Chapter 1

Review
There has been considerable attention towards the coordination chemistry of macrocyclic ligands as a fascinating area of research to inorganic chemists. The design of novel macrocyclic ligands stems out mainly in view of their use as models to elaborate the metal ions interaction and to get an inside of the coordinating sites in metallo-proteins and in biological systems. These macrocyclic ligands also serve as models to study magnetic exchange phenomena and also as therapeutic reagents in chelate therapy for the treatment of metal intoxication. Metal encapsulated derivatives help to study the guest–host interaction and in catalysis. These areas have led to a considerable efforts in developing reliable inexpensive synthetic routes for this category of compounds. Several classes of macrocyclic ligands which include saturated polyaza macrocycles, imine Schiff bases, polyoxa macrocycle, polyoxaaaza macrocycle, crown ethers, cryptands, compartmental macrocyclic ligands that form mononuclear and heteronuclear complexes, pH responsive macrocycle and macrocycle containing pendant arms have been synthesized and their reactivities towards metallic substrates have been reported. These macrocycles which contain varying combination of aza[N], oxa[O], phospha[P] and sulphha[S] ligating atoms can be tailored
to accommodate specific metal ions vis-a-vis cavity size or hole size of the macrocycle. A macrocycle is defined as a cyclic compound having at least nine, or more, heteroatomic members and with three, or more, ligating centres\textsuperscript{1-4}. They have an internal hydrophilic cavity formed by donor atoms, and an external hydrophobic framework made up of chains. The three-dimensional extension of macromonocycles in which more than one macrocycle is incorporated in the same molecule are called macropolycycles\textsuperscript{5}. An intriguing feature of macrocyclic chemistry is that the design and synthesis of macrocycles with varying ring size and donor sites, with specific properties can be achieved with relative ease. Over the past 2-3 decades an extensive series of macrocyclic ligands have been prepared and studied which are classified into various subdivisions\textsuperscript{5}. The following types are a few of the ligands classified into various different subdivisions [Figure 1.1 (I-XIV)].

(i) Coronands\textsuperscript{6,7} (I) are macrocyclic species which contain various \textbf{heteroatoms} as binding sites. The complexes of these ligands are referred to as coronate.

(ii) Crown ethers\textsuperscript{8} (II) and (III) are macrocyclic polyethers.

(iii) Macrocyclic polycarbonyls are cyclic ligands containing carbonyl functionalities, the macrocyclic oligoketones\textsuperscript{9} (IV), the polylactones\textsuperscript{10} (V) and the polylactams\textsuperscript{11} (VI).
(iv) Spherands\textsuperscript{12} (VII) and hemispherands\textsuperscript{13} (VIII) are macrocyclic ligands which consist of arrangements of phenyl groups.

(v) Calixarenes\textsuperscript{14} (IX), from the Greek meaning chalice and arene (incorporation of aromatic rings), are macrocyclic phenol–formaldehyde condensation products.

(vi) Cyclodextrins\textsuperscript{15} are naturally occurring cyclic oligomer of 1,4-glucopyranosides.

(vii) Catenands\textsuperscript{16} (X) are two separate, but interlocked macrocyclic ligands.

(viii) Cryptands\textsuperscript{17,18} (XI) and (XII) are macropolycyclic receptor molecules which provide a cavity for inclusion of a variety of substrates. Cryptate refers to their complexes.

(ix) Sepulchrates\textsuperscript{19} (XIII) are polyaza macrobicycles analogous to the cryptands.

(x) Speleands\textsuperscript{20} (XIV) are hollow, macropolycyclic molecules formed by the combination of polar binding units with rigid shaping groups. Speleale refers to the complex.
Figure 1.1 (I-XIV)
There are two main approaches to prepare such systems:

a) Conventional organic synthesis of the ligands.

b) Metal ion promoted reaction involving condensation of noncyclic components in the presence of suitable metal ion (in short termed as metal template procedure).

A great variety of azamacrocyclic complexes have been formed by condensation reactions in the presence of metal ions (metal template). The majority of such reactions have imine formation as the ring closing step. Tetrazamacroycles 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 used in the template procedure\textsuperscript{21}. The design of the ligand capable of forming stable metal complexes would not only allow further study of the coordination properties of the metal ion but also would enable to exploit in detail, certain important emerging properties of these complexes. The design of macrocyclic Schiff bases have provided their potential use as metal specific ligand allowing incorporation of even two or more metal ions simultaneously.

