CHAPTER I


INTRODUCTION


In nature, macrocyclic ligands have been known for over 65 years, e.g. nonactin, valinomycin, porphyrin and corrin ring derivatives(1). The discovery, that these naturally occurring macrocycles can form selectively stable complex, such as iron-porphyrin core in haemoglobin, cobalt corrin of vitamin $B_{12}$ and magnesium-hydroporphyrin in chlorophylls, has opened several broad chemical investigations (2-4). Synthesis of multidentate macrocycles, especially cyclicpolyether, was first interested by C.J. Pederson in 1967 (4). Then other related macrocyclic compounds have been synthesized. Now the field of macrocyclic complexes has expanded tremendously.


## 1.1 Macrocyclic Compounds and Their Chemistry


Macrocycle has been defined as a cyclic compound having nine, or more, heteroatomic members and with three, or more, ligating atoms (2).

In general, macrocyclic compounds are classified and arranged to the types of donor atoms. Representative synthetic macrocyclic compounds for the various classes are given below :

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in cyclization step.

Other macrocyclic polyamines can also be synthe-
sized by the condensation of bissulphonamides in HCONMe$_2$
in high dilution as in process [5], Scheme II. The free
amines (IV) can be obtained by acid-catalyzed hydrolysis of
the cyclic sulphonamides(III), followed by treatment of the
salts with base.

### 1.1.3 Cyclic Polythioethers

In 1969 Rosen and Busch (6-7) used the reaction
sequence in Scheme III to prepare the quadridentate macro-
cycles (VI) and (VII). The final ring-closing step gave a
38% yield. Initially the corresponding yield of (VI),
the sulfur analog of cyclam, was 7.5%, although the reac-
tion was performed at a modulate dilution. Subsequently
this yield was improved by diluting the alcohol solution
threefold used in the original preparation.

