

Transition Metal Complexes of S-Propyl-L-Cysteine

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Summary: Four transition metal complexes of the type $M(L)_2$ ($M = Co, Ni, Cu, Zn$ and $L = S\text{-Propyl-L-cysteine}$) were synthesized and characterized by elemental analysis, spectral studies, thermo-gravimetric analysis, magnetic moment measurement and EPR. The complexes are proposed to have octahedral geometry around the metal atoms due to nitrogen and oxygen atoms. The ligand acts as a bridging ligand between two adjacent metal atoms leading to the formation of polymeric complexes. The carboxylate group in the ligand acts as bridging moiety between the two metal atoms. The polymeric nature of these complexes is also confirmed by the fact that they are insoluble in ordinary solvents. XAFS was used as confirmatory technique and it also shows octahedral environment around the central metal atom due to nitrogen and oxygen and clearly rejects the involvement of sulphur in the coordination sphere. EPR and XAFS show Jahn-Teller distortion around copper in the complex.

Keywords: S-Propyl-L-cysteine, XAFS analysis, Metal complexes, Coordination polymers, Bridging ligand.

Introduction

Metal complexes are playing important roles in our lives ranging from health and industry to environment [1-4]. These roles are played through the combined effects of metals and the ligands which none of them can perform without complexing with each other. So the synthesis and study of metal complexes is an important dimension in chemistry.

Amino acids are fundamental unit of protein structures. These proteins play structural as well as functional roles in living bodies. In addition to protein synthesis, amino acids are also involved in a wide range of physiological and pathological processes necessary for optimal body function. For example, glycine alone helps with the breakdown of fat by regulating the concentration of bile acids. Glycine is also required for the biosynthesis of Heme, a key component of haemoglobin which is essential in the maintenance of red blood cell integrity and optimal oxygen carrying capacity. Glycine is used in the treatment of neuro behavioural disorders, blood sugar regulation, muscle growth, anti-aging effects, hormones regulation and cancer treatment [5-10].

S-Propyl-L-cysteine (Pcys) (Fig. 1) is an amino acid found in plants of genus *Allium* e.g. onion and garlic [11]. It has shown promising health effects like anti-oxidative, cholesterol lowering [11], prevention from drug induced injury to liver [12], anti-apoptotic protection [13], and similar effects [14]. By making complexes of this amino acid with

different biologically important metals we can produce new beneficial effects.

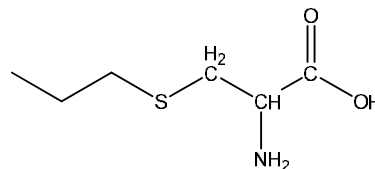


Fig. 1: S-propyl-L-cystine.

The structure elucidation of the amino acid complexes can help to correlate and understand their properties. In this project we have synthesized copper, cobalt, nickel and zinc complexes of S-propyl-L-cysteine and due to their amorphous nature, various techniques including XAFS have been used to elucidate their structure.

Experimental

Melting points of the ligand and the complexes were determined using a Gallenkamp melting point apparatus. ¹H-NMR spectrum was taken in D₂O and recorded at 500 MHz on Varian INOVA-500 instrument. (abbreviations: *s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet). Mass spectrum was recorded on Jeol MS Route and Waters micromass triple quadrupole quarto II Elctectrospray Ionization mass spectrometer. Cone voltages ranging from 5-15

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V were used for best results. IR spectra were taken on FT-IR Nicolet 6700 of Thermoscientific company. Elemental Analysis was performed using CHNS-932 LECO analyzer. UV-Vis spectra were recorded from 200-800 nm by using spectro UV-Vis double beam UVD-3500 (Labomed INC.). Magnetic moments were measured at 20 °C using Mark 1 instrument from Sherwood scientific company. Mercury tetrathiocyanatocobaltate (II) {Hg [Co (NCS)₄]} was used as a calibrant. TGA, DTA were taken by using Universal V4.2E TA instrument-SDT Q600 V8.2 Build 100 and. Analysis were made in Nitrogen environment with heating rate of 10°C min⁻¹ from 25 to 1000 °C Reagent grade materials were purchased from Aldrich Chemical Co. and used without further purification.

X-ray absorption spectra were collected from solid samples of copper complexes of S-propyl-L-cysteine diluted into cellulose powder and finely ground and pressed into 13 mm discs by the application of moderate pressure (10 Tonnes). The composition of the disc was adjusted so as to achieve a balance between the attenuation of the sample and the transmittance beyond the Cu absorption edge. For all samples the minimum transmittance was between 10 and 20% through the edge and XAFS regions.

