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# Synthesis, Structural and Biological Studies of Nickel(II), Copper(II) and Zinc(II) Chelates with Tridentate Schiff Bases Having NNO and NNS Donor Systems

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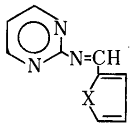
**New tridentate pyrimidine-derived NNO and NNS donor Schiff base ligands and their nickel(II), copper(II) and zinc(II) chelates have been synthesized and characterized on the basis of elemental analysis, $^1$H-NMR, IR and electronic spectral data and conductance and magnetic measurements. The synthesized ligands and their metal chelates have been screened and compared for their antibacterial action against bacterial species *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.**

**Keywords** tridentate Schiff-base; potential ligand; metal chelate; antibacterial

## Introduction

Pyrimidine-derived ligands and their transition metal chelates exhibit interesting spectral and biological properties.[1] The azomethine ($\rangle C=N-$) function, which is aided by the adjacent donor groups, can act as a versatile chelate and may make the molecule a useful participant in potentially important complex formation reactions. Also, their usefulness[2] in the separation and estimation of metal ions make them an important class of organic reagents. These considerations, as a continuation of our earlier work[3] on biologically active transition metal complexes with Schiff bases, prompted us to synthesize and report new tridentate NNO and NNS donor Schiff bases, derived from the reaction of 2-aminopyrimidine with 2-furaldehyde and 2-thiophenecarboxaldehyde to give I and II and their nickel(II), copper(II) and zinc(II) complexes. On the basis of analytical and spectral data, the synthesized complexes have been proposed to have octahedral geometry. The ligands and complexes have also been screened for their antibacterial activity against strains such as, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The antibacterial activity of the ligands has been shown to be substantially increased on chelation/complexation.



I : X=O
II : X=S

## Experimental

**Materials and Methods** All solvents used were AR grade. Metal salts (as chloride) were used for the preparation of metal complexes. Conductance was measured on a YSI model-32 conductivity bridge. Magnetic measurements were done on a Gouy balance. IR spectra were recorded in Nujol on an A-10 Hitachi spectrophotometer. $^1$H-NMR spectra of the ligands (in $d_6$-dimethyl sulfoxide ($d_6$-DMSO)) were recorded on an R10 spectrometer. Electronic spectra (in dimethylformamide (DMF)) were studied on a Hitachi double-beam U-2000 model spectrophotometer using glass cells of 1 cm thickness. Elemental CHN analyses were carried out on a Coleman automatic analyser. All melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. Metal contents of the complexes were determined by methods reported elsewhere.[4,5] Chloride was estimated gravimetrically[5] as AgCl.

**Preparation of Schiff-Bases** 2-(2-Furanylmethyleneamino) Pyrimidine (I): 2-Furaldehyde (0.83 ml, 0.96 g, 0.01 mol) was added to an ethanolic solution (20 ml) of 2-aminopyrimidine (0.95 g, 0.01 mol). Then 2—3 drops of concentrated sulfuric acid were added and this mixture refluxed for 3 h. The solution, on cooling, gave a white solid product which was filtered, washed with ethanol, then with ether and dried. The solid thus obtained was crystallized in aqueous ethanol to give (I) (47%).

2-(2-Thienylmethyleneamino) Pyrimidine (II): 2-Thiophenecarboxaldehyde (0.92 ml, 1.12 g, 0.01 mol) in ethanol was added to an ethanolic solution (20 ml) of 2-aminopyrimidine (0.95 g, 0.01 mol) at 50 °C. A few drops of concentrated sulfuric acid were then added and this mixture refluxed for 2 h. The solution on cooling gave a light yellow product which was filtered, with ethanol, then with ether and dried. The solid thus obtained was crystallized in aqueous ethanol to give (II) (58%).