Black and Mclean (8) also reported the synthesis of
an 18-membered ring in Figure 1.1. The reaction of 1,2-di-
bromoethane with the disodium salt of 3-thiapentane-1,5-di-
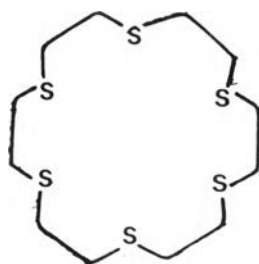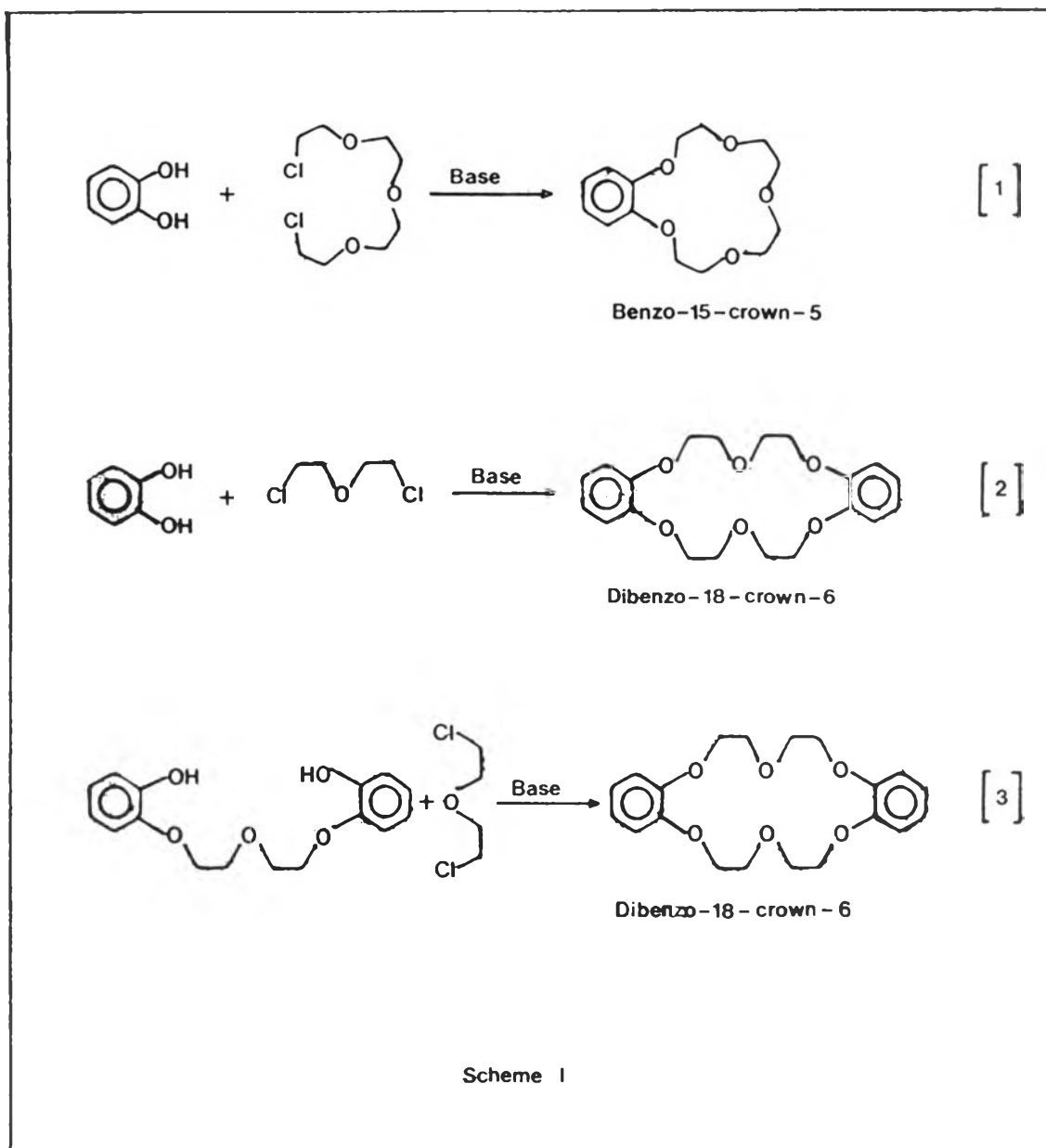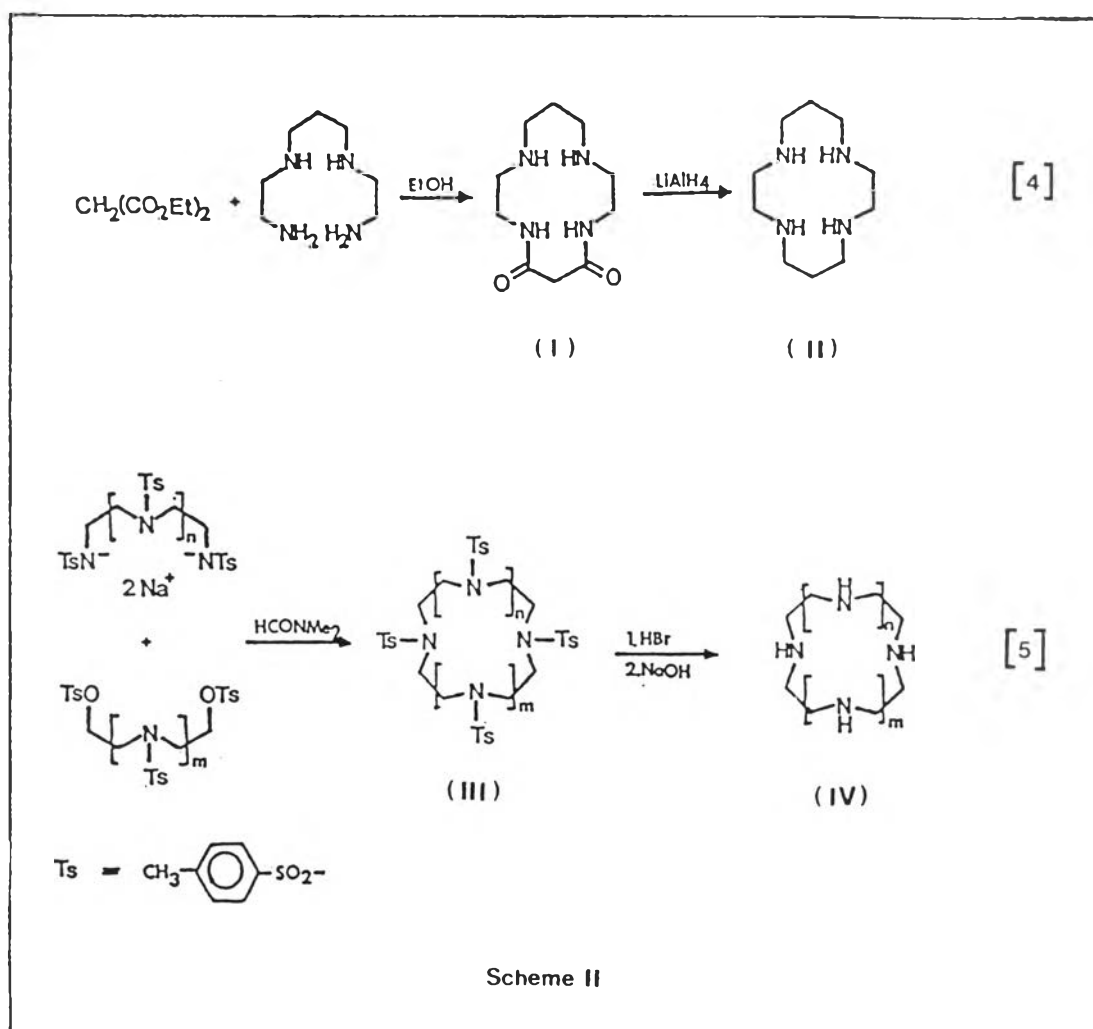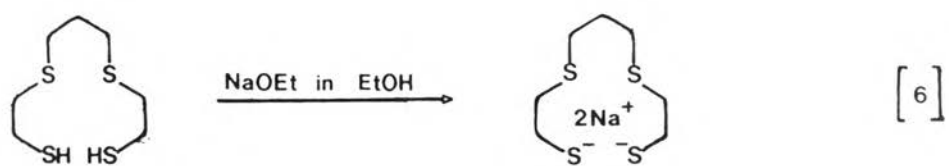thiol in ethanol at high dilution gave a yield of 31%.



