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Spectroscopic and Antimicrobial Studies of Cu(II) and Zn(II) Complexes of a Schiff Base derived from 2-Acetylpyridine with 4-Phenylthiosemicarbazide.

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Abstract

Interaction of Cu(II) and Zn(II) metal salts in (2:1 molar ratio) with a Schiff base derived from the condensation of 4-phenylthiosemicarbazide with 2-acetylpyridine in (1:1 molar ratio) ethanol, produced Schiff base (2)-*N*-phenyl-2-[1-(pyridin-2-yl)ethylidene]hydrazine-1-carbothioamide(2-acetylpyridine-4-phenylthiosemicarbazone)(AP-PTSC) Cu(II) and Zn(II) complexes. The Schiff base and its Cu(II) and Zn(II) complexes were characterized based on melting point/decomposition temperature, solubility, magnetic susceptibility, infrared spectra, molar conductance measurements, elemental and gravimetric analyses. The Cu(II) and Zn(II) complexes show moderate values of decomposition temperatures. The Schiff base and the complexes were soluble in some common organic solvents. Infrared spectral data of the Schiff base and its complexes, indicated coordination of the Schiff base to the metal (II) ion via azomethine nitrogen. The effective magnetic moment of the Cu(II) and Zn(II) complexes suggested an octahedral geometry. The molar conductance values of the complexes show that the complexes are electrolytes. The results of the elemental analysis of the ligand and its complexes are in good agreement with the calculated values, suggesting a 1:2 (metal-ligand) ratio. Antimicrobial screenings of the ligand and its complexes were conducted against gram-positive (*Staphylococcus aureus,*) and two gram-negative (*Salmonella typhii, and Escherichia coli*) bacteria specie. Also three fungi mainly (*Candida albicans*, *Mucus indicus and Aspergillus flavus*) were used. The results showed that both the ligand and the complexes are active against the specie used.

Keywords: Schiff base, 4-phenylthiosemicarbazide, 2-acetylpyridine, magnetic susceptibility, elemental analysis.

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Introduction

The easy preparation of Schiff base compounds arise interest in their study. They are prepared by condensation of primary amines with carbonyl compounds (Pierra, 1987). Schiff bases are organic compounds with varying applications in several fields of chemistry and biochemistry Singh *et al*. (1999). They serve as catalysts in the oxidation of cyclo-octene and tetraline in the presence of benzoic anhydride (Nishinaga *et al*., 1989). Ethylene diammine derivative Schiff bases have been useful in photochemical degradation of natural rubber

(Beokon *et al*., 2004). Schiff bases derived from salicylaldehydes and boronate have antifungal activities against *Aspergilus niger* and *Asperglus flavus* (Zhang *et al*., 2005).

A special class of Schiff base is that of thiosemicarbazone derivatives, as their sulphur (S) donor sites are particularly useful for transition metals in the formation complexes, (Abou-Melha *et al*., 2008). The versatile biological activity and prospective use of thiosemicarbazones and their metal complexes as drugs have been widely explored for nearly 50 years (Cowley *et al*., 2002). The ability of their molecules to chelate with traces of metals in the biological system is believed to be a reason f or their activity (Husain *et al*., 2008).2,4-dihydroxy benzaldehyde-4-phenyl 3-thiosemicarbazone (DHBPTSC) Schiff ba se with its Pd(II), Ni(II) and Cu(II) complexes exhibit some significant antibacterial and antifungal activities against *Bacillus subtilis*, *Escherichia Coli*, *Pseudomonas fluorescencs*, *Staphylococcus aureus*, Aspergillus niger and *candida albicans* (Asha-Kumar *et al.,* 2018). macrocyclic complexes of copper(II), nickel(II) and cobalt(II) derived from α and β- diketones and 2,6-diaminopyridine exhibited enhance biological activity (Singh *et al.,* 2006). copper(II) complexes obtained from condensation of salicylaldehyde and o-vanillin with 2- and 3-aminopyridine and 2- and 3-(aminomethyl) pyridine respectively, demonstrated a good antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtillis*, *Escherichia coli* and *Candida albican* using agar diffusion (Abdullahi *et al.,* 2018). 3-aminopyridine-2 carboxaldehyde thiosemicarbazone (Triapine) shows enhance *in vitro* antiproliferative activity in two human cancer cell lines (41M and SK-BR-3), (Kowol *et al*., 2009).

