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Crystallographic Evidence of Substituent Induced Stereospecificity in Mixed Ligand Complexes of Amino Acid Derivatives

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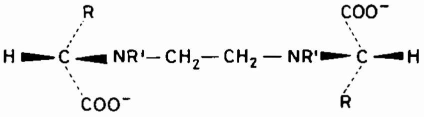
Abstract

The crystal and molecular structure of ΛΔ-cis-α-ethylenebis-α-*RR*/*SS*-aminobutyric acidato(1,2-diaminoethane)cobalt(III) perchlorate, ΛΔ-*cis*-α-[Co(*RR*/*SS*-EBABA)(en)]ClO$_4$, was determined from three-dimensional X-ray counter data. The complex crystallizes in the monoclinic system, space group $P2_1/n$ with $a = 8.514(5)$, $b = 19.482(9)$, $c = 11.610(6)$ Å, $\beta = 109.70(4)°$, $V = 1813(1)$ Å^3. For $Z = 4$, the observed and calculated densities are 1.64(1) and 1.644 g cm^{-3}, respectively. The structure was refined by block-diagonal least-squares technique to a final $R = 0.062$ for 1661 observed reflections. The geometry about the cobalt atom is roughly octahedral with the tetradentate *RR*/*SS*-EBABA, assuming *cis*-α configuration in which the complex possesses two out-of-plane amino acidate (R) rings and the backbone ethylenediamine (E) ring. The E ring conformation is δ for the Δ-*cis*-α isomer and λ for the Λ-*cis*-α isomer, respectively. On the other hand, both R rings have an asymmetric envelope conformation while the en ring has a δ conformation. As the crystal structure is centrosymmetric, it consists of a racemic mixture of Λ-$S_\mathbf{N}S_\mathbf{N}$-($\lambda_\mathbf{E}$-$e_{\mathbf{R}_1}$-$e_{\mathbf{R}_2}$)-($\delta_\mathbf{en}$)-*cis*-α-[Co(*RR*-EBABA)(en)]$^+$ and Δ-$R_\mathbf{N}R_\mathbf{N}$-($\delta_\mathbf{E}$-$e_{\mathbf{R}_1}$-$e_{\mathbf{R}_2}$)($\lambda_\mathbf{en}$)-*cis*-α-[Co(*SS*-EBABA)(en)]$^+$ enantiomers as paired complex cations. Thus the X-ray diffraction experiment has revealed stereospecific formation of both cations due to intra- and interligand interactions.

Introduction

It is well known that steric interactions are of paramount importance in determining the nature and type of complexes which can be formed with cobalt(III). We have recently made a study of stereospecificity and diastereoselectivity in mixed ligand complexes of amino acid derivatives, where we observed that stereospecificity can be correlated with the van der Waals volume of the substituent at the Cα asymmetric atom of the parent amino acid [1]. When substituents are smaller ($<C_2H_5$), non-stereospecific coordination is observed while for bulkier substituents ($>C_2H_5$) stereospecific coordination occurred. The borderline cases are derivatives of α-aminobutyric acid ($R = C_2H_5$). As the latter does not exist as a natural amino acid in the optical pure form, we have recently synthesized the EBABAH$_2$ ligand, of course in the racemic form [2]. These linear flexible ethylenebisamino acidate-type (EBAA) tetradentate ligands (**I**) are of particular interest for cobalt(III) studies not only for their interesting stereochemistry but also for the use made of these substitution-inert complexes as probes of protein structure–function relationships [3]. In this work, we have investigated the question of whether or not the 'borderline' C$_2$H$_5$ substituent can induce stereospecificity.



R' = H, R = C_2H_5 (EBABA)

I

Experimental

Preparation, separation and spectral characterization of the geometrical isomers of [Co(*rac*-EBABA)(en)]$^+$ have been previously reported [2]. Single crystals of ΛΔ-*cis*-α-[Co(*RR*/*SS*-EBABA)(en)]ClO$_4$ were prepared at room temperature by slow evaporation from ethanol/water solution; dark red plate-like crystals resulted. The density was measured by flotation in cyclohexane–bromoform mixture.

