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Synthesis, Characterization and Antimicrobial studies of Co(II), Ni(II), Cu(II), Zn(II) and Fe(III) Complexes with Isatin Derivative

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Abstract: Metal complexes of Zn(II), Co(II), Ni(II), Cu(II) and Fe(III) with Schiff base derived from benzaldehyde and isatin monohydrazone have been synthesized & characterized on the basis of elemental analyses, IR spectral, electronic spectra. The elemental analyses of the complexes confine to the stoichiometry of the type $ML_2 \cdot 2NO_2$ [$M = Zn(II), Co(II), Ni(II), Cu(II)$] and $[FeL_2 \cdot 2NO_2] \cdot NO_2$. The redox properties of the complexes were extensively investigated by electrochemical method using cyclic voltammetry (CV). The Co(II) and Cu(II) complexes exhibited quasi-reversible single electron transfer process where as Zn(II) and Fe(III) complexes shown two redox peaks of quasi-reversible one electron transfer process. All the coloured complexes have been screened for their antimicrobial activity against fungi viz. *A. niger*, *A. flavous*, *P. triticena*, *F. species* & bacteria viz. *E. coli*, *B. subtilis*, *S. typhi*, *S. aureus*. The results of antimicrobial activity shows that metal complexes of bivalent metals have more potency towards experimental fungi & bacteria. It also shows that Cu(II) complex is more toxic against bacteria *S. aureus*.

Keywords: Isatin; Benzaldehyde; Electrochemistry; Spectral characterization; Transition metals

I. Introduction

Schiff bases of isatin were reported to possess antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal, and anthelmintic activities¹. They also exhibit significant anticonvulsant activity, apart from other pharmacological properties². Isatin, an endogenous indole and its derivatives have been shown to exhibit a wide range of biological activities³⁻⁷. Isatin-thiosemicarbazone copper (II) complexes related to the antiviral drug, methisazone were prepared electrochemically or by usual condensation methods, being characterized by different spectroscopic techniques⁸. Metal complexes with Schiff bases of isatin derivatives exhibited remarkable biological activity⁹⁻¹¹. Redox properties of a drug can give insights into its metabolic fate or pharmaceutical activity^{12,13}. Although much attention has been directed to study the metal complexes of the Schiff base ligands derived from isatin¹⁴, no investigations have appeared in the literature to describe the metal complexes of the Schiff base derived from isatin monohydrazone and benzaldehyde. Thus, the aim of present work is to synthesize and characterize Zn(II), Co(II), Ni(II), Cu(II) and Fe(III) metal complexes with newly synthesized Schiff base derived from isatin monohydrazone and benzaldehyde, possessing donor sites of carbonyl oxygen and azomethine nitrogen. The electron transfer mechanism of the metal complexes is investigated by the aid of cyclic voltammetry. It is well known that the metal complexes of ligands are more biological activity than the free ligands^{15,16}.

II. EXPERIMENTAL

A. Materials

All the chemicals used were of reagent grade. Isatin was recrystallized before using.

B. Synthesis of isatin monohydrazone

Isatin (1.47 g, 10 mol) was dissolved in methanol (40 mL) and was added to a solution of mixture was refluxed for 3 hours on a water-bath. On cooling, the yellow compound that formed was filtered, washed, dried and recrystallized from methanol having m.p. 225 °C.

C. Synthesis of Schiff base

The Schiff base has been synthesized by refluxing the reaction mixture of hot methanolic solution (30 mL) of isatin monohydrazone (0.01mol) and benzaldehyde for 4-5 h with 3-4 drops of hydrochloric acid. The product

obtained after the evaporation of the solvent was filtered, washed with cold methanol and recrystallized from methanol having m.p. 274 °C.

D. Synthesis of Zn (II), Co (II), Ni (II), Cu (II) and Fe (III) complexes

Hot methanolic solution (35 mL) of Schiff base (2 mol) was mixed with hot methanolic solution (15 mL) of metal nitrate (1mol) and refluxed on water bath for 2 hours. Then, to the reaction mixture 2 mol of sodium acetate was added and refluxion was continued for 2 hours. The separated complex was filtered, washed thoroughly with water, methanol and dried in vacuum over fused CaCl₂.

