STUDIES ON THE COMPLEXES OF ISONICOTINOYL 2-CHLOROBENZALDEHYDE HYDRAZONES WITH CU II AND MN II AND THEIR ANTIMICROBIAL STUDIES

[1]O. Idoko, [2]S. Mamman, [3]P. Ukoha and [4]I. Abdullahi

[1]Chemistry Advanced Research Center, Sheda Science and Technology Complex, PMB 186, FCT, Abuja, Nigeria.
[2,4]Department of Chemistry, University of Abuja, FCT, Nigeria
[3]Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.
Email: owoichoidokos@gmail.com Phone: 07068688448

ABSTRACT

Complexes isonicotinoyl 2-chlorobenzaldehyde hydrazone with Mn II and Cu II were synthesized and characterized using UV visible spectrophotometry, Infrared spectrophotometry Atomic Absorption Spectrophotometry, melting point, solubility test, conductivity measurement, magnetic susceptibility. Some bacterial and fungal strains were used to screen for the biological activities of the ligands and complexes. The melting point of the ligand (216 – 218) °C is higher than 106 – 107.8^{0}C of the Mn complex. The Cu complex decomposed at 174°C.The solubility showed that the ligand and complexes were soluble in dimethyl sulphoxide, but insoluble in water. The conductivity test showed that the Cu complex are conductors with higher value (9.934) µS/cm, while the Mn complexes are non-conductor with lower value (1.346) µS/cm. The magnetic susceptibility measurement pointed out that the complexes are paramagnetic with unpaired electrons. There was coordination via the azomethine nitrogen and carbonyl oxygen in all the complexes with a square planar geometries stoichiometrically combined in the ratio of ML 1:2 for the metal and ligand respectively. The ligand and complexes showed appreciable activities against Methicillin resistant staphlococus aureus (MRSA), Escherichia coli, Helicobacter pylori, salmonella typhi Aspergillus fumigatus and aspergillus niger

Keywords: antimicrobial screening, characterization, complexes, hydrazides, hydrazones, ligand

INTRODUCTION

Hydrazones resemble ketones and aldehydes by the replacement of carbonyl oxygen with the NNH_2 functional group. They also have the triatomic grouping C=NN- which can be referred as Schiff bases derived from acid hydrazides [1]. They are formed usually by condensation of hydrazine and ketones or aldehydes. Hydrazones have a very high physiological activity. Their chemical and biological activities is centered on the presence of lone pair on trigonally hybridized nitrogen atom of the azomethine group [1]. It has been reported that metal complexes of hydrazones have diverse applications [1]. Many researchers synthesized hydrazones and their complexes which are used as drugs to combat diseases with minimal toxicity and maximal effects. In order to develop new antimicrobial compound, a number of hydrazones were tested for their antimicrobial activities because of the evolution of drug-resistant microbial pathogen [2]

Hydrazones having an azomethine proton (-NHN=CH-) constitute an important class of compounds for new drug development [2]. It was also reported that the azomethine N, which has a lone pair of electrons in an sp^2 hybridised orbital, is responsible for the vast biological activities of the hydrazones [3].

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Numerous scientific research have shown that Cu^{2+} and Mn^{2+} complexes possess various activities such as antiulcer, antiamoebic, antidiabetic, anticonvulsant, anti-inflamatory, antimicrobial and antitumor. In particular, anti-inflammatory, anti-microbial and anti-cancer activity of copper complexes has been studied. For a very long time, copper have been used for the treatment of arthritis [4,5]. As a result of the evolution of drug-resistant microbial pathogens, a new antimicrobial compounds; Mn II and Cu II complexes of isonicotinoyl 2-chlorobenzaldehyde hydrazone were synthesized and biologically screened against some selected organisms.

MATERIAL AND METHODS

Hydrazine monohydrate ($N_2H_4.H_2O$) (98%), ethylisonicotinate ($C_8H_9NO_2$) (98%), 2-chlorobenzaldehyde (C_7H_5ClO) (98%) were purchased from Zigma Aldrich. Copper(II) sulphate pentahydrate ($CuSO_4.5H_2O$) (98%), manganese(II) sulphate tetrahydrate ($MnSO_4.4H_2O$) (98%), ethanol (98%), methanol, and other solvents were of Analar grade.

