CHAPTER-1

Review of literature
INTRODUCTION

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. The concept of coordination chemistry was associated with complexation of metal cations (Lewis acids) by ligand (Lewis base). Metal coordination compounds are often referred to as metal complexes. Such complexes consist of a coordination center (metal or ion) and molecules that bind to it called ligand. Earlier workers considered and studied the coordination compounds of only a few metals, e.g., Pt, Co and Cr and coordination numbers of four and six. Most recent research on coordination compounds has been concerned with nearly all the metals of the periodic table with coordination numbers from two to twelve and in different oxidation states $[^1, ^2, ^{a,b,d}]$.

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, where the concept of teeth (dent) was introduced. 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 $[^1, ^{b,d}]$. 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 (Figure 1) $[^2, ^{b,d}]$. The ligands and their coordination complexes are synthesized by multi-step processes in the presence of volatile organic solvents, along with this; their limited solubility pushes the scientists and industrialists to develop biologically active coordination complexes via alternative route with desirable properties [3-5]. A metal complex can be cationic, anionic or neutral depending on the sum of the charges of the metal centers and the ligands [6]. A proliferation in this area of research is not only due to design of ligand systems with varying functionalities [7], synthetic strategies or advancement in techniques, but also due to multiple applications of these compounds in areas: medicinal $[^8, ^{a,b}]$, biochemical [9], bioinorganic [10], environmental [11], industrial [12], photochemical [13], photophysical [14], photoelectronic [15], etc.

The pioneering work carried on both trace as well as abundant elements generated coordination compounds which mimic the biologically significant metalloenzymes
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and metalloproteins [8,11], act as models to understand bio chemical effect in vitro, or in vivo [16], extending hope and promise for treatment of various diseases [8], developing photochemically driven molecular devices [17], functional model for water oxidation catalysis in photosystem-II [18], and in catalytic photocleavage of water [19], design of multinuclear structures capable of directing and modulating electron, energy transfer processes [18], also used for tanning leather, soaps, lubricants, bio fuel, paints and coatings materials [20-22]. The very success of pharmaceutical chemists in synthesizing broad ranges of carbon-based compounds tends to eliminate less common elements from their synthetic programs. The lack of experience of traditional medicinal chemists and pharmacologists in dealing with biologically active metal complexes poses a substantial activation energy barrier to their identifying active metal complexes and shepherding them to the clinic. These factors coupled with a tendency of pharmaceutical houses and government screening programs to view transition metal ions as toxic ‘heavy metals’ retards the development of metallopharmaceuticals. On the other hand, this also provides enterprising transition metal chemists with opportunities pioneer the development of exciting new drugs [23-26].

![Figure 1](image)

A tremendous amount of expansion and development in the area of coordination chemistry has exposed various facts including macrocyclic chemistry. This has led to the development of a new field of coordination chemistry, known as macrocyclic chemistry. The chemistry of macrocyclic complexes has been the subject of interest and research in recent years due to their various potential applications. They occupy much importance in the area of coordination chemistry. Macrocyclic complexes are generally prepared by template reactions, with transition
metal ions as templating agents. The metal ions direct the reaction, preferentially forming cyclic rather than oligomeric or polymeric products [26,27]. In many studies, the metal ion and host-guest studies of macrocyclic complexes are very useful. “The word macrocycle may be defined as a cyclic molecule with three or more potential donor atoms in a heteroatom ring of at least nine atoms”. It would not be an exaggeration to state that macrocyclic ligand lie at the centre of life, particularly with regard to the role of such systems in understanding and explaining the mechanism of photosynthesis [28], transport of oxygen in mammalian, and other respiratory systems and in the potency towards DNA binders with a high potential in anti-tumour therapy [29], as sensitizer for photodynamic therapy (PDT) [30] in cancers, as therapeutic reagents [31] and anti-inflammatory [32]. Apart from the biological implications, aspects of the chemistry of macrocyclic ligands are of relevance to a diverse number of other areas such as metal ion catalysis, organic synthesis, and metal ion discrimination in addition to a number of potential industrial and other applications. More recently the interest in the chemistry of macrocyclic ligands has been reborn due to their applications in supramolecular chemistry and new materials [33]. The first documented macrocycle possessing a pyrrole heterocyclic ring (Figure 2a) was synthesized in 1886 by Baeyer [34] resembling the porphyrin, via an acid catalysed condensation between pyrrole and acetone. The first macrocyclic compound prepared from a diacid was dimeric ethylene succinate reported [35] by Vorlander in 1894 (Figure 2b).

