

## COPPER(II) ACYLHYDRAZINATES. THEIR SYNTHESIS AND CHARACTERIZATION

Zahid H. Chohan<sup>\*1</sup>, M. A. Farooq<sup>1</sup> and Claudiu T. Supuran<sup>2</sup>

<sup>1</sup>Department of Chemistry, Islamia University, Bahawalpur, Pakistan

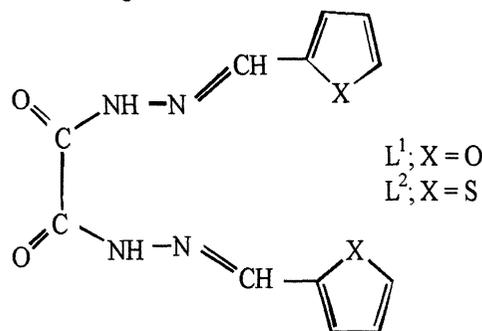
<sup>2</sup>Laboratorio di Chimica Inorganica e Bioinorganica, Università degli Studi, Via Gino Capponi 7, I-50121, Firenze, Italy

### ABSTRACT

Acylhydrazine derived furanyl and thienyl Schiff bases and their Cu(II) complexes have been prepared and characterized on the basis of their physical, spectral and analytical data. The preferred enolic form of the Schiff base function as a tetradentate ligand during coordination to the metal ion yielding a square planar complex. The Schiff bases and their complexes with different anions were tested for their antibacterial activity against bacterial species such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

### INTRODUCTION

Many studies<sup>1-4</sup> have indicated the interesting and varied ligational behavior of hydrazine and hydrazones towards transition metal ions. Their bacteriostatic properties<sup>5-9</sup> were well studied by many researchers<sup>10-12</sup>. Some hydrazones have also been found to act as potent inhibitors for DNA synthesis in a variety of cultured human cells and in particular, their Cu(II) complexes were shown to produce significant inhibition of tumor growth when administered to mice bearing a transplanted fibrosarcoma<sup>13,14</sup>. Because of such promising results, the antibacterial metallo-organic chemistry of such ligands is yet to be explored. We have previously reported<sup>15-18</sup> some antibacterial acylhydrazine derived Schiff bases and their various transition metal complexes. The present study was undertaken in order to prepare and study the metallo-organic/coordination behavior of Cu(II) with the Schiff base ligands L<sup>1</sup> and L<sup>2</sup>.



Structure of the Ligand

### EXPERIMENTAL

#### Material and Methods

All chemicals and solvents used were of Analar grade. Cu(II) salts were used as nitrate, sulphate, oxalate and acetate. 2-Furanecarboxaldehyde, 2-thiophenecarboxaldehyde, oxaloyldihydrazide were obtained from E. Merck. UV-Visible spectra were obtained on a Hitachi U-2000 double-beam spectrophotometer, IR, on a Philips Analytical PU 9800 FTIR instrument. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker 250 MHz spectrometer. C, H and N analyses were carried out by Butterworth Laboratories Ltd. Conductances of the metal complexes were determined in DMF on a YSI-32 model conductometer. Magnetic measurements were done on solid complexes using the Gouy method. Melting points were recorded on a Gallenkamp apparatus without correction.

#### Preparation of Schiff base Ligands

##### N,N-Bis(2-furanylmethylidene)oxaloyldihydrazide (L<sup>1</sup>).

2-Furanecarboxaldehyde (1.9 mL, 2.2 g, 0.02 mol) in absolute ethanol (20 mL) was added to a stirred hot ethanol solution (30 mL) of oxaloyldihydrazide (1.2 g, 0.01 mol). Then 2-3 drops of conc. H<sub>2</sub>SO<sub>4</sub> were added and the mixture was refluxed for 8 h. The reaction mixture was then cooled and left for 24 h at room temperature. During this period, a light yellow solid was formed which was recrystallized from hot ethanol to

give the desired product ( $L^1$ ) (1.8 g).  $L^2$  was prepared according to the same reported<sup>17</sup> method described as for  $L^1$ .

#### Preparation of the Metal Complexes

An ethanol solution (20 mL) of the appropriate Cu(II) salt (0.001 mol) was added to a well-stirred hot ethanol solution (20 mL) of the respective Schiff base (0.001 mol). The mixture was refluxed for 8 h. Then on cooling at room temperature; a precipitated solid product was formed. The product thus obtained was filtered, washed with ethanol, then with ether and dried. Crystallization from aqueous ethanol (50 %) gave the desired metal complexes.

