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Template-Assisted Selective Radical Addition toward Sequence-Regulated Polymerization: Lariat Capture of Target Monomer by Template Initiator

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

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

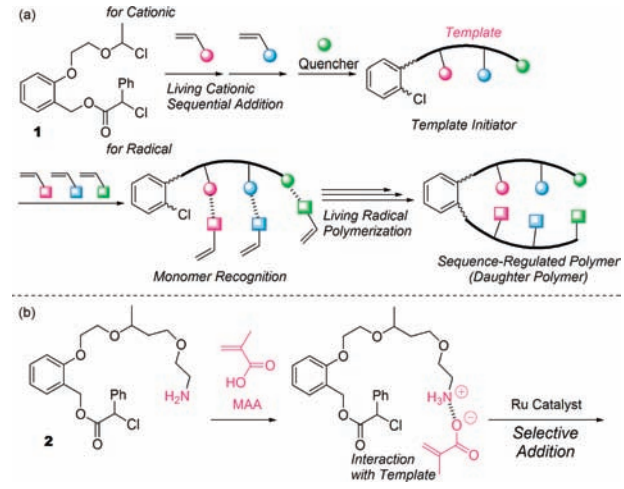
In contrast, with repeat units just randomly and averagely incorporated, conventional synthetic polymers (e.g., plastics in the solid state) mostly work as multimolecular assemblies where simple amplification of intermolecular interactions among repeat units leads to superior mechanical properties. If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

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

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

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

Scheme 1. (a) Conceptual Sequence-Regulated Radical Polymerization with a Template Initiator (**1**) Carrying Two Reactive C−Cl Bonds for Living Cationic and Radical Polymerizations; (b) Selective Radical Addition of MAA with an Amino-Functionalized Template Initiator (**2**) via Ionic Recognition



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

While starting with the same precursor **1** as before, we incorporated the recognition site via electrophilic substitution of the haloether C−Cl bond rather than electrophilic addition across a C=C bond as done previously.[3a] It should be noted that the latter is a propagation model for cationic polymerization, whereas the

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former is for cation quenching, thus showing the versatility of the haloether function in template construction.

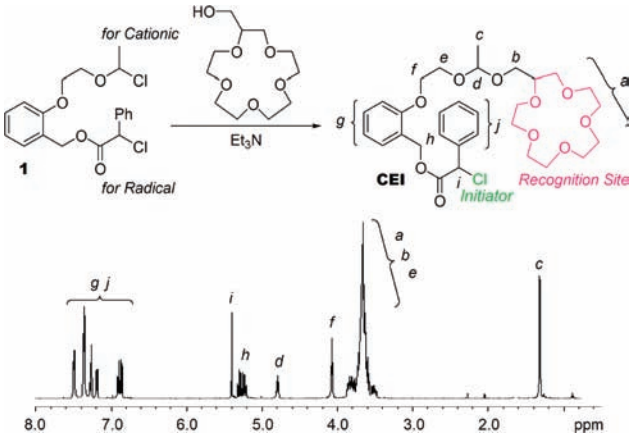
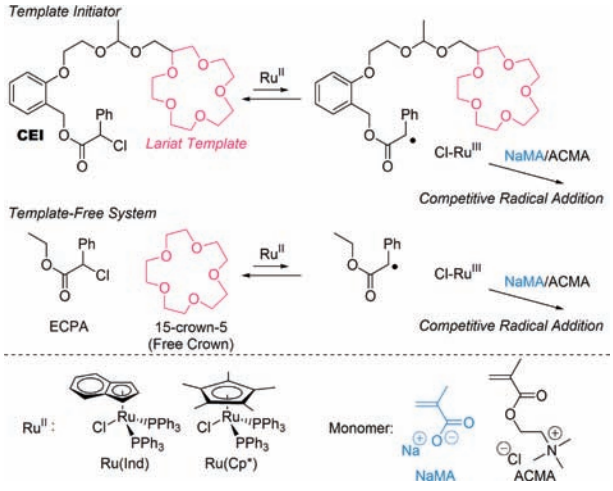


Figure 1. Synthetic scheme and ^{1}H NMR spectrum of **CEI** in $CDCl_3$.

