# Degradable Polyanhydride Networks Derived from Itaconic Acid

*Hussnain Sajjad,*[a] *Leon M. Lillie,*[a] *C. Maggie Lau,*[b] *Christopher J. Ellison,*[b*] *William B. Tolman,*[c*] *and Theresa M. Reineke,*[a*]

[a]Department of Chemistry and Center for Sustainable Polymers, University of Minnesota, Minneapolis, Minnesota 55455-0431.

[b]Department of Chemical Engineering and Materials Science, University of Minnesota, Minneapolis, Minnesota 55455-0431.

[c]Department of Chemistry, One Brookings Drive, Campus Box 1134, Washington University in St. Louis, St. Louis, MO 63130-4899.

## S.1 Experimental

### S.1.1 Materials

Anhydrous ethanol was obtained from Pharmco-AAPER (Shelbyville, KY, USA). Acetic anhydride was obtained from Fisher Scientific (Hampton, NH, USA). OMNIRAD TPO-L was obtained from IGM Resins USA, Inc. (Charlotte, NC, USA). Itaconic acid and all other reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA). Cyclopentadiene was obtained via "cracking" and fractional distillation of dicylopentadiene at 180 - 190 °C. Deuterated chloroform ($CDCl_3$) was obtained from Cambridge Isotope Laboratories (Tewksbury, MA, USA). Phosphate-buffered saline was prepared with a phosphate-buffered saline powder packet from Sigma-Aldrich (St. Louis, MO, USA), with pH of 7.4. Artificial seawater was prepared by combining 24.53 g NaCl, 5.20 g $MgCl_2$, 4.09 g $Na_2SO_4$, 1.16 g $CaCl_2$, 0.695 g KCl, 0.201 g $NaHCO_3$, and 0.101 g KBr in 1 L of DI water. All purchased compounds were used directly without further purification.

### S.1.2 Characterization Methods

Nuclear Magnetic Resonance (NMR) spectra were obtained on a Bruker Avance HD-500 in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal reference.

High-resolution mass spectrometry (HRMS) was performed on samples dissolved in methanol using a Bruker Bio-TOF II in positive mode with a $PEG_{400}$ standard.

Fourier-transform infrared (FT-IR) spectroscopy was performed on a Nicolet 6700 FT-IR spectrometer equipped with a KBr beam splitter, an MCT-A detector (Thermo Fisher Scientific, Waltham, MA), and a horizontal transmission accessory (Harrick Scientific Products, Inc., Pleasantville, NY) was used for studying the reaction conversion of the monomer mixtures. The spectrometer and horizontal transmission accessory were continuously purged with dry, $CO_2$-free air. The monomer mixtures were irradiated using a UV light source (OmniCure S1500 Spot UV Light Curing System, Excelitas Technologies) with an intensity of 50 $mW/cm^2$. The spectra were recorded with an average of 1 scan every 20 ms and a resolution of 32 $cm^{-1}$ for a total of 100 s. The samples were placed between two polished NaCl plates (diameter: 25 mm; thickness: 4 mm). The reaction was monitored based on the C=C acrylate peak of iAIAH and EtIAH at 1636 $cm^{-1}$, the C=C norbornene peak of NBiAIAH and NBEtIAH at 713 $cm^{-1}$, and the S-H peak of PETMP and DPEHMP at 2572 $cm^{-1}$. The peak heights were normalized in reference to the C=O stretch. The reaction conversion was calculated based on the initial peak intensity, $I_0$, and the peak intensity at time t, $I_t$, (i.e. Conversion = $(I_0 - I_t)/I_0$ *100%).

Thermogravimetric analysis (TGA) was performed on a TA Instruments Q500. TGA analyses were performed on 4-10 mg of sample under a nitrogen atmosphere with a heating rate of 10 °C/min from room temperature to 550 °C.

Differential Scanning Calorimetry (DSC) was performed on a TA Instruments Q-1000 on samples in hermetically sealed aluminum pans. The samples were heated and cooled at 2 °C/min and the reported spectra are from the second heating ramp.

Dynamic mechanical analysis (DMA) was performed with an RSA-G2 solid analyzer (RAS-G2, TA Instruments, USA) equipped with a film tension clamp. The temperature was controlled by a force convection oven attached with a liquid N2 cooling device, and the measurement was conducted by applying a frequency of 1 Hz and a strain of 0.05%. The specimen was cooled down to 0 °C by liquid N2 prior to the acquisition of data, and the temperature was ramped to 70 °C at 5 °C $min^{-1}$.

Electron paramagnetic resonance (EPR) spectroscopy was performed on a Bruker EleXsys E500 X-band spectrometer. Spectra of **1**-PETMP were acquired in the R4122 SHQ spherical resonator at 22 °C. Sweep width was 120 G with 1,024 points per spectrum, microwave frequency of 9.40 GHz; modulation frequency of 100 kHz, and modulation amplitude of 1.0 G.

Tensile testing was performed on a Shimadzu AFS-X at room temperature on dogbone shaped samples with the approximate gauge dimensions, 2.7 mm x 13.5 mm x 0.7 mm (W x L x T). Polyanhydride samples were extended at 5 mm/min and 5 replicate runs were averaged for analysis.

pH measurements were conducted using a Accumet Basic AB15 pH meter.

### S.1.3Synthesis of Ethyl Itaconic Acid

A 1 L round-bottomed flask (RBF) was charged with crystalline itaconic acid (200 g, 1.5 mol, 1 equivalent (equiv.)) and suspended in ethanol (575 mL, 9.8 mol, 6.5 equiv.). Acetyl chloride (5.5 g, 5 mL, 0.07 mol, 0.05 equiv.) was added to this stirred suspension and heated to reflux; solubilization occurred within 20 min. The reaction mixture was removed from the heating mantle and solvent was removed *in vacuo* to yield a slightly yellow oil. This oil was transferred to a 2 L Erlenmeyer flask and dissolved in hot toluene (400 mL, 70 °C). To this mixture, hexanes (600 mL) was added to yield a cloudy solution. After filtration, the filtrate was cooled to -20 °C for 6 h to yield large colorless crystals, which were collected via vacuum filtration and dried overnight in a vacuum oven with gentle heating (40 °C; 170 g, 70% yield). $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 11.75 (s, 1H), 6.47 (d, *J* = 1.0 Hz, 1H), 5.84 (q, *J* = 1.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.34 (d, *J* = 1.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (126

MHz, Chloroform-*d*) δ 171.61, 170.72, 133.47, 130.88, 61.20, 37.49, 14.23. HRMS (ESI-TOF, *m*/*z*) calculated for $C_7H_{10}O_4Na^+$: 181.1422; found: 181.0471. Melting Point = 56.5 °C.

