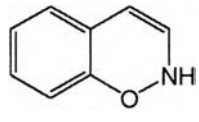
CHAPTER I
INTRODUCTION

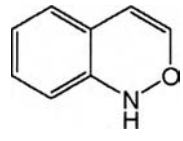
1.1 The Molecules and Chemistry of Benzoxazines

Benzoxazines are a type of heterocyclic compounds from the benzene and oxazine rings. The eight isomerism structures dependent on the position of methylene group by supplementary of H are defined as shown in Scheme I (Elderfield *et al.*, 1957).

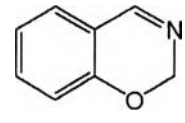
Scheme I



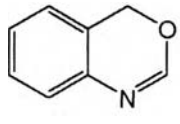
1,2-benzoxazine



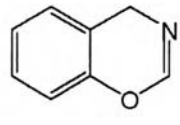
2,1-benzoxazine



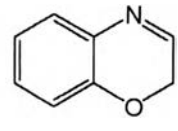
1,3,2-benzoxazine



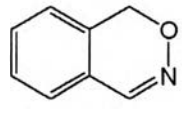
3,1,4-benzoxazine



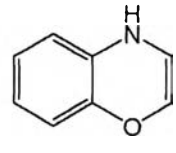
1,3,4-benzoxazine



1,4,2-benzoxazine



2,3,1-benzoxazine

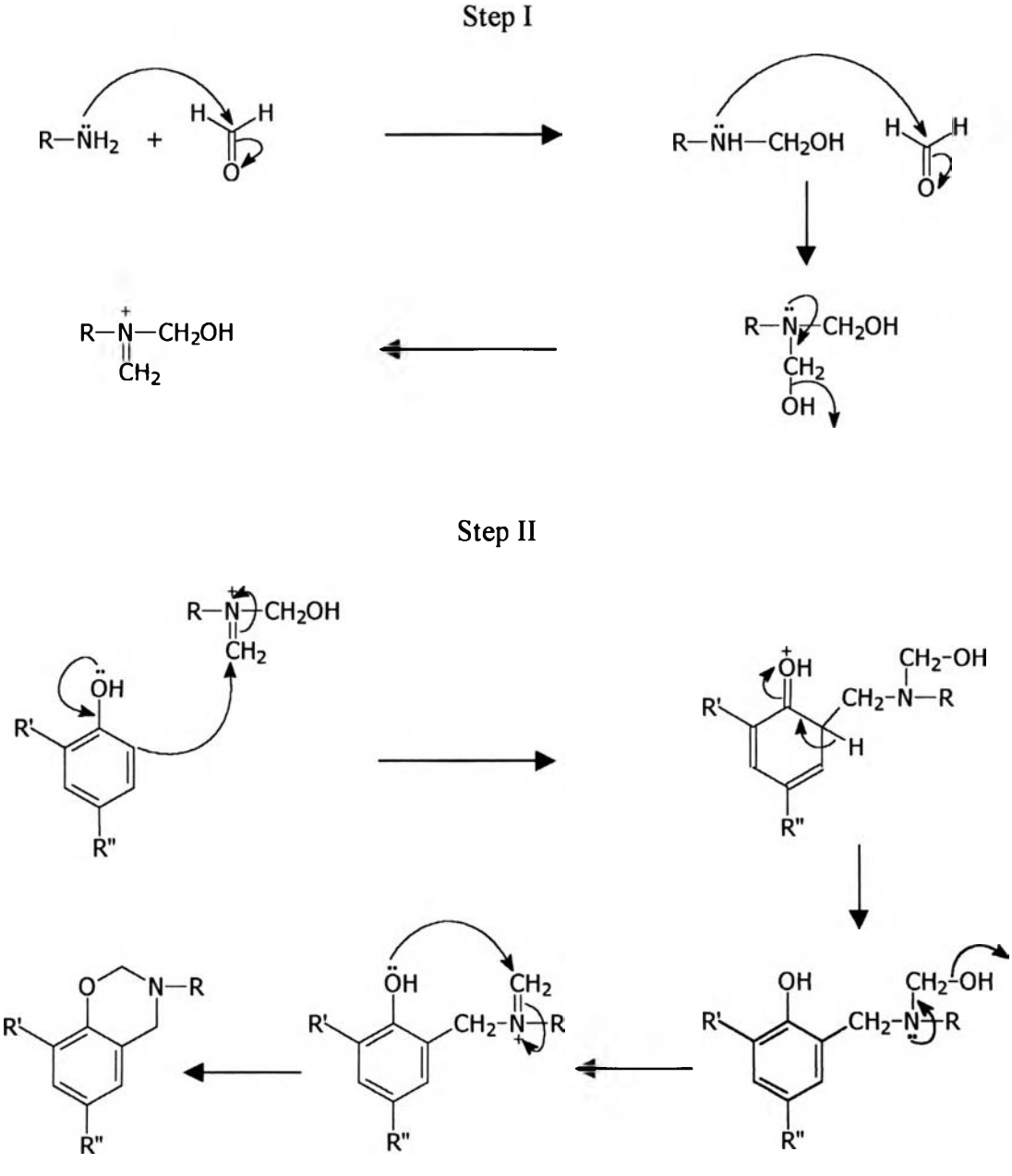


