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One-Pot Cascade Synthetic Strategy: A Smart Combination of Chemoenzymatic Transesterification and Raft Polymerization

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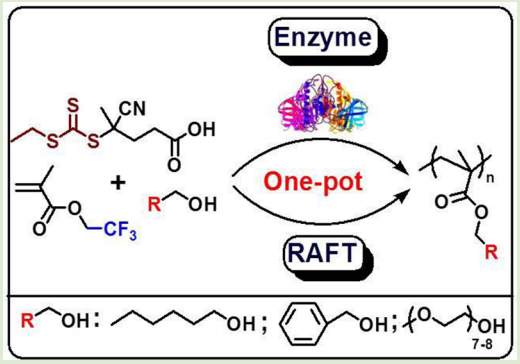
Supporting Information

ABSTRACT: Enzymatic transesterification was combined with RAFT polymerization to develop a new one-pot synthetic method for new polymer synthesis. This method contained in situ monomer transformation reaction between acyl donor monomer and primary alcohols such as hexanol and so on, followed by subsequent RAFT polymerization to get target polymers. The enzymatic reaction and RAFT polymerization tolerated each other and cooperated well to get new polymers with a completely transformed new monomer, high polymer yields, excellent control over the polymerization process, and good enzyme activity maintenance, providing a general and straightforward methodology for new polymer synthesis and modification.



Performing multiple reactions simultaneously or in tandem with polymerization represents new integrated synthetic strategies to achieve polymers with unique properties and functionalities.[1−3] The combination of different (catalytic) reactions into a one-pot system could not only avoid tedious intermediate purification steps, but provide a powerful and exquisite strategy for sophisticated polymer synthesis and modification.[4−8] For example, Kazuhiro Nakatani et al. combined metal alkoxide-catalyzed transesterification with ruthenium-catalyzed living polymerization to efficiently, conveniently produce gradient polymers in one-pot fashion.[9] Guillaume Gody et al. developed a novel one-pot methodology through a combination of polymerization and isocyanate "click" reaction to prepare α-functional polymers rapidly and versatilely.[10] These successful efforts enrich and extend the content of polymer chemistry. Due to the facile, versatile, and powerful features, the one-pot cooperation of polymerization and some compatible organic reactions to achieve polymers with expected functions is attracting more and more attention and becoming an important research topic for the development of polymerization methodology.

Enzymes are regarded as green and efficient catalysts and have been extensively used in organic synthesis.[11−13] Lipases, for instance, have shown great promise for their capability to promote transesterification and condensation reactions in organic solvents on a broad range of substrates.[14,15] Lipases are also great aids to polymer chemistry.[16] For example, lipase B from *Candida antarctica* (CALB) immobilized on acrylic macroporous resin (Novozym435) could efficiently catalyze ring open polymerization (ROP) of cyclic monomers (lactone, carbonates, etc.).[17−22] This enzyme could also catalyze the synthesis of various functional monomers, such as glycomonomers, with remarkable selectivity for the subsequent glycopolymer syntheses.[23−25] However, to get the target glycopolmer through two steps still requires laborious and time-consuming separation and purification of the intermediates. Recently, our group successfully developed a facile one-pot system to prepare new functional polymers by incorporating Novozyme435 catalyzed monomer transformation reaction in an atom transfer radical polymerization (ATRP) system.[26] The enzyme could tolerate the copper-catalyzed living radical polymerization and catalyze the transesterification reaction smoothly. These primary results encourage us to expand the enzymatic reaction with other polymerizations to develop new one-pot methodologies for a functional polymer synthesis.

Reversible addition−fragmentation chain transfer (RAFT) polymerization is a facile and metal-free approach to prepare well-defined polymers with desired molecular weights, architectures, and narrow polydispersity indices (PDIs).[27−31] RAFT can be carried out in a large range of solvents and is suitable for various monomers. Due to its excellent tolerance to many functional groups, such as hydroxyl, amide, and carboxyl groups, RAFT has been regarded as a powerful tool to facilely prepare different functional polymers.[32−38] The combination of RAFT and enzymatic ROP has been carried out by Kristofer Thurecht et al. to yield block copolymers through single or two steps, revealing the possible compatibility of RAFT and enzymatic reactions.[39]

Herein, we reported a straightforward one-pot cascade synthetic strategy through the combination of in situ enzymatic

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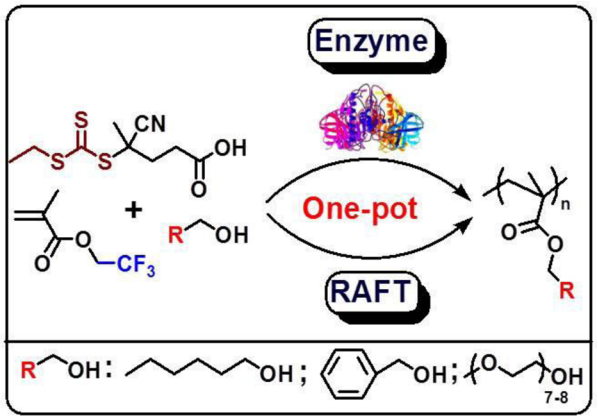
monomer transformation and RAFT polymerization. Novozym435 catalyzed the transesterification between acyl donor monomer 2,2,2-trifluoethyl methacrylate (TFEMA) and primary alcohols (ROH) to form target monomer R (meth)-acrylate (RMA). The thereby generated new monomers RMA subsequently participated in RAFT polymerization to obtain a new polymer with transformed side groups. The applied synthetic strategy in current report was schematically illustrated in Scheme 1.

