Introduction

Metal complexes play important and diversified roles in biological systems. The role of chlorophyll, haemoglobin, carbonic anhydrase, vitamin B\textsubscript{12}, xanthine oxidase, and haemocyanin illustrates the intimate linkage between inorganic chemistry and biology. Studies of these types of metal complexes are now part of the highly expanding field, bio-inorganic chemistry.

Metal complexes find interesting applications not only in the field of biology, but also in a variety of fields like catalysis and medicine. The use of inorganic substance in medicine has its origin from the time of Hippocrates. He recommended the medicinal use of metallic salts. However, the logical bases for understanding the role of inorganic species in medicine have been established only after the advances in the field of bio-inorganic chemistry.

Metal complexes have been used as diagnostic and therapeutic agents. Studies on metal based anticancer drugs and antiarthritic agents are some currently active topics of investigation in bio-inorganic chemistry. Many metal complexes, especially those of Schiff bases, have been studied from the point of view of using them as antibacterial and anticancer drugs. In this
chapter a discussion of the Schiff bases, their metal complexes and their general application is presented.

1.1 Schiff base ligands

Schiff bases are important class of ligands due to their synthetic flexibility, their selectivity and sensitivity towards the central metal atom, structural similarities with natural biological substances. Schiff base ligands are considered as ‘privileged ligands’ (1) containing azomethine group (-HC=N-). They are formed by condensation of a primary amine and carbonyl compound. The azomethine group is particularly suited for binding to metal ions via the N atom lone pair. When the Schiff bases contain one or more donor atoms in addition to -C=N- group they act as polydentate chelating ligands or macrocycles. Both aldehydes and ketones form Schiff bases; however, the formation takes place less readily with ketone than with aldehyde. Because of the versatility of the Schiff bases very large number of complexes with interesting structures are being synthesised even now. Schiff bases derived from aliphatic aldehydes are unstable and are readily polymerizable (2) while those derived from aromatic aldehydes are more stable. The common Schiff bases are crystalline and feebly basic in nature.

Generally Schiff bases are prepared under acid or base catalysis or with heat. When two equivalents of salicylaldehyde are combined with a diamine, a particular chelating Schiff base is produced. The so-called Salen ligands, with four coordinating sites and two axial sites open to ancillary ligands, are very much like porphyrins, but can be more easily prepared. The term Salen was used only to describe the tetradeionate Schiff bases derived from ethylenediamine (Figure 1.1). The more general term Salen-type is used in the literature (1) to describe the class of (O, N, N, O) tetradeionate bis-Schiff base ligands (Figure 1.2).
Chiral salen ligands have several attractive features that constitute the basis for their utility in asymmetric reactions. The Salicylaldehyde and the diamine components are synthetically accessible and their condensation to generate the salen ligand generally proceeds in nearly quantitative yield (3).

Schiff bases have been widely used in many fields, e.g., in biological, inorganic, analytical and in drug synthesis. A large number of Schiff bases and their complexes have been studied for their interesting and important properties, e.g., catalytic activity and transfer of the amino group (4), photochromic behaviour (5).
and complexing ability towards some toxic metals (6). Some Schiff bases (Figure 1.3) are employed as fluorescent indicators by spectrofluorimetric monitoring of small changes of pH (7).

![Figure 1.3. Structure of some fluorescent Schiff bases (Adopted from Ref. 7)](image)

### 1.2 Schiff base metal complexes

Schiff base metal complexes are generally prepared by treating metal halides with Schiff base ligands under suitable experimental conditions. In special cases metal alkoxides, metal amides, metal alkyls or metal acetates have been used for the synthesis. There are numerous literature reviews on the synthesis and characterisation of Schiff base metal complexes (8-11).

Generally transition metal ions are used to prepare coordination complexes, as there is possibility of synthesising a variety of complexes with variable oxidation states, different coordination geometries and interesting physicochemical properties.
A large number of tetradendate Schiff base ligands and tridendate Schiff bases are reported in literature (12-14).

The -OH or -SH groups ortho to the azomethine moiety present in the Schiff bases can induce tautomerism in the compound and give rise to different structures.

