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Dichloro, Alanine and S-Methylcysteine Cobalt (III) Complexes of Ethylenediamine-N,N'-di- α -isobutyric Acid

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Synthesis of dichloro cobalt (III) complexes of a flexible N_2O_2 -type tetradentate ligand, ethylenediamine-N,N'-di- α -isobutyric acid (eddib), has yielded two geometrical isomers, *s-cis*-(Co(eddib)Cl₂)⁻ and *uns-cis*-(Co(eddib)Cl₂)⁻. A series of substitution reactions, (Co(eddib)Cl₂)⁻ \rightarrow (Co(eddib)Cl(H₂O)) \rightarrow (Co(eddib)CO₃)⁻ \rightarrow (Co(eddib)(H₂O)₂)⁺ have been run for each of the two geometrical isomers. The reaction between the *s-cis*-(Co(eddib)Cl₂)⁻ complex and L-alanine (L-als) or S-methyl-L-cysteine (L-mcy) gave the meridional *s-cis*-[Co(eddib)(aa)] (aa = L-ala or L-mcy) complex. The S-methyl-L-cysteine was found to coordinate to cobalt (III) ion *via* the nitrogen and oxygen donor atoms.

Introduction

A linear flexible edda-type ligand (edda = ethylenediaminediacetic acid, HOOCCH₂NHCH₂CH₂NHCH₂COOH) can occupy four coordination sites with three geometric isomers possible: *s-cis*-(symmetric *cis*), *uns-cis*(unsymmetric *cis*), and *trans*(Figure 1).

Mori *et al.*¹ reported the synthesis of the *s-cis* cobalt(III) complexes of edda. Legg and Cooke² prepared both the *s-cis* and *uns-cis* isomers for the [Co(edda)(am)]⁺ (am = en, 2NH₃) as well as the cobalt(III) complexes of N-alkyl substituted analogue of edda. Kuroda³⁻⁵ observed that the coordination mode of edda depended upon the temperature. Later, Legg^{6,7} and others⁸⁻¹¹ prepared and characterized *uns-cis* isomers of [Co(edda)(L)]⁺ (L = en, S-alanine, R-propylenediamine).

The C-alkyl-substituted analogue of edda, ethylene-diamine-N,N'-di-S- α -propionate, ⁻OOCCH(CH₃)NHCH₂CH₂NHCH(CH₃)COO⁻(SS-eddp), has been prepared by Liu and Co-workers¹², in which both *s-cis* and *uns-cis* isomers of (Co(SS-eddp)(L))⁺ (L=en, R=Pn) were isolated. The cobalt(III) complexes of S-stibenediamine-N,N'-diacetate (S-sdda)¹³ gave only the *s-cis* isomer. The cobalt(III) complexes of ethylenediamine-N,N'-di-S- α -isovalerate(ven)^{14,15} yielded only the *s-cis* isomer for (Co(ven)(H₂O)NO₃), while in the case of (Co(ven)(H₂O)₃)⁺ and (Co(ven)(en))⁺ both *s-cis* and *uns-cis* isomers were found to exist. The cobalt(III) complexes of 2S, 2'S-1,1'-(ethane-1,2-diyl) bis(pyrrolidine-2-carboxylate) (pren), Co(pren)L₂⁺, have yielded only the *s-cis* isomer when L = Cl or H₂O, while both the *s-cis* and *uns-cis* isomers have been isolated when L₂ = en.^{16,17} Recently, we prepared a C-ethyl-substituted analogue of edda, ethylenediamine-N,N'-di- α -butyric acid, HOOCCH(C₂H₅)NHCH₂CH₂NHCH(C₂H₅)COOH(eddb), which yielded *s-cis*-(Co(eddb)Cl₂)⁻ complex.¹⁸

This paper will describe the preparation of the dichloro, alanine, and S-methylcysteine cobalt(III) complexes of a

C-alkyl-substituted analogue of edda, ethylenediamine-N,N'-di- α -isobutyric acid, HOOC(CH₃)₂NHCH₂CH₂NH(CH₃)₂COOH(eddib). We reported previously the synthesis of the eddib ligand and the dichloro cobalt (III) complex of eddib, in which only the *s-cis* isomer was obtained.¹⁹ We have recently been able to isolate the *uns-cis* isomer. It will be shown that both *s-cis* and *uns-cis* isomers are formed from the preparation of the dichloro cobalt(III) complexes of eddib. Complexes of the type [Co(eddib)L]⁺ (L = ClH₂O, CO₃²⁻ or 2H₂O) or Co(eddib)(aa) (aa = L-alanine or S-methylcysteine) were also prepared in this work. It will be shown that the amino acid is coordinated to the cobalt(III) ion via the nitrogen and oxygen donor atoms to give a meridional isomer.

