Complexes of 2-amino-4-thiazoleacetic acid hydrazide(ATAH), salicylaldehyhde-2-amino-4-thiazoleacetic acid hydrazone (ATASH) And acetone-2-amino-4-thiazoleacetic acid hydrazone(ATAAH) each with nickel(II)sulphate As proposed drugs

Enedoh, Margaret Chinyelu
Imo State University,
Owerri. Nigeria
megnedoh@yahoo.com

Ibe, Francis C
Imo State University,
Owerri. Nigeria
francispavo@yahoo.com

Ebosie, Patricia Ngozi
Imo State University,
Owerri. Nigeria
npebosie@gmail.com

Abstract

Complexes obtained from 2-amino-4-thiazoleacetic acid hydrazide [keto- (ATAH) and enol- (ATA) forms), salicylaldehyde- 2-amino-4-thiazoleacetic acid hydrazone (ATASH) and acetone -2-amino-4-thiazoleacetic acid hydrazone (ATAAH) were each complexed with nickel(II) sulphates. These complexes synthesized are hopefully meant to be further processed as potential drugs. The complexes were characterized by elemental analyses, conductance, infrared and electronic spectral studies. The ligands and complexes were screened for antimicrobial activity and one of the compounds was relatively active against the organism tested. The active compound is nickel-2-amino-4-thiazoleacetic acid hydrazide $[Ni(ATAH)_3]SO_4\ H_2O$. *The electronic data indicate octahedral coordination for the all the complexes synthesized. The IR spectra data are diagnostic of bidentate coordination via the carbonyl oxygen and the azomethine, the* SO_4^{2-} *anions are in their inner coordination spheres. The conductivity analyses indicate a non-electrolytic nature for the chelates.*

Key Words: Salicylaldehyde, acetone, thiazoleacetic , hydrazide, hydrazone.

INTRODUCTION

The increasing clinical importance of drug-resistant mycobacterial pathogens has lent additional urgency to microbiological research and new antimycobacterial compound development. Much attention is given to hydrazones and some other hydrazine derivatives because of their biological and physiological activities (Nwabueze, 1997), Complexes of nickel (II) with Acetone hydrazones derived from some cyclocarboxylic acids. They generally exhibit very strong antibacterial activity. This antibacterial activity is enhanced on complexation to some transition metal ions (Bontchev, Boneva, and Miter; 1981). 4-isopropylthiazole-2-carbohydrazide is known to be a novel class of potential antibacterial, antifungal and antitubercular agents (Mallikarjuna, 2008, 2009). This is due to the fact that other ligating sites may be present in addition to the carbonyl O and the azomethine N depending on the nature of R and R^1 in $RCONHNCR^1{}_2$. Hydrazones derived from 6-amino-5-formyl-1, 3-dimethyl uracil and nicotinic and isonicotinic acid hydrazides formed four – coordinate complexes with Ni^{2+} which are monomeric with three binding sites occupied by the dinegative tridentates ligand and the fourth position by water. The donor atoms are the deprotonated N of the 6- amino group, the azomethine N and the carbonyl O of the hydrazone moity. Neither the carbonyl O atoms of the uracil ring nor the endocyclic N atom of the pyridine are involved in the coordination to the metals (Enedoh and Nwabueze, 2011; Fransisco, Nuria, Illan-Cabeza, Antonio and Penas, 2000)

This work aims at synthesizing for the first time complexes of the title metal with 2-amino-4-thiazoleacetic acid hydrazide (ATAH & ATA), salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone (ATASH) and acetone -2-amino-4-thiazoleacetic acid hydrazone (ATAAH) for possible use as antibacterial agent. Then, characterizing the complexes by some physicochemical properties while subjecting the ligands and complexes to antimicrobial screening.

