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SYNTHESIS AND CHARACTERIZATION OF HETEROLEPTIC METAL COMPLEXES OF ISONIAZID AND METFORMIN

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ABSTRACT

Mixed ligand complexes of Metformin and Isoniazid have been synthesized and characterized by solubility studies, percentage metal analysis, UV-Vis spectroscopy, IR spectroscopy, magnetic moments and conductivity measurements. The infrared spectra revealed the coordination of the ligands to the metal ions [manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II)]. Meformin coordinated as a bidentate ligand via the imine nitrogen while isoniazid coordinated through its amino nitrogen (NH_2) and carbonyl oxygen (C=O). The electronic spectra and magnetic moments for the complexes strongly suggested a six coordinate octahedral geometry. The molar conductance values of the complexes are within the range 0.45-8.72 $\Omega^{-1}cm^2mol^{-1}$, and this confirms the non-electrolytic nature of the complexes.

INTRODUCTION

1,1-dimethylbiguanide hydrochloride commonly known as metformin hydrochloride is a well-known anti-diabetics drug, it is primarily used for type 2 diabetes, but is increasingly having a role in treating polycystic ovarian syndrome which can cause obesity and infertility (Aljada and Mousa, 2012). It acts by lowering blood glucose levels primarily by decreasing the amount of glucose produced by the liver. It can also decrease the amount of sugar absorbed into the body (from the diet) and can make insulin receptors in muscle tissue more sensitive, thereby helping the body respond better to its own insulin. A side effect of metformin may be diarrhea, but this is improved when the drug is taken with food, other effects include cramps, nausea, vomiting, and increased flatulence than most other anti-diabetic drugs (Bolen *et al*, 2007: Khurana and Malik, 2010).

Isonicotinylhydrazide commonly known as isoniazid was introduced into medical practice in 1952 and is used in the treatment of tuberculosis (Donald, 2010). Complexes of isoniazid have been reported to be relatively stable as well as exhibit interesting biological activities (Botarri *et al*., 2000). This has led to increased studies with respect to the synthesis and structural elucidation of metformin and isoniazid complexes (Al-Abdali *et al.*, 2015; Bamigboye *et al.*, 2012; Sharma *et al.*, 2011)

However studies on the synthesis, and structural elucidation of the mixed ligand complexes of metformin and Isoniazid, has not been reported hence this study. The results of the study are herein reported.

EXPERIMENTAL

All the chemicals and solvents used in the study were obtained from BDH and Bond Pharmaceutical, Awe, Oyo State, Nigeria. They were used without further purification. They are Isonicotinylhydrazide (Isoniazid), 1,1-dimethylbiguanide hydrochloride (Metfomin), Sodium hydroxide pellets, nitric acid, dimethyl-sulphoxide (DMSO), dimethyformamide (DMF), hexane, diethylether, acetone, acetonitrile, methanol, ethanol, perchloric acid, hydrochloric acid, copper(II) chloride dihydrate, nickel(II) chloride hexahydrate, zinc(II) chloride, cobalt(II) chloride hexahydrate, manganese(II) chloride tetrahydrate. The percentage metal content was determined using EDTA and atomic absorption spectroscopy (AAS). The infrared spectra were recorded in the 4000–400 cm^{-1} region with a Shimadzu FT-IR 8000 spectrophotometer using KBr pellets. UV-Visible spectra of the samples were measured in the range 800-200 nm using a Shimadzu UV-Vis 1800 spectrophotometer. Magnetic susceptibility measurements were carried out at room temperature using a Sherwood Scientific MXI model Gouy magnetic while the melting points of the compounds were

determined using a Gallenkamp melting point apparatus.

Synthesis of mixed ligand complexes

Solution of each of the metal salts (1.0 mmol of $CoCl_2.6H_2O$, $CuCl_2.2H_2O$, $MnCl_2.4H_2O$, $ZnCl_2$, $NiCl_2.6H_2O$) in 10 ml of methanol was added dropwise into stirring methanolic NaOH solution of metformin hydrochloride (2.0 mmol) and isoniazid (1.0 mmol). The solution was stirred for two hours, during which precipitate was formed. The product was filtered, washed with excess ethanol and dried over anhydrous calcium chloride.

