Supporting Information

for

Acid-Cleavable Poly(Oxazoline) Surfactants

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Supporting figures

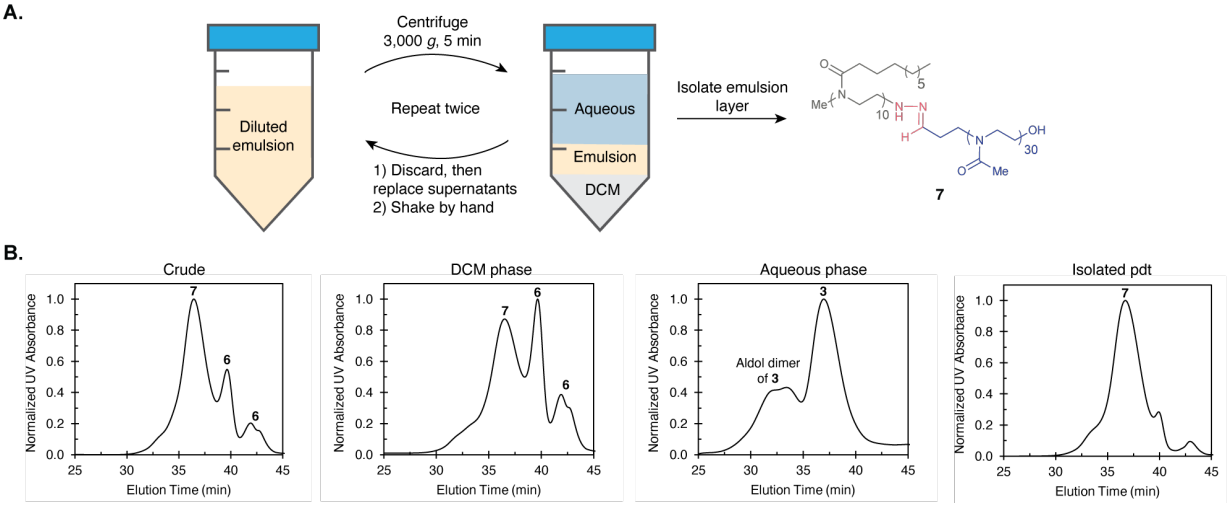
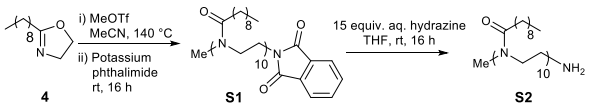


Fig. S1 Purification of surfactant **7**. (A) Schematic showing the emulsion workflow to purify surfactant **7**. (A) SEC traces (UV, 210 nm) of surfactant **7** and the impurities that were removed. The aldol dimer of **3** is a known product of poly(oxazoline)s containing aliphatic aldehydes.[1]



Scheme S1. Synthesis of P(NonOx)-NH_2.

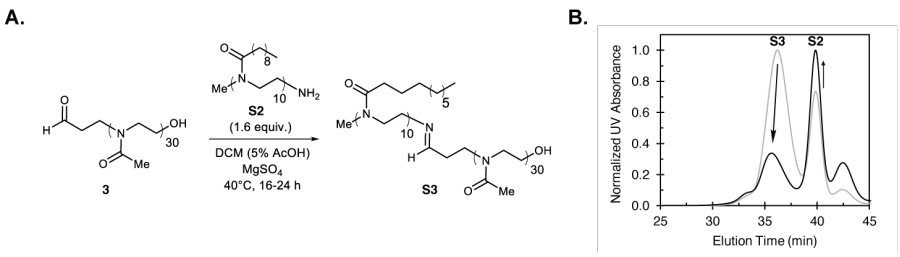


Fig. S2 Attempted isolation of imine linked surfactant. (A) Synthetic scheme to synthesize imine linked surfactant. (B) Normalized SEC traces (UV, 210 nm) of imine linked surfactant **S3** before and after the emulsion work-up.

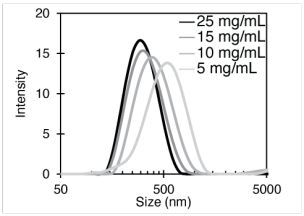


Fig. S3 DLS intensity plots of PFC-in-water nanoemulsions formulated using **7** at varying concentrations.

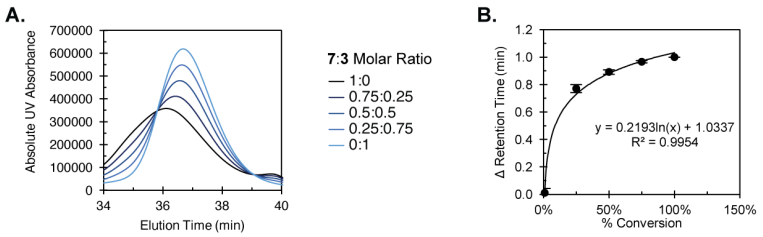


Fig. S4 Calibration curve for the SEC degradation assay. (A) Raw SEC traces (UV, 210 nm) of mixtures of **7** and **3**. (B) Change in retention time plotted over the molar percent conversion. Different percent conversions were obtained by mixing stock solutions of **7** and **3** together, maintaining a constant total molarity. Error bars represent the standard error of two measurements. Note: Nonlinearity is attributed to the difference in absorbance intensity between the **3** and **7** at the same concentration.

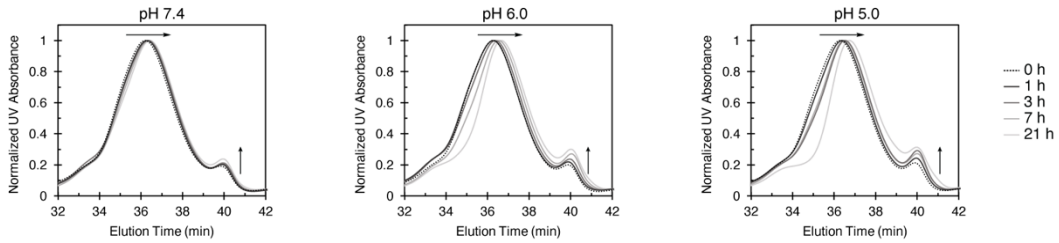


Fig. S5 SEC traces (UV, 210 nm) of time course decay of **7** in 1:1 MeOH in CPB 7.4, 6.0, or 5.0. This is representative data for **Figure 3C**.

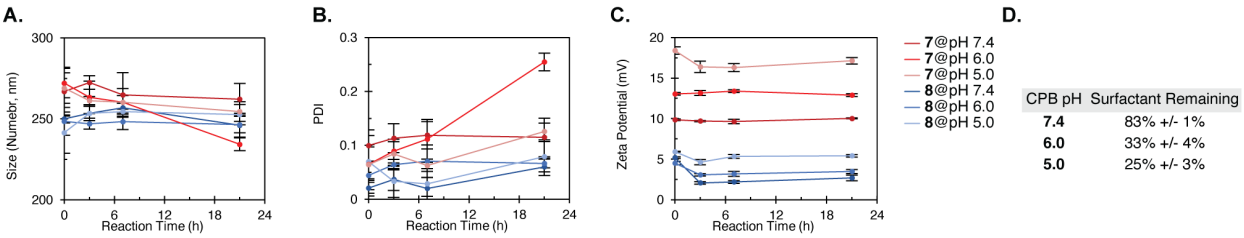


Fig. S6 DLS data for CPB treated **7** or **8** emulsions. (A) Tracking emulsion size (number) as a function of time. (B) Tracking emulsion PDI as a function of time. (C) Tracking emulsion zeta potential as a function of time. Error bars represent the standard deviation of three measurements. (D) Quantification of surfactant **7** remaining after emulsion degradation using the calibration curve shown in **Figure S2**. Error bars represent the standard error of three measurements.

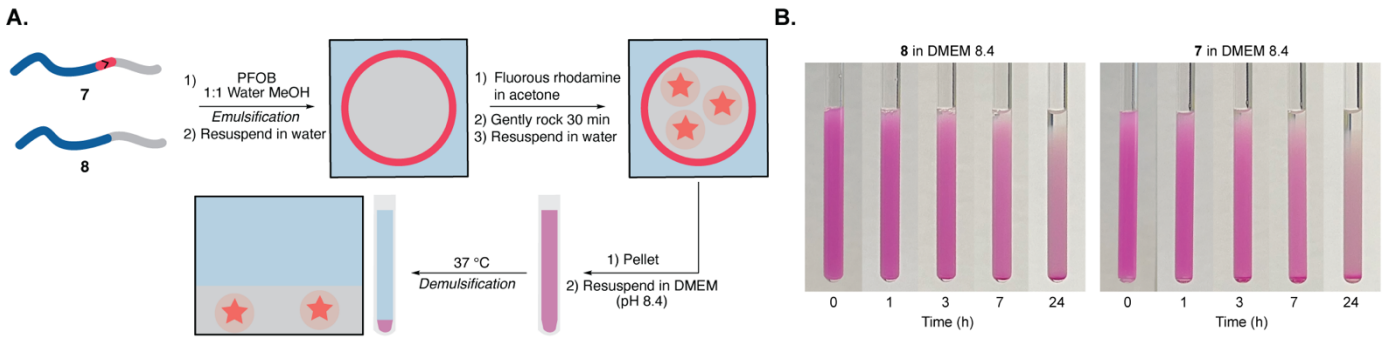


Fig. S7 Emulsion degradation assay using DMEM cell culture media at 37 °C. (A) Schematic depicting the formation of nanoemulsions and their degradation. (B) Vial photos of emulsions containing 1 mM fluorous rhodamine formulated from **7** (right) or **8** (left) in DMEM over 21 h.

General experimental procedures

Chemical reagents were purchased from Sigma-Aldrich, VWR, Alfa Aesar, Thermo Fisher, Fisher Scientific, SynQuest Laboratories, or Acros Organics. *t*-butyl carbazate was purchased from MilliporeSigma and was used without purification. 2-(2-bromoethyl)-1,3-dioxolane was purchased from Millipore sigma and was purified through column chromatography. All reagents were used without purification unless noted otherwise. 2-methyl-2-oxazoline (MeOx) was distilled over barium oxide and stored in an air free flask under N_2 gas until use. Methyl trifluoromethanesulfonate (MeOTf) was distilled under anhydrous conditions into an air free flask under N_2. 2-nonyl-2-oxazoline (NonOx) was synthesized according to literature protocol.[2] Fluorous rhodamine was prepared according to literature protocols.[3]

Anhydrous and deoxygenated acetonitrile (MeCN) and anhydrous and deoxygenated dichloromethane (DCM) were dispensed from a Grubb's-type Phoenix Solvent Drying System built by JC Meyer.[5] Solvent was removed under reduced pressure with a Büchi Rotovapor with a Welch self-cleaning dry vacuum pump and further dried with a Welch DuoSeal pump. Dialysis was performed with pre-wetted Spectra/Por 6 regenerated cellulose dialysis membranes with a 1 kDa molecular weight cutoff purchased from Spectrum Laboratories. Nuclear magnetic resonance (^{1}H-NMR, ^{13}C-NMR) spectra were taken on Bruker Avance 500 instrument and processed with MestReNova 14.2.3 software unless otherwise stated. All ^{1}H-NMR and ^{13}C-NMR peaks are reported in reference to $CDCl_3$ at 7.26 ppm and 77.16 ppm, respectively. High resolution mass spectrometry was acquired on a Waters LCT Premier TOF LC/MS coupled with an ACQUITY UPLC (Waters).

For assessment of the statistical significance of differences, a one-tailed Student's t-test assuming unequal sample variance was employed. Results were considered significant/not significant different per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$

Instrumentation

Size exclusion chromatography: Size exclusion chromatography (SEC) was performed on a Jasco GPC workstation using trifluoroethanol (TFE) as the eluent (0.5 mL min^{-1}, room temperature) with 20 mM NaTFA as an additive through a PFG analytical guard column (Linear S, 50 x 8 mm, 5 µm, Polymer Standard Service- USA, Inc.) and two PFG analytical columns (Linear S, 300 x 8 mm, 5 µm, Polymer Standard Service- USA, Inc.) in series. Poly(2-methyl-2-oxazoline) (P(MeOx), synthesized in house, see appendix 1) were validated by mass using matrix assisted laser desorption ionization (MALDI), and the number average molecular weight (M_n) values were used to build a calibration curve. Processing was performed using ChromNAV Data Analysis software (Version 2.0, Jasco). Polymers were dissolved in TFE (1 mg mL^{-1}), filtered (0.22 µm, PTFE, Filtrous), and injected using an auto-sampler (20 µL). M_n obtained from SEC was used to determine

molar amounts of product for calculating both yield, as well as stoichiometry in post polymerization modifications.

Matrix-assisted laser desorption/ionization time-of-flight: Mass spectral data for polymers were obtained on an AB SCIEX TOF TOF 5800 MS. Samples were acquired using linear positive mode. For calibrant preparation: Calibration was performed using low mass calibration standards (for calibration with MW 700 < 3500 Da). The mixture of standards was dissolved in 125 µL of 0.1% TFA in water. The mixture of standards was purchased from Bruker and contains the following peptides: Bradykinin 1-7 (MW: 757.3992 Da, average: 757.86 Da), Angiotensin II (MW: 1046.5418 Da, average: 1047.19 Da), Angiotensin I (MW: 1296.6853 Da, average: 1297.49 Da), Substance P (MW: 1347.7354 Da, average: 1348.64 Da), Bombesin (MW: 1619.8223 Da, average: 1620.86 Da), ACTH clip 1-17 (MW: 2093.0862 Da, average: 2094.43 Da), ACTH clip 18-39 (MW: 2465.1983 Da, average: 2466.68 Da), and Somatostatin 28 (MW: 3147.4710 Da, average: 3149.57 Da). Matrix solution of alpha-cyano-4-hydroxycinnamic acid (Sigma-Aldrich) was prepared in 1:2 MeCN/H_2O + 0.1% TFA (vol%) at 10 mg/mL. This matrix solution was spotted directly onto the plate, followed by the mixture of the standards. For polymer analytes: Matrix solution of *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB, Millipore Sigma, ≥99.0%) was prepared in $CHCl_3$ at 20 mg/mL. Counterion solution of sodium trifluoroacetate (NaTFA, Sigma-Aldrich, 98%) was prepared in isopropanol at 10 mg/mL. Polymer analyte solutions were prepared in $CHCl_3$ at 20 mg/mL. Solutions were combined at a 50:5:1 matrix:analyte:counter-ion ratio and mixed thoroughly on a vortex. Samples (2 µL x 10) were then spotted in duplicate on the MALDI target plate. Spectra represent the sum of 4,000 shots. The laser intensity was set to 7,000.

µwave reactor: µwave reactions were performed using a CEM Discover SP µwave synthesis reactor. All reactions were performed in glass 10 mL µwave reactor vials purchased from CEM with silicone/PTFE caps. Flea micro PTFE-coated stir bars were used in the vials with magnetic stirring set to high and 15 seconds of premixing prior to the temperature ramping. All µwave reactions were carried out at 140 °C with the pressure release limit set to 250 psi (no reactions exceeded this limit to trigger venting) and the maximum wattage set to 150 W (the power applied was dynamically controlled by the µwave instrument and did not exceed this limit for any reactions).

Dynamic light scattering: Emulsion size and zeta potential was measured with a Malvern Zetasizer Nano dynamic light scattering. Size SOP parameters: 10 runs, 10 seconds/run, three measurements, no delay between measurements, room temperature with 30 second equilibration time. Collection parameters: Lower limit = 0.6, Upper limit = 1000, Resolution = High, Number of size classes = 70, Lower size limit = 0.4, Upper size limit = 1000, Lower threshold = 0.05, Upper threshold = 0.01. Data are representative of three replicate measurements. Zeta potential analysis: Zeta potential was analyzed with a Malvern Zetasizer Nano. SOP parameters: 50 runs, 3 measurements, no delay between measurements, Model: Smoluchowski, room temperature, 20 second equilibration time. Collection parameters: Auto mode. Data are representative of three replicate

measurements. Zeta potential error bars represent the standard deviation of the measurements.

Fluorescence spectroscopy: Measurements were taken on ThermoFisher Varioskan Lux Multi-mode microplate reader (VLBL00D0). Fluorescence measurements were done in a black 96-well plate (Polystyrene, flat bottom, Genesee Scientific). Excitation was at 500 nm, with a 5 nm bandwidth. Emission was collected from 555 - 595 nm, in 1 nm steps. Measurements were taken from the top with a measurement time of 1000 ms at 50/60 Hertz.

Abbreviations

$CDCl_3$ = Deuterated chloroform; $CHCl_3$ = chloroform; CPB = citrate phosphate buffer; DCM = dichloromethane; DI water = deionized water; DLS = dynamic light scattering; MALDI-TOF = matrix assisted laser desorption ionization time of flight; MeCN = acetonitrile; MeOH = methanol; MeOx = 2-methyl-2-oxazoline; MWCO = molecular weight cut off. $NaHCO_3$ = Sodium bicarbonate; $MgSO_4$ = magnesium sulfate; CO_2 = carbon dioxide; NaTFA = sodium trifluoroacetate; NMR = nuclear magnetic resonance; NonOx = 2-nonyl-2-oxazoline; PBS = phosphate buffered saline; PFC = perfluorocarbon; PFOB = perfluorooctylbromide; P(MeOx) = poly(2-methyl-oxazoline); SEC = size exclusion chromatography; NaTFA = sodium trifluoroacetate; TFE = 2,2,2-trifluoroethanol

Emulsion formulation and characterization

Formulation: Emulsions were formulated by addition of surfactant **7** or **8** (2.5 mg) into an Eppendorf tube. A 1:1 mixture of MeOH and MilliQ water (100 μL) was added. The surfactant was thoroughly dissolved first by vortex agitation, then by heating mildly. PFOB (10 μL) was then added and the mixture was centrifuged (3200 *g* for 30 s) to ensure complete phase separation The sample was then emulsified by sonication for 90 sec at 35% amplitude on ice using a Sonica (Q125) sonicator. The emulsion was then washed with water by pelleting (3300 *g*, 3 min), resusupending in MilliQ water (100 μL), pelleting (3300 *g*, 3 min), and resuspending the appropriate buffer (100 μL). If fluorous rhodamine was used as the payload, then a varying amount of fluorous rhodamine was dissolved (concentration specified in each section) in the PFOB.

