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SCHIFF BASE FROM L-Glycine and 4-Hydroxybenzaldehyde AND ITS COMPLEXES WITH Co(II) and Cu(II): SYNTHESIS AND ANTIMICROBIAL ACTIVITY

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ABSTRACT

This study reports the synthesis and characterization of Schiff base ligands derived from 4-hydroxybenzaldehyde and L-glycine. The Schiff base was synthesized using a base catalyst (Potassium hydroxide). The derived Schiff base was reacted with metal salts (Cobalt (II) chloride pentahydrate and Copper (II) sulphate pentahydrate) to form Schiff base-metal complexes. The synthesized Schiff base, (E)-2-(4-hydroxybenzylideneamino) acetic acid and its metal complexes were characterized using Fourier Transform-Infrared (FT-IR) spectroscopy and solubility in selected solvents. The antimicrobial activity of the synthesized complexes was evaluated against strains of *Staphylococcus aureus, Escherichia coli* using standard agar diffusion method. The result demonstrated that the metal complexes exhibited enhanced antimicrobial activity compared to the Schiff base. The result shows the potential of the complexes as antimicrobial agents, highlighting the importance of metal-amino acid interactions in enhancing biological activity.

INTRODUCTION

The process by which aromatic aldehydes and primary amines combine to form imine derivatives was discovered by Hugo Schiff in 1864. Azomethine groups with the general formula R-CH=N-R are generated by reacting amines with aldehydes or ketones to create Schiff bases, a significant class of chemical compounds. Typically, Schiff bases are formed under the catalysis of acids, bases, or heat. Schiff bases are condensation products of primary amines with carbonyl compounds. Whereas Schiff bases carrying an alkyl substituent are relatively unstable, those with an aryl group are more stable and easily produced [1]. Whereas Schiff bases containing aromatic aldehydes with efficient conjugation are more stable, those containing aliphatic aldehydes are unstable and easily polymerizable [2]. A Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilizers. They are fundamental materials for the synthesis of various ligands which can be used as chiral auxiliaries in asymmetric synthesis. Metal complexes of Schiff bases have also been used in oxidation reactions [3].

Schiff bases are derived from the condensation reaction between a primary amine and a carbonyl compound. They possess an imine functional group (-C=N-), rendering them highly reactive intermediates. [4]. Schiff base is also known as imine or azomethine group. Schiff base is named after Hugo Schiff in 1864. The general structure of Schiff base is R2C=NR*, where [R* ≠ H] and [R* = alkyl or aryl] [5]. Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. and are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful catalytic transformations [6]. Schiff bases appear to be important intermediates in several enzymatic reactions involving enzyme interaction with an amino or a carbonyl group of a substrate. In bio-inorganic chemistry, the interest in the Schiff base complexes derives from their ability to provide synthetic models for metal-containing sites in metalloproteins and to contribute to developments in medicinal chemistry. Thus, Schiff bases and their complexes have a variety of applications in biological, clinical, and analytical fields [7].

The history of Schiff bases and their derivatives is rooted in the pioneering work of German chemist Hugo Schiff during the 19th century [8]. Schiff's initial investigations led to its discovery, as they are condensation products of ketones or aldehydes with primary amines. Schiff bases exhibit diverse reactivity profiles, making them valuable intermediates in organic synthesis. These compounds undergo various transformations, including nucleophilic addition, reduction, and metal coordination reactions. The nucleophilic character of the imine nitrogen makes Schiff bases susceptible to attack by electrophiles, leading to the formation of a variety of functionalized products [9].

Amino acids, the building blocks of proteins, possess both amine (-NH_2) and carboxylic acid (-COOH) functional groups, and are versatile molecules known for their diverse chemical reactivity. Amino acids can also form Schiff bases, especially when their amine group reacts with aldehydes. These Schiff base derivatives have unique properties, as they retain the amino acid's ability to coordinate metal ions, making them useful in various applications. Amino acid-derived Schiff bases can act as ligands, coordinating with metals. Since amino acids are chiral, their Schiff base derivatives maintain this chirality, which can lead to applications in asymmetric synthesis. These compounds often show interesting biological activities, such as antimicrobial, antiviral, and anticancer effects, making them useful in medicinal chemistry. An essential component in controlling biological activity is a heterocyclic molecule. Nitrogen atoms are joined to aryl and alkyl atoms by carbon-nitrogen double bonds found in Schiff bases. Schiff bases offer a variety of pharmacological properties and practical uses in industry. Aniline or o-amino phenol can be used to make Schiff bases. Schiff bases have a variety of pharmacological properties, including antibacterial, anti-inflammatory, antidepressant, and antipyretic properties [10]. High yields of Schiff bases have been produced by synthesizing them from ortho-hydroxy aryl aldehydes and aromatic or heteroaromatic amines.

