

Ni(II), Cu(II) AND Zn(II) METAL CHELATES WITH SOME THIAZOLE DERIVED SCHIFF-BASES: THEIR SYNTHESIS, CHARACTERIZATION AND BACTERICIDAL PROPERTIES

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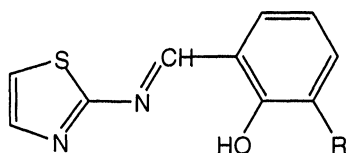
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ABSTRACT

A number of thiazole derived tridentate Schiff-bases (LH) and its metal chelates of the type $[M(L_2)X]$ where $M=Ni(II)$, $Cu(II)$ and $Zn(II)$, L =substituted salicylaldehyde (5-H, 5- CH_3 , 5- OCH_3 , 5- NO_2 and 5-Cl) and $X=Cl$ have been synthesized and characterized with the help of elemental analyses, conductivity measurements, magnetic moments, UV-Vis, IR and NMR spectral data. An octahedral structure for Ni(II) and Zn(II) and a distorted octahedral structure for Cu(II) chelates have been proposed. All the Schiff-bases and their metal chelates have been screened for their biological activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and in comparison, the metal chelates have been shown to possess more antibacterial activity than the uncomplexed Schiff-bases.

INTRODUCTION

Schiff-bases and the relevant transition metal complexes are still found to be of great interest in co-ordination chemistry¹⁻⁴ although this subject has been extensively studied⁵⁻⁸. A number of reviews have appeared on the co-ordination chemistry of Schiff-base complexes⁹⁻¹¹ which exhibit an interesting variety of stereochemical behaviors in this area. Thiazole and substituted thiazoles possess interesting biological activity probably conferred to them by the strong aromaticity of their ring system¹², which leads to great *in vivo* stability. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties could be obtained¹³. With a view to understanding such potentialities and also, the usefulness of Schiff-bases the present author has undertaken the syntheses of some thiazole derived Schiff-bases (Fig 1) by condensing some substituted salicylaldehydes (5-H, 5- CH_3 , 5- OCH_3 , 6- NO_2 and 5-Cl) with 2-aminothiazole and their metal chelates (1-15) with Ni(II), Cu(II) and Zn(II). In order to establish the biological role of metals, these prepared Schiff-bases and their metal chelates have been screened for their bactericidal activity against bacterial species such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.



R = H, CH_3 , OCH_3 , NO_2 or Cl

EXPERIMENTAL

Material and methods

All chemicals and solvents used were of Analar grade. All the metals were used as their metal(II) chlorides. 2-Aminothiazole and substituted salicylaldehyde were obtained from Aldrich. IR, 1H NMR and ^{13}C NMR spectra were recorded on a Philips Analytical PU 9800 FTIR and Bruker 250 MHz instruments. UV-Visible spectra were obtained on a Hitachi U-2000 double-beam spectrophotometer. Conductance of the metal complexes was determined in DMF at 10^{-3} dilution on a YSI-32 model conductometer. Magnetic measurements were done on solid complexes using the Gouy method. The synthesized Schiff-bases and their metal chelates were analyzed for C, H and N by microanalytical techniques and the metal contents in the chelates were estimated by standard methods. Melting points were recorded on a Gallenkamp apparatus and are uncorrected. The antibacterial studies were carried out with the help of the Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan.

Preparation of the Schiff-bases

An amount of salicylaldehyde (0.01 M) was dissolved in hot ethanol (20 mL). To this solution was added ethanolic solution of 2-aminothiazole (0.01 M, 30 mL). Then 2-3 drops of conc H_2SO_4 were added in it and the mixture, refluxed with stirring for 1 h and then left for 24 h at room temperature. During this period yellow needles precipitated. The crystals were filtered, washed with ethanol and dried at $60^\circ C$

Preparation of the Metal Complexes

An ethanol solution of appropriate metal(II) chloride (1 mmol, 20 mL) was added to a stirred hot ethanol solution of the respective Schiff-base (2 mmol, 30 mL). The resulting mixture was refluxed for 3 h. The solution was then cooled, filtered, reduced to nearly half its volume and then left for two days at room temperature. During this period the product crystallized. It was filtered, washed with ethanol and ether and dried to give desired metal complexes (1-15).

