

## Harnessing Strained Disulfides for Photocurable Adaptable Hydrogels

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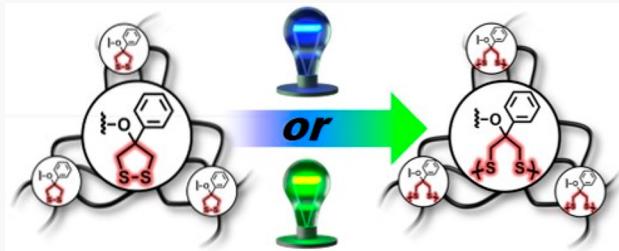
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**ABSTRACT:** We report a photomediated disulfide cross-linking strategy for the generation of adaptable hydrogels from telechelic network precursors containing strained cyclic disulfides. Exploiting the intricate stereoelectronic properties of 1,2-dithiolanes arising from the unfavorable four-electron interaction in the disulfide scaffold, amphiphilic poly(ethylene glycol)-1,2-dithiolane conjugates formed free-standing adaptable hydrogels at 10 wt % polymer content upon disulfide photolysis under UV irradiation ( $\lambda_{\text{max}} = 365$  nm). Cross-linking was achieved in less than 10 min with tunable network moduli depending on irradiation time. Investigations into the gelation mechanism suggest the formation of free thiols during light exposure accounting for the dynamic nature of the gels. Furthermore, we successfully expanded this gelation strategy to green light ( $\lambda_{\text{max}} = 515$  nm) by employing the photosensitizer eosin Y, allowing for hydrogel formation open to air.



### INTRODUCTION

Hydrogels are widely used in the biomedical field, for example, as material for contact lenses and wound dressings.<sup>1</sup> The recent convergence of dynamic-covalent chemistry<sup>2</sup> with hydrogel systems has resulted in a considerable expansion of potential hydrogel applications.<sup>3</sup> Adaptable cross-links<sup>4</sup> impart dynamic mechanical behavior to hydrogels, which renders these materials as promising platforms for drug delivery or 3D cell encapsulation and culture.<sup>1,5,6</sup>

The use of light as a stimulus in macromolecular transformations has been an important strategy in the development of adaptable hydrogels.<sup>7</sup> Photomediated reactions can alter gel properties via selective de-cross-linking,<sup>8–10</sup> postgelation patterning,<sup>11–13</sup> or network stiffening.<sup>14–16</sup> Light can also be employed for the formation of adaptable hydrogels, for example, via photoinduced thiol–ene additions<sup>17,18</sup> or copper-catalyzed alkyne–azide reactions<sup>19</sup> between monomers and presynthesized cross-linkers containing dynamic linkages or functional groups susceptible to dynamic bonding.<sup>17</sup> However, most of these approaches require photoinitiators, posing potential biocompatibility concerns. Furthermore, only a few gelation approaches exist where the dynamic cross-links that constitute the network are generated directly upon irradiation in one step. For example, Anseth and co-workers recently reported the additive-free formation of adaptable hydrazone hydrogels via the condensation of multiarm hydrazine-terminated poly(ethylene glycol) (PEG) with photoliberated 2-nitrosobenzaldehyde macromonomers.<sup>20</sup> Herein, we aim to expand the toolbox of dynamic bond-

forming photochemistry for the generation of additive-free photocurable disulfide-cross-linked hydrogels (Figure 1).

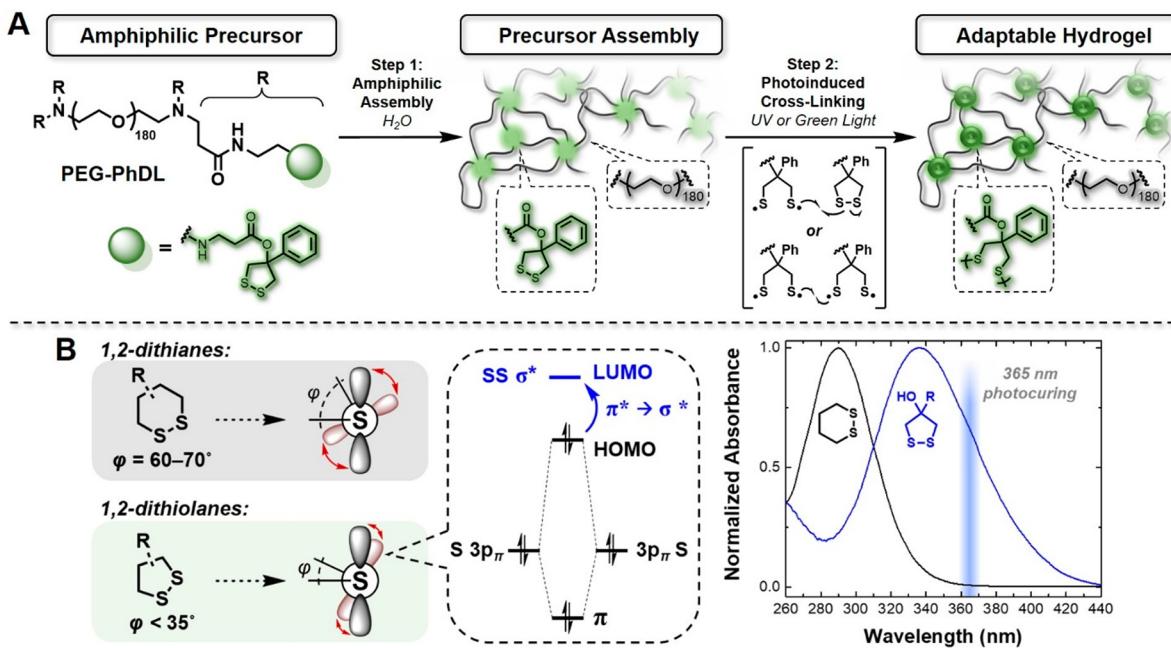
With a bond strength of approximately 63 kcal/mol,<sup>21</sup> the disulfide bond is among the strongest homonuclear single bonds; however, disulfides readily exchange with thiols<sup>22</sup> and undergo redox reactions,<sup>23</sup> making them an attractive dynamic bond for adaptable hydrogels. 1,2-Dithiolanes, five-membered cyclic disulfides, have been recognized for their versatile reactivity arising from a strained disulfide ring system.<sup>24–28</sup> For example, Waymouth and co-workers incorporated the 1,2-dithiolanes methyl asparagusic acid and lipoic acid into amphiphilic triblock copolymers prepared by ring-opening polymerization of cyclic carbonates.<sup>29,30</sup> Under selective solvent conditions, the addition of a small molecule thiol induced cross-linking of the polymer-tethered 1,2-dithiolane groups via thiol-initiated ring-opening, generating disulfide-cross-linked hydrogels with viscoelastic properties governed by a dynamic polymerization-depolymerization equilibrium. Apart from their increased reactivity, 1,2-dithiolanes exhibit unusual photoelectronic properties compared to other disulfides, as evidenced in a red-shifted UV–vis absorbance. Photolysis of linear disulfide bonds typically requires UV light at wave-

