

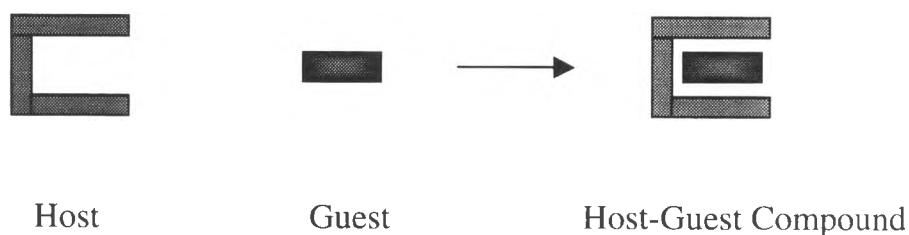
CHAPTER II LITERATURE SURVEY



2.1 Host-Guest Chemistry

Host-guest phenomena was first reported by Michael Faraday (1823) about the clathrate structure of chlorine. The concept and theory of host-guest phenomena was established when C.J. Pedersen (Kroschwitz, 1995) declared crown compounds about the synthesis, structures, and host-guest interaction of crown compounds and metal ions in the mid 1960s. The host-guest chemistry became one of the advanced research themes after C.J. Pedersen, D.J. Cram, and J.M. Lehn were the 1967 Nobel prize laureates in chemistry.

Host-guest chemistry can be explained by a model of a host concave and a guest convex relationship or lock and key model which was proposed by Fisher (1894) (Scheme 2.1). The guest can be stabilized in the host framework with secondary forces such as, van der Waals, ionic, hydrophilic, and hydrophobic interactions.



Scheme 2.1 Model of inclusion compound (Fisher, 1894).

The guest molecules are required to fit for the size and shape to accommodate the specific properties of host cavity or channel. Generally, polar guests are favored with the host cavities lined with polar groups while

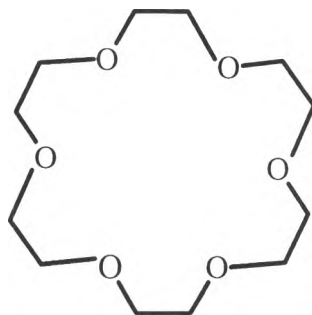
nonpolar guest with nonpolar host cavities. Concerning the size of the host cavity, most host compounds give diameters of the cavity in the range of 0.4-0.8 nm. Host channel has an affinity to entrap linear guest, while a host cage is suitable for a spherical guest. The cage cavity is more stable than the channel or layer cavity (Kroschwitz *et al.*, 1995).

2.2 Well-Known Inclusion Compounds

2.2.1 Crown Compound

Crown ether is named by C.J. Pedersen (1967) due to its crown-like structure. Crown compounds are macrocyclic compounds having methylene basic unit linked with hetero atoms such as O, N, or S as electron donor atoms in their cyclic structure.

The macrocyclic polyethers having only O atoms as the electron donors are known as crown ethers (Scheme 2.2), while azacrown ether as cyclic amino ethers where N atom substitutes for some of O atoms in crown ethers. Cyclic polyether sulfides in which S atom substitutes O atoms are called thiacycrown ethers (Hiraoka, 1982).



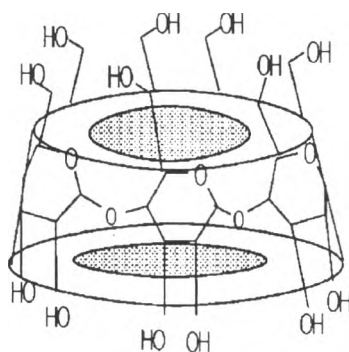
Scheme 2.2 Crown ether.

Crown compounds are reported to entrap not only alkali and alkaline earth metal ions, but also some typical and transition metals through

ion-dipole interaction helded by unshared pairs of electrons of O, N, and S atoms. The complexation ability and stability depend on cavity size, donor atom, diameter, and charge of cation. This results in function as phase-transfer catalyst and reagents (Hiraoka, 1982). Izatt *et al.* (1985) reported that crown ethers containing 5-10 oxygen atoms forming the complexes with Li^+ , K^+ , Na^+ , NH_4^+ , etc.

2.2.2 Cyclodextrin

Cyclodextrins are cyclic oligosaccharides prepared by enzymatic degradation of starch giving mainly three types of cyclodextrins, i.e., α -, β -, and γ -cyclodextrins, containing 6, 7, and 8 of α -1,4-linked D-glucopyranose units, respectively (Scheme 2.3). The circularly linked glucose units result in a molecular shape of truncated cone with an internal cavity capable for hosting organic compound guests.



