Chapter 1

An Overview of Polyaza \([N_x]\) Macrocycles: Scope and Prospects of Macrocyclic Moieties as Encapsulating/Chelating Ligands
The cyclic compounds with nine or more members including all the hetero atoms and possessed with three or more electron rich donor atoms have been termed as macrocycle systems [1]. These donor atoms are usually positioned so that upon coordination, preferably five or six membered chelate rings are formed with the metal ion. The interests in the chemistry of macrocyclic compounds have increased rapidly during the last 2 – 3 decades or so because of their many biological and industrial applications. Henceforth, macrocyclic ligands can be placed under the class of polydentate ligands containing donor atoms either incorporated in or less commonly attached to the cyclic backbone. In other words, multidentate macrocyclic ligands are cyclic molecules consisting of an organic framework interspersed with heteroatoms, which are capable of interacting with a variety of species. Macropolycyclic ligands are a three – dimensional extension of macromonocycles, in which more than one macrocycle is incorporated in the same molecule. Macrocyclic and macropolycyclic molecules display unique and excited chemistries in that they can function as receptors for substrates of widely differing physical and chemical properties and upon complexation can drastically alter these properties. Selective substrate recognition, stable complex formation, transport capabilities and catalysis are examples of the wide-ranging properties of these molecules. A review on the coordination chemistry of macrocyclic and macropolycyclic ligands cannot be comprehensive in a few pages, however, some important findings in this field are outlined here.

**Terminology:**

Useful definitions of terms occurring frequently in dealing with this chemistry are presented below.

1. A complex is an entity consisting of two or more molecular species, which interact in such a manner that they are being held together in a physically characterisable structural relationship.

2. Receptor and substrate are terms describing the species involved in complex formation. The terms receptor and substrate usually imply that the complex formed has the well – defined structural and chemical properties of a supra-
molecule, as in biological receptor-substrate associations.

3. **Host and guest** are terms covering all kinds of inter-molecular associations from the well-defined supra-molecules to loosely packed solid-state inclusion compounds.

4. Homo-nuclear refers to multi-site binding in which identical substrates are bound.

5. Hetero-nuclear refers to multi-site binding in which different substrates are bound.

6. Monotopic refers to receptors which possess only one binding subunit.

7. Ditopic or polytopic receptors are those which possess two or more binding subunits.

8. A cascade complex is one in which an additional substrate may be included between metal cations (or eventually anions) in a ditopic or polytopic ligand.

9. Macrocyclic and macropolycyclic effects designate the great thermodynamic stability of macrocyclic ligand complexes compared to non-macro cyclic analogues.

Common nomenclature has developed over the years, in particular for coronand and cryptand ligands. The crown-type ligands are commonly named according to the total number of atoms in the macrocyclic ring enclosed in brackets and preceding the classification (crown), followed by the number of oxygens.

The number of donor atoms in the macrocycle and the imposed degree of rigidity influence the nature of cavity. While a rigid framework results in a preformed cavity, flexibility allows latent cavity formation. The selectivities observed for the crown ethers and cryptands in the complexation of the alkali and alkaline earth metal ions are closely related to cavity size, although in exceedingly large cavities selectivity may become lost due to a preponderance of flexibility [2]. 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 unfavourable ligand deformation in order to achieve binding contact. This influence of

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cavity size also pertains to cylindrical cavities, for which the length of chain substrates compared to cylindrical macrocyclic cavity size has been found to be distinctly correlated to substrate selectivity and complex stability [3-5].

The incorporation of chiral units within the macrocyclic skeleton is an important route to the design of macrocyclic receptors capable of enantiomeric or chiral substrate recognition. In order to achieve this goal, the receptor must display fine structures as a result of chiral barriers, which then allows diastereomeric receptor–substrate interactions, in addition to maintaining the desired cavity properties [6-8].