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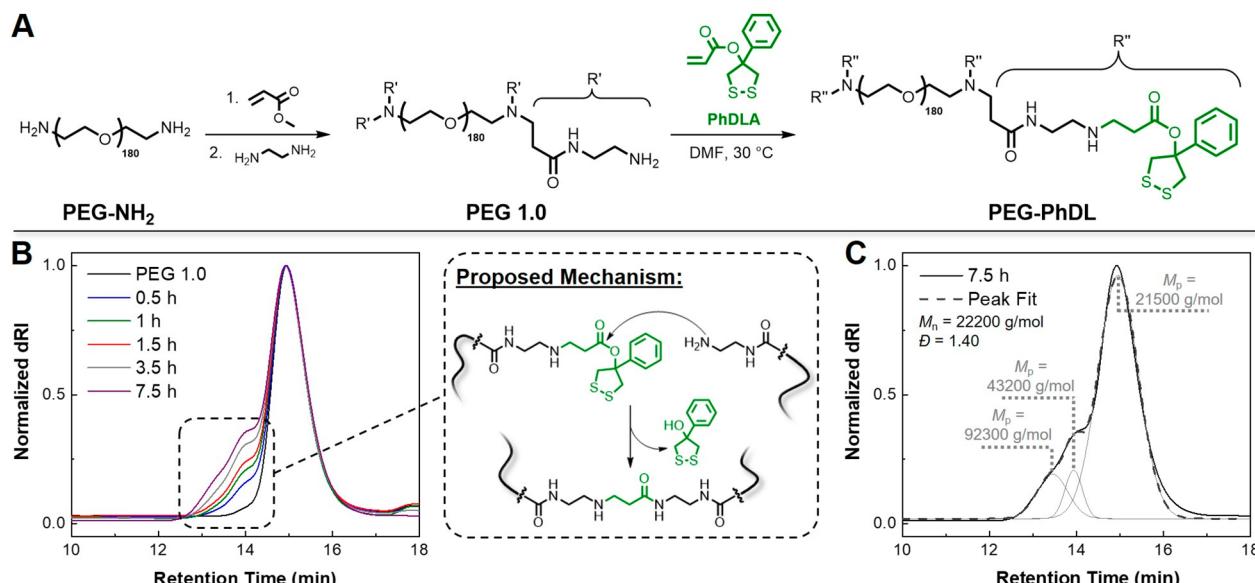
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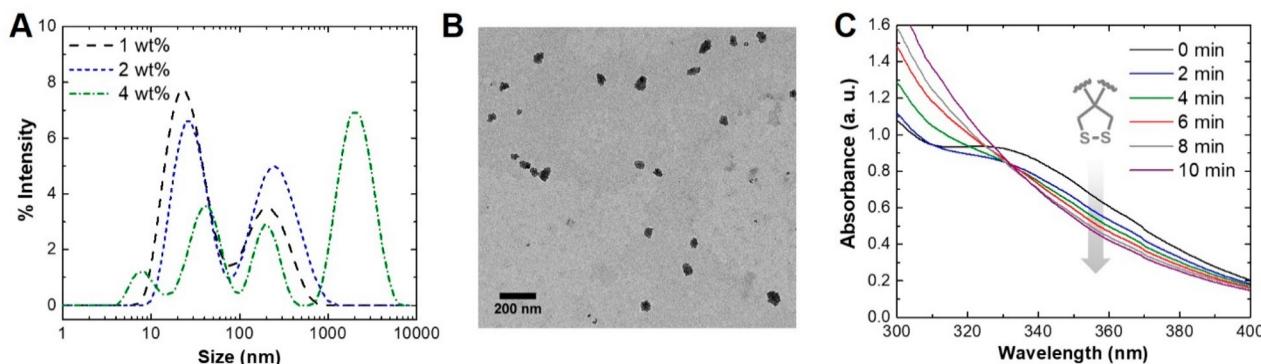
**Figure 1.** Exploiting 1,2-dithiolane photochemistry for disulfide hydrogels. (A) The gelation strategy includes the generation of latent telechelic PEG-PhDL aggregates in water with hydrophobic 1,2-dithiolane-rich cores and poly(ethylene glycol) chains in the corona. Light irradiation generates thiyl radicals that covalently cross-link the network either via ring-opening of unreacted 1,2-dithiolane units or recombination with other thiyl radicals. (B) The Fischer projections along the disulfide bond of the unstrained six-membered 1,2-dithiane with a CSSC dihedral angle ( $\varphi$ ) between 60 and 70° and a strained five-membered 1,2-dithiolane with  $\varphi$  lower than 35° reveal the sulfur 3p<sub>π</sub> orbital overlap in 1,2-dithiolanes. Both 3p<sub>π</sub> orbitals are fully occupied, thus, the asymmetric splitting into bonding  $\pi$  and antibonding  $\pi^*$  is overall destabilizing. The HOMO energy is raised, which gives rise to a bathochromic shift of the first electronic transition ( $\pi^* \rightarrow \sigma^*$ ), rendering 1,2-dithiolanes susceptible to photolysis with UV irradiation at 365 nm.



**Figure 2.** PEG-PhDL network precursor synthesis and characterization. (A) Schematic reaction sequence for the synthesis of PEG-PhDL starting from PEG-diamine (PEG-NH<sub>2</sub>). (B) The evolution of a high-molecular weight shoulder during the Michael addition of phenyl-1,2-dithiolane acrylate (PhDLA) with amidoamine PEG (PEG 1.0) at 125 mg/mL in DMF was attributed to the formation of amides via aminolysis of unhindered single PhDLA-Michael adducts with unreacted free amines. (C) Deconvolution of the final molecular weight distribution indicated formation of dimers and tetramers as the coupling products. Peak molecular weights ( $M_p$ ) were obtained relative to polystyrene standards.

lengths below 300 nm.<sup>31</sup> 1,2-Dithiolanes, however, can be photolyzed with milder UV irradiation at wavelengths around 350 nm and above,<sup>32</sup> a characteristic used in small molecule studies<sup>32–34</sup> and the cross-linking of assembled polymer structures<sup>35</sup> and networks.<sup>36</sup>

In this report, we exploited the unique electronic properties of 1,2-dithiolanes to photo-cross-link telechelic polymers into adaptable disulfide hydrogels (Figure 1A). Specifically, we modified PEG with a hydrophobic phenyl-substituted 1,2-dithiolane derivative generating the amphiphilic network



**Figure 3.** Investigation of PEG-PhDL aggregation and photolysis. (A) Dynamic light scattering of PEG-PhDL in aqueous solution showed the formation of polymer aggregates. Larger clusters of aggregates formed at higher PEG-PhDL concentrations. (B) Transmission electron microscopy of a 1 wt % solution of PEG-PhDL in water confirmed the presence of nanoparticles. (C) UV-vis spectroscopy of PEG-PhDL in water at 2 wt % after various irradiation times showed the gradual disappearance of the 1,2-dithiolane absorbance band around 330 nm due to photolysis.

precursor, denoted here as PEG-phenyl-1,2-dithiolane (PEG-PhDL). Immersion of PEG-PhDL in water promoted the formation of 1,2-dithiolane aggregates interlinked by PEG chains. 1,2-Dithiolane photolysis upon UV irradiation ( $\lambda_{\text{max}} = 365$  nm) induced radical-mediated cross-linking, most likely via ring-opening or radical recombination (Figure 1A). To further demonstrate the versatility of this hydrogel system, we developed a photocuring strategy with green light under air. The covalently cross-linked, free-standing hydrogels were shapeable, stimuli-responsive, and cell-compatible.

