N,N'-Dimethylethylenediamine-N,N'-di-α-butyric Acid Cobalt(III) Complexes Utilizing Oxidation of Sulfur of S-Methyl-L-cysteine

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The Reaction of S-methyl-S-cysteine (L-Smc) with racemic *s-cis*-[Co(dmedba)Cl_2]$^-$ **1** (H_2dmedba = N,N'-dimethylethylenediamine-N,N'-di-α-butyric acid) yields Δ-*s-cis*-[Co(dmedba)(L-Smc)] **2** with N,O-chelation. Oxidation of sulfur of **2** with H_2O_2 in a 1 : 1 mole ratio gives Δ-*s-cis*-[Co(dmedba)(L-S(O)mc)] **3** having an uncoordinated sulfenate group. Oxidation of sulfur of L-Smc with H_2O_2 in a 1 : 1 mole ratio produces S-methyl-L-cysteinesulfenate (L-S(O)mc) **5**. Direct reaction of **1** with **5** in basic medium gives an N,O-chelated Δ-*s-cis*-[Co(dmedba)(S-S(O)mc)-N,O], which turned out to be same as obtained by oxidation of **2**, while an N, S-chelated Δ-*s-cis*-[Co(dmedba)(S-S(O)mc)-N,S] complex **4** is obtained in acidic medium from the reaction of **1** with **5**. This is one of the rare [Co^{III}(N_2O_2-type ligand)(amino acid)] type complex preparations, where the reaction conditions determine which mode of N, O and N, S chelation modes is favored.

Keywords : Cobalt(III) complex, Ligand oxidation.

Introduction

N,N'-dimethylethylenediamine-N,N'-di-α-butyric acid (H_2dmedbda) and its cobalt(III) complexes have been synthesized in our laboratory.[1] Dmedba[#] is an N_2O_2-type tetradentate ligand and has been found to yield exclusively the *s-cis* (symmetric *cis*) geometrical isomer in a series of cobalt(III) complexes, [Co(dmedba)L]$^{n-}$ (L = Cl_2, $(H_2O)_2$, ClH_2O, CO_3^{2-}). The geometrical isomerism in the cobalt(III) complexes of the N_2O_2-type tetradentate ligands has been studies extensively.[2-8] When L is a symmetrical bidentate ligand such as ethylendiamine in the [Co(N_2O_2)(en)]$^-$ complexes, two geometrical isomers, *s-cis* (symmetric *cis*) and un*s-cis* (unsymmetric *cis*) are possible. When L is an asymmetric bidentate ligand such as an amino acid, however, an additional isomerism arises: *s-cis-mer* (merridional), *uns-cis-mer*, and *uns-cis fac* (facial).

Recently, the trifunctional amino acid cobalt(II) complexes of dmedba, [Co(dmedda)(aa)] (aa = S-methyl-L-cysteine, L-glutamic acid, L-aspartic acid) have been prepared from the reaction between the *cis*-[Co(dmedda)Cl_2]$^-$ complex and the amino acid.[9] These trifunctional amino acids have shown remarkable stereospecificity in their coordination to the racemic *s-cis*-[Co(dmedda)Cl_2]$^-$ to give the Δ-*s-cis-mer*-[Co(dmedda)(aa)] configuration only, in which the amino acid is chelated *via* the nitrogen and oxygen donor atoms.

