Design of Bulky and Transformable Monomers toward Sequence Control for Vinyl Polymers

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CONTENTS

# GENERAL INTRODUCTION

Background

Peptide, which is a type of natural polymers, is composed of twenty types of amino acids (i.e., comonomers) carrying different pendant groups. The order of amino acids, that is sequence, is precisely controlled based on the transcription system by mRNA template. The well-defined sequence in one chain allows formation of higher-ordered structure, leading to biological functions in our body.[1] In this way, sequence is the most important structural factor for properties and functions of peptides.

On the other hand, various types of monomers are available for syntheses of vinyl polymers via chain-growth polymerization. In particular, radical polymerization is widely used for practical applications, since some monomers can be combined in copolymerization and the resultant copolymers are useful for tuning the properties/functions by the averaged composition ratio. We can combine various methacrylate derivatives in radical copolymerization, but the sequence of the resultant copolymer is totally random. Inspired by the sequence regulation of amino acids in nature, creation of novel properties/functions could be expected, if sequence control for methacrylate units carrying different pedant groups is achieved. However, sequence of the resultant copolymer is totally random unlike peptides,
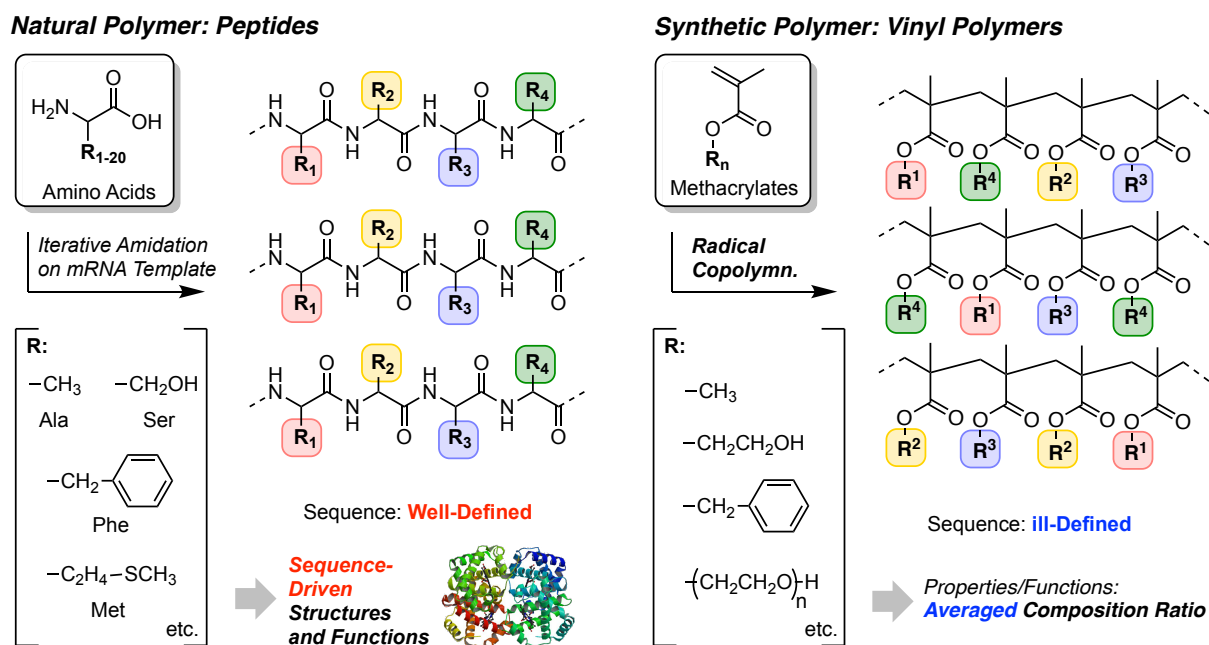
Figure 1. Sequence in Polymer Science: (A) Well-defined Nature Polymer (B) ill-defined Synthetic Polymer.
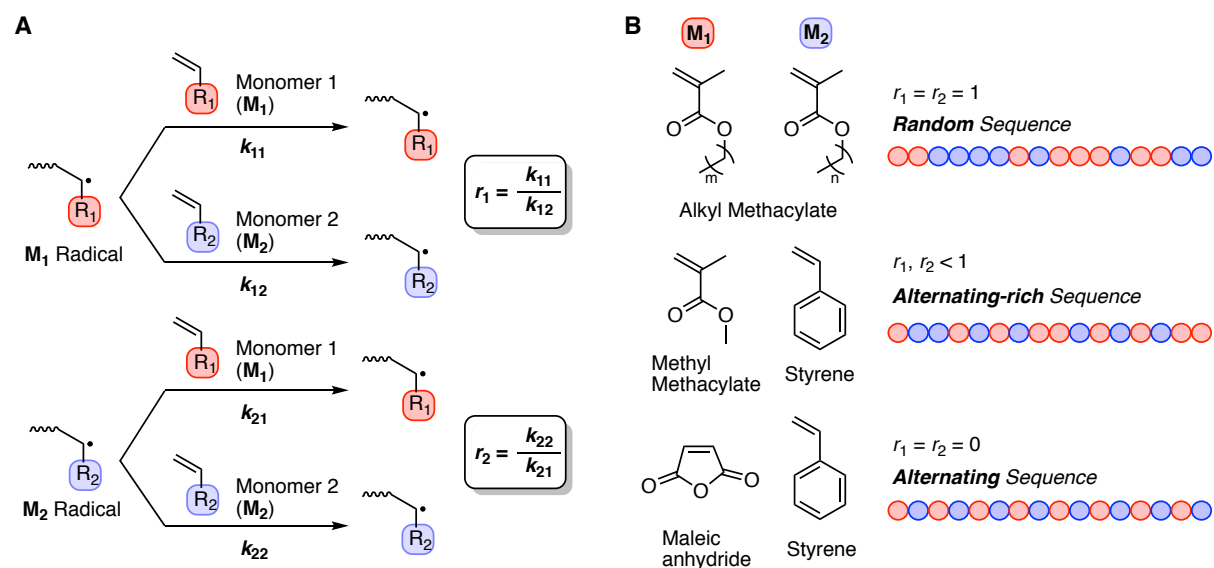
Figure 2. (A) Mayo-Lewis terminal model of radical copolymerization and reactivity ratios (r_1 and r_2) (B) The typical comonomer pairs giving random, alternating-rich, and alternating sequence and the reactivity ratios.

and the control is basically impossible due to the chain-growth mechanism.

Monomer reactivity ratios are very important in understanding copolymerization behaviors as well as predicting composition ratio/sequence of the resulting copolymers. According to the Mayo-Lewis terminal model,[2] there are four possible propagation steps in copolymerization of monomer 1 (M_1) and monomer 2 (M_2) where k_{ij} is the rate coefficient for the reaction of the M_i-ended radical adding M_j monomer (i, j = 1 and 2) (Figure 2A). The monomer reactivity ratios (r_1 and r_2) are defined as below:

$r_1 = k_{11}/k_{12}$

$r_2 = k_{22}/k_{21}$

The value of r_i represents the preference for homo-propagation (i.e., M_i-ended radical to M_i) over cross-propagation with another monomer (i.e., M_i-ended radical to M_j). The composition ratio and sequence can be predicted from the reactivity ratios to some extent (Figure 2B). For $r_1=r_2=1$, both radical species show no preference for monomers affording random sequence, and the pair of identical monomer derivatives (i.e., alkyl methacrylates) free from steric hindrance corresponds to this case. When both ratios are lower than one (r_1, r_2 <1) , the radical species prefer the comonomer giving alternating-rich sequence, as seen in the pair of methyl methacrylate and styrene. The zero of reactivity ratios allows the cross-over propagation leading to syntheses of alternating copolymers. The typical examples allowing alternating copolymerization are the combinations of styrene-maleic anhydride[3], styrene-maleimide[4,5], and styrene-pentafluoro styrene.[6]

2

In radical polymerization, the reactive radical species frequently undergo chain-transfer and termination reactions in addition to initiation and propagation, and thus it is impossible to control molecular weight of polymer.   The instant concentration of "active species" can be reduced by reversible conversion to "dormant species", which allows suppression of the side-reactions leading to control of molecular weights as well as construction of tailor-made polymers such as block copolymers, graft polymers, and end-functionalized polymers. Radical polymerizations involving dormant species are coined as reversible-deactivation radical polymerizations (RDRPs),[7] and they are mainly classified to three mechanisms: "dissociation combination", "atom transfer", and "degenerative chain transfer".   Metal-catalyzed living radical polymerization or atom transfer radical polymerization (ATRP) proceeds under the atom transfer mechanism, where radical species is reversibly capped with halogen (X) under one-redox catalysis by a transition metal complex ($Mt^n \leftrightarrow Mt^{n+1}$) (Figure 3A). Various complexes of ruthenium,[8] copper,[9] and iron[10] are available as the catalysts for ATRP.

Understandably, we use an excess amount of monomer for the initiator or chain transfer
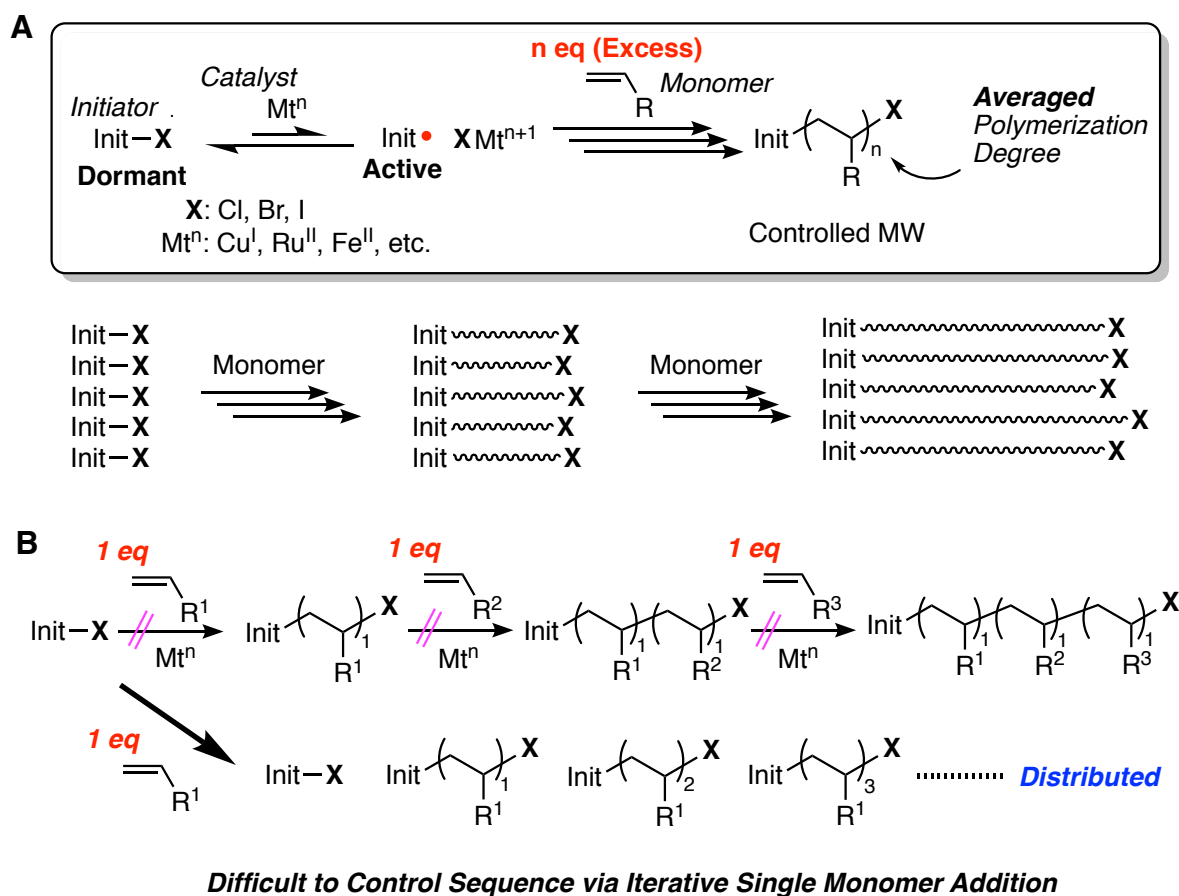
Figure 3. (A) Metal-catalyzed living radical polymerization mechanism (B) The inherent difficulty of single radical addition via living radical polymerization

agent to synthesize polymers via RDRP.   Herein, can we control the single monomer addition (SMA) via the reaction with an equimolar amount of monomer?   Unfortunately, the product is a mixture of the initiator, single, double, triple adducts and others due to the chain-growth mechanism (Figure 3B). Using non-conjugated monomer or an excess of initiator could allow the control of single monomer addition once, but it is difficult to repeat it toward construction of sequence-controlled oligomers/polymers.   We may rely on SEC purification to isolate the single-unit adduct, but this way is less efficient because it requires a lot of effort and the yield becomes low.   Despite the inherent difficulty in sequence control even with RDRP, the RDRP system must be useful because of the quantitative reaction from the initiator and suppression of undesirable reactions such as termination and chain transfer.   Here, several methodologies for synthesizing sequence-controlled copolymers based on RDRP and the characteristic features of the resultant polymers are described.

Monomer Design for Periodic Sequence Control

As mentioned above, copolymerization of common monomer pairs afforded statistical copolymers via chain-growth polymerization, and the resultant copolymer composition highly relies on monomer reactivity ratios.   Despite the inherent difficulties, several studies on periodic sequence control via monomer design have been reported.   In this section, the two strategies for periodic sequence control are reviewed: (A, B) divinyl monomer; (C, D) sequence-embedded oligo-monomer (Figure 4).

Ouchi et al. reported an asymmetric AB-type divinyl monomer (for M_1 = left monomer, M_2 = right monomer) whose both pendant groups were connected via cleavable linker.[11-14] The cyclopolymerization of the cleavable linker embedded divinyl monomer followed by cleavage of the linker affords an alternating copolymer carrying general pendant group. Crucial is the control of intermolecular propagation (i.e., M_1 radical to M_2) via cyclization reaction, which is attribute to neighboring effect from the linker design, and intramolecular propagation (i.e., M_2 radical to M_1) using the monomer reactivity ratios where the r_2 value is lower than r_1.   Two examples are shown in Figure 4A and B.   In the first design, a divinyl monomer carrying hemiacetal ester linker was designed to give alternating copolymers of methacrylic acid and 2-hydroxyethyl acrylate via the hydrolysis of the cleavable linker into carboxylic acid and hydroxy groups (Figure 4A).[12]   In another design, an active ester linker that can be transformed into amide group via post-modification (i.e., aminolysis) was used as cleavable linker (Figure 4B).[14]   The active ester acrylate was connected with another
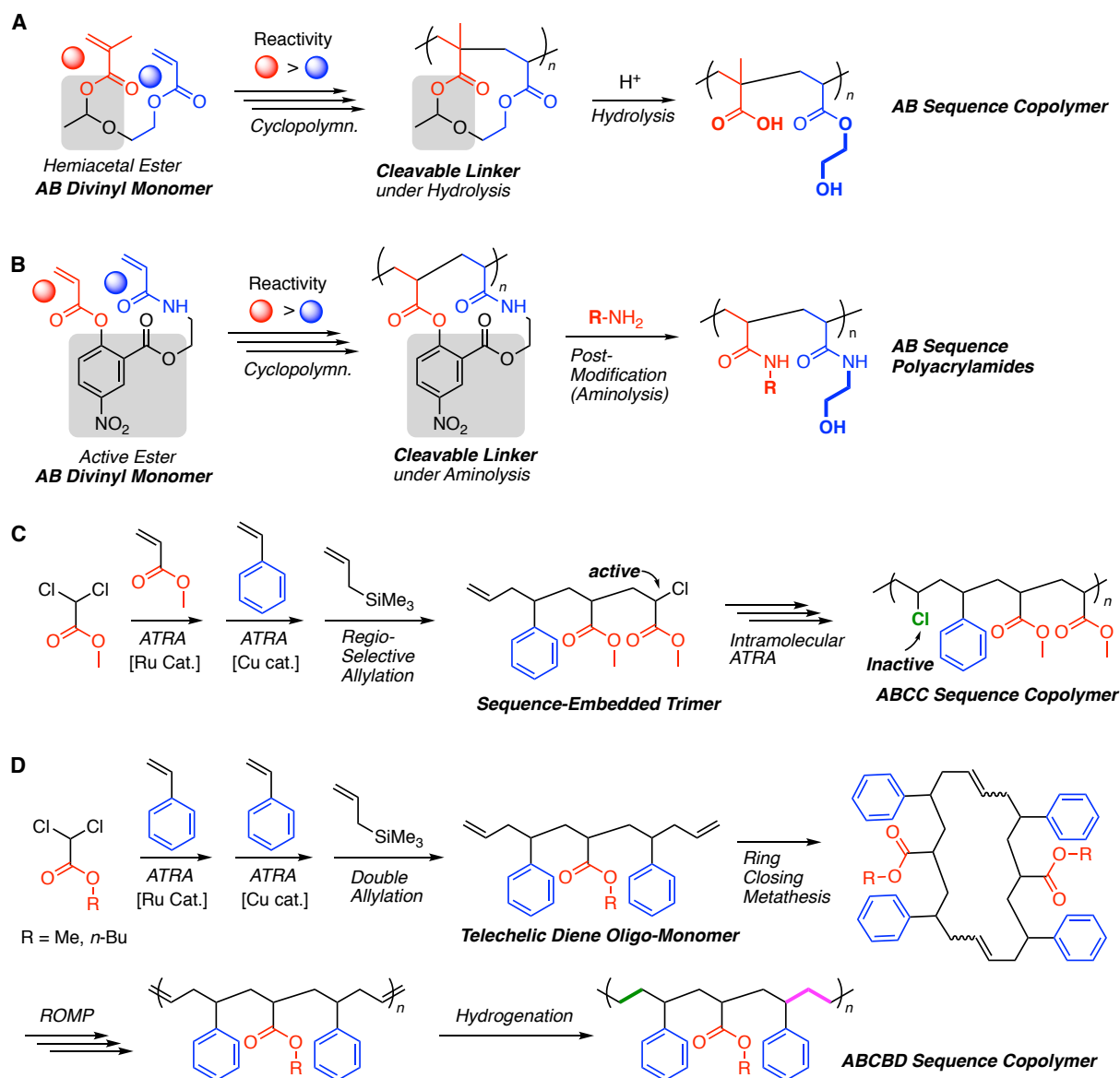
Figure 4. Monomer designs for periodic sequence control: (A, B) divinyl monomer carrying cleavable linker (C, D) sequence-embedded oligo-monomer.

acrylamide via cleavable linker.   The latter bond was placed in the opposite direction to the former to give a hydroxy pendant via the aminolysis reaction.   Thus, the aminolysis after cyclopolymerization allowed the synthesis of alternating copolymers two different pendants (i.e., amide pendant and hydroxy pendant).   However, both examples had the inherent difficulties such as the need for diluted condition to prevent cross-linking and complicated monomer synthesis.

Kamigaito et al. utilized iterative atom transfer radical addition (ATRA) to synthesize various sequence-embedded oligo-monomer with commonly used monomer such as styrene, acrylates, maleimide and acrylonitrile.[15-19]   For example, the sequence-embedded trimer was

synthesized by three consecutive reactions (Figure 4C).[15]   A first ATRA of methyl acrylate to methyl dichloroacetate catalyzed by ruthenium catalyst allowed to generate the methyl acrylate dimer containing two carbon-chloride bonds.   The second ATRA of styrene to either the two carbon-chloride bonds catalyzed by copper catalyst followed by the regio-selective allylation with allyltrimethylsilane to form sequence-embedded trimer containing active carbon-chloride. Subsequently, ABCC (A = chloride; B = styrene; C = methyl acrylate) sequence copolymers was synthesized via intramolecular ATRA of tetramers.   The activated carbon-chloride bond attacked the unconjugated carbon-carbon double bonds of another monomer to lead to step-growth propagation and the newly generated carbon-chloride bond, which is equivalent to the poly (vinyl chloride), was inactive for catalyst.   For another example, ABCBD (A = methylene; B = styrene; C = methyl (or *n*-butyl) acrylate; D = ethylene) sequence copolymers were synthesized via a combination of iterative ATRAs and olefin metathesis reactions (Figure 4D).[19]   First, they synthesized sequence-embedded trimer using ATRAs twice by metal-catalyst (i.e., ruthenium or copper) and then places olefins at both ends by allylation to obtain telechelic diene oligo-monomer.   Subsequently, the telechelic monomers could be transformed into the sequence-embedded cyclic monomer via ring-closing metathesis.   Ring opening metathesis polymerization (ROMP) of the cyclic olefin followed by hydrogenation of the resulting internal olefin successfully afforded ABCBD sequence copolymers.
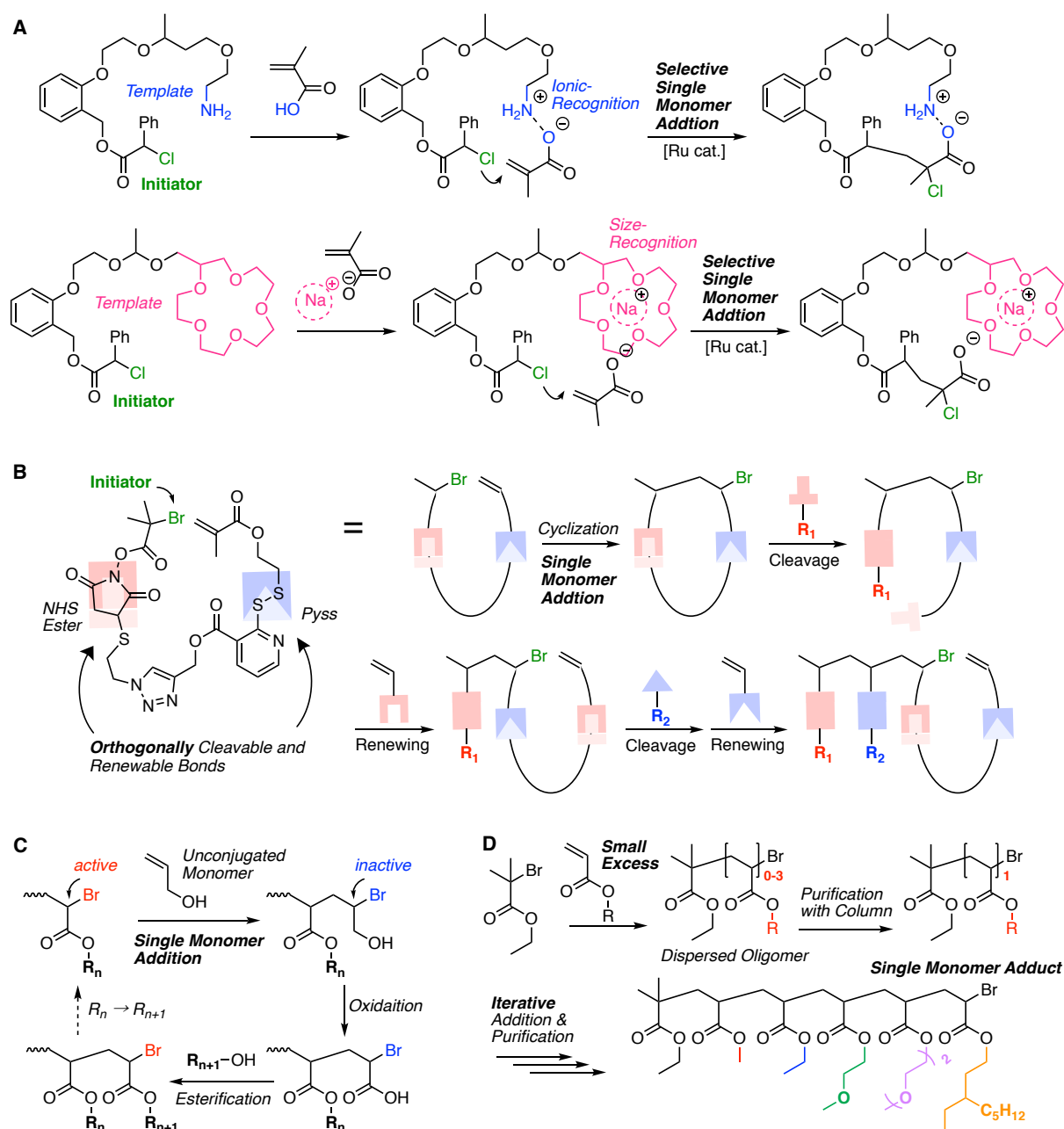
Iterative Single Monomer Addition

Solid phased peptide synthesis, developed by R. B. Merrifield, generates peptides with well-defined sequence via step-growth synthesis.[20]   The synthesis of well-defined sequences of amino acids is achieved by iterative cycles of SMA and deprotection.   Sequence-controlled vinyl polymers would be expected if this strategy can be applied to the synthesis of vinyl polymers.   Due to the chain-growth mechanism, however, the strategy of iterative SMA is not straightforward for vinyl polymers as mentioned above.

The development of the RDRP system gives a major breakthrough allowing for the iterative SMA strategies toward syntheses of sequence-defined polymers.   A monomer design for suppression of oligomerization/polymerization and RDRP system that can be reactivated from active carbon-halogen bond allow the strategy of iterative SMA.

For the template polymerization, the sequence can be controlled through the interaction between template and monomer.   The monomer is recognized to the template prior to propagation, and the recognition can be based on ionic interaction,[21] metal complexation,[22]

covalent bond,[23] and hydrogen bond.[24]   Sawamoto et al. reported a strategy of single monomer addition utilizing 'template initiator' carrying monomer recognition sites (Figure 5A).[21,22] The template initiator had two points on a benzene ring, one for recognition site and another for radical polymerization to synthesize a daughter polymer intramolecularly.   The ionic coordination of methacrylic acid (MAA) by the amine template led to selective single monomer addition of MAA via ruthenium-catalyzed radical addition.   A similar tendency was observed

Figure 5. The strategies for single monomer addition: (A) template-assisted single monomer addition (B) single monomer addition via cyclization (C) iterative cycle using unconjugated monomer (D) separation of single monomer adduct with column chromatography.

when a 15-crown-5-ether was introduced as the size-specific recognition site. The initiator exhibited selective radical addition of methacrylic acid carrying sodium cation by the size-recognition. Though this strategy showed the potentiality for the synthesis of sequence-controlled copolymers by introducing recognition sites, the two problems remained. One is synthesis of template with well-defined order of multiple recognition site, and another is control of propagation order on the templated polymerization. These problems must be resolved to realize the template polymerization for sequence-control.

The cyclization could be the key to realize iterative SMA. Ouchi et al. proposed the special inimer structure that contains cleavable and renewable linkers to realize iterative cyclization (Figure 5B).[25] The inimer had a carbon-bromine as an initiator for living radical polymerization and conjugated carbon-carbon double bond which was connected to the initiator through orthogonally cleavable and renewable linkers [i.e., *N*-hydroxysuccinimide ester (NHS ester) and pyridine disulfide (PySS)]. The bond of NHS-ester can be cleaved by the aminolysis to give an amide and NHS, and the cleaved NHS group can be regenerated to NHS-ester bond by esterification with acid halide. Similarly, PySS can also be cleaved and regenerated to S-S bond carrying conjugated carbon-carbon double bond. The SMA via cyclization was performed under the diluted condition to control selective propagation without unfavorable cross-linking. This strategy was demonstrated by the synthesis of sequence-controlled trimers.

Huang et al. achieved SMA to utilizing unconjugated vinyl monomer carrying ally alcohol via ATRP (Figure 5C).[26] The carbon-bromide bond after SMA was inactive for ATRP due to the lacking resonance stability of the allyl radical. The resultant bromide terminal was reactivated by oxidation of hydroxymethyl group into carboxyl acid followed by esterification with different pendants. Repeating the cycle of SMA and transformation steps could lead to sequence-controlled oligoacrylates, but the synthesis has not been reported since the first report.

Column chromatography techniques can utilize the synthesis of sequence-controlled polymers with highly efficient purification. Indeed, several recent studies have utilized automated flash chromatography to separate dispersed oligomers into monodispersed oligomers.[27-32] Junkers et al. reported the iterative SMA using the column chromatography (Figure 5D).[33] Small excess monomer was added into the initiator to produce dispersed short oligomers via photochemical ATRP. The resultant oligomers could be efficiently separated by column chromatography into the monodispersed oligomer, with single monomer adduct being the desired product. Repeating the cycle of addition and purification steps could allow to

synthesis of sequence-controlled oligomers.　Consequently, monodispersed oligomers with up to five units (i.e., methyl, ethyl, ethylene glycol, diethylene glycol and 2-ethylhexyl group) were successfully synthesized.　This strategy has the advantage of the broad monomer library due to independence of its characteristic monomer reactivity, but there are inherent problems that the process takes time and the overall yield gradually decreases as the cycle is repeated.

Objectives

As described above, several strategies for the synthesis of sequence-controlled polymers have been reported: design of templated initiator, cyclopolymerization of divinyl monomers connected via cleavable linker, using steric hindrance of bulky pendant, iterative SMA, and polymerization of pre-programmed monomer. However, these elaborate strategies were limited to laboratory-scale synthesis due to complicated synthesis consisting of many steps for the initiator and monomer, diluted conditions to overcome the inherent copolymerization behavior driven the reactivity ratios, and low overall yield.
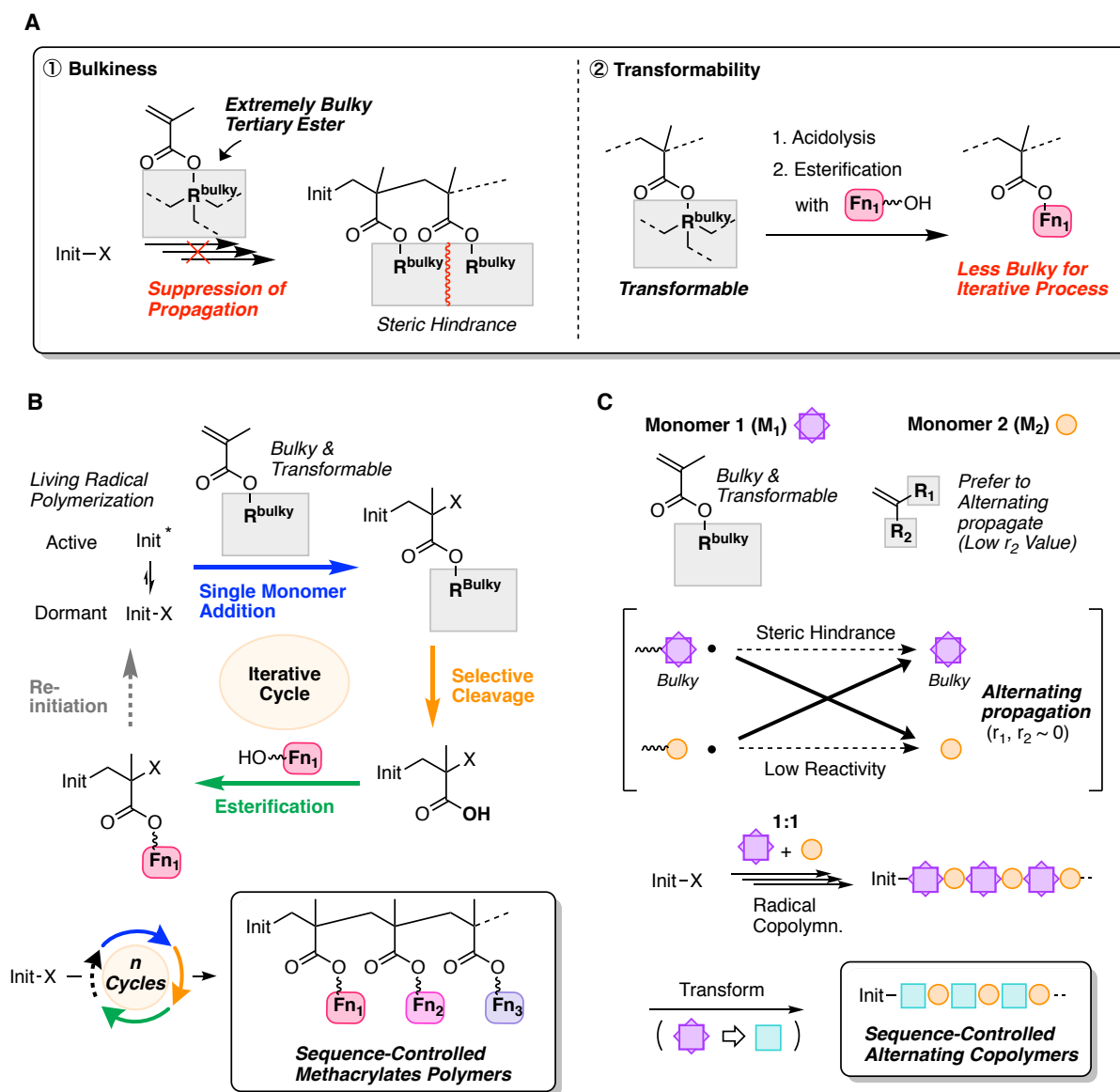

Figure 6. (A) Key concept in this thesis: bulky and transformable monomer design for sequence control (B) Iterative cycle with the bulky monomer toward the synthesis of sequence-controlled methacrylate polymers (C) Copolymerization with the bulky monomer toward a synthesis of sequence-controlled alternating copolymers.

Given these backgrounds, this thesis deals with special methacrylate monomer design for the synthesis of sequence-controlled (co)polymers. The author focused on "bulky and transformable" pendant as the component for the control of SMA under the radical polymerization. The key of this strategy is the introduction of the extremely bulky tertiary alcohol-based ester pendant to control SMA via suppression of propagation due to steric hindrance; the bulky pendant of single monomer adduct can be selectively transformed into a less bulky "desired" pendant via acidolysis and esterification for the iterative process (Figure 6A). Thus, the iterative cycle of SMA, selective cleavage, and esterification would give sequence-controlled methacrylate polymers (Figure 6B). In addition, the bulky methacrylate monomer allows for the progress of alternating copolymerization with a comonomer carrying less bulky pendant that gives a lower r_2 value for common methacrylate (M_1: methacrylate, M_2: the comonomer) because a r_1 value significantly decreases to zero due to the steric hindrance (Figure 6C). Consequently, the resultant alternating copolymers after the 1:1 radical copolymerization of bulky methacrylate and the comonomer followed by the transform of the bulky pendant would allow to synthesize sequence-controlled alternating copolymer consisting of common monomer units.

Outline of This Study

This thesis consists of two parts including four chapters: **Part I** (Chapters 1, 2) deals with design of bulky and transformable methacrylate monomer for the control of sequence-controlled oligo- or poly(methacrylate)s via the iterative cycle. This special monomer design is crucial for the precise control of SMA under living radical polymerization as well as selective transformation into less bulky desired pendants for the iterative process. **Part II** (Chapters 3, 4) focused on the control of alternating sequence with the special monomer. The unique polymerization behaviors of the special monomer, that is inactive for homopolymerization but active for copolymerization, allowed the progress of alternating copolymerization in conjunction with comonomers carrying low reactivity to common methacrylates. In addition, the resultant copolymer followed by the acidolysis of the bulky pendant afforded the alternating copolymers consisting of methacrylic acid and the comonomer units.

In PART I, ***Chapter 1*** studied a special methacrylate monomer to control sequence for vinyl polymers. The tertiary alkyl methacrylate monomer carrying isopropyl and adamantyl group (IPAMA) allowed precise control of SMA with initiator via living radical polymerization. The bulky pendant of single monomer adduct can be selectively cleaved and subsequently transformed into less bulky and non-tertiary pendant to repeat the cycle. Thus, an iterative cycle of SMA, selective cleavage, and esterification can be repeated to synthesize sequence-controlled oligo- and poly(methacrylate)s. In this chapter, the strategy utilizing special methacrylate monomer are actually demonstrated as well as the scope of applicable alcohols for the esterification process.
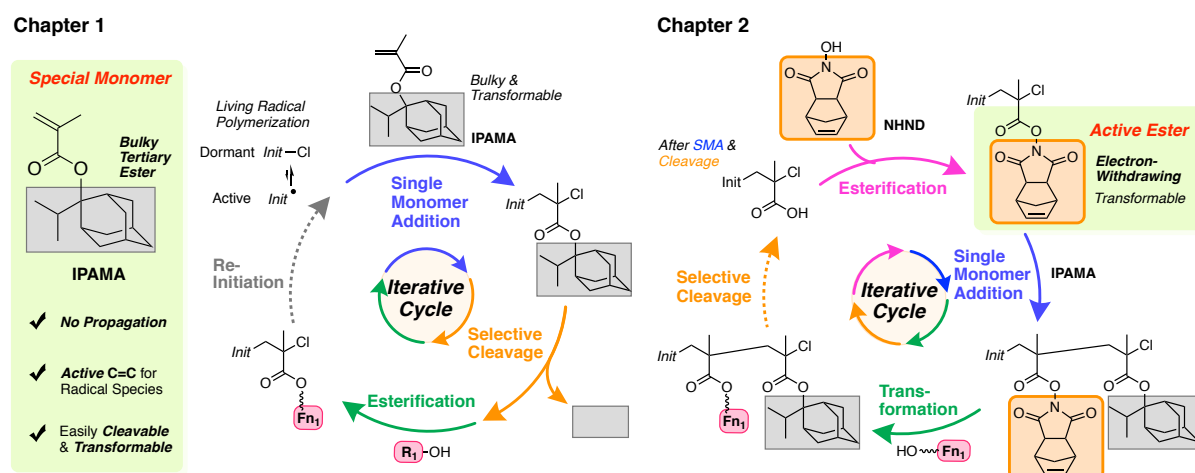

Figure 7. The overview of Part I: special monomer design for the precise control of single monomer addition toward sequence-controlled vinyl polymers (***Chapter 1***) and introduction of active ester to growing-end pendant for efficient single monomer addition (***Chapter 2***).

In *Chapter 2,* iterative SMA under ATRP was studied in detail toward syntheses of sequence-controlled oligo- and poly(methacrylate)s for higher yield. An introduction of active ester, that is electron-withdrawing and transformable by amidation or esterification, to growing-end pendant led to efficient SMA of IPAMA without unfavored reaction (i.e., termination by combination). A cycle of SMA, transformation, selective cleavage, and esterification realized effective SMA as well as iterative process with higher overall yield.

In PART II, *Chapter 3* studied a facile methodology to synthesize alternating-rich copolymers consisting of MAA and *N*-alkyl acrylamide units. Another bulky tertiary alkyl methacrylate carrying ethyl and fenchol group (EFMA) was designed for control of alternating copolymerization. The copolymerization of EFMA with *N*-hydroxy-succinimidyl acrylate (NSA) carrying electron-withdrawing substituent followed by transformation (i.e., amidation for NSA and acidolysis for EFMA) afforded alternating-rich copolymers consisting of MAA and *N*-alkyl acrylamide units. The resultant copolymers made of MAA with *N*-isopropyl acrylamide or *N*-octadecyl acrylamide showed sequence-driven solubilities and thermal response properties.

In *Chapter 4*, an alternating copolymer made of MAA and acrylonitrile (AN) was synthesized by using EFMA. The copolymerization of EFMA and AN followed by transformation (i.e., acidolysis) gave alternating-rich copolymer of MAA and AN. The resultant copolymers showed sequence-driven thermal reactivity in comparison with the corresponding 1:1 statistical copolymer.
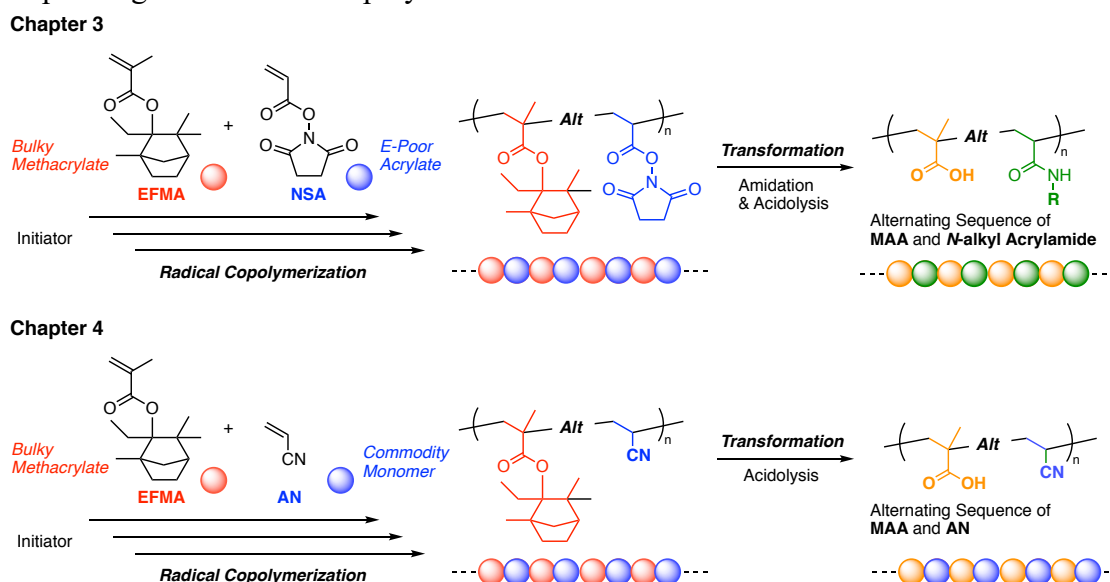
Figure 8. The overview of Part II: synthesis of the alternating copolymers made of MAA and *N*-alkyl acrylamide (*Chapter 3*) and the alternating copolymers made of MAA and AN (*Chapter 4*) utilizing the bulky methacrylate.

In summary, the author has developed new concepts and strategies for syntheses of sequence-controlled vinyl oligomers/polymers via chain-growth polymerization. The key to these strategies is design of an extremely bulky and transformable methacrylate monomer. The thesis would open the door to sequence control for vinyl polymers as well as design of sequence-driven functions of vinyl polymers in the future.