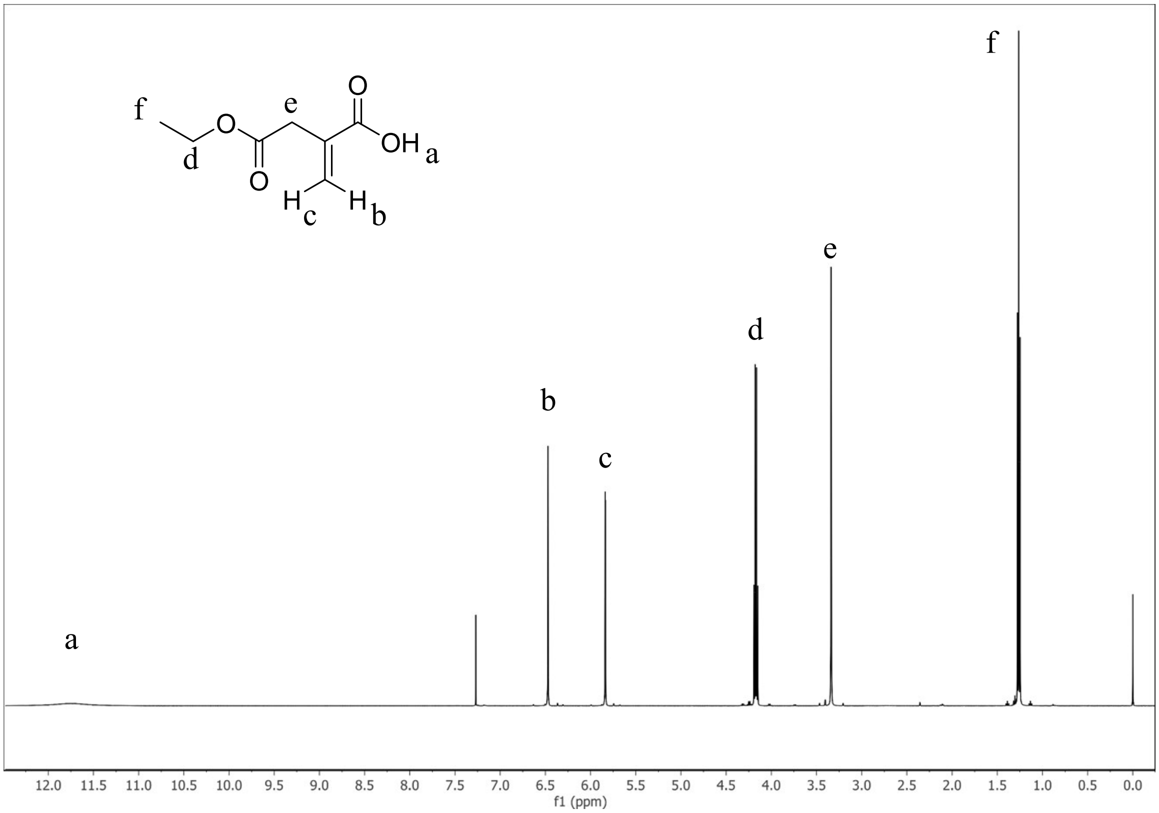


**Figure S1.** $^1$H-NMR spectrum of ethyl itaconic acid ($CDCl_3$, 500 MHz).

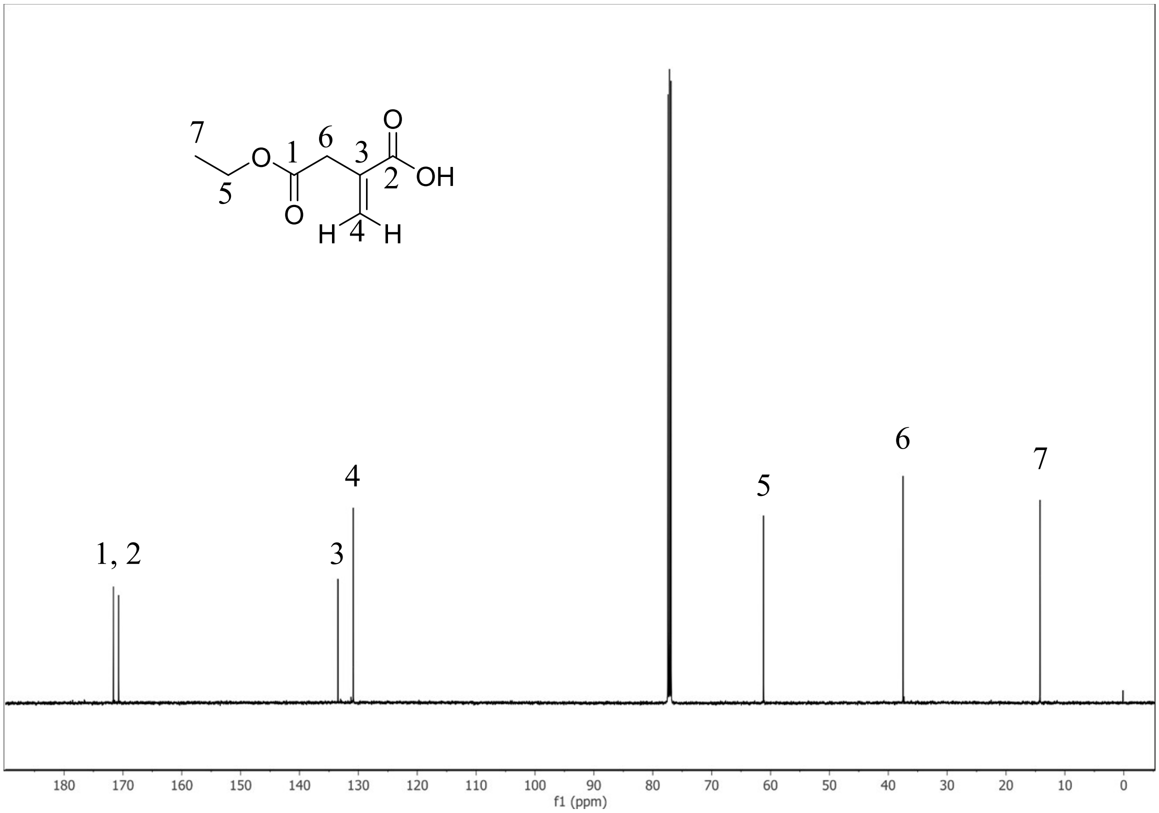


**Figure S2.** $^{13}$C-NMR spectrum of ethyl itaconic acid ($CDCl_3$, 126 MHz)

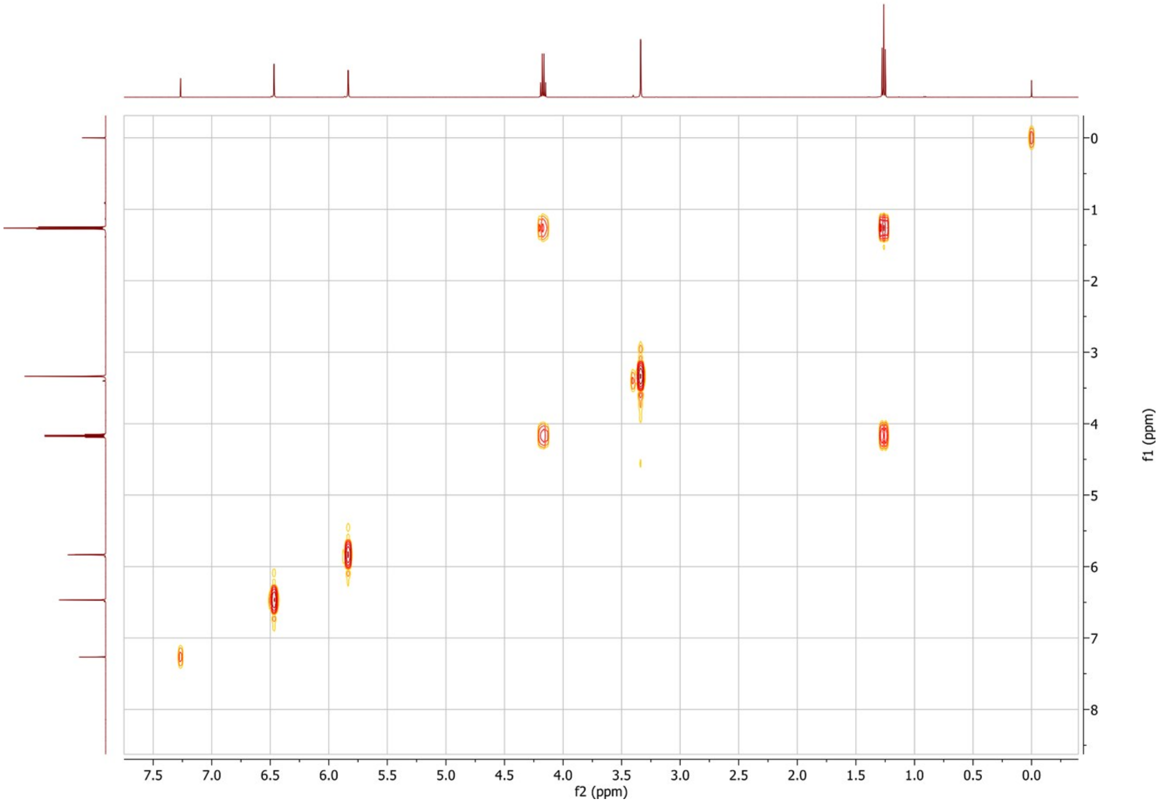


**Figure S3.** $^1$H COSY NMR spectrum of ethyl itaconic acid ($CDCl_3$, 500 MHz)

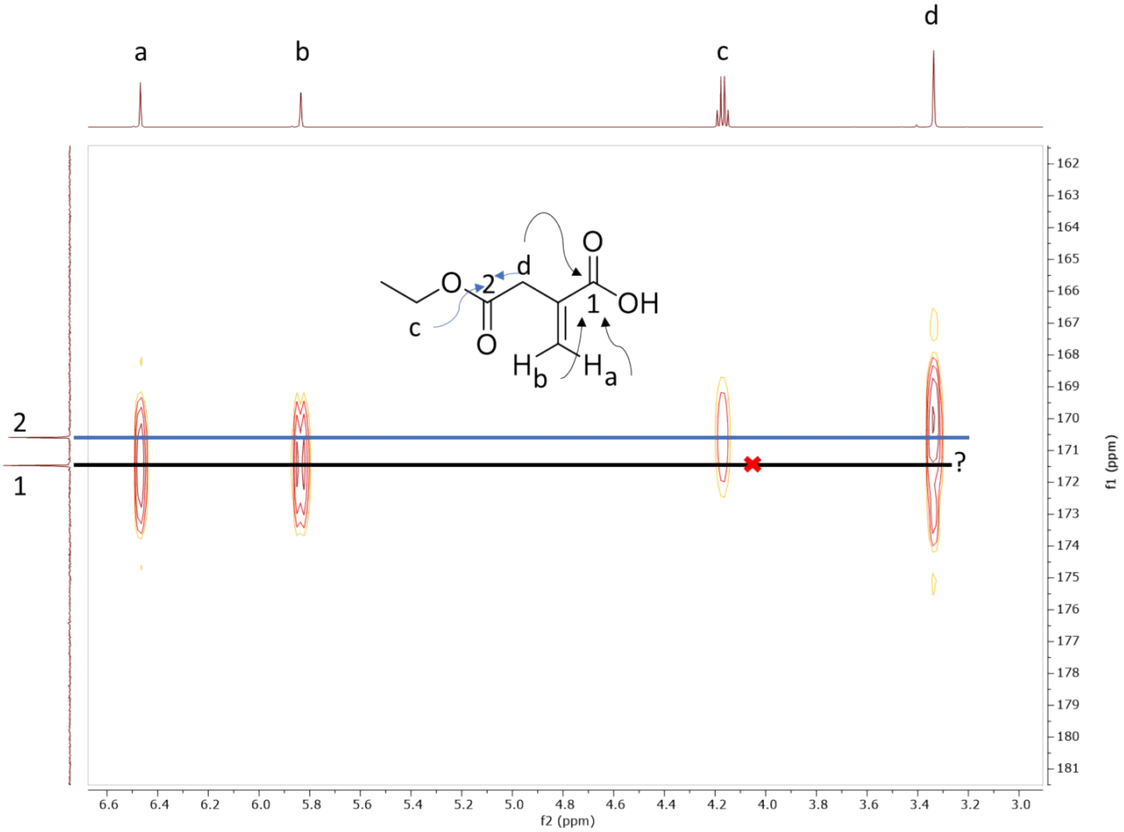


**Figure S4.** $^1$H-$^{13}$C HMBC NMR spectrum for structural confirmation of ethyl itaconic acid (500 MHz, 125 MHz).

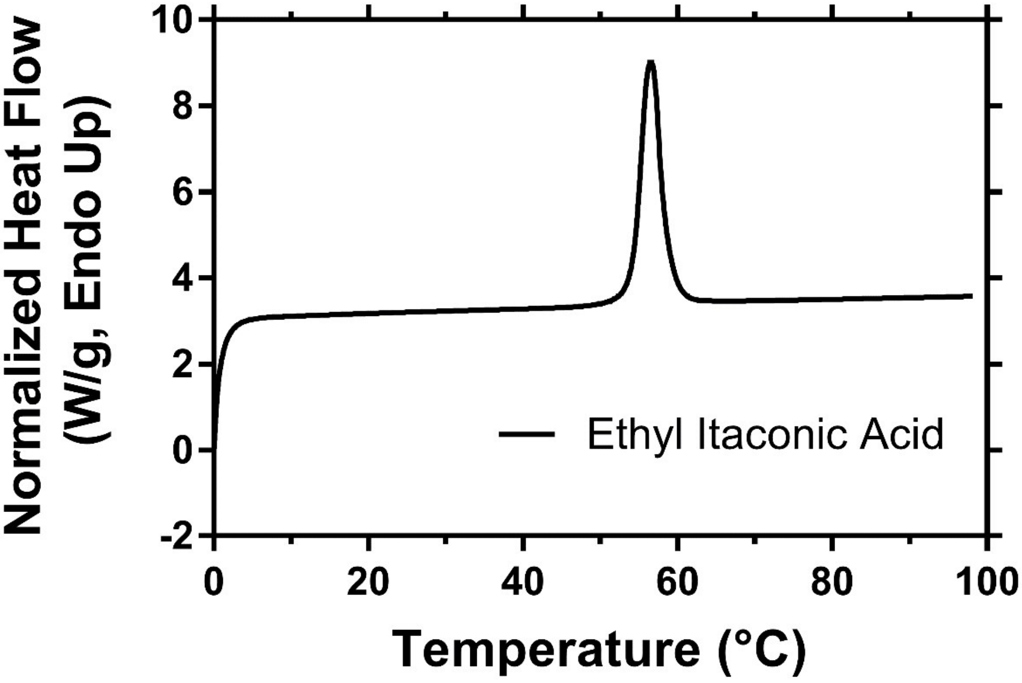


**Figure S5.** Melting point assessment of ethyl itaconic acid by differential scanning calorimetry (DSC).

### S.1.4 Synthesis of Isoamyl Itaconic Acid

A 1 L round-bottomed flask (RBF) was charged with crystalline itaconic acid (100 g, 0.77 mol, 1 equivalent (equiv.)) and suspended in isoamyl alcohol (430 mL, 4.9 mol, 6.4 equiv.). Acetyl chloride (2.5 mL, 0.04 mol, 0.05 equiv.) was added to this stirred suspension and heated to reflux; solubilization occurred within 20 min. The reaction mixture was removed from the heating mantle and solvent was removed *in vacuo* to yield a slightly yellow oil. This oil was transferred to a 2 L Erlenmeyer flask and dissolved in hot toluene (200 mL, 70 °C). To this mixture, hexanes (300 mL) was added to form a homogenous solution. The crystallization solution was cooled to -20 °C for 6 h to yield colorless crystals, which were collected via vacuum filtration and dried overnight in a vacuum oven with gentle heating (40 °C; 90.9 g, 59 % yield). $^1$H NMR (500 MHz, Chloroform-*d*) δ 6.46 (d, $J$ = 1.0 Hz, 1H), 5.83 (q, $J$ = 1.1 Hz, 1H), 4.14 (t, *J* = 6.9 Hz, 2H), 3.34 (d, *J* = 1.2 Hz, 2H), 1.68 (dp, *J* = 13.4, 6.7 Hz, 1H), 1.52 (q, *J* = 6.9 Hz, 2H), 0.91 (d, *J* = 6.6 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.80, 170.60, 133.28, 130.61, 63.76, 37.43, 37.19, 25.01, 22.41. HRMS (ESI-TOF, *m/z*) calculated for $C_{10}H_{16}O_4Na^+$: 223.2232; found: 223.0926. Melting Point = 49.3 °C.