1,4-benzoxazine

Benzoxazines can be prepared by Mannich reaction from phenols, formaldehyde and amines (Holly and Cope, 1944). The ring formation of benzoxazines is proceeded via the mechanisms shown in Schemes II and III. Burke studied extensively the synthesis of benzoxazine derivatives, 3,4-dihydro-1,3-2H-benzoxazines, in a single step from *p*-substituted phenols, formaldehyde and a primary amine in a molar ratio of 1:2:1, respectively (Scheme II). An alternative method is that the equimolar quantities of each reactant react in the first step to obtain an intermediate of o-alkylaminomethyl-*p*-substituted phenol, followed by

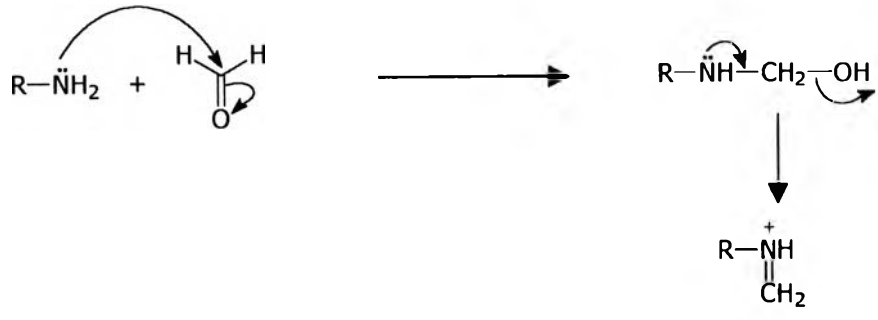
treating with formaldehyde in the presence of a basic catalyst to converse to 3,4-dihydro-3,6-disubstituted-1,3-2H-benzoxazines (Scheme III).

