

Synthesis, Characterization and Biological Activity Studies of Mixed Ligand Complexes with Schiff base and 2,2'-Bipyridine

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Abstract

Two new mixed ligand complexes of transition metals were synthesized from a Schiff base (L1) obtained by the condensation reaction of isoniazid and p- anisaldehyde as primary ligand and 2,2'-bipyridine (L2) as secondary ligand. The ligand and their metal complexes were studied using various spectroscopic methods viz. molar conductance, magnetic susceptibility measurement, IR and solution UV/Vis spectroscopic techniques. The mixed ligand complexes were found to have formulae $[M(L1)(L2)]2+(M = Cu(II) \text{ and } Ni(II))$. The resultant data revealed that the metal complexes have square- planar structure exhibiting electrolytic nature. The biological activities of the new compounds were tested against *Escherichia coli* (*E. coli*) and *Bacillus cereus* (*B. cereus*) showing the enhance activity of complexes against the species as compared to the free ligand.

Keywords: Schiff base ligands; Transition metals; 2, 2'-Bipyridine; Isoniazid; Antibacterial activity

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Introduction

Study of coordination chemistry of transition metal ions with various types of ligands has been enhanced by the current advancements in the fields of bioinorganic chemistry and medicine [1]. Through the years, Schiff bases have played a special role as chelating ligands in main group and transition metal coordination chemistry, due to their stability under a variety of oxidative and reductive conditions, and to the fact that imine ligands are borderline between hard and soft Lewis bases [2-4].

Schiff bases that arise from amino and carbonyl compounds are an important class of ligands that coordinate to metal ions through azomethine nitrogen and have been studied widely [5]. In azomethine derivatives, the (CN) linkage is necessary for biological activity; numerous azomethines have been reported to have marked antifungal, antibacterial, anticancer and antimalarial activities [6-14]. A large number of Schiff bases and their complexes have been studied for their interesting and significant properties, e.g. their ability to reversibly bind oxygen [15,16], catalytic activity in hydrogenation of olefins [17] photochromic properties [18] and complexing ability towards some toxic metals [19].

Mixed ligand complexes also play an important role in the

biological field as exemplified by many ways in which enzymes are known to be activated by metal ions [20]. Schiff bases derived from heterocyclic compounds such as P- anisaldehyde and furan- 2-carbaldehyde have attracted an increased interest in the bioinorganic chemistry field [21-23]. Isoniazid (INH), also known as isonicotinylhydrazide (INH), is a known tuberculostatic agent used as a first-line agent for the prevention and treatment of both latent and active tuberculosis. It forms metal chelates with many bivalent ions having moderate to better biological significance [24,25]. Since the discovery of bipyridine at the end of the nineteenth century, the bipyridine ligand has been used extensively in the complexation of metal ions due to its strong redox stability and ease of functionalization [26,27]. The biological activities of the Schiff base and its mixed ligand complexes were also investigated herein.

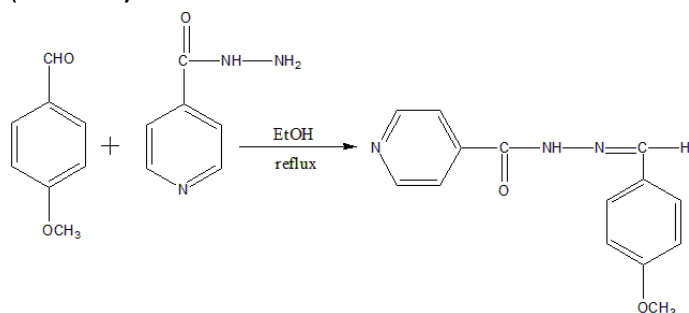
Experimental

All used chemicals were purchased from Merck and Loba chemicals. All the melting points were determined on a digital melting point apparatus. Products were characterized by comparison of spectroscopic data (UV-Visible and FT-IR) and melting points with authentic samples. The wavelength of absorbance was determined by UV-Visible spectrophotometer [JASCO 503] using a quartz cuvette and ethanol as the reference.