Scheme 1. One-Pot Cascade Strategy Combining Chemoenzymatic Transesterification and RAFT Polymerization



According to our previous study, TFEMA was selected as the acyl donor monomer due to its much higher reactivity to react with alcohols compared with other (meth)acrylates such as methyl methacrylate (MMA). We selected hexanol as the model alcohol substrate for the next detailed illustration of this one-pot cascade synthesis. 4-Cyano-4-(ethylthiocarbonothioylthio) pentanoic acid and 2,2′-azobisisoheptonitrile (ABVN) were used as the chain transfer agent (CTA) and initiator, respectively. Meanwhile, triethylamine (TEA) has been found to promote the polymerization (Figure S1a,b), thus, an equivalent amount of TEA was also added into the reaction system. Typically, TFEMA, hexanol, TEA, and Novozym435 together with CTA and initiator were added in the reaction system. The reaction was performed at 55 °C in toluene. A detailed kinetics study was conducted and Figure 1a shows the kinetics of the cascade reactions combining RAFT polymerization and in situ enzymatic monomer transformation.

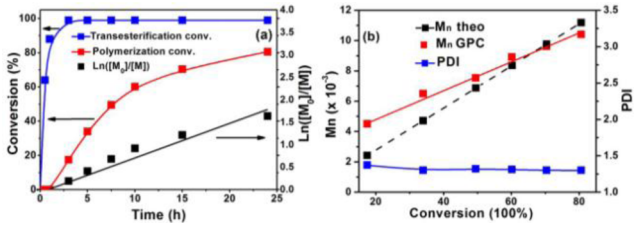


Figure 1. Kinetics study of one-pot cascade synthesis: (a) conversion and the kinetic curve vs reaction time; (b) experimental molecular weights (measured by GPC), theoretical molecular weight (calculated by polymerization conversion), and PDI vs monomer conversions. Novozym435 = 0.50 g; [CTA] = 12.0 mM; [ABVN] = 4.0 mM; $[TFEMA]_0$ = 0.9 M; $[Hexanol]_0$ = 0.9 M; [TEA] = 0.9 M in 6.5 mL of toluene at 55 °C.

In the first hour, the transesterification of TFEMA with hexanol proceeded quickly and approximately 90% of TFEMA were converted into new monomer hexyl methacrylate (HMA). However, an approximate 1 h induction period was observed in the RAFT process and no polymer formed during this time, although CTA and initiator also existed in the reaction mixture (Figure 1a). The possible reason for the induction period is attributed to the residual oxygen. RAFT process could thus be regarded as a dormant state during the induction period, and only enzymatic monomer transformation proceeded in the system.

After the one hour induction period, the transesterification was almost completed and nearly all monomers existing in the reaction mixture were newly generated HMA (Figure S2). Meanwhile, the RAFT process revived from dormant state and triggered the polymerization. The RAFT polymerization of HMA exhibited a linear pseudo-first-order kinetic plot versus time (Figure 1a); the molecular weights increased linearly with monomer conversions and all the polymers during polymerization remained narrow molecular weight distribution (PDI ~ 1.30; Figure 1b), indicative of a controllable RAFT process. According to the kinetics study, this one-pot combination of enzymatic transesterification and RAFT represents a cascade process in which in situ monomer transformation occurs first followed by subsequent RAFT polymerization of a new generated monomer to get a new target polymer.

A model reaction between CTA and hexanol was conducted to test whether CTA could maintain its integrity in the presence of Novozym 435 and hexanol. According to the ^{1}H NMR analyses, the existence of Novozym435 seemed to have no effect on the trithiolcarbonate agent (Figure S3). Thus, the CTA could still control the polymerization. With time increasing, the monomer conversion reached up to 84% after 24 h, and the GPC curves shifted to higher molecular weight positions (Figure 2a). After purification, the composition of the

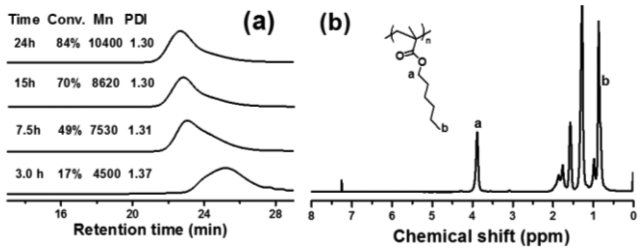


Figure 2. GPC curves of polymers during cascade RAFT polymerization (a); ^{1}H NMR spectrum (in $CDCl_3$) of the obtained polymer (b).

obtained polymer was analyzed by ^{1}H NMR, with the peak corresponding to the methylene protons of the ester group in HMA appearing clearly at 3.95 ppm (Figure 2b), no characteristic TFEMA peak was observed in the ^{1}H NMR spectrum (4.30 ppm, see Figure S1c), suggesting only a homopolymer poly(HMA) was obtained through the one-pot cascade reactions.

