

THE PREPARATION AND STEREOCHEMISTRY OF THE TERNARY COBALT(III) COMPLEX OF (2*R*,2'*S*)-2,2'-ETHYLENE-BIS-(2-AMINOBUTANOIC) ACID AND ETHYLENEDIAMINE

Milan STRAŠÁK, Milena KEDEROVÁ and Vladimír NOVÁK

Department of Analytical Chemistry,

Pharmaceutical Faculty, Comenius University, 832 32 Bratislava

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The ternary cobalt(III) complex $[\text{Co}(\text{EDDB})(\text{en})]^+$ was prepared by oxidation of an aqueous solution of a cobalt(II) salt and the ligands by an equimolar amount of PbO_2 . Chromatographic separation on a cation exchanger yielded two geometric isomers, that were characterized by their electronic absorption, ^{13}C NMR and IR spectra. Gel permeation chromatography was used to partially separate the two geometric isomers to yield the corresponding enantiomers, whose absolute configuration was found by CD.

Complexes of cobalt with flexible linear tetradentate ligands of the ethylene-bis-(aminoacid) type (EBAA) ($^-\text{OOCCH}(\text{R})\text{NHCH}_2\text{CH}_2\text{NHCH}(\text{R})\text{COO}^-$) can be employed as basic model compounds in the study of the stereochemistry of complexes of biogenic metals with peptides and proteins. These ligands can form three geometric isomers in octahedral complexes, *cis- α* , *cis- β* , and *trans* (Fig. 1). In the *trans* isomer, the central E ring and both G rings lie approximately in the equatorial plane of the octahedron, indicating considerable strain in the chelate rings. Thus, the formation of this isomer has been described only for the Pt(IV) complex¹, and its identification is rather questionable. In all other described syntheses of EBAA complexes, the *cis- α* isomer was formed in predominating amounts, for both complexes of this type of basic ligand, derived from glycine², and for its C-alkyl substituted derivatives α -alanine³, valine⁴, proline⁵, and phenylalanine⁶. However, only the *cis- α* isomer was formed in complexes of (*S*)-stilbenediamine-N,N'-diacetate⁷ and leucine derivatives⁸; similarly, the *cis- α* isomer was formed in complexes of derivatives of proline^{5,9} and valine⁴, which also contained monodentate ligands (H_2O , NO_3^- , Cl^-).

Recently, Moo-Jin Jun et al.¹⁰ described the preparation of ternary cobalt(III) complexes of (2*R*,2'*S*)-2,2'-ethylene-bis(2-aminobutanoic) acid (EDDB) with monodentate ligands Cl , H_2O and a bidentate ligand, CO_3^{2-} . They found from the ^1H NMR and electronic absorption spectra that only the *cis- α* isomer is formed in all the complexes. When en was the other ligand, a small amount of the *cis- β* isomer was formed in some cases⁴⁻⁶ and thus it was considered interesting to study the effect of this ligand on the distribution of geometric isomers in this type of ternary complexes.

EXPERIMENTAL

Chemicals

(*R, S*)- α -bromobutyric acid (Fluka) was used in the synthesis without further purification. 1,2-diaminoethane (Merck) was redistilled prior to use. All the other chemicals were of p.a. purity.

Synthesis of (*2R, 2'S*)-2,2'-ethylene-bis(2-aminobutanoic) Acid, H₂EDDB

This ligand was prepared by condensation of (*R, S*)- α -bromobutyric acid with 1,2-diaminoethane in alkaline medium¹¹, with a yield of 1.8 g (78%). Melting point, 309°C. For C₁₀H₂₀N₂O₄ (232.3) was calculated: 51.66% C, 8.68% H, 12.06% N; found: 51.58% C, 8.77% H, 12.01% N.

