

Synthesis, Characterization and Evaluation of Biological Properties of Transition Metal Chelates with Schiff base Ligands Derived from Glutaraldehyde with L-Leucine

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ABSTRACT

A nitrogen-oxygen Schiff base HL derived from Glutaraldehyde and L-Leucine has been reacted with different divalent metal ions in 2:1 molar ratio, producing neutral complexes. All compounds were characterized using physico-chemical and spectroscopic methods namely elemental analysis, melting point, magnetic moment measurement, conductivity measurement, UV-Vis, IR, ¹HNMR spectroscopy and XRD measurements. They were further analysed by thermal technique (TGA/DTA) to gain better insight about the thermal stability and kinetic properties of the complexes. The IR data demonstrated the tetradentate binding of Schiff base ligand. The molar conductivity values were relatively low, showing their nonelectrolytic nature. Room temperature magnetic susceptibility measurements revealed that the nature of Ni(II) and Cu(II) complexes were paramagnetic. The *in vitro* antimicrobial activities of all the compounds were screened against different microbial species by Disc Diffusion method and showed better activity compared to parent drug and control drug.

Keywords: Schiff base, Metal complexes, IR, XRD, Antimicrobial activity

I. INTRODUCTION

Transition metal complexes derived from Schiff bases have occupied a central role in the development of coordination chemistry. Schiff base can accommodate different metal centers involving various coordination modes thereby allowing successful synthesis of homo and hetero metallic complexes with varied stereochemistry. This feature is employed for modeling active sites in biological systems. A large number of Schiff bases and their complexes have been investigated for their interesting and important properties, such as their ability to reversibly bind oxygen, their catalytic activity in the hydrogenation of olefins, their photochromic properties and their complexing ability towards some toxic metals. Many biologically important Schiff bases have been reported in the literature possessing, antimicrobial, antibacterial, antifungal, anti-inflammatory, anti convulsant, antitumor and anti- HIV activities⁽¹⁻⁴⁾. *In vivo* studies have indicated that some biologically

active compounds may become more carcinostatic and bacteriostatic upon chelation⁽⁵⁾. Several reviews showed that the metallo-organic chemistry of such compounds greatly influence their biological action highlighting the catalytic function metal in many biological processes⁽⁶⁻⁸⁾.

Therefore, considering the above facts and continuing our interest in this field, the present work reports a study on the synthesis, characterization and antimicrobial properties of Ni and Cu complexes with the Schiff base derived from Glutaraldehyde and L-Leucine (HL).

II. EXPERIMENTAL

Materials and Physical Measurements:

All the glassware used for the preparation were cleaned with chromic mixture, distilled water and then dried in Oven at 110°C. All the chemicals such as Glutaraldehyde, L- Leucine, Cupric nitrate and Nickel

nitrate were of analytical grade and used as such without any further purification. Glutaraldehyde and L-Leucine were obtained from Sigma Aldrich, Cupric nitrate and Nickel nitrate was obtained from Merck (LTD). Solvents were purified and dried by standard methods. The solvent system used was DMSO [dimethyl Sulfoxide]. The metal contents of the complexes were determined by EDTA titration. Elemental analyses were carried out on a Vario EL 111 elemental analyzer at Sophisticated Analytical Instruments facility, CUSAT, Kochi. Thin layer Chromatography was performed on precoated Silica gel (E-Merck) 607-254 analytical plates (0.25mm). IR Spectra were recorded in KBr discs on a Perkin – Elmer FT-IR spectrometer model 1600 in the 4000-400 cm^{-1} region. The electronic spectra were recorded in a Shimadzu double beam visible spectrometer. Molar conductance of the complexes were measured in DMSO (10^{-3}M) solutions using a Systronic digital conductivity meter. Nuclear magnetic Resonance $^1\text{H-NMR}$ Spectra (300 MHz) of the samples were recorded in DMSO- d_6 by employing TMS as internal standard at NIIST, Trivandrum. XRD was recorded on a computer controlled X-ray diffractometer system JEOL JDX 8030. The magnetic susceptibility measurements at room temperature were made on Guoy's balance using Copper Sulphate as calibrant. Double distilled water was used throughout the experimental work. Thermal analysis of the metal complexes was carried out using Perkin- Elmer Diamond thermal analyzer in an inert atmosphere of nitrogen by recording the change in weight of the complexes on increasing temperature upto 900°C at the heating rate of $10^\circ\text{C} / \text{min}$. The antimicrobial activities of ligands and their mixed ligand complexes were screened by Disc Diffusion method⁽⁹⁾.

