# Supplementary Information

## Homoallylglycine residues are superior precursors to orthogonally modified thioether containing polypeptides

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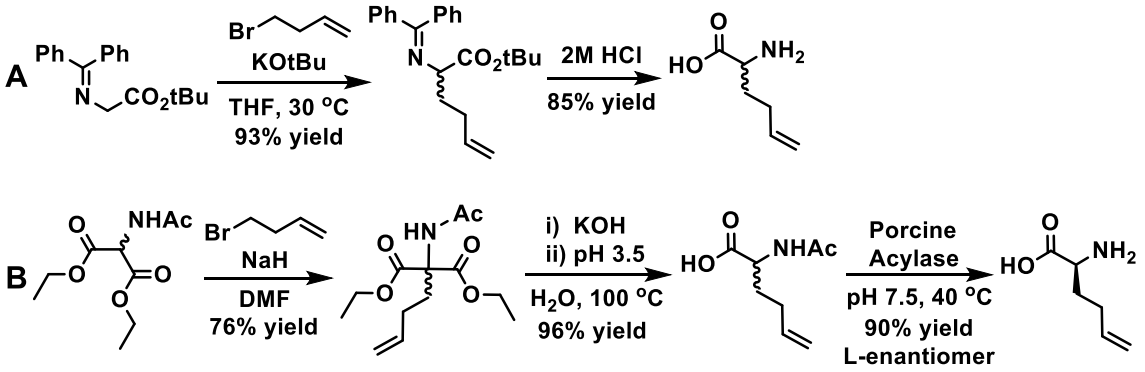
### Materials and methods

Unless specified, all post-polymerization modification chemistry was performed in glass vials under ambient atmosphere. Thiol-ene reactions were performed in 1 dram screw top glass vials capped with septa to allow sparging. An Exo Terra Repti-Glo 5.0 compact fluorescent tropical terrarium lamp was used as the ultraviolet light source. Small molecule chemistry was performed in heat-dried glassware under a nitrogen atmosphere, unless otherwise specified. THF and hexanes were degassed with dinitrogen and passed through an alumina column before use. All other reagents and solvents were used as received. Unless otherwise specified, all reactions were performed at ambient temperature (ca. 20 °C). In-house deionized water was used for all aqueous chemistry and dialysis unless otherwise specified. Circular dichroism (CD) spectroscopy was performed on samples prepared using deionized water filtered through a Millipore Milli-Q Biocel A10 filter system unless otherwise specified. CD spectra were collected using 0.1 or 0.5 mg/mL solutions of polypeptide on an Olis DSM 10 spectrophotometer using a 0.1 cm path length quartz cuvette. Percent α-helical content of polypeptides was estimated using the formula % α-helix = $100 \times (-[\theta]_{222} + 3000)/39000)$, where $[\theta]_{222}$ is the measured molar ellipticity at 222 nm. Thin-layer chromatography was performed with EMD gel 60 F254 plates (0.25 mm thickness) and spots were visualized using a UV lamp or $KMnO_4$ stain. Silicycle Siliaflash G60 silica (60-200 μm) was used for all column chromatography. Silica used for chromatographic purification of NCA monomers was dried under vacuum at 250 °C for 48 hours and then stored in a dinitrogen filled glovebox. Compositions of mobile phases used for chromatography and compositions of solvent systems used for circular dichroism are given in volume percents. Dialysis was performed with regenerated cellulose tubing obtained from Spectrum labs. NMR spectra were recorded on a Bruker AV400 instrument with chemical shifts reported relative to the deuterated solvent used. Infrared spectra of solution samples were collected using a Perkin Elmer 1605 FT-IR Spectrophotometer. Solid state FTIR spectra were collected using a Perkin Elmer Spectrum One FT-IR Spectrophotometer with a Perkin Elmer Universal ATR Sampling Accessory. DART-MS spectra were collected on a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source at the low desorption setting and a Vapur Interface (IonSense). Both the source and MSD were controlled by Excalibur v. 3.0. Analytes were dissolved 1 mg/mL in 1:3 THF:MeCN and

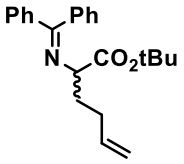
spotted onto OpenSpot sampling cards (IonSense). Ionization was accomplished using He plasma with no additional ionization agents. Mass calibration was carried out using Pierce LTQ Velos ESI (+) and (-) Ion calibration solutions (Thermo Fisher Scientific). Tandem gel permeation chromatography/light scattering (GPC/LS) was performed at 25 $^{o}$C using an SSI Accuflow Series III pump equipped with Wyatt DAWN EOS light scattering and Optilab REX refractive index detectors. Separations were achieved using 100 Å and 1000 Å PSS-PFG 7 μm columns at 30 ºC with 0.5% (w/w) KTFA in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as eluent and sample concentrations of 10 mg/ml. Enantiomeric excess of L-Hag was measured against a racemic standard using an Agilent 1260 Infinity HPLC. Separations were achieved using a Chiralpak AD-H 5 μm column with 10% isopropanol in hexanes as eluent and sample concentrations of 1 mg/ml. Melting points were measured using a DigiMelt MPA160 SRS melting point apparatus with a ramp rate of 5 $^{o}$C/minute.

*Abbreviations: N*-carboxyanhydride (NCA), degree of polymerization (DP), L-methionine (Met), poly(L-methionine) (**M**), ( L-homoallylglycine (Hag), poly(L-homoallylglycine) (**G$^{HA}$**), DL-homoallylglycine (*rac*-Hag), poly(DL-homoallylglycine) ((***rac*-G$^{HA}$**)) , 2,2-dimethoxy-2-phenylacetophenone (DMPA), α-methoxy-ω-isocyanoethyl-poly(ethylene glycol) (PEG-NCO), monomer to initiator ratio (M:I), dispersity ($M_w/M_n$ or *Đ*), methyl iodide (MeI), ultraviolet light irradiation (*h*ν), molecular weight cutoff (MWCO), deionized (DI), room temperature (RT), equivalents (eq), isopropyl alcohol (IPA), acetonitrile (MeCN), tetrahydrofuran (THF), methanol (MeOH), ethyl acetate (EtOAc), glacial acetic acid (AcOH), formic acid (HCOOH), (+/-) camphorsulfonic acid (CSA), diethyl ether ($Et_2O$), dichloromethane (DCM), potassium tert-butoxide (KOtBu), tert-butyl hydroperoxide (TBHP), *N,N*-Dimethylformamide (DMF), 2-[2-(2-methoxyethoxy)ethoxy]ethanethiol ($mEG_3SH$), 2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]ethanethiol ($mEG_4SH$), 1-mercapto-11-hydroxy-3,6,9-trioxaundecane ($EG_4SH$), $mEG_3SH$ modified poly(L-homoallylglycine) (**mEG$_3$-G$^{HA}$**), $mEG_4SH$ modified poly(L-homoallylglycine) (**mEG$_4$-G$^{HA}$**), $EG_4SH$ modified poly(L-homoallylglycine) (**EG$_4$-G$^{HA}$**), $mEG_4SH$ modified poly(DL-homoallylglycine) (**mEG$_4$-(*rac*-G$^{HA}$)**), 1-thio-β-D-glucopyranose tetraacetate modified poly(L-homoallylglycine) (**Glc(OAc)$_4$-G$^{HA}$**), 1-thio-β-D-glucopyranose modified poly(L-homoallylglycine) (**Glc-G$^{HA}$**), rotary evaporation (rotovap), broad (br), doublet (d), doublet of doublets (dd), doublet of doublet of quartets (ddq), doublet of quartets (dq), doublet of triplets (dt), multiplet (m), pentet (pent), quartet (q), singlet (s), triplet (t), Direct Analysis in Real Time Mass Spectrometry (DART-MS).

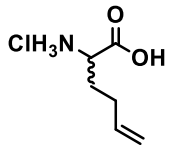
## 1. Synthesis of amino acids and NCA monomers



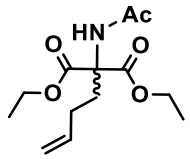

**Scheme S1.** Synthesis of homoallylglycine amino acids. (A) *rac*-Hag NCA (B) Hag NCA.



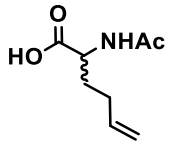

**N-(Diphenylmethylene)-DL-homoallylglycine *tert*-butyl ester.** This compound was synthesized by following a previously reported method.[1] A 10% THF solution of potassium *tert*-butoxide (1.9 g, 17 mmol) was added dropwise to a 10% THF solution of N-(diphenylmethylene)-glycine *tert*-butyl ester (2.5 g, 8.5 mmol) at -70 °C (EtOAc/liquid nitrogen bath). After 15 minutes, 2.0 mL (20 mmol) 3-butenyl bromide was added via syringe. The reaction was let warm to ambient temperature then transferred to a 30 °C water bath and let stir overnight. The reaction was then let cool to ambient temperature and quenched with 30 mL of saturated ammonium chloride solution. The resulting layers were partitioned in a separatory funnel, and the aqueous layer was then extracted with 4 x 25 mL DCM. Combined organic extracts were washed with brine, dried with anhydrous sodium sulfate, and volatiles were removed under reduced pressure. The resulting oil was purified by silica gel chromatography with 8 % EtOAc in hexanes as mobile phase. Solvent was removed under reduced pressure to yield the product as a pale yellow oil (2.8 g, 93% yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.68-7.56 (br m, 2H), 7.52-7.29 (br m, 6H), 7.21-7.12 (br m, 2H), 5.80-5.66 (dq, J = 27.2, 6.1 Hz, 1H), 5.00-4.86 (br m, 2H), 3.93, (t, J = 6.2 Hz, 1H) 2.15-1.93 (br m, 4H), 1.44 (s, 9H).



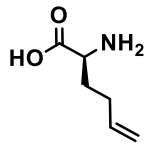

**DL-Homoallylglycine hydrochloride, *rac*-Hag.** This compound was synthesized by following a previously reported method.[1] N-(Diphenylmethylene)-DL-homoallylglycine *tert*-butyl ester (1.72 g) was suspended in 27.5 mL of 2 M aqueous HCl, and stirred rapidly at ambient temperature for 3 hours. The suspension became a clear solution in 60 minutes and a yellow oil began to separate. Organic byproducts were removed by washing the reaction mixture with 3 x 20 mL DCM. The aqueous layer was then concentrated under reduced pressure and further concentrated under high vacuum to give the product as a white solid (654 mg, 85 % yield). $^1$H NMR (400 MHz, $D_2O$, 25 °C): δ 5.82-5.71 (br m, 1H), 5.08-5.01 (dq, J = 17.2, 1.6 Hz, 1H) 5.01-4.96 (dd, J = 11.8, 8.8 Hz, 1H), 3.87 (t, J = 12.5 Hz, 1H), 2.14-2.06 (q, J = 7.0 Hz, 2H), 2.01-1.81 (br m, 2H). Spectral data were consistent with previously published results.[1]




**Diethyl 2-homoallyl-2-acetamidomalonate.** This compound was synthesized by following a previously reported method.[2] A solution of diethyl 2-acetamidomalonate (45 g, 210 mmol, 1.0 eq) in DMF (300 mL) was prepared in a round bottom flask and capped with a septum. Separately, a suspension of 60 % NaH (9.1 g, 230 mmol, 1.1 eq) in DMF (100 mL) was prepared in a Schlenk flask and stirred in an ambient temperature water bath under $N_2$ atmosphere. The malonate solution was slowly cannula transferred into the NaH suspension (caution: exothermic). The resulting mixture was stirred 10 min. 3-Butenyl bromide (23 mL, 230 mmol, 1.1 eq) was then added in one portion via syringe. The mixture was stirred for 16 h on a 60 °C oil bath, and then quenched with AcOH (2 mL) and concentrated by rotary evaporation, then using high vacuum. The residue was dissolved in $Et_2O$ (250 mL) and washed with $H_2O$ (2 x 200 mL), and then the organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. This crude material was purified by column chromatography (25-35% EtOAc/hexanes) to provide diethyl 2-homoallyl-2-acetamidomalonate as a pale yellow solid (43 g, 76 % yield). $R_F$ = 0.32; 25% EtOAc/hexanes. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.79 (s, 1 H), 5.75 (ddq, *J* = 17.1, 10.3, 6.5 Hz, 1 H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1 H), 4.97 (dq, *J* = 10.2, 1.5 Hz, 1 H), 4.25 (q, *J* = 7.1 Hz, 4 H), 2.45 (m, 2 H), 2.04 (s, 3 H), 1.92 (m, 2 H), 1.25 (t, *J* = 7.0, 6 H).

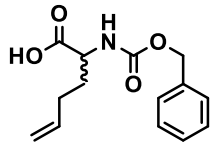



***N*-acetyl-DL-homoallylglycine.** This compound was synthesized by following a previously reported method.[2] Diethyl 2-homoallyl-2-acetamidomalonate (13 g, 49 mmol) was suspended in aqueous 1 N KOH (2.6 eq). The mixture was refluxed with vigorous stirring. The initially biphasic mixture became homogenous after *ca*. 30 min. Heating was maintained for 3 h in total. The mixture was adjusted to pH 3.5 (temperature compensated) with conc. HCl. The mixture was then refluxed for an additional 1 h. The pH was then adjusted again back to pH 3.5 using conc. HCl (*Note:* the pH rises as the decarboxylation progresses). The mixture was again refluxed for an additional 2 h then allowed to cool to ambient temperature. The solution was then concentrated to about 2/3 its original volume by rotary evaporation. The resultant amber mixture was treated with activated charcoal (12 mL of powder). After stirring for 10 min, the suspension was filtered. The colorless filtrate was adjusted to pH 2.0 with conc. HCl. This mixture was then extracted with 4 x 80 mL of EtOAc. The organic extracts were dried over $Na_2SO_4$ and concentrated by rotary evaporation to provide *N*-acetyl-DL-homoallylglycine (7.7 g, 96 % yield) as a colorless solid. $^1$H NMR (400 MHz, $D_2O$, 25 °C): δ 5.89 (ddq, *J* = 17.2, 10.3, 6.8 Hz, 1 H), 5.12 (dq, *J* = 17.2, 1.7 Hz, 1 H), 5.06 (m, 1 H), 4.35 (dd, *J* = 9.5, 4.7 Hz, 1 H), 2.21 (m, 2 H), 2.06 (s, 3 H), 2.01 (m, 1 H), 1.86 (m, 1 H).

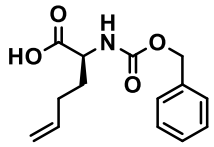



**L-Homoallylglycine.** This compound was synthesized by following a previously reported method.[2] A 300 mM aqueous solution of *N*-acetyl-DL-homoallylglycine (46 g, 290 mmol) containing 5 mM $KH_2PO_4$ was prepared in a Schlenk flask. The solution was adjusted to pH 7.5-8.0 with aqueous 4 N KOH. The mixture was placed in a 40 °C oil bath and degassed by stirring under $N_2$ for 15 min. Porcine amino acylase (4.2 U per mmol of *N*-acetyl-DL-homoallylglycine) was added and the reaction mixture was gently stirred. At selected time points 50 µL aliquots were removed and analyzed using a ninhydrin colorometric assay.[2] The pH of the solution was periodically measured and if necessary readjusted to pH 7.5-8.0 by addition of 4 N KOH. When the ninhydrin assay showed no further increase in amino acid concentration, the resolution reaction was terminated by briefly heating the mixture to 60 $^o$C followed by stirring with activated charcoal (72.5 mL of powder). The mixture was vacuum filtered to yield a colorless filtrate, which was adjusted to pH 1.5 with conc. HCl, and then washed with EtOAc (3 x 490

mL). The aqueous phase was applied onto a Dowex® 50WX8 column (490 mL) and desalted by flushing the column with $H_2O$ until the eluent reached neutral pH followed by desorption of the amino acid by eluting with aqueous 1.0 N $NH_3$. L-Homoallylglycine was recovered as a colorless solid after rotary evaporation followed by lyophilization (15.3 g, 92 % yield based on amount of *N*-acetyl-L-homoallylglycine). $^1$H NMR (400 MHz, 0.5 % TFA-d/$D_2O$, 25 °C): δ 5.80 (m, 1 H), 5.09 (m, 1 H), 5.02 (m, 1 H), 4.02 (m, 1 H), 2.15 (m, 2 H), 2.0 (m, 2 H). $[\alpha]_D^{24}$ = +27.4 (c 1.00, 1 N HCl). Spectral data were consistent with previously published results.[2]




**N-(Carbobenzyloxy)-DL-homoallylglycine.** DL-Homoallylglycine hydrochloride (104 mg, 0.64 mmol) was dissolved in DI water (9.0 mL). Sodium bicarbonate (586 mg, 7.0 mmol) was added to the resulting solution and the reaction mixture was let stir at room temperature for 10 minutes. The reaction was then cooled to 0 °C and benzyl chloroformate (144 mg, 0.84 mmol) was added dropwise. The reaction was let warm to room temperature overnight with vigorous stirring. The reaction mixture was transferred to a separatory funnel and washed with 4 x 6 mL $Et_2O$. The aqueous layer was then brought to pH 2 with 3M HCl and extracted with 4 x 5 mL EtOAc. The EtOAc extracts were dried with $Na_2SO_4$, decanted, concentrated under reduced pressure and further concentrated under vacuum to give a white solid (79.4 mg, 48 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.42-7.28 (br m, 5H), 6.02-5.68 (br m, 1H), 5.32-4.92 (br m, 5H), 4.51-4.22 (br m, 1H), 2.22-2.10 (q, J = 7.1 Hz, 2H), 2.10-1.72 (br m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 177.3, 156.1, 136.6, 136.1, 128.6, 128.3, 128.2, 116.1, 67.2, 53.3, 31.5, 29.4. MP = 104.0-105.2 °C.




**N-(Carbobenzyloxy)-L-homoallylglycine.** L-Homoallylglycine (58 mg, 0.46 mmol) was dissolved in 1M sodium bicarbonate (5 mL) and let stir for 10 minutes. The reaction was then cooled to 0 °C and benzyl chloroformate (108 mg, 0.63 mmol) was added dropwise. The reaction was let warm to room temperature overnight with vigorous stirring. The reaction mixture was transferred to a separatory funnel and washed with 4 x 3 mL $Et_2O$. The aqueous layer was then brought to pH 2 with 3M HCl and extracted

with 4 x 2 mL EtOAc. The EtOAc extracts were dried with $Na_2SO_4$, decanted, concentrated under reduced pressure and further concentrated under vacuum to give a white solid (90 mg, 75 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.40-7.29 (br m, 5H), 6.06-5.65 (br m, 1H), 5.37-4.88 (br m, 5H), 4.52-4.18 (br m, 1H), 2.25-2.09 (q, J = 7.1 Hz, 2H), 2.09-1.71 (br m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 177.3, 156.1, 136.6, 136.1, 128.6, 128.3, 128.2, 116.1, 67.2, 53.3, 31.6, 29.4. MP = 69.3-71.8 °C.

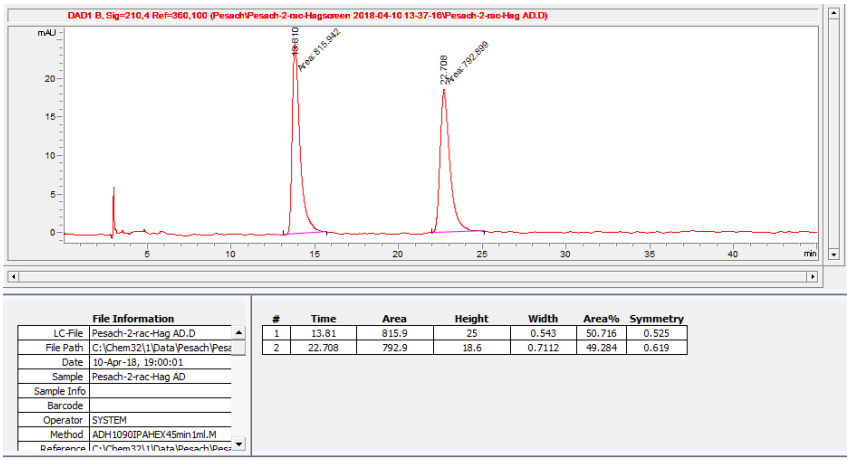



**Figure S1.** Chiral HPLC chromatogram of N-(carbobenzyloxy)-DL-homoallylglycine.

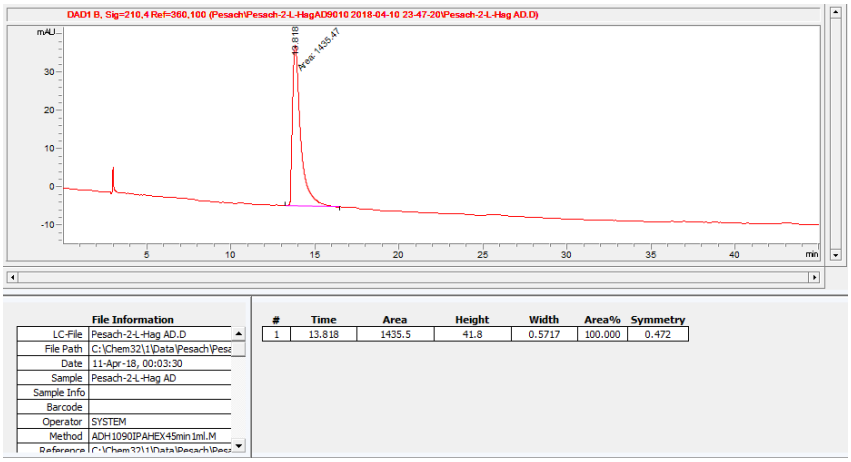
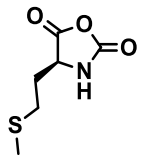


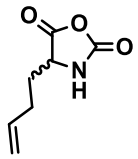

**Figure S2.** Chiral HPLC chromatogram of N-(carbobenzyloxy)-L-homoallylglycine.

**Amino acid *N*-carboxyanhydride (NCA) monomer syntheses.** NCA monomers were prepared using a previously established method.[3] ***Caution! Phosgene is extremely hazardous and all manipulations must be performed in a well-ventilated chemical fume hood with proper personal protection and necessary***

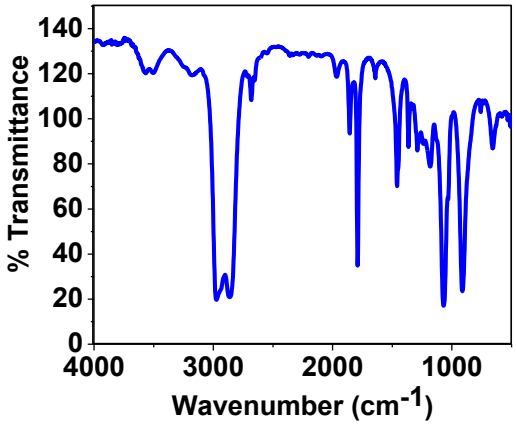
***precautions taken to avoid exposure.*** After evaporation of crude reaction mixtures to dryness using a Schlenk manifold, crude products, in sealed Schlenk flasks under vacuum, were brought into a dinitrogen filled glovebox for purification. The method of purification varied for each monomer, as detailed below.



**L-Methionine *N*-carboxyanhydride, Met NCA.** Purified via column chromatography using 33 % THF in hexanes. Spectral data were consistent with previously published results.[3]



**DL-Homoallylglycine *N*-carboxyanhydride, *rac*-Hag NCA.** Purified via column chromatography using 33 % THF in hexanes. DL-Homoallylglycine hydrochloride (590 mg) was used to prepare *rac*-Hag NCA, which was obtained as a colorless solid (408 mg, 73 % yield). $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.40 (s, 1H), 5.84-5.71 (br m, 1H), 5.18-5.08 (m, 2H), 4.37-4.31 (m, 1H), 2.33-2.20 (q, J = 6.9 Hz, 2H), 2.13-2.03 (m, 1H), 1.93 (pent, J = 7.1 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 169.7, 153.0, 135.6, 117.3, 57.1, 30.8, 29.1. DART-MS m/z = 154.05 $[M - H]^-$ (calcd for $C_7H_8O_3N$: 154.05). MP = 63.8-65.4 °C.



