BAJOPAS Volume 15 Number 1, June, 2022 **http://dx.doi.org/10.4314/bajopas.v15i1.16**

Bayero Journal of Pure and Applied Sciences, 15(1): 119 - 124
Received: April, 2022
Accepted: June, 2022
ISSN 2006 – 6996

SYNTHESIS, ANTIMICROBIAL ACTIVITIES OF METAL (II) COMPLEXES FROM SALICYLALDEHYDE AND VALINE SCHIFF BASE

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ABSTRACT
Complexes formed from the interaction of Fe(II), Co(II), Cu(II), and Zn(II) with Schiff base derived from salicylaldehyde and valine have been synthesized and characterized on the basis of melting point/decomposition temperature, solubility, molar conductance, UV spectroscopy and infrared spectral analysis. The Schiff base melted at a temperature of 208°C while the synthesized metal (II) complexes decomposed at a temperature range of 220-241°C. All the complexes were found to be soluble in water and DMSO but insoluble in acetonitrile, ether and hexane. Octahedral geometry around these metal ions has been proposed on the basis of magnetic and spectral studies. The synthesized Schiff base as well as the complexes were tested against the bacterial strains comprising Staphylococcus aureus (Gram positive), Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis and Klebsiella pneumonia (Gram negative) and two fungal species; Aspergillus fumigatus and mucor species. A comparative study of inhibition values of the Schiff base and its complexes indicated that the complexes exhibited higher antimicrobial activity than the free ligand.
Keywords: Synthesis, Amino acid, Schiff bases, salicylaldehyde, valine, antimicrobial activity.

INTRODUCTION

Amino acids are the smallest unit of protein defined as an organic molecule made of amine and carboxylic functional groups. The combination of a basic amino group and an acid carbonyl group in the same molecule result in some unique properties and reactions (Wu, 2009). They control the body's water balance, facilitate the exchange of nutrients between tissues and also provide the body with energy. Thus, amino acids are ideal chelates or ligands from both chemical and nutritional point of view as a result of their ability of forming stable complexes with transition metal ions due to the presence of oxygen and nitrogen which are donor atoms (Abu-Dief and Mohammed, 2015). The incorporation of amino acids in the Schiff base structure enables the design of ligands with enhanced chirality and multidentate functionality (Shamsi *et al*., 2014). Salicylaldehyde on the other hand, is an organic compound and has many applications in organic synthesis, biological activities and chemical industries. It is considered a good chelating and extracting agent. Salicyldoxime, a compound of salicylaldehyde is used as extractant to effect the separation and concentration in hydrometallurgical recovery of copper (Ocio *et al*., 2004).

Schiff bases derived from the reaction of salicylaldehyde with primary amines represent a versatile series of ligands. Several literature reports have confirmed the involvement of amino acid Schiff base complexes in a variety of chemical and biological processes such as the catalysis of transamination, carboxylation and racemization reactions (Fattuoni *et al*., 2020). It has also been proved that amino acid Schiff base complexes can be used as radiotracers in nuclear medicine (Abdel-Rahman *et al*., 2017) and also as anticancer and antibacterial agents (Da Silva *et al*., 2011, Li *et al*., 2020).

Here in, we present the synthesis and characterization of the Schiff base of salicylaldehyde and valine for Fe(II), Co(II), Cu(II) and Zn(II) metal complexes and also their antimicrobial applications.

EXPERIMENTAL

MATERIALS AND METHODS

All the chemicals including the metal salts used in this work 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 Gallenkamp Hot box oven at 110ºC before used. All weighing were carried out on electric metler Toledo B154 weighing balance. Magnetic susceptibility balance Sherwood MK1 was used to measure the magnetic susceptibility of the complexes. Melting point of the Schiff base as well as the decomposition temperature of the complexes were determined using Gallenkamp melting point apparatus. Infrared spectral analyses were recorded using Happ Genzel in the range of 650-4000cm^{-1}. Molar conductance of the complexes was measured using Jenway 4010 conductivity meter. Absorbance measurement was carried out using Jenway 6305 Spectrophotometer. Antimicrobial activity studies were carried out at the department of microbiology, Bayero University Kano. The isolates *Staphylococcus aureus* (Gram positive), *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Klebsiella pneumonia* (Gram negative) and fungal species *Aspergillus fumigates* and mucor species were obtained and identified at the same department.

Synthesis of the Schiff base (ligand)

The Schiff base was prepared by adding an ethanolic solution (10 ml) of salicylaldehyde (0.01 mol) to ethanolic solution (20 ml) of valine (0.0l mol) with stirring. Concentrated H_2SO_4 (2-3 drops) were added and the mixture was refluxed for 1 hr. The reaction mixture was then collected and cooled in an ice-bath which immediately gave a yellow precipitate. The product obtained was filtered, washed severally with ethanol, then with ether and dried (Zahid *et al.,* 1997).