In the present work depicted in Figure 1, the S-methyl-L-cysteine is coordinated to the racemic *s-cis*-[Co(dmedba)Cl_2]$^-$ **1** to give the *s-cis-mer*-[Co(dmedba)(L-Smc)] complex **2**, in which the stereospecificity and regioselectivity of the L-Smc ligand are to be found out. Then, the sulfur atom in the *s-cis*-[Co(dmedba)(L-Smc)] complex **2** is oxidized to become a sulfenate group. In a separate experiment, the L-Smc ligand is oxidized to become S-methyl-L-cysteine sulfenate (L-S(O)mc) **5**, which is then coordinated to **1** to afford the standard complex, *s-cis-mer*-[Co(dmedba)(L-S(O)mc)] **3**, to be compared with that prepared from oxidation reaction of **2**. It will be shown that each reaction condition gives the same structure with the same absolute configuration. Interestingly, it will be shown further that in a basic reaction condition L-S(O)mc **5** is coordinated to the cobalt(III) ion through the amine and carboxylate groups (N, O chelation) (compound **3**), while in an acidic reaction condition it is coordinated to the metal ion through the nitrogen and sulfur donor atoms (N,S chelation) (compound **4**).

[#]($^-$OOCCH(C_2H_5)N(CH_3)(CH_2)$_2$)

Experimental Section

S-methyl-L-cysteine, 2-bromobutyric acid, and N,N'-dimethylethylene-diamine were used as received (Aldrich). Dowex 50W-X4 cation exchange resin (200-400 mesh, H^+ form) and Dowex 1-80X anion exchange resin (200-400 mesh, Cl^- form) were used after repeated purifications. Electronic absorption and infrared spectra were recorded on a Shimadzu UV-240 double Beam Spectrometer and a Shimadzu IR 435 Spectrometer, respectively. Pmr spectra were measured with a 270 MHz JEOL GSX-270 Spectrometer. Circular Dichroism spectra were obtained from a JASCO J-550 Spectrometer. Elemental analyses were performed by Micro-Tech Analytical Lab., Skokie, Illinois, USA.

Preparation of *s-cis*-H[Co(dmedba)Cl_2] (1). This was prepared according to the known method.[1]

Preparation of Δ-*s-cis-mer*-[Co(dmdba)(L-Smc)-N,O] (2). 1.2 g (3 mmol) of *s-cis*-H[Co(dmedba)Cl_2] **1** was dissolved in 40 mL of water and heated at 60 °C for 20 min. 0.40 g (3.0 mmol) of S-methyl-L-cysteine was added to this solution and the pH of the solution was adjusted to 8.0, 0.1 g of activated carbon was added and the resultant reaction