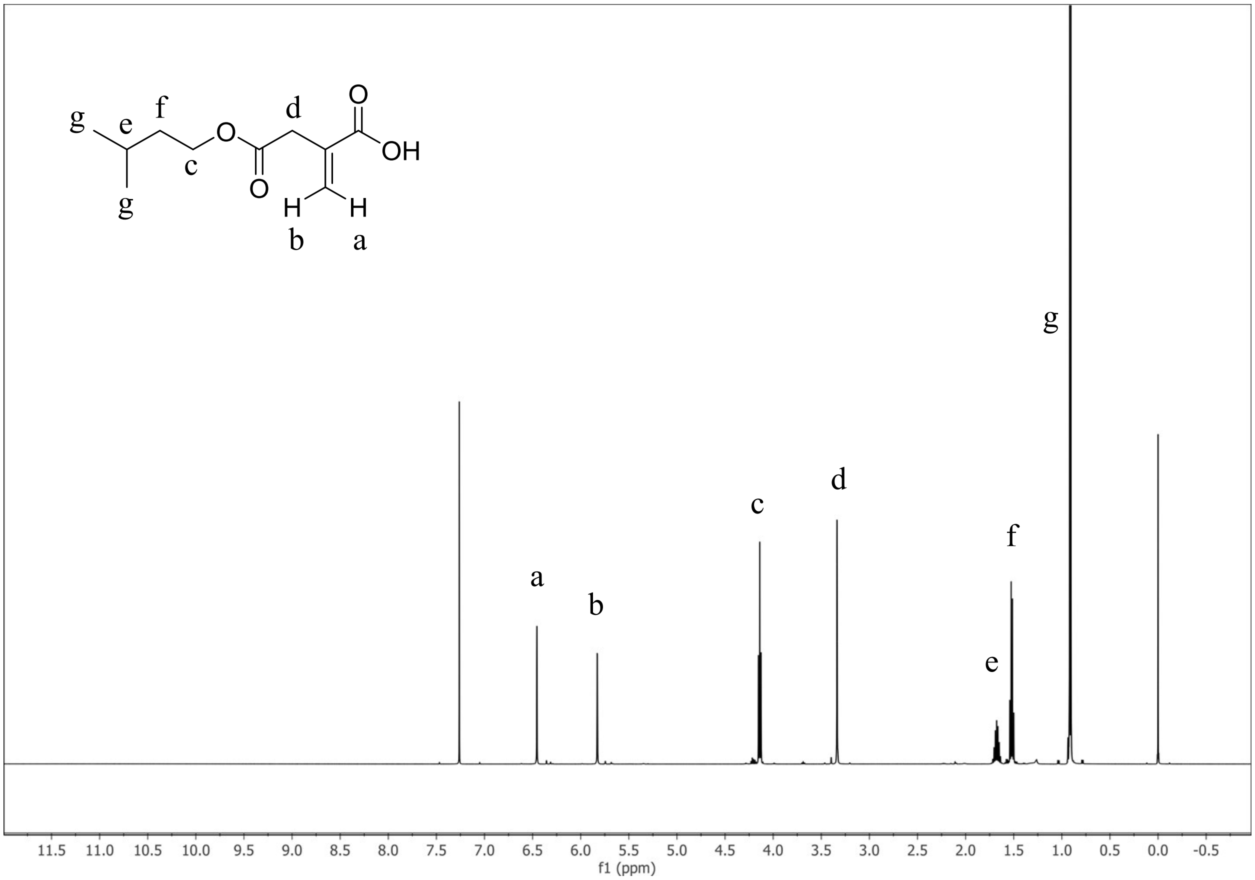


**Figure S6.** H-NMR spectrum of isoamyl itaconic acid ($CDCl_3$, 500 MHz).

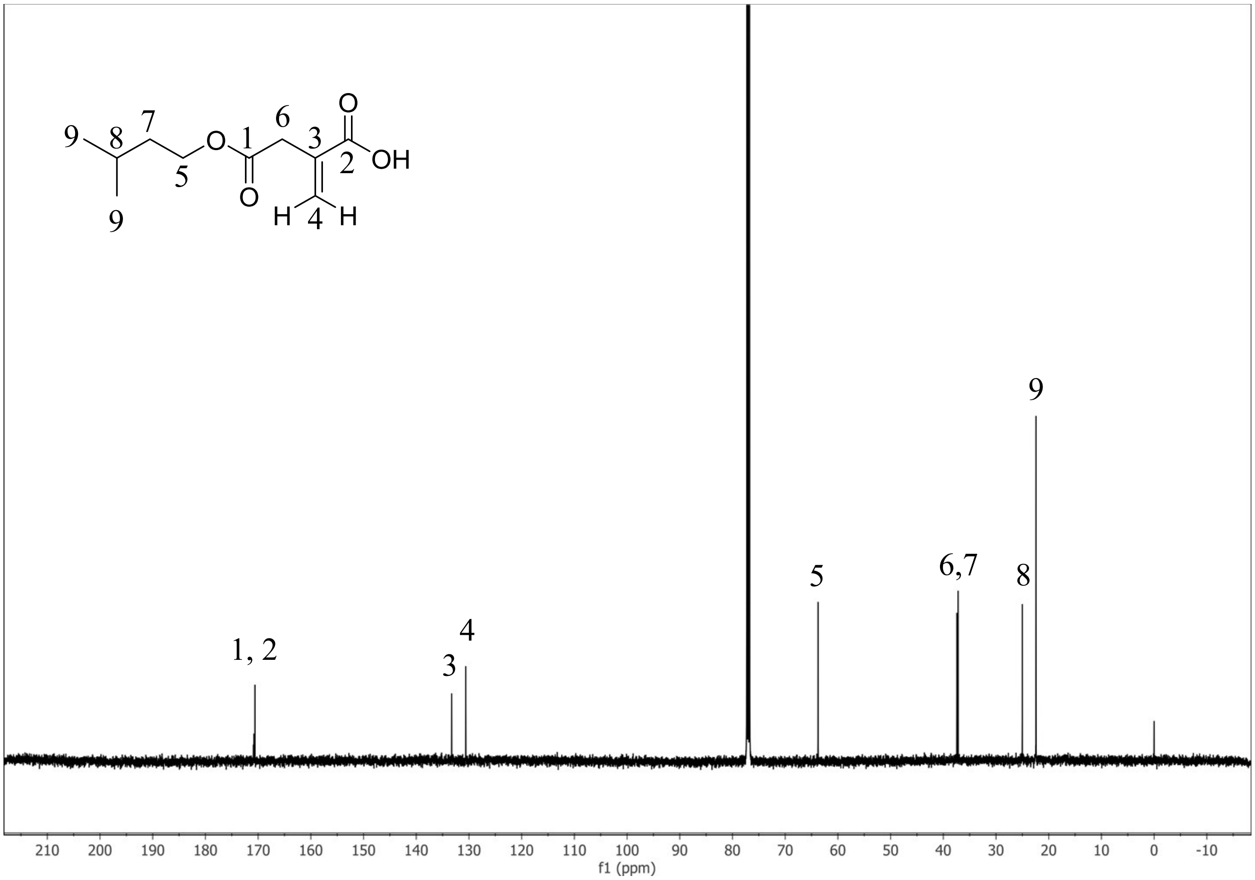


**Figure S7.** $^{13}$C-NMR spectrum of isoamyl itaconic acid ($CDCl_3$, 126 MHz)

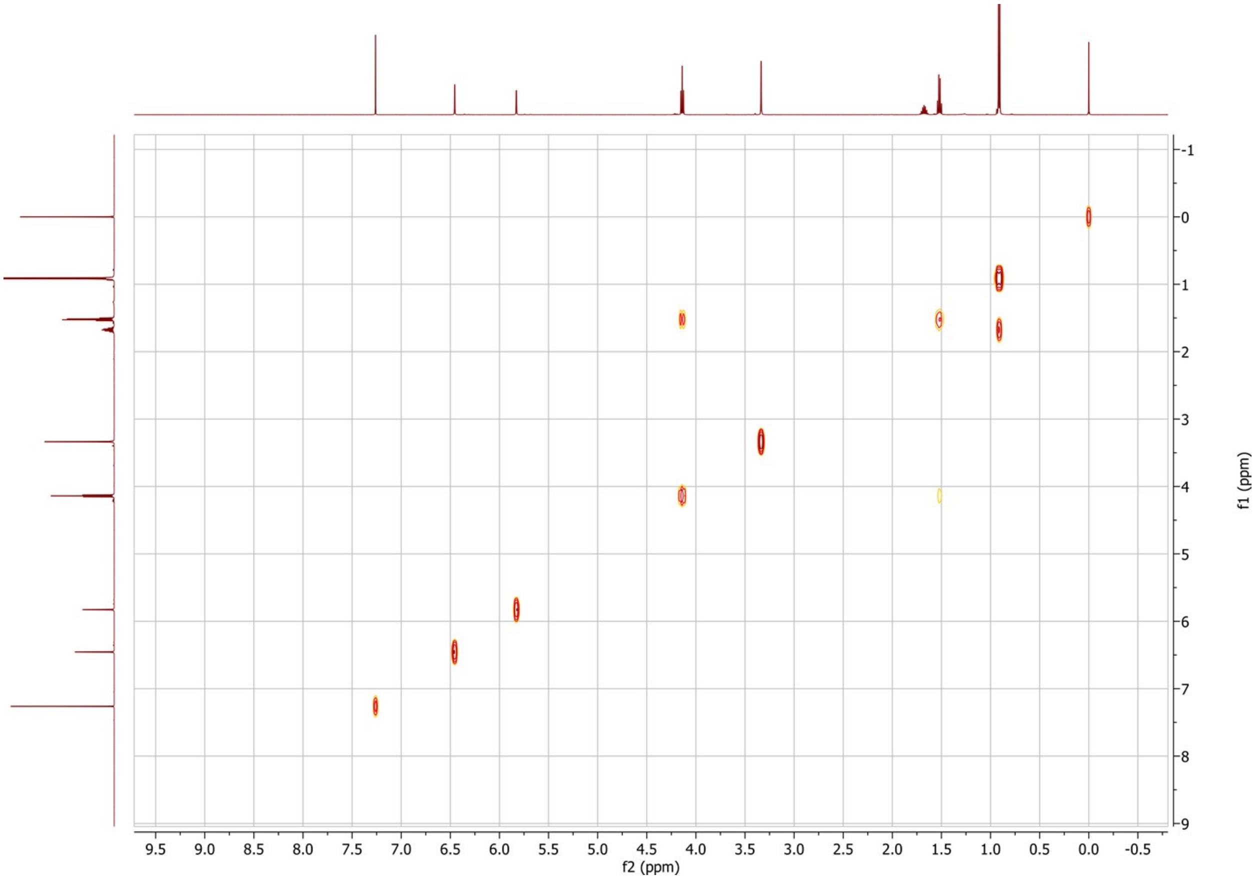


**Figure S8.** ${}^{1}$H COSY NMR spectrum of isoamyl itaconic acid (CDCl$_3$, 500 MHz)

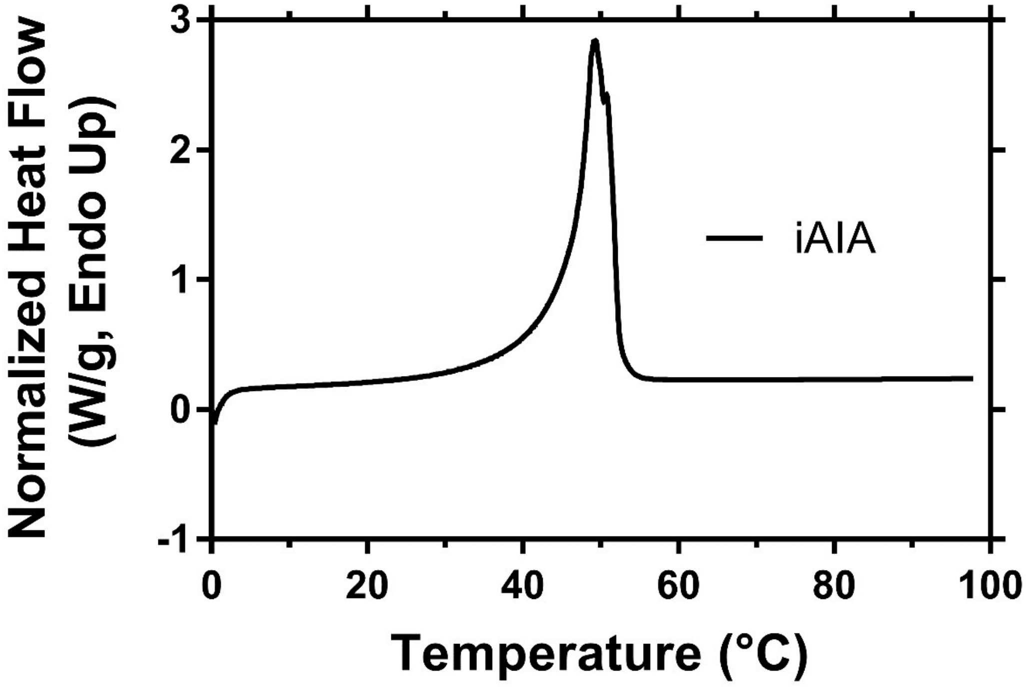


**Figure S9.** Melting point assessment of isoamyl itaconic acid by differential scanning calorimetry (DSC).

### S.1.5 Synthesis of Ethyl Itaconic Anhydride (1)

Ethyl itaconic acid (40 g, 0.25 mol, 1 equiv.) was measured into a 250 mL round bottom flask equipped with a magnetic stir bar. Acetic anhydride (120 mL, 1.3 mol, 5.0 equiv.) was added to this reaction flask, forming a suspension. The flask was attached to a reflux condenser and the suspension was heated to reflux with a heating mantle for 30 min. Upon heating, the solution became homogenous. The reaction was then removed from the heating mantle and excess acetic anhydride and acetic acid were removed *in vacuo* in two phases. The first phase was performed on a rotary evaporator (80-95 °C, 10-30 mbar) to remove the bulk of the acetic acid and anhydride. The second phase involved heating the sample oil on a high vacuum system (130 °C, 100 mtorr), with monitoring via thin-layer chromatography (TLC, silica gel, 5:1 $CH_2Cl_2$:ethyl acetate (EtAc) mobile phase, $R_{f,\ EtIAh} = 0.59$, $R_{f,mixed\ anhydride} = 0.64$, visualized with potassium permanganate TLC Stain). Subsequent color removal with an anhydrous silica gel plug with ethyl acetate resulted in 32 g of ethyl itaconic anhydride (**1**) as a yellow oil. $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 6.47 (s, 2H), 5.98 (s, 2H), 4.17 (q, *J* = 7.1, 1.5 Hz, 4H), 3.39 (s, 4H), 1.26 (td, *J* = 7.1, 1.5 Hz, 6H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.14, 161.69, 133.33, 132.19, 61.34, 37.33, 14.21. HRMS (ESI-TOF, *m*/*z*) calculated for $C_{14}H_{18}O_7Na^+$: 321.2792; found: 321.0945. $T_g$ = - 64 °C.

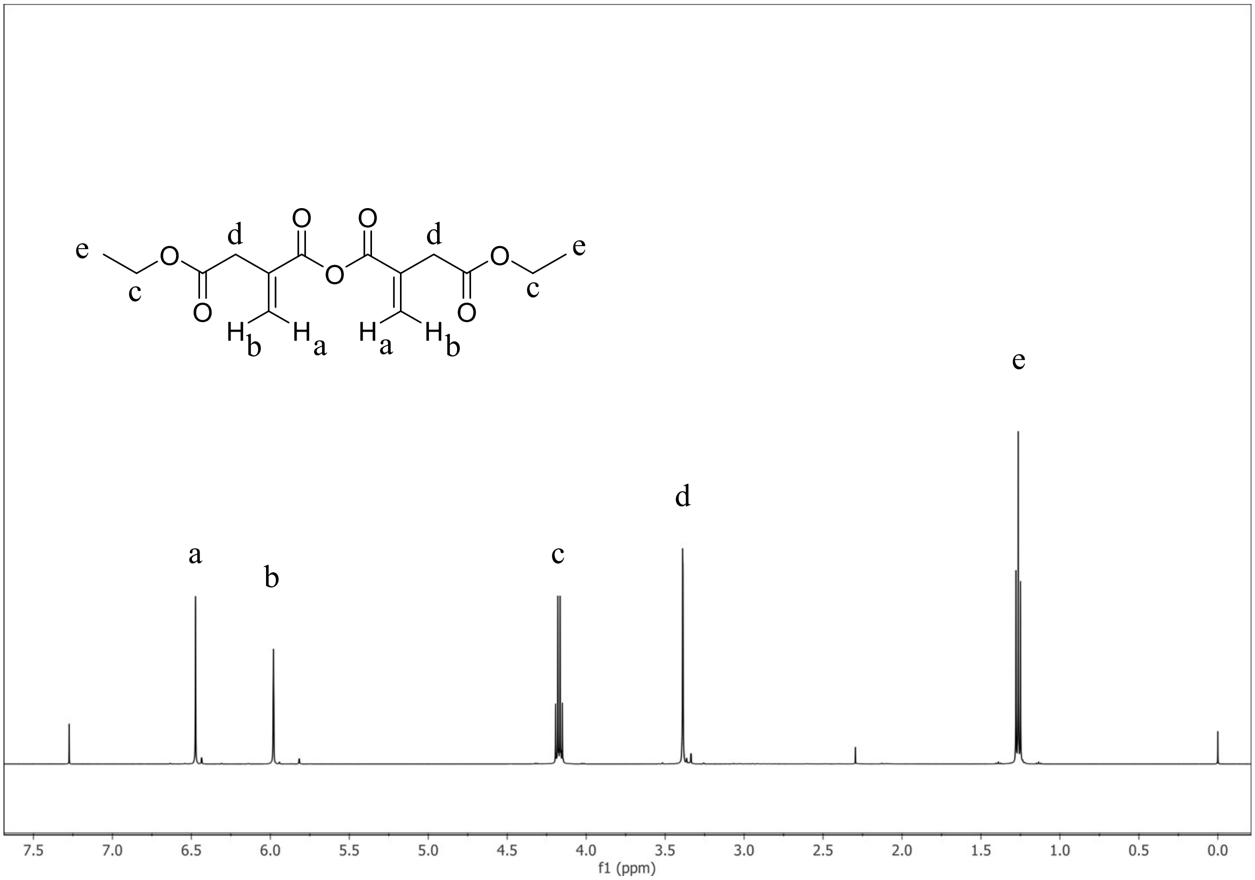


**Figure S10.** $^{1}$H-NMR spectrum of ethyl itaconic anhydride (**1**) (CDCl3, 500 MHz).

**Figure S11.** $^{13}$C-NMR spectrum of ethyl itaconic anhydride ($CDCl_3$, 126 MHz)

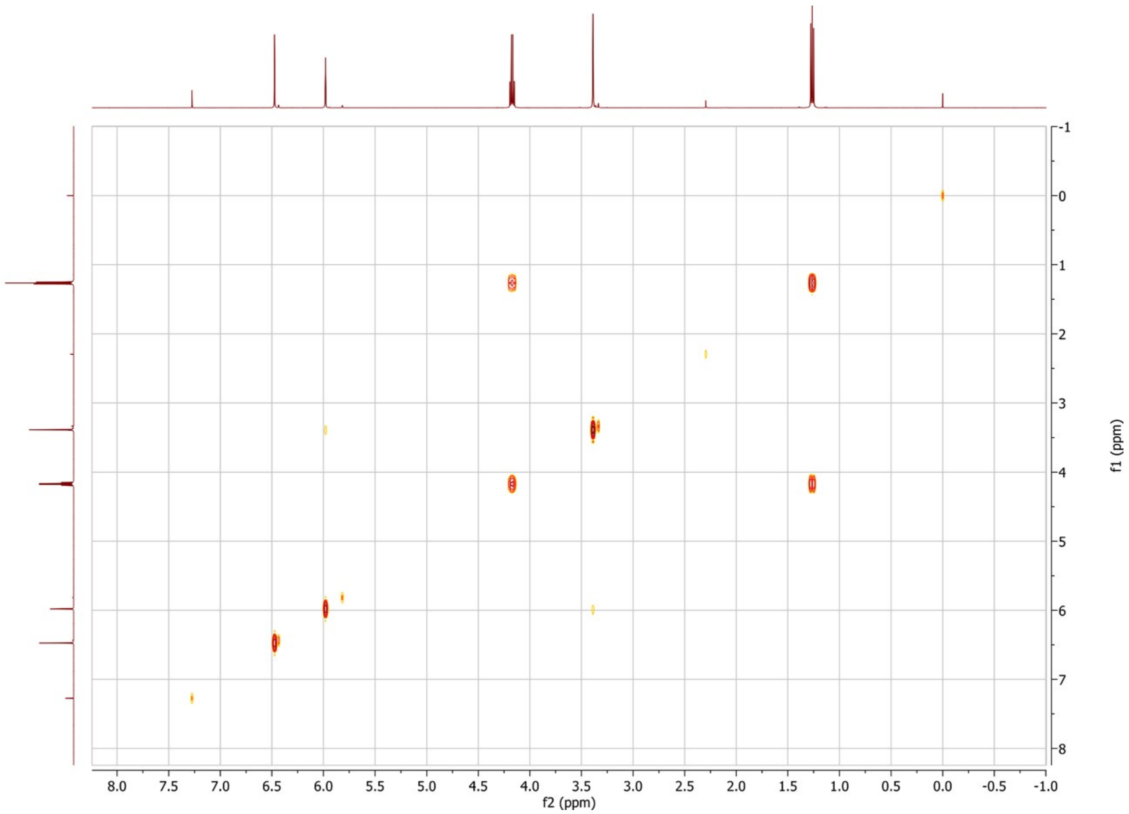


**Figure S12.** $^1$H COSY NMR spectrum of ethyl itaconic anhydride (**1**) (CDCl$_3$, 500 MHz)

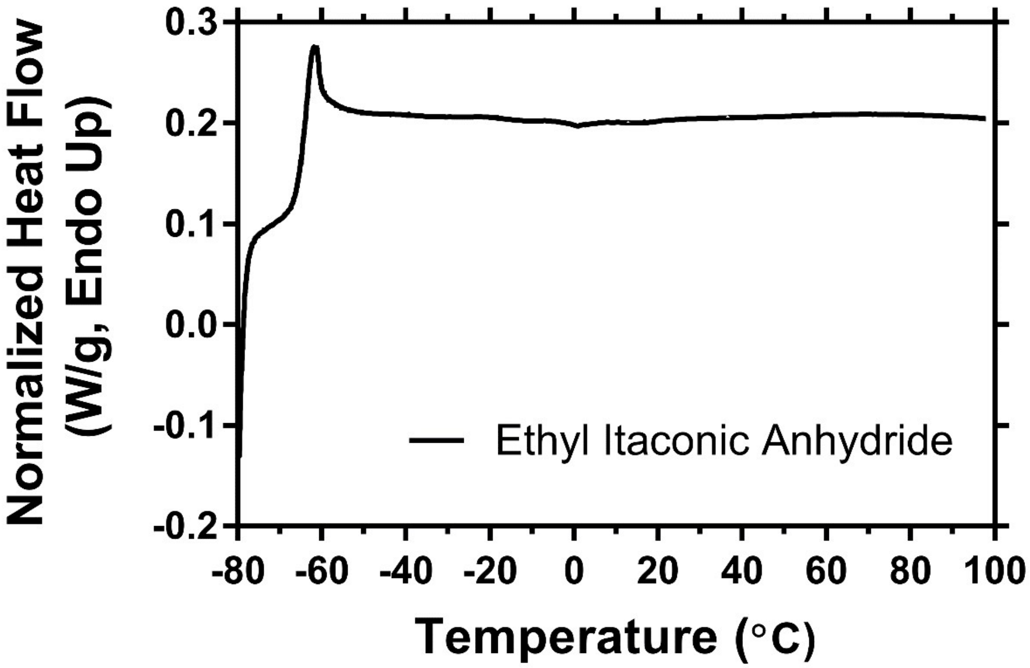


**Figure S13.** Melting point assessment of ethyl itaconic anhydride (**1**) by differential scanning calorimetry (DSC). Crystallinity was not observed during this test. Instead a glass transition was observed.

### S.1.6 Synthesis of Isoamyl Itaconic Anhydride (2)

Isoamyl itaconic acid (118 g, 0.59 mol, 1 equiv.) was measured into a 250 mL round bottom flask equipped with a magnetic stir bar. Acetic anhydride (275 mL, 2.9 mol, 4.9 equiv.) was added to this reaction flask, forming a suspension. The flask was attached to a reflux condenser and the suspension was heated to reflux with a heating mantle for 30 min. Upon heating, the solution became homogenous. The reaction was then removed from the heating mantle and excess acetic anhydride and acetic acid were removed *in vacuo* in two phases. The first phase was performed on a rotary evaporator (80-95 °C, 10-30 mbar) to remove the bulk of the acetic acid and anhydride. The second phase involved heating the sample oil on a high vacuum system (120 °C, 40 mtorr), with monitoring via thin-layer chromatography (TLC, silica gel, $CH_2Cl_2$

mobile phase, $R_{\mathrm{f,\ iAIAh}} = 0.13$, $R_{\mathrm{f,mixed\ anhydride}} = 0.34$, visualized with potassium permanganate TLC Stain). Vacuum was applied until TLC and $^1$H NMR analysis showed minimal mixed anhydride. **2** was used without any further purification and was obtained as a light yellow oil (47.9 g, quantitative yield). $^1$H NMR (500 MHz, Chloroform-*d*) δ 6.49 (s, 1H), 5.99 (d, *J* = 1.2 Hz, 1H), 4.16 (t, *J* = 6.9 Hz, 2H), 3.41 (d, *J* = 1.1 Hz, 2H), 1.69 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.63 – 1.58 (m, 0H), 1.58 – 1.50 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 7H). $^{13}$C NMR (126 MHz, Chloroform-*d*) δ 170.22, 161.69, 133.39, 132.13, 64.08, 37.35, 37.30, 25.15, 22.56. HRMS (ESI-TOF, *m*/*z*) calculated for $C_{14}H_{18}O_7Na^+$: 405.4422; found: 405.1913. $T_g$ = - 70 °C.

