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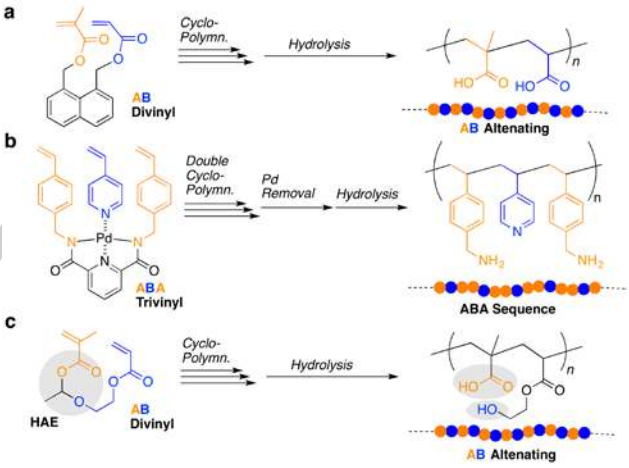
Alternating Sequence Control for Carboxylic Acid and Hydroxyl Pendant Groups via Controlled Radical Cyclopolymerization of Divinyl Monomer Carrying Cleavable Spacer

Makoto Ouchi,*[a] [b] Marina Nakano,[a] Tomoya Nakanishi,[a] and Mitsuo Sawamoto*[a]

Abstract: By utilizing features of hemiacetal ester (HAE) bond, i.e., easy formation from vinyl ether and carboxylic acid and easy cleavage into different functional groups (–COOH and –OH), we achieved control of alternating sequence for the two functional pendant groups of vinyl copolymer. Methacrylate- and acrylate-based vinyl groups were connected through HAE bond to prepare a cleavable divinyl monomer, which was cyclo-polymerized under optimized condition with ruthenium-catalyzed living radical polymerization. Subsequent cleavage of the HAE bond in the resultant cyclo-pendant led to copolymer consisting of methacrylic acid and 2-hydroxyethyl acrylate units and they were likely aligned with alternating sequence as analyzed by ^{13}C NMR. The alternating sequence of –COOH and –OH pendant specifically provided lower critical solution temperature (LCST) in an ether solvent, which was not observed with the random copolymer of same composition ratio.

In nature, “sequence” of macromolecules (i.e., DNA and peptides) is elaborately controlled, and functional substituents at well-defined positions cooperatively play an important role on their functions. Sequence control for synthetic polymers has recently attracted attentions toward more advanced functions like natural polymers,[1–6] but the control is still challenging in polymer science. Among artificial macromolecules, vinyl polymers are most interesting for this subject, because they consist of repeating units derived from comonomers carrying various functional pendant groups similar to peptides composed of amino acid-based units. Vinyl polymers are generally synthesized through addition polymerization of vinyl monomers and have been used toward plastic, fiber, and rubber as well as functional advanced materials. Monomers are easily co-polymerized via the chain growth mechanism to give statistical “random” copolymers and the properties can be tuned by combination of comonomers as well as the averaged composition ratio. Now that molecular weight and terminal groups can be controlled with living polymerization, the subject of sequence control and sequence-driven functions could be the next destination in polymer science. However, rather unfortunately, the chain-growth mechanism is less appropriate for sequence control because the propagation does not occur in stepwise.

Some concepts or methodologies to control sequence for vinyl polymers have been reported.[7–20] One simple but never easy approach is the iterative single unit addition on the basis of living polymerization.[7,13–16] These might be less satisfactory in terms of yield/efficiency because purification and/or diluted condition are required due to the statistical feature inherent in addition polymerization. Another one is relying on not addition polymerization but other polymerizations, such as polyaddition,[9] ring-opening metathesis polymerization (ROMP),[20] acyclic diene metathesis (ADMET) polymerization.[19] Monomers having information of sequence or position are connected with each other and subsequent hydrogenation (for the metathesis mechanism) to give polymers of periodic sequence equivalent for vinyl polymer structures.