The coordination chemistry of multidentate ligands has been a field of intensive research amongst inorganic chemists and bioinorganic chemists over the past decades. There is no dearth of literature on the synthetic structural or functional aspects of such ligand. Naturally, occurring macrocyclic complexes like vitamin B12, metalloporphyrins, chlorophyll and the industrially important metal-phthalocyanine have been studied for many years [1,9-12]. Synthetic ring complexes which copy [13] aspects of these naturally occurring complicated macrocyclic ring systems are known. Investigations of such compounds find an analogy with the natural systems, and were the main goal of early stage research. Although, the results obtained do not always closely parallel those in nature, the biochemical role of metal ions in the natural system is better understood through these synthetic models. At present the emphasis of research is ranged over the whole spectrum of chemistry. The wide spread interests in these molecules are due to their unique and exciting chemistries in that they can serve as receptors for the metal ions, molecular cations, neutral molecules or molecular ions of widely differing physical and chemical properties. Moreover, metal ions complexation can drastically alter these properties. They possess several desirable properties such as selective substrate recognition, stable complex formation, transport capabilities and catalysis [14].

In general, macrocyclic ligands are organic heterocyclic compounds containing between 10 to 30 atoms in a ring. They have an internal hydrophilic cavity formed by the donor atoms and an external hydrophobic cavity formed with the external hydrophobic framework made up of chains. An interesting feature of macrocyclic compounds is that the design and syntheses with varying ring sizes and donor sites, with specific properties
can be achieved with relative ease. Extensive series of macrocyclic ligands have been prepared and studied, which are classified into various subdivisions [14]. IUPAC nomenclature of these compounds is cumbersome and not illustrative. Simple but not unequivocally defined notations have been suggested for certain types of macrocycles. However, sophisticated compounds when represented by their structural formulae provide a clear picture of the macrocycles.

Macrocyclic ligands have been prepared using conventional organic synthesis as well as employing in-situ procedures involving cyclization in the presence of a metal ion [15-18]. In some reactions the presence of a metal ion is required. The metal ion is said to act as a template and such reactions have been termed as metal assisted template synthesis. Schiff base condensation between a carbonyl compound and an organic amine in presence of a metal ion [19,20] to yield an imine linkage has led to the synthesis of many aza macrocycle complexes as illustrated below in Figure 1.1.

The crown polyethers are examples of macrocycles which have been prepared [21-23] mainly by the direct synthesis as shown in Figure 1.2 a. Mixed oxa – thia crowns are obtained [24-26] from oligo (ethylene glycol) dichloride reactions with dithiol (Figure 1.2 b).
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Ether – ester macrocycles are derived [27,28] from acid chloride and oligo (ethylene glycol) (Figure 1.3).

Figure 1.2

The main target in macrocyclic design is to synthesize macrocycles, which are able to discriminate among the different metal cations. Many factors influencing the selectivities of macrocycles for cations have been determined. These include macrocyclic cavity dimensions, shape and topology, substituent effect, conformational flexibility or rigidity and donor atom type, number and arrangement [29-32]. For the first row transition metal ions the consecutive increments in radii are not large so it becomes difficult to effect discrimination solely on the cation-cavity best-fit. The other features involved are

- The natural order of stability constants.
- The metal ion-ligand donor compatibility derived from hard and soft acid and base character.
- The preferentially site symmetry required [33] by the metal ion.

The match between the cation and the macrocyclic cavity diameter is especially visible in small cryptands and other preorganized macrocycles, such as calixarenes and

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spherands. In these cases, size selectivity goes together with lack of flexibility of the ring, which is too rigid to undergo conformational changes upon complexation. The influence of the cavity shape is envisaged in some calixarenes which exhibit very high "coordination geometry selectivity" specially toward UO$_2^{2+}$ [34]. Small cryptands and other reorganized rigid type macrocycles, discriminate between cations that are either smaller or larger than the one with the optimum size i.e "peak selectivity". Macrocycles of flexible cavity type, such as larger crown ethers and cryptands, discriminate principally among smaller cations i.e "plateau selectivity" [35].

Fenton and co-workers [33,36,37] have investigated the design and synthesis of oxaaaza macrocyclic ligands with varying ring sizes and flexibilities including both weak and strong donor atoms in varied donor sets and sequences in order to define the principles underlying transition metal selectivity by the macrocyclic ligands. It was realized that discrimination for different metal ions to be structurally or stereochemically based. This behavioural trend has been well documented through the work of Tasker and co-workers [38,39]. Lindoy and co-workers [40] have developed the design strategies for new macrocyclic ligand systems, which are able to recognize particular transition and post-transition metal ions. Differences in log $k$ values were used both as a monitor and control of the ligand synthesis. Starting from a particular macrocyclic ligand which gives rise to discrimination, the related derivatives can be synthesized. This is done through a systematic tuning-up process by employing a typical three-dimensional structural matrix procedure. The macrocyclic ring substitution is achieved along another direction, and varying the donor atom type along the third dimension. This matrix procedure [41] enables the effects of incremental structural variations on log $k$ difference to be followed.

