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Selective Postmodification of Copolymer Backbones Bearing Different Activated Esters with Disparate Reactivities

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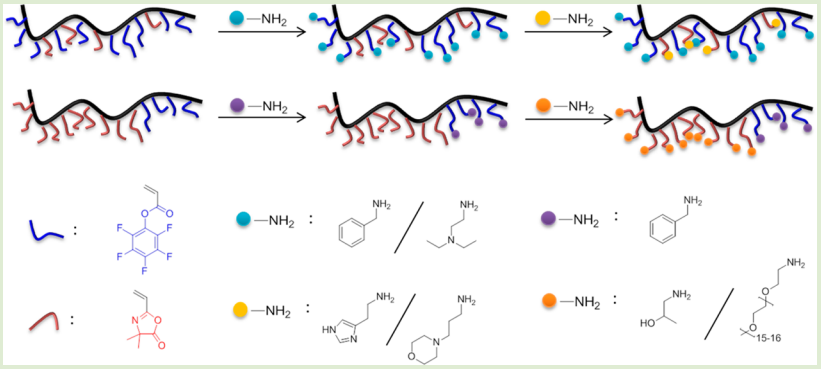
Supporting Information



ABSTRACT: In this communication, we report an easy method for introducing functional groups into polymer structures by successively reacting two different activated ester functionalities (pentafluorophenyl (PFP) ester and azlactone (AZ)) with different functional amine compounds. By exploiting the difference in reactivity of the two activated esters (PFP and AZ) toward different amino compounds, we demonstrate, for the first time, a selective modification of the different activated ester groups, thereby introducing functional groups to the polymer backbone in a controlled manner. Statistical and block copolymers of vinyl dimethyl azlactone (VDM) and pentafluorophenyl acrylate (PFPA), i.e.,(p(VDM-*stat*-PFPA)) and (p(VDM-*block*-PFPA)), were prepared using reversible addition−fragmentation transfer (RAFT) polymerization and subsequently modified using a library of amino compounds, yielding macromolecules with bespoke functionality. In additional work, the functional macromolecules were self-assembled into nanoparticles.

Reactive polymers containing functional and reactive side chain units have emerged as important building blocks for the preparation of novel materials, finding application in a wide range of biomedical[1] and materials research.[2a−f] Such polymers represent a versatile and powerful modular platform for the preparation of new materials, for application in drug delivery,[3] imaging,[4] biosensing,[5] as well as gene delivery.[6] Direct polymerization of functional monomers followed by post-modification is a common approach to build such reactive polymers.[2c,d,7]

Modern living radical polymerization methods, such as atom transfer radical polymerization (ATRP),[8] reversible addition−fragmentation chain transfer polymerization (RAFT),[9] and nitroxide-mediated polymerization (NMP),[10] have afforded many opportunities to tailor polymer architectures.[11] However, living radical polymerization techniques can be limited by the presence of incompatible groups present in the monomer; to address this challenge, the postmodification of preformed polymer scaffolds using efficient chemical reactions, to achieve well-defined and functional macromolecules, has been an active area of research over the last ten years.[2c,d,7,12] Direct postmodification using efficient 'click' reactions,[13] including azide−alkyne cycloaddition, Diels−Alder, thiol−ene, and amine/activate ester reactions, can yield functional polymer libraries. Recently, the incorporation of two reactive groups in the same polymer chain has led to the synthesis of highly complex macromolecules, using the sequential conversions of different functional groups on copolymers.[14] For example, Tunca's group described a "double click" method to introduce

