

Reverse Block Sequence in Self-Immulative Poly(benzyl ether)-Based Amphiphiles for Tailoring End Groups and Self-Assembly Behavior

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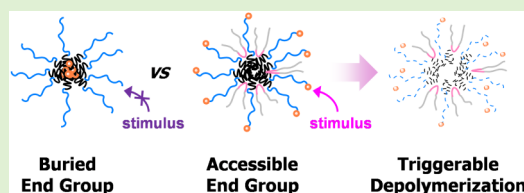


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ABSTRACT: This paper reports a modular design of self-immolative poly(benzyl ether) (PBE) amphiphiles that allows precise control over polymer chain structure, end-group placement, and degradation behavior. By tuning block sequences and exposing reactive end groups, these amphiphiles undergo efficient head-to-tail depolymerization upon external stimuli. Structural variations in the monomers enable micelle formation with end groups displayed on the surface, while the carboxylate content in the hydrophilic block influences global micelle morphology. The resulting micelles are degradable in aqueous environments and can transform into spherical structures when combined with conventional surfactants. As a proof of concept, small-molecule cargos were successfully loaded and released from the mixed micelles on demand. This design platform offers a versatile route to create functional, stimulus-responsive surfactants with tunable assembly, degradation, and controlled release capabilities.



INTRODUCTION

Polymeric micelles have core–shell-type structures comprised of well-defined hydrophobic and hydrophilic segments and are generally formed through the self-assembly of amphiphilic block copolymers. Leveraging diverse synthetic chemistry and chemical functionalities, they have been sophisticatedly engineered at the molecular level and further served as a versatile platform offering tailored solutions for a wide range of chemical, biorelated, and environmental applications, such as cargo delivery, regenerative medicine, pollutant removal, microreactor system, and cosmetics.^{1–4} These nanoassemblies are particularly effective not only in stabilizing dispersion systems by reducing interfacial free energy under aqueous conditions but also in loading and releasing cargos. In light of this, the development of degradable polymer micelles that demonstrate stimuli-responsive loading and release behavior has received considerable attention.^{5–8} To achieve this—from the perspective of polymer synthesis and engineering—(i) the chain sequence in the entire backbone is sophisticatedly controlled at the molecular level to impart amphiphilicity, (ii) robust yet labile covalent bonds (e.g., ortho esters, imides, acetals, imines, or hydrazones) are deliberately incorporated into the assembled structure, and (iii) the positions of reactive groups are appropriately arranged, causing the nanoaggregates to disintegrate in a predesigned manner upon exposure to endo- or exogenous stimuli such as chemicals, pH, reactive oxygen species (ROS), glutathione (GSH), enzymes, light, and temperature.^{9–17} However, conventional degradable micelles consist of hydrophobic segments, such as polyesters and polycarbonates, and hydrophilic segments, such as polyamides,

or polyethylene glycol—which are nondegradable—so thus these are limited by incomplete or delayed disintegration, leaving behind partially degraded oligomeric segments or short polymer fragments.¹⁸

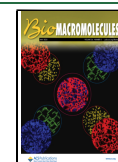
As a response to this, self-immolative polymers (SIPs) that are capable of controlled depolymerization through autonomous domino-like processes throughout their backbones have been notably widely investigated for use in degradable micelles.^{19–25} SIP-based micelles completely degrade into predesigned small-mass molecules when triggered by specific stimuli,^{18,26–28} ensuring the generation of minimal residual products and thus reducing potential side effects or the risk of long-term accumulation in the body.^{29,30} These micelles can also achieve the rapid and complete release of their payload after degradation, enhancing their therapeutic efficacy in comparison to the slower and less predictable release behavior of conventional degradable micelles.^{18,31,32} Self-immolative poly(benzyl ether)s (PBEs) are a particularly attractive type of SIP that polymerize from quinone methide monomers and then depolymerize in a head-to-tail manner via sequential quinone methide elimination,²⁷ triggered by a single equivalent of external stimulus that cleaves an end-capping unit on the PBE chain. Furthermore, owing to their synthetic flexibility,

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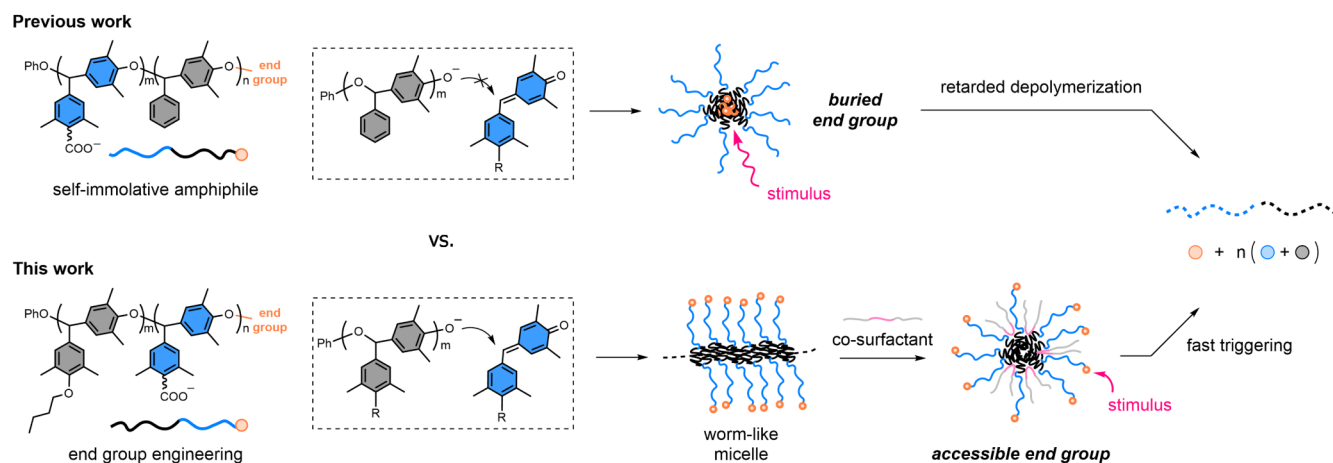


Figure 1. Schematic depiction of the conceptual design of self-immolative poly(benzyl ether) (PBE)-based amphiphiles: (top) PBE-based micelles with end groups buried within the micelle core, and (bottom) PBE-based micelles featuring accessible end groups exposed on the outside, facilitating rapid demicellization via PBE depolymerization in a head-to-tail manner, in the presence of a common cosurfactant.

various PBE chains have been designed for a wide range of functional polymeric materials (e.g., elastomers, adhesives, hydrogels, membranes, and imaging agents) with on-demand degradability.^{33–38} PBEs can also be designed as amphiphilic block copolymers that consist of hydrophilic and hydrophobic blocks, as taking advantage of living anionic polymerization.³⁹ These PBE amphiphiles self-assemble into micelles that completely degrade even in an aggregated state. However, in previously reported micelle designs,³⁹ the PBE end-caps, which initiate depolymerization throughout the backbone in response to external stimuli, are buried inside the hydrophobic core, which allows for demicellization outward from the core but prevents instant demicellization under aqueous conditions, thus reducing their suitability for practical applications. Thus, the rational molecular engineering of PBE amphiphiles is required to develop stimuli-responsive micelles with accessible end groups, enabling programmed degradation.