Scheme II

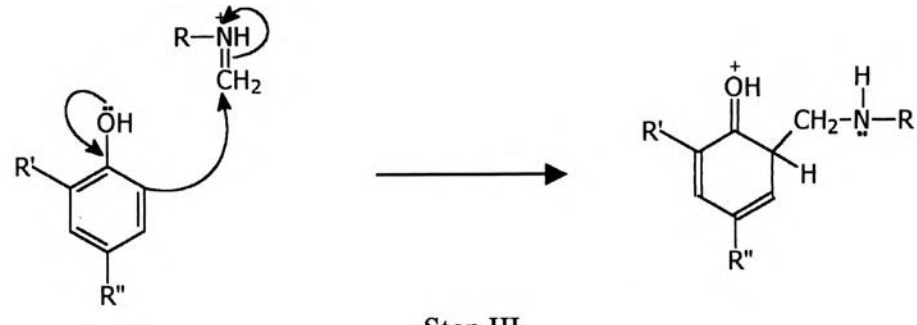


Scheme III

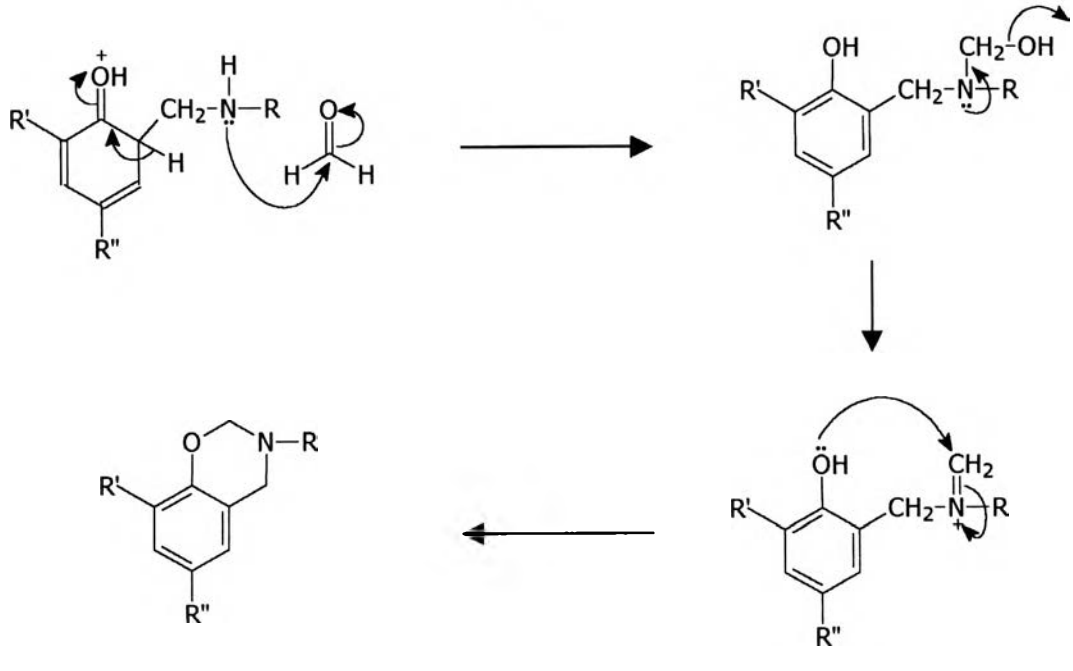
Step I



Step II



Step III

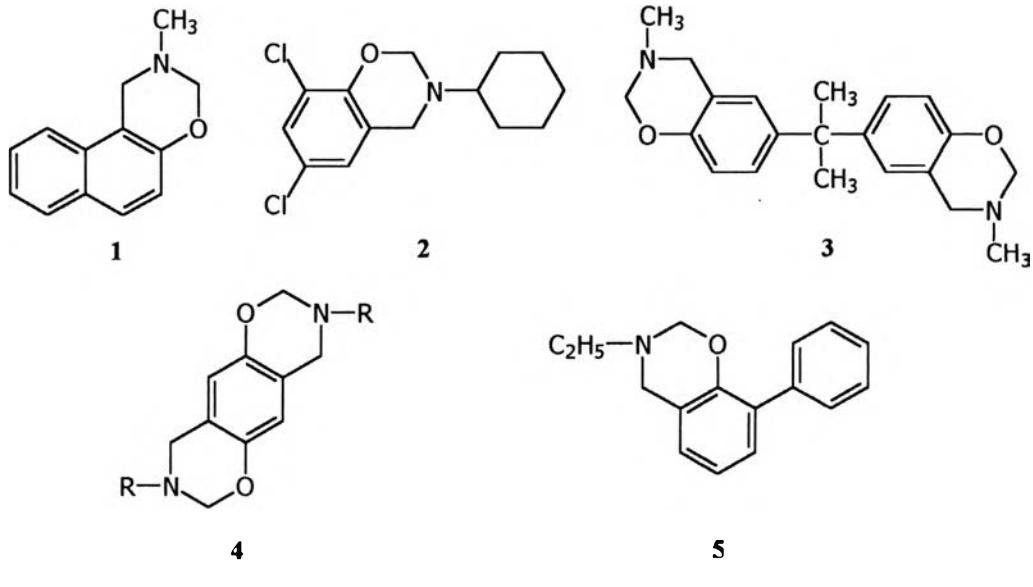


1.2 Development of Benzoxazines

Up to now, many benzoxazine derivatives, such as naphthol-based (**1**), halogen substituted phenol-based (**2**) (Burke *et al.*, 1964), bisphenol A-based (**3**) (Ning and Ishida, 1994), hydroquinone-based (**4**) (Burke *et al.*, 1961), phenylphenol-based (**5**) (Burckhalter *et al.*, 1961), etc., have been proposed. Burke *et al.* (1954) reported the condensation of 2-naphthalformaldehyde and *p*-toluidine to yield 2,3-dihydro-2-p-totyl-1H-naphth-(1,2e)-m-oxazine (**4**). Although various derivatives have been successfully prepared, the practical applications are rarely found. One of the reports about the application can be referred to naphthoxazines, the synthetic drugs for antibacterial, antifungicidal, antitumor, and antituberculosis (Burke *et al.*, 1964).

Benzoxazines are known as a type synthetic organic molecule in the 50's and 60's. It was not until Kopf and Wagner (1973) proposed the oxazine-derived phenolics as a potential precursor in synthesis of novolac resin, benzoxazines have been recognized for the thermosetting material. However, no polymerization of benzoxazine resins was reported. Benzoxazines received much more attention when Ning and Ishida (1994) exhibited a superb thermosetting novel phenolic resin material prepared from bisphenol A-based benzoxazine monomers, namely polybenzoxazines (see 1.4 Biphenol-Based Polybenzoxazines).