Data Collection

A crystal 0.30 × 0.25 × 0.10 mm was selected for data collection. Oscillation and Weissenberg photo-

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graphs showed the crystal to be monoclinic, with systematic absences $0k0$ for k odd and $h0l$ for $h+l$ odd, uniquely indicating the space group. Unit-cell parameters were refined by a least-squares fit of 2θ values of 15 high-angle reflections ($15 < 2\theta < 40°$). Intensity data were measured up to (2θ) 50° on a Syntex $P2_1$ four-circle diffractometer using graphite-monochromatized Mo Kα radiation; $2\theta - \theta$ scan method (scan rate varied from 4.88 to 29.3° min^{-1} in 2θ and the background was measured at each end of the scan for one half of the scan time). Two standard reflections monitored after every 98 scans showed no intensity deterioration. The data were averaged to give 2284 unique reflections, of which 1661 with $I \geqslant 2\sigma(I)$ were classified as observed. No correction for absorption was made.

Crystal Data

Formula weight $M_r = 448.7$ ($CoC_{12}H_{26}N_4O_8Cl$), monoclinic, space group $P2_1/n$, $a = 8.514(5)$, $b = 19.482(9)$, $c = 11.610(6)$ Å, $\beta = 109.70(4)°$, $V = 1813(1)$ Å^3, $Z = 4$, $D_m = 1.64(1)$, $D_c = 1.644$ g cm^{-3}, $F(000) = 936$, Mo Kα, $\lambda = 0.7107$ Å, $\mu = 10.6$ cm^{-1}, room temperature.

Structure Determination

The structure was determined by the heavy-atom method, the Co and Cl positions being obtained from a Patterson map and the remaining non-hydrogen atoms from subsequent Fourier syntheses. Refinement was by block-diagonal least-squares method using anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were treated as fixed contributions to structure-factor calculations, not refined; they were placed at calculated positions (C–H 1.09, N–H 1.00 Å) with isotropic thermal parameters set to 1.0 Å^2 higher than B_{eq} for associated N or C atoms. A $\Sigma w(\Delta F)^2$ function was minimized, with weighting scheme ($w = |F_o|/25$ if $|F_o| < 25$ and $w = 25/|F_o|$ if $|F_o| \geqslant 25$) being chosen to give similar values of $w(\Delta F)^2$ over ranges of $\sin\theta/\lambda$ and $|F_o|$. Scattering factors [4] for neutral atoms were used. Maximum shift in the final cycle of refinement was 0.12 times the estimated standard deviation. Maximal and minimal residual peaks in the final difference Fourier map were 0.82 (near Co) and 0.56 e Å^{-3} respectively. The final residuals were $R = 0.062$ and $R_w = 0.079$ for observed reflections (used in refinement). All calculations were performed with a local version of the NRC system [5] at the Research Computing Centre of the Comenius University, Bratislava.

Final atomic coordinates of the non-hydrogen atoms are listed in Table 1. Interatomic distances and angles are given in Table 2. See also 'Supplementary Material'.

TABLE 1. Final atomic coordinates with e.s.d.s in parentheses

Atom	x/a	y/b	z/c
Co	0.18223(6)	0.04494(3)	0.26187(5)
N(1)	0.1295(3)	−0.0538(1)	0.2452(2)
N(2)	0.4083(3)	0.0208(1)	0.2571(2)
N(3)	0.2319(3)	0.1421(1)	0.2914(3)
N(4)	−0.0470(4)	0.0696(1)	0.2515(3)
O(1)	0.2497(3)	0.0301(1)	0.4325(2)
O(2)	0.1193(3)	0.0558(1)	0.0910(2)
O(3)	0.2331(3)	−0.0424(1)	0.5743(2)
O(4)	0.2099(3)	0.0409(1)	−0.0679(2)
C(1)	0.2581(4)	−0.0878(2)	0.2048(3)
C(2)	0.4234(4)	−0.0559(2)	0.2739(3)
C(3)	0.1267(4)	−0.0804(2)	0.3674(3)
C(4)	0.2051(4)	−0.0261(2)	0.4672(3)
C(5)	0.4102(4)	0.0437(2)	0.1341(3)
C(6)	0.2320(5)	0.0462(2)	0.0404(4)
C(7)	0.1053(5)	0.1729(2)	0.3383(4)
C(8)	−0.0590(5)	0.1468(2)	0.2547(4)
C(9)	−0.0451(5)	−0.1007(2)	0.3641(4)
C(10)	−0.1026(6)	−0.1689(2)	0.2947(5)
C(11)	0.5010(5)	0.1132(2)	0.1457(4)
C(12)	0.5319(5)	0.1344(3)	0.0285(4)
Cl	0.0568(1)	0.2634(1)	0.0121(1)
O(5)	−0.0655(6)	0.2167(2)	−0.0512(4)
O(6)	0.0725(5)	0.3167(3)	−0.0649(5)
O(7)	0.2037(5)	0.2352(3)	0.0788(6)
O(8)	−0.0069(11)	0.2919(3)	0.0984(8)

