

Supporting Information to

## A versatile polypeptoid platform based on *N*-allyl glycine

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### **Supplies.**

Unless otherwise stated, all reagents were purchased and used as is from commercial sources (Sigma-Aldrich, ACROS, and/or Alfa Aesar). Anhydrous solvents (*i.e.* DMF, DMA, and benzonitrile) were either purchased in bottles with a septum over molecular sieves or distilled from a drying agent (*i.e.* calcium hydride for CH<sub>2</sub>Cl<sub>2</sub> or solid sodium for THF). All other solvents (*e.g.* dioxane, EtOAc, MeOH, etc.) were used as is from their respective commercial sources. Freshly distilled solvents were stored over activated molecular sieves (3 Å; 3–5 mm beads) and sealed under argon (flowed through a calcium chloride drying tube). Thin layer chromatography (TLC; 0.2 mm silica gel with fluorescent indicator; Polygram® SIL G/UV<sub>254</sub>) plates with visualizing agents (UV, iodine chamber, or KMnO<sub>4</sub> stain) were utilized to monitor the first two synthetic steps of the monomer synthesis. Flash chromatography techniques were utilized with nitrogen pressure to push eluent/sample mixture through silica gel (pore size 60 Å; Fluka). All laboratory equipment was cleaned and oven dried prior to use. The reaction flasks, for polymerization, were prepared by flash drying with a heat gun and reduced pressure (1.2x10<sup>-2</sup> mbar).

### **Analytical Instrumentation and methods.**

#### *Gas chromatography mass spectrometry (GC-MS).*

An Agilent Technologies GC 6890N MS 5975 equipped with an auto-sampler was utilized for analysis of compounds, purity, and detection of the monomer for polymerization monitoring. Samples were prepared in 2 mL septum-sealed vials at concentrations between 1–10 mg/mL. Enhanced ChemStation® software was utilized for the measuring program and analysis.

Monomer measuring program: An aliquot of 1 µL was injected into the heating block (200 °C), split (50:50), and flowed (He; 0.757 bar) through the heated (50–200 °C; 2 minute hold then 8 °C/min) column. After a 2 minute solvent delay, the data was captured (duration of 21.75 minutes) by the aforementioned software and sub-sequentially analyzed.

#### *Elemental analysis.*

C/H/N elemental analysis was performed using a Vario EL Elemental Analyzer.

#### *Melting point apparatus.*

The power setting of a MEL-TEMP® II apparatus, produced by Laboratory Devices Inc. (USA), was set to 4 for <100 °C and 5 for 100–200 °C.

#### *Nuclear magnetic resonance (NMR) spectroscopy.*

A Bruker DPX-400 MHz instrument was utilized for in house NMR measurements. These measurements were completed at room temperature and the samples were previously prepared in CDCl<sub>3</sub> (sub-monomer to monomer) or DMF-d<sub>7</sub> (polymers) at concentrations of ~5 or ~25 mg/mL, respectively. Topspin software was utilized for the setup, measurements, and data collection.

The Varian 600 MHz instrument, equipped with an autosampler, was utilized to measure **7d** (100% and 57% modification) at a separate facility. Samples were prepared in DMF-d<sub>7</sub> (~20 mg/mL) and measured at room temperature. The fid was then transformed into spectra via MestReC© software. The respective deuterated solvent proton peaks were identified and used as the internal shifting standard.<sup>1</sup>

#### *Fourier transform infrared spectroscopy (FT-IR).*

FT-IR measurements were completed on a Varian 1000 FT-IR, Scimitar series, equipped with an interchangeable sample head. Samples were loaded onto a diamond attenuated total reflectance (ATR) accessory and the Varian Resolutions FTS 1000 software allowed for measurements (transmittance; resolution = 4; 32 scans) and the recording of data.

#### *Size exclusion chromatography (SEC).*

SEC with simultaneous UV (270 nm) and RI detection was performed in *N*-methyl-2-pyrrolidone (NMP + 0.5 wt% LiBr) at +70 °C using a column set of two 300 × 8 mm<sup>2</sup> PSS-GRAM (spherical polyester particles with an average diameter of 7 μm) columns with porosities of 10<sup>2</sup> and 10<sup>3</sup> Å. Solutions containing ~0.15 wt% polymer were filtered through 0.45 μm filters; the injected volume was 100 μL. Calibration was done with polystyrene standards (Polymer Standards service PSS, Mainz, Germany). The NTeqGPC V6.4 software was used for data recording and handling.

#### *Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-ToF MS).*

MALDI-ToF MS was carried out with a Bruker Autoflex III Smartbeam MALDI (Bruker Daltonik), equipped with a laser working at 356 nm. Acceleration voltage was 20 kV and 4 x 500 shots at different places of the spot were recorded. Instrument software (FlexControl) and FlexAnalysis was used for data handling. Samples were prepared by applying the dried droplet method. 50 μl of matrix (T-2-(3-(4-t-Butyl-phenyl)-2-methyl-2-propenylidene)malononitrile, DCTB, 10 mg/ml in THF) were premixed with 10 μl of sample (2 mg/ml in THF). 1 μl of that mixture was dropped on the target.

#### *Thermal analysis (DSC and TGA)*

Differential scanning calorimetry (DSC) was performed on a Netzsch DSC Phoenix<sup>®</sup> in an inert nitrogen atmosphere. The samples were heated from room temperature to 250 °C, cooled to -50 °C and finally heated again to 250 °C at a heating/cooling rate of 10 K/min.

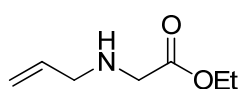
Thermogravimetric analysis (TGA) was carried out on a Netzsch TG 209 F1 at 20 K/min in a nitrogen atmosphere.

### Turbidimetry.

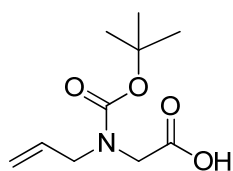
Samples (0.1 % w/w in ultra-pure H<sub>2</sub>O) were loaded into the Turbidity photometer TP1 (Tepper Analytik, Wiesbaden), via quartz cuvettes, and stirred. The instrument was programmed with a heating rate of 1 K/min between 20 and 80 °C. The transmittance (599 nm) and temperature measurements were recorded simultaneously by capturing the data as a text file via a hyper-terminal. The text data was loaded into Origin 8.6 where the temperature was converted into Celsius (raw data divided by 40) and the incremental transmittance data was divided by the maximum transmittance value and subsequently multiplied by 100%. The temperature at which the transmittance dropped to 80% was assigned as the cloud point temperature.

### Synthetic Procedures.

#### Monomer Synthesis.

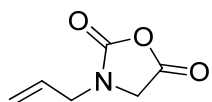


*Step i.* Ethyl 2-(allylamino)acetate (**3**). The following procedure was modified from a published procedure described by Liskamp and coworkers.<sup>2</sup> Allylamine (**1**; 22 mL; 0.294 mol) and Et<sub>3</sub>N (42 mL; 0.303 mol) were prepared in anhydrous THF (300 mL) and placed under argon. The solution was cooled to 0 °C. Ethyl bromoacetate (**2**; 28 mL, 0.255 mol) was dissolved in anhydrous THF (200 mL) and added to the allylamine solution via a dripping funnel (over 30 minutes). White precipitation was observed after the complete addition of **2**. The reaction was stirred for an additional 3-4 hours and then the solvent was removed by roto-vaporization (loss of product was observed below 200 mbar with a water bath set to 40 °C). The precipitate was washed with Et<sub>2</sub>O (3x50 mL) and filtered off. The filtrate was collected and the solvent was removed by roto-vaporization. The crude oil (55.07 g) was loaded onto a slurry packed column (1.5 kg of silica gel prepared in Et<sub>2</sub>O). Flash chromatography techniques were utilized with Et<sub>2</sub>O (5-10 L) as the eluent. Fractions of **3** were collected (R<sub>f</sub> = 0.09; KMnO<sub>4</sub> stain) and the solvent was removed by roto-vaporization. A translucent oil (35.45 g) was isolated and analyzed. The yield was adjusted down to 83% due to an observable ether impurity (<sup>1</sup>H-NMR analysis). GC-MS detects **3** (143.1 *m/z*), with a retention time of 8.5 minutes, and no other peaks (except for solvents). Further analysis correlates with Liskamp and coworkers published data.



*Step ii.* 2-(Allyl(tert-butoxycarbonyl)amino)acetic acid (**4**). The following procedure was modified from a published procedure described by Liskamp and coworkers.<sup>2</sup> Ethyl 2-(allylamino)acetate (**3**; 33.00 g; 0.200 mol<sup>3</sup>) was dissolved in 1,4-dioxane (500 mL). Boc<sub>2</sub>O (44.54 g; 0.204 mol) was added to the stirring solution and the reaction mixture was placed under argon. The reaction was followed by TLC (100% Et<sub>2</sub>O; KMnO<sub>4</sub> stain) and the protection was complete within 2-4 hours (R<sub>f</sub> change from 0.09 to 0.95). MeOH (300 mL) was poured into the stirring solution. A 4 N NaOH solution (120 mL; 0.48 mol) was added via dripping funnel (~1-2 hours). White precipitation was observed after the complete addition of NaOH. TLC indicated the consumption of the intermediate (Ethyl Boc-*N*-allylglycinoate). The mixture was diluted with H<sub>2</sub>O (~300 mL) and 1,4-dioxane was extracted in Et<sub>2</sub>O (~3x500 mL). The aqueous layer pH was adjusted to ~3 (Litmus paper) with 1 N KHSO<sub>4</sub>. Further extractions were carried out with EtOAc (3x150

mL). The collected extracts were dried over  $\text{MgSO}_4$  and concentrated down (roto-vaporization) to a white solid. This was re-dissolved in  $\text{Et}_2\text{O}$  and subsequently removed via rotovaporization (2x). High vacuum was utilized to remove trace amounts of solvents. A white crystalline powder was collected (41.27 g; 96%). Analysis with  $^1\text{H-NMR}$  and GC-MS (fragmentation pattern; 16.5 minutes) supports product **4** with no impurities and subsequently matches data presented by Liskamp and coworkers.



*Step iii.* 3-Allyloxazolidine-2,5-dione (**5**). The following procedure was modified from Zhang and Luxenhofer group's reported procedures.<sup>4, 5</sup> A reaction flask was oven dried and flushed with argon. Compound **4** (10.01 g; 0.0465 mol) was added to this flask and dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (350 mL). The stirring solution was cooled to  $0^\circ\text{C}$ .  $\text{PCl}_3$  (4.86 mL; 0.0557 mol) was injected slowly (~5 minutes) and the reaction was allowed to stir for 4-5 hours. Volatile organics were removed by a rotovaporizer connected to argon. A Criegee distillation apparatus was flashed dried under vacuum ( $1.5 \times 10^{-2}$  mbar). The remaining material was transferred to the distillation round bottom flask utilizing anhydrous THF. Solvents were cryo-condensed away. After leaving on high vacuum for ~20 minutes, the distillation flask was placed in an oil bath and well insulated with cotton. The temperature of the oil bath was initially raised to  $75^\circ\text{C}$ . Once the internal thermometer was within 15 degrees of the oil bath, the temperature was slowly raised to  $85\text{--}90^\circ\text{C}$  ( $2.0 \times 10^{-2}$  mbar).<sup>6</sup> Boiling point range of product **5** was  $73\text{--}88^\circ\text{C}$ . A translucent oil (3.6 mL; 4.82 g; 73%) was collected. Product **5** is highly reactive to impurities and must be used immediately or stored under an inert system.<sup>7</sup>  $^1\text{H-NMR}$  analysis supports product **5** in 98% purity.  $^1\text{H-NMR}$  ( $\text{DMF-d}_7$ , 400 MHz)  $\delta$  5.98-5.82 (m, 1H), 5.40 (d,  $J = 16$  Hz, 1H), 5.25 (d,  $J = 10$  Hz, 1H), 4.35 (s, 2H), 4.03 (d,  $J = 6$  Hz, 2H);  $^{13}\text{C NMR}$  ( $\text{DMF-d}_7$ , 400 MHz)  $\delta$  167.9, 153.2, 132.4, 118.6, 49.8, 46.2; FT-IR (crystal)  $\nu_{\text{max}}$  3087, 2985, 2932, 1848, 1763, 1452, 1409, 1272, 1217, 1183, 983, 939, 913, 893, 833, 749, 699, 661, 600, 549  $\text{cm}^{-1}$ ; GC-MS (MSD)  $R_t = 13.0$  min; (EI)  $m/z$  141.0 ( $\text{M}^+$ ,  $[\text{C}_6\text{H}_7\text{NO}_3]^+$ ).

