Synthesis, Characterization and antimicrobial Studies of isonicotinoyl 2-chlorobenzaldehyde Hydrazone and the Ni II and Co II complexes

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Abstract: **isonicotinoyl 2-chlorobenzaldehyde hydrazone and the Ni II and Co II complexes were synthesized and characterized via melting point, solubility test, conductivity measurement, magnetic susceptibility, UV visible spectrophotometry, Infrared spectrophotometry and metal analysis using Atomic Absorption Spectrophotometry. The antimicrobial screening was also carried out on the ligand and complexes using some bacteria and fungal strains. The melting point of the complexes are higher than the ligand. The ligand and complexes are insoluble in water, but soluble in dimethyl sulphoxide. The conductivity test showed that the ligand and complexes are non-conductors. The magnetic susceptibility measurement pointed out that the Ni II complex is diamagnetic, while the Ni II complex is paramagnetic. There was coordination via the azomethine nitrogen and carbonyl oxygen. The Ni II complex has a square planar geometry while the Co II complex has an octahedralgeometry. The ligand and complexes has appreciable activities against some of the selected organisms.**

I. INTRODUCTION

Hydrazones are related to ketones and aldehydes by the replacement of the carbonyl oxygen with the NNH_2 functional group and are characterized by the presence of the triatomic grouping C=NN- and they can be considered as Schiff bases derived from acid hydrazides[2]. They are formed usually by condensation of hydrazine and ketones or aldehydes. The most important property of hydrazones is their high physiological activity. Extensive studies have revealed that the lone pair on trigonally hybridized nitrogen atom of the azomethine group is responsible for the chemical and biological activity[2]. It has been reported that metal complexes of hydrazones have diverse applications[2]. These compounds and their complexes are being synthesized as drugs by many researchers in order to combat diseases with minimal toxicity and maximal effects. Hydrazones and their metal complexes are biologically very active compounds[2]. These predictions have provided therapeutic pathway for the development of new effective biologically active hydrazones. In an urge to develop new antimicrobial compound, a number of hydrazones were tested for their antimicrobial activities because of the evolution of drug-resistant microbial pathogen[9,10]. The aim of this research work is to synthesize, characterize and also investigate the antimicrobial properties of isonicotinoyl 2-chlorobenzaldehyde hydrazone and their Ni II and Co II complexes

II. MATERIAL AND METHODS

Hydrazine monohydrate ($N_2H_4.H_2O$) (98%), nickel(II) chloride hexahydrate ($NiCl_2.6H_2O$) (98%), ethylisonicotinate ($C_8H_9NO_2$) (98%), 2-chlorobenzaldehyde (C_7H_5ClO) (98%) were purchased from Zigma Aldrich. Anhydrous Cobalt(II) chloride ($CoCl_2$) (98%) were bought from Merck Darmstadt Germany, while 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. The infrared spectra was recorded in nujol using Thermo Scientific NICOLET iS5 FTIR in the range of 4000-400 cm^{-1}. The melting point was determined using ELECTROTHERMAL Melting Point. 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 Nwabueze[12], as shown in equation 1.

In a 250 cm^3 flat bottomed flask, 20 g of ethylisonicotinate, 6.60 g of hydrazine monohydrate and 100 cm^3 of ethanol were added and stirred. The mixture was refluxed on a steam water bath for 5 h. The refluxed mixture was poured in a 500 cm^3 beaker and allowed to stand overnight. The crystals formed were filtered, washed with 50 cm^3 absolute ethanol and dried in dessicator over fused $CaCl_2$.

Isonicotinic hydrazide (INH) was used to synthesize the isonicotinic 2-chlorobenzaldehyde hydrazone following the method of Mallikarjuna *et al.*,[8] as shown in equation 2

In a 250 cm^3 beaker, 10 g of Isonicotinic hydrazide, 10.26 g of 2-chlorobenzaldehyde and 100 cm^3 of ethanol was added. The mixture 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[8].

$$C_8H_9NO_2 + N_2H_4 \longrightarrow C_6H_7N_2O \quad 1$$

$$C_6H_7N_2O + C_6H_5OCl \longrightarrow C_{13}H_9ON_3Cl \quad 2$$

Scheme 1: Equations for the synthesis of the ligands

Synthesis of Complexes

The complexes of Ni^{2+} and Co^{2+} were synthesized according to the method described by Mallikarjuna *et al.,*[8]