Synthesis of the Schiff base complexes

The complexes were prepared by refluxing a mixture of hot ethanolic solution (20 ml) of the ligand (0.02 mol) with an aqueous solution (10 ml) of the metal (II) chloride (0.01 mol) salt for 2 hrs. The mixture obtained was then reduced to nearly half its volume and left over night which resulted in the formation of a solid precipitate. The colored precipitate obtained was then filtered, washed with cold ethanol and dried (Zahid *et al.,* 1997).

Determination of metal to ligand ratio

The number of ligand coordinated to the metal ion was determined using Job's method of continuous variation (Angelici, 1971). A 3 mmol aqueous solution of the ligand and the metal chlorides were prepared. The following ligand to metal ratio (ml); 0:16, 1:15, 3:13, 5:11, 7:9, 9:7, 11:5, 13:3, 15:1 were taken from the ligand solution and each of the metal chloride solutions respectively. A total volume of 16 ml was maintained throughout the process and the mole fraction of the ligand was calculated in each mixture. The solutions of the metal chlorides were scanned so as to find the wavelength of maximum absorption (λ_{max}) for that particular metal ion (Angelici, 1971). The machine was fixed at maximum wavelength (λ_{max}) before taking the absorbance values. The values were extrapolated against mole fraction of the ligand and the number of coordinated ligand (coordination number) was determined using the relation below:

$n = x_i / (1 - x_i)$

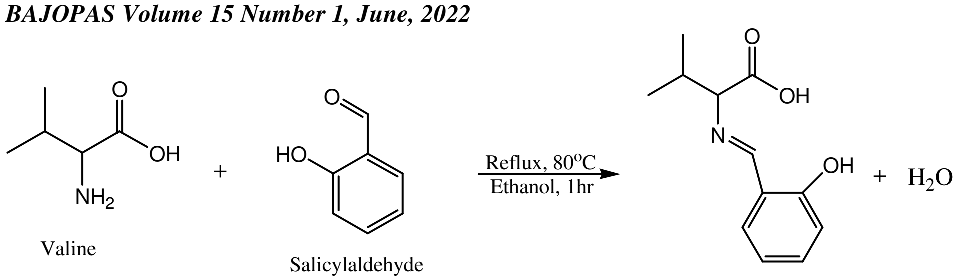
Where n= number of coordinated ligand and x_i= mole fraction at maximum absorbance.

Antimicrobial studies

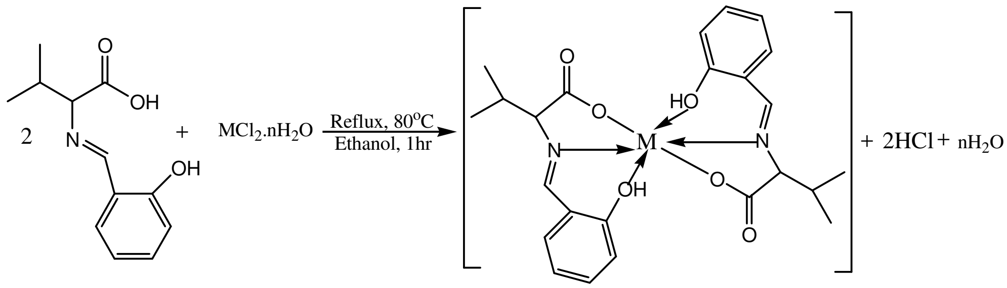
The synthesized Schiff base and its corresponding metal complexes were screened for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis* and *Klebsiella pneumonia* and fungal species, *Aspergillus fumigatus* and mucor species. The complexes and the Schiff base were dissolved in DMSO to produce three different concentrations 60, 30 and 15 µg/disc. A sterilized forceps was then used to place the prepared disc of the ligand and complexes on the already inoculated agar plates at various intervals and then incubated at 37°C for 24 hrs (Yusha'u, 2011) while for the fungal activity, the inoculated plates was left for 3 days at room temperature (Hassan *et al*., 2006). The inhibition zone of the ligand and complexes were then measured (in diameter) around the disc (NCCLS, 2008).

RESULTS AND DISCUSSION

The Schiff base was synthesized by the condensation of salicylaldehyde and valine in 1: 1 mole ratio as shown in Scheme 1. The reaction of the ligand and metal (II) salts (Scheme 2) gave compounds of various colors with an appreciable yield as shown in Table 1. The Schiff base was thermally stable with a melting point of 208°C which significantly increased on complexation as shown in Table 1.



