the warm toluene solution and reflux continued. After 1 hr the solvent and excess thionyl chloride were removed under aspirator vacuum. The crude (S)-N-phthaloylalanyl chloride was added all at once to 1 l. of an aqueous solution of ethylenediamine (51 g, 0.85 mol) and sodium bicarbonate (350 g) in an ice bath. This solution was allowed to warm to room temperature with ice cooling as necessary to control the initially vigorous reaction. The reaction mixture was allowed to stir overnight, then the excess sodium bicarbonate was neutralized with 6 M HCl. The solid material which precipitated was recrystallized from methanol to yield 340 g of N,N'-bis[(S)-phthaloylalanyl]ethylenediamine. The entire 340 g was treated with hydrazine (51 g, 1.6 mol) in refluxing ethanol. After 4 hr reflux, the mixture was placed in a refrigerator overnight to precipitate phthalhydrazide. The mixture was filtered and the residue washed several times with ethanol. The ethanol extracts were combined and the solvent was removed on a rotary evaporator to yield a solid. This crude N,N'-bis[(S)-alanyl]ethylenediamine was slurried in 1.0 l. of tetrahydrofuran then excess lithium aluminum hydride (73 g) in 500 ml of tetrahydrofuran was added at once. The mixture was refluxed gently on a steam bath overnight. After treating the mixture with 73 ml of water, 73 ml of 15% NaOH, and 220 ml of water, isolation and purification were carried out as per Asperger and Liu.[18] The yield of product was 85 g (24.8% overall), $[\alpha]^{26}$D $-3.84°$ (lit. $[\alpha]$D $-2.23°$).

(3S,10S)-3,10-Diamino-5,8-diaza-2,11-dimethyldodecane (diisopropyltrien) was prepared from (S)-valine by the same procedure as above except that the lithium aluminum hydride reduction was carried out for 8 hr in refluxing diglyme. After decomposition of the lithium aluminum hydride, the filtrate and ethanol washings were treated with HCl gas to precipitate white crystals. These were recrystallized from boiling methanol with some sodium chloride coprecipitate, $[\alpha]^{26}$D (1 M HCl) $+13.5°$ (corrected for NaCl content).

Anal. Calcd for C₁₂H₃₄N₄Cl₄: C:H:N = 4.19:1.00:1.66. Found: 4.17:1.00:1.62.

$\Lambda(-)_{436}$-α-Dinitro-2,9-diamino-4,7-diazadecanecobalt(III) Chloride Hydrate (6). Dimethyltrien tetrahydrochloride (5.0 g, 15.6 mmol) and LiOH·H₂O (1.96 g, 46.8 mmol) were dissolved in 20 ml of water. A solution of CoCl₂·6H₂O (3.71 g, 16.6 mmol) was prepared in 5 ml of water. Both solutions were cooled in an ice bath then mixed and quickly added to sodium nitrite (2.26 g, 32.7 mmol) in an ice bath. The solution was stirred rapidly while a vigorous stream of air was passed over it. After 1.5 hr aeration, the mixture was filtered and the yellow crystals were washed with a small amount of cold 1 M HCl, ethanol, and acetone and then air dried. A second crop was obtained by concentrating the filtrate, adding sodium chloride, and cooling. Total yield was 4.2 g (71%). The compound was recrystallized slowly from hot water and excess sodium chloride to give large yellow-brown crystals with $[\alpha]^{26}$D $-58°$, $[\alpha]_{436}{}^{26}$ $-2190°$.

Anal. Calcd for C₈H₂₄N₆O₅CoCl: C, 26.6; H, 6.15; N, 23.3; Co, 16.3. Found: C, 26.8; H, 6.28; N, 23.4; Co, 16.2.

$\Lambda(-)_{436}$-α-Dinitro-3,10-diamino-5,8-diaza-2,11-dimethyldodecanecobalt(III) perchlorate (13) was prepared from diisopropyltrien by the above procedure, except that after aeration sodium perchlorate was added; then the solution was stirred at 45° for 2 hr to precipitate straw yellow crystals (3.5 g, 54%), $[\alpha]_{436}{}^{26}$ $-1140°$.

Anal. Calcd for C₁₀H₂₈N₆O₅CoCl: C, 30.0; H, 6.29; N, 17.5. Found: C, 30.1; H, 6.35; N, 17.3.

$\Lambda(-)_{436}$-α-Dichloro-2,9-diamino-4,7-diazadecanecobalt(III) Chloride Hydrate (7). 6 (7.2 g, 19 mmol) was slurried with 5 ml of water in a small crystallizing dish and 10 ml of concentrated hydrochloric acid was added. The solution was placed on a steam bath and slowly evaporated. A second 10 ml of hydrochloric acid was added and the solution again taken to dryness. The purple product was placed in a soxhlet apparatus and extracted with 150 ml of methanol, containing 1 ml of 12 M HCl (to prevent solvolysis and to provide water of crystallization), until no more purple product dissolved. The solution was refrigerated overnight to yield clusters of large violet needles [yield 6.3 g, 92.6%], $[\alpha]^{26}$D 2385°, $[\alpha]^{26}_{436}$ $-860°$.

Anal. Calcd for C₈H₂₄N₄OCoCl₃: C, 27.6; H, 6.65; N, 16.07; Co, 16.9. Found: C, 27.7; H, 6.53; N, 16.03; Co, 16.7.

$\Lambda(-)_{436}$-α-Dichloro-3,10-diamino-5,8-diaza-2,11-dimethyldodecanecobalt(III) perchlorate (14) was prepared from 13 by the above procedure, $[\alpha]^{26}$D (1 M HCl) 1600°, $[\alpha]^{26}_{436}$ (1 M HCl) $-681°$.

Anal. Calcd for C₁₂H₃₀N₄CoO₄Cl₃: C, 31.43; H, 6.60; N, 12.23; Co, 12.9. Found: C, 31.56; H, 6.86; N, 12.30; Co, 13.1.

Δ(+)₄₃₆-β-Nitritonitro-2,9-diamino-4,7-diazadecanecobalt(III) Perchlorate (8a) and Δ(+)₄₃₆-β-Dinitro-2,9-diamino-4,7-diazadecanecobalt(III) Perchlorate (8b). (a) 7 (4.0 g, 11.2 mmol) and lithium carbonate (1.0 g, 13.5 mmol) were added to 20 ml of water and heated on a steam bath for 2.5 hr; then the red solution was filtered hot. Sodium perchlorate (5.5 g) was added; the solution was diluted to 200 ml with ethanol and then placed in a refrigerator. After overnight cooling, the precipitated sodium chloride was filtered off. To the red solution was then added 2.2 ml of concentrated perchloric acid and after standing 0.5 hr at room temperature a solution of 1.9 g of sodium nitrite in a small amount of water was added. After standing overnight, the straw yellow crystals were collected from the orange solution by filtration, washed three times with cold water, ethanol, then diethyl ether, and air dried. The yield of nitritonitro complex was 1.8 g, $[\alpha]^{26}_{436}$ +359°. The combined filtrate and washings were placed in a refrigerator for 2 weeks to precipitate 1.6 g of dinitro complex, $[\alpha]^{26}_{436}$ +1560°. Total yield 3.4 g, 68.7%.

Anal. Calcd for C₈H₂₂N₆O₈CoCl: C, 22.6; H, 5.22; N, 19.8; Co, 13.9. Found: C, 22.7; H, 5.24; N, 19.6; Co, 13.6.

(b) 7 (0.358 g, 1.0 mmol) and sodium chloroacetate (0.34 g, 3 mmol) were refluxed for 4 hr in ethanol. After cooling to room temperature the burgundy solution was decanted from precipitated sodium chloride and then treated with sodium nitrite (0.207 g, 3 mmol). After stirring for 1 day the yellow crystals were collected from the yellow solution by filtration, washed with ethanol and then ether, and air dried. The yield of nitritonitro complex was 0.275 g (65%). Upon heating at 45° over a period of days, an aqueous solution of nitritonitro complex slowly isomerized to the dinitro complex.