Experimental

Physical Measurements. Electronic absorption spectra, and infrared spectra were recorded on a Shimadzu UV-240 double beam Spectrophotometer and a Shimadzu IR 435 spectrophotometer, respectively. ¹H-NMR spectra were measured with a varian EM 360-L spectrometer using D₂O solvent with internal standard, Sodium 2,2-dimethyl-2-silapentane-S-sulfonate(DSS). Elemental analyses were performed by Micro-Tech Lab., Skokie, Illinois, U.S.A. 2-Amino-isobutyric acid and 1,2-dibromoethane were purchased from Aldrich and used without further purification.

Preparation of Ethylenediamine-N,N'-di- α -isobutyric Acid. This was prepared from the reaction between 2-aminoisobutyric acid and 1,2-dibromoethane.¹⁹

Preparation of Hydrogen Dichloro(ethylenediamine-N,N'-di- α -isobutyrate)cobaltate(III), H[Co(eddib)Cl₂]. In 60 ml of water 2.3g of ethylenediamine-N,N'-di- α -isobutyric acid, 0.8g of sodium hydroxide, and 2.3 g of cobalt dichloride hexahydrate were added in order. Carbon diox-

ide-free air was bubbled through the reaction mixture. 10 ml of hydrogen peroxide (30%) was added dropwise, and air bubbling was continued for ten hours, during which time the color of the solution changed from dark brown to deep red violet. 20 ml of concentrated hydrochloric acid was added and the mixture was concentrated in a water bath to a volume of about 15 ml. The reaction mixture was added to an ion-exchange column (Dowex 50 \times 4-400, 200-400 mesh, H⁺ form, 200 ml) using water as an eluent. The *s-cis* isomer was eluted first, followed by the *uns-cis* isomer. Each solution was evaporated to a small volume and 10 ml of concentrated hydrochloric acid was added. The solution was evaporated again to less than half of the original volume. Upon cooling in an ice bath the product was precipitated, which was collected and washed with methanol and ether. Yield, 0.3 g for the *s-cis* isomer and 0.2 g for the *uns-cis* isomer. Anal. Calcd for H[Co(C₁₀H₁₈O₄N₂)Cl₂]: C, 31.7; H, 5.6; N, 7.4; Cl, 18.7. Found: for the *s-cis* isomer: C, 32.0; H, 5.5; N, 7.3; Cl, 18.6 and for the *uns-cis* isomer; C, 31.9; H, 5.5; N, 7.4; Cl, 18.8.

Preparation of *s-cis*- and *uns-cis*[Co(eddib)Cl₂·H₂O] in Situ. 0.04 g of *s-cis*-H[Co(eddib)Cl₂] was dissolved in 20 ml of cold 0.01N perchloric acid and stirred at 20 °C for 12 min. At this point the electronic absorption spectrum was recorded. The *uns-cis*-[Co(eddib)Cl₂·H₂O] was obtained in the same way.

Preparation of *s-cis*- and *uns-cis*-[Co(eddib)CO₃]⁻ in Situ. The redish violet solution of *s-cis*-s-[Co(eddib)Cl₂·H₂O] was allowed to stand for 90 min., and 0.05g of NaHCO₃ was added. The color of the solution changed to violet pink after 30 min of standing, and then the electronic absorption spectrum of *s-cis*-[Co(eddib)CO₃]⁻ was taken. The *uns-cis*-[Co(eddib)CO₃]⁻ was obtained by the same method.

Preparation of *s-cis*- and *uns-cis*-[Co(eddib)(H₂O)₂]⁺ in Situ. 11.6N perchloric acid was added dropwise to the solution of *s-cis*-[Co(eddib)CO₃]⁻ with stirring until the pH of the solution was 2.

The color of the solution changed from violet pink to violet, and the electronic absorption spectrum of the *s-cis*-[Co(eddib)(H₂O)₂]⁺ was taken. The *uns-cis*-[Co(eddib)(H₂O)₂]⁺ was prepared *via* the same method as that used for the *s-cis* isomer.

