CHAPTER II
THEORETICAL BACKGROUND AND LITERATURE REVIEW

2.1 Supramolecular Chemistry

Supramolecular chemistry is termed as the chemistry of molecular assemblies and of the intermolecular bond, as "chemistry beyond the molecule" (Lehn, 1995). Supramolecules consist of many simple subunits, each designed to perform a specific task. Ideal supramolecules found in natural system are DNA, RNA, and enzymes (Ball, 1994). For the past decades, development of instruments leads to the information of natural supramolecules and enables us to imitate the natural phenomena by designing the simple molecules with the complicated two- or three-dimensional structure. For example, Lehn *et al.* (1988) proposed the double-stranded "helicates", which obtained from the complexation of Cu(I) with tris(bipyridine), BP_3 (Figure 2.1). Catenanes and rotaxanes were carried out by the donor-acceptor interactions between bipyridinium ions and both benzocrowns and

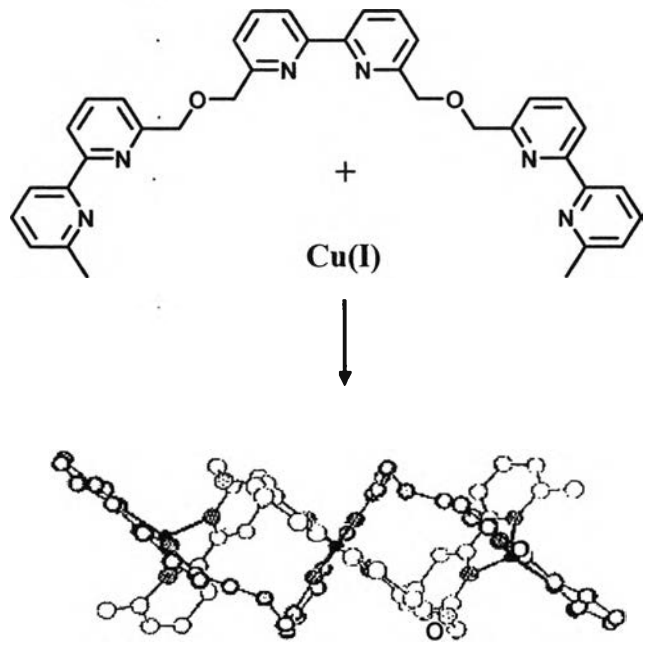
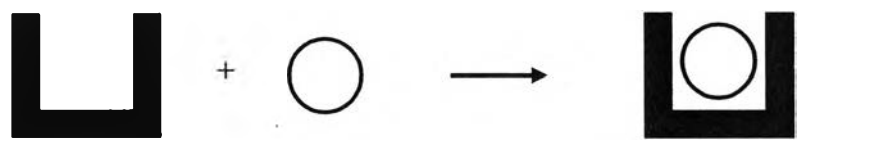


Figure 2.1 Schematic representation of the double-stranded "helicate", which result from the complexation of Cu(I) with BP_3.

naphthalenocrowns (Ortholand *et al.*, 1989). This leads to the development of synthetic supramolecules for using in many applications such as catalysts in biological systems, transporting agents in phase seperation systems, building blocks in supramolecular systems, molecular devices and machines, molecular switches (Gokel, 1999).

Considering to the supramolecular system, the components, which are host and guest molecules, are binded under the lock and key structure by intermolecular forces, but not by covalent bonds (Scheme 2.1) (Pedersen, 1967; Lehn, 1995). These intermolecular forces include van der Waals molecular interaction, electrostatic interaction, and hydrogen bonding (Fu *et al.*, 1992). The examples of well-known host molecules are crown ethers (Pedersen, 1967), cyclodextrins (Chankvetadze *et al.*, 1996), calixarenes (Böhmer, 1995), and their various derivatives. The guest species may be cations, anions, or neutral molecules (Pedersen, 1967; Lehn, 1995; Tuemmler *et al.*, 1977).

Scheme 2.1 Model of host-guest compound.



Host **Guest** **Host-Guest Compound**

2.2 Crown Ether based Macrocyclization

Crown ethers are macrocyclic compounds obtained by the cyclization of two or more different molecules under the dilute condition and/or the use of metal template. For example, 18-crown-6 and 15-crown-5 were obtained by using potassium and sodium ion as a template (Laidler *et al.*, 1989). Hydrogen bond networks of pyridazine and naphthyridine containing macrocycles were carried out via condensation (Xing *et al.*, 2005).