![Diagram](a)

![Diagram](b)

**Figure 2**
Prior to 19th century there existed only well established category of synthetic macrocyclic ligands containing nitrogen atoms, which were the highly conjugated phthalocyanines. Phthalocyanine (Figure 3) \[36^{a,b,c}\] and its derivatives bear a strong structural resemblance to the natural porphyrin systems. Until the 1960's only the phthalocynines and various isolated compounds such as Alphen's cyclam (Figure 4) \[37^{a,b}\].

Since then, lot of advances have taken place considerably in the late 60's and early 70's in the field of coordination chemistry of polyazamacrocycles by the pioneering and independent contributions \[38,39\] of eminent scientists like Curtis, Busch, Jager and Pedersen (Figure 5\[a,b,c,d\]). Charles J. Pedersen's publication \[39\] (1967) "Synthesis and Characterization of over 30 new cyclic polyether macrocycles" initiated tremendous and continuing interest in scientific community. These discoveries led to more systematic studies of macrocycles and their metal complexes.
This interest was stimulated by the possibilities which macrocycles offered to the creative chemist to investigate molecular recognition in new ways. The interest in design of novel macrocyclic ligands stems out mainly in view of their wide range of applications. For example macrocyclic compounds are commonplace in biological systems. The earliest known metal macrocyclic complexes are those incorporating the tetrapyrrole unit, found in naturally occurring biologically-active substances [40\textsuperscript{ab}], like haemoglobin [41,42], chlorophyll [40\textsuperscript{a}] and vitamin B\textsubscript{12} coenzyme [40\textsuperscript{a}]. Haemoglobin is quantitatively the most important hemoprotein in which the metal centre is located in a functionalized porphyrin ring known as a ‘haem’ group [42–43\textsuperscript{ab}]. Magnesium porphyrin complexes called chlorophyll play important roles in photosynthesis in green plants and some bacteria [43] while vitamin B\textsubscript{12} is a cobalt-binding corrin which acts as the cofactor for a number of enzymes for catalysis of substrate rearrangement [44] (Figure 6 and Figure 7). Macrocyclic compounds can also be used as anti-viral agents [45–47]. Their examples include the drugs AMD3100 [45,46] and bis (Zn(II) cyclen) [47\textsuperscript{ab}]. The drug AMD3100 is used in the treatment of patients who have cancers involving the blood and immune system. It is also one of the most potent anti-HIV agents known and has recently been in clinical trials against AIDS [48]. The Zn(II) complex of xyl-bicyclam i.e. bis(Zn (II) cyclen), has been shown to be ten times more active than the ligand alone [49] (Figure 8a) and (Figure 8b).
Particular interest in the clinical use of macrocycles has centered upon the paramagnetic complexes with lanthanides as contrast agents in magnetic resonance imaging (MRI) [50]. MRI contrast agents are paramagnetic substances which provide contrast between diseased and normal tissue in the body and/or show the status of organ function and blood flow [51]. A contrast agent has to be stable and inert at physiological pH and in blood serum. The enhanced stability of macrocyclic ligands fit these specific requirements. Derivatives of tetraazaacyclodecane, (a) dotarem (DOTA), (b) proHance (HPDO3A), and (c) Gadobutrol (DO3AB) have been used commercially in gadolinium (III) complexes for MRI [52] (Figure 9\textsuperscript{a,b,c}).

![Diagram of macrocyclic ligands](image)

**Figure 9**

The interaction between the macrocyclic ligand and the substrate can be fine-tuned by the appropriate selection of the binding site, and overall ligand topology, e.g., nature of donor atoms, donor set, donor array, the ligand substitution and the nature of the ligand backbone. Several classes of macrocyclic ligands have been synthesized with varying combination of aza (N), oxa (O), sulpho (S) and phospho (P) donor atoms. Other factors that are needed to be considered include:

**Electronic effects:** The charge, polarity and polarizability of the binding sites have the major influence on the complex stability [1,53].
Structural effects: These effects are very crucial for selective complexation of a substrate by a macrocyclic ligand. The number of binding sites, in general, should be at least equal to the coordination number of the cation [43].

Conformation: The existence of more than one conformation for a given macrocyclic ligand can be complicated by complexation. Greater complex stability is achieved when the confirmations built in the free ligand and complexes ligands are same [43, 53].

