

# Complexes of 2-amino-4-thiazoleacetic acid hydrazide(ATAH), salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone(ATASH) and acetone-2-amino-4-thiazoleacetic acid hydrazone(ATAAH), each with copper(II)sulphate

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**Abstract:** Four 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) each complexed with copper(II) sulphates have been synthesized. The complexes were characterized by elemental analyses, conductance, infrared and electronic spectral studies. The ligands and complexes were screened for antimicrobial activity and the compounds were relatively inactive against the organism tested. The electronic data indicate a square planar 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<sub>4</sub><sup>2-</sup> anions are in their inner coordination spheres. The conductivity analyses indicate a non-electrolytic nature for the chelates.

**Key Words:** acetone, 2-amino-4-thiazoleacetic acid, antimicrobial, bidentate, enol, hydrazide, hydrazone, keto, Salicylaldehyde, sulphates

## 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 [J.N. Nwabueze (1997),

Complexes of Copper (II) with Acetone hydrazones derived from some cyclocarboxylic acids, Synth. React.Inorg. Met.-Org. Chem. 27, 673.] They generally exhibit very strong antibacterial activity. This antibacterial activity is enhanced on complexation to some transition metal ions[Bontchev et al; 1981]. 4-isopropylthiazole-2-carbohydrazide is known to be a novel class of potential antibacterial, antifungal and antitubercular agents [B. P. Mallikarjuna et al, 2008, 2009]. Also of interest is the coordination mode of hydrazones. 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<sup>1</sup> in RCONHNCR<sup>1</sup><sub>2</sub>. Hydrazones derived from 6-

amino-5-formyl-1, 3-dimethyl uracil and nicotinic and isonicotinic acid hydrazides formed four – coordinate complexes with Cu<sup>2+</sup> 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 moiety. 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 et al; 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.

## Experimental

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 methods as in literature [Nwabueze et al.; 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 desiccator. (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, 0.05 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. 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 7 days to crystallize. The milky crystals obtained were filtered and were recrystallized from ethanol. 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 Cu-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 0.61g (0.0025 moles) of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the copper(II) solution and a light brown coloured crystals were formed. The crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 1.1g; 43%).

#### ***The preparation of the Cu-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 0.61g (0.0025moles) of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the copper(II) solution and a brown coloured crystals were formed. The crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 1.3g; 60%).

#### ***The preparation of the Cu-ATAAH complexes***

0.985gram (0.005mole) of acetone-2-amino-4-thiazoleacetic acid hydrazone was dissolved in 10ml of ethanol and slightly warmed, while 0.61g (0.0025 moles) of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  was dissolved in 10ml of water. The ligand was then added gently while stirring continuously into the copper(II) solution and a coffee brown coloured crystals were formed. The

crystals were filtered and dried over silica gel in a desiccator for 2 days. (Yield, 1.15g; 61%).

### ***The preparation of enolhydrazone, Cu-ATA***

This was obtained by adding a little quantity of sodium ethoxide into the mixture of copper (II) sulphate and 2-amino-4-thiazoleacetic acid hydrazone 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<sub>2</sub>.

### ***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 copper 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, klebsiella 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

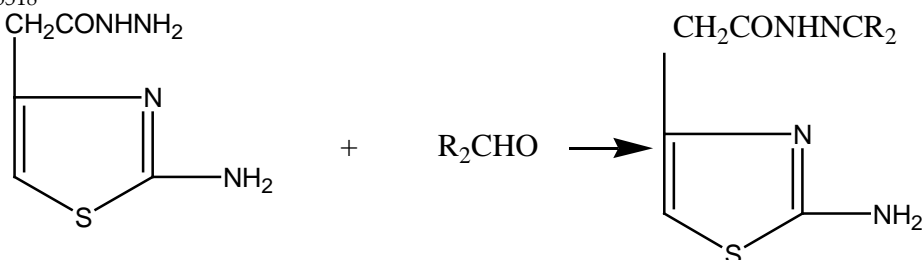
different solutions of the ligand and complexes (0.005g/ml ethanol). Drying and sterilization in the oven at a temperature of 37°C for 24 hours followed. The Petri-dishes containing already gelled nutrient agar were inoculated with the micro-organisms. These Petri-dishes were impregnated with the disks 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 thiozolehydrazone

Assignment of band above 3000cm<sup>-1</sup> are only tentative since band due to the symmetric vibrations of OH, NH and NH<sub>2</sub> groups appear in this region as unresolved [Jeffery et al; 1979]. Bands around 3400cm<sup>-1</sup> in the spectra of the hydrated complexes are assigned to  $\nu(\text{OH})$  of water of crystallization [Ikekwere et al; 1989]. The  $\nu(\text{C}=\text{O})$  band located in the spectrum of the ligand at ca 1669cm<sup>-1</sup> is lowered in the spectra of the complexes by 02 – 128cm<sup>-1</sup> indicating coordination via the carbonyl oxygen.