## RESULTS AND DISCUSSION

### Physical Properties

The Schiff bases ( $L^1$  and  $L^2$ ) (Fig. 1) were prepared by reacting the appropriate amount of 2-furanicarboxaldehyde and 2-thiophenecarboxaldehyde in hot ethanol with oxaloyldihydrazide in 1 : 2 molar ratio. The structures of these Schiff base ligands were established<sup>17</sup> with the help of IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectroscopic and microanalytical data. All the metal complexes (Table I) were prepared by the stoichiometric reaction of Cu(II) salt and Schiff base ligands in equimolar ratio (M:L=1:1). The complexes are intensely colored and stable solids, which decompose above 200°C without melting and are insoluble in common organic solvents such as ethanol, methanol, chloroform or acetone. DMSO and DMF, however, dissolved all the complexes. Molar conductance values (92-98  $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$ ) of the soluble complexes in DMF show values indicating<sup>19</sup> that they are all electrolytes.

Table I. Physical and Analytical Data of the Cu(II) Complexes

Complex	M.p (°C)	B.M ( $\mu_{\text{eff}}$ )	Calc (Found) %		
			C	H	N
1 $[\text{Cu}(L^1)_2](\text{NO}_3)_2$ $\text{C}_{12}\text{H}_{10}\text{CuN}_6\text{O}_{10}$ [461.5]	218-220	1.55	31.2 (31.6)	2.2 (2.1)	18.2 (18.5)
2 $[\text{Cu}(L^1)_2](\text{SO}_4)$ $\text{C}_{12}\text{H}_{10}\text{CuN}_4\text{O}_8\text{S}$ [433.6]	222-224	1.62	33.2 (33.4)	2.3 (2.2)	12.9 (13.0)
3 $[\text{Cu}(L^1)_2](\text{C}_2\text{O}_4)$ $\text{C}_{14}\text{H}_{10}\text{CuN}_4\text{O}_8$ [425.5]	220-222	1.57	39.5 (39.3)	2.4 (2.6)	13.2 (13.1)
4 $[\text{Cu}(L^1)_2](\text{CH}_3\text{CO}_2)_2$ $\text{C}_{16}\text{H}_{14}\text{CuN}_4\text{O}_8$ [453.5]	224-226	1.65	42.3 (42.5)	3.1 (3.5)	12.3 (12.2)
5 $[\text{Cu}(L^2)_2](\text{NO}_3)_2$ $\text{C}_{12}\text{H}_{10}\text{CuN}_6\text{O}_8\text{S}_2$ [493.7]	222-224	1.58	29.2 (29.1)	2.0 (2.2)	17.0 (17.4)
6 $[\text{Cu}(L^2)_2](\text{SO}_4)$ $\text{C}_{12}\text{H}_{10}\text{CuN}_4\text{O}_6\text{S}_2$ [433.6]	227-230	1.55	33.2 (33.6)	2.3 (2.2)	12.9 (12.6)
7 $[\text{Cu}(L^2)_2](\text{C}_2\text{O}_4)$ $\text{C}_{14}\text{H}_{10}\text{CuN}_4\text{O}_6\text{S}_2$ [457.7]	224-226	1.60	36.7 (36.9)	2.2 (2.6)	12.2 (12.1)
8 $[\text{Cu}(L^2)_2](\text{CH}_3\text{CO}_2)_2$ $\text{C}_{16}\text{H}_{14}\text{CuN}_4\text{O}_6\text{S}_2$ [485.66]	226-228	1.62	39.5 (39.3)	2.9 (2.7)	11.5 (11.3)

Model studies of these Schiff bases (Fig. 2) show that in no case can these Schiff bases exhibit tridentate behavior. They are only capable of exhibiting tetradentate (Fig. 2) behavior. However, they have a tendency to exhibit different tautomers, either as diketone [Fig. 2A], dienol [Fig. 2B] and as well as ketoenol [Fig. 2C]. In the dienol form, the ligands may coordinate metal ions through X (X=O or S) donor sites of furanyl or thienyl and through the two azomethine nitrogens (HC=N). The diketone and ketoenol forms can also behave similarly, as tetradentate ligands, coordinating through the same coordination sites as dienol form.