X-ray fluorescence measurements were made at a temperature of ca. 273K using beamline 20 B (bending magnet) at the KEK Photon Factory, Tsukuba, Japan. A channel-cut Si(1 1 1) monochromator provided an energy resolution (DE/E) of ca. 2.4_10_4, and higher order harmonics of the selected wavelength were rejected by detuning the monochromator by a factor of a half. EXAFS measurements were conducted at the Cu K-edge. Solid samples were measured in transmission mode using an ion chamber detector. Data reduction of experimental X-ray absorption spectra was performed using the program XFIT [15]. The model structure was refined using the XFIT software package, which incorporates ab initio FEFF 6.01MS curved wave calculations [16]. The number of refined variables, Nrv, in the models, including the scale factors E0 and S0 2 are listed.

Synthesis of S-n-Propyl-L-cysteine

Sodium hydroxide (30g, 0.75 mol) was dissolved in 500 ml of distilled water and was added with L-cysteine (30.25g, 0.25 mol). Then propyl iodide (42.5g, 0.25 mol) was added drop by drop and stirred for 4 hours. This solution was acidified to pH 6 with acetic acid and the precipitates obtained were

filtered and washed with ethanol and were dried in oven at 50 °C. On TLC this compound showed a single spot.

Yield 84 %, m.p. = 221-223 °C, (dec); FT-IR ν = 2965-2860, 2580, 2120 cm⁻¹ (NH₃⁺), 1585 (COO⁻), ¹H-NMR (D₂O-NaOD) δ = 3.65 (1H, *dd*, *J* = 6.29 Hz, CH at α -Carbon), δ = 2.79-2.90 (2H, *dd*, *J* = 6.5 Hz, SCH₂ on β -carbon), δ = 2.53 (2H, *t*, *J* = 7.29 Hz, SCH₂ at n-propyl), δ = 1.56 (2H, *m*, CH₂), 0.91 Hz, (3H, *t*, *J* = 7.23 CH₃). ESI-Mass *m/z* = 164.1 [M+H]⁺. Anal. Cald. for (C₆H₁₃O₂NS) (%): C, 44.17; H, 7.97; N, 8.58; S, 19.63, Found(%): C, 44.03; H, 7.85; N, 8.49; S, 19.51.

Synthesis of the Complexes

The Following procedure was used for the synthesis of the complexes (2.2a-d).

Metal chloride, MCl₂ [M= Cu, Ni, Co, Zn] (0.01mol) was dissolved in 25 ml of distilled water. Another solution was prepared by dissolving S-propyl-L-cysteine (3.26 g, 0.02 mol) in 25 ml of water. Both the solutions were mixed and stirred for 30 minutes. NaOH (0.8g, 0.02 mol) dissolved in 10 ml of distilled water was added drop by drop in the solution. The Final pH of these mixtures was adjusted between 7.5 - 8. The precipitates were filtered and washed with water and ethanol and dried over CaCl₂.

Bis(S-n-propyl-L-cysteinato)Cu(II): Cu(C₆H₁₂NO₂S)₂

Yield 92%, m.p. = Dec.>218 °C. FT-IR ν = 3283, 3234 cm⁻¹ (NH₂), 1621, 1392 cm⁻¹ (COO⁻). UV-Vis ν = 16025 cm⁻¹. μ_{eff} (B.M.) = 2.20. Anal. Cald. for Cu(C₆H₁₂NO₂S)₂ (%): C, 37.16; H, 6.19; N, 7.22; S, 16.51; Found(%): C, 37.32; H, 6.25; N, 7.23; S, 16.56.

Bis(S-n-propyl-L-cysteinato)Co(II): Co(C₆H₁₂NO₂S)₂

Yield 89 %, m.p. = Dec.>220 °C. FT-IR ν = 3339, 3270 cm⁻¹ (NH₂), 1594, 1405 cm⁻¹ (COO⁻). UV-Vis ν = 37051, 19733 cm⁻¹. μ_{eff} (B.M.) = 5.16. Anal. Cald. for Co(C₆H₁₂NO₂S)₂(%) : C, 37.59; H, 6.26; N, 7.31; S, 16.71; Found(%): C, 37.41; H, 6.24; N, 7.39; S, 16.71.