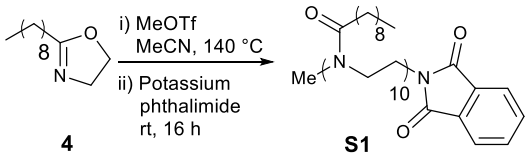
Characterization: Emulsion size was measured by dynamic light scattering. The bulk emulsion solution was diluted in MilliQ H_2O (20 μL emulsions in 2 mL MilliQ H_2O) in a plastic 1 cm cuvette. Emulsion surface charge was measured via zeta potential. The bulk emulsion solution was diluted in MilliQ H_2O (20 μL emulsions in 2 mL MilliQ H_2O) in a plastic 1 cm cuvette. The solution was then transferred to a disposable folded capillary cell for zeta potential measurements.

1-octanol partition experiment protocol

Emulsions formed from **7** or **8** were prepared on a 5x scale (12.5 mg surfactant, 500 μL solution) and loaded with rhodamine. 50 μL of acetone containing 1 mM fluorous rhodamine was used. The solution was divided into 10 aliquots (50 μL each), which were each pelleted (3300 *g* for 3 min) and resuspended in the appropriate buffer (CPB pH 7.4, 6.0, or 5.0, 50 μL each). Each buffer condition was tested in triplicate. Each emulsion solution was further diluted in 1.25 mL of the respective pH CPB buffer. 1-octanol (0.5 mL) was gently added on top of this solution. 100% payload release was determined by measuring the fluorescence of 50 μL of emulsion (after drying) in 1-octanol. Fluorescence of each experiment was taken by removing 1-octanol (200 μL) and measuring the photoluminescence in a 0.3 mL cuvette with 500 nm excitation and collection from 525–700 nm. Slits were 1 nm, step size 2 nm, integration time 0.1 s. After measurement, the 1-octanol was returned. The maximum of the fluorescence intensity measurement was used in quantification.

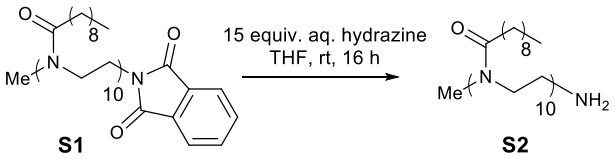
Synthetic chemistry experimental procedures

Synthesis of **S1**:



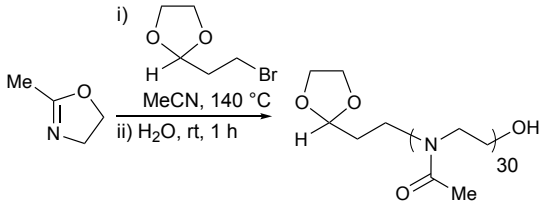
To an oven dried μwave vial, flame dry and purge / backfill x3 with N_2. MeCN (0.71 mL, anhydrous), NonOx (0.53 mL, 0.5 g, 2.5 mmol, 10 equiv.), and methyl triflate (28.7 μL, 0.042 g, 0.25 mmol, 1 equiv.) were added. The mixture was mixed gently and heated at 140 °C in the μwave for 2 min 40 s. After, the reaction was terminated with potassium phthalimide (0.167 g, 2.53 mmol, 10 equiv.). After 16 h, the reaction mixture was filtered through cotton and celite, then polymer **S1** was evaporated to dryness. The polymer **S1** was dissolved in DCM (10 mL) and the organic phase was washed with water (3 x 30 mL) in a separatory funnel. The organic layer was dried with sodium sulfate. Polymer **6** was evaporated to dryness, yielding the product as a white solid. (0.3933 g, 1.83 mmol, 73%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (m, 4H), δ 3.43 (m, 38H), 3.00-2.93 (m, 3H), 2.31-2.21 (m, 19H), 1.58 (m, 18H), 1.24 (m, 114H), 0.86 (m, 28H) ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.0, 173.4, 171.3, 168.3, 168.0, 134.3, 133.0, 123.6, 62.5, 45.3, 42.6, 33.7, 33.1, 32.9, 32.0, 29.7, 29.5, 25.5, 25.4, 22.8, 14.2. LCMS: Calculated for Me-P(NonOx)$_7$-phthalimide $[M+H]^+$: 1542.29; found: 1541.97. M_w = 0.9 kDa, M_n = 0.8 kDa, $Đ$ = 1.13. SEC: M_w = 1.2 kDa, M_n = 1.2 kDa, $Đ$ = 1.08.

Synthesis of **S2**:



To a scintillation vial, **S1** (0.27 g, 0.15 mmol, 1 equiv.) was added. Tetrahydrofuran (15 mL) was added, followed by 64 wt% aqueous hydrazine (0.11 mL, 2.2 mmol, 15 equiv.). The reaction mixture was diluted with DCM (20 mL) and added to a separatory funnel. Polymer **S2** was washed with saturated $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried with sodium sulfate. Polymer **S2** was evaporated to dryness, yielding the product as a white solid. (0.239 g, 0.120 mmol, 80%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.41 (m, 36H), 2.99-2.92 (m, 3H), 2.30-2.21 (m, 19H), 1.56 (m, 21H), 1.22 (m, 111H), 0.84 (m, 29H) ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.0, 173.3, 45.5, 33.7, 33.1, 32.9, 32.0, 29.7, 29.5, 25.5, 25.3, 22.8, 14.2. LCMS: Calculated for Me-P(NonOx)$_7$-NH_2 $[M+H]^+$: 1412.29; found: 1412.05. M_w = 1.6 kDa, M_n = 1.3 kDa, $Đ$ = 1.19. SEC: M_w = 1.5 kDa, M_n = 1.4 kDa, $Đ$ = 1.06.

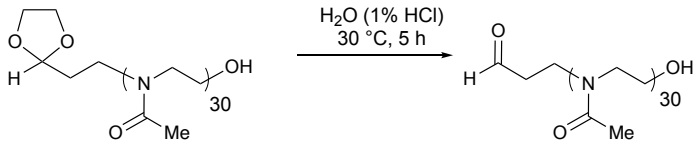
Synthesis of **2**:



1 **2**

To an oven dried μwave vial, flame dry and purge / backfill x3 with N_2. MeCN (9.38 mL, anhydrous), MeOx (5 mL, 5 g, 60 mmol, 20 equiv.), and 2-(2-bromoethyl)-1,3-dioxolane (0.3818 mL, 0.5345 g, 2.953 mmol, 1 equiv.) were added. The mixture was mixed gently and heated at 140 °C in the μwave for 8 min 18 s. After, the reaction was quenched with water (0.709 mL, 0.709 g, 39.4 mmol, 13 equiv.). After 1 h, polymer **2** was evaporated to dryness, re-dissolved in water and then dialyzed (1,000 MWCO). Polymer **2** was evaporated to dryness, yielding the pure product as a white solid. (2.104 g, 0.5508 mmol, 19%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85 (s, 1H), 4.40 (m, 1H), 3.94 (m, 2H), 3.84 (m, 2H), 3.46-3.27 (m, 159H), 2.47 (m, 2H), 2.11-1.91 (m, 125H) ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.4, 170.8, 48.0, 46.9, 45.4, 43.5, 21.3. MALDI: Calculated for dioxolane-P(MeOx)$_{15}$-OH $[M+H]^+$: 1394.85; found: 1394.76. M_w = 3.0 kDa, M_n = 2.8 kDa, $Đ$ = 1.07. SEC: M_w = 3.8 kDa, M_n = 3.3 kDa, $Đ$ = 1.15.

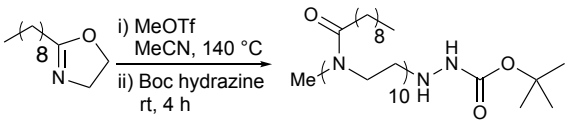
Synthesis of **3**:



2 **3**

To a 100 mL round bottom flask, **2** (1.541 g, 0.4034 mmol, 1 equiv.) was added. Water (42 mL) was added, then HCl (0.8 mL, 2 vol%) was added dropwise. The reaction was heated to 37 °C for 2 h. The crude reaction mixture was immediately dialyzed (1,000 MWCO). Polymer **3** was evaporated to dryness, yielding the pure product as a white solid (0.9382 g, 0.2433 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82-9.76 (s, 1H), 4.40 (m, 1H), 3.48-3.43 (m, 121H), 2.62 (m, 10H), 2.13-2.06 (m, 90H) ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.4, 170.8, 53.6, 47.6, 46.9, 45.4, 43.6, 21.3. MALDI: Calculated for aldehyde-P(MeOx)$_{19}$-OH $[M+H]^+$: 1691.04; found: 1693.97. M_w = 3.3 kDa, M_n = 3.1 kDa, $Đ$ = 1.07. SEC: M_w = 3.8 kDa, M_n = 3.5 kDa, $Đ$ = 1.09.

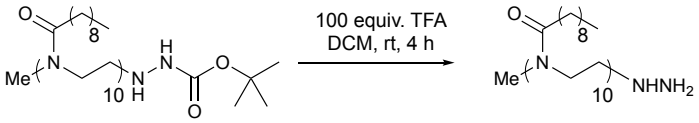
Synthesis of **5**:



4 **5**

To an oven dried μwave vial, flame dry and purge / backfill x3 with N_2. MeCN (4.53 mL, anhydrous), NonOx (2 mL, 1.964 g, 9.960 mmol, 10 equiv.), and methyl triflate (112 μL, 0.1635 g, 0.996 mmol, 1 equiv.) were added. The mixture was mixed gently and heated at 140 °C in the μwave for 3 min 54 s. To a separate 25 mL round bottom flask, flame dry and purge / backfill x3 with N_2. DCM (5 mL, anhydrous) was added through a syringe and *tert*-butyl carbazate (1.316 g, 9.960 mmol, 10 equiv.) was added under flow of N_2. Once the polymerization was complete, the polymerization solution was transferred to the 25 mL round bottom flask *via* syringe to end cap. The solution was allowed to stir at room temperature for 4 h. Polymer **5** was evaporated to dryness. Polymer **5** was purified by dissolving into DCM (5 mL) and precipitating directly into cold MeCN (10:1 v/v%). The precipitated solid was washed once more with cold MeCN (50 mL). Polymer **5** was decanted after centrifugation, then **5** was evaporated to dryness. Polymer **5** was obtained a white solid (0.9331 g, 0.6288 mmol, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.42 (m, 31H), 3.01-2.93 (m, 3H), 2.32-2.24 (m, 18H), 1.57 (m, 17H), 1.45 (s, 9H), 1.24 (m, 103H), 0.88-0.85 (t, 26H) ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.3, 45.4, 33.1, 32.9, 32.0, 29.7, 29.5, 25.6, 25.4, 22.8, 14.2. MALDI: Calculated for Me-P(NonOx)$_6$-NHNHBoc $[M+Na]^+$: 1330.17; found: 1331.13. M_w = 2.1 kDa, M_n = 1.9 kDa, $Đ$ = 1.11. SEC: M_w = 1.7 kDa, M_n = 1.6 kDa, $Đ$ = 1.06.

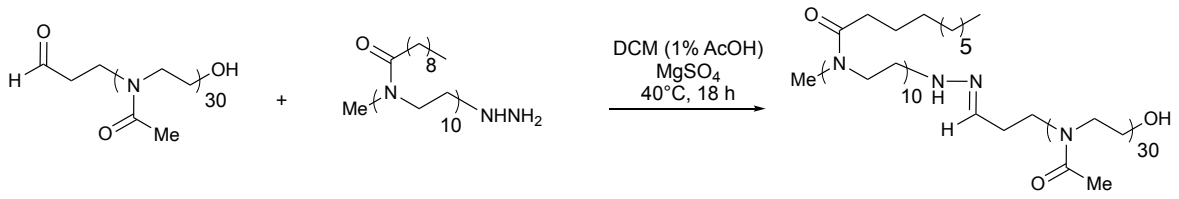
Synthesis of **6**:



5 **6**

To a scintillation vial, **5** (0.8806 g, 0.5934 mmol, 1 equiv.) was added. DCM (2.6 mL) was added, then TFA (2.6 mL, 50 vol%) was added dropwise. The reaction was allowed to stir for 5 h at room temperature. The reaction was quenched by adding the reaction mixture dropwise into saturated $NaHCO_3$ (40 mL) in a separatory funnel. Additional DCM (10 mL) was added, then the organic phase was washed with water (2 x 40 mL) and brine (1 x 40 mL). The organic layer was dried with sodium sulfate. Polymer **6** was evaporated to dryness, yielding the product as a white solid. (0.7373 g, 0.5285 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.42 (m, 34H), 3.00-2.93 (m, 3H), 2.30-2.23 (m, 19H), 1.57 (m, 19H), 1.24 (m, 115H), 0.86 (m, 29H) ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 173.3, 45.5, 33.7, 33.1, 32.9, 32.0, 29.7, 29.5, 28.9, 25.6, 25.4, 22.8, 14.2. Calculated for Me-P(NonOx)$_7$-$NHNH_2$ $[M+H]^+$: 1427.30; found: 1427.14. M_w = 2.0 kDa, M_n = 1.9 kDa, $Đ$ = 1.09. SEC: M_w = 1.6 kDa, M_n = 1.4 kDa, $Đ$ = 1.14.

Synthesis of **7**:



3 **6** **7**

To an oven dried 3 necked, 100 mL round bottom flask, flame dry and purge / backfill x3 with N_2. Aldehyde **3** (505.4 mg, 0.1311 mmol, 1 equiv.) and hydrazine **6** (308.0 mg, 0.2075 mmol, 1.6 equiv.) were added under flow of N_2. DCM (40.4 mL) and AcOH (4 mL, 9 vol%) were added through a syringe, then $MgSO_4$ (0.350 g, 2.91 mmol, 22 equiv.) was added under flow of N_2. The reaction was heated to 35 °C on an oil bath for 18 h. The reaction mixture was then filtered through a Celite plug to remove $MgSO_4$. The reaction was quenched by adding it dropwise to saturated $NaHCO_3$ in water (140 mL). The mixture was shaken intermittently during the dropwise addition to quell the evolution of CO_2 gas. The two phases were then emulsified by vigorous shaking. The emulsion was then centrifuged (3000 *g* for 3 min). A water phase, emulsion phase, and organic phase were visible and were separated from one another. The water phase was extracted by addition of DCM (20 mL) and repetition of the centrifugation (3000 *g* for 3 min). The aqueous phase was then discarded, and the organic phases were combined. The DCM phase was extracted by addition of water (60 mL) and repetition of the centrifugation (3000 *g* for 3 min). The aqueous and organic phases were discarded, and the emulsion phases were combined. The emulsion phase was then washed by addition of DCM (10 mL) and DI water (20 mL). The three phases were shaken by hand, and then centrifuged (3000 *g* for 3 min). The aqueous and organic phases were discarded. This step was repeated once more. Polymer **7** was then evaporated to dryness, yielding the pure product as an off-white solid. (0.367 g, 0.0813 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34-5.25 (m, 1H), 3.48-3.44 (m, 192H), 3.01-2.94 (m, 3H), 2.33-2.23 (m, 19H), 2.14-2.08 (m, 120H), 1.75 (m, 46H), 1.59 (m, 20H), 1.25 (m, 134H), 0.88-0.86 (t, 37H). MALDI: M_w = 5.5 kDa, M_n = 5.1 kDa, $Đ$ = 1.08. SEC: M_w = 5.1 kDa, M_n = 4.4 kDa, $Đ$ = 1.16.

Figure experimental procedures

Figure 2A. Synthesis of polymers 2, 3, 5, 6, **and** 7**.**
See supporting synthetic chemistry experimental procedures.

Figure 2E. Matrix assisted laser desorption ionization spectra of 7**.**
See Instrumentation matrix-assisted laser desorption/ionization time-of-flight section.

Figure 3A. Degradation of 7 **monitored by SEC.**
6 mg of surfactant **7** was weighted into 3 different Eppendorf tubes. To each Eppendorf tube, 0.6 mL of a 1:1 mixture of MeOH and CPB buffer (pH 7.4, 6.0, or 5.0) was added (10 mg/mL). The samples were sonicated until dissolved fully. The Eppendorf tubes were then submerged in a sand bath preheated to 37 °C. 0.1 mL aliquots were taken at 0 h, 1 h, 3 h, 7 h, and 21 h. The solvent of the aliquot was blown off using air, then the sample (1 mg) was dissolved in 1 mL of trifluoroethanol (with 20 mM NaTFA) for SEC. The fraction of change was obtained by normalizing the retention times of each measurement using the retention time of **7** as the maximum and the retention time of **3** as the minimum. The percent decrease of surfactant was obtained by dividing these values by the fraction of change of CBP pH 7.4 at 0 h.

