CHAPTER IV
STUDY ON MACROCYCLIZATION ON ACETYLENE-BASED BENZOXAZINE DIMER

4.1 Abstract

Macrocyclization between benzoxazine dimer containing alkyne group at N-position and diacid chloride selectively yields [2+1] linear oligoester and [2+2] macrocycle depending on the synthesis condition. By applying acetylene-based benzoxazine dimer, *N,N*-bis(3,5-dimethyl-2-hydroxybenxyl)propargylamine, **2**, which was obtained from benzoxazine monomer, 3,4-dihydro-6,8-dimethyl-3-propargyl-2H-1,3-benzoxazine, **1**, as a starting compound, the macrocyclization between **2** and terephthaloyl dichloride under homogeneous and interfacial polycondensation gives the main product of [2+2] benzoxazine macrocycle and traces of [2+1] linear oligoester. The heterogeneous reaction brings a linear oligoester of [2+1] instead of macrocycles. When diacid chloride is adipoyl dichloride, the macrocyclization under interfacial polymerization gives the mixture of [1+1] benzoxazine macrocycle and [2+1] linear oligomer ester.

Keywords: benzoxazine, macrocyclic ester, heterogeneous reaction, homogeneous reaction, interfacial polycondensation

4.2 Introduction

Recently, the development in the field of supramolecular chemistry has received much more attention as indicated by the large number of articles. Due to their unique properties developed from molecular recognition, host-guest system or supramolecular system is on expectation for the functions which never obtained from simple molecules. One of the examples of supramolecular system is macrocyclic which can exhibit molecular recognition properties and binding abilities with specific metal ions (Ogoshi and Harada, 2008). For example, Trippe *et al.* (2002) synthesized bis(pyrrolo)tetrathiafulvalene macrocycles which exhibited high binding affinities for Pb^{2+} and Ba^{2+} in order to induce optical or redox properties.

Macrocyclic is well-known as host species which can show unique properties. However, the preparation of those macrocyclic compounds has been limited not only the complicated synthesis and purification processes but also the problem of the low-yield product.

For the past several years, our group has established a supramolecular chemistry based on benzoxazine molecules. Ring opening reaction of mono-phenol benzoxazines inevitably brings benzoxazine dimer whereas the dimers hardly polymerized with phenol since the structure of benzoxazine is stabilized by hydrogen bond network. Benzoxazine dimers perform supramolecular chemistry which may possibly due to the resemble structure to an aza-methylene linked calixarenes (Chirachanchai, 2000). In the past, our group proposed the attractive points of supramolecular benzoxazines about their various molecular designs flexibility, effective and efficient reactions, high yield production, etc. Moreover, our group succeeded in preparing of supramolecular chemistry of benzoxazines which is under the concept of simple, efficient, and effective process for benzoxazine macrocycles with high yield (up to 85%) (Laobuthee *et al.*, 2002).

Previously, several benzoxazine monomers with specific functional groups were synthesized in order to further modify by various reactions. For example, Kiskan and Yagci (2008) reported that benzoxazines with terminal acetylene group (-C≡CH) could be prepared as benzoxazine based acetylene monomer to obtain polymer by using transition metal catalyst. Benzoxazines with triazole group via

click reaction (Ergin *et al.*, 2007) and a novel benzoxazine monomer containing diacetylene linkage by applying oxidative coupling reaction (Chernykh *et al.*, 2009) were also reported.

It comes to our question that how to design and synthesize the benzoxazine macrocycles. As monophenol benzoxazine inevitably gives monophenol dimers, the use of benzoxazine containing propargyl moieties might be a simple way to obtain macrocycles with alkyne group. It can be expected that by applying click chemistry or oxidative coupling reaction through the alkyne group, a series of benzoxazine-based macrocyclic polymers can be easily obtained.

The present work, therefore, focuses on the molecular design and synthesis condition of macrocyclic compounds by using acetylene-based benzoxazine dimer and diacid chloride as starting materials.

4.3 Experimental

4.3.1 Chemicals

Propargylamine, 2,4-dimethyl phenol, adipoyl dichloride, terephthaloyl dichloride and deuterated-chloroform ($CDCl_3$) were purchased from Aldrich, Germany. Formaldehyde was purchased from Ajax Chemical, Australia. Sodium hydroxide, sodium sulfate anhydrous, dioxane, diethyl ether, chloroform, dichloromethane, isopropanol and tetrahydrofuran (THF) were products of RCI Labscan, Thailand. Silica gel 60 for column chromatography (0.063-0.200 nm) was obtained from Merck. All chemicals were used as received.

4.3.2 Instruments

Fourier transform infrared spectra (FTIR) were recorded by a Bruker Fourier transform infrared (FTIR) in the range 4000-650 cm^{-1} at a resolution of 2 cm^{-1}. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were obtained from a Bruker Avance nuclear magnetic resonance (NMR) spectrometer (Germany) operating at Larmor frequencies of 500.13 MHz. $CDCl_3$ was used as the solvent. Mass spectroscopy was analyzed by a Bruker matrix-assisted laser desorption ionization time-of-flight mass spectrometer (MALDI-TOF MS) and a Bruker Daltonic Micro-TOF mass spectrometer (ESI-TOF) in positive ion mode.

4.3.3 Syntheses

4.3.3.1 Benzoxazine Dimer

Benzoxazine dimer, *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)propargylamine, **2**, was prepared by ring opening reaction of 3,4-dihydro-6,8-dimethyl-3-propargyl-2H-1,3-benzoxazine (benzoxazine monomer), benzoxazine monomer, **1**, as reported previously (Chirachanchai *et al.*, 2000; Laobuthee, 2002).