![Tetradendate Schiff base](Adopted from Ref. 40)

![Tridendate Schiff base](Adopted from Ref. 50)

A well known Schiff base complex, N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, known as Jacobsen’s catalyst (15) is used as an asymmetric catalyst in the epoxidation reaction. It can be prepared by separating 1, 2-diaminocyclohexane into its component enantiomers and then reacting with 3,5-di-tert-butyl-2-hydroxybenzaldehyde to form a Schiff base. Jacobsen’s catalyst can be prepared from this ligand by treatment with manganese(II) acetate followed by oxidation with air, which may be isolated as the chloro derivative after the addition of lithium chloride.
1.3 Transition metal complexes of quinoxaline Schiff base

Quinoxalines, also called a benzopyrazines, is a heterocyclic compound containing a ring complex made up of a benzene ring and a pyrazine ring containing two nitrogens in mutually para position. It is isomeric with quinazoline, phthalazine and cinnoline. Quinoxalines are used as dyes, pharmaceuticals and as antibiotics e.g echinomycin, levomycin and actinoleutin. Some studies were carried out in order to explore the antitumoral properties of quinoxaline compounds (16). Quinoxaline and its analogues have been investigated as the ligands for metal complex catalysts (17). These compounds have a wide range of applications in pharmacology, bacteriology and mycology (18-23). Most of the quinoxaline derivatives are synthesised by the condensation of 1,2-diamines with aliphatic or aromatic 1, 2-dicarbonyl compounds or benzilmonoxime using solid acid catalysts (24-27). Symmetrical and unsymmetrical 2, 3-disubstituted quinoxalines are formed by the palladium-catalyzed Suzuki-Miyaura coupling of 2,3-dichloroquinoxaline with various
boronic acids (28). Pyridine-substituted quinoxalines used as good bidentate ligands for the synthesis of metal complexes with Ru or Os (29).

Transition metal complexes of Schiff base formed by the reaction of quinoxaline-2-carboxaldehyde with orthophenylenediamine, o-aminophenol, 2-aminobenzimidazole were synthesised and characterised by Chittilappilly et al. (30). Various reports of quinoxaline-2-carboxaldehyde with diamines show that quinoxaline containing transition metal complexes have lot of applications in different fields.

1.4 Applications of Schiff base metal complexes

Schiff base complexes are more selective in catalysing various reactions, such as hydroxylation, aldol condensation and epoxidation. They are also used as catalysts in various biological systems, polymers and dyes.

1.4.1 Schiff base metal complexes used as catalysts

Schiff base complexes have been widely used in both homogeneous and heterogeneous catalysed reactions and the activity depends on different factors such as nature of ligands, coordination sites and nature of metal ions. Metal complexes with vacant coordination site can act as catalysts for two reasons. Firstly, they can have several oxidation states and can take part in electron transfer reactions. Secondly, they can provide sites at which reactions can take place. This feature gives them a high probability to form the suitable intermediates required for preceding the catalytic reactions. They can show catalytic behaviour when dissolved in solutions or in solid state and act as homogeneous or heterogeneous catalysts. Literature reports reveal that a large number of Schiff base metal complexes exhibit catalytic activities including oxidations, aryl coupling reactions, aminations and carbonylations. The Schiff base complexes of platinum group metals Ru, Rh, Pd, Os, Ir, and Pt, are used for many of these transformations. As our studies are on the oxidation reaction catalysed by
Ru(III) complexes and hydrogenation reaction catalysed by Ir(III) Schiff base complexes, the discussion in the following section is limited to oxidation reaction and hydrogenation reaction.

### 1.4.1.1 Oxidation reactions

The oxidation of primary and secondary alcohols and hydrocarbons to the corresponding carbonyl compounds plays an important role in organic synthesis (31, 32). The use of oxidants such as N-methyl morpholine-N-oxide (NMO), hydrogen peroxide and inexpensive green oxidants, such as molecular oxygen or air for converting alcohols to carbonyl compounds on an industrial scale remains an important challenge in the development of industrial processes. The selective oxidation of phenol to catechol and hydroquinones is an industrially useful process and has been carried out using transition metal complexes. The oxidation of phenol in the presence of hydrogen peroxide is normally an activation process but accomplished in presence of transition metal catalysts (33-35).

The accessibility of higher oxidation states of ruthenium makes it as an excellent candidate as catalyst for oxidation reactions. Aerobic oxidation of primary alcohols catalyzed by ruthenium complexes and copper complexes has been reported (36-38). The oxidation of cyclic alcohols such as cyclopentanol, cyclohexanol, cycloheptanol and cyclooctanol to their corresponding ketones were accomplished efficiently up to 84% by the binuclear ruthenium(III) Schiff base complexes (39). Tetradedate Schiff base complexes of Ru have shown to be a good catalyst for oxidation reactions (40-43) (Figure 1.7).
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Transition metal complexes of tridentate Schiff base complexes have been successfully used in several catalytic oxidation reactions (44-45) (Figure 1.8).

