A COMPARITIVE VIEW OVER THE SYNTHESIS OF SCHIFF BASE LIGANDS AND METAL COMPLEXES BY CONVENTIONAL AND SOLVENT FREE ROUTES

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Abstract:
In the present paper, synthesis of Schiff base ligands and the metal complexes are studied and compared by conventional and solvent free route. The synthesis of Schiff base ligands of amino acids (Glycine, Phenylalanine and Tyrosine) with salicylaldehyde and their mixed ligand ternary Cu(II) complexes are discussed. Other ligands are used in co-ordination with the schiff base is 1,10- Phenanthroline/thiourea in equimolar ratio. The environmentally efficient and modern developed method for synthesis is the solid state synthesis of salicylidene amino acids through pestle mortar synthetic procedure. This method is compared with the conventional method that require refluxing the reactant mixture for hours in an organic solvent, here ethanol. The complexes are characterized by spectral techniques IR spectroscopy and UV spectroscopy. The investigations concluded that the pestle mortar assisted method is very rapid, simple and economic for the preparation of ligands and complexes as well. The Antimicrobial studies were also performed for the complexes. The spectral data for the ligands and complexes obtained from either method, conventional and solventless procedure are in good agreement with one another. The azomethine bonding(-CH=N-) between salicylaldehyde amino acids based Schiff bases is described by the IR spectral peak around 1600 cm⁻¹.

Keywords: Salicylidene Amino Acids; 1,10- Phenanthroline; Thiourea; Azomethine.

Cite This Article: Deeksha Sharma, and Prof. Arpan Bhardwaj. (2017). “A COMPARITIVE VIEW OVER THE SYNTHESIS OF SCHIFF BASE LIGANDS AND METAL COMPLEXES BY CONVENTIONAL AND SOLVENT FREE ROUTES” International Journal of Engineering Technologies and Management Research, 4(12: SE), 107-117. DOI: 10.5281/zenodo.1163783.

1. Introduction

Schiff bases are versatile ligands synthesized from the condensation of an amino compound with carbonyl compounds and were first reported by Hugo Schiff in 1864. Nowadays, Schiff bases are used as intermediates for the synthesis of amino acids or as ligands for preparation of metal complexes having a series of different structures[1]. Many researchers and their co-workers studied a series of complexes derived from Schiff bases of salicylaldehyde and its substituted analogues[2]. Structure and mechanism of the formation of the Schiff base complexes have been discussed in several literature studied.[3] Chelating ligands containing N, S and O donor atoms show broad biological activity and are of special interest because of the variety of ways in which
they forms bonds with metal ions. Some Schiff bases and their metal complexes containing Cu, Ni, Zn and Co were synthesized from salicylaldehyde, 2,4 dihydroxy- benzaldehyde, glycine and L-alanine and possess antitumor activity and their order of reactivity with metal complexes were investigated. Amino Schiff bases derived with aromatic and heterocyclic amine possess high anti-tumor and cytotoxic activity against human tumor cell counts. They have been widely studied because they have antifungal, antibacterial, anticancer, antiviral, herbicidal and industrial applications. They also serves as models for biologically important species and find applications in biomimetic catalytic reactions.

Recently, studies have made for few mixed ligand complexes containing heterocyclic amine as secondary ligands and few Schiff base containing complexes. Salicylaldehydes reacts with a variety of primary amine to produce imine, which are often referred to as Schiff bases. Such reactions sometimes occurs spontaneously when the aldehyde and amine are mixed and the products may separate as solids or liquids. The Schiff bases described in this paper have all been derived from salicylaldehyde, which has a hydroxyl group ortho to the aldehyde group. The aldehyde group combines with the amine group of amino acid while the hydroxyl group makes possible the formation of metal derivatives of the resulting Schiff bases.

Centuries have passed to synthesize various categories of organic and inorganic compounds via general conventional synthetic routes. These preparative techniques were developed by crowd of researchers who came from different streams in the research field, and fixed a trend of synthesizing new combinations through the similar methodologies. However, their contributions could not be questioned in this new era but an alternative thinking is a necessary requirement of present environmental issues. All the conventional procedure expenses are high in terms of solvent use, consumption of time, instrumental setup expenditure and complicated laboratory and atmospheric conditions to manage till the experiments continues. Therefore the present work is focused to perform a comparative study of the synthetic procedures of our complexes.

