THE SYNTHESIS AND STEREOCHEMISTRY OF THE TERNARY COBALT(III) COMPLEX WITH A STEREOSPECIFIC LIGAND DERIVED FROM (S)-LEUCINE

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Dedicated to the Academician J. Majer on the occasion of his 60th birthday.

A new stereospecific ligand, ethylenediamine-N,N′-di(S)-α-isocapronic acid, was synthesized by condensation of (S)-leucine with 1,2-dibromoethane in alkaline aqueous medium. It follows from the ^{1}H and ^{13}C NMR spectra that the terminal methyl groups are chemically and magnetically nonequivalent. Of the four theoretically possible isomers of the ternary cobalt (III) complex with ethylenediamine, separation on catex yielded only one, whose absolute configuration was determined by a combination of ^{1}H and ^{13}C NMR, electron absorption spectroscopy and CD and IR spectroscopy.

The problem of stereoselectivity in coordination chemistry is closely connected with the known stereochemical specificity of biological systems. In addition to the many other functions fulfilled by metal ions in enzymes, such as increasing the reactivity through polarization or electron transfer, they also have a stereochemical function. They can ensure approach of reacting molecules in a coordination sphere with a definite geometry, thus increasing the probability of a given reaction or orient a reaction along a desired pathway. It can be expected that the study of the formation of ternary complexes of metal ions with various ligands[1,2] can contribute to solution of this problem.

In a study of the selectivity of the formation of diastereoisomers of ternary cobalt (III) complexes with the derivatives of amino acids, a hypothesis was formulated[3,4] according to which stereospecific formation of Δ isomers occurs only when the substituent on the α-C is larger than C_2H_5. Thus, the conformation of chelate rings can be fixed by suitable substituent selection, which then unambiguously determines the absolute configuration of the diastereoisomer[4]. To test this hypothesis, we prepared a new optically active ligand, (S, S)-EDDIC, with an isobutyl group on the α-carbon; the steric volume of this group is much greater than that of C_2H_5. It can thus be expected that only Δ isomers will be formed stereospecifically in the synthesis of the Co(III) complex.

EXPERIMENTAL

Chemicals

(S)-Leucine was the product of the Sigma company and was used as supplied. 1,2-Dibromoethane and 1,2-diaminoethane (both from Merck) were redistilled prior to the synthesis. The other chemicals were of *p.a.* purity.

Synthesis of Ethylenediamine-N,N'-di-(S)-α-isocapronic Acid, (S, S)-EDDIC

2 g (50 mmol) of NaOH dissolved in 4 ml of water were added to 6·56 g (50 mmol) of (S)-leucine dissolved in 10 ml of water. The solution was heated to the boiling point under a reflux condenser and 4·7 g (25 mmol) 1,2-dibromoethane and 3·5 g (25 mmol) K_2CO_3 were gradually added so that the pH remained between 10 and 11. The solution was then refluxed for 38 hours. After cooling, the precipitated KBr and unreacted K_2CO_3 were filtered off and the filtrate was acidified with conc. HCl to pH 9; a white substance was precipitated. The raw product was purified by repeated conversion to the sodium salt and precipitation with conc. HCl, was filtered off and recrystallized from the necessary amount of hot water. The white substance obtained was dried under vacuum at 70°C. The mother liquor was evaporated down and the product was isolated in the above manner. The yield was 4·5 g (63%). Melting point, 280°C (charring). Elemental analysis: for $C_{14}H_{28}N_2O_4$ was calculated 57·56% C, 9·81% H, 9·67% N and found 58·31% C, 9·78% H, 9·71% N.

Preparation of [Co(S, S)-EDDIC(en)] ClO$_4$. 2 H$_2$O

To a suspension of 0·72 g (2·5 mmol) (S, S)-EDDIC in 4 ml of water were added a suspension of 0·3 g (2·5 mmol) CoCO$_3$ in 20 ml water, 0·1 g of active carbon to ensure equilibrium of the isomers formed, 0·2 ml of 65% HNO$_3$ diluted to 2 ml and 0·18 ml (2·5 mmol) of 1,2-diamino-ethane diluted to 7 ml. The mixture was heated to 60°C and 0·3 ml of 30% H$_2$O$_2$ was added dropwise with intense stirring. The mixture was heated and stirred at this temperature for 6 hours. After cooling, the reaction mixture was bubbled with air overnight. The active carbon was then filtered off and the wine red solution was chromatographed through a column packed with Dowex 50W-X8 (50—100 mesh) in the Na$^+$ cycle. After washing with water (to remove any substances not adsorbed on the column), elution was carried out using 0·1 M-NaClO$_4$, yielding a single fraction. The product was freed of NaClO$_4$ by repeated evaporation to dryness on a rotating vacuum evaporator and extraction with absolute ethanol. The residue of NaClO$_4$ was removed by passing the solution through a column packed with Sephadex G-10. An amount of 0·85 g of product was obtained as light purple needles. For [Co(C$_{16}$H$_{34}$N$_4$O$_4$)] ClO$_4$. H$_2$O calculated: 35·50% C, 6·93% H, 10·38% N; found: 35·53% C, 7·07% H, 10·36% N.