As described above the most effective method for the synthesis of macrocyclic complexes involves an in-situ approach wherein the presence of metal ion in the cyclization reaction markedly increases the yield of the
cyclic product. The metal ion plays an important role in directing the steric course of the reaction and this effect has been termed as the metal-template effect\textsuperscript{22}. The first example of deliberate synthesis of a macrocycle using this procedure was described\textsuperscript{23} by Thompson and Busch (Figure 1.2),

![Figure 1.2](image1.png)

although Curtis had previously demonstrated the potential of template assembly through his observation that the reaction of Ni(en)\textsubscript{3}(ClO\textsubscript{4})\textsubscript{2} (en = 1,2-diaminoethane) and acetone yields isomeric tetraazamacrocyclic complexes\textsuperscript{24} of Ni(II) (Figure 1.3).

![Figure 1.3](image2.png)

Metal salts also facilitate the self-condensation of o-phthalonitrile to give metal-phthalocyanin complexes\textsuperscript{25} (Figure 1.4).
Schiff base condensation between a carbonyl compound and an organic diamine in the presence of a metal ion to yield an imine linkage has led to the synthesis of many azamacrocycle complexes\textsuperscript{26,27} as illustrated below by Figure 1.5.

The lighter transition metal ions (members of first transition series) have been extensively used in the template syntheses of tetradeutate macrocycles. The directional influence of the orthogonal d-orbitals is regarded as instrumental in guiding the synthetic pathway. The last two decade or so has seen an extension of this technique and successful
attempts have been made to even use organo-transition metal derivatives as templating instruments to generate a few tridentate cyclononane complexes\textsuperscript{28,29}. This has been further expanded to include the s- and p-block cations which guide the synthesis of penta- and hexa-dentate Schiff base macrocycles\textsuperscript{30,31} and a series of tetraimine Schiff base macrocycles\textsuperscript{32,33}. The smaller Schiff base macrocycles have been termed as “1+1” macrocycles and the tetraimine derivatives as “2+2” macrocycles in reference to the number of head and lateral units present\textsuperscript{32}. The metal complexes of the “2+2” macrocycles may be mono- or di-nuclear in nature.

It has been generally found that for the larger Schiff base macrocycles the transition metal cations are ineffective as templates\textsuperscript{28}. Trans-metallation reactions\textsuperscript{28,31-33} have been successfully employed for such macrocycles. This approach has been particularly successful when applied to the generation of di-nuclear Cu(II) complexes of tetraamine Schiff base macrocycles. The latter have been used as speculative models for the bimetallobiosites in cupro-proteins such as haemocyanin and tyrosinase\textsuperscript{34}. The size of the cation used as the template has proved to be of importance in directing the pathway for the Schiff base systems (Figure 1.6).

The compatibility between the size of the metal ion and the cavity size (hole) of the macrocycles contributes to the effectiveness of the
Figure 1.6 Schiff base macrocycle synthesis in the presence of non–transition metal templates
synthetic pathway and to the geometry of the resulting complexes. Furthermore, the similarity in ionic radii between the alkaline earth metal cations and lanthanide (III) cations suggests that the latter could also be used as efficient templating devices. However, the lanthanide template lacks the metal directing capabilities of the transition metals but it provides a more flexible coordination environment.