RESULTS AND DISCUSSION

The mixed ligand complexes showed high melting points and displayed a variety of colours ranging from black to blue. The complexes had high melting points with a range of 280 – 350 °C. These high melting points when compared to that of metformin and isoniazid, 223 – 226 °C and 170 – 173 °C respectively suggest high thermal stability of the synthesized complexes. The theoretical % metal in the mixed ligand complexes of metformin with isoniazid showed a fairly good correlation with the experimental values as shown in Table 1. The complexes were obtained in appreciable yield ranging from 55.71 - 75.32 %. The reaction of isoniazid and metformin hydrochloride with hydrated metal salts in methanolic sodium hydroxide produces the mixed ligand metal complexes displayed in Equation 1. All the complexes synthesized were insoluble in water and other common solvents, except dimethylsufoxide (DMSO).

$$MCl_2.XH_2O + MET + INA \xrightarrow[NaOH]{MeOH/} [M(MET)(INA)Cl_2] \text{ --------- } 1$$

Table1: Physical properties and analytical data for compounds

COMPOUNDS	Formula/(formula weight(g))	Colour	Melting point (°C)	% metal found (calc)	% yield
MET	$C_4N_5H_{11}$ (129.167)	White	223-226	-	-
INA	$C_6N_3H_7O$ (137.142)	White	170-173	-	-
$[Mn(MET)(INA)Cl_2].2H_2O$	$C_{10}N_8H_{22}O_3Cl_2Mn$ (428.249)	Black	292	13.10 (12.83)	68.13
$[Co(MET)(INA)Cl_2].2H_2O$	$C_{10}N_8H_{22}O_3Cl_2Co$ (432.239)	Dark brown	>300	14.00 (13.63)	55.71
$[Ni(MET)(INA)Cl_2]$	$C_{10}N_8H_{18}OCl_2Ni$ (396.002)	Yellow	>300	14.03 (14.82)	75.32
$[Cu(MET)(INA)Cl_2]$	$C_{10}N_8H_{18}OCl_2Cu$ (400.859)	Blue	>300	15.18 (14.54)	54.54
$[Zn(MET)(INA)Cl_2]$	$C_{10}N_8H_{18}OCl_2Zn$ (402.718)	White	>300	15.63 (16.23)	59.90

Infrared Spectra

The infrared spectra data of the metal(II) complexes of Metformin and Isoniazid are shown in Table 2, while the representative infrared spectrum is displayed in Figure 1.

From the infrared interpretation of the ligands, there are various specific bands of importance (Gunasekaran. *et al.,* 2009; Socrates, 2004). These bands are due to the amido group (N-H), carbonyl group ν(C=O), and imine group ν(C=N), found in both ligands and C-N which occurs in metformin. These bands undergo shifts on complexation which provides an evidence of coordination. Additional bands due to metal-oxygen and metal-nitrogen bond which were absent in the spectra of the ligands are usually observed in the spectra of the metal complexes which further provide further evidence for coordination (Neelamma *et al.*, 2010).

In the Isoniazid spectrum there are two vibrational bands at 3300 and 3209 cm^{-1} while the bands at 3300 and 3176 cm^{-1} in the metformin spectrum correspond to asymmetric and symmetric stretching of $-NH_2$ group. In all the metal(II) complexes, with the exception of Co(II)

and Mn(II) complexes which showed broad band of v(O–H) at 3425 and 3414 cm^{-1}, the band assigned as v(N-H) in the metformin spectrum at 3372 cm^{-1} showed a shift to lower frequencies in the complexes, strongly suggesting metal ion coordination.

The infrared spectra of the complexes revealed that isoniazid acted as a bidentate ligand coordinating through the amino nitrogen (NH_2) and carbonyl oxygen (C=O). The carbonyl v(C=O) appeared at band 1667 cm^{-1}. In the metal(II) complexes this band shifted to lower frequencies, with differences of 30 –40 cm^{-1}, thus suggesting metal coordination through the carbonyl (–C=O) group (Gunasekaran. *et al.*, 2009). On the other hand, the v(N-H) in the Isoniazid spectrum at 3114 cm^{-1} showed shifts to higher frequencies in the complexes, revealing that the amide nitrogen of the isoniazid did not take part in coordination (Gunasekaran. *et al.*, 2009). However in Co(II) and Mn(II) complexes, a broad band of v(O–H) at 3425 and 3414 cm^{-1} was observed thus confirming the presence of water molecules in the complexes.

The appearance of new bands at the low frequency region of the infrared spectra gives an evidence of coordination as the bands were assigned to M–N and M–O stretching vibrations (Kriza *et al.*, 2010).