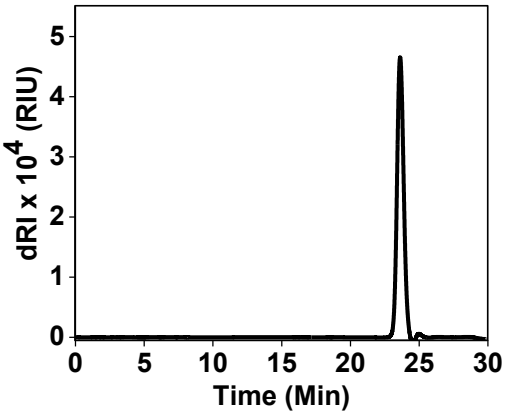
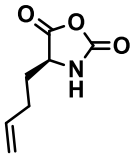
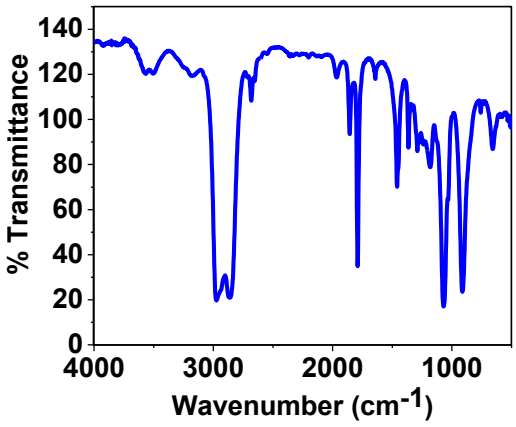



**Figure S3.** TOP: FTIR spectrum of *rac*-Hag NCA (50 mg/mL in THF). Note NCA bands at 1856 and 1790 $cm^{-1}$, and alkene stretch at 1642 $cm^{-1}$. BOTTOM: SEC Chromatogram of *rac*-Hag NCA in 0.5% (w/w) KTFA in HFIP. RIU = arbitrary refractive index units.



**L-Homoallylglycine *N*-carboxyanhydride, Hag NCA.** Purified via column chromatography using 33 % THF in hexanes, followed by 2x recrystallization from THF/hexanes at -35 °C. L-Homoallylglycine (460 mg) was used to prepare Hag NCA, which was obtained as a white solid (370 mg, 66 % yield). $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.51 (s, 1H), 5.85-5.70 (br m, 1H), 5.18-5.07 (m, 2H), 4.37-4.31 (br m, 1H), 2.33-2.20 (br m, 2H), 2.13-2.03 (m, 1H), 1.93 (pent, J = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 169.7, 153.0, 135.5, 117.4, 57.1, 30.8, 29.2 DART-MS m/z = 154.05 $[M - H]^-$ (calcd for $C_7H_8O_3N$: 154.05). MP = 41.6-43.1 °C.



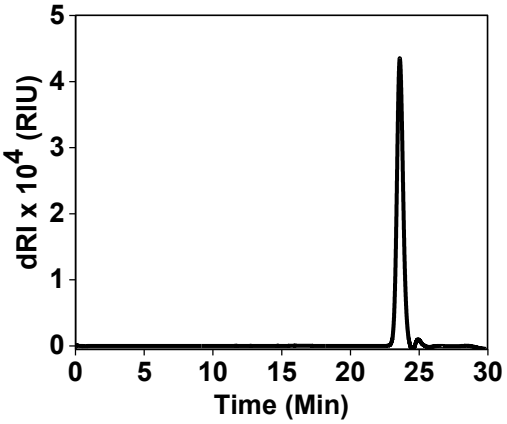



**Figure S4.** TOP: FTIR spectrum of Hag NCA (50 mg/mL in THF). Note NCA bands at 1856 and 1790 $cm^{-1}$, and alkene stretch at 1642 $cm^{-1}$. BOTTOM: SEC chromatogram of Hag NCA in 0.5% (w/w) KTFA in HFIP. RIU = arbitrary refractive index units.

## 2. Homopolymerizations of Hag and *rac*-Hag NCAs

**General Procedure for Polymerization of Hag NCA.** All polymerization reactions were performed in a dinitrogen filled glove box using anhydrous solvents. To a solution of Hag NCA in THF (164 mg, 1.05 mmol, 25 mg/mL) was added a solution of $Co(PMe_3)_4$ in THF (970 µL, 52.5 µmol). Once mixed, the reaction was let stand at ambient temperature for 1-2 h, and completion of polymerization was confirmed by FTIR. Polymerization at all different monomer to initiator feed ratios used were found to be complete within 2 h. The completed reaction was removed from the glove box and 1-2 drops of 3 M HCl were added. The polymer was then precipitated with DI water, centrifuged at 3000 rpm, and the supernatant was discarded. The pellet was washed 3 times with DI water and then lyophilized to yield poly(L-homoallylglycine), $\mathbf{G^{HA}}$, as a white solid (105 mg, 95 % yield). $^1$H NMR (400 MHz, TFA-d, 25 °C): δ 5.87-5.70 (dq, J = 17.7, 14.2 Hz, 1H), 5.17-5.01 (br m, 2H), 4.74-4.70 (dd, J = 8.4, 7.0 Hz, 1H), 2.28-2.08 (br m, 2H), 2.07-1.87 (br m, 2H).

| M:I | $M_n$ ($^1$H NMR) | DP ($^1$H NMR) | $M_w/M_n$ | Yield (%) |
|---|---|---|---|---|
| 20 | 6100 | 55 | N/A | 92 |
| 40 | 12400 | 112 | N/A | 81 |
| 60 | 18800 | 169 | N/A | 93 |
| 80 | 27200 | 245 | N/A | 90 |

**Table S1.** Synthesis of $\mathbf{G^{HA}}$ at different monomer to initiator ratios (M:I) using $Co(PMe_3)_4$ initiator in THF at 20 °C. DP = number average degree of polymerization determined for PEG-NCO end-capped chains using $^1$H NMR integrations. Yield is the total isolated yield of purified polypeptide. N/A = not determined due to insolubility of $\mathbf{G^{HA}}$ in 0.5% (w/w) KTFA in HFIP.

**General procedure for polymerization of *rac*-Hag NCA.** All polymerization reactions were performed in a dinitrogen filled glove box using anhydrous solvents. To a solution of *rac*-Hag NCA in THF (173 mg, 1.11 mmol, 25 mg/mL) was added a solution of $Co(PMe_3)_4$ in THF (1.00 mL, 55.0 μmol). Once mixed, the reaction was let stand at ambient temperature for 2 h, and completion of polymerization was confirmed by FTIR. Only polymerizations with M:I ratios up to 20:1 were found to go to completion within 2 hours, polymerizations at higher M:I ratios did not go to completion even after many hours. After 2 hours, the reaction was removed from the glove box and 1-2 drops of 3 M HCl were added. The polymer was then precipitated with DI water, centrifuged at 3000 rpm, and the supernatant was discarded. The pellet was washed 3 times with DI water and then lyophilized to yield poly(DL-homoallylglycine), **(*rac*-$G^{HA}$)**, as a white solid (100 mg, 85 % yield). $^1$H NMR (400 MHz, TFA-d, 25 °C): δ 5.92-5.72 (br m, 1H), 5.17-5.01 (br m, 2H), 4.74 (br s, 1H), 2.34-2.13 (br m, 2H), 2.13-1.89 (br m, 2H).

| M:I | Monomer Conversion | DP | $M_w/M_n$ | Yield (%) |
|---|---|---|---|---|
| 20 | Complete | 44 | 1.13 | 96 |
| 40 | Incomplete | N/A | N/A | 87 |
| 60 | Incomplete | N/A | N/A | 65 |
| 80 | Incomplete | N/A | N/A | 63 |

**Table S2.** Synthesis of **(*rac*-$G^{HA}$)** at different monomer to initiator ratios (M:I) using $Co(PMe_3)_4$ initiator in THF at 20 °C. DP = number average degree of polymerization. Yield is the total isolated yield of purified polypeptide. N/A = Not determined due to incomplete polymerization reaction.

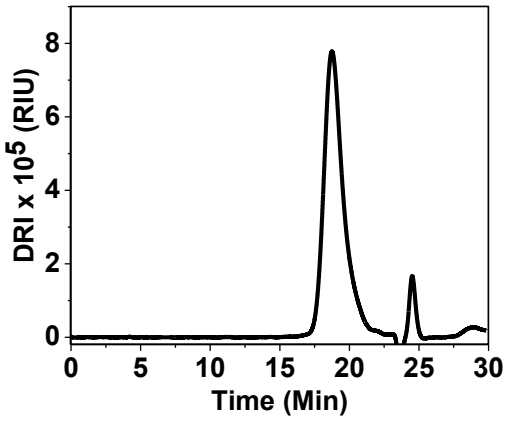



**Figure S5.** GPC Chromatogram of **(*rac*-$G^{HA}$)$_{43}$** in 0.5% (w/w) KTFA in HFIP. RIU = arbitrary refractive index units.

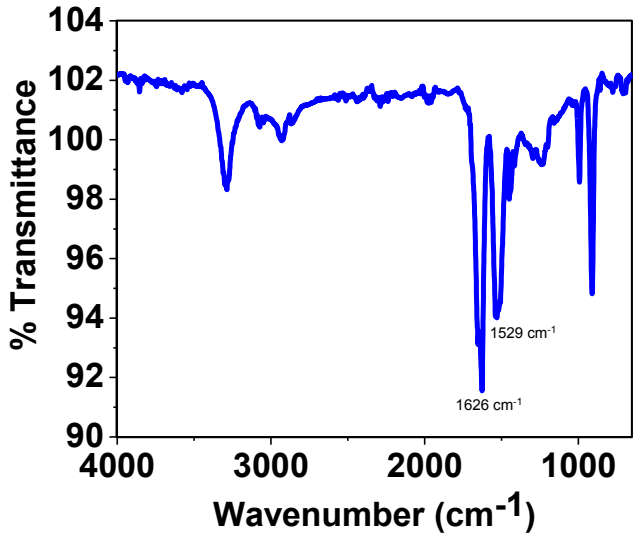
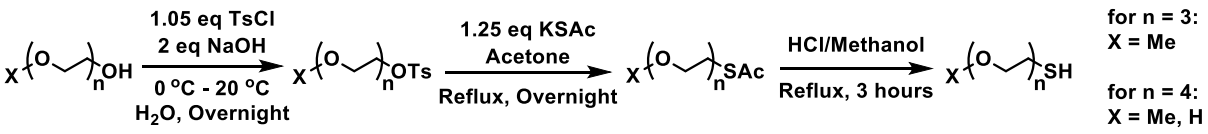


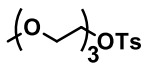

**Figure S6.** Solid state FTIR of **(*rac*-G$^{HA}$)$_{43}$**. The Amide I and Amide II bands at 1626 and 1529 cm$^{-1}$, respectively, are characteristic of a β-Sheet conformation.

**General procedure for endcapping of polypeptides with PEG chains.** The general procedure for polymerization of Hag NCA was followed. Once the reaction was determined to be complete by FTIR, a solution of α-methoxy-ω-isocyanoethyl-poly(ethylene glycol), PEG-NCO (MW = 1000 Da, 4 eq per $Co(PMe_3)_4$) in THF was added to the polymerization mixture inside a dinitrogen filled glovebox. The reaction was let stand overnight, and then removed from the glovebox. 1-2 drops of 3M HCl were then added and the reaction was precipitated with water, centrifuged at 3000 rpm and the supernatant was discarded. The pellet was washed 3 times with DI water to remove unconjugated PEG-NCO, and the resulting pellet was then lyophilized to yield PEG-endcapped polypeptide as a white solid. To determine the molecular weight of the polypeptides ($M_n$), $^1$H NMR spectra were obtained in deuterated trifluoroacetic acid (TFA-d) or deuterated chloroform ($CDCl_3$) containing 1-2 drops of TFA-d. Similar to procedures described in literature,[4] the integral of the alkene proton resonance of **G$^{HA}$** at 5.17-5.01 ppm was compared to the integral of the polyethylene glycol resonance at δ 4.01 (TFA-d) or δ 3.64 ($CDCl_3$/ TFA-d) to obtain **G$^{HA}$** lengths (see spectral data section).

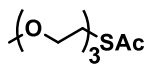
### 3. Thiol-ene modification of G$^{HA}$ and (*rac*-G$^{HA}$) homopolypeptides



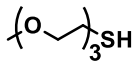

**Scheme S2.** Synthesis of oligoethylene glycol thiols.



**p-Toluenesulfonyl triethylene glycol methyl ether.** This compound was synthesized using a previously reported procedure.[5] $H_2O$ (10.0 mL) was added to triethylene glycol monomethyl ether (3.21 g, 19.5 mmol) and NaOH (1.56 g, 39.0 mmol). Tosyl chloride (2.89 g, 20.5 mmol) was dissolved in THF (10.0 mL) and added dropwise over ice with stirring. The reaction was let warm to ambient temperature overnight. Diethyl ether (20.0 mL) was then added to the reaction and the mixture was taken up into a separatory funnel and partitioned. The aqueous layer was washed with diethyl ether (3 x 5.00 mL) then the combined organic fractions were washed with $H_2O$ (3 x 20.0 mL). The organic layer was dried with anhydrous sodium sulfate, decanted and evaporated to dryness to give the product as a clear oil (4.08 g, 79 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.81-7.77 (d, J = 8.3 Hz, 2H), 7.35-7.31 (d, J = 8.0 Hz, 2H), 4.17-4.13 (m, 2H), 3.70-3.48 (br m, 10H), 3.36 (s, 3H), 2.44 (s, 3H).

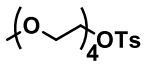


**2-[2-(2-Methoxyethoxy)ethoxy]ethanethioacetate.** This compound was synthesized using a previously reported procedure.[6] p-Toluenesulfonyl triethylene glycol methyl ether (3.80 g, 14.2 mmol) and potassium thioacetate (2.02 g, 17.7 mmol) were dissolved in a round bottom flask containing acetone (150 mL). A reflux condenser was added and the reaction was stirred vigorously overnight at 50 °C. Solvent was removed via vacuum and the resulting mixture was dissolved in a biphasic mixture of 30 mL DCM and 30 mL $H_2O$, taken up into a separatory funnel, and partitioned. The aqueous layer was washed with 2 x 30 mL DCM and combined organics were washed with 10 mL brine. The organic layer was dried with anhydrous sodium sulfate, decanted, and evaporated to dryness to give the product as a yellow oil (2.64 g, 90 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.66-3.52 (br m, 10H), 3.37 (s, 3H), 3.09 (t, J = 6.5 Hz, 2H), 2.33 (s, 3H).

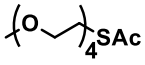


**2-[2-(2-Methoxyethoxy)ethoxy]ethanethiol, mEG$_3$SH.** This compound was synthesized using a previously reported procedure.[7] Methanol (20.0 mL) and conc. HCl (1.50 mL) were added to a sealed pressure tube containing 2-[2-(2-methoxyethoxy)ethoxy]ethanethioacetate (2.06 g, 10.0 mmol). The reaction mixture was stirred at 100 $^o$C for 3 hours. The reaction was let cool to ambient temperature and then $H_2O$ (20.0 mL) was added. This mixture was extracted with 3x 15.0 mL DCM. Combined organic extracts were then washed with 3x 15.0 mL $H_2O$ and 1x 15 mL brine, dried with anhydrous sodium

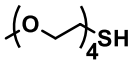
sulfate, decanted, and evaporated to dryness to give the product as a yellow oil (1.37 g, 83 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.68-3.53 (br m, 10H), 3.38 (s, 3H), 2.73-2.66 (dt, J = 8.2, 6.5 Hz, 2H), 1.58 (t, J = 8.2 Hz, 1H).



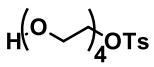
**p-Toluenesulfonyl tetraethylene glycol methyl ether.** The procedure for synthesis of p-toluenesulfonyl triethylene glycol methyl ether was followed. Tetraethylene glycol monomethyl ether (4.23 g) was used to prepare the product, obtained as a clear oil (4.18 g, 66 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 7.83-7.76 (d, J = 8.2 Hz, 2H), 7.36-7.30 (d, J = 8.1 Hz, 2H), 4.15 (t, J = 9.7 Hz, 2H), 3.70-3.51 (br m, 14H), 3.37 (s, 3H), 2.44 (s, 3H).



**2-[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]ethanethioacetate.** The procedure for synthesis of 2-[2-(2-methoxyethoxy)ethoxy]ethanethioacetate was followed. p-toluenesulfonyl tetraethylene glycol methyl ether (2.74 g) was used to prepare the product, obtained as a dark yellow oil (2.00 g, 90 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.67-3.52 (br m, 14H), 3.37 (s, 3H), 3.08 (t, J = 6.5 Hz, 2H), 2.33 (s, 3H).

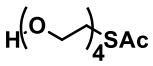


**2-[2-[2-(2-Methoxyethoxy)ethoxy]ethoxy]ethanethiol, mEG$_4$SH.** The procedure for synthesis of 2-[2-(2-methoxyethoxy)ethoxy]ethanethiol was followed. 2-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-ethanethioacetate (1.31 g) was used to prepare the product, obtained as a pale yellow oil (851 mg, 78 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.67-3.49 (br m, 14H), 3.35 (s, 3H), 2.71-2.61 (m, 2H), 1.57 (t, J = 8.2 Hz, 1H).

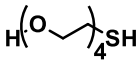


**Tetraethylene glycol monotosylate.** This compound was synthesized using a previously reported procedure.[8]. Tetraethylene glycol (23.4 g, 120. mmol) was added to 100 mL round bottom flask and dissolved in THF (4.3 mL). NaOH (727 mg, 18.2 mmol) was added as solution in 4.3 mL $H_2O$. Tosyl chloride (2.23 g, 12.0 mmol) was dissolved in THF (14.0 mL) and added dropwise over ice with stirring. The reaction was stirred at 0 $^o$C for 3 hours then diluted with ice water (70 mL). The mixture was

extracted with 3x 45 mL DCM. The combined organic fractions were washed with 2 x 130 mL DI water, dried with anhydrous sodium sulfate, decanted, and evaporated to dryness to give the product as a pale yellow oil (3.69 g, 87 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 7.82-7.77 (d, J = 8.3 Hz, 2H), 7.36-7.30 (dd, J = 8.5 Hz, 0.58 Hz, 2H), 4.16 (t, J = 4.8 Hz, 2H), 3.80-3.50 (br m, 14H), 2.44 (s, 3H) 2.17 (br s, 1H).

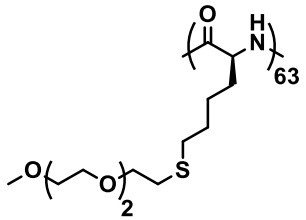



**Tetraethylene glycol monothioacetate.** The procedure for synthesis of 2-[2-(2-methoxyethoxy)-ethoxy]ethanethioacetate was followed. Tetraethylene glycol monotosylate (3.69 g) was used to prepare the product, further purification (column chromatography with 100 % ethyl acetate) was required to obtain the product as a yellow oil (1.76 g, 57 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.74-3.55 (br m, 14H), 3.09 (t, J = 6.5 Hz, 2H), 2.33 (s, 3H) 2.29 (br s, 1H).

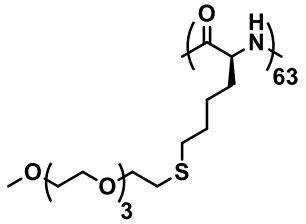



**1-Mercapto-11-hydroxy-3,6,9-trioxaundecane, $EG_4SH$.** The procedure for synthesis of 2-[2-(2-methoxyethoxy)ethoxy]ethanethiol was followed. Tetraethylene glycol monothioacetate (200 mg) was used to prepare the product, obtained as a pale yellow oil (95 mg, 58 % yield). $^1$H NMR (400 MHz, $CDCl_3$, 25 $^o$C): δ 3.75-3.55 (br m, 14H), 2.71-2.61 (dt, J = 8.1 Hz, J = 6.5 Hz, 2H), 2.11 (br s, 1H), 1.62 (t, J = 8.2 Hz, 1H).

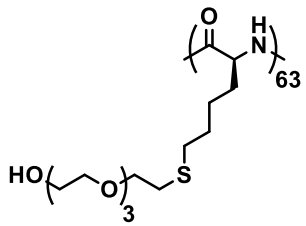
**General procedure for thiol-ene modification of $G^{HA}$.** A sample of $G^{HA}$ (*ca*. 7 mg) and DMPA (0.2 eq per $G^{HA}$ residue) were placed in a 1 dram screw top vial. THF was then added to give a 4 mg/mL polymer concentration. The desired thiol was then added via micropipette (3 eq per Hag residue) and the solution was degassed by sparging with $N_2$ for 10 minutes. The vial was then covered with parafilm and the solution was irradiated with UV light for 2.5 hours (Exo Terra Reptile Lamp) and let stir overnight. The solution was then transferred to a 2000 MWCO dialysis bag and dialyzed against methanol for 24 hours with one change of dialysate, followed by dialysis in water for 24 hours with one water change. The dialyzed polymer was lyophilized to dryness to give the product as a white solid.



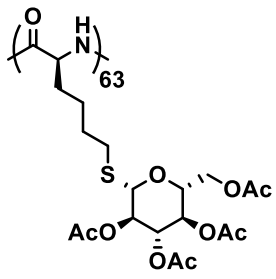
**$mEG_3$-$G^{HA}_{63}$.** The general procedure for thiol-ene modification of $\mathbf{G^{HA}}$ was followed. $\mathbf{G^{HA}_{63}}$ (6.5 mg) and $mEG_3SH$ (3 eq per Hag residue) were used to prepare the product, obtained as a white solid (14.1 mg, 83 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 4.89-4.53 (br m, 1H), 4.22-3.77 (br m, 10H), 3.75-3.02 (br m, 5H), 3.02-2.60 (br m 2H), 2.23-1.43 (br m, 6H).



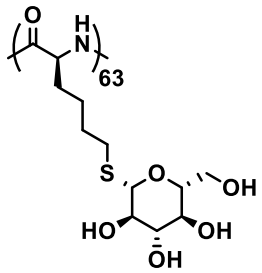
**$mEG_4$-$G^{HA}_{63}$.** The general procedure for thiol-ene modification of $\mathbf{G^{HA}}$ was followed. $\mathbf{G^{HA}_{63}}$ (7.5 mg) and $mEG_4SH$ (3 eq per Hag residue) were used to prepare the product, obtained as a white solid (16.3 mg, 89 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 4.99-4.58 (br m, 1H), 4.25-3.80 (br m, 14H), 3.80-2.55 (br m, 7H), 2.31-1.46 (br m, 6H).



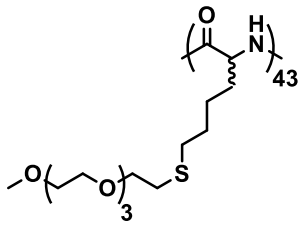
**$EG_4$-$G^{HA}_{63}$.** The general procedure for thiol-ene modification of $\mathbf{G^{HA}}$ was followed. $\mathbf{G^{HA}_{63}}$ (7.5 mg) and $EG_4SH$ (3 eq per Hag residue) were used to prepare the product, obtained as a white solid (16.3 mg, 89 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 4.95-4.50 (br m, 1H), 4.27-3.60 (br m, 14H), 3.59-2.54 (br m, 4H), 2.20-1.43 (br m, 6H).



