Synthesis of Semifluorinated Block Copolymers Containing Poly(ϵ-caprolactone) by the Combination of ATRP and Enzymatic ROP in $scCO_2$

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ABSTRACT: The synthesis of novel diblock copolymers consisting of a semifluorinated block of poly(1*H*,1*H*,2*H*,2*H*-perfluorooctyl methacrylate) (PFOMA) and a hydrocarbon block of polycaprolactone (PFOMA-*b*-PCL) was achieved by the combination of enzymatic ring-opening polymerization (eROP) and atom transfer radical polymerization (ATRP). The chemoenzymatic synthesis of diblock copolymers from a bifunctional initiator in two consecutive steps was investigated. A polycaprolactone (PCL) macroinitiator was obtained via enzymatic ring-opening polymerization initiated by the bifunctional initiator. A PFOMA block was then grown from this PCL macroinitiator. In addition, block copolymers were successfully prepared by a two-step−one-pot synthesis using a sequential monomer addition technique.

Introduction

Semifluorinated block and graft copolymers are of growing interest because of their unique properties, such as chemical inertness, solvent and high-temperature resistance, and low surface tension, that in principle may be transferred to other polymeric materials by copolymerization. The copolymerization of a fluorinated monomer with a nonfluorinated monomer usually leads to a random copolymer that exhibits properties intermediate between those of the parent homopolymers. Indeed, such materials led themselves to many applications, for example as CO_2-philic surfactants in supercritical carbon dioxide ($scCO_2$).[1] Several attempts have been reported to prepare semifluorinated copolymers by means of cationic,[2] anionic,[3] living radical,[4] and group transfer polymerization,[5] but few studies have addressed the synthesis of block copolymers composed of a hydrophilic block and a semifluorinated block. To date, the synthesis and properties of various types of fluorine-containing polymers have been reported,[6] for example, fluorinated homopolymers, where fluorine is included in the main chain, terminal chain, or side chain, and fluorinated diblock copolymers. Fluorinated homopolymers are solvophobic in many cases, whereas the presence of a solvophilic nonfluorinated polymer block increases solubility. This often leads to polymers that behave in an amphiphilic nature. The possibility of modifying some characteristics of polymeric materials by the addition of fluorine-containing monomers or by the combination of monomers with different bulk properties represents a goal of increasing importance.

Enzymatic catalysis has become an important factor in industrial synthesis since processes can be carried out under mild conditions and often result in high enantio-, regio-, and chemoselectivity. Enzymes are also often able to replace heavy metal catalysts and in some cases reduce the use of organic solvents.[7] In polymer chemistry, enzymes have a number of advantages over traditional catalysts: polymerizations can be conducted under mild conditions, immobilized enzyme can easily be removed from the reaction mixture, and most importantly enzymes are biocompatible catalysts.[8] However, polymer chemistry requires the development of compatible chemo- and biocatalytic methods. Recently, the combination of ATRP and conventional metal-catalyzed ROP has been successfully demonstrated in conventional solvents.[9] It has also been shown that a sequential two-step synthesis combining enzyme and ATRP catalysis can be achieved successfully.[10]

Recently, the use of $scCO_2$ as a polymerization medium has attracted considerable interest. In addition to being an environmentally "green" solvent, replacing volatile organic and aqueous solvents, $scCO_2$ offers several advantages as a reaction medium; e.g., it has a low viscosity, it is inert to free radicals, it has no detectable chain transfer to solvent, and its solvent strength can be finely tuned.[11]

Enzymes have been used as catalysts for organic reactions in $scCO_2$, thus demonstrating that they can function effectively under supercritical conditions.[12] A number of studies have been carried out in this field. The combination of $scCO_2$- and enzyme-catalyzed polymerization opens up a promising new area of research. Only a few publications report the combination of environmentally friendly nature of enzymes and $scCO_2$ for use in polymerizations.[13−15] In previous work, we reported the enzyme-catalyzed ring-opening polymerization (eROP) of ϵ-caprolactone (ϵ-CL) in $scCO_2$ and a simple strategy for the synthesis of block copolymers by combining the eROP of ϵ-CL with the atom transfer radical polymerization (ATRP) of methyl methacrylate (MMA) in $scCO_2$. It was demonstrated that the enzymatic polymerization and the ATRP proceeded concurrently, and better results were obtained in $scCO_2$ than in conventional solvents.[16]

Comb-shaped copolymers synthesized from polycaprolactone macromonomers combined with a perfluorinated acrylate have been shown to self-assemble at surfaces and interfaces.[17] The PCL macromonomers were synthesized by initiating ring-

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Scheme 1. Two-Step Chemoenzymatic Polymerization of PFOMA-*b*-PCL Block Copolymer

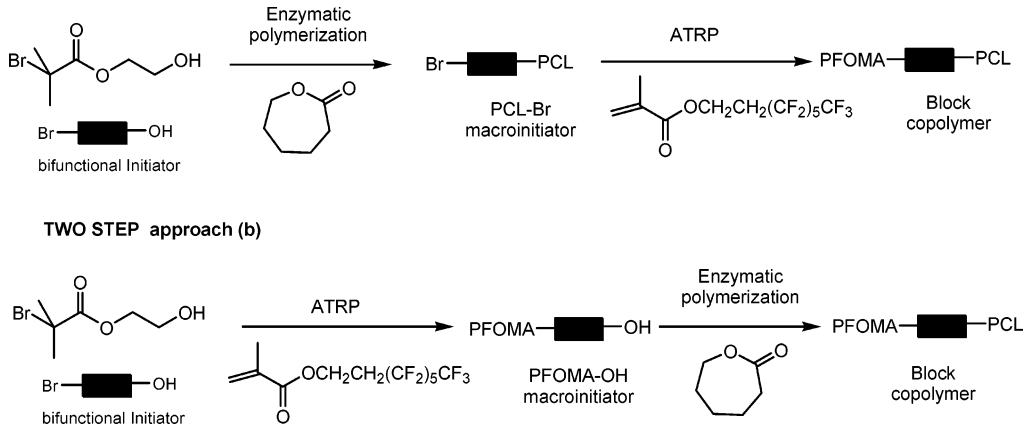

Table 1. Results for the ATRP of FOMA in $scCO_2$ Using ϵ-Caprolactone as a Cosolvent

entry	solvent[a]	% conv[b]	% yield[c]	$M_{n,cal}$[d] (kDa)	$M_{n,NMR}$[e] (kDa)	$M_{n,GPC}$ ELS (kDa)	PDI ELS	$M_{n,GPC}$ DRI (kDa)	PDI DRI
1	CO_2/CL	40	30	9.6	N/A[f]	7.0	1.03	4.0	1.23
2	CO_2/CL	35	30	9.2	12	8.6	1.04	5.0	1.11
3	CO_2/CL	55	48	8.4	15	5.0[g]	1.01	5.9	1.08
4	CO_2	0	0						

