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Functionalizable, Side Chain-Immolative Poly(benzyl ether)s

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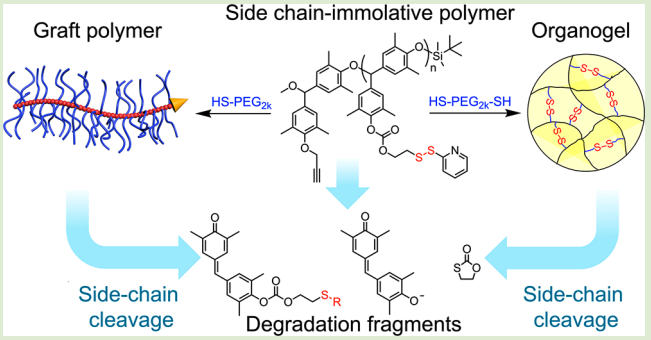
Supporting Information

ABSTRACT: Herein, we report a poly(benzyl ether)-based self-immolative polymer (SIP) with pendant pyridine disulfide groups. Cleavage of the side-chain disulfides leads to the formation of phenolates, which initiate depolymerization from the side chain. Due to the higher density of the disulfide groups compared to that of the chain-end-capping group, which normally is responsible for initiating depolymerization of SIPs, the side chain-immolative polymer (ScIP) can be readily degraded in the solid state where the mobility of polymer chains is substantially limited. The ScIP was also further modified through the thiol−disulfide exchange reaction to prepare ScIP-*g*-poly(ethylene glycol) graft polymers and organogels, which were also able to undergo complete reductive self-immolative degradation.



There has been an increasing interest in stimuli-responsive polymers due to the emerging needs for smart materials with the ability to react to external triggers, such as pH, temperature, redox conditions, ions, enzymes, and light, among others.[1−4] Self-immolative polymers (SIPs),[4,5] a unique class of stimuli-responsive materials, typically consist of a thermodynamically unstable polymer backbone at room temperature and a reactive end-cap that responds to external triggers. Once the end-cap is removed, a head-to-tail, domino-like depolymerization process takes place, completely converting the SIPs into small molecule fragments through sequential elimination or cyclization reactions. Thus far, several types of SIPs, including polycarbamates,[6−10] polycarbonates,[11,12] polythiocarbamates,[13] polythiocarbonates,[11] polyphthalaldehydes,[14−19] poly(benzyl ether)s (PBEs),[20−25] and polyglyoxylates,[26,27] have been reported. Among them, the PBE, drawing inspiration from McGrath's seminal benzyl ether oligomers,[28] can be conveniently accessed in high molecular weight (MW) from quinone methide-based monomers, which are easily obtained in high yields by oxidation of the corresponding phenols.[20] Nevertheless, we have found that, in order for the PBE backbone to undergo degradation, an anticoplanar molecular orbital alignment for the phenolate at the polymer chain-end is important.[23] As such, inflexible polymer backbones or polymers in the solid state exhibit very slow degradation rates, limiting their potential applications.

Recently, Phillips et al. have demonstrated a strategy to enable solid-state self-immolative degradation of PBEs by incorporating stimuli-responsive units onto the pendant phenoxy group of every repeating unit of the polymer.[22] This strategy greatly increases the concentration of the reactive phenolates that can initiate degradation, and allows macroscopic PBE plastics to respond to applied molecular signals in the surrounding fluid. In order to incorporate these PBEs into other polymer systems, for example, by forming cross-linked networks or graft polymers, it is desirable to modify them on the pendant groups postpolymerization. Herein, we develop a PBE-based, side chain-immolative polymer (ScIP) with the ability for postpolymerization functionalization. The ScIP is prepared using a new quinone methide monomer (**4**) with a pendant pyridine disulfide moiety (Scheme 1). We demonstrate that the ScIP can be used to form graft copolymers or organogels in the presence of mono- or bis-mercapto-terminated poly(ethylene glycol) (PEG) chains, respectively. Upon reductive cleavage of the side-chain disulfides in the presence of dithiothreitol (DTT), the graft copolymer disintegrates into the corresponding PEG chains, and the organogel quickly dissolves in solution. The degradation process was monitored by gel permeation chromatography (GPC) and ^{1}H NMR, and was compared to a computer simulation following a stochastic degradation model.

