

# Structurally Dynamic Hydrogels Derived from 1,2-Dithiolanes

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**S** Supporting Information

**ABSTRACT:** The design and generation of adaptable materials derived from structurally dynamic polymers provides a strategy for generating smart materials that can respond to environmental stimuli or exhibit self-healing behavior. Herein we report an expedient organocatalytic ring-opening polymerization of cyclic carbonates containing pendant dithiolanes (trimethylene carbonate/dithiolane, TMCDT) from poly(ethylene oxide) diols to generate water-soluble triblock (ABA) copolymers containing a central poly(ethylene oxide) block and terminal dithiolane blocks. Hydrogels generated from the triblock copolymers and a cross-linking dithiol exhibited dynamic behavior as a result of the reversible ring opening of the pendant 1,2-dithiolanes. These materials exhibit self-healing behavior, can be injected through a syringe, and rapidly recover their mechanical properties after a severe strain deformation. The dynamic properties of these gels can be modulated with the number of dithiolane units, pH, and temperature.

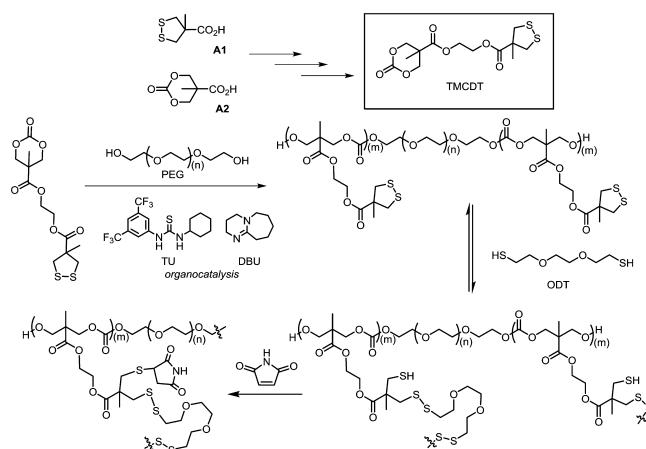
The development of controlled polymerization reactions to generate architecturally defined macromolecules has opened up new opportunities for materials design.<sup>1–6</sup> The molecular weight, composition, sequence, stereochemistry, and topology of macromolecules has a significant influence on the properties of macromolecular materials; recent attention has focused on adaptable materials derived from structurally dynamic polymers whose properties can respond to environmental stimuli or exhibit self-healing behavior.<sup>7–13</sup> Among the various chemistries that can be utilized for dynamic covalent chemistry,<sup>8–10,12,14,15</sup> disulfide exchange is particularly attractive as S–S bonds are strong, but can be cleaved by light, heat, or mechanical force and can exchange rapidly with thiols in a manner that depends on pH, temperature, and redox potential.<sup>16–23</sup> Disulfide exchange equilibria are ubiquitous in biology and are important for maintaining the tertiary structure of proteins and the intracellular redox potential.<sup>24</sup> Cyclic dithiolanes such as liponic acid also play a role in diverse intracellular catalytic functions.<sup>25</sup>

Synthetic polymers incorporating thiols or disulfides are a class of redox-sensitive, photosensitive, and mucoadhesive materials.<sup>13,17,26–29</sup> Pioneering work by Regen showed that lipids containing pendant dithiolanes could be used to cross-link and stabilize liposomes;<sup>30</sup> this strategy has also been used to generate redox-active polymeric nanoparticles.<sup>31</sup> The fast, reversible, and tunable disulfide exchange equilibria of cyclic disulfides<sup>17,32–35</sup> inspired us to investigate whether the incorporation of pendant cyclic disulfides into water-soluble polymers might generate new

classes of dynamic covalent hydrogels. Herein, we describe the synthesis of cyclic carbonates containing substituted 1,2-dithiolanes and the organocatalytic ring-opening polymerization of these monomers to generate structurally-dynamic, deformable hydrogels.

We envisioned that ABA triblock copolymers where the terminal A blocks contain pendant 1,2-dithiolanes and the B block is a flexible water-soluble PEG would, upon addition of a suitable telechelic dithiol, provide a class of structurally dynamic networks<sup>8–10</sup> whose properties could be modulated by temperature or pH or by capping of the resultant free thiols (Scheme 1).

## Scheme 1. Synthesis of TMCDT Monomer, ABA Triblock Copolymers, and Gels



We targeted an organocatalytic ring-opening polymerization<sup>36–38</sup> of dithiolane-functionalized trimethylene carbonate monomers as we anticipated that the mild conditions and high functional group tolerance of organocatalytic ring-opening polymerization<sup>2,39</sup> would provide an attractive synthetic route to these materials.