Fig. 1.1 structure of Hexathia-18-crown-6

Benzo-15-crown-5     [1]

Dibenzo-18-crown-6     [2]

Dibenzo-18-crown-6     [3]

Scheme I

Scheme II

NaOEt in EtOH

(V)

[6]

V

Br        Br

(VI)

[7]

V

CH₂Br
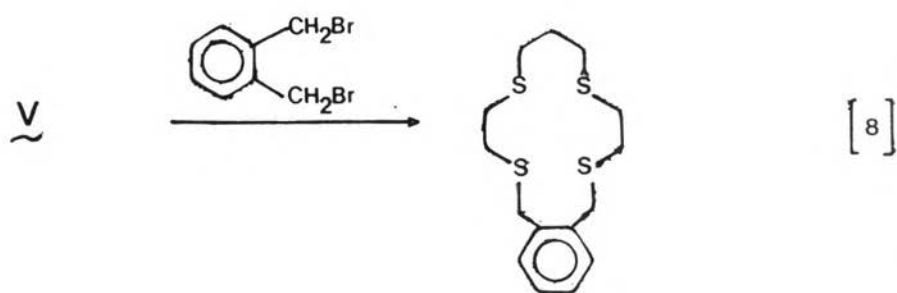
CH₂Br

(VII)

[8]
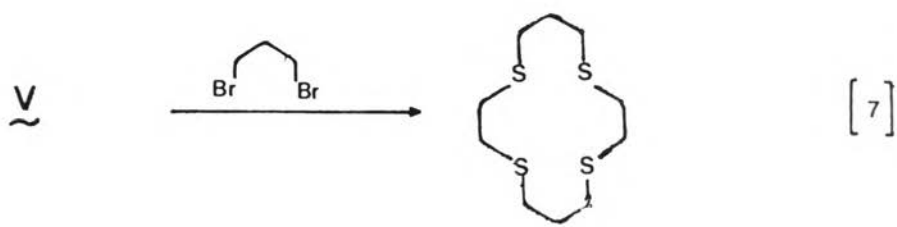
Scheme III

## 1.1.4  Mixed Donor Macrocycles

### 1.1.4.1  Macrocyclic polyether sulfide

Sulfur is the most common heteroatom ( other than oxygen) in mixed crown compounds which are easily prepared from dimercaptans or sodium sulfide and the dihalide (9-10), as shown in process [9].  The yields are often very good (25-30%).  A review of the preparation of all types of macrocyclic sulfur compounds was reported by J.S. Bradshaw and J.Y. Hui in 1974 (11-13).

$15-O_3S_2$

[9]
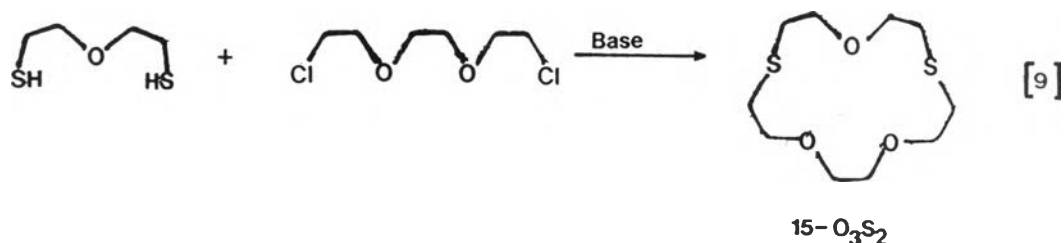
### 1.1.4.2  Macrocyclic polyether-amine (aza-crown)

Macrocyclic compound consisting of oxygen and nitrogen atoms has been called "aza-crown".  The synthesis of aza-crown compounds is of interest due to intermediate complexation properties between those of the all oxygen crowns, which strongly complex alkali and alkaline earth metal ions, and those of the all nitrogen cyclams, which strongly complex heavy metal cations.  These mixed com-

plexation properties make the aza-crowns have important uses as synthetic receptors in molecular recognization process (14). In addition the aza-crowns are important intermediates for the synthesis of cryptands (for diaza-crowns). There are a number of interesting uses of aza-crowns as catalysts in nucleophilic substitution and oxidation reactions (15-16).

