Chapter - 1

Introduction
1. **Introduction**

In nature, metal complexes and organic compounds (as ligands) are playing a vital role in growth and development of organism. The best example of the naturally occurring metal complex, chlorophyll (a green pigment found in cyanobacteria and the chloroplasts of algae and plants) is an extremely important biomolecule which helps in photosynthesis. Chemical reactions were known to man long before chemistry had attained the status of science. It was found that substances changed their properties under certain external conditions and this observation is a characteristic of chemical reactions. The ancient Egyptians found that if malachite, a green ore, was fired with charcoal, a red metal was obtained, called copper. Medicinal application of metals can be traced back to almost 5000 years [1].

Coordination chemistry, precisely, is the chemistry of metal atoms "coordinated" by atoms or molecules. Coordination chemistry has always been a challenge to the inorganic chemist. In the early days of chemistry, it seemed unusual (hence the name complexes) and seemed to defy the usual rules of valence. Today a lot of research has been done on coordination chemistry. Although the usual bonding theories can be extended to accommodate these compounds, they still provide stimulating problems to be resolved.

Coordination chemistry enjoys a prominent place in inorganic chemistry. Werner’s coordination theory was the first attempt to
explain the bonding in coordination complexes and concluded that in complexes the metal shows two different sorts of valencies *viz* primary and secondary valencies. Primary valencies are non-directional and are the number of positive charges on the complex ion. In compounds, this charge is matched by the same number of charges from negative ions. Secondary valencies are directional. In modern terms the number of secondary valencies equals the number of ligand atoms coordinated to the metal. This is called the coordination number. The development of modern medicinal inorganic chemistry, stimulated by the discovery of cis-dichlorodiammine platinum(II) [cisplatin] and its subsequent use as a drug in the treatment of several human tumors [2,3], has been facilitated by the inorganic chemist’s extensive knowledge of the coordinating property and redox properties of metal ions. Metal centres, being positively charged, are favoured to bind to negatively charged biomolecules, the constituents of proteins and nucleic acids which offer excellent ligands for binding to metal ions. The pharmaceutical use of metal complexes therefore has excellent potential.

Coordination complexes are formed by the union of a cation with one or more neutral or charged species. The neutral molecules or ions (usually anions) which are attached with the central ion in complex compounds are called ligands or coordinating groups. The term ligand, which originated from the Latin word *liogare* was first introduced by Alfred Stock in 1896, in relation to silicon chemistry. According to Lewis, in most of the complex compounds, the
ligands act as Lewis bases (electron pair donors) and central metal ion acts as a Lewis acid (electron acceptor), i.e., in most of the complexes, the ligands donate one or more electron pairs to the central metal ion (Figure 1.1)

![Figure 1.1. General metal complex equation](image)

**Fig.1.1. General metal complex equation**

The ligands are attached to the central metal ion through their donor atoms. The metallic atom with which the ligands are attached through coordinating bonds is called the central metallic atom. The metallic atom may be in zero, positive or negative oxidation state. Ligands are classified according to the number of donor atoms contained and are known as uni, di, tri, or quadridentate ligands. When a singly coordinating group or ligand occupies two or more coordination positions on the same central metal ion, a complex possessing a closed ring is formed. The phenomenon of ring formation is called chelation and ring formed is called chelate ring. The term chelate was first introduced in 1920 by Morgan and Drew [4].

In some cases, multiple bonding occurs i.e. ligands act simultaneously as donor and acceptor, for e.g., in metallic carbonyls, CO molecule can both accept and donate electron pair.
Coordination number of the central metal atom in a given complex is equal to the total number of donor atoms which are attached to the central metal atom. In other words, the coordination number of the central metal atom is equal to the number of sites at which the ligands are attached to central metal ion. In case of complex compounds that contain only monodentate ligands, the coordination number of the central metal atom is equal to the number of monodentate ligands coordinated to the metal atom. This rule does not hold good for the complexes containing polydentate ligands.

Coordination number of metallic atom predicts the geometry of the metal complex compound. Thus for coordination number equal to 2, 3, 4, 5 and 6, the geometry of the complex compound formed is linear, trigonal planar, tetrahedral or square planar, trigonal bipyramidal and octahedral respectively. Coordination number gives us an idea about the way in which the ligands are arranged around the central metallic atom.