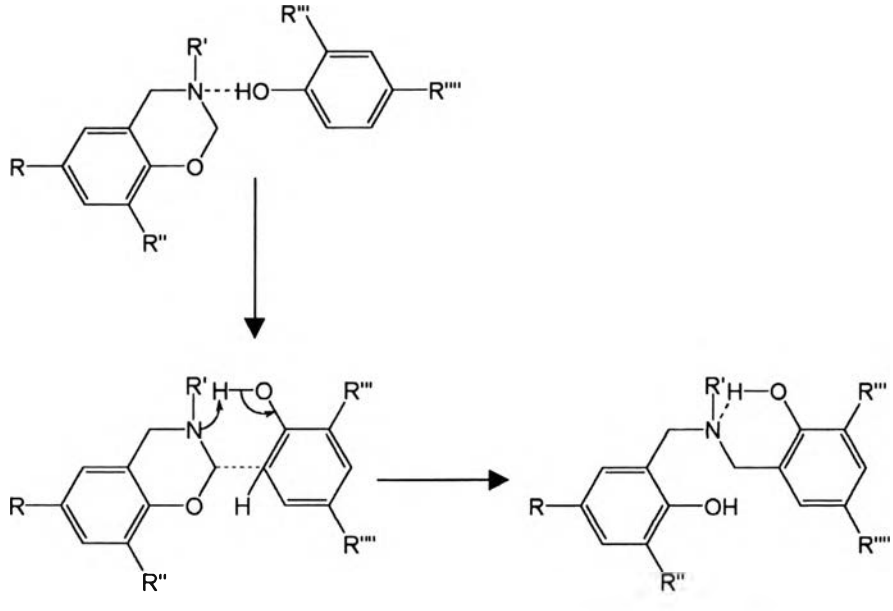
Scheme IV



1.3 Ring Opening Reaction of Benzoxazines

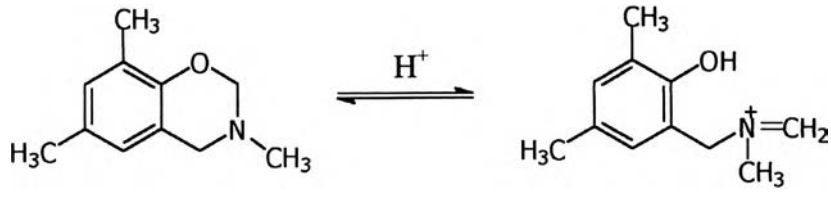
Benzoxazines are known to perform the reverse Mannich reaction as shown in Scheme V. Burke *et al.* (1965) proposed that the reaction be initiated by the approach of phenol to benzoxazines via intermolecular hydrogen bond. The initiation step gives an intermediary complex, which provides the electron movement from nitrogen atom to hydroxyl group.

Scheme V



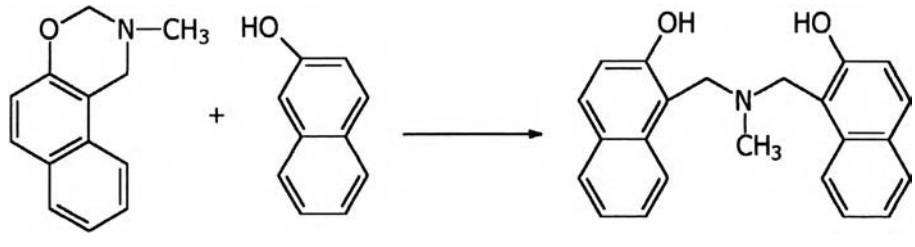
Although Kopf and Wagner (1973) reported the potential application to use benzoxazine derivatives for phenolic resin, the studies on the polymerization conditions were not established. Riess *et al.* (1985) attempted to polymerize mono-substituted benzoxazines similar to the case of polymerization of phenol by using various conditions, which are type of phenols, reaction temperatures, molar ratios, phenol initiator concentrations. The reactions were done in bulk using NMR and GPC to determine the degree of polymerization. However, the degree of polymerization was achieved at the level of low oligomers (tetramer to hexamer) even though the reaction conditions have been varied. Although the reason why polymerization terminated was not clarified, the kinetics and mechanisms were proposed. Reiss et al. suggested that there should be a step of protonation at oxygen atom of oxazine ring in the initial step (Scheme VI).

