Extreme Mechanics Letters 59 (2023) 101953

Contents lists available at ScienceDirect

Extreme Mechanics Letters

journal homepage: www.elsevier.com/locate/eml

Highly entangled hydrogels with degradable crosslinks

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ARTICLE INFO

Article history:
Received 26 October 2022
Received in revised form 21 December 2022
Accepted 21 December 2022
Available online 10 January 2023

Keywords:
Degradable
Hydrogel
Entanglement
Dynamic crosslink
Disulfide crosslink
Acrylamide

ABSTRACT

This paper studies a polymer network in which crosslinks are degradable but polymer chains are not. We show that entanglements markedly enhance the mechanical properties of the polymer network before degradation and slow down degradation. We synthesize polyacrylamide hydrogels with disulfide crosslinks. In a precursor of a low water-to-monomer molar ratio and low crosslinker-to-monomer molar ratio, the monomers are crowded and the resulting polymer chains are long, so that the entanglements greatly outnumber crosslinks. The as-synthesized hydrogels are submerged in pure water to swell to equilibrium. We show that entanglements enhance the swell resistance of the hydrogel, as well as stiffen and toughen the hydrogel. We further show that entanglements slow down degradation when the hydrogel is submerged in an aqueous solution of cysteine. This work demonstrates that entanglements substantially expand the properties space of degradable polymers.

Degradable polymers have been under development as sutures [1–4], drug-delivery carriers [5–8], and environment-friendly materials [9–11]. This paper focuses on a class of degradable polymer networks in which crosslinks degrade in response to a trigger, but polymer chains do not. For example, when a polyacrylamide network crosslinked by disulfide is submerged in an aqueous solution of cysteine, the disulfide and cysteine undergo a thiol–disulfide exchange reaction, and the polyacrylamide network dissolves into a polyacrylamide solution [12,13]. In this class of degradable polymers, polymer chains need not degrade, so that many well-established polymer networks can be repurposed as degradable polymers using degradable crosslinks [14–16].

We have recently shown that a polymer of dense entanglements and sparse crosslinks, called a tanglemer, has exceptional mechanical behavior, characterized by low hysteresis, high elastic modulus, high strength, and high toughness [17]. When such a polymer network is submerged in a solvent, the dense entanglements enhance the swell resistance of the network. When the polymer network is stretched, the dense entanglements stiffen the network. Furthermore, before a polymer chain breaks, tension is transmitted along its entire length and to many other entangled polymer chains. Breaking of a single bond on the polymer chain dissipates enormous energy stored in both the chain and the entangled chains, which toughens the polymer network. Tanglemers expand the properties space of polymer networks through topology, not chemistry.

We hypothesize that tanglemers can also expand the properties space of degradable polymers. To test this hypothesis, we prepare polyacrylamide hydrogels of disulfide crosslinks of various densities of entanglements. The precursor contains four species of molecules: monomer, water, crosslinker, and initiator. The composition of a precursor is specified by three molar ratios: water-to-monomer molar ratio W, crosslinker-to-monomer molar ratio C, and the initiator-to-monomer molar ratio I. A precursor of low values of C and I results in a polymer network of long polymer chains. All polymer networks in this work are prepared with precursors of a fixed ratio $I/C = 0.4$, but of various values of W and C. Compare two precursors of a fixed low value of C, but different values of W. In both cases, the low value of C leads to polymer networks of long polymer chains. In the precursor of high W, the monomers are sparse, resulting in a sparsely entangled polymer network (Fig. 1a). In the precursor of low W, by contrast, the monomers are crowded, resulting in a highly entangled polymer network (Fig. 1b). The two polymer networks have the same average length of chains, but different topologies of networks.

We synthesize hydrogels using one type of monomer, acrylamide, but two types of crosslinkers, N,N'-Methylenebisacrylamide (MBAA) and N,N'-Bis(acryloyl)cystamine (BACA) (Fig. 2a). In an aqueous solution of cysteine, the polyacrylamide chains and the MBAA crosslinks do not degrade, but the BACA crosslinks degrade by a thiol–disulfide exchange reaction (Fig. 2b).