4.3.3.2 Heterogeneous Reaction

Heterogeneous reaction of benzoxazine dimer, **2** with terephthaloyl dichloride was carried out as reported elsewhere (Laobuthee and Chirachanchai, 2002).

4.3.3.3 Homogeneous Reaction

Terephthaloyl chloride (101.5mg, 0.5mmol) was dissolved in THF (100 mL). A solution of **2** (161.7 mg, 0.5 mmol) and NaOH (80 mg, 2 mmol) in THF (50 mL) was added dropwisely and stirred at room temperature for 7 days. The solution obtained was collected, and washed with distilled water, followed by drying over anhydrous sodium sulfate. The solvent was removed to obtain crude product. The crude product was further purified by column chromatography. In similar procedures, the reactions were carried out but varying the concentrations of **2**, terephthaloyl dichloride and NaOH in the range of 0.5 mmol to 2 mmol.

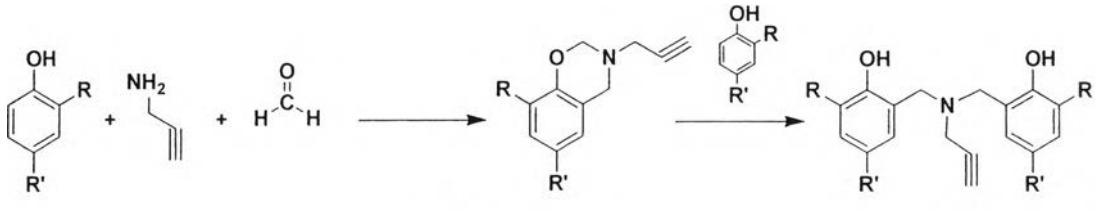
4.3.3.4 Interfacial Polycondensation

A solution of **2** (0.15 mol/L) in water in the presence of NaOH and a solution of terephthaloyl chloride (0.15 mol/L) in dichloromethane in separate syringes were added dropwisely into the mixture of dichloromethane (35 mL), water (10 mL) containing hexadecyltrimethylammonium bromide (27 mg), and left stirring at room temperature for 7 days. The solution obtained was washed with distilled water several times before vacuum drying. The product obtained was dissolve in hexane/dichloromethane (70:30) use as a sample for column chromatography. Similar procedures were carried out but using K_2CO_3 (276.4 mg, 2 mmol) and Et_3N (279 μL, 2 mmol) as a catalyst. In addition, adipoyl dichloride was also applied as a reactant with **2** under the similar reaction condition.

4.4 Results and discussion

4.4.1 Acetylene-based Benzoxazine Dimer

Benzoxazine dimer containing propargyl group (–C≡CH) were synthesized as shown in Scheme 4.1. Benzoxazine monomer, 3,4-dihydro-6,8-dimethyl-3-propargyl-2H-1,3-benzoxazine, **1**, was prepared by Mannich reaction from 2,4-dimethyl phenol, formaldehyde and propargylamine. After ring opening reaction of **1**, *N,N*-bis(3,5-dimethyl-2-hydroxybenzyl)propargylamine, benzoxazine dimer, **2**, can be obtained. The chemical structures of **1** and **2** were clarified by FTIR and ^{1}H NMR spectroscopy techniques. Compound **1** was successfully prepared as identified from (Figure 4.1(A)) the FTIR spectrum with the peaks at 1244 cm^{-1}, 933 cm^{-1}, and 3290 cm^{-1} (asymmetric stretching of Ar–O–C, -CH out of plane of benzene ring (oxazine ring), and –C≡CH of propargyl group) and (Figure 4.2(A)) the ^{1}H-NMR spectrum with the signals at 4.09 and 4.94 ppm (methylene protons in oxazine ring). Compound **2** was also successfully prepared as clarified from FTIR spectrum (Figure 4.1(B)) with the peaks at 3405 cm^{-1}(hydroxyl group), 1484 cm^{-1} (tetrasubstituted benzene), and at 3266 cm^{-1} (propagyl group) including the disappearance of the peak at 933 cm^{-1} (-CH out of plane of oxazine ring) and the ^{1}H-NMR spectrum (Figure 4.2(B)) with the signal at 3.83 ppm (methylene group in mannich bridge) including the disappearance of the signal at 4.94 ppm (methylene group in oxazine ring).