Materials and Method

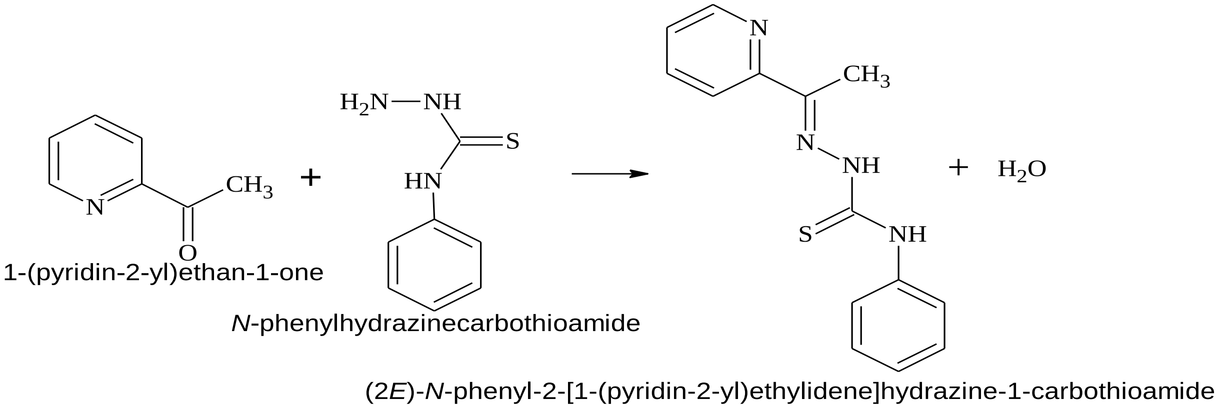
All the chemicals used in this work were of Analar Grade and were used without further purification. Glass wares used for the preparation were thoroughly washed with detergent, rinsed with distilled water and dried in an oven. The main chemicals; 4-phenylthiosemicarbazide and 2-aceltylpyridine, were all purchased from Sigma Aldrich U. K.

All weighing was carried out using Electrical Meter Balance AB 54. Magnetic susceptibility measurements of the complexes were determined using Sherwood Scientific MSB MK1 Magnetic Susceptibility Balance. Melting point/decomposition temperatures were determined using a digital WRS-IB Microprocessor Melting Point Apparatus. Infrared spectral analyses were recorded using Shimadzu FTIR-8400S Fourier Transform Infrared Spectrophotometer in the range 4500-250 cm^{-1}. Molar conductivity measurements were carried out using George Kent model 5003 conductivity meter. Metal and Elemental Analysis of C, H and N were carried out at Robertson Microlit Laboratories, New Jersey (U.S.A).

All the microbial isolates used in this study were obtained from the Department of Medical Microbiology, Aminu Kano Teaching Hospital Kano, and identified at the Department of Microbiology. The antimicrobial screening was conducted in the Department of Microbiology, Bayero University Kano. Standard drugs; Ciprofloxacin for bacteria and Ketoconozole for fungi as reference standards were obtained from Department of Microbiology, Bayero University, Kano. Mueller Hinton agar and Potato dextrose were used as growth media for the microbes.

Preparation of Schiff base (AP-PTSC)

2-acetylpyridine (0.01 mol, 1.12 cm^3) was added drop wise to a hot solution of 4-phenylthiosemicarbazone (1.67 g, 0.01 mol) in ethanol (70 cm^3), followed by the addition of 3 drops of acetic acid. The mixture was refluxed with constant stirring for 2 hours. The solution was transferred into a refrigerator at 5°C for 24 hours. The precipitate obtained was filtered off, washed several times with ether and dried over P_2O_5 in a desiccator for three days (Scovill *et al*., 1982).



Scheme 1: Preparation of AP-PTSC Schiff base

Preparation of the Schiff base metal (II) complexes

Cu(II) and Zn(II) complexes for the Schiff base (AP-PTSC) derived from 2-acetylpyridine with 4-phenyl thiosemicarbazide, were prepared by the addition of 0.002 mol of the Schiff base in 20 cm^3ethanol to the solution containing 0.001 mol of each of the metal(II) salts in 10cm^3 ethanol. Each of the mixture was then refluxed for 3 hours with stirring. On cooling, the precipitate obtained was filtered, washed with diethyl ether and dried over P_2O_5 in a desiccator for three days (Gehad *et al.*, 2006).

Determination of Melting point/ Decomposition Temperature

The melting point of the Schiff base and the decomposition temperature of the metal(II) complexes were determined using microprocessor melting point apparatus (WRS-IB) and Gallenkamp melting point apparatus (Aliyu and Zayyan, 2013).

