# SUPPORTING INFORMATION

**Acid-Triggered, Acid-Generating, and Self-Amplifying Degradable Polymers**

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1. Materials and Methods

Unless otherwise noted, all solvents were ACS reagent grade and purchased from Acros Organics, Fisher Scientific, or Sigma-Aldrich, and used without further purification. HPLC grade acetonitrile (J.T. Baker) was stored over activated 4 Å molecular sieves for at least 1 day prior to use. HPLC grade acetone (Fisher Scientific) preserved under N₂ was used without purification. Acrolein, acrylamide, allyloxy ethanol, allyl alcohol, 2,2-diethoxyacetophenone, NaI, N-hydroxyethyl acrylamide, N,N'-methylenebis(acrylamide), N-methylmorpholine-N-oxide, p-toluenesulfonic acid, potassium osmate(VI) dihydrate, triethylene glycol monomethyl ether, trimethylsilyl trifluoromethanesulfonate, and 1st generation Grubbs Catalyst were purchased from Aldrich and used as received. TMS bromide (Oakwood Chemicals), and compressed HCl (Airgas) were used as received. 1,2-Dichlorobenzene (Aldrich) was passed through a basic alumina column and stored over activated 3 Å molecular sieves under N₂. SiliaMetS dimercaptotriazine (DMT) was purchased from SiliCycle. Silica and basic alumina chromatography were performed using 230-400 mesh (40-63 μm) silica gel and activated, basic, Brockmann I, 58 Å, respectively. D₂O was purchased from Aldrich and all other deuterated solvents were purchased from Cambridge Isotope Laboratory.

¹H and ¹³C NMR spectra were recorded on a 400 or 500 MHz Varian Unity Inova spectrometer at ambient temperature. NMR spectra were processed using MestReNova software and chemical shifts were in parts per million (ppm). All ¹H and ¹³C spectra were referenced to the residual solvent peak. Integration is provided and coupling constants (J) are reported in Hertz (Hz). Electrospray ionization mass spectra (ESI-MS) were obtained by using ESI on a Waters Micromass Q-Tof spectrometer, FD on a Waters 70-VSE spectrometer. Gel permeation chromatography (GPC) experiments were carried out on a Waters system equipped with a Waters 1515 isocratic pump, a Waters 2414 refractive index detector, and a miniDAWN TREOS 3-angle laser light scattering detector (MALLS, Wyatt Technology, CA) with the detection wavelength set at 658 nm. The MALLS detector was calibrated using pure toluene and used for the determination of the absolute molecular weights. DMF containing 0.1 M LiBr was used as the mobile phase with the flow rate = 1.0 mL/min at 50 °C using a set of four Styragel columns (5 µm): two HR 2, one HR 3 and one HR 4. Absolute molecular weights of the polymers were determined based on the dn/dc value of each sample using the ASTRA software (version 6.1, Wyatt Technology CA) assuming 100% mass recovery. All pH values were measured on a Mettler Toledo FE20 FiveEasy Benchtop pH Meter using pH Electrode LE409. Characterization
of linear viscoelastic properties was performed on a combined motor/transducer DHR-3 rotational rheometer from TA Instruments using a parallel-plate geometry with a diameter of 20 millimeters and Peltier temperature control. For rheological characterization, all gels were prepared at a nominal thickness of 1 mm for loading. During measurements, the gap was continuously varied to maintain a normal force of 0.5 ± 0.1 N to avoid edge fracture and maintain contact across the geometry. A low viscosity mineral oil was applied to the exposed surface of the gel to prevent evaporation. All data was plotted and fitted using OriginPro 8. Some plots were imported into Adobe Illustrator for annotation and coloring of lines and symbols.

**Caution:** Acrolein is toxic to humans following inhalation, oral or dermal exposure. All reactions using acrolein and all polymer degradation experiments that produce acrolein should be performed in a fume hood with appropriate personal protective equipment.

2. Synthesis and Characterization

**Scheme S1.** Synthesis of compound 1.

**Compound 14.** The preparation of 14 was carried out by following reported procedures.\(^1\)\(^2\) Briefly, acrolein (7 g, 100 mmol, 1 equiv) was added dropwise into a solution of bromotrimethylsilane (15.8 mL, 120 mmol, 1.2 equiv) in benzene (120 mL) at 0 ºC. The resulting mixture was stirred for 30 min and warmed to room temperature for 60 min. The crude mixture was used directly in the next step. **Caution:** Acrolein is toxic to humans following inhalation, oral or dermal exposure.

