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COMMUNICATION

Post-Polymerization Modification of Polymethacrylates Enabled by Keto-Enol Tautomerization

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We report a post-polymerization modification strategy to functionalize methacrylic copolymers through enol-ester transesterification. A new monomer, vinyl methacryloxy acetate (VMAc), containing both enol-ester and methacryloyl functionality, was successfully copolymerized with methyl methacrylate (MMA) by selective reversible addition-fragmentation chain transfer (RAFT) polymerization. Post-polymerization modification of pendent enol esters proceeded through an "irreversible" transesterification process, driven by the low nucleophilicity of the tautomerization product, to result in high conversion under mild conditions.

The precise functionalization of macromolecules through mild and efficient means has gained much attention in recent years.[1-3] Click chemistry, for example, allows for covalent incorporation of functional components (e.g., therapeutic compounds, radical initiators, biomacromolecules) into polymeric scaffolds for an array of applications.[4-7] Although not traditionally considered a "click" reaction, transesterification reactions are operationally straightforward and often proceed to high conversion by engaging Le Chatelier's principle. Generally, transesterification reactions require a significant excess of reactant or efficient removal of competitive alcohol byproducts (e.g., methanol, ethanol, ethylene glycol) to achieve high conversion.[8-10] We, as well as others, have previously demonstrated the direct functionalization of acrylic polymers, such as poly(methyl acrylate) (PMA), whereby pendent esters readily undergo transesterification in the presence of functional nucleophiles (Figure 1A).[11-15] Although this method conveniently allows access to an array of functional polyacrylates, the requisite removal of methanol through continuous distillation at high temperatures arguably limits its overall utility and scope. We hypothesized that transesterification of enol ester pendant groups could circumvent the need for byproduct removal, and thus the requirement for high temperatures, by providing a pathway to suppress competitive transesterification (Figure 1B). Specifically, this method relies on the formation of a dormant, non-nucleophilic byproduct (i.e., acetaldehyde) via keto-enol tautomerization of vinyl alcohol to generate functionalized materials through organocatalyzed acyl substitution at room temperature.[16, 17]

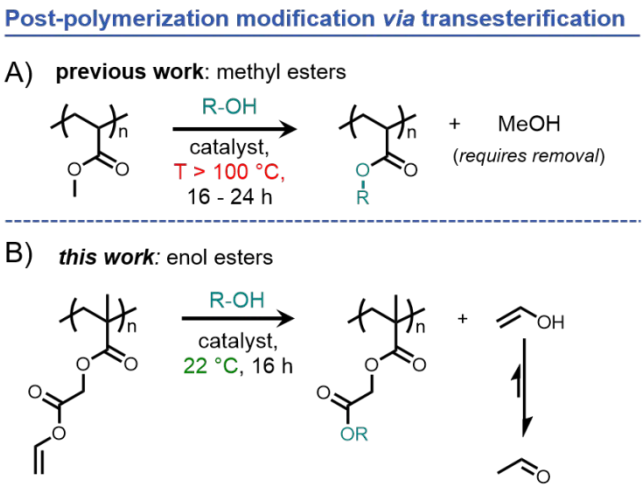

Figure 1. (A) Previous work demonstrating efficient transesterification of poly(methyl acrylate) via removal of methanol at elevated temperature. (B) Proposed method leveraging keto-enol tautomerization to promote side-chain functionalization.

We began our investigation by attempting to prepare acrylic polymers bearing pendent enol esters to be used as substrates for post-polymerization modification. However, the synthesis of enol ester-containing polymers through free-radical polymerization poses a challenge in that enol ester preservation is difficult due to their susceptibility to radical addition. Therefore, we began by studying poly(2-bromoethyl acrylate) (PBEA)[18] as a masked olefin precursor material for enol ester generation. Specifically, we hypothesized post-polymerization dehydrohalogenation of PBEA could afford access to poly(vinyl acrylate); however, this circuitous route resulted in macroscopic gelation, presumably due to base-catalyzed intermolecular enolate alkylation (Figure S2).[19] Poor control over the desired dehydrohalogenation prompted us to

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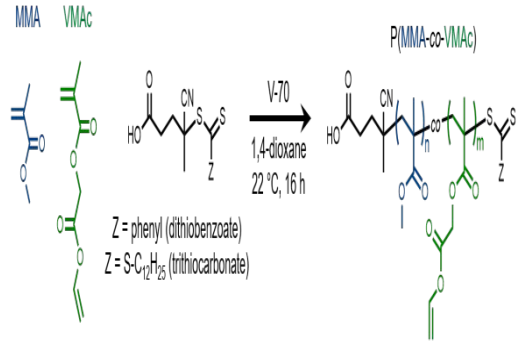


Scheme 1. RAFT copolymerization of methyl methacrylate (MMA) and vinyl methacryloxy acetate (VMAc).