Antibacterial Studies**Preparation of Discs.**

The Schiff base/complex (30 µg) in DMF (0.01 mL) was applied on a paper disc, [prepared from blotting paper (3 mm diameter)] with the help of a micropipette. The discs were left in an incubator for 48 h at 37° C and then applied on the bacteria grown agar plates.

Preparation of Agar Plates.

Minimal agar was used for the growth of specific bacterial species. For the preparation of agar plates for *Escherichia coli*, MacConkey agar (50 g), obtained from Merck, was suspended in freshly distilled water (1 L). It was allowed to soak for 15 minutes and then boiled on a water bath until the agar was completely dissolved. The mixture was autoclaved for 15 minutes at 120° C and then poured into previously washed and sterilized Petri dishes and stored at 40° C for inoculation.

Procedure of Inoculation.

Inoculation was done with the help of a platinum wire loop which was made red hot in a flame, cooled and then used for the application of bacterial strains.

Application of Discs.

A sterilized forceps was used for the application of paper disc on the already inoculated agar plates. When the discs were applied, they were incubated at 37° C for 24 h. The diameter of the zone of inhibition was then measured.

Table 1 Physical, Spectral and Analytical Data of the Schiff bases

Schiff base/ Mol. Form.	M.P. (°C)	IR (cm ⁻¹)	Calc (Found %)		
			C	H	N
R=H C ₁₀ H ₈ N ₂ OS [204.18]	163	2900(OH),1635 (HC=N),1285(C-O)	58.8 (58.5)	3.9 (4.2)	13.7 (14.1)
R=CH₃ C ₁₁ H ₁₀ N ₂ OS [218.19]	178	2905(OH),1630 (HC=N),1285(C-O)	60.5 (60.6)	4.6 (4.9)	12.8 (12.7)
R=OCH₃ C ₁₁ H ₁₀ N ₂ O ₂ S [234.19]	155	2900(OH),1635 (HC=N),1280(C-O)	56.4 (56.3)	4.3 (4.5)	12.0 (11.8)
R=NO₂ C ₁₀ H ₁₀ N ₃ O ₃ S [212.18]	186	2900(OH),1630 (HC=N),1280(C-O)	56.6 (56.6)	4.7 (4.6)	19.8 (20.1)
R=Cl C ₁₀ H ₇ ClN ₂ OS [238.63]	172	2905(OH),1635 (HC=N),1285(C-O)	50.3 (50.2)	2.9 (2.6)	11.7 (11.5)

RESULTS AND DISCUSSION**Physical properties**

The Schiff-bases were prepared by condensation of equimolar amounts of substituted salicylaldehyde and aminothiazole in ethanol. The crystallized products after characterization (Table 1, 2) were used further for the preparation of their metal complexes.

All the complexes (1-15) prepared are crystalline solids and melt with decomposition above 250° C without showing sharp melting points. The complexes are soluble in chloroform, DMF, DMSO and benzene. Their melting behaviour, solubility and crystalline nature suggests that they are non-polymeric. Elemental analyses data (Table 3) suggested 1:2 (metal:ligand) stoichiometry. Low conductance values (12-17 ohm⁻¹ cm² mol⁻¹) indicated that the complexes are non-electrolytic^{14,15} in nature.