Synthesis of Schiff base

Schiff base ligand was prepared by reacting equimolar amounts of L-Leucine (0.2mol, 2.6g) and Glutaraldehyde (0.1mol, 0.94g) in 150ml of absolute methanol. The reaction mixture was refluxed on a steam bath at 90 to 95°C for 1 hour. The reaction was examined by TLC with time to time till completion.

The solvent was partially evaporated and the yellowish mass product was precipitated by cooling and filtered off, washed with distilled water, dried, recrystallised and finally preserved in a desiccators.

Synthesis of Schiff base complexes

Metal (II) nitrates (1 mmol) was dissolved in 200cm^3 of methanol. The filtered solution was added dropwise into 20 cm^3 methanol solution of the Schiff base ligand (1mmol). The resulting mixture was refluxed and stirred for 8 hours. After, refluxing the volume of the solution was reduced to one third and the concentrate was cooled at 0°C . The precipitated complex was filtered off, washed several times with cold ethanol and dried in vacuo over anhydrous CaCl_2 .

III. RESULTS AND DISCUSSION

Metal (II) Salts react with Schiff base ligand in 1:1 molar ratio in alcoholic medium to afford dark green and greenish yellow complexes. Cu(II) complex and Ni(II) complex are normally stable at room temperature and hygroscopic in nature. The Schiff base ligand is soluble in common polar organic solvents like ethanol and methanol. The corresponding complexes are relatively well soluble in DMSO.

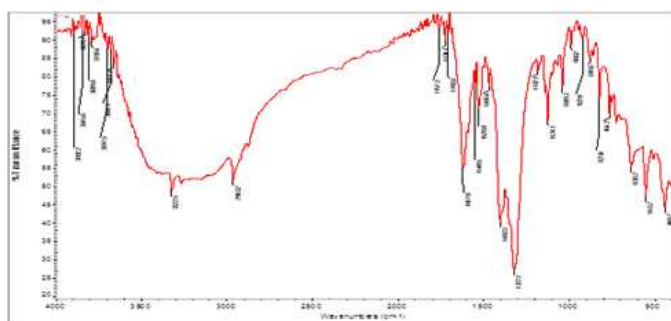
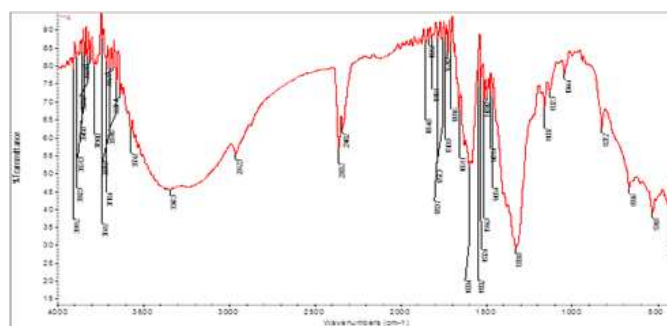
The physical and analytical data of the ligands and their complexes are given in Table 1. Elemental data of the complexes are in good agreement with theoretical values. The elemental analysis data shown in Table 1 indicates that all the metal complexes have metal to ligand ratio as 1:1 and it can be represented as $[\text{CuL}_1](\text{H}_2\text{O})_2$ and $[\text{NiL}_1](\text{H}_2\text{O})_2$ where L_1 is a Schiff base ligand obtained by the condensation of Glutaraldehyde and L-Leucine. The Cu(II) complex and Ni(II) complex have lower molar conductance value (12 and $14\text{ cm}^2\text{ mol}^{-1}$) indicating the above complexes are non electrolytes as evidenced by the non-involvement of the nitrate group in coordination⁽¹⁰⁾.

