Sequence Regulation by Molecular Programming and Template-Assisted Polymerization

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GENERAL INTRODUCTION

Background

1. Well-Defined Sequence in Biopolymers

In polymer science and molecular biology, "*sequence*" implies the order of constitutional repeat units (monomer units) along the main-chain backbone of a polymer. As symbolized in replication of deoxyribonucleic acid (DNA), *sequence is the basis of life*, by which all the information for life is replicated, inherited, and expressed from generation to generation. In living cells, for example, the sequence in a parent DNA is exactly transcribed into a ribonucleic acid (RNA), and a particular protein is specifically expressed according to the sequence information transcribed in the RNA template (central dogma).[1] These proteins are perfectly "sequence-regulated" polypeptides, although as many as 20 amino acids with the same reactive sites (amine and carboxylic acid) are employed as comonomers for the stepwise amidation. The expressed sequence (or primary structure), in turn, dictates unique tertiary (three-dimensional) structures of proteins, such as chain-folding, to express advanced functions (e.g., organocatalysis, selective transport, and immune process) (Figure 1). Most importantly, proteins and related biopolymers thus function as autonomous *single* molecules, in sharp contrast to synthetic polymers where their physical properties and functions mostly rely on their aggregates deriving from amplified intermolecular interactions among repeat units. Thus, their functions are incomparably more efficient and advanced than those of artificial polymers, and *the monomer-sequence regulation plays a central role for the functions*.

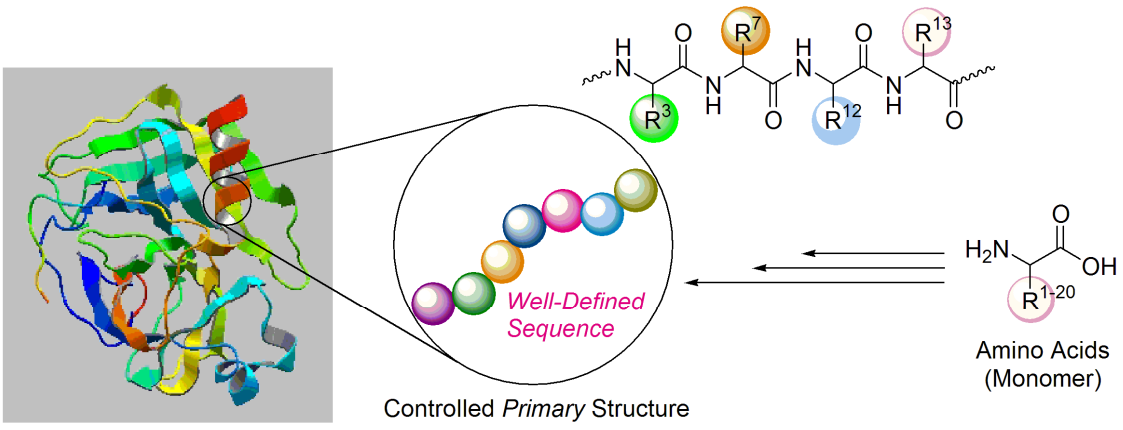


Figure 1. Sequence-regulated polymerization in nature.[2]

2. Structural Control in Synthetic Polymers

Synthetic polymers are indispensable for our modern life as chemical materials (e.g., plastics) and vastly produced with various polymerization techniques. Among them, addition polymerization of vinyl monomers is important to obtain carbon main-chain polymers. These polymers are usually a mixture of ill-defined macromolecular chains with various lengths (broad molecular weight distributions) and uncontrolled sequences of the pendent substituents or functionalities. This irregularity is derived from the poor regulation in polymerization reactions: initiation and propagation reactions randomly occur; some side reactions (termination or chain-transfer reaction) disturb the propagation; and cross-propagation with comonomers is basically stochastic and of low selectivity. However, since Szwarc discovered *living* anionic polymerization in 1956,[3] molecular weight control is now possible in most of addition polymerizations including cationic,[4] radical,[5-9] and coordination.[10]

Living polymerization is defined as a chain-growth polymerization that consists of initiation and propagation alone, free from termination or transfer reactions. The initiation starts from a specific molecule carrying an initiating site (initiator) from which the same number of polymer chains propagates without side-reactions. A suitable terminator or quencher can purposefully terminate the propagation. By its nature, the molecular weight can be controlled by the feed ratio of monomer to initiator, and the molecular weight distribution is narrow or, ideally, of a Poison distribution, when initiation is much faster than propagation. Additionally, it enables one to easily synthesize various structures such as end-functionalized, block, graft, and star polymers (Figure 2).[11]

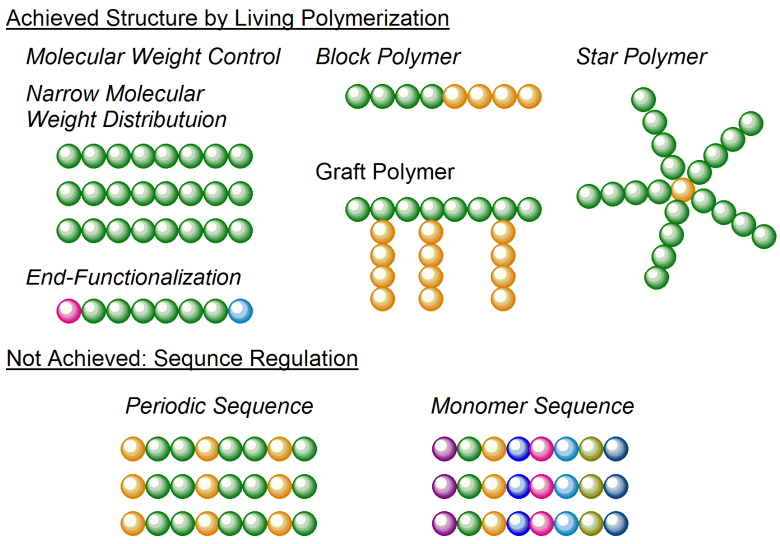


Figure 2. Achieved polymer structures obtained via living polymerizations.

The progress in living polymerization has opened a way to the precision syntheses of various functional polymers with sophisticated architecture for advanced functional materials. Even with these controlled polymerizations, however, the regularity of polymer chains is much inferior to biopolymers, especially in terms of sequence. Given these progresses as well as deficiencies, an increasing number of polymer scientists nowadays have begun seeking for the road to approach the nature's elegance and the biopolymers' accuracy by sequence-regulating polymerization. In the author's view, as discussed below, the time is now ripe for our polymer chemists to embark on the sequence control for synthetic polymers.[12]

3. Sequence Regulation in Synthetic Polymers

As discussed above, the trend in polymer chemistry is moving to discover "*sequence-regulated polymerization*".[12] The pioneer of artificial sequence-regulated polymerization is Merrifield's solid-phase synthesis of peptides.[13] This is still a useful way to synthesize sequence-defined oligopeptides but is restricted to step-growth polymerization, and the protection-deprotection procedure is cumbersome and sometimes not tolerant of functional groups.

In addition polymerization, thus far, sequence regulation has been achieved by three methods, though considerably to limited extents in terms of the number of repeat units to be controlled for specific sequences: (i) spontaneous alternating copolymerization, (ii) stepwise chain extension, and (iii) sequential monomer addition (Figure 3).

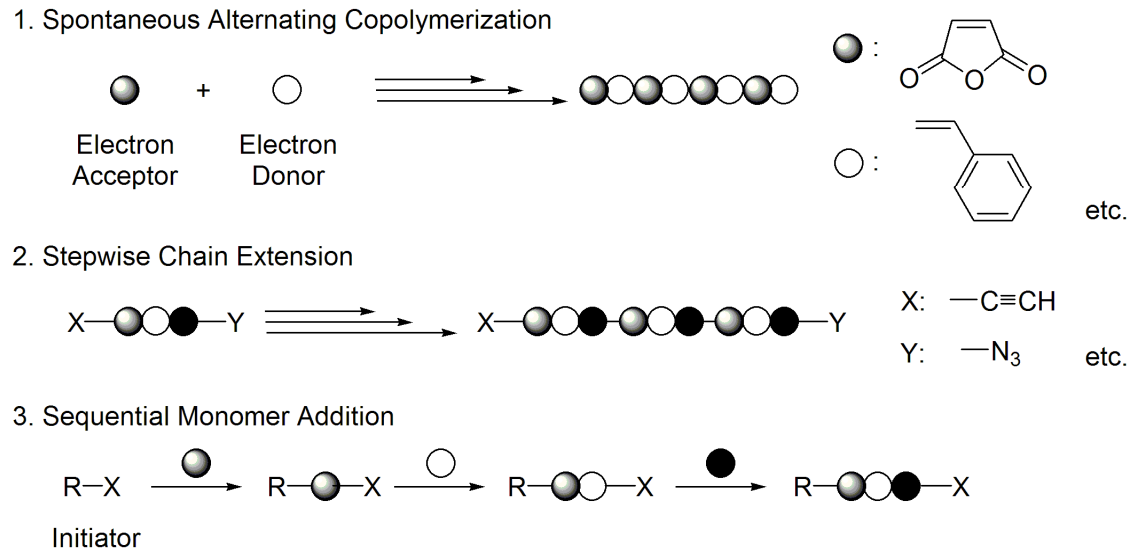


Figure 3. Sequence regulation in synthetic polymers.

Spontaneous Alternating Copolymerization. The simplest sequence regulation would be found in alternating copolymerization where sequence alternation (enhanced cross-propagation) is derived from the inherent electronic features of a specific monomer combination (Figure 3, route 1). A typical example is the radical copolymerization of a pair of an electron-acceptor and an electron-donor monomers, such as maleic anhydride and styrene, and addition of a Lewis acid promotes the alternating propagation.[14] Most of the previously reported examples in fact achieved alternating sequences but without the control of chain length (molecular weight). Quite recently, however, alternating and living radical copolymerization has been examined to obtain alternating copolymers with controlled molecular weights.[15] The feature of favoring cross-propagation has also allowed local functionalization at desired positions on a polymer chain.[16, 17]

In addition to these AB-alternating sequences, alternation of three repeat units has been reported. For example, in the course of their extensive study of spontaneous non-catalyst AB-alternating copolymerization of heterocyclic monomers, Saegusa and co-workers obtained alternating ABC-sequence copolymers by terpolymerization of ethylene phenylphosphonite, acrylonitrile, and carbon dioxide via zwitterion.[18] Recently, Kamigaito et al. achieved an AAB-alternating copolymerization of limonene and maleimide by a controlled radical polymerization (reversible addition-fragmentation chain transfer polymerization: RAFT)[6] in the presence of fluoroalcohol, which is to direct the specific sequence along with the inherently enhanced cross-propagation of the two monomers.[19]

Stepwise Chain Extension. A chain extension reaction of bifunctionally reactive monomers would lead to alternating or periodic sequences (Figure 3, route 2), where the extension process should be highly chemoselective. Recently, the so-called "click chemistry"[20, 21] has attracted attention for such chain extension methods. For example, Lutz et al. synthesized AB-oligomers from an azide-amine monomer and an alkyne-carboxylic acid monomer via repetition of two chemoselective reactions: a copper-catalyzed azide-alkyne 1,3-cycloaddition (CuAAC) and an amidification of carboxylic acids and primary amines.[22] On the other hand, Guan and co-workers designed oligopeptides carrying azide and alkyne terminals that are extended by CuAAC into sequence-controlled polypeptides with functional groups placed in a repetitive regular sequence.[23] Similarly, heterotelechelic oligostyrenes carrying α-azide and ω-alkyne terminals were synthesized where maleimide units were included at designed positions via stepwise addition of a maleimide by cross-propagation.

Subsequent click chain extension by CuAAC gave polystyrenes in which the position of the maleimide's unit (and their pendent functionality) is periodic.[17]

In another case, Kamigaito et al. performed metal-catalyzed step-growth polyaddition of specially designed monomers with a programmed sequence of subunits, such as ABCC, from common vinyl monomer building blocks.[24] Thus, the monomers are designed to carry a carbon–chlorine bond active for metal-catalyzed living radical polymerization as well as non-conjugated olefin terminals that are inactive for radical propagation but capable of a single radical addition. Once the carbon–chlorine bond is activated by a metal catalyst to give a radical species, it attacks the olefin to give a non-reactive vinyl chloride unit, and the repetition of this reaction leads to polymers of a programmed alternating sequence.

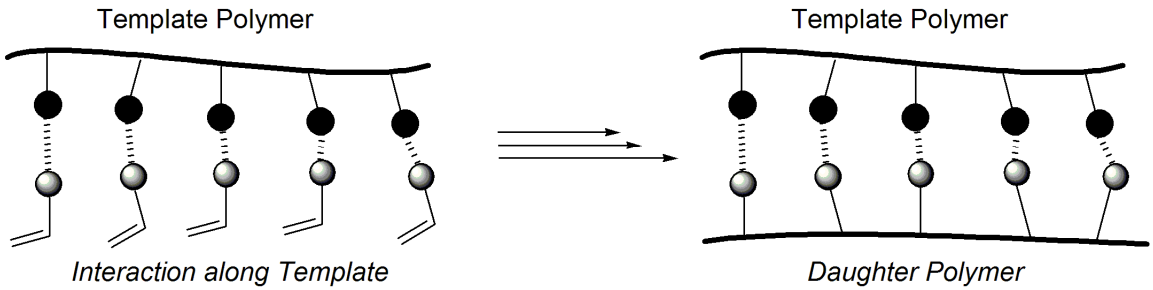
Sequential Monomer Addition. If the selective monoaddition of multiple monomers is possible in chain-growth living polymerization, repetition of such monoadditions would also allow sequence regulation (Figure 3, route 3). In the beginning of 1990s, Higashimura and co-workers applied this strategy for their living cationic polymerization of vinyl ethers.[25] The research in fact gave sequence-defined oligomers but in low yield, because multiple homoaddition obviously accompanied single additions, and fractionation was accordingly required to remove undesired products.

Though the above-discussed three approaches are very attractive to sequence regulation, they rely on specific monomers or special techniques. Therefore, more universal and convenient ways to regulate sequence are desired, and template systems are attractive in artificial systems.

4. Template Polymerization

Inspired by biological systems, in which "template" is vital to produce perfectly sequence-regulated biomolecules, some researchers have examined template-assisted organic synthesis.[26] In polymer chemistry, template polymerization (sometimes called "replica polymerization" or "matrix polymerization") has been also studied[27] since the first example was reported in 1950s.[28] In template polymerization, as with like RNA transcription and related biopolymer syntheses, component monomers interact with a template polymer, and these aligned monomers are polymerized along the template (Scheme 1). The linkage between monomers and a template is, for example, hydrogen bonding,[29] ionic interaction,[30]

covalent bond,[31] metal-coordination,[32] or stereocomplex.[33] Some positive "template effects" were reported: acceleration of polymerization; improvement of yield; and transcription of molecular weight or stereostructures from a template to a daughter polymer. Recently, some researches have been attempted to incorporate the idea of "template polymerization" into precision polymerization for advanced control.[34] However, to the author's knowledge, there has been no report on sequence regulation by template polymerization, most likely because of the unclearness of the initiating point and difficulties in synthesis of the template with a well-defined sequence.



Scheme 1. Template polymerization.

Objectives

From these backgrounds, the author has selected "sequence-regulated polymerization" through design of template molecules as the central subject of his doctoral research. Here, he carefully devised an "initiator-embedding template" or "template initiator" in which a polymerization initiating site is placed in a close vicinity of a template moiety within the same molecular framework, so that his approach is clearly distinguished from conventional template systems that lack an intramolecularly incorporated precision initiating site (Figure 4).

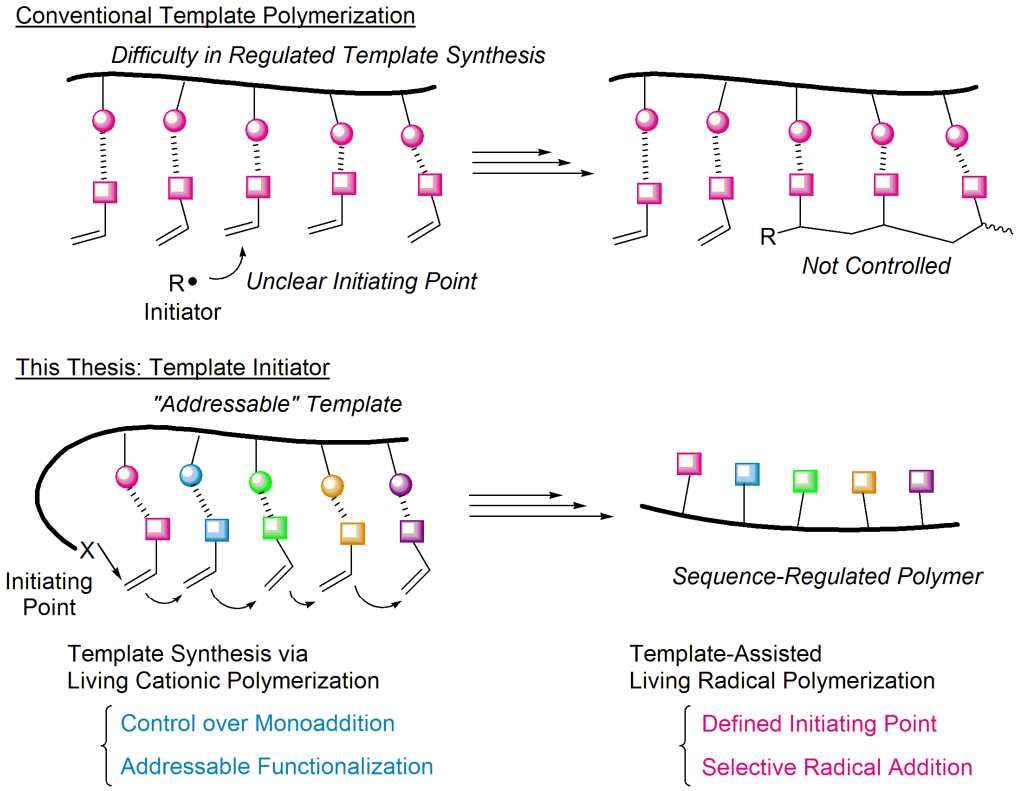


Figure 4. The strategy for template initiator-assisted sequence-regulated polymerization.

To approach "sequence-regulated polymerization" with such a "template initiator", the author considered the following points to be crucial in systems design:

Point 1. The initiating site is designed at the edge of the template to control propagation along the template.

Point 2. The template moiety should carry recognition units for monomers in a well-defined sequence.

Point 3. Polymerization should proceed quantitatively from the initiating site without

side reactions, and the active species should be tolerant of functional groups both in the template for monomer recognition and in monomers to be polymerized.

From these viewpoints, the author designed a heterobifunctional initiator **1** as the "base" initiator (Figure 5). Here, one carbon–chlorine bond (C–Cl) neighboring the ether part is an initiator for Lewis acid-catalyzed living cationic polymerization[4] to grow a template molecule (polymer), whereas another C–Cl neighboring the ester part is that for metal-catalyzed living radical polymerization[5] to target "sequence regulation". They are connected *ortho* to each other on a rigid benzene framework, so as to bring the initiating site along the template (**Point 1**). Living cationic polymerization is promising to synthesize a template molecule with well-defined sequence by tuning the condition according to monomer reactivity as shown by literature,[25] although protection/deprotection or post-functionalization is required to introduce functional groups (**Point 2**). For the backbone formation from the template-aligned monomers, metal-catalyzed living radical polymerization is suitable for "sequence regulation" because of the high tolerance of functional groups (**Point 3**).

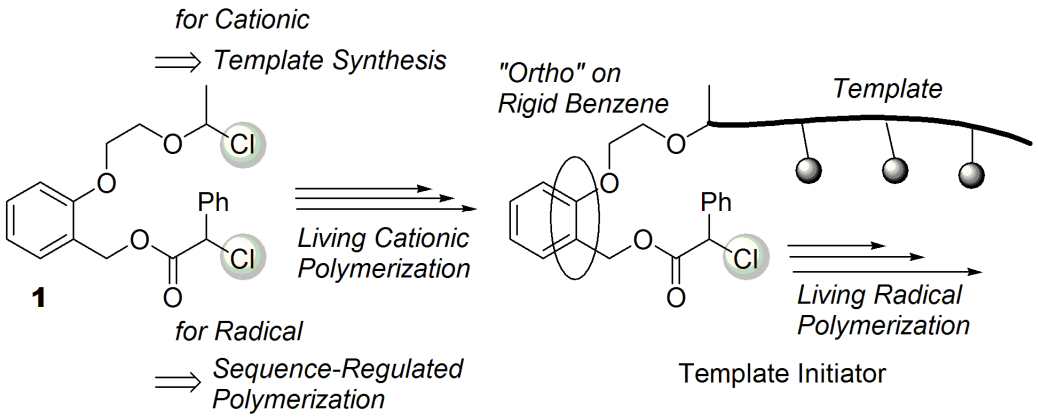


Figure 5. Design of template initiator from heterobifunctional initiator (**1**).

In this thesis, the author studied two objects to put the strategy with **1** into practice:

(1) Programmed/Addressable Living Cationic Polymerization for Template Synthesis

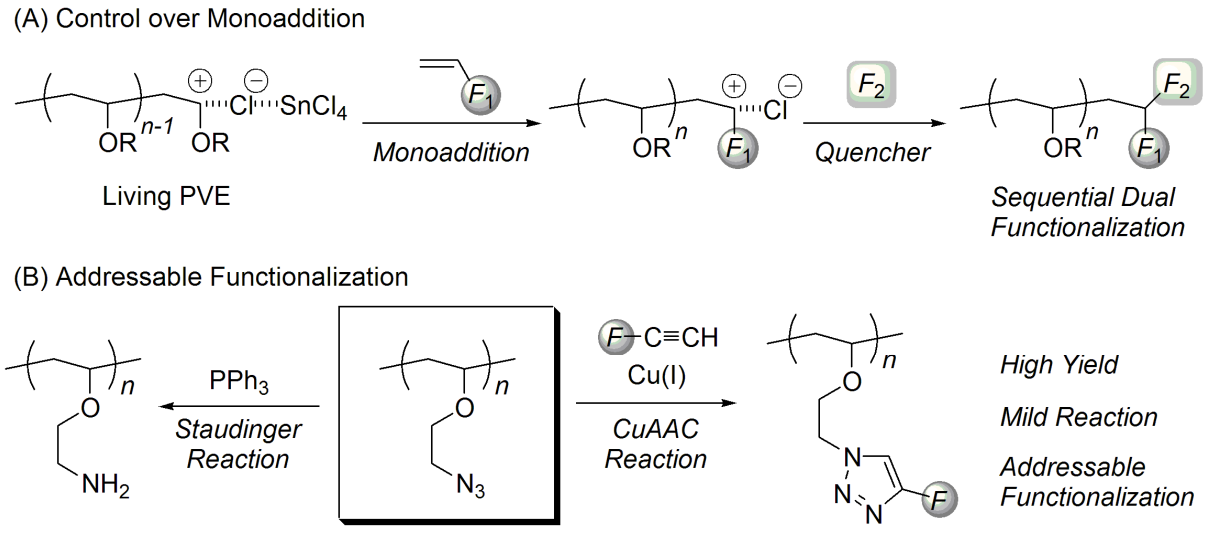
(2) Template Initiator-Assisted Radical Reactions

(1) Programmed/Addressable Living Cationic Polymerization for Template Synthesis. The first objective was directed to a more advanced control over living cationic polymerization for precision synthesis of template. Here, the author embarked on the two subjects with living cationic polymerization system: control over monoaddition of a monomer carrying protected functional side chain (Scheme 2A); and living cationic polymerization of an addressable monomer to introduce functional groups (Scheme 2B).

The control over the monoaddition of a functional monomer is fundamental, since it allows synthesis of template whose position of the functional groups is well-defined. In this thesis, the author studied a selective monoaddition for "living" polymer chain and the following end-capping reaction for sequential dual functionalization at well-defined positions, penultimate and terminal, respectively.

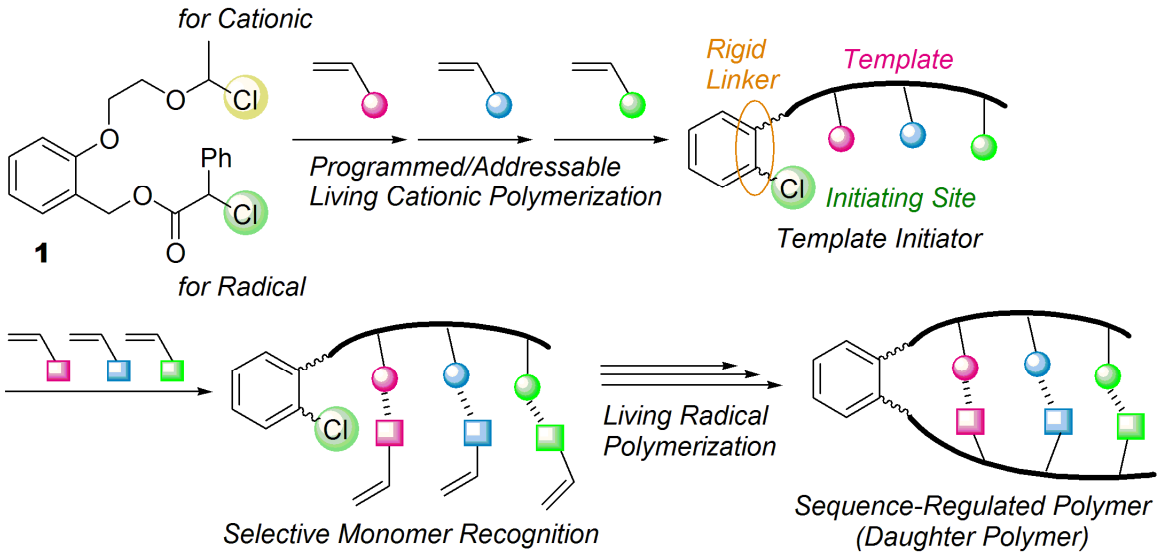
In this design, the monomer-recognition sites (e.g., hydroxy, amine, and carboxylic acid) need to be dangled on the template molecule. However, such functional groups need to be protected in the template construction but to be deprotected after the polymerization, since cationic growing species is less tolerant of such functional groups.[35-37] In some cases, protection-deprotection processes unfortunately damage other chemical bonds in a template and thereby limits the availability of recognition sites.

Therefore, more convenient ways to introduce functional groups were desired for living cationic polymerization. Thus, the author focused on an azide-containing vinyl ether as an "addressable" monomer. Since the azide group can be converted into versatile functional groups by CuAAC reaction[20] or Staudinger reaction[38] under mild conditions, the polymerization control would be useful for the template synthesis.



Scheme 2. Programmed/addressable living cationic polymerization.

