ChemSearch Journal 7(2): 34 – 39, December, 2016
Publication of Chemical Society of Nigeria, Kano Chapter

Received: 22/11/2016 Accepted: 13/12/2016
http://dx.doi.org/10.4314/csj.v7i2.7

Synthesis, Characterization and Antimicrobial Activities of a Schiff Base Derived from Phenylalanine and Acetylacetone and its Mn(II), Ni(II) and Cu(II) Complexes

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ABSTRACT

Complexes of Cu(II), Ni(II) and Mn(II) with a Schiff base derived from condensation reaction of phenylalanine and acetylacetone have been synthesized and characterized analytically and spectroscopically. Melting point of the Schiff base was 188°C and the complexes decompose within a temperature range of 210-242°C. The molar conductance values of the complexes were found to be within 15.0-60.0Ω^{-1}cm^{2}mol^{-1} range while the magnetic moment values indicated the complexes to be paramagnetic. The Infrared spectra of the Schiff base showed the azomithine peak at 1605cm^{-1} which shifted to 1595-1637cm^{-1} in the complexes. The analytical and spectral studies revealed that all the metal complexes are in 1:2 Metal-Ligand ratios, with the Schiff base acting as a tridentate ligand towards metal ion via azomethine-N, deprotonated-O of carboxylic group and enolic-O group of acetylacetone. The synthesized ligand and its respective metal (II) complexes were screened for their antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Gram-negative) bacterial strains and antifungal activity against *Candida albicans, Fusarium solani* and *Aspergillus fumigatus.* The results revealed that, the Schiff base and the metal complexes showed significant antibacterial and antifungal strength at high concentrations.

Keywords: Acetylacetone, Schiff base, complex, antimicrobial, characterization

INTRODUCTION

Amino acids are good examples of bioligands which contain a combination of an amine and a carboxylic acid group which make them versatile ligands for complex formation. The presence of amine makes amino acids good candidates for condensation reaction with an array of carbonyl compounds forming a corresponding array of Schiff bases. A number of such Schiff bases have been synthesized (Zahraa, *et al* 1012, Nursen and Perihan, 2004) and have attracted a great deal of interest in the chemistry of metal complexes for their physiological and other pharmacological applications (Prakash and Adhikari, 2011, Anna *et al* 1984). They show a significant biological activity (Abu-Dief and Mohamed, 2015) and have a great ability of forming stable complexes with transition metals ions due to the presence of oxygen and nitrogen which are excellent donor atoms.

On the other hand, acetylacetone is an organic compound that famously exists in two tautomeric forms that rapidly interconvert. It served as a building block for the synthesis of heterocyclic compounds. It may undergo condensation reaction between its ketone moiety and that of amine group of amino acid to form the desired ligand with azomethine (-HC=N-) linkage (Misbah *et al.*, 2013). The chemistry of Schiff bases and their complexes will continue to attract the interest of researchers despite their enormous report in literature (Andreea *et al* 2011, Merajuddin *et al* 2014) and several reviews have been reported (Gufta, *et al*, 2012, Prakash and Adhikari, 2011, Abu-Dief and Mohamed, 2015). These are connected to the versatility of these compounds in inorganic synthesis as well as their numerous applications in biology (Annapoorani and Krishnan, 2013), pharmacology (Cleiton *et al* 2011), industries (Shalin *et al*, 2009) etc.

In continuation of our work on the amino acids Schiff base, we here report the synthesis of phenylalanine and acetylacetone Schiff base and its complexes with Mn (II), Ni (II), and Cu (II) ion. In addition we also report the antimicrobial activities of the Schiff base and the complexes.

MATERIALS AND METHODS

All chemicals and solvents used were of analytical grade and were used without further purification. The glass wares used were washed with detergent, rinsed with distilled water and dried in an oven at 110°C before use. All weighing were carried out on an electric mettle balance model

H_3OAR, melting points/decomposition temperature were determined using Galenkemp melting point apparatus. Molar conductance measurements were carried out in DMSO using Jenway conductivity meter 4010 model. Microbial activity studies were carried out at the microbiology Department, Bayero University Kano, Nigeria.