Scheme 1. Cyclopolymerizations to control alternating sequence. (a) Cyclopolymerization of AB-type divinylmonomer with cleavable spacer into two –COOH pendants, (b) doublecyclopolymerization of ABA-type trivinylmonomer on palladium complex, (c) cyclopolymerization of AB-type divinylmonomer with HAE spacer (this work).

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On the other hand, cyclopolymerization of cleavable multivinylmonomers where the pendant groups are connected to each other via cleavable spacer could be an approach to control periodic sequence by cleaving resultant cyclo-pendant. This methodology could provide sequence control for high molecular weight polymer, though sequence pattern is limited to periodic. We have reported two examples on this concept. One is AB-divinyl monomer consisting of methacrylate and acrylate whose ester is connected via naphthalene scaffold (Scheme 1A).[11] The cyclopolymerization was controlled with metal-catalyzed

living radical polymerization under diluted condition, followed by cleavage of ester group, to give AB alternating copolymer consisting of methacrylic and acrylic acid units. A drawback of this design is using same cleavage bond (i.e., ester) resulting in an identical pendant group, i.e., carboxylic acid. Another type is ABA-trivinyl monomer built on palladium complex and the double cyclopolymerization led to the copolymer of ABA periodic sequence of amino methyl styrene (A) and 4-vinyl pyridine (B) units (Scheme 1B).[12] Although different functional groups (i.e., amine and pyridine) are aligned with ABA sequence, simultaneous control of molecular weight was not achieved because extremely lower temperature is required to maintain the π-π stacked structure during polymerization.

In this communication, we present a simple but effective design to control periodic sequence for different functional side chains as well as the molecular weight and the sequence-driven property. Crucial is an introduction of cleavable spacer between two vinyl groups in divinyl monomer and control of the cyclopolymerization. Herein, hemiacetal ester (HAE) bond is the key as a cleavable bond, since the bond is cleaved into carboxylic acid and hydroxyl groups under acidic condition as well as easily formed from vinyl ether and carboxylic acid. Given by the previous design with the combination of methacrylate and acrylate for AB alternating sequence, the two vinyl monomer components are connected via HAE bond to prepare AB divinyl monomer **1** (Scheme 1C). The cyclopolymerization of **1** followed by cleavage of HAE bond could expect to give alternating sequence of methacrylic acid and 2-hydroxyethyl acrylate (HEA).

We thus studied conditions to realize cyclopolymerization of **1**, such as selection of initiator/cocatalyst and concentrations of components, by means of ruthenium-catalyzed living radical polymerization (see Supporting Information, Table S1). First, a bromine-based initiator [H–(MMA)$_2$–Br] was used in conjunction with RuCp*(Cl)(PPh$_3$)$_2$]$_0$ (catalyst) and Al(O*i*-Pr)$_3$ (cocatalyst), and the polymerization of **1** was performed in toluene at 60˚C with the following concentration: [**1**]$_0$/[H–(MMA)$_2$–Br]$_0$/[RuCp*(Cl)(PPh$_3$)$_2$]$_0$/[Al(O*i*-Pr)$_3$]$_0$ = 100/2.0/1.0/10 mM (Entry 1). Consumptions of the both vinyl groups [i.e., methcrylate (M) and acrylate (A)] were individually determined with ^{1}H NMR, and the two vinyl groups were consumed at almost same rate, indicating control of cyclopolymerization. However, Al(O*i*-Pr)$_3$ caused ester-exchange with **1** during polymerization to give non-cyclo unit carrying an isopropyl pendant, which was observed in the conversion analysis by ^{1}H NMR. Thus, Al(O*t*-Bu)$_3$ was used as the cocatalyst, because it is known to work for MMA polymerization without ester exchange reaction (Entry 2).[21] In this polymerization, a damage of **1** due to ester exchange reaction was not observed, however the molecular weight distribution of obtained polymer was broad (M_w/M_n = 2.93). Herein, chlorine- [H–(MMA)$_2$–Cl] or iodine-based (H–EMA–I) initiator was used instead of H–(MMA)$_2$–Br (Entry 3–4). The former gave slower polymerization and broad MWD of obtained polymer (M_w/M_n = 2.65), and in contrast, the latter did faster polymerization and narrower MWD (M_w/M_n = 1.59). In spite of such acceleration, the two vinyl groups were consumed in parallel and any insoluble gel was not formed during polymerization. As the concentration of **1** or initiator was higher, the MWDs were clearly broader probably due to cross-linking reaction but moderately diluted condition allowed narrower MWDs of obtained polymers (Entry 4–6).

