METAL COMPLEXES OF NOVEL SCHIFF BASE CONTAINING ISATIN: CHARACTERIZATION, ANTIMICROBIAL, ANTIOXIDANT AND CATALYTIC ACTIVITY STUDY

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ABSTRACT

Objectives: The aim of our work was to synthesize novel mixed ligand-metal complexes and evaluation of antimicrobial, antioxidant assay, and analysis of catalytic oxidation of cyclohexane.

Methods: The complexes were characterized by means of various physicochemical techniques such as elemental analysis, molar conductance, magnetic susceptibility, infrared (IR), electronic absorption, 1H NMR (proton magnetic resonance), and mass spectral studies. The antimicrobial screening study was done by disc diffusion method. The catalytic activity of the complexes was observed in the oxidation of cyclohexane using ecofriendly hydrogen peroxide as oxidant.

Results: On comparing the 1H NMR and IR spectral data of free ligand and its complexes, it was found to be azomethine (CH=N) proton which is formed in the free ligand. During complexation, the azomethine proton is coordinated to the metal ion and the phenolic oxygen is coordinated to the metal ion by deprotonation. The analytical data and mass spectra of the ligand and the complexes confirm the stoichiometry of metal complexes as being of the (MLY)Cl type and the metal to ligand ratio is 1:1. The antimicrobial, antioxidant, and catalytic potential were evaluated and the result shows the better activity of the complexes than the ligand.

Conclusion: It was found to be copper(II) and zinc(II) complexes which are effective against all the bacteria when compared to standard drug streptomycin. Copper(II) complex was found to be effective antibacterial agent against Aspergillus niger and Aspergillus flavus in comparison to the standard drug Nystatin. The zinc complex exhibited good catalytic activity.

Keywords: Antimicrobial activity, Catalytic activity, Mixed ligand-metal complexes, Octahedral geometry, Radical scavenging activity.

INTRODUCTION

The biologically active compound isatin (indole-2,3-dione) was first obtained in 1841 from the oxidation of indigo dye by nitric and chromic acids [1]. In nature, isatin is found in plants and widely distributed in mammalian tissues and body fluids [2]. The biologically active compound isatin’s concentration in urine is to become a diagnostic marker for the clinical severity of Parkinson’s disease in humans; however, electrophysiology, synthetic, and metabolic pathways of isatin in human system are yet to be fully established. In organic synthesis, isatin and its derivatives have widely used as key intermediate due to their biological and pharmacological properties [1,3]. The multicoordination centers form stable chelates with essential metal ions which, in turn, used in human’s metabolism. Salicylaldehyde-based Schiff base metal complexes serve as high potential antibacterial agent [4]. The electrochemical determination of isatin and other nitrogen heterocycles using various electrode systems attains prominence in recent years. The derivatives of isatin were reported to show anti-HIV, anticonvulsant, antibacterial, antifungal, antiprotozoal, antiviral, and antioxidant activities [5-13].

A wide range of molecular disorder accumulated due to oxidative stress is originated as a result of an imbalance between the free radical production and antioxidant defenses [14,15]. Antioxidant acts as scavenger to prevent the damage of cell and tissue. The byproducts of normal metabolisms are O2− and OH− (reactive oxygen species) and are detected in all types of organisms [16]. In addition to phenolic compounds, aromatic heterocyclic amines showed that antioxidant properties in vitro have been discussed from the view of chemical kinetics [17].

Oxidation of cyclohexane is an important industrial reaction. Most of the industries struggle with the manufacture of cyclohexanol and cyclohexanone from cyclohexane at high temperature and pressure. To overcome these difficulties, nowadays, Schiff base metal complexes act as a catalyst toward the oxidation of cyclohexane reaction at low temperature and pressure [18]. The Schiff base derived from isatin possesses significant enhancement antibacterial, antifungal, and antioxidant activities during complexation [19].

Bearing these facts in mind, to enhance the biological and catalytic properties of Schiff base metal complexes, we are planned to synthesis the metal complexes using mixed ligand. In this concerned, the hexacoordinated mixed ligand Cu(II), Zn(II), Ni(II), and Co(II) complexes were synthesized from the diimino-tetradentate Schiff base which was derived from the condensation of isatin with ethylenediamine and bipyridine. These metal complexes showed remarkable antimicrobial and antioxidant activities which may find their importance in medicinal chemistry. The metal complexes also exhibited catalytic activity toward the oxidation of cyclohexane using environmental-friendly hydrogen peroxide as oxidant.

