

Some Metal(II) Chelates of Ni(II), Cu(II) and Zn(II) with Thiazole Derived Schiff-Base Ligand: Their Synthesis, Characterization and Role of Anions (NO_3^- , SO_4^{2-} , $\text{C}_2\text{O}_4^{2-}$ and CH_3CO_2^-) on Their Antibacterial Properties.

¹ ZAHID H. CHOCHAN* AND ²M. PRAVEEN

¹Department of Chemistry, Islamia University, Bahawalpur, (Pakistan)

²Department of Chemistry, Washington University, St. Louis 63130, (U S A)

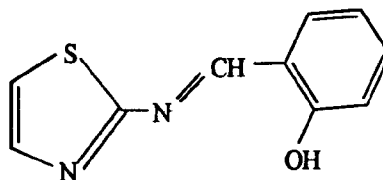
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Summary: A number of biologically active nickel(II), copper(II) and zinc(II) chelates with a novel thiazole derived salicylaldehyde having the same metal ion but different anions, e.g., nitrate, sulfate, oxalate and acetate, have been synthesized and characterized on the basis of their physical, spectral and analytical data. In order to evaluate the role of anions on their antibacterial properties, the ligand and its synthesized metal chelates with various anions have been screened against bacterial species *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The title studies have proved the role of anions in enhancing the antibacterial properties.

Introduction

Thiazoles are largely used as antibacterial [1], antifungal [2], antitumour [3], anthelmintic [4] and diuretic agents [5]. Also, various salicylaldehydes have been claimed [6,7] as potential inhibitors for DNA synthesis. Hence, if a salicylaldehyde molecule is coupled with a thiazole moiety, the resulting compound may show a more biological activity. Considering these factors, it was thought worthwhile to synthesize thiazole-derived salicylaldehyde (Fig. 1) and study its relationship with the metal ions in subsequently increasing its bactericidal activity. A remarkable correlation between biological activity and chelation has been examined [8-11] from various point of views. The connected metal centers in biologically active molecules may involve different functions such as oxygen transport, DNA inhibitor, enzymatic activity or electron transfer.

In order to gain more information and the factors responsible for enhancing the biological



(Fig 1). Structure of the Schiff-base Ligand (L)

activity, the present studies are reported to evaluate the possible role of anions (nitrate, sulfate, oxalate and acetate), which may play by staying as a counter part of the metal ion (cation) in the metal chelates. For this purpose metal(II) chelates of the type $[\text{M}(\text{L})_2]\text{X}$, where $[\text{M} = \text{Ni}(\text{II}), \text{Cu}(\text{II}) \text{ and } \text{Zn}(\text{II}), \text{L} = \text{Schiff-base (Fig. 1) and } \text{X} = \text{NO}_3^-, \text{SO}_4^{2-}, \text{C}_2\text{O}_4^{2-} \text{ and } \text{CH}_3\text{CO}_2^-]$ having the same metal(II) ion but different anions have been synthesized, characterized and screened for their antibacterial activity against bacterial species *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

*To whom all correspondence should be addressed.

Result and Discussion

Physical Properties

Schiff-base (Fig. 1) was prepared by reacting equimolar amounts of salicylaldehyde and 2-aminothiazole in ethanol. The crystallized product after characterization was further used for the preparation of its metal complexes.

All the prepared complexes (1-12) are crystalline solids which decompose above 250°. The complexes are soluble in DMF, DMSO and benzene. Their melting behavior, solubility and crystalline nature suggested that they are non-polymeric. Elemental analyses data (Table 1) indicated 1:2 (metal:ligand) stoichiometry. Molar conductance values [12] of the complexes range 120-170 ohm⁻¹ cm² mol⁻¹. In order to confirm further the nature of the anions (coordinated/free), the spectra of the nitrate complexes were studied. A coordinated nitrate group generally absorbs at ~1020 and 1250 cm⁻¹. However, no such bands were observed in the nitrate complexes, suggesting [13] the non-coordination of the anionic group.