Consequently, controlled cyclopolymerization of **1** was realized under optimized condition: [**1**]$_0$/[H–EMA–I]$_0$/[RuCp*(Cl)(PPh$_3$)$_2$]$_0$/[Al(O*t*-Bu)$_3$]$_0$ = 100/2.0/1.0/10 mM in toluene at 60˚C (Figure 2). The vinyl groups from methacrylate and acrylate units were consumed at almost same rate (Figure 2a) despite of inherently different reactivity, which is due to intramolecular propagation on the spacer connection.[22] The polymerization proceeded without giving any insoluble polymers and the propagation seemed to be controlled: the number-averaged molecular weight (M_n) was increased as the conversion increased (b) and SEC curves of obtained polymers shifted to higher molecular weight keeping the unimodal shapes (c). In addition, an iodine-based catalyst[23] was used instead of RuCp*(Cl)(PPh$_3$)$_2$ to analyze the structure of obtained polymer: there was one series of peaks whose interval is the molecular weight of **1** and the mass of each peak agreed with the molecular weight of ideal polymer (the Na$^+$ adduct) of **1** carrying the initiator moieties at the terminals. From these analyses, it was concluded that the cyclopolymerization of **1** was fairy controlled. Another type of divinyl monomer **2**, where HAE bond was introduced at different position from **1**, was also tested for cyclopolymerization under the same condition, and similar results, i.e., parallel consumption and molecular weight control, were observed (Table S1 Entry 8 and Figure S4).

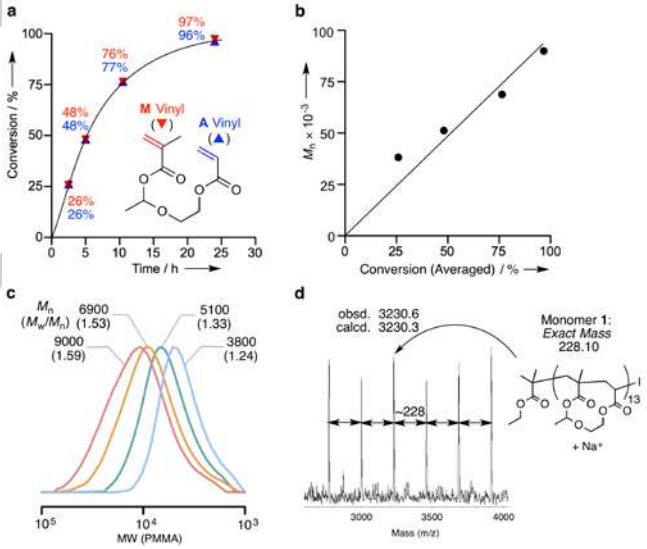

Figure 1. Ruthenium-catalyzed cyclopolymerization of **1**: [**1**]$_0$/[H–EMA–I]$_0$/[RuCp*(Cl)(PPh$_3$)$_2$]$_0$/[Al(O*t*-Bu)$_3$]$_0$ = 100/2.0/1.0/10 mM in toluene at 60˚C. (a) time-conversion plot, (b) conversion-Mn plot, (c) SEC curves of obtained polymers, (d) MALDI-TOF-MS spectrum of obtained polymer. The sample of MALDI-TOF-MS [Conv. (M) = 27%, Conv. (A) = 26%; M_n = 3700; M_w/M_n = 1.20] was prepared with iodine-based ruthenium complex instead of RuCp*(Cl)(PPh$_3$)$_2$ to avoid halogen exchange reaction: [**1**]$_0$/[H–EMA–I]$_0$/[[Cp*Ru(μ_3-I)]$_4$]$_0$/[PPh$_3$]$_0$ = 100/2.0/1.0/8.0 mM.