Scheme VI



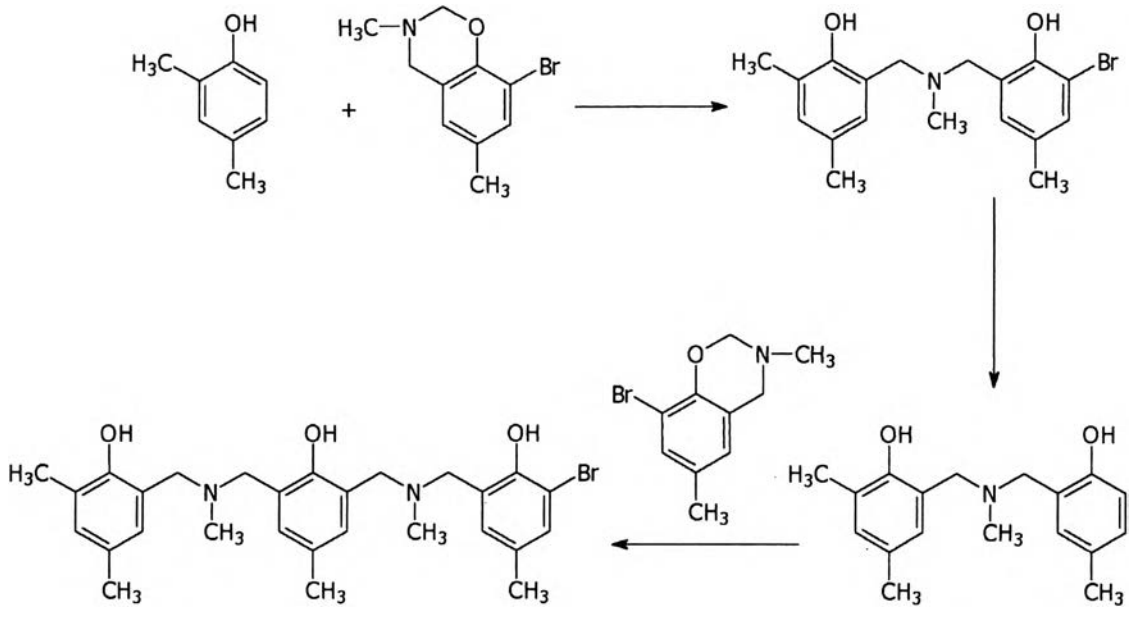
Bruke *et al.* (1965) demonstrated that by the ring opening reaction, the two units of phenol linked with azamethylene compound can be obtained, for example; 2,3-dihydro-2-methyl-1H-naphth-(1,2-e)-1,3-oxazine and 2-naphthol gives N,N-bis (2-hydroxy-1-napthylmethyl)methylamine (Scheme VII). This report is useful since 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 (Scheme VII).

Scheme VII



Until now, there is no report about the linear polymer obtained from the ring opening reaction of benzoxazines even the mechanism insists the stepwise reaction to produce a chain of aza-methylene-phenol polymer. Ishida and Krus (1998) firstly reported a unique synthesis to successfully achieve a linear chain obtained from the benzoxazines. It should be noted that the reaction was done in multisteps with the requirement to use bromophenol as a starting material. The linear chain was accomplished by alternating step of debromination and ring opening reaction (Scheme VIII).

