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SYNTHESIS, CHARACTERIZATION, AND ANTIOXIDANT ACTIVITY ON METAL(II) COMPLEXES OF A SCHIFF BASE DERIVED FROM THIOSEMICARBAZIDES AND O-VANILLIN

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ABSTRACT

A Schiff base derived from o-vanillin and thiosemicarbazide was synthesized, as well **as** its Mn(II), Fe(II), and Co(II) complexes. The Schiff base and its metal(II) complexes were characterized based on FTIR, solubility, melting/decomposition temperature, conductivity, and elemental analysis. From the analysis, the Schiff base was confirmed through the C=N IR peak (1648 cm^{-1}), and from the elemental analysis, the Schiff base to metal ratio of 1:2 was established. Molar conductivity measurement shows that all the complexes were in a range (18.0–47.0) hence they are non-electrolytic or non-ionic. Based on magnetic susceptibility measurement, the study further proposed the structure of the metal complexes to be octahedral in geometry and revealed that all the complexes were paramagnetic. Antioxidant activity of the synthesized compounds was analyzed with the DPPH free-radical–trapping process. The synthesized compounds exhibited lower antioxidant activity than the standard ascorbic acid. IC_{50} values of the synthesized molecules measured from 20.226 to 59.454. All the synthesized compounds showed moderate antioxidant activity.

Keywords: Antioxidant activity, characterization, Schiff base, metal complexes

INTRODUCTION

The chemistry of Schiff base-metal complexes has fascinated several chemists in different parts of the globe in search of promising chemotherapeutic agents for disease control. The ease with which the Schiff base ligands are designed and synthesized has made them referred to as 'fortunate ligands', possessing azomethine derivatives (C=N), which are essential for biological activity, including antibacterial, antifungal, antioxidant, anticancer, and diuretic activities. A variety of Schiff bases and their complexes studied as model molecules for biological, analytical, and industrial applications have made this part of inorganic chemistry highly interesting (Prakash and Adhikari, 2011; Bala et al., 2012; Abdel Aziz et al., 2012).

Schiff bases, named after Hugo Schiff (1834-1915), possess a functional group containing a carbon-nitrogen double bond with the nitrogen atom linked to an aryl or alkyl group, except for hydrogen (Kostova and Sasa, 2013). Schiff base compounds are condensation products of primary amines and carbonyl compounds (aldehydes and ketones) (Ashraf et al., 2011; Brodowska and Lodyga, 2014). Schiff bases are compounds containing an azomethine group (>C=N) and have the general structure $R^1R^2C=NR^{3,}$ where R^1, $R^{2,}$ and R^3 are aryl, alkyl, cycloalkyl, or heterocyclic groups that are of different substituents. They are considered an important class of compounds for various pharmacological activities (Ghosh et al., 2020). They have attracted a lot of researchers' attention due to their strong chelating properties, ease of preparation, and versatile applications (Abu Dief and Mohamed, 2015). Schiff bases of both natural and non-natural origin have exhibited a wide range of applications, including antibacterial, antitubercular, antifungal, antiparasitic, antiviral, antioxidant, anticancer, analgesic, catalytic, and anti-inflammatory properties (Ghosh et al., 2020; Noor et al., 2020).

Schiff base metal complexes are generally synthesized by treating metal halides with Schiff base ligands under suitable experimental conditions. In special cases, metal alkoxides, metal amides, metal alkyls, or metal acetates have been used for the synthesis (Pier, 2004). Generally, transition metal and lanthanide ions are used to prepare coordination complexes with different oxidation states, exhibiting interesting new physicochemical properties and coordination structures and geometries (Masaaki et al., 2003). The (-OH) hydroxyl group or (–SH) sulfhydryl group ortho to the (–C=N-) group moiety present in the Schiff bases can induce tautomerism in the compounds and give many different structures (Costamagna et al.,1992).

