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Synthesis and Preliminary Antibacterial Screening of Hydrazone Derived from Isonicotinic Acid Hydrazide and Its Cu(II), Co(II) and Ni(II) Complexes

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Abstract

Complexes of Cu(II), Co(II) and Ni(II) derived from the ligand Acetone isonicotinic acid hydrazone (AINH) have been synthesized and characterized on the basis of electronic and physico-chemical methods. The results indicate that all complexes exhibited coordination number of 6 and the ligand coordinated to metal via N and O donor. Analytical data reveal that all the complexes possess 1:2 metal–ligand ratios. Molar conductivity measurements showed non-electrolytic nature of the complexes while the solubility test on the ligand and its metal(II) complexes showed they are soluble in dimethylsulphoxide (DMSO). The complexes were evaluated for their antibacterial activity against human pathogens like gram positive *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*) and gram negative *Escherichia coli* (*E. coli*), *Salmonella typhi* (*S. typhi*) strains. The result of microbial screening showed that the complexes have moderate antimicrobial activity.

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Keywords: Synthesis, Hydrazone, Metal Complexes, Antimicrobial Activity, Magnetic Susceptibility

INTRODUCTION

Metal ions play vital roles in a vast number of biological processes. Uses of metal ions in therapeutic agents are known to accelerate drug action and their efficacy is enhanced upon coordination with a metal ion [1-4]. The antimicrobial properties of metal complexes have been recognized for centuries and have represented some of the most fundamental breakthroughs in medicinal history [5]. Developing metal-based drugs is emerging as an active area of research. Schiff base metal complexes are amongst the most widely studied coordination compounds, due to the fact that Schiff bases offers opportunities for alterating the metal center electronic factor, enhancing the stability and solubility [1-5] and are active against a wide range of organisms such as *Staphylococcus aureus, Escherichia coli, Bacillus polymyxa, Mycobacteria, Salmonella typhi, Plasmopora viticola and Trychophyton gypseum* [5].

There has been growing interest in the study of hydrazones because of their physiological activity, coordinative capability and applications in analytical chemistry [5, 6]. Compared to the simple hydrazone Schiff bases, aroyl or heteroaroyl Schiff bases have additional donor sites. This introduces a wider range of properties like antibacterial, antimycobacterial, anticonvulsant, analgesic, anti-inflammatory and antitumor activities.

The transition metal complexes are far more biologically active than uncoordinated compounds and their enhanced biological activity has been an active area of investigation among medicinal researchers, [7-12] and coordination compounds of arylhydrazones have been reported to act as enzyme inhibitor. In general, arylhydrazones act as chelating ligands with transition metal ions by binding through the N atom of azomethine group and O atom of carbonyl group, therefore this type of compounds can coordinate *in vivo* to metal ions. The aim of the present investigation is to synthesize, characterize and study the biological activity of various transition metal complexes of Schiff base derived from acetone isonicotinic acid hydrazine.

MATERIALS AND METHODS

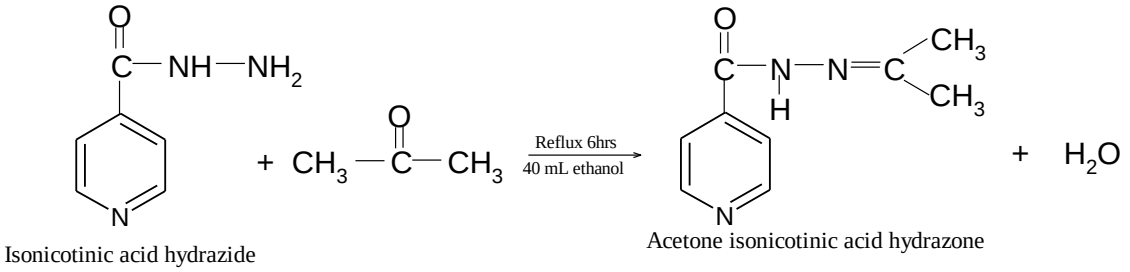
Reagents/solvents and Instrumentation: $Cu(NO_3)_2.3H_2O$, $Co(NO_3)_2.6H_2O$ and $Ni(NO_3)_2.6H_2O$, were analytical grade reagents and obtained from commercial source (Sigma-Aldrich Chemical Co.) and used without further purification. Melting points were determined on Gallenkamp melting point apparatus. The products were characterized electronically, spectroscopically and melting point determination. The wavelength of absorbance was determined by UV-Visible spectrophotometer (PD303) using a quartz cuvette and DMSO as reference. The IR spectra were recorded on FT-IR spectrophotometer (Shimadzu, FT-IR 8400S) using KBr as standard reference in wave number 4000 - 400cm^{-3}. Elemental analyses were done using Perkin Elmer 2400CHN analyzer. The magnetic susceptibilities of the complexes were measured at room temperature using a Gouy balance.