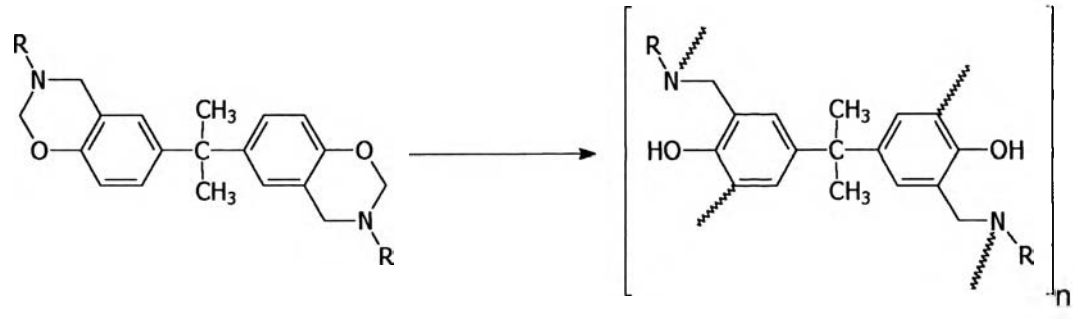
Scheme VIII



1.4 Bisphenol A-Based Polybenzoxazines

Properties of polybenzoxazines were reported for the first time when Ning and Ishida (1994) demonstrated a novel phenolic resin from bisphenol A-based benzoxazine monomer (Scheme IX). The key of the success in polymerizing bisphenol A-based benzoxazines can be referred to the crosslink structure generated from the two benzoxazine groups belonging to a single bisphenol ring. By varying the type of bisphenols and biphenols, the tremendous molecular design flexibility can be achieved. These polybenzoxazines drew strong attention when Ning and Ishida (1994) reported the unique chemical and physical properties, such as no catalyst required in polymerization, near-zero shrinkage, high glass transition temperatures, high moduli, low water adsorption, good dielectric properties, and high mechanical properties.

Scheme IX



1.5 Another Challenge: From Benzoxazines to a Novel Inclusion Compound

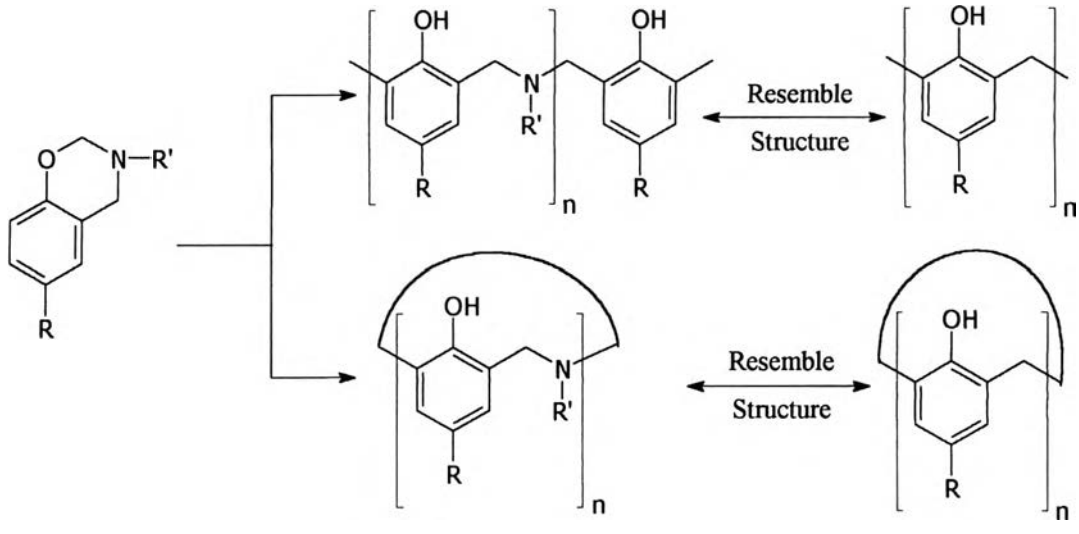
Chirachanchai *et al.* (2000) proposed that the open ring benzoxazines show the inclusion phenomena as seen in the case of acyclic phenolic resin and calixarenes (Scheme X) (Arduni *et al.*, 1986, Böhmer, V., 1995, Cram and Ho, 1986, Diemer *et al.*, 1991, Gutsche, 1989 and 1997, Lehn, 1995, and Murakami *et al.*, 1991).

The linear open ring benzoxazines can be expected for a novel host compound owing to the hints from the many reports about acyclic oligophenol-formaldehyde (Sone *et al.*, 1989), (Ohba *et al.*, 1993), and linear all-ortho oilgomers of phenol-formaldehyde resin (Yamagishi *et al.*, 1994). Previously, Sone *et al.* (1989) demonstrated acyclic oligophenol-formaldehyde as a host compound responding selectively to various types of organic molecules, such as acetone, 1,1,1-trichloroethane, methylethylketone, 1-bromo-2-chloroethane, etc. Ohba *et al.* (1993) reported that the tetramer of carbonyl-bridged analogs of acyclic *p-t*-butylphenol-formaldehyde formed an inclusion compound with the benzene molecule at 2:1 ratio. The derivatives of linear all-ortho oilgophenol-formaldehyde were reported to show the affinity toward alkali metal ions via pseudocyclic conformation (Yamagishi *et al.*, 1994).

The possibility that the macrocyclic benzoxazines exhibit the inclusion phenomena can be referred to the various reports about calixarenes. Gutshe et al. reported that calixarenes form the host-guest compound with various types of organic molecules and metal ions. Applications of calixarenes are proposed in the many areas, for example, sensors, separation, purification, and dissolvation (Diamond and McKervey, 1996). Shinkai (1993) proposed the sulfonylcalix[n]arenes which

induces a high water solubility, resulting to the dissolution of metal ion in aqueous solution.