E. Antimicrobial Activity

The biological experiments for determining antimicrobial activity of synthesized Schiff base and its Zn(II), Co(II), Ni(II), Cu(II) and Fe(III) metal complexes have been done by serial dilution method¹⁷. In this technique the solutions of different concentrations (viz. 250 ppm, 500 ppm, 750 ppm and 1000 ppm) were prepared in dimethyl formamide. The graded dilution of the test compounds in a suitable nutrient (agar) and PDA medium were inoculated with the organisms under examination using aseptic techniques in an incubator at 37 °C.

The antibacterial and antifungal activity of Schiff base and their metal complexes have been screened in vitro, against bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*) and fungi (*Aspergillus flavous*, *Aspergillus niger*, *Penicillium triticena* and *Fusarium species*). Standard antibacterial (Streptomycine) and antifungal drug (Nystatin) was used for comparison under similar conditions.

The percentage of growth inhibition was calculated by measuring the diameter of the microbial colony in the control and test plates by the following expression-

$$\% \text{ inhibition} = \frac{C - T}{C} \times 100$$

Where C = diameter of microbial colony in millimeter in control plate.

T = diameter of microbial colony in treated (test) plate.

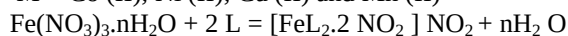
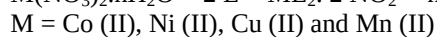
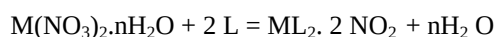
F. Physical measurements

The purity of complexes were confirmed by running their TLC on silica gel- G. The IR spectra in KBr matrix were recorded on Perkin- Elmer 842- spectrophotometer at CDRI, Lucknow & elemental analysis of C, H, N, were carried out at NCL, Pune. The accelerating voltage was 10 kV and the spectra were recorded at room temperature and m-nitrobenzyl alcohol was used as the matrix. Molar conductivity measurements were recorded on ELICO-CM-82 T Conductivity Bridge with a cell having cell constant 0.51. Electrochemical behavior of the metal complexes was investigated with CH Instruments, U.S.A (Model 1110A-Electrochemical analyzer, Version 4.01) in HPLC grade DMF containing n-Bu4NClO₄ as the supporting electrolyte.

The three-electrode system consisted of glassy carbon electrode (3 mm diameter) as a working electrode, a Ag/AgCl (3 M KCl) reference electrode and a platinum wire as auxiliary electrode was used. In order to provide a reproducible active surface and to improve the sensitivity and resolution of the voltammetric peaks, the glassy carbon electrode was polished to a mirror finish with 0.3 micron alumina on a smooth polishing cloth and then rinsed with methanol and double distilled water prior to each electrochemical measurements. The electrode cleaning procedure requires less than 3 min. All the solutions examined by electrochemical techniques were purged for 10 min. with water-saturated nitrogen. All measurements were carried out at room temperature (24 °C).

III. RESULTS AND DISCUSSION

The formation of complexes of metal nitrates with Schiff base in methanol is presented in the following reaction.



All the metal complexes are stable and non-hygroscopic in nature. The complexes are insoluble in common organic solvents but soluble in DMF and DMSO. The elemental analyses shows that, the Zn(II), Co(II), Ni(II) and Cu(II) complexes have 1:2 stoichiometry of the type ML₂·2NO₂ and Fe(III) complex is of the type [FeL₂·2NO₂]. NO₂ wherein L acts as a bidentate ligand.

The molar conductance values are too low to account for any dissociation of the complexes in DMF, indicating the nonelectrolytic nature of the complexes in DMF. The analytical & physical data of synthesized Schiff base and its Zn(II), Co(II), Ni(II), Cu(II) and Fe(III) metal complexes are given in table- I-

Table I - Analytical & physical data of synthesized Schiff base & their Metal Complexes

S.No	Compounds	Mol. wt.	Yield %	Molar Conductivity mhos cm ² mol ⁻¹	Elemental analysis (Cal.)/Found %			
					C	H	N	M
1.	(Ligand)C ₁₅ H ₁₁ N ₃ O	249		9.3	72.29	4.42 (4.19)	16.87 (15.59)	-
2.	[CoL ₂ . 2 NO ₂]	648.93	79	9.9	55.48 (54.32)	3.39 (3.04)	17.26 (16.20)	9.08 (8.82)
3.	[NiL ₂ . 2 NO ₂]	648.7	78	10.7	55.49 (54.04)	3.40 (2.80)	17.27 (15.89)	9.05 (8.98)
4.	[CuL ₂ . 2 NO ₂]	653.54	75	13.3	55.08 (54.67)	3.37 (2.09)	17.14 (16.98)	9.72 (8.03)
5.	[ZnL ₂ . 2 NO ₂]	655.37	76	15.62	54.93 (53.64)	3.35 (3.09)	17.08 (16.48)	9.98 (8.75)
6.	[FeL ₂ .2 NO ₂] NO ₂	691.8	74	19.7	52.04 (50.48)	3.18 (2.87)	18.21 (16.95)	8.06 (7.0s9)