(c) 10 was treated with sodium perchlorate and excess sodium nitrite dissolved in a small amount of water. Upon slight heating the dissolution of green 10 was accompanied by immediate precipitation of yellow needles. The ORD spectrum of this material was identical with that of the β-nitritonitro complex (8a).

(+)₅₇₈-*trans*-Dichloro-2,9-diamino-4,7-diazadecanecobalt(III) Perchlorate (10). (a) 8a was treated with concentrated hydrochloric acid and then evaporated on a steam bath to yield green crystalline 10. The product was recrystallized as long, dark needles from methanol by slow evaporation of a concentrated solution. The ORD curve in concentrated hydrochloric acid is nearly identical with that of *trans*-S,S-Co-trien Cl₂⁺.¹⁹ Nmr in 35% DCl-D₂O shows a doublet at δ 1.44 ppm, $[\alpha]^{26}_{578}$ (12 M HCl) 290°.

Anal. Calcd for C₈H₂₂N₄O₄CoCl₃: C, 23.81; H, 5.50; N, 13.89; Co, 14.60. Found: C, 23.62; H, 5.75; N, 13.72; Co, 14.45.

(b) 8b was treated with concentrated hydrochloric acid and then evaporated on a steam bath to yield a mixture of maroon crystals (Δ-β-dimethyltrien-CoCl₂⁺) and 10. The mixture was refluxed in methanol to obtain a green solution and, upon concentration and cooling, green needles of 10.

Λ(−)₄₃₆-β₂-[Dimethyltrien-Co(R)- or (S)-ala](ClO₄)₂·H₂O (5). (a) 7 (0.358 g, 1 mmol) and alanine (0.089 g, 1 mmol) were dissolved in 5 ml of hot water. The pH of this purple solution was adjusted to 7-8 with 5 M NaOH. The solution was then stirred overnight at 71°. The resulting red-orange solution was neutralized to pH 8 and heated for another 2 hr to ensure that the pH remained constant. After adding 1.0 g of sodium perchlorate, the volume was reduced to 3 ml, under moving air, then allowed to cool. After 45 min at 5°, the orange crystals were collected, washed with 95% ethanol and then diethyl ether, and air dried [yield 0.20 g, 37.2%]. For the (R)-alanine complex, $[\alpha]^{26}_D$ (1 M HCl) 120°, $[\alpha]^{26}_{436}$ (1 M HCl) −989°. For the (S)-alanine complex, $[\alpha]^{26}_D$ (1 M HCl) 50.2°, $[\alpha]^{26}_{436}$ (1 M HCl) −804°.

Anal. Calcd for C₁₁H₃₀N₅O₁₁CoCl₂ (5ₛ): C, 24.55; H, 5.62; N, 13.01; Co, 10.95. Found: C, 24.57; H, 5.59; N, 12.91; Co, 10.87.

(b) 8 (0.425 g, 1 mmol) was dissolved in 40 ml of boiling water and 0.7 ml of concentrated nitric acid was added. After simmering for 1 hr, the red-orange solution was cooled and 5 M NaOH added dropwise until the color turned to red. (S)-Alanine (0.089 g, 1 mmol) was added and the pH adjusted to 6.5-7.0. The solution turned orange while heating at low heat on a hot plate overnight. The volume was reduced to 10 ml while heating under moving air, then 1.5 g of sodium perchlorate was added. The solution was cooled at 5° for several hours to yield 0.2 g of orange crystals. The ORD curve and nmr spectrum were identical with those of 5ₛ.

Λ(−)₄₃₆-β₂-[Dimethyltrien-Co-gly]I₂·H₂O (9). This compound

(19) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *Inorg. Chem.*, 6, 1032 (1967).

was prepared from 6 and glycine in water by the procedure in (b) above. The iodide salt precipitated as orange hexagonal platelets $[\alpha]^{26}_D$ (1 M HCl) 73°, $[\alpha]^{26}_{436}$ (1 M HCl) −773°.

Anal. Calcd for C₁₀H₂₈N₅O₃CoI₂: C, 20.74; H, 4.87; N, 12.1, Co, 10.2. Found: C, 20.73; H, 4.81; N, 11.9; Co, 10.0.

Λ(−)₄₃₆-β₂-[Dimethyltrien-Co(R)-val](ClO₄)₂ (12ᵣ). 7 (0.358 g, 1.0 mmol), valine (0.117 g, 1.0 mmol), and 2 drops of 5 M sodium hydroxide were placed in 3 ml of water in a test tube. After stirring for 20 min the violet solution was placed in a 60° water bath. The pH was maintained between 6 and 7 with 5 M sodium hydroxide. After no further pH change was noted, 2 g of sodium perchlorate was added to the orange solution to get an immediate precipitate. After overnight cooling (5°) the product was collected by filtration, washed with 95% ethanol, ethanol, and ether and then air dried; yield, 0.345 g (62%); $[\alpha]^{26}_{436}$ −869°. The solubility in water with 0.1 g of NaClO₄/ml was found to be 5.84 × 10⁻⁴ M.

Anal. Calcd for C₁₃H₃₂N₅O₁₀CoCl₂: C, 28.48; H, 5.88; N, 12.78; Co, 10.75. Found: C, 28.45; H, 5.92; N, 12.75; Co, 10.93.

Λ(−)₄₃₆-β₂-[Dimethyltrien-Co(S)-val](ClO₄)₂ (12ₛ) was prepared from 7 and (S)-valine in the same manner, $[\alpha]^{26}_{436}$ −653°. The solubility in water with 0.1 g of NaClO₄/ml was found to be 1.29 × 10⁻³ M.

Anal. Calcd for C₁₃H₃₂N₅O₁₀CoCl₂: C, 28.5; H, 5.88. Found: C, 28.7; H, 5.90.

Λ(−)₄₃₆-β₂-[Diisopropyltrien-Co(R)-ala](ClO₄)₂·H₂O (16ᵣ). 14 (0.23 g, 0.5 mmol) and (R)-alanine (0.0445 g, 0.5 mmol) were stirred at 60° in 2 ml of water. The pH was maintained at 7.0 with a pH-stat using 5 M sodium hydroxide. After nearly 0.5 mmol of sodium hydroxide had been added (4 hr), 0.5 g of sodium perchlorate was added to the orange solution and the mixture cooled overnight to yield 0.200 g of orange crystals (67.5%). The crystals were recrystallized slowly from water with a small amount of sodium perchlorate to obtain long orange needles, $[\alpha]^{26}_{436}$ −1065°.

Anal. Calcd for C₁₅H₃₈N₅O₁₁CoCl₂: C, 30.3; H, 6.44; N, 11.8; Co, 9.92. Found: C, 29.9; H, 6.75; N, 11.6; Co, 9.79.

Λ(−)₄₃₆-β₂-[Diisopropyltrien-Co-(S)-ala](ClO₄)₂·H₂O (16ₛ) was prepared from 14 and (S)-alanine by the above procedure, $[\alpha]^{26}_{436}$ −924°.

Anal. Calcd for C₁₅H₃₈N₅O₁₁CoCl₂: C, 30.3; H, 6.44; N, 11.8; Co, 9.92. Found: C, 30.0; H, 6.68; N, 11.7; Co, 9.73.