**Preparation of Metal Complexes** $[M(L)_2]Cl_2$ (**1**, **2**, **3**) Where M = Ni(II), Cu(II), Zn(II) and L = (I): An ethanolic solution (10 ml) of ligand (I) (0.002 M) was added to a magnetically stirred aqueous solution (15 ml) of M(II)chloride (0.001 M). The mixture was refluxed near the boiling point for 2 h. The resulting mixture was cooled, filtered and reduced to a small volume (15 ml). The concentrated mixture was left overnight at room temperature which resulted in the formation of a solid product. The solid thus formed was filtered, washed with ethanol, then with ether, dried and crystallized in aqueous ethanol to give **1** (52%), **2** (47%) and **3** (43%).

$[M(L)_2]Cl_2$ (**4**, **5**, **6**), Where M = Ni(II), Cu(II), Zn(II) and L = (II): A hot solution of ligand (II) (0.002 M) in absolute ethanol (15 ml) was added to a magnetically stirred aqueous solution (15 ml) of M(II) chloride (0.001 M). The mixture was refluxed for 2 h. The resulting solution was then cooled, filtered and reduced to a small volume (15 ml). This solution was left overnight at room temperature which resulted in the formation of a solid product. The product thus formed was filtered, washed with ethanol, then with ether (2 × 5 ml), dried and recrystallized in

TABLE I. Physical and Elemental Analysis and Spectral Data of Ligands

| Compound No. | Mol. formula | mp (°C) | IR (cm$^{-1}$) | $^1$H-NMR (ppm) ($d_6$-DMSO) | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| I | $C_9H_7N_3O$ | 180—182 | 3304, 2928, 2024, 1640, 1610, 1542, 1378, 1112, 950, 784 | 6.9 (m, 3H, H-2, 5, 6), 8.4 (m, 4H, H-1, 3, 4, 7) | 62.42<br>(62.44 | 4.04<br>4.03 | 24.27<br>24.25) |
| II | $C_9H_7N_3S$ | 164—165 | 3308, 3164, 2869, 2020, 1944, 1642, 1610, 1544, 1350, 1054, 874 | 6.9 (m, 3H, H-2, 5, 6), 8.5 (m, 4H, H-1, 3, 4, 7) | 57.14<br>(57.18 | 3.70<br>3.72 | 22.22<br>22.24) |

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aqueous-ethanol to yield **4** (55%), **5** (47%) and **6** (43%).

**Antibacterial Studies** Antibacterial activity of the synthesized ligands and their metal complexes was evaluated with the help of the Microbiology Laboratory, Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur. Antibacterial activity against bacterial species obtained from different patients carrying the bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* was determined using the paper disc diffusion method.

Preparation of Disc: A ligand/metal complex (30 $\mu$g) in DMF (0.01 ml) was applied to a disc prepared from blotting paper (3 mm size) with the help of micropipett. The discs were left in an incubator for 48 h at 37 °C and then applied to bacteria grown on agar plates.

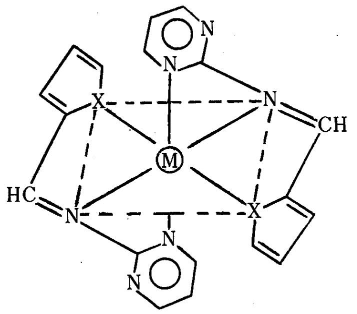
Preparation of Agar Plates: For this purpose Mac Conkey agar obtained from Merck Chemical Company was used. Mac Conkey agar (50 g) was suspended in freshly distilled water (1 l). It was allowed to soak for 15 min and then boiled with constant shaking in a waterbath until the agar was completely dissolved. The mixture was autoclaved for 15 min at 120 °C and then poured into previously washed and sterilized petri dishes and stored at 4 °C for inoculation.

Procedure of Inoculation: This was done by means of a platinum wire loop which was first made red hot on a flame, allowed to cool in air and then used for the application of previously described bacterial strains. The preculture was first prepared in 2 ml of nutrient broth by selecting a suitable bacterial colony, and later on it was transfered to a nutrient broth which was incubated for 2 h at 37 °C. Then 500 $\mu$l of the culture was spread on the agar plate, which was incubated for 24 h at 37 °C.