Shaping groups: In general saturated chains provide greater flexibility and total macrocyclic ring size is increased. However, unsaturation causes steric constraints on the molecule due to which the flexibility is at a minimum [53].

Cavity size: The number of donor atoms in the macrocyclic complexes and the imposed degree of rigidity influence the nature of the cavity. While a rigid framework results in a preformed cavity and flexibility allows latent cavity formation. During the last few decades, an extensive series of macrocyclic ligands have been synthesized and studied. These are classified into various subdivisions [1,54-64]. Some examples of macrocyclic ligands and complexes are given below (Figure 10 and Figure 11).
Macrocyclic ligands impart thermodynamic and kinetic stabilities to their complexes [65-66]. In comparison to their open chain analogs, macrocyclic ligands are far more stable as they have stereo-chemical constraints associated with their cyclic nature, which may influence their potential for metal-ion recognition [67]. The ligands coordinated to a metal ion are held in specific geometric orientations. The metal ion plays an important role in directing the steric course of the reaction and this effect is termed "metal template effect" [62]. The enhanced stability of metal complexes of macrocyclic ligands over other linear polydentate ligands is attributed to various structural effects (topological effect) such as:

Chelate effect: The linking of two donor atoms together with the metal ion results in a chelate. The linkage results in a large increase in the binding constants with metal ions as compared to the separate donor groups. This increased inertness is called as chelate effect, which is largely entropic in origin [68].

Macrocyclic effect: The enhancement of the formation constants relative to the values for the thermodynamically most favored, structurally analogous, but non cyclic-amine has been termed a macrocyclic effect by analogy with the chelate effect [62].
Cryptate effect: Addition of a second ring to a macrocyclic complexes resulting in a macrocyclic ligand, further enhances the stability of its metal complexes. The cryptate effect is often even higher than would be expected for simple addition of a second fused macrocycle. The general observation is that the affinity between the ligands of a particular kind, e.g., amines, for a given metal increases with the increasing topological constraint of the ligand system [69]. The topological constraint is in the order, simple coordination < chelation < macrocyclic effect < cryptate effect (Figure 12).

![Diagram of coordination, chelation, and cryptate effect](image)

**Figure 12**

The family of complexes with aza-macroyclic ligands has remained a focus of scientific attention for many decades [43,70,71]. To some extent the interest in macrocyclic complexes stems from the chemical properties that the macrocyclic ligands bring to the complexes. Great variety of azamacrocyclic complexes have been formed by condensation reactions in the presence of metal ions (template effect). The majority of such reactions have imine formation as ring closing step. Tetraazamacrocycles with 14 and to a lesser extent 16-membered predominate. While, amongst the various first transition series Ni(II) and Cu(II) are the most widely active metal ions in the template procedure [72]. Polyazamacrocyclic ligands are found to be very versatile ligands due to their capability of forming stable metal complexes [73] and their significant implications in analytical, biological and medicinal applications [74,75] (Figure 13a). The complexation capabilities of polyaza macrocycles are mainly governed by the macrocyclic ring size [74,75] (Figure 13b) and (Figure 13c). Among the polyazamacroycles, the tetraaza macrocyclic ligands and their metal complexes have attracted interest among the coordination chemists [76]. The important tetraazamacroycles [77-79] 14-ane N₄
(Figure 14a) 12-ane N₄ (Figure 14b) have been realized for several decades and their complexation chemistry with a large variety of metal ions has been studied thoroughly. The metal complexes of 14-ane N₄ and 12-ane N₄ represent reference systems [80] in the coordination chemistry of azamacrocycles and they are of great practical importance because the knowledge gained might be most easily transferable to the understanding of the natural products. Sulekh Chandra and co-workers have reported [74a,b,81a-b,83] the synthesis and characterization of a large number of azamacrocyclic ligands and its complexes (Figure 14c). During the past decades macrocyclic ligands have attracted widespread attention due to two unique properties: (a) their ability to discriminate among closely related metal ions based on the metal ion radius (ring size effect); (b) the significant enhancement in complex stability constant which is generally exhibited by optimally fitting macrocyclic ligands relative to their open-chain analogues (macrocyclic effect) [82,83]. The formation of macrocyclic complexes depends significantly on the dimension of internal cavity, on the rigidity of macrocycles, on the nature of its donor atoms and on the complexing properties of the anion involved in the coordination [84]. The ability to control metal ion selectivity is clearly of great interest in many areas and this selection is influenced by the nature, arrangement of donor atoms and also the ring size. There is at present a need for the investigation of selective coordination properties in novel systems [85].