(2) Template Initiator-Assisted Radical Reactions. In the second objective, the author investigated the possibility of sequence-regulated polymerization with template initiators (Scheme 3). For feasibility examination of this approach, template initiators with a single recognition site have been designed and synthesized by monoadition or end-capping. These template initiators were applied for metal-catalyzed radical addition (Kharasch addition)[39] to examine the template effect: selectivity of a recognizable monomer was evaluated over the corresponding non-recognizable monomer (e.g., methacrylic acid vs. methyl methacrylate). Also, multi-functionalized template was synthesized via the addressable living cationic polymerization to study template-assisted monomer-selective radical copolymerization. It is quite difficult to provide some selectivity for a monomer (substrate) in radical-mediated addition and polymerization, and if achieved these template effects would be landmark results to approach sequence-regulated radical polymerization.

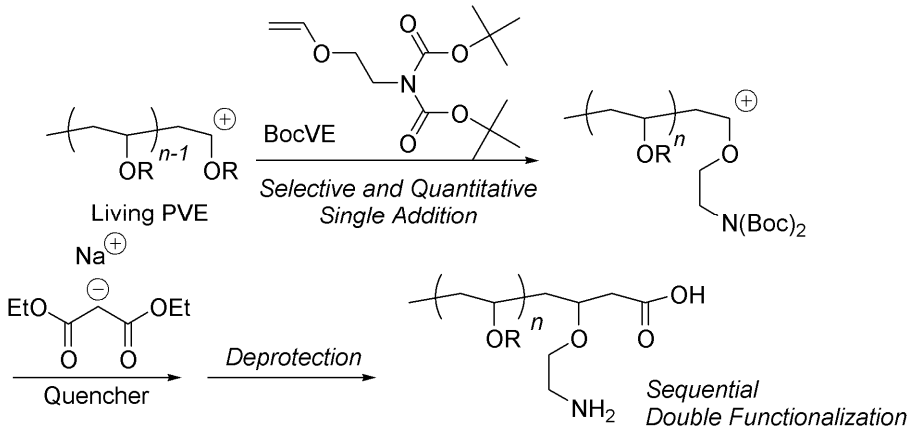


Scheme 3. Template initiator-assisted living radical polymerization toward sequence regulation.

Outline of This Study

The present thesis consists of two parts: **Part I** (Chapter 1-2) deals with the development of living cationic polymerization toward controlled template synthesis in which selective single addition and direct living polymerization of an addressable monomer for diverse functional units were discussed. **Part II** (Chapter 3-5) focused on template initiator-assisted substrate-selective radical reactions.

Chapter 1 presents selective single monomer addition in living cationic polymerization. Among the various monomers, the author found that di-*tert*-butyl {*N*-[2-(vinyloxy)ethyl]imido}dicarboxylate (BocVE) induced single addition for living cationic polymerization of *n*-butyl vinyl ether (NBVE) with $SnCl_4$. This would be due to the bulky side chain interacting with the terminal carbocation to block the further propagation. The Boc side chain, introduced at the terminal with a single unit, was quantitatively deprotected into amine, and also the combination with a conventional capping agent (e.g., sodium diethyl malonate) led to sequential double functionalization with, for example, amine and carboxylic acid (Scheme 4).



Scheme 4. Selective single addition of BocVE and sequential double functionalization in living cationic polymerization.

Chapter 2 describes direct living cationic polymerization of azide-containing vinyl ether, 2-azidoethyl vinyl ether (AzVE) with $SnCl_4$ as an activator. The molecular weights of the produced polymers were directly increased as the conversion, and the molecular weight distributions were narrow ($M_w/M_n \approx 1.2$). Importantly, quantitative functionalization of the

side groups via Staudinger reaction and CuAAC reaction under mild condition was achieved (Figure 6).

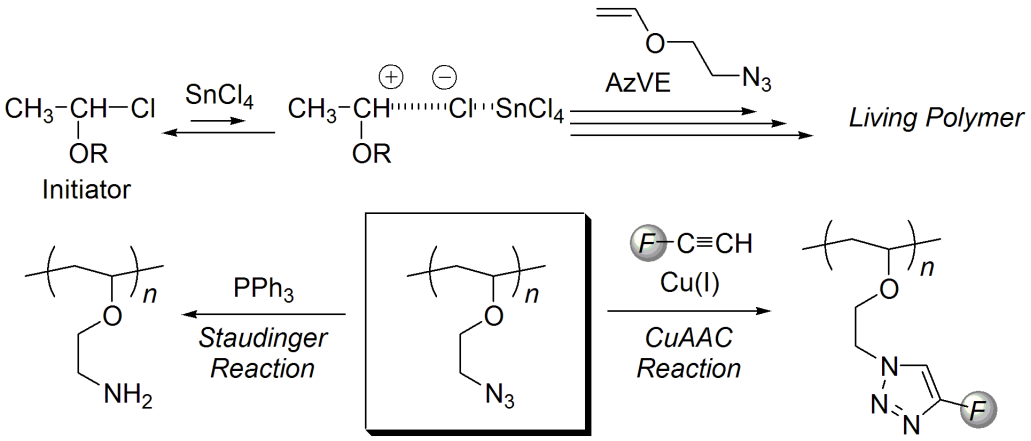
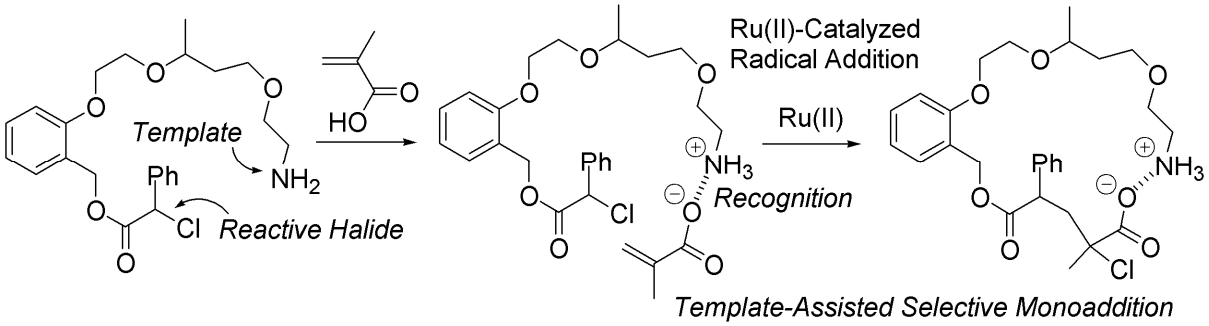


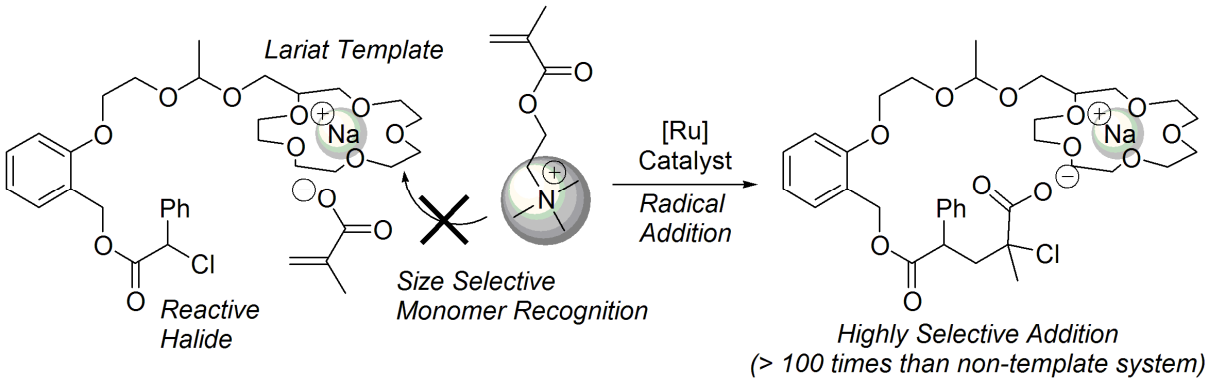
Figure 6. Direct living cationic polymerization of AzVE and addressable functionalization of azide groups by Staudinger reaction and CuAAC reaction.

Chapter 3 deals with highly selective and quantitative radical addition of methacrylic acid (MAA) by using a template initiator containing a built-in amine group as the recognition site (Scheme 5). The template initiator was synthesized via selective single addition of BocVE to the cationic site of a novel heterobifunctional initiator, **1**. In the radical addition of MAA, the specific ionic binding of MAA by the amine template led to preferential formation of 1:1 adducts. Additionally, in competitive radical addition of MAA and non-recognized monomer (methyl methacrylate; MMA), highly selective addition of MAA over MMA was observed. Quantitatively, the substrate selectivity was enhanced more than ten times relative to the result for the non-template initiator.



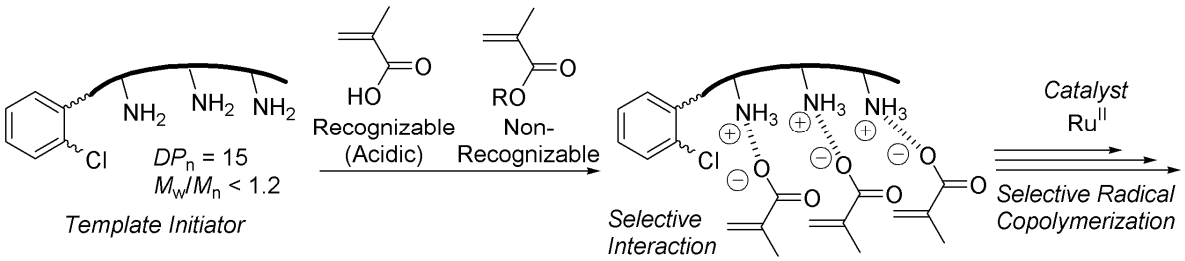
Scheme 5. Template initiator-assisted selective monoaddition of MAA.

Chapter 4 focuses on template initiator-assisted selective radical addition of sodium methacylate (NaMA) over a methacrylate carrying ammonium cation. Crucial is size-selective recognition by a lariat crown ether embedded close to the initiating site (Scheme 6). The reaction could be conducted in low temperature utilizing active ruthenium catalyst, and the selectivity reached over 100 times larger than that with the non-template system. Here, the template initiator was prepared via the electrophilic substitution on the cationic initiating site, which is the model for quenching reaction in living cationic polymerization, showing the versatility in template construction.



Scheme 6. Template initiator-assisted selective addition of NaMA by size-selective recognition by lariat capture of the crown ether template.

Chapter 5 discusses the structural adequacy of the template platform consisting of two initiating sites placed *ortho* to each other in benzene. With the platform, the author prepared the template initiators carrying single- or multi-amine recognition units and utilized them in competitive radical addition and copolymerization (Scheme 7). Comparative experiments with similar but non-template initiators indicated that the *ortho* position design and the guaranteed initiating point at the edge of the template were crucial to induce desired template effects, i.e., recognized monomers selectively reacted or polymerized.



Scheme 7. Template initiator-assisted radical copolymerization

In conclusion, this thesis presents new template-assisted reaction systems with the template initiator toward unprecedented sequence-regulated polymerization. For the template synthesis, selectivity or controllability was improved with living cationic polymerization: single addition control for polymer terminal; and polymerization control with an addressable functional monomer. The template initiators were prepared via the advanced "cationic" techniques to achieve selective radical reactions and polymerizations, coupled with ruthenium catalysts.

This study is just the beginning to realize sequence regulation in "artificial" polymerization, which has been essential in nature for the functions since the birth of life. In the bio-systems, much more elegant and sophisticated systems are programmed to produce the "well-defined" polymers, which seem to be beyond our reach. However, the author believes that our ultimate control over reactions and polymerizations would approach the essence of natural molecules, i.e., sequence regulation, and he wishes this thesis would contribute to the progress.

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PART I

Programmed/Addressable Living Cationic Polymerization for Template Synthesis

Chapter 1

Selective Single Monomer Addition in Living Cationic Polymerization: Sequential Double End-Functionalization in Combination with Capping Agent

Abstract

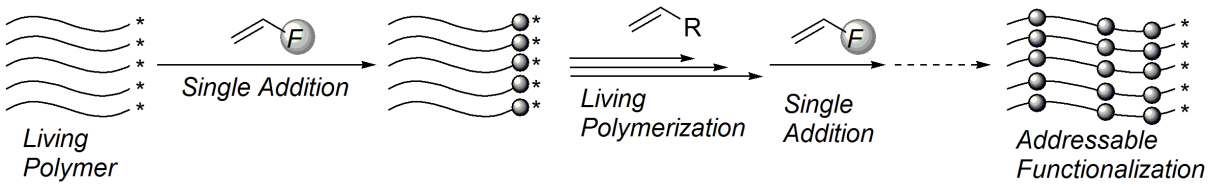
Amine-functionalized and amine–carboxylate double-functionalized polymers (**I** and **II**, respectively) have been synthesized by a selective single addition of a protected 2-aminoethyl vinyl ether (BocVE) {CH_2=CH[$OCH_2CH_2N(Boc)_2$]; Boc = *t*-butoxycarbonyl} onto a living cationic poly(*n*-butyl vinyl ether) [poly(NBVE)] initiated with the $SnCl_4$/*n*-Bu_4NCl system: (**I**) –$(NBVE)_n$–$CH_2CH(OCH_2CH_2NH_2)$–H; (**II**) –$(NBVE)_n$–$CH_2CH(OCH_2CH_2NH_2)$–CH_2CO_2H. The single addition was examined with a set of alkene monomers less reactive than NBVE, including BocVE, 2-chloroethyl vinyl ether, 2-vinyloxyethylphtalimide, and styrene. Upon addition of 10 molar excess of these alkenes onto the living ends, only BocVE led to the intended single adduct, and this was attributed to a chelating interaction of the two carboxylate groups in the terminal BocVE unit with the growing poly(NBVE) terminal, thus sterically hampering further propagation. A simple acid-catalyzed Boc-deprotection led to the amino-functionalized version **I**. Alternatively, an additional quenching the BocVE-capped living end (the precursor of **I**) with sodium malonate, followed by double deprotection of the Boc and the malonate groups gave the double-functionalized version **II**. The selective addition of a single monomer molecule is thus a new method for addressable or site-specific introduction of functional groups along polymer chains.

Introduction

Despite the recent advances in precision polymer synthesis to give block, graft, and numerous other structures, synthetic polymers are generally much inferior beyond comparison to natural polymers, in terms of primary structure control and hence functions or smartness. A particular superiority of natural polymers is found in their perfectly defined and predetermined "sequence" of constitutional repeat units that addresses structural and functional groups within macromolecules and thereby dictates developing specific higher order structure, function, and performance. Sequence control and addressable functionalization in artificial polymers is therefore most critical in approaching more advanced functions, though unprecedented yet.[1, 2]

A possible way to this goal is the selective "single" addition of a specific monomer onto the growing end in propagation, by which only one new repeat unit is connected to the growing end, and thus a particular pendent functionality in the added monomer is addressed at a predetermined position along a polymer backbone (Scheme 1).[2] The addition step herein should not only be living (free from side-reactions) but also occur only once, and the latter prerequisite is not simple to achieve in chain-growth polymerization. Namely, in most of living polymerizations, the active species are reversibly converted into dormant forms that are in dynamic equilibria with the active form. Despite the intervention of dormant species, the propagation is by nature a chain-growth process, and a single activation step usually triggers multiple propagation steps before the active end returns dormant.

If, however, the attachment of a specific monomer unit (***F***) generates a new dormant end (...-***F****) that is more stable and/or bulkier than the dormant end (...-M*) from a main monomer (M), further propagation might be temporarily stopped, even when an excess amount of ***F*** is loaded (the asterisk * indicates that the terminal is dormant). The added monomer ***F*** thereby leads to a selective and temporary "end-capping", forming ...–M-M-M-M-M-***F****. Nevertheless, though more stable, the new dormant end –***F****



Scheme 1. Selective single addition in living cationic polymerization toward addressable functionalization.

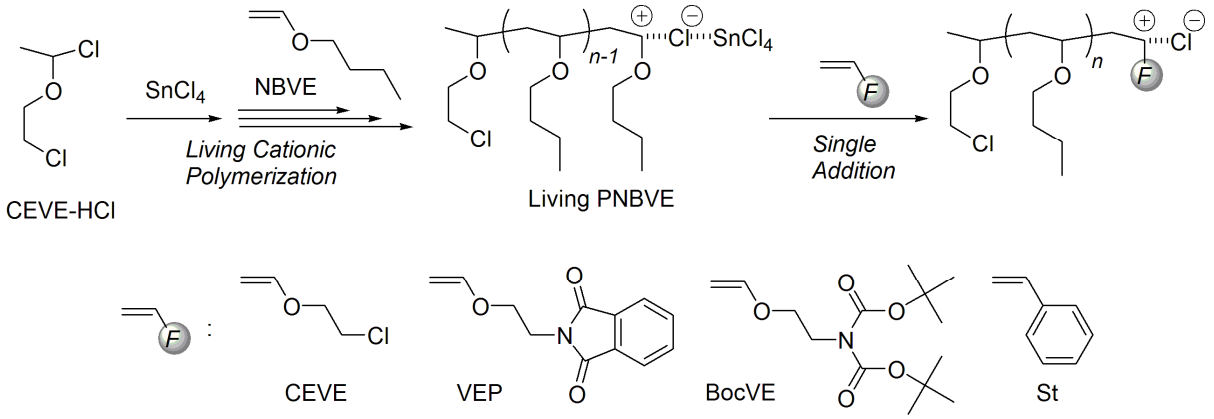
is not completely inactive and may be re-activated by one way or another (e.g., higher temperature or a more active catalyst) to resume propagation with the "main" monomer M that is to provide a longer and non-functionalized main segments, i.e., ...-M-M-M-***F***-M-M-M*. Repetition of such a programmed end-capping (single addition of ***F***) and re-activation (propagation with M) in turn enables addressable functionalization of a polymer chains at desired positions:

...-M-M-M-***F***-M-M-M-M-***F***-M-M-M-***F***-M-M-M-M-M-***F***-M-M-M...

Obviously, the success of an addressable functionalization should depend on, among other factors, the design of a specific monomer ***F*** (Scheme 1).

Thus, the author began to search specific monomers to achieve the single monomer addition for the temporary termination in Lewis acid-catalyzed living cationic polymerization of vinyl ethers (VEs).[3] 1,1-Diphenyl ethylene (DPE) might be one of the promising candidates, since the single addition has been achieved in living cationic polymerization of isobutylene.[4] However, the structure of DPE is less suitable as a functional monomer (unit) or the precursor: the re-activation from a DPE dormant end seems difficult; and introduction of functional groups into the DPE framework is not simple.

In this chapter, the author targeted electron-donating vinyl compounds that may work as a specific monomer (as ***F***) in the $SnCl_4$-catalyzed living cationic polymerization of *n*-butyl vinyl ether (NBVE) (as M) to examine the proposed addressable functionalization (Scheme 2). Potential ***F*** monomers included: 2-chloroethyl vinyl ether (CEVE), 2-vinyloxyethylphtalimide (VEP),[5] di-*tert*-butyl{*N*-[2-(vinyloxy)ethyl]imido}dicarboxylate (BocVE),[2c, 6] and styrene (St). These were selected from the viewpoints of functionality (or post-reaction functionalization) and lower reactivity relative to NBVE as functions of



Scheme 2. Single addition in living cationic polymerization of NBVE.

electronic effects as well as steric bulkiness. Note that CEVE is a precursor of functional VEs via S_N2 substitution reactions; VEP and BocVE are both protected forms of 2-aminoethyl VE but different in protecting chemistry and in steric bulk; and St is for comparison with VEs and a standard for its substituted derivatives.

Herein the author reports that BocVE is an excellent "specific" monomer that indeed achieves the single-step addition and selective end-capping upon living poly(NBVE) ends. From end-group analysis, among the candidate monomers examined, only BocVE specifically induced the single addition, while other monomers resulted in multi-step propagation (i.e., block copolymerization or oligomerization), or in no reactions. Furthermore, the terminal ...–NBVE–BocVE* is stable against NBVE propagation but active enough for electrophilic reactions and thus quantitatively reacted with sodium diethyl malonate,[7] to form ...–BocVE–(malonate) terminal, which led to a bifunctional sequence of an amine and a carboxylic acid upon double deprotection of the Boc and the malonate groups.

Experimental Section

Materials

NBVE (Tokyo Kasei; >98%) was washed with 10% aqueous sodium hydroxide and then with water, dried overnight over potassium hydroxide (pellets), and distilled twice over calcium hydride before use. CEVE was washed with 10% aqueous sodium hydroxide and then with aqueous saturated sodium chloride, dried overnight over sodium sulfate, and distilled twice over calcium hydride before use. Styrene was dried overnight over calcium chloride and distilled twice over calcium hydride before use. VEP,[5] BocVE,[6] a hydrogen chloride adduct of 2-chloroethyl vinyl ether (CEVE-HCl),[8] and sodium diethyl malonate[7] were prepared according to literature. *n*-Octane (internal standard for gas chromatography) was dried overnight over calcium chloride, and distilled twice over calcium hydride before use. Dichloromethane (CH_2Cl_2; solvent) was purified to be moisture- and oxygen-free by passing through a purification column [Solvent Dispensing System; Glass Contour] before use. $SnCl_4$ (1.0 M in CH_2Cl_2; Aldrich), *n*-Bu_4NCl (Tokyo Kasei; >98%), $LiBH_4$ (2.0 M in THF; Aldrich), and HCl (4.0 M in 1,4-dioxane; Aldrich) were used as received.

Synthesis of BocVE-Capped Poly(NBVE)

Polymerization was carried out under dry argon in baked glass flasks with three-way stopcocks. A typical example is given below: Living cationic polymerization was initiated by adding a solution of $SnCl_4$/*n*-Bu_4NCl in CH_2Cl_2 (0.50 mL) into a mixture (4.5 mL) of NBVE (200 mM) and CEVE-HCl (10 mM) in CH_2Cl_2 at –78 °C by a dry syringe. Monomer conversion was determined from the concentration of residual monomer measured by gas chromatography with *n*-octane as an internal standard. After near complete monomer consumption, BocVE (1.0 M in CH_2Cl_2; 0.5 mL) was added to the reaction mixture. The polymerization was quenched with an excess of ammonical methanol (2.0 mL) or $LiBH_4$ (2.0 M in THF; 0.80 mL) at 0 °C. In the case of the latter, after 1 h from addition of quencher, water (1.6 mL) was added to decompose residual $LiBH_4$. The quenched reaction mixture was diluted with *n*-hexane, washed with water, evaporated under reduced pressure and vacuum dried.

Synthesis of BocVE-Malonate Double Capped Poly(NBVE)

Living cationic polymerization was initiated by adding a solution of $SnCl_4$/*n*-Bu_4NCl in CH_2Cl_2 (0.50 mL) into a mixture (4.5 mL) of NBVE (200 mM) and CEVE-HCl (10 mM) in CH_2Cl_2 at –78 °C by a dry syringe. After near complete monomer consumption, BocVE (1.0 M in CH_2Cl_2; 0.50 mL) was added to the reaction mixture, and the mixture was stirred for additional 2 h. Then, a solution of sodium diethyl malonate (200 mM in 1,4-dioxane; 2.5 mL) was added, and the mixture was stirred for 1 h at 0 °C. The quenched reaction mixture was diluted with *n*-hexane, washed with water, evaporated under reduced pressure and vacuum dried.

Deprotection

The BocVE-capped poly(NBVE) (0.10 g) was treated with HCl (4.0 M in 1,4-dioxane; 1.8 mL; 200 equiv. for the Boc group) for 24 h at room temperature with stirring. The reaction mixture was diluted with ethyl ether and washed sequentially with NaOH aqueous solution (equivalent to the HCl employed) and water, followed by evaporation under reduced pressure and vacuum drying.

In the double deprotection for the BocVE and the malonate terminal units, the polymer poly(NBVE)-(BocVE)-(malonate) (0.10 g) was dissolved in ethanol (10 mL) and NaOH (5.0 equiv. to the COOEt units) was added. The mixture was magnetically stirred for 3 h, water

(10 mL) was added, and stirring was continued for an additional 3 days. The resulting sodium salt was converted into malonic acid by treatment with HCl. For subsequent decarboxylation, the acid-capped product was isolated by evaporation under reduced pressure, dissolved in 1,4-dioxane (20 mL), and kept at 90 °C for 1 h. The product was isolated by evaporation, dissolved in CH_2Cl_2 (50 mL), washed with water to remove the resulting NaCl, and then isolated by evaporation followed by vacuum-drying.

For Boc-deprotection, the decarboxylation product was treated with HCl (2.0 mL; 4 M in 1,4-dioxane; 200 equiv. for Boc group) for 24 h at room temperature with stirring. The resulting polymer was isolated by evaporation, dissolved in 1,4-dioxane, and neutralized with $NaHCO_3$ aqueous solution, followed by evaporation. Chloroform was added to the product, the soluble part was isolated by filtration, and the filtrate was evaporated to dryness, to give the final products.

Measurement

The M_n, M_w/M_n, and MWD of polymers were determined by size-exclusion chromatography in THF at 40 °C using three polystyrene gel columns (Shodex KF-400RL × 2 and KF-400RH) that were connected to a Shodex DU-H2000 precision pump, a Shodex RI-74 refractive index detector, and a Shodex UV-41 UV/vis detector set at 250 nm. The columns were calibrated against 13 standard polystyrene samples (Tosoh; M_w = 500-3,840,000; M_w/M_n = 1.01-1.14). ^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer, operating at 500.16 MHz. Polymer samples for ^{1}H NMR were fractionated by preparative SEC. MALDI-TOF-MS analysis was performed on a Shimadzu AXIMA-CFR instrument equipped with 1.2-m linear flight tubes and a 337-nm nitrogen laser.

Results and Discussion

1. Screening of "Specific" Monomers in Living Cationic Polymerization of NBVE

NBVE was first polymerized with $SnCl_4$/*n*-Bu_4NCl,[9] coupled with adduct CEVE-HCl as an initiator in CH_2Cl_2 at –78 °C: $[NBVE]_0$ = 200 mM; $[CEVE\text{-}HCl]_0$ = 10 mM; $[SnCl_4]_0$ = 10 mM; [*n*-$Bu_4NCl]_0$ = 5.0 mM. The monomer was almost quantitatively consumed within 1 min (conversion ≈ 100%), and the molecular weight and its distribution of the products were precisely controlled (M_n = 2,900; M_w/M_n = 1.08) (entry 1 in Table 1; Figure 1a). To

Table 1. Living cationic polymerization of NBVE and addition of another monomer.[a]

Entry	Added Monomer	$[SnCl_4]_{add}$ (mM)	M_n[b]	M_w/M_n[b]	
1	–	–	2,900	1.08	PNBVE (1st block)
2	CEVE	0	3,800	1.11	Polymerization
3	VEP	0	4,300	1.11	Polymerization
4	BocVE	0	3,200	1.08	Monoaddition[c]
5	BocVE	100	3,200	1.08	Monoaddition[c]
6	St	0	3,100	1.09	~ 0 St unit/chain[c]
7	St	100	3,000	1.16	*2.57* St units/chain[d]

[a] $[NBVE]_0$ = 500 mM, $[CEVE\text{-}HCl]_0$ = 10 mM, $[SnCl_4]_0$ = 10 mM, $[n\text{-}Bu_4NCl]_0$ = 5.0 mM, $[added\ monomer]_{add}$ = 100 mM in CH_2Cl_2 at –78 °C. [b] Measured by SEC. [c] Confirmed by MALDI-TOF-MS. [d] Measured by ^1H NMR.

