ACS Macro Letters
Letter
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Toward Self-Healing Hydrogels Using One-Pot Thiol–Ene Click and Borax-Diol Chemistry

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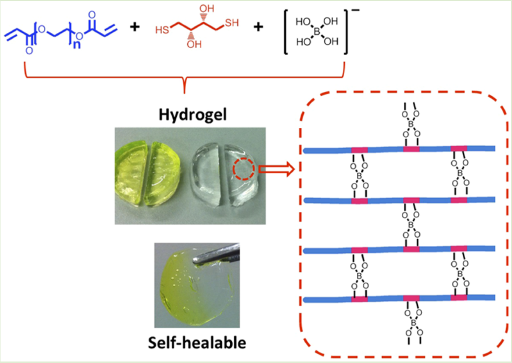
Ⓢ *Supporting Information*



ABSTRACT: Intrinsic self-healing soft materials such as hydrogels are especially promising for a variety of medical applications. Multistep preparation of starting functional polymer precursors and the expensive stock materials such as tetra-polyethylene glycol are one of the factors that limit the wider use of self-healing hydrogels. Herein, we reported a facile one-pot approach to prepare PEG based self-healing hydrogels from inexpensive commercially available components: polyethylene glycol diacrylate and dithiothreitol. For the first time, borax was used as the catalyst for a thiol–ene Michael-type polyaddition of PEG gels. Borax as the catalyst is quite efficient, allowing rapid gelation (from 40 s to 2 min) under ambient conditions and at room temperature. Essentially, as one catalyst, borax induces the formation of two classes of bonds, covalent thioether and transient boronate ester bonds, were formed at the same time. The storage modulus of the afforded PEG gel (87.5% water) reached up to 10^4 Pa, making the mechanical performance comparable with permanently cross-linked PEG gels. Additionally, the dynamic nature of the boronate ester linkages imparts the gel with self-healing properties, and the obtained gels can be healed within 30 min without external stimulus. Further, the transparent hydrogel is pH and thermal responsive. We believe that the manifold impacts of borax can open a new route to prepare hydrogels with intriguing properties, which find potential application as gel sealant, biosensors, or regenerative medicines.

Polymer hydrogels are soft and wet materials, composed of a hydrophilic polymer network structure and large amount of water (50–90%) inside the three-dimensional network.[1] Hydrogels are well-suited for biomedical applications, as they are homogeneous soft materials with hydrophilic nature, porous structure, and tailored stiffness.[2,3] They have shown promising application in a number of fields, including regenerative medicines and biomedical devices, such as biosensors, as well as separation systems.[4−6] Stimuli-responsive (SR) hydrogels have gained considerable attention, which is attributed to the manifold applications they can be used for. SR hydrogels are able to shrink or expand, to switch between solution and gel state or to change their viscosity property in response to the environmental triggers like pH, temperature,[7] or light.[1,8,9] Intensive studies have focused on boronate ester cross-linked hydrogels and constitutional dynamic polymers[10−12] because of the transient nature of the complexation between boronic acids and 1,2- or 1,3-diols, enabling the hydrogel to repair damage autonomously.[13−15] In addition to that, the formation of boronate ester cross-links is a chemical equilibrium process, which can be influenced by both temperature and pH, imparting the hydrogels consequently with thermo- and pH-responsive behaviors.[16,17] Moreover, saccharides like fructose and glucose can form stronger complexes with boric acid, endowing the hydrogels with a glucose responsive function, which enables applications in glucose sensing and self-regulated insulin release.[18]

Thiol–ene "click" reactions possess numerous unique and important features.[19−21] These include (1) a versatile library of C═C double bonds, enes, can serve as effective substrates, including activated as well as nonactivated C═C bonds; (2) the reactions are extremely fast (ranging from seconds to minutes depending on the applied catalysts and functional substrates) under ambient temperature and pressure; (3) the reactions are tolerant to the presence of air/oxygen and moisture; (4) thioethers are formed quantitatively in a regioselective way. These features make it a particularly attractive, robust, and powerful process in manufacturing soft materials like hydrogels.[22] Nucleophile/base-catalyzed thiol-Michael addition reactions allow for the formation of thick, homogeneous hydrogels, which is a critical characteristic for tissue regenerative materials. Triethylamine (TEA),[23] PBS (phosphate buffer solution),[24,25] or HEPES[26] (4-(2-hydroxy ethyl)-1-piperazineethanesulfonic acid) buffer have been explored as catalysts for the synthesis of hydrogels. The aforementioned buffer solutions, especially PBS, are exclusively studied because the reaction conditions match very well with physiological conditions (pH = 7.4, ∼330 mOsm), which are mild enough to allow in vivo biomedical applications;[24] but the