METHODOLOGY

Ethyl-2-amino-4-thiazoleacetate, acetone and salicylaldehyde were obtained from Sigma – Aldrich Chemical Company Ltd, while the copper(II) sulphates and acetates were obtained from BDH Chemical Ltd England. All were used without further purification

Preparation of 2-amino-4-thiazoleacetic acid hydrazide (ATAH)

2- amino-4-thiazoleacetic acid hydrazide was prepared from 1mole of ethyl-2-amino-4-thiazoleacetate and 1 mole of the hydrazine hydrate using standard method as in literature (Nwabueze, 1992.

25.00ml (0.40moles) of hydrazine hydrate was added to 70g (0.40moles) of ethyl-2-amino-4-thiazoleacetate in 300mls of absolute ethanol. It was refluxed on a water bath for 6 hours. The solution was left to crystallize for 3 days. The light brown crystals obtained were filtered , recrystallized from ethanol, filtered and dried over silica gel in a desiccators. (yield , 46.1g; 65.86%)

Preparation of Salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone (ATASH)
8.6g, (0.05 mole) of 2-amino-4-thiazoleacetic acid hydrazide (ATAH) was mixed with 5.3ml(6.01g,(0.0.05 moles) of salicylaldehyde in 130ml ethanol and refluxed for 4 hours in a 250ml round bottom flask on water bath. The solution was left for 24 hours to crystallize. The yellow crystals obtained were filtered and were recrystallized from ethanol.s They were then dried in a desiccator over silica gel.(Yield,9.7g; 80.78%).

Preparation of Acetone-2-amino-4-thiazoleacetic acid hydrazone (ATAAH)
8.6g, (0.05 mole) of 2-amino-4-thiazoleacetic acid hydrazide (ATAH) was mixed with 3ml (0.05 moles]) of acetone in 120ml ethanol and refluxed for 4 hours in a 250ml round bottom flask on water bath. The solution was left for 7days to crystallize. The milky crystals obtained were filtered and were recrystallized from ethanol.s They were then dried in a desiccator over silica gel.(Yield,6.1g; 40%).

Preparation of the complexes
The complexes were prepared by the reaction between aqueous solutions of the metal salts and ethanolic solutions of the ligand in a 1,2 molar ratio

The preparation of the Ni-ATAH complexes
0.86 gram (0.005mole) of 2-amino-4-thiazoleacetic acid hydrazide(ATAH) was dissolved in 10ml of ethanol and slightly warmed, while 0.64g (0.0025 moles) of $NiSO_4.6H_2O$ was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the nickel(II) solution and a light green coloured crystals were formed. The crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 0.75g; 45%).

The preparation of the Ni-ATASH complexes
1.22 gram (0.005mole) of salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone was dissolved in 10ml of ethanol and slightly warmed, while 0.64g (0.0025moles) of $NiSO_4.6H_2O$ was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the nickel(II) solution and a yellow coloured crystals were formed. The crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 0.51g; 37%).

The preparation of the Ni-ATAAH complexes
0.985gram (0.005mole) of acetone-2-amino-4-thiazoleacetic acid hydrazone was dissolved in 10ml of ethanol and slightly warmed, while 0.64g (0.0025 moles) of $NiSO_4.5H_2O$ was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the nickel(II) solution and a vsery light green coloured crystals were formed. The crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 0.89g; 53%).

The preparation of enolhydrazide, Ni-ATA
This was obtained by adding a little quantity of sodium ethoxide into the mixture of nickel (II) sulphate and 2-amino-4-thiazoleacetic acid hydrazide during the complexation

Elemental Analysis [Jeffrey et al; 1979]
Using EDTA the percentage of metals in the complexes were determined complexometrically while that of sulphur was gravimetrically determined as sulphate by precipitation using $BaCl_2$.

