Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

for

Controlling nanoemulsion surface chemistry with poly(2-oxazoline) amphiphiles

Daniel A. Estabrook,[a] Amanda F. Ennis,[a,b] Rachael A. Day[a] and Ellen M. Sletten*[,b]

[a]Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young, Dr. E., Los Angeles, CA 90095, USA.

[b]Present address: Department of Chemistry, Duke University, 124 Science Drive, Durham, NC 27708, USA.

*Prof. Ellen M. Sletten: sletten@chem.ucla.edu

Table of Contents

Supporting figures

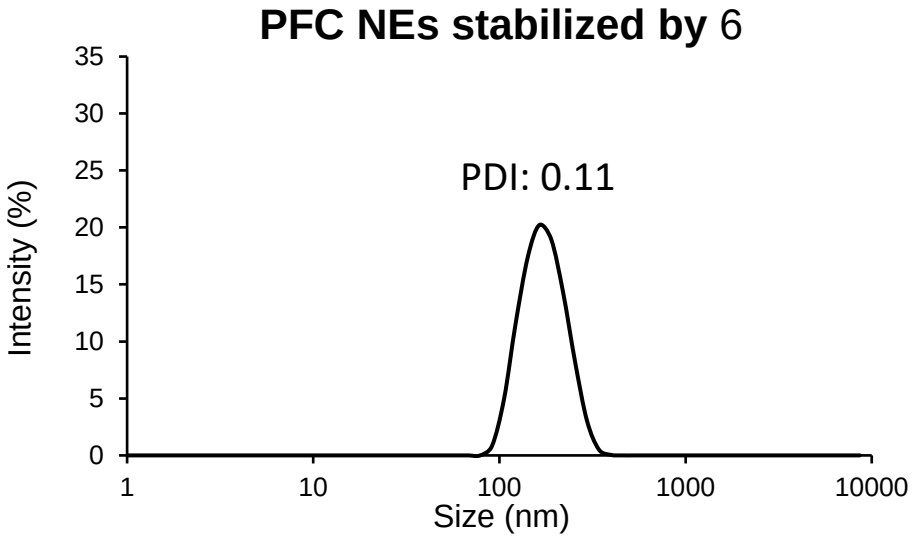


Figure S1. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **6**. Data are an average of five replicate measurements.

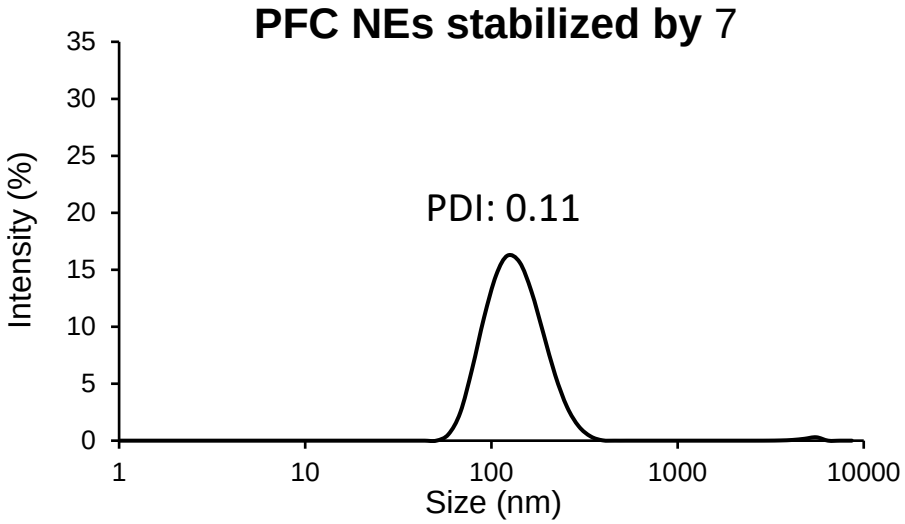


Figure S2. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **7**. Data are an average of five replicate measurements. Note: minor aggregation at ~5.6 µm, constituting 1% intensity percent by area. As intensity is proportional to diameter to the sixth power, the observed aggregation is minimal.

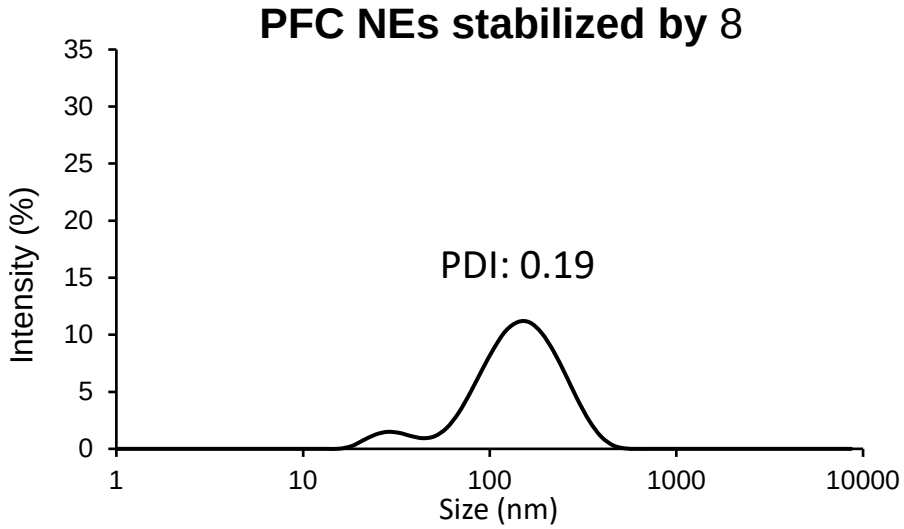


Figure S3. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **8**. Data are an average of five replicate measurements. Small population at ~50 nm corresponds to micelles.

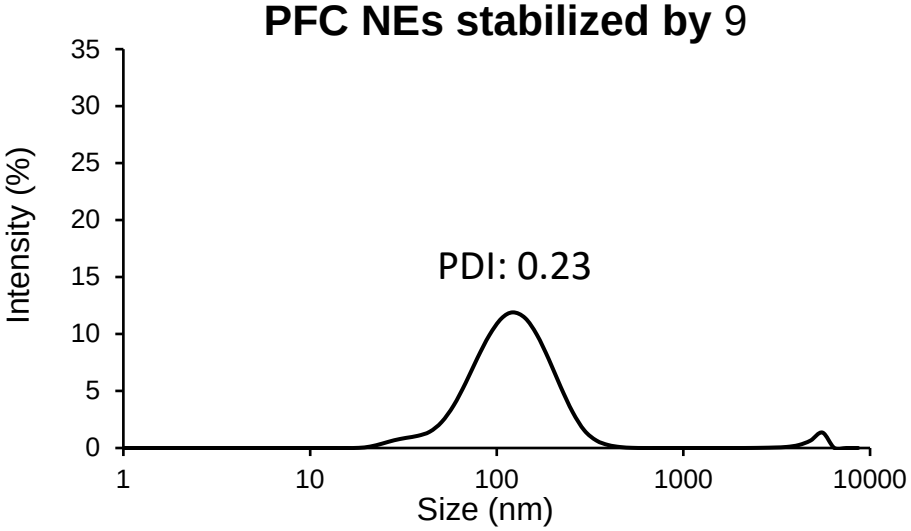


Figure S4. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **9**. Data are an average of five replicate measurements. Small population at ~50 nm corresponds to micelles. Note: minor aggregation at ~5.6 µm, constituting 2% intensity percent by area. As intensity is proportional to diameter to the sixth power, the observed aggregation is minimal.

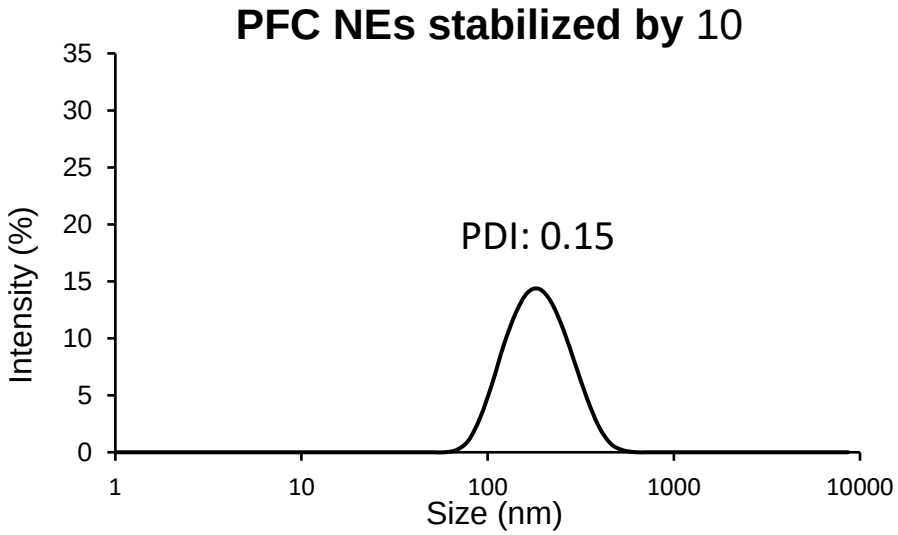


Figure S5. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **10**. Data are an average of five replicate measurements.

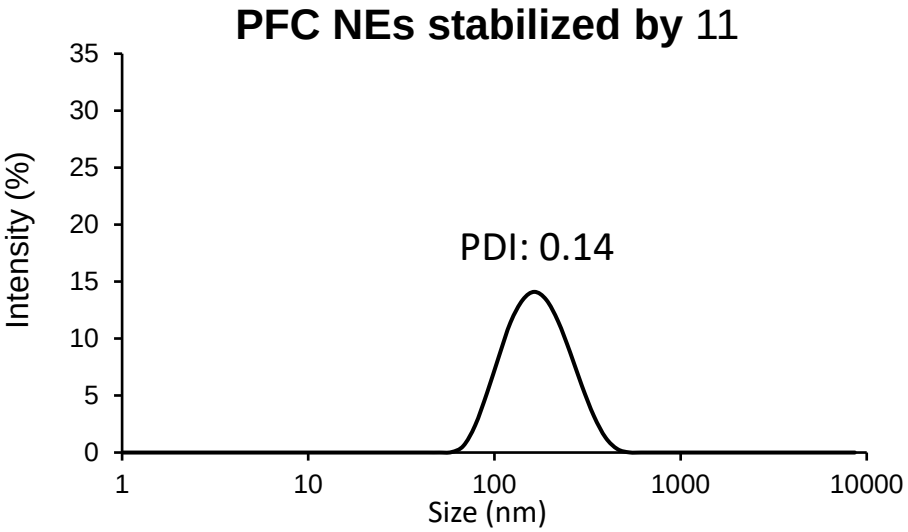


Figure S6. Dynamic light scattering data for the PFC nanoemulsions stabilized by surfactant **11**. Data are an average of five replicate measurements.

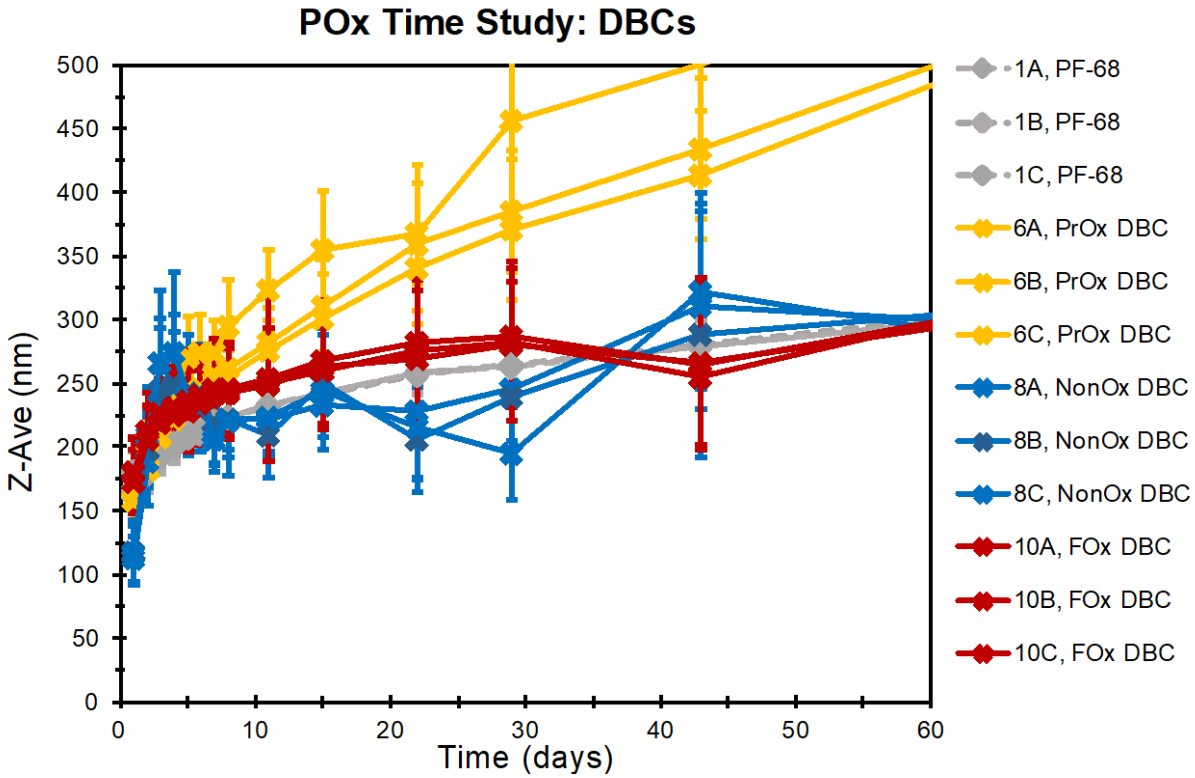


Figure S7. Size of PFC nanoemulsions stabilized by diblock copolymers (DBC) over time. The size of nanoemulsions composed of 7:3 PFD:PFTPA v/v% stabilized POx diblock copolymers **6** (yellow solid line, propyl-based, "PrOx DBC"), **8** (blue solid line, nonyl-based, "NonOx DBC"), and **10** (red solid line, fluorous-based, "FOx DBC") was measured by DLS over time. Nanoemulsions of identical composition but stabilized by **1** (grey dashed line, Pluronic F-68) were included as a control. Size measurements were performed on three independent samples (A-C), five replicates per sample. Error bars represent half-width at half-maximum.

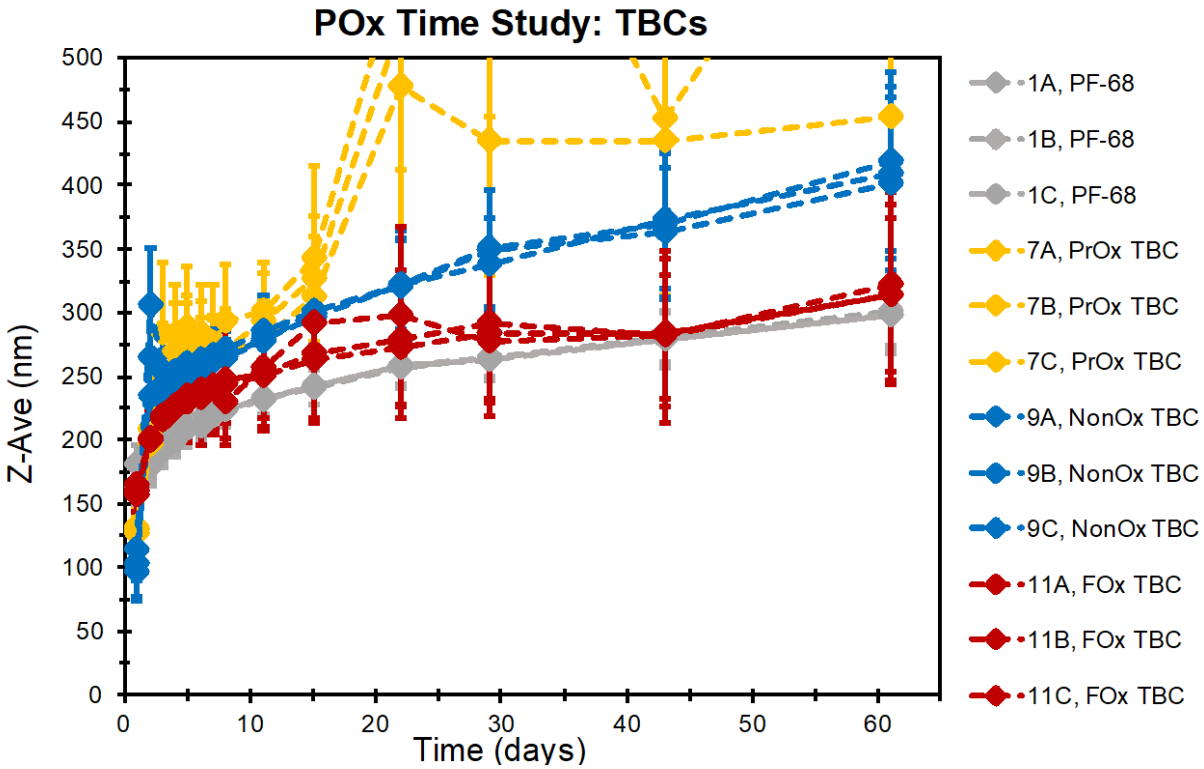


Figure S8. Size of PFC nanoemulsions stabilized by triblock copolymers (TBC) over time. The size of nanoemulsions composed of 7:3 PFD:PFTPA v/v% stabilized by POx triblock copolymers **7** (yellow dashed line, propyl-based, "PrOx TBC"), **9** (blue dashed line, nonyl-based, "NonOx TBC"), and **11** (red dashed line, fluorous-based, "FOx TBC") was measured by DLS over time. Nanoemulsions of identical composition but stabilized by **1** (grey dashed line, Pluronic F-68) were included as a control. Size measurements were performed on three independent samples (A-C), five replicates per sample. Error bars represent half-width at half-maximum.

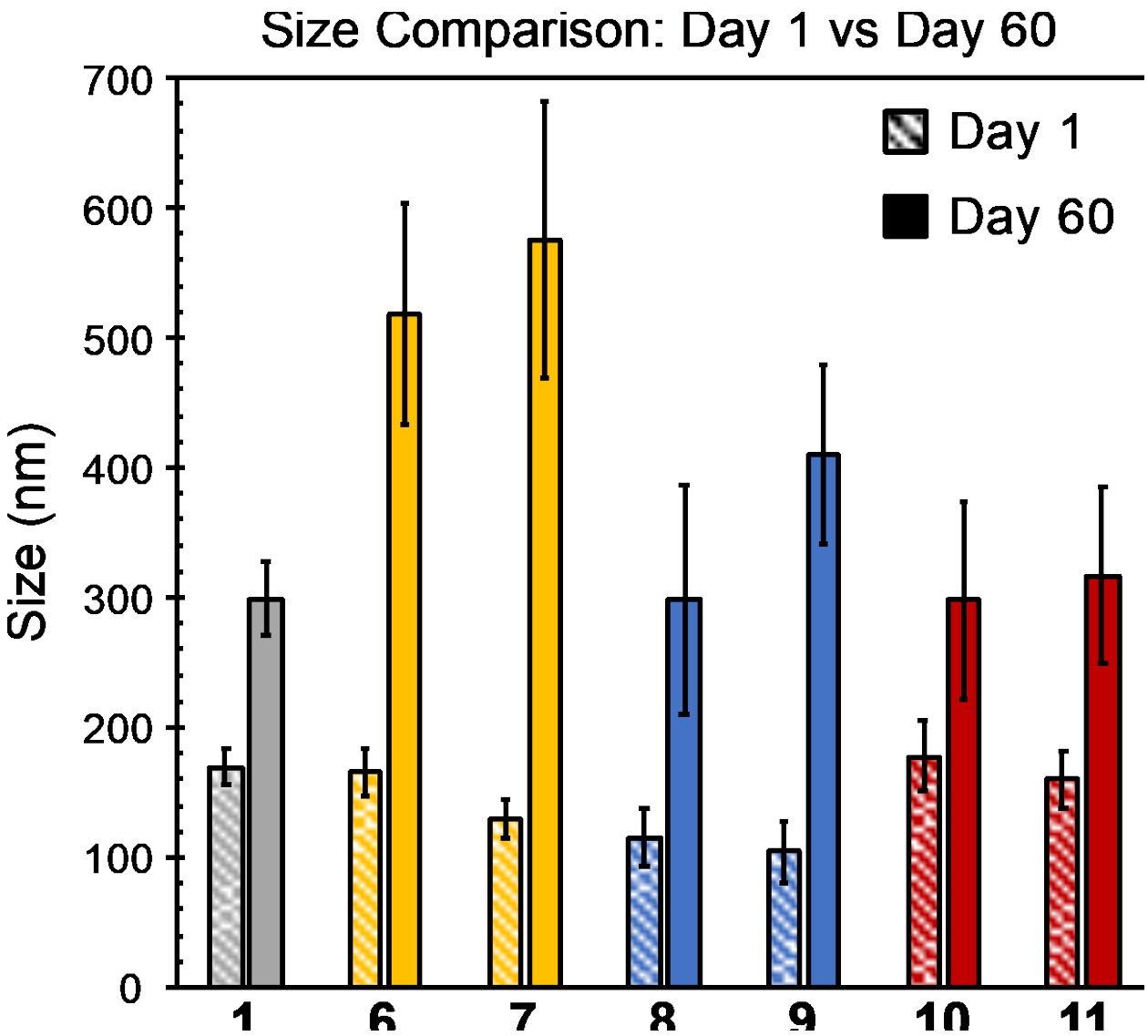


Figure S9. Initial (day 1) and final (day 60) size distributions of POx-stabilized emulsions. Emulsions were prepared by sonicating a solution of 2.8 wt% surfactant, with 10 vol% 7:3 PFD:PFTPA in phosphate buffered saline (PBS). Emulsions were diluted 1:100 in MilliQ water prior to measurements by dynamic light scattering (DLS). Data represents the average of three independent samples; error bars represent the half-width at half-maximum averaged over the three independent samples.

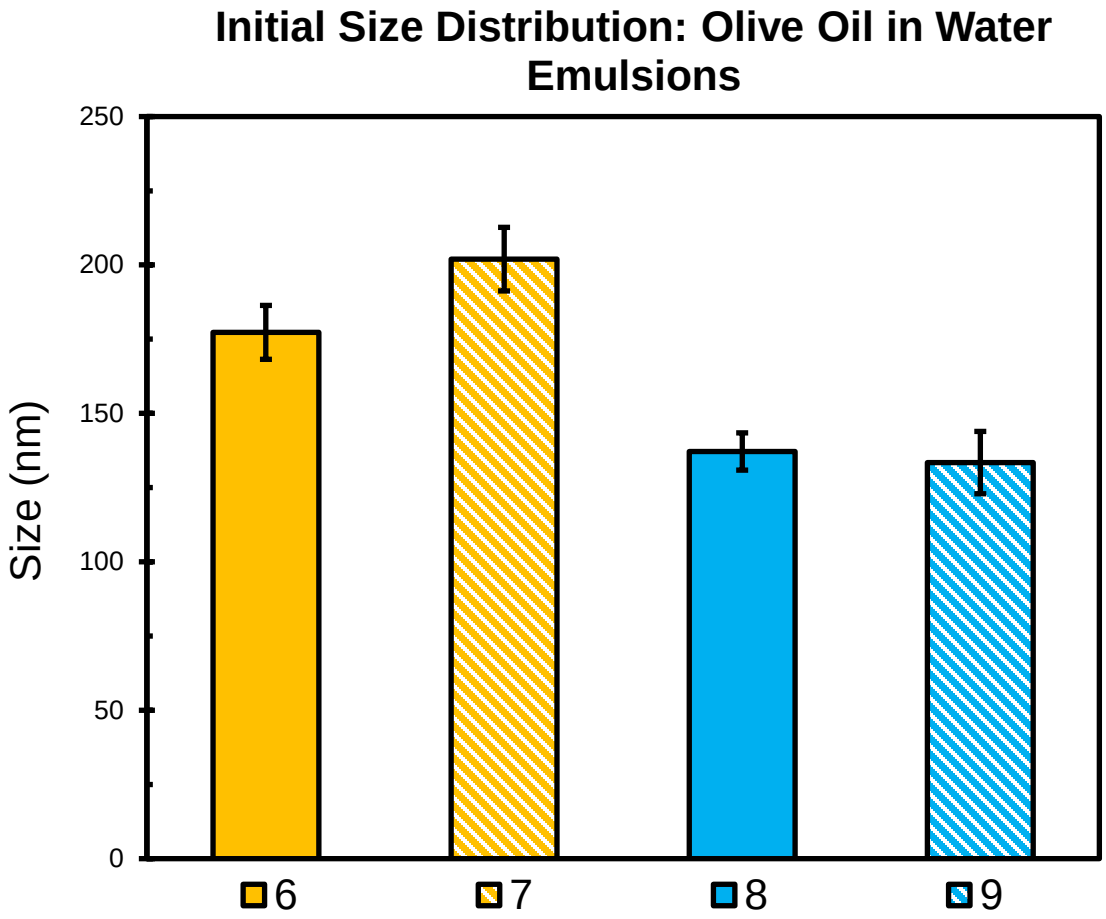


Figure S10. Dynamic light scattering data for the initial size distributions of POx-stabilized olive oil-in-water nanoemulsions. Error bars represent the half-width at half-maximum. Emulsions were prepared as described by the general emulsion procedure replacing 7:3 PFD/PFTPA with olive oil. Data are an average of three replicate measurements.

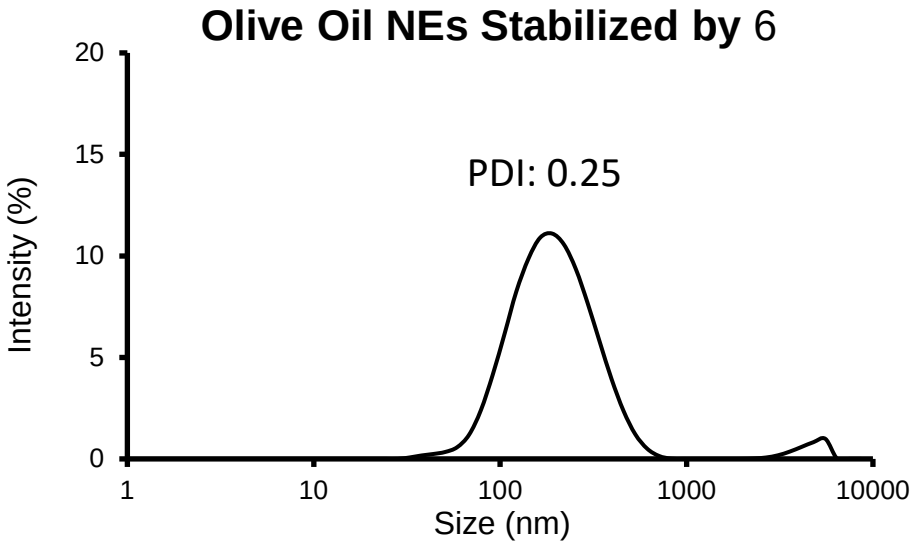


Figure S11. Dynamic light scattering data for oil-in-water nanoemulsions stabilized by surfactant **6**. Data are an average of five replicate measurements. Note: minor aggregation at ~5.6 µm, constituting 4% intensity percent by area. As intensity is proportional to diameter to the sixth power, the observed aggregation is minimal.

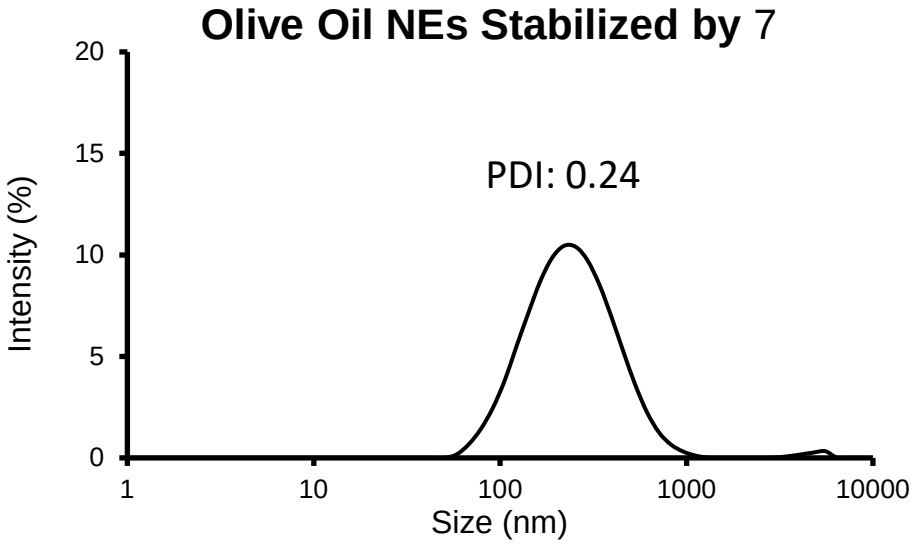


Figure S12. Dynamic light scattering data for oil-in-water nanoemulsions stabilized by surfactant **7**. Data are an average of five replicate measurements. Note: minor aggregation at ~5.6 µm, constituting 1% intensity percent by area. As intensity is proportional to diameter to the sixth power, the observed aggregation is minimal.

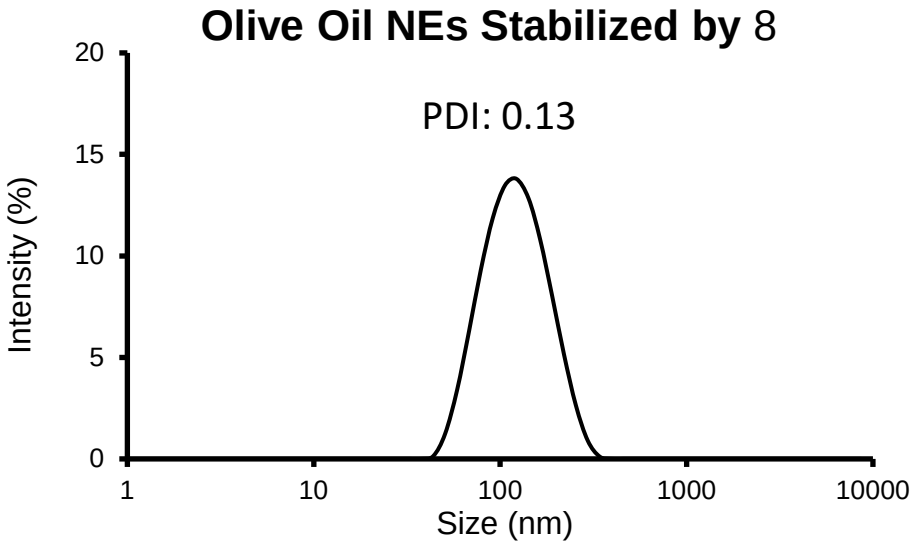


Figure S13. Dynamic light scattering data for oil-in-water nanoemulsions stabilized by surfactant **8**. Data are an average of five replicate measurements.