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PART I

# Control of Aperiodic Sequence via Iterative Single Monomer Addition

Chapter 1

Iterative Radical Addition with a Special Monomer Carrying Bulky and Convertible Pendant: A New Concept toward Controlling the Sequence for Vinyl Polymers

Abstract

Herein the author proposes a new concept to control sequence for vinyl polymers. A tertiary alkyl methacrylate monomer carrying both adamantyl and isopropyl groups (IPAMA) is very unique to allow control of single unit addition with an alkyl halide initiator for metal-catalyzed living radical polymerization due to the exceptional bulkiness. After control of the single unit addition, the bulkiness can be removed via acidolysis to further convert into the ester pendant with less bulky and nontertiary alcohol. The resultant adduct can be used as an initiator for the next single unit addition of IPAMA and the terminal ester can be selectively hydrolyzed followed by esterification similar to the first process. Namely, the cycle consisting of "radical addition of IPAMA", "acidolysis of the IPAMA side group", and "esterification of resultant carboxylic acid" can be repeated to construct sequence well-defined poly(oligo-)methacrylates. In this letter, results of the cycle and the iterative process with the special methacrylate monomer are actually demonstrated as well as the scope of applicable alcohols for the esterification process toward sequence control with functional units.
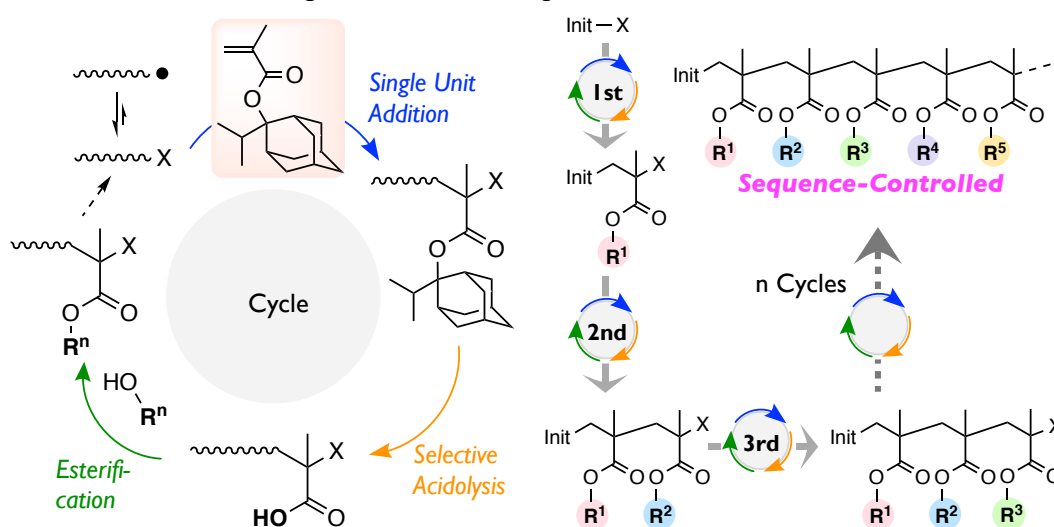
Introduction

For natural polymers such as DNA and peptides, "sequence" or an order of repeating units (i.e., nucleotides and amino acids) is an essential structural factor governing higher-order structures as well as the functions. The side groups, that is, nucleobases and amino acid residues, are arranged with well-defined order along the main chain for the identifiable molecular information. Similar macromolecular structures consisting of repetitive units and side groups can be seen in vinyl polymers that are artificially synthesized via chain-growth polymerization of vinyl monomers: typically, side groups are dangled from every other carbon on the carbon-based main chain or polyethylene. Development of precision polymerizations has allowed control of main chain length (i.e., molecular weight) and terminal groups for vinyl polymers by means of living polymerizations and that of direction of the side group (i.e., tacticity) by stereospecific polymerizations.[1] Unfortunately, the chain growth mechanism is totally unsuitable for sequence control, because growing active species would lead to statistical chain reactions with existing monomers. Indeed, organisms in nature do not use chain growth mechanism but iterative process to achieve sequence control for macromolecules taking advantage of sophisticated template system.

There has been a growing interest in sequence control for synthetic macromolecules in recent years and some methodologies have been reported:[2,3] polymerization of programmed monomer,[4-9] utilizing inherent monomer reactivity, and iterative process along with protection/deprotection of reactive sites.[10-14] Although these are elaborate methodologies, some issues have been left toward sequence-driven functional macromolecules, likely due to that sequence patterns (periodic vs aperiodic) and introduced functional groups are still limited. One of ultimate goals in this field should be "desired" sequence control for vinyl copolymers consisting of repetitive units with various side groups to provide sequence-oriented functions like natural peptides.

Some attempts have been reported toward "desired" sequence control for vinyl polymers. One pioneering research is iterative single monomer addition on the basis of living cationic polymerization of vinyl ethers.[15] Quite recently, such iterative addition process for sequence control has been studied by means of living radical polymerization or reversible deactivation radical polymerization.[16,17] In these researches, living polymerization is essential to maintain the activity of growing terminal through reversible capping with suitable leaving group (halogen or thioester) after single unit addition. However, the inherent statistical addition feature due to chain-growth mechanism forces purification after each addition process

for removal of side products where no monomer or more than one unit is inserted. The author's group has quite recently reported a new concept to control sequence in which single monomer addition is controlled via cyclization and the iterative process is realized by introduction of two types of cleavable/ renewable linkers.[18] The concept is interesting, but there still remains a problem of poor efficiency in the syntheses. Huang's approach with aryl alcohol seems to be promising toward sequence-controlled vinyl polymer, where the nonconjugated vinyl compound is expected to allow control of single unit addition under ATRP process due to the lower propagation ability and the alcohol side group could be converted into conjugated ester after the addition.[19] Thus, a chance could arise to generate controlled radical species under ATRP condition, leading to the iterative process consisting of radical addition and side-group transformation. However, the further study has been not reported after the conceptual report, likely due to low efficiency in addition of aryl alcohol.

In this work, the author proposes a new methodology to control sequence for vinyl polymer segment consisting of methacrylate units. Crucial is introduction of very bulky side-group to control single unit addition by restraining continuous propagation and that the side group is selectively cleavable after the single unit addition into less bulky and noncleavable ester pendant to repeat the cycle (Figure 1a). Thus, the iterative cycle consisting of radical addition, cleavage, and functionalization would give methacrylate-based sequence- controlled segment (Figure 1b).

A matter of prime importance in this approach is the selection of such a special methacrylate monomer fulfilling both bulkiness and selective cleavability. The latter is essential to realize selective transformation of the monomer side group into functional group at terminal without damaging other functionalized side groups. The author focused on tertiary
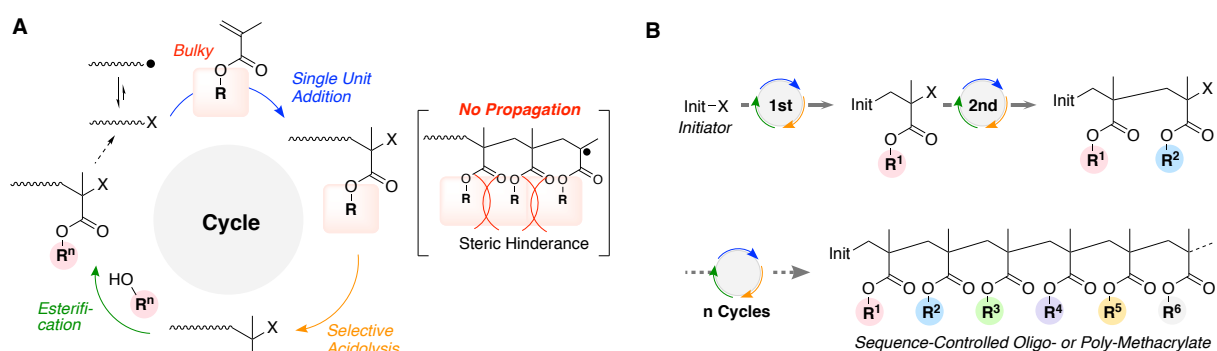
Figure 1. (A) A cycle consisting of "single unit addition", "selective acidolysis", and "esterification" with a special methacrylate monomer carrying very bulky and convertible pendant. (B) The iterative cycle to construct sequence-controlled oligo-or poly-methacrylate.

(3°) ester to realize the selective cleavage because such a tertiary (3°) ester side group is known to be cleavable into −COOH under acidolysis, as applied for photoresist applications.   Unless very bulky or tertiary alcohol is used for the esterification process, it is expected that the cycle can be repeated.

Experimental

Materials

The following reagents were used as received: α-chlorophenylacetyl chloride (Aldrich, >90%), 1-dodecanol (TCI, >99.0%), 2-isopropyl-2-adamantyl methacrylate (IPAMA; TCI, >98.0%), trifluoroacetic acid (TFA: Wako, >98.0%), methanol (Wako, >99.8%), ethanol (Wako, >99.5%), 3-phenyl-1-propanol (TCI, >98.0%), propargyl alcohol (Aldrich, >99.0%), 3-buten-1-ol (TCI, >98.0%), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC-HCl: TCI, >98.0%), *N,N'*-diisopropylcarboiimide (DIC;: TCI, >97.0%), 4-dimethylaminopyri-dine (DMAP: TCI, >99.0%).   Triethylamine (TCI, >99.0%) was dried overnight over calcium chloride and distilled before use.   Column chromatography was carried out using Wakosil C300 (Wako) as the stationary phase.

All reagents for ruthenium catalyst, listed below, were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inter-gas-systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere (H_2O < 0.1 ppm; O_2 < 0.1 ppm): Ruthenium(III) Chloride hydrate (Wako, > 99.9%), 1,2,3,4,5-penta-methylcyclopentadiene (TCI, > 93%), lithium triethylhydridoborate (Aldrich, 1.0 M solution in THF), 1,2-bis(diphenylphosphino)-ethane monoxide (BPMO Ligand: Aldrich, > 97%).   The ruthenium precursor [Cp*Ru(μ_3-Cl)]$_4$ was synthesized as described in the literature.[20]

Toluene (Kishida kagaku, Osaka, Japan; purity 99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 30 min immediately before use. 1,2,3,4-tetrahydrousnaphthalene (tetralin; internal standard for ^{1}H NMR) were dried over calcium chloride and distilled from calcium hydride.   Unless stated otherwise, all the solvents were purchased from Wako Pure Chemical Industries and used without further purification.

Measurement

The product for each step was purified by preparative recycling SEC (column: Jasco

KF-5001) connected to a Jasco PU-2086 precision pump, a Jasco RI-2031 refractive-index detector and a Jasco UV-2075 ultraviolet detector.   ^{1}H NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer, operating at 500.125 MHZ. Electrospray-ionization mass spectra (ESI-MS) were measured on a Waters Quattro micro API.

Synthesis

Hydrolysis of IPAMA

IPAMA (0.105 g, 0.40 mmol) were placed in glass tube and dissolved in dichloromethane (DCM, 10 mL).   To this resultant solution, TFA (0.15 mL, 2.0 mmol) were added at 0 ˚C while stirring for 30 min.   After the reaction mixture was concentrated under reduced pressure at 40 ˚C, and subsequently measured with ^{1}H NMR (Figure 2C).

Selective Acidolysis of IPAMA

IPAMA (0.105 g, 0.40 mmol) and MMA (0.043 mL, 0.40 mmol) were placed in glass tube and dissolved in DCM (10 mL).   To this resultant solution, TFA (0.15 mL, 2.0 mmol) were added at 0 ˚C while stirring for 30 min.   Subsequently, the reaction mixture was measured with ^{1}H NMR (Figure 2D).

Synthesis of dodecyl 2-choloro-2-phenylacetate (DCPA: Initiator)

Triethylamine (25.4 mL, 183 mmol) and 1-dodecanol (34.1 mL, 152 mmol) were placed in round-bottom flask under argon and then dissolved in DCM (500 mL).   To the resultant solution, α-chlorophenylacetyl chloride (26.3 mL, 166 mmol) was gradually added at 0 ˚C, while stirring for 30 min.   The reaction solution was warmed to room temperature and stirred overnight.   To the solution, 600 mL of Et$_2$O were added, followed by addition of 600 mL of sat. NaHCO$_3$ solution.   The organic layer was washed with brine 3 times and dried on Na$_2$SO$_4$. After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane : ethyl acetate = 95:5).   The product was obtained as slightly yellow oil (153 mmol, 92 %). The ^{1}H NMR spectrum was shown in Figure S1: ^{1}H NMR (in CDCl$_3$): 7.49 (dd, 2H), 7.41-7.33 (m, 3H), 5.34 (s, 1H), 4.15 (t, 2H), 1.60 (quint, 2H), 1.34-1.17 (m, 18H), 0.88 (t, 3H).   The ESI-MS: observed; 361.20 m/z, calculated (+ Na); 361.19 m/z.

Ruthenium-catalyzed radical addition of IPAMA with DCPA in 1st cycle

The typical procedure is given as below: [Cp*Ru(μ$_3$-Cl)]$_4$ (0.31 g, 0.29 mmol) and

BPMO ligand (0.96 g, 2.3 mmol) were placed in round-bottom flask under argon and dissolved in toluene (280 mL).   The solution was heated to 80 ˚C for 1 h to prepare ruthenium complex: here, the color changed from black-red to yellow-brown.   Separately, IPAMA (15.2 g, 57.9 mmol) was placed in another round-bottom flask under argon.   After cooling the ruthenium complex solution to room temperature, the solution was transferred to IPAMA.   To the resultant solution, tetralin (1.40 mL) and DCPA (initiator, 2.0 mL, 5.80 mmol) was added and subsequently stirred for 4 h at 100 ˚C.   After the reaction mixture was concentrated under reduced pressure at 40 ˚C, the crude product was passed through a neutral silica column chromatography (hexane : ethyl acetate = 1:4) to remove Ru catalyst, followed by purification with preparative recycling SEC technique.   The product (**I**) was obtained as slightly yellow oil (4.93 mmol, 85 %).   The ^{1}H NMR spectrum was shown in Figure S2: ^{1}H NMR (in CDCl$_3$): 7.34-7.21 (m, 5H), 4.12-3.96 (m, 2H), 3.94-3.76 (m, 1H), 3.18-3.02 (m, 1H), 2.73-2.40 (m, 4H), 2.00-1.58 (m, 15H), 1.54 (quintet, 2H), 1.34-1.17 (m, 18H), 1.02-0.97 (dt, 6H), 0.88 (t, 3H). The ESI-MS: observed; 623.40 m/z, calculated (+ Na); 623.40 m/z.

Selective acidolysis of the single unit adduct of IPAMA in 1st cycle

The typical procedure of cleavage is given as below: the IPAMA adduct (**I**, 0.73g, 1.22 mmol) were placed in glass tube under argon and dissolved in DCM (30 mL).   To this resultant solution, TFA (0.47 mL, 6.14 mmol) was added at 0 ˚C while stirring for 30 min.   After the reaction mixture was concentrated under reduced pressure at 40 ˚C, the crude product was purified with preparative recycling SEC technique. The methacrylic acid product **II** was obtained as slightly yellow oil (1.13 mmol, 93 %).   The ^{1}H NMR spectrum was shown in Figure S3: ^{1}H NMR (in CDCl$_3$): 7.34-7.21 (m, 5H), 4.09-3.99 (m, 2H), 3.94-3.85 (m, 1H), 3.13-2.92 (m, 1H), 2.58-2.37 (m, 1H), 1.79-1.72 (d, 3H), 1.54 (sext, 2H) 1.34-1.14 (m, 18H), 0.88 (t, 3H).   The ESI-MS: observed; 447.21 m/z, calculated (+ Na); 447.23 m/z.

Esterification with methanol in 1st cycle

The typical procedure of cleavage is given as below: the methacrylic acid adduct (**II**, 0.785 g, 1.85 mmol) and DMAP (22.6 mg, 0.19 mmol) were placed in round-bottom flask under argon and dissolved in DCM (60 mL).   To this resultant solution, DIC (0.43 mL, 2.77 mmol) and methanol (0.75 mL, 18.5 mmol) were added at 0 ˚C and subsequently stirred for 1 h.   The solution was warmed to room temperature and stirred for 24h.   After the reaction mixture was concentrated under reduced pressure at 40 ˚C, the crude product was purified with preparative

recycling SEC technique to remove DIC and DMAP, followed by purification with a neutral silica column chromatography (eluent: ethyl acetate) to remove by-product (activated ester or carboxylic anhydride).   The methanol-esterified product was obtained as slightly yellow oil (1.23 mmol, 69 %).   The ^{1}H NMR spectrum was shown in Figure S4: ^{1}H NMR (in CDCl$_3$): 7.34-7.21 (m, 5H), 4.08-3.98 (m, 2H), 3.92-3.84 (m, 1H), 3.68-3.4 (d, 3H), 3.09-2.86 (m, 1H), 2.58-2.34 (m, 1H), 1.73 (d, 3H), 1.53 (quintet, 2H), 1.34-1.14 (m, 18H), 0.88 (t, 3H).   The ESI-MS: observed; 461.21 m/z, calculated (+ Na); 461.24 m/z.

Procedures for 3 steps (radical addition, acidolysis, and esterification) in 2nd and 3rd cycles were also done similar to those in 1st cycle. ^{1}H NMR and ESI-MS spectrum of products are shown below (Figure S5-13).

Result and Discussion

The author focused on an adamantyl group for the bulkiness to screen five kinds of tertiary ester methacrylates carrying adamantyl group (ADMA, IAM, MAMA, EAMA, and IPAMA) for the polymerization ability in ruthenium-catalyzed living radical polymerization at 100 °C (Figure 2A).[21]   It is assumed that the special monomer suitable for this concept is hardly polymerized.   When the tertiary carbon of adamantyl group is directly connected to ester (i.e., ADMA), the monomer was smoothly polymerized [Figure 2(A-1)], as reported.[22] The monomer in which adamantyl group is not connected directly to the ester (IAM) was also polymerized easily.   On the other hand, the polymerization ability was remarkably decreased when the secondary carbon of adamantyl group was connected to ester in conjunction with alkyl chain [−CH$_3$, MAMA; −CH$_2$CH$_3$, EAMA; −CH(CH$_3$)$_2$, IPAMA].   Above all, IPAMA was hardly polymerized under this condition.   However, this methacrylate was fairly copolymerized with methyl methacrylate (MMA) [Figure 2(A-2)].   These results indicate that the pendant of IPAMA is too bulky to sequentially propagate but the double bond is active enough for radical species.

Then, radical addition behaviors of IPAMA were studied under conditions for ruthenium-catalyzed living radical polymerization [Figure 2(A-1)].[23]   The solutions containing a chlorine-based initiator (DCPA)[24] and an excess amount of IPAMA (2, 5, and 10 equiv.) was heated at 100 °C in conjunction with ruthenium catalyst and conversions of IPAMA were   plotted against time.   The monomer was consumed under every condition, but
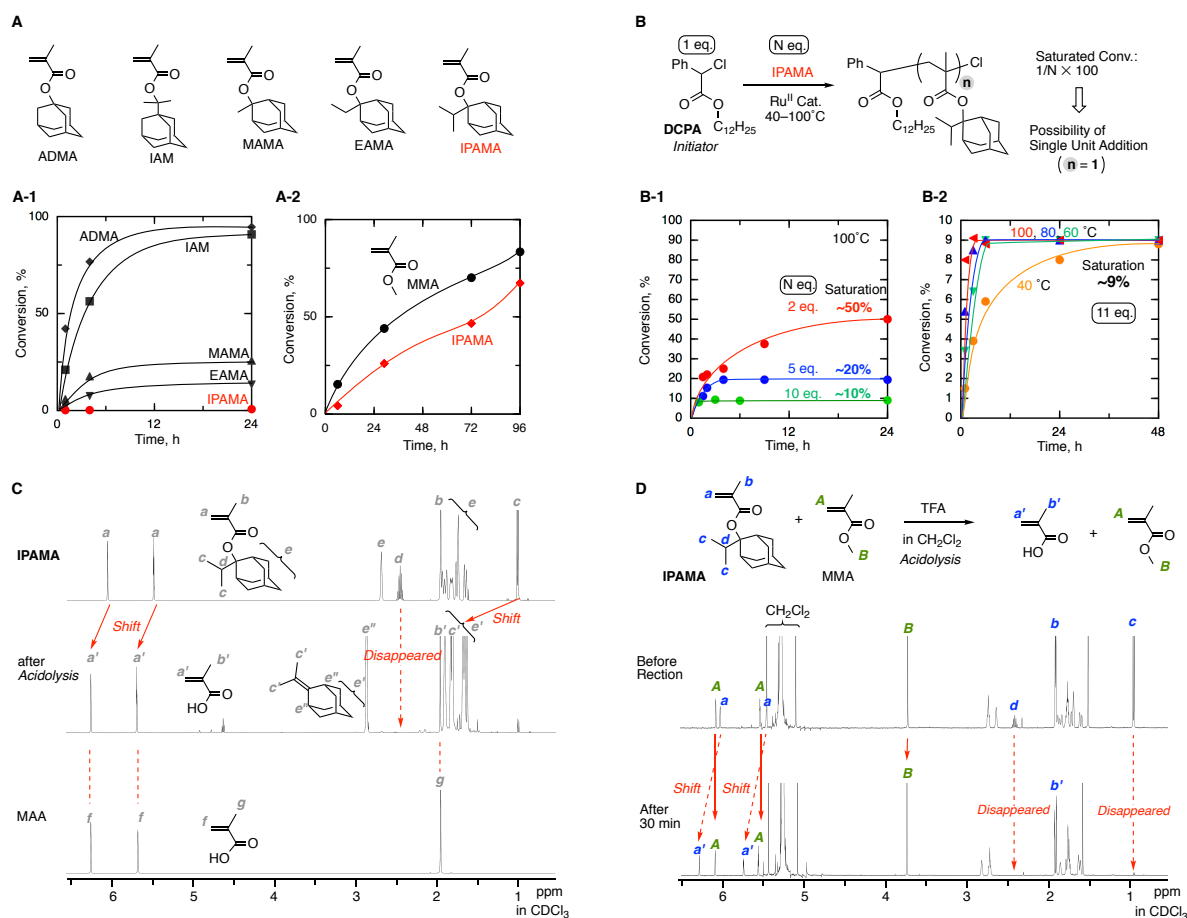
Figure 2. (A-1) Radical polymerizations of various methacrylate monomers carrying adamantly group: $[Monomer]_0/[DCPA]_0/[[Cp*Ru(\mu_3-Cl)]_4]_0/[BPMO\ Ligand]_0 = 2000/20/4.0$ mM in toluene at 100°C. (A-2) Radical copolymerization of IPAMA with MMA: $[MMA]_0/[IPAMA]_0/[ECPA]_0/[Ru(Ind)Cl(PPh_3)_2]_0/[n\text{-}Bu_3N]_0 = 2000/2000/20/2.0/\ 20$ mM in toluene at 80°C. (B) Radical addition of IPAMA: (B-1) $[IPAMA]_0/[DCPA]_0/[[Cp*Ru(\mu_3-Cl)]_4]_0/[BPMO\ Ligand]_0 = 40,\ 100,$ or $200/20/1.0/8.0$ mM in toluene at 100°C. (B-2) $[IPAMA]_0/[DCPA]_0/[[Cp*Ru(\mu_3-Cl)]_4]_0/[BPMO\ Ligand]_0 = 220/\ 20/1.0/8.0$ mM in toluene at 40–100°C. (C) Hydrolysis of IPAMA: $[IPAMA]_0/[TFA]_0 = 40/200$ mM in DCM at 0°C. (D) Selective Acidolysis of IPAMA: $[IPAMA]_0/[MMA]_0/[TFA]_0 = 40/200$ mM in DCM at 0°C.

interestingly, the conversion was saturated around 50, 20, and 10%, respectively. These values of saturated conversions showed good agreement with those assuming single unit additions were controlled (i.e., $1/N \times 100$; $N = [IPAMA]_0/[initiator]_0$). Next, to see effects of temperature on the behaviors, the radical reactions were performed at various temperatures under 11 equiv. condition ($[IPAMA]_0/[initiator]_0 = 11$) [Figure 2(B-2)]. As the temperature was decreased, the reaction was slower, but the conversions were saturated around 9% regardless of the temperature, which is also consistent with that single unit addition was

controlled.

The cleavable ability of the ester in IPAMA was also studied.   An addition of trifluoroacetic acid (TFA) into the IPAMA solution induced acidolysis of the side group to give methacrylic acid quantitatively (Figrue 2C).   To confirm the selectivity for the acidolysis, the reaction was performed in the presence of MMA with primary ester pendant (Figrue 2D). Consequently, IPAMA was transformed into methacrylic acid, whereas MMA remained unchanged.

Given results of the preliminary reactions shown above, the first cycle was actually performed by starting at the radical reaction of IPAMA with DCPA at 100 °C, where 10 equiv. of IPAMA and DCPA were injected in conjunction with Ru(II) catalyst.   After the conversion was saturated at about 10%, the product was purified to remove excess IPAMA and catalyst,
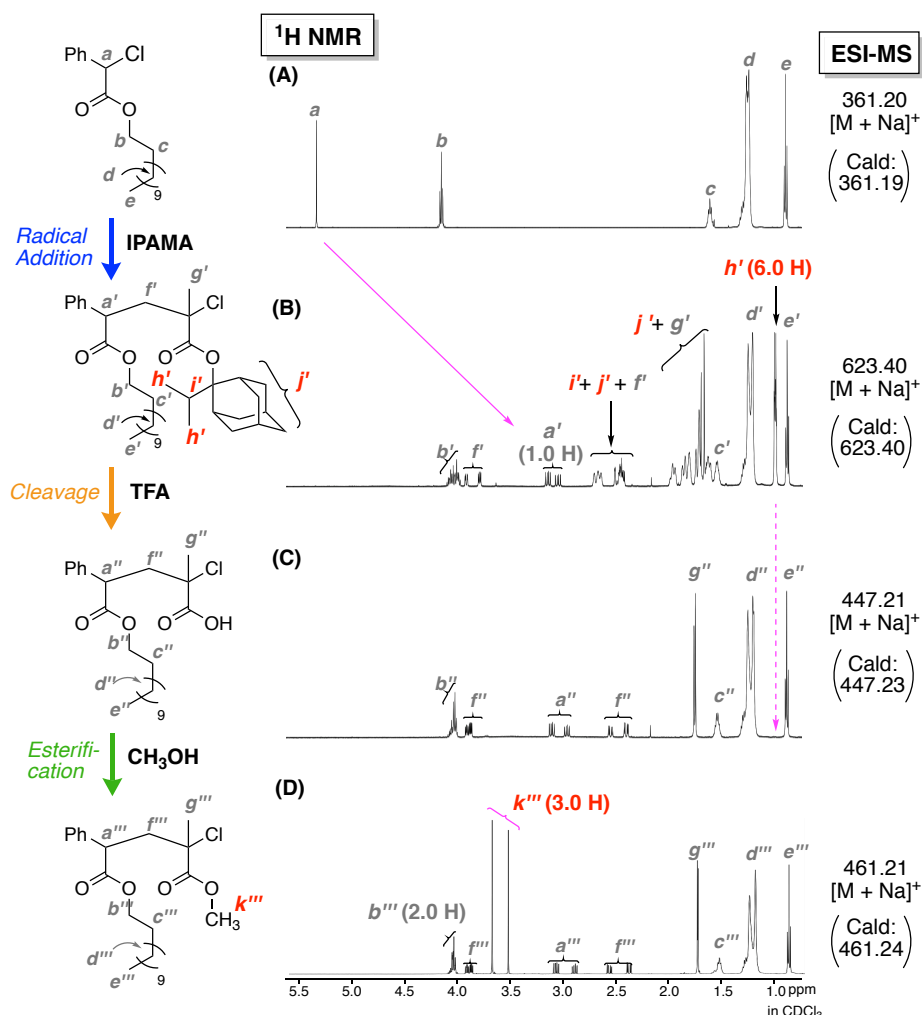
Figure 3. ^{1}H NMR analyses of products in the 1st cycle: (A) DCPA (Initiator) (B) the adduct of DCPA with IPAMA after ruthenium-catalyzed radical addition (C) hydrolyzate of the adduct (D) product by esterification of hydrolyzed product with methanol.

followed by structure characterization with ^{1}H NMR (Figure 3). The peak from methine proton neighboring to chlorine [a in (A)] quantitatively shifted to upper field [a' in (B)], and many peaks appeared from protons of IPAMA pendant group. Importantly, the peak integration ratio between protons from DCPA and IPAMA indicated that the single unit adduct of IPAMA to DCPA was actually formed: a'/h' = 1.0:6.0. The ESI-MS analysis of the product also supported the formation of the 1:1 adduct.

For the 1:1 adduct, TFA was treated to cleave the IPAMA side group via acidolysis. The cleavage quantitatively proceeded, as characterized by ^{1}H NMR (Figure 3C) and ESI-MS. Note that the primary ester derived from the initiator survived through the acidolysis process and only IPAMA derived ester was decomposed. For the next esterification, methanol was tested as the alcohol for condensation to the −COOH side group after the acidolysis to give the adduct of MMA unit. In the ^{1}H NMR spectrum of product (Figure 3D), peaks from methoxy side group[25] newly appeared with the reasonable integration ratio (b'''/k''' = 1.0:3.0) and the mass was increased for that of methoxy (CH$_3$O−) substituent. Consequently, the esterification was fairly performed to give the MMA adduct (Init-MMA-Cl).
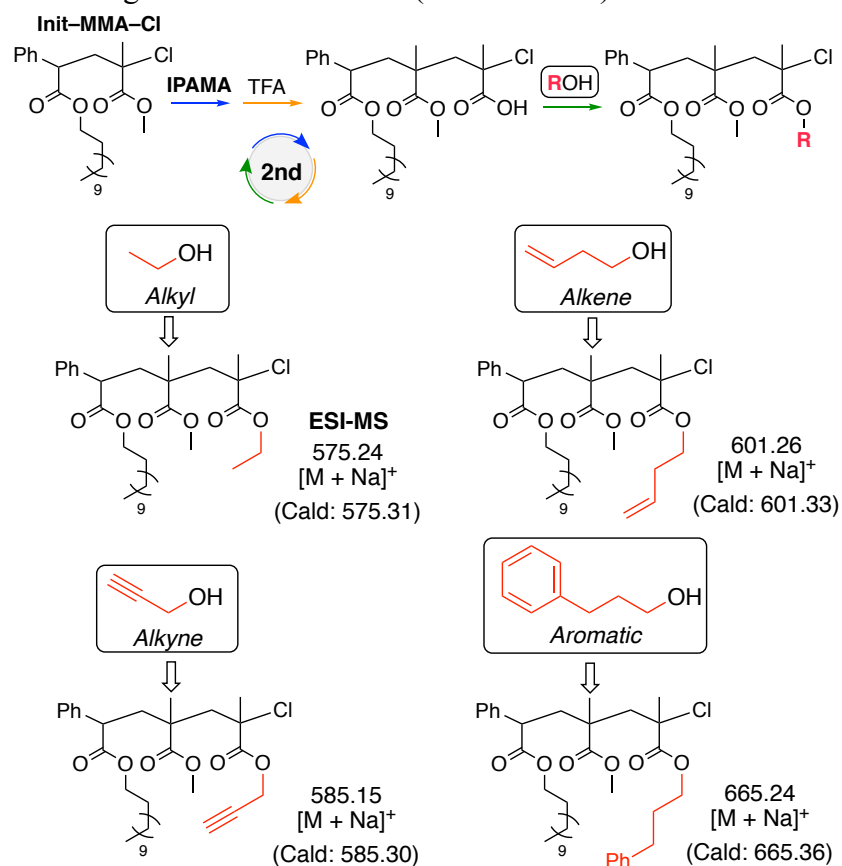
Figure 4. 2nd Cycle starting from radical addition of IPAMA with the product (Init–MMA–Cl) obtained via 1st cycle. Four kinds of alcohols were used for the esterification process.

Then, the second cycle was studied using the product (Init- MMA-Cl) after first cycle including esterification with methanol (Figure 4). By fears of unfavorable side reactions at higher temperature, the radical addition of IPAMA with Init-MMA-Cl was performed at lower temperature (80 °C). The single unit addition was controlled even in the second cycle to give the single unit of IPAMA adduct (Init-MMA-IPAMA-Cl). The IPAMA side group can be selectively cleaved into −COOH, followed by esterification with four kinds of alcohols (ethanol, 3-butenyl alcohol, propargyl alcohol, and 3-benzenepropanol) for study on scope of alcohols for the esterification process. As a result, they were quantitatively introduced, supported by ^{1}H NMR and ESI-MS. It is important that alkene and alkyne can be introduced because they are useful for post-functionalization via click-type reactions toward sequence-control with functional groups.

To confirm the reproducibility of this concept, the third cycle was finally studied using
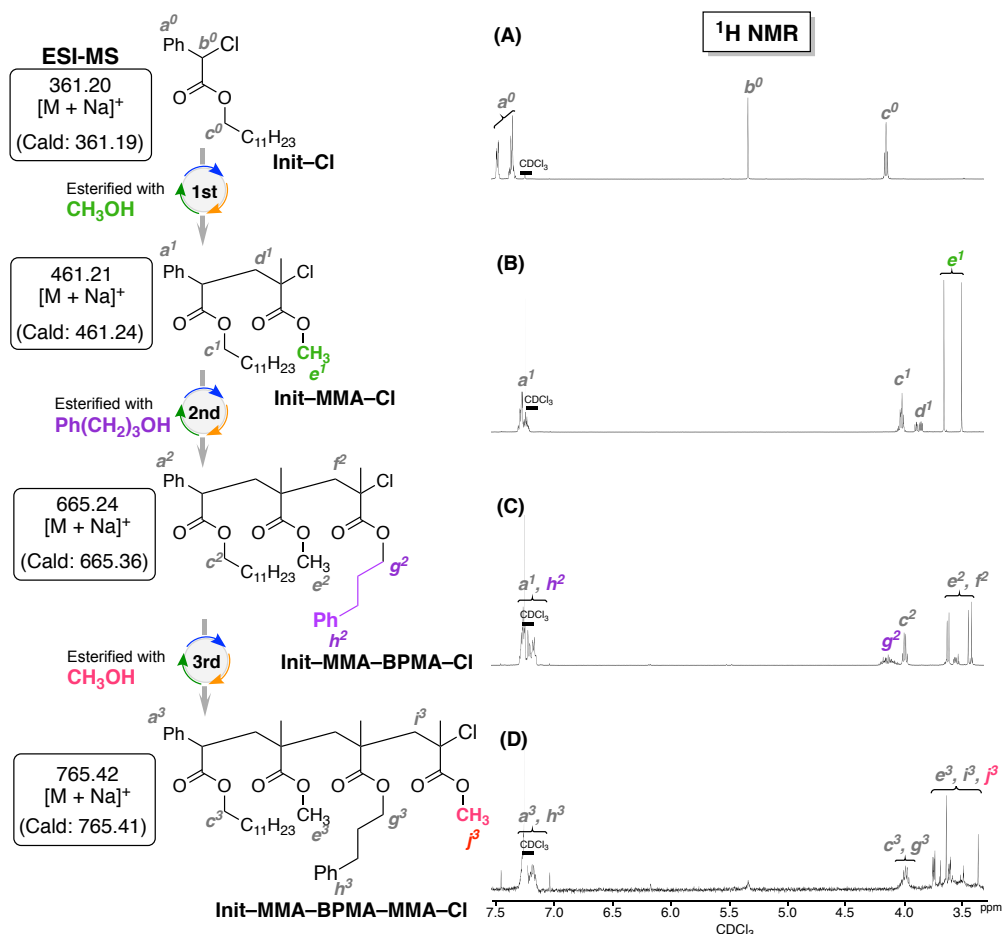
Figure 5. ^{1}H NMR spectra and ESI-MS analyses of the initiator (A: Init–Cl), the product after 1st cycle via esterification with methanol (B: Init–MMA–Cl), that after 2nd cycle with 3-benzenepropanol (C: Init–MMA–BPMA–Cl), and that after 3rd cycle with methanol (D: Init–MMA–BPMA–MMA–Cl).

the adduct after the second cycle with aromatic alcohol (Init-MMA-BPMA-Cl).   The reaction conditions for the three reactions (i.e., radical addition, acidolysis, and esterification) in the third cycle were the same as those in the second, and finally, methanol was used for the esterification.   The single unit of MMA was certainly incorporated without damaging the last three units (initiator, MMA, and BPMA), which was characterized by ^{1}H NMR and ESI-MS (Figure 5).

Conclusion

The author has developed a new concept to control sequence for methacrylate units. The key molecule is a very bulky and convertible methacrylate monomer, IPAMA.   The monomer is active enough to undergo radical addition reaction but too bulky to sequentially propagate, and thus single unit addition can be controlled under condition of living radical polymerization.   The tertiary ester group is easily hydrolyzed under acidic condition to convert into carboxylic acid, followed by ester pendants with less bulky and nontertiary substituents. These unique features allow an iterative cycle consisting of radical addition, acidolysis, and esterification, which could lead to sequence-controlled vinyl polymers.   As the radical addition is controlled under mechanism of living radical polymerization, combination of living radical polymerization would allow syntheses of new type of polymers, such as block copolymer carrying sequence-controlled segment on the interface.   This concept could open the door to sequence control for vinyl polymers as well as design of sequence-driven functions of vinyl polymers.

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(23) The long alkyl chain was intentionally introduced for easier purification in the iterative process shown later.

(24) Two peaks were observed due to the chiral carbon neighboring to chlorine.