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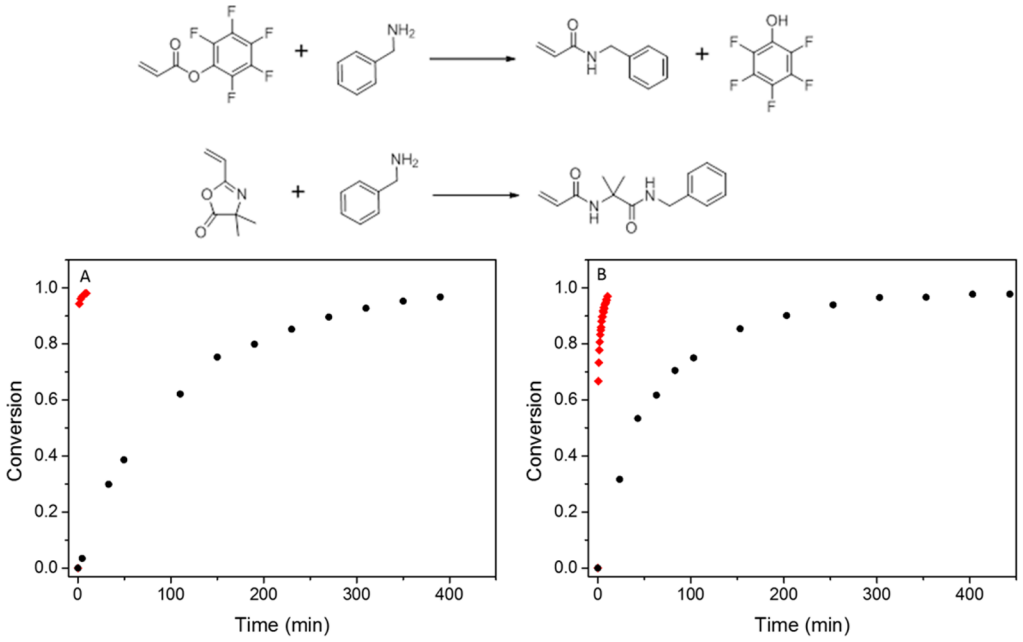

Figure 1. (top) Schematic representation of the amidation reaction of PFPA and VDM with benzylamine; (bottom) pentafluorophenyl ester (PFP, red diamond) and azlactone (AZ, black circle) conversion versus time in (A) DMSO-d_6 and (B) CD_3CN. *Note: PFP conversion was determined using ^1H and ^{19}F NMR analysis and AZ conversion using ^1H NMR analysis (see* Supporting Information *for details).*

different functional groups to a polymer chain.[15] The combined use of "click" (or efficient) chemistry can facilitate the synthesis of complex macromolecule architectures, such as graft copolymer, comb-polymers, miktoarm star polymers, or multifunctional polymers, as demonstrated by several groups.[16]

Amine/activated ester reactions (amidations) have, to some extent, been underused relative to other popular "click" transformation reactions, despite having several positive attributes. Amidation can be conducted at room temperature using a wide range of solvents without side reactions, leading to amidation yields of 100% even when a 1:1 ratio is used (even in the absence of solvent). In addition, a large range of amino compounds are commercially available. The only drawback of amidation is the formation of side products when some activated esters are employed. *N*-(Meth)acryloxysuccinimide activated ester groups were initially used in polymer modification reactions in the 1970s by Ferruti[17] and Ringsdorf,[18] and later Whitesides' group[19] successfully employed anhydride functional polymers for the preparation of biomedical materials. More recently, pentafluorophenyl ester containing monomers were polymerized to synthesize glycopolymers, responsive polymers, and functional polymers by Theato and co-workers,[20] Klok and co-workers,[21] and our group.[22] The azlactone group (AZ) was also recently successfully employed in the synthesis of various functional polymers by Haddleton's group[23] and Fontaine and co-workers[24] using 2-vinyl-4,4-dimethylazlactone (VDM) as monomer.

Our objective in this work was to explore the use of selective functionalization, exploiting the differing reactivity toward amines, of different activated ester functionalities. Specifically, the synthetic strategy we adopted was to exploit the difference in amine reactivity between two activated esters: pentafluorophenyl ester (PFP) and azlactone (AZ). First, we investigated the reactivity of these two activated esters in different solvents (DMSO and acetonitrile) using model compounds. Subsequently, we synthesized different statistical and block copolymers by RAFT copolymerization of vinyl dimethyl azlactone (VDM) and pentafluorophenyl acrylate (PFPA). The resultant copolymers were then reacted with a library of amine compounds using successive addition, thereby introducing functional groups to the polymer chains in a specific manner.

