CHAPTER II
LITERATURE REVIEW

2.1 Supramolecular Chemistry

Supramolecular chemistry is defined as 'chemistry beyond a single molecule' under the lock and key structure (Scheme 1) (Diemer *et al.*, 1995). Considering the component of supramolecules, we always pay attention on how two or more chemical species be associated as an assembly or host-guest system under the inter and intramolecular bonds (Steed, 2004). The function of supramolecules is based on the molecular recognition which host molecules selectively bind with guest species. The concept, the functions, and potential applications have been well accepted when D. J. Cram, J.-M. Lehn, and C. J. Pedersen are Nobel Laureates in 1987 (Frangsmyr and Malmstrom, 1992). Various types of compounds are reported as supramolecules either macrocyclic molecules such as crown ether (Patai and Rappoport, 1989), cyclodextrin (Bender and Komiyama, 1978), and calixarenes (Vicens and Boehmer, 1991; Gutsche, 1989, 1997) or assemblies of individual small molecules, such as nucleic acids (Fletcher *et al.*, 2003; Wengel, 2004) and steroids (Sada *et al.*, 2001). The guest species may be cation, anion, or neutral molecules (Vogtle, 1991).

Scheme 1

2.2 Calixarene

Calixarene is one of the synthetic supramolecules which can be obtained from a specific reaction of phenols and formaldehydes as exemplified in Figure 1 (Vicens and Boehmer, 1991). The compound and its derivatives are clarified for inclusion phenomena to accept various types of guests such as metal ions and organic molecules (Gutsche, 1989, 1997). Up to now, many researchers have developed the calixarenes chemistry to clarify the synthesis pathways and the derivatives as well as the functions about the guest sensitivity and selectivity. For example, the association constant of calixarene complex determined by NMR and the formation of 1:2 calix[n]aryl acetate-alkali metal ion complex proven by mass spectroscopy were reported (Shinkai *et al.*, 1988; Inokuchi *et al.*, 1993). Hexahomotriazacalix[3]arenes derivatives (Grannas *et al.*, 1994) show the binding of metal ions and alkylammonium ions whereas *N*-(2-picolyl)-hexahomotriazacalix[3]arenes (Takemura, 2002) perform their selectivity in binding with lanthanide ions.

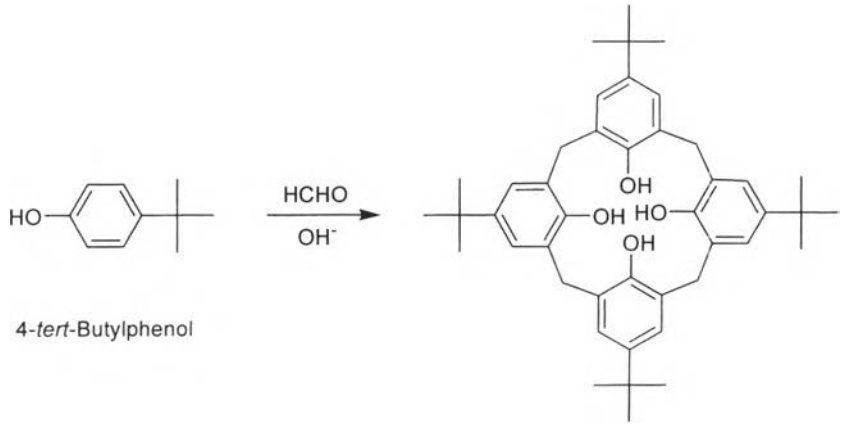
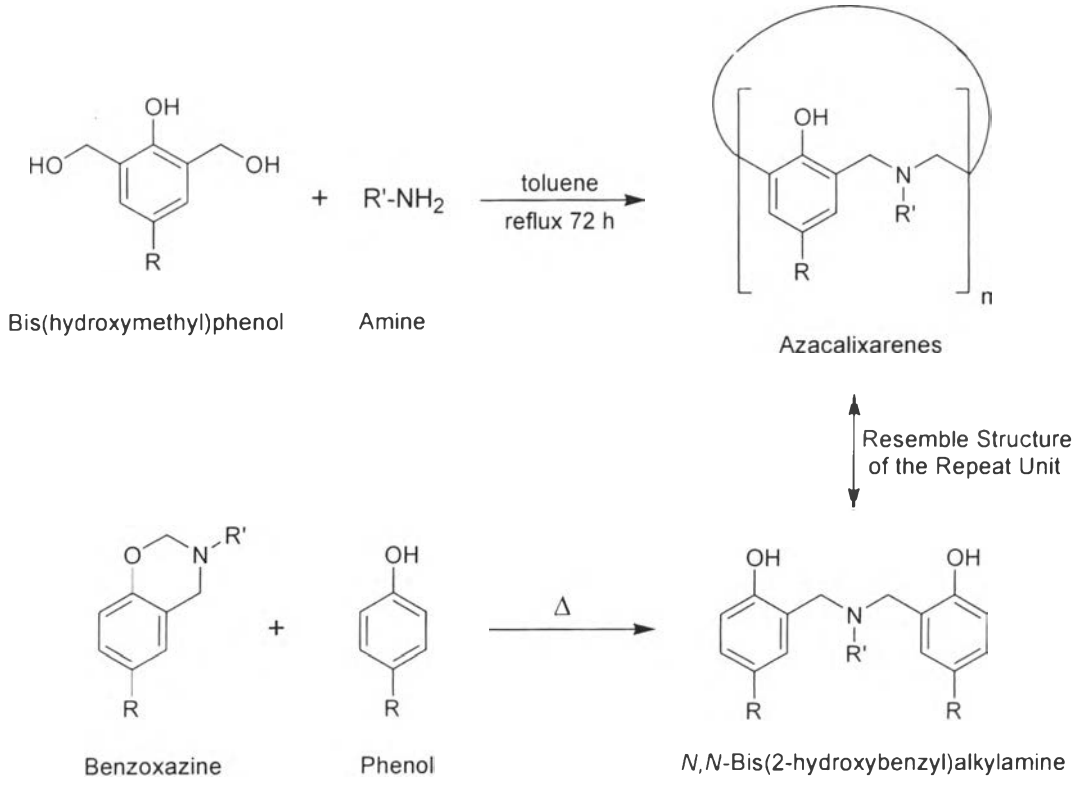