Bis(S-n-propyl-L-cysteinato)Ni(II): Ni(C₆H₁₂NO₂S)₂

Yield 88 %, m.p. = Dec.>219 °C. FT-IR ν = 3355, 3267 cm⁻¹ (NH₂), 1596, 1402 cm⁻¹ (COO⁻). UV-Vis ν = 27106, 16081 cm⁻¹. μ_{eff} (B.M.) = 3.41. Anal. Cald. for Ni(C₆H₁₂NO₂S)₂ (%) : C, 37.63; H,

6.27; N, 7.31; S, 16.72; Found(%): C, 37.58; H, 6.37; N, 7.28; S, 16.83.

Bis(S-n-propyl-L-cysteinato)Zn(II): $Zn(C_6H_{12}NO_2S)_2$

Yield 91 %, m.p. = Dec.>218 °C. FT-IR ν = 3315, 3242 cm^{-1} (NH_2), 1609, 1404 cm^{-1} (COO^-). Anal. Cald. for $Zn(C_6H_{12}NO_2S)_2$ (%) : C, 36.98; H, 6.16; N, 7.19; S, 16.43; Found(%): C, 36.75; H, 6.14; N, 7.28; S, 16.35.

Results and Discussion

FTIR Spectroscopy

Depending on the pH and metal atom, amino acids can act as monodentate, bidentate and tridentate ligands and they can be either bridging or non-bridging ligands [17-19]. Amino acids show IR pattern characteristic of ionic carboxylate and amine salt as they exist in zwitterionic form in their solid states.

The broad band of NH_3^+ is composed of asymmetric and symmetric stretches, combination and overtones overlapping with each other [20]. This region becomes wider due to participation of C-H stretching vibrations. This region becomes even wider in ionic salts of the amino acids as NH_3^+ is deprotonated here and N-H vibrational frequencies rise due to increase of N-H bond strength. Furthermore hydrogen bonding involved also contributes to the band widening [21].

Similarly, the ionized carboxylic group shows absorption bands due to asymmetric and symmetric carboxylate (COO^-) stretches around 1580 and 1410 cm^{-1} , respectively. The protonated carboxylic group e.g., in hydrochloride salt, absorbs between 1700-1750 cm^{-1} [20, 21].

Upon coordination of the amino acids to the metal, following changes can be observed in IR absorption frequencies for amino (NH_2), carboxylate (COO^-).

1. Coordination of amino group is shown by the presence of two well resolved peaks in the region 3000-3400 cm^{-1} . Amino group coordination is also attested by absence of band in the region 2050-2150 cm^{-1} . This band is present in free amino acid and their basic salts and is assigned to non-coordinated NH_2 group. [22] The absence of $\delta_{as}(NH_3^+)$ band in the complex is another proof of NH_2 coordination.

In free ligand this band is present at 1505 cm^{-1} [21].

2. Coordination of carboxylate (COO^-) group to metal causes the asymmetric frequency to increase and symmetric frequency to decrease. The amount of increase and decrease depends on the metal involved which in turn depends upon the strength of M-O bond. Stronger the M-O bond, the more is the increase in asymmetric frequency [21].

IR frequencies for metal-oxygen and metal-nitrogen bond are also an important proof for coordination of the ligands with metals. For the metals of first transition series in +2 oxidation state, the M-N stretching frequency occurs between 400-500 cm^{-1} and the M-O frequency occurs between 280-400 cm^{-1} . These frequencies decrease as the atomic radius of the metal involved increases and vice versa.

Another parameter for the metal complexes is $\Delta\nu$, which is the difference between the asymmetric and symmetric vibration frequencies of the carboxylate group of the amino acid, [$\Delta\nu = \nu_{as} - \nu_s$ (COO^-)]. When an amino acid coordinates, the asymmetric vibration frequency increases and the symmetric vibration frequency decrease as compared to the free ionic state, which, in turn, depends on the metal oxygen (M-O) bond strength. The stronger the M-O bond, the greater is the shift in asymmetric and symmetric frequencies. Nakamoto provided the following order of metals for the increase in the separation of the two frequencies on coordination [21].

$Ni(II) < Zn(II) < Cu(II) < Co(III) < Pd(II) \approx Pt(II) < Cr(III)$

$\Delta\nu$ not only tells about the strength of the M-O bond but also about the mode of the coordination of the carboxylate group. The carboxylate group can coordinate either in a monodentate fashion (only one oxygen coordinating) or bidentate fashion (with both the oxygen atoms involved in coordination). The monodentate coordination gives rise to higher $\Delta\nu$ values while bidentate coordination gives rise to $\Delta\nu$ closer to ionic carboxylate group, e.g., in potassium salts of the amino acids [21].