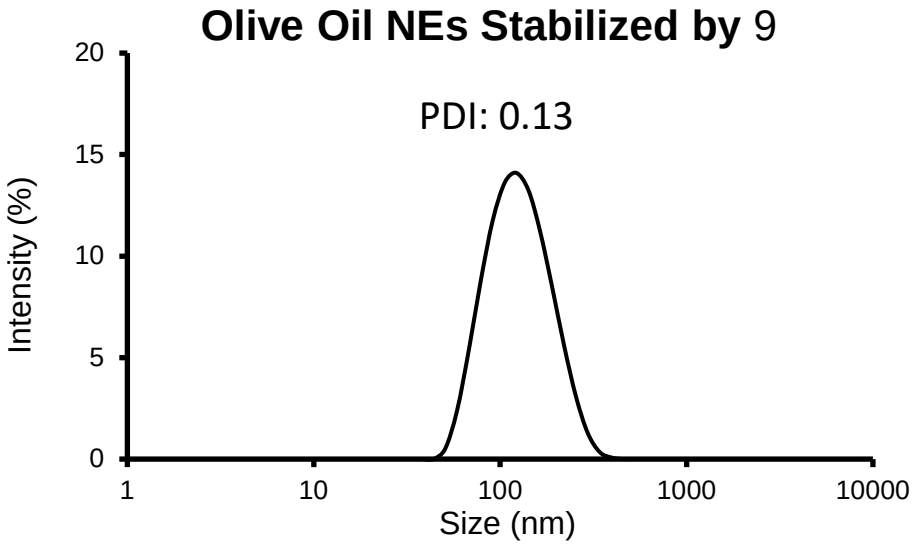


Figure S14. Dynamic light scattering data for oil-in-water nanoemulsions stabilized by surfactant **9**. Data are an average of five replicate measurements.

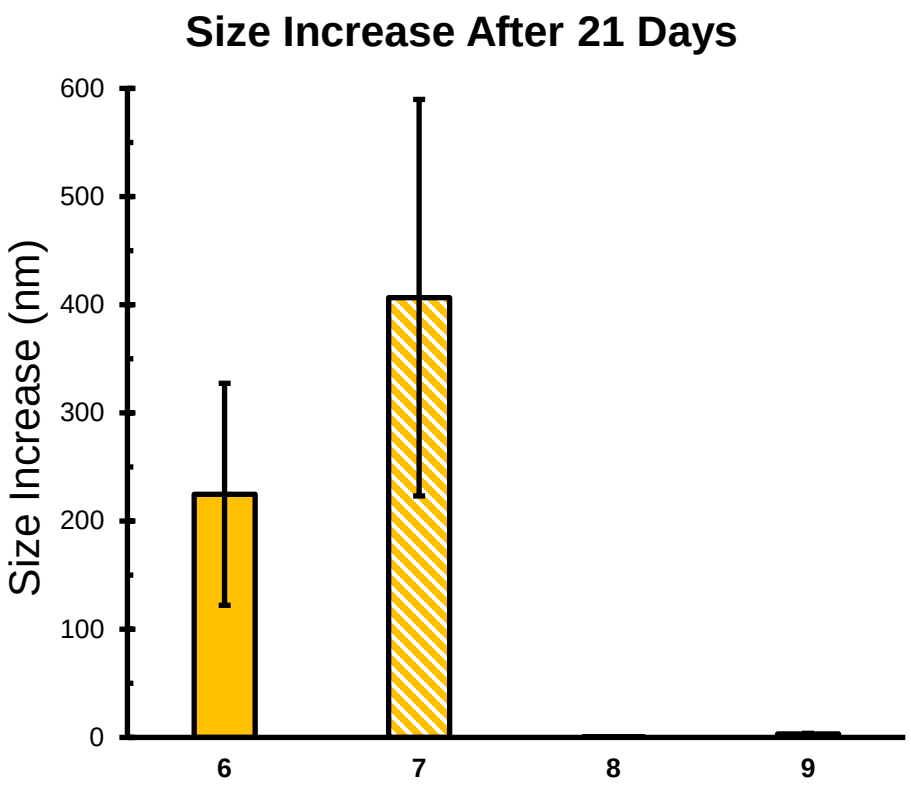


Figure S15. Size change of olive oil-in-water nanoemulsions over 21 days, stabilized by POx surfactants **6** (yellow solid bar, propyl-based diblock copolymer), **7** (yellow dashed bar, propyl-based triblock copolymer), **8** (blue solid bar, nonyl-based diblock copolymer), and **9** (blue dashed bar, nonyl-based triblock copolymer). Size measurements represent average of duplicate samples, three replicates per sample. Error bars represent the standard deviation of the size changes for duplicate samples.

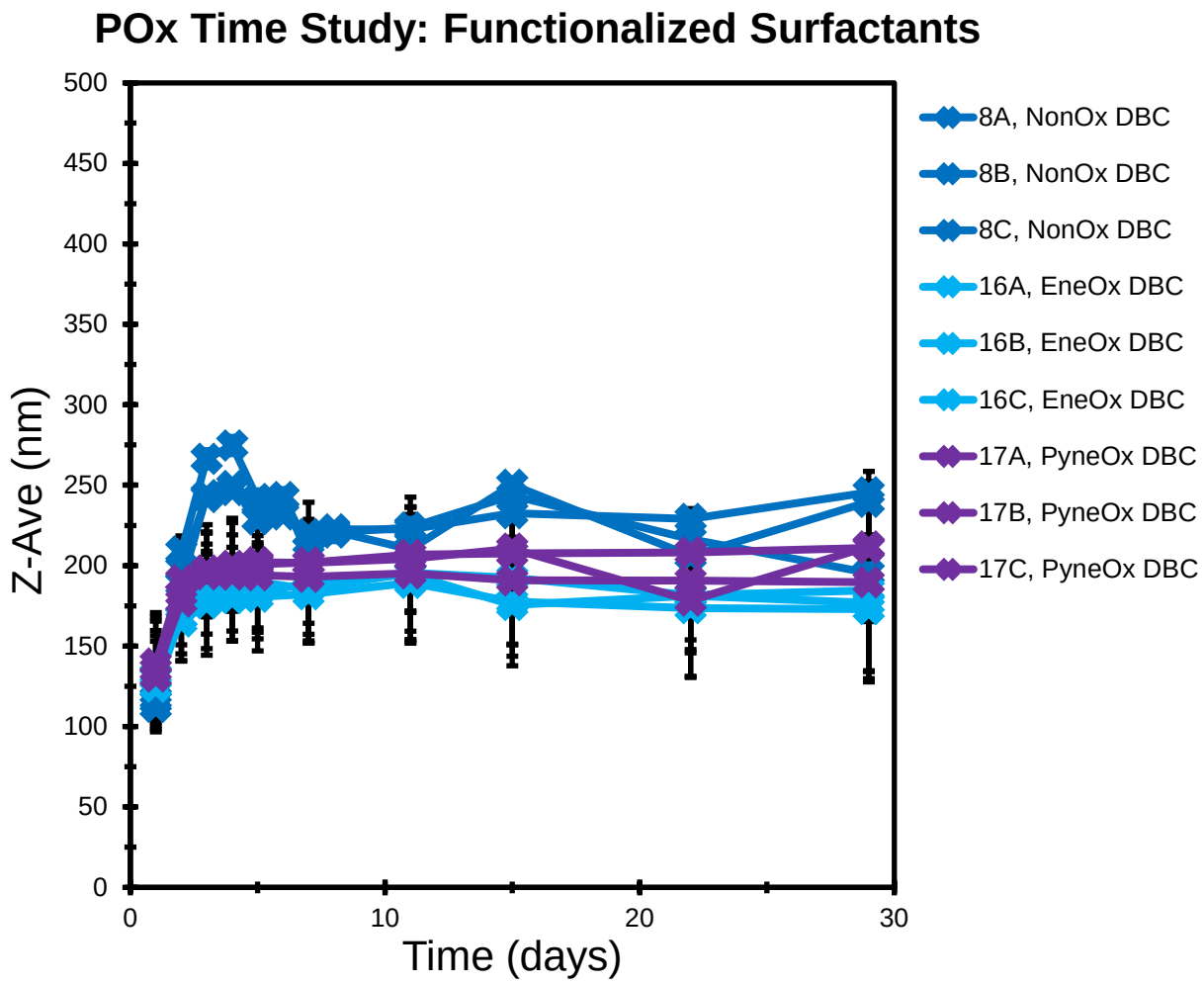


Figure S16. Size of PFC nanoemulsions prepared with functionalized surfactants over time. The size of nanoemulsions composed of 7:3 PFD:PFTPA v/v% stabilized by functionalized POx diblock copolymers **16** (light blue solid line, alkene-containing comonomer, "EneOx DBC") and **17** (purple dashed line, alkyne-containing comonomer, "PyneOx DBC") or unfunctionalized POx diblock **8** (dark blue solid line, nonyl-based, "NonOx DBC"), was measured by DLS over time. Size measurements were performed on three independent samples (A-C), five replicates per sample. Error bars represent half-width at half-maximum.

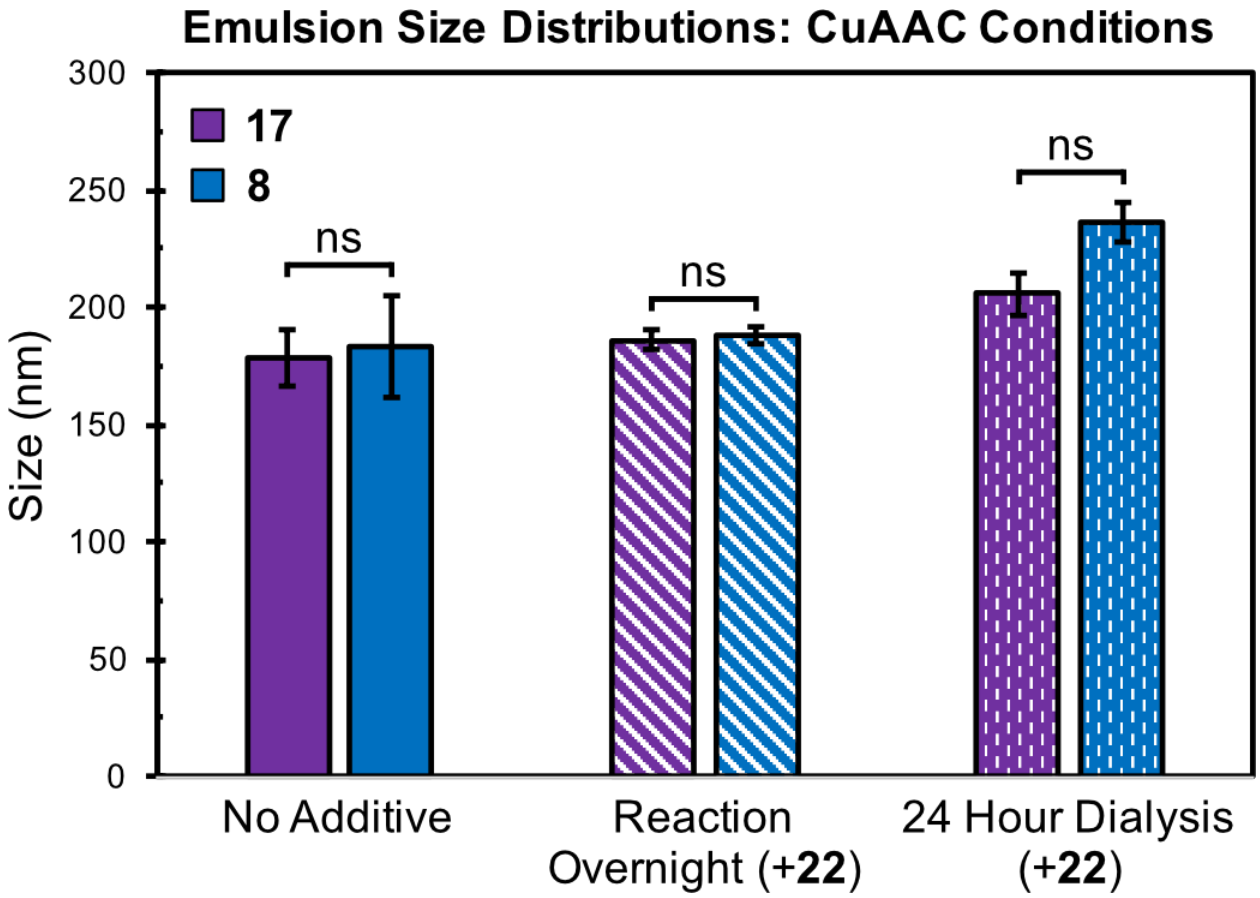


Figure S17. Dynamic light scattering data for alkyne-containing surfactant **17** (purple) and unfunctionalized surfactant **8** (blue) before (solid) and after (diagonal stripes) overnight CuAAC reaction with azidorhodamine **22**, followed by 24-hour dialysis (vertical stripes). Size measurements represent average of duplicate samples, three replicates per sample. Error bars represent the standard deviation of the size changes for duplicate samples. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$. Statistical significance was done by comparing the two sets of emulsions at identical conditions.

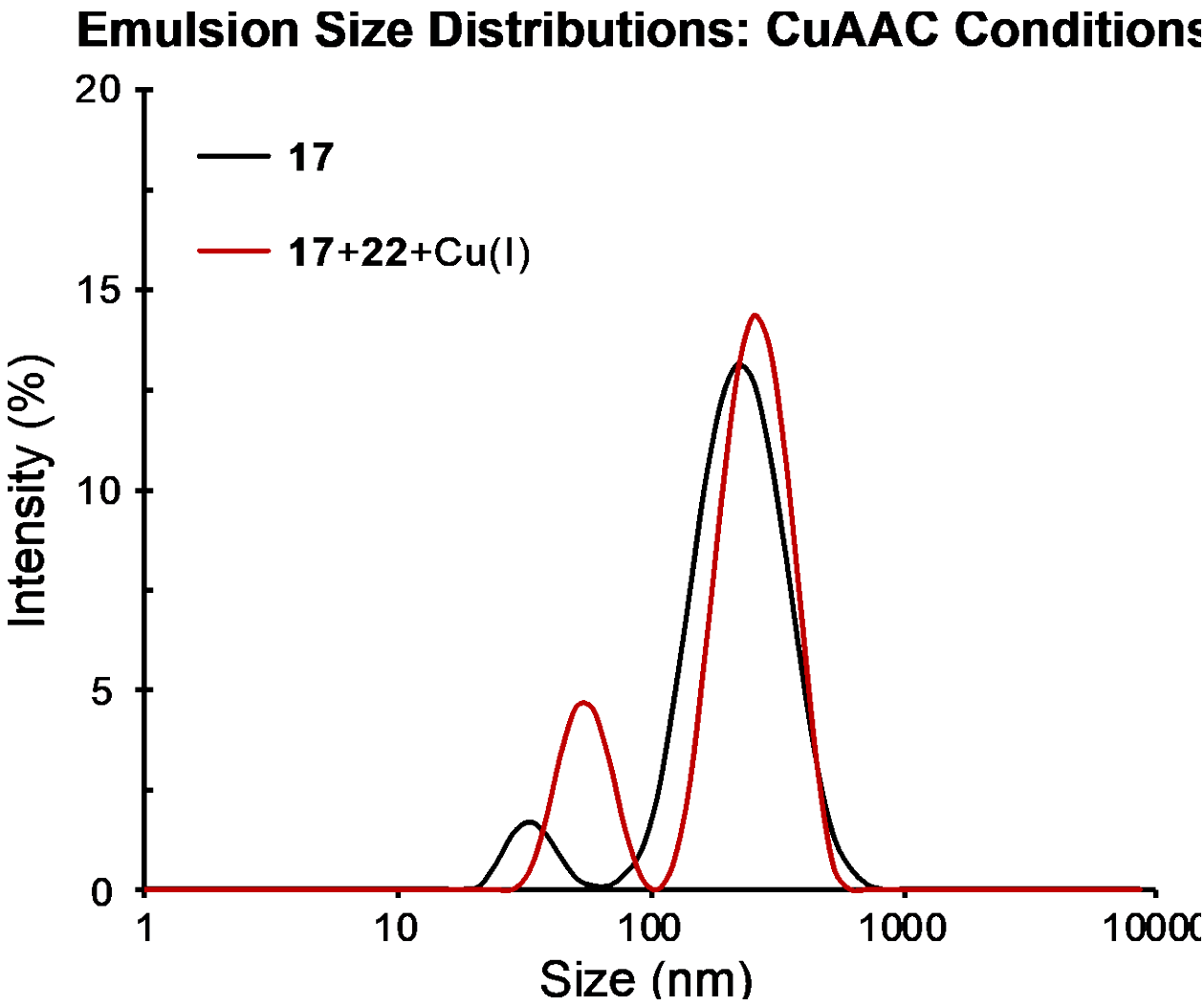


Figure S18. Dynamic light scattering data for the PFC nanoemulsions stabilized by alkyne-containing surfactant **17** before (black) and after (red) overnight CuAAC reaction with azidorhodamine **22**. Small population at ~50-70 nm corresponds to micelles; the observed increase in micelle size after conjugation with rhodamine **22** could be due to a change in hydrophilic-hydrophobic balance of the dye-micelle conjugate. Data are an average of three replicate measurements.

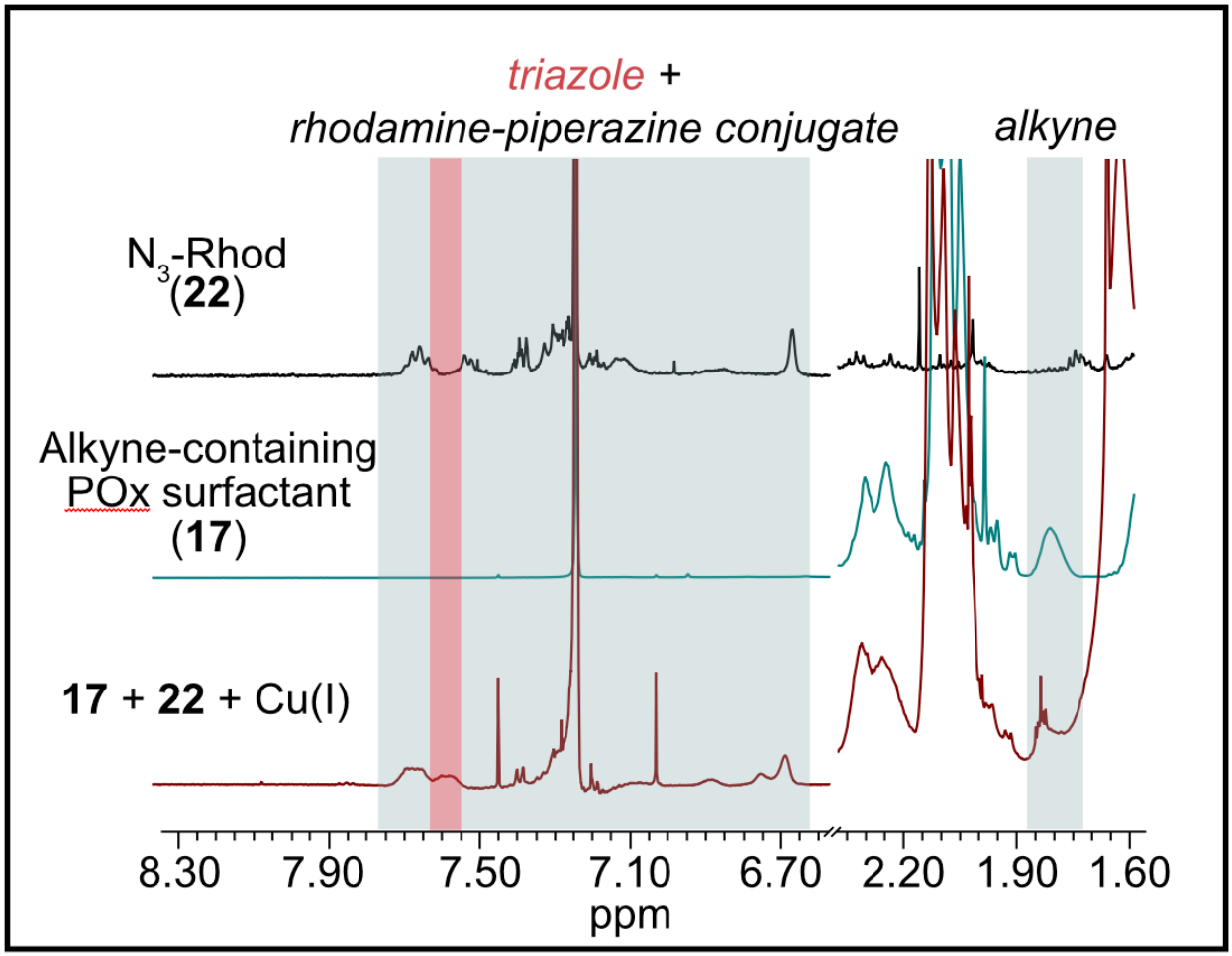


Figure S19. ^{1}H NMR ($CDCl_3$) of isolated surfactant from post-emulsion modification of **17** with azidorhodamine **22**, overlaid in relevant regions with starting materials **17** and **22**, as demonstrated in Figure 4C. Evolution of triazole peak in **17** + **22** can be seen at 7.60 ppm (highlighted red region), agreeing with the triazole peak that appears in reaction of **17** with model azide ethylazidoacetate **20** (Figure 3C,E). Full ^{1}H NMR of purified, modified surfactant is provided in Figure S20.

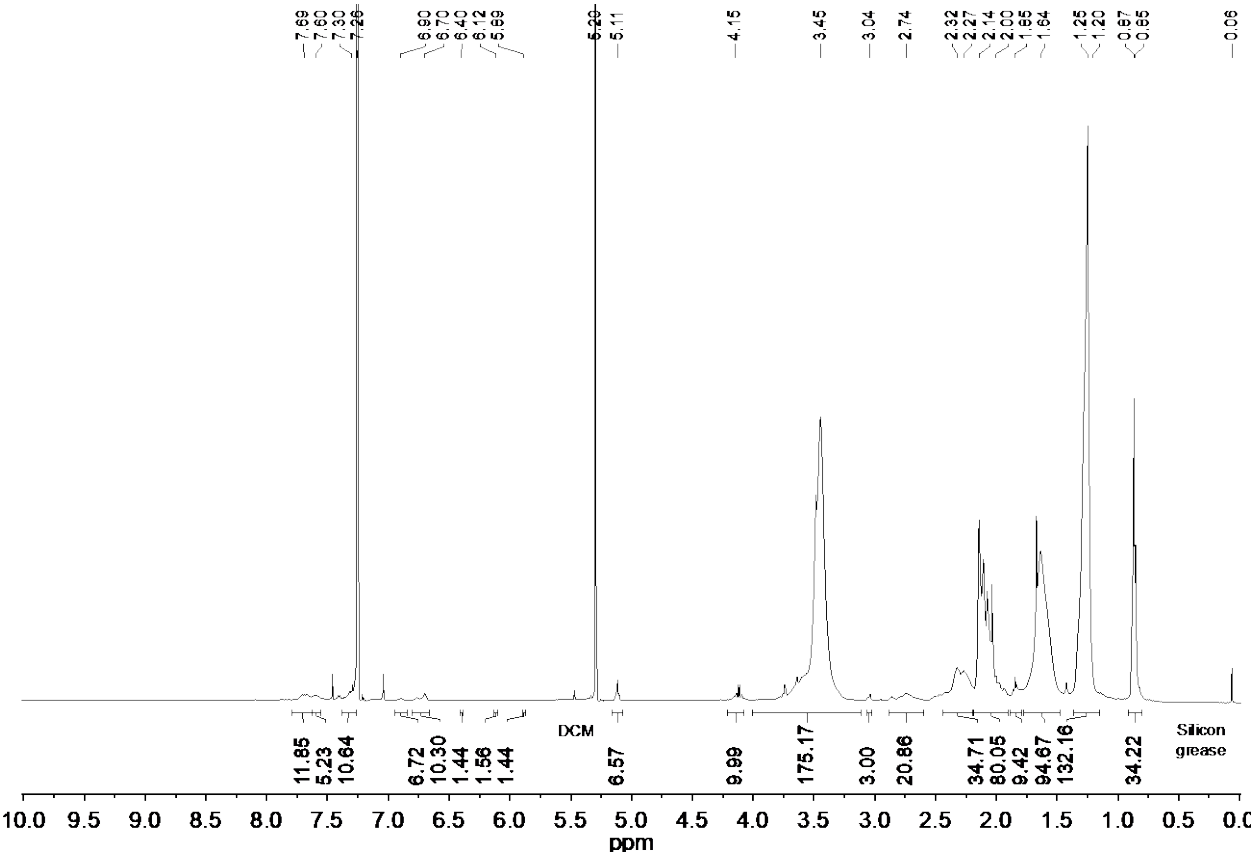


Figure S20. ^{1}H NMR of isolated and dialyzed surfactant from post-emulsion modification of **17** with azidorhodamine **22**, as demonstrated in Figure 4C.

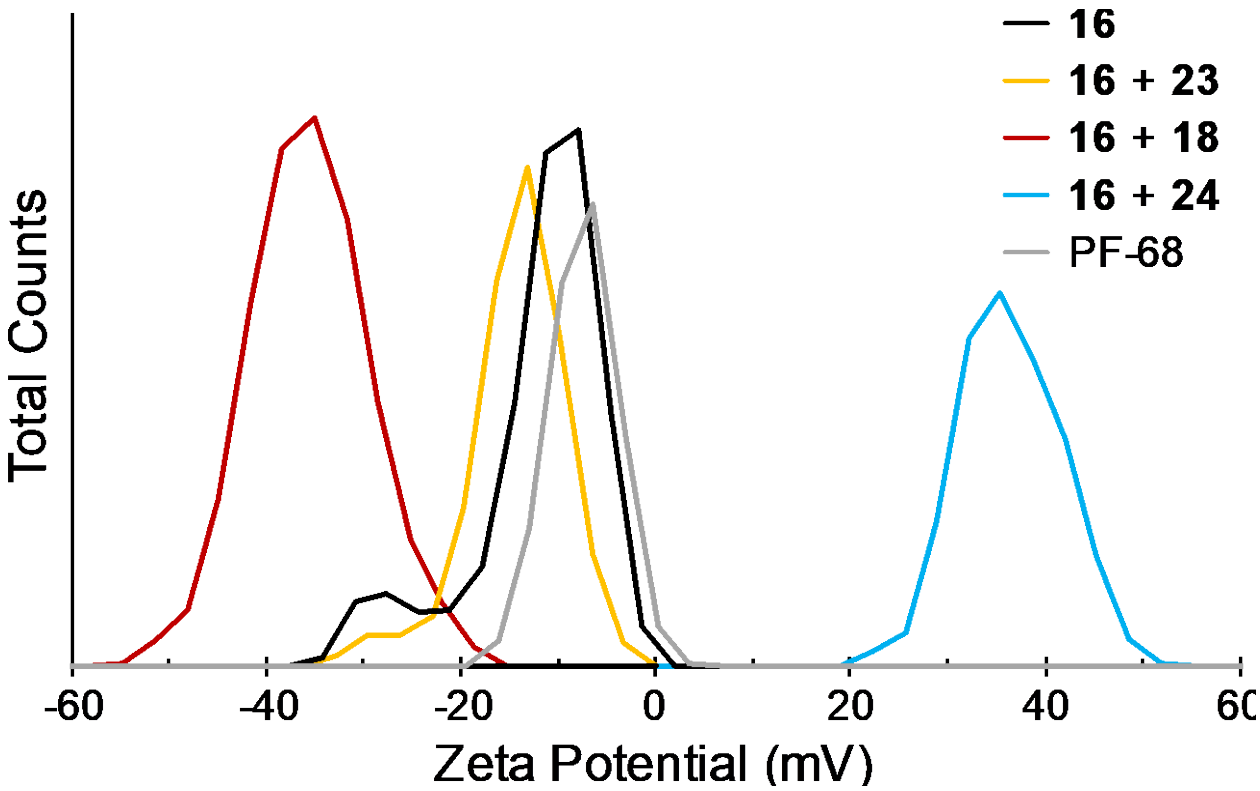


Figure S21. Zeta potential distributions for **16**-stabilized PFC emulsions modified with thiols (**18**, **23**, or **24**) before and after thiol-ene couplings, as shown in Figure 4E,F. Zeta potential traces for emulsions stabilized with functionalized surfactant **16** before (black) or after thiol-ene coupling with the following thiols: **23** (methylmercaptoacetate, yellow), **18** (mercaptoacetic acid, red) or **24** (2-dimethylaminoethanethiol, blue). Emulsions stabilized with Pluronic F-68 (**1**, PF-68, grey) were used as controls. Plotted is the zeta potential of the resulting emulsions at pH 7.4

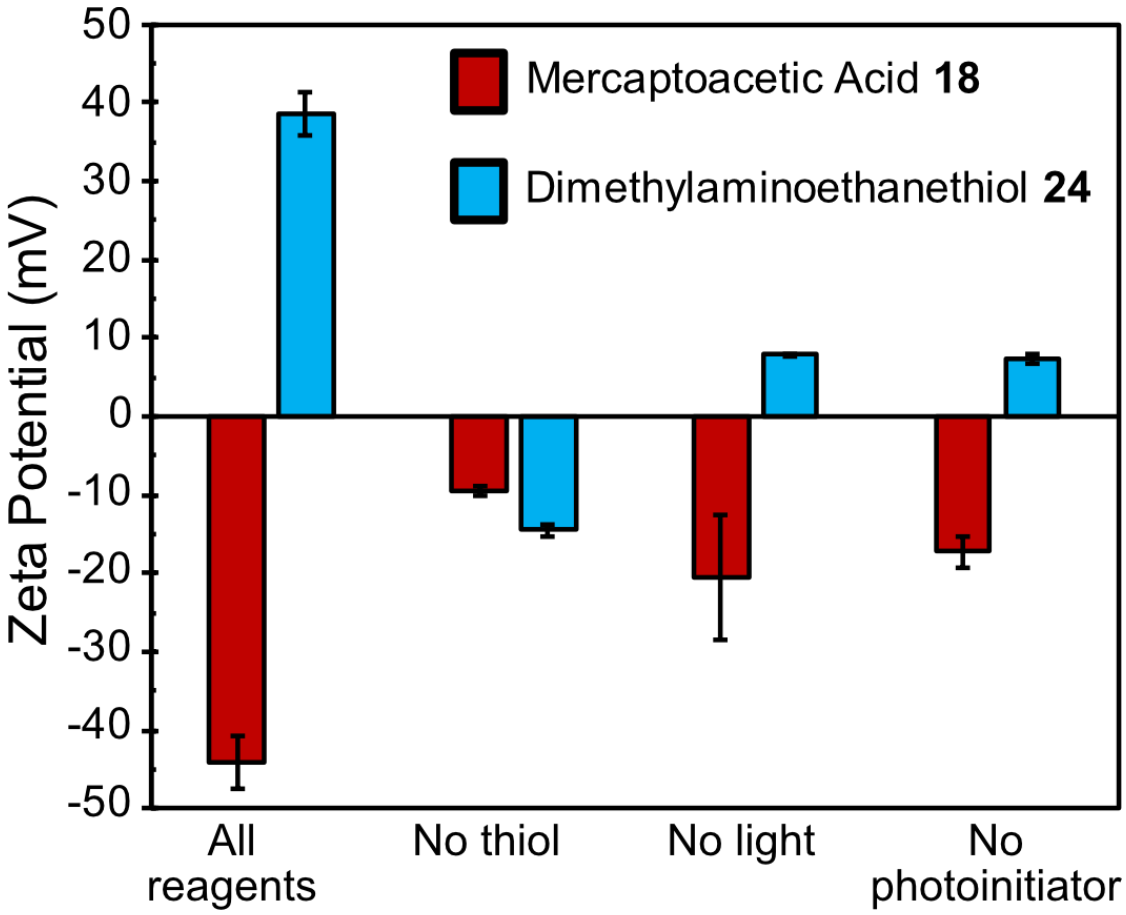


Figure S22. Zeta potentials for thiol-ene coupling controls. Emulsions were prepared with surfactant **16** and modified according to general nanoemulsion modification procedure using thiols **18** and **24**, with noted exceptions for lack of reagent. Plotted is the zeta potential of the resulting emulsions at pH 6. Data is representative of five replicate measurements. Error bars represent the standard deviation of five measurements.