[a] All polymerizations were carried out at 45 °C and at 1500−1700 psi (10.3−11.7 MPa). Two different initiators were used: monofunctional initiator (ethyl 2-bromoisobutyrate) (entry 1) or bifunctional initiator (entries 2−4). [b] Conversion was obtained by NMR from the ratio between the olefinic $(CH_3)C{=}CH_2$ proton (5.60 or 6.14 ppm) for FOMA monomer and the methylene 1,1-dihydro protons $O{-}CH_2CH_2{-}CF_2$ (4.29 ppm) for PFOMA. [c] Yield was obtained gravimetrically from the dried polymer after purification. [d] Theoretical M_n was calculated according to the equation M_n = [FOMA]/[I] × MW(FOMA) × conv + MW(I). [e] $M_{n,NMR}$ determined by ^{1}H NMR by taking the ratio of the 1,1-dihydro protons $O{-}CH_2CH_2{-}CF_2$ at 4.29 ppm in the fluoroalkyl group to the methylene protons (3.85 ppm) in the bifunctional initiator. [f] End group not detectable by NMR. [g] M_n = 5.4 kDa obtained by a HFIP TripleSec system using hexafluoro-2-propanol as a solvent.

opening polymerization of ϵ-caprolactone with 2-hydroxyethyl methacrylate. This resulted in a polyester capable of free-radical polymerization, allowing copolymerization with a heptadecafluorodecyl acrylate to yield graft copolymers.

In this paper, we extend the $scCO_2$ methodology to the synthesis of novel diblock copolymers consisting of a semifluorinated block of poly(1*H*,1*H*,2*H*,2*H*-perfluorooctyl methacrylate) and a hydrocarbon block of polycaprolactone (PFOMA-*b*-PCL) by the combination of e-ROP and ATRP (Scheme 1). We describe the optimization of the ATRP of fluorinated monomers and the synthesis of block copolymers. The synthesis of amphiphilic copolymers based on caprolactone units and fluorinated moieties is attractive to prepare polymers potentially useful in biomedical applications or with the potential to be used as emulsifiers and surfactants in $scCO_2$.[18]

Experimental Section

Materials. ϵ-Caprolactone (ϵ-CL, 99%) was purchased from Aldrich, dried over CaH_2 for 24 h under nitrogen, distilled under reduced pressure with three freeze, pump, thaw cycles, and stored under nitrogen until use. 1*H*,1*H*,2*H*,2*H*-Perfluorooctyl methacrylate (FOMA, 95%) was obtained from Fluorochem and purified by passing through an alumina column.

2,2′-Bipyridine (bpy, 99+%) was purchased from Lancaster, copper(I) bromide (98%) was purchased from Aldrich, and 1,4-dioxane was purchased from Fisher and used as received. Novozym-435 (10 wt % Lipase B from *Candida antarctica* on a macroporous acrylic resin) was purchased from Novozymes. 1,1,2-Trichloro-1,2,2-trifluoroethane (Freon-113) was purchased from Aldrich. Molecular sieves (3 Å) were dried in an oven at 400 °C prior to use. SFC grade carbon dioxide (99.99%) was purchased from BOC gases. The bifunctional initiator was synthesized as described elsewhere.[19] The high-pressure reactions were conducted in a 12.5 mL volume clamp seal autoclave, equipped with a magnetic stirrer bar. The autoclave was placed on a hot plate stirrer to allow the reaction to be stirred.[16,20,21]

General Procedure for the ATRP of FOMA Using ϵ-CL as a Cosolvent in $scCO_2$ (Entry 3, Table 1). The reactor was charged with copper(I) bromide (30 mg, 0.20 mmol) and bpy (62 mg, 0.40 mmol). It was then purged with a flow of CO_2 for 5 min. Degassed FOMA (3 mL, 10 mmol), ϵ-CL (7 mL, 63 mmol), and the bifunctional initiator (36 μL, 0.26 mmol) were added to the autoclave using a syringe under a flow of CO_2 to prevent the ingress of any moisture into the system. The autoclave was sealed and heated to the required temperature, and the pressure of CO_2 increased to the desired level (1800 psi (12.4 MPa)). Agitation was achieved via a magnetic stirrer bar placed inside the body of the autoclave. The reaction was terminated at 24 h by placing the vessel into a dry ice/acetone bath to freeze the contents. Once the pressure had fallen to atmospheric pressure, the autoclave was opened and the solid CO_2 was allowed to sublime from the polymer product. The polymeric material in the autoclave was dissolved in a mixture of chloroform and Freon-113 and passed through an alumina column to remove the Cu catalyst. The polymer was separated from the resulting mixture by precipitation in cold methanol.

Synthesis of the PCL-Br Macroinitiator. The PCL-Br macroinitiator was synthesized by enzyme-catalyzed ring-opening polymerization catalyzed by Novozym-435. The polymerizations were carried out in two different reaction media: $scCO_2$ (yielding PCL-Br 2) and in bulk using glassware (yielding PCL-Br 1).