Λ(−)₄₃₆-β₂-[Dimethyltrien-Co-(R)-aminomethylmalonate]-ClO₄·½H₂O (3ᵣ). (a) Dry potassium aminomethylmalonate, prepared by neutralizing α,α-aminomethylmalonic acid (0.133 g, 1.0 mmol) with KOH, and 7 (0.358 g, 1.0 mmol) were refluxed in 150 ml of anhydrous (over Mg) methanol. While refluxing, disappearance of the malonate salt was accompanied by precipitation of an orange solid. When precipitation was complete (20 hr), the solid was collected from the orange solution by filtration, washed with ethanol and ether, and then air dried. In order to allow for coprecipitated potassium perchlorate, the yield was determined spectrophotometrically to be 74.2%. The compound was recrystallized from water with an excess of sodium perchlorate to yield orange needles of perchlorate hemihydrate, $[\alpha]^{26}_D$ (1 M HCl) 75°, $[\alpha]^{26}_{436}$ (1 M HCl) −933°. The CD curve of the recrystallized complex was identical with that of the crude material.

Anal. Calcd for C₁₂H₂₈N₅O₈.₅CoCl: C, 30.48; H, 5.97; N, 14.82; Co, 12.46. Found: C, 30.68; H, 5.99; N, 14.74; Co, 12.58.

(b) The synthesis was performed in refluxing "reagent" methanol directly from the reagent bottle to give a 57.4% yield of pure 3ᵣ.

(c) The synthesis was performed in refluxing methanol (reagent) with 15% excess KOH to give a 40.7% yield of pure 3ᵣ.

(d) 7 (0.358 g, 1.0 mmol), α,α-aminomethylmalonic acid (0.133 g, 1.0 mmol) and triethylamine (0.66 g, 6.6 mmol) were refluxed in 150 ml of ethanol. During 2 hr reflux the solution turned from burgundy to orange as orange crystals precipitated; yield, 0.267 g (65%).

Decarboxylation of 3. A nearly saturated solution of 3 in 1 M HCl (~0.1 M) was prepared in an nmr tube. The tube was placed in a steam bath for 0.5 hr during which time gas evolution was evident. The nmr spectrum of the decarboxylated product closely resembled that of Λ(−)₄₃₆-β₂-[dimethyltrien-Co-(S)-ala]²⁺ (see Figure 8). The nmr spectrum exhibited no further change upon continued heating.

Chromatography. The filtrates from the preparation of 3 were taken to dryness and subjected to chromatography on a 25 cm × 1 cm column of AG50WX2 cation exchange resin in the sodium form. In each case, elution was begun with 500 ml of 0.5 M NaCl then

Scheme I
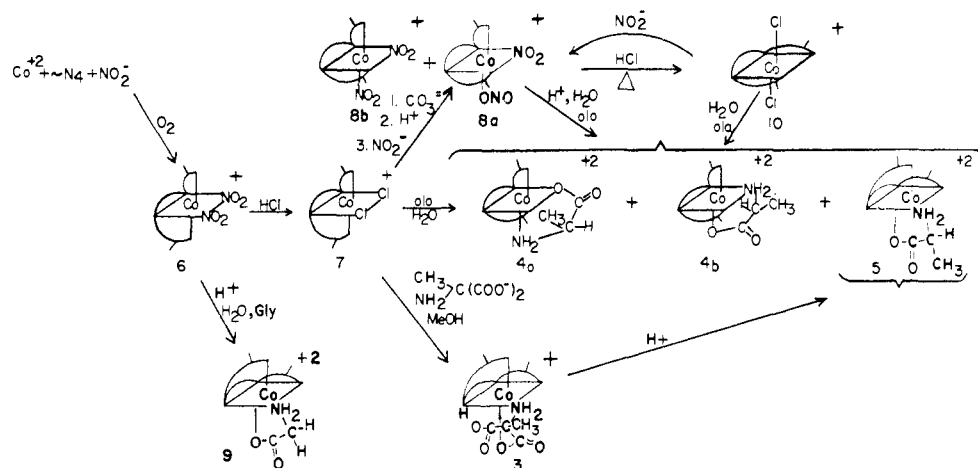
finished with 1.5 M NaCl. Products were identified by visible spectra, ORD, and CD. The first fraction off the column was the singly charged Δ-β-malonates (2). The second fraction was the singly charged Λ-β-malonate (3), if present. The third fraction, eluted with 1.5 M NaCl, was doubly charged alaninates (5) arising from decarboxylation of 3 (the ORD curve of this fraction was identical with Figure 8). A fourth, slow-moving fraction represents Δ-β-aquo species, i.e., Δ-β-[-dimethyltrien-Co(H_2O)(OH^-)]$^{2+}$.

Preparation and Decarboxylation of Λ($-$)$_{436}$-β-[2,9-Diamino-4,7-diazadecanecobaltaminoisopropylmalonate]$^+$ **(11).** 7 (0.179 g, 0.5 mmol), α,α-aminoisopropylmalonic acid (0.806 g, 0.5 mmol), and triethylamine (0.44 g, 4.4 mmol) were refluxed for 5 hr in methanol. No precipitate had formed from the orange solution. The solvent and excess triethylamine were removed on a rotary evaporator. The residue was dissolved in 3 ml of water and 0.3 g of sodium perchlorate and 0.3 ml of concentrated perchloric acid were added. The solution was warmed on a steam bath with vigorous effervescence as carbon dioxide was liberated. After 45 min heating, during which orange crystals had begun to form, the solution was cooled to room temperature. After standing overnight the crystals were collected by filtration, washed with methanol (to remove any Δ-β complex) until washings were colorless, and air dried; yield, 0.078 g of mixed Λ($-$)$_{436}$-β_2-[dimethyltrien-Co-(R) and (S)-val]$^{+2}$.

Preparation and Decarboxylation of Λ($-$)$_{436}$-β-[3,10-Diamino-5,8-diaza-2,11-dimethyldodecanecobaltaminomethylmalonate]$^+$ **(15).** 14 (0.23 g, 0.5 mmol), α,α-aminomethylmalonate (0.06659, 0.5 mmol), and triethylamine (0.4 g, 4 mmol) were refluxed in 50 ml of methanol for 1.5 hr. The solvent was then removed from the orange solution on the rotatory evaporator. The residue was dissolved in 2.5 ml of water and treated with sodium perchlorate (0.5 g) to obtain an immediate, pale orange precipitate. This was recrystallized from water to give orange platelets. The nmr spectrum exhibited the malonate methyl singlet at δ 1.77 ppm. The crystals (0.05 g) were dissolved in 1 M hydrochloric acid and heated on a steam bath 0.5 hr to ensure decarboxylation (the methyl singlet had become a doublet as expected).

Kinetics. Solutions of hydrochloric acid of concentrations between 7.38 and 0.1 M were prepared. Buffers were prepared as 1.0 M solutions from betaine hydrochloride, glycine, and sodium formate. Ionic strength was maintained in the pH range at 1.0 with KCl. The H_0 scale[20] was used for acid concentrations of 1.0 M and above while for the other solutions pH was determined by a glass electrode. Decarboxylation reactions were followed at 81.6° on a Perkin-Elmer Model 141 polarimeter with recorder attachment. Increasing rotation changes averaging 0.6°, for solutions of about 0.005 M substrate concentration, were observed at a wavelength of 546 nm.