Hexa-coordinated ruthenium (III) complexes, [RuX(EPh₃)₂(L)] (where X = Cl or Br; L = dibasic tridentate Schiff base ligand; E = P or As) and [RuX(EPh₃)(L)] (where L = dianion of the tetradentate Schiff base) are found to be good catalyst for the oxidation of benzyl alcohol and cyclohexanol in the presence of N-methylmorpholine-N-oxide (46,47). The relatively higher product yield obtained for the oxidation of benzyl alcohol than that for cyclohexanol was
due to the fact that the $\alpha$-CH moiety of benzyl alcohol is more acidic than that of cyclohexanol (48). Ruthenium(II) Schiff base complexes containing triphenylphosphine/ triphenylarsine (49-51) and ruthenium(III) Schiff base complexes with bidentate N, O/S donor ligands exhibited catalytic activity for the oxidation of benzyl alcohol to benzaldehyde in presence of NMO (52). The complex $[\text{Ru}^{\text{III}}(\text{amp})(\text{bipy})(\text{H}_2\text{O})]^+$ (where $\text{H}_2\text{amp}=N$-(2-hydroxyphenyl)salicyldimine and bipy= 2,2$'$-bipyridyl) is found to be an effective catalyst in the oxidation of benzene to phenol by using tert-butylhydroperoxide ($t$-BuOOH) (53).

Triphenylphosphine complexes and chalconate complexes of Ru have been found to be efficient catalysts for the aerobic oxidation of alcohols (54,55). Ruthenium(III) Schiff base complexes have two N$_2$O$_2$ metal binding sites, which are linked to each other with a biphenyl bridge and acts as potential catalyst for oxidation of wide range of primary and secondary alcohols to corresponding aldehydes or ketones with moderate to high conversion in the presence of N-methylmorpholine-N-oxide (NMO) (56) (Figure 1.9).

Figure 1.9. Structure of binuclear ruthenium(III) Schiff base complexes (Adopted from Ref. 56)
The complex, \([\text{Ru(CO)}(\text{EPh}_3)(\text{B})(\text{L})] \) \((\text{E} = \text{P or As}; \text{B} = \text{PPh}_3, \text{AsPh}_3, \text{py or pip}; \text{L} = \text{dianion of the Schiff bases derived from thiosemicarbazone with acetoacetanilide, acetoacet-o-toluidide and o-chloro acetoacetanilide})\) is reported to have catalytic activity for the oxidation of benzyl alcohol and cyclohexanol in presence of NMO (51). Schiff base complexes of Palladium containing triphenylphosphine was found to be an efficient catalyst for the oxidation of alcohols (57). Schiff base complexes containing palladium was an effective catalyst in the direct oxygenation of unfunctionalized hydrocarbons and phenols (58-61).

Cobalt (II) Schiff base complex shows high catalytic activity for the aerobic oxidation of secondary alcohols to ketones (62). Iron(III) complex with tridentate Schiff base, acetylacetone and N-hydroxyphenyl-salicylideneamine was found to act as a homogeneous catalyst in the oxidation of sulfides (63). Manganese(III) Schiff-base complex act as a catalyst for oxidation of sulfides to sulfoxides using hydrogen peroxide (64).

There have been many attempts to anchor Schiff base metal complexes to polymer supports with a view to have the advantages of heterogeneous catalysts. Polymer-supported Schiff base complexes of metal ions show high catalytic activity in oxidation reactions (65). The polymer-anchored Schiff base complexes of Cu(II), Co(II), Ni(II), Mn(II) and Fe(III) exhibited good catalytic activity for the oxidation of cyclohexene (66).

### 1.4.1.2 Hydrogenation reaction

Ruthenium-based catalytic systems are found to be effective in the transfer hydrogenation of ketones and imines (67). Although the well known BINAP–Ru(II) complex as catalyst (BINAP = 2,20-bis (diphenylphosphine)-1, 10-binaphthyl) have proved to be extremely efficient for the asymmetric hydrogenation of functionalized ketones, it has been unable to hydrogenate simple ketones that lack hetero atoms anchoring the ruthenium metal (68). A ruthenium(II)
Schiff base complex system containing diphosphine and 1,2-diamine ligands in the presence of a base and 2-propanol was proved to be an efficient catalyst for the hydrogenation of ketones under mild conditions (69). Ru(II) Schiff base complexes were also found to act catalysts for the reduction of benzene (70).

The complex [RuX(EPh₃)(L)₂] (where, E = P or As, X = Cl or Br and L = O, N donor Schiff bases) was an efficient catalyst in the transfer hydrogenation of imines to amines (71) (Figure 1.10).