EXPERIMENTAL

Materials
All chemicals used in the present work, namely, isatin, salicylaldehyde, ethylenediamine, bipyridine, copper, zinc, cobalt, and nickel chloride were of analytical reagent grade (Merk, Germany). Solvents were purified according to the standard procedures described in Weisenburg series [20] and in quantitative analysis by Vogel [21].
Potato dextrose agar was used as medium for the evaluation of the products was noted. The catalytic oxidation of cyclohexane was carried out in methanol as solvent by DPPH radical scavenging activity assay [25]. The catalytic activities were expressed as percentage scavenging activity and were calculated by the following formula.

\[
\text{% Radical scavenging activity} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100
\]

Catalytic activities

The oxidation of cyclohexane has always been an area of intensive research because it is one of the essential steps in the production of nylon. The catalytic oxidation of cyclohexane was carried out in acetonitrile solvent using hydrogen peroxide as an oxidant in the presence of mixed ligand-metal complex [MLY][Cl] as catalyst. In a typical reaction, about 0.1 mol H₂O₂ was added to the mixture of 0.01 mol cyclohexane and 0.001 mol [MLY][Cl] in acetonitrile and the reaction mixture was stirred for 5 h at 343 K. The reaction progress and its completion were checked by analyzing the reaction mixture using thin-layer chromatography by withdrawing small aliquots of the reaction mixture at specific interval of time. The percentage yield of the products was noted.

RESULTS AND DISCUSSION

Analytical studies

The complexes of the type [MLY]Cl, where, M=Cu(II), Zn(II), Ni(II), and Co(II) were synthesized by the reaction of tetradentate ligand, metal(II) chloride, and bipyridine in a 1:1:1 molar ratio in methanol. In DMSO, the complexes showed higher molar conductance value indicates the electrolytic nature.
Three different concentrations (25 µg/ml, 50 µg/ml, and 75 µg/ml) of the compounds have been tested for antibacterial activity against B. subtilis, S. aureus, E. coli, and P. mirabilis. The Cu(II) and Zn(II) complexes exhibited enhanced activity against all the bacteria examined than the standard drug streptomycin. The enhanced activity of the complexes may be attributed to chelation of Schiff base with metal ion [36]. The partial sharing of positive charge with the donor groups and possible π-electron delocalization within the chelate ring system makes the metal ion as less polar. Due to this reduced polarity of the metal ion, the lipophilicity of the complex increases, and hence, diffusion of metal ion through cell membrane becomes easier. Thus, chelating effect makes the metal complex as powerful antibacterial.

Antibacterial studies

The antibacterial efficacy of the ligand and its metal complexes was tested against the human pathogens such as B. subtilis, S. aureus, E. coli, and P. mirabilis. Three different concentrations (25 µg/ml, 50 µg/ml, and 75 µg/ml) of the compounds have been tested for antibacterial assay. The results are presented in Table 1. The results of the antibacterial activity showed that all the complexes possess good activity against B. subtilis, S. aureus, E. coli, and P. mirabilis. The Cu(II) and Zn(II) complexes exhibited enhanced activity against all the bacteria examined than the standard drug streptomycin. The enhanced activity of the complexes may be attributed to chelation of Schiff base with metal ion [36]. The partial sharing of positive charge with the donor groups and possible π-electron delocalization within the chelate ring system makes the metal ion as less polar. Due to this reduced polarity of the metal ion, the lipophilicity of the complex increases, and hence, diffusion of metal ion through cell membrane becomes easier. Thus, chelating effect makes the metal complex as powerful antibacterial.

IR spectra

The IR spectrum of the free ligand showed a band at 1618 cm⁻¹ which can be attributed to azomethine moiety. This band is shifted to lower frequency around 1606–1598 cm⁻¹ in the spectra of complexes which indicate the coordination of metal to the azomethine nitrogen. The absorption band appeared at 1757 cm⁻¹ is due to νC=O. This band shifted to lower wavenumber in the complexes indicates involvement of νC=O with metal center during complexation. The ligand showed that a band at 3400 cm⁻¹ is due to phenolic OH group. The absence of νOH band in all the complexes suggests subsequent deprotonation of phenolic group and coordination of phenolic oxygen to the metal ion. The band at 3160 cm⁻¹ in the spectrum of free ligand assigned to vN-H stretching vibration. The position of this band remains nearly the same frequency in the spectra of metal complexes suggesting the uncoordination of this group [26]. The band at 1260 cm⁻¹ is due to phenolic C-O. This band shifted to lower wavenumber in the complexes indicates coordination of metal to the phenolic C-O. The appearance of two new bands in the regions 545–525 cm⁻¹ and 459–422 cm⁻¹ in the spectra of complexes was due to νM-N and νM-O stretching vibrations, respectively [27].