Selected data of IR spectrum of the S-propyl-L-cysteine complexes is given in Table-1.

In all the complexes two well resolved peaks in the region 3100-3400 cm^{-1} indicates the coordination of amino group to the metals. Similarly, the absence of a band in the region 2050-2150 cm^{-1} and around 1505 cm^{-1} is also an evidence of coordination of an amino group.

Table-1: FT-IR data (cm⁻¹) of S-n-propyl-L-cysteine complexes.

Complex	NH ₃ ⁺ /NH ₂	v _{as} COO ⁻	v _s COO ⁻	Δv*
S-propyl-L-cysteine	3230-2670	1580	1403	177
Potassium salt	(br. band)			
Cu Peys	3283, 3234	1621	1392	229
Co Peys	3339, 3270	1594	1405	189
Ni Peys	3355, 3267	1596	1402	194
Zn Peys	3315, 3242	1609	1404	205

*Δv = v_{as} - v_s (COO⁻)

Table-2: UV-Vis. Data of S-propyl-L-cysteine complexes.

Sr. No.	Complex	λ _{max} (nm)	Band Assignment
1.	Bis(S-propyl-L-cysteinato) Cu(II)	624	d _{xy, yz, xz} → d _{x²-y²}
2.	Bis(S-propyl-L-cysteinato) Co(II)	506	⁴ T _{1g} → ⁴ T _{1g} (P)
		1011	³ A _{2g} → ³ T _{2g}
3.	Bis(S-propyl-L-cysteinato) Ni(II)	615	³ A _{2g} → ³ T _{1g}
		369	³ A _{2g} → ³ T _{1g} (P)

Changes in the carboxylate group frequencies prove its coordination to metals. Δv clearly indicates that the carboxylate group is coordinated in a bidentate fashion.

Metal ligand vibration frequencies for Ni, Co, Cu and Zn can be found at 301, 313, 376, 399 cm⁻¹ for metal-oxygen (M-O) and 443, 455, 461, 481 cm⁻¹ for metal-nitrogen (M-N) respectively.

Thermal Analysis

Bis(S-n-propyl-L-cysteinato)Cu(II): Cu(C₆H₁₂NO₂S)₂

The thermogram of the copper propyl cysteine complex (Fig. 2) shows one step decomposition near 220 °C. This single step actually seems to be composed of two steps because this step broadens immediately after traveling a half way down ward. DTG shows similar behaviour around 220 °C. The residue after TGA was CuO and hence TGA suggests formula of the complex to be Cu(C₆H₁₂NO₂S)₂.

No coordinated water detected in the thermogram.

Bis(S-n-propyl-L-cysteinato)Co(II): Co(C₆H₁₂NO₂S)₂

In this complex, the decomposition occurs in two steps. (Fig. 3) The first step is considered to be the removal of the two thio-ether chains (-CH-CH₂-S-CH₂-CH=CH₂) and second step is the removal of the rest of the groups. DTG confirms this pattern. The final residue was CoO hence the molecular formula was suggested to be Co(C₆H₁₂NO₂S)₂. No coordinated water was detected in the thermogram.

Bis(S-n-propyl-L-cysteinato)Ni(II): Ni((C₆H₁₂NO₂S)₂)

In this complex the decomposition consists of only one step which is at higher temperature than

the copper and the cobalt complexes (Fig.4). Whole of the ligand breaks up as one unit. DTG confirms this pattern. The final residue was NiO hence the molecular formula was suggested to be Ni(C₆H₁₂NO₂S)₂. No coordinated water was detected in the thermogram.

Bis(S-n-propyl-L-cysteinato)Zn(II): Zn((C₆H₁₂NO₂S)₂)

According to TGA, the decomposition of zinc complex proceeds in two steps (Fig. 5). Here the thioether chain is removed at 260 °C and rest of the molecule is removed at 400 °C. The final residue was ZnO hence the molecular formula was suggested to be Zn(C₆H₁₂NO₂S)₂. No coordinated water was detected in the thermogram.

Magnetic Moment

Magnetic moments of Bis(S-propyl-L-cysteinato)Cu(II), Bis(S-propyl-L-cysteinato)Co(II) and Bis(S-propyl-L-cysteinato)Ni(II) complexes were found to be 2.20, 5.16 and 3.14 respectively. Cobalt, Nickel and Copper have d⁷, d⁸, d⁹ configuration respectively and here cobalt has high spin configuration. An octahedral geometry is proposed with the support of UV-Vis data for these complexes [23].