The metal complexes usually are synthesized by the reaction of the required metal ions with the preformed ligands. However, there are potential disadvantages, if this method is adopted for the preparation of metal complexes of preformed macrocycles. The synthesis of a macrocycle in the free form (non-template) results in a low yield of the desired product with a number of side reactions in which polymerization predominates. In order to circumvent this problem the ring closure step in the synthesis may be carried out under conditions of high dilution [47] or a rigid group be introduced to restrict
rotation in the open-chain precursors [43-45], thereby, facilitating cyclization. An effective method for the synthesis of macrocyclic complexes involves an in-situ approach wherein the presence of metal ion in the cyclization reaction enhances the yield of the cyclic product. The metal ion play an important role in directing the steric course of the reaction and this effect is termed as "metal template effect" [46]. The metal ion may direct the condensation preferentially to cyclic rather than polymeric products (the kinetic template effect) or stabilize the macrocycle once formed (the thermodynamic template effect). In another attempts the presence of mineral acids like HCl, HNO₃ or HClO₄ in place of metal ions [46] has also facilitated the cyclization step by minimizing the unwanted side reactions.

Substitution of the coordinated metal ion by other metal ions, which are not effective as templates, has also been achieved by the transmetalation (metal exchange) reaction. In this way a wide range of mono- and di- nuclear complexes [44] have been prepared. A metal ion which can not serve as a template for a particular macrocycle can effectively coordinate to form stable complexes if reacted with the free macrocycles. For the large Schiff base macrocycles, the transition metal ions often are ineffective as templates. Consequently, the kinetic stability of the metal ions present in the macrocyclic complexes of the s- and p- block cation some times enable the generation of corresponding transition and inner- transition metal complexes by transmetallation with a second 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. In this way a range of Ni³⁺ and Cu²⁺ complexes (Figure 1.5) of macrocycles have been obtained which are not accessible by the direct template methods [47-57].

The transmetallation is the resultant of the stability difference 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 [47-50] to synthesize a range of di-nuclear complexes of 2:2 macrocycles from the corresponding mononuclear complexes. However, in some cases transmetallation is accompanied by a change
in geometry of the resulting complex. In some transmetallation reactions new types of microcyclic ligands arising from ring expansion or contraction are also obtained which depends on the demands and the size of the transmetallating ions [47,58,59].

The kinetic lability of the lanthanide complexes has also been exploited to generate the corresponding complexes of the transition metals. For examples, reactions of the lanthanum (III) complexes of 1.5 as well as of 1.6 with Cu$^{2+}$ yield di-nuclear copper (II) complexes depending on the reaction conditions [60] as shown in the following equations.

\[
\begin{align*}
[\text{La(L)(NO}_3)_3] + 2 \text{Cu(ClO}_4)_2.6\text{H}_2\text{O} & \xrightarrow{\text{EtOH}} [\text{Cu(}L\text{(OH)}_2]\text{(ClO}_4)_3.3\text{H}_2\text{O} + \text{La(NO}_3)_3 \\
[\text{La(L)(NO}_3)_3] + 6 \text{Cu(ClO}_4)_2.6\text{H}_2\text{O} & \xrightarrow{\text{EtOH}} [\text{Cu(}L\text{(μ-OH)}_2]\text{(ClO}_4)_3 + \text{La(NO}_3)_3 \\
\end{align*}
\]

where \(L = 1.5\) or 1.6.
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The kinetic lability of the metals present in the generation of macrocyclic complexes derived from the use of alkaline earth and main group template agents has enabled the generation of the corresponding transition metal complexes through transmetallation reaction [47,48,50,51,57]. This approach has been particularly successful when applied to the generation of dinuclear copper(II) complexes of tetraimine Schiff base macrocycles, used as speculative models for the bimetallobiosites in cupro-proteins such as haemocyanin and tryosinase [61]. The size of the cation used as template has proved to be of importance in directing the synthetic pathway in the Schiff base systems, shown by the scheme in Figure 1.7.

