

solution of the purified complex: UV (0.2 M  $\text{NH}_4\text{HCO}_3$ )  $\lambda$  302, 425 nm (see Figure 1).

Upon standing in the dark for 10 days at 4 °C, the complex had decomposed completely to the enneagold cluster: UV  $\lambda$  317, 357 (s), 385, 447 nm (see Figure 2).

**Tricyanoheptakis[4,4',4''-phosphinidynetri(benzenemethanamine)]undecagold (9b).** A suspension of 80 mg (0.36 mmol) of AuCN and 311 mg (0.36 mmol) of the tris(tosylate) **6** in 10 mL of 95% ethanol was stirred for 1 h, when almost all of the AuCN had dissolved. The mixture was filtered, neutralized with KOH, and treated with 14 mg (0.36 mmol) of  $\text{NaBH}_4$ . After 1 h, the ruby-red solution was quenched with 0.1 mL of acetone, concentrated at room temperature, and chromatographed in 0.05 M  $\text{K}_2\text{HPO}_4$  on Bio-Gel P-6 (100–200 mesh, 4 × 50 cm column, 1.2 mL/min), affording an approximately  $10^{-4}$  solution of purified complex: UV (0.05 M  $\text{K}_2\text{HPO}_4$ )  $\lambda$  303, 420 nm (see Figure 3). Upon standing at 4 °C, this solution deposited a sparingly soluble, dark red, amorphous solid; the supernatant was lyophilized for storage of the remaining material.

**Acknowledgment.** Support for this research was provided by the National Institutes of Health through Grants GM-15971 and GM-21612. We also thank Professor John Hearst for the sedimentation-equilibrium measurements.

## References and Notes

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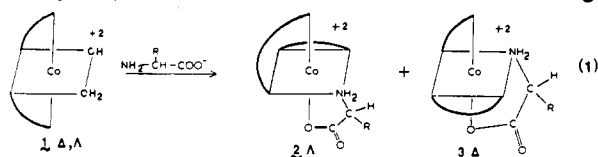
## Amino Acid Mediated Asymmetric Transformation and Catalytic Asymmetric Transformation of the $\alpha$ -Triethylenetetraminecobalt(III) Moiety

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**Abstract:** A high degree of asymmetric transformation is realized upon treatment of racemic  $\alpha$ -dichlorotriethylenetetraminecobalt(III) chloride (**5**) with (*S*)-proline and triethylamine in refluxing methanol and ethanol when up to 94.5% of the cobalt appears in the products as  $\Delta(+)$  $_{436-\beta_2}$ -[triethylenetetraminecobalt(III) (*S*)-prolinate] $^{2+}$ . A similar asymmetric transformation is observed when racemic **5** is treated with a symmetrical amino acid,  $\alpha,\alpha$ -aminomethylmalonic acid, and triethylamine in refluxing methanol with only catalytic amounts of various chiral acids to produce  $\Lambda(-)$  $_{436-\beta_2}$ -[triethylenetetraminecobalt(III) (*R*)-aminomethylmalonate] $^{2+}$  (the purity of which was proven by a resolution via cation-exchange chromatography).

In recent years considerable research has been directed toward the synthesis and isolation of tetraminocobalt(III)-amino acid complexes. A typical reaction between a racemic tetraminocobalt(III) moiety and an  $\alpha$ -amino acid is shown in eq 1 to produce two amino acid complexes. Because product isolation could be greatly simplified, a desirable and useful case of this type of synthesis would be one in which the unwanted isomer is not produced. This situation could be brought about in two ways: (1) a kinetic differentiation wherein the incoming



amino acid reacts preferentially with either the  $\Lambda$  or  $\Delta$  form of the tetramine; (2) a thermodynamic differentiation in which equilibrium is established between the two products and the more stable one predominates. A kinetic resolution involving **1** and glutamic acid had been proposed and subsequently disproven.<sup>1,2</sup> Little stereospecificity was found in the synthesis of  $\beta_2$ -[trien-Co (*S*)-Pro] $^{2+}$  <sup>3</sup> from  $\beta$ -[trien-Co(OH)(OH<sub>2</sub>)] $^{2+}$  and (*S*)-proline under kinetically controlled conditions.<sup>4</sup> Kinetic differentiation has been claimed in the complexation of **1** with the N-terminus of chiral dipeptides, but no evidence is presented to preclude thermodynamic equilibration upon hydrolysis of the peptide linkage to produce **2** and **3**.<sup>5</sup> Neither has a thermodynamic differentiation been conclusively demonstrated for an amino acid complex. However, Busch has presented conditions under which the ethylenediamine groups in

**Table I.** Distribution of the  $\Delta$  and  $\Lambda$  Isomers in the Precipitate and the Mother Liquors of the Reactions to Produce **6** on a 4-mmol Scale

mL of ethanol <sup>a</sup>	precipitate		Mother liquor	overall yield
	$\Delta$ -6, mmol	$\Lambda$ -6, mmol	$\Delta$ -6, mmol	$\Delta$ -6, %
90	3.57	0.03	0.21	94.5
60	3.45	0.04	0.29	93.5
45	2.94	0.01	0.46	85.0
30	2.44	0.01	0.53	74.3
0	2.11	0.05	0.75	71.5
90 <sup>b</sup>	2.22	0.18		

<sup>a</sup> Volume of methanol added was [90 mL - (volume of ethanol)].