The complex combinations of Co(II) and Ni(II) with Schiff base obtained through the condensation of (*E*)-methyl 2-amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c] pyridine-3-carboxylate with 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) were prepared. The antioxidant, antimicrobial, and plasmid DNA cleavage activities were investigated. The antibacterial effects of the Co(II) complex on Gram-positive and Gram-negative bacteria were identified to be higher than those of the ligand. The complexes were found to have higher radical scavenging potential on 1,1-diphenyl-2-picryl-hydrazyl (DPPH). In comparison with the ligand, the binding affinity of the Ni(II) complex was higher than that of the ligand (Turan et al., 2019).

Schiff base complexes of different types of transition metals in the form Cu(II), Co(II), Mn(II), and Zn(II) were synthesized. The Schiff base used as a ligand was derived from the condensation reaction between 5-aminosalicylic acid with *o*-vanillin in methanol. Schiff base used as ligand was named as (*Z*)-2-hydroxy-5-[(2-hydroxy-3-methoxy benzylidene) amino] benzoic acid. The antimicrobial activity of the synthesized complexes against *Escherichia coli, Pseudomonas aersginosa, Staphylococcus aureus, Shigella flexneri, Protious vulgaris,* and *Bacillus subtilus* was carried out with clarithromycin as a standard drug at 100 ppm and 200 ppm concentrations of the complexes (Shaheen et al., 2019).

Schiff-base bearing new bis(thiosemicarbazone) derivatives were prepared from terephthalaldehyde and various thiosemicarbazides. The *in vitro* antioxidant activity of the synthesized compounds was analyzed with the 1,1-diphenyl-2-picryl hydrazyl free-radical–trapping process. The synthesized compounds exhibited lower antioxidant activity than the standard ascorbic acid. Among the synthesized compounds, (2,2')-1,4-Benzenedicarboxaldehyde-1-methanylylidene-bis(4-(4-nitrophenyl) thiosemicarbazone had the best antioxidant activity because of the nitro group, which reduces the bond strength between nitrogen and hydrogen atoms, thereby decreasing electron density (Yakan, 2020).

New complexes $[NiL_2(H_2O)_2]\ 3H_2O$ (L:1-{4-[(2-hydroxy-3-methoxybenzylidene) amino] phenyl} ethanone) were prepared, and their thermal decomposition confirmed the existence of lattice and coordinated water molecules in them. Enzyme inhibition of complexes was evaluated against carbonic anhydrase isoenzymes and acetylcholinesterase. The best inhibition enzyme was the Ni(II) complex with 62.98±18.41, 86.17±23.62 Ki (Inhibition constant) values, whereas this inhibition effect showed ligand with 24.53±2.66 Ki value for the enzyme (Buldurum et al., 2019).

Macrocyclic Schiff bases were synthesized by condensation of acetyl acetone with semicarbazide hydrochloride and thiosemicarbazide in the presence of methanol. Their oxovanadium complexes have been synthesized by using vanadium acetylacetone. The synthesized compounds were screened for *in vitro* growth-inhibiting activity against different strains of bacteria, viz., *Staphylococcus aureus*, *Bacillus licheniformis*, *Escherichia coli,* and *Micrococcus luteus* (ATCC), and were compared with the standard antibiotic ofloxacin. Also *in-vitro* antioxidant activity of all compounds was determined by nitric acid free radical scavenging assay (Pawar et al., 2011).

A Schiff base was synthesized using compounds like 5-amino-4H-1,2,4-triazole-3-thiol and 3-hydroxy-4-methoxybenzaldehyde and used as a ligand for the synthesis of transition metal complexes of Cu(II), Co(II), Mn(II), Zn(II), and Ni(II). The synthesized complexes were used for biological testing of antibacterial activity against gram-negative bacteria (*Klebsiella pneumonia*, *Enterobacter aerogenes*, *Escherichia coli*, *Pseudomonas fluorescens*, *Pseudomonas aeruginosa,* and *Salmonella enteritidis)* as well as gram-positive bacteria *(Bacillus cereus*, *Micrococcus luteus*, *Staphylococcus aureus)* using amoxicillin as a standard drug. The results obtained were positive for many of the bacteria. Mn(II) complexes were able to inhibit bacteria as shown by their zone inhibition (mm) results, and showed positive results for gram-positive bacteria like *Micrococcus luteus* and *Staphylococcus aureus,* and for gram-negative bacteria like *Klebsiella pneumonia*, *Enterobacter aerogenes,* and *Pseudomonas aeruginosa*. Further studies were conducted on the antioxidant activity, where free radical scavenging activity was performed using DPPH, ABTS, and superoxide. Almost all complexes showed positive results for radical scavenging activities at different levels for each metal complex. Antioxidant activity order for metal complexes and ligand was in order of Zn> Ni> Cu>Mn>Co>ligand. The results of the inhibitory effects on inhibitory effects on alpha-amylase and yeast alpha-glucosidase additionally carried out revealed the inhibition order for the metal and ligand to be Zn>Ni>Cu>Mn>Co>ligand (Vinusha et al., 2019).

