



## BIOLOGICAL AND CATALYTIC ACTIVITY OF MIXED LIGAND TRANSITION METAL COMPLEXES

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### Abstract

A new series of Cr(III), Mn(II), Fe(II), Fe(III), Co(II), Ni(II) and Zn(II) ternary complexes derived from lornoxicam and 1,10-phenanthroline (Phen) have been synthesized. The two ligands, in comparison to ternary metal complexes are screened for their antimicrobial and anticancer activity. The results showed that the metal complexes be more active than the parent LOR ligand but less active than 1,10-phenanthroline free ligand. The Co(II) and Cu(II) metal complexes completely missed anticancer activity. Similarly Chiral mixed ligand (CML) metal complexes are synthesized. The CMLCo(II)/Ni(II) complexes, synthesized and characterized in the present work, have been used as catalysts decomposition of hydrogen peroxide. The study on catalytic decomposition of hydrogen peroxide deals with the use of these complexes as two different types of catalysts i.e. heterogeneous and homogeneous catalysts heterogenised on alumina. It has been observed that complexes adsorbed on alumina (heterogenized) are better catalysts as compared to non-adsorbed complexes (heterogeneous catalysts).

**Keywords:** Lornoxicam; 1,10-phenanthroline, ternary metal complexes; spectroscopy, Mixed ligand metal complexes, isonitrosopropiophenone Benzil, bis (thiosemicarbazone), Fe(II), Zn(II) Benzaldehyde, Catalyst, Hydrogen Peroxide, Oxidation



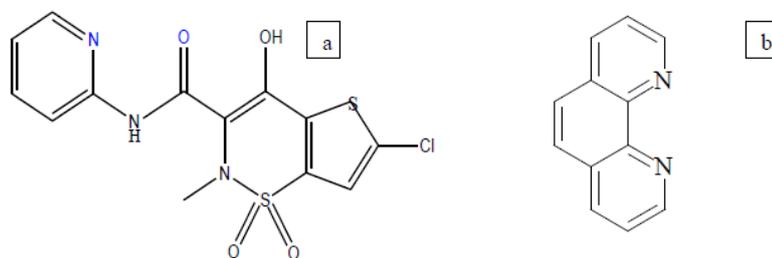
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### 1.1 Introduction

In recent years, there has been renewed interest in the synthesis and study of mixed ligand transition metal complexes. The utility aspects of these complexes have received their share of attention as these have found applications in diverse fields. Chiral metal complexes are well known for their use as catalysts, especially in asymmetric synthesis asymmetric epoxidations or Sharpless epoxidations and resolution of racemic compounds. Light catalyzed inversion and diastereoisomeric equilibration in chiral metal complexes have been studied extensively. Metal-based drugs are a research area of increasing interest for inorganic, pharmaceutical and medicinal chemistry and have concentrated much attention as an approach to new drug

development. As far as we know, the selection of appropriate metal ions and organic ligands is the key in the construction of complexes. Metal ions, especially their radii and coordination geometry, determine the extending direction and coordination modes of the organic ligands, which is important for the structure of the complexes.

Among the metal complexes, those of 1,10-phenanthroline have attracted line.1,10-phenanthroline as chelating nitrogen donor ligands is among the most efficient chelators for transition and post-transition metal ions with which it form stable complexes in solution. The presence of aromatic and/or heteroaromatic groups into the structure of nitrogen donors gives these ligands with additional properties. For instance, poly nitrogen donors containing aromatic and/or heteroaromatic groups conjugate the ligational ability with the photophysical properties typical of these groups and, accordingly, they have been widely used as chemosensors for metal ions in solution, since their coordination may affect the properties of the photosensitive group giving rise to an optical response. It is well known been also reported that some ternary complexes of 1,10-phenanthroline (phen) e.g. [Cu(phen)] have an antitumor activity where it inhibited DNA or RNA polymerase activities. Microbial infections often produce pain and Inflammation. Chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. Anti-inflammatory, analgesic and antipyretic activities are known for some Pyridine and phenol derivatives. These compounds are able to block cartilage destruction during the inflammatory process and thus are a promising class of anti-inflammatory compounds. Lornoxicam drug (Fig.1) is a member of non-steroidal anti-inflammatory drugs (NSAIDs) that characterized by rapid and complete uptake in the bloodstream and in turn, the presence of the metallic ions can affect bioavailability of the drug thus possessing a fast analgesic action.