Figure 1. Synthesis of *p-tert*-butylcalix[4]arene.

2.3 Azacalixarene and the Related Structure of Benzoxazine Derivatives

Azacalixarene is a derivative of calixarenes prepared from bis(hydroxymethyl)phenol and amine (Scheme 2). In general, the aza group performs well in cation binding leading to the specific interaction with guest species (Liu *et al.*, 1998). For example, the efficient uranyl and lanthanide ion extraction of hexahomotriazacalix[3]arene and *N*-(2-picolyl)-hexahomotriazacalix[3]arenes were reported by Takemura *et al.* (1992, 2002). It is important to note that the repeating unit of azacalixarenes consists of phenol and aza-methylene unit. The structure of this repeating unit is similar to what we obtain from the ring opening reaction of benzoxazine.

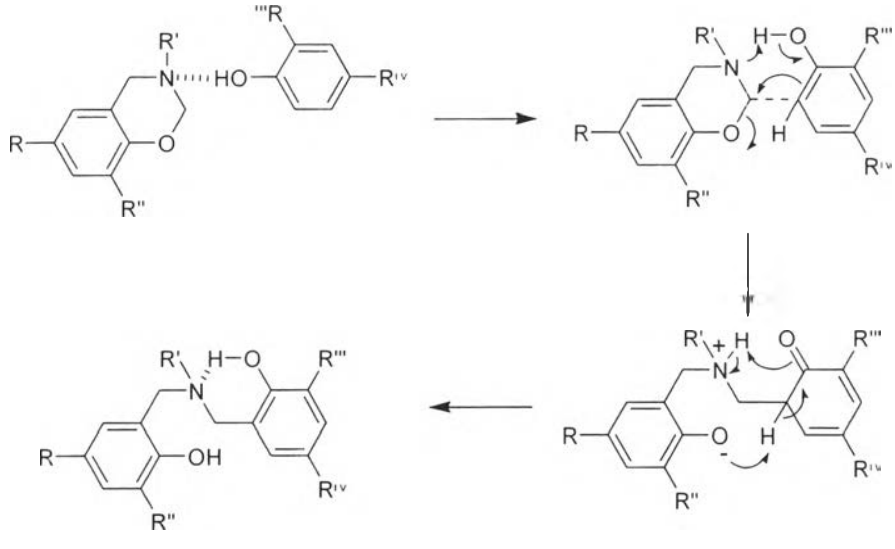
Scheme 2



2.4 Chemistry of Benzoxazine

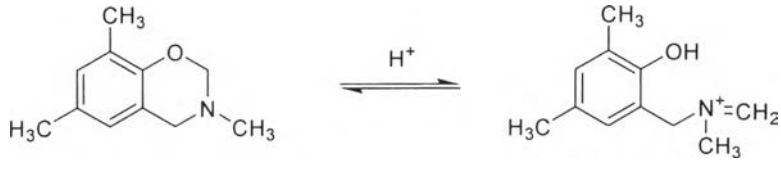
Benzoxazine is known to perform the reverse Mannich reaction via intermolecular hydrogen bond as shown in Scheme 3. The initiation step gives an intermediate, which provides the electron movement from nitrogen atom to hydroxyl group. It is proven that the ring opening reaction occurs specifically at the ortho position of phenolic group, which can be a guideline to design the many open ring benzoxazines (Bruke *et al.*, 1965).

Scheme 3



Another mechanism of which the protonation at oxygen atom in oxazine ring is the initial step (Scheme 4) to follow by the phenol unit addition was proposed (Reiss *et al.*, 1985).

Scheme 4

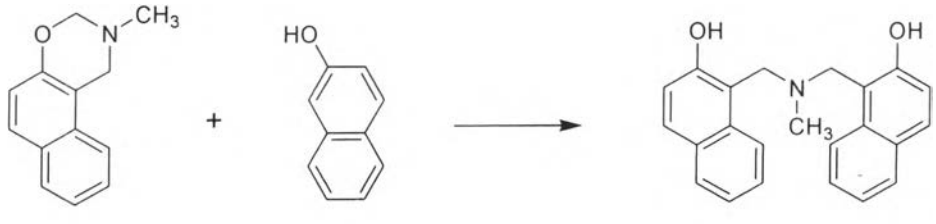


2.5 Chemistry of *N,N*-Bis(2-hydroxybenzyl)alkylamine

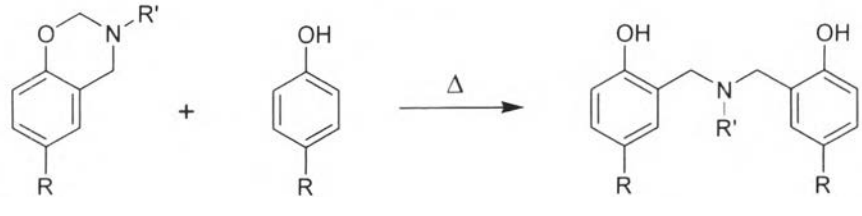
It is important to note that, with a single ring opening, benzoxazine gives a derivative of two phenols with methylene-aza-methylene linkage (Bruke *et al.*, 1965). For example, the reaction between 2,3-dihydro-2-methyl-1H-naphth-(1,2-e)-1,3-oxazine and 2-naphthol gives *N,N*-bis(2-hydroxy-1-napthylmethyl)methylamine (Scheme 5).

Based on its theoretical reaction pathway, it is natural to expect for a linear polymer from monophenol benzoxazine. However, up to now, there has been no report about linear polybenzoxazine. For the past few years, Laobuthee (2002) has focused on the ring opening reaction of benzoxazines to conclude that the chemistry of ring opening reaction of monophenol based benzoxazine is so unique. It gives mainly *N,N*-bis(2-hydroxybenzyl)alkylamine and rarely provides the linear polymer (Scheme 6). The structural characterization by FTIR, NMR, and single crystal X-ray analysis (Figure 1 in Chapter I) proved that the compounds are stabilized by intra- and intermolecular hydrogen bond networks (Laobuthee *et al.*, 2001). In addition, an inevitable asymmetric reaction via Mannich reaction was occurred even excess amount of formaldehyde and amine derivatives were used (Scheme 7).