**Glc(OAc)$_4$-G$^{HA}_{63}$.** The general procedure for thiol-ene modification of **G$^{HA}$** was followed. **G$^{HA}_{63}$** (10.8 mg) and 1-Thio-β-D-glucose tetraacetate (3 eq per Hag residue) were used to prepare the product, obtained as a white solid (38.6 mg, 84 % yield). $^1$H NMR (400 MHz, $CDCl_3$/TFA-d, 25 $^o$C): δ 5.32 (t, J = 9.3 Hz, 1H), 5.15 (t, J = 9.6 Hz, 1H), 5.03 (t, J = 9.6, 1H), 4.59-4.48 (br d, J = 10. Hz, 1H), 4.43 (br s, 1H), 4.24 (br s, 2H), 3.83-3.70 (br d, J = 9.8 Hz, 1H), 2.75-2.55 (br d, J = 6.8 Hz, 2H), 2.20-1.97 (br m, 12H), 1.78-1.17 (br m, 6H).




**Glc-G$^{HA}_{63}$.** This deprotection follows a previously reported method that was used for a different glycopolymer.[9] **Glc(OAc)$_4$-G$^{HA}_{63}$** (10 mg) was dissolved in 1:2 DCM:MeOH (1 mL). An aqueous solution of hydrazine monohydrate (65 % (w/w), 4 eq per acetyl group) was added via syringe and the mixture was stirred. Shortly after the addition of hydrazine monohydrate, a white precipitate formed. The reaction was let stir overnight, after which 1-2 drops of acetone were added to quench excess hydrazine. $Et_2O$ (2 mL) was added, the product was centrifuged at 3000 rpm, and the supernatant was discarded. The pellet was washed with ether (2 mL). Solvent was removed via vacuum and the product was dissolved in DI water, transferred to a 2000 MWCO dialysis bag, and dialyzed for 48 hours with 2 water changes daily. The dialyzed polymer was lyophilized to dryness to give the product as a white solid (6.2 mg, quantative yield). $^1$H NMR (400 MHz, $D_2O$, 25 $^o$C): δ 4.48-4.34 (br d, J = 9.1 Hz, 1H), 3.95 (br s, 1H), 3.82-3.71 (br d, J = 11.4 Hz, 1H), 3.66-3.54 (br m, 1H), 3.44-3.25 (br m, 3H), 3.25-3.15 (br m, 1H), 2.67 (br s, 2H), 2.04-1.09 (br m, 6H).




**mEG$_4$-(*rac*-G$^{HA}$)$_{43}$.** The general procedure for thiol-ene modification of **G$^{HA}$** was followed. **(*rac*-G$^{HA}$)$_{43}$** (8.0 mg) and $mEG_3SH$ (6 eq per *rac*-Hag residue) were used to prepare the product, obtained as a white solid (16.3 mg, 68 % yield). (93 % functionalization, determined by comparison of alkene 2H integral

(5.17 ppm) to the integral from the oligoethylene glycol group (4.37-3.82)). $^{1}$H NMR (400 MHz, TFA-d, 25 $^{o}$C): δ 5.05-4.53 (br m, 1H), 4.37-3.82 (br m, 14H), 3.82-2.59 (br m, 7H), 2.30-1.50 (br m, 6H).

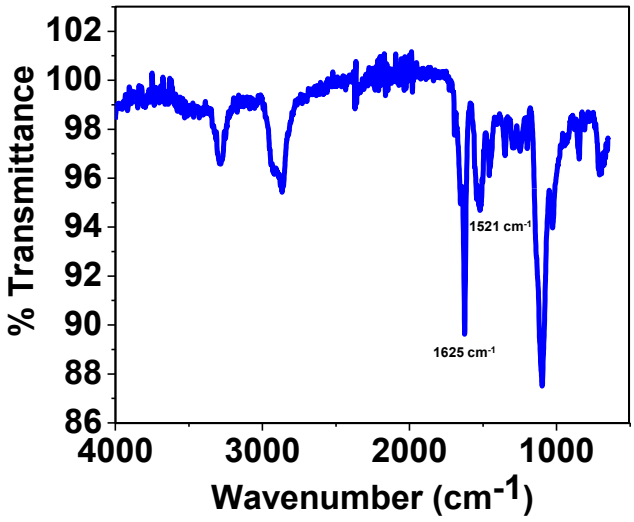



**Figure S7.** Solid state FT-IR of **mEG$_4$-(*rac*-G$^{HA}$)$_{43}$**. The Amide I and Amide II bands at 1625 and 1521 cm$^{-1}$, respectively, are characteristic of a β-Sheet conformation.

**Secondary modification of thiol-ene conjugated polypeptides**

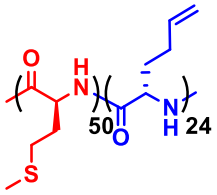
**mEG$_4$-G$^{HAM}_{63}$. mEG$_4$-G$^{HA}_{63}$** (6.6 mg) was suspended in 0.2 M formic acid (330 µL). Methyl iodide was added via syringe (6 eq per mEG$_4$-Hag residue), the reaction was then covered and stirred vigorously for 72 hours. The reaction mixture was transferred to a 2000 MWCO dialysis bag and dialyzed against 0.1 M NaCl for 24 hours, followed by DI water for 24 hours with 2 water changes daily. The dialyzed polymer was then lyophilized to dryness to give the product as a translucent white solid (7.5 mg, 99 % yield). $^{1}$H NMR (400 MHz, $D_2O$, 25 $^{o}$C): δ 4.36 (br s, 1H), 4.05 (br t, J = 5.1 Hz, 3H), 3.84-3.53 (br m, 14H), 3.53-3.27 (br m, 5H), 3.00 (s, 3H), 2.05-1.45 (br m, 6H).

**mEG$_4$-G$^{HAO}_{63}$. mEG$_4$-G$^{HA}_{63}$** (11 mg) and CSA (1.6 mg) were dissolved in DI water (1.1 mL). An aqueous solution of TBHP (70 % (w/w), 16 eq per mEG$_4$-Hag residue) was then added. The reaction was let stir overnight and quenched with 1-2 drops of a saturated aqueous sodium thiosulfate solution. The reaction mixture was transferred to a 2000 MWCO dialysis bag and dialyzed against DI water for 48 hours with 2 water changes daily. The dialyzed polymer was lyophilized to dryness to give the product as

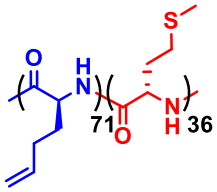
a white solid (8.7 mg, 75 % yield). $^1$H NMR (400 MHz, $D_2O$, 25 $^o$C): δ 4.19 (br s, 1H), 3.93-3.44 (br m, 14H), 3.27 (s, 3H), 3.13-3.00 (br m, 1H), 3.00-2.90 (br m, 1H), 2.90-2.72 (br m, 2H), 1.81-1.29 (br m, 6H).

**4. Synthesis and modification of block copolypeptides**

**Example diblock copolypeptide syntheses**



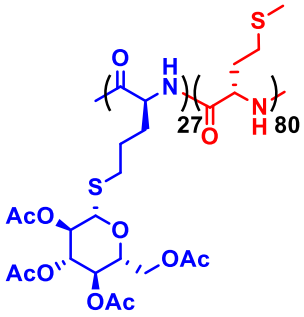
**Poly(L-methionine)$_{50}$-*block*-poly(L-homoallylglycine)$_{24}$, $M_{50}G^{HA}_{24}$.** All polymerization reactions were performed in a dinitrogen filled glove box using anhydrous solvents. To a solution of Met NCA in THF (98.0 mg, 550 μmol, 50 mg/mL) was added a solution of $Co(PMe_3)_4$ in THF (515 μL, 28 μmol). Once mixed, the reaction was let stand at ambient temperature for 1 hour and completion of polymerization was confirmed by FTIR. An aliquot (203 μL) was removed from the reaction and endcapped with PEG-NCO to determine DP of the first block (found DP = 50) (see method above). To the remaining polymerization solution was added a solution of Hag NCA in THF (39.8 mg, 2.60 μmol, 50 mg/mL). The reaction was let stand for 1 hour and completion of polymerization was confirmed by FTIR. The reaction was removed from the glove box and 1-2 drops of 3 M HCl were added. The polypeptide was then precipitated with DI water, centrifuged at 3000 rpm, and the supernatant was discarded. The pellet was washed 3 times with DI water and then lyophilized to yield poly(L-methionine)$_{50}$-*block*-poly(L-homoallylglycine)$_{24}$, $\mathbf{M_{50}G^{HA}_{24}}$ (composition determined by $^1$H NMR), as a white solid (94.4 mg, 99 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 5.92-5.72 (br m, 1H), 5.19-5.05 (br m, 2H), 5.00-4.88 (br m, 2H), 4.79-4.70 (m, 1H), 2.90-2.64 (br m, 4H), 2.40-2.13 (br m 12H), 2.10-1.90 (br m, 2H).



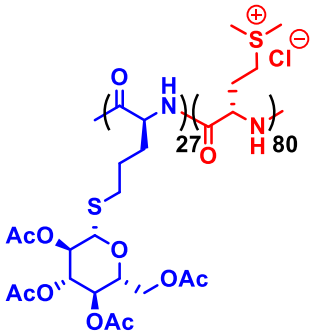
**Poly(L-homoallylglycine)$_{71}$-*block*-poly(L-methionine)$_{36}$, $G^{HA}_{71}M_{36}$.** All polymerization reactions were performed in a dinitrogen filled glove box using anhydrous solvents. To a solution of Hag NCA in THF (20.1 mg, 130 μmol, 25 mg/mL) was added a solution of $Co(PMe_3)_4$ in THF (119 μL, 6.47 μmol). Once mixed, the reaction was let stand at ambient temperature for 1 hour and completion of polymerization was confirmed by FTIR. An aliquot (370 μL) was removed and endcapped with PEG-NCO to determine DP

of the first block (found DP = 71). To the remaining polymerization solution was added a solution of Met NCA in THF (6.83 mg, 39.0 µmol, 50 mg/mL). The reaction was let stand for 1 hour and completion of polymerization was confirmed by FTIR. The reaction was removed from the glove box and 1-2 drops of 3 M HCl were added. The polymer was then precipitated with DI water, centrifuged at 3000 rpm, and the supernatant was discarded. The pellet was washed 3 times with DI water and then lyophilized to yield Poly(L-homoallylglycine)$_{71}$-*block*-poly(L-methionine)$_{36}$, $\mathbf{G^{HA}_{71}M_{36}}$ (composition determined by $^1$H NMR) as a white solid (13.4 mg, 97 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 5.92-5.72 (br m, 2H), 5.19-5.05 (br m, 4H), 5.00-4.88 (br m, 1H), 4.81-4.65 (br m, 2H), 2.90-2.66 (br m, 2H), 2.36-2.13 (br m, 9H), 2.10-1.90 (br m, 4H).

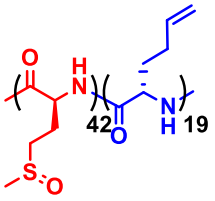
**Modifications of diblock copolypeptides**



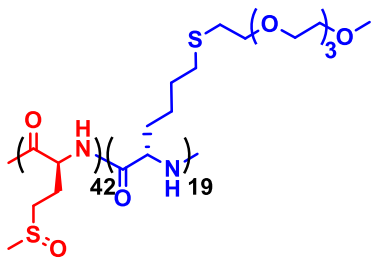

**Glc(OAc)$_4$-G$^{HA}_{27}$M$_{80}$.** $\mathbf{G^{HA}_{27}M_{80}}$ (14.4 mg), 1-Thio-β-D-glucose tetraacetate (8 eq per Hag residue) and DMPA (2.92 mg, 0.4 eq per Hag residue) were placed in a 1 dram screw top vial. THF was then added to give a copolymer concentration of 10 mg/mL. The solution was then degassed via sparging with $N_2$ for 10 minutes. The vial was then covered with parafilm and the solution was irradiated with UV light for 2.5 hours (Exo Terra Reptile Lamp) and let stir overnight. The solution was then transferred to a 2000 MWCO dialysis bag and dialyzed against methanol for 24 hours with one change of dialysate, followed by dialysis against water for 24 hours with one water change. The dialyzed polymer was lyophilized to dryness to give the product as a white solid (20.4 mg, 82 % yield). $^1$H NMR (400 MHz, $CDCl_3$/TFA-d, 25 $^o$C): δ 5.34 (t, J = 9.2 Hz, 1H), 5.18 (t, J = 9.6 Hz, 1H), 5.05 (t, J = 9.6, 1H), 4.61-4.50 (br d, J = 9.6 Hz, 1H), 4.43 (br s, 1H), 4.26 (br s, 5H), 3.83-3.70 (br d, J = 10.1 Hz, 1H), 2.80-2.47 (br m, 8H), 2.33-2.01 (br m, 27H), 1.78-1.21 (br m, 6H).



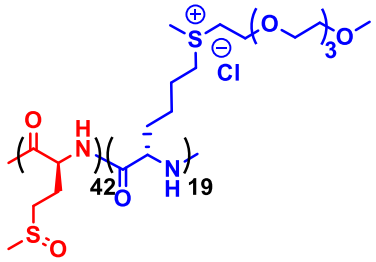
**$Glc(OAc)_4$-$G^{HA}_{27}M^{M}_{80}$.** **$Glc(OAc)_4$-$G^{HA}_{27}M_{80}$** (11.7 mg) was suspended in DI water (1.2 mL). Methyl iodide was added via syringe (6 eq per Met residue), the reaction was then covered and stirred vigorously for 72 hours. The reaction mixture was transferred to a 2000 MWCO dialysis bag and dialyzed against 0.1 M NaCl for 24 hours, followed by DI water for 24 hours with 2 water changes daily. The dialyzed polymer was then lyophilized to dryness to give the product as a translucent white solid (13.0 mg, 95 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 5.80-5.59 (br m 1H), 5.58-5.41 (br m, 1H), 5.41-5.28 (br m, 1H), 5.25-4.94 (br m, 3H), 4.94-4.80 (br m, 1H), 4.80-4.61 (br m, 1H), 4.61-4.41 (br m, 2H), 4.19-3.98 (br m, 1H), 3.97-3.50 (br d, J = 45.2 Hz, 6H), 3.23-3.04 (br d, J = 5.8 Hz, 18H), 2.99-2.49 (br m, 8H), 2.37-2.25 (br m, 12H), 2.10-1.37 (br m, 6H).



**$M^{O}_{42}G^{HA}_{19}$.** A solution of hydrogen peroxide:acetic acid in DI water (3 %:1.5 % (v/v), 2.61 mL) was added to a vial containing **$M_{42}G^{HA}_{19}$** (31.3 mg). The suspension was stirred vigorously overnight, briefly vortexed after 18 hours and let stir for 6 more hours. The reaction was quenched with 1-2 drops of aqueous saturated sodium thiosulfate solution and then transferred to a 2000 MWCO dialysis bag. The reaction mixture was dialyzed against water for 48 hours with two water changes daily. Lyophilization yielded the product as a white, fluffy solid (32.2 mg, 95 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^o$C): δ 5.88-5.72 (br m, 1H), 5.18-5.06 (br m, 2H), 5.05-4.86 (br m, 2H), 4.80-4.64 (br m, 1H), 3.59-3.15 (br m 5H), 3.05-2.95 (br d, J = 7.9 Hz, 7H), 2.81-2.41 (br m , 5H), 2.34-1.89 (br m, 4H).



**$M^{O}_{42}mEG_4\text{-}G^{HA}_{19}$.** **$M^{O}_{42}G^{HA}_{19}$** (8.0 mg), and DMPA (1.9 mg, 0.4 eq per Hag residue) were placed in a 1 dram screw top vial. A mixture of 25% THF in AcOH was then added to give a polymer concentration of 4 mg/mL. $mEG_4SH$ was then added via micropipette (10 eq per Hag residue) and the solution was degassed via sparging with $N_2$ for 10 minutes. The vial was then covered with parafilm and the solution was irradiated with UV light for 2.5 hours (Exo Terra Reptile Lamp) and let stir overnight. The solution was then transferred to a 2000 MWCO dialysis bag and dialyzed against methanol for 24 hours with one change of dialysate, followed by dialysis in water for 24 hours with one water change. The dialyzed polymer was lyophilized to dryness to give the product as a white solid (10.3 mg, 86 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^{o}$C): δ 5.08-4.89 (br m, 2H), 4.85-4.60 (br m, 1H), 4.30-3.79 (br m, 14H), 3.76-3.22 (br m, 9H), 3.07-3.00 (br d, J = 8.1 Hz, 6H), 2.99-2.65 (br m , 4H), 2.65-2.43 (br m, 2H), 2.18-1.49 (br m, 6H).



**$M^{O}_{42}mEG_4\text{-}G^{HAM}_{19}$.** **$M^{O}_{42}mEG_4\text{-}G^{HA}_{19}$** (7.7 mg) was suspended in 0.2 M formic acid (520 µL). Methyl iodide was added via syringe (6.6 eq per $mEG_4$-Hag residue), the reaction was then covered and stirred vigorously for 72 hours. The reaction mixture was transferred to a 2000 MWCO dialysis bag and dialyzed against 0.1 M NaCl for 24 hours, followed by DI water for 24 hours with 2 water changes daily. The dialyzed polymer was then lyophilized to dryness to give the product as a translucent white solid (8.3 mg, 99 % yield). $^1$H NMR (400 MHz, TFA-d, 25 $^{o}$C): δ 5.08-4.86 (br m, 2H), 4.83-4.61 (br m, 1H), 4.24-3.80 (br m, 14H), 3.76-3.56 (br m, 5H), 3.14-3.06 (br s, 3H), 3.04-2.97 (br d, J = 7.9 Hz, 6H), 2.83-2.63 (br m , 2H), 2.60-2.42 (br m, 2H), 2.28-1.56 (br m, 6H).

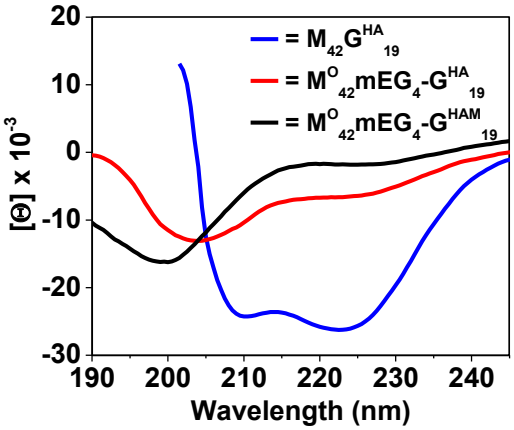



**Figure S8.** Circular dichroism spectra of $\mathbf{M_{50}G^{HA}_{24}}$ and its derivative block copolypeptides at 0.1 mg/mL, 20 °C. $\mathbf{M_{42}G^{HA}_{19}}$ (blue, in THF), $\mathbf{M^{O}_{42}mEG_4\text{-}G^{HA}_{19}}$ (red, in DI water, 25% α-helix), $\mathbf{M^{O}_{42}mEG_4\text{-}G^{HAM}_{19}}$ (black, in DI water, 12% α-helix). The derivative $\mathbf{M^{O}_{42}G^{HA}_{19}}$ possessed poor solubility in both organic and aqueous solvents and was not analyzed.

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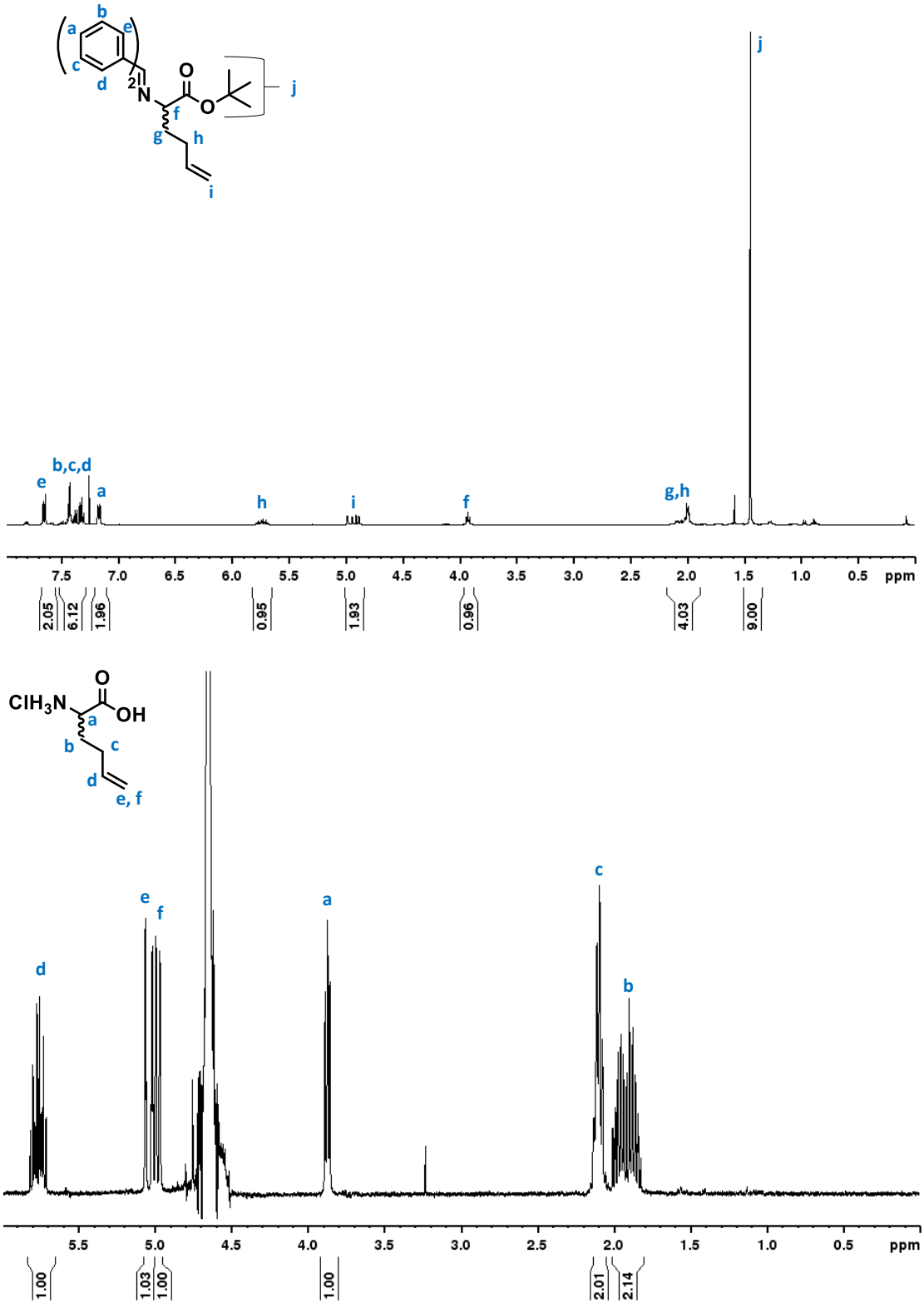
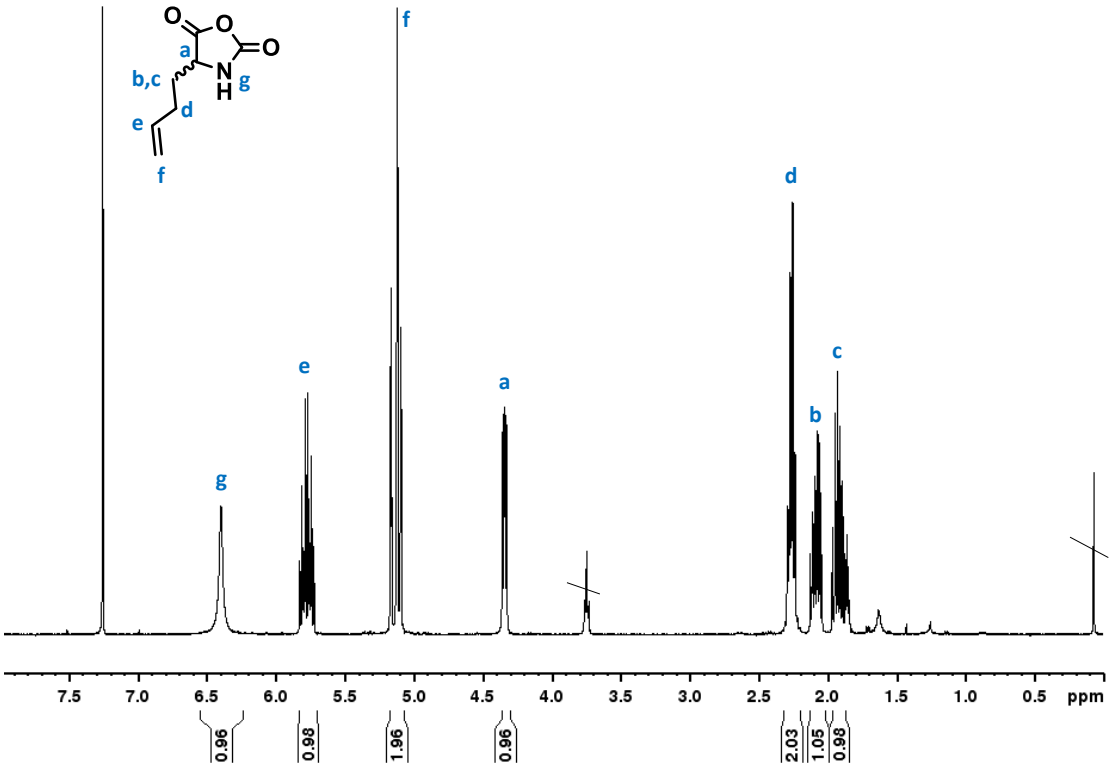
## NMR Spectral Data