The as-prepared hydrogels are then submerged in pure water to swell to equilibrium. Both MBAA-crosslinked hydrogels and

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https://doi.org/10.1016/j.eml.2022.101953
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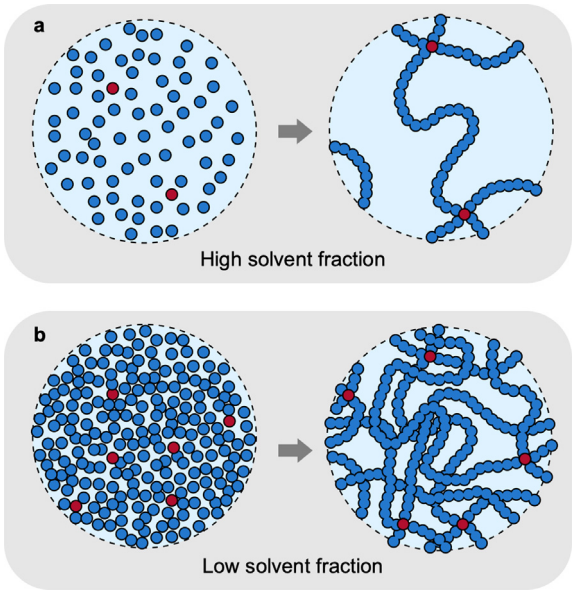

Fig. 1. Densify entanglements by using a precursor in which monomers are crowded. (a) In a precursor of a high water-to-monomer molar ratio, monomers are sparse, resulting in a sparsely entangled polymer network. (b) In a precursor of a low water-to-monomer molar ratio, monomers are crowded, resulting in a highly entangled polymer network. The two precursors have the same value of the crosslinker-to-monomer molar ratio.

BACA-crosslinked hydrogels reach equilibrium in pure water, indicating that they do not degrade in pure water. We subject the equilibrium hydrogels to various tests. Consider hydrogels prepared with precursors of a fixed value of $C = 1 \times 10^{-4}$. A precursor of low W leads to an as-prepared hydrogel with a high density of entanglements, so that the equilibrium hydrogel has a high polymer content (Fig. 3a) and high stiffness (Fig. 3b).

The toughness of the hydrogels is insensitive to W (Fig. 3c). In principle, the toughness depends on both the polymer chain length and the polymer content [18,19]. Recall that all these hydrogels have a fixed value of C, and therefore a similar average length of polymer chains. The toughness scales with the polymer content $\Gamma \sim$(polymer content)$^{2/3}$ [18]. As the polymer content varies from 2.5% to 15% when W varies from 25 to 2, the toughness is expected to change by a factor of $\sim$3. The measured toughness of the hydrogels varies somewhat with W. However, toughness scatters by a factor of $\sim$2, so that we do not study the scaling relation between toughness and polymer content.

Next, we fix $W = 2$ and vary C in the precursors, in which the monomers are crowded. The as-prepared hydrogels are submerged in pure water to swell to equilibrium. We measure the polymer content, elastic modulus, and toughness of the equilibrium hydrogels as functions of C (Fig. 3d–3f). When $C < 1 \times 10^{-5}$, the as-prepared hydrogel swells excessively and becomes a viscous liquid, so the material properties are not measured. When C exceeds a critical value, $\approx 1 \times 10^{-5}$, the amount of crosslinks is high enough to hold elasticity, and the hydrogels are solid-like. When $1 \times 10^{-5} < C < 1 \times 10^{-3}$, the polymer content and elastic modulus both plateau, suggesting that many entanglements exist for each polymer chain between two crosslinks. When $C > 1 \times 10^{-3}$, the polymer content and elastic modulus increase with C, indicating that the number of crosslinks is comparable to or greater than that of entanglements. That is, each chain has entanglements equivalent to $C = 1 \times 10^{-3}$. The number of monomers between adjacent entanglements can be approximated by the number of monomers between adjacent crosslinks at $C = 1 \times 10^{-3}$. As two crosslinks form a chain and one crosslink connects four chains, the number of monomers between adjacent crosslinks is $(2C)^{-1}$, which corresponds to the entanglement molecular weight of 35,000 g/mol.

Our estimated entanglement molecular weight of the polyacrylamide hydrogel can be compared with the entanglement molecular weight of polyacrylamide melt, which is 9,100 g/mol [20]. We synthesized hydrogels with precursors with different values of W. When W is high, monomers are dilute and the entanglements are sparse. When W is low, monomers are crowded and the entanglements are dense. The lowest W in this study is 2, which corresponds to about 50% of the mass fraction of water