Synthesis of the Schiff base (ligand)

Acetylacetone (0.12 g, 1.2 mmol), phenylalanine (1.0 mmol) and potassium hydroxide (0.056 g, 1.0 mmol) were mixed in 50mL methanol. The mixture was then magnetically stirred under reflux for 6 hours. The volume of the obtained solution was reduced on water bath, the precipitate obtained was filtered and then washed with cold ethanol and then with anhydrous diethyl ether at room temperature and then dried in air (Zahraa *et al*, 2012).

Synthesis of the Schiff base complexes

A hot solution (60°C) of the appropriate metal (II) chloride (1 mmol) in an ethanol (25 mL) was added to the solution of the Schiff base (2 mmol) in the same solvent (25mL). The resulting mixture was stirred under reflux for 3hrs where upon the complexes precipitated. It was collected by filteration, washed with ethanol, followed by diethyl ether and dried in an oven at 110°C (Gehad *et al*, 2006).

Antibacterial activity test

The ligand and complexes were dissolved separately in DMSO to have three different concentrations (250µg, 500µg and 1000µg) per disc. They were placed on the surface of the culture media (nutrient agar) and incubated at 37°C for 24hrs. Then *in vitro* antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa and Klebsiella pneumoniae* (Gram-negative) of the ligand and its complexes were carried out by disc diffusion method. The diameter of zone of inhibition produced by the ligand and complexes were compared with the standard (Yusha'u and Sadisu, 2011).