## RESULTS AND DISCUSSION

**1,2-Dithiolane Photochemistry.** The absorbance redshift of five-membered disulfide ring systems can be rationalized with simplified molecular orbital (MO) theory.<sup>37</sup> The Bergson model<sup>37</sup> invoked here involves significant simplifications; however, detailed molecular orbital calculations have verified the results qualitatively.<sup>38</sup> Linear disulfides usually reside in a gauche conformation with a CSSC dihedral angle ( $\varphi$ ) around 90°, minimizing the overlap of the fully occupied sulfur 3p<sub>π</sub> orbitals.<sup>37,39</sup> When the disulfide bond is incorporated into a cyclic structure,  $\varphi$  decreases, and the sulfur 3p<sub>π</sub> orbitals begin to overlap. While six-membered disulfides (i.e., 1,2-dithianes) are flexible enough to maintain an almost unstrained conformation with  $\varphi$  around 60°, the 3p<sub>π</sub> orbitals in 1,2-dithiolanes are forced into a nearly eclipsed conformation at  $\varphi$  values lower than 35°, resulting in significant orbital interaction (Figure 1B).<sup>21</sup> Due to the asymmetric splitting of the fully occupied sulfur 3p<sub>π</sub> orbitals into bonding  $\pi$  and antibonding  $\pi^*$  MOs, the destabilization of the electrons in  $\pi^*$  dominates, thus weakening the S–S bond. Additionally, the first electronic transition shifts to lower energies (i.e., to longer wavelengths) due to the raised HOMO energy, enabling 1,2-dithiolane photolysis with UV irradiation around 365 nm (Figure 1B),<sup>37,40</sup> which we aim to leverage for photoinduced network formation.

**Network Precursor Synthesis.** PEG-PhDL was synthesized via Michael addition between phenyl-1,2-dithiolane acrylate (PhDLA) and amidoamine poly(ethylene glycol) (PEG 1.0). PEG 1.0 was readily obtained from poly(ethylene glycol) diamine (PEG-NH<sub>2</sub>) after a Michael addition-aminolysis reaction sequence with methyl acrylate and ethylene diamine (Figure 2A). Successful 1,2-dithiolane conjugation was confirmed via <sup>1</sup>H NMR, UV-vis, and Raman spectroscopy (Figures S2–S4 of the Supporting

Information, SI). When the reaction was conducted at moderate polymer concentrations (25 mg/mL) in *N,N*-dimethylformamide (DMF) with methanol (MeOH) as a cosolvent for better solubility of PEG 1.0, only the single acrylate-amine Michael adduct was obtained even after elongated reaction times (30 h) at elevated temperature (50 °C). We attributed this observation to the steric hindrance around the secondary amine after the first addition (Figure S5). Increasing the concentration to 125 mg/mL and switching to DMF as the only solvent resulted in a faster conjugation reaction and higher 1,2-dithiolane incorporation, which should further promote assembly due to the enhanced hydrophobic character of the chain ends and thus facilitate subsequent network formation. However, the formation of high molecular weight species was observed by size exclusion chromatography (SEC) at longer reaction times (Figure 2B). Peak deconvolution of the SEC trace indicated that dimers and tetramers with the doubled and 4-fold molecular weights relative to the unimer PEG-PhDL were causing the high molecular weight shoulder (Figure 2C). Treatment with the disulfide reducing agent tributylphosphine<sup>41</sup> resulted in no significant change of the molecular weight distribution (Figure S6), which led us to the conclusion that intermolecular disulfide formation via 1,2-dithiolane ring opening is not occurring. Instead, we hypothesize that irreversible amide bond formation via aminolysis of PhDLA-amine Michael adducts and unreacted primary amines resulted in polymer chain coupling (Figure 2B). Notably, the formation of high molecular weight species was relatively insensitive to polymer concentration, as indicated by similar SEC patterns observed for reactions carried out at 25 and 125 mg/mL in DMF (Figures 2B and S7A). Alternatively, monomodal SEC traces were observed in DMF/MeOH at 25 mg/mL (Figure S7B), suggesting that aggregation of PEG 1.0 in DMF, also evident from a hazy reaction mixture, is a determining factor for interchain coupling.

We found that multimodal PEG-PhDL network precursors obtained from DMF generally yielded hydrogels at much lower polymer loadings than the monomodal PEG-PhDL from DMF/MeOH. This is likely due to the dimeric and tetrameric 1,2-dithiolane-conjugates acting as multifunctional bridging units between multiple smaller polymer assemblies, thus lowering the network percolation threshold (Figure S8). For consistency, all hydrogels in this report were formed from the same PEG-PhDL network precursor containing dimers and

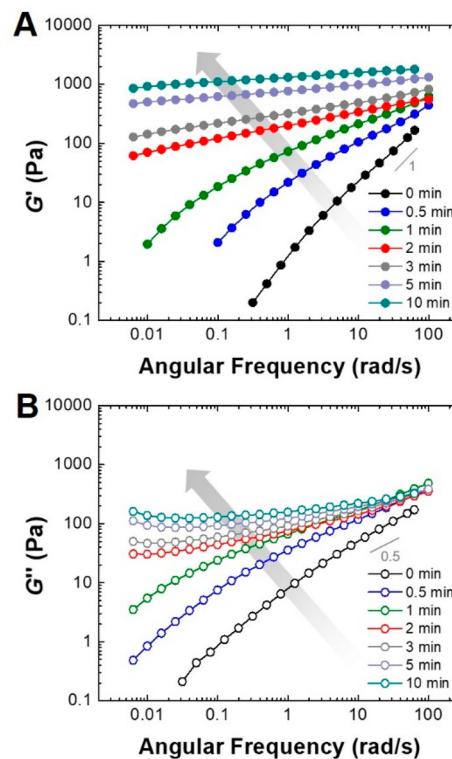
tetramers synthesized from DMF with a number-average molecular weight ( $M_n$ ) of 22 200 g/mol, a dispersity ( $D$ ) of 1.40, and 68% 1,2-dithiolane incorporation (Figures 2, S3, and S4).

**Aggregation and Photolysis of PEG-PhDL.** The accumulation of 1,2-dithiolane moieties in the hydrophobic regions of assembled networks is critical for efficient disulfide cross-linking.<sup>30</sup> To assess the assembly behavior of PEG-PhDL, we performed dynamic light scattering (DLS) on aqueous solutions of PEG-PhDL at 1, 2, and 4 wt % (Figure 3A). At the concentrations tested, DLS showed the formation of PEG-PhDL aggregates with multiple size distributions. Transmission electron microscopy (TEM) of aggregates formed at 1 wt % showed spherical and elongated nanoparticles with diameters ranging from 20 to 70 nm (Figures 3B and S9), matching with the first major size distribution observed by DLS. These results suggest that the hydrophobicity of the tethered 1,2-dithiolane moieties is sufficient to induce aggregation into nanoparticles with 1,2-dithiolane units in the core and hydrophilic PEG chains in the corona. Higher concentrations of PEG-PhDL led to larger structures, which can be attributed to the increased clustering of PEG-PhDL aggregates via bridging PEG chains.<sup>30</sup>

To investigate 1,2-dithiolane photolysis in PEG-PhDL aggregates, we monitored the disappearance of the 1,2-dithiolane absorbance band around 330 nm by UV-vis spectroscopy after regular time intervals of UV light exposure under argon atmosphere (Figure 3C). The decreasing absorbance with increasing irradiation time confirmed photo-induced cleavage of the strained disulfide bond.<sup>29,35</sup> The evolution of a new absorbance band above 300 nm, which most likely arises from the formation of new linear disulfide linkages, prevented absolute quantification of 1,2-dithiolane photolysis. However, we tried to mitigate the impact of this band overlap by determining the relative 1,2-dithiolane absorbance ( $A_t/A_0$ ) after various irradiation times at a wavelength (i.e., 380 nm) that is separated from the overlap region (Figure S10). Both PEG-PhDL concentrations (i.e., 2 and 4 wt %) showed comparable rates of 1,2-dithiolane absorbance decrease, which we believe is due to a similar local concentration of 1,2-dithiolane units inside the cores of the PEG-PhDL aggregates.

