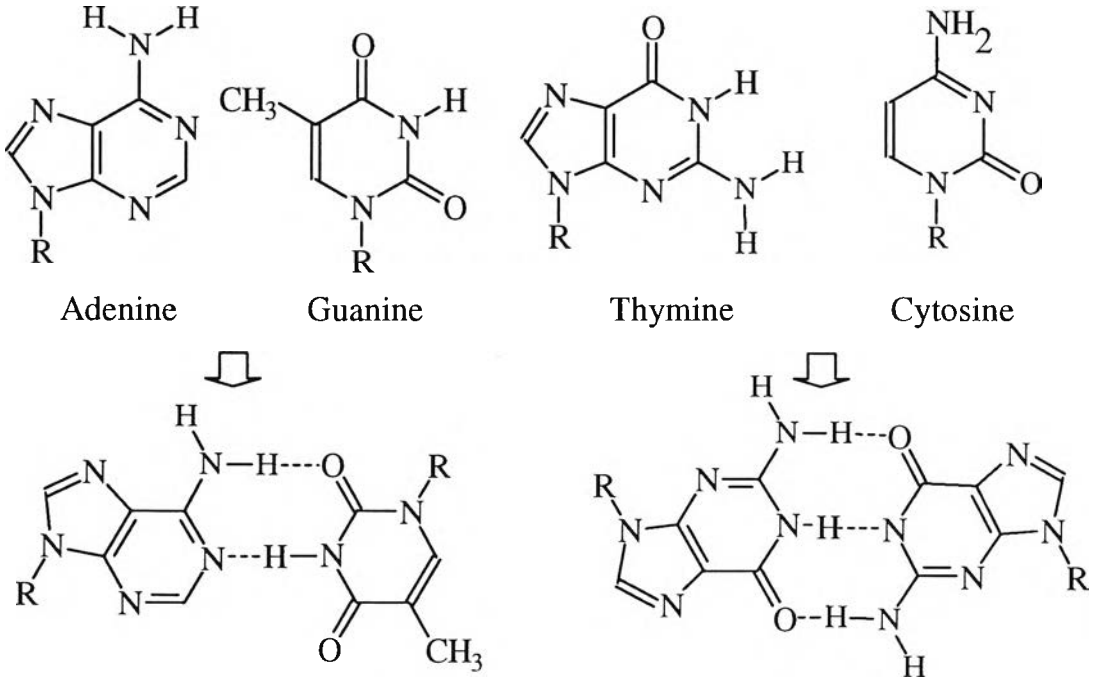
CHAPTER II

LITERATURE SURVEY

2.1 Supramolecular Chemistry; The Definition

Supramolecular chemistry was received much attention for the first time when Watson and Crick, the Nobel Laureates in 1962, reported the unique structure of nucleic bases pairing and their double helix secondary structure. In the later time, it is known that the molecules perform the function of genetic code, such as translation, transcription and transformation in 1953 (Scheme 2.1). Based on the understanding at the molecular level, the simple molecules of adenine, guanine, cytosine, and thymine are known to form the base pairing to each other by using the hydrogen bonding and the π–π stacking conformation between purine and pyrimidine heterocyclic.

Scheme 2.1 Four principal nucleic acid bases and base pairing



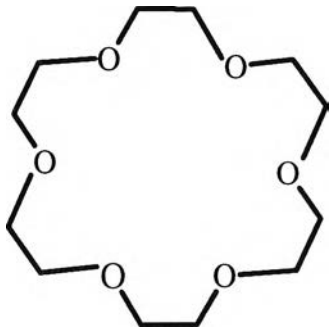
The base paring is considered to be an ideal supramolecule which inspires a new concept of chemistry under the name of "Molecular Assembly", "Inclusion or Host-Guest Compound", Molecular Recognition", and Biomimetic Chemistry". Conceptually, supramolecular chemistry is defined as "lock and key" of the two individual molecules stabilized each other by the non covalent bonding, or in another words, the secondary forces, i.e., van der Waals, dipole-dipole interaction, ionic interaction, and hydrogen bonding. Two individual molecules are called "host" and "guest" molecules, while the asset of host and guest molecules is called "Inclusion Compound".