Electronic Spectroscopy

As all of the complexes of S-propyl-L-cysteine were insoluble in common solvents, their electronic spectra were recorded as a homogenous paste in Nujol sandwiched between two glass slits as a thin film (Table-2). These absorption values are characteristic of an octahedral geometry as similar results have been obtained for other octahedral systems of related copper, cobalt and nickel complexes [23, 18].

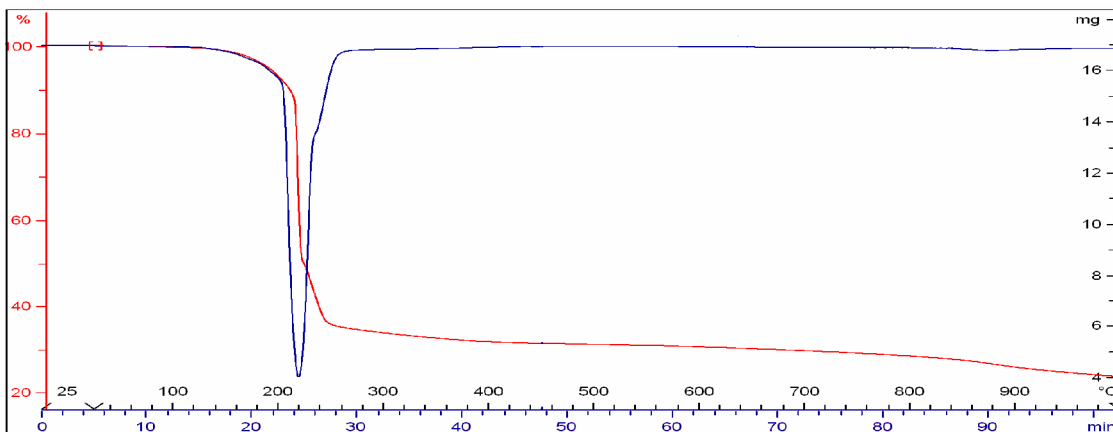


Fig. 2: TGA and DTG of Bis(S-propyl-L-cysteinato)Cu(II).

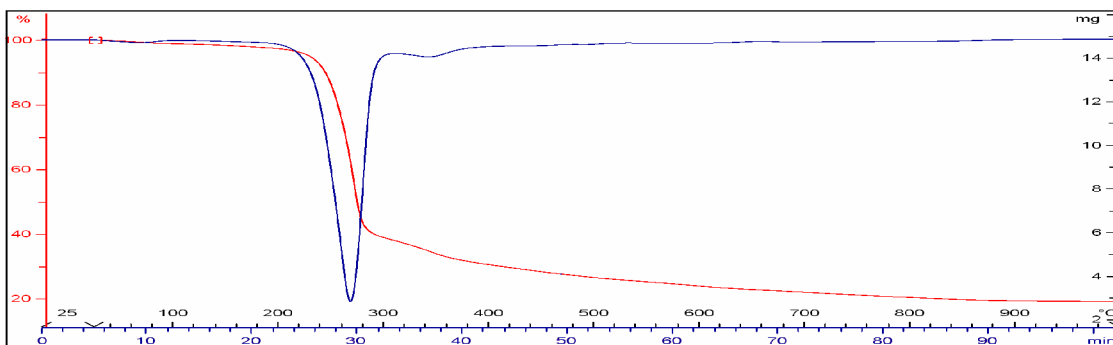


Fig. 3: TGA and DTG of Bis(S-propyl-L-cysteinato)Co(II).