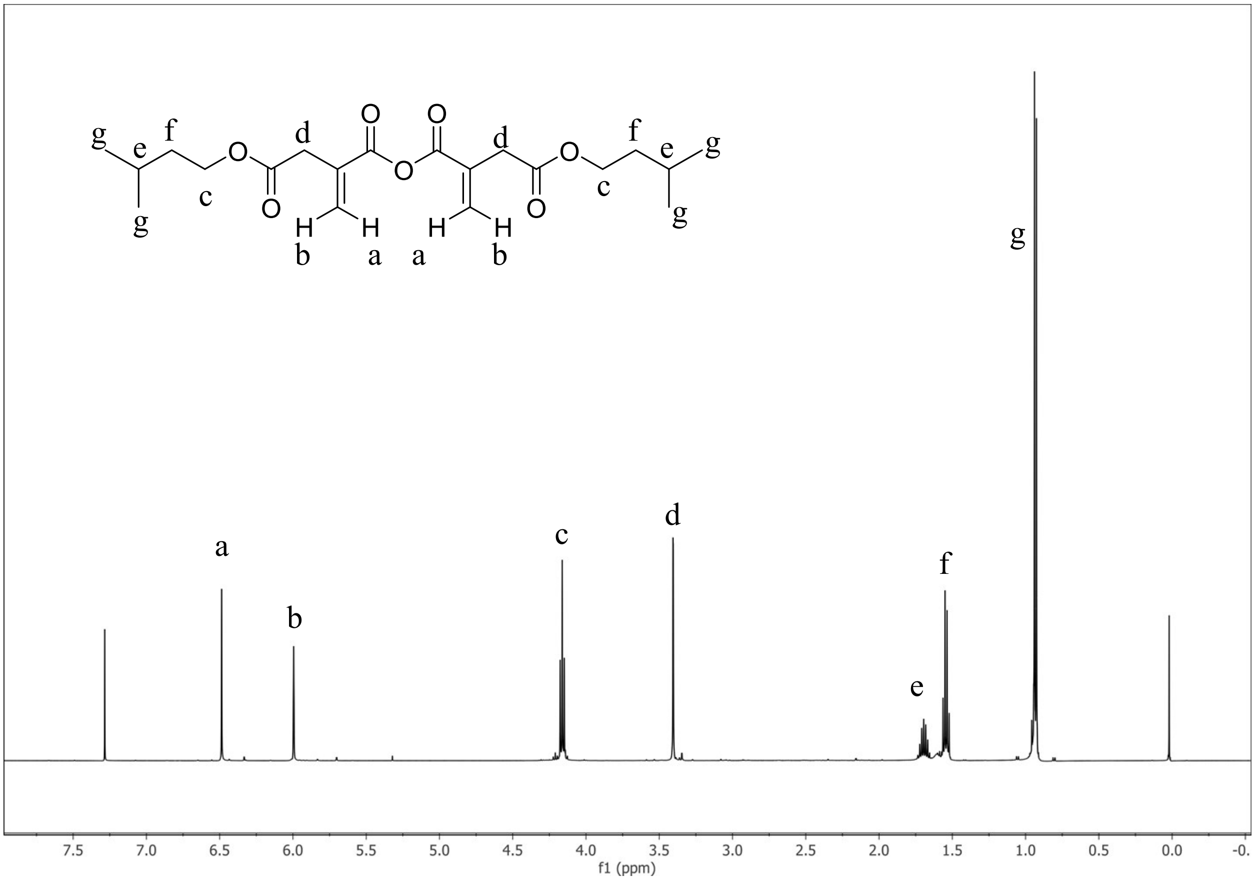


**Figure S14.** $^1$H-NMR spectrum of isoamyl itaconic anhydride (**2**) ($CDCl_3$, 500 MHz).

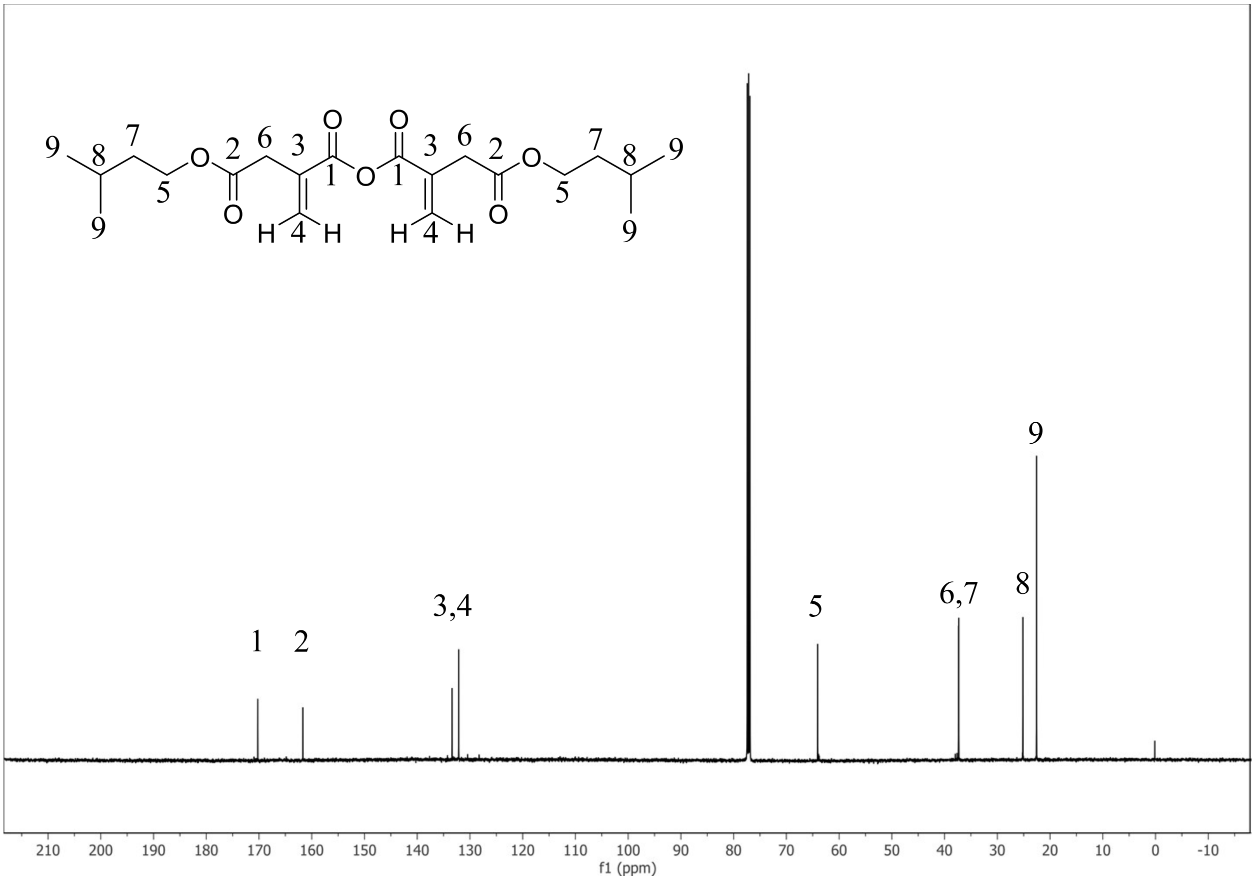


**Figure S15.** $^{13}$C-NMR spectrum of isoamyl itaconic anhydride (**2**) ($CDCl_3$, 126 MHz)

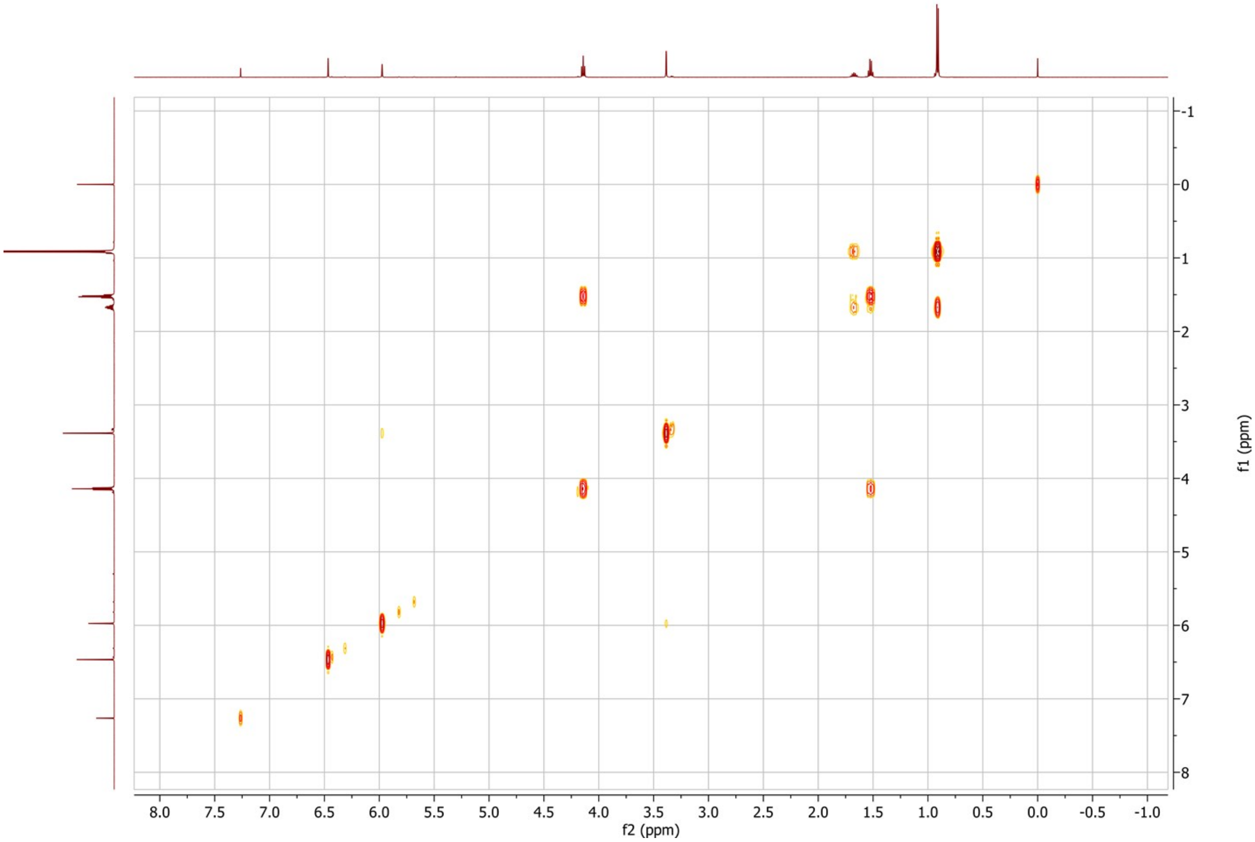


**Figure S16.** $^1$H COSY NMR spectrum of isoamyl itaconic anhydride (**2**) (CDCl$_3$, 500 MHz)

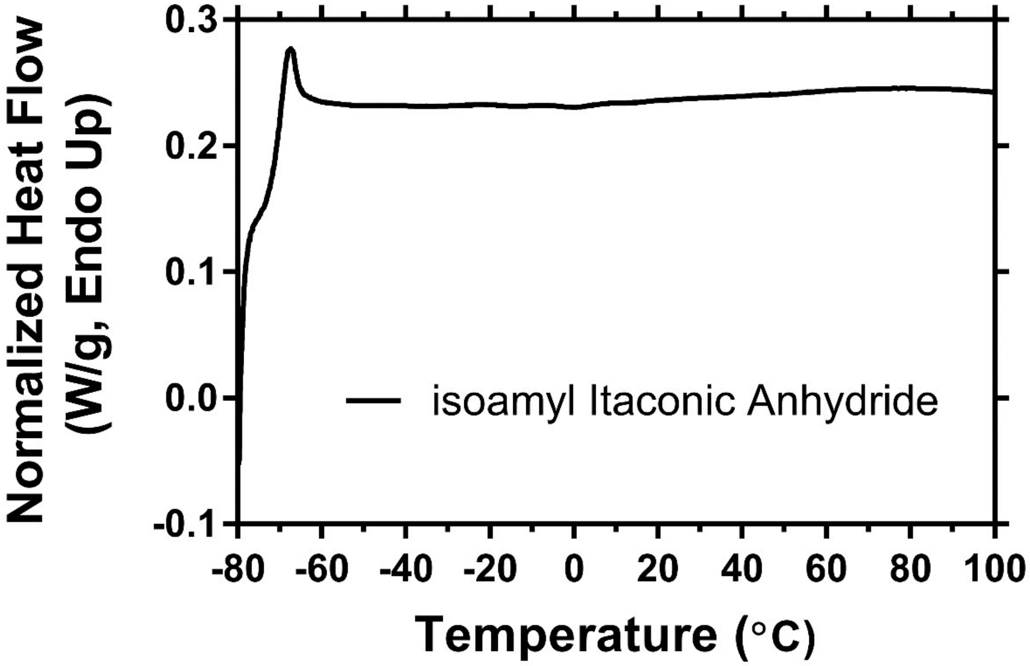


**Figure S17.** Melting point assessment of isoamyl itaconic anhydride (**2**) by differential scanning calorimetry (DSC). Crystallinity was not observed during this test. Instead a glass transition was observed.

### S.1.7 Synthesis of Norbornene-Ethyl Itaconic Anhydride (3)

Ethyl Itaconic Anhydride (10 g, 33.5 mmol) and freshly distilled cyclopentadiene (5.54 g, 83.8 mmol) were added to a 25 mL round bottom flask. The flask was sealed with a glass stopcock and the reagents were stirred at 50 °C for 16 h. The flask was then connected to a Schlenk line and the excess cyclopentadiene and dicylopentadiene byproduct were removed under reduced pressure at 50 °C (monitored via $^1$H NMR spectroscopy). The resultant yellow viscous liquid was used without further purification (14.3 g quantitative yield). HRMS (ESI-TOF, *m/z*) calculated for $C_{24}H_{30}O_7Na^+$: 453.1883; Observed: 453.1902.