While writing the structural formula of a given compound, the central metal atom and ligands attached with it are always written in a square bracket, called coordination or inner sphere. The portion outside the coordination sphere is called ionization or outer sphere. Thus in \([\text{Co(NH}_3\text{Cl)}\text{Cl}_2]\), the square bracket which contains the central metal ion \(\text{Co}^{+3}\) and the ligands of five ammonia molecules and one chloride ion, is coordination sphere and the portion that contains two chloride ions is ionization sphere.
Over the past twenty-five years, the uses of Schiff base ligands have been extensive in inorganic chemistry. Schiff base can be represented by the general formula RCH=NR₁ where R and R₁ are various substituents. These compounds are formed by the condensation of a primary amine with compounds containing active carbonyl group (Scheme 1.1). It was named after the scientist Hugo Schiff. Since the seminal work by Schiff and co-workers, metal chelate Schiff base complexes have continued to play the role of one of the most important stereochemical models in main group and transition metal coordination chemistry due to their preparative accessibility, diversity and structural variability [5-6].

**Scheme 1.1 Schematic representation of the general reaction for obtaining Schiff bases**

Schiff bases play an important role in biological systems with several applications. They act as anticancer [7-9], antibacterial [10-16], antifungal [17-20], antiviral [21], antiparasitic agents [11]. Schiff bases are the key intermediates in a large number of synthetic and biological reactions are of considerable interest due to their various magnetic, catalytic and biological applications. Thus, for researchers in bioinorganics, the complexes containing Schiff bases provide structural models to know coordination sites around the metal ion in metalloproteins or in enzymes.
The cryomagnetic properties of binuclear complexes originating from Schiff base ligands have permitted the understanding of the mechanism by which the magnetic coupling between the two metallic centers is established, an information that has crucially contributed to the development of this research domain. As for catalysis, the emphasis is mainly placed on the complexes containing chiral Schiff bases, which are efficient in various organic reactions.

Schiff bases can display tautomeric isomerism based on the phenol-imine (O–H···N) and keto-amine(O···H–N) coupling, depending on the nature of intramolecular hydrogen bond [22, 23]. The shifting of the tautomeric equilibrium is strongly affected by the chosen solvent. Thus, protic and aprotic solvents governed by high dielectric constants shifts the equilibrium towards the quinonic derivative.

The coordination chemistry of Schiff bases is of considerable interest due to their various magnetic, catalytic and biological applications. Ligands containing sp² hybridized nitrogen atoms, when present in the aromatic system, show extensive coordination, especially when they are bi or tridentate ligands. Metal derivatives of Schiff bases have been known since 1840, but the synthetic study of complexes was commenced by Pfeiffer and coworkers in 1931.
1.1 Literature review

1.1.1 Enrofloxacin

Enrofloxacin is a member of the family of 6-fluoro-7-piperazinyl-4-quinolones. This antibiotic is highly lipophilic and the addition of a carboxic acid and a tertiary amine contributes to the amphoteric properties of enrofloxacin. Enrofloxacin is bactericidal and has excellent activity against both Gram-positive and Gram-negative pathogens. This antibiotic has also been used to control certain intracellular pathogens. Modification of the 4-quinolone ring has enhanced the antimicrobial activity of this compound. Oral bioavailability of enrofloxacin is excellent in monogastric mammals and preruminant calves, with up to 80% of the ingested dose being absorbed into systemic circulation. Enrofloxacin does not readily complex with plasma proteins, which enables metabolites to readily cross cell membranes. In humans, approximately 10% to 40% of the fluoroquinolones are bound to plasma proteins. As a group, the fluoroquinolones are widely distributed throughout the body, including the kidneys, liver, bile, uterus, fallopian tubes, bone, and inflammatory tissues [24-26].

Interestingly, enrofloxacin is the best ligand for the synthesis of metal complexes due to its bioactive properties.

Walaa El-Shwiniy et al., reported that titanium (IV), yttrium (III), zirconium (IV), palladium (II) and cerium (IV) with deprotonated endrofloxacin leads to the formation of the neutral or cationic
mononuclear complexes (Figure 1.2). These complexes are found to be antibacterial agents[27].

![Diagram](image.png)

**Fig.1.2. The coordination of metal ions with Enrofloxacin.**

Nadia El-Gamel and *et al*, reported the synthesis and characterization of both binary Co(II)-(1), Ni(II)-(2) complexes with enrofloxacin drug and ternary Co(II)-(3), Ni(II)-(4) complexes in presence of DL-alanine (H₂L₂) using physico-chemical techniques (Figure 1.3). Antimicrobial activity of these complexes were screened against two gram-positive and two gram-negative bacteria[28].
Eleni K. E and co-worker brilliantly explained that Enrofloxacin and Sparfloxacine act as bidentate deprotonated ligands bound to the metal through the pyridone oxygen and one carboxylate oxygen. The central metal ions of molybdenum and vanadyl in complexes are six-coordinate and have slightly distorted octahedral geometry (Figure 1.4). The lowest energy model structures of each complex were proposed with molecular modeling calculations. Later they have studied antimicrobial activity, DNA binding and cleavage of the complexes was reported [29,30].
Fig. 1.4. The structures of the complexes (MoO$_2$ (erx)$_2$) and VO (erx)$_2$ (H$_2$O).