To investigate the reactivity of the two different activated ester groups, i.e., azlactone and pentafluorphenyl ester, we adopted VDM and PFPA monomers, as model compounds, in reactions with benzylamine. The amidation reaction was carried out at 25 °C in DMSO-d_6 or in acetonitrile-d_3 and monitored by NMR and FT-IR. To aid in the identification of the NMR shifts after amidation, two separate reactions were carried out with PFPA and VDM in the presence of benzylamine overnight (Figure 1). The reactions were performed in DMSO at room temperature using a stoichiometric amount of benzylamine and activated ester. After reaction, the products were purified by column chromatography and analyzed by ^1H NMR spectroscopy. After reaction of the AZ group with benzylamine, signal shifts of the methyl group from 1.37 to 1.41 ppm and the vinyl group from 6.0, 6.2, and 6.5 ppm to 5.5, 6.1, and 6.4 ppm were observed (Figure S1 in the Supporting Information), while FT-IR showed the absence of any signal at 1820 cm^{-1} attributed to the azlactone ring (Figure S2 in the Supporting Information). The presence of signals at 7.0 and 3.7 ppm confirmed a successful reaction. After reaction of the PFP group with benzylamine, a signal shift from the acrylic protons 6.4, 6.5, and 6.6 ppm to 5.6, 6.2, and 6.3 ppm by ^1H NMR spectroscopy was noted, while ^{19}F NMR spectroscopy showed the release of pentafluorophenol by the appearance of new signals at −165, −172, and −178 ppm (Figure S1 in the Supporting Information). The disappearance of the ester signal at 1780 cm^{-1} confirmed a complete amidation reaction (Figure S2 in the Supporting Information). In a second step, we decided to monitor the reaction of AZ and PFP toward benzylamine using online NMR analysis using DMSO or acetonitrile. In both solvents, PFP is more reactive than AZ as a complete conversion of PFP was observed in less than 3 min, while AZ