Infrared spectra

The IR spectra of the ligand showed a broad band at ~ 3120 cm⁻¹ due to νOH and νC=N mode occurred at ~ 1635 cm⁻¹ respectively [14-16]. These bands were shifted in the spectra of its complexes. This shifting of νOH towards higher frequency (~ 3125-3130 cm⁻¹) and lowering of νC = N (~ 1585-1610 cm⁻¹) suggested that the co-ordination of the Schiff-base occurred through the oxygen of the phenolic -OH group and nitrogen of the azomethine (HC = N) group. Further conclusive evidence of the co-ordination of the ligand with the metals was confirmed by the appearance of weak low frequency

Table 1. Physical and Analytical Data of Metal(II) Chelates

No	Metal chelate/ Mol. Formula	M.P. ^o (C) (dec)	Cal (Found)%			B.M (μm)
			C	H	N	
1	[Ni(L) ₂](NO ₃) ₂ C ₂₀ H ₁₆ NiN ₆ O ₈ S ₂ [590.8]	261-263	40.6 (40.8)	2.7 (2.5)	14.2 (14.3)	3.05
2	[Ni(L) ₂](SO ₄) C ₂₀ H ₁₆ NiN ₄ O ₆ S ₃ [562.9]	258-260	42.6 (42.9)	2.8 (2.6)	10.0 (10.2)	3.11
3	[Ni(L) ₂](C ₂ O ₄) C ₂₂ H ₁₆ NiN ₄ O ₆ S ₂ [554.8]	262-264	47.6 (48.0)	2.9 (2.8)	10.1 (10.0)	3.12
4	[Ni(L) ₂](CH ₃ CO ₂) ₂ C ₂₄ H ₂₂ NiN ₄ O ₆ S ₂ [584.8]	264-266	49.2 (49.3)	3.8 (3.5)	9.6 (9.8)	3.13
5	[Cu(L) ₂](NO ₃) ₂ C ₂₀ H ₁₆ CuN ₆ O ₈ S ₂ [593.7]	251-253	40.3 (40.0)	2.7 (2.5)	14.1 (14.1)	1.90
6	[Cu(L) ₂](SO ₄) C ₂₀ H ₁₆ CuN ₄ O ₆ S ₃ [567.8]	248-250	42.3 (42.7)	2.6 (2.5)	9.9 (10.2)	1.87
7	[Cu(L) ₂](C ₂ O ₄) C ₂₂ H ₁₆ CuN ₄ O ₆ S ₂ [569.7]	250-252	46.3 (46.6)	2.8 (2.6)	9.8 (10.1)	1.88
8	[Cu(L) ₂](CH ₃ CO ₂) ₂ C ₂₄ H ₂₂ CuN ₄ O ₆ S ₂ [589.7]	255-257	48.8 (49.1)	3.7 (3.9)	9.5 (9.4)	1.92
9	[Zn(L) ₂](NO ₃) ₂ C ₂₀ H ₁₆ ZnN ₆ O ₈ S ₂ [597.5]	265-267	40.2 (40.1)	2.7 (2.8)	14.1 (14.1)	Dia
10	[Zn(L) ₂](SO ₄) C ₂₀ H ₁₆ ZnN ₄ O ₆ S ₃ [569.6]	258-260	42.1 (42.3)	2.8 (2.7)	9.8 (9.9)	Dia
11	[Zn(L) ₂](C ₂ O ₄) C ₂₂ H ₁₆ ZnN ₄ O ₆ S ₂ [561.5]	264-266	47.0 (47.4)	2.8 (2.5)	10.0 (10.3)	Dia
12	[Zn(L) ₂](CH ₃ CO ₂) ₂ C ₂₄ H ₂₂ ZnN ₄ O ₆ S ₂ [591.5]	267-269	48.7 (48.5)	3.7 (3.3)	9.5 (9.4)	Dia

bands at ~ 480-510 and ~ 345-370 cm⁻¹ (Table 2) due to metal-oxygen and metal-nitrogen stretching vibrations [15] in the metal complexes and not observable in the spectra of Schiff-base.