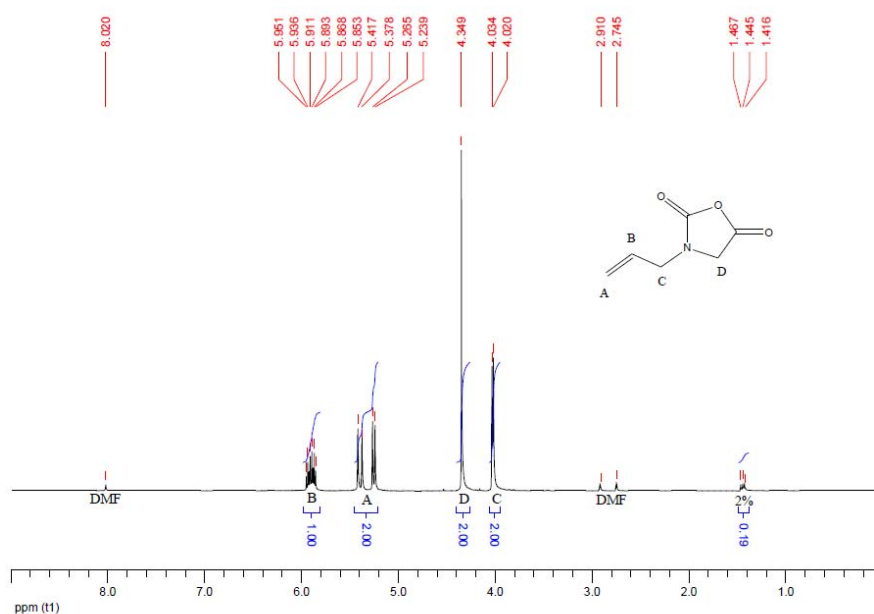


Figure SI-1.  $^1\text{H NMR}$  spectrum of **5** in  $\text{DMF-d}_7$ .

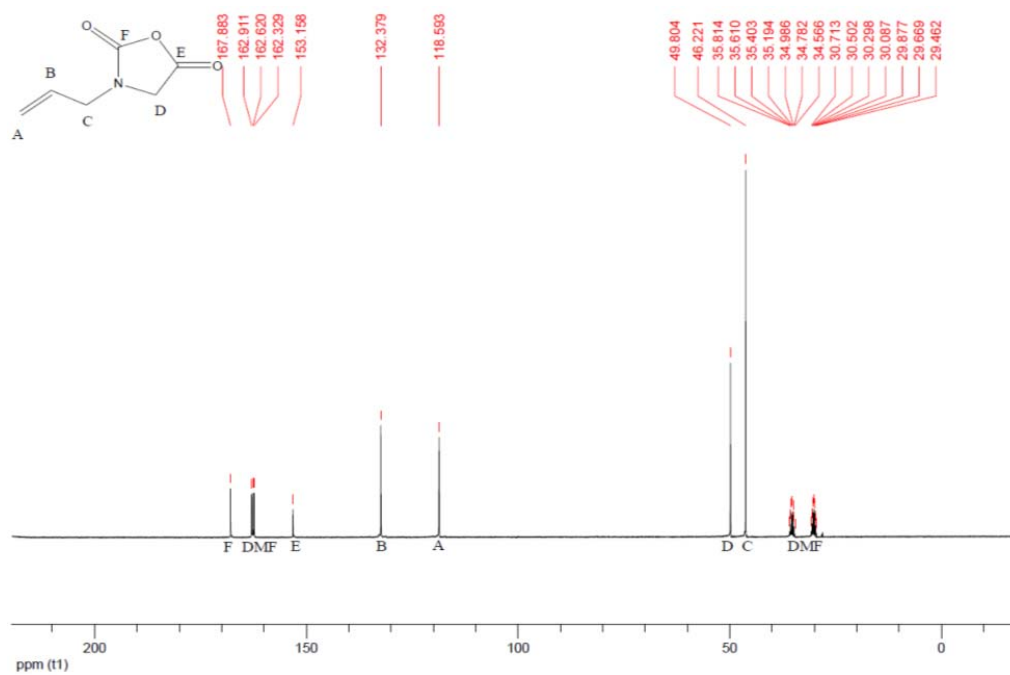


Figure SI-2.  $^{13}\text{C}$  NMR spectrum of 5 in  $\text{DMF-d}_7$ .

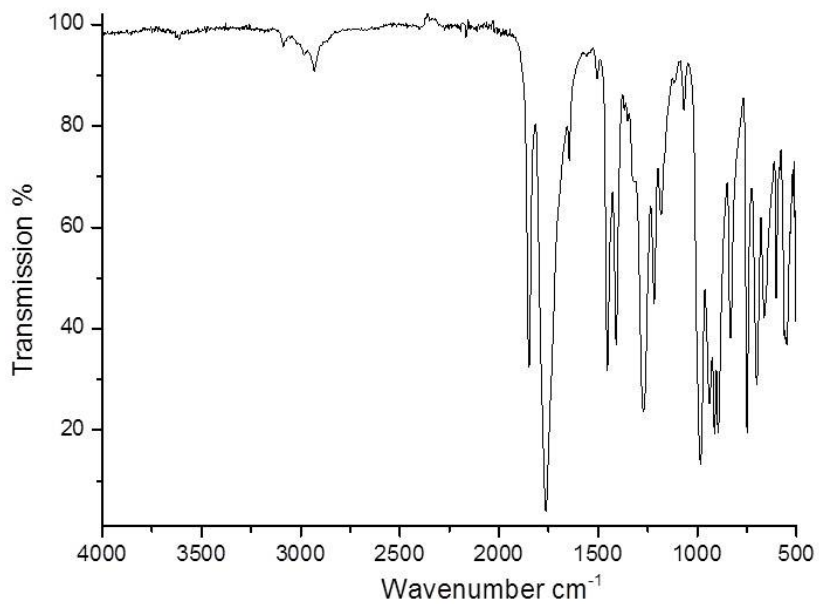


Figure SI-3. FT-IR spectrum of 5 neat.

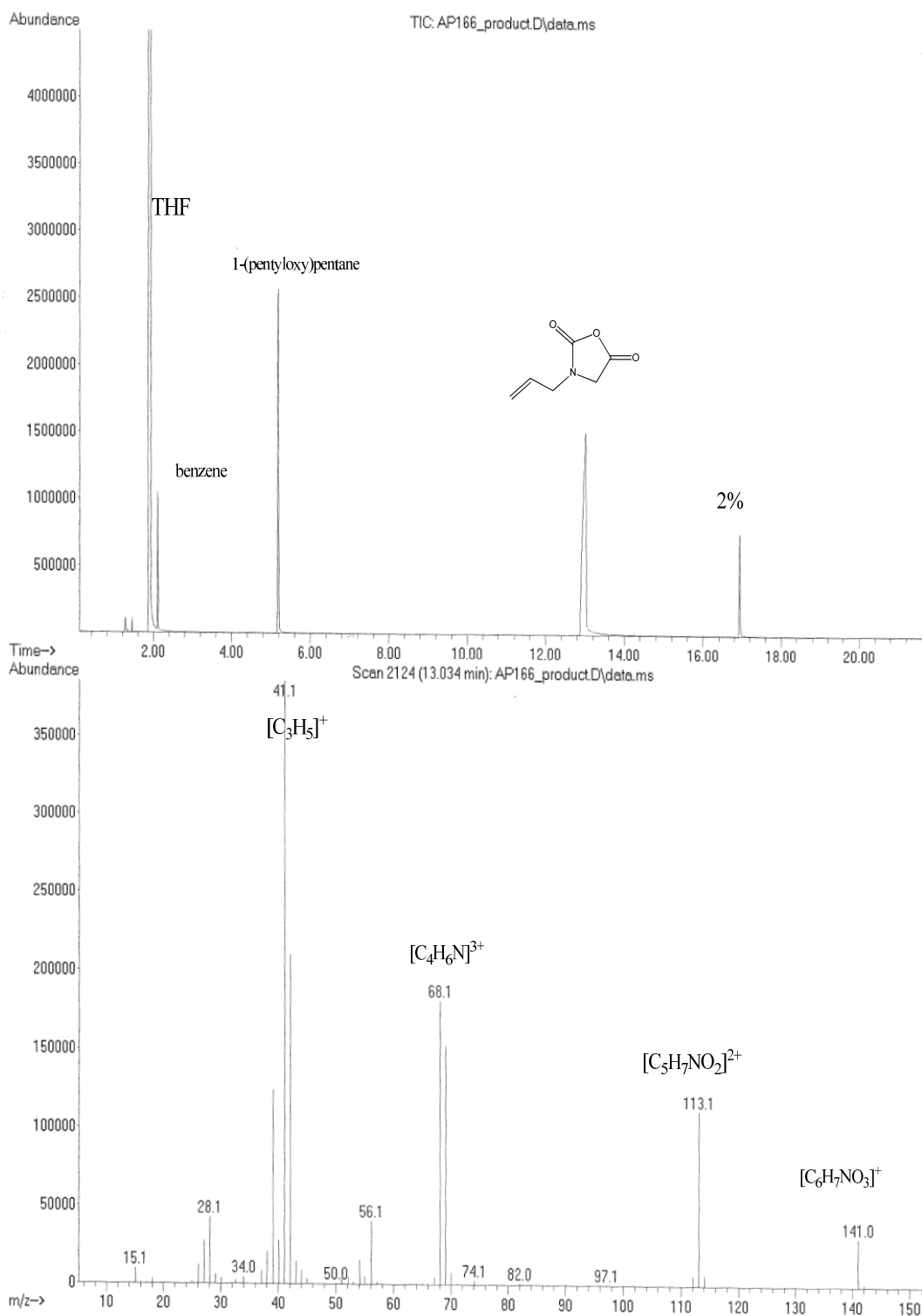
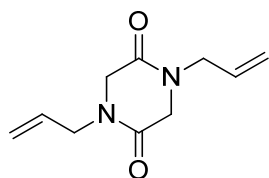


Figure SI-4. GC-MS spectrum of 5.



*Step iv.* 1,4-Diallylpiperazine-2,5-dione (**6**). The diketopiperazine (DKP) **6** was detected as a side product created during the purification of NCA **5** (previous attempts). Improper insulation/vacuum of a short path distillation caused **5** to reflux (110-130 °C) in the crude mixture (O=PCL<sub>2</sub>, PCl<sub>3</sub>, HCl, etc.) over 3-4 hours.

The oil bath temperature was then raised to 140-150 °C and the exterior of the distillation apparatus was heated above 100 °C. NCA **5** (0.41 g; 6%) and DKP **6** (2.88 g; 31%) were collected as an oil and white crystalline material (mp = 98 °C), respectively. Noteworthy, Katsu and coworkers observed **6** as a competing by-product of the cyclization of a tripeptide into the target compound *N,N',N''*-triallyl-*cyclo*-triglycine but did not describe any characterization.<sup>8</sup> We herein disclose the full characterization of **6**. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.76-5.66 (m, 1H), 5.25 (dd, J = 10, 19 Hz, 2H), 4.01 (d, J = 6 Hz, 2H), 3.94 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 163.2, 130.8, 119.6, 49.2, 48.2; FT-IR (crystal) ν<sub>max</sub> 2976, 2941, 2913, 2862, 2841, 1652, 1486, 1438, 1410, 1334, 1290, 1193, 1138, 1076, 1010, 938, 779, 631 cm<sup>-1</sup>; GC-MS (MSD) R<sub>t</sub> = 20.5 min; (EI) *m/z* 194.4 (M<sup>+</sup>, C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub>); elemental analysis C 61.7%, H 6.9%, N 14.3% (found), C 61.8%, H 7.2%, N 14.4% (calculated).