**Figure 1. Structures of (a) lornoxicam and (b) 1,10-phenanthroline.**

## **1.2 Preparation of mixed ligand complexes**

The mixed complexes were prepared by mixing equal amounts (0.01 mol) of hot saturated ethanolic solution of the first ligand (lornoxicam) and second ligand (1,10-phenanthroline)

with the same ratio of metal chloride or borate salts. The mixture was refluxed for three hours. The resulting complexes were filtered and washed several times with hot ethanol until the filtrates become clear. The solid complexes then dried in desiccator over anhydrous calcium chloride. The yield ranged from 74-91%.



M(II) = Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) ; M(III) = Cr(III), Fe(III)

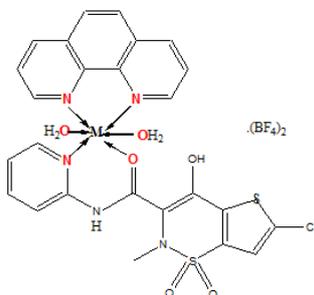
L<sup>1</sup> = lornoxicam; L<sup>2</sup> = 1,10-phenanthroline

The dried complexes were subjected to elemental and spectroscopic analyses. The obtained complexes are soluble in ethanol, DMF and DMSO. All melting points of the complexes were measured and found to be >200 °C.

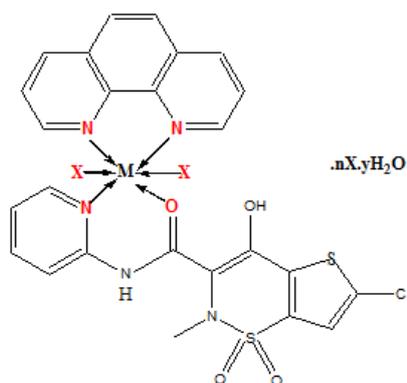
### 1.3 Structural interpretation

The structure of all complexes may be interpreted with a similar distribution of like coordinating sites, which coordinated to M(II)/(III) ions and takes place via the pyridyl N and carbonyl O atom. The structures proposed are based on octahedral geometry. The proposed structural formulas of the above complexes are summarized as three types of coordination as follow:

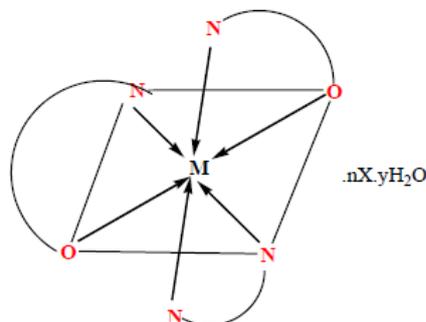
a) In case of Fe(II), Co(II) and Zn(II) complexes:



b) In case of Cr(III), Ni(II) and Cu(II) complexes (where n = 1, y = 2 for Cr(III) complex, n = 0, y = 1 for Ni(II) complex and n = 0, y = 2 for Cu(II) complex) :



c) In case of Fe(III) and Mn(II) ternary complex (where  $n = 3$ ,  $y = 0$  for Fe(III) complex and  $n = 2$ ,  $y = 2$  for Mn(II) complex)