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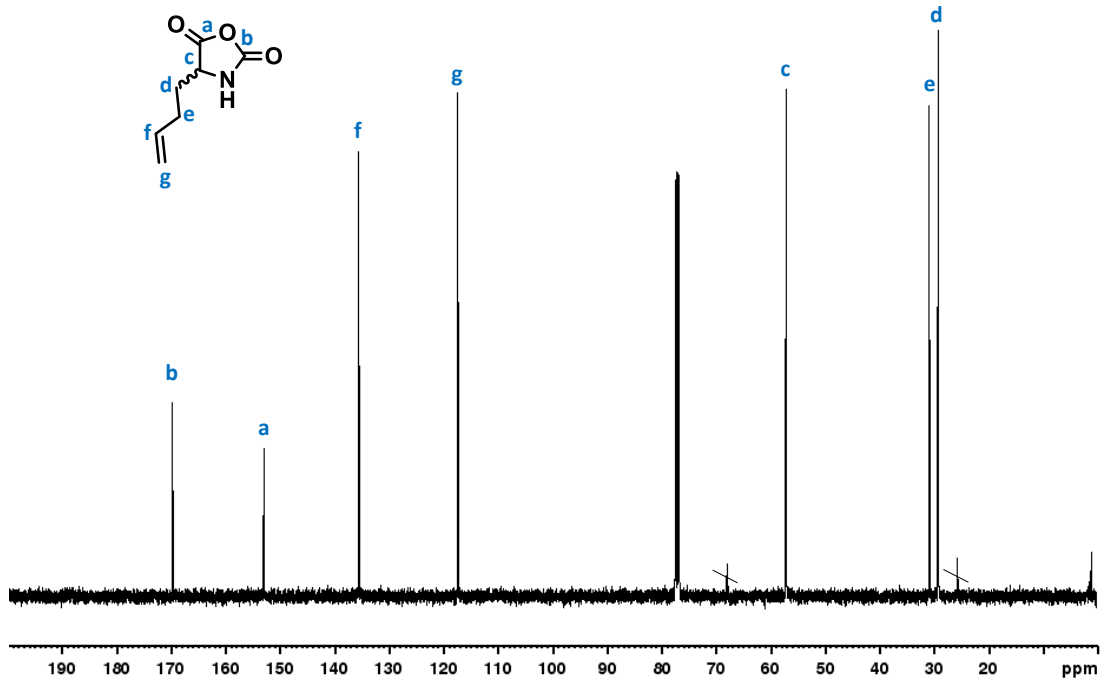
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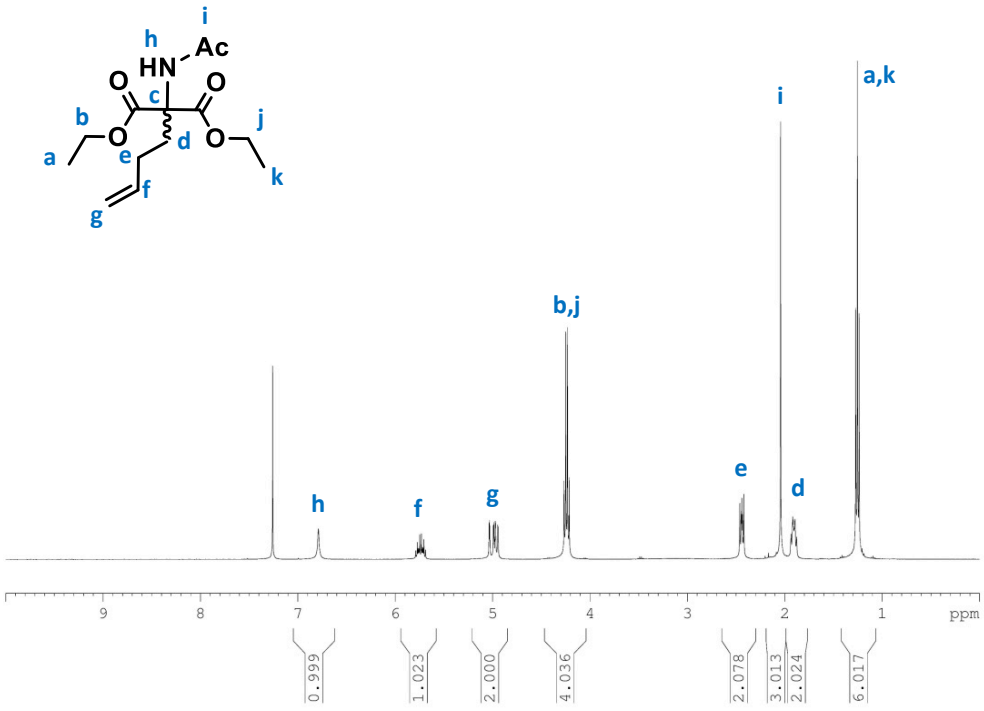
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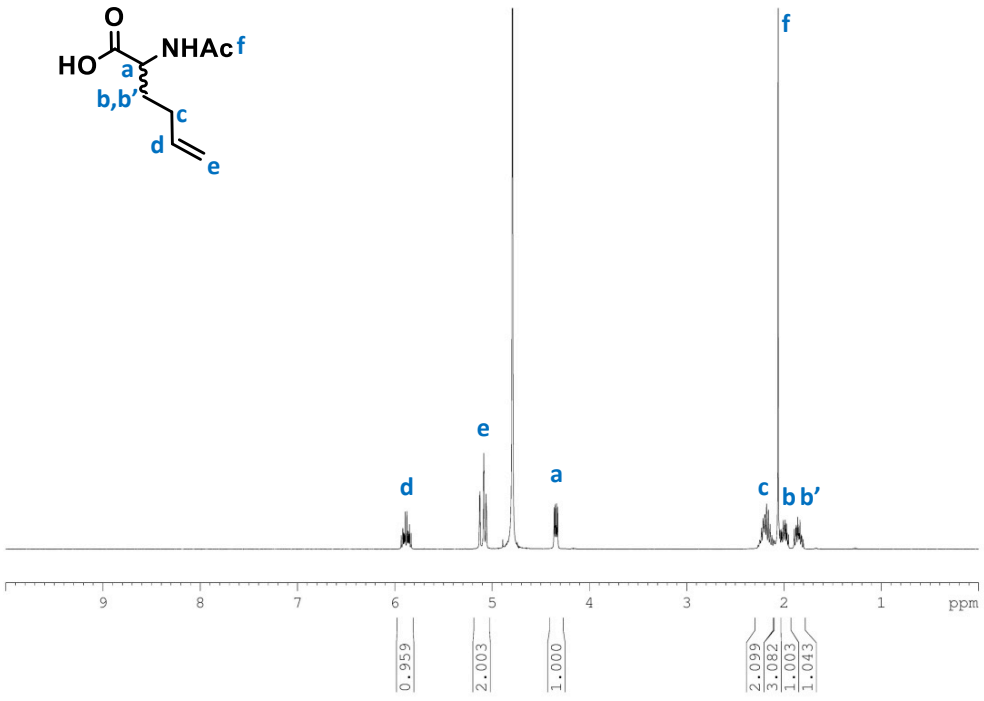
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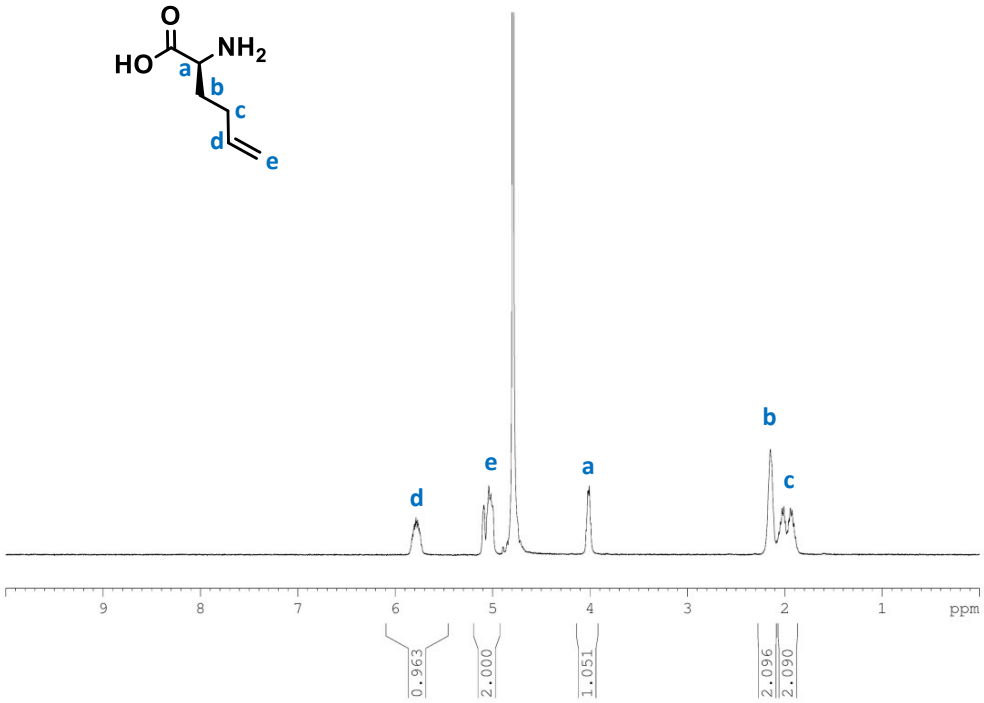
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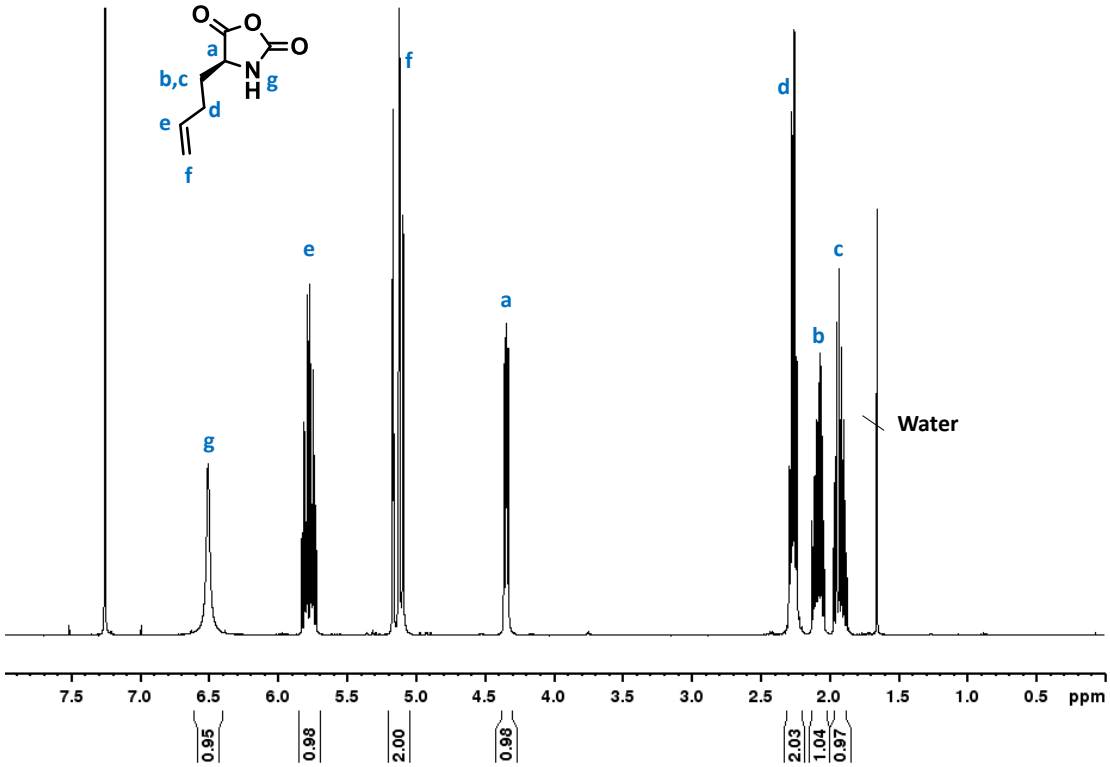
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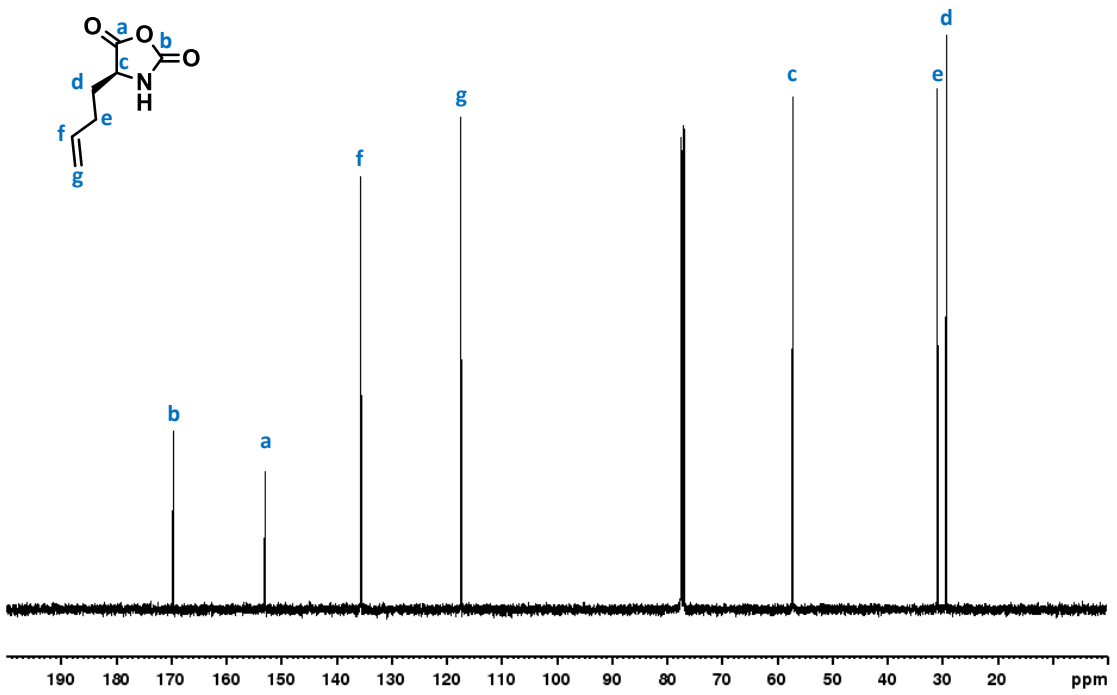
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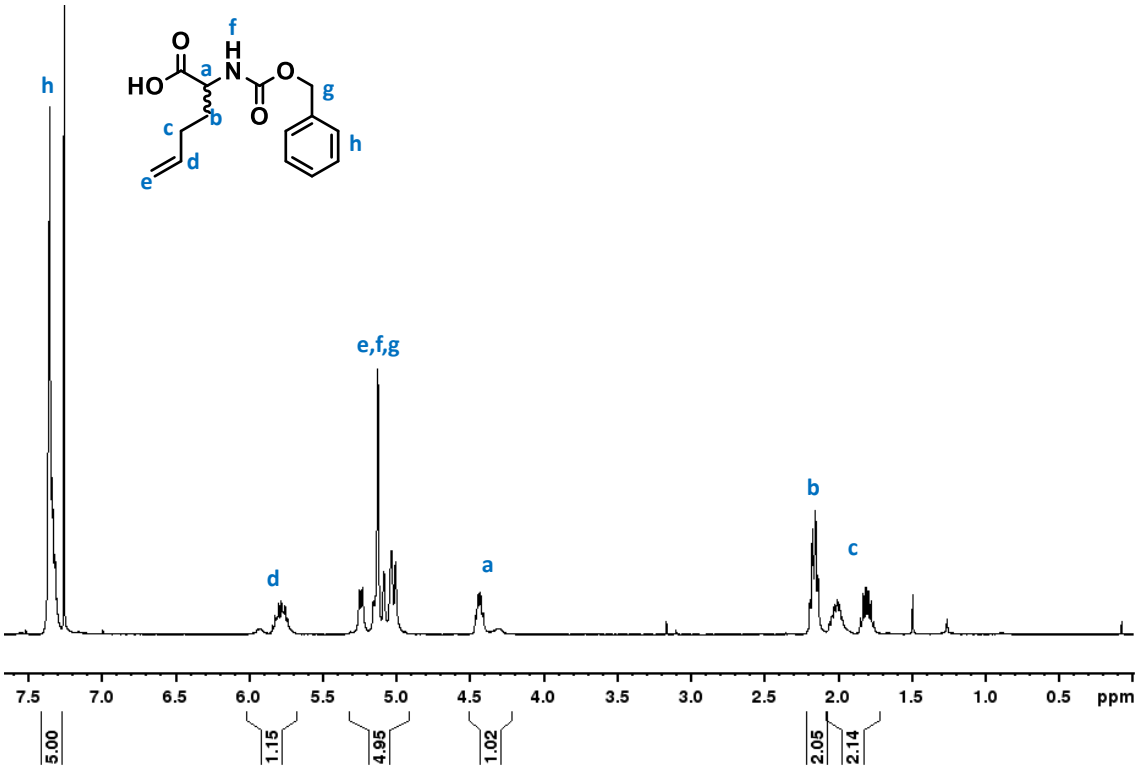
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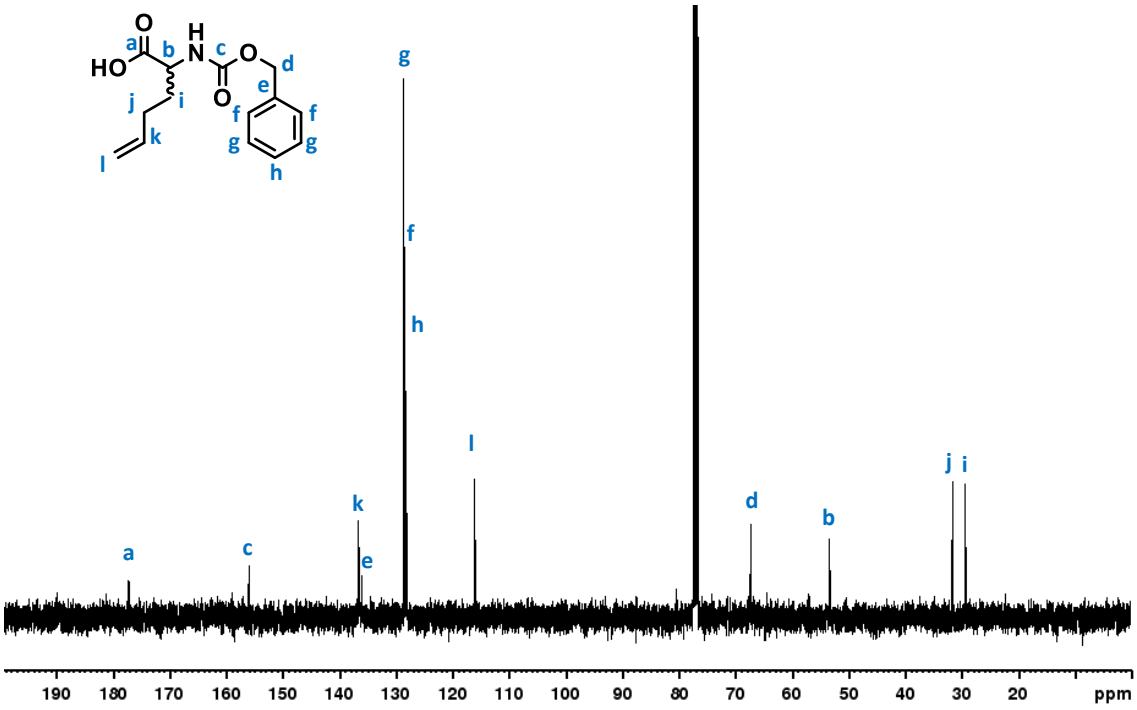
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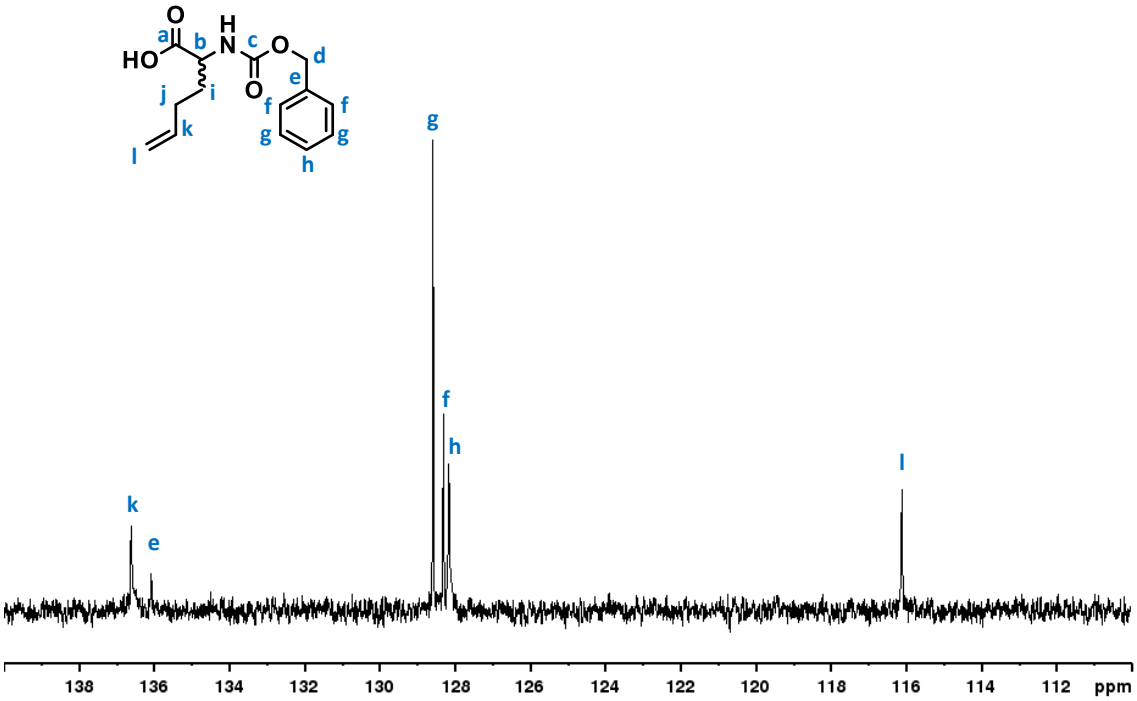
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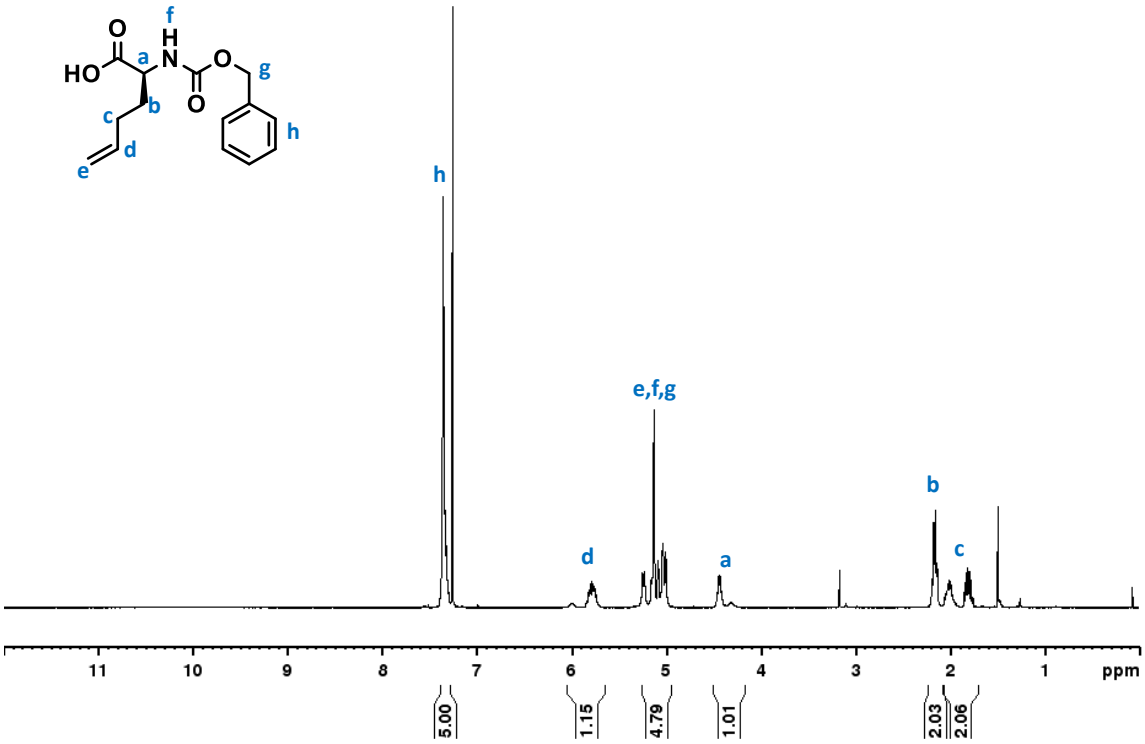
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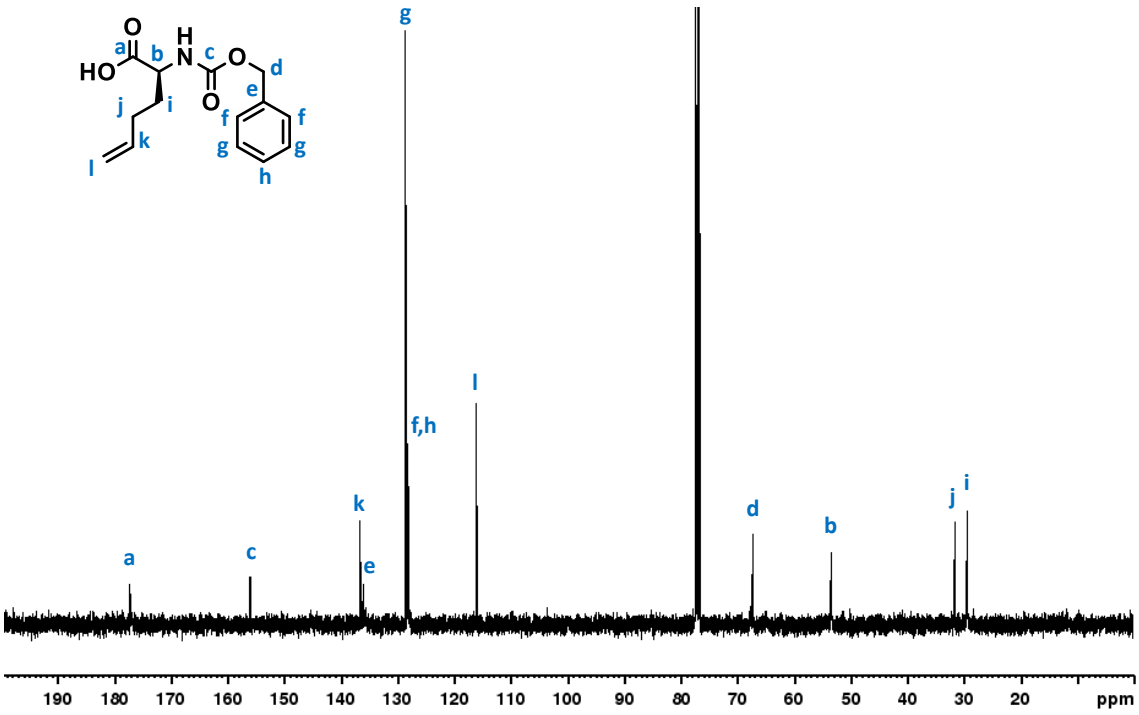
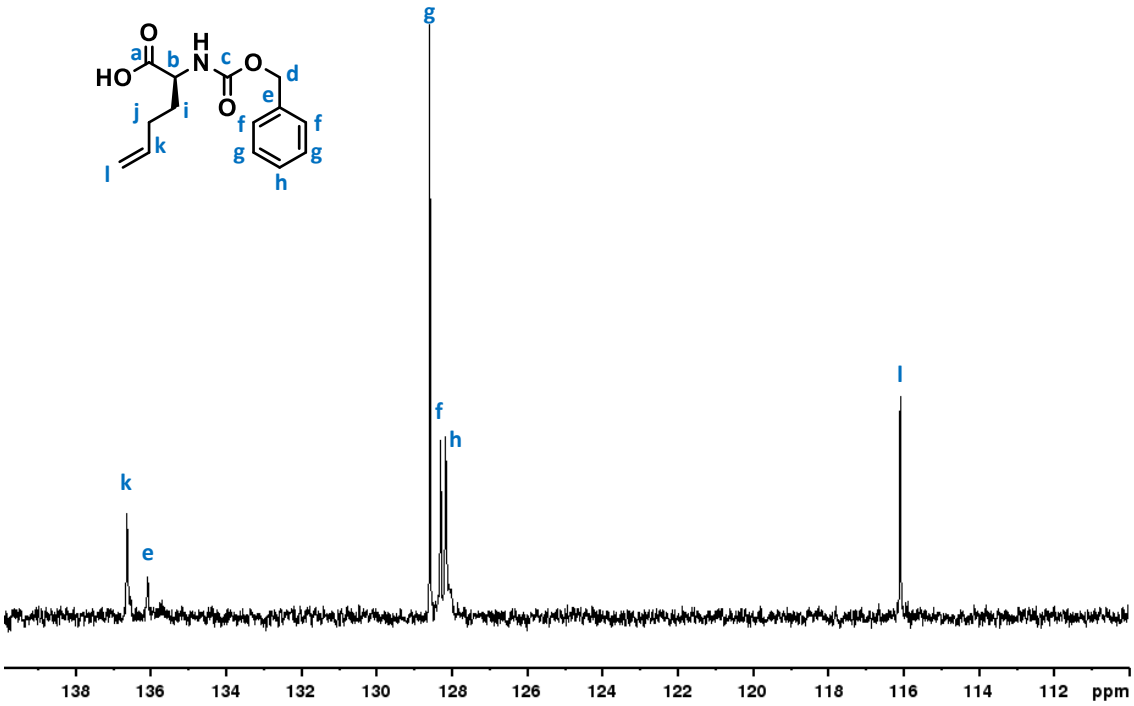
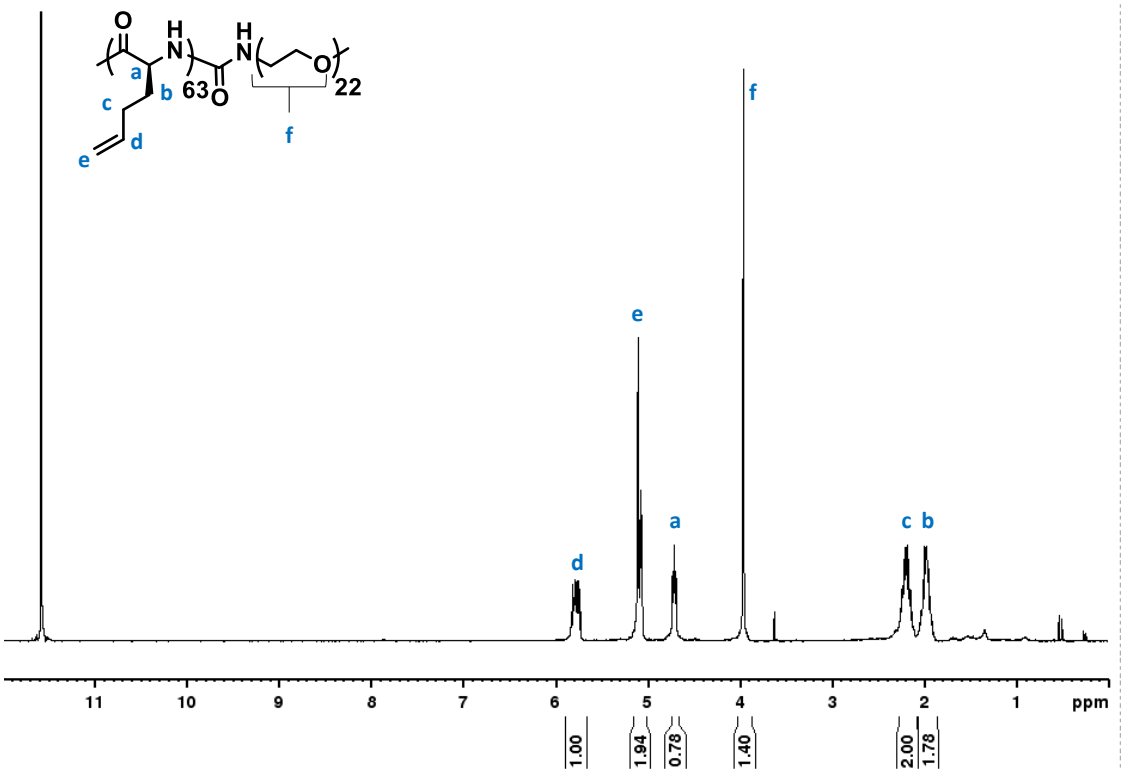
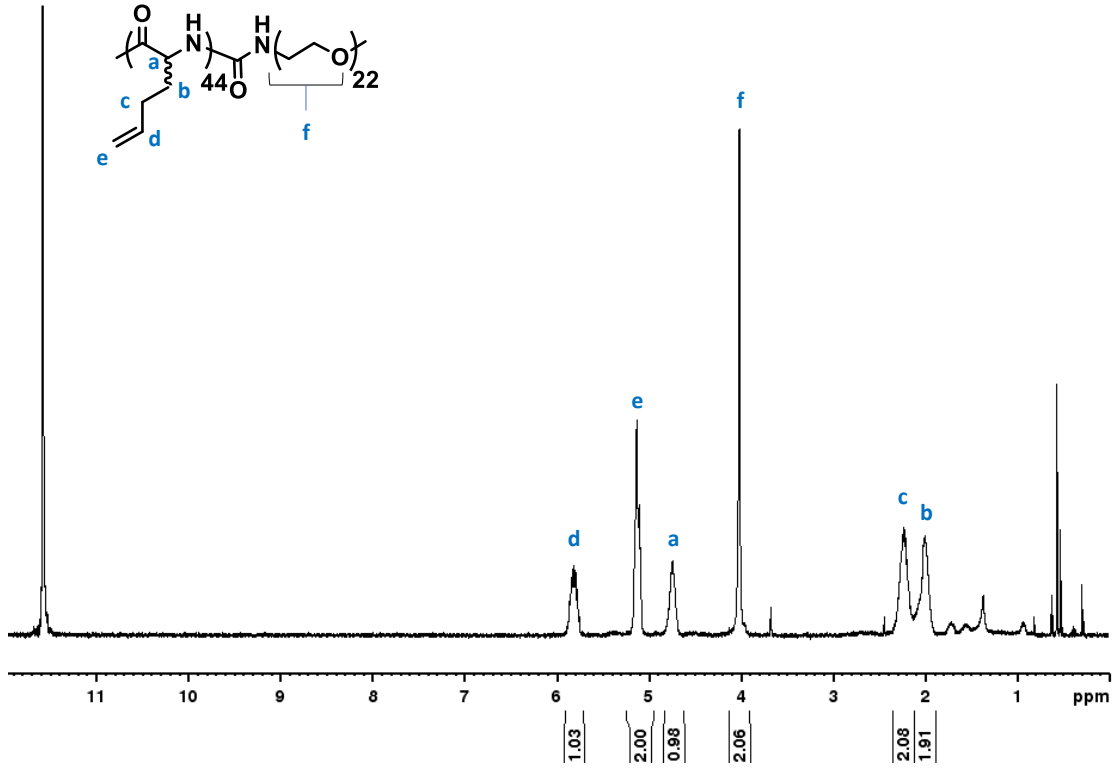
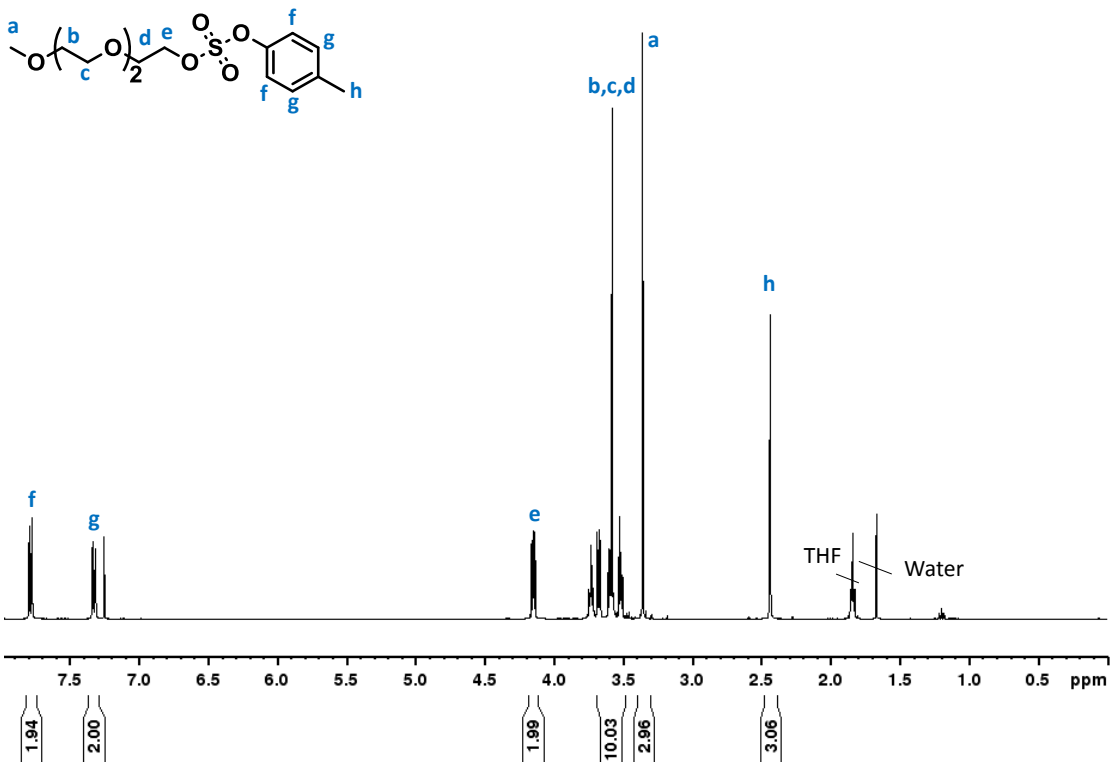
2.06