Application of Disc: Sterilized foreceps were used for the application of paper discs to the already-inoculated agar plate. When the discs were applied, they were then incubated for 24 h at 37 °C.

## Results and Discussion

The Schiff bases (I) and (II) were synthesized by adopting a procedure similar to that reported earlier.$^{6)}$ The metal complexes were prepared by the stoichiometric (1 : 2) reaction (M : L) of metal and ligand. The analytical data and physical properties of the metal chelates are summarized in Table II. The complexes are all insoluble in organic solvents except DMF and DMSO. The conductance measurements of the complexes ($0.54\times10^2$—$0.038\times10^2$ Siemens/cm$^2$/mol) in aqueous solution were low, suggesting them to be non-electrolytic in nature.$^{7,8)}$



M = Ni(II), Cu(II), Zn(II)

X = O = L$_{\mathrm{I}}$
S = L$_{\mathrm{II}}$

Fig. 1. Proposed Structure for Metal Chelates

**Magnetic Properties** At room temperature the magnetic moments of the nickel(II) complexes were found to be in the range 3.15—3.21 BM (Table II) which are indicative of their six-coordinated octahedral geometry.$^{9,10)}$ The Cu(II) complexes show normal $\mu_{\mathrm{eff}}$ values, 1.78—1.82 BM, indicating the presence of one unpaired electron. The slightly higher BM probably results from spin-orbit coupling. However, $\mu_{\mathrm{eff}}$ values 1 : 2 (M : L) stoichiometry suggest a distorted octahedral geometry$^{11,12)}$ of the complexes.

**Electronic Spectra** The electronic spectra of nickel(II) complexes show bands at 25500—26200, 16100—16200 and 9500—10200 cm$^{-1}$ due to the transitions $^3A_{2g}(\mathrm{F})\rightarrow{}^3T_{2g}(\mathrm{F})(\nu_1)$, $^3A_{2g}(\mathrm{F})\rightarrow{}^3T_{1g}(\mathrm{F})(\nu_2)$ and $^3A_{2g}(\mathrm{F})\rightarrow{}^3T_{2g}(\mathrm{p})(\nu_3)$; these are consistent with an octahedral$^{13)}$ configuration. The Cu(II) complexes show three broad bands in the region 26500—28100, 22555—24200 and 16200—17700 cm$^{-1}$. The low energy band may be assigned for Cu(II) complexes in octahedral configuration$^{14)}$ corresponding to the transition $^2E_g\rightarrow{}^2T_{2g}$. The band around 22000 cm$^{-1}$ can be attributed to symmetry forbidden ligand→metal charge transfer.

**Infrared Spectra** A comparison of the spectra of ligands and their metal chelates (Table II) indicated that ligands are coordinated to the metal in three ways. The ligands mainly show two absorption bands, one at 1640 cm$^{-1}$ due to the stretching mode of the acyclic azomethine ($>$C=N–) group and the other at *ca.* 1610 cm$^{-1}$ due to the –N=C$<$ of the heterocyclic ring. However, a negative shift of *ca.* 10 cm$^{-1}$ in the azomethine band ($>$C=N–) and in the (–N=C$<$) band of the heterocyclic ring indicates bonding through these groups. Conclusive evidence$^{15)}$ which confirmed the coordination of the metal atom with ligand was obtained when new bands at *ca.* 720 and *ca.* 570 cm$^{-1}$ assigned to (M–S) and (M–O) stretching, were found in the spectra of the metal complexes but absent from the spectra of ligands. It is, therefore concluded from the above observations that ligands I and II are respectively coordinated to the metal atoms through NNO and NNS donor groups

