

福井大学工学審査

学位論文[博士(工学)]

**Synthesis of Biocompatible/Biodegradable Block Copolymers  
Using Metal-Free Living Cationic Polymerization**  
(メタルフリーリビングカチオン重合を用いた生体適  
性/生分解性ブロックコポリマーの合成)

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*Dedicated to my beloved parents.....*

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## Preface

The flourishing of macromolecule synthesis falls on nineties, however the term of controlled polymerization, offering narrow molecular weight distribution with predetermined molecular weights of polymers and copolymers, appeared in 1956.<sup>1,2</sup> Michael Szwarc discovered at that time an anionic polymerization carried out in the absence of termination reaction thus introduced the term of `living polymerization`. The growing anionic end stabilized by e.g. anthracene, was converted to a dormant, covalent species by a reversible reaction. Similar invention but in the case of cationic polymerization appeared much later. Higashimura and Sawamoto demonstrated the cationic living polymerization of vinyl ethers using hydrogen chloride and iodine initiating system.<sup>3</sup> At the same time Kennedy and Faust by applying another initiating system, tertiary acetate/boron trichloride, polymerized isobutylene with quite narrow polydispersity index, unambiguously proving that the strong interactions between the elongating carbocation and the carboxylate counteranion plays a crucial role in forming living polymers.<sup>4</sup> Penczek et al. established livingness in ring-opening polymerization of cyclic acetals in 1980, whereas employing dynamic equilibrium between growing free radical and dormant species was brought with the work of Otsu in 1982.<sup>5,6</sup> Next approaches to achieve control over polymer architecture via radical polymerization led to commercial applications.

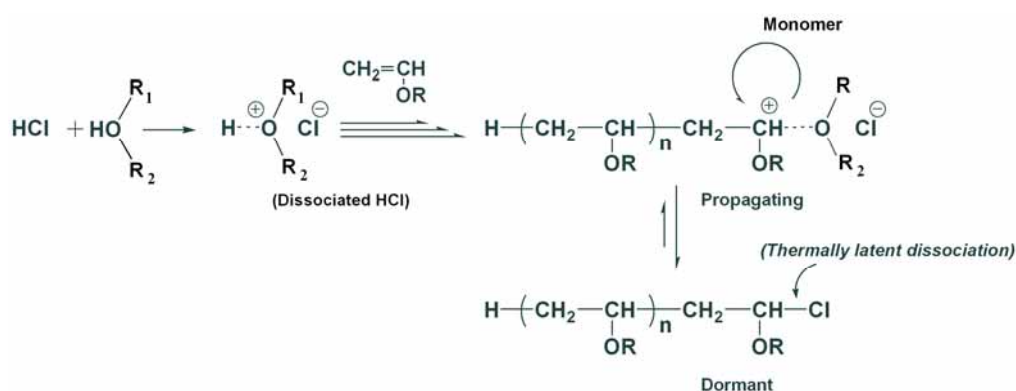
Nowadays, numerous studies are dictated by a better control of polymerization process which required detailed investigations of the reaction mechanisms and finding new effective initiating systems. The cationic living polymerization allows to

obtain the products with high molecular weights, is not as well explored as radical and anionic because of the difficulties involved in the experimental part (proceeds at very high rates and is extremely sensitive to the presence of small concentration of impurities) thus became of a deep interest of a current investigation. Due to the increasing importance of eliminating metallic residues from the reaction system the object of present study led to development of metal-free living cationic polymerization method.

Chapter 1 concerns about general background of controlled polymerization taking into special consideration living cationic system. The discussion raises metal-free initiating system problem giving variety of examples of their improvements at the turn of the last century.

Chapter 2 provides a detailed research on metal-free living cationic polymerization of alkyl vinyl ethers, vinyl ethers with electron-donating groups in pendant and vinyl ethers with bulky group next to the electron-donating substituent in the pendant.

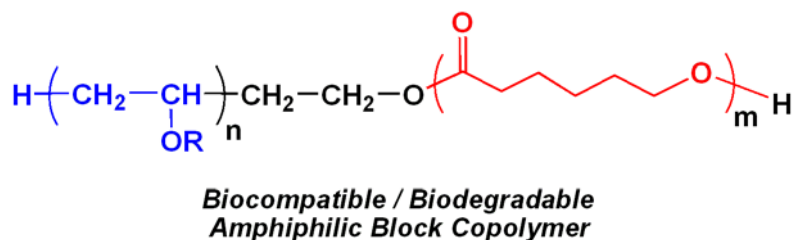
Chapter 3 presents the effects of structure of ethers dissolving HCl.



Ethers ( $\text{R}_1\text{R}_2\text{O}$ ):  $\text{Et}_2\text{O}$ ,  $n\text{Bu}_2\text{O}$ ,  $i\text{Pr}_2\text{O}$ ,  $\text{DO}$ ,  $\text{THF}$ ,  $\text{CPME}$

Chapter 4 reports the synthesis and characterizations of Poly(isobutyl vinyl ether)-*block*-Poly( $\epsilon$ -caprolactone) using metal-free living cationic polymerization. Thus this study focuses on a) preparation of monofunctional poly(butyl vinyl ether) of predicted molecular weights applying HCl · Et<sub>2</sub>O and b) ring opening polymerization of  $\epsilon$ -caprolactone initiated by hydroxyl endgroups in the presence of the already adopted complex.

Chapter 5 describes the synthesis of polyvinyl alcohol-*block*-poly( $\epsilon$ -caprolactone). Linking two segments took place by the use of the functional terminating poly(TBVE) created by HCl · Et<sub>2</sub>O initiating system. By the fact that polyTBVE could be hydrolyzed to PVA, diblock PVA-co-PCL has been examined.



## **Chapter 1**

### General Introduction

## Living Cationic Polymerization

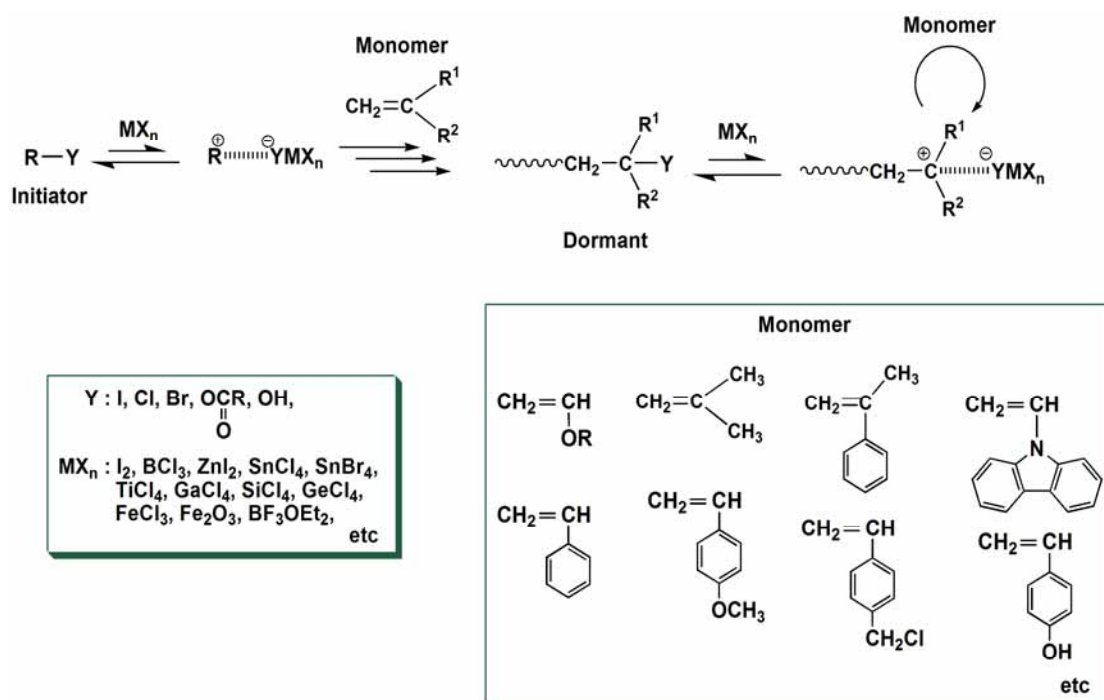
The living cationic polymerization is a special case of chain polymerization. The conventional chain polymerization is comprised of three steps: initiation, propagation and termination which carry out constantly during overall reaction. In a strict sense in every moment of the process the growing chains of the polymer have just started while other ones could become already non-active as a consequence of a termination reaction. The degree of polymerization is almost constant with the time and does not depend on a current conversion of monomer.

The living cationic polymerization definition assumed elimination of all termination reactions which means that once positively charged active centers are created could lifetime forever. Once growing chain ends are activated the propagation reaction occurs by nucleophilic attacks of the monomer (active chain ends mechanism) or involves a neutral growing chain end and cationic species generate reversibly from monomer (activated monomer mechanism). Even if the lack of monomer supervened in the reaction system polymerization could be resumed by the addition of a new charge of monomer.

To suppress the unfavorable reactions such as transfer or termination during polymerization process several conditions have to be fulfilled. Principally a counteranion cannot be too nucleophilic because it may result in covalent bonding with carbenium ions (vinyl polymerization) or onium ions (ring opening polymerization). Another way to control over too nucleophilic counteranion is the application of such initiation system or polymerization conditions (e.g. nature of monomer, solvents, temperature) which can properly tune its nucleophilicity. Thus



the growing cationic species, which are highly reactive, are converted to a dormant covalent species by a reversible reaction and in doing so equilibrium is sustained. Therefore it does not undergo termination reaction namely it extend its lifetime. The conventional mechanism of vinyl living cationic polymerization of vinyl compounds is shown below.



Scheme 1-1. Conventional Mechanism of Living Cationic Polymerization.

The controlled polymerization is performed by the activation of dormant species (halides) by the addition of Lewis acid in such way that exchange between them and growing carbocation unfolds fast thus the rate of initiation reaction is higher than the one of overall reaction of propagation.



been found to be the key factor.<sup>8</sup> It caused suppressing of dissociation of ionic species, which in result provides to the shifting of the equilibrium to covalent species and converts to living polymerization again. Scheme 1-2 presents described above initiating systems. Another class of initiating systems involves  $\text{EtAlCl}_2$  which plays role as an initiator in the presence of added bases.<sup>9</sup> The living process using ethylaluminium dichloride follows the concept so-called “stabilization of the growing carbocation by added bases”. In order to clarify the assumption Higashimura et al. provided the polymerization with externally added ethers which stabilized unstable growing carbocation with conjugation of anion generated by  $\text{EtAlCl}_2$ . The addition of ethers to the polymerization mixture, resulted in increasing of livingness. The investigations indicated as well, that the addition of relatively small amount of ether has a significant influence on the living character of the polymerization, this because there is high concentration of ether functions present in the form of monomer and formed polymer. In elucidating this phenomenon the following course was adopted: added ether provides a better ability to form the dormant oxonium ion. The equilibrium between dormant and active species is more shifted to the dormant with the added ether than in case of isobutyl vinyl ether from the monomer or from the polymer.

The initiating system that leads to uncontrolled polymerizations can be slowed down and transformed into controlled polymerization also by addition of esters and sulfides.<sup>10,11</sup> For instance, a trifluoromethane sulfonic acid led into the uncontrollable polymerizations but when carried out in the presence of a dialkyl sulfide such as tetrahydrothiophene the polymerization returns to its livingness. In this case the sulfide transforms the carbenium ions into sulfonium ions which are

the dormant of the growing species.

The fine control over polymerization process is manifested not only in molecular weight and its distribution but also in stereoregularity of obtained polymer. It was found that by a proper designing of the Lewis acid components which affect the electronic nature of counteranion as well as bulkiness and its spatial shape, the goal may be obtained. The application of titanium chlorides with the combination of aromatic substituents brought interesting observations.

As shown in Figure 1-3 the symmetry around the Lewis acid's metal centers from which the counteranion is formed appeared to be an important factor indicating the stereoregularity. It is noteworthy that in the case of diisopropyl molecule 83% of *meso* content was obtained.<sup>12</sup>

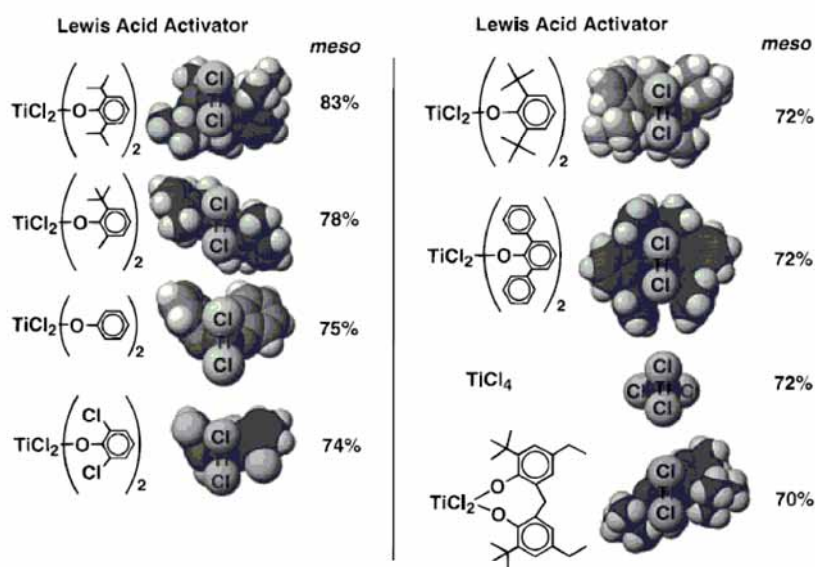


Figure 1-3. Meso diad contents of poly(IBVE) obtained with IBVE-HCl/MX<sub>n</sub> in toluene at -78 °C and computer-generated molecular models of titanium compounds. Polymerization conditions: [M]<sub>0</sub> = 0.38 M; [1]<sub>0</sub> = 5.0 mM; [TiCl<sub>2</sub>(OAr)<sub>2</sub>]<sub>0</sub> = 10 mM (2.0 mM only for TiCl<sub>4</sub>).

Living cationic polymerization may control the molecular weight, molecular weight distribution and stereoregularity like above.

The development of cationically polymerizable products (having predictable molecular weights and narrow molecular weight distributions) has opened the way to produce a large variety of block copolymers. Vinyl ethers led to evaluation of these new materials for specific applications. The properties might be simply varied by the correct choice of lateral group of vinyl ether and its co-monomer. A few examples of model copolymerizations are indicated below.

The concern of selection of appropriate Lewis acid and the additives is one of the factors of successful synthesis of block copolymers due to the fact that tuning cation activity enables the generations of stronger nucleophilic counteranions. The significant advancement on the area cationic polymerization in the matter of coupling two chemically different blocks was brought by Faust et al. The given method allowed to form poly(isobutyl vinyl ether)-*block*-poly(isobutylene)(PIBVE-PIB).<sup>13</sup> The method involves end-capping of living PIB chains with 1,1-diphenylethylene(DPE) followed by modification of cation reactivity, using the Lewis acid(TiCl<sub>4</sub>).