<sup>b</sup> Reaction was stopped after 4 h.

racemic  $\text{en}_3\text{Co(III)}^+3$  are labilized and, using 1 equiv of *d*-tartrate as resolving agent, was able to cause precipitation of the  $\Lambda$ - $\text{en}_3\text{Co}$  *d*-tartrate while isomerizing the more soluble  $\Delta$ -diastereomer to a  $\Lambda, \Delta$  mixture.<sup>6</sup> The limiting yield in this case becomes 100% because all of the  $\Delta$  isomer may potentially be converted into the  $\Lambda$  diastereomer as precipitation causes the  $\Lambda, \Delta$  equilibrium to shift. One drawback of this type of second-order asymmetric transformation is the requirement of at least 1 equiv of resolving agent.<sup>7</sup>

The purpose of this research is to demonstrate conditions under which a high degree of transformation of the racemic trien-Co(III) moiety can be effected using 1 equiv of an optically active amino acid [(*S*)-proline] as a chiral agent and then to utilize similar conditions to demonstrate transformation in a system using a symmetrical amino acid ( $\alpha, \alpha$ -aminomethylmalonic acid) with only catalytic amounts of chiral agents.

### Experimental Section

NMR spectra were obtained on Varian T-60 and EM 360 spectrometers with sodium dimethylsilapentanesulfonate (DSS) as internal standard. CD spectra were obtained in 1 M HCl on a Cary 60 spectropolarimeter and reproduced with the aid of a Hewlett-Packard 9821 desk calculator. Rotations were taken on a Perkin-Elmer 241 polarimeter in 10-cm cells and are uncorrected. The cation-exchange resin was Bio-Rad AG50-WX2, 200-400 mesh. (*S*)-Proline was purchased from Aldrich Chemical Co.  $\alpha, \alpha$ -Aminomethylmalonic acid (**4**) and  $\alpha$ -trien-CoCl<sub>3</sub> (**5**) were prepared by literature procedures.<sup>8,9</sup> Potassium antimonytartrate was standard drug-store grade tartar emetic.

**Isomerization of  $\Lambda(-)_{436}\text{-}\beta_2\text{-(2S,9S)-2,9-Diamino-4,7-diazadecanecobalt(III)(S)-Alaninate}$ ] Chloride (**8**).**<sup>10</sup> **8** (0.349 g) was dissolved in 90 mL of methanol and 1.5 mL of triethylamine was added. The solution was refluxed for 24 h and then the solvent evaporated under moving air. The CD spectrum was obtained on a portion of the residue which had been dissolved in water and acidified with 1 M HClO<sub>4</sub>.

**$\Delta(+)_436\text{-}\beta_2\text{-(Triethylenetetraminecobalt(III)(S)-Prolinate)}$  Iodide (**6**).** (*S*)-Proline (0.46 g, 4.0 mmol), **5** (1.25 g, 4.0 mmol), 1.5 mL of triethylamine, and 1.4 g of NaI were placed in a solvent composed of *x* mL of ethanol and (90 - *x*) mL of methanol (see Table I). The mixture was refluxed until several hours beyond the point when the violet starting material **5** was no longer in evidence. The mixture was then allowed to cool and stand at room temperature for 36 h. The precipitate (pink-orange powder in the reactions with mostly ethanol solvent and well-formed orange crystals otherwise) was collected, washed with ethanol and ether, then air-dried, and ground in a mortar to assure homogeneity. Repeated crystallizations from water led to slightly increasing rotations which became constant at  $M_{\alpha 436}(\text{H}_2\text{O}) = 3990 \pm 20^\circ$ .<sup>11</sup> The CD spectrum was identical to that reported in the literature<sup>12</sup> with  $M_{\alpha 493} = -4070^\circ$ . Drying the water-recrystallized samples to constant weight at 110 °C produced a weight loss of 5.9%, indicating two waters of crystallization,  $\epsilon_{438}$  148.8 (lit.<sup>12</sup> 158).

The experiment in 90 mL of ethanol was repeated, but reflux was stopped after only 4 h while there was still a considerable amount of unreacted **5**. Pink powder (1.87 g, 2.4 mmol) was collected.

For each of the mother liquors from the above reaction the solvent was evaporated under a stream of moving air. The residue was then

**Table II.** Results from Treating **5** with **4** in the Presence of Various Chiral Agents

chiral agent	% yield of <b>7</b>	% $\Lambda$ - <b>7</b>	overall yield of $\Lambda$ species, %
( <i>S</i> )-phenylalanine (5.5 mg)	69	91.7	79
( <i>S</i> )-phenylalanine (50 mg)	55	90.1	72
<i>d</i> -tartaric acid (6.3 mg)	51	98.5	75
( <i>S</i> )-glutamic acid (5.7 mg)	57	96.8	77
( <i>S</i> )-aspartic acid (6.6 mg)	69	78.5	70
( <i>S</i> )-alanine (6.8 mg)	53	68.9	60
none	60	50.1	50

dissolved in a measured amount of water, and the CD and visible spectra were obtained.

**$\Lambda(-)_{436}\text{-}\beta_2\text{-(Triethylenetetraminecobalt(III)(R)-Aminomethylmalonate)}$  Chloride (**7**).** **4** (0.399 g, 3.00 mmol), **5** (0.935 g, 3.00 mmol), and triethylamine (1.5 mL, 15 mmol) were placed in 90 mL of methanol with a silicon carbide boiling stone. A catalytic amount of chiral agent (see Table II) was then added and refluxing commenced. Several hours of refluxing produced a deep-red solution. Further refluxing (12-20 h) yielded an orange solution and initiated precipitation of orange crystals. Refluxing was continued until it appeared that no further precipitate was forming (36-80 h). The precipitate was collected immediately from the hot solvent, washed with methanol and petroleum ether, and then air-dried. The presence or absence of the sharp methyl singlet of methanol at  $\delta$  2.0 ppm in the NMR spectrum revealed that the product crystallized with either 1.0 or no solvent molecules. Anal. (C<sub>10</sub>H<sub>24</sub>N<sub>5</sub>O<sub>4</sub>CoCl<sub>2</sub>) Calcd for C, H, N: 17.16. Found 16.76. Repeated crystallizations from ethanol/water as the perchlorate salt led to rotations increasing to a constant value at  $M_{\alpha 436}(\text{1M HCl}) = -4610^\circ$  and  $M_{\alpha 436}(\text{H}_2\text{O}) = -5380^\circ$ . Care must be taken to keep the pH high during recrystallization to avoid precipitation as the partially protonated salt. The NMR spectrum exhibits a methyl singlet at  $\delta$  -1.11 ppm;  $\epsilon_{478}$  142(H<sub>2</sub>O), 148(1M HCl),  $\epsilon_{348} = 161(1\text{M HCl})$ .