Figure 2a shows ^{1}H NMR spectrum of the cyclopolymer (40% conversions for the two vinyl groups, M_n = 6400; M_w/M_n = 1.30). Some peaks derived from the repeating unit protons were observed, but the shapes were much broader than common

vinyl (co)polymers due to the cyclostructure. Importantly, methine (*c*) and methyl (*d*) in repeating HAE bond were clearly identified, indicating the HAE bond was maintained during the radical polymerization process. Minor peaks around 6.4 ppm were likely attributed to unreacted acrylate (*h'*, *g'*) branched on the copolymer. This implies the cyclopropagation was not perfect, however, the "apparent" error ratio was estimated as less than 5%, and so the degree of cyclopropagation was relatively high.

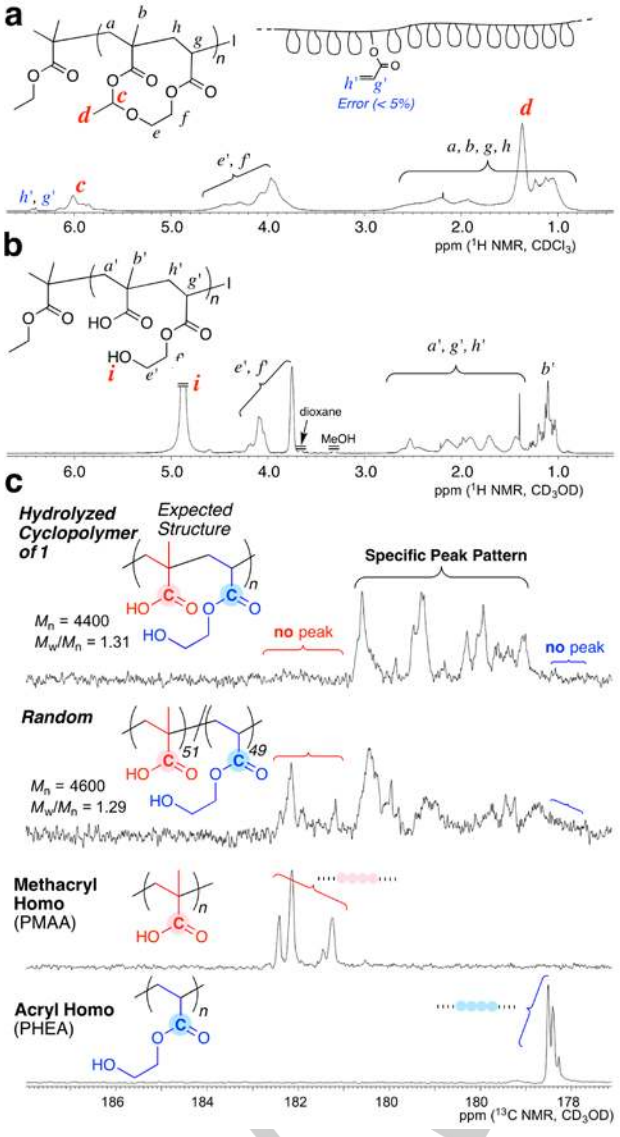

Figure 2. ^{1}H NMR spectrum of obtained cyclopolymer of **1** (a) and the hydrolysed copolymer (b). ^{13}C NMR spectra (178–187 ppm, c) of the hydrolysed copolymer **1**, random copolymer, homopolymer of MAA, and homopolymer of HEA.