Table 2: Infrared spectral data of complexes of metformin with isoniazid (cm^{-1})

Compounds	$\nu_{(O-H)}$	$\nu_{(N-H)}$	$\nu_{(N-H)}$	$\nu_{(C=O)}$	$\nu_{C=N)}$	$\nu_{(C-N)}$	$\nu_{(en)py}$	$\nu_{(M-N)}$	$\nu_{(M-O)}$
MET	-	3372w	3300, 3176m	-	-	1170m	-	-	-
INA	-	3114	3300, 3204	1667	1334	-	1635, 1557	-	-
$[Mn(MET)(INA)Cl_2].2H_2O$	3414b	-	-	1645	1383	1188	1681, 1546	611w	515w
$[Co(MET)(INA)Cl_2].2H_2O$	3425b	-	-	1645	1384	1188	1681, 1548	626w	561w
$[Ni(MET)(INA)Cl_2]$	-	3180	3365, 3269	1643	1367		1681, 1518	646w	545w
$[Cu(MET)(INA)Cl_2]$	-	3057	3360, 3263	1633	1392	1195	1672, 1566	621w	530w
$[Zn(MET)(INA)Cl_2]$	-	3373	3497, 3450	1633	1392	1195	- 1554	640w	572w

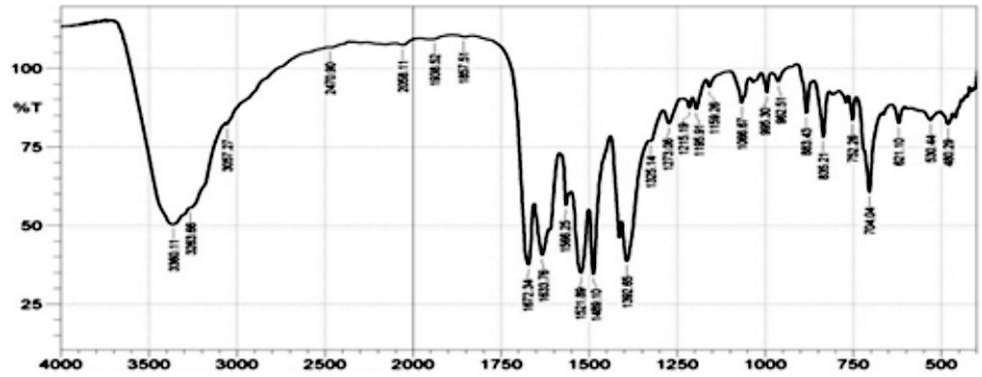

Figure 1: Infra-red spectrum of [Cu(MET)(ISN) Cl_2]

Electronic Spectra

The electronic spectral data measured in dimethylsulfoxide (DMSO) for the synthesized mixed ligand complexes is shown in Table 3, while the electronic spectrum of the copper complex is displayed in Figure 2.

A comparison of the electronic spectra of the free ligands with those of their corresponding metal complexes show some shifts that can be considered as evidence for complex formation (Refat and El-Metwaly, 2012). Upon complexation, the ligand centered bands ($n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$,) undergo an intensity increase with a slight shift relative to the ligand and d-d transitions which are responsible for the characteristic colours of these complexes.

In the UV spectrum of Metformin ligand, a prominent band at 234 nm is assigned for the intraligand $n\rightarrow\pi^*$ transition in the amide group moiety. The ligand INA showed a sharp band at 263 nm which is assigned to $\pi\rightarrow\pi^*$.

The visible spectrum copper(II) complex of metformin mixed with isoniazid showed a single band at 678 nm and a shoulder at 528 nm due to Jahn-Teller distortion. This is consistent with the $^{2}T_{2g} \leftarrow {}^{2}E_{g}$ transition in an octahedral environment (Lee, 1996).

In the ligand field spectrum of Co(II) complex of MET mixed with INA two d–d bands (486, 552 nm) are observed. The lowest energy band (high wavelength) at 552 nm is assigned to the $^{4}T_{2}g \leftarrow {}^{4}T_{1}g$ transition, this assignments supports the proposed octahedral geometry for the complex (Cakir *et al.*, 2001; Lee, 1996).

