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SYNTHESIS, CHARACTERIZATION, AND IN VITRO ANTIMICROBIAL STUDIES ON NICKEL (II) AND COPPER (II) COMPLEXES OF SCHIFF BASE DERIVED FROM ISATIN (1H-INDOLE-2,3-DIONE) ANDS THIOSEMICARBAZONE

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ABSTRACT

The Schiff base ligand was obtained from the condensation of Isatin and Thiosemicarbazide. Its Nickel(II) and Copper(II) complexes were synthesized by the solutions of the ligand and that of the chloride of the correspond metal in the ratio of 2:1. The complexes obtained were characterized by FTIR, melting point/decomposition temperature determination, atomic absorption spectroscopy (AAS), magnetic susceptibility, and molar conductance and solubility tests. The complexes showed moderate values of decomposition temperatures. Infrared spectral data of the ligand and the complexes indicated coordination of the ligand to the metal (II) ion via azomethine nitrogen, indole oxygen and thionine sulphur; thus acting as a tridentate ligand. The complexes showed an effective magnetic moments of 3.34 BM and 0.94 BM for the NI(II) and Cu(II) respectively which suggests an octahedral geometry. The molar conductivities of 17.1 $\Omega^{-1}cm^2mol^{-1}$ for the Ni(II) and 9.1 $\Omega^{-1}cm^2mol^{-1}$ for Cu(II) complexes indicated that these complexes are non-electrolytic. The results of the AAS and the empirical formula indicated that, the Schiff base is monobasic and tridentate towards the metal ions. The ligand and the complexes were tested for antimicrobial activity against Staphylococcus aureus, Salmonella typhimurium, Escherichia coli (bacteria); Aspergillus flavus, Aspergillus fumigatus and Mucor species (fungi). Amoxicillin and Ketoconazole were used as positive control for the bacteria and fungi isolates respectively. The results showed that the complexes are more active than the free ligand but not as active as the standard drugs.

Keywords: Ligand Schiff base, Thiosemicarbazide, Isatin, molar conductivity, magnetic susceptibility, Empirical Formula

INTRODUCTION

Thiosemicarbazones are special class of Schiff base with two N and two S donors which are of great interest owing to their significant antibacterial, antiviral, antimalarial, antiinflammatory activity, anti-leprotic, and anti-cancer activities (Shawish *et al., 2014*). Thiosemicarbazones usually are chelating ligands capable of coordinating with transition metal ions. They coordinate to the metal ion through sulfur and nitrogen of the hydrazine (Chandra *et al.,* 2007and Salman *et al.,* 2014). This class of compounds has received great interest from chemist and other scientist due to their bonding modes, biological activities, structural diversity, and ion-sensing ability (Mishra *et al.*, 2013). Moreover, due to the presence of various manageable sets of sulfur and nitrogen atoms capable of donating electrons pair, which makes them useful as chelating ligands in the preparation of metal complexes (Singh *et al.,* 2001).

Thiosemicarbazone compounds are synthesized by condensation reaction of thiosemicarbazide or its derivative and an aldehyde or a ketone. In this paper, we report the synthesis of thiosemicarbazone from isatin (1H-indole-2,3-dione) and thiosemicarbazide (hydrazinecarbothioamide). The Ni(II) and Cu(II) complexes were also synthesized using hydrated Ni (II) and Cu (II) chlorides. The investigation of their biological activity was also carried out using some pathogenic bacteria and fungi.

MATERIALS AND METHODS

Materials

All reagents used in this study were of analytical grade and were used without further purifications. The infrared spectra of the ligand and the complexes were recorded as KBr discs on Shimadzu FTIR-8400S Fourier Transform Spectrophotometer in the range of 400 – 4000 cm^{-1}. The magnetic susceptibilities of these complexes were measured using Magnetic Susceptibility balance MK1. Molar conductance of the complexes were measured using Janway 4010 conductivity meter. The metal content in the complexes was determined using AAS Buck Scientific 210 VGP. All glassware were washed thoroughly with detergent and rinsed several times with distilled water and kept at 110^oC in an oven for 3 hours.