**UV Photocuring of PEG-PhDL.** Having established a protocol for 1,2-dithiolane cross-linking at low PEG-PhDL concentrations, we increased the polymer concentration to 10 wt %, resulting in macroscopic gelation after 2 min irradiation. The minimum polymer content for gelation was found to be around 7 wt %, and solutions containing less—albeit showing an increase in viscosity—failed to form macroscopic networks, most likely due to insufficient percolation of PEG chains between the amphiphilic polymer assemblies. In this report, all hydrogels discussed below were formed at 10 wt % PEG-PhDL in water. No gelation could be observed in nonselective solvents such as methanol or dimethyl sulfoxide, which agrees with the findings by Waymouth and co-workers that assembly of 1,2-dithiolane units is necessary for network formation.<sup>29,30</sup>

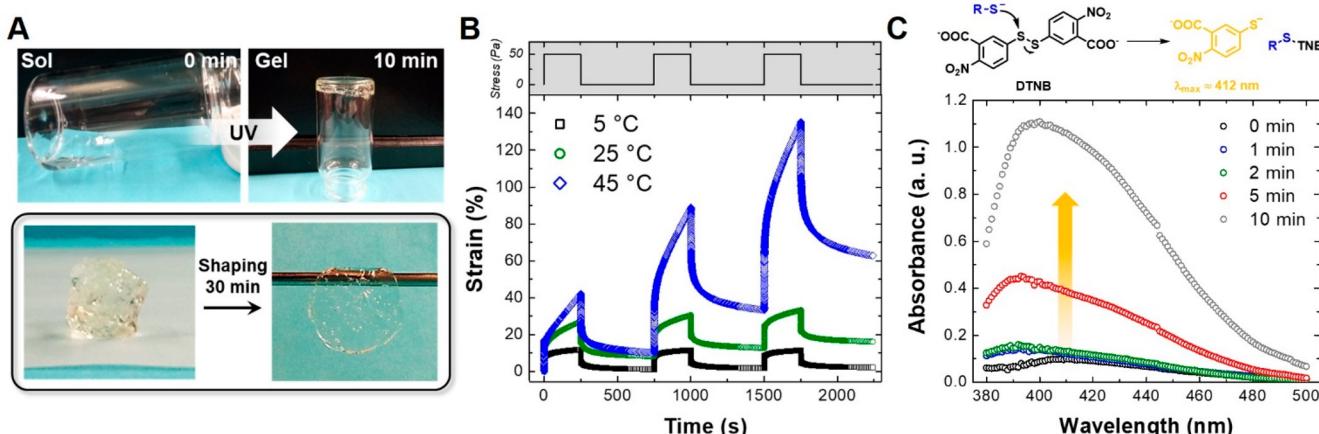
To characterize the cross-linking process, we studied the mechanical properties of PEG-PhDL hydrogels as a function of irradiation time using small-amplitude oscillatory shear rheology (Figure 4).<sup>42</sup> In oscillatory shear measurements, a small sinusoidal deformation is applied to the sample, resulting in a complex response, which can be separated into a storage modulus ( $G'$ ) and a loss modulus ( $G''$ ). Conceptually,  $G'$  is related to the energy stored reversibly in the network (i.e., the



**Figure 4.** Oscillatory shear rheology of UV-cured PEG-PhDL hydrogels at 25 °C and 1% strain. (A) Evolution of storage modulus ( $G'$ ) and (B) loss modulus ( $G''$ ) with increasing irradiation time. The more pronounced increase of  $G'$  over  $G''$  is indicative of covalent network formation.

elastic response), and  $G''$  represents the amount of energy being dissipated as heat (i.e., the viscous response). After determining the linear viscoelastic region for each sample with strain sweep experiments (Figure S12), we studied the viscoelastic properties of the hydrogels at different irradiation times at 1% strain and 25 °C via angular frequency ( $\omega$ ) sweeps (Figure 4). Prior to UV exposure,  $G''$  was found to be higher than  $G'$  until the high-frequency limit ( $\omega \sim 50$  rad/s), indicating predominantly viscous behavior (Figures 4 and S13). After 1 min of irradiation,  $G'$  and  $G''$  were congruent and exhibited similar frequency scaling ( $G', G'' \approx \omega^{0.3}$ ), two characteristics that are typically observed at the gel point of a network (Figure S13).<sup>43</sup> Upon further UV irradiation,  $G'$  continued to increase more than  $G''$ , indicating successful covalent network formation. We also tested thiol-induced cross-linking via the addition of 10 mol % (with respect to 1,2-dithiolane units) of 2-mercaptoethanol, analogous to the report by Waymouth and co-workers.<sup>30</sup> The hydrogels obtained via this method showed almost the same viscoelastic properties as the photocured gels (Figure S14), supporting our hypothesis that ring-opening and subsequent disulfide cross-linking caused network formation.

Generally, dynamically cross-linked materials exhibit time-dependent viscoelastic behavior.<sup>44</sup> At time scales longer than the terminal relaxation time ( $\tau_{\max}$ ), network rearrangements enabled by bond exchange can effectively dissipate energy, resulting in a predominantly viscous response upon deformation (i.e.,  $G' < G''$ ). If the deformation is applied on time scales shorter than  $\tau_{\max}$  then the lifetime of the dynamic bond is too long to contribute significantly to the relaxation spectrum and



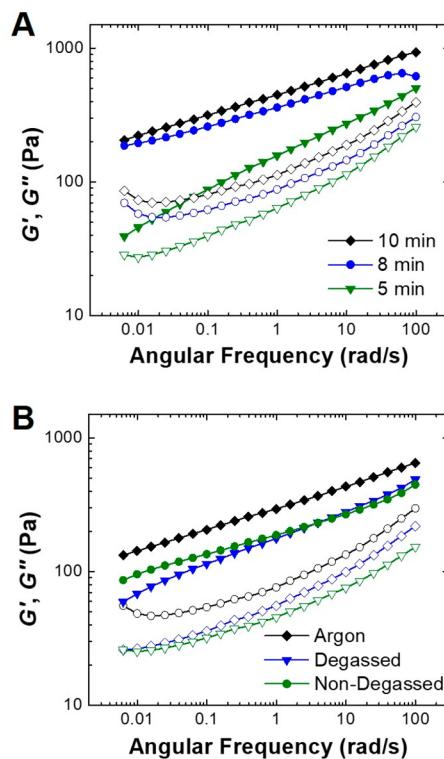
**Figure 5.** Shape adaptability of PEG-PhDL hydrogels. (A) Photographs of PEG-PhDL in water before and after UV irradiation (top); the free-standing transparent hydrogels could be shaped into plates (bottom). (B) Step creep experiments at different temperatures indicated temperature-dependent bond exchange. (C) Ellman's reagent dithionitrobenzoic acid (DTNB) exchanges with thiols forming the colored 2-nitro-5-thiobenzoate. UV-vis spectroscopy of Ellman's assay on PEG-PhDL hydrogels after varying irradiation times showed an increasing absorbance at 412 nm, indicative of thiol formation.

the viscoelastic response becomes mostly elastic (i.e.,  $G' > G''$ ). Therefore, in an ideal dynamically cross-linked material, we expect the viscoelastic spectrum to be separated into a predominantly viscous region at lower frequencies and a mostly elastic region at higher frequencies with a moduli crossover at  $\tau_{\max}$ . For hydrogels prepared from PEG-PhDL after 10 min UV irradiation,  $G'$  stayed fairly constant, around 1300 Pa across the probed frequency range, and  $G''$  remained approximately at 200 Pa (Figures 4 and S13). Such a time-independent mechanical response is usually associated with elastic materials. However, the free-standing PEG-PhDL hydrogels showed self-healing behavior and could be readily shaped into plates (Figure 5A), indicating dynamic bond exchange in the material. Furthermore, assuming a Maxwell model to calculate the ratio of energy stored and dissipated per unit volume (SI S4),<sup>45,46</sup> we estimated that about 70% of the total energy was dissipated via network relaxation at the lowest frequency measured (0.006 rad/s), suggesting significant viscous character at this time scale. Additionally, such a convex shape of  $G''$  (Figures 4B and S13) is often observed in frequency sweep curves of dynamic networks at frequencies above the crossover frequency, suggesting that dynamic bond exchange is occurring, but not on the investigated time scales.<sup>47</sup>