Then, the HAE bond in the repeating unit is cleaved with trifluoroacetic acid (TFA) and structure of the resultant copolymer was characterized with ^{1}H NMR (in CD_3OD, Figure 2b). The peaks from HAE bond disappeared, and instead a peak (*i*) from proton of the resultant hydroxyl group appeared. An integration ratio of the characteristic peaks (*b*' and *e*', *f*) certainly supported formation of the copolymer of MAA and HEA with 1:1 composition ratio.

To verify the sequence of MAA and HEA units, the structure was analyzed with ^{13}C NMR (Figure 3). Herein, peaks from carbonyl group (C=O) were compared with those for the random copolymer of MAA and HEA with 1:1 composition ratio as well as for respective homopolymers of MAA and HEA. The random copolymer was prepared via ruthenium-catalyzed living radical polymerization of *tert*-butyl methacrylate (TBMA) and HEA, followed by deprotection of TBMA unit in the resultant random copolymer: M_n = 4600, M_w/M_n = 1.29, $DP_{n,TBMA}$: $DP_{n,HEA}$ = 51 : 49 (before deprotection, see Supporting Information). Importantly, the copolymer from **1** provided no peaks from MAA sequential homo unit at around 182 ppm, in sharp contrast to the random copolymer. As for peak from HEA sequential unit at around 178 ppm, the analysis was vague due to the lower S/N ratio but almost no peaks were observed around this region. In addition, peaks at 179–181 ppm were quite different from those for the random copolymer. Considering the polymerization behaviors together, such as parallel consumption of the two vinyl groups and no formation of insoluble product, these structural analyses with ^{13}C NMR likely support alternating sequence of MAA and HEA.

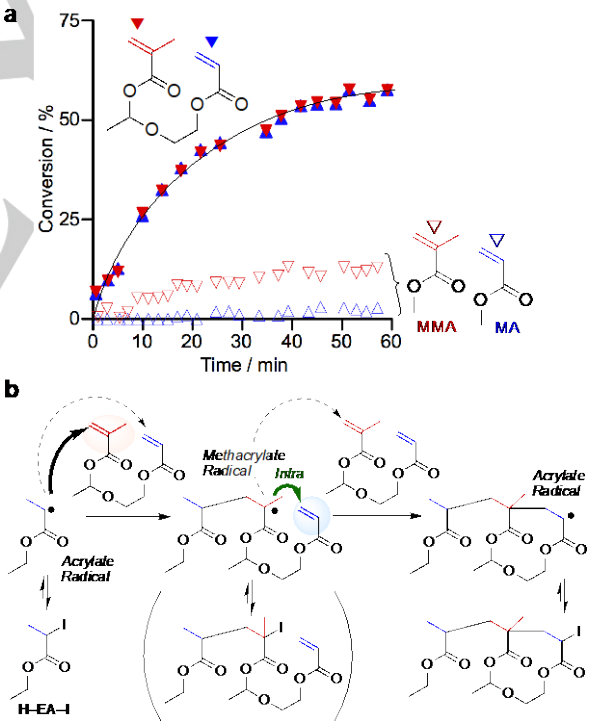

Figure 3. Ruthenium-catalyzed radical addition reaction of **1** with EA–I as a model reaction: [**1**]$_0$/[EA–I]$_0$/[RuCp*(Cl) $(PPh_3)_2$]$_0$/[Al(O*t*-Bu)$_3$]$_0$ = 10/10/1.0/10 mM in toluene-d_8 at 60˚C. Control experiment: MMA and MA were used instead of **1**; [MMA]$_0$/[MA]$_0$/[EA–I]$_0$/[RuCp*(Cl)$(PPh_3)_2$]$_0$/[Al(O*t*-Bu)$_3$]$_0$ = 10/10/10/1.0/10 mM in toluene-d_8 at 60˚C. (a) Time conversion plots, (b) plausible propagation mechanism with **1**.