## 1.4 Antimicrobial activity

### 1.4.1 Antibacterial activities

The Lornoxicamligand has no activity at all towards *Bacillus subtilis* and *Escherichia coli*. This is attributed to its very versatile nutritional capability, adaptability to various hydrocarbon rings, and the possession of pump mechanism which ejects metal complexes as soon as they enter the addition, *Bacillus subtilis*, *Staphylococcus aureus*, *Beisseriagonorrhoeae* and *Escherichia coli* cell. In *coli* are sensitive to all the complexes, with the exception of the Ni(II) complexes, and an inhibitory zone of its positive charge with donor groups of the ligand and possible  $\pi$ -electron delocalisation on the aromatic rings. This increased the lipophilic character, favouring its permeation into the bacterial range of 10.0-20.0 mm (Fig.2 ). In all cases, the metal complexes are more active than the LOR ligand expectedly due to chelation, which reduced the polarity of the metal atom, mainly because of partial sharing membrane, causing the death of the organisms. A look at the antibiotic, Amikacin, activities against the various bacterial isolates relative to the metal complexes showed that the activities of the former are much lower, with optimum activity being about half of metal complexes against all the bacterial organisms. When the antimicrobial activity of metal complexes is investigated, the following principal factors should be considered: (i) the chelate effect of the ligands; (ii) the nature of the N-donor ligands; (iii) the total charge of the complex; (iv) the existence and the nature of the ion neutralizing the ionic complex and (v) the nuclearity of the metal center in the complex. This is probably one of the reasons for the diverse antibacterial activity shown by the complexes while the nature of the metal ion coordinated to LOR ligand may have a significant role to this diversity. In general, all the complexes exhibit better inhibition than free LOR against *Bacillus subtilis*, *Staphylococcus aureus*, *Beisseriagonorrhoeae* and *Escherichia coli*. More specifically, Mn(II) and Co(II)

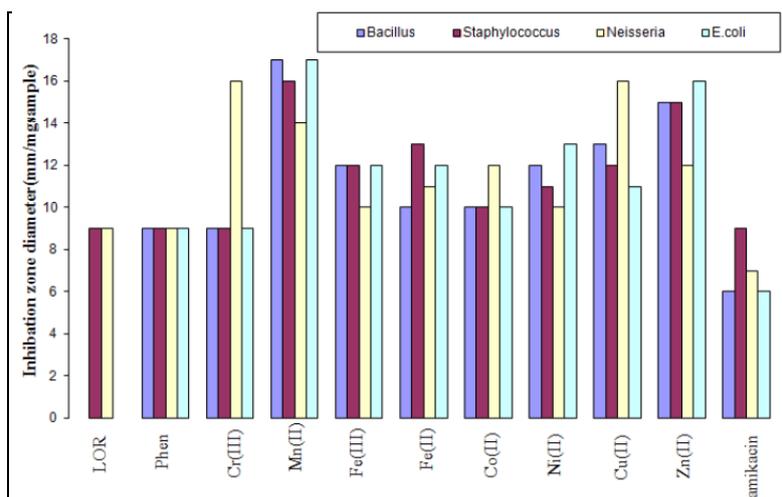
complexes show the best inhibition among all the complexes in this study and it is one and halt to twenty times more active than LOR against all the microorganisms used, indicating that the coordination of the LOR ligand to Co(II) and Mn(II) has enhanced its antimicrobial activity. On the other hand, the rest complexes present higher antimicrobial activity to LOR against the four microorganisms.

### 1.4.2 Antifungal activities

The preliminary fungitoxicity screening of the LOR, 1,10-phenanthroline and ternary complexes were performed against the *Candida albicans* in vitro by the diffusion technique . LOR drug and all the metal complexes showed no fungal growth inhibition except Mn(II) complex. The Mn(II) complex in this study is nearly two times more active than Ketokonazole standard against *Candida albicans* microorganism used.

### 1.4.3 Anticancer activity

Cancer, of which there are over 100 different forms, is a leading cause of death. The clinical success of cis-platin, and related platinum based drugs, as anti-cancer agents constitutes the most impressive contribution to the use of metals in medicine. However major problems associated with these anti-cancer metallo-drugs include serious toxicity and other side-effects, and major problems with resistance. New potent and selective anti-cancer drugs are urgently required. Recently novel metal based compounds containing metals such as titanium, copper, ruthenium, tin and rhodium have been reported with promising chemotherapeutic potential, and which have different mechanisms of vacation to the platinum based drugs.