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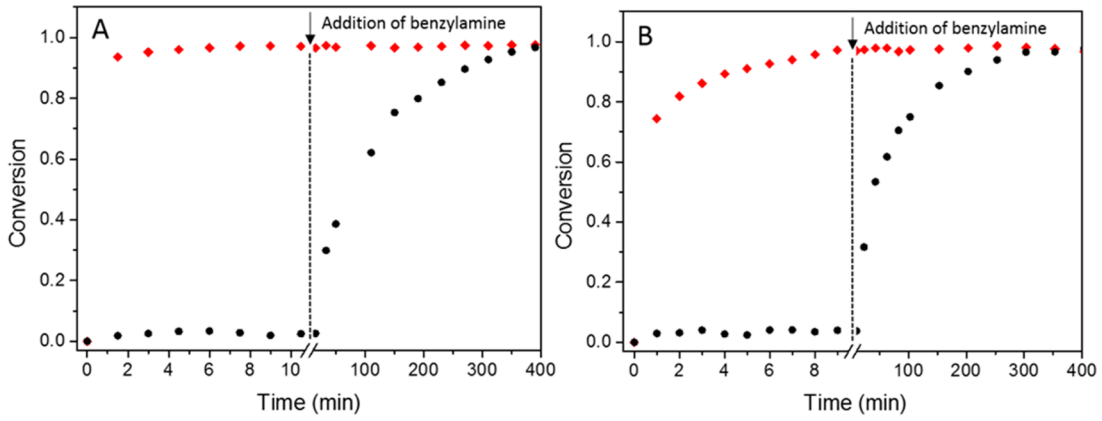
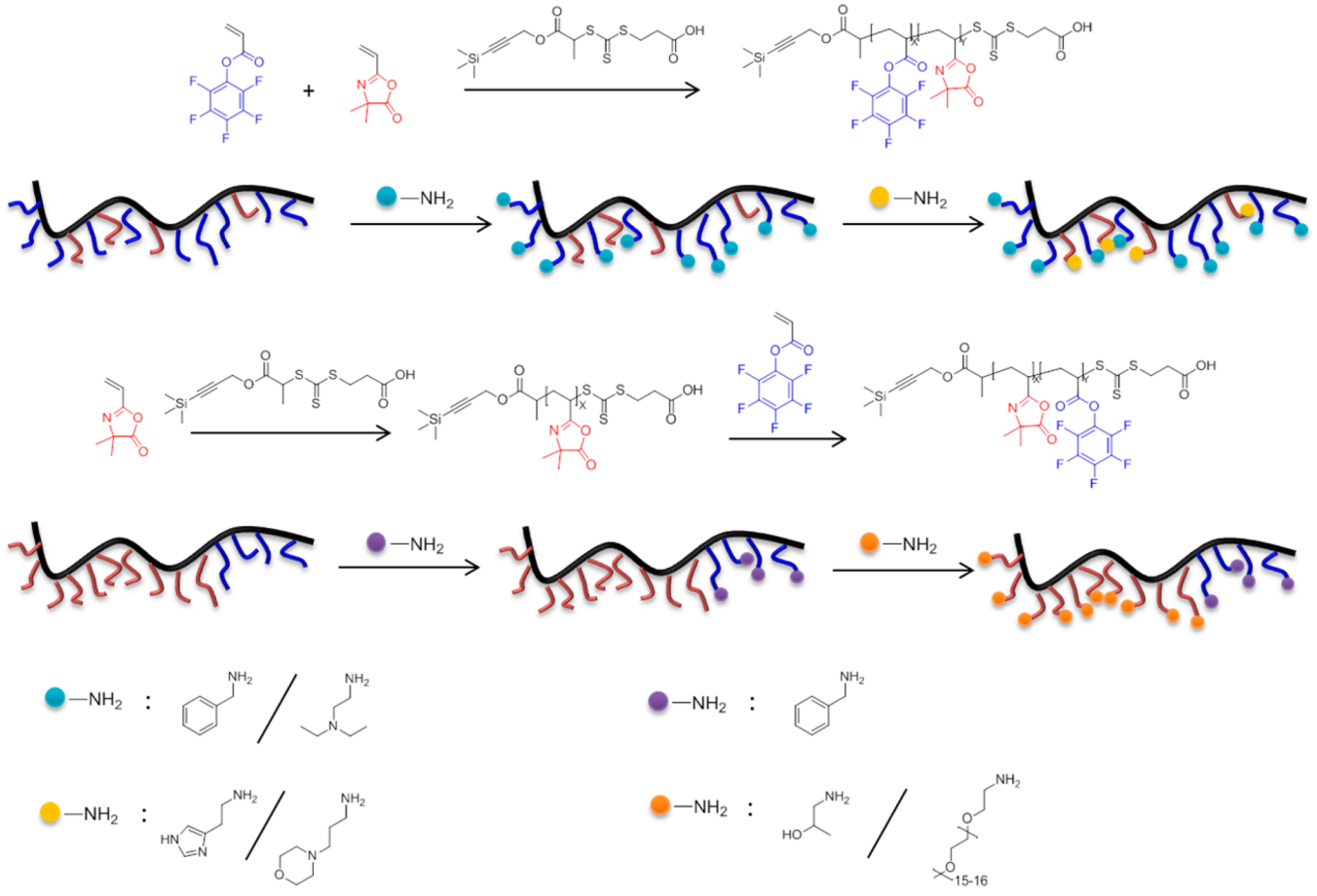


Figure 2. Kinetics of PFP (red diamond) and AZ (black circle) in the presence of benzylamine in (A) DMSO-d_6 and (B) CD_3CN-d_3. Note: In the first step of the reaction, [PFP]:[AZ]:[Benzylamine] = 1: 1:1 was used. After 30 min, an additional aliquot of benzylamine was added to the reaction mixture (final ratio: [PFP]:[AZ]:[Benzylamine] = 1:1:2). *Note: PFP conversion was determined using ^1H and ^{19}F NMR analysis and AZ conversion using ^1H NMR analysis (see* Supporting Information *for details).*

Scheme 1. Schematic Representation of Functionalization of Different Polymers Using PFP and AZ Activate Ester Groups



required 400 min to reach full conversion (Figure 1). Interestingly, the reactions performed in DMSO presented the fastest kinetics for PFP, while the reaction of amidation using PFP in acetonitrile was slightly slower than the reaction performed in DMSO. These results motivated us to carry out the amidation reaction in DMSO.