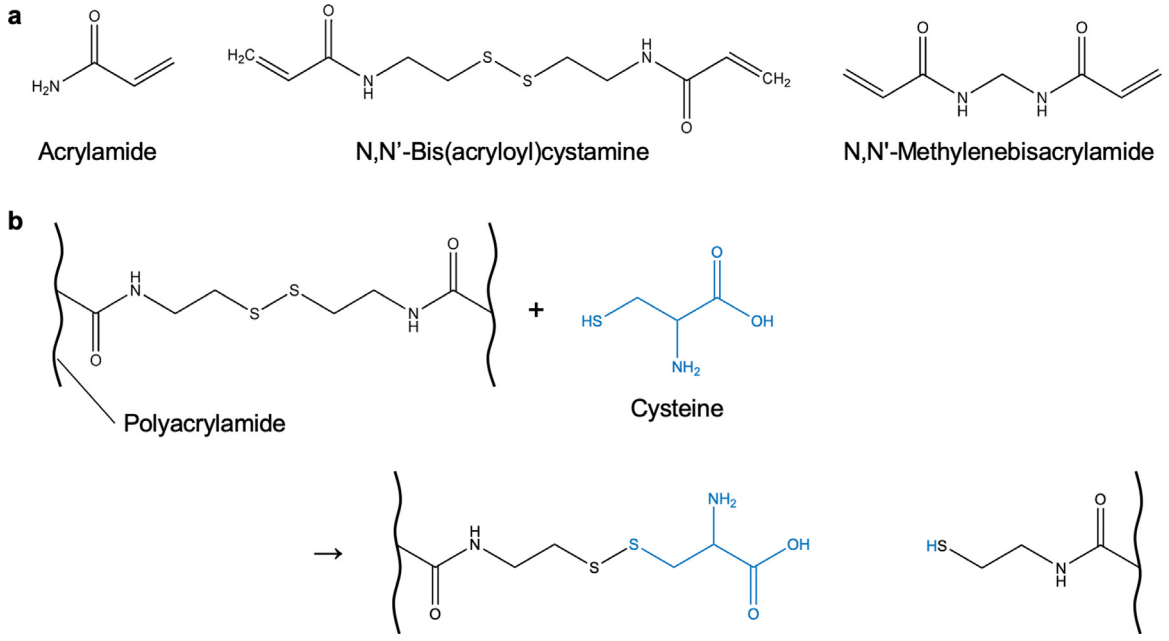

Fig. 2. Hydrogels with non-degradable crosslinks and degradable crosslinks. (a) Acrylamide is used as the monomer for all hydrogels in this work. N,N'-Bis(acryloyl)cystamine (BACA) is used as the degradable crosslinker, and N,N'-Methylenebisacrylamide (MBAA) is used as the non-degradable crosslinker. (b) In an aqueous solution of cysteine, the disulfide crosslink dissociates by a thiol–disulfide exchange reaction.

