1.8, at 0.035 *M* Hg^{2+}; 1.4, at 0.073 *M*; 2.7, at 0.145 *M*. The irregular variation probably arises from nonuniform changes in activity coefficients in this region of high ionic strength.
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(31) One anomaly should be noted: within this group of chelates IV–VI, rate variations, while minor, lie in the order saloph > salen > Me_2salen (relative rates 1.6:1.2:1.0), whereas by both of the criteria referred to a trend in exactly the reverse order would have been expected. The differences in any of the parameters is so small, that we regard small changes within the group IV–VI as not particularly significant.

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Reaction of Acetaldehyde with Some Optically Active Cobalt(III) Complexes Containing Coordinated Glycine

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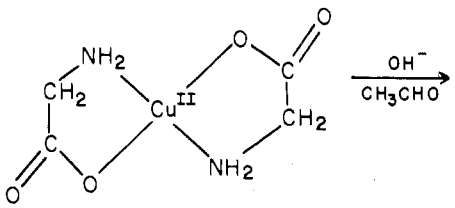
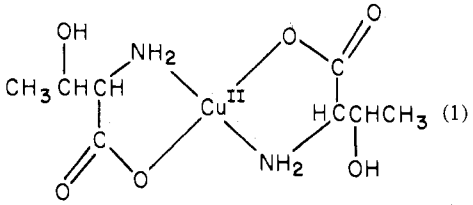
The resolution and assignment of absolute configuration of the isomers of $[Co(en)(gly)_2]^+$ is reported. The optically active cations (+)-$[Co(en)_2(gly)]^{2+}$, (+)-*trans*(*O*)-, (+)-β-*cis*(*O*)-, and (+)-α-*cis*(*O*)-$[Co(en)(gly)_2]^+$ react with acetaldehyde in an aldol-type condensation reaction to give optically active threonine and allothreonine. Using kinetically controlled conditions, the reaction yields products with relatively high optical purities (16–35%). The isolated threonine and allothreonine contain an excess of the *S* isomer indicating that the aldehyde prefers to attack the *S* "side" of the coordinated glycine in these cations. However, analysis of the amino acid distribution suggests that the diversity of geometric environments exhibited by the cations has little effect on the stereochemical course of the reaction. Finally, the product distribution found reinforces the assignment of the absolute configuration of the cations based on circular dichroism arguments.

Introduction

The chemical reactivity of the amino acid glycine coordinated to a transition metal ion has been recognized for some time. Akabori and coworkers[1] demonstrated that the glycine molecules in bis(glycinato)copper(II), $Cu(gly)_2$, react with acetaldehyde in an aldol-type condensation reaction to give threonine and allothreonine (eq 1). The structures of the *S*





(1)

forms of threonine and allothreonine are shown in Figure 1.

Acetaldehyde has also been shown to react with the geometric isomers[2] of $[Co(gly)_3]$ as well as the *N*-salicylideneglycinatoaquocopper(II) complex.[3] Various other reactants such as formaldehyde, benzaldehyde, and pyruvic acid[4] have been used in this reaction to produce serine, β-phenylserine, and β-hydroxy-β-methylaspartic acid, respectively.

Recognizing the stereochemical possibilities of this reaction, Murakami and Takahashi[5] examined the condensation products obtained from the reaction of acetaldehyde with two optically active Co(III) complexes. They found that the reaction of the optically active cation (−)-$[Co(en)_2(gly)]^{2+}$ with acetaldehyde yields product amino acids with low optical activity (8% asymmetric synthesis). We have reexamined the stereospecificity of this reaction with the enantiomer of (−)-$[Co(en)_2(gly)]^{2+}$ as well as the optically pure geometric isomers of $[Co(en)(gly)_2]^+$ (Figure 2). This series of complexes provides an opportunity to study the product distribution obtained from the reaction as a function of changes in complex geometry.

Experimental Section

Reagents and Equipment. All chemicals were reagent grade unless otherwise noted. The amino acids glycine and (*S*)-threonine were purchased from Nutritional Biochemicals Corp., Cleveland, Ohio. Reagent grade acetaldehyde was purified just prior to use by distillation (under N_2) of 10 ml of aldehyde acidified with 2 drops of H_3PO_4. All uv–visible spectra were obtained using a Cary 14 spectrophotometer. The optical rotatory dispersion (ORD) spectra were obtained with a Beckman DU spectrophotometer, fitted with a Keston polarimeter attachment. Circular dichroism (CD) spectra were obtained using a Cary 60 spectrophotometer. A Sargent pH-Stat fitted with a Sargent miniature combination electrode was used for the reactions. The pH-Stat was standardized at pH's of 7.00 and 10.00 with standard buffers prior to each run.

The proton magnetic resonance (pmr) spectra were recorded using a Varian A-60 spectrometer with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as a reference. The pmr samples were prepared by dissolving 80–100 mg of the complex in 0.5 ml of D_2O. Exchange of the NH_2 protons was accomplished by addition of 1.0 *N* NaOD until the solution turned basic (pH 10) followed immediately by the addition of 1 drop of 6 *N* DCl.