The utilized enzyme, Novozym435, is immobilized CALB on acrylic macroporous resin, which can be easily separated after polymerization through centrifugation or filtration. Moreover, the enzyme can be operated at an elevated temperature without significant activity loss.[40] In the current work, the retained enzyme activity was also tested through the enzymatic transesterification between 4-nitrophenyl acetate (4-NPA)

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and methanol.[41] As shown in Table 1 (No. 1), the enzyme maintained most activity (~81%) after RAFT polymerization,

Table 1. One-Pot Cascade Synthesis via RAFT Polymerization and In Situ Monomer Transformation[a]

No.	alcohol	poly conv.[b] (%)	trans conv.[b] (%)	M_n[c]	PDI[c]	retained enzyme activity[d] (%)
1	hexanol	84	100	12200	1.24	81 ± 8
2	BzOH	75	100	9700	1.30	83 ± 9
3	mPEG$_{350}$	71	100	6780	1.10	85 ± 9

[a]Novozym435 = 0.50 g; [CTA] = 12 mM; [ABVN] = 4 mM; $[TFEMA]_0$ = 0.9 M; $[Hexanol]_0$ = 0.9 M; [TEA] = 0.9 M in 6.5 mL of toluene at 55 °C, 24 h. [b]Calculated by ^{1}H NMR. [c]Determined by GPC. [d]Determined by enzymatic hydrolytic activity of 4-NPA.

which is desirable for the possible recycle use of this biocatalyst. The easy separation and excellent enzyme activity maintenance provide additional advantages to the chemoenzymatic cascade synthesis for future large-scale manufacture.

Taking the excellent results into account, we believed that the one-pot chemoenzymatic cascade synthesis combining RAFT polymerization and enzymatic transformation might be a general methodology for polymer synthesis via in situ monomer transformation. To test that, we used two other primary alcohols, benzyl alcohol (BzOH) and poly (ethylene glycol) methyl ether (molecular weight ~ 350, mPEG$_{350}$), respectively, as substrates for enzymatic transesterification to generate new monomers (Table 1, Nos. 2 and 3). Similarly, the in situ transesterification and RAFT polymerization cooperated well with these two alcohols. The monomer transformation occurred with high yield (~100%), and the polymers were obtained with high polymerized monomer conversions (>70%) and narrow molecular weight distributions (PDI ≤ 1.30). Meanwhile, the purified polymers were also almost homopolymers of transformed new monomers according to the ^{1}H NMR analyses (Figure 3). Furthermore, the enzyme retained excellent activity in both cases (>80%, Table 1, Nos. 2 and 3). All these data suggested the combination of enzymatic monomer transformation reaction and RAFT is a general methodology for new polymer synthesis.

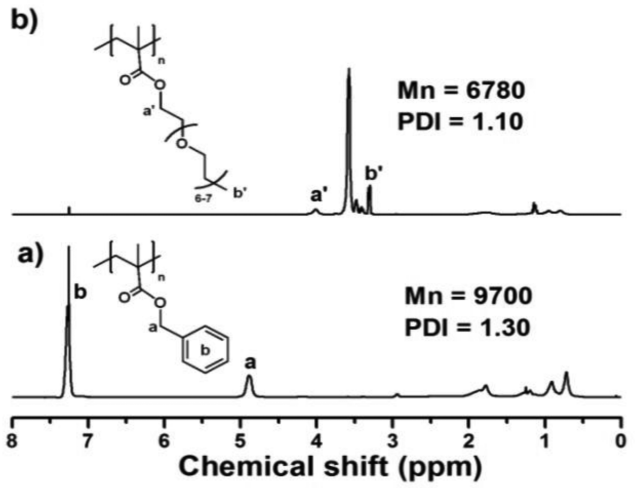

Figure 3. ^{1}H NMR spectra ($CDCl_3$) of (a) poly(BzMA) and (b) poly(mPEG$_{350}$MA).

In conclusion, a novel one-pot cascade reaction system combining RAFT polymerization and enzymatic transformation has been developed by the combination of RAFT and enzymatic transesterification between TFEMA and primary alcohols. This new synthetic strategy involves a tandem process that contains an in situ monomer transformation followed by subsequent RAFT polymerization. The two reaction systems cooperate well with complete monomer transformation efficiency, high yield of polymers, excellent control over polymerization, and good enzyme activity maintenance. Moreover, the one-pot cascade synthesis is a general method, suited to various primary alcohol substrates. Considering the facile and versatile feature, this synthetic strategy provides an alternative choice for polymerization methodology and might have potential application for sophisticated polymer synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, ^{1}H NMR spectrum during polymerization, ^{1}H NMR of model reaction product of Novozym435, CTA, and hexanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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