1 : R = -CH$_3$, R' = -CH$_3$ **2** : R = -CH$_3$, R' = -CH$_3$

Scheme 4.1

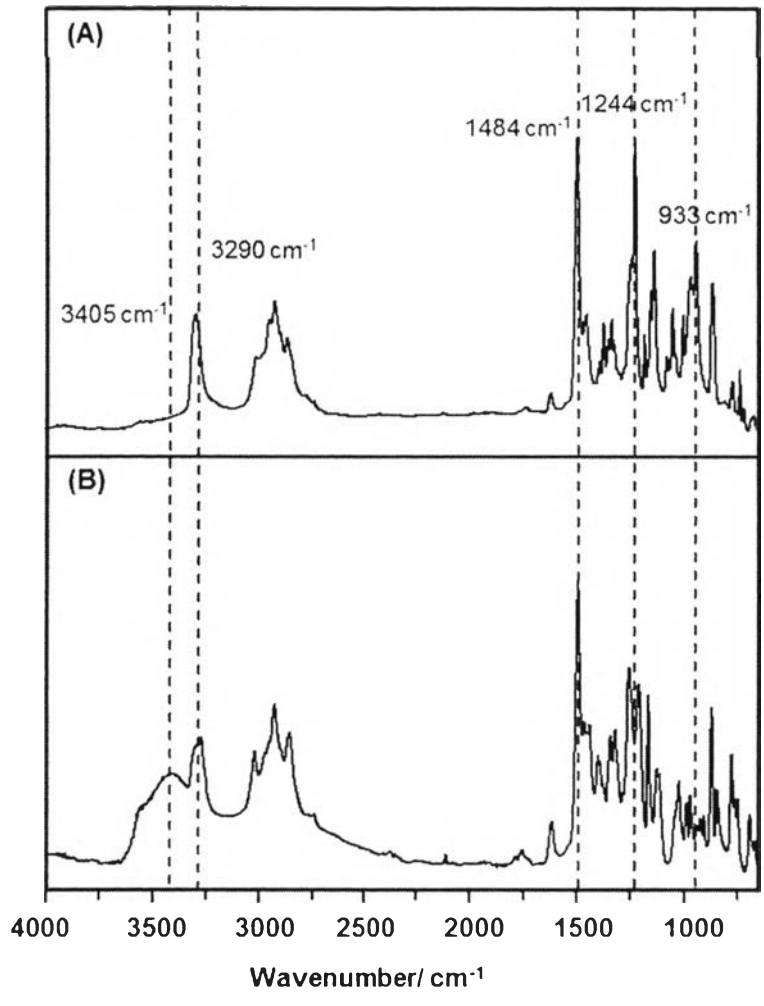


Figure 4.1 FTIR spectra of (A) **1**, and (B) **2**.

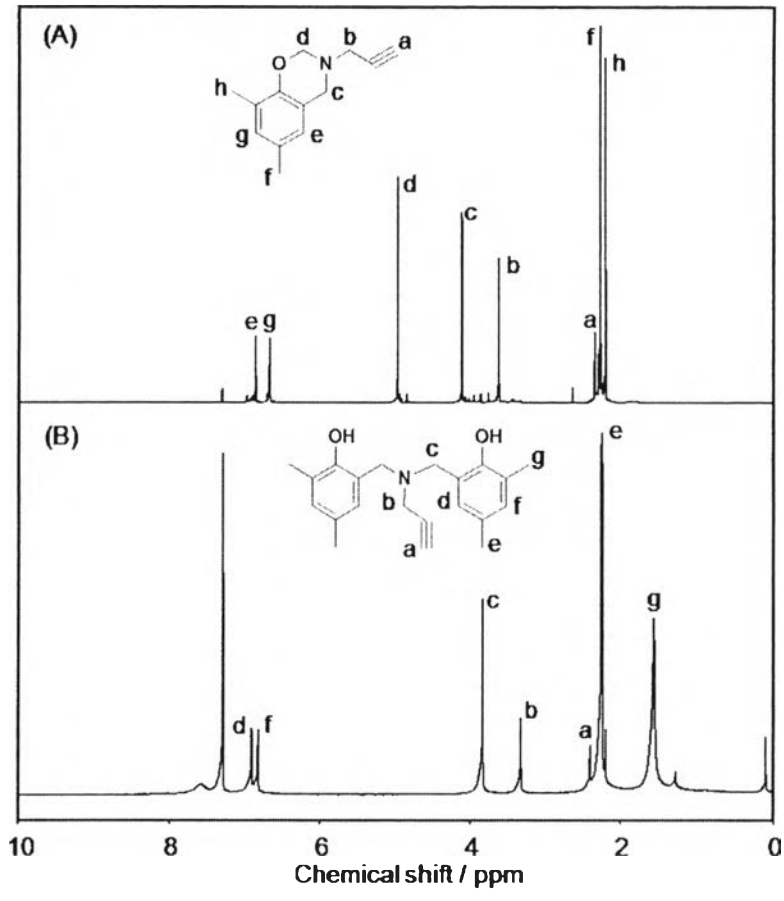


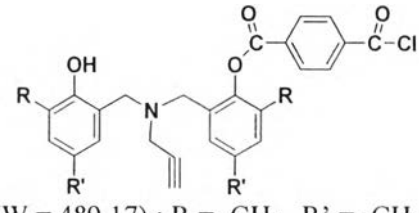
Figure 4.2 ^{1}H-NMR spectra of (A) **1**, and (B) **2**.

4.4.2 Benzoxazine-based Macrocycle: Heterogeneous Reaction

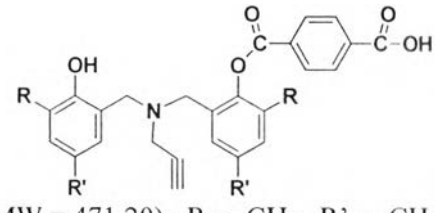
It is known that the macrocyclization was carried out under the high dilution condition with or without using metal ion template (Dietrich *et al.*, 2004; Xing *et al.*, 2005). High dilution techniques combining with a slow addition of reactants to the system (Jiang *et al.*, 1997) favors intramolecular reaction more than intermolecular side reaction (Malesevic *et al.*, 2004). However, as the macrocyclization can be obtained only from the specific reaction, in the most cases, the dilution condition brings several products and the yield is rather low.

In the past, Laobuthee and Chirachanchai (2002) demonstrated that [2+2] macrocyclic compound can be easily produced in a single step of esterification between benzoxazine dimer and terephthaloyl dichloride with the use of alkaline metals or basic conditions. In this work, similar procedures were applied. It is

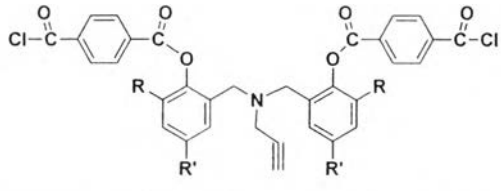
important to note that esterification of **2** with terephthaloyl dichloride may possibly give several compounds, i.e. **5-11** via [1+1], [2+2], and other linear oligoester benzoxazines as shown in Scheme 4.2.