Crucial to realize alternating sequence with this approach is the combination of different vinyl groups, i.e., methacrylate and acrylate. Given by reactivity ratios for combination of methacrylate and acrylate [e.g., r_1 = 2.15, r_2 = 0.40 for methyl methacrylate (MMA: M_1) and methyl acrylate (MA: M_2)],[24] both radical species from methacrylate and acrylate prefer to react with methacrylate-based vinyl group. Herein, selectivity on cyloclopolymerization of **1**, i.e., propagation order of the two vinyl groups, was studied with the model reaction under similar condition to the above polymerization. An acrylate-based iodine initiator (H–EA–I) was used for the reaction with an equimolar of **1** under ruthenium catalysis in toluene-d^8 at 60˚C and the conversions of two vinyl groups (i.e., methacrylate and acrylate) were directly observed: $[H–EA–I]_0/[\mathbf{1}]_0$ = 10/10 mM. As shown in the time-conversion plots (Figure 4a), both of the vinyl groups were smoothly consumed and the rate was almost same as each other (parallel consumption), like the polymerization. Similar model reaction was also performed with an equimolar mixture of MMA and MA instead of **1**: $[H–EA–I]_0/[MMA]_0/[MA]_0$ = 10/10/10 mM. In sharp contrast to the reaction with **1**, only MMA was consumed, whereas MA was hardly done through the reaction, and the consumption rate of MMA was much slower than **1**. From these model reactions, the following mechanism was proposed (Figure 4b): the acrylate-based radical species from EA–I could preferably react with methacrylate vinyl group over acrylate, which is supposed from the model reaction with MMA and MA. From the result of same consumption for both of the vinyl groups in **1**, the resultant methacrylate radical species could intramolecularly react with the acrylate vinyl group, independent of the inherent preference to methacrylate, due to the neighboring effect and/or enthalpy gain via the cyclization. Most probably, the intramolecular propagation on **1** smoothly proceeded without going through methacrylate-based dormant species that is formed via halogen capping to methacrylate-based radical species by Ru^{III}. The resultant acrylate radical or the dormant species could repeat the cyclopropagation with the order from methacrylate to acrylate, eventually to give the alternating sequence.[25]

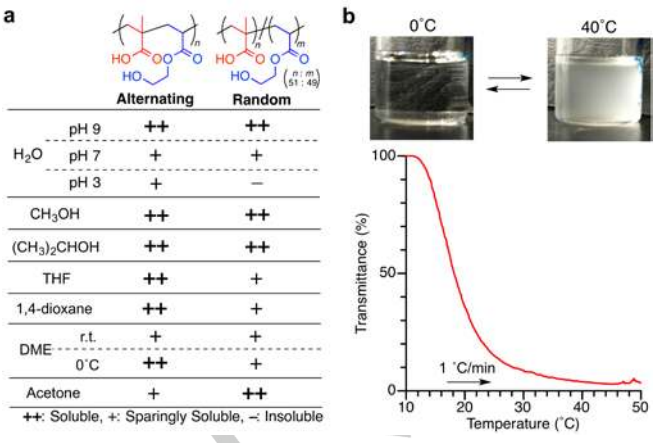

Figure 4. (a) Comparison of solubilities between alternating and random copolymer of MAA and HEA, (b) transmittance measurement of DME solution of the alternating copolymer (8 mg/ml) as a function of temperature. Heating process at 1 ˚C/min from 10˚C to 50˚C.

Finally, solubility of the resultant alternating copolymer of MAA and HEA (M_n = 4400, M_w/M_n = 1.31 before HAE cleavage) was examined in comparison with the random copolymer, which was used for the sequence analysis by ^{13}C NMR.