In a 250 cm^3 beaker, 0.5 g of isonicotinic 2-chlorobenzaldehyde hydrazone was dissolved in 20 cm^3 ethanol by slight heating on hot plate. Between 0.420 - 0.475 g of the metal salts were also dissolved in 20 cm^3 deionized water and added to the hydrazone solutions. The mixture 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 $CaCl_2$[8]. The equations for the preparation of the complexes are shown in Scheme 2

$$CoCl_2 + 2C_{13}H_9ON_3Cl \longrightarrow [Co(C_{13}H_9ON_3Cl)_2Cl_2] \quad 3$$

$$NiCl_2.6H_2O + 2C_{13}H_9ON_3Cl \longrightarrow [Ni(C_{13}H_9ON_3Cl)_2]Cl_2 + 6H_2O \quad 4$$

Scheme 1: Equations for the preparation of the complexes (Mallikarjuna *et al.,* 2015).

Assessment of Antimicrobial Potentials 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.

In a 100 cm^3 beaker, 0.001 mg of the compound was added and dissolved in 10 cm^3 of DMSO to obtain a concentration of 100 µg/cm^3. This was the initial concentration of the compound used to determine its antimicrobial activities. Diffusion method was the method used for screening the compound. Mueller Hinton agar and Sabouraund dextrose agar were used as the growth medium for the microbes. The media were prepared according to the manufacturer's instructions, sterilized at 121 °C for 15 min, poured into sterile Petri dishes and was allowed to cool and solidify. The Mueller Hinton agar was seeded with 0.1 cm^3 of the standard inoculum of the test bacteria 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 sterilecork 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 compound of the concentration of 100µg/ml was then introduced into the well on the inoculated medium. Incubation was made at 37 ^oC 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[3].

Minimum Inhibition Concentration (MIC), MFC and MBC

The minimum inhibition concentration of the complex was determined using the broth dilution method. Muller Hilton broth and sabouraud dextrose broth were prepared; 10 cm^3 of the broth was dispensed into test tubes and was sterilized at 121 °C for 15 min, the broth was allowed to cool. Mc-Farland turbidity standard scale number 0.5 was prepared to give turbid solution. Normal saline was prepared, l0 cm^3 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 concentration of about $1.5x10^8$ 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. Having obtained the different concentrations of the compound in the sterile broth, 0.1 cm^3 of the test microbe in the normal saline was then introduced into the different concentrations, the bacteria was introduced into Mueller Hinton broth while the fungi was introduced into sabouraud dextrose broth incubation was made at 37 °C for 24 h for the bacteria and 30 °C for 1-7 days for the fungi, after which the test tube of the broth were observed for turbidity (growth) the lowest concentration of the compound in the broth, which shows no turbidity was recorded as the minimum inhibition concentration, while the plates with lowest concentration of the sample without colony growth gave the MBC and MFC respectively[3].

III. RESULTS AND DISCUSSION

Table 1: Analytical and Physical Data of the Ligand and Complxes

Formular	Yield %	Metal Cal(Exp)%	Melting point °C	Conductivity µS/cm	Colour
2-INHH	75.32	-	210 – 212	0.351	Milky
$[Ni(2INHH)_2]Cl_2$	45.36	10.19(10.23)	218 - 220	1.284	Light blue
$[Co(2INHH)_2Cl_2]$	50.84	9.10(10.09)	217 – 219	1.346	Off-white

Table 2: Electronic Spectral data and magnetic susceptibility of 2-INHH, $[Ni(2INHH)_2]Cl_2$ and $[Co(2INHH)_2Cl_2$

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	$n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$	-	-
$[Ni(2INHH)_2]Cl_2$	365 574 663	27397.26 17421.60 15082.95	323.35 169.76 266.11	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$	Square Planar	Diamagnetic
$[Co(2INHH)_2Cl_2]$	360 592	25777.77 15220.89	323.46 252.62	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$	Octahedral	1.84

Table 3: Infrared spectral bands of the 2-INHH, $[Ni(2INHH)_2]Cl_2$, $[Co(2INHH)_2Cl_2]$, $[Mn(2INHH)_2]SO_4$ and $[Cu(2INHH)_2]SO_4$

Samples	vNH	v C=O	vC=N	M-N	M-O	M-Cl
$C_{13}H_9ON_3Cl$	3350.0	1676	1601.3	-	-	
$[Ni(2INHH)_2]Cl_2$	3349.9	1678.3	1601.2	465.7	530.53	
$[Co(2INHH)_2Cl_2$	3351.1	1677.1	1600.7	462.9	509.6	402.8

Table 5: Zone of inhibition of 2-INHH, $[Ni(2INHH)_2]Cl_2$ and $[Co(2INHH)_2Cl_2]$.

