CHAPTER I
INTRODUCTION

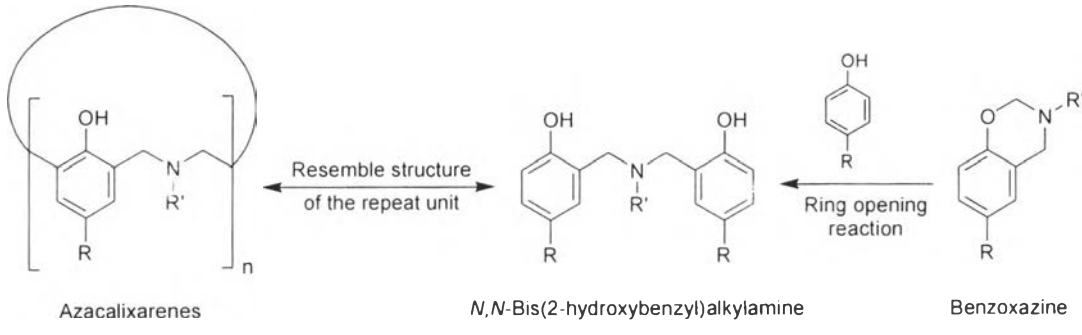
Supramolecular chemistry has received much attention for the unique molecular recognition and the related inclusion phenomena for decades (Pedersen, 1967; Pedersen and Frensdroff, 1972; Lehn, 1995; Tummler *et al.*, 1977; Vogtle, 1991; Nassimbeni, 2004). With the advance of instrumentation technology, not only cyclics but also acyclics are clarified for supramolecular structure to accept guest species based on either non-covalent interactions such as van der Waals (Knight *et al.*, 2002), dipole-dipole (Yasuda *et al.*, 1999), π-π stacking (Min and Suh, 2001), or hydrogen bonding (Raymo *et al.*, 2001; Desiraju, 2004). Various approaches to obtain supramolecular structured compounds are proposed starting from molecular modeling (Grotjahn *et al.*, 2004), template controlled reaction (Busch, 2004), and functionalization (Hoogenboom *et al.*, 2003). These systematical challenges cover the fundamental molecular designs to synthesis pathways. Up to now, various host molecules such as urea, cholic acid, cyclodextrin, crown ether, calixarene, and their derivatives have been developed and clarified for the molecular recognition (Diemer *et al.*, 1995).

Calixarene is one of the most well-known hosts of which various derivatives such as mercaptocalix[4]arenes, hexaamide calix[6]arenes, and bridged calix[8]arenes as well as the inclusion phenomena are reported (Ikeda and Shinkai, 1997). Calixarene consists of phenol unit and methylene linkage in macrocyclic structure. Azacalixarene is a derivative with aza group in between the phenol and methylene groups. It should be noted that the ring opening reaction of benzoxazine gives a repeat unit of phenol-methylene-aza which is resemble to that of azacalixarenes (Scheme 1). On this viewpoint, for the past few years, we have originally focused on the benzoxazine chemistry and aimed to clarify the inclusion phenomena as a novel host based on the molecular design and synthesis as well as the studies on supramolecular structure either in solution or solid state.

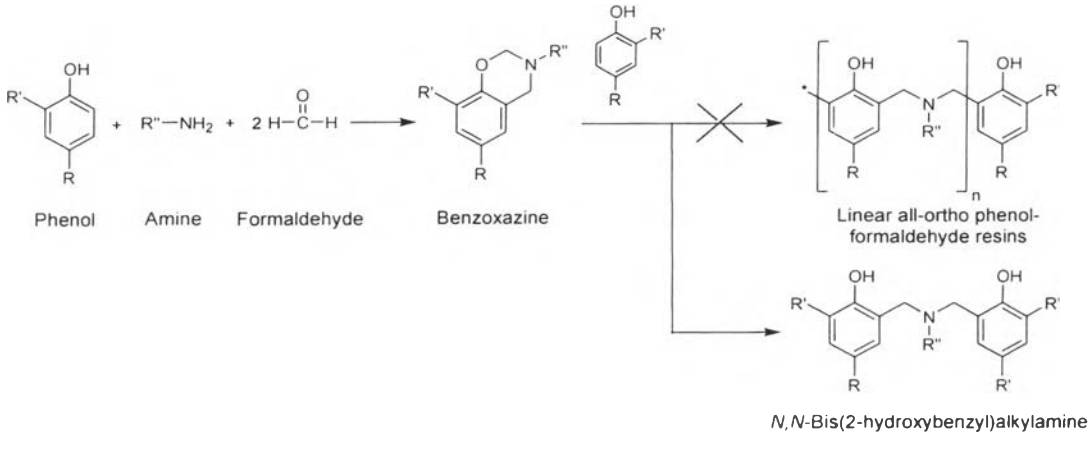
Benzoxazine is a heterocyclic prepared from the Mannich reaction of phenol, formaldehyde, and amine derivatives. The ring opening reaction of

benzoxazine proceeds easily under acid catalyst. In the past, our group declared that the ring opening of benzoxazine with the corresponding phenol is difficult to provide a linear polymer but quantitatively produces *N,N*-bis(2-hydroxybenzyl)alkylamine derivative possibly due to a single time of ring opening reaction (Scheme 2) (Laobuthee *et al.*, 2003). The structural characterization on the *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives by single crystal X-ray analysis (Figure 1), nuclear magnetic resonance (NMR), and Fourier transform infrared spectroscopy (FTIR) proved that the compounds are stabilized under the inter- and intramolecular hydrogen bond network (Laobuthee, 2002), as a result, only a single ring opening is promoted.

