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

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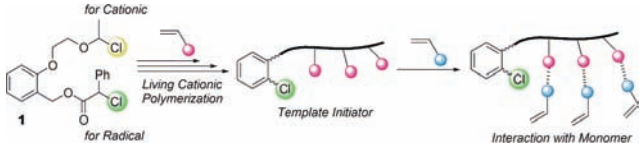
In recent years, template-assisted synthesis has been directed toward perfecting structural control of molecules, as inspired by biological macromolecules (typically, DNA and proteins) that are finely defined in terms of not only molecular weight but also "sequence" of repeat units or functionality along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

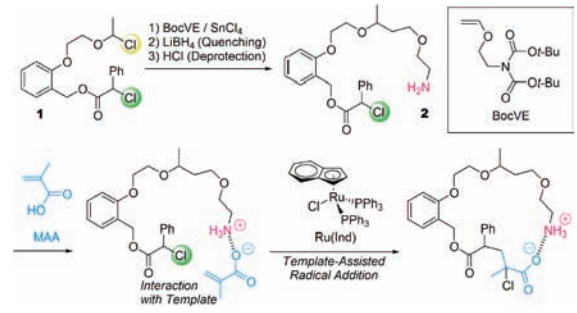
For the former target, we have pioneered two precision polymerizations, Lewis acid-catalyzed living cationic[2] and metal-mediated living radical[3] polymerizations, both of which allow syntheses of well-defined polymers with controlled molecular weights and narrow molecular weight distributions. Notably,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

Scheme 1. Template Initiators from a Heterobifunctional Halide for Template-Assisted Living Radical Polymerization



This communication reports our initial approach toward sequence control in our living radical polymerization via template-bearing initiators coupled with metal catalysts; the synthesis of the "template" initiator is based on our living cationic polymerization (Scheme 1). Prior to sequence control in polymerization, we examined the template-effect for metal-catalyzed radical addition (Kharash reaction),[6] a model for our living radical polymerization (Scheme 2). Though conventional radical reactions are performed with excess halide relative to alkene substrate in order to prevent oligomerization, we herein deliberately performed a radical addition under equimolar conditions ($[\text{halide}]_0 = [\text{alkene substrate}]_0$) to demonstrate the adequacy and potential of this template model.

Scheme 2. Radical Addition of MAA with the Template Halide



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

For the template introduction, we first performed living cationic polymerization from the precursor **1** using di-*tert*-butyl {*N*-[2(vinyloxy)ethyl]imido}dicarboxylate (BocVE), a vinyl ether with a protected pendant amino function. The reaction was catalyzed with $SnCl_4$ in conjunction with $(n\text{-Bu})_4NCl$ as an additive.[7] Rather unexpectedly, some specific conditions turned out to allow a selective single monomer addition to the cationic site generated from the haloether in **1**: $[\text{BocVE}]_0 = 50$ mM; $[\mathbf{1}]_0 = 10$ mM; $[SnCl_4]_0 = 10$ mM; $[(n\text{-Bu})_4NCl]_0 = 5.0$ mM in CH_2Cl_2 at −78 °C [Scheme 2; see the Supporting Information (SI)]. Quenching of the cationic intermediate with $LiBH_4$, followed by deprotection of the Boc site with excess HCl to afford the corresponding amine, gave the target template initiator **2**, as verified by ^1H NMR analysis (see the SI). Importantly, the haloester moiety in **1** remained intact during these addition and workup steps.

With the template-bearing halide **2**, radical addition of methacrylic acid (MAA) was initiated in toluene at 80 °C (1:1 **2**/MAA molar ratio) with the ruthenium complex catalyst RuCl(Ind)-

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$(PPh_3)_2$ (Ind = η-C_9H_7), one of the most useful catalysts for metal-catalyzed living radical polymerization[8] and radical addition.[9] Through its acid function, MAA is expected to be "recognized" by the amine template located in the vicinity of the initiating site.

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

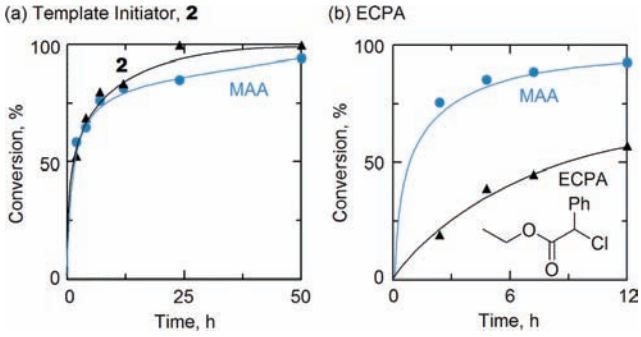

Figure 1. Time−conversion curves in radical additions of halides (C−Cl compounds) to MAA in toluene at 80 °C, based on consumption of (▲) the C−Cl bond in the halide [(a) **2**; (b) ECPA] and (●) the C═C bond in MAA. Conditions: $[halide]_0 = [MAA]_0 = 100$ mM; $[RuCl(Ind)(PPh_3)_2]_0 = 4.0$ mM; $[n\text{-}BuNH_2]_0$ = (a) 0 and (b) 100 mM.

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

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

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

When the MAA/MMA competitive addition was performed under the identical conditions but with the template-free initiator (ECPA/*n*-$BuNH_2$), MAA reacted just a little faster than MMA [k'(MAA)/k'(MMA) = 2.99]. Therefore, in terms of substrate selectivity expressed via the rate ratio, the template recognition enhanced MAA incorporation by more than 10 times relative to MMA. Such a template effect was also observed in other solvents (see the SI). Because the recognition is based on ionic interactions, the template effect would be sensitive to solvent polarity. The concentrations of substrates would also be crucial in the selective

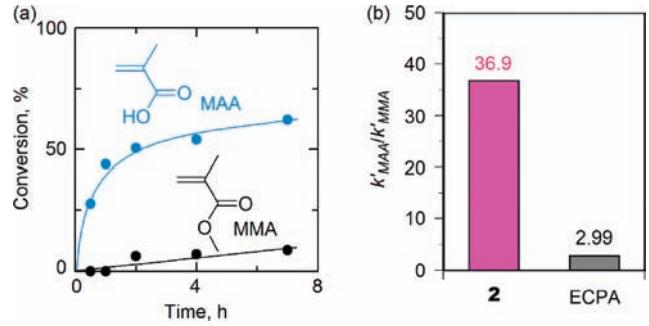

Figure 2. (a) Time−conversion curves using template **2** and (b) comparison of the reaction selectivities determined by kinetic analysis using **2** and ECPA for competitive radical addition between MAA and MMA in toluene at 80 °C: $[MAA]_0 = [MMA]_0 = [$**2** or ECPA$]_0 = 50$ mM; $[RuCl(Ind)(PPh_3)_2]_0 = 4.0$ mM; $[n\text{-}BuNH_2]_0 = 0$ or 50 mM (for ECPA).

addition, where oligomerization might also occur. In fact, additional experiments indicated that less-polar solvents (e.g., toluene) and lower concentrations (<50 mM) facilitate the specific monoaddition.

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

These results for the model addition reactions are now being extended to "template-assisted" polymerizations, by which further control over the repeat-unit sequence will be examined and possibly demonstrated.

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Supporting Information Available: Experimental details, ^{1}H 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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