The synthesis of TMCDT was carried out in two steps from the known carboxylic acids A1<sup>40</sup> and A2<sup>36</sup> (Scheme 1, see Supporting Information for details). The organocatalytic ring opening of TMCDT with the DBU/TU<sup>39,41</sup> cocatalyst system (5 mol %) from telechelic PEG diols ( $M_n = 4.6, 14, 20,$  and  $35$  kDa; Table 1) occurred readily in  $\text{CH}_2\text{Cl}_2$  to generate triblock copolymers of p(TMCDT-PEG-TMCDT), containing short TMCDT sequences ( $m \approx 4–6$ , Scheme 1). Analysis of the resulting block copolymers by <sup>1</sup>H NMR and GPC demonstrated efficient initiation from PEG and revealed the dithiolane ring to

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**Table 1. Telechelic Polymerization of TMCDT with PEG**

Copoly.	PEG $M_n$ (kDa)	DP <sup>a</sup>	$M_n^a$ (kDa)	$M_w/M_n^b$
1	4.6	10	8.1	1.16
2	14	8.5	16.9	1.18
3	14	9.8	17.5	1.15
4	14	11.7	18.1	1.19
5	20	8.8	23.2	1.35
6	35	10.2	38.5	1.17

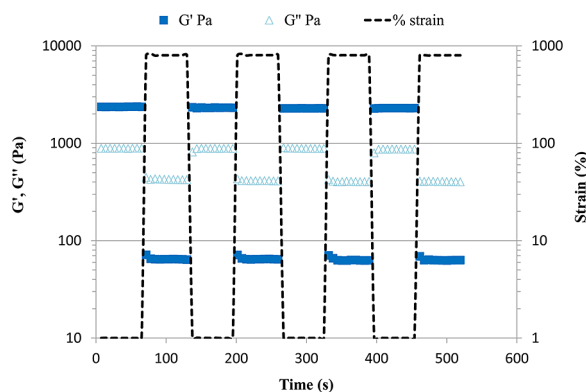
<sup>a</sup>Degree of polymerization of TMCDT, determined by <sup>1</sup>H NMR.

<sup>b</sup>Determined by GPC in THF with polystyrene calibration.

be intact with no sign of ring opening under the reaction conditions (see Supporting Information).

Triblock copolymers 1–6 are soluble in chloroform; copolymers 2–4 are soluble in water at 10 wt %. Addition of 3,6-dioxa-1,8-octanedithiol (ODT, 0.5 equiv relative to TMCDT) to an aqueous dispersion of copolymers 2–4 results in rapid gelation. A minimum copolymer concentration of approximately 10 wt % was optimal for stable gel formation. Copolymers 2, 3, and 4 were selected for further studies due to their higher solubility in water compared to 1 and the relative ease of preparing and manipulating 10 wt % solutions compared to those of 5 and 6. Hydrogels prepared from 10 wt % aqueous solutions of 3/ODT could be readily removed from vials, and were deformable and could easily be shaped and cut with a spatula (Figure S1, Supporting Information). The hydrogel exhibits shear-thinning behavior and can be injected through a syringe (movie S1, Supporting Information).

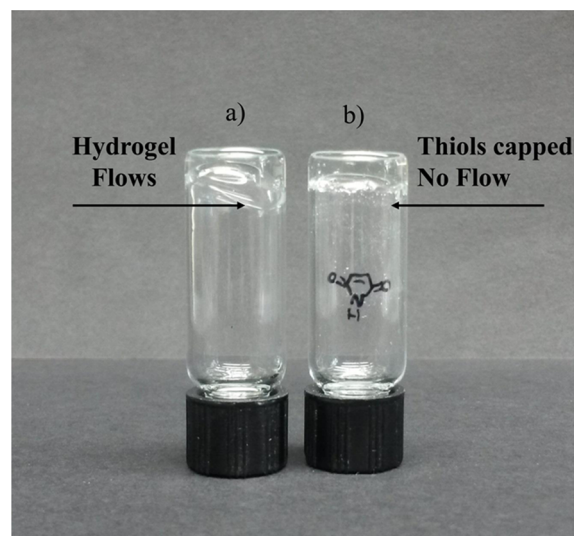
Small amplitude oscillatory shear rheometry was carried out to provide further information on the dynamic behavior of these hydrogels.<sup>42</sup> Strain sweeps at a constant oscillatory frequency of 1 Hz at 25 °C revealed that the hydrogel derived from 3/ODT exhibited linear viscoelastic behavior from 0.1% strain up to ~90% strain with a constant storage modulus ( $G'$ ) of 2180 Pa and a loss modulus ( $G''$ ) of 860 Pa (Figure S2, Supporting Information). At higher applied strains ( $\gamma > 100\%$ ) both  $G'$  and  $G''$  drop and  $G'$  decreases below  $G''$  at approximately  $\gamma = 125\%$  applied strain, indicative of a transition from gel-like to liquid-like behavior at high strain.<sup>43</sup> The gel can rapidly recover its mechanical properties after severe strain deformation, as evidenced by a dynamic step-strain test (Figure 1). When a 10 wt % 3/ODT hydrogel at 1% strain is subjected to an 800% step strain,  $G'$  drops substantially from  $G' = 2300$  Pa to  $G' = 65$  Pa. Reversing the strain to 1% results in rapid recovery (<10 s) to the



