Asymmetric Synthesis of Alanine using Cobalt(III) Complexes of (3*R*)-3-Methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane and (3*S*)-3-Methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane

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Upon decarboxylation Λ-*cis*-β-$[CoL^1(amm)]^{2+}$ yielded Λ-*cis*-β-$[CoL^1(R\text{-alaO})]^{2+}$, while Δ-*cis*-β-$[CoL^2(amm)]^{2+}$ gave Δ-*cis*-β-$[CoL^2(S\text{-alaO})]^{2+}$; where L¹ = (3*R*)-3-methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane, L² = (3*S*)-3-methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane, amm = α-amino-α-methylmalonate and alaO = alaninate. The asymmetrically synthesized alanines were isolated but with extensive racemization *via* the decomposition of the decarboxylated complexes.

An asymmetric synthesis of alanine was accomplished by Asperger and Liu [1] using a dissymmetric cobalt(III) complex and α-amino-α-methylmalonate (amm) as the precursor of alanine. The ligands, (3*R*)-3-methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane (L¹) and (3*S*)-3-methyl-1,6-bis[(2*S*)-pyrrolidin-2-yl]-2,5-diazahexane (L²), were shown to be highly stereoselective and yielded, respectively, Λ-*cis*-β-$[CoL^1Cl_2]^+$ and Δ-*cis*-β-$[CoL^2Cl_2]^+$ in the *cis* geometry,[2] which have been used in this work in an attempted asymmetric synthesis of alanine.

Experimental

Λ-cis-β-$[CoL^1(amm)]Cl_2{\cdot}H_2O$.—A solution of Λ-*cis*-β-$[CoL^1Cl_2]ClO_4$ (1.58 g) [2] in water (15 cm³) was heated on a steam-bath for 30 min and then cooled to room temperature. The compound NH_4(amm) (0.39 g) [2] dissolved in water (30 cm³) was added and the resultant solution was heated at 80 °C for 5 h. It was cooled to room temperature and evaporated under a stream of air until crystals separated. The red product was filtered off and recrystallized from water and ethanol (Found: C, 39.15; H, 7.35; Cl, 13.65; N, 13.40. $C_{17}H_{36}Cl_2CoN_5O_4{\cdot}H_2O$ requires C, 39.10; H, 7.35; Cl, 13.55; N, 13.40%).

Δ-cis-β-$[CoL^2(amm)]Cl_2{\cdot}H_2O$.—This was prepared *via* the same method described above using Δ-*cis*-β-$[CoL^2Cl_2]ClO_4{\cdot}0.5H_2O$ [2] (Found: C, 39.00; H, 7.30; Cl, 13.50; N, 13.45. $C_{17}H_{36}Cl_2CoN_5O_4{\cdot}H_2O$ requires C, 39.10; H, 7.35; Cl, 13.55; N, 13.40%).

Λ-cis-β-$[CoL^1(alaO)]Cl_2{\cdot}H_2O$.—The complex Λ-*cis*-β-$[CoL^1(amm)]Cl_2{\cdot}H_2O$ (0.71 g) was dissolved in water (15 cm³). The pH was adjusted to 7.5 using dilute LiOH and the solution heated at boiling for 15 min. It was cooled to room temperature and the solution was evaporated to dryness under a stream of air. The product was recrystallized from water and ethanol (Found: C, 39.95; H, 7.55; N, 14.60. $C_{16}H_{34}Cl_2CoN_5O_2{\cdot}H_2O$ requires C, 40.35; H, 7.60; N, 14.70%).

Δ-cis-β-$[CoL^2(alaO)]Cl_2{\cdot}H_2O$.—This was obtained from the same method described above using Δ-*cis*-β-$[CoL^2(amm)]Cl_2{\cdot}H_2O$ (Found: C, 40.30; H, 7.50; N, 14.60. $C_{16}H_{34}Cl_2CoN_5O_2{\cdot}H_2O$ requires C, 40.35; H, 7.60; N, 14.70%).