Paper Electrophoresis

Paper electrophoresis without glass vessels was used to verify the purity and charge magnitude for the complex ion obtained. Platinum electrodes were used for measurements in the pH range 2—9. Paper Whatman No 2 was used at a constant ionic strength (0·10 M-KNO$_3$). The concentration of the complex was of the order of 10^{-2} mol dm^{-3}.

Spectral Measurements

Electronic absorption spectra were measured on a Specord UV VIS spectrophotometer in the

range 200—800 nm using 1 and 3 cm quartz cuvettes. The concentration was adjusted according to conditions.

The IR spectra were measured on a Perkin–Elmer 337 instrument using the KBr technique in the region $4\,000 - 400\,cm^{-1}$.

The CD spectra were measured on a CNRS Rousel Jouan Dichrograph III instrument in the region 200—700 nm. The concentration of the aqueous solutions was of the order of 10^{-4} mol . . dm^{-3}. Measurements were carried out in 5 mm cuvettes.

The ^{1}H and ^{13}C NMR spectra were measured using c. 10% solutions in D_2O (pD > 7). The internal standard was sodium 3-(trimethylsilyl)propionate (TSP) for ^{1}H NMR and dioxane for ^{13}C NMR. The ^{1}H and ^{13}C NMR spectra were measured using a Jeol FX-100 FT NMR pulse spectrometer at a working frequency of 99·55 MHz for ^{1}H and 25·047 MHz for ^{13}C NMR.

All measurements were carried out at a laboratory temperature.

RESULTS AND DISCUSSION

The Conformation of Ethylenediamine-N,N'-di-(S)-α-isocapronic Acid

The linear tetradentate ligand (S, S)-EDDIC was prepared from (S)-leucine with a known configuration. As the condensation did not occur on the optically active carbon atoms, it can be assumed that the absolute configuration of the synthesized (S, S)-EDDIC will be:
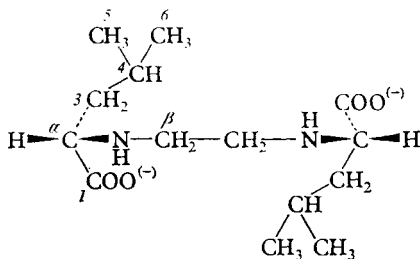
The structure of the newly synthesized ligand was confirmed on the basis of IR, ^{1}H and ^{13}C NMR spectra (Figs 1*a* and 3*a*). The signals for protons bonded to carbon atoms can be seen on the ^{1}H NMR spectrum (Fig. 1*a*). The signal for the proton bonded to the α-carbon atom appears at the lowest magnetic field intensity (3·10 ppm) as a triplet, as for leucine alone[7]. As this proton interacts with two nonequivalent CH_2 protons of leucine, this signal shape is probably the result of a small difference in the vicinal coupling constants $^{3}J_{AX}$ and $^{3}J_{BX}$ (both ~7 Hz). This value is close to that for the analogous coupling constant for the leucine anion[7] (6·70 Hz). As the value observed here is larger than the ^{3}J value for free rotation[7] (6·35 Hz), it would appear that, of the three possible rotamers (Fig. 2), rotamers *I* and *II* are present in equal amounts in (S, S)-EDDIC, and rotamer *III* is present in a smaller amount. The signal for the β-CH_2 protons, which are equivalent, appears as a singlet at

