



Synthesis, Characterization and Biological Activity of Cu(II) and Ni(II) Complexes of 3-Hydroxy- 4-(Pyridine-2-yl-Methylene Amino) Benzoic Acid

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ABSTRACT

The synthesis, characterization and biological activity of Cu(II) and Ni(II) complexes derived from tridentate Schiff base ligand 3-hydroxy-4-(pyridine-2-yl methylene amino) benzoic acid (HL) was obtained by the condensation of 2-Pyridine carboxaldehyde with 4-amino 3-hydroxy benzoic acid has been described. The complexes were characterized based on elemental analyses, molar conductivity measurements, FT-IR, UV-vis and thermogravimetric analysis. The Schiff base acts as tridentate mono basic donor, coordinating through the azomethine nitrogen, phenolic OH and pyridynyl nitrogen. The ligand and their metal complexes were screened against bacteria and fungi. Data obtained showed that metal complexes have shown higher biological activity Schiff base ligand.

Key words: Schiff base; Copper; Nickel; Transition metal complexes; Biological activity.

INTRODUCTION

Transition metal complexes have attracted attention of inorganic, metallo-organic as well as bio-organic chemists because of their extensive applications in wide ranging areas from material science to biological sciences¹. Metal complexes of Schiff bases are extensively studied due to synthetic flexibility, selectivity and sensitivity towards a variety of metal atoms². Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis and as polymer stabilizers³. The

efficacy of the various organic therapeutic agents can often be enhanced⁴ upon coordination with a suitable metal ion. In many cases, the pharmacological activity has been found to be highly dependent on the identity of the donor sequence of the ligands, as different ligands show widely different biological activities although they may vary only slightly in their molecular structure⁵. There is a real perceived need for the discovery of new compounds endowed with antimicrobial activities. Schiff bases and their metal complexes are known to be biologically important and interesting because of their anti-inflammatory, anti-carcinogenic,

antipyretic, anti-diabetic, anti-bacterial and antifungal properties^{6,7}. It has been found that the tridentate Schiff base ligands with a flexible donor atom, in comparison with the bidentate ligands, are more suitable ligand systems for stabilizing organo-metal complexes because of the coordination of the additional donor atom. Metal complexes of pyridine carboxylic acids and some of the derivatives have also been successfully used as model systems for the design of new metallo-pharmaceutical compounds⁸. Pyridine derivative plays an important role in many bio-chemical reactions. 2-pyridine carboxaldehyde has been found involved in enzyme reactions as medicine^{9,10}. The Copper(II) and nickel(II) complexes of Schiff base ligands have played a vital role in the development of coordination chemistry¹¹.

In view of the above considerations, we have synthesized and characterized Cu(II) and Ni(II) complexes of Schiff base (HL) derived from 2-pyridine carboxaldehyde and studied the biological activity of the complexes.

EXPERIMENTAL

Materials and Physical Measurement

Analytical or chemically pure grade chemicals were used for the preparation of ligands and metal complexes. Elemental analysis was carried out on Euro elemental analyzer. The IR spectra were recorded of (Thermo Nicolet FT-IR, Nicolet-200, USA) spectrometer in the 4000-400 cm^{-1} region using KBr pellets. Thermogravimetric analysis was carried out on a STA 409 PC analyzer under the flow of nitrogen gas. Electronic spectral studies of the compounds were carried out using Shimadzu UV 1800 spectrophotometer. The molar conductance of the complexes in DMF solution (10^{-3}) at room temperature was measured using a direct reading conductivity meter.

Synthesis of ligand HL

As shown in scheme 1, synthesis of the ligand was based on the following method: 4-amino-3-hydroxy benzoic acid (0.001 mol) dissolved in ethanol was added to the ethanolic solution of 2-pyridine carboxaldehyde (0.001 mol). Then the mixture was refluxed for 24 hrs with constant stirring at a temperature of 50 to 60°C. The solvent was

removed by rotavaporation. The brown coloured compound that obtained was washed with hexane and dried. The compound was recrystallised from hot ethanol..