\[ M = \text{Cr(III)}, \ X = \text{Cl or NO}_3 \] and \[ \text{Ph} = \text{C}_6\text{H}_5 \]

(a)
M = Mn(II), Co(II), Ni(II), Cu(II), Fe(III) and Cr(III), R = CH₃, X = Cl

Figure 13
The synthesis of macrocycles is an art in itself. There are four main approaches to prepare macrocyclic ligand systems:

2. Metal ion promoted reactions, involving condensation of noncyclic components in the presence of suitable metal ion (Template effect).
4. High dilution technique.

The preparation of the free macrocycles has certain advantages in many cases. The purification of the organic product may be more readily accomplished than purification of its complexes, and further the characterization by physical techniques becomes easier.

But the free macrocycles are often of low yield for the desired product and may have side reactions. To overcome this problem the ring closure step in the synthesis may be carried out under conditions of high dilution [86] or another way is that a rigid group may be introduced to restrict rotation in the open chain precursors which facilitates cyclization [87,88]. One of the most effective methods for the synthesis of macrocyclic complexes involves an \textit{in-situ} approach where the presence of metal ion in the cyclization reaction markedly increases the yield of the cyclic product. The metal ion may direct the condensation preferentially to cyclic rather than the polymeric products. The metal ion and the anion are important to the template process because the balance between the size of the cation and anion will determine the degree of dissociation of the metal salt in the reaction medium [89].
Macrocycles of the rigid types such as small cryptands and other preorganized macrocycles discriminate between cations that are either smaller or larger than the one with optimum size—"peak selectivity". Macrocycles of flexible type, such as larger crown ethers and cryptands discriminate principally among smaller cations—"plateau selectivity" [90]. The number, kind and arrangement of donor atoms also play an important role in macrocyclic selectivities. The oxygen donors in classical crown ethers have the largest affinities for alkali, alkaline earth and lanthanide cations. The nitrogen donor atoms favor transition metal cations and sulfur donor atoms favor Ag⁺, Pb²⁺, and Hg²⁺ [90]. The incorporation of benzene, cyclohexane, pyridine rings and other constituents into flexible macrocyclic skeletons lead to their stiffening and may alter both ligand binding strength and selectivity.

A variety of crown ethers and mixed oxathia crown have been prepared mainly by the direct synthesis [91-93]. Polyazathia macrocycles have been synthesized by reacting an appropriate polythiane with a dibromoalkane. The reaction may be sometimes aided by metal template [91,94-96] (Scheme 1 and 2).

Scheme 1

Scheme 2
Rosen and Busch [97] have been synthesized of Nickel(II) complexes of some tetradeionate thioethers as the exclusive donors. These new materials include the first low-spin nickel(II) complexes having four thioethers as the donors, and a number of tetragonal complexes formed from one of these low-spin complexes by coordination of various axial ligands (Scheme 3).

![Scheme 3](image)

(Scheme 3)

Sulfur acts as a very good ligating atom when in the form of the sulfide ion or as mercaptide ion, but complexes of sulfur as a thioether are much less abundant [1,98], though in cyclic polyether analogs, the metal ion could be coordinated in the expected enclosed fashion for several metal ions including the nickel(II) complex [99] (Figure 15) or in exodentate form found for niobium(IV) and mercury(II) chloride [1,100,101], respectively (Figure 16 and Figure 17).

![Figure 15](image)

![Figure 16](image)
Polyazathia macrocycles have been synthesized by reacting an appropriate polythiane with a dibromoalkane. The reaction may be sometimes aided by metal template [102] (Scheme 4). Broer de Groot et al. [103] synthesized large ring meta- and orthothiacyclopahnes ditopic macrocycles containing six sulphur atoms (Scheme 5). To fully encircle a first row transition metal ion a macrocycle ring size of between 13 and 16 members is required provided that the nitrogen donors are spaced such that five-, six-, or seven-membered chelate rings are produced on coordination [62,104].

\[
\text{Scheme 4}
\]
The majority of all nitrogen donor macrocycles that have been studied were tetraazamacrocycles but later on a large number of pentaazamacrocycles have also been studied. H. Keypour and co-workers have recently reported a novel series of pentaaza macrocyclic complexes (Figure 18a) [105\textsuperscript{a}] and also reported (Figure 18b) [105\textsuperscript{b}] Schiff base Mn(II) macrocycles with two 2-pyridyliclymethyl pendant arms by the metal ion-templated [1+1] cyclocondensation of 2,6-diacetylpyridine with three different branched hexadentate amines.