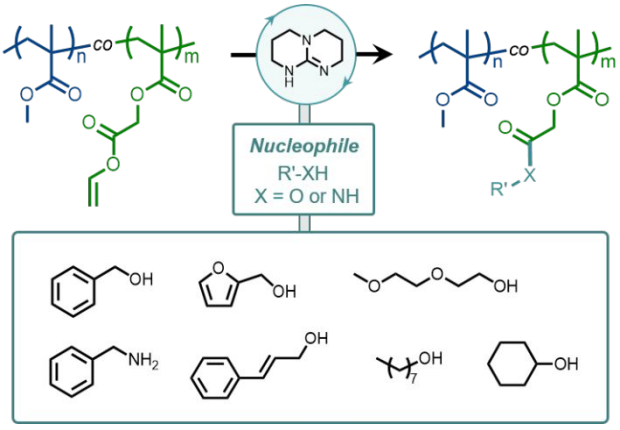
pursue a more direct route to access enol ester-containing polymer substrates. Therefore, we synthesized a new methacrylic monomer, vinyl methacryloxy acetate (VMAc), designed to contain a polymerizable methacryloyl fragment and a sterically unhindered enol ester fragment capable of undergoing post-polymerization organocatalyzed acyl substitution.

Free-radical copolymerization of methyl methacrylate (MMA) and VMAc was achieved through reversible addition-fragmentation chain transfer (RAFT) polymerization (Scheme 1).[20, 21] Wooley and co-workers have successfully demonstrated selective RAFT polymerization of divinyl monomers to prepare well-defined copolymers bearing pendent alkene functionality.[22, 23] We reasoned a similar strategy could be adopted to promote methacrylic homo-propagation in the presence of pendent enol esters. Vinyl acetate (VAc), which mimics the enol ester group of VMAc and is arguably the most well-studied enol ester, is known to exhibit poor copolymerization behavior with a variety of more activated monomers.[24] Importantly, the reactivity ratios between MMA and vinyl acetate (r_{MMA} = 27.8, r_{VAc} = 0.014 at 40 °C)[25] exhibit a temperature dependence whereby an increase in methacrylic homo-propagation is observed at lower reaction temperatures (r_{MMA} = 39, r_{VAc} = 0.001 at 20 °C).[26] Therefore, we chose to conduct RAFT copolymerizations at room temperature to selectively bias the polymerization of VMAc to the methacryloyl fragments while preserving the enol ester functionality necessary for subsequent transformations.

Copolymerizations of MMA and VMAc (1:1 molar ratio of MMA to VMAc) were carried out at room temperature in the presence of 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70). As expected, linear copolymers were obtained after 16 h as evidenced by monomodal GPC chromatograms of purified P(MMA-*co*-VMAc) RAFT copolymers (Figure S3). The use of a dithiobenzoate chain transfer agent resulted in narrower molecular weight distributions as compared to copolymerizations mediated by a trithiocarbonate. Copolymerizations resulting in higher monomer conversions ($p > 0.35$) led to significant branching; therefore, copolymerizations were optimized to produce linear copolymers by quenching the reaction at low monomer conversion. Interestingly, reactions quenched by exposure to atmospheric oxygen resulted in significant branching presumably due to peroxyl radical addition to pendent vinyl esters (Figure S4). However, upon addition of butylated hydroxytoluene (BHT) at the end of the reaction, linear copolymers could be isolated. Additionally, ^{1}H NMR spectroscopy of purified copolymers revealed near-equimolar comonomer composition (Figures S6-S14), agreeing well with initial comonomer feed ratios.

Having prepared well-defined P(MMA-*co*-VMAc) copolymers of suitable molecular weight, we then sought to evaluate these substrates for acyl substitution catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[27, 28] Formation of the activated TBD-amide upon release of vinyl alcohol should facilitate esterification or transamidation with an appropriate *O*- or *N*-nucleophile, respectively. Importantly, base-catalyzed tautomerization of vinyl alcohol to acetaldehyde (K_{enol} = [enol]/[keto] ≈ 3.0 × 10^{-7} at 25 °C)[29] will sufficiently render the byproducts of the substitution to be non-nucleophilic (Figure S5). This ensures the equilibrium will heavily favor formation of the desired functionalized copolymer without the constraint of removing competitive alcohol byproducts.

We examined several functional alcohol and amine nucleophiles to probe the generality of this method (Scheme 2). First, we investigated benzyl alcohol as a model nucleophile



Scheme 2. General scheme for TBD-catalyzed transesterification and amidation of P(MMA-co-VMAc) in the presence of various functional nucleophiles.