A large variety of block copolymers containing vinyl ethers have been synthesized by sequential addition of monomers. Alkyl substituted vinyl ethers are characterized by similar reactivities so the order of monomer addition can be optional. According to the reactivities of vinyl ethers with polar pendant groups adjusting the reaction conditions become significant. Those with polar group in pendant derived their reactive abilities from their alkyl substituted counterparts. In this case the copolymerization initiating system is usually comprised from HI/I<sub>2</sub> or HX/ZnX<sub>2</sub>.<sup>14</sup>

Combinations of polar and nonpolar vinyl ethers lead to the formation of amphiphilic block copolymers. In many cases the postpolymerization modifications of one of the blocks may be omitted.

Amphiphilic block copolymers comprised of vinyl ethers might be synthesized by sequential living cationic polymerization of IBVE and a vinyl ether with 1,2:5,6-diisopropylidene-D-glucose side group. The HCl adduct of isobutyl vinyl ether, IBVE-Cl was used as an initiator in the presence of  $ZnI_2$ . The molecular weight distribution of the final block copolymers was narrow, and the experimentally determined molecular weights and compositions targets agreed with the theoretical ones<sup>15</sup>).

Another method of synthesis copolymers was represented by isobutylene-b-methyl vinyl ether. At the beginning isobutylene was polymerized. After quantitative conversion of first monomer, second was added in the presence of  $TiCl_4$ . Final product had relatively narrow molecular weight distribution<sup>16</sup>).

Demonstrated methods manifested the application of various initiating systems. Proposed complexes refined their utility over a considerable period however there is still difficulty concerning their metallic nature.

### **Metal-free living polymerization**

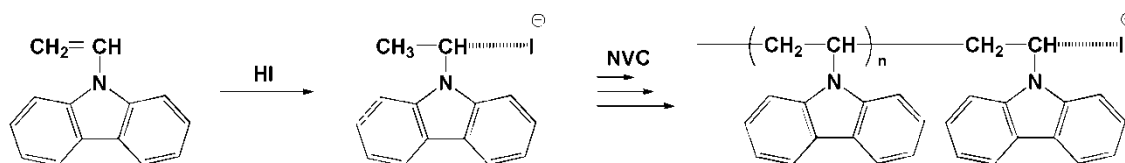
Since not a metal catalyst or initiator is used in the reaction, metal-free living polymerization may be applicable in the field of bio-, resist or electronic materials where metal residues are objectionable. Examples of the metal free living polymerization are indicated below.

Till 1983 there was no concept on metal-free living polymerization when Webster announced a new method of polymerization of methyl methacrylate using so-called Group Transfer Polymerization using silyl ketal acetals under ambient temperature.<sup>17</sup> After that Reetz et al. using tetrabutyl thiolates and malonates as initiators officially introduced the term of metal-free initiators. Using same strategy Sivaram<sup>18</sup> and Fieberg<sup>19</sup>, with tetrabutylammonium ion serving as counteraction obtained acrylonitrile and acrylates. Another report on metal-free living polymerization was presented by Zagala and Hogen-Esch.<sup>20</sup> By using the tetraphenylphosphonium counteraction ( $\text{Ph}_4\text{P}^+$ ) at ambient temperature in THF polymerization of MMA was succeeded resulting in narrow molecular weight distribution and high initiator efficiency  $f( M_n(\text{calc})/M_n(\text{exp})$ .

Controlled radical polymerization namely the polymerization in the presence of TEMPO (2,2,6,6-tetramethylpiperidinoxyl) as well as variety examples of RAFT (reversible addition fragmentation chain transfer) present the reactions with no metal impurities<sup>21-25</sup>.

Special interest has been devoted to metal-free ring-opening polymerization of lactides according their broad range of applications (packaging, surgery or pharmacology).<sup>26-27</sup> Hedrick et al. first applied nucleophilic organocompounds (4-aminopyridines, phosphines, *N*-heterocyclic carbenes) in association with an alcohol as an initiator.<sup>28</sup> Many approaches have been dedicated to acid-catalyzed ROP however controlled cationic polymerization succeeded only for  $\delta$ -valerolactone and  $\epsilon$ -caprolactone, using as a catalyst HCl or an organic acid.<sup>29</sup> Interesting achievement was obtained by using trifluoromethanesulfonic acid ( $\text{HOTf}$ )<sup>30</sup> and protic reagent initiating system under room temperature obtaining well defined

polymers. In comparison, Kricheldorf et al. catalyzed ROP by acid only resulting in a poor control of obtained products even applying the optimum conditions, assured ipso facto of a critical influence of the protic initiator.<sup>31</sup> Recently, TBD (triazabicyclodecene) has been presented as an effective catalyst of the polymerization of cyclic esters and lactides leading to products with narrow molecular weight distributions.<sup>32-33</sup> Another approaches treated of organocatalytic ring-opening polymerization. For example *N*-hetero cyclic carbene with assorted alcohol as an initiator brought well defined poly cyclic ethers. In this case the nucleophilic *N*-hetero cyclic carbene activates the monomer toward attack from initiating/propagating alcohol.



Scheme 2-1

The living cationic polymerization of vinyl ethers in terms of applying non-metal initiating system was considered as not polymerizable for a long time. Sawamoto and Higashimura announced the possibility of living polymerization of NVC (*N*-vinylcarbazole) by HI alone.<sup>34</sup> A reaction formula of this polymerization system was indicated in Scheme 2-1.



The polymerization was possible according to the fact that HI is a weak protonic acid therefore the conjugation with stable NVC cation provided to living propagation. As mentioned in a previous subheading that for IBVE the polymerization proceeded with HI in the presence of ammonium salts and by superstrong acid or triflic acid.

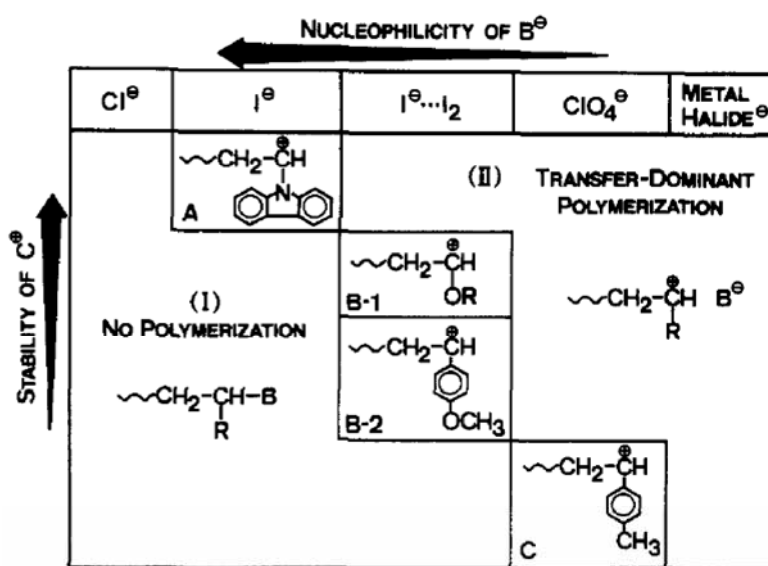


Figure 2-1. Scope of living cationic polymerization of vinyl monomers. Boxes A, B-1, B-2, and C indicate the monomer/initiator combinations for living polymerization.

Except those few examples on metal-free living cationic polymerization of vinyl ethers there were no proofs on initiating system consist of protonic acid without Lewis acid which role was to activate the cationogen. The explanation of this mechanism is presented in the Figure 2-1.

Surprising results however were obtained recently by using  $\text{HCl} \cdot \text{Et}_2\text{O}$  initiating system.<sup>36</sup> It turned out that abovementioned system in ethers plays triple role as initiator, activator and stabilizer. Details concerning the new system will be described in the next chapter.

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## Chapter 2

Metal-Free Living Cationic Polymerization of Various Vinyl Ethers Using  
Hydrogen Chloride with Ether: The effects of Monomer

## ABSTRACT

A highly effective initiating system has been achieved for living cationic polymerization of vinyl ethers consisting of HCl alone without Lewis acid. Present investigations intended to determine effects of the monomer on the already adopted complex  $\text{HCl} \cdot \text{Et}_2\text{O}$ . The monomers are classified into three categories: alkyl vinyl ethers, vinyl ethers with electron-donating groups in pendant and vinyl ethers with bulky group next to the electron-donating substituent in the pendant. It was shown that in case of alkyl vinyl ethers polymerization proceeded smoothly without induction phase giving narrow polydispersity index. Different behavior was observed with monomer possessing electron-donating groups in pendant where rate of polymerization underwent essential changes. However the  $\text{HCl} \cdot \text{Et}_2\text{O}$  was applicable to the polymerization of all kinds of monomers it was found that those with electron donating groups influenced on induction phase of the process. Furthermore obtained polymers have been verified by  $^{13}\text{C}$  NMR. It was demonstrated that structures of poly(IBVE), poly(TBVE), poly(SiEVE), poly(SiPVE), and poly(SiBVE) were relatively meso rich.

## INTRODUCTION

In general, the response to different catalysts types correlates with the electron displacement by the substituents attached to an ethylene group.<sup>1</sup> In case of *N*-vinylcarbazole its electron-donating carbazolyl pendant allows to polymerize with controlled molecular weight and narrow molecular weight distribution. Stabilization of propagating NVC cation occurs by carbazolyl pendant which provides a conjugating system where the positive charge is delocalized.<sup>2</sup> Complying with the same polymerization conditions, I<sub>2</sub> initiating system in the presence of common ion salt (n-Bu<sub>4</sub>NI) didn't give desired products in point of other vinyl ethers due to their non stability of growing carbocations.<sup>3,4</sup> Thus investigation of the effect of monomer appeared to be significant.

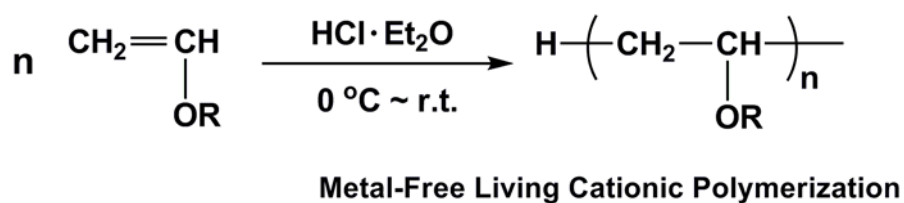
Numerous proposals have been made for the living cationic polymerization of vinyl ethers using Lewis acid as an activator.<sup>5</sup> For instance, alkyl vinyl ethers such as NPVE, NBVE, IBVE, SBVE, TBVE using e.g. 1-(isobutoxy)ethyl acetate/EtAlCl<sub>2</sub> initiating system in the presence of methyl acetate it was found that by increasing chain branching of alkyl groups polymerization rates increase while MWDs of the obtained polymers broadens. The electron donating power of the side alkyl groups through the inductive effect caused difference in the reactivity of monomer. It was noteworthy that steric crowding near to the growing center caused low stability of propagating species of TBVE through its weakened interaction with the added base.

So far various vinyl ether monomers yielded in high cationic polymerizability however the initiation system provided their products has had limited success in the term of its metal inherency. Since new demands concerning the area of a drug



delivery system or microelectronics impose to perform the polymerization without metallic contaminants, finding an accurate synthesis method became the priority. It was found that HCl alone in diethyl ether (Et<sub>2</sub>O) provides well defined products.<sup>6</sup> The overall equation has been showed in Scheme 1. HCl · Et<sub>2</sub>O in ethers plays triple role as initiator, activator, and stabilizer by Et<sub>2</sub>O for carbocation.

Present chapter arises on the effect of the structure of monomer on cationic polymerization initiated by HCl · Et<sub>2</sub>O. The object of study was discussed in term of stability of propagating carbocation. Thus various vinyl ether monomers containing electron-donating groups in pendant and bulky groups next to the electron-donating substituent in the pendant were chosen for investigation. Verification of obtained products took place by means of <sup>13</sup>C NMR.



**Scheme 1.**

## EXPERIMENTAL

### Materials

For monomers, isobutyl vinyl ether (IBVE, TCI), cyclohexyl vinyl ether (CHVE, TCI) *n*-butyl vinyl ether (NBVE, TCI), *tert*-butyl vinyl ether (TBVE, Aldrich), 2-chloroethyl vinyl ether (CEVE, TCI), and 2-methoxyethyl vinyl ether (MOVE, donated by Maruzen Petrochemical) were distilled twice over calcium hydride and were stored in a brown ampoule under dry nitrogen. 2-(*tert*-Butyldimethylsilyloxy)ethyl vinyl ether (SiEVE), 3-(*tert*-butyldimethylsilyloxy)propyl vinyl ether (SiPVE), and 4-(*tert*-butyldimethylsilyloxy)butyl vinyl ether (SiBVE) were prepared and distilled according to the literature method.<sup>7</sup> For initiating system HCl in Et<sub>2</sub>O (HCl·Et<sub>2</sub>O, Aldrich; 1.0 M). Hexane and toluene were washed by usual methods and were distilled over calcium hydride just before use.

### Polymerization Procedures

Polymerization was typically carried out at 0 °C under a dry nitrogen atmosphere in a glass tube equipped with a three-way stopcock baked at 250 °C for 10 min before use. The reaction was initiated by the addition of HCl·ether solution into a mixture of a monomer in hexane or toluene at 0 °C by a dry medical syringe. For another method, monomer was directly added to HCl in Et<sub>2</sub>O (including hexane or toluene) to initiate. After quenching the polymerization by methanol containing a small amount (0.1 vol%) of aqueous ammonia, the reaction mixture was washed by water. The product polymer was recovered from the organic layer by evaporation

and vacuum-dried. The conversion of a monomer was determined by gravimetry.

## Polymer Characterization

The molecular weight distribution (MWD) of the polymers was measured by size exclusion chromatography (SEC) in tetrahydrofuran at 38 °C on three polystyrene gel columns [TSK gel G-MH<sub>HR</sub>-M × 2 or × 3 (exclusion limit: 4 × 10<sup>6</sup> (polystyrene, PSt)); 7.8 mm i.d. × 300 mm each; flow rate 1.0 mL/min] connected to a Tosoh AS-8020 auto-injector, a CCPM-II dual pump, a UV-8020 UV detector and a RI-8011 refractive detector with a LS-8000 LALLS. The main detector is RI-8011. The number-average molecular weight ( $M_n$ ) and  $M_w/M_n$  were calculated from SEC curves on the basis of a PSt calibration. Polymer structure was confirmed by <sup>1</sup>H NMR (500 MHz) or <sup>13</sup>C NMR (125 MHz) using JEOL JNM-EX500 spectrometer.

