Trifunctional Amino Acid–Cobalt(III) Complexes of *N,N'*-Dimethylethylenediamine-*N,N'*-diacetic Acid

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Abstract

Cobalt(III) complexes of *N,N'*-dimethylethylenediamine-*N,N'*-diacetic acid (dmedda) and trifunctional amino acids, [Co(dmedda)(aa)] (aa = S-methyl-L-crysteine, L-glutamic acid, L-aspartic acid) have been prepared from the reaction between the s-*cis*-$[Co(dmedda)Cl_2]^-$ complex and the amino acid. The amino acids have been found to coordinate through the amine and carboxylate groups. The glutamic acid and aspartic acid are coordinated to the cobalt(III) ion via formation of the five-membered glycinate chelate ring. The optically active amino acids have shown a remarkable stereoselectivity in their coordination to the racemic s-*cis*-$[Co(dmedda)Cl_2]^-$ giving the Δ-s-*cis*-[Co(dmedda)(aa)] absolute configuration only.

Introduction

Cobalt(III) complexes of the *N,N'*-dimethylethylenediamine-*N,N'*-diacetate ion (dmedda) have been investigated in the past years [1–4]. The flexible tetradentate dmedda is an ONNO type ligand like the ethylenediamine-*N,N'*-diacetate ion (edda) except that the former has the methyl substitution at the nitrogen donor atoms. The cobalt(III) complexes of dmedda have been obtained in the s-*cis* geometry only, while those of edda have been isolated in both geometries, uns-*cis* and s-*cis* [1, 5–9]. On the other hand, Douglas *et al.* have prepared the tmdda (trimethylenediamine-*N,N'*-diacetate) ligand containing a larger diamine backbone. The cobalt(III) complexes of tmdda have been yielded in the uns-*cis* geometry only except for the [Co(tmdda)(en)]$^+$ complex [10–13].

The dmedda cobalt(III) complexes of trifunctional amino acids such as S-methyl-L-cysteine (L-smc), L-glutamic acid (L-glu), and L-aspartic acid (L-asp) have been of particular interest because only two of the three functional groups present in those amino acids can bind to the cobalt(III) complexes of dmedda. For cysteine, $HSCH_2CH(NH_2)COOH$, both sulfur-to-metal and oxygen-to-metal bonds have been found to exist in solid complexes of Zn(II), Cd(II), and Hg(II) [14], whereas sulfur and nitrogen appear to be the ligating atoms toward Ni(II) in aqueous solution [15]. With methionine, $CH_3SCH_2CH_2CH(NH_2)COOH$, the formation constants in aqueous solution indicate that coordination occurs via the $-NH_2$ and $-COO^-$ groups for a number of transition and post-transition metal ions [16–18].

S-methyl-L-cysteine, L-glutamic acid and L-aspartic acid can, when coordinated to a metal ion, form a five-, six- (asp), or seven-membered (glu) chelate ring depending on the mode of coordination. Although the trifunctional amino acids have been observed to coordinate to a metal ion mostly through the $-NH_2$ and $-COO^-$ groups [19], we have undertaken to study the chelate systems of the cobalt(III) complexes containing the dmedda and trifunctional amino acids of S-methyl-L-systeine, L-glutamic acid, and L-aspartic acid to observe (i) the mode of coordination resulting from the reaction between the $[Co(dmedda)Cl_2]^-$ complex and the trifunctional amino acids, and (ii) whether or not the optically active amino acids coordinate stereoselectively in their reaction with racemic $[Co(dmedda)Cl_2]^-$.

Experimental

Preparation of Barium N,N'-Dimethylethylenediamine-N,N'-diacetate (Badmedda)

This was prepared essentially by the method of Legg and Cooke with some modification as described previously [4].

Preparation of s-cis-Hydrogen(N,N'-dimethylethylenediamine-N,N'-diacetato) Dichloro Cobaltate(III), s-cis-H[Co(dmedda)Cl$_2$] [4]

1.6 g of barium *N,N'*-dimethylethylenediamine-*N,N'*-diacetate was dissolved in 20 ml of water.

