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

M. C Enedoh (megnedoh@yahoo.com)
Department of Chemistry, Imo State University, P.M.B. 2000, Owerri, Nigeria.

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 SO42- 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 R¹ in RCONHNCR¹². Hydrazones derived from 6-amino-5-formyl-1, 3-dimethyl uracil and nicotinic and isonicotinic acid hydrazides formed four – coordinate complexes with Cu²⁺ 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 1 mole of ethyl-2-amino-4-thiazoleacetate and 1 mole of the hydrazine hydrate using standard method as in literature [Nwabuezeto; 1992]. 25.00 ml (0.40 moles) of hydrazine hydrate was added to 70 g (0.40 moles) of ethyl-2-amino-4-thiazoleacetate in 300 ml 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, 46.1 g; 65.86%)

Preparation of Salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone (ATASH)
8.6 g, (0.05 mole) of 2-amino-4-thiazoleacetic acid hydrazide (ATAH) was dissolved in 130 ml of ethanol and refluxed for 4 hours in a 250 ml 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, 9.7 g; 80.78%).

Preparation of Acetone-2-amino-4-thiazoleacetic acid hydrazone (ATAAH)
8.6 g, (0.05 mole) of 2-amino-4-thiazoleacetic acid hydrazide (ATAH) was mixed with 3 ml (0.05 moles) of acetone in 120 ml of ethanol and refluxed for 4 hours in a 250 ml 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, 6.1 g; 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 (0.005 mole) of 2-amino-4-thiazoleacetic acid hydrazide (ATAH) was dissolved in 10 ml of ethanol and slightly warmed, while 0.61 g (0.0025 moles) of CuSO₄·5H₂O was dissolved in 10 ml 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, 1.1 g; 43%).

The preparation of the Cu-ATASH complexes
1.22 gram (0.005 mole) of salicylaldehyde-2-amino-4-thiazoleacetic acid hydrazone was dissolved in 10 ml of ethanol and slightly warmed, while 0.61 g (0.0025 moles) of CuSO₄·5H₂O was dissolved in 10 ml 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, 1.3 g; 60%).

The preparation of the Cu-ATAAH complexes
0.985 gram (0.005 mole) of acetone-2-amino-4-thiazoleacetic acid hydrazone was dissolved in 10 ml of ethanol and slightly warmed, while 0.61 g (0.0025 moles) of CuSO₄·5H₂O was dissolved in 10 ml 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 enolhydrazide, 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 hydrazide during the complexation.

**Elemental Analysis [Jeffery 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 BaCl₂.

**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 thiozolehydrazide

Assignment of band above 3000cm⁻¹ are only tentative since band due to the symmetric vibrations of OH, NH and NH₂ groups appear in this region as unresolved [Jeffery et al; 1979]. Bands around 3400cm⁻¹ in the spectra of the hydrated complexes are assigned to ν(OH) of water of crystallization [Ikekwere et al; 1989]. The ν(C=O) band located in the spectrum of the ligand at ca1669cm⁻¹ is lowered in the spectra of the complexes by 02 – 128cm⁻¹ indicating coordination via the carbonyl oxygen.

The ν(C=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⁻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.
These complexes are monometric non-electrolytes, proved by their solubility in common organic solvents, insolubility in H₂O, not too high melting points and very low conductivity [Ikekwere 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

<table>
<thead>
<tr>
<th>Compound</th>
<th>υ(OH)</th>
<th>υ(NH)</th>
<th>υ(C=O)</th>
<th>Δυ(C=O)</th>
<th>υ(C=N)</th>
<th>Δυ(C=N)</th>
<th>υ(SO₄²⁻)</th>
<th>υ(M-O)</th>
<th>υ(M-N) (H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAH</td>
<td>3322</td>
<td>3120</td>
<td>1701</td>
<td>1508</td>
<td></td>
<td></td>
<td>600</td>
<td>423</td>
<td></td>
</tr>
<tr>
<td>ATASH</td>
<td>3788</td>
<td>1750</td>
<td>1589</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>423</td>
<td></td>
</tr>
<tr>
<td>ATAAH</td>
<td>3395</td>
<td>1628</td>
<td>1528</td>
<td></td>
<td></td>
<td></td>
<td>432</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Cu(ATAH)₃]SO₄</td>
<td>3310</td>
<td>3124</td>
<td>1627</td>
<td>-74</td>
<td>1522</td>
<td>+14</td>
<td>1119</td>
<td>599</td>
<td>423</td>
</tr>
<tr>
<td>[Cu(ATA)₂]H₂O</td>
<td>3308</td>
<td>3112</td>
<td>1626</td>
<td>1521</td>
<td>603</td>
<td>510</td>
<td>693</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Cu(ATASH)₂SO₄·H₂O</td>
<td>3382</td>
<td>3131</td>
<td>1622</td>
<td>-128</td>
<td>1521</td>
<td>-68</td>
<td>1104</td>
<td>614</td>
<td>460</td>
</tr>
<tr>
<td>[Cu(ATAAH)]SO₄</td>
<td>3312</td>
<td>3139</td>
<td>1630</td>
<td>-02</td>
<td>1516</td>
<td>-12</td>
<td>1130</td>
<td>412</td>
<td>698</td>
</tr>
</tbody>
</table>
Electronic spectra

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

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>λ nm</th>
<th>Assignment</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  [Cu(ATAH)₃]SO₄</td>
<td>610</td>
<td>d → d</td>
<td>Square planar</td>
</tr>
<tr>
<td>2. [Cu(ATA)₂]H₂O</td>
<td>670</td>
<td>d → d</td>
<td>Square planar</td>
</tr>
<tr>
<td>3. [Cu(ATASH)₂]SO₄.H₂O</td>
<td>682</td>
<td>d → d</td>
<td>Square planar</td>
</tr>
<tr>
<td>4 [Cu(ATAAH)]SO₄</td>
<td>680</td>
<td>d → d</td>
<td>Square planar</td>
</tr>
</tbody>
</table>

The spectra of the copper(II) complexes show a single band located at 610 nm, 670 nm, 682 nm and 680 nm. 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**

<table>
<thead>
<tr>
<th>COMPOUNDS</th>
<th>S.aureas</th>
<th>E.coli</th>
<th>S.spp</th>
<th>K.aerogenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ATAH</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>2. ATASH-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. ATAAH-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>4. [Cu(ATAH)₃]SO₄</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>5. [Cu(ATASH)₂]SO₄.H₂O</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6. [Cu(ATAAH)]SO₄</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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.

References

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