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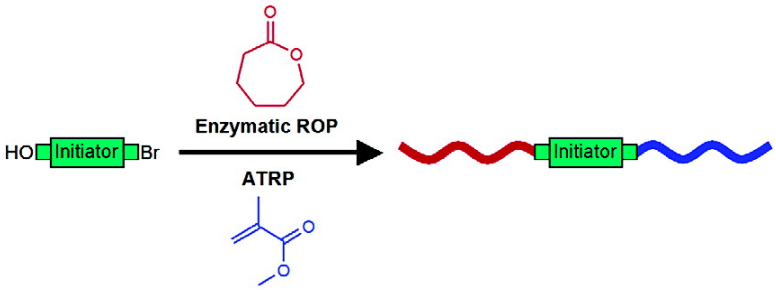

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Can Block Copolymers Be Synthesized by a Single-Step Chemoenzymatic Route in Supercritical Carbon Dioxide?

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We report for the first time a simple strategy for a single-step, simultaneous, one-pot synthesis of block copolymers by combining the enzymatic ring-opening polymerization (ROP) of ϵ-caprolactone (ϵ-CL) with the atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA). The success of the process can be attributed to the use of supercritical carbon dioxide ($scCO_2$). We demonstrate that both enzyme- and metal-based ATRP catalysts function concurrently in $scCO_2$. Use of ϵ-CL as a cosolvent allows the ATRP-catalyzed growth of the PMMA block to proceed with good control, despite the fact that the ϵ-CL cosolvent is being consumed by the enzymatic ROP.

The combination of two different living polymerization strategies in one pot (i.e., ATRP and conventional metal catalyzed ROP) has been reported using conventional solvents.[1] Others have shown sequential two-step syntheses combining enzyme and ATRP catalysts.[2] However, the results were not as successful when the polymerizations were attempted simultaneously in conventional solvents.[3]

Enzymes are used as catalysts in a wide variety of reactions because they can be highly active and selective, while also being more environmentally acceptable than some conventional catalysts.[4] There has been a great deal of interest in the use of enzymes to mediate polymerizations.[5,6] In particular, lipases have been found to be effective in ROPs.[7] Recently, there have been concerted efforts to increase the versatility of enzymes to produce block copolymers. A combination of enzymatic polymerization with an alternative polymerization method can allow the stepwise formation of block copolymers of very different monomers by use of a central bifunctional initiator.[2]

Supercritical fluids are environmentally acceptable replacements for organic solvents. $scCO_2$ has been widely studied because it is inexpensive, inert, nontoxic, and nonflammable, and because its critical parameters are easily accessible ($T_c = 31.0$ °C, $p_c = 7.38$ MPa).[8] While $scCO_2$ has been demonstrated to be a suitable solvent for some enzyme-catalyzed reactions[9] and chemically catalyzed polymerizations,[10,11] very little work has been carried out combining the environmentally friendly nature of enzymes and $scCO_2$ for use in polymerizations.[12−14] Our strategy toward the simultaneous one-pot synthesis is outlined in Scheme 1 (route 1). The reactions were carried out in $scCO_2$ at 35 °C, 1500 psi (10.3 MPa) using MMA (1.5 mL) and ϵ-CL (5 mL). An immobilized enzyme catalyst (Novozym-435) was used for the ROP. However, the key to success is to ensure that the ATRP process remains homogeneous in $scCO_2$. This is not normally the case (vide infra), but here we find that ϵ-CL acts as a very effective cosolvent, while also supplying the monomer for consumption by the enzymatic polymerization. The use of ϵ-CL as the solvent for ATRP reactions has been reported previously.[15] Intriguingly, in our work, control over the ATRP reaction was preserved, despite the consumption of the ϵ-CL cosolvent as it polymerized to form the second block (Table 1). A key advantage of the use of $scCO_2$ is that the ATRP can occur in the $scCO_2$ plasticized PCL that is formed, as well as in the ϵ-CL monomer/$scCO_2$ solution. The two catalysts do not appear to have any adverse effect on each other; both PCL and PMMA peaks were clearly observed in the ^{1}H NMR spectrum of the product. From the NMR analysis, the block copolymers were found to be approximately 15 mol % PMMA. GPC analyses showed polydispersities very similar to those of the block copolymers produced using the consecutive two-step methods (Scheme 1, routes 2 and 3, vide infra). To demonstrate block copolymer formation, the product was hydrolyzed. GPC analysis of the product clearly shows a shift to lower molecular weight, implying the removal of the PCL from the block copolymer (Figure 1). Additionally, ^{1}H NMR shows definitively the disappearance of the PCL from the product, leaving just the PMMA block of the copolymer. Further data from DSC, MALDI-TOF, and electrospray mass spectrometry also suggest a PCL-*b*-PMMA structure. In addition, analysis by GPC and DSC confirmed that levels of homopolymer were less than 10 wt %.

Control of the molecular weights of the constituent blocks can also easily be achieved in situ. The molecular weights of the PMMA and PCL blocks both increase with time, demonstrating that the two polymerizations occur simultaneously. Reducing the amount of ATRP catalyst (Table 1, entry 4) reduced the length of the PMMA block. Similarly, reducing the level of enzyme catalyst (entry 5) reduced the size of the PCL block produced.

To investigate the simultaneous single-step polymerization, the constituent polymerization steps have been studied in isolation (Scheme 1, routes 2 and 3). Enzymatic ROP of ϵ-CL, initiated from the hydroxyl group of the initiator, was carried out in $scCO_2$ (35 °C, 1500 psi (10.3 MPa)) using identical reaction conditions but without addition of the ATRP catalysts (20 h, $M_w = 28\,000$, PDI $= 1.6$). ^{1}H NMR demonstrated that the initiator was indeed bound to the PCL.