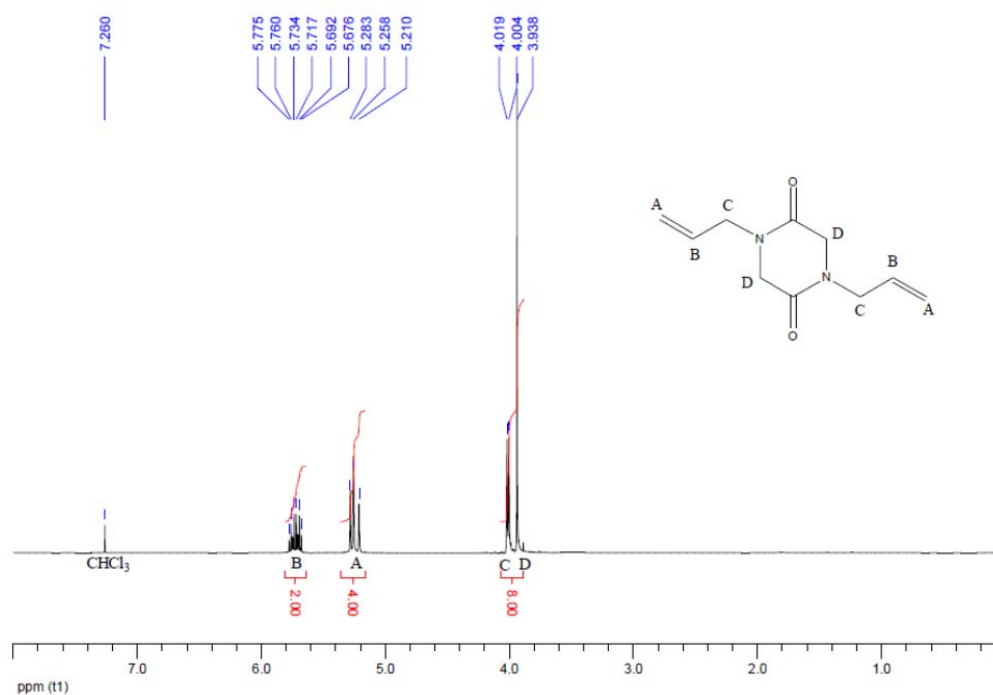


Figure SI-5. <sup>1</sup>H NMR spectrum of **6** in CDCl<sub>3</sub>.

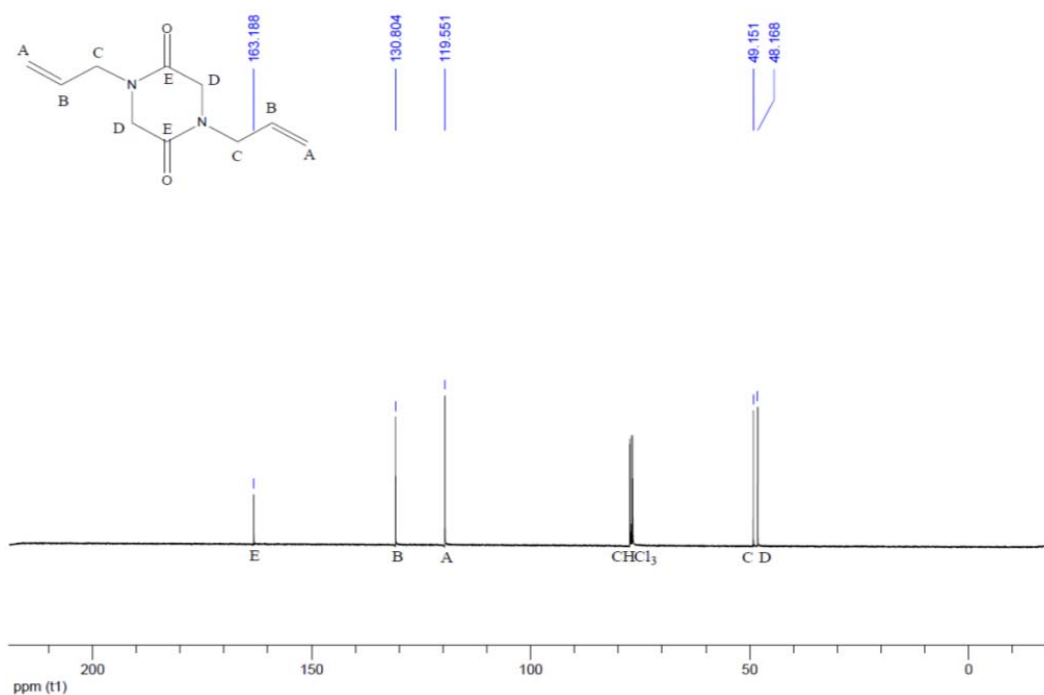


Figure SI-6.  $^{13}\text{C}$  NMR spectrum of **6** in  $\text{CDCl}_3$ .

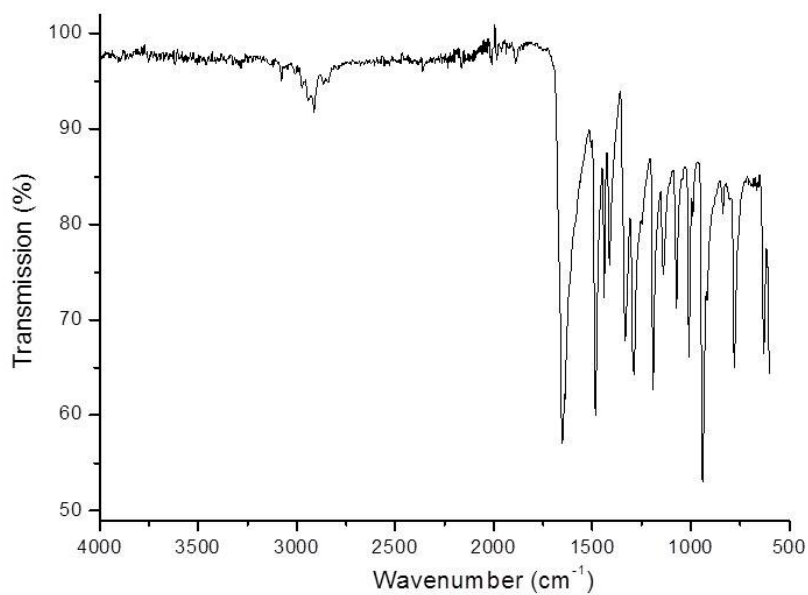


Figure SI-7. FT-IR spectrum of **6** neat.



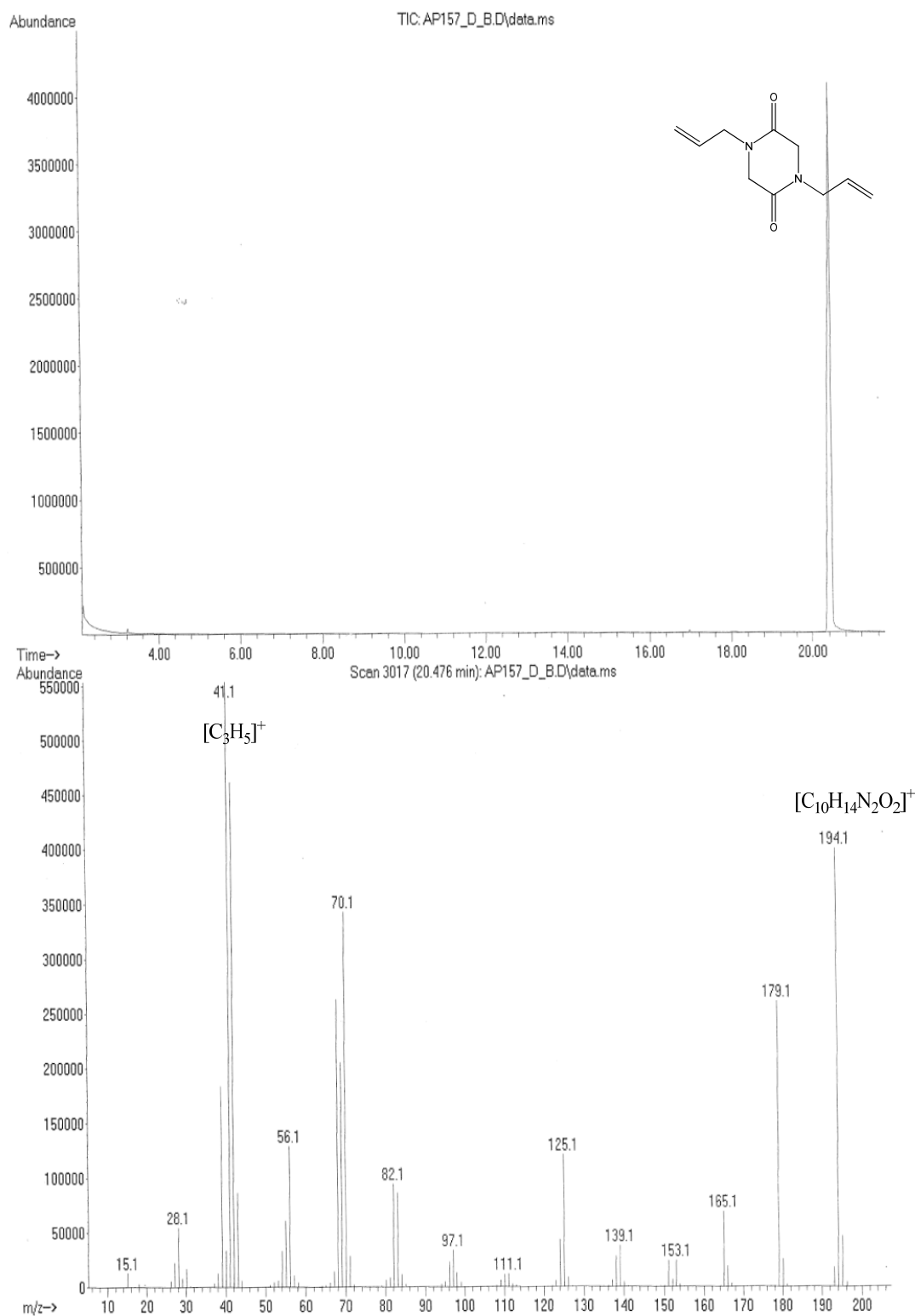
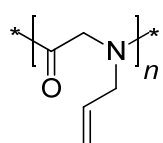


Figure SI-8. GC-MS spectrum of **6**.

### Preparation of poly(*N*-allyl glycine).



**Homogeneous phase preparation of poly(*N*-allyl glycine) (7a-d).** A sealable reaction flask was flashed dried on a Schlenk line. Freshly distilled NCA **5** was dissolved in anhydrous THF and transferred into the reaction flask (under streaming argon). Low vapor volatiles were removed by cryo-condensation and the remaining oil was left on continuous vacuum ( $1.5 \times 10^{-2}$  mbar) for ~30 minutes. Under streaming argon, anhydrous solvent<sup>9</sup> (DMA; benzonitrile; ~1-2 wt %)<sup>10</sup> was transferred into the reaction flask followed by the initiator (a 1 M solution of benzylamine in NMP;  $[5]_0/[BnNH_2]_0 = 100$  and 20). The pressure was reduced to  $2.0 \times 10^{-2}$  mbar and the reaction flask was resealed. The reactions were monitored by GC-MS.<sup>11</sup> Complete consumption of the monomer was only detected when low molecular weights were targeted in benzonitrile. Acetic anhydride was utilized to terminate the end group's activity. The solvent was distilled off (under vacuum) and the crude oil was redissolved in a miniscule amount of THF. The polymers were then precipitated into petroleum ethers. Centrifugation and decantation were utilized in isolating the precipitates. High vacuum was utilized for removing residue solvents. **7d** exemplary example: Duration of 4 days; Gravimetric yield = ~100%; SEC (PS):  $M_n = 2.0$  kg/mol, PDI = 1.07; <sup>1</sup>H-NMR (DMF-d<sub>7</sub>, 400 MHz)  $\delta$  7.30 (br, 5 H, C<sub>6</sub>H<sub>5</sub>-), 5.84 (br, 14 H, -CH=), 5.28 (br, 27 H, =CH<sub>2</sub>), 4.28 (br, 29 H, allyl[-CH<sub>2</sub>-]), 3.98 (br, 27 H,  $\alpha$ [-CH<sub>2</sub>-]), 1.98 (m, 4H, -CH<sub>3</sub>); <sup>13</sup>C NMR (DMF-d<sub>7</sub>, 400 MHz)  $\delta$  169.9, 169.2, 134.2, 133.9, 128.8, 128.0, 117.4, 116.9, 50.3, 50.0, 48.2; FT-IR (crystal)  $\nu_{max}$  3079, 2981, 2933, 1645, 1469, 1408, 1348, 1283, 1211, 1189, 1125, 992, 915, 837, 695 cm<sup>-1</sup>; DSC inflection point 55 °C.

