



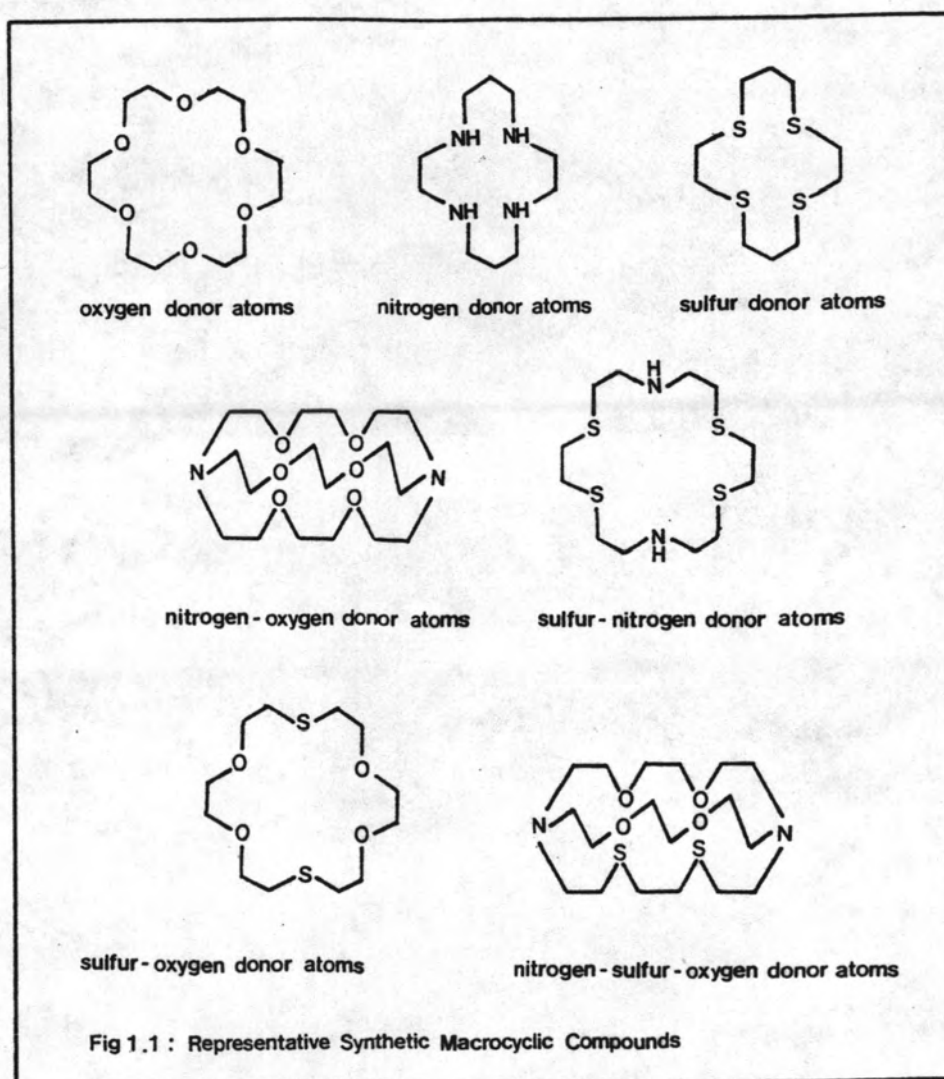
Chapter I

Introduction

1.1 Macrocyclic Compounds and their Chemistry

Although metal complexes of naturally occurring macrocyclic ligands have been known for over 50 years e.g., porphyrin, corrin ring derivatives and phthalocyanines, it is only during the past three decades, since the first publication by Pedersen (1), a large number of synthetic macrocyclic compounds; polyethers, polyamines, polythioethers and other related molecules have been synthesized (Fig 1.1). The field of macrocyclic complexes has expanded tremendously and the number of papers published per year dealing with this class of compounds is still growing.

These novel macrocycles typically contain central hydrophilic cavities ringed with either electronegative or electropositive binding atoms and exterior flexible frameworks exhibiting hydrophobic behavior. These show a pronounced ability to bind a wide variety of cations or anions and in many cases to undergo marked conformational changes during binding. Their hydrophobic exteriors allow them to solubilize ionic substances in nonaqueous solvents and in membrane media. Particularly, they have been shown to possess very interesting and unusual way on binding with a wide variety of cations including ammonium ion and in a few specific cases with anions. The factors affecting the formation and thermodynamic stabilities of these



ion - macrocycle complexes include (2,3) :

1. the type(s) of binding site in the ring
2. the number of binding sites in the ring
3. the relative sizes of the ion and the macrocyclic cavity
4. the physical placement of the binding sites
5. the steric hindrance in the ring
6. the solvent and extent of solvation of the ion and the binding sites
7. the electrical charge of the ion.