Preparation of Ethylenediamine-(*2R, 2'S*)-ethylene-bis-(2-aminobutanoato) Cobalt(III) Perchlorate, [Co(EDDB)(en)]ClO₄

A suspension of 1.0 g (4.3 mmol) H₂EDDB in 20 ml water was adjusted to pH 9 with 1M-NaOH. Then a solution containing 1.02 g (4.3 mmol) CoCl₂.6 H₂O in 7 ml water was added, along with 1.03 g (4.3 mmol) PbO₂ and 0.1 g of active carbon to accelerate the formation of an equilibrium mixture of the isomers. This mixture was heated with stirring to 60°C and maintained at this temperature for 1 hour. The mixture was cooled to laboratory temperature, the active carbon was filtered off and the wine-red solution was chromatographed on Dowex 50W-X8 (50—100 mesh, Na⁺ cycle). The mixture of isomers formed a compact layer in the upper part of the column; washing with water yielded a pink eluate. The complex was eluted with 0.2M-NaClO₄ at a flow rate of about 1 ml min⁻¹. The two purple layers A-I and A-II were eluted in this order. Electronic absorption spectroscopy indicated that eluates A-I and A-II contained the *cis*- α -[Co(EDDB)(en)]⁺ and *cis*- β -[Co(EDDB)(en)]⁺ isomers, respectively, in a ratio of c. 6 : 1. Both eluates were condensed on a rotating vacuum evaporator and the precipitated NaClO₄ was filtered off. Repetition of this procedure resulted in removal of most of the NaClO₄. The remainder of the NaClO₄ was removed by gel permeation chromatography on a column

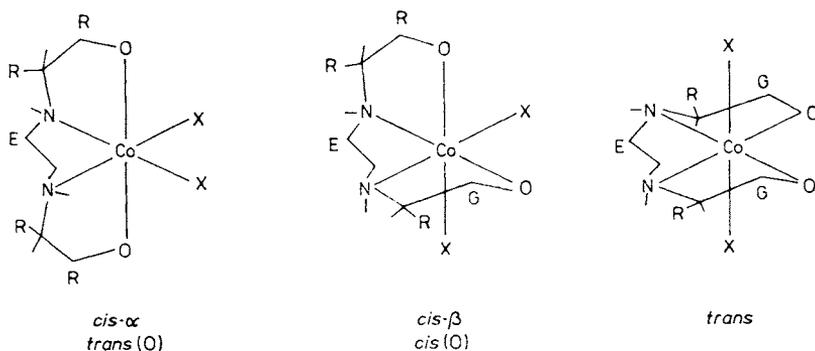


FIG. 1

Possible geometric isomers of the cobalt(III) complex with the flexible linear tetradentate ligand EBAA. (R = out-of-plane or "relaxed" ring, G = in-plane or "girdling" ring, E = central "ethylenediamine" ring)

packed with Sephadex G-10. It was observed in this procedure that the coloured bands corresponding to the *cis*- α and *cis*- β geometric isomers separated into two layers (A-I-1, A-I-2 and A-II-1, A-II-2). Measuring of the optical rotation $[\alpha]_{\lambda}$ indicated that all four components exhibit optical activity. All the eluates were condensed to a small volume, ethanol was added and the solutions were left to stand in a refrigerator for several days. The precipitated purple crystals were washed with cold ethanol and acetone and filtered off, followed by elemental analysis. For $\text{Co}(\text{C}_{12}\text{H}_{26}\text{N}_4\text{O}_4)\text{ClO}_4 \cdot \text{H}_2\text{O}$ (466.6) calculated: 30.86% C, 6.05% H, 12.01% N; found for A-I-1: 30.47% C, 6.21% H, 12.13% N; for A-I-2: 30.89% C, 5.14% H, 12.15% N; for A-II-1: 30.54% C, 6.14% H, 12.10% N; for A-II-2: 30.58% C, 6.12% H, 12.11% N.

Paper Electrophoresis

The purity and charge magnitude of the isomers obtained were found by using paper electrophoresis. Whatman No. 2 paper was used in the pH region pH 5–7 at a constant ionic strength of 0.1M-KNO₃. The complex concentration was of the order of 10⁻² mol dm⁻³. A solution of 0.05 mol dm⁻³ antipyrin with 0.02 mol dm⁻³ tetrathylammonium iodide was used as a mobility standard. The standard was detected using Dragendorf reagent and the complexes using a 0.01% solution of dimethylglyoxime in ethanol.