An F & M (Hewlett-Packard, Stokie, Ill.) Model 402 gas–liquid chromatograph (glc) with dual column flame ionization detectors was used for the amino acid analyses. The elemental analyses of the complexes were done by Galbraith Laboratories, Knoxville, Tenn.

Syntheses. ***trans*(*O*)-$[Co(en)(gly)_2]Cl\cdot 2H_2O$ and β-*cis*(O)-$[Co(en)(gly)_2]Cl\cdot H_2O$.** The synthesis and characterization of these

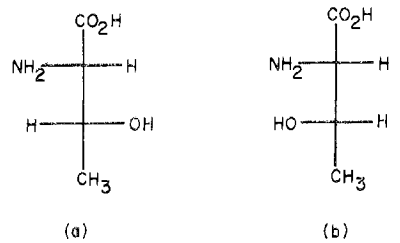


Figure 1. (a) (*S*)-Threonine (*S*-thr); (b) (*S*)-allothreonine (*S*-allo); *S* refers to the absolute configuration of the α-carbon atom.

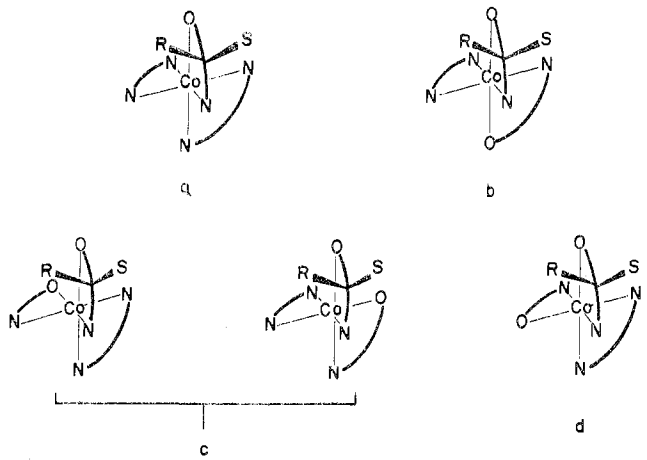


Figure 2. (a) Λ(+)-[Co(en)$_2$(gly)]$^{2+}$; (b) Λ(+)-*trans*(*O*)-[Co(en)-(gly)$_2$]$^+$; (c) Λ-β-*cis*(*O*)-[Co(en)(gly)$_2$]$^+$; (d) Λ(+)-α-*cis*(*O*)-[Co(en)-(gly)$_2$]$^+$; where gly is $NH_2CH_2CO_2^-$, N–O, and en is $NH_2CH_2CH_2$-NH_2, N–N. In each case the *R* and *S* "sides" of the coordinated glycine molecule are shown. The β-cis(O) isomer has nonequivalent glycine molecules.

complexes have been previously reported.[6,7] Part of the following is a modification of the method of Matsuoka, *et al.*[6,7] To 80 ml of 10 *N* NaOH was added 46.0 g (0.163 mol) of [CoCl(gly)H$_2$O(en)]Cl and 60.0 g (0.810 mol) of glycine. Two hundred milliliters of water was added and the solution stirred for 3 days at room temperature. The solution was concentrated to 200 ml in a stream of air and cooled in an ice bath, and the pH of the dark red solution adjusted to 7 by careful addition of concentrated perchloric acid. Upon standing of the mixture in a refrigerator for 1 hr, 15 g of the crude dark red trans(O) isomer precipitated and was removed by filtration. Addition of 50 ml of methanol to the filtrate and refrigeration for 10 hr yielded 18.3 g of a pink precipitate containing principally the β-cis(O) isomer.

The crude trans(O) precipitate was washed with several 50-ml portions of a 3:1 water–ethanol solution, dissolved in water, and converted to the chloride salt by passing the solution through a Dowex 1-X8 anion-exchange resin. The yield of *trans*(*O*)-[Co(en)(gly)$_2$]-Cl·2H$_2$O was 11 g.

A 6.0-g portion of the impure β-cis(O) isomer was separated from small amounts of the trans(O) and α-cis(O) isomers using Dowex 50W-X8 cation-exchange resin and eluting with 0.3 *N* NaClO$_4$. The eluting agent was removed from the pure β-cis(O) isomer by washing with absolute ethanol. As with the trans(O) isomer the perchlorate salt was converted to the chloride salt using an anion-exchange resin. The yield of β-*cis*(*O*)-[Co(en)(gly)$_2$]Cl·H$_2$O was 3 g.

The visible absorption and pmr spectra of both complexes were identical with those previously reported.[7] Pmr (D$_2$O, DSS): *trans*(*O*)-[Co(en)(gly)$_2$]$^+$, δ 2.64 (s, 4 H, CH_2CH_2), 3.61 (s, 4 H, gly CH_2); β-*cis*(*O*)-[Co(en)(gly)$_2$]$^+$, δ 2.72, 2.86 (m, 4 H, CH_2CH_2), 3.44 s, 3.61 s (4 H, gly CH_2).

