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MICROWAVE INDUCED SYNTHESIS AND CHARACTERIZATION OF BIOLOGICAL ACTIVE MIXED LIGAND COPPER CHLORIDE COMPLEXES

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ABSTRACT

Mixed Ligand Copper Chloride Complexes of (2-carboxyphenyl)-pyridine-2-ylethyleneamine and 1, 10-Phenanthroline; and 1, 10-Phenanthroline!" have been synthesized by microwave method. This compound have been characterized by elemental analysis, FT-IR, FAB-mass, molar conductance, electronic spectra, Electrochemical, magnetic susceptibility, electrical conductivity and Antimicrobial analysis. The complex is green and stable in air. Analytical data revealed that all the complex exhibits 1:1 (metal:ligand) ratio with the coordination number 6. FAB-mass and Electrochemical data show the present copper (II) complexes undergo quasi-reversible on electron reduction (CuII/CuI) redox process. The Antimicrobial analysis reveals that mixed ligand Copper Chloride complex prepared by (2-carboxyphenyl)-pyridine-2-yl ethylene amine is more active than (2-carboxyphenyl)-pyridine-2-yl ethylene amine Ligand.

Keywords: Microwave synthesis; Mixed Ligand; Copper complex; Antimicrobial;

1. INTRODUCTION

The Schiff bases have high affinity to chelate with the transition metal ions, hence are attracting attention due to potential applications in areas viz. biology, catalysis, thermal, electrical, optical, magnetic etc. Metal complexes are suitable to molecular materials, on the basis of electronic properties associated with the metal center [1-3]. Schiff base ligands containing O and N donor atoms play an important role in coordination chemistry related to catalysis and enzymatic reaction, magnetism and molecular architecture. [1-3] Microwave reactions under solvent free and less solvent conditions are attractive offering reduced pollution, low cost and offer high yields together with simplicity in processing and handling. The salient features of microwave approach are shorter reaction times, simple reaction conditions and enhancements in yields [4,5]. In this study, we report the synthesis, physicochemical characterization and biological significances of Cu (II) complexes with ligands derived from (2-

carboxyphenyl)-pyridine-2-ylethyleneamine and 1, 10-Phenanthroline; (Fig. 1). The reaction was carried out by microwave methods. The metal complex formed with this new ligand may be used as precursors for the synthesis of new compounds, exhibit interesting physical, chemical and biological properties.

2.1 CHEMICALS AND REAGENTS

2.1.1 Purification of solvents

The solvents used, methanol, ethanol, in this research were obtained from Sd-fine and were purified and dried by conventional methods. All products were dried in vacuum while all the glass wares were dried overnight in an oven. Chemicals was reagent grade and purchased from Aldrich. Solvents were reagent grade and used with no other purification, other than drying over the specified molecular sieves when required.

Microwave assisted synthesis were carried out in open glass vessel on a modified microwave oven model 2001 ETB with rotating tray and a power source 230 V, microwave energy output 800 W and

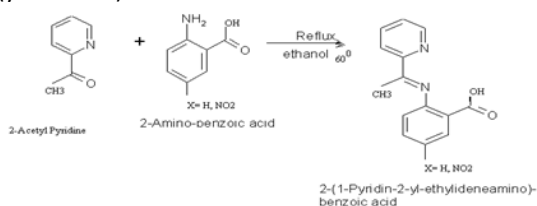
microwave frequency 2450 MHz. A thermocouple device was used to monitor the temperature inside the vessel of the microwave. The microwave reactions were performed using on/off cycling to control the temperature.

2.1.2 Commercially available compounds

2- Acetyl pyridine from Lanckester Anthranilic acid, from Alfa Aesar. 1, 10-phenanthroline, from Merck. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ from SD-fine. DMSO, Dimethylformamide, DCM, Acetonitrile from SD-fine.

2.1.4 Synthesis of Ligands (L_1) Scheme: [(L_1)]

Microwave method for the synthesis of Schiff bases: The equimolar (1:1) ratio of 2-(1-Pyridine-2-yl-ethylideneamino)-benzoic acid (L_1), synthesized by mixing of a solution 2-Acetyl-pyridine (0.121 g, 1 mmol) in 10 ml of ethanol with solution of 2-aminobenzoic acid (0.137 g, 1mmol) dissolved in 10 ml of absolute ethanol while stirring. The reaction mixture was then irradiated by the microwave oven by taking 5 mL of dry ethanol as a solvent. The reaction was completed in a short time (6 min) with higher yields. The resulting product was recrystallised with ethanol and finally dried under reduced pressure over anhydrous CaCl_2 in a desiccator. The progress of the reaction and purity of the product was monitored by TLC using silica gel G (yield: 81%).