TABLE 2. Bond lengths (Å) and angles (°) with e.s.d.s in parentheses

Co–N(1)	1.970(3)	C(4)–O(3)	1.226(4)
Co–N(2)	2.000(3)	C(3)–C(9)	1.504(6)
Co–N(3)	1.944(3)	C(9)–C(10)	1.544(6)
Co–N(4)	1.974(3)	N(2)–C(5)	1.502(4)
Co–O(1)	1.890(2)	C(5)–C(6)	1.541(5)
Co–O(2)	1.884(2)	C(6)–O(2)	1.297(5)
N(1)–C(1)	1.485(5)	C(6)–O(4)	1.211(4)
C(1)–C(2)	1.500(5)	C(5)–C(11)	1.541(5)
C(2)–N(2)	1.508(5)	C(11)–C(12)	1.526(6)
N(1)–C(3)	1.518(4)	N(3)–C(7)	1.488(5)
C(3)–C(4)	1.544(5)	C(7)–C(8)	1.497(6)
C(4)–O(1)	1.269(4)	C(8)–N(4)	1.509(4)
N(1)–Co–N(2)	87.6(1)	C(4)–O(1)–Co	116.6(2)
N(1)–Co–O(1)	86.1(1)	C(3)–C(4)–O(3)	118.2(3)
N(2)–Co–O(2)	86.1(1)	O(1)–C(4)–O(3)	124.6(3)
N(3)–Co–N(4)	85.7(1)	N(1)–C(3)–C(9)	112.8(3)
N(1)–Co–O(2)	91.8(1)	C(4)–C(3)–C(9)	111.7(3)
N(1)–Co–N(3)	175.3(1)	C(3)–C(9)–C(10)	112.0(4)
N(1)–Co–N(4)	92.5(1)	C(1)–N(1)–C(3)	112.8(3)
N(2)–Co–O(1)	92.2(1)	Co–N(2)–C(5)	106.0(2)
N(2)–Co–N(4)	175.2(1)	N(2)–C(5)–C(6)	110.9(3)
N(2)–Co–N(3)	94.6(1)	C(5)–C(6)–O(2)	112.8(3)
N(3)–Co–O(1)	89.6(1)	C(6)–O(2)–Co	118.1(2)

(continued)

TABLE 2. *(continued)*

N(3)–Co–O(2)	92.6(1)	C(5)–C(6)–O(4)	120.1(3)
N(4)–Co–O(1)	92.6(1)	O(2)–C(6)–O(4)	127.1(3)
N(4)–Co–O(2)	89.1(1)	N(2)–C(5)–C(11)	110.1(2)
O(1)–Co–O(2)	177.3(1)	C(6)–C(5)–C(11)	112.3(3)
Co–N(1)–C(1)	107.4(2)	C(5)–C(11)–C(12)	113.1(3)
N(1)–C(1)–C(2)	107.8(3)	C(2)–N(2)–C(5)	113.0(3)
C(1)–C(2)–N(2)	108.6(3)	Co–N(3)–C(7)	108.4(2)
C(2)–N(2)–Co	105.7(2)	N(3)–C(7)–C(8)	105.0(3)
Co–N(1)–C(3)	108.4(2)	C(7)–C(8)–N(4)	107.3(3)
N(1)–C(3)–C(4)	109.2(3)	C(8)–N(4)–Co	108.3(2)
C(3)–C(4)–O(1)	116.9(3)		