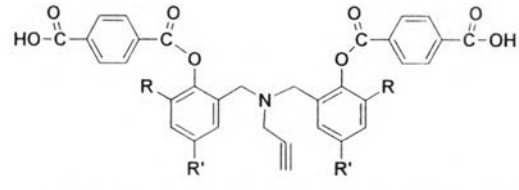
5 (MW = 489.17) : R = -CH_3, R' = -CH_3



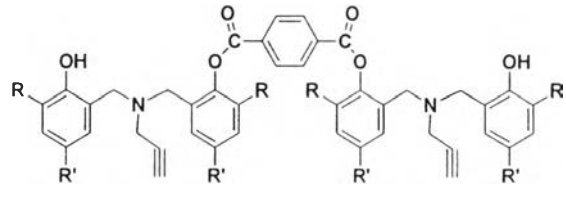
6 (MW = 471.20) : R = -CH_3, R' = -CH_3



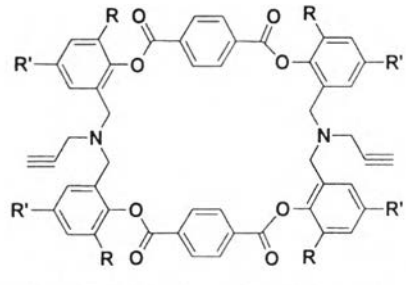
7 (MW = 655.15) : R = -CH_3, R' = -CH_3



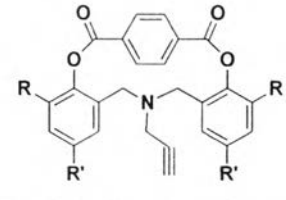
8 (MW = 619.22) : R = -CH_3, R' = -CH_3



9 (MW = 776.38) : R = -CH_3, R' = -CH_3



10 (MW = 906.39) : R = -CH_3, R' = -CH_3



11 (MW = 453.19) : R = -CH_3, R' = -CH_3

Scheme 4.2

The product obtained from heterogeneous reaction shows a new peak of C=O stretching of ester group at 1737 cm^{-1} (Figure 4.3). However, the broad peak at 3300-

3500 cm^{-1} implies hydroxyl groups remained in the structure. ^{1}H-NMR shows three different methylene protons at 3.28, 3.89 and 3.91 ppm and four equivalent aromatic protons of terephthaloyl dichloride at 8.46 ppm. The results above suggest the possible product of [2+1] linear oligoester, **9**. The structure was further confirmed by ESI-MS. The parent peak ($M+H^+$) at *m/z* = 777 reflects the molecular weight of **9** (Figure 4.4).

From heterogeneous reaction, it is confirmed that an esterification of **2** with terephthaloyl dichloride provides **9** in high yield (85%) whereas on macrocycles, such as **10** was identified.

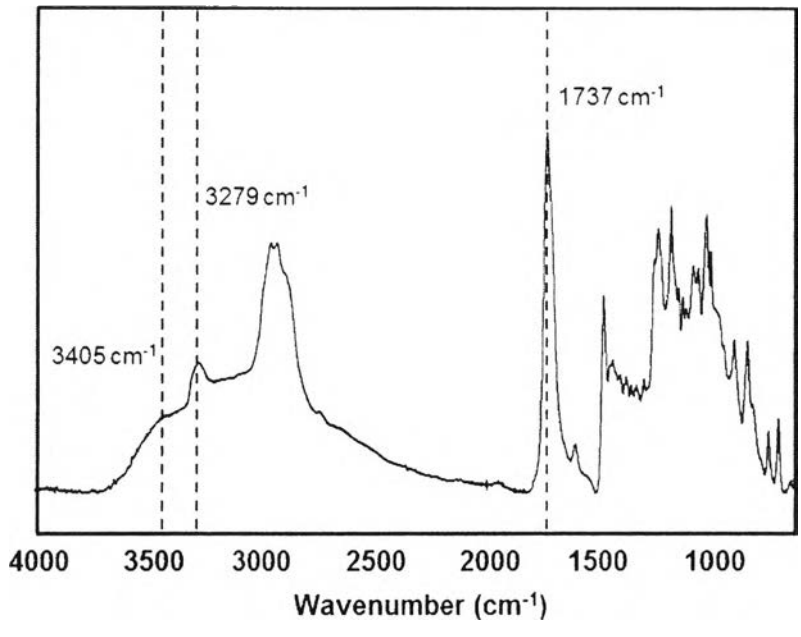


Figure 4.3 FTIR spectrum of **9**.