α-*cis*(*O*)-[Co(en)(gly)$_2$]Cl. Since only a trace of this isomer was detected in the above approach, the reaction scheme was modified. The preparation of the trans(O) and β-cis(O), isomers was repeated, but after adjustment of the pH to 7, the solution was refrigerated for 10 hr yielding 30.2 g of the mixed isomers. This mixture was triturated with 47 g (0.63 mol) of KCl and 200 ml of water and the KClO$_4$ which formed was collected by filtration and washed with two 5-ml portions of ice water. After combining the washings with the filtrate, 5.0 g of activated charcoal was added and the suspension was stirred at room temperature for 15 min. All traces of the charcoal were removed using filter aid. The red filtrate was triturated with 142 g (0.63 mol) of AgClO$_4$·H$_2$O for 2 min and immediately filtered to remove the silver halide and a small amount of the sparingly soluble trans(O) perchlorate. This isomer was recovered from the silver salt by washing with 500 ml of water. The volume was reduced to 100 ml by evaporation at reduced pressure at 40° and then placed in an ice bath for 1 hr. About 15 g of the trans(O) and β-cis(O) isomers was recovered from the dark red solution. The α-cis(O) isomer was isolated using a Dowex 50W-X8 cation-exchange resin in the sodium form and eluting with 0.3 *N* NaClO$_4$. The work-up was the same as that used for the β-cis(O) isomer. This procedure was repeated three times until a sufficient quantity of material was available for resolution.

The visible absorption and pmr data were identical with those reported earlier for this complex.[7] Pmr (D$_2$O, DSS): δ 2.62 (s, 4 H, CH_2CH_2), 3.53 (s, 4 H, gly CH_2).

(+)- and (−)-*trans*(*O*)-[Co(en)(gly)$_2$]X·H$_2$O, Where X$^-$ = I$^-$, Cl$^-$. To a flask shielded from the light, containing a suspension of 2.21 g (0.015 mol) of *d*-tartaric acid and 5.35 g (0.015 mol) of silver *d*-tartrate[8] in 140 ml of water, was added 100 ml of a solution containing 9.35 g (0.039 mol) of racemic *trans*(*O*)-[Co(en)-(gly)$_2$]Cl·2H$_2$O. After stirring of the mixture for 30 min, the silver chloride was removed by filtration and washed once with 10 ml of water, and the volume of the filtrate and washings was reduced under vacuum at 40° to 80 ml. Slow evaporation in the air produced 2.2 g of the impure (+) disastereoisomer. The material was washed once with 5 ml of ice water and then recrystallized from about 20 ml of water taking care so as not to heat above 40°; yield 0.96 g; [M]$_D$ +3430°. Further recrystallization did not change the rotation.

After recovery of the (+) diastereoisomer, the volume was reduced to 40 ml under a stream of air to yield 1.35 g of the impure (−) diastereoisomer. The yield after recrystallization was 0.60 g; [M]$_D$ −3270°.

The (+) diastereoisomer, 0.96 g, was ground in a mortar with 10 ml of water. After addition of 1.7 g of sodium iodide the mixture was triturated for 2 min. The iodide salt of the complex was removed by filtration and washed once with 3 ml each of water, ethanol and finally acetone; the yield of (+)-*trans*(*O*)-[Co(en)(gly)$_2$]I·H$_2$O was 0.65 g. *Anal.* Calcd for [CoC$_6$H$_{16}$O$_4$N$_4$]I·H$_2$O: C, 17.49; H, 4.40; N, 13.60. Found: C, 17.58; H, 4.69; N, 13.49.

The (−) diastereoisomer was similarly converted to the iodide salt using 6 ml of water and 1.1 g of sodium iodide; the yield of (−)-*trans*(*O*)-[Co(en)(gly)$_2$]I·H$_2$O was 0.40 g.

The (+) iodide was suspended in 30 ml of water and converted to the chloride salt by addition of 1.2 g of freshly prepared silver chloride. A check of the rotation of the isolated chloride gave a value identical with that of the iodide salt.

(+)- and (−)-β-*cis*(*O*)-[Co(en)(gly)$_2$]X·2H$_2$O Where X$^-$ = I$^-$, Cl$^-$. The resolution was done in a manner identical with that for the trans(O) isomer on 4.76 g of β-*cis*(*O*)-[Co(en)(gly)$_2$]Cl·H$_2$O. The (+) diastereoisomer ([M]$_{470}$ +5000°) was crystallized first and after conversion to the iodide salt yielded 0.50 g of (+)-β-*cis*(*O*)-[Co-(en)(gly)$_2$]I·2H$_2$O. *Anal.* Calcd for [CoC$_6$H$_{16}$O$_4$N$_4$]I·2H$_2$O: C, 16.76; H, 4.69; N, 12.89. Found: C, 16.42; H, 4.68; N, 12.89.

The rotation of the (−) diastereoisomer was [M]$_{470}$ +5850°; the yield was 0.40 g as the iodide salt.