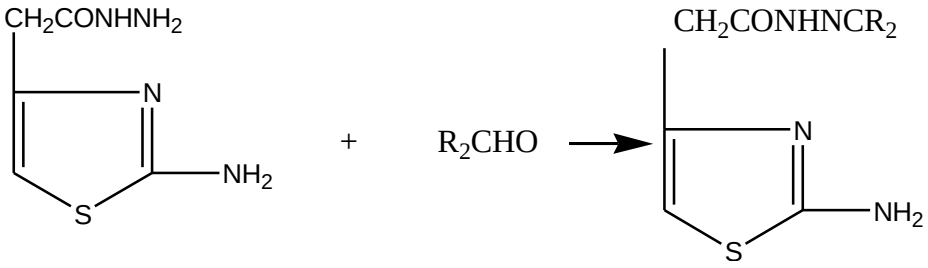
Instrumental Measurement
IR spectra in nujol were taken using 8400S Fourier Transform Infrared Spectrophotometer. Electronic absorption spectra of the ligand and complexes were done in ethanol solution using Spectronic 21D Milton Roy UV – VIS SpectrophotometeR. The conductivity measurement in EtOH of the complexes were made using the pH/ conductivity meter, JENWAY 430.

Antimicrobial Screening

Antimicrobial screening of the ligands, the nickel salts and the complexes in aqueous methanol was carried out using nutrient Agar. *In-vitro* susceptibility testing of the chemicals were carried out on four types of micro-organisms viz *staphylococcus aureus, Escherichia coli, streptococcus, klebsialla aero genes.* Disks were sterilized in the oven at a temperature of 60°C for one hour and allowed to cool and then they were coated accordingly with the different solutions of the ligand and complexes(0.005g/ml ethanol).Drying and sterilization in the oven at a temperature of 37°C for 24 hours followed. The Petri-dishes containing already gelled nutrient agar were innoculated with the micro-organisms. These Petri-dishes were impregnated with the disks containing the solutions of the ligands and the complexes differently and separately. They were arranged radially from the centre of the dishes and incubation was done for 24 hours. This was done in duplicate . Antibacterial activity was measured as zone diameter of inhibition around the disk.

RESULT AND DISCUSSION

The chemical equation below represents the preparation of the thiozolehydrazone from the thiozolehydrazide



The reaction between the ligand and the metal salts yield complexes with 1:1, 2:1, or3:1 stoichiometries

The analytical data and some physical constants for the complexes are shown in table 1

TABLE I: Analytical data and some Physical Constants of the Ligands and Complexes

S/N	COMPOUNDS	FORMULAR	FM. WT	COLOUR	MPT/DEC	%YIELD	%M	$\%SO_4^{2-}$	Conductivity Ω^{-1} cm^2 mol^{-1}
1.	ATAH	$C_5H_8N_4OS$	172	Light brown	134°	66	-	-	-0.276
2.	ATA	$C_5H_7N_4OS$	171	Light brown	102°	21	.-	-	0.207
3	ATASH	$C_{12}H_{12}N_4OS$	276	Yellow	210°	81	-	-	0.289
4	ATAAH	$C_8H_{12}N_4OS$	212	Milky	198°	40	-	-	0.199
5	$[Ni(ATAH)_2]SO_4.H_20$	$C_{10}H_{18}N_8O_6S_2Ni$	516.5	Dirty Green	126°	45..	10.20(11.00)	18.50(18.60)	0.287
6	$[Ni(ATA)_2]H_2O$	$C_{10}H_{16}N_8O_7S_2Ni$	589.5	Yellow Green	198°	41..	9.77(9.90)		0.291
7	$[Ni(ATASH)_3SO_4.H_2O$	$C_{15}H_{23}N_{12}O_8S_4Ni$	1000.5	Yellow	132°	37..	4.10(5.80)	9.50(9.60)	0.301
8	$[Ni(ATAAH)_2]SO_4.H_2O$	$C_{21}H_{38}N_{12}O_8S_4Ni$	817.5	Light Green	128°	53..	7.00(7.00)	11.60(11.70)	0.275

These complexes are monometric non-electrolytes, proved by their solubility in common organic solvents, insolubility in H_2O, not too high melting points and very low conductivity [Ikekwere et al 1989]

Infrared Data

Assignment of band above 3000cm^{-1} are only tentative since band due to the symmetric vibrations of OH, NH and NH_2 groups appear in this region as unresolved (Jeffery, Basset, Nendham and Dennry, 1979]. Bands around 3400cm^{-1} in the spectra of the hydrated complexes are assigned to υ(OH) of water of crystallization [Ikekwere et al; 1989]. The υ(C=O) band located in the spectrum of the ligand at ca1669cm^{-1} is lowered in the spectra of the complexes by[(- 02) – (-75)]cm^{-1} indicating coordination via the carbonyl oxygen.

