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Antimicrobial and antioxidant studies on some transition metal complexes derived from the Schiff base ligand, 4-hydroxypent-3-en-2-ylideneaminophenol

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ABSTRACT

A series of metal complexes have been synthesised using the Schiff base ligand, 4-hydroxypent-3-en-2-ylideneaminophenol, (L_1) derived from the condensation reaction of 2-aminophenol with acetyl acetone in ethanol. This series of $M-L_1$ complexes ($M=Fe(III), Co(II), Mn(II), Cu(II)$ and $Zn(II)$) were characterized by spectroscopic techniques (IR, UV-visible), elemental analysis, and conductivity measurement. The analytical results reveal that the Schiff base acted as a tridentate ligand and coordinated to the metal ion in a 1:1 $M:L$ stoichiometric ratio. The $Fe(III)$, $Mn(II)$ and $Co(II)$ complexes showed octahedral geometry, while the $Zn(II)$ and $Cu(II)$ complexes showed tetrahedral geometry. *In vitro* antibacterial activity of the Schiff base ligand and its metal complexes carried out on four bacterial strains (*E. coli*, *P. aeruginosa*, *S. typhi*, *S. aureus*) and four fungal strains (*C. albicans* ATCC 12C, *C. albicans* ATCC P37037, *C. albicans* ATCC P37039, *C. neoformans*) showed higher activity of the complexes compared to the ligand. The Schiff base and its metal complexes showed antioxidant (free radical scavenging) activities when compared to garlic acid.

Keywords: Schiff base ligand, Metal complexes, antimicrobial, antioxidant activity.

INTRODUCTION

Schiff's bases are an important class of organic compounds due to their excellent coordination chemistry and their wide range of industrial and biological applications [1-3]. They are excellent coordinating compounds forming stable complexes with transition metal ions. Schiff's bases and their metal complexes have been used as catalysts for the epoxydation of olefins, photo-stabilisation of polymers [2, 3] and for the polymerisation of metals complexes. They have also been shown to exhibit a broad range of antifungal, anti-inflammatory, and antituberculosis properties [1, 4-6].

The common structural feature of Schiff's base ligands is the azomethine group, $RHC=NR'$ where R and R' are alkyl or aryl groups. The presence of the imine group in Schiff's bases has been shown to account for the observed biological activities [7- 9]. Coordination of the Schiff bases to different metal atoms has shown to enhance the observed biological activity [9].

In recent decades, the incidence of bacterial resistance to existing drugs has become a major worldwide concern and necessitating the development of new molecules to fight this drug resistance by pathogens.

In this paper we report the synthesis of some metal complexes of the Schiff base ligand, 4-hydroxy-3-(2-ylideneaminophenyl)phenol, (L_1) derived from 2-aminophenol and acetyl acetone as well as their antimicrobial properties. The free radical scavenging activity of the Schiff base ligand L_1 and that of the transition metal complexes is evaluated and compared to that of Garlic Acid (GA).

MATERIALS AND METHODS

All chemicals are of reagent grade and were used without further purification. The solvents were purified by standard methods. Elemental analysis for C, H, N were carried out on a Fisons instrument 1108 CHNS/O analyser while quantitative estimation of metals was done using the atomic absorption technique on the Perkins-Elmer model 2400 series II instrument. Infrared spectra were recorded on an Alpha-Bruke and Perkins Elmer spectrometer while UV-visible spectra were recorded on a HACH DR 3900 spectrophotometer. Conductivity measurements were made on 10^{-3} M solutions of the complexes in water at 25°C using the HANNA, Hi9811-5. Melting points were determined using Stuart Melting point Apparatus. Thermogravimetric analysis was carried out using Perkin-Elmer Pyris 6 TGA up to 900°C in a closed perforated aluminium pan.