In 1979 Kulstad and Malmsten (17-18) reported a re-markable synthesis of cryptand [2.2.1] and 1,10-diaza-18-crown-6 from the reaction of 1-iodo-8-chloro-3,6-dioxaoctane and 1,8-diiodo-3,6-dioxaoctane respectively. The iodo starting material gave the cryptand while the diiodo com-pound gave the diaza-18-crown-6. In the former case, the iodide reacted much faster than the chloride, allowing the formation of an intermediate amine with three branches, this product then cyclized into the cryptand(VIII) as shown in process [10].



( VIII )
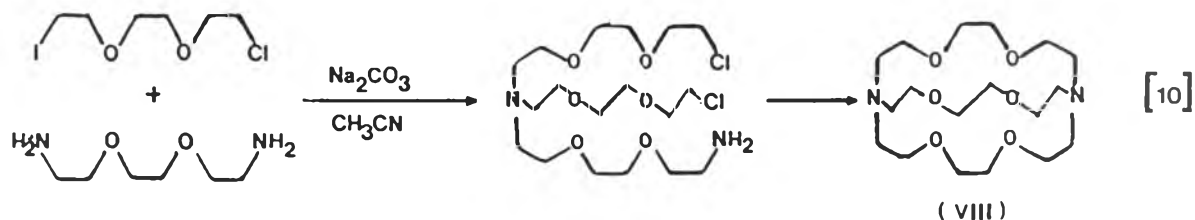
When the diiodo starting material was used ,the di-aza-crown resulted from a simultaneous reaction with both iodides in the presence of a template cation. The formation of the cryptand was also controlled by template and solvent effects. The best solvent was found to be acetonitrile.

Sodium carbonate was the best catalyst because sodium ion fits into the cryptand [2.2.2]. The assignment for common names to cryptands are done by counting number of oxygen atoms in each chain (17-18) as shown in Fig.1.2.
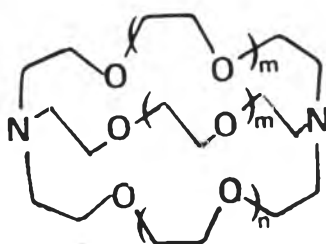


[1.1.1]   when   m = n = 0

[2.1.1]   when   m = 0, n = 1

[2.2.1]   when   m = 1, n = 0

[2.2.2]   when   m = n = 1

[3.2.2]   when   m = 1, n = 2

[3.3.2]   when   m = 2, n = 1

[3.3.3]   when   m = n = 2

Fig. 1.2   Common name assignments for cryptands

## 1.2   The Nature of Macrocyclic Ligand and Their Complexes

The geometry of the larger macrocyclic ligands is usually more flexible than that of smaller size molecules, because of decreasing ring strain. The factors affecting the complexation of metal ions by macrocyclic ligand are listed as follow (19-20):

1.  the relative cation and ligand cavity sizes.

2.  the binding sites within the macrocyclic
    compound  such as nitrogen (-aza compounds),
    oxygen (-oxa compounds), and  sulfur (-thia
    compounds).

3.  the oxidation number and the size of cation.

4.  steric hindrance in the ring.

5.  solvent effect.

Complex stability constants are controlled by  the
nature of ion-ligand interaction, such as  the  ion-dipole
and charge-induced dipole type (21).  The cation selectivi-
ty of a macrocyclic ligand is affected by the "fit"of cat-
ions in the ligand  cavity  only  among  cations which can
enter the ligand cavity.  However,both stability and selec-
tivity of complexation are also strongly affected by solva-
tion and counter ion (22).

In 1980  J.D. Lamb  and  co-workers (23)  reported
stability constants (log K) for interaction  of some crown
ether compounds with monovalent cations in methanol at 25 C
and  found that the  selectivity  order  of  15-crown-5 in
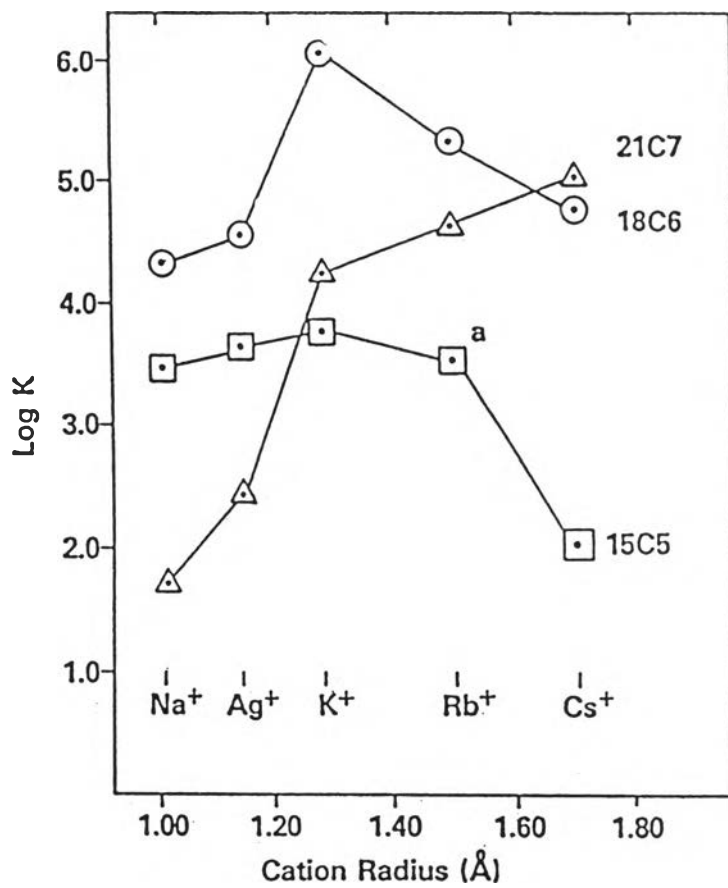methanol was $K^+ > Ag^+ > Na^+ > Cs^+$ as shown in Figure 1.3