Scheme X



Chirachanchai *et al.* (2000) pointed out that the expectation for inclusion property of the open ring benzoxazines is from the fact about the specific structure, where hydrophilic hydroxyl group and the hydrophobic benzene ring, as well as the lone pair electrons from heteroatoms are in the same molecule. Here, the electron density of benzoxazines may even be stronger than that of calixarenes owing to the combination of oxygen and nitrogen atoms (Scheme X). It is important to note that the hydrophobicity of the open ring benzoxazine can be controlled from the functional group R and R' (see 1.6 Molecular Design of Controlled Structure Benzoxazines).

Previously, Chirachanchai *et al.* (2000) clarified the above suggestion from the studies on inclusion phenomena of bisphenol A-based oligobenzoxazine. It was found that the bisphenol A-based oligobenzoxazine exhibits the ion extraction ability dependent on the solubility parameter of the organic solvent (χ_{ab}). The studies provide meaningful information in terms of not only showing that the open ring benzoxazine molecules be a novel host compound but also the host-guest formation

of benzoxazines be under the molecule assembly structures (Chirachanchai *et al.*, 2000).

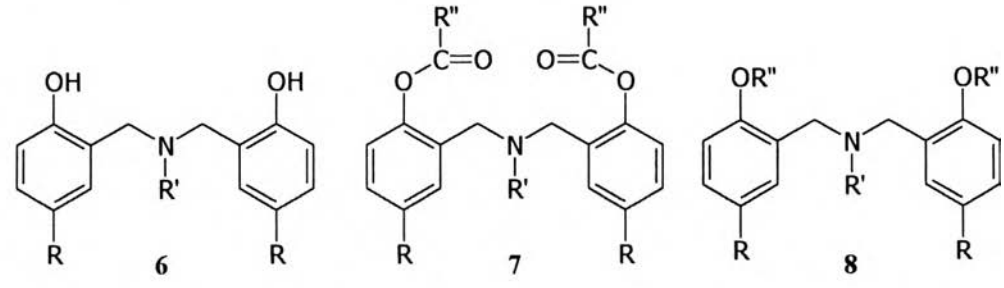
1.6 Molecular Design of Controlled Structure Benzoxazines

As described in 1.5, in order to achieve the open ring benzoxazine as host compound, a well-defined structure is the most important point to be considered. In the case of linear open ring benzoxazines (Scheme XI), the simplest molecules are *p*-substituted phenol-based open ring linear benzoxazines, such as dimer (**6**), trimer, etc. The other derivatives can be obtained by modifying the hydroxyl group by esterification (7) and etherification (**8**). The oligoesters (**9**) and oligoethers (**10**) are the interesting compounds, which can be prepared from the reaction of *p*-substituted open ring benzoxazine with diacid chloride and dialkylhalide. By varying the types of *p*-substituted phenols and amines, many derivatives differing in hydrophilicity and hydrophobicity can be obtained.

Theoretically, benzoxazine-based macrocyclics can be achieved via the synthesis pathways similar to that of calixarenes. One of the approaches is to synthesize the compound in the dilute condition where the molecules tend to accomplish intramolecular cyclization (Steed and Atwood, 2000). It is also known that the cyclization will be much more effective when the metal ion is added to function as a template to align each molecule in a cyclic manner (Steed and Atwood, 2000).

The benzoxazine-based macrocyclics can be obtained either as symmetric cyclic compounds (**11-12**), ester and ether linkage cyclics that can be easily obtained from esterification and etherification of *p*-substituted dimer (**13-14**).

Scheme XI



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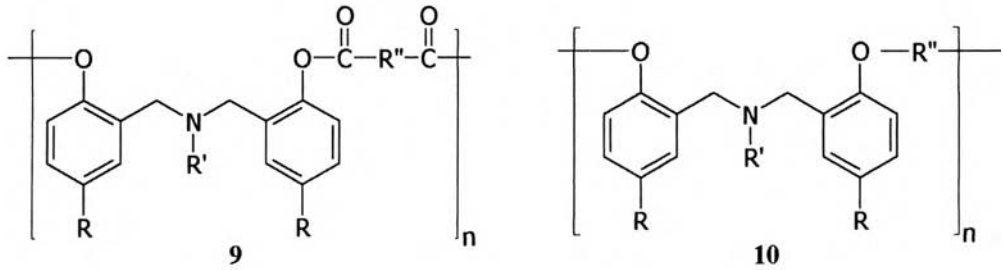