Scheme 2.1.4: Synthesis of L_1 : Where $x = \text{H}, \text{NO}_2$; Reagents and Conditions; Ethanol-60 °C; (b) reflux for 5h.

Fig. 1 Structure of Schiff base ligands

Microwave method for the synthesis of metal complexes: The ligand, phen and the metal salt were mixed in 1:1:1 (metal:ligand) ratio in a grinder. The reaction mixture was then irradiated by the microwave oven by taking 5 mL of dry ethanol as a solvent. The reaction was completed in a short time (8 min) with higher yields. The resulting product was then recrystallized with ethanol and ether and

finally dried under reduced pressure over anhydrous CaCl_2 in a desiccator. The progress of the reaction and purity of the product was monitored by TLC using silica gel G (yield: 81%).

Mm- microwave method

[L_1]: - Yield 72% (81%); m.p. 148°C; Colour: Golden brown; Anal. Calc. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$: C, 66.99,(67%); H, 5.03,(5.5%); N, 11.18,(11.80%); Found: C, 66.99,(66.9%); H, 5.03,(5.04%); N, 11.18,(11.20%); IR (KBR) (cm^{-1}) 1617 $\nu(\text{C}=\text{N})$; 1672 $\nu(\text{C}=\text{O})$; Uv-Vis: 250nm, 270nm, 330nm $\lambda_{\text{max}}(\text{nm})$; ^1H NMR: (CDCl_3) (400 MHz) δ CH_3 : 2.48 ppm and Ar-H6.5 -8.3 ppm; Azomethine (C=N):8.5 ppm.

2.2 ANALYSIS OF COMPLEXES

2.2.1 Estimation of Carbon, Hydrogen, and Nitrogen : Elemental analysis (C, H, and N) were estimated on a Thermo Finnegan FLASH EA-112 CHNS analyzer at IISc, Bangalore. The carbon, hydrogen and nitrogen provide correct picture about the molecular formula as well as the purity of the compounds.

2.2.2 Estimation of metal content : Metal contents of the complexes were estimated after decomposing the complexes with 1:1 mixture of conc. nitric acid and perchloric acid [4, 5]. The solution was evaporated repeatedly and the residue was extracted with dilute hydrochloric acid and water. The amounts of metal ion in the solution obtained were determined by standard method. [10]

2.3. PHYSICO - CHEMICAL METHODS

^1H NMR: Nuclear magnetic resonance is powerful tool for investing nuclear structure. Nuclear magnetic resonance is technique that enables us to shape and structure of molecules. In particular it reveals the different chemical environment of the various forms of hydrogen present in molecule, from which we are dealing. It is method of both qualitative and quantitative analysis. ^1H NMR spectra were recorded on a Bruker ACF 300 MHz spectrometer using $[\text{TMS}(\text{CH}_3)_4\text{Si}]$ as the internal reference. Chemical shifts were measured on the δ (ppm) scale and are reported in ppm. NMR data were collected on a Brüker Avance 500 spectrometer at 500 MHz Data were collected in $\text{DMSO}-d_6$ at 25°C unless stated otherwise. Solvent references were either tetramethylsilane (TMS). ^1H

NMR was used to characterize the compound. When necessary, elemental analyses were obtained to determine purity. [11]. The proton NMR spectra of the Schiff base ligands were recorded in DMSO-d₆ solution using TMS as internal standard. The ¹H-NMR spectra of the L₁ ligand show multiplet at δ 7.127-7.652 ppm due to aromatic protons while the azomethine proton resonates as singlet at δ 8.5. The phenolic OH groups have signals at δ 12.243 ppm which are disappeared on coordination.