Amino acids in Schiff bases retain the ability to coordinate with metal ions, especially through the imine nitrogen and carboxyl oxygen. This is useful for synthesizing metal complexes with potential biological activity. The most common metals involved in such complexes are transition metals like copper, cobalt, zinc, nickel, and manganese. The resulting metal complexes often have enhanced biological and catalytic properties. These Schiff bases can form stable complexes with metals, which are used in fields like catalysis and medicine. For example, copper (II) complexes with amino acid Schiff bases are known for their antimicrobial properties. These reactions have been shown to stabilize when aldehydes and amino acids can form two five membered rings chelated to the metal ion. It was suggested that atoms of amino acid will hold in the plane of the aromatic ring when they are coordinated to the metal ions [11]. Metal complexes derived from amino acids have attracted much more attention because of its inorganic and biological importance [12]. They show wide applications as anti-cancer, anti-tumor, anti-bacterial, anti-fungal, and anti-inflammatory agents [13].
Amino acid derivative Schiff bases exhibit significant biological activities, including antimicrobial, antiviral, antifungal, anticancer, and enzyme inhibitory properties. These properties make Schiff bases and their metal complexes promising candidates for drug development and biomedical research [14]. Recently, there has been considerable interest in the chemistry of amino acid derived Schiff base compounds due to their potential in nuclear medicine application [15]. However, the drug resistances against antibacterial agents may pose a problem in their use with medical purposes [16]. The problem could be overcome by the preparation of metal complexes, by a process of chelation with the coordination of transition metal ions. It is well known that N and O atoms play a key role in the coordination of metals. Amino acid derived Schiff bases have N and O atoms as their basic elements. Schiff base derivatives containing donor atom can act as good chelating agents for the transition of metal ions [17].

MATERIALS AND METHODS

The reagents used in this work are of analytical grade and were used as purchased without purification. Glass wares were washed and dried in an oven at 1100 °C overnight before use. FTIR was carried out using Fourier Transform Infrared spectroscopy machine (Carry 630 by Agilent Technology) from 400 to 4000cm^{-1}.

Apparatus and Equipment

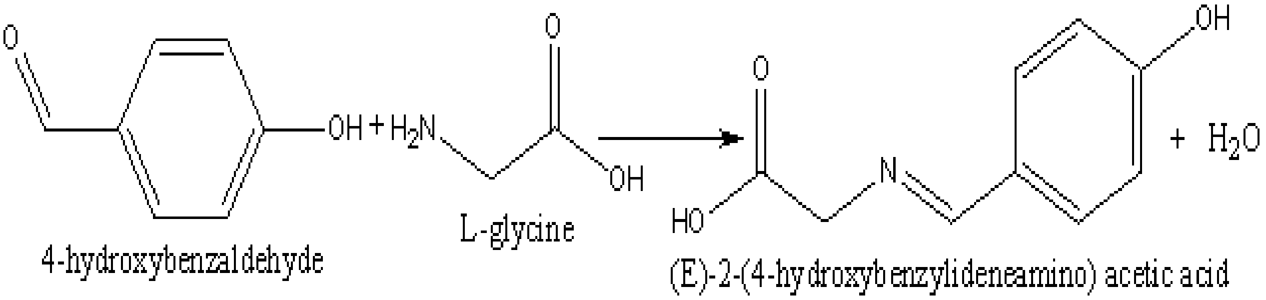
Conical flasks, volumetric flask, measuring cylinder, beakers, glass funnel, filter paper, capillary tubes, nose mask, analytical weighing balance, foil paper, thermometer, spatula, petri-dish, sample bottle and gloves. Magnetic stirrer, flat bottom flask, reflux condenser, IR spectrophotometer, sterile swabs, sterile filter paper discs or wells.

Reagents

4-hydroxylbenzaldehyde ($C_7H_6O_2$), L-glycine ($C_2H_5NO_2$), potassium hydroxide (KOH), glacial acetic acid, copper (II) sulphate pentahydrate ($CuSO_4.5H_2O$), cobalt (II) chloride pentahydrate ($CoCl_2.5H_2O$), ethanol, methanol, distilled water, plant extract, McFarland standard (0.5), Mueller Hinton agar, sterile saline or broth, test organisms (bacteria).