It is well known that nature prefers macrocyclic derivatives for many fundamental biological functions such as photosynthesis and transport of oxygen in mammalian and other respiratory system\textsuperscript{35}. Generally, such derivatives have higher thermodynamic and kinetic stability than a cyclic ones\textsuperscript{3}. Studies of the geometry around the metal centre present in the active sites and its electronic and magnetic behaviour are highly cumbersome due to the fact that the metal ion is embedded in a biopolymer backbone\textsuperscript{36}. Therefore, the synthesis and studies of model systems are important which may provide more insight about the cooperative phenomenon, electron transfer and magnetic interaction between metal centres\textsuperscript{37,38}. Macrocyclic ligand have been successfully exploited for diverse processes such as separation of ions by transport through artificial and natural membranes, liquid–liquid, solid–liquid phase transfer reactions, preparation of ion selective electrodes, isotope separation and in the understanding of some natural processes through mimicry of metallo-enzymes\textsuperscript{39}. The use of macrocyclic ligands for
selective metal complex formation has received considerable attention over many years\textsuperscript{40}. Attempts have also been made by workers to investigate the interaction of mixed donor macrocyclic ligands incorporating four, five and eight potential donor sites with a range of latter first row transition and post transition metal ions\textsuperscript{40}. These studies were aimed to achieve metal ion discrimination within the respective ligand series and to understand the reason for such discrimination when it was observed. The strategies employed in such studies were to investigate metal ion behaviour across a "matrix" of ligands, whose structures vary in stepwise manner\textsuperscript{40}. Parameters such as the macrocyclic ring size, donor atoms set and degree of ligand substitution were varied to form the required matrix.

The crown poly-ethers are examples of macrocycles which have been prepared mainly by the direct synthesis\textsuperscript{8,41,42} (Figure 1.7) employing non-template procedure.

![Figure 1.7](image)

Mixed oxa-thia crowns are obtained from oligo (ethylene glycol) dichloride reactions with dithiols\textsuperscript{43-45} (Figure 1.8).
Another series of ether-ester and ether-ester-amide macrocycles are derived from acid chlorides and oligo (ethylene glycols) or ethylene diamine typified\(^{46,47}\) by Figure 1.9.

Polythia macrocycles are obtained by reacting an appropriate polythiane with a dibromoalkane (Figure 1.10). In some cases the reactions are metal template\(^{23,48}\) assisted (Figure 1.11).
The phosphorus macrocycles are made via template condensation\textsuperscript{49} of coordinated polyphosphine ligands and a dibromoalkane (Figure 1.12).

Template assisted single-stage ring closure methods are also reported\textsuperscript{50} (Figure 1.13).
The arsenic donor macrocycles are synthesized\textsuperscript{51} by reacting lithiated polyarsene with dichloroalkane (Figure 1.14).

![Figure 1.14](image)

Macropolycycles are in general made by progressive construction of the framework through a series of reactions of the appropriate reactants\textsuperscript{16-18,52-55}.

It is now understood that there is a need in several areas for a rational approach towards ligand design for selective complexation of metal ion in solution\textsuperscript{56}. A major determinant of the metal ions specificity is expected to be the nature of the metal binding residues. Metal binding studies have shown the importance of ligand field stabilization energy and hard-soft acid-base effects\textsuperscript{57} in determining metal ion specificity. Macrocycles containing 'hard' ether-oxygen centers show binding preferences towards 'hard' alkali and alkaline earth cations, but shift their preference towards 'soft' heavy metal ions\textsuperscript{58-61} with incorporation of 'soft' sulfide or amine linkages in place of ether linkages. The selection of appropriate 'shaping groups' and hetero-atom at the binding site is crucial for selective complexation of substrate by a macrocyclic ligand.
Macrocycles with saturated chains and large cavity sizes have greater flexibility\textsuperscript{1-4}. Unsaturation imposes steric constraints on the molecule to the extent that when donor atoms are connected via an aromatic system e.g. pathalocyanines, flexibility is at minimum. The nature of cavity is influenced by the number of donor atoms in the macrocycle and its degree of flexibility. While a rigid framework results in a preformed cavity, flexibility allows latent cavity formation. The selectivities observed for the crown ether and cryptands in the complexation of the alkali and alkaline earth metal ions are closely related to the cavity size, although in exceedingly large cavities, selectivity may become lost due to preponderance of flexibility\textsuperscript{1-4}.