Received: May 20, 2015
Accepted: June 8, 2015
Published: June 10, 2015

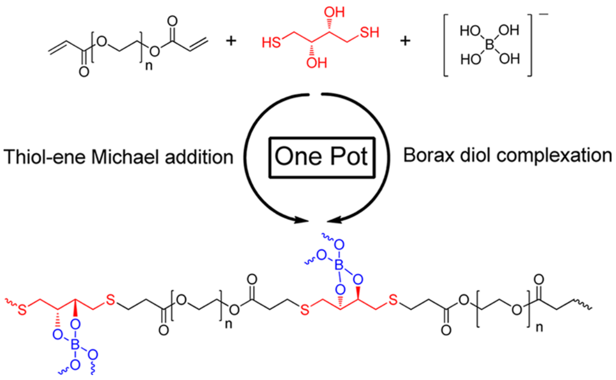
DOI: 10.1021/acsmacrolett.5b00336
ACS Macro Lett. 2015, 4, 673−678

achieved cell safety is in the sacrifice of gelation rate. The gelation time of (meth)acrylate −Michael addition varies from tens of minutes to hours. TEA is a very effective catalyst for the gelation of maleimide functionalized macromolecular precursors. Cell encapsulation tests show that catalytic amount of TEA-mediated maleimide functionalized PEG-Michael addition hydrogels that allowed a cell spreading comparable to the natural collagen matrix, showing that a very small amount of TEA (4 mM) is acceptable even for highly sensitive cell types.[23] In contrast, Borax possesses a much higher LD50 value (4500−6000 mg/kg) than TEA (460 mg/kg), which means its toxicity is much lower than that of TEA.[27] Researchers also showed that most boronic acids present no particular toxicity compared to the other organic compounds[28] and recently reported a guanosine-borate hydrogel has a potential for a variety of biomedical applications.[29] Moreover, although it has been rarely mentioned, borax is indeed an efficient metal-free catalyst for hetero-Michael addition reactions in aqueous media.[30]

Polyethylene glycol (PEG) hydrogels possess intrinsic low-protein absorption properties, a minimal inflammatory profile and well-proved safety for in vivo use. Further, it is easy to incorporate a wide range of biologically active moieties derived from commercially available reagents. These features make PEG hydrogels the "gold standard" in the field of regenerative medicine and biomedical devices.[23,31] This information motivated us to explore borax as an alternative catalyst for the synthesis of PEG hydrogels. PEG diacrylate and dithiothreitol were explored as the gelation precursors in the present study. We believe that the manifold impacts of borax can open a new route to prepare hydrogels with intriguing properties, which has potential application as gel sealants, biosensors, or regenerative medicines.