Figure 4C. Rhodamine Loaded Nanoemulsion Demulsification.
See emulsion formation and characterization section. For each experimental condition 12.5 mg of surfactant, 500 µL of 1:1 MeOH MilliQ water, and 50 µL of PFOB were used. 50 µL of acetone containing 1 mM fluorous rhodamine was used.

Figure 4D. Zeta potential of emulsions in varying pH CPB.
See emulsion formation and characterization section and instrumentation dynamic light scattering procedure. No payload was encapsulated within the nanoemulsion.

Figure 5B. Quantification of Payload Release by Fluorescence
See 1-octanol partition experiment protocol.

Supplemental figure experimental procedures

Figure S1A. Emulsion Purification Protocol.
See supporting synthetic chemistry experimental procedures.

Scheme S1. Synthesis of P(NonOx)-NH_2.
See supporting synthetic chemistry experimental procedures.

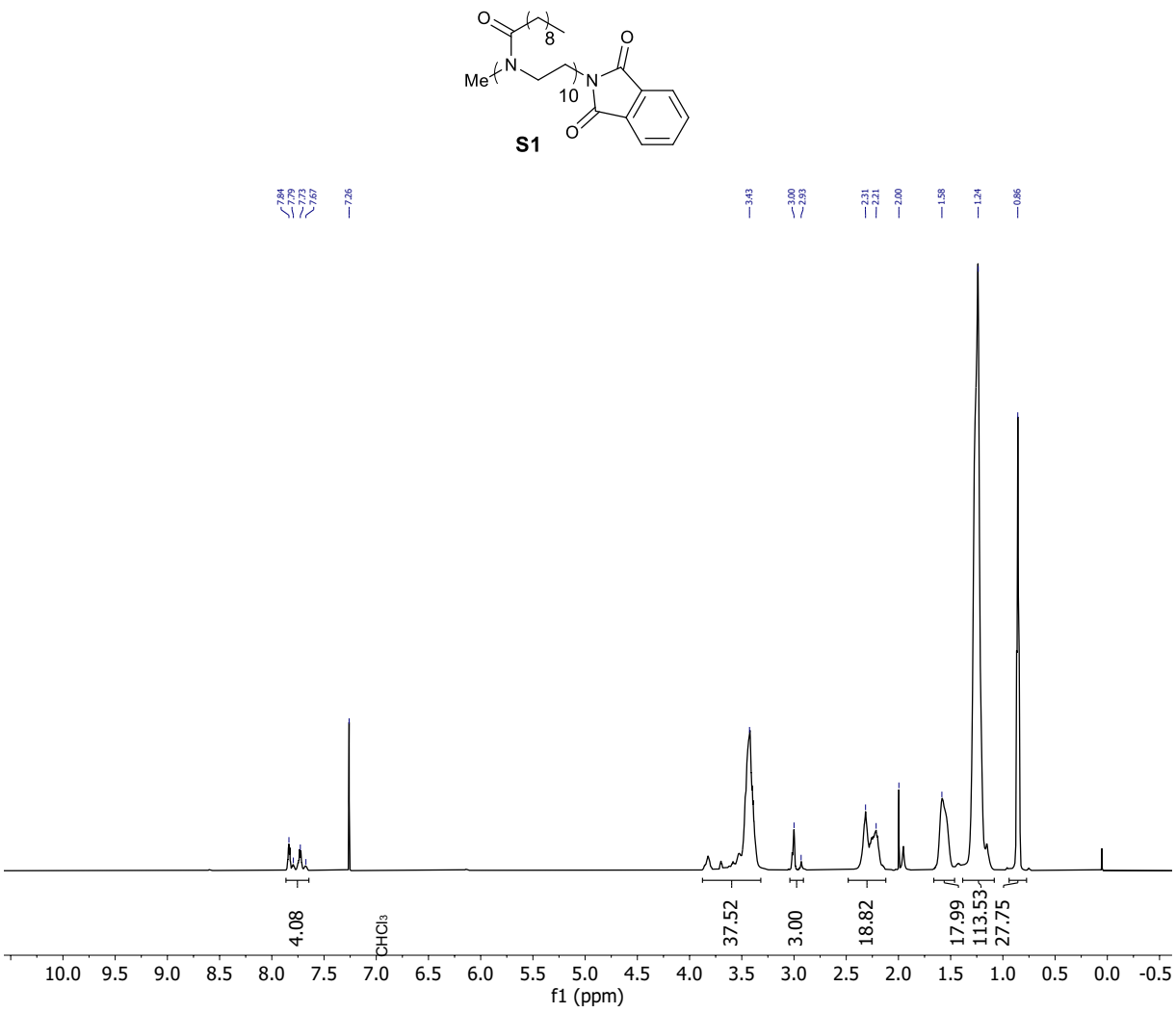
Figure S5. Degradation of 7 monitored by SEC.
6 mg of surfactant **7** was weighted into 3 different Eppendorf tubes. To each Eppendorf tube, 0.6 mL of a 1:1 mixture of MeOH and CPB buffer (pH 7.4, 6.0, or 5.0) was added (10 mg/mL). The samples were sonicated until dissolved fully. The Eppendorf tubes were then submerged in a sand bath preheated to 37 °C. 0.1 mL aliquots were taken at 0 h, 1 h, 3 h, 7 h, and 21 h. The solvent of the aliquot was blown off using air, then the sample (1 mg) was dissolved in 1 mL of trifluoroethanol (with 20 mM NaTFA) for SEC.

Figure S6A-C. Dynamic Light Scattering and Zeta potential of emulsions in varying pH CPB.
See emulsion formation and characterization section and instrumentation dynamic light scattering procedure. No payload was encapsulated within the nanoemulsion.

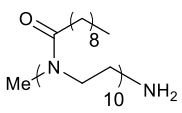
Figure S6D. Degradation of 7 in emulsions monitored by SEC
See emulsion formation and characterization section and instrumentation dynamic light scattering procedure. No payload was encapsulated within the nanoemulsion. After 21 h of incubation at 37 °C, 100 µL of the emulsion was removed. The solvent of the aliquot was blown off using air, then the sample (1 mg) was dissolved in 1 mL of trifluoroethanol (with 20 mM NaTFA) for SEC.

Figure S7. Rhodamine Loaded Nanoemulsion Demulsification in DMEM.
See emulsion formation and characterization section and instrumentation dynamic light scattering procedure. For each experimental condition, 12.5 mg of surfactant, 500 µL of 1:1 MeOH MilliQ water, and 50 µL of PFOB were used. 50 µL of acetone containing 1 mM fluorous rhodamine was used. DMEM was used.

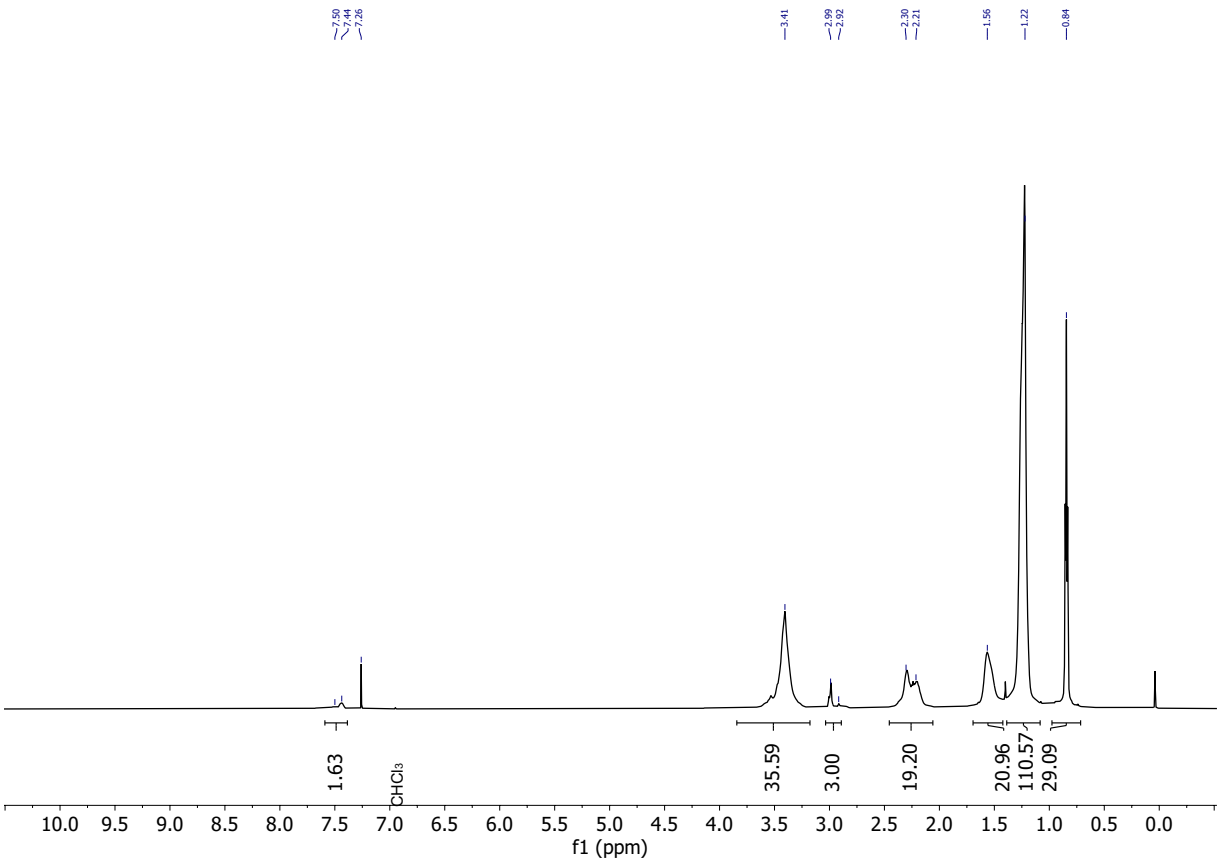
^{1}H NMR spectra



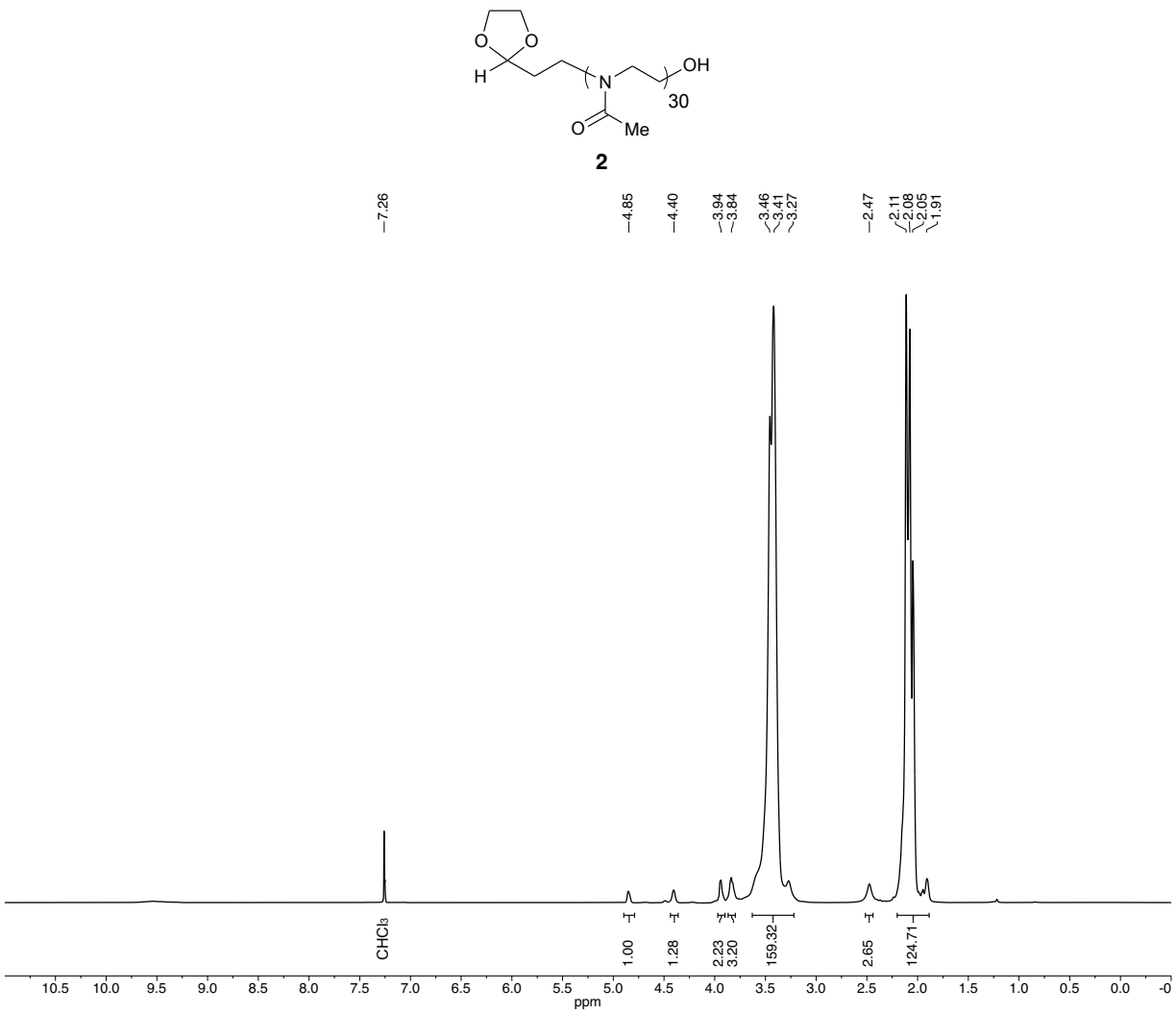
^{1}H NMR (500 MHz, $CDCl_3$) of **S1**.



S2

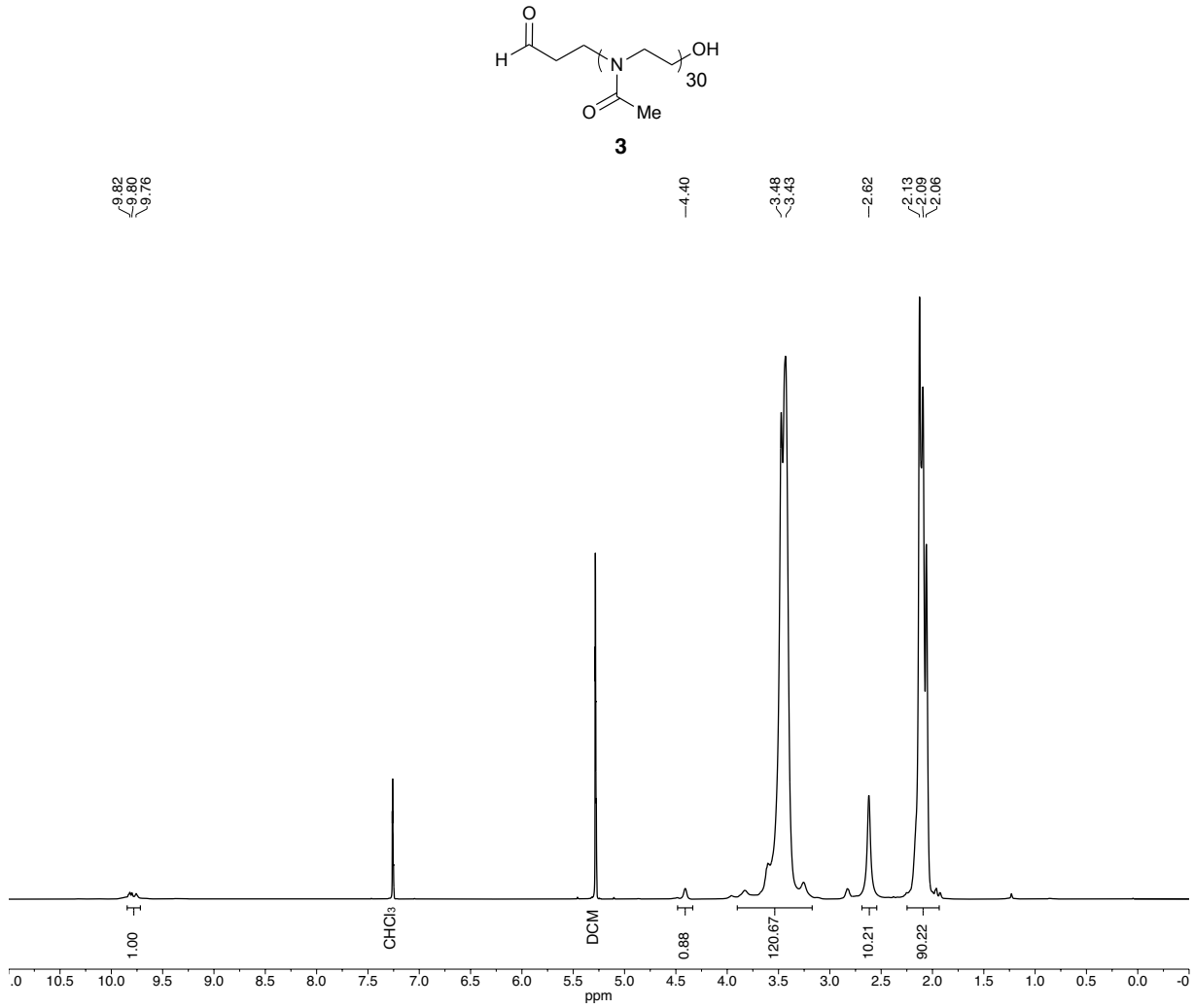


^{1}H NMR (500 MHz, $CDCl_3$) of **S2**.