2·60 ppm. A multiplet centred at 1·42 ppm corresponds to the CH and CH_2 protons of leucine. The signal for the methyl protons are two doublets at 0·90 and 0·91 ppm, indicating that the methyl groups are not equivalent, similarly as in ethylenediamine--N,N'-di-(S)-α-isovaleric acid[5] ((S, S)-EDDIV). This non-equivalence of the terminal methyl groups is also apparent from the ^{13}C NMR spectra (Fig. 3a) and may be
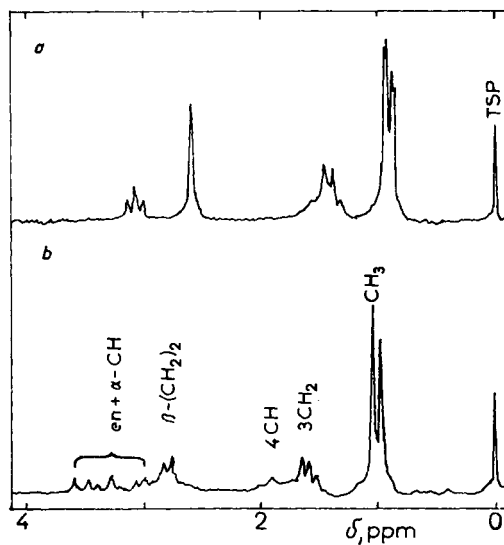
FIG. 1

The ^1H NMR spectrum of a (S, S)-EDDIC and b Δ-cis-α-[Co((S, S)-EDDIC)(en)]ClO₄ . . 2 H₂O in D₂O
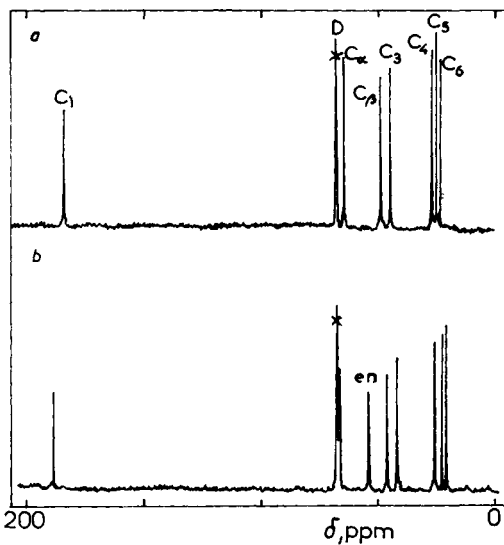
FIG. 3

The ^{13}C NMR spectrum of a (S, S)-EDDIC and b Δ-cis-α-[Co((S, S,)-EDDIC)(en)]ClO₄. . 2 H₂O in D₂O

the result either of steric hindrance preventing free rotation of the rather bulky isobutyl groups and/or of the presence of the asymetric α-carbon atoms. Conformational analysis of (S, S)-EDDIV indicate[6] that this nonequivalence is the result of asymmetric sites at the α-carbon atoms and not of originally claimed steric hindrance[5].

The Stereochemistry of the Complex

The synthesized complex is the optically active analogue of the octahedral $[Co(EDDAA)(en)]^+$ complexes (EDDAA = ethylenediaminediacetic acid), which can exist as four different isomers (Fig. 4). Because of the tetrahedral coordination of the tetravalent nitrogen, the out-of-plane chelate rings in the cis-β-isomers are more strained and distorted from the plane containing the nitrogen atoms, so that it can be expected that this geometric isomer will be less stable than the cis-α-isomer. The conformation of the chelate rings lying in the equatorial plane (the E rings[8]) is given by the configuration of the secondary nitrogen atoms, while the chelate rings connecting the equatorial and polar coordination sites (R, G rings[8]) seem to be sufficiently flexible to assume either the λ or δ conformation regardless of the configuration of the nitrogen atoms[9]. The same number of ^{13}C signals for the co-ordinated and uncoordinated (S, S)-EBL ligands (Fig. 3) indicates that both the (out-of-plane) chelate R rings are equivalent — i.e. the cis-α-isomer is present. It is also apparent from Fig. 3 that coordination of (S, S)-EBL to Co(III) leads to downfield shift in the signal of the carboxyl C_1 and α-carbon atoms. A similar effect, resulting from a decrease in the electron density on the C_1 and α-C atoms as a result of coordination of neighbouring (N, O) atoms can be seen in the ^{1}H NMR spectrum in Fig. 1.
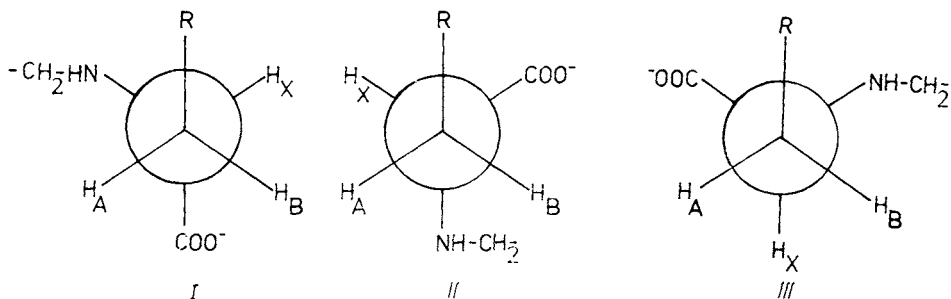