**Compound 5.** The crude mixture containing 14 was treated with p-toluenesulfonic acid, monohydrate (500 mg) and 4 (14.3 g, 140 mmol, 1.4 equiv). The mixture was refluxed in a Dean-Stark apparatus for 20 h. The product was diluted with benzene (50 mL), washed with an aqueous 5% (w/w) solution of NaHCO\(_3\) (2 × 250 mL) and water (250 mL), dried over MgSO\(_4\), concentrated, and purified by column chromatography (SiO\(_2\), EtOAc:hexanes, 10:90) resulting in 17.45 g of product (54% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.86 (m, 2H), 5.30 – 5.07 (m, 4H), 4.77 (t, \(J = 5.7, 1\)H), 3.97 (d, \(J = 5.7, 4\)H), 3.77 – 3.59 (m, 4H), 3.55 (t, \(J = 5.0, 4\)H), 3.41 (t, \(J = 6.7, 2\)H), 2.15 (td, \(J = 6.8, 5.6, 2\)H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 134.85, 117.23, 101.80,
72.36, 69.56, 65.53, 36.70, 28.87. m/z LRMS (ESI) calculated for [M+Na]+: 346.08; found: 346.08. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

**Compound 1.** Compound 5 (5.3 g, 0.023 mol, 1 equiv) was dissolved in acetone (30 mL) and treated with NaI (4.2 g, 0.028 mol, 1.25 equiv) at room temperature for 20 h. The reaction was diluted with diethyl ether (60 mL) and cooled to -20 °C to precipitate NaI and NaCl. This cold solution was quickly filtered through a sintered glass funnel. The filtrate was concentrated, redissolved in hexanes (100 mL), washed with an aqueous 10% (w/w) Na₂S₂O₃ (2 × 50 mL) and brine (50 mL), dried with Na₂SO₄, concentrated, and purified by column chromatography (SiO₂, EtOAc:hexanes, 20:80). The slightly-yellow product was further purified by passing through another column (basic alumina, EtOAc:hexanes, 15:85) to afford 7.32 g of product in 86% yield. ¹H NMR (400 MHz, CDCl₃) δ 5.91 (m, 2H), 5.36 – 5.13 (m, 4H), 4.73 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 5.7, 4H), 3.77 (dt, J = 10.7, 4.8 Hz, 2H), 3.72 – 3.64 (m, 2H), 3.59 (t, J = 4.8 Hz, 4H), 3.20 (t, J = 7.1 Hz, 2H), 2.18 (td, J = 7.1, 5.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 134.85, 117.23, 117.21, 103.29, 72.36, 69.57, 65.46, 37.35, 0.42. m/z LRMS (ESI) calc for [M+Na]+: 393.06; found: 393.05. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

**Scheme S2.** Synthesis of compound 2.

**Compound 16.** The crude mixture of 14 was prepared as previously mentioned and used directly to synthesize 16. Briefly, acrolein (7 g, 100 mmol, 1 equiv) was added dropwise into a solution of bromotrimethylsilane (15.8 mL, 120 mmol, 1.2 equiv) in benzene (120 mL) at 0 °C. The resulting mixture was stirred for 30 min and warmed to room temperature for 60 min. Then, the crude mixture was treated with p-toluenesulfonic acid, monohydrate (500 mg) and 15 (20 mL, 17 g, 294 mmol, 2.9 equiv). The mixture was refluxed using a Dean-Stark apparatus for 24 h. The product washed with an aqueous 5% (w/w) solution of NaHCO₃ (2 × 250 mL) and water (250 mL), dried over MgSO₄, concentrated, and purified by column chromatography (SiO₂, EtOAc:hexanes, 10:90) resulting in 14.5 g of product (62% yield). ¹H NMR (400 MHz, CDCl₃) δ 5.92 (m, 2H), 5.30 (m, 2H), 5.19 (m, 2H), 4.79 (t, J = 5.5 Hz, 1H), 4.19 – 4.01 (m, 4H), 3.45 (t, J = 6.7 Hz, 2H), 2.20 (td, J = 6.7, 5.5 Hz, 2H). Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.
**Compound 17.** Compound 16 (5.3 g, 22.5 mmol, 1 equiv) was dissolved in acetone (30 mL) and treated with NaI (4.2 mg, 28.2 mmol, 1.25 equiv) at room temperature for 12 h. The reaction was diluted with diethyl ether (60 mL) and cooled to -20 °C for 2.5 h. This cold solution was quickly filtered through a sintered glass funnel. The filtrate was concentrated, re-dissolved in hexanes (100 mL), washed with an aqueous 10% (w/w) Na$_2$S$_2$O$_3$ (100 mL) and brine (100 mL), dried with Na$_2$SO$_4$, and concentrated. The product was purified by column chromatography (SiO$_2$, EtOAc:hexanes, 7:93) and then passed through basic alumina to afford 5.4 g (85% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.92 (m, 2H), 5.30 (m, 2H), 5.19 (m, 2H), 4.70 (t, $J$ = 5.5 Hz, 1H), 4.15 – 4.02 (m, 4H), 3.19 (t, $J$ = 7.1 Hz, 2H), 2.18 (td, $J$ = 7.1, 5.5 Hz, 2H). *Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.*