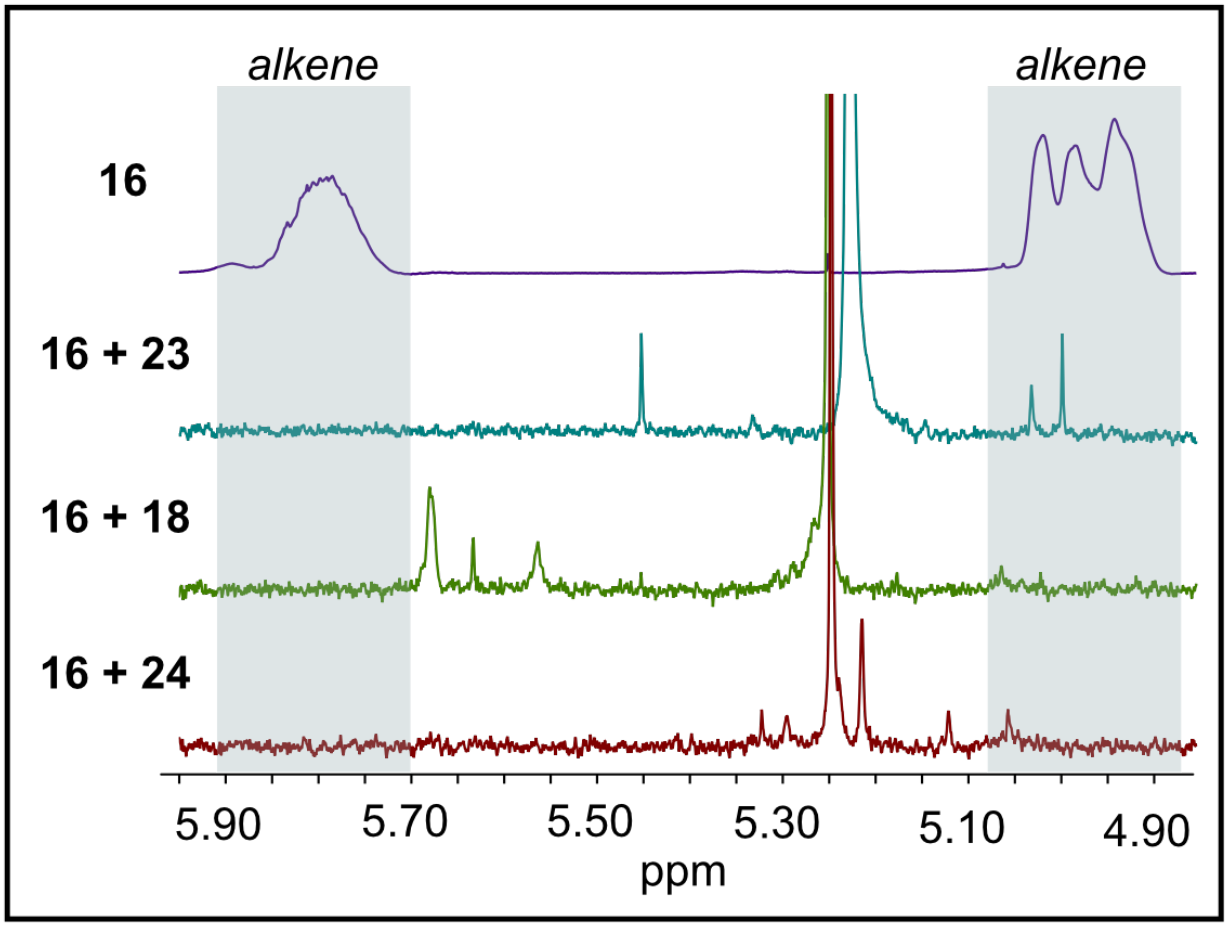


Figure S23. ^{1}H NMR of isolated surfactant from post-emulsion modification of **16** with thiols **18**, **23** and **24**, as demonstrated in Figure 4E,F. Overlaid region demonstrates full conversion of alkene functionality. Full ^{1}H NMR spectra of crude, modified surfactant are provided in Figures S24-S26.

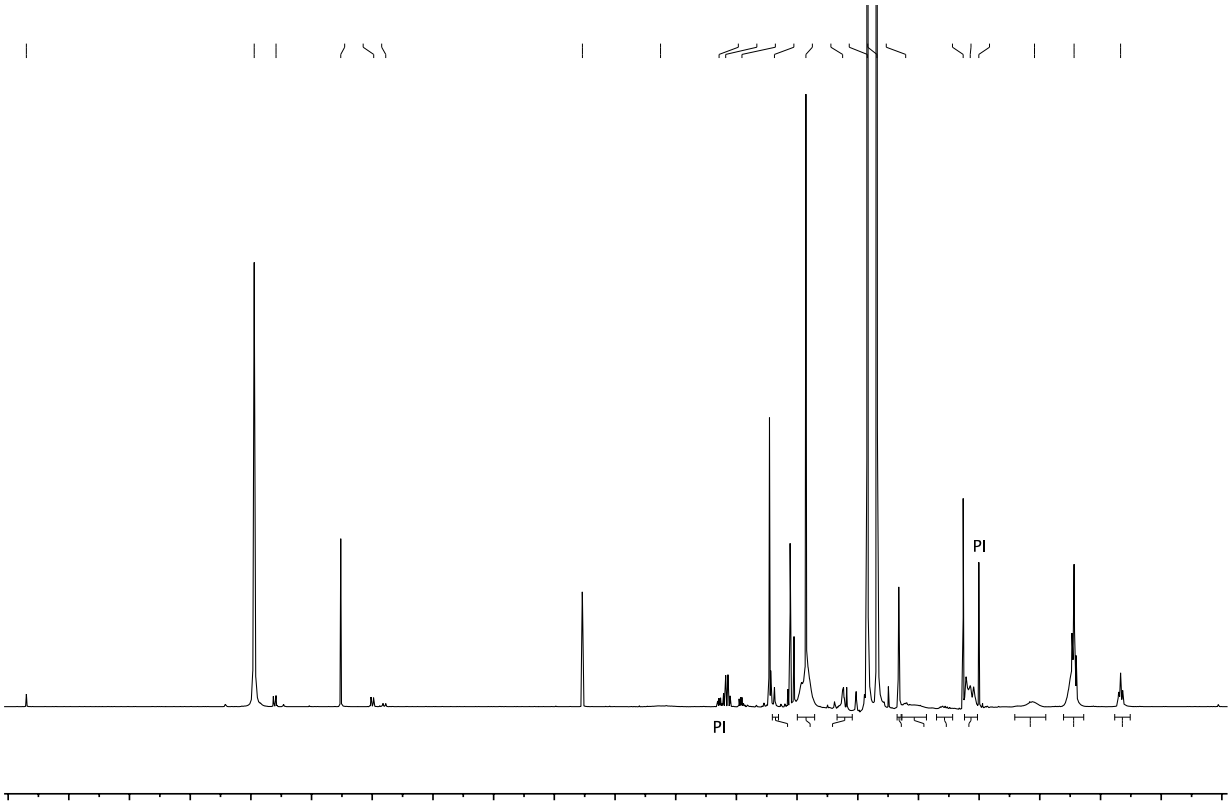


Figure S24. Crude ^{1}H NMR of isolated surfactant from post-emulsion modification of **16** with thiol **23**, as demonstrated in Figure 4E,F. PI = photoinitiator (irradiated Irgacure D-2959).

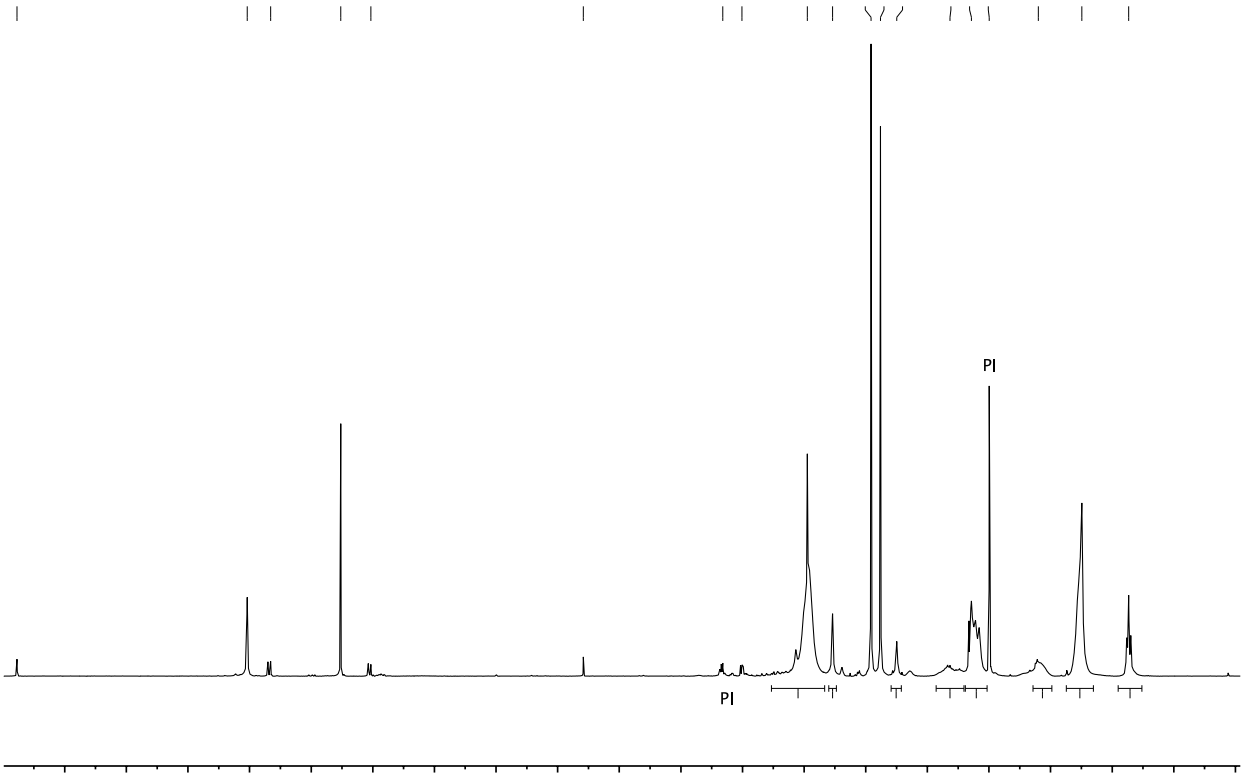


Figure S25. Crude ^{1}H NMR of isolated surfactant from post-emulsion modification of **16** with thiol **18**, as demonstrated in Figure 4E,F. PI = photoinitiator (irradiated Irgacure D-2959).

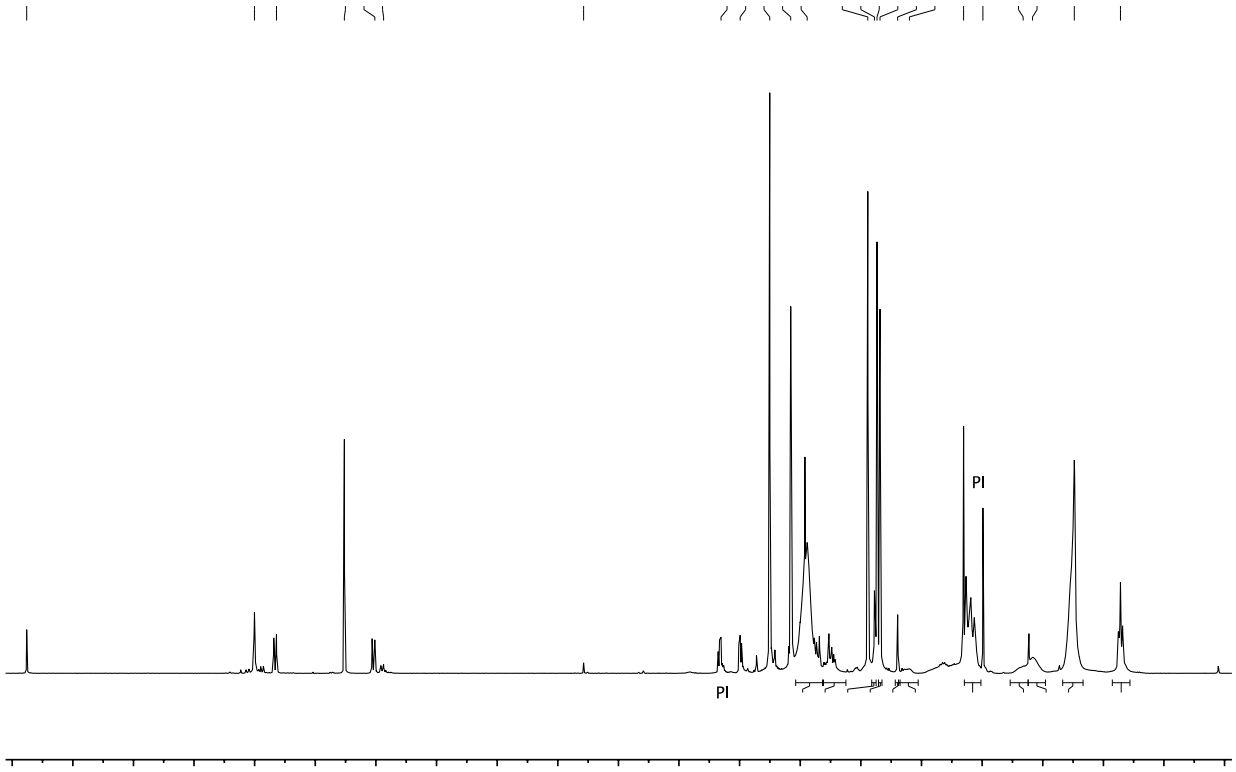


Figure S26. Crude ^{1}H NMR of isolated surfactant from post-emulsion modification of **16** with thiol **24**, as demonstrated in Figure 4E,F. PI = photoinitiator (irradiated Irgacure D-2959).

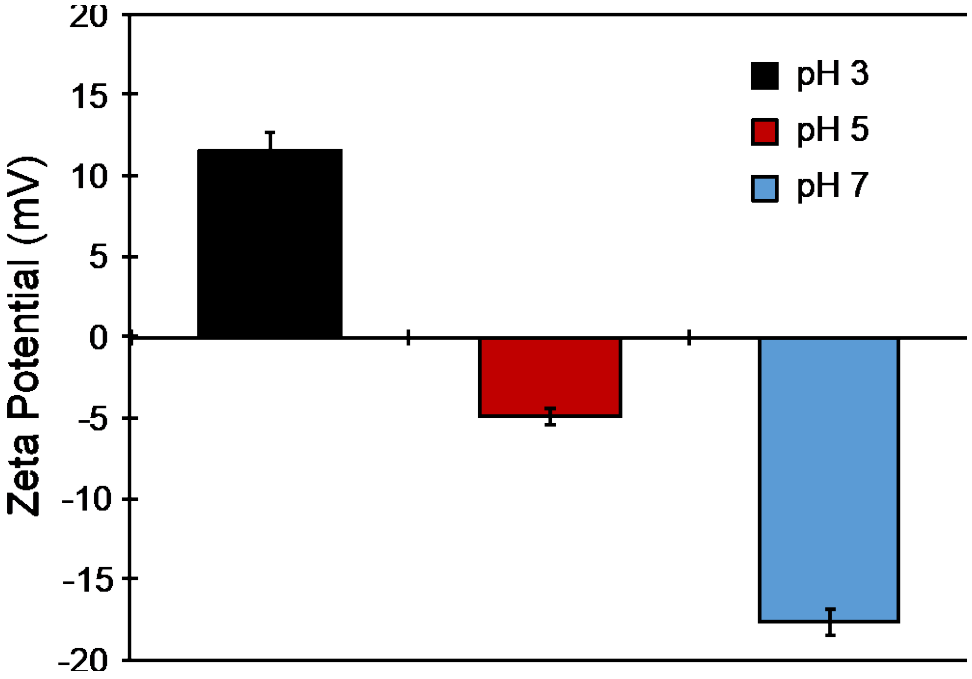


Figure S27. Dependence of zeta potential on pH for PFC emulsions stabilized by unmodified **16**. Data is representative of five replicate measurements. Error bars represent the standard deviation of five measurements.

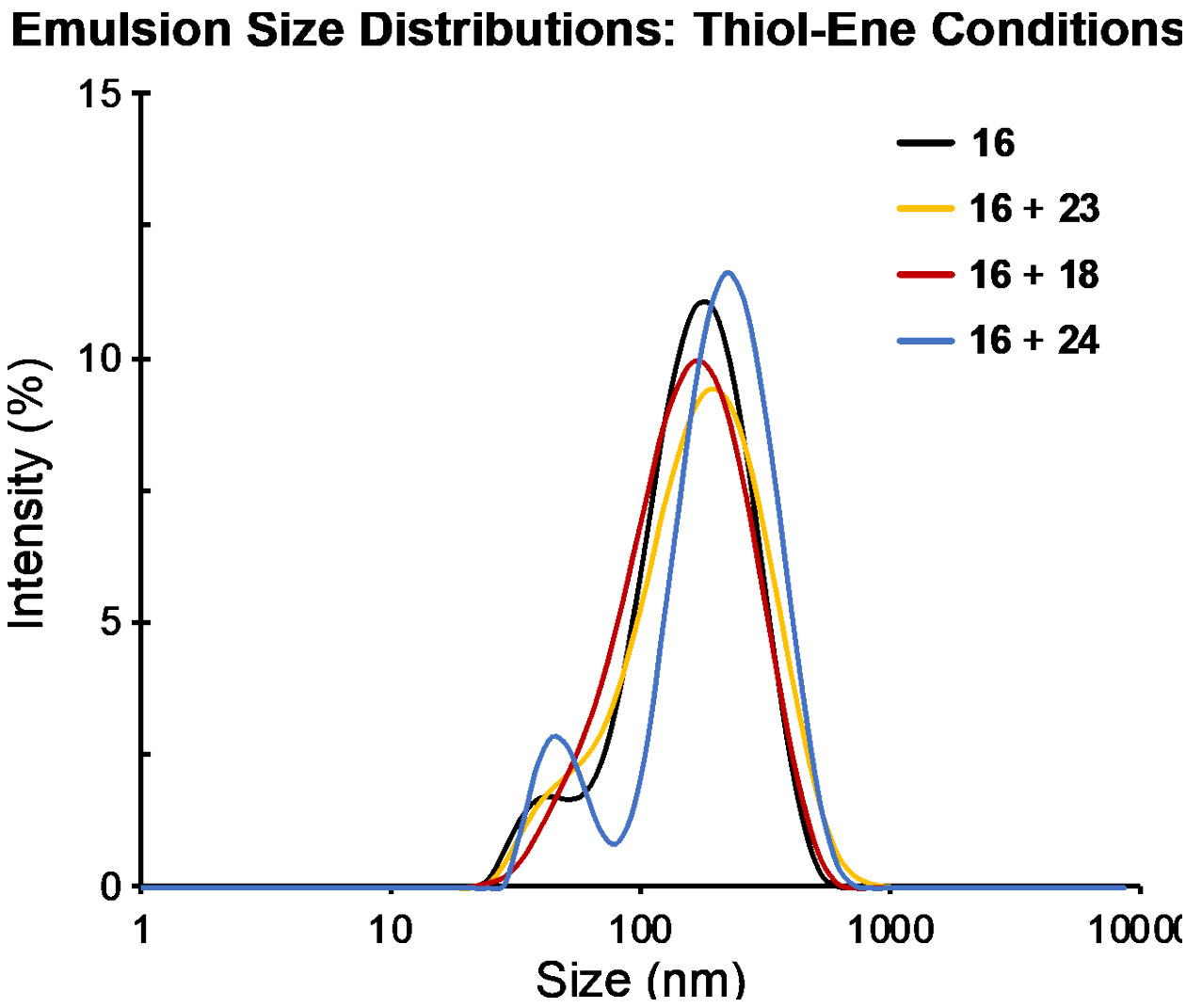


Figure S28. Dynamic light scattering data for the PFC nanoemulsions stabilized by alkene-containing surfactant **16** before (black) and after thiol-ene coupling with the following thiols: **23** (methylmercaptoacetate, yellow), **18** (mercaptoacetic acid, red) or **24** (2-dimethylaminoethanethiol, blue). Small population at ~50 nm corresponds to micelles. Data are an average of three replicate measurements.

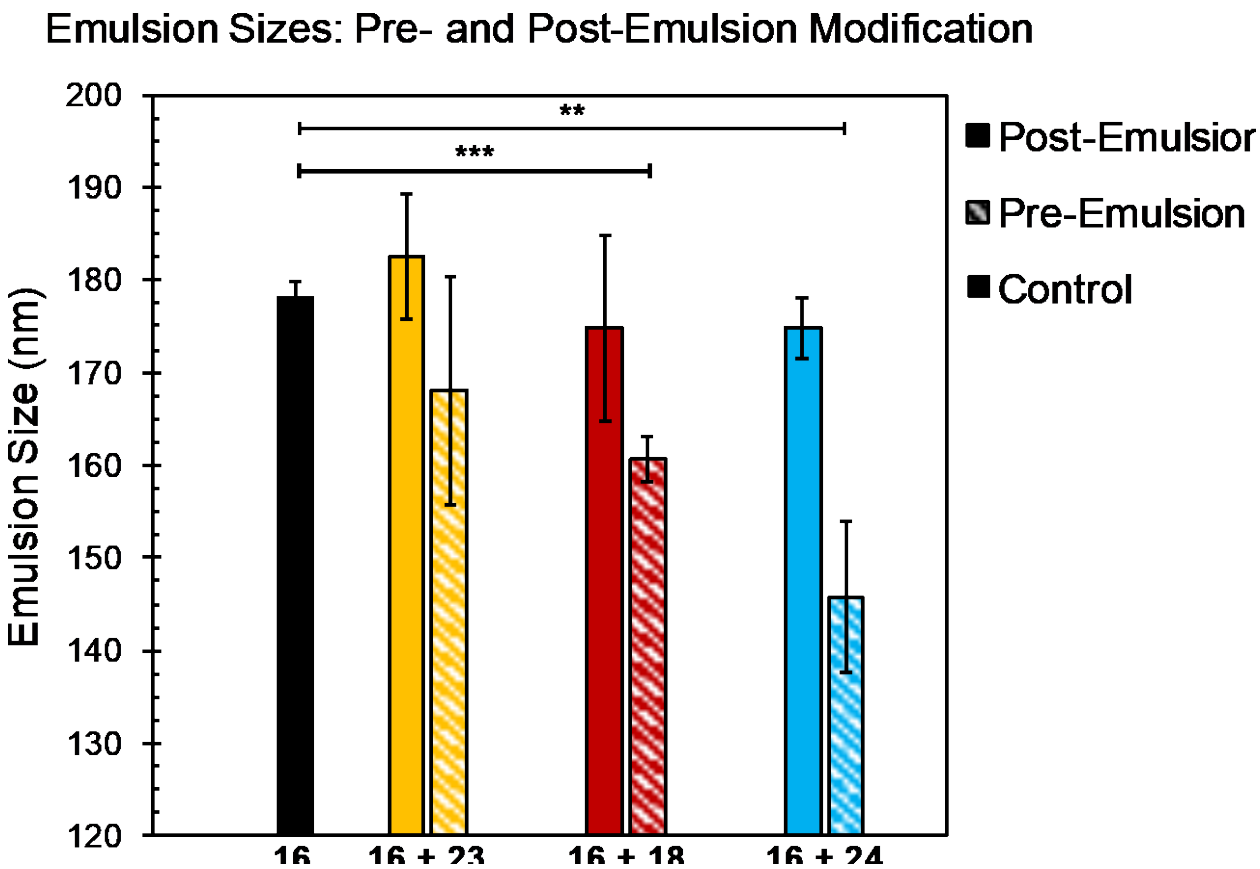


Figure S29. Emulsions modified through either a pre- or post-emulsion modification method as presented in Figure 5A,B. Thiol-ene chemistries were performed on surfactant **16** with thiols **18**, **23** or **24** either before (conditions in Figure 3B) or after emulsification (conditions in Figure 4E). The emulsions were diluted 1:100 in MilliQ water and analyzed by DLS. Plotted are nanoemulsion sizes. Size data are representative of the average of three independent samples, with three replicate measurements; error bars represent the standard deviation of the three independent samples. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$. Statistical significance was done for each emulsion with reference to control emulsion stabilized by unmodified **16**.

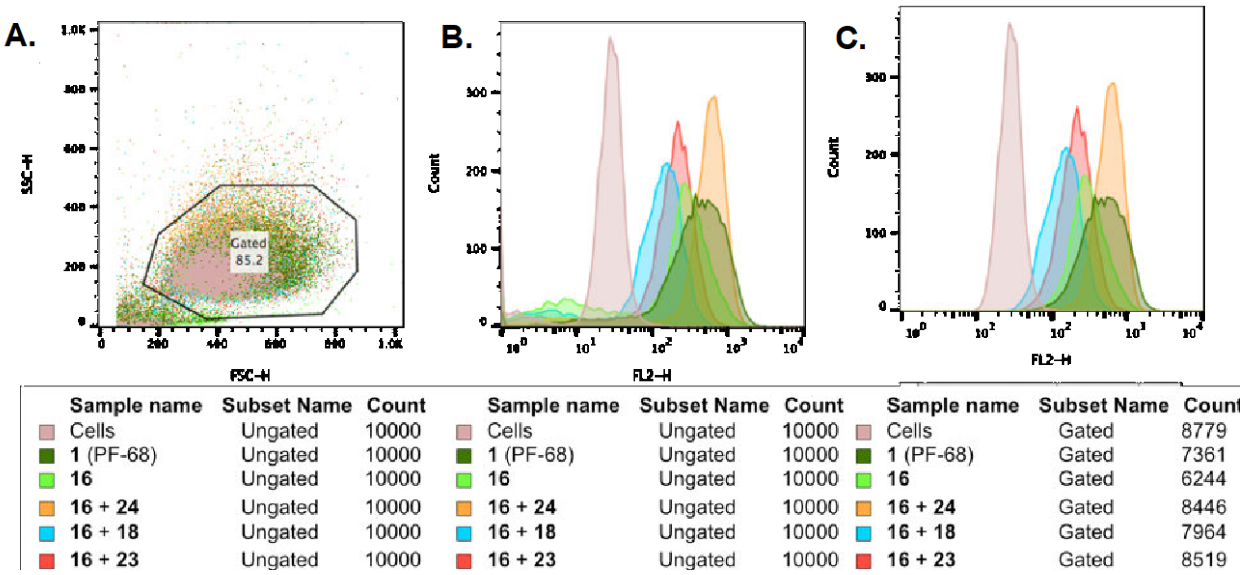
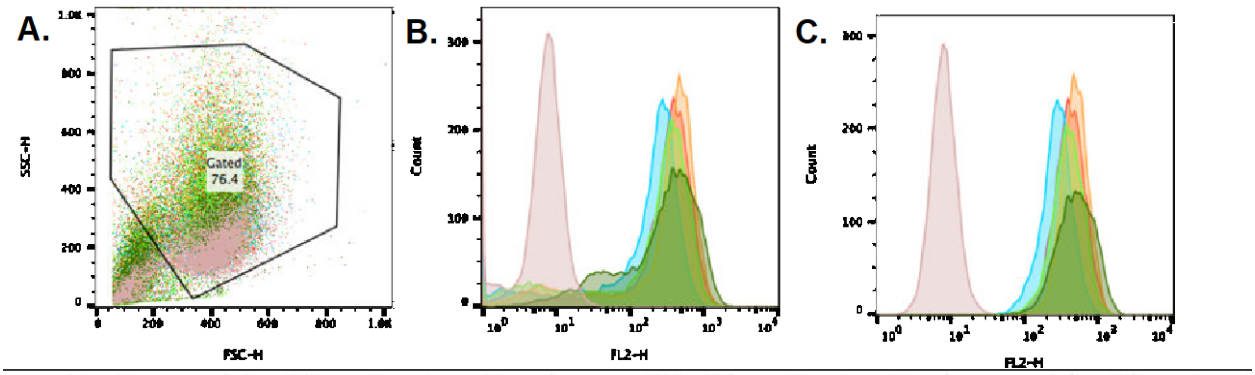


Figure S30. Histograms for A375 cell uptake flow cytometry data in Figure 6C.
(A) Side scatter (SSC) vs forward scatter (FSC) overlay of A375 cells incubated for 3 hours with emulsions and washed. The gate employed for Figure 6C is shown. (B) Representative FL-2 histograms of each sample, ungated. (C) Representative FL-2 histograms of each sample, gated.