Results

The interrelations of the dimethyltrien Co system are shown in Scheme I. Oxidation of a mixture of (2S,9S)-2,9-diamino-4,7-diazadecane, cobaltous ion, and nitrite
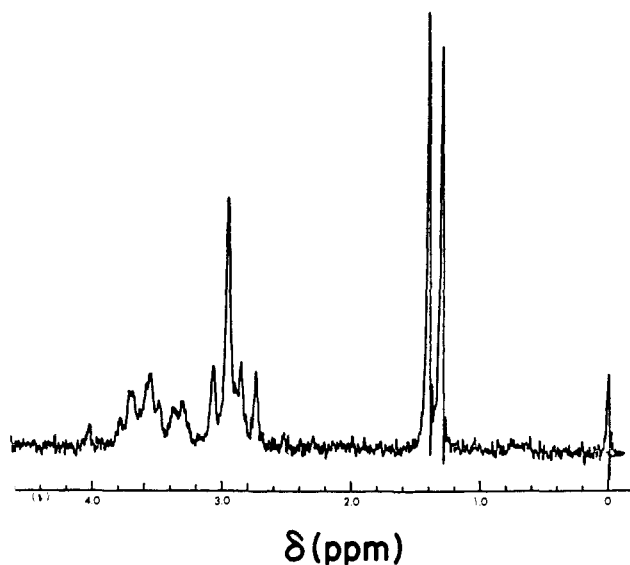
(20) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

δ (ppm)

Figure 1. Nuclear magnetic resonance spectrum of Λ($-$)$_{436}$-α-dinitro-2,9-diamino-4,7-diazadecanecobalt(III) chloride (6) in D_2O.

ion could conceivably lead to three isomers: cis-α (6), cis-β (8), and trans (10). However, Sargeson and Searle[21] have shown that for the quite similar triethylenetetramine ligand, the conditions employed here gave a high yield of only the cis-α isomer (6). The infrared spectrum of 6 exhibits a doublet at 820 cm^{-1} supporting its formulation as a dinitro complex.[22] A dinitrito complex would be expected to exhibit no resonance in this area while a nitritonitro complex would be expected to exhibit a singlet due to the nitro group. The nmr spectrum of 6 (Figure 1) exhibits a doublet at δ 1.37 ppm, as would be expected for the equivalent methyl groups on the dimethyltrien ligand, each being split by a single proton. The dichloro complex (7), obtained by treating 6 with hydrochloric acid, exhibits an nmr spectrum nearly identical with that obtained by Asperger and Liu for cis-α-dichlorodimethyltrienecobalt(III).[23] The ORD curve for 6 (Figure 2) exhibits a positive Cotton effect in the 450–550-nm region, thus

(21) A. M. Sargeson and G. H. Searle, *Inorg. Chem.*, **6**, 787 (1967).

(22) R. B. Penland, F. J. Lane, and J. V. Quagliano, *J. Amer. Chem. Soc.*, **78**, 887 (1956).

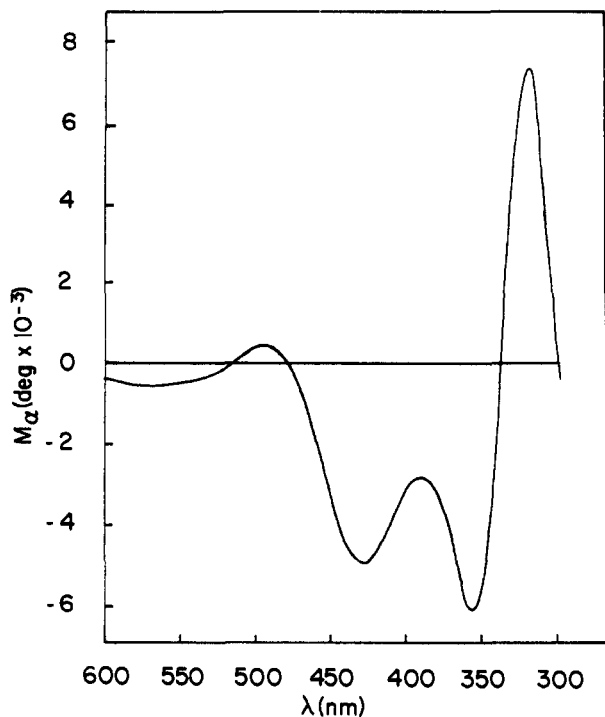(23) R. G. Asperger and C. F. Liu, *J. Amer. Chem. Soc.*, **89**, 708 (1967).

Figure 2. Rotatory dispersion curve of $\Lambda(-)_{436}$-α-dinitro-2,9-diamino-4,7-diazadecanecobalt(III) chloride (6) in D_2O.
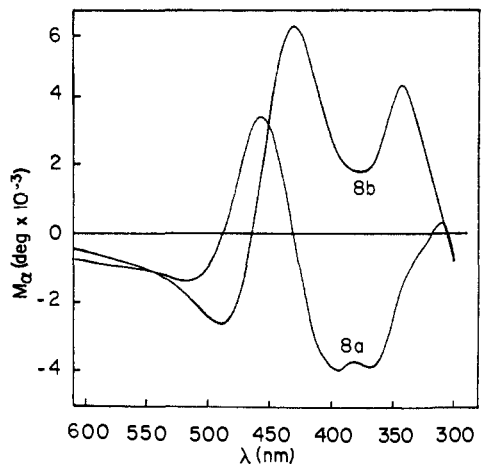

Figure 3. Rotatory dispersion curve of $\Delta(+)_{436}$-β-nitronitro-2,9-diamino-4,7-diazadecanecobalt(III) perchlorate (8a) and $\Delta(+)_{436}$-β-dinitro-2,9-diamino-4,7-diazadecanecobalt(III) perchlorate (8b) in H_2O.

allowing us to assign the Λ configuration to the complex.[24] Repeated crystallization of 6 from water does not alter the ORD curve indicating that it is a pure diastereomer and supporting the contention that dimethyltrien binds stereospecifically.[23]

Sargeson and Searle have shown that cis-α-triethylenetetraminecobalt(III) undergoes stereochemical inversion to the cis-β complex in basic solution.[21] Accordingly, 7 was treated with lithium carbonate, perchloric acid, then sodium nitrite in water and ethanol to give a Δ-cis-β-nitritonitro (8a) and a Δ-cis-β-dinitro complex (8b) whose ORD's exhibit a negative Cotton effect in the 450–550-nm region (Figure 3). (The intermediate Δ-β-carbonato complex was not isolated.) A singlet

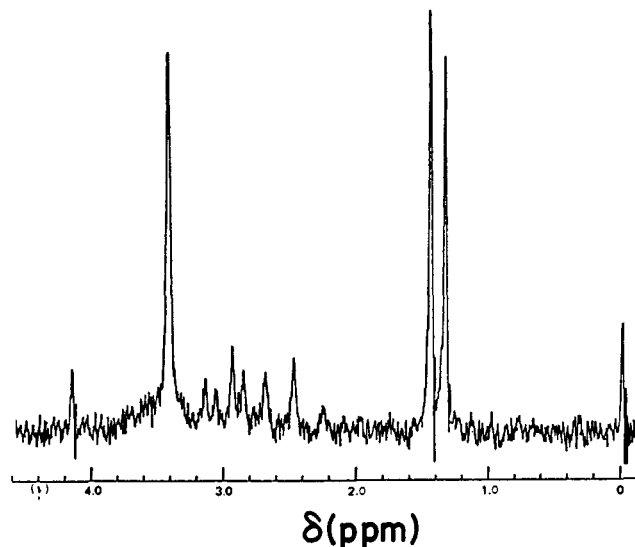(24) A. M. Sargeson and G. H. Searle, *Inorg. Chem.*, 4, 45 (1965).

Figure 4. Nuclear magnetic resonance spectrum of $\Delta(+)_{436}$-β-nitritonitro-2,9-diamino-4,7-diazadecanecobalt(III) perchlorate (8a) in D_2O.

at 830 cm^{-1} in the infrared spectrum of the former suggests formulation as the nitritonitro complex.[22] In warm water, this compound isomerizes to the dinitro complex (8b) as evidenced by the doublet at 825 cm^{-1} in the infrared spectrum. This is in accord with results obtained by Pearson, *et al.*, for cis-nitritonitrobis(ethylenediamine)cobalt(III) nitrate.[25] (8a also results when pure $trans$-[dimethyltrien-CoCl$_2$]$^+$ (10) is treated with nitrite ion.) The nmr spectrum of 8a (Figure 4) exhibits a doublet at δ 1.4, arising from the two methyl groups of the dimethyltetramine. Apparently, the asymmetry of the complex does not place these methyl groups in environments sufficiently different to perturb the spectrum.