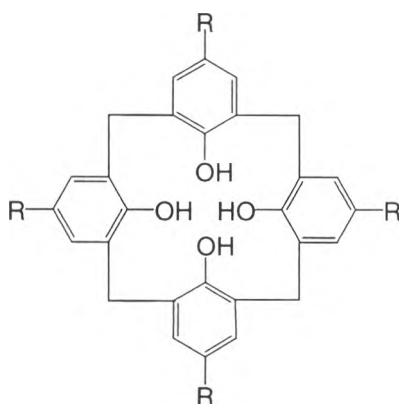
Scheme 2.3 Cyclodextrin.

Hydrophilic hydroxy groups located at outer rim make cyclodextrin dissolvable in water. The inner rim of their cavity lined by hydrogen atoms and the glycosidic oxygen bridges results in hydrophobic cavity (Chankvetadze *et al.*, 1996). Intramolecular hydrogen bonds formed between 2-hydroxy and 3-hydroxy groups of adjacent glucose units maintain

the remarkably rigid structure. Moreover, each D-glucose unit in cyclodextrin structure contains five chiral carbon atoms, to be a chiral macrocyclic compound. All of these properties lead to wide range applications, such as, solubilizers, diluents in pharmaceutical industries, flavor stabilizers in food industries, catalysts, and separation media in chemical industries (Chankvetadze *et al.*, 1996).

2.2.3 Calixarenes

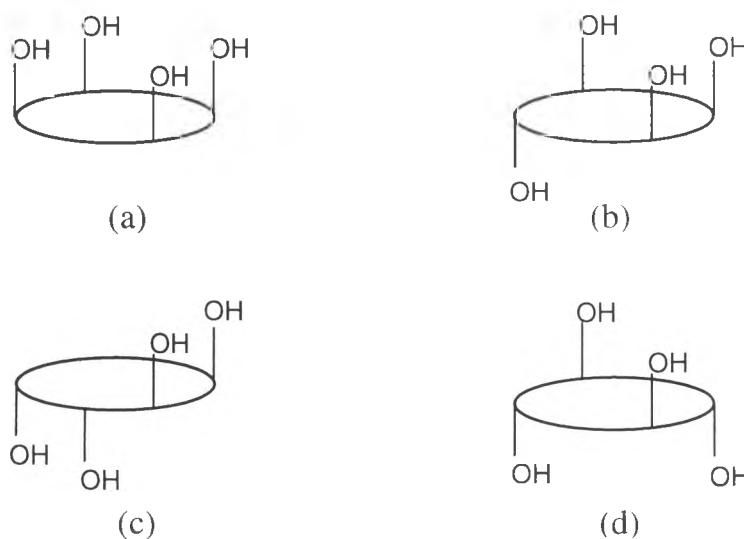
Calixarenes have received attention for the host guest chemistry owing to its cone- or calix-like conformation. The unique structure can be explained as a phenol chain linked by methylene bridges. The improvement of synthesis procedures makes it possible to prepare a selective calix[4]arenes (Scheme 2.4), calix[6]arenes, and calix[8]arenes. The compounds obtained are known to include various types of organic molecules and metal ions in the cavities.



Scheme 2.4 Calix[4]arenes.

The higher homologous (calix[6]- and calix[8]arene) are known to be more flexible. Gutsche introduced four possible conformations (Scheme 2.5) of calixarenes that are cone, partial cone, 1,2-alternate, and 1,3-alternate.

The potential applications range from the specific ligands, sensors (Diamond *et al.*, 1996), and medical diagnostic, decontamination of waste water, construction of artificial enzymes, synthesis new materials for nonlinear optics or for ultrathin layer, and sieve membranes with molecular pores (Böhmer, 1995).



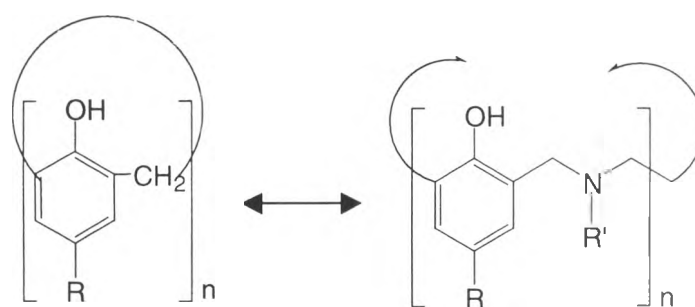
Scheme 2.5 Four possible conformations of calixarenes (a) cone, (b) partial cone, (c) 1,2-alternate, and (d) 1,3-alternate (Shinkai, 1993).