Up to now, various kinds of crown ethers have been proposed. For example, Monoazathiacrown ethers were carried out by the reaction of bis(2-chloroethyl)amine with dithiol derivatives (Tanaka *et al.*, 2001). Diaza-18-crown-6

and diaza-12-crown-4 were achieved by the cyclization of a ditosylate with the substituted diols (Zhang *et al.*, 1995). Fluorescent acridono-18-crown-6 was prepared by the cyclization of acridono derivatives and tetraethylene glycol ditosylated (Huszthy *et al.*, 2001). Although various kinds of crown ethers were carried out, the yields were limited at about 10-45% because of the purification process, e.g., column chromatography, extraction, and recrystallization.

Among many reports on the macrocyclization of crown ethers, the cyclization with tosyl derivatives under the presence of base was a good approach to obtain selective macrocycles. For example, Charbonnière *et al.* (2000) proposed the synthesis of novel crown ethers, i.e., cyclic di[(o-polyethyleneglycoxy)phenyl]amine by treating diarylamine with ditosylated tri-, tetra-, or pentaethyleneglycol using Cs_2CO_3 as the base. Ágai *et al.* (1996) reported on the preparation of dibenzo-monoaza crown ethers from cyclization phenol-aza-phenol derivatives with ditosylated compounds under the presence of K_2CO_3. In all cases, the cyclization of crown ring with various chain lengths of ditosylated compound gave only a single type of macrocycle, i.e., [1+1] macrocycle.

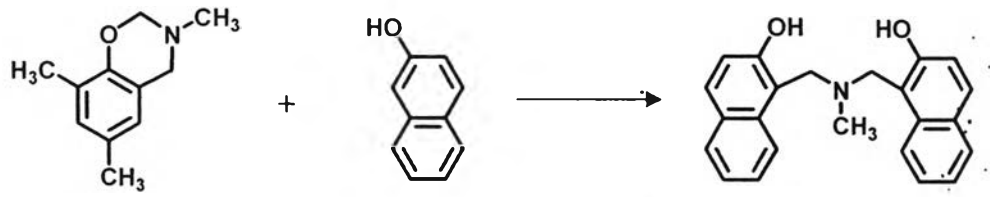
2.3 Inclusion Phenomena of Crown Ether and Its Derivatives

Crown ether and its derivatives are well-known as the host molecules to accept the guest species for both cationic and anionic guest species. For cationic guest species, the ions such as alkali (Izatt *et al.*, 1991; Demirel *et al.*, 2003), alkali earth (Buschmann *et al.*, 2000), lanthanide cations (Saleh *et al.*, 1999), and transition metal ions (Szalay *et al.*, 2004), were reported. In the case of anionic guest species, the protonated structure of crown ether was proposed. For example, Singh *et al.* (2005) reported about the chromate anion recognition of charged diaza 12-crown-4 and 18-crown-6. Božić *et al.* (2005) proposed the protonated 15-membered macrocyclic ligands for including various anion guest species, i.e., picrate, perchlorate, and thiocyanate anions. Based on the inclusion properties of these macrocyclic compounds, this leads to widely use in many applications such as phase transfer, selective cation, and sensor systems (Vogtle, 1991).

2.4 Chemistry of *N,N*-Bis(2-hydroxyalkylbenzyl)alkylamine

Burke *et al.* (1965) reported on the preparation of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives via a single ring opening of benzoxazine. For example, *N,N*-bis(2-hydroxy-1-napthylmethyl)methylamine was carried out by the ring opening reaction of 2,3-dihydro-2-methyl-1H-naphth-(1,2-e)-1,3-oxazine with 2-naphthol (Scheme 2.2).

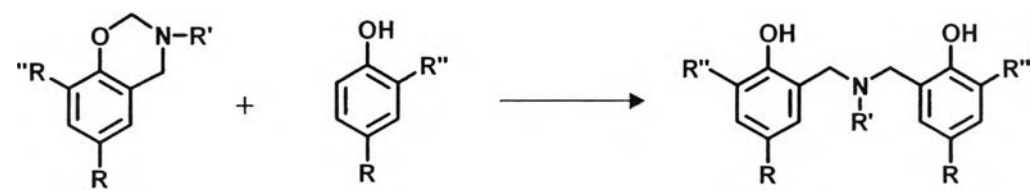
Scheme 2.2 Ring opening reaction of 2,3-dihydro-2-methyl-1H-naphth-(1,2-e)-1,3-oxazine with 2-naphthol.



In the case of para-substituted phenol based benzoxazines, linear polymer should be obtained. However, Riess *et al.* (1985) found that the polymerization proceeded with a limit of four to six repeat units. At that time, the involved factors and the mechanisms controlling the polymerization have not been clarified.