NMR Spectra

The ¹H NMR and ¹³C NMR spectra of the free ligand and its metal complexes support the conclusion derived from the IR spectra. The ¹H

Table 2. IR Spectral Data of the Metal(II) Chelates

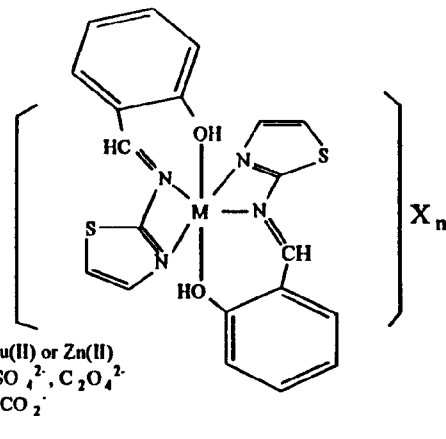
No	IR (cm ⁻¹)	λ _{max} (cm ⁻¹)	
1	3125 (OH), 1610 (HC=N), 485 (M-O), 355 (M-N)	29225, 23775, 13545, 8245	
2	3130 (OH), 1605 (HC=N), 480 (M-O), 345 (M-N)	28250, 24115, 14555, 8170	
3	3130 (OH), 1585 (HC=N), 495 (M-O), 350 (M-N)	29300, 23790, 14285, 8550	
4	3128 (OH), 1610 (HC=N), 490 (M-O), 355 (M-N)	28355, 24200, 14570, 7975	
5	3125 (OH), 1602 (HC=N), 505 (M-O), 365 (M-N)	27245, 14530	
6	3130 (OH), 1590 (HC=N), 510 (M-O), 370 (M-N)	27245, 14530	
7	3125 (OH), 1595 (HC=N), 505 (M-O), 365 (M-N)	26500, 14877	
8	3125 (OH), 1610 (HC=N), 490 (M-O), 360 (M-N)	28170, 15100	
9	3130 (OH), 1605 (HC=N), 495 (M-O), 355 (M-N)	27250	
10	3125 (OH), 1610 (HC=N), 495 (M-O), 345 (M-N)	27250	
11	3125 (OH), 1605 (HC=N), 485 (M-O), 370 (M-N)	27250	
12	3125 (OH), 1610 (HC=N), 510 (M-O), 365 (M-N)	28445	

NMR spectra of the ligand exhibit [17] peaks at δ 7.9 (s) and δ 12.8 (s) ppm due to azomethine (CH = N) and hydroxyl (OH) protons. The azomethine and hydroxyl proton signals in the spectra of complexes display an upfield-shifted proton resonance indicating involvement of these groups in coordination. Thiazole proton of free ligand at δ 7.8 ppm also showed a downfield shift in the spectra of complexes providing an evidence of coordination of thiazole nitrogen to the metal. The other aromatic and heteroaromatic protons were found as expected [18] in their region. Similarly, ^{13}C NMR spectra of the ligand showed azomethine carbon resonance at δ 165.2 ppm and one of the thiazole carbon resonance at δ 143.2 ppm which shifted to downfield in the complexes attributed [18] to the coordination of azomethine and thiazole nitrogens with the metal atom.

UV-Visible spectra and Magnetic moments

The electronic spectra of the Ni(II) complexes exhibited four bands at 7975-8550, 13545-14570, 23725-24200 and 28250-29300 cm^{-1} . The first three bands were assigned to the spin-allowed transitions $\nu_1^3\text{A}_{2g} \rightarrow ^3\text{T}_{2g}$, $\nu_2^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{F})$ and $\nu_3^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{P})$ respectively. The fourth band at 28250-29300 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) complexes [19]. The magnetic moments of the complexes lie in the range 3.05-3.13 B.M (Table 1) also confirm the octahedral geometry [20]. 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 $^2\text{E}_g \rightarrow ^2\text{T}_{2g}$ transitions in the octahedral geometry and a sharp band of high intensity at 26500-28170 cm^{-1} assigned to Ligand-metal charge-transfer [20].

The Cu(II) complexes of tetrahedral geometry or octahedral geometry [22,23] normally exhibit magnetic moments in the range 1.80-1.95 B.M. The magnetic moments of the present Cu(II) complexes lie in the range 1.87-1.92 B.M. On the basis of electronic spectra and magnetic susceptibility data, a distorted octahedral geometry [21] is proposed for the complexes. The electronic spectra of the Zn(II) complexes exhibit only a high intensity band at 27250-28445 cm^{-1} assigned [22-25] to ligand-metal charge-transfer.