Methodology

Preparation of Isatin-thiosemicarbazone

The ligand was obtained by addition of an ethanolic solution containing 0.105 g (10 mmol) of thiosemicarbazide in 10 ml of ethanol to a solution 10 mmol of 1H-indole-2,3-dione in 10 cm^3 of ethanol followed by the addition of 0.5 cm^3 of acetic acid. This mixture was refluxed for 2 hours to obtain a yellow precipitate which was filtered off, washed with ice-cold ethanol and dried in a desiccator over P_2O_{10}. (Nur Nadia *et al.,* 2015).

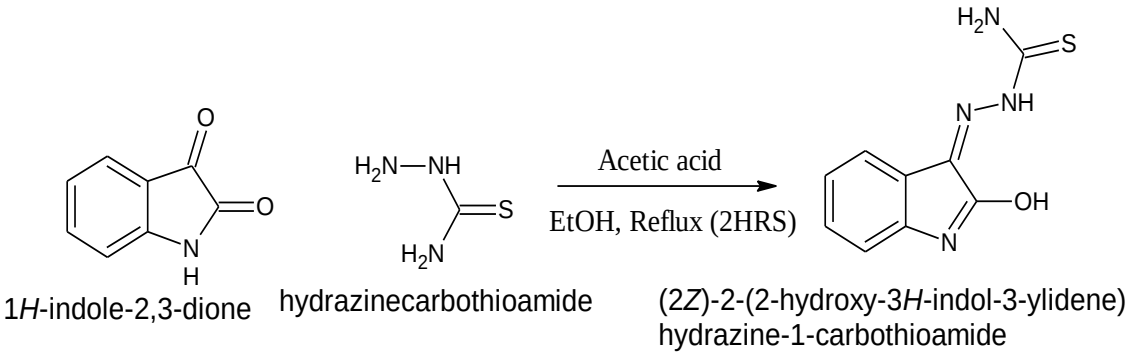

Figure 1: schematic representation of Thiosemicarbazone synthesis

Preparation of M (II) thiosemicarbazone complexes (M= Ni or Cu)

The complexes were obtained by addition of 5 cm^3 of 0.8 M ethalonic NaOH to an ethanolic solution (30 cm^3) of the ligand (0.8810 g, 4 mmol) followed by the addition of a solution of 2 mmol hydrated M (II) chloride in 20 cm^3 of ethanol. The resulting mixture was refluxed for 3 hrs and the precipitate formed was filtered off, rinsed with hot ethanol and dried in a desiccators over P_2O_{10} (Nur Nadia *et al.*, 2015). The synthesis of these complexes is represented schematic in the following equation:

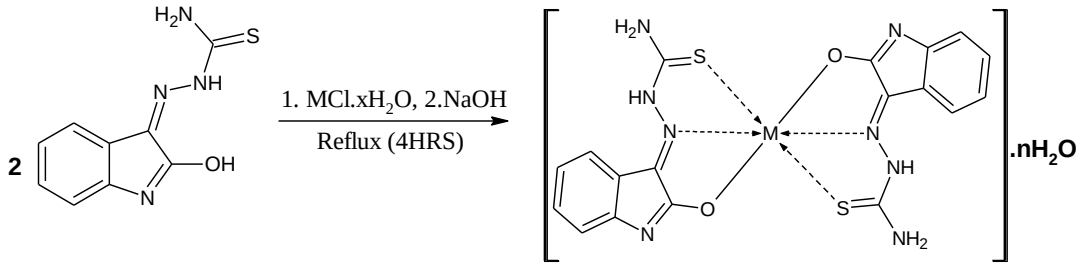

Figure 2: Schematic syntheses of the metal complexes. (M= Ni or Cu)

Estimation of the metal content in the complexes

To determine the metal content in the complexes 0.0100 g of each metal complex was digested with 15cm^3 of 33% aqueous HCl solution. Using distilled water, the volume was made to 100 cm^3 and the working solutions were prepared by serial dilution of this stock solution with distilled water. The amount of metals in the complexes were measured against bank solution using AAS machine (Hassan *et al.*, 2013).