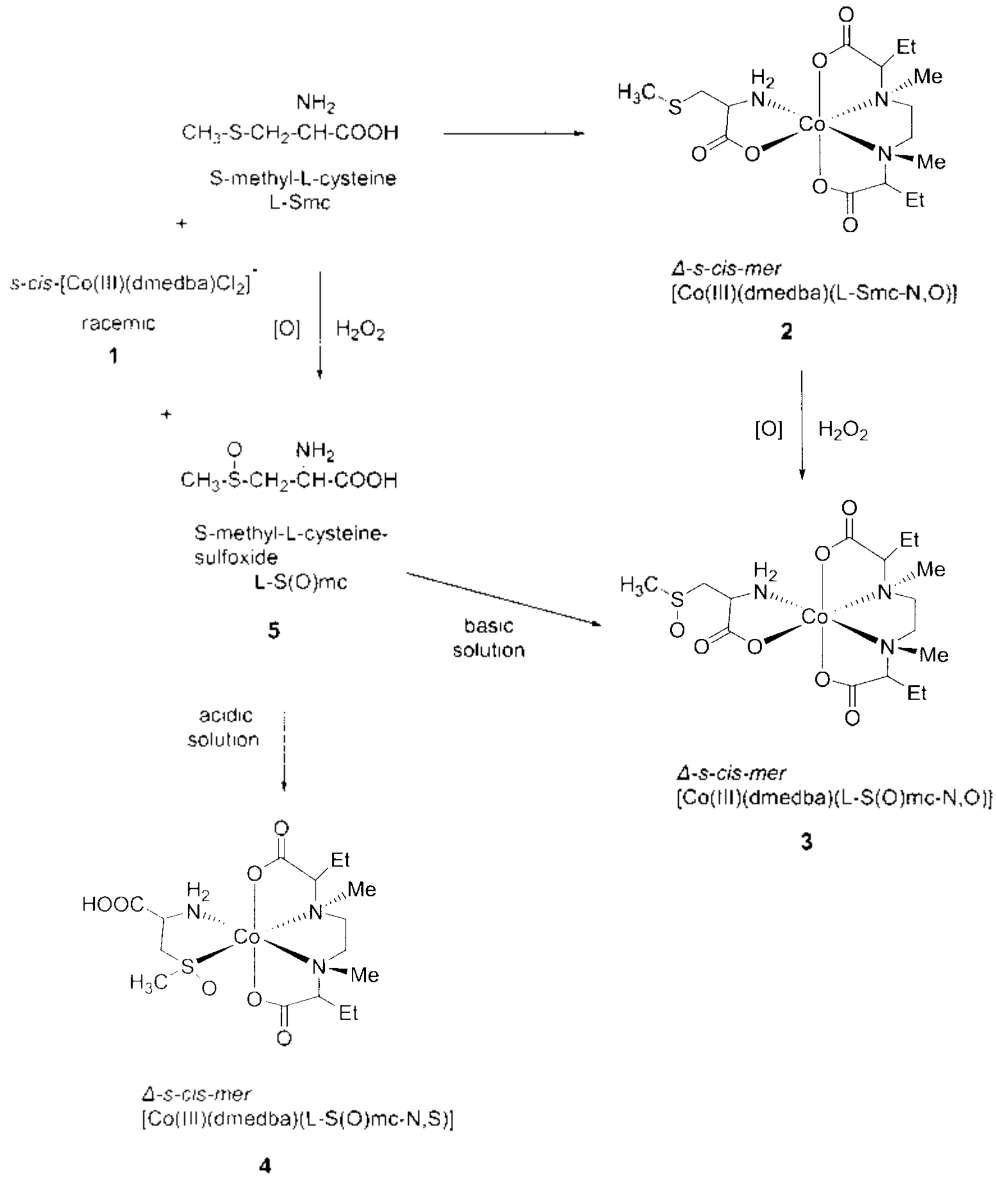

Figure 1. Synthetic Reactions to prepare compounds 2, 3, 4, and 5.

mixture was stirred at 60 °C for 8h. The reaction mixture was cooled and filtered to remove all the solid materials. The filtrate was concentrated to remove solvent with a rotary evaporator. The precipitates were dissolved in ethanol and filtered to remove white solid materials. Ether was added to the filtrate, which was then stored in a cold palce for a day. The violate product was collected by filtration, and recrystallized once from ethanol and ether. Yield: 0.23 g (17%). Anal. Calcd. for $C_{16}H_{30}CoN_3O_6S$: C, 42.57; H, 6.70; N, 9.31. Found: C, 42.66; H, 6.75; N, 8.97; S, 7.12. ^{1}H-NMR (δ): 1.2 (brs t), 1.7-2.2 (two m), 2.1(two s), 2.5(s), 2.8(s), 3.0-4.0 (brs. m).

Prepartion of Δ-*s-cis-mer*-[Co(dmedba)(L-S(O)mc)-N,O] (3). *(a) Via Oxidation of Δ-s-cis-mer-[Co(dmedba) (L-Smc)-N,O]:* 1.1 g (2.3 mol) of **2** was dissolved in 20 mL of water and stirred for 10 min. at room temperature. A solution of 0.26 mL of 30% H_2O_2 (2.3 mmol) diluted in 10 mL of water slowly added for 50 min. The red violet solution was evaporated under reduced pressure. The solid obtained was dissolved in ethanol, which was filtered and evaporated again under reduced pressure. The product was dissolved in 5 mL of water, which was admitted to a column packed with Dowex 50W-X8 cation exchange resin (200-400 mesh, H⁻ form). Two bands were detected by elution with water. The violet first band fraction was the remaining reactant. The red violet second band fraction was collected and concentrated until precipitates were formed. The red violet solid product was washed with ethanol and ether. Yield; 0.45 g (42%). Anal. Calcd. for $C_{16}H_{30}CoN_3O_7S$: C, 41.41; H, 6.47; N, 8.99. Found: C, 41.05; H, 6.49; N, 8.85; S, 6.81.