**$\Delta(+)_436\text{-}\beta_2\text{-(Triethylenetetraminecobalt(III)(S)-Aminomethylmalonate)}^{2+}$  (**7<sub>s</sub>**).** Racemic **7** (150 mg) was dissolved in 1 mL of water and sorbed onto a 46 × 1.1 cm cation-exchange column in the potassium form. Elution was carried out with a saturated solution of potassium antimonyl tartrate. Two bands began immediately to separate. By the time the first band had traversed 90% of the column length, a clean separation was evident. As the first band began to elute, the eluent was changed to 0.2 M NaCl. Fractions of 4 mL each were collected, and the absorbance at 478 nm and rotations at 436 nm were monitored. A plot of the ratio of these values (which is directly proportional to the specific rotation) clearly shows the separation between bands. The limiting value for the second band shows  $M_{\alpha 436} = +5260^\circ$ .

**Mother Liquors.** The mother liquors from several reactions to produce **7** were combined and evaporated to dryness in moving air. The residue was dissolved in a minimum amount of water and sorbed onto a 3.2 × 90 cm cation-exchange column in the sodium form. Elution was initiated with 0.5 M NaCl to bring one small fraction (a) down the column much faster than a +1 species. Two bands moved at rates consistent with +1 ions (b, c). After the second +1 band had been eluted, the column was washed with water and two overlapping +2 bands brought down with 1.5 M HCl (d, e).

**Isomerization of **7**.** (a) Three milligrams of **7** was placed in 3 mL of hot methanol with several drops of triethylamine. Sufficient water was added to effect solution and the sample was placed in a jacketed 10-cm polarimeter cell thermostated at 63 ± 2 °C. The rotations at 546 and 436 nm were monitored. The reaction appeared to be biphasic with an initial rapid decrease in rotation over the first few minutes followed by a more leisurely decline. The half-time for disappearance of optical activity during the slow phase was 2.8 × 10<sup>4</sup> s. (b) Ten milligrams of **7** was dissolved in 10 mL of 0.2 M HCO<sub>3</sub><sup>-</sup>/CO<sub>3</sub><sup>2-</sup> buffer at pH 10.0. The rotations were monitored as above at 65 ± 2 °C. An initial rapid increase in rotation was observed followed by a slow decline. The half-time for disappearance of optical activity during the slow phase was 1.0 × 10<sup>5</sup> s.

### Results

The molar ellipticity at 505 nm of  $\Lambda\text{-}\beta_2\text{-[dmt-Co(S)-Ala]}^{2+}$

**Table III.** Parameters<sup>a</sup> of the Component Gaussian Cotton Effects for **7**<sup>b</sup>

	i	ii	iii	iv	v	vi
<i>a</i>	484.9	445.8	348.4	338.8	250.7	532.0
<i>b</i>	34.7	33.4	22.2	20.0	28.3	39.9
<i>C</i>	5188	2422	-969	-92	-3360	-235

<sup>a</sup> As defined previously.<sup>13</sup> <sup>b</sup> *a* is peak location in nm, *b* is the half-width at 1/*e* of maximum peak height, and *C* is the maximum ellipticity in degrees.

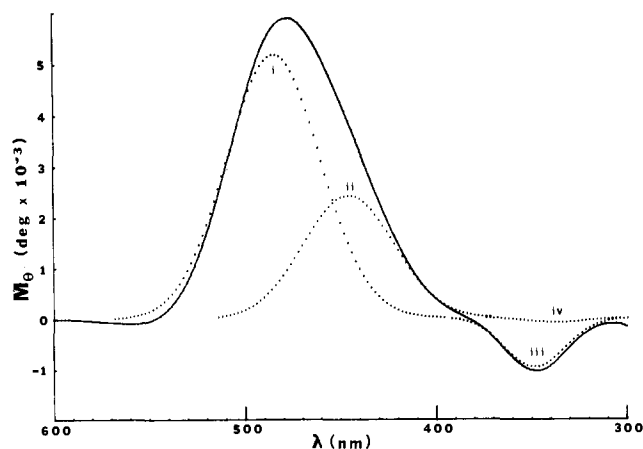
**Table IV.** Components of the Mother Liquor from the Synthesis of **7**

species	% of total cobalt in solution
$\Delta$ - $\beta$ -[trien-Co( <i>R</i> )-MAM] <sup>+</sup>	7.4
$\Delta$ - $\beta$ -[trien-Co( <i>S</i> )-MAM] <sup>+</sup>	19.5
$\Delta$ - $\beta$ -[trien-Co( <i>R</i> )-MAM] <sup>+</sup>	4.9
$\Delta$ - $\Delta$ -[trien-Co( <i>S</i> )-MAM] <sup>+</sup>	21.8
	total $\Delta$ species = 50.1%
$\Delta$ - $\beta$ -[trien-Co( <i>R</i> )-Ala] <sup>2+</sup>	11.0
$\Delta$ - $\beta$ -[trien-Co( <i>S</i> )-Ala] <sup>2+</sup>	6.3
$\Delta$ - $\beta$ -[trien-Co( <i>R</i> )-Ala] <sup>2+</sup>	6.3
$\Delta$ - $\beta$ -[trien-Co( <i>S</i> )-Ala] <sup>2+</sup>	11.0
(amino acidate) <sub>3</sub> Co(III)	11.7
	total $\Delta$ species = 49.9%