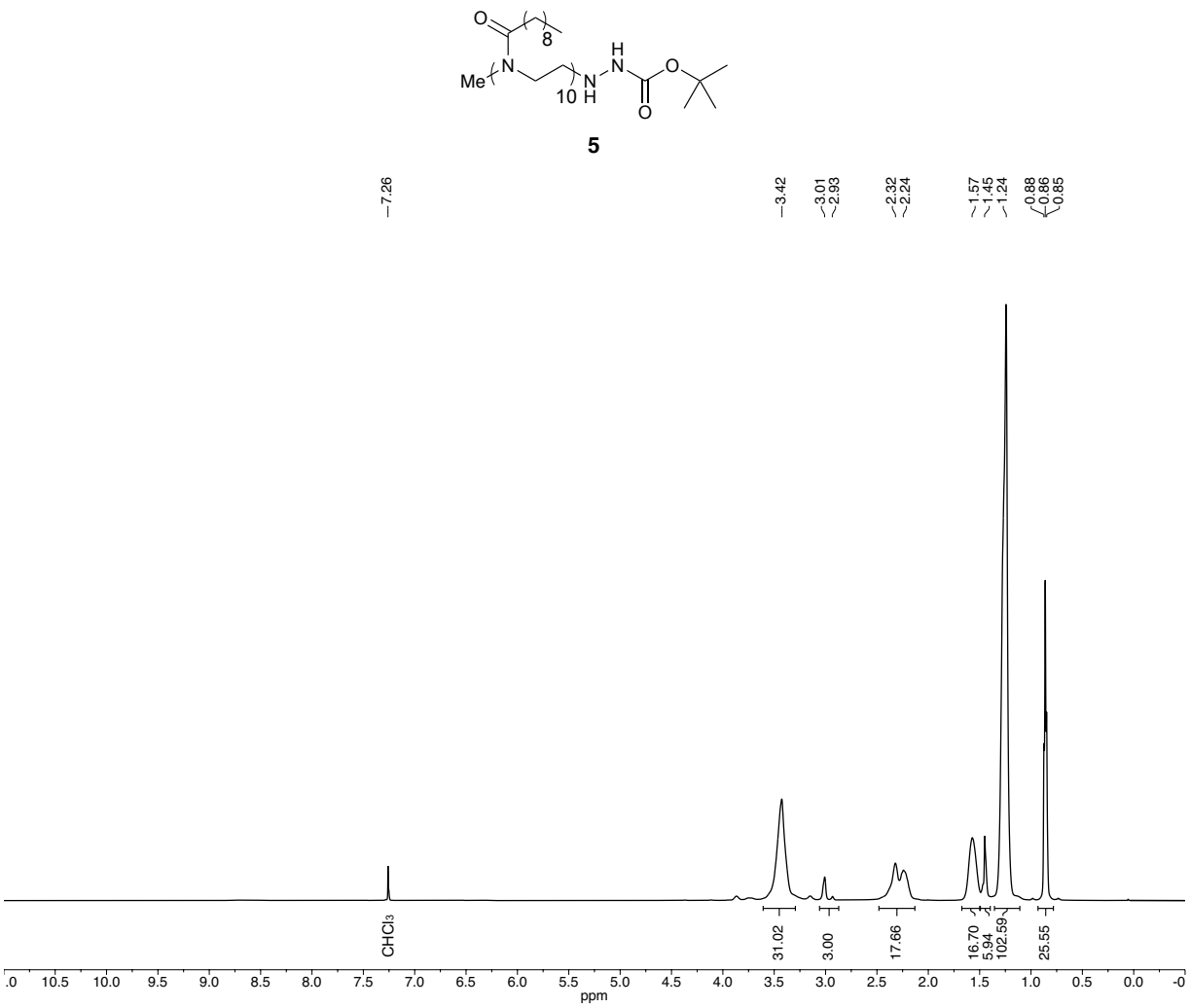


2

^{1}H NMR (500 MHz, $CDCl_3$) of **2**.



^{1}H NMR (500 MHz, $CDCl_3$) of **3**.



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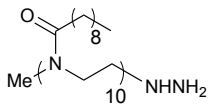
^{1}H NMR (500 MHz, $CDCl_3$) of **5**.



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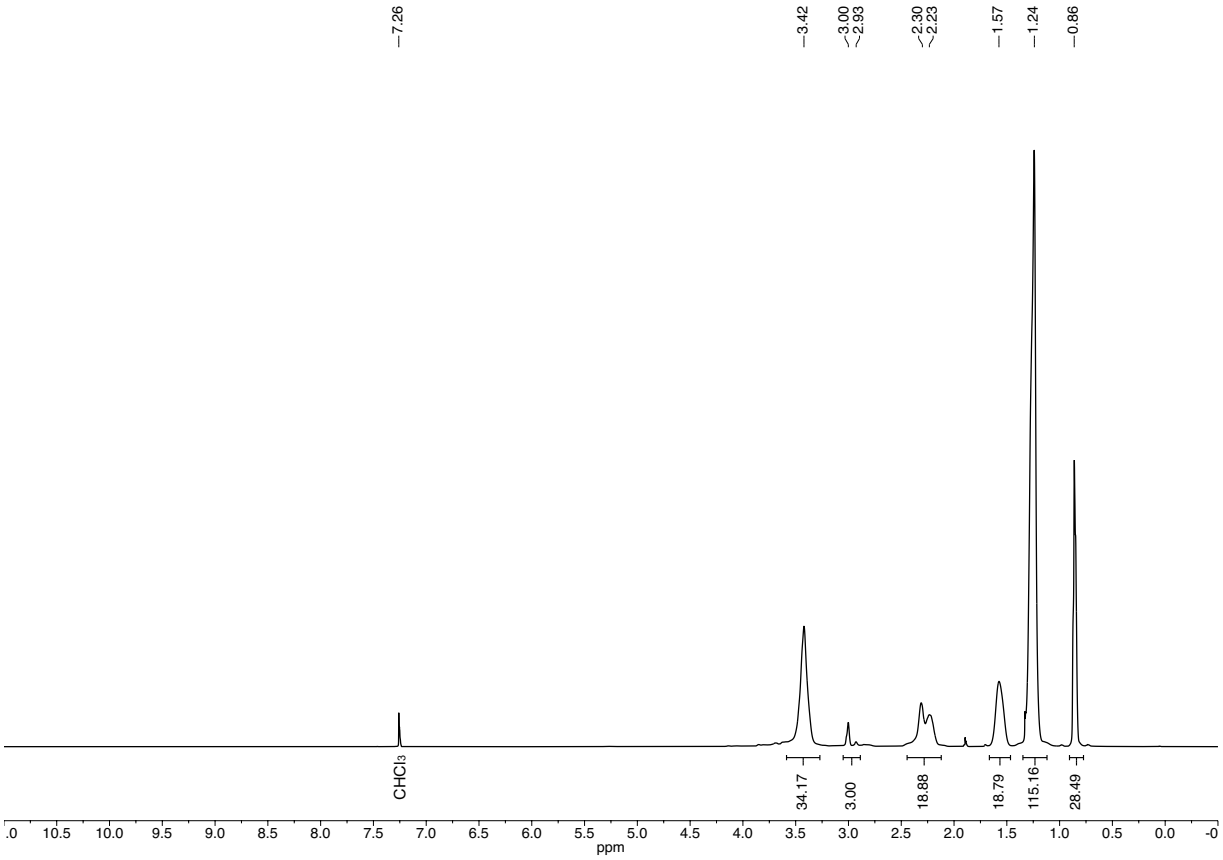
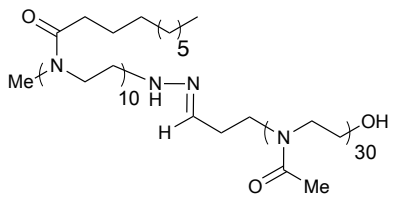


^{1}H NMR (500 MHz, $CDCl_3$) of **6**.



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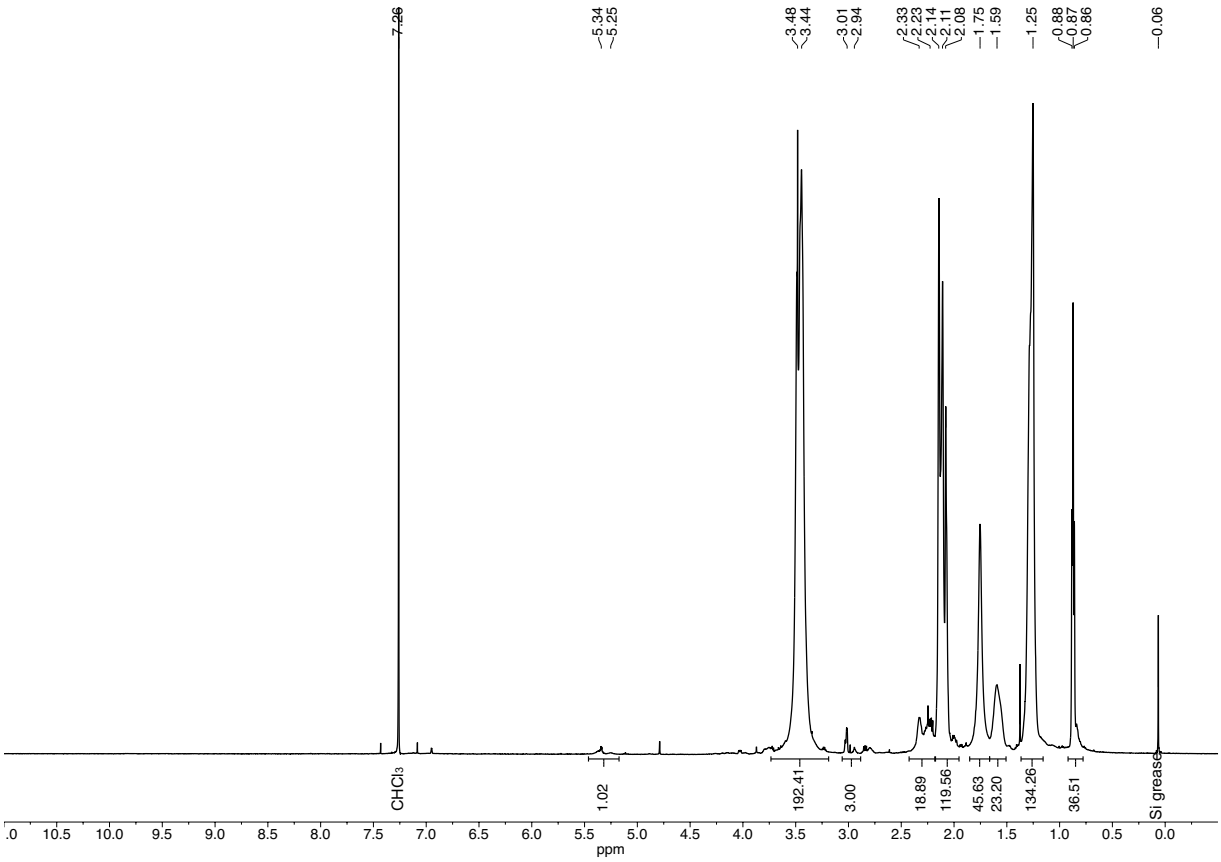
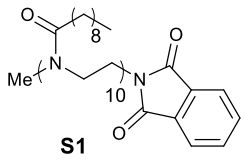
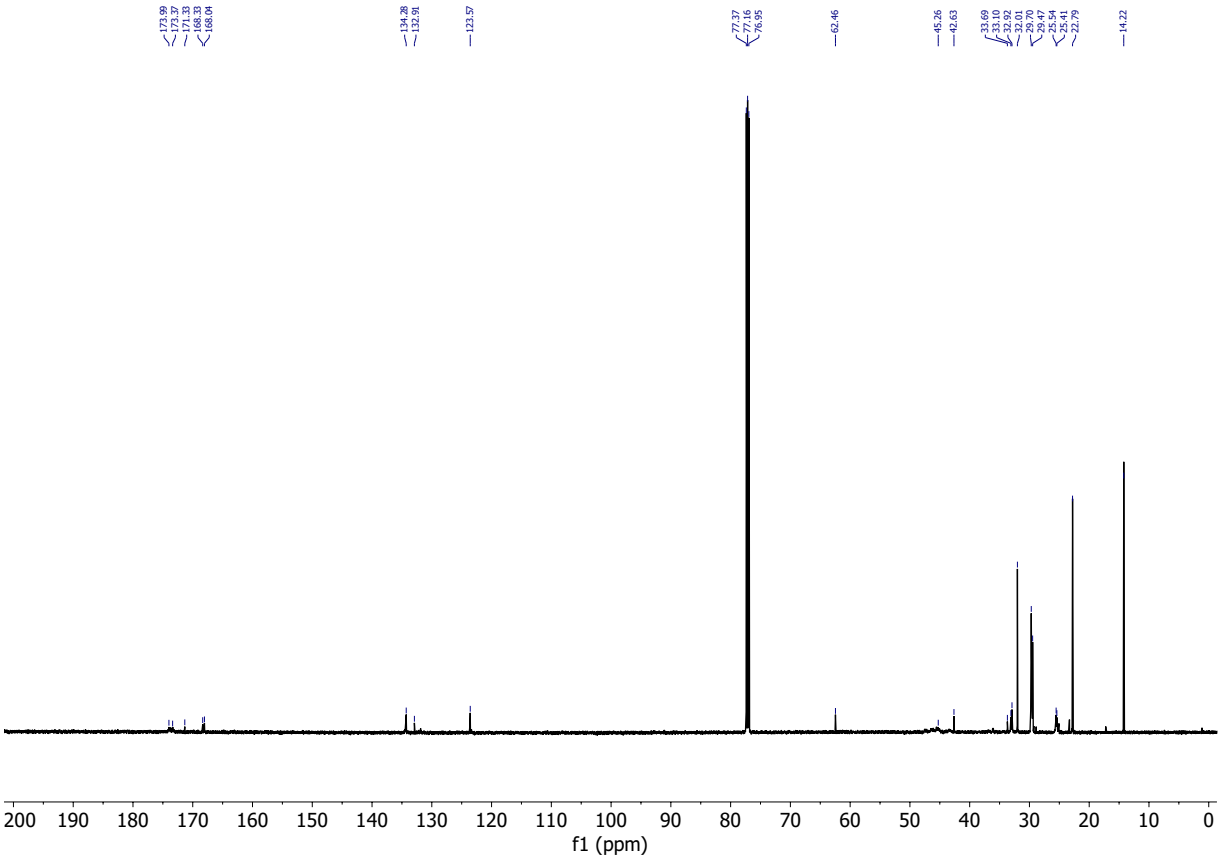


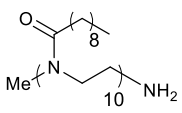
^{1}H NMR (500 MHz, $CDCl_3$) of **7**.