Chapter 1 Supporting Data
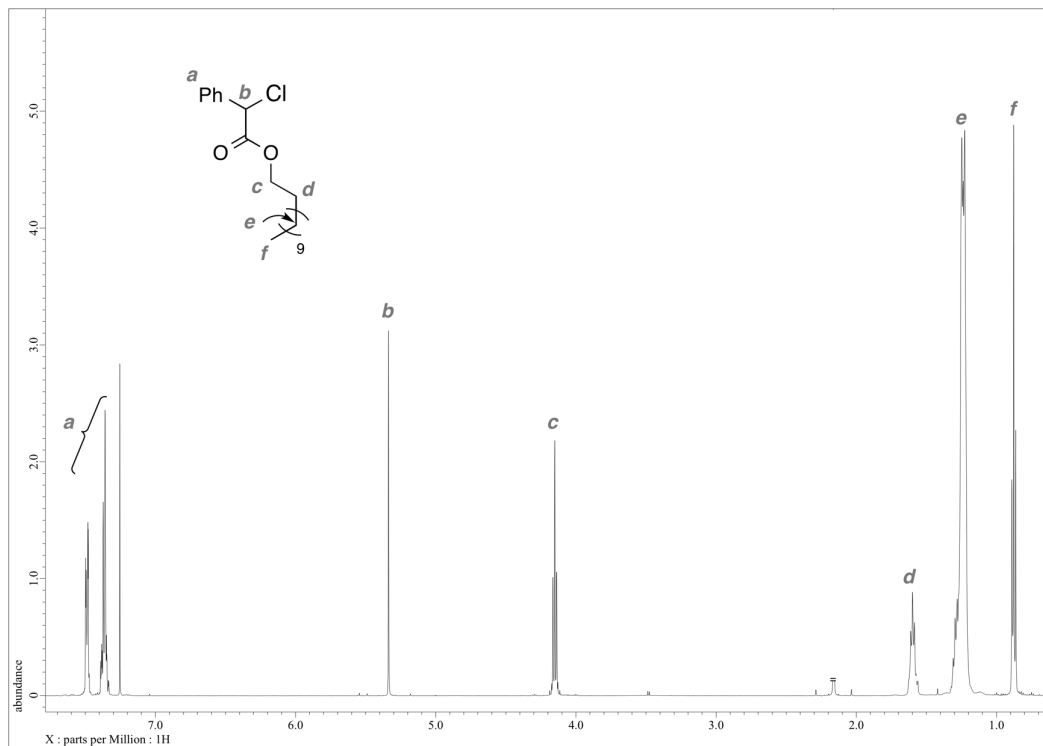
Figure S1. ^{1}H NMR spectrum of initiator
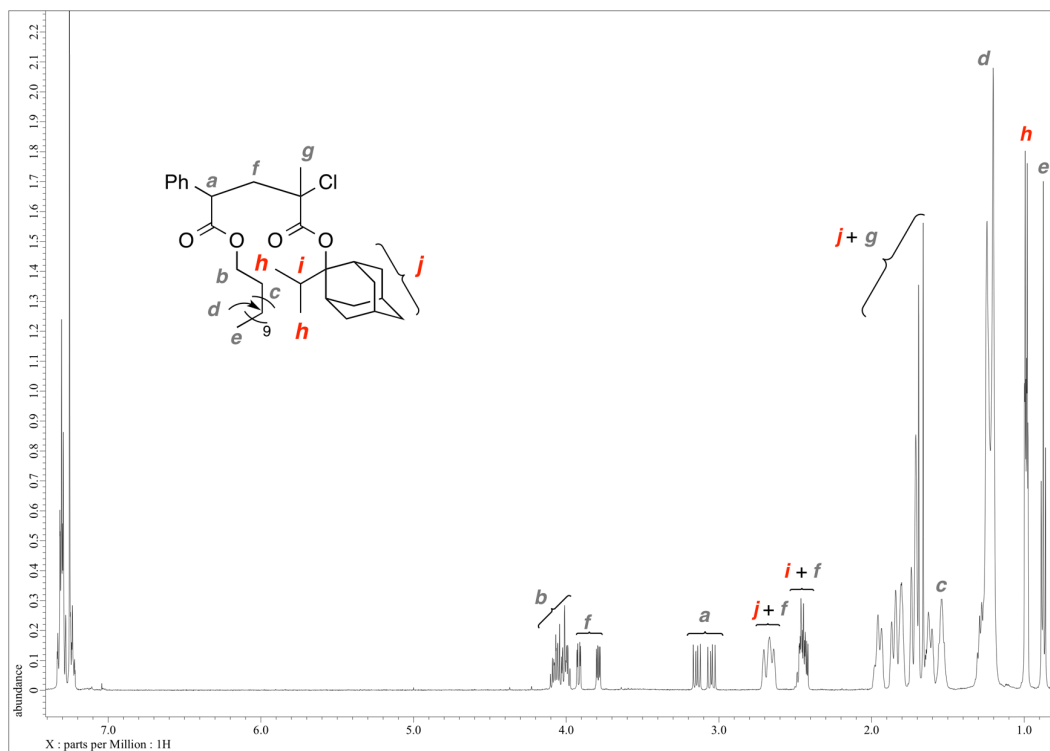
Figure S2. ^{1}H NMR spectrum of single monomer adduct (1st Cycle)
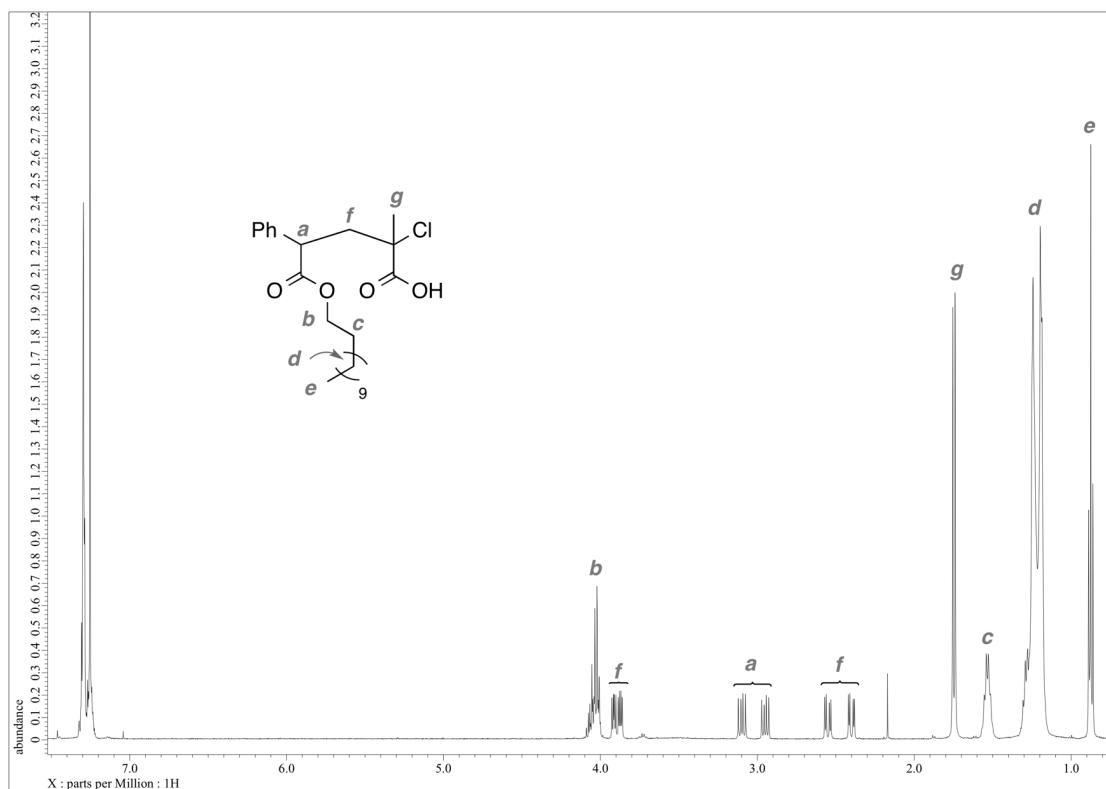
Figure S3. ^{1}H NMR spectrum of product after selective cleavage (1st Cycle)
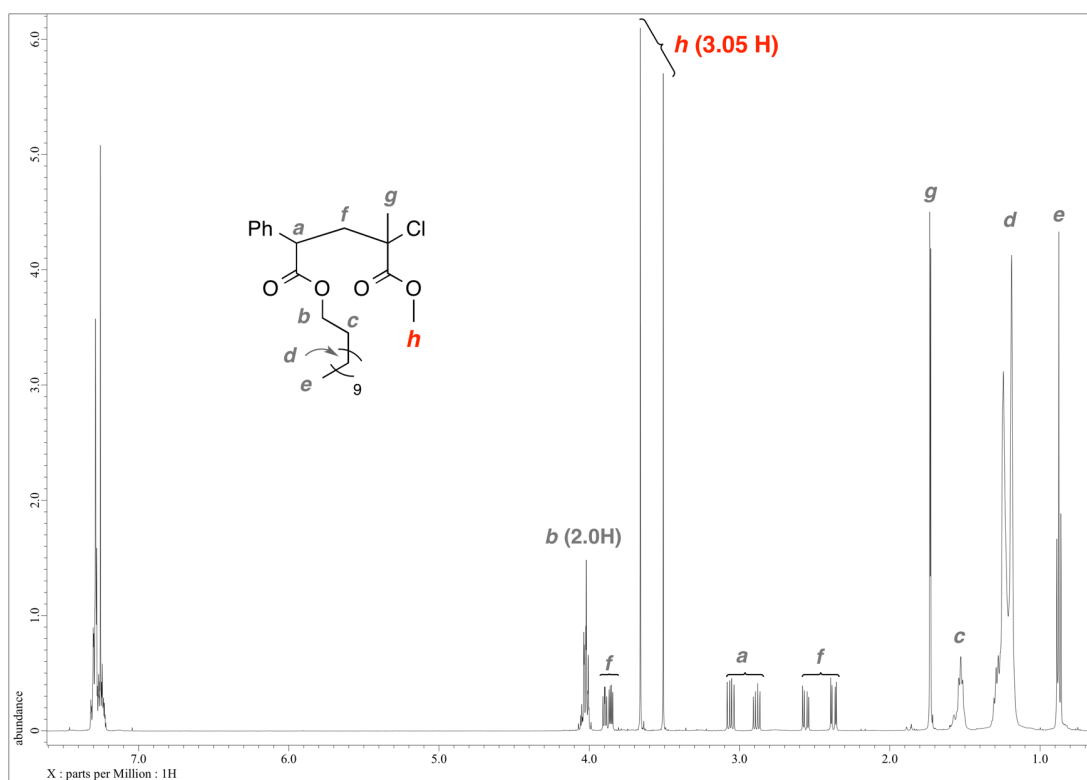
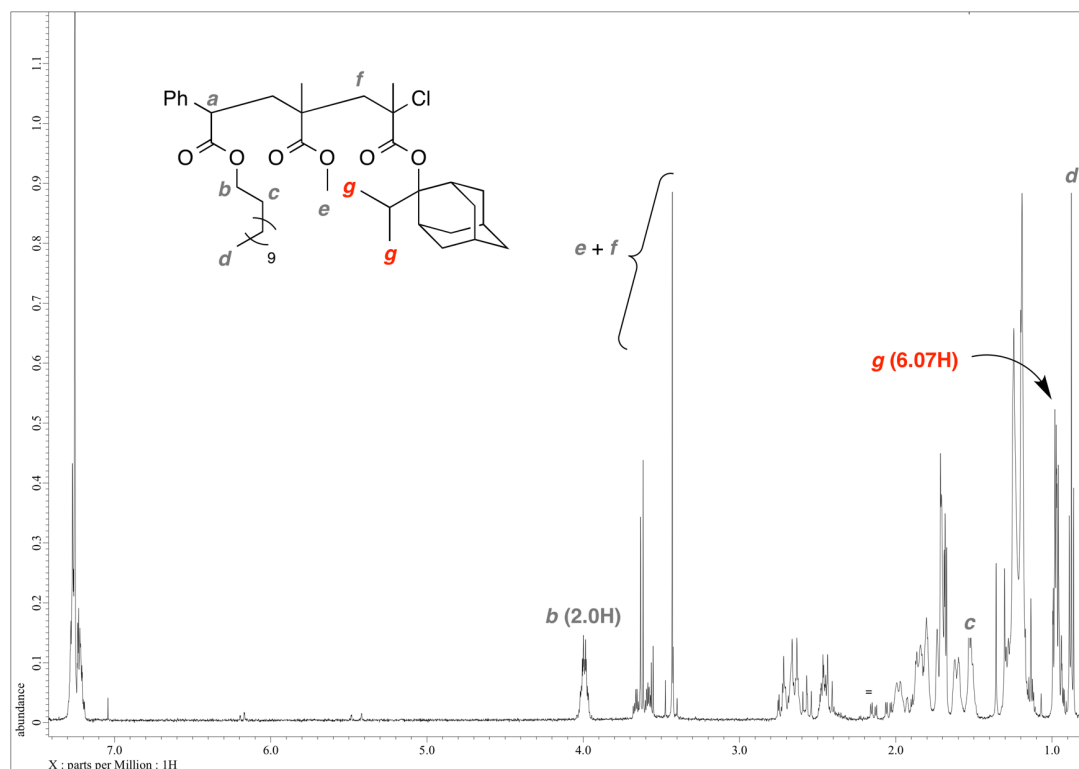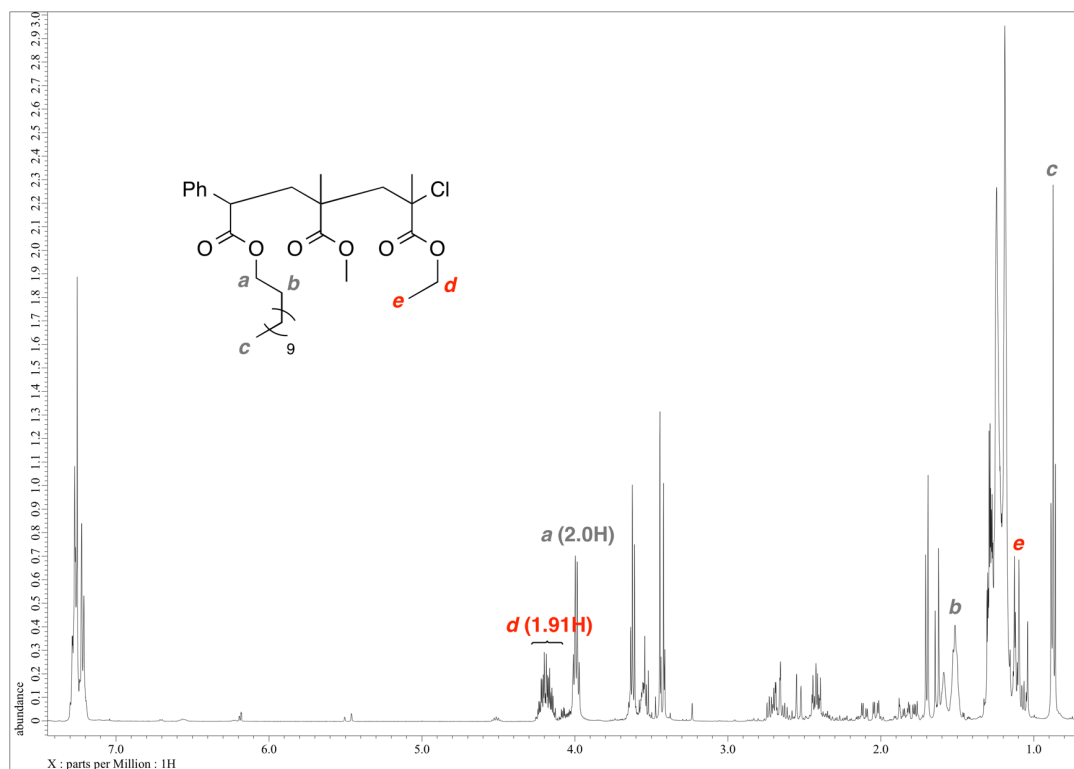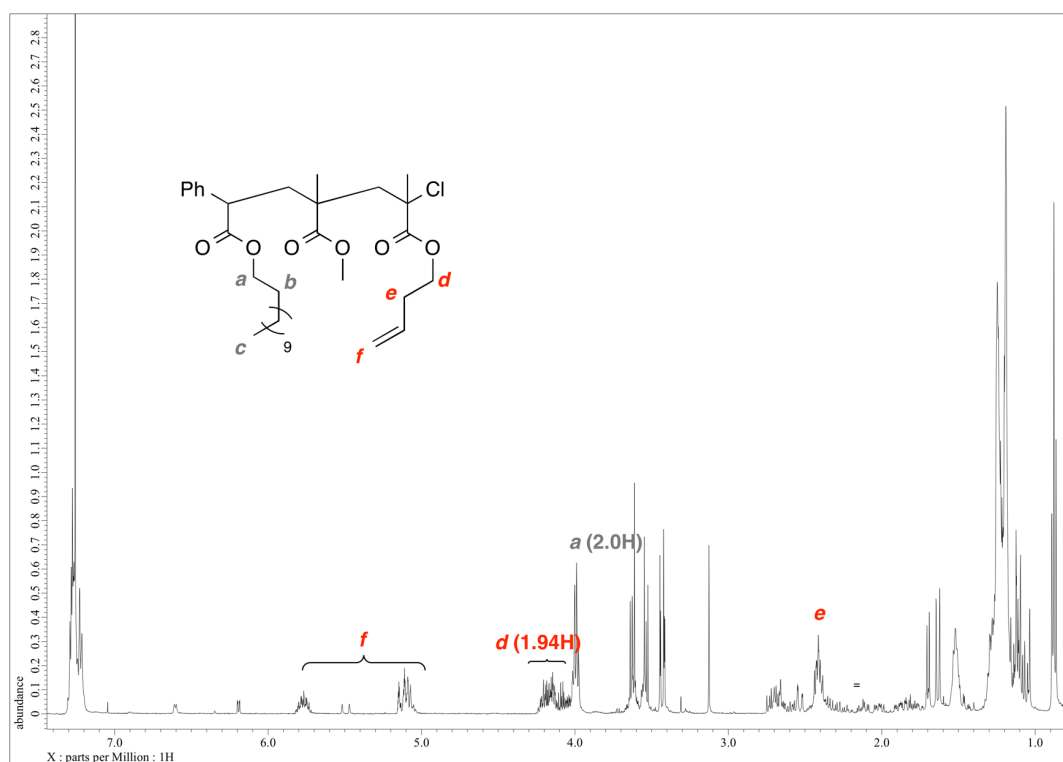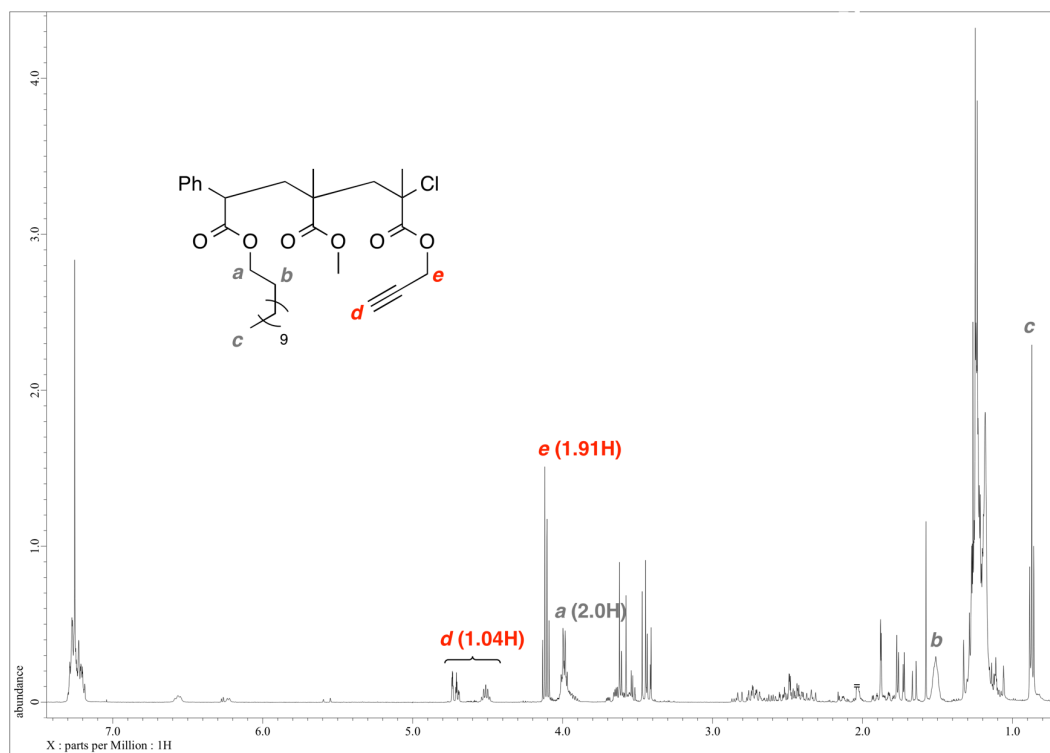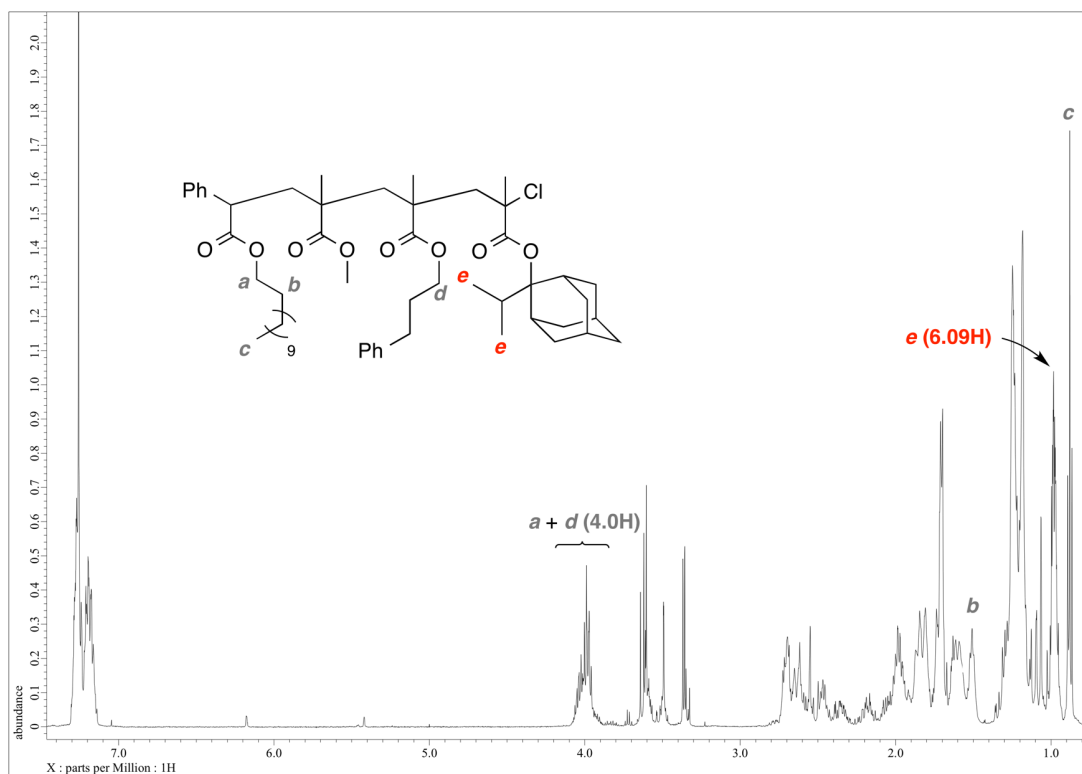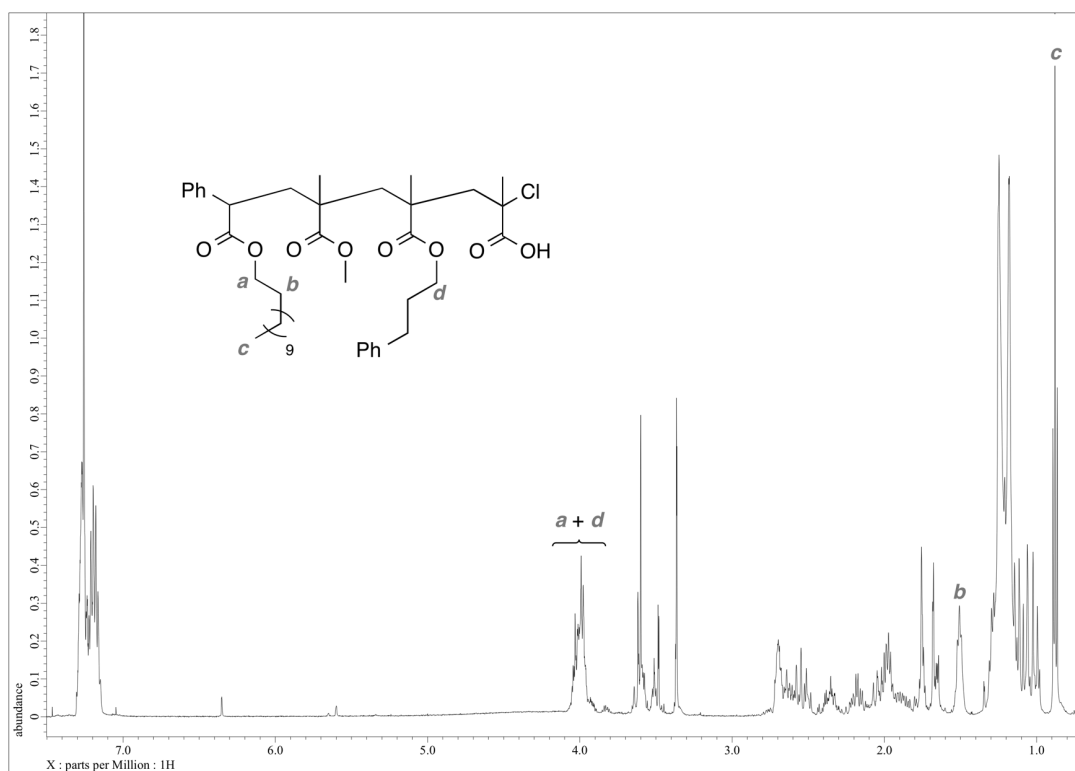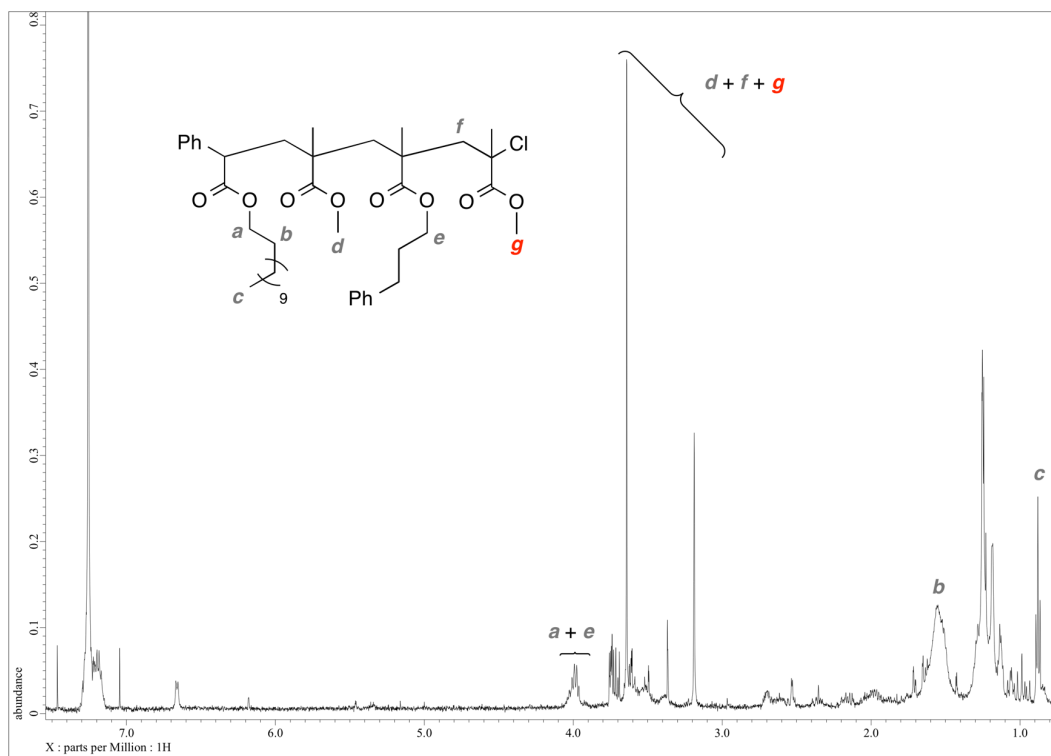**Figure S4.** ^{1}H NMR spectrum of product after esterification with methanol (1st Cycle)

Figure S5. ^{1}H NMR spectrum of single monomer adduct (2nd Cycle)

Figure S6. ^{1}H NMR spectrum of product after selective cleavage (2nd Cycle)

Figure S7. ^{1}H NMR spectrum of product after esterification with ethanol (2nd Cycle)

Figure S8. ^{1}H NMR spectrum of product after esterification with 3-buten-1-ol (2nd Cycle)

Figure S9. ^{1}H NMR spectrum of product after esterification with propargyl alcohol (2nd Cycle)
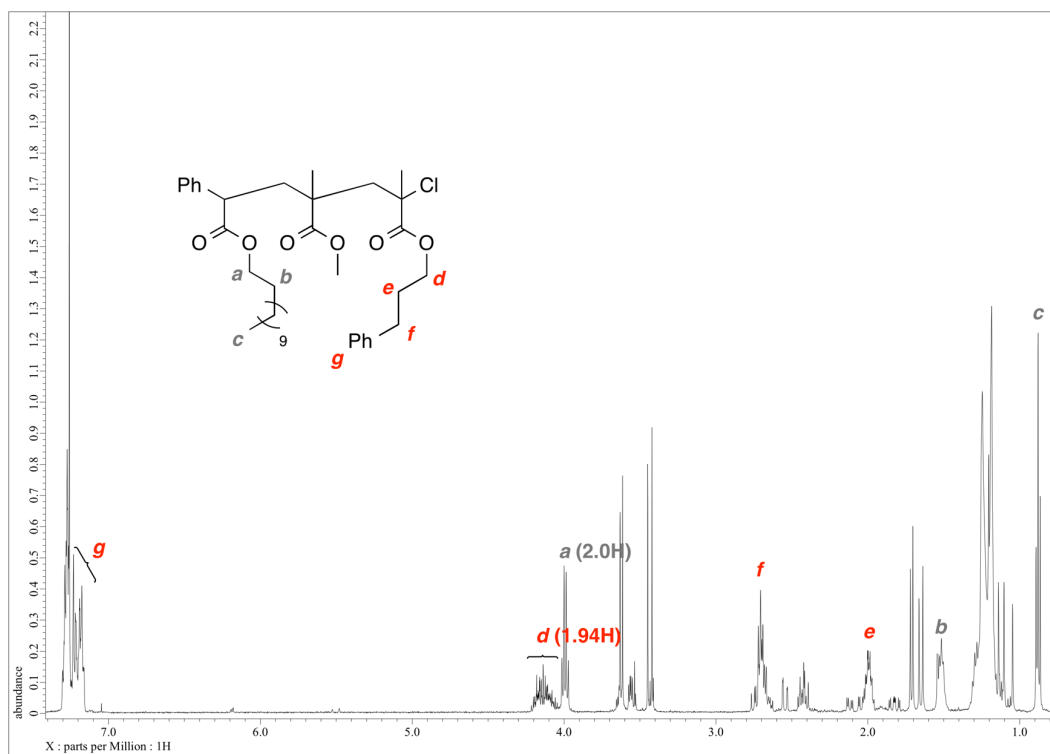
Figure S10. ^{1}H NMR spectrum of product after esterification with 3-phenyl-1-propanol (2nd Cycle)

Figure S11. ^{1}H NMR spectrum of single monomer adduct (3rd Cycle)

Figure S12. ^{1}H NMR spectrum of product after selective cleavage (3rd Cycle)

Figure S13. ^{1}H NMR spectrum of product after esterification with methanol (3rd Cycle)

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PAPER
Makoto Ouchi *et al.*
Precise control of single unit monomer radical addition with
a bulky tertiary methacrylate monomer toward sequence-
defined oligo- or poly(methacrylate)s *via* the iterative
process

Chapter 2

Precise Control of Single Unit Monomer Radical Addition with a Bulky Tertiary Methacrylate Monomer toward Sequence-Defined Oligo- or Poly(methacrylate)s via the Iterative Process

Abstract

Iterative single unit monomer radical addition with a bulky tertiary methacrylate monomer, adamantyl and isopropyl pendant methacrylate (IPAMA), under ATRP conditions was studied in detail toward the syntheses of sequence-defined oligo- or poly(methacrylate)s in higher yields. The introduction of an activated ester for the alkyl halide or the adduct was effective in improving the accuracy of the single unit addition of IPAMA without forming unfavorable products. Thus, a cycle consisting of 4 steps, "radical addition", "transformation", "selective cleavage", and "active esterification", was established to realize the circumstances for effective single unit monomer addition and the iterative process along with pendant modification. The cycle was actually repeated to synthesize 2 units of adduct in high yield.
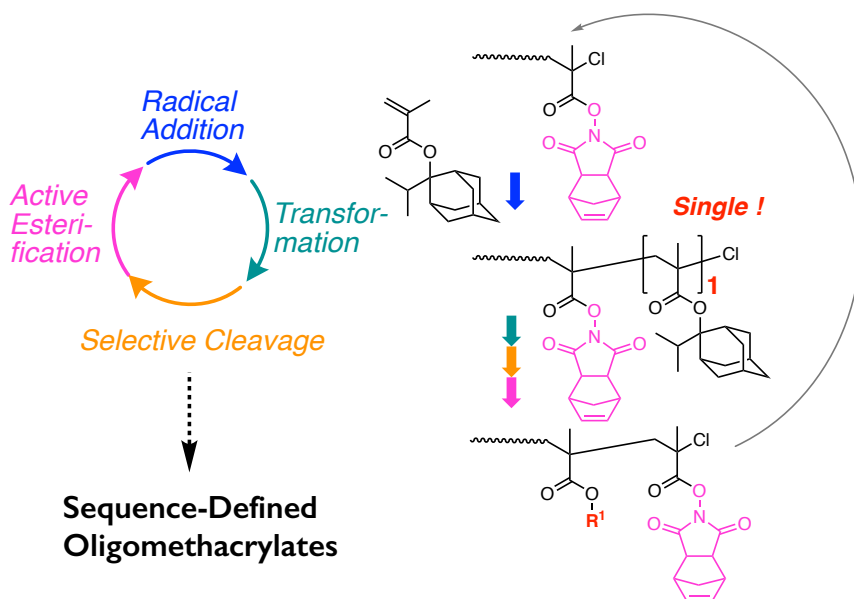
Introduction

Thanks to the establishment of reversible deactivation radical polymerization (RDRP)[1] allowing control over molecular weight as the occasion demands, the "sequence" or the order/ position of repeating monomer units has attracted attention as the structural factor to use to obtain more precise synthetic polymers over the last decade.[2–7]   For natural polymers, i.e., DNA or proteins, the sequence is an essential structural factor determining higher order structures, leading to smart and effective functions far superior to those of artificial counter-parts.   Herein, control over the order of the pendant groups (i.e., nucleobases or amino acid residues) regularly dangling from a main chain composed of a single type of repeating units is crucial.   In this regard, synthetic copolymers consisting of the same monomer derivatives carrying various side chains, such as (meth)acrylates, styrenes, or acrylamides, are similar to natural polymers.   However, the chain-growth mechanism for synthesis of such copolymers is inherently unsuitable for sequence control, and the difficulty is more marked with the same monomer derivatives.   Thus, polymer chemists are aware that sequence control for the same kinds of repeating units is extremely challenging unless some iterative addition process is developed.

The development of RDRP has enabled us to control chain length or molecular weight as well as the terminal groups for vinyl polymers.   The deactivation process contributes to the temporal conversion of growing active (radical) species into dormancy, leading to the suppression of irreversible chain transfer and termination reactions. For example, in the case of atom transfer radical polymerization (ATRP) or metal-catalyzed living radical polymerization,[8,9] a halogen is provided from a higher oxidant metal complex to deactivate radical species, and the resultant carbon–halogen bond can be reversibly activated via one-electron redox of the catalyst.

The RDRP feature that growing chains can continue to grow without irreversible termination would be required even for sequence control.   However, some additional regulation is necessary to overcome the problem that distributed adducts are generated due to the chain-growth mechanism.   In this context, the author have proposed using a special methacrylate monomer carrying an extremely bulky and transformable pendant to control single monomer addition and repeat it (Figure 1).[10]   Specifically, adamantyl and isopropyl pendant tertiary (3°) methacrylate (IPAMA) was found to be the special monomer meeting the
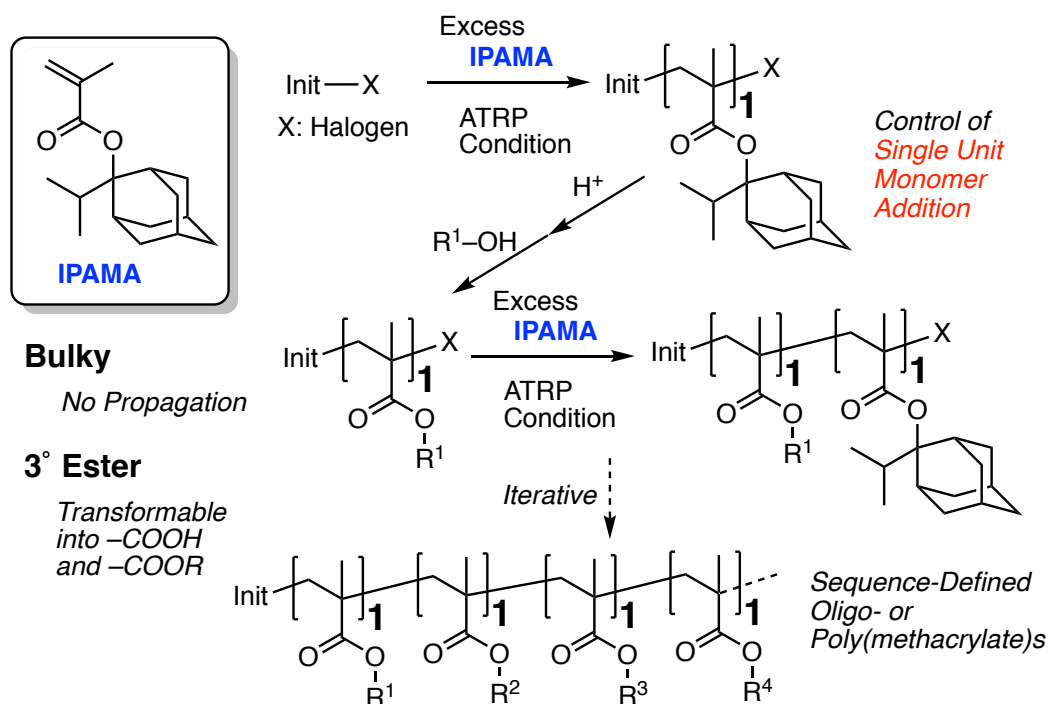
Figure 1. Iterative single unit monomer addition with IPAMA to construct sequence-defined oligo-or poly(methacrylate)s

demand.   The pendant is too bulky to react with itself for propagation, but the monomer can react with alkyl halide to yield a single unit adduct capped by halogen under optimized ATRP conditions.   The tertiary ester pendant in the resultant adduct is transformed into carboxylic acid via cleavage with a strong protonic acid, and the resultant acidic pendant can be esterified with 1° or 2° alcohol (R^n–OH) giving a less bulky methacrylate unit.   The 1° or 2° ester is tolerant of the acidic conditions for the later cleavage process.   For the resultant single methacrylate unit adduct, the chance arises to undergo radical addition with IPAMA.   If the single unit adduct is quantitatively synthesized for the initiator or halogen-capped product, the methodology would allow the construction of sequence-defined oligo- or poly(methacrylate)s in high yield.

Such single monomer addition has been investigated by some groups.   Moad et al. utilized kinetic parameters with reversible addition–fragmentation chain-transfer (RAFT) polymerization to demonstrate the synthesis of a dimer of *N*-isopropylacrylamide (NIPAM) and styrene, but the overall yield was low (about 30%).[11]   Junkers et al. synthesized sequence-defined oligoacrylates by repeating equimolar addition of acrylate monomer and purification of the single unit adduct on the basis of RAFT and photo-induced ATRP.[12–15]   This methodology is simpler, but faces a yield issue due to the necessity of isolating the single unit

adduct from the dispersed product at each reaction.   Recently, Xu and Boyer et al. have reported single monomer addition via a photo-induced electron transfer (PET)-RAFT system.[16–19]   The selective activation by an organic photo-redox catalyst or selective cross-over propagation based on comonomer reactivity ratios is crucial.

Although the author's methodology is rational in principle for realizing a defined sequence, a problem also remains to be solved: the single unit monomer radical addition of IPAMA is partially imperfect in the strict sense, resulting in a small amount of unfavorable product (*vide infra*).   The process for removal of the side product might cause a low yield of the ideal single unit adduct.   As high a yield as possible in one cycle is required, because it accumulates via an iterative process.   Thus, in this work, the author focused in detail on the radical addition of IPAMA with a halogen compound or the adduct to improve the efficiency of the single unit addition.   Consequently, the author found that an electronic effect of the alkyl halide is important to control the radical addition of the bulky monomer. One more step was necessary to change the electron density of the halogen terminal, but the efficiency of single unit addition was improved.

Experimental

Materials

The following reagents were used as received α-chlorophenylacetyl chloride (Aldrich, >90%), 1-dodecanol (TCI, >99.0%), *N*-hydroxy-5-norbornene-2,3-dicarboximide (NHND: TCI, >99%), 2-isopropyl-2-adamantyl methacrylate (IPAMA; TCI, >98.0%), 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD: TCI, >98%), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU; TCI, >98%), trifluoroacetic acid (TFA: Wako, >98.0%), COMU (Aldrich, >97.0%), *N,N*-diisopropylethylamine (DIEA; TCI, >99%), methanol (Wako, >99.8%).   Triethylamine (TCI, >99.0%) was dried overnight over calcium chloride and distilled before use.   Column chromatography was carried out using Wakosil C200 (Wako) as the stationary phase.

The catalyst reagents (precursor, complex, ligand, etc.) for the radical reaction were used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inter-gas-systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere ($H_2O < 0.1$ ppm; $O_2 < 0.1$ ppm): chloro(indenyl)bis(triphenylphosphine) ruthenium(II) (Ru(Ind); Strem, >98%), pentamethylcyclopentadieneylbis(triphenylphosphine) ruthenium(II) chloride (RuCp*; Aldrich), 1,2-bis(diphenyl phosphino)-ethane monoxide (Wako, >97%), copper(I) bromide (CuBr; Aldrich, >98%), 4,4'-dinonyl-2,2'-bipyridyl (dNbpy; TCI,

>98%).   The ruthenium precursor [Cp*Ru(μ$_3$-Cl)]$_4$ was synthesized as described in the literature.[20, 21]

Toluene (Kishida kagaku, Osaka, Japan; purity >99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for more than 30 min immediately before use.   Unless stated otherwise, other solvents were purchased from Wako Pure Chemical Industries and used without further purification.   1,2,3,4-tetrahydrousnaphthalene (tetralin; internal standard for ^{1}H NMR) was distilled over calcium chloride.

Measurement

Size exclusion chromatography (SEC) was measured at 40°C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404) connected to DU-H2000 pump, 74S-RI refractive-index detector, and 41-UV ultraviolet detector (Shodex).   The columns were calibrated against 12 standard poly(methyl methacrylate) standards (PSS Polymer, M_n =730-1650000; M_w/M_n = 1.04-1.15).   The product for each step was purified by preparative recycling SEC in chloroform as an eluent on polystyrene-gel column (Shodex KF-5001) connected to PU-2086 precision pump, RI-2031 refractive-index detector, and UV-2075 ultraviolet detector (Jasco).   ^{1}H NMR spectra were recorded on JEOL JNM-ECA500 spectrometer, operating at 500.125 MHZ.   Electrospray-ionization mass spectra (ESI-MS) were measured on Thermo Fisher Scientific Exactive Plus.

Synthesis

Synthesis of dodecyl 2-choloro-2-phenylacetate (DCPA: Initiator)

Triethylamine (25.4 mL, 183 mmol) and 1-dodecanol (34.1 mL, 152 mmol) were placed in round-bottom flask under argon and then dissolved in dichloromethane (DCM)(500 mL). To the resultant solution, α-chlorophenylacetyl chloride (26.3 mL, 166 mmol) was gradually added at 0 °C, while stirring for 30 min.   The reaction solution was warmed to room temperature and stirred overnight.   To the solution, 600 mL of Et$_2$O were added, followed by addition of 600 mL of sat. NaHCO$_3$ solution.   The organic layer was washed with brine 3 times and dried on Na$_2$SO$_4$.   After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane : ethyl acetate = 95:5).   The product was obtained as slightly yellow oil (51.7 g, 153 mmol, 92 %).   ^{1}H NMR (in CDCl$_3$): 7.49 (dd, 2H), 7.41-7.33 (m, 3H), 5.34 (s, 1H), 4.15 (t, 2H), 1.60 (quint, 2H), 1.34-1.17 (m, 18H), 0.88 (t, 3H).

Synthesis of hydroxy-5-norbornene-2,3-dicarboxyimidyl-2-choloro-2-phenylacetate (NHND-CPA: Initiator)

Triethylamine (4.8 mL, 34.2 mmol) and NHND (5.6 g, 31.4 mmol) were placed in round-bottom flask under argon and then dissolved in DCM (50 mL). To the resultant solution, α-chlorophenylacetyl chloride (4.5 mL, 28.5 mmol) was gradually added at 0 ˚C, while stirring for 30 min. The reaction solution was warmed to room temperature and stirred for 1h. To the solution, 200 mL of Et_2O were added, followed by addition of 200 mL of deionized water. The organic layer was washed with brine 3 times and dried on Na_2SO_4. After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane : ethyl acetate = 80:20). The product was obtained as white powder (6.6 g, 18.3 mmol, 58 %). ^{1}H NMR (in $CDCl_3$): 7.51 (dd, 2H), 7.44-7.38 (m, 3H), 6.20 (s, 2H) 5.61 (s, 1H), 3.44(s, 2H), 3.30 (s, 2H), 1.77 (s, 1H), 1.51 (d, 1H).

Ruthenium-catalyzed radical addition of IPAMA with DCPA in 1st cycle
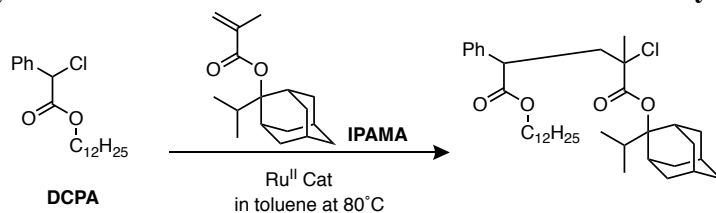
[Cp*Ru(μ$_3$-Cl)]$_4$ (0.0033 g, 0.0030 mmol) and 1,2-bis(diphenylphosphino)-ethane monoxide (0.010 g, 0.024 mmol) were placed in round-bottom flask under argon and dissolved in toluene (2 mL). The solution was heated to 80 ˚C for 1 h to prepare the ruthenium complex. IPAMA (0.16 g, 0.60 mmol) was placed in another round-bottom flask under argon. After cooling the ruthenium complex solution to room temperature, the solution was transferred to the IPAMA solution. Subsequently, tetralin (0.10 mL) and DCPA (initiator, 0.020 g, 0.060 mmol) were added and the solution was heated at 80˚C. After 24 hours, the reaction mixture was concentrated under reduced pressure at 35 ˚C, and the crude product was passed through a neutral silica column chromatography (hexane : ethyl acetate = 20:80) to remove Ru catalyst, followed by purification with a preparative recycling SEC apparatus. The product was obtained as slightly yellow oil (0.031 g, 0.051 mmol, 85 %). ^{1}H NMR (in $CDCl_3$): 7.34-7.21 (m, 5H), 4.12-3.96 (m, 2H), 3.94-3.76 (m, 1H), 3.18-3.02 (m, 1H), 2.73-2.40 (m, 4H), 2.00-1.58 (m, 15H), 1.54 (quintet, 2H), 1.34-1.17 (m, 18H), 1.02-0.97 (dt, 6H), 0.88 (t, 3H).

Ruthenium-catalyzed radical addition of IPAMA with NHND-CPA in 1st cycle
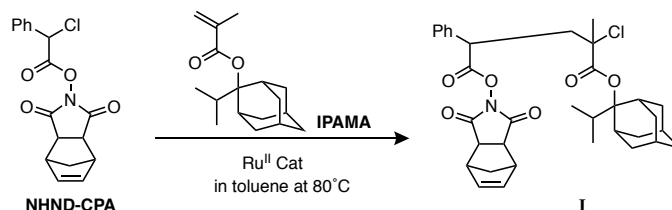
[Cp*Ru(μ_3-Cl)]$_4$ (0.11 g, 0.10 mmol) and 1,2-bis(diphenylphosphino)-ethane monoxide (0.34 g, 0.80 mmol) were placed in round-bottom flask under argon and dissolved in toluene (95 mL).   The solution was heated to 80 ˚C for 1 h to prepare the ruthenium complex. IPAMA (5.25 g, 20.0 mmol) was placed in another round-bottom flask under argon.   After cooling the ruthenium complex solution to room temperature, the solution was transferred to the IPAMA solution.   Subsequently, tetralin (0.50 mL) and NHND-CPA (initiator, 0.66 g, 2.0 mmol) were added and the solution was heated at 80 ˚C.   After 24 hours, the reaction mixture was concentrated under reduced pressure at 35 ˚C, and the crude product was passed through a neutral silica column chromatography (hexane : ethyl acetate = 75:25) to remove Ru catalyst, followed by purification with a preparative recycling SEC apparatus.   The product **I** was obtained as slightly yellow oil (1.13 g, 1.9 mmol, 95 %). ^{1}H NMR (Figure 5, in CDCl$_3$): 7.37-7.23 (m, 5H), 6.16 (s, 2H), 4.28-4.06 (dddd, 1H), 3.40 (s, 2H), 3.28 (s, 2H), 3.27-3.13 (m, 1H), 2.75-2.62 (d, 2H), 2.61-2.42 (m, 3H), 2.00-1.46 (m, 14H), 1.01-0.96 (m, 6H).