Test Organisms	2-INHH	Co-2INHH	Ni-2INHH	SF	CF	FL	FU
MRSA	25	26	28	32	0	0	0
VRE	26	24	27	30	32	0	0
S. aureus	0	0	0	35	29	0	0
S. Pyogene	0	27	0	30	0	0	0
E. coli	26	28	27	0	32	0	0
H. pylori	0	0	0	30	29	0	0
S. typhi	23	26	25	32	32	0	0
C. albican	24	28	27	0	0	34	32
C. krusei	0	0	0	0	0	32	0
A. fumigatus	20	26	23	0	0	0	34
A. niger	23	24	25	0	0	0	31

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

Table 6 : MIC and MBC/MFC of [2-INHH], $[Ni(2INHH)_2]Cl_2$ and $[Co(2INHH)_2Cl_2]$.

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

Physical and Analytical Data of Ligand and Complexes

The analytical and physical data of the ligand and complexes are shown in Table 1. The different shades of colour of the complexes different from the white colour of the ligand could be an indication that complexation has taken place[13].

The 2-chlorobenzaldehyde isonicotinoyl hydrazone, 2-INHH was synthesized after refluxing for 4 h as shown in Scheme 3.1. It precipitated as a milky powder, which was in agreement with some works that also synthesized the ligand[8]. The yield of the ligand is 75.32 % which was lower than a similar work which gave a yield of 98.8% [1,8], but slightly higher than another similar work done by Mallikarjuna and co-workers[1]. Ni^{2+}, and Co^{2+} complexes of 2-INHH were also synthesized with different colours as light-blue and off-whit respectively. The complexes gave a yield between the range of 45.36 – 70.38 % as shown in Table 4.1. The melting of the ligand, 2-INHH is lower than the values for the complexes, Ni[2-INHH] and Co[2-INHH] [1,8]. The analytical data for 2-INHH and its metal complexes also supported the ML_2 type complexes. The conductivity of the ligand and complexes are presented in Table 1. The low conductivity values of 2-INHH, Ni[2-INHH] and Co[2-INHH] in the range of 0.351 – 1.435 µS/cm in DMSO is an indication that they are non-electrolytes[5]. The ligand, 2-INHH and the complexes, Ni[2-INHH] and Co[2-INHH] are soluble in DMSO, but insoluble water, ethanol, and hexane.

The metal composition of the complexes are shown in Table 1. The metals, Ni and Co in the complexes were determined using Atomic Absorption Spectroscopy method[17]. The experimental values of the metal analysis of the complexes were in agreement with the calculated values though with

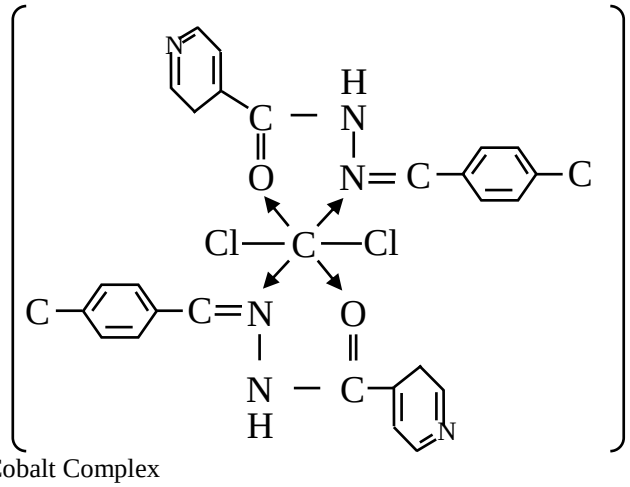
slight differences. Qualitative analysis was carried out on the ligand and complexes for the presence of chloride. The qualitative test chloride gave a positive result for the Ni^{2+} complex only and could be as result of the presence of the anion outside the coordination sphere[15].