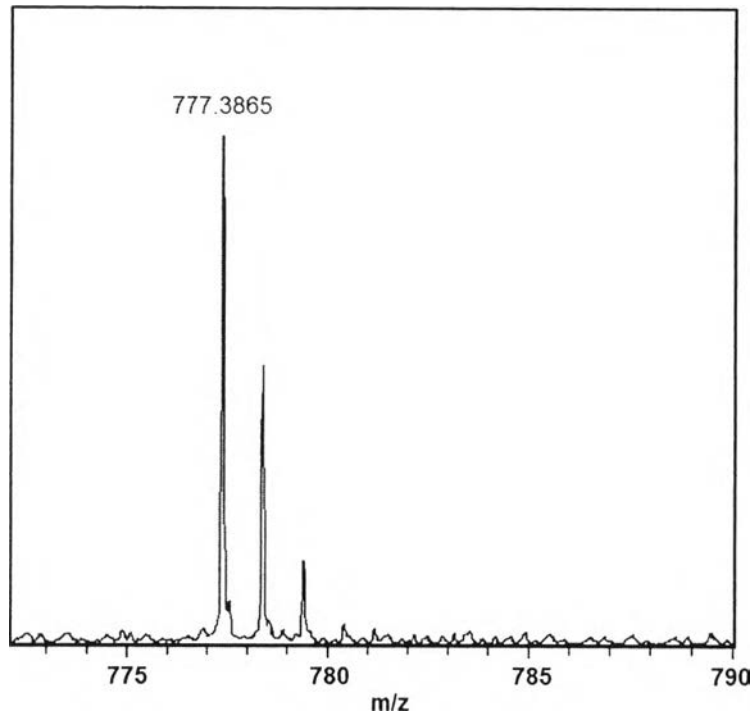


Figure 4.4 ESI mass spectrum of **9**.

4.4.3 Benzoxazine-based Macrocycle: Homogeneous Reaction

In order to study on macrocyclization of **2**, homogeneous reaction was also considered instead of heterogeneous reaction. In this case, the concentration of the reactant was also studied. For conditions 1 and 2, the products obtained show C=O stretching of ester group at 1736 cm^{-1} and 1737 cm^{-1}, respectively (Figures 4.4(A), (B), and (C)). The broad peak of hydroxyl group at 3300-3500 cm^{-1} is disappeared. However, the broad peak at 3300-2800 cm^{-1} and the peak at 3639 cm^{-1} imply intramolecular H-bond and free hydroxyl group, respectively. ^{1}H-NMR of condition 1 shows the important signals of four equivalent aromatic protons of diacid chloride at 8.47 ppm and three different methylene protons at 3.29, 3.75 and 3.84 ppm. This result indicates the formation of **9**. In the case of condition 2 and 3, ^{1}H-NMR spectrum of **10** shows the important signals at 8.33, 3.58 and 3.12 ppm assigned to the four equivalent aromatic protons and two different methylene protons, respectively. The products obtained from conditions 1, 2 and 3 were further confirmed by MALDI-TOF MS to find the parent peak ($M+H^+$) at *m/z* = 777

indicating the structure of **9**. However, the MALDI-TOF MS of the product obtained from condition 2 and 3 shows the parent peak ($M+H^+$) at *m/z* = 777 and 907 indicating the formation of **9** and **10**, respectively.

The data suggest that the concentration plays an important role to control the macrocyclization. As in Table 4.1, the condition 2 and 3 lead to [2+2] macrocycle, **10**, and [2+1] linear oligoester, **9** whereas the condition 1 provides only [2+1] linear oligoester, **9**.

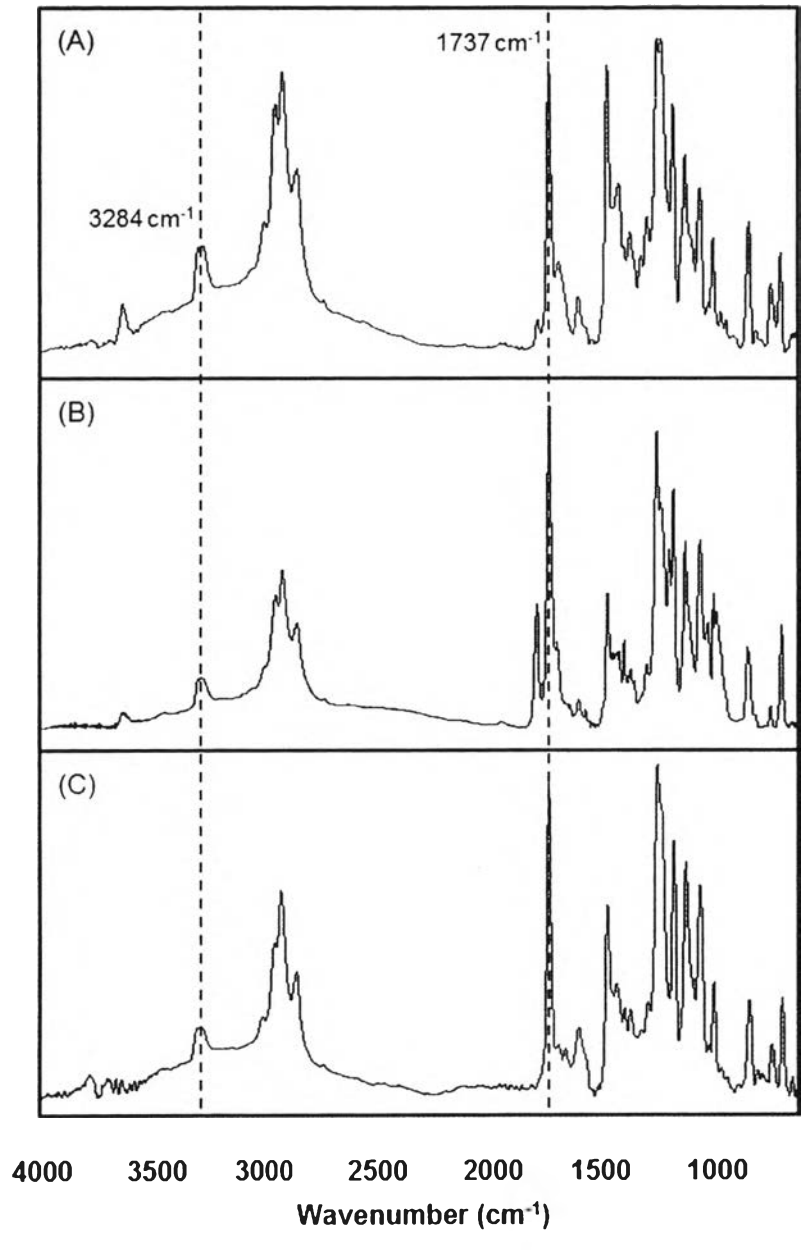
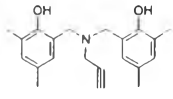


Figure 4.5 FTIR spectra of the product obtained from homogeneous reaction; (A) condition 1, (B) condition 2, and (C) condition 3.