Our group demonstrated the single ring opening of benzoxazine was terminated under dimer level to obtain high yield (80%-90%) of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives (Scheme 2.3) (Laobuthee *et al.*, 2001, 2003; Phongtamrug *et al.*, 2004, 2005, 2006). Considering the structure of these derivatives, the single crystallography analysis pointed out the unique structures with inter- and intramolecular hydrogen bonds network (Figure 2.2) to provide asymmetric reaction (Laobuthee *et al.*, 2001).

Scheme 2.3 Single ring opening reaction of benzoxazines with phenol derivatives.



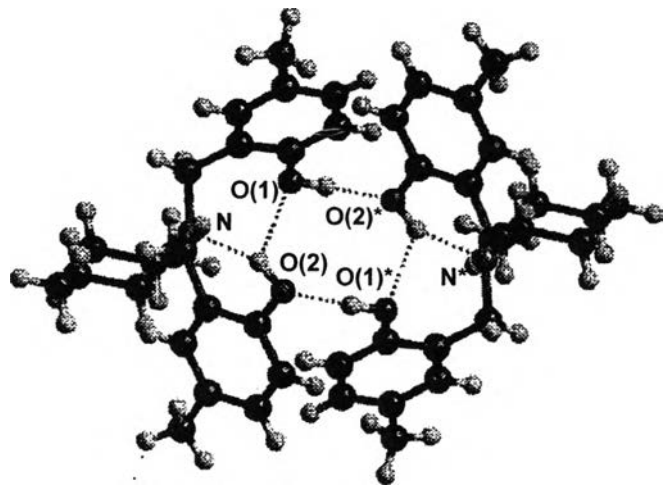
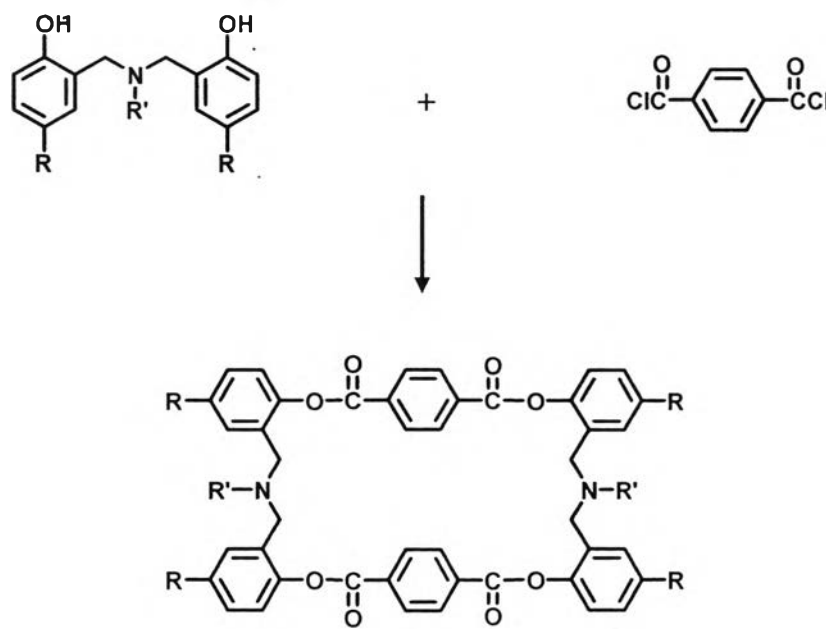


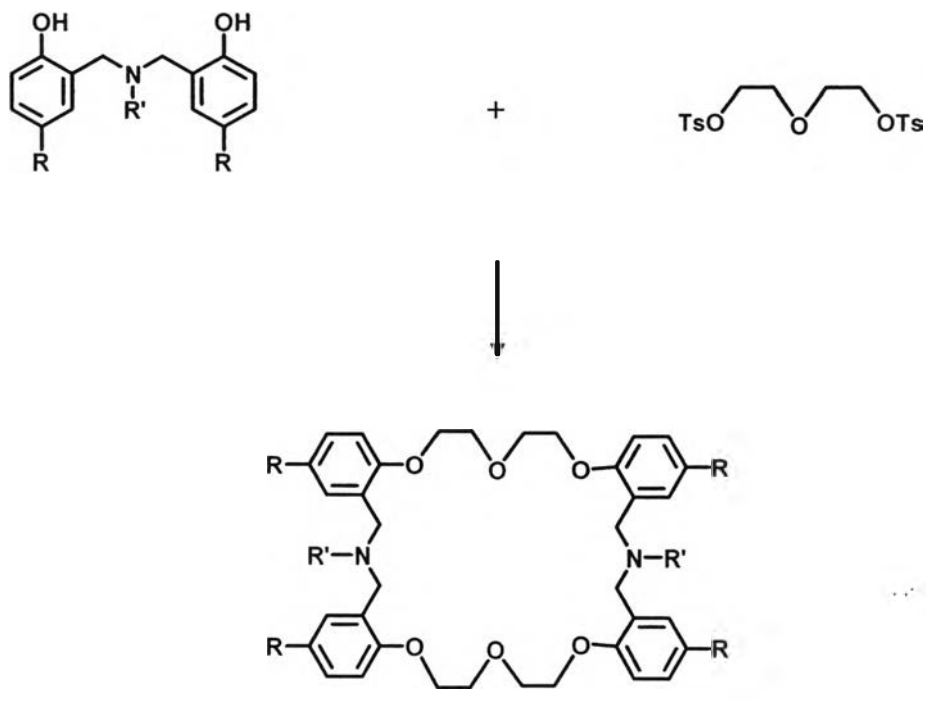
Figure 2.2 Crystal structure of *N,N*-bis(5-methyl-2-hydroxybenzyl)cyclohexylamine.