In the present study, we demonstrate the modular design of PBE amphiphiles and their self-assembly behavior into degradable micelles with enhanced degradability. The alignment of the structure of the quinone methide monomers leads to the formation of sequence-controlled block copolymers without generating steric effects or changing the reactivity of the monomers. As a result, the end groups are positioned on the hydrophilic segment, thus producing biocompatible micellar structures with exposed end-caps, which allows that molecular demicellization occurs via depolymerization from the outside to the inside. The content of the hydrophilic moieties in the PBE chains also determines the global morphology of the assembled structure, with a transition from worm-like to discontinuous configurations, while mixing with a commercial surfactant leads to the formation of spherical mixed micelles into which cargo molecules can be loaded and then released when the micelles are exposed to a specific stimulus.

Figure 1 summarizes the proposed design concept for degradable micelles with accessible end groups and compares it with a previously reported design.³⁹ In a past study, we developed self-immolative PBE-based amphiphiles that formed stable micelles under aqueous conditions and underwent on-demand demicellization via triggered depolymerization. The micelles could then be used to encapsulate cargo molecules and release them when exposed to a specific stimulus.

However, due to the unfavorable electronic structure of monomers and challenging polymerization route, the blocks in PBE chains could not be swapped, limiting the introduction of the end-capping unit to only the hydrophobic segment. These PBE amphiphiles self-assembled with their end groups oriented toward the interior of the micelle core, which retarded their depolymerization behavior by restricting their response to hydrophobic fluorinating agents such as Fluolead (i.e., 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride). Therefore, to enhance the accessibility of the end groups and improve the degradability of these micelles, end-group engineering of the PBE chain was conducted in the present study, resulting in exposed end groups on the exterior of responsive micelles. To achieve this, two types of quinone-methide monomers were deliberately employed and sequentially polymerized, which allowed for the formation of the PBE block copolymers and the placement of the end group on the hydrophilic segment. The resultant amphiphiles formed worm-like structures under aqueous conditions before transforming into spherical micelles when combined with a conventional polymer surfactant. As designed, both of these structures readily reacted with a hydrophilic trigger owing to the enhanced accessibility of the end groups, producing the initial quinone methide monomers via head-to-tail depolymerization. In this proof-of-concept study, we primarily aim to develop the chemical design of the degradable amphiphiles and manipulate their self-assembled structures, rather than focusing on their practical use. Nonetheless, we anticipate that the proposed modular design of degradable micelles has the potential to incorporate additional functional moieties with target-specific or therapeutic effects, to be used with conventional surfactants that exhibit complementary properties, and/or carry other macromolecular payloads such as enzymes or genes for theranostic purposes or to act as a self-regulating platform with programmed behavior.

MATERIALS AND METHODS

Materials. All reactions were performed in flame-dried glassware under positive pressure and a nitrogen atmosphere unless otherwise noted. Air- and moisture-sensitive liquids were transferred using a syringe or stainless-steel cannula. The quinone methides **1**³⁰ and **2**³⁶ were prepared as reported previously. The monomer precursors **7**³⁴ and 4-(4-(allyloxy)-3,5-dimethylbenzyl)-2,6-dimethylphenol³⁹ were prepared as reported previously.

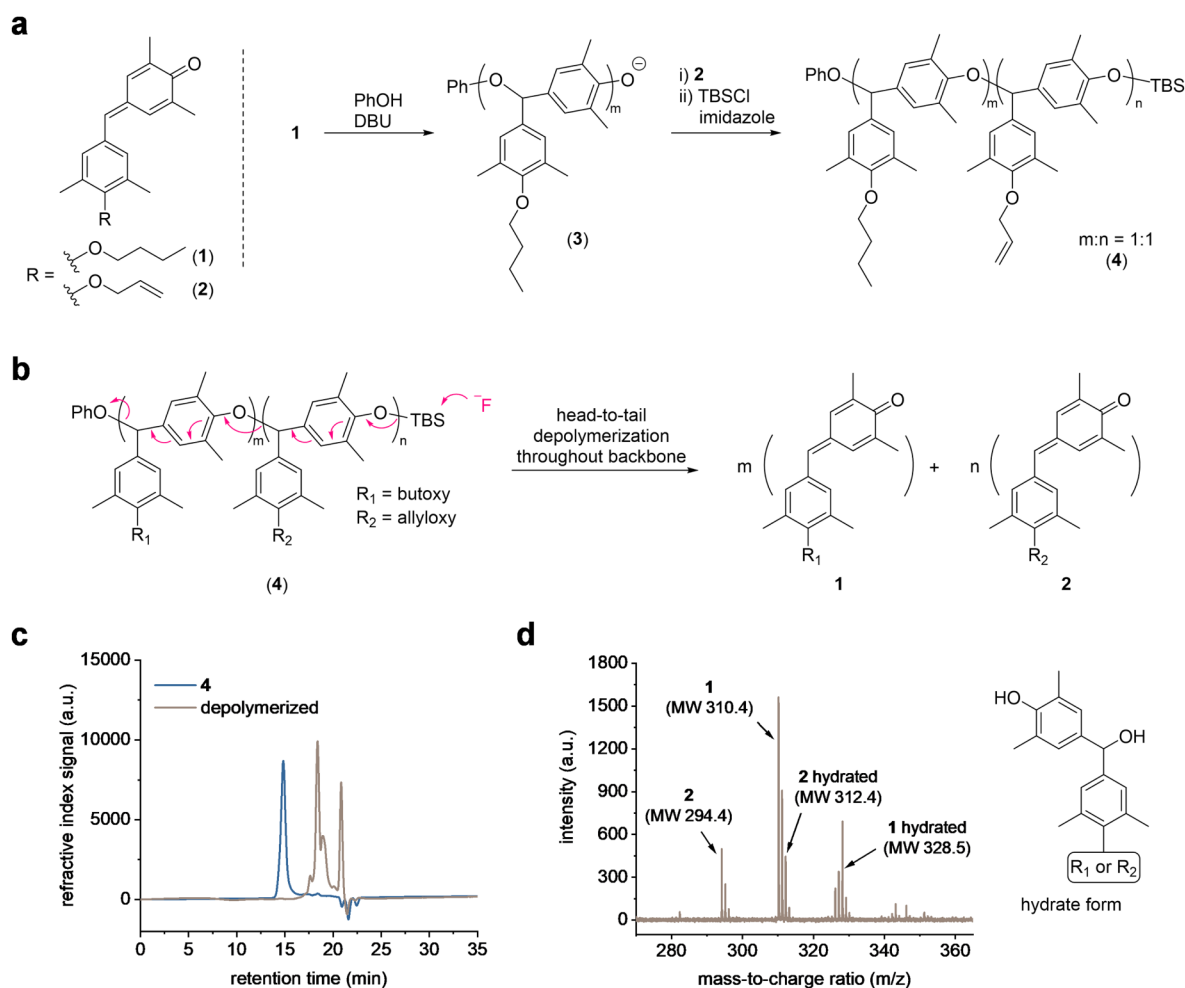


Figure 2. (a) Synthetic route for self-immolative poly(benzyl ether)-based block copolymer **4** from monomers **1** and **2** via sequential anionic polymerization. TBS = *tert*-butyldimethylsilyl. (b) Depolymerization of **4** in response to fluoride (2 equiv), resulting in the formation of monomers **1** and **2**. (c) GPC chromatograms of **4** before and after exposure to fluoride. (d) Mass spectrum obtained after depolymerization (left), identifying the formation of **1** and **2** and their hydrates (right).