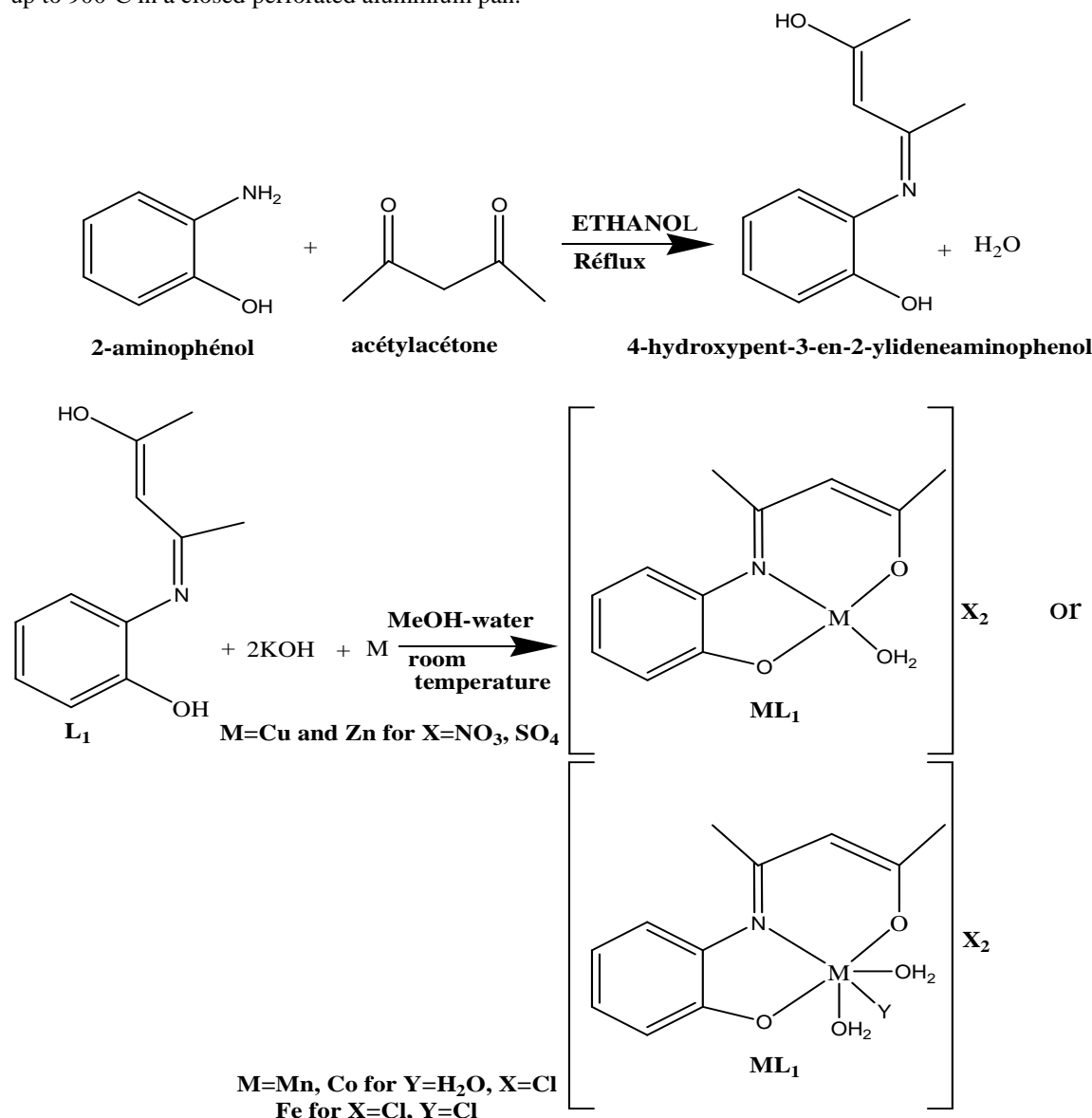


Figure 1: Schematic representation of the synthesis of the ligand, L_1 and its complexes

Synthesis

Synthesis of Schiff base

2-aminophenol (4.4 g; 40 mmol) was dissolved in 20 mL of ethanol in a 100 mL beaker at 50-60°C. A solution of acetylacetone (4.12 mL; 40 mmol) predissolved in 5 mL of ethanol was added drop wise to the 2-aminophenol solution while stirring. The mixture was heated under reflux for 5 hours in a water bath at a temperature of 80°C and

allowed to cool. A yellow precipitate was obtained, which was filtered, dried and weighed ($m = 5.54$ g representing a yield of 72 %).