The visible spectrum of Ni(II) complex of metformin mixed with isoniazid shows three band at 688, 610, and 418 nm. The bands are due to $^{3}T_{1g} \leftarrow {}^{3}A_{2g}$, $^{3}T_{1g}(F) \leftarrow {}^{3}A_{2g}$, $^{3}T_{1g}(P) \leftarrow {}^{3}A_{2g}$ transitions respectively. The assignments also support octahedral geometry. The Mn(II) complexes of metformin mixed with isoniazid showed weak absorption in the visible region, which is due to spin forbidden transitions (Lee, 1996). There was an absence of bands in the visible region for zinc complexes as they do not undergo d–d transitions (Lee, 1996).

Table 3: The electronic spectral data of complexes of metformin with isoniazid

Compounds	Intraligand transition (nm)	Charge transfer (nm)	Ligand field d-d transition (nm)	Assignment	Proposed geometry
MET	234	-	-	-	-
INA	263	-	-	-	-
$C_{10}N_8H_{22}O_3Cl_2Mn$	-	417	620, 650, 671	Low intensity spin forbidden transitions	Octahedral
$C_{10}N_8H_{22}O_3Cl_2Co$	367	-	486 552	$^{4}T_{1}g \leftarrow {}^{4}A_{2}g$ $^{4}T_{1}g \leftarrow {}^{4}T_{2}g$	Octahedral
$C_{10}N_8H_{18}OCl_2Ni$	340	-	418 610 688	$^{3}T_{1g}(P) \leftarrow {}^{3}A_{2g}$ $^{3}T_{1g}(F) \leftarrow {}^{3}A_{2g}$, $^{3}T_{1g} \leftarrow {}^{3}A_{2g}$,	Octahedral
$C_{10}N_8H_{18}OCl_2Cu$		358	608(sh), 678	$^{2}T_{2g} \leftarrow {}^{2}E_{g}$	Octahedral
$C_{10}N_8H_{18}OCl_2Zn$	298	-	-	-	Octahedral

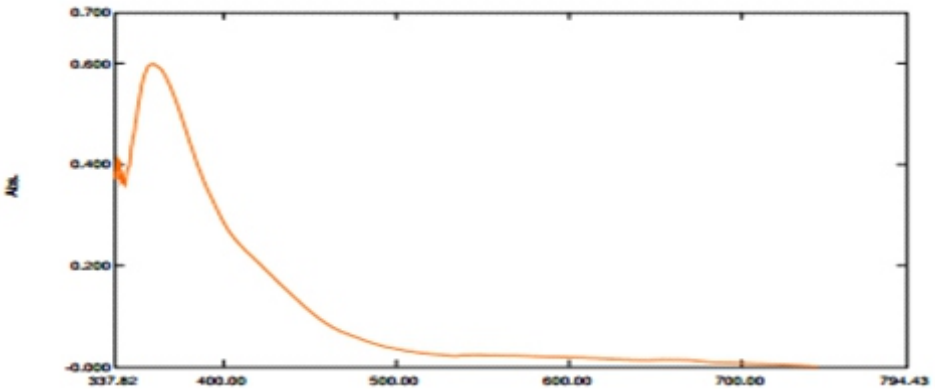

Figure 2: Electronic spectrum of [Cu(MET)(ISN)Cl_2]

Magnetic Moment

All the complexes are paramagnetic while the Zn(II) complex is diamagnetic. This is shown by the magnetic moment values obtained for the complexes as shown in Table 4. The spin only magnetic moment for copper complex is 1.73 BM. The magnetic moment values for copper(II) complex was 1.34 BM which reveals its mononuclear nature and suggests an octahedral geometry. The low value suggests antiferromagnetism (Osowole *et al*., 2014). The magnetic moment values of 3.18 BM and 2.00 BM for cobalt and nickel complexes respectively supports octahedral geometry, however the values also reveal the likelihood of antiferromagnetism as they are lower than the spin only magnetic moment expected for these complexes (Lee, 1996; Akinyele *et al*. 2019). The magnetic moment value for manganese complex was 5.95 BM this strongly suggests an octahedral geometry (Lee, 1996). The values derived from the UV-Visible spectroscopic data and magnetic moments suggest an octahedral geometry for the complexes.