Of the alkaline earth cations only magnesium generates the pentadentate “1:1” macrocycle but it is ineffective in generating the hexadentate “1:1” macrocycle which is readily synthesized in the presence of the large cations Ca\(^{2+}\), Sr\(^{2+}\), Ba\(^{2+}\) and Pb\(^{2+}\). These cations, however, generate the “2:2” macrocycle derived from the components giving the “1:1” macrocycle with magnesium [50,51,55]. A further size related effect is metal-induced ring contraction. If the metal ion is too small for the macrocyclic cavity and there is a functional group (=NH or –OH) available for addition to the imine bond then this can add to produce a smaller, more accommodating cavity for the available metal ions [62,63]. Most of the early work featured the use of transition metal ions in the template synthesis of tetradentate macrocycles. The directional influence of the orthogonal d-orbital is also instrumental in guiding the synthetic pathway. The last two decade has seen an extension of this technique, which was further extended to include the use of organo-transition metal derivatives to generate tridentate cyclononane complexes [64,65]. The smaller Schiff base macrocycles have been termed “1:1” macrocycles. The metal complexes of “2:2” macrocycles may be mono- or di-nuclear in nature.

Macrocycles with pendant groups represented a class of ligands (deliberately synthesis) to achieve metal ion discrimination. Macrocycles with pendant groups bearing neutral oxygen donors have been synthesized in abundance mainly due to the synthetic simplicity [66-72]. The hydroxy ethyl pendant groups produce a marked decrease in complex stability for small metal ions and a moderate increase in complex stability for the large Pb\(^{2+}\) ion and so. This is in accordance with the rule regarding the effect of
neutral oxygen donors on the complex stability in relation to metal ion size. This led to a simple generalization that in order to increase the selectivity of macrocycles for large metal ions, all that is necessary is to add groups bearing neutral oxygen donors [73]. The synthesis of highly functionalized macrocyclic receptors is an important initial step in the investigation of molecular recognition properties of these large ring compounds [74].

Condensation reactions between a diamine and ethylene diamine tetraacetic acid (EDTA) dianhydride or diethylenetriaminepentaacetic acid (DTPA) dianhydride give dioxopolyazacyclo alkanes with differing ring size and with a different number of pendant carboxymethyl groups [74]. The use of 1,3-diaminopropane as a diamine gives 13-membered [75] macrocycles (Figure 1.8). These macrocyclic ligands form ionic metal chelates with bivalent and trivalent metal ions respectively. The partial double-bond character of the C – N bond in an amide group decreases the flexibility of the macrocyclic ring and defines the conformation of the ligands. When an additional

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A great deal of interest has been directed to synthesize functionally modified macrocycles. Modified ligands, achieved by variation of the heteroatoms or ring substituents as well as ring size can greatly influence observed selectively patterns. The ability of certain molecules to bind specifically a closely related species in biological systems is of great significance. Macrocyclic polyamines are one among such class of compounds that have been structurally modified to develop ligands with specific properties.

The secondary amine donors in macrocyclic polyamines can synthetically be substituted with amides or with other heteroatoms, which may also act as characteristic donors. These simple structural modifications would dramatically alter the complexing behaviour [76]. An amide group offers two potential binding atoms, the oxygen and nitrogen for complexation of protons and metal ions. They are planar with 40% double – bond character in carbon – nitrogen bond and strongly favours the trans form as shown below:
A free or unconnected amide is a weak coordinating group due to the weakly basic amide oxygen atom and weak acidity of hydrogen. With such weakly basic O- atoms (pKa = 1) [77,78] strong metal complexation will not occur at that site. The metal ion interaction with the neutral nitrogen atom also provides only the weak complexes. 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) [79,80] implies that alkali and alkaline earth metal ions will not effect its removal. Transition metal ions promise to be more effective in substituting nitrogen bound amide hydrogen but they suffer metal ion hydrolysis and precipitation in neutral and basic solutions [81]. Therefore, metal ion must be capable of substituting a nitrogen bound amide hydrogen. To do so in neutral solutions, metal ions require an effective anchor (primary ligating sites) to inhibit metal ion hydrolysis [81].