The IR spectrums were recorded on FT-IR spectrophotometer [JASCO, FT-IR/4100] Japan using dry KBr as the standard reference. The magnetic susceptibility of the complexes was measured at room temperature using a Gouy balance.

General Procedure for Synthesis of N-(4-methoxybenzylidene) isonicotinohydrazone Schiff base Ligand, L1

INH (1.37 g, 10.0 mmol) was mixed with absolute ethanol (15 mL) and the mixture brought to the boil, producing a slurry. Barely sufficient additional ethanol was then added to give a homogeneous solution at reflux. P-anisaldehyde (1.22 mL, 10 mmol) was added drop-wise over 5 minutes and washed with 5 mL of ethanol. The reaction mixture was refluxed for 4 hours then allowed to cool slowly and to stand overnight. Finally, it produces a white crystalline solid which was filtered off and dried (**Scheme 1**).



Scheme 1: Synthesis of Schiff base ligand L1.

Experimental procedure for synthesis of mixed ligand complexes

To the warm methanolic solution (10 mL) of primary ligand L1 (0.255 g, 1 mmol), 10 mL warm methanolic solution (0.257 g, 1 mmol) of nitrate salt of metal Cu(II) and Ni(II) were added. After 30 minutes 5 mL warm methanolic solution of 2,2'-bipyridine (0.156 g, 1 mmol) was added drop-wise as a secondary ligand (L2) and the resulting mixture was refluxed for about 3-4 hours.

The obtained precipitate was filtered, washed with methanol and dried under vacuum on anhydrous CaCl_2 .

Antimicrobial activity

The ligand (L1) and its mixed ligand complexes with (L2) were screened for in vitro antimicrobial activity in DMSO against gram-negative *Escherichia coli* (*E. coli*) and gram-positive *Bacillus cereus* (*B. cereus*) strains by Kirby Bauer's disc diffusion technique. A uniform suspension of test organism of 24 hours old culture was prepared in a test tube containing the sterile saline solution. Sterile nutrient agar was then added in each of the Petri dishes. The dishes were related to ensuring the uniform mixing of the microorganism in the agar medium which was then allowed to solidify. Sterile Whatmann filter paper discs were dipped in the solution of each compound and placed on the labeled plates. The DMSO was used as a control of the solvent. Kanamycin was used as a standard compound for comparison. Plates were kept in the refrigerator for half an hour for diffusion and incubated at 37°C for 24 hours. The diameter of the zone of inhibition around each disc was measured by scale and results were recorded in terms of mm. The observed data of antimicrobial activity of the L1, mixed ligand complexes and the standard drugs are given in **Table 4**.

Results and Discussion

By the reaction of Cu(II) and Ni(II) with ligand (L1) and 2,2'-bipyridine (L2), complexes of the type $[\text{M}(\text{L1})(\text{L2})]^{2+}$ were obtained. These complexes have a different color, stable at room temperature, insoluble in common polar solvent but soluble in DMSO and DMF, do not have the sharp melting point but decompose above 250°C . The measurement of molar conductivity at 10^{-3} M concentration carried out in DMSO at room temperature. The molar conductivity values show that the nitrate complexes were 1:2 electrolytes [28]. The analytical and physical data (color, melting point, molar conductivity and magnetic moment) of the complex are given in **Table 1**. For the Cu(II) and Ni(II) complexes the magnetic moments were 1.83 BM and 0.22 BM indicating paramagnetic and diamagnetic nature

Table 1 Analytical and physical properties data of L1 and its mixed ligand complexes with L2.