FIG. 2

Newmann projection of the three rotamers of the (S,S)-EDDIC fragment, where R is an isobutyl group

^{1}H NMR spectroscopy[6,10-12] was successfully used to determine the absolute configuration of the [Co(EDDAA)(en)]$^+$ complexes. Proton signals were observed for the α-C protons in the region 3·37 — 3·54 ppm (H^b, axial proton) and 3·93 to 4·19 ppm (H^a, equatorial protons) in the analogous spectra of the EDDA[10,11] and ethylenediamine-N,N'-di-(S)-α-propionic acid[12] (EDDP) complexes. The chemical nonequivalence was interpreted here in terms of the magnetic anisotropy of the C—N bond. Of the two α-CH$_2$ protons, that lying above the C—N bond is more shielded, *i.e.* the axial (in plane) H^b proton (Table I). The chemical shift values for the protons on the α-C atom of the coordinated (S, S)-EDDIC ligand indicate that this proton lies in the region shielded by the C—N bond (H^b, axial), so that the isobutyl group is oriented equatorially (*exo*) to the plane of the five-membered ring. The isomer yielding this spectrum was assigned the Δ-configuration for (S, S)--EDDP (ref.[12]). As it has been found that the configuration on the α-C atom is decisive for the overall absolute configuration of this type of ternary complex, it follows from the ^{1}H NMR spectrum (Fig. 1b) that the absolute configuration of the isolated isomer is Δ-*cis*-α-[Co((S, S)-EDDIC)(en)]$^+$. This conclusion is in agreement with the results of CD measurements (Fig. 5).

Δ-*cis*-α   Λ-*cis*-α
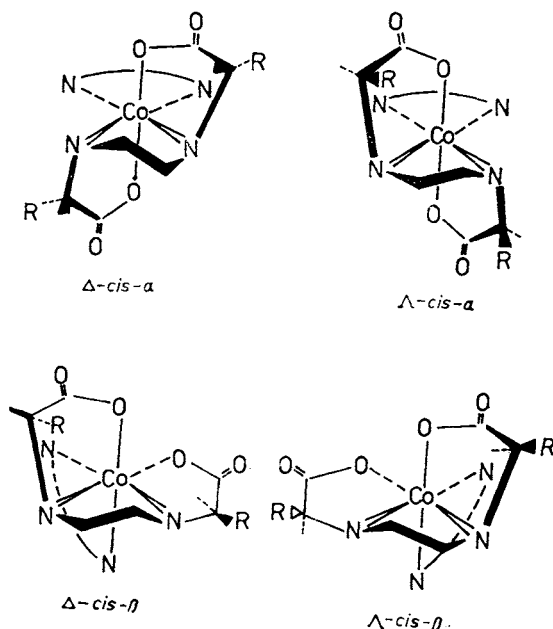
Δ-*cis*-β   Λ-*cis*-β

FIG. 4

Four possible isomers of the [Co((S, S)EDDIC)(en)]$^+$ cation

The *cis*-α-isomer obtained is chiral[13] as the result of configurational dissymmetry, conformational dissymmetry and vicinal effects resulting from the asymmetric α-C and N atoms, so that theoretically four diastereoisomers can be expected, as depicted in Fig. 4. In actual fact, only one isomer was obtained, whose CD spectrum (Fig. 5) exhibits two Cotton effects in the $^1A_{1g} \rightarrow {}^1T_{1g}$ region; one negative, stronger at a longer wavelength (530 nm) and a second, positive effect at a shorter wavelength (460 nm). The compound studied here is of the *cis*-α-[Co(EDDAA)X$_2$] type, where X$_2$ is chelated ethylenediamine. It was found for these types of complexes, for (S, S)-EDDP (ref.[12]), (S, S)-EDDIV and ethylenediamine-N,N'-di-(S)-pyrrolidine--α-carboxylic acid ((S, S)-EDDPC) (refs[14,15]), that a negative Cotton effect at longer wavelengths corresponds to absolute configuration Δ. This has been confirmed[16] on the basis of X-ray structural analysis of the Δ-*cis*-α-[Co((S, S)-EDDPC)(en)]. .ClO$_4$. 2 H$_2$O complex.