The conventional synthetic methods include heating a mixture of metal salt and ligands selected in a solvent system. The materials produced from this method are thermally unstable or reactive to solvent used sometimes and this could lead to breaking of co-ordination bonds or creation of metal sites for other species could also be possible. While the unconventional methods are the mechanochemically initiated reactions comparable to those of solvent reactions. The method is known to be environmentally-friendly and can possibly give high yield of products. The physical effects of grinding on molecular crystals results in frictional heating in the reaction vessel followed by intimate mixing of reactants through introducing amorphous form of the material.

Therefore, a vast knowledge of the interaction between biologically active molecules and metals is required to study the model species such as the simple amino acids, heterocyclic bases such as 1,10-Phenanthroline and Thiourea for interpretation of more complex system. Amino acid has the neutral donor N at one end and acidic replaceable H at the other end and is sufficient length to span two adjacent coordinating site and the resulting complexes is a chelate or inner complex compound. Such metal chelates are characterized by great thermal stability, are intensely colored, insoluble or partially soluble in water but soluble in organic solvents are of practical importance. Amino acids form complexes with metal atoms and exhibit significant biological
and enzymatic activities. Herein, report have been presented on the synthesis and characterization of several new mixed ligand complexes of Cu(II) with salicylaldehyde bound amino acid as primary ligand and heterocyclic amine base as secondary ligand. Thiourea and substituted thiourea are soft donor ligands in which the thioamide group is an important common characteristics and have considerable co-ordination potential. They are capable of forming co-ordinate bonds through both sulphur and nitrogen atoms. Therefore the ease of thiourea in co-ordination makes an attractive approach to study for new metal complexes.

2. Material and Methods

Reagents and Chemicals: The reagents were obtained commercially from CDH chemicals which are of analytical grade and used as received. The chemicals used during experimental procedure includes amino acids, L-Glycine, L-Phenylalanine and L-Tyrosine, Salicylaldehyde, Potassium hydroxide is used as a base catalyst for the synthesis of Schiff base ligand, 1,10-Phenanthroline monohydrate is used as a heterocyclic secondary ligand, Thiourea is used as an alternative ligand. Metal salt Cu(NO$_3$)$_2$.3H$_2$O is used to form mixed ligand complexes. Ethanol is used as a solvent for organic reagents and double distilled water for dissolving polar compounds such as amino acids.

Synthesis of Schiff Base Ligand: The synthetic procedures for Schiff base ligands were performed by two ways. They are discussed as under:

a) By Solvo-Thermal Method, The above mentioned starting materials were used in the preparation of Schiff base ligand SalAA by conventional routes as reported in literature$^{[14]}$ in a reflux condenser at 40°C for 2-3 hours in an ethanol solvent. The equimolar quantity of salicylaldehyde and amino acids (3 mmol.) were condensed in the presence of KOH (3 mmol.) as a base catalyst. Pale yellow coloured solution is obtained in the reaction mixture which was precipitated on freezing for 5-7 days. The precipitate was filtered and washed with ethanol and recrystallized to get the pure crystals. The crystals were dried in a vaccum dessicator over anhydrous CaCl$_2$. This dried crystalline solid is the required shiff base ligand of salicylaldehyde amino acids.

b) By Solvent-Free method, This is the alternative method used for the preparation of Schiff base ligands assisted by a mortar and a pestle made of porcelain. The procedure is completely free of solvent and big experimental setup. Similar reagents of same molar quantity are combined in a mortar and grinded for 10 min.or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continous grinding for 20-30 minutes. The product was finally washed and recrystallized from ethanol and dried in air and vaccum dessicator over anhydrous calcium chloride.