Symbol of Compounds	Complexes	M.P or De (Decomposition Temp) / $^\circ\text{C}$	Solubility			μ_{eff} in B.M
			Color	DMSO & DMF	Molar conductance $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$	
Ligand (L1)	$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$	143	White	(+) ve	5	
$[\text{Cu}(\text{L1})(\text{L2})](\text{NO}_3)_2$	$[\text{Cu}(\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2)(\text{C}_{10}\text{H}_8\text{N}_2)](\text{NO}_3)_2$	275 (De)	Brown	(+) ve	156	1.83
$[\text{Ni}(\text{L1})(\text{L2})](\text{NO}_3)_2$	$[\text{Ni}(\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2)(\text{C}_{10}\text{H}_8\text{N}_2)](\text{NO}_3)_2$	285 (De)	Yellow	(+) ve	149	Dia

Table 2 Key infrared bands (cm^{-1}) of L1 and its mixed ligand complexes with L2.

Symbol of Compound	Compound	ν (C=O)	ν (C=N)	ρ (Py) bending	ν (M-O)	ν (M-N)
Ligand (L1)	$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$	1658.84	1598.69			
Ligand L2	$\text{C}_{10}\text{H}_8\text{N}_2$		1642 m	650		
$[\text{Cu}(\text{L1})(\text{L2})](\text{NO}_3)_2$	$[\text{Cu}(\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2)(\text{C}_{10}\text{H}_8\text{N}_2)](\text{NO}_3)_2$	1636.35	1592.95	678.73	528.02	433.99
$[\text{Ni}(\text{L1})(\text{L2})](\text{NO}_3)_2$	$[\text{Ni}(\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2)(\text{C}_{10}\text{H}_8\text{N}_2)](\text{NO}_3)_2$	1628.82	1571.41	681.68	534.71	426.92

Table 3 UV- Visible spectrum of the Ligand L1 and its mixed ligand complexes with L2.

Symbol of Compound	Compound	λ in nm	Assignment
Ligand (L1)	$C_{14}H_{13}N_3O_2$	283	$\pi-\pi^*$
		333	$n-\pi^*$
$[Cu(L1)(L2)](NO_3)_2$	$[Cu(C_{14}H_{13}N_3O_2)(C_{10}H_8N_2)](NO_3)_2$	270	$\pi-\pi^*$
		367	C.T
$[Ni(L1)(L2)](NO_3)_2$	$[Ni(C_{14}H_{13}N_3O_2)(C_{10}H_8N_2)](NO_3)_2$	269	$\pi-\pi^*$
		370	C.T

Table 4 Antibacterial screening results of Ligand L1 and its mixed ligand complexes with L2.

Compounds	Antibacterial Zone of Inhibition (in mm)	
	Gram Negative	Gram Positive
	<i>Escherichia coli</i>	<i>Bacillus cereus</i>
Kanamycin	32	35
Ligand (L1)	4	4
$[Cu(L1)(L2)](NO_3)_2$	20	22
$[Ni(L1)(L2)](NO_3)_2$	18	15

respectively. These values correspond to the square- planar geometry of both the mixed ligand complexes [29,30].

IR spectral studies

The IR spectrum of the primary ligand (L1) showed in **Table 2 and Figure 1**, exhibited characteristic bands at $1658.84.5\text{ cm}^{-1}$ and 1598.69 cm^{-1} assigned to $\nu(C=O)$ and $\nu(C=N)$ respectively **Figures 1-4** [31]. The band at $1658.84.5\text{ cm}^{-1}$ attributable to the $\nu(C=O)$ stretching vibration of the Schiff base ligand is shifted to another region $1628-1637\text{ cm}^{-1}$ in the complexes of Cu(II) and Ni(II) indicating coordination of the carbonyl oxygen to the metal ions (**Figures 2-3**). The presence of band at $528-535\text{ cm}^{-1}$ in the IR spectra of complex is due to M-O stretching vibration