Synthesis of Schiff Base

Schiff base was prepared by dissolving L-glycine (2.5 g) and potassium hydroxide (1.85 g) in methanol (25 mL), 4-hyroxylbenzaldehyde (4.05 g) was prepared in methanol (25 mL). The latter solution is added to the first solution, which was stirred for 1 hour 30 minutes at room temperature. The colour of the solution changed to yellow with orange precipitate. The precipitate was filtered and air-dried. During the drying, the colour of the residue changed from orange to yellow. The product weighed 4.15 g (yield = 70%).



Scheme 1: Synthesis of (E)-2-(4-hydroxybenzylideneamino) acetic acid

Reaction of Schiff base with Copper Salt

Copper complex is prepared by adding ethanol (20 mL) to copper sulphate (1.5 g) in a clean beaker, this solution is then reacted with solution of the prepared Schiff base (0.01mol) in ethanol alongside sodium hydroxide and then mixed over a magnetic stirrer for 5 hours at room temperature. After mixing the Schiff bases and copper sulphate solution a green coloration was observed, and the green color changed to dark blue in 5 minutes. The solid filter was precipitated and washed with diethyl ether. and the complex was dried in a vacuum.

Reaction of Schiff base with Cobalt Salt

The cobalt complex was prepared by adding ethanol (20 mL) to the cobalt chloride (2.314 g) in a clean beaker, this solution is then reacted with solution of the prepared Schiff base (0.01mol) in ethanol. The reaction mixture was refluxed for three hours, filtered, washed with distilled water and methanol and dried with desiccator.

Characterization of the Samples

The Schiff base ligand and the two complexes were characterized using infrared spectroscopy and solubility in some selected solvents. The dried samples were collected in the sample bottles and labelled as 'SB' for the Schiff base, 'M-Co' for the Cobalt complex, and 'M-Cu' for the Copper complex.

Infrared Spectroscopy

The samples were crushed with KBr (5 mg) separately. The samples were placed in a holder in the path of the IR source. A detector read the analogue signal and converted the signal to a spectrum. A computer was used to analyse the signals and identify the peaks.

The FT-IR analysis was carried out using Agilent technologies, Germany, (Cary 360, 2015) at TETfund Chemistry Laboratory, FUNAAB.

Solubility Test

The Schiff base was tested for its solubility in different solvents. A measured quantity of the prepared Schiff base (0.05 g) was transferred into a test tube to which about 2 mL of the corresponding solvent was added, and the solubility was observed and recorded.

Antimicrobial Analysis

A well-prepared McFarland 0.5 standard was compared to the inoculum with standard visually. Mueller-Hinton Agar (MHA) was poured into the sterile petri dishes and allowed to solidify, dried for 15 minutes to remove excess moisture. The surface of the MHA plate was evenly streaked with the swab to ensure uniform growth of the bacteria using a sterile cotton swab dipped into the bacterial suspension (McFarland standard) [18].

The antimicrobial activity was carried out by an adapted agar well-diffusion method. The antimicrobial activity of the synthesized compounds was determined against (*Staphylococcus aureus, Escherichia coli*) microbial stain. The sterile cork borer was used to punch wells (6-8 mm) into the inoculated MHA plate, the well was filled with the plant extract solution and incubated at 37 °C for 18-24 hours. The activity was determined and recorded by measuring the growth inhibitor zone using ruler.

RESULT AND DISCUSSION

The color and yield of the Schiff base product and its complexes with Cobalt and Copper is given in Table 1.

Table 1: Color and yield of the Schiff base/Metal complexes

Complexes	Color	Yield (%)
Cobalt	Purple	65.85
Copper	White	69.37
Schiff Base	Yellowish	70.00

Fourier Transform Infrared Radiation (FTIR) Spectroscopic Analysis of Sample Schiff Base, M-Co and M-Cu

The samples were analyzed between the range of 4500- 400 cm^{-1} and the spectrum was obtained. The result of the IR spectra of the samples shows the sharp absorption in functional group and fingerprint region, the absorption band. The IR spectra are plot of transmittance and wavenumber in cm^{-1}.