Sample name	Subset Name	Count
Cells	Ungated	10000
1 (PF-68)	Ungated	10000
16	Ungated	10000
16 + 24	Ungated	10000
16 + 18	Ungated	10000
16 + 23	Ungated	10000

Sample name	Subset Name	Count
Cells	Ungated	10000
1 (PF-68)	Ungated	10000
16	Ungated	10000
16 + 24	Ungated	10000
16 + 18	Ungated	10000
16 + 23	Ungated	10000

Sample name	Subset Name	Count
Cells	Gated	7913
1 (PF-68)	Gated	5885
16	Gated	6738
16 + 24	Gated	7332
16 + 18	Gated	7245
16 + 23	Gated	7641

Figure S31. Histograms for RAW cell uptake flow cytometry data in Figure 6D. (A) Side scatter (SSC) vs forward scatter (FSC) of RAW cells incubated for 3 hours with emulsions and washed. The gate employed for Figure 6D is shown. (B) Representative FL-2 histograms of each sample, ungated. (C) Representative FL-2 histograms of each sample, gated.

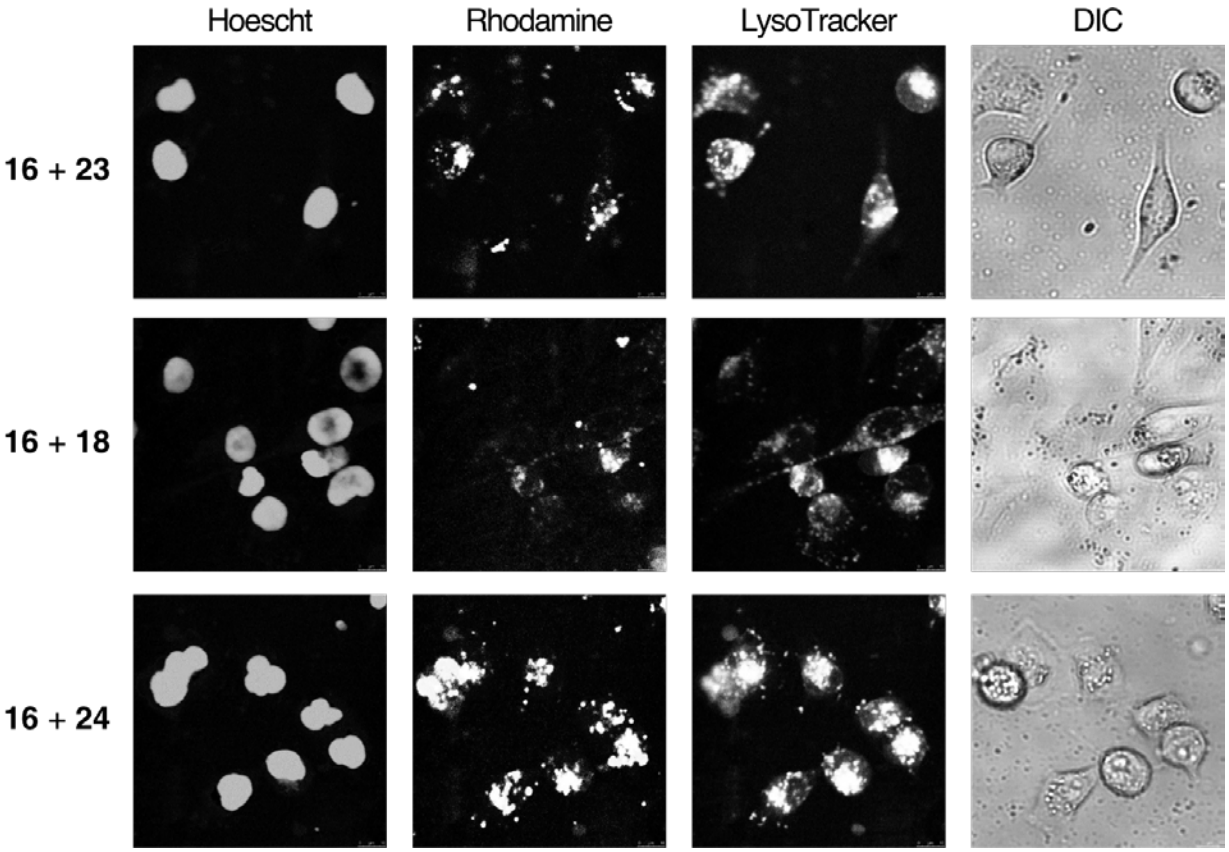


Figure S32. Single channel images for Figure 6E (confocal microscopy of A375 cells). PFC nanoemulsions with modified surface charges were prepared via the thiol-ene modification of emulsions formed from **16** as described in Figure 4E,F. Excess reagents were removed via thrice centrifugation and resuspension in MilliQ H_2O. After the final wash, the emulsions were resuspended in PBS and **25** in acetone was added. The emulsions were rocked for 1 min then introduced to A375 cells for 1 hour. The cells were washed 5x (3x media, 2x FACS buffer) to remove excess emulsions, lifted with trypsin and transferred to an FBS-treated microscope slide, incubated for 1 h in media, stained with Hoescht dye and LysoTracker Green and imaged via confocal microscopy. The cells were analyzed for rhodamine (Ex 532 nm) and Lysotracker Green (Ex 488 nm). Scale bar indicates 10 μm. Images are representative of two independent experiments.

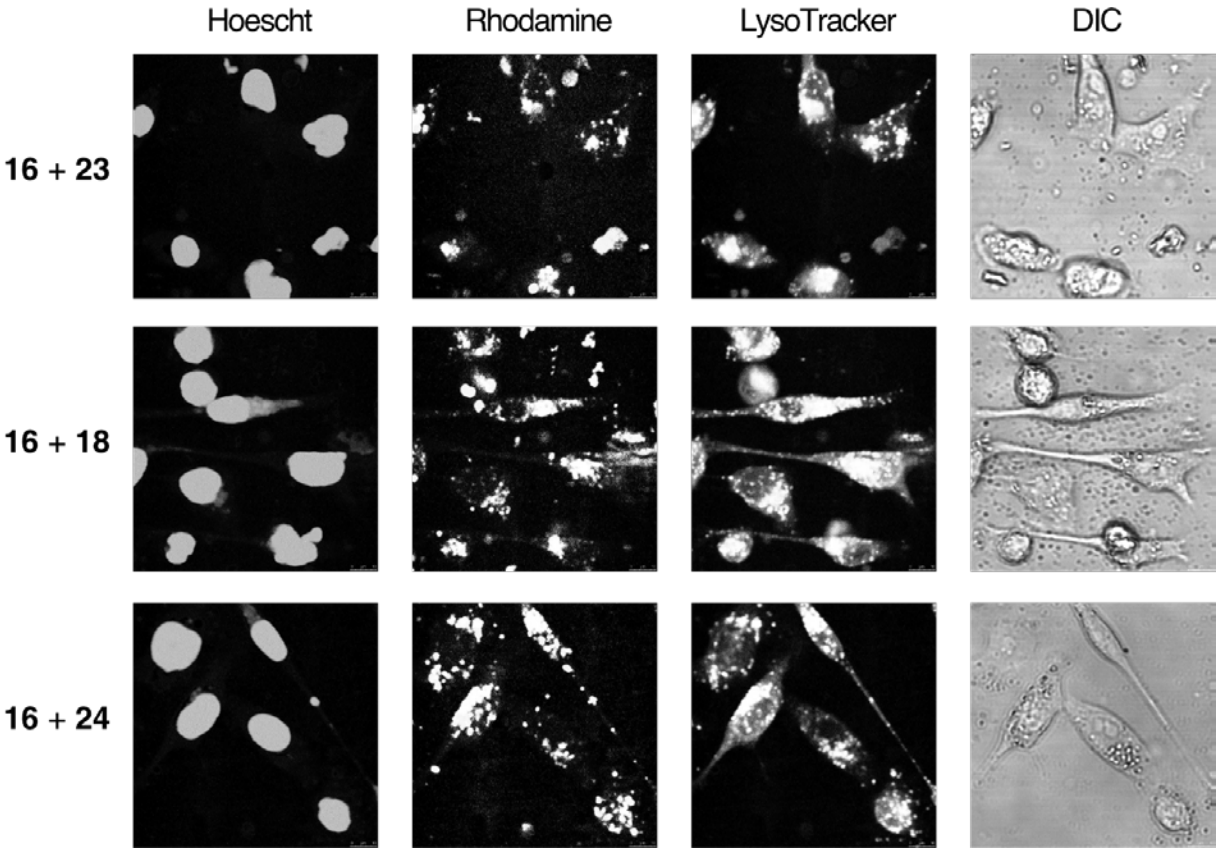


Figure S33. Single channel images for Figure 6F (confocal microscopy of RAW cells). PFC nanoemulsions with modified surface charges were prepared via the thiol-ene modification of emulsions formed from **16** as described in Figure 4E,F. Excess reagents were removed via thrice centrifugation and resuspension in MilliQ H_2O. After the final wash, the emulsions were resuspended in PBS and **25** in acetone was added. The emulsions were rocked for 1 min then introduced to RAW cells for 1 hour. The cells were washed 5x (3x media, 2x FACS buffer) to remove excess emulsions, lifted with trypsin and transferred to an FBS-treated microscope slide, incubated for 1 h in media, stained with Hoescht dye and LysoTracker Green and imaged via confocal microscopy. The cells were analyzed for rhodamine (Ex 532 nm) and Lysotracker Green (Ex 488 nm). Scale bar indicates 10 µm. Images are representative of two independent experiments.

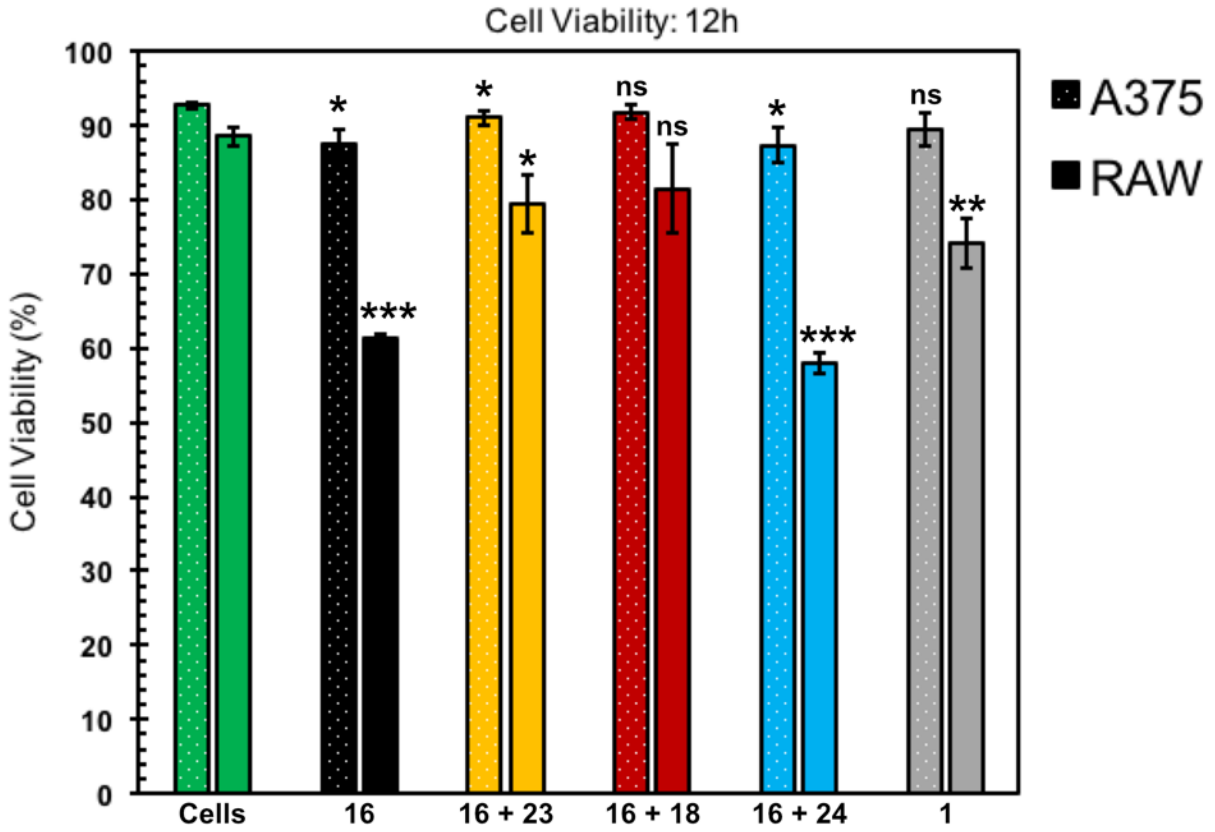


Figure S34. Cellular viability studies for RAW and A375 cells incubated with PFC nanoemulsions with modified surface charges over 12 hours. Surfactant concentration is ~7.0 mg/mL. Green = control cells; Black = emulsions stabilized by **16**; Yellow = emulsions stabilized by **16** and modified by **23**; Red = emulsions stabilized by **16** and modified by **18**; Blue = emulsions stabilized by **16** and modified by **24**; Grey = emulsions stabilized by **1**. Error bars represent the standard deviation of three replicate samples. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$. Statistical significance was done for each emulsion with reference to control cell (cell with no emulsion).

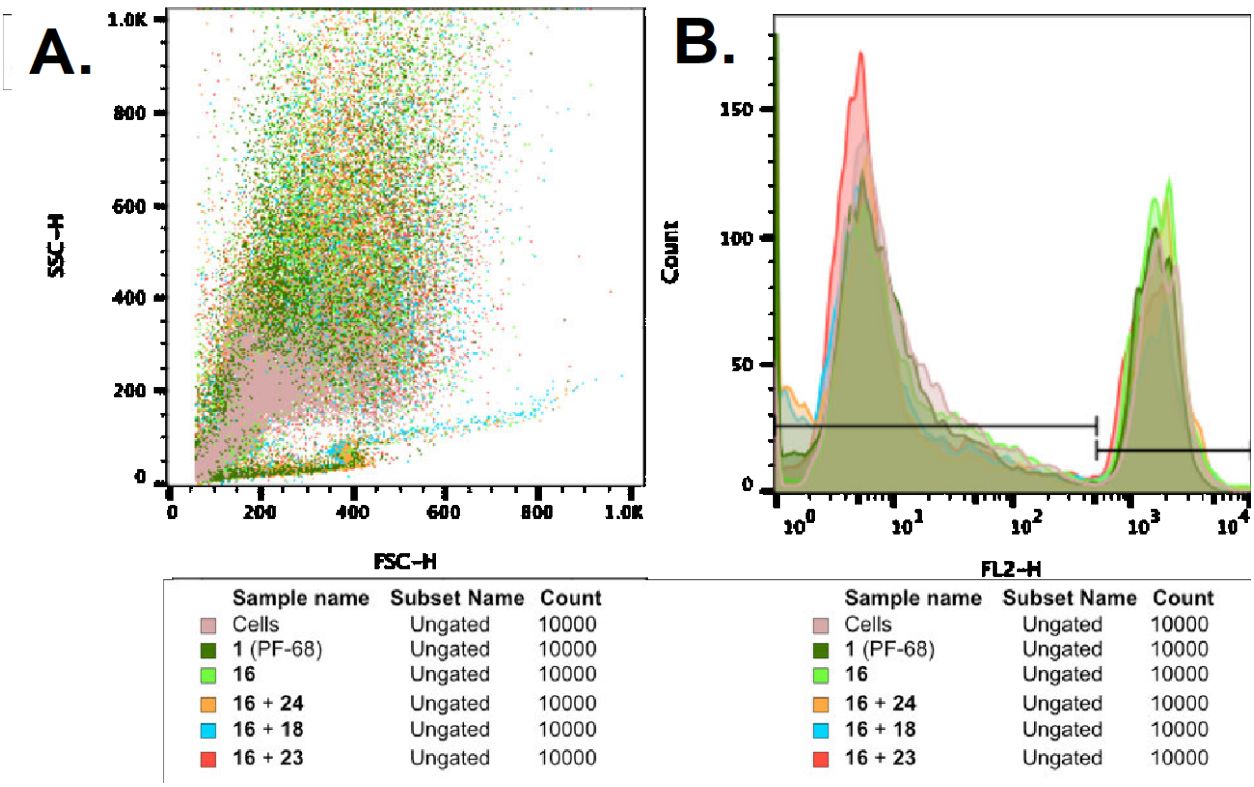


Figure S35. Histograms for RAW cellular viability flow cytometry data in Figure S34. (A) side scatter (SSC) vs forward scatter (FSC) overlay of RAW cells incubated for 12 hours with emulsions. (B) Representative FL-2 of each sample.

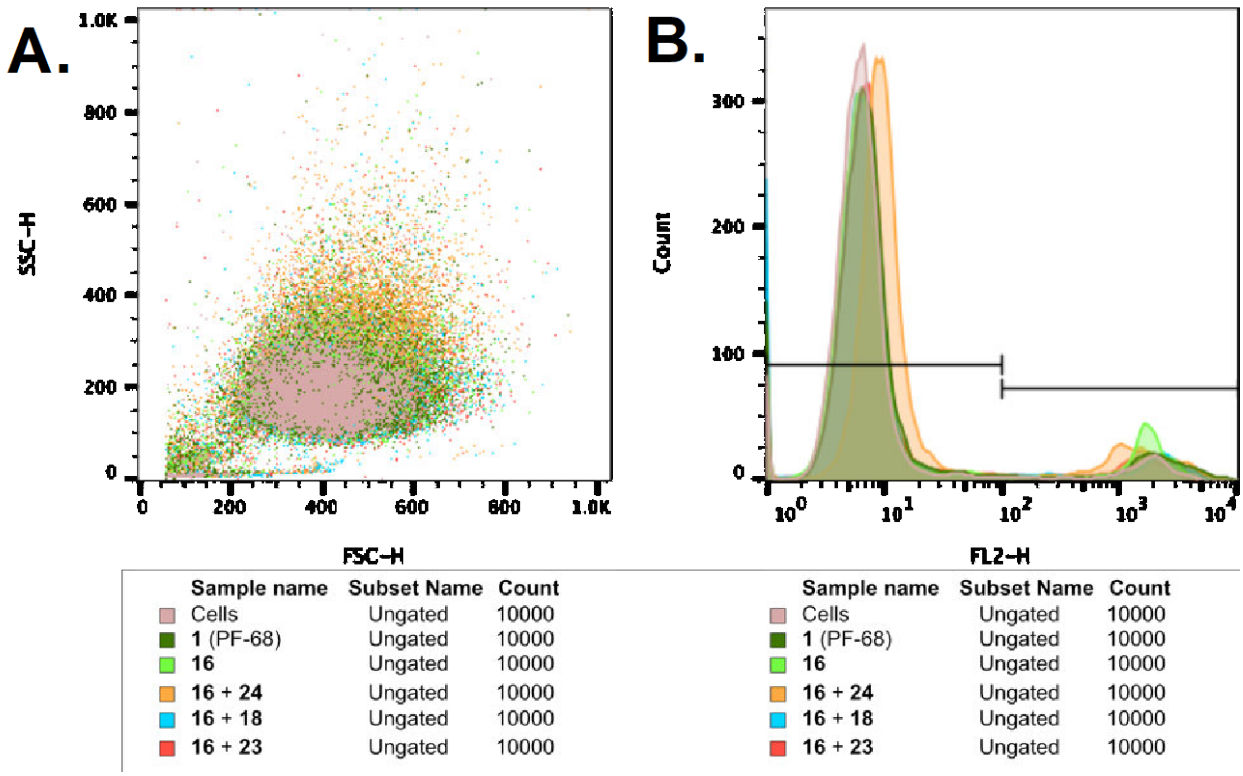


Figure S36. Histograms for A375 cellular viability flow cytometry data in Figure S34. (A) side scatter (SSC) vs forward scatter (FSC) overlay of A375 cells incubated for 12 hours with emulsions. (B) Representative FL-2 of each sample.

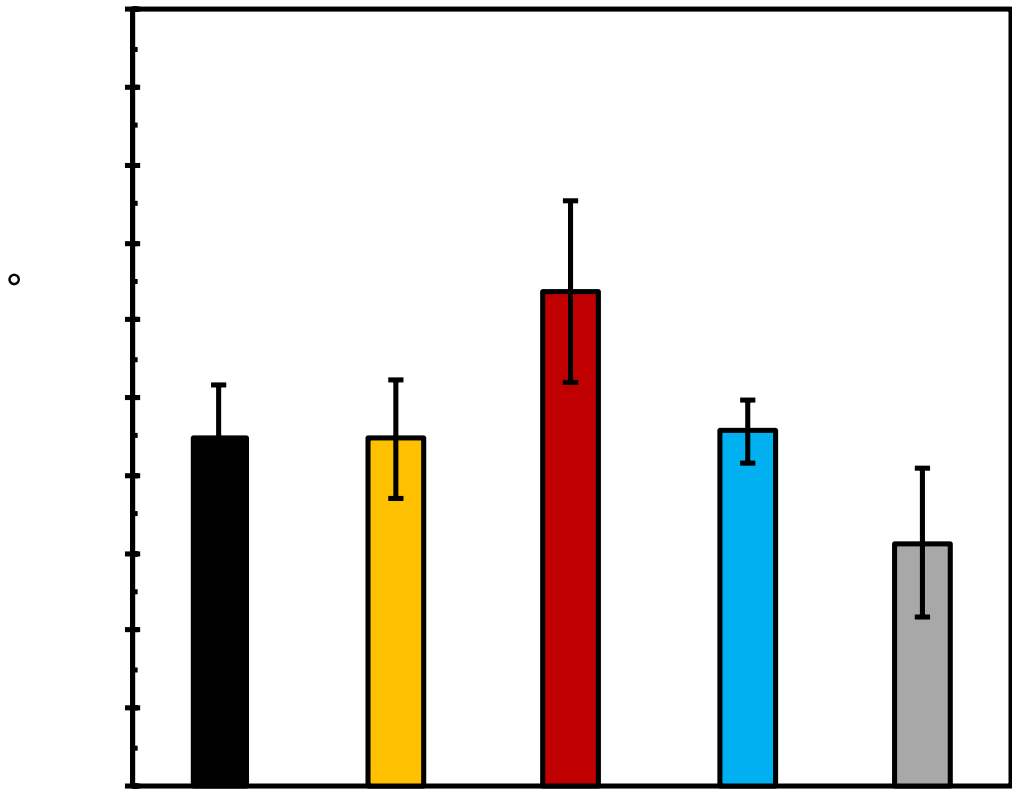


Figure S37. Inhibition of cellular (A375) uptake at 4 °C versus 37 °C. Black = emulsions stabilized by **16**; Yellow = emulsions stabilized by **16** and modified by **23**; Red = emulsions stabilized by **16** and modified by **18**; Blue = emulsions stabilized by **16** and modified by **24**; Grey = emulsions stabilized by **1**. Percent inhibition was determined as a ratio of cellular uptake (FL-2 fluorescence) at 4 °C versus uptake at 37 °C for one hour. Error bars represent the absolute uncertainty in uptake measurements, with three replicate samples at each temperature.

Supporting tables

Table S1. Characterization of functionalized amphiphilic poly(2-oxazoline)s

#	Polymer	M_n[a] (kDa)	$Đ$[b]
16	P((MeOx$_{30}$-*stat*-EneOx$_5$)-*b*-NonOx$_{11}$)	5.2	1.25
17	P((MeOx$_{29}$-*stat*-PyneOx$_5$)-*b*-NonOx$_{11}$)	5.2	1.25

PyneOx = 2-(4-pentynyl)-2-oxazoline; EneOx = 2-(3-butenyl)-2-oxazoline
[a]Number-average molecular weight (M_n) determined by ^{1}H-NMR end-group analysis of terminal CH_3 group to polymeric backbone
[b]Dispersity index ($Đ$) determined by SEC analysis (eluent: $CHCl_3$, DMF + 0.1M LiBr, or hexafluoroisopropanol)

Supporting equations

Determining surface area and volume of emulsions stabilized with **11**:

Knowns:
- Diameter of nanoemulsions: 120 nm

$$Surface\ area\ of\ nanoemulsion = 4\pi * (120\ nm)^2 = 3600\ nm^2$$
$$Volume\ of\ nanoemulsion = \frac{4}{3}\pi * (120\ nm)^3 = 9.1 * 10^5\ nm^3$$

Determining number of emulsions stabilized with **11**:

Knowns:
- Volume of inner phase (fluorocarbon or hydrocarbon oil): 20 µL

$$\#\ of\ emulsions = \frac{volume\ of\ solvent}{volume\ of\ avg\ emulsion} = \frac{2.00 * 10^{19}\ nm^3}{9.1 * 10^5\ nm^3} = 2.2 * 10^{13}\ emulsions$$

Determining number of alkene molecules used in surfactant:

Variables:
- EneOx (**16**) polymer weight (M_n): 5152 Da
- Alkene = 12.2 mol% of total polymer

$$mols\ alkene\ monomer = \frac{5.60\ mg\ polymer}{5152\ Da} = 1.09 * 10^{-6}\ mols\ polymer$$

$$(1.09\ mols\ polymer)(12.2\ mol\%\ alkene) = 1.32 * 10^{-7}\ mols\ alkene$$

$$(1.32 * 10^{-7}\ mols\ alkene)(6.02 * 10^{23}\ molecules * mol^{-1}) = 7.95 * 10^{16}\ alkene\ molecules$$

Determining number of alkene molecules per emulsion:

Assumptions:
- All surfactant in solution is assembled at the liquid-liquid interface

$$\frac{\#\ of\ alkenes\ in\ surfactant}{\#\ of\ emulsions} = \frac{7.95 * 10^{16}\ alkenes}{2.2 * 10^{13}\ emulsions} = 3600\ alkenes\ per\ emulsion$$

General experimental procedures

Chemical reagents were purchased from Sigma-Aldrich, Alfa Aesar, Fisher Scientific, or Acros Organics and used without purification unless noted otherwise. Anhydrous dimethyl sulfoxide (DMSO) was obtained from a Sure-SealTM bottle (Aldrich). Anhydrous and deoxygenated solvents dichloromethane (DCM), acetonitrile (MeCN), methanol (MeOH), and tetrahydrofuran (THF) were dispensed from a Grubb's-type Phoenix Solvent Drying System. Anhydrous but oxygenated 1-butanol and chlorobenzene was prepared by drying over 4 Å molecular sieves for at least 3 days. Thin layer chromatography was performed using Silica Gel 60 F254 (EMD Millipore) plates. Flash chromatography was executed with technical grade silica gel with 60 Å pores and 40–63 μm mesh particle size (Sorbtech Technologies). 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. Bath sonication was performed using a Branson 3800 ultrasonic cleaner. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) spectra were taken on Bruker Avance 500 (^{1}H NMR and ^{13}C NMR) or AV-300 (^{19}F NMR) instruments and processed with MestReNova software. All ^{1}H NMR peaks are reported in reference to $CDCl_3$ at 7.26 ppm. Size Exclusion Chromatography (SEC)/Gel Permeation Chromatography (GPC), unless otherwise noted, was conducted on a Shimadzu high performance liquid chromatography (HPLC) system with a refractive index detector RID-10A, one Polymer Laboratories PLgel guard column, and two Polymer Laboratories PLgel 5 μm mixed D columns. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min). Calibration was performed using near-monodisperse poly(methyl-methacrylate) PMMA standards from Polymer Laboratories. Masses for analytical measurements were taken on a Sartorius MSE6.6S-000-DM Cubis Micro Balance. Microwave reactions were performed using a CEM Discover SP microwave synthesis reactor. All reactions were performed in glass 10 mL microwave 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 microwave 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 250W (the power applied was dynamically controlled by the microwave instrument and did not exceed this limit for any reactions). Irradiation with light was performed with BI365 nm Inspection UV LED lamp, purchased from Risk reactor (Output power density >5000μW/cm² at 15" (38cm), voltage range 90-265V ac, output power: 3*325mW at 365nm peak).

Abbreviations

DCM = dichloromethane; DMSO = dimethylsulfoxide; EtOH = ethanol; MeCN = acetonitrile; MeOH = methanol; THF = tetrahydrofuran; PFD = perfluorodecalin; PFTPA = perfluorotripropylamine; POx = poly(2-oxazoline); DBC = diblock copolymer; TBC = triblock copolymer; MeOx = 2-methyl-2-oxazoline; NonOx = 2-nonyl-2-oxazoline, FOx = 2-(perfluorohexyl)ethyl-2-oxazoline; PyneOx = 2-(4-pentynyl)-2-oxazoline; EneOx = 2-(3-butenyl)-2-oxazoline; MMA = methylmercaptoacetate; MAA = mercaptoacetic acid; DMAET = 2-dimethylaminoethanethiol.

General photophysics procedure

Absorbance spectra were collected on a JASCO V-770 UV-Visible/NIR spectrophotometer with a 4000 nm/min or 2000 nm/min scan rate after blanking with the appropriate solvent. Quartz cuvettes (1 cm or 0.33 cm) were used for absorbance and photoluminescence measurements.

General nanoemulsion formation procedure

Polymer surfactant (5.6 mg) was dissolved in DMF (20 μL) and sonicated in a bath sonicator (~15 minutes) until fully dissolved, at which point 7:3 perfluorodecalin:perfluorotripropylamine (10 vol%, 20 μL) or olive oil (10 vol%, 20 μL) was added, followed by PBS buffer pH 7.4 (200 μL). The mixture was sonicated at 35% amplitude for 15 minutes at 0 °C on a QSonica (Q125) sonicator. Sonication was performed by lowering the probe directly at the liquid-liquid interface of the two immiscible solvents.

General nanoemulsion analysis procedure

Size analysis: 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. Size was analyzed with a Malvern Zetasizer Nano dynamic light scattering. SOP parameters: 10 runs, 10 seconds/run, three measurements, no delay between measurements, 25 °C with 120 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. Size error bars represent the half-width at half-maximum of the measurements.

Zeta potential analysis: 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. Solution was then transferred to a disposable folded capillary cell for zeta potential measurements. Zeta potential was analyzed with a Malvern Zetasizer Nano. SOP parameters: Minimum: 10 runs, Maximum: 100 runs, 5 measurements, no delay between measurements, Model: Smoluchowski, 25 °C, 120 second equilibration time. Collection parameters: Auto mode. Data are representative of five replicate measurements. Zeta potential error bars represent the standard deviation of the measurements.

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 = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.

General nanoemulsion modification procedure via thiol-ene

Functionalized surfactant **16** containing ~8 wt% alkene (11.2 mg, 2.20 mmol) was dissolved in DMF (40 µL) and samples were sonicated in a bath sonicator (~15 minutes) until dissolved. A 7:3 mixture of perfluorodecalin:perfluorotripropylamine (10 vol%, 40 µL) was added, followed by PBS buffer pH 7.4 (400 µL). The biphasic mixture was sonicated at 35% amplitude for 90 seconds according to the general nanoemulsion formation procedure. The size was analyzed with Malvern Zetasizer Nano dynamic light scattering according to the general nanoemulsion analysis procedure.

