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# Co(II) and Cu(I) Complexes of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole: Synthesis, Characterization and Antibacterial studies

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**Abstract**
(O-Carboxybenzoyl)-p-aminophenylsulfonamido thiazole belongs to the group of drugs called sulfonamides. The drug is a broad spectrum antimicrobial that can treat different types of infections including intestinal infections. The drug is indicated in treatment of dysentery, colitis, gastroenteritis and intestinal surgery. Co(II) and Cu(I) complexes of this drug have been synthesized. The melting point, solubility, colour and yield were determined. The metal complexes were characterized based on electonic and infrared spectroscopy. Electronic spectrum of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole showed intraligand charge transfer transition (ILCT). The electronic spectra of the metal complexes showed intraligand charge transfer transition (ILCT), ligand to metal charge transfer (LMCT) and d-d transition. Infrared spectra studies suggested coordination through the S=O and OH functionalities in the complexes.Tetrahedral geometry have been proposed for the complexes. Using continuous variation method, metal:ligand ratio for the complexes suggested 1:2 ratio. (O-Carboxybenzoyl)-p-amino phenylsulfonamidothiazole showed no inhibitory activity against *Escherichia coli, Stapylococcus aureus, Klebsiella pneumoniea and Salmonella enterica*. Inhibition was observed in the complexes. Copper complex showed the highest inhibition zone diameter and minimum inhibition concentration against *Salmonella enterica* at 15.00±0.00 and 0.59±0.06 mg/ml respectively. Cobalt complex showed higher inhibition zone diameter and minimum inhibition concentration against *Escherichia coli* at 23.00±0.00 mm and 0.34±0.00 mg/ml respectively. These showed that both metal ions were able to introduce a new feature into the drug.

***Keywords:*** Complexes, ligand, infrared, electronic, drug, antibacterial.

## 1. Introduction

The field of medicinal inorganic chemistry can be divided into two main classes: firstly, chelating agents as drugs which target metal ions, whether free or protein-bound; and secondly, metal-based drugs that target receptors where the central metal ion is usually the key feature of the mechanism of action[1]. Silver and mercury complexes have been reported as antibacterial agents [2 – 4]. Silver sulfadiazene [5] finds use for treatment of severe burns; the polymeric compound slowly releases Ag ion. In many countries silver nitrate is still used to prevent ophthalmic disease in newborn babies [6]. The mechanism of action of Ag and Hg is through slow release of the active metal ion. These metal ions inhibit thiol in bacterial cell walls. The medicinal uses of coordination compounds are of increasing biological, clinical, pharamaceutical and industrial importance. Colorectal cancer has been treated with fluorouracil-oxaliplatin complex in Europe and the USA[7, 8].Peptic ulcer and ulcers associated with Helicobacter pylori has been managed with ranitidine-bismuth citrate complex, marketed in the USA as ranitidine bismutrex [9]. The use of complexing agents in the treatment of Wilson's disease is a good example of how excess (CuII) toxicity may be ameliorated by chelating agents [10] Antiparasitic activity of gold and ruthenium complexes of chloroquine and clotrimazole have been investigated [11, 12]. Furthermore, it was found that some chloroquine complexes are useful even in chloroquine-resistant cases. It has been [13] reported that copper–cephalexin complex exhibited a good anti-inflammatory activity and had more antibacterial effect than the free cephalexin. The effect of metal ions on drug activity

was confirmed by several studies [14, 15]. Fe(II) and Mn(II) complexes of 2-[({4-[(1,3-thiazol-2ylamino) sulfonyl]phenyl}amino)carbonyl]benzoic acid have been investigated to be more potent than the free ligand againt *Escherichia coli* and *Stapylococcus aureus* [16]. Transition metal complexes offer advantages over common organic base drugs because the transition metal ion provides an alternative route in the drug receptor machanism. Cisplatin, a platinum complex is one of the world's best selling anticancer drug [17].

Based on the therapeutic properties of metal complexes, we have decided to synthesize, characterize and determine the antibacterial activity of Co(II) and Cu(I) complexes of (o-carboxy benzoyl)-p-amino phenylsulfonamidothiazole.

## 2. Materials and methods

2.1 All reagent used were of analytical grade. (o-carboxybenzoyl)-p-aminophenylsulfonamidothiazole was purchased from, Co(II) chloride hexahydrate and Cu(II) chloride dihydrate were purchased fron BDH Chemical Ltd Poole England. UV-visible 2500PC Series Spectrophotometer was used for electronic studies while SHIMADZU FTIR-8400S Fourier Transform Infrared Spectrophotometer was employed for the functional group studies.