Transformation of the single unit adduct in 1st cycle
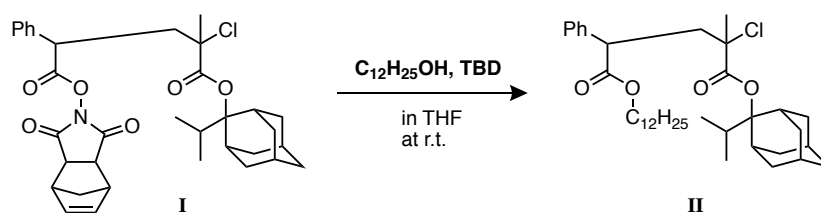
The IPAMA adduct (**I**, 27 mg, 0.045mmol) were placed in glass tube under argon and dissolved in THF (1 mL).   To this resultant solution, 1-dodecanol (0.10 mL, 0.45 mol) and TBD (9.5 mg, 0.068 mmol) were added, and subsequently stirred for 2 h at room temperature. The reaction mixture was neutralized with acetic acid, and concentrated under reduced pressure at room temperature.   The crude product was purified with a preparative recycling SEC apparatus.   The product **II** was obtained as slightly yellow oil (26 mg, 0.043 mmol, 95 %). ^{1}H NMR (Figure 5, in CDCl$_3$): 7.34-7.21 (m, 5H), 4.12-3.96 (m, 2H), 3.94-3.76 (m, 1H), 3.18-3.02 (m, 1H), 2.73-2.40 (m, 4H), 2.00-1.58 (m, 15H), 1.54 (quintet, 2H), 1.34-1.17 (m, 18H), 1.02-0.97 (dt, 6H), 0.88 (t, 3H).

**Selective acidolysis of the single unit adduct of IPAMA in 1st cycle**
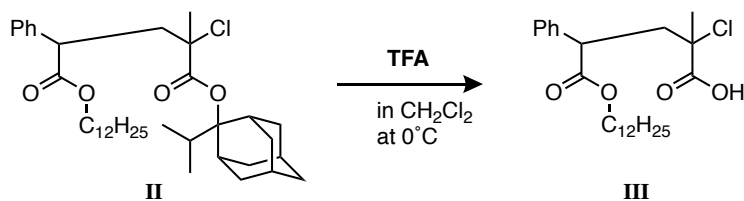
The IPAMA adduct (**II**, 4.54 g, 7.56 mmol) were placed in glass tube under argon and dissolved in CH_2Cl_2 (190 mL). To this resultant solution, TFA (2.93 mL, 37.8 mmol) was added at 0 ˚C while stirring for 30 min. After the reaction mixture was concentrated under reduced pressure at 35 ˚C, and the crude product was purified with a preparative recycling SEC apparatus. The methacrylic acid adduct product **III** was obtained as slightly yellow oil (3.21 g, 7.56 mmol, 100 %). ^1H NMR (Figure 5, in $CDCl_3$): 7.34-7.21 (m, 5H), 4.09-3.99 (m, 2H), 3.94-3.85 (m, 1H), 3.13-2.92 (m, 1H), 2.58-2.37 (m, 1H), 1.79-1.72 (d, 3H), 1.54 (sext, 2H) 1.34-1.14 (m, 18H), 0.88 (t, 3H).

Esterification with NHND in 1st cycle
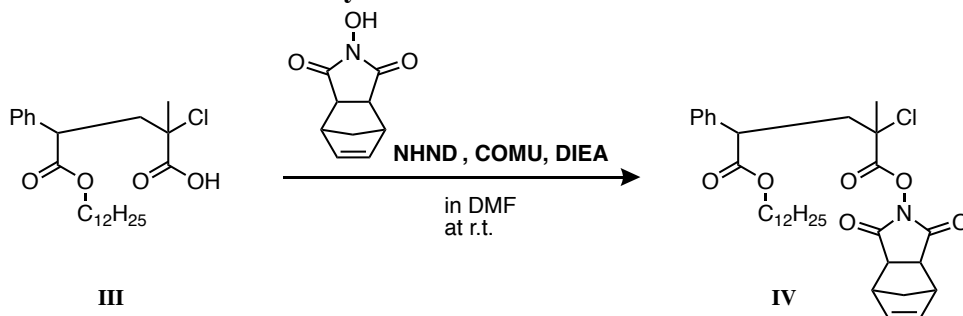
The methacrylic acid adduct (**III**, 1.88 g, 4.44 mmol) was placed in round-bottom flask under argon and dissolved in DMF (110 mL). To this resultant solution, COMU (2.28 g, 5.33 mmol) and DIEA (1.51 mL, 8.88 mmol) were added, and subsequently stirred for 30 min. Separately, NHND (15.9 g, 88.8 mmol) was placed in another round-bottom flask under argon. And then, the solution was transferred to NHND and stirred for 24h. To the solution, 100 mL of hexane was added, followed by addition of 100 mL of deionized water. The organic layer was extracted with hexane 3 times and dried on Na_2SO_4. After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane : ethyl acetate = 90:10). The NHND-esterified product **IV** was obtained as slightly yellow oil (2.47 g, 4.22 mmol, 95 %). ^1H NMR (Figure 5, in $CDCl_3$): 7.34-7.21 (m, 5H), 6.21 (s, 2H), 4.11-3.99 (m, 2H), 3.95-3.81 (dd, 1H), 3.49-3.29 (d, 4H), 3.24-3.14 (m, 1H), 2.57-2.47 (m, 1H), 1.83-1.74 (t, 4H), 1.53 (s, 3H), 1.34-1.14 (m, 18H), 0.88 (t, 3H).

**Ruthenium-catalyzed radical addition of IPAMA in 2nd cycle**

IV → V
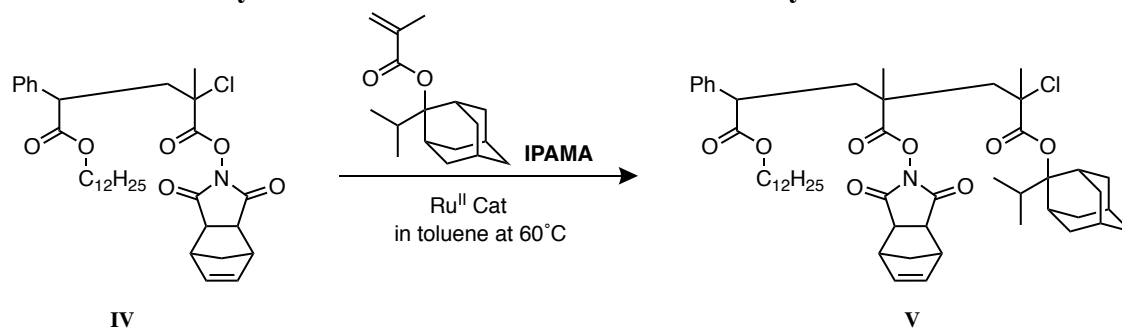
[Cp*Ru(μ_3-Cl)]$_4$ (0.20 g, 0.18 mmol) and 1,2-bis(diphenylphosphino)-ethane monoxide (0.63 g, 1.48 mmol) were placed in round-bottom flask under argon and dissolved in toluene (170 mL).   The solution was heated to 80 ˚C for 1 h to prepare the ruthenium complex. IPAMA (9.70 g, 36.95 mmol) and the NHND-esterified product (**IV**, 2.16 g, 3.70 mmol) were placed in another round-bottom flask under argon.   After cooling the ruthenium complex solution to room temperature, the solution was transferred to IPAMA solution.   Subsequently, tetralin (0.4 mL) was added and the solution was heated at 60 ˚C.   After 7 hours, the reaction mixture was concentrated under reduced pressure at 35 ˚C, and the crude product was passed through a neutral silica column chromatography (hexane : ethyl acetate = 75:25) to remove Ru catalyst, followed by purification with a preparative recycling SEC apparatus.   The product **V** was obtained as slightly yellow oil (3.01 g, 3.55 mmol, 96 %). ^{1}H NMR (Figure 7, in CDCl$_3$): 7.38-7.18 (m, 5H), 6.22 (s, 2H), 4.10-3.95 (m, 2H), 3.93-3.82 (m, 1H), 3.45 (s, 2H), 3.31 (s, 2H), 2.89-2.40 (m, 6H), 2.18-1.48 (m, 20H), 1.42-1.15 (m, 21H), 1.02-0.92 (dt, 6H), 0.88 (t, 3H).

Transformation of the single unit adduct in 2nd cycle

V → VI
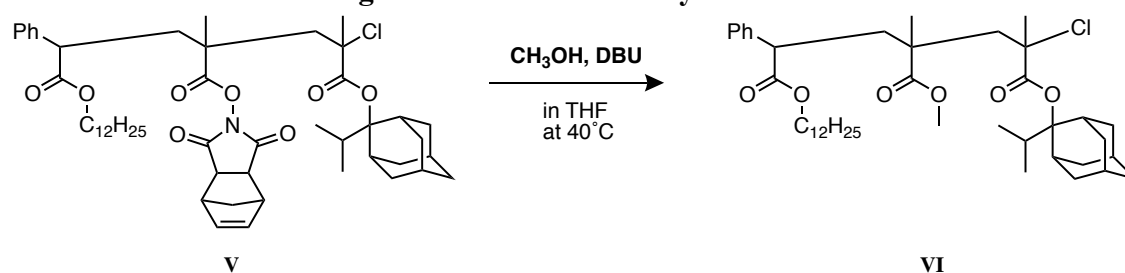
The IPAMA adduct (**V**, 30.8 mg, 0.036 mmol) were placed in glass tube under argon and dissolved in THF (0.30 mL).   To this resultant solution, methanol (0.014 mL, 0.36 mmol) and DBU (0.027 mL, 0.18 mmol) were added, and subsequently stirred for 24h at room temperature.   The reaction mixture was neutralized with acetic acid, and concentrated under reduced pressure at room temperature.   The crude product was purified with a preparative

recycling SEC apparatus. The product **VI** was obtained as slightly yellow oil (22.7 mg, 0.033 mmol, 90 %). ^{1}H NMR (Figure 8, in CDCl$_3$): 7.31-7.18 (m, 5H), 4.06-3.93 (m, 2H), 3.68-3.56 (m, 1H), 3.63-3.61 (d, 1.5H), 3.42 (s, 1.5H), 2.85-2.38 (m, 6H), 2.00-1.58 (m, 16H), 1.52 (s, 2H), 1.36-1.12 (m, 21H), 1.00-0.92 (dt, 6H), 0.86 (t, 3H).

Selective acidolysis of the single unit adduct of IPAMA in 2nd cycle
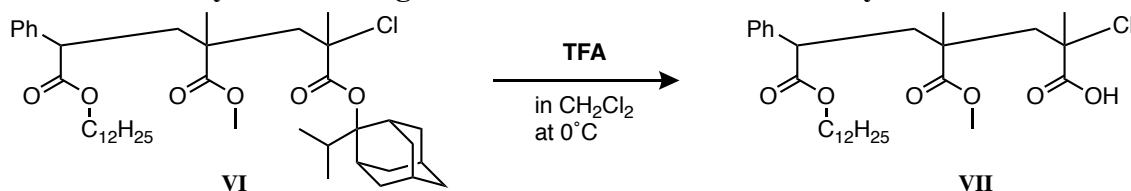
The IPAMA adduct (**VI**, 0.28 g, 0.40 mmol) were placed in glass tube under argon and dissolved in CH$_2$Cl$_2$ (10 mL). To this resultant solution, TFA (0.15 mL, 1.99 mmol) was added at 0 ˚C while stirring for 30 min. After the reaction mixture was concentrated under reduced pressure at 35 ˚C, and the crude product was purified with a preparative recycling SEC apparatus. The methacrylic acid adduct **VII** was obtained as slightly yellow oil (0.21 g, 0.40 mmol, 100 %). ^{1}H NMR (Figure S6, in CDCl$_3$): 7.30-7.19 (m, 5H), 4.04-3.94 (q, 2H), 3.69-3.56 (m, 1H), 3.62-3.60 (d, 1.5H), 3.41-3.39 (d, 1.5H), 2.80-2.30 (m, 3H), 2.18-1.68 (m, 4H), 1.52 (s, 2H), 1.32-1.10 (m, 21H), 0.88 (t, 3H).

Esterification with NHND in 2nd cycle
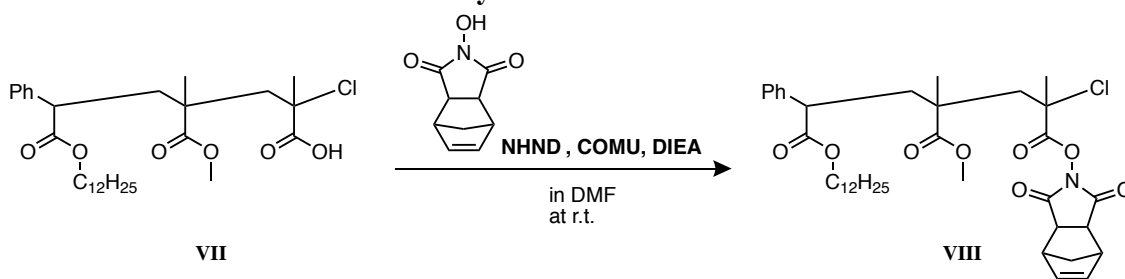
The methacrylic acid adduct (**VII**, 0.21 g, 0.40 mmol) was placed in round-bottom flask under argon and dissolved in DMF (10 mL). To this resultant solution, COMU (0.20 g, 0.48 mmol) and DIEA (0.13 mL, 0.80 mmol) were added, and subsequently stirred for 30 min. Separately, NHND (3.54 g, 20 mmol) was placed in another round-bottom flask under argon. And then, the solution was transferred to NHND and stirred for 24h. To the solution, 100 mL of hexane was added, followed by addition of 100 mL of deionized water. The organic layer was extracted with hexane 3 times and dried on Na$_2$SO$_4$. After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane : ethyl

acetate = 90:10).   The NHND-esterified product **VIII** was obtained as slightly yellow oil (0.26 g, 0.38 mmol, 96 %). ^{1}H NMR (Figure S6, in CDCl$_3$): 7.31-7.19 (m, 5H), 6.21 (s, 2H), 4.04-3.94 (q, 2H), 3.69-3.56 (m, 1H), 3.62-3.60 (d, 1.5H), 3.45 (s, 2H), 3.41-3.39 (d, 1.5H), 3.31(s, 2H), 2.92-2.31 (m, 3H), 2.18-1.68 (m, 5H), 1.55-1.47 (d, 3H), 1.44-1.12 (m, 21H), 0.89 (t, 3H).

Result and Discussion
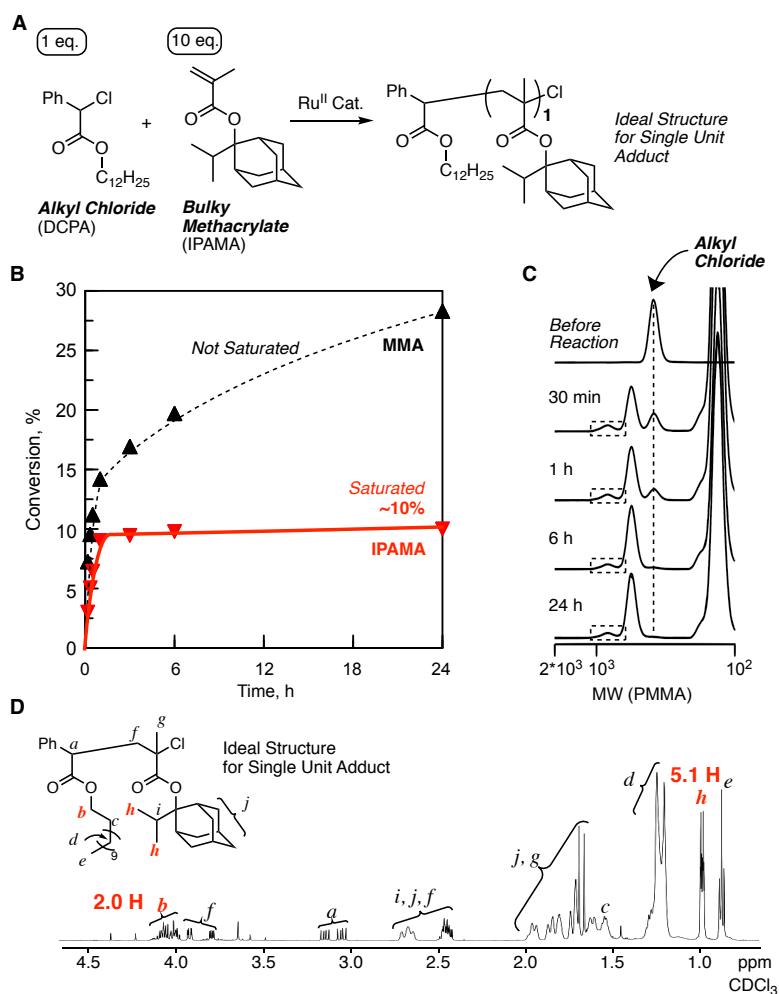
Figure 2. Radical addition of IPAMA with DCPA: [IPAMA]$_0$/[DCPA]$_0$/[[Cp*Ru(μ$_3$-Cl)]$_4$]$_0$/[BPMO ligand]$_0$ = 200/20/1.0/8.0 mM in toluene at 80°C.   (A) Scheme; (B) time-conversion; (C) SEC curves of the products; (D) ^{1}H NMR spectrum of the product.   BPMO ligand: 1,2-bis(diphenylphosphino)ethane monoxide.

The radical addition with IPAMA was studied in more detail (Figure 2).   Here, dodecyl 2-chloro-2-phenylacetate (DCPA) was used as the alkyl halide or the initiator (A), because this type of phenyl acetate halide allowed better efficient radical generation due to the lower bond energy than that of a simple methacrylate-based halide.[22]   A long alkyl chain (C$_{12}$H$_{25}$–) was introduced to detect the product by SEC.   The radical addition reaction of 10 equivalents of

IPAMA with DCPA was performed with a Cp*/bisphosphine monoxide-based ruthenium catalyst upon heating (80°C)[10, 23] and the reaction was monitored by ^{1}H NMR. The resultant products over time were analyzed by SEC.

As shown in Figure 2B, IPAMA was initially consumed after the solution was heated, but the conversion was saturated at around 10%: further consumption was not observed even after a long interval. For the SEC analysis (Figure 2C), the relative intensities of the peaks from alkyl halide gradually decreased, whereas a higher molecular weight (MW) peak likely from the single unit adduct was observed.   Finally, this peak was principally observed and the alkyl halide peak disappeared.   However, another minor peak of higher molecular weight (dotted line square) was also observed.   The product was purified by preparative SEC for removal of the lower molecular weight compounds (*e.g.*, the excess IPAMA and catalyst residues) and the higher MW product was analyzed by ^{1}H NMR.   The spectrum nearly supported an ideal structure of the single unit adduct, but the integration ratio from the IPAMA side chain to the initiator moiety was inconsistent with the ideal value for assuming that the 1 unit adduct was formed [Figure 2D: the ideal integration of the methyl protons (h) is 6.0 for the methylene protons (2H) in the DCPA unit].   Considering that the integration ratio is less than the ideal value and the minor peak of higher MW is observed in the SEC analysis, a bimolecular coupling reaction between DCPA likely accompanied the main reaction and a small amount of the
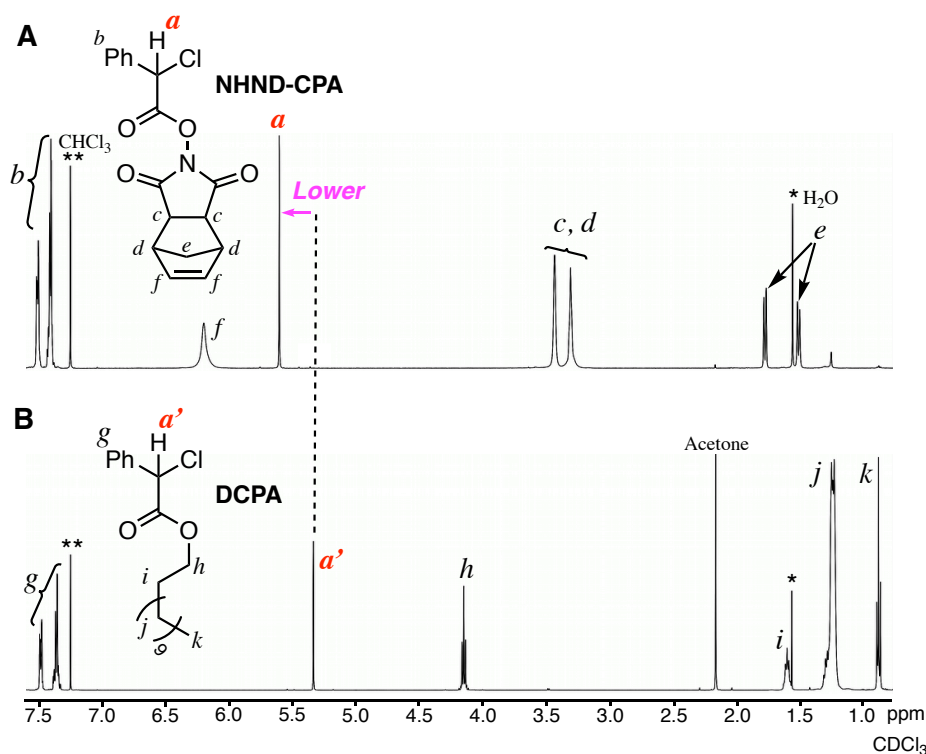

Figure 3. ^{1}H NMR spectrum of NHND-CPA (A) and DCPA (B) (r.t., CDCl$_3$)

coupled compound was contained in the product.

Suppression of the unfavorable coupling reaction was studied by changing the reaction conditions, i.e., catalyst, con- centration, and temperature (Figure S1), but the unfavorable peak did not disappear completely. The author then decided to replace the dodecyl ester of the chloride with an activated ester[24] in anticipation that the coupling reaction between the corresponding electron-deficient radical species could be avoided.   An *N*-hydroxy-5-norbornene-2,3-dicarboxyimide (NHND)-based ester[25] was selected among the various types of activated ester, because the relatively high molecular weight is suitable for SEC analysis. Thus, NHND-CPA was designed as the new initiator.   Figure 3 shows the ^{1}H NMR spectrum of NHND-CPA in comparison with DCPA.   The lower shift in the methine proton next to chlorine than for DCPA indicated the electron-with- drawing effect of the NHND-based ester. Such an activated ester can be transformed into an alkyl ester or amide via a reaction with alcohol or amine.   Thus, the concept of repeating the cycle via post modification is still available, although one more step in a cycle is required.

The newly synthesized halide initiator (NHND-CPA) was used for the ruthenium-catalyzed radical reaction with 10 eq. of IPAMA (Figure 4).   Saturated conversion at 10% (Figure 4A) and the peak shift in SEC analysis (Figure 4B) were observed, similar to DCPA, indicating the progress of the single unit monomer addition.   Importantly, no coupling peak was observed in the SEC trace.   The quantitative formation of the single unit adduct was proved by the ^{1}H NMR spectrum (Figure 4C): the integration ratio of the methyl protons of the IPAMA unit (h, 6H) to those of olefin protons from the NHND moiety (d, 2H) was exactly 3 : 1.   The H–H COSY 2D NMR and ESI-MS spectra also corresponded to the formation of a
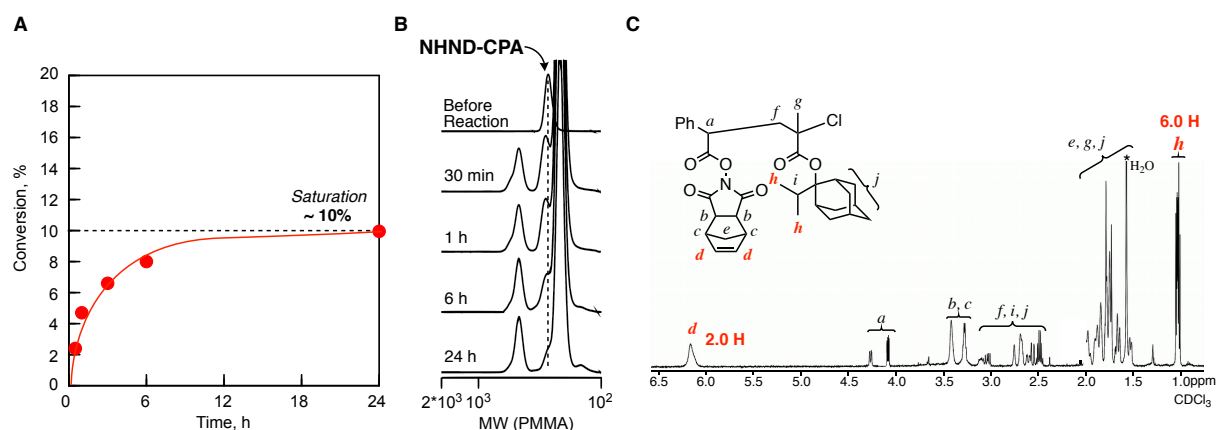
Figure 4. Radical addition of IPAMA with NHND-CPA: [IPAMA]$_0$/[NHND-CPA]$_0$/ [[Cp*Ru(μ_3-Cl)]$_4$]$_0$/[BPMO Ligand]$_0$ = 200/20/1.0/8.0 mM in toluene at 80˚C.   (A) time-conversion (B) SEC curves of the products (C) ^{1}H NMR spectrum of the product.

single unit adduct (Figure S2 and S3).

Thus, the activated ester-based halide was found to be effective in controlling the single unit addition with IPAMA. To always realize such reaction circumstance in the iterative cycle, the steps in a cycle were modified, as shown in Figure 5A. Namely, after control of single unit addition, the penultimate NHND-based unit was transformed into an alkyl methacrylate unit via transformation, and afterwards the terminal IPAMA unit was selectively cleaved under acidic conditions to convert it into a methacrylic acid unit. Finally, NHND was introduced via esterification to form the activated ester-based halide terminal that is effective in controlling the next single unit radical addition with IPAMA. The step number in a cycle is one more than conventionally used (Figure 5B), but the process is also advantageous in that the circumstances of the radical addition always identical in the iterative process (*i.e.*, the reaction between the NHND-terminal halide and IPAMA).
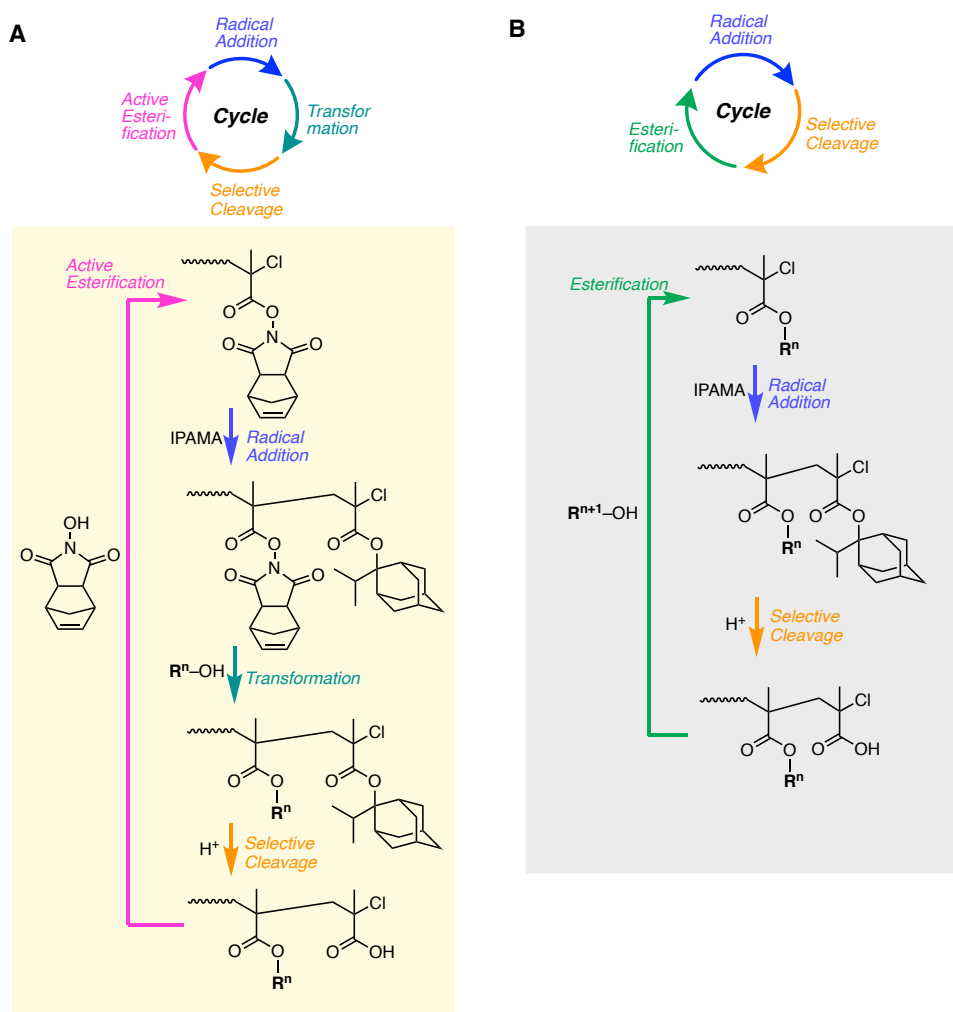
Figure 5. A new cycle with activated ester (A) in comparison with the previous cycle (B).

Thus, one cycle consisting of 4 steps, *i.e.*, "radical addition", "transformation", "selective cleavage", and "active esterification", was actually performed, and the structure of the product obtained at each step was characterized by ¹H NMR (Figure 6). For the transformation of the IPAMA-adduct, dodecyl alcohol was used in conjunction with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as the base. The peak from the double bond of the NHND pendant disappeared completely, and instead peaks from the dodecyl ester pendant (k, m, n) appeared with reasonable integration ratios for the quantitative transformation. The transformation product was fully sup- ported with the assistance of H–H COSY 2D NMR (Figure S4). Interestingly the peaks from the methine proton neighboring the phenyl group clearly shifted to higher field (*a'* vs. *a''*) via the transformation due to a change in electronic environment. The splitting of single peak (a) into two peaks (*a'* and *a''*) was due to the
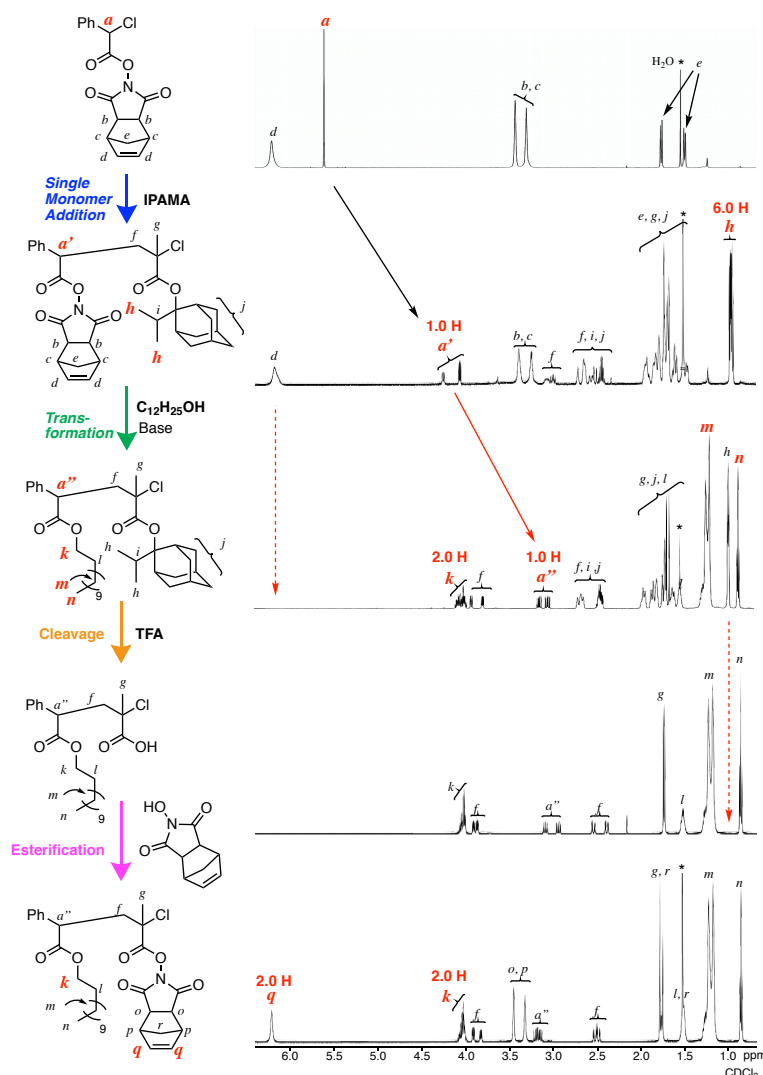
Figure 6. Structural analyses by ¹H NMR for the products after all the steps. See supporting information for reaction conditions.

formation of two diastereoisomers caused by the chiral carbon neighboring the chlorine atom. Then the product was treated with trifluoroacetic acid (TFA) for cleavage of the IPAMA unit. Consequently, the peak from isopropyl methyl protons vanished, while the peaks from the dodecyl ester pendant survived quantitatively, indicating the quantitative and selective cleavage. Finally, NHND was reacted with the methacrylic acid adduct to convert it into an activated ester-based halide terminal.

The reaction also occurred quantitatively, which was sup- ported by the appearance of the peak derived from the double-bond protons of the NHND pendant.   Note that the isolation yield for each step in the cycle was over 95%.   Most probably, the reaction yield is almost 100%.

The obtained NHND-ester pendant adduct was used as the initiator for the 2nd radical addition of IPAMA (Figure 7). When the reaction was performed at 80°C similar to the 1st radical addition, a slightly higher conversion (10.7%) was observed than the saturated value (10%), assuming control of single unit addition.   In addition, unknown peaks were observed at a lower molecular weight than the starting initiator.   The trend was more remarkable at 100°C.   Probably, some side reactions, such as decomposition of the initiator, took place at
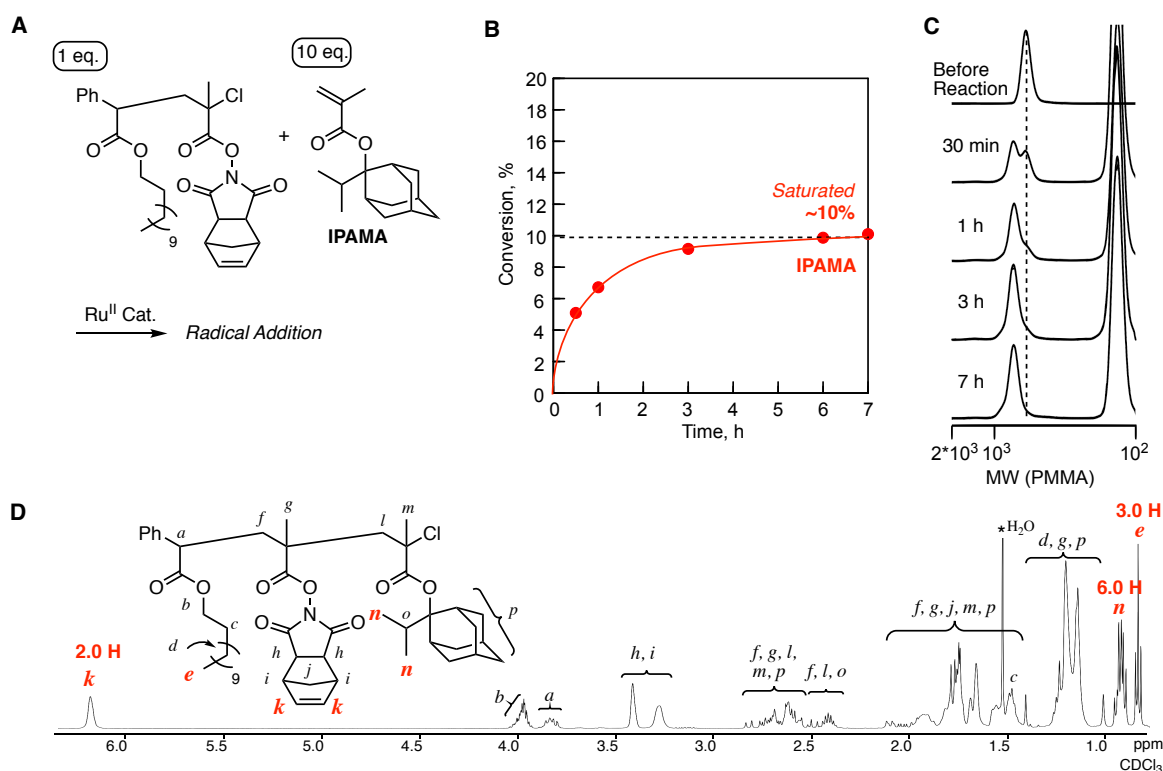
Figure 7. 2nd radical addition reaction of IPAMA with the chlorine-capped product obtained by 1st cycle: (A) scheme, (B) time-conversion, (C) SEC curves, (D) ^{1}H NMR spectrum for the product after the reaction in 7 hours.   See supporting information for reaction conditions.

such a higher temperature.   However, when the reaction temperature was decreased to 60 °C, the conversion was saturated at 10% (Figure 7B) and the unfavorable peaks were not observed in SEC (Figure 7C).   Indeed, the 1H NMR spectrum of the product totally supported the formation of the ideal adduct consisting of three kinds of ester pendant: *i.e.*, dodecyl (*e*), NHND (*b*), and isopropyl (*n*) (Figure 7D).

   The NHND-ester pendant in the middle unit was transformed into a methyl ester, *i.e.*, an MMA unit via the reaction with methanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[26]   The transformation was characterized by ^{1}H NMR (Figure 8).   The peak (*k*) from the olefin protons in the NHND pendant disappeared completely, and instead the methoxy proton peaks (*h*) were observed with a reasonable integration ratio for the quantitative transformation.   The resultant spectrum was very complicated due to the existence of some chiral carbons.   The formation of the methyl pendant product was fully supported with the assistance of H–H COSY 2D NMR (Figure S5).
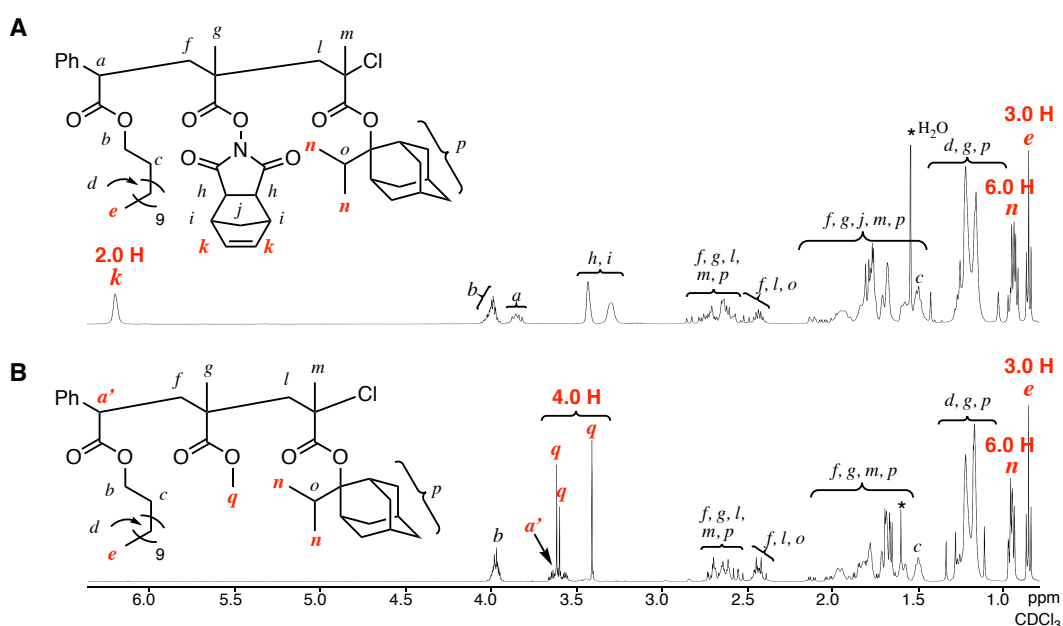
Figure 8. Structural analyses by ^{1}H NMR for the products in the 2nd cycle: (A) after radical addition of IPAMA; (B) after transformation with methanol.

   The MMA-converted product after the transformation underwent selective cleavage under acidic conditions, followed by active esterification with NHND for the IPAMA unit, similar to the 1st cycle.   These reactions also proceeded quantitatively to give the corresponding product (Figure S6 for ^{1}H NMR and Figure S7 for ESI-MS), which are ready for the next radical addition in the 3rd cycle.