Synthesis of Precursor Block Copolymer 4. In a flame-dried round-bottom flask, **1** (50 mg, 0.16 mmol, 1.0 equiv) was dissolved in dry DCM (0.25 mL) and cooled to 0 °C, after which a solution of phenol (0.01 mg, 0.2 μmol, 0.001 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.02 mg, 0.2 μmol, 0.001 equiv) in DCM (0.1 mL) was added. The polymerization reaction was carried out at 0 °C for 2 h. After the addition of monomer **2** (95 mg, 0.32 mmol, 2.0 equiv), the mixture was polymerized at 0 °C for an additional 2 h. After this, *tert*-butyldimethylsilyl chloride (88.67 mg, 0.59 mmol, 1.2 equiv) and imidazole (40.05 mg, 0.59 mmol, 1.2 equiv) were sequentially added to the reaction mixture to induce the end-capping reaction. The mixture was stirred at 23 °C for 24 h and isolated using precipitation in MeOH and subsequent filtration. After redissolving it in DCM and reprecipitating it in MeOH twice, the desired polymer **4** was obtained as a white powder (72%; M_n , 28 kDa; $\bar{D}$, 1.16). ^1H NMR (CDCl_3 , 400 MHz): δ 6.96–6.86 (m, 8 H), 6.09 (m, 1 H), 5.52 (br s, 2 H), 5.37 (d, 1 H, J = 16 Hz), 5.23 (d, 1 H, J = 8.0 Hz), 4.29 (br s, 2 H), 3.73 (br s, 2 H), 2.22 (m, 12 H), 1.84 (m, 12 H), 1.76 (m, 2 H), 1.53 (m, overlap, 2 H), 0.98 (m, 3 H).

Synthesis of Amphiphilic Copolymer 5. Copolymer 4 (100 mg, 3.6 μ mol) was dissolved in dry DCM (1 mL) in a flame-dried 20 mL vial. Subsequently, 3-mercaptopropionic acid (21 mg, 0.2 mmol, 1 equiv to allyl moieties) and the photoinitiator Irgacure 2595 (5 mg, 0.02 mmol, 0.1 equiv to allyl moieties, total 5 wt %) were added. The mixture was degassed via nitrogen bubbling for 15 min and then exposed to UV-light irradiation (365 nm) for 300 s. After stirring at 23 °C for 24 h, the resulting mixture was subjected to precipitation in

MeOH followed by filtration. The resulting solid underwent redissolution in DCM and reprecipitation in MeOH twice to yield the desired polymer **5** in its acidic form as a white powder (45%; M_n , 29 kDa; D , 1.36) with a 20% substitution yield. ^1H NMR (CDCl_3 , 400 MHz): δ 6.96–6.86 (m, 8 H), 6.09 (m, 1 H), 5.52 (br s, 2 H), 5.41 (d, 0.8 H, J = 16 Hz), 5.23 (d, 0.8 H, J = 8.0 Hz), 4.29 (br s, 2H), 3.73 (br s, 2H), 2.22 (m, 12 H), 1.84 (m, 12 H), 1.76 (m, 2 H), 1.53 (m, overlap, 2 H), 0.98 (m, 3 H).

Synthesis of Proton-end-capped Homopolymer 3. This control polymer was prepared in a similar manner for **4** except for adding acetic acid instead of the second monomer **2**. In a flame-dried round-bottom flask, **1** (200 mg, 0.64 mmol, 1.0 equiv) was dissolved in dry DCM (1 mL) and cooled to 0 °C. To which, a solution of phenol (0.04 mg, 0.8 μmol, 0.001 equiv) and DBU (0.08 mg, 0.8 μmol, 0.001 equiv) in DCM (0.1 mL) was then added. The polymerization reaction proceeded at 0 °C for 2 h. Then, acetic acid (39 mg, 0.77 mmol, 1.2 equiv) was introduced in one portion. After stirring at 23 °C for 24 h, an aliquot of the mixture was taken for the estimation of monomer conversion without isolation. The remaining crude polymer was isolated by precipitation in MeOH and subsequent filtration and further purified by redissolving DCM and reprecipitating twice in MeOH. A white powder (92%; M_n , 20 kDa; $\bar{D}$, 1.14). ^1H NMR (CDCl_3 , 400 MHz): δ 6.94–6.84 (m, 4 H), 5.53–5.52 (d, 1 H, $J = 4$ Hz), 3.74–3.72 (t, 2 H, $J = 8$ Hz), 2.24–2.19 (m, 6 H), 1.85–1.83 (m, 6 H), 1.77–1.74 (m, 2 H), 1.53–1.52 (m, overlap, 2 H), 0.99–0.96 (m, 3 H).

Synthesis of 8. To a solution of 4-(4-(allyloxy)-3,5-dimethylbenzyl)-2,6-dimethylphenol (400 mg, 1.35 mmol, 1.0 equiv) in DMF (1 mL) were added 3-mercaptopropionic acid (3MPA) (172 mg, 1.62 mmol, 1.2 equiv) and azobis(isobutyronitrile) (AIBN) (111 mg, 0.68 mmol, 0.5 equiv). After degassed by nitrogen bubbling for 15 min, the reaction mixture was stirred at 80 °C for 12 h. After cooled to room temperature, the mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over NaSO₄, and concentrated under reduced pressure. The desired product was purified by column chromatography (gradient elution with 0–20% ethyl acetate in hexanes) to afford **8** as a yellow oil (320 mg, 0.82 mmol, 61%). IR (cm⁻¹): 3493, 3005, 2929, 1700, 1449, 1174; ¹H NMR (CDCl₃, 400 MHz): δ 6.80–6.79 (d, 4 H, *J* = 4 Hz), 3.82–3.80 (t, 2 H, *J* = 8 Hz), 3.71 (s, 2 H), 2.84–2.79 (m, 4 H), 2.70–2.67 (m, 4 H), 2.22–2.21 (d, 12 H, *J* = 4 Hz); ¹³C NMR (CDCl₃, 500 MHz): δ 177.2, 171.3, 153.8, 150.4, 137, 132.9, 130.5, 129, 128.8, 123, 70.1, 40.4, 34.5, 30.2, 28.8, 16.2, 15.4; HRMS (TOF MS FD+, *m/z*): calculated for C₂₃H₃₀O₄S (M⁺) 402.18593; found 402.18609.