The UV spectra was recorded using Agilent Technologies Cary 300 UV Vis in the range of 190 – 1000 nm. using Thermo Scientific NICOLET iS5 FTIR in the range of 4000-400 cm^{-1} was to determine the infrared spectra of the complexes and ligand. The melting/decomposition point was determined using ELECTROTHERMAL melting point equipment. Molar conductance of the complexes was determined in dimethylsulphoxide using JENWAY Conductivity/pH meter. Magnetic susceptibility values were measured at room temperature using Sherwood Scientific Magnetic Susceptibility Balance. Guoy's method using $Hg[Co(NCS)_4]$ as a calibrant type magnetic balance. The metal analysis was carried out using Thermo Scientific Atomic Absorption Spectrometer iCE 3000.

Synthesis of the Ligands

Isonicotinic hydrazide (INH) was synthesized according to the method described by [6], as shown in equations 1 and 2.

A solution of 20g of ethylisonicotinate and 6.60g of hydrazine monohydrate in 100 cm^3 of ethanol was refluxed on a steam water bath for 5 hr. The refluxed mixture was allowed to stand overnight for the complete formation of the crystals. The crystals formed was washed with ethanol and dried in a desiccator.

Synthesis of Isonicotinic 2-Chlorobenzaldehyde Hydrazone

Isonicotinic hydrazide (INH) was used to synthesize the isonicotinic 2-chlorobenzaldehyde hydrazone following the method of [7] as shown in equations 1 and 2

A solution of 10 g of Isonicotinic hydrazide (INH), and 10.26 g of 2-chlorobenzaldehyde in 100 cm^3 of ethanol was heated on a water bath for 5 min to dissolve completely the content. The mixture was stirred and allow to stand for 5 min. The white crystals formed were filtered, washed with 50 cm^3 absolute ethanol and dried in a dessicator [7].

Synthesis of complexes

The complexes of Cu^{2+} and Mn^{2+} were synthesized according to the method described by [7].

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A solution of 0.5 g of isonicotinic 2-chlorobenzaldehyde hydrazone in 20 cm^3 ethanol was added to the solution of 0.475 g of the metal salts in 20 cm^3 deionized water was stirred with a stirring rod for 1 min and allowed to stand overnight. The crystals formed was filtered, washed with 50 cm^3 absolute ethanol and dried in a dessicator over fused $CaCl_2$ [7]. The equations for the preparation of the complexes are shown in Scheme 1

$$CuSO_4 \cdot 5H_2O + 2C_{13}H_9ON_3Cl \rightarrow [Cu(C_{13}H_9ON_3Cl)_2]SO_4 + 5H_2O \quad 1$$

$$MnSO_4 \cdot 4H_2O + 2C_{13}H_9ON_3Cl \rightarrow [Mn(C_{13}H_9ON_3Cl)_2]SO_4 + 4H_2O \quad 2$$

Scheme 1: Equations for the preparation of the complexes [7].

Antimicrobial activities of compounds

The antimicrobial activities of the ligands and complexes were determined using some bacteria and fungi such as Methicillin resistant staphlococus aureus (MRSA), vancomycin resistant *enterococci (VRE), staphylococcus aureus, streptococcus pyogenes, Escherichia coli,* Helicobacter pylori, salmonella typhi. Others are Candida albicans, Candida krusei, Aspergillus fumigatus and aspergillus niger.

A solution of 0.001 mg of the complex in 10 cm^3 of DMSO to obtain a concentration of 100 µg/cm^3 was prepared which was used for the antimicrobial activities. Diffusion method was used as follows; Mueller Hinton agar and Sabouraund dextrose agar were used as the growth medium for the microbes. The media were sterilized at 121 °C for 15 min, poured into sterile Petri dishes and was allowed to cool and solidify. The standard inoculum of the test bacteria was prepared by seeding 0.1 cm^3 of Mueller Hinton agar, while the Sabouraund dextrose agar was seeded with 0.1 cm^3 of the standard inoculum of the fungi. The inoculum was spread evenly over the surface of the media by the use of a sterile swab. By the use of a sterile cork borer of 6 mm in diametres, a well was cut at the centre of each inoculated medium. About 0.1 cm^3 of the solution of the complex with the concentration of 100µg/ml was then introduced into the well on the inoculated medium. Incubation was made at 37 °C for 24 h for the bacteria and at 30 °C for 1-7 days for the fungi, after which the plates of the medium were observed for the zone of inhibition of growth. The zone was measured with a transparent ruler and the result recorded in millimeters [9].