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1.4 g of cobaltous sulfate heptahydrate dissolved in 20 ml of water was added to this solution and the reaction mixture was maintained at 50 °C for 30 min. Barium sulfate was removed from the reaction mixture by filtration. 2.0 ml of 30% H_2O_2 was carefully added to the filtrate. 30 ml of concentrated hydrochloric acid was added to this solution and then the resulting solution was concentrated to a volume of 20 ml, which was added to an ion-exchange column filled with 200–400 mesh Dowex 1-8X anion exchange resin. The eluent was 0.1 N HCl solution. The first band showed a purple color, which turned out to be the [Co(dmedda)Cl(H_2O)] complex, and the second band showed a green color which was the H[Co(dmedda)Cl_2] complex. The green complex was obtained by evaporating the solution to dryness on a water bath.

Preparation of s-cis-(S-methyl-L-cysteinato)(N,N'-dimethylethylenediamine-N,N'-diacetato) Cobalt(III), s-cis-[Co(dmedda)(L-smc)]

A solution containing 1.0 g (0.003 mol) of s-*cis*-H[Co(dmedda)Cl_2] in 30 ml of water was heated at 60 °C for 20 min. To this solution was added a solution containing 0.40 g (0.003 mol) of s-methyl-L-cysteine in 10 ml of water. The pH of the solution was adjusted to 8.5 by addition of 1 M NaOH aqueous solution. After 0.15 g of activated charcoal had been added to the solution, the mixture was mechanically stirred at 60 °C for 8 h. The charcoal and insoluble material were removed by filtration and washed with hot water. The combined filtrate and washings were concentrated to *ca.* 5 ml with a rotary evaporator. The resulting violet solution was poured into a column containing cation-exchange resin (Dowex 50 W-X4, 200–400 mesh, H^+ form). The mixture of products absorbed at the top of the column and pink impurities were eluted with water. Only one fraction gave 0.2 g of the required product. Yield: 0.2 g (17%). *Anal.* Calc. for $CoC_{12}H_{22}O_6N_3S$: C, 36.5; H, 5.6; N, 10.6. Found: C, 36.4; H, 5.5; N, 11.0%.

Preparation of s-cis-(N,N'-Dimethylethylenediamine-N,N'-diacetato)(L-hydrogen glutamato) Cobalt(III), s-cis-[Co(dmedda)(L-glu)]

The complex was prepared and separated into only one isomer in the same procedure as that used for [Co(dmedda)(L-smc)] using L-glutamic acid in place of s-methyl-L-cysteine. The reaction solution was concentrated and chromatographed on an cation-exchange column. The complex was eluted with distilled water. The substance was then obtained by evaporating the solution to dryness on a water bath. Yield: 0.34 g (27%). *Anal.* Calc. for $CoC_{13}H_{21}O_8N_3 \cdot H_2O$: C, 34.9; N, 5.2; N, 9.4. Found: C, 34.8; H, 5.2; N, 9.5%.

Preparation of s-cis-(N,N'-Dimethylethylenediamine-N,N'-diacetato)(L-hydrogen aspartato) Cobalt(III), s-cis-[Co(dmedda)(L-asp)]

The complex was prepared in the same way as that used for [Co(dmedda))L-glu)] using L-aspartic acid. Yield: 0.41 g (32%). *Anal.* Calc. for $CoC_{12}H_{19}O_8N_3 \cdot 1.5H_2O$: C, 32.6; H, 5.0; N, 9.5. Found: C, 32.7; H, 5.0; N, 9.6%.

Physical Measurements

Electronic absorption spectra were obtained with a Shimadzu UV-240 Spectrophotometer. PMR spectra were recorded on a Varian EM 360L Spectrometer. Infrared spectra were taken with a Hitachi 270-30 Spectrophotometer. Elemental analyses were performed by Korea Advanced Institute of Science and Technology. Circular dichroism spectra were measured using a Jasco J-550C Automatic Recording Spectropolarimeter.

Results and Discussion

The dichloro cobalt(III) complex of dmedda has yielded only one isomer of s-*cis* geometry [4]. Therefore, the trifunctional amino acid cobalt(III) complexes of dmedda have been prepared from the reaction between the s-*cis*-[Co(dmedda)Cl_2]$^-$ complex and one of the amino acids used here, s-methyl-L-cysteine, L-glutamic acid, and L-aspartic acid.