Scheme 1. Valine derived Schiff base formation



Scheme 2: Synthesis of Valine derived Schiff base-metal complexes

Magnetic susceptibility was measured for the complexes and the result presented in Table 1. The values show that all the complexes were paramagnetic with magnetic moment values of 4.08, 1.70 and 2.85 B.M for the Co(II), Cu(II) and Fe(II) complexes respectively which are within the range observed for octahedral complexes (Gehad *et al.*, 2006, Dharam *et al.*, 2011). However, Zn(II) complex was found to be diamagnetic with a negative magnetic moment. The results are in agreement with increasing number of unpaired electrons available in these complexes.

Table 1: Physical Properties of the Ligand and its metal (II) Complexes

Compound	Colour	μ_{eff} (BM)	Decpt. Temp. (°C)	Melting Point (°C)	Percentage Yield(%)
$C_{12}H_{15}NO_3$	Yellow	–	–	208	63.83
$[Co(C_{12}H_{14}NO_3)_2]$	Pink	4.08	241	–	44.97
$[Cu(C_{12}H_{14}NO_3)_2]$	Blue	1.70	221	–	66.80
$[Fe(C_{12}H_{14}NO_3)_2]$	Brown	2.85	220	–	53.96
$[Zn(C_{12}H_{14}NO_3)_2]$	White	–	226	–	76.50

The Schiff base and the complexes were found to be soluble completely in water and DMSO, sparingly soluble in ethanol and methanol but insoluble in hexane, acetonitrile and ether (Table 2).

Results of conductivity measurements of the complexes in DMSO are presented in Table 3. The low values recorded indicated that all the complexes are non-electrolyte as evident by low values obtained for all the complexes which were within the range of 10-18Ω^{-1} cm^2 mol^{-1} when compared with molar conductance of strong electrolytes like NaCl (123.7Ω^{-1} cm^2 mol^{-1}) and $AgNO_3$ (130.5Ω^{-1} cm^2 mol^{-1}) (Gupta, 2012).

Table 2: Solubility test of the Ligand and its metal (II) complexes

Compound	Water	Ethanol	Methanol	DMSO	DMF	Hexane	Acetonitrile	Ether
$C_{12}H_{15}NO_3$	S	S	S	S	S	IS	IS	IS
$[Co(C_{12}H_{14}NO_3)_2]$	S	SS	SS	S	SS	IS	IS	IS
$[Cu(C_{12}H_{14}NO_3)_2]$	S	SS	SS	S	S	IS	IS	IS
$[Fe(C_{12}H_{14}NO_3)_2]$	S	SS	SS	S	SS	IS	IS	IS
$[Zn(C_{12}H_{14}NO_3)_2]$	S	SS	S	S	S	IS	IS	IS

KEY: S-Soluble, SS-Sparingly soluble, IS-Insoluble

Table 3: Conductivity measurement of complexes in 1×10^{-3} DMSO

Complex	Concentration ($Moldm^{-3}$)	Specific conductance ($Ohm^{-1}cm^{-1}$)	Molar conductance ($Ohm^{-1} cm^2 mol^{-1}$)
$[Fe(C_{12}H_{14}NO_3)_2]$	1×10^{-3}	16.20×10^{-6}	16.2
$[Co(C_{12}H_{14}NO_3)_2]$	1×10^{-3}	16.89×10^{-6}	16.89
$[Cu(C_{12}H_{14}NO_3)_2]$	1×10^{-3}	18.12×10^{-6}	18.12
$[Zn(C_{12}H_{14}NO_3)_2]$	1×10^{-3}	10.0×10^{-6}	10.0

IR spectral Studies

IR spectral of the Schiff base complexes (Table 4) showed a shift of the azomethine peak to the range of 1606-1622cm^{-1} in all the metal complexes which is an indication of the participation of the azomethine nitrogen ν(C=N) in coordination to the metal ions (Byeong-Goo *et al.,* 1996). Also the -OH group peak at 3174cm^{-1} in the spectral of the Schiff base, shifted towards higher frequency side in the complexes which also is an indication of the participation of (-OH) group in bond formation. New absorption bands in the range of 775-788 and 533-564cm^{-1} in the metal (II) complexes indicated the formation of M-N and M-O bonds respectively. These overall data suggest that the azomethine -N, O of phenol and O of carboxylato are involved in coordination with the metal ion in the complexes formation.

