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Abstract: Complexes of isonicotinic acid hydrazide with Cu(II), Co(II) and Ni(II) have been prepared and characterized by analytical and physico-chemical techniques, such as elemental analysis, melting point and solubility studies, magnetic susceptibility and conductivity measurements, electronic and IR spectral studies. The infrared spectral studies revealed the bidentate nature of the Schiff base in the complexes; the ligand acting as neutral bidentate donor coordinating to the metal through the carbonyl O and the azomethine N. An octahedral geometry is suggested for all the complexes. The compounds were subjected to antimicrobial screening using serial broth dilution method and they show moderate antimicrobial activity.

Keywords: Antimicrobial activity, hydrazide, reflux, transition metal complex, synthesis

Introduction

Hydrazides and their derivatives are well known biologically active substances used in medicine as therapeutic drug and their efficacy is enhanced upon coordination with a metal ion (Anderson *et al.*, 2004; Casanova *et al.*, 1993; Ogunniran *et al.*, 2007). This had led to investigations on metal-drug interactions and more studies on complexes of metal hydrazides with the aim of discovering more effective chemotherapeutic agents to fight diseases (Obaleye *et al.*, 2000).

There has been increasing interest in the study of hydrazides due to their physiological activity, coordinative capability and applications in analytical chemistry (Dnyandeov *et al.*, 2015; Sule and Nwabueze, 2013). Compared to the simple hydrazide Schiff bases, aryl or heteroaryl Schiff bases have additional donor sites. This introduces a wider range of properties like antibacterial, anticonvulsant, analgesic, anti-inflammatory and antitumor activities. In general, acid hydrazides R-CO-NH-NH₂, acts as chelating ligands with transition metal ions by binding through the N atom of azomethine group and O atom of carbonyl group and therefore this type of compounds can coordinate *in vivo* to metal ions. The aim of the present investigation is to synthesize various transition metal complexes of Schiff base derived from isonicotinic acid hydrazide.

Materials and Methods

Reagents/solvents and instrumentation

All chemicals used were of analytical grade bought from Sigma-Aldrich Chem. Co. and used without further purification. The decomposition temperature and melting point of the ligand and complexes was taken using Gallenkamp apparatus. Conductivity measurements were also carried out using HANNA instrument conductivity meter for the freshly prepared solutions in DMSO solvent while magnetic susceptibility measurement were also taken using a Gouy balance. The electronic spectra of the ligand and complexes were determined in DMSO solvent using PD303 UV spectrophotometer. Infrared spectra was taken using Shimadzu FT-IR Spectrometer 8400S (4000 - 400 cm⁻¹) using KBr pellets.

Preparation of isonicotinic acid hydrazide (INH)

The ligand (INH) was prepared using standard method (Salawu *et al.*, 2015). 15.1 mL (15 g, 0.30 mol) of hydrazine hydrate was added to 45.35 mL (45 g, 0.3 mol) of ethylisonicotinate in 100 mL of absolute ethanol and refluxed for six hours in a 250 mL round-bottom flask. The mixture was transferred into a beaker and was left overnight to

crystallize. The resulting crystals were recrystallized from absolute ethanol and finally dried over CaCl₂ in a desiccator and weighed.

Preparation of metal complexes

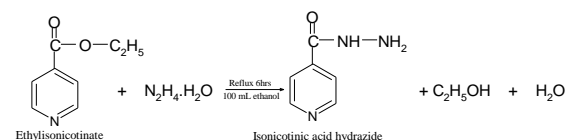
The metal complexes were prepared by using standard method (Salawu *et al.*, 2015). The metal complexes have been prepared by mixing the ethanolic solution of Cu(NO₃)₂·3H₂O, Co(NO₃)₂·6H₂O and Ni(NO₃)₂·6H₂O to the ethanolic solution of the hydrazide placed on a magnetic stirrer with a constant stirring for about 10 min after which it was left for about 1 hour to cool. The crystals obtained were filtered and dried in a CaCl₂ desiccator and weighed.

Antibacterial studies

The antibacterial activity of the ligand and its complexes was evaluated by the serial broth dilution method in a medium of agar nutrient on gram-positive bacteria (*Streptococcus* and *Staphylococcus*) and gram-negative bacteria (*Escheria coli* and *Salmonella*) using nutrient agar.