Theoretically, host guest compound is defined as follows. 1) "The spontaneous assembly of molecules into structured, stable, noncovalently joined aggregates (Whiteside *et al.*, 1991)". 2) "The nonconvalently interaction of two or more molecular subunits to form an aggregate whose novel structure and properties are determined by the nature and positioning of the components (Hamilton *et al.*, 1990)". 3) "The spontaneous formation of higher-ordered structure (Lindsey 1991). The specific interaction between host and guest, which can occur under a certain condition, is known as a "Molecular Recognition". For the past three decades, the structures of host-guest compounds have been clarified and well-understood year by year owing to the improvement of the analytical instruments. In the present era, it comes to the point of how we can design a particular molecule satisfying the conditions to form the host guest compound, so called the molecular architecture research, and how we can control the structure of host guest compound, so called the molecular recognition. The extension of these researches in this area is to find the new molecules under the concept of supramolecular chemistry by imitate the biosystem or natural supramolecules, so called biomimetic chemistry. The development of biomimetic chemistry enables us to obtain the unique functions in the new host molecules that can introduce to practical applications.

2.2 Complexation of Well-known Host Compounds

Artificial or synthetic host guest compound has been received much attention since the clarification of cyclic structure of crown ether (Scheme 2.2)

Scheme 2.2 Crown ether



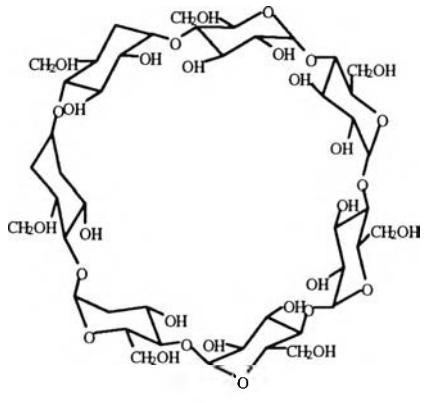
Crown ether is a cyclic oligoether that provides the polar cavity to form complexes with metal ions. Before that time, less studied were dealt with the possible structure of polyether and its related complex formation properties until Pedersen demonstrated the feasibility of synthesizing large cyclic polyethers, containing more than one benzoyl group, by the condensation methods of diol and divalent organic groups. Pedersen reported the simple crown ethers forming the complex with ammonium and alkylammonium salts (Pedersen, 1967). The general preparation of oxycrown compound was reported to be achieved by refluxing diol and divalent organic groups, with the different ratio and reaction time. There are many types of crown ethers reported, such as oxycrown, azacrown, or thiacrown compounds (Hiraoka, 1982). The size of cavity and ion dipole interaction was known to be dependent on the number of O or electron rich atoms in crown structures. Izatt, S. R. *et al.* (1985) found that crown ether host contained 5-10 oxygen atoms forming the complexes with Li^+, K^+ and NH_4^+, etc. *t*-Butylcyclohexyl-15-crown-5 and cyclohexyl-21-crown-7 were reported to entrap alkali metal

ions. Owing to their specific structures, there are many applications of crown ethers,i.e., organic synthesis catalyst, ion separation, or ion transportation

Marchand *et al.* (1999) studied the capability of alkali-crown ethers and alkali-cryptands complexation to find the selectivity toward the extraction of Li^+ and Na^+ picrates. Cage-functionalized diaza (17-crown-5) ethers were found to show the high selectivity toward the complexation with K^+ and Rb^+ picrate solutions.

The second generation of inclusion compound can be raised for cyclodextrin. Cyclodextrins are natural products from enzymatic degradation of starch which is composed of six to eight glucopyranoside units bound head to tail in cycle at 1- and 4-positions. Cyclodextrin can be devided into 3 types, α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin (Scheme 2.3). The key factors making cyclodextrin as host compound can be mentioned as the cyclic or ring structure, the hydrophilicity and hydrophobicity of the cavity and the specific size of the cavity, depended on the number of dextrins. The cavity size of cyclodextrin is in the level to entrap neutral molecules, such as α-cyclodextrin can entrap with benzene or phenol, β-cyclodextrin can include naphthalene or 1-anilino-8-naphthalene-sulphonate and γ-cyclodextrin can incorporate anthracene.