**Figure 2. Biological activity of LOR, 1,10-phenanthroline and ternary complexes.**

### **1.5.1 Catalytic activity of transition metal complexes ligand**

Thiosemicarbazones are an important class of N,N,S,S donors which have pharmacological interest due to their significant antibacterial, antiviral, antimalarial, antileprotic, and anticancer activities. Thiosemicarbazones usually are chelating ligands with transition metal ions, bonding through sulfur and hydrazine nitrogen. The chemistry of iron and zinc receives attention primarily because of the fascinating electron transfer and energy transfer properties displayed by the complexes of this metal. Transition metal complexes offer a wide range of oxidation states and reactivity of the iron and zinc complexes depend on the stability and inter convertibility of these oxidation states, which in turn depend on the nature of the ligand bound to the metal. Transition metal complexes are effective catalysts in cross-coupling reactions, but their use as catalysts for aryl-aryl coupling has not been much studied. Mild and efficient aromatic couplings have been reported. Selective oxidation of alcohols to aldehydes and ketones is a key reaction in organic synthesis. The development of new procedures that can use air or molecular oxygen as oxidant is environmentally attractive. The oxidation of organic compounds with an ecofriendly oxidant, aqueous hydrogen peroxide is a challenging goal of catalytic chemistry. In recent years, a considerable amount of research was dedicated to the preparation of various transition metal complexes catalysts and their application for oxidations of various organic compounds. Homogeneous catalysis by ruthenium and osmium compounds has been reported by several workers but the use of [Fe(II)BBTSC] and [Zn(II)BBTSC] as homogeneous catalyst in acidic medium has not yet been reported. In the present system good yield is obtained with substrate catalyst ratio ranging from 85400 to 341250:1 and it oxidizes a wider range of organic compounds, and it is a more convenient, eco-friendly and economical compared to many other systems. To explore the potential of the present system for conversion of various other groups in aqueous acetic acid medium, here in the oxidation of benzaldehyde by 30% H<sub>2</sub>O<sub>2</sub> in the presence of traces of [Fe(II)BBTSC] and [Zn(II)BBTSC] is reported.

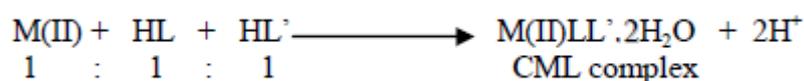
Some metal ligand complexes are found to catalyze reactions such as oxidation, oxidative cleavage, hydroformylation, etc. and have shown *catalyses* like activity in decomposition of hydrogen peroxide. Phthalocyanines have found wide applications in diverse areas. It is well established that ternary complexes play a decisive role in the activation of enzymes and also in the storage and transport of active substances. The binary and ternary transition metal complexes have shown biological activity. Mixed ligand complexes of transition metals are commonly found in biological systems. During recent years metal complexes of some N/O donor ligands have attracted considerable attention because of their greater antifungal and

antibacterial activities than those of the parent ligands. Ternary complexes containing an amino acid as a secondary ligand are of significance as they are potential models for enzyme-metal ion substrate complexes.

Here we concentrate on the synthesis and characterization of chiral mixed ligand Co(II)/Ni(II) complexes prepared by using HINPP as a primary ligand (HL) and various chiral saccharides as secondary ligands (HL'). These complexes have also been employed as catalysts in reactions such as decomposition of hydrogen peroxide and hydrolysis of esters.

### 1.5.2 Characterization of metal complexes

The synthesis of CML complexes may be represented as shown in equation:



(Where HL is HINPP and HL' is a chiral saccharide ligand).

All of the complexes are non-hygroscopic stable solids. They are colored and thermally stable, indicating a strong metal-ligand bond. The elemental analysis data of metal complexes is consistent with their general formulation as mixed ligand complexes  $\text{MLL}' \cdot 2\text{H}_2\text{O}$ . The molar conductance values of the complexes in methanol at  $10^{-3}$  M concentration are very low ( $<1$ ), indicating their non-electrolytic nature. The specific rotation values for the complexes with (+)-glucose in methanol solution (0.01%) were found to be positive. The value for the complex with (-)-fructose was found to be negative. This indicates that the specific rotation of the complexes is due to the corresponding chiral saccharide moiety.