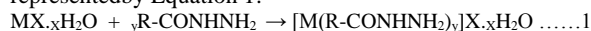
Results and Discussion

The preparation of the hydrazide as ligand from ethylisonicotinate and hydrazine hydrate was represented by the reaction in scheme 1:



Scheme 1: Preparation of isonicotinic acid hydrazide

The reaction of the metal(II) salts and the hydrazide from the equation above, to form metal complexes can be represented by Equation 1:



Where M = Cu, Co, Ni, x = 1/4, X = NO₃, y = 1/2

Complexes of type [M(INH)₂(H₂O)₂](NO₃)₂ were obtained upon the reaction of Cu(II), Co(II) and Ni(II) nitrate with the ligand [INH]. All the complexes were colored, solid and partially soluble in common polar solvents but soluble in DMSO. They decompose on heating at high temperature. The elemental analysis is in good agreement with the chemical formula proposed for complexes. The molar conductance in DMSO of the complexes are 0.16, 0.26 and 0.25 mScm²mol⁻¹, respectively for Cu(II), Co(II) and Ni(II) complexes of [INH]. The very low conductance value shows the non-electrolytic

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nature of the complexes (Dnyandeo *et al.*, 2015; Kamalakev *et al.*, 2015). The analytical and physical data (melting point, color and molar conductivity) of the complexes are shown in Table 1.

Table 1: Physical and analytical data of Ligand and metal complexes

Compound/Molecular weight (Colour)	Yield (%)	Λ_m mScm ² mol ⁻¹	M.P. °C	Elemental analysis found/ Calculated (%)				
				C	H	N	M	NO ₃ ⁻
[INH]	3.24	–	171	51.45	4.98	30.55	–	–
137.000 (White)	(82)			(52.56)	(5.11)	(30.66)		
[Cu(INH) ₂ (H ₂ O) ₂](NO ₃) ₂ 497.546 (Green)	1.21	0.16	198	28.91	3.58	21.88	12.80	25.00
	(68)			(28.94)	(3.62)	(22.51)	(13.00)	(25.17)
[Co(INH) ₂ (H ₂ O) ₂](NO ₃) ₂ 492.933 (Pale red)	1.08	0.26	200	29.20	3.52	21.72	11.81	25.10
	(63)			(29.21)	(3.65)	(22.72)	(11.96)	(25.15)
[Ni(INH) ₂ (H ₂ O) ₂](NO ₃) ₂ 492.693 (Purple)	1.03	0.25	220	28.99	3.53	22.70	11.90	25.10
	(66)			(29.22)	(3.65)	(22.73)	(11.92)	(25.16)

INH = Isonicotinic acid hydrazide

Infrared spectra

The IR band assignment of ligand and complexes is shown in Table 2. The broad band absorption in the region 3439-3408 cm⁻¹ in the complex is ascribed to water (Roman and Chundak, 2014). In the IR spectra of INH, the average intensity band which appear at 3113 cm⁻¹ was assigned to ν (N-H) vibration (Reddy *et al.*, 2015). The vibration frequencies ν N-H are strongly displaced in all complexes. The displacements suggest the involvement of the azomethine nitrogen in coordination with metallic ions (Amudat, 2010). In accordance with this is the fact that the vibration frequency ν N-N is displaced towards lower values in IR spectra of hydrazides complexes.

A strong band was observed at 1654 cm⁻¹ in INH assignable to ν (C=O). The band position of ν (C=O) has shifted to lower frequency by 14-17 cm⁻¹ in the complexes on coordination of metal ions indicating the involvement of the carbonyl group in bonding to metal (Dianu *et al.*, 2009). The free ligand INH also exhibited a strong band at 1556 cm⁻¹ which was assigned to ν (C=N). This band shifts to higher energy region by 6-62 cm⁻¹ in the complexes. It suggests bonding through the azomethine Nitrogen (Dnyandeo *et al.*, 2015). In the IR spectra of complexes, a very intense band appears at 1384 cm⁻¹ which is assigned to NO₃⁻ anion (Dianu *et al.*, 2009). In the region 600-400 cm⁻¹ range, bands associated to ν (M-N) and

ν (M-O) have been assigned and are in good agreement with data found in the literature (Nakamoto, 1992).

Electronic spectra

From Table 3, the UV/Visible spectra of the ligand isonicotinic acid hydrazide shows two bands at 360 and 440 nm. These bands have been shifted to longer wavelengths in the metal complexes which indicate complexation (Kamalakev *et al.*, 2015).

The electronic spectrum of [Cu(INH)₂(H₂O)₂](NO₃)₂ presents two bands at 355 and 560 nm, which can be attributed to the $d_{xy} \rightarrow d_{x^2-y^2}$ and $d_{z^2} \rightarrow d_{x^2-y^2}$ transitions, respectively; while the magnetic moment is 2.20 BM proper for an octahedral geometry. In the spectrum of [Co(INH)₂(H₂O)₂](NO₃)₂, bands were also located at 350 and 530 nm which were assigned to $n \rightarrow \pi^*$ and ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}$, respectively while the magnetic moment is 5.44 BM. This information is in favour of an octahedral geometry. The absorption band of [Ni(INH)₂(H₂O)₂](NO₃)₂ consists of three bands and a shoulder located at 358, 508, 608 and 750 nm which were assigned to $n \rightarrow \pi^*$, ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$, ${}^3A_{2g} \rightarrow {}^3T_{1g}$ and ${}^3A_{2g} \rightarrow {}^3T_{2g}$, respectively while the magnetic moment is 3.12 BM. Thus the octahedral geometry is also suggested for this complexes (Ababei, 2012).