[28,32]. The azomethine band at 1598.69 cm^{-1} of Schiff base was shifted to lower frequency ranging of $1571-1593\text{ cm}^{-1}$ in the spectra of the complexes, confirming the participation of the azomethine nitrogen atom in the coordination of the metal ion. In the IR spectra of this complex, the new bands which appear in the $426-434\text{ cm}^{-1}$ region are assigned to the $\nu(M-N)$ vibration [28,32]. The strong sharp band observed at 1384 cm^{-1} in the complex can be assigned to uncoordinated nitrate ion [28]. The band at 650 cm^{-1} is assigned to $\nu(C=N)$ of pyridine for secondary ligand, L2. This band is shifted to $671-682\text{ cm}^{-1}$ for mixed ligand complexes [33,34]. All of these IR data confirm ligands coordinated in Cu(II) and Ni(II) metal complexes through their O and N atoms respectively.

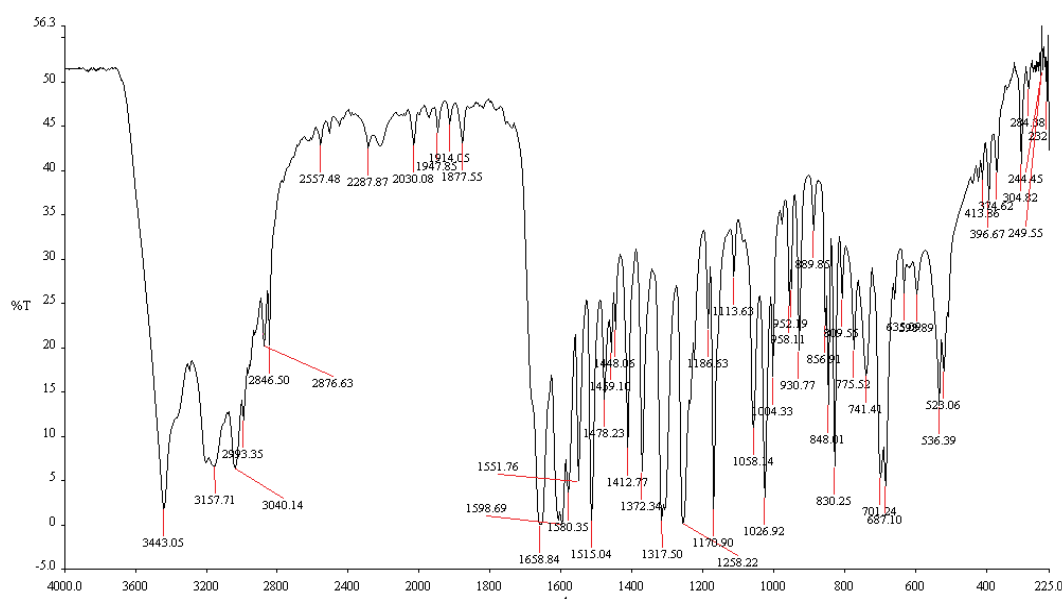


Figure 1 IR Spectrum of L1.