## RESULTS AND DISCUSSION

### Metal-Free Living Cationic Polymerization of Various Vinyl Ethers

To study the effects of the monomer structure on polymerization behavior, vinyl ether monomers were classified into 3 categories as shown in Chart 1 and their polymerizations using HCl·Et<sub>2</sub>O were investigated. The monomers are grouped as follow: (A) alkyl vinyl ether, (B) vinyl ether with electron-donating groups in the pendant, and (C) vinyl ether with bulky group, *tert*-butyldimethylsilyl group, next to the electron-donating substituent in the pendant. The category A includes the monomer for poly(CHVE) with high glass transition<sup>8</sup> and for polyvinyl alcohol

precursor, poly(TBVE).<sup>9</sup> The categories B and C include MOVE and SiBVE, 2-hydroxybutyl vinyl ether with protecting group, which are utilized to form thermoresponsive polymers in water.<sup>7,11</sup>

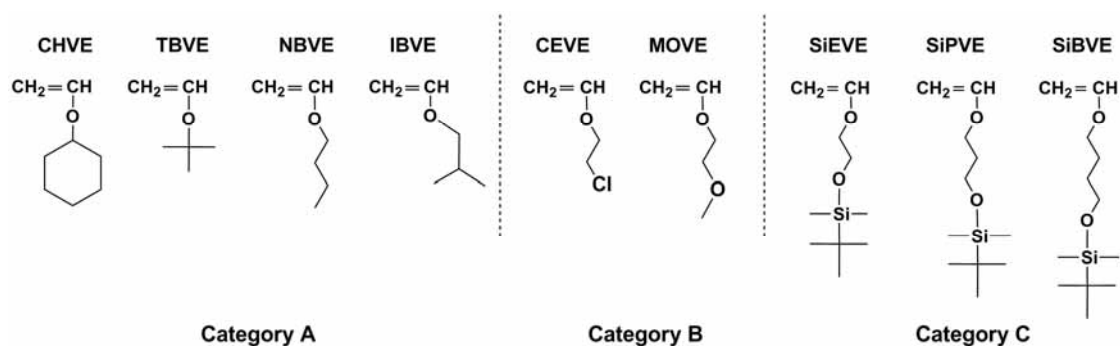


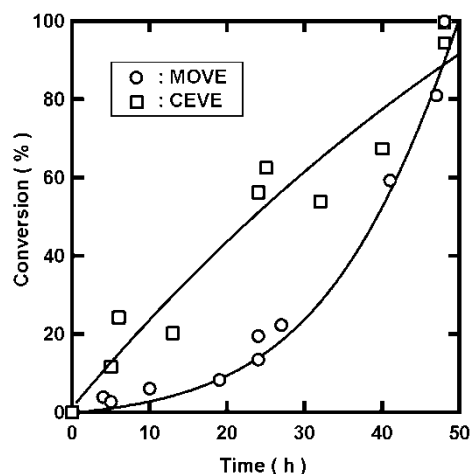
Chart 1.

### Polymerization for Vinyl Ethers in Category A and B

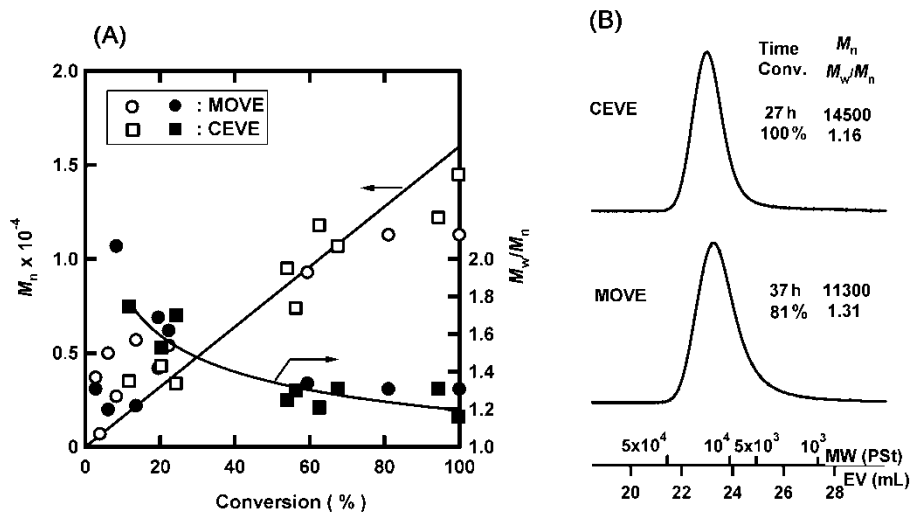
The polymerization of alkyl vinyl ethers (category A) were carried out in hexane at 0 °C with HCl·Et<sub>2</sub>O: [alkyl vinyl ether]<sub>0</sub> = 0.76 or 0.80 M; [HCl]<sub>0</sub> = 4.0 mM; [Et<sub>2</sub>O]<sub>0</sub> = 0.96 M (this is corresponding to 1/9 volume of solvent). All systems induced homogenous polymerizations, whereas the rate depended on monomer structures [16]. Irrespective of different structures of alkyl chain, all monomers were consumed quantitatively without an induction period to give quantitative conversion within 45 min (CHVE:  $M_n = 17400$ ,  $M_w/M_n = 1.33$  at conv. = 80 %; TBVE<sup>10</sup>, NBVE<sup>6</sup>, and IBVE<sup>6</sup>:  $M_w/M_n \leq 1.15$  at conv. > 85 %).

Next, the polymerizations of vinyl ethers with electron-donating groups in the

pendant (category B) were investigated under the same initiator condition as for the alkyl vinyl ether in toluene at 0 °C:  $[\text{monomer}]_0 = 0.8 \text{ M}$ ;  $[\text{HCl}]_0 = 4.0 \text{ mM}$ ;  $[\text{Et}_2\text{O}]_0 = 0.96 \text{ M}$ . CEVE has a chlorine moiety and MOVE has an ether group (methoxy group) in the pendant. Figure 1 shows time-conversion curves for the polymerizations. For CEVE, the polymerization proceeded smoothly without an induction period and was completed around 50 h. However, different results were obtained for MOVE. This may be due to interaction between  $\text{H}^+$  and electron donating moiety at the initiation stage. Figure 2(A) shows the relationship between monomer conversion and  $M_n$  or the  $M_w/M_n$  ratio of the polymers for poly(CEVE) and poly(MOVE). For the both polymerizations, without a low conversion range,  $M_n$  increased in direct proportion to the monomer conversion, and the MWDs of the resulting polymers were quite narrow for poly(CEVE) ( $M_w/M_n = 1.16$  at conv. 100 %) and were relatively narrow for poly(MOVE) ( $M_w/M_n = 1.31$  at conv. 81 %) as shown in Figure 2(B).



**Figure 1.** (A) Time-conversion curves for the polymerization of CEVE and MOVE by  $\text{HCl}\cdot\text{Et}_2\text{O}$  in toluene with 1/9 volume of  $\text{Et}_2\text{O}$  at 0 °C:  $[\text{HCl}]_0 = 4.0 \text{ mM}$ ,  $[\text{Et}_2\text{O}]_0 = 0.96 \text{ M}$ ,  $[\text{monomer}]_0 = 0.80 \text{ M}$ .

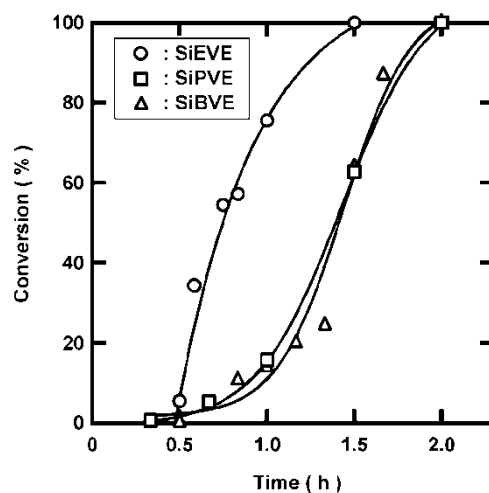


**Figure 2.** (A)  $M_n$  and  $M_w/M_n$  for the polymerization of CEVE and MOVE by HCl·Et<sub>2</sub>O in toluene with 1/9 volume of Et<sub>2</sub>O at 0 °C: [HCl]<sub>0</sub> = 4.0 mM, [Et<sub>2</sub>O]<sub>0</sub> = 0.96 M, [monomer]<sub>0</sub> = 0.80 M. (B) The MWD curves for PCEVE and PMOVE.

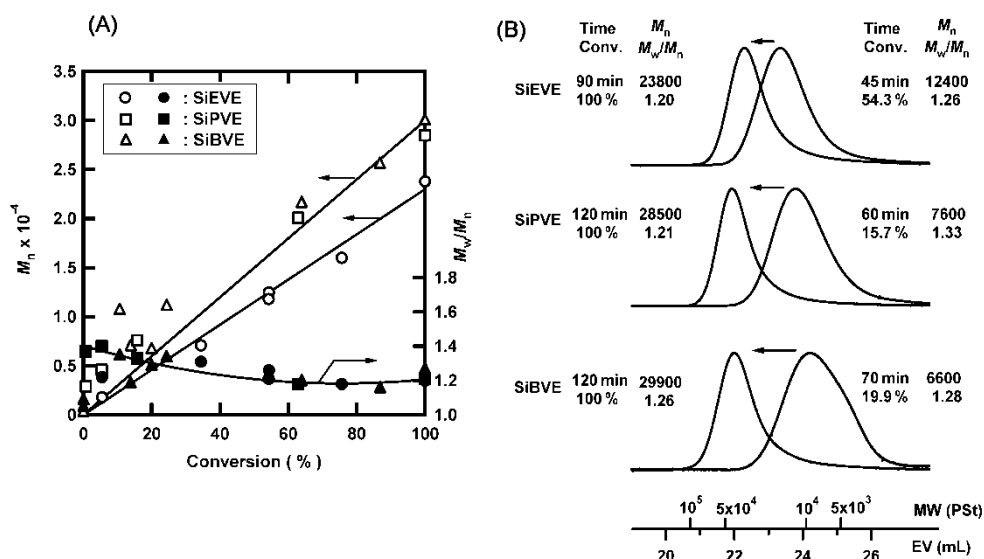
### Polymerization for Vinyl Ethers in Category C

On the basis of polymerization for MOVE, the polymerizations of vinyl ethers with bulky group next to the electron-donating substituent in the pendant (category C) were performed under the same condition in toluene at 0 °C with HCl·Et<sub>2</sub>O. These monomers have the same ether oxygen but different spacer lengths. Alternatively, degrees of interaction between H<sup>+</sup> and ether oxygen in the pendant are smaller than that of MOVE due to bulky *tert*-butyldimethylsilyloxy group, which interactions should be stronger with increasing the length of spacer alkyl groups. Figure 3(A) shows time-conversion curves for these polymerizations. In a similar fashion for MOVE, all polymerizations have an induction period during 30 min. However, after the induction period, smooth polymerization occurred and all monomers were consumed quantitatively to give quantitative conversion within 2 h. No effects of

steric hindrance on polymerization were observed because the induction period was still present in all monomers in category C. However, the polymerization rate decreased with the length of the alkyl chain between vinyl ether and *tert*-butyldimethylsilyloxy group. This is an inverse result from the polymerization using metal Lewis acids such as  $\text{Et}_{1.5}\text{AlCl}_{1.5}$  <sup>7</sup>, may be unique for the  $\text{HCl}\cdot\text{Et}_2\text{O}$  polymerization system. Figure 4(A) shows the relationship between monomer conversion and  $M_n$  or the  $M_w/M_n$  ratio of the polymers. Although all monomers polymerized with induction period,  $M_n$  increased in direct proportion to the monomer conversion. The MWDs of the resulting polymers were monodispersal during polymerization and relatively narrow as shown in Figure 4(B). These results for monomers suggested that  $\text{HCl}\cdot\text{Et}_2\text{O}$  system is applicable for the polymerization of various vinyl ethers as shown in Chart 1, however, the structure around electron-donating groups such as isolated ether oxygen contributes the polymerizations rate and induction period.



**Figure 3.** Time-conversion curves for the polymerization of SiEVE, SiPVE, and SiBVE by  $\text{HCl}\cdot\text{Et}_2\text{O}$  in toluene with 1/9 volume of  $\text{Et}_2\text{O}$  at 0 °C:  $[\text{HCl}]_0 = 4.0 \text{ mM}$ ,  $[\text{Et}_2\text{O}]_0 = 0.96 \text{ M}$ ,  $[\text{monomer}]_0 = 0.80 \text{ M}$ .



**Figure 4.** (A)  $M_n$  and  $M_w/M_n$  for the polymerization of SiEVE, SiPVE, and SiBVE by HCl·Et<sub>2</sub>O in toluene with 1/9 volume of Et<sub>2</sub>O at 0 °C: [HCl]<sub>0</sub> = 4.0 mM, [Et<sub>2</sub>O]<sub>0</sub> = 0.96 M, [monomer]<sub>0</sub> = 0.80 M. (B) The MWD curves for the obtained polymers at the 100% and lower conversion.

### Polymer structure

The structure of poly(IBVE) obtained using HCl·ether was examined by <sup>1</sup>H NMR and <sup>13</sup>C NMR. From the <sup>1</sup>H NMR results (not shown) for all polymerizations of IBVE, we concluded that the end group of poly(IBVE) have been transformed from carbocation or -Cl from dormant to -OCH<sub>3</sub> after quenching the polymerization by methanol. From <sup>13</sup>C NMR, the steric structure (dyad) of various poly(vinyl ether)s were examined, which were obtained by HCl·Et<sub>2</sub>O ([Et<sub>2</sub>O]<sub>0</sub> = 0.96 M). These structures were relatively meso rich; the meso/raceme ratios were 63/37, 64/36, 58/42, 68/32, and 68/32, for poly(IBVE), poly(TBVE), poly(SiEVE), poly(SiPVE), and



poly(SiBVE), respectively (conv.  $\geq$  89.3 %, samples obtained at the highest conversion). These results were almost the same as that of usual cationic polymerization<sup>7,12</sup>.

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## Chapter 3

Metal-Free Living Cationic Polymerization of Various Vinyl Ethers Using  
Hydrogen Chloride with Ether: The effects of Ether Structure

## ABSTRACT

Detailed research on  $\text{HCl} \cdot \text{Et}_2\text{O}$  and the effect given by the monomer structure on the polymerization has been extended to examine a behavior of various ethers in the conjugation with chloride acid. It was shown that among ethers subjected to synthesis initiation reaction may be achieved by ethers efficiently dissolving HCl with specification of symmetrical ones. Ethers such as *n*Bu<sub>2</sub>O, *i*Pr<sub>2</sub>O, Et<sub>2</sub>O, CPME, DO, and THF were chosen for investigation. Considered ethers lead to propagation via living fashion. The effect of the structure was examined based on computer-generated model calculated by MM2.