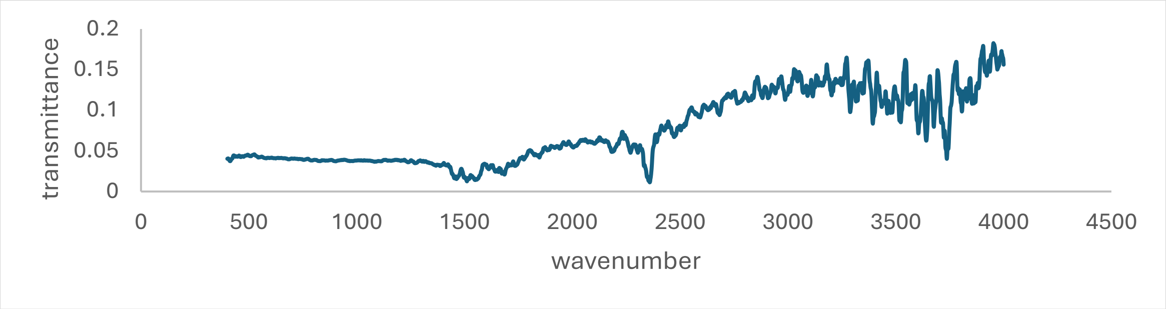


Figure 1: FT-IR spectrum of Schiff Base

Figure 1 shows the FT-IR analysis of the synthesized Schiff base. It exhibits characteristic vibration stretches peaks of v (C=N) at 1655 cm^{-1}, v (C=O) at 1735 cm^{-1}, v (C=C$_{arene}$) at 1556 cm^{-1}, v (C$_{arene}$-H) at 3073 cm^{-1}, v (C$_{aryl}$-O) at 1270 cm^{-1}, v (O-H$_{(carboxyl)}$) at 3222 cm^{-1}, v (O-H$_{(free)}$) at 3604 cm^{-1}.

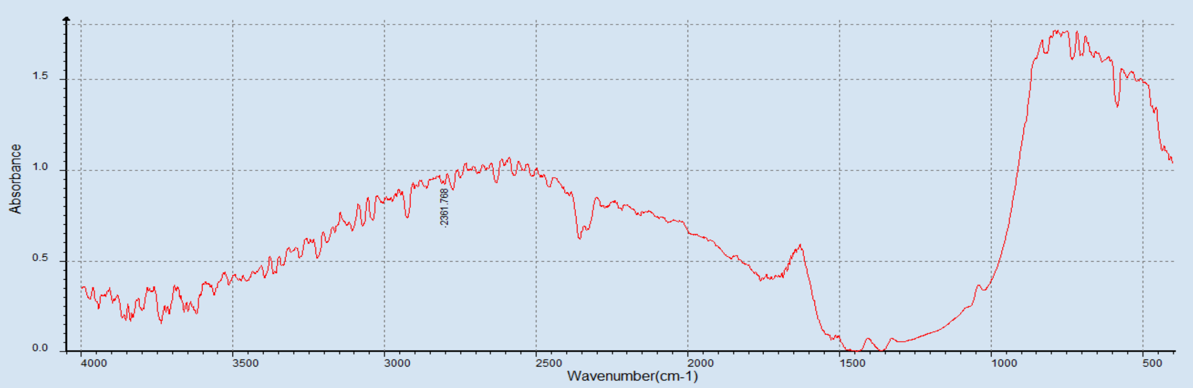


Figure 2: FT-IR spectrum of Cobalt Complex

Figure 2 shows the FT-IR analysis of the synthesized Cobalt (II) complex. It exhibits characteristic vibrational stretches peaks of v Co-N) at 523 cm^{-1}, v (Co-O) at 569 cm^{-1}, v (C=N) at 1620 cm^{-1}, v (C=O) at 1711 cm^{-1}, v (C=C$_{(arene)}$) at 1555 cm^{-1}, v (C$_{arene}$-H) at 3073 cm^{-1}, v (C$_{aryl}$-O) at 1281 cm^{-1}, v (O-H$_{(free)}$) at 3644 cm^{-1}.