Herein, we propose a novel one-pot approach to synthesize PEG-based self-healable hydrogels. Essentially, borax plays two roles in the gelation process: (1) as a catalyst for thiol−acrylate Michael polyaddition; (2) formation of boronate ester cross-links with 1,2-diols along DTT (dithiothreitol). This novel synthetic route has the following characteristics: (a) the starting materials are commercially available and cheap; (b) the gel is formed in situ due to the rapid gelation rate (around 2 min); (c) it is a one-pot reaction, which is easy to handle; (d) the obtained gel is cross-linked by boronate ester bonds, which possesses the features of self-healable, pH, and temperature, as well as glucose sensitive. To the best of our knowledge, this is the first reported case to use borax as the catalyst for thiol-Michael polyaddition PEG hydrogel. Essentially, one catalyst, two classes of bonds−thioether covalent bond and transient boronate ester bond are formed at the same time. PEGDA (M_n = 700 g/mol) was chosen as a simple model polymer to construct a hydrogel, because it is water-soluble and commercially available at cheap price. DTT was selected because it contains dithiol functionality, is water-soluble, features a 1,2-diol group, and is commercially available. As shown in Scheme 1, two classes of reactions are expected to proceed during the gelation process: (1) borax catalyzed the linear step growth polymerization of PEGDA and DTT, that is, a polyaddition; (2) the complexation between tetrahedral borate anion $B(OH)_4^-$ and 1,2-diols of DTT incorporated in the formed polymer chain. When adding a borax solution to a homogeneous aqueous solution containing a stoichiometric ratio of PEGDA and DTT, a hydrogel was obtained shortly after vigorous mixing at 25 °C. The gelation time varied from 40 s to 2 min, depending on the concentration of borax and polymer precursors (Table S1, video S1), which can be considered as a reasonable time range suitable for injectable hydrogels.[1] For a first comparison, hydrogels were formed at a polymer concentration of 12.5% wt. Hydrogels obtained from lower borax concentrations (less than 0.02 mol/L) appeared as deformable semisolids that still flow under gravity over several minutes. Increasing the borax concentration yielded hydrogels that appeared as brittle, elastic gels, which behaved like typical covalently cross-linked hydrogels. The difference in behavior at different borax concentrations is attributed to the lower cross-linking density in the polymer network. Further examination of the morphology of the hydrogel by SEM (Figure S1) revealed that the hydrogel showed typical porous structures.

Scheme 1. Schematic Illustration of a "One-Pot" Preparation of Thiol−Ene PEG-Based Hydrogels



In order to confirm the borax-catalyzed thiol−ene Michael addition reaction, the obtained hydrogel was lyophilized prior to FT-IR analysis. As shown in Figure 1A, in which the absorption of C═C stretch at 1625 cm^{-1} and the S−H stretch located at 2549 cm^{-1} almost disappeared after the addition reaction (bottom red line), indicating that the functional groups were fully consumed during the reaction. The ability of borax catalyzing thiol-Michael addition reaction was further proven by a model reaction using DTT and di(ethylene glycol)ethyl ether acrylate (molar ratio 1:2). The reaction was monitored by ^{1}H NMR. As shown in Figure 1B, the multiple peaks (**a**) ranging from 6.0 to 6.5 ppm attributed to the CH_2═CH- protons completely disappeared after 15 min. Meanwhile, a new sharp peak appeared around ∼5.0 ppm, originating from the methylene protons (-CH_2COO−) of the Michael addition adduct. ^{1}H NMR directly proved that the activated C═C double bond is fully consumed in short time, indicating that the reaction is quantitative at room temperature. This suggested that borax is indeed a very efficient catalyst for thiol-Michael addition reaction in aqueous solution, allowing the formation of macromolecules based on borax-catalyzed step-growth polyaddition.

In order to document the catalytic efficiency, the molecular weights of Michael addition adducts made from step-growth polyaddition of DTT-PEGDA catalyzed by either borax or PBS were compared. Identical molar amounts of PEGDA and DTT (molar ratio 1:1) were applied for both reactions. In the case of a PBS-catalyzed reaction, the ^{1}H NMR was checked after 30 min. As shown in Figure 2A, the multiple peaks (**a**) ranging from 6.0 to 6.5 ppm attributed to the CH_2═CH- protons disappeared almost completely, indicating that the reaction occurred in >99% conversion. It is worthy to note that, after the Michael addition reaction between DTT and PEGDA, a