A. Infrared Study

In comparison with the spectra of the Schiff base, all the Zn(II), Co(II), Ni(II), Cu(II) and Fe(III) complexes exhibited the band of (HC=N) in the region 1596-1603 cm⁻¹; showing the shift of band to lower wave numbers indicating that, the azomethine nitrogen is coordinated to the metal ion^{19, 20}. The band of (C=O) in the region 1697-1704 cm⁻¹ in the metal complexes showing the shift to lower wave numbers confirms that, the carbonyl oxygen is coordinated to the metal ion^{20, 21}. The unaltered position of a band due to (NH) and (C=N) in all the metal complexes indicates that, these groups are not involved in coordination. The new bands in the region of 452-480 and 510-530 cm⁻¹ in the spectra of the complexes are assigned to stretching frequencies of (M-N) and (M-O) bonds respectively²². Other strong bands around 1360 cm⁻¹ & 860 cm⁻¹ in all complexes, suggest monodentate coordination of -NO₂ group in the complexes²³. Thus the IR spectral results provide strong evidences for the complexation of Schiff base with metal ions in bidentate mode. The important frequencies of Schiff base & its metal complexes are given in table II-

Table II The important infrared frequencies (in cm⁻¹) of Synthesized Schiff base and its metal complexes

Compounds	ν (CH=N)	ν (N-H) Indol ring	ν (C=O) Lactonyl	ν (C=N)	ν (M-N)	ν (M-O)	ν (M-NO ₃)
C ₁₅ H ₁₁ N ₃ O	1621	3190	1722	1612	-	-	-
[CoL ₂ . 2 NO ₂]	1600	3186	1710	1610	440	510	1340, 855
[NiL ₂ . 2 NO ₂]	1605	3192	1712	1614	458	520	1350, 865
[CuL ₂ . 2 NO ₂]	1598	3193	1698	1610	467	532	1345, 843
[ZnL ₂ . 2 NO ₂]	1610	3190	1704	1614	449	515	1320, 865
[FeL ₂ .2 NO ₂] NO ₂	1596	3187	1710	1612	542	526	1332, 840

B. Electronic Spectral and magnetic studies

Electronic spectra of the Zn(II) complex display weak absorption bands at 18615 (λ_1), 23684 (λ_2), 27769 (λ_3) and 38890 cm^{-1} (λ_4) characteristic of octahedral geometry corresponding to $6A_{1g} \rightarrow 4T_{1g}(4G)$, $6A_{1g} \rightarrow 4E_g(4D)$, $6A_{1g} \rightarrow 4T_{1g}(4P)$, $6A_{1g} \rightarrow 4E_g(G)$ transitions, respectively. The complex shows magnetic moment in the range 5.92 B.M. The electronic spectra of Co(II) complex exhibited absorption bands in the region 8000-10000 cm^{-1} and 18000-20000 cm^{-1} corresponding to λ_1 and λ_3 transitions respectively, which are attributed to the transitions $4T_{1g}(F) \rightarrow 4T_{2g}(F)$ (λ_1); $4T_{1g}(F) \rightarrow 4T_{1g}(P)$ (λ_3). In the present investigation, brownish Co (II) complex show the absorption bands at 9542 and 19282 cm^{-1} corresponding to λ_1 and λ_3 transitions respectively. These bands are the characteristic of high spin octahedral Co (II) complex²⁴. However, λ_2 band is not observed because of its proximity to strong λ_3 transition. The magnetic measurement of Co (II) complex exhibited magnetic moment value of 4.76 which is within the octahedral range of 4.3-5.2 BM.²⁵ The greenish Ni(II) complex exhibited three bands at 10415, 15645 and 26342 cm^{-1} which are attributed to the $3A_{2g} \rightarrow 3T_{2g}$ (λ_1); $3A_{2g} \rightarrow 3T_{1g}(F)$ (λ_2) and $3A_{2g} \rightarrow 3T_{1g}(P)$ (λ_3) transitions respectively indicating octahedral geometry around Ni(II) ion²⁶. Ni (II) complex showed the magnetic moment value of 3.28 which is within the range of 2.8-3.5 BM suggesting²⁵ consistency with their octahedral environment.