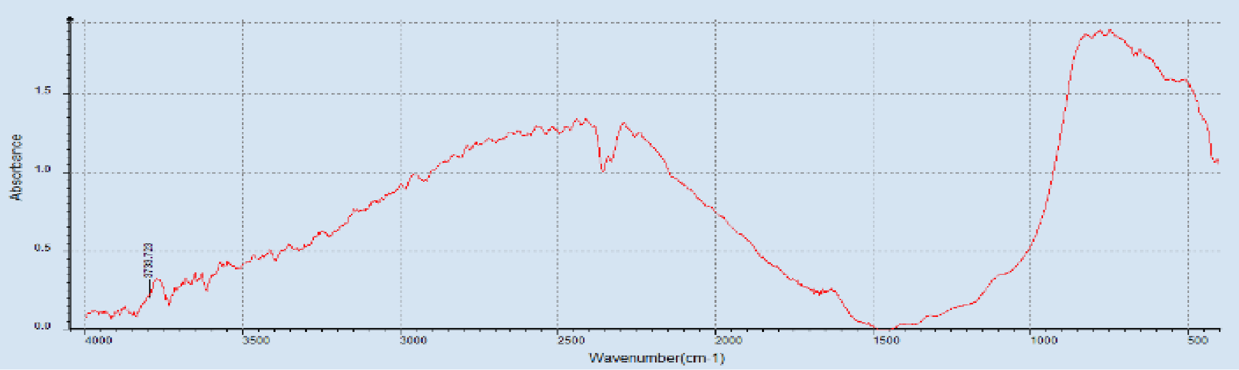


Figure 3: FT-IR spectrum of Copper Complex

The FT-IR analysis of the synthesized Copper (II) complex is shown in Figure 3. It exhibits characteristic vibrational stretches peaks of v (Cu-N) at 493 cm^{-1}, v (Cu-O) at 552 cm^{-1}, v (C =N) at 1625 cm^{-1}, v (C=O) at 1719 cm^{-1}, v (C=C$_{(arene)}$) at 1563 cm^{-1}, v (C$_{arene}$-H) at 3080 cm^{-1}, v (C$_{aryl}$-O) at 1298 cm^{-1}, v (O-H$_{(free)}$) at 3668 cm^{-1}.

In the IR spectra of the complexes, the stretching band of C=N displayed a shift lower to the Schiff base, 1620 cm^{-1} and 1625 cm^{-1} of complexes compared to the 1655 cm^{-1} of the Schiff base ligand. This could be due to the weakening in the C=N bond of the imine during complexation, the imine nitrogen donating electron to the metal empty d-orbital. Disappearance of v (O-H) at ~3222 cm^{-1} indicates the deprotonation of the hydroxyl group of the carboxyl (-COOH) to form carboxylate ion (-COO-) which coordinate with the metal ion to form the v (M-O) at 552 cm^{-1} & 562 cm^{-1} for the cobalt and copper coordination to the oxygen respectively. The v (C=C) vibration stretches for the aromatic ring at 1563-1555 cm^{-1} in the Schiff base and the two complexes, and the (C-H) of the arene stretches at 3080-3073 cm^{-1}. The free (O-H) connected to the aromatics group stretches at 3668-3604 cm^{-1} in the three samples.

Solubility test

The solubility test was carried out to identify the solubility of the Schiff base and its metal complex in various solvent. The solvents used were diethyl ether, ethanol, methanol and distilled water. The results are shown in Table 2.

Table 2: Solubility test for the complexes and Schiff base

S/N	Solvent	Cobalt complex	Copper complex	Schiff base
1	Distilled water	Soluble	Slightly Soluble	Highly Soluble
2	Ethanol	Soluble	Soluble	Soluble
3	Methanol	Soluble	Soluble	Slightly Soluble
4	Diethyl ether	Insoluble	Insoluble	Insoluble

The Schiff base and the complexes are soluble in distilled water and polar organic solvents like methanol and ethanol but insoluble in diethyl ether, a non-polar solvent. The result shows that polar organic solvent is the most suitable solvent for the applications of the Schiff base and its Co and Cu complexes. This is similar to what was observed in the study of the metal complexes of benzaldehyde and glycine [19].

Antimicrobial activity of the Schiff base and the Co and Cu complexes

The antimicrobial activities of E-[2-(4-hydroxybenzylidene) amino] acetic acid and the Co & Cu complexes were studied against Staphylococcus aureus and E. coli. The results obtained are recorded and shown in Table 3.

Table 3: Antimicrobial activity of Schiff Base and metal complexes

S/N	Compounds	Zones of inhibition (mm) *S. aureus*	Zones of inhibition (mm) *E. coli*
1	Schiff Base	18	-

2	Cobalt	15	18
3	Copper	18	20

The table shows that the Schiff base and metal complexes have a high inhibition zone and are highly active against *Escherichia coli* and *Staphylococcus aureus.* This shows that the Schiff base and metal complexes have high anti-bacterial activity.

CONCLUSION

In conclusion, this study successfully synthesized Schiff base from 4-hydroxybenzaldehyde and L-glycine. Schiff base-metal complexes were synthesized by the reaction of prepared Schiff base with Co(II) and Cu(II) compounds. The microbial studies of the Schiff base and metal complexes reveal that the complexes have high antibacterial activities. The results highlight the potential of these complexes as effective agents against various microbial pathogens.

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