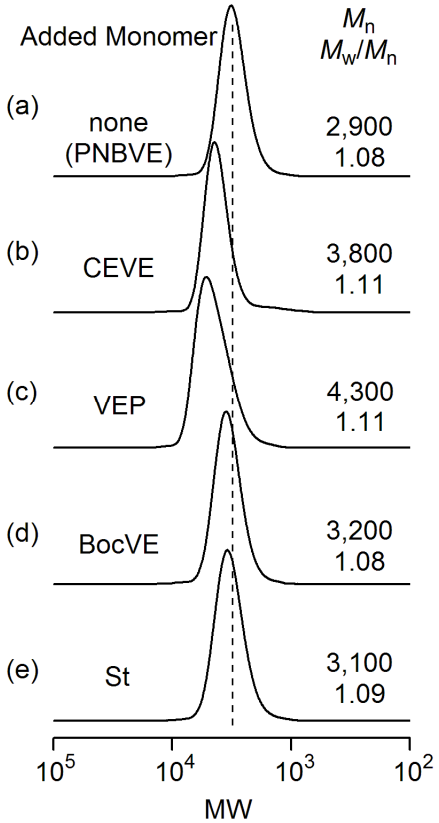


Figure 1. SEC curves of PNBVEs (a) before and (b-e) after addition of other monomers with (b) CEVE, (c) VEP, (d) BocVE, and (e) St. See Table 1 for the reaction conditions.

these living polymer solutions was added an excess of a "specific" monomer candidate (CEVE, VEP, BocVE, or St) (10 molar equiv. to polymer-end or the initiator), and the mixtures were kept at –78 °C for additional 2 h. After quenching ammonical methanol, the resultant polymers were analyzed with SEC and ^{1}H NMR.

For CEVE and VEP, SEC curves of the polymers obviously shifted to higher molecular weights keeping the narrow MWD (entry 2 and 3 in Table 1; Figures 1b and 1c). This indicates that not a single addition but a block copolymerization occurred. In contrast, with BocVE and St, SEC curves of the products neither shifted nor broadened (entry 4 and 6 in Table 1; Figures 1d and 1e).

The molecular weights and the terminal structures of the polymers before and after BocVE or St addition were more closely analyzed by MALDI-TOF-MS (Figure 2). In the poly(NBVE) samples before the additions (Figure 2a), only a single peak series was detected, with a uniform interval of about 100 corresponding to an NBVE repeat unit. The absolute

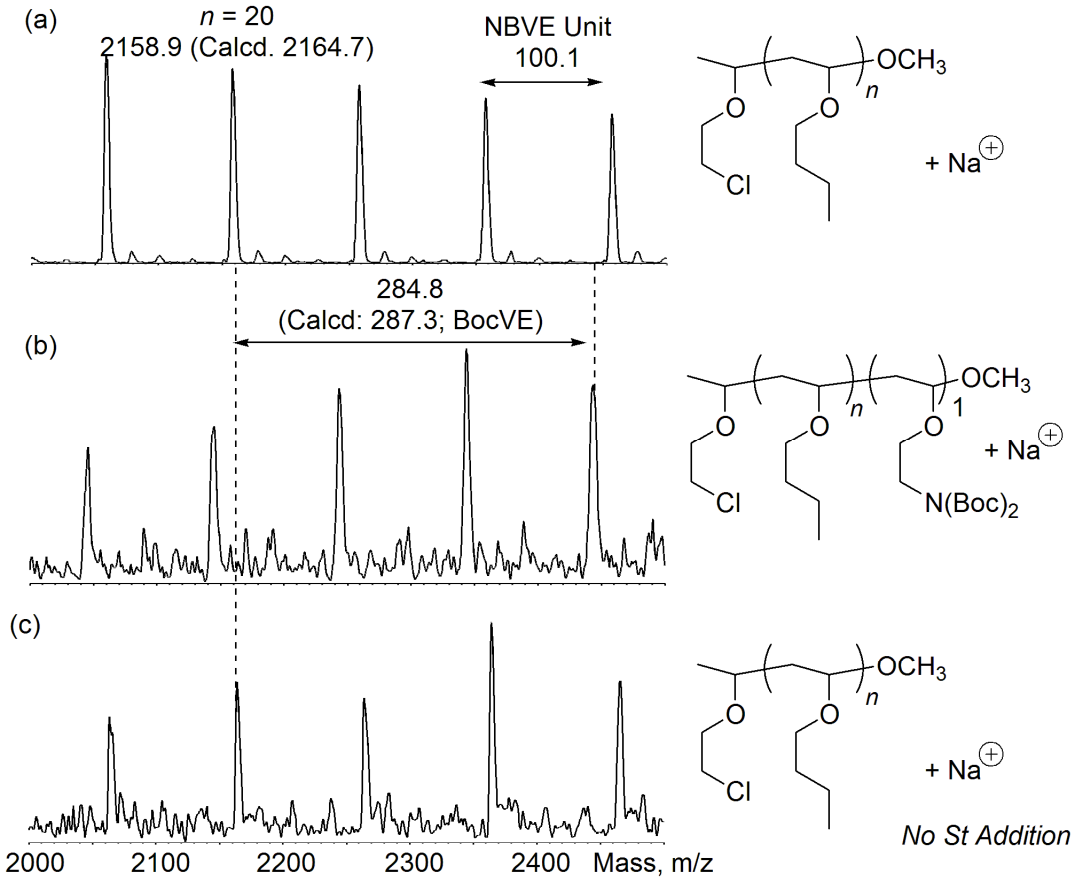


Figure 2. MALDI-TOF-MS spectra of PNBVEs (a) before and (b, c) after addition of other monomers with (b) BocVE and (c) St. The measured samples are same as entry 1, 4, and 6 of Table 1.

mass number of each peak agreed with that for the structure expected for living NBVE polymers: H–CEVE–$(NBVE)_n$–OCH_3[10] with sodium cation.

The BocVE-treated sample gave a clearly differing MALDI profile (Figure 2b) where the peak interval was 100, the same as for the pristine poly(NBVE), but the peaks were totally shifted with about 285, close to the mass of a single BocVE unit (287.3). This result demonstrates the single-unit addition of BocVE to all the poly(NBVE) living chains.

The St-treated samples, in contrast, showed no such a mass change before and after the atempted reaction (Figure 2c), and presumably no reaction took place between living poly(NBVE) and styrene.

Addition experiments with BocVE and St were also performed under more vigorous conditions i.e., 10 times of the catalyst was injected upon addition of the new monomers ($[SnCl_4]_{add}$ = 100 mM; $[monomer]_{add}$ = 100 mM). After a 1-hour stirring, the reactions were

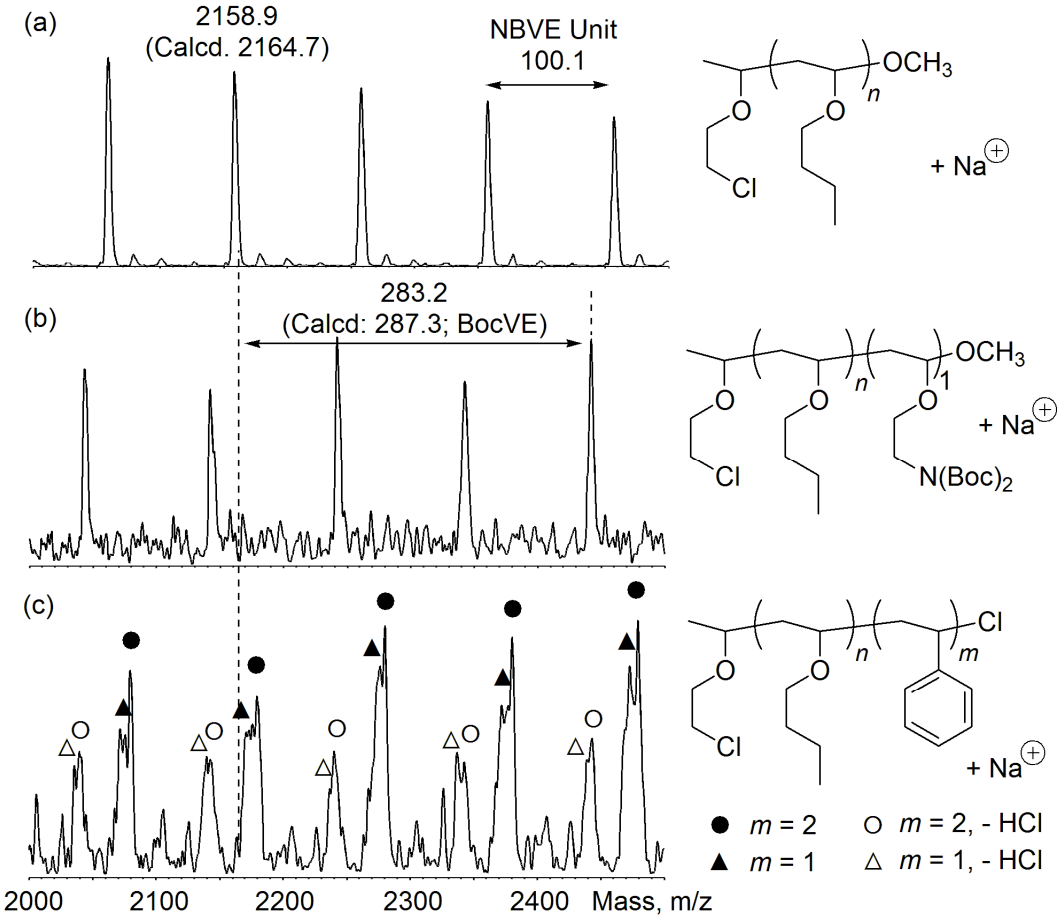


Figure 3. MALDI-TOF-MS spectra of PNBVEs (a) before and (b, c) after addition of other monomers with (b) BocVE and (c) St along with $SnCl_4$. The measured samples are same as entry 1, 5, and 7 of Table 1.

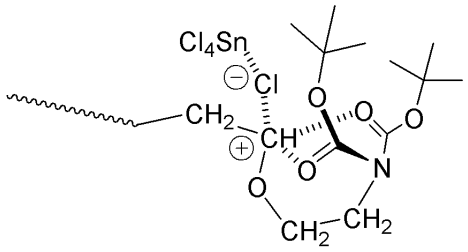


Figure 4. Proposed structure of growing carbocation after an addition of BocVE

quenched with ammonical methanol and the resultant polymers were analyzed with MALDI-TOF-MS. Even upon the co-addition of the catalyst, BocVE quantitatively underwent a selective single-unit addition onto the poly (NBVE) (Figure 3b), very similar to the reaction without Lewis acid addition (Figure 2).

For styrene, the original peaks of poly(NBVE) disappeared, and multiple series of peaks newly appeared instead (Figure 3c), indicative of the addition of one and two monomers (●, ▲) with the increased concentration of catalyst. The additional peak series (○, △) originate from the laser-induced terminal dehydrochlorination of the styrene-capped poly(NBVE).

Thus, BocVE was found to be quite unique to induce a selective monoaddition onto the growing living poly(vinyl ether) carbocation. The author speculates that the specificity is brought about by the following electronic and steric features that would effectively keep the BocVE-capped cation from further propagation. Electronically, as illustrated in Figure 4, the geminal Boc pendent groups in the terminal BocVE unit, as a built-in "added base",[11] would intramolecularly stabilize the growing carbocation through a double carbonyl coordination. Sterically, the coordination of the two bulky Boc groups renders the circumference around the cationic end too crowded for approaching BocVE.

2. Amine-Capped Poly(NBVE) Terminal via Deprotection

The single BocVE terminal unit was then deprotected to obtain an amine-capped poly(NBVE). Quenched with methanol, the precursor polymer [...–$(NBVE)_n$–(BocVE)–OMe] carries an acid-sensitive acetal terminal, while the usual Boc deprotection applies acidic conditions, and therefore the terminal acetal was first hydrogenated with $LiBH_4$ at a final stage of living cationic polymerization of NBVE.[12] Subsequently, an excess amount of HCl (200 equiv. to the Boc group) was added at room temperature into a solution of the hydride-capped PNBVE (M_n = 3,400, M_w/M_n = 1.09), and the solution was stirred for

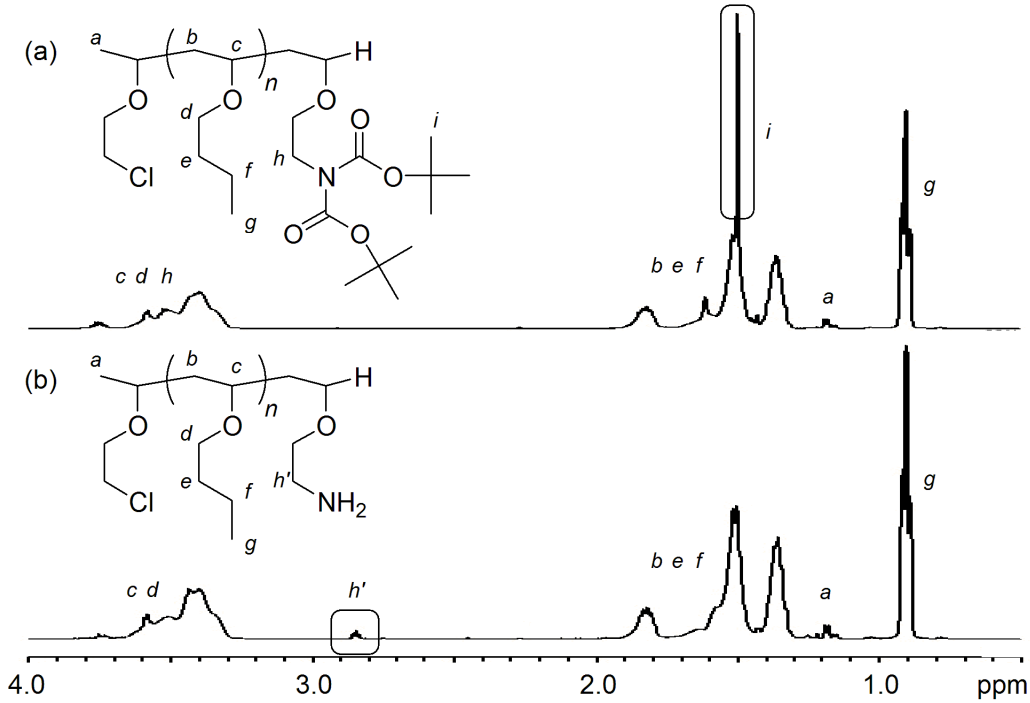


Figure 5. ^{1}H NMR spectra (in $CDCl_3$) of PNBVEs obtained via (a) living cationic polymerization of NBVE and addition of BocVE, and (b) deprotection of Boc group. Polymerization: $[NBVE]_0$ = 200 mM; $[CEVE\text{-}HCl]_0$ = 10 mM; $[SnCl_4]_0$ = 10 mM; $[n\text{-}Bu_4NCl]_0$ = 5.0 mM; $[BocVE]_{add}$ = 100 mM in CH_2Cl_2 at –78 °C. Quenching: $[LiBH_4]_{add}$ = 300 mM at 0 °C. Deprotection: HCl (200 eq for Boc groups) was treated in 1,4-dioxane at r.t. for 24 h.

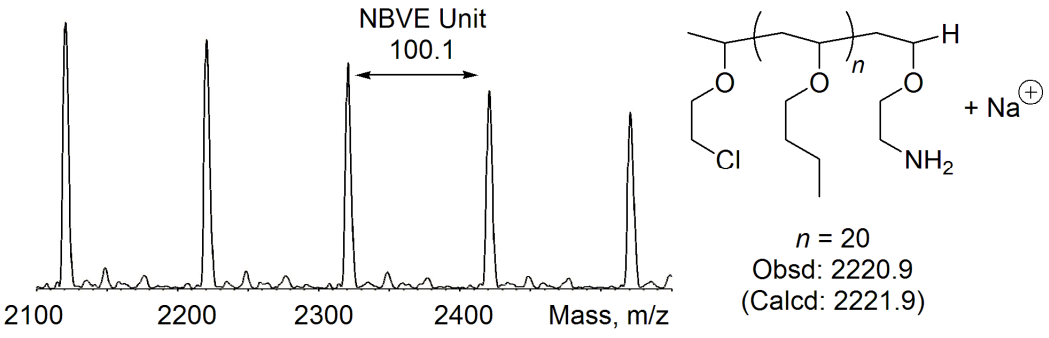


Figure 6. MALDI-TOF-MS spectrum of PNBVE via addition of BocVE, quenching with $LiBH_4$ and deprotectino of Boc group (M_n = 3,400; M_w/M_n = 1.09 before the deprotection). See caption of Figure 5 for the conditions.

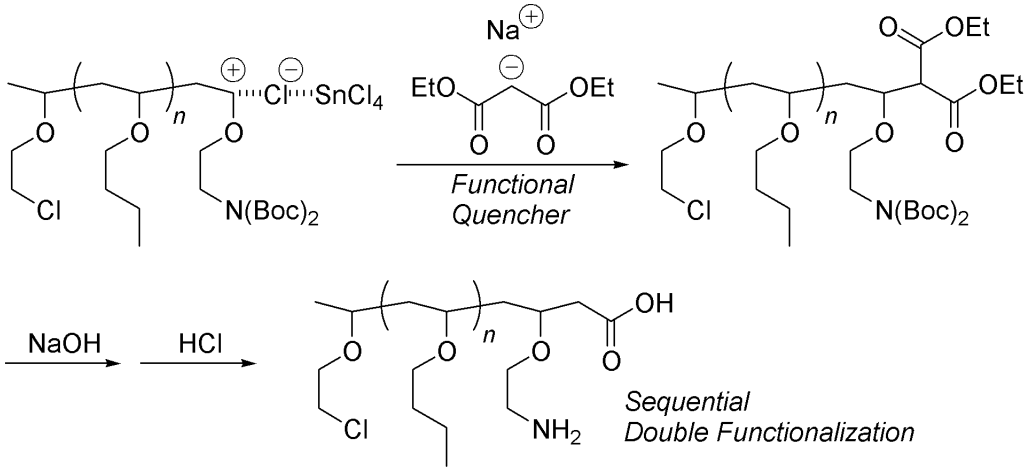
24 h. ^{1}H NMR analysis of the polymers before and after the HCl treatment confirmed a quantitative and complete deprotection; namely, the sharp peak attributed to the *t*-butyl unit of the Boc group (1.5 ppm) disappeared, and instead a new peak, assignable to the methylene protons adjacent to an amino group, was appeared at 2.8 ppm (Figure 5). Furthermore, MALDI-TOF-MS assay strongly supported the quantitative formation of amine, since the absolute mass agreed with that of the ideal structure with one unit of amino ethyl vinyl ether unit (sodium cation adduct) (Figure 6).

Thus, the author achieved the quantitative amination of PNBVE terminal by the selective single addition of BocVE and the subsequent deprotection.

3. Combination with Conventional Capping: Double Functionalization of the Terminal

Finally, a conventional terminal capping was sequentially performed for the BocVE-capped PNBVE with sodium diethyl malonate,[7] since the growing end should be still electrophilic even after the single addition of a BocVE unit. This would lead to the double functionalization of the terminal by an amine (from the terminal BocVE unit) and a carboxylic acid (from the malonate capping) via double deprotection for each protecting groups (Scheme 3).

After the living cationic polymerization of NBVE and sequential addition of BocVE (10 eq. to the living ends), sodium diethyl malonate (10 eq.) was allowed to react for 1 h at 0 °C. Molecular weight of the produced polymer was fairly controlled (M_n = 3,100 and M_w/M_n = 1.08), without any adverse effects of the capping agent, and the quantitative "double" introduction of a single unit of BocVE and a terminal malonate group was



Scheme 3. Double functionalization of PNBVE with amine and carboxylic acid terminal.

confirmed by ^{1}H NMR, as indicated by the peaks of the Boc *t*-butyl group (*i*, 1.5 ppm) and those of the malonate's methyl (*k*, 1.3 ppm) and methylene protons (*j*, 4.2 ppm) (Figure 7a). The terminal structure was also supported by the MALDI-TOF-MS *m*/*z* values of the products (a single series of peaks separated by the NBVE *m*/*z* unit) (Figure 8).

The malonate terminal was converted into carboxylic acid via hydrolysis with NaOH and subsequent heating for decarboxylation. Then, the Boc group was deprotected to amine by the treatment with excess HCl. Clean proceedings of both deprotection steps were confirmed by ^{1}H NMR, where the characteristic precursor peaks were completely disappeared

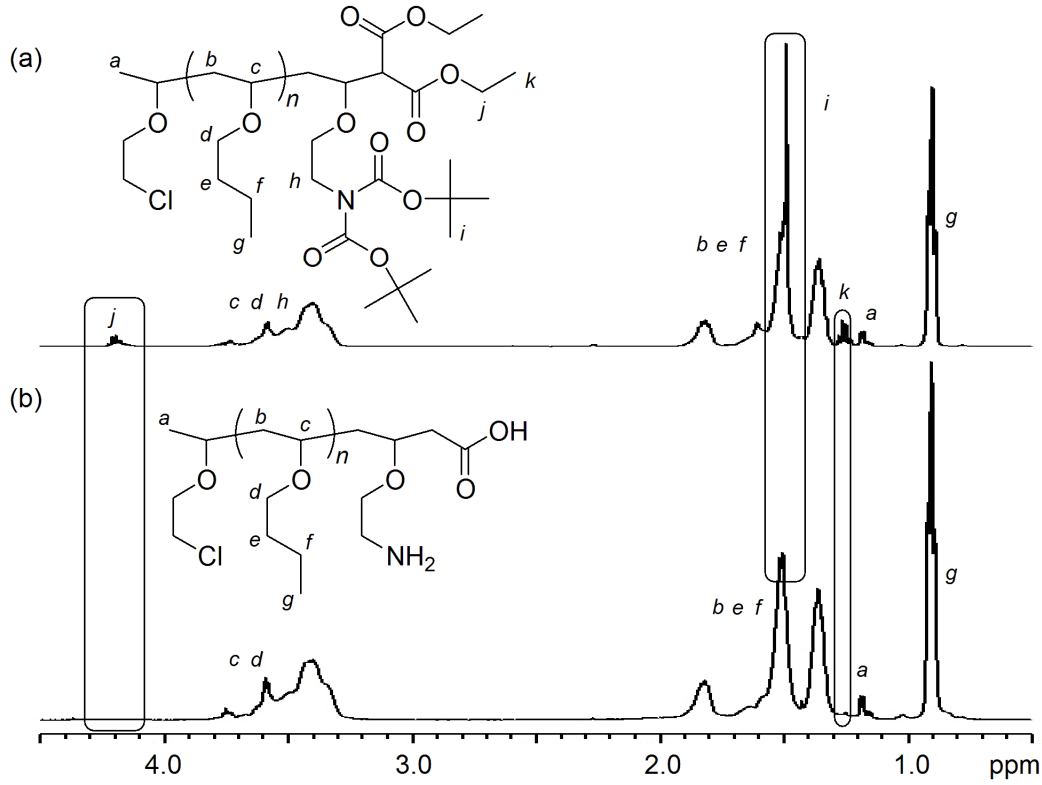


Figure 7. ^{1}H NMR spectra (in $CDCl_3$) of PNBVEs obtained via (a) addition of BocVE and capping of sodium diethyl malonate, and (b) after deprotections of the malonate terminal and the Boc group. Polymerization: $[NBVE]_0$ = 200 mM; $[CEVE\text{-}HCl]_0$ = 10 mM; $[SnCl_4]_0$ = 10 mM; $[n\text{-}Bu_4NCl]_0$ = 5.0 mM; $[BocVE]_{add}$ = 100 mM in CH_2Cl_2 at –78 °C, quenched with 10 eq. (for polymer chain number) of sodium diethyl malonate at 0 °C. Deprotection of malonate group: NaOH (5 eq. for –COOEt) was treated in ethanol/water at r.t. for 3 days, and heated in 1,4-dioxane at 90 °C for 1 h. Deprotection of Boc groups: HCl (200 eq. for Boc group) was treated in 1,4-dioxane at r.t. for 24 h.

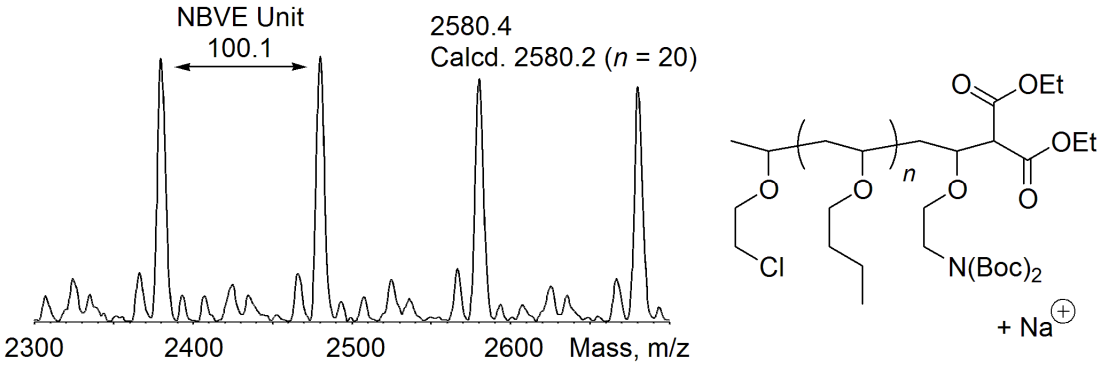


Figure 8. MALDI-TOF-MS spectrum of PNBVE via addition of BocVE and capping of sodium diethyl malonate (M_n = 3,200; M_w/M_n = 1.08). See caption of Figure 7 for the condition.

(*i*-*k*, Figure 7b). As a result, the terminal structure of the PNBVE was sequentially regulated with a carboxylic acid and an amine.

Conclusion

BocVE was found to be a unique monomer to induce a single and selective addition at a growing end in the living cationic polymerization of NBVE with $SnCl_4$. This would be due to the bulky pendent group that specifically interacts with the terminal carbocation, via double coordination of the two Boc carbonyls (Figure 4), thereby to prohibit further propagation. The Boc group, introduced at the terminal with a single unit, was quantitatively deprotected into an amine, and also the combination with a conventional capping agent (e.g., sodium diethyl malonate) led to a sequential double functionalization with, for example, an amine and a carboxylic acid.