Table 4: Magnetic susceptibility data of the complexes of metformin with isoniazid

Compounds	Temp. (K)	μ_{eff} (BM)	μ_s (BM)
$C_{10}N_8H_{22}O_3Cl_2Mn$	298	5.95	5.92
$C_{10}N_8H_{22}O_3Cl_2Co$	298	3.18	3.87
$C_{10}N_8H_{18}OCl_2Ni$	298	2.00	2.83
$C_{10}N_8H_{18}OCl_2Cu$	298	1.34	1.73
$C_{10}N_8H_{18}OCl_2Zn$	298	Diamagnetic	0.00

Conductivity measurements

The conductivity measurement of each complex was done using DMSO and the results are presented in Table 5. The molar conductivities in DMSO for all the complexes are in the range 0.45 – 8.72 Ω^{-1} cm^2mol^{-1}, indicating their non-electrolytic nature (Geary, 1971). The low values of molar conductance indicate that the metal complexes did not dissociate in the solvent, while the chloride ion satisfied both the primary and secondary valencies of the metals as shown in Figure 3.

Table 5: Molar conductance values of complexes of metformin with isoniazid in ($\Omega^{-1}cm^2mol^{-1}$)

Compounds	Λm ($\Omega^{-1}cm^2mol^{-1}$)	Solvent
[Cu(MET)(ISN) Cl_2]	8.72	DMSO
[Fe(MET)(ISN) Cl_2]	6.50	DMSO
[Ni(MET)(ISN)Cl_2]	3.80	DMSO
[Mn(MET)(ISN)Cl_2].2H_2O	0.45	DMSO
[Co(MET)(ISN)Cl_2].2H_2O	6.30	DMSO
[Zn(MET)(ISN)Cl_2]	4.94	DMSO

CONCLUSION

The synthesis and characterization of Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) complexes of metformin mixed with isoniazid was carried out. The compounds were characterized by UV-Visible spectroscopy, infrared spectroscopy, metal analysis, conductivity and magnetic measurements.

The complexes were insoluble in water and display varying degree of solubility in six common solvents including dimethylsulfoxide (DMSO). The infrared spectra revealed coordination of the ligand to the metal ion via the amine nitrogen (NH_2), carbonyl (C=O) of Isoniazid, and the imine (C=N) nitrogen of metformin. The electronic spectra in conjunction with the magnetic moments suggested a six coordinate octahedral geometry. These observations were supported by the molar conductance values which also suggested the non-electrolytic nature of the complexes.

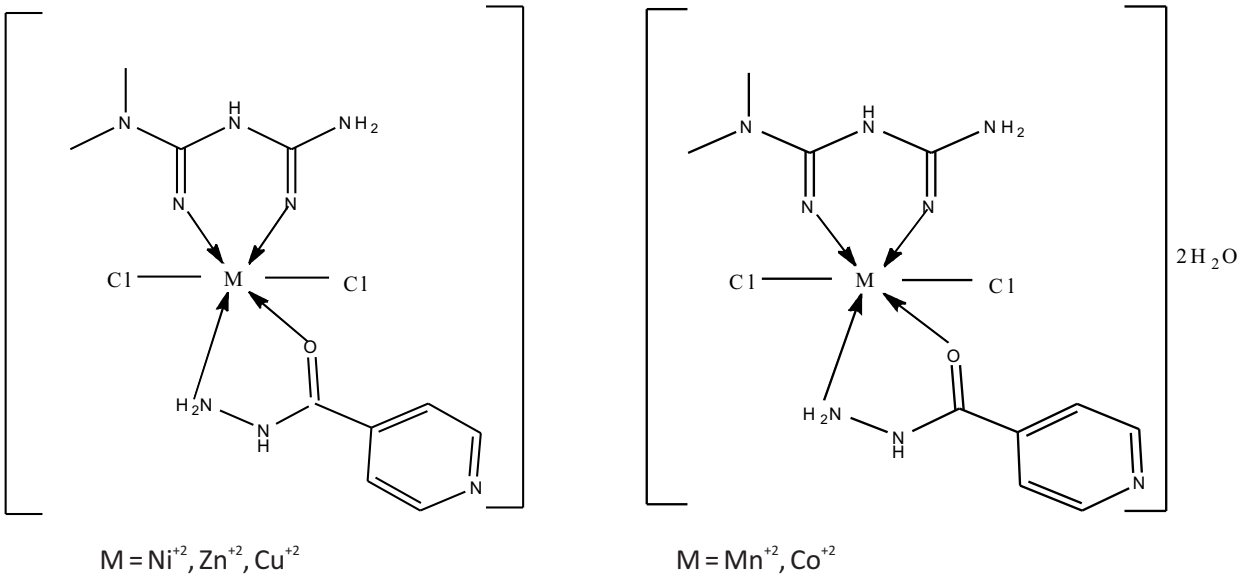

Figure 3: Proposed Structure of Mixed Ligand Metal Complexes of Metformin with Isoniazid

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