Solubility Test

The solubility of the Schiff base and each of its metal(II) complexes was tested using common organic solvents and distilled water. 20 mg of each compound was tested in 5 cm^3 of each of the corresponding solvent in a test tube, shaken thoroughly (Saha *et al.*, 2009).

Magnetic Susceptibility Measurement

The magnetic susceptibility (χ_g) of complexes was determined using magnetic susceptibility balance MKI Sherwood science Ltd via equation 1 (Lancashire, 2000).

$$\chi_g = \frac{CL\,(R_1-R_0)}{m\times10^9} \;\ldots\ldots\ldots (1)$$

Where; m= sample mass (g) = $W_1 - W_0$, W_0 = weight of empty capillary tube, W_1 = weight of the capillary tube and the complex, R_o = initial reading from the balance for empty capillary tube, R_1= reading from the balance for the loaded capillary tube, L = length of the complex in the capillary tube (cm). C = balance calibration constant (C = 1).

Infrared Measurements

Shimadzu FTIR-8400S Fourier Transform Infrared Spectrophotometer in the range 250-4500cm^{-1} was used. A small amount of powder sample (about 1-2% of KBr amount) was taken and mixed with KBr powder and then analyzed using infrared analyzer. The results obtained are shown in Table 4.

Molar Conductance Measurement

Molar conductivity measurements were carried out on 1 x 10^{-3} $moldm^{-3}$(0.001M) solution of each of the metal complexes in Dimethyl Formamide (DMF) at 25°C. The molar conductance is calculated using equation 4, (Mohd, *et al.*, 2013).

$$\Lambda_M = \frac{1000L}{C} \ldots\ldots.(4)$$

Where Λ_M = molar conductance, L = specific conductance and C = concentration of the complex.

Elemental Analysis

The analysis was carried out using Perkin-Elmer CHN 2400 Elemental Analyzer based on the classical Pregl-Dumas method. About 20 mg of each of the samples for analysis was encapsulated in an aluminium vial and inserted automatically into the Combustion Zone of the analyser using a single-sample auto injector. In the presence of excess oxygen and combustion reagents, the samples were combusted completely and reduced to the elemental gases CO_2, H_2O and N_2. All the results were computed automatically and were given as percent weight of each element.

Estimation of Metals in the Complexes

About 0.2000 g of each metal complex was placed in a 100 cm^3 beaker followed by 12.5 cm^3 of 20% nitric acid and heated to about dryness. The content of the beaker was allowed to cool to room temperature and 12.5 cm^3 of distilled water was added while stirring. The content of the beaker was filtered and the filtrate was subjected to further analysis (Vogel, 1972).

Estimation of Copper (II) ion in $[Cu(AP\text{-}PTSC)_2]Cl_2$

The percentage composition by weight of copper in the complex was calculated using gravimetric factor in equation 2 and the results obtained are shown in Table 6.

Estimation of Zinc (II) ion in $[Zn(AP\text{-}PTSC)_2]Cl_2$

The percentage composition by weight of zinc in the complex was calculated using gravimetric factor in equation 3 and the results obtained are shown in Table 6

$$\text{G. F of Zn} = \frac{\text{Atomic weight of Zn}}{\text{Molar mass of Zn}[Hg(SCN)4]} \ldots\ldots\ldots (3)$$

Antimicrobial Test

The *In vitro* antimicrobial activity of the ligand (AP-PTSC) and its complexes were tested against Gram-positive (S*taphylococcus aureus*,) and two Gram-negative (*Salmonella typhii*, and *Escherichia coli*) pathogenic bacteria. Also three fungi mainly (*Candida albicans*, *Mucus indicus* and *Aspergillus flavus*) were used. Muller Hilton Agar media for bacteria while Potato Dextrose Agar (PDA) for fungi were used and were prepared in distilled water. The ligands and the complexes were dissolved separately in Dimethyl Sulphoxide (DMSO) to obtain three different concentrations (15 µg/ml, 30 µg/ml and 60 µg/ml), which were used to check the antimicrobial activities by well diffusion method. The discs were saturated with the dissolved compounds in Dimethylsulfoxide (DMSO) and then placed in petridishes containing the culture media. The petridishes were incubated at 37ºC and the inhibition zone was measured after 24hours for bacterial strain and 48hours for fungal isolates and compared with standard drugs (Ciprofloxacin for bacteria and Ketoconozole for fungi), Tables 7 and 8, (Sheikh *et al.*, 2004). The magnetic susceptibility as presented in (Tables 3) is 1.9BM for $[Cu(AP\text{-}PTSC)_2]Cl_2$, indicating a paramagnetic high spin octahedral geometry but $[Zn(AP\text{-}PTSC)_2]Cl_2$ has 0.0BM , showing its diamagnetic nature (Gehad *et al.*, 2006).