The emulsion solution was aliquoted (4x115 µL), giving solutions **A**-**D** (2.8 mg 16 per solution at ~8 wt% ≈ 0.3 mg EneOx, 2.1 µmol, 1.0 equiv.). To solution **A**, methyl mercaptoacetate was added (23, 4.0 µL, 41 µmol, 20 equiv.). To solution **B**, mercaptoacetic acid (**18**, 3.5 µL, 41 µmol, 20 equiv.) was added. To solution **C**, dimethylaminoethanethiol was added (**24**, 4.3 mg, 41µmol, 20 equiv.). A photoinitiator stock solution was made by dissolving Irgacure D-2959 (3.374 mg, 15 µmols) in MilliQ water (1 mL). Photoinitiator stock solution (115 µL, 1.6 µmol, 0.8 equiv.) was added to solutions **A**-**C**. All solutions were illuminated with 365 nm light overnight. The following morning, the emulsion size and charge was determined according to the general nanoemulsion analysis procedure.

General nanoemulsion modification procedure via CuAAC

Emulsions stabilized by surfactant **17** were prepared according to the general nanoemulsion procedure. A stock solution of azidorhodamine **22** (38.2 mg/mL) was prepared by dissolving azidorhodamine **22** (21 mg/mL) in MilliQ water (300 µL) and MeOH (250 µL).

A portion of the bulk emulsion solution (130 µL) was diluted with MilliQ water (290 µL) and $CuSO_4$ (0.08 mg, 0.5 µmol, 0.3 equiv.), sodium ascorbate (0.168 mg, 0.815 µmol, 0.50 equiv.) were added followed by azidorhodamine **22** (80 µL of stock solution, 3.0 mg, 4.9 µmol, 3.0 equiv.). The reaction was stirred overnight. The following morning, the emulsion size was analyzed as described in the general nanoemulsion analysis procedure.

Cell culture experimental procedures

RAW cells were donated by the lab of Professor Alexander Hoffman. A375 cells were purchased from ATCC.

RAW cells and A375 cells were cultured in Dulbecco's Modified Eagle Media (DMEM, Life Technologies, cat# 11995073) supplemented with 10% fetal bovine serum (Corning, lot# 35016109) and 1% penicillin-streptomycin (Life Technologies, cat# 15070063). Cells were washed with PBS, or PBS supplemented with 1% fetal bovine serum (FACS buffer). Cells were detached with trypsin digest solution (*i.e.* 0.25% trypsin, 2.21 mM EDTA (1X), (-) sodium bicarbonate (Corning, lot# 12317008). Cells were incubated at 37 °C, 5% CO_2, during treatments and throughout culturing, in HERACell 150i CO_2 incubators. Cells were pelleted through use of Sorvall ST 40R centrifuge (3x, 526xg, 3 min). All cell work was performed in 1300 Series A2 biosafety cabinets. Confocal microscopy was performed on a TCS SPE Leica confocal microscope containing 405 nm, 488 nm, 532 nm and 635 nm lasers.

General cell labeling procedure

Fluorous rhodamine **25** was synthesized as previously reported[1]. A stock solution of 9.37 mg/mL in acetone (4.29 mM) was prepared.

PF-68-stabilized emulsions were prepared as described by the general nanoemulsion formation and modification procedures. POx-stabilized emulsions were prepared and functionalized as described by the general nanoemulsion formation and modification procedures. After size and zeta potential measurements had been taken, emulsions were washed by centrifugation and suspension (3x 900*g* followed by resusupension in 100 μL PBS). On the last wash, emulsions were resuspended in PBS buffer (100 μL). Fluorous rhodamine **25** stock (10 μL) was then added to each emulsion solution. Solutions were then rocked and lightly vortexed for ~1 minute to encapsulate **25**.

RAW or A375 cells were placed in a 96-well plate (50,000 cells per 200 μL/well) and incubated in DMEM media (37 °C, 5% CO_2, overnight) (Note: incubation of cells and thiol-ene reaction were performed over the same night). The next day, cells were washed 3x in FACS buffer (PBS + 1% FBS) by continually adding and removing 125 μL FACS buffer to the adherent cells. On the last removal of FACS buffer, the cells were suspended in 75 μL FACS buffer and then treated with 25μL **25**-loaded emulsions (total volume = 100 μL per well). The cells were incubated in the presence of emulsions (37 °C, 5% CO_2,) for 3 h. Following incubation, the cells were washed three times by PBS to remove residual emulsions (add + remove 150 μL PBS 3x) followed by addition of trypsin digest solution (100 μL, total well volume = 200 μL). The cells were incubated for 5-10 minutes at 37 °C, pipetted vigorously until cells were detached (for RAW cells, process was more difficult). Wells were then quenched by addition of DMEM media (100 μL) and the lifted cells were transferred to a 96-well V-bottom plate. Cells were then pelleted down by centrifugation (526 x *g*, 3 min, 4 °C) and resuspended in FACS buffer (200 μL), and the process was repeated three times.

Flow cytometry

On the last resuspension, cells were transferred to 1.2mL microtiter tubes with a final volume of 400 μL FACS buffer. Flow cytometry was performed on a BDBiosciences FACSCalibur equipped with 488 nm and 635 nm lasers. Fluorous rhodamine **25** fluorescence was measured on FL2 channel to measure cellular uptake. Fluorescence across cell lines was normalized to background control cell FL-2 fluorescence. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.

Microscopy

The general cell labeling procedure was followed with the following modifications:
Cells were plated at 30,000 cells/200 μL well, a 1 hour incubation was performed instead of 3 hours. Following incubation in FACS buffer (100 μL), cells were washed (3x DMEM media, 2x PBS) before lifting with trypsin. Washes in the v-bottom 96-well plate were performed with DMEM media (3 x 200 μL).

On last resuspension, the two identical wells were combined, and cells were transferred to a single-well glass microscope slide (VWR 10118-600) that had been treated with FBS (~2 mL, 30 min) and allowed to dry at rt in a biosafety cabinet to maintain sterility. The cells were allowed to adhere to slide (37 °C, 5% CO_2, 1 hour). Cells were stained with Hoechst (1 drop/1mL media, 15 min) and LysoTracker Green (100μL stock, stock: 0.2 μL probe in 4 mL FACS) before confocal images were taken.

Confocal settings were as follows: Rhodamine (532 laser-55%, 1150 gain, offset -0.6, collection 540-700nm), Hoechst (405 laser-55%, 1150 gain, offset -0.6, collection 420-500nm), LysoTracker Green (488 laser-55%, 1150 gain, offset -0.6, collection 500-540 nm), DIC (scan-BF, 575 gain, offset -0.4). Scale bar represents 10 μm. Images were processed in ImageJ.

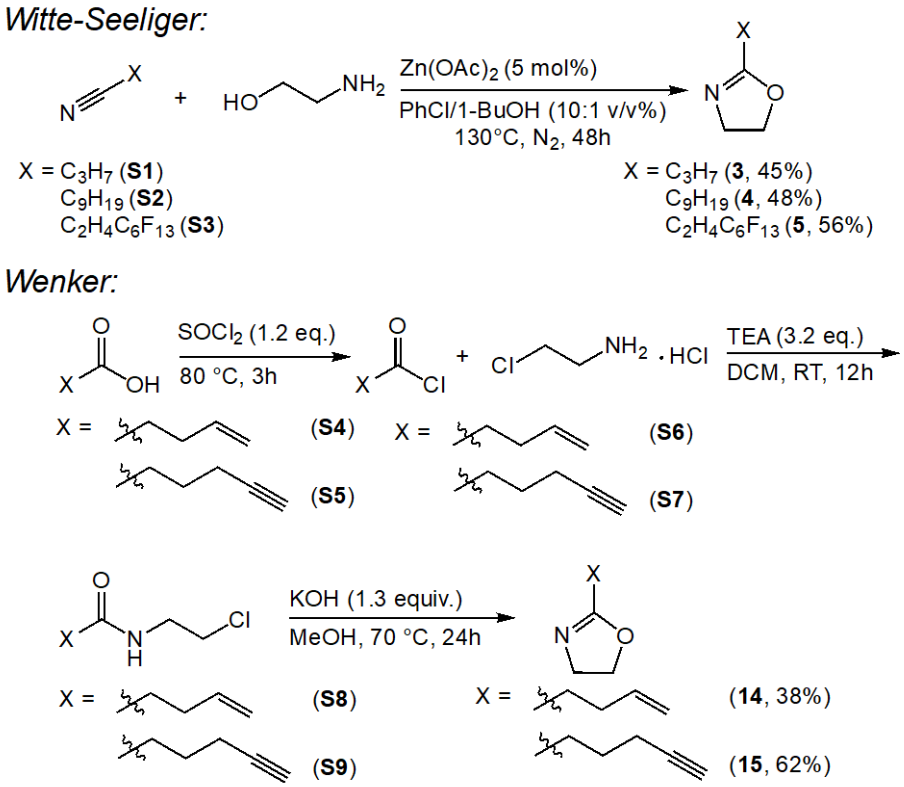
Cell viability

The general cell labeling procedure was followed with the following modifications:
The emulsions were not loaded with rhodamine **25** and the incubation time was 12 hours instead of 3 hours. On the last resuspension, cells were transferred to 1.2mL microtiter tubes with a final volume of 400 μL FACS buffer (PBS + 1% FBS). Propidium iodide solution (0.5 μL, 1 mg/mL in PBS) was added to each well. Cells were incubated on ice for 15 minutes prior to flow cytometry measurements.

Live and dead controls (heat killed at 70 °C for 1 min) were used to set the range of the FL2 channel. Data were analyzed by splitting the population at ~10^2 as a live/dead line. Flow cytometry was performed as described above.

Synthetic chemistry experimental procedures

Witte-Seeliger and Wenker routes to aliphatic, fluorous and functionalized 2-substituted-2-oxazolines:



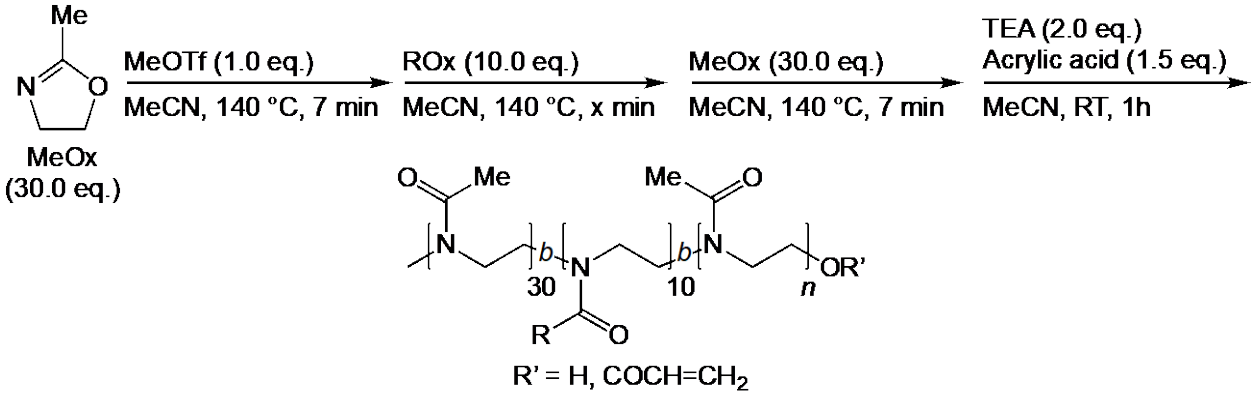
PrOx (**3**) and NonOx (**4**) were synthesized according to literature procedure.[2]

2 - (1H,1H′ ,2H,2H′ - perfluorohexyl) - 2 - oxazoline (FOx, **5**) was synthesized according to a modified literature procedure.[3] To a flame dried 2-neck round bottom flask fit with a reflux condenser, chlorobenzene (2.2 mL, anhydrous) and 1-butanol (0.2 mL, anhydrous) were added followed by zinc acetate (20 mg, 0.1 mol, 0.05 equiv.), and 1H,1H,2H,2H-perfluorohexylnitrile (826 mg, 2.21 mmol, 1.00 equiv.). The reaction mixture was heated to130 °C to dissolve zinc acetate, and then monoethanolamine (162 mg, 2.66 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 48 hours, at which point it was cooled to rt and purified by flash chromatography on silica gel, eluting with a 2:1 Hex:EtOAc solvent system + 8% triethylamine. This procedure resulted in pure FOx **5** (498 mg, 1.2 mmol, 54%). ^{1}H- and ^{19}F-NMR agreed with literature values[3–5]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28 (t, *J* = 9.5 Hz, 2H), 3.85 (t, *J* = 9.4 Hz, 2H), 2.66–2.41 (m, 4H). ^{19}F NMR ($CDCl_3$): δ -80.77 (s, 3F), -115.01 (s, 2F), -121.88 (s, 2F), -122.88 (s, 2F), -123.55 (s, 2F), -126.12 (2F).

2-(3-butenyl)-2-oxazoline (EneOx, **14**) was synthesized according to literature procedure.[6] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (m, 1H), 5.06 (m, 2H), 4.26 (t, *J* = 9.4 Hz, 2H), 3.86 (t, *J* = 9.4 Hz, 2H), 2.41 (m, 4H).

2-(4-pentynyl)-2-oxazoline (PyneOx, **15**) was synthesized according to literature procedure.[7] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (t, *J* = 9.3 Hz, 2H), 3.82 (t, *J* = 9.3 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.28 (td, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.87 (quin, *J* = 7.2 Hz, 2H).

Synthesis of poly(2-oxazoline) block copolymers **6**-**11**:



6, R = C_3H_7; n = 0 **9,** R = C_9H_{19}; n = 10
7, R = C_3H_7; n = 10 **10**, R = $C_2H_4C_6F_{13}$; n = 0
8, R = C_9H_{19}; n = 0 **11**, R = $C_2H_4C_6F_{13}$; n = 10

P(MeOx$_{30}$-*b*-PrOx$_7$) (6)

To a flame dried microwave vial, MeCN (1.2 mL, anhydrous) and MeOx (200 μL, 0.200 g, 2.35 mmol, 30.0 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.078 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, PrOx (90 μL, 89 mg, 0.78 mmol, 10 equiv.) was added under N_2 and heated to 140 °C for 15 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16 mg, 0.16 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**6**) as a white solid. Polymer **6** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (179 mg, 0.050 mmol, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.84 (dd, *J* = 8.7, 1.6 Hz, 1H), 3.45 (m, 148H), 3.04 (m, 3H), 2.34 (m, 14H), 2.14 (m, 91H), 1.64 (m, 13H), 0.94 (s, 20H). SEC: M_w = 5.4 kDa, M_n = 4.4 kDa, $Đ$ = 1.26. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

P(MeOx$_{30}$-*b*-PrOx$_7$-*b*-MeOx$_{30}$) (7)

To a flame dried microwave vial, MeCN (1.2 mL, anhydrous) and MeOx (200 μL, 0.200 g, 2.40 mmol, 30 equiv.) were added and deoxygenated via freeze-pump-thaw (x2).

Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.080 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, PrOx (90 μL, 89 mg, 0.78 mmol, 10 equiv.) was added under N_2 and heated to 140 °C. After 15 minutes, MeOx (200 μL, 0.200 g, 2.35 mmol, 30 equiv.) was added under N_2 and heated to 140 °C for 7 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16 mg, 0.16 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**7**) as a white solid. Polymer **7** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (420 mg, 0.060 mmol, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.84 (dd, *J* = 8.7, 1.6 Hz, 1H), 3.43 (m, 262H), 3.03 (m, 3H), 2.33 (m, 17H), 2.13 (m, 181H), 1.64 (m, 15H), 0.94 (s, 21H). SEC: M_w = 6.4 kDa, M_n = 4.9 kDa, $Đ$ = 1.29. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

P(MeOx$_{30}$-*b*-NonOx$_{12}$) (8**)**

To a flame dried microwave vial, MeCN (1.2 mL, anhydrous) and MeOx (200 μL, 0.200 g, 2.40 mmol, 30 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.078 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, NonOx (155 μL, 155 mg, 0.783 mmol, 10 equiv.) was added under N_2 and heated to 140 °C for 3 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16.0 mg, 0.157 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**8**) as a white solid. Polymer **8** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (102 mg, 0.020 mmol, 29% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.84 (dd, *J* = 8.7, 1.6 Hz, 1H), 3.44 (m, 162H), 3.03 (m, 3H), 2.32 (m, 23H), 2.13 (m, 91H), 1.58 (m, 24H), 1.24 (m, 133H) 0.86 (t, *J* = 6.6 Hz, 36H). SEC: M_w = 5.0 kDa, M_n = 4.1 kDa, $Đ$ = 1.24. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

P(MeOx$_{30}$-*b*-NonOx$_{10}$-*b*-MeOx$_{30}$) (9**)**

To a flame dried microwave vial, MeCN (1.2 mL, anhydrous) and MeOx (200 μL, 0.200 g, 2.4 mmol, 30 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.080 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, NonOx (155 μL, 155 mg, 0.783 mmol, 10 equiv.) was added under N_2 and heated to 140 °C. After 3 minutes, MeOx (200 μL, 0.20 g, 2.4 mmol, 30.0 equiv.) was added under N_2 and heated to 140 °C for 7 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16 mg, 0.16 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**9**) as a white solid. Polymer **9** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness

(363 mg, 0.050 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.84 (dd, *J* = 8.7, 1.6 Hz, 1H), 3.43 (m, 279H), 3.00 (m, 3H), 2.31 (m, 28H), 2.12 (m, 177H), 1.57 (m, 21H), 1.23 (m, 120H), 0.85 (t, *J* = 6.6 Hz, 31H). SEC: M_w = 9.2 kDa, M_n = 6.8 kDa, *Đ* = 1.29. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

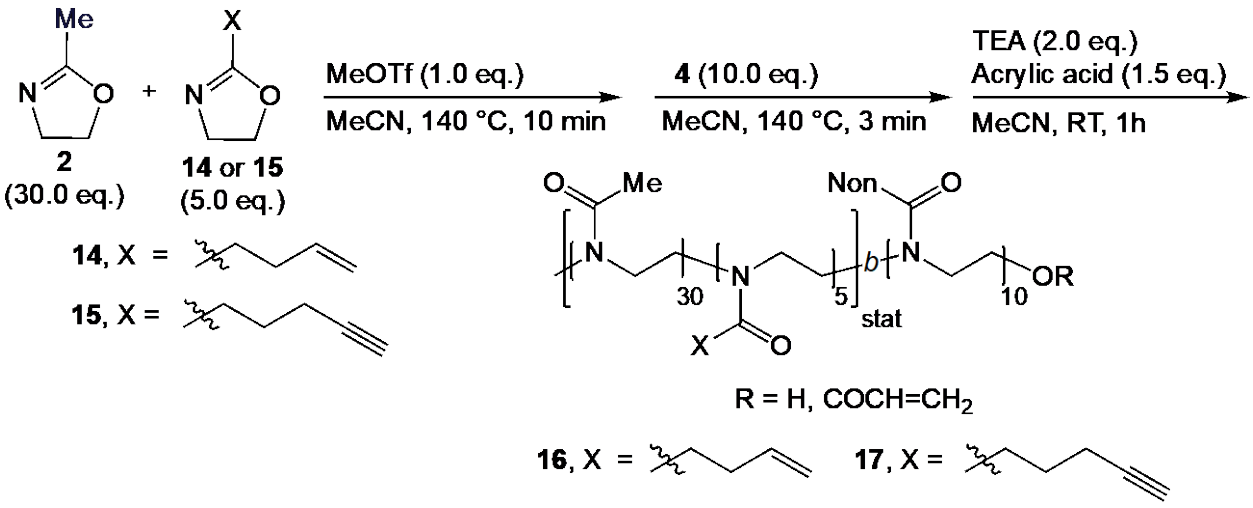
P(MeOx$_{29}$-*b*-FOx$_9$) (10**)**

To a flame dried microwave vial, MeCN (0.6 mL, anhydrous) and MeOx (100 μL, 0.10 g, 1.2 mmol, 30 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (4.4 μL, 6.0 mg, 0.039 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, FOx (98.0 μL, 163 mg, 0.392 mmol, 10 equiv.) was added under N_2 and heated to 140 °C for 25 minutes, at which point the polymerization was quenched with acrylic acid (4 mg, 0.06 mmol, 1.5 equiv.), followed by triethylamine (8 mg, 0.08 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**10**) as a white solid. Polymer **10** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (130 mg, 0.020 mmol, 49% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47 (m, 148H), 3.03 (m, 3H), 2.91-2.36 (m, 36H), 2.13 (m, 87H). ^{19}F NMR (300 MHz, $CDCl_3$): δ -81.97 (s, 3F), -115.65 (s, 2F), -123.02 (s, 2F), -124.01 (s, 2F), -124.67 (s, 2F), -127.30 (s, 2F). SEC: M_w = 14.0 kDa, M_n = 12.0 kDa, *Đ* = 1.16. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

P(MeOx$_{29}$-*b*-FOx$_9$-*b*-MeOx$_{29}$) (11**)**

To a flame dried microwave vial, MeCN (0.6 mL, anhydrous) and MeOx (100 μL, 0.10 g, 1.2 mmol, 30 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (4.4 μL, 6.0 mg, 0.040 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 7 minutes, FOx (98.0 μL, 163 mg, 0.392 mmol, 10 equiv.) was added under N_2 and heated to 140 °C. After 25 minutes, MeOx was added (100 μL, 0.10 g, 1.2 mmol, 30 equiv.) under N_2 and heated to 140 °C for 7 minutes, at which point the polymerization was quenched with acrylic acid (4 mg, 0.06 mmol, 1.5 equiv.), followed by triethylamine (8 mg, 0.08 mmol, 2 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**11**) as a white solid. Polymer **11** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (220 mg, 0.020 mmol, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 (m, 261H), 3.06 (m, 3H), 2.91-2.36 (m, 29H), 2.11 (m, 173H). ^{19}F NMR (300 MHz, $CDCl_3$): δ -82.03 (s, 3F), -115.69 (s, 2F), -123.07 (s, 2F), -124.04 (s, 2F), -124.73 (s, 2F), -127.36 (s, 2F). SEC: M_w = 5.6 kDa, M_n = 4.5 kDa, *Đ* = 1.09. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 cm^{-1} (CH_x-CO) (s).

Synthesis of functionalized poly(oxazoline) block copolymers **16** and **17**:



P(MeOx$_{30}$-*r*-EneOx$_5$-*b*-NonOx$_{11}$) (16)

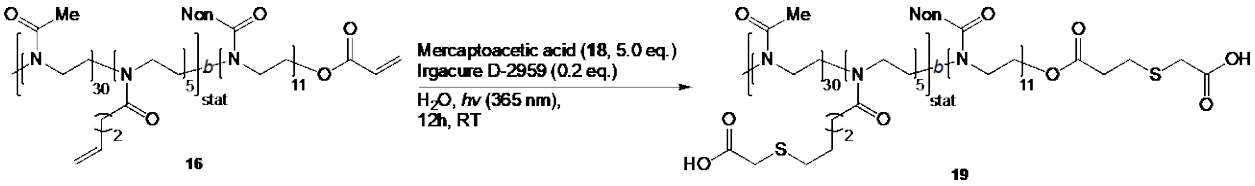
To a flame dried microwave vial, MeCN (1.2 mL, anhydrous), MeOx (200 μL, 0.20 g, 2.4 mmol, 30 equiv.), and EneOx (30 μL, 29 mg, 0.24 mmol, 3 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.080 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 10 minutes, NonOx (155 μL, 155 mg, 0.783 mmol, 10 equiv.) was added under N_2 and heated to 140 °C for 3 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16 mg, 0.16 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was evaporated to dryness to yield crude polymer (**16**) as a white solid. Polymer **16** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (204 mg, 0.040 mmol, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.84 (dd, *J* = 8.7, 1.6 Hz, 1H), 5.81 (m, 5H), 5.06 (m, 9H), 3.44 (m, 179H), 3.06 (m, 3H), 2.46 (m, 5H), 2.34 (m, 32H), 2.13 (m, 90H), 1.58 (m, 22H), 1.25 (m, 127H) 0.86 (t, *J* = 6.6 Hz, 33H). SEC: M_w = 5.2 kDa, M_n = 6.5 kDa, $Đ$ = 1.25. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 (CH_x-CO) (s), 917 cm^{-1} (=C-H bend).

P(MeOx$_{29}$-*r*-PyneOx$_5$-*b*-NonOx$_{11}$) (17)

To a flame dried microwave vial, MeCN (1.2 mL, anhydrous), MeOx (200 μL, 0.20 g, 2.4 mmol, 30 equiv.), and PyneOx (30 μL, 0.032 g, 0.235 mmol, 3 equiv.) were added and deoxygenated via freeze-pump-thaw (x2). Following deoxygenation, MeOTf (8.9 μL, 13 mg, 0.078 mmol, 1.0 equiv.) was added and the mixture was heated at 140 °C in the microwave. After 10 minutes, NonOx (155 μL, 155 mg, 0.783 mmol, 10 equiv.) was added under N_2 and heated to 140 °C for 3 minutes, at which point the polymerization was quenched with acrylic acid (8.0 mg, 0.12 mmol, 1.5 equiv.), followed by triethylamine (16 mg, 0.16 mmol, 2.0 equiv.) 30 minutes later. The reaction mixture was

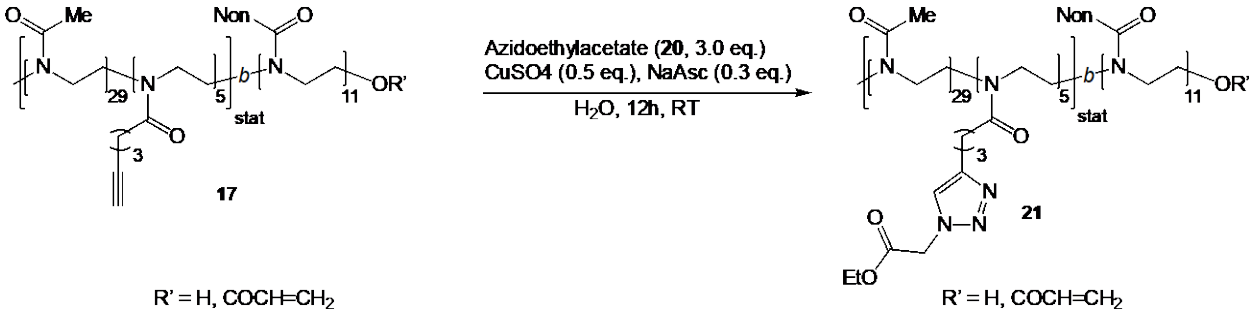
evaporated to dryness to yield crude polymer (**17**) as a white solid. Polymer **17** was purified by precipitation by dissolving in a minimal amount of DCM and dropwise addition to cold Et_2O (20:1 v/v%), collected and evaporated to dryness (380 mg, 0.070 mmol, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (dd, 0.5H), 6.04 (dd, 0.5H), 5.80 (dd, 0.5H), 3.44 (m, 180H), 2.97 (m, 3H), 2.63 (m, 10H), 2.43 (m, 26H), 2.20 (m, 92H), 1.77 (m, 6H), 1.58 (m, 22H), 1.18 (m, 129H) 0.80 (t, J = 6.6 Hz, 32H). SEC: M_w = 6.4 kDa, M_n = 5.1 kDa, $Đ$ = 1.25. FT-IR: 2930 (C-H str) (w), 1620 (C=O str, amide I) (vs), 1420 (CH_x-CO) (s), 639 cm^{-1} (≡C-H bend).

Functionalization of poly(2-oxazoline) block copolymer **16** with thiol **18**:



Surfactant **16** was modified based on thiol-ene conditions previously reported.[6,8] All reagent equivalents were calculated with respect to alkene. Briefly, functionalized surfactant **16** (10.6 mg ~8 wt% alkene, 1.0 equiv.) was dissolved in acetone + MeOH (1:1, 400 μL total). To this solution mercaptoacetic acid (**18**, 3.1 mg, 34 μmol, 5 equiv.) and Irgacure D-2959 (0.30 mg, 1.4 μmol, 0.20 equiv.) were added and briefly purged with nitrogen. The resulting mixture was irradiated with 365 nm light (power density: >5000μW/cm² at 15") at RT overnight. After the reaction had been run overnight, polymer was concentrated down, dissolved in DCM, and washed with water (x3). After drying on high vacuum, polymer **19** was analyzed by ^{1}H NMR and compared to polymer **16** (Figure 3D).

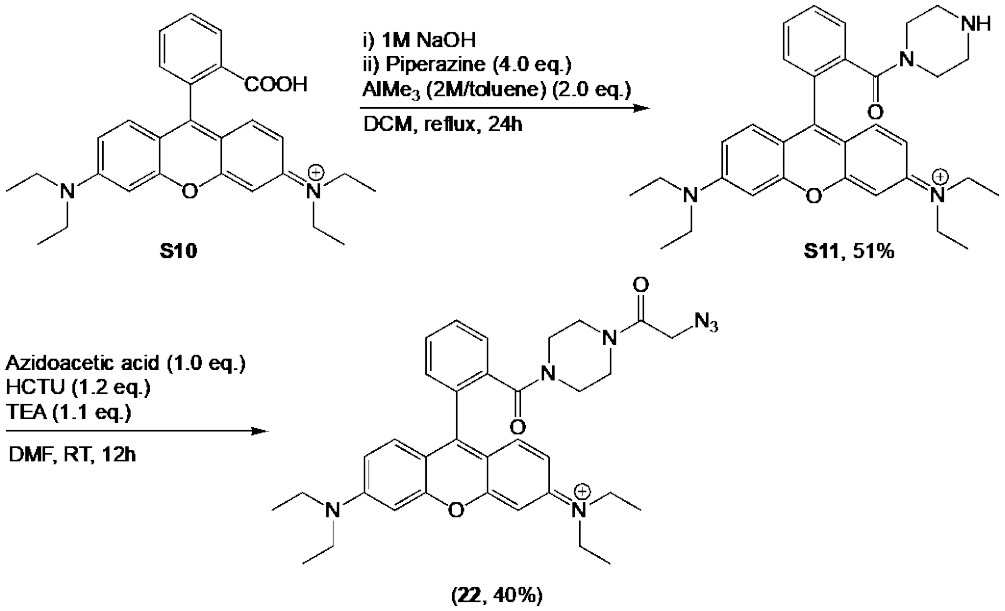
Functionalization of poly(2-oxazoline) block copolymer **17** with azide **20**:



Surfactant **17** was modified based on CuAAC conditions previously reported.[7] All reagent equivalents were calculated with respect to alkyne. Briefly, functionalized surfactant **17** (10.6 mg, ~8 wt% alkyne, 1.0 equiv.) was dissolved in tBuOH + H_2O (1:1, 400 μL total). To this solution sodium ascorbate (0.6 mg, 3 μmol, 0.5 equiv.), copper sulfate (0.3 mg, 2 μmol, 0.3 equiv.) and azidoethylacetate (**20**, 4.0 mg, 31 μmol, 5.0 equiv.) were added and stirred at RT overnight. After the reaction had been run overnight, polymer was

concentrated down, dissolved in DCM, and washed with water (x3). After drying on high vacuum, polymer **21** was analyzed by ^{1}H NMR and compared to polymer **17** (Figure 3E).