Preparation of PCL-Br 2 by eROP of ϵ-CL in $scCO_2$ (Entry 2, Table 2). The reactor was charged with Novozym-435 (400 mg), after which the autoclave was sealed and heated to 35 °C while under vacuum for 2 h in order to dry the enzyme beads. After 2 h, the vacuum was released by filling the autoclave with low-pressure CO_2. ϵ-CL (5 mL, 45 mmol) and bifunctional initiator (66 μL, 48 mmol) were then added to the autoclave by syringe, under a flow of CO_2, to prevent the ingress of moisture into the system. After all the liquid reagents had been added, the autoclave was sealed, the stirring started, and the pressure of CO_2 increased to 1500 psi (10.3 MPa). After 16 h reaction, the autoclave was placed into a dry ice/acetone bath to freeze the contents. Once the pressure had fallen to atmospheric pressure, the autoclave was opened, and the whole mixture in the autoclave was dissolved in chloroform and

Table 2. Conditions and Results of the Synthesis of Diblock Copolymers

entry	ratio[d] PFOMA/PCL	conv (%)[e]	yield (%)[f]	$M_{n,theo}$[g] (kDa)	$M_{n,NMR}$[h] (kDa)	$M_{n,GPC}$ ELS (kDa)	PDI ELS	$M_{n,GPC}$ DRI (kDa)	PDI DRI	$M_{n,GPC}$ HFIP (kDa)	PDI HFIP
1 PCL-Br 1		100	70		20	21.5	1.39	20.0	1.47		
2 PCL-Br 2		63	40		14.2	15.5	1.29	14.0	1.51		
3[a]	12/88	50	30	26.5	N/A	18.0	1.21	15.3	1.49		
entry 3 after hydrolysis			15		8.6	3.0	1.09	6.1	1.08		
4[b]	45/55	70	57	82.9	N/A	30.4	1.24	33.2	1.26	17.8	1.87
entry 4 after hydrolysis			N/A		N/A	4.9	1.08	7.5	1.18		
5[a]	38/62	54	32	51.7	N/A	19.9	1.26	20.3	1.42	17.1	1.92
entry 5 after hydrolysis			54		8.6	3.9	1.03	5.6	1.06	11.3	2.26
6[c]	20/80		37		N/A	13.0	1.39	15.8	1.51	8.08	3.08
entry 6 after hydrolysis			N/A		10.8	4.6	1.04	5.4	1.16	5.01	2.27

[a] Polymerization carried out at 40 °C at 1700 psi (11.7 MPa) using PCL-Br 2 as a macroinitiator. [b] Polymerization carried out at 40 °C at 1700 psi (11.7 MPa) using PCL-Br 1 as a macroinitiator. [c] Two-step−one-pot polymerization. [d] Ratio PFOMA/PCL in the block copolymer calculated by NMR. [e] Conversion calculated from NMR. [f] Yield was obtained gravimetrically after purification from the dried polymer. [g] Theoretical M_n according to the equation M_n = [FOMA]/[macroinitiator] × MW(FOMA) × conv + MW(macroinitiator). [h] $M_{n,NMR}$ determined by ^{1}H NMR, by taking the ratio of the methylene protons O−*CH*$_2$(CH$_2$)$_3$−CH$_2$−CO at 4.15 ppm in PCL block and the methylene protons at 4.20 ppm in the bifunctional initiator for PCL-Br macroinitiator (entries 1 and 2) and by taking the ratio of the 1,1-dihydro protons O−*CH*$_2$CH$_2$−CF$_2$ at 4.29 ppm in the fluoroalkyl group to the methylene protons (3.85 ppm) in the bifunctional initiator.

the Novozym-435 removed by filtration. The polymer was precipitated from cold methanol and dried overnight under vacuum at 50 °C. Yield = 40%.

Preparation of PCL-Br 1 by eROP of ϵ-CL in Bulk (Entry 1, Table 2). Novozym-435 (550 mg) and molecular sieves (3 Å) were added to a flask, which was previously dried in the oven at 100 °C for 24 h. The mixture was exposed to vacuum for 2 h at 60 °C in order to dry the enzyme beads, after which ϵ-CL (6.8 mL, 62 mmol) and the bifunctional initiator (140 μL, 1.02 mmol) were added separately to the flask by syringe. The reaction was terminated after 15 h, and the reaction mixture was dissolved in chloroform and the Novozym-435 removed by filtration. The polymer was precipitated from cold methanol and dried overnight under vacuum at 50 °C. Yield = 70%.

General Procedure for the ATRP of FOMA with PCL-Br Macroinitiator (Entry 3, Table 2). The reactor was charged with PCL-Br macroinitiator (500 mg), copper(I) bromide (32 mg, 0.22 mmol), and bpy (70 mg, 0.45 mmol), and the autoclave was sealed and heated to 35 °C while under vacuum for 2 h. After 2 h, the vacuum was released by filling the autoclave with low-pressure CO_2. ϵ-CL (5 mL, 45 mmol) and FOMA (1.5 mL, 5.2 mmol) were then added to the autoclave by syringe, under a flow of CO_2, to prevent the ingress of moisture into the system. After all the liquid reagents had been added, the autoclave was sealed and heated at 45 °C, the stirring started, and the pressure of CO_2 increased to 1500 psi (10.3 MPa). After 20 h of reaction, the autoclave was placed into a dry ice/acetone bath to freeze the contents. Once the pressure had fallen to atmospheric, the autoclave was opened, and the contents of the vessel were dissolved in a mixture of chloroform and Freon-113. The resulting solution was passed through an alumina column to remove the catalyst, and the polymer was precipitated from cold methanol.