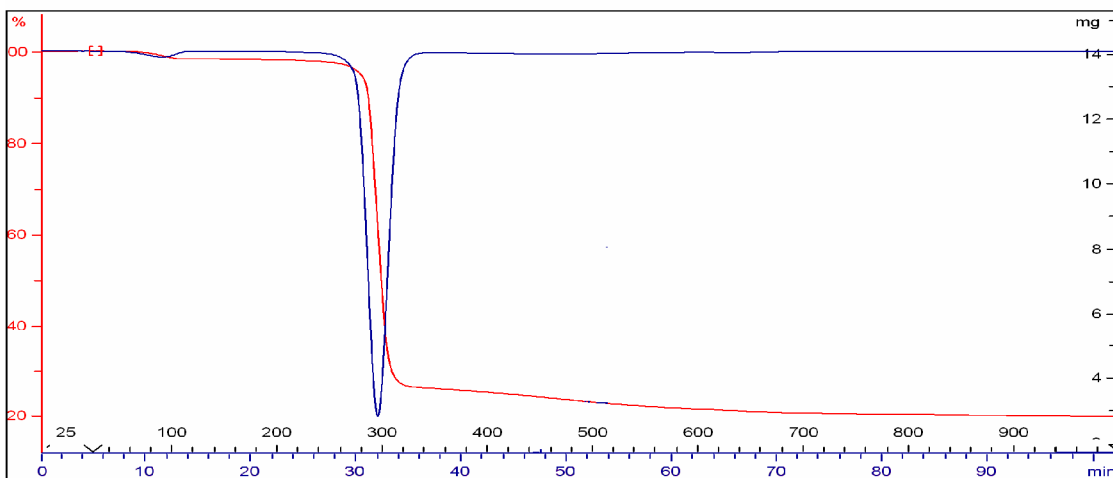


Fig. 4: TGA and DTG of Bis(S-propyl-L-cysteinato)Ni(II).

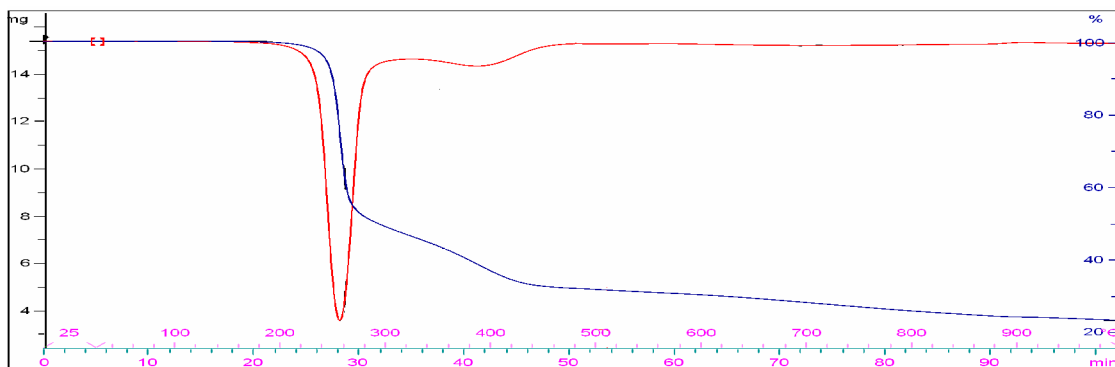


Fig. 5: TGA and DTG of Bis(S-propyl-L-cysteinato)Zn(II).

EPR Spectroscopy

The EPR spectra for Bis(S-propyl-L-cysteinato)Cu(II) showed values for g_1 and g_2 to be 2.06 and 2.18, respectively. The g_1 and g_2 values for the similar reported tetragonally distorted complexes, e.g., the copper complex of methionine sulfoxide are 2.05 and 2.21 respectively. Similarly, the g_1 and g_2 values for $[\text{Cu}(\text{H}_2\text{O})_4(\text{HCO}_2)_2]$ are 2.06 and 2.31 [24]. Similar values have also been reported for the other tetragonally distorted octahedral copper complexes [25]. So, a comparison of the above reported data with the published literature values indicates a tetragonally distorted octahedral geometry due to the Jahn-Teller effect for the copper complex.

XAFS Analysis

Description of the Model

Since the primary interest of the study is the characterization of the primary coordination sphere of the copper atom, a simple model with minimal degrees of freedom was used to analyse the XAFS data. In this case, pairs of identical atoms were located along the Cartesian axes where the Cu-ligand distance for pairs of ligands was constrained to be equal. Consequently, each of the three ligand types was associated with one positional parameter and these, together with the energy offset (E_0) and scale factor (S_0^2), gives a total of 8 parameters. The information content of the data is commonly reported as the number of independent points (N_{idp}), and is given by the relation $(2 + 2 \cdot R \cdot k / \Delta)$. The R (1 – 2.75 Å) and k range (2 – 14 Å⁻¹) used for the analysis

gives N_{idp} of 15.6, this being approximately twice the number of refined parameters.

Working

Three alternative refinements were conducted; (i) all six donor oxygen atoms with each of the three pairs of ligands having different Cu-O bond lengths; (ii) four oxygen, two nitrogen and (iii) four oxygen, two sulphur coordination. In each case, the Cu-ligand bond distance was constrained to be equal for pairs of ligands along an axis. A summary of the structural results together the fitting statistics obtained for Bis(S-n-propyl-L-cysteinato)Cu(II) using the three models is given in Table-3. The figures for these fits are shown (Figs. 6-8). The input file used for fit is given in appendix. Consideration of the fitting statistics leads to the conclusion that the immediate coordination sphere about the copper does not include sulphur, but consists of six first-row p-block elements, most likely, either CuO_4N_2 or CuO_6 . As expected for the d^9 ion, copper (II), strong Jahn-Teller effects are apparent, with a significant lengthening of two of the Cu-O distances.

