Supporting information for:

^{19}F MRI of Polymer Nanogels Aided by Improved Segmental Mobility of Embedded Fluorine Moieties

Oyuntuya Munkhbat [1], Mine Canakci [2], Shaokuan Zheng [3], Weiguo Hu [4], Barbara Osborne [2,5], Alexei A. Bogdanov *[,3] and S. Thayumanavan *[1,2,5]

[1]*Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003, United States*
[2]*Molecular and Cellular Biology Program, University of Massachusetts, Amherst, Massachusetts 01003, United States*
[3]*Department of Radiology and the Laboratory of Molecular Imaging Probes, and The Chemical Biology Interface Program, University of Massachusetts Medical School, Worcester, Massachusetts 01655, United States*
[4]*Department of Polymer Science and Engineering, University of Massachusetts, Amherst, Massachusetts 01003, United States.*
[5]*The Center for Bioactive Delivery, Institute for Applied Life Sciences, University of Massachusetts, Amherst, Massachusetts 01003, United States*

Materials:

All chemicals and reagents were purchased from commercial sources and were used as received, unless otherwise mentioned. Polyethylene glycol monomethyl ether acrylate (PEGA; 480), 2,2,2-trifluoroethyl methacrylate (TFEMA), 3,5-bis(trifluoromethyl)benzoic acid, 2-hydroxyethyl methacrylate, nonafluoro-tert-butyl alcohol, tert-butyl acrylate, 2-tetrahydropyranyl acrylate, pentaerythritol, DL-dithiothreitol (DTT), folic acid, fluorescein isothiocyanate isomer I, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI) were obtained from Sigma-Aldrich. 2,2′-Azobis(2-methylpropionitrile) (AIBN) was purchased from Sigma-Aldrich and purified by recrystallization in cold methanol for three times. Cyclohexyl acrylate (CHA) and docetaxel were purchased from TCI America. Pyridyl disulfide ethyl acrylate (PDSA) and Compound **3** were synthesized according to previously reported procedures.[1,2] Thiolated version of folic acid (FA-SH) and fluorescein isothiocyanate (FITC-SH) were prepared using to the previously reported procedures.[1,3]

Methods: Synthesis protocol:

Synthesis of P1:

PEGA (0.398 g, 0.83 mmol), PDSA (0.1 g, 0.415 mmol), THPA (0.194 g, 1.245 mmol) and AIBN (4.5 mg, 0.0277 mmol) were weighed into small round bottom flask and purged with argon. Reaction mixture was dissolved in 0.75 mL of previously degassed dry THF. TFEMA (40 µL, 0.277 mmol) was separately degassed (15 min) and added with syringe. After that the reaction mixture was sealed and transferred to preheated oil bath at 65 °C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 96%. GPC (THF) Mn:16 kDa. *Đ*:3.71. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42, 7.64, 7.07, 5.90, 4.42-4.13, 3.80, 3.60-3.34, 2.98, 2.31-1.01. Tentative assignments for the NMR peaks are shown below. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 159.6, 149.2, 138.0, 124.6, 122.1, 120.5, 101.1, 100.2, 98.6, 94.9, 72.1, 70.7, 69.1, 63.9, 63.5, 63.1, 60.9, 59.1, 53.5, 45.5, 41.2, 37.2, 32.0, 31.0, 30.8, 25.4, 20.3, 19.9, 19.5, 19.1.

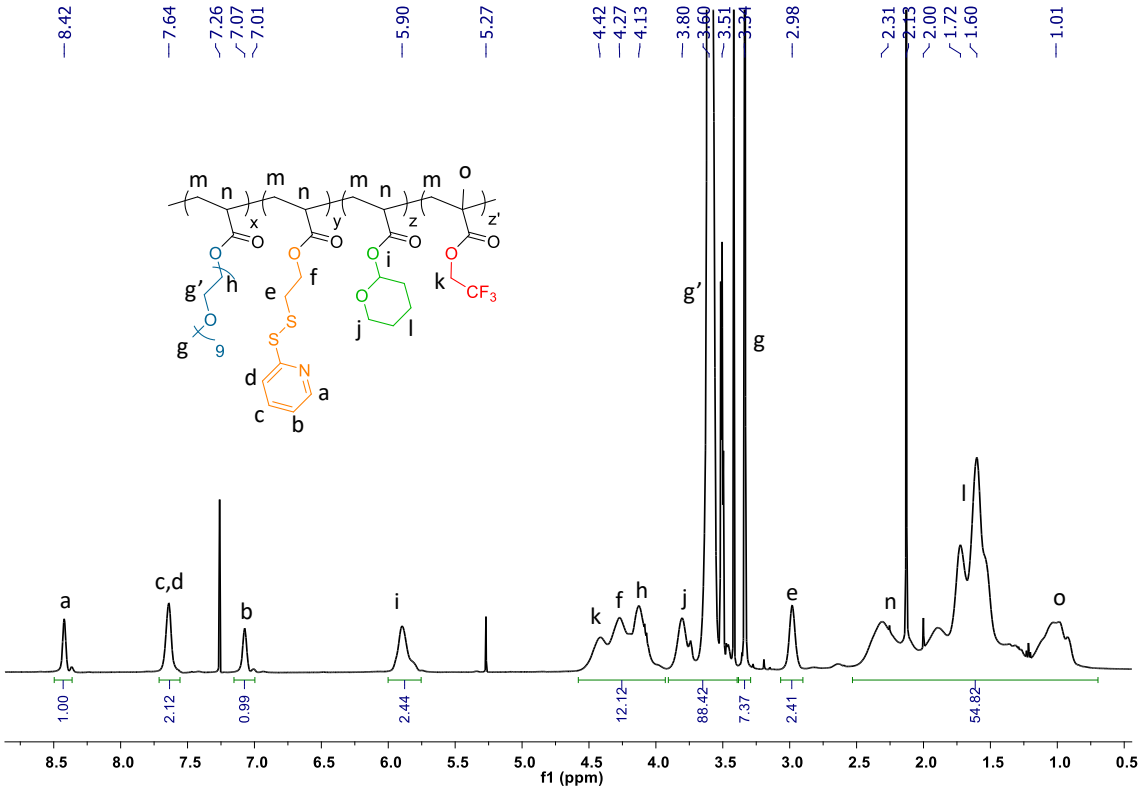


Figure S1: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P1**.

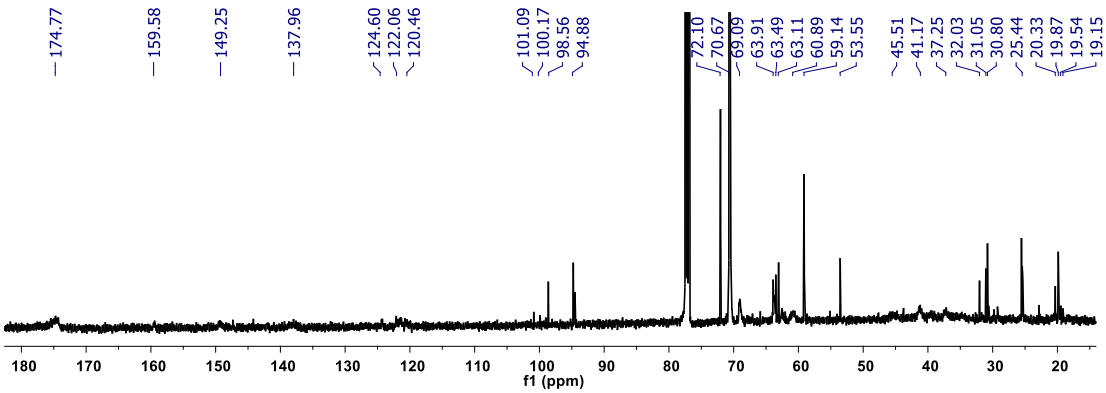


Figure S2: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P1.**

Synthesis of P2:

PEGA (0.398 g, 0.83 mmol), PDSA (0.1 g, 0.415 mmol), THPA (0.152 g, 0.968 mmol) and AIBN (4.5 mg, 0.0277 mmol) were weighed into small round bottom flask and purged with argon. Reaction mixture was dissolved in 0.75 mL of previously degassed dry THF. TFEMA (79 µL, 0.553 mmol) was separately degassed (15 min) and added with syringe. After that the reaction mixture was sealed and transferred to preheated oil bath at 65 ^{o}C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 97%. GPC (THF) Mn:18000 Da. *Đ*:3.88. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44, 7.65, 7.09, 5.91, 4.42-4.14, 3.82, 3.63-3.35, 2.99, 2.32-1.01. Tentative assignments for the NMR peaks are shown below. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 159.6, 149.8, 144.3, 137.7, 124.3, 122.4, 121.1, 120.0, 100.9, 99.9, 98.7, 94.6, 93.1, 72.1, 70.7, 68.8, 65.9, 64.0, 62.1, 60.9, 59.3, 55.2, 45.9, 41.5, 37.2, 32.0, 30.8, 25.8, 22.9, 20.5, 19.5, 18.3, 8.8.

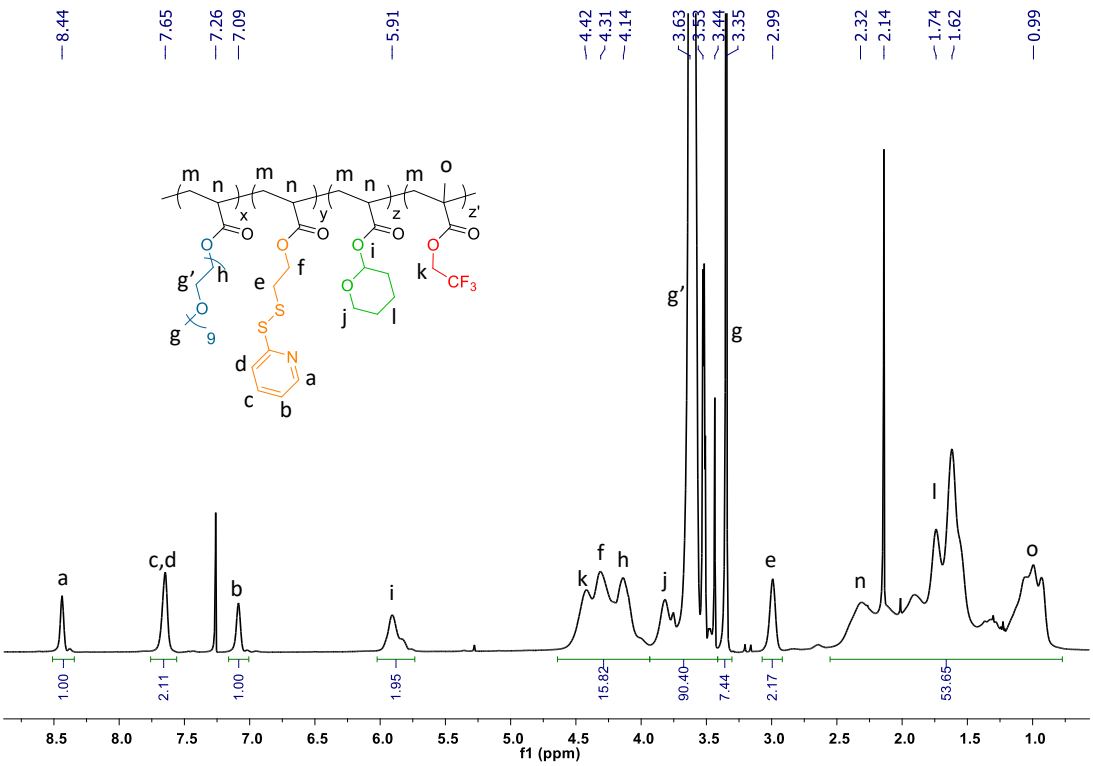


Figure S3: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P2**.