Fig. 1.3 Relation between magnitude of stability constant(log K) and relative sizes of the crown ether cavity and monovalent cations.

## 1.3  Ligand Solvation and The Macrocyclic Effect

The enhanced stability of the metal ion complex of macrocyclic ligands as compared to their open-chain analogues, has been termed the "macrocyclic effect"(24). This effect has been firstly attributed to the smaller configurational entropy of the macrocyclic ligands(25). The most frequently suggestions postulate that the stability of macrocyclic complexes arises from:

1.   the "prestrained" conformation of cyclic ligands, which are already in a conformation most suitable for complex formation (26-27).

2.   the steric hindrance to solvation of the donor atoms, which are oriented into the ring cavity in the center of the ligand (28-29).

However, the main source of macrocyclic effect was attributed to (a) the internal interactions of metal and donor groups (b) the external interactions between the cyclic ligand and the solvent molecules, which lead to the "ligand solvation effect". The effect of ligand solvation on metal ion complex stability constant should be very important in biological systems, the donor groups are frequently forced to be close to one another or in some way are shielded from solvation. As with the macrocyclic effect, the cause of enhanced metal binding, is a combina-

tion of more favorable enthalpy terms from diminished solvation of donor groups and smaller loss of ligand configurational entropy. The magnitude of metal binding constants to larger molecules could be increased by many orders. It is due to these factors as well as the possibility that steric hindrance might have just the opposit effect. In an aqueous solution, the complex is supposed to be less hydrated than the metal ion because of the ligand coordination.

## 1.4 Stoichiometry of Salt Complexes

The cyclic polyethers have been found to form primarily 1:1 metal:polyether complexes with a large array of metal ions by J.C.Pederson in 1967 (4). The later work showed that the stoichiometry is not as simple as originally assumed, depending on the ratio of the diameter of the cavity and metal ion diameter (30-33). The original concept of a 1:1 complex is shown in Figure 1.4
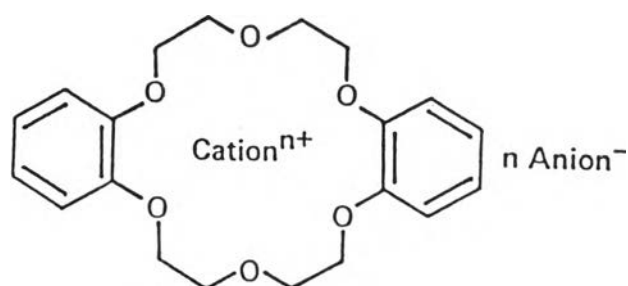


Fig. 1.4  1:1 Salt complex of dibenzo-18-crown-6

There is also structural evidence indicating that
in many cases the relative size of the polyether cavity
and the metal ion control the stoichiometry of the resul-
ting complex. The ionic diameters of some cations and the
estimated sizes of the holes of selected cyclic polyethers
are given in table 1.1

Table 1.1 Diameters of selected cations and cyclic
polyether cavities (34)

| Cation | Ionic diameter($\overset{o}{A}$) | Polyether | Dimeter of cavity ($\overset{o}{A}$) |
|--------|---------|-----------|----------------|
| Lithium | 1.20 | All 14-crown-4 | 1.2 - 1.5 |
| Sodium | 1.90 | All 15-crown-5 | 1.7 - 2.2 |
| Potassium | 2.66 | All 18-crown-6 | 2.6 - 3.2 |
| Rubidium | 2.96 | All 21-crown-7 | 3.4 - 4.3 |
| Cesium | 3.34 | | |
| Silver | 2.52 | | |
| Barium | 2.70 | | |

The 1:1 complexes are generally assumed to be con-
sist of the metal ion bound in the cavity of the polyether
ring (35-38). The fact that a metal ion forms a 1:1
complex with cyclic polyether does not always indicate
that the metal ion is located in the cavity of the poly-

ether.    The metal ion   may have   directed valencies which
preclude bonding to all the oxygen atoms   or it may be too
large or too small to fit "exactly"in the hole. Apparently
the former is  the case  for  the  solid complex of cobalt
chloride and the cyclic polyether (dicyclohexyl-18-crown-6)
,(IX) in Figure 1.5 , where based on and  magnetic  moment
data (39), two possible structures were postulated:


    1.  a sandwich type structure with two cobalt ions
located between two cyclic polyether molecules,(X), and

    2.  a chain  type  polymer  with  an   alternating
array of cobalt cations and cyclic polyether molecules,(XI)


    These structures are possible only if each  cyclic
polyether  contributes  three  oxygen atoms to each cobalt
ion to form an octahedral complex.   In  the  absense  of
X-ray crystallographic data, it cannot be predicted which,
if either,of these structure is correct.