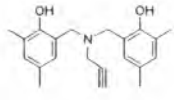
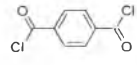
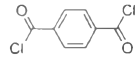
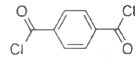
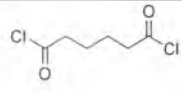
Table 4.1 Reaction condition of the products obtained from homogeneous reaction

Dimer	Condition	Concentration	Product	
		Dimer(mmol)/ 150 mL	FTIR (cm^{-1})	MALDI-TOF/ compound (*m/z*)
 **2**	1	0.5	1736 (-C=O)	777/ **9**
	2	1	1737 (-C=O)	777/ **9** 907/ **10**
	3	2	1737 (-C=O)	777/ **9** 907/ **10**

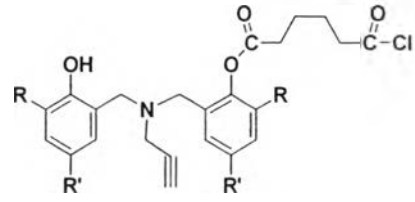
4.4.4 Benzoxazine-based Macrocycle: Interfacial Polycondensation

Previously, Ishizu and Ichimura (1998) demonstrated that interfacial polycondensation can increase ring closure efficiency due to the limited field of the reaction at the interface region. Jiang *et al.* (1997) reported that a series of macrocyclic arylate dimers can be synthesized with high yield by interfacial polycondenzation of *o*-phthaloyl dichloride with bisphenol-A. In our cases, interfacial polycondensation of **2** with terephthaloyl dichloride was carried out and various types of catalysts were applied. The results are summarized in Table 4.2. Surprisingly, the esterification of **2** with terephthaloyl chloride using NaOH, K_2CO_3 and Et_3N resulted in [2+2] macrocyclic compound, **10** and [2+1] linear oligoester, **9**, as confirmed by FTIR, ^{1}H-NMR and ESI MS.

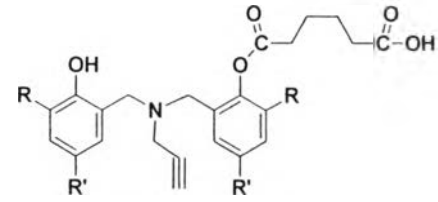
Table 4.2 Reaction condition of the products obtained from interfacial polycondensation of **2**

Dimer	Condition	Diacid Chloride	Catalyst	Product	
				FTIR (cm^{-1})	ESI/ compound (*m/z*)
 **2**	4		NaOH	1737 (-C=O)	777/ **9** 907/ **10**
	5		K_2CO_3	1736 (-C=O)	777/ **9** 907/ **10**
	6		Et_3N	1737 (-C=O)	777/ **9** 907/ **10**
	7		NaOH	1755 (-C=O)	434/ **18** 757/ **16**

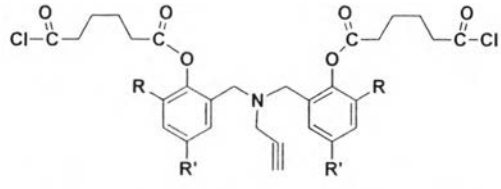
In the past, Bradshaw and Thompson (1978) demonstrated that the esterification of diacidchloride with various glycols gave [1+1] macrocyclic diester except the esterification of tetraethylene glycol with terephthaloyl chloride gave [2+2] macrocyclic compound. Based on this point, adipoyl dichloride was used instead of terephthaloyl dichloride to study on macrocyclization (Table 4.2, Condition 7). Interfacial polycondensation of **2** with adipoyl dichloride possibly give [1+1], [2+2] macrocyclic products and/or linear oligoester as shown in Scheme 4.3. FTIR, ^{1}H-NMR and MALDI-TOF MS were applied to clarify the structure of the product obtained to find a new peak of C=O stretching mode of ester group at 1755 cm^{-1} and the disappearance of OH peak at 3500 cm^{-1}, whereas the result of ESI MS shows the parent peak ($M+H^+$) at *m/z* = 434 and 757. This leads to the structures of **18** and **16**, respectively.



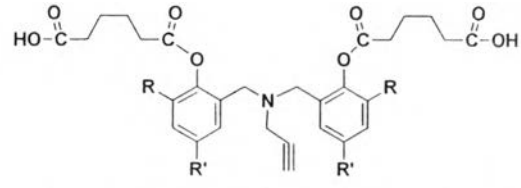
12 (MW = 469.20) : R = -CH_3, R' = -CH_3



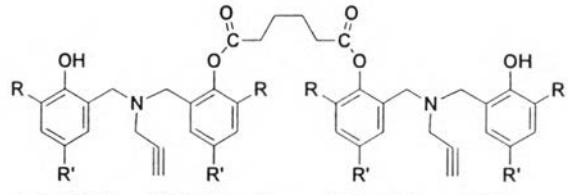
13 (MW = 451.24) : R = -CH_3, R' = -CH_3