Recently, Yan- Jun Wang et al., reported the two new La(III) and Sm(III) complexes with Enrofloxacin (Figure 1.5). Both of the complexes are triclinic system with space group P1. The structure of the complexes show that each rare earth atom in both complexes was nine-coordinated. Two of the enrofloxacin ions acted as tridentate chelate and bridging ligands, while the others as bidentate chelate ligands. The binding reaction between the complexes and bovine serum albumin (BSA) were studied by UV-vis absorption spectra and fluorescence spectroscopy [31].
Fig. 1.5. The coordination model of the complexes (Ln(III) = La(III), Sm (III))

1.1.2 8-hydroxyquinoline Ligand

8-hydroxyquinoline and its derivatives are widely used as analytical reagents [32-34] and anti-amoebic agents. 8-hydroxyquinoline (oxine) behaves as bidenate (N,O\(^-\)) univalent ligand to form chelates with several metal ions [35].

Liheng Feng and co-worker reported the luminescent properties of metal complex, (OXHQ)\(_3\)Al, with 8-hydroxyquinoline aluminum and electron-transporting 1,3,4-oxadiazole (Figure 1.6). The photophysical processes was investigated by UV–vis absorption and fluorescence emission spectra in dilute solution. The results showed that the luminescence quantum yield of (OXHQ)\(_3\)Al was 0.67 in DMSO and it
emitted blue light with the band gap of 3.13 eV estimated from the onset absorption [36].

Fig. 1.6. The complex of (OXHQ)$_3$Al

The metal complexes of mixed ligands of 8HQ-uracils (Figure 1.7) have been reported to provide significant cytotoxicity against human cancer cells i.e., HepG2, A549, HuCCA-1, and MOLT-3 [37].

Fig. 1.7 Structure of 8-hydroxyquinoline-uracil metal complexes

8HQ-4-benzenesulfonamide (HQMABS), shown in Figure 1.8, is a hybrid of 8HQ and sulfanilamide and was reported to be a ligand for metal complexes. This study showed that HQMABS exhibited more
potent antimicrobial activity with higher sensitivity against Gram-positive bacteria as compared to their individual parent compounds (ie, 8HQ and sulfanilamide). This demonstrates that there is a synergistic effect of 8HQ and sulfanilamide that facilitates the penetration of HQMABS into the site of action in bacterial cells. Therefore, HQMABS exhibited antimicrobial effects through a similar mechanism to that of 8HQ, as a membrane active agent via metal ion chelation. On the other hand, all metal complexes of HQMABS displayed weak to moderate activity as compared to their respective free ligand, HQMABS. Moreover, the antimicrobial activity of these compounds is dependent on the concentration, lipophilicity of the compound, nature of metal ions, geometry of the complex, and coordinate sites [38, 39].

![Chemical structures of HQMABS and metal complexes](image)

**Fig. 1.8. Chemical structures of HQMABS and metal complexes**

Ketan Patel *et al* reported the synthesis of mixed ligand complexes of transition metal with 8-quinolinols and 5-propoxymethyl-8-quinolinol (Figure 1.9). These metal complexes
proven to be active against two bacterial strains Gram +ve, two Gram–ve and two fungal strains. The activities of other compounds are moderate in compared to the standard drugs [40].

**Fig. 1.9. Chemical structures of metal complexes**

### 1.1.3. Isoniazid Ligand

The front-line drugs used in the treatment of Tuberculosis (TB) prophylaxis are isoniazid (INH), rifampicin (RF), ethambutol (ETB) and pyrazinamide (PZA). INH (C₆H₇ON₃) is the hydrazide of isonicotinic acid and was first reported in 1952 [41]. It was the most potent drug of a series of compounds based on carboxylic acid hydrazides [42]. Actually, INH is a pro-drug and is oxidatively activated by the enzyme KatG *in vivo* [43]. However, its mechanism of action is not fully understood [44].

Maria Freitas and co-worker reported synthesis of new Zn (II) complex of the mycobactericidal drug isoniazid. The complex is constituted by two isoniazid (INH) molecules, six hydration water molecules and two perchlorate counter-ions for each metal center (C₁₂H₂₆N₆Cl₂O₁₆Zn). Zinc(II) adopts a distorted octahedral geometry,
where two INH molecules coordinate in a bidentate manner through the hydrazide group (N, O) and the other two isoniazid residues complete the coordination sphere of zinc(II) through their aromatic nitrogen atoms [45].

![Possible structure of metal complexes](image)

**Fig. 1.10. Possible structure of metal complexes**

Sorkin *et al* found that the copper(II) complex of isoniazid, C$_6$H$_{11}$N$_3$SO$_7$Cu, is up to 10 times more active than free INH ligand against tubercle bacilli [46]. Toxicity against *A.salina* demonstrates a good correlation with the cytotoxic activity for some human solid tumors [47].