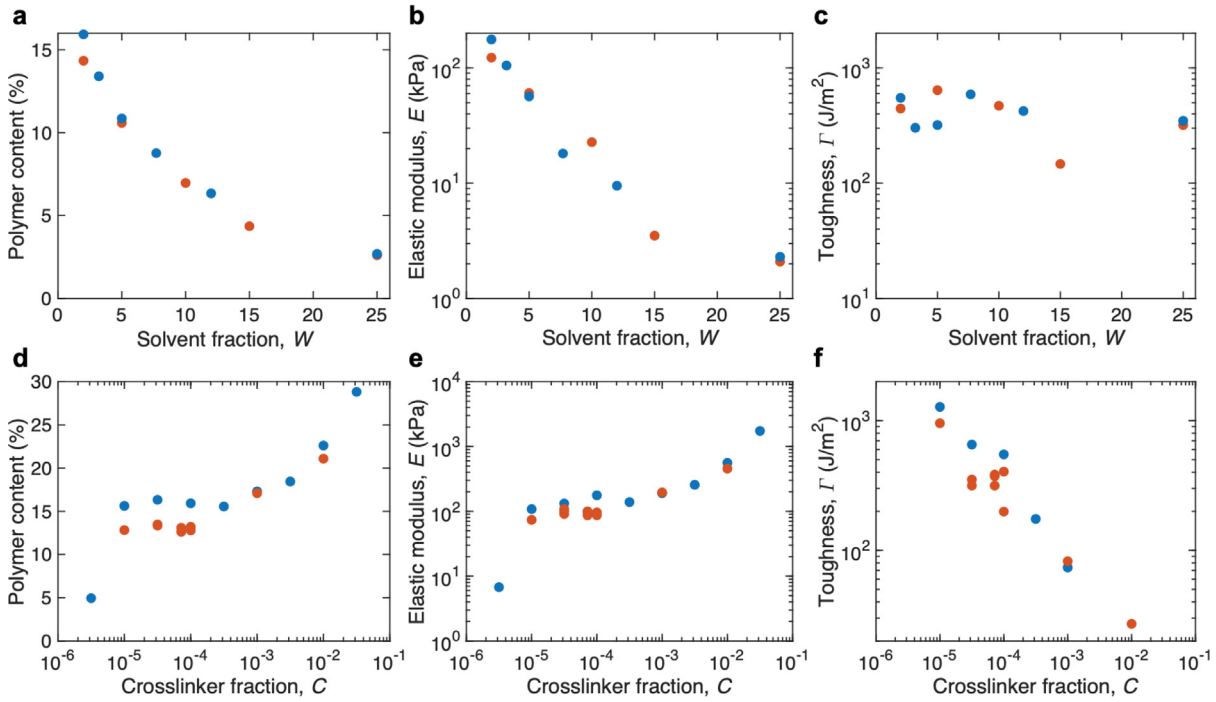

Fig. 3. Degradable hydrogels before degradation (red) and non-degradable hydrogels (blue) have comparable properties. (a–c) The hydrogels are prepared with precursors of $C = 1 \times 10^{-4}$ and various values of W. (d–f) The hydrogels are prepared with precursors of $W = 2$ and various values of C. All hydrogels are swollen in pure water to equilibrium before being tested. The data for the non-degradable hydrogels are from literature [17]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in the precursor. Therefore, the entanglement molecular weight will be higher than that of pure melt of linear polyacrylamide ($W = 0$).

The toughness of the hydrogel decreases as C increases. The toughness varies about 10^2 times while C varies 10^4 times and a clear scaling relation is observed despite the scatter. According to the Lake–Thomas model, toughness Γ scales with $l^{1/2}$, in which l is the length of the polymer chain [19]. As the number of monomer units per polymer chain is $(2C)^{-1}$, $l \sim C^{-1}$ and $\Gamma \sim C^{-1/2}$. At $C = 1 \times 10^{-5}$, the polymer content $\approx$ 13%, the modulus $\approx$ 100 kPa, and the toughness $\approx$ 1,000 J/m^2.

The hydrogels of the degradable crosslinker BACA synthesized in this work are compared to those of the non-degradable crosslinker MBAA synthesized in previous work [17] (Fig. 3). For the given values of W and C, the two types of hydrogels have near-identical properties. The polymer content and modulus are governed by the entropic elasticity of the polymer networks. Their values are almost the same for the hydrogels of two types of crosslinks, indicating that the two types of crosslinkers have similar reaction efficiency. This similarity is unsurprising, given the similarity in the chemical structures of the two types of crosslinkers. The two types of hydrogels have near-identical toughness also, even though the two types of crosslinkers have different bonding energies, 215 kJ/mol for S–S and 345 kJ/mol for C–C [21]. It is likely that the difference in the bonding energies is small compared to the scatter in the toughness.

We confirm that the cysteine dissociates BACA and does not degrade polyacrylamide. We prepare MBAA-crosslinked hydrogels and BACA-crosslinked hydrogels using precursors of $W = 25$ and $C = 1 \times 10^{-4}$. The as-prepared hydrogels are first submerged in pure water to swell to equilibrium, and then submerged in an aqueous solution of cysteine of a concentration of 0.1 M. Whereas the MBAA-crosslinked hydrogel maintains the shape for 72 h (Fig. 4a), the BACA-crosslinked hydrogel dissolves within 4 h (Fig. 4b).

Next, we synthesize a hydrogel of degradable crosslinks using a precursor of $W = 2$ and $C = 1 \times 10^{-4}$. The as-prepared hydrogel is submerged in pure water to swell to equilibrium. The swollen hydrogel is then submerged in an aqueous solution of cysteine of a concentration of 0.1 M at room temperature. The hydrogel swells further 1.4 times by mass in 24 h and does not fully degrade over 72 h (Fig. 4c).

We prepare fresh samples of the three hydrogels to quantify further the effects of the degradable crosslinker and entanglements. The as-prepared hydrogels are submerged in pure water to swell to equilibrium, and then submerged in an aqueous solution of cysteine of a concentration of 0.1 M at room temperature. When a hydrogel degrades by cysteine, the disassociated polymer chains dissolve in the solution from the surface of the hydrogel. Consequently, the hydrogel becomes inhomogeneous and the boundary of the hydrogel becomes unclear. Therefore, it is not appropriate to characterize the degradation by using the degree of swelling or rheology properties. Instead, we measure the elastic moduli of the three hydrogels as functions of time (Fig. 4d). For the hydrogel prepared using a precursor with MBAA and $W = 25$, the elastic modulus does not change over time. For the hydrogel prepared using a precursor with BACA and $W = 25$, the elastic modulus drops as the crosslinks degrade, and the hydrogel dissolves within 4 h. For the hydrogel prepared using a precursor with BACA and $W = 2$, the elastic modulus decreases over time, but the hydrogel does not fully dissolve for 160 h.