Minimum Inhibition Concentration (MIC)

The minimum inhibition concentration of the complex was assessed using the broth dilution method as follows; Muller Hilton broth and sabouraud dextrose broth were prepared by dispensing 10 cm^3 of the broth into test tubes and sterilized at 121 °C for 15 min and the broth was allowed to cool. Mc-Farland turbidity standard scale number 0.5 was prepared to give turbid solution. About l0 $cm^3$of the normal saline was dispensed into sterile test tube and the test microbe was inoculated and incubated at 37 °C for 6 h. Dilution of the test microbe was done in the normal saline until the turbidity marched that of the Mc-Farland's scale by visual comparison at this point the test microbe has a

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concentration of about 1.5 x 10^8 cfu/cm^3. Two-fold serial dilution of the compound was done in the sterile broth to obtain the concentrations of 100 µg/cm^3, 50 µg/mlcm^3, 25 µg/cm^3,12.5 µg/cm^3 and 6.25 µg/cm^3. The initial concentration was obtained by dissolving 0.001 mg of the complex in 10 cm^3 of the sterile broth followed by adding 0.1 cm^3 of the test microbe in the normal saline was introduced into the different concentrations of the complexes and ligand, the bacteria was added into Mueller Hinton broth and placed in the incubator at 37 °C for 24 h while, the fungi was introduced into sabouraud dextrose broth made at 30 °C for 1-7 days. The test tubes of the broths were observed for turbidity (growth). The lowest concentration of the compound observed which shows no turbidity was recorded as the minimum inhibition concentration [10].

Minimum Bactericidal Concentration/Minimum Fungicidal Concentration (MBC/MFC)

The Mueller Hinton agar and sabouraud dextrose agar prepared and sterilized at 121 °C for 15 min were poured into sterile petri dishes and allowed to cool and solidify. The bacteria strain was sub-cultured on the Mueller Hinton agar while the fungi was sub-cultured on the Sabouraud dextrose agar and incubated at 37 °C for 24 h for bacteria, and that of the fungi was incubated at 30 °C between 1-7 days after which the plates of the media were checked for colony growth, MBC/MFC were determined by the plates with the lowest concentration of the compounds without colony growth [10].

RESULTS AND DISCUSSION

The results of the work are presented in the Tables 1 - 6 below.

Table 1. **Physical Property Data of the Ligand and Complexes**

Formula	Yield %	Metal Cal (Exp)%	Melting point °C	Conductivity µS/cm	Colour
2-INHH	75.32	-	216 – 218	0.351	Milky
$[Cu(2INHH)_2]SO_4$	70.38	12.22(13.01)	174*	9.934	Bluish Green
$[Mn(2INHH)_2]SO_4$	52.82	12.41(11.59)	106 – 107.8	1.346	white

Physical Property Data of Ligand and their Complexes

The synthesized 2-chlorobenzaldehyde isonicotinoyl hydrazone, 2-CBIH precipitated as a milky powder, which was in agreement with a work that also synthesized the ligand [7]. The yield of the ligand turn out to be 75.32 % which was lower than a similar work which produced a yield of 98.8% [7][11], but higher than the value (70.05%) of another similar work done by [7] and co-workers [11]. Mn^{2+} and Cu^{2+} complexes of 2-CBIH were also synthesized precipitating as a white and buish-green colour respectively. The complexes turn out to produce a yield between the range of 52.82 – 70.38 % as shown in Table 1. The melting point of the 2-CBIH as shown in Table 1 is in the range of 216 – 218 °C which is lower than the values for the complex Mn[2-CBIH], while complex Cu[2-CBIH] decomposed at 183 °C. The physical data for 2-CBIH and its metal complexes also supported the ML_2 type complexes. The low conductivity values of 2-CBIH, Ni[2-CBIH], Co[2-CBIH] and Mn[2-CBIH] in the range of 0.351 – 1.435 µS/cm in

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DMSO and in the range of 0.009 – 1.403 µS/cm in DMF is an indication that they are non-electrolytes while that of Cu[2-CBIH] (10.29) µS/cm is electrolytic [12]. The ligand, 2-CBIH and the complexes, Mn[2-CBIH] are soluble in DMSO, but insoluble water, ethanol, and hexane while the Cu[2-CBIH] is partially soluble in DMSO, but insoluble in water, ethanol and hexane. The metals, Ni, Co, Mn and Cu in the complexes were determined using Atomic Absorption Spectroscopy method

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Table 2. Electronic Spectral data and magnetic susceptibility of 2-INHH, $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$

Compounds	Wave Length nm	Wave No. cm^{-1}	Molar Absorptivity $mol^{-1}cm^{-1}$	Assignment	Geometry	μ_{eff} B.M
$C_{13}H_9ON_3Cl$	353	28328.61	1292.65	$n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$	-	-
$[Mn(2INHH)_2]SO_4$	361	27700.83	10.33	d-d	Square Planar	1.97
	515	19417.47	35.54	d-d		
	608	16447.36	28.39	d-d		
$[Cu(2INHH)_2]SO_4$	365	27397.26	290.27	$^2B_{1g}\rightarrow{}^2B_{2g}$	Square Planar	1.77
	536	18656.71	232.21	$^2B_{1g}\rightarrow{}^2E_g$		