Colour: Brown Yield: 75-78 %, m.p.: 152, Anal. Calc. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3$; C, 64.46, H, 4.16, N, 11.56, O, 19.82; Found C, 64.40, H, 4.12, N, 11.52, O, 19.79. FTIR (KBr) cm^{-1} ; 3358 $\nu(\text{O-H})$, 1578 $\nu(\text{C=N})$, 1441 (pyridine ring). $^1\text{H-NMR}$ (DMSO- d_6); δ 9.60 (1H, s, Ar-OH), δ 12.52 (1H, s, carboxylic acid-OH), δ 8.73 (1H, d, pyridine), δ 7.55-7.97 (5H, m, phenyl), δ 8.73 (1H, s, NCH). Uv/Vis (DMF, nm); 274, 297, 327.

Synthesis of Metal Complexes

The metal complexes were synthesized by the following general procedure, a solution of the appropriate metal salt (4 mmol) dissolved in 20 mL ethanol was added to a hot ethanolic solution of the ligand (0.1 g, 4 mmol). The mixture was refluxed for 3 to 4 hrs at a temperature of 50-60 °C. On cooling, colored complexes were precipitated out. They were filtered, washed with ethanol and dried under vacuum over P_4O_{10} .

[Cu(L)(OAc)]

Color: dark green, Yield: 76 %, m.p. 238 °C. Anal. calc. for $\text{C}_{15}\text{H}_{13}\text{CuN}_2\text{O}_5$. C, 49.38, H, 3.59, Cu, 17.42, N, 7.68, O, 21.93 % Found, C, 49.86, H, 3.98, N, 7.72; O, 22.04 Cu, 17.49; FT-IR (KBr, cm^{-1}); 3390 $\nu(\text{O-H})$, 1541 $\nu(\text{C=N})$, 1419 (pyridine ring), 480 $\nu(\text{M-N})$, 745 (M-O). Uv/Vis (DMF, nm); 318, 353, 390.

[Ni(L)Cl₂.H₂O]

Colour: Reddish brown, Yield: 73%, m.p.: 254 °C. Anal. Calc. for $\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}_4\text{Ni}$; C, 40.16, H, 2.85, Cl, 18.24, N, 7.20, Ni, 15.09, O, 16.46 %; Found, C, 40.09, H, 2.80, Cl, 18.21, N, 7.18, Ni, 15.05, O, 16.41. FTIR (KBr) cm^{-1} ; 3345 $\nu(\text{O-H})$, 1595 $\nu(\text{C=N})$, 1427 (pyridine ring), 515 $\nu(\text{M-N})$, 590 $\nu(\text{M-O})$. Uv/Vis (DMF, nm); 295, 313, 350.

Antimicrobial activity

The ligand and its metal complexes were screened against bacteria and fungi using paper disc diffusion method [12-15]. The bacterial and fungal organisms used were, *Pseudomonas aeruginosa* (gram +Ve), *Escherichia Coli* (gram – Ve), *Aspergillus Niger* and *Rhizoptonia Solani*

respectively. The compounds were tested at a concentration of 30 µg/0.01mL in DMF solution. Nutrient agar was used as culture medium for bacteria and potatodextrose agar for fungi. The zones of inhibition formed were measured in millimeters. DMF was used as control and gentamycine was used as a standard drug.

RESULTS AND DISCUSSION

3-hydroxy-4-(pyridine-2-yl methylene amino) benzoic acid was synthesized from 2-pyridine carboxaldehyde and 4-amino-3-hydroxy benzoic acid as shown in Scheme 1. The metal complexes Cu(II) and Ni(II) were obtained by the reaction of metal chloride /acetate with tridentate ligand in 1:1 molar ratios. The analytical data shown in Table 1 of the complexes are consistent with proposed molecular formulas. Molar conductance values of the soluble complexes in DMF showed low values $\sim 20 \text{ cm}^{-1} \text{ mol}^{-1}$ indicating them to be non-electrolytic in nature. The complexes are coloured, non-hygroscopic and are soluble in DMF, DMSO and other common organic solvents like methanol and ethanol.