A trifunctional amino acid ligand offers an additional interesting question as to which functional groups are utilized in chelation. There are three possible modes of chelation when the S-methyl-L-cysteine(L-smc) reacts with s-*cis*-[Co(dmedda)Cl_2]$^-$ as shown in Fig. 1: N, S chelation (**I**), S, O chelation (**II**), and N, O chelation (**III**).

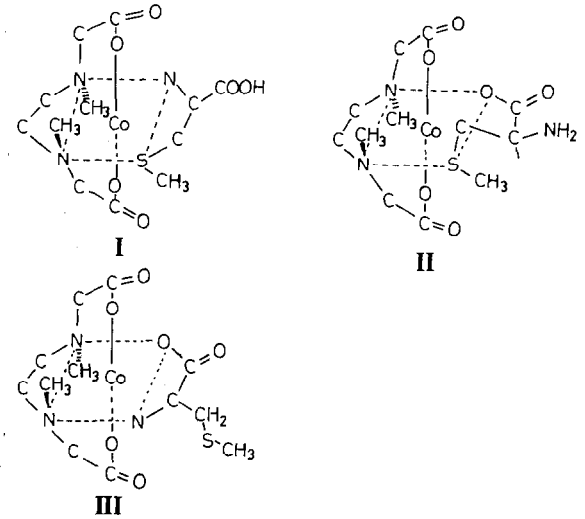

Fig. 1. The geometrical isomers of the [Co(dmedda)(L-smc)] complex.

TABLE I. The COO Stretching Frequencies of the Cobalt(III) Complexes

Compound	$_{as}$OCO	$_{s}$OCO (cm^{-1})
dmedda	1735[a]	1440
s-*cis*-[Co(dmedda)Cl_2]$^-$	1630	1365
s-*cis*-[Co(dmedda)(L-smc)]	1640	1360
s-*cis*-[Co(dmedda)L-glu)]	1730[a], 1650	1370
s-*cis*-[Co(dmedda)(L-asp)]	1730[a], 1650	1370

[a]Uncoordinated COOH stretching band.

Table I shows the COO stretching frequencies for the dmedda ligand and the complexes prepared in this work. While the dmedda ligand shows the free –COOH group at 1735 cm^{-1}, the [Co(dmedda)(L-smc)] indicates the coordinated $-COO^-$ at 1640 cm^{-1}, which rules out structure **I** [20].

The electronic absorption spectra are particularly helpful in distinguishing the coordinating donor atoms of N, O, and S [21, 22]. In the visible spectrum of [Co(dmedda)(L-smc)] (Table II, also see Fig. 6 below) the d–d transitions occur at 540 and 360 nm. The band at longer wavelength is assigned to the transition $A_{1g} \rightarrow T_{1g}$, and the one at shorter wavelength to $A_{1g} \rightarrow T_{2g}$. If a S atom is coordinated, the visible spectrum of either $[CoN_3O_2S]$ or $[CoN_2O_3S]$ (structure **II** in Fig. 1) would have shown the d–d transitions at much longer wavelengths (~600 nm) than those observed in this work, reflecting the relative positions of the groups in the spectrochemical series, $-S^- <$ amine $< -CO_2^-$ [21, 22]. Therefore, structure **II** in Fig. 1 is eliminated, and in the [Co(dmedda)(L-smc)] complex the coordination of the S-methyl-L-cysteine ligand takes place through the amino and carboxylate groups (structure **III**).

TABLE II. Electronic Spectral Data for Aqueous Solutions of the Cobalt(III) Complexes

Compound	Absorption maxima (nm) (ϵ ($M\ cm^{-1}$))
s-*cis*-[Co(dmedda)Cl_2]	597(75), 411(57)
s-*cis*-[Co(dmedda)(L-smc)]	540(62), 500 sh, 360(127)
s-*cis*-[Co(dmedda)(L-glu)]	542(97), 503 sh, 375(142)
s-*cis*-[Co(dmedda)(L-asp)]	542(84), 500 sh, 376(112)

In the s-*cis*-meridional isomer like structure **III** in Fig. 1, the holohedrized symmetry is rhombic, with the average contribution being different along all three axes. This loss of symmetry of the s-*cis*-*mer*-$[CoN_3O_3]$ system is expected to cause a splitting or at least a broadening of the lowest energy absorption [23]. A definite shoulder is found for the lower energy absorption band of s-*cis*-*mer*-[Co(edda)(L-ala)] [24]. Such phenomena are also observed in structure **III** of our s-*cis*-*mer*-[Co(dmedda)(L-smc)].