Magnetic Susceptibility and Electronic Data of Ligand and Complexes

The UV spectra and effective magnetic susceptibility results are shown in Table 2. The 2-chlorobenzyldehyde isonicotinoyl hydrazone, 2-INHH showed absorption peak at the uv region of 28,328.61 cm^{-1} with the molar absorptivity of 1292.65 mol^{-1} cm^{-1} corresponding to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ ligand transition [13].

The complex $[Mn(2INHH)_2]SO_4$ showed weak absorption peaks at 16,447.36 cm^{-1}, 19,417.47 cm^{-1} and 27700.83 cm^{-1} with molar absorptivities of 10.33, 28.39 and 35.54 mol^{-1} cm^{-1}. These transitions are forbidden and weak and could be due to d-d transitions within the metal d-orbitals [14]. The effective magnetic susceptibility of the complex is 1.97 BM slightly higher than the spin only value of 1.73 BM for one unpaired electron. This also suggested a square planar geometry [15][16]. The complex, $[Cu(2INHH)_2]SO_4$ showed two absorption peaks at 18,656.71 and 27,397.26 cm^{-1} with molar absorptivities of 232.21 and 290.27 mol^{-1} cm^{-1} respectively. These transitions are allowed and could be assigned to $^2B_{1g}\rightarrow{}^2B_{2g}$ and $^2B_{1g}\rightarrow{}^2E_g$ suggesting a square planar geometry [17][18]. The magnetic susceptibility of the complex, $[Cu(2INHH)_2]SO_4$ is 1.77 BM which corresponds to one unpaired

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electron of a d^9 system. This also indicates that the complex is square planar [19][20].

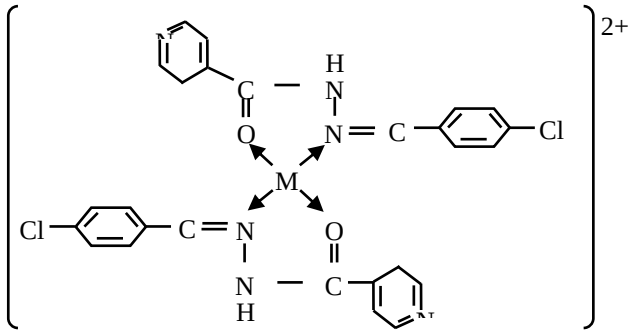
Table 3. Infrared spectral bands of the 2-INHH, $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$

Samples	vNH cm^{-1}	v C=O cm^{-1}	vC=N cm^{-1}	M-N cm^{-1}	M-O cm^{-1}	M-Cl cm^{-1}
$C_{13}H_9ON_3Cl$	3350.0	1676	1601.3	-	-	
$[Mn(2INHH)_2]SO_4$	3352.5	1676.9	1601.2	426.7	510.2	
$[Cu(2INHH)_2]SO_4$	3393.5	1656.9	1595.4	447.2	558.3	

M = Mn^{2+} or Cu^{2+}

Infrared Spectral Analysis of Ligand and Complexes

The infrared spectral of the ligands and complexes are outlined in Table 3. The υ(NH) band was found at 3350.02 cm^{-1} for the ligand, 2-INHH and appeared in the same region in the complexes of Mn^{2+} and Cu^{2+}. The M-N absorption bands of $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$ complexes were located at 426.7 cm^{-1} and 447.2 cm^{-1} respectively. The complexes also showed absorption bands corresponding to M-O 426.72 cm^{-1} and 447.27 cm^{-1} respectively. This is typical of a complex with a square planar geometry [14].



M = Mn or Cu

Scheme 2. Structure of the complexes

Table 4: Zone of inhibition of 2-INHH, $[Cu(2INHH)_2]SO_4$ and $[Mn(2INHH)_2]SO_4$

Test Organisms	2-INHH mm	Cu-2INHH mm	Mn[2-INHH] mm	SF mm	CF mm	FL mm	FU mm
MRSA	25	26	26	32	0	0	0
VRE	26	28	29	30	32	0	0
S. aureus	0	0	0	35	29	0	0
S. Pyogene	0	0	0	30	0	0	0
E. coli	26	29	28	0	32	0	0
H. pylori	0	0	0	30	29	0	0