Conclusion

As shown above, the introduction of an activated ester pendant for the chloride initiator allowed efficient radical addition of the bulky methacrylate. One more step is required to realize the reaction circumstances in the iterative cycle for the construction of sequence-defined oligo- or poly(methacrylate)s, but the progress of single unit radical addition without unfavorable side reactions is particularly significant in this strategy. Figure 9 summarizes the yields for all the cycles in the 1st and 2nd cycles demonstrated in this work. Note that the high values are yields of actual isolated products after purification for removal of excess reactants (IPAMA, alcohol) and catalysts *etc*. The reaction yields are probably close to 100% in all the steps, though the purification process could be a bottle- neck for large-scale synthesis. For a more practical process, the introduction of some supporter (solid resin or a soluble polymer chain carrying a cleavable spacer[27]) would be required, and this is now under investigation.
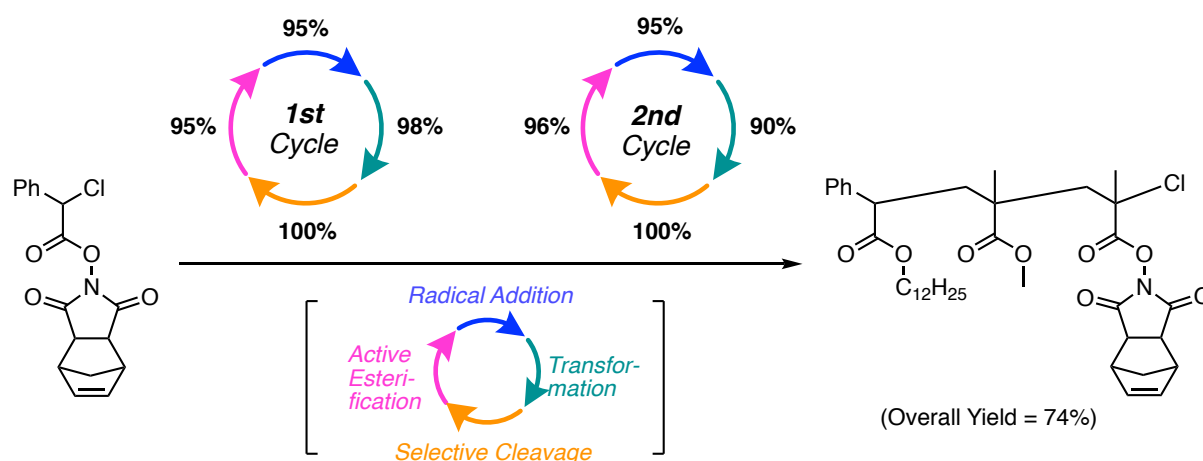
**Figure 9.** Yields for all the steps in 1st and 2nd cycle

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Chapter 2 Supporting Data
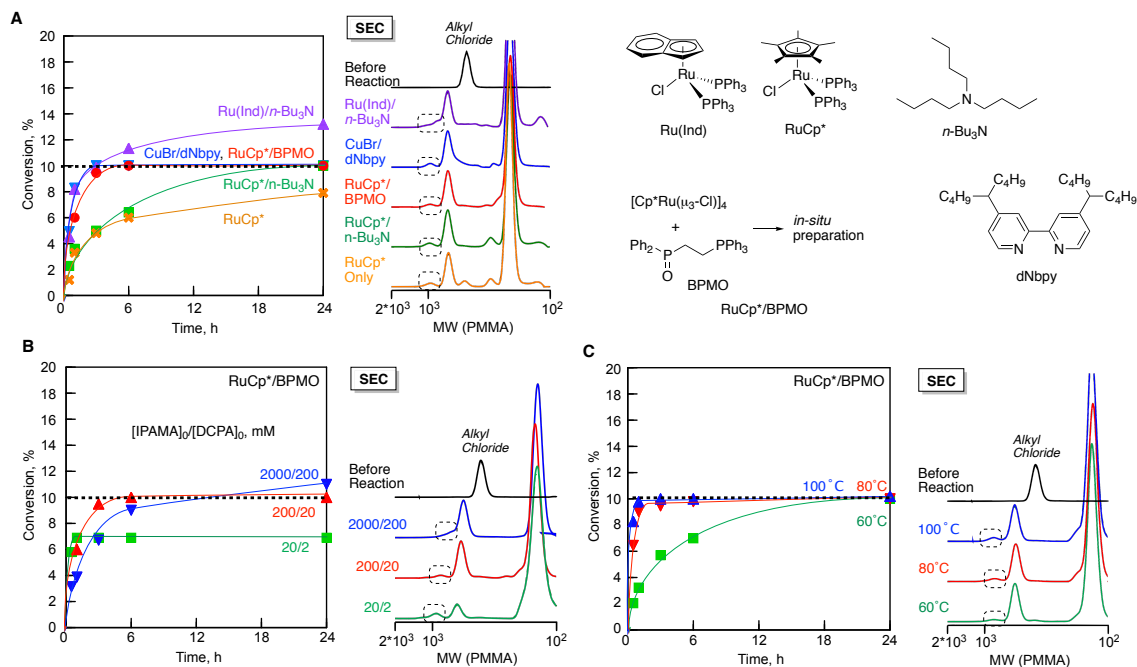
Figure S1. Effects of conditions (A: catalyst, B: catalyst amount, C: temperature) on the radical addition of IPAMA with DCPA. (A) [Ru Catalyst]$_0$/[n-Bu$_3$N]$_0$ = 4.0/40 mM; [[Cp*Ru(μ_3-Cl)]$_4$]$_0$/[BPMO]$_0$ = 1.0/8.0 mM; [CuBr]$_0$/[dNbpy]$_0$ = 20/20 mM for [IPAM A]$_0$/[DCPA]$_0$ = 200/20 mM in toluene at 80˚C.   (B) [IPAMA]$_0$/[DCPA]$_0$ = 2000/200, 200/20, and 20/2.0 mM for [[Cp*Ru(μ_3-Cl)]$_4$]$_0$/[BPMO]$_0$ = 1.0/8.0 mM in toluene at 80˚C.   (C) [IPAMA]$_0$/[DCPA]$_0$/ [[[Cp*Ru(μ_3-Cl)]$_4$]$_0$/[BPMO]$_0$ = 200/20/1.0/8.0 mM in toluene at 60, 80 or 100˚C.
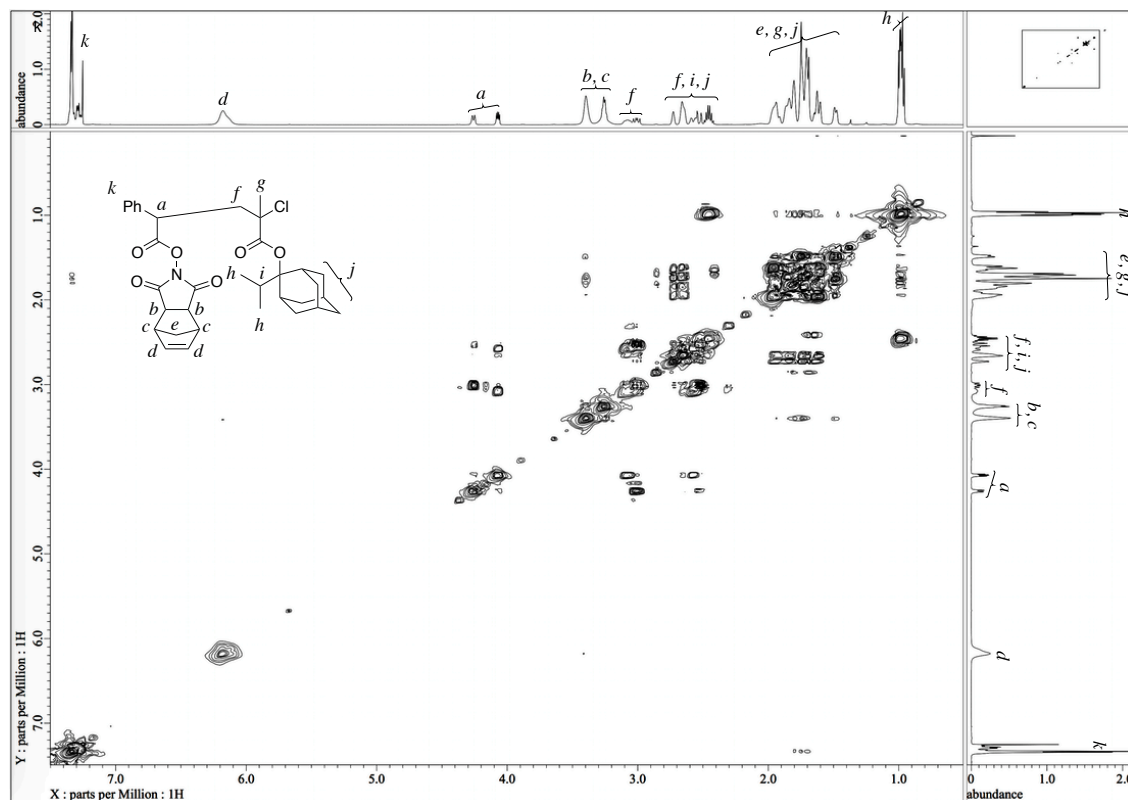
Figure S2. $^1H-^1H$ COSY Spectrum of the product after Single Monomer Addition with IPAMA (1st cycle).
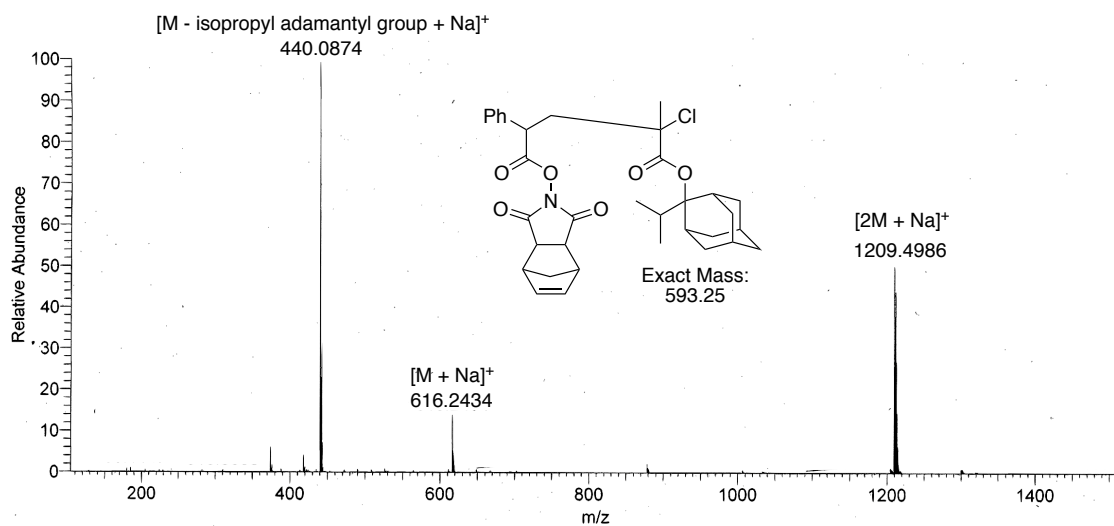
Figure S3. ESI-MS Spectrum of the product after radical addition of IPAMA with NHND-CPA (1st cycle)
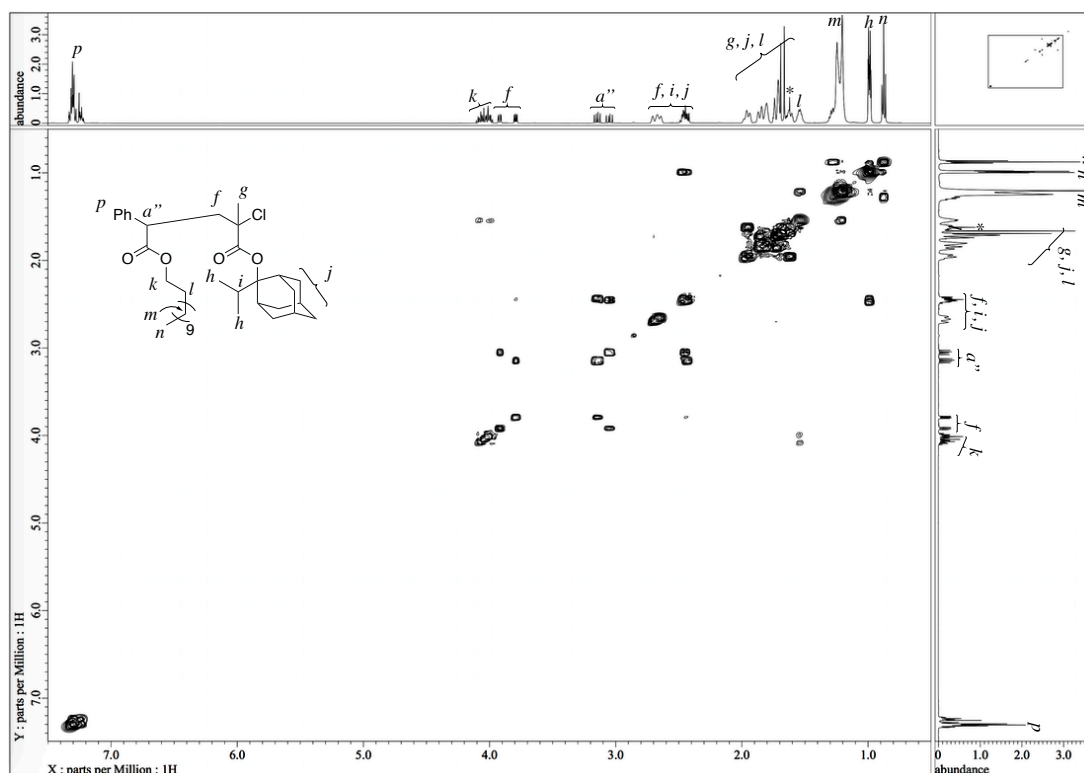
Figure S4. ^{1}H−^{1}H COSY spectrum of the product after Transformation with dodecyl alcohol (1st cycle).
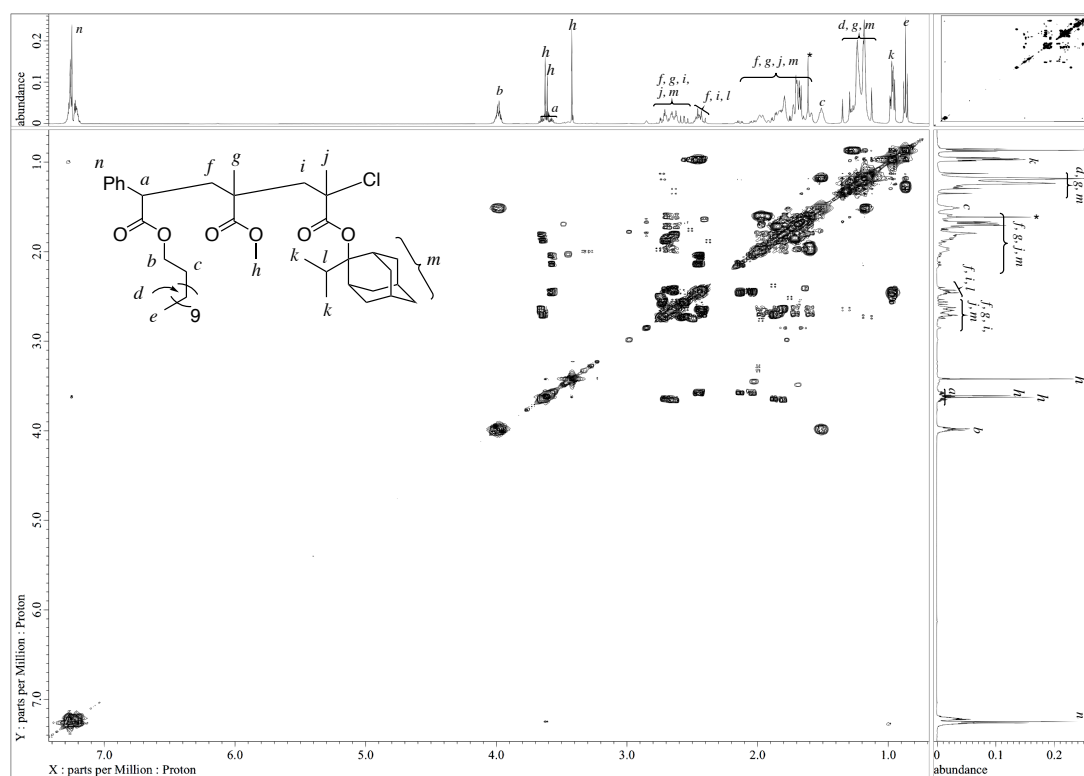
Figure S5. ^{1}H−^{1}H COSY spectrum of the product after transformation with methanol
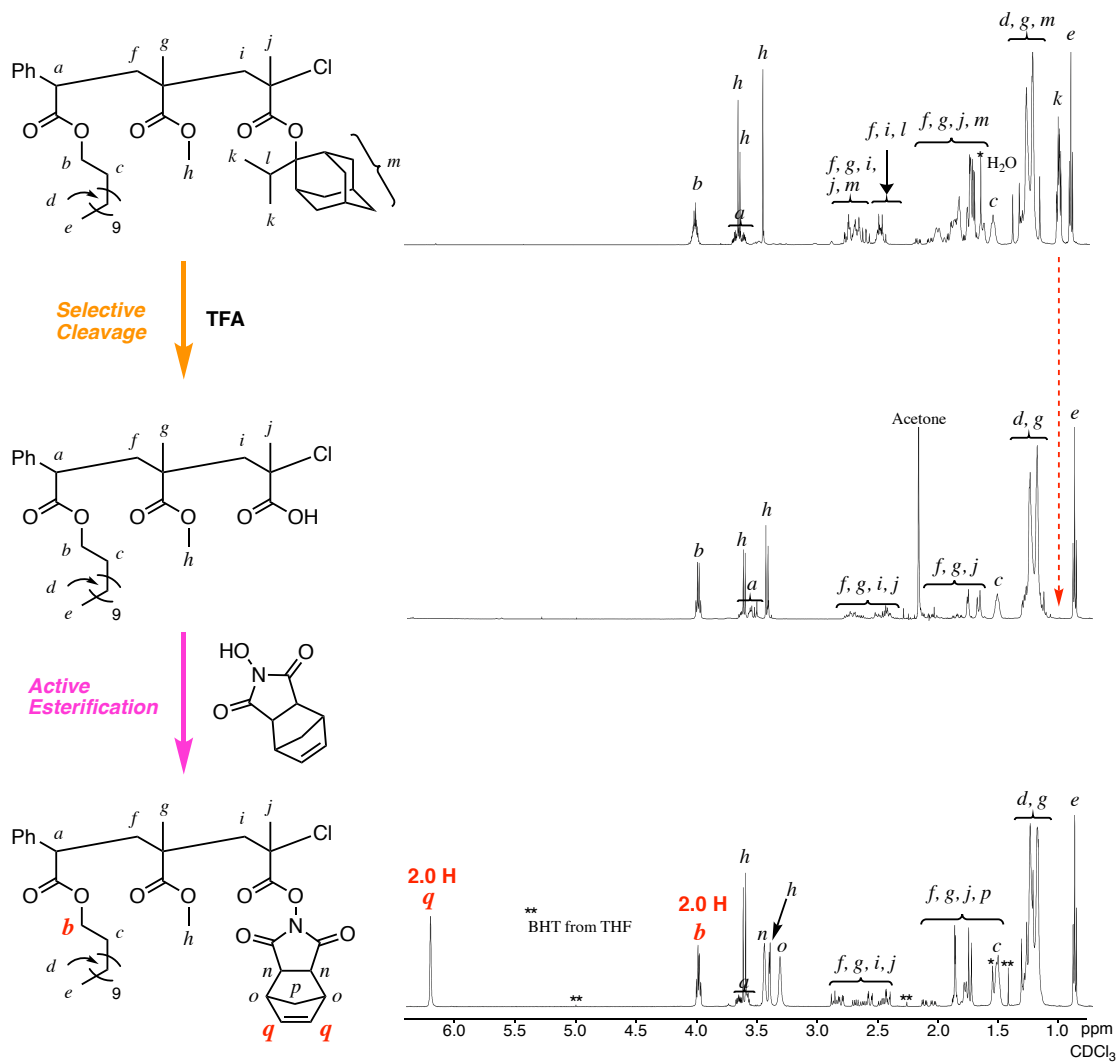
Figure S6. Structural analyses by ¹H NMR for the products after selective cleavage and esterification (2nd cycle).
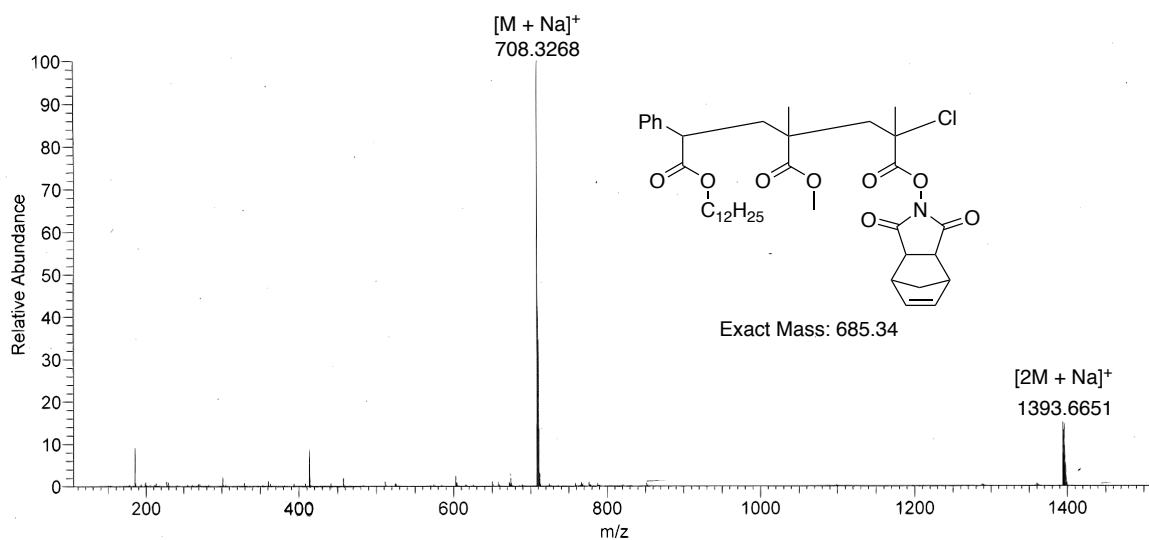
Figure S7. ESI-MS spectrum of product after esterification with NHND (2nd cycle).

PART II

# Control of Alternating Sequence
via Radical Copolymerization

Chapter 3

Unusual Radical Copolymerization of Supra-Bulky Methacrylate with *N*-Hydroxysuccinmide Acrylate: Facile Syntheses of Alternating-Rich Copolymers of Methacrylic Acid and *N*-Alkyl Acrylamide

Abstract

In this work, the author provides a facile methodology to synthesize AB alternating-rich copolymers made of methacrylic acid (MAA) and alkyl acrylamide units. An extremely bulky 3˚-ester methacrylate carrying ethyl and fenchol substituents (EFMA) was newly designed as a special monomer that is inactive for homopolymerization but active for copolymerization in radical polymerization. Indeed, EFMA showed unique radical copolymerization behaviors to the bulkiness, which was quite different from a general methacrylate (i.e., MMA). The copolymerization of EFMA with an electron-deficient acrylate carrying a *N*-hydroxysuccinimide substituent (NSA) followed by post reactions (i.e., acidolysis and amidation) for both units afforded alternating-rich copolymer of MAA and alkyl acrylamide units. The sequence was characterized by ^{13}C NMR analyses in comparison with the statistical copolymers and homopolymers. The reactivity ratio values also supported progress of the alternating copolymerization. Thus-obtained alternating-rich copolymers of MAA with isopropyl acrylamide (NIPAM) or octadecyl acrylamide (C18Am) showed sequence-driven solubilities and thermal response properties.
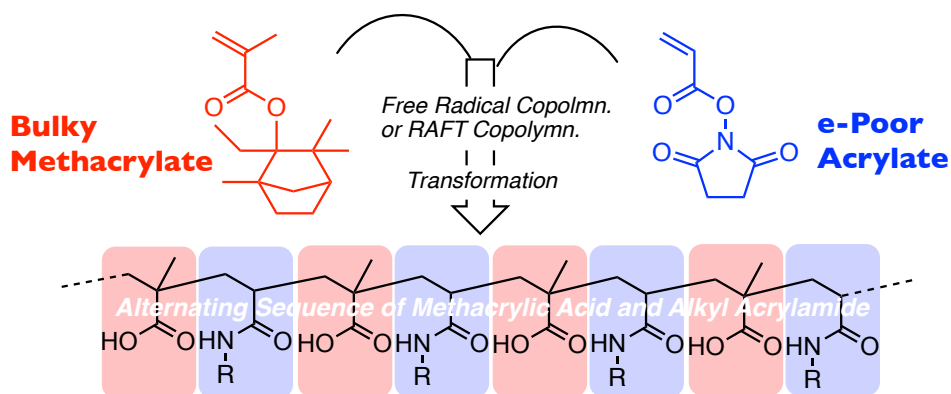
Introduction

Radical copolymerization has been studied for long and the extensive studies led to lots of data of reactivity ratios for various combinations of comonomers as shown in Polymer Handbook.[1]   The values are useful for predicting the averaged composition ratio of obtained copolymer.   The copolymerization behavior or the statistic trend generally depends on the combination of type of the comonomers such as styrene, (meth)acrylate, acrylamide as well as an electronic factor by the substituent from the pendant.   It is not so easy to change the trend dramatically. In general, the product is the mixture of chains having various composition ratios and thus the resultant copolymers are less uniform in terms of the composition due to the statistical feature of chain-growth copolymerization.   One exception is "alternating copolymerization" realized with a specific combination giving $r_1 = r_2 = 0$, such as vinyl ether and maleic anhydride.[2]   The electronic effect is significant in the alternating copolymerization and the cross-over propagation selectively takes place due to the large difference in electron density: propagating radical species selectively react with another monomer rather than itself. A fact that alternating sequence is enhanced by an addition of Lewis acid through interaction with carbonyl group on side chain[3] also explains the importance of electronic effect.

On the other hand, sequence control for synthetic polymers has attracted attentions during the past decade.[4-12]   Especially, the control for carbon-main chain polymers alternately carrying pendant group(s) has awakened curiosity for those who have treated synthetic polymers, because some functionalities could be introduced via the side chains in well-defined order.[11,12] Radical polymerization is particularly useful as the polymerization tool in terms of monomer diversity: both monomer types and pendant functional groups can be designed and combined according to the purpose.   However, sequence control by radical polymerization for general monomers such as styrene, (meth)acrylate, and acrylamide is challenging due to the less selectivity of the corresponding radical species to the comonomer as well as difficulty in control of definite single unit addition and the repetition.   So far, some efforts to control sequence with radical polymerization have been studied through templated system,[13-15] selective cyclopolymerization,[16-20] and iterative single unit addition.[21-29]   However, some cases require complicated synthesis consisting of many steps for the initiator and monomer and/or diluted condition for the polymerization to control sequence beyond the inherent copolymerization tendency based on the reactivity ratios.   Alternatively, applicable monomers are often limited to those inherently showing alternating propagation abilities such as styrene and maleimide derivatives.   Toward clarification of sequence-oriented properties and the

practical application, sequence control for general monomer units as well as the scalable approach is required.

In this work, given by these backgrounds, the author has focused on pendant bulkiness of monomer for more applicable sequence control beyond inherent copolymerization ability. The author has recently found a methacrylate carrying adamantyl and isopropyl (IPAMA) is a unique monomer allowing single unit radical addition with reversible deactivation radical polymerization (ruthenium-catalyzed living radical polymerization) due to the bulkiness (Figure 1A).[24,29] The tertiary pendant ester can be converted into less bulky group after the addition enabling the repetition of single unit addition, which could lead to synthesis of sequence-defined poly(oligo) methacrylates. The low homo polymerization ability of such a bulky methacrylate might affect copolymerization behavior to lead to alternating copolymerization with a comonomer (Figure 1B). Indeed, some examples on unique copolymerization peculiar to bulkiness have been reported in anionic polymerization.[30-32] For ring-opening metathesis polymerization (ROMP), some bulky and strained cyclic monomers induced alternating copolymerization in conjunction with less strained monomers.[33-35]
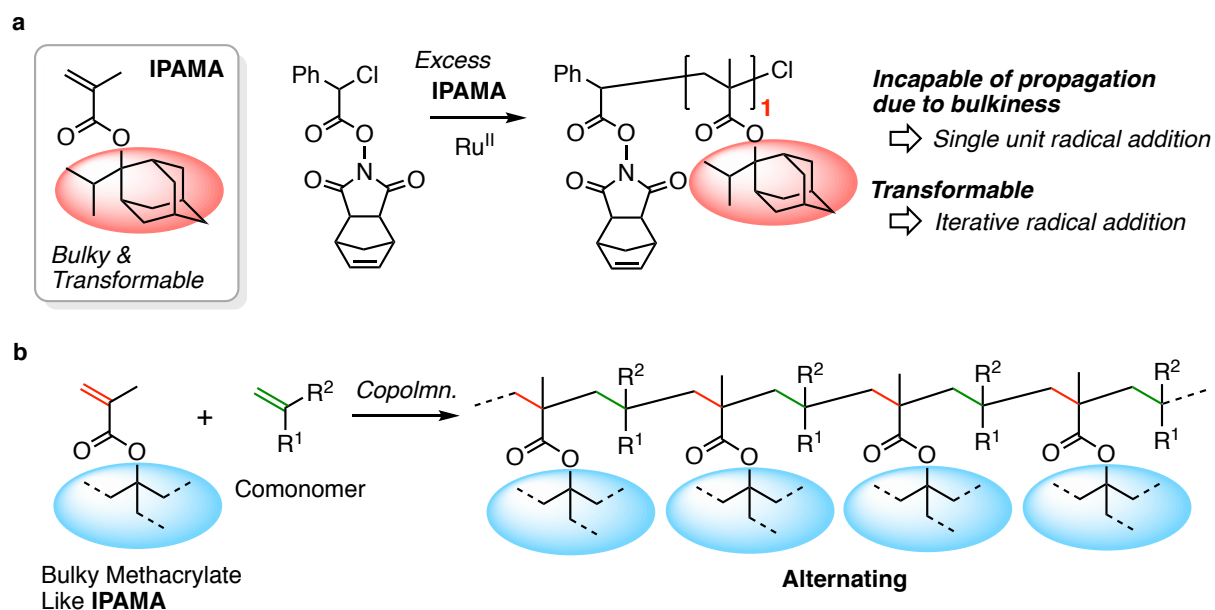
Figure 1. (a) Ruthenium-catalyzed single unit radical addition of a bulky and transformable methacrylate (IPAMA) for a chlorine compound. (b) Radical copolymerization of a bulky methacrylate with a comonomer toward control of alternating sequence.

Experimental

Materials

The following reagents were used as received: 2,2'-azobis(isobutyronitrile) (AIBN; TCI, >98.0%), 2,2'-azobis(*N*-butyl-2-methylpropionamide) (VAm-110; wako, >95.0%), 2-cyano-2-propyl benzodithioate (CP-BDT; Aldrich, >97%), fenchyl alcohol (TCI, >96.0%), 2-ethyl fenchol (Aldrich, >97.0%), triethylamine (TCI, >99.0%), methacryloyl chloride (TCI, >90.0%), isopropyl amine (TCI, >99.0%), butyl amine(TCI, >99.0%), stearyl amine (TCI, >85.0%), trifluoroacetic acid (TFA; Wako, >98.0%), 2-isopropyl-2-adamantyl methacrylate (IPAMA; TCI, >98.0%), *N*-succinimidyl acrylate (NSA; TCI, >98.0%), methacrylic acid (Wako, >99.0%). *N*-Isopropylacrylamide (NIPAM; TCI, 98.0%, stabilized with MEHQ) was purified by recrystallization two times from the hexane solution. Methyl methacrylate (MMA; TCI, >99.8%, stabilized with 6-tert-butyl-2,4-xylenol), *tert*-butyl methacrylate (tBMA: TCI, >98%), butyl vinyl ether (BVE; TCI, >98.0%, stabilized with KOH), styrene (TCI, >99.0%, stabilized with TBC), methyl acrylate (MA; TCI, >99.0%, stabilized with MEHQ), and 1-vinyl-2-pyrrolidone (NVP; TCI, >99.0%, stabilized with *N,N'*-Di-sec-butyl-p-phenylenediamine) were dried overnight over calcium chloride and distilled before use. Column chromatography was carried out using Wakosil C200 (Wako) as the stationary phase. Sodium hydride dry (Aldrich, >90.0%) was used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inter-gas-systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere (H_2O < 0.1 ppm; O_2 < 0.1 ppm).

Toluene (Kishida kagaku, Osaka, Japan; purity >99.5%) was dried and purified by passing through purification columns (Solvent Dispensing System, SG Water USA, Nashua, NH; Glass Contour) and bubbled with dry nitrogen for 15 min before use. Unless stated otherwise, other solvents were purchased from Wako Pure Chemical Industries and used without further purification. 1,2,3,4-tetrahydrousnaphthalene (tetralin; internal standard for ^{1}H NMR) was distilled over calcium chloride.

Characterization

Structure calculations were carried out using Gaussian 16.[36] Size exclusion chromatography (SEC) was measured at 40°C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404) connected to DU-H2000 pump, 74S-RI refractive-index detector, and 41-UV ultraviolet detector (Shodex). The columns were calibrated against 12 standard poly(methyl methacrylate) standards (PSS Polymer, M_n =730-1650000; M_w/M_n = 1.04-1.15).

^{1}H NMR spectra were recorded on JEOL JNM-ECA500 spectrometer, operating at 500.125 MHz.   Temperature-variable transmittance of polymer solutions was measured on UV-1800 (Shimadzu, optical path length = 1.0 cm, λ = 670 nm, heating (or cooling) rate: 1 ˚C/min).   The polymer samples for thermal response and transmittance measurement were dehydrated via freeze dry from the water or 1,2-dimethoxyethane solution.   The polymer solutions were put in a refrigerator (about 2˚C) overnight before the thermal response evaluations.

Monomer Synthesis

Synthesis of 2-fenchyl methacrylate (FMA)
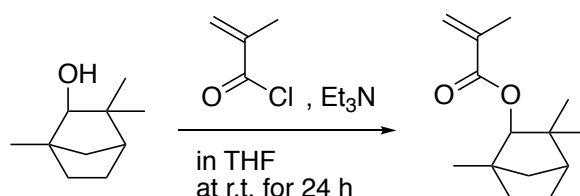
Fenchyl alcohol (5.0 g, 32.4 mmol) and triethylamine (5.4 mL, 39.0 mmol) were placed in round-bottom flask under argon and then dissolved in THF (60 mL).   To the resultant solution, methacryloyl chloride (3.3 mL, 33.8mmol) was gradually added at 0 ˚C, while stirring for 30 min.   The reaction solution was warmed to room temperature and stirred overnight. The reaction was quenched with methanol (5 mL). To the solution, 200 mL of Et$_2$O were added, followed by addition of 200 mL of sat. NaHCO$_3$ solution.   The organic layer was washed with brine 3 times and dried on Na$_2$SO$_4$.   After concentration under reduced pressure, the crude product was purified with silica column chromatography (hexane:ethyl acetate = 95:5).   The product was obtained as slightly yellow oil (2.5 g, 11.3 mmol, 35 %).   ^{1}H NMR (in CDCl$_3$): 6.12 (s, 1H), 5.53 (s, 1H), 4.42 (s, 1H), 1.96 (s, 3H), 1.81-1.68 (m, 3H), 1.63-1.57 (d, 1H), 1.49-1.42 (m, 1H), 1.23-1.16 (d, 1H), 1.15-1.07 (m, 4H), 1.05 (s, 3H), 0.77 (s, 3H).

Synthesis of 2-ethyl-2-fenchyl methacrylate (EFMA)
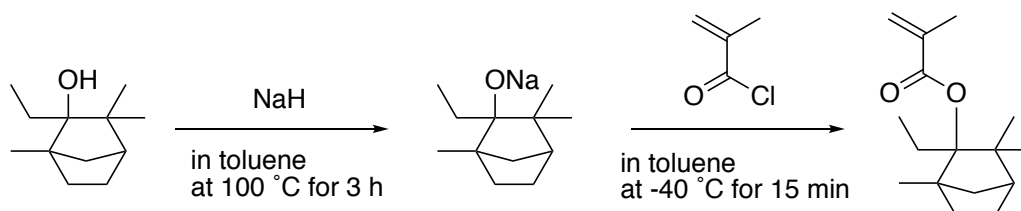
Sodium hydride (0.75 g, 31.3 mmol) were placed in round-bottom flask under argon and then dissolved in toluene (14 mL).   To the resultant solution, 2-ethyl fenchol (5.0 mL, 26.2 mmol) was gradually added at 0 ˚C, while stirring for 30 min.   The reaction solution was

warmed to 100 ˚C and stirred for 3h.   After cooling the solution, methacryloyl chloride (2.6 mL, 27.1 mmol) was gradually added at -40 ˚C, while stirring for 15 min.   The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, followed by purification with silica column chromatography (hexane:ethyl acetate = 99:1).   The product was obtained as slightly yellow oil (4.2 g, 16.8 mmol, 64%). ^{1}H NMR (in CDCl$_3$): 6.05 (s, 1H), 5.47 (s, 1H), 2.21-2.13 (sext, 1H), 2.05-1.98 (sext, 1H), 1.93 (s, 3H), 1.79-1.68 (m, 3H), 1.59-1.56 (d, 1H), 1.50-1.40 (m, 1H), 1.24 (s, 3H), 1.13 (s, 3H), 1.11-1.08 (d, 2H), 1.06 (s, 3H), 0.83-0.73 (t, 3H).

Synthesis of stearyl acrylamide (C18AAm)
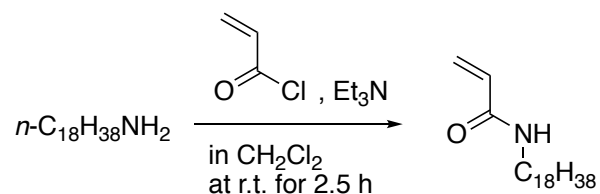
Stearylamine (13.6 g, 50.6 mmol) and triethylamine (8.5 mL, 55.6 mmol) were placed in round-bottom flask under argon and then dissolved in CH$_2$Cl$_2$ (50 mL).   To the resultant solution, acryloyl chloride (4.5 mL, 55.0 mmol) was gradually added at 0 ˚C, while stirring for 30 min.   The reaction solution was warmed to room temperature and stirred for 2.5 hours.   The reaction mixture was quenched with methanol (3 mL), and then concentrated under reduced pressure.   The reaction mixture was dissolved in THF and the filtrate was concentrated under reduced pressure.   The crude product was purified by recrystallization in methanol.   The product was obtained as white powder (12.5 g, 38.7 mmol, 77%). ^{1}H NMR (in CDCl$_3$): 6.26 (d, 1H), 6.08 (q, 1H), 5.73 (brs, 1H), 5.61 (d, 1H), 3.31 (q, 2H), 1.52 (quin, 2H), 1.24 (m, 30H), 0.87 (t, 3H).

Free radical copolymerization of methacrylate (EFMA or MMA) and comonomer

Copolymerization of EFMA or MMA (M$_1$) with a comonomer (M$_2$) were performed by changing the injection ratio (M$_2$ = BVE, Styrene, NVP, or MA).   Typical procedure of the copolymerization (EFMA and MA) is as follows: EFMA (0.75 g, 3.0 mmol), AIBN (9.9 mg, 0.060 mmol), and tetralin (0.2 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved in 1,4-dioxane (1.6 mL).   To the solution, methyl acrylate (0.27 mL, 3.0 mmol) was added in this order at room temperature.   For immediately after mixing, the reaction solution was warmed to 60˚C.   The reaction was terminated according to the progress

of copolymerization by cooling the solution to –78˚C.   The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with tetralin as an internal standard. M_n and M_w/M_n of obtained copolymers in 24 h were determined by SEC (Table 1).

Table 1. Free Radical Copolymerization of methacrylate (EFMA or MMA) and comonomer (BVE, NVP, styrene, and MA)[a]

Methacrylate (M$_1$)	Comonomer (M$_2$)	Conv$_{M1}$, %	Conv$_{M2}$, %	M_n	M_w/M_n
EFMA	BVE	17.3	8.0	700	2.45
	NVP	54.5	26.7	7400	2.06
	Styrene	37.9	48.8	16,800	1.71
	MA	80.0	72.1	14,300	2.09
MMA	BVE	100	21.1	11,900	2.69
	NVP	100	80.0	23,300	2.01
	Styrene	59.8	57.4	16,700	2.01
	MA	100	84.0	17,200	2.57

[a][methacrylate]$_0$/[comonomer]$_0$/[AIBN]$_0$ = 1000/1000/20 mM in 1,4-dioxane at 60˚C

Procedures to determine monomer reactivity ratio

　　Copolymerization of EFMA (M$_1$) and NSA (M$_2$) were performed with AIBN by changing the monomer ratio (M$_1$:M$_2$ = 9:1, 7:3, 5:5, 3:7, and 1:9). Typical procedure of copolymerization is as follows: EFMA (0.25 g, 1.0 mmol), NSA (0.17 g, 1.0 mmol), AIBN (3.3 mg, 0.020 mmol), and anisole (0.1 mL, internal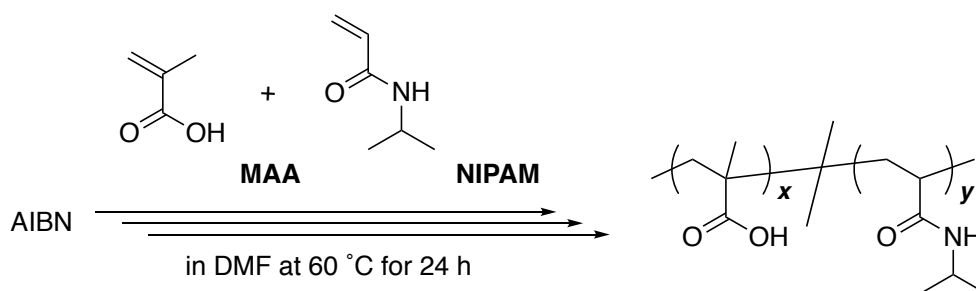 standard) were placed in Schlenk tube under argon, and then dissolved in DMF (1.0 mL) (5:5 injection condition).   The solution was warmed to 60˚C for initiating the radical copolymerization.   The reaction was terminated by cooling the solution to –78˚C.   The composition ratio [$F = DP_{M1}/(DP_{M1} + DP_{M2})$] was determined from the monomer conversion ratio [Conv$_{M1}$, Conv$_{M2}$] by ^{1}H NMR with anisole as an internal standard.   The actual monomer feed ratio [$f = [M_1]_0/([M_1]_0 + [M_2]_0)$] was also determined by ^{1}H NMR before reaction.   The monomer reactivity ratios were then calculated via Fineman-Ross plot with the F and f values (Table 2 and Figure 4).   The monomer reactivity ratios for MMA and NSA were similarly determined.

Table 2. Free Radical Copolymerization of Methacrylate (M_1: EFMA or MMA) with NSA (M_2) for Determination of the Reactivity Ratio[a]

M_1	f[b]	Time (min)	$Conv_{M1}$[c](%)	$Conv_{M2}$[c](%)	F[d]
EFMA	0.12	10	16.9	7.2	0.23
	0.30	10	9.0	5.0	0.43
	0.50	20	6.8	6.8	0.50
	0.69	20	2.4	4.9	0.52
	0.90	10	0.7	4.0	0.56
MMA	0.09	5	9.0	3.5	0.20
	0.30	5	12.1	5.2	0.49
	0.46	5	3.6	1.9	0.62
	0.69	5	1.9	1.6	0.73
	0.89	5	2.4	3.3	0.86

[a] $[M_1+M_2]_0/[AIBN]_0 = 2000/10$ mM in DMF at 60˚C.

[b] Actual monomer feed ratio ($f = [M_1]_0/([M_1]_0 + [M_2]_0)$) determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR.

[d] Calculated from f, $Conv_{M1}$ and $Conv_{M2}$.

Synthesis of alternating-rich copolymer of MAA and NIPAM *via* free radical copolymerization and side-chain transformation
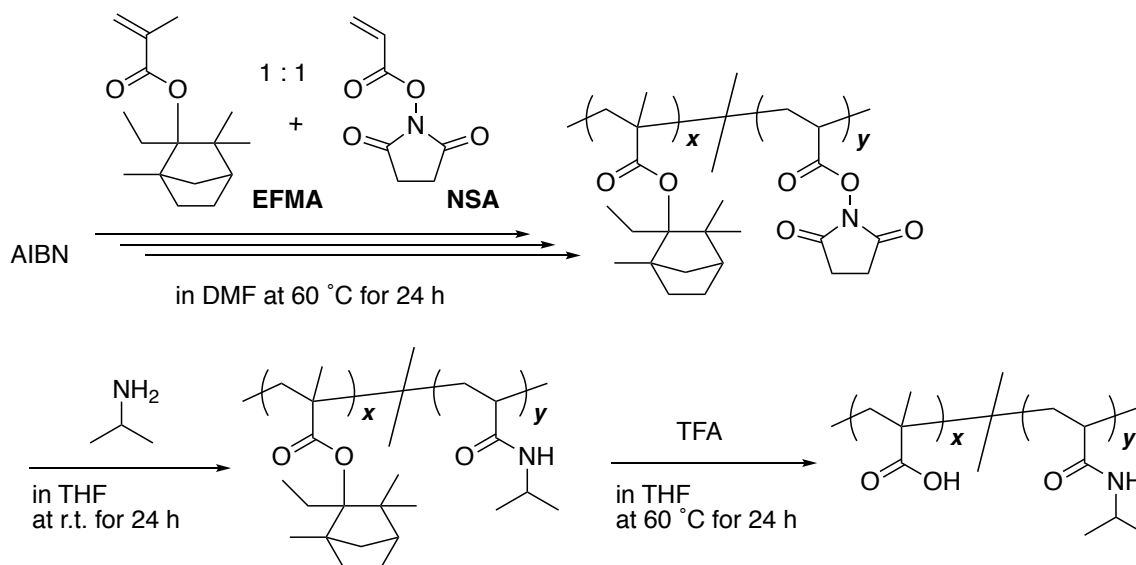
EFMA (0.75 g, 3.0 mmol), NSA (0.50 g, 3.0 mmol), AIBN (9.9 mg, 0.060 mmol), and anisole (0.1 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved

in DMF (3 mL). The reaction solution was warmed to 60˚C for initiating the radical copolymerization. The reaction was terminated in 4.5 hours by cooling the solution to –78˚C. The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with anisole as an internal standard (Conv$_{EFMA}$ = 72.3 %, Conv$_{NSA.}$ = 72.9 %). The reaction mixture was purified via dialysis in DMF for removal of residue monomer, and DMF was evaporated under reduced pressure to obtain the copolymer (0.96 g, $M_{n\,(GPC)}$ = 16000, M_w/M_n = 1.94). The averaged composition ratio (x : y) was 49 : 51 (by ^{1}H NMR: Figure 5).