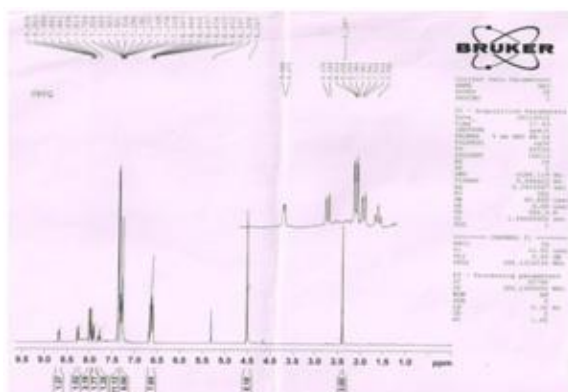


Fig. 2

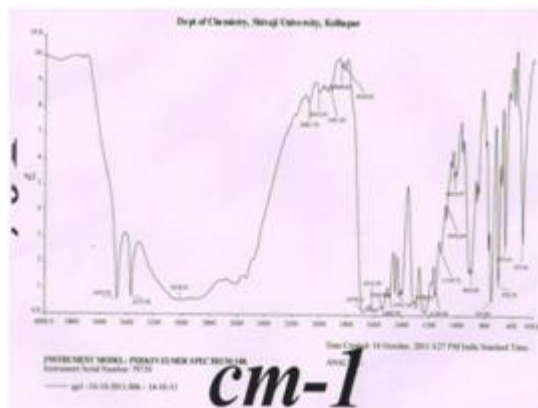
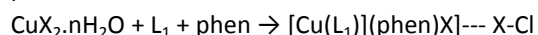


Fig. 3

3. RESULTS AND DISCUSSION

The metal complex is coloured, solid and stable towards air and moisture at room temperature. They decompose on heating at high temperature and less soluble in common organic solvents. Study results obtained by microwave assisted synthesis is that reactions was completed within 8 min by the microwave irradiation technique and yields have been improved by 81%. The result of microwave methods, with analytical and physical data of the compound is given in the Table 1. The metal chelate have 1:1 (metal:ligand) stoichiometry.

The observed molar conductance of the complexes in DMSO at room temperature is consistent with the non-electrolytic nature of the complex. The synthesized compounds is crystalline colored, nonhygroscopic, soluble in Dimethylformamide(DMF)and Dimethyl sulfoxide (DMSO). They were obtained with excellent yield because of the intramolecular hydrogen bond between the fairly acidic phenolic hydrogen and the azomethine nitrogen atom in 2-ACETYL PYRIDINE or its derivatives, which Catalyzes the condensation reactions. The coordination of the Cu metal of the Tridentate (ONN) ligands is realized by means of PYRIDINE nitrogen atom and AZOMETHINE of the ligands and ONE oxygen of the ligands. Composition and identity of the assembled system were deduced from elemental analysis and IR, Uv-Vis, NMR, CV and molar conductance. The analytical data of the complex indicated 1:1 metal to ligand stoichiometry. Possible compositions of the complex is calculated and compared with the experimental values as presented in Table 1. The Schiff base could coordinate to the metal atoms through the phenolate oxygen, imines' nitrogen, and pyridyl nitrogen atoms. The Cu (II) complex adopts octahedral geometry by following synthesis procedure.



3.1 Magnetic Moments and Electronic Spectra :

Magnetic moments and electronic spectra of the metal complexes are listed in table. The electronic spectra of the free ligands L₁ shows two weak bands at 30303-37037 cm⁻¹ and 24390-30769 cm⁻¹ which are assigned to the n→π, π→π* transitions respectively. The broad band centered at 15267-13793 cm⁻¹ appearing as an envelope in the Cu (II) complexes assigned to the ²E_g and ²T_{2g} transition reveals the octahedral geometry. The ²E_g and ²T_{2g} states of the octahedral Cu (II) (d⁹) split under the influence of Tetrahedral distortion and distortion can be such as to cause three transition ²B_{1g}→²B_{2g}; ²B_{1g}→²E_g and ²B_{1g}→²A_{1g} to remained unresolved in the spectra. The octahedral geometry of Cu (II) ion in complex is confirmed by the measured magnetic moment value is 1.74 μ_B which is in harmony with the reported value. The complexes were dissolved in

DMF and the molar conductivities of 10^{-3} M of their solutions at room temperature were measured. Table 2 shows the molar conductance values of the complexes. It is concluded from the results that complex is found to have molar conductance values in the range of $16 \text{ ohm}^{-1} \text{ mol}^{-1} \text{ cm}^2$ indicating the non-electrolytic nature of these complex. [5]