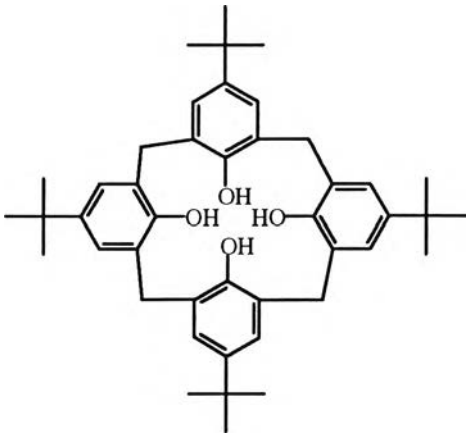
Scheme 2.3 Cyclodextrin



γ-Cyclodextrin was applied with digoxin as a drug for controlled release system (Iwamoto, 1978) and found that it maintained the effective amount and time owing to the improvement of solubility of digoxin by cyclodextrin in blood.

Calixarenes, as shown in Scheme 2.4, are known as the third generation of host compound by phenol-formaldehyde condensation. The structures of calixarenes were analyzed to be cone, partial, 1,2 alternate, and 1,3 alternate conformations (Knop and Pilato (1985)). The number of arenes in the calixarenes can be controlled by the reaction condition. The unique structure of calixarenes can be claimed to the hydrophobic and hydrophilic parts arranging on the top and bottom of the ring.

Scheme 2.4 Calixarenes



Gutsche (1989) reported that calixarenes and their cyclic oligomers between *p*-substituted phenol and formaldehyde can form the host-guest complexes with various types of organic molecules and metal ions. Applications of calixarenes are expected in many areas, such as catalyst, seperation, isolation, purification and dissolvation. Arduini *et al.* (1986) reported p-*t*-butylcalix[4]arenes and the sodium selectivity via extraction experiment. Pulpoka and his coworkers (1996) clarified the structures of

calix[4]arenes bridged by a cryptand unit and a crown ether chain in 1,3-alternative conformation and demonstrated ion entrapment property by varying alkali picrate salts. Ungaro, R. *et al.* (1996) reported the conformational properties of calix[4]arenes derivatives and proposed as a new receptor for the selective encapsulation of metal ions and neutral molecules. Calix[4]arenes with 1,3-alternate structure was known as the selectivity potassium ionophores. Sone *et al.* (1997) reported that sulfur-bridged calixarenes can trap the neutral guests, such as acetone, benzene or dioxane.

2.3 Clarification of Inclusion Compound

There are many techniques that can be used to clarify the host guest compound, depending on the nature of guest species, i.e., ionic and neutral species. In the case of ions as guest species, the host guest interaction can be identified whether it is in liquid or solid state. UV/Vis can be applied to clarify the ion interaction ability. Smid (1972) reported that UV spectra clarified the changing of host and guest about electron surroundings as can be observed from the peak shifting. NMR technique is good for quantitative analysis on the host guest ratio. Cram and Ho (1986) noted that the chemical shift of picrate proton was around 8.8 ppm via ^{1}H-NMR. Pulpoka *et al.* (1996) reported that the peak of aromatic protons on calix[4]cryptand crown-6 was shifted and concluded that the potassium was located in the cryptand cavity. Lamsa *et al.* (1998) also reported that ^{1}H-NMR can clarify the guest entrapped inside the host system. Arbuini *et al.* studied cone conformation of p-t-butylcalix[4]arenes to entrap with K^+. TGA and XRD were applied to study the host guest ratio and host guest structure, respectively. Mass spectroscopy is another method that gives the information about host-guest complexation and the molecular assembly when the host and the guest form a cluster. Leize *et al.* noted that electrospray mass spectrometry exhibited the metal complexes between their compound entrapped with Cu^{2+}. Shiina and Kinumaki (1997)

reported the complexation by using mass spectrometry and showed the differences in fragmentation between $[M+H]^+$ and $[M+Li]^+$.