The Electronic spectra of Cu(II) complex display two prominent bands. A low intensity broad band around 14476 cm^{-1} is assignable to $2T_{2g} \rightarrow 2E_g$ transition. Another high intensity band at 25562 cm^{-1} is due to symmetry forbidden ligand metal charge transfer. On the basis of electronic spectra distorted octahedral geometry around Cu (II) ion is suggested²⁷. The Cu (II) complex showed magnetic moment 1.76 BM is slightly higher than the spin-only value 1.73 BM expected for one unpaired electron, which offers possibility of an octahedral geometry²⁸. The electronic spectra of the Fe (III) complex showed strong bands at 17932 and 13122 cm^{-1} . It was not possible to identify the type of the d-d transition. This is due to a strong charge-transfer (CT) band tailing from the UV-region to the visible region. The magnetic moment of the Fe (III) complex was observed is 5.04 B.M., lower than the magnetic moment of the high spin octahedral complex. Generally, a tentative interpretation expects the structure of Fe(III) to be an octahedral geometry²⁹.

C. Electrochemical studies

A cyclic voltammogram of Zn(II) complex is presented in Figure 1. The redox property of the Zn(II) complex was studied in the potential range of +1.7 to -1.9 V. The Zn(II) complex is electroactive with respect to the metal center and exhibited two redox processes, each reduction is associated with a single-electron transfer process at room temperature^{30,31}. For both responses, the cathodic and anodic peak heights are equal, and vary as the square root of the scan rate; E_{pc} and E_{pa} are virtually independent of the scan rate. Two well-defined quasi-reversible one-electron cyclic responses were observed at $E_{pc} = -1.4706$ with a corresponding oxidation peak at $E_{pa} = -0.6632$ V and at $E_{pc} = -0.5975$ with a corresponding oxidation peak at $E_{pa} = 0.8168$ V respectively at a scan rate of 100mV/s.

The electrochemical behavior shows moderately high reduction potentials. E_p values for the first redox couple, 0.8279V is higher than for the second redox couple, 0.2201V. E_p value is higher for the complex due to the difference between the original complex and the reduced species.

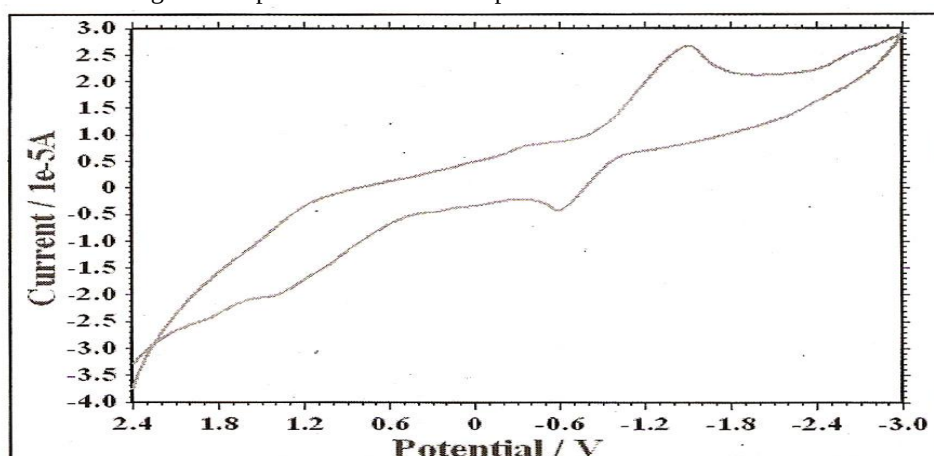


Figure 1. Cyclic voltammogram of Zn(II) complex

Cyclic voltammogram of Co (II) & Ni(II) complexes are presented in Figure 2 & 3. The Co (II) & Ni(II) complexes exhibit one electron quasi reversible transfer process with a reduction peak at $E_{pc} = -1.6$ V with a corresponding oxidation peak at $E_{pa} = -0.8$ V at a scan rate of 50mV/s. The peak separation (ΔE_p) of this couple

is 0.7V. With the increasing scan rates, E_p value also increases giving further evidence for the quasi-reversible Co(II)/Co(I) couple.