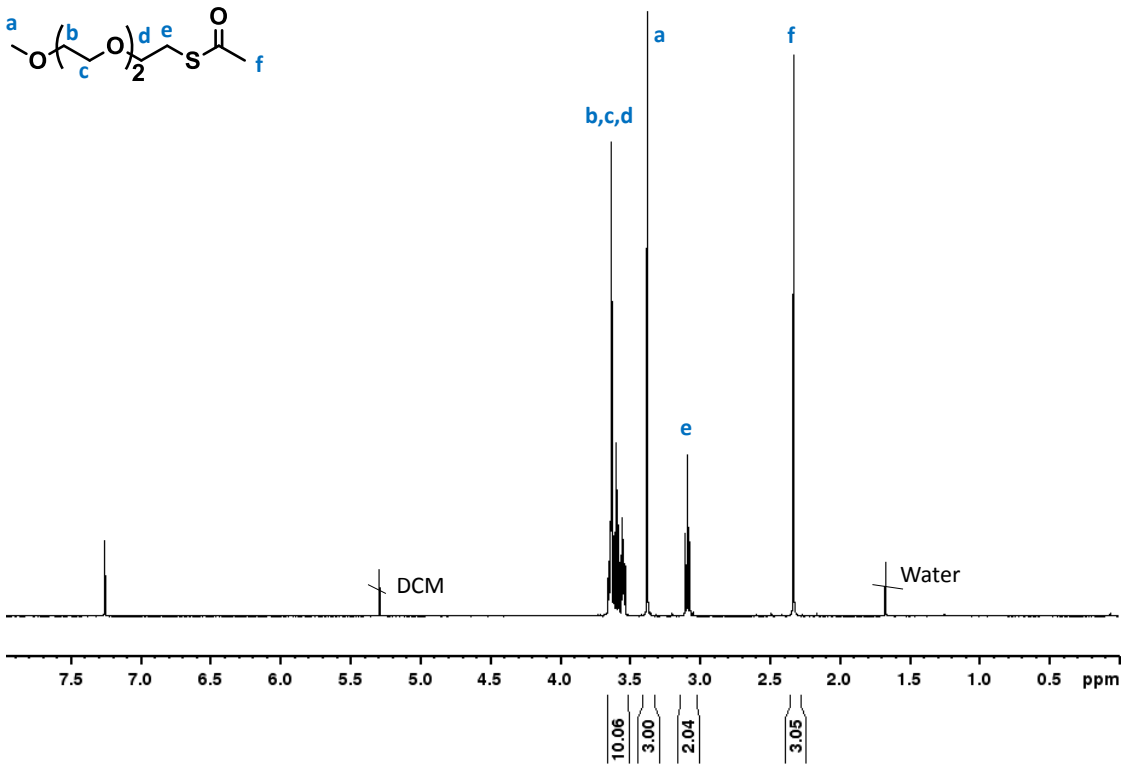

HO
O
a
b
H
N
c
O
d
e
f
g
h
i
j
k
l
f,h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

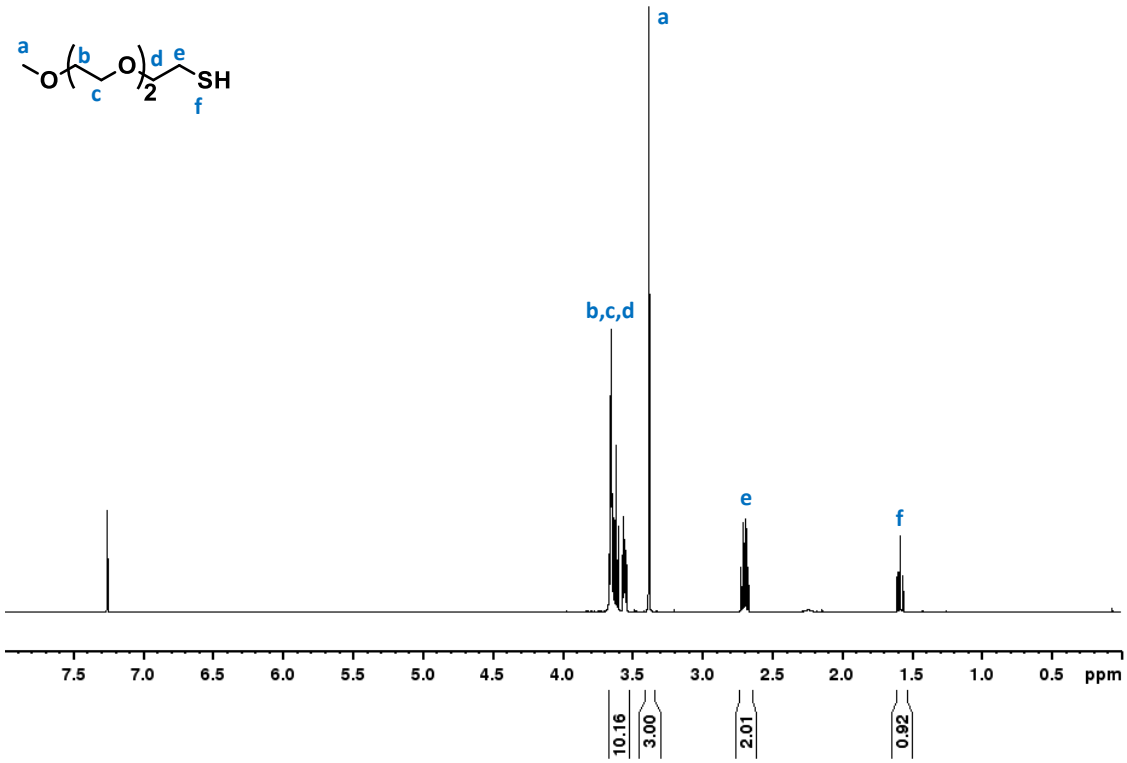

HO
O
a
b
H
N
c
O
d
e
f
g
h
i
j
k
l
138
136
134
132
130
128
126
124
122
120
118
116
114
112
ppm