Results and Discussion

Reaction between4-phenylthiosemicarbazide with 2-acetylpyridine in (1:1 molar ratio) in ethanol produced a Schiff base; 2-acetylpyridine-4-phenylthiosemicarbazone (AP-PTSC). Cu(II) and Zn(II) complexes were synthesized from this Schiff base in (2:1 molar ratio) in ethanol.

Physico-Chemical Properties of the Schiff Base and its Metal(II) Complexes.

The Schiff base is yellow powder with a yield of 86.8% and a melting point of 170ºC. The complexes $[Cu(AP\text{-}PTSC)_2]Cl_2$ and[$Zn(AP\text{-}PTSC)_2]Cl_2$ are green and pale yellow with decomposition temperature of 232ºC and 265ºC, a yield of 82.4% and 75.5% (Table 1). The variation in colour of the Schiff base with its corresponding complexes indicates coordination of the Schiff base with the metal ions. The colour of the compounds is attributed to 'd-d' orbital transition of electron between one energy level to another, by their magnitude of splitting, which in turn depends on the geometry of the complex, the nature of the ligand and charge transfer (Rodgers, 1994). The decomposition temperatures of the complexes are relatively high, indicating good thermal stability of the complexes.

Both the Schiff base and its complexes are soluble in acetone, dichloromethane, chloroform and DMSO but slightly soluble in methanol and ethanol (Tables 2). The solubility of the Schiff bases and their metal(II) complexes in the common solvents indicated their low polarity which can be used to determine the suitable solvents that could be utilized for subsequent spectroscopic measurements (Jones and Fleming, 2010).

The magnetic susceptibility as presented in (Tables 3) is 1.9BM for $[Cu(AP\text{-}PTSC)_2]Cl_2$, indicating a paramagnetic high spin octahedral geometry but $[Zn(AP\text{-}PTSC)_2]Cl_2$ has 0.0BM , showing its diamagnetic nature (Gehad *et al*., 2006).

Table 1: Physical Properties of (AP-PTSC) Schiff Base and its Metal (II) Complexes

Ligand/Complex	Colour	Melting point (°C)	Decomposition Temperature (°C)	Percentage (%) Yield
AP-PTSC	Yellow	170	-	86.8
$[Cu(AP\text{-}PTSC)_2]Cl_2$	Green	-	232	82.4
$[Zn(AP\text{-}PTSC)_2]Cl_2$	pale yellow	-	265	75.5

AP-PTSC = Schiff base derived from 2-acetylpyridine and 4-phenylthiosemicarbazide.
$[M(AP\text{-}PTSC)_2]Cl_2$ = Metal (II) complex for the Schiff base derived from 2-acetylpyridine and 4-phenylthiosemicarbazide, where M = Cu or Zn(II) ion.

Table 2: Solubility Data of (AP-PTSC) Schiff Base and its Metal(II) Complexes

Ligand/Complex	Water	Methanol	Ethanol	n-hexane	Ether	Acetone	Dichloromethane	Chloroform	DMSO	Benzene
AP-PTSC	IS	SS	SS	IS	IS	S	S	S	S	IS
$[Cu(AP\text{-}PTSC)_2]Cl_2$	IS	SS	SS	IS	IS	S	S	S	S	IS
$[Zn(AP\text{-}PTSC)_2]Cl_2$	IS	SS	SS	IS	IS	S	S	S	S	IS

Key: IS => Insoluble, SS =>Slightly Soluble, S => Soluble

Table 3: Magnetic Susceptibility Values of AP-PTSC Metal (II) Complexes

Complex	Gram susceptibility $(X_g)10^{-6}$	Molar Magnetic Susceptibility $(Xm)10^{-3}$	Magnetic Moment μ_{eff}(B.M)	Magnetic Property
[Cu(AP-PTSC)2]Cl2	2.38	1.59	1.9	Paramagnetic
[Zn(AP-PTSC)2]Cl2	−0.35	-24.2	0.0	Diamagnetic

$[M(AP\text{-}PTSC)_2]Cl_2$,=>Metal (II) complexes of Schiff base derived from 2-acetylpyridine and 4-phenylthiosemecarbazide, where M= Cu or Zn(II) ion.