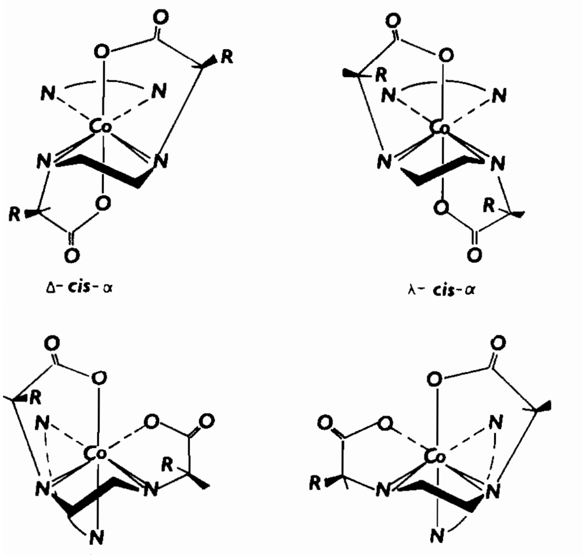

Fig. 1. The four possible isomers of the [Co(EBAA)(en)]$^+$ ion.

Results and Discussion

For the [Co(EBAA)(en)]$^+$ system two geometrical isomers are possible and further there are two optical isomers Δ and Λ for both the *cis-α* and *cis-β* forms (Fig. 1). Because of the tetrahedral stereochemistry of four-covalent nitrogen, the puckered chelate rings in the *cis-β* isomer are somewhat strained and slightly distorted from the plane containing the donor N and O atoms, so that this isomer might be expected to be less favorable than the *cis-α* one [6].

If coordination of EBAA is non-stereospecific, both Δ and Λ enantiomers are formed. This non-stereospecificity has been observed for EBG* and *SS*-EBA (R = CH_3) ligands [1], indicating the possibility of both equatorial and axial positions of the methyl groups. For bulkier substituents (i-C_3H_7 [1], i-C_4H_9 [7] and benzyl [8]) however stereospecific coordination forming only Δ enantiomers for *SS*-EBAA has been observed because these bulky substituents can be placed exclusively in an equatorial position.

Description of the Complex Cation

The geometry of the complex cation, tentatively assigned as ΛΔ-*cis*-α-[Co(*RR*/*SS*-EBABA)(en)]$^+$ on the basis of previous chemical and spectroscopic studies [2], is confirmed by the structure determined. As the crystal structure is centrosymmetric, it consists of a racemic mixture of Λ-*cis*-α-[Co(*RR*-EBABA)(en)]$^+$ and Δ-*cis*-α-[Co(*SS*-EBABA)(en)]$^+$ enantiomers as paired complex cations. Thus the X-ray diffraction experiment has revealed that the complex cation *cis*-α-[Co(*RR*-EBABA)(en)]$^+$ is formed stereospecifically with absolute configuration Λ [9] and complex cation *cis*-α-[Co(*SS*-EBABA)(en)]$^+$ with configuration Δ. The overall configuration of the Λ-isomer is displayed in Fig. 2, which also shows the numbering of the atoms.

The geometry around the cobalt atom is approximately octahedral, the ligating atoms being two O atoms in *trans* positions, two N atoms from the *RR*-EBABA ligand and two N atoms from en. The *RR*-EBABA ligand is tetradentate. Coordinating with the cobalt(III) ion it forms three five-membered chelate rings: one central ethylenediamine ring, which lies in the plane of the two coordinated N atoms (E ring) and two amino acidate rings, lying outside this plane (R rings) [10]. Hence the configuration is *cis*-α, as predicted on the basis of absorption and NMR spectroscopy [2]. From inspection of Table 2 it is seen that the bond length distortions are minimal. The Co–O(1) and Co–O(2) bond lengths are similar to those found in Cα-unsubstituted EBAA complexes [11, 12] or *SS*-EBP complexes [6, 13]. On the contrary to the above mentioned complexes, there are highly significant differences (10σ) within the Co–N(EBAA) and Co–N′(en) bond lengths respectively.

The torsion angles in the rings are given in Table 3. The conformation of the chelate is such that both amino acidate R rings adopt forced, energetically unfavorable, envelope conformation (Co-envelope for R_1 and Cα-envelope for R_2 ring), while the central E ring has staggered conformation of λ chirality. The E ring torsion angle N(1)–C(1)–C(2)–N(2) is −53.4(4)°. In a number of ethylenediamine complexes this value is also about 50° [14]. Absolute configurations of the two asymmetric N atoms are *SS*. The values for the dihedral angles about the Cα–C′ [15] bonds for the two R amino acidate rings are 3.0(5) and 26.0(4)°, respectively. The X-ray structural studies have shown that these angles are

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*Abbreviations used: EBG, ethylenebisglycinate = EDDA; EBA, ethylenebis-α-alaninate; EBP, ethylenebisprolinate.