### Infrared Spectra

The IR spectra of the Schiff bases and their Cu(II) complexes were recorded in KBr and are reported in Tables I with some tentative assignments of their important characteristic bands. All these Schiff bases showed the absence of the bands at  $\sim 3420\text{ cm}^{-1}$  and  $1730\text{ cm}^{-1}$  due to characteristic  $\nu(\text{NH}_2)$  and  $\nu(\text{C}=\text{O})$  stretching vibrations of the respective hydrazinoamine and aldehyde. Instead, a new band at  $\sim 1635\text{ cm}^{-1}$  assigned<sup>20</sup> to the azomethine (HC=N) linkage appeared in the spectra of all of the proposed Schiff base

ligands. Also a band at  $1020\text{ cm}^{-1}$  due to a HN-N vibration appeared in the spectra of  $L^1$  and  $L^2$ . This observation suggested<sup>21</sup> that the hydrazinoamine and aldehyde moieties of the starting reagents are no longer present and that condensation to the respective Schiff bases has taken place.

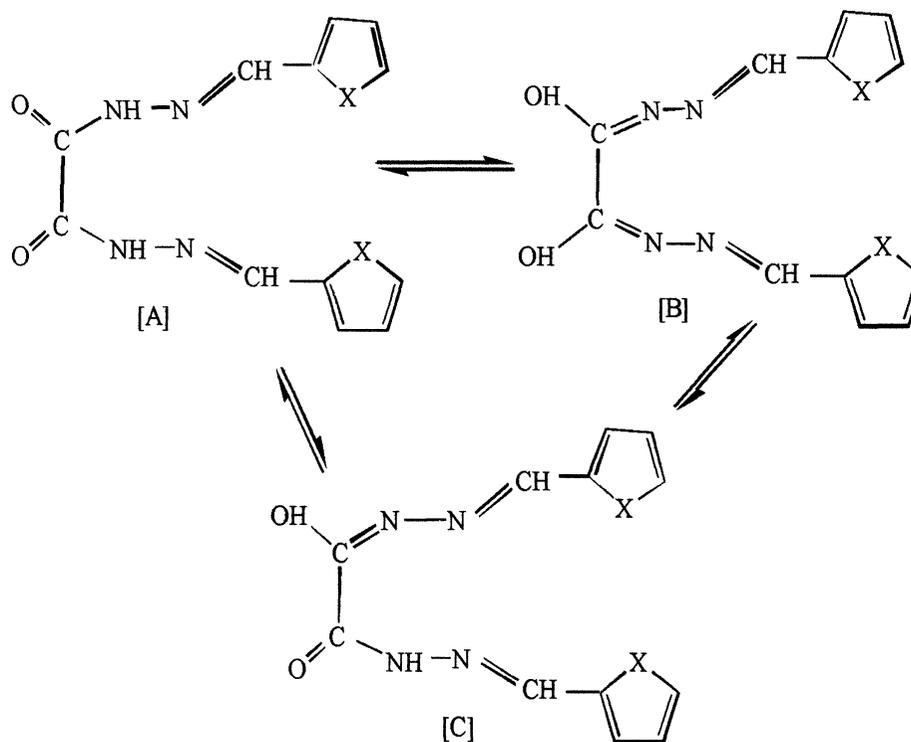


Fig. 2 Tautomeric forms of the investigated ligands

A comparison of the infrared spectra of the Schiff bases and their metal complexes indicated<sup>21,22</sup> that the Schiff bases are tetradentately coordinated to the metal ions. The band due to  $\nu(\text{C}=\text{O})$  was absent in the spectra of the complexes suggesting<sup>23</sup> enolization of the Schiff bases during complexation. This is supported by the evidence that the band due to  $\nu(\text{OH})$  in the spectra of these complexes was observed at  $\sim 3315\text{ cm}^{-1}$ . These facts suggested that the Schiff bases  $L^1$  and  $L^2$  remained in the keto form in the solid state as uncomplexed ligands but in solution the keto and enol forms were in equilibrium<sup>24</sup>, as shown in Fig. 2B. The amide-II band was split, displaced to higher frequency and reduced in intensity. Shift ( $5\text{--}10\text{ cm}^{-1}$ ) to higher frequency of the  $\nu(\text{N-N})$  band at  $1025\text{ cm}^{-1}$  and its splitting indicated coordination of the azomethine nitrogen. Moreover, a low frequency shift ( $10\text{--}15\text{ cm}^{-1}$ ) of the band due to the azomethine ( $\text{HC}=\text{N}$ ) linkage at  $1635\text{ cm}^{-1}$  indicated involvement of the azomethine nitrogen in coordination. The appearance of weak, low frequency new bands at  $\sim 360$  and  $\sim 455\text{ cm}^{-1}$  were assigned<sup>25</sup> to metal-sulfur  $\nu(\text{M-S})$  in the thienyl and metal-oxygen  $\nu(\text{M-O})$  in the furanyl ligands. These bands were only observable in the spectra of the metal complexes and not in the spectra of their Schiff bases which in turn confirmed the participation of the heteroatoms X (S or O) in the coordination. These observations, in turn, suggested<sup>22,26</sup> a square planar geometry for the Cu(II) complexes (Fig. 3).