Spectral Measurements

The IR spectra were measured using a Perkin-Elmer 337 instrument by the KBr technique, with measurements in the range 4 000–400 cm⁻¹.

Electronic absorption spectra were measured in the region 350–700 nm on a Specord UV-VIS instrument in 1 cm glass cuvettes. The concentrations of the aqueous solutions, of the order of 10⁻² mol dm⁻³, were adjusted according to the conditions.

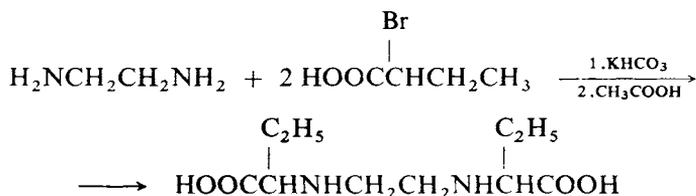
The specific rotation was measured on a Perkin-Elmer 141 instrument at four wavelengths (436, 546, 578, and 589 nm). The CD spectra were measured using a Jobin-Yvon Dichrograph III in the region 350–800 nm in quartz cuvettes. The concentrations of the aqueous solutions of the measured complexes were found from the appropriate absorption spectra and atomic absorption spectroscopy.

The ¹³C NMR spectra were measured on a Varian VXR-300 instrument at a working frequency of 75 MHz. The appropriate compounds were employed to prepare 10% solutions in ²H₂O. Dioxane was used as a standard.

All measurements were carried out at laboratory temperature.

RESULTS AND DISCUSSION

The linear tetradentate EDDB ligand was prepared by condensation of (2*R*,2'*S*)- α -bromobutyric acid with 1,2-diaminoethane in alkaline medium.



The structure of this ligand was confirmed by IR and ^{13}C NMR spectroscopy (Fig. 2a). When flexible, linear tetradentate ligands of this type exhibit octahedral coordination, they can have three geometric isomers, as depicted in Fig. 1. It was found from X-ray structural analysis^{12,13} that the strain in the chelate ring in Co(III) complexes with EBAA decreases in the order $E > G > R$. Consequently, the formation of the octahedral complex with two R rings (*cis- α*) will be energetically more favourable than the formation of the complex with one G and one R ring (*cis- β*). The *trans* isomer cannot be formed because the second bidentate ligand is en.

The geometric isomers formed were identified by ^{13}C NMR spectroscopy. Comparison of the measured spectra (Fig. 2 and Table I) indicated that the *cis- α* isomer

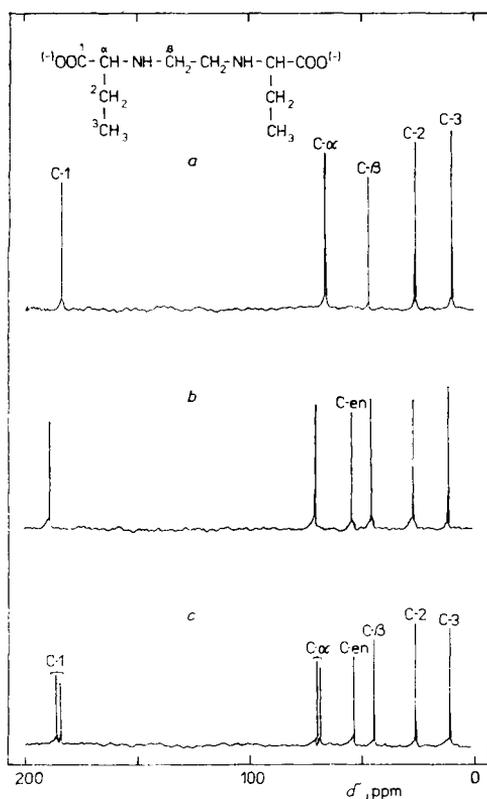


FIG. 2
The ^{13}C NMR spectra of *a* the DL-EDDB ligand, *b* *cis- α* -[Co(EDDB)(en)]⁺, *c* *cis- β* -[Co(EDDB)(en)]⁺ in $^2\text{H}_2\text{O}$