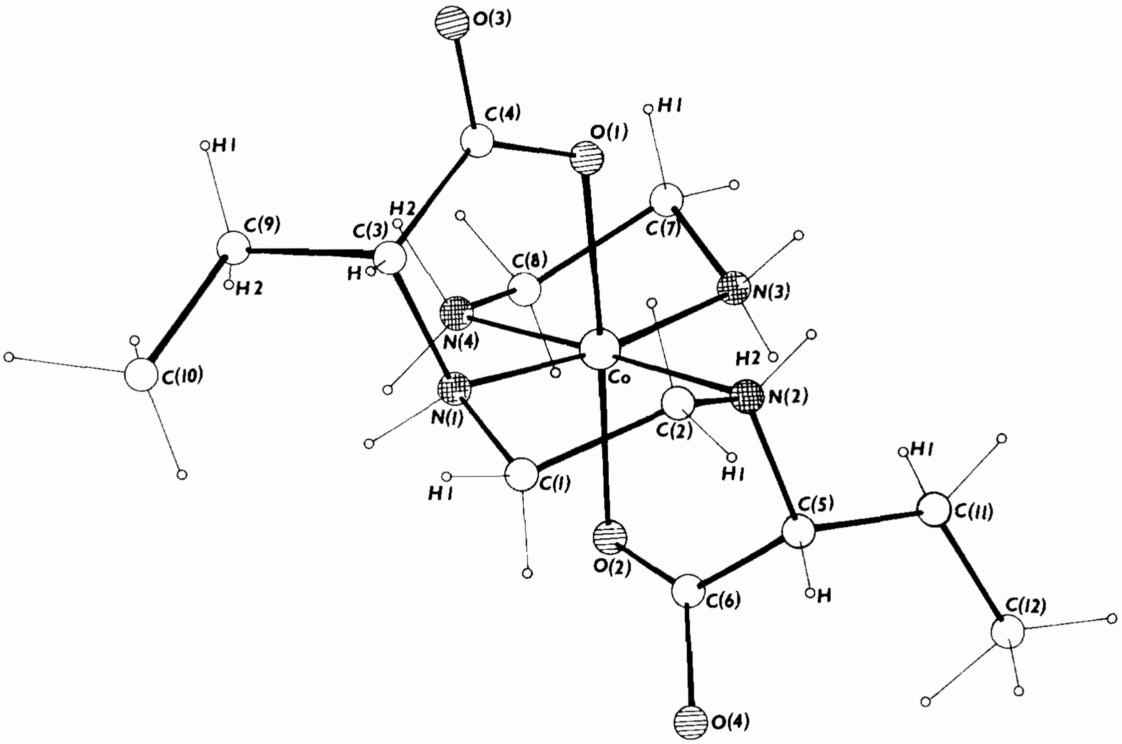

Fig. 2. Molecular structure of Λ-$S_N S_N$-(λ_E-e_{R_1}-e_{R_2})(δ_{en})-*cis*-α-[Co(*RR*-EBABA)(en)]$^+$. Only hydrogen atoms involved in significant non-bonding interactions are labelled for clarity.

TABLE 3. Selected torsion angles (°) with e.s.d.s in parentheses

Co–N(1)–C(1)–C(2)	40.6(3)	N(3)–C(7)–C(8)–N(4)	53.3(4)
N(1)–C(1)–C(2)–N(2)	−53.4(4)	C(7)–C(8)–N(4)–Co	−35.4(4)
C(1)–C(2)–N(2)–Co	38.7(4)	C(8)–N(4)–Co–N(3)	7.4(2)
C(2)–N(2)–Co–N(1)	−13.0(2)	N(4)–Co–N(3)–C(7)	22.3(3)
N(2)–Co–N(1)–C(1)	−15.2(2)	C(2)–C(1)–N(1)–C(3)	−78.8(3)
Co–N(1)–C(3)–C(4)	−13.0(4)	C(1)–C(2)–N(2)–C(5)	−76.7(4)
N(1)–C(3)–C(4)–O(1)	3.0(5)	C(1)–N(1)–C(3)–C(4)	105.8(3)
C(3)–C(4)–O(1)–Co	9.7(4)	C(1)–N(1)–C(3)–C(9)	−129.4(3)
C(4)–O(1)–Co–N(1)	−14.4(3)	O(1)–C(4)–C(3)–C(9)	−122.5(4)
O(1)–Co–N(1)–C(3)	14.7(2)	N(1)–C(3)–C(4)–O(3)	−170.7(3)
Co–N(2)–C(5)–C(6)	−25.0(3)	N(1)–C(3)–C(9)–C(10)	73.9(4)
N(2)–C(5)–C(6)–O(2)	26.0(4)	C(2)–N(2)–C(5)–C(6)	90.3(3)
C(5)–C(6)–O(2)–Co	−13.3(4)	C(2)–N(2)–C(5)–C(11)	−144.8(3)
C(6)–O(2)–Co–N(2)	−1.3(2)	O(2)–C(6)–C(5)–C(11)	−97.7(4)
O(2)–Co–N(2)–C(5)	15.2(2)	N(2)–C(5)–C(6)–O(4)	−155.4(3)
Co–N(3)–C(7)–C(8)	−46.9(3)	N(2)–C(5)–C(11)–C(12)	171.0(3)