*(b) In Basic Solution from the Reaction between s-cis-H[Co(dmedba)Cl₂] **1** and S-Methyl-L-cysteinesulfenate **5**:* 1.2 g (3 mmol) of **1** was dissolved in 50 mL of water and

heated at 60 °C for 20 min. 0.46 g (3 mmol) of **5** was added to this solution. The pH of solution was adjusted to 8 with 1 M aqueous NaOH solution and stirred for 5 hrs at 60 °C. The solution was evaporated under reduced pressure to obtain the red violet precipitates. The solid materials Obtained were dissolved in 5 mL of water, which was admitted to a column packed with Dowex 50W-X8 cation exchange resin (200-400 mesh, H^+ form). Two bands were detected by elution with water. The violet first band fraction was the remaining reactant. The red violet second band fraction was colleted and evaporated reactant. The violet solid was washed with ethanol and ether. Yield: 1.10 g (77%). Anal. Calcd. for $C_{16}H_{30}CoN_3O_7S$; C, 41.11; H, 6.47; N, 8.99; S, 6.86. Found: C, 41.09; H, 6.48; N, 8.89; S, 6.90. ^{1}H-NMR (δ): 1.2 (brs t), 1.8(m), 2.1(m), 2.6(s), 3.4(m).

Preparation of Δ-*s-cis-mer*-[Co(dmedba)(L-S(O)mc)-N,S] (4). 0.10 g (0.25 mmol) of **1** was dissolved in 30 mL of water and heated at 60 for 20 min. 0.04 g (0.25 mmol) of S-methyl-L-cysteinesulfenate **5** was added to this solution and the pH of the solution was adjusted to 3.0 with 1 N HCl. Stirring was continued at 60 °C for 2h. The solution was evaporated under reduced pressure to obtain the blue precipitates. The precipitates were dissolved in 2 mL of water and admitted to Dowex cation exchange column. Two bands were detected by elution with water. The violet first band fraction was discarded. The blue second band fraction was collected and evaporated to yield the blue product, which was washed with ethanol and ether. Yield: 0.10 g (86%). Anal. Calcd. For $C_{16}H_{31}CoN_3O_7S\cdot 1H_2O$: C, 39.50; H, 6.84; N, 8.64; S, 6.59. Found: C, 39.45; H, 6.79; N, 8.61; S, 6.55. ^{1}H-NMR (δ): 3.1(s), 3.4(m), 4.6(m).

Preparation of S-Methyl-L-cysteinesulfenate (L-S(O)mc) (5). This compound was prepared via the similar method known in the literature.[10] 4.0 g (30 mmol) of S-methyl-L-cysteine was dissolved in 60 mL of acetic acid. The solution was cooled to 12 °C and stirred, to which 3.5 mL of 30% H_2O_2 (30 mmol) was slowly added for 4h. The solution was filtered and the filtrate was concentrated to *ca* 30 mL. 30 mL of acetone was slowly added and the solution was stored in cold place overnight. The solution was filtered to collect the white product and air-dried. white solids were recrystallized from water and ethanol. Yield: 2.90 g (64%). Anal. Calcd. for C_4HNO_3S: C, 31.78; H, 6.00; N, 9.26; S, 21.21. Found: C, 31.79; H, 6.06; N, 9.24; S, 21.19. ^{1}H-NMR (δ): 1.2(brs t), 1.9(m), 2.3(s), 2.9(s), 3.0(s), 3.4(m).