Electronic absorption spectra and magnetic measurement

The electronic spectra of ligand and its complexes were recorded in methanol. The ligand shows two bands at 40823 and 32787 cm⁻¹ assigned for π π* and n π* electronic transitions, respectively [28]. Nickel(II) complex exhibits three bands at 12.919, 15.924, and 20.833 cm⁻¹ attributed to A₂g(F) →T₁g(F), A₁g(F) →T₁g(F), and A₁g(F) →T₂g(F) transitions indicating octahedral geometry. The nickel(II) complex showed magnetic moment value of 3.14 B.M corresponding to two unpaired electrons in an octahedral environment [29]. Copper complex shows a band at 16,556 cm⁻¹ assigned for T₁g(F) →T₁g(F) transition suggesting a distorted octahedral geometry [30] which was further supported by its magnetic moment value of 1.88 B.M. The cobalt(II) complex exhibits two bands at 33,003 and 21,368 cm⁻¹ assigned to T₁g(F) →T₁g(F) and T₂g(F) →A₁g(F) transitions. The magnetic moment value of Co(II) complex was 4.86 B.M., which favors octahedral geometry [31]. Zn(II) complex does not show d-d transition due to its diamagnetic nature [32].

Proton magnetic resonance spectra

The proton magnetic resonance spectra of ligand and its Zn(II) complex were recorded in DMSO-d₆. The ¹H NMR spectrum of ligand and its zinc(II) complex exhibited signals at 10.3 ppm and 2.6 ppm due to NH proton of isatin moiety [33] and N-CH₃ protons [34]. The phenyl multiplet appeared at 6.8–7.2 ppm. The spectrum of the free ligand exhibited a signal at 13.3 ppm due to phenolic protons [35]. However, in the spectrum of zinc(II) complex, the azomethine (CH=N) proton showed a downfield shift at 8.9 ppm, thereby suggesting the coordination of these to Zn(II) ion by deprotonation. The signals at 7.60–7.76 and 8.20–8.39 ppm were assigned to bipyridine protons. The proton magnetic resonance spectra of ligand and its Zn(II) complex are given in Figs. 2 and 3.

Mass spectra

The ESI mass spectra of the ligand and its Zn(II) complex were recorded in methanol. The ligand shows two bands at 40823 and 32787 cm⁻¹ assigned for π π* and n π* electronic transitions, respectively [28]. Nickel(II) complex exhibits three bands at 12.919, 15.924, and 20.833 cm⁻¹ attributed to A₂g(F) →T₁g(F), A₁g(F) →T₁g(F), and A₁g(F) →T₂g(F) transitions indicating octahedral geometry. The nickel(II) complex showed magnetic moment value of 3.14 B.M corresponding to two unpaired electrons in an octahedral environment [29]. Copper complex shows a band at 16,556 cm⁻¹ assigned for T₁g(F) →T₁g(F) transition suggesting a distorted octahedral geometry [30] which was further supported by its magnetic moment value of 1.88 B.M. The cobalt(II) complex exhibits two bands at 33,003 and 21,368 cm⁻¹ assigned to T₁g(F) →T₁g(F) and T₂g(F) →A₁g(F) transitions. The magnetic moment value of Co(II) complex was 4.86 B.M., which favors octahedral geometry [31]. Zn(II) complex does not show d-d transition due to its diamagnetic nature [32].

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Antioxidant studies
The capability of DPPH to receive an electron or hydrogen from antioxidant molecule makes it become a stable diamagnetic molecule [37,38]. The antioxidant assay is a dynamic method to anticipate the scavenging ability of metal complexes, tested with respect to different concentrations (100, 50, 25, and 12.5 µg/ml) of Cu(II), Zn(II), Ni(II), and Co(II) metal complexes with DPPH radical. The data revealed that Cu(II) and Zn(II) complexes exhibited potent antioxidant activity even in minimum concentration (12.5 µg/ml) level than the Ni(II) and Co(II) complexes. The free radical scavenging ability of the metal complexes is presented in Table 3.

Antifungal studies
The antifungal activity was carried out by disc diffusion method. The ligand and its Cu(II), Zn(II), Ni(II), and Co(II) complexes have been tested for their antifungal activity at 100 µg/ml concentration. The results showed that copper complex exhibits enhanced activity against A. niger and A. flavus more than the standard drug nystatin and it showed moderate effect on R. bataticola and C. albicans. Nickel and cobalt complexes exhibited moderate activity against niger, A. flavus, R. bataticola, and C. albicans. Nickel and cobalt complexes exhibited moderate activity against A. niger, A. flavus, R. bataticola, and C. albicans. Copper and zinc complexes exhibited good activity against A. niger, A. flavus, R. bataticola, and C. albicans.