Synthesis of Azidorhodamine **22** (*N*-(9-(2-(4-(2-azidoacetyl)piperazine-1-carbonyl)phenyl)-6-(diethylamino)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium):



Azidorhodamine **22** was synthesized according to a modified literature procedure from rhodamine B piperazine amide (**S11**)[9], and ^{1}H-NMR was compared to literature[10].

To flame-dried dram vial, azidoacetic acid (9.0 mg, 97 µmol, 1.0 equiv.), *N*-hydroxysuccinimide (11.3 mg, 98.2 µmol, 1.10 equiv.) and *N*-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (20.4 mg, 106 µmol, 1.10 equiv.) were added followed by DMF (1.5 mL, anhydrous). The reaction was stirred at rt under N_2 for 2 hours. After 1 hour, to a separate flame-dried dram vial, rhodamine B piperazine amide **S11** (49.5 mg, 90.7 µmol, 1.00 equiv.) dissolved in DMF (0.5 mL, anhydrous) was added, followed by addition of triethylamine (14 µL, 100 µmol, 1.1 equiv.). The reaction was stirred at rt for 1 hour. The **S11**/triethylamine reaction mixture was then transferred to the azidoacetic acid vial, and rinsed with the remaining 0.5 mL DMF. The reaction was stirred under N_2 at rt overnight and purified by flash chromatography on silica gel, eluting with 40:1 DCM:MeOH. ^{1}H NMR agreed with literature values.[10] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62-7.78 (m, 3H), 7.53-7.60 (m, 1H), 7.30-7.41 (m, 4H), 6.67 (s, 2H), 4.17 (m, 2H), 3.40 – 3.70 (m, 12H), 2.60 (br m, 4H), 1.22-1.29 (s, 12H).

Figure experimental procedures

Figure 2A.
Poly(2-oxazoline)s were synthesized via microwave protocol using kinetics previously reported in the literature.[11–13] See supporting synthetic chemistry experimental procedures for synthetic details.

Figure 2B/C. Perfluorocarbon nanoemulsion formation and stability
Emulsions were prepared as described by the general nanoemulsion formation procedure, using surfactants **6**-**11**. Three independent solutions of each emulsion were made (400 μL scale). At each time point, solutions were vortexed (~45 seconds) to resuspend the emulsions. Size was analyzed per the general nanoemulsion analysis procedure. Note: Data are representative of five replicate measurements.

Figure 3A. Synthesis and reactivity of functionalized POx surfactants 16 **and** 17
Functionalized polymers were synthesized via microwave protocol using kinetics previously reported in the literature [6,7,11,12]. See supporting experimental procedures for synthetic details.

Figure 3B-E. Modification of surfactant 16 **through thiol-ene coupling**
See supporting synthetic chemistry experimental procedures for synthetic details.

Figure 4B. PFC nanoemulsion with surfactants 8**,** 16**, and** 17
Emulsions stabilized by surfactants **8**, **16**, and **17** were formed as described by the general nanoemulsion formation procedure. Size was analyzed per the general nanoemulsion analysis procedure to confirm similar emulsion size distributions.

Figure 4C. Emulsion surface modification: CuAAC of 22 **with surfactant** 17
Emulsions stabilized by surfactants **8**, and **17** were formed as described by the general nanoemulsion formation procedure. Size was analyzed per the general nanoemulsion analysis procedure to confirm similar emulsion size distributions. Both **8** and **17** were subjected to the general CuAAC modification procedures.

Figure 4D. Analysis of absorbance of emulsions following CuAAC with 22
Pre-dialysis (solids lines): After reaction with **22**, the emulsion solutions were diluted 1:100 and transferred to a quartz cuvette for fluorimeter measurements. Emission settings: Ex: 560 nm; Em. range: 565-700 nm; Ex. slit: 3 nm; Em. slit: 3 nm; Step size: 1; Integration: 0.01. Absorbance measurements were then taken after transferring solution to plastic cuvette.

Post dialysis (dotted lines): Emulsion solutions were then subjected to 24-hour dialysis against DI H_2O using a 3 kDa membrane cutoff dialysis tubing. Sample volumes were recorded before and after dialysis to account for possible dilution. The DI H_2O was exchanged three times. After accounting for diluting, appropriate amount of emulsion solution was transferred to a quartz cuvette and diluted to 2 mL MilliQ H_2O. For instance, prior to dialysis, solution of emulsions stabilized by surfactant **8** was 478 μL—after dialysis,

the total volume was 550 µL (15% dilution); to account for this, 23 µL of solution (rather than 20 µL) was diluted to 2 mL.

Fluorescence and absorbance measurements were taken as previously described. Absorbance measurements were then taken after transferring solution to plastic cuvette.

Figure 4E/F. Emulsion surface modification: Thiols with surfactant 16
Emulsions stabilized by surfactant **16** were formed, functionalized, and analyzed as described by the general nanoemulsion formation, modification and analysis procedures.

Figure 5B. Size distribution of emulsions functionalized through pre- and post-emulsion modification
Emulsions were functionalized through either pre- or post-emulsion modification routes using the following procedures:

In the pre-emulsion route, surfactants were modified through thiol-ene couplings as described in the synthetic chemistry experimental procedures (Figure 3B,D). After isolating modified surfactant, surfactant was employed for nanoemulsion formation as described by the general nanoemulsion formation procedure. The resulting emulsions were analyzed as described by the general nanoemulsion analysis procedure.

In the post-emulsion modification route, emulsions were formed, functionalized and analyzed as described by the general nanoemulsion formation, modification and analysis procedures.

Plotted are the size changes as determined by the absolute difference between size distributions of the resulting emulsions and control emulsions formulated with unmodified **16**. Size data are representative of the average of three independent samples, with three replicate measurements; error bars represent the standard deviation of the three independent samples. Statistical significance was done with regards to control emulsions. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$.

Figure 6C/D. Emulsion surface modification and cellular uptake studies:
Emulsions were prepared, functionalized and analyzed as described by the general nanoemulsion formation, modification with thiol-ene and analysis procedures. Emulsions were then incubated with RAW and A375 cells and analyzed by flow cytometry according to the procedures found in general cell culture experimental procedure section.

Figure 6E/F. Confocal microscopy of A375 or RAW cells stained and incubated with emulsions for 1 h, washed, and stained with Hoescht dye and LysoTracker Green.
Emulsions were prepared, functionalized and analyzed as described by the general nanoemulsion formation, modification with thiol-ene and analysis procedures. Emulsions were then incubated with RAW and A375 cells and analyzed by microscopy according to the procedures found in general cell culture experimental procedure section.

Figure S1-6. Size of PFC nanoemulsions stabilized by POx surfactants.
Emulsions were prepared as described by the general nanoemulsion formation procedures and analyzed as described by the general nanoemulsion analysis procedure. Data are an average of five replicate measurements.

Figure S7-S9. Size of PFC nanoemulsions over time.
See Figure 2C.

Figure S10-14. Initial size distributions of POx-stabilized olive oil-in-water nanoemulsions.
Olive oil emulsions were prepared according to the general nanoemulsions formation procedure and analyzed as described by the general nanoemulsion analysis procedure.

Figure S15. Size of olive oil-in-water nanoemulsions over time.
Emulsions prepared in Figures S10-S14 were analyzed over time as described in Figure 2C. After ~21 days, propyl-containing surfactants (**6**, **7**) visually phase separated, and were no longer tracked.

Figure S16. Size of PFC nanoemulsions over time stabilized by functionalized surfactants 16 **and** 17
Emulsions prepared in Figure 4B were analyzed over time as described in Figure 2C.

Figure S17A/B. Size data for emulsions before and after modification by CuAAC
"No Additive" (solid): Emulsions composed of **8** and **17** were prepared according to the general nanoemulsion procedure and their size was analyzed according to the general analysis procedure (raw data, Fig. S18).
"Reaction Overnight" (diagonal stripes): Emulsions from above were subjected to conditions according to the general modification procedure with CuAAC, as described in Figure 4C. Following this procedure, their size was analyzed according to the general analysis procedure (raw data, Fig. S18).
"24 Hour Dialysis" (vertical stripes): Emulsions from above underwent 24 hours of dialysis as described in Figure 4D. After dialysis, the size of the emulsions was analyzed according to the general analysis procedure.

Figure S19-S20. NMR analysis of isolated surfactant from emulsions that underwent post-emulsion modification with CuAAC
Following the procedure described for Figure 4C, emulsions were destabilized by vortexing a biphasic mixture of aqueous emulsions and DCM (1:10 vol%). The aqueous

layer was removed and the remaining mixture evaporated to dryness. The resulting product was then dissolved in DCM (~6 mL) and washed water (3 x ~2 mL). After drying on high vacuum, polymer was analyzed by ^{1}H NMR to determine modification **17** + **22** (bottom spectra) which was compared to isolated spectra for **22** (top) and **17** (middle). Broadening of aromatic peaks and disappearance of alkyne are indicative of conjugation.

Figure S21. Zeta potential data for emulsions modified with different thiols.
Emulsions were prepared according to the general emulsion formation, modified according to the general thiol-ene modification procedure, and analyzed according to the general nanoemulsion analysis procedure.

Figure S22. Controls for thiol-ene modification of nanoemulsions.
Emulsions were prepared with surfactant **16** according to the general nanoemulsion formation procedure. Emulsions were modified according to general nanoemulsion modification by thiol-ene chemistry procedure using thiols **18** and **24**, with noted exceptions for lack of reagent. Emulsions were analyzed as described by the general nanoemulsion analysis procedure.

Figure S23-S26. NMR analysis of isolated surfactant from emulsions that underwent post-emulsion modification with thiol-ene.
Following the procedure described for Figure 4F, emulsions were destabilized by vortexing the biphasic mixture of aqueous emulsions and (1:10 vol%). The aqueous layer was removed and the remaining mixture evaporated to dryness. The resulting product was then dissolved DCM (~6 mL) and washed water (3 x ~2 mL). After drying on high vacuum, polymer was analyzed by ^{1}H NMR to determine modification of **16** with thiols **18**, **23**, and **24**. The quantitative disappearance of alkene peaks is indicative of conjugation.

Figure S27. Size analysis of emulsions modified through pre- or post-emulsion modification.
Same experiment as 5B except full emulsion size plotted instead of size change. 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 per the following definitions: ns = $p > 0.05$, significant = $p < 0.05$, * = $p \leqslant 0.05$, ** = $p \leqslant 0.01$, *** = $p \leqslant 0.001$. Statistical significance was done for each emulsion with reference to control emulsion stabilized by unmodified **16**.

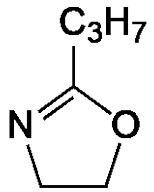
Figures S30,S31. Histograms for flow cytometry cell uptake experiments.
See Figure 6C and 6D.

Figures S32,S33. Single channel images for Figure 6E, 6F.
Confocal microscopy experiments were performed as described in the cell culture procedures.

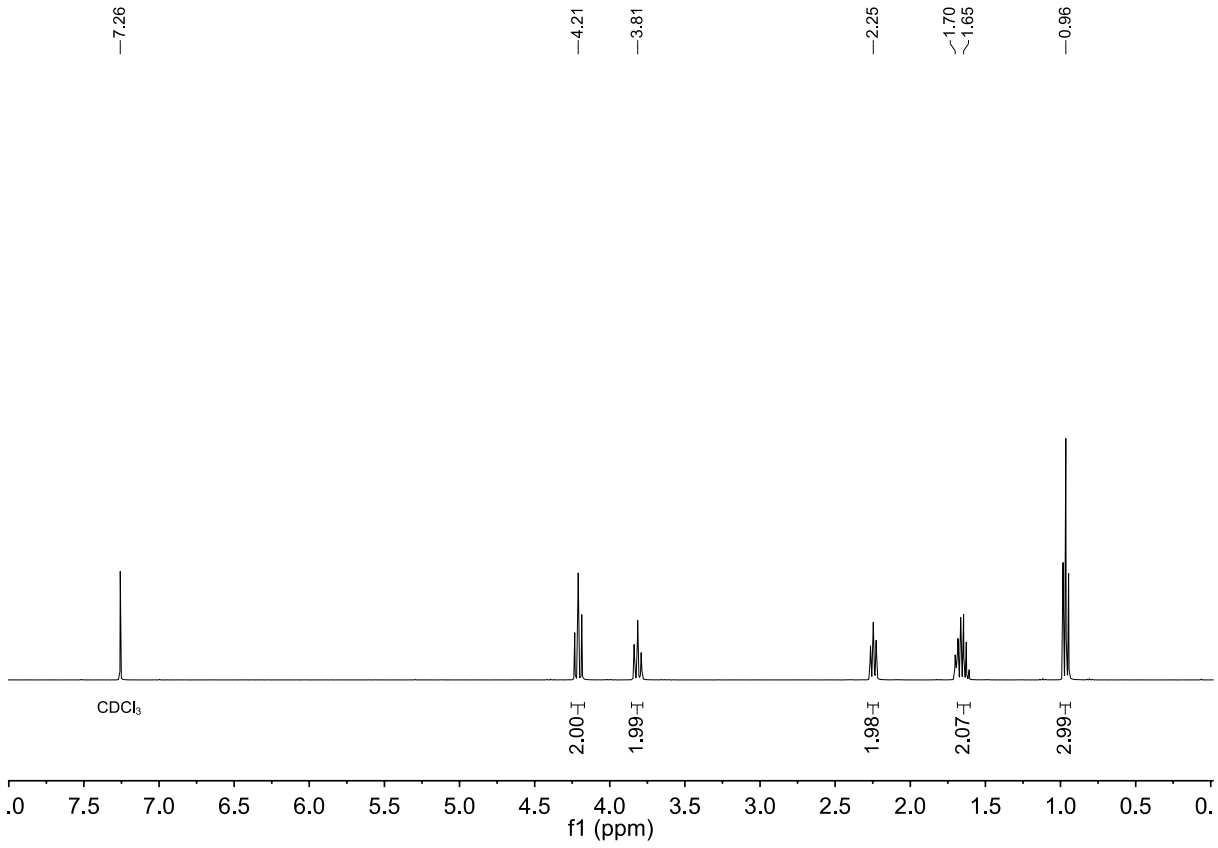
Figures S34-S36. Cellular viability studies for RAW and A375 cells incubated with PFC nanoemulsions with modified surface charges.
Cell viability experiments were performed as described in the cell culture procedures.

Figure S37. Inhibition of cellular (A375) uptake at 4 °C versus 37 °C.
Emulsions were prepared, functionalized and analyzed as described by the general nanoemulsion formation, modification with thiol-ene and analysis procedures. Emulsions were then incubated with A375 cells and analyzed by flow cytometry according to the procedures found in the general cell culture experimental procedure section. Followed general cell labeling procedure for measurements at 4 °C with the following alterations: A375 cells were pre-incubated in cold (4 °C) media for 30 minutes prior to treatment with emulsions. Emulsion incubation was carried out for one hour in a refrigerator set at 4 °C. Emulsions were then washed according to protocol, with media and FACS buffer pre-chilled at 4 °C.

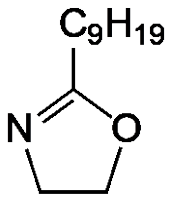
^{1}H-NMR spectra



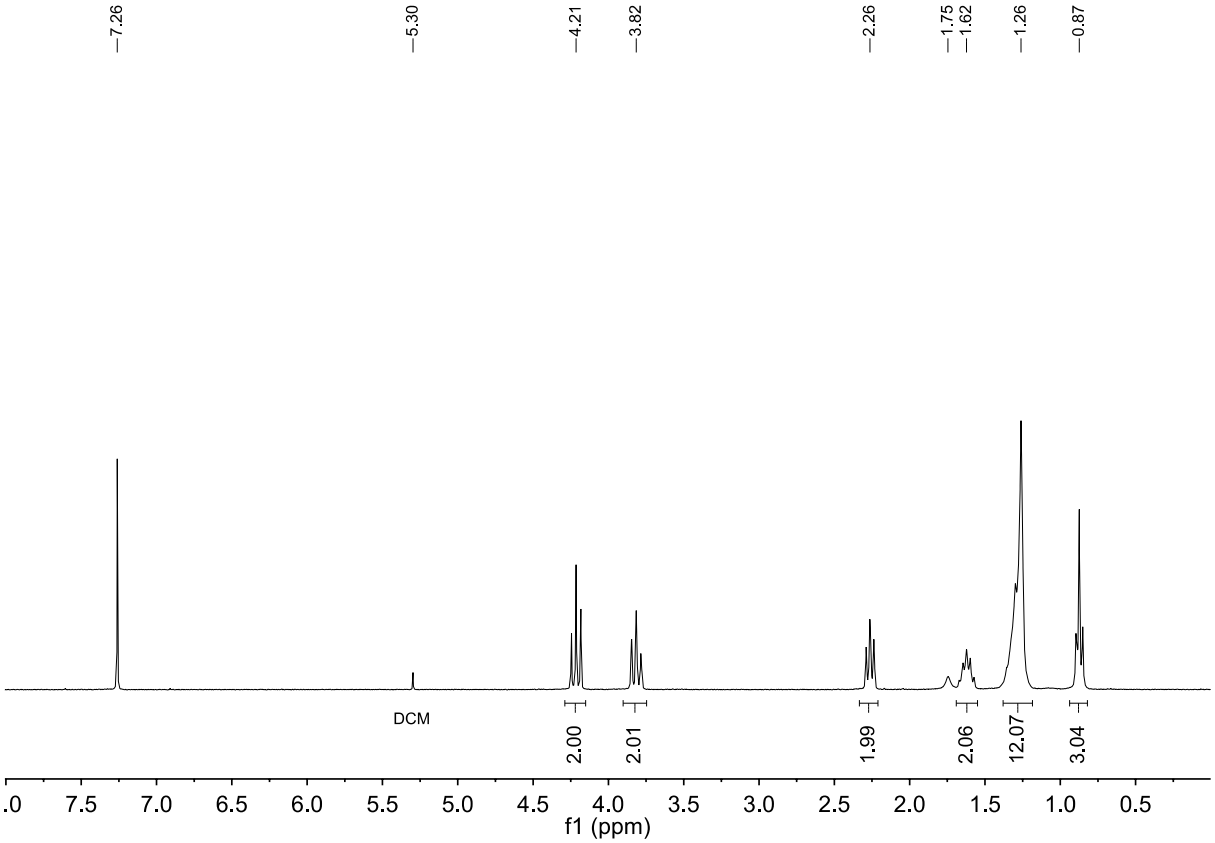
2-propyl-2-oxazoline (**3**)



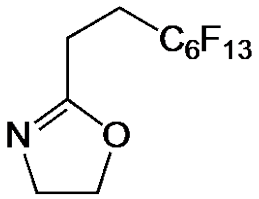
^{1}H NMR (300 MHz, $CDCl_3$) of monomer **3** 2-propyl-2-oxazoline.



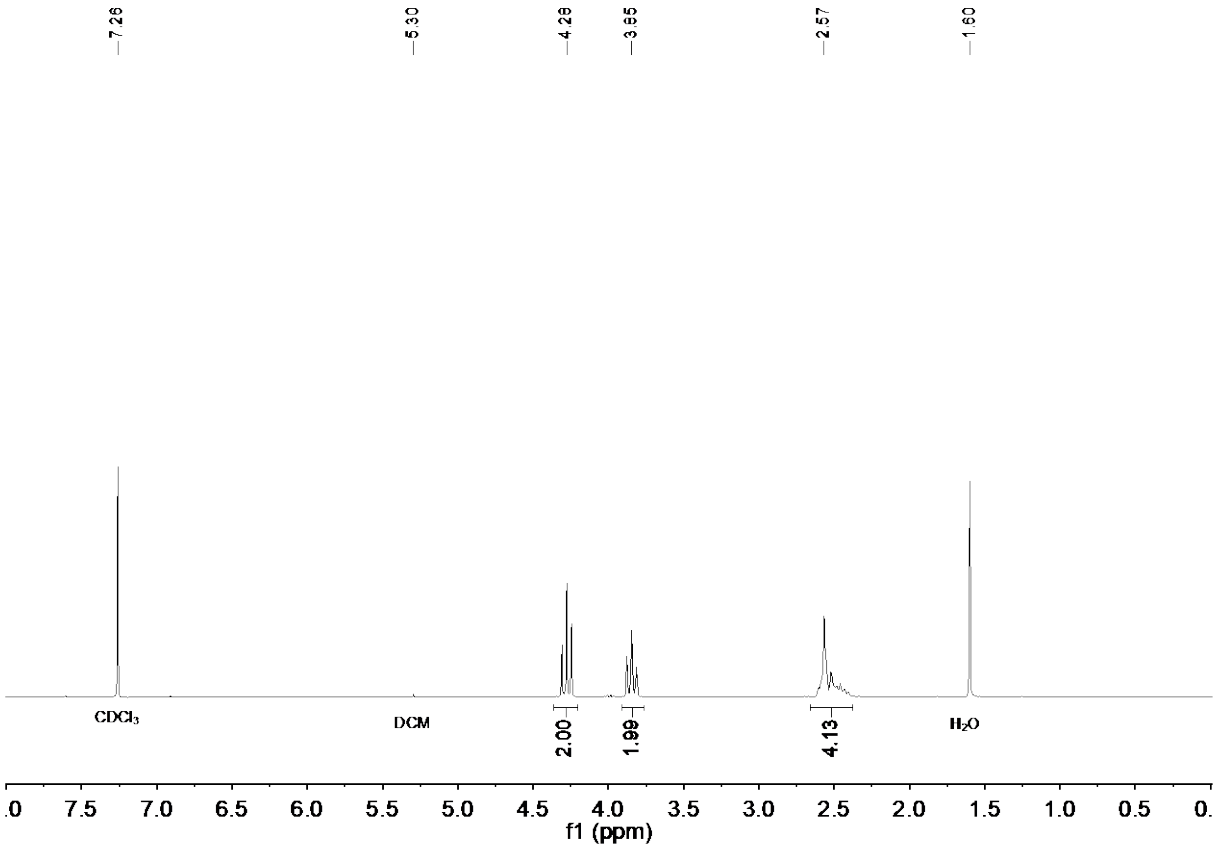
2-nonyl-2-oxazoline (**4**)



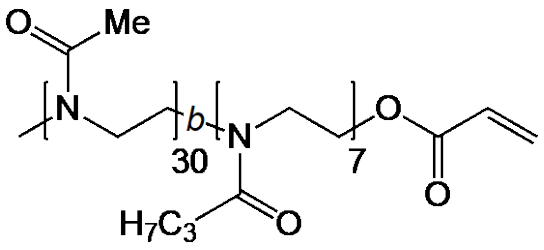
^{1}H NMR (300 MHz, $CDCl_3$) of monomer **4** 2-nonyl-2-oxazoline.



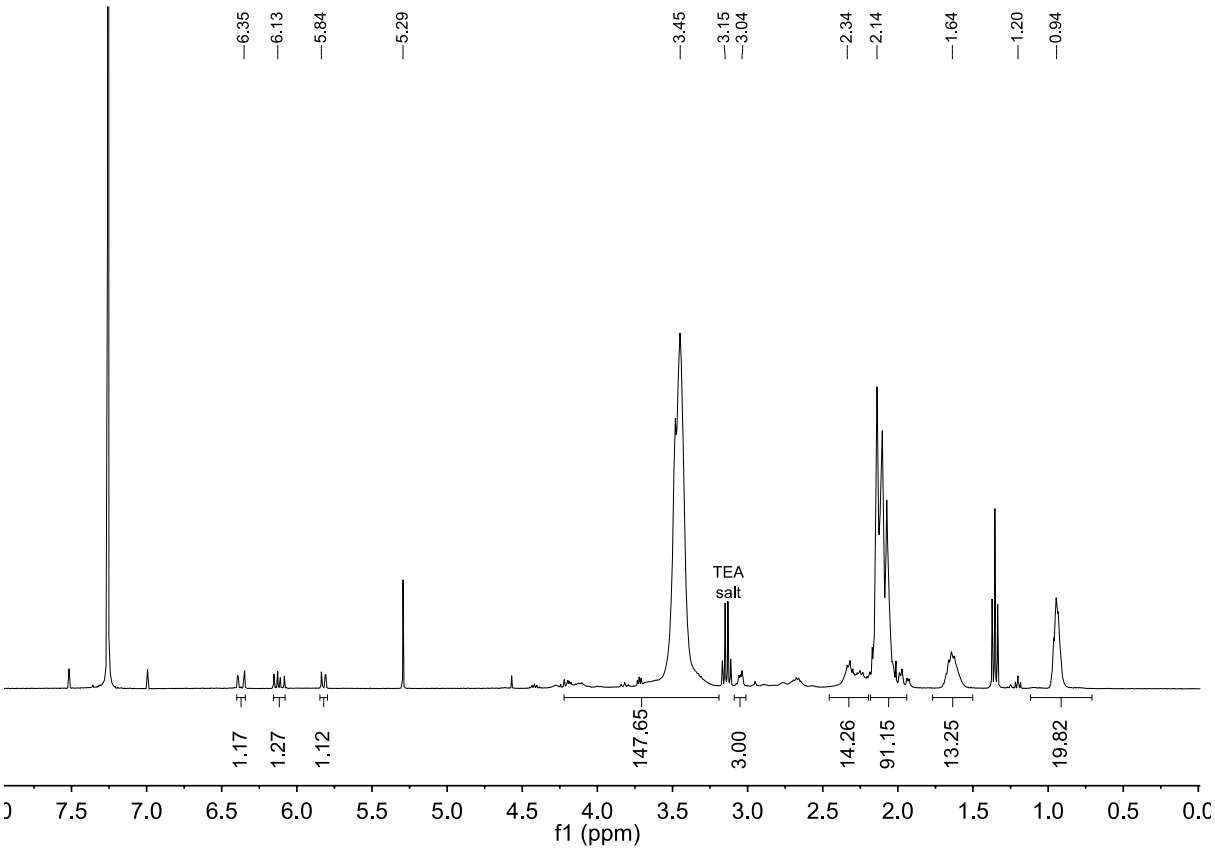
2-(perfluorohexyl)ethyl-2-oxazoline (**5**)



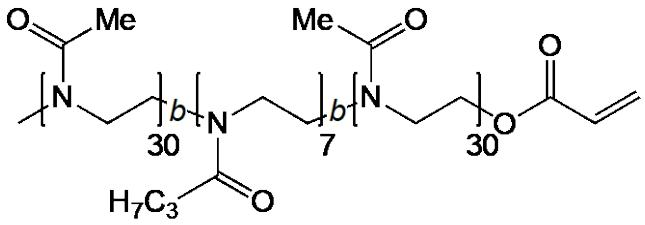
^{1}H NMR (300 MHz, $CDCl_3$) of monomer **5** 2-(perfluorohexyl)ethyl-2-oxazoline.



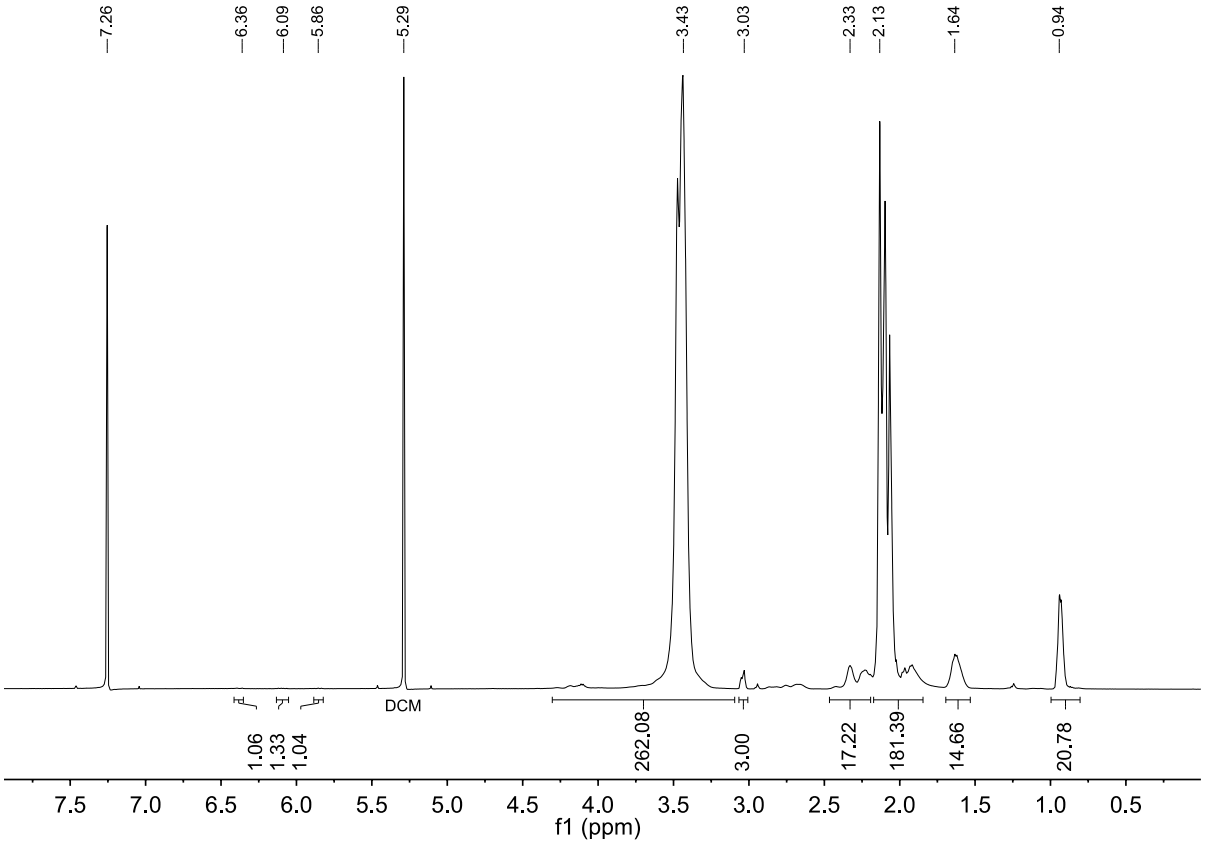
P(MeOx)$_{30}$-*b*-P(PrOx)$_7$ (6)



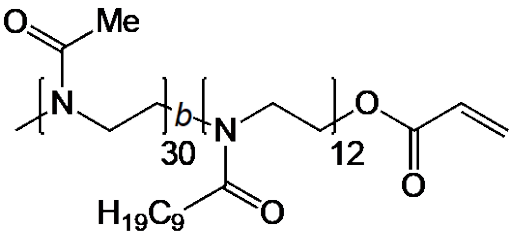
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **6** P(MeOx$_{30}$-*b*-PrOx$_7$).