If a substrate is too small for a given ligand cavity the resulting complex will be destabilized by substrate-receptor repulsions and ligand deformation. On the other hand, for a substrate that is too large for a macrocycle, destabilized complexes will result due to poor ligand-substrate binding contact or unfavorable ligand deformation in order to achieve binding contact. Ligand flexibility and shape are also controlled by the dimensionality of the macrocycles. The dimensionality of a macrocycle is defined\textsuperscript{1-5} in terms of the highest number of edges to which a vertex is attached. A vertex is mostly a donor atom, but not always. Simple unappended monocycles are bidimensional while the bi- as well as tri-cyclic systems are tridimensional. Macrobicyclic ligands are inherently
more rigid than their monocyclic analogues. Flexibility can be increased by increasing the chain length. The incorporation of functional groups such as amide, ester, thioester, urethane and thiourea provides polar binding sites and additional ligand stiffening. Macrocycles with chiral units in their skeleton serves as receptors for chiral substrates. A wide range of ligands can be designed of desired properties from a thorough knowledge of binding sites and its environment, and topology that determines the ease of complex formation. As polydentate ligands, the macrocycles are capable of interacting with a broad range of metal ions as well as non-metal ions (complex cations, anions, neutral molecules). The macrocyclic ligands offer unusually high ligand field strengths to those metal ions having the ionic diameter matched to the macrocyclic cavities. The resulting complexes are extremely stable thermodynamically and kinetically. Macrocyclic ligands are also efficient in stabilizing high oxidation states of metal ions that are not readily attainable such as Cu(III) and Ni(III). This property enables them to undergo a diverse array of chemical reactions, such as ligand oxidative dehydrogenation, metal alkylation, ligand substitution and hydrogenation. The success of some of these reactions is closely linked with the ability of higher and lower oxidation states of metal ions in these complexes to function as reactive intermediates.
The enhanced stability of metal complexes of macrocyclic ligands over other linear polydentate ligands is attributed to various structural effects namely, macrocyclic effect, chelate effect, cryptate effect and multiple juxtapositional fixedness (MJF)\(^{72}\). These effects which have been found to give stronger complexes arise from the structural factors, size, shape or geometry, connectedness or topology and rigidity of the macrocycle. Figure 1.15 displays the general observation that the affinity between ligands of a particular kind, amines in the example, and a given metal increases with the increasing topological constraint of the ligand system. The topological constraint is in the order, simple coordination < chelation < macrocyclic effect < cryptate effect.

**Increasing Topological Constraint**

Coordination → Chelation → Macrocycle Effect → Cryptate Effect

**Topology and the Chelate, Macrocycle and Cryptate Effect**

Figure 1.15
Figure 1.15 also illustrates the chelate effect, which increases with the number of donors linked together through the series ethylenediamine (en), diethylenetriamine and N,N′-bis(2-aminoethyl)-1,3-diaminopropane, the macrocyclic effect for the case of the tetra-aza cyclotetradecane and the cryptate effect for the last structure. These topological effects are displayed in both kinetic and thermodynamic properties. This is manifested in equilibrium constants and is accompanied by exceptional kinetic inertness. Cabbiness and Margerum were the first to name the ‘macrocyclic effect’ while reporting the first quantitative study of the relative thermodynamic and kinetic stability of tetra-aza macrocycles. Subsequent studies on tetra-thia macrocycles, alkali metal complexes of crown ethers and various metal ion derivatives of cryptates have confirmed the macrocyclic effect for macrocyclic ligands. Dissociation of the macrocycle from the metal complex is not an easy process because a macrocycle has no terminal groups. It would then require some profound change in the conformation of the chelated macrocycle to occur for the displacement process, probably, by the folding of the ligand. This shows that there is a substantial barrier in the way of macrocycle dissociation. Quantitative studies have shown that the rates of dissociation of macrocyclic ligands are much more greatly retarded than the corresponding rates of simple complex formation.
Martell and Hancock have pointed out the fact that molecular organization is higher with macrocycles than with linear tetratdentate ligands. The increased molecular organization associated with the macrocyclic ligand will raise it to a high energy state with respect to conformation, dipole-dipole repulsion and solvation. The cost in energy for complex formation can then, in fair measure, be prepaid during the synthesis of preorganized ligands or hosts\textsuperscript{80}. The benefit of increasingly rigid structures of preorganized ligands presently called preorganization\textsuperscript{81} was earlier labelled multiple juxtapositional fixedness\textsuperscript{82,83}. The extent to which this is realized depends on the topology\textsuperscript{78,80} and rigidity of the ligand and on the complimentarity (size, geometry, electronics) of the metal ion. Complementarity\textsuperscript{78,80} provides the minimal requirements for strong affinity while topology and rigidity constraints are the design factors available for arbitrarily enhancing affinity.