### NMR Spectra

The NMR spectra of the free ligands and some of their metal complexes have been recorded in  $\text{DMSO-d}_6$ . The features of the free ligands are already reported<sup>27</sup> elsewhere which have shown the NMR spectra of the free ligands in support to the conclusions derived from the IR spectra as expected. In the spectra of the Cu(II) complexes (Table III), these proton signals appeared much more downfield, as expected, due to increased conjugation during coordination<sup>28,29</sup>

Table II. IR and UV-Visible Data of the Cu(II) Complexes

No	IR (cm <sup>-1</sup> )	$\lambda_{\max}$ (cm <sup>-1</sup> )
1	3315 (b, OH), 1625 (s, HC=N), 1025 (m, N-N), 455 (m, M-O).	14680, 16390, 27320
2	3320 (b, OH), 1620 (s, HC=N), 1025 (m, N-N), 455 (m, M-O).	14675, 16385, 27335
3	3317 (b, OH), 1625 (s, HC=N), 1025 (m, N-N), 455 (m, M-O).	14685, 16380, 27330
4	3315 (b, OH), 1625 (s, HC=N), 1025 (m, N-N), 455 (m, M-O).	14680, 16395, 27335
5	3317 (b, OH), 1620 (s, HC=N), 1025 (m, N-N), 360 (m, M-S).	14690, 16385, 27325
6	3317 (b, OH), 1620 (s, HC=N), 1025 (m, N-N), 360 (m, M-S).	14685, 16380, 27335
7	3315 (b, OH), 1625 (s, HC=N), 1025 (m, N-N), 360 (m, M-S).	14675, 16390, 27325
8	3320 (b, OH), 1625 (s, HC=N), 1025 (m, N-N), 360 (m, M-S).	14680, 16385, 27330

s = sharp, m = medium, b = broad

Table III. NMR Spectral Data of the Cu(II) Complexes

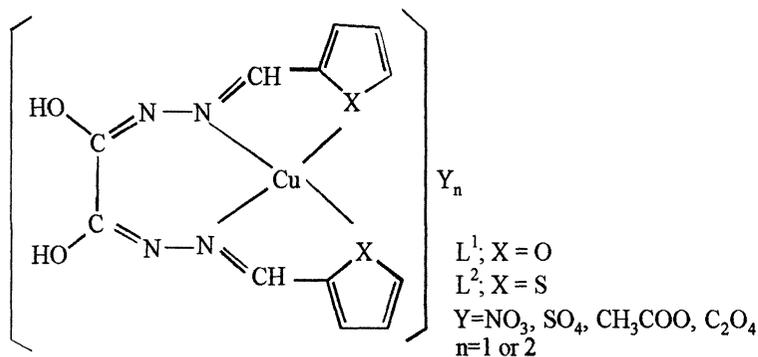
Complex	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) (ppm)	<sup>13</sup> C NMR (DMSO-d <sub>6</sub> ) (ppm)
1	4.8 (s, 1H, OH), 5.0-5.2 (m, 1H, furanyl), 5.4 (m, 1H, furanyl), 5.9 (m, 1H, furanyl), 8.2 (s, 1H, HC=N).	82.8 (C-O), 105.9, 113.1, 121.8, 124.2 (furanyl), 153.1 (HC=N).
2	4.9 (s, 1H, OH), 5.1-5.3 (m, 1H, furanyl), 5.5 (m, 1H, furanyl), 5.9 (m, 1H, furanyl), 8.3 (s, 1H, HC=N).	82.9 (C-O), 105.9, 113.3, 121.8, 124.3 (furanyl), 153.2 (HC=N).
3	4.8 (s, 1H, OH), 5.2-5.3 (m, 1H, furanyl), 5.4 (m, 1H, furanyl), 5.9 (m, 1H, furanyl), 8.2 (s, 1H, HC=N).	82.8 (C-O), 105.9, 113.2, 121.9, 124.3 (furanyl), 153.1 (HC=N).
4	4.9 (s, 1H, OH), 5.1-5.2 (m, 1H, furanyl), 5.4 (m, 1H, furanyl), 5.9 (m, 1H, furanyl), 8.3 (s, 1H, HC=N).	82.9 (C-O), 105.9, 113.2, 121.8, 124.2 (furanyl), 153.3 (HC=N).
5	4.7 (s, 1H, OH), 5.1-5.2 (m, 1H, thienyl), 5.3 (m, 1H, thienyl), 5.8 (m, 1H, thienyl), 8.1 (s, 1H, HC=N).	82.6 (C-O), 105.8, 113.1, 121.7, 124.1 (thienyl), 153.1 (HC=N).
6	4.8 (s, 1H, OH), 5.1-5.2 (m, 1H, thienyl), 5.4 (m, 1H, thienyl), 5.8 (m, 1H, thienyl), 8.2 (s, 1H, HC=N).	82.5 (C-O), 105.7, 113.3, 121.7, 124.1 (thienyl), 153.2 (HC=N).
7	4.8 (s, 1H, OH), 5.0-5.2 (m, 1H, thienyl), 5.4 (m, 1H, thienyl), 5.8 (m, 1H, thienyl), 8.3 (s, 1H, HC=N).	82.8 (C-O), 105.8, 113.2, 121.7, 124.2 (thienyl), 153.3 (HC=N).
8	4.8 (s, 1H, OH), 5.1-5.3 (m, 1H, thienyl), 5.4 (m, 1H, thienyl), 5.7 (m, 1H, thienyl), 8.2 (s, 1H, HC=N).	82.7 (C-O), 105.7, 113.3, 121.6, 124.1 (thienyl), 153.2 (HC=N).