### 1.5.3 Catalytic Activity of Complexes

The study on catalytic decomposition of hydrogen peroxide deals with the use of these complexes as two different types of catalysts i.e. heterogeneous catalysts and homogeneous catalysts heterogenised on alumina.

#### Decomposition of Hydrogen Peroxide

The use of CML cobalt (II) complexes in the kinetic study of catalytic decomposition of  $\text{H}_2\text{O}_2$  is studied recently. In the present studies CML Co(II)/Ni(II) complexes have been employed in the kinetic study of catalytic decomposition of  $\text{H}_2\text{O}_2$ . The CML Co (II)/Ni (II) complexes were used in the form of heterogeneous catalysts and homogeneous catalysts heterogenised on alumina support in the catalytic decomposition of  $\text{H}_2\text{O}_2$ . The reactions were studied at two different volume strengths (3 and 5 V) and at three different temperatures (35, 55 and 60 °C). The method adopted for the purpose consisted essentially of following the

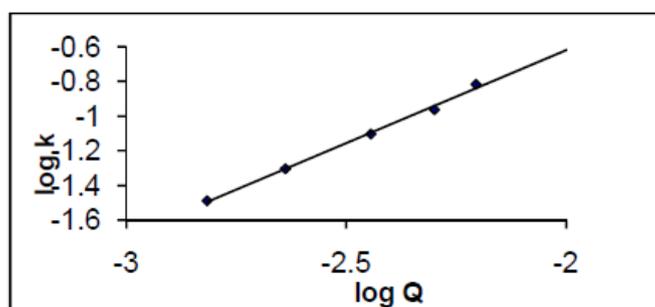
kinetics of catalytic decomposition of H<sub>2</sub>O<sub>2</sub> using a gasometrical technique involving the measurement of the volume of oxygen evolved.

**A) CML Co (II) and Ni (II) Complexes as Heterogeneous Catalysts:**

The kinetic studies of catalytic decomposition of H<sub>2</sub>O in presence of CML Co(II)/Ni(II) complexes, used as heterogeneous catalysts, have been carried out at three different temperatures (35, 55 and 60 °C) and at two different volume strengths (3 and 5 V) of H<sub>2</sub>O<sub>2</sub>. The catalytic nature of the reaction was confirmed by recovering the complexes unchanged, both in amount and composition, at the end of the reaction. The FTIR spectra of some of the complexes recorded before and after the reaction are almost identical indicating that the catalysts do not suffer any irreversible, compositional or structural change. The cobalt(II) as homogeneous ion in the form of its chloride solution shows a very low catalytic activity with respect to the decomposition of H<sub>2</sub>O<sub>2</sub>, the specific reaction rates at 35, 55 and 60 °C being 0.195 × 10<sup>-2</sup>, 0.702 × 10<sup>-2</sup> and 0.832 × 10<sup>-2</sup> min<sup>-1</sup>, respectively. However, in presence of the present CML Co (II)/Ni (II) complexes in heterogeneous phase, the rate of catalytic disproportionation is enhanced considerably, as can be easily inferred from the observed specific reaction rates. It follows, therefore, that complexation and heterogenization of Co(II)/Ni(II) have an enhanced effect on the catalytic decomposition of H<sub>2</sub>O<sub>2</sub>, especially at higher temperatures. All the CML Co(II) complexes with tetrahedral geometry show almost similar catalytic activities. This would be expected on the basis of the similar structures proposed for the complexes. Normally, more stable complexes should show higher E and lower k values. However, the values of activation energy, E, and various thermodynamic parameters depicted, indicate that lower k values are found to be associated with relatively lower E values. It has also been reported that when a system passes into a transition state, accompanied by an increase in entropy, then notwithstanding the high activation energy, the reaction will proceed at faster rates. Conversely, therefore, a reaction accompanied by decrease in entropy will be expected to proceed slowly, notwithstanding the low activation energy. The effect of change of metal ion during complexation interestingly affects the rate of the reaction when it has been observed that octahedral Ni(II) complexes with dextrose and fructose show lower k values as compared to the tetrahedral and octahedral Co(II) complexes. Obviously, the Co(II) complexes are catalytically more active than the Ni(II) complexes. It is observed that DH<sup>‡</sup> values are closer to E values in accordance with absolute reaction rate theory for solution. The value of DG<sup>‡</sup> has been found to be higher in all the cases and not much difference has been found in both the systems. The values of DS<sup>‡</sup> were found to be negative in all the cases indicating that molecules in transition state are more ordered than the