General Procedure for the Two-Step−One-Pot Copolymerization (Entry 6, Table 2). The reactor was charged with Novozym-435 (220 mg), copper(I) bromide (39 mg, 0.28 mmol), and bpy (72 mg, 0.46 mmol), and the autoclave was sealed and heated to 35 °C while under vacuum for 2 h in order to dry the enzyme beads. After 2 h, the vacuum was released by filling the autoclave with low-pressure CO_2. ϵ-CL (5 mL, 45 mmol) and bifunctional initiator (66 μL, 48 mmol) were then added to the autoclave by syringe, under a flow of CO_2, to prevent the ingress of moisture into the system. After all the liquid reagents had been added, the autoclave was sealed, the stirring started, and the pressure of CO_2 increased to 1500 psi (10.3 MPa). After 16 h of reaction, the autoclave was placed into a dry ice/acetone bath to freeze the contents. Once the pressure had fallen to atmospheric pressure, an autoclave valve was opened, and the contents were allowed to heat to room temperature. A positive pressure of CO_2 was maintained to prevent the ingress of air or moisture in the vessel. For the synthesis of the second block, FOMA (2 mL, 6.9 mmol) was then immediately added to the autoclave by syringe, under a flow of CO_2, to prevent the ingress of moisture into the system. The autoclave was sealed and heated to 35 °C, the stirring started, and the pressure of CO_2 increased back up to 1500 psi (10.3 MPa). After 20 h, the autoclave was placed into a dry ice/acetone bath to freeze the contents. Once the pressure had fallen to atmospheric pressure, the autoclave was opened, and the contents of the autoclave were dissolved in a mixture of chloroform and Freon-113. The resulting solution was passed through an alumina column to remove the CuBr catalyst, and the polymer was precipitated from cold methanol.

Hydrolysis. The block copolymer (0.30 g) was dissolved in 1,4-dioxane (15 mL) at 85 °C in a 100 mL flask. 1.0 mL of concentrated hydrochloric acid was added to the solution, which was left stirring for 20 h. The hydrolyzed polymer was obtained by precipitating the solution into cold methanol.

Characterization. IR spectra were measured on a Nicolet Avatar 360 FTIR spectrometer in a KBr disk.

^{1}H NMR spectra of the PFOMA homopolymers and also the PFOMA-*b*-PCL block copolymers were obtained in a mixed solvent of Freon-113 and $CDCl_3$. ^{1}H NMR spectra were recorded using a Bruker DPX-300 spectrometer (300 MHz). Analysis of the spectra was carried out using Mestre-C Software.

GPC was performed using a LC 1120 HPLC pump (Polymer Laboratories) with chloroform as the solvent at 30 °C, two PLgel 5 μm Mixed-D columns (Polymer Laboratories), and an evaporative light scattering detector (Polymer Laboratories PL-ELS 1000). Calibration was carried out using polystyrene standards. Both the sample analysis and the calibration were conducted at a flow rate of 1 mL min^{-1}. The samples were also analyzed on a PL-GPC-120 system using THF as eluent (elution rate of 1 mL min^{-1}), calibrated using polystyrene standards and with a refractive index detector. Interestingly, the PCL and the PFOMA moieties give opposite signals on the RI detector. Finally, some of the samples were also analyzed on an HFIP TripleSec system using 1,1,1,4,3,3,3-hexafluoro-2-propanol as eluent (elution rate of 0.8 mL min^{-1}), calibrated using poly(styrene) standards and with a four detector system: Waters, 2487, dual wavelength UV detector, Viscotek 270 (light scattering (RALS/LALS) and viscometry), and Waters 2414, differential refractive index detector 35 °C.

DSC: A TA-2920 modulated DSC (TA Instruments), calibrated with an indium standard, was used to analyze the polymers. The crystallization temperature of polymers was also determined with each run typically ranging from −50 to 160 °C for two cycles. The heating program starts with the equilibration at −50 °C, then ramp 10 °C/min to 160 °C, isothermal for 5 min, ramp 10 °C/min to −50 °C, and the same steps for the second cycle. The samples were analyzed again using a Mettler Toledo DSC-30 system from −100 to 200 °C with a ramp 20 °C/min in order to observe the T_g.

MALDI TOF MS analysis was carried out on a Voyager-DE-STR spectrometer using a dithranol matrix with NaI additive. The

analysis was performed with the spectrometer in positive reflector mode.

Results and Discussion

Atom transfer radical polymerization (ATRP) has been used successfully for a large range of monomers, including (meth)-acrylates, styrenes, and many others, resulting in a well-controlled polymerization and low polydispersities.[22]

We report our initial work on radical polymerization carried out in $scCO_2$ for the synthesis of semifluorinated homopolymers (PFOMA). In addition, we extend our technique to the synthesis of semifluorinated block copolymers containing a hydrocarbon block. Perrier et al. reported the synthesis and the homopolymerization of perfluoroalkylethyl methacrylate (FEMA). In the attempted polymerization of FEMA by copper-mediated living radical polymerization in toluene, the initial reaction was homogeneous. However, as polymerization proceeded, phase separation occurred. Unreacted monomer remained in the upper toluene layer, and the lower solid was the polymer.[23] Xia et al. used ATRP to polymerize fluorinated monomers, such as 1,1-dihydroperfluorooctyl methacrylate, using fluorinated catalysts.[24] The fluorinated reagents were required to create a homogeneous solution in $scCO_2$ during the reaction. In the work described herein, a much simpler cosolvent approach is adopted to create a homogeneous system. Previously, we found that ϵ-caprolactone acts as a very effective cosolvent for ATRP of MMA, allowing the polymerization to remain homogeneous in $scCO_2$. The use of ϵ-CL as the solvent for ATRP reactions has been reported previously in conventional solvents.[25]

The results for the ATRP of FOMA in $scCO_2$ using ϵ-caprolactone as a cosolvent are summarized in Table 1. High-pressure polymerizations were also carried out in a view cell equipped with sapphire windows. This afforded visual observation of the phase behavior during the polymerization and allowed the solubility of the components to be observed. The monomers FOMA and ϵ-CL, copper bromide, and bipyridine were added in the same ratios as for the polymerizations and pressurized with CO_2. The polymerization medium was observed to be a homogeneous brown solution with no visible precipitation at any time during the polymerization. The PFOMA product plasticizes in $scCO_2$ at 45 °C and 1100 psi (7.6 MPa) and is completely soluble in the ϵ-CL/$scCO_2$ mixture at 45 °C and 1100 psi (7.6 MPa). The ATRP of FOMA in $scCO_2$ without ϵ-CL failed in the production of the homopolymer (entry 4, Table 1).

The conversion of the reaction was calculated from the ^{1}H NMR data using the integrated area for the olefinic $(CH_3)C{=}CH_2$ proton (5.60 or 6.14 ppm) for FOMA monomer as compared to the methylene 1,1-dihydro protons $O{-}CH_2CH_2{-}CF_2$ (4.29 ppm) for PFOMA.