Lehn and Sauvage have reported\textsuperscript{84} the advantage of the cryptate (macropolycyclic) effect on the affinities for the hard alkali and alkaline earth metal ions. This macrobicyclic ligands exhibit remarkably larger stabilization than an ordinary macrocycle does.

Virtually, all types of metal ions have been complexed with macrocyclic ligands\textsuperscript{1-4}. Complexes of transition metal ions have been studied extensively with tetra-aza macrocycles\textsuperscript{85}, naturally occurring porphyrin and porphyrin related complexes\textsuperscript{86-89}.
Complexes of crown ethers$^{8,41}$ and cryptands figure prominently with alkali and alkaline earth metal ions. Macro cyclic complexes of lanthanides and actinides are now attracting much attention.$^{90}$ Macrocyclic complexes of lanthanides have now many medical applications such as radio-immunoscintigraphy ($\gamma$-Scintigraphy)$^{91,92}$ and positron emission tomography$^{93,94}$ as contrast-enhancing agents in magnetic resonance imaging and other clinical applications$^{95}$.

The template potential of metal ions in the formation of macrocycle depends on the preference of the cations for sterochemistries i.e. octahedral, tetragonal, square planner or square pyramidal in which the bonding d-orbitals are in orthogonal arrangements. This has been observed when condensation of 2,6-diacetylpyridine with triethylenetetraamine,$N,N'$-bis-(3-aminopropyl)ethylene diamine, or $N,N'$-bis(2-aminoethyl)-1,3-propanediamine using Cu(II) or Ni (II) ions were found unsuccessful. However, for these reactions the metal ions Mg(II), Mn(II), Fe(II), Co(II), Zn(II), Cd(II) and Hg(II) served as effective templating agents leading to the formation of 7-co ordinate complexes of the macrocycles shown in Figures 1.16 and 1.17.
It is therefore, apparent that 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\textsuperscript{90,96}.

It is, well, established that template condensation of Ni(II) and Cu(II) acyclic tetra-amine complexes with formaldehyde and nucleophiles is a convenient way to prepare functionalized macrocyclic complexes\textsuperscript{97}. The use of primary amines as nucleophiles in these reactions results in the formation of complexes of azacyclam ligands possessing non-coordinated nitrogen atoms in the macrocyclic backbone\textsuperscript{98}. Such molecules are unstable in the free i.e. non-coordinated state owing to the hydrolytic instability of the diaminomethylene fragments\textsuperscript{99}. This feature restricts their applicability for the preparation of complexes with metals other than Ni or Cu. From this point of view, the employment of C–H
acid, which form C–C bonds upon interaction with formaldehyde, as nucleophiles seems more preferable, but their assortment is rather limited. However, variety of substituted nitroalkane and malonic acid esters have been exploited as locking fragments in the preparation of a number of functionalized macrocycles$^{98,100}$. However, reactions using malonic acid ester as locking agent usually result in low yields of the desired product. The barbituric acid as capping agent has been successfully employed in formaldehyde–amine condensation to result in macrocyclic compounds$^{101}$ as shown in Figure 1.18.

(i) Barbituric acid, HCHO, MeOH - $\text{H}_2\text{O}$ (6:1 v/v), reflux 4 h. Axial $\text{H}_2\text{O}$ and $\text{ClO}_4$ in 2 are omitted.

Figure 1.18

Ideally, the complex is formed by adding the required metal ion to a preformed macrocycle but there are disadvantage to this approach as the synthesis of the macrocycle often results in a low yield of the desired product with side reaction e.g. polymerization etc. In order to avoid this problem the ring closure step in the synthesis may be carried out under condition of “high dilution”$^{102}$ or “rigid groups” may be introduced to
restrict rotation and internal entropy losses in the open-chain precursors$^{103-105}$ and so facilitates cyclization.