Thus, there exist unusual opportunities for the synthesis of macrocyclic molecules which exhibit a high degree of selectivity in metal binding. For example, certain cyclic polyethers not only strongly bind particular alkali and alkaline earth metals but selectively bind one or more of these ions in preference of the others in each series (4).

More recently, binucleating ligands, a term that describes a polydentate ligand capable of simultaneously binding two metal ions, have been systematically synthesized (5-8). The original aim of this work was directed towards the activation of small molecules such as N_2 , O_2 , CO, CO_2 , and NO by binuclear transition metal complexes (9). From this work very interesting new chemistry has evolved concerning magnetostructural correlation in spin - exchange coupled homo- and heterobinuclear systems. Systematic redox studies on such compounds using a variety of electrochemical methods are increasingly published. Systems with an even higher nuclearity than two are presently being studied in several laboratories.

The synthetic flexibility of macrocycles is now used to prepare low-molecular-weight compounds of bioinorganic relevance (10). In metalloproteins, the transition metals are often incorporated (fixed) via nitrogen atoms of amino acids of polypeptide chains, for example, histidine residues. These bonds may be modeled by use of macrocyclic ligands. In order to understand spectroscopic properties and the reactivity of transition metal centers in metalloproteins, it is useful and intellectually challenging to design and synthesize low-molecular-weight model complexes, where macrocycles mimic the binding of the metal ions to the protein. Quite spectacular results have been obtained using synthetic porphyrins and their iron(II) complexes to understand the factors governing the reversible oxygen uptake of hemoglobin (11). Macrocycles are very useful tools not only in bioinorganic chemistry but also in other fields of chemistry. For example, they are also promising agents for uses in removing or separating metals in solution in processes such as saline water purification and solution mining.