**Compound 2.** The dihydroxylation of 17 was carried out by following reported procedures.$^{3,4}$ Briefly, 17 (1.41 g, 5 mmol, 1 equiv) was dissolved in a mixture of water (18 mL) and acetone (60 mL). N-methyl morpholine N-oxide (NMO, 1.76 g, 15 mmol, 3 equiv) and K$_2$OsO$_4$•H$_2$O (0.073 g, 0.2 mmol, 0.04 equiv) were added and the reaction was stirred at room temperature for 2 h. The product was washed with diethyl ether (3 x 25 mL), saturated with NaCl, extracted with chloroform/isopropanol (1:1, 3 x 25 mL), concentrated, and purified by column chromatography (SiO$_2$, DCM:MeOH, 9:1) resulting in 0.77 g of product (44% yield). $^1$H NMR (400 MHz, D$_2$O) δ 4.65 (t, $J$ = 5.8 Hz, 1H), 3.83 (p, $J$ = 5.9, 5.5 Hz, 2H), 3.76 – 3.40 (m, 8H), 1.70 – 1.52 (m, 2H), 1.33 (h, $J$ = 7.5 Hz, 2H), 0.87 (t, $J$ = 7.4 Hz, 2H). *Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.*

**Scheme S3.** Synthesis of compound 3.

**Compound 18.** Acrolein (6.64 mL, 0.1 mol) was added to toluene (200 mL) and diethyl ether (60 mL). Dicinnamalacetone (5 mg) was added to the mixture as an indicator. Gaseous HCl was bubbled through the mixture for 2 h as the light-yellow solution turned bright orange. A $^1$H NMR of the crude reaction mixture indicated ~97% conversion of acrolein to 18. The mixture was concentrated under reduced pressure to remove the ether and used directly in the next reaction. *Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.*

S5
**Compound 19.** Triethylene glycol monomethyl ether (40 mL, 0.25 mol) and p-toluenesulfonic acid, monohydrate (230 mg, 1.2 mmol) were added to the crude mixture containing 18. The solution was refluxed for 20 h using a Dean-Stark trap. The solvent was removed under reduced pressure. The residue was re-dissolved in ethyl acetate (100 mL), washed with hexanes (100 mL), and an aqueous solution containing 5% (w/w) K₂CO₃ and 10% (w/w) NaCl (300 mL). The product was extracted with ethyl acetate (2 × 100 mL) and the organic layers washed with brine and dried over Na₂SO₄. The solution was concentrated under reduced pressure to provide 45 g of crude 2, which was used directly in the next reaction without purification. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

**Compound 3.** The crude 19 (24 g, 0.06 mol) was dissolved in acetone (200 mL). NaI (39 g, 0.26 mol) and NEt₃ (0.83 mL, 0.006 mol) were added and the solution was stirred at 45 °C for 20 h. Diethyl ether (200 mL) was added and the reaction was cooled to -20 °C to precipitate NaI and NaCl. This cold solution was quickly filtered through a sintered glass funnel. The filtrate was concentrated under reduced pressure, re-dissolved in hexanes (200 mL), and washed with an aqueous 10% (w/w) Na₂S₂O₃ solution (2 × 100 mL). The product was back extracted, washed with brine, dried over Na₂SO₄, concentrated to get a light brown viscous oil, and purified by column chromatography (SiO₂, EtOAc:hexanes, 50:50). Further purification was accomplished by a second column (basic alumina, EtOAc:hexanes, 50:50) to provide 16.4 g of product in 55% yield. ¹H NMR (400 MHz, CDCl₃) δ 4.73 (td, J = 5.6, 1.1 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.76 – 3.63 (m, 20H), 3.59 (ddd, J = 5.7, 3.8, 1.2 Hz, 4H), 3.42 (d, J = 1.1 Hz, 5H), 3.33 – 3.18 (m, 2H), 2.26 – 2.16 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 134.88, 117.25, 103.27, 72.36, 69.57, 65.46, 37.35, 0.48. m/z LRMS (ESI) calculated for [M+H₂O+H]⁺: 517.14; found: 517.13. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