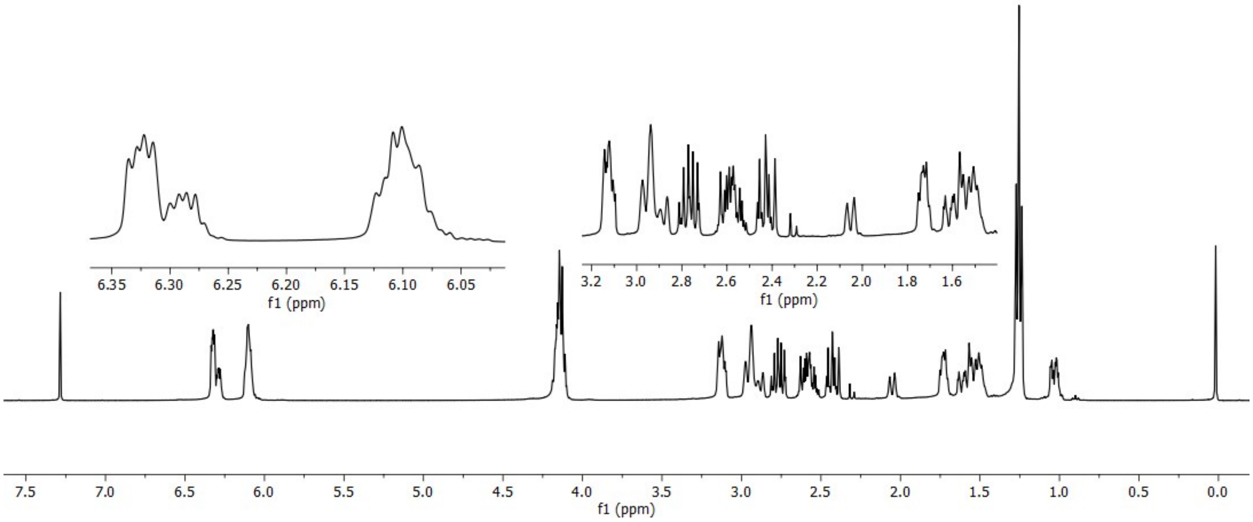


**Figure S18**. $^1$H-NMR spectrum of norbornene-ethyl itaconic anhydride (**3**) ($CDCl_3$, 500 MHz).

### S.1.8 Synthesis of Norbornene-Isoamyl Itaconic Anhydride (4)

Isoamyl Itaconic Anhydride (10 g, 26.1 mmol) and freshly distilled cyclopentadiene (4.32 g, 65.4 mmol) were added to a 25 mL round bottom flask. The flask was sealed with a glass stopcock and the reagents were stirred at 50 °C for 16 h. The flask was then connected to a Schlenk line and the excess cyclopentadiene and dicylopentadiene byproduct were removed under reduced pressure at 50 °C (monitored via $^1$H NMR spectroscopy). The resultant yellow viscous liquid was used without further purification (13.3 g quantitative yield). HRMS (ESI-TOF, *m/z*) calculated for $C_{30}H_{42}O_7Na^+$: 537.2823; Observed: 537.2847.

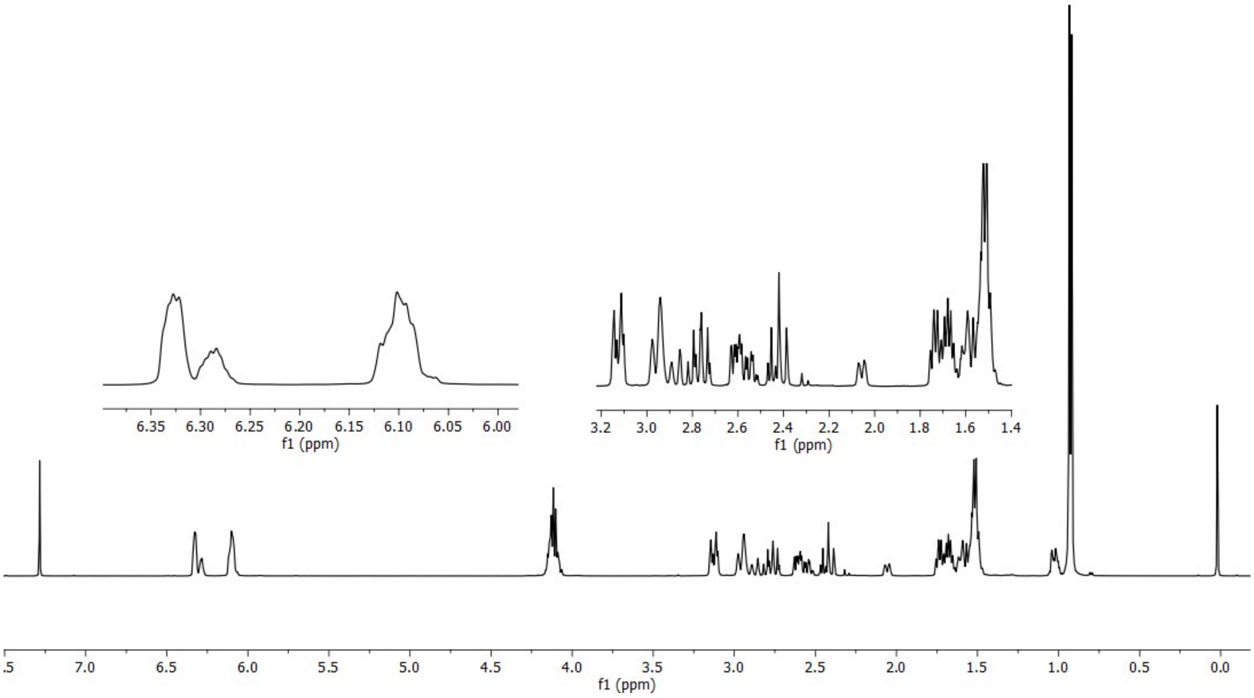


**Figure S19**. $^1$H-NMR spectrum of norbornene-isoamyl itaconic anhydride (4) ($CDCl_3$, 500 MHz).

## S.2 Representative Thiol-ene Polymerization of Itaconic Anhydrides

Itaconic acid anhydride and thiol monomers were mixed such that the ratio of the [ene]:[thiol] end groups was kept at 1:1. **3** (0.50 g, 1.16 mmol), PETMP (0.28 g, 0.58 mmol.), and TPO-L (39 mg, 5 wt%) were added to a 5 mL glass scintillation vial and shaken using a vortex device for 5 -10 minutes to ensure solution homogeneity. This mixture was then pipetted into silicon dog-bone molds (2.7 mm x 13.5 mm x 0.7 mm (W x L x T))) for curing with a 36 W MelodySusie® UV Nail Dryer. Samples were exposed to UV light for 2 minutes, flipped over, and exposed for an additional 2 minutes and then stored in a desiccator until use.

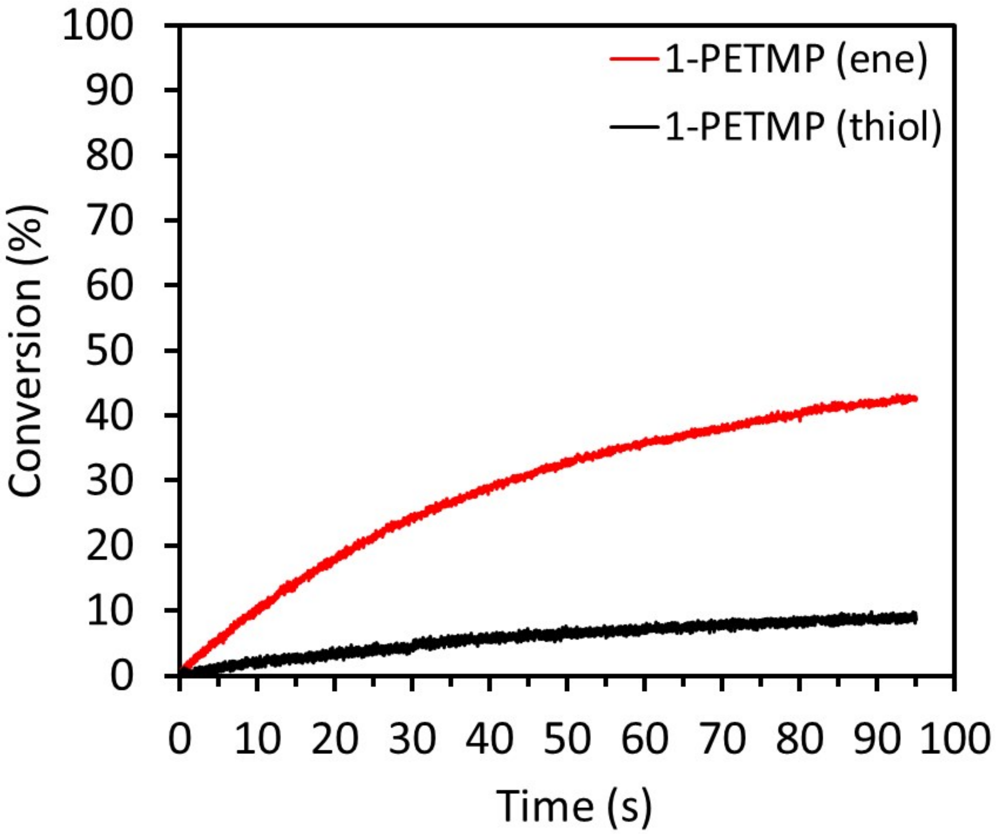


**Figure S20.** Photopolymerization kinetic curves of the alkene (red) and thiol (black) conversion in **1**-PETMP. The mismatch in overall conversions of the functional groups indicate that a thiol-ene mechanism is not exclusively obeyed during polymerizations.

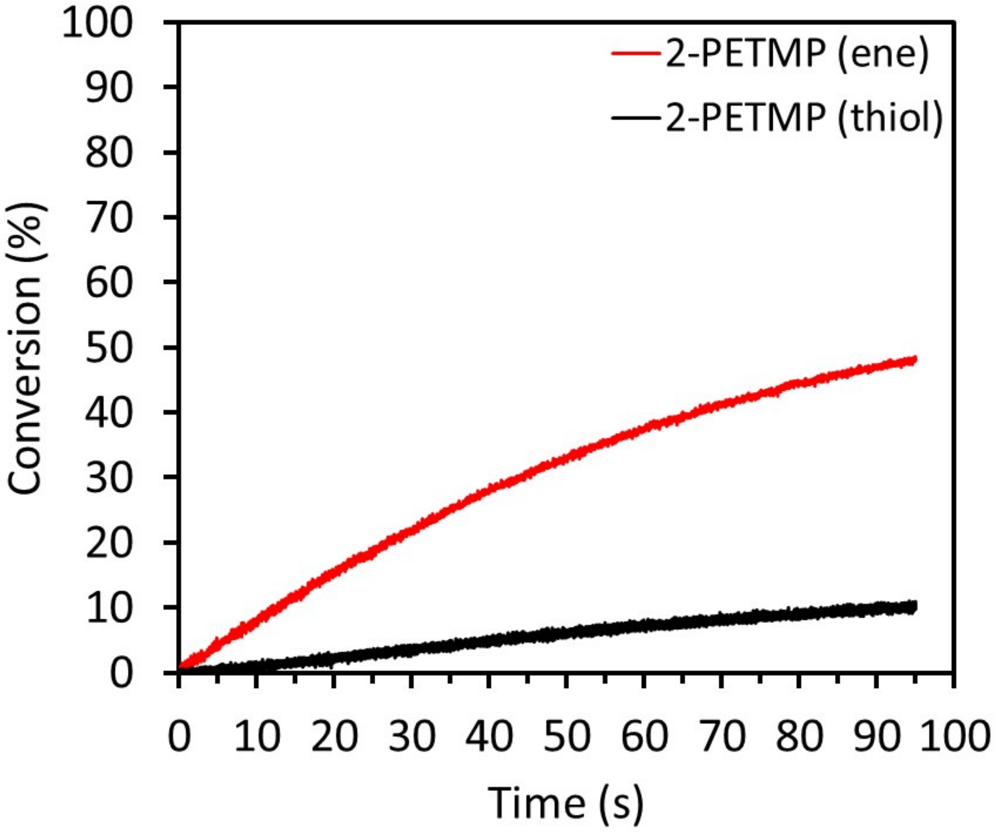


**Figure S21.** Photopolymerization kinetic curves of the alkene (red) and thiol (black) conversion in **2**-PETMP. The mismatch in overall conversions of the functional groups indicate that a thiol-ene mechanism is not exclusively obeyed during polymerizations.

Determining gel point for thiol-acrylate reaction:

$$(\bar{f}_{ene}-1)\frac{k_p 2}{k_{ct} r}p_\alpha + p_\alpha^2(\bar{f}_{th}-1)(\bar{f}_{ene}-1)\left(1+\frac{k_p 1}{k_{ct} r}\right)=1 \tag{1}$$

$$\left(\bar{f}_{ene}=2; \bar{f}_{th}=4; \frac{k_p}{k_{ct}}=1.5; r=1\right)$$

Since the thiol-acrylates undergo both step-growth and chain-growth reaction, the gel point was determined using equation S1 where $\bar{f}_i$ is the number of "i" functional groups, $p_\alpha$ is the gel point, r is the ratio of thiol:ene functional groups, and $k_p/k_{ct}$ is the ratio of reaction rate constants of polymerization ($k_p$) and chain transfer ($k_{ct}$) which was determined to be 1.5 for thiol-acrylate reactions. For 1-PETMP and 2-PETMP, the gel points were calculated to be 21.6 %.