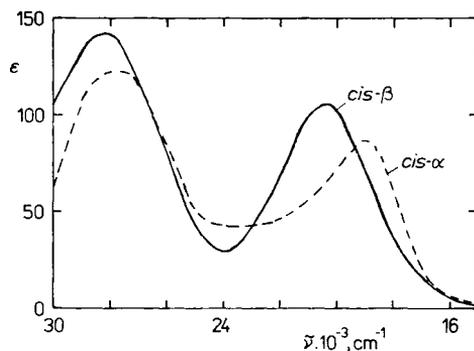


FIG. 3
The electronic absorption spectrum of *cis- α* -[Co(EDDB)(en)]⁺ (-----) and *cis- β* -[Co(EDDB)(en)]⁺ (—)

(C_2 symmetry) yields a simple spectrum with the same number of lines as the ligand alone. As the *cis-β* isomer contains three different chelate rings, its symmetry is decreased (C_1) and some split signals are observed in the spectrum.

The isomer geometry can also be found from the visible absorption spectra (Fig. 3 and Table II), which have been described in detail for the $[\text{Co}(\text{EBAA})(\text{en})]^+$ complexes. This type of compound has CoN_4O_2 holohehedral structure. Because of the tetragonal symmetry, the first excited state of the cobalt d^6 low-spin complex $T_{1g}(O_h)$ is split to the 1A_2 and 1E levels. Thus the ${}^1A_{1g} \rightarrow {}^1E_g$ and ${}^1A_{1g} \rightarrow {}^1A_{2g}$ transitions can be expected for the low-energy absorption band. The decreased symmetry of this band as a result of the splitting of the D_{4h} component in the *cis-α* isomer is apparent in Fig. 3, while the *cis-β* isomer exhibits a symmetric band in this region. It could be expected from the lower symmetry of the *cis-β* isomer that this isomer will have a higher molar absorption coefficient value than the more symmetric *cis-α* isomer; this was found experimentally to be true.

TABLE I
The ^{13}C chemical shifts of the studied compounds in ${}^2\text{H}_2\text{O}$

Compound	δ , ppm ^a
H_2EDDB	182.8, 65.7, 46.9, 26.3, 10.0
<i>cis-α</i> - $[\text{Co}(\text{EDDB})(\text{en})]\text{ClO}_4 \cdot \text{H}_2\text{O}$	188.0, 70.7, 54.3, 46.2, 26.5, 11.7
<i>cis-β</i> - $[\text{Co}(\text{EDDB})(\text{en})]\text{ClO}_4 \cdot \text{H}_2\text{O}$	185.8, 184.3, 69.7, 69.5, 54.0, 44.3, 26.3, 10.6

^a For assignment, see Fig. 2.

TABLE II
Electronic and CD spectra of isomers

Isomer	Ligand field spectra, $\lambda_{\text{max}}(\epsilon)^a$		CD, $\lambda_{\text{max}}(\Delta\epsilon)^a$
	${}^1A_{1g} \rightarrow {}^1T_{2g}$	${}^1A_{1g} \rightarrow {}^1T_{1g}$	
Δ - <i>cis-α</i>	361 (123)	527 (88)	540 (-0.70)
Λ - <i>cis-α</i>	361 (123)	527 (88)	540 (+0.11)
Δ - <i>cis-β</i>	355 (144)	480 (107)	495 (-0.04)
Λ - <i>cis-β</i>	355 (144)	490 (107)	495 (+0.05)

^a The values of λ_{max} are given in nm, those of ϵ or $\Delta\epsilon$ in $1 \text{ mol}^{-1} \text{ cm}^{-1}$.

Both of the geometric isomers of the EDDB racemic ligand could be partially resolved to yield the corresponding enantiomers using gel permeation chromatography on Sephadex G-10. This procedure has been used successfully for cationic¹⁴ and anionic¹⁵ Co(III) complexes and is especially useful as partial resolution of the racemates is accompanied by purification of the complex with separation of inorganic salt used as an elution agent in the chromatographic separation of the geometric isomers. Table II gives the degree of optical purity of the enantiomers obtained after a single passage through the column.