In the PMR spectrum of s-*cis*-*mer*-[Co(dmedda)(L-smc)] (Fig. 2) the methyl protons at the sulfur atom are shown as a singlet at 1.7 ppm, and the two β-methylene hydrogens of the S-methyl-L-cystene exhibit a doublet at 3.0 ppm. The single hydrogen on the α-carbon atom and four methylene hydrogens in the R ring are shown at 3.2–4.2 ppm. The methyl protons attached to the nitrogen atoms show two singlets at 2.2–2.4 ppm.

It is very interesting to observe that coordination in the [Co(dmedda)(L-smc)] complex takes place through the amino and carboxylate groups in spite of the strong ligating properties of the sulfide. Because the S atom (soft base) [25] differs markedly in its donor properties from the N atom of an amino group and the O atom of a carboxylate group (hard base), the S-methyl-L-cysteine may tend to coordinate with a cobalt(III) ion (hard acid) using the pair of hard base atoms (N and O).

In the s-*cis*-[Co(dmedda)(aa)] (aa = L-aspartic acid and L-glutamic acid) there are three possible geometrical isomers resulting from different modes of coordination of the amino acids (Fig. 3). Structure **IV** would not occur because of the excessively large chelate rings. Structure **V** involves a chelate ring formed by the amino group and the non-α-carboxylate group, while structure **VI** has a chelate ring formed by the amino and α-carboxylate groups.

Infrared spectra of both s-*cis*-[Co(dmedda)(L-glu)] and s-*cis*-[Co(dmedda)(L-asp)] show an uncoordinated –COOH at 1730 cm^{-1} and a co-

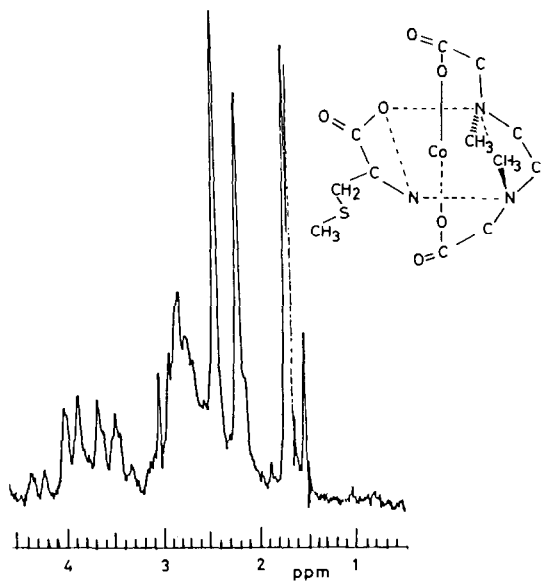

Fig. 2. The PMR spectrum of s-*cis*-[Co(dmedda)(L-smc)] in D_2O.

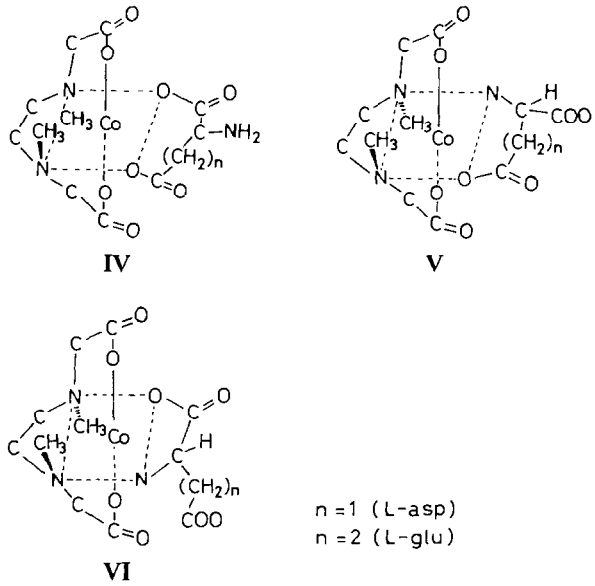

Fig. 3. The geometrical isomers of [Co(dmedda)(L-aa)] where aa is aspartic or glutamic acid.