(Fig 2). Proposed Structure of the Metal(II) chelate

In the light of the above discussion an octahedral structures for the Ni(II) and Zn(II) chelates and a distorted octahedral structure for the Cu(II) chelates is proposed. It is tentatively proposed that the Schiff-base ligand coordinates 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 Studies

The antibacterial activity of Schiff-base in comparison to its metal chelates having the same metal atom but different anions was studied against bacterial species *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Paper disc diffusion method reported [26,27] earlier was adopted for screening. The Schiff-base and its complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The antibacterial results reproduced in Table 3 evidently show that the activity of the Schiff-base became more pronounced when co-ordinated with the metals. When the same metal chelate having different anions was individually screened the degree of bactericidal activity also varied. For example, the Ni(II) complex having nitrate as anion was more bactericidal than the Ni(II) complex with sulfate, oxalate or acetate anions. Similarly, the Ni(II) complex of oxalate anion was more antibacterial than the complex with acetate, chloride or sulfate anions. The same results were found for Cu(II) and Zn(II) complexes. From

Table 3 Antibacterial Activity Data

Schiffbase/ Chelate	M i c r o b i a l S p e c i e s		
	a	b	c
L	++	+	+
1	+++	+++	+++
2	+++	+++	+++
3	+++	++++	+++
4	+++	++	++
5	++++	+++	+++
6	+++	+++	+++
7	++++	+++	+++
8	++	+++	+
9	+++	+++	++++
10	+++	+++	+++
11	+++	++++	++
12	++	++++	+++

a= *Escherichia coli*,b= *Staphylococcus aureus*,c= *Pseudomonas aeruginosa*

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.

the obtained data, it was generally observed that the order of potency in comparison to the metal complexes having chloride anions evaluated and reported earlier [28] and to the results of the present studies against the tested bacterial species was found to follow the order as:



On the basis of these results, it is strongly claimed that different anions do effect the biological behavior of the metal chelates. It is however, suspected that factors such as solubility, conductivity, dipole moment and cell permeability mechanisms (influenced by the presence of anions) may be the possible reasons for increasing this activity.

Experimental

All chemicals and solvents used were of Analar grade. IR, ¹H NMR and ¹³C NMR spectra were recorded on 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 on a YSI-32 metal conductometer. Magnetic measurements were

done on solid complexes using the Gouy method. Analyses were carried out by Butterworth Laboratories Ltd. 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 Ligand

An amount of salicylaldehyde (0.01 M) in hot ethanol (20 mL) was added to ethanolic solution (20 mL) of 2-aminothiazole (0.01 M, 30 mL). Then 2-3 drops of conc. H₂SO₄ were added and the mixture was refluxed with stirring for 1 h and then left for 24 h at room temperature. During this period yellow crystalline needles precipitated. The crystals were filtered, washed with ethanol and dried at 60°C to give Schiff-base (L), m.p 163°C. IR (KBr, cm⁻¹) 3120 (OH), 1635 (C = N), 1530, 1465, 955. ¹NMR (DMSO-d₆) δ 6.9 (m, 2H, aromatic), 7.3 (m, 1H, aromatic), 7.5 (m, 1H, aromatic), 7.9 (s, 1H, CH = N), 7.4 (d, 1H, heteroaromatic), 7.8 (d, 1H, heteroaromatic), 12.9 (s, 1H, OH). ¹³CNMR (DMSO-d₆) δ 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). Analyses calculated C, 58.8; H, 3.9; N, 13.7 for C₁₀H₈N₂OS C, 58.5; H, 4.2; N, 13.9 %.

Preparation of Metal Complexes

An ethanolic solution of appropriate metal(II) salt (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 (67 %), 2 (60 %), 3 (65 %), 4 (65 %), 5 (62 %), 6 (65 %), 7 (65 %), 8 (60 %), 9 (62 %), 10 (63 %), 11 (65 %) and 12 (65 %).

Antibacterial Studies

The synthesized metal chelates in comparison to the free ligand were screened for their antibacterial activity against bacterial species *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The paper disc diffusion

method was used for the determination of antibacterial activity as reported [10,11] elsewhere.

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