When attempts were made to synthesize the aminomethylmalonate complex (3) from 7 in water, a mixture of isomers resulted from which only $\Delta(+)_{436}$-β-[dimethyltrien-Co-malonate]$^+$ (2a)[26] was readily isolable. ORD evidence suggests that, in aqueous solution, much Λ-α to Δ-β isomerization occurs, even before complexation. Accordingly, we performed the reaction in methanol using 7 and the dipotassium salt of aminomethylmalonate, to achieve a quite satisfactory yield (74.2%) of 3. The structure of 3 was confirmed by X-ray crystallography in Dr. Jenny Glusker's laboratory and will be reported separately.

The CD curve of 3 exhibits its principle Cotton effect at 500 nm as do the curves of 5_R and 5_S, supporting their formulation as N–O bound complexes. That the uncoordinated carboxylate group is nonprotonated is confirmed by the elemental analysis, which indicates the presence of only one perchlorate anion. Protonation of the free carboxylate group in 3 is quite evident from the pronounced change in the nmr spectrum upon going from H_2O or D_2O to 1 M HCl in H_2O. (The isolated methyl resonance shifts 0.13 ppm downfield while the

(25) R. G. Pearson, P. M. Henry, J. G. Bergman, and F. Basolo, *J. Amer. Chem. Soc.*, 76, 5920 (1954).

(26) Only one Δ-cis-β-[dimethyltrien-Co-malonate]$^+$ has been isolated in pure crystalline form. The nmr spectrum (resembling that of 3_R) exhibits the singlet at δ 1.90 and the pair of doublets centered at δ 1.60 ppm. The CD curve exhibits a strong negative Cotton effect at 500 nm representing the optical inversion that one would expect in going from Λ-cis-α to Δ-cis-β.
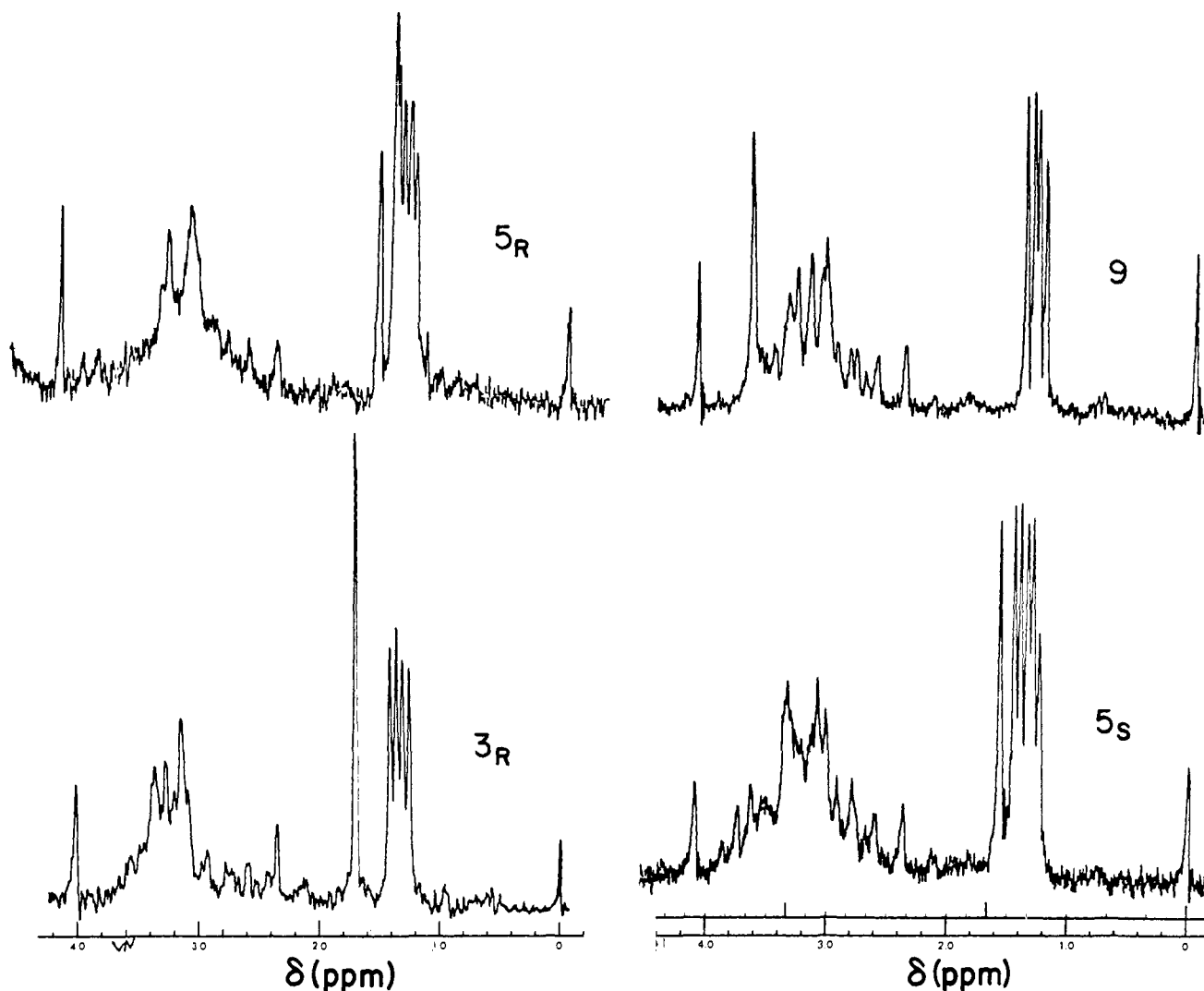
Figure 5. Nuclear magnetic resonance spectra of $\Lambda(-)_{436}$-β_x-[dimethyltrien-Co-aminoacidate]$^{n+}$ (3$_R$, 5$_S$, 5$_R$, and 9) in D_2O.

other pair of methyl doublets coalesces to one with broad peaks centered at δ 1.4 ppm.)

Comparison of the CD curves of the products from the reaction of (R)- and (S)-alanine with 7 with those of Δ- and Λ-β_2-trien-Co-(S)-ala^{+27} led to their formulation as $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-ala]($ClO_4)_2 \cdot H_2O$ complexes. This assignment was confirmed upon establishing the identity of the ir, CD, ORD, and nmr spectra of 5 with the decarboxylation product of 3. The synthesis of 5$_R$ and 5$_S$, by reaction of (R)- and (S)-alanine with 7 in water, yielded appreciable amounts of the $\Delta(+)_{436}$-β complexes (4a,b) also, as ions in solution which were identified by ORD.[27] The yield of 5 (37.2%) was not affected by order of addition of the reactants, by carrying out the reaction at lower pH or by adding the alanine after aquation of 7. The same yield was obtained when $\Delta(+)_{436}$-β-[dimethyltrien-Co(NO$_2)_2$]ClO_4 (8b) was used as a starting material.

When an amino acid is coordinated to either the Λ-β- or Δ-β-dimethyltrien-Co moiety (2, 3, 4, 5, 9, 12) the dimethyltrien methyl groups are no longer in equivalent environments; thus, we expect the nmr spectrum to exhibit a pair of doublets in the olefinic region instead of just one doublet as in 6. This is quite evident

(27) C. Lin and B. E. Douglas, *Inorg. Chim. Acta*, 4, 3 (1970).

in the nmr spectrum of the glycine complex (9) (Figure 5). The alanine adducts (5$_S$,5$_R$) would be expected to exhibit another doublet due to the α-methyl group. Thus, these two complexes should exhibit six peaks in the olefinic region (Figure 5). The α-methyl group in the malonate complex (3) should be a singlet so we would expect only five peaks in the olefinic region (Figure 5). The visible spectra of 5$_S$, 5$_R$ and 3 each exhibit peaks at 348 and 480 nm with extinction coefficients as shown in Table I.