Sodium methacrylate (NaMA) was selected as a targeting monomer for the 15-crown-5-ether site, as sodium cation is known to be specifically recognized by this crown ether via its ion-fitting size. Methacryloyloxyethyltrimethylammonium chloride (ACMA) was examined as a competing ionic monomer carrying an unfitted larger cation. First, the size-specific recognition by 15-crown-5 was monitored by ^{1}H NMR spectroscopy in EtOH-d_6 at 40 °C (Figure S-1 in the Supporting Information). When NaMA was mixed with an equimolar amount of the ether ([NaMA] = [15-crown-5] = 50 mM), the methylene peak *d* of the latter was clearly shifted downfield from 3.64 to 3.70 ppm, and those of the NaMA olefin (*a*) were shifted upfield from 5.73/5.13 to 5.70/5.10 ppm (Figure S-1a,c,d). These shifts show some interaction between the two components and most likely indicate capture of the sodium cation into the cyclic ether moiety. On the other hand, such peak shifts were not observed with ACMA (Figure S-1b,c,e), indicating that no recognition or capture of the ammonium cation occurred. More importantly, and relevant to competitive reactions with the two monomers (see below), the selective recognition of NaMA occurred even in the presence of ACMA (Figure S-1f).

Scheme 2. Ruthenium-Catalyzed Competitive Radical Addition of NaMA and ACMA with Crown Template Initiator or Template-Free Initiator (ECPA)



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

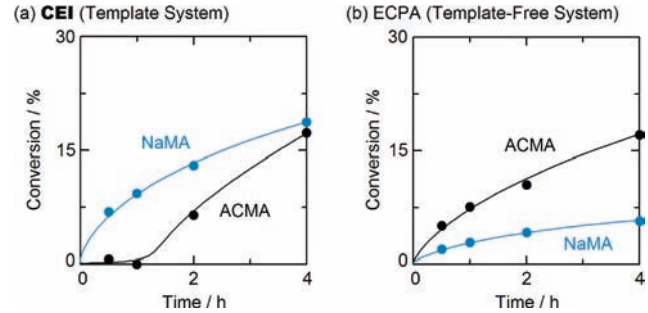


Figure 2. Time−conversion curves for the competitive radical addition of NaMA and ACMA with (a) **CEI** and (b) ECPA in EtOH at 40 °C. Conditions: $[NaMA]_0 = [ACMA]_0 = [initiator]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[15\text{-crown-5}]_0 = 50$ mM (only when ECPA was used as the initiator).

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

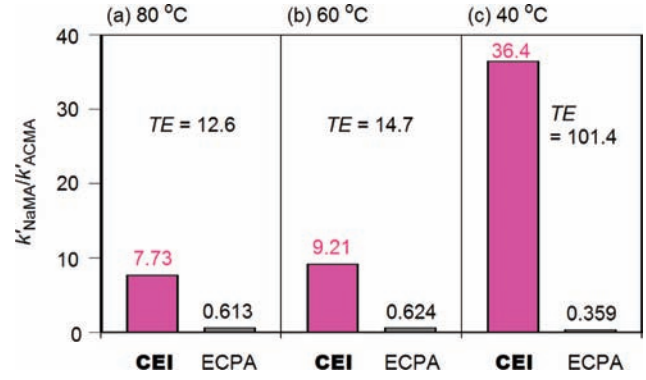


Figure 3. Monomer selectivity in competitive radical addition of NaMA and ACMA with **CEI** or ECPA in EtOH at (a) 80, (b) 60, and (c) 40 °C. Conditions: $[NaMA]_0 = [ACMA]_0 = [initiator]_0 = 50$ mM; $[Ru(Ind)Cl(PPh_3)_2]_0 = 4.0$ mM; $[15\text{-crown-5}]_0 = 50$ mM (only when ECPA was used as the initiator).