The synthesis of functionalized macarocycle is an important step in the investigation of molecular recognition properties of large ring compounds [82]. Functionalized polyazamacrocycles with pendant arms or exocyclic substituents are reported [83], 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. Kimura and Kodama have reported detailed studies of macrocyclic polyamines with one-, two- and three- substituted amide groups [84] (Figure 1.10). These classes of compounds are known as macrocyclic oxopolyamines. Their structures bear the dual features of macrocyclic polyamines and oligopeptides. As polyamines donor ligands, they have affinities for a broad range of heavy metal ions and transition metal ions. Certain macrocyclic polyamines can enclose alkali and alkaline earth metal ions [85,86].

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 [84]. Until early 1970’s macrocyclic polyamines (e.g. cyclam) had been used mostly as chelating agents for transition metal ions of basic
coordination chemistry [87,88]. They possess some common properties as those of nitrogen-containing bifunctional molecules (Figure 1.11, a-d) such as porphyrins [87],

\[
\begin{align*}
X = Y = Z = H_2 \\
X = O, Y = Z = H_2 \\
X = Y = O, Z = H_2 \\
X = Y = Z = O
\end{align*}
\]

Figure 1.10

peptides (e.g. Gly-Gly-His) [89,90] or biogenic polyamines (e.g. spermine) and even more variety of functions [91,92].

Highly functionalized macrocycles can be designed by considering the properties of macrocyclic polyamines, which arise mainly from the composite nitrogen donors and their basicities [76], for example very distorted metal complexes could be constructed due to extraordinary macrocyclic stabilities. There are reports [93,94] 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 intermediates or reaction transition states that are extremely reactive molecules may also

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be designed. In other words, new metal catalysts of metallo-enzyme models may be easily tailored from the basic macrocyclic structures [76].

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) [79,80] 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 [81]. To avoid this hydrolysis, an effective anchor ligand (Primary Ligating site) bound to metal is required to inhibit metal ion hydrolysis [81]. If a macrocycle does not contain amide bonds, amine groups within the ring or terminal groups, drastic condition are needed for complex formation.

![Diagram](image)

Figure 1.12

Polyamine macrocycles possess cavity capable of providing a favourable environment for transition metal ions [95]. The strength of the ion binding is determined by ion size, macrocyclic cavity size, and ligand conformation [96,97]. Typically the 14-membered tetraamine macrocycles, cyclam, monooxocyclam and dioxocyclam (mono- and di-amide macrocycles) (Figure 1.12, a-c) incorporate metal ions into their cavities and form a stable square-planar complex with several configuration [97,98] like that known for porphyrins and corrins. Macrocyclic oxopolyamines are unique metal chelators, their structure bears dual features of macrocyclic polyamines and oligo-peptides.

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[99-102]. The oxopolyamines owing to their important biological functions and some unusual properties have been extensively studied and structural features are well recognized [85.99-102]. The two amido groups in macrocyclic dioxotetraamines are equivalent when coordinated to 3d metal ion, the amido groups get deprotonated simultaneously [85] as the presence of a non-deprotonated or a singly deprotonated complexes is unlikely [102].

Certain macrocyclic polyamines can enclose alkali and alkaline earth metal ions [85,86]. In contrast, oligopeptides such as triglycine (Figure 1.13 a-b) and tetraglycine (Figure 1.13 c) complex with a very limited number of metal ions i.e. Cu$^{2+}$, Ni$^{2+}$, Co$^{2+}$ and Pd$^{2+}$ and the resulting complex dissociate easy and fast [103,104].

Complexation studies [89,90,102-107] with the variety of macrocyclic oxopolyamines 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.