Three Schiff base ligands have been synthesized with the condensation of salicylaldehyde and amino acids, i.e, salicylidene glycine (salgly), salicylidene phenylalanine (salphyala) and salicylidene tyrosine (saltyr). The condensation was proceeded through two ways and interest was focused on the comparison of the synthesis of ligand as well as complexes by conventional and advanced solventless methods. All the reactants and catalyst are similar in either procedures instead the reaction time is reduced from hours to few minutes and the product yield is noticed to increase to a considerable amount.
Synthesis of Cu(II) complexes: Six ternary Cu(II) complexes of the type [Cu(II)(salAA)(L)], where primary ligand is salAA= salicylidene glycine (salgly), salicylidene phenylalanine (salphyala) and salicylidene tyrosine (saltyr) and secondary ligand is L(a,b) a= 1,10-phenanthroline, b= Thiourea. The complexes with different ligand combinations were prepared by following two different ways:

**Synthesis of [Cu(salgly)1,10-phenanthroline]NO_3:** To a mixture of L-Glycine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of 1,10- phenanthroline and 10 ml aqueous solution of Cu(NO_3)_2.3H_2O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in dessicator. Yield: 66%

An alternative solvent free method is followed for synthesizing the above mixed ligand copper complexes. The amino acid glycine, KOH and salicylaldehyde of equimolar quantity (3mmol) is combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this mixture equimolar 1,10 phenanthroline and Cu(NO_3)_2.3H_2O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum dessicator over anhydrous calcium chloride.

**Synthesis of [Cu(salphyala)1,10-phenanthroline]NO_3:** To a mixture of L-Phenylalanine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of 1,10- phenanthroline and 10 ml aqueous solution of Cu(NO_3)_2.3H_2O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in dessicator. Yield: 73%

The amino acid phenylalanine, KOH and salicylaldehyde of equimolar quantity (3mmol) are combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this mixture equimolar 1,10 phenanthroline and Cu(NO_3)_2.3H_2O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum dessicator over anhydrous calcium chloride.

**Synthesis of [Cu(saltyr)1,10-phenanthroline]NO_3:** To a mixture of L-Tyrosine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of 1,10- phenanthroline and 10 ml aqueous solution of Cu(NO_3)_2.3H_2O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in dessicator. Yield: 77%

The amino acid tyrosine, KOH and salicylaldehyde of equimolar quantity (3mmol) are combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this
mixture equimolar 1,10 phenanthroline and Cu(NO$_3$)$_2$.3H$_2$O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum desiccator over anhydrous calcium chloride.

**Synthesis of [Cu(salgly)thiourea]NO$_3$:** To a mixture of L-Glycine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of thiourea and 10 ml aqueous solution of Cu(NO$_3$)$_2$.3H$_2$O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in desiccator. Yield: 65%

The amino acid glycine, KOH and salicylaldehyde of equimolar quantity (3mmol) is combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this mixture equimolar thiourea and Cu(NO$_3$)$_2$.3H$_2$O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum desiccator over anhydrous calcium chloride.

**Synthesis of [Cu(salphyala)thiourea]NO$_3$:** To a mixture of L-Phenylalanine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of thiourea and 10 ml aqueous solution of Cu(NO$_3$)$_2$.3H$_2$O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in desiccator. Yield: 67%

The amino acid phenylalanine, KOH and salicylaldehyde of equimolar quantity (3mmol) is combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this mixture equimolar thiourea and Cu(NO$_3$)$_2$.3H$_2$O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum desiccator over anhydrous calcium chloride.

**Synthesis of [Cu(saltyr)thiourea]NO$_3$:** To a mixture of L-Tyrosine (3mmol) and KOH (3mmol) in 10 ml distilled water add 10 ml ethanolic solution of salicylaldehyde (3mmol) and reflux the reaction mixture for 3 hours at 40°C. To this mixture, add dropwise 10 ml ethanolic solution of thiourea and 10 ml aqueous solution of Cu(NO$_3$)$_2$.3H$_2$O (3mmol). Again reflux the solution for 2-3 hours at 40°C. A green precipitate was obtained which was isolated by filtration, recrystallisation and finally dried in desiccator. Yield: 78%

The amino acid tyrosine, KOH and salicylaldehyde of equimolar quantity (3mmol) are combined in a mortar and grinded for 10 min. or more with a pestle. The pale yellow coloured paste is obtained which changes to a solid powder on continuous grinding for 20-30 minutes. To this mixture equimolar thiourea and Cu(NO$_3$)$_2$.3H$_2$O was added and grinded well for 15 minutes. A dark green solid product is obtained which was finally washed and recrystallized from ethanol and dried in air and vacuum desiccator over anhydrous calcium chloride.
3. Result and Discussion

The preparations were preceded through two ways and interest was focused on the comparison of the synthesis of ligand as well as complexes by conventional and advanced solventless methods. All the reactants and catalyst are similar in either procedures instead the reaction time is reduced from hours to few minutes and the product yield is noticed to increase to a considerable amount shown in Table-1. The complexes were soluble in DMF, DMSO and methanol while sparingly soluble in water. They are very stable in solid and dry atmosphere while hygroscopic at lower temperature. Therefore they are stored in a dessicator over anh. CaCl₂.