was observed to decrease from 7000° to 1800° while refluxing for 24 h with triethylamine in methanol. The CD spectrum of an acidified sample looked nearly like the vicinal effect of (*S*)-alanine.<sup>13</sup> To evaluate the composition more precisely, published CD parameters of  $\Delta$ - $\beta_2$ -[dmt-Co(*S*)-Ala]<sup>2+</sup><sup>13</sup> and of  $\Delta$ - $\beta_2$ -[dmt-Co(*S*)-Ala]<sup>2+</sup><sup>14</sup> were used to construct a family of CD curves of varying proportions. The curve of best fit represented 57%  $\Delta$  isomer and 43%  $\Delta$  isomer. Thus, the tetramine ligand had isomerized from 100%  $\Delta$ - $\beta$  to 57%  $\Delta$ - $\beta$ .

It had been reported that  $\Delta$ - $\beta_2$ -(*R,R*)-[trien-Co(*S*)-Pro]I<sub>2</sub> was insoluble in methanol, while the corresponding  $\Delta$ - $\beta_2$ -(*S,S*) isomer was soluble.<sup>12</sup> When racemic  $\alpha$ -[trien-CoCl<sub>2</sub>]Cl was treated with (*S*)-proline in refluxing methanol with excess sodium iodide, under conditions which caused isomerization of the above-mentioned dmt complex, a pink-orange crystalline precipitate was obtained. The CD spectrum of this complex had characteristics identical with that for  $\Delta$ - $\beta_2$ -(*R,R*)-[trien-Co(*S*)-Pro].<sup>12</sup> The compound crystallized as a dihydrate but underwent rapid efflorescence. On the basis of the molar ellipticity of this sample and the published value for the  $\Delta$ - $\beta_2$ -(*S,S*)-[trien-Co(*S*)-Pro]I<sub>2</sub><sup>11</sup> the composition of the precipitates from carrying out the reaction in various methanol-ethanol mixtures was determined (Table I). As the fraction of ethanol in the solvent was increased, more precipitate was formed. At ethanol fractions of two-thirds and above, sodium chloride was also precipitated. A table of the concentration ratio of  $\Delta$ - $\beta_2$  isomer to  $\Delta$ - $\beta_2$  isomer vs.  $\theta_{493}/\theta_{450}$  was constructed from literature CD values<sup>12</sup> and used to determine the amount of  $\Delta$ - $\beta_2$ -(*R,R*)-[trien-Co(*S*)-Pro]<sup>2+</sup> in each mother liquor (Table I). One reaction was halted while one-third of the starting  $\alpha$ -[trien-CoCl<sub>2</sub>]Cl had not yet reacted. The product from this reaction was still greater than 92% pure  $\Delta$ - $\beta_2$ -(*R,R*)-[trien-Co(*S*)-Pro]<sup>2+</sup>. The total yield of  $\Delta$ - $\beta_2$  product varied from 71.5% in pure methanol solvent to 94.5% in pure ethanol, indicating that an asymmetric transformation had certainly taken place.

When racemic  $\alpha$ -[trien-CoCl<sub>2</sub>]Cl is treated with the symmetrical amino acid  $\alpha$ , $\alpha$ -aminomethylmalonic acid in refluxing methanol with triethylamine and a small amount of naturally occurring chiral acid, an orange crystalline precipitate of high optical activity is formed. The stoichiometry of the complex satisfies its formulation as [trien-Co MAM]Cl<sub>2</sub> (**7**). The region

**Figure 1.** Circular dichroism spectrum of  $\Delta$ (-)<sub>436</sub>- $\beta_2$ -[trien[Co(III)-(*R*)-MAM]<sup>2+</sup> in 1.0 M HCl (—) and component Gaussian Cotton effects (···).

between 990 and 1100 cm<sup>-1</sup> in the IR has been used to characterize trien-Co(III)-amino acid complexes.<sup>15</sup> The IR spectrum exhibits peaks at 1065, 1058, 1036, and 1002 cm<sup>-1</sup> (with intensities decreasing in that order) which is of a pattern most nearly matching the spectrum of  $\Delta$ - $\beta_2$ -(*S,S*)-[trien-Co AA]<sup>2+</sup> in that region.<sup>15</sup> The CD spectrum of this complex is shown in Figure 1. With the aid of program CURFIT,<sup>16</sup> the spectrum was deconvoluted into six Gaussian Cotton effects (Table III), the summation of which reproduces the spectrum to within instrumental error over the 600–300-nm region. As demonstrated previously,<sup>13</sup> the sign of the Cotton effects labeled as i and ii in Figure 1 allow us respectively to assign the  $\Delta$  configuration to the tetramine chelate and the *R* configuration to the bound aminomethylmalonate ligand. The location of the CD maximum (below 500 nm) further establishes the complex as  $\beta_2$ .<sup>15</sup> Final confirmation of the structure of **7** comes upon acid-catalyzed decarboxylation. It has been shown that decarboxylation of aminomethylmalonate bound to a Co(III) tetramine leads to an alanine complex.<sup>10,17</sup> The CD spectrum of the alanine complex formed upon acid-catalyzed decarboxylation of **7** is identical to the published spectrum of  $\Delta$ - $\beta_2$ -[trien-Co(III)Ala]<sup>2+</sup> with  $M_{\theta 490} = 7250^\circ$ .<sup>12</sup> The molar rotation of the purified **7** was used to establish the purity of the products from reactions carried out in the presence of small amounts of various naturally occurring chiral acids (Table II). In all cases, the  $\Delta$ - $\beta$  isomer was the predominant species. In most cases, the yield of  $\Delta$  product exceeded 50%, indicating that an asymmetric transformation had taken place. Reflux was always continued for several hours after it was judged that no further precipitate was forming. If reflux were continued for up to several days beyond this point, extensive decarboxylation of **7** into (*R*)- and (*S*)-alanine complexes ensued (as evidenced by the appearance of alanine methyl doublets in the NMR). The collected mother liquors were subjected to cation-exchange chromatography. Fraction a was a small amount of an uncharged species (perhaps tris[aminoacidate cobalt(III)]). The concentration was estimated by assuming an  $\epsilon$  of ca. 150 for the absorption maximum at 480 nm and appears in Table IV as a percentage of the total cobalt species in solution. Fraction c exhibited a CD spectrum which was the mirror image of **7** but smaller in magnitude; therefore, it was adjudged to be a mixture of  $\Delta$ - $\beta_2$ -[trien-Co(*S*)-MAM]<sup>+</sup> and **7**, with **7** as the minor component. The enantiomeric composition of this fraction was readily calculated from the known ellipticities of **7**. Fraction b exhibited a CD spectrum in which the first principal Cotton effect (i in Figure 1) was positive (therefore denoting  $\Delta$ ), but Cotton effect ii was negative [denoting (*S*)-aminomethylmalonate]. It was therefore adjudged