The resultant copolymer (0.61 g) was placed in Schlenk tube under argon, and then dissolved in DMF (2.0 mL). To the solution, isopropyl amine (0.5 mL, 5.4 mmol) was gradually added at 0 ˚C for transformation into NIPAM unit. The reaction solution was warmed to room temperature and stirred for 24 hours. Then, the reaction mixture was purified via dialysis in DMF and DMF was evaporated under reduced pressure to obtain the NIPAM copolymer (0.48 g).

The NIPAM copolymer (0.24 g) was placed in Schlenk tube under argon, and then dissolved in THF (5 mL). To the solution, TFA (1.5 mL, 20.0 mmol) was gradually added at 0 ˚C. The reaction solution was warmed to 60 ˚C and stirred for 24 hours. Then, the reaction mixture was evaporated for removal of TFA, followed by dialysis in DMF. Finally, DMF was evaporated under reduced pressure to obtain the copolymer of MAA and NIPAM (0.091 g).

Synthesis of MAA-NIPAM statistical copolymers via free radical copolymerization

MAA-NIPAM statistical copolymers were synthesized via free radical copolymerization of MAA and NIPAM with AIBN by changing the monomer ratio ([MAA]$_0$:[NIPAM]$_0$ = 3:1, 1:1, and 1:3). Typical procedure of the copolymerization ([MAA]$_0$:[NIPAM]$_0$ = 1:1) is as follows: NIPAM (0.45 g, 4.0 mmol), AIBN (13.1 mg, 0.080 mmol), and anisole (0.1 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved in DMF (3.5 mL). To the solution, MAA (0.34 mL, 4.0 mmol) was added at room temperature. Immediately after mixing, the reaction solution was warmed to 60˚C.

The reaction was terminated in 24 hours by cooling the solution to –78˚C.   The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with anisole as an internal standard (Conv$_{MAA}$ = 100 %, Conv$_{NIPAM.}$ = 100 %).   The reaction mixture was purified via dialysis in DMF and DMF was evaporated under reduced pressure to obtain the copolymer (0.62 g).   The averaged composition ratio (x : y) was 51 : 49 (by ^{1}H NMR).   Other statistical copolymers [(x : y) = 92 : 8 and 10 : 90) were also synthesized with the similar process and the averaged composition ratio was determined by ^{1}H NMR.

Synthesis of alternating-rich copolymer of MAA and NIPAM *via* RAFT copolymerization and side-chain transformation
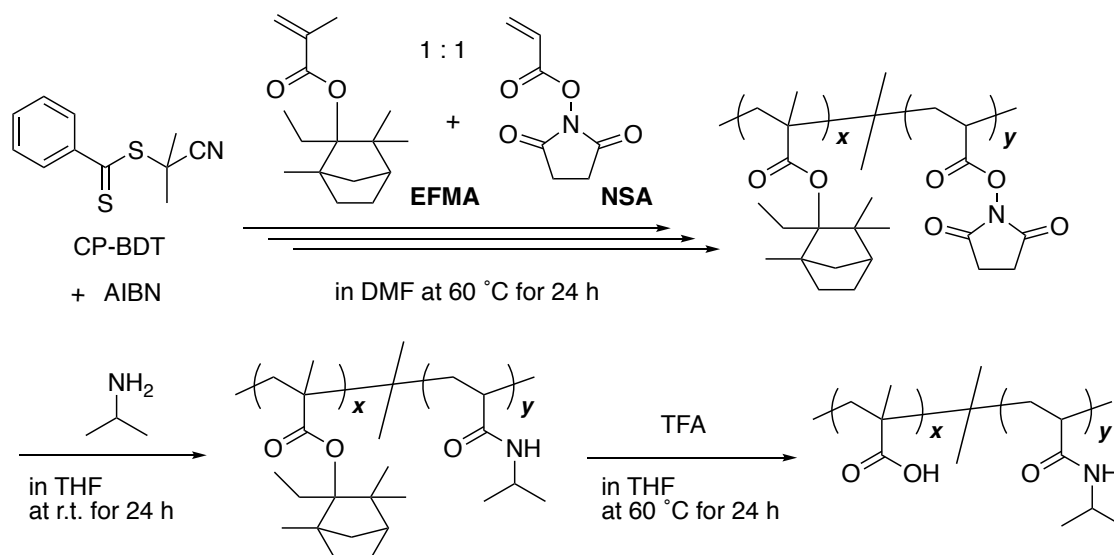
EFMA (0.75 g, 3.0 mmol), NSA (0.50 g, 3.0 mmol), CP-BDT (13.3 mg, 0.060 mmol), AIBN (1.0 mg, 0.006 mmol), and anisole (0.1 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved in DMF (2 mL).   The reaction solution was warmed to 60˚C for initiating the radical copolymerization.   The reaction was terminated in 24 hours by cooling the solution to –78˚C.   The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with anisole as an internal standard (Conv$_{EFMA}$ = 85.3 %, Conv$_{NSA.}$ = 87.4 %).   The reaction mixture was purified via dialysis in DMF for removal of residue monomer and DMF was evaporated under reduced pressure to obtain the copolymer (1.04 g, M_n = 8200, M_w/M_n = 1.26).   The averaged polymerization degree was determined by ^{1}H NMR (x = 54, y = 55: Figure 7c).

The resultant copolymer (0.40 g) was placed in Schlenk tube under argon, and then dissolved in DMF (10 mL).   To the solution, isopropyl amine (1.0 mL, 10.8 mmol) was gradually added at 0 ˚C.   The reaction solution was warmed to room temperature and stirred

for 24 hours.   Then, the reaction mixture was purified via dialysis in DMF and DMF was evaporated under reduced pressure to obtain the NIPAM copolymer (0.30g).

The NIPAM copolymer (0.25 g) was placed in Schlenk tube under argon, and then dissolved in THF (5 mL).   To the solution, TFA (1.5 mL, 20 mmol) was gradually added at 0 °C.   The reaction solution was warmed to 60 °C and stirred for 24 hours.   Then, the reaction mixture was evaporated for removal of TFA, followed by dialysis in DMF.   Finally, DMF was evaporated under reduced pressure to obtain the copolymer of MAA and NIPAM (**Alt**$_{MAA-NIPAM}$-**1**, 0.084 g).

Synthesis of alternating-rich copolymer of MAA and C18Am *via* RAFT copolymerization and side-chain transformation
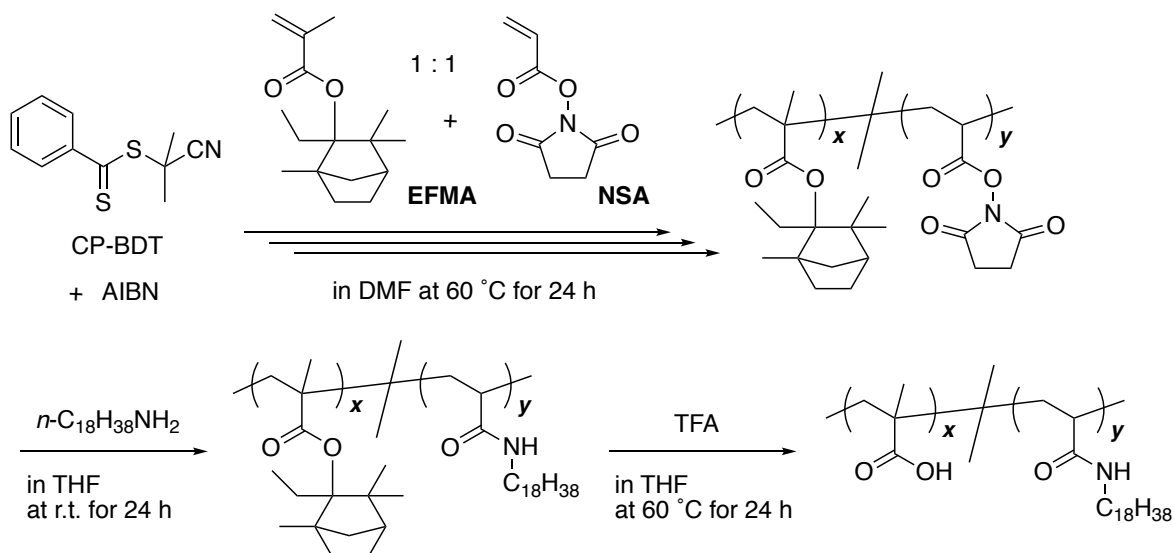
The EFMA-NSA copolymer obtained via RAFT copolymerization (see above, 0.38 g) was placed in Schlenk tube under argon, and then dissolved in THF (20 mL).   To the solution, stearyl amine (2.5 g, 9.3 mmol) was gradually added at 0 °C.   The reaction solution was warmed to room temperature and stirred for 24 hours.   Then, the reaction mixture was purified via dialysis in DMF and DMF was evaporated under reduced pressure to obtain the C18Am copolymer (0.42 g).

The C18Am copolymer (0.30 g) was placed in Schlenk tube under argon, and then dissolved in THF (10 mL).   To the solution, TFA (1.5 mL, 20 mmol) was gradually added at 0 °C.   The reaction solution was warmed to 60 °C and stirred for 24 hours.   Then, the reaction mixture was evaporated for removal of TFA, followed by dialysis in THF.   Finally, THF was evaporated under reduced pressure to obtain the copolymer of MAA and C18Am (**Alt**$_{MAA-C18Am}$, 0.18 g)

Synthesis of MAA-C18Am statistical copolymers *via* RAFT copolymerization
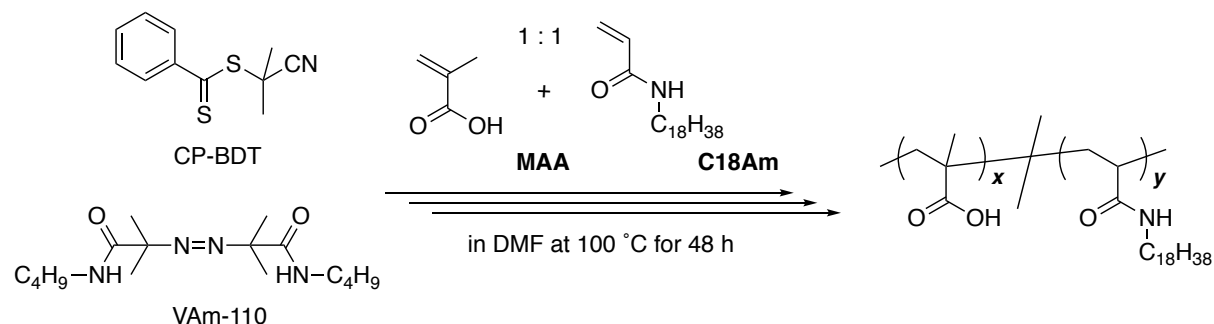
MAA-C18Am statistical copolymers were synthesized via RAFT copolymerization of MAA and C18Am with AIBN by changing the monomer ratio ($[MAA]_0$:$[C18Am]_0$ = 3:1, 1:1, and 1:3). Typical procedure of the copolymerization ($[MAA]_0$:$[C18Am]_0$ = 1:1) is as follows: C18Am (0.65 g, 2.0 mmol), CP-BDT (22.1 mg, 0.10 mmol), VAm-110 (3.1 mg, 0.010 mmol), and anisole (0.1 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved in DMF (2 mL).   To the solution, MAA (0.17 mL, 2.0 mmol) was added at room temperature (1:1 injection condition).   Immediately after mixing, the reaction solution was warmed to 100°C for initiating the RAFT copolymerization.   The reaction was terminated in 48 hours by cooling the solution to –78°C.   The conversion of vinyl group was determined by ^{1}H NMR in THF-d_8 with anisole as an internal standard ($Conv_{MAA}$ = 88.1%, $Conv_{C18AAm.}$ = 81.8%).   The reaction mixture was purified via dialysis in THF for removal of residue monomers and THF was evaporated under reduced pressure to obtain the MAA-C18Am copolymer (**Stat$_{50/50}$**, 0.10 g).   The number-averaged polymerization degrees were determined by ^{1}H NMR: x = 64, y = 65.   Other statistical copolymers (**Stat$_{20/80}$** and **Stat$_{70/30}$**) were also synthesized with the similar process and the composition ratios indicated by the subscript were determined by ^{1}H NMR.

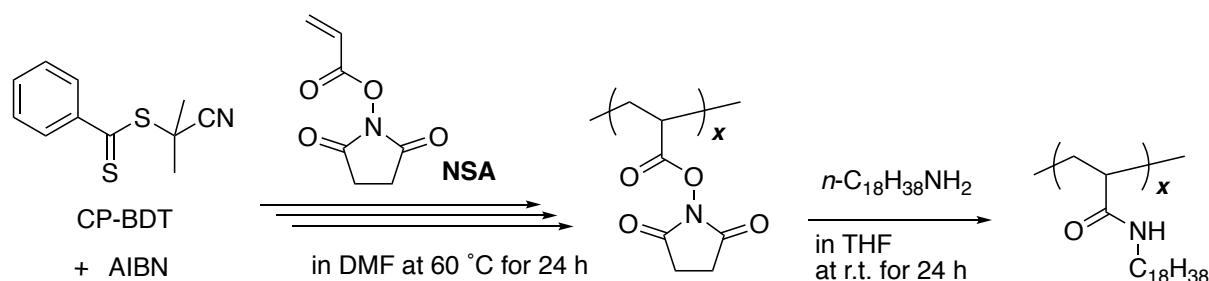**Synthesis of PMAA *via* RAFT polymerization of tBMA and deprotection**
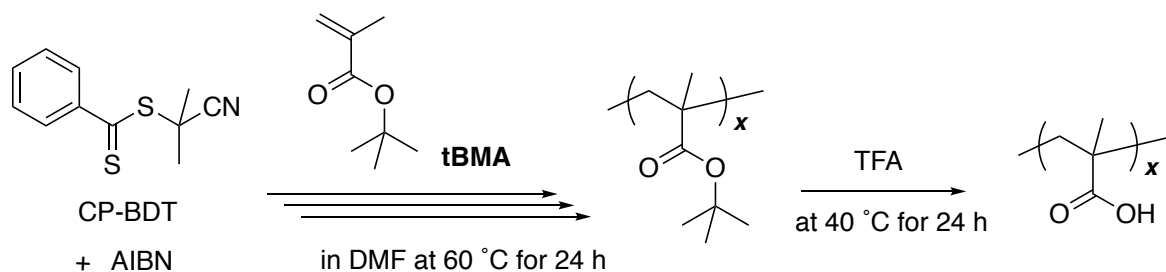
CP-BDT (33.2 mg, 0.15 mmol), and AIBN (2.4 mg, 0.015 mmol) were placed in Schlenk tube under argon. Then, tBMA (0.97 mL, 6.0 mmol), anisole (0.1 mL, internal standard) and DMF (2.0 mL) were added in this order at room temperature.   Immediately after

mixing, the reaction solution was warmed to 60˚C. The reaction was terminated in 24 hours by cooling the solution to –78˚C. The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with anisole as an internal standard (Conv. = 89.4 %). The reaction mixture was purified via dialysis in DMF for removal of residue monomer and DMF was evaporated under reduced pressure to obtain poly(tBMA) (0.28 g, M_n = 6800, M_w/M_n = 1.14). The number-averaged polymerization degree of was determined by ^{1}H NMR (DP_n = 47).

TFA (10 mL) was directly added to the polymer (0.28 g) and the solution was subsequently stirred at 40˚C for 24 hours. Then, TFA was evaporated, followed by dialysis in DMF. Finally, DMF was evaporated under reduced pressure to obtain PMAA (0.11 g,)

Synthesis of poly(C18AAm) *via* RAFT polymerization

NSA (1.0 g, 6.0 mmol), CP-BDT (33.2 mg, 0.15 mmol), and AIBN (2.4 mg, 0.015 mmol) were placed in Schlenk tube under argon. Then, anisole (0.1 mL, internal standard) and DMF (2.5 mL) were added in this order at room temperature. Immediately after mixing, the reaction solution was warmed to 60˚C for initiating the RAFT polymerization. The reaction was terminated in 24 hours by cooling the solution to –78˚C. The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with anisole as an internal standard (Conv. = 85.8 %). The reaction mixture was purified via dialysis in DMF for removal of residue monomer and DMF was then evaporated under reduced pressure to obtain poly(NSA) (0.24 g, M_n = 7600, M_w/M_n = 1.27). The number-averaged polymerization degree was determined by ^{1}H NMR (DP_n = 45).

Poly(NSA) (0.13 g) and n-C$_{18}$H$_{37}$NH$_2$ (2.5 g , 9.3 mmol) were placed in Schlenk tube under argon, and they were then dissolved with 30 mL of THF. The solution was stirred at room temperature for 24 hours. Then, the reaction mixture was purified via dialysis in THF and evaporated under reduced pressure to obtain poly(C18Am) (0.36g).

Result and Discussion
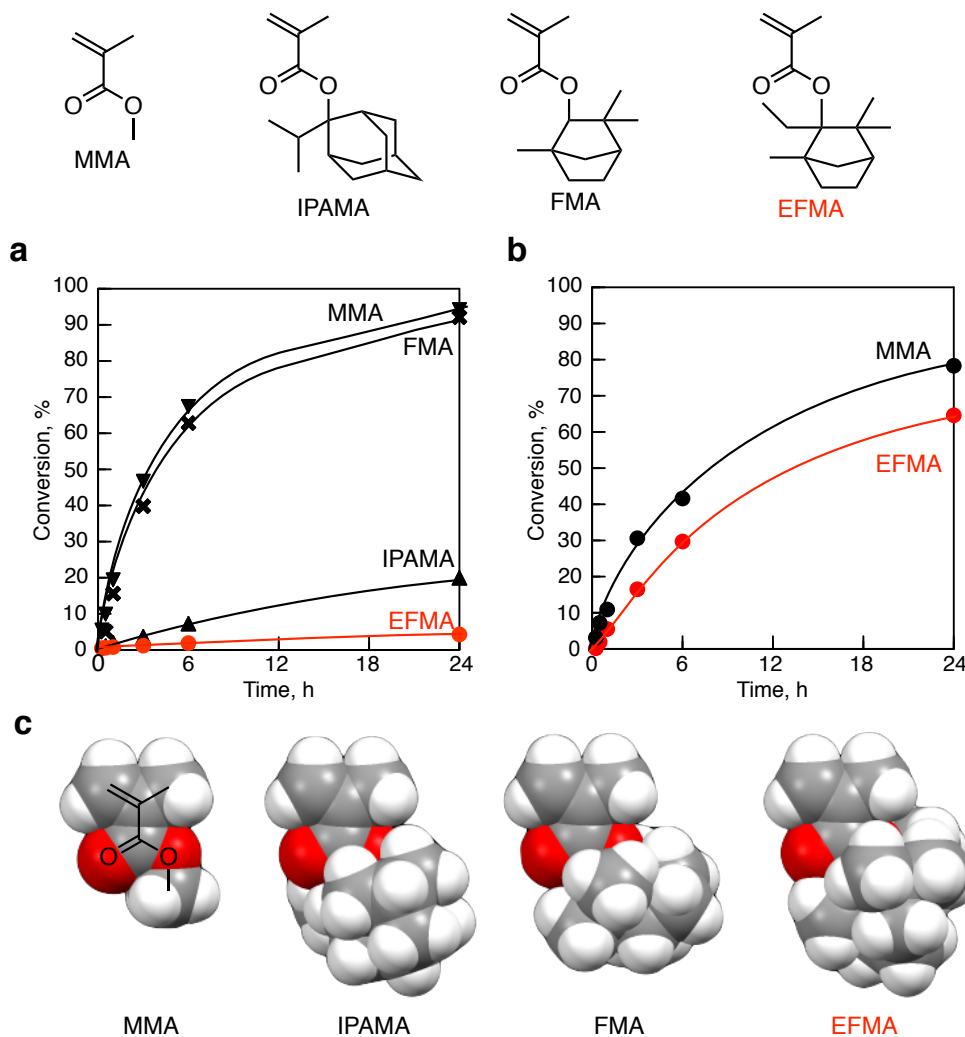
Figure 2. (a) Time-conversion curves for free radical polymerizations of various methacrylate monomers (MMA, IPAMA, FMA, and EFMA): $[\text{monomer}]_0/[\text{AIBN}]_0 = 2000/20$ mM in toluene at 60˚C. (b) Time-conversion curves for free radical copolymerization of MMA and EFMA: $[\text{MMA}]_0/[\text{EFMA}]_0/[\text{AIBN}]_0 = 1000/1000/20$ mM in toluene at 60˚C. (c) Space-filling models of the methacrylate monomers.

The author found IPAMA shows low homo-polymerization ability in radical polymerization in previous studies on control of the single unit addition.[24] The homo polymerization was actually inhibited at higher temperature (i.e.,100˚C). However, the bulkiness seemed to be insufficient for suppression of the homo-polymerization at lower temperature. For instance, the condition at 60˚C suitable for a most common radical initiator, azobisisobuthylronitorile (AIBN), induced oligomerization of IPAMA (Figure 2A: Conv. = 20% in 24 hours, $M_n = 1500$, $M_w/M_n = 1.83$). The author thus designed bulkier methacrylate monomers whose polymerization ability was poorer even at 60˚C. The author took notice of

a fenchol-based methacrylate, because fenchol is a bicyclic alcohol consisting of many branches in the structure.   The methacrylate substituted with only fenchol (FMA) was smoothly polymerized similar to MMA, whereas that carrying both of fenchol and ethyl substituent at the root carbon neighboring to carbonyl group (EFMA) was not polymerized: the conversion in 24 hours was 4%.   In the SEC curve of the product, the peak from the oligomer/polymer was definitely negligible, which was remarkable in comparison with IPAMA.   Importantly, despite of the little homo-polymerization ability of EFMA, EFMA was consumed in copolymerization with MMA to give the corresponding copolymer (Figure 2B: Conv.EFMA = 65%; Conv.MMA =78%; M_n = 31600, M_w/M_n = 1.89).   The progress of copolymerization with MMA indicates the double bond of EFMA was active enough to less hindered methacrylate-type radical species. The relative bulkiness of EFMA to the other methacrylates was shown in the space-filling models, which was optimized by the density functional theory (DFT) calculation at the B3LYP/6-31G* level of theory (Figure 2C).   The oxygen atom derived from fenchol in EFMA was found to be covered by the substituents in this model.

The author then performed copolymerization of EFMA with some types of comonomers, i.e., styrene, methyl acrylate (MA), *n*-butyl vinyl ether (BVE), and *N*-vinyl pyrrolidone (NVP) (Figure 3A) and compared with those with MMA instead of EFMA (Figure 3B).   The condition is as follows: [EFMA or MMA]0/[comonomer]0/[AIBN]0 = 1000/1000/20 mM in 1,4-
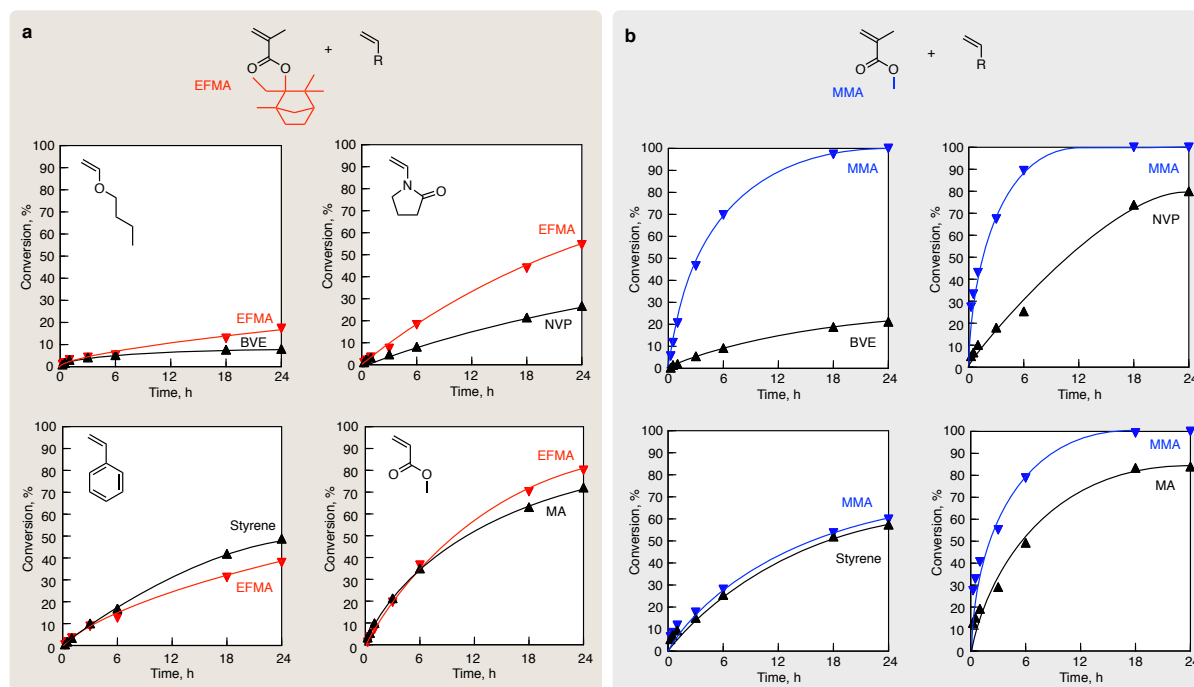
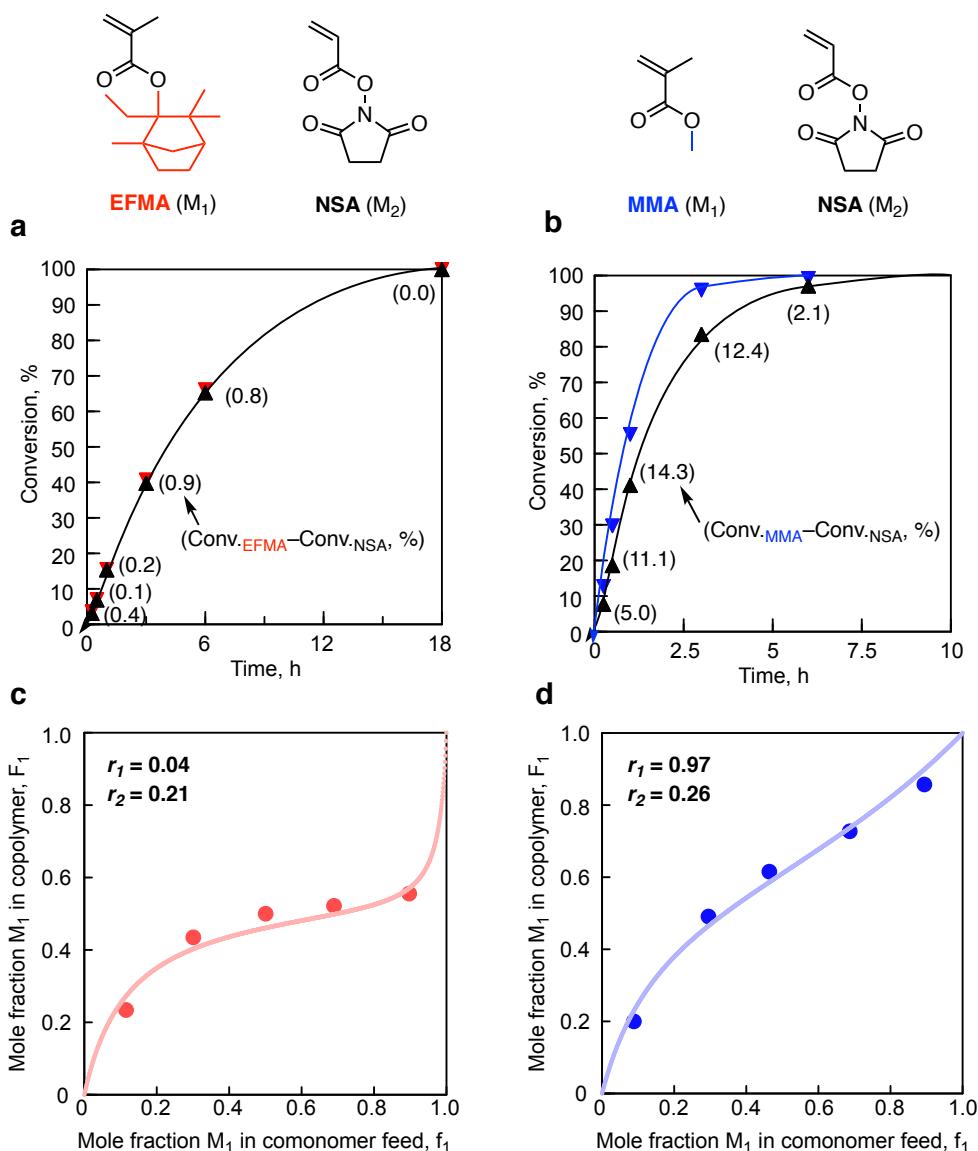

Figure 3. Free radical copolymerizations of EFMA (a) or MMA (b) with a comonomer: [EFMA or MMA]0/[comonomer]0/ [AIBN]0 = 1000/1000/20 mM in 1,4-dioxane at 60˚C.

dioxane at 60°C. The consumption rates of both EFMA and comonomers were lower than the case with MMA, which is attributed to low ability of consecutive growth of EFMA. It was expected that the combination with a comonomer giving lower r_2 value for MMA (M_1 monomer) could be alternately copolymerized with EFMA, if the inherent reactivity of EFMA is similar to MMA in terms of electronic factor. The copolymerization with non-conjugated monomers (BVE or NVP) is the case, according to the reactivity ratios ($r_1 = 37$, $r_2 = 0.1$ for M_1: MMA and M_2: ethyl vinyl ether; $r_1 = 4.78$, $r_2 = 0.006$ for M_1: MMA and M_2: NVP).[1] These values indicate methacrylate radical species tend to prefer methacrylate monomer to the comonomer. Indeed, conversion of MMA was much higher than that of BVE or NVP. On the other hand, in the case with EFMA, the difference was small, but the consumption rates of both comonomers were obviously decreased. The cross-over propagation of the bulky methacrylate radical species with the non-conjugated comonomer would be still hard even though the consecutive propagation is inhibited due to the steric hinderance. In addition, the molecular weights of the copolymers were relatively low (Table 1). On the other hand, the copolymerization with conjugated comonomer (styrene or MA) smoothly proceeded, and even in those cases the rates were slightly decreased relative to that with MMA (Figure 3).

The copolymerization of EFMA with MA seemed to proceed most smoothly giving highest conversion among the four types of copolymerization. In the earlier stage, both monomers were consumed in parallel but the trend was disturbed at the later stage, indicating the copolymerization is not alternating. The author thus changed the electron density of the comonomer toward control of alternating sequence for the resultant copolymer. Acrylic acid *N*-hydroxysuccinimide ester (NSA) is known as a useful monomer for post-functionalization via amidation to the activated ester[37] and the electron density of the double bond is poorer than general alkyl acrylates due to the highly electron-withdrawing character of the *N*-hydroxysuccinimide group.

DMF was used as a solvent for the radical copolymerization of EFMA with NSA because the resultant copolymer was insoluble in less polar solvent such as 1,4-dioxane. The copolymerization smoothly proceeded and both of the comonomers were consumed. Interestingly, both of the conversions were same during the copolymerization up to high conversion, where the difference of the two conversions were less than one (Figure 4a). Since such parallel consumption was not observed for the pair of MMA and NSA (Figure 4b), the copolymerization behavior is peculiar to the combination of the very bulky methacrylate and the highly electron deficient acrylate.

Figure 4. Comparison between EFMA and MMA on free radical copolymerizations with NSA. Time-conversion curves of 1:1 copolymerization of EFMA/NSA (a) and MMA/NSA (b): $[\text{EFMA or MMA}]_0/[\text{NSA}]_0/[\text{AIBN}]_0 = 1000/1000/20$ mM in DMF at 60˚C. Fitted injection ratio–composition curves for the copolymerizations of EFMA/NSA (c) and MMA/NSA (d): $[\text{total comonomers}]_0/[\text{NSA}]_0/[\text{AIBN}]_0 = 2000/20$ mM in DMF at 60˚C. The Reactivity ratios were determined with nonlinear least-squares method: the dots represent the experimental values (Table 2).

To discuss the copolymerization of EFMA and NSA, the reactivity ratios were determined and compared with the case of MMA (Figure 4c, d). The value of r_1 for EFMA/NSA was almost zero ($r_1 = 0.04$) and much lower than for MMA/NSA ($r_1 = 0.97$). Most probably, the dramatic decrease in the r_1 value is caused by the low homo polymerization ability of the bulky methacrylate. The value of r_2 was not zero and almost same as with MMA

(r_2 = 0.21 for EFMA/NSA; r_2 = 0.26 for MMA/NSA).   The value implies NSA-based radical species to prefers methacrylate over NSA but the consecutive propagation of NSA can take place depending on the injection ratio in both copolymerizations.   But the result with totally same conversions of EFMA and NSA for the 1:1 injection ratio could indicate that the copolymerization proceeds in a highly alternating fashion.

For the resultant copolymer (Conv.$_{EFMA}$ = 72.3% Conv.$_{NSA}$ = 72.9%, M_n = 20000, M_w/M_n = 1.73), isopropyl amine was treated to convert the NSA unit into *N*-isopropylacrylamine (NIPAM), followed by acidolysis for ester cleavage of the EFMA unit to lead to the copolymer of NIPAM and methacrylic acid (MAA).   The author's group has synthesized the alternating copolymer of NIPAM and MMA by different approach via selective cyclopolymerization of a transformable divinyl monomer and the post-transformation of the cyclopolymer.[20]   The alternating copolymer showed a unique thermo-response to the sequence in water: the solution was gradually turbid as the temperature was increased, different from poly(NIPAM) showing sharp response as well as the random copolymer.   Thus, the copolymer of EFMA and NSA was actually transformed into the same type of NIPAM-MAA copolymer for study of the thermal response feature in water as well as the sequence analysis.

The transformation of the both units was characterized by ^{1}H NMR.   In the spectrum of the starting copolymer, the characteristic peaks to both units of EFMA (*e*) and NSA (*k*) were clearly observed along with broad peaks derived from other protons (Figure 5a).   The integration ratio of the two peaks led to almost 1:1 ratio of the two units [*x* : *y* = 49 : 51 (x = $DP_{n,EFMA}$; y = $DP_{n,NSA}$)].   After the reaction with isopropyl amine, the peak from methylene protons of the NSA unit (*k*) disappeared, and instead the peak from methine proton (*l*) from NIPAM unit clearly appeared (Figure 5b).   When the resultant product was treated with TFA, the peak from EFMA unit (typically, *e*) disappeared, and the whole spectrum was similar to that of random copolymer of MAA and NIPAM (Figure 5c, Figure S1).   In addition, even after the transformation, the 1:1 composition ratio of MAA and NIPAM units was supported by integration ratio of the observed peaks.

To characterize sequence of the obtained copolymer, ^{13}C NMR was measured and peaks derived carbonyl carbons were compared with those of the homopolymers as well as the statistical copolymers of some composition ratios (*x* : *y* = 100:0, 0:100, 51:49, 92:8, and 10:90).

Some peaks attributed to carbonyl carbons in the resultant copolymer were observed over a wide range from 174-181 ppm (Figure 6a).   Shape and position of the peaks were quite different from those for the 1:1 statistical copolymer of NIPAM and MAA (b, *x* : *y* = 51 : 49).
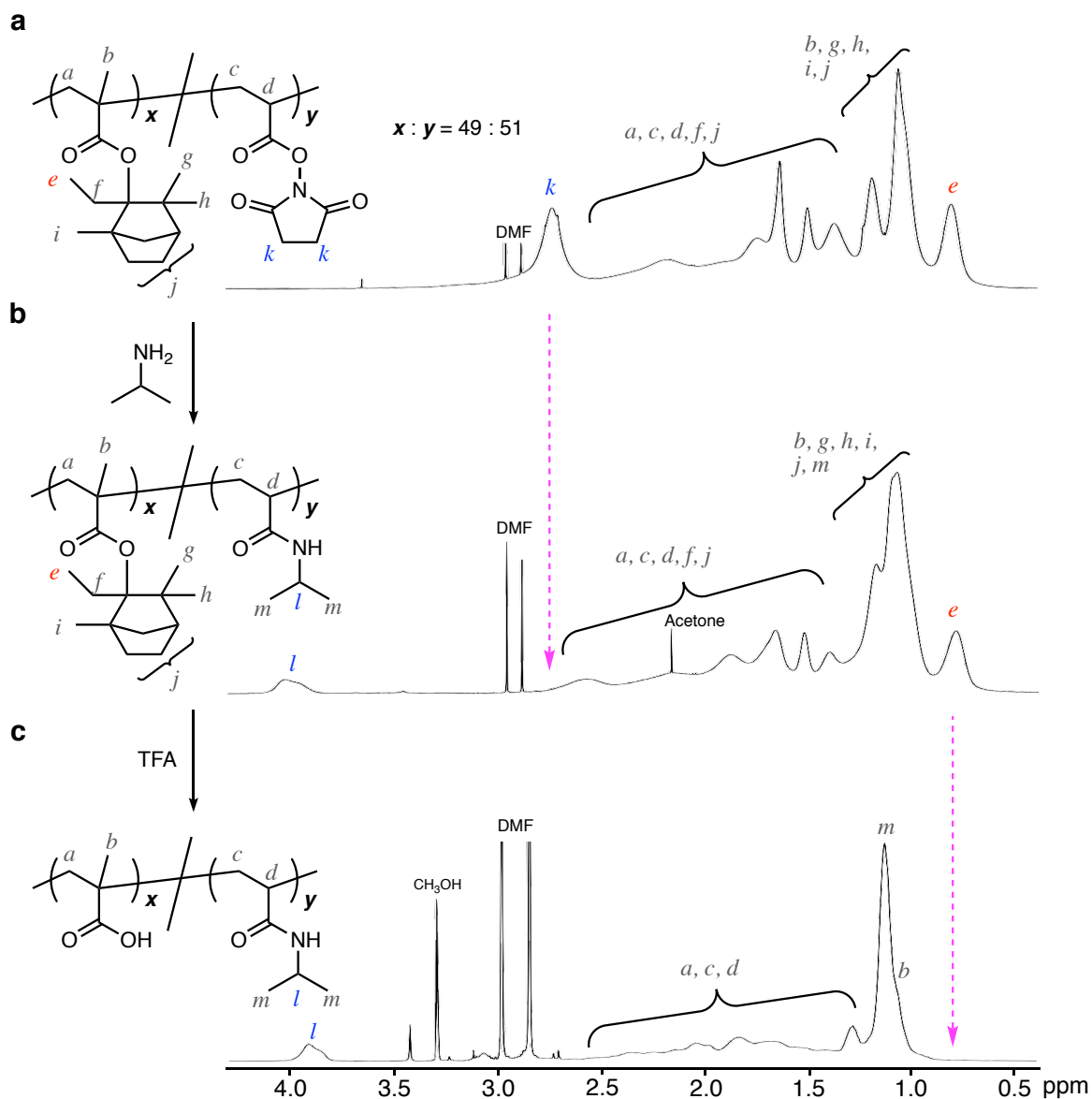
Figure 5. Structural analyses by ^{1}H NMR [500 MHz, CDCl$_3$ (a, b) or CD$_3$OD (c), r.t.] for side-chain transformation. (a) the copolymer of EFMA and NSA; (b) the copolymer after the reaction with isopropyl amine; (c) the copolymer after the TFA treatment for acidolysis of EFMA unit.

In the statistical copolymer, peaks were observed at same position as those for homopolymers (c, 180-181 ppm for PMAA; f, 174-175 ppm for PNIPA), whereas the copolymer from EFMA and NSA showed little peaks at these positions.   The main peaks are located at same positions as the minor peak observed in the statistical copolymers having small ratio of either composition unit [$x : y$ = 92:8 (d) or 10:90 (e)], which could belong to each unit neighboring to another one.   In addition, the peak shape is very similar to that for the alternating copolymer obtained by different approach via selective cyclopolymerization and transformation.[20]   The
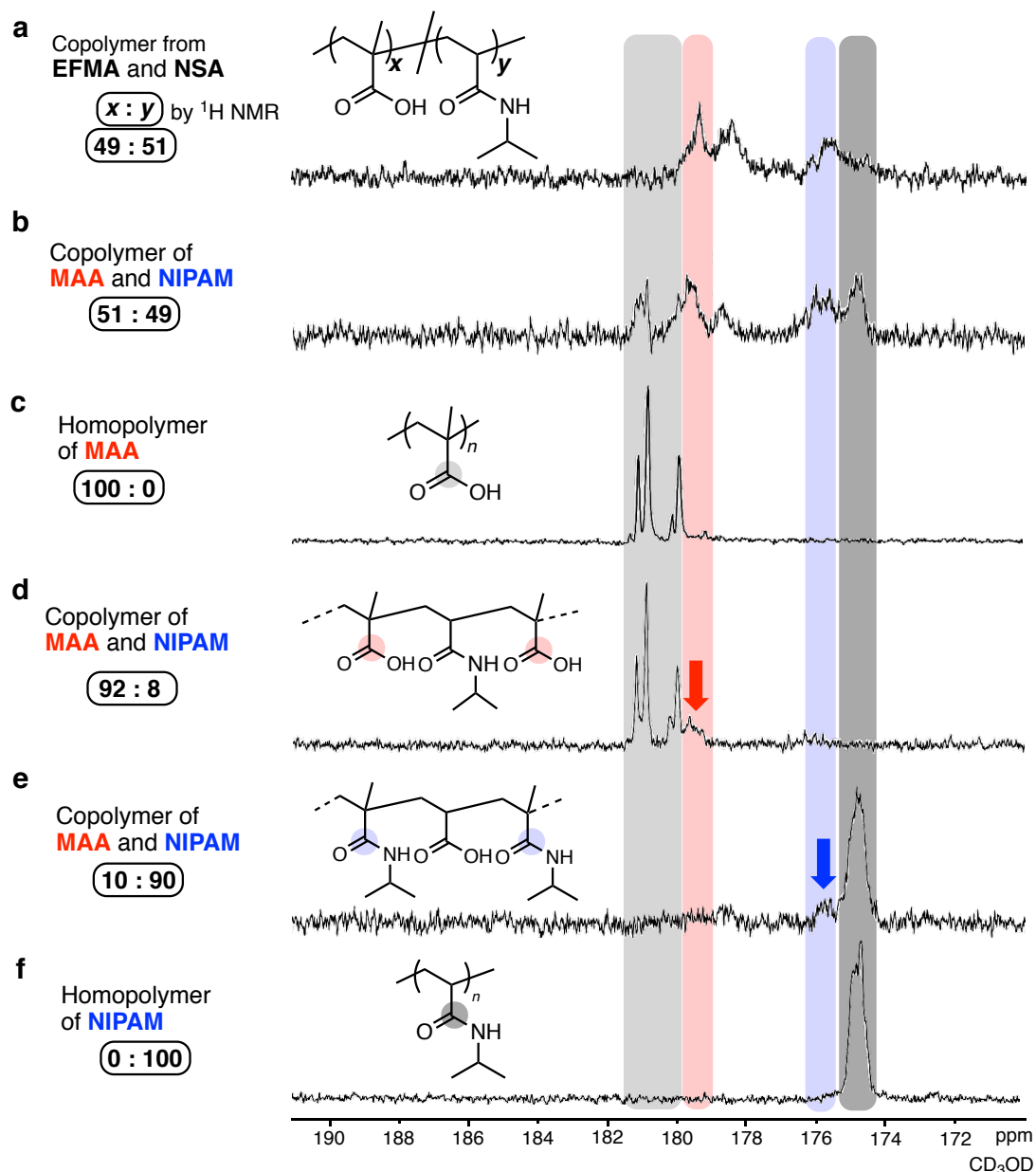
Figure 6. ^{13}C NMR (172-190 ppm, 125 MHz, CD3OD, r.t.) spectrum for sequence analyses of the MAA-NIPAM copolymer obtained by copolymerization of EFMA and NSA and transformation via amidation with isopropyl amine and acidolysis with TFA (a) in comparison with the statistical copolymers of MAA/NIPAM of 51/49 (b), 92/8 (d), and 10/90 (e) and the homopolymers [PMAA (c) and PNIPAM (f)].

peak analyses led to the conclusion that the sequence of the copolymer from EFMA and NSA is highly alternating.