Krishna Sharma and co-worker reported that two new isoniazid Schiff bases, *N*-isonicotin amido-2-furanketimine(INH-F$^1$) and *N*-isonicotinamido-5-methyl-2-furanketimine (INH-F$^2$), possessing potential N and O coordination sites have been prepared by the reaction of isoniazid with 2-acetylfuran and 2-acetyl-5-methylfuran, respectively. Complexes were studied for their antimicrobial and antimycobacterial activities [48].
Fig. 1.11. Possible structures of metal complexes

Prasanna et al reveals, the Cu(II), Zn(II) and Co(II) complexes were synthesized using metal salts with different anions (Figure 1.12). The ligand acts as dibasic tridentate in copper and zinc complexes and monobasic bidentate in cobalt complexes. The ligands show keto-enol tautomerism and the enol form was involved in complexation. The ligands and complexes were subjected for antitumor, antifungal studies and also, antitubercular activities of the ligands were predicted using the PASS prediction server [49].

Fig. 1.12. Reported structures of metal complexes
Singh et al reported the synthesis and biological studies of metal complexes containing ligands such as acetophenone salicyloylhydrazone, 4-hydroxyaceto-phenonesalicyloylhydrazone (4-HOASH) and 4-hydroxyacetophenone isonicotinoylhydrazone (Figure 1.13). Resulting complexes were studied for their antimicrobial activities [50].

![Diagram of metal complex structure](image)

**Fig.1.14. Reported structures of metal complexes**

Ozturk and coworker synthesized binuclear complexes which have the general formula \([\text{M(INH)(SO}_4(\text{H}_2\text{O})_2]}_2\), \(\text{M}= \text{Co(II)}, \text{Ni(II)}, \text{Mn(II)}\) (Figure 1.14). The obtained complexes were thermally stable and they are insoluble in common organic solvents (methanol, ethanol, acetone, DMF and acetonitrile). The spectral, thermal and magnetic susceptibility data show that in all complexes, the metallic ions are in an octahedral environment and the ligand acts as neutral bidentate being coordinated through the imine nitrogen and carboxylic oxygen. All four complexes were in dimer forms [51].
1.1.4. Quinoline

In coordination chemistry, ligational behavior of multidentate ligands, especially with different donors is of interest. A coordination cavity created by oxygen, nitrogen, and sulfur donors can provide a better fit in terms of size and flexibility for transition metal(II) ions. Structural features of a heterocyclic or acyclic core molecule which contain these donors play an important role in the coordination behavior [52]. Metal complexes derived from the S, N and O donor ligands are of interest because of their versatile structural and functional properties and their applications in biochemistry, catalysis, medicine, and material research [53–55]. The task of constructing bicompartamental NO donor ligands and their complexes is of immense interest. The recent decades have seen that medicinal chemist have devoted significant effort to develop various derivatives of quinoline as antimicrobial agents. These ring system are often incorporated into drugs designed for analgesic [56],
antimalerial [57], antitubercular [58], antimicrobial [59], antiviral [60] and antihistaminic [61] activities.

Pulin Nath and coworker reported that, Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of two new multi-dentate ligands such has 3-\{(2E)-2-[(2-hydroxyquinolin-3-yl)methylidene] hydrazinyl\} quinoxalin-2-ol(QZOH) and 3-\{(2E)-2-[(2-sulfanylquinolin-3-yl)methylidene]hydrazinyl\} quinoxalin-2-ol(QZSH) were synthesized and the ligand QZOH de-protonates to give a monobasic ONO donor and binds to the divalent metal ions in bis-tridentate fashion, using two ONO donor sites. The other ligand QZSH also de-protonates to give a monobasic SNO donor and binds to the divalent metal ions in bis-tridentate fashion, using two SNO donor sites (Fig.1.16). The geometry of complexes was Octahedral and preliminary studies showed that they possess potential antimicrobial activity [62].

![Fig.1.16. The structures of metal(II) complexes](image-url)
1.2 Aim and Objectives

- Enlightened by previous works and in search of new molecules with potential biological activities the proposed title was undertaken.
- Some new Schiff bases were synthesized to be utilized as ligands and to study the ligands and their metal complexes from a structural point of view.
- These ligands with a variety of bonding interactions, tautomeric phenomena of bonding modes and hydrogen bonding interactions, were expected to provide stimulating results.
- In pursuit of new compounds with potent biological activity, mixed ligand transition metal complexes were synthesized from Enrofloxacin, 8-hydroxy quinoline and Isoniazid along with Schiff base metal complexes.
Reference