^{13}C NMR spectra

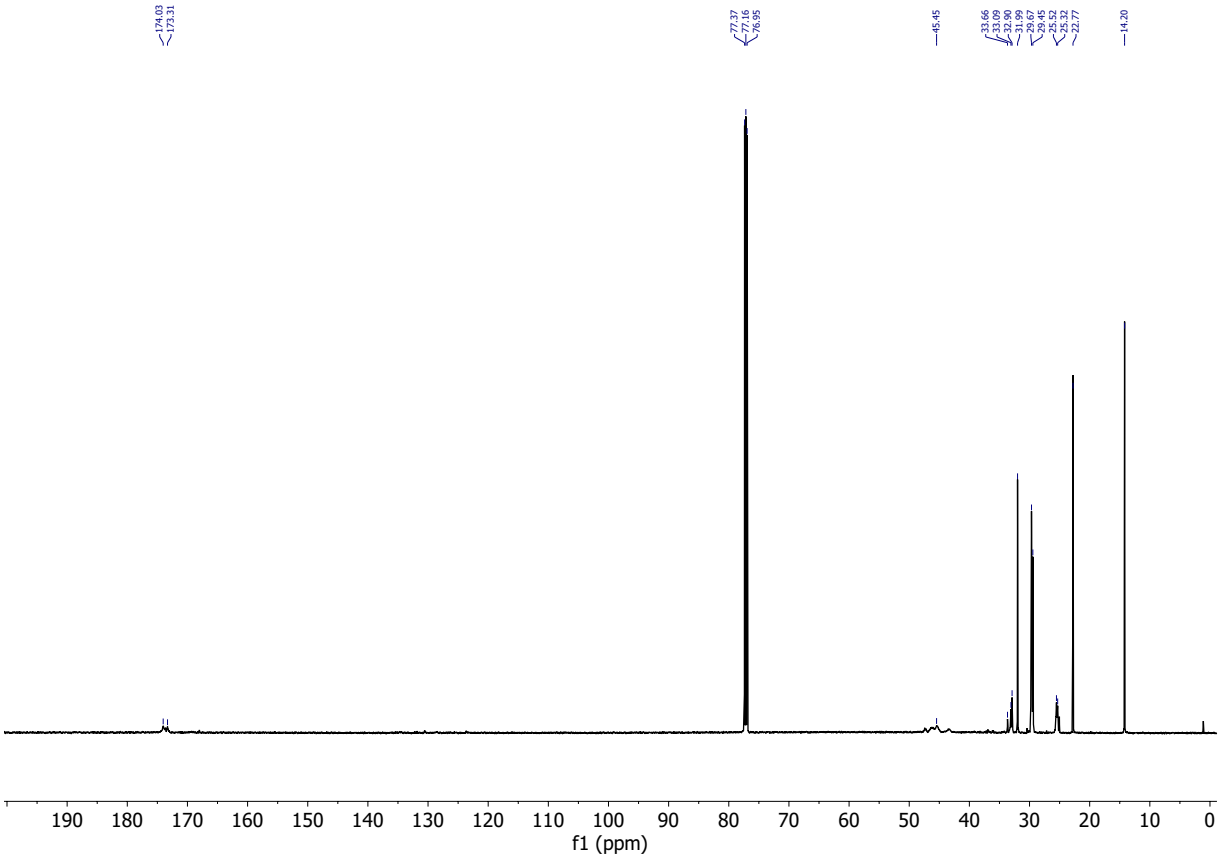




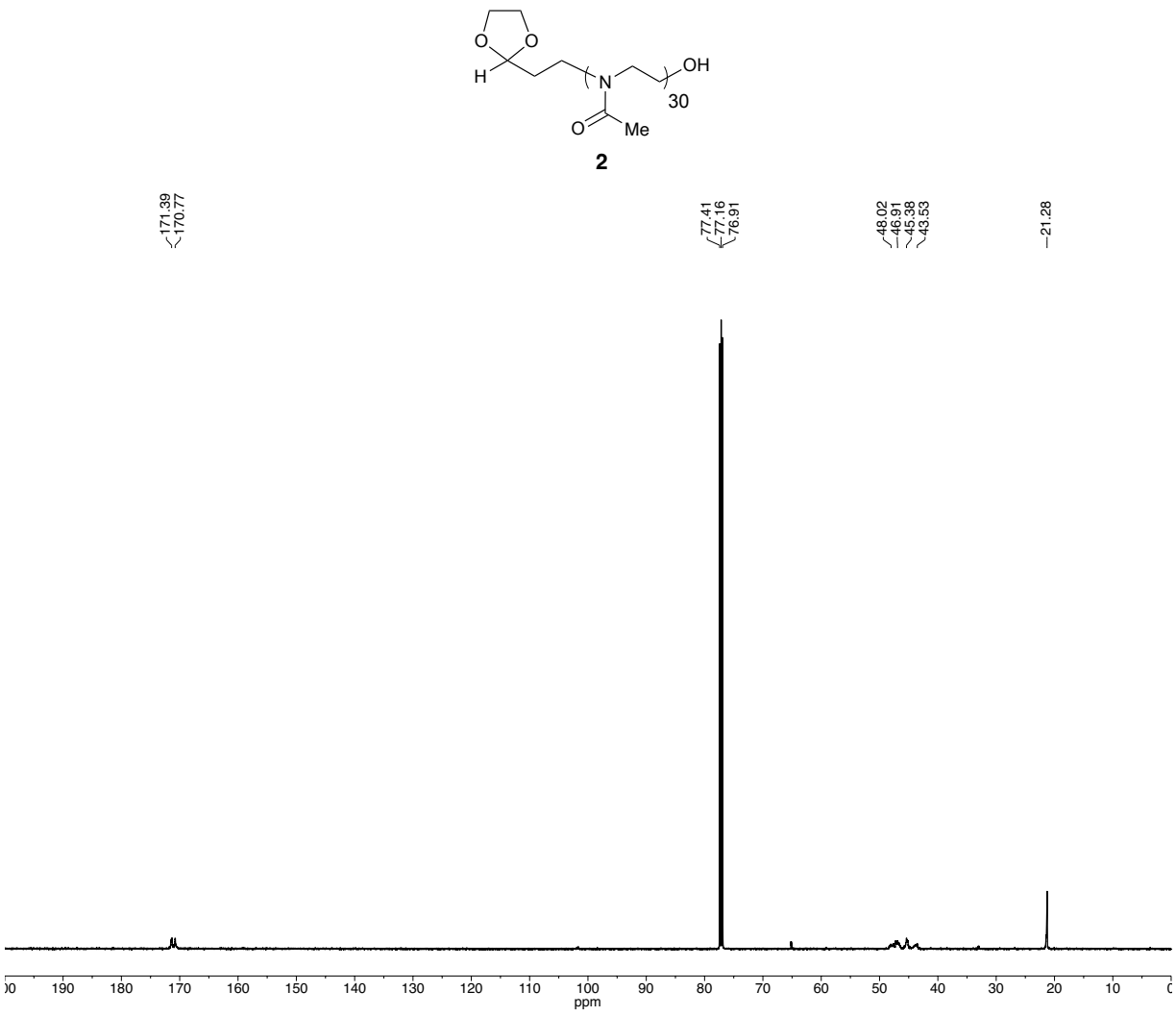
^{13}C NMR (126 MHz, $CDCl_3$) of **S1**.



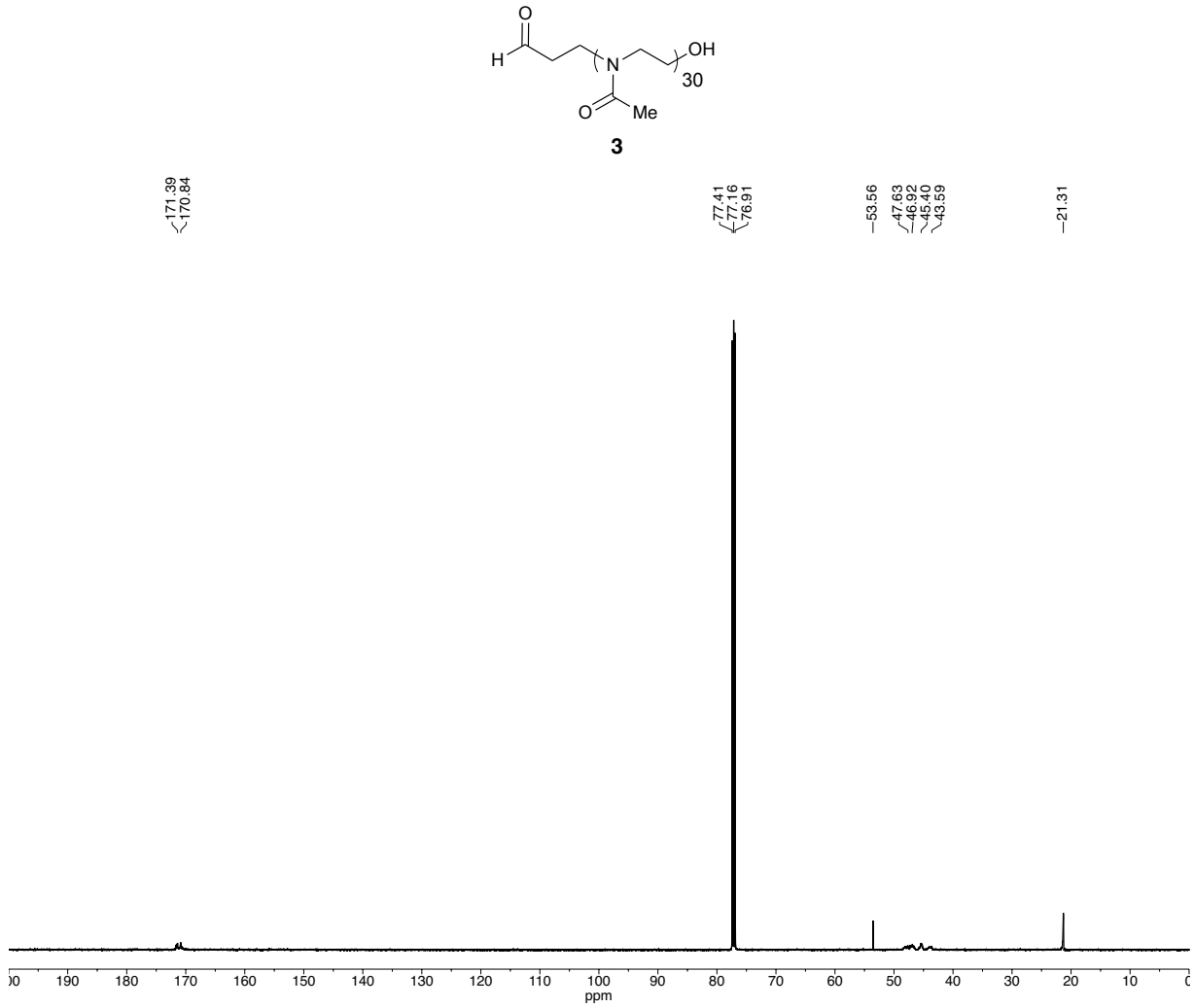
S2



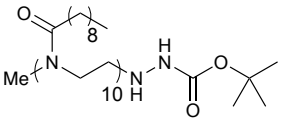
^{13}C NMR (126 MHz, $CDCl_3$) of **S2**.



^{13}C NMR (126 MHz, $CDCl_3$) of **2**.



^{13}C NMR (126 MHz, $CDCl_3$) of **3**.



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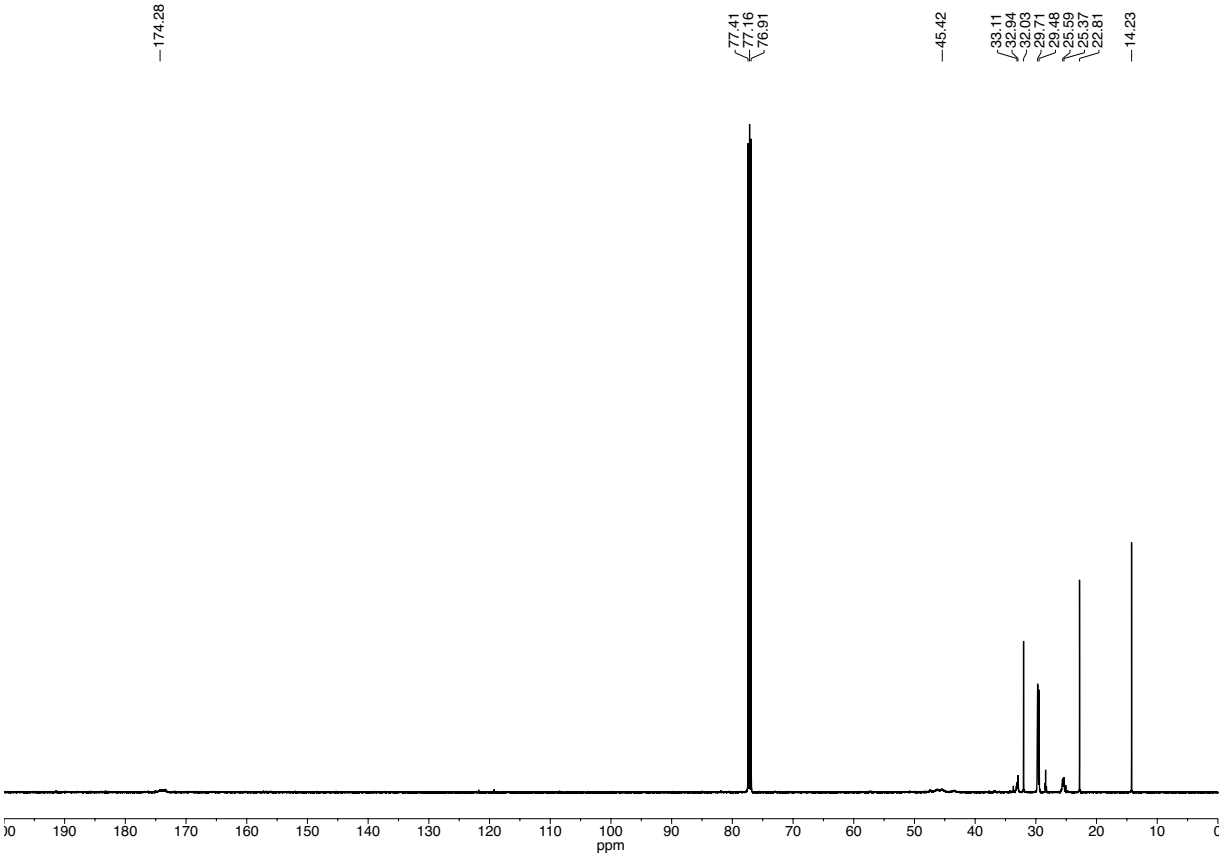
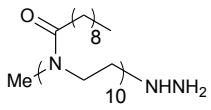


^{13}C NMR (126 MHz, $CDCl_3$) of **5**.



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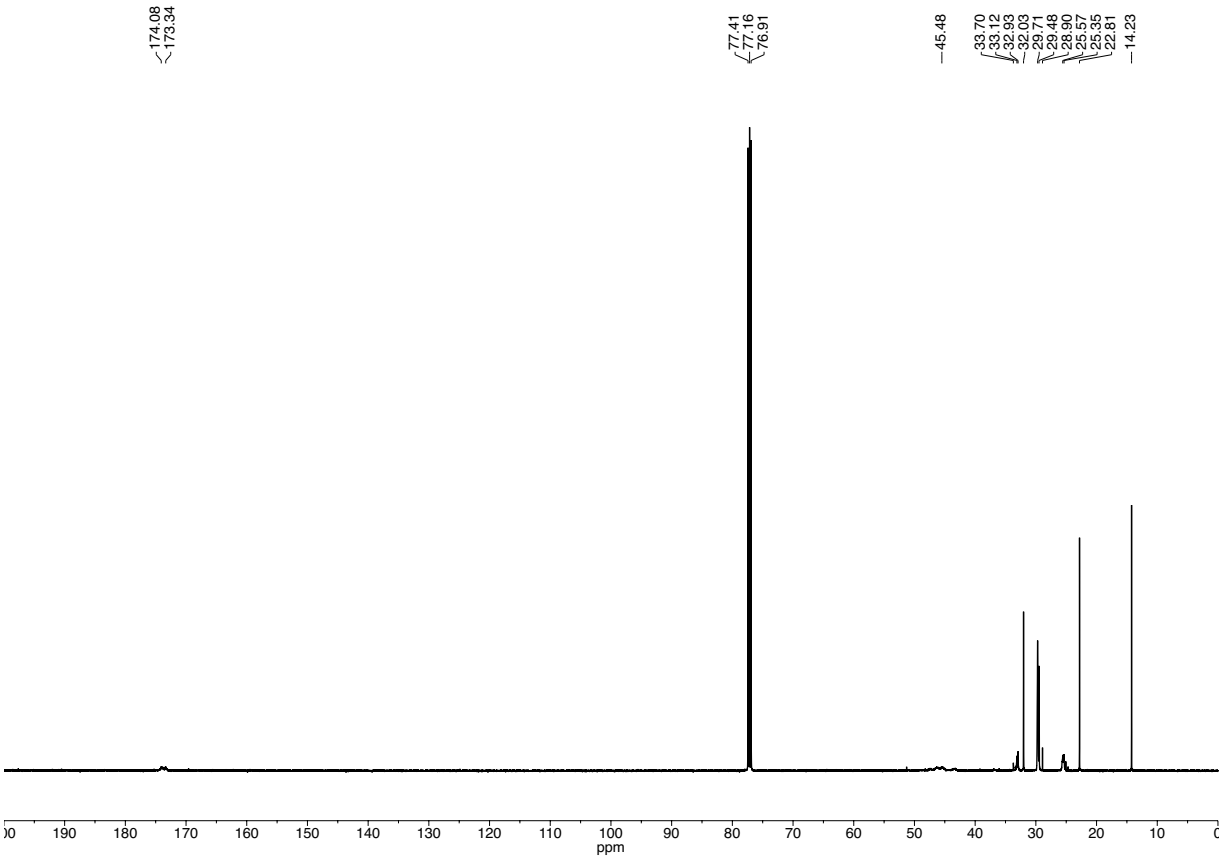
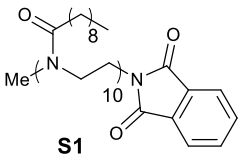
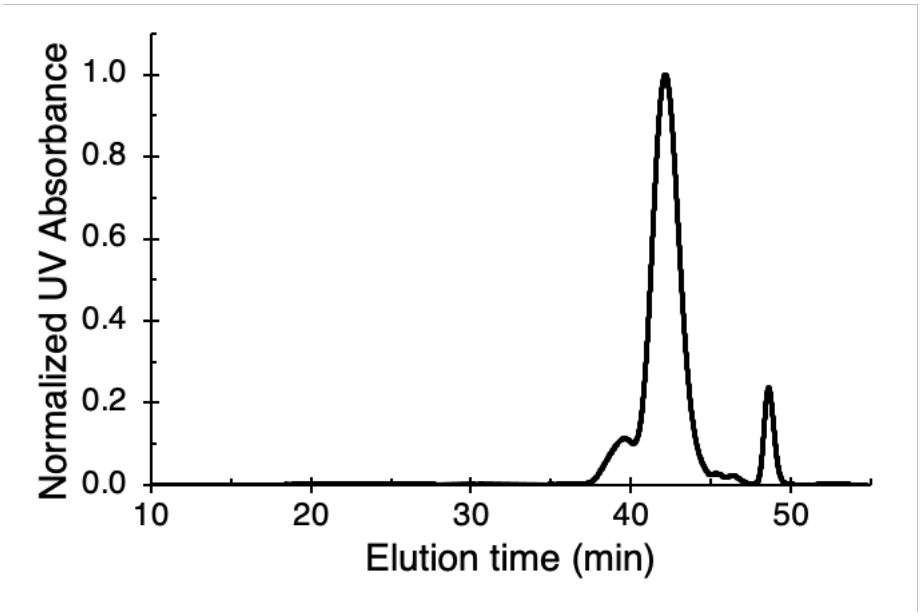


^{13}C NMR (126 MHz, $CDCl_3$) of **6**.