Infrared spectra

The characteristic IR bands of the Cu(II) and Ni(II) complexes differ from their free ligand and provide significant indications regarding the coordination and binding sites of the ligand to the metal ion. The FT-IR spectra of Cu(II) complex is shown in Fig. 1. The IR-spectral data of the ligand and its metal complexes are presented in Table 2. The $\nu(\text{C}=\text{N})$ composed mode observed at 1578 cm^{-1} in the spectra of free ligand, shifted to 1541 and 1595 cm^{-1} in the spectra of Cu(II) and Ni(II) complexes respectively, indicating the coordination of azomethine nitrogen to the metal. The IR spectrum of the ligand showed a broad peak at 3358 cm^{-1} which is attributed to $\nu(\text{O}-\text{H})$ vibration. In case of Cu(II) and Ni(II) complexes this peak was shifted slightly downwards to 3339 and 3345 cm^{-1} respectively, which is an indicative of the presence of $\nu(\text{O}-\text{H})$ vibration. Pyridine ring shows absorption band at 1441 cm^{-1} in the spectra of free ligand. This band was shifted to 1419 and 1427 cm^{-1} in those of the complexes Cu(II) and Ni(II), suggesting participation of pyridynyl nitrogen in complexation¹⁶.

Table 1: Analytical data and other details of the ligand and metal complexes

S. No	Molecular formula	Formula weight	Colour	M.P	C	H	N	O	M	Cl	Molar conductance ($\text{ohm}^{-1} \text{ mol}^{-1} \text{ cm}^2$)
1	HL	242.27	Brown	152	64.46 (64.40)	4.16 (4.12)	11.56 (11.52)	19.82 (19.79)	-	-	-
2	Cu(L)(OAc)	364.8	Bluish green	238	49.86 (49.38)	3.98 (3.59)	7.72 (7.68)	22.04 (21.93)	17.49 (17.42)	-	18
3	Ni(L) Cl ₂ .H ₂ O	353.38	Reddish brown	254	40.09 (40.16)	2.80 (2.85)	7.18 (7.20)	16.41 (16.46)	15.05 (15.09)	18.21 (18.24)	23

Table 2: FT-IR spectral data for HL ligand and its metal complexes.

Compound	$\nu(\text{O-H})$	$\nu(\text{C=N})$	Pyridine	$\nu(\text{M-N})$	$\nu(\text{M-O})$	$\nu(\text{C=C})$
HL	3358	1578	1441	-	-	739
Cu(L)(OAc)	3390	1541	1419	480	745	772
Ni(L)Cl ₂ .H ₂ O	3345	1595	1427	515	590	748

Table 3: Antimicrobial activity of HL ligand and its metal complexes

Compound	Bacteria tested		Fungus tested	
	<i>E.coli</i>	<i>P.aeruginosa</i>	<i>R.solani</i>	<i>A.niger</i>
HL	+	+	+	+
Cu(L)(OAc)	+++	+++	++	-
Ni(L)Cl ₂ .H ₂ O	++	++	++	++

Note: Maximum zone of inhibition was represented as +++ (20-35mm)

Medium zone of inhibition was represented as ++ (10-20mm)

Minimum zone of inhibition was represented as + (5-10mm).

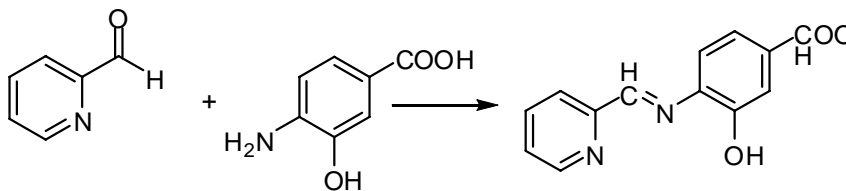
From the above information, it is evident that the ligand is bonded to metal ion through azomethine nitrogen, aromatic OH and nitrogen atom of pyridine ring.