Preparation of *s-cis*-L-Alaninato(ethylenediamine-*N,N'*-di- α -isobutyrate)cobalt(III), *s-cis*-[Co(eddib)(L-ala)]. 1.8g of *s-cis*-H[Co(eddib)Cl₂] was dissolved in 30 ml of water and was heated at 60 °C. 0.48g of L-alanine was added and the pH of the solution was adjusted to 5 with 1N NaOH. Heating was continued for 5 hrs. The solution was concentrated to a volume of about 5 ml on a rotatory evaporator. It was then added to an ion exchange column full of 200-400 mesh Dowex 50 \times 4-400 in H⁺ form. Elution with water at a flow rate of 2 ml/min gives two bands. The upper band was turned out to be [Co(eddib)(H₂O)₂]⁺. The concentration of the lower band solution yielded the redish purple product. Yield 0.72g. Anal. Calcd for CoC₁₃H₂₄O₆N₃: C, 42.5; H, 6.6; N, 11.4. Found: C, 42.0; H, 6.9; N, 11.3.

Preparation of *s-cis*-S-Methyl-L-cysteinato(ethylenediamine-*N,N'*-di- α -isobutyrate)cobalt(III), *s-cis*-[Co(eddib)(L-mcy)]. 1.8g of *s-cis*-H[Co(eddib)Cl₂] was dissolved in 30 ml of water. After heating at 60 °C, 0.67g of S-methyl-L-cysteine was added. The pH of the solution was

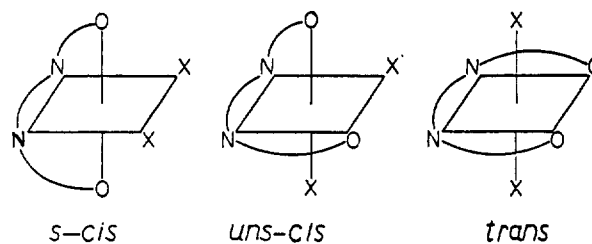


Figure 1. The possible geometric isomers of the [Co(edda)X₂]ⁿ⁺ complexes.

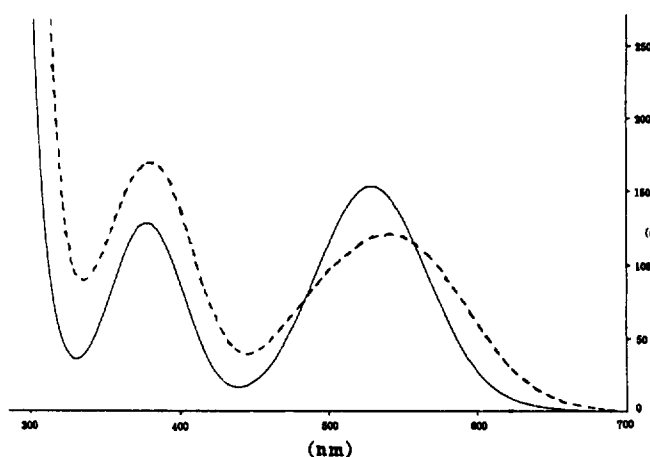


Figure 2. Electronic absorption spectra of *s-cis*-[Co(eddib)Cl₂]⁻ (—) and *uns-cis*-[Co(eddib)Cl₂]⁻ (----).

adjusted to 11 with 1 N NaOH. Heating was continued for 5 hrs, and then the solution was concentrated on a rotatory evaporator to a volume of about 5 ml. It was added to a cation exchange resin column full of Dowex 50 \times 4-400 (200-400 mesh, H⁺ form). One fraction was obtained by elution with water using a flow rate of about 2 ml/min. The product was obtained by evaporating the solution to dryness in a water bath. Yield, 0.88g. Anal. Calcd for CoC₁₄H₂₆O₆N₃S: C, 39.7; H, 6.2; N, 9.9. Found: C, 39.6; H, 6.2; N, 10.0.

Results and Discussion

Two geometrical isomers, *s-cis*- and *uns-cis*-[Co(eddib)Cl₂]⁻, were obtained during the course of our preparation. The electronic absorption spectra of these complexes are shown in Figure 2. In the case of the *s-cis* isomer, the band I and band II, which are due to the d-d transitions in the octahedral CoN₂O₂Cl₂ system, appear between 350-600 nm. The shape of the first band at 530 nm is nearly symmetrical and the intensity of the second band is somewhat lower than the first one. If the complex has the *trans* geometry, a split in the first band region would be observed. The d-d transitions are also observed between 350-600 nm for the *uns-cis* isomer. When the complex has an *uns-cis* configuration, two atoms of the same kind (Cl-Cl, N-N, O-O) are at the *cis* positions so that the intense absorption at band II would be expected, since the ligand field around the central metal atom is highly unsymmetrical. In Figure 2 the absorption intensity of band II is higher than band I, and this was also the case for the *uns-cis*-[Rh(SS-eddp)Cl₂]⁻ complex.²⁰ Thus, the assignments of the *s-cis* and *uns-cis* con-