![Figure 1.10. Structure of ruthenium(III) bis-bidentate Schiff base complexes (Adopted from Ref.71)](image)

Mono and dinuclear Pd(II) complexes of Schiff bases having sterically constrained tertiary butyl groups on the salicyl ring exhibit very good catalytic activity towards hydrogenation of nitrobenzene and cyclohexene (72,73). The polymer-supported palladium(II) Schiff base complexes are found to be an efficient catalyst for hydrogenation reactions (74-76). Hydrogenation of a variety of ketones catalyzed by rhodium complexes was also reported (77). Au(III) Schiff base complex was effective for the hydrogenation of 1,3-butadiene into the butenes (78).

### 1.4.2 Biological Activities

Antimicrobial and antifungal studies of Schiff base ligands and their metal complexes are reported (79-82). The biological activity of Schiff bases either increase or decrease upon chelation with metal ions.
1.4.2.1 Antimicrobial activity

Ruthenium(II) carbonyl complexes of the type [RuCl(CO)(PPh$_3$)(B)(L)] (where B = PPh$_3$, pyridine, piperidine or morpholine; L= anion of bidentate Schiff bases) exhibit antibacterial activity against $S$. aureus and gram-negative $E$. Coli. (83). Cr(III) and Zn(II) Schiff base complexes containing ethyl2-((1-hydroxynaphthalen-2-yl)methyleneamino)-5,6-dihydro-4H-cyclopenta[b] thiophene-3-carboxylate are reported to be active against pathogenic strains Listeria monocytogenes and Staphylococcus aureus (84). Co(II), Ni(II), Cu(II) and Zn(II) complexes of the Schiff base derived from vanillin and DL-α-aminobutyric acid found to exhibit higher antibacterial activity compared to the free Schiff bases (85). Cu, Ni, Fe and Zn Schiff base complexes derived from salicylaldehyde and o-amino benzoic acid shows good antibacterial activity against several pathogenic bacteria, such as Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumonia and Staphylococcus aureus (86). Zn(II), Cd(II), Ni(II) and Cu(II) complexes of furfurylidene diamine Schiff bases show antibacterial activities (87). N-5 chloro-salicylidiene tauriene Schiff bases and its Cu(II), Ni(II), complexes show antibacterial activities of Colibacillus and Pseudomonas aeruginosa (88).

Several mono and binuclear transition metal complexes of the Schiff bases derived from phenylaminoaceto hydrazide and dibenzoylemethane shows more potent bactericides and fungicides properties than those of the ligands (89). Platinum (IV) complexes [Pt(L)$_2$Cl$_2$] [where, L = benzyl-N-thiohydrazide, (benzyl-N-thio)-1, 3-propanediamine, benzaldehyde-benzyl-N-thiohydrazone and salicylaldehyde-benzyl-N-thiohydrazone] show antibacterial activity (90). Pd(II) complexes with N-substituted thiosemicarbazone show antibacterial activity against Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Vibrio cholerae (91). Various metal complexes in II$^{nd}$ and IV$^{th}$ oxidation states of Schiff bases derived from aniline show varying activities with different types of bacteria (92-94).
All the Schiff base ligands in the present study contain quinoxaline ring and quinoxaline compounds are known to have antibacterial properties. Quinoxaline derivatives are fragments of many biologically active and pharmacologically important compounds, including riboflavin (vitamin B$_2$), flavoenzymes. Quinoxaline ring is a part of a number of synthetic medicines. The well-known antibiotics echinomycin, leromycin, actinomycin and triostins are known to inhibit the growth of gram positive bacteria and active against various tumors also (95-98). The structure of the quinoxaline ligand is recognized from a great number of natural compounds such as riboflavin and molybdopterines, and can be used as antibacterial, antiviral, anticancer and insecticidal agent (99). In addition, it adopts a planar conformation when chelates to a metal ion (100-102).

1.4.2.2 Antifungal activities

Schiff bases and their metal complexes formed between furan or furyl glycoxal with various amines shows antifungal activities against helminthosporium gramineum (103). Cu(II), Ni(II), Co(II), Mn(II), Zn(II), VO(IV), Hg(II) and Cd(II) complexes of Schiff base derived from acetoacetanilido-4-aminoantipyrine with 2-aminobenzoic acid shows antifungal activities against Aspergillus niger, Aspergillus flavus, Rhizopus stolonifer, Candida albicans, Rhizoctonia bataicola and Trichoderma harizanum (104). Diethylphthalate and benzidin with Cu(II) complex shows antifungal activity against Aspergillus niger, A. flavus, Trichoderma harizanum, T. Viridae and Rhizoctonia solani (105).