Drug Loading into the Mixed Micelles. Copolymer **5** (2 mg, 0.1 μmol) was dissolved in dry DMF (0.5 mL) in the presence of the commercial polymer surfactant Pluronic F-127 (1 mg, 0.1 mM). A solution of DOX·HCl (5 mg, 0.01 mmol) and triethylamine (0.01 mL, 74 μmol) was then separately prepared in DMF (0.5 mL) and added to the previous DMF solution, followed by the addition of NaOH (0.04 mg, 1 μmol, 1 equiv to the carboxylic acid group in **5**) in DI water (0.1 mL). The DOX-loaded mixed micelles were formed after adding DI water (9 mL), and untrapped DOX molecules were removed using dialysis with a regenerated cellulose membrane tube (MWCO, 2 kDa) in DI water (500 mL) for 2 d at 23 °C. The resulting product was further filtered through a hydrophilic nylon membrane syringe filter (pore size, 0.45 μm) to yield the loaded mixed micelles. The loading capacity (%) of the mixed micelles was estimated as follows: (total weight of the loaded drug)/(total weight of the vector) × 100.

Triggered Drug Release via Depolymerization. DOX-loaded mixed micelles consisting of **5** and F127 were prepared in 5 mL DI water at a concentration of 16 mg mL⁻¹. A solution of Ishikawa's reagent (1 mL, 6 mmol, 2000 equiv to the TBS end group) dissolved in dry DMF (1 mL) was prepared to trigger the drug release. After transferring the micelles to a regenerated cellulose membrane tube (MWCO, 2 kDa) under dialysis conditions in DI water (500 mL) with the trigger, the release of DOX from the micelles was monitored at 23 °C for 2 d under gentle stirring. At desired time intervals, 3 mL aliquots of the reaction medium were removed and analyzed to determine the amount of DOX released by measuring the absorbance intensity at 485 nm using UV–vis spectrometry.

Theoretical Estimation of Drug Release Profiles. The release behavior of DOX was estimated using Higuchi and first-order kinetic models, expressed in eqs 1 and 2, respectively, as follows:

$$Q = K_H \cdot t^{1/2} \quad (1)$$

where *Q*, *K_H*, and *t* mean the cumulative percentage of the cargo molecule, Higuchi rate constant, and time, respectively, and,

$$C = C_0 \cdot e^{-kt} \quad (2)$$

where *C* and *C₀* mean the concentration of the cargo molecule released at *t* and its initial concentration, and *k*, rate constant, respectively.

RESULTS AND DISCUSSION

In the proposed macromolecular design of depolymerizable amphiphiles, the PBE-based block copolymer **4** played a vital role, as it was capable of head-to-tail depolymerization throughout the backbone and contained allyl moieties that induced a hydrophilic block after the postpolymerization thiol–ene reaction, leading to the formation of degradable micelles under aqueous conditions. To synthesize **4**, we employed quinone-methide monomers **1** and **2**, which have *n*-

butyl and allyl groups, respectively (Figure 2a). These monomers offered comparable electrophilicity during nucleophilic addition polymerization due to the similarity of their substituents—one alkoxy and two methyl groups on each phenyl pendent unit.^{41,42} To strategically place the end-capping unit on the hydrophilic end, we first polymerized **1** to form hydrophobic PBE block **3** via anionic polymerization initiated by a phenol (PhOH) with DBU at 0 °C. Due to the living nature of polymer **3**, we were able to add a DCM solution of an excess of monomer **2** (two equivalents to **1**), generating a second PBE block with a degree of polymerization (DP) of 45, similar to that of the first block (DP, 47). The kinetic chain length of each PBE block was relatively short compared to the initiator concentration, presumably due to incompleteness of PhOH deprotonation and/or the reversible nature of monomer addition and elimination (i.e., 1,6-addition vs 1,6-elimination) during PBE chain propagation in the absence of end groups, which affected the consumption of both monomers. After end-capping the phenolate active center with the *tert*-butyldimethylsilyl (TBS) group, we obtained the precursor polymer **4** with a molecular weight (*M_n*) of 28 kDa (Đ, 1.16; DP, 92) when measured using gel permeation chromatography (GPC) (Figure S1). In addition, the 1:1 incorporation ratio of both monomers in **4** was confirmed using proton nuclear magnetic resonance spectroscopy (¹H NMR), which revealed the equal integration of benzylic protons in the PBE backbone and terminal vinylic protons of allyl moieties in the second block being developed at 5.52 ppm and 5.21–5.41 ppm, respectively (Figure S2). In comparison, when a stoichiometric amount of **2** (i.e., a 1:1 feed ratio of 1/2) was added to a solution of **3**, the growth of the second block was greatly hindered, resulting in a PBE chain (*M_n*, 29 kDa; DP, 97) composed primarily of **1** with only a trace of **2** (10 mol %). (The obtained GPC and NMR data for this case are exhibited in Figures S3 and S4). We further analyzed the intermediate homopolymer **3** by end-capping it with a proton, instead of adding **2**. The in situ monomer conversion of **1** was determined to be 86% by NMR based on a comparison of the peak at 5.52 ppm (benzylic protons in the PBE backbone) and the peak at 0.98 ppm (terminal methyl protons of butyl moieties in **1** and **3**) (Figure S5). After isolation via precipitation, the *M_n* of the proton-end-capped **3** was measured to be 20 kDa (DP, 66) by GPC (Figure S6). Based on these data, it can be inferred that some repeat units of **1** underwent depolymerization upon the addition of **2**, likely due to the decrease in concentration. Nonetheless, these results not only highlight the reversibility of the PBE chain growth and the competitive consumption of both monomers for **4** before the end-capping reaction but also supports the necessity of using an excess amount of **2** to shift the equilibrium toward the formation of the second block.

Figure 2b presents the depolymerization behavior of **4** in response to fluoride. Because the TBS group at the chain end of **4** can be easily cleaved due to the strong interaction between Si and F,⁴³ exposure to a trace of fluoride initiates the spontaneous depolymerization of **4** via a sequential elimination reaction throughout its backbone. This head-to-tail depolymerization completely unravels the polymer chain and produces the initial monomers **1** and **2**. After treating **4** with 2 equiv of tetra-*n*-butylammonium fluoride (TBAF) in DCM for 0.5 h at 23 °C, the GPC peak for **4** completely disappeared at a retention time of 14.8 min, with the emergence of new peaks for the small-mass products after 18 min (Figure 2c). The