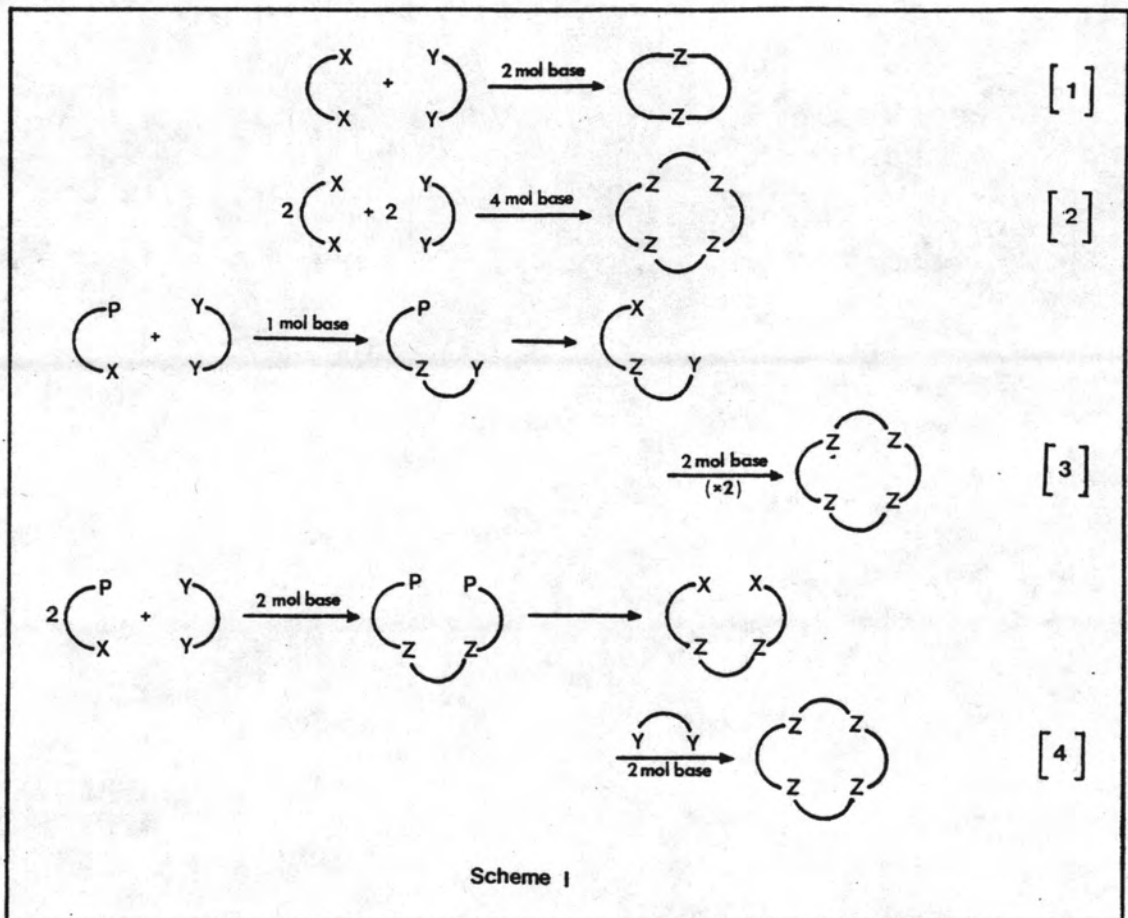
1.2 Synthesis of Free Macrocycles

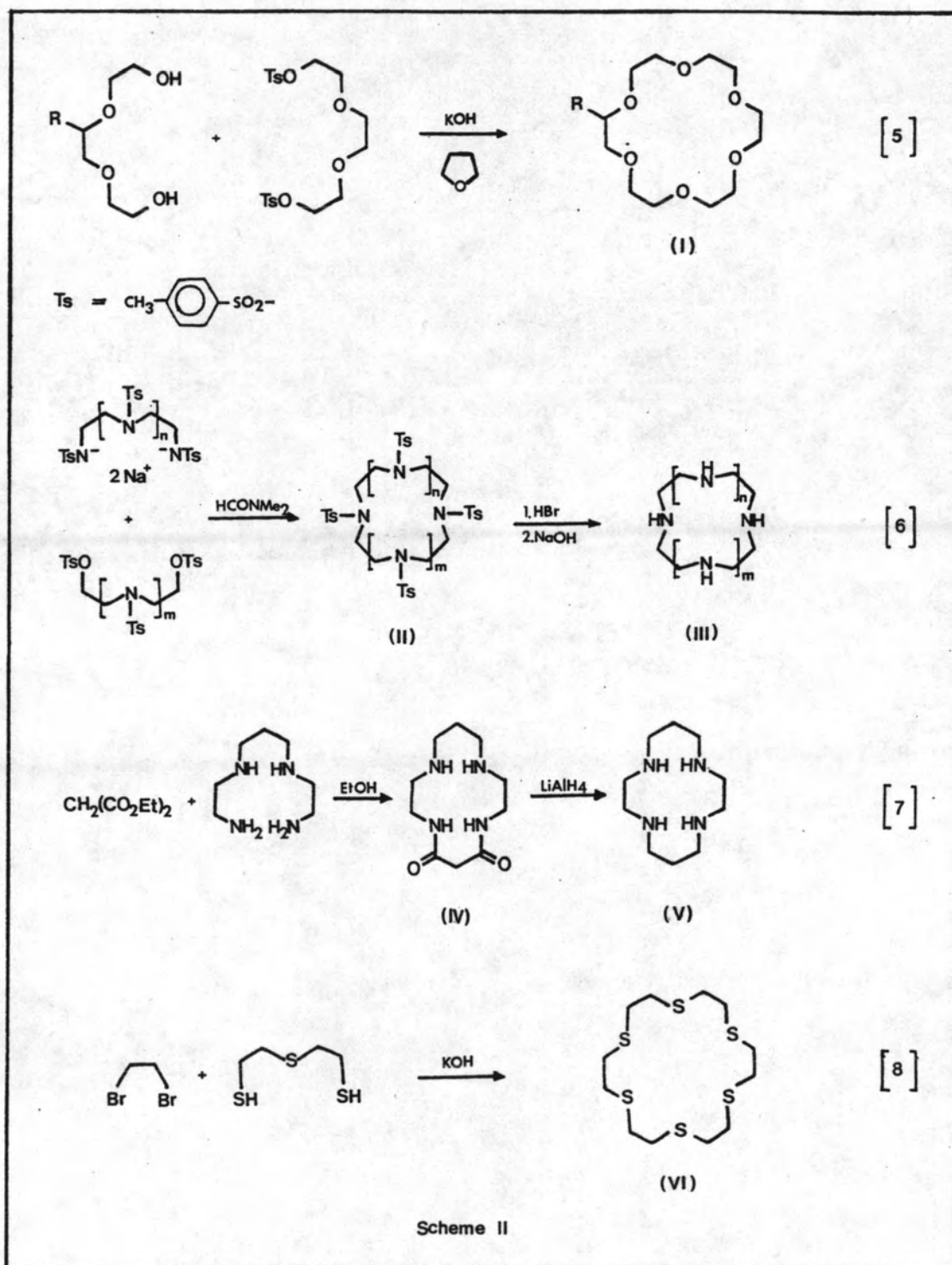
Originally, the synthesis of many new macrocyclic compounds has been facilitated by means of the so - called coordinate template effect. This effect consists of a metal ion being used in a reaction to direct the steric course of the process leading to the synthesis of species not readily obtained in the absence of the metal ion. Many macrocycles formed in this manner have only been isolated in the form of their complexes with the templating metal ions, particularly the synthesis of cyclic polyamines (12-14).