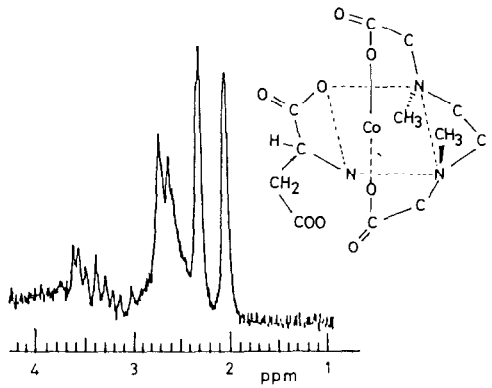

Fig. 4. The PMR spectrum of s-*cis*-[Co(dmedda)(L-asp)] in D_2O.

ordinated –COO at 1650 cm^{-1} indicating the fact that the complexes prepared in this work have either structure **V** or structure **VI**. The electronic absorption spectra are not particularly helpful in distinguishing the structures because structures **V** and **VI** are of the CoN_3O_3 type. The PMR spectra of the complexes prepared in this work, however, give strong evidence for the existence of a five-membered chelating in the complex (structure **VI**). In the PMR spectrum of [Co(dmedda)(L-asp)] (Fig. 4) the methylene protons at the α-carbon atom (marked b) are centered at 2.6 ppm, the methine proton (marked a) and the two methylene protons in the R ring (outside chelate ring) are shown in the 3.0–4.0 ppm region. A similar spectral behavior was also observed for $[Co(NH_3)_4(L\text{-asp})]^{2+}$ as a model for assigning the more complex spectra [19]. The methyl protons at the nitrogen donor atoms

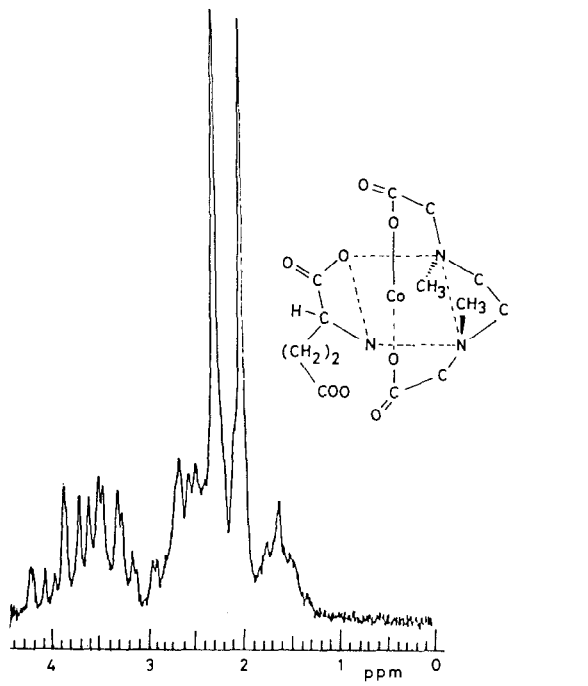

Fig. 5. The NMR spectrum of s-*cis*-[Co(dmedda)(L-glu)] in D_2O.

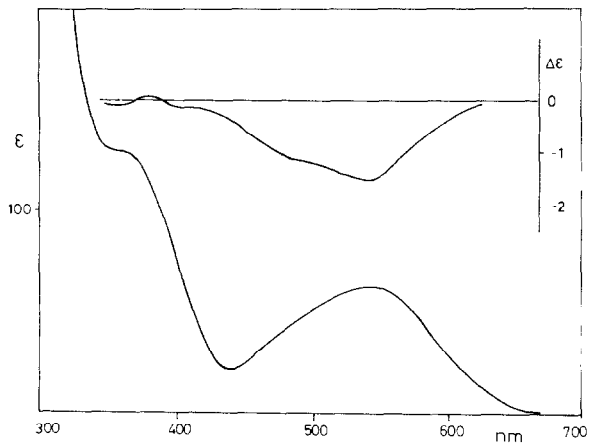

Fig. 6. CD spectrum and electronic absorption spectrum of s-*cis*-[Co(dmedda)(L-smc)].