    Considering all these facts relating to stoichiome-
try,the structures depicted in Figure 1.6  were thought to
represent roughly the 1:2 and 2:3 complexes.   A "sandwich"
structure was  suggested as  the  most  probable  one  for
the 1:2 complex, in which the metal ion is located between
ligand molecules. A "club sandwich"  structure   was pos-
tulated  for the 2:3 complex  when three ligand  molecules
are arranged flatwise in three tiers, each separated  from
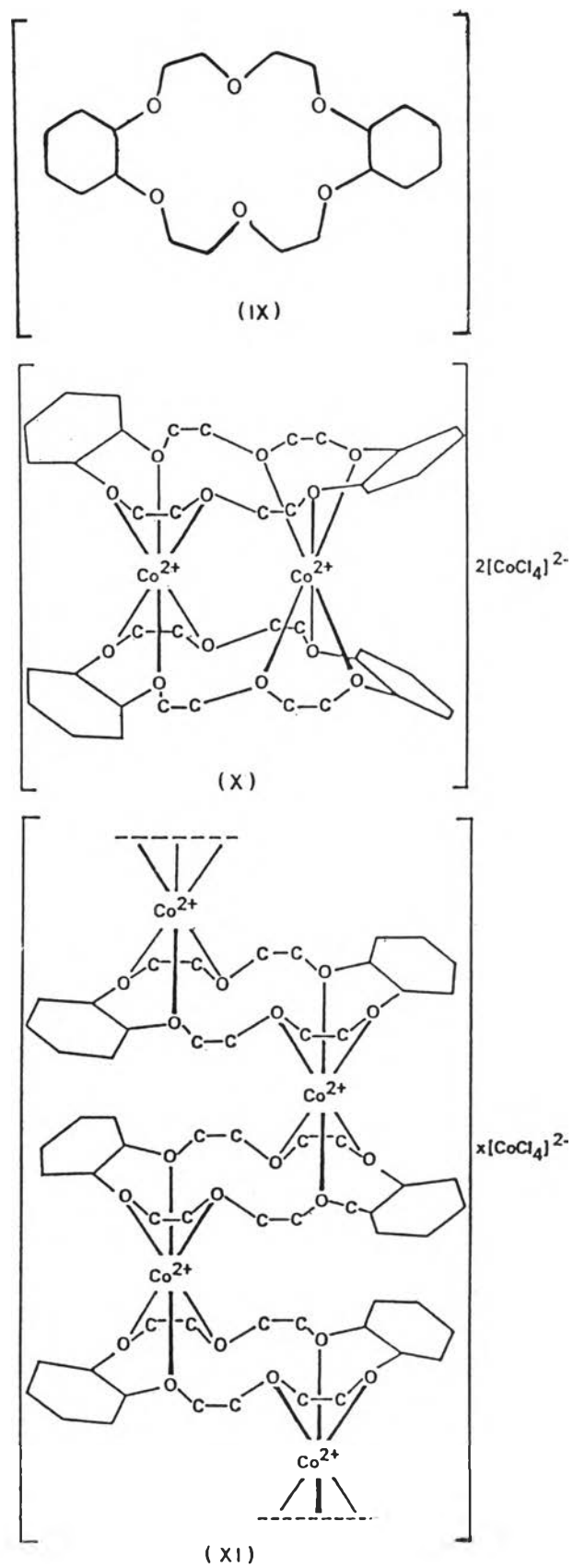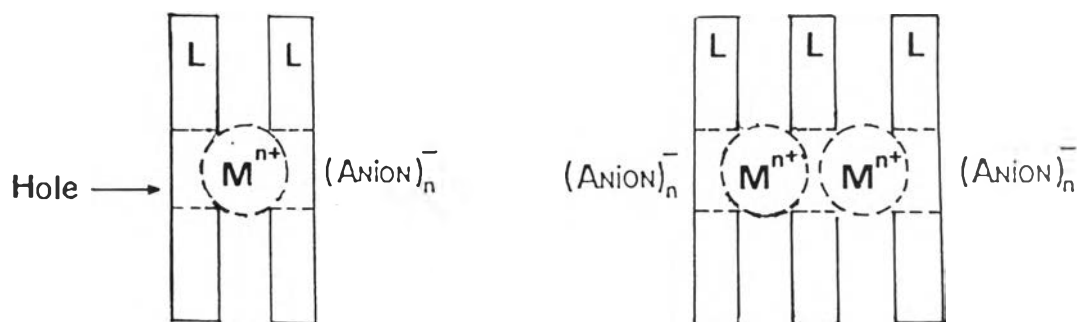the  next by a metal ion.