(+)- and (−)-α-*cis*(*O*)-[Co(en)(gly)$_2$]Cl·H$_2$O. A solution of the complex, 4.44 g (0.139 mol) in 100 ml of water, was added dropwise to 5.45 g (0.139 mol) of silver antimonyl *d*-tartrate[9] which was suspended in 250 ml of water in a darkened flask. The silver chloride which was formed was removed by filtration and the red solution condensed under a stream of air to 70 ml followed by the addition of 40 ml of absolute ethanol. After the mixture stood in the refrigerator (5–10°) for several days, a very hard red tar formed which was coated with 2.0 g of the nearly pure (+) isomer. The compound was removed from the tar and purified by heating momentarily at 30° in about 20 ml of water. After cooling and slow evaporation under a stream of air, crystallization occurred. After two crystallizations the rotation did not change; [M]$_{480}$ −10,400°. The yield was 1.01 g.

The (+) diastereoisomer was converted to the chloride salt by suspending it in 11 ml of water and slowly adding concentrated hydrochloric acid until the initially formed SbOCl dissolved. An equal volume of water was added, the SbOCl was removed, and the filtrate was evaporated to dryness at reduced pressure at 30°. The red material was purified by dissolving in 5 ml of water and adding acetone

until precipitation occurred. The procedure was repeated twice to yield 0.50 g of (+)-α-*cis*(*O*)-[Co(en)(gly)$_2$]Cl·H$_2$O. *Anal.* Calcd for [CoC$_6$H$_{16}$O$_4$N$_4$]Cl·H$_2$O: C, 22.47; H, 5.66; N, 17.47. Found: C, 22.47; H, 5.37; N, 17.54.

All efforts to isolate the (−) isomer from the red tar failed, and silver antimony *l*-tartrate[9] was synthesized and used as the resolving agent. Thus, the red tar, $[M]_{480}$ +1770°, was dissolved in 50 ml of water and converted to the chloride salt by passage through a column containing Dowex 1-X8 resin in the chloride form. Isolation and purification for the (−) isomer as the antimonyl *l*-tartrate was the same as before. The yield was 0.77 g as the chloride salt.

(+)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]Cl·H$_2$O and (−)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]I, Where *S*-thr is the (*S*)-Threonine Anion. The procedure described for the preparation of the trans(O) and β-cis(O) glycine analogs was followed by treating (*S*)-threonine with [CoCl(gly)H$_2$O(en)]Cl. Potassium hydroxide was used as the base and a fivefold molar excess of the amino acid was employed instead of an eightfold one. The pH of the resulting solution did not exceed 9.0. In attempting to precipitate the desired complexes from the reaction mixture as their perchlorate salts, only a cream white solid was obtained (possibly KClO$_4$). This material was removed by filtration and the filtrate placed on a column containing Dowex 50W-X8 resin in the H$^+$ form. Because of the large concentration of other ions present, the positively charged cobalt complexes did not form a tight band at the top of the resin but streaked badly making it impossible to do an effective separation of the desired compounds. Upon elution with 0.5 *N* HCl, the amino acid complexes which carried a 1+ charge and had oxygen atoms in the trans position easily separated from their cis-oxygen counterparts and from compounds having higher positive charge. The acidic solution containing the trans(O) isomers was collected and evaporated to dryness at reduced pressure (40°). The residue was dissolved in 75 ml of water and KCl was removed by the dropwise addition of a 3.0 *N* AgClO$_4$ solution to the chilled (0–5°) deep red liquid until precipitation ceased. After removal of the AgCl and KClO$_4$ by filtration, a careful separation was performed on the filtrate using Dowex 50W-X8 ion-exchange resin in the H$^+$ form and eluting with 0.3 *N* HCl. After 40–50 days of slow eluting, four bands were clearly visible. The third band from the bottom of the column, which was the broadest and most intense, contained the two glycinato-*S*-threoninato compounds. Using a fraction collector, 322 15-ml fractions were collected and several tubes checked for optical purity by recording the ratios of the observed rotation at 480 mμ to the optical absorbance at 530 mμ. The more soluble (+)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]$^+$ cation eluted first. After evaporation to dryness, the crude (+) diastereoisomer was redissolved in water and converted to the iodide salt by passing it over Dowex 1-X8 anion-exchange resin in the iodide form. Evaporation as before and crystallization from about 20 ml of water afforded 1.2 g of the diastereoisomer. *Anal.* Calcd for [CoC$_8$H$_{20}$O$_4$N$_4$]I: C, 21.90; H, 5.02; N, 12.80. Found: C, 21.90; H, 5.41; N, 13.31.

Recovery and purification of the less soluble (−) diastereoisomer were as before but conversion to the iodide salt was unnecessary. The yield was 0.7 g. *Anal.* Calcd for [CoC$_8$H$_{20}$O$_4$N$_4$]Cl·H$_2$O: C, 26.30; H, 6.04; N, 15.39. Found: C, 26.15; H, 6.15; N, 15.35.