TABLE I

Resonance frequencies (ppm) of the α-CH$_2$ protons in *cis*-α-[Co(EDDAA)(en)]$^+$ isomers

Complex	δ(α-CH$_2$)		Ref.
	H^a	H^b	
[Co(EDDA)(en)]$^+$	4·22	3·38	11
[Co((S,S)-EDDP)(en)]$^+$	—	3·53	12
[Co((R,R)-EDDP)(en)]$^+$	3·99	—	12
[Co((S,S)-EDDIV)(en)]$^+$	—	3·14	6
[Co((S,S)-EDDIC)(en)]$^+$	—	~3·20	this work
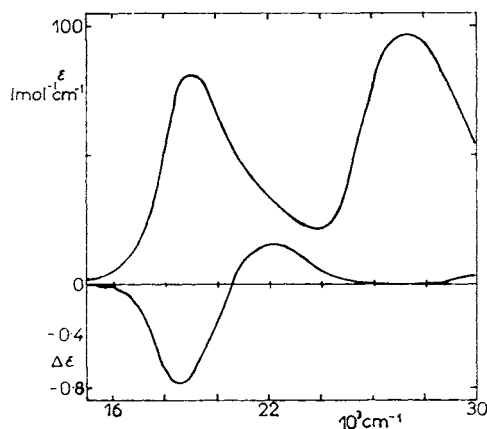
FIG. 5

The absorption (ε) and CD ($\Delta\varepsilon$) spectra of an aqueous solution of Δ-*cis*-α-[Co((S, S). .EDDIC)(en)]ClO$_4$. 2 H$_2$O

The carboxyl group of EBAA can, in principle, coordinate either as a monodentate V or bidentate VI ligand.

$$\begin{array}{ccc} -\tfrac{1}{2}\,\text{O} & \text{M}-\text{O} & \text{O} \\ \quad\diagdown\!\!\!\diagup\text{C}- & \quad\diagdown\!\!\!\diagup\text{C}- & \text{M}\diagdown\!\!\!\diagup\text{C}- \\ -\tfrac{1}{2}\,\text{O} & \text{O} & \text{O} \\ \text{IV} & \text{V} & \text{VI} \end{array}$$
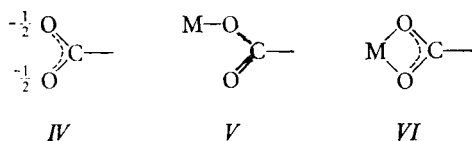
The free IV anion has relatively low symmetry (C_{2v}), so that no great decrease in this symmetry as a result of coordination can be expected. In the (S, S)-EBL ligand, both the C—O bonds are equivalent and antisymmetrical and the symmetrical COO valence vibration appears at values of 1 580 and 1 408 cm^{-1}. Formation of the complex leads to changes in the structure of the carboxyl groups. During symmetrical coordination (VI), both the COO valence vibrations will be shifted in the same direction, while asymmetrical coordination will result in a shift of the antisymmetrical COO valence vibration to higher wavenumbers and of the symmetrical COO valence vibration to lower wavenumbers. The difference Δv will be proportional to the strength of the Co—O bond. The values found, v_{as} COO (1 638) and v_s COO (1 369) cm^{-1} confirm that the carboxyl group is coordinated asymmetrically (V).

The substituents can be ordered in series according to the magnitude of the decrease in the chemical shift of the α-CH proton: $CH_3 > H > CH_2CH(CH_3)_2 > CH(CH_3)_2$; this is exactly opposite to the order of increasing diastereoselectivity in ternary EBAA complexes. A greater chemical shift is observed for the equatorial H^a atoms than the axial H^b atoms for coordinated amino acids[17] and their derivatives (Table I). The fact that a signal was observed for the axial proton on the ^{1}H NMR spectrum of coordinated EBAA indicates that the more bulky substituents attempt to assume the energetically more favourable equatorial position. The size of the substituent on the α-C atom and the chirality of the ligand determine the stereospecific coordination of amino acids and their derivatives. This is reflected in the formation of only a single diastereoisomer in spite of the fact that the synthesis occurred under conditions leading to formation of an equilibrium mixture of isomers.

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