Two new chiral thiosemicarbazide ligands and their Cu(II), Ni(II), Pd(II), and Zn(II) complexes were synthesized and characterized by nuclear magnetic resonance (NMR) (only for ligand) (Basaran et al., 2019), Fourier transform infrared (FT-IR), ultraviolet visible (UV-Vis), mass, and elemental analysis. The antioxidant activity of ligands and their metal complexes was examined. It was found that the antioxidant activity of metal complexes was better than their ligands. In addition, the antioxidant activity, as reflected by free radical scavenging, was evaluated. Besides, Pd(II) complexes exhibited better antioxidant activity than Ni(II), Cu(II), and Zn(II) complexes.

This study is aimed at the synthesis, characterization and study of the antioxidant activity of metal(II) complexes of a Schiff base derived from thiosemicarbazide and o-vanillin.

MATERIALS AND METHODS

All the reagents used in the research were of analytical grade, used without further purification, and were all obtained from Sigma Aldrich.

The glassware was washed and dried in the Gallen Kamp hot box oven at 110 °°C before use. The melting point of the Schiff base, as well as the decomposition temperature of the complexes, was determined using the Guaoming R-Y2 melting point tester. Infrared spectral analyses were recorded using an Agilent Technologist FTIR Cary 630 spectrophotometer. Magnetic susceptibility was carried out using the Sherwood MKI magnetic susceptibility balance at Umaru Musa Yar'adua University to measure the magnetic properties of the complexes. Molar conductance of the complexes was measured using a Jenway 4010 conductivity meter at Bayero University, Kano. Elemental analyses were conducted at Organic Elemental Analysis OEA laboratories in England, using a Thermo Scientific Flash Elemental AnalyzerAnti-oxidant activity of the Schiff base and metal complexes was carried out at the Department of Pure and Industrial Chemistry, Bayero University, Kano.

Synthesis of the Schiff Base

O-Vanillin (1.52 g, 0.01 mol) solution in ethanol was added to an ethanolic solution of thiosemicarbazide (0.9114 g, 0.01 mol) with continuous stirring until there was a visible color change. Two drops of acetic acid were added 10 minutes after refluxing was commenced, and the coloration deepened. The mixture was then refluxed for 2 hours. The resulting mixture was allowed to cool overnight, and the creamy crystalline precipitate obtained was filtered off, washed with ethanol, and dried in a desiccator over phosphorous pentoxide (Al Shemary et al., 2017).

Synthesis of the Complexes

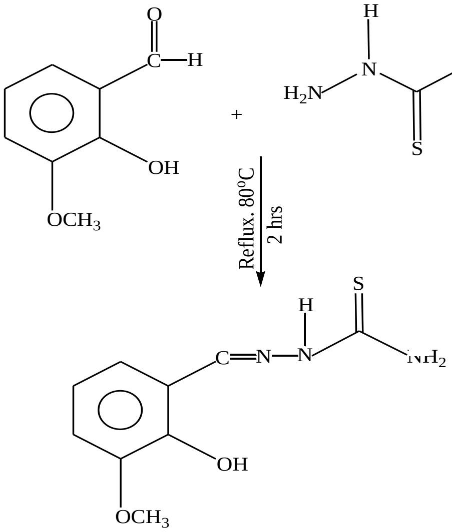
Schiff base (1.12 g, 0.005 mol) in 20 ml of ethanol and a methanolic solution of the metal(II) chloride (0.59g/ 0.0025mol) were mixed in a molar ratio of 1:2, respectively. For the synthesis of Co(II), Fe(II), and Mn(II) complexes, two drops of ammonium hydroxide were added 10 minutes after the commencement of refluxing. The reflux was then carried out for 2 hours. The product obtained was allowed to cool, filtered off, washed with ethanol, and dried in a desiccator over phosphorous pentoxide (Al Shemary et al., 2017).