Determination of water of crystallization

0.2g of each complex was placed in a cleaned crucible of known weight and kept in an oven at 110ºC until constant weight was obtained (Vogel, 1972). The percentage of water in the complexes was calculated using the following equation

$$\%\ of\ water = \frac{loss\ in\ mass}{Mass\ complex\ taken} \times 100\%$$

Magnetic Susceptibility Measurement

This was achieved by placing each of the complexes into a capillary tube of known mass (m_o) up to 1.5 to 2.5cm length. The capillary tube and its content were weighed and the mass (m_1) was recorded. The gram magnetic susceptibility was calculated from the equation:

$$X_g = \frac{LC(R_1 - R_o)}{m \times 10^9}$$

Where

Ro = readings from the balance for empty capillary

R_1 = readings from the balance for loaded capillary tube

L = the length (in cm) of the complex in the capillary tube,

C = the balance calibration constant (C = 1) and

m = is the mass of the complex taken.

Antimicrobial Studies

The antibacterial activity of the synthesized ligand and its Ni(II) and Cu (II) complexes were carried out *in vitro* by disc diffusion method as described by Khan *et al*, (2014) using cultures of *Salmonella typhimurium*, *Escherichia coli* and *Staphylococcus aureus*, and amoxicillin was used as standard drugs, while a DMSO-wetted disk was used as negative control. *Aspergillus flavus, Aspergillus niger and Mucor species (inducus)* are the three pathogenic fungi used for the antifungal activity of the ligands and complexes. Various concentrations of these compounds were used. Ketoconazole and DMSO wetted disks were used as standard fungicide (Positive Controls) negative control respectively.

RESULTS AND DISCUSSION

The Schiff base was prepared as reported. It is a yellow flaky product with good yield of 83.23% and melting point of 240ºC. The Ni(II) complex is brown whereas Cu(II) complex is green. The decomposition temperatures of these complexes were found to be 280ºC and 255ºC respectively, which is high, suggesting good stability (Table 1). The effective magnetic moments of at room temperature were determined to be 3.37 BM and 0.94 BM for Ni(II) and Cu(II) complexes respectively, which suggested that the complexes are paramagnetic in nature. The molar conductivity values obtained were found to be 9.1 and 17.3 $ohm^{-1}cm^2mol^{-1}$ for the Ni(II) and Cu(II) complexes respectively, very low values, suggesting their non-electrolytic nature (Spînu, *et al.*, 2008). All these are presented in Table 1.

Table 1: Some Physical Characteristics of the ligand and the Metal complexes`

Ligand/ Complexes	Formula Weight	Color	M.P/DT (ºC)	yield (%)	$\mu_{eff\ (BM)}$	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)
$C_9H_8N_4OS$	220.25	Yellow	240	83.23	-	-
$[Ni(C_9H_7N_4OS)_2].3H_2O$	549.21	Brown	280	76.55	3.37	9.1
$[Cu(C_9H_7N_4OS)_2].3H_2O$	554.06	Green	255	76.90	0.94	17.3