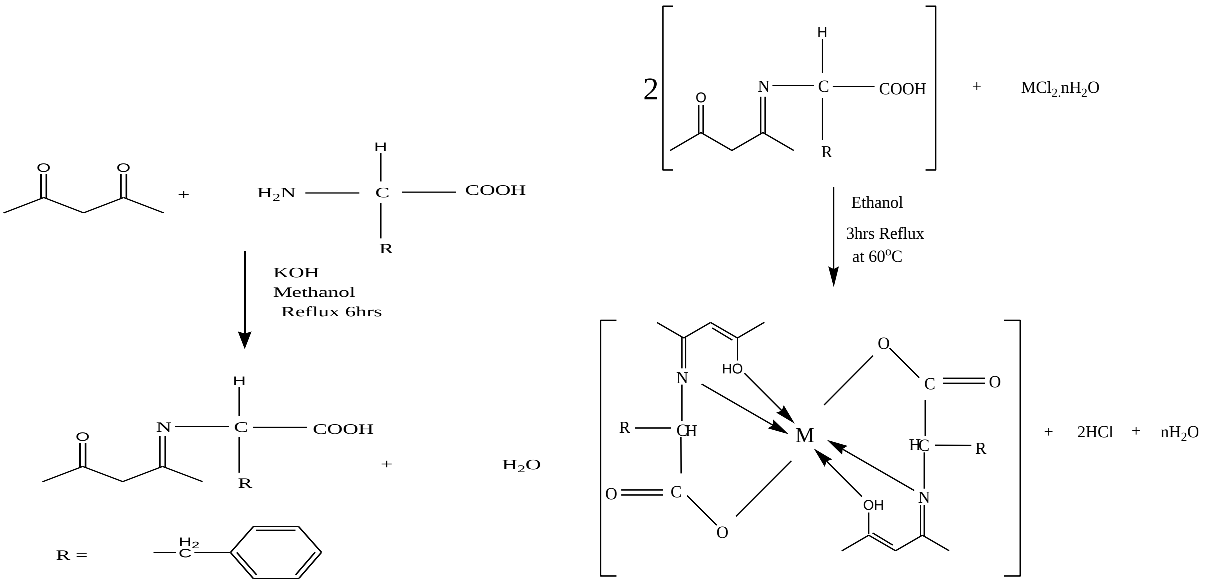
Antifungal activity test

The ligand and complexes were dissolved separately in DMSO to have three different concentrations (250µg, 500µg and 1000µg) per disc. They were placed on the surface of the culture media (sabouraud dextrose agar) and incubated at room temperature for 48hrs. Then in vitro antifungal activity against *Candida albicans, Fusarium solani and Aspergillus fumigatus* of this ligand and complexes were carried out by disc diffusion method. The diameter of zone of inhibition produced by the ligand and complexes were compared with the standard (Hassan *et al.*, 2006).

RESULTS AND DISCUSSION

Synthesis and physicochemical studies

The Schiff base and the Mn(II), Ni(II) and Cu(II) complexes were synthesized according to scheme 3.1. The formation of the Schiff base was marked with appearance of coloured precipitate from clear colourless starting materials. The observed physical data of the Schiff base and the complexes are as shown in Table 3.1.



Scheme 3.1: Synthesis of the Schiff Base and the Metal Complexes

Table 3.1: Physical properties of Schiff base and its metal (II) complexes

Compound	% Yield	Colour	Melting Point Temp (^oC)	Decomposition Temp (^oC)
$C_{14}H_{17}NO_3$	74.49	Brown	188	-
$[Cu(C_{14}H_{16}NO_3)_2]$	65.29	Deep green	-	210
$[Ni(C_{14}H_{16}NO_3)_2]$	64.29	Light green	-	290
$[Mn(C_{14}H_{16}NO_3)_2]$	64.97	Light brown	-	242

The Schiff base was reasonably thermally and air stable with melting point of 188°C which greatly improved on complexation as can be seen in Table 3.1. The metal complexes were soluble in water, methanol, ethanol and DMSO but insoluble n-hexane and ether (Table 3.2). This clearly indicated that the ligand and its complexes are soluble in polar solvent but insoluble in non polar solvent, which might be connected to the carboxylic polar end of the Schiff base and the strong polar nature of the complexes.

Molar conductance of the complexes was determined using procedure reported by Geary, 1971 and the results obtained indicated a low value for all the complexes synthesized. The values are within the range of 4.50-60$\Omega^{-1}cm^2mol^{-1}$ suggesting their non electrolytic status (Table 3.3) in agreement with similar complexes in the literature (Gufta *et al*, 2012).

Table 3.2: Solubility test of Schiff base and its metal (II) complexes

Solvent	$C_{14}H_{17}NO_3$	$[Cu(C_{14}H_{16}NO_3)_2$	$[Ni(C_{14}H_{16}NO_3)_2$	$[Mn(C_{14}H_{16}NO_3)_2$
Water	S	S	S	S
Methanol	S	S	S	S
Ethanol	S	S	S	S
Ether	IS	IS	IS	IS
DMSO	S	S	S	S
n-hexane	IS	IS	IS	IS
DMF	S	S	S	S
Chloroform	S	S	S	S
Dichloromethane	SS	S	SS	S
Acetonitrile	IS	SS	IS	SS

Key: S-Soluble SS- Slightly Soluble IS- Insoluble

Values of room temperature magnetic susceptibility measurements (Table 3.4) shows that the metal (II) complexes synthesized herein were all paramagnetic. Cu(II) complex has the magnetic moment value of 2.12B.M which is within the range normally observed for octahedral Cu(II) complexes (Gehad *et al*., 2006). Ni(II) complex magnetic moment value of 3.05B.M also as expected is within the normal range of values observed for octahedral Ni(II) complexes (Gehad *et al*., 2006). The Mn(II) complex was found to have the highest magnetic moment value of 5.50B.M which is consistent with d^5 system and are also within the range of values obtained for octahedral Mn(II) complexes (Nora, 2011). The results are in good agreement with increasing number of unpaired electrons available in these complexes.