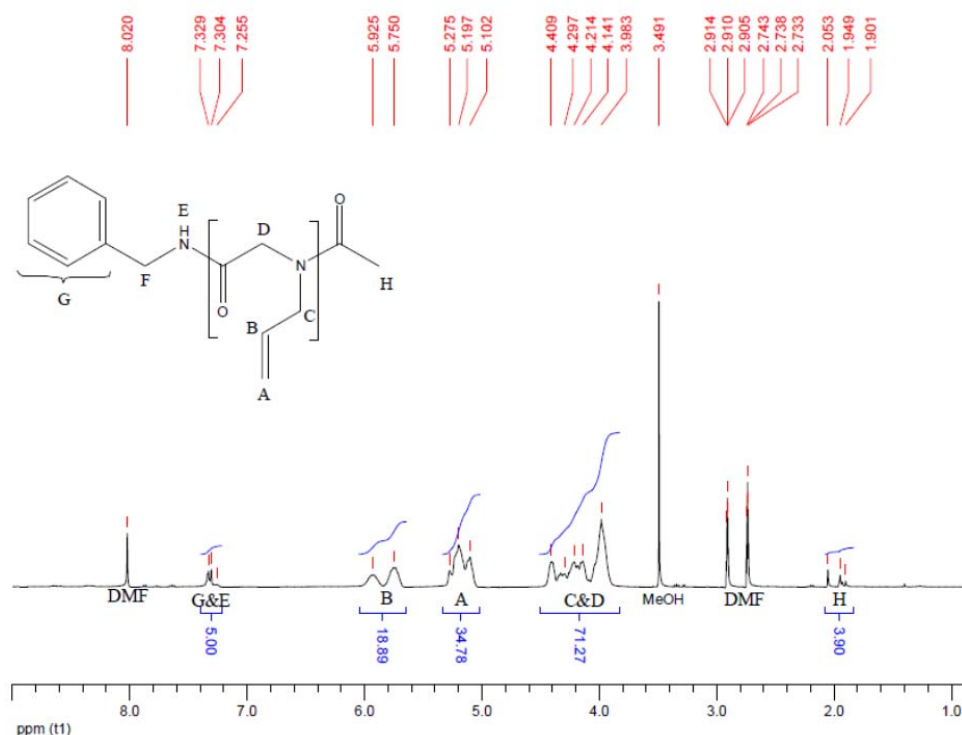


Figure SI-9. <sup>1</sup>H NMR spectrum of **7d** in DMF-d<sub>7</sub>.

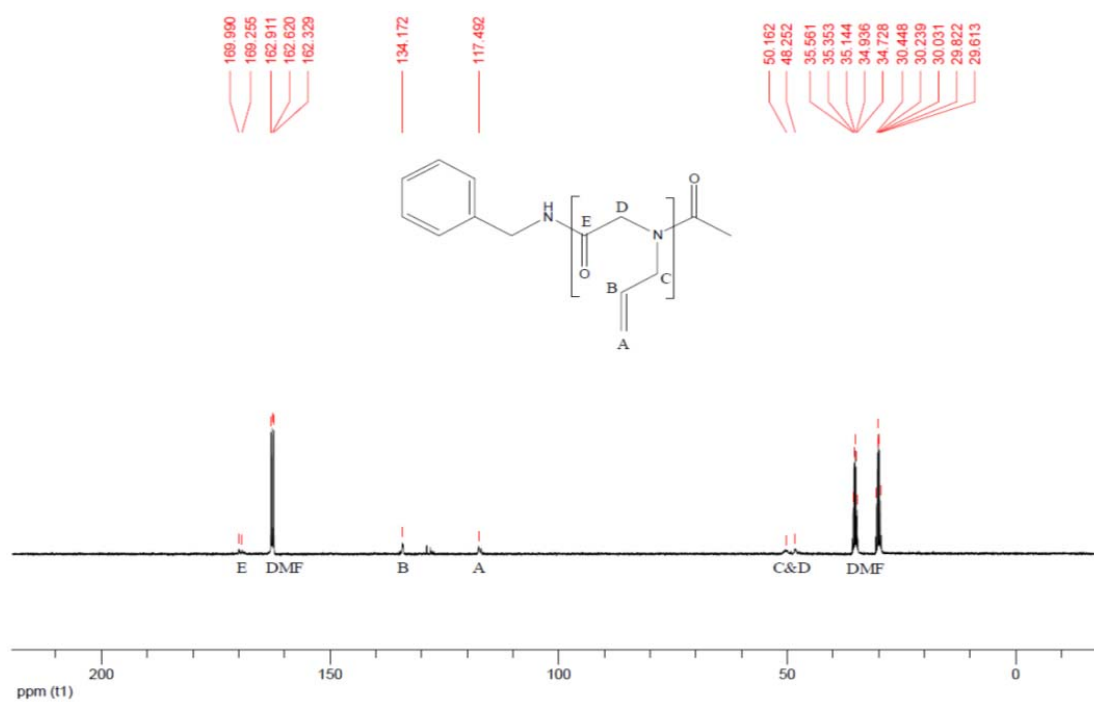


Figure SI-10.  $^{13}\text{C}$  NMR spectrum of **7d** in  $\text{DMF-d}_7$ .

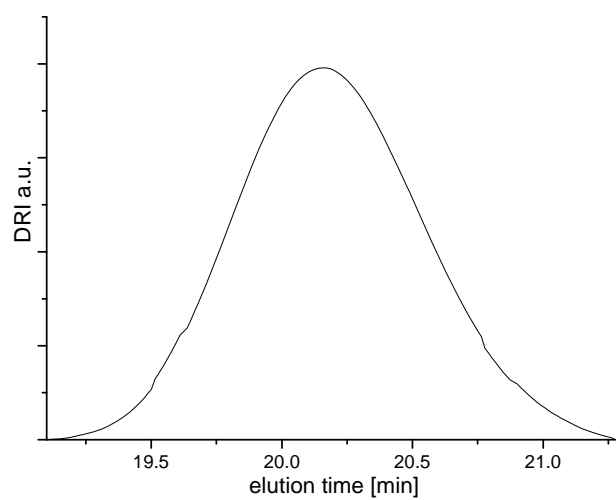


Figure SI-11. SEC trace of **7d** in NMP.

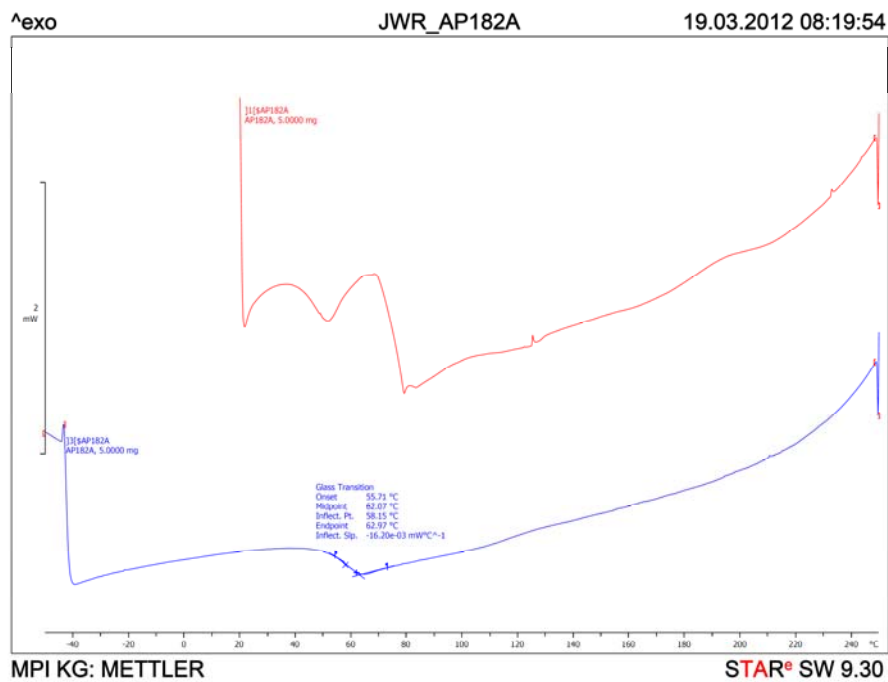


Figure SI-12. DSC heating curves (blue: 2<sup>nd</sup> heating) of **7d** neat.

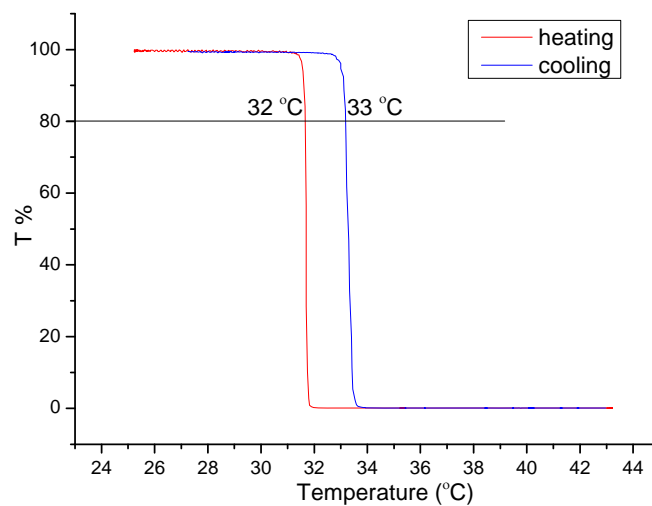
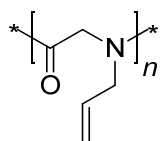
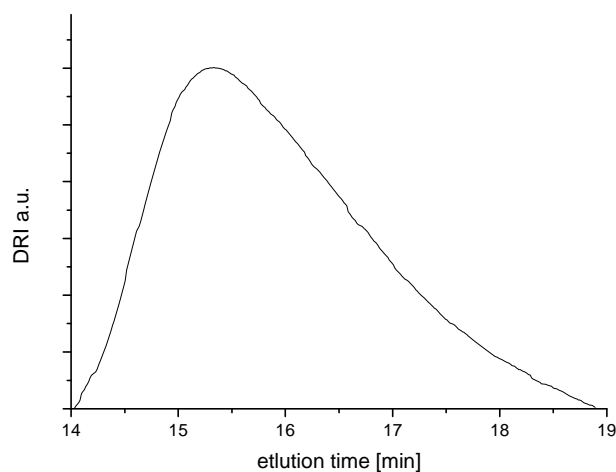


Figure SI-13. Turbidity curves of **7d** at 0.1% w/w in H<sub>2</sub>O.



*Heterogeneous phase preparation of poly(N-allyl glycine) (7e-g).* Three flasks (A, B, C) were dried and flushed with argon. Heptanes (30 mL) were injected into each flask and bubbled with argon. While under positive argon pressure (balloon), NCA **5** (0.6 mL; 5.70 mmol) was injected into each flask. High stirring was set for flask A (~20 minutes prior to initiation). Benzylamine (1 M in NMP; 14  $\mu$ L;  $[5]_0/[BnNH_2]_0 = 400$ ) was injected into the stirring mixture in flask A, into the stagnant layer of heptanes in flask B, and directly into the monomer layer in flask C. In 1 hour, a milky white layer was observed at the hetero phase for flask B whereas small bubbles were immediately produced in flask C. The respective reactions were terminated after 12 hours with acetic anhydride (0.1 mL; 1.06 mmol) and left in their current status for another 3-4 hours. The liquid phase was decanted off and the remaining material was dried on high vacuum overnight. **7g** exemplarily example: Gravimetric yield = ~100%; SEC (PS):  $M_n = 28.9$  kg/mol, PDI = 1.39;  $^1H$ -NMR (DMF- $d_7$ , 400 MHz)  $\delta$  7.32 (br, 5 H,  $C_6H_5^-$ ), 5.84 (br, 114 H,  $-CH=$ ), 5.20 (br, 207 H,  $=CH_2$ ), 4.35 (br, 195 H, allyl $[-CH_2-]$ ), 3.98 (br, 208 H,  $\alpha[-CH_2-]$ ), 2.02 (m, 14H,  $-CH_3$ );  $^{13}C$  NMR (DMF- $d_7$ , 400 MHz)  $\delta$  169.7, 169.2, 166.6, 133.9, 117.5, 50.5, 48.4; FT-IR (crystal)  $\nu_{max}$  3074, 2981, 2925, 1640, 1469, 1404, 1344, 1283, 1211, 1186, 1121, 992, 915, 841, 691  $cm^{-1}$ ; TGA thermally stable until 321  $^{\circ}C$ ; DSC inflection point 60  $^{\circ}C$ .