The analysis of PFOMA homopolymer was difficult because of its very low solubility in conventional solvents. The polymer was only completely soluble in a mixture of Freon-113 and organic solvents such as chloroform or THF. The GPC analysis was attempted with $CHCl_3$ as the eluent using a PL-ELS 1000 detector. Improved solubility was sometimes observed upon addition of few drops of Freon-113. However, the molecular weight values obtained for the polymers by GPC are inherently misleading due to the aggregation of the polymer in chloroform. Other authors have also suggested that the molecular weight of semifluorinated polymers measured by GPC is often inaccurate due to the special properties of this class of polymer.[26] It was noted that the $M_{n,GPC}$ (determined by GPC) were lower than the $M_{n,Cal}$ (calculated from the equation), presumably because of the reduced hydrodynamic volume of the fluorinated blocks in chloroform solvent relative to the calibration. The same samples were also analyzed by GPC using THF as eluent and a DRI detector given similar results. As shown in Table 1, M_n obtained for the fluorinated polymers are lower than the theoretical value. Only entry 3 (Table 1) was also analyzed by a HFIP TripleSec system using the solvent hexafluoro-2-propanol and a multidetector system. HFIP is known to be a good solvent for fluorinated acrylic polymers. The value obtained for M_n is close to the data obtained using the other GPC systems. The molecular weight of PFOMA was determined by ^{1}H NMR by taking the ratio of the 1,1-dihydro protons $O{-}CH_2CH_2{-}CF_2$ at 4.29 ppm in the fluoroalkyl group to the methylene protons (3.85 ppm) in the bifunctional initiator (Figure 1). The results obtained for the M_n of PFOMA (GPC, NMR, and theoretically) are summarized in Table 1. The close agreement between the different methods for determining M_n indicates that controlled polymerizations were achieved using ATRP in $scCO_2$.

MALDI-TOF mass spectroscopy was used to complete the characterization of the homopolymers. The main peaks have a separation of 432 Da, corresponding to one FOMA unit, and the average molecular weight was ~5−6 kDa (Figure 2). Only one distribution of peaks can be easily identified in the spectrum.

We now turn our attention to the introduction of the enzymatic ring-opening polymerization (eROP). We have shown that block copolymers PCL-*b*-PMMA can be obtained by the combination of eROP and ATRP in a one-step procedure in supercritical carbon dioxide. This paper reports a one-pot−two-step reaction for the synthesis of a novel type of block copolymer containing a semifluorinated block.

Bifunctional initiators were employed for the combination of eROP with ATRP. The initiators combine a primary hydroxy functional group for initiation of eROP and an activated bromide group for initiation of controlled radical polymerization. This initiator design allows the synthesis of block copolymers without an intermediate transformation step.

A two-step reaction was carried out (Scheme 1). This macroinitiator method has proven to be an effective tool to prepare block copolymers. One method involves isolation and purification of the first block, which is then used as a macroinitiator. A second method involves the simple addition of a second monomer to the reaction medium after nearly complete consumption of the first monomer.

Initially, the bromine end-capped macroinitiator PCL-Br was obtained by eROP in the presence of the bifunctional initiator and characterized by GPC and NMR. The end-group structure analysis of the product was conducted to ensure the absence of homopolymerization of ϵ-CL initiated by a species other than the bifunctional initiator. Water can induce nucleophilic initiation of the eROP of ϵ-CL with the inevitable formation of homopolymers with carboxylic acid end groups. The product was derivatized with oxalyl chloride.[27] The amount of homopolymer with carboxylic acid groups determined by ^{1}H NMR was negligible. The water concentration in the reaction medium has been reduced to minimum by drying the enzyme under vacuum and at 35 °C. Consequently, no formation of PCL homopolymer was observed. This drying method effectively removes most of the free and loosely bound water reducing the water-initiated polymerization.[28] This experiment demonstrates exclusively initiation from the bifunctional initiator leading to the block copolymer. The ATRP of FOMA for the block copolymerization was then performed using the bromine-terminated PCL macroinitiator in a ϵ-CL/$scCO_2$ system with

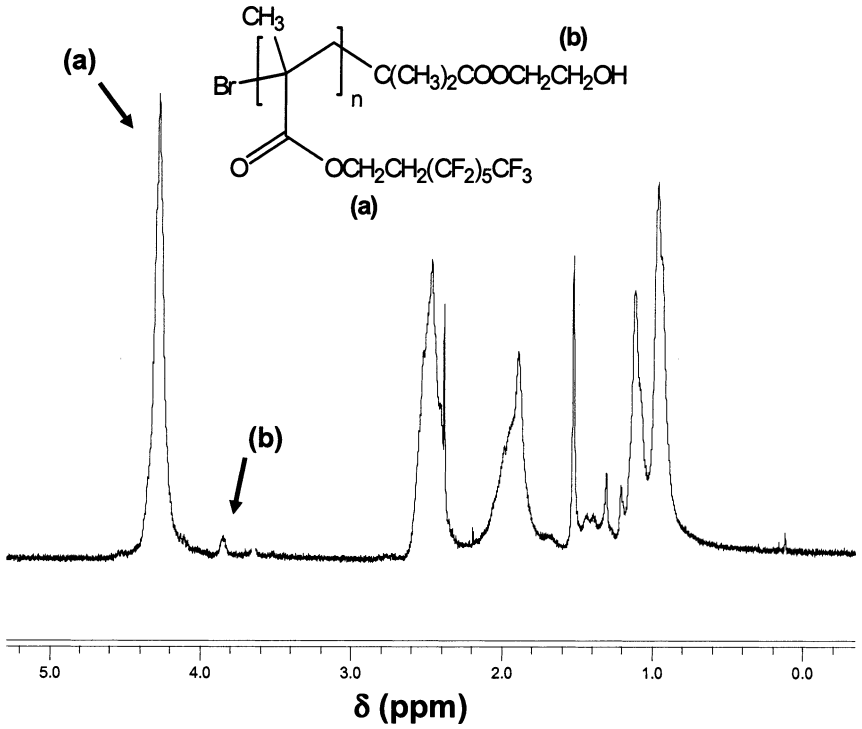

Figure 1. [1]H NMR spectra of PFOMA. The block length of PFOMA was determined by taking the ratio of protons (a) and (b).