Table 3.3: Molar conductivity test of metal (II) complexes

Compound	Electrical Conductivity ($\Omega^{-1}cm^{-1}$)	Molar Conductivity ($\Omega^{-1}cm^{2}mol^{-1}$)
$[Cu(C_{14}H_{16}NO_3)_2]$	15.00×10^{-6}	15.00
$[Ni(C_{14}H_{16}NO_3)_2]$	60.00×10^{-6}	60.00
$[Mn(C_{14}H_{16}NO_3)_2]$	21.00×10^{-6}	21.00

Table 3.4: Magnetic Susceptibility value of the metal (II) complexes

Complex	Xg (g^{-1})	Xm (mol^{-1})	μ_{eff} (B.M.)
$[Cu(C_{14}H_{16}NO_3)_2]$	3.40×10^{-6}	0.0019	2.12
$[Ni(C_{14}H_{16}NO_3)_2]$	6.83×10^{-6}	0.0038	3.01
$[Mn(C_{14}H_{16}NO_3)_2]$	23.2×10^{-6}	0.0127	5.50

IR spectral Studies

The IR spectra of the free Schiff base ligand and that of the complexes are as shown in Table 3.5. Upon comparison, the azomethine stretching vibration on the Schiff base at 1605cm^{-1} has shifted up to 1636cm^{-1} in the complexes suggesting participation of the azomethine nitrogen in coordination. Two new absorption bands at 743-837cm^{-1} and 527-623cm^{-1} absent in the free Schiff base support the formation of M-N and M-O bonds. These data suggest that the azomethine –N, carboxylate –O and enolic –O groups are involved in coordination with the metal (II) ion in the complexes.

Table 3.5: IR Spectral Data for Schiff base and its Metal (II) Complexes

Compound	v(C=N) cm^{-1}	v(M-O) cm^{-1}	v(M-N) cm^{-1}
$C_{14}H_{17}NO_3$	1605	–	–
$[Cu(C_{14}H_{16}NO_3)_2]$	1636	623	837
$[Ni(C_{14}H_{16}NO_3)_2]$	1627	565	825
$[Mn(C_{14}H_{16}NO_3)_2]$	1595	527	743

Antimicrobial Studies

The results of the antibacterial activity tests for the Schiff bases and their metal (II) complexes are as shown in Table 3.6. It has been observed that the ligands (Schiff bases) showed minimal activity against all tested organisms at all concentrations. However, the complexes show some degree of activity which increases with increase in concentration. Among the isolates tested, growth of *Staphylococcus aureus* was most hindered as evident from the higher inhibition zone recorded but *Escherichia coli* and *Klebsiella pneumoniae* are the least affected iosolates by all the compounds. Cu(II) complex recorded the highest activity against the isolates, with its activity against *Staphylococcus aureus* even surpassing the activity of the control (Ciproflaxacin) used (Andreea *et al* 2011 and Gehad *et al* 2006).

Sensitivity of fungal isolates to the ligand and its respective metal (II) complexes were also determined and the results are contained in Table 3.7. Similarly, the Schiff base showed minimal activity against all the fungal isolates tested. The Cu (II) complex continues its good activity even against the fungal isolates, as higher inhibition zone was observed when compared with other complexes (Cleiton *et al* 2011 and Gupta *et al* 2012).