(Scheme 5)
Figure 18

The hexaaazamacrocycles are interesting and versatile receptor molecules being capable to coordinate one or two metal ions and in addition their protonated forms can also encapsulate anionic guests via electrostatic interactions or/and hydrogen bonds [106]. Rothermel et al. synthesized and studied hexaaazamacrocycles and it has been shown that the role of the metal ion size is essential in controlling the conformation of this type of macrocycle [107,108] (Figure 19 and 20). Octaaazamacrocycles also exhibit interesting co-ordination properties in spite of the large cavity size formed by the macrocyclic backbone, capable of forming stable mono and binuclear metal complexes, as well as stabilize various anions in their protonated form [109].

Figure 19

Figure 20
The phosphorus macrocycles have been made via template condensation of coordinated polyphosphine ligands and α,α'-dibromo-o-xylene [110] (Scheme 6). Template assisted single-stage ring closure methods have also been reported [111] (Scheme 7). A variety of mono and binuclear octaazamacrocyclic complexes have been prepared by the template condensation reaction [112,113] (Scheme 8 and 9).
\[ 4\text{NH}_2 - \text{NH}_2\text{H}_2\text{O} + 2\text{HCHO} + \text{MX}_2 + 2\text{Br(CH}_2)_n\text{Br} \]
\[
\text{MeOH}
\]

\[ M = \text{Co(II), Ni(II), Cu(II) and Zn(II), X = Cl or NO}_3; \ n = 2 \text{ or } 3 \]

Scheme 8

\[ \text{NH}_2 - \text{NH}_2 + \overset{\text{R}}{\text{R}}\overset{\text{R}}{\text{R}}\overset{\text{R}}{\text{R}} \rightarrow \overset{\text{R}}{\text{R}}\overset{\text{R}}{\text{N}}\overset{\text{N}}{\text{N}}\overset{\text{R}}{\text{R}} \]
\[ \text{R} = \text{H, glyoxal} \]
\[ \text{R} = \text{CH}_3, \text{biacetal} \]

\[ \overset{\text{R}}{\text{R}}\overset{\text{R}}{\text{R}}\overset{\text{R}}{\text{R}} + \overset{\text{Y}}{\text{Y}}\overset{\text{Y}}{\text{Y}}\overset{\text{Y}}{\text{Y}} \rightarrow \overset{\text{M}}{\text{M}}^{2+} \]
\[ \text{L}_1, \text{R} = \text{CH}_3; \text{Y} = (\text{CH}_2)_2 \]
\[ \text{L}_2, \text{R} = \text{CH}_3; \text{Y} = (\text{CH}_2)_3 \]

\[ M = \text{Co(II), Ni(II), Zn(II), X = Cl or NO}_3 \]

Scheme 9
A new pendant-arm hexaazamacrocyclic ligand, L bearing four ethyldioxolane pendant groups has been reported recently by a group of researchers (Figure 21). The complexation capability of L in a 1:1 metal-ligand molar ratio towards the transition [Co(II), Ni(II) and Cu(II)], post-transition [Zn(II), Cd(II)] and lanthanide [La(III), Ce(III), Nd(III), and Er(III)] metal ions has been investigated [114].

![Figure 21](image)

A variety of macrocyclic complexes which have adjacent nitrogen atoms (cyclic hydrazines, hydrazone or diazines) are formed by condensation of hydrazine, substituted hydrazines or hydrazones with carbonyl compounds. Tetradentate and pentadentate aza macrocycles are formed by condensation of 2,6-diacetylpyridine with hydrazine [115,116] (Figure 22) or with dihydrazines (Figure 23).