Antioxidant Activity

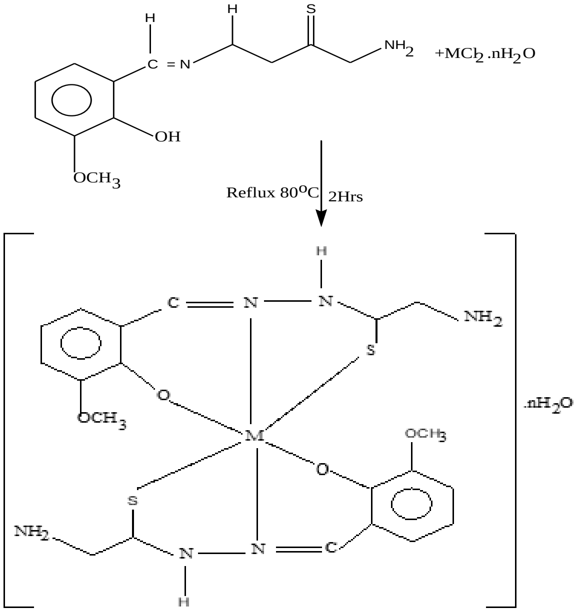
Anti-oxidant activity of Schiff base and complexes was determined using stable free radical 1,1-diphenyl-2- picryl hydrazyl (DPPH) and the IC_{50} value was recorded 0.003 g of each of the complexes was weighed and diluted in 5ml of ethanol with occasional shaking and stirring, and then used as working solution, using double serial dilution of 1000, 500, 250, 125, 62.5, 31.25, 15.625, 7.8 µg/ ml. 50 µL of the working solution was taken into the spectrophotometer, and the absorbance was recorded at 517 nm. 100 µl of DPPH was then added, and the absorbance was also recorded. The sample was incubated in the dark at room temperature for 30min then the absorbance of the mixture was taken at 517nm. The observed values were used to calculate the % inhibition and the IBM SPPS software was used to determine the IC_{50} values representing the antioxidant activity (Yakan, 2020).

RESULTS AND DISCUSSION

The Schiff base described in this research has been derived from Thiosemicarbazide and o-vanillin. It was prepared by refluxing an appropriate amount of o-vanillin and Thiosemicarbazide in methanol for 2 hours (Scheme 1). It gave a precipitate, which might probably be an indication of the formation of the Schiff base.



Scheme 1: Preparation of Schiff base



Where n=1 for Mn(II), Fe(II); n=2 for Co(II)
Scheme 2: Preparation of Metal (II) Complexes

The complexes obtained were with varying colors (Table 1), with an appreciable percentage yield in the range of 74 -80. Co(II) complex recorded the highest yield at 80.4%, while the Mn(II) complex has the least yield (74%). The Schiff base was found to melt at 120 °C. However, the metal(II) complexes were found to have decomposition temperatures in the range of (252-219)°C. These high decomposition temperature values indicate that the complexes are stable.

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

Compound	**Color**	**Percentage Yield (%)**	**Melting point/ Decomposition Temperature (°C)**
Ligand	Creamy	92	120
$[MnL_2]. H_2O$	Yellow	74	235
$[FeL_2]. H_2O$	Dark brown	76	219
$[CoL_2]$ $2H_2O$	Yellowish green	80	252

Ligand = ($C_9H_{11}N_3O_2S$)

The solubility test was carried out on the Schiff base and its corresponding complexes (Table 2) in solvents such as distilled water, methanol, ethanol, chloroform, carbon tetrachloride, acetonitrile, dimethyl formamide, and dimethyl sulphoxide to determine their nature in the solvents. Results revealed that the Schiff base and the metal complexes are soluble in most of the highly polar solvents but poorly soluble in non-polar solvents.