Results and Discussion

The schematic depiction of reaction in this work is shown in Figure 1. **1** is prepared as a racemic mixture.[1] **2** is obtained from the reaction between the racemic *s-cis*-$[Co(dmedba)Cl_2]^-$ **1** and L-Smc ligand. **3** is prepared upon the oxidation of sulfur of **2** by the stoichiometric amount of H_2O_2 to give S-methyl-L-cysteinsulfenate (L-S(O)mc). The direct reaction of this L-S(O)mc with **1** in basic solution gives **3**, which is turned out to afford the same compound as that obtained by the oxidation reaction of **2**. N, O-chelated complexes, **2** and **3** have same absolute configuration. If the direct reaction L-S(O)mc and **1** is accomplished in an acidic solution, on the other hand, an N, S-chealated Δ-*s-cis-mer*-[Co(dmedba)(L-S(O)mc)-N,S] complex **4** is obtained.

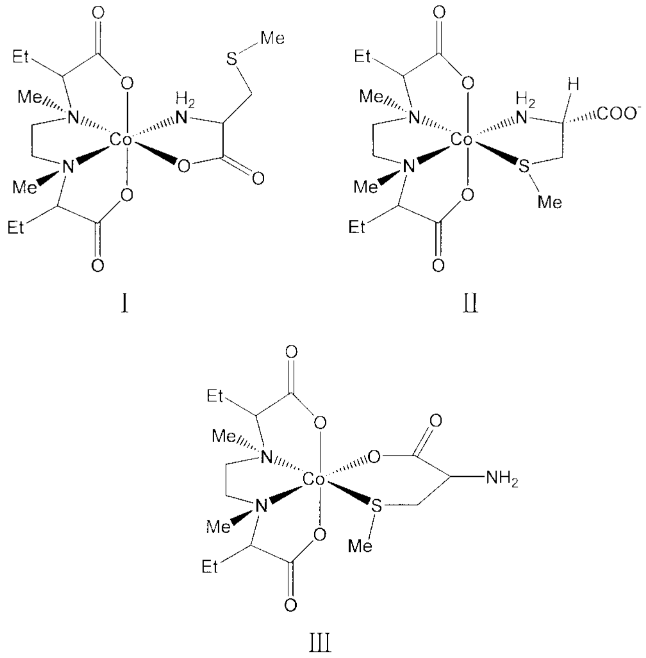

Figure 2. The geometrical isomer of *s-cis*-[Co(dmedba)(L-Smc)] complex.

The L-Smc ligand has three different donor atoms (N, O, S), and thus can have three geometrical isomers theoretically in the *s-cis*-[Co(dmedba)(L-Smc)] complex as shown in Figure 2. The infrared spectrum of **2** (Figure 4) shows the coordinated COO stretching band as 1640 cm^{-1}, which rules out the structure (Figure 2). The electronic absorption spectra are particularly helpful in distinguishing the coordinated donor atoms of N, O and S.[11-13] In the visible spectrum of **2** (Figure 3) the d-d transitions are observed at 542 and 355 nm. If the S donor atom is coordinated, the visible spectrum of either $[CoN_3O_2S]$ (structure II) or $[CoN_2O_3S]$ (structure III) would have shown d-d transition at much longer wavelengths (~600 nm),[2,13] than those observed in thin work, reflecting the position of the group in this spectrochemical series $S^- <$ amine $< COO^-$. Therefore, the structure III is also elimination, and in the *s-cis*-[Co(dmedba)(L-Smc)] complex the coordination of L-Smc take place through the amine and carboxylate group (structure I) to the merridional N, O chelation.