Separation of Alanine from Λ-cis-β-$[CoL^1(alaO)]Cl_2{\cdot}H_2O$.—To a solution of Λ-*cis*-β-$[CoL^1(alaO)]Cl_2{\cdot}H_2O$ (2.5 g) in water (30 cm³) an excess of sodium sulphide was added and the solution warmed at 50 °C in an oil-bath for 20 min. The solution rapidly turned dark brown. A saturated solution of $CoCl_2{\cdot}6H_2O$ (1.26 g) was slowly added to the solution with stirring. The precipitate formed was separated out, the solution acidified with HCl, and air was bubbled through for 30 min. The solution was passed through a Dowex 21K (20—50 mesh) resin in the chloride form which was then washed with water (2 dm³); 2 mol dm⁻³ HCl was used to elute the alanine. Upon evaporation to dryness the alanine was isolated and recrystallized from water and acetone. Yield: 0.196 g (42%). The optical rotation of the alanine measured with 2 mol dm⁻³ HCl was $\alpha_{obs.}$(HCl, 295 K, 589 nm) −0.036°; $\alpha_m = -3.0°\ cm^3\ dm^{-1}\ g^{-1}$ {$\alpha_m = -15.1°\ cm^3\ dm^{-1}\ g^{-1}$ for pure *R*-alanine measured with 2 mol dm⁻³ HCl} (Found: C, 28.65; H, 6.50; N,11.20. $C_3H_7NO_2{\cdot}$ HCl requires C, 28.70; H, 6.40; N, 11.15%).

Separation of Alanine from Δ-cis-β-$[CoL^2(alaO)]Cl_2{\cdot}H_2O$.—This was accomplished following the same method described above using Δ-*cis*-β-$[CoL^1(alaO)]Cl_2{\cdot}H_2O$. Yield: 0.23 g (48%) (Found: C, 28.60; H, 6.40; N, 11.15. $C_3H_7NO_2{\cdot}$HCl requires C, 28.70; H, 6.40; N, 11.15%). The optical rotation of the alanine measured with 2 mol dm⁻³ HCl was $\alpha_{obs.}$(HCl, 295 K, 589 nm) +0.028°; $\alpha_m = +2.8$ {$\alpha_m = +15.1°\ cm^3\ dm^{-1}\ g^{-1}$ for pure *S*-alanine}.

Λ-cis-β-$[CoL^1(R\text{-alaO})]Cl_2{\cdot}H_2O$.—The complex Λ-*cis*-β-$[CoL^1Cl_2]ClO_4$ (0.864 g) was dissolved in water (10 cm³) and heated on a steam-bath for 30 min. After cooling *R*-alanine (0.164 g) was added to the solution. The pH of the solution was adjusted to 8.0 with a LiOH solution and then heated on a steam-bath for 25 min. The solution was cooled and evaporated to dryness under a stream of air. The precipitate was washed with acetone. The product was recrystallized from water and ethanol (Found: C, 40.25; H, 7.70; N, 14.65,

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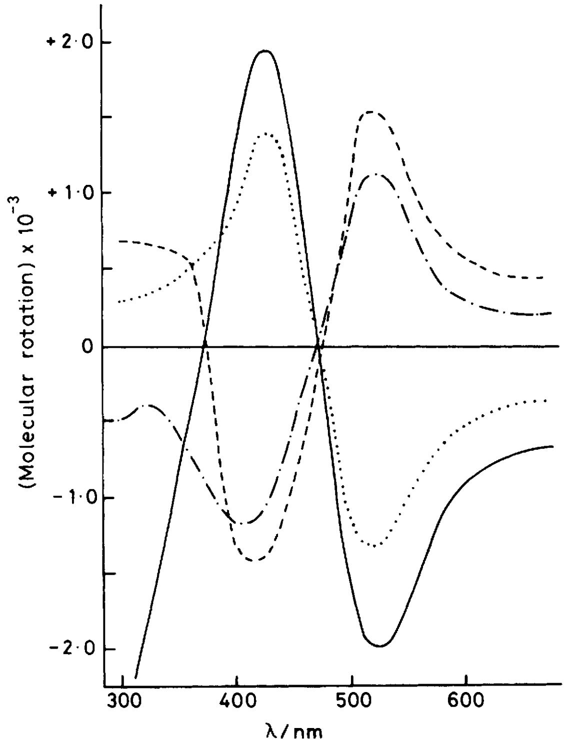
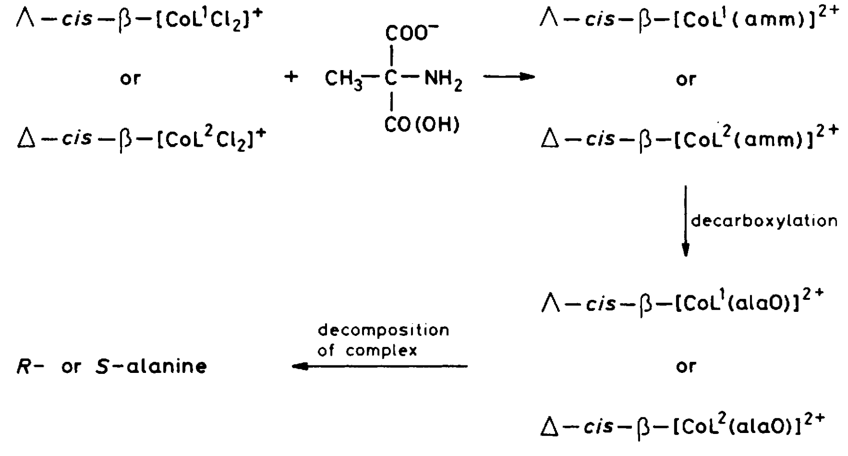