Table 4: Infrared Spectra Data of AP-PTSC and its Metal (II) Complexes

Compounds	**υ (C=N) (cm^{-1})**	**υ (N-H) (cm^{-1})**	**υ (C=S) (cm^{-1})**	**υ(M-N) (cm^{-1})**	**υ(M-S) (cm^{-1})**
AP-PTSC	1648	3296	766	-	-
[Cu(AP-PTSC)$_2$]Cl$_2$	1592	3315	759	569	397
[Zn(AP-PTSC)$_2$]Cl$_2$	1622	3403	754	453	394

AP-PTSC=> Schiff base derived from 2-acetylpyridine and 4- phenylthiosemecarbazide, [M(AP-PTSC)$_2$]Cl$_2$,=>Its Metal (II) complexes where M= Co, or Ni(II) ion.

Table 5: Molar Conductance Measurement for AP-PTSC Metal (II) Complexes

Compound	**Conc. Moldm^{-3} x 10^{-3}**	**Specific Conductance x 10^{-4} SΩ^{-1}**	**Molar Conductance Ω^{-1}cm^{2}mol^{-1}**
[Cu(AP-PTSC)$_2$]Cl$_2$	2.07	2.87	138.41
[Zn(AP-PTSC)$_2$]Cl$_2$	2.36	1.98	83.78

AP-PTSC=> Schiff base derived from 2-acetylpyridine and 4- phenylthiosemecarbazide, [M(AP-PTSC)$_2$]Cl$_2$,=>Its Metal (II) complexes where M= Co, or Ni(II) ion.

Table 6: Elemental Analysis of AP-PTSC and its Metal(II) Complexes

Ligand/Complex	%C (Calc) Found	%H (Calc) Found	%N (Calc) Found	%M (Calc) Found
AP-PTSC	(62.20) 62.40	(5.22) 5.70	(20.72) 20.80	
[Cu (AP-PTSC)$_2$]Cl$_2$	(49.81) 49.60	(4.18) 4.30	(16.60) 16.40	(9.41) 9.22
[Zn (AP-PTSC)$_2$]Cl$_2$	(49.67)	(4.17)	(16.55)	(9.66) 9.84

Table 7: Zone of Inhibition (mm) for Antibacterial of AP-PTSC and its Metal(II) Complexes

Isolate	*Staphylococcus aureus* (µg/disc)			*Escherichia coli* (µg/disc)			*Salmonella typhirium* (µg/disc)		
Compd/conc.	15	30	60	15	30	60	15	30	60
AP-PTSC	6	8	11	7	9	11	6	8	10
[Cu(AP-PTSC)$_2$]Cl$_2$	6	9	14	8	13	15	9	11	13
[Zn(AP-PTSC)$_2$]Cl$_2$	6	6	6	9	11	13	6	9	14
Ciproflaxacin (At all conc.)		34			40			43	

Table 8: Zone of Inhibition (mm) for Antifungal of AP-PTSC and its Metal(II) Complexes

Isolate	*Mucus (indicus specie)* (µg/disc)			*Aspergillus flavus* (µg/disc)			*Candida Albican* (µg/disc)		
Compd/conc.	15	30	60	15	30	60	15	30	60
AP-PTSC	7	8	11	6	6	6	7	10	13
$[Cu(AP\text{-}PTSC)_2]Cl_2$	8	12	13	8	10	15	9	11	15
$[Zn(AP\text{-}PTSC)_2]Cl_2$	6	8	11	6	7	9	8	13	15
Ketoconozole (At all conc.)		27			32			38	

AP-PTSC=> Schiff base derived from 2-acetylpyridine and 4- phenylthiosemecarbazide, $[M(AP\text{-}PTSC)_2]Cl_2$,=>Its Metal (II) complexes where M= Co, or Ni(II) ion.