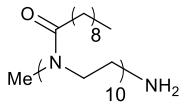
SEC traces



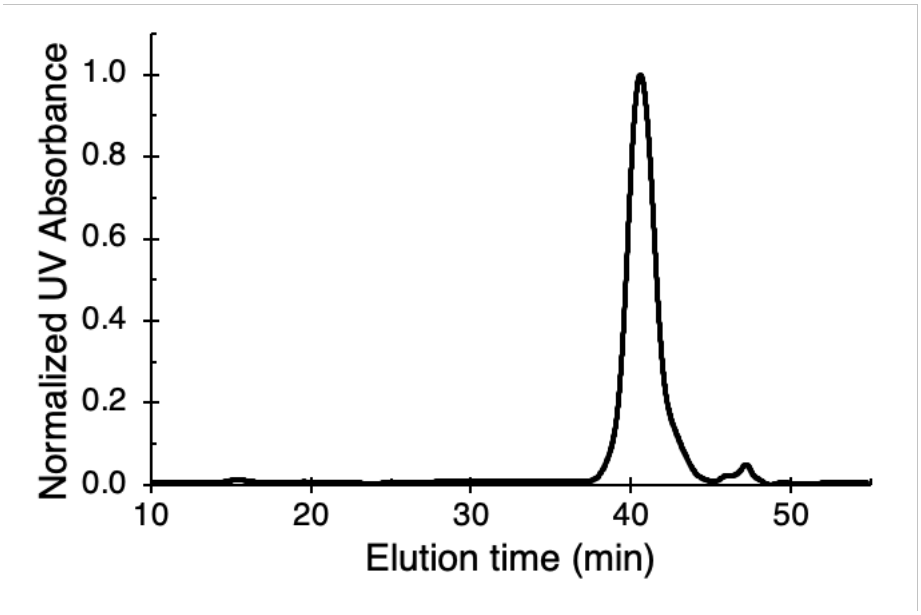
S1



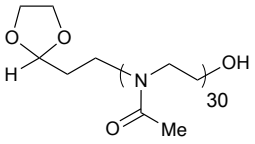
SEC of polymer **S1**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm.



S2



SEC of polymer **S2**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm.



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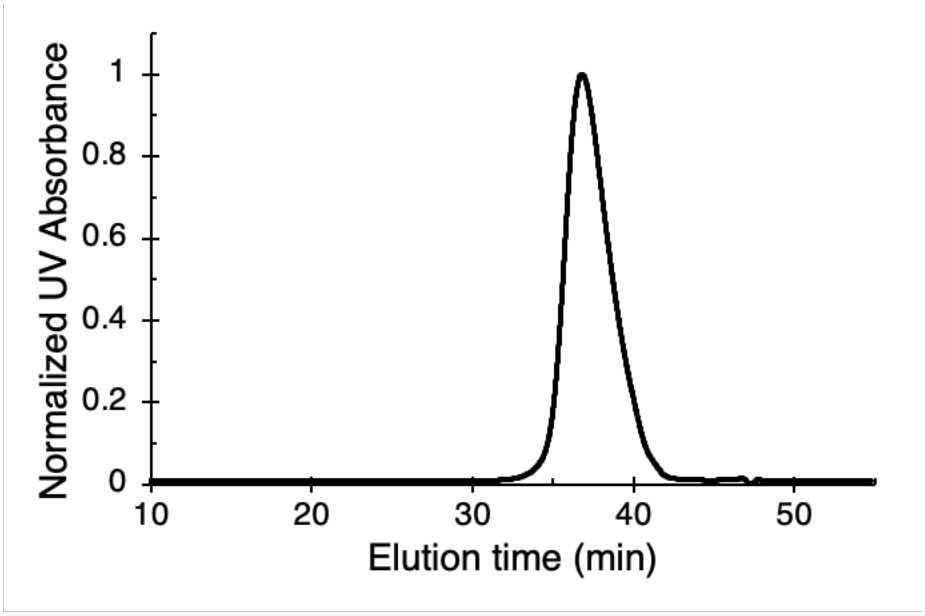
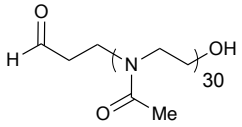


SEC of polymer **2**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm.



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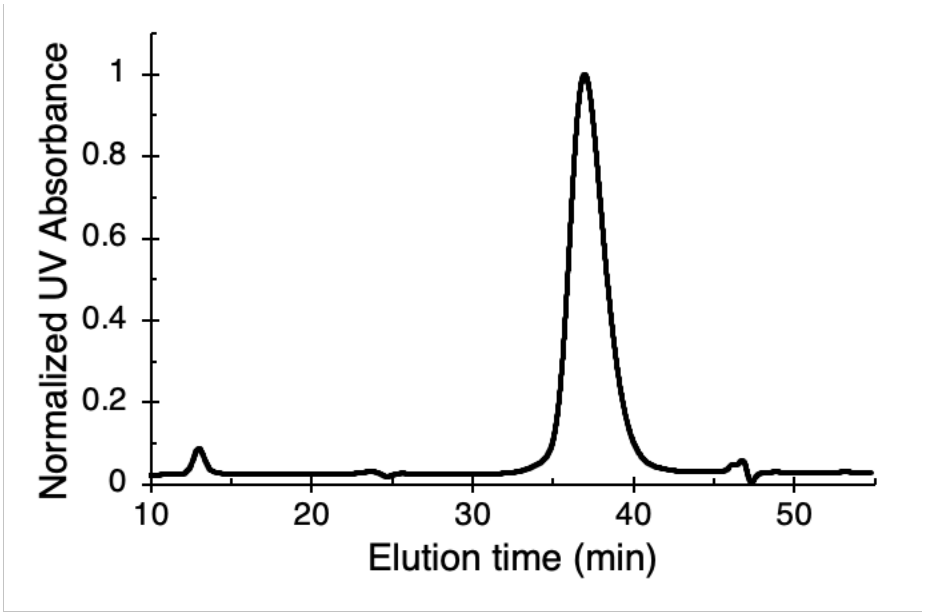
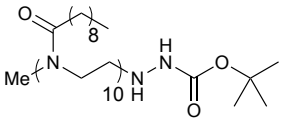


SEC of polymer **3**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm.



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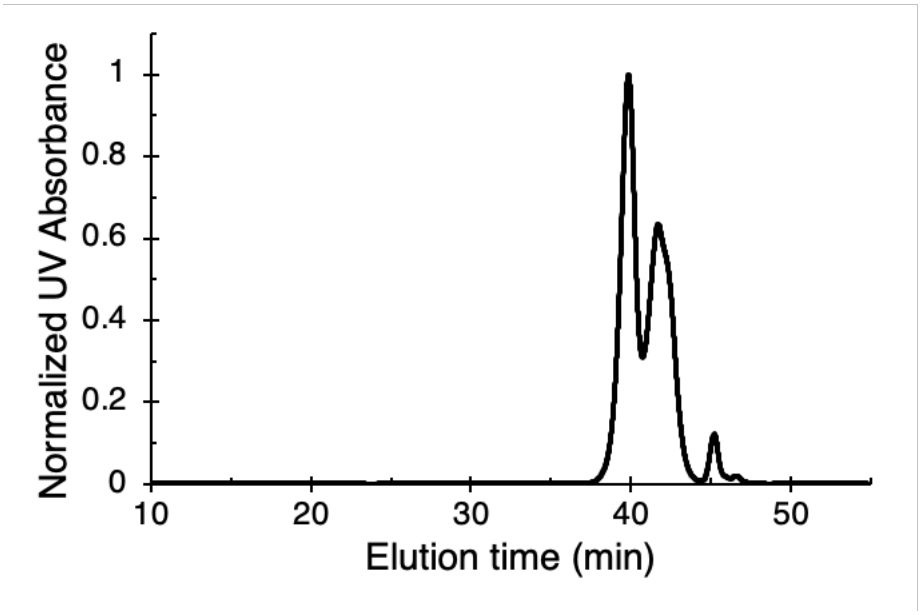
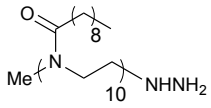


SEC of polymer **5**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm. Note: Bimodality was reproducible across all batches of the same polymerization.



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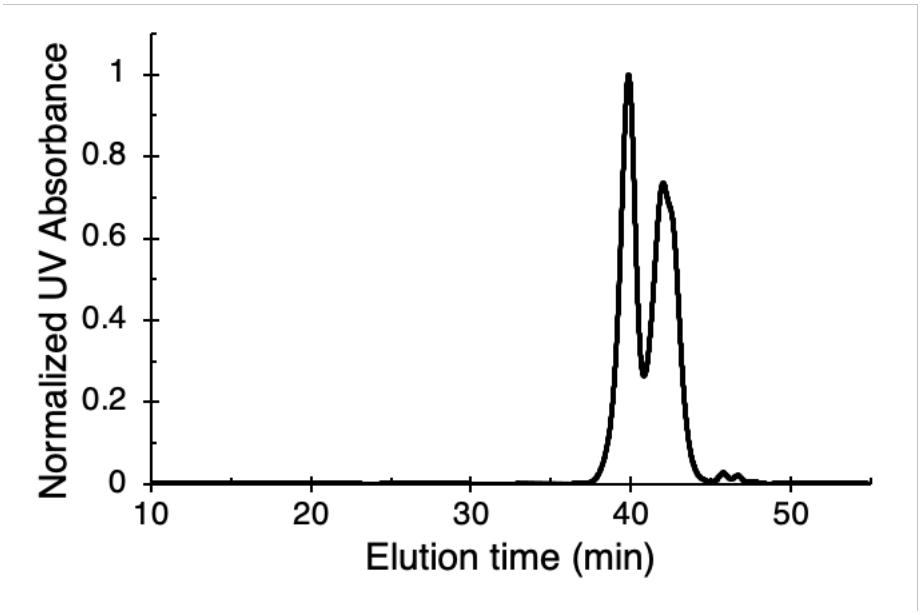
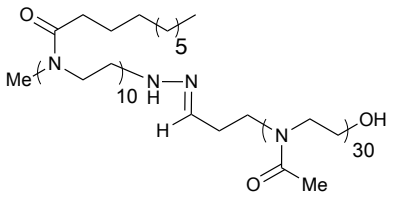


SEC of polymer **6**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm. Note: Bimodality was reproducible across all batches of the same polymerization.



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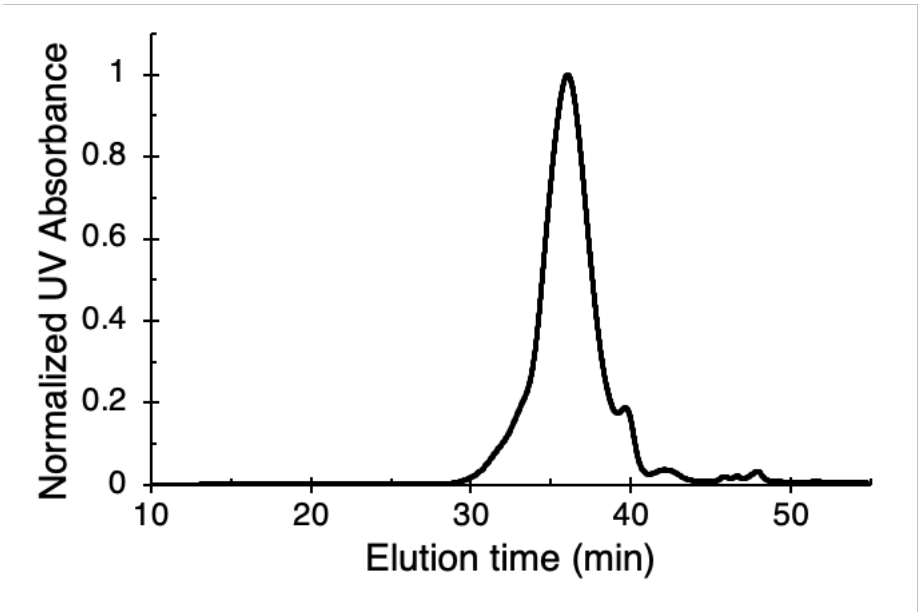
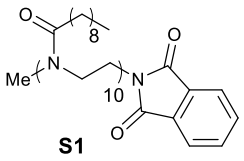
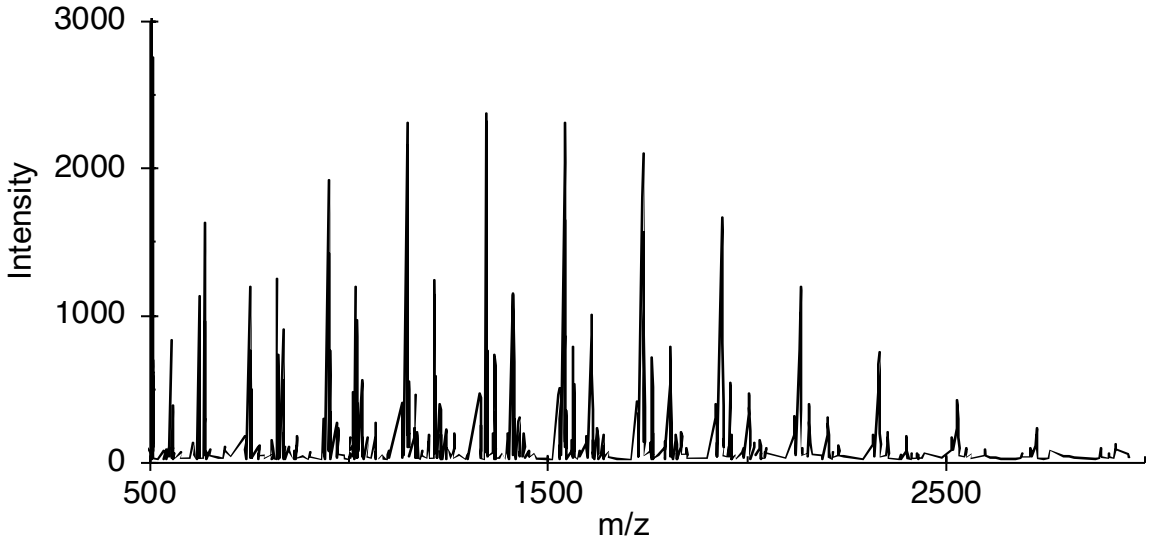


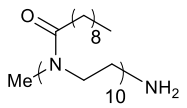
SEC of polymer **7**. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate). UV trace was acquired at 210 nm.

LCMS spectra

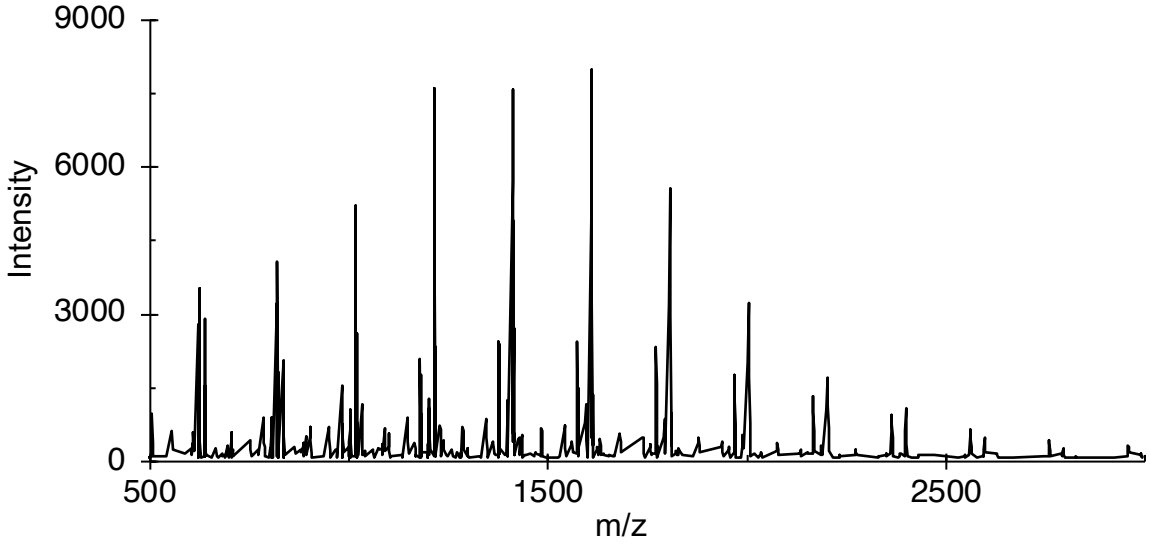




LCMS spectrum of polymer **S1**.

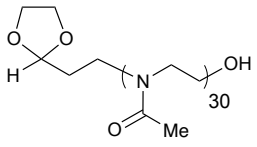


S2



LCMS spectrum of polymer **S2**.

MALDI spectra



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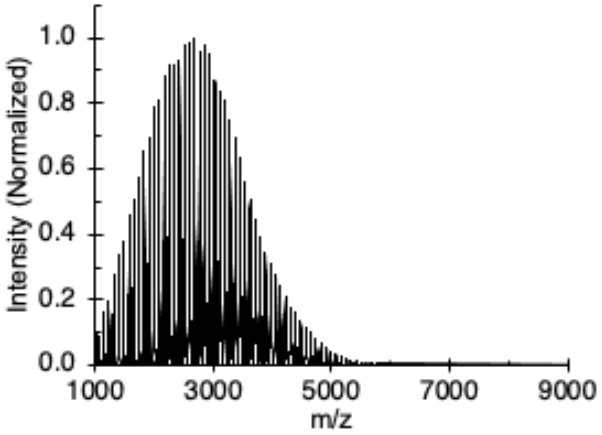
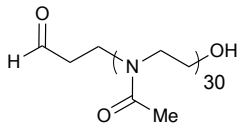


MALDI spectrum of polymer **2**.