![Figure 22](image)  ![Figure 23](image)

There has been considerable interest in the chemistry of binucleating macrocycles capable of holding two transition metal ions in close proximity. A number of such complexes have been reported earlier due to their potential relevance in bioinorganic chemistry [117,118], coordination chemistry [119-121] and homogeneous catalysis [122]. These macrocycles with a large cavity, accommodating
two metal ions can be used to bind the metal centre at fixed distances. In these systems there is often an additional internal or external bridging group, which completes the structure of the binuclear species which has the advantage of being relatively rigid and thus gives structurally well defined moieties [123]. Many metalloenzymes contains two copper ions in their active site that operate cooperatively [124]. Binuclear macrocyclic complexes having similar and dissimilar coordination sites are of particular interest because such macrocyclic complexes are thermodynamically stabilized and kinetically retarded with regard to metal dissociation and metal substitution relative to metal complexes of acyclic ligands [125]. In physicochemical aspects these binuclear copper complexes have noteworthy significance as new inorganic materials showing various magnetic properties with anti-ferromagnetic coupling depending upon the bridge angle and degree of distortion [126,127]. Dinuclear copper containing proteins play an important role in biology, including dioxygen transport or activation, electron transfer, reduction of nitrogen oxides and hydrolytic chemistry [128]. A group of researchers have reported [129,130] wide variety of binuclear macrocyclic complexes. In order to obtain binuclear macrocyclic complexes, three main synthetic strategies have been pursued (i) synthesis of large macrocycles or macrobicycles able to incorporate two metal ions [131], (ii) synthesis of bis (macrocycles) [132] and (iii) use of chelating agents bridging two macrocyclic units [133]. Each metal centre can interact with the other one directly by electrostatic forces or chemical bonding and indirectly via electron delocalization through the macrocyclic framework or bridging ligands. A variety of binuclear macrocyclic ligands with two similar and dissimilar metal centers have been reported [134,135] (Figure 24 and 25).

\[ M = \text{Co(II), Ni(II), Cu(II) and Zn(II)} \]
\[ X = \text{Cl or Br} \]

Figure 24

\[ X = \text{Cl}^-, \text{Br}^-, \text{NO}_3^- \text{ or NCS}^- \]

Figure 25
Schiff base macrocycles have been of remarkable versatility in macrocyclic and supramolecular chemistry [136,137]. They were among the first artificial macrocyclic complexes to be synthesized. These macrocycles have played a vital role in the development of synthetic macrocycles. Condensation of carbonyl compounds with primary amines was discovered in 1864 by Hugo Schiff [137,138]. Macrocyclic Schiff base complexes have attracted much attention since early 1980s [139]. However, template synthesis of the macrocyclic Schiff bases on metal ions has two substantial disadvantages. First, rather often it does not allow one to synthesize metal-free macrocyclic Schiff bases. The common structural feature of these compounds is the azomethine group with a general formula, RHC=NR', (R and R' alkyl, aryl, cyclo alkyl or heterocyclic groups) which may be variously substituted. Presence of lone pair of electron in an sp² hybridised orbital of nitrogen atom of the azomethine group is of considerable chemical importance and impart excellent chelating ability especially when used in combination with one or more donor atoms close to the azomethine group [137,140]. The effective method for the synthesis of Schiff base macrocyclic complexes which involves the condensation reaction between suitable dicarbonyl compounds and primary diamines carried out in the presence of appropriate metal ions which serve as templates in directing the steric course of the reaction. In this metal template effect the metal ion-through coordination organizes the linear substrates to facilitate the condensation process which may lead toward either [1+1] or [2+2] macrocyclic products (Figure 26). Whether the cyclization proceeds through an intramolecular condensation to give a [1+1] macrocycle or through the bimolecular steps leading to a [2+2] macrocycle depends on the relative proportions of linear substrates, the nature of the cation and reactants (chain length number and position of donor atoms), the ratio of the template ionic radius to the cavity size, conformation of acyclic intermediates and coordination properties of counter ions [141-143].

Substitution of the coordinated metal ion by other metal ions which are not effective as templates has also been achieved by the transmetallation [144,145] (metal exchange) reaction. In this way a wide range of mono- and dinuclear complexes have been prepared. A metal which cannot serve as a template for particular macrocycle can effectively coordinate to form stable complexes if reacted with the free macrocycles.
For the larger Schiff base macrocycle, transition metal ions are ineffective as templates. Consequently the kinetic lability of the metal ions present in the macrocyclic complexes of the s- and p- block cations enable the generation of the corresponding transition and inner-transition metal complexes by transmetallation reactions. On treating the kinetically labile complexes with a second metal ion, the liberated macrocycle is captured and stabilized by coordination to the new metal ion before decomposition [147-149].