DT= Decomposition temperature

The Infrared spectroscopy of the ligand its Ni(II) and Cu(II) complexes were recorded on KBr discs using FTIR-8400S Fourier Transform Infrared spectrophotometer from 400 – 4000 cm^{-1}. The band at 1681cm^{-1} and 1134cm^{-1} in the spectrum of the ligand were assigned to the azomethine group i.e C=N and ν(C=S) stretching frequencies respectively. The band assigned to ν(C=N) in the spectrum of the ligand disappeared completely in the spectra of the complexes and new bands appear at 1504 cm^{-1} and 1519 cm^{-1} in the spectrum of Ni(II) complex and Cu(II) complex respectively. This is a strong evidence that the azomethine nitrogen coordinated with these metal ions. Another evidence to support this, is the appearance of some new peaks in the range of 447 - 509 cm^{-1} which could be assigned to ν(M-N) stretching frequencies (Bennie *et al.,* 2014). The band at 1643 cm^{-1} was assigned to ν(C=N) of the indole ring remained intact in the spectra of the free ligand and itscomplexes (Hussain *et al.,* 2014). The FTIR results are contained in Table 2.

The ν(C=S) stretching band underwent an upward shift by 15-23 cm^{-1} upon complexation, indicting the coordination of the thionine sulfur with these metal ion (Ingale, 2014). The broad band at 3417 cm^{-1} in the spectrum of the ligand which was assigned to ν(-OH) of the indole ring disappeared in the spectra of the complexes. This is an evidence of the coordination of this group with these metal ions after deprotonation. The assigned to ν(C-O) was located at 1296 cm^{-1} in the spectrum of the ligand (Tawfiq, 2010 and Ceyhan *et al.,* 2015) shifted to 1319 cm^{-1} in the spectra of the complexes which is another supporting evidence for the coordination of indolic oxygen to the metal ions (Khan *et al.,* 2015). The new broad band at 3402 cm^{-1} in the spctra of the complexes was assigned to the ν(OH) of water of crystallization (Tawfiq, 2010).

Table 2: Infrared spectral data of the ligand and its complexes

Schiff base & Complexes	ν (C=N) (cm^{-1})	ν (C=N) (Ring) (cm^{-1})	ν (C=S) (cm^{-1})	ν (O-H) (cm^{-1})	ν (H_2O) (cm^{-1})	ν (C-O) (cm^{-1})	ν (M-N) (cm^{-1})
$C_9H_8N_4OS$	1681	1643	1134	3417	-	1233	-
$[Ni(C_9H_7N_4OS)_2].3H_2O$	1504	1643	1157	-	3466	1298	447
$[Cu(C_9H_7N_4OS)_2].3H_2O$	1519	1643	1149	-	3417	1240	455

L= $C_9H_7N_4OS$

Determination of metal content

The metal component in these complexes was determined using AAS. The absorbance of Ni(II) and Cu(II) complexes were 0.002 and 0.113 respectively. These absorbance values were used to extrapolate and obtain the respective metal concentrations. The percentages of metal ions compositions in these complexes were determined using the equation

$$\%\ of\ Metal = \frac{concetration\ obtained}{cocentration\ prepared} \times 100\%$$

The percentages of nickel and copper in the respective complexes were found to be 10.52 and 11.18% respectively (Table 3).

Table 3: Percentages of Ni(II) and Cu(II) ions in the complexes

Complex	Absorbance	Conc. (ppm)	% of metal %
$[Ni(C_9H_7N_4OS)_2].3H_2O$	0.002	10.52	10.52
$[Cu(C_9H_7N_4OS)_2].3H_2O$	0.113	11.18	11.18

The synthesized complexes were found to be hydrated and the water content in them was determined. The percentage of water was found to be 10.60% and 9.10% for the Ni(II) and Cu(II) complexes respectively. This is as shown in Table 4.

Table 4: Percentage of water of crystallization in the Ni(II) and Cu(II) complexes

Complex	Intial mass (g)	Final mass (g)	Loss in mass (g)	% of water
$[Ni(C_9H_7N_4OS)_2].3H_2O$	0.2018	0.1804	0.0214	10.60
$[Cu(C_9H_7N_4OS)_2].3H_2O$	0.2000	0.1818	0.0182	9.10

From the results of the above analyses and the information available from the literature, the empirical formulae of these complexes were determined. The results obtained suggested the general formula $[ML_2].3H_2O$ where M = Ni^{2+} or Cu^{2+} as presented in Table 5.