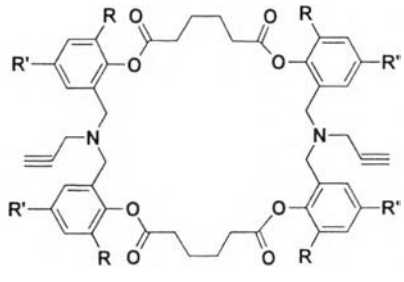
14 (MW = 615.22) : R = -CH_3, R' = -CH_3



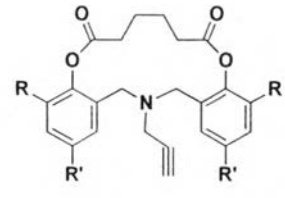
15 (MW = 579.28) : R = -CH_3, R' = -CH_3



16 (MW = 756.41) : R = -CH_3, R' = -CH_3



17 (MW = 866.45) : R = -CH_3, R' = -CH_3



18 (MW = 433.23) : R = -CH_3, R' = -CH_3

Scheme 4.3

Table 4.2 demonstrates that the catalytic interfacial polycondensation of **2** with terephthaloyl chloride by strong or weak bases can provide [2+2] macrocyclic benzoxazines. The use of adipoyl dichloride suggests that by simply using the flexible chain of diacid chloride, it is possible to obtain [1+1] benzoxazine-based macrocyclic compound.

4.4.5 Types and contents of Macrocyclization

As indicated above, although the reactions seem to give selective types of the products, it is important to identify the types and the contents of the products, especially, in the case of macrocyclic compounds. NMR spectroscopy is one of powerful technique which used to obtain not only qualitative but also quantitative analysis result. In our case, NMR technique was applied in order to find the contents of [2+2] macrocycle and [2+1] linear oligoester obtained from each condition. The method is based on integration of the NMR signals of the four protons in terephthaloyl dichloride of [2+1] linear oligoester at 8.47 ppm (I_a) relative to the NMR signal of [2+2] macrocycle at 8.33 ppm ($I_{a'}$) by using Eg (1) – (3).

$$Proportion\ of\ macrocycle = \frac{I_a}{I_{a'}} \quad (1)$$

$$Total\ compounds = 1 + proportion\ of\ macrocycle \quad (2)$$

$$Possibility\ of\ macrocycles = \frac{proportion\ of\ cycle}{Total\ compounds} \times 100 \quad (3)$$

Where 1 corresponds to one compound of [2+1] linear oligoester.

The possibility of macrocyclization of each condition is shown in Figure 4.6. For the heterogeneous and homogeneous reactions (condition 1), the [2+2] linear oligoester is obtained. In the case of the condition 2-7 (Table 4.2), the contents of macrocyclization were found to be 27%, 74%, 79%, 28%, 60% and 35%, respectively.

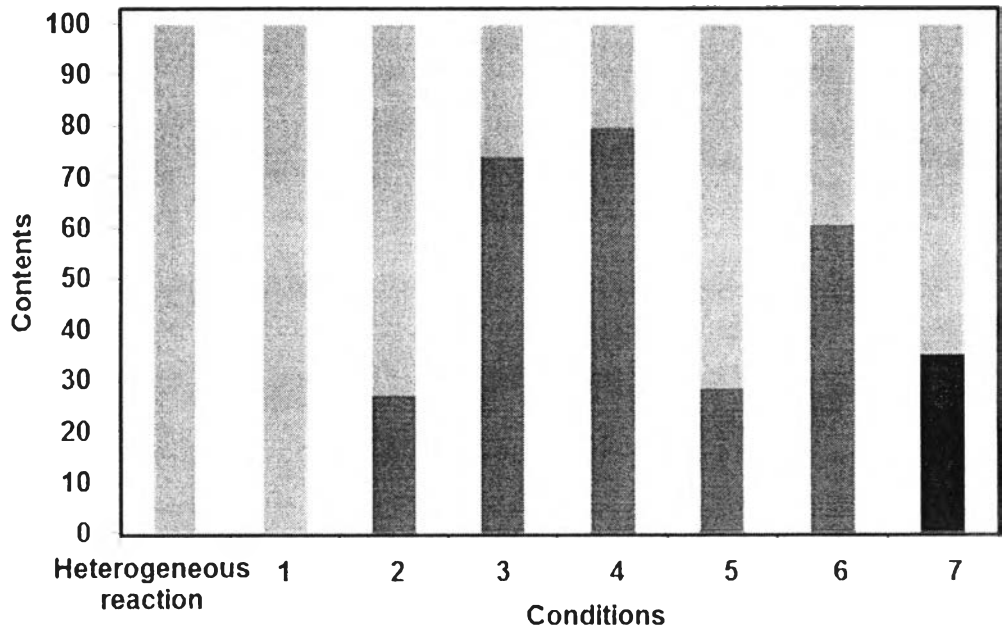


Figure 4.6 Types and contents of macrocyclization: (▦) [2+1] linear oligoester, (■) [2+2] macrocycle, and (■) [1+1] macrocycle.

In the case of homogeneous reaction (condition 1-3), the concentration of **2** was also studied by varying the concentration in the range of 0.5 mmol to 2 mmol as shown in Figure 4.7. It is important to note that an increase in the concentration of **2** leads to the higher content of macrocycle from 0% to 74%. Therefore, the concentration of the reactant is a key factor in order to control the macrocyclization.