Coordination compounds containing macrocyclic ligands can now be prepared by an astonishing variety of powerful synthetic methods (15-30). They can be synthesized either in a "free" form or bound to a given metal ion. The preparation of the free macrocycle has certain advantages in many cases, such as purification and characterization. However, the preparation of the free macrocycle also has a disadvantage in that the method usually gives only low yield of the desired product .

The most general, simple and efficient synthesis of 9 to 21 membered saturated macrocycles containing three to seven heteratoms (nitrogen and/or oxygen) was reported by Richman and co-workers (31) in 1974. Thus the exploration of the chemistry of this type of ligand becomes feasible on a large scale. The preparation of monocyclic multidentate ligands are illustrated in Scheme I. Equations [1]-[4] which — = carbon chain, X = a leaving group, Y = -OH, -NH, -SH, Z = a heteroatom and P = a base-stable protecting group illustrate the general approaches employed in the assembly of macrocyclic compounds. The base employed is typically NaH, NaOH, KOH or $(\text{Me})_3\text{CCK}$. The solvent is typically $\text{Me}(\text{CH}_2)_3\text{OH}$, Me_3COH , $\text{MeOCH}_2\text{CH}_2\text{OMe}$, Me_2SO , NCONMe_2 or tetrahydrofuran. Reactions are usually conducted at room temperature or just above. Experimentally, the approaches illustrated in equations [1] and [2] represent the most facile "one - pot" methods. Despite the low yields in general, these approaches are preferable for the synthesis of "simple" monocyclic multidentate ligands. The approach indicated in equation [3] suffers from the disadvantage that the intermediate X-Z-Y may undergo intramolecular cyclization as intermolecular cyclization. The

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stepwise approach outlined in equation [4] is a versatile one and usually affords good yields of macrocyclic ligands. The approaches depicted in equations [3] and [4] are important in preparing macrocyclic ligands incorporating a variety of different structural features.

Scheme II illustrates the synthetic examples of macrocyclic compounds such as cyclic polyethers. 18-crown-6 and its derivatives (I) were obtained (32) from condensation of triethyleneglycol with its ditosylate in tetrahydrofuran as depicted in equation [5].

Macrocyclic polyamine compounds (II) were synthesized (33) by condensation of α,ω -bissulphonamides in HCONMe_2 in high dilution as shown in equation [6]. The free amines (III) can be obtained by acid-catalyzed hydrolysis of the cyclic sulphonamides, followed by treatment of the salts with base. The yields of the final detosylation step are rather low due to acid-catalyzed C-O and C-S bond cleavage reaction.

Macrocyclic polyamines can also be obtained by other approach as shown in equation [7] i.e. reduction of bislactam precursors which are readily available from the condensations of α,ω -diamines with diesters. For example, reaction of 1,3-bis-[(2'-aminoethyl)amino]propane with diethylmalonate in ethanol under reflux (34) gives the cyclic bislactam (IV) which affords the tetraaza-14-crown-4 derivative (V) on LiAlH_4 reduction. The chief disadvantage of this reaction is the polymeric side products which are formed in large amounts for the cyclization step.