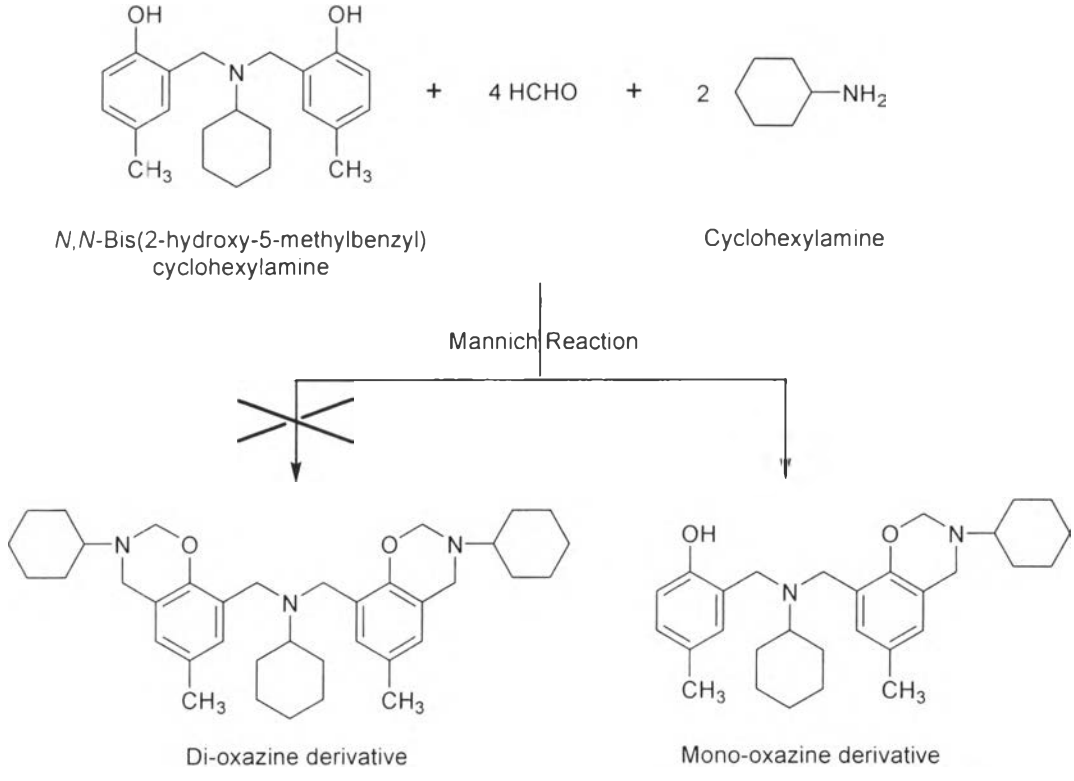
Scheme 5



Scheme 6



Scheme 7



2.6 Development of *N,N*-Bis(2-hydroxybenzyl)alkylamine for Supramolecules

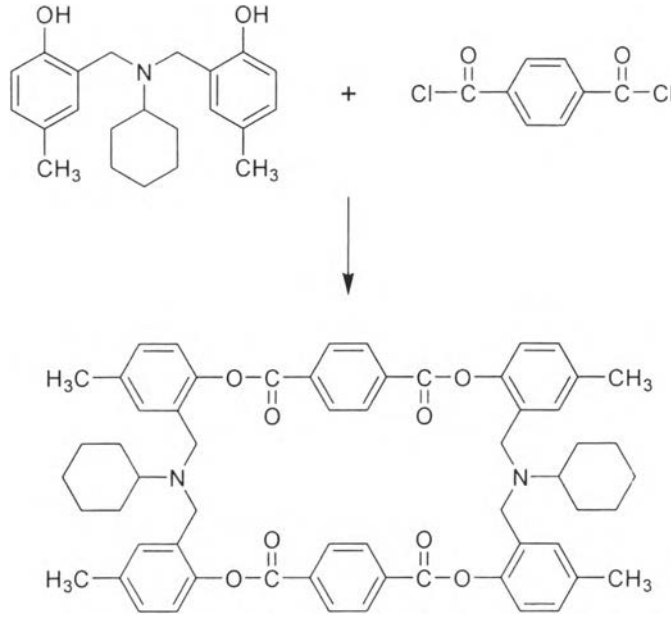
Considering the structure of *N,N*-bis(2-hydroxybenzyl)alkylamine, it can be pointed out that its structure is resemble to the repeating unit of azacalixarenes. For the past few years, our group has paid attention on the supramolecular structures and inclusion phenomena of *N,N*-bis(2-hydroxybenzyl)alkylamine.