Here we expediently define the ratio of k'_{NaMA}/k'_{ACMA} with **CEI** (templated) to k'_{NaMA}/k'_{ACMA} with ECPA (nontemplated) as the "template effect factor" (*TE*). Thus, *TE* was evaluated as 101.4 for the above-described competition reactions at 40 °C. As expected,

decreasing the reaction temperature increased *TE* (Figure 3 and Table S1 in the Supporting Information), but at all of the temperatures examined, the template effect was indeed operable ($TE \gg 1$) and beyond the experimental error.

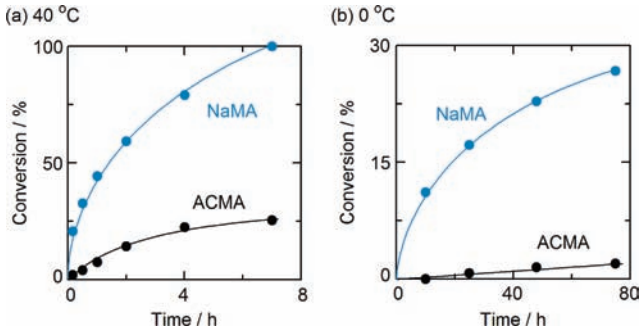


Figure 4. Time−conversion curves in competitive radical addition of NaMA and ACMA with **CEI** in EtOH at (a) 40 and (b) 0 °C. Conditions: $[NaMA]_0 = [ACMA]_0 = [\mathbf{CEI}]_0 = 50$ mM; $[Ru(Cp^*)Cl(PPh_3)_2]_0 = 4.0$ mM.

We recently found that in living radical polymerization, pentamethylcyclopentadienyl ruthenium complexes $[Ru(Cp^*)Cl(PR_3)_2$; $Cp^* = \eta^5\text{-}C_5(CH_3)_5$; R = phenyl, etc.] are active enough to catalyze living radical polymerization in ethanol even at a temperature as low as 40 °C.[12] Therefore, $Ru(Cp^*)Cl(PPh_3)_2$ was next employed for the NaMA/ACMA competitive addition at temperatures lower than 60 °C (Figure 4). For example, as shown in Figure 4a, NaMA was smoothly and quantitatively consumed at 40 °C (conv. ≈ 100% in 7 h) with $k'_{NaMA} = 1.27\ h^{-1}$, which is larger than the value using $Ru(Ind)Cl(PPh_3)_2$ at 60 °C ($0.855\ h^{-1}$). On the other hand, ACMA reacted more slowly (conv. ≈ 30% in 7 h at 40 °C; $k'_{ACMA} = 0.108\ h^{-1}$); the selectivity k'_{NaMA}/k'_{ACMA} was thus estimated to be 11.8.

At 0 °C (Figure 4b), the rate difference between NaMA and ACMA was more outstanding: the former reacted smoothly and had $k'_{NaMA} = 0.0157\ h^{-1}$, whereas the latter was hardly consumed and had $k'_{ACMA} = 0.0003\ h^{-1}$, leading to a much higher selectivity ($k'_{NaMA}/k'_{ACMA} = 52.3$). A similar trend was obtained at 25 °C (Figure S-4). All of these results demonstrate a superior recognition effect of **CEI** for NaMA.

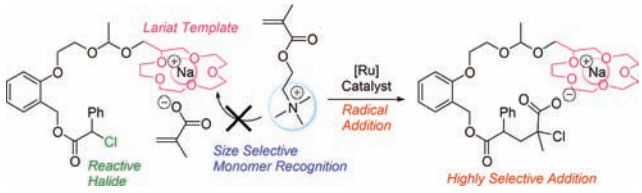


Figure 5. Size-selective monomer recognition by lariat capture of **CEI**.

In summary, we have demonstrated a highly selective radical addition with a template initiator (**CEI**) that carries a crown ether embedded close to a radical initiating site. Such a "lariat capture" of the sodium cation monomer (NaMA) by a crown macrocycle is therefore crucial for the observed size-specific molecular recognition (Figure 5), and the proximity effect allows surprisingly high substrate selectivity ($TE > 100$) in comparison with the nontemplated system. We are now further developing this concept toward sequence-regulated oligomerization and polymerization, which will be presented in the near future.

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Supporting Information Available: Experimental details, ^1H NMR spectra, and kinetic analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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