The ATRP step was also performed in $scCO_2$ as an isolated reaction, under identical conditions using the bromine group of the same bifunctional initiator, but in the absence of enzyme. There is only one previous report of ATRP in $scCO_2$, the focus of which was the use of fluorinated reagents to produce homogeneous, controlled reactions.[16] Here, we demonstrate that ϵ-CL (the comonomer) is a suitable cosolvent for the ATRP step in $scCO_2$. Our strategy takes advantage of the fact that both ϵ-CL and MMA are miscible with liquid and $scCO_2$. View cell measurements demonstrated the homogeneity of the reaction system throughout the duration of the experiment, with no visible precipitation. Exhaustive studies demonstrated that the ATRP reaction could proceed effectively at 35 °C in a CO_2/ϵ-CL mixture (30 vol % ϵ-CL)

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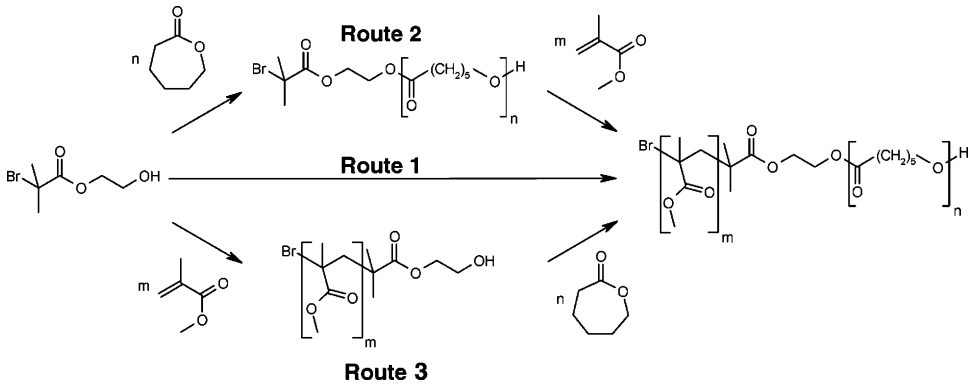
Scheme 1. Synthetic Routes To Form PCL-*b*-PMMA from a Bifunctional Initiator[a]



[a] Route 1, simultaneous, single-step polymerization combining ATRP of MMA and ROP of ϵ-CL. Two-step routes: Route 2, the ROP of ϵ-CL followed by the ATRP of MMA. Route 3, the ATRP of MMA followed by the ROP of ϵ-CL.

Table 1. Simultaneous One-Pot Block Copolymerizations of MMA and ϵ-CL[a]

			block copolymer[c]		hydrolyzed[c]	
entry	time (h)	% yield[b]	M_w	PDI	M_w	PDI
1	4	39	9400	1.28	3900	1.14
2	12	46	23000	1.26	5400	1.08
3	20	60	41000	2.11	10000	1.07
4[d]	20	58	24000	1.47	4100	1.13
5[e]	20	30	23000	1.20	8400	1.12

[a] Reactions performed with 0.4 g of Novozym-435, 0.22 mmol CuBr, and 0.45 mmol 2,2′-bipyridine unless otherwise stated. [b] Polymerization yield determined gravimetrically. [c] Molecular weight determined by GPC, against polystyrene standards. [d] Reaction carried out using half the amount of CuBr (0.11 mmol) and 2,2′-bipyridine (0.23 mmol). [e] Reaction carried out using half the amount of enzyme (0.2 g).

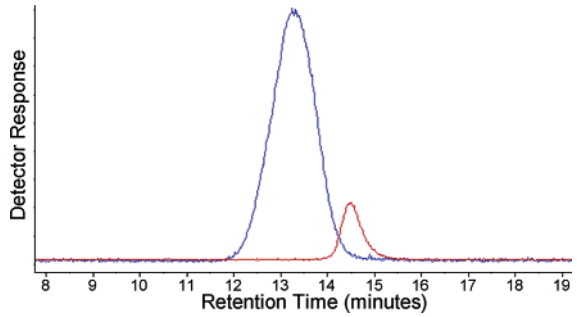


Figure 1. GPC traces for the block copolymer (entry 2) before (blue) and after (red) hydrolysis of the PCL block. Concentration of the hydrolyzed sample is approximately 10 mol % relative to that of the block copolymer.

using nonfluorinated catalysts and MMA monomer (20 h, M_w = 7200, PDI = 1.04). GPC data show molecular weight control with time, although the molecular weight of the PMMA product was found to be greater than the theoretical value. The polydispersity (PDI) was very narrow (typically 1.05−1.10), even before precipitating the polymer from solution. As expected, in the absence of initiator, there was a negligible yield of PMMA. In the absence of ϵ-CL cosolvent, PMMA rapidly precipitated from the $scCO_2$ solution, leading to a complete loss of control. GPC analysis showed a very broad, asymmetric molecular weight distribution. Detailed results from these experiments will be discussed in a future publication.

After carrying out the second steps (Scheme 1, routes 2 and 3), both PMMA and PCL were found to be present (^{1}H NMR analysis). GPC analysis showed that the molecular weights of the macroinitiators had increased. As with the simultaneous samples (route 1) the block copolymer structure was further confirmed by hydrolysis. In addition, no evidence for initiator transesterification was seen, which would lead to significant levels of homopolymer.

We have demonstrated that a simultaneous one-pot combination of enzymatic and chemical polymerization systems in $scCO_2$ leads to controlled synthesis of block copolymers. Moreover, the data clearly show that the two catalyst systems are robust under these conditions and can tolerate each other. We believe that this methodology can be extended to provide a very simple route to a wide range of block copolymers incorporating monomers with very different physical and chemical properties.

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