**Figure SI-14.** SEC trace of **7g** in NMP.

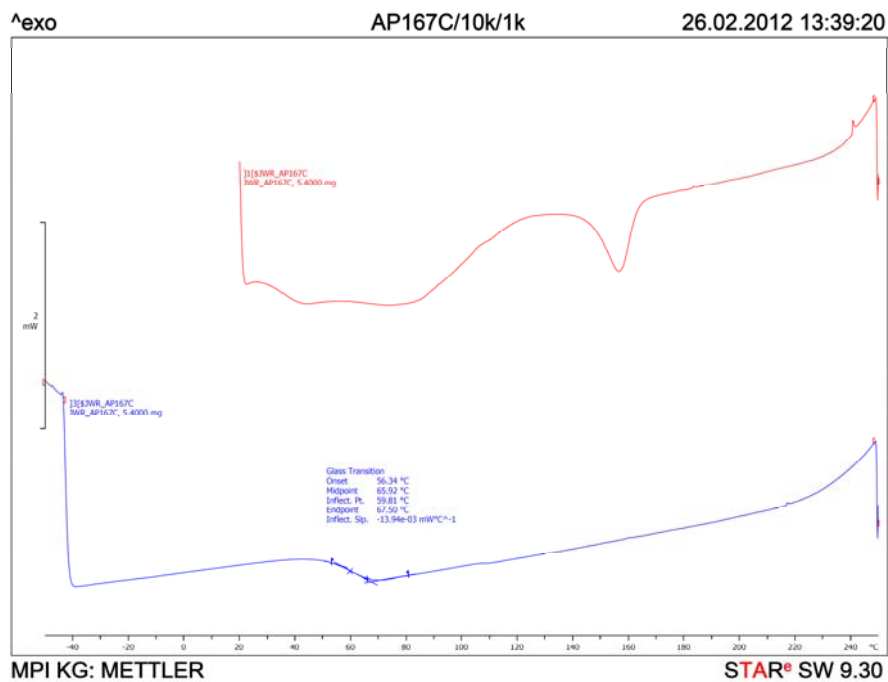


Figure SI-15. DSC heating curves (blue: 2<sup>nd</sup> heating) of **7g** neat.

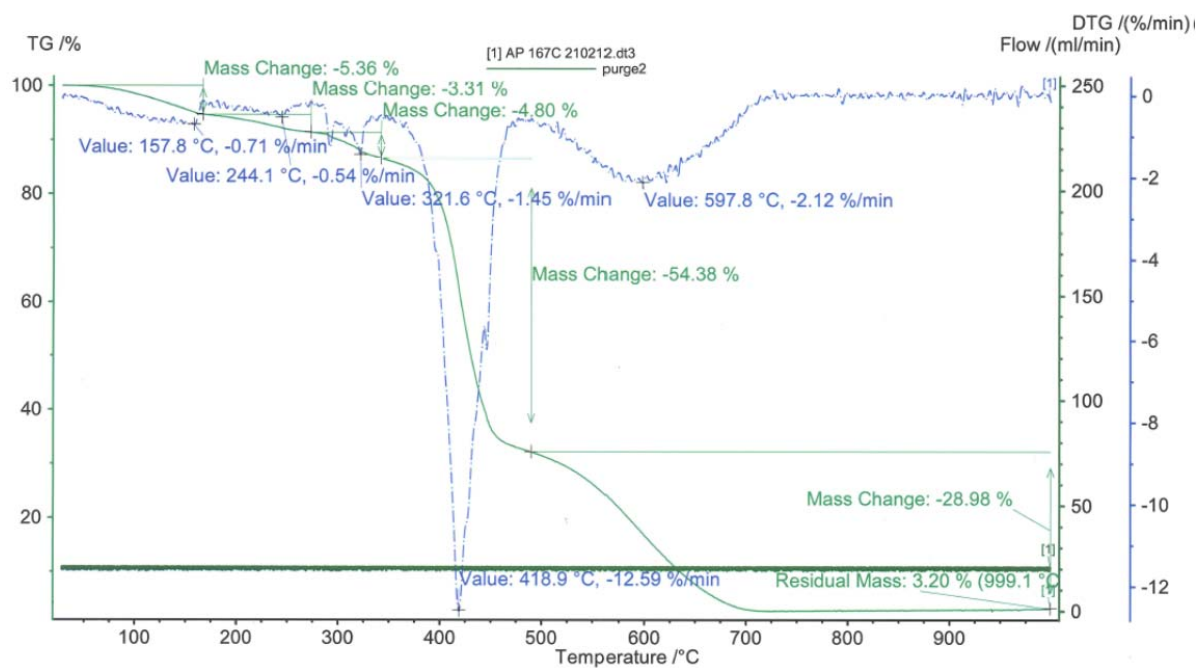


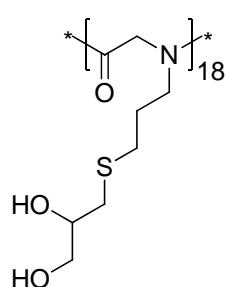
Figure SI-16. TGA curve of **7g** neat.

**Table SI-1.** Solubility profile of glycine-based polymers.<sup>a</sup>

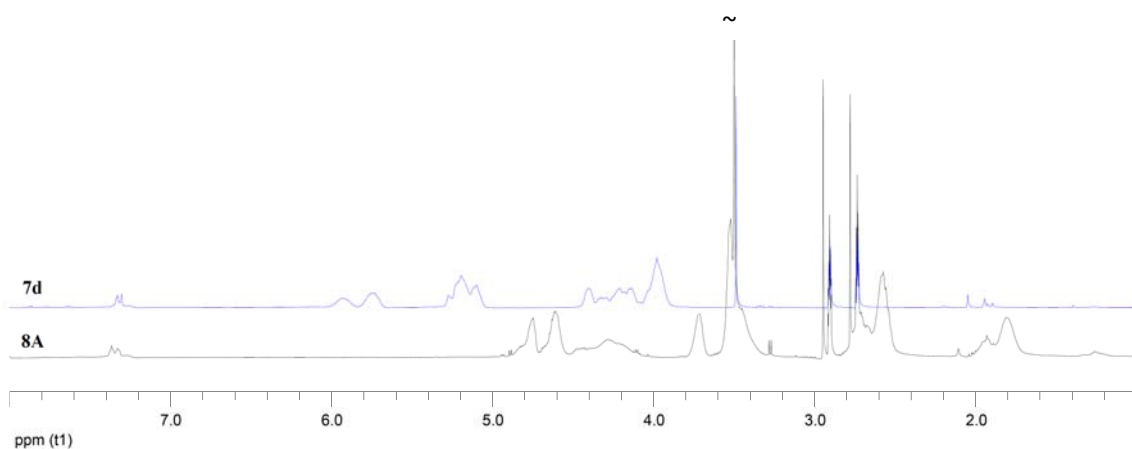
solvent	7d	7g	8A	8B	9
Acetone	+ <sup>b</sup>	- <sup>f</sup>	-	+	-
Acetonitrile	+	+ <sup>b</sup>	-	+	-
Benzonitrile	+	+	-	+	-
Chloroform	+	+	-	+	- <sup>g</sup>
Cyclohexane	- <sup>c</sup>	-	-	-	-
Methylene chloride	+	+	-	+	- <sup>g</sup>
Diethyl ether	-	-	-	-	-
N,N-dimethyl acetamide	+	+	+	+	-
N,N-dimethyl formamide	+	+	+	+	-,+ <sup>h</sup>
Dimethyl sulfoxide	+	- <sup>e</sup>	+	+	-
1,4-dioxane	+ <sup>b</sup>	- <sup>f</sup>	-	+	-
Ethanol	+	+ <sup>b</sup>	-	-	- <sup>f</sup>
Ethyl acetate	- <sup>d</sup>	-	-	+	-
Methanol	+	+	-	-	-
N-methyl-2-pyrrolidone	+	+	+	+	-,+ <sup>h</sup>
Tetrahydrofuran	+ <sup>b</sup>	+ <sup>b</sup>	-	+	-
H <sub>2</sub> O, distilled	- <sup>e</sup>	-	+	-	-
0.1 M NaOH	- <sup>f</sup>	-	+	-	- <sup>d</sup>
0.1 M HCl	- <sup>e</sup>	-	+	-	-

<sup>a</sup>1-5 mg of polymer was placed in a dram vial with 0.2 mL of 'solvent' at r.t. and lightly agitated for 12 hours; <sup>b</sup>light turbidity; <sup>c</sup>gellation; <sup>d</sup>turbid with precipitates; <sup>e</sup>sticks to the inner walls; <sup>f</sup>suspended particles; <sup>g</sup>precipitation; <sup>h</sup>precipitates dissolve with heat.

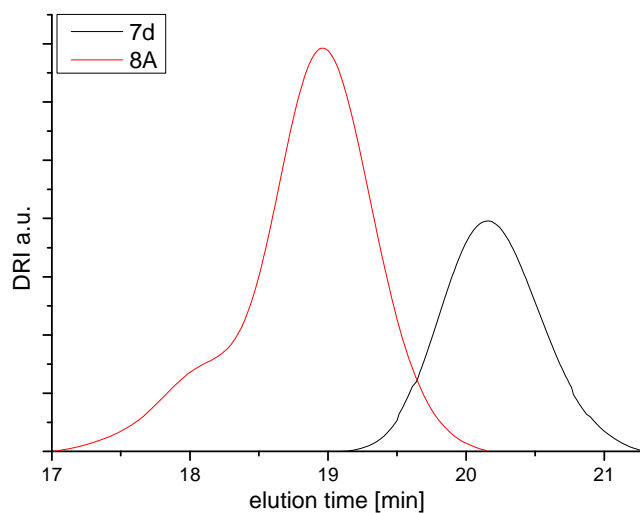
Modification of scaffold.



*Side chain modification of 7d with 1-thioglycerol to 8A.* **7d** (0.221 g; 2.27 mmol) was dissolved in DMF (2.2 mL) with 1-thioglycerol (0.24 mL; 2.75 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA; 7.3 mg; 0.028 mmol). The round bottom flask was flushed with argon and sealed with a glass stopper. The reaction mixture was then irradiated with UV light for 12 hours. The polymer was precipitated in Et<sub>2</sub>O, isolated by centrifugation and decantation, redissolved in MeOH and transferred to a new flask where the volatiles were removed by vacuum. **8A** was collected as a transparent waxy material (0.468 g; ~100%).

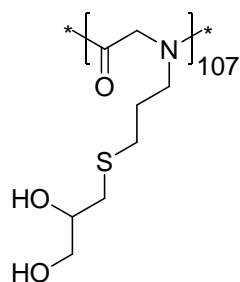


**Figure SI-17.** <sup>1</sup>H NMR spectrum of **8A** compared to **7d** in DMF-d<sub>7</sub>.



**Figure SI-18.** SEC trace of **8A** compared to **7d** in NMP.





**7g** (0.116 g; 1.19 mmol) was dissolved in DMF (2.2 mL) with 1-thioglycerol (0.12 mL; 1.38 mmol) and 2,2-dimethoxy-2-phenylacetophenone (DMPA; 10.8 mg; 0.04 mmol). The dram vial was flushed with argon and sealed. The reaction mixture was then irradiated with UV light for 24 hours. The reaction mixture was precipitated into Et<sub>2</sub>O. Centrifugation and decantation was utilized to isolate precipitate (**8A'**). Redissolved in H<sub>2</sub>O and transferred to a new flask where it was freeze dried.