The transmetallation is the resultant of the stability differentials of the parent complex and the complex of the transmetallating ion. Thus, for the transmetallation to be feasible the stability of the complex of the transmetallating ion should be greater than that of the parent complex. Transmetallation has been exploited to synthesize a range of dinuclear complexes of [2+2] macrocycles from the corresponding mononuclear complexes. The sequence of reaction involving ring closure by transmetallation with a concomitant ring contraction and reduction in ligand denticity and subsequent ring expansion in the presence of larger metal ions (Scheme 10). Thus it has been observed that when the metal ion is too small for the macrocyclic cavity, ring contraction takes place by transmetallation with a concomitant reduction in
ligand denticity and ring size. The complex of the ring contracted macrocycle undergoes ring expansion in presence of large metal ions [150-154].

Scheme 10

The metal complexes of multidentate Schiff base ligands are quite interesting due to their ability to bind with one, two or more metal centers [155-157]. The chemistry of nickel complexes with multidentate Schiff base ligands has attracted particular attention, as this metal is able to exhibit several oxidation states in the complexes [156]. Such complexes with different oxidation states have a strong role in bioinorganic chemistry and may provide the basis of models for active sites of biological systems [157, 158]. These complexes can also act as potential catalysts [159-161]. The instant and enduring popularity of Schiff base ligands undoubtedly stem from the ease with which they can be synthesized, their bewildering versatility and their wide ranging complexing ability once formed. The literature clearly shows that the study of this diverse ligand system is linked with many of the key advances made in inorganic chemistry. Not only have they played a seminal role in the development of modern coordination chemistry, but they can also be found at key points in the development of inorganic biochemistry [162]. They have also been extensively employed in the understanding of molecular
processes occurring in biochemistry, material science, catalysis, encapsulation, activation, hydrometallurgy, transport and separation phenomena [163]. A broad variety of Schiff base macrocycles can be utilized for metal biosites modeling [164], catalyst for many organic reactions, models of reaction centers of metalloenzymes [165], non-linear optical materials [166], effective catalysts in asymmetric synthesis [167], luminescence materials [168], DNA binding and cleavage reagents etc [169]. The template potential of a metal ion in the formation of a Schiff base macrocycle depends on the preference of the cations for stereochemistries (octahedral, tetragonal, square planar or square pyramidal) in which the bonding d-orbital are in orthogonal arrangements. The size of the cation is important to direct the Schiff base condensation, as there should be compatibility between the radius of the templating cation and the hole or cavity of the macrocyclic framework. As indicated by Cation-Cavity “Best fit” the smaller metal ion favors the formation of “1+1” macrocycle while a larger metal ion favors the “2+2” macrocycle. Recently, H. Khanmohammadi et al. have reported [170] the synthesis of new asymmetric heptaaza Schiff base macrocyclic complex of Mn(II) ion by templated [1+1] cyclocondensation of N,N,N',N'-tetrakis (2-aminoethyl) propane-1,2-diamine with 2,6-diacetylpyridine (Scheme 11).

![Scheme 11](image)

Abdallah and co-workers reported a new Schiff base ligand and its metal complexes with transition metal ions (Figure 27 and Figure 28) [138,171]. Sinha et al. reported heterocyclic Schiff base derived from the condensation reactions of indole-3-carboxaldehyde with different L-amino acids [172]. Damagk et al. reported mononuclear copper complexes and in vivo antitumor activity (Figure 29 and Figure 30) [173,174^ab]. Another interesting macrocyclic copper complex (Figure 31) was active in vitro and in vivo against P 388 leukaemia and B16 melanoma cells [175].
A variety of hexaazamacrocyclic complexes bearing pendant arm were synthesized by template condensation of 1,2-diaminobenzene and 1,4-phenylenediamine through formaldehyde in the presence of transition metal ions \([176^a]\) (Figure 32a). Tetraazamacrocyclic complexes formed by [2+2] template condensation reaction of diphenylglyoxal and 3,4-diaminotoluene with Co(II), Ni(II), Cu(II) and Zn(II) ions. These complexes were tested for their \emph{in vitro} antibacterial activity against gram-positive and gram-negative bacterial strains (Figure 32b) \([176^b]\).