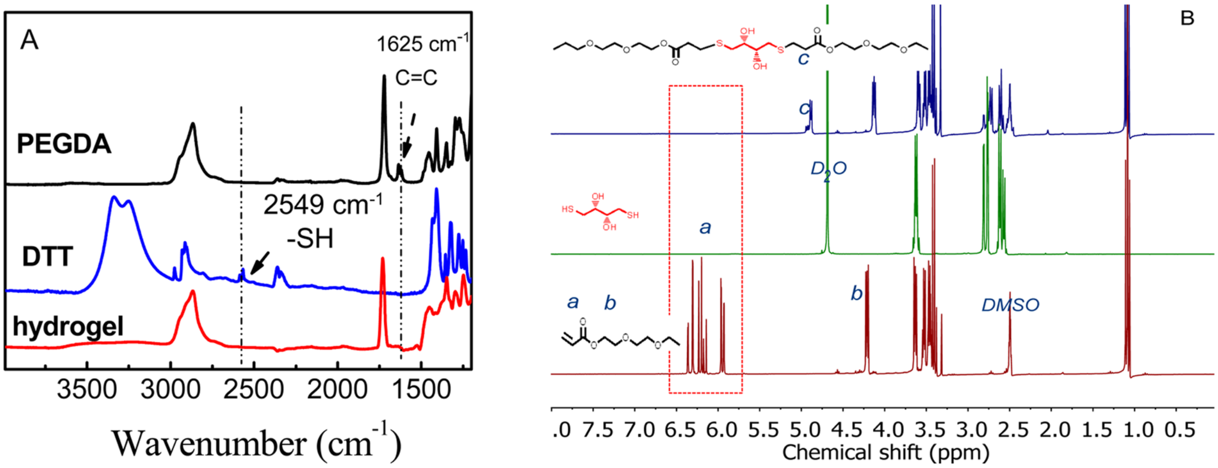


Figure 1. (A) FT-IR spectra of PEGDA (top black line), DTT (middle blue line), and lyophilized hydrogel (bottom red line) formed from 0.14 mM PEGDA, 0.14 mM DTT, and 0.02 mM borax in 1 mL of water; (B) ^{1}H NMR (300 MHz) of di(ethylene glycol)ethyl ether acrylate (bottom red line), DTT (middle green line), and the mixture of di(ethylene glycol)ethyl ether acrylate (0.28 mM/mL, 2 equiv) and DTT (0.14 mM/mL, 1 equiv) with a concentration of borax (0.02 mmol/mL) in D_2O at 25 °C for 15 min.

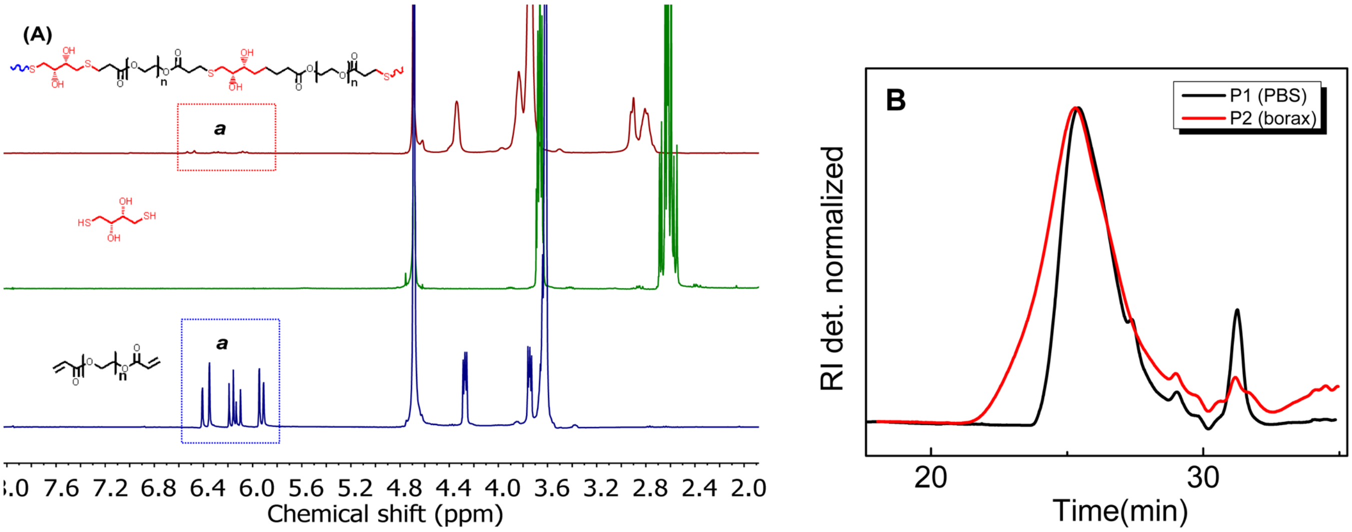


Figure 2. (A) ^{1}H NMR of thiol−ene Michael addition reaction; ^{1}H NMR (300 MHz) of PEGDA (bottom red line), DTT (middle green line), and the mixture of PEGDA (0.14 mM/mL, 1 equiv) and DTT (0.14 mM/mL, 1 equiv) with a concentration of PBS (pH 7.4) in D_2O at 25 °C for 30 min; (B) GPC (poly(hydroxyl methacrylate), acetonitrile/water = 1:4 volume) curves for thiol−ene Michael addition polymerization of PEGDA and DTT using PBS (**P1**, black curve) and borax (**P2**, red curve) as catalysts. **P1** (M_n = 7720 g/mol, M_w = 14000 g/mol), PDI 1.8; **P2** (M_n = 9100 g/mol, M_w = 25080 g/mol), PDI 2.75.