1.4.3 Other applications

The iridium(III) complexes containing 2,3-diphenylquinoxalines are highly efficient and pure-red emitting materials for electrophosphorescent organic light-emitting diodes (106). Organometallic complexes possessing a third-row transition-metal element are crucial for the fabrication of highly efficient organic light-emitting diodes (OLEDs). Schiff base complexes containing Zn(II) are now a days used as electroluminescent materials eg;bis[salicylidene(4-dimethylamino)aniline]zinc(II)
complex exhibits very good light emission and charge transporting performance in organic light emitting diodes (OLEDs).

A novel electroluminescent material, 6,7-dicyano-2,3-di-[4-(2,3,4,5-tetraphenylphenyl)phenyl]quinoxaline (CPQ), which can be used as a multifunctional material in organic light-emitting diodes (OLEDs) (107) (Figure 1.11).

![Figure 1.11. Structure of CPQ in OLEDs (Adopted from Ref. 107)](image)

Metal complexes of Schiff bases have wide application in asymmetric epoxidation of unfunctionalised olefins (108,109), used in dye industry (110), antifertility and enzymatic agents (111) and used as catalysts for polymerisation reactions (112).

1.4.4 Antitumor and Cytotoxic activities

Interaction of DNA with transition metal complexes has gained considerable current interest due to its various applications in cancer research and nucleic acid chemistry (113-116). To understand clearly the binding
behaviour DNA with Schiff base metal complexes, a brief description about structure of DNA, nucleic acid and heredity, DNA binding modes and DNA cleavage is given below.

1.4.4.1 Structure of DNA

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. In a person’s body each cell has the same DNA. Most of the DNA molecules located in the cell nucleus are called nuclear DNA but a small amount of DNA can also be found in the mitochondria as mtDNA). The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases. More than 99 percent of these bases are the same in all people. The most widely accepted model for the structure of DNA molecule was proposed by Watson and Crick in 1953 for which he was awarded the Nobel Prize for Medicine in 1962. According to him the DNA molecule is a double helix (Figure.1.12). The molecule is formed by two antiparallel polynucleotide strands which are spirally coiled round each other in a right-handed helix. The two strands are held together by hydrogen bonds. The double stranded helical molecule has alternated major and minor grooves. Each strand is a long polynucleotide of deoxyribonucleotides. The two strands are complementary to each other with regards to the arrangement of the bases in the two strands. Thus, in the double helix, purines and pyrimidines exist in base pairs, i.e., (A and T) and (G and C). As a result, if the base sequence of one strand of DNA is known, the base sequence of its complementary strand can be easily deduced. The backbone of the strand is formed by alternately arranged deoxyribose sugar and phosphate molecules which are joined by the phosphodiester linkages.

The DNA molecule that Watson and Crick described was in B form. However DNA can exist in other forms also. A, B and C forms have right handed helix while Z form has left handed helix. B is the major form that is found in the cell.
The following table (1.1) summarises the features of the different forms of DNA and figure 1.13 shows different forms of DNA.

**Figure 1.12. Structure of DNA.**

**Table 1.1. Some features of DNA Forms**

<table>
<thead>
<tr>
<th>Geometry attribute</th>
<th>A-form</th>
<th>B-form</th>
<th>Z-form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helix sense</td>
<td>right-handed</td>
<td>right-handed</td>
<td>left-handed</td>
</tr>
<tr>
<td>Repeating unit</td>
<td>1 bp</td>
<td>1 bp</td>
<td>2 bp</td>
</tr>
<tr>
<td>bp/turn</td>
<td>11</td>
<td>10.5</td>
<td>12</td>
</tr>
<tr>
<td>Pitch/turn of helix</td>
<td>28.2 Å (2.82 nm)</td>
<td>33.2 Å (3.32 nm)</td>
<td>45.6 Å (4.56 nm)</td>
</tr>
<tr>
<td>Diameter</td>
<td>23 Å (2.3 nm)</td>
<td>20 Å (2.0 nm)</td>
<td>18 Å (1.8 nm)</td>
</tr>
</tbody>
</table>
1.4.4.2 Nucleic acids and heredity

DNA is the basis for the storage, transmission and expression of genetic-information, any reaction or damage caused to it will have important consequences. An organism’s genetic information is stored as a sequence of deoxyribonucleotides stung together in the DNA chain. A mechanism exists for reading the DNA, for decoding the instructions contained therein, and for implementing those instructions to carry out the myriad biochemical processes to sustain life.