By using high dilution technique, macrocyclic polythioether, hexathia-18-crown-6 (VI), can be isolated from the reaction between the dimercaptan and $\text{BrCH}_2\text{CH}_2\text{Br}$, shown in equation [8], in the presence of KOH (35-36).

Other mixed heteroatom macrocycles (37-40) can also be obtained by using similar approaches involving both alkylation and acylation - reduction as shown in the cases of polyethers, polyamines and polythioethers.

1.3 Cation Binding Properties

One of the most interesting features of the macrocyclic compounds is the ability of these compounds to selectively bind various metal ions. Because of the unique way in which metal ions are bound in the cavities of the macrocycles, it is not surprising that the stabilities of the complexes formed are strongly influenced by the relative cavity and metal ion sizes. In many cases the relative sizes of the macrocyclic cavity and the metal ion control the stoichiometry of the resulting complex. The relative size is not the only factor influencing the configuration of the complex, there are also other factors to control the selectivity as described in section 1.1. In general, the metal is located in the cavity of the macrocycle to form a 1:1 complex. This "metal in the hole" picture has been substantiated by an X-ray crystallographic technique. Where the metal ion is too large or too small to fit "exactly" in the hole, 1:2, 2:3 and 1:3 complexes are formed. A "sandwich" structure, in which the metal ion is located between two macrocycles has been suggested as

the most probable structure for the 1:2 complex. A "club sandwich" structure has been postulated for the 2:3 complex where three macrocycles are arranged as plane in three tiers, each separated from the next by a metal ion. For example, the alkali metal thiocyanate complexes of dibenzo-18-crown-6 have been found (41-42) to have, for a given metal, the following ratios of polyether to metal ion : sodium and potassium, 1:1 ; rubidium, 1:1 and 2:1 ; and cesium, 2:1 and 3:2.

1.3.1 Cyclic Polyethers

Of all the macrocyclic compounds, the cyclic polyethers have been the most extensively investigated with respect to ion binding. Over 60 cyclic polyethers have been synthesized with ring structures containing from 9 to 60 total atoms, from 3 to 20 oxygen atoms and from 1 to 4 attached hydrocarbon rings. It has been found that cyclic polyethers have an affinity for alkali and alkaline earth metal ions (43-52). The relationship between ring size and cation size has been investigated by determining log K values of the reactions of mono- and bivalent cations with dicyclohexyl-18-crown-6. The results are shown in Figure 1.2 (53-56). Where the ratios of cation to cavity diameters are less than 0.5 little complex formation is observed. Whereas at ratio greater than 0.5 there is a rapid increase in the degree of interaction with a maximum between the ratio values of 0.75 and 0.9. This increase is followed by a decrease in the extent of interaction as the ratio of cation to cavity diameter increases. A charge effect is also seen in that bivalent ions generally have larger binding constants than monovalent ions having the same ratio value do. The bivalent ions are also more selectively