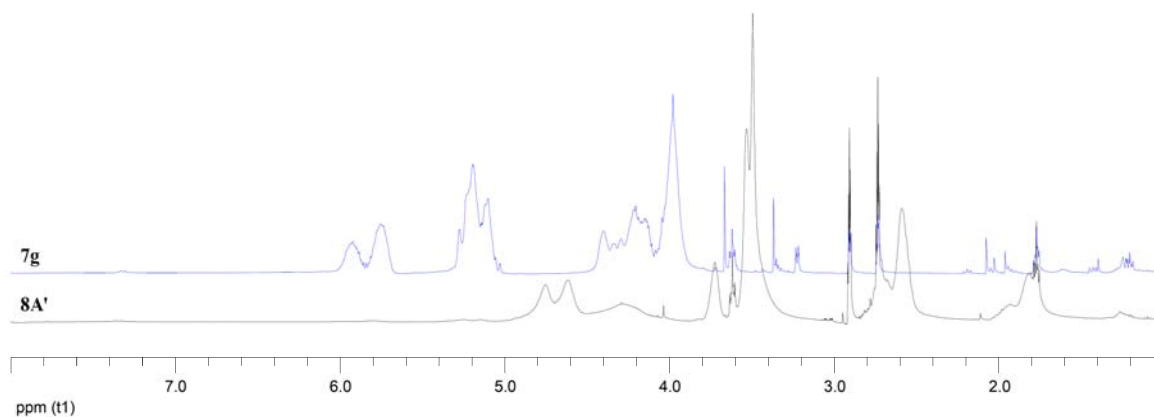


Figure SI-19. <sup>1</sup>H NMR spectrum of **8A'** compared to **7g** in DMF-d<sub>7</sub>.

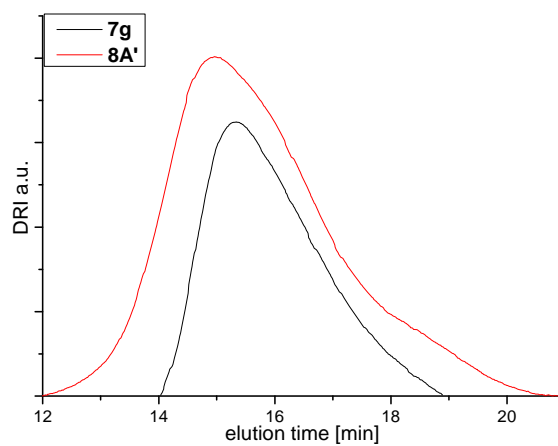


Figure SI-20. SEC trace of **8A'** compared to **7g** in NMP.

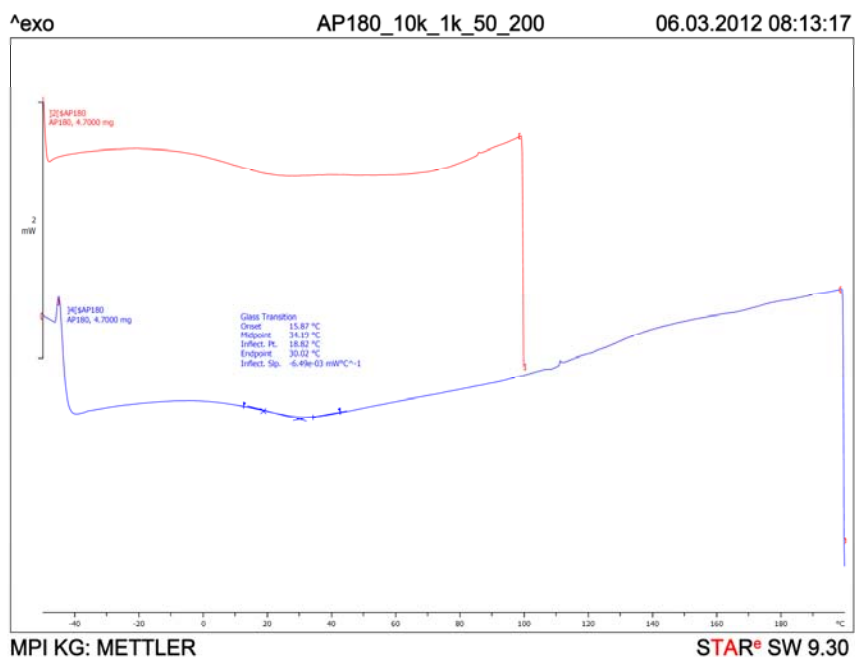


Figure SI-21. DSC heating curves (blue: 2<sup>nd</sup> heating) of **8A'** neat.

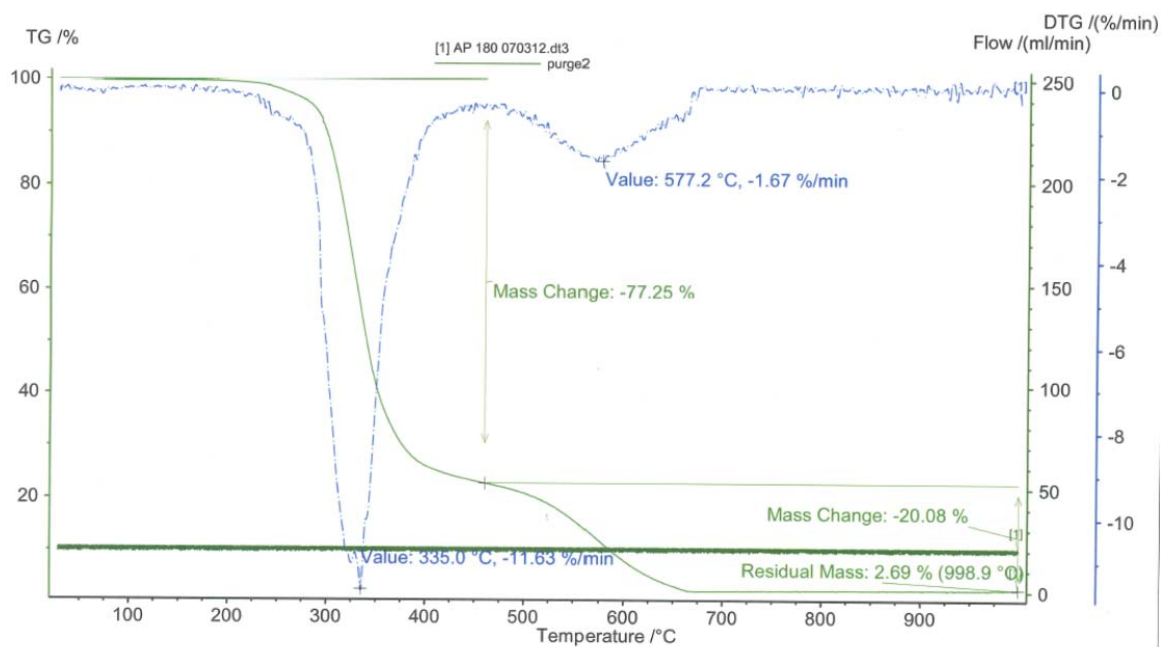


Figure SI-22. TGA curve of **8A'** neat.

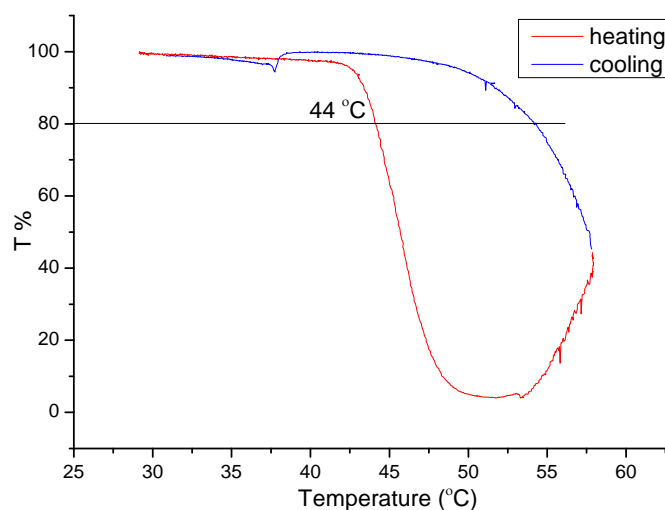
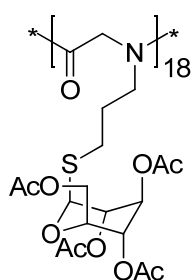


Figure SI-23. Turbidity curve of **8A'** at 0.1% w/w in H<sub>2</sub>O.



Side chain modification of **7d** with 1-thio- $\beta$ -D-glucose tetraacetate to **8B**. **7d** (0.240 g; 2.47 mmol) was dissolved in DMF (2.4 mL) and prepared in an Erlenmeyer flask under argon. 1-Thio- $\beta$ -D-glucose tetraacetate (1.06 g; 2.91 mmol) was added and the mixture was allowed to stir (~20 min). Then DMPA (7.9 mg; 0.03 mmol) was added and the reaction mixture was sealed with a glass stopper and placed under UV irradiation for 12 hours. Collected a white crystalline material (**8B**; 1.13 g; ~99 %). <sup>1</sup>H-NMR confirms product with a conversion of ~100%.

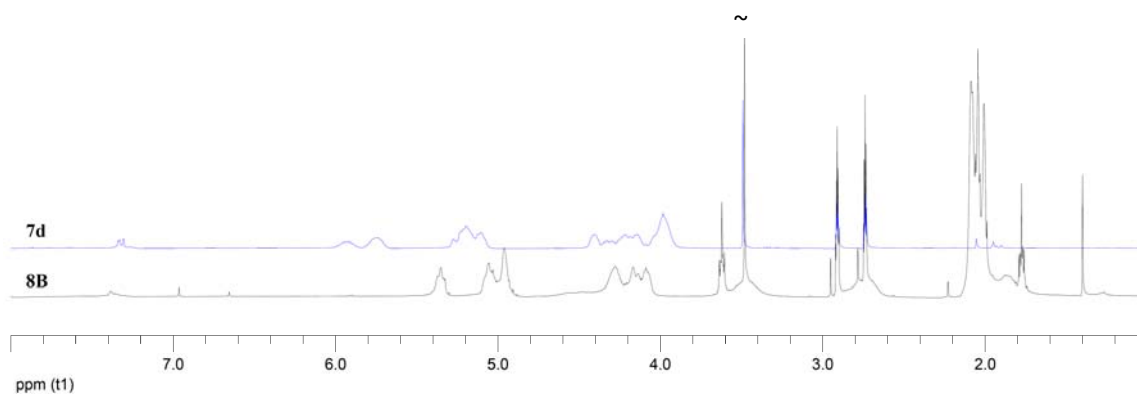


Figure SI-24. <sup>1</sup>H NMR spectrum of **8B** compared to **7d** in DMF-d<sub>7</sub>.

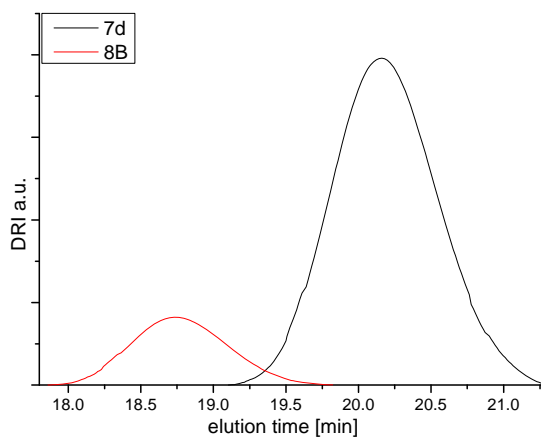


Figure SI-25. SEC trace of **8B** compared to **7d** in NMP.