We prepare hydrogels of degradable crosslinks using precursors of $W = 2$, 5, 10, and 15. All precursors have the value of $C = 1 \times 10^{-4}$. The as-prepared hydrogels are submerged in pure water to swell to equilibrium at room temperature. The final thicknesses of hydrogels in equilibrium are comparable. We then accelerate degradation by submerging the equilibrium hydrogels in the 0.1 M cysteine solution at 65 °C, and observe the change of the hydrogels with time (Fig. 5). The time required to fully degrade the hydrogels is about 19 days for $W = 2$, 14 days for $W = 5$, and 3 days for $W = 10$ and 15. Recall that a

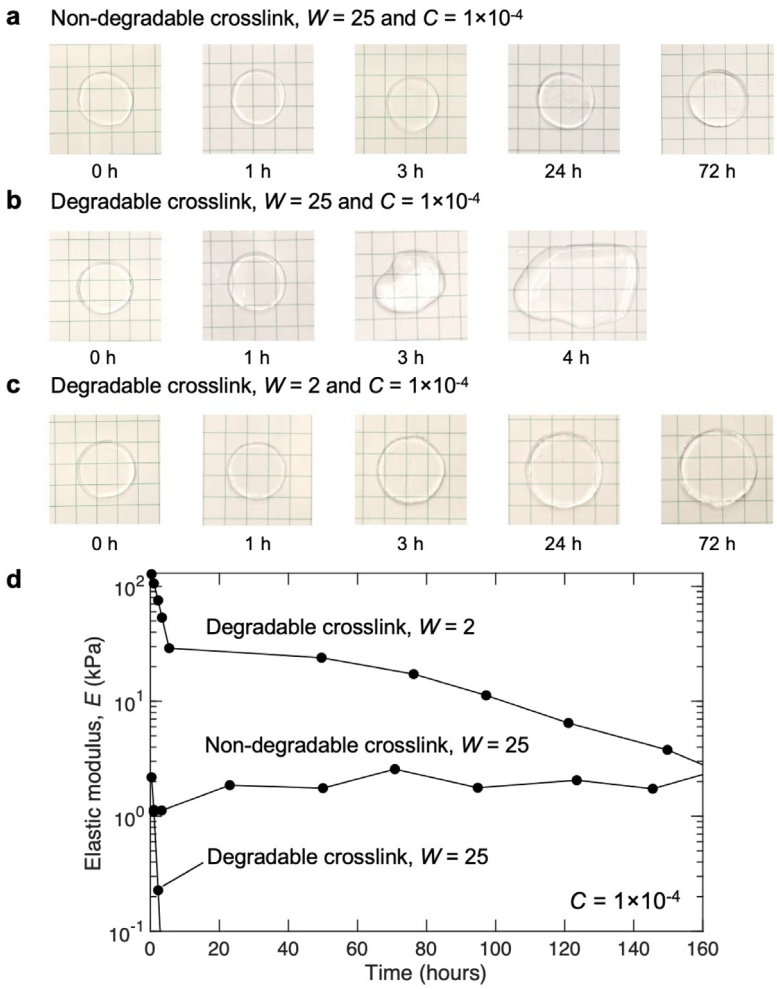

Fig. 4. Three types of hydrogels submerged in a cysteine solution. (a). A hydrogel prepared using a precursor with MBAA (non-degradable crosslinks) and $W = 25$ does not degrade over time. (b). A hydrogel prepared using a precursor with BACA (degradable crosslinks) and $W = 25$ degrades over time. (c). A hydrogel prepared using a precursor with BACA and $W = 2$ degrades slowly. The dimension of the grid is 6 mm × 6 mm. (d). The moduli of the three hydrogels as functions of time.

hydrogel prepared with a precursor of a low value of W is highly entangled. These observations confirm that the highly entangled hydrogels degrade slower than the regular hydrogels. After the as-prepared hydrogels are submerged in pure water to swell to equilibrium, the highly entangled hydrogel has higher polymer content than the regular hydrogels. Furthermore, the swelling in pure water does not degrade crosslinks, and therefore, does not disentangle polymer chains. Is the slow down of degradation due to the polymer content or entanglement density? This question is not studied in the present work, because the polymer content and entanglement density are not independent variables, but are both set by the value of W.