The NIPAM-MAA alternating copolymer obtained by the different approach was soluble in water at lower temperature and the solution was turbid as the temperature increased.[20] Contrary to the author's expectation, thus obtained copolymer consisting of NIPAM and MAA

was not soluble in water at all even at lower temperature. Note that the 1:1 copolymer of NIPAM and MAA that was synthesized via direct copolymerization of the two comonomers with AIBN up to 100% conversion of both monomers (in 24 hours) was also insoluble in water. It was assumed that the higher molecular weight of the copolymer in this work caused the different solubility. The author's effort was then directed to control of molecular weight for the copolymer by reversible-addition fragmentation chain-transfer (RAFT) polymerization. The copolymerization of EFMA with NSA was performed with 2-cyano-2-propyl benzodithioate (CP-BDT) as the chain-transfer agent in conjunction with AIBN. Consequently, the two monomers were consumed at same rate even in the RAFT system (Figure 7a). The molecular weight distributions were relatively broad but SEC curves shifted to higher molecular weight as the copolymerization proceeded, keeping the unimodal shape (Figure 7b). In the ^{1}H NMR spectrum of the product, the peak from phenyl group at the terminal was observed, and a
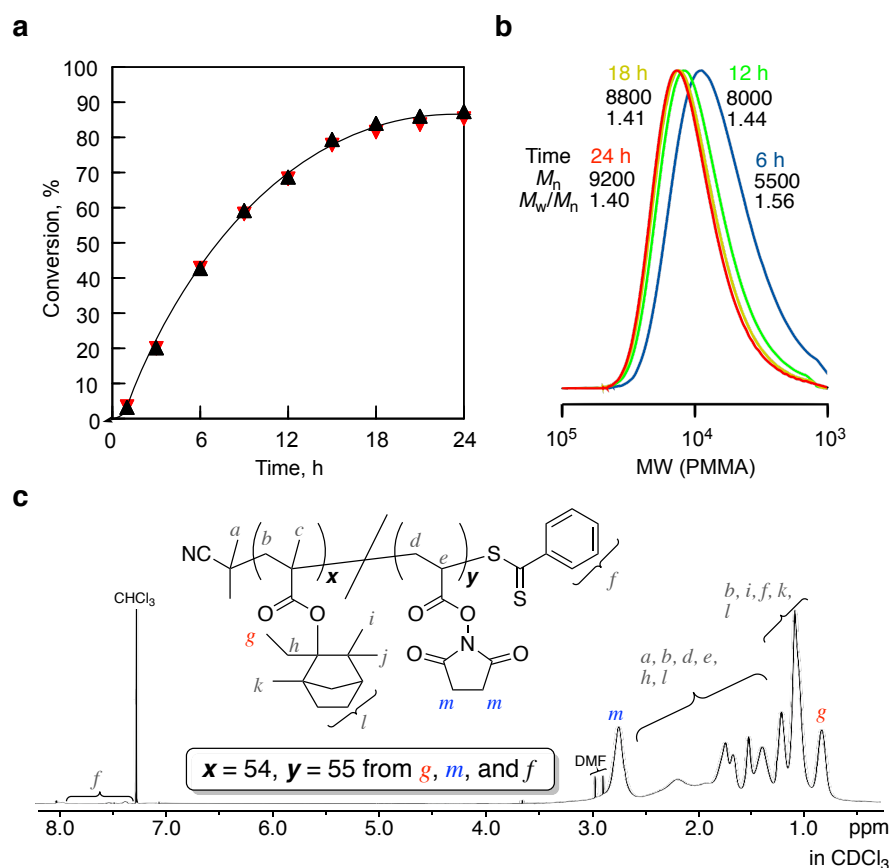
Figure 7. RAFT copolymerization of EFMA and NSA with CP-BDT as a chain-transfer agent in conjunction with AIBN: $[EFMA]_0/[NSA]_0/[CP-BDT]_0/[AIBN]_0 = 1000/1000/20/2$ mM in DMF at 60 °C: (a) time-conversion plot; (b) SEC curves of the obtained copolymers; and (c) ^{1}H NMR spectrum (500 MHz, CDCl$_3$, r.t.) of the purified copolymer (Conv.$_{EFMA}$ = 85.3%, Conv.$_{NSA}$ = 87.3%, M_n = 9200, M_w/M_n = 1.40).

number-averaged polymerization degree of each unit was estimated from the integration ratio to that of each unit: $x = 54$, $y = 55$.

Similarly, two more samples of higher molecular weight were synthesized by adjusting the injection ratio and conversions: $(x, y) = (136, 139)$ and $(191, 193)$ (Figure 8a). ^{1}H NMR spectra of the two samples before the transformation were same except the peak intensity from the terminal phenyl group (Figure S2). After the transformation, the ^{1}H NMR spectrum (Figure S3) as well as the peak patterns from the carbonyl groups in ^{13}C NMR (Figure S4) were
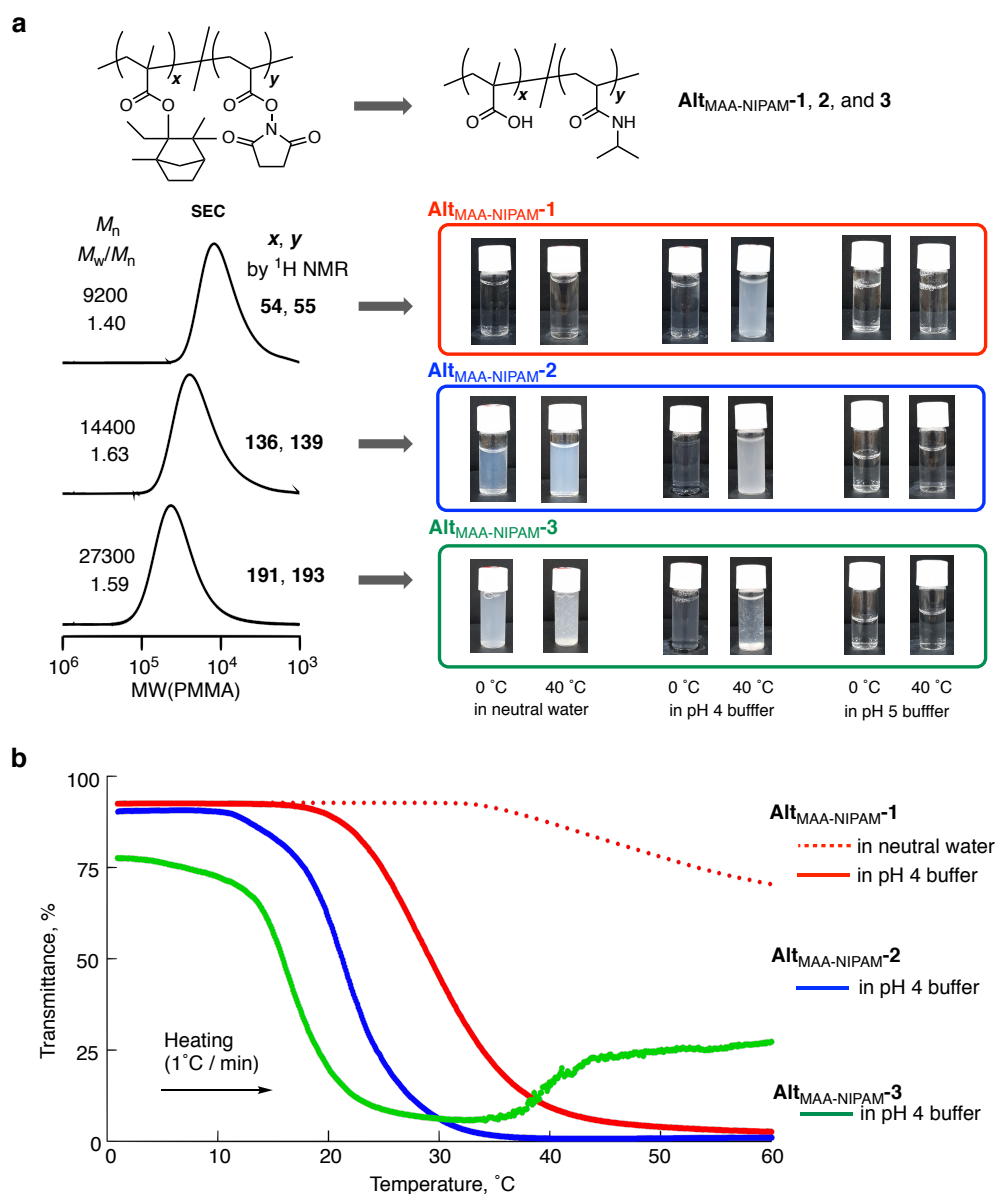
Figure 8. (a) Syntheses of alternating-rich MAA-NIPAM copolymers of different molecular weights (**Alt$_{MAA-NIPAM}$-1, -2**, and **-3**) and the solubilities in neutral water and buffer (pH 4 and 5) at 0°C and 40°C. (b) Temperature-variable transmittance measurement by UV-Vis ($\lambda = 670$ nm) on heating process (1°C/min) with 1 mg mL^{-1} solutions in neutral water or pH 4 buffer.

also similar to those of the lower molecular weight copolymer.   For the thus-obtained three alternating-rich copolymers (**Alt**$_{MAA-NIPAM}$**-1-3**) of different molecular weight, the solubilities were first tested with neutral water.   The two samples of higher molecular weight (**Alt**$_{MAA-NIPAM}$**-2, -3**) were insoluble in neutral water regardless of temperature, similar to the copolymer obtained via free radical copolymerization.   On the other hand, the copolymer of lowest molecular weight (**Alt**$_{MAA-NIPAM}$**-1**) was soluble at room temperature.   Furthermore, the solution showed thermal response: the transparent solution turned into turbid upon heating to 40˚C.   The response was reversible, and the turbid solution at 40˚C became transparent as the solution was cooled, which was also confirmed by temperature-variable transmittance measurement by UV-Vis (Figure S5 for 2 mg mL^{-1} solution).   The thermal response behavior was very similar to the alternating copolymer of similar molecular weight obtained by different approach via selective cyclopolymerization and transformation.[20]   The result indicates the degree of alternating sequence of the copolymer is high equally to the previous sample and the solubility and thermal response in neutral water depends on the molecular weight. Interestingly, when acidic water (pH 4 buffer, with $C_8H_5KO_4$-NaOH) was used, **Alt**$_{MAA-NIPAM}$**-2** became soluble at lower temperature and showed thermal response.   **Alt**$_{MAA-NIPAM}$**-3** was insoluble in the buffer solution of pH 4 but partially soluble at lower temperature.   A pH5 buffer solvent solubilized all the three copolymers and the solutions showed no thermal response.   Figure 8b shows heating process of temperature-variable transmittance measurement for 1 mg mL^{-1} solutions.[38]   For the solution in pH4 buffer, the temperature where the solution began to become cloud was higher as the molecular weight was lower, and both of **Alt**$_{MAA-NIPAM}$**-1** and **-2** eventually gave turbid solution of 0 % transmittance.   On the other hand, **Alt**$_{MAA-NIPAM}$**-3** resulted in particle precipitation or macroscopic separation, which caused the rise in transmittance at higher temperature.   Thus, the aqueous solution of the alternating-rich copolymer was found to show unique thermal response according to the molecular weight and pH.   Probably, the ionization degree of MAA unit being arranged with NIPAM unit in alternating fashion seems to be suppressed as the unit number is increased, resulting in lower solubility, but the detailed mechanism is now under investigation.   Anyhow, note that such unique thermal response dependence on molecular weight was not revealed until alternating sequence and molecular weight and were simultaneously controlled.

        Finally, the author decided to introduce an octadecyl group ($C_{18}H_{37}$–) pendant via the reaction on the NSA unit with octadecyl amine ($C_{18}H_{37}NH_2$), expecting the unique property to the alternating sequence of the highly hydrophobic chain and the hydrophilic carboxylic acid

group.   For the alternating-rich copolymer of EFMA and NSA [synthesized by RAFT copolymerization; $(x, y) = (54, 55)$], an excess of octadecyl amine was treated, followed by cleavage of the EFMA unit by TFA (Figure 9a).   Thus, an alternating-rich copolymer of MAA and octadecyl acrylamide (C18Am) was synthesized ($Alt_{MAA-C18Am}$).   The resultant copolymer showed totally different solubility from that of *N*-isopropyl pendant with same polymerization
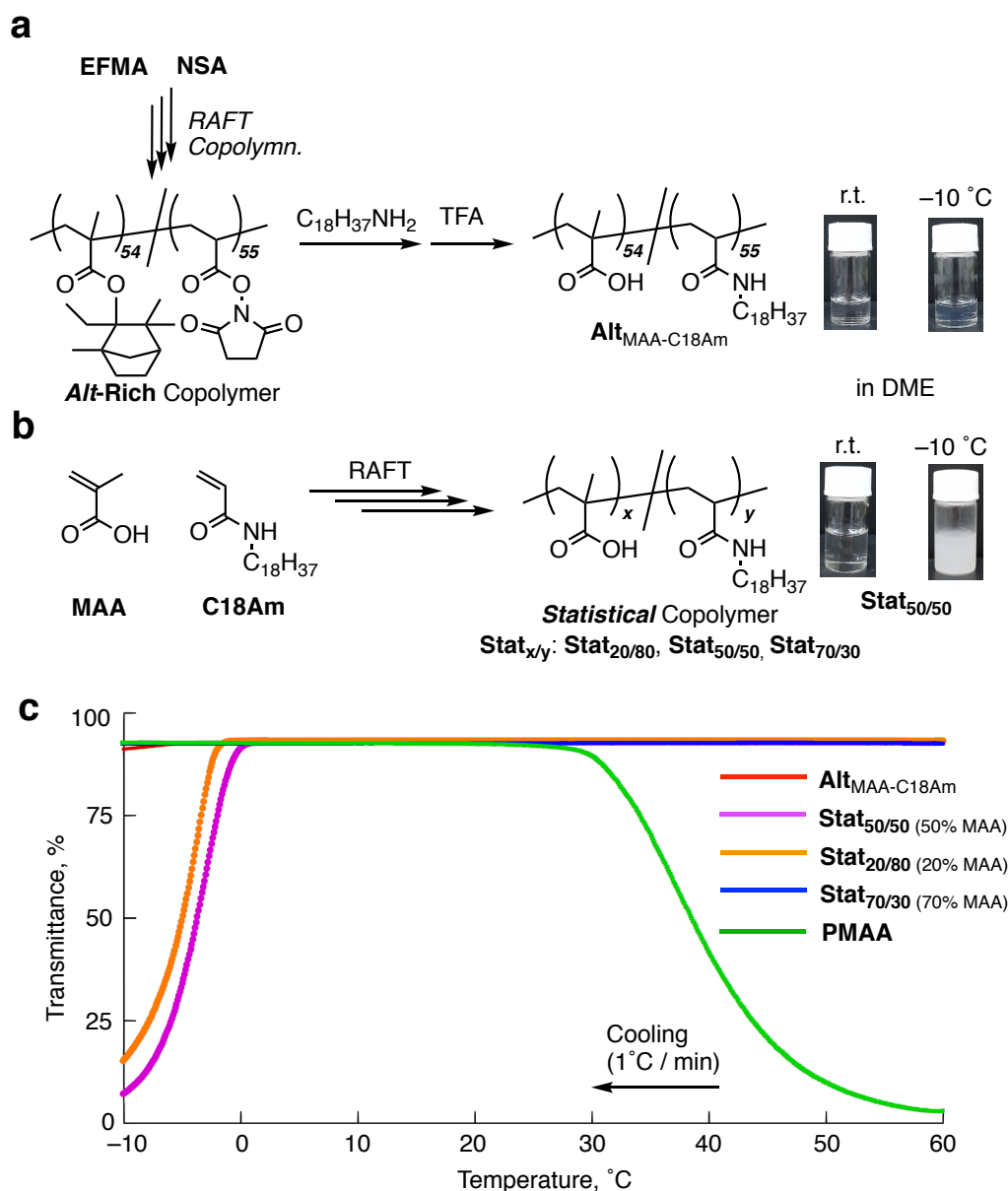
Figure 9. (a) Synthesis of alternating-rich MAA-C18Am copolymer ($Alt_{MAA-C18Am}$) obtained by RAFT copolymerization of EFMA and NSA and transformation via amidation with octadecyl amine and acidolysis with TFA.   (b) Syntheses of MAA-C18Am statistical copolymers ($Stat_{20/80}$, $Stat_{50/50}$, and $Stat_{70/30}$) of different composition ratios.   (c) Temperature-variable transmittance measurement by UV-Vis ($\lambda = 670$ nm) on cooling process (1°C/min) with 2 mg mL^{-1} solutions in DME.

degree (**Alt**$_{MAA-NIPAM}$**-1**): the former was obviously hydrophobic, whereas the latter was hydrophilic (Figure S6).

To clarify effects of sequence on the solubility, statistical copolymers of MAA and C18Am of different composition ratios (**Stat**$_{20/80}$, **Stat**$_{50/50}$, and **Stat**$_{70/30}$) (Figure 9b) as well as the homopolymers (**PMAA** and **PC18Am**) were also synthesized with RAFT system by changing the injection comonomer ratios (see Supporting Information). Consequently, **Stat**$_{50/50}$ was soluble in 1,2-dimethoxyethane (DME) at room temperature and the solutions turned into turbid at −10°C: the copolymer showed UCST-type thermal response in DME. On the other hand, **Alt**$_{MAA-C18Am}$ was totally soluble in DME even at lower temperature, despite same averaged composition ratio as **Stat**$_{50/50}$. The difference was clearly observed in temperature-variable transmittance measurement (Figure 9c, cooling process from 60°C to −10°C for 2 mg mL^{-1} solutions): no change in transmittance with **Alt**$_{MAA-C18Am}$, whereas a decrease around 0°C with **Stat**$_{50/50}$. As recently reported,[39] **PMAA** was insoluble in DME at higher temperature but were gradually solubilized on the cooling process: it showed LCST-type thermal response in DME. Such response was not observed in all the copolymers and **PC18Am** was insoluble in DME regardless of temperature. C18Am-rich statistical copolymer (**Stat**$_{20/80}$) also showed UCST-type thermal response similar to **Stat**$_{50/50}$, whereas MAA-rich copolymer (**Stat**$_{70/30}$) did no response (soluble at any temperature). Thus, the UCST-type response is likely attributed to existence of C18Am-rich segment. The lack of thermal response of the alternating-rich copolymer (**Alt**$_{MAA-C18Am}$) is probably due to absence of consecutive sequence of the C18Am unit, which is a significant difference from the statistical copolymer of same averaged compositions (**Stat**$_{50/50}$).

Conclusion

The author found the extremely bulky tertiary methacrylate (EFMA) can be copolymerized with the NHS-ester based acrylate (NSA) affording the alternating-rich copolymer transformable into general and functional monomer units, that is, methacrylic acid and alkyl acrylamide. Free radical polymerization, as well as RAFT polymerization, is available for the copolymerization. Most importantly, diluted condition and multi-step monomer synthesis is not required for the sequence control, which is distinguished from another approach using selective cyclopolymerization allowing synthesis of same type of alternating copolymer. The resultant alternating-rich copolymer of methacrylic acid and alkyl acrylamide

showed unique thermal response to the alternating sequence or absence of the consecutive sequence. The facile methodology allows syntheses of various alternating copolymers by changing the amine substituent, from which other sequence-oriented properties are expected in the future. This is now under investigation in the author's group.

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Chapter 3 Supporting Data
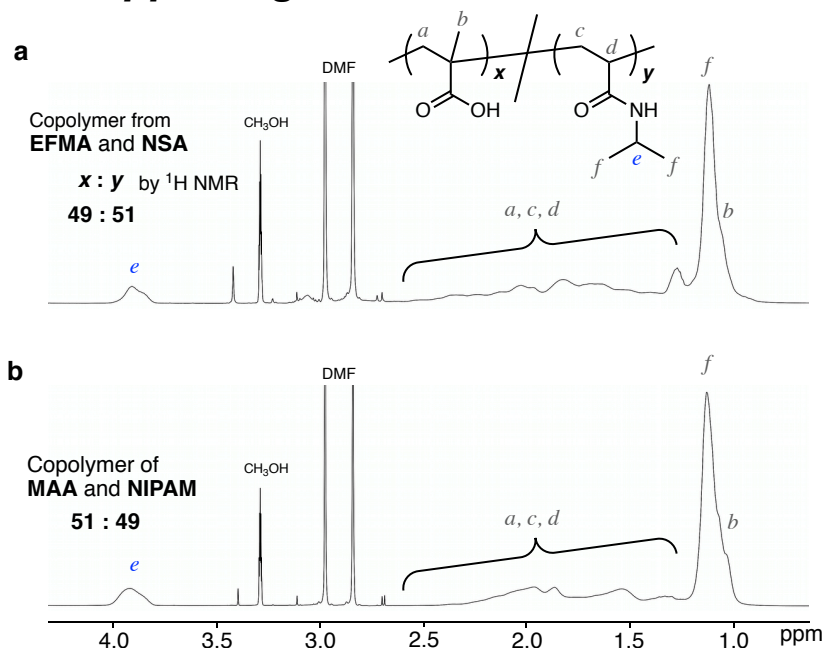
Figure S1. ¹H NMR spectra of a) copolymer from EFMA and NSA and b) copolymer from copolymerization of MAA and NIPAM
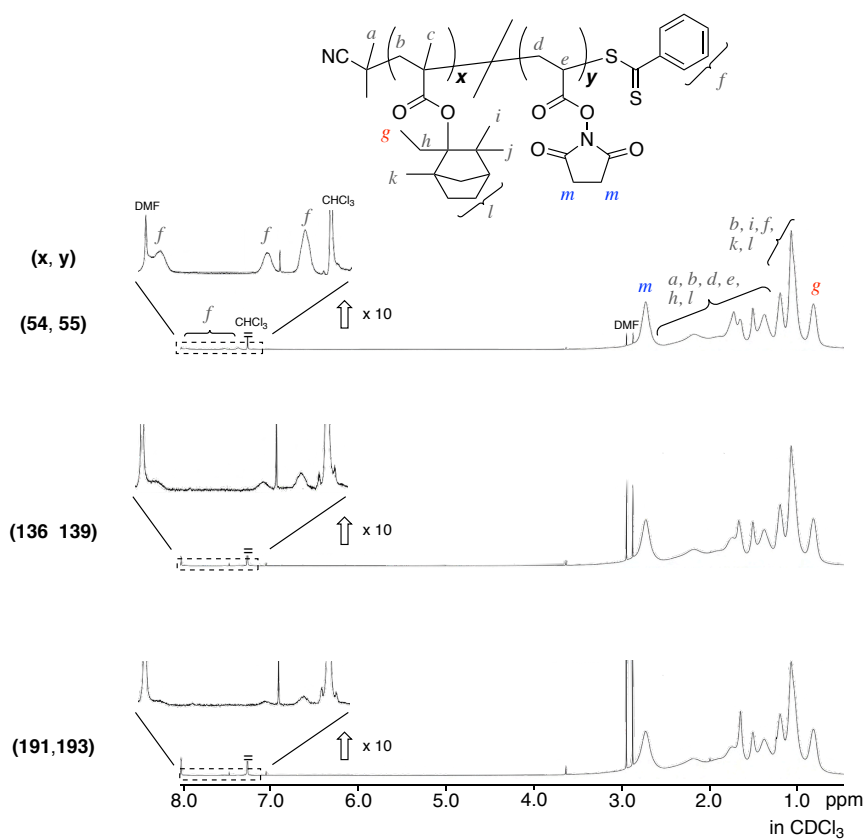
Figure S2. ¹H NMR spectra of the copolymers of EFMA and NSA with different polymerization degrees: (*x, y*) = (54, 55), (136, 139) and (191, 193).

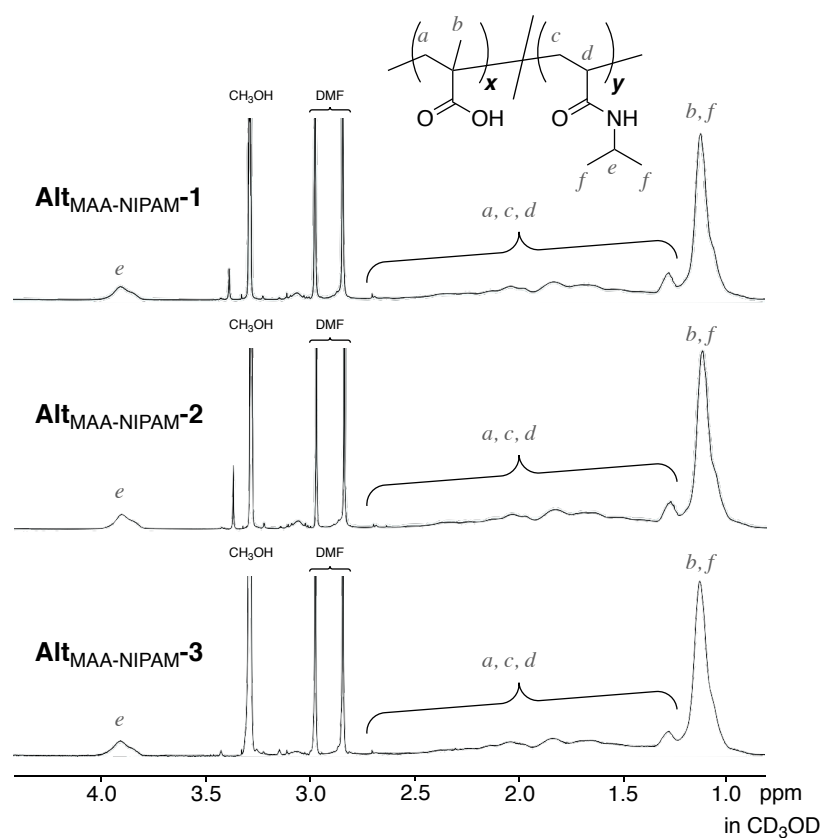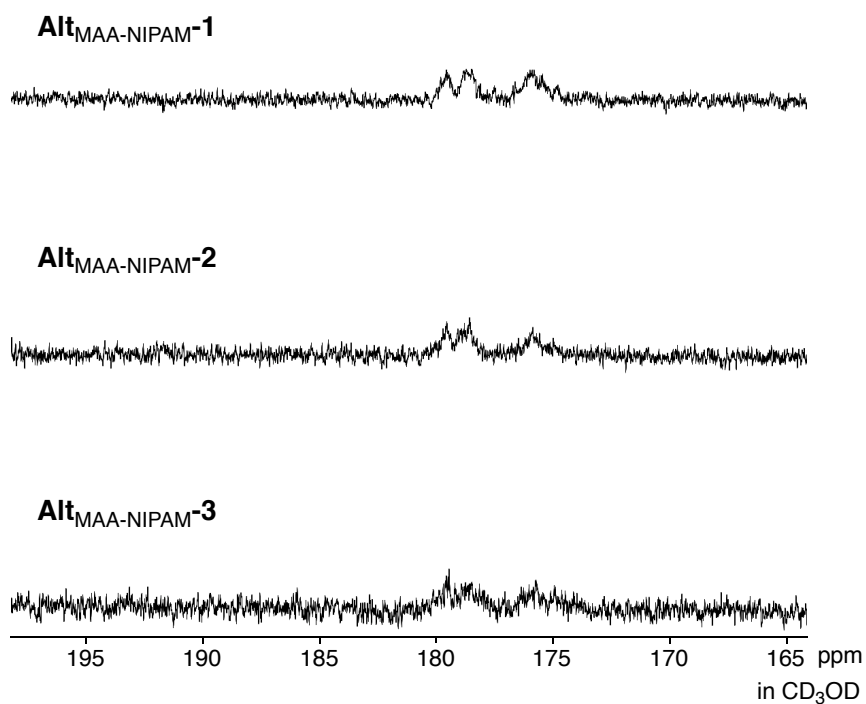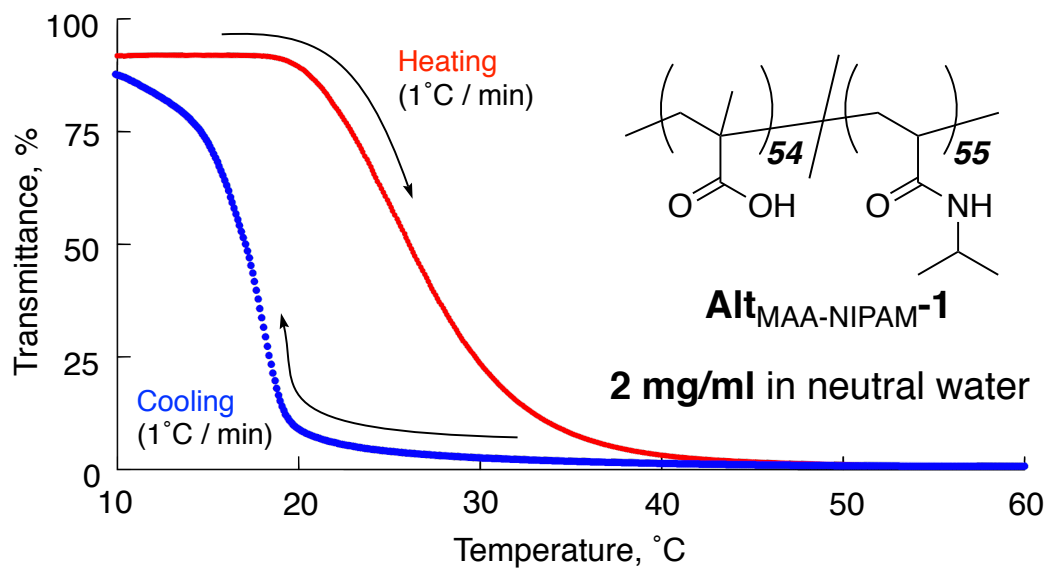**Figure S3**. ^{1}H NMR spectra of the alternating-rich copolymers (**Alt**$_{MAA-NIPAM}$-**1**–**3**).

Figure S4. ^{13}C NMR spectra from 174 to 184 ppm (carbonyl groups) of the alternating-rich copolymers (**Alt**$_{MAA-NIPAM}$-**1**–**3**).

Figure S5. Thermal response in pure water of the alternating-rich copolymer (**Alt**_{MAA-NIPAM}**-1**) that was synthesized from EFMA and NSA (concentration: 2 mg mL^{-1}).

	Alt$_{MAA-C18Am}$	**Alt**$_{MAA-NIPAM}$**-1**
Water	*Insoluble*	*Soluble*
Methanol	*Insoluble*	*Soluble*
DME	*Soluble*	*Insoluble*
1,4-Dioxane	*Soluble*	*Insoluble*
Diethyl Ether	*Soluble*	*Insoluble*
Toluene	*Soluble*	*Insoluble*
n-Hexane	*Insoluble*	*Insoluble*

Figure S6. Comparison of solubility between **Alt**$_{MAA-C18Am}$ and **Alt**$_{MAA-NIPAM}$**-1**: polymer concentration: 2 mg mL^{-1}, r.t.

Chapter 4

Synthesis of Methacrylic Acid-Acrylonitrile Alternating Copolymer Using an Extremely Bulky Methacrylate and the Sequence-Dependent Thermal Reaction Behaviors

Abstract

In this work, the author achieved the synthesis of the alternating copolymer composed of commodity monomer units, methacrylic acid (MAA) and acrylonitrile (AN), by using a bulky and transformable methacrylate carrying 2-ethylfenchyl ester group (EFMA).   The low propensity of EFMA in radical homopolymerization and the high reactivity of AN radical to methacrylate monomer in radical copolymerization allowed the peculiar alternating propagation, which was supported by the low reactivity ratios [$r_1 = 0.03$, $r_2 = 0.23$ for EFMA (M$_1$) and AN (M$_2$).   The resultant EFMA-AN alternating copolymer was quantitatively transformed into the MAA-AN counterpart via acidolysis as supported by ^{1}H and ^{13}C NMR analyses in comparison with the corresponding 1:1 statistical copolymer.   The MAA-AN alternating copolymer underwent thermal reaction between pendant groups in controlled sequence, which was different from the statistical copolymer composed of various sequence patterns.
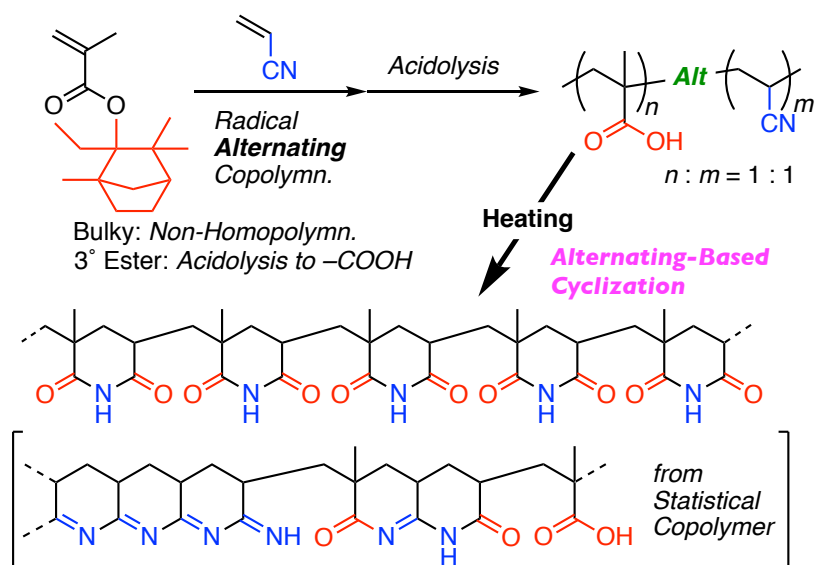
Introduction

Acrylonitrile (AN) is a typical polar vinyl monomer and is categorized as an electron-poor monomer due to the electron-withdrawing cyano pendant (–C≡N). The cyano group of poly(AN) exhibits thermal reactivity, and the most representative application is production of carbon fiber via intramolecular crosslinking and carbonization upon heating. The pendant of poly(AN) also shows reactivities for other chemical reactions, such as nucleophilic addition,[1-6] reduction,[7] hydrolysis[8] and cycloaddition.[9,10] AN is one of commodity monomers in polymer materials and is often used in radical copolymerization as a comonomer for property tuning, as symbolized by poly(acrylonitrile-co-styrene) (SAN), poly(acrylonitrile-co-butadiene-co-styrene) (ABS), poly(acrylonitrile-co-styrene-co-acrylate) (ASA), and nitrile butadiene rubber (NBR).[11] Sequence-control for synthetic copolymers has recently attracted attentions, but to the author's knowledge, there have been little examples on syntheses of sequence-controlled polymers containing AN unit.

The author's group has studied some methodologies to control sequence of commodity monomer units in copolymers synthesized via radical polymerization.[12] One approach is using a monomer whose double bond is active for radical species but incapable of propagation due to bulkiness in radical copolymerization for control of alternating copolymerization.[13-16] Herein, if the bulky pendant is transformable to commodity pendant after copolymerization, the resultant alternating copolymer would be more valuable because the properties are evaluated through comparison with the corresponding homopolymers and statistical copolymers. Methacrylate carrying 2-ethyl fenchyl pendant (EFMA) is the monomer suitable for this strategy.[13] It shows no homopolymerization ability due to the bulkiness and the tertiary ester pendant can be transformed into carboxylic acid. Therefore, the copolymerization with a comonomer whose radical species inherently shows high cross-over propagation feature for methacrylate monomer could proceed in the alternating fashion. The EFMA unit in the resultant alternating copolymer is transformable into methacrylic acid (MAA) one via acidolysis after copolymerization, and the unit is commonly used in copolymer design for acidic property. We found that *N*-succinimidyl acrylate (NSA) was available as comonomer for radical alternating copolymerization of EFMA and the resultant alternating copolymer underwent aminolysis and acidolysis leading to the alternating copolymer of MAA and *N*-alkyl acrylamide (Figure 1A).[13] Quite recently, Matyjaszewski et al. also utilized EFMA for alternating copolymerization with n-butyl acrylate (BA) to synthesize the alternating copolymer of methyl methacrylate (MMA) and BA through acidolysis and methylation.[17]

In this study, the author focused on AN as a comonomer for the radical copolymerization of EFMA in anticipation of progress of alternating copolymerization (Figure 1B). The subsequent acidolysis reaction could afford the alternating copolymer of MAA and AN, and both are commodity monomers units for copolymers in radical copolymerization. It is known that the pendants of MAA-AN statistical copolymer undergo cyclization reactions upon heating to give some types of cyclo-units.[18] His effort was thus directed to the study in thermal reactivity of the resultant MAA-AN alternating copolymer affording relatively uniform cyclo-units. The author clarified the sequence-oriented reactivity through comparison with the corresponding statistical copolymer (Figure 1C).
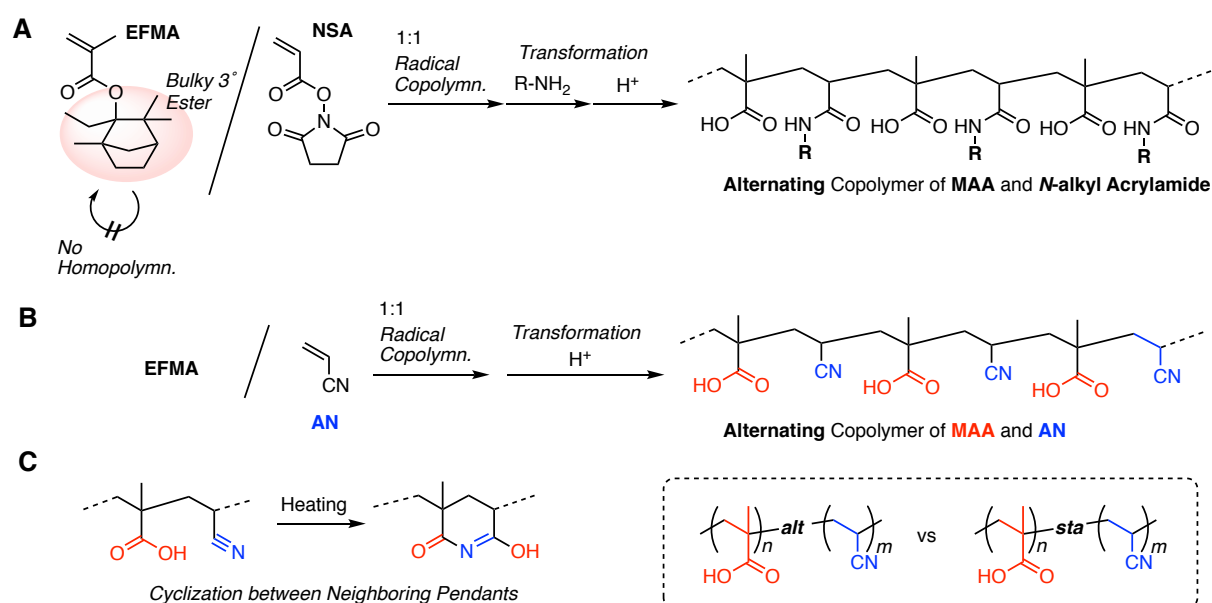
Figure 1. (A) Synthesis of alternating copolymer MAA and *N*-alkyl acrylamide via radical copolymerization of EFMA with NSA followed by aminolysis and acidolysis. (B) Synthesis of an alternating copolymers of MAA and AN via radical copolymerization of EFMA and AN followed by acidolysis. (C) Cyclization between MAA and AN units upon heating for alternating and statistical copolymers of MAA and AN.

Experimental

Materials

The following reagents were used as received: 2,2'-azobis(isobutyronitrile) (AIBN; TCI, >98.0%), 2-ethyl fenchol (Aldrich, >97.0%), triethylamine (TCI, >99.0%), methacryloyl chloride (TCI, >90.0%), trifluoroacetic acid (TFA; Wako, >98.0%), acrylonitrile (AN; TCI,

>99.0%, stabilized with MEHQ), methacrylic acid (MAA;Wako, >99.0%). Methyl methacrylate (MMA; TCI, >99.8%, stabilized with 6-tert-butyl-2,4-xylenol) was dried overnight over calcium chloride and distilled before use. Column chromatography was carried out using Wakosil C200 (Wako) as the stationary phase. Sodium hydride dry (Aldrich, >90.0%) was used as received without further purification and handled in a glovebox (MBraun Labmaster 130, M. Braun Inter-gas-systeme GmbH, Garching, Germany) under a moisture- and oxygen-free argon atmosphere (H_2O < 0.1 ppm; O_2 < 0.1 ppm).

All solvents were purchased from Wako Pure Chemical Industries and used without further purification. 1,2,3,4-tetrahydrousnaphthalene (tetralin; internal standard for ^{1}H NMR) was distilled over calcium chloride.

Measurement

Size exclusion chromatography (SEC) was measured at 40°C in THF as an eluent on three polystyrene-gel columns (Shodex LF-404) connected to DU-H2000 pump, 74S-RI refractive-index detector, and 41-UV ultraviolet detector (Shodex). The columns were calibrated against 12 standard poly(methyl methacrylate) standards (PSS Polymer, M_n =730-1650000; M_w/M_n = 1.04-1.15). NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer operating at 500.16 MHz (^{1}H) and 125.04 MHz (^{13}C) at ambient temperature.

Thermogravimetric analysis (TGA) of the polymer samples (ca. 5 mg in aluminum pan) was measured under dry nitrogen flow on a STA 2500 Regulus (NETZSCH). The heating rate was at 10°C/min from ambient temperature (ca. 25°C) to 500°C.

Fourier transform infrared spectroscopy (FT-IR) measurements were performed on a Cary 630 FT-IR spectrometer (Agilent). The solid polymer samples were directly used. The samples after thermal reaction were prepared as follows: the purified polymer samples (ca. 10 mg) on petri dish were annealed in the preheated dryer (ETTAS AVO-200SB) at 190°C for 30 min. The annealed samples were removed from the dryer, followed by cooling to room temperature.

Monomer Synthesis
Synthesis of 2-ethyl-2-fenchyl methacrylate (EFMA)

EFMA was synthesized according to the literature.[13] Sodium hydride (1.5 g, 63.5 mmol) were placed in round-bottom flask under argon and then dissolved in toluene (12.6 mL). To the resultant solution, 2-ethyl fenchol (11.0 mL, 57. 5 mmol) was gradually added at 0°C,

while stirring for 30 min. The reaction solution was warmed to 100°C and stirred for 3h. After cooling the solution, methacryloyl chloride (5.3 mL, 54.8 mmol) was gradually added at -40°C, while stirring for 15 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, followed by purification with silica column chromatography (hexane : ethyl acetate = 99:1). The product was obtained as slightly yellow oil (7.8 g, 31.2 mmol, 57%). ^{1}H NMR (in CDCl$_3$): 6.05 (s, 1H), 5.47 (s, 1H), 2.21-2.13 (sext, 1H), 2.05-1.98 (sext, 1H), 1.93 (s, 3H), 1.79-1.68 (m, 3H), 1.59-1.56 (d, 1H), 1.50-1.40 (m, 1H), 1.24 (s, 3H), 1.13 (s, 3H), 1.11-1.08 (d, 2H), 1.06 (s, 3H), 0.83-0.73 (t, 3H).