2.2 Synthesis of Cobalt (II) (o-carboxybenzoyl)-p-aminophenylsulfonamidothiazole complex: methanolic solution (50ml) of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole (8.06g) was prepared. Methanolic solution (50ml) of cobalt compound (4.76g) was added to the (o-carboxy benzoyl)-p-aminophenylsulfonamidothiazole solution and stirred gently for 45 minutes. The mixture was refluxed for 4 hours. The precipitate was dried in a desiccator and the yield was recorded.

2.3 Synthesis of Copper (II) (o-carboxybenzoyl)-p-aminophenylsulfonamidothiazole complex: methanolic solution of (50ml) of (o-carboxy benzoyl)-p-aminophenylsulfonamidothiazole (8.06g) was prepared. Methanolic solution (50ml) of manganese compound (2.69g) was added to the (o-carboxybenzoyl)-p-aminophenylsulfonamidothiazole solution and stirred gently for 45 minutes. The mixture was refluxed for 4 hours. The precipitate was dried in a desiccator and the yield recorded.

2.4 Media preparation: The media used for the antimicrobial sensitivity testing was Muller Hinton agar. It was prepared by weighing out 38g of the powdered agar into 100ml of distilled water in a conical flask. This was sterilized in an autoclave at 121$^{o}$ C for 15 minutes, after autoclave, the media was poured into sterile petri dish and allowed to gel (cool).

2.5 Determination of antimicrobial activity.The organisms used are *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniea and Salmonella enterica* gotten from stock culture in Michael Okpara University of Agriculture's microbiology laboratory. Organisms were inoculated into the already prepared Muller Hinton agar. Using a cork borer, well (7mm in diameter and 2.5mm deep) was bored into the inoculated agar and 50µl of each of the complex at a concentration of 1g/ml was delivered into the wells. The plates were incubated and read after 18 - 24 hours. The diameter zone of inhibition produced by the complexes were measured with a transparent meter rule in mm

2.6 Determination of minimum inhibitory concentration (MIC): The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial extract that can be able to inhibit the visible growth of a microorganism after overnight incubation. To determine the MIC 0.95 mL of Mueller Hinton Broth was transferred into 9 test tubes.1ml of the complex at 50mg/ml was pipetted into the first tube and properly mixed.1ml was taken from the first test tube into the second test tube and mixed. This was continued up to the 7$^{th}$ tube to give concentrations of 50, 25, 12.5, 6.25, 3.12 and 0.78mg/ml. The 8$^{th}$ tube was labeled the organism control which contained only the organisms and Mueller Hinton Broth but no complex. The 9$^{th}$ tube was labeled antibiotic control which contained the organism, Mueller Hinton Broth and antibiotic. 0.05ml (50ul) of the organism suspension was transferred into each test tube using a micropipette. The tubes were incubated and result read after 18-24

hours. The MIC was the tube that prevented visible growth of the organism after the period of incubation.

2.7. Stoichiometric determination: Metal: ligand ratio was determine using Job's method of continuous variation method [18]

## 3. Results and discussion

3.1 Physical data of the ligand and complexes are shown in Table 1. The solubility data is shown in Table 2. Antibacterial activity and minimum inhibition concentration are presented in Tables 3 and 4 respectively. Infrared and elctronic spectra are shown in Figures 1 – 6.

Table 1: Physical data for the ligand and complexes.

| Properties | L | CoL | CuL |
|---|---|---|---|
| Appearance | Solid | Solid | Solid |
| Melting point ($^oC$) | 272-277 | 322-320 | 278-280 |
| Color | White | Pink | Blue |
| Yield (%) | - | 278-280 | 322-320 |

L = (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole

Table 2: Solubility data for the ligand and metal complexes

| Compound | $CH_3OH$ | $C_6H_{14}$ | $C_2H_5OH$ | $H_2O$ | DMSO |
|---|---|---|---|---|---|
| L | IS | IS | SS | SS | S |
| CoL | IS | IS | SS | SS | S |
| CuL | IS | PS | SS | SS | S |

IS = insoluble, PS = partially soluble, SS = sparingly soluble, S= Soluble
L = (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole

Table 3: Antibacterial studies of the ligand and complexes

| | L | CuL | CoL |
|---|---|---|---|
| Bacteria Strain | IZD(mm) | IZD(mm) | IZD(mm) |
| *Escherichia coli* | 0.00 ±0.00 | 0.00 ± 0.00 | 23.00±0.00 |
| *Staphylococcus aureus* | 0.00±0.00 | 0.00±0.00 | 19.00±0.00 |
| *Klebsiella pneumoniea* | 0.00 ± 0.00 | 0.00 ± 0.00 | 15.00±0.00 |
| *Salmonella enterica* | 0.00 ± 0.00 | 15.00±0.00 | 0.00±0.00 |