### Magnetic Moment and Electronic Spectra

The UV-Visible spectral bands of the Cu(II) complexes are recorded in Table I. The copper(II) complexes exhibited<sup>30</sup> magnetic moment of 1.55-1.65 B.M at room temperature. These values are quite close to the spin-allowed values expected for a  $S=1/2$  system and the complexes attain a square planar geometry around the copper(II) ion. These copper(II) complexes (Table II) display a broad band at  $\sim 14680 \text{ cm}^{-1}$  due to  ${}^2B_{1g} \rightarrow {}^2E_g$  and two bands at  $\sim 16395$  and  $\sim 27320 \text{ cm}^{-1}$  assigned<sup>31,32</sup> due to d-d transitions and a charge transfer band, confirming their square planar environment<sup>33</sup> (Fig. 3).

### Antibacterial Properties

Antibacterial properties of the ligands and their metal complexes were studied against bacterial species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. These were tested at a concentration of  $30 \mu\text{g}/0.01 \text{ mL}$  in DMF solution using a paper disc diffusion method devised and reported<sup>34-37</sup> earlier. The results of these studies reproduced in Table IV indicated that both the Schiff-base ligands and their metal complexes individually exhibited varying degrees of inhibitory effects on the growth of the testing bacterial species. The antibacterial results evidently show that the activity of the unchelated compounds became more pronounced and prominent when chelated with the metal ion. When the same metal chelate having different anions was individually screened, the degree of bactericidal activity/potency also varied.



(Fig. 3) Proposed Structure of the Cu(II) Complex

From the obtained data, it was generally observed that the order of potency in comparison to the metal chelate having chloride anion evaluated and reported earlier<sup>38</sup> and to the results of the present studies against the same tested bacterial species under the same conditions were found to follow the order as



On the basis of these results, it is therefore, strongly claimed<sup>39,40</sup> that different anions dominantly effect the biological behavior of the metal chelates. It is, however, expected that factors such as solubility, conductivity, dipole moment and cell permeability mechanisms are certainly influenced by the presence of these anions in the chelate and may cause in increasing this activity. These studies provide a useful information about the biological activity of compounds influenced by the anions which stay outside the coordination sphere of the chelated complex.

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Table IV Antibacterial Activity Data

Ligand/ complex	M i c r o b i a l S p e c i e s			
	a	b	c	d
L <sup>1</sup>	++	++	+	++
L <sup>2</sup>	+	++	-	++
1	++++	+++	++	++
2	+++	+++	+++	++
3	+++	+++	++	+++
4	+++	++	+++	++
5	+++	++	+++	+++
6	++	+++	+	++
7	+++	+++	++	+++
8	++	+++	++	+++

a=*Escherichia coli*, b=*Staphylococcus aureus*, c=*Pseudomonas aeruginosa* d=*Klebsiella pneumoniae*. Inhibition zone diameter mm (% inhibition): +, 6-10 (27-45 %); ++, 10-14 (45-64 %); +++, 14-18 (64-82 %); +++++, 18-22 (82-100 %). Percent inhibition values are relative to inhibition zone (22 mm) of the most active compound with 100 % inhibition.

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