**Scheme S4.** Synthesis of polymer 10.

**Polymer 9.** A dry two-neck round-bottom flask (25 mL) was equipped with a condenser and connected to a vacuum pump (0.2 mmHg) and N₂ via Schlenk line. The flask was charged with a small stir bar, dry 1,2 dichlorobenzene (2 mL), and 5 (500 mg, 1.35 mmol) under positive N₂ flow. The other neck was closed with a rubber septum and copper wire. The reaction mixture
was degassed by applying vacuum for 20 min at 0 ºC. The flask was brought to room temperature, refilled with N₂ and first-generation Grubbs Catalyst (28.5 mg, 0.035 mmol, 2.5 mol%) was added under positive N₂ flow. The polymerization was carried out under gradient of vacuum and temperature. The reaction mixture was stirred at 30 ºC for 30 min with partial opening to the vacuum line to minimize spluttering. Under this condition, the solvent evaporates gradually along with ethylene gas to result in a condensed reaction mixture. This was further heated under maximum opening of the vacuum line at 50 ºC for 1 h followed by 60 ºC for 2.5 h. The reaction mixture was cooled to room temperature, dissolved in chloroform (5 mL), and ethyl vinyl ether (5 mL) was added to quench the catalyst. The mixture was stirred for 30 min at room temperature followed by precipitation in 10 mL of hexane. Upon centrifugation and drying under reduced pressure, the product (405 mg) was obtained as a highly viscous dark brown product with \( M_n \approx 13,000 \) and \( M_w/M_n \approx 1.2. \) **Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.**

**Polymer 10.** In a 50 mL round-bottom flask charged with a magnetic stirring bar, 9 (405 mg, 1.14 mmol, 1 equiv) was dissolved in a mixture of acetone (10 mL) and *tert*-butanol (6 mL). Separately, K₂OsO₄•H₂O (24 mg, 0.065 mmol, 0.57 equiv) was dissolved in DI water (2 mL) and added to the flask. N-methyl morpholine N-oxide (NMO, 335 mg, 2.86 mmol, 2.5 equiv) was added and the mixture stirred at room temperature for 5 h. A saturated aqueous solution of Na₂SO₃ (0.6 mL) was added and the mixture stirred for 2 h. The organic layer was placed in a 50 mL round-bottom flask and stirred for 1 h with SiliaMetS (1 g) to remove residual heavy metals. The mixture was filtered, concentrated, and dried over Na₂SO₄. The crude polymer was dispersed in chloroform (2 mL), precipitated into acetone to remove residual NMO, re-dissolved in methanol (2 mL), precipitated into diethyl ether, filtered, and dried to give the product (270 mg) as a golden brown solid. **Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.**

**Scheme S5.** Synthesis of compound 20.

\[
\begin{align*}
\text{O} & \quad \text{TMSCI} \\
\text{DCM, TEA} & \quad 0 \degree \text{C to rt, 13 h} \\
\text{20} & \quad 20%
\end{align*}
\]

**Compound 20.** \( N \)-hydroxyethyl acrylamide (31.0 mL, 269 mmol), triethylamine (100 mL, 716 mmol), and DCM (250 mL) were added to a round-bottom flask. The reaction was stirred for 30
min under N_2. The mixture was cooled to 0 °C and trimethylsilyl chloride (105 mL, 827 mmol) was cannulated into an addition funnel and added dropwise to the mixture over 45 min. The reaction was warmed to room temperature and stirred for 12 h. The mixture was poured into ice water (500 mL) and extracted with DCM (3 × 150 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and the solvent removed via rotary evaporation. Column chromatography was used to purify the crude compound (SiO_2, 100% DCM to 1:2 EtOAc:hexanes). A clear yellow oil was obtained in 68% yield (34.3 g). ^1H NMR (400 MHz, CDCl_3) δ 6.27 (dd, J = 16.9, 1.5 Hz, 1H), 6.11 (dd, J = 16.9, 10.3 Hz, 1H), 5.63 (dd, J = 10.3, 1.5 Hz, 1H), 3.67 (t, J = 5.3 Hz, 1H), 3.46 (q, J = 5.2 Hz, 1H). ^13C NMR (125 MHz, CDCl_3) δ 166.1, 131.5, 126.9, 61.8, 42.2, 0.0. m/z LRMS (ESI) calculated for [M+H]^+: 187.31; found: 188.11.

Scheme S6. Synthesis of Gel 13.

Compound 18. Acrolein (1 mL, 15 mmol, 1 equiv) and 1 M HCl in diethyl ether (30 mL) were added to a round-bottom flask and stirred for 2 h under N_2. The mixture was placed in dry ice/acetonitrile bath and used directly in the next step without purification. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