(Table 1, entry 1). After 16 h at room temperature, quantitative transesterification was observed (Figure S6) when using TBD (10 mol%) as an organocatalyst. However, when the reaction was performed in the absence of TBD, low conversion was observed (Table 1, entry 2, Figure S7), even at high stoichiometric ratios. The enol ester does not appear sufficiently reactive towards primary alcohols such as benzyl alcohol; however, when benzyl amine was used in the absence of TBD, high conversion (*ca.* 84%) was achieved (Table 1, entry 4, Figure S9). Due to the

Table 1. Summary of organocatalyzed transesterification of P(MMA-co-VMAc) with various functional nucleophiles[a]

Entry	Nucleophile	Equiv.	Solvent	Conv. (%)
1	Benzyl alcohol	1.5	DCM	>95
2[b]	Benzyl alcohol	5.0	DCM	5
3	Benzylamine	1.5	DCM	>95
4[b]	Benzylamine	5.0	DCM	84
5	Cinnamyl alcohol	1.5	DCM	>95
6	Furfuryl alcohol	1.5	DCM	>95
7	Diethylene glycol monomethyl ether	1.5	DCM	>95
8	1-Octanol	1.5	DCM	92
9[c]	Cyclohexanol	1.5	Anisole	39

[a]All reactions were carried out at 22 °C for 16 h in the presence of 10 mol% TBD. [b]No catalyst. [c]Performed at 80 °C.

increased nucleophilicity of *N*-nucleophiles compared to *O*-nucleophiles, sufficient reactivity was observed. Although catalyst-free amidation revealed to be efficient, yet non-quantitative, the addition of TBD (10 mol%) to the reaction facilitated quantitative formation of the amidated copolymer (Table 1, entry 3, Figure S8).

A variety of other primary alcohols were studied, namely cinnamyl alcohol, furfuryl alcohol, and diethylene glycol monomethyl ether (Table 1, entries 5-7, respectively). All examples resulted in quantitative organocatalyzed transesterification at room temperature (Figure S10 – S12). This result is consistent with previous work involving TBD-catalyzed transesterification of PMA.[11] High, yet non-quantitative conversion was observed in the case of 1-octanol (Table 1, entry 8, Figure S13). Functionalization with a secondary alcohol, cyclohexanol, resulted in low conversion even at higher reaction temperatures (Table 1, entry 9, Figure S14) and is likely a result of steric hindrance. This agrees with our previous work detailing TBD-catalyzed polyacrylate substitution.[11] Therefore, it is anticipated the use tertiary alcohols (e.g., tert-butanol) and phenols will be similarly unreactive.

Conclusions

In conclusion, we have developed a method for achieving room temperature transesterification of enol ester-containing polymethacrylates. Room-temperature RAFT copolymerization of MMA and VMAc allowed for the selective consumption of methacrylic vinyl groups and ultimately resulted in well-defined P(MMA-*co*-VMAc) copolymers bearing enol ester functionality. Organocatalyzed transesterification of the synthesized copolymers exhibited high conversion at room temperature due to the formation of dormant acetaldehyde. Given the sufficient reactivity exhibited at low temperatures, we envision this approach could be a useful tool for protein-polymer bioconjugation as well as incorporating other thermally-sensitive functionalities.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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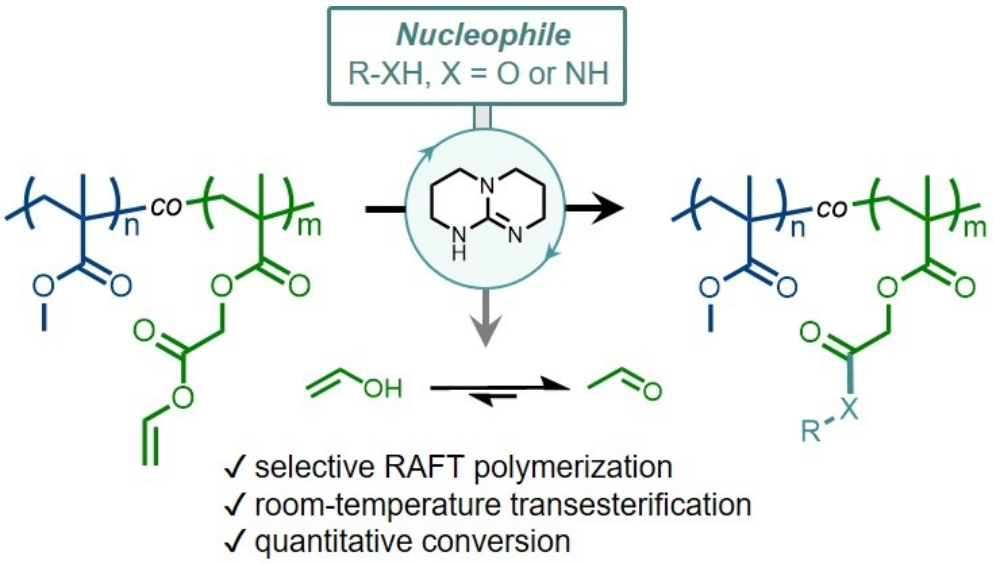

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