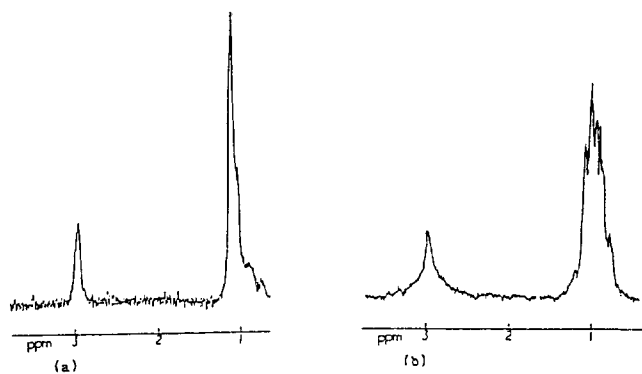


Figure 3. Pmr spectra of (a) *s-cis* isomer and (b) *uns-cis* isomer of $[\text{Co}(\text{eddib})\text{Cl}_2]^-$.

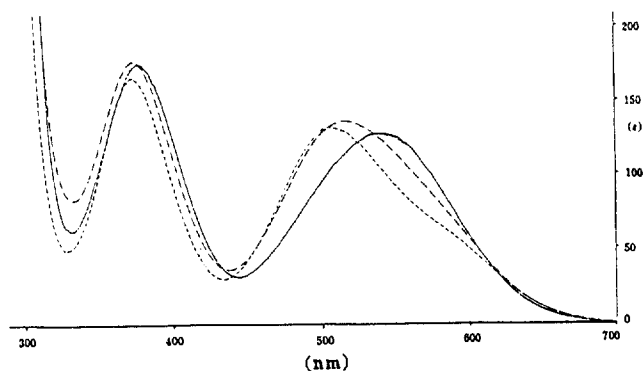


Figure 4. Electronic absorption spectra of *s-cis*- $[\text{Co}(\text{eddib})\text{ClH}_2\text{O}]$ (—), *s-cis*- $[\text{Co}(\text{eddib})\text{CO}_3]^-$ (----), and *s-cis*- $[\text{Co}(\text{eddib})(\text{H}_2\text{O})_2]^+$ (-----).

figurations to the dichloro complexes prepared in this work are reasonable, though the evidence from the electronic absorption spectra alone is not conclusive.

The *s-cis*- and *uns-cis*- $[\text{Co}(\text{eddib})\text{Cl}_2]^-$ isomers are clearly distinguished in the pmr spectra shown in Figure 3. The pmr spectrum of the *s-cis* isomer shows the methylene protons between two nitrogen atoms at 2.96 ppm as a singlet. The shift of this peak to the higher field from 3.64 ppm for the free ligand to 3.06 ppm for the complex is due to the magnetic anisotropic effect of the carbon-nitrogen bond.^{21, 22} The two isobutyrate arms of the *s-cis*- $[\text{Co}(\text{eddib})\text{Cl}_2]^-$ isomer are equivalent and the methyl protons of the butyrate arms resonate at 1.11 ppm as a singlet. If the complex has a *uns-cis* configuration, it has C_1 symmetry and two butyrate arms are no longer equivalent. In other words, one butyrate arm exists as an R ring²³ which is above the plane containing Co metal ion and two nitrogen atoms of eddib, and the other butyrate arm is placed in the G ring which is in the plane containing Co metal ion and two nitrogen atoms of eddib. In addition, one of the two methyl groups in each of G or R ring is located within the ring and the other is located out of the ring. Therefore, four methyl singlets can be expected in the *uns-cis* isomer. In the pmr spectrum of the *uns-cis* isomer (Figure 4) four methyl singlet peaks appear between 0.9 and 1.2 ppm. Also, methylene protons between the coordinated nitrogen atoms are not equivalent in the *uns-cis* isomer and resonate at 2.96 ppm as an overlapped multiplet because of four types of flexible four protons.

Figure 4 shows the electronic absorption spectrum for the

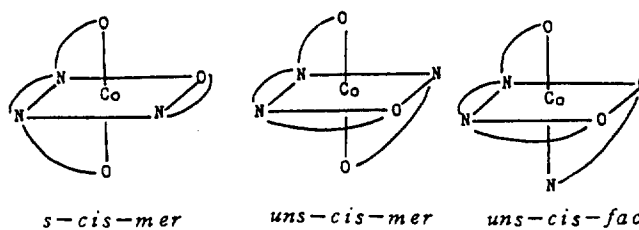


Figure 5. Configurational isomers of $[\text{Co}(\text{edda})(\text{aa})]^{n+}$ complexes (aa = amino acid).