Figure 1. R.d. curves for the standard complexes: Λ-*cis*-β-[CoL^1(*S*-alaO)]$^{2+}$ (— · — · —), Λ-*cis*-β-[CoL^1(*R*-alaO)]$^{2+}$ (– – – –), Δ-*cis*-β-[CoL^2(*S*-alaO)]$^{2+}$ (——), and Δ-*cis*-β-[CoL^2(*R*-alaO)]$^{2+}$ (· · · ·)

$C_{16}H_{34}Cl_2CoN_5O_2{\cdot}H_2O$ requires C, 40.35; H, 7.60; N, 14.70%). The following standard complexes were also prepared in the same way using the appropriate dichloro complexes and the optically pure alanine: Λ-*cis*-β-[CoL^1(*S*-alaO)]$Cl_2{\cdot}H_2O$, Δ-*cis*-β-[CoL^2(*S*-alaO)]$Cl_2{\cdot}H_2O$, and Δ-*cis*-β-[CoL^2(*R*-alaO)]$Cl_2{\cdot}H_2O$.

Results and Discussion

The asymmetric synthesis of alanine in this work proceeded as shown below.



The infrared spectra of both Λ-*cis*-β-[CoL^1(amm)]$Cl_2{\cdot}H_2O$ and Δ-*cis*-β-[CoL^2(amm)]$Cl_2{\cdot}H_2O$ showed a single carboxyl peak at 1 650 cm^{-1}, indicating that both carboxyl groups of amm are co-ordinated to the cobalt(III) ion.

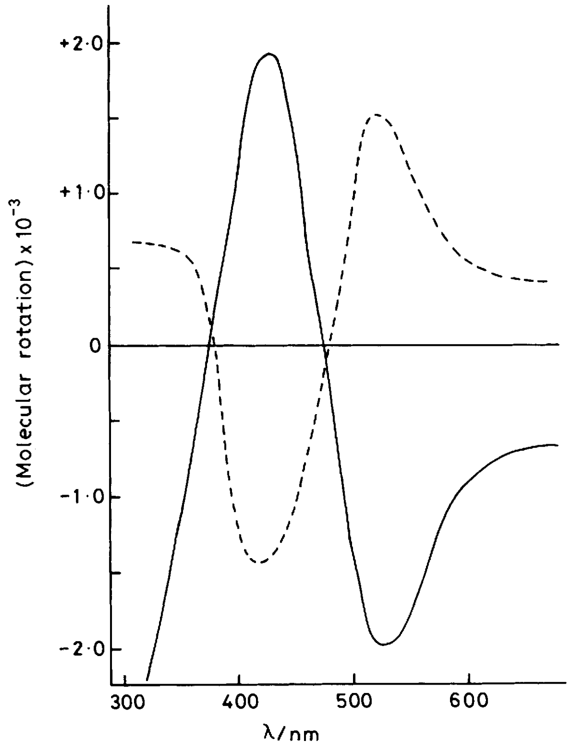


Figure 2. R.d. curves for Λ-*cis*-β-[CoL^1(alaO)]$^{2+}$ (– – – –) and Δ-*cis*-β-[CoL^2(alaO)]$^{2+}$ (——) obtained from the decarboxylation reaction