## INTRODUCTION

Summing up the conclusions arrived in the previous chapter it may be said that monomer structure, namely electron density location substantially influences rate of the polymerization using  $\text{HCl} \cdot \text{Et}_2\text{O}$  initiating system.<sup>1</sup> Present work is directed towards effect of ether structures on living cationic polymerization. The effects of ethers on polymerization process using typical three-component initiating systems (e.g. catiogen, activator and carbocation additives) showed that lack of ether base resulted in non-living polymerization. Observation indicated that the more basic the ether is, the less is needed to achieve the same reaction rate.<sup>2,3</sup>

The notion “stabilization of the growing carbocation by bases” in case of  $\text{HCl} \cdot$  ether implies that living polymerization may proceed where an ether stabilizes an unstable growing carbocation. We intend to clarify this assumption by examination of structure as well as nucleophilicity of applied ethers (*n*Bu<sub>2</sub>O, *i*Pr<sub>2</sub>O, Et<sub>2</sub>O, CPME, DO, and THF).

## EXPERIMENTAL

### Materials

Isobutyl vinyl ether (IBVE, TCI) was distilled twice over calcium hydride and was stored in a brown ampoule under dry nitrogen. For HCl in ether (HCl•ether), HCl in Et<sub>2</sub>O (HCl•Et<sub>2</sub>O, Aldrich; 1.0 M), in 1,4-dioxane (HCl•DO Aldrich; 1.0 M), and in cyclopentyl methyl ether (HCl•CPME Watanabe Chemical Industries; 4.0 M) was used as commercially supplied. HCl in di-*n*-butyl ether (HCl•*n*Bu<sub>2</sub>O), in di-isopropyl ether (HCl•*i*Pr<sub>2</sub>O), and in tetrahydrofuran (HCl•THF) was prepared by bubbling of dry HCl gas into the corresponding dehydrated ether. These dehydrated ethers for adjusting concentrations were obtained as commercially supplied for Et<sub>2</sub>O (Wako) and *i*Pr<sub>2</sub>O (Kanto Kagaku) or as distilled twice over calcium hydride or sodium for *n*Bu<sub>2</sub>O, CPME (donated by ZEON), DO, THF. Hexane and toluene were washed by usual methods and were distilled over calcium hydride just before use.

### Polymerization Procedures

Polymerization was typically carried out at 0 °C under a dry nitrogen atmosphere in a glass tube equipped with a three-way stopcock baked at 250 °C for 10 min before use. The reaction was initiated by the addition of HCl•ether solution into a mixture of a monomer in hexane or toluene at 0 °C by a dry medical syringe. For another method, monomer was directly added to HCl in Et<sub>2</sub>O (including hexane or toluene) to initiate. After quenching the polymerization by methanol containing a small amount (0.1 vol%) of aqueous ammonia, the reaction mixture was washed by

water. The product polymer was recovered from the organic layer by evaporation and vacuum-dried. The conversion of a monomer was determined by gravimetry.

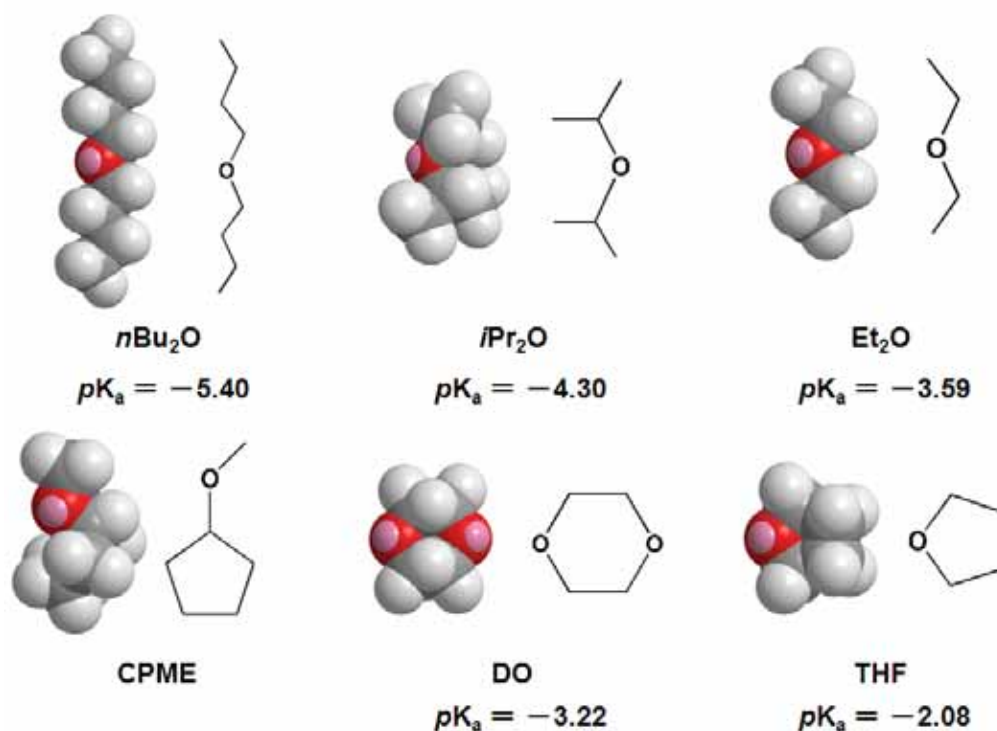
### **Polymer Characterization**

The molecular weight distribution (MWD) of the polymers was measured by size exclusion chromatography (SEC) in tetrahydrofuran at 38 °C on three polystyrene gel columns [TSK gel G-MH<sub>HR</sub>-M × 2 or × 3 (exclusion limit: 4 × 10<sup>6</sup> (polystyrene, PSt)); 7.8 mm i.d. × 300 mm each; flow rate 1.0 mL/min] connected to a Tosoh AS-8020 auto-injector, a CCPM-II dual pump, a UV-8020 UV detector and a RI-8011 refractive detector with a LS-8000 LALLS. The main detector is RI-8011. The number-average molecular weight ( $M_n$ ) and  $M_w/M_n$  were calculated from SEC curves on the basis of a PSt calibration. Polymer structure was confirmed by <sup>1</sup>H NMR (500 MHz) or <sup>13</sup>C NMR (125 MHz) using JEOL JNM-EX500 spectrometer.

## **RESULTS AND DISCUSSION**

### **Effects of Structures of Ether Dissolving HCl**

In order to investigate the effects of structure of ether dissolving HCl on polymerization system, we have examined a series of oxygen based nucleophiles (ethers) such as *n*Bu<sub>2</sub>O, *i*Pr<sub>2</sub>O, Et<sub>2</sub>O, CPME, DO, and THF. Herein, only IBVE was used as a monomer for comparisons. In Figure 1, these ether structures are represented as the most stable computer-generated models calculated by MM2 and  $pK_a$  values<sup>4</sup> are also shown.

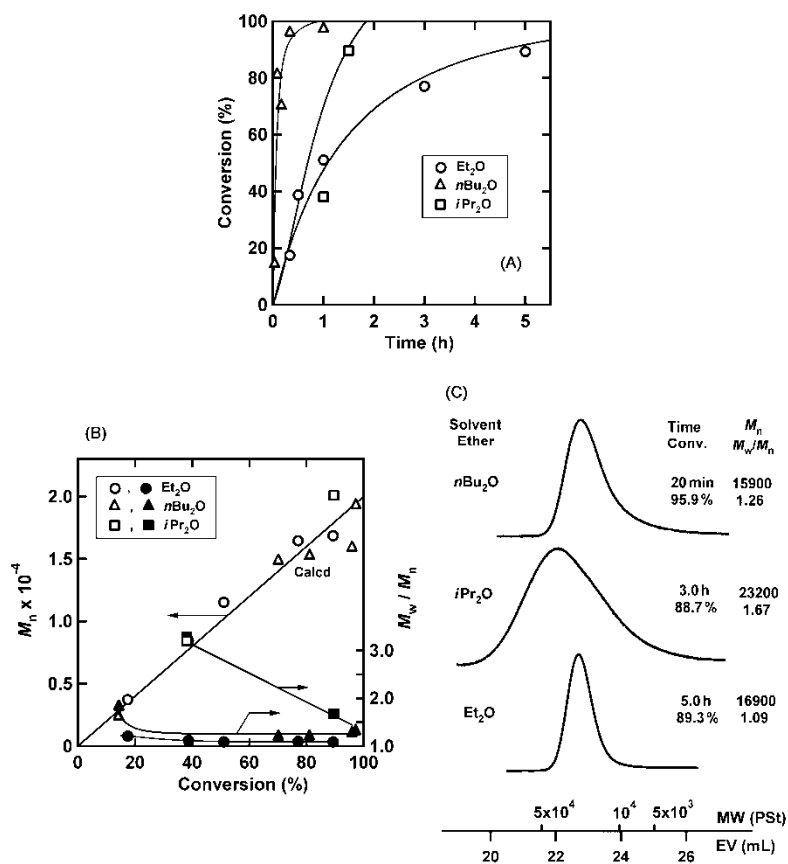


**Figure 1.** Ether structures as the most stable computer-generated model (MM2) and  $pK_a$  values.

The previous research<sup>1</sup> revealed that  $\text{Et}_2\text{O}$  could control both  $M_n$  and  $M_w/M_n$  as increasing the concentration of  $\text{Et}_2\text{O}$  though the polymerization rate was slow. Alternatively,  $\text{Et}_2\text{O}$  solely as a solvent without toluene and hexane can be polymerized in living fashion. On the basis of those results, the  $\text{HCl}$ -ether induced living cationic polymerizations of IBVE which were demonstrated using various ether concentrations and temperatures. Figure 2 shows the polymerization results in  $n\text{Bu}_2\text{O}$ ,  $i\text{Pr}_2\text{O}$ , and  $\text{Et}_2\text{O}$  using  $\text{HCl}$  at  $0\text{ }^\circ\text{C}$  ( $[\text{IBVE}]_0 = 0.76\text{ M}$ ,  $[\text{HCl}]_0 = 4.0\text{ mM}$ ) in conjugation with  $\text{HCl}$  initiating system. Figure 2 (A) shows time-conversion curves, (B) indicates the relationship between monomer conversion and  $M_n$  or the  $M_w/M_n$  ratio of the polymers, (C) summarizes all MWDs. Each polymerization proceeded



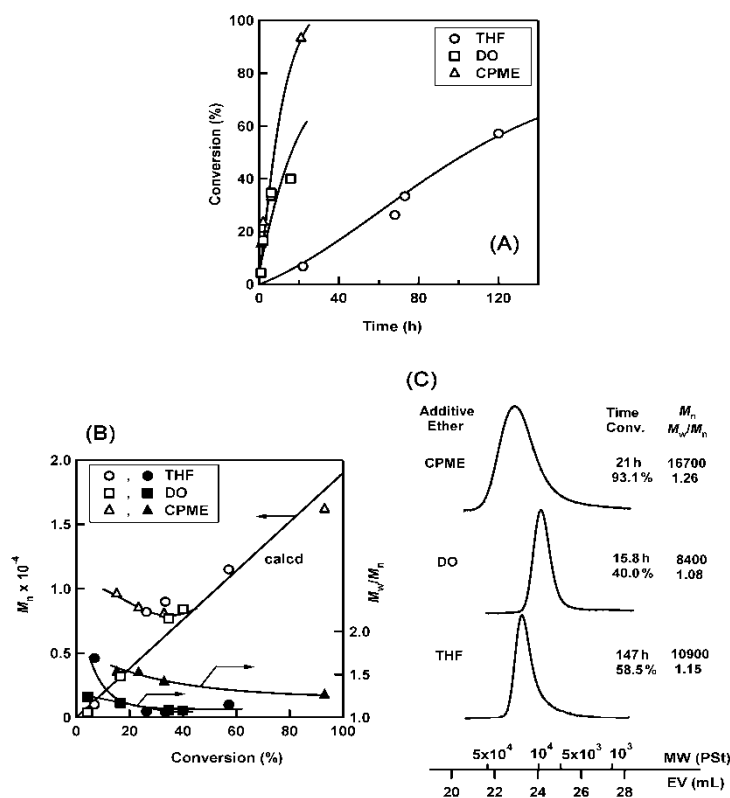
smoothly proceeded in living fashion. For example, *n*Bu<sub>2</sub>O has the lowest  $pK_a$  value as shown in Figure 1. In spite of the lowest  $pK_a$  value, polymerization proceeded without an induction period as well as the case of Et<sub>2</sub>O and completed about 20 min, though *n*Bu<sub>2</sub>O was used as a solvent. The  $M_w/M_n$  of the final polymer has relatively narrow MWD which is slightly larger than that of Et<sub>2</sub>O. ( $M_w/M_n = 1.26$  at conv. 95.9 %). In using *i*Pr<sub>2</sub>O as an added base with metal Lewis acid for polymerization of IBVE, non-living polymerization usually occurred.<sup>5</sup> Thus, this is small effect as an added base for living cationic polymerization. However, the application of *i*Pr<sub>2</sub>O provided “living” polymerization (with slightly broad MWDs) as shown in Figure 2. The  $M_n$  increased in direct proportion to the monomer conversion. The living polymerization is characteristic for HCl·ether inducing living cationic polymerizations and may be occurred due to fast dissociation of HCl, because oxygen atom is protruding from ethers as shown in Figure 1.



**Figure 2.** (A) Time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  for the polymerization of IBVE by HCl in various ether (Et<sub>2</sub>O, nBu<sub>2</sub>O, and iPr<sub>2</sub>O) at 0 °C: [HCl]<sub>0</sub> = 4.0 mM, [IBVE]<sub>0</sub> = 0.76 M. (C) The MWD curves for the obtained polymers at the highest conversion.

For CPME, DO, and THF, cationic polymerization was demonstrated at 0 or 30 °C in consideration of their melting points. In the case of HCl·CPME, polymerization was carried out under various conditions such as [CPME]<sub>0</sub> = 9.44 mM, 0.21 M and as a solvent at 0 or 30 °C, even though could not be controlled perfectly at the region of low conversion. Figure 3 shows the polymerization results complying with following conditions: [IBVE]<sub>0</sub> = 0.76 M, [HCl]<sub>0</sub> = 4.0 mM, [CPME]<sub>0</sub> = 0.21 M in

toluene at 0 °C. As shown in Figure 3(B), initial polymerization could not be controlled. The cause may be due to non-perfect dissociation of HCl in CPME, because CPME has a steric hinderance of cyclopentyl moiety next to oxygen atom of the ether, which can be explained using the structure shown in Figure 1. In the case of HCl·DO and HCl·THF, living cationic polymerization has been achieved at a slower rate than that of Et<sub>2</sub>O because of their high p*K*<sub>a</sub> values. These results for additive ethers suggested that cationic initiation can be successfully achieved using ether effectively dissociating HCl, especially symmetrical ether. Furthermore, propagation can be successfully occurred in living fashion.



**Figure 3.** (A) Time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  for the polymerization of IBVE by HCl·ether in hexane at 0 °C for CPME or 30 °C for THF and DO:  $[HCl]_0 = 4.0$  mM,  $[IBVE]_0 = 0.76$  M,  $[ether]_0 = 0.21$  M. (C) The MWD curves for the obtained polymers at the highest conversion.

In conclusion, we have provided detailed investigation on ether structures for HCl·ether induced polymerization system. The initiation reactions can be successfully achieved using ether effectively dissociating HCl, especially symmetrical ether. The HCl·ether induced cationic polymerization can be widely applied for various vinyl ethers in living fashion.