The υ(C=N) group is also affected because the azomethine N is used for ligation (Ikekwere, Patel and Nwabueze, 1989; Nwabueze 1999). Uncoordinated sulphate group has infrared active vibration located around 1120cm^{-1}. Whenever this anion coordinated, it lowers its Td symmetry and split this band. As the sulphate band is split in all the relevant complexes, it indicates that the anion is in the inner coordination sphere. The diagnostic IR bands for the ligands and complexes are shown in Table 2

Table 2 Diagnostic IR Band for the Ligands and Complexes

Compound	υ (OH)	υ (NH)	υ (C=O)	Δυ (C=O)	υ (C=N)	Δυ (C=N)	υ (SO_4^{2-1})	υ (M-O)	υ (M-N)
ATAH	3322	3120	1701		1508			600	423
ATASH	3788		1750		1589		423		
ATAAH	3395	1628		1528		432			
$[Ni(ATAH)_3]SO_4.H_2O$	3342	3114	1626	-75	1504	-04	1173	623	443
$[Ni(ATA)_2]H_2O$	3294	3125	1599		1447				
$[Ni(ATASH)_2SO_4.H_2O$	3395	1701	-49	1508	-81	1137	432		
$[Ni(ATAAH)]SO_4.H_2O$	3258		1630	+02	1511	-17	1109	615	410

Electronic Spectra

The electronic spectra data for the complexes are shown in table 3

TABLE 3: Electronic Data for the Complexes

Compound	λnm	Assignment	Stereochemistry
$[Ni(ATAH)_3]SO_4..H_2O$	382	$^3A_2g \rightarrow {}^3T1g(F)$	Octahedral
$[Ni(ATA)_2]H_2O$	442	$^3A_2g \rightarrow {}^3T1g(F)$	Octahedral
$[Ni(ATASH)_2]SO_4.H_2O$	370	$^3A_2g \rightarrow {}^3T1g(F)$	Octahedral
$Ni(ATAAH)]SO_4$	500	$^3A_2g \rightarrow {}^3T1g(F)$	Octahedral

The spectra of the nickel(II)complexes show a single band located at 382nm, 442nm, 370nm and 500nm. This is the $^3A_2g \rightarrow {}^3T1g(F)$ band which indicates an octahedral geometry for the complexes [Nwabueze; 1997, Nicholis; !974]

Antimicrobial Screening

The result of the antimicrobial screening of thr compounds is shown in table 4

TABLE 4 : Antimicrobial Test Results for the Ligands and Complexes

Compounds	*S.aur*	*E.c.*	*S.sp*	*K.aeroge*
ATAH	-	-	+	-
ATASH-	-	-		-
ATAAH-	+	+		+
$[Ni(ATAH)_3]SO_4 H_2O$	+	++	-	+
$[Ni(ATASH)_2]SO_4.H_2O$	-	-	+	-
$[Ni(ATAAH)]SO_4$	-	+	-	-

Key - resistance, + (fairly active) ++ (active)

The microbial activity of the compounds is insignificant, probably due to the presence of few nitrogen atoms except however for $[Ni(ATAH)_3]SO_4 H_2O$ which is relatively active.

CONCLUSION

The ligands (1). 2-amino-4-thiazoleacetic acid hydrazide (2). salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone and (3). acetone-2-amino-4-thiazoleacetic acid hydrazone with their complexes which was each done with nickel (II) sulphate was successfully synthesized.

The ligands acted as a neutral bidentate donor via the azomethine N and the carbonyl O. The anions apparently are in the inner coordination sphere. No significant antimicrobial activity was shown by the compounds.