Compound 11. The crude reaction mixture containing 18 was treated with trimethylsilyl trifluoromethane sulfonate (92 mL) via syringe followed by dropwise addition of a solution of 20 (5 g, 27 mmol, 1.8 equiv) dissolved in DCM (10 mL). The reaction was stirred for 3 h and quenched with triethylamine (3 mL). The mixture was washed with a saturated aqueous solution of NaHCO_3 (100 mL) and extracted with DCM (4 × 250 mL). The organic layer was collected, dried over sodium sulfate, filtered, and dried using rotary evaporation. The product was purified using column chromatography (SiO_2, EtOAc:DCM 80:20 to MeOH:DCM 3:97) resulting in the product as a partially impure clear yellow oil (1.1 g) that was used directly in the next step. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.
**Compound 12.** Sodium iodide (5.4 g, 36 mmol, 10 equiv), 11 (1.1 g, 3.6 mmol, 1 equiv), and acetone (35 mL) were combined in a flask and stirred under N₂. Using a condenser, the reaction mixture was heated to 45 ºC for 26 h and then quenched by pouring directly into a saturated NaHCO₃ solution (100 mL). The product was extracted using DCM (5 × 250 mL). The organic layer was collected, dried over sodium sulfate, and the solvent removed by rotary evaporation. The product was purified using column chromatography (SiO₂, MeOH:DCM 3:97). An orange viscous oil was collected as the product in 94% yield (0.940 mg). ¹H NMR (500 MHz, CDCl₃) δ 6.31 (dd, J = 17.0, 1.5 Hz, 2H), 6.15 (dd, J = 17.0, 10.2 Hz, 4H), 5.66 (dd, J = 10.2, 1.6 Hz, 2H), 4.63 (t, J = 5.5 Hz, 1H), 3.85 – 3.44 (m, 8H), 3.16 (t, J = 6.9 Hz, 2H), 2.12 (td, J = 6.9, 5.4 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 166.4, 131.2, 127.4, 104.1, 77.8, 65.7, 40.2, 37.3. m/z LRMS (EI) calculated for [M+Na]+: 419.22; found: 419.04. **Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.**

**Gel 13.** Gel preparation was carried out similar to a reported procedure. Briefly, crosslinker 12 (40.4 mg, 0.1 mmol, 3 equiv) was dissolved in 0.3 mL of a 2,2-dioethoxyacetophenone (DEAP) photoinitiator solution (0.3 mL of DEAP dissolved in 10 mL DMSO) and diluted with Millipore water (5 mL) in a buffer-washed scintillation vial. Acrylamide (241.5 mg, 3.4 mmol, 100 equiv) and KCl (5 mg) were added, the mixture was vortexed, and polymerized under a mercury UV lamp (Blak-Ray longwave lamp B-100AP, 365 nm, 100 W) for 1 h. **Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.**

**Scheme S5.** Synthesis of polyacrylamide hydrogel.

**Polyacrylamide hydrogel.** The polyacrylamide hydrogel (PAAm) was prepared using reported procedures. Briefly, N,N’-methylenbisacrylamide (15.7 mg, 0.1 mmol, 3 equiv) was dissolved in 0.3 mL of a 2,2-dioethoxyacetophenone (DEAP) photoinitiator solution (0.3 mL of DEAP dissolved in 10 mL DMSO) and diluted with Millipore water (5 mL) in a buffer-washed scintillation vial. Acrylamide (241.5 mg, 3.4 mmol, 100 equiv) and KCl (5 mg) were added, the mixture was vortexed, and then polymerized under a mercury UV lamp (Blak-Ray longwave lamp B-100AP, 365 nm, 100 W) for 1 h. **Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.**
3. Degradation of 3 Monitored by $^1$H NMR

To monitor the degradation by NMR, two sets of solutions of 3 (48 mM) were prepared in D$_2$O at pD 5.5. For the acid amplification study, D$_2$O of pD 5.5 was prepared by adding p-toluenesulfonic acid to D$_2$O. For the control experiment, 0.1 M acetate buffer of pD 5.5 in D$_2$O was prepared. The pD value of a solution made in D$_2$O was obtained by adding a constant of ca. 0.4 to pH*, which was measured from the direct reading in a H$_2$O-calibrated pH-meter. This adjustment between pD and pH* is based on the measurements of acids and/or bases dissolved at the same concentrations in H$_2$O and D$_2$O. For each set of NMR experiments, several NMR tubes containing 0.7 mL of the solution were capped and sealed with parafilm and heated to 70 °C. One NMR tube was taken out at each time point and the reaction was quenched by immersing the NMR tube in an ice bath. The conversions were calculated by integrating the signal at 1.9 ppm (2 proton at 0 min) with respect to the signal at 3.2 ppm (6 protons, constant throughout). These experiments were run in triplicate and the data was fitted to obtain rate constants. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

![Figure S1. $^1$H NMR analysis of the degradation kinetics of 3 in a 48 mM solution in D$_2$O.](image-url)
4. Degradation of 3 Monitored by pH

To monitor degradation by pH, 3 (0.27 mL) was added to a conical screw cap vial and dissolved in Millipore water (15 mL) to make a 48 mM aqueous solution. The solution was sonicated briefly and heated at the desired temperature. 1 mL aliquots were taken out via syringe at each time point and quenched by immediate cooling in an ice bath. The pH values of the aliquots were measured at room temperature by the pH meter calibrated for pH 4 and 7. KCl (1 mg/ml) was added to each aliquot to increase their ionic strength to improve the precision and response time of the measurement. For instantaneous degradation, the starting pH of 3 was obtained by adding external p-toluenesulfonic acid. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.