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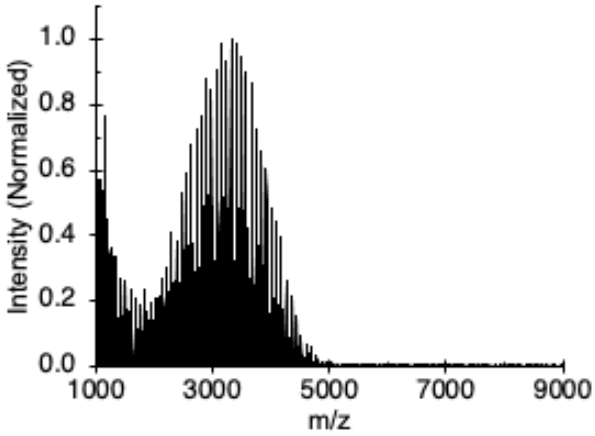
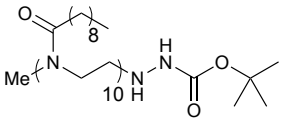
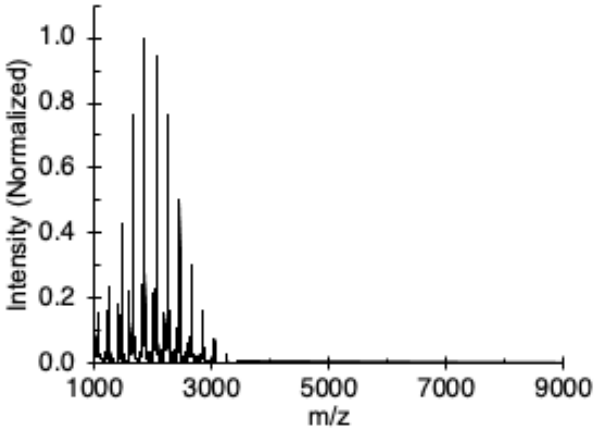


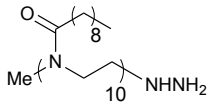
MALDI spectrum of polymer **3**.



5



MALDI spectrum of polymer **5.**



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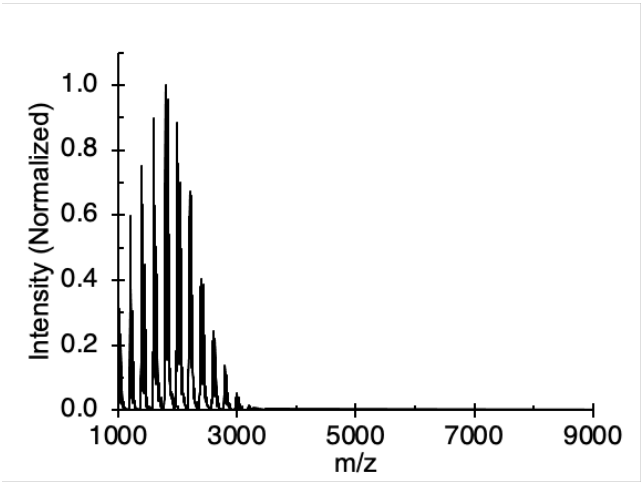
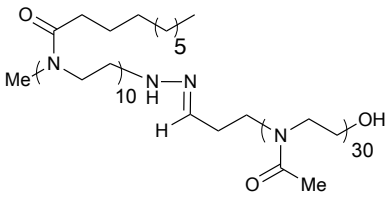


MALDI spectrum of polymer **6**.



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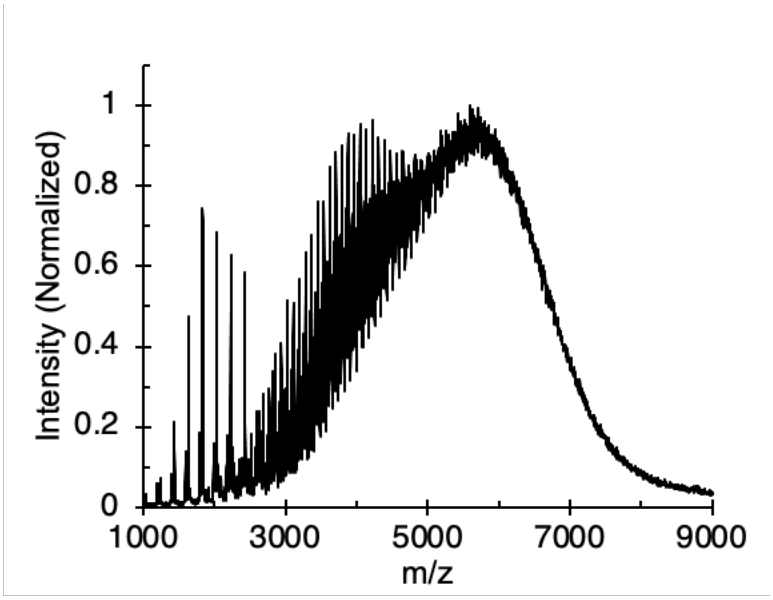


MALDI spectrum of polymer **7**.

Supplemental references:

1 C. Legros, M.-C. De Pauw-Gillet, K. C. Tam, S. Lecommandoux and D. Taton, *Eur Polym J*, 2015, **62**, 322–330.

2 H. Witte and W. Seeliger, *Angewandte Chemie International Edition in English*, 1972, **11**, 287–288.

3 E. M. Sletten and T. M. Swager, *J Am. Chem. Soc*, 2014, **136**, 13574–13577.

4 M. A. Miller and E. M. Sletten, *Org Lett*, 2018, **20**, 6850–6854.

5 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518–1520.

Appendix 1: Poly(2-methyl-oxazoline) GPC Calibration:

Molecular weight calibration was done using μwave synthesized azide end-capped poly(2-methyl-2-oxazoline) standards ranging 1 – 6 kDa (n = 11 to 70). Termination with sodium azide was chosen because it has well-established procedures and produces quantitative end-capping. Characterization was done via Matrix Assisted Laser Desorption Ionization (MALDI) to obtain M_n, M_w and dispersity ($Đ$) values.

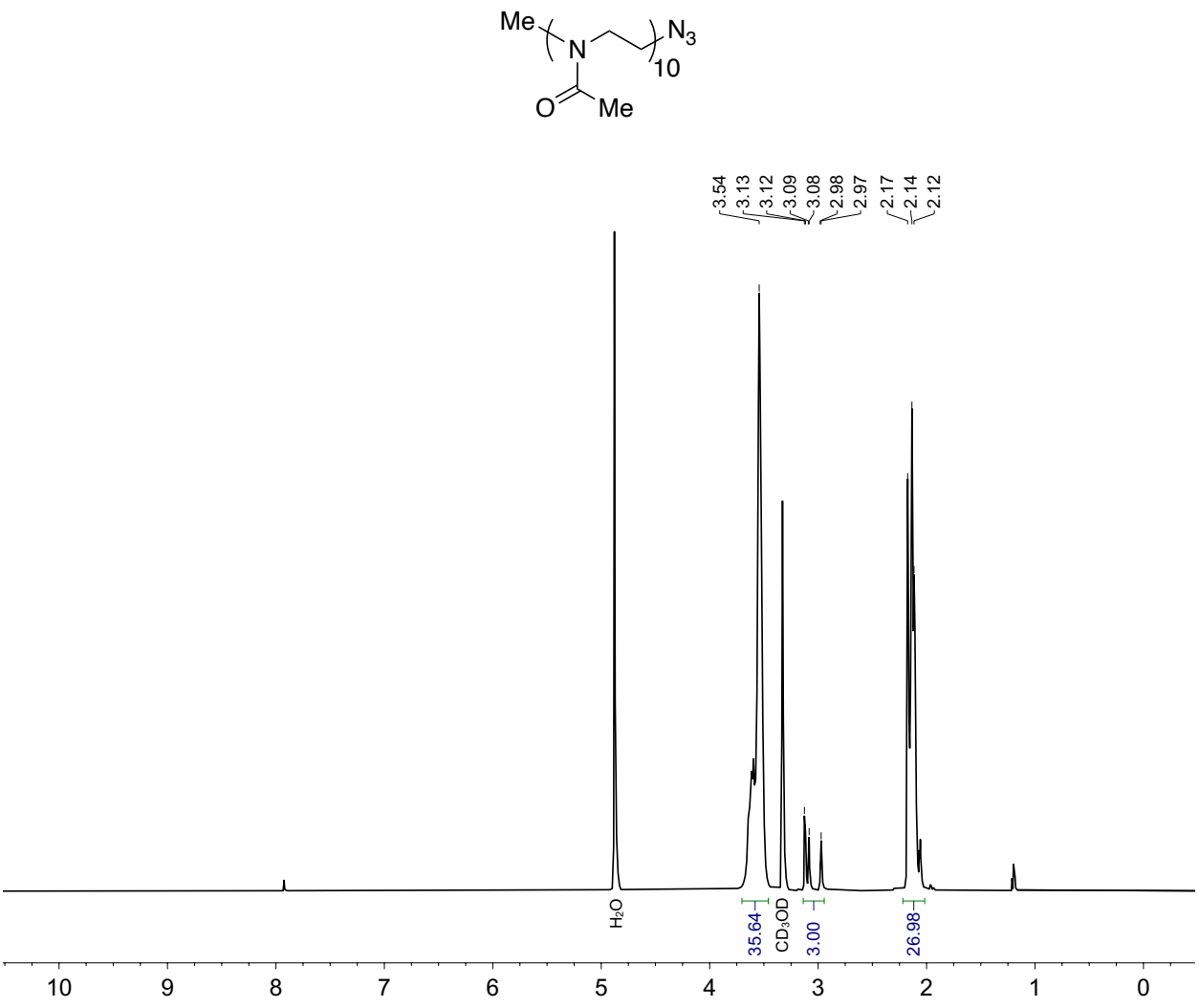
General Me-P(MeOx)$_n$–N_3 polymerization.

In a flame-dried μwave vial under N_2, methyl 2-oxazoline (11, 23, 47, or 70 equiv.), MeCN (4 M), and MeOTf (1 equiv.) were added. μwave reactions were conducted to 98% monomer consumption. Living polymer chains were end-capped immediately with sodium azide (10 equiv.) at 40 °C for three hours to obtain functionalized polymers. After removal of excess salts through filtration and removal of solvent under vacuum, the polymers were re-dissolved in $CHCl_3$ and precipitated in diethyl ether three times. For polymers above molecular weights of 1.5 kDa, dialysis was subsequently done for a minimum of one day. Samples were prepared for MALDI in 50:5:1 mixtures of 20 mg/mL *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile in $CHCl_3$, 20 mg/mL polymer in $CHCl_3$, and 10 mg/mL NaTFA in isopropyl alcohol.

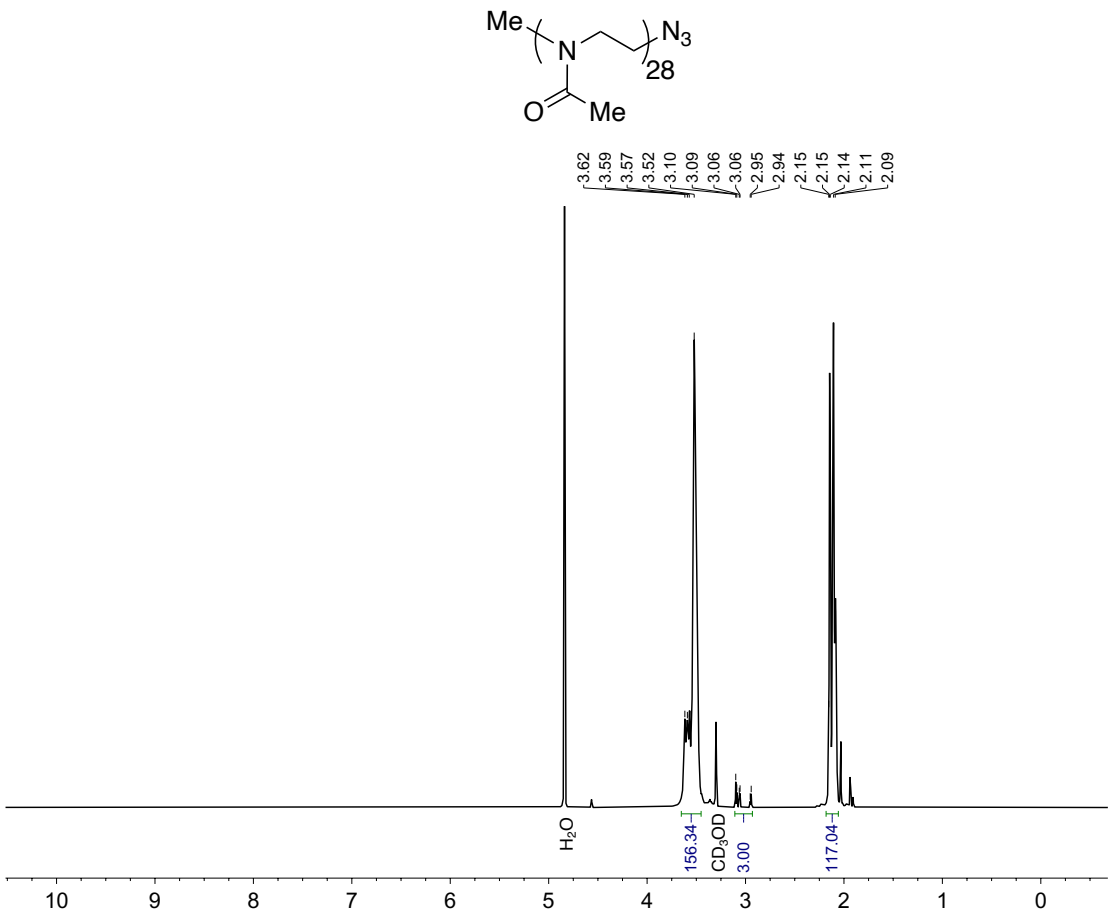
Target Molecular Weight	Actual n	M_n (MALDI)	M_w (MALDI)	$Đ$
993 Da	n = 10	901	956	1.06
2,013 Da	n = 28	2427	2616	1.08
4,054 Da	n = 44	3834	4119	1.07
6,010 Da	n = 57	4932	5285	1.07

Table 1: MALDI values used as calibrants for Me-P(MeOx)$_n$-N_3 standards.