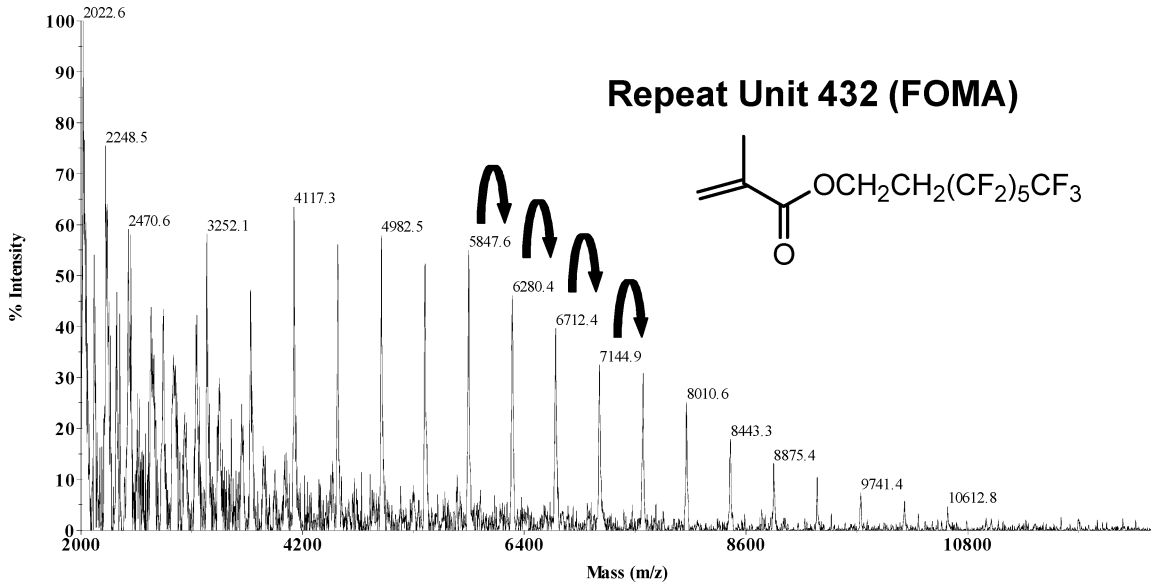

Figure 2. MALDI-TOF mass spectra of PFOMA homopolymer obtained by ATRP. Only one series of peaks is present in the MALDI-TOF spectra with a repeat unit of 432 g/mol.

CuBr/bpy as the catalyst. Two different PCL-Br macroinitiators were synthesized and purified by removing the enzyme and precipitation (Table 2, entries 1 and 2), and the PFOMA-*b*-PCL copolymers were prepared from these different macroinitiators (Table 2, entries 3−5). The synthesis of the diblock copolymer was also achieved by a sequential monomer addition technique (entry 6). In the first step, PCL was polymerized by eROP in the high-pressure reactor. After 20 h, the autoclave was depressurized, and a fresh feed of purified FOMA monomer was subsequently added to allow the ATRP to proceed. This experiment constitutes a "nearly simultaneous" one-pot reaction in the synthesis of block copolymer, without any intermediate step of purification and isolation.

GPC analysis of the block copolymer was conducted. Addition of a long hydrocarbon block was expected to improve the solubility of the block copolymer and suppress the tendency of micelle formation. However, despite the improved solubility, the analysis of the copolymers was still difficult due to their amphiphilic character and the very different solubility properties for each block. It is a well-understood phenomenon for block copolymers to form a micellar structure if one of the segments is insoluble in a given solvent.[29] The molecular weights measured by GPC for the block copolymers will almost certainly have some error—particularly at high FOMA content. A very high molecular weight (ca. 10^6 g/mol) species was occasionally observed because the formation of micelles in the GPC solvent. This peak was no longer visible by GPC as the concentration of the polymer sample was reduced. The results are summarized in Table 2. The data generally show that the FOMA block, left after hydrolysis, corresponds to the increase in molecular weight

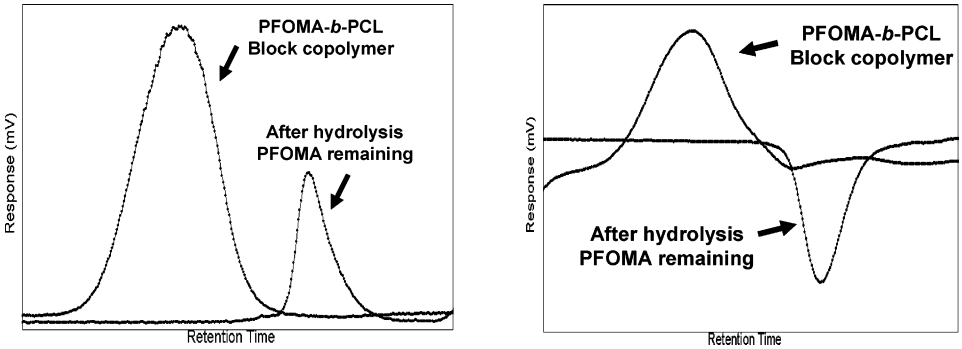

Figure 3. GPC traces for the block copolymer before and after hydrolysis of the PCL block. GPC-ELS analysis on the left; GPC-DRI analysis on the right. Note that in each case the traces demonstrate loss of the PCL block.