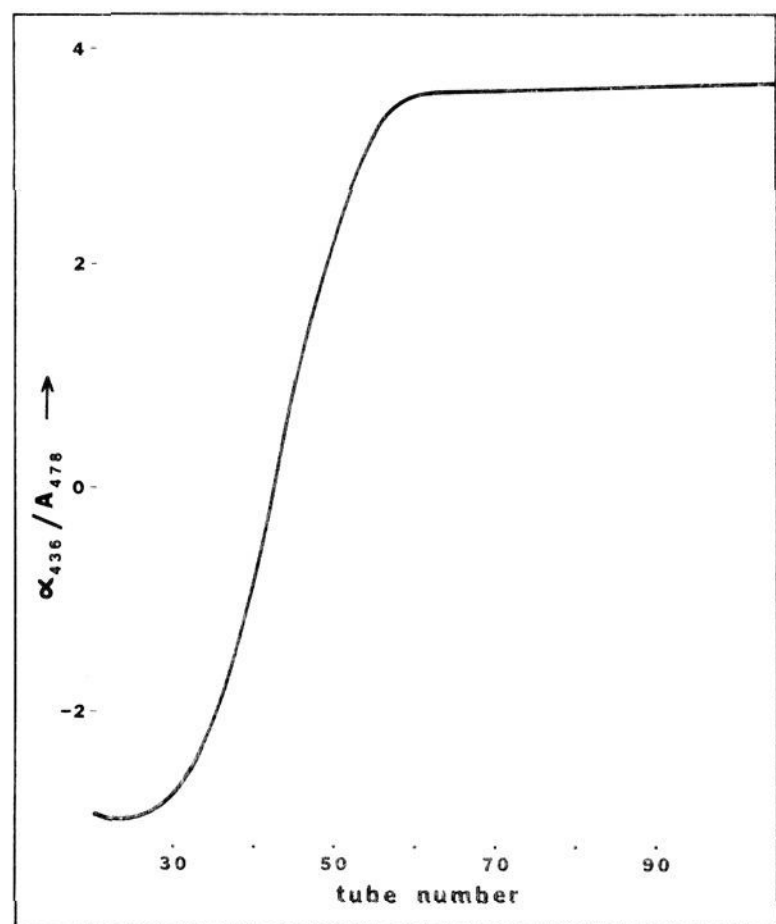


Figure 2. Plot of  $\alpha_{436}/A_{478}$  near the overlap region fractions from the chromatographic resolution of racemic  $\beta_2$ -[trien-Co(III)MAM] $^{2+}$ .

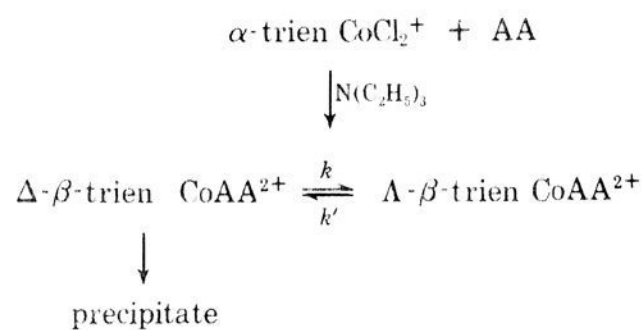
that fraction b consisted of the enantiomeric pair of  $\Lambda$ - $\beta$ -[trien-Co(III)(*S*)-MAM] $^{+}$  and  $\Delta$ - $\beta$ -[trien-Co(III)-(*R*)-MAM] $^{+}$ , with the  $\Lambda$ - $\beta$  isomer predominating. In order to determine the relative concentrations of each species, an estimate of the ellipticity for pure  $\Lambda$ - $\beta$ -[trien-Co(III)-(*S*)-MAM] $^{+}$  was necessary. From previous literature<sup>12</sup> it is seen that the vicinal effect of (*S*)-alanine offers no contribution to the CD curve of  $\beta_2$ -trien-Co(III) complexes at 567 and 534 nm. If the same is expected of the aminomethylmalonate species, the molar ellipticity observed for 7 should be an excellent approximation to that of  $\Lambda$ - $\beta$ -[trien-Co(III)-(*S*)-MAM] $^{+}$  at these wavelengths. The calculated concentrations of all of the +1 species are listed as percentages of total cobalt in solution in Table IV. Fractions d and e showed practically no optical activity and were identified respectively as the enantiomeric pairs  $\Lambda$ - $\beta_2$ -[trien-Co(*R*)-Ala] $^{2+}$  ( $\Delta$ - $\beta_2$ -[trien-Co(*S*)-Ala] $^{2+}$ ) and  $\Lambda$ - $\beta_2$ -[trien-Co(*S*)-Ala] $^{2+}$  ( $\Delta$ - $\beta_2$ -[trien-Co(*R*)-Ala] $^{2+}$ ) on the basis of the NMR methyl doublet at -1.47 and -1.51 ppm, respectively, and by comparison of visible spectra with known  $\beta_2$ -[trien-Co Ala] $^{2+}$  complexes.<sup>12</sup> The concentrations were estimated using known absorption coefficients and are listed in Table IV as percentages of total cobalt species in solution.