We further prepare hydrogels using precursors of $W = 2$, 5, 10, and 15 without crosslinks ($C = 0$). The average molecular weight of the polymer chains can be estimated from the number of initiators. Under UV light, an initiator triggers polymerization and becomes one end of the growing chain. The growing chain can be terminated by either disproportionation or combination pathway. In the case of combination, two initiators form a single chain. Assuming the fraction of combination is comparable to or greater than that of disproportionation, the number of monomers per chain is estimated as $1/(2I)$. The estimated molecular weight of the polymers is 888,000 g/mol. We then submerge the as-prepared hydrogels in pure water at 65 °C, and observe their changes over time (Fig. 6). A hydrogel prepared with a precursor of low W dissolves slower than the hydrogel prepared with a precursor of high W. This observation confirms a well-established fact. Even for a polymer solution with no crosslinks, entanglements by themselves retard the migration of polymer chains. Also observe that the dissolution of the hydrogels without crosslinks in pure water is much faster than the dissolution of the hydrogels with degradable crosslinks in the cysteine solution. Both the crosslinks and entanglements retard degradation.

The degradation involves three kinetic processes: migration of cysteine from the external solution into the hydrogel, the thiol–disulfide exchange reaction to break the disulfide bonds, and migration of polymer chains from the hydrogel to the external solution. We estimate the time scales of the three kinetic processes as follows. The diffusion coefficient of small molecules like cysteine in an aqueous environment is estimated by the Stokes–Einstein relation $D = k_B T/(6\Pi\eta r)$, where $k_B T$ is the temperature in the unit of energy, r is the radius of the molecule and η is the viscosity of water [22]. Taken $r \approx 10^{-10}$ m, $\eta = 10^{-3}$ Pa s, and $k_B T = 4 \times 10^{-21}$, the estimated diffusivity is $D \approx 10^{-9}$ m^2/s. When the thickness of the hydrogel layer is $H \approx 10^{-3}$ m, the time scale of the migration of cysteine is on the order of $H^2/D \approx 10^3$ s. In the thiol–disulfide exchange reaction, a cysteine molecule RSH and a disulfide crosslink R'SSR" react, producing a R"SH group on one polymer chain and a RSSR' group on the other polymer chain: RSH + R'SSR" ⇆ RSSR' + R"SH. The rate constant of the forward reaction is $k = 0.8$ M^{-1}s^{-1}, where k is defined by d[R'SSR"]/dt = -k[RSH][R'SSR"] [23]. At a constant

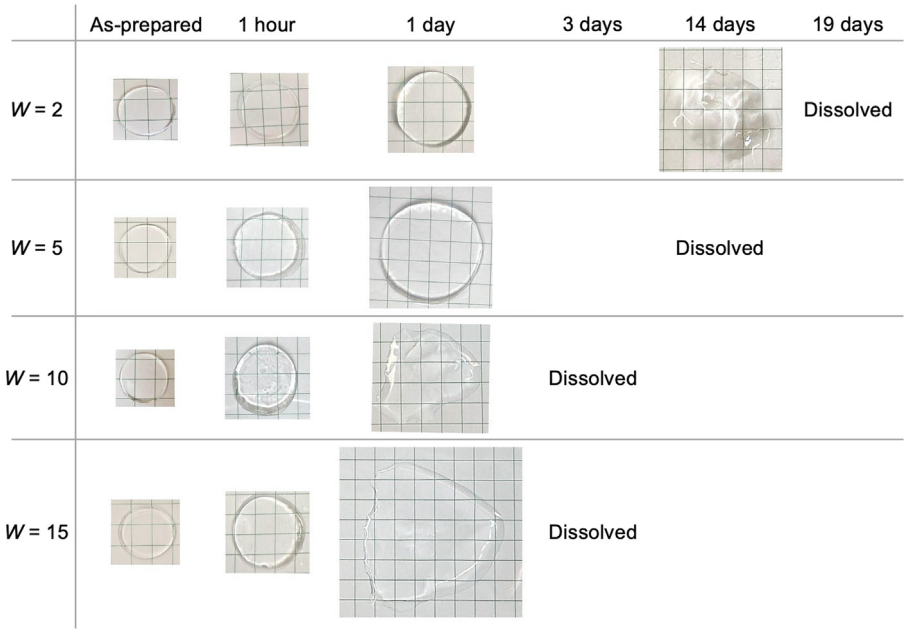

Fig. 5. Degradation of hydrogels with degradable crosslinks depending on the value of W. The value of C is 1×10^{-4} in all cases. The as-prepared hydrogels are submerged in an aqueous solution of 0.1 M cysteine at 65 °C. The dimension of the grid is 6 mm × 6 mm.