between 0 and 30°, in accordance with energy minimalization calculations [14].

Displacement of the corresponding atoms from the best least-squares planes through the carboxylato groups shows that they are planar in the range of e.s.d. The mean planes of the two R rings are approximately perpendicular to the mean plane of the E ring; the corresponding angles being 85.9 and 90.8° for E/R_1 and E/R_2 respectively.

The second ligand en has the δ conformation. These complexes would be taken approximately as analogues of *trans*-[Co(en)$_2$a$_2$] complexes, in which the conformations of en are either λλ or δδ, and the *meso* form, in which the conformation is δλ. Although there is no enthalpy preference for one isomer, the *meso* form is preferred statistically over the chiral isomers with an energy difference of 1.7 kJ mol^{-1} at 298 K.

Description of the Unit Cell

The crystal structure consists of centrosymmetric pairs of [Co(*RR*-EBABA)(en)]$^+$ and [Co(*SS*-EBABA)(en)]$^+$ complex cations and perchlorate anions. There are only two important hydrogen-bonding interactions (<3.0 Å): N(3)...O(6) ($\frac{1}{2}+x$, $\frac{1}{2}-y$, $\frac{1}{2}+z$) 2.929(6) and O(4)...N(1) ($-x$, $-y$, $-z$) 2.939(4) Å; the latter linking the cations into spirals extending along the 2_1 screw axes. Other forces are predominantly ionic in nature, acting between the cations and anions.

Substituent Induced Stereospecificity

In comparison to 1,2-diamines the five-membered chelate rings of amino acids are much less puckered. Conformational analysis shows only small interactions between the methyl substituent at the Cα and the other part of the EBAA ligand [1]. Therefore no substantial stability difference should exist between different conformations with the α-methyl in a pseudo-equatorial or pseudo-axial position. Consequently, no stereospecificity is observed for coordination of EBG and *SS*-EBA [1].

It was established from X-ray analysis that ethyl substituent at the Cα of both R rings is placed in a pseudo-equatorial position. Then both R rings adopt envelope conformation which is forced for steric reasons (Table 4).

From Table 4 it is obvious that interligand interactions between the ethyl groups and both $-NH_2$ and $-CH_2-$ groups of the second ligand en represent a specific discriminating factor in the [Co(*RR*-EBABA)(en)]$^+$ system, determining, on the basis of steric requirements, stereospecificity. In addition to these interactions, one has also to consider intraligand interactions between the axial methylene hydrogen atoms of the central E and both R rings. Hence from steric considerations it is obvious that the most important factor determining stereospecificity is the tendency of the ethyl group to occupy a pseudo-equatorial position. We may conclude that a suitable choice of substituents at asymmetric Cα of the parent amino acid will allow fixing of the conformation of the chelate rings and the absolute configuration of a given geometric isomer.

TABLE 4. Significant non-bonding interactions (Å)[a]

Interligand		Intraligand	
H2(N3)...H1(C11)	1.932	H1(C1)...H(C3)	2.100
H2(N4)...H2(C9)	2.192	H1(C2)...H(C5)	2.153
H1(C7)...H1(C9)	1.921		

[a]For numbering see Fig. 2.

Supplementary Material

The F_o and F_c tables, anisotropic temperature factors and calculated H-atom positions are available from the authors on request.

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