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## Chapter 4

Synthesis and Characterization of Block Copolymers of Poly(Isobutyl Vinyl Ether)-*block*-Poly( $\epsilon$ -Caprolactone) Using Metal-Free Living Cationic Polymerization.

## ABSTRACT

As mentioned in previous study  $\text{HCl} \cdot \text{Et}_2\text{O}$  provides an entry into metal free polymerization of various vinyl ethers with well defined structures. This chapter makes progress in the term of synthesis and characterization of hydroxyethyl functional poly(IBVE) and block copolymers comprised of poly(isobutyl vinyl ether) and poly( $\epsilon$ -caprolactone). Using mentioned initiating system in hexane at  $0^\circ\text{C}$  hydroxyethyl functionals of predicted molecular weights have been prepared. Furthermore, those primary hydroxyl end functionalities utilizing as a macroinitiator in a ring opening polymerization of monomer such as  $\epsilon$ -caprolactone led thereby into block copolymerization.

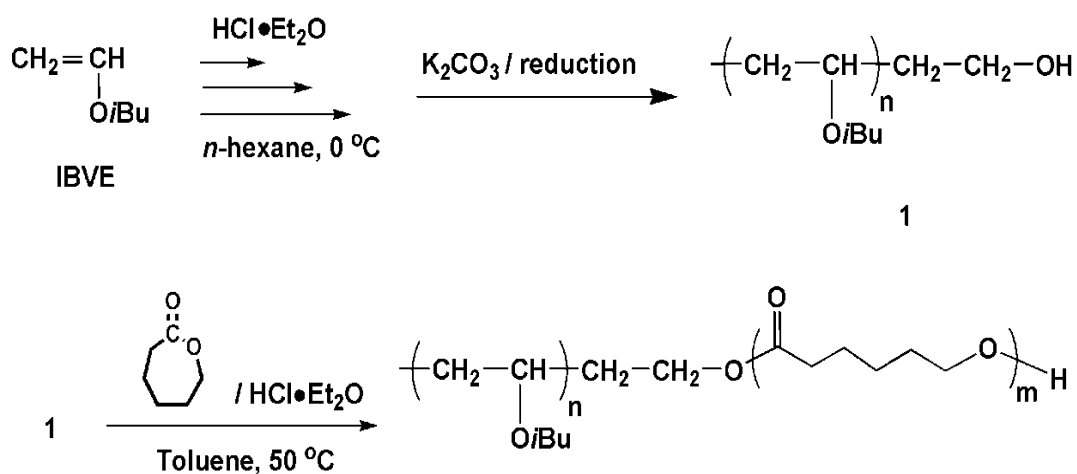
## INTRODUCTION

The formation of cationically polymerizable products having predictable molecular weights and narrow molecular weight distributions gave experimental proofs for elimination of termination and chain transfer reactions in this system. Advances in cationic methodology opened the way for well defined block copolymers (e.g. determined molecular weights, narrow distribution, and tailored architectures). Among possible methods for the preparation functional terminated polymers, living polymerization appeared to be the simplest and the most effective. By forming monofunctional poly(vinyl ether) oligomers of predicted molecular weights linking two chemically dissimilar segments may be accomplished. Many accounts have been reported on synthesis of vinyl ether with conjugation of aliphatic ester e.g. using HI/ZnI<sub>2</sub> for homopolymer synthesis and stannous octanoate as a catalyst for copolymerization.<sup>1,2,3</sup> However block copolymers with well defined architecture were obtained, a defect in the shape of metallic contaminates still remained. Referring to metal free polymerization, which widens the range of potential applications of obtained polymers concerning e.g. surgery and pharmacology<sup>4-7</sup>, promising results were shown by the application of acid (HCl · Et<sub>2</sub>O) and protic agent (alcohol and water).<sup>8,9</sup> ROP of  $\delta$ -valerolactone or  $\epsilon$ -caprolactone initiated by hydroxyl end-capped polyethers (MPEG, PEG) led to well controlled copolymers. Polymerization of cyclic carbonate with 7-membered ring was found to proceed utilizing abovementioned system.<sup>10</sup> Hydroxy-terminated prepolymer initiated a diblock copolymerization.

This investigation has been concentrated on polymerization of poly(IBVE)



possessing functional end groups such as hydroxyethyl groups with predicted molecular weights and utilized them as a macroinitiator in activated monomer cationic polymerization of  $\epsilon$ -caprolactone with  $\text{HCl} \cdot \text{Et}_2\text{O}$  as a ring-opening polymerization. This combination method is a metal free living polymerization. Monofunctional poly(IBVE) has been prepared by termination of leaving moieties using  $\text{K}_2\text{CO}_3$  in water, and then reducing formed aldehyde. The reaction route is shown in Scheme 1.



Scheme 1.

## EXPERIMENTAL

### Materials

Toluene and hexane were washed by usual methods and then distilled over calcium hydride under nitrogen prior to use. Isobutyl vinyl ether (IBVE, TCI) was distilled twice over  $\text{CaH}_2$  and stored in brown ampoules under nitrogen.  $\text{HCl} \cdot \text{Et}_2\text{O}$  (1.0M HCl in  $\text{Et}_2\text{O}$ ) was purchased from Aldrich and used without further purification. The concentration of HCl was estimated by titmetric determination using 0.1 M NaOH aqueous solution. Dehydrated  $\text{Et}_2\text{O}$  (Wako) was used as commercially supplied.  $\text{NaBH}_4$ , ethyl alcohol and  $\text{K}_2\text{CO}_3$  were used as received. CL (Naclai Tesque) was purified by distillation over calcium hydride under reduced pressure.

### Measurements

The molecular weight distribution (MWD) of the polymers was measured by size exclusion chromatography (SEC) in tetrahydrofuran at 38 °C on three polystyrene gel columns [TSK gel G-MH<sub>HR</sub>-M × 3 (exclusion limit:  $4 \times 10^6$  (polystyrene, PSt)); 7.8 mm i.d. × 300 mm each; flow rate 1.0 mL/min] connected to a Tosoh AS-8020 auto-injector, a CCPM-II dual pump, a UV-8020 UV detector and a RI-8011 refractive detector with a LS-8000 LALLS. The main detector is RI-8011. The number-average molecular weight ( $M_n$ ) and  $M_w/M_n$  were calculated from SEC curves on the basis of a PSt calibration.  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  by means of JEOL JNM-AL 300, so that the polymer structure was confirmed.

## **Polymerization of Monofunctional Vinyl Ethers**

Polymerizations were carried out at 0 °C under a dry nitrogen atmosphere in the glass flasks which were heated at 250 °C for 10 min before use. To a solution of monomer in hexane,  $\text{HCl} \cdot \text{Et}_2\text{O}$  was added in order to initiate the reaction. After the polymerization proceeded to desired conversion, the termination was completed by addition of  $\text{K}_2\text{CO}_3$  in water resulting in the aldehyde end groups. Due to reduction of aldehyde groups to the hydroxyethyl one in the end groups,  $\text{NaBH}_4$  in ethanol/hexane (4/1 v/v) was added into the reaction mixture. After 12 h of stirring was sequentially washed with dilute HCl and water to remove the initiator residues and neutralized. The obtained product was next evaporated and vacuum dried overnight.

## **Block Copolymerization from PIBVE.**

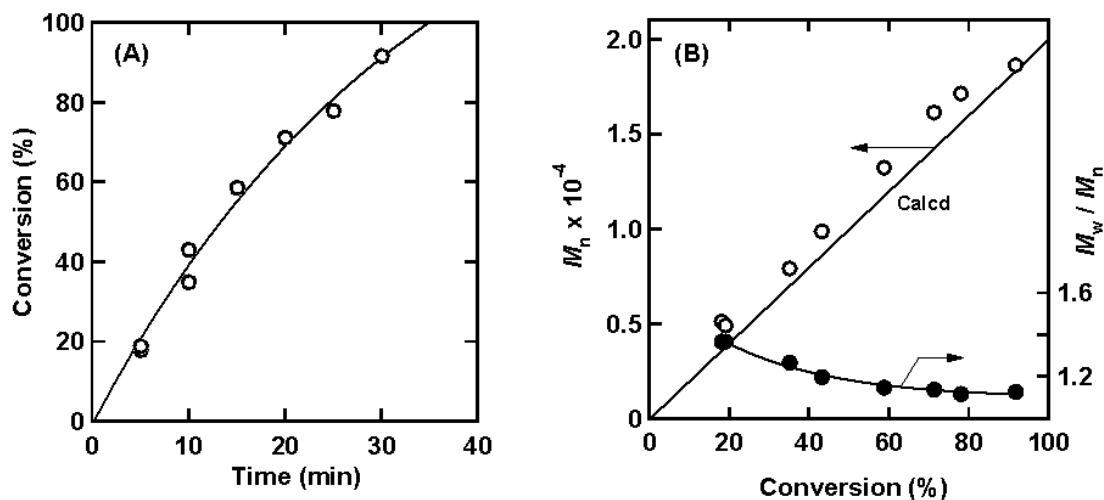
Poly(vinyl ether)s possessing functional end groups were dried under vacuum at 50 °C for 6 h, then placed under a nitrogen atmosphere. After the addition of dry toluene CL was introduced. The polymerization was initiated by  $\text{HCl} \cdot \text{Et}_2\text{O}$  and was carried out at 50 °C. In certain time, reaction mixture was diluted by dichloromethane and washed by water to remove the initiator residues. Obtained solution was then poured into methanol to precipitate the polymer. Precipitant was filtered and dried under vacuum, resulting in a powdery polymer.

## RESULTS AND DISCUSSION

### Synthesis of PIBVE Using HCl•Et<sub>2</sub>O

According to the previous study HCl•Et<sub>2</sub>O initiating system allows to polymerize various vinyl ethers. The detailed polymerization mechanism has been described, which is the facile metal-free method. HCl is dissociated by Et<sub>2</sub>O only, presented complex serves as an initiator and activator, respectively. Due to obtained results, we assumed living nature of formed polymers. The focus of this study was to investigate the optimum conditions for preparing PIBVE that is why the particular attention was directed to their polymerization characteristics. In particular, IBVE is a conventional monomer for cationic polymerization, the isobutyl moiety are more stable for HCl or HBr than *tert*-butoxy group.

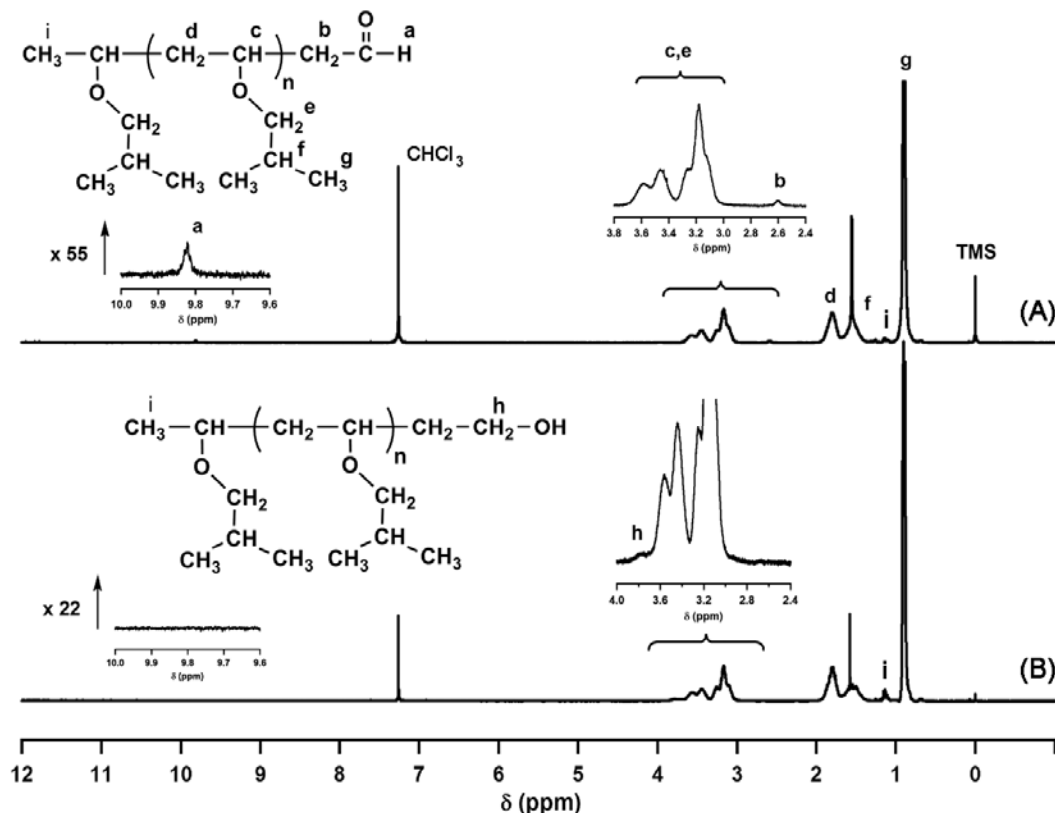
Figure 1 shows the typical example for metal-free living cationic polymerization of IBVE. Figure 1(A) depicts time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  dependents for the polymerization of IBVE by HCl•Et<sub>2</sub>O in hexane with 1/9 volume of Et<sub>2</sub>O at 0 °C: [IBVE]<sub>0</sub> = 0.76 M, [HCl]<sub>0</sub> = 4.0 mM, [Et<sub>2</sub>O]<sub>0</sub> = 0.96 M. The polymerization proceeded smoothly without induction period and completed within 40 min. The  $M_n$  increased in direct proportion to the monomer conversion, and the MWDs of the resulting polymers were narrow ( $M_w/M_n \sim 1.1$ ). Thus, the cationic polymerization of IBVE using HCl•Et<sub>2</sub>O defined as living polymerization.



**Figure 1.** (A) Time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  for the polymerization of IBVE by  $\text{HCl} \cdot \text{Et}_2\text{O}$  in hexane with 1/9 volume of  $\text{Et}_2\text{O}$  at 0 °C:  $[\text{IBVE}]_0 = 0.76 \text{ M}$ ,  $[\text{HCl}]_0 = 4.0 \text{ mM}$ ,  $[\text{Et}_2\text{O}]_0 = 0.96 \text{ M}$ .

In order to synthesize poly(vinyl ether)-*b*-PCL using metal-free living cationic polymerization abovementioned, preparation of monofunctional PIBVE was investigated in details. This was obtained by first addition of 25 wt%  $\text{K}_2\text{CO}_3$  in water resulting in aldehydic ends and then by reduction those groups using 1.6 equivalent of  $\text{NaBH}_4$  in ethanol/hexane (4/1 v/v). The reaction progress was shown by  $^1\text{H}$  NMR spectra. The presence of the aldehydic protons **a** around 9.8 ppm in  $\text{CDCl}_3$  confirmed the termination reaction in Figure 2(A). The signal observed around 1.1 ppm is assigned to the methyl proton **i** from HCl initiator. The amount of **i** is just equal to that of one third of **a**, indicating quantitative formation of terminal aldehyde (the end-functionality is almost 1). Then again the addition of the reduction agent in ethanol was accompanied with their disappearance and broadening peak next to the oxygen in the polymer backbone around 3.8 ppm in

Figure 2(B). The estimated structures were shown respectively in Figure 2.