Next, both activated esters were mixed together and simultaneously reacted with benzylamine using the following reaction ratio [AZ]:[PFP]:[benzylamine] = 1.0:1.0:1.0. The reaction was monitored online via ^1H and ^{19}F NMR analysis (Figures S3 and S4 in the Supporting Information). Figure 2 shows the conversion of both activated ester groups in DMSO and acetonitrile using ^1H and ^{19}F NMR spectroscopy. In both solvents, PFP reacted rapidly, while AZ concentration changed minimally. When benzylamine had been fully reacted, we decided to introduce a second aliquot of benzylamine to the reactional mixture. We observed that the AZ group started to react. Importantly, the AZ groups did not react with benzylamine until all the PFP groups were fully consumed (Figure 2).

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Table 1. Macromolecular Characteristics of the Polymers Synthesized in This Work

polymer	$M_{n,theor}$[a] (g mol^{-1})	$M_{n,GPC}$[b] (g mol^{-1})	PDI[b]	f_{VDM}[c]	f_{PFPA}[c]	F_{VDM}[d]	F_{PFPA}[d]
VDM-*stat*-PFPA	9720	9600	1.20	30	70	30	70
VDM	9730	12000	1.16	100	-	100	-
VDM-*block*-PFPA	17000	15800	1.20	74	26	74	26

[a]Calculated by the equation: $M_{n,theor} = [M_n]_0/[CTA]_0 \times MW^{Monomer} \times \alpha^{Monomer} + MW^{CTA}$. [b]Assessed by GPC in DMAC (0.03% w/v LiBr, 0.05% BHT) using a conventional calibration curve with narrow PS standards. [c]Molar initial feed ratio (%). [d]Molar composition (%).

VDM and PFPA were (co)polymerized in the presence of 3-(trimethylsilyl)prop-2-yn-1-yl 2-((((3-propionic acid)thio)-carbonothioyl)thio)propanoate (TSPPA) as a RAFT agent and AIBN as initiator in acetonitrile at 60 °C yielding statistical and block copolymers (Scheme 1). The presence of the two different activated ester groups was exploited to react sequentially with two different amino compounds with the goal of preparing functional block polymers.

Statistical and block copolymers were precipitated in diethyl ether before analyses using DMAC GPC, ^{1}H NMR and ^{19}F NMR, and ATR-FTIR. The presence of NMR signals attributable to both monomers in p(VDM-*stat*-PFPA) confirmed successful copolymerization. The synthesis of block copolymers proved slightly difficult; initially, we synthesized PFPA homopolymer and, subsequently, chain extended with VDM. Unfortunately, GPC analysis failed to show any increase in molecular weight after chain extension. However, an increased PDI was observed. Alternatively, we chain extended p(VDM) homopolymers with PFPA and GPC analysis demonstrating a shift to lower retention times with low PDI (<1.2). A collation of all the molecular weights and compositions of the copolymers are given in Table 1. The copolymer molecular weights, obtained by DMAC GPC, were in relatively good accord with both theoretical expectations and NMR data. Moreover, GPC results confirmed the synthesis of copolymers with low polydispersities (PDIs). ^{1}H NMR analysis (Figure S5 in the Supporting Information) showed characteristic signals of CH_3 at 1.4 ppm and CH_2 at 2.5 ppm attributable to the dimethyl azlactone ring (AZ) and $-CH_2-$ of the PFPA backbone. Using both signals, we were able to calculate the final copolymer composition (Table 1). In addition, ^{19}F NMR analysis (Figure S6 in the Supporting Information) confirmed the expected signals at −155, −160, and −165 ppm attributable to the PFPA. Using trifluoroethanol as a standard, we were able to determine the composition by ^{19}F NMR analysis. Both results obtained by ^{1}H and ^{19}F NMR analysis were in good agreement. In both statistical and block polymers, ATR-FTIR of the polymers confirmed the presence of the VDM cyclic ring (AZ) and PFP ester at 1820 and 1780 cm^{-1}, respectively (Figure S7 in the Supporting Information). Statistical and block copolymers were reacted sequentially with functional amino compounds to yield well-defined functional polymers and block copolymers. First, the p(VDM-*stat*-PFPA) copolymer was modified with different amounts of benzylamine in DMSO to test the reactivity of both activated ester groups in the copolymers. The conversion of the activated ester groups was monitored by FT-IR spectroscopy using the characteristic absorptions at 1780 and 1820 cm^{-1} (Figure 3) and ^{19}F NMR analysis. The PFP group reacted exclusively first, while the AZ group remained completely unreacted, confirming our previous results obtained using model compounds (Figure S8 in the Supporting Information).