Values are written as Mean±S.D
L = (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole

Table 4: Minimum inhibition Concentration (MIC) of the ligand and complexes

| | L | CuL | CoL |
|---|---|---|---|
| Bacteria Strain | MIC(mg/ml) | MIC(mg/ml) | MIC(mg/ml) |
| *Escherichia coli* | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.34±0.00 |
| *Staphylococcus aureus* | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.49±0.00 |
| *Klebsiella pneumoniea* | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.22±0.00 |
| *Salmonella enterica* | 0.00 ± 0.00 | 0.59±0.06 | 0.00±0.00 |

Values are written as Mean±S.D
L = (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazol

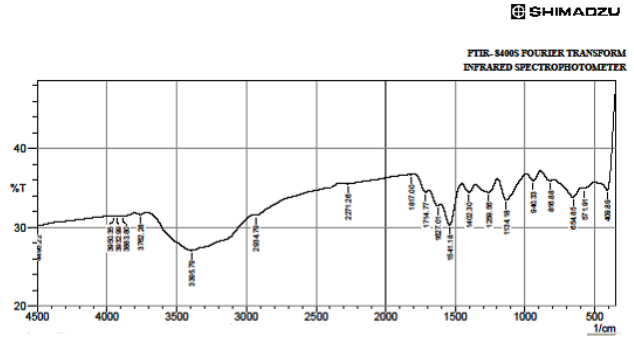


Figure 1: FTIR spectrum of (O-Carboxybenzoyl)-p-amino phenyl sulfonamidothiazole

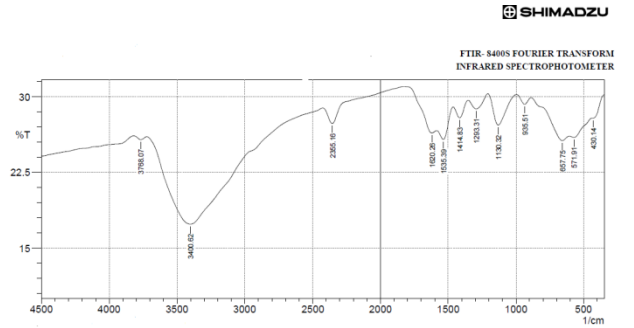


Figure 2: FTIR spectrum of Co(II) (O-Carboxybenzoyl)-p-aminophenyl sulfonamido thiazole complex

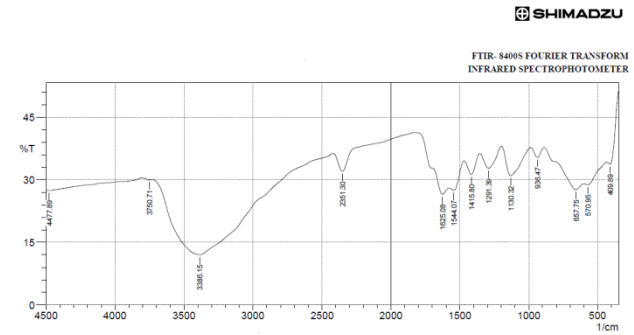


Figure 3: FTIR spectrum of Cu(I)(O-Carboxybenzoyl)-p-aminophenyl sulfonamido thiazole complex

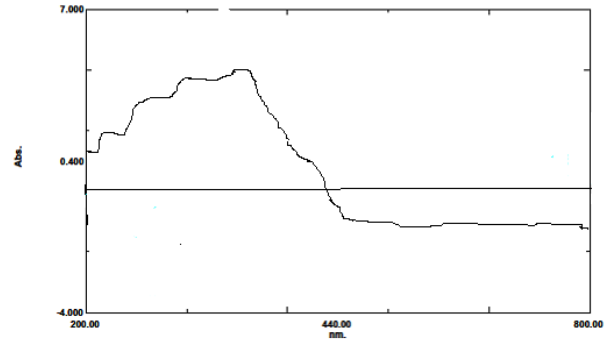


Figure 4: UV-visible of (O-Carboxybenzoyl)-p-aminophenyl sulfonamidothiazole

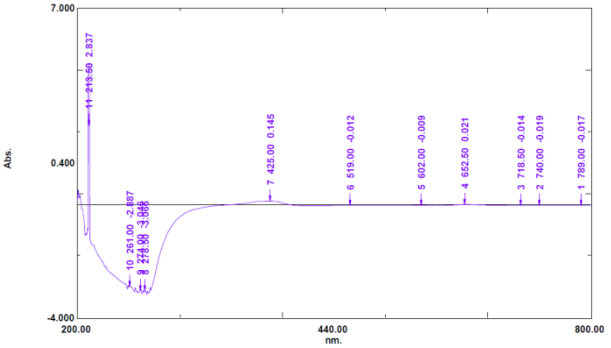


Figure 5: UV-visible of Cu(I) (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole

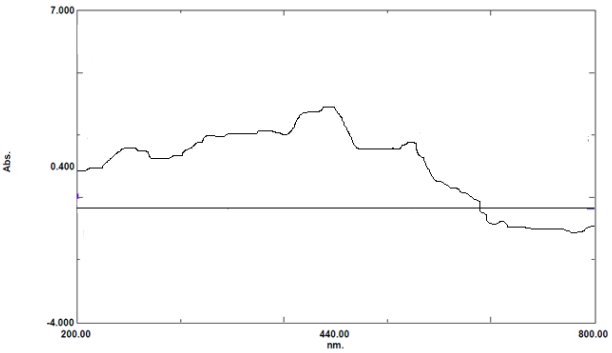


Figure 6: UV-visible of Co(II) (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole

3.2 The colour of copper and cobalt complexes are blue and pink respectively. The change in colour suggested the formation of metal complexes, since transition metal complexes are coloured. The melting point of (O-Carboxybenzoyl)-p-aminophenyl sulfonamidothiazole is 272-277 $^{o}$C, the melting point of copper complex was 278-280 $^{o}$C while that of cobalt complex was 322-320 $^{o}$C. The changes in melting point suggested the formation of metal complexes.

3.3 The C-O vibrational frequency appeared at 1259.56cm$^{-1}$ in the infrared spectrum of the ligand. The C-O vibrational frequency shifted in the metal complexes (1293.31cm$^{-1}$ in cobalt complex and 1291.39 cm$^{-1}$ in copper complex). These shifts suggest the involvement of C-O in coordination which is a as a result of decrease in electron density which decreases the C-O bond length and consequently increases the vibrational frequency. In the IR spectrum of the ligand, the OH stretch of the carboxylic acid was found to be 3395.75cm$^{-1}$. The OH vibrational frequency in the copper complex shifted upfield 3386.15 cm$^{-1}$ while in the cobalt complex it shifted downfield 3400.62 cm$^{-1}$. These shifts suggest the involvement of OH group of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothia zole in complexation. In the infrared spectrum frequency of the ligand, the S=O frequency was found at 1402.03cm$^{-1}$. In the spectra of the metal complexes the S=O frequency was found at 1414cm$^{-1}$ and 1415cm$^{-1}$ in cobalt and copper complexes. These shift in the metal complexes suggest involvement of the S=O group in coordination to the metal. The decrease in electron density decrease the S=O bond length and consequently increases it vibration frequency. C=N stretching frequency appeared at 1627.01cm$^{-1}$ in the ligand, there was no significant shift in the both complexes (Co 1620.26$^{-1}$cm and Cu 1625.08cm$^{-1}$).

3.4 Observation of the electronic spectrum of the ligand showed $\lambda$ max at 365nm. This band has been assigned $\pi - \pi^{*}$ transition. This transition could be as a result of chromophores in the ligand. The chromophores are C = O, S = O, C = C and C = N. There was no transition in the visible region (400 – 800 nm). Electronic spectra of the metal complexes revealed three types of transitions. These transitions are intra ligand charge transfer transition(ILCT) , the ligand to metal charge transfer (LMCT) and d – d transition. In the copper complex electronic spectrum, 425.00 and 652.50 nm have been attributed to ligand to metal charge transfer and d – d transition respectively. Cobalt complex electronic spectrum

showed λ maximum at 450.00 and 520.00 nm. These bands have been assigned ligand to metal charge transfer and d – d transition respectively.

(O-Carboxybenzoyl)-p-aminophenylsulfonamido thiazole showed no inhibition against *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniea and Salmonella enterica*.. The inhibition zone diameter (IZD) and minimum inhibition concentration(MIC) of copper(I) (O-carboxy benzoyl)-p-aminophenylsulfonamidothiazole complex against *Salmonella enterica* was found to be 15.00±0.00 mm and 0.59±0.06 mg/ml respectively. copper(I)(O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole complex did not inhibit *Escherichia coli, Staphylococcus aureus and Klebsiella pneumoniea.* Cobalt(II)(O-carboxy benzoyl)-p-aminophenylsulfonamidothiazole complex inhibited Escherichia coli, Staphylococcus aureus and Klebsiella pneumoniea.. The inhibition zone diameter (mm) and minimum inhibition concentration were 23.00±0.00 mm, 19.00±0.00 mm, 15.00±0.00 mm, 0.34±0.00 mg/ml, 0.49±0.00 mg/ml and 0.22±0.00 mg/ml respectively.