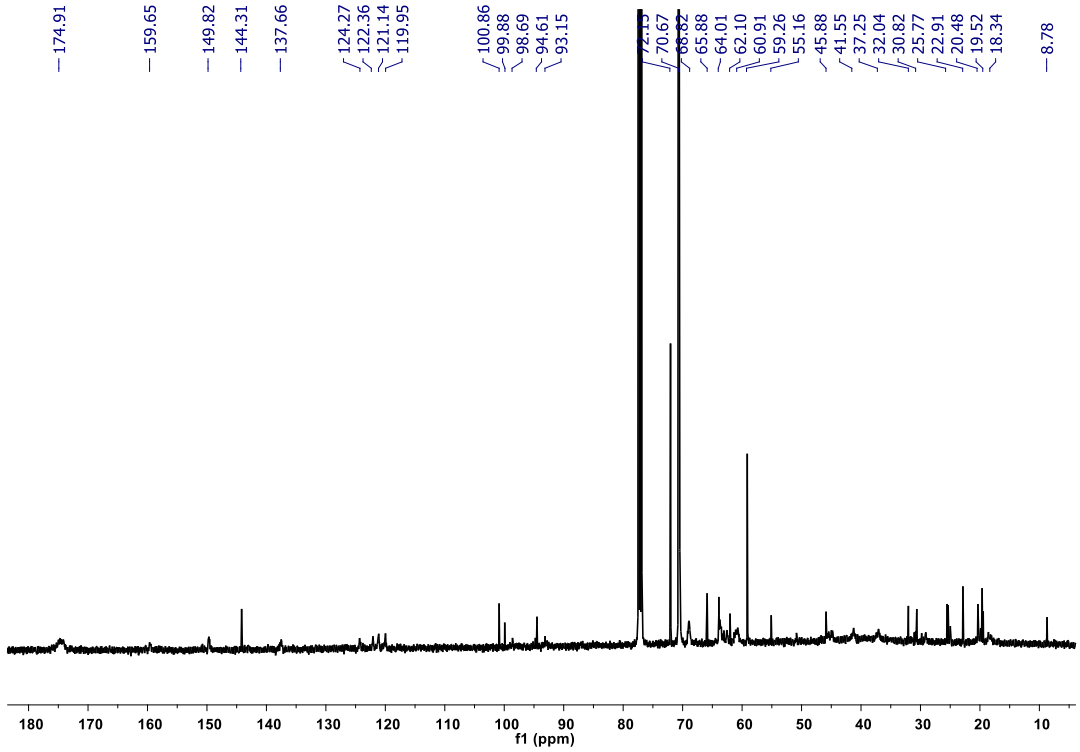


Figure S4: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P2**.

Synthesis of P3:

PEGA (0.398 g, 0.83 mmol), PDSA (0.1 g, 0.415 mmol), THPA (0.108 g, 0.692 mmol) and AIBN (4.5 mg, 0.0277 mmol) were weighed into small round bottom flask and purged with argon. Reaction mixture was dissolved in 0.75 mL of previously degassed dry THF. TFEMA (118 µL, 0.830 mmol) was separately degassed (15 min) and added with syringe. After that the reaction mixture was sealed and transferred to preheated oil bath at 65 °C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 98%. GPC (THF) Mn:16000 Da. *Đ*:3.05. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43, 7.64, 7.08, 5.90, 4.41-4.13, 3.81, 3.61-3.34, 2.98, 2.30-0.92. Tentative assignments for the NMR peaks are shown below. ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0, 159.5, 149.8, 144.3, 137.6, 124.5, 122.1, 121.2, 120.1, 100.8, 98.6, 94.5, 72.0, 70.7, 68.9, 65.9, 64.0, 62.6, 61.0, 59.1, 45.4, 44.8, 41.2, 39.3, 37.3, 32.1, 31.1, 30.7, 25.3, 22.9, 20.3, 19.7, 18.2.

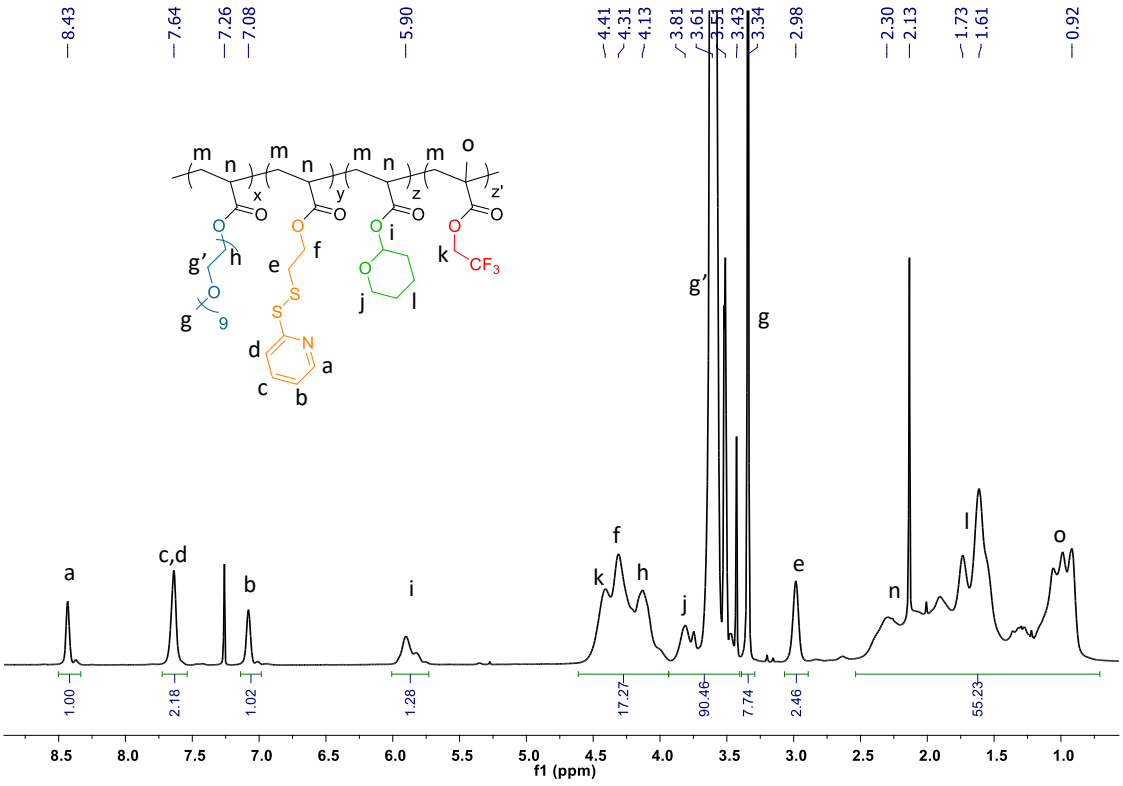


Figure S5: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P3**.

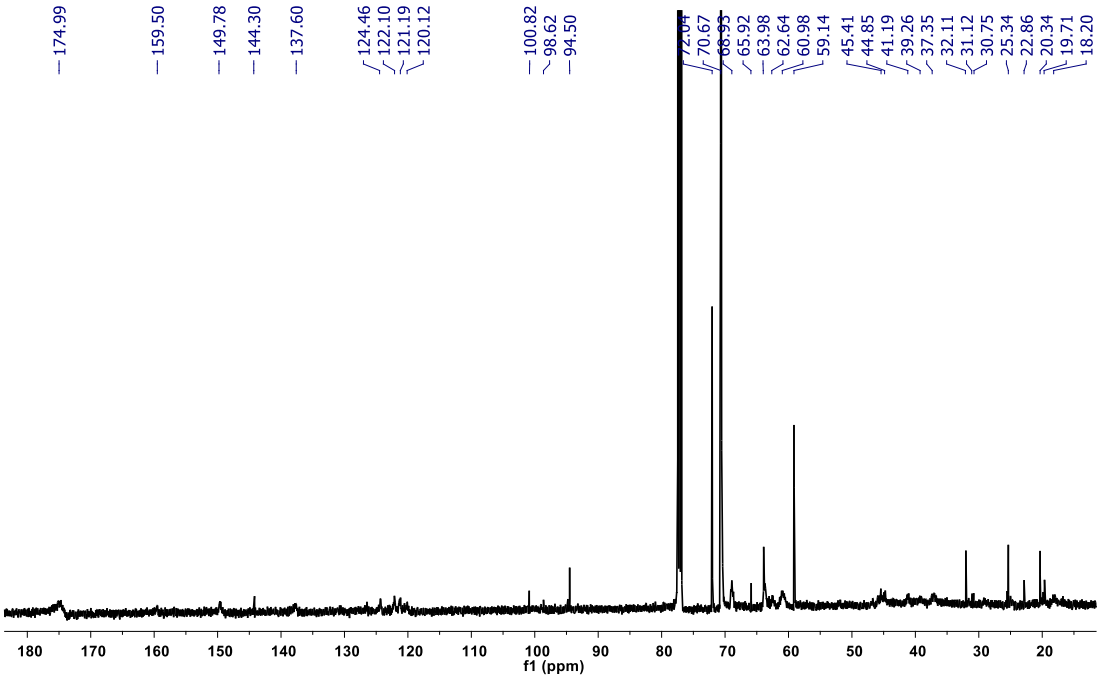


Figure S6: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-TFEMA), **P3**.

Synthesis of PC:

PEGA (0.398 g, 0.83 mmol), PDSA (0.1 g, 0.415 mmol), CHA (0.128 g, 0.692 mmol) and AIBN (4.5 mg, 0.0277 mmol) were weighed into small round bottom flask and purged with argon. Reaction mixture was dissolved in 0.75 mL of previously degassed dry THF. TFEMA (118 µL, 0.830 mmol) was separately degassed (15 min) and added with syringe. After that the reaction mixture was sealed and transferred to preheated oil bath at 65 °C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 83%. GPC (THF) Mn:11700 Da. *Đ*:2.57. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45, 7.65, 7.09, 4.69, 4.42-4.15, 3.76, 3.63-3.36, 3.00, 2.26-0.94. Tentative assignments for the NMR peaks are shown below. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 159.6, 149.7, 137.6, 124.5, 121.7, 121.2, 120.0, 73.1, 72.0, 70.5, 69.0, 63.6, 62.5, 61.0, 59.1, 45.6, 41.2, 37.1, 31.6, 25.4, 23.8, 20.0, 18.0.