To confirm this hypothesis, we employed step creep recovery experiments, probing the viscoelastic behavior of the PEG-PhDL gel after 10 min irradiation at different temperatures and longer experimental time scales (Figure 5B). At 5 °C, the hydrogel showed little permanent deformation (2% over three steps). Upon increasing the temperature, creep increased significantly, and the permanent deformation reached 16% at 25 °C and 63% at 45 °C (both over three steps). We believe that this distinct temperature dependence of creep (Figure S15) is most likely due to thermally activated bond exchange. Two mechanisms for bond exchange in disulfide-cross-linked materials can be envisioned: disulfide metathesis and thiol–disulfide exchange. Metathesis of alkyl disulfides usually requires higher temperatures<sup>48–50</sup> or UV light.<sup>51,52</sup> Thiol–disulfide exchange, however, is known to occur also at ambient temperatures.<sup>22,53</sup> Considering the substantial creep observed at room temperature, we tested the

gels for thiols after varying irradiation times via Ellman's assay combined with UV-vis spectroscopy (Figures 5C and S16). The increasing absorbance around 412 nm clearly indicated the presence of thiols after irradiation, implying that the dynamic character of PEG-PhDL hydrogels can likely be attributed to thiol–disulfide exchange. Early work by Barltrop<sup>32</sup> and Brown<sup>33</sup> suggests hydrogen abstraction by thiyl radicals from C–H bonds in  $\alpha$ -position to oxygen atoms, however, the structure of the proposed products was not fully determined. Recently, Bertrand and co-workers unambiguously showed that thiyl radicals undergo hydrogen transfer with  $\alpha$ -C–H bonds in aliphatic amines,<sup>54,55</sup> benefiting from favorable polar effects between the electron-poor thiyl radical and the electron-rich C–H bond in  $\alpha$ -position to the nitrogen.<sup>56</sup> On the basis of these reports we propose that in the PEG-PhDL hydrogel system, some of the thiyl radicals formed via UV-induced photolysis of 1,2-dithiolane units are reduced to thiols via  $\alpha$ -C–H abstraction from secondary and tertiary amines present in the polymer structure (Figure 2A).

**Green Light Photocuring of PEG-PhDL.** Hydrogel cross-linking strategies that employ UV light can substantially limit their utility in biological systems.<sup>9</sup> Moreover, longer-wavelength light allows for enhanced curing depths. On the basis of work by Glorius and co-workers, who demonstrated the photocatalytic activation of disulfides under blue light,<sup>57</sup> we hypothesized that the weakened S–S bond in 1,2-dithiolanes could undergo cleavage and cross-linking upon photoinduced electron/energy transfer (PET) from a suitable photocatalyst combined with visible light. To test this hypothesis, we employed eosin Y (EY) as a biocompatible<sup>58,59</sup> and water-soluble photocatalyst<sup>60</sup> in 10 wt % PEG-PhDL solution with green light irradiation ( $\lambda_{\max} = 515$  nm). Cross-linked hydrogels formed with 0.01 mol equiv of EY with respect to 1,2-dithiolane units under an argon atmosphere (Figure 6A). Without the addition of EY, no cross-linking was observed even after elongated irradiation times. Similar to the UV-curing approach, we observed a gradual modulus increase with irradiation time, however, the EY gels were significantly weaker than the UV gels. This suggests that the hydrogels generated with green light have a lower cross-link density than those prepared during UV irradiation, which is further reflected in



**Figure 6.** Oscillatory shear rheology at 25 °C and 1% strain of hydrogels formed with 0.01 mol equiv eosin Y (relative to 1,2-dithiolane units) under green light. (A) Storage ( $G'$ ) and loss ( $G''$ ) moduli increase with increasing irradiation time, showing covalent cross-linking. (B) Modulus comparison of hydrogels formed under argon, in a degassed solution but open to air (Degassed), and in a non-degassed solution open to air (Non-Degassed).

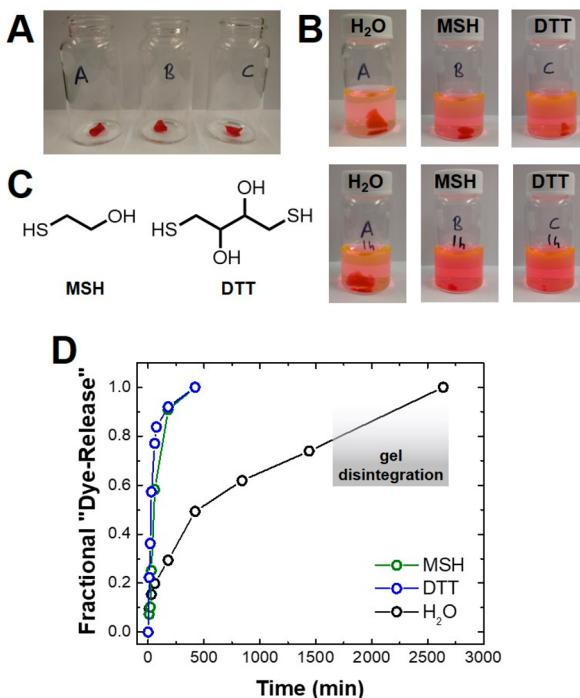
the more pronounced frequency dependence of  $G'$  in these gels. EY loading had a significant effect on network formation (Figure S17). Specifically, lower EY loadings failed to produce a cross-linked network.

We also observed considerable photobleaching of EY, which does not correlate with a catalytic PET sequence. Since matching redox potentials of the substrate and the excited state photocatalyst are crucial for PET reactions,<sup>61</sup> we conducted cyclic voltammetry experiments on a 1,2-dithiolane small molecule analog to assess the susceptibility of photoinduced reductive disulfide cleavage in our system (Figure S18). Critically, we found that the peak reduction potential ( $E_{p,red}$ ) of the 1,2-dithiolane model compound ( $E_{p,red} = -1.83$  V against SCE) is substantially lower than the reported reduction potential of excited state EY\* [ $E_{red}$  (EY<sup>+</sup>/EY\*) = -1.1 V against SCE],<sup>61,62</sup> which renders a catalytic PET reaction between those two reaction partners unfavorable. Instead, we believe that EY, in synergy with the amines tethered to the polymer structure, acts as a radical photoinitiator for 1,2-dithiolane ring-opening.<sup>63</sup> EY-amine photoinitiator systems have been widely applied for the polymerization of vinyl monomer-based hydrogel films.<sup>64–66</sup> The mechanism of EY-amine photoinitiation includes a single electron transfer from the nitrogen lone pair to the excited state EY\* followed by proton abstraction from the amino radical cation, with the resulting  $\alpha$ -amino radical initiating polymerization.<sup>67,68</sup>

The ability to cross-link under ambient conditions (i.e., room temperature and air atmosphere) is a highly sought-after feature in designing novel hydrogel systems. EY is known to

bestow oxygen tolerance upon radical polymerizations via the reduction of oxygen to the superoxide anion.<sup>62</sup> Therefore, we tested gelation of PEG-PhDL with EY in a degassed solution but in an open vial (Degassed, Figure 6B), and in a non-degassed solution open to air (Non-Degassed). Both conditions led to the formation of hydrogels with similar mechanical properties, albeit with lower moduli than hydrogels cured with EY under argon atmosphere, which is most likely due to increased oxygen-induced radical termination events.