3.2 FT-IR : The IR spectra of Schiff base ligand L_1 show band at 1672 cm^{-1} , may be assigned to the $\nu_{\text{C=O}}$ (carboxylic group), However, the spectra of complex show absence of this band accompanied by the appearance of two characteristic bands at $1591\text{-}1325 \text{ cm}^{-1}$ attributed to asymmetric and symmetrical stretching of the carboxylic group respectively, indicating the involvement of the carboxylic oxygen atom in the complex formation. The mode of coordination of carboxylate group has often been deduced from the magnitude of the observed separation between the $\nu_{\text{sy}}(\text{COO}^-)$ and $\nu_{\text{asy}}(\text{COO}^-)$, the separation value (Δ) between $\nu_{\text{asy}}(\text{COO}^-)$ in metal complexes was more than 200 cm^{-1} (266 cm^{-1}) suggests the coordination of carboxylate group in metal complex in a monodentate fashion.

The azomethine $\nu(\text{C=N})$ bands in the IR spectra of the ligands appear in the range 1617 cm^{-1} , shifting of this band towards the lower frequency region by $15\text{-}25 \text{ cm}^{-1}$ in complexes indicates involvement of azomethine nitrogen in coordination

with metal ion. The pyridine ring deformation mode at $\sim 620 \text{ cm}^{-1}$ in these spectra of the free ligands is shifted to higher wave numbers in the spectra of the complexes indicating coordination of the complexes indicating coordination of the pyridine ring nitrogen atom to the copper(II). [11] The 1,10-phenanthroline bands at 717 cm^{-1} shows their involvement in the complexes.

3.3 Cyclic Voltammetry: The electrochemical properties of the present complex have been studied by cyclic voltammetry (CV) under a nitrogen atmosphere in DMSO solution containing 0.1M NaClO_4 as the supporting electrolyte at a platinum working electrode. The electrochemical properties of metal complex particularly have been studied in order to minor spectral changes accompanying electron transfer. These complex, a negative scan initiated at 1200mV in the potential range 1500 to -1200mV , yielded a quasireversible on electron reduction ($\text{Cu}^{\text{II}}/\text{Cu}^{\text{I}}$) process in the potential range 0.458 to 0.575V against Ag/AgCl electrode. In this case, the cathodic peak potential and difference increase as the scan rate is increased. Constancy of E° shows that both peaks are complementary to each other. The pertinent redox couples are represented in the following electron transfer series (8):

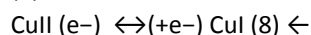


Table 1 Analytical and physico-chemical data of the metal complexes

Complex	M. F.	Colour	Yield%	M.P. °C	Analytical data % Found				Λ_M $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$	μ_{eff}
					(calculated)					
					Cu	C	H	N		
L_1	$\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$	brown	70			66.99	5.03	11.66		
$[\text{Cu}L_1(\text{phen})\text{Cl}]$	$\text{C}_{26}\text{H}_{19}\text{N}_4\text{O}_2\text{ClCu}$	green	70	>230	12.26 [12.4]	60.23 [66.5]	3.69 [3.71]	10.81 [10.86]	16	1.74

Table 2: Infrared spectral data of the ligands and metal complexes

Compound	$\nu_{\text{C=N}}$	COO^-	1, 10- phenanthroline	Cl-	Py-N
L_1	1617	1672			659
$[\text{Cu}L_1(\text{phen})\text{Cl}]$	1614	1591, 1325	15,381,409,869,717		644

Table 3 Electronic spectral data and magnetic moment values of the metal complexes

Compound	μ_{eff}	$\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions and charge transfer transitions (cm^{-1})	d \rightarrow d transitions (cm^{-1})
	μ_B		
L1		252, 275, 345	
[CuL ₁ (phen)Cl]		250, 275	650, 730

Table 4. Antibacterial screening data for the ligands and their complexes

Compound	<i>E. coli</i>						<i>S. aureus</i>					
	Diameter of inhibition zone (in mm)			b% Activity index			Diameter of inhibition zone (in mm)			b% Activity index		
	25a	50a	100a	25a	50a	100a	25a	50a	100a	25a	50a	100a
L1	14	15	16	77	67	71	10	13	15	67	67	70
L1PhenCuCl	18	22	25	89	90	87	18	20	24	88	78	90
Streptomycin (Standard)	21	23	28	100	100	100	18	23	25	100	100	100