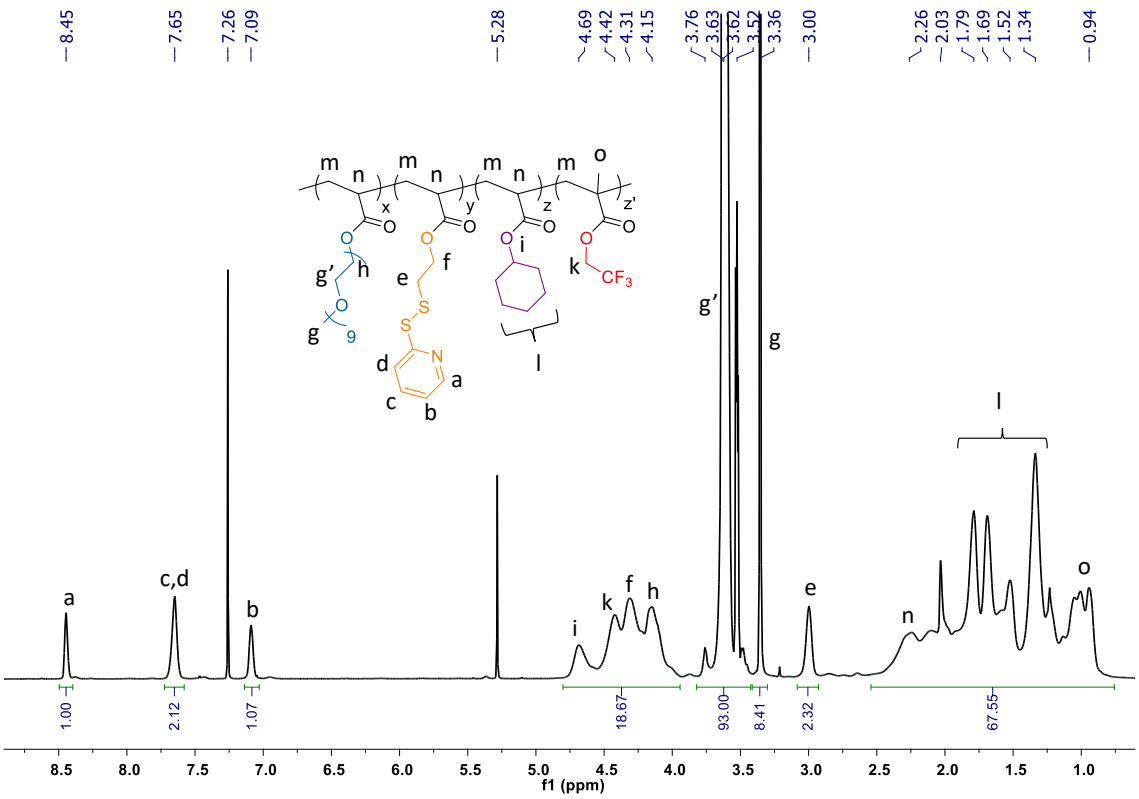


Figure S7: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-CHA-co-TFEMA), **PC**.

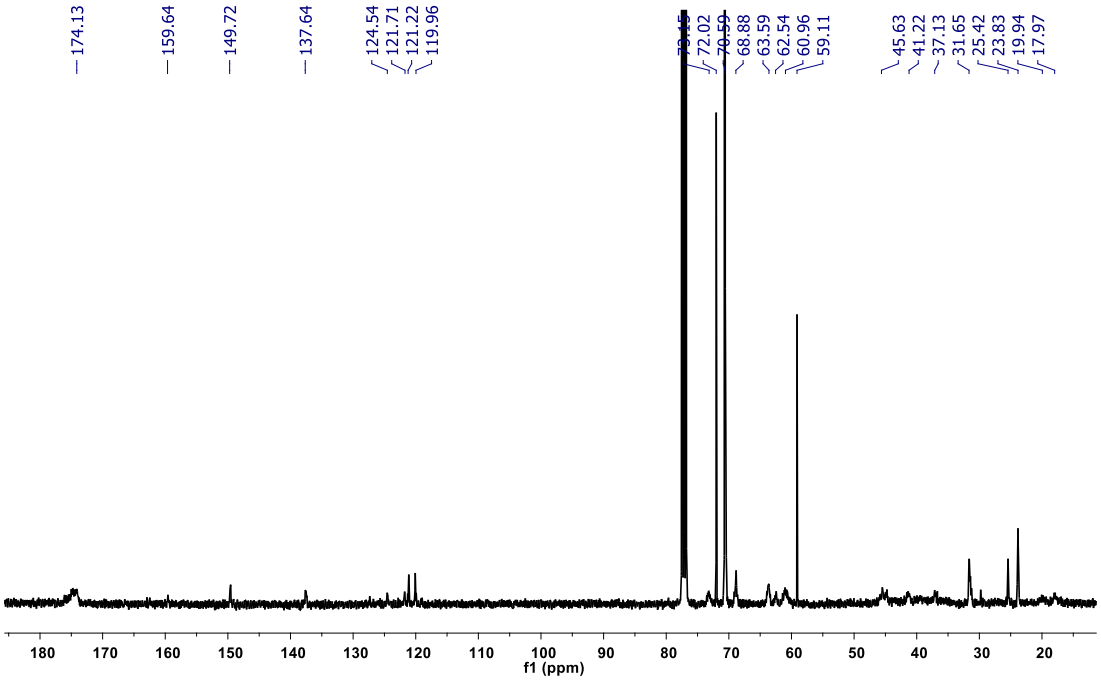
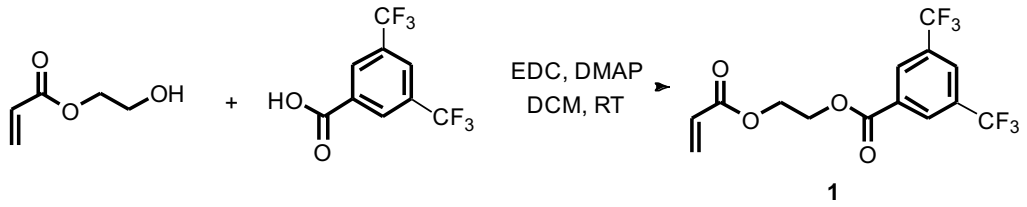


Figure S8: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-CHA-co-TFEMA), **PC**.

Synthesis of P4:



1

2-(Acryloyloxy) ethyl 3,5-bis(trifluoromethyl)benzoate (Compound **1**) To a solution of 3,5-bis(trifluoromethyl)benzoic acid (3.0 g, 11.62 mmol) in dry dichloromethane was added 2-Hydroxyethyl acrylate (1.04 g, 8.94 mmol) and cooled to 0 °C in ice bath. To this mixture N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.23 g, 11.62 mmol) and 4-(dimethylamino) pyridine (0.13 g, 1.07 mmol) were added. The reaction mixture was stirred for 3 hours at room temperature. Distilled water was added to the reaction mixture and extracted three times with dichloromethane. Combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to yield 1.23 g (39%) of pure compound **1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2H), 8.07 (s, 1H), 6.45 (d, J = 17.3 Hz, 1H), 6.16 (dd, J = 17.3, 10.4 Hz, 1H), 5.88 (d, J = 10.4 Hz, 1H), 4.64 (d, J = 4.8 Hz, 2H), 4.54 (d, J = 4.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.9, 132.4 (q, J_{C-F} = 34 Hz), 132.2, 131.9, 130.1, 127.8, 126.8-126.7 (m), 124.3, 121.6, 119.0, 64.0, 62.0.

Compound **1** (0.309 g, 0.868 mmol), PEGA (0.5 g, 1.042 mmol), PDSA (0.139 g, 0.578 mmol), CHA (0.189 g, 1.215 mmol), Cyanomethyl dodecyl trithiocarbonate (27.6 mg, 0.0868 mmol) and AIBN (3.0 mg, 0.0173 mmol) were weighed into small Schlenk flask and dissolved in 1 mL of dry toluene. Reaction mixture is degassed through three cycles of freeze-pump-thaw, transferred to preheated oil bath at 80 °C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product (**P4**) was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 79%. GPC (THF) Mn:13100 Da. *Đ*:1.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47, 8.04, 7.68, 7.12, 6.03, 4.57, 4.40-4.14, 3.76, 3.63-3.36, 3.02, 2.41, 1.84-1.69, 1.24, 0.86. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 163.7, 158.6, 149.5, 137.9, 131.9, 130.0, 126.6, 124.1, 121.4, 120.0, 118.8, 99.0, 98.4, 94.5, 71.8, 70.4, 68.9, 63.5, 62.2, 59.1, 41.1, 36.8, 34.8, 32.0, 29.8, 29.4, 25.4, 22.9, 20.3, 14.3.

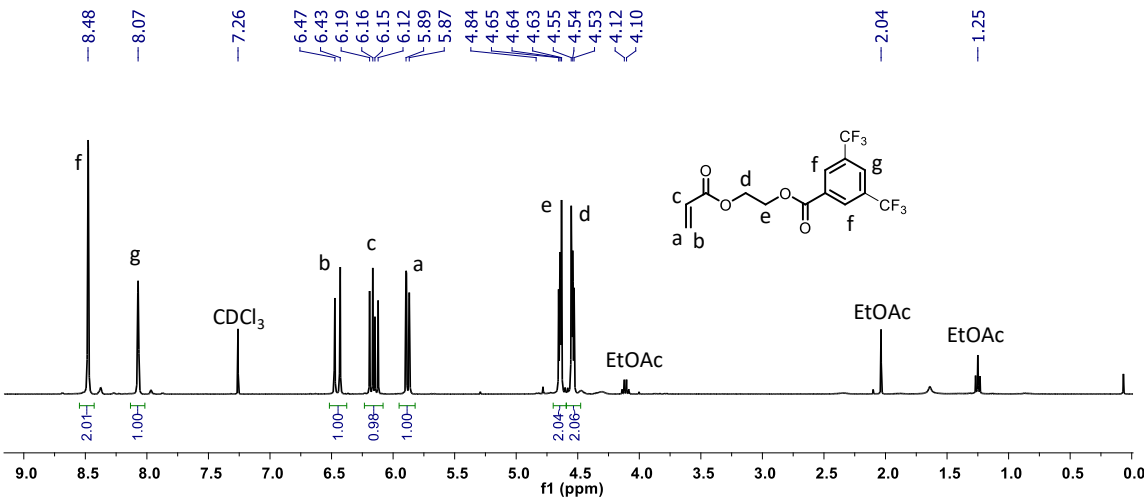


Figure S9: ^{1}H NMR spectrum of compound **1**.