Figure 1 shows the r.d. spectra of the standard complexes of optically active alanine independently prepared for comparison, while the r.d. spectra of the complexes obtained from the decarboxylation reaction are shown in Figure 2. The r.d. spectrum of the Λ-*cis*-β-[CoL^1(alaO)]$^{2+}$ ion obtained from the decarboxylation of Λ-*cis*-β-[CoL^1(amm)]$^{2+}$ is almost same as that of the Λ-*cis*-β-[CoL^1(*R*-alaO)]$^{2+}$, which indicates that the precursor of the alanine (amm) has been stereoselectively decarboxylated to become *R*-alanine. The alanine isolated from the decarboxylated complex, however, showed a specific rotation of only −3.0, representing a 20% excess of *R*-alanine over *S*-alanine. On the other hand, the decarboxylation of Δ-*cis*-β-[CoL^2(amm)]$^{2+}$ yielded stereoselectively an *S*-alanine in the resultant Δ-*cis*-β-[CoL^2(alaO)]$^{2+}$ ion. The specific rotation of the alanine isolated from this complex was +2.8, showing an 18% excess of *S*-alanine over the *R*-antipode.

The relatively low specific rotation of alanine from the decarboxylated complexes must be due to racemization occurring during the isolation process of each alanine as observed by Asperger and Liu[1] and other investigators.[3] It is interesting to observe that during the decarboxylation step the Λ-*cis*-β isomer yielded an *R*-alanine, while the Δ-*cis*-β isomer an *S*-alanine. Such stereoselectivity observed during the decarboxylation process is due to the directing power of the dissymmetric complexes of amm, which is in turn due to the strong conformational preferences of the stereoselective tetra-amine ligands.[4–6] The directing power is also enhanced by the pyrrolidine rings located at the outside chelate rings of the tetra-amine ligand L.

When a bidentate chelating agent replaces the chloro ligands of cobalt(III) complexes of L^1 or L^2, its conformation should be such that non-bonding interactions may be minimized. Three principal sources for non-bonding interactions can be considered in such complexes:[4] interactions between chelate rings, interactions between a chelate ring and the substituents on the other chelate ring (methyl group and axial hydrogen atoms), and interactions between substituents (axial hydrogen atoms on the carbon and nitrogen, and asymmetrical methyl group). In the case of the complexes of ligands L^1 and L^2 an additional source of non-bonding interactions should be considered due to the presence of the pyrrolidine ring which will not only complicate the non-bonding interactions but also bring about some stereorigidity to the molecule. Therefore, a study using molecular models shows that for an incoming bidentate chelate agent one chelate ring conformation will be favoured slightly owing to such non-bonding interactions. In the case of Λ-*cis*-β-$[CoL^1(alaO)]^{2+}$ the favoured chelate ring conformation for the alanine ligand is thought to be λ, in which the methyl group will be able to take the equatorial position. Since the *R*-alanine should be selected for such a chelate ring conformation, it is reasonable to believe that an *R* absolute configuration is imparted when the Λ-*cis*-β-$[CoL^1(amm)]^{2+}$ complex undergoes a stereoselective decarboxylation reaction. In the case of Δ-*cis*-β-$[CoL^2(amm)]^{2+}$ on the other hand, the slightly favoured chelate ring conformation appears to be δ, in which the methyl group will also be able to take up an equatorial position. Since the *S*-alanine can take the δ ring conformation under such circumstances, it is reasonable to conclude that an *S* absolute configuration is obtained when Δ-*cis*-β-$[CoL^2(amm)]^{2+}$ is subjected to a stereoselective decarboxylation reaction.

Acknowledgements

Financial support of this work from the Korea Science and Engineering Foundation is gratefully acknowledged. Thanks are also due to the Korean-American Educational Commission (to M. J. J.) for support.

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Received 5th April 1982; *Paper* 2/576