Three fundamental processes take place in the transfer of genetic information:

(a) Replication is the process by which a replica or identical copy of DNA is made so that information can be preserved and handed down to offspring. This occurs when DNA double helix unwinds, complementary deoxyribonucleotides line up in order, and two new DNA molecules are produced (Fig.16)
(b) Transcription is the process by which the genetic message contained in DNA are read or transcribed and carried out of nucleus to parts of the cells called ribosomes, where protein synthesis occurs. This occurs when a segment of the DNA double helix unwinds and ribonucleotides line up to produce messenger RNA [mRNA].

(c) Translation is the process by which the genetic messages are decoded and used to build proteins. Each mRNA, which directs protein synthesis, has segments called codons along its chain. These codons are ribonucleotide triads that are recognised by small amino acids carrying molecules of transfer RNA [tRNA], which then deliver the appropriate aminoacids needed for protein synthesis.

Figure. 1.14. DNA replication
1.4.4.3 DNA Binding Modes

DNA is an important genetic material in organisms and the basis of gene expression. Small molecules can interact with DNA (117-120) through intercalative binding, groove binding, electrostatic binding/external binding (figure 1.15).

Intercalative binding results when small molecules or the drug intercalate into the nonpolar interior of the DNA helix. Aromatic group is stacked between the base pairs in this type of binding and this happens when ligands of an appropriate size and chemical nature fit themselves in between base pairs of DNA. The ligands suitable for intercalation are mostly polycyclic, aromatic, and planar, and therefore often make good nucleic acid stains. There is a current interest in designing and synthesising DNA strand, as these molecules might function as chemotherapeutic agents.

Groove binding interactions involve direct interactions of the bound molecule with edges of base pairs in either of the major (G-C) or minor (A-T) grooves of the nucleic acids. The antibiotic netropsin is a model groove binder in which methyl groups prevents intercalation (121). Binding within the major groove of the double helix is rare for small molecules.

Electrostatic interaction happens in the case of positively charged molecules. They electrostatically interact with the negatively charged phosphates backbone of DNA chain. Electrostatic attraction is generally weak under physiological conditions. Cations such as Mg\(^{2+}\) usually interact in this way (122).

The two most common binding modes are intercalation into the base pair stack at the core of the double helix, and insertion into the minor groove. Intercalation is typically observed for cationic molecules having planar aromatic rings. The positive charge need not be part of the ring system, but rather could be on a substituent. This binding mode requires two adjacent base pairs to separate from one another to create a binding pocket for the ligand (123). Minor groove binders, on the other hand, usually have at least limited flexibility since this
allows the molecule to adjust its structure to follow the groove as it twists around the central axis of the helix (124,125). Binding in the minor groove requires substantially less distortion of the DNA compared with intercalative binding. The commonly used methods to provide insight into the binding modes of small molecules are spectroscopy, UV-vis spectroscopy, fluorescence spectroscopy, circular dichroism (CD), and linear dichroism (LD).

Figure 1.15. Binding modes of DNA
Binding to DNA will often cause a change in the absorption maximum or peak extinction coefficient. But this is insufficient to determine a binding mode, equilibrium binding constants can be determined based on the concentration dependence of any observed shifts. Fluorescent small molecules not only can exhibit changes in wavelength or quantum yield upon binding, but are often able to act as energy acceptors from the DNA bases. In these experiments, the DNA is excited with UV light and one looks for fluorescence from the ligand.

Circular dichroism measures the differential absorption of right- and left-handed circularly polarized light. Circular dichroism (CD) is a useful technique for an assessment of DNA-binding mode. When a ligand is bound to the chiral DNA, CD is induced \((126,127)\). The actual sign and magnitude of the induced CD signal is complicated and depends on the binding mode, DNA sequence, and orientation of the transition dipole of the ligand. However, intercalators will often exhibit lower intensity CD spectra compared with groove binders and this is most likely due to the fact that a groove binder contacts a larger part of the helix, around 4–6 base pairs. In contrast, a simple intercalator only contacts two base pairs.

1.4.4.4 DNA Cleavage

DNA cleavage by metal complexes generally proceeds via two major pathways by oxidative pathway and hydrolytic pathway. The DNA cleavage activity of metal complexes can be targeted towards different constituents of DNA: the heterocyclic bases, deoxyribose sugar moiety and phosphodiester linkage. Oxidative cleavage of DNA takes place in the presence of additives or photo-induced DNA cleavage. Photo-cleavers require the presence of a photosensitizer that can be activated on irradiation with UV or visible light.