solution was obtained when catalyzed with PBS, whereas in the case of borax, a transparent gel was obtained instead of clear solution. It is expected that in the case of borax, the step-growth polyaddition proceeded simultaneously with a borax-diol cross-linking reaction. The borax complexation is labile under acidic conditions; therefore, a very small amount of hydrochloric acid was added to the gel, adjusting the pH to 3, which resulted in dissolution of the gel. After the gel dissolved, the solution was lyophilized and a small sample was taken to measure aqueous GPC. GPC analysis showed that linear polymers were obtained by the borax-catalyzed polyaddition with a slightly higher molecular weight (M_n = 9100 g/mol) than PBS-mediated polyaddition (M_n = 7720 g/mol). Considering the fact that the employed starting compounds may not possess a 100% degree of bis-functionality (e.g., DTT purity ≥ 99%), the small amount of missing functional groups has a significant influence on the molecular weight of step growth polymerization,[19] which naturally limits the theoretically achievable molecular weight. All in all, GPC data showed that polymers with similar molecular weights were obtained via borax or PBS catalysis, thereby indicating that both have a comparable catalytic efficiency for thiol-Michael addition reaction.

Borax complexation is usually specific for vicinal cis diols, that is, molecules[18] with hydroxyl groups in a cis-type arrangement. Since DTT features a flexible chain, the conformations of the adjacent C−O vectors are conceivably possible. Consequently, to study the complexation chemistry in the gel system, ^{11}B NMR using DTT directly instead of the linear thioether polymer were conducted at first. ^{11}B NMR of DTT and borax with varied ratios and under different pH values were investigated. As shown in Figure 3, the ^{11}B NMR spectrum of a 1:2 mixture of borax and DTT at pH 9 (top blue line) revealed a prominent peak at 19.0 ppm, corresponding to the free boric acid; a peak with a chemical shift of 9.8 ppm,

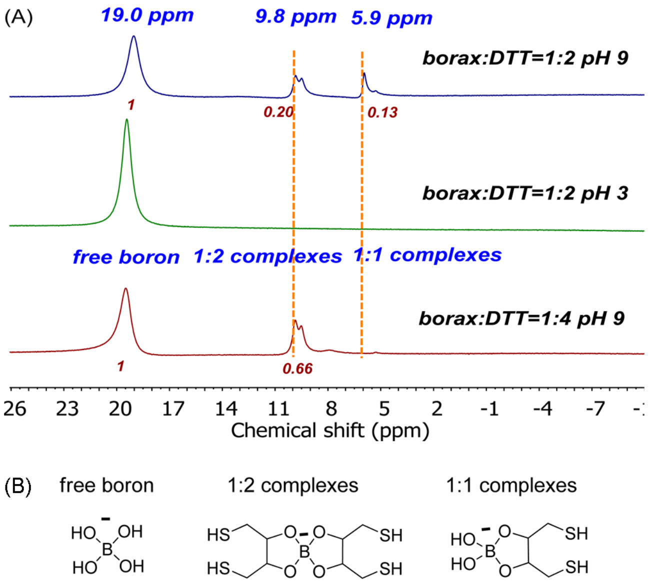


Figure 3. (A) ^{11}B NMR of borax/DTT = 1:2 at pH = 9 (top red line) and pH = 3 (bottom blue line), as well as borax/DTT = 1:4 at pH = 9 (middle green line); (B) schematic structures of boron species.