In order to isolate the  $\Delta$  isomer of 7, a resolution by cation-exchange chromatography was carried out. A relatively short column (46 cm) proved effective when the eluent was saturated potassium antimonyl tartrate. In order to keep the  $\Delta$  fraction clear of optically active contaminants, the eluent was changed to 0.2 M NaCl as soon as a definite clean separation of bands was observed. The effectiveness of the separation is illustrated by plotting the ratio of  $\alpha_{436}/A_{478}$  (which is directly proportional to  $M_\alpha$ )<sup>18</sup> vs. fraction number in the overlap region (Figure 2). The  $M_{\alpha_{436}}$  calculated from the upper asymptote is opposite in sign and in good agreement with the  $M_\alpha$  calculated for the  $\Lambda$ - $\beta_2$  complex 7.

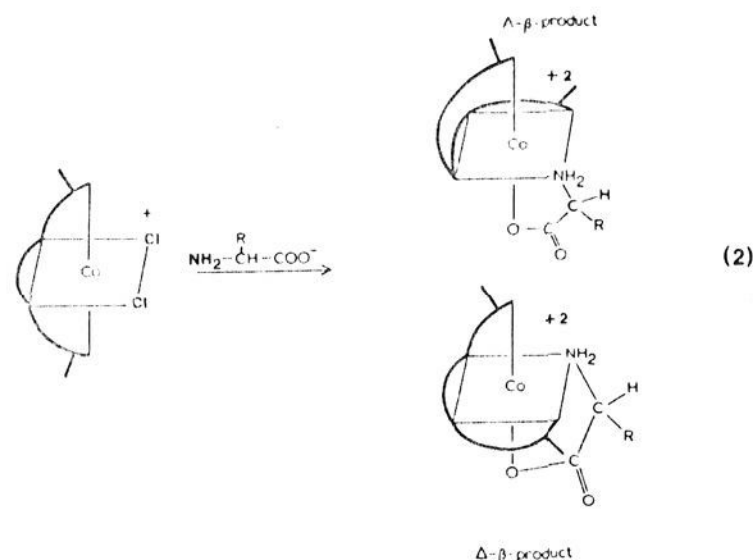
## Discussion

It had previously been reported that the product from treatment of pure  $\Lambda$ - $\alpha$ -[dimethyltrien-Co(III)Cl<sub>2</sub>]Cl with amino acids in aqueous solution produced both the  $\Delta\beta$  and  $\Lambda\beta$

## Scheme I



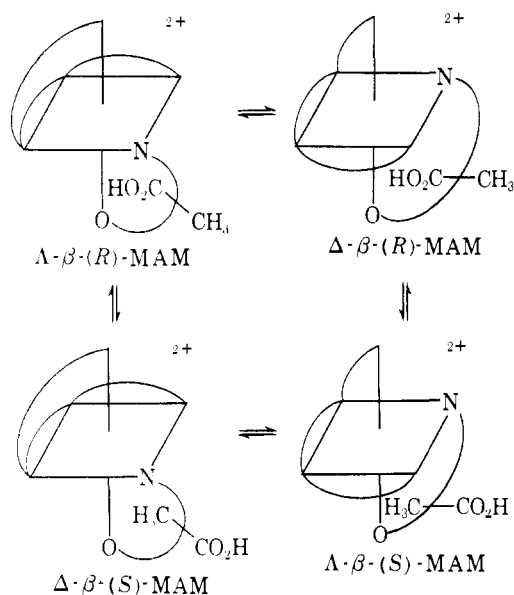
isomers (eq 2).<sup>10</sup> Higher yields of  $\Lambda$ - $\beta$  product were obtained in refluxing alcohol. It seemed reasonable to suppose that if significant amounts of both  $\Delta$ - $\beta$  and  $\Lambda$ - $\beta$  amino acid complexes could be produced an equilibrium between these two species might have been established. Accordingly, 8 was placed in



refluxing methanol in the presence of an amine base, and isomerization of the tetramine ligand was observed.

After thus demonstrating the lability of a tetramine ligand, it seemed appropriate to determine whether this relatively facile isomerization could be used to advantage in effecting an asymmetric synthesis of a trien-Co(III)-amino acid complex from racemic trien-Co(III) starting materials. The idea would be to have the unwanted product transform into the desired one as fast as it was formed. In order to shift the equilibrium in favor of the desired product, it would be necessary to remove this product rapidly from the reaction site. This could be accomplished most readily by precipitation. The process is outlined diagrammatically in Scheme I (where AA =  $\alpha$ -amino acid). If a chiral amino acid is used for AA, diastereomeric products are formed, and ready advantage can be taken of solubility differences to remove one from solution. In order for the process to be effective and to prevent excessive product contamination, the  $\Delta$ - $\Lambda$  isomerization must be sufficiently rapid that the unwanted isomer not be able to exceed its solubility. It has been observed previously that  $\Lambda$ - $\beta_2$ -[trien-Co(*S*)-Pro] $_2$  is more soluble in methanol than the diastereomeric  $\Delta$ - $\beta_2$  complex.<sup>12</sup> Therefore, (*S*)-proline was chosen as the amino acid and excess sodium iodide was added to provide the counteranion. When the reaction of Scheme I was carried out at reflux in pure methanol, a definite asymmetric transformation was observed (i.e., the yield of  $\Delta$ - $\beta$  isomer was greater than 50%, Table I). However, the products were so soluble that 44% of the cobalt species remained in solution. In order to decrease the product solubility, a portion of the solvent was replaced with ethanol in succeeding reactions. As the proportion of ethanol was increased, the yield of  $\Delta$ - $\beta$  product increased (up to 94.5% in pure ethanol), while the purity of the product remained at a high level (99.2% pure  $\Delta$ - $\beta$  from 100% ethanol). It has been previously demonstrated that the  $\Delta$ - $\beta_2$  isomer is more thermodynamically stable than the  $\Lambda$ - $\beta_2$  isomer, although no interconversion of the isomers had been achieved.<sup>4</sup> When the reaction of  $\alpha$ -[trien-CoCl<sub>2</sub>] $^{+}$  and (*S*)-proline is