Table-3: Structural parameters obtained from fitting the XAFS of Bis(S-propyl-L-cysteinato)Cu(II).

Model	Model 1	Model 2	Model 3
	$L_x, L_y, L_z = \text{O}$	$L_x, L_y = \text{O}$ $L_z = \text{N}$	$L_x, L_y = \text{O}$ $L_z = \text{S}$
Cu- $L_x/\text{Å}$	1.96 (0.019)	1.98 (0.03)	1.96 (0.03)
$\sigma^2(L_x)/\text{Å}^2$	0.0008 (0.0008)	0.0008 (0.0008)	0.0007 (0.0009)
Cu- $L_y/\text{Å}$	2.70 (0.03)	2.70 (0.03)	2.16 (0.09)
$\sigma^2(L_y)/\text{Å}^2$	0.0030 (0.0028)	0.0033 (0.0028)	0.0248 (0.0092)
Cu- $L_z/\text{Å}$	1.88 (0.02)	1.90 (0.02)	1.90 (0.03)
$\sigma^2(L_z)/\text{Å}^2$	0.0055 (0.0056)	0.0047 (0.0048)	0.0046 (0.0071)
E_0	0.49 (0.90)	0.49 (0.88)	0.02 (0.96)
S_0^2	0.99 (0.15)	1.01 (0.08)	0.85 (0.15)
σ^2	5.85	5.67	14.76
R / %	21.1	20.8	33.6

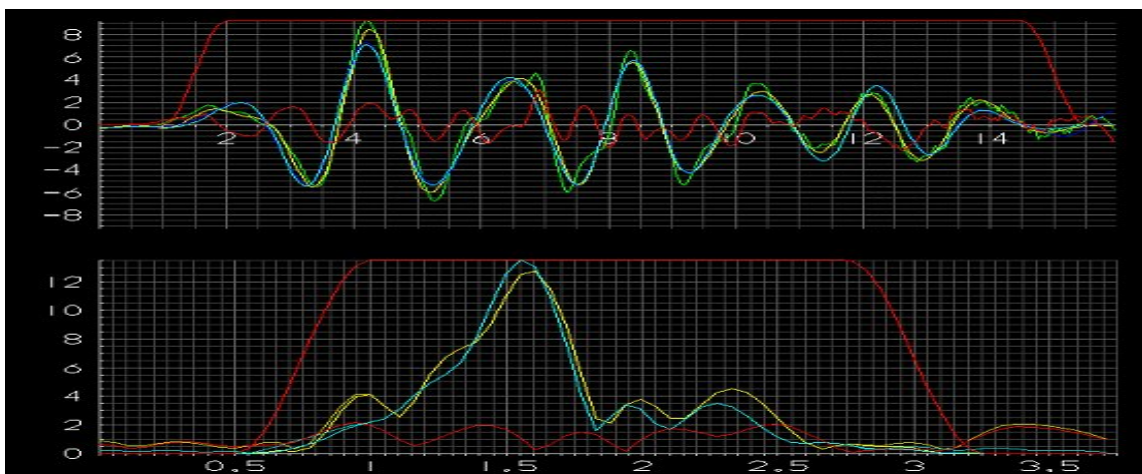


Fig. 6: When all the atoms around copper are oxygen.