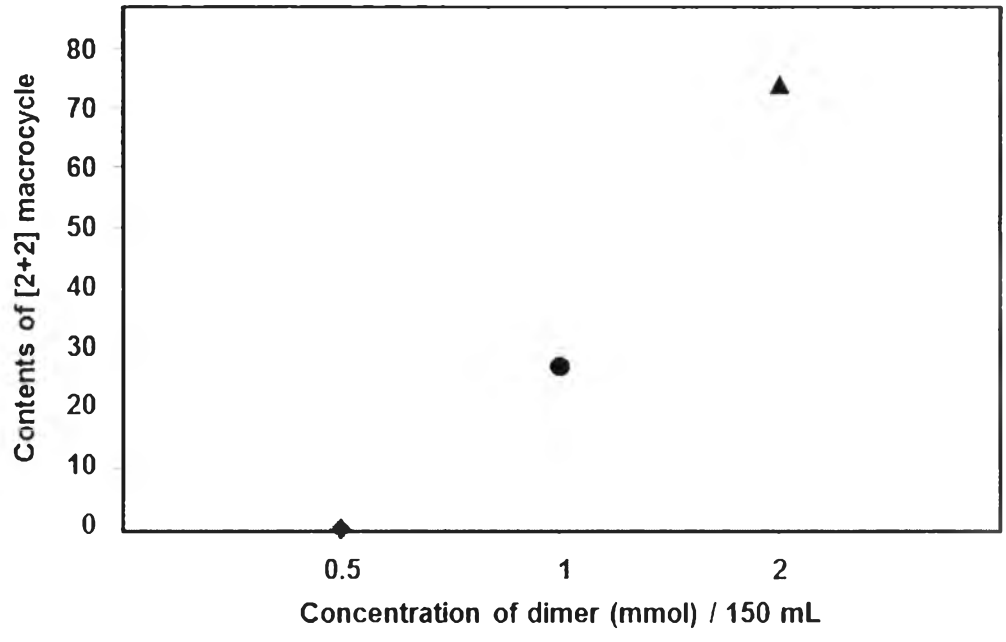


Figure 4.7 Contents of [2+2] macrocycle from homogeneous reaction: (◆) 0.5 mmol / 150 mL, (●) 1 mmol / 150 mL, and (▲) 2 mmol / 150 mL.

4.5 Conclusions

Esterification of acetylene-based benzoxazine dimer with diacidchloride was applied as a main reaction to prepare macrocyclic compounds. In the case of heterogeneous reaction, [2+1] linear oligoester was obtained. By using homogeneous reaction and an interfacial polycondensation, the reactions provided [2+1] linear oligoester and [2+2] macrocycle. Moreover, diacid chloride with flexible chain can control the macrocyclization to obtain [1+1] macrocycle and [2+1] linear oligoester as seen in the case of adipoyl dichloride.

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4.7 References

Bradshaw, J. S. and Thompson, M. D. (1978). Synthesis of Macrocyclic Polyether-Diester Compounds with an Aromatic Subcyclic Unit. Journal of Organic Chemistry, 43 (12), 2456-2460.

Chirachanchai, S., Laobuthee, A., Ishida, H., Tashiro, K. (2000). 26th Congress on Science and Technology of Thailand. Thailand, 737.

Dietrich, B., Atwood, J. L., Steed, J. W. (2004). In Encyclopedia of Supramolecular Chemistry. Marcel Dekker: New York.

Dietrich, B., Viout, P., Lenh, J. M. (1993). Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry. VCH: Weinheim.

Jiang, H., Chen, T., Xu, J. (1997). Synthesis, Structure, and Ring-Opening Polymerization of Macrocyclic Aromatic Esters: A New Route to High-Performance Polyarylates. Macromolecules, 30, 2839-2842.

Jiang, H., Chen, T., Xu, J. (1997). Synthesis, Structure, and Ring-Opening Polymerization of Macrocyclic acrylates containing phthalic unit. Science in China (Series B), 40(5), 495-502.

Laobuthee, A. (2002). Ph.D. Thesis in Polymer Science, The Petroleum and Petrochemical College, Chulalongkorn University. Bangkok, Thailand.

Laobuthee, A., Chirachanchai, S. (2002). A Simple, Effective, and Selective Synthesis Route for Difunctional 30-Membered Macrocyclic Ester and Linear Oligoester Derived from Benzoxazine Dimers. Chemical Letter, 31(6), 613-614.

Laobuthee, A., Chirachanchai, S., Ishida, H., Tashiro, K. (2001). Asymmetric Mono-oxazine: An Inevitable Product from Mannich Reaction of Benzoxazine Dimers. Journal of the American Chemical Society, 123(41), 9947-9955.

Malesevic, M., Strijowski, U., Bachle, D., Sewald, N. (2004). An improved method for the solution cyclization of peptides under pseudo-high dilution conditions. Journal of Biotechnology, 112, 73-77.

Ogoshi, T., Harada, A. (2008). Chemical sensor Based on Cyclodextrin Derivatives. Sensors. 8, 4916-4982.

Rungsimanon, T., Laobuthee, A., Miyata, M., Chirachanchai, S. (2008). [1+1] and [2+2] crown ethers derived from N,N-bis(2-hydroxyalkylbenzyl)alkylamine and their inclusion phenomena with metal ions. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 62, 333-338.

Trippe, G., Levillain, E., Derf, F. L., Gorgues, A., Salle, M., Jeppesen, J. O., Nielsen, K., Becher, J. (2002). Electrochemical Recognition of Cations By Bis(pyrrolo)tetrathiafulvalene Macrocycles. Organic letters, 4, 2461-2464.

Xing, L., Ziener, U., Sutherland, T. C., Cuccia, L. A. (2005) Hydrogen Bond Directed Synthesis of Pyridazine and Naphthyridine. Chemical Communication, 5751-5753.