The visible absorption spectra and absolute configurations of these two cations were found to be identical with those which have been previously reported.[10] Pmr (D$_2$O, DSS): (+)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]$^+$, δ 1.47 (d, J = 7.0 Hz, 3 H, CH$_3$), 2.89 (s, CH$_2$CH$_2$), 3.63 (d, 2 H, gly CH$_2$), 3.63 (d, 1 H, thr α-CH), 4.38 (m, 1 H, thr β-CH); (−)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]$^+$, δ 1.44 (d, 7.0 Hz, 3 H, CH$_3$), 2.87 (s, 4 H, CH$_2$CH$_2$), 3.64 (d, 2 H, gly CH$_2$), 3.75 (d, 1 H, thr α-CH), 4.37 (m, 1 H, thr β-CH).

(+)- and (−)-[Co(en)$_2$(gly)]Cl$_2$. This complex was prepared and resolved according to the procedure described by Liu and Douglas.[11] *Anal.* Calcd for (+)-[CoC$_6$H$_{20}$O$_2$N$_5$]Cl$_2$: C, 22.30; H, 6.18; N, 21.70. Found: C, 22.47; H, 6.32; N, 22.00. The visible absorption and circular dichroism spectra agree with those previously reported.[11]

Reactions of the Complexes with Acetaldehyde. All of the condensation reactions were carried out under nitrogen gas using a pH-Stat.

To 10 ml of doubly distilled, degassed water was added 0.3 mmol of the optically active complex and the temperature of the resulting solution adjusted to 25 ± 0.5°. After addition of 1.0 ml of an aqueous solution containing the aldehyde, the pH was automatically adjusted to a constant value by the addition of 0.08 *N* carbon dioxide free NaOH. Reaction termination was accomplished by the addition of 1 drop of concentrated acetic acid. The solvent and the unreacted aldehyde were removed under vacuum (30°) and the residue was redissolved in 40 ml of water. A 1-ml portion of this solution was reserved for determining the mole per cent of glycine reacted using glc methods.[12,13] The cobalt(III) complexes present in the remaining 39 ml of solution were destroyed by acidifying with 2 drops of concentrated acetic acid and purging with H$_2$S gas for 10 min. Addition of 5 drops of concentrated aqueous NH$_3$ caused the immediate precipitation of CoS. The sulfide was removed by filtration using filter aid and washed twice with 2-ml portions of water, and the clear or very light brown filtrate was evaporated to dryness at water aspirator pressure (50°). The residue was taken up in 3–5 ml of water and the solution was placed on a small chromatography column containing 10–12 ml of Dowex 1-X8 resin in the OH$^-$ form. After washing with 30 ml of water to remove the ethylenediamine, the amino acids were released from the resin by addition of 50 ml of 1.0 *N* HCl. The acidic solution was evaporated to dryness at reduced pressure (50°) leaving a mixture of amino acid hydrochloride salts which was analyzed for the optical isomers of threonine and allothreonine using glc.[14]

The 1.0-ml portion described above containing a small amount of product complexes was placed in a 3.0-ml centrifuge tube and the complexes were destroyed with H$_2$S as before. After centrifuging, the supernatant liquid was removed and evaporated to dryness by heating (100°) under a stream of N$_2$ gas. The residue containing ethylenediamine and the amino acids was analyzed for the relative amounts of glycine, threonine, and allothreonine using glc.[12,13]

Except for the β-cis(O) isomer where only one reaction was carried out, the amino acid distribution reported is based on two duplicate reactions (each an average of three chromatograms) on each complex. In the case of the *trans*(*O*)-[Co(en)(gly)$_2$]$^+$ cation, reactions were carried out on both the (+) and (−) isomers, and within experimental error enantiomeric amino acid distributions were obtained. The error in each of the relative mole per cent values of the four amino acids forms (*S*)- and (*R*)-threonine and (*S*)- and (*R*)-allothreonine was about ±5%.

In case of the *trans*(*O*)-[Co(en)(gly)$_2$]Cl complex the monocondensation product complexes could be cleanly separated from the other possible products using ion-exchange chromatography. After termination of the reaction, the acidified reaction mixture was separated using a Dowex 50W-X8 cation-exchange resin in the H$^+$ form. Eluting for 5 days with 0.1 *N* HCl yielded four separate bands. Visible absorption spectra of the intact complexes and glc analysis of the ligands established that the first and second bands (fastest moving) contained the four diastereomeric monocondensation products, *trans*(*O*)-[Co(en)(thr or allo)(gly)]$^+$. The third broad band was composed of the dicondensation products, *trans*(*O*)-[Co(en)(thr or allo)$_2$]$^+$, while the fourth band correspond to the unreacted *trans*-(*O*)-[Co(en)(gly)$_2$]$^+$ cation.

Results and Discussion

Absolute Configuration of the Complexes. Circular dichroism (CD) forms the basis for the assignment of absolute configuration of all of the complexes shown in Figure 2. The visible absorption and CD data for the optically active bis(glycinato) complexes are given in Table I.