Table 2 ^1H NMR and ^{13}C NMR Data of the Schiff bases

R	^1H NMR (DMSO- d_6) (ppm)	^{13}C NMR (DMSO- d_6) (ppm)
H	6.9(m,2H,aromatic), 7.3(m,1H,aromatic), 7.5(m,1H,aromatic), 7.9(s,1H,HC=N), 7.4(d,1H,heteroaromatic), 7.8(d,1H,heteroaromatic), 12.8(s,1H,OH).	116.5, 118.2, 118.7(aromatic), 131.6, 132.3, 160.7(aromatic), 118.6, 143.2, 155.9(heteroaromatic), 165.2(HC=N).
CH ₃	2.3(s,3H,CH ₃), 7.1(m,2H,aromatic), 7.3(m,1H,aromatic), 7.5(m,1H,aromatic), 8.0(s,1H,HC=N), 7.4(d,1H,heteroaromatic), 7.8(d,1H,heteroaromatic), 12.9(s,1H,OH).	31.1(CH ₃), 116.6, 118.2, 118.5(aromatic), 131.6, 132.3, 160.7(aromatic), 118.6, 143.2, 155.9(heteroaromatic), 165.2(HC=N).
OCH ₃	3.8(s,3H,CH ₃), 6.9(m,2H,aromatic), 7.3(m,1H,aromatic), 7.5(m,1H,aromatic), 8.0(s,1H,HC=N), 7.4(d,1H,heteroaromatic), 7.8(d,1H,heteroaromatic), 12.8(s,1H,OH).	31.1(OCH ₃), 116.6, 118.2, 118.5(aromatic), 131.6, 132.3, 160.7(aromatic), 118.6, 143.2, 154.9(heteroaromatic), 165.2(HC=N).
NO ₂	6.9(m,2H,aromatic), 7.4(m,1H,aromatic), 7.5(m,1H,aromatic), 8.1(s,1H,HC=N), 7.4(d,1H,heteroaromatic), 7.8(d,1H,heteroaromatic), 13.0(s,1H,OH).	116.6, 118.2, 118.5(aromatic), 131.6, 132.3, 165.7(aromatic), 118.6, 143.2, 155.9(heteroaromatic), 165.2(HC=N).
Cl	6.8(m,2H,aromatic), 7.4(m,1H,aromatic), 7.5(m,1H,aromatic), 8.1(s,1H,HC=N), 7.4(d,1H,heteroaromatic), 7.8(d,1H,heteroaromatic), 12.9(s,1H,OH).	31.1(CH ₃), 116.6, 118.2, 118.5(aromatic), 131.6, 132.3, 160.7(aromatic), 118.6, 143.3, 155.9(heteroaromatic), 165.2(HC=N).

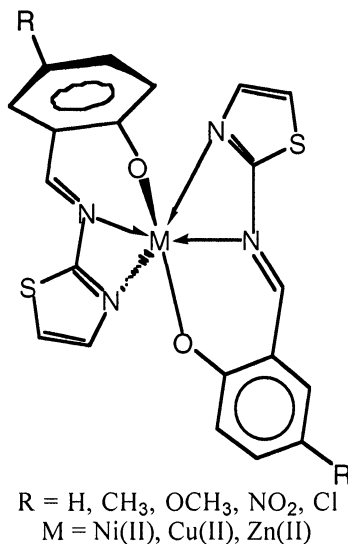


Figure 2: Structure proposed for the metal chelates

Infrared and NMR spectra

The IR spectra of the ligands (Table 1) show a weak and broad band at $\sim 2900\text{ cm}^{-1}$ instead of a strong band at 3100 cm^{-1} (expected due to phenolic $-\text{OH}$ group). This might be due to intramolecular hydrogen bonding between the hydroxyl hydrogen and nitrogen of the azomethine group forming a six membered ring¹⁶. The absence of νOH in the complexes suggested the deprotonation of the phenolic $-\text{OH}$ of the Schiff base and its co-ordination through the O atom. Moreover, the $\nu\text{C-O}$ and $\nu\text{C=N}$ modes which occurred at ~ 1285 and $\sim 1640\text{ cm}^{-1}$ respectively in the Schiff bases were shifted in the complexes. This shifting of $\nu\text{C-O}$ towards higher frequency ($\sim 1330\text{-}1342\text{ cm}^{-1}$) and lowering of $\nu\text{C=N}$ ($\sim 1580\text{-}1610\text{ cm}^{-1}$) suggested that the co-ordination of the Schiff-bases occurred through the deprotonated oxygen of the phenolic $-\text{OH}$ group and nitrogen of the azomethine (HC=N) groups¹⁶. Further conclusive evidence of the co-ordination of the ligands with the metals was confirmed by the appearance of weak low frequency bands at $\sim 480\text{-}510$ and $\sim 345\text{-}370$

cm⁻¹ (Table 4) due to metal-oxygen and metal-nitrogen stretching vibrations¹⁷⁻²¹ in the metal complexes and not observable in the spectra of Schiff-bases.

The NMR spectra are also proved to have considerable diagnostic values when compared with the reported²² related values. According to ¹H and ¹³C NMR spectra features of the Schiff-bases (Fig 1) are shown in Table 2 which are in agreement with the proposed structures.