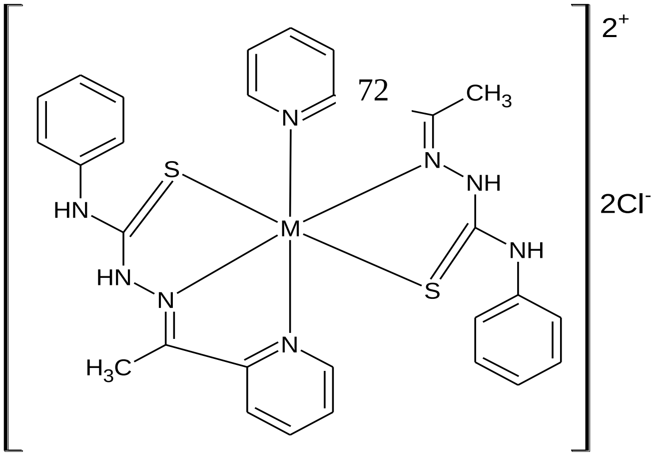
The Schiff base shows a broad band spectrum at 1648cm^{-1}, that is attributable to υ(C=N) stretching vibration, which is shifted downward in the spectra of the complexes at range of 1592-1622 cm^{-1}. This indicates coordination of the Schiff base to the metal ions via azomethine nitrogen. The spectrum of the Schiff base at 3296 cm^{-1} assignable to υ(N-H) stretching vibration shifted upward in the spectra of the complexes at 3315 cm^{-1} and 3402 cm^{-1}, which resupports coordination of the Schiff base to the metal(II) ion. The band spectra of the complexes at region of 453-569 cm^{-1} and 394-397 cm^{-1} are assignable to υ(M-N) and υ(M-S) respectively, is another indication for the coordination of the Schiff base to the metal(II) ion, (Awadelkareem *et al.*, 2012), (Tables 4).

The molar conductivities of $[Cu(AP\text{-}PTSC)_2]Cl_2$ and $[Zn(AP\text{-}PTSC)_2]Cl_2$ were carried out in DMF and their 10^{-3} M solutions are 138.41Ω^{-1}cm^{2}mol^{-1} and 83.78 Ω^{-1}cm^{2}mol^{-1} respectively as shown in (Table 5). These values indicate electrolytic nature of the complexes, (Gehad *et al.*, 2006; Mohd, *et al.,* 2013).

The results of the elemental analysis (C, H and N) of the Schiff base and its respective metal(II) complexes are as presented in Table 6. The values are in agreement with the proposed formulas of the ligand, and its corresponding metal complexes, suggesting 2:1(ligand-metal ratio).

Antimicrobial test of the AP-PTSC Schiff base and its metal(II) complexes were carried out against three bacteria isolates; Gram-positive (*Staphylococcus aureus,*), Gram-negative (*Salmonella typhii, and Escherichia coli*) and three fungi (*Candida albicans, Mucus indicus and Aspergillus flavus*). Concentrations of 15, 30 and 60(µg/disc) were used, standard drugs ciproflaxacin and ketoconozole for bacteria and fungi, were served as controls, (Tables 7-8). The results of the tests indicated moderate antimicrobial activity against the tested microorganisms when compared with the standards, and this activity increases by increasing concentration. Also the metal complexes showed higher activity than free ligand except for $[Zn(AP\text{-}PTSC)_2]Cl_2$ whose antibacterial activity against *Staphylococcus aureus* at all concentrations is lower than that of its Schiff base and its antifungal activity against *Mucus indicus* at concentration 15(µg/disc) is also lower than that of the Schiff base. However, the activities of both the ligand and the complexes are less than that of the standard drugs used. The activities of the synthesized compounds can be explained on the basis of chelation theory, which states that; the chelation tends to make the complex acts as a more powerful and potent bactericdal or bacteriostatic agent than the ligand (Sengupta *et al.,* 1998).

From the results of analysis of the complexes and the available literature data, the general molecular structure below is proposed:



Where M= Co or Ni,

Figure 1: Proposed Structure of 2-acetylpyridine-4-phenylthiosemicarbazone (AP-PTSC) Metal(II) Complexes.

Conclusion

Schiff base (2)-*N*-phenyl-2-[1-(pyridin-2-yl) ethylidene] hydrazine-1-carbothioamide i.e (2-acetylpyridine-4 phenylthiosemicarbazone) (AP-PTSC) together with its Cu(II) and Zn(II) complexes were successfully synthesized and characterized. The decomposition temperature indicates the good stability of the complexes. The IR values assignable to υ(N-H) and υ(C=N) stretching vibrations show coordination of the ligand to the metal ion via azomethine nitrogen. Molar conductance values range from 138.41 $\Omega^{-1}cm^2mol^{-1}$ and 83.78 $\Omega^{-1}cm^2mol^{-1}$, showing that the solutions of the complexes are electrolytes. The values of the magnetic susceptibility of the complexes indicated an octahedral geometry. The elemental analysis values indicate 2:1(ligand-metal ratio). The antimicrobial test shows that both the ligand and the complexes have good activities against the isolates used, finally the structures of the complexes have been proposed.

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