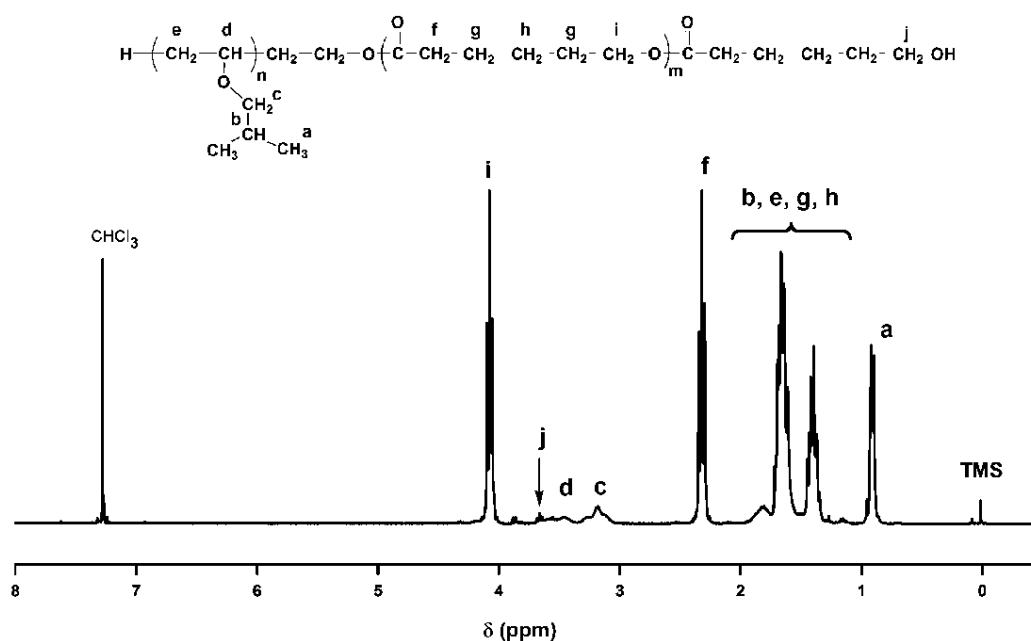


**Figure 2.** <sup>1</sup>H NMR spectra (300 MHz,  $CDCl_3$ , r.t) of (A) PIBVE (DP  $\sim$  50) terminated by aqueous  $K_2CO_3$  solution, and (B) PIBVE after reduction of (A) possessing a hydroxyethyl group.

### Diblock Copolymers Consist of PIBVE and PCL.

Diblock copolymer of PIBVE and PCL were synthesized by the combination of metal-free living cationic polymerization of IBVE and ROP as an activated monomer cationic polymerization of CL.<sup>11</sup> Applied method is illustrated in Scheme 1. The chain-end of PIBVE was used to initiate for ROP. When inadequate dried

PIBVE was used in preliminary investigation, PCL homopolymer initiated from H<sub>2</sub>O were partly obtained. To reduce the influence of water content on ratios of PVE-*b*-PCL as well as water in HCl•Et<sub>2</sub>O<sup>12</sup>, the obtained PIBVE was vacuum dried overnight. The course of the reaction was followed by <sup>1</sup>H NMR spectrum. Figure 3 depicts typical diblock copolymer bands. Signals **a-e** are derived from macroinitiator, PIBVE. After copolymerization with PCL, new signals revealed: **f, g, h, and i**, which are observed at 2.3, 1.4, 1.2, and 4.1 ppm, respectively, as shown in Figure 3.



**Figure 3.** <sup>1</sup>H NMR spectrum (300 MHz, CDCl<sub>3</sub>, r.t.) of PIBVE-*b*-PCL (No. 2 in Table1).

The signal assignable to the methylene proton next to the hydroxyl group which belongs to the prepolymer formation observed at 3.8 ppm (signal **h** in Figure 2 (B)) disappeared. While new **j** assignable to the methylene proton next to the ester

oxygen at 3.6-3.7 ppm appeared confirming that no homopolymer impurity derived from the macroinitiator, occurred.

In the course of the experiments we examined series compositions of block copolymers. Table 1 summarizes the conversion, CL length,  $M_n$ ,  $M_w/M_n$  of obtained polymers. Variations of homopolymer and CL lengths chain as well as regulating  $[CL]_0/[HCl]_0$  feed ratio, composed the factors of easily controlled diblock copolymerization process. In view of IBVE<sub>20</sub> (namely, degree of polymerization is 20 for IBVE or DP 20 for IBVE) in Table 1, monomer to initiator was fixed at 40 or 50 (No. 1, 2) and the temperature was set at 50 °C, diblock copolymers kept relatively narrow MWDs ( $M_w/M_n = 1.19$  or  $1.29$ ) with expected molecular weights. The expected molecular weight is usually lower than that determined with polystyrene, the experimental  $M_n$  determined for PCL is ca. 0.45 times lower than that calculated without any correction from the polystyrene standards.<sup>13</sup> For example, the  $M_n$  of No. 2 using the SEC of the PCL segment, which is calculated by subtraction  $M_n$  of the PIBVE macroinitiator from that of PIBVE-*b*-PCL, is in good agreement with a ca. 0.45 times lower  $M_n$  than the target molecular weight. Complying with similar conditions (No. 3) with increased temperature which naturally accelerates the reaction,  $M_w/M_n$  in the range of 1.20 was obtained. In order to investigate the influence of the homopolymer length chain, IBVE<sub>50</sub> was prepared while  $[CL]_0/[HCl]_0$  was set at 40. The MWD depicted unimodal diblock copolymer. Furthermore the peaks measured by SEC with dual RI and UV detectors appeared at the same elution time which indicates that CL was introduced into PIBVE chain (Figure 4). Different behaviors have been found in case of No.4 when  $[CL]_0/[HCl]_0 = 10$ , which was too high concentration of HCl for CL



to polymerize CL. The MWD shifted to the higher molecular weight region, however, second elution volume peak corresponding to the prepolymer and/or oligomer macromolecules appeared indicates their not incorporation in the diblock. The molecular weight as determinate by SEC deviated substantially from the theoretical value.

Table 1. ROP Results for PIBVE-*b*-PCL Using PIBVE Macroinitiator<sup>a</sup>

No.	Target composition	[CL] <sub>0</sub> /[HCl] <sub>0</sub>	[HCl] <sub>0</sub> /[PIBVE] <sub>0</sub>	Temp. (°C)	Time (h)	Conv. <sup>b</sup> (%)	CL length in polymer <sup>c</sup>	<i>M<sub>n</sub></i> (SEC) <sup>d</sup>		<i>M<sub>w</sub></i> / <i>M<sub>n</sub></i> (SEC) <sup>d</sup>	
								Homo	Diblock	Homo	Diblock
1	IBVE <sub>20</sub> - <i>b</i> -CL <sub>50</sub>	50	1	30	40	41.5	21	3000	4700	1.35	1.29
2	IBVE <sub>20</sub> - <i>b</i> -CL <sub>200</sub>	40	5	50	24	80.9	162	3000	11000	1.35	1.19
3	IBVE <sub>20</sub> - <i>b</i> -CL <sub>240</sub>	60	4	60	12	46.4	108	3000	7000	1.35	1.20
4	IBVE <sub>50</sub> - <i>b</i> -CL <sub>50</sub>	10	5	50	36	78.2	29	6300	4100	1.22	1.69
5	IBVE <sub>50</sub> - <i>b</i> -CL <sub>200</sub>	40	5	50	36	70.0	139	6300	13100	1.22	1.25
6	IBVE <sub>50</sub> - <i>b</i> -CL <sub>645</sub>	65	10	50	36	76.6	450	6300	12000	1.22	1.37

<sup>a</sup> Polymerization condition: [PIBVE]<sub>0</sub> = 7.2 mM in toluene.

<sup>b</sup> Conversion for CL polymerization from corresponding macroinitiator of PIBVE.

<sup>c</sup> Calculated from the molar ratio of CL and PIBVE in block copolymer by <sup>1</sup>H NMR.

<sup>d</sup> Polystyrene calibration.

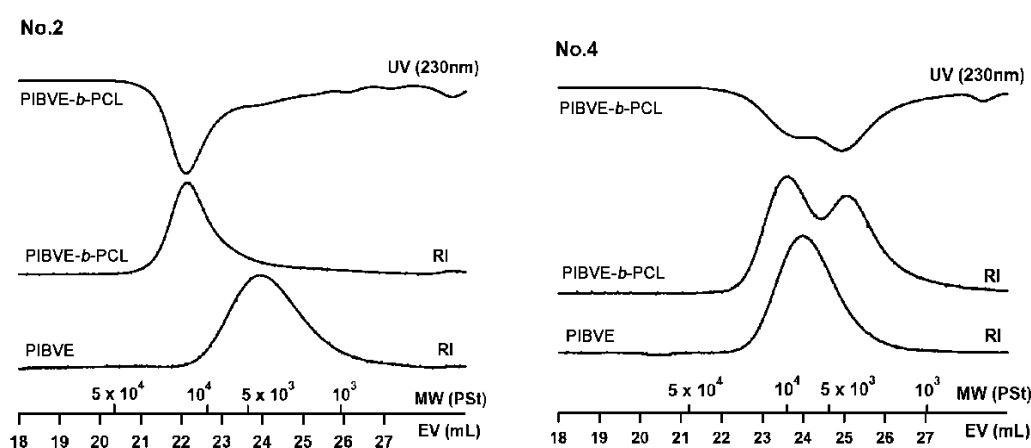
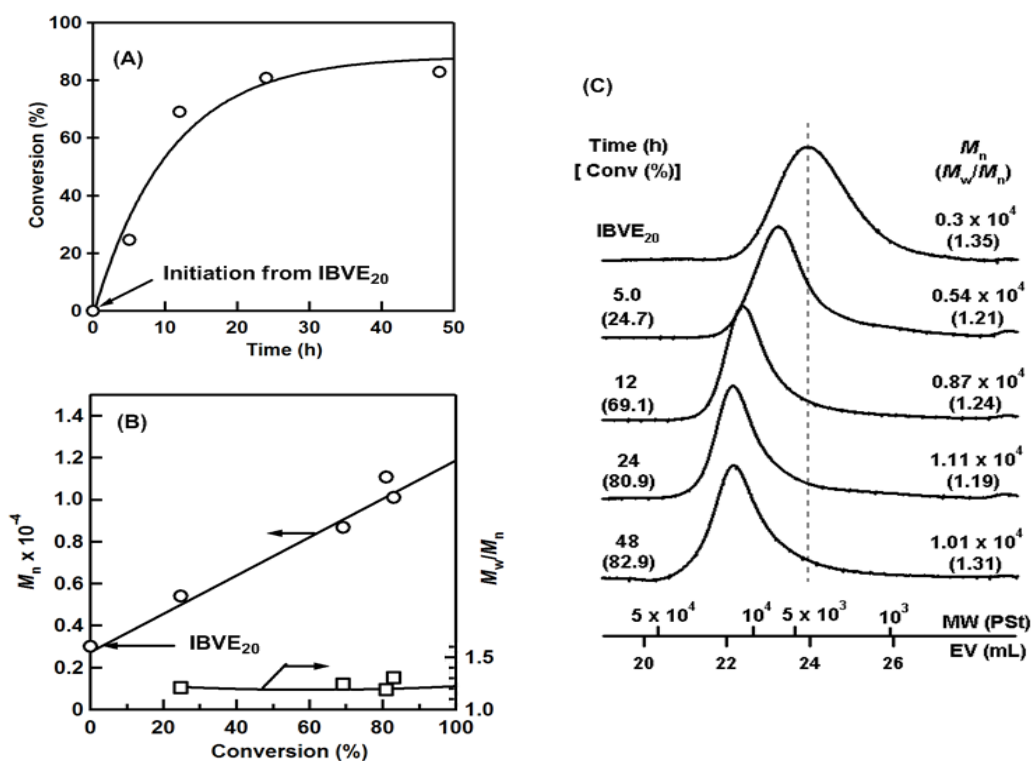


Figure 4. MWDs curves [UV (230 nm) and RI] of PIBVE-*b*-PCL of No. 2 and No. 4 with RI data for corresponding PIBVE macroinitiator obtained by metal-free living cationic polymerization using HCl • Et<sub>2</sub>O (see polymerization condition in Table 1).

On the basis of these results, using the optimum following conditions for block polymerization:  $[\text{IBVE}]_0 = 0.76 \text{ M}$ ,  $[\text{HCl}]_0 = 38 \text{ mM}$  for homopolymerization and  $[\text{CL}]_0/[\text{PIBVE}]_0/[\text{HCl}]_0 = 200/1/5$  ( $[\text{PIBVE}]_0 = 7.2 \text{ mM}$ ) in toluene with 1/9 volume of  $\text{Et}_2\text{O}$  at  $50 \text{ }^\circ\text{C}$ , the living nature of diblock copolymerization was verified.



**Figure 5.** (A) Time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  for the polymerization, and (C) MWD curves (RI data) obtained by ROP of CL using  $\text{HCl} \cdot \text{Et}_2\text{O}$  in toluene at  $50 \text{ }^\circ\text{C}$ :  $[\text{PIBVE}]_0 = 7.2 \text{ mM}$ ,  $[\text{CL}]_0/[\text{PIBVE}]_0/[\text{HCl}]_0 = 200/1/5$ ,  $[\text{Et}_2\text{O}]_0 = 1/9$  volume.

Figure 5 shows the polymerization results at various times. The block copolymerization proceeded smoothly from PIBVE (Figure 5(A)), and the  $M_n$  increased in direct proportion to the conversion of initiated CL and the MWD became lower at higher conversion ( $M_w/M_n = 1.19$  at conv. 80.9 %). Moreover, the MWDs of the block copolymer shifted to the higher molecular weight region

compared to the PIBVE (Figure 5(C)). Obtained compositions of PIBVE-*b*-PCL against the conversions are in a good agreement with the target compositions by  $^1\text{H}$  NMR.

In conclusion, we have demonstrated a versatile and facile route for the synthesis of functionalized initiators by metal free living cationic polymerization. The method affords polymers of controlled molecular mass and narrow molecular mass distribution. Furthermore obtained polymers free from metal contaminants were used as macroinitiators in the block copolymerizations of PIBVE-*b*-PCL.

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12. Firstly, HCl•Et<sub>2</sub>O were prepared from dry Et<sub>2</sub>O (Aldrich) with dry HCl gas after passing through desiccant agents (CaCl<sub>2</sub>). Although we compared the difference between prepared and purchased HCl•Et<sub>2</sub>O, almost the same polymerization results were obtained in this study.
13. Biela, T.; Duda, A.; Penczek, S. *Macromol Symp* 2002, 183, 1-10.