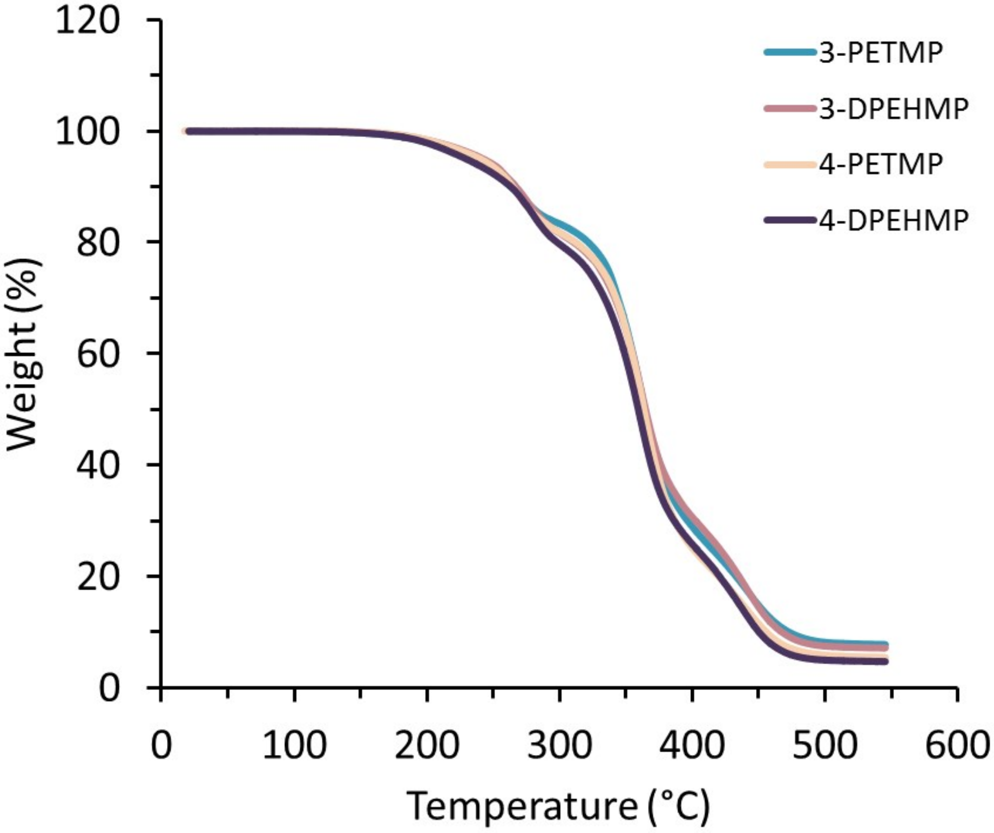


**Figure S22.** TGA thermograms of anyhydride networks at a heating rate of 10 °C·min$^{-1}$.

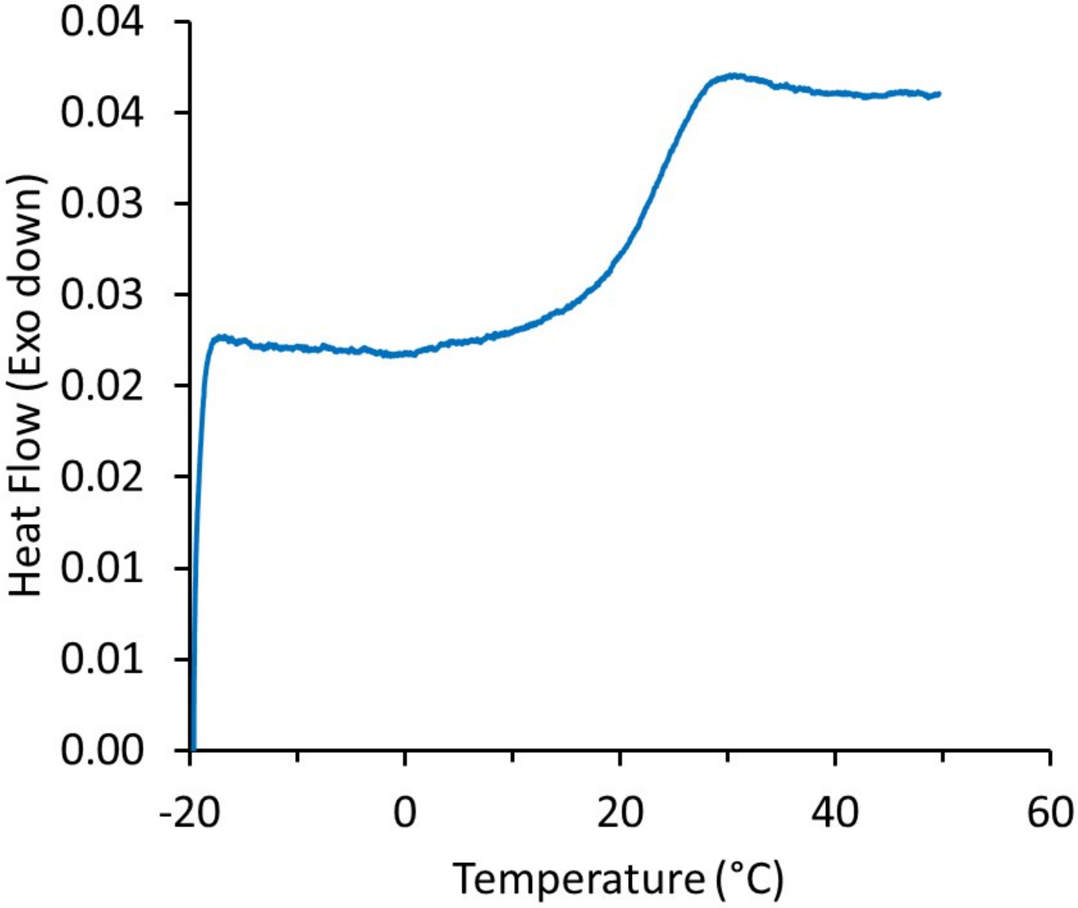


**Figure S23.** DSC thermogram of **3**-PETMP at a heating rate of 10 °C·min$^{-1}$.

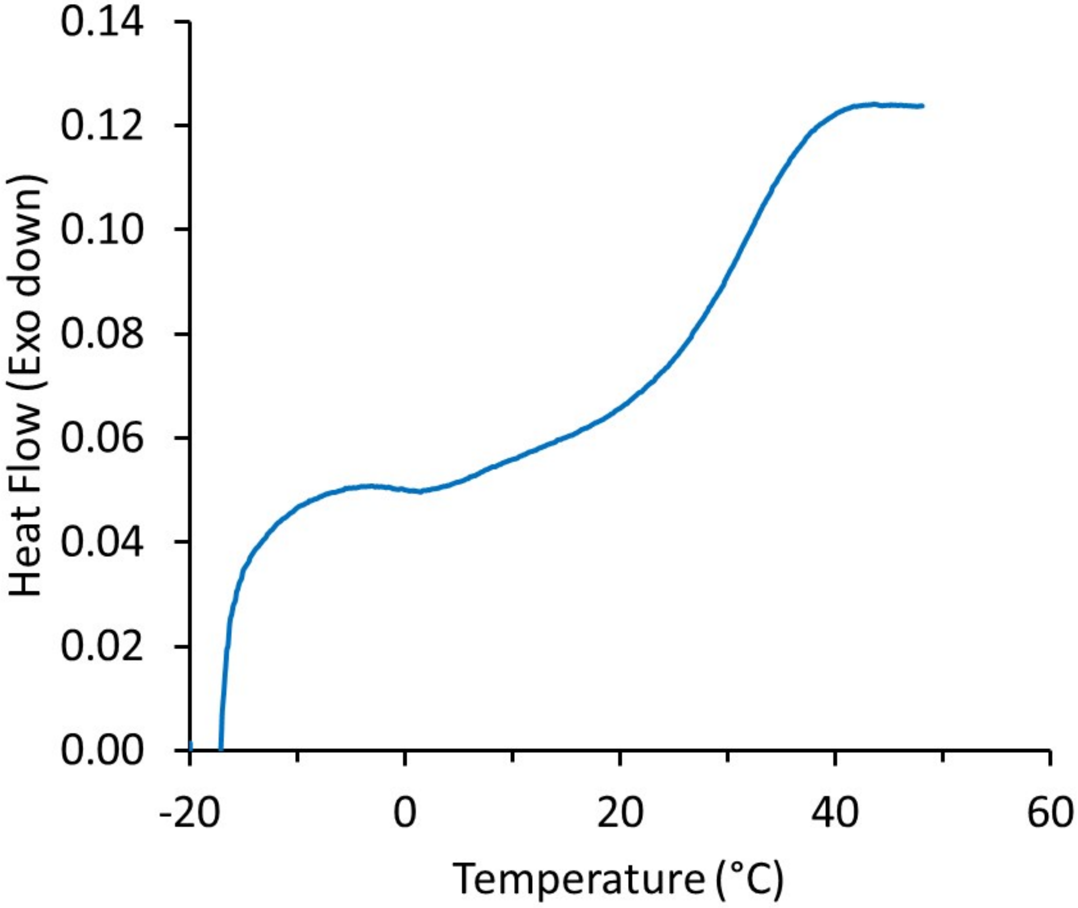


**Figure S24.** DSC thermogram of **3**-DPEHMP at a heating rate of 10 °C·min$^{-1}$.

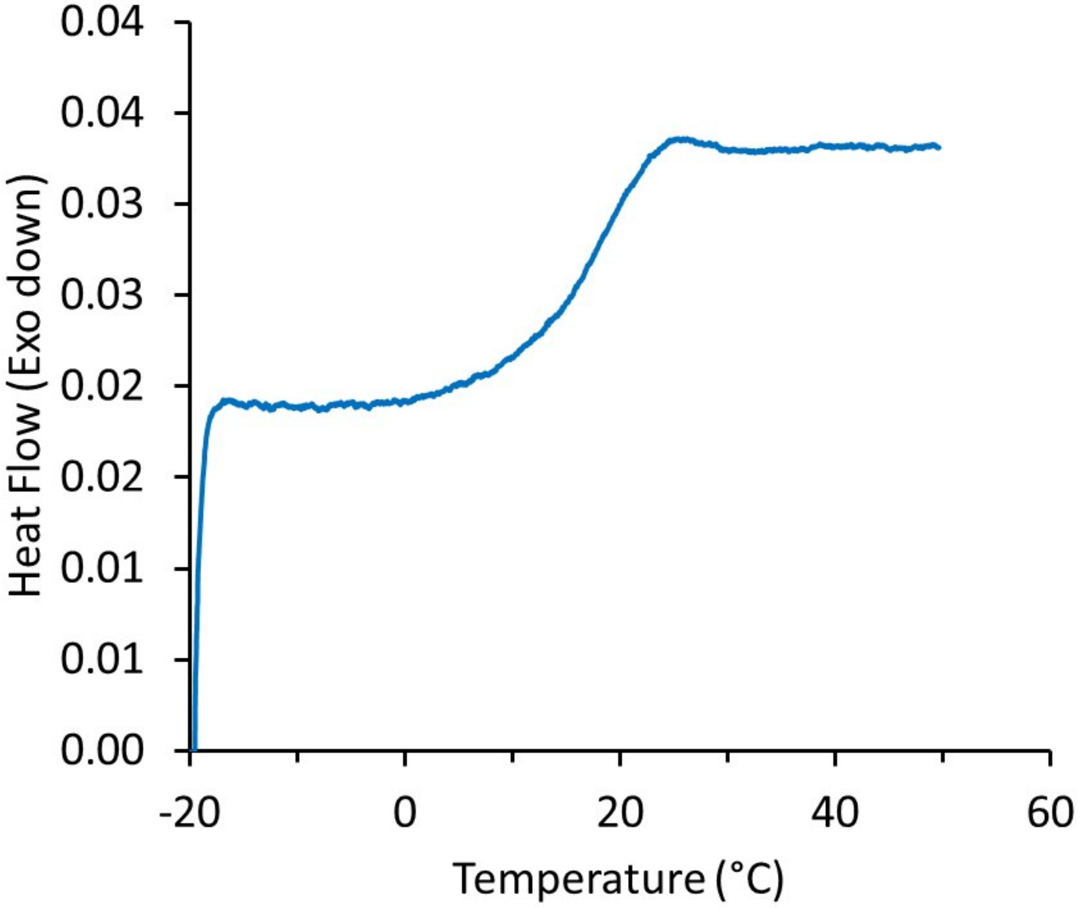


**Figure S25.** DSC thermogram of **4**-PETMP at a heating rate of 10 °C·min$^{-1}$.

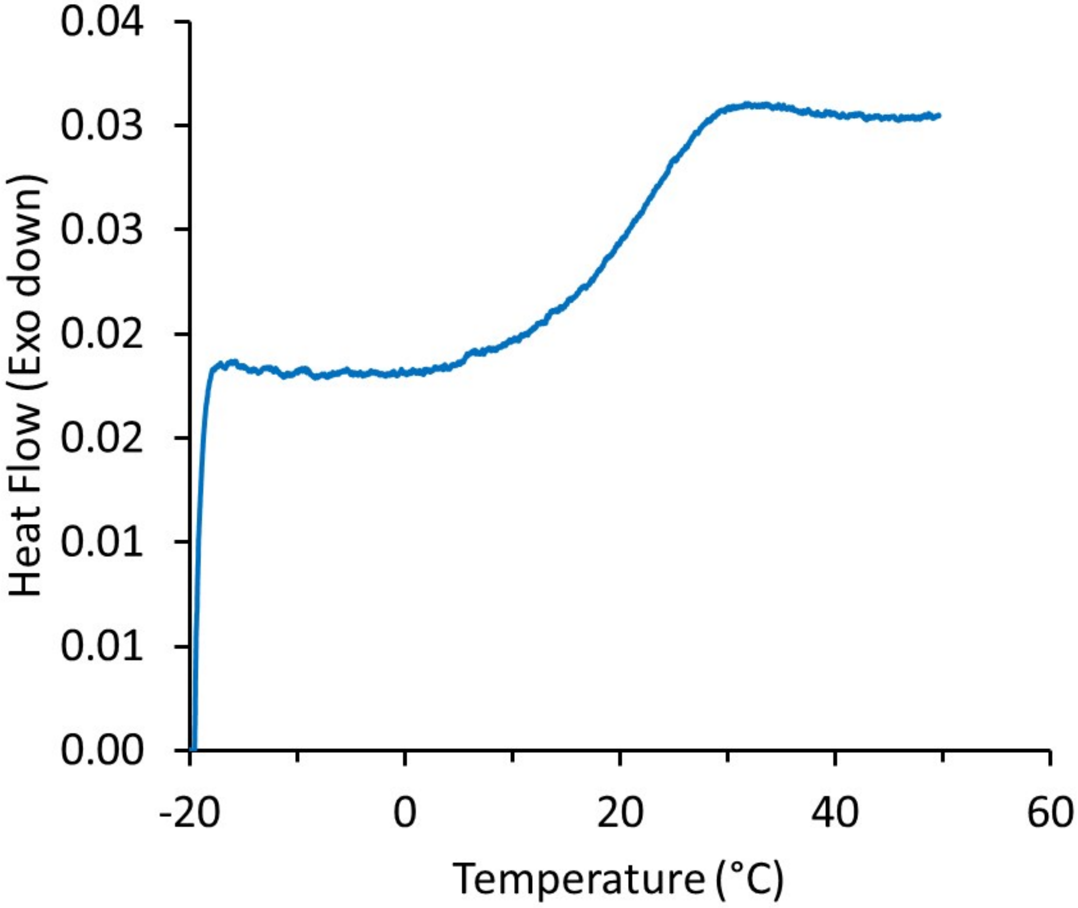


**Figure S26.** DSC thermogram of **4**-DPEHMP at a heating rate of 10 °C·min$^{-1}$.

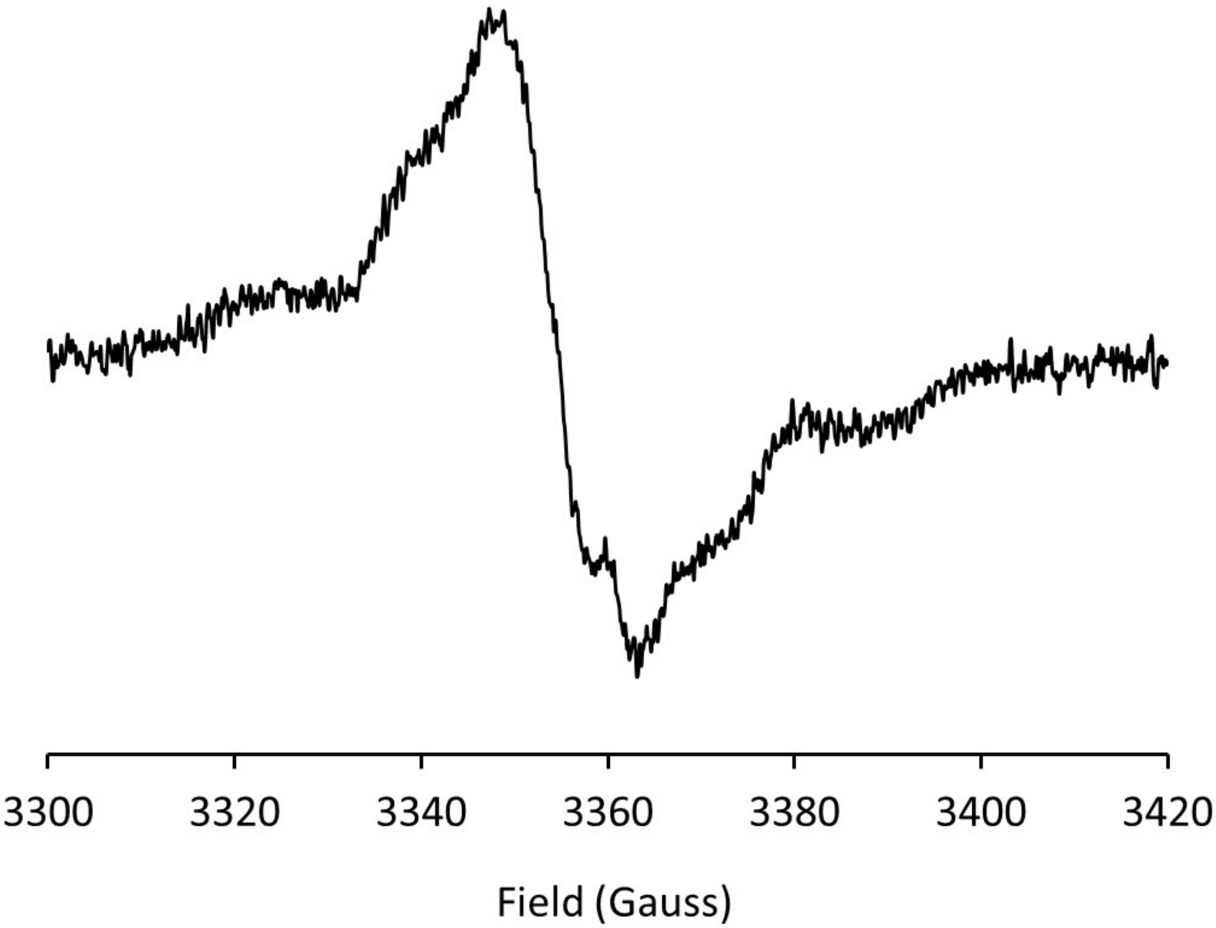


**Figure S27.** EPR spectrum acquired immediately after the photopolymerization of **3**-PETMP indicating the presence of "trapped" radicals in the polymer matrix. Operation conditions for the acquisition: microwave frequency, 9.40 GHz; modulation frequency, 100 kHz; modulation amplitude, 1.0 G.