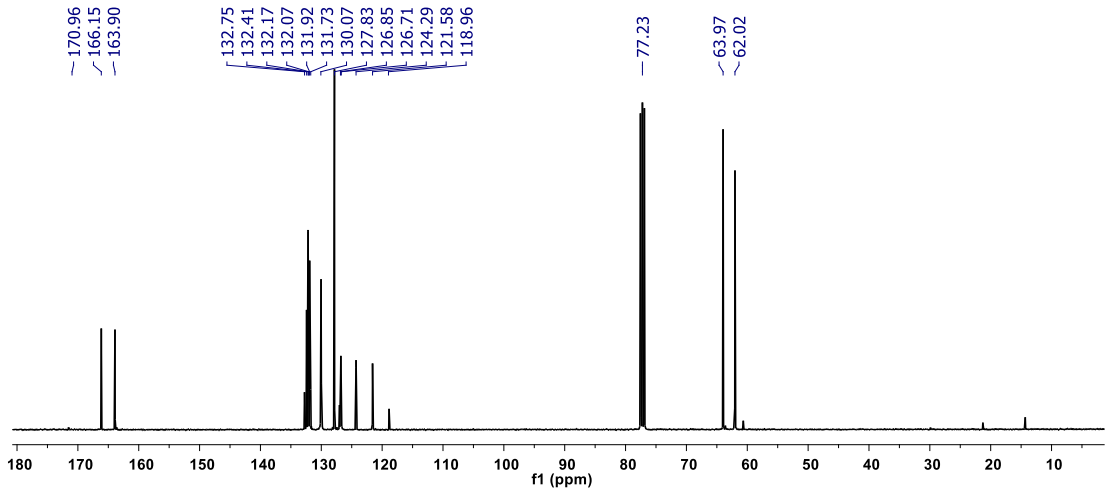


Figure S10: ^{13}C NMR spectrum of compound **1**.

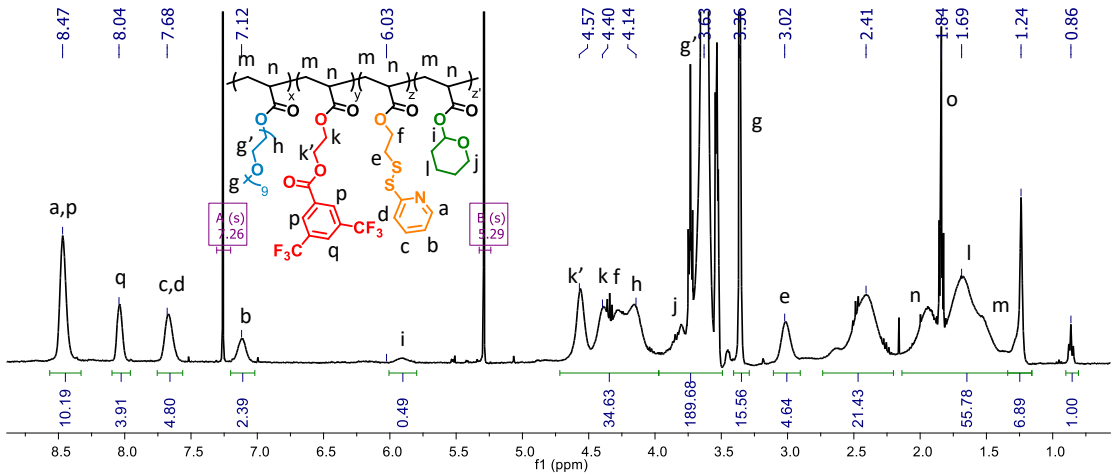


Figure S11: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-$(CF_3)_2$A), **P4.**

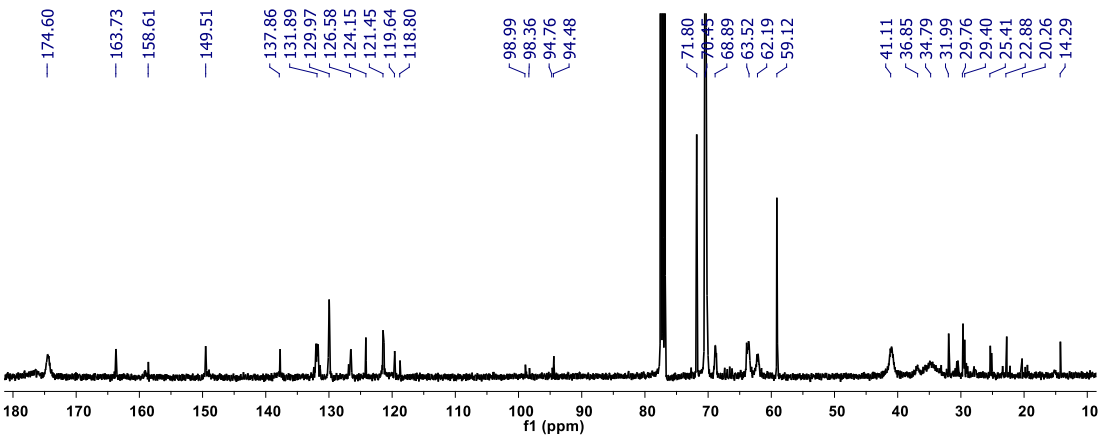
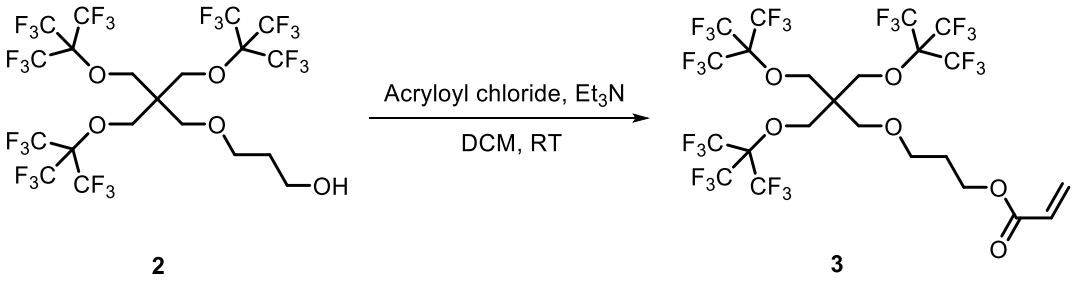


Figure S12: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-$(CF_3)_2$A), **P4.**

Synthesis of P5:



Compound **2** was prepared according to previously reports procedure.[2] To a solution of Compound **2** (2.36 g, 2.78 mmol) in dry dichloromethane was added triethylamine (0.46 mL, 3.33 mmol) and cooled to 0 °C in ice bath. To this mixture acryloyl chloride (0.25 mL, 3.06 mmol was added. The reaction mixture was stirred for 4 hours at room temperature. Distilled water was added to the reaction mixture and extracted three times with dichloromethane. Combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was purified by silica gel column chromatography using ethyl acetate/hexane as eluent to yield 0.92 g (37%) of pure compound **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, J = 17.3, 1.5 Hz, 1H), 6.10 (dd, J = 17.3, 10.4 Hz, 1H), 5.82 (dd, J = 10.4, 1.5 Hz, 1H), 4.20 (t, J = 6.4 Hz, 2H), 4.04 (s, 6H), 3.48 (t, J = 6.3 Hz, 2H), 3.38 (s, 2H), 1.92 (p, J = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 131.1, 128.3, 124.5 (q, $J_{C\text{-}F}$ = 292.5 Hz), 79.4 (m), 67.8, 65.4, 64.8, 61.4, 46.4, 28.7.

Compound **3** (25 mg, 0.0277 mmol), PEGA (0.2 g, 0.416 mmol), PDSA (67 mg, 0.277 mmol), THPA (0.104 g, 0.666 mmol) and AIBN (2.3 mg, 0.0138 mmol) were weighed into small round bottom flask and purged with argon. Reaction mixture was dissolved in 0.4 mL of previously degassed dry THF. After that the reaction mixture was sealed and transferred to preheated oil bath at 65 °C and stirred for 20 hours. Polymerization was stopped by cooling down the flask in cold water. Product (**P5**) was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield: 97%. GPC (THF) Mn:9800 Da. *Đ*:1.96. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41, 7.64, 7.06, 5.88, 4.25-3.98, 3.77, 3.59-3.50, 3.32, 2.98, 2.31-1.59, 1.120. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 159.3, 149.5, 144.0, 137.6, 121.4, 121.1, 119.6, 118.6, 100.9, 98.8, 94.7, 94.3, 92.6, 71.8, 70.44, 68.9, 65.8, 63.8, 63.5, 62.3, 59.1, 41.1, 36.8, 35.1, 31.8, 31.0, 29.0, 25.2, 24.8, 22.6, 20.3, 19.5, 18.3.

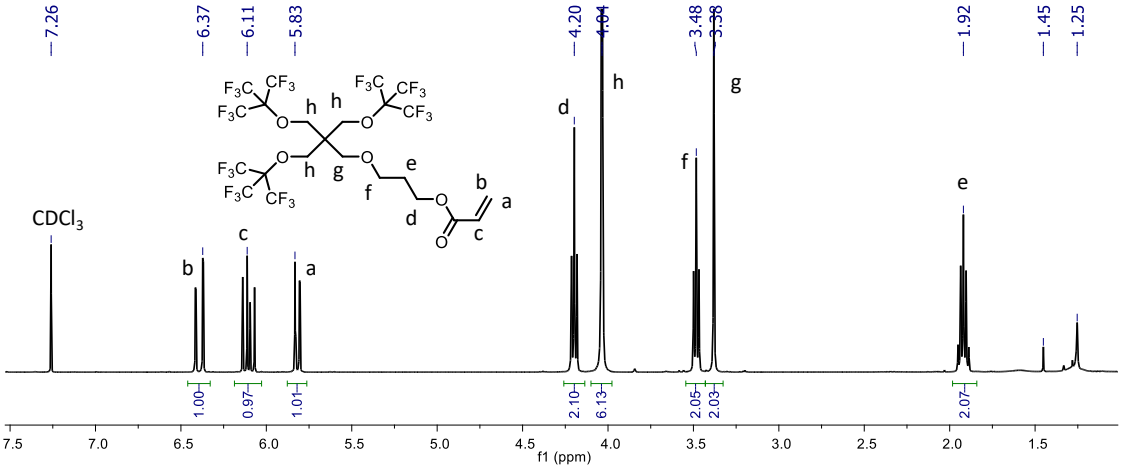


Figure S13: ^{1}H NMR spectrum of compound **3**.

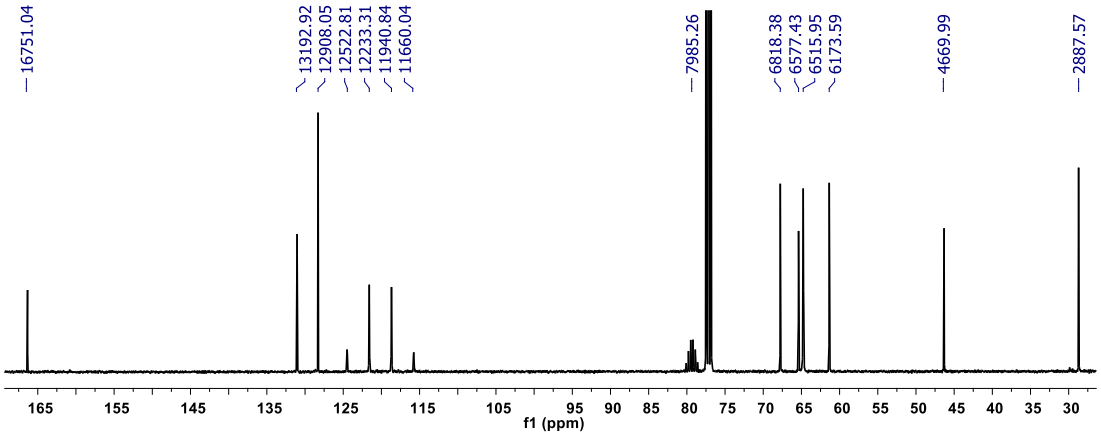


Figure S14: ^{13}C NMR spectrum of compound **3**.