Synthesis of metal Complexes

All complexes were prepared by gradually adding a methanol solution of the ligand to an aqueous solution of the corresponding metal salt. The preparation of the Cobalt(II) complex will illustrate this synthesis. A solution of 4-hydroxypent-3-en-2-ylideneaminophenol (L_1) (0.78 g; 2.8 mmol) and KOH (0.11 g; 5.6 mmol) in 20 mL methanol was added gradually with stirring to a 10 mL aqueous solution of cobalt (II) nitrate (2.8 mmol). The mixture was stirred for (3-4) hrs at 25°C. The resulting solution was allowed to stand at room temperature until the solvent evaporated to half its volume. The coloured complexes separated out and the product was filtered, washed several times with ethanol and recrystallized from hot ethanol and air dried at room temperature (yield 58-80 %). Figure 1 represents the scheme for the synthesis of the ligand and its complexes.

Antimicrobial activities

Antibacterial activities of ligand (L_1) and complexes were carried out against *E. coli*, *P. aeruginosa*, *S. typhi*, *S. aureu* and antifungal activities against *C. albicans* ATCC 12C, *C. albicans* ATCC P37037, *C. albicans* ATCC P37039, *C. neoformans* using Mueller Hilton agar solidified medium for bacterial strains and Sabouraud dextrose agar for the fungal strains. The disks impregnated test products were deposited on the surface of petri dishes seeded and incubated aerobically at 37°C for bacterial strains and at 25°C for fungal strains for 24 hours. The diameter (mm) of the area of inhibition around each disc was measured after 24 hours.

Antioxidant activity by DPPH radical scavenging activity

The 1, 1-Diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity was measured by spectrophotometric method at 517 nm. To a methanolic solution of DPPH (0.01 mmol) and garlic acid (GA), ligand(L_1) and complexes were added separately at different concentrations (0.5, 1.5, 2, 2.5 mg/mL) and an equal amount of methanol (2 mL) was added as control. After 30 min at 30°C, absorbance was measured. The activity was compared with that of garlic acid which was used as a standard antioxidant. The percentage of free radical scavenging was calculated by using the following equation.

$$\text{Percentage of scavenging activity} = \frac{A_o - A_e}{A_o} \times 100$$

Where A_o corresponds to the absorbance of DPPH without sample and A_e corresponds to the absorbance of sample with complex or ligand. A_o is the absorbance of sample containing only DPPH (blank). The % inhibitions were plotted against the respective concentrations used and from the graph, the the concentration causing 50% inhibition IC_{50} values were calculated [10-12].

RESULTS AND DISCUSSION

Complexes obtained by reaction of the some metals ions with 4-hydroxypent-3-en-2-ylideneaminophenol show different melting points than the ligand indicating that new compounds are formed. They are all coloured, non-hygroscopic and thermally stable suggesting a strong metal-ligand bond. The complexes are soluble in common polar solvents such as water, ethanol, methanol and acetone. The molar conductance values of complexes measured in water range from 121.2-277.1 $\Omega^{-1}\text{cm}^2 \text{mol}^{-1}$ suggesting that they are either 1:1 or 1:2 type electrolytes [13]. All analytical and physical data are shown in Table 1.

The azomethine IR band of the free ligand occurs at 1650 cm^{-1} . This band is shifted to 1610-1637 cm^{-1} on coordination, indicating the involvement of the azomethine nitrogen in coordination.