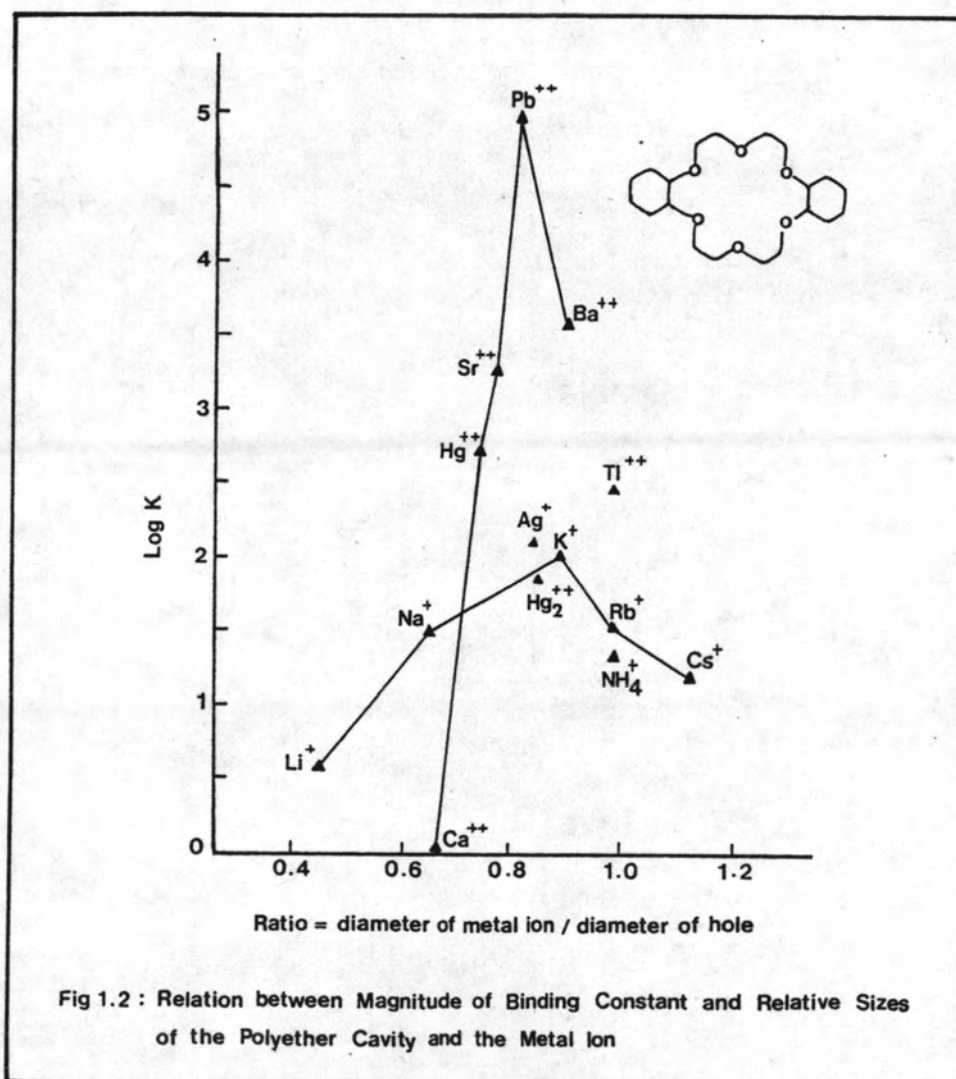


Fig 1.2 : Relation between Magnitude of Binding Constant and Relative Sizes of the Polyether Cavity and the Metal Ion

complexed than the monovalent ions. In addition, the optimum is at a somewhat smaller cation size in the case of the bivalent cations. Figure 1.2 also shows that dicyclohexyl-18-crown-6 is extremely selective toward certain cations. For example, the difference in stability constants between the Ca^{2+} and Pb^{2+} complexes of dicyclohexyl-18-crown-6 is about 10^5 .

1.3.2 Cyclic Polyamines

A large variety of cyclic polyamines having 3 to 6 functional groups in the ring have been synthesized. However, most of the cyclic polyamines have 4 functional groups which are more or less evenly spaced in a ring containing between 12 and 16 atoms (57-62). The majority of the monocyclic polyamine complexes have structures similar to (VII ; page 19) where four, more or less, equivalent nitrogen atoms are coordinated in a single plane about the metal ion while two variable ionic groups are bound in the axial sites above and below that plane. X-ray crystallographic analysis on several macrocycles containing four or five nitrogen atoms (63-71) indicates that the metal ion is located in the cavity of the ring.

The stability constants of macrocyclic polyamine complexes are higher than the similar noncyclic nitrogen containing molecules. This effect has been called "the macrocyclic effect" (72-73). Table 1.1 compares $\log K$ of 1,4,8,11-tetraazacyclotetradecane (VIII; page 19) with those of noncyclic amines.

Table 1.1 Log K Values for the Formation of Several 1:1 Cu²⁺ - tetramine Complexes

Ligand	Log K	Temp °C
Macrocyclic :		
1,4,8,11 -tetraazacyclotetradecane	28	25
Noncyclic :		
N[(CH ₂) ₃ NH ₂] ₃	13.1	25
NH ₂ (CH ₂) ₃ NH(CH ₂) ₂ NH(CH ₂) ₃ NH ₂	17.3	20
N[(CH ₂) ₂ NH ₂] ₃	18.8	20
NH ₂ (CH ₂) ₂ NH(CH ₂) ₂ NH(CH ₂) ₂ NH ₂	20.1	25
NH ₂ (CH ₂) ₂ NH(CH ₂) ₃ NH(CH ₂) ₂ NH ₂	23.9	25

It has been suggested that because of the high stability of the complexes it might be possible to trap some of the more uncommon oxidation states of the transition metal by reduction or oxidation of the complexes containing the metals in their normal oxidation states (74-79), for example, the studies of Co, Ni and Cu complexes of tetrabenzo[b,f,j,n],[1,5,9,13-tetraazacyclotetradecane (IX ; page 19), hereafter called TAAB]. The polarographic data (80) for a number of the complexes of TAAB and related macrocyclic ligands showed that four of the reduction products, TAAB derivatives of formally divalent Co, monovalent Cu and Ni and zerovalent Ni, have been isolated and characterized as pure materials due to the special ability of TAAB to stabilize the products of two, three and perhaps even more electrons addition.