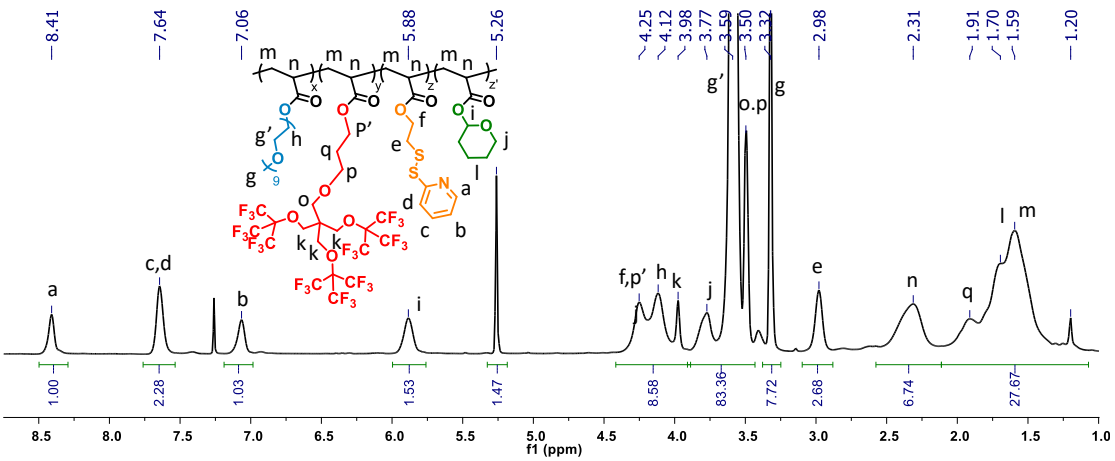


Figure S15: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-$(CF_3)_9$A), **P5.**

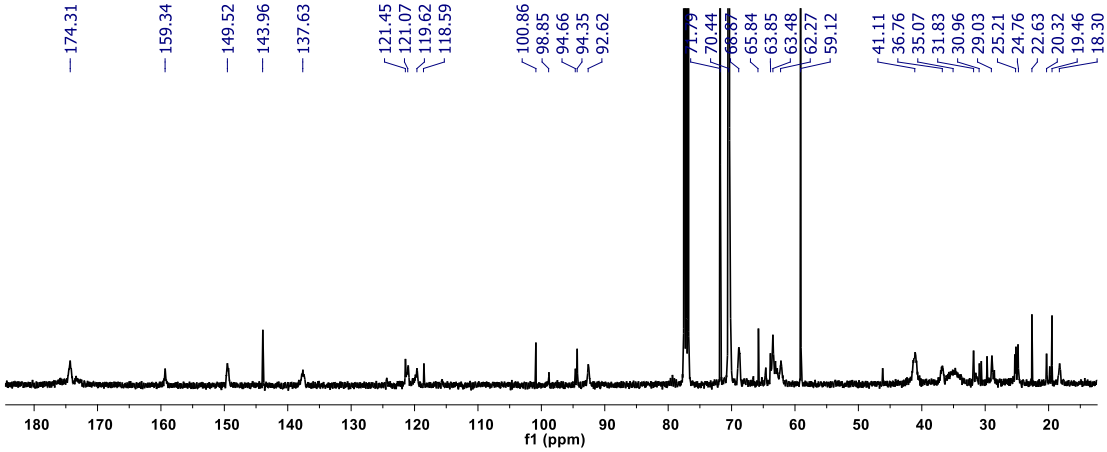


Figure S16: ^{13}C NMR spectrum of p(PEGA-co-PDSA-co-THPA-co-$(CF_3)_9$A), **P5.**

Synthesis of P6:

PEGA (0.2 g, 0.415 mmol), PDSA (0.2 g, 0.830 mmol), TFEMA (20 µL, 0.138 mmol), Cyanomethyl dodecyl trithiocarbonate (5.8 mg, 0.0184 mmol) and AIBN (0.6 mg, 0.0037 mmol) were weighed into small schlenk flask and dissolved in 0.4 mL of dry THF. Reaction mixture is degassed through three cycles of freeze-pump-thaw, transferred to preheated oil bath at 65 °C and stirred for 24 hours. Polymerization was stopped by cooling down the flask in cold water. Product (**P6**) was purified with extensive dialysis against DCM:MeOH (3:1, v/v) for three days. Yield:

68%. GPC (THF) Mn:12600 Da. *Đ*:1.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40, 7.63, 7.05, 4.42-4.11, 3.60-3.43, 3.34, 2.97, 2.32-1.51, 1.22.

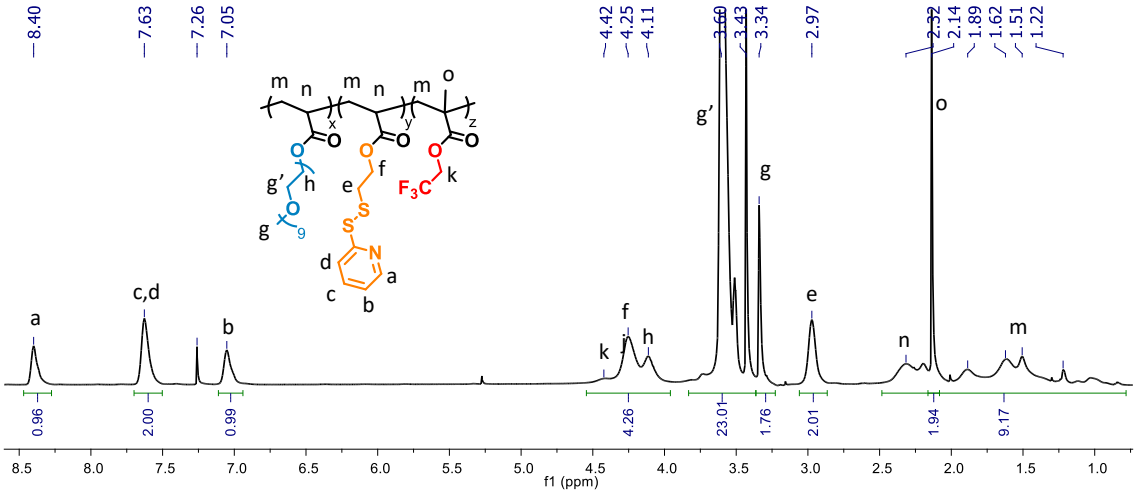


Figure S17: ^{1}H NMR spectrum of p(PEGA-co-PDSA-co-co-TFEMA), **P6.**

Gel permeation chromatography (GPC) for P1, P2, P3 and PC

Average molecular weight of all random copolymers were estimated by GPC (THF) using poly(methyl methacrylate) (PMMA) standards with a refractive index detector.

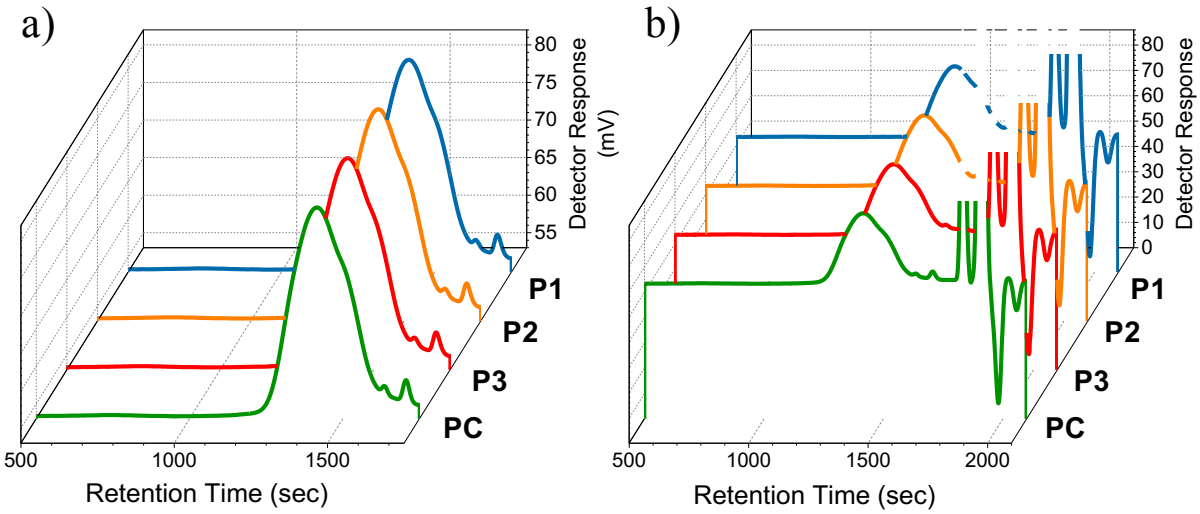


Figure S18. GPC of **P1**, **P2**, **P3** and **PC;** a) Polymer peaks are zoomed in. b) Complete GPC run of 35 min.

Dynamic light scattering (DLS) for P1, P2, P3 and PC

Table S1. Polymer characterization via GPC and ^{1}H NMR. Size change of polymer assemblies in response to crosslinking and acid degradation.

				Size (nm)[c]		
polymer	Mn (PDI)[a]	Comonomer feed ratio (OEG:PDS:THP:CF_3)	Actual monomer ratio (OEG:PDS:THP:CF_3)[b]	Polymer assembly	Polymer nanogel	Acid Degraded nanogel
P1	8 800 (1.77)	30:15:45:10	30:12:29:29	6	8	9
P2	11 900 (2.50)	30:15:35:20	25:10:20:44	8	9	10
P3	11 200 (2.35)	30:15:25:30	27:10:13:50	8	9	10
PC	11 700 (2.57)	30:15:25:30[d]	27:10:22:41[d]	13	13	13

[a]Mn measured by GPC. [b]Actual ratio is calculated based on ^{1}H NMR acquired in $CDCl_3$. [c]Size distribution is measured via DLS. [d]CHA instead of THP for PC polymer.

Table S2. Size change of polymer assemblies in response to crosslinking and acid degradation by DLS measurement.