The  $\nu(\text{C}=\text{N})$  group is also affected because the azomethine N is used for ligation [Ikekwere et al; 1989, Nwabueze 1999]. Uncoordinated sulphate group has infrared active vibration located around 1120cm<sup>-1</sup>. 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 reaction between the ligands and the metal salt yield complexes with 1:1, 2:1, or 3:1 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
1.	ATAH	C <sub>5</sub> H <sub>8</sub> N <sub>4</sub> OS	172	Light brown	134°	66	-
2.	ATA	C <sub>5</sub> H <sub>7</sub> N <sub>4</sub> OS	171	Light brown	102°	21	-
3	ATASH	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> OS	276	Yellow	210°	81	-
4	ATAAH	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> OS	212	Milky	198°	40	-
5	[Cu(ATAH) <sub>3</sub> ]SO <sub>4</sub> ·	C <sub>15</sub> H <sub>24</sub> N <sub>12</sub> O <sub>7</sub> S <sub>4</sub> Cu	677.5	Dark brown	125°	65..	9.00(9.30)
6	[Cu(ATA) <sub>2</sub> ]H <sub>2</sub> O	C <sub>10</sub> H <sub>16</sub> N <sub>8</sub> O <sub>7</sub> S <sub>2</sub> Cu	423.5	Brown	205°	43..	14.72(15.20)
7	[Cu(ATASH) <sub>2</sub> ]SO <sub>4</sub> ·H <sub>2</sub> O	C <sub>10</sub> H <sub>14</sub> N <sub>8</sub> O <sub>6</sub> S <sub>3</sub> Cu	711.5	Brown	222°	60..	8.20(8.90)
8	[Cu(ATAAH)]SO <sub>4</sub>	C <sub>7</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub> Cu	371.5	Coffee brown	179°	61..	16.50(17.00)

Figures In parenthesis are theoretical values

These complexes are monomeric non-electrolytes, proved by their solubility in common organic solvents, insolubility in H<sub>2</sub>O, not too high melting points and very low conductivity [Ikekwe et al 1989]

### Infrared data

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	ν(OH)	ν(NH)	ν(C=O)	Δν(C=O)	ν(C=N)	Δν(C=N)	ν(SO <sub>4</sub> <sup>2-</sup> )	ν(M-O)	ν(M-N)	(H <sub>2</sub> O)
ATAH	3322	3120	1701		1508			600	423	
ATASH			1750		1589				423	
ATAAH	3395		1628		1528				432	
[Cu(ATAH) <sub>3</sub> ]SO <sub>4</sub> ·	3310	3124	1627	-74	1522	+14	1119	599	423	699
[Cu(ATA) <sub>2</sub> ]H <sub>2</sub> O	3308	3112	1626		1521			603	510	693
[Cu(ATASH) <sub>2</sub> ]SO <sub>4</sub> ·H <sub>2</sub> O	3382	3131	1622	-128	1521	-68	1104	614	460	
[Cu(ATAAH)]SO <sub>4</sub>	3312	3139	1630	-02	1516	-12	1130		412	698

### Electronic spectra

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

**TABLE 3: Electronic data for the complexes**

Compound	$\lambda_{nm}$	Assignment	Stereochemistry
1 [Cu(ATAH) <sub>3</sub> ]SO <sub>4</sub> .	610	d → d	Square planar
2. [Cu(ATA) <sub>2</sub> ]H <sub>2</sub> O	670	d → d	Square planar
3. [Cu(ATASH) <sub>2</sub> ]SO <sub>4</sub> .H <sub>2</sub> O	682	d → d	Square planar
4 [Cu(ATAAH)]SO <sub>4</sub>	680	d → d	Square planar

The spectra of the copper(II) complexes show a single band located at 610nm, 670nm, 682nm and 680nm. This is the d→d band which indicates a square planar

geometry for the complexes [Nwabueze; 1997, Nicholis; 1974]

### Antimicrobial screening:

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

**TABLE 4 :Antimicrobial test results for ligands and complexes**

COMPOUNDS	<i>S.aureas</i>	<i>E.coli</i>	<i>S.spp</i>	<i>K.aerogenes</i>
1. 1. ATAH	-	-	++	-
2. ATASH-	-	-	-	-
3. ATA AH-	+	+	-	+
4. [Cu(ATAH) <sub>3</sub> ]SO <sub>4</sub>	+	+	-	++
5. [Cu(ATASH) <sub>2</sub> ]SO <sub>4</sub> .H <sub>2</sub> O	-	-	+	-
6. [Cu(ATAAH)]SO <sub>4</sub>	-	+	-	-

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

The microbial activity of the compounds is insignificant, probably due to the presence of few nitrogen atoms.

### 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 copper (II) sulphate was successfully synthesized. The ligands acted as a neutral bidentate donor via the azomethine

N and the carbonyl O. The copper complexes are square planar. The anions apparently are in the inner coordination sphere. No significant antimicrobial activity was shown by the compounds.

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