5. Degradation of 10 Monitored by \(^1\text{H} \text{NMR}\)

A solution of 10 (3 mM) was prepared in a solvent mixture containing 40\% CD\(_3\)CN in D\(_2\)O of pD 5.5 with DMSO (8 mM) as an internal standard (see arrow). The pD value of a solution made in D\(_2\)O was found by adding a constant of 0.4 to the pH value,\(^6\) which is obtained from the direct reading in a H\(_2\)O-calibrated pH-meter. An NMR tube containing 0.25 mL of the solution was capped, sealed with parafilm. The sample was inserted after equilibration to to 70 °C and time points were taken every 5 min. The conversions of acetal were calculated by integrating the signal at 5.05-5.28 ppm (acetal signal, 1 proton at 0 min) with respect to the signal at 3.25 ppm (DMSO internal standard, constant throughout). These experiments were run in triplicate and the data was fitted to obtain rate constants. Caution: Acrolein is toxic to humans following inhalation, oral or dermal exposure.
Figure S2. $^1$H NMR analysis of the degradation kinetics of 10 in a 48 mM solution in D$_2$O.

6. Degradation of 10 Monitored by GPC

A solution of 10 (0.35 M) was prepared in a solvent mixture containing 40% CH$_3$CN in H$_2$O with DMSO (8 mM). Vials containing the solution were capped, sealed with parafilm, and heated to 70 °C. One vial was taken out at each time point and the reaction was quenched by immediately immersing in an ice bath. Solutions were concentrated, dried under high vacuum, and re-dissolved in DMF containing 0.1 M LiBr to result in 30 mg/mL solution. The solutions were passed through 0.45 µm syringe filters and analyzed by GPC. Peak deconvolution was performed to obtain retention times.

Figure S3. GPC traces of the degradation of 10 from a 0.35 mM solution in 40% CH$_3$CN in H$_2$O at 70 °C.
**Figure S4.** Deconvolution results for the GPC traces of the degradation of 10 in 40% CH$_3$CN in H$_2$O at 70 ºC.

7. Degradation of 13 Monitored by pH

A Canon EOS Rebel T3 Digital SLR Camera with EF-S 60 mm lens was used to take pictures of the hydrogel degradation every 5 min using an Aputure remote shutter release timer. Hydrogels were polymerized vertically on the side of a 20 mL scintillation vial for visualization of the degradation process. Pictures were taken through an oil bath that was set to 90 ºC.
Figure S5. Visual observation of the degradation of 13 compared to polyacrylamide control at 90 °C.

Measurements of solution pH were taken before polymerization and after depolymerization for each system. The pHs were measured at room temperature by the pH meter calibrated for pH 4 and 7. KCl (1 mg/ml) was added to each sample to increase their ionic strength to improve the precision and response time of the measurement. The polyacrylamide hydrogel was measured after 24 h such that sufficient hydrolysis had taken place to achieve an accurate pH measurement. All values are an average of three separate samples.

Table S1. Monitoring hydrogel pH before and after degradation.

|          | pH before    | pH after    |
|----------|--------------|-------------|
| 13       | 4.73 ± 0.04  | 1.83 ± 0.02 |
| Polyacrylamide hydrogel | 5.19 ± 0.05  | 4.53 ± 0.04 |

8. Degradation of 13 Monitored by Rheology

Characterization of linear viscoelastic properties was performed on a combined motor/transducer DHR-3 rotational rheometer from TA Instruments using a parallel-plate geometry with a diameter of 20 millimeters and Peltier temperature control. For rheological characterization, all gels were prepared at a nominal thickness of 1 mm for loading. During measurements, the gap was continuously varied to maintain a normal force of 0.5 ± 0.1 N to avoid edge fracture and maintain contact across the geometry. A low viscosity mineral oil was applied to the exposed surface of the gel to prevent evaporation. All samples were heated from
25 °C to the final temperature at a rate of 5 °C per minute in a linear temperature ramp test. To obtain the viscoelastic storage and loss moduli, G' and G'', samples were held at the final temperature and probed at a frequency of 1 rad/s and an oscillatory strain amplitude of 3% or below which was in the linear deformation regime. For all samples, before any significant change in the moduli of the material, the ratio of G'' to G' (i.e. \( \tan(\delta) = G''/G' \)) was always less than 0.1. For the samples that undergo a dramatic decrease in G', during and after the decrease, \( \tan(\delta) \) was always less than 1. G'' and \( \tan(\delta) \) are omitted from plots for clarity. All rheological plots begin once the final temperature is reached by the Peltier temperature controller. At short times, slight increases in moduli are observed for all materials; we attribute this to temperature equilibration of the sample. Little frequency dependence was observed for any of the materials across the range of 0.1 to 30 rad/s. These experiments were run in triplicate and the data was fitted to obtain rate constants.