REFERENCES

Bontchev P.R, Boneva M., and Miter M, (1981): "Copper (II) complexes of hydrazides" ,Journal of Inorganic and Nuclear Chemistry, 43, 3163

Enedoh M. C and Nwabueze J. N (2011): "Complexes of 4-Cyanobenzaldehydecyclohexylacetic acid hydrazone with some M(II) sulphates and Acetates. (M= Ni, Cu, Co, Zn)". Zuma Journal of Pure & Applied Sciences. 9, 1

Francisco H.N, Nuria A, Illan-Cabeza M, Antonio N and Penas-Chamorro L (2000): "Ni(II), Cu(II), Zn(II) and Cd(II) complexes of di negative N, O-tridentate uracil derived hydrazones" Acta Chimica Slovakia; 47, 481.

Ikekwere P.O, Patel K.S and Nwabueze J.N (1989): "Complexes of copper(II) sulphate with some cyclocarboxylic acid hydrazides" Synthesis and Reactivity in Inorganic Metal Organic, 19, 599

Ikekwere P.O, Patel K.S and Nwabueze J.N (1989): "Complexes of cobalt(II) sulphate with some cyclocarboxylic acid hydrazides" Synthesis and Reactivity in Inorganic Metal Organic, 19, 893

Jeffrey G.H, Basset J, Nendham J. and Dennry R.C (1979): " Vogel's Textbook of Qualitative Inorganic Analysis". 4th Ed. Longman, London pp 504

Mallikarjuna B.P, Sastry B.S, Rajendraprasad Y and Chandrashekar S.M, Sathisha K (2009): "Synthesis of new 4-isopropylthiazole hydrazide analogs and some derived clubbed triazole, oxadiazole ring systems--a novel class of potential antibacterial, antifungal and antitubercular agents" To insert individual citation into a bibliography in a word-processor, select your preferred citation style below and drag-and-drop it into the document. European Journal of Medicinal Chemistry 10, 1016

Mallikarjuna B.P, Sastry B.S, Suresh Kumar G.V, Rajendraprasad Y and Chandrashekar S.M, Sathisha K..(2008): "Synthesis of new isopropylthiazole hydrazide analogs and some derived clubbed triazole, oxadiazole ring systems--a novel class of potential antibacterial, antifungal and antitubercular agents". Department of Medicinal Chemistry, PES College of Pharmacy, Hanumantha Nagar, BSK Ist Stage, Bangalore 560050, Karnataka, India. mallibp@gmail.com

Nwabueze J. (1992): " Studies on some metal (II) sulphate chelates of acetone benzoyl and acetone salicyloylhydrazones". Journal of the Chemical Society of Nigeria, 17, 41.

Nwabueze J.N (1999): "Mixed ligand of cobaloxime with hydrazones derived from cyclocarboxylic acids" Zuma Journal of Pure and Applied Sciences, 2, 35

Nwabueze J.N, (1997): "Complexes of copper (II) with acetone hydrazones derived from some cyclocarboxylic acids" Synthesis and Reactivity in Inorganic Metal Organic Chemistry. 27, 673

BIODATA

Rev Sr. (Dr.) Enedoh, Margaret Chinyelu Njideka is a religious sister of the Immaculate Heart of Mary, Mother of Christ Religious institute. She attended Our Lady's High School Effurun Warri and came out with division one. She had her first degree in Industrial Chemistry from the University of Nigeria, Nsukka in 1998 and was the second best chemistry graduand of that year. In 2004 and 2014, she got her second and third degrees respectively in Inorganic Chemistry from the University of Abuja, Abuja. She has much interest in Complexometric Chemistry. Rev. Sr. (Dr) Enedoh is presently a lecturer of inorganic chemistry in the Imo State University, Owerri. She is a full member of many professional Associations. These include: National Science Teachers Association of America (NSTA), American Chemical Society (ACS), Chemical Society of Nigeria (CSN), Science Teachers Association of Nigeria (STAN), Indeed, she is currently the National Chairperson of the Chemistry Panel of STAN.