The CD spectrum of **2** (Figure 3), which was produced from the reaction between the racemic and the optically active L-Smc, shows the negative dominant Cotton effect in the T_{1g} region indicating the fact that **2** has been stereospecifically yielded with a Δ absolute configuration.[14-16] The optically active L-Smc ligand has shown a remarkable sterospecificity to give the Δ stereoisomer in its coordination to the racemic *s-cis*-$[Co(dmedba)Cl_2]^-$ complex since it has reacted with only the Δ isomer out of two (Δ and Λ) optical isomers. Such stereospecific reaction can be utilized to

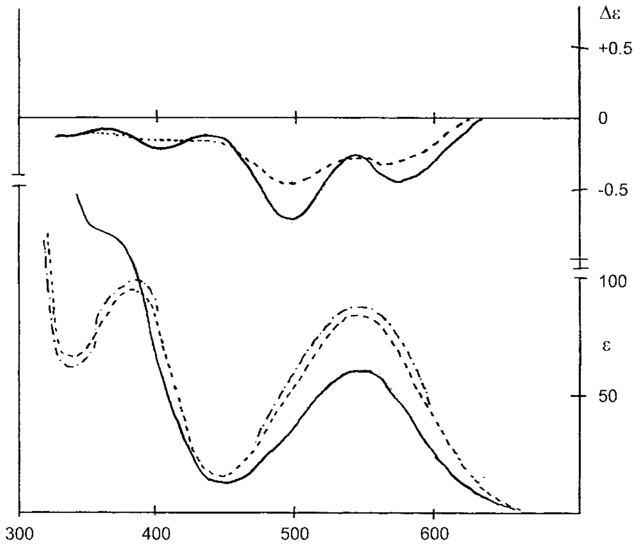

Figure 3. Electronic absorption and CD spectra of *s-cis-mer*-[Co(dmedba)(L-Smc) (2) (—), *s-cis*-[Co(dmedba)(L-S(O)mc)] (3) (---) *via* oxidation of by H_2O_2, and electronic absorption spectrum of *s-cis*-[Co(dmedba)(L-S(O)mc)] (4) by reaction between *s-cis*-$[Co(dmedba)Cl_2]^-$ and L-S(O)mc in basic solution (·—·).

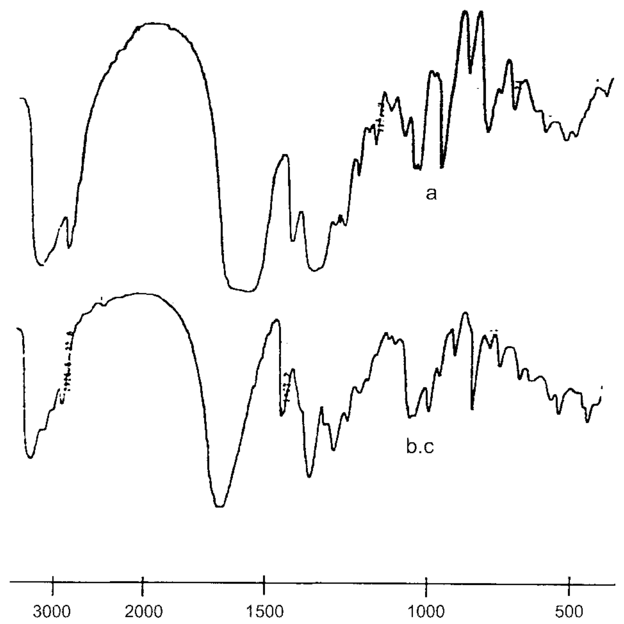

Figure 4. IR spectra of (a) *s-cis-mer*-[Co(dmedba)(L-Smc) (2), (b) *s-cis*-[Co(dmedba)(L-S(O)mc)] (3) *via* oxidation of 2 by H_2O_2, and (c) *s-cis*-[Co(dmedba)(L-S(O)mc)] (4) by reaction between *s-cis*-$[Co(dmedba)Cl_2]^-$ and L-S(O)mc in basic solution.