TABLE II. Physical and Elemental Analysis and Spectral Data of Metal Chelates

| Complex No. | Mol. formula | mp (°C) (dec.) | BM ($\mu_{\mathrm{eff}}$) | IR (cm$^{-1}$) | $\lambda_{\max}$ (cm$^{-1}$) | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 1 | Ni(L$_{\mathrm{I}}$)$_2$Cl$_2$ | 240—242 | 3.15 | 3304, 2928, 2730, 1630, 1602, 1464, 1380, 994, 570 | 25500, 16200, 9500 | 45.43<br>(45.41 | 2.94<br>2.93 | 17.65<br>17.65) |
| 2 | Ni(L$_{\mathrm{II}}$)$_2$Cl$_2$ | 228—230 | 3.21 | 3286, 2932, 2734, 1630, 1600, 1602, 1467, 987, 720 | 26200, 16100, 10200 | 42.56<br>(42.56 | 2.75<br>2.73 | 16.53<br>16.50) |
| 3 | Cu(L$_{\mathrm{I}}$)$_2$Cl$_2$ | 214—216 | 1.78 | 3192, 2936, 1876, 1630, 1605, 1466, 1380, 884, 570 | 26500, 22555, 17700 | 44.97<br>(44.99 | 2.91<br>2.91 | 17.47<br>17.46) |
| 4 | Cu(L$_{\mathrm{II}}$)$_2$Cl$_2$ | 198—200 | 1.82 | 3394, 2932, 2860, 1998, 1625, 1602, 1467, 987, 725 | 28100, 24200, 16200 | 42.16<br>(42.16 | 2.73<br>2.70 | 16.38<br>16.39) |
| 5 | Zn(L$_{\mathrm{I}}$)$_2$Cl$_2$ | 210—213 | Dia | 3288, 3144, 2940, 2696, 1625, 1600, 1380, 946, 572 | 29200, 26700 | 44.80<br>(44.81 | 2.90<br>2.90 | 17.41<br>17.39) |
| 6 | Zn(L$_{\mathrm{II}}$)$_2$Cl$_2$ | 205—207 | Dia | 3388, 2926, 2860, 1620, 1600, 1467, 1380, 876, 725 | 30000, 27200 | 42.67<br>(42.66 | 2.72<br>2.74 | 16.32<br>16.32) |

Table III. Antibacterial Activity Data of Ligands and Complexes

| Ligand[a)]/Complex No.[b)] | Microbial species | | |
|---|---|---|---|
| | a | b | c |
| I | + + | + + | + |
| II | + | + + | + + |
| **1** | + + + | + + + | + + + |
| **2** | + + | + + + | + + |
| **3** | + + + + | + + + | + + |
| **4** | + + | + + + | + + + |
| **5** | + + + | + + + | + + + |
| **6** | + + | + + + | + + |

*a)* Uncomplexed ligands (I, II). *b)* Same numbering as in Table II. a = *Escherichia coli*, b = *Pseudomonas aeruginosa* and c = *Klebsiella pneumoniae*. Inhibition zone measured in diameter, +, 6—10 mm; + +, 10—16 mm; + + +, 16—20 mm; + + + +, >20 mm.

thus acting as tridentate ligands. It is also proposed, on the basis of electronics and magnetic studies, that all the complexes show an octahedral geometry in which the two ligands possibly accommodate themselves to bind with the central metal atom in such a way that a stable configuration of the complex is formed.

**Antibacterial Activity** The present ligands I and II and their metal complexes were screened for antibacterial activity. Antibacterial activity was tested against bacteria such as, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* by paper disc diffusion methods devised in this laboratory and reported elsewhere.[16,17] As expected, the Schiff bases I and II and their metal chelates have significant bactericidal properties. In comparison with the unchelated ligands, the results of antibacterial activity (Table III) show that the metal chelates are more potent and bactericidal. At this stage we are not completely aware of the role of metal ions in increasing the biological activity/potency of such biologically active compounds. However, many factors such as chelation theory,[18] electrostatic metal binding ability, formation constants and cell permeability may be involved in this mechanism. At present, *in vivo* studies on biological systems are in progress which will help us determining the actual factors involved in these biochemical reactions.

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