The gray region in Fig. 4b indicates the range below which shear modulus data cannot be trusted, since this corresponds to the low-torque limits of the instrument. Data in this region is usually noisy, and an estimate of the limits can be obtained from \( G_{\text{min}} = \frac{F_r T_{\text{min}}}{\gamma_0} \), where \( F_r \) is a geometry dependent conversion factor to go from torque signals (which is actually measured by the instrument) to stress, \( T_{\text{min}} \) is the low-torque limit of the instrument (specified by the manufacturer), and \( \gamma_0 \) is the strain amplitude employed in the experiment. The minimum torque limit specified by TA instruments is 0.5 nNm, but as a rule of thumb, to have sufficient margin of safety, the actual limit used in the calculation was 10 times this, so we have used \( T_{\text{min}} = 5 \) nNm. Using this, the minimum shear (storage) modulus that can be measured is 0.17 Pa.

9. Kinetic Analysis

Degradation kinetics were analyzed following previously reported examples using the rate law for autocatalytic reactions. In summary, the reaction rate can be expressed as

\[
\text{rate} = k_1[R] + k_2[R][P],
\]

where \( R \) is the reactant, \( P \) is the product, and \( k_1 \) and \( k_2 \) are the rate constants that describe the non-autocatalytic and autocatalytic mechanisms, respectively. This equation can be written as
\[- \frac{dc}{dt} = k_1 c + k_2 c (c_0 - c) , \]  

(S2)

where \( c \) represents the concentration of the degradable moiety with its initial value being \( c_0 \). To express the rate as a function of the initial concentration and a measured concentration as a function of time, integration of Equation S2 leads to the following rate law

\[
\ln \left[ \frac{k_1 + k_2 c_0 - k_2 c}{c} \right] = (k_1 + k_2 c_0) t + \ln \left[ \frac{k_1}{c_0} \right].
\]

(S3)

Finally, rearrangement and simplification of Equation S3 leads to

\[
\frac{c}{c_0} = \frac{k_1 + k_2 c_0}{k_1 e^{(k_1 + k_2 c_0)t} + k_2 c_0},
\]

(S4)

which is an explicit equation for reaction conversion as a function of time. This equation can be used to fit \( k_1 \) and \( k_2 \) by least-squares regression of the normalized acetal amount.

In the case of the hydrogel, \( k_1 \) and \( k_2 \) must be extracted from the normalized storage modulus. Using the phantom model of rubber elasticity\textsuperscript{10,11} and assuming a network functionality of \( f = 4 \) (as expected for a bifunctional crosslinker), the plateau modulus \( G_0 \) and the number density of elastically active crosslinks (\( \mu \)) are related by \( G_0 = (v - \mu) k_B T = \mu k_B T \), where \( v = \mu \cdot f / 2 \) is the number density of elastically active network strands and \( k_B T \) is the thermal energy.\textsuperscript{12-15} In the case of fitting \( G/G_0 \) (Given that \( \mu \equiv N_A c \)),

\[
c = \frac{G}{k_B T N_A} \quad \text{and} \quad c_0 = \frac{G_0}{k_B T N_A}.
\]

(S5)

Substituting Equation S5 into S4,

\[
\frac{G}{G_0} = \frac{k_1 + \frac{k_2 G_0}{k_B T N_A}}{k_1 e^{(k_1 + \frac{k_2 G_0}{k_B T N_A}) t} + \frac{k_2 G_0}{k_B T N_A}}.
\]

(S6)
Thus, for each degradation profile, \( k_1 \) and \( k_2 \) were found using least-squares regression of either the normalized acetal (using Equation S4) or normalized storage modulus (using Equation S6). The values from each triplicate measurement were averaged and reported in Table 1. A plot of \( \ln[(k_1 + k_2c_0 - k_2c)/c] \) versus time is shown for visual representation to give a straight line based on the relationship provided in Equation S3. For polymer samples, it should be noted that concentration must be calculated from the moles of total degradable agents in the solution rather than simply the moles of polymer. The \( c_0 \) values used were 0.048 M for 3, 0.045 M for 10, and 0.050 M, 0.022 M, or 0.037 M for 13. In addition, the hydrogel \( k_2 \) values calculated from storage modulus neglect the effects of loops and other inactive cleavage sites. These could be accounted for in the rate equation by assuming a constant ratio of elastically inactive cleavage sites \( \phi = c_{\text{inactive}}/c_{\text{active}} \), where \( c_{\text{total}} = c_{\text{inactive}} + c_{\text{active}} \). Equation S2 is true for \( c_{\text{active}} \) but can be rewritten to account for inactive crosslinking by substituting \( c_{\text{total}} = (1 + \phi)c_{\text{active}} \). We have assumed that \( \phi = 0 \), so \( k_2 \) from our fit may be larger than the true rate constant by a factor of \( 1 + \phi \). In comparing the rates between systems, we found that the \( k_1/k_2c_0 \) value for all systems is \( \ll 1 \) as is characteristic of autocatalytic reactions (3, 10, and 13 are 0.00064, 0.0012 and 0.00014, respectively).