According to the structure of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine consisting of two phenol units, this compound has been modified for good macrocyclic structure via esterification (Scheme 2.4) (Laobuthee *et al.*, 2002) and etherification (Scheme 2.5) (Chirachanchai *et al.*, 2003).

Scheme 2.4 Esterification of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives with terephthaloyl dichloride.



Scheme 2.5 Etherification of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives with ditosylated diethylene glycol.



2.5 Inclusion Phenomena of *N,N*-Bis(*2*-hydroxyalkylbenzyl)alkylamine and Its Derivatives

According to the repeat unit of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine resembling to that of calixarene, this derivative can perform as host compound to accept various kinds of guest species. For example, our group reported about the inclusion phenomena of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives with alkaline picrate salts (Laobuthee *et al.*, 2003). We demonstrated the copper ion binding properties of the derivatives under the double-oxygen-bridged dimeric system (Phongtamrug *et al.*, 2006). We also proposed the existence of multiguest species, i.e., ion and neutral molecules, in a single host-guest framework (Phongtamrug *et al.*, 2005, 2006). In the case of macrocyclic compound based *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine, we exhibited the stoichiometric host-guest ratio of these macrocycles with alkaline picrate salts (Chirachanchai *et al.*, 2003).

2.6 Points of the Present Work

Our group succeeded in preparing *N,N*-bis(2-hydroxyalkylbenzyl) alkylamine and its derivatives in high yield (80-90%) via simple reaction conditions. We also clarified the supramolecular structure of *N,N*-bis(2-hydroxyalkylbenzyl) alkylamine derivatives in acceptance guest species. Based on the advantages of these derivatives, this brings us to modify this derivative to be macrocyclic host compounds.

We carried out the modification of *p*-substituted phenol based *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives to obtain [2+2] macrocyclic host compound showing the stoichiometric host-guest ratio with alkali picrate salts (Chirachanchai *et al.*, 2003). However, at that time, the factors to control the selective macrocyclization have not been identified. Chapter III focuses on an investigation of the ortho-substituted group in phenol group of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine in the selective crown ethers based macrocyclization. We also extend the works to the inclusion phenomena of these macrocycles with alkali ions.

According to the works reported by Charbonnière *et al.* (2000) and Ágai *et al.* (1996), the cyclization of crown ring with various chain lengths of ditosylated compound gave only a single type of macrocycle, i.e., [1+1] macrocycle. Currently, we found that the reaction of a derivative of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine with various chain lengths of ditosylated compound not only gives [1+1] macrocycle but also [2+2] one. In the Chapter IV, we aim to demonstrate how the structure of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine induce the selective macrocyclization to provide both [1+1] and [2+2] macrocycles.

As the approaches to achieve the good cyclic structure are using metal template (Dietrich, 2004; Reinhoudt *et al.*, 1976; Busch, 1992). When the backbone molecules are in a H-bond network, the non-template macrocyclic synthesis is also an effective pathway (Xing *et al.*, 2005). It should be ideal if we could design the reaction in which both a specific metal template and H-bonds synergistically function in macrocyclization. In the Chapter V, the work concentrates on the synergistic

effects of a specific metal template and H-bonds in controlling macrocyclization of *N,N*-bis(2-hydroxyalkylbenzyl)alkylamine derivatives.

Although we have reported the inclusion properties of [1+1] and [2+2] macrocycles (Chirachanchai *et al.*, 2003; Rungsimanon *et al.*, 2006), comparative studies on the structural factors related to the ion acceptance abilities have not yet been carried out. The present work (Chapter VI), therefore, focuses on dibenzo-monoaza-crowns and how their structures are involved with the metal ion selectivity.