The quinone methide monomer is based upon 4,4′-methylenebis(2,6-dimethylphenol) (**2**, Scheme S1), which was synthesized by condensing 2,6-dimethylphenol with formaldehyde under acid catalysis. Compound **2** was used to

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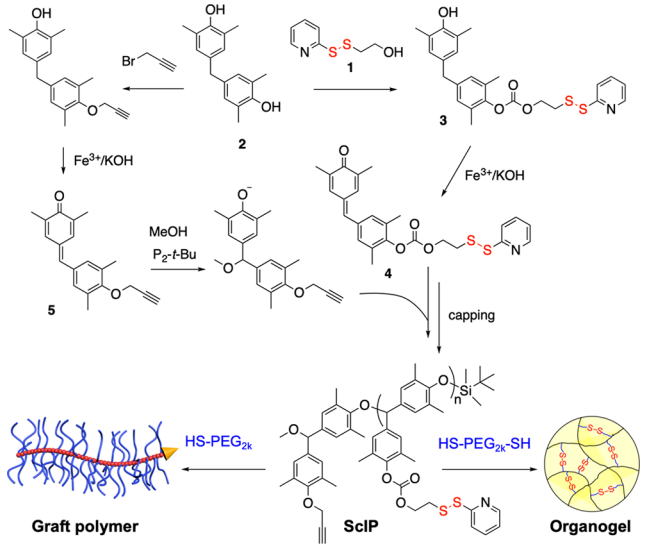
Scheme 1. Synthetic Scheme of the PBE-Based ScIP and Subsequent Functionalization



form a carbonate (**3**) with 2-(pyridin-2-yldisulfanyl)ethanol in the presence of triphosgene, which was then oxidized by potassium ferricyanide in an alkaline solution to give the final monomer, **4**. The overall yield was ∼38%, mainly due to loss during the carbonate formation step. We attempted direct anionic polymerization of monomer **4** at 0 or −20 °C with methanol and 1-*t*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi (phosphazene) (P_2-*t*-Bu) as the initiating system. However, a low degree of polymerization (∼11) was observed, regardless of monomer/initiator ratio, likely a consequence of the side reaction between the reactive methoxide species and the side-chain carbonate electrophiles (the exact mechanism causing the low molecular weight is unclear). Therefore, a two-step initiation process was developed (Scheme 1). First, an alkyne-modified quinone methide[23] (**5**, 2 equiv) was initiated by methanol (1 equiv) and P_2-*t*-Bu (1 equiv) for 45 min at 20 °C, to generate a bulky, less nucleophilic anion. The alkyne functionality is unimportant for the initiation but may be used for further chain-end functionalization. The resulting light green initiator solution was then transferred to a solution of monomer **4** (50 equiv) that was precooled to −20 °C. Successful initiation is evidenced by an instantaneous color change from bright yellow to fuchsia. The polymerization was allowed to continue for 1 h, before a chain-capping agent was added. Initially, *t*-butyldimethylsilyl chloride (TBSCl) and imidazole was used as the capping agent. However, inconsistent capping was observed. Changing the base to triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) resulted in reliable capping, as evidenced by ^{1}H NMR showing characteristic peaks of the TBS methyl groups (0.2 and 1.0 ppm) (Figure S16). Peak integration comparing chain-end methyl (both α and ω) and side-chain pyridine groups indicates that the number-average molecular weight (M_n) for a typical polymerization is 14−17 kDa (DP_n: 30−33). These results are corroborated by tetrahydrofuran (THF) GPC, showing a typical M_n of 13−18 kDa and a polydispersity index (PDI) of 1.5−1.8 (Table S1).

Next, we studied the response of the ScIP to reductive conditions in both the solution and the solid state. When the disulfide linkage is reductively cleaved, the resulting sulfhydryl anion can backbite the carbonate group to form a cyclic thiocarbonate and a phenolate anion, which then initiates the depolymerization (Figure 1). When treated with DTT in the