Synthesis of the ligand: The ligand [AINH] was prepared via the acid hydrazide. Isonicotinic acid hydrazide (3.04 g, 0.02 mole) with 2.7 ml (3.67 g, 0.06 mole) of acetone and 10 ml of absolute ethanol were refluxed for 4 hours in a 250 ml round-bottom flask after which it was transferred into a beaker and it was left for two days to crystallize. The resulting crystals were recrystallized with absolute ethanol and finally dried over $CaCl_2$ in a desiccator and weighed.

Preparation of metal complexes: The metal complexes were prepared by mixing the ethanolic solution of $Cu(NO_3)_2.3H_2O$, $Co(NO_3)_2.6H_2O$ and $Ni(NO_3)_2.6H_2O$ to the ethanolic solution of acetone isonicotinic acid hydrazone. The mixtures were placed on a magnetic stirrer, stirred constantly for about 10 minutes and left for about 1 hour to cool. The crystals obtained were filtered and dried over $CaCl_2$ in a desiccator and weighed.

RESULTS AND DISCUSSION

The preparation of the hydrazone as ligand from isonicotinic acid hydrazide and acetone was represented by the reaction in scheme 1:



Scheme 1: Preparation of Acetone isonicotinic acid hydrazone

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

$MX.{}_xH_2O + 2R\text{-}CONHNC(CH_3)_2 \rightarrow [M((R\text{-}CONHNC(CH_3)_2)_2]X.{}_xH_2O$ ……. 1

Where M= Cu, Co, Ni, x= 1 /4, X= NO_3,

By the reaction of Cu(II), Co(II) and Ni(II) nitrate with the ligand [AINH], complexes of type $[M(AINH)_2(H_2O)_2](NO_3)_2$ were obtained, where M = Cu, Co and Ni. All the complexes were colored, solid and partially soluble in common polar solvents but completely soluble in DMSO. The elemental analysis is in good agreement with the chemical formula proposed for complexes. The molar conductance in DMSO of the complexes are 0.22, 0.18 and 0.33 $mScm^2mol^{-1}$ respectively for Cu(II), Co(II) and Ni(II) complexes of [AINH]. The low conductance value supports the non-electrolytic nature of the complexes [8, 10]. The analytical and physical data (color, melting point and molar conductivity) of the complexes are given in Table 1.

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

Compound/Molecular weight (Colour)	Yield (%)	Λ_m $mScm^2mol^{-1}$	M.P. °C	Elemental analysis found/ Calculated (%)				
				C	H	N	M	NO_3^-
[AINH]	1.77	_	135	59.55	6.66	22.97	_	_
177.000 (Milky)	(76)			(60.67)	(6.74)	(23.60)		
$[Cu(AINH)_2(H_2O)_2](NO_3)_2$	1.12	0.22	191	36.20	4.44	19.30	10.87	20.40
577.546 (Green)	(57)			(37.40)	(4.50)	(19.39)	(10.99)	(21.47)
$[Co(AINH)_2(H_2O)_2](NO_3)_2$	1.83	0.18	162	37.50	4.44	18.45	10.22	22.12
572.933 (Brown)	(61)			(37.70)	(4.54)	(19.55)	(10.29)	(21.64)
$[Ni(AINH)_2(H_2O)_2](NO_3)_2$	1.36	0.33	155	37.50	4.50	19.50	10.20	23.91
572.693 (Purple)	(54)			(37.72)	(4.54)	(19.56)	(10.25)	(21.65)

Key: AINH = Acetone isonicotinic acid hydrazine

Table 2: IR bands of ligand and its complexes

Compound	υ(C=N)	υ(N-H)	υ(N-N)	υ(C=O)	υ(M-O)	υ(M-N)	υ(OH)	υ(NO_3)
AINH	1537	3190	1030	1654	-	-	-	-
$[Cu(AINH)_2(H_2O)_2](NO_3)_2$	1552	3240	1058	1654	466	570	3423	1384
$[Co(AINH)_2(H_2O)_2](NO_3)_2$	1546	3076	1080	1639	437	569	3431	1384
$[Ni(AINH)_2(H_2O)_2](NO_3)_2$	1599	3142	1066	1651	478	555	3439	1384

All the metal complexes have 1:2 (metal:ligand) stoichiometry. Magnetic moments of the complexes were measured at room temperature and the values obtained correspond with octahedral geometry as given in Table 3 [1].

FT-IR Spectra Studies

Table 2 shows the most important IR assignments in the spectra of the free ligand as well as the bonding site in the metal complexes. The broad band absorptions in the region 3439-3408 cm^{-1} which were absent in the spectra of the free ligand indicates the presence of water molecules in complexes. In the IR spectra of AINH, the average intensity band appeared at 3190 cm^{-1} which was assigned to ν(N-H) vibration [3]. The vibration frequencies νN-H are strongly displaced in all complexes. The displacements suggest the involvement of the azomethine nitrogen in coordination with metallic ions [2]. In accordance with this is the fact that the vibration frequency νN-N is displaced towards higher values in IR spectra of hydrazone complexes.

A strong band was observed at 1668 cm^{-1} assignable to ν(C=O). The band position of ν(C=O) has shifted to lower frequency by 14-17 cm^{-1} in the complex on coordination of metal ions indicating the involvement of the carbonyl group in bonding to metal [1]. The free ligand AINH also exhibited a strong band at 1537 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 [10].