Table 5: Determination of empirical formulae of the complexes

Species	**Ni**	**L**	**H_2O**	**Cu**	**L**	**H_2O**
% by mass	10.52	78.88	10.60	11.18	79.72	9.10
Moles	0.18	0.36	0.59	0.18	0.36	0.51
Mole ratio	1.0	2.0	3.3	1.0	2.0	2.8
Empirical Formula		**$[NiL_2].3H_2O$**			**$[CuL_2].3H_2O$**	

L= $C_9H_7N_4OS$

The ligand and the complexes were evaluated for antibacterial activities using three bacteria isolate namely, *salmonella typhirium, Staphylococcus Aureus* and *Escherichia Coli.* Amoxicillin as standard drug to serve as positive control. A comparative study on the antimicrobial activities of these compounds indicated that the metal complexes exhibited higher antibacterial activity than the ligand but lower antibacterial activity compared with the standard. These compounds were tested for antifungal activity against *mucor spp, aspergillus niger and aspergillus flavus* using Ketoconazole as standard. The result revealed that all the synthesized compounds were active on the three organism. The result further indicated that complexes exhibited higher potential as antifungal growth inhibition compared to the ligand, but less so less active than ketoconazole. These results are similar to that of Nair and Joseyphus, 2010, Ahmed *et al.,* 2011and Kothari, 2015 and are recorded in Table 6.

Table 6: Zone of inhibition (mm) for Antibacterial assay of the ligand and its Ni(II) and Cu(II) complexes

Antimicrobial analysis	**Antibacterial (Inhibition zone in mm)**						**Antifungal (Inhibition zone in mm)**					
Isolate	***E. Coli***		***S. typhi***		***S. Aureus***		***Mucus (indicus specie)***		***A. flavus***		***A. Niger***	
Compd/conc. (µg/disc)	200	300	200	300	200	300	200	300	200	300	200	300
Ligand	10	13	12	13	9	10	14	16	6	6	12	13
$[NiL_2].3H_2O$	10	14	14	15	10	14	15	18	9	11	10	11
$[CuL_2].3H_2O$	13	15	13	14	10	12	14	17	7	8	12	13
Amoxicillin	21	29	20	25	17	24	-	-	-	-	-	-
Ketoconazole	-	-	-	-	-	-	20	26	18	27	19	23

From the results of the analyses on these compounds and the information available in the literature, we suggest the following general structure for these complexes as presented in figure 3:

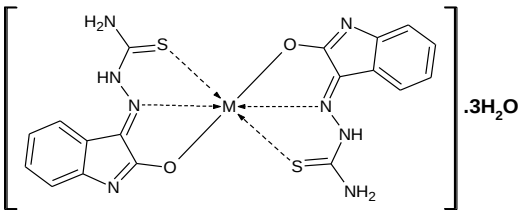

Figure 3: The proposed structure of the complexes M = Ni^{2+} and Cu^{2+},

CONCLUSION

We have successfully synthesized the thiosemicarbazone from the condensation of from 1H-indole-2,3-dione (Isatin) and thiosemicarbazide. Ni(II) and Cu(II) complexes of were synthesize from the ligand successfully. The ligand and complexes were characterized using various spectroscopic techniques; and their antibacterial and antifungal activities were studied using Amoxicillin and ketoconazole as standards respectively. The results of the antimicrobial studies revealed that the ligand and the complexes are more active on *E. coli* and *S. typhirium* than they are on *S. aureus* though they are not as active as Amoxicillin. As for the anti-fungal activity, the ligand shows no activities on *A. flavus* and *mucur spp* respectively, while Ni (II) complex show no effect on *A. niger*. The antimicrobial activities of these compounds are less than that of Ketoconazole that was used as standard drug.

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