In recent years, a further aspect of synthesis of macrocyclic polyamines has received a great deal of attention. By introducing additional ligating groups into a macrocycle, its properties are modified and more stable complexes are formed. N-functionalized derivatives of azamacrocycles are readily synthesized, and their coordination chemistry is currently actively investigated for a variety of reasons; for example, the specificity in metal-ion binding may be increased or its solubility is changed. Interesting kinetic phenomena are studied, such as intramolecular binding and dissociation process of one or more pendant arms of a modified macrocycle (81-83).

1.3.3 Cyclic Polythioethers

The first thiacycrown compounds were described over 40 years ago, some 30 years before the preparation of the oxygen analogues by Pedersen. Thiacycrown ethers are known to show great affinity for softer metal ions, such as transition or heavy metal ions, than alkali and alkaline earth metal ions (84-92). The replacement of oxygen by sulfur causes a decrease in cavity size of crown ethers. The high affinity of thiacycrown ethers for soft metal ions was observed in the study of liquid-liquid extraction of various metal ions with 1,4,8,11-tetrathiacyclotetradecane (TTCT; X; page 19) (93). The data for percent extraction (%E) and logarithmic distribution ratio ($\log D$) for each metal could be mutually compared. Class A metals were not extracted at all and of the class AB metals only copper(II) was extracted. Class B metals were extracted but their extractabilities varied considerably. This indicates that the extract-

abilities of metal ions depend on various factors such as the type of the metal ions, the anion selected to form the ion pair, the extraction solvent and probably other factors also.

This has been confirmed by the study of copper(I) - TTCT system. The results showed that the copper(I) - TTCT cation was completely extracted at $\text{pH} > 4.0$ as an ion pair with perchlorate, picrate or tetraphenylborate and the extraction of copper(I) with TTCT and picrate into different solvents decreased in the order nitrobenzene > 1,2-dichloroethane > chloroform > carbontetrachloride. This is consistent with the order of the dielectric constants of the solvents.

1.3.4 Mixed Donor Macrocycles

The effect of substituting nitrogen for oxygen on the metal binding properties of 18-crown-6 (XI ; page 19) and dibenzo-18-crown-6 (XII ; page 19) with potassium and silver ions has been studied (94-95). The results are shown in Table 1.2. Complexing of potassium is weakened appreciably as nitrogen is substituted in the ring and the stability constant falls in the order of decreasing electronegativity of the substituted group, $\text{O} > \text{NR} > \text{NH}$. The effect on silver(I) complexing is exactly the opposite with the stability increasing with substitution. It has been concluded that only electrostatic bonding exists in the potassium complexes whereas the silver (I) complexes have both electrostatic and covalent bondings.

Table 1.2 Equilibrium Constants for the Interaction of Potassium and Silver (I) with Mixed Dentate Macrocycles at 25°C

Ligand	Donor Atom		Log K	
	A	B	K in methanol	Ag (I) in water
XI	O	O	6.10	1.60
XII	O	O	5.00	
XII	NR	O	4.10	
XI	NH	O	3.90	3.3
XII	NH	O	3.20	
XI	NH	NH	2.04	7.8
XII	NH	NH	1.63	

To this end, Table 1.3 (96) illustrated the results of solvent extraction in chloroform / water solvent system for bis- and poly-(thiacrown ether)s (XIV ; page 19) and (XV ; page 19) respectively, compared with the monomer analogue (XIII ; page 19).