Table 2: IR bands of Ligands and their complexes

Compound	ν (N-H)				ν (M-O)	ν (M-N)	ν (OH)	ν (NO ₃)
INH	1556	3113	1062	1668	-	-	-	-
[Cu(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	1550	3205	1058	1654	468	626	3416	1384
[Co(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	1597	3142	1018	1651	472	557	3408	1384
[Ni(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	1597	3144	1020	1651	478	557	3416	1384

Table 3: Electronic spectral/magnetic moment data for the ligands and complexes

Compound	λ , nm	Assignment	Geometry	M.M (B.M)
INH	360 440	–	–	–
[Cu(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	355 560	$d_{xy} \rightarrow d_{x^2-y^2}$ $d_{z^2} \rightarrow d_{x^2-y^2}$	Octahedral	2.20
[Co(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	350 530	$n \rightarrow \pi^*$ ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}$	Octahedral	5.44
[Ni(INH) ₂ (H ₂ O) ₂](NO ₃) ₂	358 508 608 750	$n \rightarrow \pi^*$ ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g} \rightarrow {}^3T_{1g}$ ${}^3A_{2g} \rightarrow {}^3T_{2g}$	Octahedral	3.12

Antimicrobial activity

In an urge to develop new antimicrobial compound, a number of hydrazides were tested for their antimicrobial activities against

two gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two gram-negative bacteria

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(*Escherichia coli* and *Salmonella typhi*) because of the evolution of drug-resistant microbial pathogens.

The compounds are found to show low bactericidal behavior against most of the bacterial culture and resistance towards the other. In general the results reveal that the activity of the ligand was found to enhance on complexation with metal. The inhibition effect of the ligand and its metal complexes on the growth of various bacteria is summarized in Table 4.

Table 4: Zones of inhibition of bacteria in the presence of ligand and complexes

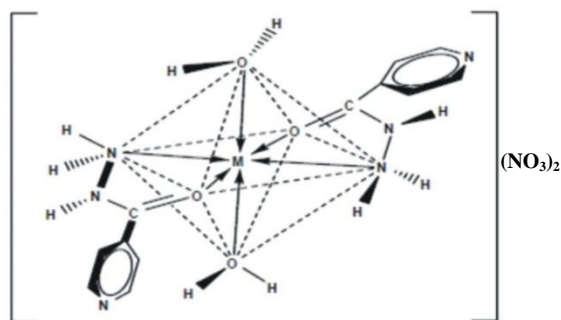
Complex	Zone of inhibition (mm)	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>E. coli</i>	<i>S. typhi</i>
INH		4	R	7	R
[Cu(INH) ₂ (H ₂ O) ₂](NO ₃) ₂		R	R	8	10
[Co(INH) ₂ (H ₂ O) ₂](NO ₃) ₂		R	15	6	R
[Ni(INH) ₂ (H ₂ O) ₂](NO ₃) ₂		10	R	5	R

R = Resistance, INH = Isonicotinic acid hydrazide

The result shows that isonicotinic acid hydrazide is slightly active to only *Staphylococcus aureus* and *Escherichia coli*. But for the complexes, [Ni(INH)₂(H₂O)₂](NO₃)₂ is active against *Staphylococcus aureus* while the other complexes were resistant to *Staphylococcus aureus*. [Co(INH)₂(H₂O)₂](NO₃)₂ was sensitive to *Streptococcus pyogenes* while the remaining complexes were non-sensitive. All the complexes were sensitive to *Escherichia coli*. Only [Cu(INH)₂(H₂O)₂](NO₃)₂ was active to *Salmonella typhi*. Hence, the result of these studies showed that all the metal complexes are more effective antibacterial than the ligand against the tested species. It was observed that metal chelation has affected significantly the antimicrobial behaviour of the ligand (Anderson *et al.*, 2004; Casanova *et al.*, 1993; Ogunniran *et al.*, 2007). The results indicate that the ligand and the complexes have antibacterial activity against some of the tested microorganisms.

Conclusions

The ligand synthesized is acting as bidentate NO, coordinating the metallic ion through the carbonyl oxygen atoms and the azomethine nitrogen atoms. All the studies suggest an octahedral surrounding of the Cu(II), Co(II) and Ni(II) metal ions. From all the available data, the probable structures for the complexes have been proposed as shown in Scheme 2.



M = Cu(II); Co(II); Ni(II)

Scheme 2: Proposed structure of Cu(II), Co(II), and Ni(II) for octahedral geometry

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