**Figure 1.** Dynamic strain amplitude cycles ( $\gamma = 1\%$  or  $800\%$ ) of 10 wt % hydrogel 3/ODT at 25 °C, illustrating reversible shear-thinning behavior.

original modulus. This recovery process is reversible over several cycles, suggesting a good self-healing ability of the gels.

A vial inversion experiment showed that the hydrogel derived from 3/ODT flows over the course of 1.5 h (Figure 2a). In



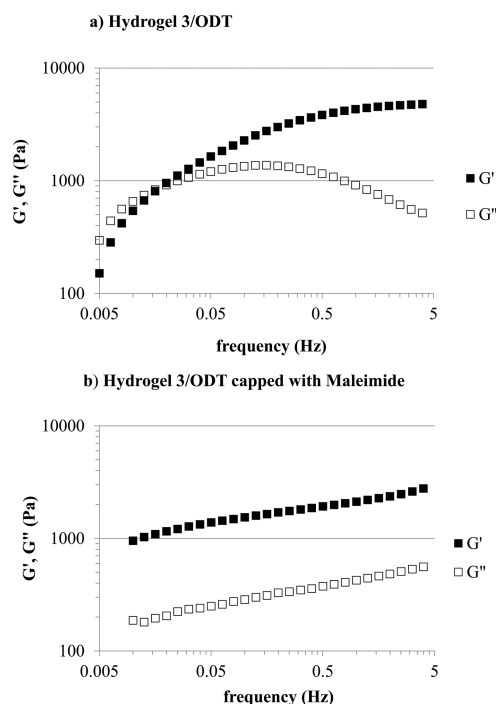
**Figure 2.** (a) Hydrogel 3/ODT exhibiting flow (1.5 h); (b) hydrogel 3/ODT treated with maleimide does not flow (1.5 h).

contrast, an analogous gel treated with excess maleimide, a reagent known to react rapidly with free thiols, was more stable and did not flow over the same time period (Figure 2b). This behavior suggests that the ability of the uncapped hydrogels to flow is due to the reversible exchange of free thiols and reformation of dithiolane rings.

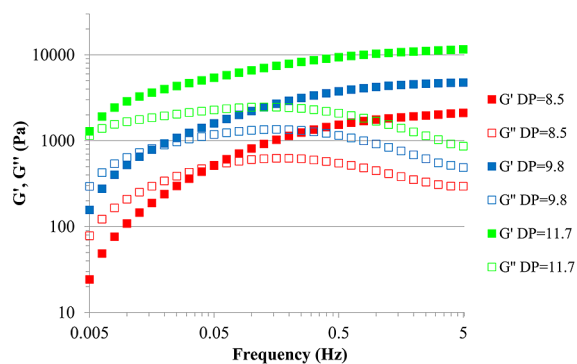
The frequency-dependent moduli  $G'$  and  $G''$  (25 °C) for the hydrogel derived from 3/ODT is shown in Figure 3a. At high frequencies, the storage modulus  $G'$  is higher than the loss modulus  $G''$ , as expected for a cross-linked network. At lower frequencies, a crossover in the storage and loss moduli occurs, consistent with liquid-like behavior at long time scales. This behavior is typical of transient networks<sup>10,44,45</sup> and consonant with the visual observations that the gels flow at longer times (Figure 2a). At 25 °C, the crossover frequency where  $G' = G'' \approx 880$  Pa is 0.017 Hz, indicating that, at frequencies below 0.017 Hz, disulfide exchange occurs at a rate that allows for dynamic restructuring of the gel.<sup>10,44–46</sup>

In contrast, hydrogels 3/ODT treated with an excess of a 1 M aqueous solution of maleimide display a higher storage modulus than loss modulus at all accessible frequencies (Figure 3b). This change to a predominantly elastic response over this range of frequencies suggests that removal of free thiols by reaction with maleimide prevents the dynamic restructuring of the gels, and is consistent with the lack of observed flow in capped hydrogels (Figure 2b).