The absolute configuration of the isomers obtained was found by measuring the CD spectra on the basis of the Cotton effect observed for the ${}^1A_{1g} \rightarrow {}^1T_{1g}$ transition. It was confirmed on the basis of correlation of the stereochemical data for these complexes with the X-ray diffraction data^{12,13} that the negative Cotton effect corresponds to the Δ absolute configuration and the positive effect to the Λ configuration. The two dominant structural sources of dissymmetry in the $[\text{Co}(\text{EDDA})\text{X}_2]$ and $[\text{Co}(\text{EDDB})\text{X}_2]$ complexes are the spatial arrangement of the chelate rings and the configuration of the asymmetric N atom. It can be seen from Table II that the CD bands for the *cis- α* isomer are more intense than those for the *cis- β* isomer, in agreement with observations for the $[\text{M}(\text{EDDA})\text{X}_2]$ complex, where M = Co(III), Cr(III) (ref.¹⁶).

EDDB and both of its complexes exhibit two intense absorption bands in the IR spectra in the region $1\,500\text{--}1\,800\text{ cm}^{-1}$. The free ligand has an antisymmetric stretching vibration of COO^- at $1\,580\text{ cm}^{-1}$ and a symmetric stretching vibration at $1\,395\text{ cm}^{-1}$. The corresponding bands for the *cis- α* isomer lie at values of $1\,627$ and $1\,370\text{ cm}^{-1}$ and for the *cis- β* isomer at $1\,635$ and $1\,374\text{ cm}^{-1}$. Thus, the difference $\nu(\text{COO}^-) = \nu_{\text{as}}(\text{COO}^-) - \nu_{\text{s}}(\text{COO}^-)$ is greater for the isomers than for the pure ligand, as coordination leads to a shift of $\nu_{\text{as}}(\text{COO}^-)$ to higher wavenumbers and of $\nu_{\text{s}}(\text{COO}^-)$ to lower wavenumbers. This behaviour in the IR spectra is typical for the asymmetrically coordinated COO^- group, which acts as a monodentate ligand in these complexes.

As mentioned above, the *cis- α* isomer was formed in approximately a six-fold excess over the *cis- β* isomer. It follows from the study of models that this is a result of nonbonding repulsive interactions between the hydrogen atoms of en and EDDB, that prevent formation of a larger amount of the *cis- β* isomer. When these steric interactions between ligands that have been postulated for the diamine analogue are eliminated in the *cis- β* isomer by using a different type of bidentate ligand (carbonate, oxalate, malonate) or monodentate ligand (H_2O , Cl^- , etc.), a much larger amount of the *cis- β* isomer is obtained¹⁶. Therefore, it is surprising that Moo-Jin Ju et al.¹⁰ obtained only the *cis- α* isomers in the preparation of ternary Co(III) complexes with EDDB and monodentate ligands. Similarly, these authors¹⁷ obtained stereoselectivity only the Δ -*cis- α* isomer of $[\text{Co}(\text{EDDP})\text{Cl}_2]^-$ in the preparation of the ternary Co(II) complex with (2*S*,2'*S*)-2,2'-ethylene-bis(2-aminopropanoic) acid

(EDDP). The diastereoselectivity of the complexes is strongly affected by the preparation procedure. In both syntheses, these authors employed oxidation with atmospheric oxygen in alkaline medium with subsequent acidification with HCl and evaporation of the solution obtained. It was recently found¹⁸ that the oxidation of cobalt salts with atmospheric oxygen in the presence of EBAA in alkaline medium leads to the formation of double-bridge μ -hydroxo- μ -peroxo-dicobalt(III) complexes of the $\text{Co}_2\text{L}_2\text{O}_2\text{OH}^-$ type, where L = EBAA. These complexes are relatively stable but decompose in acid medium to form the *cis*- α - $[\text{Co}(\text{EBAA})\text{X}_2]^+$ complexes with release of H_2O_2 . From this point of view, the stereoselective formation of the *cis*- α -isomers described in refs^{10,17} is not surprising.

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