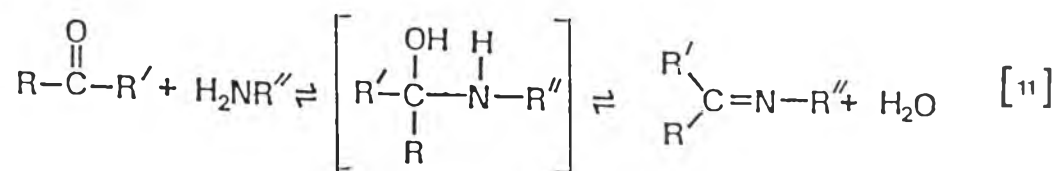Fig. 1.5 Crystalline complex of dicyclohexyl-18-crown-6 and $CoCl_2$

"Sandwich" Complex (1:2)      "Club Sandwich" Complex (2:3)

Fig. 1.6  Rough approximations of 1:2 and 2:3 complexes

## 1.5  Schiff-Base and Their Chemistry

### 1.5.1  Definition of Schiff-base

Schiff-bases are the compounds containing the azomethine group (-RC=N-) and are usually formed by the condensation of a primary amine with an active carbonyl compound, as shown in process [11]. Bases which are effective as coordinating ligands bear a functional group, usually -OH, sufficiently near the site of condensation that a five- or six-membered chelate ring can be formed upon reaction with a metal ion (40).

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-R' + H_2NR'' \rightleftharpoons \left[ R'-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-\overset{\overset{\displaystyle H}{|}}{N}-R'' \right] \rightleftharpoons \overset{\displaystyle R'}{\underset{\displaystyle R'}{}}C=N-R'' + H_2O \qquad [11]$$
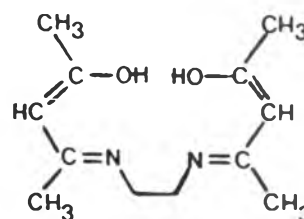
Because of the great synthetic flexibility of Schiff-base formation, many ligands of diverse structural types can be synthesized. Some examples of Schiff-base compounds are shown below ; N-salicylideneanthranilicacid (XII),2-Hydroxyethylsalicylaldimine(XIII),bis(acetylacetone) ethylenediimine(XIV)
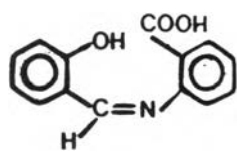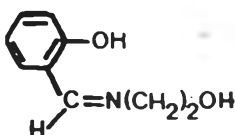


(XII)     (XIII)     (XIV)

## 1.5.2 Salicylaldimine complex

Of all Schiff-bases complexes, those derived from salicylaldimine have been by far the most thoroughly studied. Schiff (41) discovered the exceedingly important synthetic technique of preparing salicylaldimine complexes by reaction of the preformed metal salicylaldehyde compounds with primary amines.

The advantage of Schiff-bases for studying coordination chemistry is the capability to form complexes with various metals. In 1931, Dubsky and Sokol (42) isolated N,N'-bis(salicylidene)ethylenediamino Cu(II), Ni(II) and correctly formulated their structures as (XV).
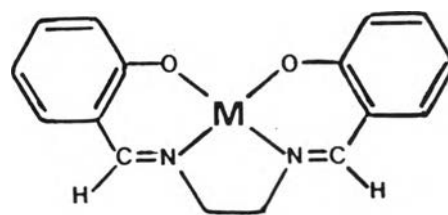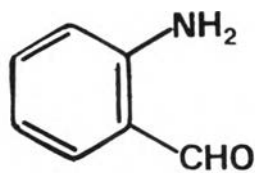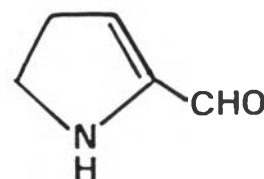
(XV)

In the period 1931-1942, Pfeiffer and his co-workers (42) produced a prodigious number and variety of complexes derived from Schiff-bases of salicylaldehyde and its substitution product (XVI), 0-aminobenzaldehyde (XVII), and pyrrole-2-aldehyde, (XVIII)
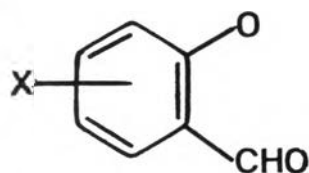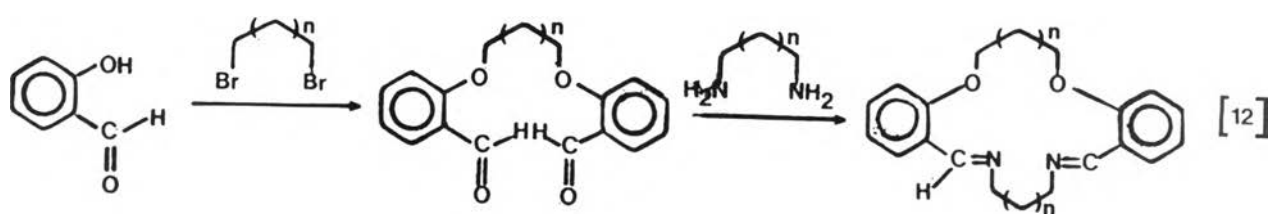