**Dye Release and Cytotoxicity.** To further prove the dynamic nature of the PEG-PhDL networks, we tested the thiol-triggered de-cross-linking of the gels by monitoring the release of the dye rhodamine 6G after incorporation into the hydrogel matrix (Figure 7). Dye-encapsulated gels were



**Figure 7.** Thiol-triggered dye release from UV-cured PEG-PhDL gels. (A) Photograph of rhodamine 6G-encapsulated hydrogels. (B) Chemical structures of the thiol triggers 2-mercaptoethanol (MSH) and dithiothreitol (DTT). (C) Photographs of the hydrogels immersed in 10 mL H<sub>2</sub>O, aqueous MSH (9  $\mu$ M), and aqueous DTT (9  $\mu$ M), after 5 min (top) and 60 min (bottom). (D) Full dye release profile of the gels.

generated by mixing rhodamine 6G into a solution of PEG-PhDL (0.02 wt % rhodamine 6G content), followed by curing under UV light (Figure 7A). Rhodamine 6G does not absorb light at wavelengths below 435 nm; thus, no interference with the photo-cross-linking process was expected, as corroborated by the similar mechanical properties of gels with and without rhodamine 6G. In water, the gel swelled substantially (Figure 7B), resulting in mostly diffusive dye release<sup>69,70</sup> for the first 30 h (~65% release). After 30 h, we observed gel disintegration due to slow thiol–disulfide exchange in the network originating from residual thiols formed during UV irradiation. In the presence of excess 2-mercaptoethanol (MSH; Figure 7C), which readily exchanges with disulfide cross-links, the gel completely dissolved in 150 min concomitant with a fast release of rhodamine 6G (Figures 7D and S19). Notably, the gel seemed to undergo surface erosion rather than bulk

swelling (Figure 7C), indicating that network de-cross-linking through thiol–disulfide exchange with excess MSH is faster than water diffusion into the gel.<sup>69,70</sup> Using the highly potent disulfide reducing agent dithiothreitol (DTT), even faster network dissolution and surface erosion were observed (Figure S19), which is consistent with more rapid disulfide cross-link cleavage by DTT. These results not only provide further evidence for the presence of dynamic disulfide cross-links in photocured PEG-PhDL gels, but also show that network degradation and cargo release can be triggered upon exposure to free thiols.

Finally, we investigated the cell-compatibility of PEG-PhDL hydrogels with NIH-3t3 cells (Figures S20 and S21). When cells were plated with fully cured PEG-PhDL hydrogels, ~80% of the cells were alive after 6 h (Figure S20), suggesting that photocured PEG-PhDL hydrogels could be used in applications that require triggered de-cross-linking or the release of a molecular cargo in the presence of living systems such as cells.

## CONCLUSIONS

We have demonstrated that the photophysical properties of strained cyclic disulfides in conjunction with telechelic polymer assembly can be leveraged for the design of an adaptable hydrogel system that undergoes a light-triggered disulfide-forming cross-linking reaction. Amphiphilic PEG-based polymers, modified with 1,2-dithiolane end-groups, show covalent network formation under UV light without any additives, or under green light in the presence of the photosensitizer EY. The disulfide-cross-linked free-standing hydrogels exhibit dynamic character at longer time scales due to thiol–disulfide exchange.

Irradiation time can be used to tune the mechanical properties of the gels, where longer irradiation times result in stiffer hydrogels. We believe this spatiotemporal control over cross-linking and network modulus can be a versatile feature in the realm of 3D-printing and photopatterning.

Importantly, this report illustrates how the careful design of macromolecular building blocks enables the development of advanced soft materials.<sup>71,72</sup> For the future, we envision that molecular manipulations of the 1,2-dithiolane groups,<sup>30,73</sup> together with variations of polymer amphiphilicity,<sup>74,75</sup> will lead to a diverse design of hydrogel performance, where robustness, biocompatibility, and stimuli-responsiveness can be discretely tuned.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.macromol.0c00604>.

Materials, experimental procedures, calculations, supporting figures, and characterization data (PDF)

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The authors declare no competing financial interest.

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## REFERENCES

- (1) Seliktar, D. Designing Cell-Compatible Hydrogels for Biomedical Applications. *Science* **2012**, *336*, 1124–1128.
- (2) Wojtecki, R. J.; Meador, M. A.; Rowan, S. J. Using the dynamic bond to access macroscopically responsive structurally dynamic polymers. *Nat. Mater.* **2011**, *10*, 14–27.
- (3) LeValley, P. J.; Kloxin, A. M. Chemical Approaches to Dynamically Modulate the Properties of Synthetic Matrices. *ACS Macro Lett.* **2019**, *8*, 7–16.
- (4) Scheutz, G. M.; Lessard, J. J.; Sims, M. B.; Sumerlin, B. S. Adaptable Crosslinks in Polymeric Materials: Resolving the Intersection of Thermoplastics and Thermosets. *J. Am. Chem. Soc.* **2019**, *141*, 16181–16196.
- (5) Wang, H.; Heilshorn, S. C. Adaptable hydrogel networks with reversible linkages for tissue engineering. *Adv. Mater.* **2015**, *27*, 3717–3736.
- (6) Rosales, A. M.; Anseth, K. S. The design of reversible hydrogels to capture extracellular matrix dynamics. *Nat. Rev. Mater.* **2016**, *1*, 15012.
- (7) Chatani, S.; Kloxin, C. J.; Bowman, C. N. The power of light in polymer science: photochemical processes to manipulate polymer formation, structure, and properties. *Polym. Chem.* **2014**, *5*, 2187–2201.
- (8) Kloxin, A. M.; Kasko, A. M.; Salinas, C. N.; Anseth, K. S. Photodegradable Hydrogels for Dynamic Tuning of Physical and Chemical Properties. *Science* **2009**, *324*, 59–63.
- (9) Kabb, C. P.; O'Bryan, C. S.; Deng, C. C.; Angelini, T. E.; Sumerlin, B. S. Photoreversible Covalent Hydrogels for Soft-Matter

Additive Manufacturing. *ACS Appl. Mater. Interfaces* **2018**, *10*, 16793–16801.

(10) Azagarsamy, M. A.; McKinnon, D. D.; Alge, D. L.; Anseth, K. S. Coumarin-Based Photodegradable Hydrogel: Design, Synthesis, Gelation, and Degradation Kinetics. *ACS Macro Lett.* **2014**, *3*, 515–519.

(11) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. Sequential click reactions for synthesizing and patterning three-dimensional cell microenvironments. *Nat. Mater.* **2009**, *8*, 659–664.

(12) Chen, M.; Gu, Y.; Singh, A.; Zhong, M.; Jordan, A. M.; Biswas, S.; Korley, L. T.; Balazs, A. C.; Johnson, J. A. Living Additive Manufacturing: Transformation of Parent Gels into Diversely Functionalized Daughter Gels Made Possible by Visible Light Photoredox Catalysis. *ACS Cent. Sci.* **2017**, *3*, 124–134.

(13) LeValley, P. J.; Neelarapu, R.; Sutherland, B. P.; Dasgupta, S.; Kloxin, C. J.; Kloxin, A. M. Photolabile Linkers: Exploiting Labile Bond Chemistry to Control Mode and Rate of Hydrogel Degradation and Protein Release. *J. Am. Chem. Soc.* **2020**, *142*, 4671–4679.