The (+)-*trans*(*O*)-[Co(en)(gly)$_2$]$^+$ cation is assumed to have pseudo-D_{4h} symmetry, Dq(O) < Dq(N), with the $^1A_{1g} \rightarrow {}^1E_g$ transition most probably occurring at 18.3 kK.[15] Using the same approach as Mason, *et al.*,[16] the positive CD absorption (+1.98) for this transition suggests that the (+)-*trans*(*O*)-[Co(en)(gly)$_2$]$^+$ ion can be related to (+)-[Co(en)$_3$]$^{3+}$ which has the Λ absolute configuration. The same configuration has been assigned to (+)-*trans*-[Co(*l*-pn)(gly)$_2$]$^+$.[17] Pmr arguments based on the diastereomeric *trans*(*O*)-[Co(en)(AA)$_2$]$^+$ and *trans*(*O*)-[Co(en)(AA)(gly)]$^+$ complexes, where AA is an optically active amino acid, further support the absolute configuration assignment.[10]

Arguments involving lower symmetry should apply to the β-cis(O) and α-cis(O) isomers. However, the visible spectra and CD absorptions for these two isomers show little splitting. Only the α-cis(O) isomer has more than one CD absorption in the $T_{1g}(O_h)$ transition region. Similar CD patterns were found for (+)-[Co(en)$_2$(CO)$_3$]$^+$ and (+)-[Co(en)$_2$(C$_2$O$_4$)]$^+$

Table I. Electronic Absorption and Circular Dichroism Data for the $[Co(en)(gly)_2]^+$ Cations[a]

Complex	Absorption[b]	CD[c]
Λ(+)-*trans*(*O*)-$[Co(en)(gly)_2]I\cdot H_2O$	18.8 (90), 22.2 sh (45), 27.9 (135)	18.3 (+1.98) 21.5 (+0.66) 27.8 (−0.41)
Λ(+)-β-*cis*(*O*)-$[Co(en)(gly)_2]I\cdot 2H_2O$	19.9 (125), 27.9 (138)	19.0 (+1.92) 25.7 (+0.08) 27.8 (−0.11) 30.4 (+0.14)
Λ(+)-α-*cis*(*O*)-$[Co(en)(gly)_2]Cl\cdot H_2O$	19.9 (106), 27.9 (142)	19.5 (+2.90) 22.5 (−0.30) 27.4 (−0.07) 30.2 (+0.10)

[a] Data were measured in aqueous solutions at approximately 10^{-2} *M*. [b] The band position is given in kK followed by the molar extinction coefficient. [c] The CD band position is given in kK followed by $(\epsilon_l - \epsilon_r)$.

which were assigned the Λ absolute configuration.[16] On the basis of the sign of the dominant CD band for the $T_{1g}(O_h)$ transition region we have assigned the Λ configuration to (+)-β-*cis*(*O*)-$[Co(en)(gly)_2]^+$ and (+)-α-*cis*(*O*)-$[Co(en)(gly)_2]^+$.

Liu and Douglas[11] resolved and assigned the Λ configuration to the $(-)_{546}$-$[Co(en)_2(gly)]^{2+}$ cation. This assignment was later amended[18] on the grounds that the dominant CD peak for this complex should be related to the ^1E_a transition of $[Co(en)_3]^{3+}$ and not the $^1A_2$ transition. Using pseudo-D_3 symmetry the correct assignment of $(+)_D$-$[Co(en)_2(gly)]^{2+}$ is Λ. The configuration of all of the cations used in this study is shown in Figure 2.

Reaction Conditions. The reaction conditions used for the condensation of the aldehyde with the metal complexes were carefully controlled. It became apparent that the maximum amount of stereochemical information could be gained by considering at least four important points.

Of prime importance to the stereochemical analysis was the stability of the optically active complexes in the basic reaction medium. Maintaining the integrity of the optically active templates during the course of the reaction was essential to maximizing the optical purity of the products. All of the cations studied were stable in basic media (no detectable racemization or decomposition at pH 11.0) for periods up to 12 hr. These conditions proved to be more severe than those actually used for the condensation reactions.

In order to compare the product distribution obtained from (+)-$[Co(en)_2(gly)]^{2+}$ with the three isomers of $[Co(en)(gly)_2]^+$, it was desirable to synthesize only the monocondensation products of the latter. Following the stereochemical course of the reaction by analyzing a mixture of mono- and discondensation products would be unnecessarily complicated. The steric effects exerted by coordinated threonine or allothreonine on a second molecule of attacking aldehyde would be difficult to predict.

In a series of trial reactions in which the pH and aldehyde to complex ratio were varied, the order of reactivity of the cations was established. The complexes were found to react with the aldehyde in the order (+)-$[Co(en)_2(gly)]^{2+}$ > (+)-*trans*(*O*)-$[Co(en)(gly)_2]^+$ > (+)-β-*cis*(*O*)-$[Co(en)(gly)_2]^+$ > (+)-α-*cis*(*O*)-$[Co(en)(gly)_2]^+$. The 1+ cation with the fastest reaction rate, *trans*(*O*)-$[Co(en)(gly)_2]^+$, proved to be very useful in establishing the optimum reaction conditions for the formation of only monocondensation products.