which is consistent with the formation of tetrahedral boron in a structure of 2:1 complexes; as well as a peak at 5.9 ppm, which is identified as boron in a structure of 1:1 complexation with DTT. These peak assignments are in agreement with the reported ^{11}B NMR spectra from borax and 2,3-butanediol.[32] Consequently, it can be argued that cross-linking is caused by the formation of 1:2 borax/diol complexes and, hence, is the chemical basis for the gelation. When the pH was adjusted to 3, the peaks at 9.8 and 5.9 ppm disappeared, and the peak intensity at 19.0 ppm correspondingly increased (middle green line). These changes suggest that the borax complexes were destroyed, which is expected because of the labile character of common borax complexes under acidic conditions. Further increasing the ratio of borax/DTT to 1:4 (bottom red line) resulted in an increased peak intensity at 9.8 ppm, indicating the preferred formation of 1:2 borax/diol complexes. It is interesting to note that even at ratios higher than the ideal stoichiometry (1:2), free species of borax were present. This can be attributed to the dynamic bonding nature of the borax/diol complexes, which fluctuates continuously between the borax complexes and dissociated states. Overall, ^{11}B NMR clearly proved that there borax/diol complexes formed successfully between borax and DTT.

In order to provide direct proof that the formation of borax/DTT complexes is the chemical basis for the gelation, linear polymers were first prepared via PBS-catalyzed Michael polyaddition reaction between DTT and PEGDA, vide supra. Afterward, solutions were prepared containing an identical polymer concentration (12.5 wt %) and a varying borax concentration ranging from 0.07 to 0.50 ($n_{\mathrm{borax}}/n_{\mathrm{DTT}}$) was added. As shown in Figure S2, the linear polymer solutions (**P0**) became viscous semisolid solutions or elastic hydrogels after the addition of borax, indicating that borax/DTT complexes acted as cross-linkers in these PEG hydrogels.

In order to gain a first insight into the properties of the hydrogels, the network structure and deformation behavior of the prepared hydrogels was investigated with small amplitude oscillatory shear flow (SAOS) experiments. The frequency dependence of the storage modulus G' and the loss modulus G'' at different borax/DTT molar ratios is shown in Figure 4. The network of the hydrogels is transient, caused by the dynamic chemical nature of the borate cross-linking. The reversible association–dissociation mechanism leads to an observable lifetime τ_0 of the transient netpoints. As a result, the hydrogel behaves like a chemically cross-linked gel at short time scales below τ_0 and like a viscoelastic Maxwell fluid at longer time scales above τ_0, in which the relaxation process of the gel can be observed.[33] This transient behavior of the netpoints is also the main reason for the self-healing properties of the measured hydrogels, vide infra. The storage modulus of the afforded PEG gel (87.5% water) reached up to 10^4 Pa, which is comparable with permanently cross-linked PEG gels.[22]

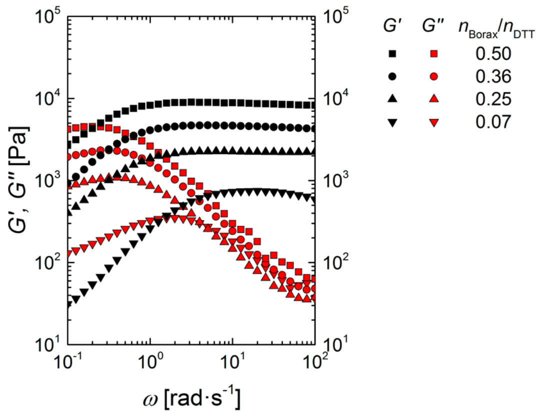


Figure 4. Storage modulus G' and the loss modulus G'' as functions of the angular frequency for polymer solutions (c = 12.5 wt %) with different borax/DTT molar ratios.

The frequency independent rubber-elasticity plateau of the storage modulus G' as a measure for the gel strength increases with the borax/DTT molar ratio. This increase was expected, because the amount of borate netpoints increased. The network parameters were calculated from the rubber-elastic plateau according (see eqs 1–3 in Supporting Information) and are shown in Table S2.

The cross-linking density υ_e increased with higher borax concentration, and therefore, the cross-link distance ξ between two netpoints decreased. The calculated molecular weight between netpoints M_e^* gives a rough idea of the number of effective borax netpoints/interactions per chain. The relaxation time τ of the network was determined from the angular frequency at the maximum of the loss modulus G'' ($\tau = \omega_{\mathrm{max}}^{-1}$) according to a study from Ide et al.,[33] which corresponds to the crossover point of the storage modulus G' and the loss modulus G''. The network relaxation time τ as a function of the borax/DTT molar ratio is shown in Figure S3. A direct linear relationship between the relaxation time τ and the borax/DTT molar ratio can be observed. It is understandable that the relaxation time τ increases with the ratio, because the chain relaxation is more constrained at higher cross-linking densities.