	Peak 1	**Volume %**	**Peak 2**	**Volume %**	**Z-Average**	**PDI (d.nm)**	**Intercept**
P1	6.1	99.9	107	0.1	20.87	0.755	0.885
P1X	7.9	99.9	108	0.1	17.39	0.521	0.885
P1H	8.5	100	-	-	22.52	0.661	0.900
P2	7.7	100	-	-	12.32	0.316	0.872
P2X	9	100	-	-	13.58	0.284	0.888
P2H	9.5	100	-	-	18.29	0.399	0.929
P3	8.5	100	-	-	13.22	0.309	0.890
P3X	9.3	100	-	-	14.27	0.297	0.931
P3H	9.9	100	-	-	17.09	0.386	0.931
PC	13.3	100	-	-	17.08	0.159	0.934
PCX	13.39	99.9	794.8	0.1	22.38	0.335	0.887
PCH	12.56	100	-	-	15.98	0.145	0.922

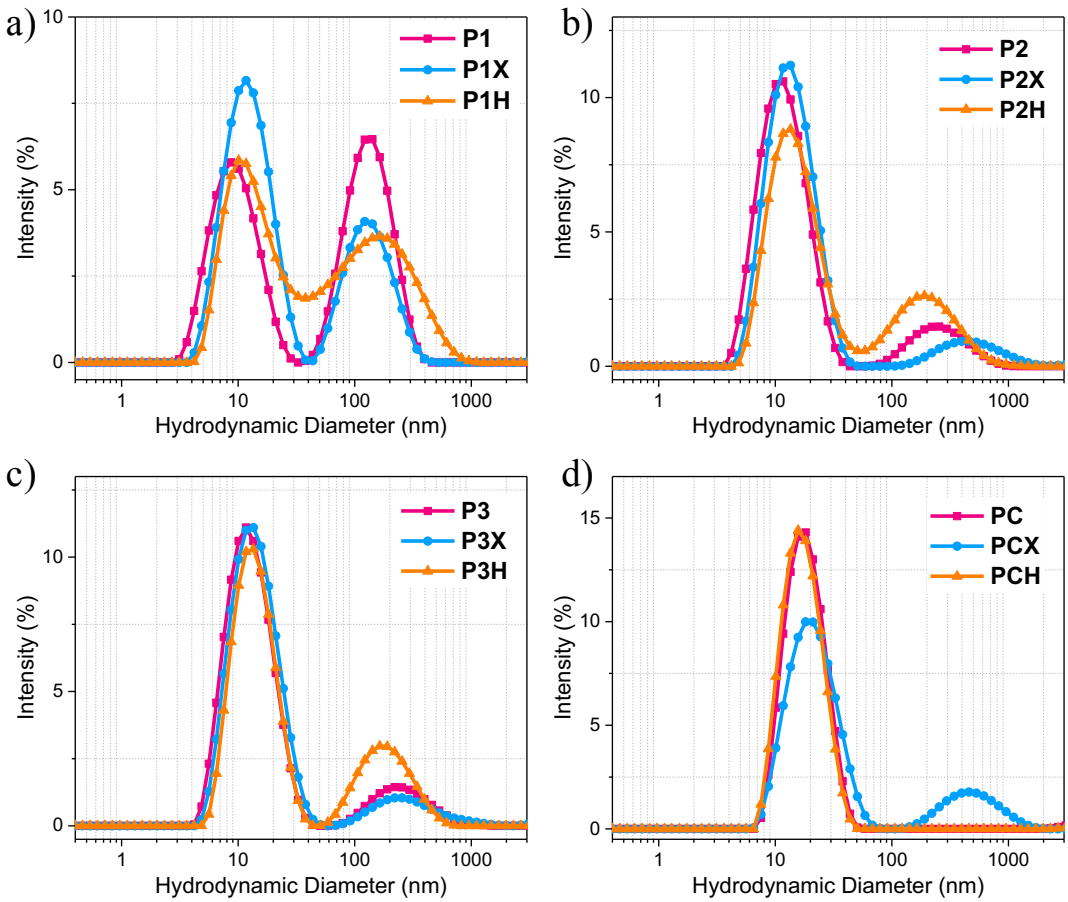


Figure S19. Intensity% weighted DLS size distribution of polymer assembly, polymer nanogel and acid degraded polymer nanogel of **P1-P3** and **PC**.

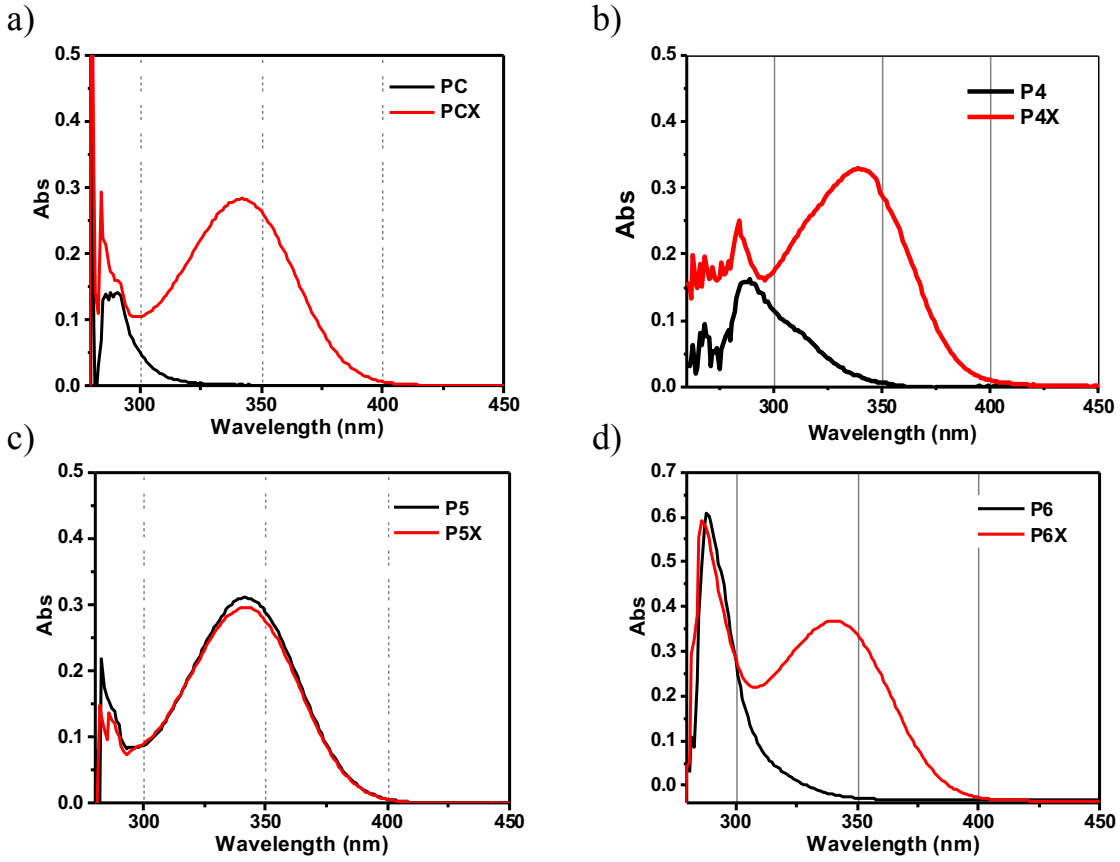


Figure S20. Absorption spectra of pyridothione at 342 nm, confirming the formation of polymer nanogel for **PC**, and **P4-P5**.

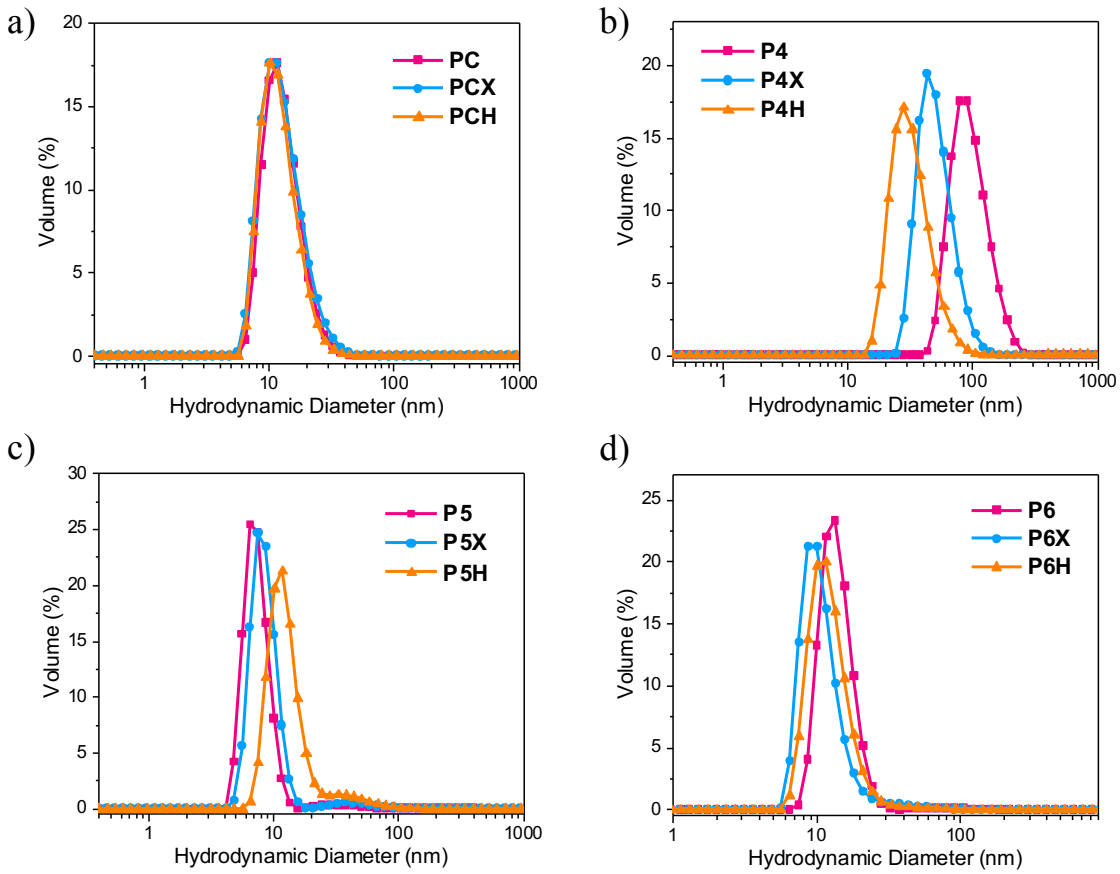


Figure S21. Volume% weighted DLS size distribution of polymer assembly, polymer nanogel and acid degraded polymer nanogel for **PC** and, **P4-P6**. There is no size change observed for **PC** after crosslinking and acid hydrolysis, which could be due to lack of THP acid degradable groups. For **P4**, **P5** and **P6**, it was challenging to obtain stable polymer assembly because of their high hydrophobicity. Therefore, size change in response to crosslinking and hydrolysis were not as consistent as other polymer series.

Table S3. Size change of polymer assemblies **PC**, **P4**, **P5** and **P6** in response to crosslinking and acid degradation by DLS measurement.

	Size (nm)[a]		
polymer	Polymer assembly	Polymer NG	Hydrolyzed NG
PC	13	13	13
P4	99	52	33
P5	8	7	12
P6	14	12	13

[a]Size distribution is measured via DLS

^{19}F NMR of P4, P5 and P6.