Such a single addition of BocVE has also opened a way to construct a template molecule for a selective radical addition reaction where the selectively introduced amine unit is essential to develop a "template-assisted" monomer recognition and a preferential propagation of a recognized monomer over a non-recognizable counterpart.[2c] Alternatively, re-initiation (re-polymerization) of NBVE and related monomers from the BocVE-capped terminal would be ideal for the introduction of mid-chain functionalities at addressable positions.

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Chapter 2

Living Cationic Polymerization of an Azide-Containing Vinyl Ether toward Addressable Functionalization of Polymers

Abstract

The author first achieved the living cationic polymerization of azide-containing monomer, 2-azidoethyl vinyl ether (AzVE), with $SnCl_4$ as a catalyst (activator) in conjunction with the HCl adduct of a vinyl ether [H–CH_2CH(OR)–Cl; R = CH_2CH_2Cl, $CH_2CH(CH_3)_2$]. Despite the potentially poisoning azide group, the produced polymers possessed controlled molecular weights and fairly narrow distributions ($M_w/M_n \approx 1.2$) and gave block polymers with 2-chloroethyl vinyl ether. The pendent azide groups are easily converted into various functional groups via mild and selective reactions, such as the Staudinger reduction and copper-catalyzed azide-alkyne 1,3-cycloaddition (CuAAC; a "click" reaction). These reactions led to quantitative pendent functionalization into primary amine ($–NH_2$), hydroxy (–OH), and carboxyl (–COOH) groups, at room temperature and without any acidic or basic treatment. Thus, poly(AzVE) is a versatile precursor for a wide variety of functional vinyl ether polymers with well-defined structures and molecular weights.

Introduction

The Lewis acid-catalyzed living cationic polymerization of vinyl ethers [CH_2=CH(OR); VE] offers a versatile precision synthesis of pendent-functionalized polymers of controlled architectures.[1] Therein 2-chloroethyl vinyl ether (CEVE) serves as a convenient, versatile precursor (parent) monomer from which a large variety of functionalized VE monomers can be obtained by simple but widely applicable nucleophilic substitution reactions of the pendent chloroethyl group; note that the intervening ethylene spacer well insulates the vinyl ether moiety from the steric and electronic effects of the potentially hazardous functionality thus introduced.

However, as with the conventional counterparts, this living polymerization is not always tolerant of polar functions (OH, NR_3, CO_2H, etc.) that often induce side-reactions with the growing carbocations, and sometimes Lewis acidic catalysts are also deactivated (poisoned) by these functionalities. Thus most of useful functions should be protected in the monomer stage before polymerization.[2-4] From these mostly protected functional VEs, a wide variety of pendent-functionalized, block or end-functionalized polymers with well-defined structures and molecular weights have already been synthesized. Despite these achievements, the protection–deprotection of the pendent functional groups is of course cumbersome, and, more seriously, rigorous acidic or basic conditions are often required therein, which sometimes deteriorate the polymer backbone and/or other coexisting functional groups.

An attractive alternative for the protected monomer method is a direct living polymerization of a pro-functional precursor monomer followed by a post-polymerization transformation of its pendent groups into desired functionalities. This pendent-transformation of course involves the post-polymerization modification and, therefore, would suffer from its general drawbacks such as poor transformation efficiency and the so-called negative neighboring-group participation; namely, the reaction of a particular pendent group is severely disturbed by the nearest neighbor that has already undergone the same transformation process.[5] It follows that the key to the success of this alternative method is to find an excellent precursor monomer.

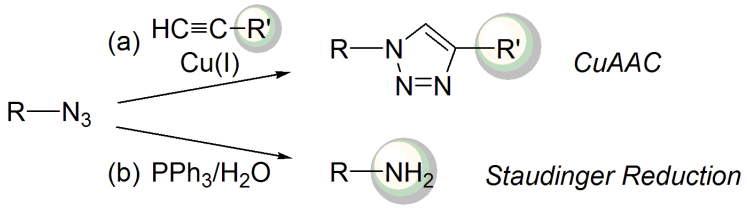
The design criteria for the precursor monomer obviously includes that the pendent pro-functional group should not interfere its living polymerization and that its post-polymerization reaction should be selective and quantitative under mild conditions

without deteriorating the parent polymer architecture. In this regard, CEVE would be a potential candidate: Its chloroethyl group is already known to be perfectly compatible to living cationic polymerization, and as demonstrated, a wide variety of pendent transformation is already established. However, nucleophilic substitution is much less productive in poly(CEVE) than in its monomer stage, and the author soon discarded this option for the polymer-reaction method.

Azide ($–N_3$) is a versatile reactive group for dipolarophiles, nucleophiles, and electrophiles because of the unique mesomeric structure ($–N=N^+=N^- \leftrightarrow –N^–N^+\equiv N \leftrightarrow –N^–N=N^+$).[6] For example, an azide compound behaves as a dipole to induce azide-alkyne 1,3-cycloaddition.[7] Especially, the copper-catalyzed azide-alkyne 1,3-cycloaddiion (CuAAC; Scheme 1A) is highly chemoselective and efficient under mild conditions or in aqueous media, which is now regarded as the most popular "click" reaction and is finding widespread applications in introducing a functional group via an azide or an alkyne precursor [N_3–R and HC≡C–R', respectively] .[8]

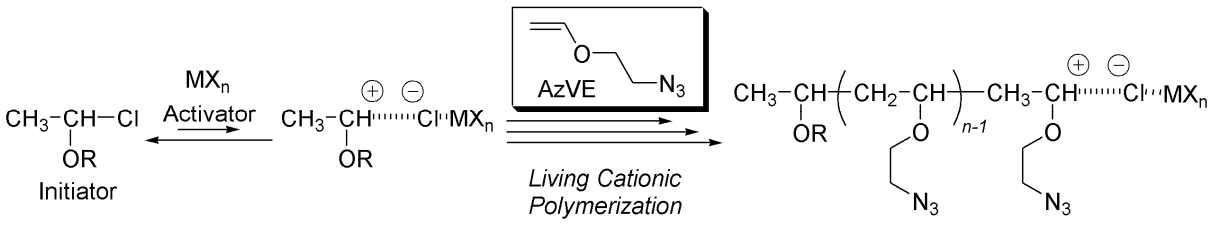
Azides also react with a phosphorous nucleophile (PR_3) to give an iminophosphorane ($–N=PR_3$), which may spontaneously be converted into a primary amine ($–NH_2$) in the presence of water (the Staudinger reduction; Scheme 1B).[9] All these examples show that azide is a very useful precursor for various functional groups, in terms of versatility, unusually high chemoselectivity, and, above all, fast and quantitative reactions.

It is therefore not surprising that CuAAC has been applied for the construction of well-defined functional polymers in living (controlled) polymerization.[10] For example, an azide may be incorporated into a monomer[11] or an end-group[12] in living radical polymerizations, and thereby block,[13] star,[14] and macrocyclic polymers[15] have been obtained. In living cationic polymerization, however, the azide-based functionalization has much less frequently examined,[16] and to the author's knowledge, no direct living cationic polymerization of azide-carrying monomers has been reported.



Scheme 1. Functionalization of azide groups: (a) CuAAC reaction, and (b) Staudinger reduction.

This chapter reports the first Lewis acid-catalyzed living cationic polymerization of an azide-carrying monomer, 2-azidoethyl vinyl ether (AzVE) (Scheme 2), with tin(IV) tetrachloride ($SnCl_4$) as a catalyst and the HCl adduct of an alkyl vinyl ether as an initiator. AzVE is in fact an excellent precursor monomer for the synthesis of pendent-functionalized polymers by the post-polymerization method, as demonstrated herein by the Staudinger reduction into amino pendants. The poly(AzVE) has been reacted by CuAAC with alkynes containing either hydroxyl or carboxyl groups, respectively to give functionalized poly(VE)s. The conditions for these transformation reactions, were much milder than those for conventional methods with protected monomers. The azide-based VE and its living cationic polymerization have thus opened a versatile way for not only pendent-functionalization but also the construction of more complicated structures such as graft polymers. Relative to the functionalized monomer method, the post-transformation approach, coupled with living polymerization, provides a family of pendent- and/or end-functionalized polymers as well as block polymers, statistically random copolymers, and star branched polymers with varying functional groups, all derived from a single identical parent precursor such as poly(AzVE). Importantly, the members of these families constitute unprecedentedly unique functional polymers which are by definition identical and well-defined in all of the following factors directly inherited from the parent precursor, except for their functionalities: the degrees of polymerization (DP) and narrow polydispersity of the main-chain and/or the segment(s); and the compositions and the sequences of pendent and/or terminal functionalities. With such uniformity in multiple structural parameters, in turn, this method will provide a unique set of "standard" functional polymers that can be rigorously compared in terms of their physical properties and functions without being affected by the variations in their fundamental structures.



Scheme 2. Living cationic polymerization of AzVE.

Experimental Section

Materials

Commercial CEVE and isobutyl vinyl ether (IBVE) were washed with 10% aqueous sodium hydroxide and then with aqueous saturated sodium chloride, dried overnight over sodium sulfate, and distilled twice over calcium hydride before use. Their hydrogen chloride adducts (CEVE-HCl and IBVE-HCl, respectively) were prepared according to literature.[17] Tetralin (1,2,3,4-tetrahydronaphtalene; an internal standard for ^{1}H NMR) was dried overnight over calcium chloride, and doubly distilled from calcium hydride under reduced pressure before use. *n*-Octane (an internal standard for gas chromatography) was purified in the same way but distilled under atmospheric pressure. Dichloromethane (CH_2Cl_2; solvent) was purified to moisture- and oxygen-free by passing through a purification column (Solvent Dispensing System; Glass Contour) before use. Sodium azide (Wako; 98%), $SnCl_4$ (1.0 M in CH_2Cl_2; Aldrich), $EtAlCl_2$ (1.0 M in *n*-hexane; Kanto Kagaku), *n*-Bu_4NCl (Tokyo Kasei; >98%), $LiBH_4$ (Aldrich; 2.0 M in THF), triphenylphosphine (Wako; >97%), CuBr (Wako; >99.9%), propargyl alcohol (Aldrich; 99%), and 4-pentynoic acid (Alfa Aesar; 98%) were used as received.

2-Azidoethyl Vinyl Ether (AzVE)

A solution of CEVE (29.5 mL; 0.290 mol) in *N,N*-dimethylformamide (175 mL) was added under dry argon into sodium azide (21.2 g; 0.326 mol) placed in a round-bottom flask. The mixture was stirred at 80 °C for 4 h, cooled to room temperature, poured into water (200 mL), and extracted with diethyl ether (500 mL). The organic phase was washed twice with water (500 mL each) and evaporated into dryness under reduced pressure. The crude product was purified by silica-gel column chromatography [eluent: chloroform/methanol, 10/1 (v/v)]. The isolated product was dissolved in CH_2Cl_2 (300 mL), dried with Na_2SO_4 overnight, and evaporated to dryness under reduced pressure to give AzVE (purity, >99.5% by NMR; isolated yield, 61%). ^{1}H NMR ($CDCl_3$): δ 6.50 (dd, 1H, CH_2=C*H*–), 4.23 (dd, 1H, *cis*-C*H*$_2$=CH–), 4.08 (dd, 1H, *trans*-C*H*$_2$=CH–), 3.86 (t, 2H, –O–C*H*$_2$–CH_2–N_3), 3.50 (t, 2H, –O–CH_2–C*H*$_2$–N_3). ^{13}C NMR ($CDCl_3$): δ 151.2 (CH_2=*C*H–), 87.4 (*C*H_2=CH–), 66.6 (–O–*C*H_2–CH_2–N_3), 50.1 (–O–CH_2–*C*H_2–N_3).

Polymerization

Polymerization was carried out under dry argon in baked glass flasks with three-way stopcocks. A typical example is given below. The reaction was initiated by adding a solution of $SnCl_4$ in CH_2Cl_2 into a mixture of AzVE and CEVE-HCl in CH_2Cl_2 at –78 °C by a dry syringe. Monomer conversion was determined from the residual monomer concentration measured by ^{1}H NMR for AzVE with tetralin as an internal standard or by gas chromatography for CEVE with *n*-octane as an internal standard. The polymerization was quenched with an excess of ammonical methanol or $LiBH_4$. In the latter case, the quencher addition was at –78 °C, but the termination reaction was run at 0 °C for 30 minutes, and water was subsequently added to decompose the residual $LiBH_4$. The quenched reaction mixture was diluted with toluene, washed sequentially with dilute hydrochloric acid, aqueous sodium hydroxide, and water, evaporated under reduced pressure, and vacuum dried.

Staudinger Reduction

Poly(AzVE) [M_n = 2,750, DP_n = 23.1 (by ^{1}H NMR)] (44 mg; 0.37 mmol of azide groups) and triphenylphosphine (0.20 g; 0.76 mmol) were dissolved into a THF/methanol mixed solvent (1.5 mL each). Water (0.15 mL) was added, and the mixture was stirred for 24 h at room temperature. The solvent was evaporated, and the crude product was dissolved in a small amount of methanol and precipitated into toluene. The precipitated polymer was filtered off and vacuum dried.

CuAAC Reaction

CuAAC reaction was conducted under dry argon in round-bottomed flask with three way stopcocks. Poly(AzVE) [70 mg; M_n = 3,620; DP_n = 31.0 (calculated from ^{1}H NMR)], an alkyne (propagyl alcohol or 4-pentynoic acid; 1.5 equiv. to the azide groups in the substrate), and CuBr (0.1 equiv.) were dissolved into DMSO (4.2 mL). The reaction mixture was stirred at room temperature for 24 h, was concentrated into a small amount by evaporation, and poured into excess toluene to precipitate the product.

Measurements

The M_n, and M_w/M_n of the polymers were determined by size-exclusion chromatography (SEC) in THF at 40 °C using three polystyrene gel columns (Shodex KF-400RL × 2 and KF-400RH) that were connected to a Shodex DU-H2000 precision pump,

a Shodex RI-74 refractive index detector, and a Shodex UV-41 UV/vis detector set at 250 nm. The columns were calibrated against 13 standard polystyrene samples (Tosoh; M_w = 500-3,840,000; M_w/M_n = 1.01-1.14). ^{1}H NMR spectra were recorded in $CDCl_3$ or CD_3OD at room temperature on a JEOL JNM-LA500 spectrometer operating at 500.16 MHz. MALDI-TOF-MS analysis was performed on a Shimadzu AXIMA-CFR instrument equipped with 1.2-m linear flight tubes and a 337-nm nitrogen laser; the matrix was dithranol.

Results and Discussion

1. Cationic Polymerization of AzVE: Effect of Lewis Acids

$SnCl_4$ and $EtAlCl_2$, representative Lewis acidic catalysts, were employed for cationic polymerization of AzVE in conjunction with CEVE-HCl as an initiator in CH_2Cl_2 at –78 °C: $[AzVE]_0$ = 0.20 M; $[catalyst]_0$ = 20 mM; $[initiator]_0$ = 10 mM (Figure 1). Both catalysts induced near quantitative polymerizations but at clearly different rates: 3 min ($SnCl_4$) vs 5 h ($EtAlCl_2$) for ~90% conversion. For the $SnCl_4$-catalyzed system, molecular weight distributions (MWDs) of the products were relatively narrow and shifted to higher molecular weight with monomer conversion, indicating the intervention of long-lived propagating species. On the other hand, such a peak shift was hardly observed with the aluminum system, and MWD was obviously broader than with $SnCl_4$.

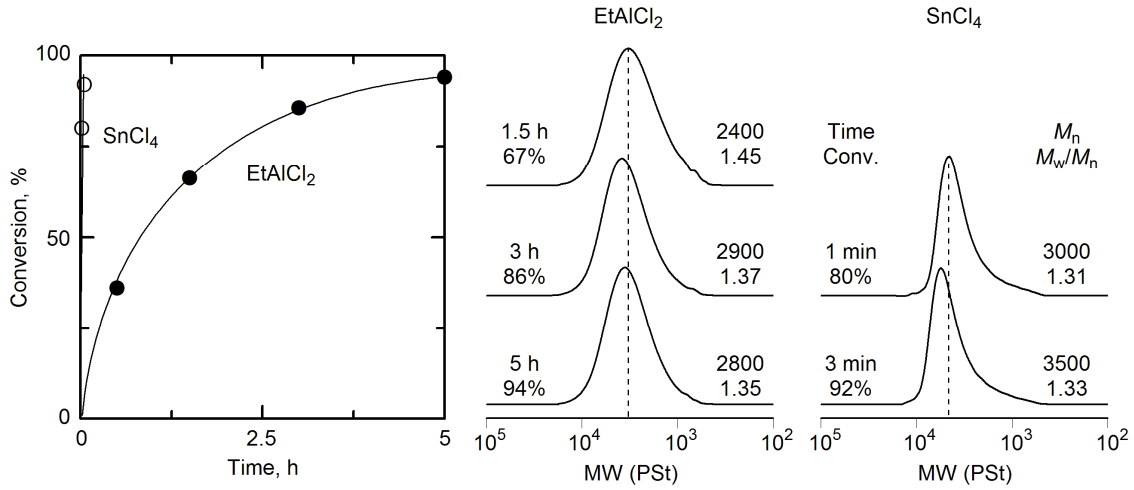


Figure 1. Comparison between $SnCl_4$ and $EtAlCl_2$ as a Lewis acid activator for living cationic polymerization of AzVE with CEVE-HCl in CH_2Cl_2 at –78 °C: $[AzVE]_0$ = 0.20 M; $[CEVE\text{-}HCl]_0$ = 10 mM; $[Lewis\ acid]_0$ = 20 mM.

The observed catalytic difference between $SnCl_4$ and $EtAlCl_2$ may be understood by considering their "chlorine affinity" (or "chlorophilicity") and the alternation of their Lewis acidity (electrophilicity) in the presence of an electron-donor: Recently, Aoshima et al. have reported that, in the ionization of a dormant poly(VE)–Cl terminal, the "chlorine affinity" or "chlorophilicity" is greater for $SnCl_4$ than for $EtAlCl_2$.[18] In the polymerization of AzVE, the electron-rich pendent azide group (either in monomer or in polymer) should interact with a Lewis acid, to in-situ weaken the acidity and thereby to require a higher amount of the catalyst.[19] Therefore, though both $SnCl_4$ and $EtAlCl_2$ are regarded as strong or electron-deficient Lewis acids in cationic polymerization, they may work as Lewis acids too mild to catalyze an efficient ionization of a terminal carbon–chlorine bond as well as its fast exchange equilibirum with the active cationic species (i.e., a lower reaction rate and a broader MWD).

The second factor is most likely the case for $EtAlCl_2$, which induced the slow and poorly controlled polymerization. For $SnCl_4$, however, its chlorophilicity is high enough to overcome its reduced acidity and in turn to mediate a fast and efficient dissociation of the terminal carbon–chlorine bond, albeit it is employed at a high concentration.

2. Cationic Polymerization of AzVE with $SnCl_4$

Effects of the $SnCl_4$ concentration were thus examined (Table 1). For two initiators of different reactivity (CEVE-HCl < IBVE-HCl), the catalyst concentration was accordingly higher for the former (> 10 mM; entry 1-3) than for the latter (< 5.0 mM; entry 4-5). At the highest concentration (100 mM; entry 1), the observed M_n (< 1000) was much lower than the calculated value from the monomer/initiator feed ratio and monomer conversion, which would be caused by an undesired initiation from impurity water and/or by the chain-transfer via β-H elimination, both facilitated by the excess catalyst (or too much ionization of the dormant end). Under these conditions, the polymerization solution was turbid, indicative of a considerable complexation of the tin catalyst by the azide group.

As the catalyst concentration was decreased, the polymerization decelerated, and too low of a dose (2.0 mM; entry 5) did not induce polymerization. In the intermediate range (5.0–20 mM), reasonably controlled molecular weights[20] and fairly narrow MWDs (M_w/M_n ~ 1.3) were achieved. Figure 2 shows the conversion–M_n plot and the SEC curves of produced polymers with 10 mM of $SnCl_4$. The molecular weight increased linearly in proportion to conversion, and the MWD was consistently narrow and shifted to high molecular weight.

Table 1. Cationic polymerization of AzVE with $SnCl_4$[a]

Entry	Initiator	[$SnCl_4$] (mM)	Time	Conv. (%)	M_n	M_w/M_n
1	CEVE-HCl	100	1 min	90	870	1.22
2		20	3 min	92	3,500	1.33
3		10	5 min	91	3,400	1.26
4	IBVE-HCl	5.0	2 h	100	3,500	1.31
5		2.0	24 h	5.4	—	—

[a] $[AzVE]_0$ = 200 mM, $[Initiator]_0$ = 10 mM in CH_2Cl_2 at –78 °C.

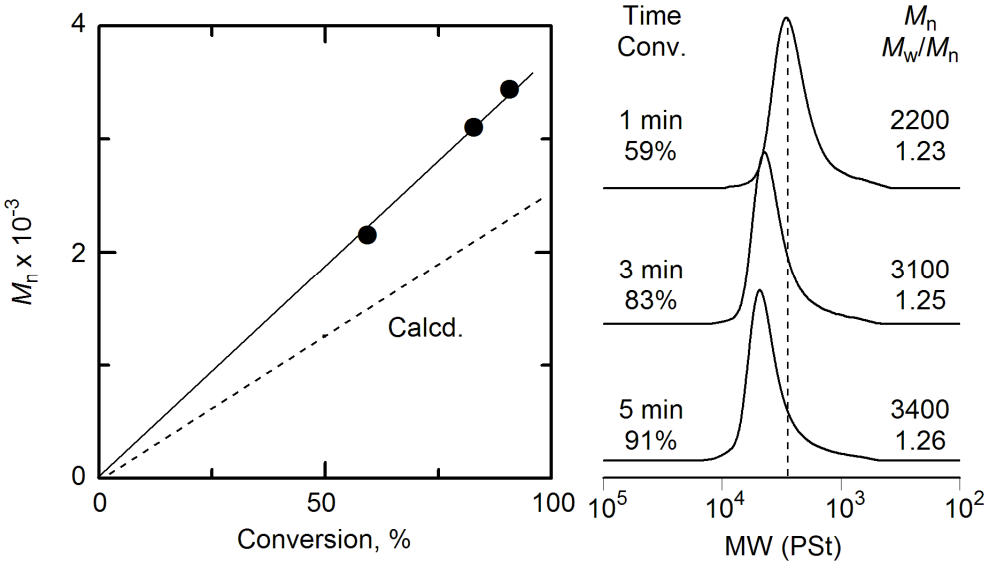


Figure 2. Conversion-M_n plot and SEC curves for living cationic polymerization of AzVE with CEVE-HCl/$SnCl_4$ in CH_2Cl_2 at –78 °C: $[AzVE]_0$ = 0.20 M; $[CEVE\text{-}HCl]_0$ = 10 mM; $[SnCl_4]_0$ = 10 mM.

The product was analyzed by MALDI-TOF-MS (Figure 3). Although the signal-noise ratio was low, only a single series of peaks was observed at an almost constant interval close to the monomer mass, 113.2. The absolute *m/z* value of each peak corresponded to the mass of the poly(AzVE) with an initiator fragment [CH_3–$CH(OC_2H_4Cl)$–] at the α-end and a methoxy terminal (–OCH_3) at the ω-end derived from the methanol quencher. These results indicate that the polymerization was well controlled without side reactions.

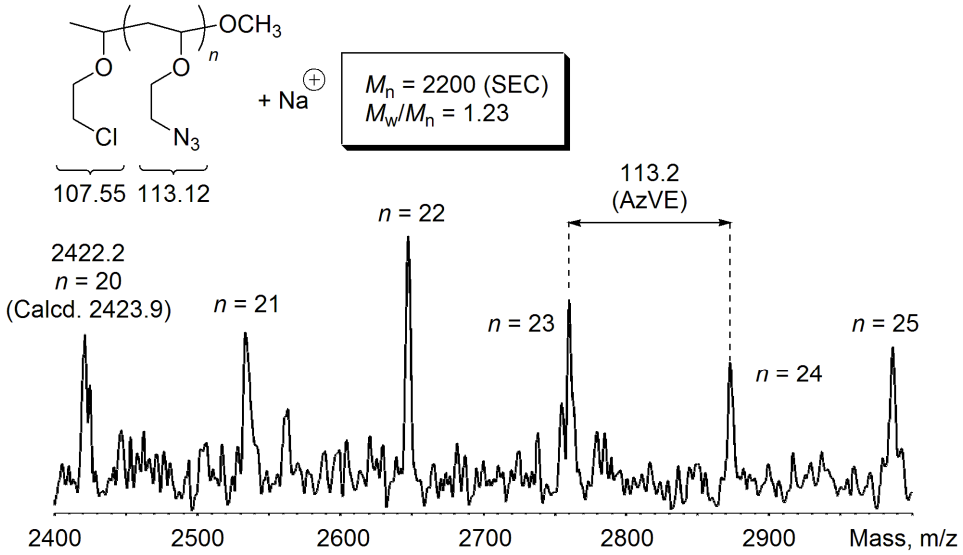


Figure 3. MALDI-TOF-MS spectrum of poly(AzVE) obtained with CEVE-HCl/$SnCl_4$ in CH_2Cl_2 at –78 °C (conversion 59%). Condition: see caption of Figure 2.

3. Block Polymerization

To further examine the "living" nature of the polymerization, block polymerization with CEVE was conducted (Figure 4). When the first-stage polymerization of AzVE was almost completed (conversion ~90%), neat CEVE was added to the reaction solution. The second monomer was also smoothly consumed, and its conversion reached 88% in an additional 90 min. The SEC curves shifted to higher molecular weight, while keeping narrow distributions ($M_w/M_n \approx 1.2$), indicating an almost quantitative block copolymerization.

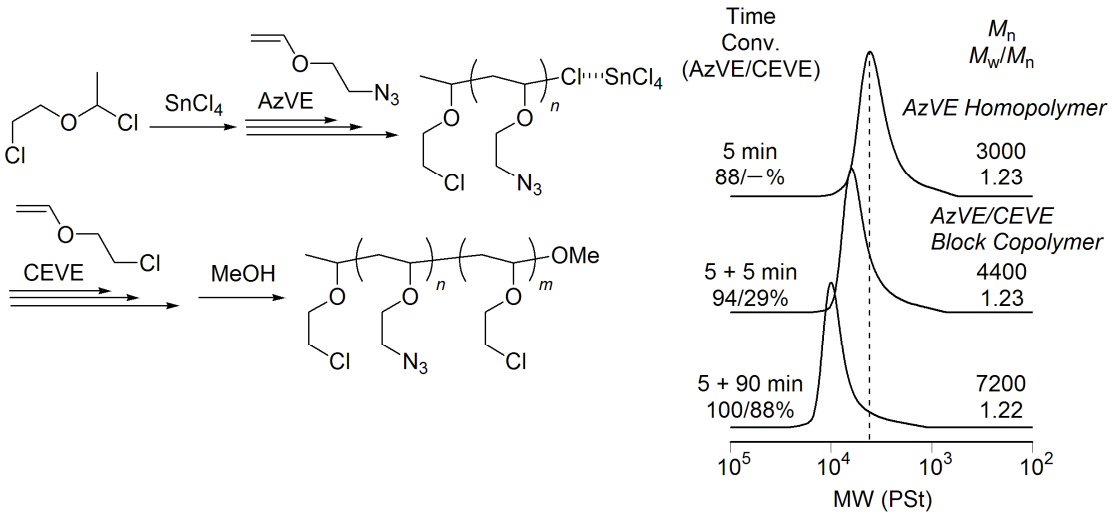


Figure 4. Block copolymerization of AzVE and CEVE with CEVE-HCl/$SnCl_4$ in CH_2Cl_2 at –78 °C: $[AzVE]_0 = [CEVE]_{add} = 0.20$ M; $[CEVE\text{-}HCl]_0 = 10$ mM; $[SnCl_4]_0 = 10$ mM.