2.4 Inclusion Compounds and the advanced Applications

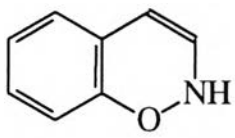
Due to molecular recognition properties, the applications of inclusion compounds can be classified into 2 stages, specific and advanced applications. According to the specific properties, such as ion dissociation and selective separation, host guest compounds can be applied as catalysts and ultrahigh purification. The molecular recognition of host guest compounds brings the advanced application such as, phase-transfer system, streospecific controlled polymerization, separation and shielding, and stabilization of unstable species. Inclusion compound can be used in a chemical transportation. Lehn (1995) noted that the ability of 18-crown-6 macrocyclic polyethers could bind primary ammonium ions to induce chemical transformation on such substrates as seen in enzymatic model studies. Recently, the advanced applications based on biomimetic concept have received much attention.

2.5 Development of Benzoxazines

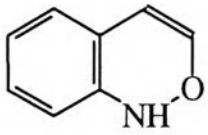
Benzoxazines, a type of phenolic materials, have eight isomerism structures (Scheme 2.5) depending on the position of methylene group by supplementary of H as defined by Elderfield and his colleagues. Holly and Cope (1944) studied the reaction between *o*- and *p*-halogen-substituted phenols with formaldehyde and primary aliphatic amine in the condensation reaction. Burke (1947) studied the synthesis of 3,4-dihydro-1,3,2H-benzoxazines using *p*-substituted phenols, formaldehyde and primary amine in the molar ratio of 1:2:1 respectively. The reaction of 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxoazines, formaldehyde and primary amine was

proposed to form N,N-dimethylolamine leading to further reaction with phenol derivative to obtain benzoxazine monomers (Scheme 2.6).

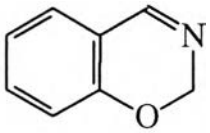
Scheme 2.5 Isomeric structures of benzoxazines