Table I. Extinction Coefficients of 3, 5$_S$, and 5$_R$ in 1 M HCl

Complex	ϵ_{348}	ϵ_{480}
5$_S$	159.2	155.9
5$_R$	159.4	154.4
3$_R$	169.4	154.3

The CD curve of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-ala]$^{2+}$ (5$_S$) (Figure 6) exhibits four well-defined bands in the 600–300-nm region [498 nm (+), 437 (−), 368 (+), and 322 nm (−)]. The CD curve of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(R)-ala]$^{2+}$ (5$_R$) (Figure 6) reveals that the band at 437 nm has changed sign and is included
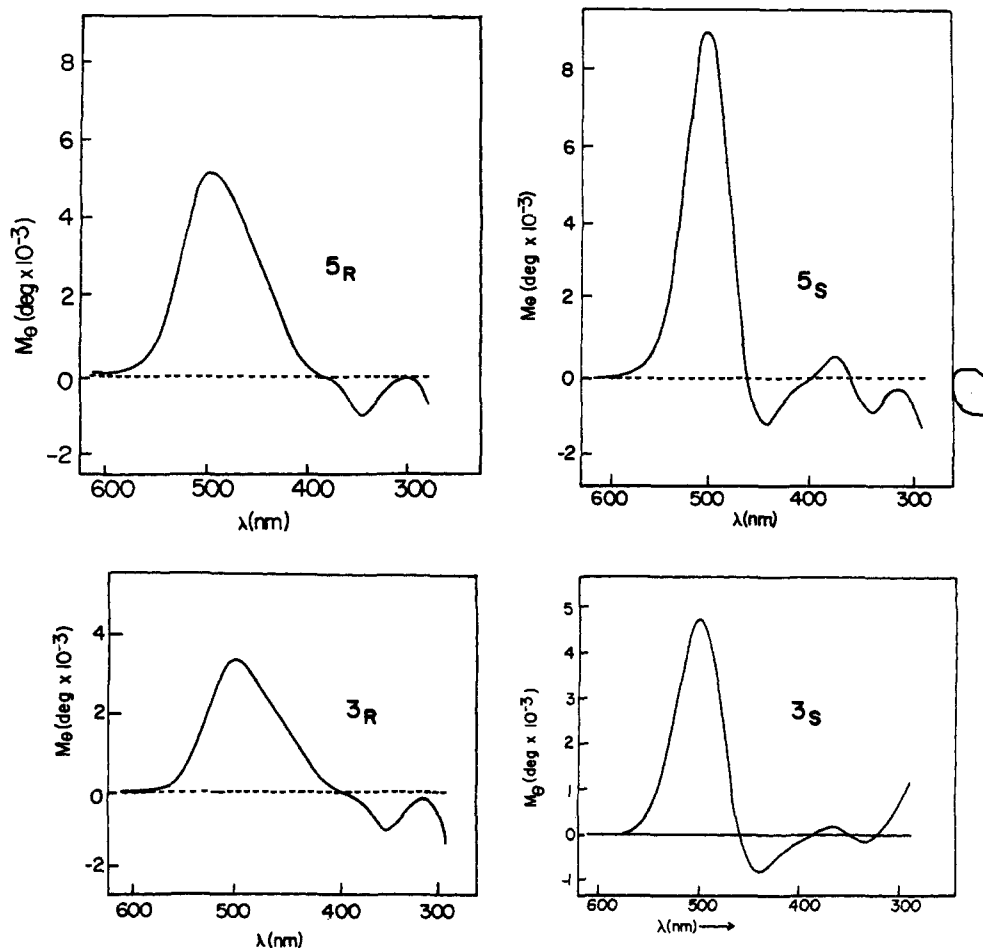
Figure 6. Circular dichroism curves of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-aminoacidate]$^{n+}$ (3_S, 3_R, 5_S, and 5_R) in 1 M HCl. 3_S was obtained only in presence of excess base.
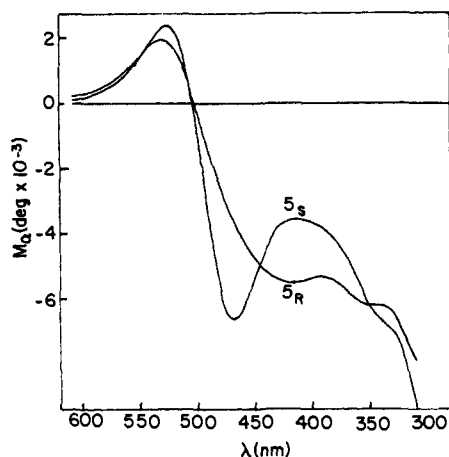

Figure 7. Rotatory dispersion curves of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)- and (R)-alaninate]$^{2+}$ (5_S and 5_R) in 1 M HCl.

under the envelope of the principal CD band at 498 nm; the band at 368 nm has either changed sign or disappeared completely. The CD curve of 3_R (Figure 6), except for the magnitude of the ellipticity, is identical with that of 5_R, clearly revealing that the malonate moiety possesses the R configuration (in the sense that if the free carboxyl group were replaced by a proton (R)-alanine would result). Examination of the nmr, CD (Figure 6), and ORD curves (Figure 7) reveals that

the composition of a mixture of 5_R and 5_S can be determined accurately and easily.

The results of the chromatography of the residues from the reaction to prepare **3** from **7** and aminomethylmalonate in methanol are shown in Table II. The

Table II. By-Products in Synthesis of 3

Product	Sol. reagent CH$_3$OH cont. stoich. KOH, %	Sol reagent CH$_3$OH cont. 15% over stoich. KOH, %	Sol. anhydrous CH$_3$OH cont. stoich. KOH, %
3_R	57	40	74.2
2a, b	3	54	
5	40	0	
cis-β-Dimethyltrien-Co(OH)(H$_2$O)$^{2+}$	0	4	
3_S[a]	0	2	

[a] Obtained only with excess base.

residue from the reaction in anhydrous methanol was a brown tar. Note that when a stoichiometric amount of KOH is used in wet methanol there is a significant amount of decarboxylation of **3** to **5**. However, when excess KOH is added to retard decarboxylation, more Δ-β products are formed (**2a,2b**), along with some of
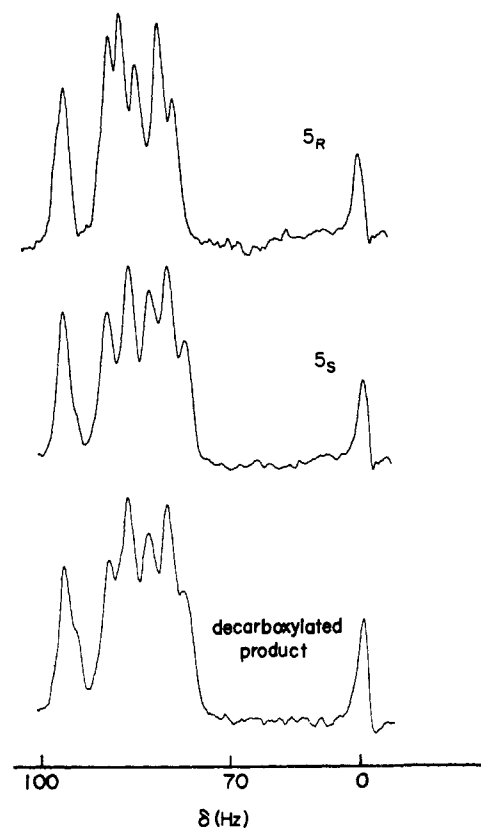
Figure 8. Comparison of the nuclear magnetic resonance spectra of 5_S and 5_R with decarboxylated 3_R in the olefinic region (1 M HCl).