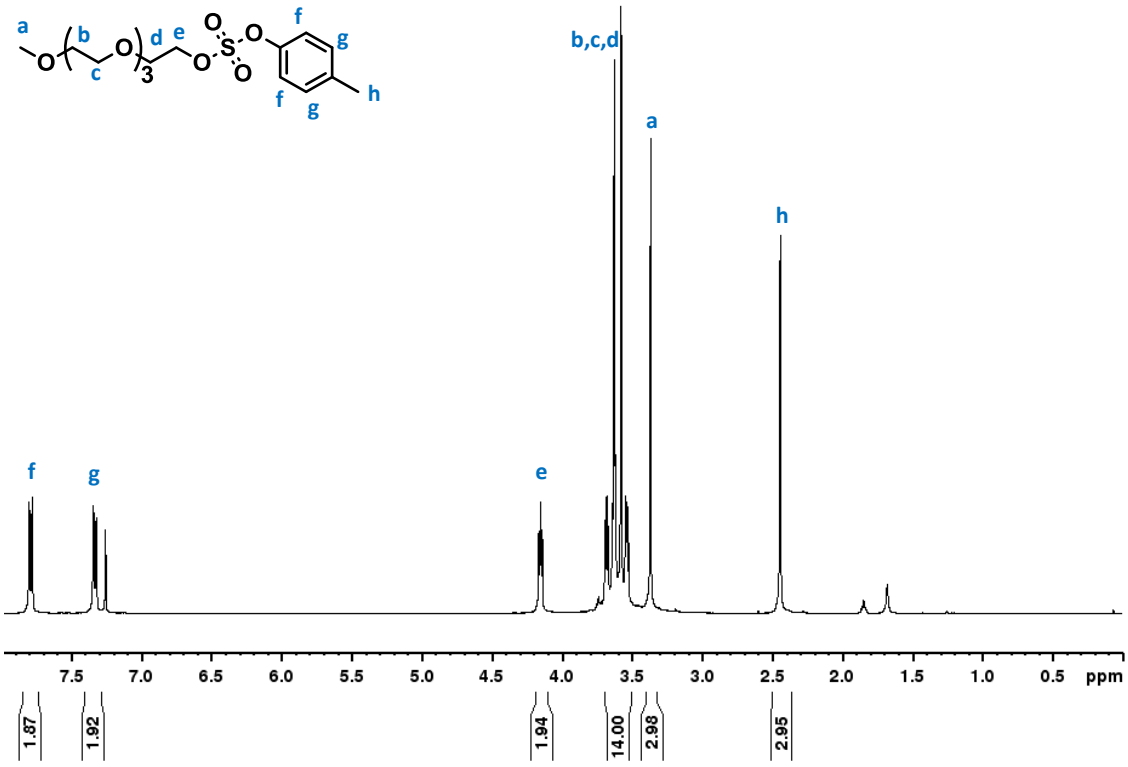

O
H
N
63
O
H
N
O
22
a
b
c
d
e
f
f
e
a
d
c b
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.94
0.78
1.40
2.00
1.78

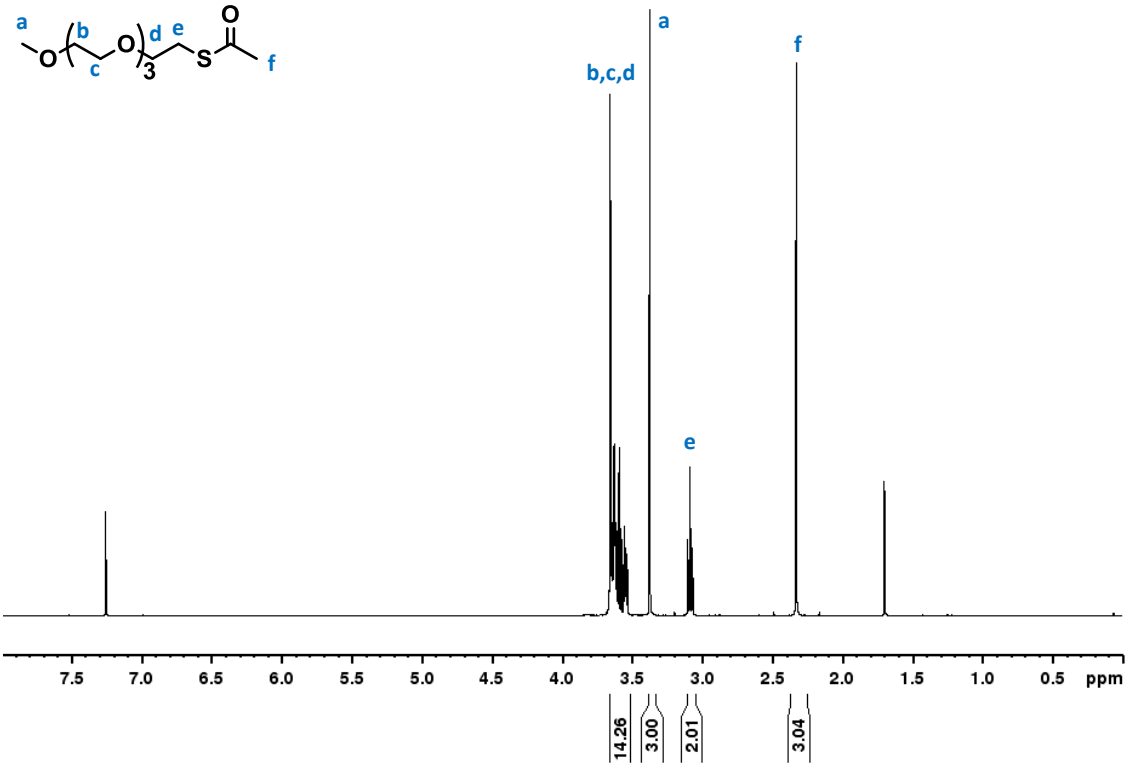

O
H
N
44
O
H
N
O
22
a
b
c
d
e
f
f
e
d
a
c
b
11
10
9
8
7
6
5
4
3
2
1
ppm
1.03
2.00
0.98
2.06
2.08
1.91

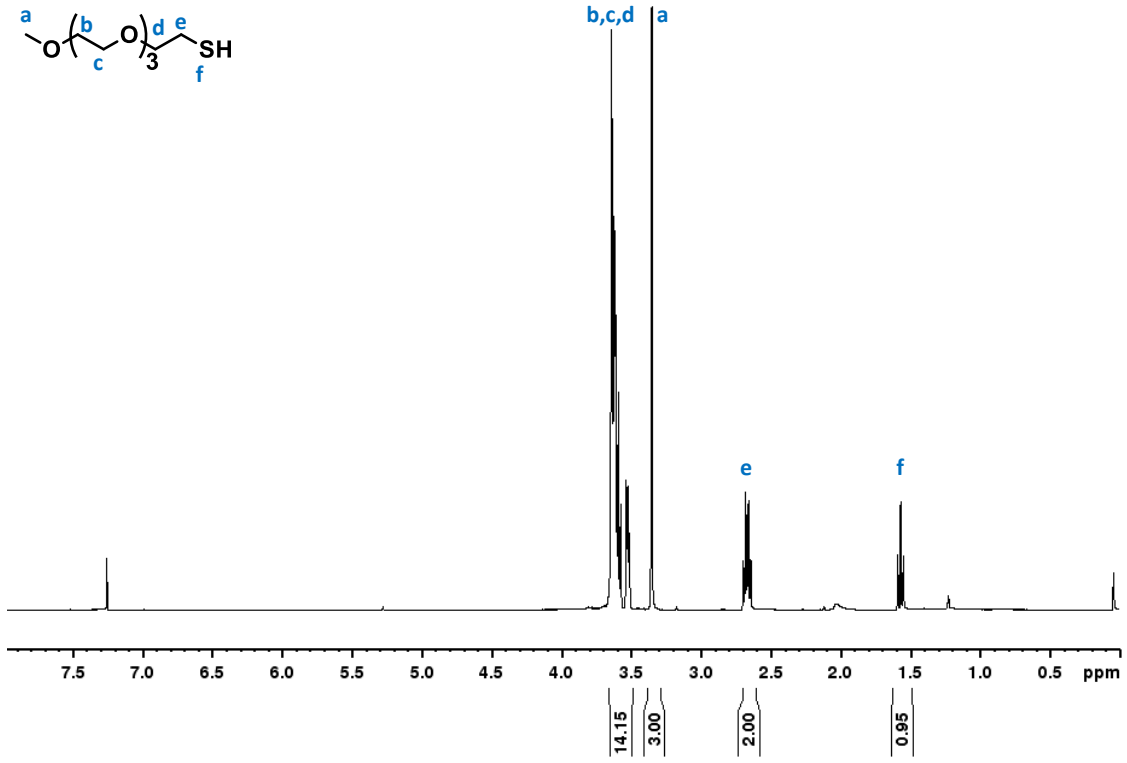

a
b
c
d
e
f
g
h
b,c,d
THF
Water
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.94
2.00
1.99
10.03
2.96
3.06

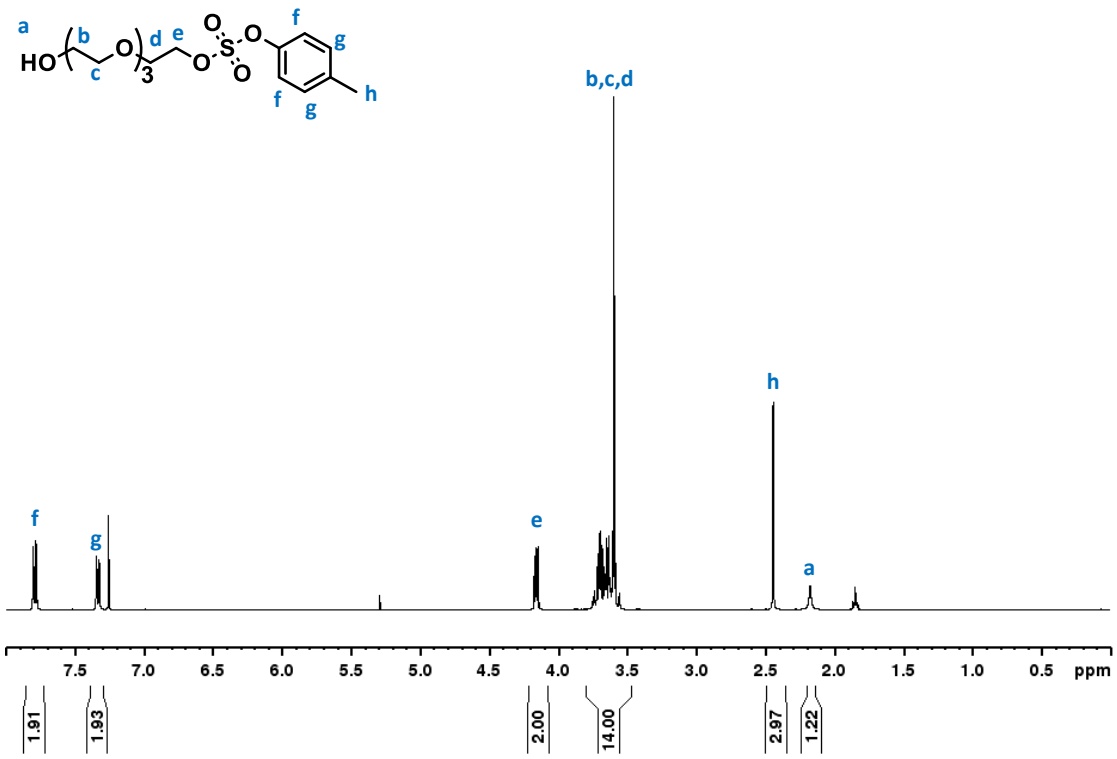

a
b
c
d
e
f
b,c,d
DCM
Water
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
10.06
3.00
2.04
3.05

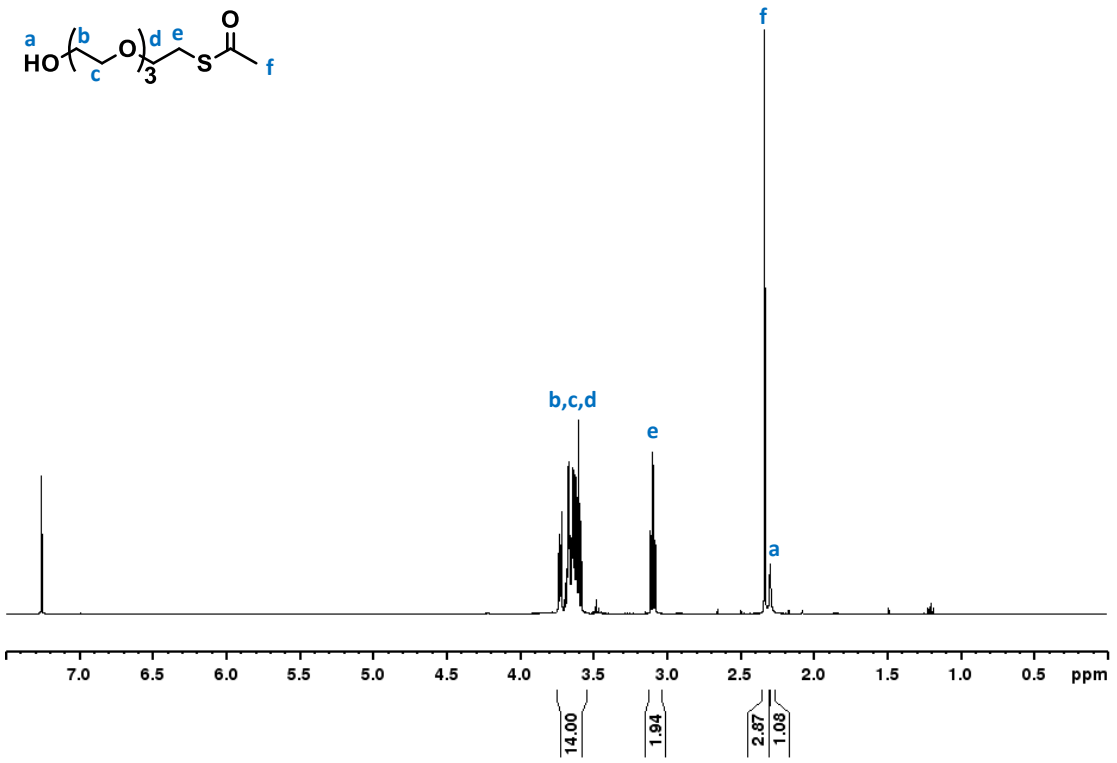

a
b
c
d
e
f
SH
2
a
b,c,d
e
f
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
10.16
3.00
2.01
0.92

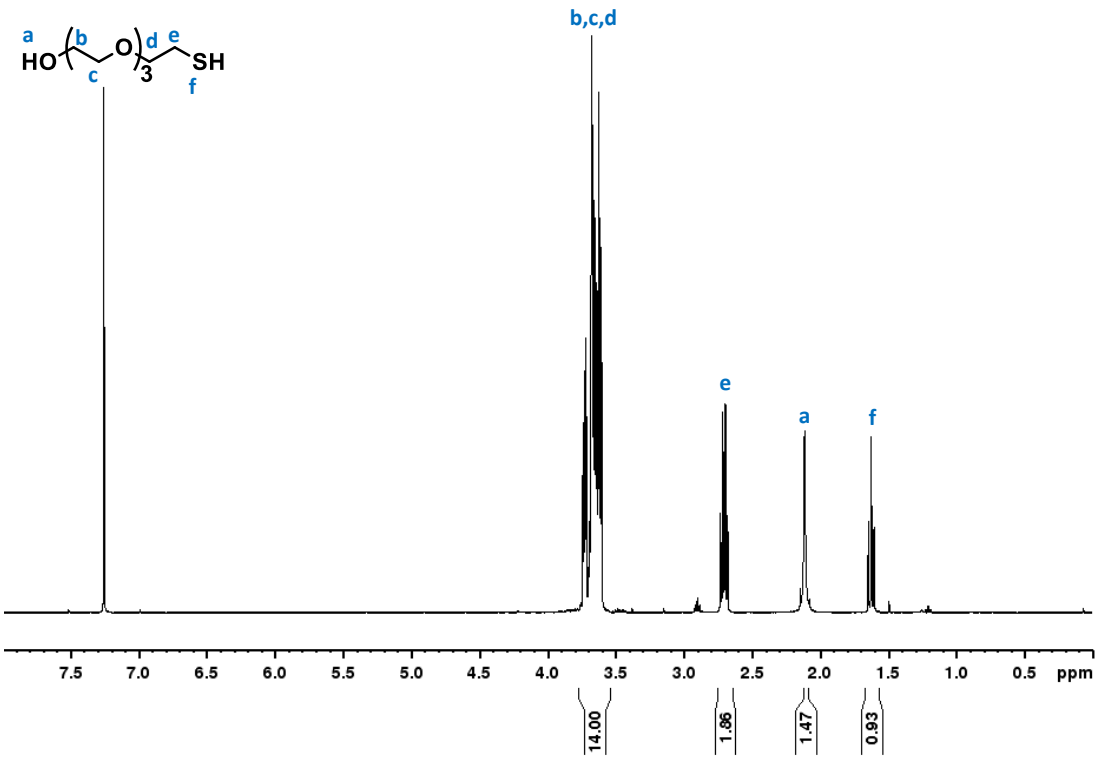

a
b
c
d
e
O
S
O
O
O
3
f
g
h
f
g
b,c,d
a
h
f
g
e
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.87
1.92
1.94
14.00
2.98
2.95

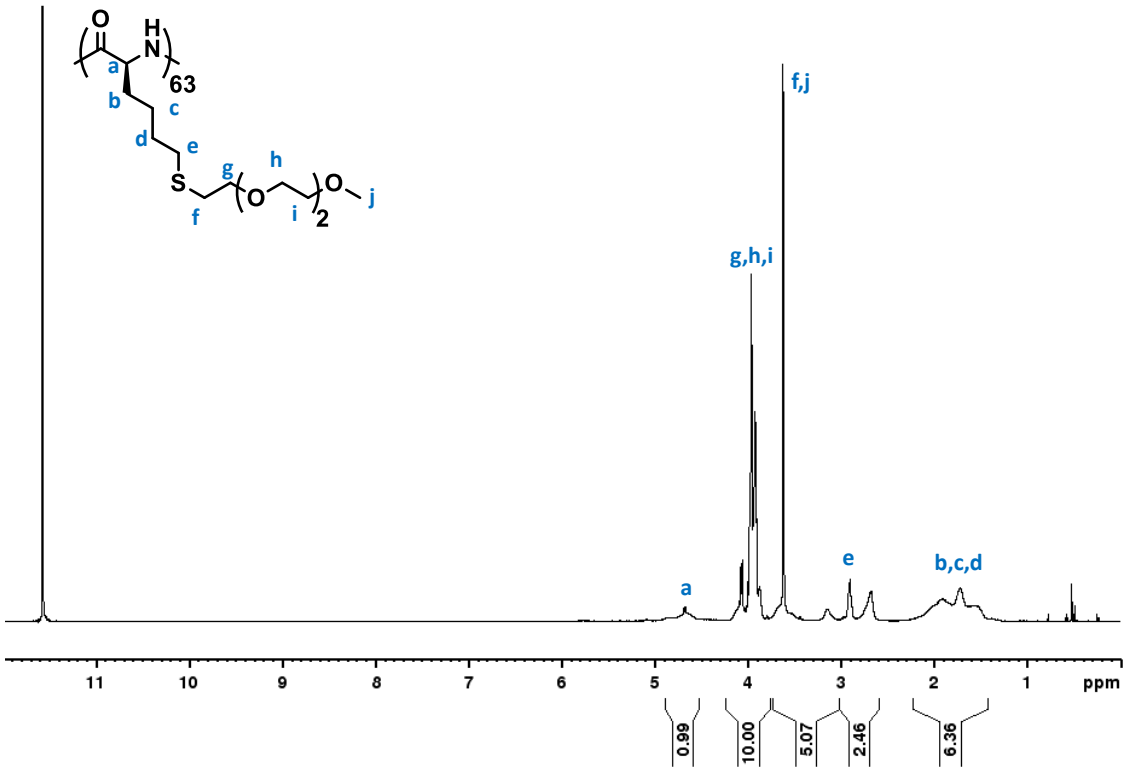

a
b
c
d
e
f
3
O
S
b,c,d
a
f
e
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
14.26
3.00
2.01
3.04

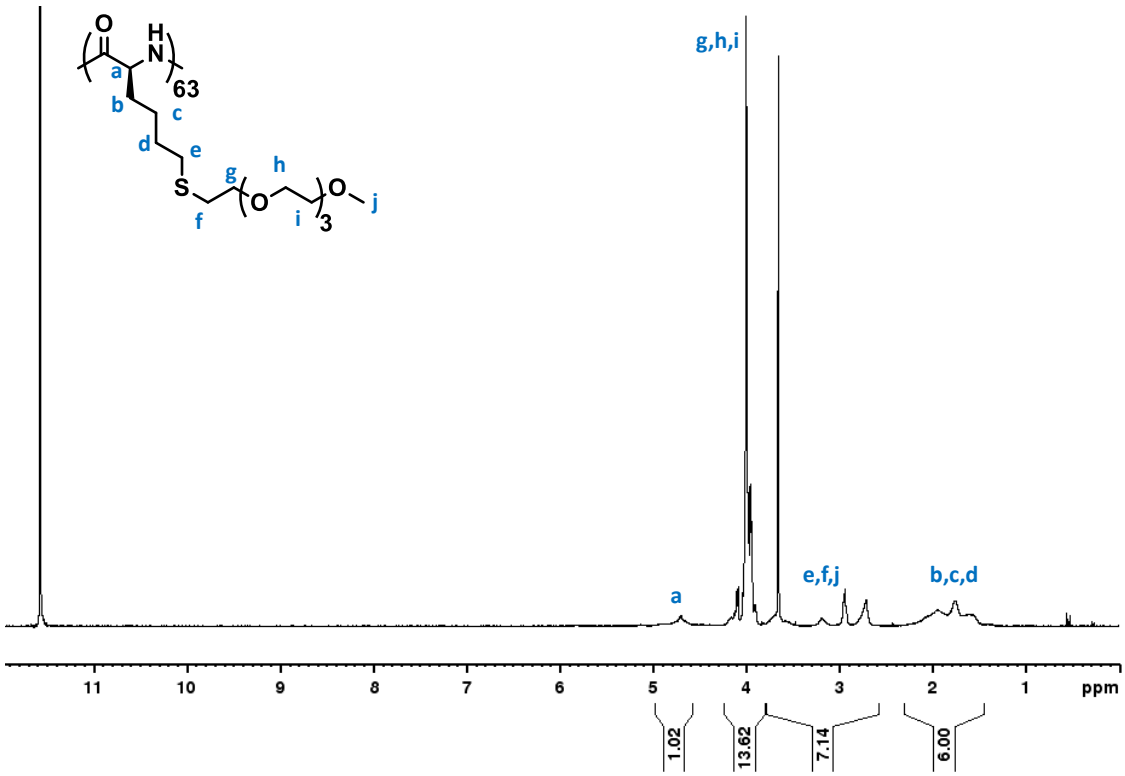

a
b
c
d
e
f
3
SH
b,c,d
a
e
f
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
14.15
3.00
2.00
0.95