Electronic Data and Magnetic Susceptibility of Ligands and Complexes

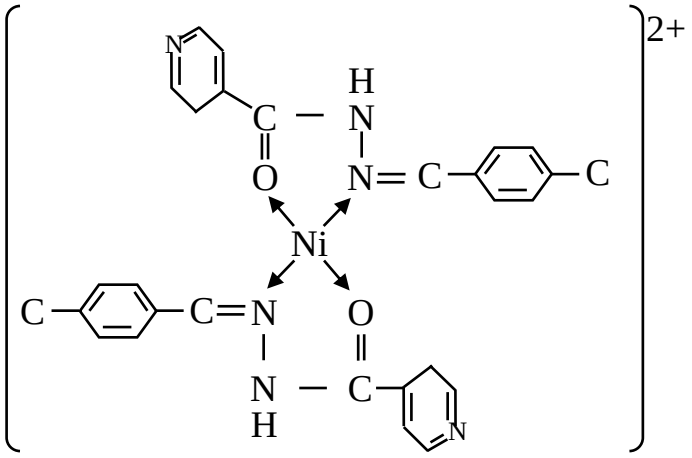
The electronic data and magnetic susceptibility of ligands and complexes are presented in Table 2. The 2-chlorobenzyldehyde isonicotinoyl hydrazone, 2-INHH showed absorption peak at the uv region of 28,328.61 cm^{-1} with the molar absorptivity of 1292.65 mol^{-1} cm^{-1} corresponding to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ ligand transition. The absorption peaks and molar absorptivities were observed at 15,082 – 27,397.31 cm^{-1} and 64.02 – 323.35 mol^{-1} cm^{-1} respectively for the $[Ni(2INHH)_2]Cl_2$ complex. The three absorption peaks are spin allowed and could be attributed to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F)\rightarrow {}^3T_{1g}(P)$ transitions. These suggests a square planar geometry [4,16]. The complex, $[Ni(2INHH)_2]Cl_2$ is diamagnetic with all the eight electrons paired.

Infrared Spectral Analysis of Ligands and Complexes

Infrared Spectral Analysis of Ligands and Complexes are presented 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 Ni^{2+} and Co^{2+}. The M-N absorption bands of $[Ni(2INHH)_2]Cl_2$ and $[Co(2INHH)_2Cl_2]$ complexes are located at 653.68 cm^{-1} and 574.87 cm^{-1} respectively. The complexes also showed absorption bands corresponding to M-O at 425.88 cm^{-1} and 451.28 cm^{-1} respectively. The complex $[Co(2INHH)_2Cl_2]$ showed evidence of coordination between the metal and the chloride ion (M-Cl) at 402.88 cm^{-1}. This is typical of a complex with a square planar geometry[15].



Cobalt Complex



Nickel Complex

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 5 and 6**.** 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 50 µg/ml respectively compared to the ligand which is consistent with a work reported by Mallikarjuna[8].

The complex $[Co(2INHH)_2Cl_2]$ is active against *Aspergillus niger* with zone of inhibitions of 26 mm. The ligand 2-INHH and its complexes are active against *Helicobacter pylori* with zone of inhibition ranging from 20 – 27 mm. 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, $[Ni(2INHH)_2]Cl_2$ against VRE are 25 mm and 27 mm respectively, and it is in agreement with a similar work (Fasina *et al.*, 2016), while the zone of inhibition of of 2-INHH, $[Ni(2INHH)_2]Cl_2$ against *Salmonella typhi* are 22 mm and 24 mm respectively. $[Mn(2INHH)_2]SO_4$ do not, while the complexes $[Ni(2INHH)_2]Cl_2$, $[Co(2INHH)_2Cl_2]$ and the ligand 2-INHH have activity against *Staphlococcus aureus* Their zone of inhibitions are in the range of 24 – 28 mm. The MIC and MBC for $[Ni(2INHH)_2]Cl_2$ and $[Co(2INHH)_2Cl_2]$ complexes against *Staphlococcus aureus* are 12.5 µg/ml and 25 µg/ml respectively.

V. CONCLUSION

At the end of this research work, isonicotinoyl 2-chlorobenzaldehyde (2-INHH), with complexes of Ni^{2+} and

Co^{2+} were synthesized. From the Job's plot, the molar ratio of the complexes were determined to be ML_2 type. The stability constants of the complexes are high indicating that all the complexes are very stable. From the conductivity measurements, it showed that the ligand and all the complexes are non-electrolytes. There is evidence of coordination via azomethine nitrogen and carbonyl oxygen. The Co^{2+} complex is diamagnetic while the Ni^{2+} complex is paramagnetic. Octahedral and square planar geometries were suggested for the $[Co(2INHH)_2Cl_2]$ and $[Ni(2INHH)_2]Cl_2$ respectively.

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