SUPPORTING INFORMATION

Embedding Well-Defined Responsive Hydrogels with Nano-Containers: Tunable Materials from Telechelic Polymers and Cyclodextrins

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1. Materials and Characterization.

4-Cyano-4-(phenylcarbonothioylthio)pentanoic acid , 3-buten-1-ol, 4-dimethylaminopyridine (DMAP), 2-hydroxyethyl methacrylate (HEMA), di(ethylene glycol) methyl ether methacrylate (DEGMA), 2,2′-azobis(2-methylpropionitrile) (AIBN), 4,4'-azobis(4-cyanovaleric acid) (ACVA), 2,2-dimethoxy-2-phenylacetophenone (DMPA), pentaerythritol tetrakis(3-mercaptopropionate) (PETMP) and 5,5'-dithio-*bis*-(2-nitrobenzoic acid) were purchased from Sigma-Aldrich Co. (USA) and used as received. 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was obtained from Alfa Aesar Co. (USA). Other chemicals and solvents were purchased from Merck Co. (Germany) and used as obtained without further purification unless otherwise noted. Synthesis of furan-protected maleimide containing alcohol[1] (**1**), 4-(3-Hydroxypropyl)-10-oxa-4-azatricyclo[5,2,1,$0^{2,6}$]dec-8-ene-3,5-dione (Azo-M)[2] and thiol-functionalized β-cyclodextrin (β-CD$(SH)_7$)[3] were conducted according to the reported procedures. The gel permeation chromatography (GPC) measurements of polymers were carried out using a Shimadzu GPC analysis system with PSS WinGPC Unity software. PSS Gram (length/ID 300 mm × 8 mm, 10 μm particle size) column was calibrated with polymethyl methacrylate standards, using refractive index detector (RID-10A). DMAc was used as eluent at a flow rate of 1 mL/min at 30 ^{o}C. NMR spectra were recorded on a Varian 400-MHz spectrometer.

2. Synthesis of Thiol Reactive Functional Group-containing CTAs and Azo Compounds.

Synthesis of Furan Protected Maleimide-Functionalized CTA (CTA-FM):

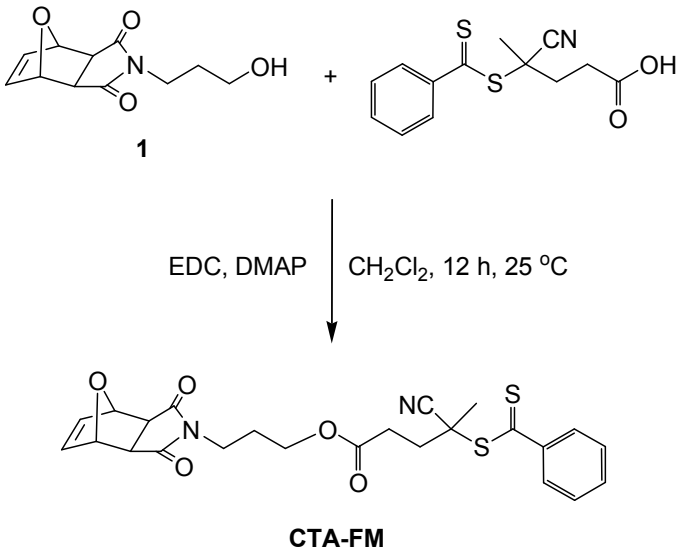


Figure S1. Synthesis of furan protected maleimide-functionalized CTA (CTA-FM).

In a 10 mL round-bottom flask equipped with a stir bar, a solution of 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (200.0 mg, 0.72 mmol), alcohol (**1**) (210.0 mg, 0.94 mmol), and DMAP (18.0 mg, 0.15 mmol) in 4 mL of CH_2Cl_2 was cooled to 0 °C under N_2. In another flask, EDC (150.0 mg, 0.78 mmol) was dissolved in 2 mL of CH_2Cl_2 and added dropwise to the reaction flask. The reaction was stirred at 0 °C for one hour and then allowed to warm to room temperature overnight. Then, the reaction medium was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated to give viscous oil. The crude product was purified by column chromatography on silica with hexane and EtOAc (1:1) affording the final product as a red oil (284.0 mg, 81 %). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.87-7.93 (m, 2H); 7.52-7.59 (m, 1H); 7.35-7.44 (m, 2H); 6.50 (s, 2H); 5.25 (s, 2H); 4.07 (t, 2H, J = 6.4 Hz); 3.59 (t, 2H, J = 7.2 Hz); 2.84 (s, 2H); 2.40-2.74 (m, 4H); 1.95 (s, 3H); 1.90-1.97 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 222.3, 176.1, 171.4, 144.5, 136.4, 132.9, 128.5, 126.7, 118.5, 80.9, 61.8, 47.4, 45.7, 35.6, 33.4, 29.7, 26.5, 24.1. Anal. Calcd. [$C_{24}H_{24}N_2O_5S_2$]: C, 59.48; H, 4.99; N, 5.78; S, 13.23. Found: C, 60.11; H, 5.09; N, 5.66; S, 12.88.