Figure 9. Rotatory dispersion curve of decarboxylated 3_R in 1 M HCl.

Figure 10. Simulated ORD curves of 5_R and 5_S and mixtures of 5_R and 5_S.

the Λ-β complex containing malonate in the S configuration (3_S). Presence of excess base in wet methanol represents the only condition which allows for the isolation of 3_S. The $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-malonate]$^+$ (3_S) was identified by its CD curve (Figure 6) which, except for the magnitude of M_θ, resembles that of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-ala]$^{+2}$ (5_S) in the 600–300-nm region, by nmr (singlet at δ 1.70 ppm, doublet centered at δ 1.23 ppm), and by the fact that it moved on the cation exchange column as a singly charged ion.

When a nearly saturated solution of **3** in 1 M HCl is heated, rapid gas evolution is evident. The nmr spectrum of the product resembles that of $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-ala]$^{2+}$ and not $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(R)-ala]$^{2+}$ (Figure 8). Closer examination reveals that the spectrum is not that of pure $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-ala]$^{2+}$ since the resonances appear to be slightly shifted and a shoulder appears (at δ 1.56 ppm) on the isolated methyl resonance (at δ 1.59 ppm). Careful counting of squares under this peak leads to the estimation that the decarboxylation product is $^2/_3$-$\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(S)-ala]$^{2+}$ (5_S) and $^1/_3$-$\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-(R)-ala]$^{2+}$ (5_R). More quantitative evaluation of the composition comes from examination of the ORD curve of the decarboxylation product (Figure 9). A polynomial regression program[28] was used to fit the ORD curves of 5_S, 5_R and of the mixture from decarboxylation of 3_S between 525 and 410 nm. The calculator was then programmed to draw a family of curves by mixing those of 5_S and 5_R. It was found that a difference in concentration of 1%
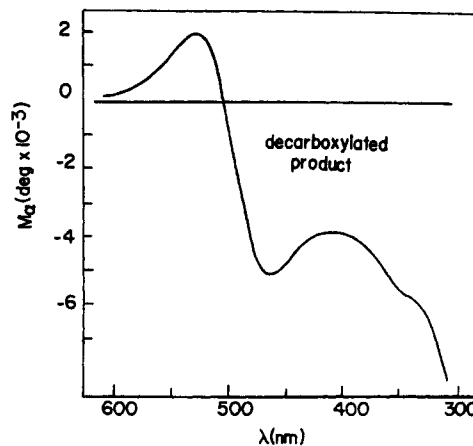
(28) Hewlett-Packard, Model 20 STAT PAC, I-9.

could easily be discerned. The derived curve of best fit corresponded to a mixture of 65% 5_S and 35% 5_R (representative calculator plots are shown in Figure 10). The efficacy of this method lies in its emphasis on matching curve shape and its tendency to minimize the importance of base-line fluctuations. $\Lambda(-)_{436}$-β-[Diisopropyltrien-Co-aminomethylmalonate]$^+$ (**15**) was prepared and decarboxylated in the same manner to yield 31.5% 16_R and 68.5% 16_S.

Since $\Lambda(-)_{436}$-β_2-[dimethyltrien-Co-aminoisopropylmalonate]$^+$ (**11**) would not crystallize readily, it was decarboxylated in the crude reaction mixture. The precipitated perchlorate salts were washed with methanol, to remove any Δ-β-dimethyltrien-Co-valinates, then ground to assure homogeneity. The mixture was analyzed by the above procedure, then corrected for the slight solubility of the components, and found to contain 64% 12_R and 36% 12_S, a result the reverse of the other two experiments. These results are summarized in Table III.

The kinetics of the decarboxylation of $\Lambda(-)_{436}$-β_2-[~N$_4$Co-(R)-aminomethylmalonate]$^+$ (3_R) were investigated polarimetrically (81.6°; μ = 1.0) at constant acidity over a 10^6 variation of hydrogen ion (pH 3.46 to $H_0 = -2.64$). The values of log ($\alpha_\infty - \alpha_t$) vs. $t_{1/2}$ are presented in Figure 11 employing (for display pur-
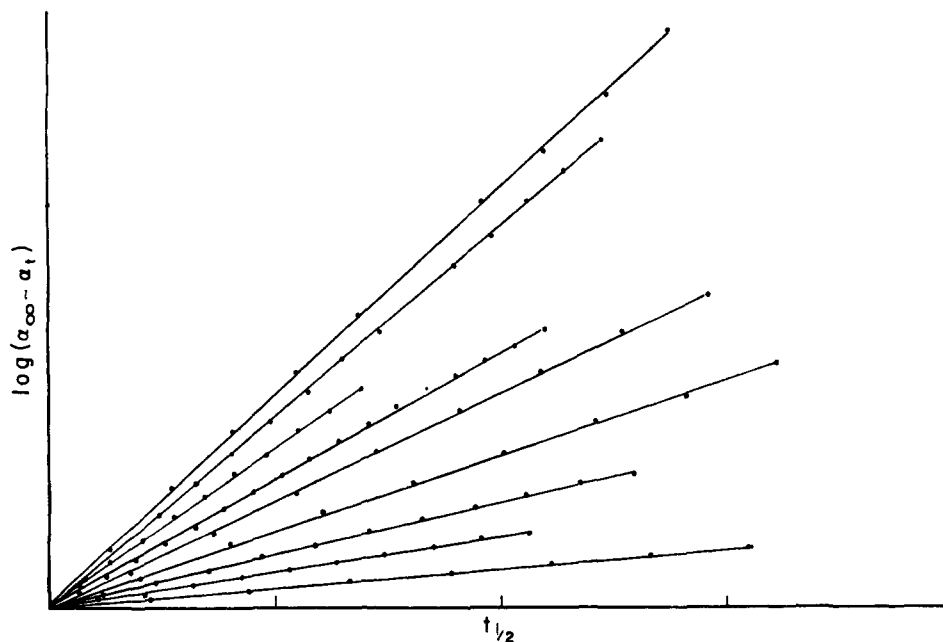
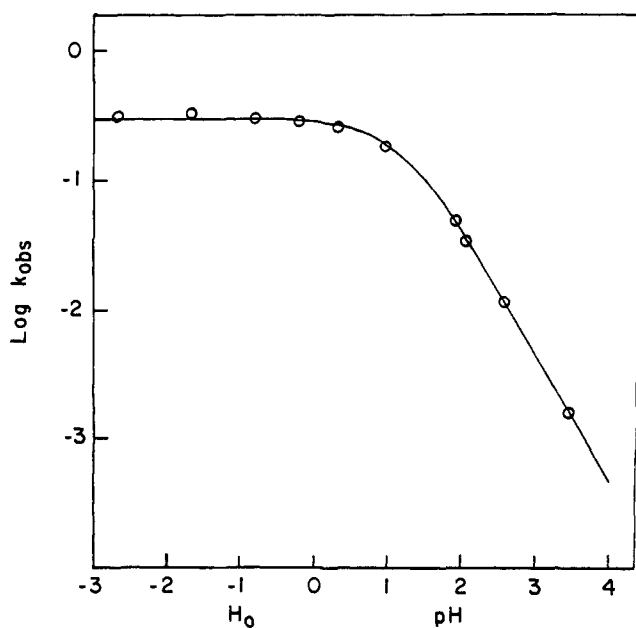Figure 11. First-order plots determined at constant pH (H_0) for the decarboxylation of 3_R.