Considering that all cross-links within the hydrogels were expected to be reversible dynamic-covalent bonds as a result of their rapid exchange of the borax/diol complex formation, the self-healing characteristics of the hydrogels were investigated. As a qualitative evaluation of self-healing, cut-and-heal tests were conducted with the hydrogels. As depicted in Figure 5, two disks of hydrogels were prepared and sliced into two halves, respectively. One hydrogel disk was colored with a dye

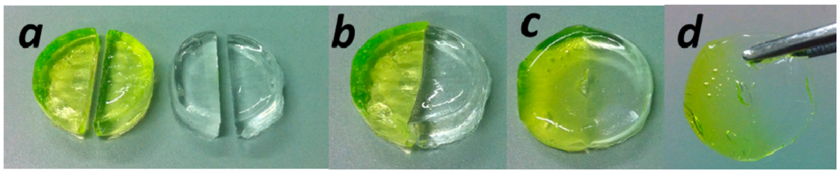


Figure 5. Photographs showing the self-healing behavior of PEG hydrogels: (a) two pieces of original hydrogel with and without fluorescence dye; (b) self-healing hydrogel upon bringing two pieces of hydrogels in contact; (c) self-healed after 30 min; (d) self-healed hydrogel suspended its own weight.

to provide better contrast. These pieces were then placed in contact to allow healing at room temperature. In all cases, the gels healed within 30 min, as evidenced by the disappearing of the scar at the damage site. The healed gels could support easily their own weight after healing. These behaviors suggested that the transient borate ester bond across the damage interface allowed healing of the hydrogels due to the dynamic nature of the borate bonds. These observations of healing were repeated three times on the same sample and healing was independent of the position where the cut was made. More healing cycles are expected to be possible due to the gel being cross-linked by transient boronate ester bonds.

Considering that the number of cross-links is determined by the chemical equilibrium among boric acid, borax/DTT complexes, it can be influenced by both pH and temperature. As depicted in Figure S4, the transparent hydrogel can be dissociated at pH = 3 and regenerated by adjusting the pH value to 9. In addition, the formation of cross-links is exothermic;[18] thus, the gel can be dissociated by heating to 80 °C and regenerated when cooling down to 18 °C (Figure S5). The gel to solution transition induced by temperature or pH is fully reversible, even after three cycles.

In summary, we provided a straightforward way to synthesize novel PEG-based self-healable hydrogels. Hydrogels were prepared by a one-pot reaction of PEGDA, DTT, and borax. FT-IR, ^{1}H NMR, and GPC results showed that borax performs dual functions: it is capable of catalyzing the thiol−ene Michael polyaddition reaction with its catalytic efficiency comparable to PBS. In addition to that, borax forms boronate ester cross-links with the vicinal hydroxyl groups of DTT along the polymer chains, which resulted in the formation of hydrogels. Rheology showed that the hydrogel possesses a transient network structure and the hydrogel strength as well as the cross-linking density depending on the borax concentration, which can be seen as a further proof that boronate ester bonds are responsible for the polymer network. The mechanical performance of the transient bond cross-linked hydrogel is comparable with those gels formed by permanent covalent bond, which provides the required mechanical support as hydrogel scaffolds. Due to the dynamic nature of boronate ester cross-links, the obtained hydrogels are self-healable and pH- and temperature-responsive. Noteworthy, the utilized components are readily commercially available at cheap prices, and therefore, these self-healable hydrogels are very attractive candidates for numerous applications. For example, our one-pot thiol−ene PEG-based self-healable hydrogels are an attractive candidate for various biomedical applications, such as hydrogel sealants, or for environmental applications like hydrogel sensors. Current studies are underway to further explore the possibilities of hydrogels based on this facile one-pot synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and supporting figures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00336.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Christian Bernstein for help with GPC measurements. L.H. gratefully acknowledges the China Scholarship Council (CSC, Grant 201206240006) for partial support of this work.

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