Table 1: Antibacterial activity of ligand and its metal(II) complexes (zone of inhibition in mm)

| Compound | B. subtilis (25 µg) | B. subtilis (50 µg) | B. subtilis (75 µg) | S. aureus (25 µg) | S. aureus (50 µg) | S. aureus (75 µg) |
|----------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| HL       | 8±0.4              | 11±0.55             | 13±0.65             | 13±0.65             | 15±0.75             | 17±0.85             |
| [CuLY]Cl | 21±1.05            | 24±1.2              | 28±1.4              | 25±1.25            | 27±1.35             | 28±1.4              |
| [ZnLY]Cl | 17±0.85            | 20±1                | 23±1.15             | 20±1                | 23±1.15             | 26±1.3              |
| [NiLY]Cl | 13±0.85            | 14±0.7              | 17±0.85             | 16±0.8             | 17±0.85             | 18±0.9              |
| [CoLY]Cl | 12±0.6             | 13±0.65             | 15±0.75             | 18±0.9             | 22±1.1              | 24±1.2              |
| Streptomycin | 13±0.65          | 15±0.75             | 20±1                |                     |                     |                     |

*All the experiments were repeated independently 3 times and the values were represented as an average mean±standard deviation. A. niger: Aspergillus niger, A. flavus: Aspergillus flavus, R. bataticola: Rhizoctonia bataticola, C. albicans: Candida albicans

Table 2: Antifungal activity of ligand and its metal(II) complexes

| Compound | Zone of inhibition in mm | A. niger | A. flavus | R. bataticola | C. albicans |
|----------|--------------------------|---------|----------|--------------|-------------|
| HL       | 7±0.35                   | 5±0.25  | 6±0.3    | 9±0.45       |
| [CuLY]Cl | 15±0.75                  | 13±0.65 | 10±0.5   | 14±0.7       |
| [ZnLY]Cl | 12±0.6                   | 7±0.35  | 9±0.45   | 13±0.65      |
| [NiLY]Cl | 10±0.5                   | 7±0.35  | 6±0.3    | 12±0.6       |
| [CoLY]Cl | 9±0.45                   | 10±0.5  | 7±0.35   | 10±0.5       |
| Nystatin | 14±0.7                   | 12±0.6  | 13±0.65  | 16±0.8       |

*All the experiments were repeated independently 3 times and the values were represented as an average mean±standard deviation. A. niger: Aspergillus niger, A. flavus: Aspergillus flavus, R. bataticola: Rhizoctonia bataticola, C. albicans: Candida albicans

Table 3: Antioxidant activity metal(II) complexes

| Concentration (µg/ml) | % of radical scavenging activity | Cu(II) | Zn(II) | Ni(II) | Co(II) |
|-----------------------|----------------------------------|-------|--------|--------|--------|
| 100                   | 71.3                             | 57.1  | 50.4   | 69.5   |
| 50                    | 60.1                             | 48.0  | 41.3   | 58.3   |
| 25                    | 49.5                             | 39.2  | 32.0   | 47.1   |
| 12.5                  | 39.0                             | 27.5  | 24.6   | 36.3   |
| IC_{50} (µM)          | 48.4                             | 123.8 | 183.9  | 59.6   |

Catalytic activities
The catalytic activities of the synthesized metal complexes were examined for their activity toward the oxidation of cyclohexane using H_{2}O_{2} as the oxidant in CH_{2}CN. The major and minor products were found to be cyclohexanone and cyclohexanone, respectively. No significant amount of adipic acid was obtained. In the absence of catalyst, no oxidation products were produced. This indicates that hydrogen peroxide alone is unable to oxidize cyclohexane. The results are given in Table 4.

Table 4: Catalytic oxidation of cyclohexane by [MLY]Cl

| Compound | Products (% yield) |
|----------|--------------------|
| Cyclohexanol | Cyclohexanone |
| [CuLY]Cl | 3.1                 | 10.1               |
| [ZnLY]Cl | 3.5                 | 11.0               |
| [NiLY]Cl | 2.75                | 9.5                |
| [CoLY]Cl | 29.6                | 9.3                |

CONCLUSION
In this work, a new series of novel Schiff base ligand and its metal complexes of Cu(II), Zn(II), Ni(II), and Co(II) were reported and their potential of antimicrobial, antioxidant, and catalytic activity was also explored. The structure of these complexes was investigated by UV-Vis, IR, proton NMR, and mass spectral studies and they exposed the octahedral nature of the complexes. The high molar conductance value revealed the electrolytic nature of the complexes. The antibacterial and antifungal activities of the free ligand and its complexes showed efficient biocidal and fungicidal activity. Copper and zinc complexes...
exhibited efficient biocidal activity compared to the free ligand and other complexes even than the standard drug streptomycin. Copper complex exhibited enhanced activity against A. niger and A. flavus than the standard drug nystatin. It was found that all the complexes are good potential antioxidants. Especially, Cu(II) and Zn(II) complexes possessed enhanced antioxidant activity. The catalytic activity of the synthesized mixed ligand-metal complexes was tested in the cyclohexane oxidation reaction using \( \text{H}_2\text{O}_2 \) as oxidant. It was found to be zinc complex exhibits good catalytic activities than the other complexes.

**AUTHORS' CONTRIBUTIONS**

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**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest concerning the publication of this paper.

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