It is noted that the poly- and bis(thiacrown ether)s extracted Ag(I) effectively. This is also the case for the corresponding monocyclic analogue but the poly- and bis(thiacrown ether)s are higher in the extractability. The poly- and bis(thiacrown ether)s also show great affinity for Hg(II) but not the monocyclic analogue. The complex formation between AgNO₃ and bis(thiacrown ether)s (XIV) and the monomeric analogue (XIII) have been investigated conducto-

metrically and the results indicate that the formation of 2:1 and 1:1 thiocrown ether to Ag(I) complexes, respectively. The poly (thiocrown ether)s (XV) is considered to form a Ag(I) complex with the same stoichiometry as the corresponding bis(thiocrown ether)s.

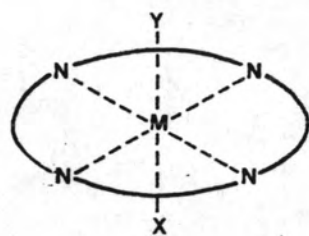
Table 1.3 Percent Extraction of Various Kind of Metals by Thiocrown Ethers.

Thiocrown Metals	Percent extraction (%E)		
	(XIII)	(XIV)	(XV)
Cu(II)	0.0	0.6	0.8
Ag(I)	70.3	86.7	90.6
Zn(II)	0.4	1.3	1.4
Hg(II)	0.0	25.1	90.4
Pb(II)	0.9	1.5	1.5

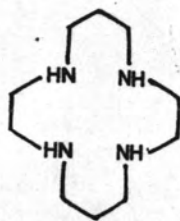
1.4 Reason for Undertaking this Work

It can be clearly seen that macrocyclic compounds have the ability to form stable complexes with specific metal cations. This property has been found useful for separation, purification, and analysis of metal ions in the field of analytical chemistry such as solvent extraction (97-100), ion - selective electrode (101-107), and liquid chromatography (108-112).

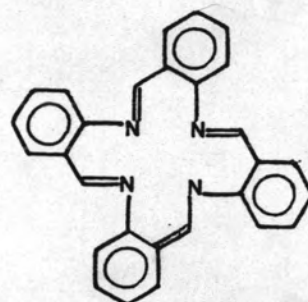
Although the work on synthesis and application of macrocyclic polyether compounds has been extensively studied, only little has been reported on polyamine compounds. Due to the great affinity for transition metal ions it is interesting to find use of the polyamine crown compounds in separating metal ions. As crown ether modified silica has proven to serve as a better separating agent for metal ions than the corresponding crown ethers, there has been no work done on either synthesis or application of similar type for polyamine compounds. This work describes an attempt to synthesize some polyamine macrocyclic compounds with functional group that can function as a precursor either in polymerization reaction of the polyamine crown compounds or for polyamine crown derivatized silica. The metal binding property and extracting ability are also investigated and compared among polyamine crown compounds with different functional groups.



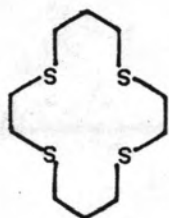
(VII)



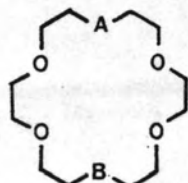
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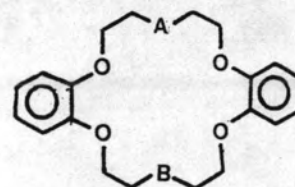
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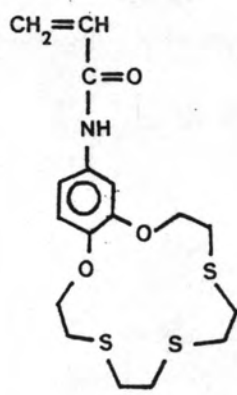
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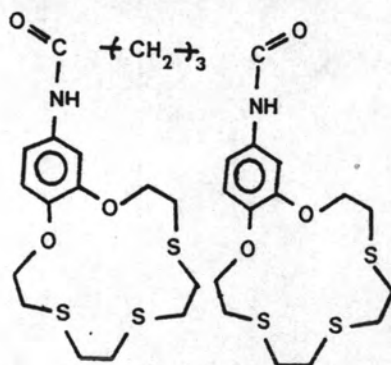
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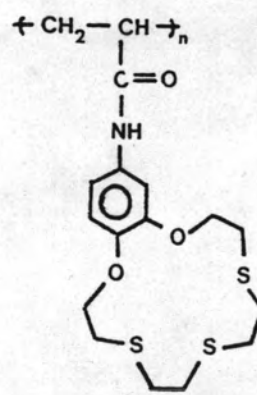
(XII)



(XIII)



(XIV)



(XV)