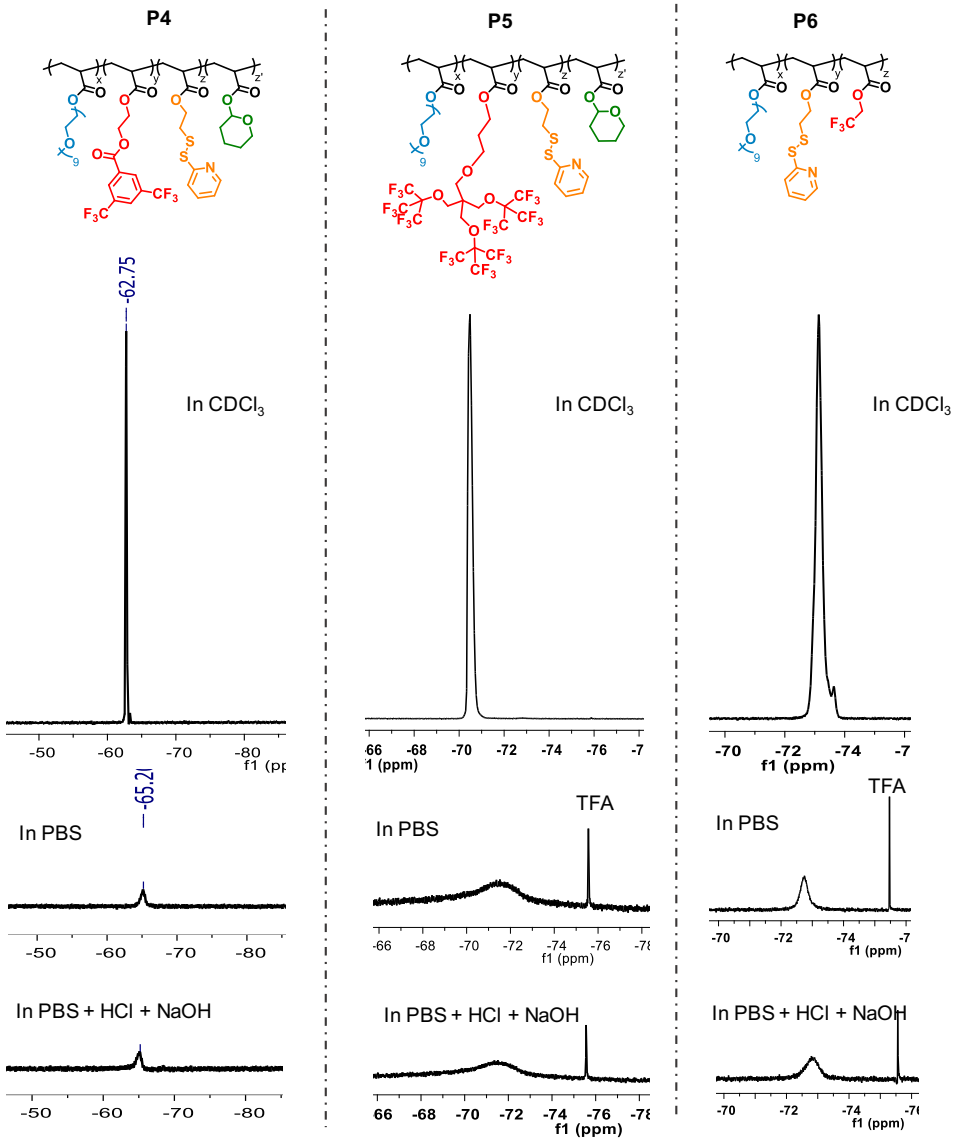


Figure S22. ^{19}F NMR of **P4**, **P5** and **P6** in $CDCl_3$ and PBS buffer.

^{19}F NMR of P1, P2, P3 and PC.

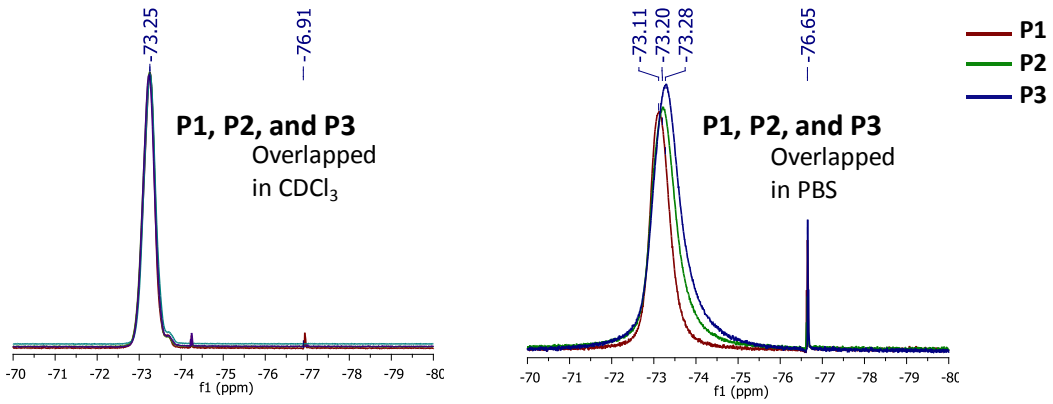


Figure S23. Stacked ^{19}F NMR of **P1**, **P2**, **P3** and **PC** in $CDCl_3$ and PBS buffer

Table S4. Evolution of T_1 in **P1**, **P2**, **P3** and **PC** in response to addition of DTT and HCl

	T_1 Relaxation time (ms)			
polymer	Polymer in $CDCl_3$	Polymer assembly (**P**)[a]	Polymer nanogel (**PX**)[a]	Acid Degraded Nanogel (**PH**)[a]
P1	518	360	358	406
P2	520	362	358	371
P3	526	363	357	380
PC	533	360	357	381

[a]Measurements were done in PBS/D_2O (90/10, v/v)

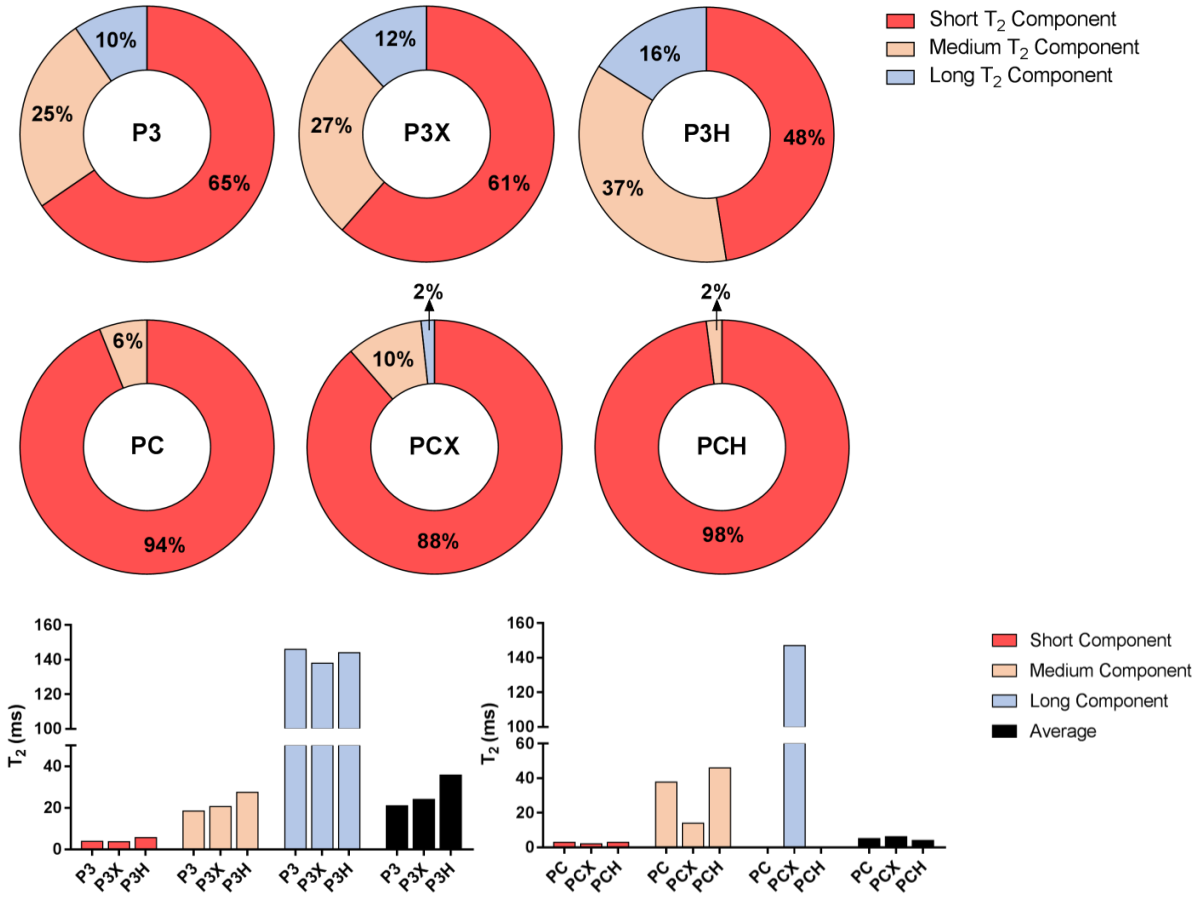
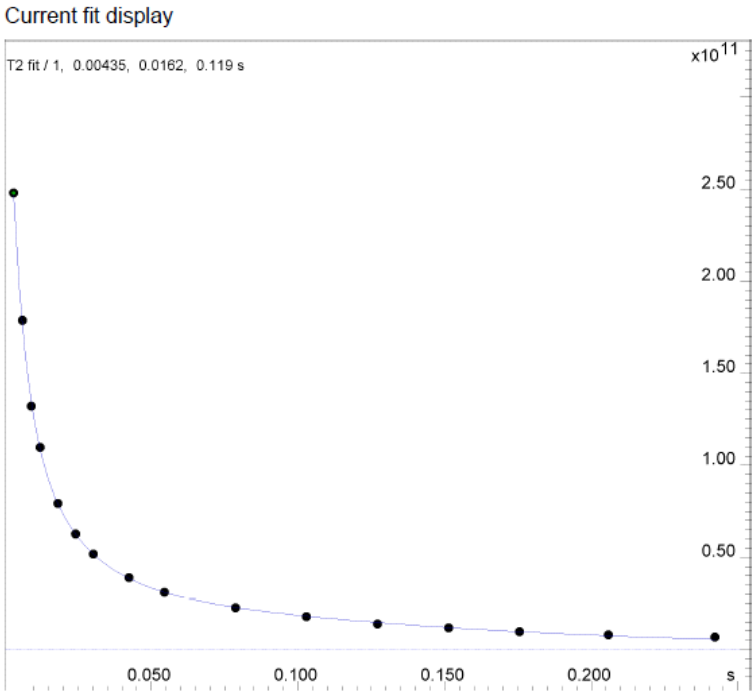


Figure S24. Evolution of T2 in P3 and PC upon DTT crosslinking and acid degradation. Graph is designed to represent the increase of T2 value for all component, increase of relative intensity for the longer T2 component and the decrease of relative intensity for the shorter T2 component resulting in increased overall T2 value for P3.