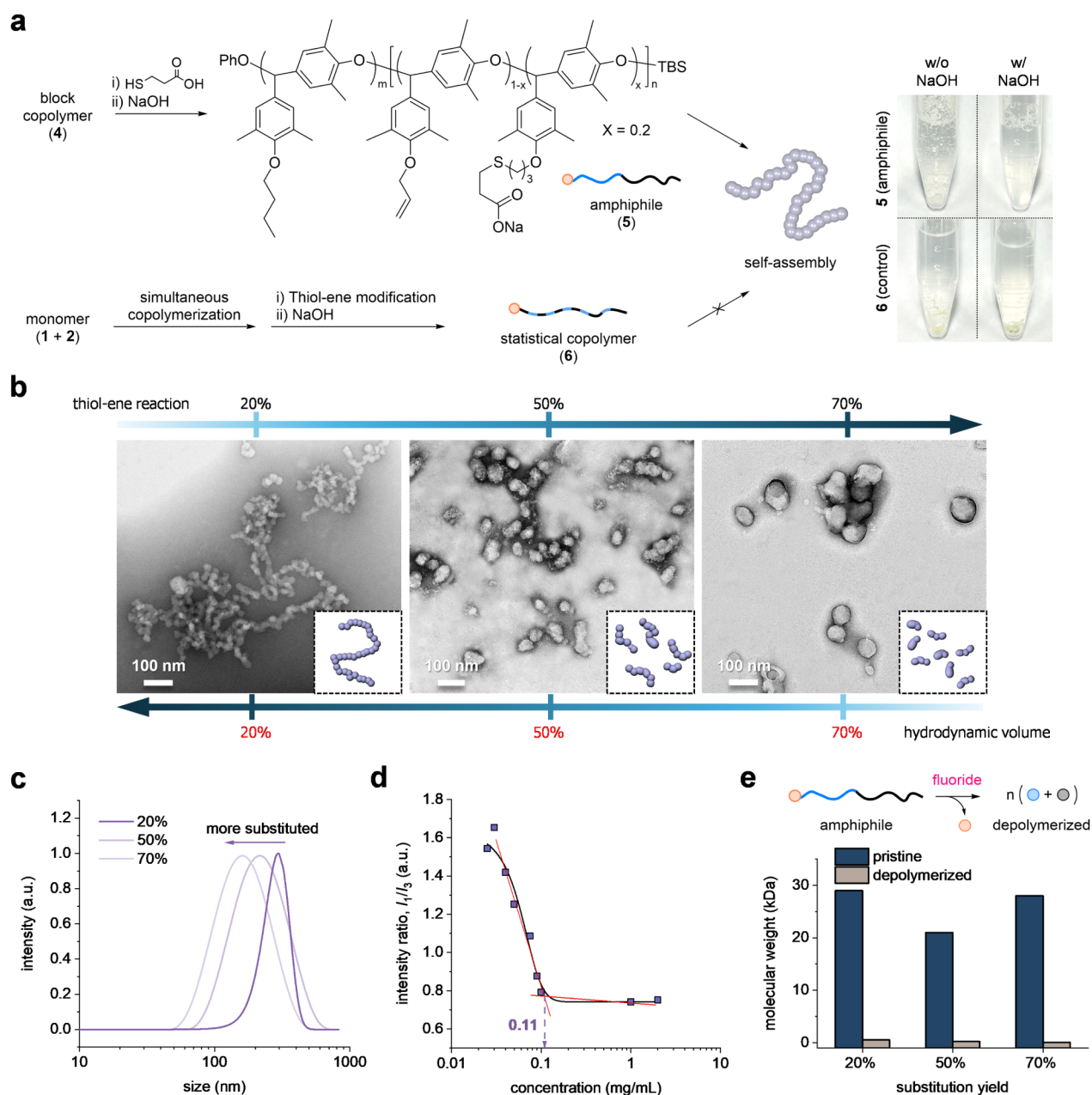


Figure 3. (a) Postpolymerization reaction for amphiphilic copolymer **5** derived from **4** via the thiol–ene reaction. The synthesis of statistical copolymer **6** is shown for comparison. The inset photographs of **5** (top) and **6** (bottom) in a conical tube under aqueous conditions without (left) or with (right) NaOH. (b) TEM images of assembled structures of **5** with varying carboxylate content, measured after stained with phosphotungstic acid. The insets depict a schematic illustration of each structure. (c) Size distribution of the assembled structures estimated using DLS in DI water. (d) Determination of the critical micellar concentration (CMC) of **5** with 20% carboxylate in the presence of pyrene. (e) Change in the molecular weight of **5** before and after depolymerization in response to fluoride.

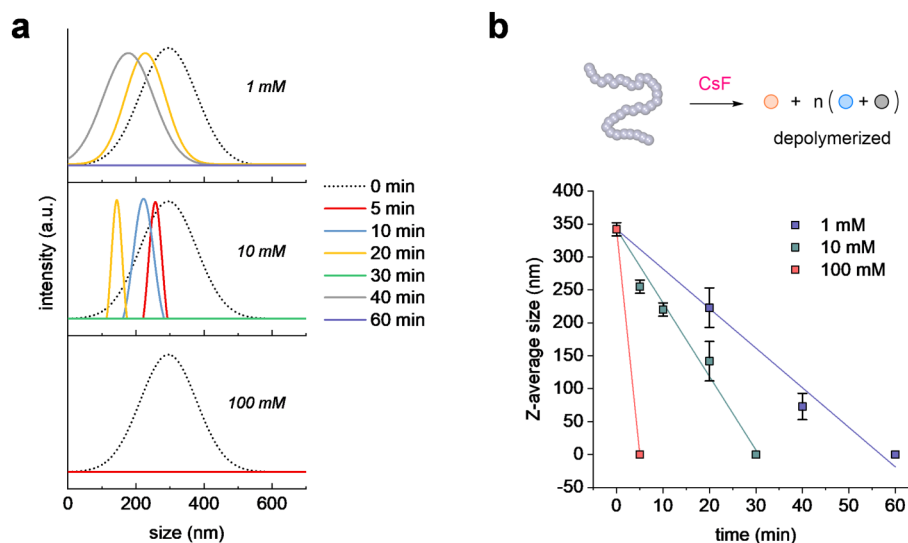
reaction products were examined using high-resolution mass spectrometry (HRMS), consequently identifying **1** and **2** and their respective hydrate forms (Figure 2d).

Postpolymerization thiol–ene modification of **4** generated amphiphilic copolymer **5** (Figure 3a). To increase the hydrophilicity of **4**, carboxylate groups were introduced to the second block of **4** using 3-mercaptopropionic acid (3MPA) and NaOH. The stoichiometric addition of 3MPA with respect to the dangling allyl moieties in the chain (i.e., a 1:1 molar ratio of 3MPA/allyl group) led to a 20% conversion rate of allyl moieties into carboxylates as determined using ^1H NMR (Figure S7), while its molecular weight slightly increased to 29

kDa as measured using GPC (Figure S8). The resulting **5** self-assembled under aqueous conditions, leading to a clear solution, in contrast to the white precipitate that formed without NaOH (top inset, Figure 3a). As a comparison, we synthesized a statistical copolymer **6** via the simultaneous polymerization of **1** and **2** at a feed ratio of 1:1. ^1H NMR and GPC analysis revealed that the polymer chain had an equimolar incorporation of both monomers and a molecular weight of 32 kDa, respectively. However, after thiol–ene substitution at a yield of 89%, the resulting **6** (M_n , 28 kDa) no longer self-assembled under the same conditions despite its structural similarity to **5**, with precipitates observed irrespective