Many metal complexes have been studied to understand their capability in the hydrolytic cleavage of DNA which involves hydrolysis of phosphodiester bond. Nucleophilic activation is required for hydrolytic cleavage of phosphodiester bond.
due to unusual stability of the diester bond in DNA. Among several types of DNA cleavage reactions, those occurring under photoactivation are of particular importance in highly targeted chemotherapeutic applications. The reagents showing photo induced DNA cleavage have major advantage over chemical nucleases, as the latter requires a reducing agent and/or $\text{H}_2\text{O}_2$ for its activity. The reagents cleaving DNA on photoactivation generally show localised effect as they are otherwise non toxic and such compounds should be useful in the photodynamic therapy (PDT), which has emerged as a promising tool against cancer. The FDA approved PDT drug photophrin, which is a mixture of hematoporphyrin derivatives and is currently used for the treatment of lung and oesophageal cancers.

1.5 Transition metal complexes as chemical probes for DNA

The design of molecules that exhibit strong binding affinity to DNA is a challenging area of research. Such molecules can act as excellent chemotherapeutic reagents that exert their biological activity through interactions with DNA (128-133). Interactions with DNA are not the only the factors that determine the biological activity of these molecules, but their reactivity and selectivity are often correlated with their mode of binding with DNA. Therefore a better understanding of the factors that govern the interactions of small molecules with DNA has an important role in the rational design of various DNA-targeted chemotherapeutic agents and molecular probes for DNA. Of these small molecules, the bifunctional derivatives that can undergo photo induced electron-transfer processes have attracted much attention in recent years for their use in DNA detection, analysis, and cleavage (134-139). Stable and inert complexes containing active metal centres are extremely valuable as probes of biological systems.

Gupta and co-workers reported DNA binding properties of a series of transition metal complexes having potential NNO-tridentate donor Schiff bases
derived from the condensation of 2, 6-dibenzoyl 4-methylphenol with diamines (140-145). Transition metal complexes, copper (146), ruthenium (147,148) and palladium complexes (149) are used now-a-days extensively to study metal complex–DNA interactions.

Pd(II) complexes with benzothiazole-2-thiolate and bipyridyl ligands found to interact with fish sperm DNA through intercalation (150). Tetra nuclear palladium(II) complex \([\text{Pd}_4(\text{phen})_4(\mu-\text{pydc})_4].10\text{H}_2\text{O}\) where, \((\text{phen}=1, 10\text{-phenanthroline}, \text{pydc} = \text{pyridine-3,4-dicarboxylate})\) binds with FS-DNA in an intercalative way (149). Octahedral polypyridyl ruthenium complexes have excellent DNA binding and DNA cleavage abilities as well as rich photophysical and photochemical properties (151, 152). Lincoln and Norden studied the DNA binding studies for Ru(II) complexes containing 1, 10-phenanthroline (phen) and 2,2'-bipyridine as ligands (153). Lippard et al, established that square planar platinum(II) complexes containing an aromatic heterocyclic ligand could bind DNA by intercalation (154). Platinum(IV) complexes are widely applied in the treatment of various types of cancers such as testicular, ovarian and bladder carcinomas (155-159). Platinum (IV) complexes \([\text{Pt}(\text{L})_2\text{Cl}_2]\) \(\text{where, L}=\text{benzyl-N-thiohydrazide}, (\text{benzyl-N-thio})-1, 3\text{-propanediamine}, \text{benzaldehyde-benzyl-N-thiohydrazone\ and\ salicylaldehyde-benzyl-N-thiohydrazone}\) show cytotoxic activity (160). The Pt complex, \([(5,6\text{-dimethyl-1,10-phenanthroline}) (1S,2S\text{-diaminocyclohexane})\text{platinum (II)}]^2+\) shows cytotoxicity 100-fold greater than that of cisplatin in the L1210 (murine leukemia) cell line (161).

Cu(II) complexes of this Schiff base interact with native calf thymus DNA by groove or intercalating binding mode (162). Binuclear copper(II) complexes having the Schiff base ligand, N,N’-bis(3,5-tert-butylsalicylidene-2- hydroxy)-1, 3-propanediamine, are found to be effective in the cleavage of plasmid DNA in the presence of hydrogen peroxide at pH = 7.2 and 37 °C. Cu(II) Schiff base
complexes derived from diethylenetriamine and 2-thiophene-carboxaldehyde/2-furaldehyde/2-pyrrole-2-carboxaldehyde are reported to interact with DNA through a simple mode of coordination (163). Some copper complexes of the Schiff base formed between benzaldehyde and alanine have shown the ability to suppress superoxide anion free radicals (O$_2^-$) which may cause inflammation or cancer in humans (164). Copper(II) complex of Schiff bases synthesised from salicylaldehyde, 2,4-dihydroxy-benzaldehyde and glycine possess antitumor activity (165). Complete cleavage of double stranded pUC19 DNA by the Cu(II) complex, [Cu(dpq)$_2$(H$_2$O)](ClO$_4$)$_2$ (where dpq = dipyridoquinoxaline) reported by Shanta Dhar et al. (166).