Table 1. Physical & analytical data of the schiff base ligand and its complexes

Compound	Formula	Colour	Found [Cal] (%)			
			C	H	N	M
L ₁	C ₁₇ H ₃₀ N ₂ O ₄	Yellow	62.32 (62.5)	9.12 (9.26)	8.14 (8.58)	-
[CuL ₁ (H ₂ O) ₂]	C ₁₇ H ₃₀ N ₂ O ₆ Cu	Dark green	47.84 (47.92)	8.01 (8.03)	6.48 (6.57)	14.55 (14.91)
[NiL ₁ (H ₂ O) ₂]	C ₁₇ H ₃₀ N ₂ O ₆ Ni	Yellowish green	47.91 (48.46)	7.95 (8.12)	6.45 (6.65)	13.81 (13.94)

Infra-red Spectra

The schiff base ligand show $\nu(\text{C}=\text{N})$ azomethine band observed at 1634 cm^{-1} . On complexation, this band was shifted to 1598 cm^{-1} and 1600 cm^{-1} regions⁽¹¹⁾ due to the co-ordination of azomethine nitrogen to the Cu(II) ion and Ni(II) ion. In the spectra of Schiff base ligand, the peptide band was observed at 1530 cm^{-1} . On complexation, this band was shifted to 1525 cm^{-1} region in Cu(II) complex and to 1518 cm^{-1} region in Ni(II) complex, indicating the linkage between metal ion and peptide nitrogen atom. The IR spectra of the complexes also shows some other bands at 1318 and 1355 cm^{-1} , which may be ascribed to the presence of free NO_3 group. New bands observed at 544 cm^{-1} , 546 cm^{-1} and 486 cm^{-1} , 466 cm^{-1} which are not seen in the spectrum of the free ligand can be attributed to $\nu(\text{M}-\text{O})$ and $\nu(\text{M}-\text{N})$ vibrations respectively⁽¹²⁾. The spectra of the complexes illustrate broad bands in 3454 and 3318 cm^{-1} assigned to the presence of water molecules⁽¹³⁾ in CuL₁ and NiL₁ complexes.

**Figure 1.** IR spectra of CuGlu(leu)₂.2H₂O**Figure 2.** IR spectra of NiGlu(leu)₂.2H₂O

UV/Vis Spectra

The electronic spectra are often very useful in the evaluation of results furnished by other methods of structural investigation. The electronic spectral measurements are used for assigning the stereochemistries of metal ions in the complexes based on the positions and number of d-d transition peaks⁽¹⁴⁾. The electronic spectra of the metal complexes were recorded at room temperature in the UV region which exhibit intraligand and charge transfer transitions. The Schiff base ligand L₁ show the absorption band at 275 nm which is assigned to $\pi \rightarrow \pi^*$ transition of the $\text{C}=\text{N}$ Chromophore. On complexation, this band was shifted to lower wavelength region at 250 nm suggesting the co-ordination of azomethine nitrogen with Cu(II) and Ni(II) ions⁽¹⁵⁾. The spectra also shows the other transition is in the range of 325 and 335 nm which can be assigned to $n \rightarrow \pi^*$ transition. Another transition is in the range of 350 and 360 nm which may be due to the charge transfer transition. The spectra also shows certain absorption band at 600 and 630 nm which is in accordance with d-d transition. The magnetic moment value of Cu(II) complex is 1.8 BM , which is slightly higher than the spin-only value 1.73 BM , offers possibility of an distorted Octahedral geometry around the metal ion⁽¹⁶⁾. The Ni(II) complex has magnetic moment value of 3.32 BM which is

within the range of 2.8-3.5 BM indicating a Spin- free octahedral configuration.

¹H NMR Spectra

Proton nuclear magnetic resonance spectral analysis was performed for the synthesized ligand and metal complexes which provided further evidence for the structural characteristics of the metal complexes. The ¹H-NMR spectra of the Schiff base complexes in DMSO exhibits signals at 8.44, 7.9 ppm and 8.03, 7.44 ppm, attributed to CH=N- and -NH protons respectively. The multisignals within 3.53, 3.4, 2.4 and 1.5 ppm are assigned to the -CH₃, -CH₂ and -CH groups respectively. The azomethine proton signal in the spectrum of the corresponding complexes is shifted downfield compared to the free ligand, suggesting deshielding of the azomethine group due to the coordination with the metal ion. There is no appreciable change in all other signals of the complexes. The n.m.r results obtained further supports the i.r inferences.