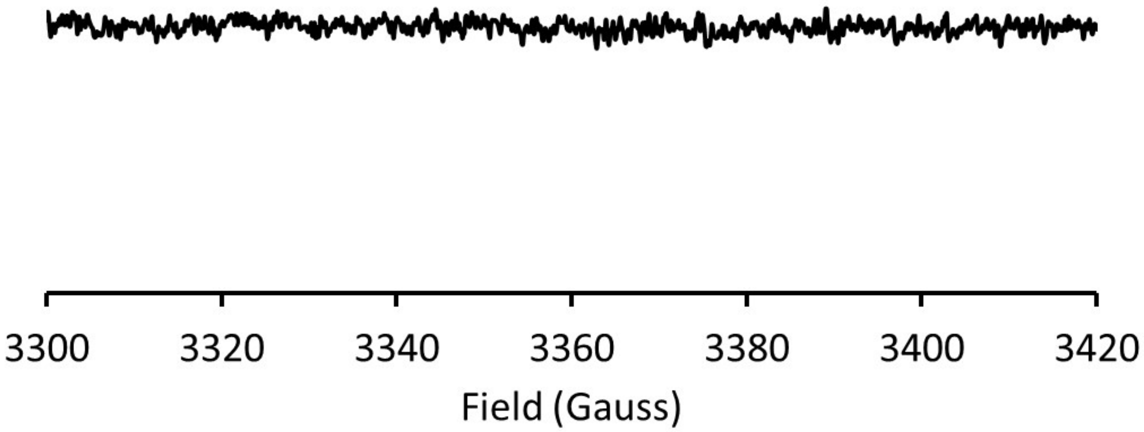


**Figure S28.** EPR spectrum of **3**-PETMP with post-curing thermal treatment at 100 °C for 24 hours. Operation conditions for the acquisition: microwave frequency, 9.40 GHz; modulation frequency, 100 kHz; modulation amplitude, 1.0 G.

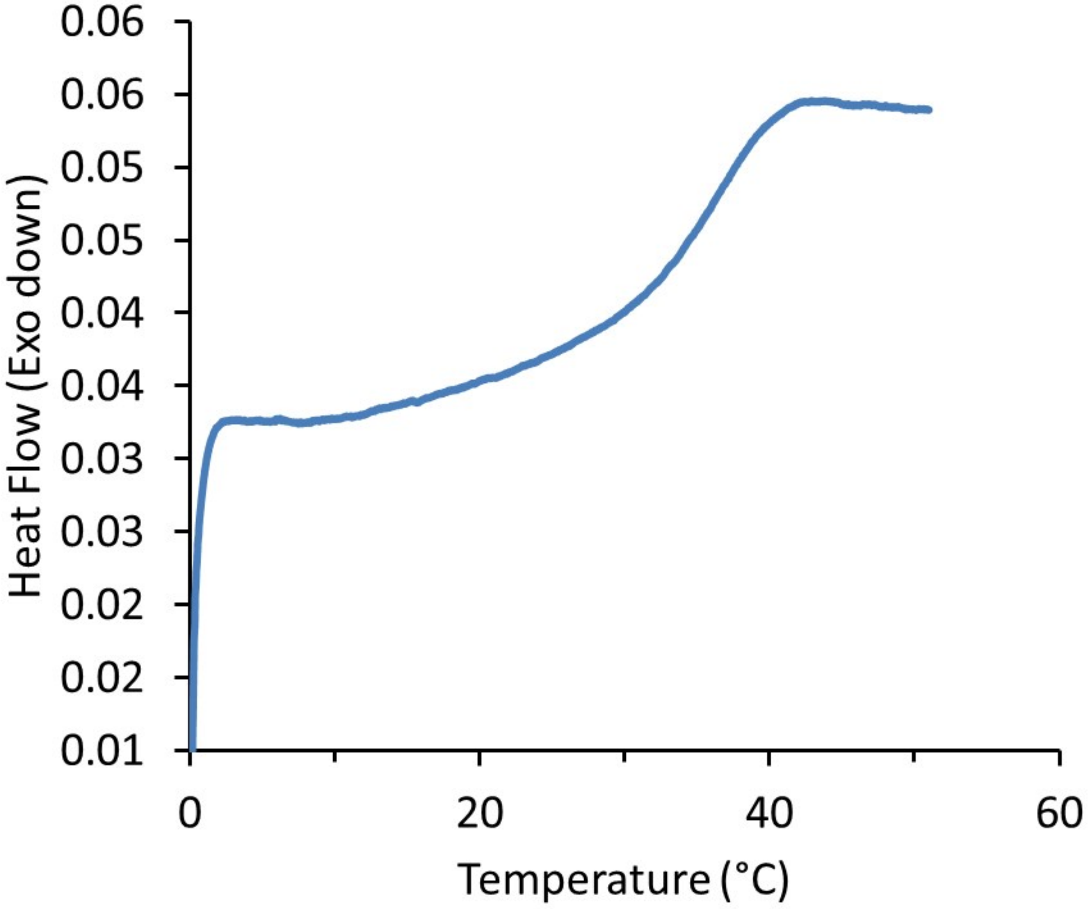


**Figure S29.** DSC thermogram (heating rate of 10 °C·min$^{-1}$) of **3**-PETMP with post-curing thermal treatment at 100 °C for 24 h.

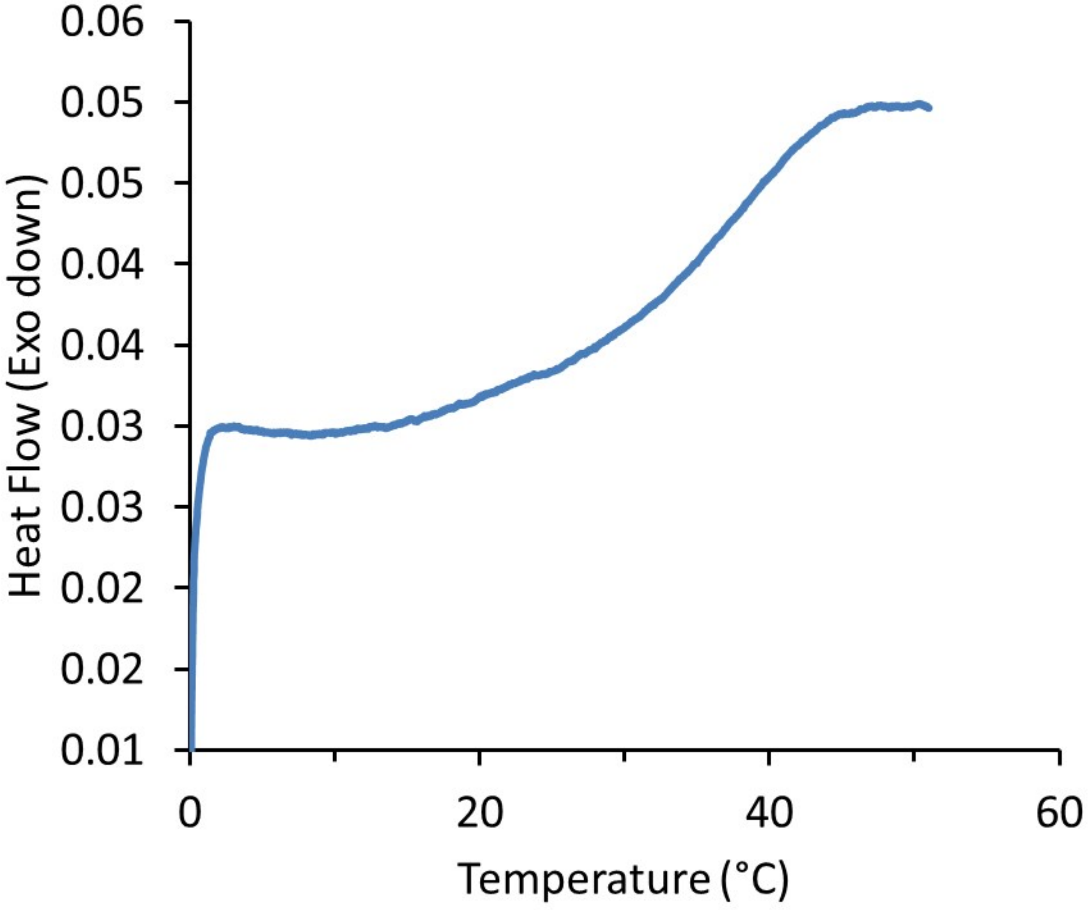


**Figure S30.** DSC thermogram (heating rate of 10 °C·min$^{-1}$) of **3**-DPEHMP with post-curing thermal treatment at 100 °C for 24 h.

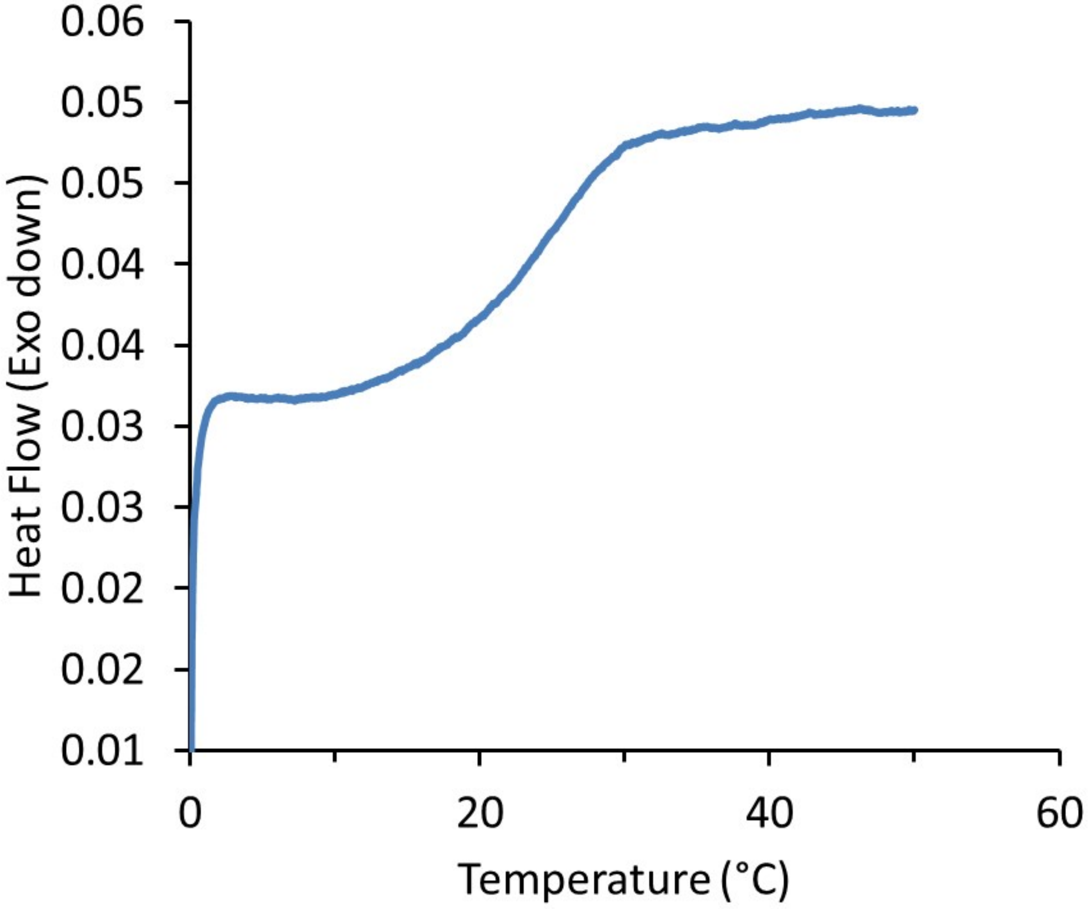


**Figure S31.** DSC thermogram (heating rate of 10 °C·min$^{-1}$) of **4**-PETMP with post-curing thermal treatment at 100 °C for 24 h.

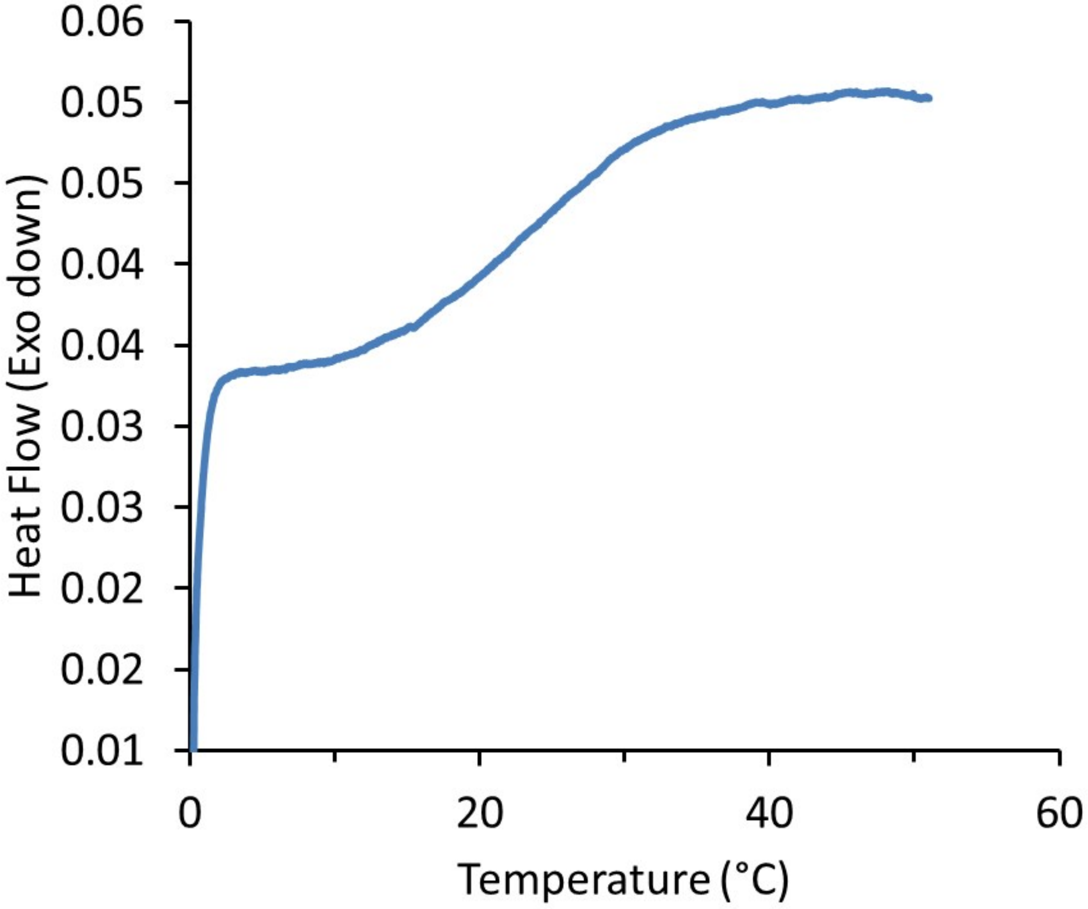


**Figure S32.** DSC thermogram (heating rate of 10 °C·min$^{-1}$) of **4**-DPEHMP with post-curing thermal treatment at 100 °C for 24 h.

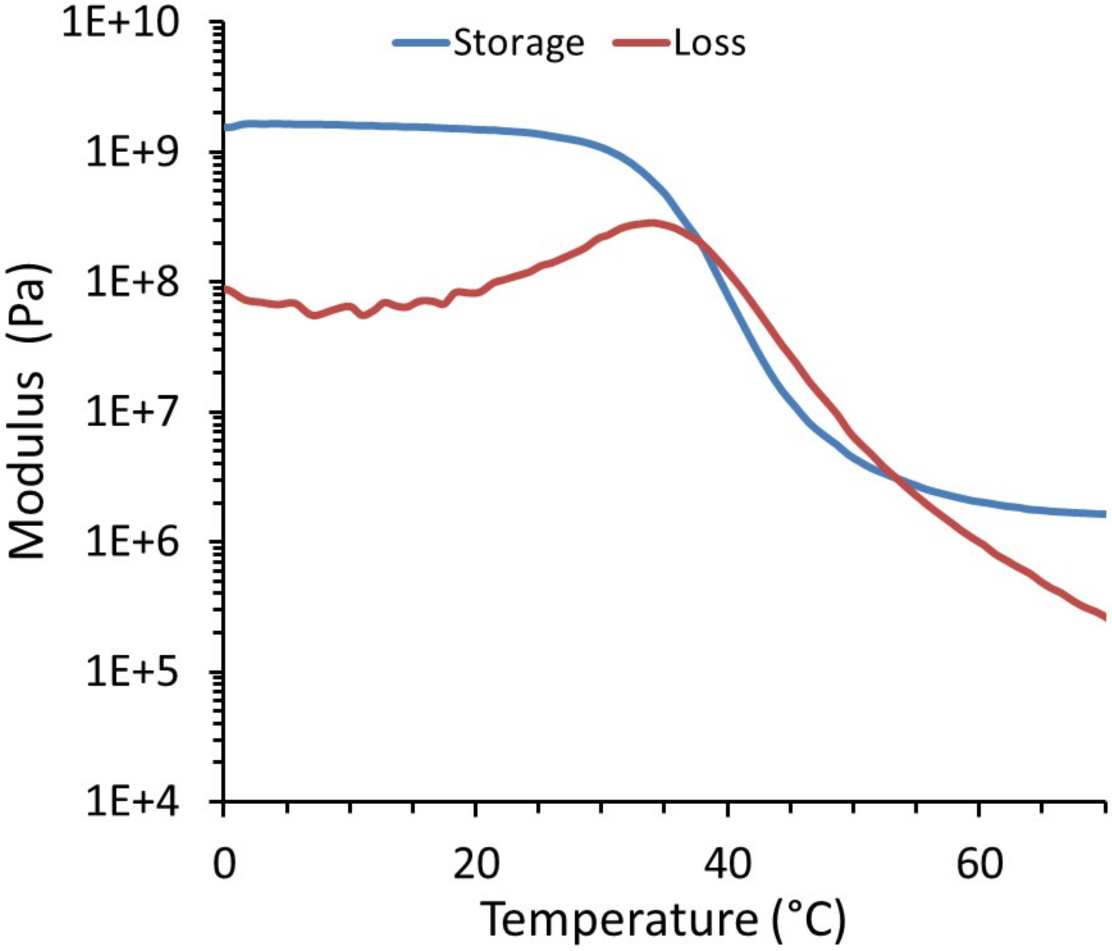


**Figure S33.** Storage and loss moduli measured via DMA of **3-**PETMP with post-curing thermal treatment at 100 °C for 24 h.