Subsequently, we decided to extend our synthetic approach to the postmodification of copolymers using a range of

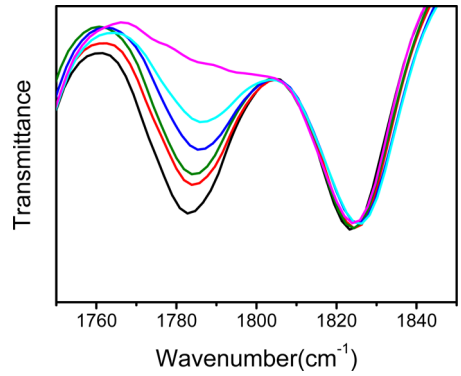

Figure 3. FT-IR spectra of p(VDM-*stat*-PFPA) copolymer versus time. p(VDM-*stat*-PFPA) copolymer was reacted in the presence of benzylamine at room temperature in DMSO using the following ratio: [PFP]:[AZ]:[benzylamine] = 1.0:1.0:1.0.

commercially available amines, including *N*,*N*-diethylethylenediamine, 3-morpholinopropylamine aminopropan-2-ol, methoxypolyethylene glycol amine, furfuryl amine, and benzylamine, to yield a library of functional copolymers. p(VDM-*stat*-PFPA) and p(VDM-*block*-PFPA) copolymers were reacted with an initial amine (A) for 1 h (Scheme 1). Subsequently, a second amine (B) was added to the reaction mixture to react with azlactone groups. Both sequential reactions were monitored using FT-IR and NMR analyses. FT-IR data confirmed successive reactions by confirming the disappearance of the PFP ester signal at 1780 cm^{-1} following reaction with the first amine, and the disappearance of the AZ cyclic ester signal at 1820 cm^{-1} was only observed after reaction with the second amine (Figure S17 in the Supporting Information). These results are in good agreement with those from our previous model reactions. After the postmodification, the copolymers were purified by dialysis and analyzed by GPC (Figure S18 in the Supporting Information) and NMR. ^{1}H and ^{19}F NMR (Figures S9−S16 in the Supporting Information) showed a successful amidation reaction. NMR analyses on purified copolymers allowed us to determine the copolymer compositions after reaction with amines A and B (Figures S10, S12, S14, and S16 in the Supporting Information). The copolymer composition was very close to the initial PFPA:VDM feed composition demonstrating that the postmodification is quantitative (Table 2).

Block copolymers modified successively by benzylamine and NH_2-PEG formed an amphiphilic block copolymer that potentially could self-assemble in water to yield nanoparticles. To demonstrate the potential of our approach to prepare nanoparticles, we self-assembled amphiphilic copolymers previously prepared by the slow addition of water. Dynamic light scatting (DLS) and transmission electron microscopy (TEM) were employed to determine the size and the shape of the nanoparticles (Figure 4). DLS shows the formation of micelles with a size of ∼20 nm with a very low dispersity (0.1 in

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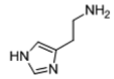
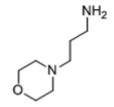
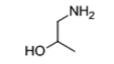
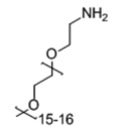
Table 2. Different Amines Used for Post Modification in This Study[c]