4. Staudinger Reduction

With a controlled poly(AzVE) sample thus obtained with the CEVE-HCl/$SnCl_4$ system [M_n = 2,750, DP_n = 23.1 (by ^{1}H NMR)], the transformation of the azide pendent groups into amines was then examined by the Staudinger reduction. Triphenylphosphine (PPh_3), two equivalents to the pendent azide groups, was added into a polymer solution in THF/methanol, and then a small amount of water (5 vol-%) was injected. After stirring at room temperature for 24 h, the polymer was precipitated into toluene, and the recovered product was analyzed by ^{1}H NMR (Figure 5). The azide peak at 3.3 ppm (-C*H*$_2$-N_3, *e*; Figure 5a), abundant in the precursor, completely disappeared upon the treatment, and a new peak appeared at 2.8 ppm, attributable to a pendent amine (-C*H*$_2$-NH_2, *e'*; Figure 5b). The integration ratios of the main polymer peaks (*b*-*e*, *b'*-*e'*) to the α-end (*a*, *a'*) were consistent with the quantitative transformation of azide to amine without changing the degree of polymerization (DP_n) or the overall structures of the polymers. Thus, the transformation was quantitative and highly selective even under mild conditions, in sharp contrast to the conventional amination (hydrazinolysis) of phtalimides, which requires high temperature and toxic hydrazine.

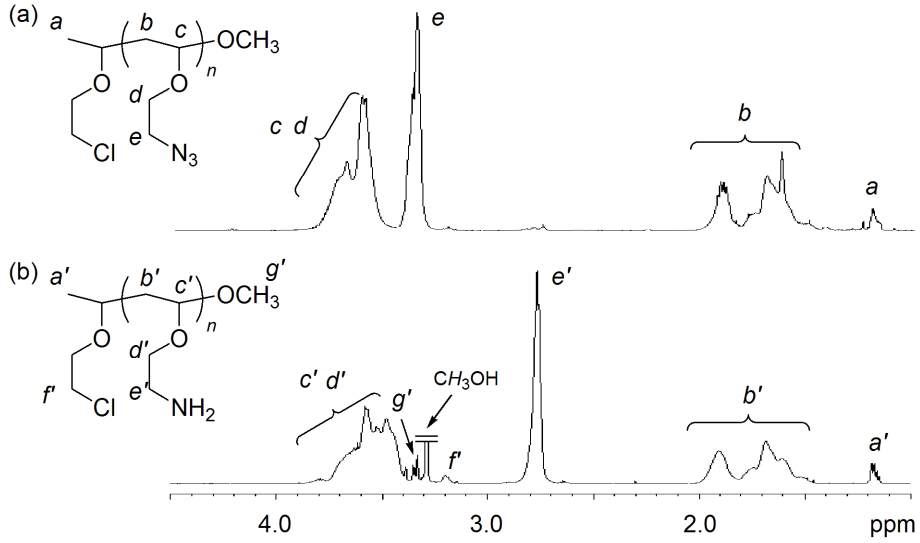


Figure 5. ^{1}H NMR spectra of (a) poly(AzVE) (in $CDCl_3$), and (b) polymer obtained by Staudinger reduction for amination (in CD_3OD).

5. CuAAC Functionalization

Finally, the author performed CuAAC for poly(AzVE) to demonstrate versatile functionalization of the azide side chain. Two alkynes with hydroxy (propargyl alcohol) and carboxylic group (4-pentynoic acid) were employed as reactants, in conjunction with CuBr (without a ligand)[11a] as catalyst in DMSO.[21] If the "click" reactions successfully proceed, the azide should be converted into a triazole carrying a hydroxyl or a carboxyl function.

After the reaction at room temperature for 24 h, the product was recovered via reprecipitation into toluene, as with the Staudinger reduction. ^{1}H NMR analyses confirmed quantitative transformations with both alkynes: the azido-methylene at 3.3 ppm (*e*, Figure 6a) disappeared, and instead the characteristic triazole methyne emerged around at 7.8 ppm

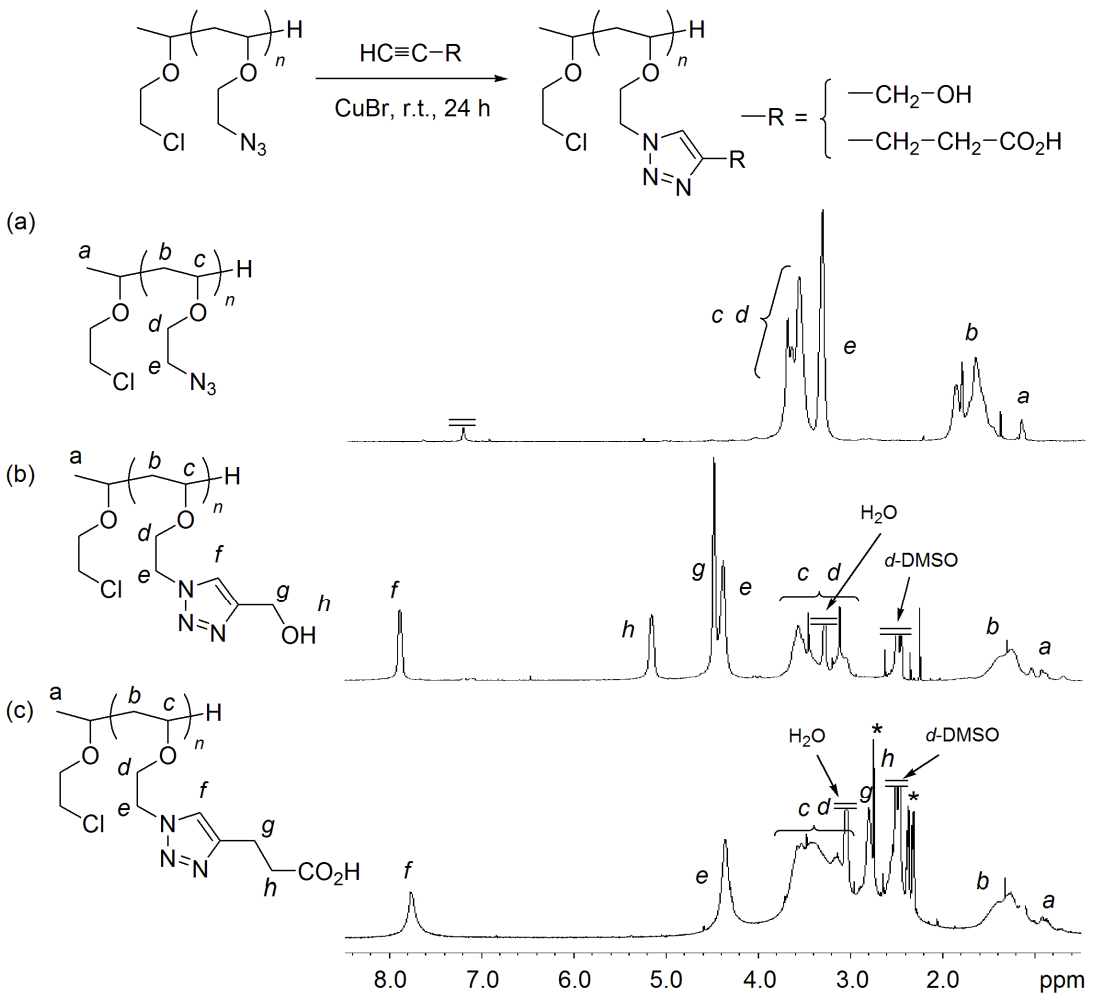


Figure 6. ^{1}H NMR spectra of poly(AzVE) [(a), in $CDCl_3$] and converted polymers by CuAAC with propargyl alcohol [(b), in DMSO-d_6] and 4-pentynoic acid [(c), in DMSO-d_6]. *from unreacted 4-pentynoic acid.

(Figures 6b and 6c). For the reaction with propargyl alcohol, in addition, distinctive peaks of the hydroxyl methyl (-C*H*$_2$OH) were observed at 4.5 and 5.2 ppm (*g* and *h*, Figure 6b) whose relative intensity is consistent with the unaltered main chain. In the case with 4-pentynoic acid, a broad carboxyl peak was certainly observed at 10-14 ppm, but unfortunately it was ambiguous whether this originated from the polymer side chains or from the unreacted substrate.[22] However, as a peak from the methylene next to the ring (triazole-C*H*$_2$-CH$_2$-COOH) was observed at 2.8 ppm (*g*, Figure 6c) along with the triazole methyne (*f*), the carboxyl introduction should be quantitative.

Conclusion

The author first achieved living cationic polymerization of azide-carrying vinyl ether (AzVE) with the $SnCl_4$/VE-HCl adduct initiating system, to give not only homopolymers but block polymers with CEVE. The azide pendent groups therein were quantitatively and mildly converted into amine, hydroxyl, and carboxyl by the Staudinger reduction or CuAAC. This system will open a new way to construct functionalized VE polymers. The method will be extended into the precision synthesis of more complicated structures in conjunction with other controlled polymerizations.

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(21) As such functional groups possibly cause some undesirable reaction with the methoxy capped acetal terminal to make the structural analysis complicated, the author used hydrogen terminal polymer.

(22) With 4-pentynoic acid, unreacted substrate was obviously remained even after the reprecipitation, as observed in the NMR spectrum. The copper catalyst or the related residue would be dangled on the pendant carboxyl groups of the resultant polymer, and the unreacted acid be also attached through coordination on the copper. This would cause the difficulty in the removal.

PART II

Template Initiator-Assisted Radical Reactions toward Sequence-Regulated Polymerization

Chapter 3

Template-Assisted Radical Addition: Ionic Recognition with Amine-Carrying Template Initiator

Abstract

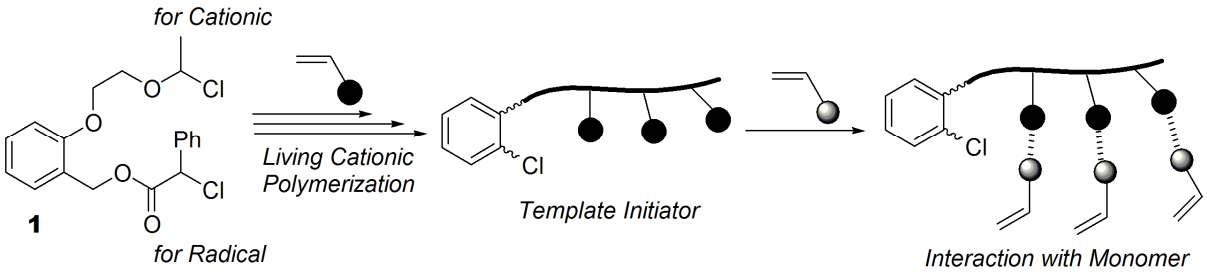
A ruthenium(II)-catalyzed highly selective and quantitative radical addition of an alkene (methacrylic acid; MAA) has been achieved by using a template halide (**2**) where an amine group is built-in as a recognition site for the carboxyl group of the substrate. The specific ionic binding of MAA by the amine template (1:1 mole ratio) led to preferential formation of the MAA–**2** 1:1 adduct, whereas a similar halide without a template induced MAA oligomerization even in the presence of an externally added amine. A competitive radical addition of MAA versus its ester form (methyl methacrylate; MMA) on the halide further demonstrated that the substrate selectivity [k'_{MAA}/k'_{MMA}] for **2** is enhanced over 10 times by the intramolecular introduction of the template, relative to for the non-template halide. These specificities are most likely triggered by the specific interaction (recognition) of the carboxyl group in MAA via the acid-selective template amine, implanted in the close vicinity of the radical addition site in **2**. These results intimate possibility of control in repeat-unit sequence in precision polymerization.

Introduction

In recent years, template-assisted synthesis has been directed toward perfecting structural control of molecules, as inspired by biological macromolecules (typically, DNA and proteins) that are finely defined in terms of not only molecular weight but "sequence" of repeat units or functionality along the backbone.[1] For such systems, one needs to achieve at least two targets: a controlled synthetic reaction of perfect chemo- and regio-selectivity and a method (or a reaction field) where a particular substrate (monomer) is specifically recognized, allowing structural input to be transcribed and expressed. For the latter, a promising approach is a template-assisted system in which target substrates are efficiently recognized via such interactions as hydrogen-bonding, coordination, or ionic or hydrophobic interactions for sequence expression.

For the former target, Sawamoto and co-workers have pioneered two precision polymerizations, Lewis acid-catalyzed living cationic[2] and metal-mediated living radical[3] polymerizations, both of which allow syntheses of well-defined polymers with controlled molecular weight and narrow molecular weight distribution. Notably, the radical system is important in terms of the wide variety of applicable monomers and tolerance of functional groups. Nevertheless, the sequence of constitutional repeat units along the polymer backbone is far more challenging and to date has not been controlled even in these living processes, except for rather simple AB- and ABC-alternating copolymerizations.[4] Previous attempts at so-called template polymerizations are abundant but, to the author's knowledge, without remarkable sequence control.[5]

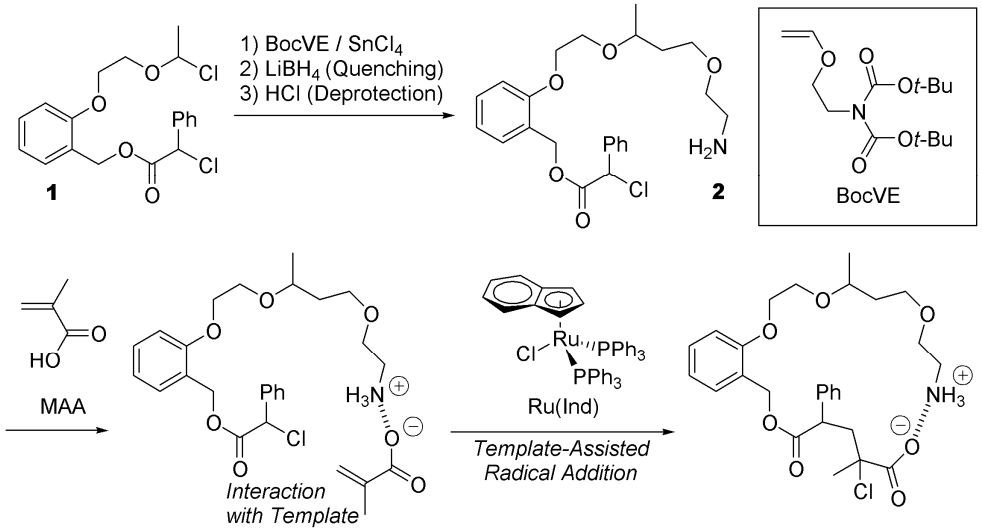
This chapter reports the author's initial approach toward the sequence control in living radical polymerization via template-bearing initiators coupled with metal catalysts; and the



Scheme 1. Template initiators from a heterobifunctional halide for template-assisted living radical polymerization.

synthesis of the "template" initiator is based on living cationic polymerization (Scheme 1). Prior to sequence control in polymerization, the author examined the template-effect for metal-catalyzed radical addition (Kharash reaction),[6] a model for living radical polymerization (Scheme 2). Though conventional radical reactions are performed with an excess amount of a halide over an alkene substrate in order to prevent oligomerization, the author herein deliberately performed a radical addition under equimolar conditions ($[\text{halide}]_0 = [\text{substrate alkene}]_0$), to demonstrate the adequacy and potential of this template model.

Like the transcription and expression of sequence information in natural polymers, the introduction of a template into a polymerization field would provide clues about sequence control in artificial polymer synthesis. For this purpose, the author has designed *template* initiators (**2**) in which a template unit is built into a relatively rigid framework, allowing a particular monomer to be recognized and thereby specifically incorporated into the growing chain via living radical propagation (Scheme 1). To construct such a model system, the author employed a new heterobifunctional halide (**1**) derived from 2-hydroxybenzyl alcohol, in which two different initiating sites (C–Cl bonds) are placed *ortho* to each other. The haloether part is for living cationic polymerization to generate an oligomeric template component, whereas the haloester part is for a subsequent living radical polymerization to be regulated by the neighboring template segment placed in the hairpin-shaped rigid framework. In the template segment, the author introduced an oligomeric unit of pendant aminoethyl group(s) that would selectively recognize acid-bearing monomers (Scheme 2).



Scheme 2. Radical addition of MAA with the template halide.

Experimental Section

Materials

2-Hydroxybenzyl alcohol (2-HBA; Aldrich; 99%), 2-chloroethyl vinyl ether (CEVE; Tokyo Kasei; >97%), potassium hydroxide (Wako; >85%), and *n*-Bu_4NBr (Tokyo Kasei; >99%) were used as received. α-Chlorophenyl acetyl chloride (Aldrich; 90%) was distilled under reduced pressure before use. Triethylamine was dried overnight over calcium chloride and distilled before use.

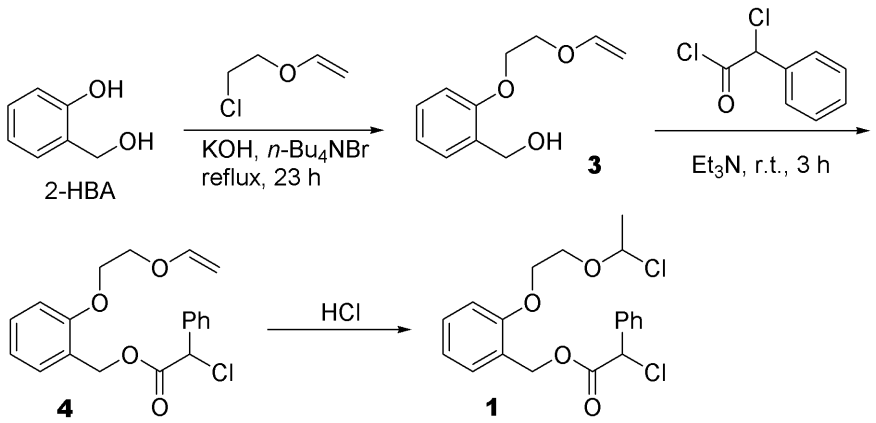
Di-*tert*-butyl {*N*-[2-(vinyloxy)ethyl]imido}dicarboxylate (BocVE) was prepared according to literature.[7] Chromatography-grade dichloromethane (CH_2Cl_2; solvent) and toluene (solvent) were purified to moisture- and oxygen-free by passing through a purification column (Solvent Dispensing System; Glass Contour) before use. $SnCl_4$ (1.0 M in CH_2Cl_2; Aldrich), *n*-Bu_4NCl (Tokyo Kasei; >98%), $LiBH_4$ (2.0 M in THF; Aldrich), and HCl (4.0 M in 1,4-dioxane) were used as received.

Methacrylic acid (MAA; Tokyo Kasei; >99%) was dried overnight over calcium chloride and distilled under reduced pressure before use. Methyl methacrylate (MMA; Tokyo Kasei; >99%) was dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. $Ru(Ind)Cl(PPh_3)_2$ (Strem; >98%) was used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere (H_2O < 1 ppm; O_2 < 1 ppm). Ethyl 2-chloro-2-phenylacetate (ECPA; Aldrich; >97%) was distilled under reduced pressure before use. Butylamine (*n*-$BuNH_2$; Tokyo Kasei; >99%) was degassed by bubbling dry nitrogen for more than 15 min before use. Tetralin (1,2,3,4-tetrahydronaphtalene; ^1H NMR internal standard for MAA and MMA) was dried overnight over calcium chloride and doubly distilled from calcium hydride under reduced pressure before use.

The precursor initiator (**1**) was synthesized via three steps as shown below (Scheme 3).

{2-[2-(Vinyloxy)ethoxy]phenyl}methanol (3)

2-HBA (10 g, 80 mmol) was dissolved in 15 ml of KOH_{aq} (22 wt-%). To the solution were added CEVE (12.2 mL, 120 mmol) and *n*-Bu_4NBr (0.54 g; 1.66 mmol), and the mixture was heated to reflux for 24 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with water for three times, and evaporated to dryness under reduced pressure. The crude product was purified by silica-gel column chromatography [eluent: chloroform/MeOH,



Scheme 3. Synthesis of a hetero bifunctional halide, **1**.

100/3 (v/v)]. The isolated product was dissolved in CH_2Cl_2 (300 mL), dried with Na_2SO_4 overnight, and evaporated to dryness under reduced pressure to give **3**: yield, 68%. ^{1}H NMR ($CDCl_3$): δ 7.26 (m, 2H, Ar-*H*), 6.96 (t, 1H, Ar-*H*), 6.90 (d, 1H, Ar-*H*), 6.52 (dd, 1H, CH_2=C*H*-), 4.67 (d, 2H, Ar-CH_2-OH), 4.25-4.06 (m, 6H, CH_2=CH-O-CH_2-CH_2-), 2.75 (t, 1H, -O*H*). ^{13}C NMR ($CDCl_3$): δ 156.62, 129.84, 129.03, 128.89, 121.29, 111.77 (-O-C_6H_4-CH_2-), 151.73 (CH_2=*C*H-O-), 87.38 (*C*H_2=CH-), 66.78 (CH_2=CH-O-CH_2-*C*H_2-O-), 66.33 (CH_2=CH-O-*C*H_2-CH_2-O-), 62.16 (Ar-*C*H_2-OH).

2-[2-(Vinyloxy)ethoxy]benzyl 2-chloro-2-phenylacetate (4)

To a solution of **3** (10.5 g, 54.3 mmol) and triethylamine (9.86 mL, 81.4 mmol) in dry THF (280 mL) at 0 °C was slowly added α-chlorophenyl acetyl chloride (8.14 ml, 51.5 mmol) dropwise under dry argon. The solution was stirred at 0 °C for 30 min and then at room temperature for an additional 3 h. The reaction was quenched with 250 mL of water. The quenched solution was diluted with CH_2Cl_2 (500 mL), washed with water for three times, and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography (eluent: chloroform). The product was dissolved in CH_2Cl_2 (300 mL), dried with Na_2SO_4 overnight, and evaporated to dryness under reduced pressure to give **4**: yield, 73%. ^{1}H NMR ($CDCl_3$): δ 7.50 (m, 2H, Ar-*H*), 7.36 (m, 3H, Ar-*H*), 7.30-7.22 (m, 2H, Ar-*H*), 6.94-6.88 (m, 2H, Ar-*H*), 6.48 (dd, 1H, CH2=C*H*-), 5.41 [s, 1H, Ar-C*H*(Cl)-CO], 5.28 (q, 2H, Ar-CH_2-O), 4.23 (dd, 1H, *cis*CH_2=CH-), 4.15 (t, 2H, Ar-O-CH_2-), 4.06 (dd, 1H, *trans*CH_2=CH-), 3.94 (t, 2H, CH_2=CH-O-CH_2-). ^{13}C NMR ($CDCl_3$): δ 168.1 [-O-*C*O-CH(Cl)-], 156.5, 135.8, 129.8, 129.7, 129.2, 128.7, 128.0, 123.8, 120.9, 111.7 (-C_6H_4-O-CO-CH(Cl)-C_6H_5), 151.7 (CH_2=*C*H-O-), 87.1 (*C*H_2=CH-), 66.8

(-CH_2-*C*H_2-O-C_6H_4-), 66.4 (CH_2=CH-O-*C*H_2-), 63.6 [-CO-*C*H(Cl)-C_6H_5], 59.1 (-C_6H_4-*C*H_2-O-).

2-[2-(1-Chloroethoxy)ethoxy]benzyl 2-chloro-2-phenylacetate (1)

Compound **1** was prepared by bubbling dry HCl gas into a CH_2Cl_2 solution of **4**, as reported.[8]

Precursor (5) of the Template Initiator

Living cationic "addition" of BocVE was carried out under dry argon in baked glass flasks equipped with a three-way stopcock. The reaction was initiated by adding a solution of $SnCl_4$/*n*-Bu_4NCl (in CH_2Cl_2) into a mixture of **1** and BocVE in CH_2Cl_2 at –78 °C by a dry syringe ($[\mathbf{1}]_0$ = 10 mM; $[BocVE]_0$ = 50 mM; $[SnCl_4]_0$ = 10 mM; $[n\text{-}Bu_4NCl]_0$ = 5.0 mM). After an hour, $LiBH_4$ (3 equiv. for **1**) was added, and the reaction mixture was stirred at room temperature for an additional 30 min, followed by addition of water was to decompose the residual $LiBH_4$. The quenched reaction mixture was diluted with *n*-hexane, washed with water, evaporated under reduced pressure, and finally vacuum dried: crude **5** (100% conversion). The crude product was further purified by preparative size-exclusion chromatography (column, Shodex KF-5001; eluent, THF): isolated yield, 60%. ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 2H), 7.36 (m, 3H), 7.30-7.18 (m, 2H), 6.89 (m, 2H), 5.39 (s, 1H), 5.24 (q, 2H), 4.03 (m, 2H), 3.75-3.50 (m, 9H), 1.74-1.63 (m, 2H), 1.48 (s, 18H), 1.15 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 168.30, 156.87, 152.81, 136.00, 129.87, 129.59, 129.35, 128.92, 128.16, 123.77, 120.72, 111.75, 82.33, 73.22, 69.05, 67.98, 67.70, 66.98, 63.77, 59.26, 45.57, 36.95, 28.19, 19.94.

Template Initiator (2).

The precursor **5** was treated with HCl (4 M in 1,4-dioxane; 200 equiv. to the Boc group in **5**) for 24 h at room temperature with stirring. The product was isolated by evaporation, dissolved in 1,4-dioxane, treated with $NaHCO_3$ aqueous solution for neutralization, and then isolated by evaporation. Chloroform was added to the product and the soluble part was isolated by filtration. Then the filtrate was evaporated to dryness to obtain **2**: yield, 89%. ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 2H), 7.34-7.18 (m, 5H), 6.89 (m, 2H), 5.40 (s, 1H), 5.30 (m, 2H), 4.01 (m, 2H), 3.72-3.48 (m, 7H), 2.98 (s, 2H), 1.69 (m, 2H), 1.13 (m, 3H). LR MS (ESI) (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{30}ClNO_5$, 436.18; found, 436.0.