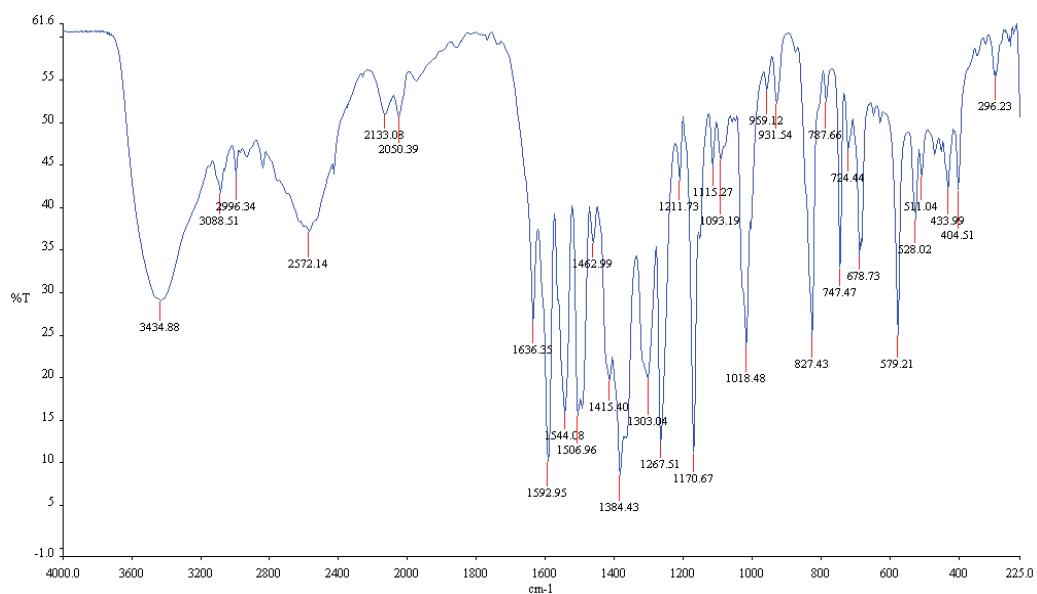


Figure 2 Spectrum of $[Cu(L1)(L2)](NO_3)_2$.

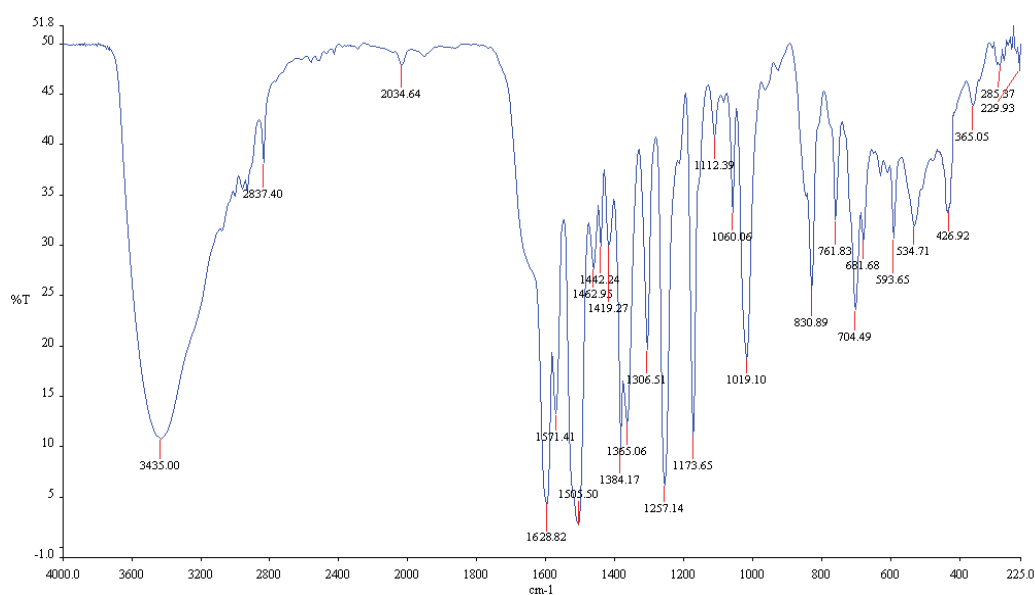


Figure 3 IR Spectrum of $[Ni(L1)(L2)](NO_3)_2$.

UV- visible spectra

The UV-Visible spectra of the ligand L1 shows two bands at 281 and 347 nm which are assigned to $\pi-\pi^*$ and $n-\pi^*$ transition respectively. All the complexes showed the charge transfer transitions which can be assigned to charge transfer from the ligand to metal (LMCT) and vice versa. For complexes, absorption bands at the range of 367– 370 nm may be associated with $L \rightarrow M$ charge transfer and vice versa ($M \rightarrow L$) [29-30]. In the UV-region, the complexes showed absorption band at 269–270 nm (Figure 4) which may be assigned to $\pi-\pi^*$ transition. The spectra of all the complexes exhibiting bands assigned to $\pi-\pi^*$

and $M \rightarrow L$ charge transfer, the metals normally prefer square-planar geometry [29,30]. All observations were summarized in the Table 3.