(14) Tamate, R.; Ueki, T.; Kitazawa, Y.; Kuzunuki, M.; Watanabe, M.; Akimoto, A. M.; Yoshida, R. Photo-Dimerization Induced Dynamic Viscoelastic Changes in ABA Triblock Copolymer-Based Hydrogels for 3D Cell Culture. *Chem. Mater.* **2016**, *28*, 6401–6408.

(15) Brown, T. E.; Silver, J. S.; Worrell, B. T.; Marozas, I. A.; Yavitt, F. M.; Gunay, K. A.; Bowman, C. N.; Anseth, K. S. Secondary Photocrosslinking of Click Hydrogels To Probe Myoblast Mechano-transduction in Three Dimensions. *J. Am. Chem. Soc.* **2018**, *140*, 11585–11588.

(16) Accardo, J. V.; Kalow, J. A. Reversibly tuning hydrogel stiffness through photocontrolled dynamic covalent crosslinks. *Chem. Sci.* **2018**, *9*, 5987–5993.

(17) Cash, J. J.; Kubo, T.; Bapat, A. P.; Sumerlin, B. S. Room-Temperature Self-Healing Polymers Based on Dynamic-Covalent Boronic Esters. *Macromolecules* **2015**, *48*, 2098–2106.

(18) Cash, J. J.; Kubo, T.; Dobbins, D. J.; Sumerlin, B. S. Maximizing the symbiosis of static and dynamic bonds in self-healing boronic ester networks. *Polym. Chem.* **2018**, *9*, 2011–2020.

(19) Adzima, B. J.; Tao, Y.; Kloxin, C. J.; DeForest, C. A.; Anseth, K. S.; Bowman, C. N. Spatial and temporal control of the alkyne-azide cycloaddition by photoinitiated Cu(II) reduction. *Nat. Chem.* **2011**, *3*, 256–259.

(20) Azagarsamy, M. A.; Marozas, I. A.; Spaans, S.; Anseth, K. S. Photoregulated Hydrazone-Based Hydrogel Formation for Biochemically Patterning 3D Cellular Microenvironments. *ACS Macro Lett.* **2016**, *5*, 19–23.

(21) Steudel, R. Properties of Sulfur-Sulfur Bonds. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 655–664.

(22) Houk, J.; Whitesides, G. M. Structure-Reactivity Relations for Thiol-Disulfide Interchange. *J. Am. Chem. Soc.* **1987**, *109*, 6825–6835.

(23) Vogt, A. P.; Sumerlin, B. S. Temperature and redox responsive hydrogels from ABA triblock copolymers prepared by RAFT polymerization. *Soft Matter* **2009**, *5*, 2347–2351.

(24) Burns, J. A.; Whitesides, G. M. Predicting the stability of cyclic disulfides by molecular modeling: effective concentrations in thiol-disulfide interchange and the design of strongly reducing dithiols. *J. Am. Chem. Soc.* **1990**, *112*, 6296–6303.

(25) Singh, R.; Whitesides, G. M. Degenerate Intermolecular Thiolate-Disulfide Interchange Involving Cyclic Five-Membered Disulfides Is Faster by Than That Involving Six- or Seven-Membered Disulfides. *J. Am. Chem. Soc.* **1990**, *112*, 6304–6309.

(26) Zhang, Q.; Shi, C.-Y.; Qu, D.-H.; Long, Y.-T.; Feringa, B. L.; Tian, H. Exploring a naturally tailored small molecule for stretchable, self-healing, and adhesive supramolecular polymers. *Sci. Adv.* **2018**, *4*, No. eaat8192.

(27) Bang, E. K.; Gasparini, G.; Molinard, G.; Roux, A.; Sakai, N.; Matile, S. Substrate-initiated synthesis of cell-penetrating poly(disulfide)s. *J. Am. Chem. Soc.* **2013**, *135*, 2088–2091.

(28) Yu, H.; Wang, Y.; Yang, H.; Peng, K.; Zhang, X. Injectable self-healing hydrogels formed via thiol/disulfide exchange of thiol functionalized F127 and dithiolane modified PEG. *J. Mater. Chem. B* **2017**, *5*, 4121–4127.

(29) Barcan, G. A.; Zhang, X.; Waymouth, R. M. Structurally dynamic hydrogels derived from 1,2-dithiolanes. *J. Am. Chem. Soc.* **2015**, *137*, 5650–5653.

(30) Zhang, X.; Waymouth, R. M. 1,2-Dithiolane-Derived Dynamic, Covalent Materials: Cooperative Self-Assembly and Reversible Cross-Linking. *J. Am. Chem. Soc.* **2017**, *139*, 3822–3833.

(31) Klepel, F.; Ravoo, B. J. Dynamic covalent chemistry in aqueous solution by photoinduced radical disulfide metathesis. *Org. Biomol. Chem.* **2017**, *15*, 3840–3842.

(32) Barltrop, J. A.; Hayes, P. M.; Calvin, M. The Chemistry of 1,2-Dithiolane (Trimethylene Disulfide) as a Model for the Primary Quantum Conversion Act in Photosynthesis. *J. Am. Chem. Soc.* **1954**, *76*, 4348–4367.

(33) Brown, P. R.; Edwards, J. O. Effect of solvent on the photolysis of alpha-lipoic acid. *J. Org. Chem.* **1969**, *34*, 3131–3135.

(34) Whitney, R. B.; Calvin, M. Chemical and Photochemical Studies on 6,8-Thioctic Acid and 1,2-Dithiolane (Trimethylene Disulfide). *J. Chem. Phys.* **1955**, *23*, 1750–1756.

(35) Margulis, K.; Zhang, X.; Joubert, L. M.; Bruening, K.; Tassone, C. J.; Zare, R. N.; Waymouth, R. M. Formation of Polymeric Nanocubes by Self-Assembly and Crystallization of Dithiolane-Containing Triblock Copolymers. *Angew. Chem., Int. Ed.* **2017**, *56*, 16357–16362.

(36) Song, L.; Zhang, B.; Gao, G.; Xiao, C.; Li, G. Single component Pluronic F127-lipoic acid hydrogels with self-healing and multi-responsive properties. *Eur. Polym. J.* **2019**, *115*, 346–355.

(37) Bergson, G. Molecular orbital treatment of the 3p(pi) interaction in five-membered cyclic disulphides. *Ark. Kemi* **1958**, *12*, 233–237.

(38) Boyd, D. B. Conformational dependence of the electronic energy levels in disulfides. *J. Am. Chem. Soc.* **1972**, *94*, 8799–8804.

(39) Zysman-Colman, E.; Harpp, D. N. Comparison of the structural properties of compounds containing the XSSX moiety (X = H, Me, R, Cl, Br, F, OR). *J. Sulfur Chem.* **2004**, *25*, 291–316.

(40) Bergson, G.; Claeson, G.; Schotte, L.; Block-Bolten, A.; Toguri, J. M.; Flood, H. Ultraviolet Absorption Spectra of Disulphides and Diselenides. *Acta Chem. Scand.* **1962**, *16*, 1159–1174.

(41) Humphrey, R. E.; Potter, J. L. Reduction of Disulfides with Tributylphosphine. *Anal. Chem.* **1965**, *37*, 164–165.

(42) Yan, C.; Pochan, D. J. Rheological properties of peptide-based hydrogels for biomedical and other applications. *Chem. Soc. Rev.* **2010**, *39*, 3528–3540.

(43) Winter, H. H.; Chambon, F. Analysis of Linear Viscoelasticity of a Crosslinking Polymer at the Gel Point. *J. Rheol.* **1986**, *30*, 367–382.

(44) Leibler, L.; Rubinstein, M.; Colby, R. H. Dynamics of reversible networks. *Macromolecules* **1991**, *24*, 4701–4707.