Table 1. Summary for the Synthesized Poly(benzyl ether)s

polymer	architecture	carboxylate substitution	M_n (kDa)	$\bar{D}$	DP	CMC (mg mL ⁻¹)	Z-average size
4	block	0%	28	1.16	92	— ^a	— ^a
5	block	20%	29	1.36	92	0.11	296 nm
		50%	21	1.52		0.09	220 nm
		70%	28	1.16		0.77	164 nm
6	statistical	0%	32	1.29	106	— ^a	— ^a
		89%	28	1.13		— ^a	— ^a

^aAssembled structures not formed.**Figure 4.** (a) Change in size distribution of the worm-like micellar structure of **5** when exposed to different CsF concentrations recorded at various time intervals over 1 h. (b) Demicellization via depolymerization (top) and the change in the Z-average size of the micellar structure over time (bottom).

of NaOH (bottom inset, Figure 3a). This confirmed the formation of a hydrophilic block in **5** that allowed the entire chain to self-assemble under aqueous conditions. The NMR and GPC data for the synthesis of **6** are presented in Figures S9–S12.

The assembled structure of **5** and the effect of thiol–ene substitution on this structure were investigated using transmission electron microscopy (TEM) (Figure 3b). With 20% of the allyl moieties replaced with carboxylates, **5** formed a continuous worm-like structure with a measured diameter of 31 ± 3 nm, attributable to the presence of unreacted allyl moieties in the hydrophilic segment. An increase in the carboxylate content of **5** led to morphological changes, with 50% substitution, achieved using 3 equiv of 3MPA in regard to the allyl moieties, leading to a shorter continuous structure and a larger diameter (58 ± 12 nm). The compound then exhibited an irregular round shape with an average diameter of 73 ± 12 nm with 70% substitution, achieved using 5 equiv of 3MPA. In contrast, the overall hydrodynamic size of **5** decreased with an increase in the yield substitution when estimated using dynamic light scattering (DLS). The scattered light intensity-based size distributions of **5** were exhibited in Figure 3c. The average globular diameter was 295 nm for 20% substitution, falling to 220 nm at 50% and 164 nm at 70%. The worm-like globule thus had the largest hydrodynamic volume, with the structure becoming smaller due to the enhanced hydrophilicity of the second block.

We also investigated the critical micelle concentration (CMC) of the structures assembled from **5** using fluorescence

spectroscopy in the presence of pyrene as a fluorescent probe (Figure 3d).⁴⁴ The CMC of **5** with 20% substitution was found to be 0.11 mg mL⁻¹ in DI water, which was determined based on the change in the ratio between the emission peaks of I_1 and I_3 appearing at 373 and 383 nm under excitation at 334 nm, respectively, arising from the capture of the pyrene probe in the hydrophobic core of the micelle. In contrast, the CMC values of **5** at 50% and 70% substitution yields were 0.09 and 0.77 mg mL⁻¹, respectively. The carboxylate content thus not only influenced the hydrophilicity of **5** but also altered the packing arrangement of the aggregated structures. By comparing the obtained CMCs, the packing shape of **5** could be similar at 20% and 50% substitution but considerably different at 70%, presumably due to the incorporation of more hydrophilic groups.⁴⁵ Nevertheless, the CMC values were illustrative of the self-assembly capability of the PBE-based amphiphilic block copolymers. Changes in the emission spectra of pyrene as a function of the concentration of **5** and the corresponding CMC values are presented in Figures S13 and S14, respectively.

We also investigated whether the PBE backbone retained its depolymerization ability with varying levels of tethered carboxylate in **5** (Figure 3e). The PBE amphiphiles exhibited slight variation in their molecular weight due to differences in the carboxylate content and the radius of gyration. However, after exposure to 0.04 M TBAF in DCM for 0.5 h at 23 °C, the molecular weight of all of the amphiphiles significantly decreased, as measured using GPC. In particular, the initial GPC peaks completely disappeared, with new peaks