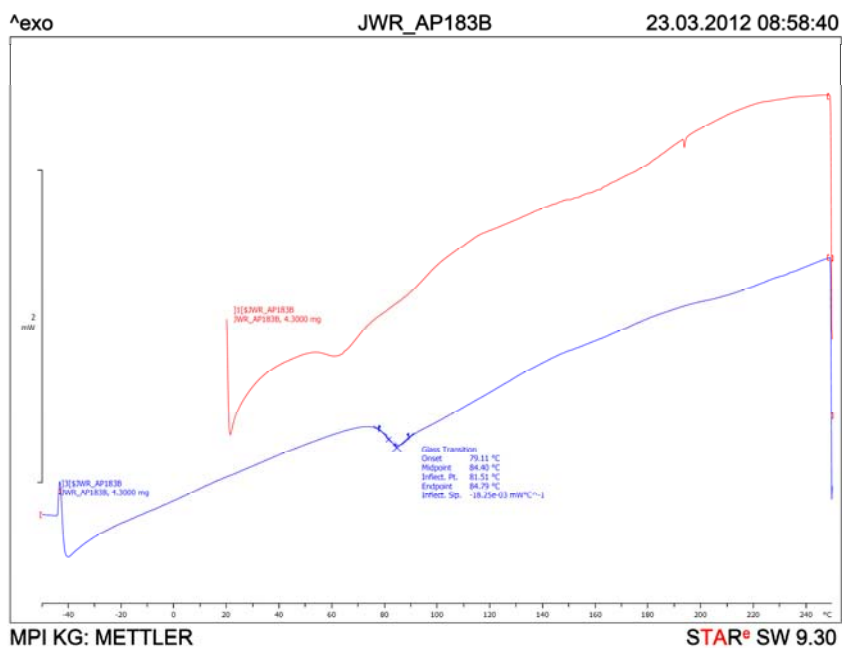
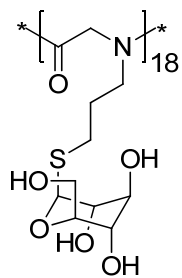
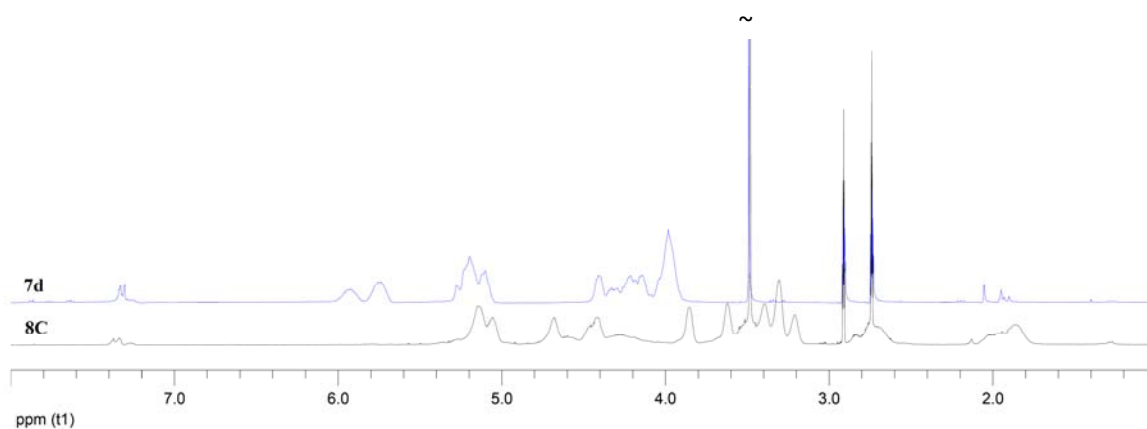


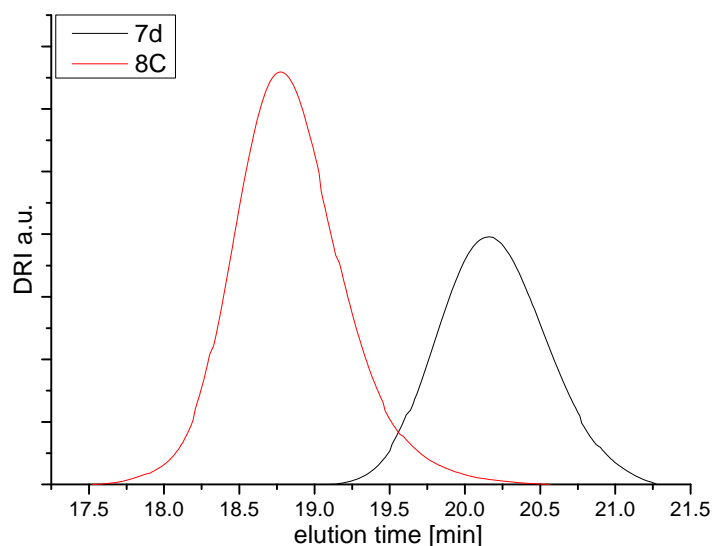
Figure SI-26. DSC heating curves (blue: 2<sup>nd</sup> heating) of **8B** neat.



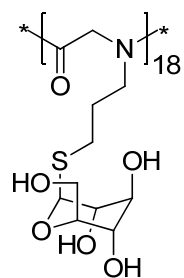
*Side chain modification of 7d with 1-thio-β-D-glucose to 8C.* **7d** (0.124 g; 1.28 mmol) was dissolved in H<sub>2</sub>O (12 mL) and prepared in an Erlenmeyer flask under argon. 1-Thio-β-D-glucose (0.559 g; 2.56 mmol) was added and the mixture was allowed to stir (~20 min). Then 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropio-phenone (HEMP; 6.8 mg; 0.03 mmol) was added followed by glacial acetic acid (0.8 mL) until the aqueous solution was slightly acidic (Litmus paper). The mixture was then irradiated for 24 hours by UV light. The crude mixture was purified with a dialysis membrane (500 Da) against H<sub>2</sub>O. Freeze drying was utilized to remove water. A white material was collected (**8C**; 0.302 g; 75%) and analyzed. <sup>1</sup>H-NMR confirms product with a conversion of ~100%.



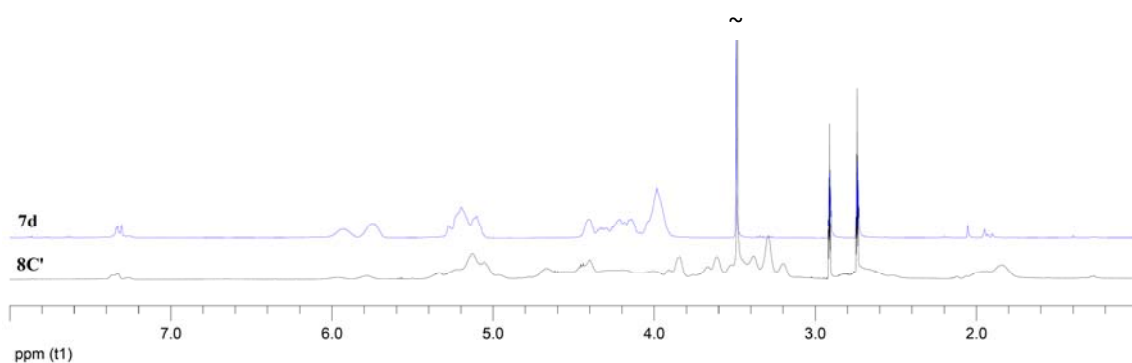
**Figure SI-27.** <sup>1</sup>H NMR spectrum of **8C** compared to **7d** in DMF-d<sub>7</sub>.



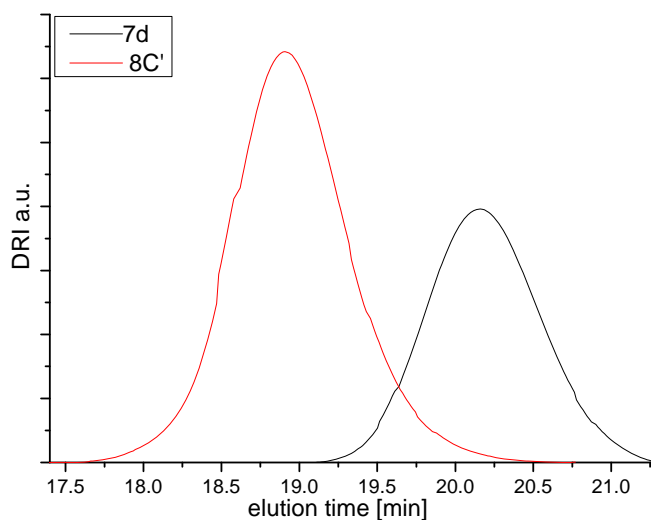
**Figure SI-28.** SEC trace of **8C** compared to **7d** in NMP.



*Side chain modification of 7d with 1-thio- $\beta$ -D-glucose to 8C'. 7d* (0.106 g; 1.09 mmol) was dissolved in H<sub>2</sub>O (10 mL) and prepared in an Erlenmeyer flask under argon. 1-Thio- $\beta$ -D-glucose (0.480 g; 2.20 mmol) was added and the mixture was allowed to stir (~20 min). Then glacial acetic acid (0.8 mL) was added until the aqueous solution was slightly acidic (Litmus paper). The mixture was then irradiated for 24 hours by UV light. The crude mixture was purified with a dialysis membrane (500 Da) against H<sub>2</sub>O. Freeze drying was utilized to remove water. A white material was collected (**8C'**; 0.273 g; 80%) and analyzed. <sup>1</sup>H-NMR confirms product with a conversion of 57%.



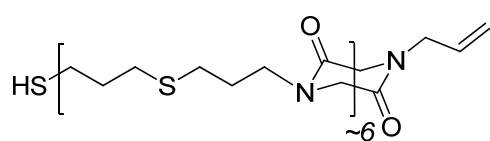
**Figure SI-29.** <sup>1</sup>H NMR spectrum of **8C'** compared to **7d** in DMF-d<sub>7</sub>.



**Figure SI-30.** SEC trace of **8C'** compared to **7d** in NMP.

### Preparation of polydiketopiperazine (**9**).

ADMET attempt to make Poly(hex-3-ene)diketopiperazine (PHKP). The procedure described by Masuda and coworkers was utilized here with the Hoveyda-Grubbs type 2 catalyst.<sup>12</sup> No polymerization was detected by GPC. GC-MS, TLC, and <sup>1</sup>H-NMR all indicate that the monomer is still present with some other by-products which could be the monomer interacting with the catalyst. Masuda and coworkers described in their publication that a six member deactivation state could form with the Ruthenium catalyst and therefore the methylenes should be elongated until such complexes are not possible.



Thio-ene step growth synthesis of Poly(dipropyl-thioether)-diketopiperazine (PSKP<sub>6</sub>). **6** (0.510 g; 2.62 mmol) was combined with 1,3-propanedithiol (0.290 g; 2.68 mmol) in an EtOH:H<sub>2</sub>O (2.5 mL; 2:0.5) mixture. The reaction solution was

then exposed to UV irradiation. Precipitation was observed within 1 hour and the reaction was allowed to stir for an additional 3 hours. The liquids were removed by centrifugation and decantation. The remaining white powder was washed with EtOH (3x) and isolated by the aforementioned technique. High vacuum was utilized to 'dry' the product. Although there was some loss due to a laboratory mishap, we were able to isolate a white powder (**9**; 0.381 g; 24%). <sup>1</sup>H-NMR (DMF-d<sub>7</sub>, 400 MHz) δ 6.53-6.43 (m, 1 H), 6.00 (br t, 1.5 H), 4.76 (br s, 23 H), 4.73 (s), 4.67 (s), 4.23 (t, 20 H), 3.36 (t, 22 H), 3.27 (t, 21 H), 2.60 (q, 32 H), 2.12 (t, 1 H), 2.03 (d, 1.5 H); <sup>13</sup>C NMR (DMF-d<sub>7</sub>, 400 MHz) δ 164.6, 132.9, 118.1, 50.5, 47.8, 45.2, 34.5, 34.14, 27.4, 23.4; FT-IR (crystal) ν<sub>max</sub> 2912, 1640, 1478, 1438, 1335, 1283, 1216, 1156, 1017, 983, 876, 837, 764, 725 cm<sup>-1</sup>; TGA thermally stable until 300 °C; DSC inflection point 6 °C.