In the area of synthesis, a simple, selective, and effective macrocyclization of *N,N*-bis(2-hydroxybenzyl)alkylamine (Schemes 8-9) was developed (Laobuthee, 2002). The macrocyclic compound obtained from etherification performed inclusion with alkali picrate salt in stoichiometric ratio (Chirachanchai *et al.*, 2003)

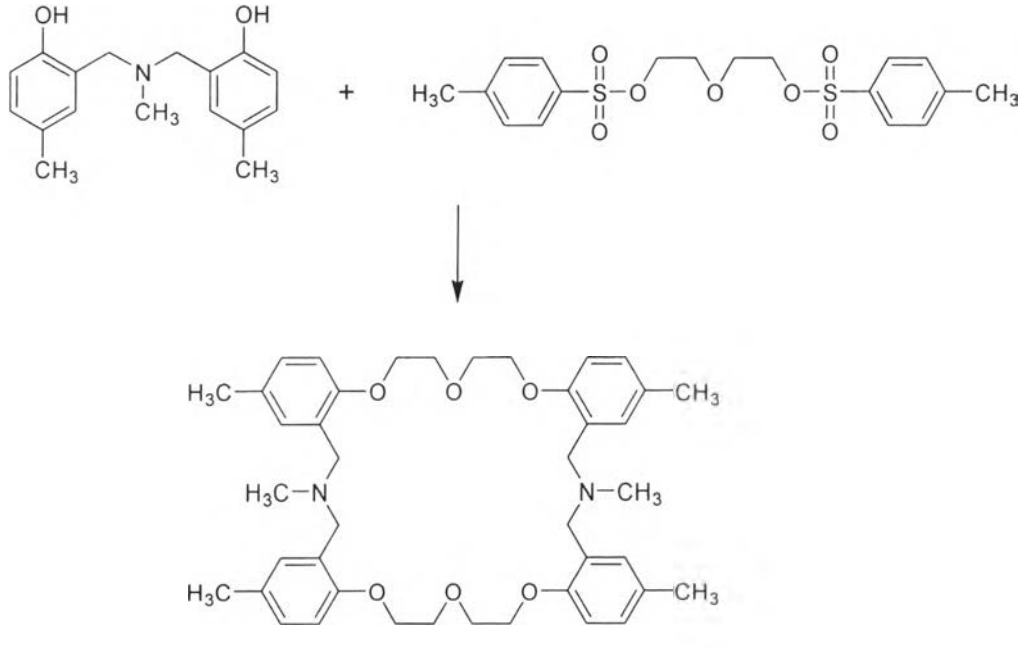
In the area of inclusion phenomena, the ion responsive properties of the ring opening structured bisphenol-A based benzoxazines with various alkali and alkaline earth metal ions was reported (Siripatanasarakit, 1997). *N,N*-Bis(2-hydroxybenzyl)alkylamine was systematically developed as a simple model to study

the inclusion phenomena with metal ions. The esterification of *N,N*-bis(2-hydroxybenzyl)alkylamine at hydroxyl group with terephthaloyl chloride gives a novel host to interact with alkali metal was demonstrated (Laobuthee *et al.*, 2003).

Scheme 8



Scheme 9



2.7 Supporting Evidences for Supramolecular Structure of *N,N*-Bis(2-hydroxybenzyl)alkylamine

The single crystal of *N*-[(2-hydroxylato-5-methyl)benzyl-(2'-hydroxylato-3',5'-dimethylbenzyl)]ethyl amine dicopper (II) (Figure 2) of which the host structure is similar to that of *N,N*-bis(2-hydroxybenzyl)alkylamine was reported (Malathy Sony *et al.*, 2002). It is important to note that the structure of bis[(3,5-dimethyl,2-hydroxy)-2'-hydroxy-5'-methyl]benzylethylamine can be defined as a derivative of *N,N*-bis(2-hydroxybenzyl)alkylamine. Although, the work emphasizes on the complexation with copper, the work gives us some supporting evidences about the supramolecular complexation of *N,N*-bis(2-hydroxybenzyl)alkylamine. The bis(μ_2-phenoxide)-bridged macrocyclic dinuclear copper (II) complexes by condensation of diformylphenol, diaminoalkane, and copper ion (Figure 3) was shown (Thompson *et al.*, 1996). In this case, the supramolecular structure of dinuclear copper (II) complex is an important information when we consider that the two phenols of a unit of *N,N*-bis(2-hydroxybenzyl)alkylamine might perform similar structure in accepting metal ions.