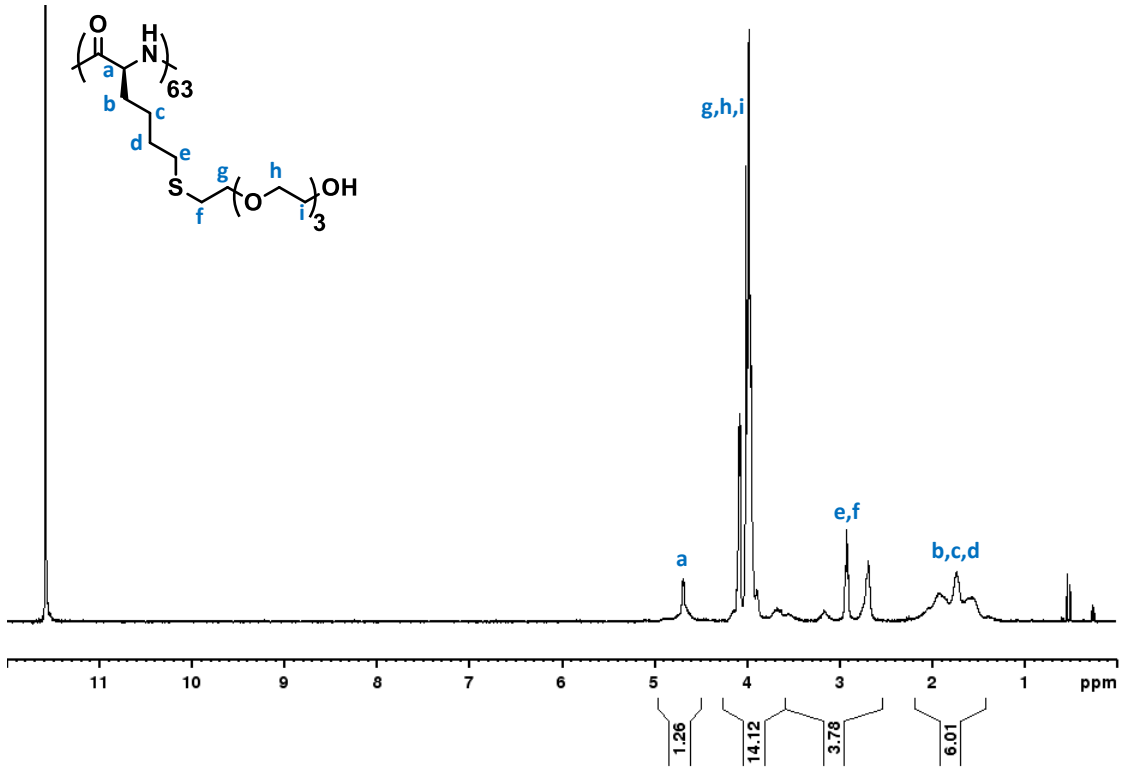

a
b
c
d
e
f
g
h
HO
O
S
b,c,d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.91
1.93
2.00
14.00
2.97
1.22

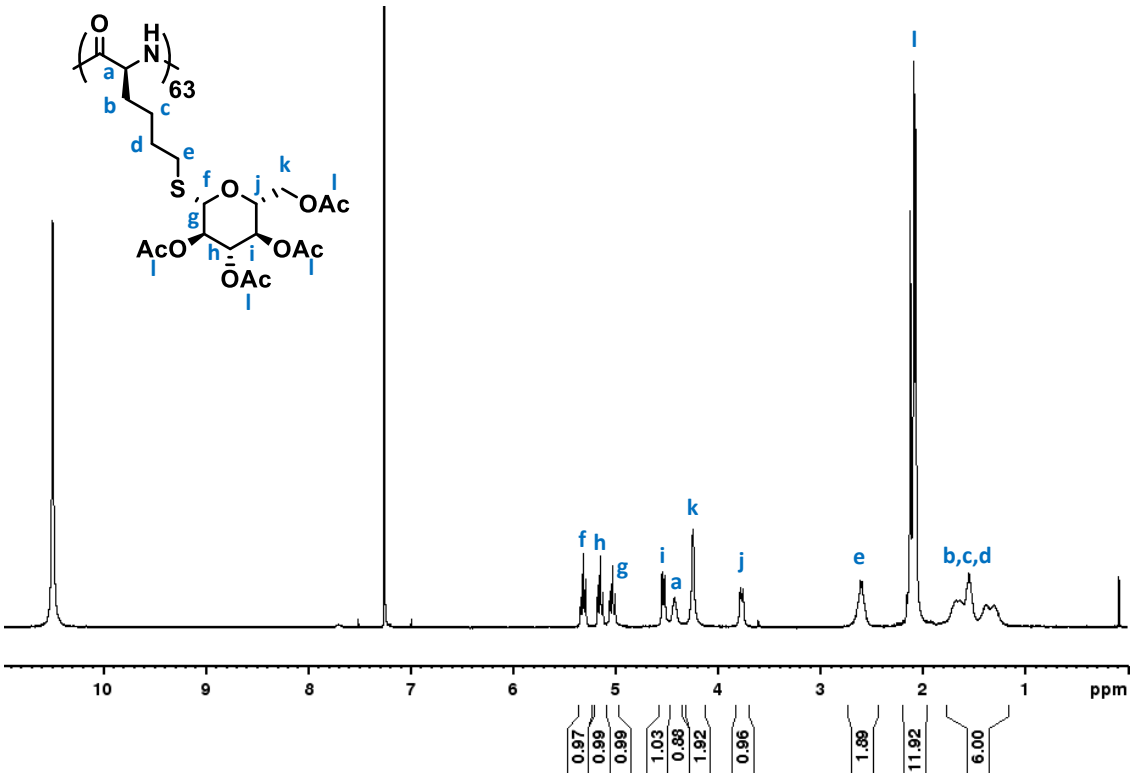

a
b
c
d
e
f
HO
O
S
b,c,d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
14.00
1.94
2.87
1.08

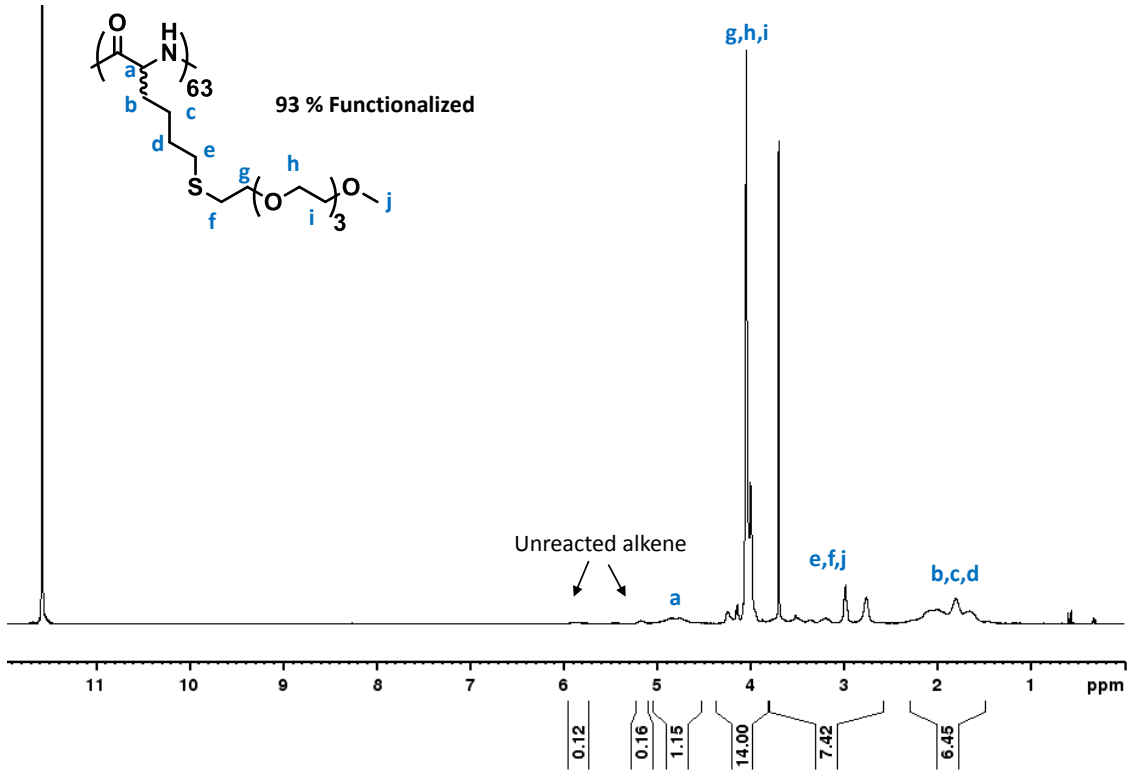

a
b
c
d
e
f
HO
O
3
SH
b,c,d
e
a
f
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
14.00
1.86
1.47
0.93

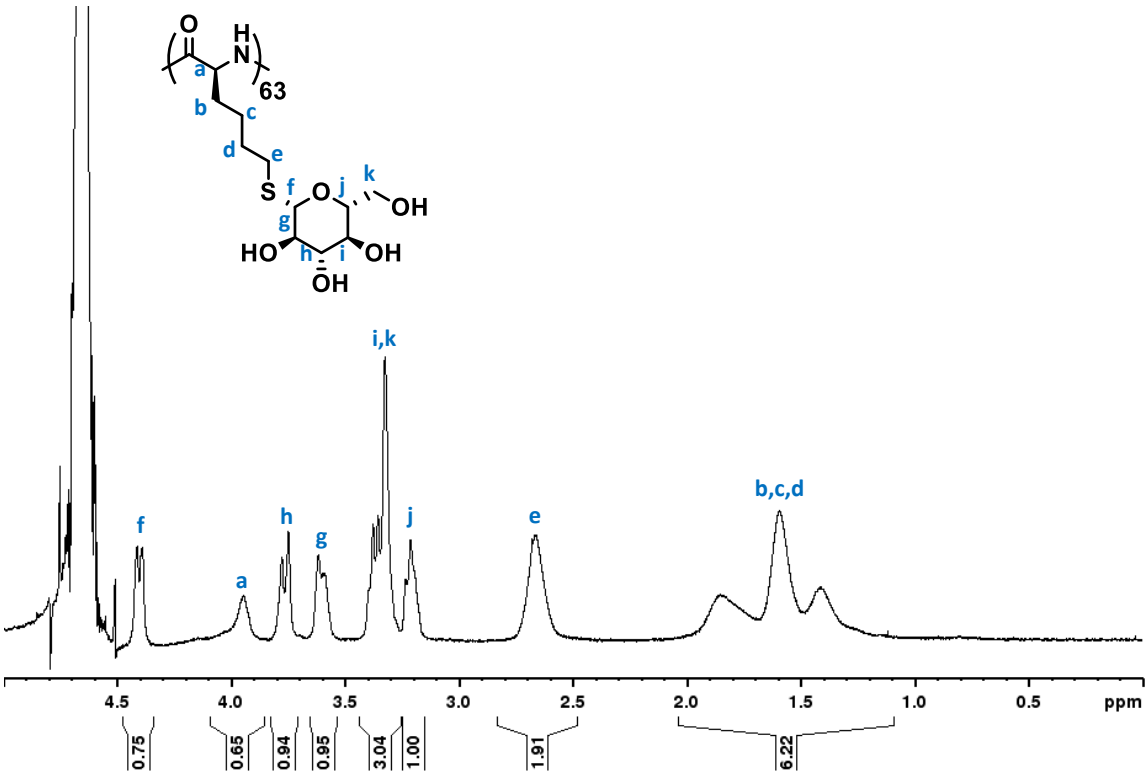

O
H
N
63
a
b
c
d
e
f
g
h
i
j
S
O
2
f,j
g,h,i
a
e
b,c,d
11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
10.00
5.07
2.46
6.36

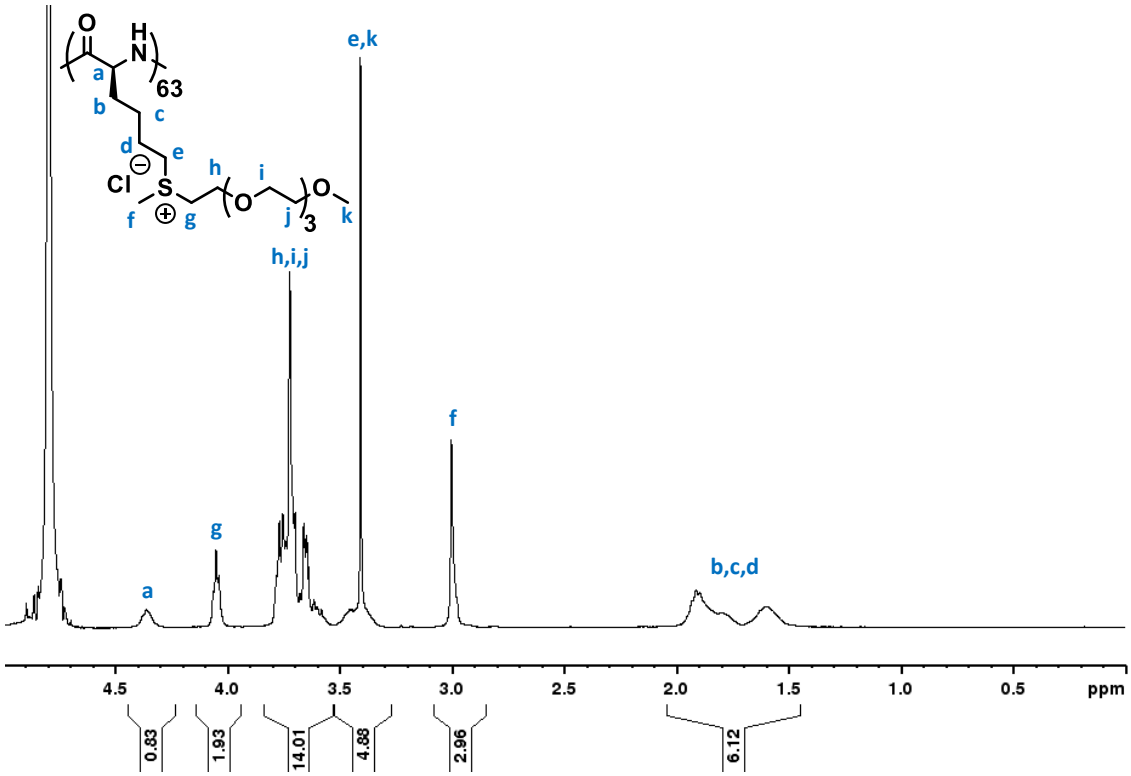

O
H
N
63
a
b
c
d
e
S
f
g
h
O
i
3
O
j
g,h,i
a
e,f,j
b,c,d
11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
13.62
7.14
6.00

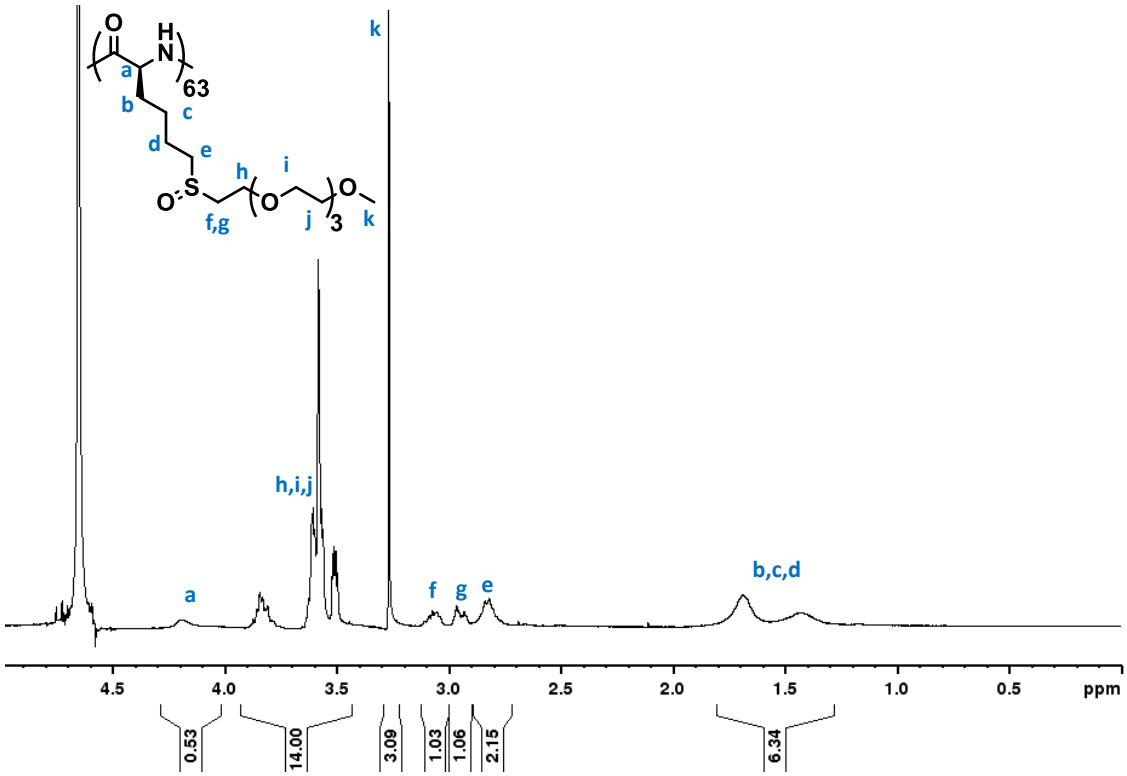

O
H
N
63
a
b
c
d
e
S
f
g
h
O
i
3
OH
g,h,i
a
e,f
b,c,d
11
10
9
8
7
6
5
4
3
2
1
ppm
1.26
14.12
3.78
6.01

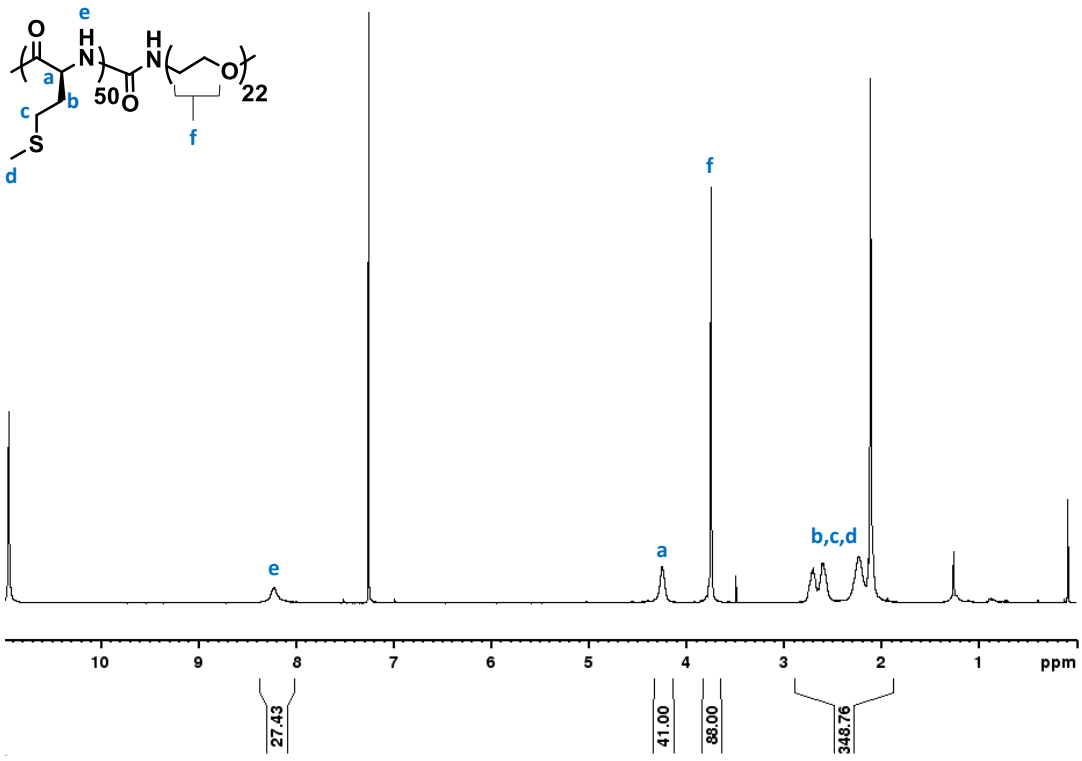

63
OAc
AcO
OAc
OAc
f h g i a k j e l b,c,d
10 9 8 7 6 5 4 3 2 1 ppm
0.97 0.99 0.99 1.03 0.88 1.92 0.96 1.89 11.92 6.00

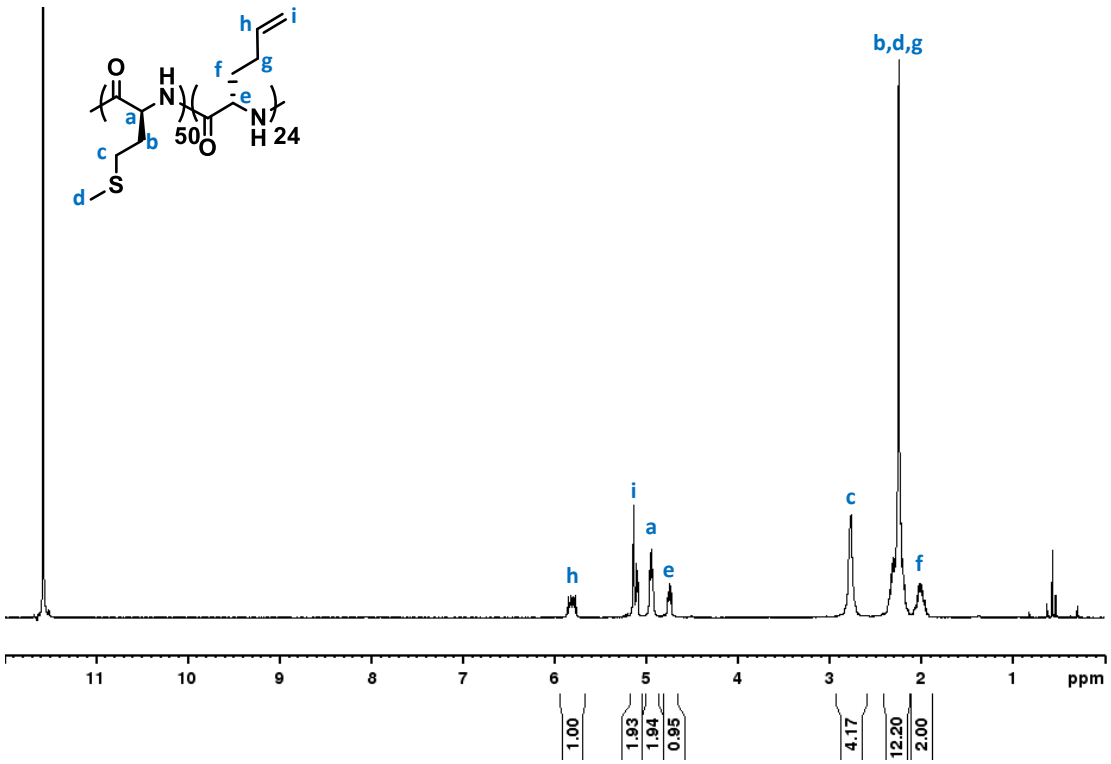

63
93 % Functionalized
3
g,h,i
Unreacted alkene
a
e,f,j
b,c,d
11 10 9 8 7 6 5 4 3 2 1 ppm
0.12 0.16 1.15 14.00 7.42 6.45