The difference between forward and backward peak potentials can provide a rough evaluation of the degree of the reversibility. The ratio of cathodic to anodic peak height was less than one. However, the peak current increases with the increase of the square root of the scan rates. This establishes the electrode process as diffusion controlled.

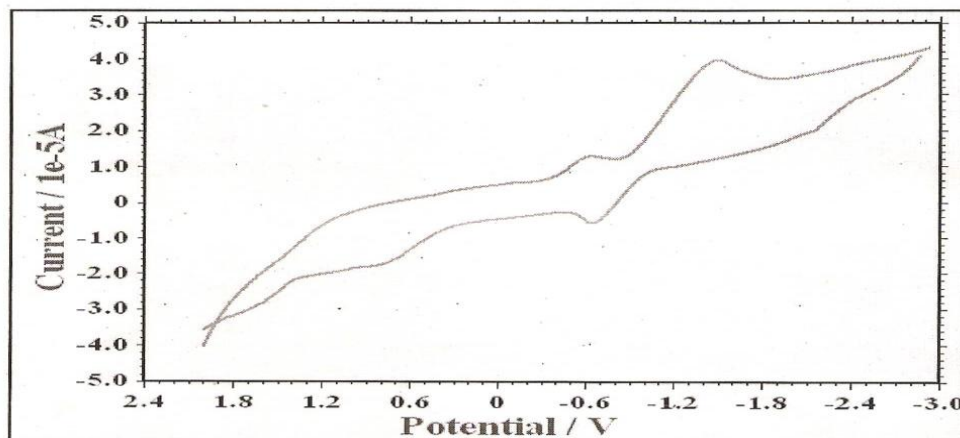


Figure 2. Cyclic voltammogram of Co(II) complex

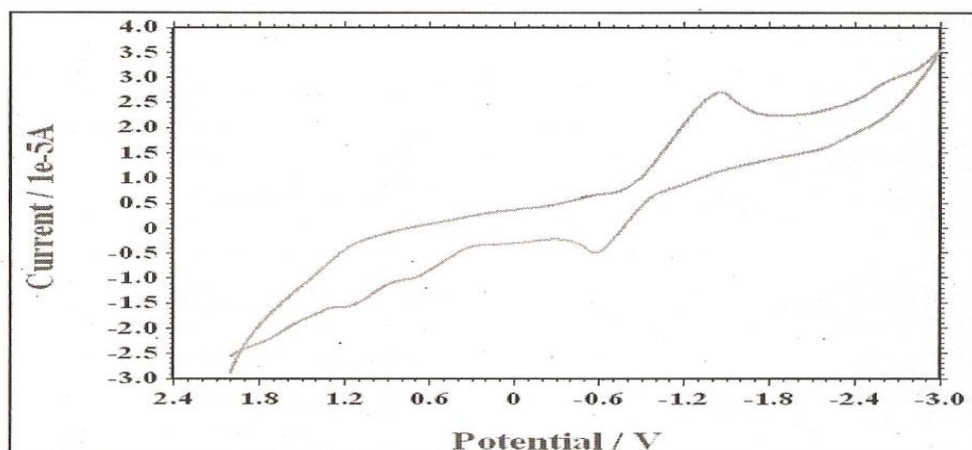


Figure 3. Cyclic voltammogram of Ni(II) complex

A cyclic voltammogram of Cu (II) complex is presented in Figure 4. Voltammogram displays a reduction peak at $E_{pc} = -1.4V$ with an associated oxidation peak at $E_{pa} = -0.6V$ at a scan rate of 50mV/s. The peak separation of this couple (E_p) is 0.8V and increases with scan rate. The E_p is 1.1 and 1.4 at scan rates 100mV/s and 200mV/s respectively. Thus, the analyses of cyclic voltametric responses at different scan rate give the evidence for quasi-reversible one electron reduction. The most significant feature of the Cu(II) complex is the Cu(II)/Cu(I) couple. The ratio of cathodic to anodic peak height was less than one. However, the peak current increases with the increase of the square root of the scan rates. This establishes the electrode process as diffusion controlled³².