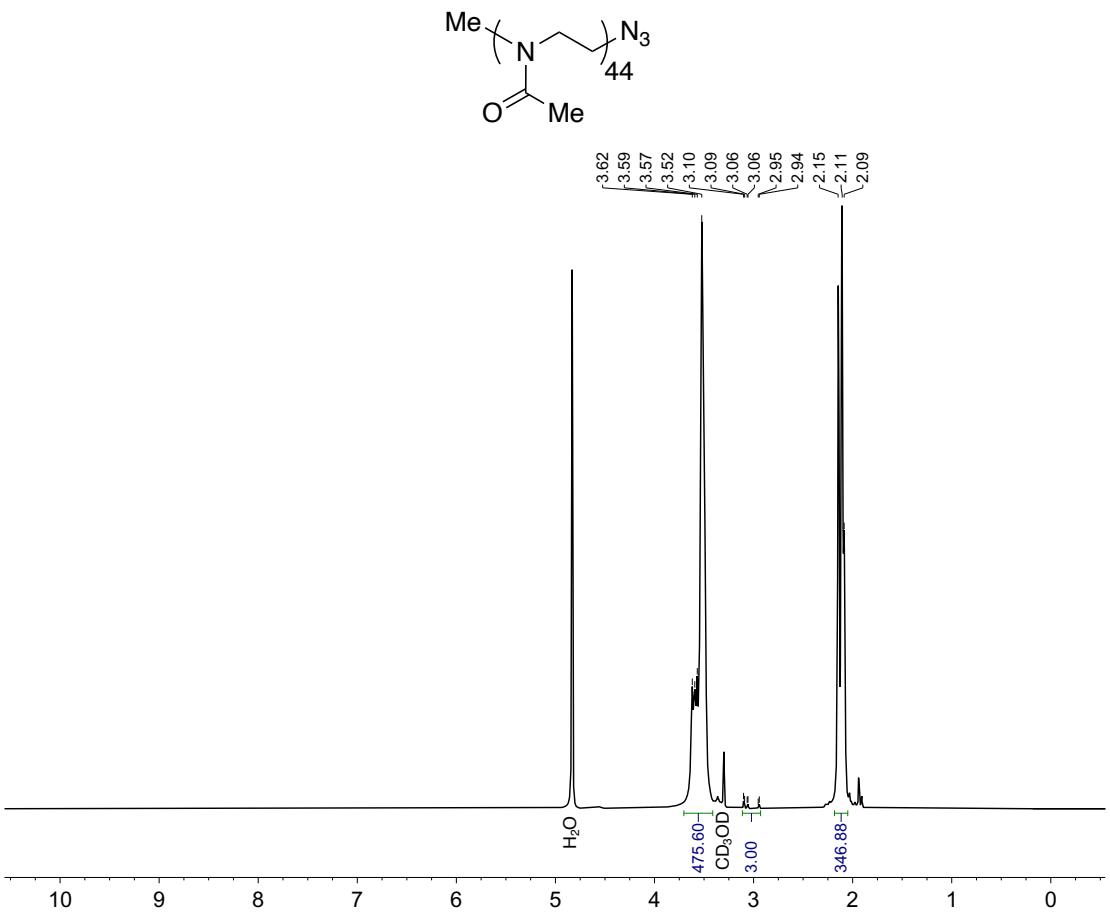
Appendix 1: ^{1}H NMR spectra



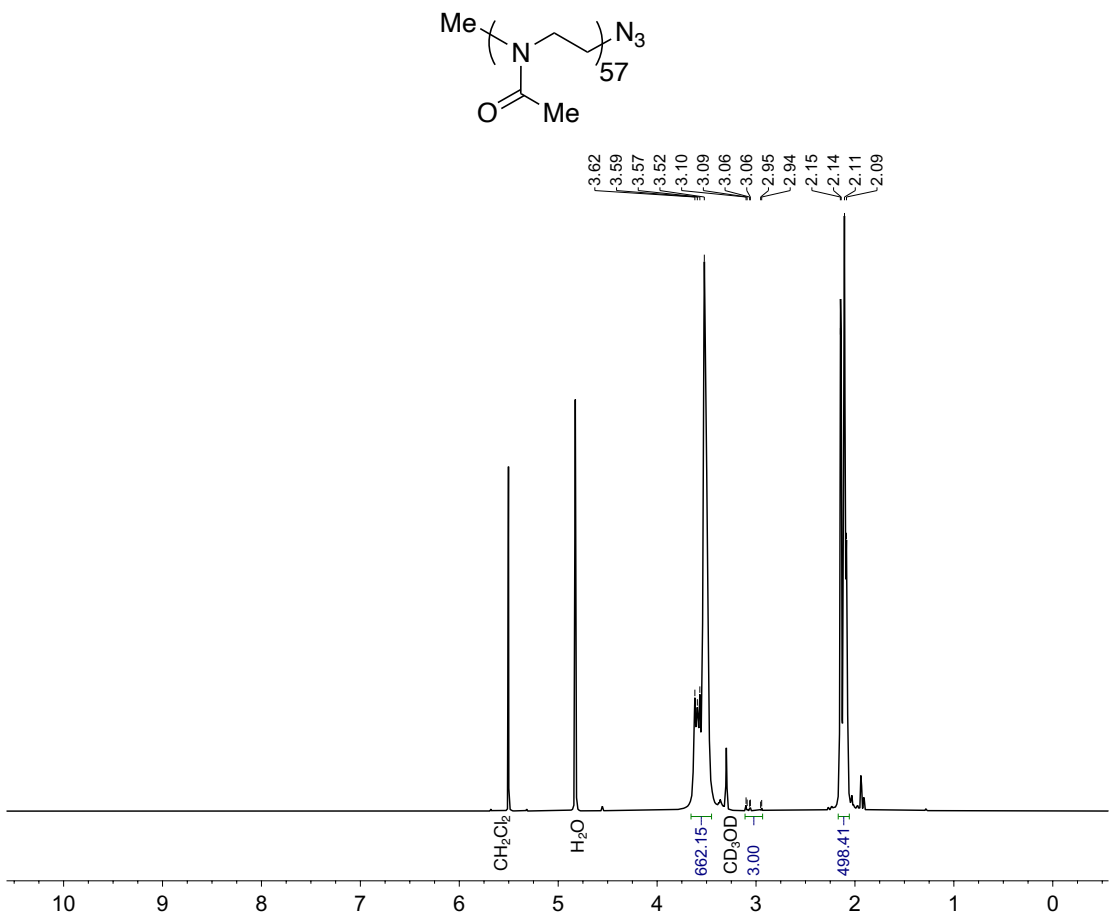
^{1}H NMR (500 MHz, D_4-MeOH) of Me-P(MeOx)$_{10}$-N_3.



^{1}H NMR (500 MHz, D_4-MeOH) of Me-P(MeOx)$_{28}$-N_3.

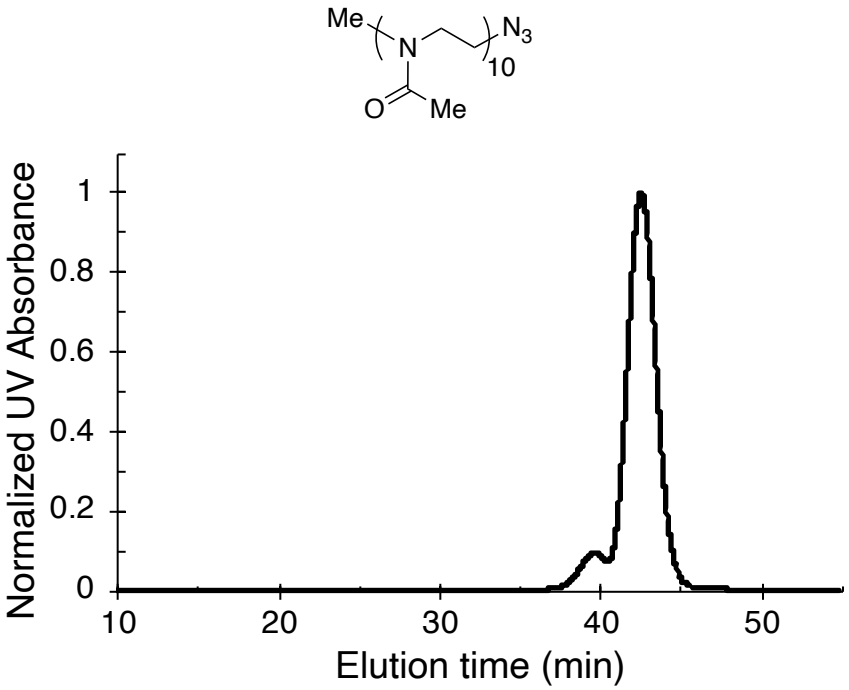


^{1}H NMR (500 MHz, D_4-MeOH) of Me-P(MeOx)$_{44}$-N_3.

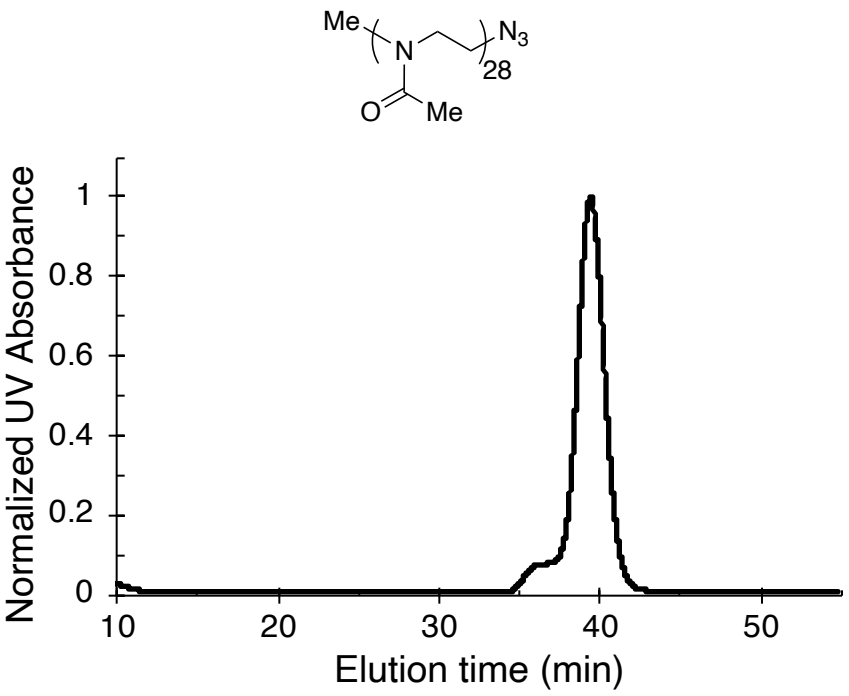


^{1}H NMR (500 MHz, D_4-MeOH) of Me-P(MeOx)$_{57}$-N_3.

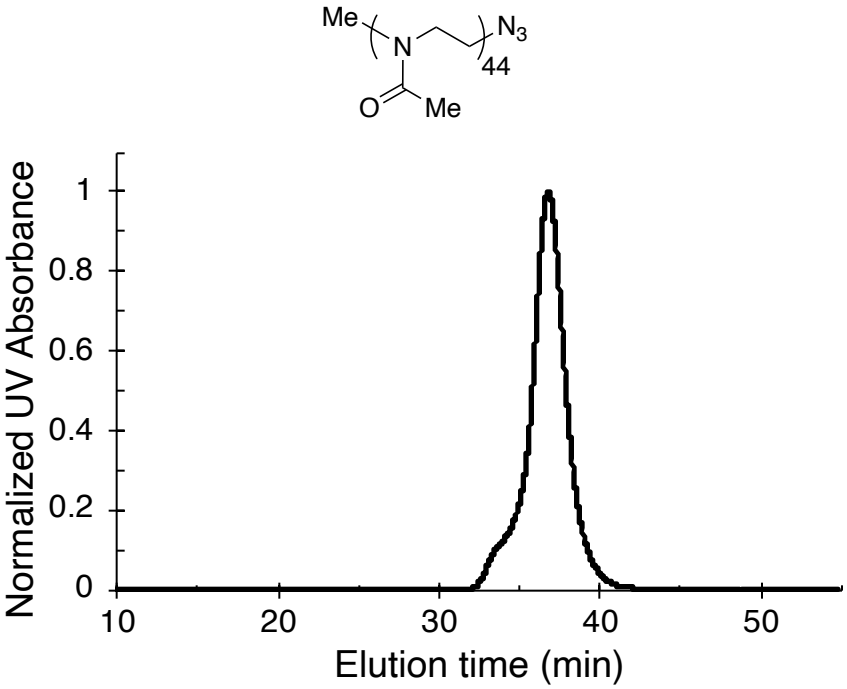
Appendix 1: SEC traces



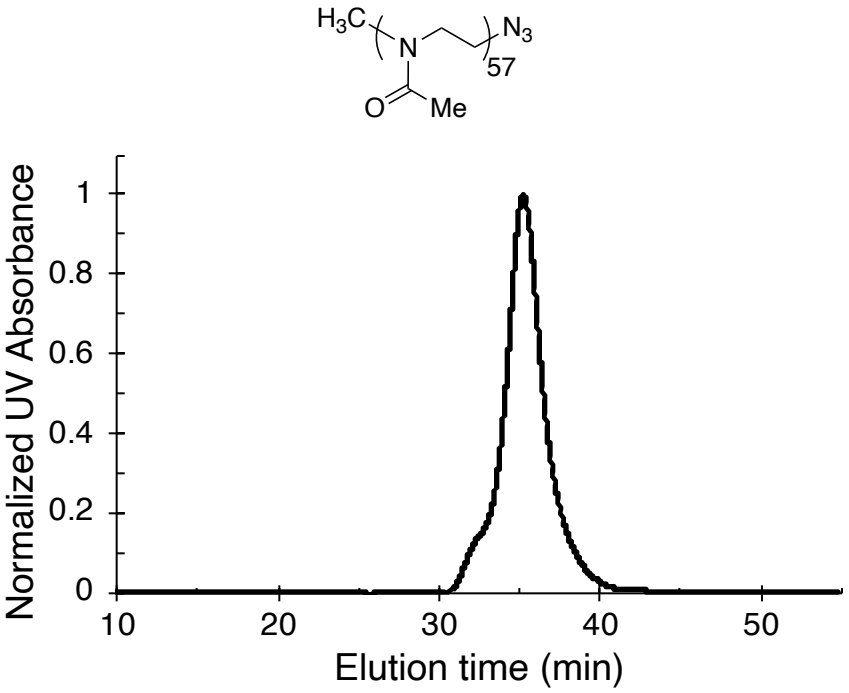
SEC of Me-P(MeOx)$_{10}$-N$_3$. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate).



SEC of Me-P(MeOx)$_{28}$-N$_3$. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate).

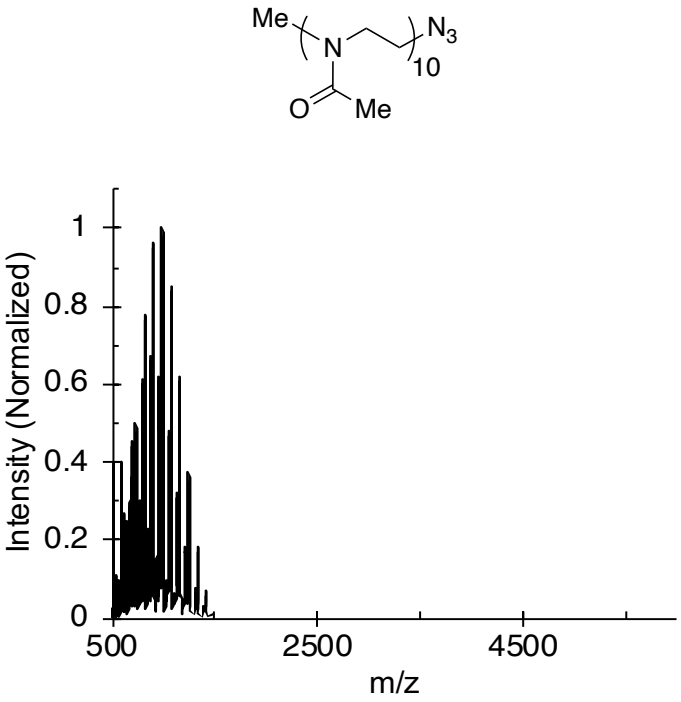


SEC of Me-P(MeOx)$_{44}$-N$_3$. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate).

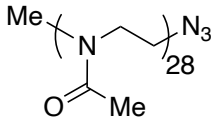


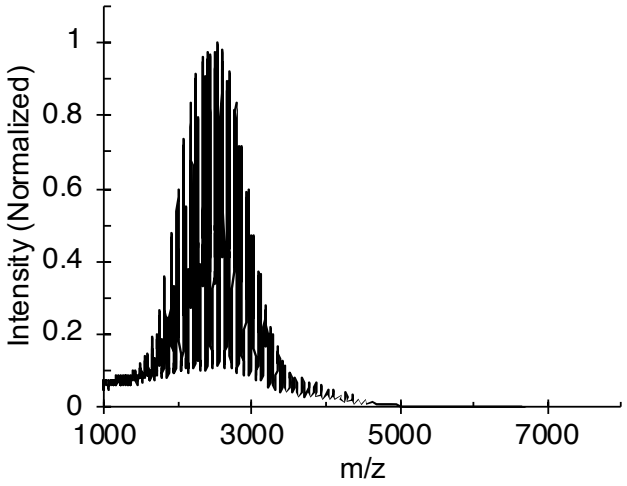
SEC of Me-P(MeOx)$_{57}$-N$_3$. Eluent was 20 mM NaTFA in TFE run at room temperature (0.5 mL min^{-1} flow rate).

Appendix 1: MALDI spectra

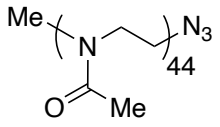


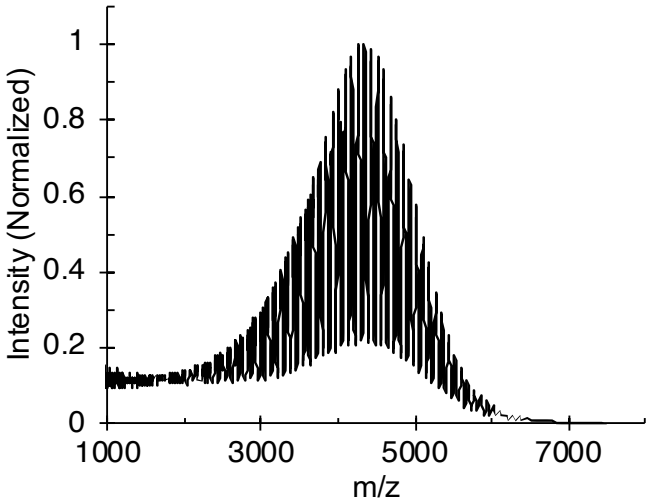
MALDI spectrum of Me-P(MeOx)$_{10}$-N$_3$.



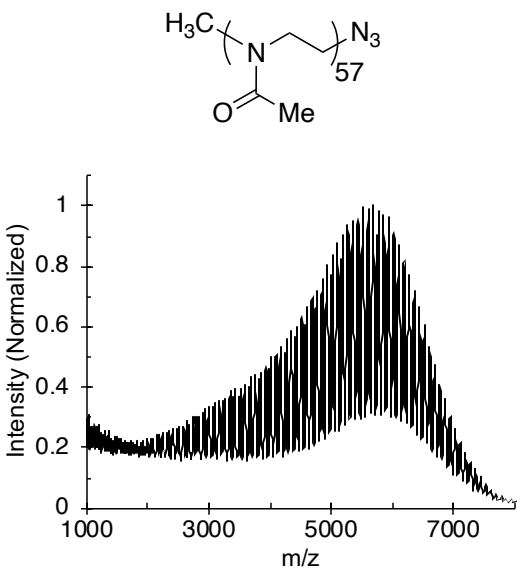


MALDI spectrum of Me-P(MeOx)$_{28}$-N$_3$.





MALDI spectrum of Me-P(MeOx)$_{44}$-N$_3$.



MALDI spectrum of Me-P(MeOx)$_{57}$-N$_3$.