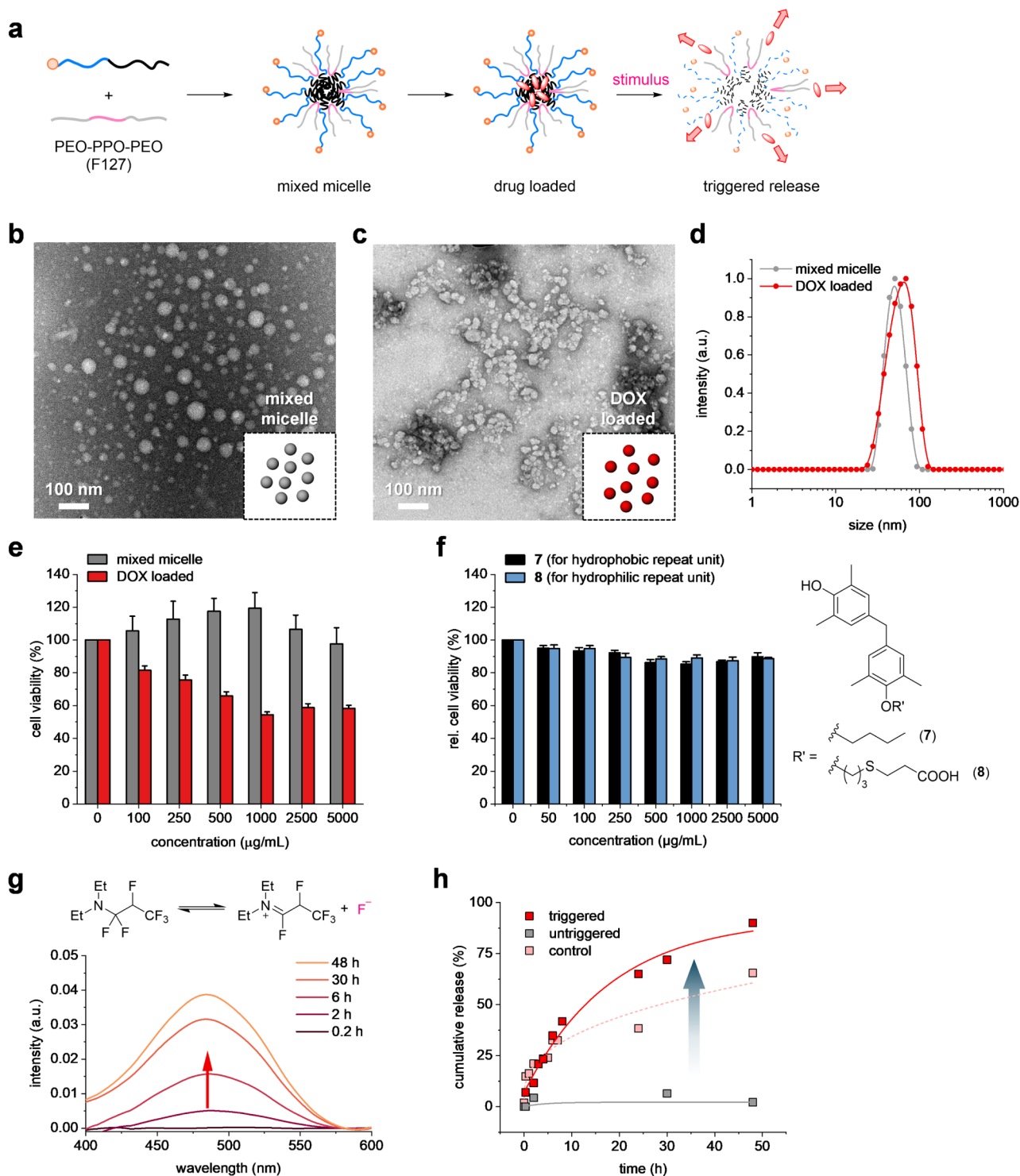


Figure 5. (a) Schematic description of the formation of a mixed spherical micelle when **5** is combined with the common polymer surfactant Pluronic F-127 (F127) at a ratio of 2:1 **5**/F127 (w/w) and its drug loading and release behavior via triggered depolymerization. (b, c) TEM images of (b) unloaded mixed micelles and (c) those loaded with doxorubicin (DOX), measured after stained with phosphotungstic acid. The inset images present a schematic diagram of the micelle structure. (d) Particle size distribution of the mixed micelles with and without DOX. (e, f) Relative viability of RAW 264.7 cells when incubated for 24 h with various concentrations of (e) the mixed micelles with and without DOX and (f) both repeat units in hydrophobic and hydrophilic segments (their structures are shown in on the right). (g) Absorption spectra measured for the DOX-loaded mixed micelles upon exposure to Ishikawa's reagent (shown in the inset). (h) Cumulative amounts of DOX released via triggered depolymerization (red) and its natural release from mixed micelles without the trigger (gray). For comparison, the release pattern for a previously reported PBE micelles is shown (dotted peach).

corresponding to monomeric products appearing at retention times of >18 min (Figure S15), which was similar to the results

observed for the depolymerization of **4** before thiol–ene modification. These results confirmed that the dangling

carboxylates do not significantly affect the cleavage of the TBS end-cap or the subsequent depolymerization of the PBE backbone. The measured properties of the synthesized polymers are summarized in Table 1.

The triggered depolymerization capability of **5** led to the molecular demicellization of the assembled structures. The deliberate positioning of the reactive end groups on the exterior allowed for the facile degradation of the micellar form of **5** in response to common fluoride sources such as CsF. The worm-like structure of **5** with 20% substitution was exposed to various CsF concentrations under aqueous conditions at 23 °C to monitor changes in its size distribution over time using DLS (Figure 4a). With 1 mM CsF, a gradual decrease in the average size of the micellar form was observed followed by the complete disappearance of the size distribution signal after 1 h, indicating that no aggregates remained. When the CsF concentration was increased to 10 mM, the size distribution shifted more rapidly, disappearing entirely within 30 min. At 100 mM, the DLS signal disappeared within 5 min, which was attributed to rapid depolymerization occurring across the entire micelle surface shortly after exposure to fluoride. These results indicate the presence of a demicellization pathway that begins at the micelle surface and proceeds inward through the depolymerization of **5**, leading to a gradual decrease in the size of the micelle and the formation of depolymerization products (Figure 4b, top). The change in the average size of the overall structures is also presented at the bottom of Figure 4b. The Z-average size of the worm-like micelles linearly decreased at 1 mM CsF as the depolymerization of **5** progressed after being triggered by the fluoride. The rate of demicellization increased by a factor of 2 and 11 when the CsF concentration was increased to 10 mM and 100 mM, respectively, which was attributed to the more rapid triggering of the exposed end groups and surface-initiated depolymerization.

Though the amphiphile **5** inherently formed a worm-like or discontinuous structure depending on the carboxylate content, it had the potential to assemble into spherical micelles when mixed with a polymer surfactant. We demonstrated this using Pluronic F-127 (hereafter F127), a nontoxic, nonionic, triblock copolymer consisting of a hydrophobic poly(propylene oxide) (PPO) block flanked with two hydrophilic poly(ethylene oxide) (PEO) blocks at either end. Using **5** with 20% substitution, mixed spherical micelles were generated at a **5**/F127 (w/w) mixing ratio of 2:1. These micelles could be loaded with cargo molecules in a manner similar to conventional micelles, which could then be released on demand when exposed to a specific stimulus via the triggered depolymerization of **5** (Figure 5a). Using 0.1 mg mL⁻¹ F127, mixed micelles formed under aqueous conditions at 23 °C for a total concentration of 0.3 mg/mL. To investigate the assembly behavior of the proposed amphiphile, the global morphology of the resulting micelles was evaluated using TEM (Figure 5b). Overall, spherical mixed micelles with an average diameter of 37 ± 3 nm were observed. The size of the micelles was also estimated using DLS, with the diameter found to be 55 nm (Figure 5d). Given that the concentration of F127 used to induce the mixed micelles was below its inherent CMC,^{46–48} this change in the shape of **5** could be ascribed to coaggregation with F127, and the free F127 could be liberated from the mixed micelles once depolymerization occurred. For comparison, we examined coassembly behavior of **5** with 50% or 70% carboxylate content in the presence of F127. At 50% substitution, the discontinuous structure similarly transformed

into spheres with an average diameter of 76 nm (by TEM) and 112 nm (by DLS), almost twice the size of those by **5** with 20% substitution. Contrarily, no distinct morphology was found from **5** with 70% substitution (Figure S16). These results highlight the significance of the carboxylate content on the coassembly behavior with F127 and reinforced our focus on **5** with 20% substitution, which caused uniform small mixed spheres. We also employed sodium dodecyl sulfate (SDS), an anionic small-mass surfactant, to form mixed micelles with **5** (20% substitution) and observed spherical micelles with an average diameter of ~30 nm in the presence of SDS at 1 mM (below its CMC) as confirmed using TEM and DLS (Figure S17a). However, unlike when F127 was used, these micelles were nondegradable in response to fluoride (Figure S17b); only the size distribution of the micelles was found to broaden owing to inconsequential depolymerization, while the average diameter remained, as shown in DLS data. This is likely because the ionic surfactant induced undesirable surfactant synergism that can influence packing structures even at a low concentration and further position the end groups internally,⁴⁹ which retarded the triggering event of the end group to some degree. However, this highlights the significance of positioning the end group on the exterior and the importance of selecting an appropriate nonionic cosurfactant for the formation of degradable mixed micelles. Furthermore, the CMC value of the mixed micelles was measured to be 0.14 mg mL⁻¹ (Figure S18), which is slightly larger than that of the worm-like micelles of **5** owing to the morphological change along with F127.