(XVI)          (XVII)          (XVIII)

The synthesis of macrocyclic Schiff-base of dibenzo -containing aza-crowns from salicylaldehyde or its deriva- tives has been reported first by Lindoy and co-workers (43-44). The salicylaldehyde was first reacted with di- halide followed by condensation with a diamine to form an imine, illustrated in process[12].



[12]

In 1985 Wild and co-workers (45) prepared a dibenzo
diaza-14-crown-4 with a *trans* arrangment  of the $N_2O_2$ donor
groups.  The hydroxymethyl  group  of the starting material
was first oxidized to the  aldehyde, which  condensed  with
the primary amine of another molecule of starting material.
The resulting Schiff-base was reduced  to  form  the  final
dibenzodiaza-crown, as depicted in process[13]
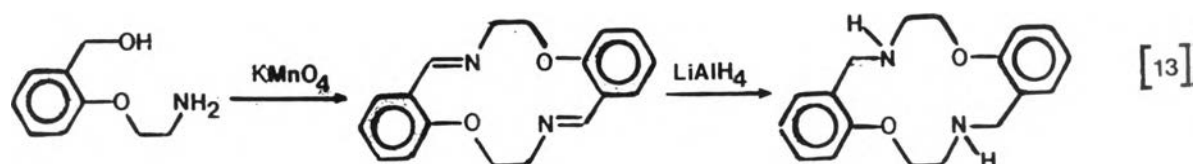


## 1.6  Macrocycle as Complexing Agent in Analytical Chemistry

Macrocyclic molecules can selectively  solubilize
ions and  form stable complexes with  specific  metal ions.
They have considerable potential for separation, purifica-
tion and  analysis of metal ion in the field of analytical
chemistry, such as separation of ions by transport through
artificial  and  natural  membrane  (46-50), liquid-liquid
extraction(51-52), preparation of ion selective electrodes
(54-56),using as stationary phase in liquid chromatography
,and phase-transfer catalyst (57).

Extractions are the most completely developed for large-scale up,dissolution in apolar solvents of metal and organic salts (53) as in Figure 1.7. Membrane and catalyst are promising areas as yet publicly described only at bench scale.
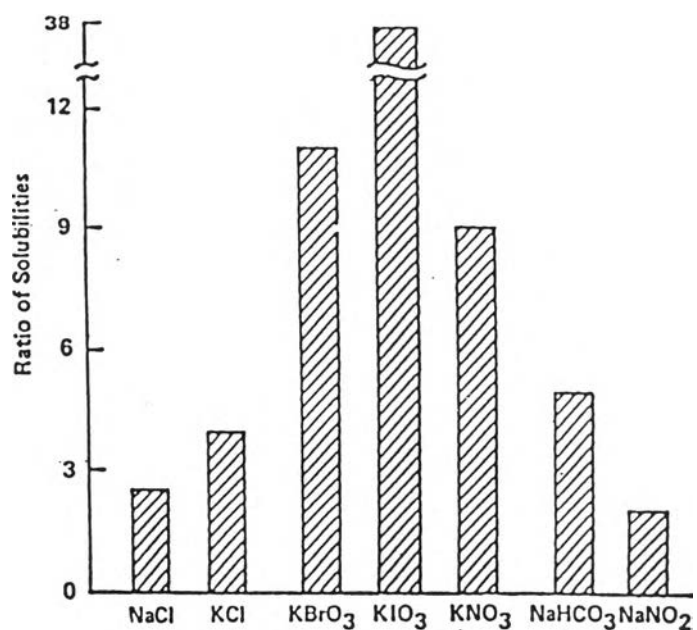


Fig 1.7   Increase in the solubility of alkali salts
in methanol.  The solubility of these salts
in greatly increased by the presence of di-
benzo-18-crown-6.

## 1.7 Objectives of This Study

Although the work on synthesis of macrocyclic and open-chain Schiff-base compounds have been extensively studied, most was investigated in the field of coordination chemistry and ability of complexation. There has been no work reported on using Schiff-base , either as open- chain or as macrocyclic, in extracting metal ions, specifically transition metal ions or as complexing agent in analytical chemistry.

In summary, the aims of this study are:

1. to synthesize free macrocyclic and open-chain Schiff-base compounds of similar structure.

2. to study the cation-binding properties and the extracting ability of the synthesized compounds

3. to study the possibility of using some Schiff-base compounds as spectrometric reagent in quantitative analysis of metal ion.