Table 3 Physical Data of Metal Chelates

No	Metal chelate/ Mol. Formula	M.P(°C) (dec.)	B.M. (μ_{eff})	Calc (Found)%		
				C	H	N
1	[Ni(L ¹) ₂ (Cl) ₂] C ₂₀ H ₁₄ NiCl ₂ N ₄ O ₂ S ₂ [535.93]	252-254	3.07	44.8 (44.5)	2.6 (2.5)	10.4 (10.5)
2	[Ni(L ²) ₂ (Cl) ₂] C ₂₂ H ₁₈ NiCl ₂ N ₄ O ₂ S ₂ [563.95]	248-250	3.12	46.9 (47.0)	3.2 (3.6)	9.9 (10.2)
3	[Ni(L ³) ₂ (Cl) ₂] C ₂₂ H ₁₈ NiCl ₂ N ₄ O ₄ S ₂ [595.95]	273-275	3.10	44.33 (44.67)	3.0 (2.9)	9.4 (9.3)
4	[Ni(L ⁴) ₂ (Cl) ₂] C ₂₀ H ₁₂ NiCl ₂ N ₆ O ₆ S ₂ [625.93]	266-268	3.13	38.37 (38.71)	1.9 (2.0)	13.4 (13.6)
5	[Ni(L ⁵) ₂ (Cl) ₂] C ₂₀ H ₁₂ NiCl ₃ N ₄ O ₂ S ₂ [569.38]	257-260	3.13	42.5 (42.3)	2.1 (2.2)	9.8 (9.2)
6	[Cu(L ¹) ₂ (Cl) ₂] C ₂₀ H ₁₄ CuCl ₂ N ₄ O ₂ S ₂ [540.96]	255-257	1.83	44.4 (44.8)	2.6 (2.3)	10.4 (10.1)
7	[Cu(L ²) ₂ (Cl) ₂] C ₂₂ H ₁₈ CuCl ₂ N ₄ O ₂ S ₂ [568.78]	251-253	1.90	46.45 (46.18)	3.2 (3.9)	9.8 (9.7)
8	[Cu(L ³) ₂ (Cl) ₂] C ₂₂ H ₁₈ CuCl ₂ N ₄ O ₄ S ₂ [600.78]	271-273	1.88	44.0 (44.7)	3.0 (3.5)	9.3 (9.2)
9	[Cu(L ⁴) ₂ (Cl) ₂] C ₂₀ H ₁₂ CuCl ₂ N ₆ O ₆ S ₂ [630.76]	268-270	1.95	38.0 (38.1)	2.1 (2.5)	13.3 (13.1)
10	[Cu(L ⁵) ₂ (Cl) ₂] C ₂₀ H ₁₂ CuCl ₃ N ₄ O ₂ S ₂ [574.21]	252-254	1.96	41.8 (41.9)	2.1 (2.0)	9.8 (9.5)
11	[Zn(L ¹) ₂ (Cl) ₂] C ₂₀ H ₁₄ ZnCl ₂ N ₄ O ₂ S ₂ [542.59]	274-276	Dia	44.3 (44.4)	2.6 (2.5)	10.3 (10.9)
12	[Zn(L ²) ₂ (Cl) ₂] C ₂₂ H ₁₈ ZnCl ₂ N ₄ O ₂ S ₂ [570.61]	262-264	Dia	46.3 (46.5)	3.2 (3.1)	9.8 (9.2)
13	[Zn(L ³) ₂ (Cl) ₂] C ₂₂ H ₁₈ ZnCl ₂ N ₄ O ₄ S ₂ [602.61]	257-259	Dia	43.8 (43.4)	3.0 (3.6)	9.3 (9.2)
14	[Zn(L ⁴) ₂ (Cl) ₂] C ₂₀ H ₁₂ ZnCl ₂ N ₆ O ₆ S ₂ [632.59]	269-171	Dia	38.0 (38.2)	1.9 (2.2)	13.3 (13.0)
15	[Zn(L ⁵) ₂ (Cl) ₂] C ₂₀ H ₁₂ ZnCl ₃ N ₄ O ₂ S ₂ [576.04]	278-280	Dia	41.7 (41.9)	2.1 (2.5)	9.7 (10.1)

UV-Visible spectra and Magnetic moments

Electronic spectra of the Ni(II) complexes exhibit four bands at 8000-9885, 13545-15555, 23775-24100 and 27245-29300 cm⁻¹. The first three bands were assigned to the spin allowed transitions ³A_{2g}(v₁) → ³T_{2g}, ³A_{2g}(v₂) → ³T_{1g}(F) and ³A_{2g}(v₃) → ³T_{1g}(P) respectively. The fourth band at 27245-29300 cm⁻¹ was of high intensity and was due to ligand-metal charge-transfer. The occurrence of three spin-allowed transitions

supports the octahedral geometry for the Ni(II) complexes²³. The magnetic moments of the complexes lie in the range 3.06-3.13 B.M (Table 4) and also confirms the octahedral geometry²⁴.