Shinkai *et al.* proposed the sulfonate ion of calix[n]arenes to induce the high water solubility. The compounds obtained performed inclusion complexation with several organic molecules and cation in aqueous solution. Ungaro, McKervy, and Chang indicated a series of calixaryl esters having superb alkali metal affinity.

2.3 From Calixarenes to Benzoxazine

Concerning the structure of calixarenes, factors that induce the host guest properties can be summarized as follows (Scheme 2.6 (a)).

1. The hydrophilic site of hydroxyl group
2. The hydrophilic site of R in phenol group
3. The methylene linkage
4. The controlled chains of oligomers
5. The lone pair electrons of oxygen atom.



(a) Calixarenes

(b) Oligobenzoxazine

Scheme 2.6 Structures of (a) calixarenes, and (b) oligobenzoxazine.

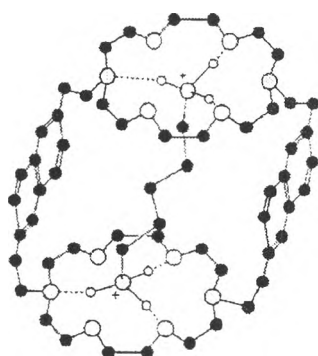
As shown in Scheme 2.6 (b), the open ring structure of benzoxazine can be claimed as aza-methylene phenol chain which resembles that of cyclic methylene phenol or calixarenes. Here, it is expected that the nitrogen atom of the tertiary amine linkage provides additional lone pair electrons to exhibit the inclusion properties.

2.4 Molecular Design

Supramolecules in natural systems induce the complicated molecular recognition under the simple molecular structures and interactions. The requirements of supramolecules can be concluded as an asset of molecules that has a specific structure where the secondary forces are formed. As a result, the specific channel or cavity for guest molecules, i.e., ions, monomers, and

neutral molecules. Thus, the key of success to design biomimic inclusion compound is known as an obtain of simple molecule which can form specific structure by its pseudocyclic and/or cyclic structure. In most cases, hydrogen bonding, π - π interaction, and hydrophobic interaction are the main secondary forces. The shape and size of the cavity induced by the specific structure, then, play an important role in selectivity (Ball, 1994). In the case of host molecules accepting the metal ions, the structure requires electron donors to entrap metal ions such as heteroatoms which provide lone pair electrons. A single cyclic unit of crown ether was developed for the ion binding ability and selectivity to be bicyclic, and tricyclic of cryptand and triazacrown as proposed by Lehn.

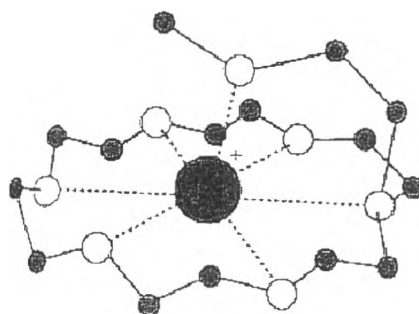
Another approach to improve the molecular interaction is to design the molecules where the cavity formed is resemble to the guest structure. In the case of pencil-case molecule, two units of azacrown linked by two linear spacer groups to form a pencil-like cavity (Scheme 2.7). In this case, a linear diamine molecule, which is a pencil-like compound, can be entrapped perfectly (Ball, 1994).



Scheme 2.7 Two azacrown rings joined by hydrocarbon spacer groups (pencil-like compound).

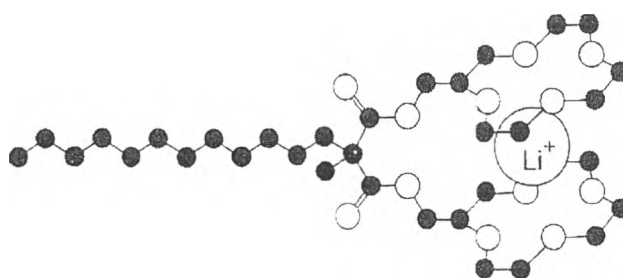
Gokel proposed a Lasso-like compound which is an azacrown having a linear hydrocarbon chain with additional electron donor group (usually an

ether group) attached to the N atom (Scheme 2.8). When metal ion is entrapped in the ring, the ether group of hydrocarbon chain will bind such metal ion more tightly.



Scheme 2.8 Lasso-like compound.