(45) Goodwin, J. W.; Hughes, R. W. Linear Viscoelasticity I: Phenomenological Approach. *Rheology for Chemists: An Introduction*, 2<sup>nd</sup> ed.; Royal Society of Chemistry: Cambridge, 2008; pp 102–103.

(46) Macosko, C. W. Linear Viscoelasticity. *Rheology: Principles, Measurements, and Applications*; Wiley-VCH: New York, 1994; pp 122–123.

(47) Brown, T. E.; Carberry, B. J.; Worrell, B. T.; Dudaryeva, O. Y.; McBride, M. K.; Bowman, C. N.; Anseth, K. S. Photopolymerized dynamic hydrogels with tunable viscoelastic properties through thioester exchange. *Biomaterials* **2018**, *178*, 496–503.

(48) Lafont, U.; van Zeijl, H.; van der Zwaag, S. Influence of Cross-linkers on the Cohesive and Adhesive Self-Healing Ability of Polysulfide-Based Thermosets. *ACS Appl. Mater. Interfaces* **2012**, *4*, 6280–6288.

(49) Canadell, J.; Goossens, H.; Klumperman, B. Self-Healing Materials Based on Disulfide Links. *Macromolecules* **2011**, *44*, 2536–2541.

(50) Imbernon, L.; Oikonomou, E. K.; Norvez, S.; Leibler, L. Chemically crosslinked yet reprocessable epoxidized natural rubber

via thermo-activated disulfide rearrangements. *Polym. Chem.* **2015**, *6*, 4271–4278.

(51) Michal, B. T.; Jaye, C. A.; Spencer, E. J.; Rowan, S. J. Inherently Photohealable and Thermal Shape-Memory Polydisulfide Networks. *ACS Macro Lett.* **2013**, *2*, 694–699.

(52) Otsuka, H.; Nagano, S.; Kobashi, Y.; Maeda, T.; Takahara, A. A dynamic covalent polymer driven by disulfide metathesis under photoirradiation. *Chem. Commun.* **2010**, *46*, 1150–1152.

(53) Pepels, M.; Pilot, I.; Klumperman, B.; Goossens, H. Self-healing systems based on disulfide-thiol exchange reactions. *Polym. Chem.* **2013**, *4*, 4955–4965.

(54) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. Thiyl Radical Mediated Racemization of Non-activated Aliphatic Amines. *J. Org. Chem.* **2006**, *71*, 7288–7292.

(55) Routaboul, L.; Vanthuyne, N.; Gastaldi, S.; Gil, G.; Bertrand, M. Highly Efficient Photochemically Induced Thiyl Radical-Mediated Racemization of Aliphatic Amines at 30 °C. *J. Org. Chem.* **2008**, *73*, 364–368.

(56) Roberts, B. P. Polarity-reversal catalysis of hydrogen-atom abstraction reactions: concepts and applications in organic chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

(57) Teders, M.; Henkel, C.; Anhäuser, L.; Strieth-Kalthoff, F.; Gómez-Suárez, A.; Kleinmans, R.; Kahnt, A.; Rentmeister, A.; Guldin, D.; Glorius, F. The energy-transfer-enabled biocompatible disulfide-ene reaction. *Nat. Chem.* **2018**, *10*, 981–988.

(58) Niu, J.; Lunn, D. J.; Pusuluri, A.; Yoo, J. I.; O’Malley, M. A.; Mitragotri, S.; Soh, H. T.; Hawker, C. J. Engineering live cell surfaces with functional polymers via cytocompatible controlled radical polymerization. *Nat. Chem.* **2017**, *9*, 537–545.

(59) Tucker, B. S.; Coughlin, M. L.; Figg, C. A.; Sumerlin, B. S. Grafting-From Proteins Using Metal-Free PET-RAFT Polymerizations under Mild Visible-Light Irradiation. *ACS Macro Lett.* **2017**, *6*, 452–457.

(60) Figg, C. A.; Hickman, J. D.; Scheutz, G. M.; Shanmugam, S.; Carmean, R. N.; Tucker, B. S.; Boyer, C.; Sumerlin, B. S. Color-Coding Visible Light Polymerizations To Elucidate the Activation of Trithiocarbonates Using Eosin Y. *Macromolecules* **2018**, *51*, 1370–1376.

(61) Majek, M.; Filace, F.; Wangelin, A. J. v. On the mechanism of photocatalytic reactions with eosin Y. *Beilstein J. Org. Chem.* **2014**, *10*, 981–989.

(62) Xu, J.; Shanmugam, S.; Duong, H. T.; Boyer, C. Organophotocatalysts for photoinduced electron transfer-reversible addition-fragmentation chain transfer (PET-RAFT) polymerization. *Polym. Chem.* **2015**, *6*, 5615–5624.

(63) Gruber, H. F. Photoinitiators for free radical polymerization. *Prog. Polym. Sci.* **1992**, *17*, 953–1044.

(64) Hill-West, J. L.; Chowdhury, S. M.; Slepian, M. J.; Hubbell, J. A. Inhibition of thrombosis and intimal thickening by in situ photopolymerization of thin hydrogel barriers. *Proc. Natl. Acad. Sci. U. S. A.* **1994**, *91*, 5967–5971.

(65) Lilly, J. L.; Gottipati, A.; Cahall, C. F.; Agoub, M.; Berron, B. J. Comparison of eosin and fluorescein conjugates for the photo-initiation of cell-compatible polymer coatings. *PLoS One* **2018**, *13*, No. e0190880.

(66) Kizilel, S.; Pérez-Luna, V. H.; Teymour, F. Photopolymerization of Poly(Ethylene Glycol) Diacrylate on Eosin-Functionalized Surfaces. *Langmuir* **2004**, *20*, 8652–8658.

(67) Zakrzewski, A.; Neckers, D. C. Bleaching products of rose bengal under reducing conditions. *Tetrahedron* **1987**, *43*, 4507–4512.

(68) Valdes-Aguilera, O.; Pathak, C. P.; Shi, J.; Watson, D.; Neckers, D. C. Photopolymerization studies using visible light photoinitiators. *Macromolecules* **1992**, *25*, 541–547.

(69) Li, J.; Mooney, D. J. Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071.

(70) Siepmann, J.; Göpferich, A. Mathematical modeling of bioerodible, polymeric drug delivery systems. *Adv. Drug Delivery Rev.* **2001**, *48*, 229–247.

(71) Kabb, C. P.; O’Bryan, C. S.; Morley, C. D.; Angelini, T. E.; Sumerlin, B. S. Anthracene-based mechanophores for compression-activated fluorescence in polymeric networks. *Chem. Sci.* **2019**, *10*, 7702–7708.

(72) Niu, W.; Gonsales, S. A.; Kubo, T.; Bentz, K. C.; Pal, D.; Savin, D. A.; Sumerlin, B. S.; Veige, A. S. Polypropylene: Now Available without Chain Ends. *Chem.* **2019**, *5*, 237–244.

(73) Carmine, A.; Domoto, Y.; Sakai, N.; Matile, S. Comparison of lipoic and asparagusic acid for surface-initiated disulfide-exchange polymerization. *Chem. - Eur. J.* **2013**, *19*, 11558–11563.

(74) Chen, L.; Ci, T.; Li, T.; Yu, L.; Ding, J. Effects of Molecular Weight Distribution of Amphiphilic Block Copolymers on Their Solubility, Micellization, and Temperature-Induced Sol-Gel Transition in Water. *Macromolecules* **2014**, *47*, 5895–5903.

(75) Cui, S.; Yu, L.; Ding, J. Thermogelling of Amphiphilic Block Copolymers in Water: ABA Type versus AB or BAB Type. *Macromolecules* **2019**, *52*, 3697–3715.