The alternating copolymer exhibited good solubility for alcohol, such as methanol and isopropanol, which was same as the random copolymer. However, it showed different solubility from the random copolymer for ether solvents, i.e., tetrahydrofuran (THF), 1,4-dioxane, and dimethyl ether (DME), as well as for acetone: the alternating copolymer was more soluble for the ether solvents but opposite tendency was observed for acetone. Such a solubility difference was also seen with acidic water (pH 3). Most interestingly, the solution of the alternating copolymer in DME was obviously turbid at room temperature, but it became transparent when it was put in ice bath. The thermosensitive solubility in DME was then evaluated with temperature-dependent UV/vis measurements, where transmittance of the solution was monitored at λ = 670 nm upon heating process ([polymer] = 8 mg/mL, heating speed = 1 °C/min). Consequently, the solution was phase-separated in DME upon heating, though the response was not so quick. On the other hand, the DME solution of the random copolymer was completely turbid regardless of temperature.

The detailed mechanism of the LCST behavior by the alternating sequence is currently unclear, but most probably it is related to balance of the following two hydrogen bonding interactions: intra-chain interaction between neighboring pendants, i.e., –COOH and –OH; inter-chain interaction between –COOH pendants (so-called “carboxlic dimer”) that would cause precipitation or phase separation. The neighboring hydroxyl group could affect the later interaction between –COOH pendants through its hydrogen bonding with the acid and/or its solvation, and the interaction preference might be changed depending on temperature in DME solution, leading to LCST behavior. In general, LCST behavior of polymer solution in organic solvent is not so common, and specific combination of polymer structure and solvent are required, such as poly(vinyl ether) having ionic liquid pendant in chloroform,[26] PEG pendant polymethacrylate in hydrofluorocarbon,[27] and polyether in ionic liquid.[28] It should be noted that the LCST behavior in this work was observed by using very simple structures composed of MAA and HEA units in the ether solvent and was specific to the “alternating” sequence.

In conclusion, the simple connection of methacrylate and acrylate via HAE bond in side chain could lead to alternating sequence for –COOH and –OH pendant groups through the cyclopolymerization and the cleavage of HAE bond in repeating cyclo-units. The alternating sequence for the two functional groups provided unique solubility behavior, which was different from the random sequence of same composition ratio. This approach would open the door to development of sequence control for vinyl copolymers not only as the methodology but also toward creation of sequence-oriented functions or properties.

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Keywords: sequence• radical polymerization • cyclopolymerization • template • lower critical solution temperature (LCST)

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[23] The iodine-based ruthenium catalyst was used only for MALDI-TOF-MS analysis to suppress halogen exchange reaction making the analysis complicated. See Table S1 Entry 7. Usually $RuCp^*(Cl)(PPh_3)_2$ was used because it is commercially available.
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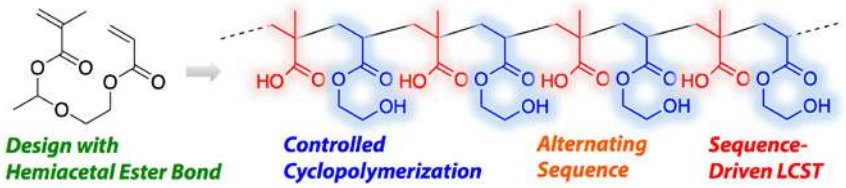
COMMUNICATION



Controlled cyclopolymerization of hemiacetal ester (HAE) bond-connected divinylmonomer and subsequent cleavage of HAE in the cyclo-pendant led to alternating copolymer consisting of methacrylic acid and 2-hydroxyethyl acrylate units. The resultant copolymer showed lower critical solution temperature (LCST) in an ether solvent, which was specific to the alternating sequence.

Makoto Ouchi, Marina Nakano, Tomoya Nakanishi, and Mitsuo Sawamoto**

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Alternating Sequence Control for Carboxylic Acid and Hydroxyl Pendant Groups via Controlled Radical Cyclopolymerization of Divinyl Monomer Carrying Cleavable Spacer