Table 2: Solubility Test of Ligand and its Complexes

Compounds	**Distilled water**	**Methanol**	**Ethanol**	**Chloroform**	**Carbon**	**Nitrobenzene**	**Acetonitrile**	**DMF**	**DMSO**
Ligand	IS	SS	SS	IS	IS	SS	IS	S	S
$[MnL_2]. H_2O$	SS	SS	SS	IS	IS	SS	IS	S	S
$[FeL_2]. H_2O$	SS	SS	SS	IS	IS	SS	IS	S	S
$[CoL_2]$ $2H_2O$	IS	SS	SS	IS	IS	SS	IS	SS	S

Ligand = ($C_9H_{11}N_3O_2S$)
Where;
S = Soluble
IS = Slighlty Soluble
SS = Insoluble

Molar conductance measurements (Table 3) in DMSO solution carried out on the metal(II) complexes are in the range of (47.0-14.05) $ohm^{-1}cm^2mol^-$. These low conductivity values show that all the complexes are non-electrolytes.

Table 3 Conductivity Measurement of Metal (II) complexes in DMSO

Compounds	Concentration (mol/dm^{-3})	Specific conductance (ohm^{-1}cm^{-1})	Molar conductance (ohm^{-1}cm^{2}mol^{-1})
[MnL$_2$]. H$_2$O	1 x 10^{-3}	25.2 x 10^{-6}	25.2
[FeL$_2$]. H$_2$O	1 x 10^{-3}	14.05 x 10^{-6}	14.05
[CoL$_2$] 2H$_2$O	1 x 10^{-3}	47.0 x 10^{-6}	47.0

Ligand = ($C_9H_{11}N_3O_2S$)

The important FTIR spectral results of the ligand and complexes are displayed in table 4 below. The absorption band at 1648 cm^{-1} is assigned to the formation of the azomethine group of the ligand. The shift in the absorption band of the azomethine group in the spectra of all the complexes (1603, 1592, and 1599 cm^{-1} for Mn(II), Fe(II), and Co(II) complexes, respectively) confirms the coordination of the metals to the ligand. The absorption bands assigned to v(C-O) cm^{-1} were found in the range of 1212 – 1283 cm $^{-1}$. The bands between 545 and 627 are assigned to v (M-N) cm^{-1} and those in the range of 441 – 583 cm $^{-1}$ belong to *v* (M-O) cm^{-1}.

Table 4 FTIR Analysis of Ligand and its Complexes

Compounds	*v* (C=N) cm^{-1}	*v* (C-O) cm^{-1}	*v* (M-N) cm^{-1}	*v* (M-O) cm^{-1}	*v* (OH) cm^{-1}
Ligand	1648	1261	601	512	3029
[MnL$_2$]. H$_2$O	1603	1223	593	493	3164
[FeL$_2$]. H$_2$O	1592	1212	627	583	3156
[CoL$_2$] 2H$_2$O	1599	1216	545	441	3622

Ligand = ($C_9H_{11}N_3O_2S$)

The magnetic susceptibility measurement of the complexes has a BM of (5.55, 5.6, 4.5), which are for Mn, Fe, and Co respectively. This shows that the complexes are within the agreement for the octahedral geometry for the magnetic moment of the complexes, with the exception of diamagnetic zinc complexes. this is in accordance with a previously reported study by Turan et al. (2019.

Table 5: Magnetic susceptibility of complexes

Compounds	Magnetic Susceptibility (cm^3/g)	Molar Magnetic Susceptibility (cm^3/mol)	Bohr Magneton (μ_{eff})	
[MnL$_2$]. H$_2$O	6.97X10^{-5}	0.0365	5.55	Paramagnetic
[FeL$_2$]. H$_2$O	8.8096X10^{-5}	0.0462	5.60	Paramagnetic
[CoL$_2$] 2H$_2$O	4.324X10^{-5}	0.0235	4.50	Paramagnetic

Ligand = ($C_9H_{11}N_3O_2S$)

The results of the UV analysis of the synthesized compounds are shown in Table 6. The results reveal bands associated with intra-ligand and non-bonding electronic transitions. The bands in the range of 217.63nm – 235nm are associated with intra ligand (π – π*) electronic transitions, and those in the range of 358.32nm – 422.88nm are associated with non-bonding (n – π*) electronic transitions.