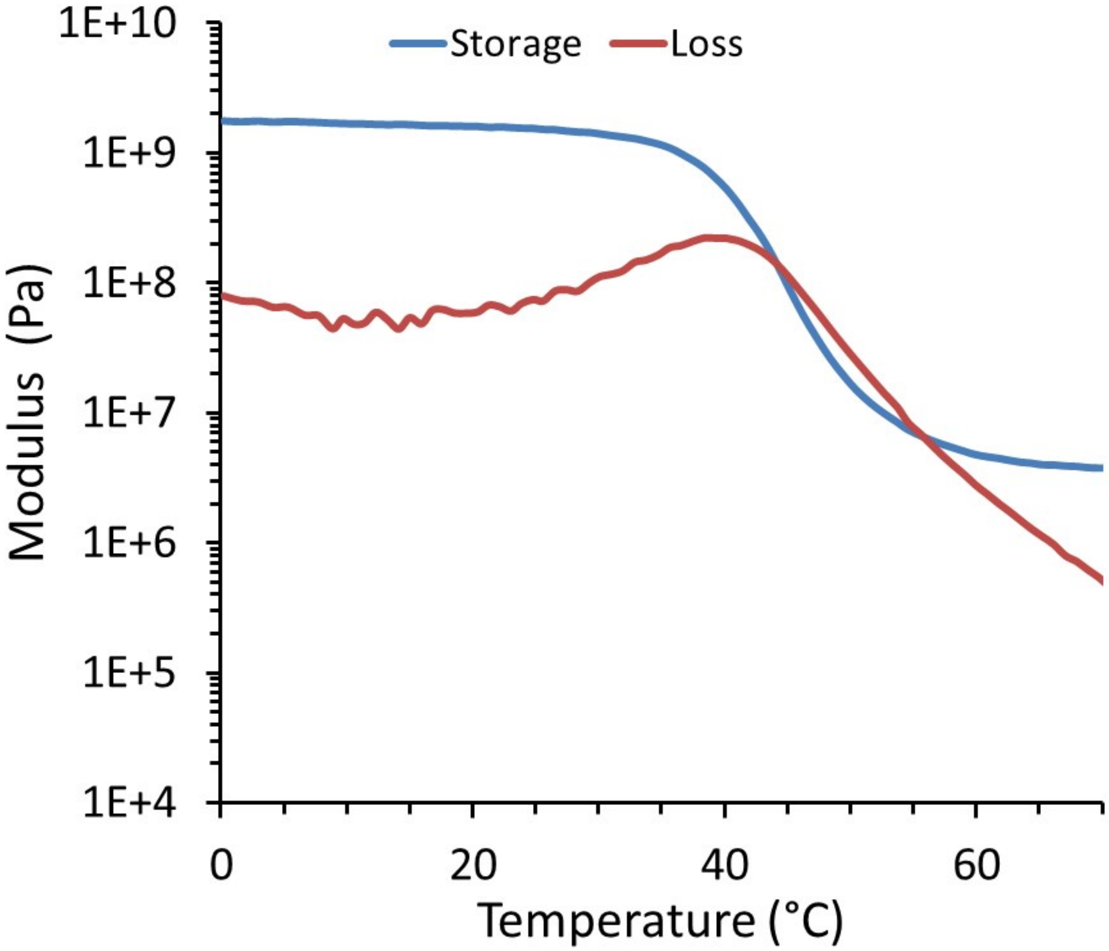


**Figure S34.** Storage and loss moduli measured via DMA of **3-**DPEHMP with post-curing thermal treatment at 100 °C for 24 h.

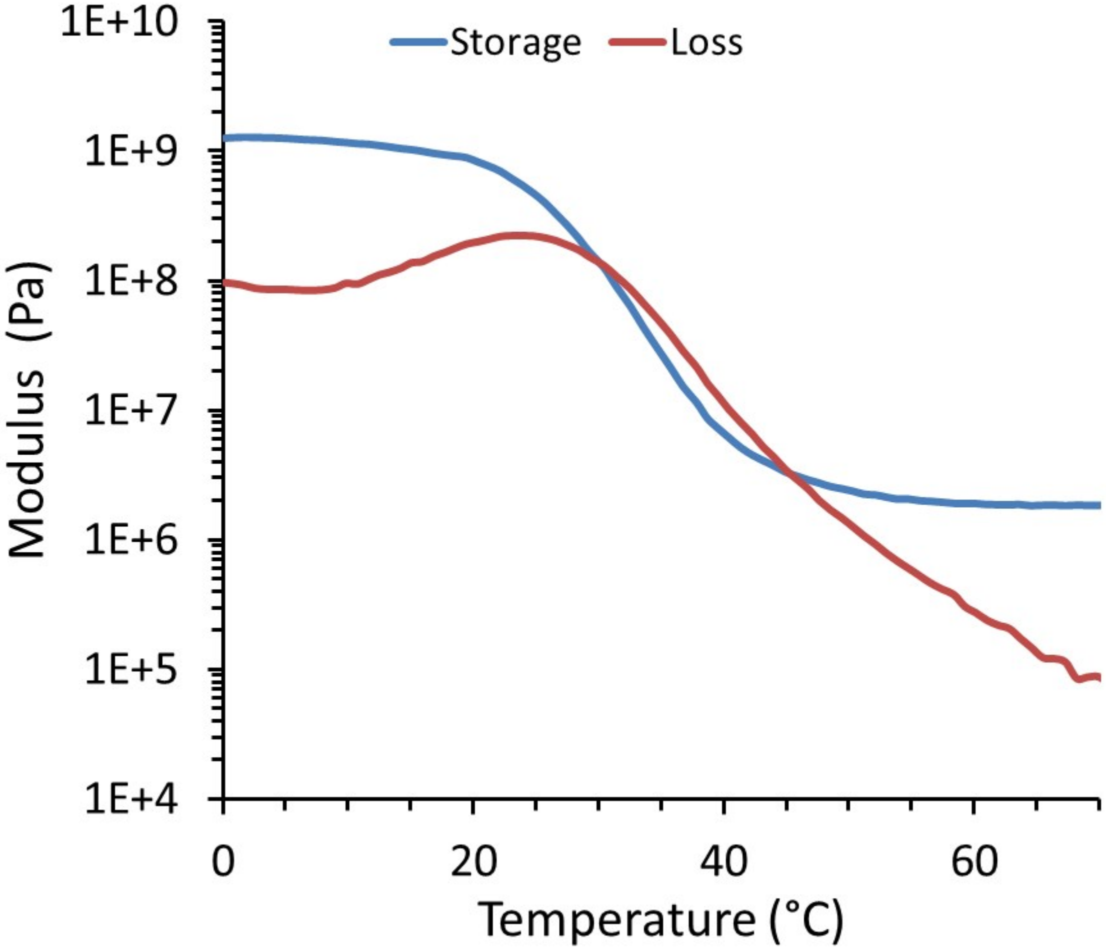


**Figure S35.** Storage and loss moduli measured via DMA of **4-**PETMP with post-curing thermal treatment at 100 °C for 24 h.

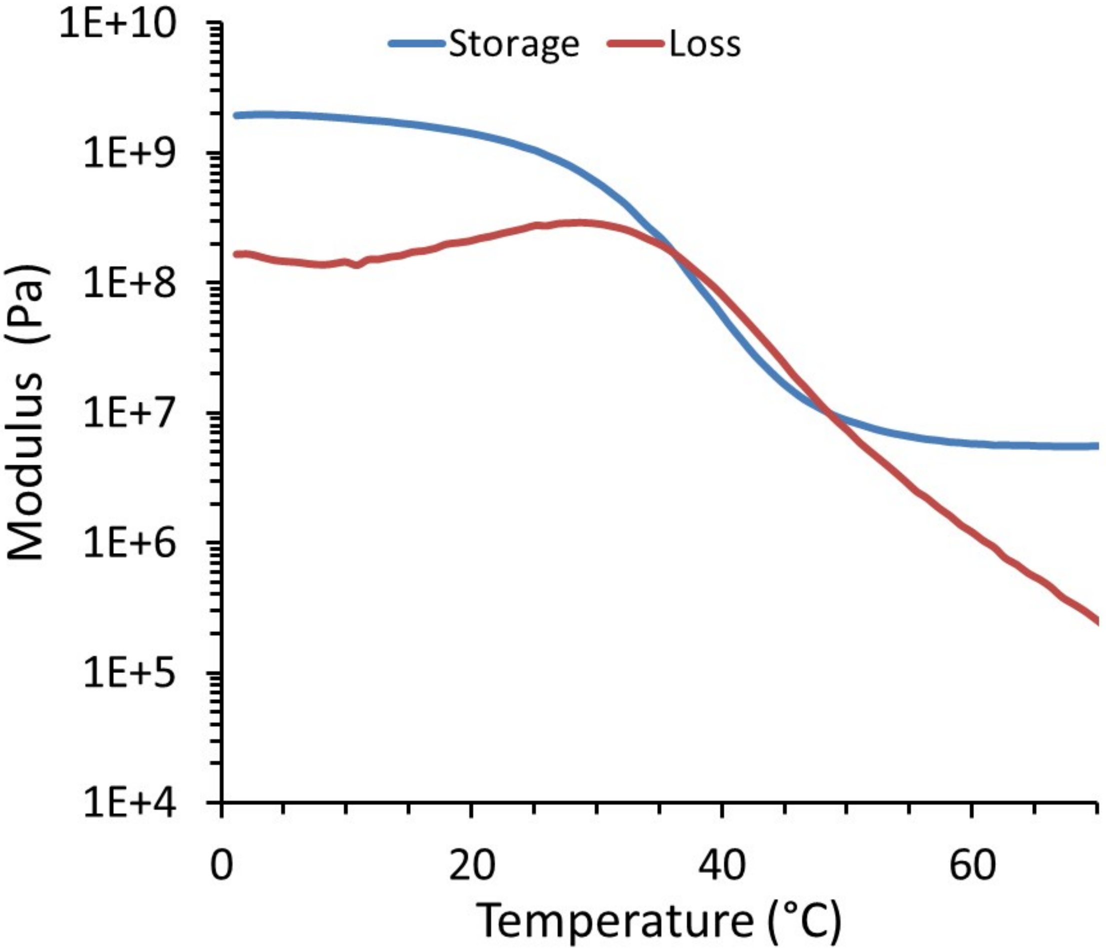
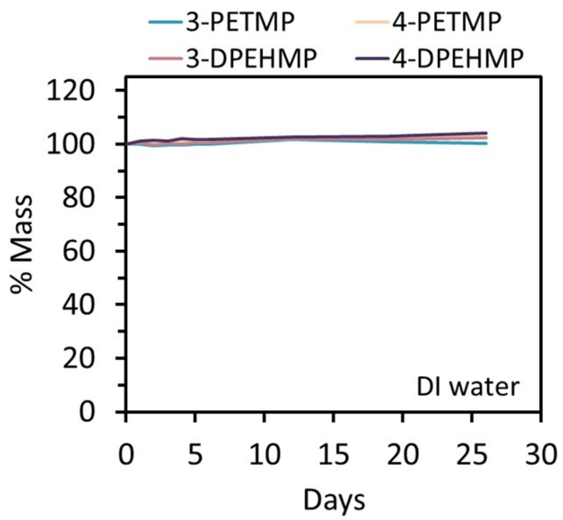
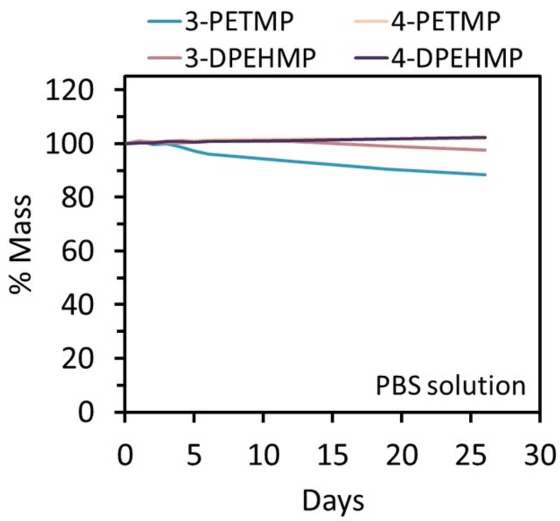


**Figure S36.** Storage and loss moduli measured via DMA of **4-**DPEHMP with post-curing thermal treatment at 100 °C for 24 h.

### S.3 Hydrolytic Stability Testing

Samples of the anhydride networks (~30 mg) were added to 5 mL scintillation vials and used for hydrolytic stability testing in triplicate in DI water (pH ~7), phosphate-buffered saline (PBS) solution (pH 7.4), and artificial seawater (pH 7.8). The vials were placed in a dish filled with aluminum beads heated to 50 °C. Mass measurements were performed by removing the submerged sample from the vials, blotting them dry with a KimWipe, and recording the mass using a balance. The solutions were changed every two weeks.


3-PETMP
4-PETMP
3-DPEHMP
4-DPEHMP
% Mass
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Days
DI water


3-PETMP
4-PETMP
3-DPEHMP
4-DPEHMP
% Mass
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Days
PBS solution

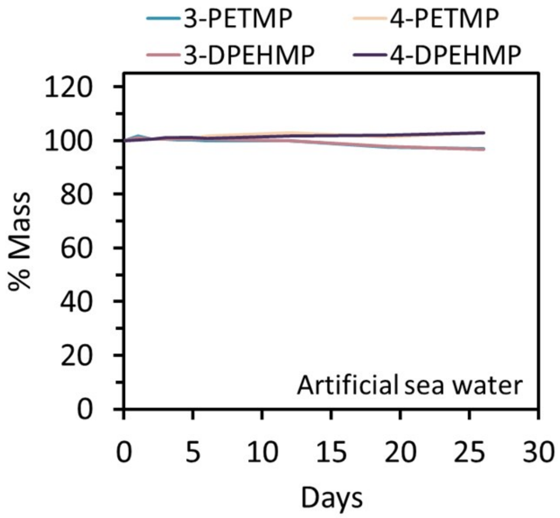

3-PETMP
4-PETMP
3-DPEHMP
4-DPEHMP
% Mass
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Days
Artificial sea water

**Figure S37**. Hydrolytic stability tests of the polyanhydride networks at 22 °C in DI water (pH 7.0), phosphate buffer saline (PBS) solution (pH 7.4), and artificial sea water (pH 7.8).

**Table S1**. pH values of the degradation solutions after completion of degradation studies at 50 °C

| | DI Water* | PBS solution | Artificial SW |
|---|---|---|---|
| **3**-PETMP | 3.5 | 5.6 | 3.4 |
| **3**-DPEHMP | 3.1 | 5.0 | 3.4 |
| **4**-PETMP | 3.3 | 5.1 | 4.3 |
| **4**-DPEHMP | 3.2 | 5.6 | 3.7 |

*pH values were measured after complete degradation of samples in PBS solution and artificial SW. Samples in DI water were not fully degraded after 51 days.