This is also confirmed by the presence of new bands around 491-409 cm^{-1} assigned to metal-Nitrogen bond [14]. The absence of the phenolic (-OH) band in all the spectra of the metal complexes suggests the involvement of the phenolic oxygen in bonding through deprotonation of the OH group. The band at 1250 cm^{-1} in the free ligand attributed to the =C-O stretch is shifted to about 1200 cm^{-1} in the complexes while new bands are observed at 528-580 cm^{-1} which could be assigned to the metal-oxygen bond.

The electronic absorption spectra of Mn(II) and Fe(III) complexes revealed bands at 23,809 cm^{-1} and 22,936 cm^{-1} respectively which can be attributed to the ${}^6A_{1g} \rightarrow {}^4T_{2g}$ (G) transition suggesting octahedral environment[15]. The spectrum of cobalt revealed two bands at 22,471 cm^{-1} and 19,230 cm^{-1} attributed for the ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transition also suggesting the octahedral geometry [15]. The electronic spectrum of Cu(II) complex shows bands at 22,727 cm^{-1} assigned ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transition indicated the square-planar geometry. The absence of any band below 10000 cm^{-1} excludes the possibility of tetrahedral geometry [16].

Table 1: Physical Properties and Elemental analytical data for L₁ and its Metal Complexes

Compound	Colour	Melting point °C	Molar conductance (ohm ⁻¹ cm ² mol ⁻¹)	Elemental analyses Expt. (Calc.)		
				C	H	N
L ₁ = C ₁₁ H ₁₃ NO ₂	Yellow	192 °C	—	69.21.(69.09)	6.75.(6.85)	7.35(7.32)
[MnL ₁ (H ₂ O) ₂]Cl ₂ (MnL ₁)	Reddish brown	>260 °C	131.7	37.52.(37.63)	4.13(4.31)	4.42(3.99)
[Fe L ₁ Cl(H ₂ O) ₂]Cl ₂ .H ₂ O (FeL ₁)	Rust brown	>260 °C	277.1	32.85(32.58)	3.92(4.23)	3.95(3.45)
[ZnL ₁ H ₂ O]SO ₄ .5H ₂ O (ZnL ₁)	Pale yellow	>260 °C	121.2	28.96(28.80)	4.35(5.05)	3.02(3.05)
[Co L ₁ (H ₂ O) ₃] Cl ₂ (CoL ₁)	Dark brown	160°C	138.4	35.48(35.41)	4.46(4.59)	3.72(3.75)
[Cu L ₁ H ₂ O](NO ₃) ₂ (CuL ₁)	Green	> 360 °C	134.7	34.85(33.47)	2.88(3.32)	10.85(10.64)

Thermo gravimetric analysis

The Thermogravimetric analysis of Fe(III) complex is used to exemplify the decomposition of these metal complexes and shows a mass loss at 78°C corresponding to the loss of lattice water molecule. The second mass loss obtained at 210°C (80 %) corresponds to the loss of Schiff base ligand which is probably decomposed into gases. At 465°C, the thermogram shows a residue representing 4% mass corresponding to the metal oxide residue [17-20].

The differential thermal analysis (DTA) curve shows endothermic processes at 75-110°C consistent with the loss of lattice water molecule and the endothermic processes at 150-250°C corresponding to the decomposition of Schiff base ligand and the formation of iron oxide residue.

Antimicrobial activity

The antimicrobial activities of the ligand L₁ and the transition metal complexes were evaluated for their *in vitro* antibacterial activities against *E. coli*, *P. aeruginosa*, *S. typhi*, *S. aureus*, and antifungal activities against *C. albicans* ATCC 12C, *C. albicans* ATCC P37037, *C. albicans* ATCC P37039 and *C. Neoformans*.

Antimicrobial activity was evaluated by measuring the diameter of the inhibition zones (mm) observed with respect to each microbial strain, using a calliper. Each test was performed three times and the results are shown on Table 2.