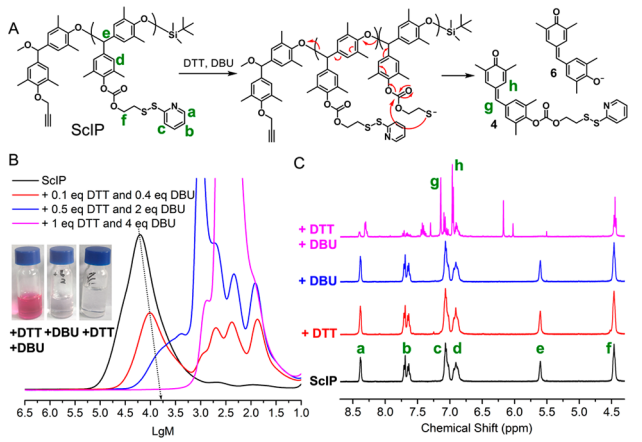


Figure 1. Reductive degradation of unmodified ScIP. (A) Schematics showing the degradation pathway. (B) THF GPC chromatograms of ScIP treated with various substoichiometric amounts of DTT and DBU. Inset: color change associated with the formation of phenolates and the lack of response when DTT or DBU alone is used (reaction time: 20 min). (C) ^{1}H NMR spectra of the ScIP and those treated with DTT, DBU, or both.

presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the ScIP THF solution turned fuchsia immediately, suggesting the formation of phenolate anions. DBU was used to deprotonate DTT and also prevent residue water in the solvent from capping the chain-end phenolate. Other bases tested include triethylamine, pyridine, and piperidine; none were effective in promoting the self-immolative reaction. In the absence of DBU, DTT alone did not induce depolymerization in THF, possibly because the free thiol group of DTT lacks the necessary nucleophilicity to exchange with disulfides. THF GPC reveals that the ScIP peak decreases in height and shifts toward the lower MW end as the concentration of DTT/DBU increases. There is also a series of rising, low MW peaks corresponding to the added DTT, DBU, and fragments of the degraded polymer. Two main degradation products, **4** and **6**, were observed by electrospray ionization−mass spectrometry (ESI-MS; Figures S15 and S16), which is consistent with the predicted self-immolation mechanism. ^{1}H NMR in THF-d_8 confirms that the ScIP is completely degraded after 1 min of DTT/DBU treatment, as evidenced by the disappearance of the polymer backbone -$OAr_2(CH)$- peaks and the sharpening of all peaks, which result from the much higher diffusion rates of the fragments versus the polymer in solution. In contrast, when DBU and DTT were used separately to treat the polymer, no apparent changes in ^{1}H NMR were observed. These data confirm that the reductive cleavage of the side chain disulfides can rapidly lead to complete polymer backbone degradation in solution. In order to test the ability of the ScIP to undergo depolymerization in the solid state, a pellet of the polymer was placed in acetonitrile, a poor solvent for the polymer, but a good solvent for the monomer. Next, DTT (0.2 mM) and DBU (0.8 mM) were introduced, and photographs of the pellet were acquired over time (Figure 2). The polymer pellet changed its color to purple minutes after the addition of DTT/DBU (but not when DBU alone was added) and almost completely disappeared in 5 h. In contrast,

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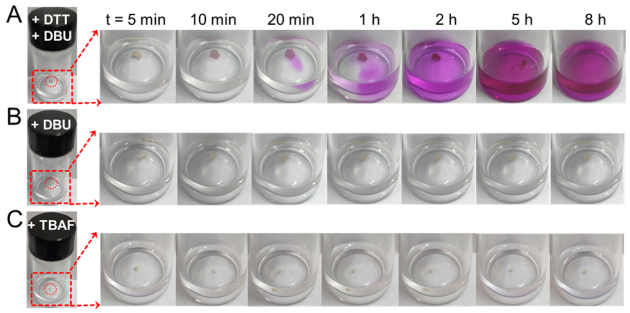

Figure 2. Time-course photographs showing the depolymerization of solid-state ScIP pellet in acetonitrile containing (A) 0.2 mM DTT and 0.8 mM DBU; (B) 0.8 mM DBU; (C) 0.2 mM TBAF.

when tetra-*n*-butylammonium fluoride (TBAF, 0.2 mM) was used to treat the polymer pellet, which otherwise would cleave the polymer end-cap and cause rapid degradation in solution (as demonstrated in THF by ^{1}H NMR, Figure S20), no color change or dissolution of the pellet was observed in 8 h. These results support our previous finding that the mobility of the SIP backbone is key in facilitating fragmentation of the polymer, and the side chain-immolative strategy can successfully enable solid-state use of these SIPs.