Radical Addition

The reaction was carried out under dry argon in baked and sealed glass tubes. A typical example with the template initiator **2** is given below: In a 50-mL round-bottomed flask was placed **2** (0.085 g), and toluene (3.42 mL), tetralin (0.100 mL), solutions of MAA (1 M in toluene; 0.195 mL) and MMA (1 M in toluene; 0.195 mL) were added sequentially in this order at room temperature under dry argon. The resulting mixture was totally transferred by syringe under dry argon to a 50-mL round-bottomed flask containing $Ru(Ind)Cl(PPh_3)_2$ (12.1 mg). The total volume of the reaction mixture was thus 3.90 mL. Immediately after mixing, aliquots (0.40 mL each) of the solution were injected into baked glass tubes, which were then sealed and placed in an oil bath kept at 80 °C. At predetermined intervals, the reaction was terminated by cooling the reaction mixtures to –78 °C. Monomer conversion was determined from the concentration of residual monomer measured by ^{1}H NMR with tetralin as an internal standard.

Measurements

^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer, operating at 500.16 MHz. Electrospray-ionization mass spectra (ESI-MS) were measured on a Waters Quattro micro API.

Results and Discussion

1. Synthesis of Template Initiators

For the template introduction, the author first performed living cationic polymerization from the precursor **1** using di-*tert*-butyl {*N*-[2-(vinyloxy)ethyl]imido}dicarboxylate (BocVE), a vinyl ether with a protected amino pendent function.[7] The reaction was catalyzed with $SnCl_4$ in conjunction with *n*-Bu_4NCl as an additive.[9] As shown in Chapter 1, some specific conditions turned out to allow a selective single monomer addition to the cationic site generated from the haloether in **1**: $[BocVE]_0$ = 50 mM; $[\mathbf{1}]_0$ = 10 mM; $[SnCl_4]_0$ = 10 mM; $[n\text{-}Bu_4NCl]_0$ = 5.0 mM in CH_2Cl_2 at –78 °C (**5**; Figure 1a). Quenching of the cationic intermediate with $LiBH_4$, followed by deprotection of the Boc site with excess HCl to afford the corresponding amine, gave the target template initiator **2**, as verified by ^{1}H NMR analysis (Figure 1b). Importantly, the haloester moiety in **1** remained intact during these addition and work-up steps.

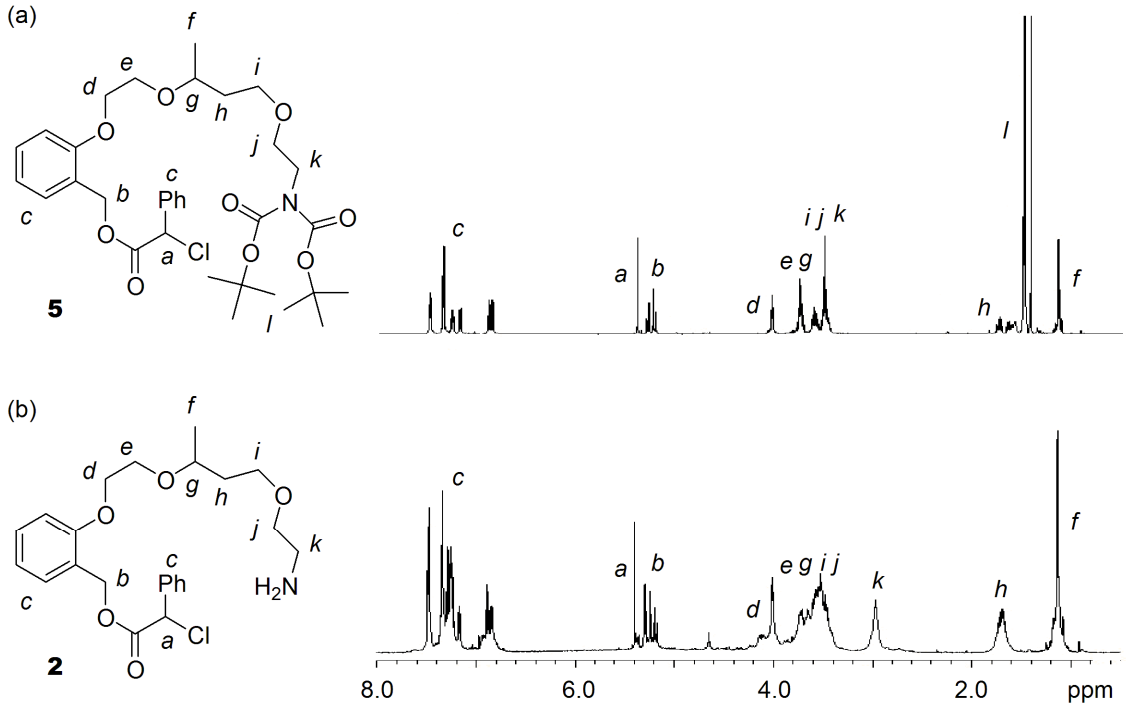


Figure 1. ^{1}H NMR spectra (in $CDCl_3$) of (a) the precursor halide, **5**, and (b) the template halide, **2**.

2. Selective Radical Addition via Template Recognition

With the template-bearing halide **2**, radical addition of methacrylic acid (MAA) was initiated in toluene at 80 °C (1:1 **2**/MAA molar ratio) with the ruthenium complex catalyst [Ru(Ind)Cl(PPh_3)$_2$; Ind = η^5-C_9H_7], one of the most useful catalysts for metal-catalyzed living radical polymerization[10] and radical addition.[11] Through its acid function, MAA is expected to be "recognized" by the amine template located in the vicinity of the initiating site.

MAA was consumed at almost the same rate as the halide, as monitored by ^{1}H NMR spectroscopy, suggesting the predominant formation of a 1:1 adduct, rather than oligomeric products (Figure 2a). On average, the isolated product contained 1.22 units of MAA per haloester moiety in **2** (Figure 3). Furthermore, the molecular mass determined by electrospray ionization mass spectrometry (ESI-MS) was 522.0, close to 522.2 for $[M+H]^+$ of the adduct.

In sharp contrast, in a control radical addition with a haloester without a built-in template amino group [ethyl 2-chloro-2-phenylacetate (ECPA)] in the presence of an externally added amine (*n*-$BuNH_2$), MAA was consumed much faster than the initiating site, resulting in oligomers rather than a 1:1 adduct (Figure 2b). Actually, ESI-MS analysis detected only a minor amount of the adduct.

From these results, the preferential formation of the 1:1 addition is most likely triggered by the specific interaction (recognition) of the template amine with the acid in MAA, which brings the monomer into the close vicinity of the radical site in **2**. Separate ^{1}H NMR experiments also confirmed the specific acid-base interaction between MAA and the amine in **2** (Figure 4).

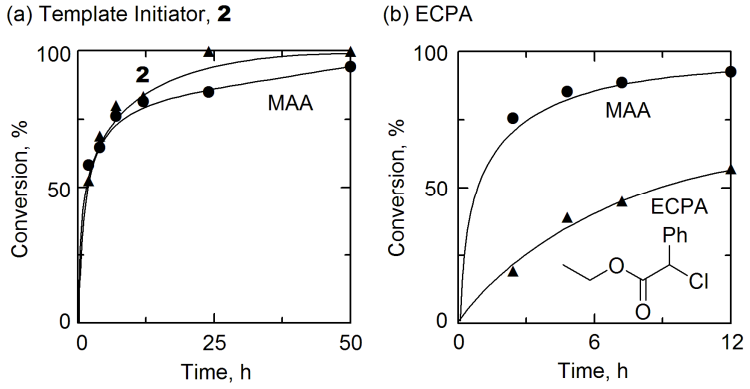


Figure 2. Time-conversion curves in radical addition of a halide (C-Cl compound) to MAA in toluene at 80 °C, based on consumption of C-Cl bond in halide (▲) and C=C bond in MAA (●). $[halide]_0 = [MAA]_0 = 100$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[n\text{-}BuNH_2]_0$ = (a) 0 or (b) 100 mM.

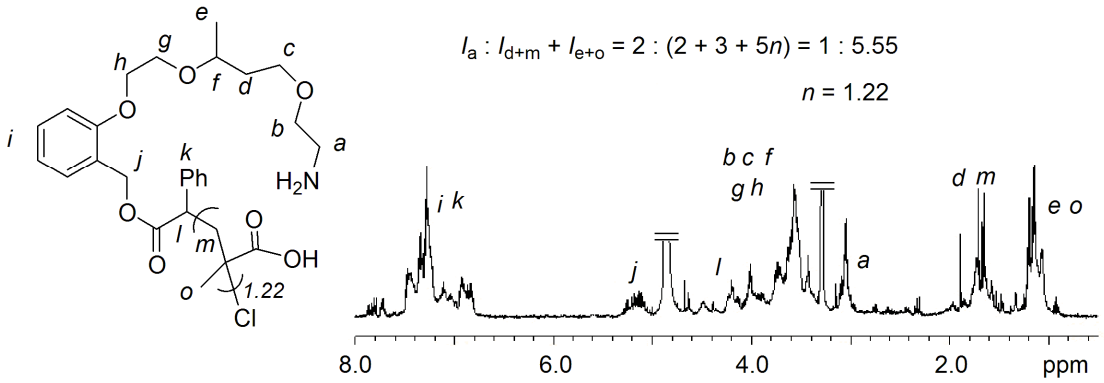


Figure 3. ^{1}H NMR spectra (in CD_3OD) of the product obtained by template initiator-assisted radical addition of MAA in toluene at 80 °C: $[MAA]_0$ = 100 mM; $[\mathbf{2}]_0$ = 100 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 4.0 mM. The average number of MAA units per halide was calculated from the integral ratio of *a*, *d*, *e*, *m*, and *o*.

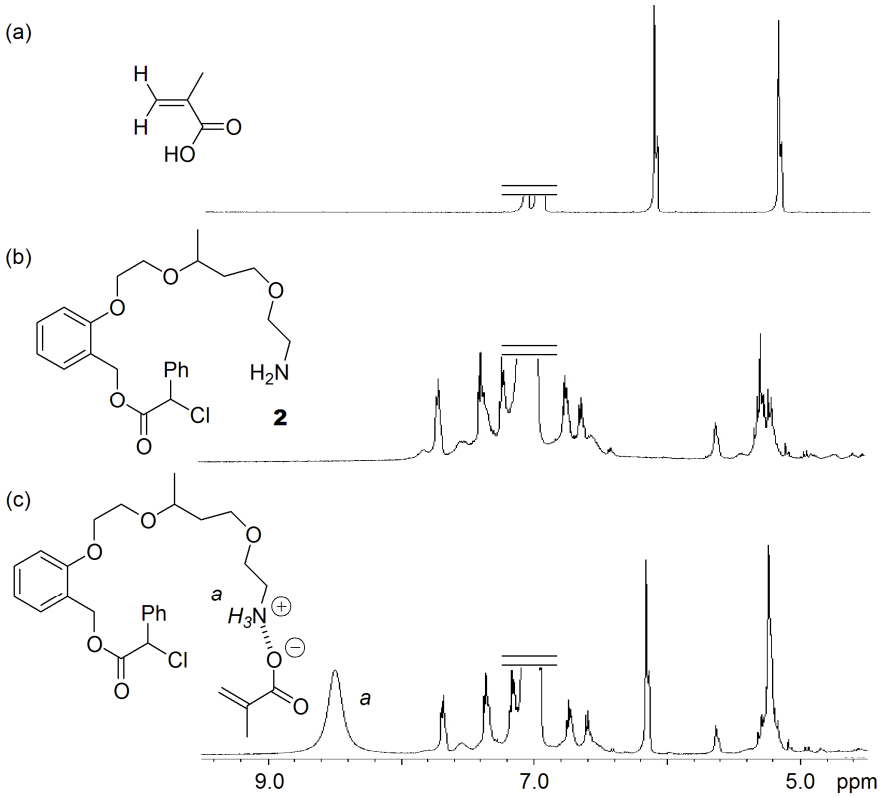


Figure 4. ^{1}H NMR spectra of MAA with amine-template halide (**2**) in toluene-d_8 at room temperature: (a) [MAA] = 100 mM; (b) [**2**] = 100 mM; (c) [**2**] = [MAA] = 100 mM.

3. Competitive Radical Addition via Template Recognition

To further prove the template effect, the author examined the competitive radical addition to **2** of MAA and methyl methacrylate (MMA) in toluene at 80 °C [1:1:1 MAA/MMA/**2** molar ratio, $Ru(Ind)Cl(PPh_3)_2$ catalyst]. As shown in Figure 5a, the acid monomer reacted much faster than the ester counterpart. More quantitatively, the initial first-order rate constant (k') was ~40 times greater for the acid form: $k'_{MAA} = 0.679\ h^{-1}$; $k'_{MMA} = 0.0184\ h^{-1}$; $k'_{MAA}/k'_{MMA} = 36.9$ (Figure 5c).

When the MAA/MMA competitive addition was performed under the identical conditions but with a template-free initiator (ECPA/*n*-$BuNH_2$), MAA reacted just a little faster than MMA [$k'_{MAA}/k'_{MMA} = 2.99$] (Figure 5b, c). Therefore, in terms of substrate selectivity expressed via the rate ratio, the template recognition enhanced MAA incorporation by more than 10 times relative to MMA. Such a template effect was also observed in other solvents (Table 1). Because the recognition is based on ionic interactions, the template effect would be sensitive to solvent polarity. The concentrations of substrates would also be crucial in the selective addition, where oligomerization might also occur. In fact, additional experiments indicated that less polar solvents (e.g., toluene) and lower concentrations (< 50 mM) facilitate the specific monoaddition (Table 1 and 2).

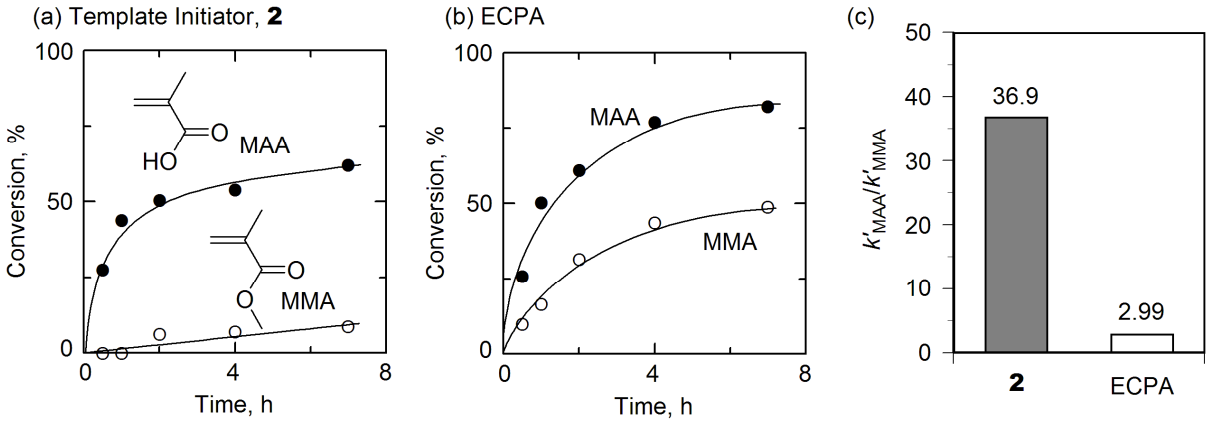


Figure 5. (a, b) Time-conversion curve with (a) template (**2**) and (b) ECPA, and (c) comparison of reaction selectivity determined by kinetic analysis between **2** and ECPA for competing radical addition with MAA and MMA in toluene at 80 °C: $[MAA]_0 = [MMA]_0 = [\mathbf{2}\text{ or ECPA}]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[n\text{-}BuNH_2]_0 = 0$ or 50 mM (for ECPA).

Table 1. Template-assisted competitive radical addition of MAA and MMA with concentration of 50 mM.[a]

Entry	Halide/Additive	Solvent	k'_{MAA} (h^{-1})	k'_{MMA} (h^{-1})	Selectivity[b]	Template Effect[c]
1	**2**	toluene	0.679	0.0184	36.9	12.3
2	ECPA/*n*-$BuNH_2$		0.657	0.220	2.99	
3	**2**	THF	0.182	0.0375	4.85	4.11
4	ECPA/*n*-$BuNH_2$		0.511	0.430	1.18	
5	**2**	DCE[d]	0.575	0.338	1.70	1.34
6	ECPA/*n*-$BuNH_2$		0.481	0.378	1.27	
7	**2**	EtOH	0.365	0.332	1.10	1.28
8	ECPA/*n*-$BuNH_2$		0.570	0.663	0.859	

[a] Reaction conditions: $[MAA]_0 = [MMA]_0 = [halide]_0 = 50$ mM $[n\text{-}BuNH_2]_0 = 0$ or 50 mM, $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM at 80 °C. [b] [Selectivity] = k'_{MAA}/k'_{MMA}. [c] The ratio of Selectivity between the template system and the corresponding non-template one; [Template Effect] = $[Selectivity]_2/[Selectivity]_{ECPA}$. [d] dichloroethane.

Table 2. Template-assisted competitive radical addition of MAA and MMA with concentration of 100 mM.[a]

Entry	Halide/Additive	Solvent	k'_{MAA} (h^{-1})	k'_{MMA} (h^{-1})	Selectivity[b]	Template Effect[c]
1	**2**	toluene	0.857	0.172	4.98	1.49
2	ECPA/*n*-$BuNH_2$		1.62	0.485	3.34	
3	**2**	THF	0.251	0.0897	2.80	2.15
4	ECPA/*n*-$BuNH_2$		0.463	0.357	1.30	
5	**2**	DCE[d]	0.254	0.0781	3.25	1.43
6	ECPA/*n*-$BuNH_2$		0.862	0.379	2.27	
7	**2**	EtOH	0.324	0.183	1.77	1.95
8	ECPA/*n*-$BuNH_2$		0.454	0.500	0.908	

[a] Reaction conditions: $[MAA]_0 = [MMA]_0 = [halide]_0 = 100$ mM $[n\text{-}BuNH_2]_0 = 0$ or 100 mM, $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM at 80 °C. [b] [Selectivity] = k'_{MAA}/k'_{MMA}. [c] The ratio of Selectivity between the template system and the corresponding non-template one; [Template Effect] = $[Selectivity]_2/[Selectivity]_{ECPA}$. [d] dichloroethane.

Conclusion

The author has demonstrated a quantitative and highly selective radical addition using a *template initiator* (**2**) containing a built-in amine group as the recognition site for the carboxyl group of the substrate in the close vicinity of the radical-forming site. Obviously, the designed placement of the recognition site is important, and it should also be noted that both the radical formation and the subsequent addition are finely controlled by the ruthenium complex, are free from undesirable side-reactions, and maximize the expression of template recognition. Another contributing factor is that the template initiator can be cleanly and conveniently synthesized by living cationic addition/polymerization reactions.

These results for the model addition reactions were extended to "template-assisted" polymerizations as described in Chapter 5.

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Chapter 4

Template-Assisted Radical Addition: Size-Selective Lariat Capture with Crown Ether Template Initiator

Abstract

Surprisingly high monomer selectivity was demonstrated in competitive radical addition with two kinds of methacrylates carrying sodium and ammonium cation. Crucial is size-specific recognition by lariat crown ether, embedded close to reactive halide in a designer template initiator. Especially, a combination with active ruthenium catalyst led to outstanding selectivity at low temperature. This template system will open the way to unprecedented sequence-regulated polymerization.

Introduction

The repeat-unit sequence, or monomer sequence, in proteins, genes, and other natural polymers is perfectly controlled by template molecules that carry predetermined sequence information through which substrate monomers are selectively recognized and connected ("sequence-regulated" polymerization). Sequence regulation in macromolecules implies that functional groups are placed at specific positions in a polymeric framework in order to express specific structures (conformations) and, in turn, particular functions. Thus, sequence-regulated macromolecules may work as autonomous single molecules that function without depending on assembly, aggregates, or other multimolecular architectures.

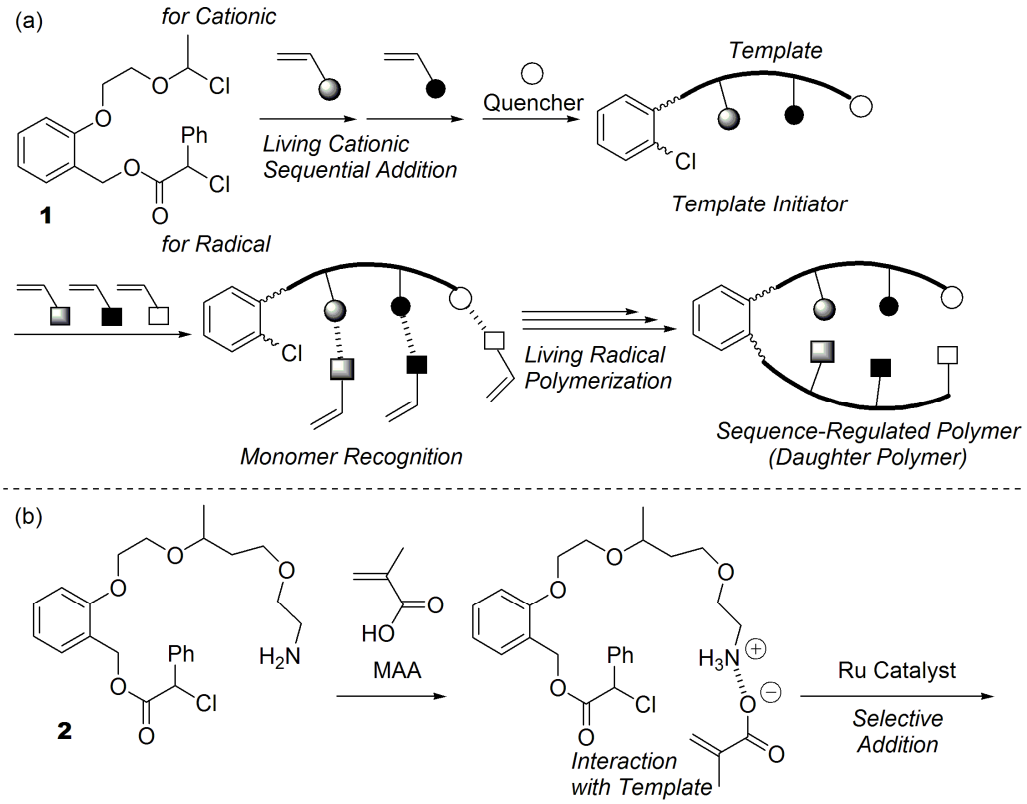
In contrast, with repeat units just randomly and averagely incorporated conventional synthetic polymers (e.g., plastics in solid state) mostly work as a multimoleular assemblies where simple amplification of intermolecular interactions among repeat units leads to superior mechanical properties. If the repeat-unit sequence is precisely controlled in artificial polymers, more sophisticated and perhaps unprecedented functions or properties may emerge, rivaling natural polymers. Therefore, sequence regulation is no doubt one of the most challenging subjects in contemporary polymer science, and some efforts, including the author's,[1-4] have now been directed to achieve this ultimate goal, although it has not yet been perfectly achieved.

In Chapter 3, the author started to examine the possibility of template-assisted[5] sequence regulation in chain-growth polymerizations (Scheme 1a).[3a] Therein the author utilized living polymerizations[6, 7] with "template initiators" that carry not only an initiating site but also a built-in template for sequence regulation. Such initiators may be synthesized from a heterobifunctional precursor (**1**) carrying two carbon–chlorine bonds *ortho* to each other in a rigid benzene framework: the haloether part is for embedding of a template molecule by living cationic polymerization or related reactions, and the haloester is for metal-assisted living radical propagation toward sequence control. Obviously, the close proximity of the template and the radical-growing sites within the rigid aromatic framework is designed to maximize the so-called "template effect" in sequence regulation.

As illustrated in Scheme 1a, living cationic polymerization is promising for template synthesis, as it allows precise single monomer-additions, as the author's group demonstrated;[2, 3b] moreover living radical polymerization is suitable for template-assisted propagation because the growing radicals are highly tolerant of polar functionalities within the monomers

and templates.

The author's first study in this lines[3a] in fact demonstrated a clear template effect in a selective radical addition[8] of methacrylic acid (MAA) over methyl methacrylate with an amino-functionalized template initiator (**2**; Scheme 1b). Specifically, the built-in amino group recognized the acid monomer over the ester derivative via ionic interaction and thereby enhanced the former's radical reactivity by more than an order of magnitude relative to the corresponding non-template systems. In order to achieve a truly sequence-controlled polymerization, however, this heralding finding should be generalized, i.e., the substrate–template "recognition combination" should be diversified beyond the acid–amine pair.



Scheme 1. (a) Conceptual sequence-regulated radical polymerization with a template initiator (**1**) carrying two reactive C–Cl bonds for living cationic and radical polymerizations; (b) Selective radical addition of MAA with an amino-functionalized template initiator (**2**) via ionic recognition.

Experimental Section

Materials

Heterobifunctional (radical/cationic) initiator **1** was prepared as reported in Chapter 3.[3a] Triethylamine was dried overnight over calcium chloride and distilled before use. Chromatography-grade dichloromethane (CH_2Cl_2) was purified to moisture- and oxygen-free by passing through a purification column (Solvent Dispersing System; Glass Contour) before use. 2-Hydroxymethyl-15-crown 5-ether (Tokyo Kasei) was used as received.

Sodium methacrylate (NaMA; Aldrich, >99%), methacryloyloxyethyltrimethyl-ammonium chloride (ACMA; Wako; >97%), $Ru(Ind)Cl(PPh_3)_2$ (Strem, >98%) and $Ru(Cp^*)Cl(PPh_3)_2$ (Aldrich) was used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere (H_2O < 1 ppm; O_2 < 1 ppm). Ethyl 2-chloro-2-phenylacetate (ECPA; Aldrich; >97%) was distilled under reduced pressure before use. Tetralin (1,2,3,4-tetrahydronaphtalene; ^1H NMR internal standard for NaMA and ACMA) was dried overnight over calcium chloride and doubly distilled from calcium hydride under reduced pressure before use. Ethanol (solvent; Wako; >99.5%) was degassed by bubbling dry nitrogen for more than 15 min before use. 15-Crown-5 (Alfa Aesar; 98%) was used as received.

Template initiator, CEI

To a solution of 2-hydroxymethyl-15-crown 5-ether (0.90 g, 3.60 mmol) and trimethylamine (0.502 mL, 3.60 mmol) in CH_2Cl_2 (9.14 mL) was added a solution of **1** (840 mM in CH_2Cl_2; 2.86 mL) at r.t. under dry argon, and the solution was subsequently stirred for 6 h (100% conversion). The solvent was evaporated under reduced pressure, and the crude product was purified by preparative size-exclusion chromatography (column, Shodex KF-5001; eluent, THF): isolated yield, 57%. ^1H NMR ($CDCl_3$): δ 7.49 (m, 2H), 7.35 (m, 3H), 7.30-7.18 (m, 2H), 6.88 (m, 2H), 5.40 (s, 1H), 5.27 (m, 2H), 4.79 (m, 1H), 4.07 (t, 2H), 3.90-3.47 (m, 23H), 1.32 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 168.14, 156.66, 135.84, 129.74, 129.46, 129.21, 128.78, 128.01, 123.68, 120.68, 111.66, 78.83, 71.33, 71.10, 70.92, 70.81, 70.59, 70.54, 70.51, 70.37, 70.23, 67.71, 65.24, 63.57, 59.11, 19.54. A representative ^1H NMR spectrum is shown in Figure 1. LR MS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{30}H_{41}ClO_{10}$, 619.24; found 619.1.