Figure 12. Log rate $vs.$ pH profile for the decarboxylation of 3_R.

Table III. Results of Decarboxylation of
Various Tetraminecobaltaminomalonates

Compd	% R	% S
3_R	35	65
11	64	36
15	31.5	68.5

poses) a varying scale on the y axis. Examination of Figure 11 reveals that decarboxylation follows first-order kinetics (eq 9) throughout the period of observa-

$$d[3_R]/dt = k_{obsd}[3_R] \qquad (9)$$

tion (1–3 half-lives). The log k_{obsd} values (log of slopes of the plots of Figure 11) are plotted $vs.$ the acidity indexes pH and H_0 in Figure 12. The points of

Figure 12 are experimental with the theoretical curve being generated from eq 10 where a_H is the hydrogen

$$k_{obsd} = k_r[a_H/(K_a' + a_H)] \qquad (10)$$

ion activity determined by the glass electrode or H_0 values, K_a' the apparent acid dissociation constant of the carboxyl group of 3_R, and k_r the first-order rate constant for decarboxylation of the carboxylic acid in the undissociated form. The values of k_r and pK_a' employed to generate the curve of Figure 12 are 0.295 and 1.2 min^{-1}, respectively. That the decarboxylation reaction is not subject to general catalysis is indicated by the insensitivity of k_{obsd} to buffer concentration at constant pH. Thus, at concentrations of betaine buffer of 1.0 M (pH 1.94), 0.125 M (pH 1.92), and 0.10 M (pH 2.08) the values of k_{obsd} for decarboxylation were found to be 4.77 × 10^{-2}, 4.83 × 10^{-2}, and 3.29 × 10^{-2} min^{-1}, respectively. At completion of the kinetic experiments the only Co^{III} products in solution were shown to be 5_R and 5_S by nmr and ORD spectra.

Discussion

The main objective of this work was to ascertain the degree of chiral recognition that an asymmetric cobalt moiety would have for the "equivalent" carboxyl groups in an aminoalkylmalonic acid and to determine the species that undergoes decarboxylation in the ensuing complex as well as the degree of induced asymmetry in the decarboxylation product. The synthesis and experiments necessary to establish structural–spectra relationships are outlined in Scheme I. Notably, treatment of 7 with aminomethylmalonic acid yields primarily Λ-β and some Δ-β products but no Λ-α complex. This is in line with other investigators' ability to isolate only β complexes upon treatment of α-trien-CoCl$_3$ with amino acids.[27,29] (A feasible mechanism for the isomerization is discussed elsewhere.[30])

(29) L. G. Marzilli and D. A. Buckingham, *Inorg. Chem.*, **6**, 1042 (1967).

(30) J. P. Glusker, H. L. Carrell, R. Job, and T. C. Bruice, *J. Amer. Chem. Soc.*, to be submitted for publication.

The evidence (CD, X-ray) strongly implies that the dimethyltrien-Co-aminomethylmalonate complex (3) contains the N–O bound malonate moiety exclusively in the R configuration. This signifies that the dimethyltrien-Co moiety coordinates one carboxylate group to the complete exclusion of the other, identical, carboxylate group. Unless excess base is added, no other $\Lambda(-)_{436}$-β-malonate complex is isolated. *These results represent the first instance of absolute*[31] *chiral recognition of a prochiral center by a small molecule* (a characteristic common in enzymic catalysis).

The structure of 3 (Scheme I) reveals a hydrogen bond between one carboxylate group and the proton on a secondary nitrogen of the dimethyltrien ligand. It is evident that in actuality there exists three-point binding of the malonate moiety; *i.e.*, the metal system has provided a template, which can accept only one configuration for substrate binding, as suggested by Ogston[32] in his three-point hypothesis for enzyme systems. In this light it is not surprising that such a high degree of chiral recognition should exist.

Decarboxylation of 3 in acidic solution (81.6°) yields 65% 5_S and 35% 5_R. The reaction has been established to be first order in the species of 3 in which the carboxyl group not coordinated to the Co^{III} moiety is protonated. In analogy to the decarboxylation of other undissociated carboxylic acids possessing β,γ unsaturation[33] it is reasoned that decarboxylation of 3 involves a cyclic transition state to yield, as a metastable intermediate, an "enol"-like product in which the asym-

metric carbon of 3 has become sp^2 (eq 11). That 5_S is
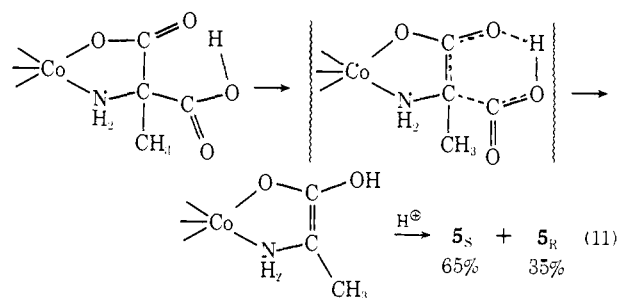
observed in 30% excess over 5_R must then require considerable asymmetric induction on protonation of the sp^2 intermediate by the dissymmetric cobalt center. The experiments aimed at ascertaining the effects of bulkier substituents, both on the malonate moiety and on the tetramine ligand, proved discouraging (Table III) in that the extent of asymmetric induction does not become much greater with increase in steric demand. In the case of the isopropyl malonate complex the order of asymmetry was actually reversed (Table III) indicating that bulkiness in the malonate substituent is perhaps of more significance than on the tetramine ligand.

In conclusion, the most important aspect of this study is the establishment that a small chiral metal complex may recognize, in an absolute sense, a prochiral center. Of less importance but considerable interest is our finding that the stereospecifically formed malonate complex decarboxylates with appreciable asymmetric induction from the dissymmetric cobalt moiety.

(31) Within experimental error. We estimate that our chromatographic technique could easily have detected 0.5% of 3_S.
(32) A. G. Ogston, *Nature (London)*, 162, 963 (1948).
(33) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill, New York, N. Y., 1962, p 72.

Ring Strain and General Acid Catalysis of Acetal Hydrolysis. Lysozyme Catalysis

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Abstract: The hydrolysis of 2-methoxy-3,3-dimethyloxetane (7) occurs with general acid catalysis as attested to by: (1) dependence of observed rate constant upon the concentrations of acid species in solution (Brønsted $\beta = -0.65$); (2) the near identity of catalytic coefficients for dihydrogen phosphate anion and imidazolium ion; and (3) the values of the deuterium solvent kinetic isotope effects for H_3O^+ and $H_2PO_4^-$ ($k_D/k_H = 1.8 \pm 0.9$ and 0.50 ± 0.10, respectively). These results establish that the proposed ring strain in the Phillips mechanism for lysozyme would allow general acid catalyzed hydrolysis of the glycosidic bond.

In 1965, Phillips[2] announced the elucidation of the three-dimensional structure of lysozyme, the first enzyme whose tertiary structure had been reported in detail. Lysozyme catalyzes hydrolysis of β (1–4)

glycosidic bonds in polysaccharides made up of N-acetylglucosamine or alternating N-acetylglucosamine and N-acetylmuramic acid residues. A model of an enzyme–substrate complex showed[3] that the only functional groups in the active site which might reasonably be catalytically active are the carboxyl groups Glu-35 and

(1) Work carried out by R. F. Atkinson while on sabbatical leave from The Department of Chemistry, Grand Valley State College, College Landing, Allendale, Mich. 49401.
(2) (a) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature (London)*, 206, 757 (1965); (b) L. N. Johnson and D. C. Phillips, *ibid.*, 206, 761 (1965).

(3) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. Phillips, and V. R. Sarma, *Proc. Roy. Soc., Ser. B*, 167, 378 (1967).