In the IR spectra of complexes, a very intense band appears at 1384 cm^{-1} which is assigned to NO_3^- anion [4]. 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 [13].

Therefore, it can be concluded that [AINH] ligand binds to the metal ions through azomethine N and the carbonyl O atom.

Electronic spectra and magnetic moment

The electronic spectral data of the metal complexes in DMSO solution are given in Table 3. The electronic spectrum of $[Cu(AINH)_2(H_2O)_2](NO_3)_2$ presents three bands located at 352, 499 and 626 nm which can be attributed to Laporte forbidden d-d transition [14]. The magnetic moment is 1.94 B.M. Thus the octahedral geometry has been suggested for this complex. The spectrum of $[Co(AINH)_2(H_2O)_2](NO_3)_2$ consists of bands at 355, 499 and 699 nm which are due to parity forbidden transition, that is , d-d transition [14]. The magnetic moment is 4.50 B.M. These findings support an octahedral geometry for the Co(II) complex. $[Ni(AINH)_2(H_2O)_2](NO_3)_2$ showed bands at 359, 506 and 659 nm which were assigned to $n\rightarrow\pi^*$, $^3A_{2g}\rightarrow{}^3T_{1g}(P)$ and $^3A_{2g}\rightarrow{}^3T_{1g}$ transitions respectively. The magnetic moment is 2.98 BM. These findings are in favor of an octahedral geometry for the Ni(II) complex of [AINH] [13, 14].

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

Compound	λ,nm	Assignment	Geometry	M.M (B.M)
AINH	356			
	506	-	-	-
	650			
$[Cu(AINH)_2(H_2O)_2](NO_3)_2$	352	$dxy\rightarrow dx^2\text{-}y^2$		
	499	$dz^2\rightarrow dx^2\text{-}y^2$	Octahedral	1.94
	626	$^2E_g\rightarrow{}^2T_{2g}$		
$[Co(AINH)_2(H_2O)_2](NO_3)_2$	355	$n\rightarrow\pi^*$		
	499	$^4T_{1g}(F)\rightarrow{}^4A_{2g}$	Octahedral	4.50
	699	$^4T_{1g}\rightarrow{}^4T_{1g}(P)$		
$[Ni(AINH)_2(H_2O)_2](NO_3)_2$	359	$n\rightarrow\pi^*$		
	506	$^3A_{2g}\rightarrow{}^3T_{1g}(P)$	Octahedral	2.98
	659	$^3A_{2g}\rightarrow{}^3T_{1g}$		

Antimicrobial Activity

The results of the antibacterial activities of the ligand and its metal complexes are presented in Table 4. The antibacterial activities of the ligand and their complexes were tested against

two gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes)* and two gram-negative bacteria (*Escherichia coli* and *Salmonella typhi)* using nutrient agar. It was observed that the standard drug chloramphenicol was more potent than the ligand and metal complexes. All the metal complexes have higher antibacterial activities compared to the ligand.

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

Complex	Zone of inhibition (mm)			
	S. aureus	S. pyogenes	E. coli	S. typhi
AINH	3	6	4	NA
$[Cu(AINH)_2(H_2O)_2](NO_3)_2$	NA	10	NA	NA
$[Co(AINH)_2(H_2O)_2](NO_3)_2$	20	13	10	NA
$[Ni(AINH)_2(H_2O)_2](NO_3)_2$	5	NA	5	10

Key: NA = No activity, AINH = Acetone isonicotinic acid hydrazine

The results show that acetone isonicotinic acid hydrazone is slightly active to *Staphylococcus aureus, Streptococcus pyogenes* and *Escherichia coli*. But for the complexes, $[Ni(AINH)_2(H_2O)_2](NO_3)_2$ and $[Co(AINH)_2(H_2O)_2](NO_3)_2$ are active against *Staphylococcus aureus* while $[Cu(AINH)_2(H_2O)_2](NO_3)_2$ showed no activity towards the bacterial. $[Cu(AINH)_2(H_2O)_2](NO_3)_2$ and $[Co(AINH)_2(H_2O)_2](NO_3)_2$ were sensitive to *Streptococcus pyogenes* while $[Ni(AINH)_2(H_2O)_2](NO_3)_2$ was non-sensitive. All the complexes except $[Cu(AINH)_2(H_2O)_2](NO_3)_2$ were sensitive to *Escherichia coli*. Only $[Ni(AINH)_2(H_2O)_2](NO_3)_2$ was active to *Salmonella typhi*. From the results, it can be seen that $[Co(AINH)_2(H_2O)_2](NO_3)_2$ has a broad spectrum, which proved to be active against almost all the tested microbial strains. 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 or bioactive behaviour of the ligand [15-20]. The results indicate that the ligand and the complexes have antibacterial activity against the tested microorganisms.

CONCLUSION

We synthesized three complexes of Cu(II), Co(II), and Ni(II) with hydrazone derived from isonicotinic acid hydrazide. These complexes have been characterized by elemental analysis, magnetic and conductometric measurements, IR and also electronic spectra. The ligand 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.

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