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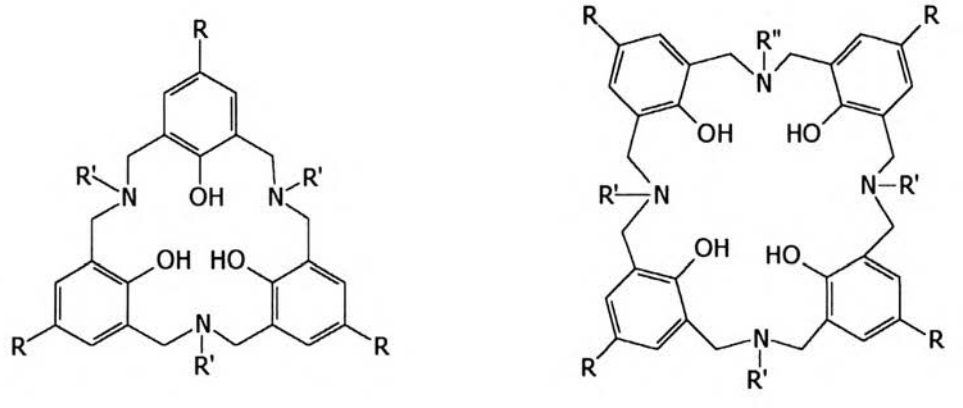
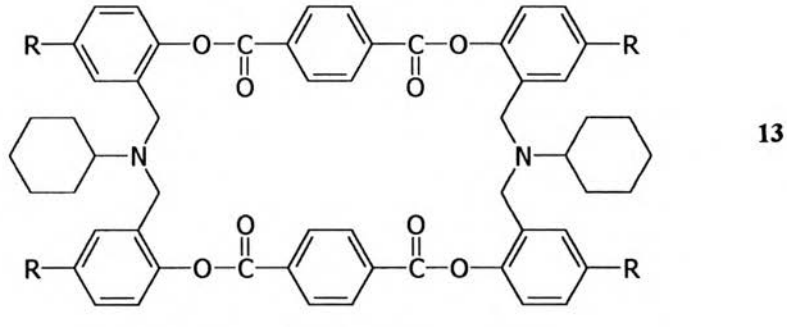


11 12



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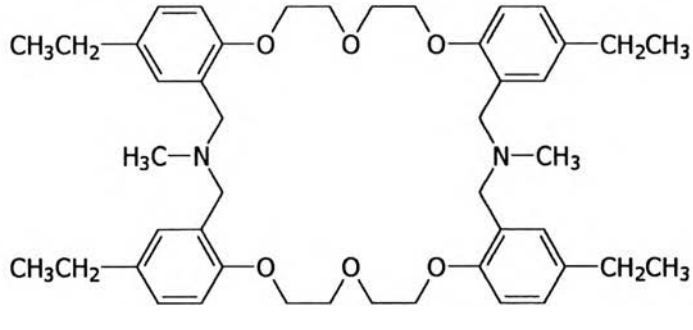

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1.7 The Scope of the Present Work

Although the chemistry of benzoxazines have been known for half a century, there are many questions needed to be answered. Does the ring opening of benzoxazines indeed give us polymer chains? Will the open ring structure of *p*-substituted phenol-based benzoxazines show an inclusion property?

In other words, the present work stands on the molecular designs and syntheses of monosubstituted phenol-based benzoxazines. Starting from these compounds, we can not only achieve a series of well-defined molecules but also study the possibility whether or not the molecules exhibit the inclusion phenomena.

To achieve the above aims, the present dissertation is divided into two major parts which are;

(i) verify the ring opening reaction of *p*-substituted phenol-based benzoxazine monomers and the strategies to obtain other potential host compounds, especially the macrocyclic molecules, and

(ii) clarify the host-guest properties of the compounds obtained from (i) including the effects involved in the molecular interaction between these compounds with other molecules or ions.

Thus,

Chapter II bases on the studies on the ring opening reaction of *p*-substituted phenol-based benzoxazines in order to clarify whether we can achieve the linear oligomer or polymer or not.

Chapter III deals with the strategy to overcome the problem in the ring opening reaction of benzoxazines. This chapter is important since it is the first time that we demonstrated an asymmetric structure obtained from a unique molecule of the open ring benzoxazine.

Chapter IV is about the unique products obtained from the aza-methylene-phenol, namely, benzoxazine dimer.

Chapter V clarifies whether the compounds obtained from II-IV show the inclusion phenomena or not. This chapter focuses on using benzoxazine dimers as host compounds and the metal ion as guest species.