Scheme II



carried out in more dilute methanolic solution and in the absence of iodide (so that no precipitation occurs), the initial ratio of  $\Delta$  to  $\Lambda$  product is 1:1, while after 48 h the ratio has leveled off at 3.2:1.<sup>19</sup> Thus, as is commonly the case, the degree of second-order asymmetric transformation (represented by the product ratio in the precipitate) far exceeds the degree of first-order asymmetric transformation (represented by the product ratio in solution).<sup>20</sup>

If a symmetrical amino acid is used for AA in Scheme I, the products which it is desired to separate will be enantiomeric. One way of separating enantiomeric compounds from solution is by isomorphous seeding.<sup>21</sup> Since it had been shown that  $\alpha,\alpha$ -aminomethylmalonic acid produces a  $\Lambda\text{-}\beta_2\text{-[trien-Co(III)(R)-MAM]}^+$  complex which is only slightly soluble in methanol,<sup>10</sup> that amino acid was chosen as the symmetrical AA in Scheme I. The problem then became one of providing an isomorphous seed for a compound that had not previously been prepared. The reaction was carried out in refluxing methanol in clean glassware to give a 60% yield of optically inactive product which was shown to be a mixture of  $\Lambda\text{-}\beta_2\text{-[trien-Co(III)(R)-MAM]}^{2+}$  and  $\Delta\text{-}\beta_2\text{-[trien-Co(III)(S)-MAM]}^{2+}$ . When the reaction was repeated with a small amount (1.4 mol%) of *d*-tartaric acid added, a 51% yield of product which was 98.5%  $\Lambda\text{-}\beta_2\text{-[trien-Co(III)(R)-MAM]}^{2+}$  was obtained. The synthesis was repeated using other naturally occurring acids which were at hand with similar results (Table II). The addition of (*S*)-phenylalanine (1.1 mol%) provided the most effective reaction with a 69% yield of product, which was 91.7%  $\Lambda\text{-}\beta_2\text{-[trien-Co(III)(R)-MAM]}^+$ , and a 79% overall yield of  $\Lambda$  products. The reaction efficiency did not increase upon adding the (*S*)-phenylalanine up to a concentration of 10 mol %. The yields reported in Table II are typical, with the reactions containing *d*-tartaric acid giving the purest product and those containing (*S*)-alanine the least pure. The yields in this reaction were hindered by the fact that up to 14% of the cobalt species ended up as an alanine complex brought about by decarboxylation of the aminomethylmalonate over the extensive reaction periods. The purities presented in Table II are based on comparison with a sample of high rotation which was repeatedly crystallized until constant rotation was reached. To ensure that this did indeed produce an optically pure product, a racemic sample of **7** was chromatographed on a cation-exchange column with optically active eluent and the pure  $\Delta\text{-}\beta$  fraction was collected. The rotation of this sample was nearly equal in magnitude and opposite in sign to the recrystallized **7**, thereby establishing its purity.

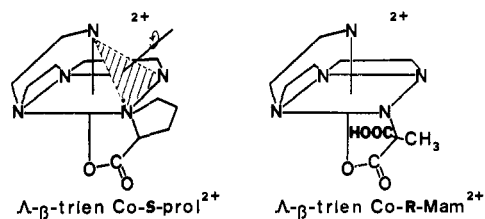
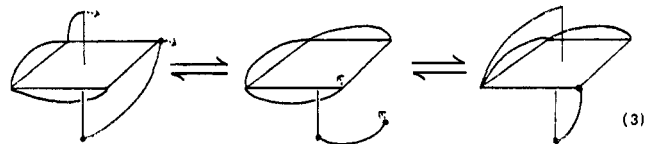


Figure 3. The  $\Delta\text{-}\beta_2\text{-trien-Co(III)}$  complexes of the amino acids studied in this work.

### Mechanism

Although the detailed mechanism is the subject of another effort,<sup>19</sup> certain conclusions can be drawn from the experiments presented here.

The  $\Lambda\text{-}\beta_2\text{-[trien-Co AA]}^{2+}$  complexes studied are depicted in Figure 3. In order to isomerize the  $\Lambda\text{-}\beta_2$  complex to the  $\Delta\text{-}\beta_2$  complex for AA = proline, a simple Bailar twist,<sup>22</sup> about the pseudo  $C_3$  axis protruding from the shaded octahedral face, is adequate (concurrent with a conjugate base mechanism on the secondary N atoms to allow them to isomerize). Since aminomethylmalonic acid is a prochiral molecule, the situation for **7** is more complicated. In order to racemize **7**, not only the configuration of the tetramine be inverted, but one carboxyl group (Figure 3) must become dissociated from the metal and replaced by the other one. Thus, while a dissociative mechanism would seem to be preferred in either case,<sup>23a</sup> it becomes mandatory for **7**. Such a dissociative mechanism can easily be visualized as proceeding through an intermediate containing a planar tetramine ligand (eq 3).<sup>23a,b</sup> Assuming that the sec-