Table 6 UV Analysis of Ligand and Complexes

Compounds	Wavelength of Intra-ligand π – π* Transition	Wavelength of Non-bonding n – π* Transition
Ligand	217.63nm	358.32nm
[MnL$_2$]. H$_2$O	228.86nm	361.94nm
[FeL$_2$]. H$_2$O	220.33nm	364.01nm
[CoL$_2$] 2H$_2$O	235.00nm	422.88nm

Ligand = ($C_9H_{11}N_3O_2S$)

The percentage composition of carbon, nitrogen, and hydrogen in the compounds was determined by elemental analysis. The results obtained along with the calculated values are shown in Table 4.7 below.

Table 7 Elemental Analysis of Ligand and its complexes [% Found (Calculated]

Compounds	C	H	N	S
Ligand	42.79 (47.98)	4.21 (4.92)	16.31 (18.65)	12.32 (14.23)
[MnL$_2$]. H$_2$O	38.13 (41.45)	3.92 (4.25)	14.42 (16.11)	11.68 (12.29)
[FeL$_2$]. H$_2$O	40.01 (41.380)	4.02 (4.23)	14.15 (16.08)	10.59 (12.27)
[CoL$_2$] 2H$_2$O	36.25 (39.78)	3.71 (4.08)	12.08 (15.57)	9.75 (11.79)

Ligand = ($C_9H_{11}N_3O_2S$)

The antioxidant activity of the synthesized compounds and the standard used is shown in Table 8. From the result, it can be seen that all the complexes have lower antioxidant activity than ascorbic acid, with an IC$_{50}$ value of 0.00. All the complexes have shown moderate antioxidant activity. This is from a previously reported study (Yakan, 2020).

Table 8 Antioxidant Activity of Ligand and its complexes.

Compounds	IC$_{50}$
Ascorbic Acid	0.000
Ligand	25.518
[MnL$_2$].H$_2$O	20.597
[FeL$_2$].H$_2$O	59.454
[CoL$_2$]2H$_2$O	20.226

Ligand = ($C_9H_{11}N_3O_2S$).
Where AA is ascorbic acid

Conclusion

Schiff base and its metal(II) complexes were synthesized successfully using o-vanillin and thiosemicarbazide. The coordination of azomethine nitrogen of the Schiff base ligand to the metal ions has been confirmed via FTIR data comparison ligand with those of the metal(II) complexes. The bonding of the Schiff base through the (C=N) nitrogen to the metal ion was further confirmed by the appearance of new bands due to the v(M-N) bond in the metal complexes' spectra. Conductivity measurements showed that the complexes are non-electrolytes. The decomposition temperature of these Schiff base complexes revealed high values, which is an indication of high stability. The solubility test carried out in various solvents showed that the compounds synthesized were all soluble in DMSO. The positive values of the magnetic susceptibility of the complexes show they are paramagnetic in nature, with the exception of the Zinc complex, which has a negative value, hence its diamagnetic nature. The elemental analysis of Schiff base and their metal complexes shows a 1:2 metal-to-ligand ratio. Based on the results of the various analyses carried out, the structure of the Schiff base and complexes was proposed. Results from the antioxidant activity carried out revealed that Ni(II) complex has the highest antioxidant activity, while the remaining compounds showed moderate activities when compared with the standard used (Ascorbic acid)

Conclusively, this study describes a prominent and economic way for a better synthesis of Schiff base complexes and their metal(II) with very good yield products. Hence, the methodology will be useful for various syntheses of Schiff bases with several substituents on the aromatic aldehyde and the amine and their metal(II) complexes.

Recommendation

Based on the results carried out for various analyses such as IR, analytical and spectroscopic data the structure of the Schiff base. However, further analysis such as 13C NMR, X-ray crystallography, should be carried out to further investigate and confirm the structure of the synthesized complexes.

Further studies into the biological activities could be established as some of the complexes could be potential drugs. Toxicity studies of the Schiff base and its complexes should also be carried out to establish their non-toxicity.

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