## Chapter 5

Synthesis of Biocompatible and Biodegradable Block Copolymers of Polyvinyl Alcohol-*block* -Poly( $\epsilon$ -Caprolactone) Using Metal-Free Living Cationic

## ABSTRACT

As described in previous chapter the synthesis of block copolymer comprised of PIBVE and PCL via metal free living polymerization has been fully succeeded. Hence the research has been extended to build PTBVE-*b*-PCL. Since the formation of poly(isobutyl vinyl ether)-*b*-poly( $\epsilon$ -caprolactone) (PIBVE-*b*-PCL) and poly(*tert*-butyl vinyl ether)-*b*-poly( $\epsilon$ -caprolactone) (PTBVE-*b*-PCL) was performed from two vinyl ethers and CL, novel amphilic, biocompatible, and biodegradable block copolymers comprised of polyvinyl alcohol and PCL, namely PVA-*b*-PCL, were synthesized by transformation of acid hydrolysis of *tert*-butoxy moiety of PTBVE in PTBVE-*b*-PCL. The synthesized copolymers showed a well defined structure and a narrow molecular weight distribution. The structure of resulting block copolymers were confirmed by  $^1\text{H}$  NMR, size-exclusion chromatography, and differential scanning calorimetry.

## INTRODUCTION

Although non-biodegradable polymers play a crucial role in the plastics industry, their disadvantages in the shape of large-scale commodity packaging accumulating in the environment, influenced researchers to open a new area of the polymer synthesis. The advances achieved in the last 30 years of research on these materials respond not only to environmental needs but beyond this for medical applications, the new materials have been utilized to prepare the controlled release for drugs and proteins.<sup>1,2</sup> According to the unique properties of biodegradability and biocompatibility, since we also deal with the systems of living organisms, amphiphilic block copolymers and the development of their potential applications has received considerable attention especially in the case of achieving the requirements for medical devices or for wound dressings<sup>3,4</sup> in which concerns of immunogenicity are important.<sup>5</sup> Much research has been done on preparing polyester-*b*-polyether, while hydrophobic segments were represented by aliphatic polyesters such as poly(lactide)<sup>6</sup>, poly(lactide-*co*-glycolide)<sup>7</sup>, and hydrophilic sites by poly(ethylene glycol)<sup>8</sup>, which were synthesized via ring-opening polymerization (ROP).

The focus of this study was to form an amphiphilic, biocompatible, and biodegradable diblock polymer via metal-free living cationic polymerization. In particular, the recent development of metal-free ROP by activated monomer cationic polymerization<sup>9</sup> using  $\text{HCl} \cdot \text{Et}_2\text{O}$ <sup>10</sup>, and of anionic ROP with thiourea-tertiary amine catalyst<sup>11</sup>, and with *N*-heterocyclic carbenes<sup>12</sup>, helped us to synthesize the diblock copolymers.





## EXPERIMENTAL

### Materials

Toluene and hexane were washed by usual methods and then distilled over calcium hydride under nitrogen prior to use. *Tert*-butyl vinyl ether (TBVE, TCI) was distilled twice over CaH<sub>2</sub> and stored in brown ampoules under nitrogen. HCl•Et<sub>2</sub>O (1.0M HCl in Et<sub>2</sub>O) was purchased from Aldrich and used without further purification. The concentration of HCl was estimated by titmetric determination using 0.1 M NaOH aqueous solution. Dehydrated Et<sub>2</sub>O (Wako) was used as commercially supplied. NaBH<sub>4</sub>, ethyl alcohol and K<sub>2</sub>CO<sub>3</sub> were used as received. CL (Naclai Tesque) was purified by distillation over calcium hydride under reduced pressure. HBr gas was prepared via mixing sulfuric acid and sodium bromide, and then was passed through calcium chloride directly into the reaction mixture.

### Measurements

The molecular weight distribution (MWD) of the polymers was measured by size exclusion chromatography (SEC) in tetrahydrofuran at 38 °C on three polystyrene gel columns [TSK gel G-MH<sub>HR</sub>-M × 3 (exclusion limit: 4 × 10<sup>6</sup> (polystyrene, PSt)); 7.8 mm i.d. × 300 mm each; flow rate 1.0 mL/min] connected to a Tosoh AS-8020 auto-injector, a CCPM-II dual pump, a UV-8020 UV detector and a RI-8011 refractive detector with a LS-8000 LALLS. The main detector is RI-8011. The number-average molecular weight ( $M_n$ ) and  $M_w/M_n$  were calculated from SEC curves on the basis of a PSt calibration. <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> by means of JEOL JNM-AL 300, so that the polymer structure was confirmed.

Particularly its stereoregularity was measured by  $^1\text{H}$  NMR in deuterated dimethyl sulfoxide ( $\text{DMSO-}d_6$ ). Differential scanning calorimetry (DSC) thermograms were recorded at a rate of  $5\text{ }^\circ\text{C}/\text{min}$  in heating by means of Perkin Elmer differential scanning calorimeter DSC7. Melting and decomposition temperatures, which are respectively  $T_m$  and  $T_d$ , were determined as the peaks observed in the thermograms.

### **Polymerization of Monofunctional Vinyl Ethers**

Polymerizations were carried out at  $0\text{ }^\circ\text{C}$  under a dry nitrogen atmosphere in the glass flasks which were heated at  $250\text{ }^\circ\text{C}$  for 10 min before use. To a solution of monomer in hexane,  $\text{HCl}\cdot\text{Et}_2\text{O}$  was added in order to initiate the reaction. After the polymerization proceeded to desired conversion, the termination was completed by addition of  $\text{K}_2\text{CO}_3$  in water resulting in the aldehyde end groups. Due to reduction of aldehyde groups to the hydroxyethyl one in the end groups,  $\text{NaBH}_4$  in ethanol/hexane (4/1 v/v) was added into the reaction mixture. After 12 h of stirring was sequentially washed with dilute HCl and water to remove the initiator residues and neutralized. The obtained product was next evaporated and vacuum dried overnight.

### **Block Copolymerization from PTBVE**

Poly(vinyl ether)s possessing functional end groups were dried under vacuum at  $50\text{ }^\circ\text{C}$  for 6 h, then placed under a nitrogen atmosphere. After the addition of dry toluene CL was introduced. The polymerization was initiated by  $\text{HCl}\cdot\text{Et}_2\text{O}^{13}$  and

was carried out at 50 °C. In certain time, reaction mixture was diluted by dichloromethane and washed by water to remove the initiator residues. Obtained solution was then poured into methanol to precipitate the polymer. Precipitant was filtered and dried under vacuum, resulting in a powdery polymer.

### **Preparation PVA-*b*-PCL by Acid Hydrolysis with HBr**

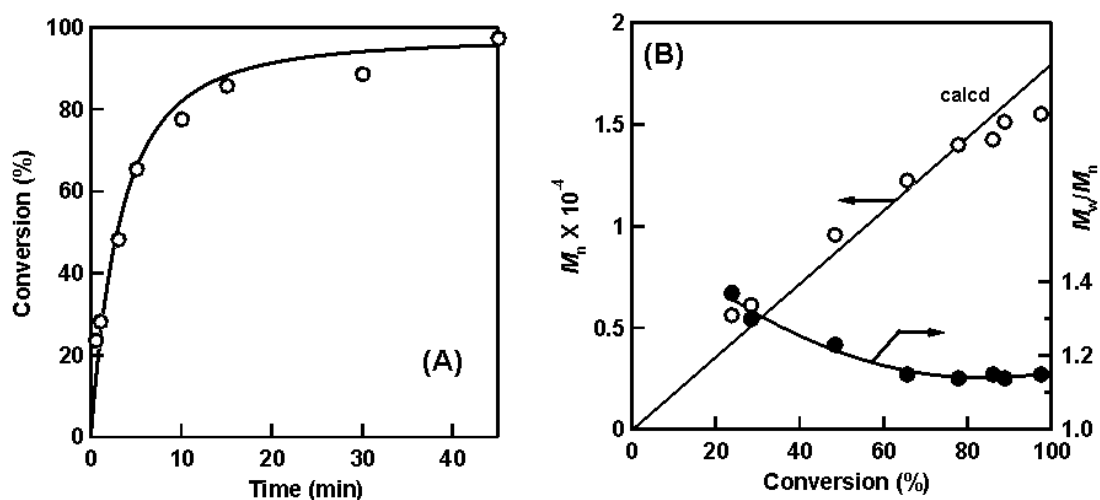
PTBVE-*b*-PCL was converted into PVA-*b*-PCL with HBr gas. After stirring the 1.0 wt% of the PTBVE-*b*-PCL in toluene was treated by dry nitrogen for 10 min in order to remove oxygen dissolved in the solution. Dry HBr was then introduced into reaction mixture during 2 h and next added into ammonical methanol. The precipitate was collected by filtration, washed by methanol, and dried under vacuum.

### **Synthesis of PTBVE Using HCl·Et<sub>2</sub>O**

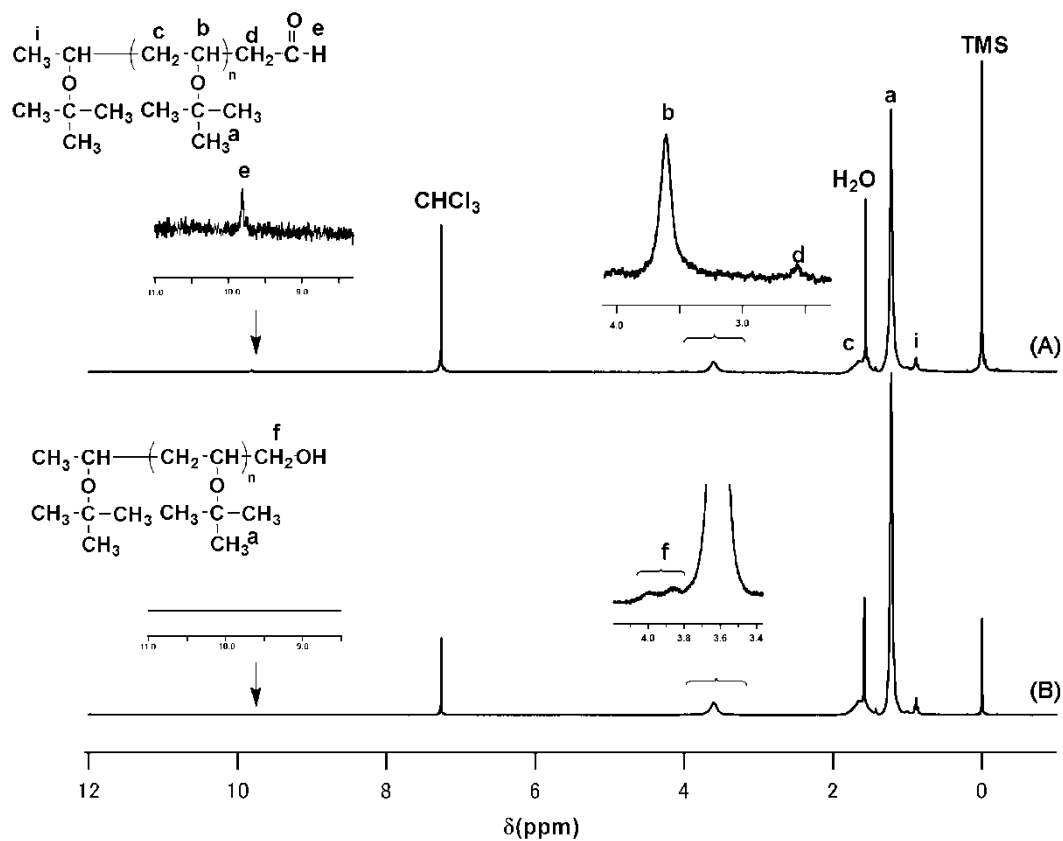
In a similar way for PIBVE, we carried out polymerization of TBVE using HCl·Et<sub>2</sub>O.

Figure 1 shows the typical polymerization results for TBVE. The polymerization proceeded smoothly without an induction period and completed around 45 min. From linear increasing in  $M_n$  against conversion as shown in Figure 1(B), unambiguously living polymers were obtained. These polymer end groups, hydroxyethyl moieties, were prepared by termination using aqueous K<sub>2</sub>CO<sub>3</sub> solution and NaBH<sub>4</sub> with ethanol under the same condition of PIBVE. Figure 2 shows the

NMR spectra of PTBVE obtained with various terminal groups. In the  $^1\text{H}$  NMR spectra, the presence of the aldehydic protons, **e**, around 9.8 ppm in Figure 2(A) and then the signal **f** assignable to  $-\text{CH}_2\text{-OH}$  group was observed around 4.0 ppm in Figure 2(B). In Figure 2(A), the signal observed around 0.9 ppm is assigned to the methyl proton **i** from HCl initiator. The amount of **i** is just equal to that of one third of **e**, indicating PTBVE with a quantitative end-functionality as well as PIBVE.



**Figure 1.** (A) Time-conversion curves, (B)  $M_n$  and  $M_w/M_n$  for the polymerization of TBVE by  $\text{HCl} \cdot \text{Et}_2\text{O}$  in hexane with 1/9 volume of  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$ :  $[\text{TBVE}]_0 = 0.76 \text{ M}$ ,  $[\text{HCl}]_0 = 4.0 \text{ mM}$ ,  $[\text{Et}_2\text{O}]_0 = 0.96 \text{ M}$ .



**Figure 2.**  $^1\text{H}$  NMR spectra (300 MHz,  $\text{CDCl}_3$ , r.t) of (A) PTBVE (DP ~ 50) terminated by aqueous  $\text{K}_2\text{CO}_3$  solution, and (B) PTBVE after reduction of (A) possessing a hydroxyethyl group

### Diblock Copolymers Consist of PTBVE and PCL.

Table 2 and Figure 3 summarize the diblock copolymerization of TBVE with CL. As tabulated results show the polymerization of series target compositions of block copolymers was characterized by conversion,  $M_n$ , and  $M_w/M_n$  obtained. In all the cases temperature was set at 50 °C. In case of TBVE with DP 20, CL to initiator was fixed at 40 at high conversion (71.8 %) along with expected molecular weights were obtained. Applying the same target composition but with increased monomer

to initiator ratio to 200 and polymerization time, caused narrow MWD ( $M_w/M_n = 1.17$  for No.2). No. 3 and 4 show that the ratio  $[HCl]_0/[PTBVE]_0$  essentially affected the polymer structure. Abovementioned results were supplemented by SEC. Even though the MWDs shifted to the higher molecular weight region in all the cases, bimodal nature is observed only No. 1 which may be induced by graft polymerization at partially hydrolyzed PTBVE due to high concentration of HCl. The result is different between PIBVE-PCL and PTBVE-PCL, which may be due to stabilization of pendants in vinyl ethers for HCl or HBr.