Figure S6. Representative data fitting for monitoring the disappearance of acetal functionality of 3 by \(^1\)H NMR as a 48 mM solution in D\(_2\)O at 70 °C. Dashed lines are fits of the data to Equation S4 (\( R^2 = 0.997 \)) and dotted lines are provided to guide the eye.
Figure S7. Representative data fitting for monitoring the disappearance of acetal functionality of 10 by $^1$H NMR as a 3 mM solution in D$_2$O/CD$_3$CN at 70 °C. Dashed lines are fits of the data to Equation S4 ($R^2 = 0.983$) and dotted lines are provided to guide the eye.

Figure S8. Representative data fitting for monitoring the disappearance of acetal functionality of 13 by rheology at 90 °C. Data points are shown as small faded circle symbols. Dashed lines are fits of the data to Equation S6 ($R^2 = 0.997$) and dotted lines are provided to guide the eye.
10. References

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11. Supplemental Comparison of ADMET Control Polymer Degradation

An attempt was made to prepare a control polymer with the same $M_n$ as 10 but lacking the halogen. Poly(PTPD)-hydroxyl was prepared with a significantly lower molecular weight. A preliminary comparison of its degradation by NMR is shown below.

![Graph showing preliminary comparison of hydrolysis rates of ADMET polymer with and without I.](image)

**Figure S9.** Preliminary comparison of hydrolysis rates of ADMET polymer with and without I.

12. Supplemental Synthesis and Degradation of 21

Encouraged by the degradation behavior of 13, we applied the 3-iodopropyl acetal moiety to another polyol hydrogel. Hydrogel 21 was synthesized following the procedure below. When 21 was incubated in H$_2$O at 70 ºC in acetate buffered solutions (pH 5.35) and un-buffered solution (pH 5.5), an amplified degradation behavior of the hydrogel was observed. Thermoresponsive collapse (opacity) of the hydrophobic domains within the hydrogel structure was observed and no significant degradation was observed after 53 h of incubation. However, complete disappearance of the hydrogel occurred in the following 16 h. Comparatively, no visible degradation of the hydrogel occurred over the 69 h incubation period for the buffered system. Although, we cannot exclude the influence of the polyurethane structure or acid diffusion through the gel as it degrades, this qualitative result is in good agreement with our hypothesis that only when the acid amplifying unit is allowed to proliferate, and not be quenched by buffering conditions, will the macroscopic auto-catalytic degradation be realized.
Scheme S6. Synthesis of 21.

Compound 21. To a nitrogen purged 4 mL glass screw-cap vial containing 0.25 g (0.714 mmol) of 3 was added to 0.48 g (0.476 mmol) anhydrous 3-ARM PEG (MW: 1,014), 8.5 μL dibutyltin dilaurate, 1 mL anhydrous THF, and 0.23 mL (1.43 mmol) of hexamethylene diisocyanate while using vortexing and nitrogen to mix and purge the reaction vial between additions. The mixture was allowed to stand at room temperature for ~10 min until the transparent yellow liquid solution turned to a yellow opaque gel. The reaction was left for an additional 3 h at room temperature to ensure complete gelation. The gel was cut in half and dialyzed against nanopure water for 2 d (MWCO: 12-14 kD). The resulting translucent gels were lyophilized until constant weight and stored covered at 0 °C. ATR IR (1/cm): 3320, 2930, 2860, 1690, 1530, and 1250.

Figure S9. (a) Photos displaying acid triggered self-amplified degradation of 21 in pH 5.5 H₂O at 70 °C. (b) Photos displaying minimal acid triggered self-amplified degradation of 21 in acetate buffer at 70 °C.
13. Supplemental GPC Traces

![GPC traces with molecular weight and Mn values](image)

14. Supplemental NMR Spectra

![NMR spectrum with chemical shifts](image)
Crude $^1$H NMR (CDCl$_3$, 400 MHz)
$^1$H NMR (CDCl$_3$, 400 MHz)