reactants in ground state. The plot of  $\log(a-x)$  against  $t$  for the complexes is linear indicating that the decomposition of  $H_2O_2$  in the presence of catalyst follows first order kinetics. Keeping the quantity of the catalyst and  $H_2O_2$  constant, when the temperature was varied in the range  $35-60^\circ C$ , the value of  $k$  increased with increase in temperature. By comparing the  $k$  values with those obtained with  $5 V H_2O_2$  it can be inferred in general, that the rate of the reaction decreases with increase in the concentration of  $H_2O_2$ , though discrepancies are observed in a few cases. Keeping the quantity of  $H_2O_2$  and the temperature constant, when the quantity of catalyst was varied in the range

0.01-0.05 g, the value of  $k$  increased with increase in the quantity of the catalyst. The plot of  $\log k$  against  $\log [Co(INPP)(Dex).2H_2O]$  is linear with a slope of 0.8, indicating that the order of the disproportionation reaction is almost unity (Fig. 3).

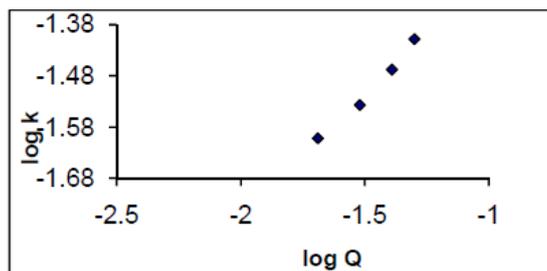


**Fig .3 Plot of  $\log k$  against  $\log \{Quantity\ of\ [Co(INPP)(Dex)].2H_2O\}$ .**

### **B) CML Co(II)/Ni(II) Complexes as Heterogenized Catalysts**

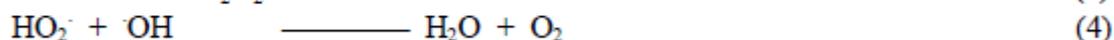
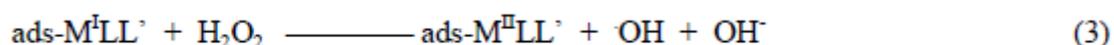
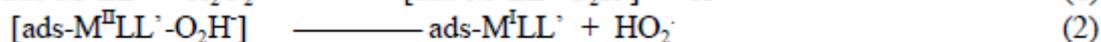
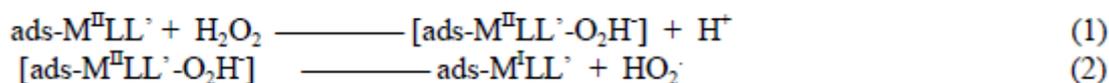
It is known that a catalyst, when attached to a support i.e. when heterogenized, enhances the catalytic activity. In the following section, we report the results of kinetics of disproportionation of hydrogen peroxides catalyzed by CML Co(II)/Ni(II) complexes adsorbed on alumina. It is reported that alumina, duly processed acts as a catalyst in the decomposition of hydrogen peroxides. Therefore, when experiments were carried out with alumina under identical conditions, the volume of oxygen evolved was found to be negligible. Experiments carried out using alumina treated with a solution of HINPP or saccharides revealed no activity at all. This shows that when alumina, HINPP or saccharides are used individually, they show much less or no catalytic activity in the decomposition of hydrogen peroxide. However, activity increases considerably when the complex is adsorbed on alumina. Thus it can be inferred that the CML Co(II)/Ni(II) complex adsorbed on alumina is responsible for the fast  $H_2O_2$  decomposition reaction. Keeping the quantity of the catalyst and  $H_2O_2$  constant, when the temperature was varied in the range  $35-60^\circ C$ , the value of  $k$  was found to increase with increase in temperature. The plot of  $\log k$  against  $\log$