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S. typhi	23	27	26	32	32	0	0
C. albican	24	0	25	0	0	34	32
C. krusei	0	0	0	0	0	32	0
A. fumigatus	20	27	26	0	0	0	34
A. niger	23	26	28	0	0	0	31

SF-Sparfloxacin CF-Ciprofloxacin FL- Fluconazole FU- Fulcin

Table 5: MIC and MBC/MFC of [2-INHH], $[Mn(2INHH)_2]SO_4$and $Cu(2INHH)_2]SO_4$

Test Organism	[2-INHH] MIC (μg/ml)	[2-INHH] MFC/MBC (μg/ml)	Mn-2INHH MIC (μg/ml)	Mn-2INHH MBC/MFC (μg/ml)	Cu-2INHH MIC (μg/ml)	Cu-2INHH MBC/ MFC (μg/ml)
M R S A	25	50	25	50	25	50
V R E	25	50	12.5	25	12.5	25
S. aureus	-	-	-	-	-	-
S. pyogen	-	-	-	-	-	-
E. Coli	25	50	12.5	25	12.5	25
H. pylori						
S. typhi	50	100	25	50	12.5	25
C. albican	50	100	25	50	-	-
C. krusei	-	-	-	-	-	-
A. fumigat	50	100	25	50	12.5	25
A. niger	50	100	12.5	25	25	50

The Antimicrobial Assay of the Ligands and the Complexes

The zone of inhibition, MIC and MBC/MFC of the ligand and complexes are presented in Tables 4 and 5**.** The test organisms are: Methicillin resistant *Staphlococus aureus* (MRSA), Vancomycin resistant *enterococci* (VRE), *Staphylococcus aureus, streptococcus pyogenes, Escherichia coli, Helicobacter pylori, Salmonella typhi.* Others are *Candida albicans, Candida krusei*, *Aspergillus fumigatus* and *Aspergillus niger*.

The ligand 2-INHH and its complexes show no activity against *Streptococcus pyogenes, Candida albicans* and *Candida krusei.* They all have activity against *Aspergillus fumigatus* with zone of inhibitions that ranged from 22 – 25 mm. Upon complexation, the MICs and MBCs of the complexes of 2-INHH reduces to 25 µg/ml and

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50 µg/ml respectively compared to the ligand which is consistent with a work reported by [7]. The complex, $[Cu(2INHH)_2]SO_4$ was active against *Aspergillus niger* with zone of inhibitions of 23 mm. The ligand 2-INHH and its complexes are active against *Helicobacter pylori* with zone of inhibition ranging from 20 – 27 mm. The MIC and MBC of the complex $[Cu(2INHH)_2]SO_4$ is lower than the other complexes of 2INHH. The complex, $[Co(2INHH)_2Cl_2]$ does not have activity against Vancomycin resistant *enterococci* (VRE) and *Salmonella typhi*. The zone of inhibition of 2-INHH, $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$ against VRE are 25 mm, 27 mm and 26 mm respectively, and it is in agreement with a similar work [16], while the zone of inhibition of of 2-INHH, $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$ against *Salmonella typhi* are 22 mm, 24 mm and 24 mm respectively. $[Mn(2INHH)_2]SO_4$ do not have any activity against *Staphlococcus aureus,* while the complex $[Cu(2INHH)_2]SO_4$, and the ligand 2-INHH have activity. Their zone of inhibitions are in the range of 24 – 28 mm. The standard drugs used are Sparfloxacin, Ciprofloxacin, Fluconazole and Fulcin. The 2-INHH, Cu and Mn have 23mm, 27 and 26 zone of inhibitions respectively against s. Typhi compared to the standard drugs Sparfloxacin, Ciprofloxacin with 32mm zone of inhibitions. The Cu complex do not have activity against c. Albicans, while the ligand and the Mn complex have 24mm and 25mm zone of inhibitions respectively against C. Albicans. The standard drugs (Fluconazole and Fulcin) have zone of inhibitions of 34mm and 32mm against C. Albicans respectively.

CONCLUSION

At the end of the research work, Mn II and Cu II complexes of isonicotinoyl 2-chlorobenzaldehyde hydrazone was synthesised. The spectrophotometric analysis suggested a square planar geometry with coordination via the azomethine nitrogen and carbonyl oxygen in all the complexes. The complexes are paramagnetic and non-polar in nature. The antimicrobial screening carried out on the ligand and complexes using some bacterial and fungal strains showed appreciable activities against *Methicillin resistant staphlococus aureus* (MRSA), *Escherichia coli*, *Helicobacter pylori, salmonella typhi Aspergillus fumigatus* and *aspergillus niger*.

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