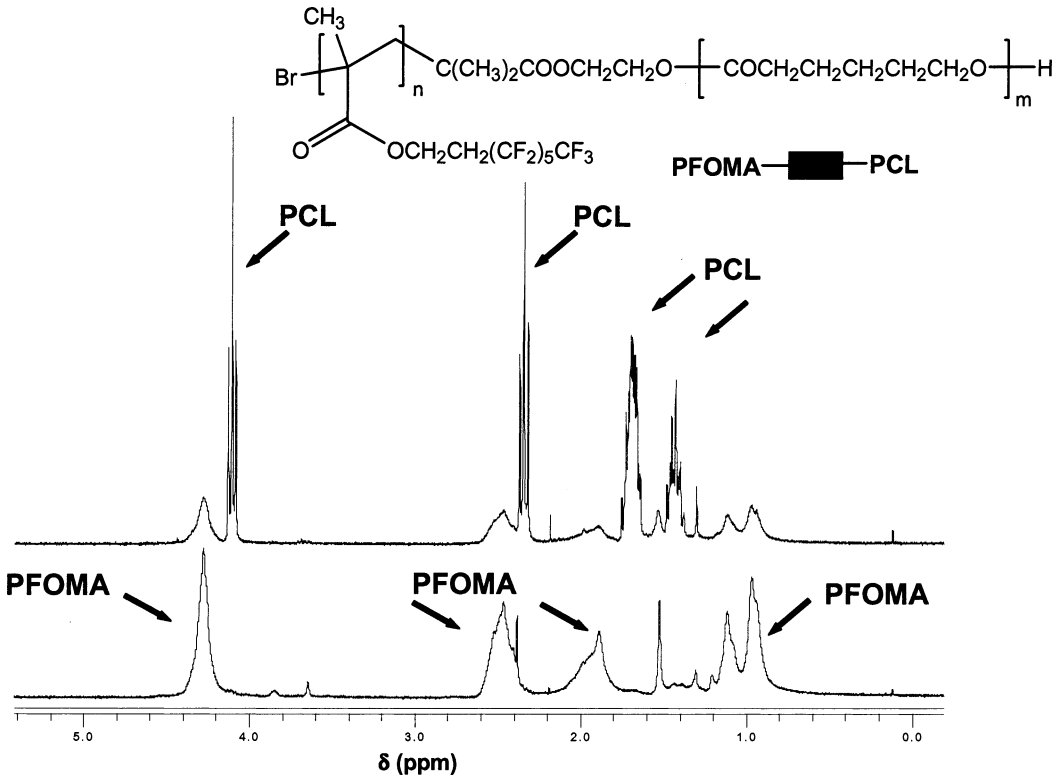

Figure 4. ^{1}H NMR spectra of (a) PFOMA-*b*-PCL block copolymer and (b) the remaining PFOMA block after hydrolysis.

after the addition of the second block. Samples were also analyzed by GPC using HFIP as a mobile phase in the attempt of an accurate estimation of the molecular weight distribution for the copolymers. As seen in the Table 2, there are some differences between the data sets obtained by the three different GPC systems.

The IR and the ^{1}H NMR spectra indicated the successful polymerization of both monomers. On the basis of the ratio of the area of the two peaks (4.29 ppm for $-CH_2CH_2CF_2-$ for the FOMA block and the 4.14 ppm for $-OCH_2CH_2-$ for the PCL block), the chemical composition was calculated to give a ratio PFOMA/PCL 12/88, 45/55, and 62/38, respectively, for entries 3, 4, and 5. In the IR spectra for the block copolymer (see Supporting Information), the first region of interest lies between 1500 and 1000 cm^{-1}, which is dominated by bands associated with the motion of CF_2 groups at 1260 and 1160 cm^{-1}. In addition, the band at 1220 cm^{-1} is attributed to stretching and bending of the carbon skeleton of the fluorocarbon block. The second region of interest is between 600 and 800 cm^{-1}, where the peak of 648 cm^{-1} was assigned to the CF_2 wagging vibration in the helical conformation.

To demonstrate block copolymer formation, the PCL block of the product was hydrolyzed. GPC analysis of the product shows a shift to lower molecular weight, implying the removal of the PCL from the block copolymer (Figure 3). ^{1}H NMR shows definitively the disappearance of the PCL from the product, leaving just the PFOMA block of the copolymer (Figure 4).

DSC analysis was performed by means of a Mettler Toledo DSC-30 in the range from −100 to 200 °C. To minimize the effect of recrystallization from the solution, two thermal scans were collected for each sample. The evaluation of the crystallinity content was performed on the second thermal scan. The crystallinity of the block copolymer is attributed to the PCL block. PCL homopolymer has a crystallization temperature (T_c) of 41.5 °C, whereas, PFOMA homopolymer is an amorphous material which does not show any crystallization temperature. The DSC thermograms for the PCL homopolymer and for the block copolymers are shown in Figure 5. The crystallinity of the copolymer decreases when the molecular weight of the PFOMA block increases. With a longer PFOMA block in the copolymer, lower crystallinity and also a lower T_c are observed.

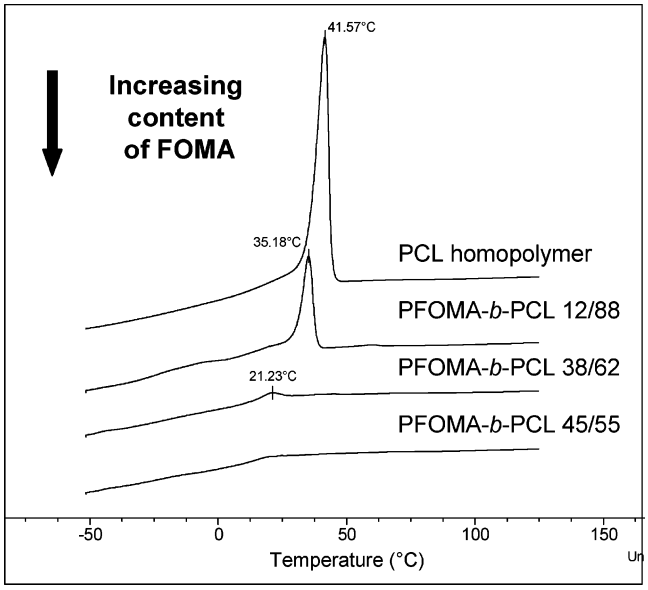

Figure 5. DSC thermogram of the PCL homopolymer and the block copolymers PFOMA-*b*-PCL. PCL homopolymer: $T_c = 41.5$ °C, block copolymer PFOMA/PCL 12/88: $T_c = 35.2$ °C, block copolymer PFOMA/PCL 38/62: $T_c = 21.6$ °C, block copolymer PFOMA/PCL 45/55: T_c not observed.