The synthesis of macrocycle in a non-template procedure has been achieved by established procedure$^{106}$ i.e. utilizing Schiff base condensation of the respective dialdehydes and the appropriate linear di- or tri-amine derivates in methanol giving the corresponding cyclic products. A similar non-template reaction procedure was also employed to obtain the related four-, five- and eight-donor macrocycles$^{107-109}$. It has been mentioned by these authors that it is not necessary to carry out the ring closing reaction under high dilution condition as a prerequisite for the non-template procedure. In most of the previous attempts use of linear polyamines in Schiff base condensation reactions sometimes resulted in a non-terminal (secondary) amine reacting in concert with a primary amine and an aldehyde group to yield a 1,3-diazacyclopentane or a 1,3-diazacyclohexane (aminal) derivative$^{110}$.

The synthesis of functionalized macrocycle is an important step in the investigation of molecular recognition properties of large ring compounds$^{111}$. Functionalized polyazamacrocycles with pendant arms or exocyclic substituents are reported$^{26}$, which exhibit flexibility and possess big cavity sizes to effectively encapsulate large cations or metal ions. The ability of certain molecules to bind specifically, a closely related species in biological system is of great significance. Macropolyamines are one
among such class of compounds that have been structurally modified to develop ligands with specific properties. Macrocyclic polyamines containing 1, 2 and 3 carbonyl functions whose structure bear dual feature of macrocyclic polyamines and oligopeptides show more selectivity as compared to the carbonyl free systems. Until early 1970's macrocyclic polyamines (e.g. cyclam) had been used mostly as chelating agents for transition metal ions for study of basic coordination chemistry. They possess some common properties as those of nitrogen-containing bifunctional molecules (Figure 1.19 I-IV) such as porphyrins, peptides (e.g. Gly-Gly-His), or biogenic polyamines (e.g. spermine) and even more variety of functions.

Highly functionalized macrocycles can be designed by considering the properties of macrocyclic polyamines which arises mainly from the composite nitrogen donor and their basicities. For example very distorted metal complexes could be constructed due to extraordinary
macrocyclic stabilities. There are reports\textsuperscript{120,121} that metal ions bigger than the expected cavity size of the macrocycles lie out of the macrocyclic basal plane and chelation/coordination is achieved by distorting the geometry. Reaction intermediate or reaction transition states are extremely reactive molecules may also be designed. In other words, new metal catalysts of metallo enzyme model may be easily tailored from the basic macrocyclic structures\textsuperscript{119}.

It is apparent that the structural variations that occurs between individual macrocyclic ligands tends to be reflected in a predictable manner by the respective log k values for metal complex formation. Thus, for example, the individual log k values show the expected dependence on the nature of the donor set present\textsuperscript{122}. The magnitude of a particular log k value tends to be strongly influenced by the number of secondary nitrogen donors present in the corresponding ligand. If one restricts comparison to mixed oxygen-nitrogen donor system having identical back bone structure, then the log k values for the complexes of a given metal with ligand strongly reflects the number of nitrogen present in the respective mixed donor sets which are in accord with the expected weak donor capacity of ether oxygen towards the metal ions\textsuperscript{123-128}.

A free amide is a weak coordinating group due to weakly basic amide oxygen atom and weak acidity of hydrogen. This results in weak complexation at that site. On the other hand substitution of nitrogen
bound hydrogen by a metal ion should create a very strong bond. However, the very weak acidity of hydrogen (pKa 15)\textsuperscript{129,130} implies that alkali and alkaline earth metal ion will not effect its removal. Transition metals are more effective as compared to alkali and alkaline earth metals but suffer metal ion hydrolysis and precipitation in neutral and basic solutions\textsuperscript{131}. To avoid this hydrolysis an effective anchor ligand (primary ligating site) bound to metal ion is required to inhibit metal ion hydrolysis\textsuperscript{131}. If a macrocycle does not contain amide bonds, amine groups within the ring or terminal groups, drastic condition are needed for complex formation.