Using UV–vis spectrometry and a linear calibration plot for DOX, it was found that the spherical micelles that formed with F127 could be loaded with doxorubicin (DOX) at a loading capacity of ~13% (Figure S19), leading to a ~1.2-fold increase in their average diameter as measured using TEM (45 ± 7 nm) (Figure 5c). This loading capacity was comparable to that reported for previous PBE-based amphiphile owing to their structural similarities.³⁹ The size of the micelles after DOX loading was increased twice, reaching 110 nm as measured by DLS (Figure 5d), which was in good agreement with the TEM results. In addition, the zeta potential of the micelles did not greatly change with the loading of DOX. The unloaded micelles had a surface potential of –22 mV due to the carboxylate groups on the surface, and this rose slightly to –36 mV after loading with DOX (Figure S20), confirming the encapsulation of DOX in the hydrophobic core of the micelles.

We also tested the DOX loading properties of the mixed micelles using cell viability experiments with RAW 264.7 cells (Figure 5e). The unloaded mixed micelles were noncytotoxic to a concentration of 0.5 mg mL⁻¹, with a relative viability for RAW 264.7 of above 100%. In contrast, only slight cytotoxicity was observed with the DOX-loaded micelles, with a cell viability of 75% at 0.5 mg mL⁻¹. Given that free DOX molecules are cytotoxic for RAW 264.7 even at a low concentration of 5 μg mL⁻¹,⁵⁰ as demonstrated in Figure S21, these results indicated that DOX was tightly entrapped in the micelle core without significant leakage, highlighting the mixed micelles as a potentially biocompatible, responsive vector. In addition, we prepared each repeat unit in both hydrophobic and hydrophilic segments and evaluated their cytotoxicity (Figure 5f). Both were found to be noncytotoxic, further revealing the potential biocompatibility of the PBE amphiphiles even after depolymerization.

Ishikawa's reagent, a fluorinating agent that releases fluoride under aqueous conditions, was subsequently tested as another potential trigger for micelle degradation and the on-demand release of DOX (Figure Sg). So, the trigger was added to a suspension of the loaded mixed micelles (0.16 mg mL^{-1}) to induce the release of DOX, resulting in the final trigger concentration of 12 mM. UV-vis spectrometry revealed that the characteristic absorption peak of DOX molecules at 485 nm increased over time. Overall, nearly 90% of the loaded DOX molecules were released from the micelle core over a period of 2 d at 23 °C via the depolymerization of **5** under neutral conditions (Figure Sh). In contrast, no significant release of DOX was observed over time in the absence of the trigger, confirming the thermodynamic stability of the micelles. In fact, DOX could be released from the micelles under acidic conditions, due to the destabilization of the micelles via protonation of carboxylate moieties. However, only ~60% of DOX released over 48 h in a phosphate buffer at pH 3, supporting the effectiveness of the triggered release. Also, the DOX leakage was not observed at pH 10, owing to the stability of the micelles under basic conditions (Figure S22). Meanwhile, the triggered drug release behavior of the mixed micelles was more effective than that exhibited by the control DOX-loaded micelles that had buried TBS end-caps in the core (0.05 mg mL^{-1}), which required 5 d to release ~90% of their DOX loading in the presence of a hydrophobic trigger at a concentration of 40 mM, ~three times higher than that used for this study (Figure S23).^{39,40} However, the DOX release kinetics was sluggish compared to the degradation of worm-like structures observed above. This can be attributed not only to the reagent's tendency to transfer fluoride rather than generate free fluoride but also to the potentially limited accessibility of the end groups in the PBE chains within the mixed micelles. Presumably, employing a spatiotemporal stimulus, such as light, in combination with a suitably designed end group on the PBE chains could help overcome accessibility-related challenges.

The release characteristics of the proposed micelle delivery system were also estimated using the Higuchi model, which describes the diffusion-controlled release of drugs from matrix systems. In particular, this model effectively describes the sustained drug release kinetics of polymeric systems.^{51–54} The Higuchi rate constant (K_H) was measured to be $13.6 \pm 0.7 \text{ h}^{-0.5}$, which was 1.2-fold higher than that from the control previous micelles (K_H , $11.2 \pm 0.3 \text{ h}^{-0.5}$). In addition, we assessed the release kinetics using the first-order kinetic model, which is widely applied to the concentration-dependent dissolution of drugs from matrices.⁵⁵ A rate constant (k) of $0.07 \pm 0.01 \text{ h}^{-1}$ was obtained from the mixed micelles, ~7 times higher than that from the control micelles (k , $0.01 \pm 0.01 \text{ h}^{-1}$). The linear plots obtained for the estimations are displayed in Figure S24. The enhanced release behavior of the mixed micelles could be primarily attributed to the positioning of the TBS groups on the exterior of the assembled structure, which improved their accessibility for the applied external stimuli. This facilitated on-demand demicellization via the spontaneous depolymerization of the individual amphiphiles. In addition, we demonstrated a variety of fluorinating agents, such as TBAF, CsF, and Ishikawa's reagent, to trigger the depolymerization of the micelles. However, once the final application of these designed micelles is determined, we can introduce a relevant end group instead of TBS, apply an appropriate stimulus including biorelated signals, and further

optimize the demicellization behavior under physiological conditions by considering factors such as pH, temperature, medium, etc.

CONCLUSIONS

In the present study, we demonstrated a molecular strategy for end-group engineering for self-immolative PBEs. Employing the structural similarity of the selected quinone methide monomers, we successfully synthesized a block PBE copolymer through the sequential addition of the monomers via living anionic polymerization, followed by functionalization with a reactive end group. This end group could be positioned at either chain end during the termination process and initiate complete head-to-tail depolymerization of PBEs in response to a specific stimulus. Selective tethering of carboxylate groups to one block of the PBE backbone via a thiol-ene reaction not only differentiated the hydrophobic and hydrophilic blocks but also imparted amphiphilic characteristics on the PBE backbone. The resulting PBE amphiphiles self-assembled under aqueous conditions with their end groups positioned on the exterior of the assembled structure to facilitate enhanced degradability. The amphiphiles formed worm-like micelles capable of on-demand demicellization via the in situ depolymerization of PBE when triggered by a fluoride stimulus. The PBE amphiphiles also formed degradable spherical micelles when mixed with a trace amount of the commercial copolymer surfactant F127. These spherical mixed micelles were biocompatible and able to stably encapsulate DOX as a cargo molecule, which was subsequently released when exposed to fluoride. The design concept for micelles proposed in the present study has the potential to be improved further by incorporating synergistic functionalities or a variety of end groups that are reactive to endogenous signals (e.g., pH, GSH, or ROS). This could lead to the development of functional polymer surfactants for use in specific biomedical and environmental applications that can advantage of their controlled micellization–demicellization behavior.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.biomac.4c01845>.

Synthetic procedures, experimental details, NMR spectra, GPC chromatograms, TEM images, emission spectra, DLS data, and supporting graphs (PDF)

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Notes

The authors declare no competing financial interest.

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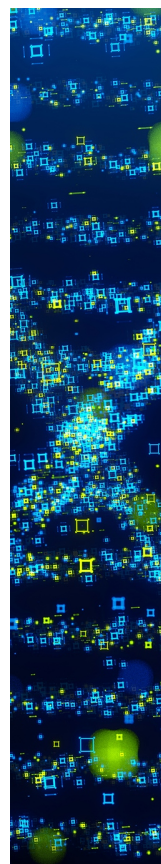
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