Antimicrobial screening result

The Schiff-base ligand L1 and its mixed ligand complexes with L2 reported here were evaluated for antibacterial activity against *Escherichia coli* and *Bacillus cereus*. The values of zone inhibition were measured in millimeter. The data of antibacterial activities of ligand L1 and its mixed ligand complexes with L2 are given in Table 4.

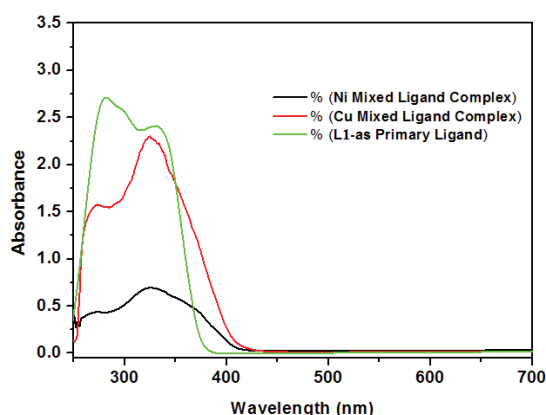


Figure 4 UV- Visible Spectrum of the L1 and its Mixed Ligand Complexes.

Based on the above results the expected structures of the Schiff base complexes may be represented as shown in the Figure 5.

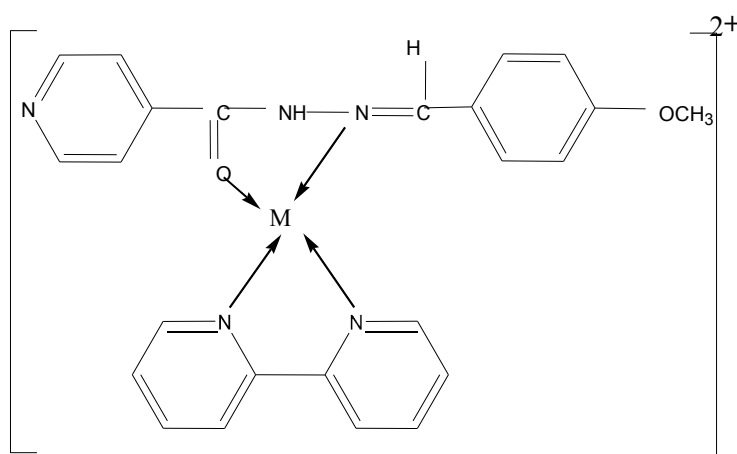


Figure 5 The proposed geometry of M- mixed ligand complexes for L1 and L2 (where, M= Cu(II) and Ni(II)).

The inhibitory zone data reveals that the ligand L1, as well as its mixed ligand complexes with L2, shows good to moderate good antibacterial activity. The biological activity of Schiff base ligand arises from the presence of imine group which imports in elucidating the mechanism of transformation reaction in biological systems. However, mixed ligand complexes with L2 showed remarkable antibacterial activity as a result of chelation of metal with organic ligands synergistically increasing its effect [28, 31, 32, and 35]. The DMSO control did not show any antimicrobial activity against the tested bacterial strains whereas the tested compounds were found to be active.

Conclusion

The Schiff base ligand L1 and its Cu(II) and Ni(II) mixed ligand complexes with L2 were prepared and characterized using various

spectral and other techniques. The IR spectral data indicated that Schiff base (L1) and 2,2'-bipyridine (L2) ligand coordinated to the metal ions by carbonyl oxygen, N of azomethine and pyridine respectively indicating the square-planar geometry of the complexes. It has been observed that the mixed ligand complexes showed more antibacterial activity than Schiff base ligand L1. Although with respect to standard, the tested compounds were found to be moderately active.

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