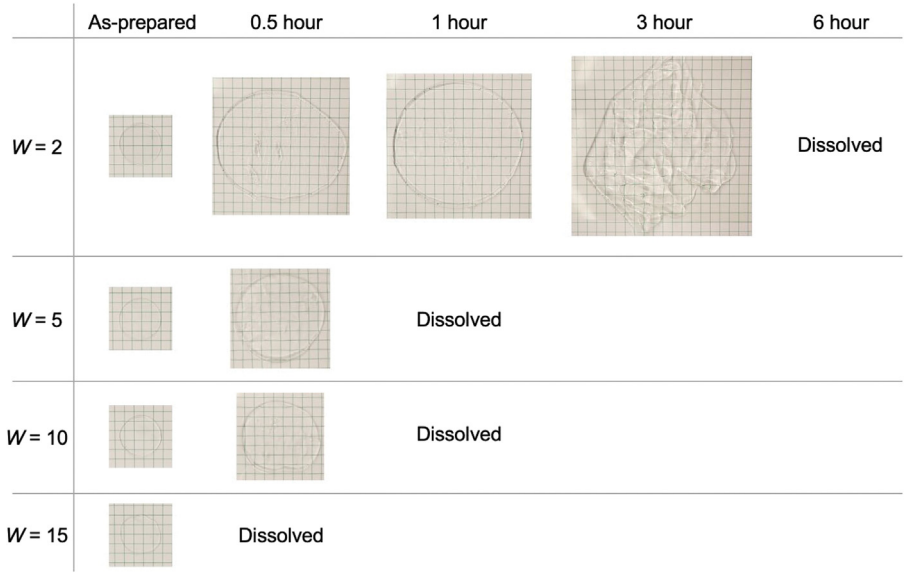

Fig. 6. Dissolution of uncrosslinked hydrogels depending on the value of W. For all cases, $C = 0$ and $I = 4 \times 10^{-5}$. The as-prepared hydrogels are submerged in pure water at 65 °C. The dimension of the grid is 6 mm × 6 mm.

concentration of the cysteine [RSH], the kinetic equation is a first-order ordinary differential equation for the concentration of the disulfide crosslinks [R'SSR"], giving a time scale of reaction $(k[\mathrm{RSH}])^{-1}$. Take the concentration of the cysteine to be the same as that in the external solution in our experiment, [RSH] = 0.1 M, and the time scale of the forward reaction is on the order of 10^1 s. The reverse reaction has the rate constant of the same orders of magnitude, suggesting that the reaction reaches equilibrium in the time scale of 10^1 s. The polymer chains also migrate by diffusion, whose rate can be estimated by the following scaling analysis [24]. The Rouse model provides the diffusivity of the unentangled polymer chains $D_{\mathrm{Rouse}} \approx k_B T/(N\eta b)$, where b is the size of the repeating unit of the polymer chain and N is the number of repeating units. The Rouse model has been modified by the reptation model to include the effect of entanglements and solvent, giving $D_{\mathrm{rep}} \sim D_{\mathrm{Rouse}}(N_e/N)\phi^{-7/3}$, where N_e is the number of the repeating units between adjacent entanglements, ϕ is the volume fraction of the polymers, and the solvent is a theta-solvent. Taking $k_BT = 4 \times 10^{-21}$ J, $\eta = 4 \times 10^{-4}$ Pa s at 65 °C, $b = 4 \times 10^{-10}$ m, $N = 5{,}000$, $N_e/N = 0.1$, and $\phi = 0.15$, we obtain that $D_{\mathrm{rep}} \approx 10^{-11}$ m^2/s. The above estimates indicate that the reaction is much faster than the migration of cysteine, and the migration of cysteine is much faster than the migration of polymer chains.

We next compare these theoretical considerations to the experimentally observed times of degradation. For uncrosslinked hydrogels, the time for degradation is on the order of 10^4 s when $W = 2$, and on the order of 10^2 s when $W = 15$ (Fig. 6). According to our measurement, for these two hydrogels of $W = 2$ and 15, ϕ is different by a factor of three and N_e is different by a factor

of about ten because the number of repeating units scales with E^{-1}. Therefore, D_{rep} is expected to be different by a factor of 10^2, which corresponds to the measured times of degradation. These observations illustrate the significance of W on the time scale of the migration of polymers.