The pendant pyridine disulfide groups of the ScIP can be further chemically modified through the thiol−disulfide exchange reaction (Scheme 1).[29,30] By treating the ScIP with an excess (1.5 equiv to the disulfide group) of α-mercapto-methoxyPEG$_{2k}$, and subsequent GPC purification, a graft polymer (ScIP-*g*-PEG$_{2k}$) was prepared (Figure S17). When a bis-mercapto-terminated PEG$_{2k}$ (thiol/disulfide = 1.5:1, molar ratio) was used to react with the ScIP, an organogel with a gel content of 55 ± 5% was formed. Next, we examined the degradation of these ScIP-containing materials in response to DTT/DBU (Figure 3). When the graft polymer was exposed to varying concentrations of the reducing agent, an instant color changes to fuchsia was observed. THF GPC indicates the production of intermediate-length polymer fragments as well as

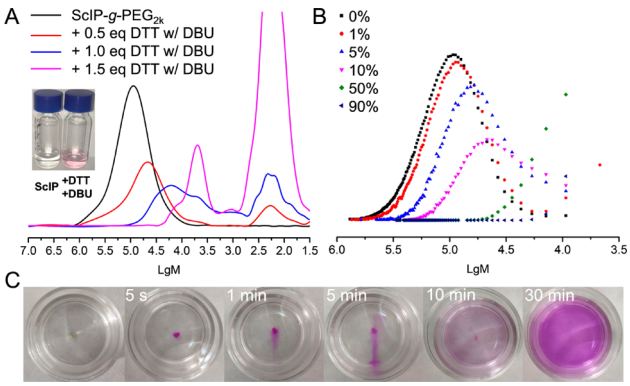

Figure 3. Self-immolative degradation of modified ScIPs. (A) THF GPC chromatograms of brush-type ScIP graft polymer treated with various amounts of DTT and DBU. Inset: color change associated with the formation of phenolates (degradation intermediate). (B) Simulated molecular weight distribution of the graft polymer after various percentages of random cleavages of the disulfides followed by complete degradation from the cleavage sites to the α-end. The initial molecular weight distribution is that of ScIP-*g*-PEG$_{2k}$. (C) Time-course photographs of a piece of ScIP-based organogel immersed in acetonitrile containing 0.2 mM DTT and 0.8 mM DBU.

free PEG chains when the graft polymer was partially degraded. It is worth noting that the side chain-initiated depolymerization is different from the chain end-initiated process in terms of expected degradation products. If the polymer is degraded from the chain-end, given sufficient reaction times, complete conversion to the corresponding monomer is expected, resulting in loss of a portion of the polymer, but no change in the molecular weight for the remaining polymers. However, if a side chain (at position x along the backbone) initiates the degradation, the segment between the polymer α-end and x is degraded, but the segment between x and the ω-end remains intact, which leads to both loss of polymer mass and reduction of molecular weight. We modeled the cleavage of the disulfides as a stochastic event and predicted the molecular weight distributions of the degraded ScIP as a function of % disulfide cleaved (Figures 3B, Scheme S4). The simulation reveals an increase of PDI and a decrease of MW as the % disulfide cleaved increases. These trends nicely match those observed with GPC, corroborating the proposed degradation mechanism. Similar to the graft copolymer, the ScIP organogel responded instantly to the addition of DTT (0.2 mM) and DBU (0.8 mM) in THF, as evidenced by the rapid color change to fuchsia and complete dissolution within 1 h (Figure S21). Interestingly, the dissolution of the gel was even faster when carried out in acetonitrile (Figure 3C), despite it being a poor solvent for the ScIP backbone, possibly due to improved ScIP backbone mobility as a result of better solvation of PEG chains in acetonitrile.

In summary, we have developed a quinone methide monomer and the corresponding anionic polymerization process to prepare a side chain-immolative and functionalizable polymer. With a high content of stimuli-responsive units, these ScIPs not only rapidly degrade in solution under reductive conditions but also undergo self-immolation in the solid state. The pendant pyridine disulfides enable postpolymerization modification to produce graft polymers and cross-linked organogels, which also respond to reductive conditions. With their syntheses and degradation demonstrated, these functionalizable ScIPs pave the way for further chemical investigations as well as technological applications (for example, ScIP systems that work in neutral pH, aqueous buffers for drug delivery, sensing, etc.).

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, additional characterization data, and supporting figures (PDF)

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Author Contributions

The manuscript was written by K.Z. and Y.X. through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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