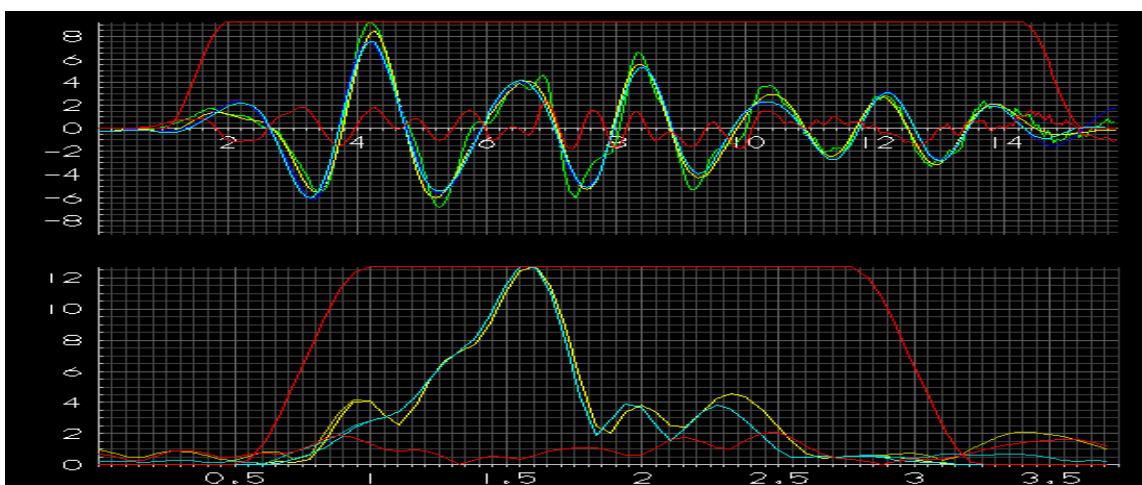


Fig. 7: When four atoms are oxygen and two atoms are nitrogen around copper.

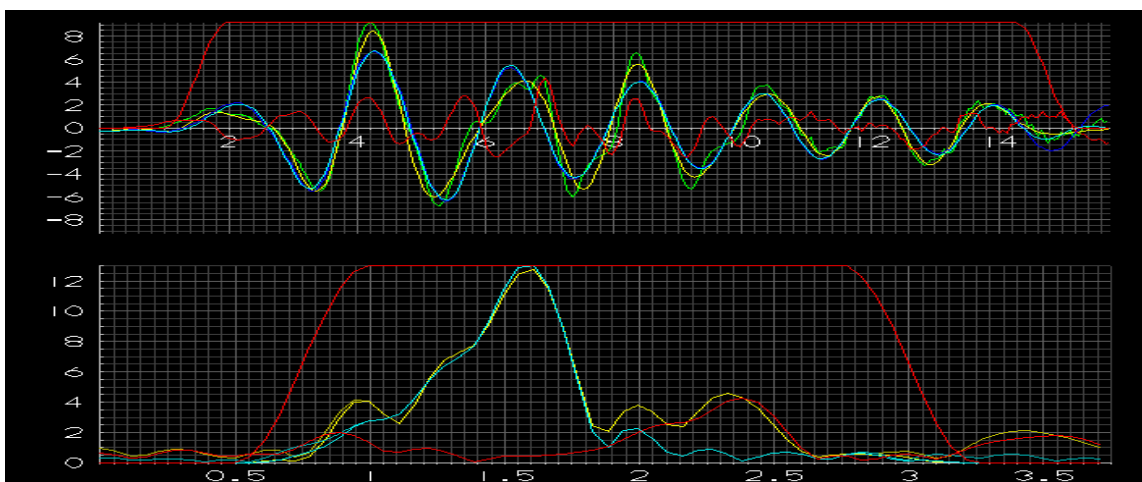


Fig. 8: When four atoms are oxygen and two atoms are sulfur around copper.

Conclusion

Based on the spectral and the physical data, the following polymeric structure for the metal complexes of S-Propyl-L-cysteine has been suggested (Fig. 9). The polymeric nature of these complexes is also confirmed by insolubility of these complexes in ordinary solvents. The metal atom has the octahedral geometry of the ligand atoms around it. The copper complex also shows a Jahn-Teller distortion. XAFS analysis was done on the copper complex and XAFS confirmed the above stated results obtained by other techniques. So in analogy with the copper complex results, we can expect the similar coordination environment in rest of the complexes which is supported by other techniques too.

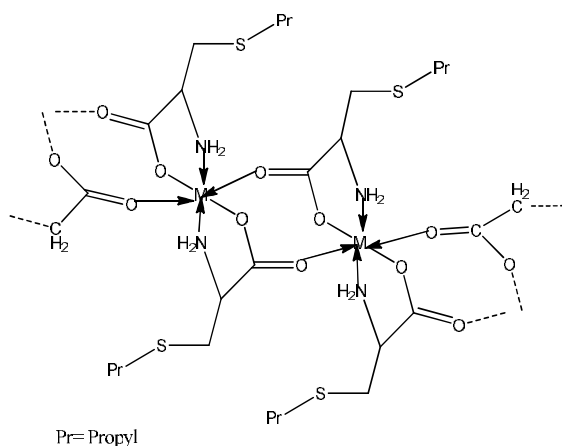


Fig. 9: Structure of S-Propyl-L-cystine metal complexes.

Acknowledgments

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