ondary N atoms are allowed to isomerize to the thermodynamically most stable configurations,<sup>15,24</sup> it is seen that the essential equilibria involved in the isomerization of **7** can involve four  $\beta_2$  species (abbreviated as in Scheme II), each of which was found upon chromatographic analysis of the mother liquors. While carboxylate dissociation can lead to isomerization of both the tetramine and the malonate ligands (eq 3), the relative abundances of the malonate species in solution (Table IV) make it apparent that carboxylate dissociation cannot be the only operating mechanism. If carboxylate dissociation were the dominant mechanism, one would expect to find the  $\Delta$ - to  $\Lambda$ -tetramine concentration ratio in the mother liquors to be the same as that of the (*R*)-MAM to (*S*)-MAM complexes. However, the ratio of the  $\Delta$ - to the  $\Lambda$ -tetramine species in solution is 1:1 (Table IV); therefore, the tetramine is completely racemized. Meanwhile, the ratio of the total (*R*)-MAM species in solution to the total (*S*)-MAM species is 1:3.4, representing a severe depletion of (*R*)-MAM species which has not been made up by racemization. Clearly, the tetramine ligand isomerizes significantly more rapidly than the malonate. This can be accounted for by invoking a pathway which proceeds via amino group dissociation as the predominant mechanism in eq 3. This would be in accord with the available data on monodentate amino acids in Co(III)-amine complexes, where it was found that N-coordinated amino acid complexes decompose rapidly in solution<sup>25</sup> while O-coordinated amino acid complexes are stable over extended periods.<sup>26</sup>

### Conclusion

This research has demonstrated that a second-order asymmetric transformation process wherein a chiral amino acid acts

upon a racemic cobalt(III)-tetramine moiety can give excellent asymmetric yields of tetraminecobalt(III)-amino acid complex. Furthermore, under the same conditions, a reasonably high asymmetric yield may be obtained using a symmetric amino acid with only catalytic amounts of chiral material present in the original reaction mixture. Since **7** undergoes acid-catalyzed decarboxylation to give an asymmetric yield of an alanine complex,<sup>14</sup> this leads to an asymmetric amino acid synthesis using only catalytic amounts of chiral agents.

**Acknowledgment.** Support provided by the Research Corporation, the Colorado State University Experiment Station, and by Biomedical Sciences Support Grants is gratefully acknowledged.

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## Oxidation-Reduction Reactions of Organoselenium Compounds. 1. Mechanism of the Reaction between Seleninic Acids and Thiols<sup>1</sup>

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**Abstract:** In aqueous dioxane benzeneseleninic acid, PhSeO<sub>2</sub>H, reacts with 3 mol of an alkanethiol, RSH, to yield 1 mol each of the corresponding selenenyl sulfide PhSeSR and disulfide RSSR. Over the pH range 0.2-10.0 and with the thiol present in large stoichiometric excess over the seleninic acid, the reaction takes place in two distinct stages, both of which exhibit a first-order dependence on thiol concentration. In the first stage the thiol and PhSeO<sub>2</sub>H react to form an intermediate having a  $\lambda_{\max}$  at 265 nm, and which is believed to be the thioiseleninate PhSe(O)SR. In the second stage this intermediate then reacts with the thiol to initiate a reaction sequence leading to PhSeSR and RSSR as the final products. The pH-rate profiles associated with the two stages of the reaction are quite different. For the first stage at pH  $\leq 2$  the kinetically dominant pathway for formation of the intermediate is reaction of RSH with PhSeO<sub>2</sub>H<sub>2</sub><sup>+</sup>, from pH 2.5 to 4.5 it is reaction of RSH with PhSeO<sub>2</sub>H, and above pH 5 it is reaction of RS<sup>-</sup> with PhSeO<sub>2</sub>H. The rates of all these processes are only slightly slower when the thiol is *t*-BuSH than they are when it is *n*-BuSH. The pH-rate profile for the second stage indicates that above pH 5 the kinetically important process is reaction of the intermediate with the thiolate ion RS<sup>-</sup>, while below pH 2 it is reaction of RSH with a protonated form of the intermediate. For both these reactions the rate of reaction in the *t*-BuSH system is over 10<sup>4</sup> slower than in the *n*-BuSH system. This very large rate difference indicates that the rate-determining step of the reaction of the intermediate PhSe(O)SR with RS<sup>-</sup> (or of the protonated intermediate with RSH) involves attack on the sulfur atom of the intermediate, the complete mechanism for the second stage being as shown in Scheme II. While the intermediate PhSe(O)SBu-*t* is quite stable thermally in dilute solution in aqueous dioxane, it decomposes rapidly at room temperature in concentrated solution in anhydrous acetone. Possible reasons for its surprising difference in stability under these different conditions are briefly discussed.

Research in recent years has shown that certain reactions of organoselenium compounds can be used to effect a number of valuable synthetic transformations.<sup>2-8</sup> These developments, plus the important physiological effects of selenium, either definitely established<sup>9</sup> or tentatively hypothesized,<sup>10</sup> have greatly heightened interest in organoselenium chemistry. With this increased interest it becomes highly desirable to learn much more about the detailed mechanisms of reactions of organoselenium compounds, a subject that has received only very limited attention in the past.

Aromatic seleninic acids, ArSeO<sub>2</sub>H, are moderately strong oxidizing agents and can be reduced to diselenides, ArSeSeAr, by a variety of reagents,<sup>11-14</sup> including thiols. According to Rheinboldt and Giesbrecht<sup>11</sup> the stoichiometry of the thiol-seleninic acid reaction is as shown in the equation



Because of the current interest<sup>10</sup> in the physiological chemistry of selenium and the ubiquitous nature of thiol groups in biological systems investigation of the mechanism of the reduction