All the synthesized compounds have been characterized by spectroscopical and physiochemical techniques such as UV-Vis spectroscopy and IR spectroscopy and molecular weight measurements of ligand and complexes. The main results achieved in the course of the present investigation by either methodologies have been discussed and compared with each other on the basis of analytical data obtained. IR spectra were recorded on FT-IR spectrometer Bruker’s model in KBr pellets in the range 4000-400 cm⁻¹.

Table 1: Comparative study of Ligands and Complexes synthesized by two methodologies.

| Compound Ligand/Cu Complex | M.P (°C) | Colour    | Mol. Wt. (calcu.) | % Yield (Reflux4-5hrs) | % Yield (Grinding30-45min.) |
|---------------------------|---------|-----------|------------------|------------------------|-----------------------------|
| SalGlycine                | 188     | yellow    | 179.2            | 62                     | 85                          |
| Salphenylalanine          | 192     | pale yellow | 287.31         | 57                     | 80                          |
| SalTyrosine               | 210     | pale yellow | 303.31         | 64                     | 89                          |
| [Cu(salgly)phen]NO₃       | 310     | green     | 618.99           | 66                     | 76                          |
| [Cu(salphyala)phen]NO₃    | >360    | dark green | 727.13           | 59                     | 80                          |
| [Cu(saltyr)phen]NO₃       | >360    | dark green | 743.13           | 77                     | 82                          |
| [Cu(saltyr)tu]NO₃         | 206     | light green | 496.89         | 65                     | 85                          |
| [Cu(salphyala)tu]NO₃      | 280     | green     | 605.03           | 67                     | 88                          |
| [Cu(salgy)tu]NO₃          | 325     | green     | 621.03           | 78                     | 84                          |

3.1. IR Spectral Studies

IR spectral studies of ligands explains the formation of azomethine linkage (C=N) which is observed at 1640-1590 cm⁻¹ for different salicylaldehyde based ligands. These regions of vibrational stretching are characteristic to the synthesis of Schiff bases. The green synthesis technique in the absence of solvent also shows the bands in similar regions. A broad band in the region 3400-3200 cm⁻¹ is due to phenolic OH group which coincides with the presence of OH in the amino acid. The carboxylic C=O vibrational modes, symmetric and asymmetric were found at 1580-1420 cm⁻¹. The phenolic C-O stretching is observed at 1243 cm⁻¹.

In the comparison of the spectrum of complex and ligand, we find that complex exhibits absorption band of imine group at lower wave number by 14- 20 cm⁻¹. This shift of band at lower wave number indicates that the azomethine nitrogen is coordinated to the metal through its lone pair of electrons. The absorption band of phenolic –OH group is lost in the spectrum of complex,
it indicates that phenolic –OH group is deprotonated and metal binds through phenolic oxygen. Also the phenolic C-O vibrations are increased to 1290-1320 cm\(^{-1}\) in metal complex spectra to suggest the coordination of ligand to the central metal ion. While the bands due to asymmetric and symmetric COO\(^{-}\) stretching in the region 1580 and \(1420\) cm\(^{-1}\) were lowered to 1517 and 1382 cm\(^{-1}\) representing the coordination of carboxylic group to the metal ion complex formation.

The heterocyclic ligand 1,10-phenanthroline ring stretching peaks were found at higher frequency range 1515 cm\(^{-1}\) due to co-ordination of nitrogen atoms to the metal. The coordination of thiourea is proposed to occur through lone pair of electrons on nitrogen. A shift from 2962 cm\(^{-1}\) of free thiourea is observed to 3007 cm\(^{-1}\) for N-H vibrations. All these shifts were reported in the complexes synthesized by conventional reflux techniques are in good agreement with the solvent free synthesis.

Figure 1-4 shows the IR spectra and coordination affects on streching vibrations of mixed ligand Cu(II)complex containing primary salicylaldehyde amino acid Schiff base ligand along with secondary NO donor ligands 1,10-phenanthroline/Thiourea by reflux and grinding synthetic methods.