Table 4: Infrared spectral data of the Ligand and their metal (II) complexes

Compound	C=N v (cm^{-1})	(-OH) v (cm^{-1})	(M – N) v (cm^{-1})	(M-O) v (cm^{-1})
$C_{12}H_{15}NO_3$	1604	3174	–	–
$[Fe(C_{12}H_{14}NO_3)_2]$	1608	3145	788	540
$[Co(C_{12}H_{14}NO_3)_2]$	1606	3180	775	535
$[Cu(C_{12}H_{14}NO_3)_2]$	1613	3198	775	564
$[Zn(C_{12}H_{14}NO_3)_2]$	1611	3176	779	533

The estimation of the ligand to metal ratio was carried out by Job's method of continuous variation. The plot of the absorbance against mole fraction in each case at maximum absorbance corresponding to the ligand mole fraction suggest 1:2 metal-ligand ratio for all the complexes, indicating $[M(L_2)]$ (M=Co(II), Cu(II), Ni(II), Fe(II) or Zn(II), L= ligand) molecular formula for the complexes.

Antimicrobial studies

The antibacterial activity for the Schiff base and its metal (II) complexes were determined using disc difusion method. The diameters of zone of inhibition (mm) were measured for each treatment. The Schiff base ligand showed little or no activity against all the tested organisms at all concentrations (Table 5). Bacterial strain of *Staphylococcus aureus* was found to resist Fe(II) and Zn(II) metal complexes whereas *Klebsiella pneumonia* and *Escherichia coli* were more prone to attack by all the complexes. However, *Pseudomonas aeruginosa* was resistant to all the tested complexes at lower concentrations which improves to significant activity at higher concentration especially Cu(II) and Fe(II) complexes.

Table 5: Antibacterial activities of the Schiff base and its complexes against some bacterial species

Test organisms	Compound	Zone of inhibition(mm)/Concentration (μg/disc)		
		60	**30**	**15**
S. aureus	$C_{12}H_{15}NO_3$	10	08	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	06	06	06
	$[Co(C_{12}H_{14}NO_3)_2]$	22	12	06
	$[Cu(C_{12}H_{14}NO_3)_2]$	13	11	30
	$[Zn(C_{12}H_{14}NO_3)_2]$	06	06	06
E. coli	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	06	06	06
	$[Co(C_{12}H_{14}NO_3)_2]$	30	27	16
	$[Cu(C_{12}H_{14}NO_3)_2]$	13	11	30
	$[Zn(C_{12}H_{14}NO_3)_2]$	06	06	06
P. aeruginosa	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	14	06	06
	$[Co(C_{12}H_{14}NO_3)_2]$	06	06	06
	$[Cu(C_{12}H_{14}NO_3)_2]$	13	10	23
	$[Zn(C_{12}H_{14}NO_3)_2]$	13	10	08
K. pneumonia	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	09	07	07
	$[Co(C_{12}H_{14}NO_3)_2]$	23	21	18
	$[Cu(C_{12}H_{14}NO_3)_2]$	13	10	23
	$[Zn(C_{12}H_{14}NO_3)_2]$	13	10	08
Proteus mirabilis	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	13	10	06
	$[Co(C_{12}H_{14}NO_3)_2]$	11	09	06
	$[Cu(C_{12}H_{14}NO_3)_2]$	09	09	11
	$[Zn(C_{12}H_{14}NO_3)_2]$	09	06	06

Similarly, antifungal activity of the schiff base and the complexes were determined and the results presented in Table 6. Valine Schiff base was found to be inactive at all concentrations. However, Co(II) and Cu(II) complexes have shown appreciable activity even at lower concentration on *Aspergillus fumigates* while Fe(II) and Zn(II) complexes were relatively inactive against the two fungal isolate tested. Generally, the metal complexes were observed to be more active than their corresponding Schiff base. This increase in activity may be due to the coordination to the metal ion which improves the activity of the ligand.

Table 6: Antifungal activity of the metal complexes against some fungal species

Test organisms	Compound	Zone of inhibition(mm)/Concentration (μg/disc)		
		60	**30**	**15**
Aspergillus fumigatus	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	06	06	06
	$[Co(C_{12}H_{14}NO_3)_2]$	10	09	06
	$[Cu(C_{12}H_{14}NO_3)_2]$	13	10	08
	$[Zn(C_{12}H_{14}NO_3)_2]$	06	06	06
Mucor speies	$C_{12}H_{15}NO_3$	06	06	06
	$[Fe(C_{12}H_{14}NO_3)_2]$	11	09	06
	$[Co(C_{12}H_{14}NO_3)_2]$	10	09	06
	$[Cu(C_{12}H_{14}NO_3)_2]$	12	09	07
	$[Zn(C_{12}H_{14}NO_3)_2]$	09	07	06

CONCLUSION

Complexes of Fe(II), Co(II), Cu(II) and Zn(II) with Schiff base derived from the condensation reaction of salicylaldehyde and valine have been successfully synthesized and characterised. based on spectral and electronic studies. The structure as shown in Scheme 2 may be proposed for all the synthesized complexes. Some of the metal (II) complexes synthesized showed significant antibacterial and antifungal activity at high concentrations with Co(II) complex showing excellent activity against *Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumonia.*

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