Stoichiometric ratio base on Jobs method of continous varation [18] showed that the Metal:ligand ratio for the complexes was 1:2.

The structure of the ligand is shown in Figures 7.

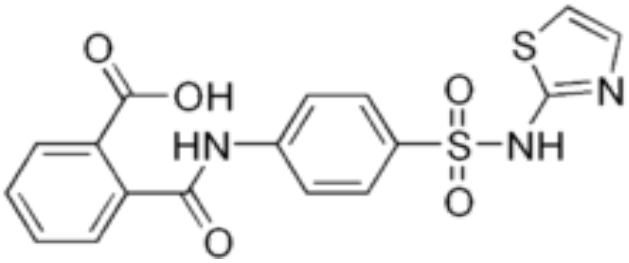

Figure 7: Structure of (O-Carboxybenzoyl)-p-aminophenylsulfo namidothiazole

Based on the electronic, infrared characterization, and continuous variation method, the following structures Figures 8 and 9 have been proposed for the metal complexes.

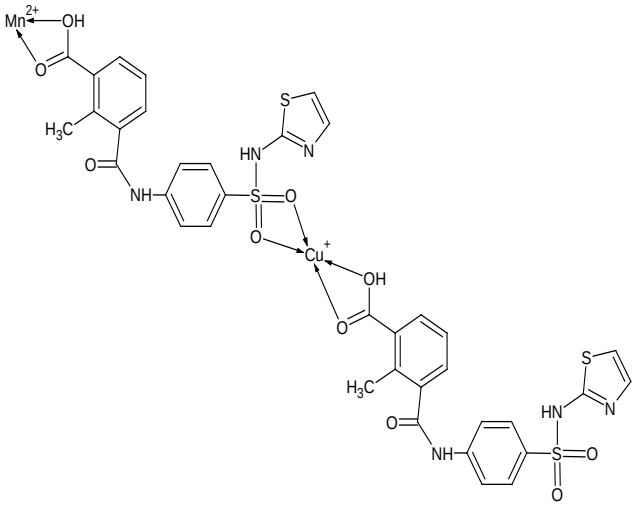

Figure 8: Suggested structure for Cu(I) (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole complex

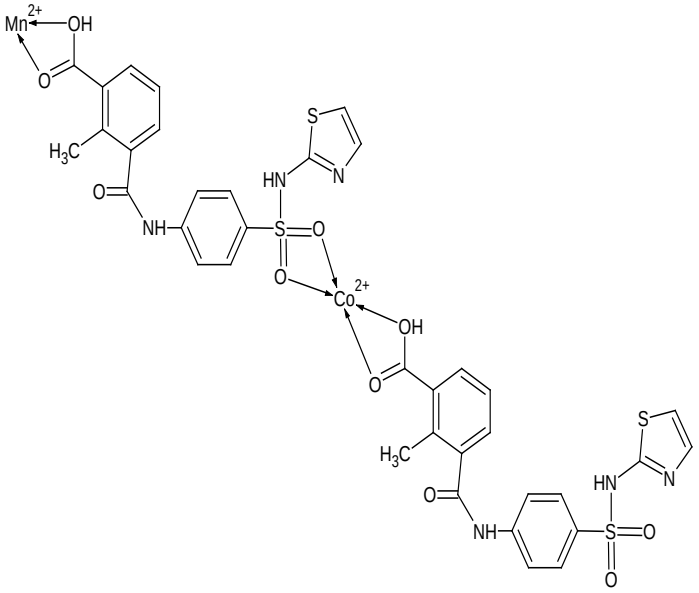

Figure 9: Suggested structure for Co(II) (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole complex

## 4. Conclusions

Co(II) and Cu(I) complexes of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole have been synthesized. FT-IR, electronic characterization, and stoichiometric determination suggested tetradentate complexes The ability of (O-Carboxybenzoyl)-p-aminophenylsulfonamidothiazole to coordinate Co(II) and Cu(I) have been assured.. The complexes

were more potent than (o-carboxyben zoyl) -p-aminophenylsulfonamidothiazole.

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