For disulfide-crosslinked hydrogels, the time for degradation is on the order of 10^6 s when $W = 2$, and on the order of 10^5 s when $W = 15$ (Fig. 5). A comparison between Figs. 5 and 6 shows that crosslinks slow down degradation. How can a fast reaction slow down the migration of polymer chains? We interpret this observation as follows. Disassociated polymer chains stay in the network for times much longer than the reaction time. The reaction reaches the equilibrium locally and the reverse reaction re-crosslinks the polymer chains. The thiol–disulfide exchange reaction has an equilibrium constant of $[R''SH][RSSR'][RSH]^{-1}[R'SSR'']^{-1} = 0.43$ [23]. Consequently, when the cysteine concentration is 0.1 M, 0.3% of crosslinks remain bonded. Given that there are about 10^2 crosslinkers per polymer chain, the reverse reaction may slow down the migration of polymer chains. We are unaware of a quantitative model of this synergy between reaction and migration of polymers.

In summary, we have synthesized polymers of degradable crosslinks, and show that entanglements greatly improve the mechanical properties before degradation and substantially slow down degradation. Both mechanical properties and degradation rate are important objects in the development of degradable polymers. By varying the composition of precursors, one can prepare polymer networks of the same chemistry but different topologies. Since the effect of the topology is general, the improvement of the mechanical properties and the delay of degradation are expected in other polymer networks, unless entanglements can readily slip and de-concentrate the tension. The density of entanglements provides an additional parameter to expand the properties space of degradable polymers.

Experimental Section

Materials

Acrylamide (AAm, A8887) is used as a monomer and 2-Hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (Irgacure 2959, 410896) is used as a photoinitiator. N,N'-Bis (acryloyl)cystamine (BACA, A4929) is used as a degradable crosslinker, and N,N'-Methylenebisacrylamide (MBAA, 146072) is used as a non-degradable crosslinker. L-Cysteine (168149) is used as a trigger of degradation. All chemicals are purchased from Sigma-Aldrich.

Synthesis

The monomer and crosslinker are dissolved in water, and the photoinitiator is dissolved in ethanol. The three solutions are then mixed to prepare a precursor of certain values of W, C, and I. The precursor is mixed using a vortex mixer (VWR digital vortex mixer 120V), and is put in an ultrasonic bath (Bransonic CPX1800H) for 3 mins to get rid of bubbles. The precursor is poured into a rectangular mold (89 mm × 51 mm × 0.8 mm), and then covered with a glass sheet and clamped with clips. The precursor is cured under an ultraviolet lamp (1.5 mW/cm^2, 10 ea, Sankyo Denki, F8T5BL) for 3 h. The as-prepared hydrogel is peeled off the mold.

The mass of the as-prepared hydrogel m_0 is measured right after curing. The as-prepared hydrogel is submerged in pure water for over 24 h to swell to equilibrium. The mass of the equilibrium hydrogel m is measured. The swelling ratio is defined by $R = m/m_0$. The thickness of the equilibrium sample is calculated by multiplying $R^{1/3}$ to the thickness of the as-prepared hydrogel. The polymer content is the mass ratio of the polymer to the equilibrium hydrogel.

Measurement of mechanical properties

The equilibrium hydrogel is then cut into a rectangular shape (89 mm × 38 mm). Two sides of the sample are glued with grippers made of acrylic sheets (8560K257) using Krazy glue. The size of the testing area is 89 mm × 12.7 mm. Each sample is pulled using a tensile tester (Instron 5966) to fracture at a stretch rate of 0.0079s^{-1}, and the force is recorded as a function of displacement. The elastic modulus is measured using samples without a pre-crack, and is 3/4 times the initial slope of the stress–stretch curve. To measure the toughness, a crack of a length of 12.7 mm is introduced by a razor blade to the edge of a sample. The experiment records the critical stretch when the sample fractures, λ_c. The toughness of the hydrogel is calculated by $w(\lambda_c)H$, where $w(\lambda)$ is the energy density of the uncracked sample and H is the height of the sample.

Degradation

In one set of experiments, the equilibrium hydrogel is cut and glued with grippers in the same way used for the elastic modulus measurements. Then the sample is immersed in an aqueous solution of 0.1 M L-cysteine at room temperature. The elastic modulus is measured as a function of time. In another set of experiments, the equilibrium hydrogel is cut into a disk, immersed in the aqueous solution of 0.1 M L-cysteine, and stored in an oven at 65 °C. The shapes of the sample are recorded over time.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

J. K. was supported by Kwanjeong Lee Chong Hwan Educational Foundation of Korea (KEF-2017). M.S. is a visiting student at Harvard University supported by the China Scholarship Council.

Funding

This work was supported by MRSEC, USA (DMR-2011754) and by the Air Force Office of Scientific Research, USA (FA9550-20-1-0397).

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