\(M = \text{Co(II), Ni(II), Cu(II) and Zn(II)} \quad X = \text{Cl or NO}_3\)
Transition metal complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) with Schiff base ligand, derived from condensation of vanillin with 2-aminophenol were synthesized in alcoholic medium (Figure 33) [177]. K. Mohanan et al. reported synthesis, characterization and antimicrobial activity of ligands and their trivalent metal complexes of cobalt(III), manganese(III) and iron(III) (Figure 34) [178].
M = Co(III), Fe(III) or Mn(III); X = Cl/OAc/NO₃

Figure 34

Recently template synthesis of mononuclear 18-membered zinc(II) tetraiminemacro cyclic complexes by the Schiff base condensation of 2,6-diformyl-4-methylphenol with 4-nitro-, 4-chloro- and 4-methyl-o-phenylenediamines in the presence of hydrated zinc(II) nitrates was studied. All the synthesized complexes were screened for their antibacterial activity against Staphylococcus epidermidis, Staphylococcus aureus, Klebsiella pneumoniae and Salmonella typhi and were found to be active antibacterial agents. (Figure 35a,b,c) [179].
F. Arjmand have reported new enantiomeric Cu(II) and Zn(II) L-\(\beta\)-fluorobenzothiazole benzothiazole Schiff base-valine complexes as chemotherapeutic agents and studied DNA binding profile, cleavage activity, MTT assay and cell imaging studies (Figure 36) [180].

\[ M = \text{Cu(II) and Zn(II)} \]

S. Tabassum et al. synthesized and characterized of Cu\(\text{II}\\/\text{Ni}^{\text{II}}\\/\text{Sn}^{\text{IV}}\) heterobimetallic complexes which act as antitumor chemotherapeutics. The cleavage activity of diphenyltin analog supports its potential use as cancer chemotherapeutic agent particularly selective for human leukemic cell line K-562 (Figure 37) [181].
Figure 37

D. Kumar and Sandhya have been reported eight new bivalent tetraazamacroyclic complexes which have been synthesized by the reaction of oxaloyldihydrazide and benzyl/acetylacetone by adopting template method. Synthesized dihydrazide and all complexes were screened for antimicrobial activity against two bacteria Staphylococcus aureus and Escherichia coli and two fungi Aspergillus niger and Aspergillus flavus. The Cu(II) complexes were found most active against both bacteria while Zn(II) complex was most active against both fungi [182].

Tahir et al. have reported a number of macrocycles and their transition metal complexes of varying ring sizes [183] (Figure 38), bis macrocycles [184] (Figure 39), Schiff base complexes [185] (Figure 40), aromatic macrocyclic complexes [186] (Figure 41), mixed donors [187,188] (Figure 42 and Figure 43), and also reported Schiff base macrocyclic ligands and their complexes prepared by condensation reaction between 2'-methylacetocetanilide and aliphatic diamines and their comparative study of interaction of calf thymus DNA with copper(II) complexes (Figure 44) [189], DNA binding study of copper complex of 18-membered tetraethia macrocyclic complex Figure 45 [190], and also reported anticancer studies of Schiff base complexes Figure 46 [191].
M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II), X = Cl or NO₃

**Figure 38**

M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II), X = Cl or NO₃

**Figure 39**

M = Co(II), Ni(II), Cu(II) and Zn(II), X = Cl or NO₃

**Figure 40**
Chapter-1

\[ \text{Figure 41} \]

\[ \text{Figure 42} \]

\[ \text{Figure 43} \]
M = Co(II), Ni(II), Cu(II) and Zn(II)

Figure 44

M = Co(II), Ni(II), Cu(II) and Zn(II), X = Cl or NO₃

Figure 45

M = Co(II), Ni(II), Cd(II) and Sn(II), Ph = C₆H₅, X = Cl or NO₃

Figure 46
Chapter-1

The brief introduction in the area of coordination chemistry discussed in the above paragraphs does not enumerate the holistic coverage. Therefore, only the relevant and parallel work has been included in introduction of the Ph.D. thesis. In view of the fact that macrocyclic coordination chemistry still forms the basis of extensive research due to multiple applications, it was thought worth to develop this research area by synthesizing and characterizing coordination compounds of transition metal complexes to explore their structural features and to investigate their potential biological applications. This Ph.D. thesis deals with the synthesis and characterization of 13-membered pentaaza bis (macrocyclic) complexes, 15-membered tetraaza Schiff base complexes, 16-membered octaazamacrocyclic complexes of transition metals and their biological studies: in vitro antimicrobial (antibacterial and antifungal) and anticancer activities.
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CHAPTER-2
Experimental Methods