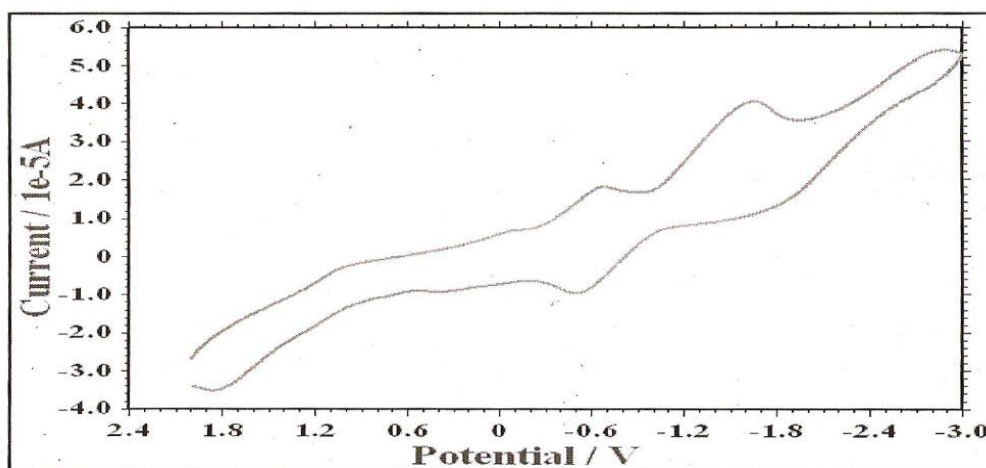


Figure 4. Cyclic voltammogram of Cu(II) complex

A cyclic voltammogram of Fe(III) complex is presented in Figure 5. The Fe (III) complex exhibited two quasi-reversible peaks. A cyclic voltammogram of Fe (III) displays two reduction peaks, first one at $E_{pc} = -0.7213$ V with an associated oxidation peak at $E_{pa} = 0.4162$ V and second reduction peak at $E_{pc} = -1.6721$ V with an associated oxidation peak at $E_{pa} = -0.5839$ V corresponding to the Fe (III)/Fe (II) and Fe (II)/Fe (I) respectively at a scan rate of 0.2V/s. The value of E_p is 0.3051 and 1.0882 for first and second redox couples respectively and increases with scan rate giving evidence for quasi-reversible nature associated with one electron reduction.

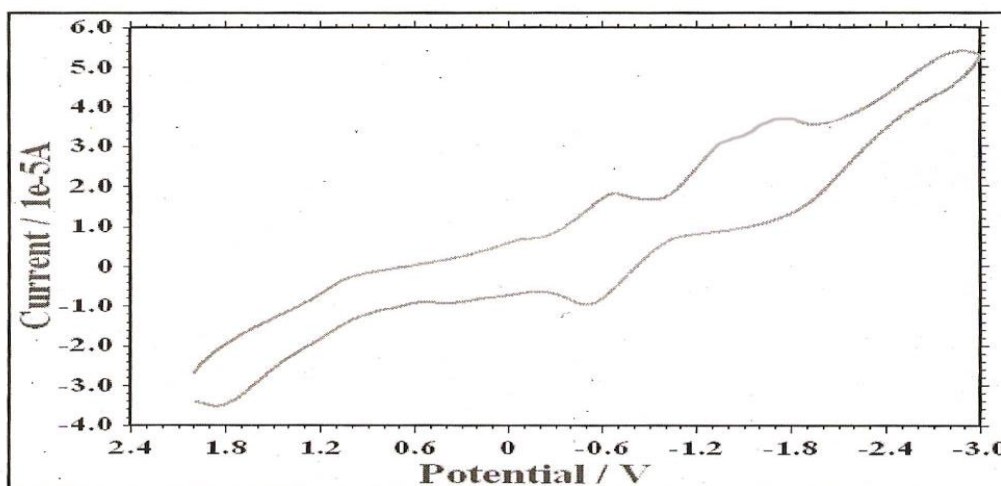


Figure 4. Cyclic voltammogram of Fe(III) complex

D. Antimicrobial Studies

The antibacterial and antifungal activity of synthesized Schiff base and its metal complexes were screening in vitro, against bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*) and fungi (*Aspergillus flavous*, *Aspergillus niger*, *Penicillium triticena* and *Fusarium species*). The results are recorded in Table III and IV. The results of biocidal activities show that the percentage of zone of inhibition of 500 ppm concentration is the best. The percentage of growth inhibition capacities of metal complexes follow the following order against different bacteria and fungi-