{[Co(INPP)(Dex)].2H<sub>2</sub>O adsorbed on alumina} is linear with a slope of 1.0, indicating that the order of the disproportionation reaction with respect to quantity of catalyst is unity (fig. 4)

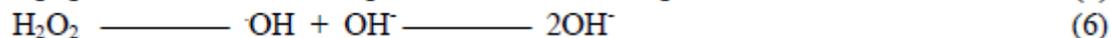
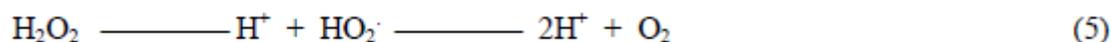


**Fig. 4 Plot of log k against log {Quantity of [Co(INPP)(Dex)].2H<sub>2</sub>O adsorbed on alumina}.**

It has been observed that heterogenized CML complexes show more activity than heterogeneous CML complexes as catalysts. This is due to the increase in the concentration of adsorbed reactant molecules on the surface of the catalyst, which according to the law of mass action, enhances the rate of the reaction. The surface-active complex, recovered during the reaction after washings, was however found to decolorize a dilute solution of potassium permanganate, indicating that it is a peroxy species. Based on the above experimental observations, the following reaction mechanism may be suggested and may involve the initial steps of interaction of the surface complex with H<sub>2</sub>O<sub>2</sub> or OOH<sup>-</sup> ion. The decomposition of H<sub>2</sub>O<sub>2</sub> in presence of the catalysts may proceed through steps (1)-(6) shown in Scheme.



The mechanism in above scheme has been proposed utilizing the oxidation and reduction of H<sub>2</sub>O<sub>2</sub> by steps (5) and (6) respectively, as reported elsewhere.



the formation of free radicals  $\cdot\text{OH}$  and  $\text{HO}_2'$  as the intermediates in homogeneous metal ion catalysed decomposition of H<sub>2</sub>O<sub>2</sub>.

## 1.6 Conclusion

The work described in this paper involved the synthesis and spectroscopic characterization of a series of chromium, manganese, ferrous, ferric, cobalt, nickel, copper and zinc ternary complexes with LOR and 1,10-phenanthroline ligands. These complexes were characterized by using different physiochemical techniques. The IR spectra revealed that LOR behaves as neutral bidentate ligand coordinated to the metal ions through amide –CO and pyridine–N groups, also 1,10-phenanthroline behaves as neutral bidentate ligand coordinated to the metal ions through two pyridine–N groups. The magnetic moment and solid reflectance spectral measurements confirm the presence of all these chelates in octahedral geometry. The ESR spectra gave good evidence for the proposed structure and the bonding for all studied complexes.

Also based on the above discussion and information available in the literature, the following conclusions may be drawn for catalytic activity of transition metal complexes ligand

1. Higher decomposition temperature and electrical conductance studies show the presence of strong metal-ligand bonding and non-electrolytic nature of the complexes, respectively.
2. Specific rotation measurement studies are indicative of the chirality of the complexes.
3. Magnetic studies are indicative of tetrahedral geometry for Co(II) complexes and octahedral geometry for Ni(II) complex, which is confirmed by crystal field transitions shown by the electronic spectra.
4. IR spectra show bonding of the metal ion through N/O and O of the two ligands and presence of water of crystallization, confirmed by thermal analysis.
5. In both the reactions, Co(II) complexes are catalytically more active than Ni(II) complexes.
6. Octahedral Co(II) complexes are catalytically more active than tetrahedral Co(II) complexes in decomposition of H<sub>2</sub>O<sub>2</sub> while in hydrolysis of esters tetrahedral Co(II) complexes are catalytically more active.
7. Catalytic activity of octahedral Co(II) complexes is more than octahedral Ni(II) complexes in both the reactions.
8. Generally, CML Co(II)/Ni(II) complexes adsorbed on alumina (heterogenized) are better catalysts as compared to non-adsorbed complexes (heterogeneous catalysts).

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