¹H-NMR spectra

The ¹H NMR signals of the HL and their Cu(II) and Ni(II) complexes are recorded in DMSO. The ligand has signals at δ 9.60, 12.52, 8.73, 7.55-7.97 and 8.73 ppm, which are due to Ar-OH, carboxylic acid-OH, pyridine ring, phenyl and N=CH respectively. In the complexes, signals due to -OH are absent supporting the coordination of ligand to metal through phenolic oxygen. The low field position of -CH (δ =8.73) could be attributable to the deshielding caused by the pyridine ring and the remaining group adjacent to the -CH=N- moiety.

UV-Vis spectra

The UV-Vis absorption spectra of the ligand and its metal complexes were recorded in DMF solution. The electronic spectrum of the ligand exhibited intra-ligand transitions at 274 and 297 nm due to π - π^* transitions and at 327 nm due to n - π^* transition of azomethine group. On complexation these bands suffered considerable shifts due to coordination to respective metal ions. The electronic spectrum of Cu(II) complexes exhibited absorption bands at 318, 353-390 nm. On complexation, the band due to azomethine group at 327 nm which corresponds to n - π^* transition was shifted to 318nm. This shows that azomethine group is involved in complexation. The band observed at 353-390 nm is assignable to a combination of ligand-Metal charge transfer (L-MCT) and d-d bands.



Scheme 1: Synthesis of ligand HL

The electronic spectra of Ni(II) complex shown in Fig. 2, exhibited bands at 295, 313 and 350 nm, which may be assigned to $\pi-\pi^*$, $n-\pi^*$ (azomethine nitrogen) and L-MCT from phenolate oxygen to an empty d-orbital and d-d transitions¹⁷.

TG-DTA

Thermogravimetric (TG) and differential thermal analysis (DTA) were used to describe thermal behaviour of the prepared complexes. The TG and DTA studies of the complexes were carried