The ligand L₁ shows moderate activity on the bacteria *E. coli*, *P. aeruginosa*, *S. aureus*, and on the fungi strains, *C. albicans* ATCC12C because the DZI range between 10-24 mm.

The MnL₁ complex (L₁ =4-hydroxypent-3-en-2-ylideneaminophenol) showed low activity on both bacterial and fungal strains while CoL₁ and CuL₁ complexes exhibited moderate activity on most of the bacterial strains. FeL₁, CoL₁ and ZnL₁ complexes also showed moderate activity on some of the fungal strains. CuL₁ complex exhibited antifungal activities which were higher than the reference antibiotic.

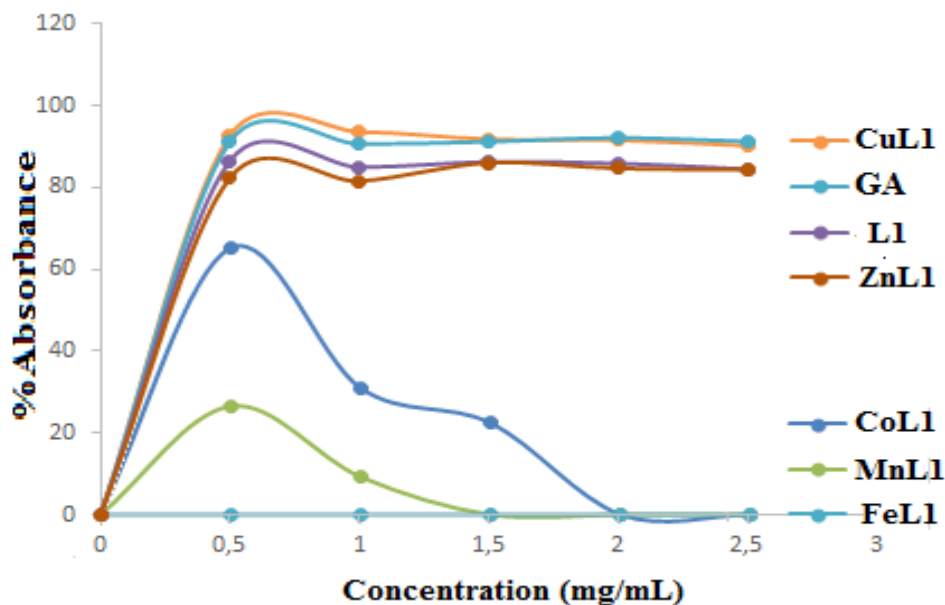
The DZI values of show that most of the metal complexes with 4-hydroxypent-3-en-2-ylideneaminophenol as ligand are active on the bacteria and yeast strains used for this study. It is clear from this study that coordination of the Schiff base affects the biological activity of the ligand. Coordination enhances the activity for CuL₁ while CoL₁, ZnL₁, FeL₁ and MnL₁ complexes showed less activity compared to the reference antibiotics and the ligand.

Table 2: Growth Inhibition Zone of Microbes in mm.