The product complexes from a series of aldehyde condensation reactions involving the trans(O) cation were isolated using ion-exchange chromatography. This technique allowed the separation of the mixture into the two types of condensation products. Separate bands were observed for the monocondensation products (two bands, four isomers), dicondensation products (one broad band, ten isomers), and the unreacted trans(O) cation. Amino acid analysis of the destroyed complexes[12,13] provided a means of identifying the composition of the bands. The conditions ultimately chosen for the reaction were found by maximizing the amount of monocondensation products synthesized and at the same time preventing the formation of any detectable amount of dicondensation products. This occurred at pH 9.5 (25°) with an aldehyde to complex ratio of 1:1. In a period of 3 hr, 12% of the coordinated glycine in *trans*(*O*)-$[Co(en)(gly)_2]^+$ reacted to form threonine and allothreonine.

Using the same conditions established for the trans(O) isomer, the cis(O) isomers reacted with the aldehyde at a slow rate. The slowest to react, α-cis(O), yielded only a trace (1–2% reacted glycine) amount of product. Attempts to improve the yield obtained from this complex by lengthening the reaction time led to a geometric isomerization. Ion-exchange separation of the complexes formed over 12–24-hr reaction periods showed that the trans(O) (visible absorption 18.8 and 22.2 kK) and possibly β-cis(O) (extinction coefficients of the d–d bands) geometries were present. The fact that the α-cis(O) complex was stable to racemization and isomerization in basic media in the absence of the aldehyde suggests that monocondensation products themselves are unstable. The products from extended reaction times are being further investigated.

A third important factor was the possibility of racemization about the α center of the coordinated threonine and allothreonine. The lability of the methylene or methine protons of coordinated amino acids in basic media appears to be general.[19] Sargeson, *et al.*,[20] have shown that the α asymmetric center in certain cobalt(III)–(*S*)-alanine and –(*S*)-valine complexes is susceptible to racemization in basic media. As a check on the importance of this factor in the condensation reaction, the stability of two of the four possible trans(O) monocondensation products was studied.

The reaction of the aldehyde with Λ(+)-*trans*(*O*)-$[Co(en)(gly)_2]^+$ produces four diastereoisomeric complexes: Λ(+)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]$^+$, Λ(+)-*trans*(*O*)-[Co(en)(*R*-thr)(gly)]$^+$, Λ(+)-*trans*(*O*)-[Co(en)(*S*-allo)(gly)]$^+$, and Λ(+)-*trans*(*O*)-[Co(en)(*R*-allo)(gly)]$^+$. Two of these complexes Λ(+)- and Δ(−)-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]$^+$, the latter being enantiomeric to Λ(+)-*trans*(*O*)-[Co(en)(*R*-thr)(gly)], were synthesized from optically pure (*S*)-threonine and separated using ion-exchange chromatography. At pH 9.5 (3.0 hr) no change in the stereochemistry about the α center was detected. Inversion about this asymmetric center leads to formation of allothreonine (epimerization) which would have been easily detected using glc.[12–14] Although not synthesized and examined directly, the (+)- and (−)-*trans*(*O*)-[Co(en)(*S*-allo)(gly)]$^+$ cations are very likely stable to inversion under the same conditions also.

The possibility of epimerization of the four $[Co(en)_2$(thr or allo)$]^{2+}$ complexes was discounted by consideration of the α-proton exchange rate[20] of (−)-$[Co(en)_2(S\text{-ala})]^{2+}$. The initial step in the racemization process is the deprotonation of the asymmetric carbon atom. Assuming a close similarity between the 2+ cations formed in the condensation reaction and (−)-$[Co(en)_2(S\text{-ala})]^{2+}$, the $t_{1/2}$ based on pseudo-first-order kinetics is about 100 hr at pH 9.5. The rate of epimerization at this pH should be very slow and is assumed not to affect the product analysis.

Finally, the reaction was carried out at constant pH in the absence of a buffer system. Mason, *et al.*,[21] have given evidence that highly charged anions of the kind normally found in buffers (CO_3^{2-}, PO_4^{3-}) can form outer-sphere complexes with certain cobalt(III) complexes. The presence of such outer-sphere structures in the aldehyde condensation reaction may have an effect on the stereochemical course of the reaction

Table II. Product Distribution from the Reaction of Acetaldehyde with Some Optically Active Glycine Complexes

Complex	% threonine[a]	% allothreonine[a]	% glycine reacted	Temp (°C), pH	Ref
$\Lambda(+)$-$[Co(en)_2(gly)]^{2+}$	26 (16, *S*)	74 (35, *S*)	12	25, 9.5	This work
$\Lambda(+)$-$[Co(en)_2(gly)]^{2+}$ [c]	78 (8, *S*)	22	90	RT,[b] 11[d]	5
$\Lambda(+)$-*trans*(*O*)-$[Co(en)(gly)_2]^+$	33 (33, *S*)	67 (31, *S*)	11	25, 9.5	This work
$\Lambda(+)$-*β*-*cis*(*O*)-$[Co(en)(gly)_2]^+$	28 (21, *S*)	72 (28, *S*)	6	25, 9.5	This work
$\Lambda(+)$-*α*-*cis*(*O*)-$[Co(en)(gly)_2]^+$	36[e]	64[e]	1-2	25, 9.5	This work
$[Co(l\text{-pn})_2(gly)]^{2+}$ [f]	69 (1, *S*)	31	95	RT, 11[d]	5