show two peaks between 2.03 and 2.23 ppm. The occurrence of two bands is probably due to the steric interaction between the N-methyl group and the non-α-carboxylate arm. The PMR spectrum of s-*cis*-[Co(dmedda)(L-glu)] (Fig. 5) shows the same pattern as observed for s-*cis*-[Co(dmedda)(L-asp)]. The similarity in the chemical shifts of the N-methyl protons in the complexes of L-glutamic acid, L-aspartic acid, and S-methyl-L-cysteine may result from the protons being in the same chemical environment in those complexes as would be expected if the complexes have a five-membered chelate ring.

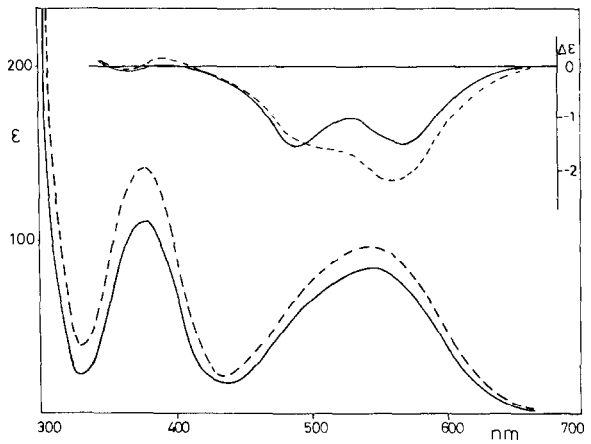

Fig. 7. CD spectrum and electronic absorption spectrum of s-*cis*-Co(dmedda)(L-asp) and s-*cis*-Co(dmedda)(L-glu).

Our assignment that s-*cis*-[Co(dmedda)(L-asp)] and s-*cis*-[Co(dmedda)(L-glu)] have structure **VI** is substantiated by the observation that the glutamic and aspartic acids are coordinated exclusively via the five-membered glycinate ring in the [Co(tmdda)-(L-glu)] and [Co(tmdda)(L-asp)] complexes [13, 19].

s-*cis*-$[Co(dmedda)Cl_2]^-$ has been obtained as a racemic mixture and has not been resolved in this work. The dmedda cobalt(III) complexes of S-methyl-L-cysteine, L-glutamic acid and L-aspartic acid have been prepared from the reaction between the racemic s-*cis*-$[Co(dmedda)Cl_2]^-$ complex and the optically active amino acids. The CD spectra of the complexes prepared in this work (Figs. 6 and 7) show the negative dominant peak in the T_{1g} region, indicating the fact that all the L-amino acid complexes of s-*cis*-[Co(dmedda)(aa)] have the Δ configuration [26–28]. The optically active L-amino acids have shown remarkable stereoselectivity to give the stereoisomer exclusively in their coordination to racemic s-*cis*-$[Co(dmedda)Cl_2]^-$ out of two possible stereoisomers of Λ-s-*cis* and Δ-s-*cis* (Fig. 8). Such stereoselective reactions can be utilized to resolve racemic mixture of complexes such as, for example, s-*cis*-$[Co(dmedda)Cl_2]^-$, since Δ-s-*cis*-$[Co(dmedda)Cl_2]^-$ should be obtained when the amino acid in Δ-s-*cis*-[Co(dmedda)(aa)] is replaced by two chloro ligands. Further work on such stereoselective reactions is currently going on.

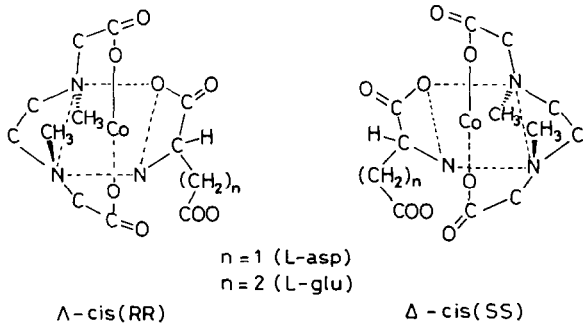

Fig. 8. s-*cis*-Configurational isomers of [Co(dmedda)(L-aa)] where aa is aspartic or glutamic acid.

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