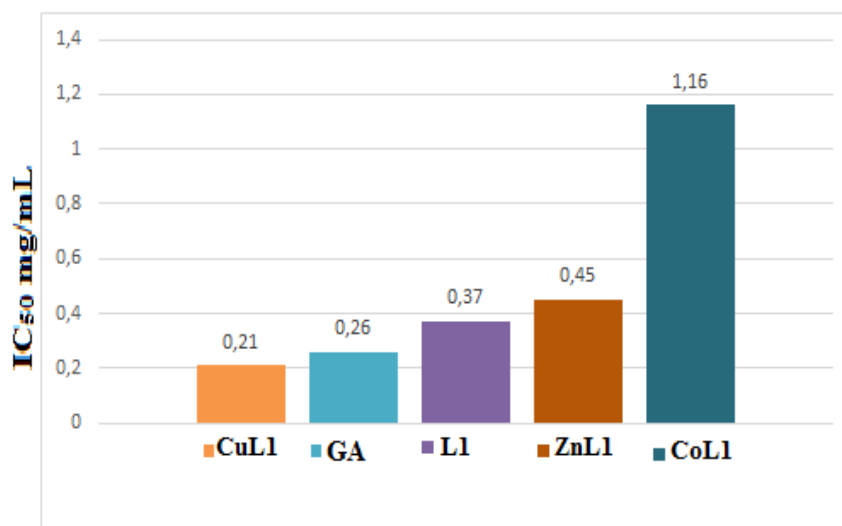
Compound	Bacteria				Fungi			
	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Salmonella typhi</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i> ATCC 12C	<i>Candida albicans</i> ATCC P37037	<i>Candida albicans</i> ATCC P37039	<i>Cryptococcus neoformans</i>
L ₁	17,5±0,70	12±0	0±0	11,5±0,70	24±0	5±7,07	0±0	6±0
MnL ₁	6±0	6±0	10,33±0,57	7±0	6±0	6±0	6±0	6±0
FeL ₁	7,66±1,15	6±0	11,33±0,57	6±0	12,66±1,15	13,66±1,15	6,66±0,57	6±0
CoL ₁	20±0	14±0	10±0	12,5±0,70	10,5±0,70	15,5±2,12	14±1,41	12,5±0,70
CuL ₁	12±1,41	12±0	0±0	11,5±0,70	30±5,65	22,5±2,12	26±0	10±0
ZnL ₁	7,33±0,57	6±0	6±0	8,66±1,15	9±0	13,33±0,57	7±0	6±0
Ciprofloxacin	14±0	28±1,73	30±0	29±1,73	/	/	/	/
Doxycycline	12±0	28,5±2,12	29±1,73	13,33±1,52	/	/	/	/
Fuconazole	/	/	/	/	19±3,46	19,66±0,57	29,66±0,57	12,66±1,15
Nystatine	/	/	/	/	28,33±1,52	12,33±0,57	19±1	15±0

The antioxidant (radical scavenging) activity of 1, 1- Diphenyl-2-picryl hydrazyl (DPPH)

Figures 1(a) and 1(b) show the free radical scavenging activity of Garlic Acid (GA), the Schiff base ligand L_1 and the transition metal complexes. At a concentration of 5 mg /mL, the scavenging activities of the CuL_1 , L_1 , ZnL_1 , CoL_1 and MnL_1 are 92.58, 86.44, 82.30, 66.02, 27.75% respectively, while at the same concentration, the activity of garlic acid (reference antioxidant) is 91.13 %. This means that CuL_1 , L_1 and ZnL_1 exhibited significant free radical scavenging activity. The scavenging activities of CoL_1 and MnL_1 were less significant. The IC_{50} of CuL_1 , L_1 , ZnL_1 , and CoL_1 are 0.21, 0.37, 0.45 and 1.16 mg/mL respectively. The IC_{50} of CuL_1 is less than the IC_{50} of GA which is 0.26 mg/mL suggesting that CuL_1 complex is more active. The order of the IC_{50} is thus, $CuL_1 > GA > L_1 > ZnL_1 > CoL_1$ with CoL_1 exhibiting the least antioxidant activity.



4a) The scavenging activity of the DPPH radical

4b) IC_{50} for GA, L_1 and M- L_1 complexesFigure 4: Free radical scavenging activity of the Garlic Acid (GA), the Schiff base ligand L_1 and the transition metal complexes**CONCLUSION**

The metal complexes of 4-hydroxyphenyl-3-en-2-ylideneaminophenol have tetrahedral and octahedral geometry and exhibited strong to moderate antibacterial activities. Cu(II) and Co(II) complexes are more effective as antibacterial agents than their precursor ligand. These compounds can serve as good targets for the design of antimicrobial

agents. All the compounds showed varying antioxidant (free radical scavenging) activities when compared to garlic acid.

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