Scheme 1



Scheme 2



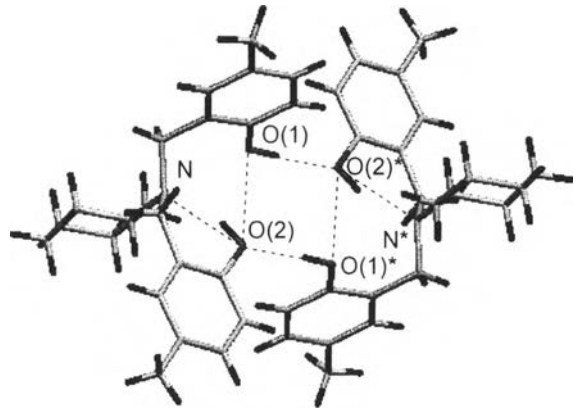


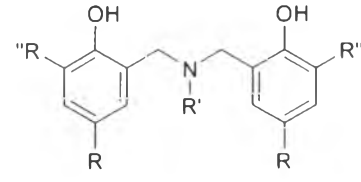
Figure 1. Crystal structure of *N,N*-bis(2-hydroxy-5-methylbenzyl)cyclohexylamine with the atomic numbering scheme (Laobuthee *et al.*, 2001).

Our challenge in supramolecular chemistry of *N,N*-bis(2-hydroxybenzyl)alkylamine derivative is started when we found the inclusion phenomena of the derivative with alkali and alkaline earth metals studied by ultraviolet visible spectroscopy (UV-Vis) technique (Laobuthee *et al.*, 2003). However, how the interaction of *N,N*-bis(2-hydroxybenzyl)alkylamine derivative with transition metal ions be established is left unclarified. Here, Chapter 3 aims to investigate the interaction with transition metal ions of *N,N*-bis(2-hydroxybenzyl)alkylamine. The inclusion phenomena of *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives, **1-5**, (Scheme 3) with transition metal ions are reported based on the qualitative and quantitative analyses by various analytical techniques, i.e., UV-Vis, NMR, FTIR, WAXD, differential scanning calorimetry (DSC), and electrospray ionization mass spectroscopy (ESI-MS).

It is important to note that single crystal analysis is the most useful technique to determine the precise structure of host-guest compound (Vogtle, 1991), thus, Chapter 4 focuses on the single crystal analyses of *N,N*-bis(2-hydroxybenzyl)alkylamine host interacting with copper guest. It should be note that although various transition metal ions were considered, the single crystal was obtained only in the case of copper ion. In this work, the crystallography work, computational calculation, and simulation (Cerius^2 and MS modeling) are applied to

demonstrate how the charge transfer system of host-guest is formed using copper ion as a model case. In this Chapter, the unique host structure to accept copper ion without structural changes is also clarified from the superimposed approach.

Scheme 3



N,N-Bis(2-hydroxybenzyl)alkylamine

1: R= CH_3, R'= CH_3, R"= H
2: R= CH_3, R'= C_3H_7, R"= H
3: R= CH_3, R'= C_6H_{11}, R"= H
4: R= C_2H_5, R'= CH_3, R"= H
5: R= CH_3, R'= CH_3, R"= CH_3

It should be noted that the crystallography analysis of *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine, **5**, after inclusion with copper ions declares the cases that solvent and/or water molecules existed in the packing structure. This leads to pay an attention on the concerted inclusion of guest species, i.e., ion species and neutral molecules, in a single host-guest unit. Chapter 5 describes simultaneous interaction of *N,N*-bis(2-hydroxy-3,5-dimethylbenzyl)methylamine with copper ion species, methanol and water molecules.

One of the most attractive points in modifying *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives is the cyclization for macrocycles. The potential reactions are those occurring at hydroxyl groups of phenol units. In the previous study, we reported for the first time about the simple but selective and effective synthesis pathway to obtain [2+2] macrocyclic compounds (Laobuthee and Chirachanchai, 2002; Chirachanchai *et al.*, 2003). Chapter 6 reviews how we challenged the novel macrocyclic compounds, dibenzo-monoaza-12-crown-3 derivatives (Figure 2), obtained from [1+1] of effective and selective one-pot synthesis route based on *N,N*-bis(2-hydroxybenzyl)alkylamine derivatives.

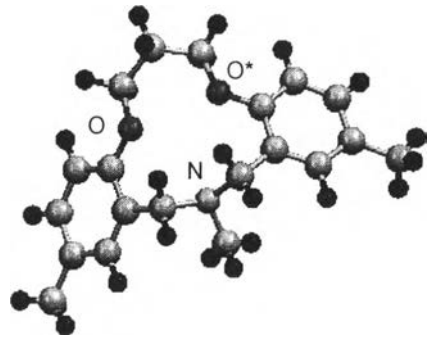


Figure 2. Crystal structure of dibenzo-monoaza-12-crown-3 derivative.

In conclusion, the present dissertation declares how *N,N*-bis(2-hydroxybenzyl)alkylamine obtained from a single ring opening benzoxazine gives us a novel host compound. The originality of the work is not only the host-guest structural analysis by single crystal X-ray technique but also the clarification about unique host structure which accepts both ion species and neutral molecules as guests at the same time. The work also covers the development of molecular design and synthesis of *N,N*-bis(2-hydroxybenzyl)alkylamine by clarifying that a dibenzo-monoaza-12-crown-3 can be selectively obtained in high yield via a simple but effective reaction condition.