[a] The per cent amino acid found is given, followed by the per cent asymmetric yield, $|S-R/S+R| \times 10^2$, and the configuration of the enantiomer in excess. [b] RT is room temperature. [c] This work treats the reaction of $\Delta(-)$-$[Co(en)_2(gly)]^{2+}$ with aldehyde. The data in the table have been adjusted to correspond to the products from the $\Lambda(+)$ isomer. [d] pH not specified in the original work. The value in the table has been measured from solutions identical with those described in ref 5. [e] Insufficient sample available for the analysis of the optical isomers of threonine and allothreonine. [f] Optically active but the isomer used in the reaction was not specified.

which would be difficult to assess.

Stereochemical Analysis of the Products. Table II shows that using relatively mild conditions substantial amounts of asymmetric synthesis can be achieved. The three complexes for which the per cent asymmetric synthesis was determined show that changes in geometry (Figure 2) have little effect on the product distribution. Similar asymmetric yields and product distributions were obtained for all of the compounds.

Since the reaction conditions did not allow the racemization of the α center of the coordinated amino acid (epimerization), the stereochemistries of the products reflect the direction of the attacking aldehyde. The data in Table II show that the direction of attack of the aldehyde is probably not influenced by changes in the local environment of the coordinated glycine molecule. In every case an excess of the *S* amino acid was produced. Figure 2 shows that the glycine molecules in $\Lambda(+)$-$[Co(en)_2(gly)]^{2+}$ and $\Lambda(+)$-*trans*(*O*)-$[Co(en)(gly)_2]^+$ have primary amine functions as near-neighbor donor groups. The *β*-cis(O) geometry, on the other hand, contains two nonequivalent glycine molecules each of which has different donor atoms as near neighbors ($-NH_2$, $-NH_2$ *vs.* $-NH_2$, $-CO_2^-$). Presumably both molecules of glycine in the *β*-cis(O) compound react with the aldehyde but the distribution of products from this complex is essentially the same as that produced from $\Lambda(+)$-$[Co(en)_2(gly)]^{2+}$ and Λ-*trans*(*O*)-$[Co(en)(gly)_2]^+$. The complex $\Lambda(+)$-*α*-*cis*(*O*)-$[Co(en)(gly)_2]^+$ should provide the most effective test of this type of near-neighbor effect but unfortunately the reaction with aldehyde was very slow (1–2% glycine reacted). Without significantly modifying the glc analytical procedure[14] a quantitative analysis of the isomer distribution was not possible. However, one glc technique[13] did permit the determination of the relative amounts of the two distereomers. Values similar to those of the other three isomers were found.

The product distribution for the aldehyde condensation with $\Lambda(+)$-$[Co(en)_2(gly)]^{2+}$ at pH 9.5 contrasts markedly with that reported by Matsuoka, *et al.*[6] The reason for the low optical purity (1–8%) and the different product distribution observed (threonine:allothreonine = 2:1) in the earlier work is not clear. However, the possibility of racemization (epimerization) of optically active products cannot be discounted. The effect of pH, reaction time, and temperature on the product distribution is being investigated.

Finally, the ability of the aldehyde to recognize the ring system of three of the complexes in the same way reinforces the assignments of absolute configuration. However, the utility of this reaction as a means of assigning the absolute configuration of other glycine-containing systems should await a thorough dilineation of the aldehyde recognization process.

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Registry No. $\Lambda(+)$-*trans*(*O*)-$[Co(en)(gly)_2]I$, 54003-40-6; $\Delta(-)$-*trans*(*O*)-$[Co(en)(gly)_2]I$, 54053-69-9; $\Lambda(+)$-*β*-*cis*(*O*)-$[Co(en)(gly)_2]I$, 54003-41-7; $\Delta(-)$-*β*-*cis*(*O*)-$[Co(en)(gly)_2]I$, 54053-70-2; $\Lambda(+)$-*α*-*cis*(*O*)-$[Co(en)(gly)_2]Cl$, 54053-71-3; $\Delta(-)$-*α*-*cis*(*O*)-$[Co(en)(gly)_2]Cl$, 54053-72-4; $\Lambda(+)$-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]I, 54003-42-8; $\Delta(-)$-*trans*(*O*)-[Co(en)(*S*-thr)(gly)]Cl, 54036-72-5; $[CoCl(gly)H_2O(en)]Cl$, 15559-96-3; glycine, 56-40-6; acetaldehyde, 75-07-0; $\Lambda(+)$-$[Co(en)_2(gly)]Cl_2$, 54003-28-0; $\Lambda(+)$-*trans*(*O*)-$[Co(en)(gly)_2]$(*d*-tartrate), 54003-30-4; $\Delta(-)$-*trans*(*O*)-$[Co(en)(gly)_2]$(*d*-tartrate), 54053-66-6; $\Lambda(+)$-*α*-*cis*(*O*)-$[Co(en)(gly)_2]$(antimonyl *d*-tartrate), 54053-68-8.

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