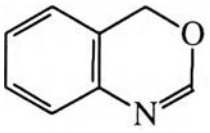
1,2-benzoxazine



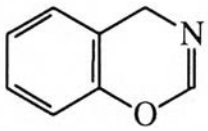
2,1-benzoxazine



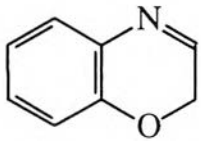
1,3,2-benzoxazine



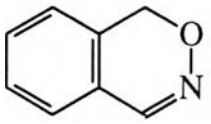
3,1,4-benzoxazine



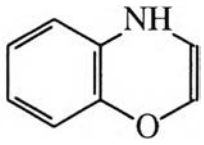
1,3,4-benzoxazine



1,4,2-benzoxazine



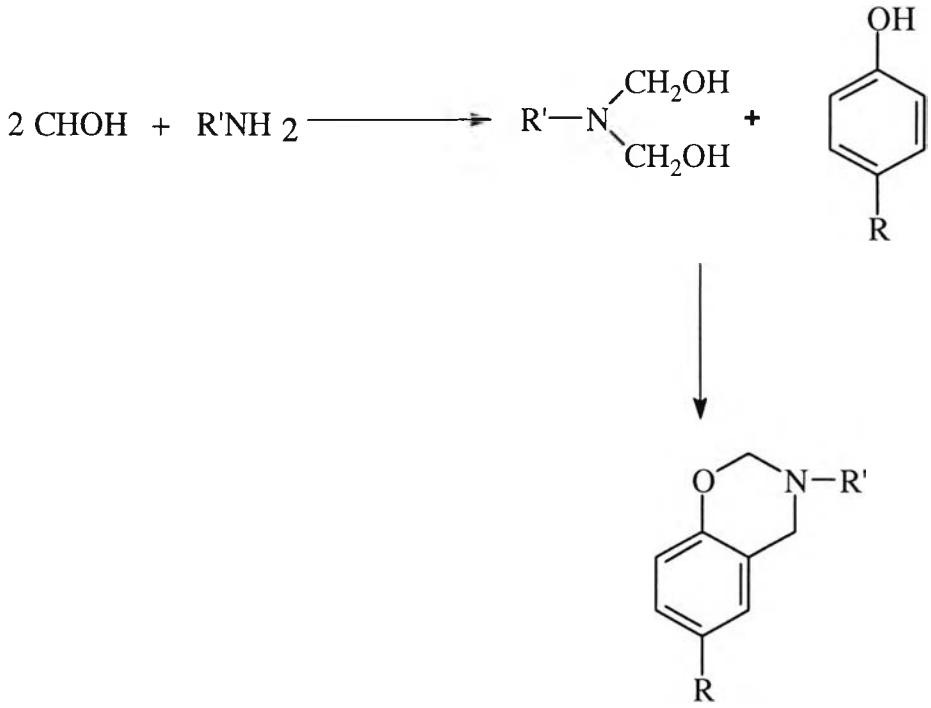
2,3,1-benzoxazine



1,4-benzoxazine

Burckhalter (1952) also focused on Mannich reaction with ortho-phenylphenol to form dimer with methylene-amine-methylene bridge or Mannich base position for antimararial study. The reaction was proceeded by using dioxane as a solvent.

Scheme 2.6 Preparation of benzoxazine monomer



2.6 The related Structure of Benzoxazines and Calixarenes

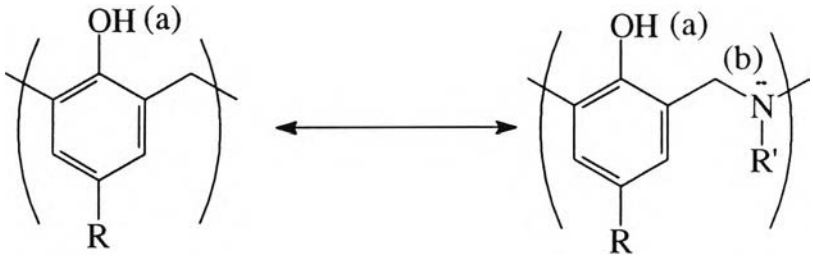
Chirachanchai *et al.* (1998) proposed benzoxazines as a novel type of host compound since the open ring structure of benzoxazine is somewhat similar to that of calixarenes. Thus, benzoxazine, which has both oxygen and nitrogen atoms containing the lone pair electrons, is also expected to show the phenomena like calixarenes (Scheme 2.7). Siripattanasarakit *et al.* reported that benzoxazine monomer synthesized from bisphenol-A and aniline (B-A) could entrap metal ion by its assembly.

2.7 Benzoxazine and its Guest Responsive Property

Siripattanasarakit (1997) studied the liquid/liquid extraction systems of benzoxazines to find the properties as ionophores forming complexes with

various metal ion types. Evaluation by Pedersen's technique was found that both monomers and oligomers of benzoxazine exhibit ion extraction in high percent yield. The ion extraction percentage was strongly controlled by the solubility parameter of the solvent. Benzoxazines displayed much more significant ion affinity than the reported hosts, i.e., calixarenes. pseudocyclic calixarenes crown ether.

Scheme 2.7 Structures of Calixarenes (I) and Benzoxazines (II)



(I) (II)

(a) hydroxy group

(b) aza methylene linkage

Phongtamrug (1998) reported that the different functional groups on benzene ring group had the effect on the ion extraction ability of benzoxazine monomers and leaded to the molecular assembly formation. Moreover, owing to the steric effect of benzoxazine monomer, the molecular assembly was proposed as loose or/and flexible structure allowing the ability for the metal ion entrapment.

Techakamolsuk (1999) presented the open ring of benzoxazine dimers and their modified structures and clarified the effects of the bulkiness in the dimers. The effects of intramolecular hydrogen bonding and electron lone pairs played the role in the ion extraction step.

2.8 The Scope of the Present Work

Although Siripatanasarakit found that benzoxazine monomer (Ba-A) showed ion extraction ability, the factor induced was not clarified. Thus, in the first part of the present work, a series of benzoxazine monomers were tailored with the variation of bulky groups at benzene ring and aza group, in order to proceed the systematical studies on ion extraction ability. Meanwhile, in the previous work the ion interaction property was studied by using a series of alkali metal picrate ions. Thus, it is another objective of the present work to study the possibility of other metal salt interaction. With the various aspects of the database about host-metal inclusion compound of benzoxazine, the origin of host-guest interaction will be clarified.