Figure 1: IR spectra of \([\text{Cu(salygly)}\text{phen}]\text{NO}_3\) complex (Reflux synthesis)
Figure 2: IR spectra of [Cu(salgly)phen]NO$_3$ complex (Grinding)

Figure 3: IR spectra of [Cu(salphenylalanine)phen]NO$_3$ complex (Grinding)
UV–vis Spectral Studies

UV–vis absorption spectra of ligand and complexes is carried using 1cm quartz micro cuvettes in DMF solvent in the wavelength range of 200-800nm show λmax at 285nm for Cu phenanthroline complex. In the UV region, band at 380 nm is due to the n-π* transitions of azomethine (C=N) function of Schiff base. This supports the coordination of metal with the azomethine nitrogen. The remaining bands in the UV region at 205 nm and 270 nm are due to the π-π* transitions of benzene rings present in coordinated phenanthroline observed at higher wavelength (red shift) upon complexation. The band showing intensity at 680nm regions were due to d-d transition. Generally d-d transition of the copper (II) complex exhibits a band at 685 nm. The transition of unpaired electrons from ground state to the excited state in the d orbital is responsible for the coloured complexes. This transition is greatly affected by ligand coordinated with the metal ion and to the energies of d orbitals.14

Antimicrobial Studies

Antimicrobial screening of the complexes prepared by both the methods were carried out using well diffusion method. The prepared culture plates were inoculated with different selected strains of bacteria and fungi such as Staphylococcus aureus, and E.coli and Candida albicans and Aspergillus niger using streak plate method. Wells were made on the agar surface with 6 mm cork borer. The extracts were poured into the well using sterile syringe. The plates were incubated at 37 °C+2 °C for one day for bacterial and 25±2 °C for 2–4 days for fungal activity. The plates were observed for the zone clearance around the wells.15-16 The zone of inhibition was calculated by measuring the diameter of the inhibition zone around the well (in mm)
including the well diameter. All ligands and its metal complexes show good antibacterial and antifungal activity against most of the species of bacteria and fungi in the range of 11mm - 30 mm diameter inhibition zone.

4. Conclusion

The investigations concluded that the pestle mortar assisted method is very rapid, simple and economic for the preparation of both ligands and Cu(II) complexes . Three Schiff base ligands have been synthesized with the condensation of salicylaldehyde and amino acids, i.e, salicylidene glycine (salgly), salicylidene phenylalanine (salphyala) and salicylidene tyrosine (saltyr). The condensation was preceded through two ways conventional solvo thermal method and non-conventional solvent free method. Six Cu(II) mixed ligand green coloured complexes were synthesized \[[\text{Cu(salgly)}\text{phen}]\text{NO}_3\], \[[\text{Cu(salphyala)}\text{phen}]\text{NO}_3\], \[[\text{Cu(saltyr)}\text{phen}]\text{NO}_3\], \[[\text{Cu(salgly)}\text{tyr}]\text{NO}_3\], \[[\text{Cu(salphyala)}\text{tyr}]\text{NO}_3\], \[[\text{Cu(saltyr)}\text{tyr}]\text{NO}_3\] using reflux and grinding procedures. The reflux method involves excessive application of laboratory equipments, conditions, solvent and time consuming reaction steps with average product yields. Contrary to this, the pestle mortar assisted synthesis is very fast and requires lesser laboratory conditions such as glasswares, instruments etc. It is completely free of solvent which is the demanding subject of green chemistry.

The comparison of the synthesis of ligand and complexes performed through physiochemical and spectroscopic techniques, i.e, IR, UV-Vis spectral data obtained from either method, conventional and solventless procedure are in good agreement with one another. The azomethine linkage(-CH=N-) between salicylaldehyde amino acids based Schiff bases is described in the spectral studies and the shifts were observed due to the complexation of ligands with metal ions. The Antimicrobial studies were also performed for the complexes prepared by both the routes are in good agreement to each other. Also, attempt has been made to replace heterocyclic ligand with thiourea as they act as soft donor ligands in which the thioamide group is an important common characteristics and have considerable co-ordination potential. They are capable of forming co-ordinate bonds through both sulphur and nitrogen atoms. Therefore the ease of thiourea in coordination makes an attractive approach to study for novel metal complexes.

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