![Cu(II) complex for the cleavage of pUC19 DNA](Adopted from Ref. 166)

Chromium(III) complexes derived from chiral binaphthyl Schiff base ligands (R- and S-2,2'-bis (salicylideneamino)1, 10-binaphthyl) are also interact with CT-DNA through groove binding (167). The interaction of chromium(III) Schiff base complexes, [Cr(salen)(H$_2$O)$_2$]$^+$ where salen = N,N’-ethylenebis (salicylideneimine) and [Cr(salprn)(H$_2$O)$_2$]$^+$ where salprn = N,N’-ropylenebis(salicylideneimine) with calf thymus DNA (CT-DNA) has been reported (168). 5-triethyl ammonium methyl salicylidene ortho-phenylendiimine ligand with Ni(II) strongly interacts with DNA (169). Various metal complexs of dppz, [Co(phen)(qdppz)]$^{3+}$ and [Ni(phen)qdppz]$^{2+}$ were found to be good intercalators of DNA due to the extensively $\pi$-conjugated and planar structure of this novel ligand (170). The cobalt(II) and nickel(II) complexes of salicylaldehyde-2-phenylquinoline-4-
carboxylhydrazone interact with calf-thymus DNA through groove binding (171). The interaction between [Fe(salen)]Cl and calf thymus DNA through an electrostatic binding between the Fe(Salen)$^{2+}$ cation and the phosphate groups of DNA (172). The Mn(II) complex, MnL (L=sodium(E)-3-(1-carboxyethylimino)methyl)-4-hydroxybenzenesulfonate), is also capable of intercalating into the double-stranded salmon sperm DNA (173).

1.6 Objectives and scope of the present work

The metal complexes of Schiff bases find interesting application in medicine, material science and catalysis. Hence there is a continuing interest in the synthesis of new Schiff bases and their complexes. It was therefore considered worthwhile to synthesise some new complexes of Schiff bases and study their physicochemical properties and application as oxidation catalyst, hydrogenation catalyst and DNA cleaving agents.

The work presented in this thesis is mainly concerned with metal complexes of Schiff bases containing quinoxaline ring. These Schiff bases with an electron withdrawing heterocyclic system would be interesting, as their ligand field strengths are expected to be weaker than the Schiff bases derived from salycylaldehyde. Further the complexes of these ligands are expected to behave quite differently from the salen complexes in catalytic and DNA cleaving properties. Further it was expected that complexes containing heterocyclic ring, quinoxaline, quinoline and indazole could bind DNA by intercalation and might be more effective towards DNA cleavage. Most of the complexes reported efficiently for DNA cleaving were those of palladium(II) and copper(II). Therefore the complexes of Pd(II) and copper(II) were synthesised to study DNA cleaving properties. Ru(III) and Ir(III) complexes find application in catalysis, and therefore the complexes of these metals were also synthesised. Thus the work presented in this thesis was carried out with the following objectives.
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- To synthesise Schiff bases which contain heterocyclic rings and are capable of having electronic properties in their complexes different from those of salen ligand.
- To study the nature of coordination of such Schiff bases with metal ions like Pd(II), Cu(II), Ir(III) and Ru(III)
- To study the DNA binding and cleaving ability the complexes, particularly those of Pd(II) and Ir(III).
- To undertake a qualitative study of activity of the complexes as catalysts in oxidation and hydrogenation reaction.

The following ligands were selected for the study

a) quinoxaline-2-carboxalidine-5-aminoindazole (qc5in)
b) quinoxaline-2-carboxalidine-6-aminoindazole (qc6in)
c) 3-hydroxy-quinoxaline-2-carboxalidene-5-aminoindazole (hqc5in)
d) 3-hydroxy-quinoxaline-2-carboxalidene-6-aminoindazole (hqc6in)
e) 3-hydroxyquinoxaline-2-carboxalidine-8-aminoquinolidene (hqaqn)

New complexes of Pd(II), Ru(III), Ir(III) and Cu(II) with the above mentioned ligands were synthesised and characterised. Further their DNA binding and cleaving ability and catalytic activity of the complexes in a typical oxidation and hydrogenation reaction were also studied. Details of these studies are embodied in this thesis.

1.7 References

Chapter 1


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