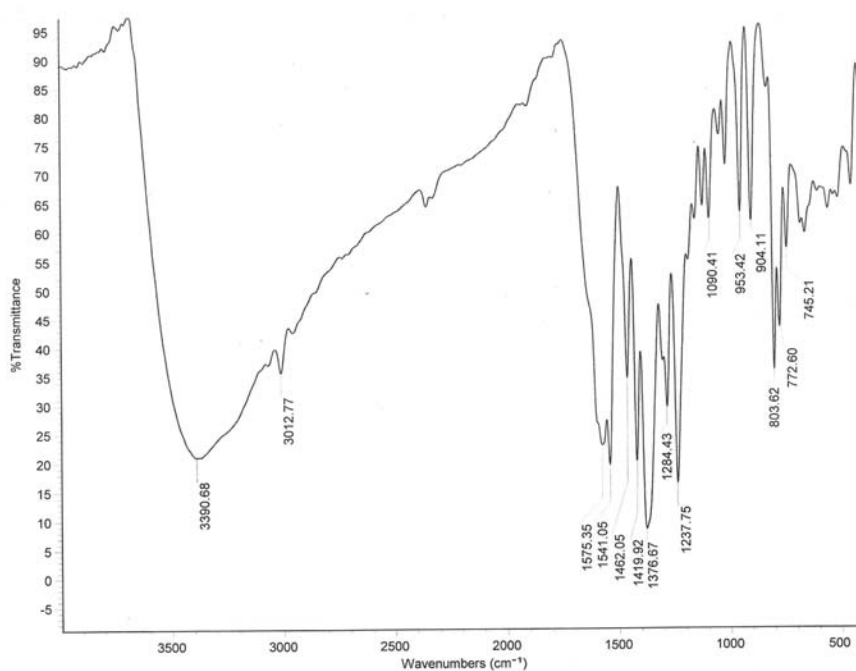


Fig. 1: FT-IR spectra of Cu(II) complex

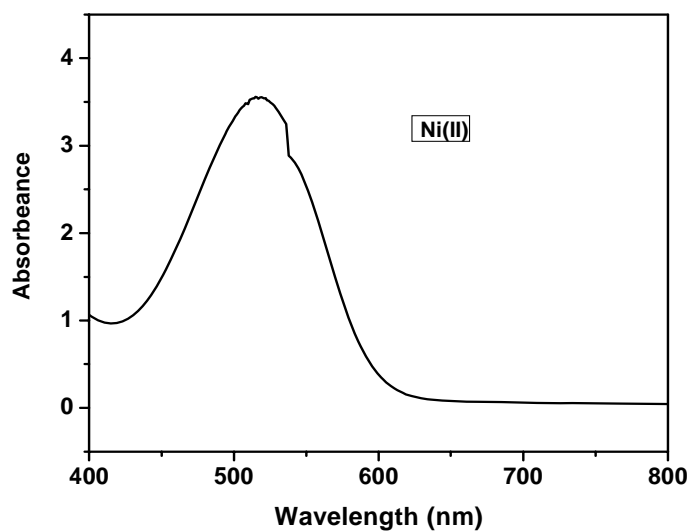


Fig. 2: UV-Vis absorption spectra of Ni(II) complex

out in the temperature range 300-1000 °C with a sample heating rate 5 °C/min in a static nitrogen atmosphere. The TGA curve of the Cu(II) complex Fig. 3, showed three decomposition steps. The first decomposition step occurred at a narrow temperature range of 310-380 °C, which corresponds to the removal of coordinated anions. Second decomposition step occurred at 450-550 °C due to the loss of half part of the ligand. The third decomposition step occurred at a temperature range 940-960 °C due to the loss of remaining part of the ligand leaving CuO as final residue. This process is accompanied by two broad exothermic peaks and one endothermic peak. Exothermic peaks are observed at 500 °C and endothermic peak was observed at 950 °C.

The TGA curve of the Ni(II) complex presented two decomposition steps. The first step of decomposition occurred with in the temperature range 340-380 °C. This step corresponds to the breakage of coordinated bond and the decomposition of the ligand. The second decomposition step occurred between 500-600 °C. The degradation of the complex was accompanied by three exo-effects, one broad exothermic peak between 490-590 °C and two sharp exothermic peaks at 600-650 °C.

Biological activity

The ligand and their metal complexes were evaluated for their antimicrobial activity against the bacteria and fungi. The biological activity results are

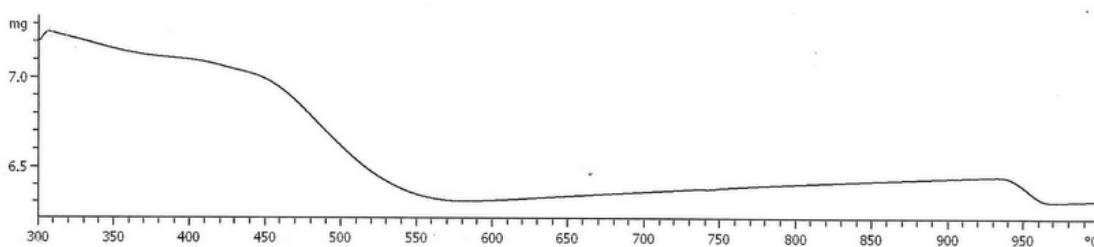


Fig. 3: The TGA curve of the Cu(II) complex

presented in Table 3. The increased activity of the metal complexes can be explained on the basis of chelation theory¹⁸. Increased activity enhances the lipophilicity of complexes due to delocalization of π -electrons in the chelate ring¹⁹. Cu(II) complex was found to be highly active against *E. Coli* and *P. aurogynosa* and showed moderate activity against *R. Solani* (fungus). Ni(II) complex exhibited moderate activity against both bacteria and fungi. The results of anti fungal and anti bacterial screening, indicate that Cu(II) complex showed more activity than the Ni(II) complex.

CONCLUSION

Reactions of schiffbase derived from 2-Pyridine Carboxaldehyde and 4-amino 3-hydroxy

benzoic acid with Cu(II) and Ni(II) ions yielded mono nuclear complexes. The structure of these complexes was elucidated by elemental analyses, FT-IR, UV-Vis spectra, TG-DTA as well as conductivity measurements. The coordinating sites are phenolic oxygen, azomethine nitrogen and pyridynyl nitrogen. The metal complexes showed antibacterial and antifungal activities. The Cu(II) metal complex showed a higher antibacterial and antifungal effect than the free ligand and Ni(II) metal complex.

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