Radical addition

The reaction was carried out under dry argon in sealed glass tubes. A typical example with the template initiator **CEI** is given below: In a 50-mL round bottomed flask was placed **CEI** (97.9 mg), Ru(Ind)Cl(PPh_3)$_2$ (27.6 mg), NaMA (48.0 mg), ACMA (92.3 mg), and then ethanol (8.72 mL), tetralin (0.10 mL) and ECPA (0.075 mL) were added sequentially in this order at room temperature under dry argon. The total volume of the reaction mixture was thus 8.90 mL. Immediately after mixing, aliquots (0.40 mL each) of the solution were injected into baked glass tubes, which were then sealed and placed in an oil bath kept at 80-40 °C or ice bath kept at 0 °C. At predetermined intervals, the reaction was terminated by cooling the reaction mixtures to –78 °C Monomer conversion was determined from the concentration of residual monomer, measured by ^{1}H NMR with tetralin as an internal standard.

Measurements

^{1}H NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500.16 MHz. Electrospray-ionization mass spectra (ESI-MS) were measured on a Waters Quattro micro API.

Results and Discussion

1. Synthesis of CEI

In this chapter, a crown ether moiety was newly embedded as an alternative recognition site in the template initiator (**CEI**; Figure 1) to recognize ionic monomers according to their cation size.[9] Thus, a crown ether alcohol, 2-hydroxymethyl-15-crown 5-ether, was allowed to react with the haloether C–Cl bond in **1**, at room temperature in the presence of triethylamine, to give the target initiator **CEI** in high yield (Figure 1).

While starting with the same precursor **1** as before, the author incorporated the recognition site the electrophilic substitution of the haloether C–Cl bond rather than electrophilic addition across a C=C bond as done previously.[3a] It should be noted that the latter is a propagation model for cationic polymerization, whereas the former is for cation-quenching, thus showing the versatility of the haloether function in template construction.

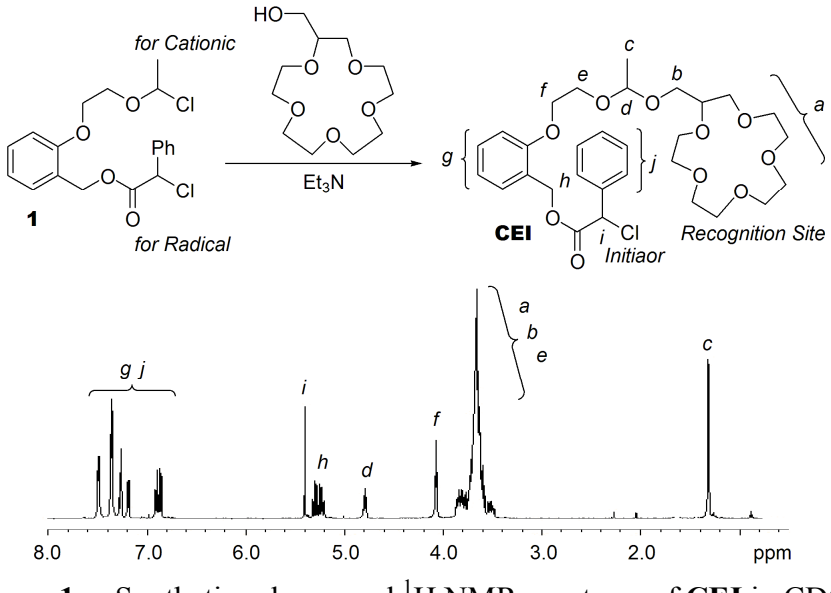


Figure 1. Synthetic scheme and ^{1}H NMR spectrum of **CEI** in $CDCl_3$.

2. Competitive Radical Addition via Size-Selective Template Recognition

Sodium methacrylate (NaMA) was selected as a targeting monomer for the 15-crown 5-ether site, as sodium cation is known to be specifically recognized by this crown ether via its ion-fitting size. Methacryloyloxyethyltrimethylammonium chloride (ACMA) was examined as a competing ionic monomer carrying an unfitted larger cation. First, the size-specific recognition by 15-crown-5 was monitored by ^{1}H NMR spectroscopy in EtOH-d_6

at 40 °C (Figure 2). When NaMA was mixed with an equimolar amount of the ether ([NaMA] = [15-crown-5] = 50 mM), the methylene peak *d* of the latter was clearly shifted downfield from 3.64 to 3.70 ppm, and those of the NaMA olefin (*a*) were shifted upfield from 5.73/5.13 to 5.70/5.10 ppm (Figure 2a, c, d). These shifts show some interaction between the two components and most likely indicate capture of the sodium cation into the cyclic ether moiety. On the other hand, such peak shifts were not observed with ACMA (Figure 2b, c, e), indicating that no recognition or capture of the ammonium cation occured. More importantly, and relevant to competitive reactions with the two monomers (see below), the selective recognition of NaMA occurred even in the presence of ACMA (Figure 2f).

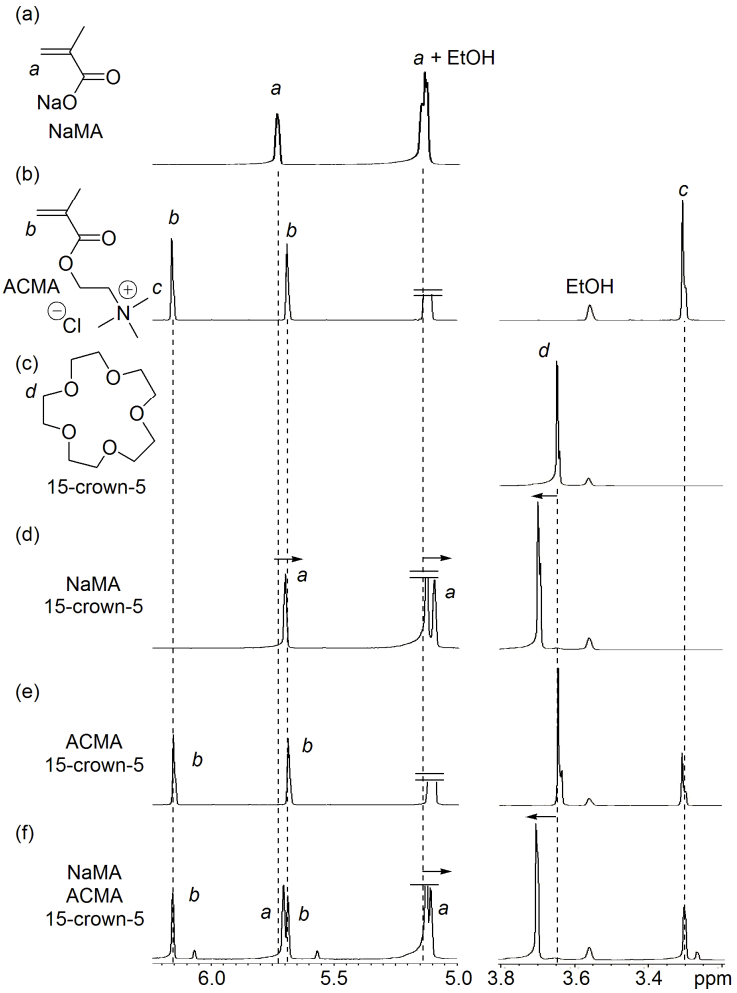
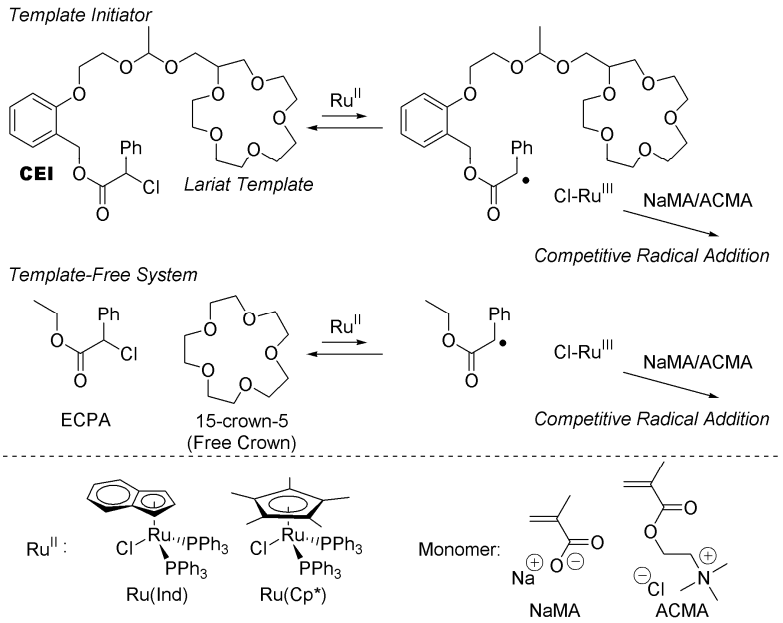


Figure 2. ^{1}H NMR spectra of cationic monomers and 15-crown-5 in EtOH-d_6 at 40 °C: (a) [NaMA] = 50 mM; (b) [ACMA] = 50 mM; (c) [15-crown-5] = 50 mM; (d) [NaMA] = [15-crown-5] = 50 mM; (e) [ACMA] = [15-crown-5] = 50 mM; (f) [NaMA] = [ACMA] = [15-crown-5] = 50 mM.

Encouraged by these findings, the author carried out a competitive radical addition of NaMA and ACMA with **CEI** in ethanol at 40 °C via coupling with $Ru(Ind)Cl(PPh_3)_2$ (Ind = η^5-C_9H_7), one of the active catalysts for radical addition[10] and living radical polymerization[11] (Scheme 2). Figure 3a shows time–conversion curves during the initial 4 h. NaMA was smoothly consumed, while an induction period was observed for the consumption of ACMA during which only the sodium monomer was specifically incorporated into the radical site of **CEI**. The apparent rate constants (k') of the two monomers were calculated from the initial slopes of first-order plots and found to have the values: $k'_{NaMA} = 0.186\ h^{-1}$ and $k'_{ACMA} = 5.10 \times 10^{-3}\ h^{-1}$. These results show that NaMA reacted ~36 times faster than ACMA ($k'_{NaMA}/k'_{ACMA} = 36.4$).

As a control experiment, a similar competitive reaction was performed with a template-free initiator, ethyl 2-chloro-2-phenylacetate (ECPA), in the presence of 15-crown-5 (Figure 3b). Importantly, a definitely opposite tendency was observed: NaMA consumption was slower than that of ACMA ($k'_{NaMA} = 4.28 \times 10^{-2}\ h^{-1}$, $k'_{ACMA} = 0.119\ h^{-1}$, $k'_{NaMA}/k'_{ACMA} = 0.359$), and thus, the selectivity enhancement by the template was more than 2 orders of magnitude: 36.4/0.359 = 101.4. From these results, the crown ether moiety on the initiator was found to selectively accelerate the addition of NaMA via specific recognition (template effect) by the crown ether, which approximates the substrate to the radical reaction site (or its dormant C–Cl form).



Scheme 2. Ruthenium-catalyzed competitive radical addition of NaMA and ACMA with crown template initiator or template-free initiator (ECPA).

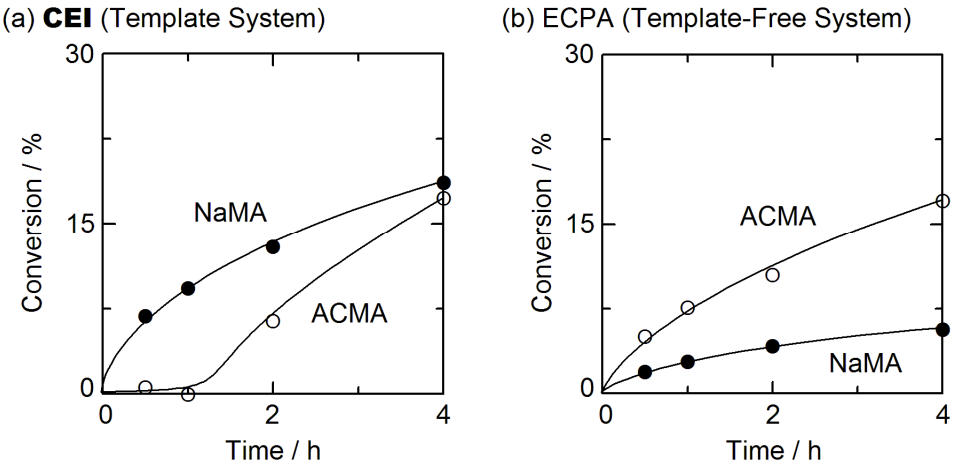


Figure 3. Time–conversion curves in competitive radical addition of NaMA and ACMA with (a) **CEI** and (b) ECPA in EtOH at 40 °C: $[NaMA]_0 = [ACMA]_0 = [initiator]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[15\text{-crown-5}]_0 = 50$ mM (only when ECPA was used as an initiator).

Here the author expediently defines the ratio k'_{NaMA}/k'_{ACMA} with **CEI** (template) to that with ECPA (non-template) as "template effect factor (*TE*)". Thus, *TE* was evaluated as 101.4 for the above-described competitive reactions at 40 °C. As expected, decreasing the reaction temperature increased *TE* (Figure 4 and Table 1), but at all of the temperatures examined, the template effect was indeed operable (*TE* >> 1) and beyond the experimental errors.

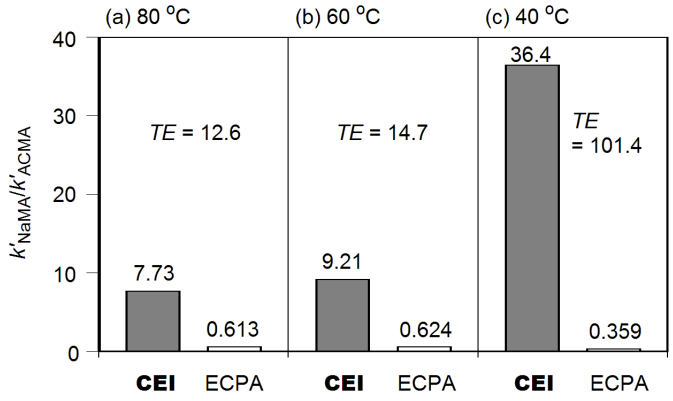


Figure 4. Monomer selectivity on competitive radical addition of NaMA and ACMA with **CEI** or ECPA in EtOH at (a) 80, (b) 60, and (c) 40 °C: $[NaMA]_0 = [ACMA]_0 = [initiator]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[15\text{-crown-5}]_0 = 50$ mM (only when ECPA was used as an initiator).

Table 1. Template-assisted competitive radical addition of NaMA and ACMA with $Ru(Ind)Cl(PPh_3)_2$.[a]

Entry	Initiator	Temp (°C)	k'_{NaMA} (h^{-1})	k'_{ACMA} (h^{-1})	Selectivity[b]	Template Effect[c]
1	**CEI**	80	4.06	0.526	7.72	12.6
2	ECPA		0.724	1.18	0.613	
3	**CEI**	60	0.855	0.0928	9.21	14.7
4	ECPA		0.211	0.338	0.624	
5	**CEI**	40	0.186	0.00510	36.4	101.4
6	ECPA		0.0428	0.119	0.359	

[a] Reaction conditions: $[NaMA]_0 = [ACMA]_0 = [initiator]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[15\text{-crown-5}]_0 = 50$ mM (only when ECPA was used). [b] [Selectivity] = k'_{NaMA}/k'_{ACMA}. [c] The ratio of Selectivity between the template system and the corresponding non-template one; [Template Effect] = $[Selectivity]_{CEI}/[Selectivity]_{ECPA}$. [d] $[Ru(Ind)Cl(PPh_3)_2]_0 = 10$ mM.

3. Competitive Radical Addition with Active Catalyst in Lower Temperature

Sawamoto and co-workers recently found that in living radical polymerization pentamethylcyclopentadienyl ruthenium complexes [$Ru(Cp^*)Cl(PR_3)_2$; $Cp^* = \eta^5\text{-}C_5(CH_3)_5$; R = phenyl etc.] are active enough to catalyze living radical polymerization in ethanol even at a temperature as low as 40 °C.[12] Therefore, $Ru(Cp^*)Cl(PPh_3)_2$ was next employed for the NaMA/ACMA competitive addition at temperatures lower than 60 °C (Figure 5). For example, as shown in Figure 5a, NaMA was smoothly and quantitatively consumed at 40 °C (conv. ≈ 100% in 7 h), with $k'_{NaMA} = 1.27\ h^{-1}$, still higher than that with $Ru(Ind)Cl(PPh_3)_2$ at 60 °C ($0.855\ h^{-1}$). On the other hand, ACMA reacted slower (conv. ≈ 30% in 7 h at 40 °C; $k'_{ACMA} = 0.108\ h^{-1}$): the selectivity k'_{NaMA}/k'_{ACMA} was thus estimated to be 11.8.

At 0 °C (Figure 5b), the rate difference between NaMA and ACMA was more outstanding: the former reacted smoothly and had $k'_{NaMA} = 0.0157\ h^{-1}$, whereas the latter was hardly consumed and had $k'_{ACMA} = 0.0003\ h^{-1}$, leading to a much higher selectivity ($k'_{NaMA}/k'_{ACMA} = 52.3$). A similar trend was obtained at 25 °C (Table 2). All of these results demonstrate a superior recognition effect of **CEI** for NaMA.

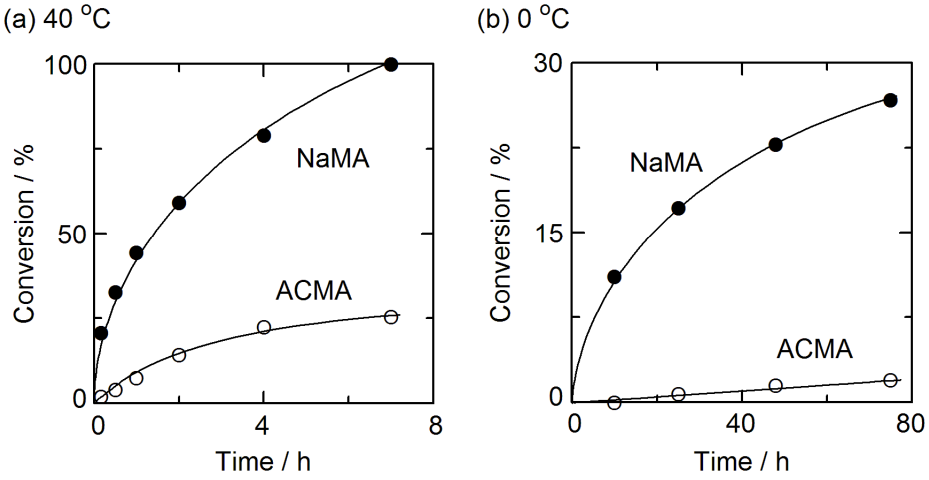


Figure 5. Time-conversion curves in competitive radical addition of NaMA and ACMA with **CEI** in EtOH at (a) 40 and (b) 0 °C: $[NaMA]_0 = [ACMA]_0 = [\mathbf{CEI}]_0 = 50$ mM; $[Ru(Cp^*)Cl(PPh_3)_2]_0 = 4.0$ mM.

Table 2. Template-assisted competitive radical addition of NaMA and ACMA with $Ru(Cp^*)Cl(PPh_3)_2$.[a]

Entry	Temp. (°C)	k'_{NaMA} (h^{-1})	k'_{ACMA} (h^{-1})	Selectivity[b]
1	40	1.27	0.108	11.8
2	25	0.197	0.0074	26.6
3	0	0.0157	0.0003	52.3

[a] Reaction conditions: $[NaMA]_0 = [ACMA]_0 = [\mathbf{CEI}]_0 = 50$ mM; $[Ru(Cp^*)Cl(PPh_3)_2]_0 = 4.0$ mM. [b] [Selectivity] = k'_{NaMA}/ k'_{ACMA}.

Conclusion

The author has demonstrated a highly selective radical addition with a template initiator (**CEI**) that carries a crown ether embedded close to a radical initiating site. Such a "lariat capture" of the sodium cation monomer (NaMA) by a crown macrocycle is therefore crucial for the observed size-specific molecular recognition (Figure 6), and the proximity effect allows surprisingly high substrate selectivity (*TE* > 100) in comparison with the non-template system.

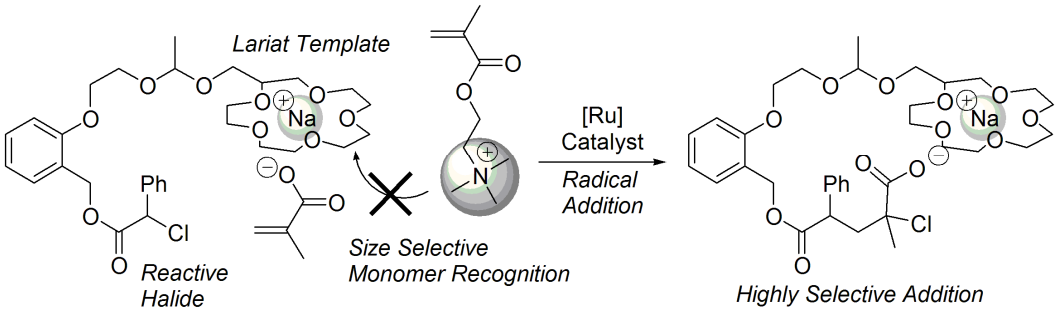


Figure 6. Size selective monomer recognition by lariat capture of **CEI**.

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Chapter 5

Template-Assisted Radical Addition and Copolymerization: Adequate System Design of Template Initiators for High Substrate Selectivity

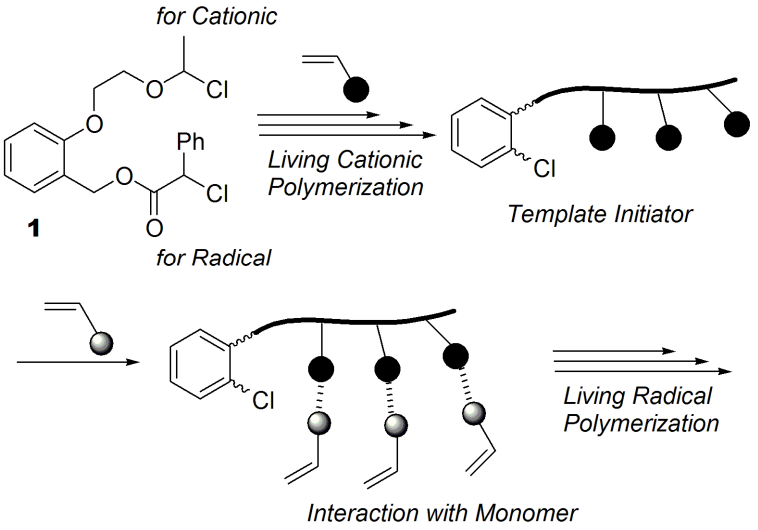
Abstract

"Template initiator" platforms (**1**) have been designed for expressing the sequence information in a template in radical polymerization. Thus, the author demonstrated the structural adequacy of **1** consisting of two initiating sites placed *ortho* to each other in benzene: one for living cationic polymerization to introduce a template carrying substrate-recognition tags, and the other for metal-catalyzed living radical polymerization to achieve sequence regulation. For example, for two positional isomers with an amine template for an acid monomer, only the *ortho* initiator induced selective radical addition of methacrylic acid (MAA; recognizable) over methyl methacrylate (MMA; non-recognizable). Another version was an oligo(vinyl ether) with a multiple amine template, which demonstrated template effects for MAA recognition over benzyl methacrylate (BzMA) in copolymerization.

Introduction

Nature skillfully utilizes template systems to produce well-defined biopolymers, and they possess incomparably more advanced functions than synthetic polymers. Among the controlled structural factors typical in biopolymers, monomer sequence (the order of constitutional repeat-units along a polymer backbone) is essential to express specific three-dimensional structures and thereby the structure-based functions. On the other hand, in artificial polymerizations, the sequence control is still undeveloped, although the precision control of chain length as well as terminal, block (segmental), and branch structures have been achieved by living polymerization techniques.[1, 2] Recently, sequence regulation in polymerization has begun to be intensively investigated,[3-6] but, no general and efficient ways have been achieved yet.

A promising way to realize sequence control would be to mimic template systems in nature. The author has thus embarked template-assisted living radical polymerization with designer "template initiators" carrying recognition units (template) in the vicinity of a radical initiating site (Scheme 1).[5a, 5c] "Template polymerization" has indeed been studied for some time with templates that are mostly added into a polymerization mixture separately from an initiating system, but their so-called template effects are limited to enhancement of polymerization rate or yield and rather minor stereochemical control.[7] To the author's knowledge, there have been few reports on the sequence regulation by template systems, presumably because of difficulty in template synthesis and in demonstrating a truly template-driven substrate-selective polymerization.



Scheme 1. Template-assisted living radical polymerization.

In Chapter 3 and 4, the author has proposed "template initiator" platforms, heterobifunctional (radical/cationic) initiators (**1**) that carry two vicinal carbon–chlorine bonds placed *ortho* to each other in a rigid aromatic framework. In the author's strategy, "template" is synthesized and built-in within the platform via living cationic polymerization from the chloroether part, and sequence control is to be achieved via metal-catalyzed living radical polymerization from the neighboring chloroester that triggers a quantitative initiation from the edge of the *ortho*-template within the same platform. Here, as the author's group demonstrated,[4, 5c] the cationic system is suitable for the construction of a template, since it allows a controlled single addition of a selected monomer (or "step-growth" propagation) that is also functionally tolerant and precisely tunable in accordance with the substrate's reactivity and/or bulkiness.

The author has already reported the initial work in this line to demonstrate the "template effect" on monomer selectivity with a template initiator carrying one amino unit (**2**; Figure 1) for ruthenium-catalyzed competitive radical addition of methacrylic acid (MAA; recognizable) over methyl methacrylate (MMA; non-recognizable).[5a] Namely, the template-amino moiety recognized the acid monomer via an ionic interaction ($–NH_3^+ ... ^-OCO–$) to allow its preferential incorporation.

In this chapter, the author now examined the structural design adequacy of his template initiators, especially for the proximity effect of the *ortho*-positioned template and radical initiating site. Thus, the author prepared the *meta* counterpart (**3**) consisting of the same template and initiator components, chemically identical but positionally different, to compare with the *ortho* isomer in terms of the monomer selectivity in competitive radical addition. Also, to examine the template effects in a "polymerization" with this platform, the author newly prepared an oligo(vinyl ether) (**4**) to which multiple amino pendent groups as a template are introduced via living cationic polymerization, and employed it for the ruthenium-catalyzed radical copolymerization of MAA and benzyl methacrylate (BzMA).