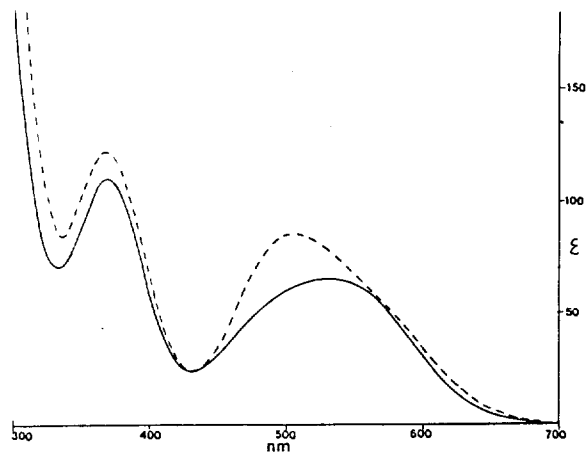
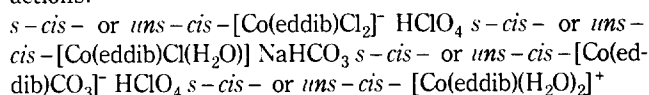


Figure 6. Electronic absorption spectra of *s-cis-mer*- $[\text{Co}(\text{eddib})(\text{L-ala})]$ (—) and *uns-cis-mer*- $[\text{Co}(\text{eddib})(\text{L-mcy})]$ (-----).

uns-cis complexes obtained from the following series of reactions.



In these spectra the absorption maxima shift to shorter wavelengths as the labile chloro ligands are substituted with aqua chloro, carbonato, and two aqua ligands. Such observation is in accordance with the spectrochemical series of chloro, carbonate, and aqua ligands.

The substitution reaction between *s-cis*- $[\text{Co}(\text{eddib})\text{Cl}_2]^-$ and L-alanine or S-methyl-L-cysteine has resulted in isolation of the corresponding amino acid complex. Three geometrical isomers, *s-cis-mer* (meridional), *uns-cis-mer*, and *uns-cis-fac* (facial) are possible an amino acid (aa) is coordinated in the $[\text{Co}(\text{eddib})(\text{aa})]^{n+}$ complex (Figure 5). In the electronic absorption spectrum of $[\text{Co}(\text{eddib})(\text{L-ala})]$ (Figure 6) the band I and band II appear between 350 and 580 nm. The splitting pattern of the first band having a shoulder at 490 nm indicates that the $[\text{Co}(\text{eddib})(\text{L-ala})]$ complex has a meridional geometry of either *s-cis* or *uns-cis*. The pmr spectrum of the $[\text{Co}(\text{eddib})(\text{L-ala})]$ complex has the methyl protons at near 1.6 ppm, the pattern of which shows an *s-cis* geometry.

Although the S-methyl-L-cysteine has three donor atoms (N,O,S), the IR spectrum of the $[\text{Co}(\text{eddib})(\text{L-mcy})]$ complex shows the coordination of the nitrogen and oxygen donor atoms. The COO stretching band occurs at 1640cm^{-1} as is typical of the coordinated carboxylate groups. The electronic absorption spectrum (Figure 6) of this complex shows a similar pattern as the alanine complex, a CoN_3O_3 system

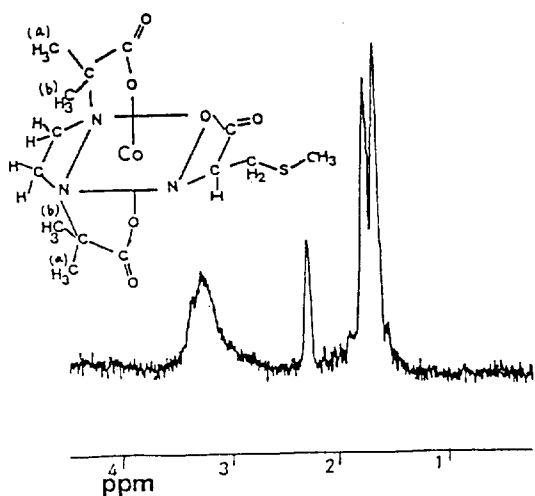


Figure 7. PMR spectrum of *s-cis-mer*-(Co(eddib)(SMCys) in D_2O .

with a meridional configuration. In the pmr spectrum of the complex (Figure 7) the S-methyl proton is shown at 2.2 ppm and the methyl protons at near 1.7 ppm, indicating that the complex has an *s-cis* geometry. If the complex had an *uns-cis* geometry, its pmr spectrum would have shown more complicated pattern. Therefore, the L-alanine or S-methyl-L-cysteine cobalt(III) complex of eddib is shown to have the meridional *s-cis* configuration.

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