The electronic spectra of the Cu(II) complexes exhibit two bands, a broad unsymmetrical band in the visible region at 14530-15100 cm^{-1} may be due to ${}^2E_g \rightarrow {}^2T_{2g}$ transitions in the octahedral geometry and a sharp band of high intensity at 26500-28170 cm^{-1} assigned to Logan-metal charge-transfer²⁴. The Cu(II) complexes of tetrahedral geometry or octahedral geometry^{25,26} normally exhibit magnetic moments in the range ~ 1.9 B.M. The magnetic moments of the present Cu(II) complexes lie in the range 1.81-1.96 B.M. On the basis of electronic spectra and magnetic susceptibility data, a distorted octahedral geometry²⁷ is proposed for the complexes. The electronic spectra of the Zn(II) complexes exhibit only a high intensity band at 27250-28500 cm^{-1} assigned²⁸ to ligand-metal charge-transfer.

Table 4 Spectral and Analytical Data of Metal Chelates

No	IR (cm^{-1})	λ_{max} (cm^{-1})
1	1330(C-O),1610(HC=N),480(M-O),345(M-N)	29205,23775,13545,8245
2	1335(C-O),1580(HC=N),485(M-O),355(M-N)	28255,24100,15555,
3	1342(C-O),1585(HC=N),495(M-O),350(M-N)	29300,23890,14285
4	1340(C-O),1605(HC=N),498(M-O),365(M-N)	28375,24005,14972
5	1341(C-O),1602(HC=N),510(M-O),345(M-N)	27650,23995,15345
6	1337(C-O),1590(HC=N),512(M-O),370(M-N)	27245,14530
7	1335(C-O),1595(HC=N),505(M-O),367(M-N)	26500,14877
8	1340(C-O),1610(HC=N),492(M-O),365(M-N)	28170,15100
9	1342(C-O),1605(HC=N),495(M-O),355(M-N)	27270,14655
10	1338(C-O),1595(HC=N),480(M-O),345(M-N)	27220,14995
11	1335(C-O),1610(HC=N),495(M-O),370(M-N)	27250
12	1342(C-O),1600(HC=N),510(M-O),365(M-N)	28445
13	1335(C-O),1610(HC=N),510(M-O),360(M-N)	28500
14	1337(C-O),1598(HC=N),505(M-O),361(M-N)	27780
15	1340(C-O),1595(HC=N),500(M-O),365(M-N)	27555

Table 5 Antibacterial Activity Data

Schiff-base/-Chelate	M i c r o b i a l S p e c i e s			
	a	b	c	d
HL ¹	++	+	+	++
HL ²	+	++	++	+
HL ³	++	+	-	+
HL ⁴	+	++	+	+
HL ⁵	++	+	+	++
1	+++	+++	+++	+++
2	+++	+++	+++	+++
3	+++	++++	+++	++
4	+++	++	++	++
5	++++	+++	+++	+++
6	+++	+++	+++	++
7	++++	+++	+++	+++
8	++	+++	+	++
9	+++	+++	++++	+++
10	+++	+++	+++	+++
11	+++	++++	++	+++
12	++	++++	+++	+++
13	+++	+++	+++	++
14	++++	+++	++	++++
15	+++	++	++	+++

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.

In the light of the above discussion octahedral structures for Ni(II) and Zn(II) complexes and distorted octahedral structure for Cu(II) complexes is proposed. It is tentatively proposed that the Schiff-base ligands coordinate through the nitrogen of the azomethine group, nitrogen of thiazole ring and oxygen of phenolic group forming a stable chelate ring structure (Fig 2).

Antibacterial activity

The antibacterial activity of Schiff-bases and their complexes was studied against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* bacterial species. Paper disc diffusion method devised and reported^{29,30} earlier was adopted for screening. All the Schiff-bases and its complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The antibacterial results are reproduced in Table 5 which evidently show that the activity of the Schiff-bases became more pronounced when co-ordinated with the metals.

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