In the *ortho* versus *meta* adequacy comparison, little selectivity was observed with the *meta*-based initiator, as with a non-template model initiator, indicating that the *ortho* placement within **2** is critical to induce a selective radical addition through the proximity effect of the recognition site (amine) relative to the initiating site (C–Cl). With the multiple tag system (**4**), the recognizable monomer (MAA) was consumed clearly faster than the non-recognizable partner (BzMA). This specific trend was definitely opposite to the copolymerizations with a non-templated model initiator.

Experimental Section

Materials

Methacrylic acid (MAA; Tokyo Kasei; >99%) was dried overnight over calcium chloride and distilled under reduced pressure before use. Methyl methacrylate (MMA; Tokyo Kasei, >99%) was dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. Benzyl methacrylate (BzMA; Tokyo Kasei; >98%) was purified by passing through an inhibitor removal column (Aldrich) and was subsequently degassed by triple vacuum-argon bubbling cycles before use. 2-Azidoethyl vinyl ether (AzVE),[8] a heterobifunctional initiator (**1**),[5a] a hydrogen chloride adduct of 2-chloro ethyl vinyl ether (CEVE-HCl),[9] and an amine-carrying template radical initiator (**2**)[5a] were prepared according to literatures. *Meta*-substituent model initiator (**3**) was synthesized as same as **2**, starting from 3-hydroxybenzyl alcohol. Ethyl 2-chloro-2-phenylacetate (ECPA; Aldrich; >97%) was distilled under reduced pressure before use. $Ru(Ind)Cl(PPh_3)_2$ (Ind = η^5-C_9H_7; Strem; >98%) was used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere (H_2O < 1 ppm, O_2 < 1 ppm). Butylamine (*n*-$BuNH_2$; Tokyo Kasei; >99%) and ethanol (solvent) were degassed by bubbling dry nitrogen for more than 15 min before use. Tetralin (1,2,3,4-tetrahydronaphtalene, ^{1}H NMR internal standard for MAA, MMA and BzMA) was dried overnight over calcium chloride and doubly distilled from calcium hydride under reduced pressure before use. Chromatography-grade dichloromethane (CH_2Cl_2; solvent) and toluene (solvent) were purified to moisture- and oxygen-free by passing through a purification column (Solvent Dispensing System; Glass Contour) before use. $SnCl_4$ (1.0 M in CH_2Cl_2; Aldrich), $LiBH_4$ (2.0 M in THF; Aldrich), and triphenylphosphine (Wako; >97%) were used as received.

Template Macroinitiator (4) and Initiator-Free Template (5)

Living cationic polymerization of AzVE was performed under dry argon in baked glass flasks equipped with a three-way stopcock. A typical one is given below. The reaction was initiated by adding a solution of $SnCl_4$ (in CH_2Cl_2) into a mixture of an initiator (**1**) and AzVE in CH_2Cl_2 at –78 °C by a dry syringe ($[\mathbf{1}]_0$ = 10 mM; $[AzVE]_0$ = 100 mM; $[SnCl_4]_0$ = 20 mM). After 5 min, $LiBH_4$ (3 equiv. for the initiator) was added, and the reaction mixture was stirred at 0 °C for an additional 30 min, followed by addition of water to decompose the residual $LiBH_4$. The quenched reaction mixture was diluted with

toluene/*n*-hexane [1/1 (v/v)], washed sequentially with dilute hydrochloric acid and aqueous sodium chloride, evaporated under reduced pressure, and finally vacuum dried. The crude polymer was further purified by preparative size-exclusion chromatography (column: Shodex KF-5003; eluent, THF). The obtained polymer [M_n = 1,860, DP_n = 13.4 (by ^{1}H NMR), M_w/M_n = 1.18] (0.167 g; 1.20 mmol of azide groups) and triphenylphosphine (0.644 g; 2.45 mmol) were dissolved into DMF (5.0 mL). Hydrochloric acid (36 wt.-%; 0.25 mL) was added, and the mixture was stirred for 24 h at room temperature. The solvent was evaporated, and the crude product was dispersed in 1,4-dioxane, treated with $NaHCO_3$ aqueous solution for neutralization, and then isolated by evaporation. Methanol was added to the product and the soluble part was isolated by filtration. Then, the filtrate solution was concentrated by evaporation, and doubly precipitated into toluene.

Radical Addition/Polymerization

The reaction was carried out under dry argon in baked and sealed glass tubes. A typical example with the template initiator **2** is given below: In a 50-mL round-bottomed flask was placed **2** (0.085 g), and toluene (3.42 mL), tetralin (0.100 mL), solutions of MAA (1 M in toluene; 0.195 mL) and MMA (1 M in toluene; 0.195 mL) were added sequentially in this order at room temperature under dry argon. The resulting mixture was totally transferred by syringe under dry argon to a 50-mL round-bottomed flask containing $Ru(Ind)Cl(PPh_3)_2$ (12.1 mg). The total volume of the reaction mixture was thus 3.90 mL. Immediately after mixing, aliquots (0.40 mL each) of the solution were injected into baked glass tubes, which were then sealed and placed in an oil bath kept at 80 °C. At predetermined intervals, the reaction was terminated by cooling the reaction mixtures to –78 °C. Monomer conversion was determined from the concentration of residual monomer measured by ^{1}H NMR with tetralin as an internal standard.

Measurements

The M_n and M_w/M_n of the polymers were determined by size-exclusion chromatography (SEC) in THF at 40 °C using polystyrene gel columns (Shodex KF 400RL × 2 and KF-400RH) that were connected to a Shodex DU-H2000 precision pump, a Shodex RI-74 refractive index detector, and a Shodex UV-41 UV/vis detector set at 250 nm. The columns were calibrated against 13 standard polystyrene samples (Tosoh; M_w = 500-3,840,000; M_w/M_n = 1.01-1.14). ^{1}H NMR spectra were recorded on a JEOL

JNM-LA500 spectrometer, operating at 500.16 MHz.

Results and Discussion

1. Template effects in competitive radical addition: *Ortho* versus *Meta* Template Placement

Competitive radical additions of MAA and MMA were performed with three initiators, i.e., the *ortho*-templated (**2**), its *meta* isomer (**3**), and a non-templated version (ECPA) with an identical initiating site, in conjunction with a ruthenium catalyst $[Ru(Ind)Cl(PPh_3)_2$ (Ind = η^5-C_9H_7)][10] in toluene at 80 °C: $[initiator]_0 = [MAA]_0 = [MMA]_0 = 50$ mM; $[Ru(Ind)]_0 = 4.0$

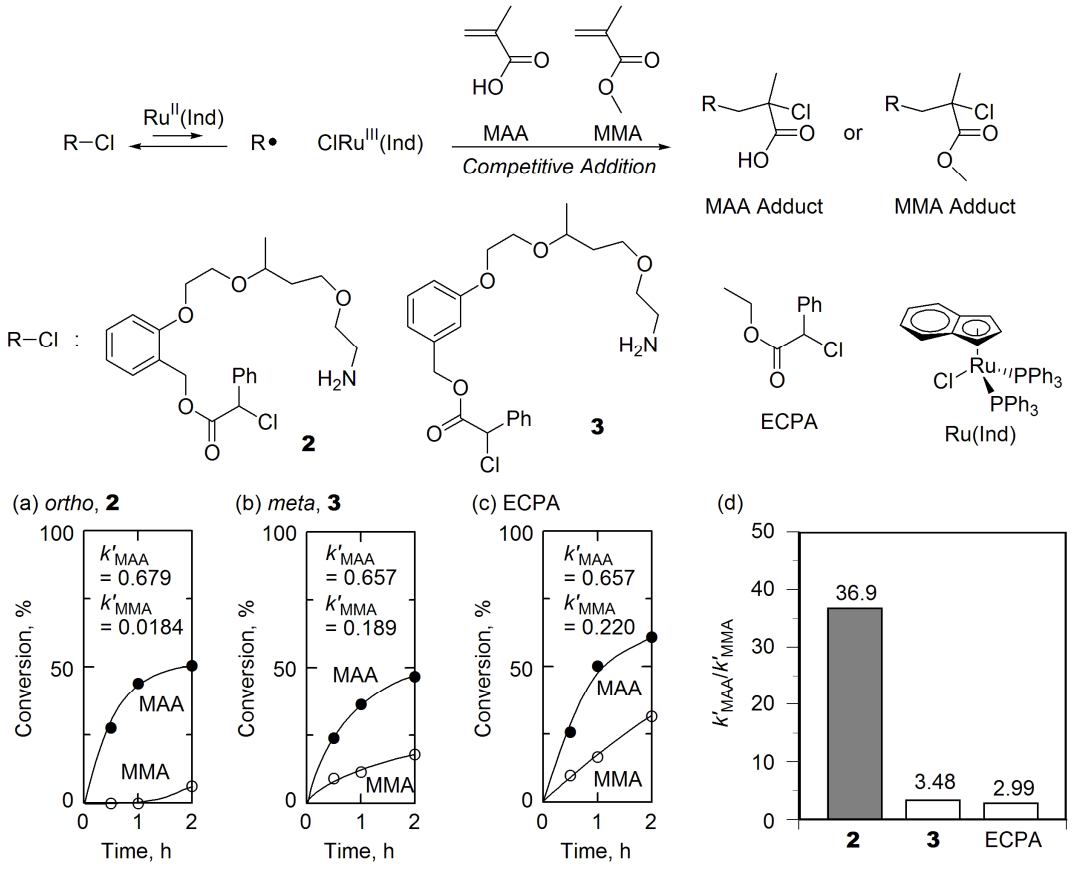


Figure 1. Template initiator-assisted competitive radical addition of MAA and MMA with $Ru(Ind)Cl(PPh_3)_2$ in toluene at 80 °C: (a-c) Time–conversion curves using the various initiator [(a) **2**, (b) **3**, and (c) ECPA] and (d) comparison of the reaction selectivity using various initiating systems: $[Initiator]_0 = [MAA]_0 = [MMA]_0 = 50$ mM; $[n\text{-}BuNH_2]_0 = 50$ mM (when using ECPA as the initiator); $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM.

mM. The reactions were conducted deliberately under equimolar conditions to evaluate template effects, different from typical metal-catalyzed radical additions in which an excess amount of an initiator (halide) was used over monomers to prevent oligomerization.[11] The template initiators (**2** and **3**) were synthesized via cationic selective monoaddition of a Boc-protected vinyl ether with the dual initiator platform (**1**) and the subsequent deprotection to embed a single unit of an amino group.[5a, 5c]

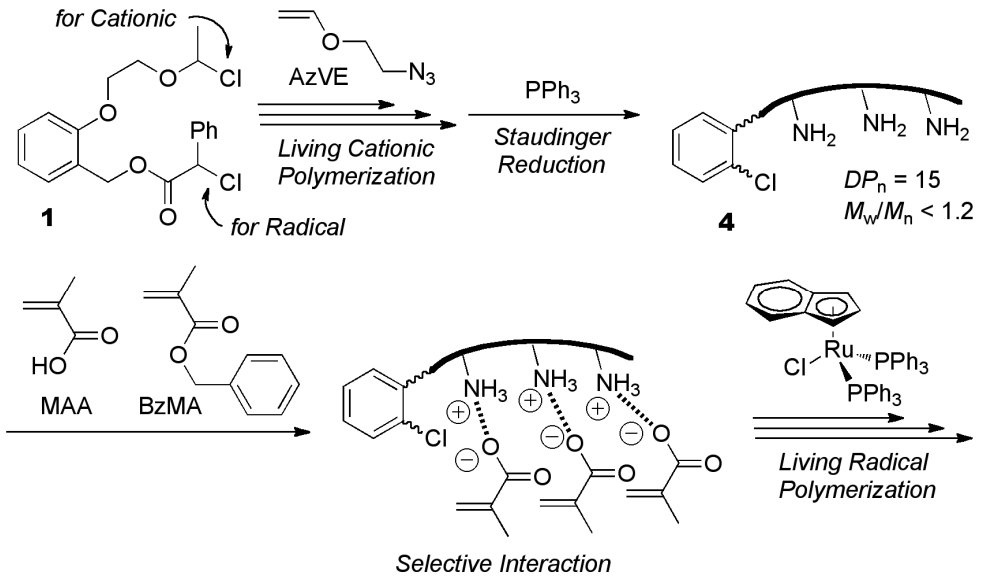
As shown in Figure 1a, with the *ortho* initiator (**2**), the addition of MMA was inhibited during the first one hour, while MAA was smoothly consumed. The selectivity for MAA over MMA, estimated from the ratio of the initial-first order rate constant (k'_{MAA}/k'_{MMA}), reached about 40 (k'_{MAA}/k'_{MMA} = 36.9: k'_{MAA} = 0.679; k'_{MMA} = 0.0184; Figure 1d). On the other hand, in the case with the *meta* initiator (**3**), MMA reacted without such an induction period, although the rate was smaller than MAA (Figure 1b). The calculated selectivity (k'_{MAA}/k'_{MMA}) was about 3.48 (k'_{MAA} = 0.657; k'_{MMA} = 0.189), which was similar to that with non-template initiator [ethyl 2-chloro-2-phenyl acetate (ECPA)] in the presence of *n*-$BuNH_2$ (k'_{MAA}/k'_{MMA} = 2.99: k'_{MAA} = 0.657; k'_{MMA} = 0.220; Figure 1c). These results indicate that the distance between the recognition site (amine) and the reactive site (C–Cl), or the proximity to the recognition site, is essential to induce the high selectivity of **2**.

2. Template effects on radical copolymerization of MAA and BzMA

To establish a truly sequence-controlled "polymerization" with the template initiator platform (**1**), ideally, an array of multiple and different recognition sites should be sequentially introduced into the template part via living cationic polymerization from the haloether initiator site. Here, prior to such a promising but laborious attempt, a single kind of a recognition group (amine) was repetitively embedded into the template to examine the "template effects" on copolymerization of a recognizable monomer (methacrylic acid: MAA) with a non-recognizable comonomer (benzyl methacrylate: BzMA) (Scheme 2).

Multiple amine groups were embedded via direct living cationic polymerization of an azide-carrying vinyl ether (AzVE), which was developed by the author toward a universal syntheses of functional poly(vinyl ether)s.[8] The pendent azide groups in poly(AzVE) can be converted into amines by Staudinger reduction under mild conditions.[12]

Living cationic polymerization of AzVE with **1** was carried out in conjunction with $SnCl_4$ (catalyst) in CH_2Cl_2 solvent at –78 °C: $[AzVE]_0$ = 100 mM; $[\mathbf{1}]_0$ = 10 mM; $[SnCl_4]_0$ = 20 mM (Scheme 2). The obtained poly(AzVE) was well-controlled with narrow molecular



Scheme 2. Synthesis of the template macroinitiator and ruthenium-catalyzed radical copolymerization of MAA and BzMA.

weight distribution (M_n = 2,200; M_w/M_n = 1.18; Figure 2). The pendent azides were then converted into primary amines with two equivalents of triphenylphosphine in DMF/HCl_{aq}; the acidic condition was essential to avoid a decomposition of the α-haloester radical initiating site. The quantitative conversion into amine groups was verified by ^{1}H NMR spectroscopy, to show that the resultant template macroinitiator (**4**) possessed on average 15 amine units per molecule (Figure 3).

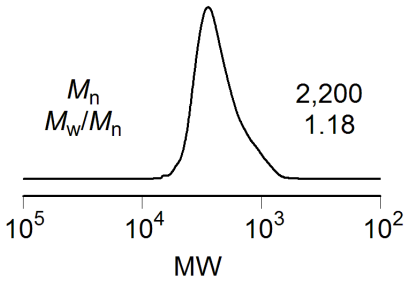


Figure 2. SEC curve of the poly(AzVE) as the precursor for the template macroinitiator synthesized by $SnCl_4$-mediated living cationic polymerization of AzVE in CH_2Cl_2 at -78 °C: $[AzVE]_0$ = 100 mM; $[\mathbf{1}]_0$ = 10 mM; $[SnCl_4]_0$ = 20 mM.

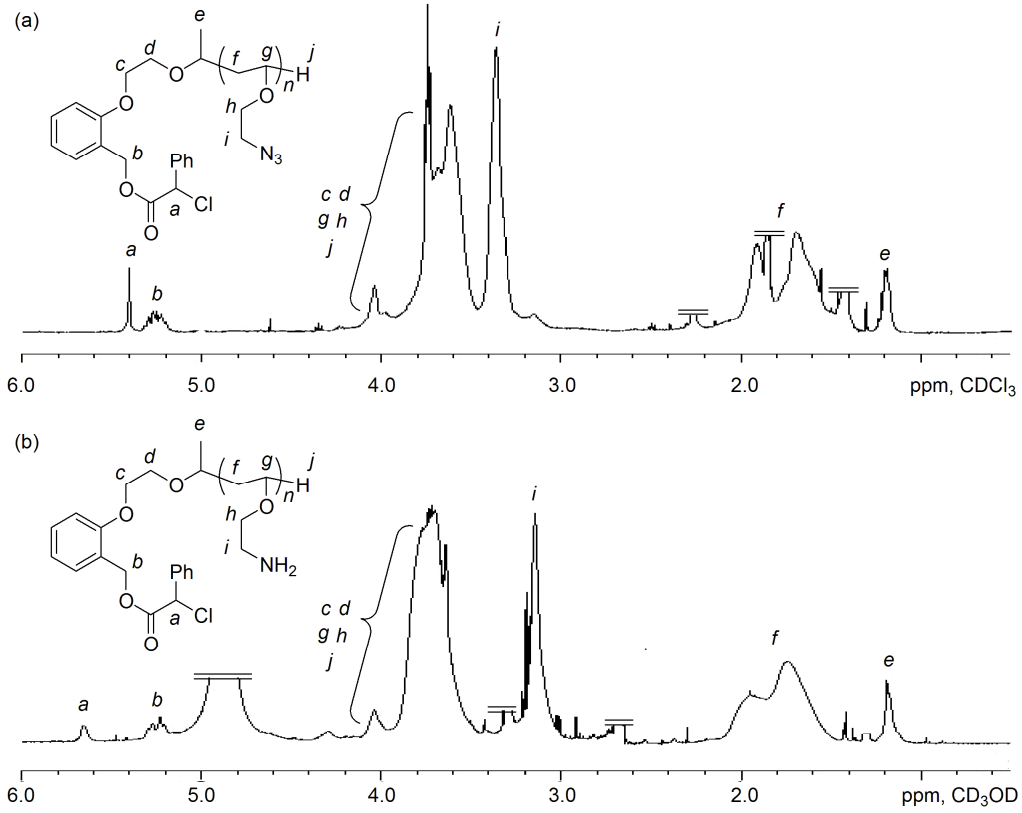


Figure 3. ^{1}H NMR spectra of (a) the precursor poly(AzVE) in $CDCl_3$ and (b) the template macroinitiator in CD_3OD.

Using this macroinitiator (**4**), 1:1 radical copolymerization of MAA and BzMA was examined under the catalysis by $Ru(Ind)Cl(PPh_3)_2$ in ethanol (Scheme 2). The initiator concentration was set so that the pendent amine in **4** be equimolar to MAA and BzMA: $[MAA]_0 = [BzMA]_0 = 150$ mM; $[\mathbf{4}]_0 = 10$ mM (i.e., the total amine concentration is 150 mM for the initiator with $DP_n = 15$). As shown in Figure 4a, the conversion of MAA was fast and smooth, whereas that of BzMA was slow and retarded. On the other hand, the copolymerization with a non-template initiator (ECPA) gave a diametrically opposite tendency: BzMA was more reactive than MAA (Figure 4b). Such a reactivity inversion with the macroinitiator would indicate a template effect: MAA was selectively recognized by the template via ionic interaction with the pendent amines and was thereby condensed around the initiating site or the growing radical.

Importantly, the template initiator system with **4** should be differentiated from more conventional "initiator-free" template systems where a template and an initiator are separate

molecules. Thus, MAA–BzMA copolymerization was carried out with ECPA, a template-free initiator with the identical initiating site as in **4**, in the presence of a poly(vinyl ether) carrying pendent amino groups [**5**; M_w/M_n = 1.15 (SEC); DP_n = 11.2; M_n = 1100 (^{1}H NMR)] as a template for MAA (Figure 4c). Although the conversion of MAA was a little higher with the ECPA/**5** pair than with ECPA alone without **5**, the relative reactivity order for the former was opposite (BzMA > MAA) to that for the system with **4**. In the ECPA/**5** system, the initiating site and the template were separate from each other, rendering specific substrate recognition by **5**, if any, less effectively expressed in the reaction.

These comparative experiments demonstrate the placement of the initiating site close to the recognition sites (as in **4**) to be essential to express template effects as well as specific monomer recognition. This point should be more important when template initiator platforms are applied for sequence-regulated polymerization.

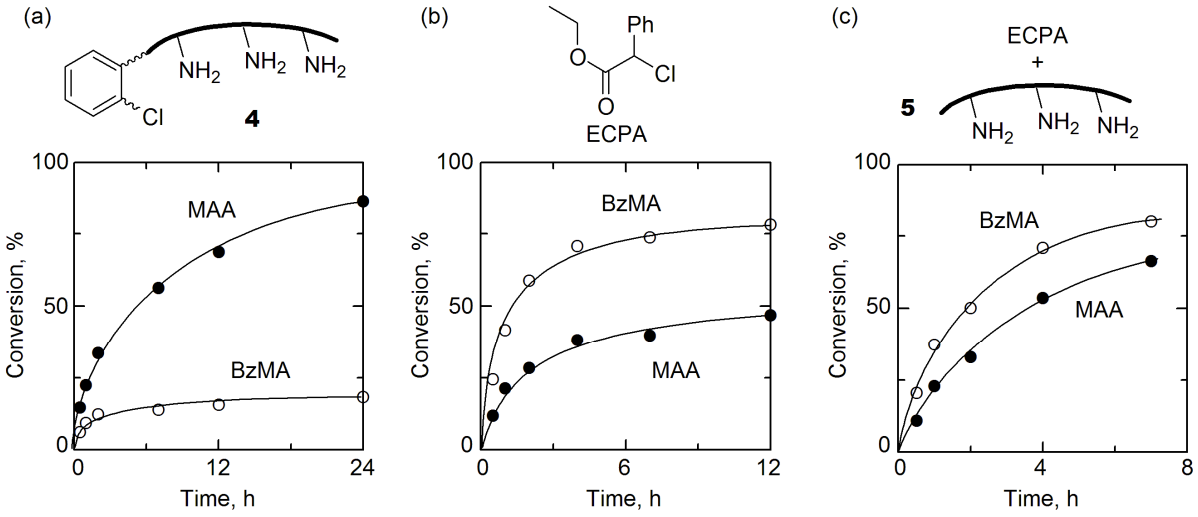


Figure 4. Time–conversion curves of ruthenium-catalyzed radical copolymerizaion of MAA and BzMA with various initiating systems in ethanol at 80 °C: $[MAA]_0 = [MMA]_0$ = 150 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 4.0 mM; (a) the template initiator: $[\mathbf{4}]_0$ = 10 mM; (b) non-template system: $[ECPA]_0$ = 10 mM; $[n\text{-}BuNH_2]_0$ = 150 mM; (c) initiator-free template: $[ECPA]_0$ = 10 mM; [pendent amine]$_0$ = 150 mM.

Conclusion

The structural adequacy of the template initiator platform (**1**) was studied in regard to sequence-controlled polymerization. Comparative experiments with similar but non-templated initiators in competitive radical addition and copolymerization indicated that the *ortho* position design and the guaranteed initiating point at the edge of the template were crucial to induce desired template effects, i.e., recognized monomers selectively reacted or polymerized. In the future, more sophisticated design and synthesis of the template component in **1** would open the door to truly sequence-regulated polymerization.

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Chapter 1

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Shohei Ida, Takaya Terashima, Makoto Ouchi, Mitsuo Sawamoto
J. Polym. Sci. Part A: Polym. Chem., **2010**, *48*, 3375-3381.

Chapter 2

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Chapter 3

"Selective Radical Addition with a Designed Heterobifunctional Halide: A Primary Study toward Sequence-Controlled Polymerization upon Template Effect"
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Chapter 4

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Chapter 5

"Designer Template Initiator for Sequence Regulated Polymerization: Systems Design for Substrate-Selective Metal-Catalyzed Radical Addition and Living Radical Polymerization"
Shohei Ida, Makoto Ouchi, and Mitsuo Sawamoto
Macromol. Rapid Commun., *in press*.

ACKNOWLEDGMENTS

This thesis presents the studies which the author carried out from 2005 to 2011 at the Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University under the direction of Professor Mitsuo Sawamoto.

The author would like to express his sincere gratitude to Professor Mitsuo Sawamoto for his continuous guidance and encouragement throughout the course of this work. He is also grateful to Associate Professor Makoto Ouchi and Dr. Takaya Terashima for their helpful and convincing suggestions, and stimulating discussions.

The author thanks sincerely to Ms. Kimiko Nishi (Sharp Co., Ltd) for her discussion and kind guidance in experimental technique in the early phase of this research. It is pleasure to express his appreciation to Dr. Muneki Ishio (Kuraray Co., Ltd), Mr. Kazuhiro Nakatani, and all the members of Sawamoto laboratory for useful suggestion and their friendship during the course of research. The author is also obliged to Ms. Miro Takayama for her assistance during the author's school life.

The author acknowledges Mr. Kenichi Nakamura (Toagosei Co, Ltd) for his technical support on the synthesis of heterobifunctional initiator (Chapter 3-5) and Mr. Tetsuro Yamamoto (Kaneka Co., Ltd) for his technical support on the synthesis of sodium diethyl malonate (Chapter 1).

The author wishes to thank for Professor Yoshio Okamoto (Nagoya University; Harbin Engineering University), Professor Sadahito Aoshima (Osaka University), Professor Eiji Yashima (Nagoya University), Professor Masami Kamigaito (Nagoya University), Professor Yoshitsugu Hirokawa (The University of Shiga Prefecture), Associate Professor Shokyoku Kanaoka (Osaka University), Associate Professor Kotaro Satoh (Nagoya University), Associate Professor Tsuyoshi Ando (Nara Institute of Science and Technology), and all "ORION" members of their laboratory, especially to Mr. Hiroaki Shimomoto and Ms. Yukari Oda, for their meaningful discussion and kind encouragement.

The author would like to express his special thanks to Professor Axel H. E. Müller (Universität Bayreuth) for kind support and valuable suggestions during the author's stay in Germany.

The author is very grateful to Japan Society for Grant-in-Aid for research assistant of the Global COE Program, "International Center for Integrated Research and Advanced Education in Materials Science" of Kyoto University (2008-2011) and Teijin Kumura Scholarship (2006-2011).

Finally, the author wishes to express his deep appreciation to his parents, Mr. Yoshio Ida and Mrs. Isako Ida, his sister Ms. Nanako Ida and his all family for their constant care and affectionate encouragement.

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March, 2011