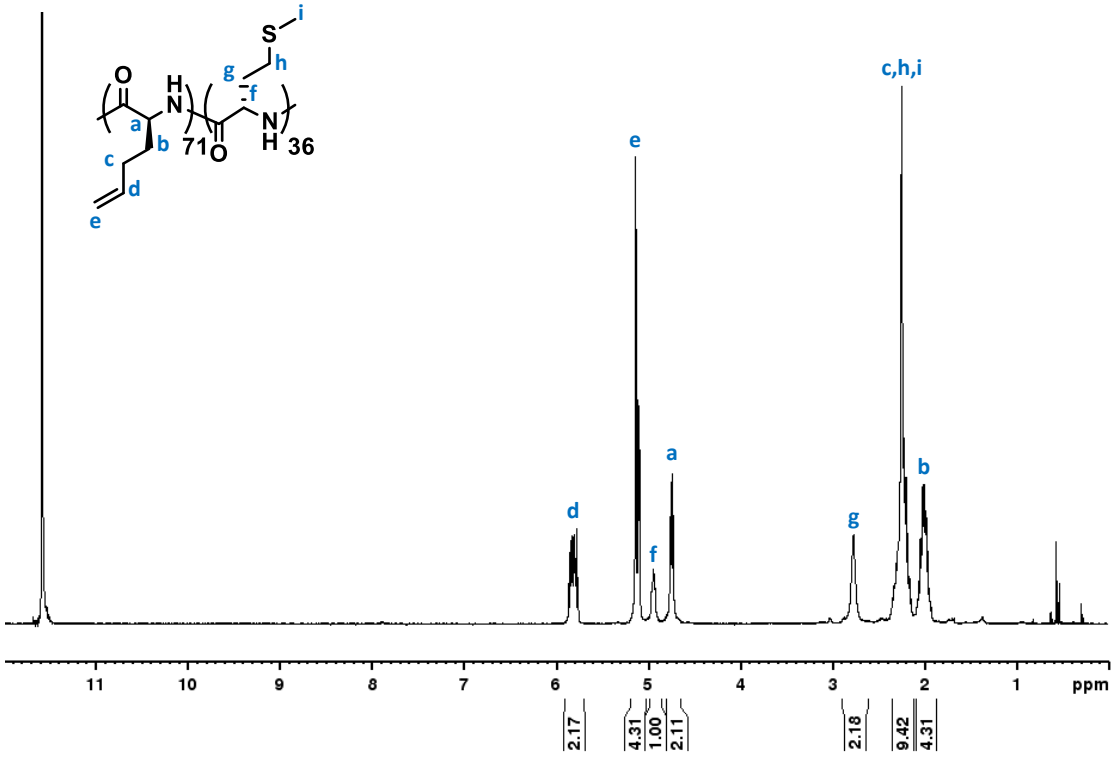

i,k
f
h
g
j
e
b,c,d
a
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.75
0.65
0.94
0.95
3.04
1.00
1.91
6.22

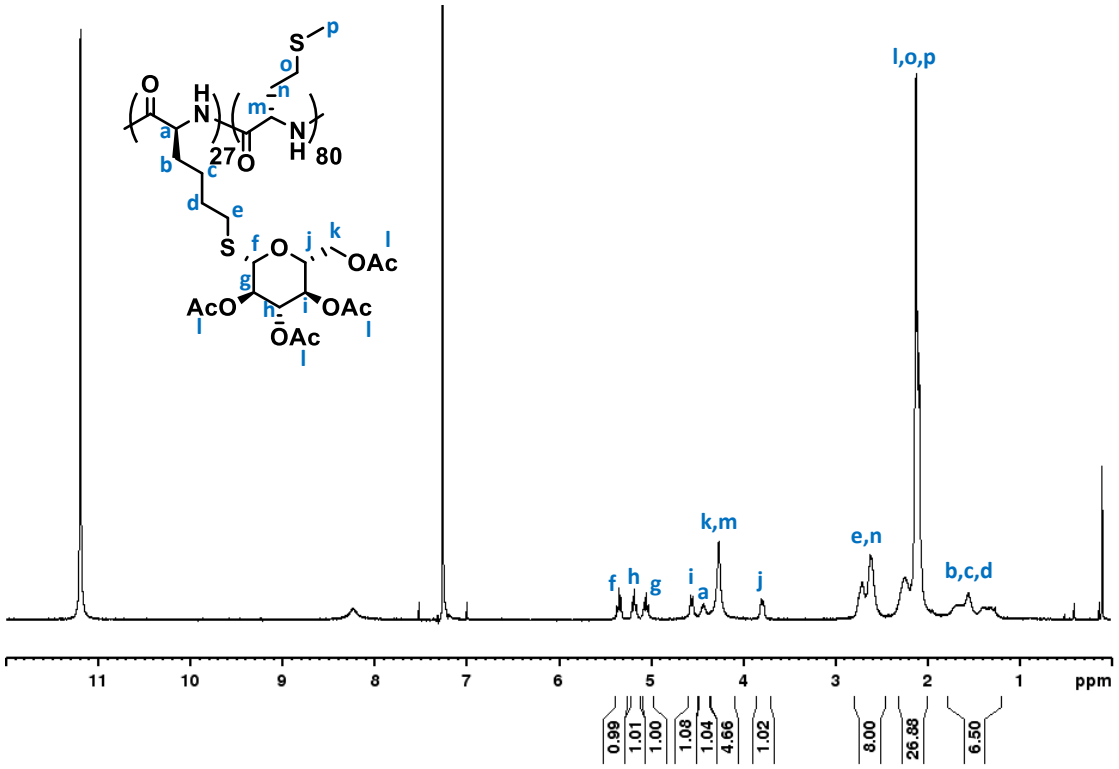

e,k
h,i,j
f
g
a
b,c,d
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.83
1.93
14.01
4.88
2.96
6.12

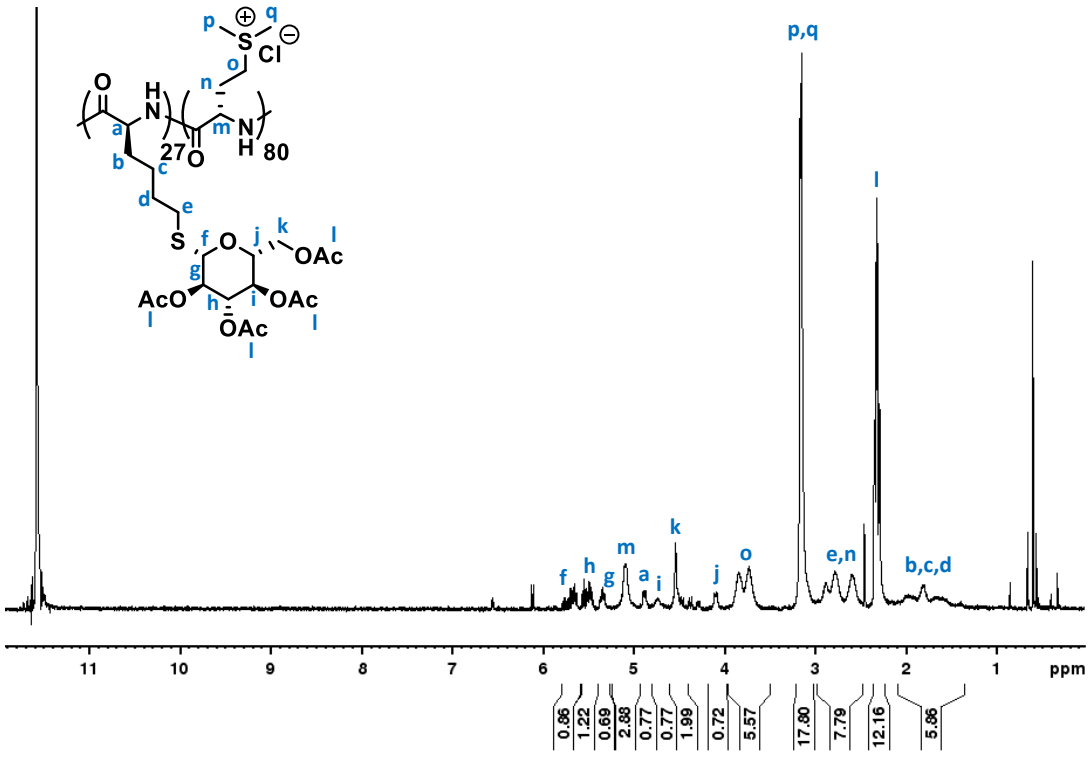

k
h,i,j
a
f
g
e
b,c,d
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.53
14.00
3.09
1.03
1.06
2.15
6.34

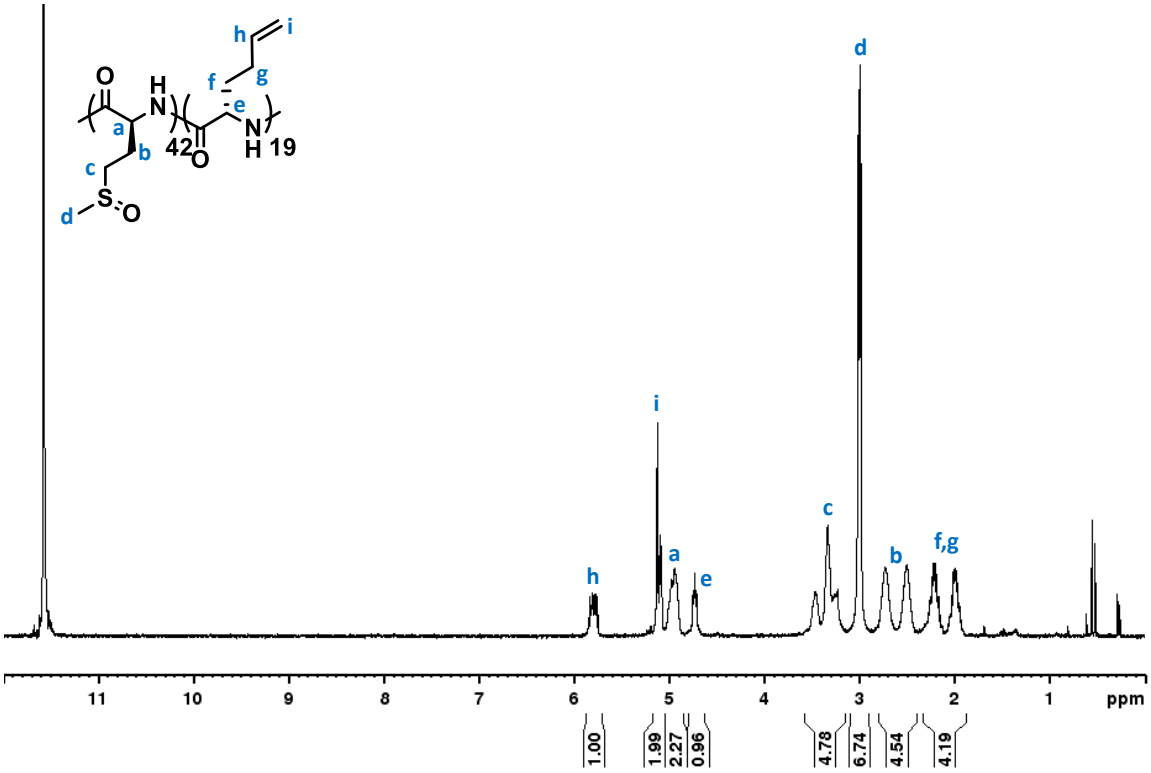

e
f
a
b,c,d
10
9
8
7
6
5
4
3
2
1
ppm
27.43
41.00
88.00
348.76

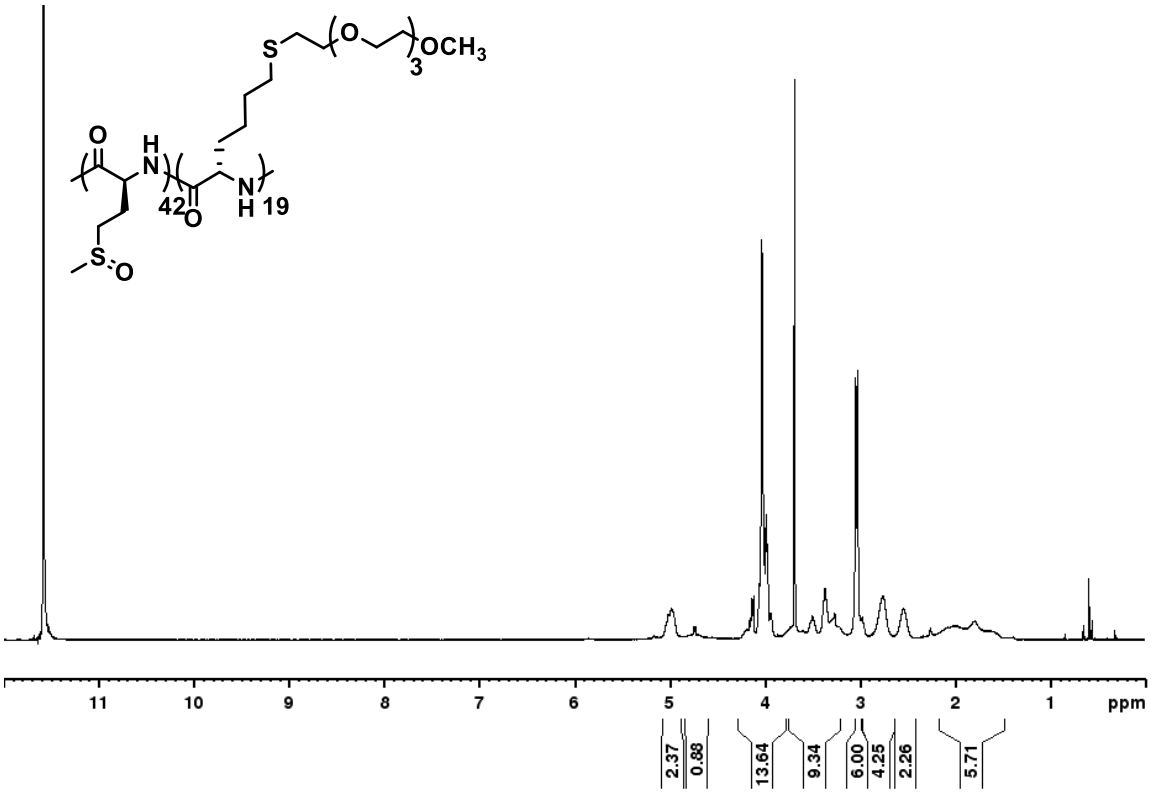

h
i
f
g
e
a
b
c
d
50
24
b,d,g
i
a
h
e
c
f
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.93
1.94
0.95
4.17
12.20
2.00

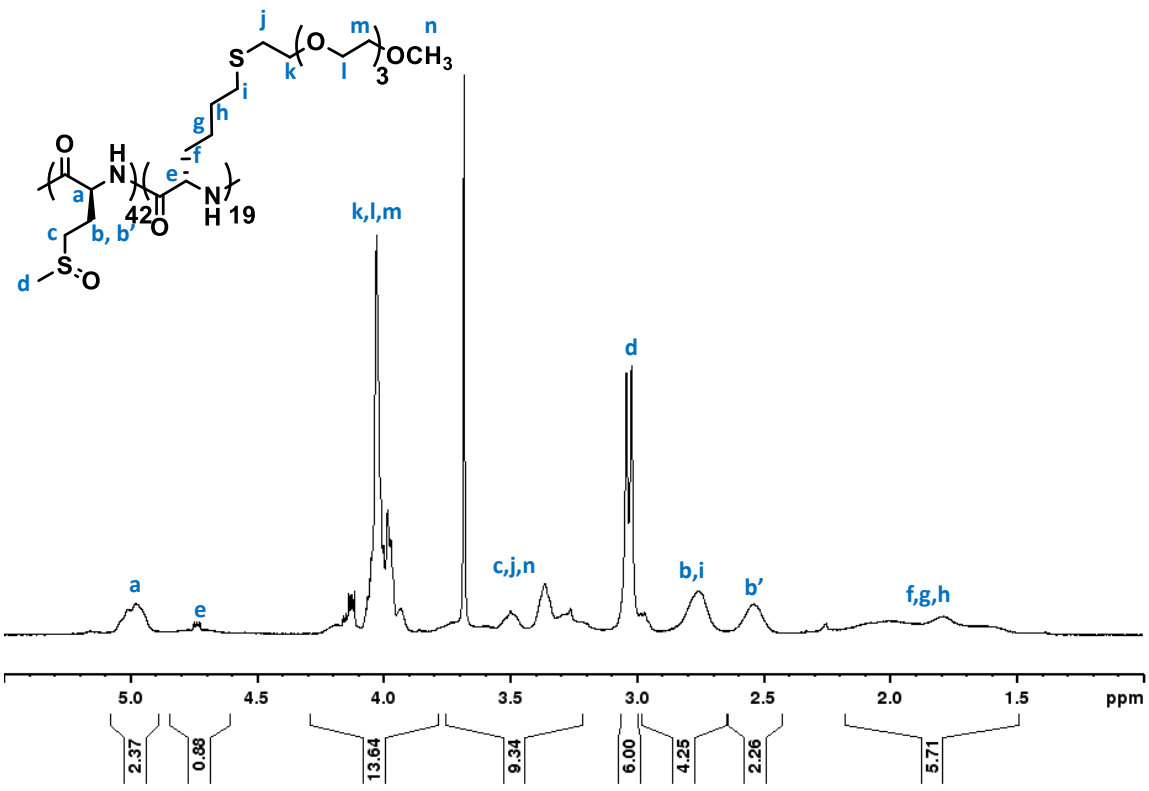

i
S
g
h
f
a
b
71
36
c
d
e
c,h,i
e
a
d
f
g
b
11
10
9
8
7
6
5
4
3
2
1
ppm
2.17
4.31
1.00
2.11
2.18
9.42
4.31

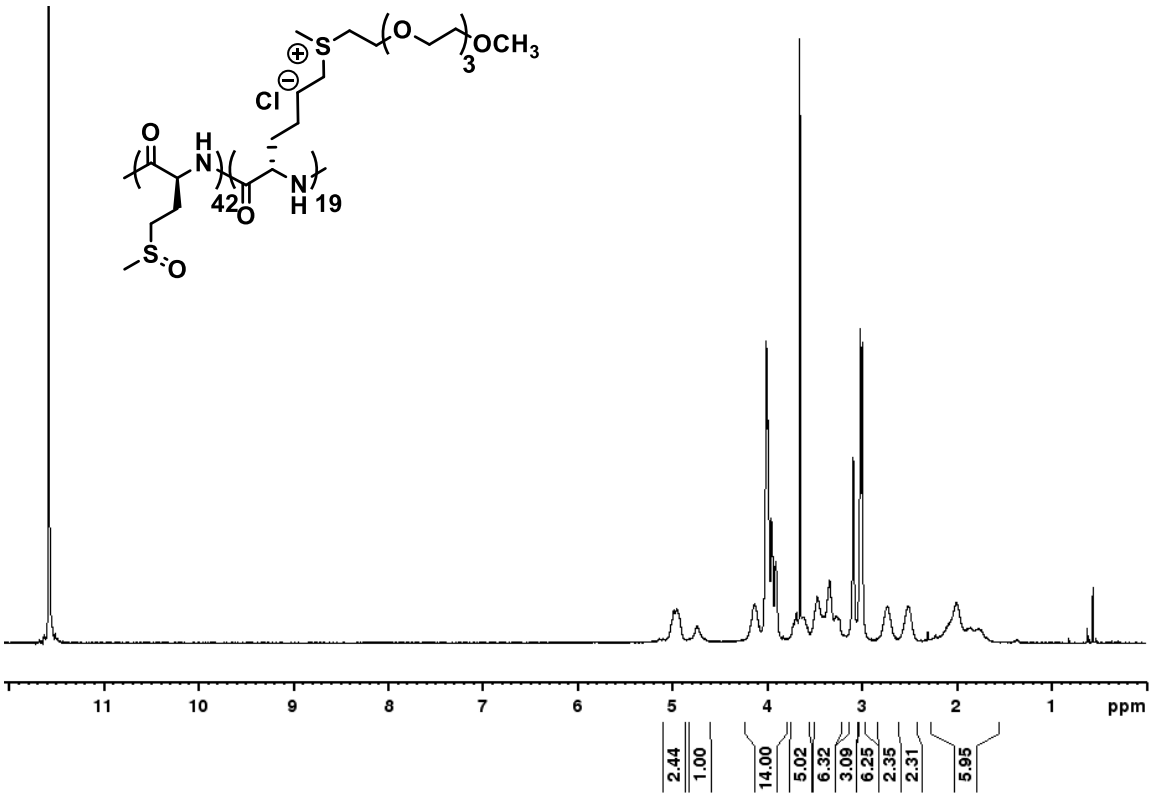

l,o,p
k,m
e,n
b,c,d
f
h
g
i
a
j
11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.01
1.00
1.08
1.04
4.66
1.02
8.00
26.68
6.50

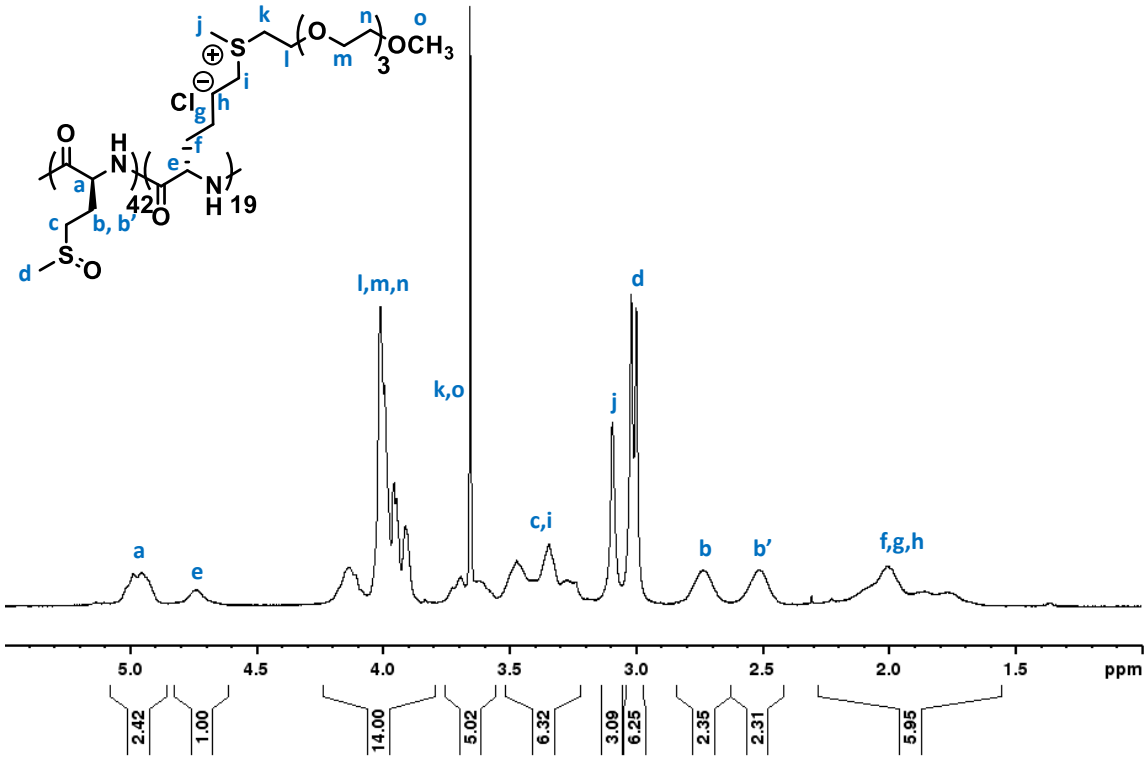

p,q
l
k
m
o
e,n
b,c,d
f
h
g
a
i
j
11
10
9
8
7
6
5
4
3
2
1
ppm
0.86
1.22
0.69
2.88
0.77
0.77
1.99
0.72
5.57
17.80
7.79
12.16
5.06


h
i
d
i
c
h
a
e
b
f,g
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.99
2.27
0.96
4.78
6.74
4.54
4.19


11
10
9
8
7
6
5
4
3
2
1
ppm
2.37
0.88
13.64
9.34
6.00
4.25
2.26
5.71


a
e
k,l,m
c,j,n
d
b,i
b'
f,g,h
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.37
0.88
13.64
9.34
6.00
4.25
2.26
5.71


11
10
9
8
7
6
5
4
3
2
1
ppm
2.44
1.00
14.00
5.02
6.32
3.09
6.25
2.35
2.31
5.95


j
k
n
o
S
l
m
OCH3
3
i
Cl
g
h
O
H
N
f
e
a
42
N
H 19
O
c
b, b'
S
O
d
l,m,n
k,o
d
j
c,i
a
e
b
b'
f,g,h
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.42
1.00
14.00
5.02
6.32
3.09
6.25
2.35
2.31
5.95