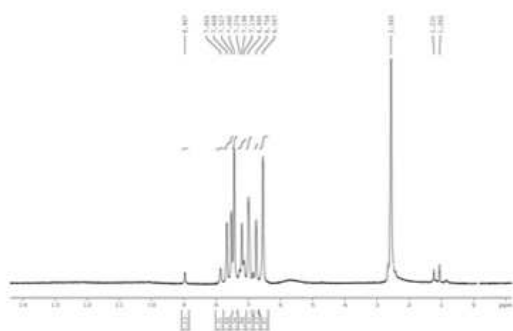


Figure 3. ¹H NMR of CuGlu(leu)₂.2H₂O

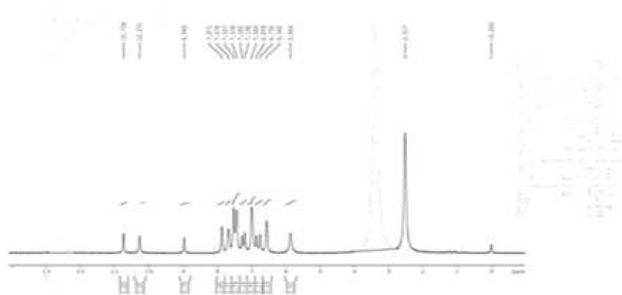


Figure 4. ¹H NMR of NiGlu(leu)₂.2H₂O

Powder XRD study

X-ray Diffraction data was recorded by using Cu K α radiation(1.5406 Angstrom). The intensity data was collected over a 2 θ range of 4-60°. All the

diffraction peaks in the X-ray diffraction pattern of the Schiff base metal complexes agreed with the reported standard data and no characteristic peaks were obtained. The mean grain size of the particles were determined from the XRD line broadening measurement using Scherre's equation (1)

$$d_{XRD} = 0.9 \lambda / \beta \cos \theta \quad (1)$$

Where λ is the wavelength (Cu K α), β is the full width at half maxima (FWHM) and θ is the diffraction angle. A definite line broadening of the diffraction peak is an indication that the synthesized material is microcrystalline. The diffractogram and associated data depicted the 2 θ value for each peak, relative intensity and inter-planar spacing. XRD diffractogram shows that CuGlu(leu)₂.2H₂O and NiGlu(leu)₂.2H₂O complexes has the crystallite size of 41 nm and 46 nm suggesting the microcrystalline nature.

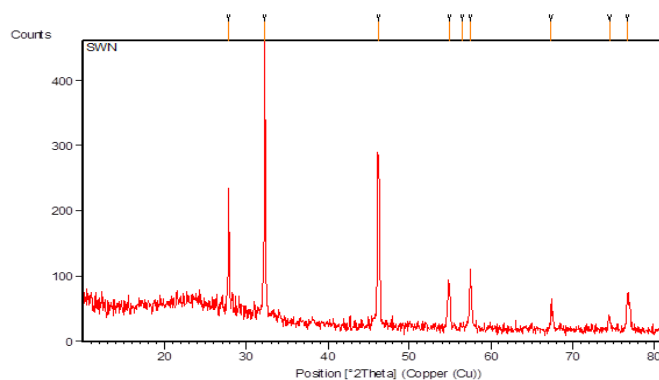


Figure 5. Powder XRD pattern of CuGlu(leu)₂.2H₂O

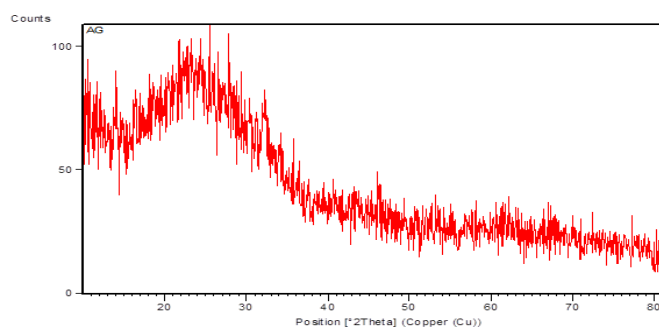


Figure 6. Powder XRD pattern of NiGlu(leu)₂.2H₂O

Thermogravimetric analysis:

The dynamic TGA with the percentage mass loss at different steps have been recorded. The elimination of

lattice and coordinated water molecules take place in the first step. The TGA and DTA analysis of Cu(II) and Ni(II) complexes were conducted in air in the range of 25 -900°C at 10 / min rate. The complexes lose their weight in the temperature range 140-240°C and 135-260°C corresponding to two coordinated water molecules with an endothermic peak in DTA curve. After the total loss of water, the organic moiety decomposes at 750°C and 650°C and the observed residue corresponds to the respective oxide. The occurrence of endothermic peak and elimination of the two water molecules at comparatively higher temperature unambiguously confirm our earlier observation based upon the IR spectrum that the water molecules are coordinated in the metal complexes.