Copolymers containing sufficiently long blocks of PFOMA lead to a material that does not exhibit any crystallization temperature.

As reported previously in the literature, the T_gs of PCL homopolymer and of PFOMA homopolymer are −60 and 46 °C, respectively. DSC analysis of the block copolymers showed the T_g for the hydrogenated phase PCL and the T_g for the perfluorinated phase PFOMA to be similar to the homopolymers. Although sometimes the T_g for the PFOMA can be hidden for the melting peak of the PCL. No observable glass transition in the region in between those values was observed. This fact suggests the immiscibility of the polymers. A biphasic morphology caused by the segregation of the fluorinated and the hydrogenated moieties could be evident for the block copolymer. It is important to note that some of glass transition is not clearly evident from the DSC curves. Therefore, the interpretation of the thermal behavior of the block copolymers is much more complex. A slight difference is observed in the measured melting temperatures. As expected, the T_m value of the copolymers increases with increasing CL content. However, the melting temperature varied only a few degrees, from 57 to 61 °C.

An alternative approach is to first synthesize the PFOMA-OH macroinitiator in $scCO_2$ and then to carry out eROP from this (Scheme 1b). The macroinitiator formation was conducted successfully in $scCO_2$ by ATRP using the bifunctional initiator as shown previously in this paper. However, when this material was then used to initiate eROP of PCL in $scCO_2$, we obtained little success. PCL homopolymer was produced almost exclusively, presumably from water initiation from adventitious water in the high-pressure reactor. Exhaustive efforts to reduce water content failed to improve the situation, although on one occasion a bimodal product was obtained which suggested the unreacted PFOMA homopolymer of ca. 5 kDa or a PCL block of that M_w—but this material was only a minor product alongside homopolymer PCL. The lack of reactivity cannot be attributed to poor solubility since PFOMA-OH is very soluble in $scCO_2$. Thus, one would predict that the enzyme should have good access to the hydroxy functionality to initiate eROP of PCL, as was found previously for the analogous PMMA-OH macroinitiator.[16] Alternatively, it could be that although the PFOMA-OH appears to be well solubilized in the $scCO_2$/ϵ-CL mixture, it is actually micellized such that access to the hydroxy functionality is extremely inhibited. This would prevent formation of the block copolymer. Alternatively, steric hindrance by the FOMA moieties could exacerbate the same effect.

The one-pot synthesis in the presence of FOMA and ϵ-CL was also attempted without success. The reaction was carried out in $scCO_2$ at 35 °C (or 45 °C) at 1700 psi (11.7 MPa) using ϵ-CL and FOMA of varying initial feed ratios, the ATRP catalysts Cu(I)Br/bipy, and Novozym-435. No block copolymer was obtained. The resulting mixture contained homopolymers of both PCL and of PFOMA and a very small amount of block copolymer. The homopolymers could be separated by means of their different solubility in conventional solvents. The NMR spectra clearly identified both polymers. However, GPC analysis showed a bimodal distribution, indicating the presence of two homopolymers rather than a block copolymer structure.

A comparison was made with polymerization of the semifluorinated block copolymers in conventional solvents. The ATRP of FOMA was carried out using the same bromine end-capped macroinitiator (PCL-Br) in toluene with CuBr/bipy as catalyst and working at temperature of 80 °C (see Supporting Information for detailed experiments). Initially, the FOMA was miscible with toluene, and a brown homogeneous solution was produced. However, this quickly separated into two phases, presumably as the PFOMA block formed. This same phase separation and poor solubility was also observed by Perrier when carrying out the polymerization of FEMA in toluene.[23] The product obtained after purification showed a very broad molecular weight distribution, which was consistent with a very low yield of block copolymer and unreacted PCL-Br homopolymer. As reported by others, we found that the synthesis of the fluorine-containing block copolymers is limited by the solubility of these materials in common organic solvents and would normally require the use of fluorinated solvents (e.g., trifluorotoluene or Freon 113).[30,31] The polymerization was also carried out in bulk, in the absence of any additional solvent. PCL-Br homopolymer was found to be insoluble in the liquid FOMA monomer, even at high temperatures (80 °C). Therefore, the polymerization in bulk could not be performed. To conclude, the polymerizations in $scCO_2$ are much more controlled and with higher yields than those obtained using conventional liquid solvents. These data clearly show that $scCO_2$ is exceptionally good solvent for the preparation of fluorinated block copolymers, and moreover, the same $scCO_2$ can be used to ensure the activity and recyclability of the enzymatic reaction.

Conclusion

Amphiphilic block copolymers of a hydrocarbon block and semifluorinated PFOMA block were synthesized using PCL macroinitiator containing chain ends with ATRP functionality. It has been demonstrated that PCL macroinitiators polymerize FOMA effectively, leading to a PFOMA block with controlled molecular weight. In addition, we demonstrated that the chemoenzymatic synthesis of block copolymers combining eROP and ATRP can be also achieved by a sequential monomer addition technique using a bifunctional initiator. Detailed analysis of the obtained polymer confirmed the presence of predominantly block copolymer structures. PFOMA-*b*-PCL block copolymer offers some interesting features because of the combination of the biodegradability of PCL and the capacity of surface modification of the semifluorinated block PFOMA. We believe that this combination of polymerization strategies

in $scCO_2$ could open up the synthesis of a wide range of novel block copolymers that up until now have not easily been accessible using conventional methods.

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Supporting Information Available: IR spectra of (a) PCL-Br macroinitiator, (b) PFOMA homopolymer, and (c) diblock copolymer PFOMA-*b*-PCL; detailed experimental part for the general procedure for the ATRP of FOMA with PCL-Br macroinitiator in toluene; GPC traces for the polymerization of FOMA using the bromine end-capped macroinitiator PCL-Br in toluene. This material is available free of charge via the Internet at http://pubs.acs.org.

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