A Tong-like molecule, designed by Richard Bartsch, can entrap metal ions between its jaws (Scheme 2.9). The size of jaws is appropriate with lithium ion, thus making it useful for selective extraction of lithium.



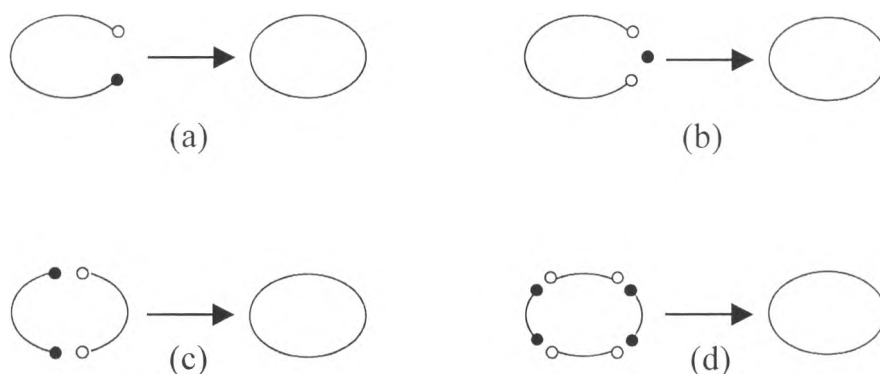
Scheme 2.9 Tong-like compound.



2.5 Cyclization

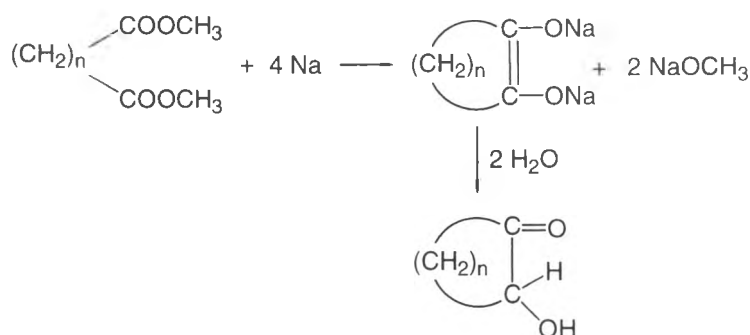
The term cyclization is defined as any interaction or reaction taking place between two ends of a chain (Dietrich *et al.*, 1993). Macrocycle can be formed in several ways that are;

1. Simple cyclization (Scheme 2.10 (a)),
2. Cyclization in conjunction with another molecule (capping) (Scheme 2.10 (b)),
3. Condensation of two or four either identical or different units (Scheme 2.10 (c), and (d)).



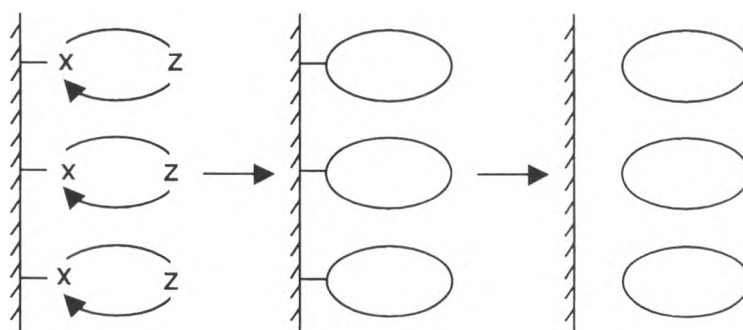
Scheme 2.10 Cyclization method (Dietrich *et al.*, 1993).

The cyclization can be induced when intramolecular reaction is more favorable than intermolecular reaction. High dilution technique is one of the ring closure methods. The concept of this technique was first formulated and applied by P. Ruggli (1912) who studied the formation of cyclic amides. For two components reaction, the two solutions of reactant are added dropwisely into large quantity of solvent with vigorous stirring. The key point of such technique is that the concentration of intermediate should be as dilute as possible. High dilution cyclization can be carried out in either homogeneous or heterogeneous medium. Acyloin cyclization is an example using heterogeneous method developed by Prelog and Stoll (Scheme 2.11).



Scheme 2.11 Heterogeneous method of acyloin cyclization (Herceg *et al.*, 1972).

In addition, solid-liquid heterogeneous medium (Scheme 2.12) with polymer support as a site for the reaction is another useful technique used in cyclopeptide synthesis.



Scheme 2.12 Cyclization in solid-liquid heterogeneous medium on a polymer support (Dietrich *et al.*, 1993).