E. Bactericidal activities of metal complexes

E. coli : Cu (II) > Zn (II) > Co (II) > Ni (II) > Fe(III)
 S. typhi : Cu (II) $\approx$ Zn(II) > Co (II) > Ni (II) > Fe(III)
 S. aureus : Cu (II) > Zn (II) $\approx$ Co (II) > Ni (II) > Fe(III)
 B. subtilis: Mn (II) $\approx$ Zu (II) > Co (II) $\approx$ Ni (II) > Fe(III)

F. Fungicidal activities of metal complexes

A. flavous : Cu (II) > Zn (II) > CO (II) > Ni (II) > Fe(III)

A. niger : Cu (II) > Zn (II) > Co(II) > Ni (II) > Fe(III)
P. triticea : Cu (II) > Zn (II) > Co (II) ≈ Ni (II) > Fe(III)
F. species: Cu (II) > Zn (II) > Co (II) > Ni (II) > Fe(III)

The results indicate that the Cu (II) complex is more toxic compared to other complexes, as well as Cu (II) complex is more effective towards bacteria *S. aureus* compared to other microbes. The over all results obtained from the above studies confirm that with increase in the concentration of the complexes the activity almost remains unchanged or is slightly increase. This enhancement in the activity of the metal complexes can be explained on the basis of chelation theory³³. It is, however, known that the chelating tends to make the Schiff base act as more powerful and potent bacteriostatic agents, thus inhibiting the growth of bacteria and fungi more than the parent Schiff base³⁴⁻³⁶.

(Table III) - Percentage of zone of inhibition of Ligands & their Metal Complexes against Fungi

Compounds	A. flavous				A. niger				P. triticea				F. species			
	% Conc. In ppm				% Conc. In ppm				% Conc. In ppm				% Conc. In ppm			
	250	500	750	1000	250	500	750	1000	250	500	750	1000	250	500	750	1000
C ₁₅ H ₁₁ N ₃ O	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[CoL ₂ . 2 NO ₂]	39.50	69.13	71.55	75.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00
[NiL ₂ . 2 NO ₂]	39.50	62.66	69.13	71.55	39.50	62.66	69.13	71.55	39.50	62.66	64.00	69.13	39.50	62.66	64.00	69.13
[CuL ₂ . 2 NO ₂]	39.50	69.13	69.13	71.55	39.50	71.55	71.55	75.00	39.50	69.13	71.55	71.55	39.50	69.13	71.55	75.00
[ZnL ₂ . 2 NO ₂]	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	69.13	71.55
[FeL ₂ . 2 NO ₂]	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00

(Table IV) - Percentage of zone of inhibition of Ligands & their Metal Complexes against Bacteria

Compounds	E. coli				S. typhi				S. aureus				B. subtilis			
	% Conc. In ppm				% Conc. In ppm				% Conc. In ppm				% Conc. In ppm			
	250	500	750	1000	250	500	750	1000	250	500	750	1000	250	500	750	1000
C ₁₅ H ₁₁ N ₃ O	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00
[CoL ₂ . 2 NO ₂]	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00	39.50	54.00	62.66	64.00
[NiL ₂ . 2 NO ₂]	39.50	62.66	69.13	71.55	39.50	62.66	69.13	71.55	39.50	62.66	64.00	69.13	39.50	62.66	64.00	69.13
[CuL ₂ . 2 NO ₂]	39.50	62.66	64.00	69.13	39.50	62.66	69.13	71.55	54.00	75.00	75.00	75.00	39.50	69.13	69.13	71.55
[ZnL ₂ . 2 NO ₂]	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00
[FeL ₂ . 2 NO ₂]	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00	39.50	69.13	71.55	75.00

IV. CONCLUSIONS

In this study, the synthesis of Zn(II), Co(II), Ni(II), Cu(II), and Fe(III) complexes with Schiff base derived from benzaldehyde and isatin monohydrazone and characterized. The Schiff base act as versatile bidentate ligand. The electrochemical properties of the metal complexes revealed the quasi-reversible one electron/two electron transfer redox process. The Schiff base and some of the metal complexes were found to be active against some of the representative bacterial and fungal strains. The results of microbial studies indicate that the Cu (II)

complex is more toxic compared to other complexes, as well as Cu (II) complex is more effective towards bacteria *S. aureus* compared to other microbes.

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