![Figure 1.13](image)

A combination of amide groups and soft donors (e.g. sulfur donors) in the macrocyclic skeleton accommodates only nobel metal ions, Pt$^{2+}$ and Pd$^{2+}$, but not the common transition metal ions [108,109]. 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

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nitrogens. The $\text{Cu}^{2+}$ and $\text{Ni}^{2+}$ macrocyclic complexes, in general, are kinetically more stable and hence their lives are longer than peptide complexes [84]. A fundamental knowledge of oxo-(mono/di) macrocyclic complexes have been found applicable in the oxygenase model [110] and the superoxide dismutase model [111,112]. 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 [113]. Subsequent deprotonation of the amide protons give the stable macrocyclic complexes [114]. Although mono-, di- and tri-amide macrocycles derived form cyclam are now well known, however, those bearing exclusively amide donor groups (i.e. tetraamine 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 [114,115] the detailed study of a macrocyclic tetrapeptide complexation (Figure 1.14a) with $\text{Cu}^{2+}$. 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 $\text{Cu(OH)}_2$. Similar approach adopted by Collins and co-workers for effecting metal insertion into macroyclic tetraamides (Figure 1.14 b,c) reported by them was not successfull for any of the first row metals from Chromium to Copper [116]. They have reported the reactions of these macrocycles with the divalent metals including Chromium [117], manganese [118,119], Iron [120], Cobalt [121], nickel [122] and copper [123]. 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 [116]. The tetraamido-N ligands are strongly donating upon tetra-deprotonation and resistant to oxidative destruction. The isolation and characterization of several higher oxidation states metal complexes implied that the macrocycles possess the property of being compatible with strongly oxidizing coordination environments. Such ligands would

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allow the isolation and characterization of the reactive intermediates formed at the reaction transition states in the homogeneous catalytic oxidation processes [118,123].

Metal complexes containing saturated polyaza macrocyclic ligands bearing pendant donors functions, often N-carboxymethyl groups, appear in a wide range of applications, including MRI imaging agents and other therapeutic agents requiring bifunctional chelates [124]. Pendant – arm chelating macrocycles also form a class of ligand intermediate between simple macrocycle and fully encapsulating ligands with a three – dimensional framework [125]. The pendant – arm macrocycles are usually synthesized prior to coordination. Fully alkylated ligands, which possess only tertiary nitrogen can be relatively straight forward synthesized while partially alkylated macrocycles which contain both secondary and tertiary nitrogen are more difficult to achieve [126]. The low yields and the formation of mixture of partially alkylated product are main problems in the synthesis of such compounds in some cases mixture of isomers and indeed some geometric some isomer has to be inaccessible [127].

The use of macrocyclic ligands for selective metal complex formation has received considerable attentions over the last many years [128]. Synthetic macrocyclic ligands are useful models for the study of biologically important metallo-proteins or enzymes. The availability of a number of structural derivatives and the ability to complex a large number of metal ions in different oxidation states have made this class of ligands

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attractive and a potential subject to further investigations. The template method [19] has been exploited extensively for isolating metal inclusion derivatives. However, metal ion free macrocyclic ligand may be obtained [129] in fair yields employing cyclocondensation reactions in the absence of metal ions as templating agent. In non-template procedures, cyclization is facilitated only under high dilution conditions, and in some cases the presence of H\(^+\) ions is necessary for the precipitation of stable salts of the macrocyclic ligand.

Several synthetic approaches have been proposed to design discrete polynuclear complexes. One of them consists of the ingenious use of compartmental ligands, which are organic molecules able to hold together two or more metal ions. The Schiff bases derived from 2,6-diformyl-4-methylphenol (Robson–type ligands) and from 3-formylsalicylic acid are among the most popular ligands belonging to this family [130,131]. These ligands are especially appropriate to generate either homo-binuclear complexes, symmetrical or un-symmetrical or hetero-binuclear complexes. The ligands (Figure 1.15 a and Figure 1.15 b), which were obtained starting from 3-formylsalicylic acid [131] usually produced binuclear complexes in which the ligand

![Figure 1.15](image)

\(\text{(a)} \quad \text{(b)}\)

\(\text{Figure 1.15}\)

\(\text{(b)}\) is a compartmental acyclic side–off ligand possessing dissimilar compartments. The latter is excellent ligand for stepwise synthesis of heterobinuclear complexes [132]. The

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unsymmetrical tetradeutate schiff – base ligands derived from 3-formylsalicylic acid (Figure 1.16) has been shown to be suitable precursor for the design of homo- and hetero-trinuclear systems.

Figure 1.16

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