The dynamic properties of these hydrogels can be readily tuned by changing the architecture of the copolymers, pH, and concentration of the cross-linker (Figures 4, S3–S4, Supporting Information). The rheological properties are very sensitive to the number of dithiolane repeat units of the copolymer. Triblock copolymers 2, 3, and 4 with the same PEG block length but slightly different TMCDT block lengths exhibit measurable differences in their frequency-dependent moduli  $G'$  and  $G''$  (Figure 4). The moduli of the hydrogels increase with increasing length of the TMCDT block ( $2 < 3 < 4$ ), and the  $G' = G''$



**Figure 3.** (a) Frequency-dependent viscoelastic behavior of hydrogel 3/ODT illustrating crossover frequency of 0.017 Hz ( $G' = G''$ ); (b) hydrogel 3/ODT treated with maleimide shows no crossover of the storage and loss modulus.



**Figure 4.** Influence of TMCDDT block length (Copolymer 2/ODT, red; 3/ODT, blue; 4/ODT, green) on the storage ( $G'$ ) and loss ( $G''$ ) moduli.

crossover shifts to lower frequency; i.e., the gel becomes stiffer and relaxes more slowly with increasing number of TMCDDT repeat units.

The solution pH also has a significant influence on the rheological properties of these hydrogels. A 10 wt % hydrogel derived from polymer 2/ODT generated at pH 7 and acidified with a drop of pH 1 water exhibited a higher storage modulus than loss modulus at all accessible frequencies, analogous to the behavior observed for the maleimide-capped gels at pH 7. In contrast, an analogous sample analyzed at pH 7 exhibited a crossover frequency at 0.012 Hz ( $G' = G'' = 329$  Pa). A sample treated with a drop of pH 10 water exhibited a crossover frequency of 0.040 Hz and a crossover modulus of  $G' = G'' = 398$  Pa. These data suggest that the dynamics of disulfide exchange can be readily tuned by pH, as expected based on solution studies of dithiol exchange.<sup>34,47</sup>

Hydrogels 3/ODT exhibit thermoreversible behavior. Hydrogels 3/ODT generated at room temperature were observed to flow upon heating but reverted to a gel upon cooling to room temperature. The temperature-dependent moduli of 3/ODT hydrogels were recorded from 25 to 55 °C at a heating rate of 1 °C/min (Figure S5, Supporting Information). Both storage ( $G'$ ) and loss moduli ( $G''$ ) decreased with increasing temperature, and a crossover ( $G' = G''$ ) was observed at 42.6 °C, which was identified as the sol–gel transition temperature. This behavior could also be followed by UV–visible spectroscopy.<sup>48,49</sup> A 10 wt % aqueous solution of triblock polymer 3 containing intact dithiolane rings exhibits a temperature-independent absorbance from ~330–410 nm. In contrast, the hydrogel 3/ODT exhibits an increase in absorbance at ~370 nm with increasing temperature that is fully reversible over several thermal temperature cycles (Figure S6, Supporting Information). As both the rate and equilibrium of dithiolane ring opening are likely to be temperature dependent, this temperature-dependent dynamic behavior merits further study; nevertheless, these data illustrate how the properties of the TMCDDT-based hydrogels can be easily tuned by parameters such as block length, pH, cross-linker concentration, or temperature.

Preliminary studies indicate that the TMCDDT hydrogels 3/ODT are stable under ambient aerobic conditions, at least up to 72 h. Hydrogel samples kept under ambient air in sealed containers (to minimize evaporation of water) without any special precautions for the exclusion of oxygen exhibit comparable rheological and UV/vis behavior to freshly prepared samples (Figures S7–S8, Supporting Information). These data suggest that if any oxidative disulfide formation occurs, it does not appreciably alter the hydrogel properties over these time periods.

In summary, we report a new class of structurally dynamic hydrogels derived from the reversible cross-linking of pendant 1,2-dithiolanes with dithiols. These materials are a class of transient networks that are injectable and rehealable as well as exhibit shear-thinning and dynamic flow behaviors that depend on the architecture, temperature, and pH. While ABA triblock copolymers with hydrophilic B blocks and hydrophobic A blocks are known to self-assemble in water to form transient networks,<sup>50–54</sup> the clear differences observed when the free thiols in these networks are “capped” with maleimides (Figures 2, 3, S9) strongly implicate that the rapid and reversible ring opening of the pendant cyclic disulfides contributes to the dynamic behavior of these hydrogels. It is likely that the dynamic properties observed are a result of a transient network of hydrophobically associated TMCDDT blocks that is stabilized and modulated by thiol exchange with the cyclic disulfides.

The hydrogel properties may be of interest for applications requiring shaping and molding of gels at the point of introduction or where network rearrangement over time is required. The shear-thinning and self-healing behaviors of the hydrogels make them attractive candidates for injectable carriers for drug/cell delivery.<sup>55,56</sup> Further work on the reversible alkylation/dealkylation of free thiols in the gel could provide access to unique materials that undergo triggered degradation upon exposure to external stimuli.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Procedures for the preparation of previously unreported compounds as well as spectral data and GPC traces; movie of hydrogel behavior. The Supporting Information is available free



of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02161.

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### Notes

The authors declare no competing financial interest.

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