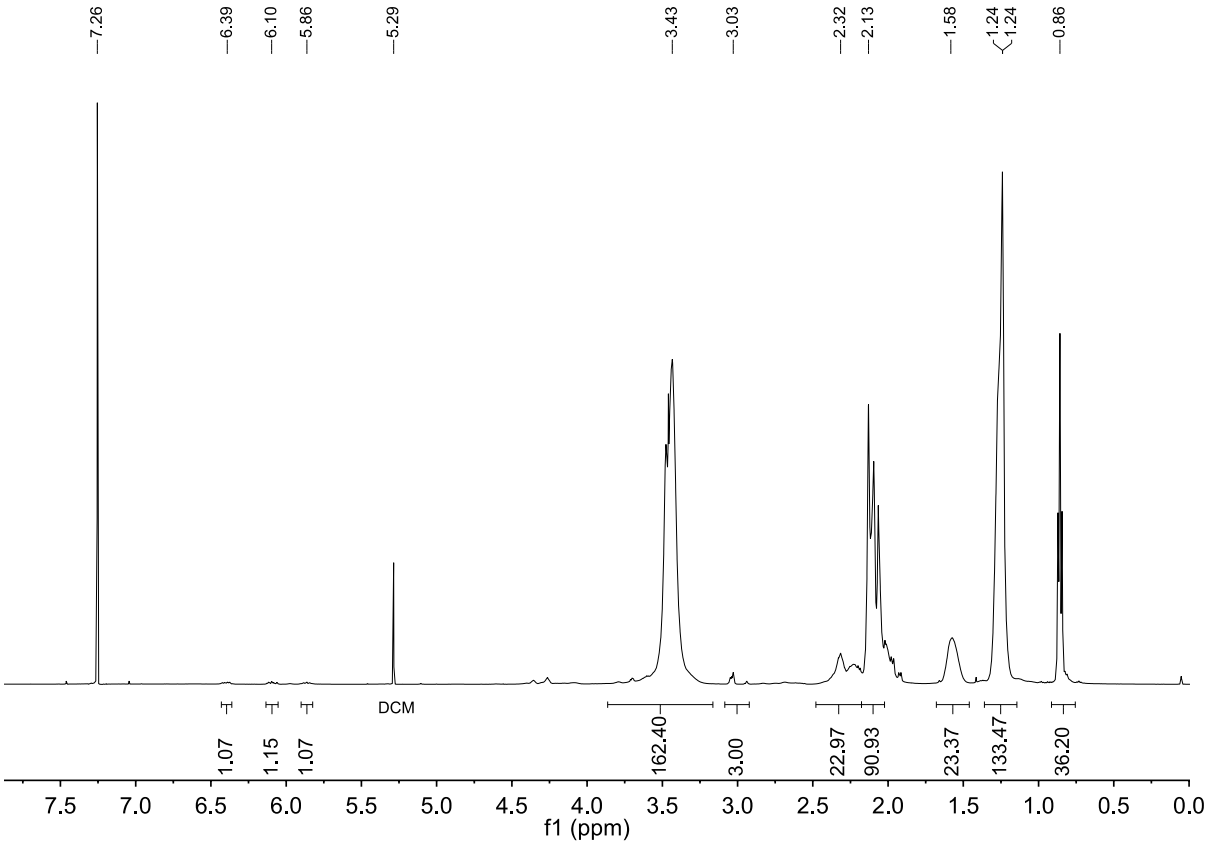
P(MeOx)$_{30}$-*b*-P(PrOx)$_7$-*b*-P(MeOx)$_{30}$ (**7**)



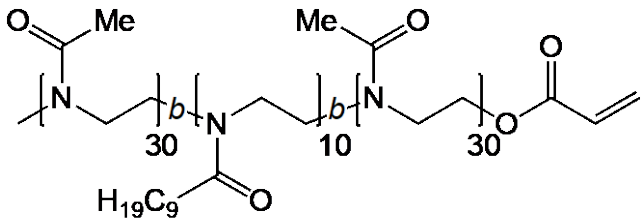
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **7** P(MeOx$_{30}$-*b*-PrOx$_7$-*b*-MeOx$_{30}$).



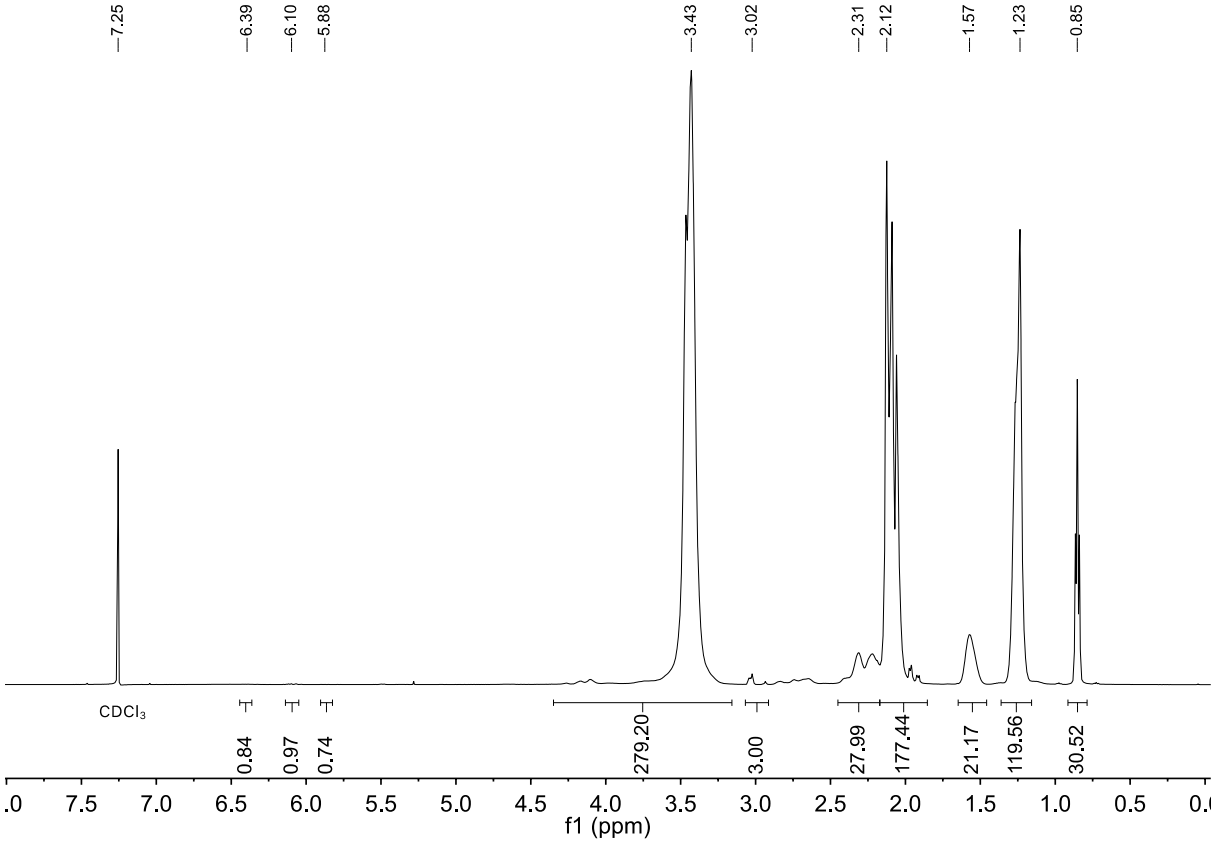
P(MeOx)$_{30}$-*b*-P(NonOx)$_{12}$ (8)



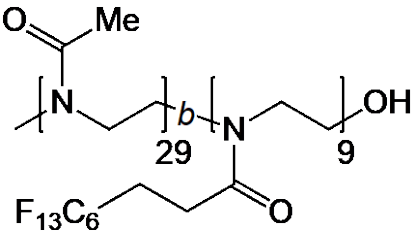
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **8** P(MeOx$_{30}$-*b*-NonOx$_{12}$).



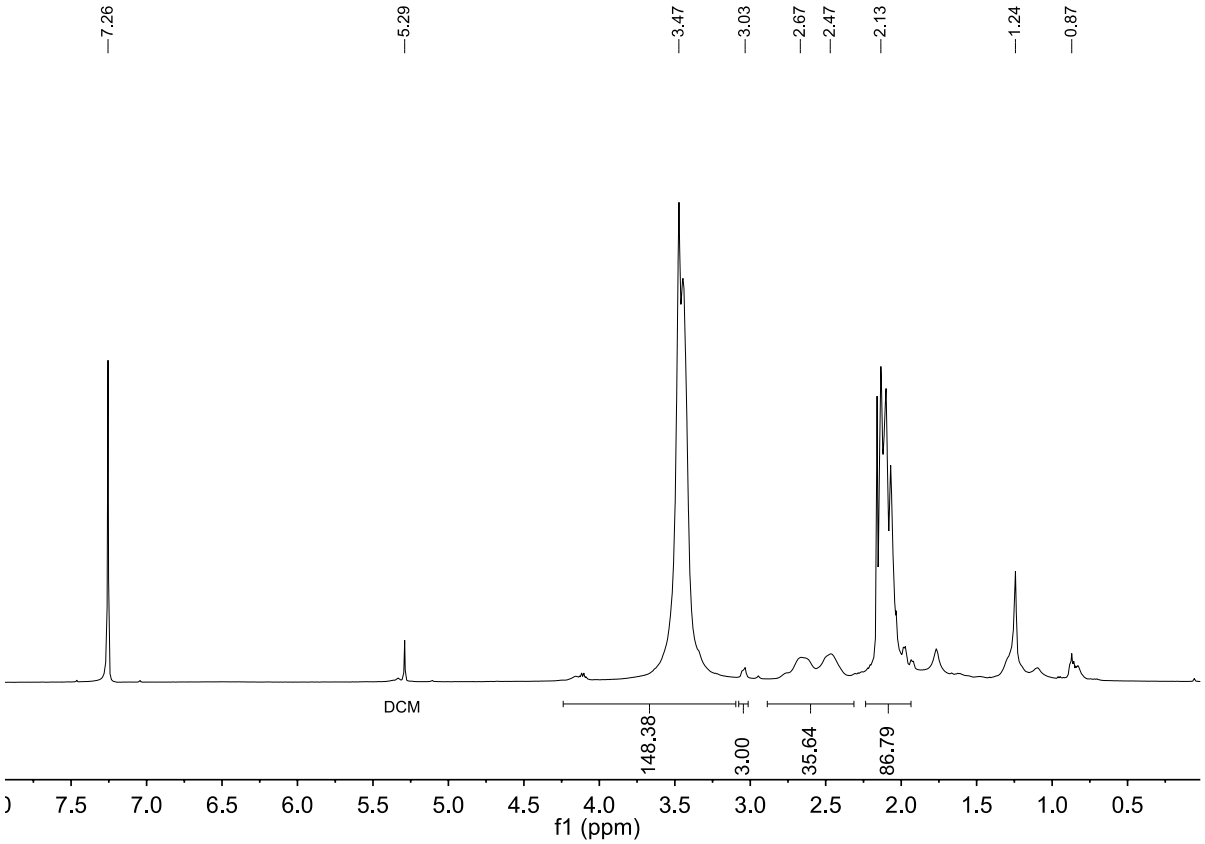
P(MeOx)$_{30}$-*b*-P(NonOx)$_{10}$-*b*-P(MeOx)$_{30}$ (**9**)



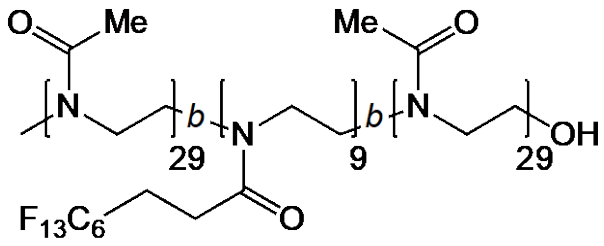
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **9** P(MeOx$_{30}$-*b*-NonOx$_{10}$-*b*-MeOx$_{30}$).



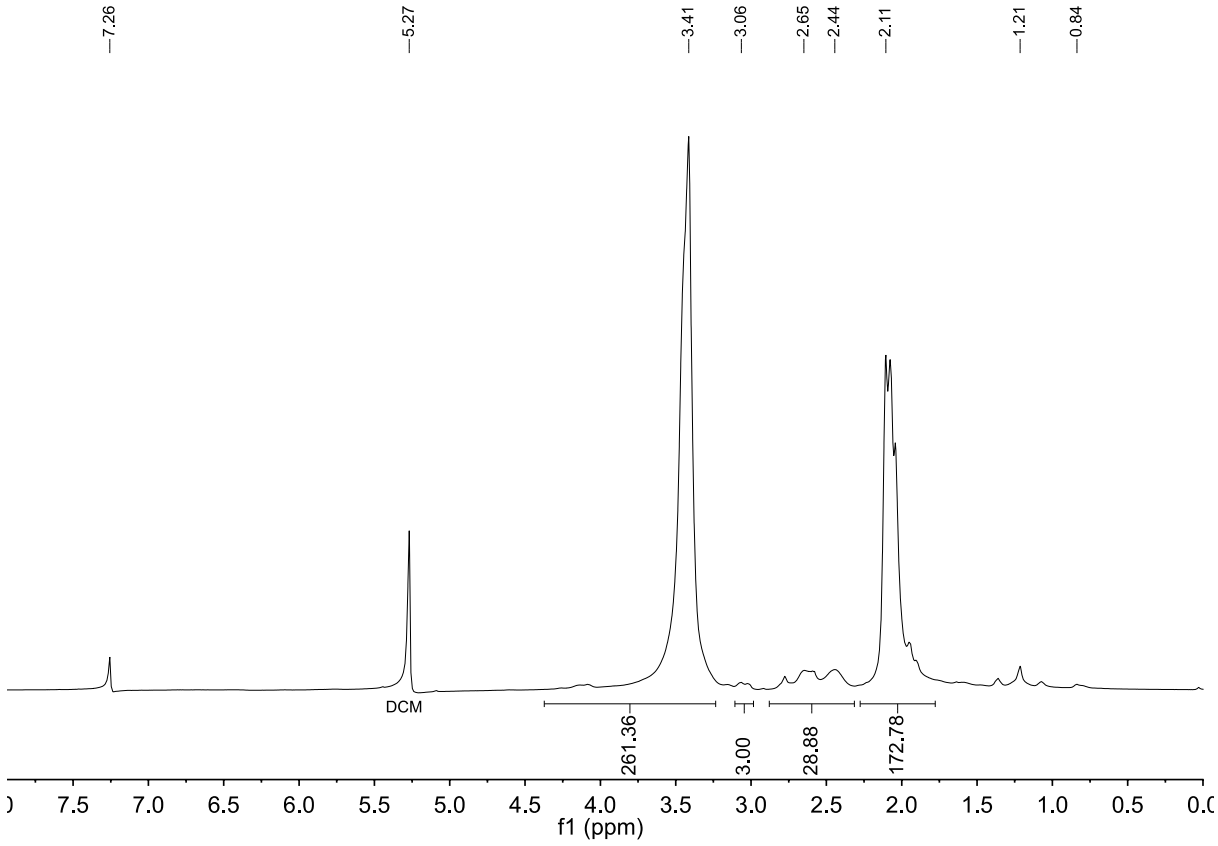
P(MeOx)$_{29}$-*b*-P(FOx)$_9$ (10)



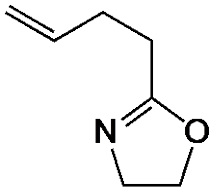
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **10** P(MeOx$_{29}$-*b*-FOx$_9$).



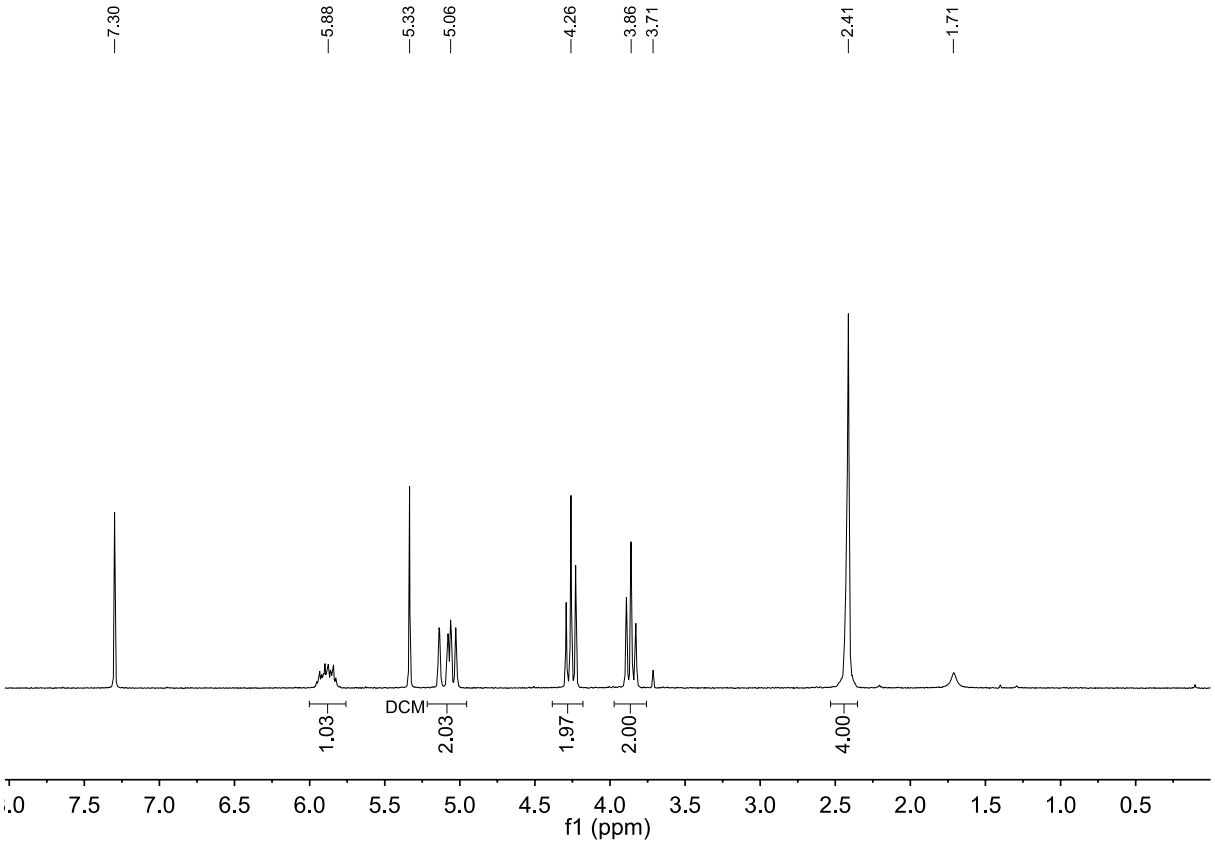
P(MeOx)$_{29}$-*b*-P(FOx)$_9$-*b*-P(MeOx)$_{29}$ (11)



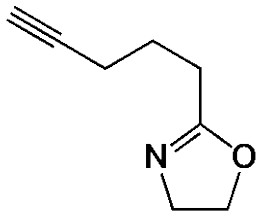
^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **11** P(MeOx$_{29}$-*b*-FOx$_9$-*b*-MeOx$_{29}$)



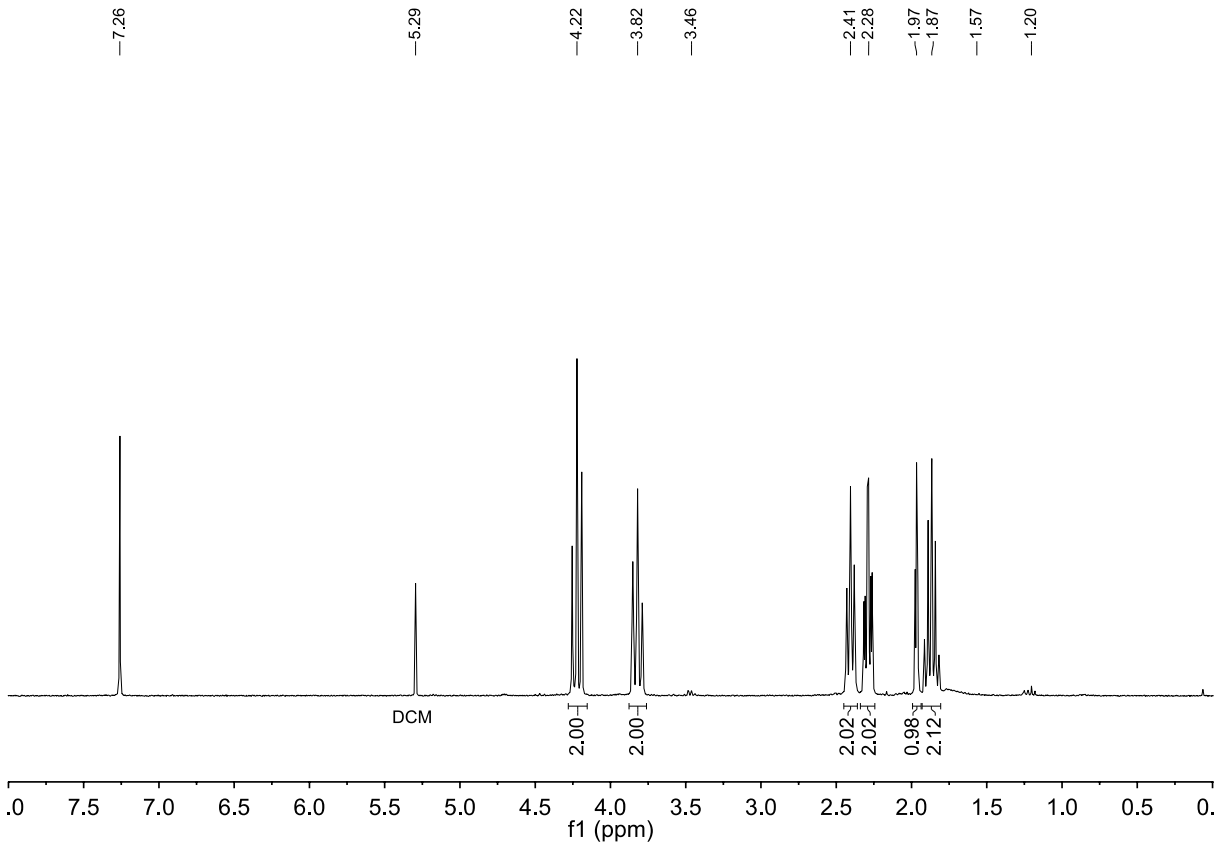
2-(3-butenyl)-2-oxazoline (**14**)



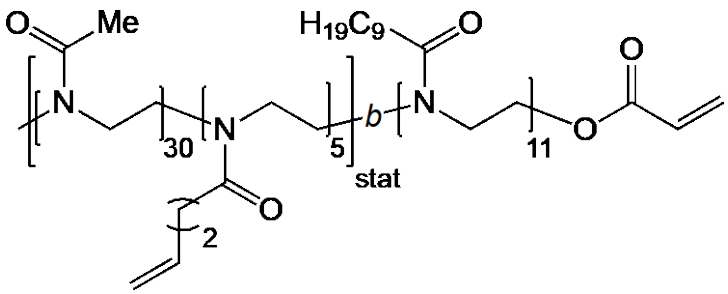
^{1}H NMR (300 MHz, $CDCl_3$) of functional comonomer **14** (2-(3-butenyl)-2-oxazoline (EneOx)).



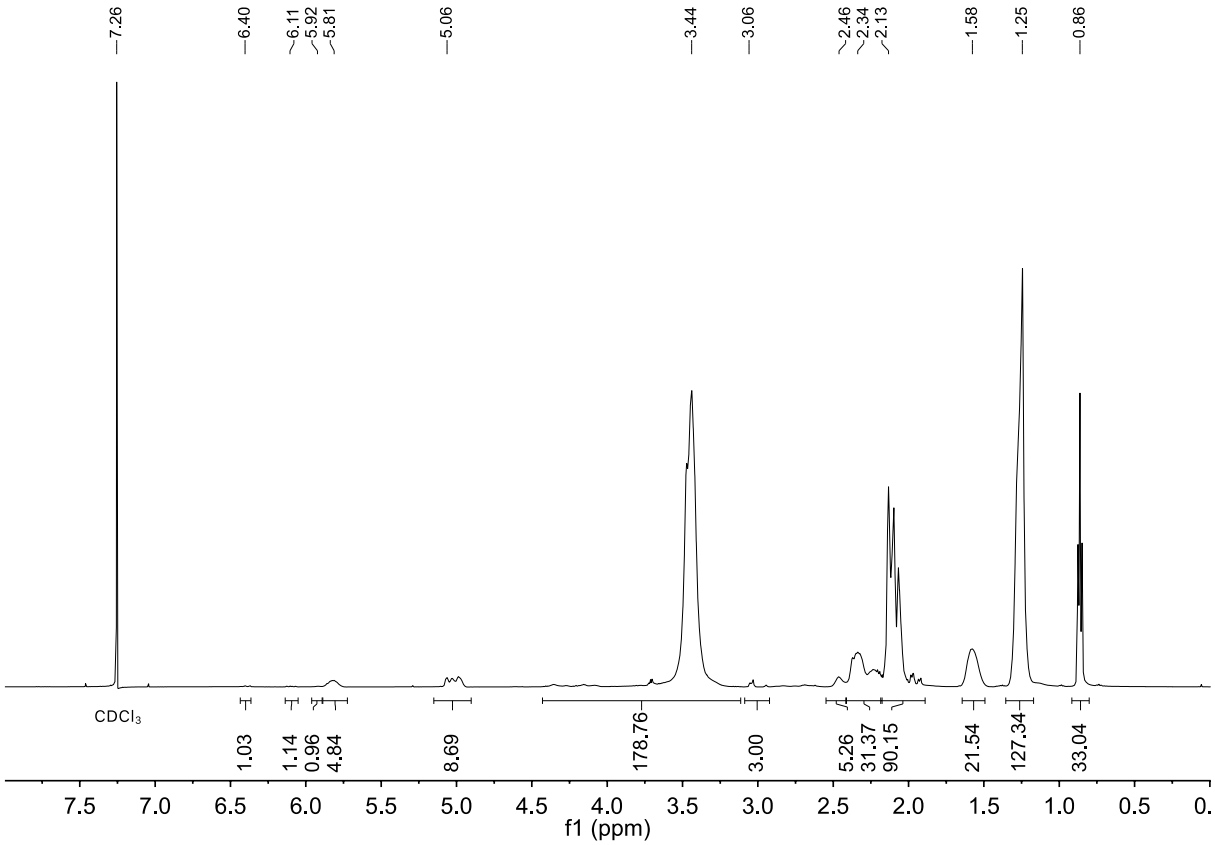
2-(pent-4-ynyl)-2-oxazoline (**15**)



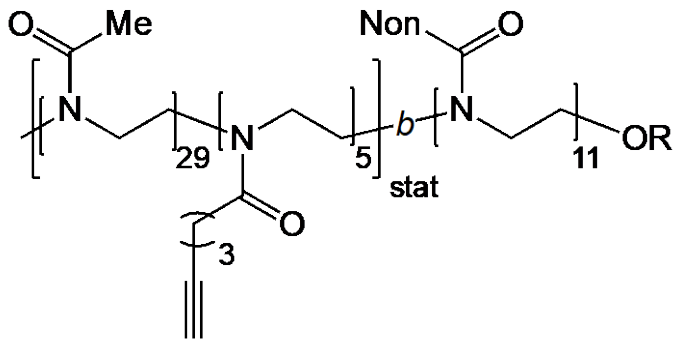
^{1}H NMR (300 MHz, $CDCl_3$) of functional comonomer **15** (2-(4-pentynyl)-2-oxazoline (PyneOx)).