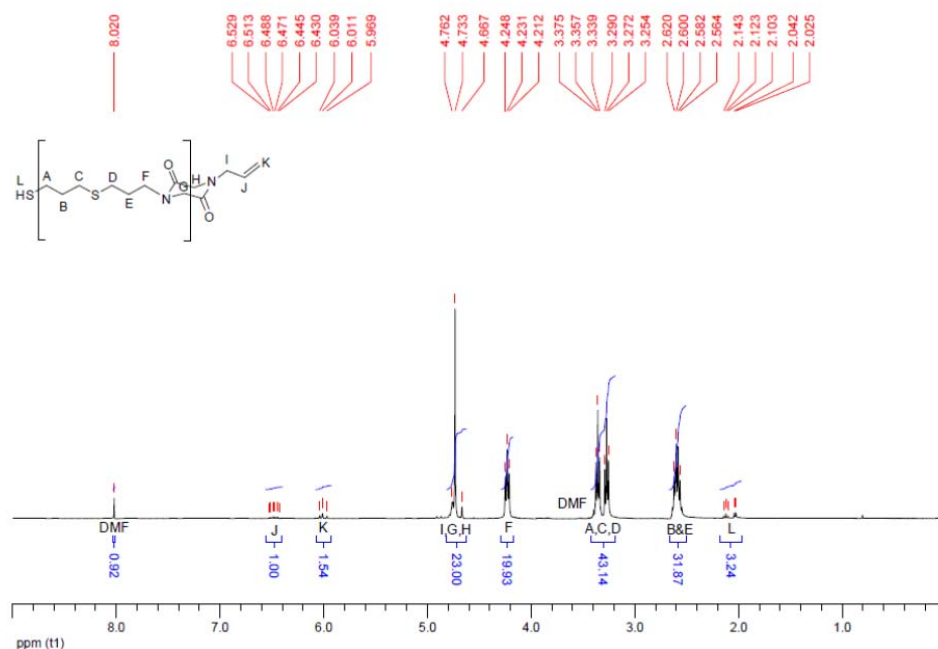


Figure SI-31. <sup>1</sup>H NMR spectrum of **9** in DMF-d<sub>7</sub>.

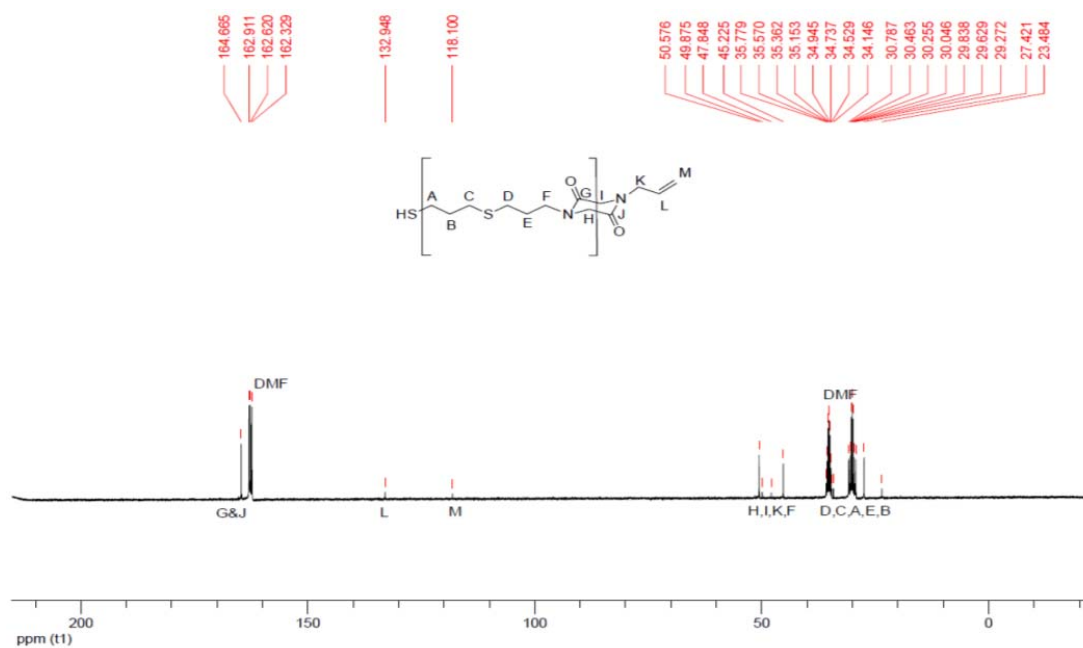


Figure SI-32.  $^{13}\text{C}$  NMR spectrum of 9 in DMF- $d_7$ .

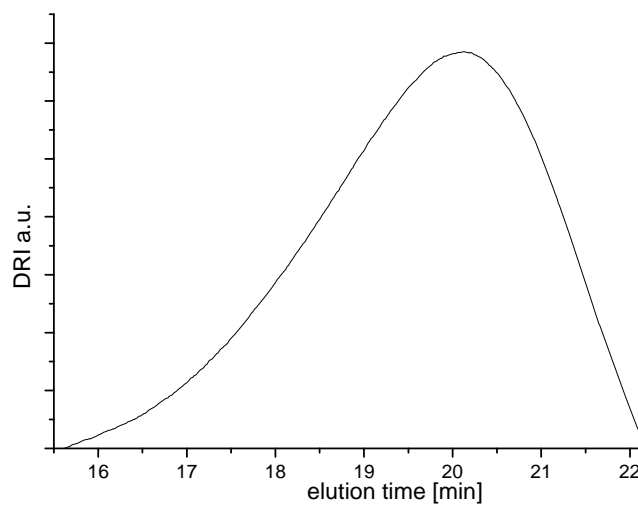


Figure SI-33. SEC trace of 9 in NMP.



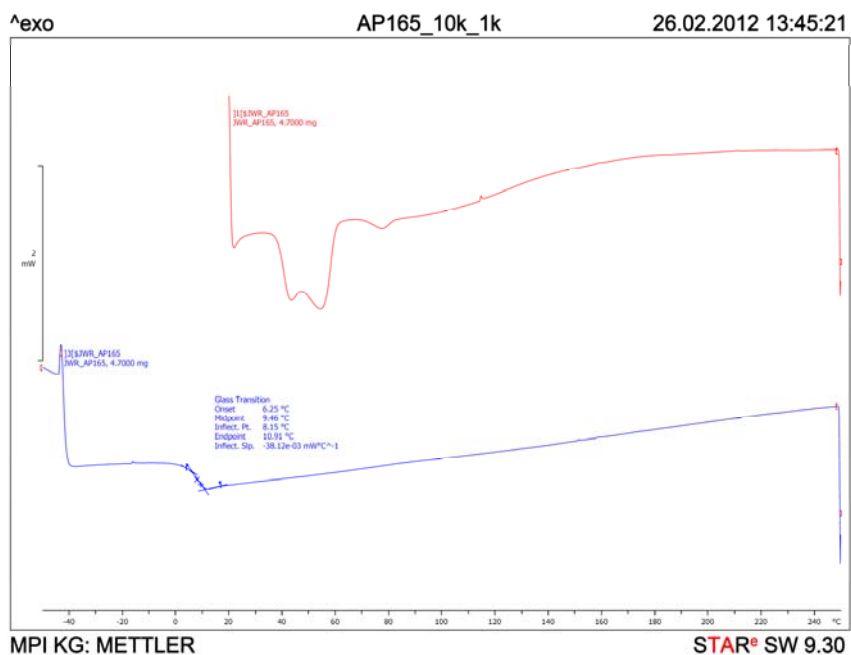


Figure SI-34. DSC heating curves (blue: 2<sup>nd</sup> heating) of 9 neat.

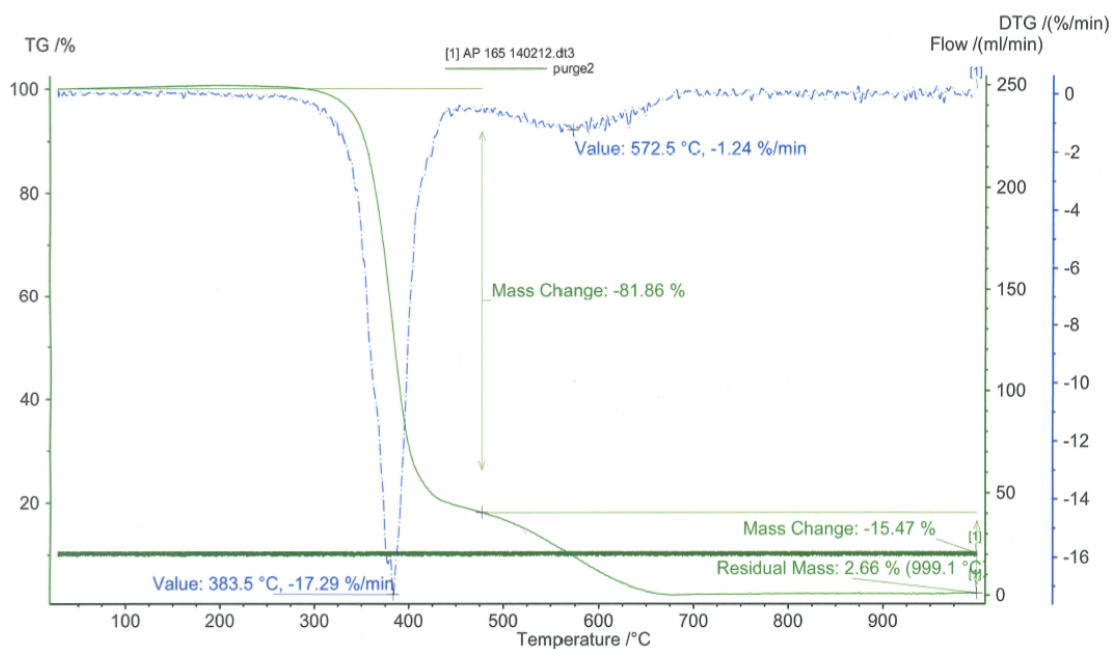


Figure SI-35. TGA curve of 9 neat.

## References and notes

1. H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J Org Chem*, 1997, **62**, 7512-7515.
2. J. F. Reichwein and R. M. J. Liskamp, *Eur. J. Org. Chem.*, 2000, 2335-2344.
3. Adjusted moles to account for previously mentioned diethyl ether impurity.
4. L. Guo and D. H. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 18072-18074.
5. C. Fetsch, A. Grossmann, L. Holz, J. F. Nawroth and R. Luxenhofer, *Macromolecules*, 2011, **44**, 6746-6758.
6. Slow and careful heating improves the separation of product **5** (73 °C) from by-product (bp 65 °C).
7. *N*-allyl glycine NCA would readily lead to oligomerization, and unknown side products, upon exposure to air contact and/or impurities found in solvents. Interestingly, our investigations with *N*-methyl and *N*-propargyl glycine NCAs indicate a greater stability to ambient conditions. In general, all glassware should be clean and dry. Also, scratched glassware should be avoided, or treated with a silylating agent. We have found that the *N*-allyl glycine NCA can be stored at -20 °C, in a properly prepared flask, under argon and heptanes, for up to 6 months without decomposition. Alternatively, the crude cyclization mixture (CH<sub>2</sub>Cl<sub>2</sub>, PCl<sub>3</sub>, etc.) allows for short term storage (1 month) at 5 °C.
8. H. Hioki, H. Kinami, A. Yoshida, A. Kojima, M. Kodama, S. Takaoka, K. Ueda and T. Katsu, *Tetrahedron Letters*, 2004, **45**, 1091-1094.
9. *N*-methyl glycine NCA was originally utilized to determine the "ideal solvent" conditions for these *N*-substituted polyglycines. The preliminary investigations suggested that out of the solvents explored (THF, 1,4-dioxane, DMF, NMP, and CH<sub>2</sub>Cl<sub>2</sub>) dichloromethane readily produced well defined polymers with near full incorporation and with polydispersities <1.2. Although, the monomer to initiator feed ratio was targeting low molecular weights (20 to 40 repeating units). Further work with *N*-allyl glycine NCA suggested that the polymerization does not proceed past ~46 repeating units due to unknown side reactions with the monomer. This work was omitted.
10. Luxenhofer's recent publication suggested that utilizing 10% by w/w for targeting 50 repeating units leads to high incorporation of less sterically hindered NCAs. Our investigations with **7g** suggest that the polymers are highly soluble in benzonitrile. We were able to obtain concentrations as high as 15% w/w.
11. The internal pressure of the reaction flask was reduced everytime a sample was taken for analysis.
12. K. Terada, E. B. Berda, K. B. Wagener, F. Sanda and T. Masuda, *Macromolecules*, 2008, **41**, 6041-6046.