resolve the racemic mixtures of metal complexes. Structure of **1** and **2** are also elucidated by ^{1}H nmr data. In the ^{1}H nmr spectrum of **1**, the methyl and methylene protons of the ethyl group on the α-carbon are shown at, respectively, 1.4 ppm as a triplet and 1.4 ppm as a quartet, the N-methyl protons at 3.1 ppm as a singlet, and the methylene protons between two nitrogen donor atoms at 3.7 ppm as a singlet, while the α-carbon methylene proton at 4.2 ppm as a triplet. Substitution of chloro ligands for L-Smc lowers the symmetry of the complex from C_2 to C_1. The S-methyl protons of **2** are shown at 2.1 ppm as two singlets, while the methylene protons of the coordinated L-Smc ligand 2.8 ppm as a doublet. The methyl and methylene protons of the ethyl group on the α-carbon of dmedba of **2** are shown at, respectively, 1.2 ppm as a broad triplet (essentially two triplets) and 1.8-2.2 ppm as two quartets.

The oxidation of **2** with H_2O_2 in a 1 : 1 mole ratio have yielded a sulfenato complex of **3** as a red violet solid. The infrared spectrum of **3** (Figure 4) shows the S-O stretching vibration at 1010 cm^{-1} as opposed to the S=O stretching band of the free L-S(O)mc at 1016 cm^{-1}. Such sulfenate stretching vibration has been shown at 953 cm^{-1} for $[Co(en)_2(cysteinesulfenato)]^-$ and at 960-998 cm^{-1} for $[Co(en)_2(sulfenato)]^-$ complexes,[17,18] in which the sulfur atom is coordinated to cobalt(III) ion. In our compound 3 the sulfenato group is not coordinated but remains as a free sulfenate group. The λ_{max} in the visible for **3** (Figure 3) is 545 nm, which is the same as that for **2**, and thus H_2O_2 oxidation of **2** occurs without disruption of the primary coordination sphere of the cobalt center. The CD curve for **3** is somewhat different from that for **2** because of the contribution from the sulfur atom which becomes a chiral center upon oxidation. The ^{1}H pmr spectrum of **3** shows a downfield shift of S-methyl protons from 2.1 ppm in **2** to 2.6 ppm. Such downfield shifts also observed N-methyl protons and methylene protons.

Oxidation of L-Smc with H_2O_2 in a 1 : 1 mole ratio gives the S-methyl-L-cysteine sulfenate **5**. The S-O stretching absorption of **5** is shown at 1015 cm^{-1} and the ^{1}H pmr spectrum shows the downfield shift of s-methyl singlet from 2.2 ppm of the unoxidated L-Smc to 3.1 ppm.

The direct reaction of **1** with **5** in basic aqueous solution at pH 8 has yielded **3**. The electronic absorption spectra (Figure 3) and ^{1}H nmr, IR (Figure 4) convince that this direct method gives the same complex as that obtained by oxidation reaction of **2** with stoichiometric H_2O_2.

In an acidic aqueous solution at pH 3, however, the reaction of **1** with **5** has produced a very different complex, in which the sulfenato sulfur has coordinated to cobalt(III) ion as a donor atom. The visible spectrum of **4** (Figure 3) clearly shows that the N, S chelation has occurred, where the λ_{max} of $A_1g \rightarrow T_{1g}$ (O_h) visible absorption shows a red shift to 575 nm from the λ_{max} of 5454 nm for **3** with the coordination of sulfur atom to cobalt(III) ion.[13,19] The IR spectrum of **4** shows the uncoordinated -COOH vibration at 1730 cm^{-1} along with the coordinated -COO vibration of dmedba ligand at 1640 cm^{-1}. The S-O vibration is shown at 1070 cm^{-1}. ^{1}H nmr spectrum of **4** also shows a pattern suitable for the sulfur coordinated complexes.

It is noted that in our reaction between the S-methyl-cysteine sulfenato ligand system having three (N, O, S) donor atom and dichloro cobalt(III) complex of dmedba, both N,O-chelation and N, S-chelation, have been observed for the first time in this work in the [Co(N_2O_2-type ligand)(amino acid)] type complex preparation depending upon the basicity or acidity of the reaction system. Studies to observe such phenomena further are under way.

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