[P(MeOx)$_{30}$-*r*-P(EneOx)$_5$]-*b*-P(NonOx)$_{11}$ (16)

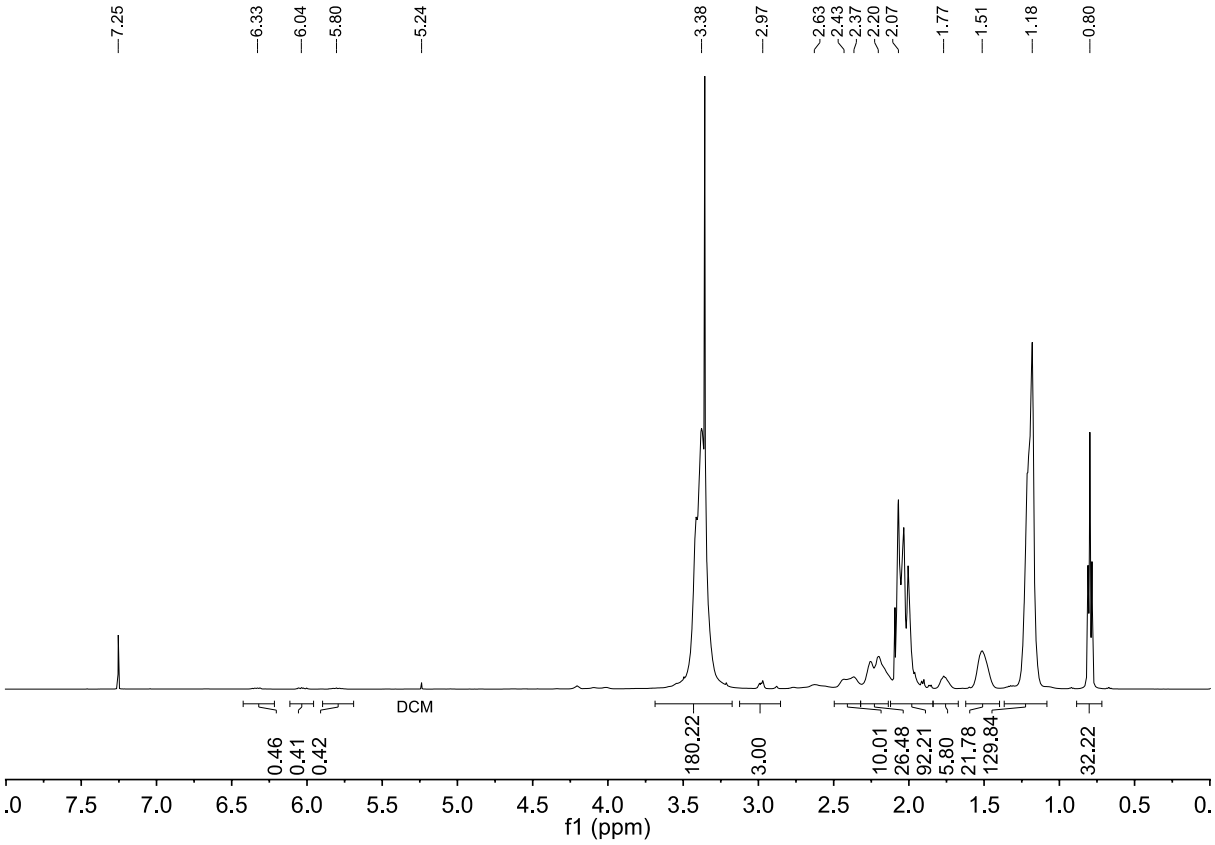


^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **16** P(MeOx$_{30}$-*r*-EneOx$_5$-*b*-NonOx$_{11}$)



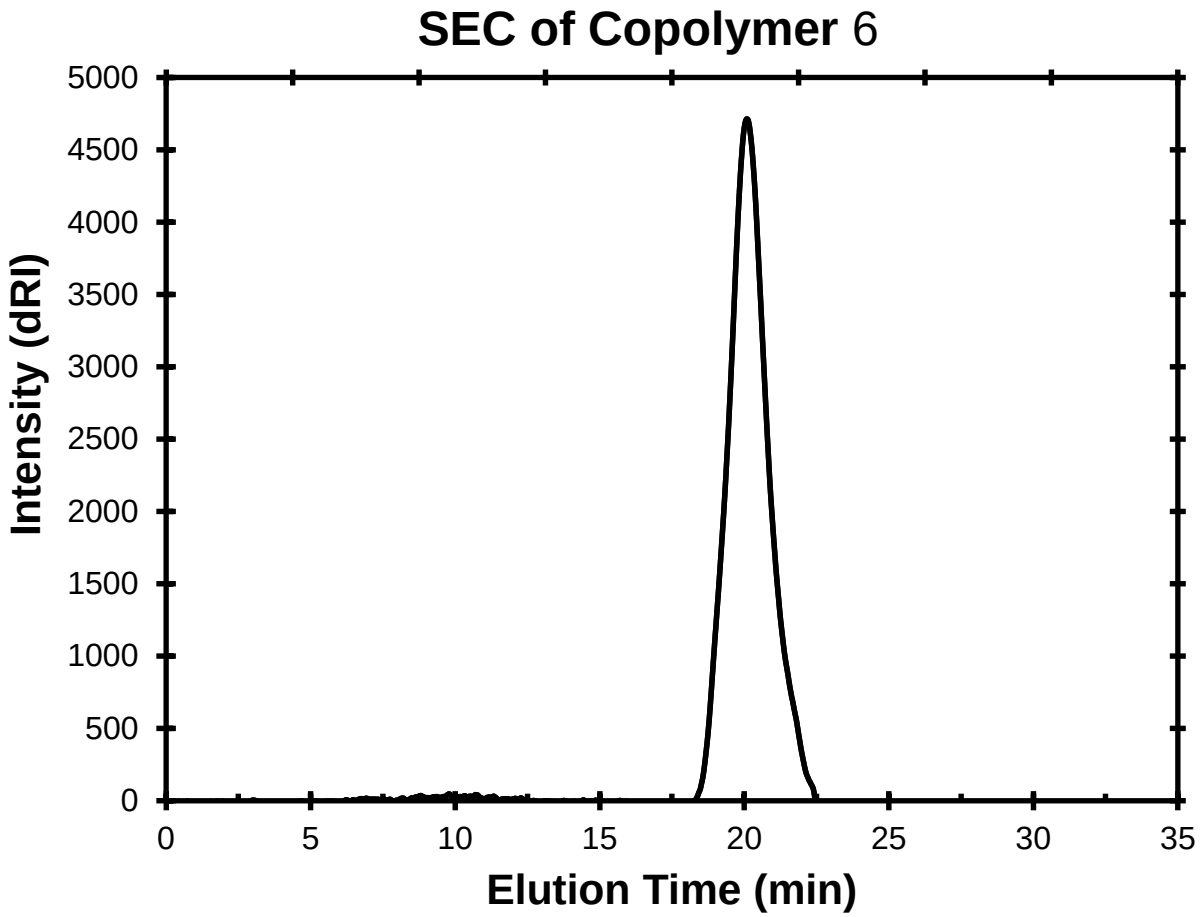
R = H, $COCH=CH_2$

$[P(MeOx)_{29}$-*r*-$P(PyneOx)_5]$-*b*-$P(NonOx)_{11}$ (**17**)

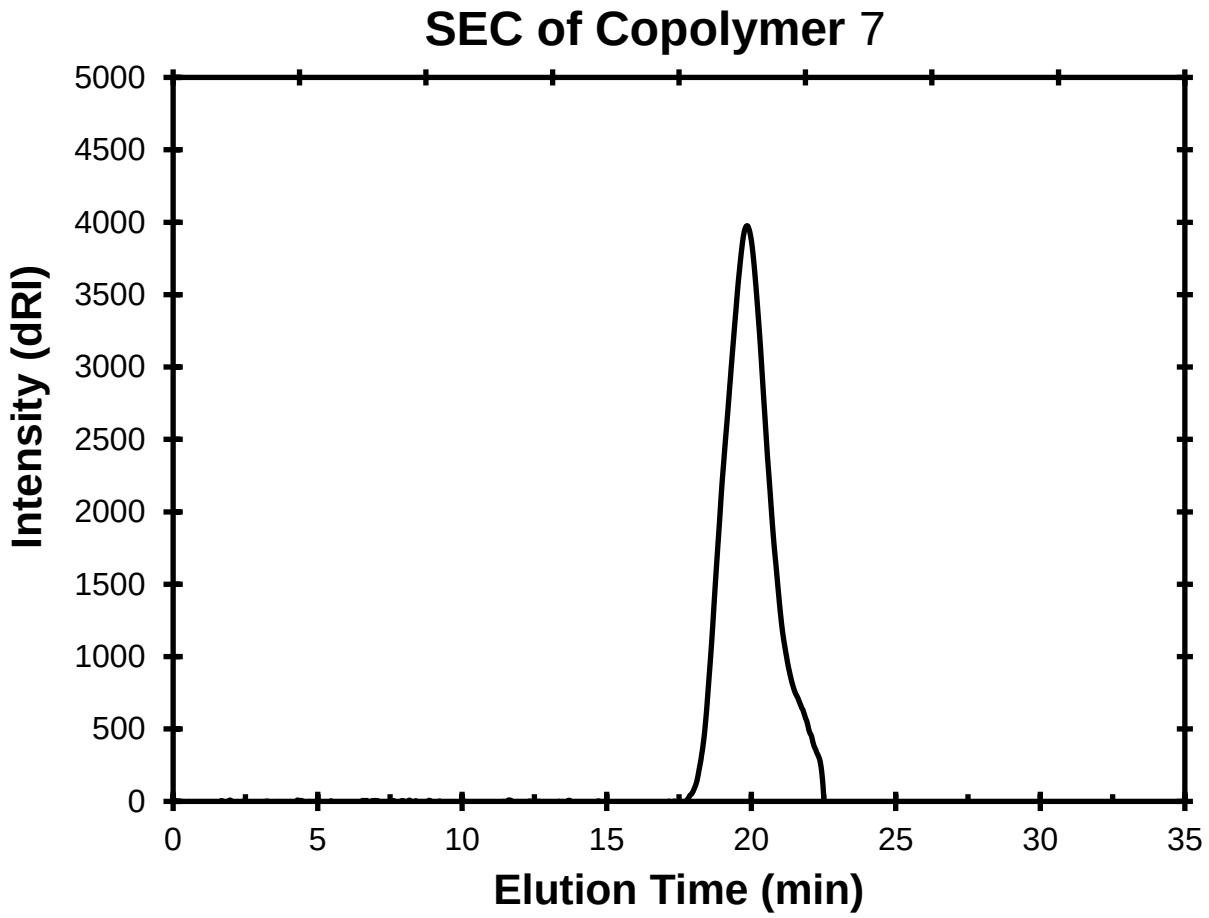


^{1}H NMR (500 MHz, $CDCl_3$) of copolymer **17** $P(MeOx_{29}$-*r*-$PyneOx_5$-*b*-$NonOx_{11})$.

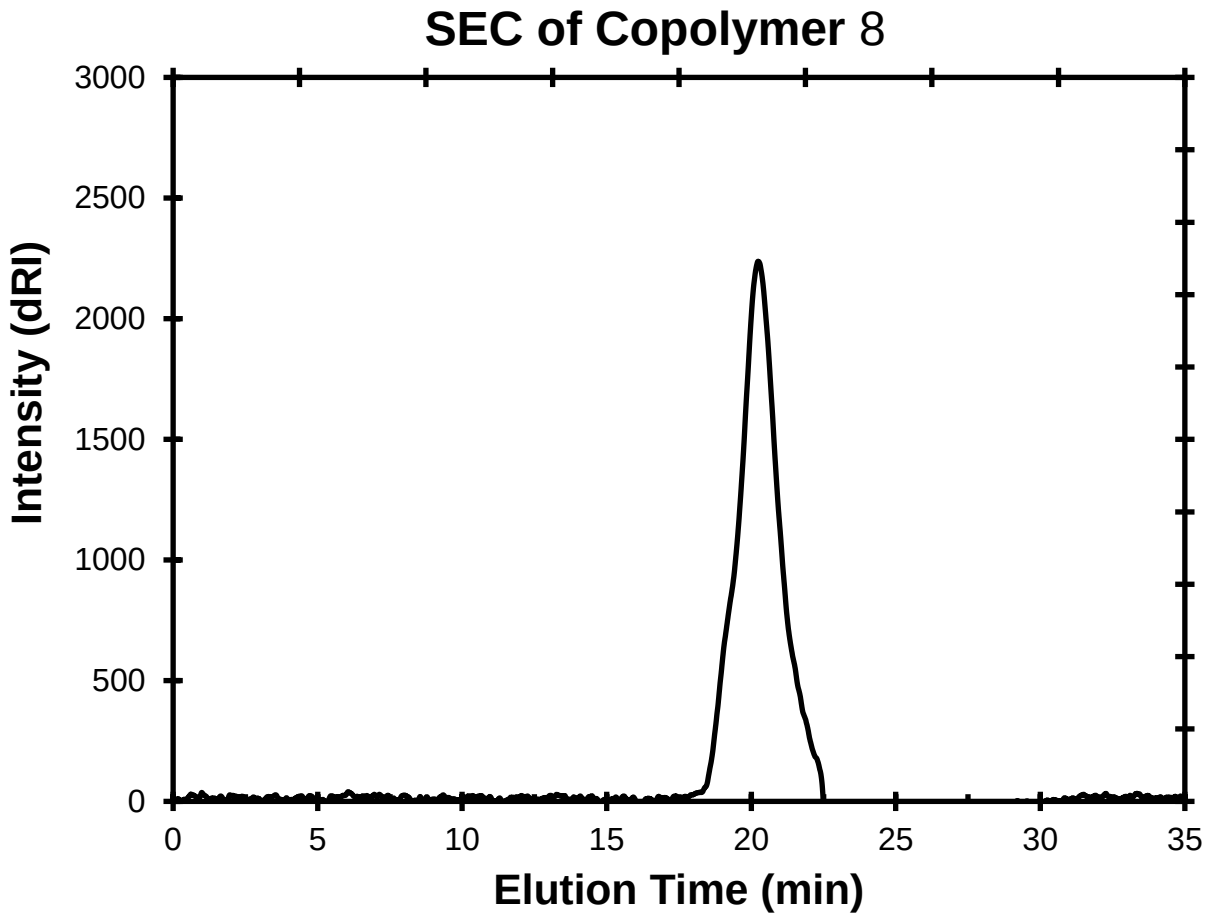
SEC analysis



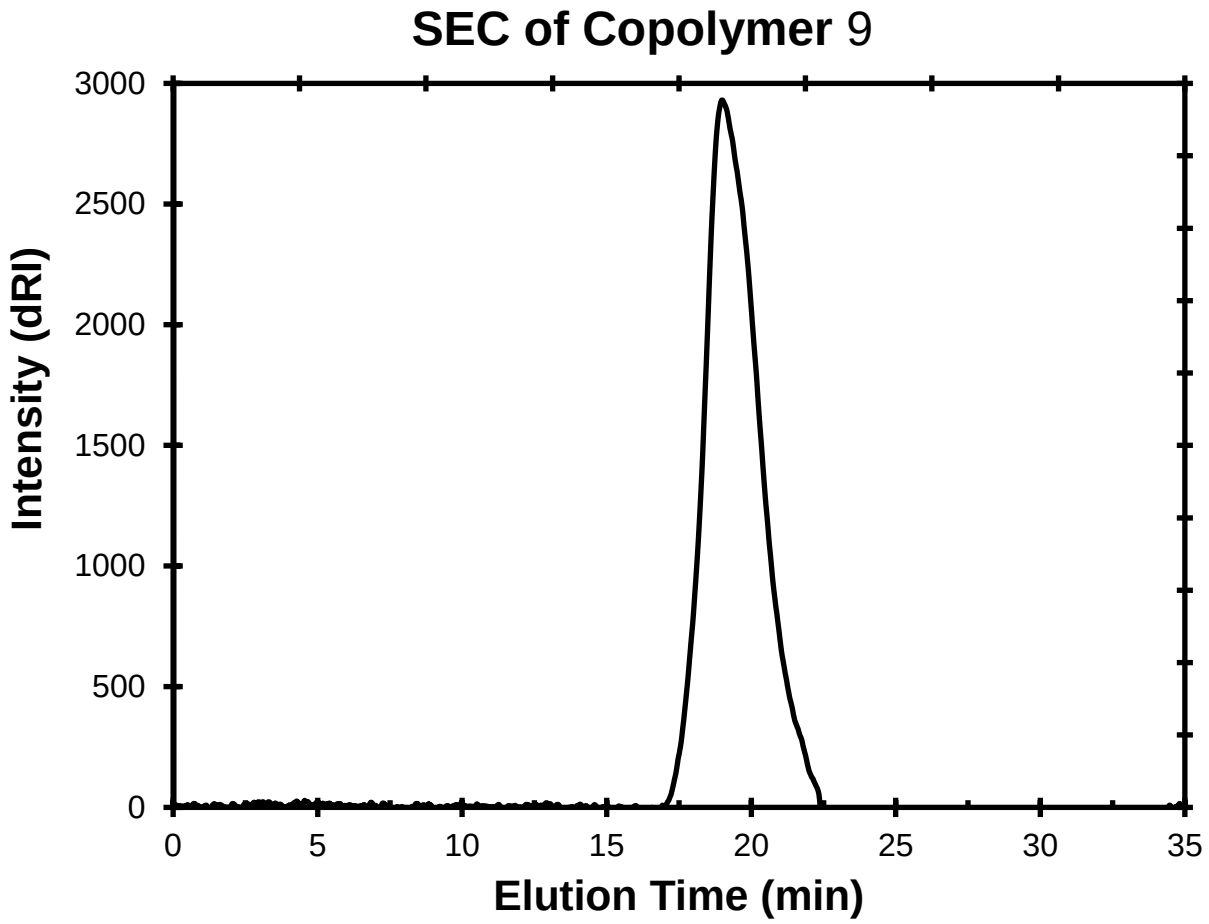
Size exclusion chromatogram of **6**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min).



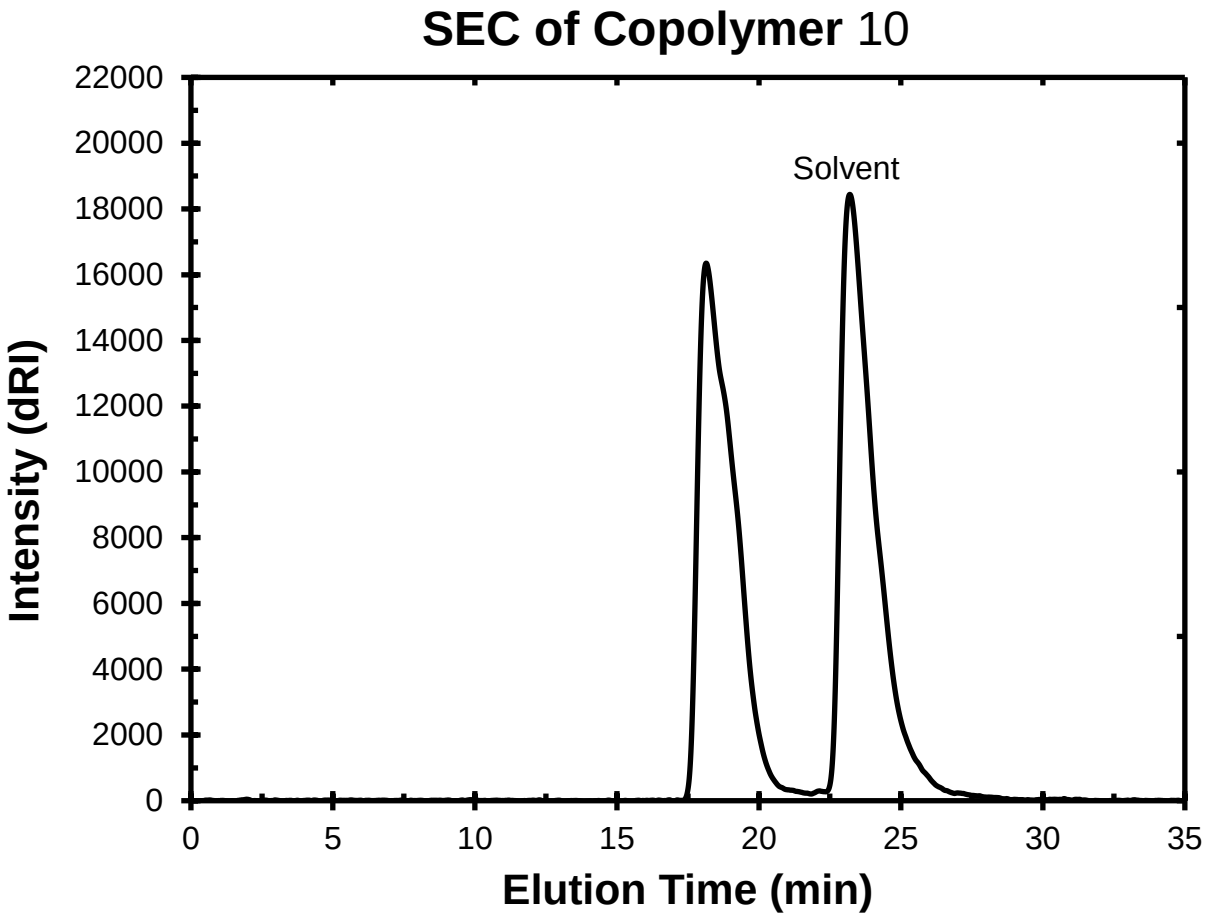
Size exclusion chromatogram of **7**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min).



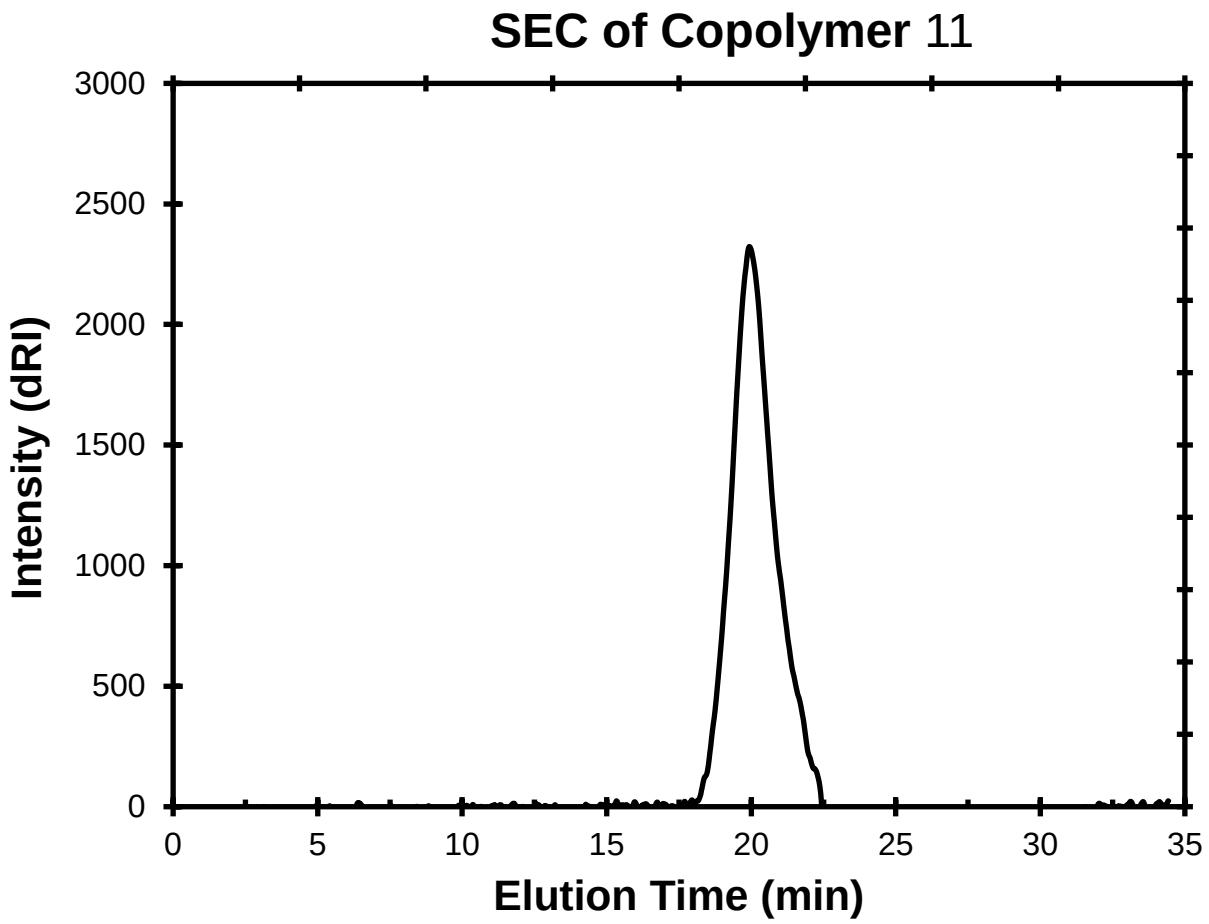
Size exclusion chromatogram of **8**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min).



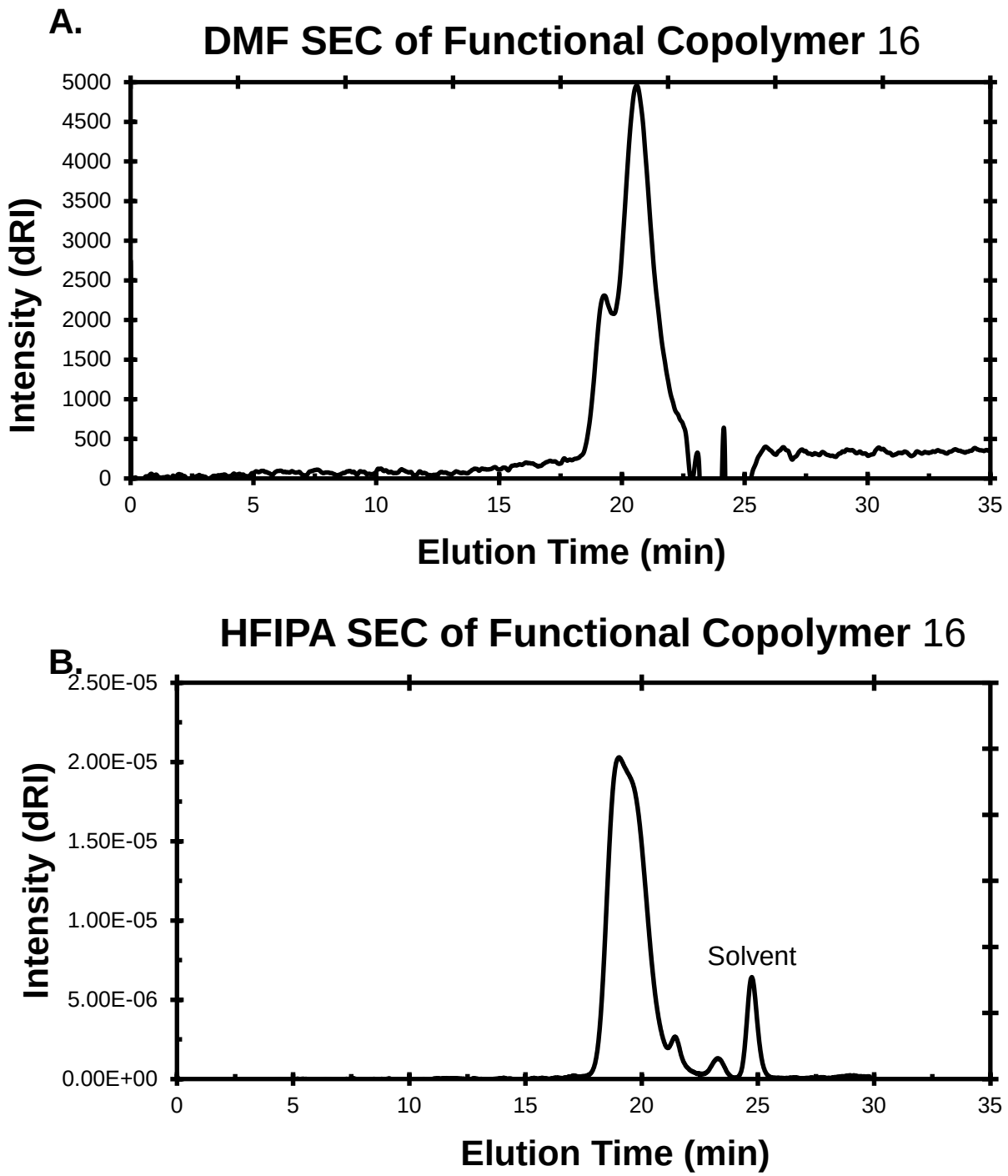
Size exclusion chromatogram of **9**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min).



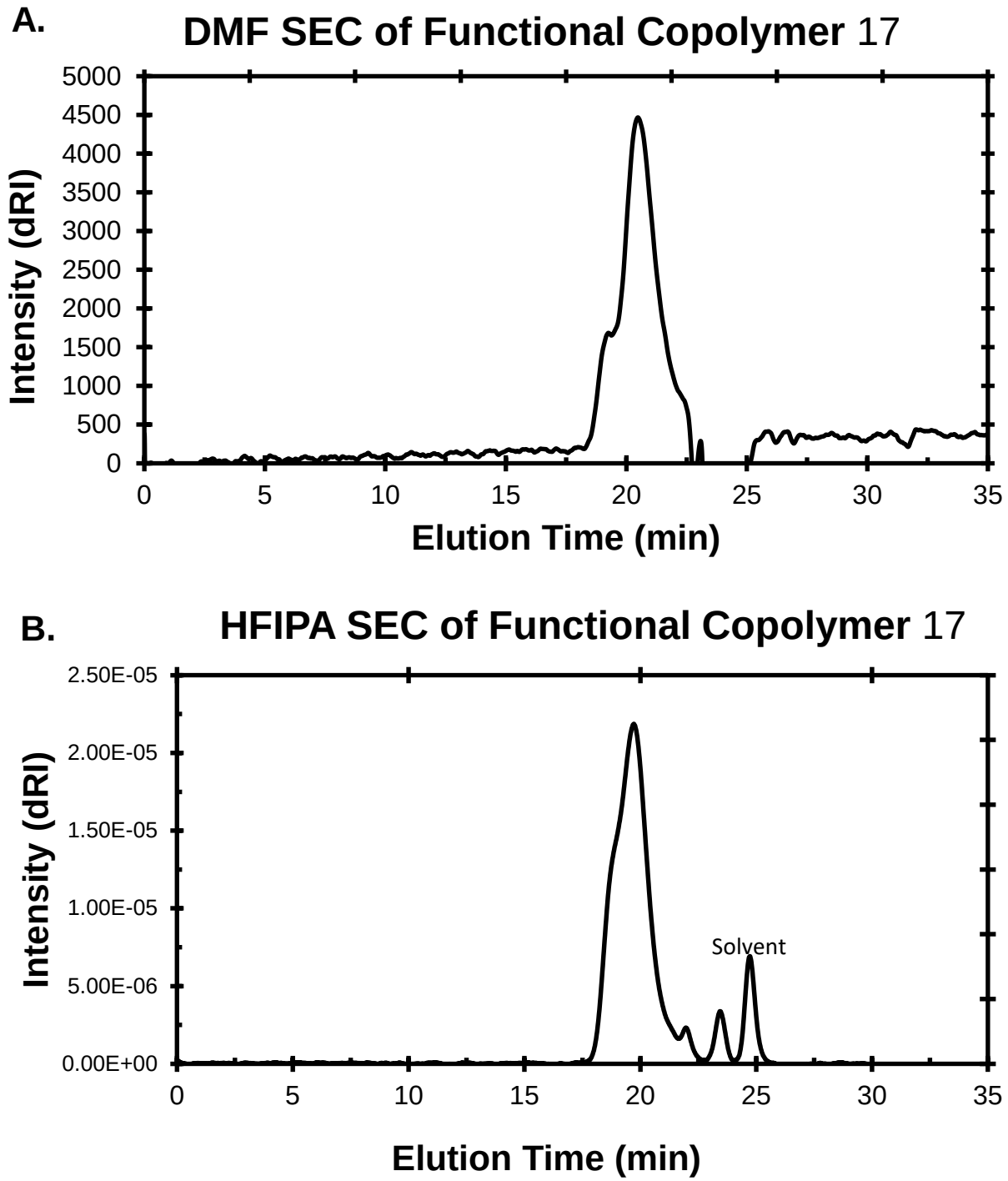
Size exclusion chromatogram of **10**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/min). Trace was negative due to refractive index of incorporated fluorous oxazoline. Reported data were then flipped horizontal and analyzed. Solvent peak can be seen at ~23 minutes due to this inversion.



Size exclusion chromatogram of **11**. Eluent was DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min).



Size exclusion chromatogram of **16**. Eluent was either (A) DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min), negative peak at ~23 minutes is solvent, or (B) HFIPA at 25 °C (flow rate: 0.75 mL/min), peaks at ~23.3, 24.8 minutes are solvent. Shoulders have previously been observed in poly(2-oxazoline)s and may be attributed to aggregation, sample-column interactions,[7,14] or either extrinsic or intrinsic chain transfer/coupling side reactions that may occur at high monomer conversion and high reaction temperatures.[11,15]



Size exclusion chromatogram of **17**. Eluent was either (A) DMF with LiBr (0.1 M) at 50 °C (flow rate: 0.80 mL/ min), negative peak at ~23 minutes is solvent, or (B) HFIPA at 25 °C (flow rate: 0.75 mL/min), peak at ~23.3, 24.8 minutes are solvent. Shoulders have previously been observed in poly(2-oxazoline)s and may be attributed to aggregation, sample-column interactions,[7,14] or either extrinsic or intrinsic chain transfer/coupling side reactions that may occur at high monomer conversion and high reaction temperatures.[11,15]

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