	Amine-A	Amine B	f_{PFPA}[a]	f_{VDM}[a]	$F_{Amine\text{-}A}$[b]	$F_{Amine\text{-}B}$[b]
VDM-stat-PFPA$_{M1}$			70	30	73	27
VDM-stat-PFPA$_{M2}$			70	30	69	31
VDM-block-PFPA$_{M1}$			26	74	24	76
VDM-block-PFPA$_{M2}$			26	74	27	73

[a]Molar composition (%) before the modification, calculated by ^{1}H and ^{19}F NMR (Figures S5 and S6 in the Supporting Information). [b]Molar composition (%) after the modification, calculated by ^{1}H NMR (Figures S9, S11, S13, and S15 in the Supporting Information). [c]Note: The reaction time with Amine-A was carried out for 4 h, and subsequently, amine-B was introduced and reacted for 16 h, respectively. All samples were purified by dialysis against acetone and then water.

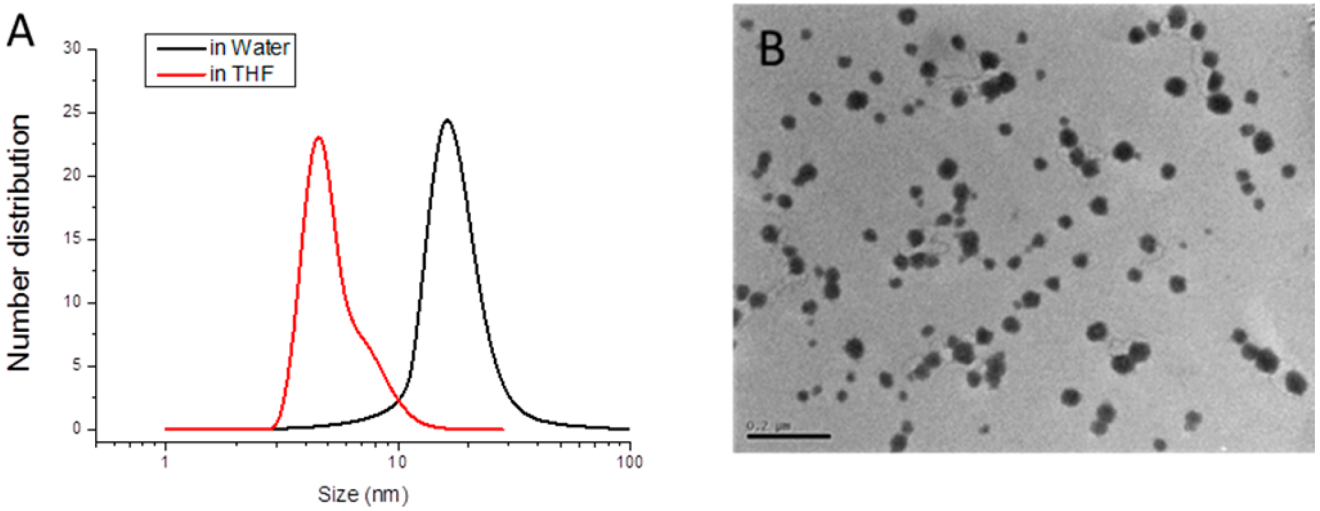


Figure 4. (A) DLS size measurement of copolymers modified with NH_2−PEG and benzylamine in THF and in water. (B) TEM image of self-assembled nanoparticles.

good agreement with TEM data). Using our one-pot modification reaction yielding a block copolymer, followed by self-assembly, we got AB block micelles. The formation of micelles not only proves that we can fully control the postmodification of different blocks but also indicates that the synthetic approach is potentially useful for generating nanostructures, such as micelles for potential application as drug vehicles.

In this communication, we explored a successive post-modification reaction using the difference in reactivity between two activated ester groups. The amine reactivity of two activated esters (AZ and PFP) was well studied, and different amine functional moieties were reacted with the polymers to yield functional block copolymers. These copolymers were assembled into more complex structures such as a micelle.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of RAFT agents, model reactions, synthesis of RAFT agents, VDM and PFPA monomers, homopolymer, statistical copolymers, and block copolymer. 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 interest.

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