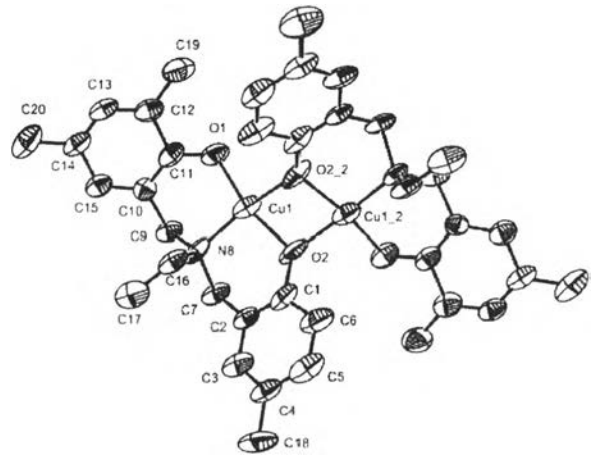


Figure 2. Perspective view of *N*-[(2-hydroxylato-5-methyl)benzyl-(2'-hydroxylato-3',5'-dimethylbenzyl)]ethyl amine dicopper (II) showing the thermal ellipsoids at 30% probability level (Malathy Sony *et al.*, 2002).

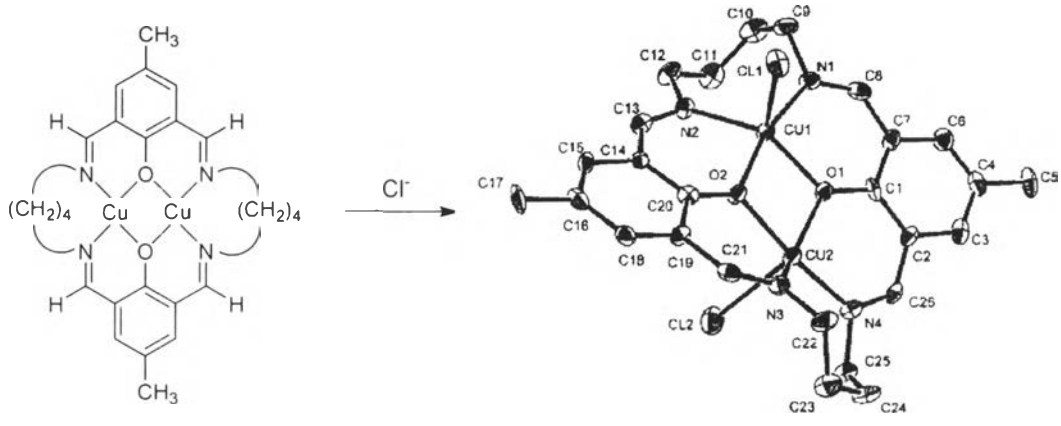


Figure 3. Bis(μ_2-phenoxide)-bridged macrocyclic dinuclear copper (II) complex (Thompson *et al.*, 1996).

2.8 Scope of the Present Work and Its Originality

The present work is initiated from the question about the inclusion formation of *N,N*-bis(2-hydroxybenzyl)alkylamine with transition metal ions. In order to find out how *N,N*-bis(2-hydroxybenzyl)alkylamine forms complex with transition metal ions in solution state, the simple approach is done by using various analytical techniques, i.e., UV-Vis, NMR, ESIMS, FTIR, XRD, and DSC. However, the absolute clarification of the host-guest compound from a single crystal X-ray analysis to determine the host-guest structure is also a goal in this work.

Based on the hydroxyl group and nitrogen atom in the structure of *N,N*-bis(2-hydroxybenzyl)alkylamine, non-covalent bonding such as ionic (Wohrle and Pomogailo, 2003), coordination (Beauchamp and Loeb, 2004), and hydrogen bonds with metal ions and/or neutral molecules (Lehn, 1995) is expected. Here, an attempt to discover any feasible conditions for metal and neutral guests entrapment are included in the work.

One of the most attractive points in modifying *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives is the cyclization for macrocyclic molecules. Since *N,N*-bis(2-hydroxybenzyl)alkylamine consists of diphenol, the reactions of phenol chemistry are focused. In this work, an effective and selective one-pot synthesis for [1+1] macrocyclization of *N,N*-bis(2-hydroxybenzyl)alkylamine and

1,3-bis(tosyloxy)propane to obtain dibenzo-monoaza-12-crown-3 is originally proposed.

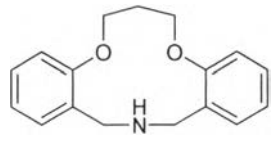


Figure 4. Structure of dibenzo-monoaza-12-crown-3.