Polymer Synthesis

Synthesis of alternating-rich copolymer of MAA and AN *via* free radical copolymerization and side-chain transformation
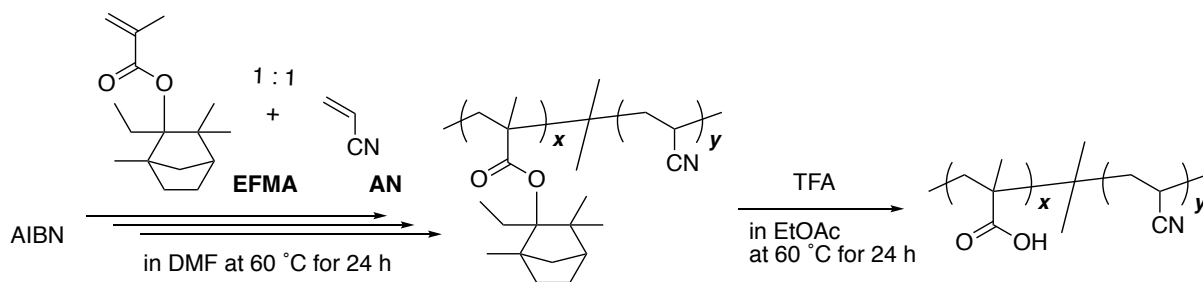
AIBN (9.8 mg, 0.060 mmol) was placed in Schlenk tube under argon. Then, *N,N*-dimethylformamide (DMF) (3 mL), EFMA (0.75 g, 3.0 mmol), AN (0.19 mL, 3.0 mmol), and 1,4-dioxane (0.1 mL, internal standard) were added in this order at room temperature. Immediately after mixing, the reaction solution was warmed to 60°C for initiating the radical copolymerization. The reaction was terminated in 24 hours by cooling the solution to –78°C. The conversion of vinyl group was determined by ^{1}H NMR in CDCl$_3$ with 1,4-dioxane as an internal standard (Conv$_{EFMA}$ = 59.8 %, Conv$_{AN.}$ = 58.5 %). The reaction mixture was diluted by THF and purified *via* reprecipitation in hexane 3 times for removal of residue monomers. Finally, the precipitate was evaporated under reduced pressure to remove residue solvent. The copolymer of EFMA and AN was obtained as white solid (0.45 g, $M_{n\ (GPC)}$ = 17100, M_w/M_n = 1.48). The averaged composition ratio (x : y) was 49 : 51 (by ^{1}H NMR: Figure 3B).

The resultant copolymer (0.45 g) was placed in Schlenk tube under argon, and then dissolved in ethyl acetate (EtOAc) (26.6 mL). To the solution, TFA (11.4 mL, 0.15 mol) was added at 0°C, and the reaction solution was warmed to 60°C for 24 hours. The precipitate was filtered through PTFE filter (pore size 0.45μm) and washed by ethyl acetate several times.
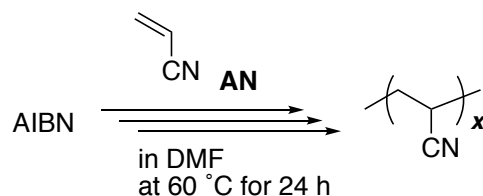
Then, the filtered solid was dissolved in dimethyl sulfoxide (DMSO) and purified via reprecipitation in chloroform.   Finally, chloroform was evaporated under reduced pressure to obtain the alternating copolymer of MAA and AN as white solid (0. 15 g, yield = 72.3%).   The progress of acidolysis was confirmed by ^{1}H NMR.

Synthesis of 1:1 Statistical copolymer of MAA and AN *via* free radical bulk copolymerization
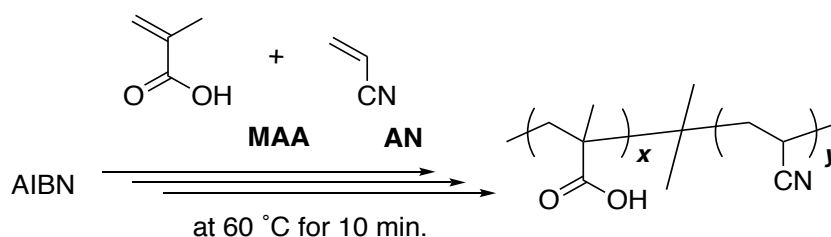
The 1:1 statistical copolymer of MAA and AN was synthesized in reference to the literature.[19]   AIBN (98.4 mg, 0.60 mmol) was placed in Schlenk tube under argon.   Then, MAA (1.01 mL, 12.0 mmol), AN (3.14 mL, 48.0 mmol), and tetralin (0.1 mL, internal standard) were added in this order at room temperature.   Immediately after mixing, the reaction solution was warmed to 60°C.   The reaction was terminated in 10 minutes by cooling the solution to –78°C.   The conversion of vinyl group was determined by ^{1}H NMR in DMSO-d_6 with tetralin as an internal standard (Conv$_{MAA}$ = 20.2 %, Conv$_{AN.}$ = 4.5 %).   The reaction mixture was diluted by DMSO and reprecipitation in chloroform 3 times for removal of residue monomers. Finally, chloroform was evaporated under reduced pressure to obtain statistical copolymer of MAA and AN as white solid (0.19 g).   The averaged composition ratio (x : y) was 49 : 51 (by ^{1}H NMR: Figure 3C).

Synthesis of polyacrylonitrile (PAN) *via* free radical polymerization

AIBN (16.4 mg, 0.10 mmol) were placed in Schlenk tube under argon. Then, DMF (4.4 mL), AN (0.66 mL, 10.0 mmol) and 1,4-dioxane (0.1 mL, internal standard) were added in this

order at room temperature.   Immediately after mixing, the reaction solution was warmed to 60°C.   The reaction was terminated in 24 hours by cooling the solution to –78°C.   The conversion of vinyl group was determined by ^{1}H NMR in DMSO with tetralin as an internal standard (Conv. = 90.0 %).   The reaction mixture was purified via reprecipitation in chloroform 3 times for removal of residue monomer.   Finally, chloroform was evaporated under reduced pressure to obtain PAN as white solid (0.32 g).   The ^{1}H NMR spectrum was shown in Figure S1.

Synthesis of poly(methacrylic acid) (PMAA) *via* free radical polymerization
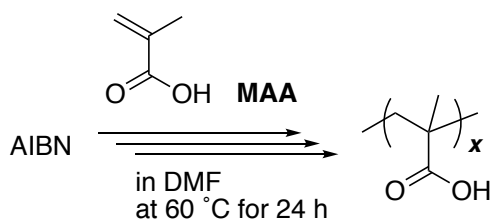
AIBN (16.4 mg, 0.10 mmol) were placed in Schlenk tube under argon. Then, DMF (4.2 mL), MAA (0.84 mL, 10.0 mmol) and 1,4-dioxane (0.1 mL, internal standard) were added in this order at room temperature.   Immediately after mixing, the reaction solution was warmed to 60°C.   The reaction was terminated in 24 hours by cooling the solution to –78°C.   The conversion of vinyl group was determined by ^{1}H NMR in DMSO-d$_6$ with tetralin as an internal standard (Conv. = 98.0 %).   The reaction mixture was purified via reprecipitation in chloroform 3 times for removal of residue monomer.   Finally, chloroform was evaporated under reduced pressure to obtain PMAA as white solid (0.65 g).   The ^{1}H NMR spectrum was shown in Figure S2.

Procedures to determine monomer reactivity ratio

Copolymerization of EFMA (M_1) and AN (M_2) were performed with AIBN by changing the monomer ratio (M_1:M_2 = 9:1, 7:3, 5:5, 3:7, and 1:9). Typical procedure of copolymerization is as follows: EFMA (0.75 g, 3.0 mmol), AN (0.19 ml, 3.0 mmol), AIBN (9.8 mg, 0.060 mmol), and 1,4-dioxane (0.1 mL, internal standard) were placed in Schlenk tube under argon, and then dissolved in DMF (3.0 mL) (5:5 injection condition).   The solution was warmed to 60°C for initiating the radical copolymerization.   The reaction was terminated by cooling the solution to –78°C.   The composition ratio [$F = DP_{M1}/(DP_{M1} + DP_{M2})$] was determined from the monomer conversion ratio [Conv$_{M1}$, Conv$_{M2}$] by ^{1}H NMR with 1,4-dioxane as an internal

standard.   The actual monomer feed ratio [$f = [M_1]_0/([M_1]_0 + [M_2]_0)$) was also determined by ^{1}H NMR before reaction.   The monomer reactivity ratios were then calculated via Fineman-Ross plot with the F and f values (Table 1 and Figure 2).   The monomer reactivity ratios for MMA and AN were similarly determined.

Table 1. Free Radical Copolymerization of Methacrylate (M_1: EFMA or MMA) with AN (M_2) for Determination of the Reactivity Ratio[a]

M_1	f[b]	Time (min)	$Conv_{M1}$[c] (%)	$Conv_{M2}$[c] (%)	F[d]
EFMA	0.10	10	7.9	3.1	0.23
	0.33	15	4.4	3.1	0.41
	0.49	30	3.9	4.0	0.48
	0.65	15	0.3	0.6	0.52
	0.88	10	1.0	6.0	0.55
MMA	0.11	7	5.9	3.6	0.17
	0.31	7	3.7	2.1	0.44
	0.51	7	2.4	1.5	0.63
	0.71	7	6.5	5.2	0.76
	0.91	7	2.9	3.8	0.89

[a][M_1+M_2]_0/[AIBN]_0 = 2000/10 mM in DMF at 60°C.

[b] Actual monomer feed ratio ($f = [M_1]_0/([M_1]_0 + [M_2]_0)$) determined by ^{1}H NMR.

[c] Determined by ^{1}H NMR.

[d] Calculated from f, $Conv_{M1}$ and $Conv_{M2}$.

Result and Discussion

The author first performed free radical copolymerization of EFMA with AN using AIBN as an initiator in DMF at 60°C: [EFMA]_0/[AN]_0/[AIBN]_0 = 1000/1000/20 mM (Figure 2A). The copolymerization smoothly proceeded and the consumption rates of both EFMA and AN reached approximately 60% in 24h.   In addition, both monomers were consumed at the same rate suggesting progress of alternating propagation given the fact that EFMA shows no polymerization ability in the absence of comonomer.   The author also performed the radical copolymerization with MMA instead of EFMA to see effects of EFMA.   In this case, the
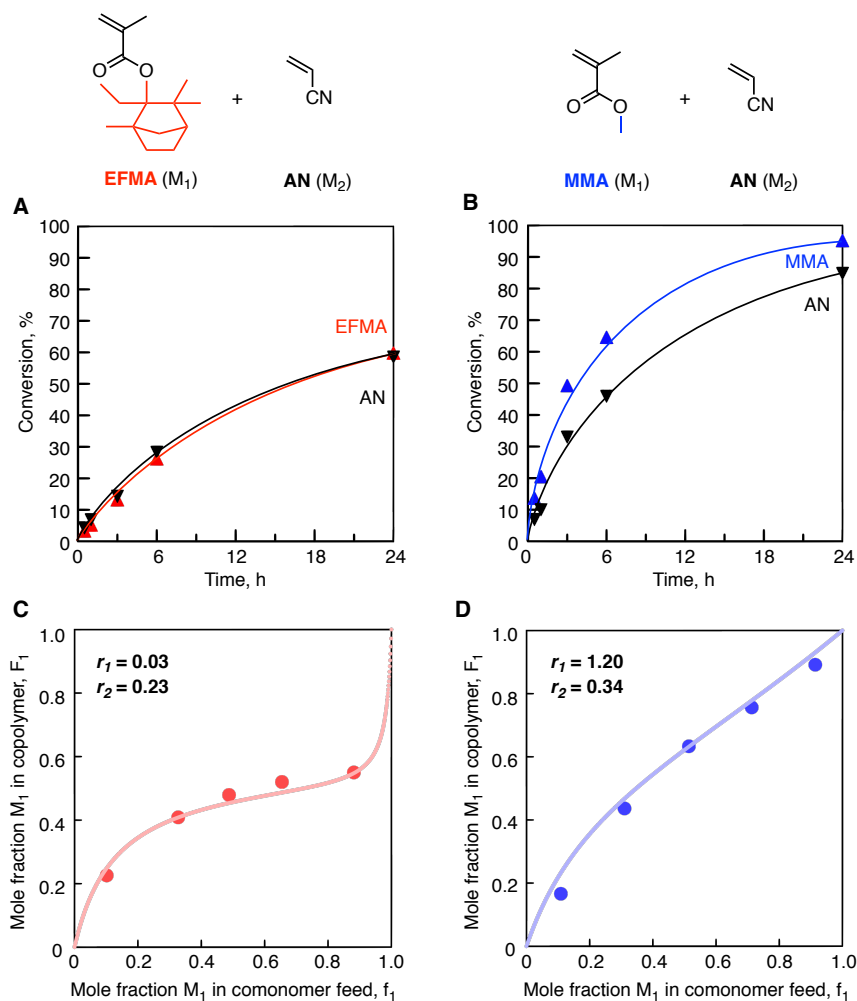
Figure 2. Comparison between EFMA and MMA on free radical copolymerization with AN. Time-conversion curves of 1:1 copolymerization of EFMA/AN (A) and MMA/AN (B): [EFMA or MMA]$_0$/[AN]$_0$/[AIBN]$_0$ = 1000/1000/20 mM in DMF at 60°C. Fitted injection ratio - composition curves for the copolymerization of EFMA/AN (C) and MMA/AN (D): [total comonomers]$_0$/[AN]$_0$/[AIBN]$_0$ = 2000/20 mM in DMF at 60°C.

parallel consumption behavior was not observed, and the copolymerization progressed faster.

To discuss the copolymerization behavior in more detail, the author determined the monomer reactivity ratios for the pair of EFMA/AN in comparison with MMA/AN (M$_1$: methacrylate, M$_2$: AN, Figure 2C, D). The r_1 value for EFMA/AN was almost zero (r_1= 0.03), whereas that for MMA/AN was higher than 1 (r_1= 1.20). The remarkable difference in the r_1 value was consistent with the inability of EFMA to propagate in succession due to the bulkiness. The not so high value of r_1 for MMA/AN indicates the inherent cross-propagation ability of methacrylate radical species for the AN monomer, and thus the propagation of EFMA radical species to AN could take place. As for the value of r_2, it was not completely zero but low (r_2
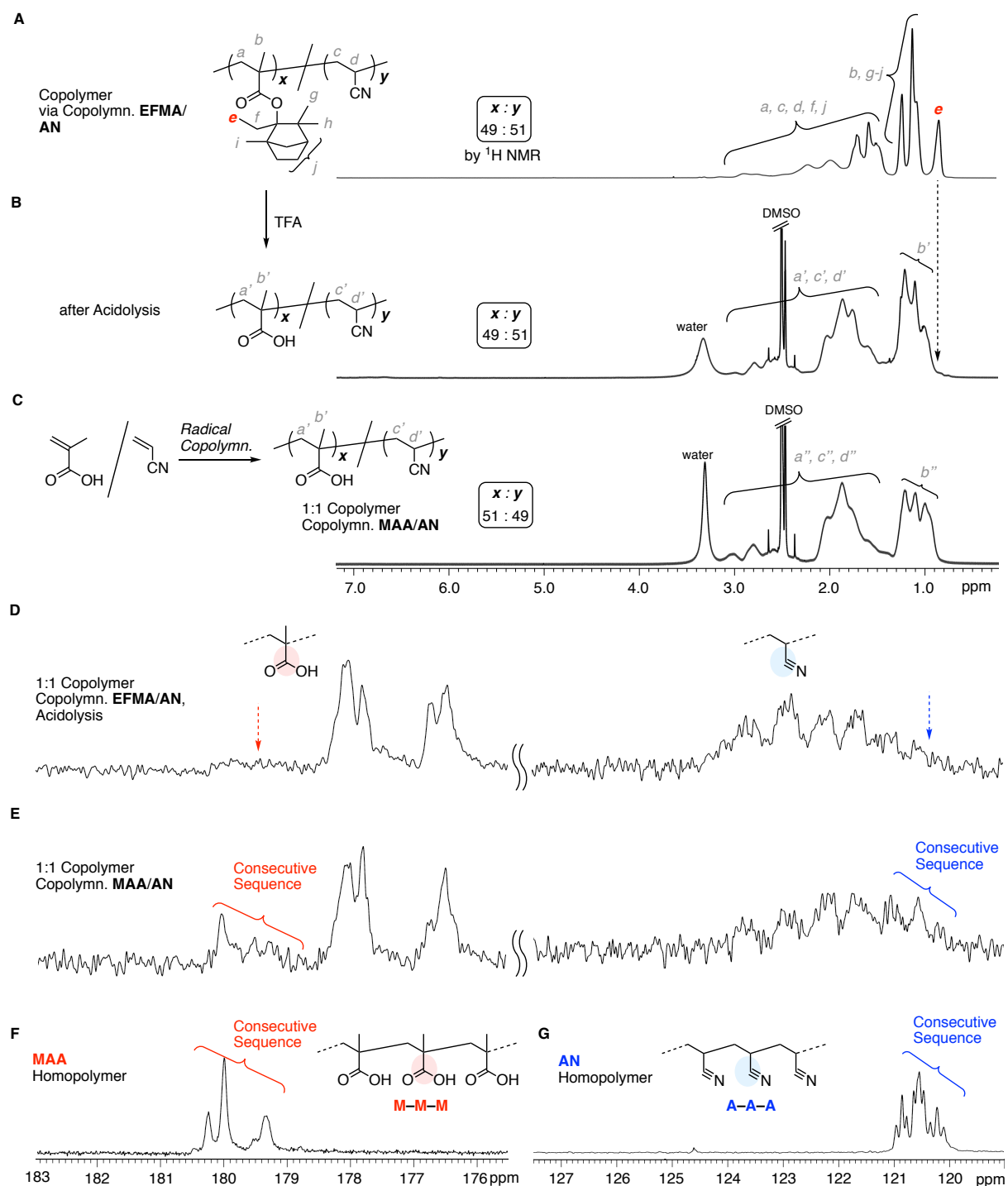
Figure 3. Structural analyses by ^{1}H NMR [500 MHz, CDCl$_3$ (A) or DMSO-d$_6$ (B, C), room temperature (r.t.)]: (A) the copolymer of EFMA and AN; (B) the copolymer after the TFA treatment for acidolysis of the EFMA units; (C) the copolymer of MAA an AN. Sequence analyses by ^{13}C NMR [125 MHz, DMSO-d$_6$, r.t.]: (D) the copolymer obtained by acidolysis of the copolymer of EFMA and AN in comparison with (E) the 1:1 statistical copolymer, and the homopolymers [(F) PMAA and (G) PAN]

= 0.23) and similar to that for MMA/AN (r_2 = 0.34). The low value shows the preference of AN radical species to methacrylate monomer, which is suitable for control of alternating sequence. Given the reactivity ratios as well as the parallel consumption behavior, the 1:1 radical copolymerization of EFMA and AN likely afforded the alternating copolymer.

The 1:1 radical copolymerization of EFMA and AN was quenched in 24 h (Conv.$_{EFMA}$ = 59.8%, Conv.$_{AN}$ = 58.5%) followed by purification with reprecipitation, and subsequently the resultant copolymer (M_n =17100, M_w/M_n = 1.48) was subjected to acidolysis with TFA for transformation of the EFMA unit to MAA. The transformation was characterized by ^{1}H NMR (Figure 3). The peak (e) characteristic to methyl group of the EFMA side chain was clearly observed around 0.8 ppm in CDCl$_3$ before the acidolysis treatment, and the integration ratio i ndicated the 1:1 composition ratio [x:y = 49:51 (x = DP$_{n, EFMA}$, y = DP$_{n, AN}$)] (Figure 3A). The copolymer after acidolysis became insoluble in CDCl3 and the structure was characterized with DMSO-d$_6$ (Figure 3B). The EFMA methyl peak obviously disappeared, and the spectrum was similar to that of statistical copolymer (x:y = 51:49) that was directly obtained via 1:1 radical copolymerized of MAA and AN (Figure 3C). The peak derived from α-methyl group of MAA units (b') was clearly observed, and the integration ratio of the peak to others indicated the same composition ratio for MAA and AN units (x:y = 49:51) as that before acidolysis. These analyses supported the quantitative transformation of EFMA unit into MAA in the alternating copolymer.

The sequence of the resultant copolymer was characterized by ^{13}C NMR in comparison with the 1:1 statistical copolymer and the homopolymers [i.e., PMAA, PAN]. The author focused on two regions where the carbonyl carbon peaks from MMA unit (*C*=O, 176.0-180.6 ppm) and cyano carbon ones from AN (*C*≡N, 119.7-125.0 ppm) were observed. The carbonyl peak of the copolymer from EFMA/AN was different from that of the statistical copolymer: peaks at lower magnetic field (179-180 ppm) were hardly observed. The correspondence of the peaks to PMAA suggests that they are derived from the consecutive sequence of MAA unit and no such homo arrangement exist in the copolymer from EFMA/AN as expected. As for the cyano carbon peaks, the trend of little peaks from the consecutive sequence of AN unit was supported, though the trend was not so clear due to the broad peaks. Thus, structural analysis of the copolymer after acidolysis transformation also supported the alternating sequence.

As described above, the MAA-AN statistical copolymers are known to exhibit thermal reactivities upon heating through cyclization between pendant groups. Scheme 1 shows the possible thermal reactions of different sequence segments: consecutive MAA sequence
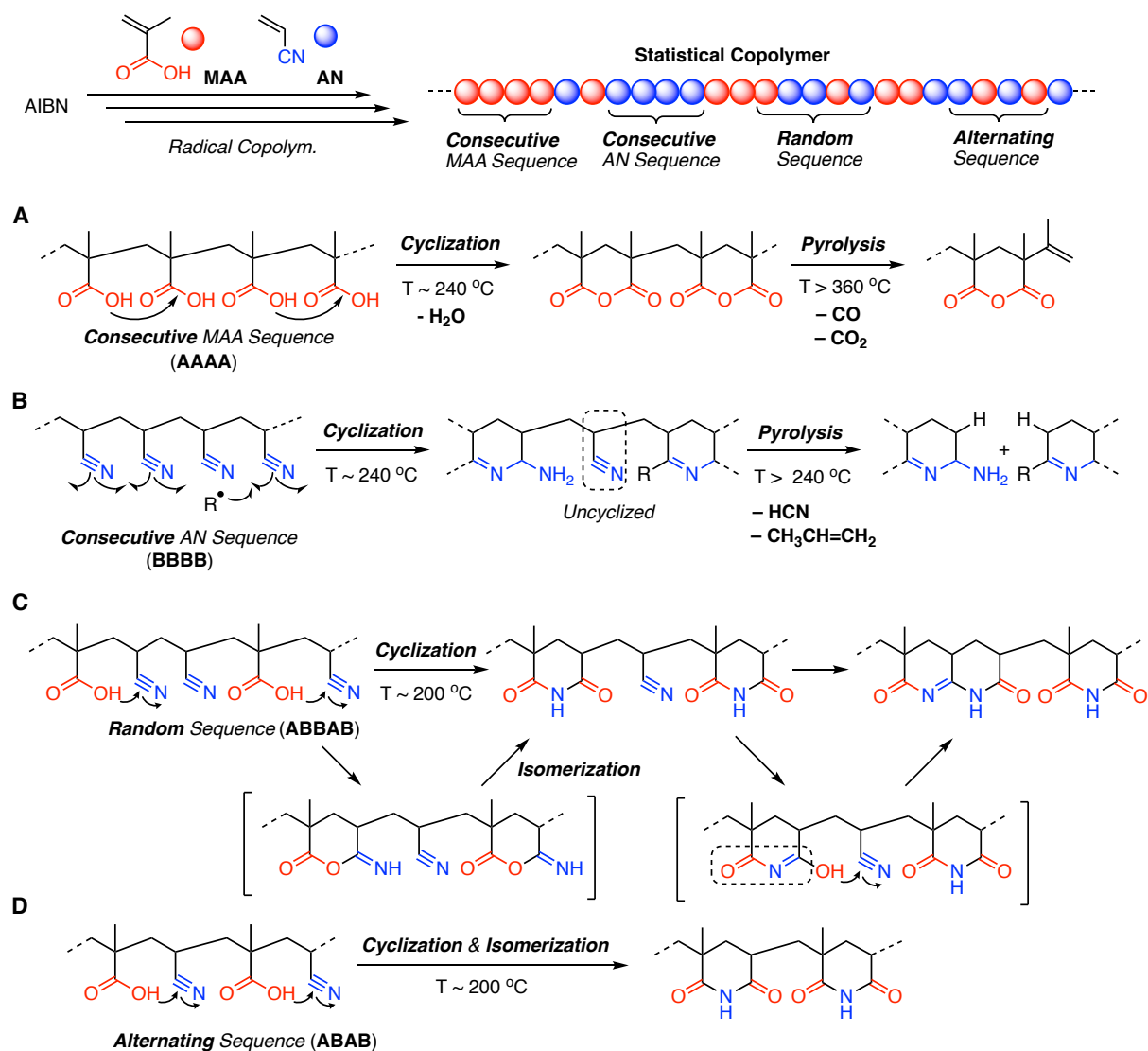
Scheme 1. Possible thermal reactions of different sequence segments in MAA-AN statistical copolymer: (A) consecutive MAA sequence (**AAAA**); (B) consecutive AN sequence (**BBBB**); (C) random sequence (**ABBAB**); (D) alternating sequence (**ABAB**).

(**AAAA**); consecutive AN sequence (**BBBB**); random sequence (**ABBAB**); alternating sequence (**ABAB**). The consecutive MAA sequence undergoes two step thermal reactions along with the weight loss, as clarified by thermogravimetric analysis of PMAA.[20] Initially, two neighboring carboxylic acids of the consecutive MAA sequence are cyclized via dehydration to form a glutaric anhydride-type six-membered ring. Further increasing temperature (i.e., temp.> 360°C) causes release of CO_2 and CO gas from the anhydride ring structure of the cyclopolymer resulting in fragmentation (Scheme 1A). As for the consecutive AN sequence, the segment undergoes cyclization and pyrolysis through thermal processing, as reported for PAN by Houtz et al.[21] Some radical species attack the triple bond of the cyano group (C≡N) to be transformed into the double bond (C=N) and the intramolecular chain-

reaction affords a kind of ladder segment composed of pyridine-type six-membered ring. The thermal reaction proceeds without weight change unlike consecutive MAA sequence resulting in dehydration-based cyclization. However, further heating at higher temperature (i.e., temp.> 240°C) causes the pyrolysis reaction: the ladder chain was decomposed from the unreacted AN unit via release of hydrogen cyanide (HCN) and propylene leading to weight loss (Scheme 1B).

In the case of the random sequence, the thermal reaction between neighboring groups becomes more complicated. The carboxylic acid pendant of MAA attacks the cyano group of neighboring AN to generate six-membered ring structure through an ionic mechanism upon thermal process, followed by isomerization to the imide structure, according to the previous studies.[18,22,23] If the AN unit exists neighboring to the cyclic imide unit, further cyclization proceeds via tautomerization resulting in ladder-type structure (Scheme 1C). The two-step cyclization does not take place for the **AB** repetitive alternating sequence (Scheme 1D) but for the **ABB** sequence.

Given the possible thermal reactions of the MAA-AN statistical copolymer, the author considered that the MAA-AN alternating copolymer exhibited the sequence-specific thermal reactivity different from the statistical analogue and thus investigated the thermal reaction behaviors.
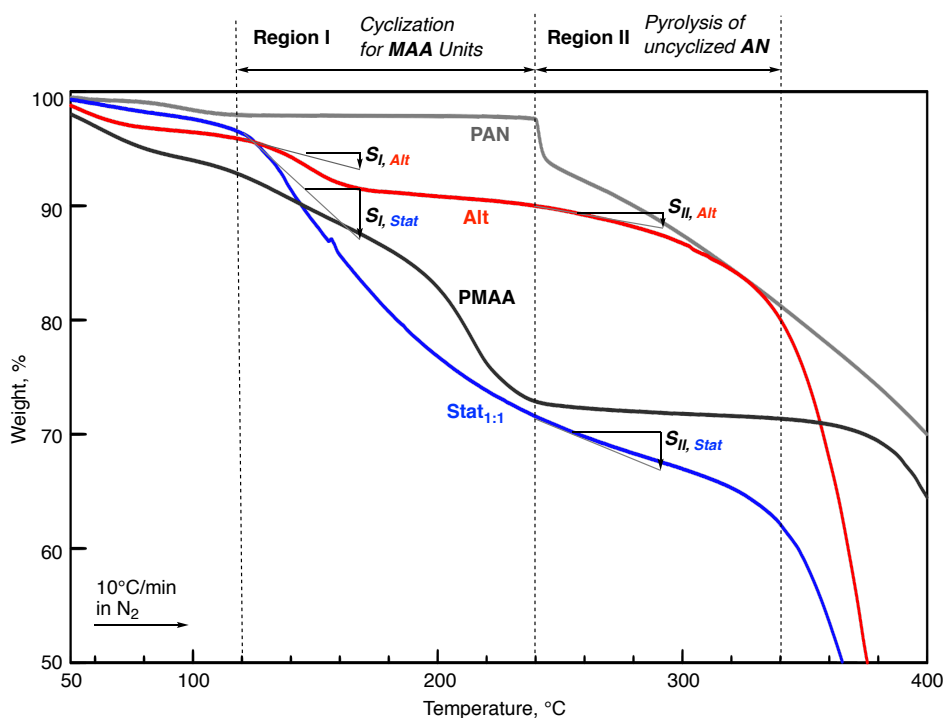
Figure 4. Thermal analyses of the MAA-AN alternating copolymers (**Alt**) by TGA on the heating process (10°C/min) from 50°C to 400°C under nitrogen gas in comparison with the 1:1 statistical polymer (**Stat₁:₁**) and homopolymers (**PMAA** and **PAN**).

The weight loss of the MAA-AN alternating copolymer (**Alt**) was then evaluated by simultaneous thermogravimetry/differential thermal analysis (TG-DTA) in comparison with the corresponding 1:1 statistical copolymer (**Stat$_{1:1}$**) and the homopolymers (**PMAA** and **PAN**) (Figure 4). **Alt** obviously showed superior thermal stability to **Stat$_{1:1}$** in the temperature range from 120℃ to 340℃. To discuss the difference in more detail, the chart was divided into two regions (I and II), where the weight of **PMAA** or **PAN** was largely decreased probably due to dehydration of MMA units and pyrolysis of uncyclized AN units, respectively:

Region I (120-240°C): Dehydration of MMA units for **PMAA**

Region II (240-340°C): Pyrolysis of uncyclized AN units for **PAN**

Table 2. Values of the and initial slope and weight loss on the Region I and II

Polymer	Region I (120-240°C)		Region II (240-340°C)	
	Initial Slope, S_I (% °C^{-1})	Weight$_{240°C}$ (%)	Initial Slope, S_{II} (% °C^{-1})	Weight$_{340°C}$ (%)
Alt	-0.060	90.0	-0.034	80.0
Stat$_{1:1}$	-0.19	71.6	-0.94	62.0

In Region I, **Alt** gave the lower initial slope ($S_{I,Alt}$ = 0.060, Table 2), which was about one third of **Stat$_{1:1}$** ($S_{I,Sta}$ = 0.19). The weight of **Alt** at 240˚C ($W_{Alt,240°C}$) was 90.0%, which was higher than that of **Stat$_{1:1}$** ($W_{Sta,240°C}$ 71.6%). The significant differences were likely attributed to the fact that there are few ratios of consecutive MAA sequence in **Alt** causing dehydration via cyclization of the neighboring MAA units. The thermally stable feature of **Alt** was also observed in region II: $S_{II,Alt}$ = 0.034 vs $S_{II,Sta}$ = 0.94; $W_{Alt,340°C}$ = 80.0% vs $W_{Sta,340°C}$ = 62.0%. The differences were derived from that **Alt** contains fewer uncyclized AN unit than **Stat$_{1:1}$**.

The structural change of **Alt** upon heating was evaluated by FT-IR in comparison with Stat1:1 (Figure 5A and B). The samples were thermally annealed at 190°C, which is a middle temperature of Region I, for 30 min. In the spectrum before heating, the characteristic peaks to the stretching vibration of the cyano bond (C≡N) and the carbonyl bond (C=O) were clearly observed at 2243 cm^{-1} and 1700 cm^{-1}, respectively. After the heat treatment, the cyano peak disappeared, whereas the carbonyl peak slightly shifted to 1688 cm^{-1}. These changes were consistent with that the cyclic imide units were efficiently formed from the alternating sequence. On the other hand, **Stat$_{1:1}$** gave completely different spectra. Some additional peaks highlighted by gray square, which were not detected in **Alt**, were observed, and they were likely derived from the random sequence. Interestingly, the peak corresponding to the stretching vibration of C-O-C bond in the cyclic carboxylic acid anhydride appeared at 946 cm^{-1} after the
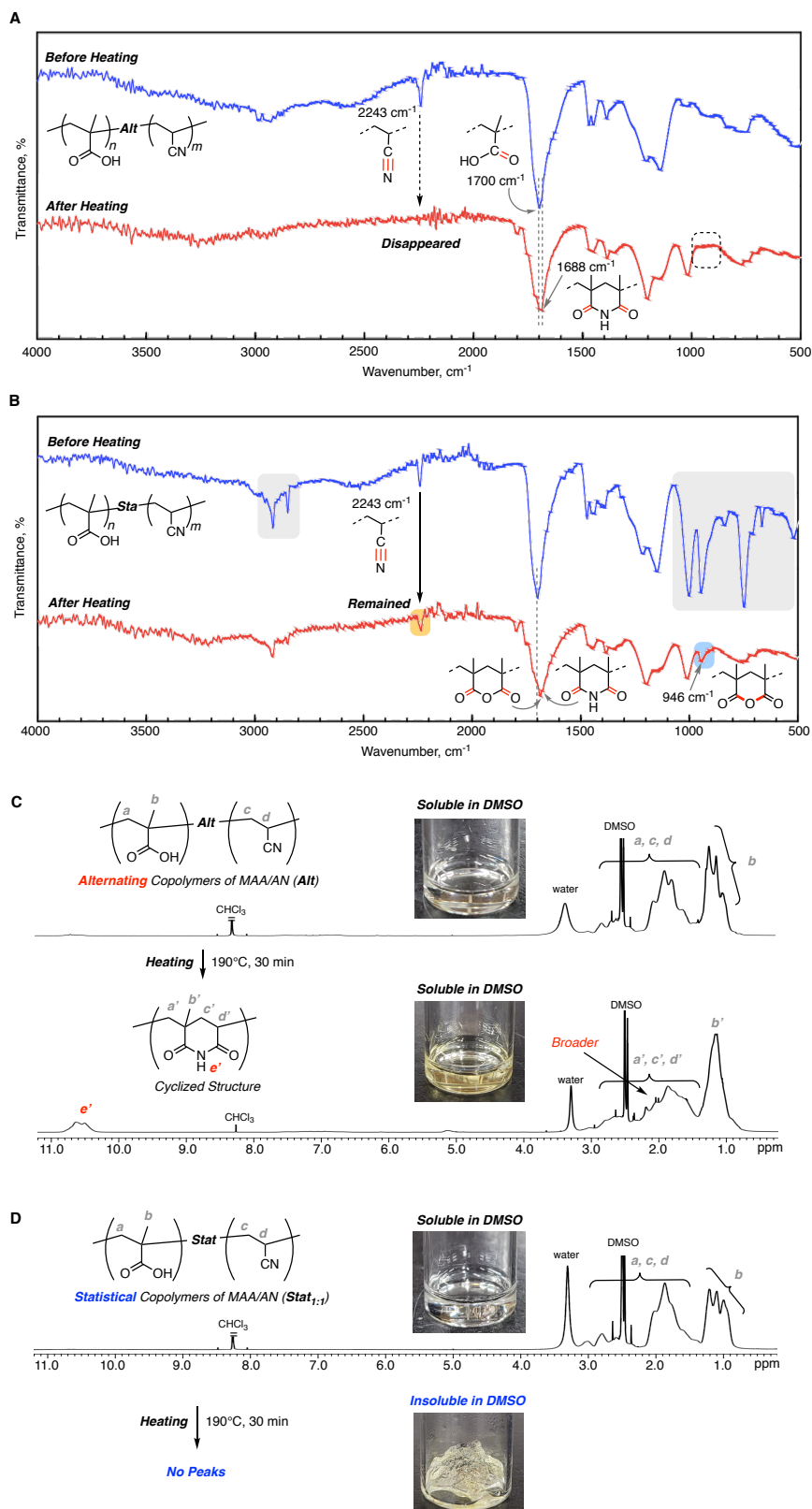
Figure 5. Structural analyses of the copolymers before and after heating at 190°C for 30 min by FT-IR [**Alt** (A) and **Stat**$_{1:1}$ (B)] and ^{1}H NMR (500 MHz, DMSO-d$_6$, room temperature) [**Alt** (C) and **Stat**$_{1:1}$ (D)]. **Stat**$_{1:1}$ became insoluble in DMSO after heating.

heating process, and the cyano peak remained.   The notable difference was also in agreement with that the thermal cyclization reactions of the homo sequences of MAA and AN in the statistical copolymer took place (Scheme 1A and B).

To examine the structural change upon heating in more detail, the author characterized the structures of the copolymers after heating by ^{1}H NMR.   The peak derived from the imide proton was clearly observed around 10.7 ppm, and the peaks from the backbone protons became boarder (Figure 5C).   In contrast, the statistical copolymer turned into insoluble in any solvent including DMSO after the heating treatment due to more complicated reactions giving some types of cyclized structures, and the NMR analysis was thus inaccessible (Figure 5D).   The author thus clarified the alternating copolymer afforded the sequence-specific thermal reactions different from the statistical analogue through these structural analyses.

Conclusion

In summary, the author precisely synthesized the MAA-AN alternating copolymer via radical copolymerization of the bulky tertiary methacrylate (EFMA) and subsequent hydrolysis reaction.   The obtained alternating copolymer showed the unique thermal reaction behaviors to afford the imide-based cyclopolymer, which was totally different from the corresponding 1:1 statistical copolymer resulting in different types of cyclo-structures, typically the cyclic carboxylic acid anhydride unit.   The sequence-specific thermal reaction behavior of the alternating copolymer is based on the absence of consecutive sequence of MAA and AN.

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Chapter 4 Supporting Data
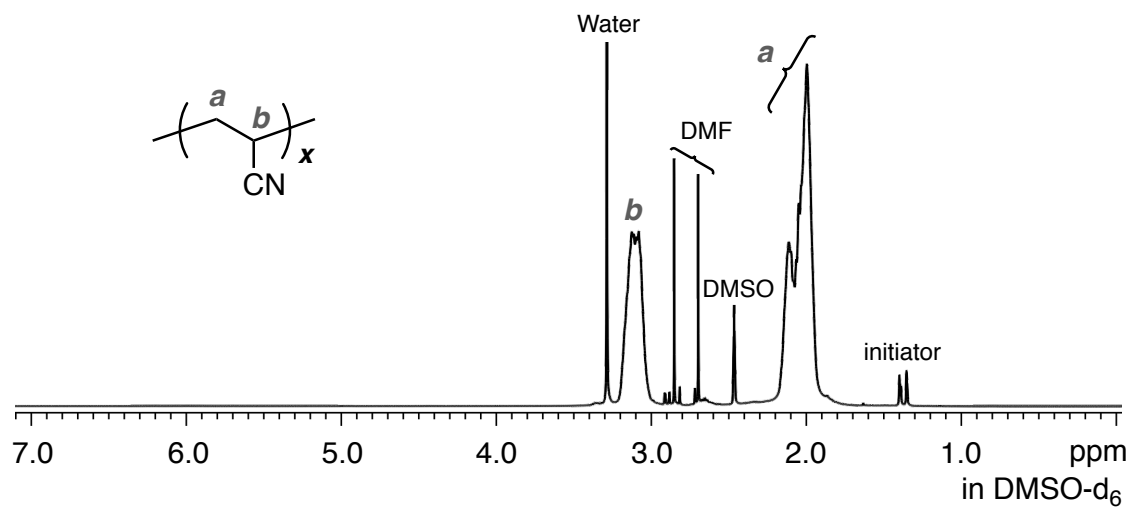
Figure S1. ^{1}H NMR (DMSO-d$_6$, r.t,) spectrum of PAN
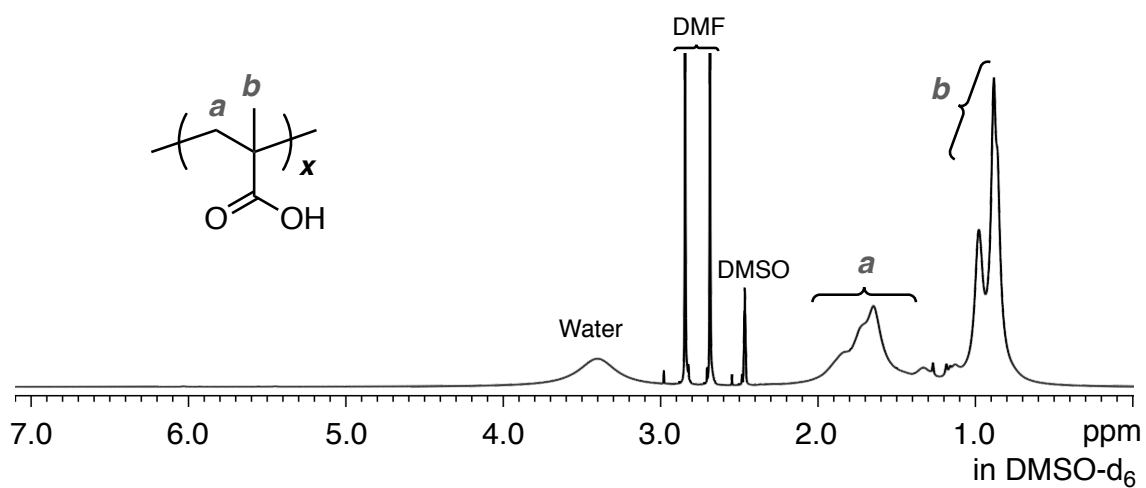
Figure S2. ^{1}H NMR (DMSO-d$_6$, r.t,) spectrum of PMAA.

List of Publications

Part I

Chapter 1

"Iterative Radical Addition with a Special Monomer Carrying Bulky and Convertible Pendant: A New Concept toward Controlling the Sequence for Vinyl Polymers"

<u>Dongyoung Oh</u>, Makoto Ouchi, Tomoya Nakanishi, and Mitsuo Sawamoto

ACS Macro Lett., **2016**, *5*, 6, 745-749.

Chapter 2

"Precise Control of Single Unit Monomer Radical Addition with a Bulky Tertiary Methacrylate Monomer toward Sequence-Defined Oligo- or Poly(methacrylate)s via the Iterative Process"

<u>Dongyoung Oh</u>, Mitsuo Sawamoto, and Makoto Ouchi

Polym. Chem., **2019**, *10*, 1998-2003.

Part II

Chapter 3

"Unusual Radical Copolymerization of Suprabulky Methacrylate with *N*-Hydroxysuccinmide Acrylate: Facile Syntheses of Alternating-Rich Copolymers of Methacrylic Acid and *N*-Alkyl Acrylamide"

<u>Dongyoung Oh</u>, Yousuke Furuya, and Makoto Ouchi

Macromolecules, **2019**, *52*, 22, 8577-8586.

Chapter 4

"Synthesis of Methacrylic Acid-Acrylonitrile Alternating Copolymer Using an Extremely Bulky Methacrylate and the Sequence-Dependent Thermal Reaction Behaviors"

<u>Dongyoung Oh</u> and Makoto Ouchi

Submitted.

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