![Figure 1.20 (I-III)](attachment:image)

Polymine macrocycles possess cavity capable of providing a favourable environment for transition metal ions\textsuperscript{132}. The strength of the ion binding is determined by ion size, macrocyclic cavity size, and ligand conformation\textsuperscript{133,134}. Typically the 14-membered tetraamine macrocycles cyclam, monooxocyclam, and dioxocyclam (mono- and di-amide
macrocycles) (Figure 1.20 I-III) incorporate metal ions into their cavities and form a stable square planer complex with several configurations like that known for porphyrins and corrins. Macrocyclic oxopolyamines are unique metal chelators, their structure bears dual features of macrocyclic polyamines and oligopeptides. The oxopolyamines owing to their important biological functions and some unusual properties have been extensively studied and structural features are well recognized. The two amido groups in macrocyclic dioxotetramines are equivalent when coordinated to 3d metal ion, amido groups get deprotonated simultaneously as the presence of a non-deprotonated or a singly deprotonated complex is unlikely.

Certain macrocyclic polyamines can enclose alkali and alkaline earth metal ions. In contrast, oligopeptides such as triglycine (Figure 1.21 I) and tetracycline (Figure 1.21 II and III) complex with a very limited number of metal ions i.e. Cu(II), Ni(II), Co(II) and Pd(II) and the resulting complex dissociate easy and fast.

![Diagram](image)

**Figure 1.21 (I-III)**

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Complexation studies with variety of macrocyclic oxo-polyamines in reference to oxo free polyamines have led to the conclusion that the macrocyclic oxo-tetraamine, in general, are more selective than oxo free systems in interaction with metal ions.

A combination of amide groups and soft donors (e.g. sulfur donors) in the macrocyclic skeleton accommodates only noble metal ions, Pt(II) and Pd(II), but not the common transition metal ions. The stability of the complexes formed varies with the ring sizes, which are more stable than the corresponding peptide complexes. The thermodynamic stability of the macrocyclic system is suggested to result from the unusual slow dissociation (or substitution) rates. It is well recognized that organic amide group stabilize high oxidation states of metal ions when coordinated with the deprotonated nitrogens. The Cu(III) and Ni(III) macrocyclic complexes, in general, are kinetically more stable and hence their lives are longer than peptide complexes. A fundamental knowledge of oxo-(mono/di) macrocyclic complexes have been found applicable in the oxygenase model and the superoxide dismutase model. Their distinctive properties have found wider scope of chemical and biochemical applications in fields such as selective metal ion transport, as redox enzymes models and stabilization of unusual oxidation states of metal ions. Subsequent deprotonation of the amide protons give the stable macrocyclic complexes. Although mono-, di-
and tri-amide macrocycles derived from cyclam are now well known, however those bearing exclusively amide donor groups (i.e. tetraamide macrocycles) are quite rare. The possibility of effecting metal insertions into polyamide macrocycles free of any accessible donor groups is usually, difficult and this has been one of the reasons hindering the development of this area.

Margerum and Rybka have reported\textsuperscript{153,154} the detailed study of a macrocyclic tetrapeptide complexation (Figure 1.22 I) with copper(II). This important contribution demonstrated that metal insertion to give a tetraamido-N complex is possible for a macrocyclic tetraamide. In this system metal insertion was performed in the presence of aqueous sodium hydroxide using freshly precipitated Cu(OH)\textsubscript{2}. Similar approach adopted by Collins and co-workers for effecting metal insertion into macrocyclic tetraamides (Figure 1.22 II, III) reported by them was not successful for any of the first row metals from chromium to copper\textsuperscript{155}. They have reported the reactions of these macrocycles with the divalent metals including chromium\textsuperscript{156}, manganese\textsuperscript{157,158}, iron\textsuperscript{159}, cobalt\textsuperscript{160}, nickel\textsuperscript{161}, and copper\textsuperscript{162}. The key features of their method included the use of an anhydrous solvent (THF), low temperature when bases strong enough to decompose THF are employed, strong bases to deprotonate the ligand prior to metal addition and the use of divalent transition metal salts which have some solubility in THF\textsuperscript{155}. The tetraamido-N ligands are strongly
donating upon tetra-deprotonation and resistant to oxidative destruction. The isolation and characterization of several higher oxidation state metal complexes implied that the macrocycles possess the property of being compatible with strongly oxidizing coordination environments. Such ligands would allow the isolation and characterization of the reactive intermediates formed at the reaction transition states in the homogeneous catalytic oxidation processes$^{157,162}$.

Figure 1.22 (I-III)
References