P1



P1X

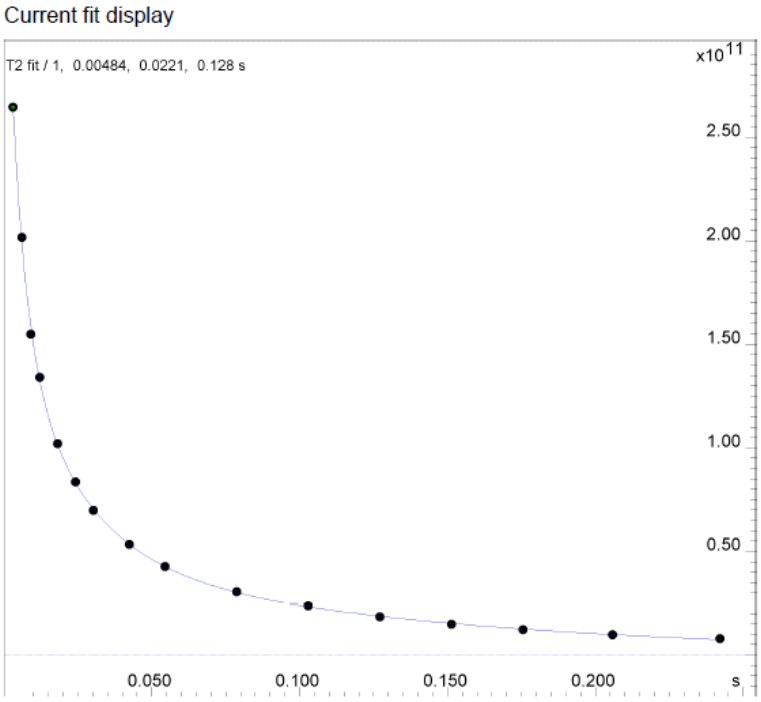


Figure S25. Exponential curve fitting in T_2 for **P1, P1X**.

P1H

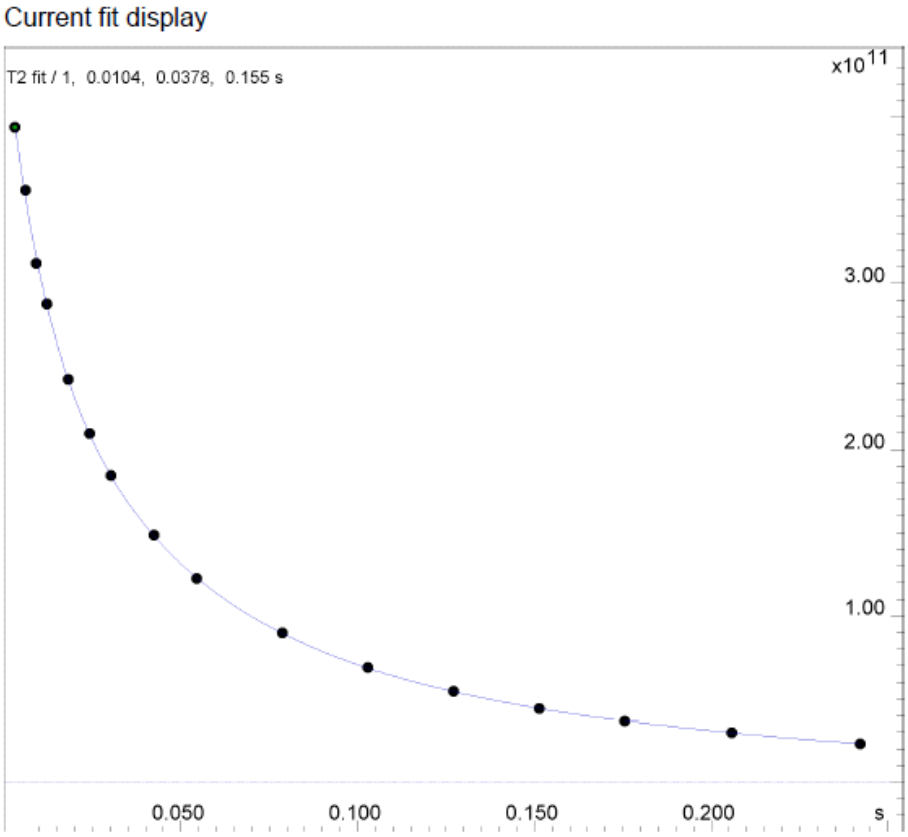


Figure S26. Exponential curve fitting in T_2 for **P1H**.

Diffusion NMR of P1 and P1H

Table S5. Fraction (f) and hydrodynamic diameter (D) of each component from the two-component fitting of diffusion NMR data for samples P1 and P1H.

	f_a (%)	D_a (nm)	f_b (%)	D_b (nm)
P1	54	3.6	46	9.8
P1H	57	4.4	43	12.6

^{1}H and ^{19}F MRI Phantom Imaging

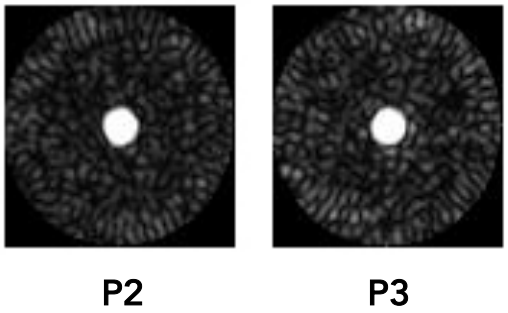


Figure S27. ^{19}F MRI phantom images of **P2** and **P3** at 15mM concentration in H_2O.

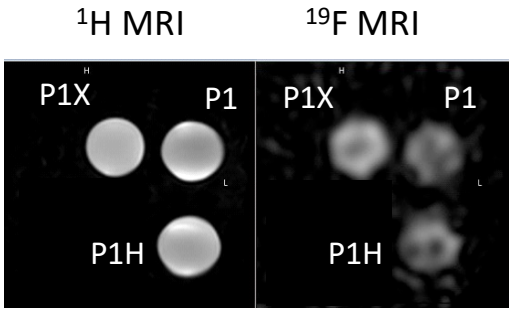


Figure S28: (a) ^{1}H and ^{19}F phantom MRI images of P1 series at 20 mg/mL concentration in PBS buffer.

^{1}H and ^{19}F MRI Animal Imaging

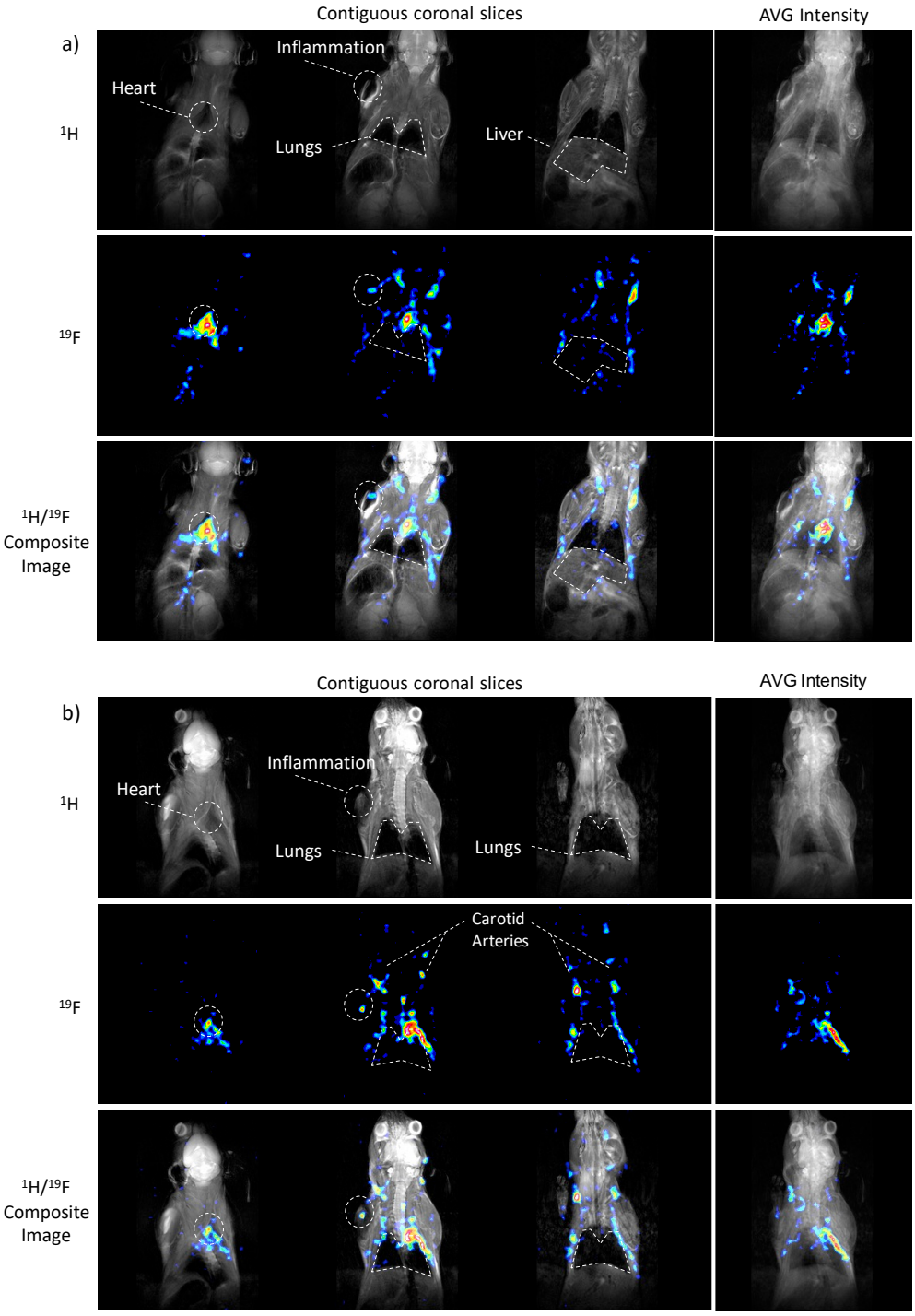


Figure S29: *In vivo* ^{1}H and ^{19}F contiguous coronal slices of mouse after 2 hours (a) or 72 hours (b).

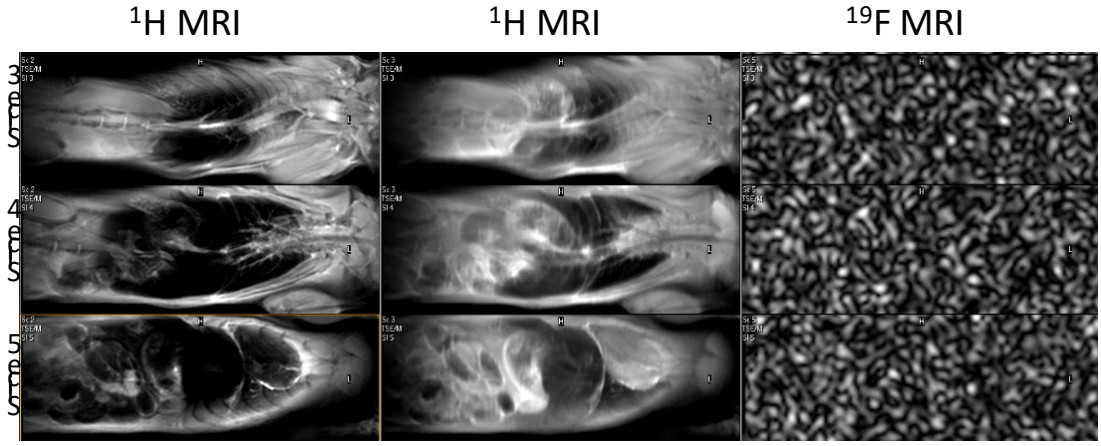


Figure S30: *In vivo* ^{1}H and ^{19}F MRI images of mouse without any polymer injection, eliciting that there is no ^{19}F signal inherent to animal body.

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