Antimicrobial activity:

The invitro antimicrobial activity of the compounds was tested against the bacteria *Klebsiella* sps, *Escherichia coli*, *Staphylococcus aureus* and fungi *Candida* sps, *Aspergillus niger*, and *Aspergillus fumigatus* by Disc Diffusion method. The minimum inhibitory concentration (MIC) values of the compounds are summarized in Table 2. From the MIC values obtained, it was found that the complexes exhibit higher antimicrobial activity than the free

ligand. Compounds containing C=N group have enhanced antimicrobial activity than C=C group. The corresponding Cu and Ni complexes show enhanced antimicrobial activity. This may be ascribed to the increased lipophilic nature of the complexes arising due to chelation. Against all the bacterial species, the Schiff base ligand does not show any activity. Among all organisms, CuL₁ complex was found to be moderately active in the bacterial species of *Klebsiella* sps and *Staphylococcus aureus*. However Cu complex was found to have more activity in the species of *E. coli*. Moreover, the results of the bacterial activity of Ni complex points out that the Ni complex shows moderate activity in the bacterial species of *Klebsiella* sps and *Staphylococcus aureus* at the same time it shows less activity in the species of *E. coli*. The results on antifungal activity of the ligands show very less activity towards all the fungal species such as *Candida* sps, *Aspergillus niger* and *Aspergillus fumigatus*. The CuL₁ complex possesses higher activity in *Candida* sps, and slightly less active in *Aspergillus niger* and *Aspergillus fumigatus* than in *Candida* sps. In the same way, the NiL₁ complex shows higher activity towards *Aspergillus niger* and *Aspergillus fumigatus* and shows slightly less active in *Candida* sps.

Table 2. Antimicrobial data of the ligand and their complexes

Schiff base/ Complex	Zone of inhibition					
	<i>Klebsiella</i> sps	<i>Escherichia</i> <i>coli</i>	<i>Staphylococcus</i> <i>aureus</i>	<i>Candida</i> sps	<i>Aspergillus</i> <i>niger</i>	<i>Aspergillus</i> <i>fumigatus</i>
L ₁	5	6	5	4	5	6
Cu L ₁	11	12	10	12.5	11.5	11.5
Ni L ₁	13	12	13	20	21	21

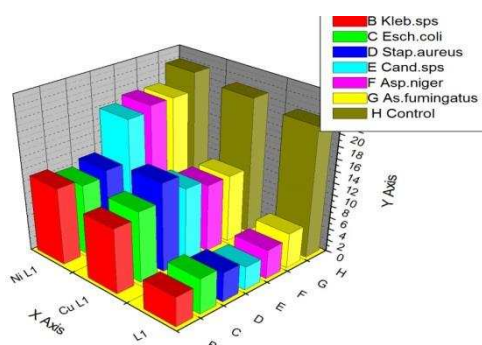


Figure 3.7. Zone of inhibition of the ligand and their complexes

IV. CONCLUSION

In this paper, coordination chemistry of a Schiff base ligand, obtained from the reaction of Glutaraldehyde and L-Leucine is described. Cu(II) and Ni(II) complexes have been synthesized using the above Schiff base ligand and characterized on the basis of analytical, magnetic and Spectral data. The Schiff base complexes exhibit Octahedral geometry.

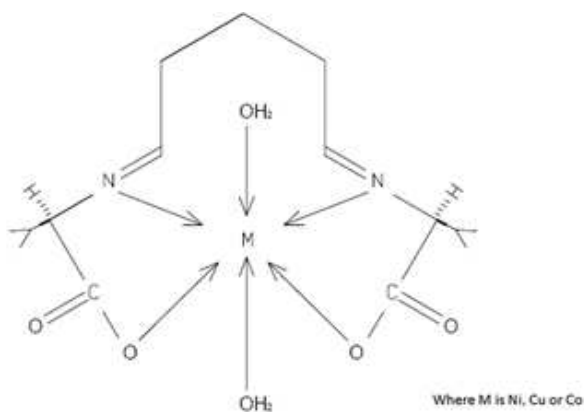


Figure 8. Structure of Schiff base Metal Complex

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