Table 5. Antifungal screening data for the ligands and their complexes

Compound	<i>A. niger</i>			<i>C. albicans</i>		
	Diameter of inhibition zone (in mm)			Diameter of inhibition zone (in mm)		
	25a	50a	100a	25a	50a	100a
L1	13	14	20	16	16	18
L1PhenCuCl	19	23	27	18	21	23
Miconazole (Standard)	22	25	30	24	24	28

3.4 UV-VIS ANALYSIS

The UV-vis spectra of the complex in DMF are reported in Table 3. They show essentially three sets of common bands, falling in the range 270 to 780 nm. The very intense bands at low wavelengths have been assigned to charge transfer transition, for complexes with aromatic bridges these bands occur at longer wavelengths, as expected from the higher aromaticity of the ligands which eases delocalization of electron density. On the other hand, the observed new shoulder around 450 nm in the spectra of the complexes solutions can be likely ascribed to an intermolecular transition from the ligands molecules to the vacant orbitals localized on the coordinated metal ions, that is, LMCT. The weaker band in the region 650 to 730 nm in the spectra of complexes

with aliphatic imines is assigned to unresolved transitions from the four low-lying empty dxy orbital (Hoyt and Everett, could not be observed for complexes with aromatic imines bridges since it is masked by the high charge transfer transitions.[6]

3.5 Antimicrobial activities : The *in vitro* antimicrobial activity of the synthesized Schiff base ligands and their corresponding metal complexes on selected bacteria *E. coli* and *S. aureus* and two fungi *A. niger* and *C. albicans* was carried out. All of the tested compounds showed good biological activity against microorganism. The bactericidal and fungicidal investigation data of the compounds are summarized in Tables 4 and 5. Moreover, all the complexes are moderately active as compared to the standard bactericide and fungicide

(Streptomycin and Miconazole). A comparative study of the ligands and their transition metal complexes indicates that the complexes are more active than their respective ligands, the activity increases upon coordination. The increased activity of the metal chelates than those of the ligands can be explained on the basis of Overtone's concept and Chelation theory. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of the π -electrons over the whole chelating ring and enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. There are other factors also, which increase the activity viz. solubility, lipophilicity/hydrophilicity, conductivity and M-L bond length[18].

a Concentration in ppm; b% Activity Index= Zone of inhibition by test compound (diameter) / 100 Zone of inhibition by standard (diameter)

3.6 Biological activity: The *in-vitro* biological activity of the investigated Schiff base and their metal complexes was tested against the bacteria *Escherichia coli* and *Staphylococcus aureus* by disc diffusion method using nutrient agar as medium and streptomycin as control. The antifungal activities of the compounds were also tested by the Well diffusion method against the fungi *Aspergillus niger* and *Candida albicans*, on potato dextrose agar as the medium and miconazole as control. Each of the compounds was dissolved in DMSO and solutions of different concentrations (25, 50 and 100 ppm) were prepared separately. In a typical procedure, a well was made on agar medium inoculated with microorganism. The well was filled with the test solution using a micropipette and the plate was incubated 24 h for bacteria at 37°C and 72 h for fungi at 30°C. During this period, the test solution diffused and the growth of the inoculated microorganism was affected. The inhibition zone was developed, at which the concentration was noted. All determinations were performed in thrice.

4. CONCLUSION

In case of microwave assisted synthesis, it was observed that the reaction time decreased from hours to minutes and availability of the product with better yield as compared to the conventional method. Use of solvent is also minimized. In this work, the coordination chemistry of the three Schiff base ligands, L₁ and metal complex with copper(II) Cl⁻ And 1,10-phenanthroline as secondary ligand were described and characterized on the basis of analytical, magnetic and spectra data as well as Electrochemical studies. The Schiff bases ligand act as monobasic tridentate, coordinated to the metal ions in a tri dentate manner with ONN donor sites of the carbonyl oxygen, azomethine nitrogen, and pyridine nitrogen along with anion and two Nitrogen of 1, 10-phenantroline in the complex formation and in ligands, the coordination mode of carboxylate group is unidentate mode, correlating the experimental data, one can suggest the octahedral geometry for the prepared metal complexes. The present copper (II) complexes undergo quasi-reversible on electron reduction (CuII/CuI) redox process. The antimicrobial data showed that the metal complexes to be more biologically active compared to those parents Schiff base ligands against all pathogenic species. Such studies may assist to search some novel chemotherapeutics to answer the emerging problem of drug resistance in health sciences

5. ACKNOWLEDGEMENT

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