Table 2. ROP Results for PTBVE-*b*-PCL Using PTBVE Macroinitiator<sup>a</sup>

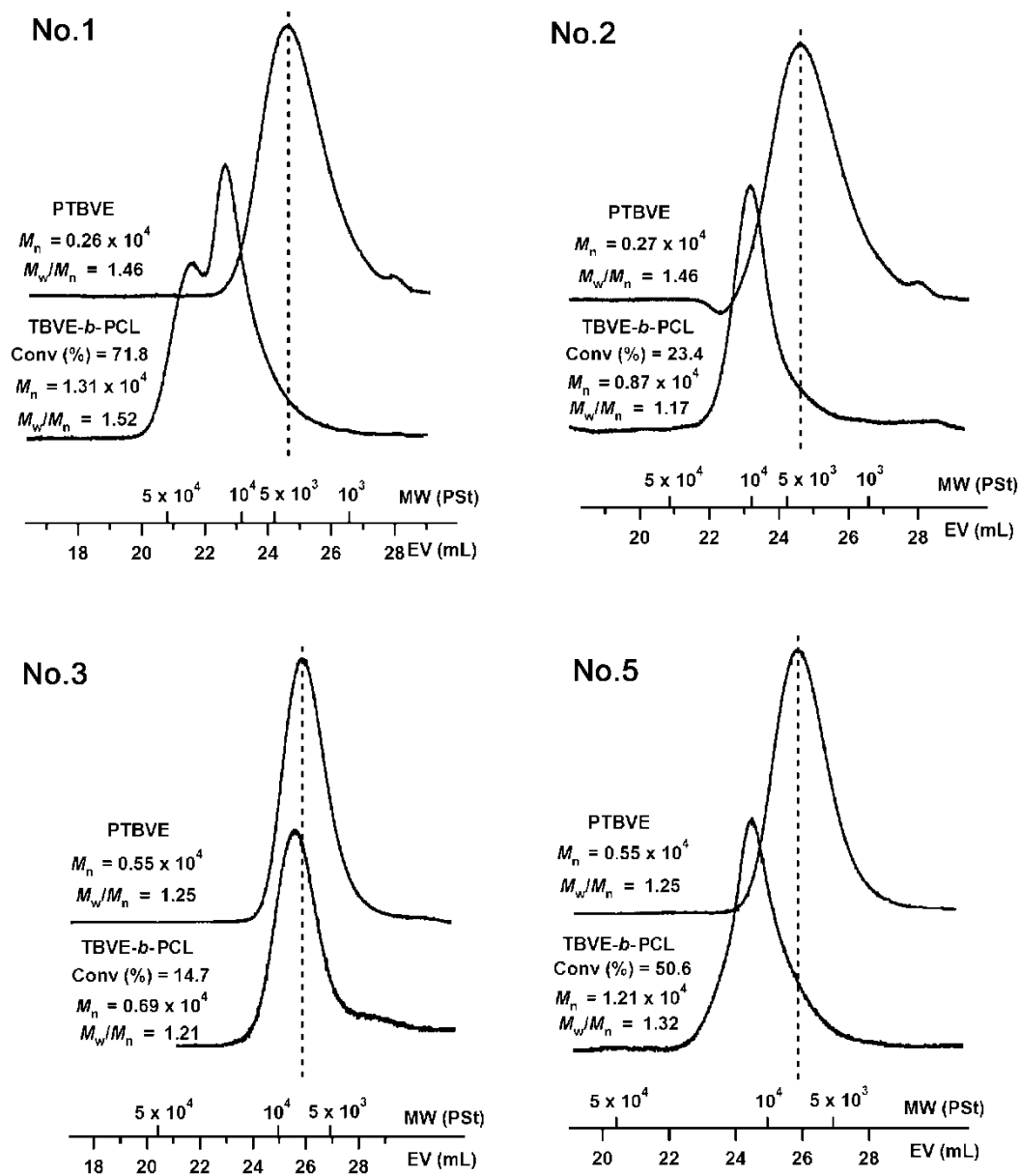
No.	Target composition	$[CL]_0/[HCl]_0$	$[HCl]_0/[PTBVE]_0$	Temp. (°C)	Time (h)	Conv. <sup>b</sup> (%)	CL length in polymer <sup>c</sup>	$M_n$ (SEC) <sup>d</sup>		$M_w/M_n$ (SEC) <sup>d</sup>	
								Homo	Diblock	Homo	Diblock
1	TBVE <sub>20</sub> - <i>b</i> -CL <sub>200</sub>	40	5	50	24	71.8	141	2600	13100	1.46	1.52
2	TBVE <sub>20</sub> - <i>b</i> -CL <sub>200</sub>	200	1	50	77	23.4	49	2700	8700	1.46	1.17
3	TBVE <sub>50</sub> - <i>b</i> -CL <sub>50</sub>	50	1	50	65	14.7	8	5500	6800	1.25	1.21
4	TBVE <sub>50</sub> - <i>b</i> -CL <sub>100</sub>	50	2	50	63	30.6	33	5500	8100	1.25	1.31
5	TBVE <sub>50</sub> - <i>b</i> -CL <sub>200</sub>	100	2	50	65	51.0	92	5500	12100	1.25	1.32

<sup>a</sup> Polymerization condition:  $[PTBVE]_0 = 7.2$  mM in toluene

<sup>b</sup> Conversion for CL polymerization from corresponding macroinitiator of PTBVE

<sup>c</sup> Calculated from the molar ratio of CL and PTBVE in block copolymer by <sup>1</sup>H NMR.

<sup>d</sup> Polystyrene calibration.

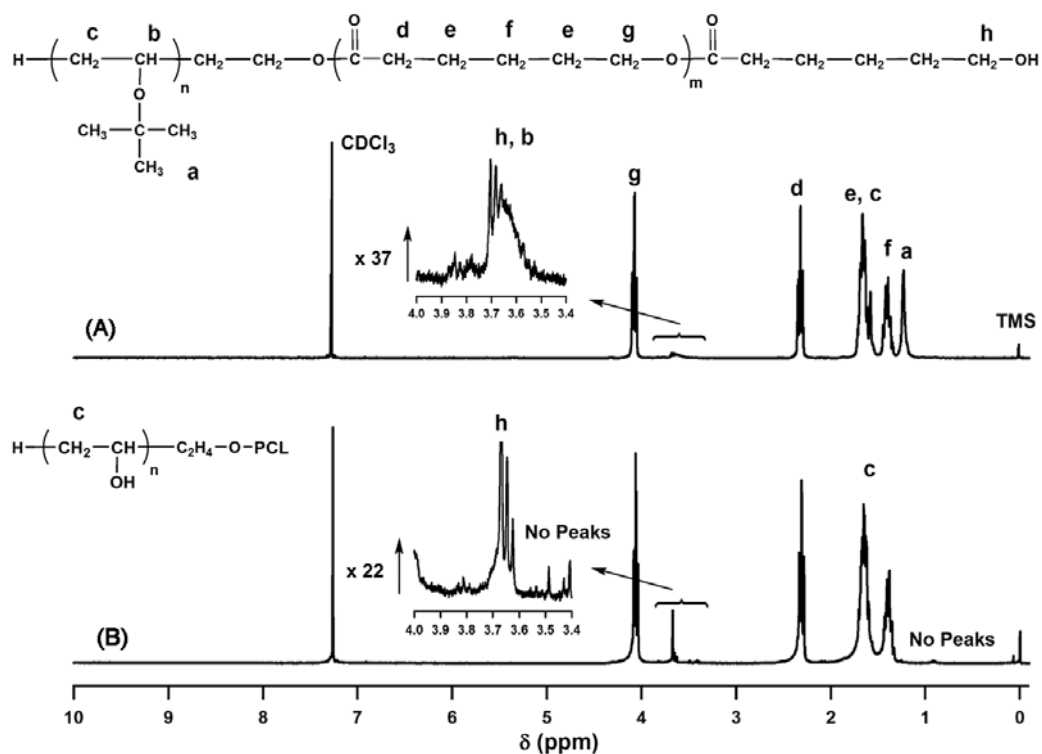


**Figure 3.** MWDs curves (RI data) of PTBVE-*b*-PCL of No. 1, No. 2, No. 3, and No. 5 with corresponding PTBVE macroinitiator obtained by metal-free living cationic polymerization using  $\text{HCl} \cdot \text{Et}_2\text{O}$  (see polymerization condition in Table 2).

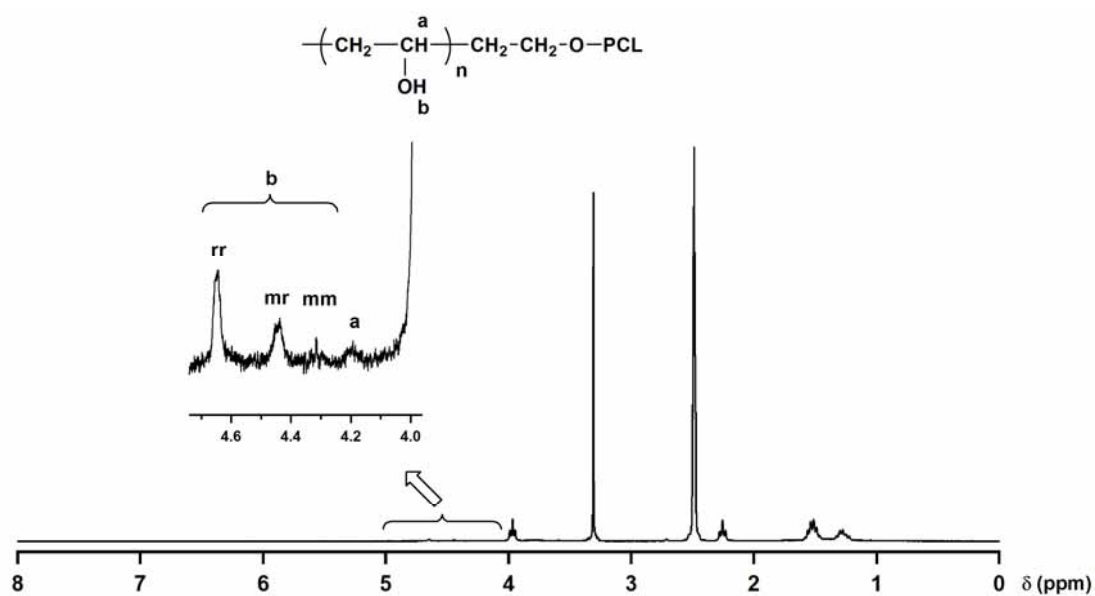
## Transformation into PVA

In attempt to attain the conversion from PTBVE into PVA, dry HBr gas as a hydrolysis agent was applied.  $[\text{TBVE}]_0/[\text{HBr}]_0$  corresponding to 1/4 molar ratio has been examined, which applied time was 25 min. Based on the peak intensity of the two blocks in their  $^1\text{H}$  NMR spectrum showed that the transformation into the PVA equaled 41.0 % only. Applying substantial excess of HBr ( $[\text{TBVE}]_0/[\text{HBr}]_0 = 1/70$ ), PVA units appeared in still small quantity (50.6 %), that is why in order to prevent the blowing excess of HBr, 1/20 molar ratio has been investigated with increasing the time (2 h) of reaction. Complying with these conditions peaks assignable to PTBVE terminals at 1.2 ppm and methylene protons on the *tert*-butoxy moiety in PTBVE at 3.6 ppm disappeared as shown in Figure 4. Comparison of the amounts of **c**, **e**, and **f** in Figure 9 (A) and (B) also reveals that no cleavage of the main-chain ester bond occurred under this condition. The PVA formation existence was also verified by  $^1\text{H}$  NMR in  $\text{DMSO}-d_6$  which depicted that the hydroxyl proton absorption in TBVE splits into three separate peaks belonged to PVA (Figure 5) with predominance of the *mm/mr/rr* sequence fraction-58.3/29.6/12.1. This is due to highly isotactic PVA, which values are close to the steric structure of PTBVE (DP ~ 190), meso = 64 %.<sup>18)</sup> The obtained PVA-*b*-PCL (from No. 2 in Table 2) has  $T_m$  55 °C and  $T_d$  312 °C by means of DSC(Figure 6), which are derived from PCL and PVA, respectively. The obtained  $T_m$  for PCL in block copolymer showed almost the same temperature as PCL homopolymer. However, in comparison with  $T_d$  of PVA homopolymer<sup>19</sup>, it is likely that the thermal stability of PVA was improved by blocking the PCL segments.

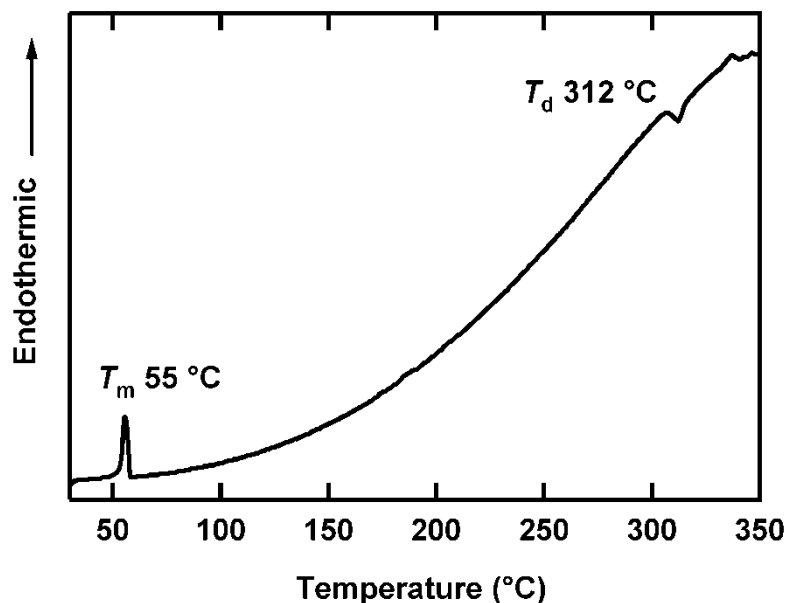




**Figure 4.**  $^1\text{H}$  NMR spectra (300 MHz,  $\text{CDCl}_3$ , r.t) of (A) PTBVE-*b*-PCL (No. 2 in Table 2) and (B) PVA-*b*-PCL obtained after acid hydrolysis of (A).



**Figure 5.**  $^1\text{H}$  NMR spectra (300 MHz,  $\text{DMSO-}d_6$ , 30  $^\circ\text{C}$ ) of PVA-*b*-PCL (the same sample shown in Figure 4(B)), *mm*, *mr*, and *rr* are stereostructures for PVA.



**Figure 6.** DSC thermogram for PVA-*b*-PCL (obtained from No. 2 in Table 2).

In conclusion, we have formed a polyTBVE possessing hydroxyl groups which serves as a macroinitiator in the block copolymerization of PTBVE-*b*-PCL. The living nature of the block was indicated by relatively narrow MWDs and linear increase in molecular weight with conversion. This procedure has advantages over the current preparative methods according to lack of metal residues which are difficult to remove. Abovementioned functional-end polymer was linked with ester formation, and as a result biocompatible, biodegradable, amphiphilic block copolymer PVA-*b*-PCL was prepared.

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