Table 3.6: Antibacterial activity of Schiff base and its metal (II) complexes

Test organism	Compound	Zone of Inhibition (mm)/Concentration (µg/disc)			Control (mm) Ciproflaxacin 5µg/disc
		250	500	1000	
Eschericia coli	$C_{14}H_{17}NO_3$	07	07	08	25
	$[Cu(C_{14}H_{16}NO_3)_2]$	08	09	10	
	$[Ni(C_{14}H_{16}NO_3)_2]$	08	09	10	
	$[Mn(C_{14}H_{16}NO_3)_2]$	07	07	08	
Pseudomonas aeruginosa	$C_{14}H_{17}NO_3$	06	06	08	29
	$[Cu(C_{14}H_{16}NO_3)_2]$	10	13	15	
	$[Ni(C_{14}H_{16}NO_3)_2]$	08	08	10	
	$[Mn(C_{14}H_{16}NO_3)_2]$	08	10	15	
Staphylococcus aureus	$C_{14}H_{17}NO_3$	08	09	10	25
	$[Cu(C_{14}H_{16}NO_3)_2]$	45	50	60	
	$[Ni(C_{14}H_{16}NO_3)_2]$	10	24	30	
	$[Mn(C_{14}H_{16}NO_3)_2]$	09	10	12	
Proteus mirabilis	$C_{14}H_{17}NO_3$	06	08	10	25
	$[Cu(C_{14}H_{16}NO_3)_2]$	10	12	16	
	$[Ni(C_{14}H_{16}NO_3)_2]$	10	12	15	
	$[Mn(C_{14}H_{16}NO_3)_2]$	10	12	15	
Klebsiella aeruginosa	$C_{14}H_{17}NO_3$	06	06	06	06
	$[Cu(C_{14}H_{16}NO_3)_2]$	08	10	14	
	$[Ni(C_{14}H_{16}NO_3)_2]$	06	06	06	
	$[Mn(C_{14}H_{16}NO_3)_2]$	06	06	08	

Table 3.7: Antifungal activity of Schiff base and its metal (II) complexes

Test organism	Compound	Zone of Inhibition (mm)/Concentration (µg/disc)			Control (mm) Mancozef 10mg/ml
		250	500	1000	
Candida albicans	$C_{14}H_{17}NO_3$	06	06	08	30
	$[Cu(C_{14}H_{16}NO_3)_2]$	15	20	28	
	$[Ni(C_{14}H_{16}NO_3)_2]$	08	10	12	
	$[Mn(C_{14}H_{16}NO_3)_2]$	08	10	14	
Fusarium solani	$C_{14}H_{17}NO_3$	06	06	08	33
	$[Cu(C_{14}H_{16}NO_3)_2]$	14	18	20	
	$[Ni(C_{14}H_{16}NO_3)_2]$	08	10	14	
	$[Mn(C_{14}H_{16}NO_3)_2]$	10	11	14	
Aspergillus fumigatus	$C_{14}H_{17}NO_3$	06	06	08	25
	$[Cu(C_{14}H_{16}NO_3)_2]$	10	15	30	
	$[Ni(C_{14}H_{16}NO_3)_2]$	06	08	10	
	$[Mn(C_{14}H_{16}NO_3)_2]$	08	08	10	

The antimicrobial data reveal that the Schiff base and the complexes exhibited varying degrees of inhibition on the growth of the tested organisms. The results further indicated that, activity of the Schiff base is enhanced on coordination to the metal ions this trend was observed with other Schiff base metal complexes (Cleiton *et al* 2011).

CONCLUSION

Complexes of Mn(II), Ni(II) and Cu(II) with Schiff base derived from acetylacetone and phenylalanine have been successfully synthesize and characterized. The complexes were found to be non electrolyte. IR, spectral and electronic studies confirm that, the metal (II) ions are coordinated to the Schiff base through the azomethine-N, deprotonated-O of carboxylic group and enolic-O group of acetylacetone, thus confirming the structure in scheme 3.1. The Schiff base and the respective metal (II) complexes were evaluated *in vitro* against five bacterial (four Gram-negative, one Gram-positive) and three fungal strains. The metal (II) complexes synthesized showed significant antibacterial and antifungal activity at high concentrations, with Cu(II) complex showing an excellent activity against *Staphylococcus aureus*. This Cu (II) complex when fully developed could reasonably be used for the treatment of some common disease caused by *Staphylococcus aureus*.

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