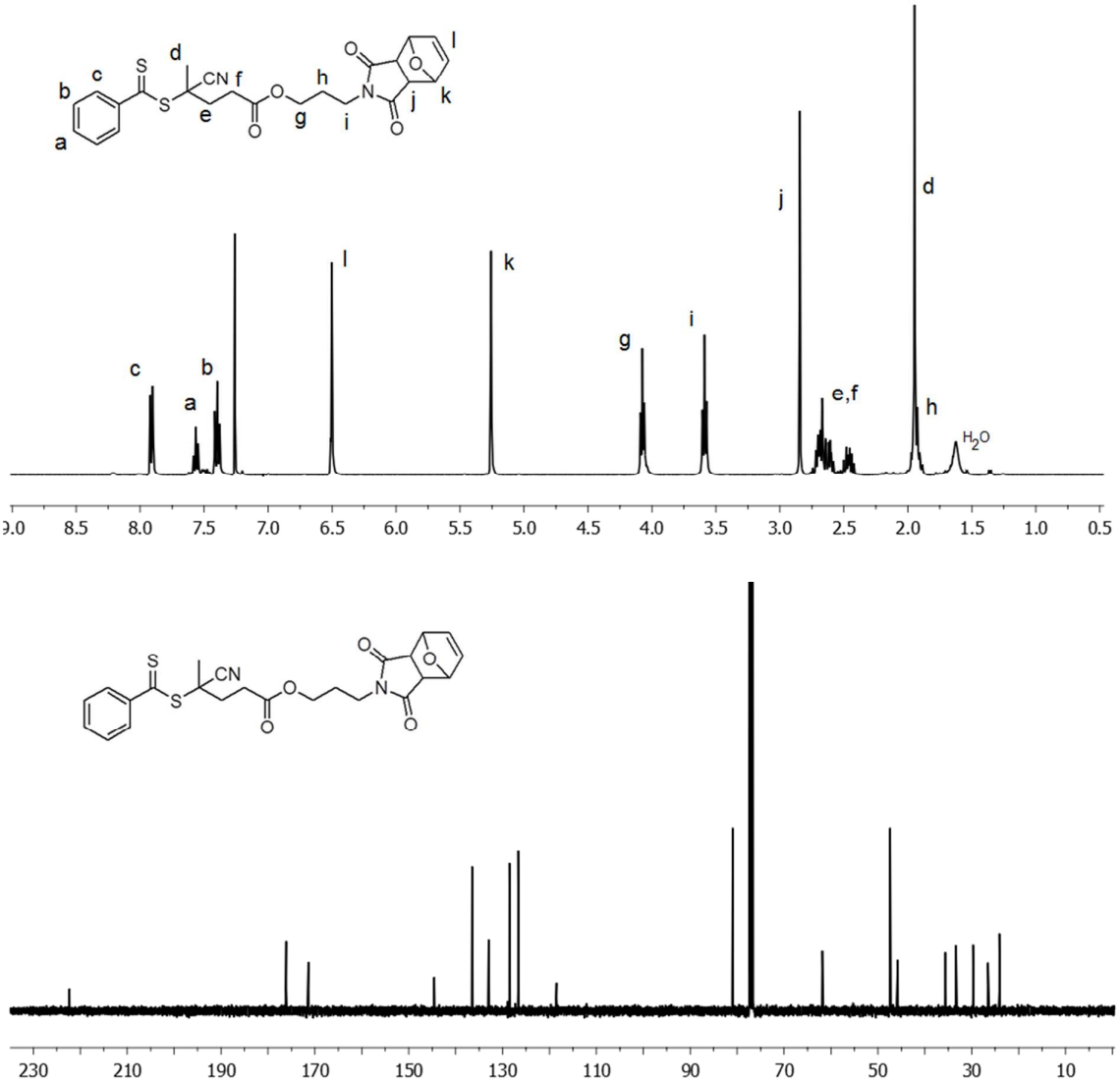


Figure S2. ^{1}H and ^{13}C NMR spectra of CTA-FM.

Synthesis of Vinyl-Functionalized CTA (CTA-V):

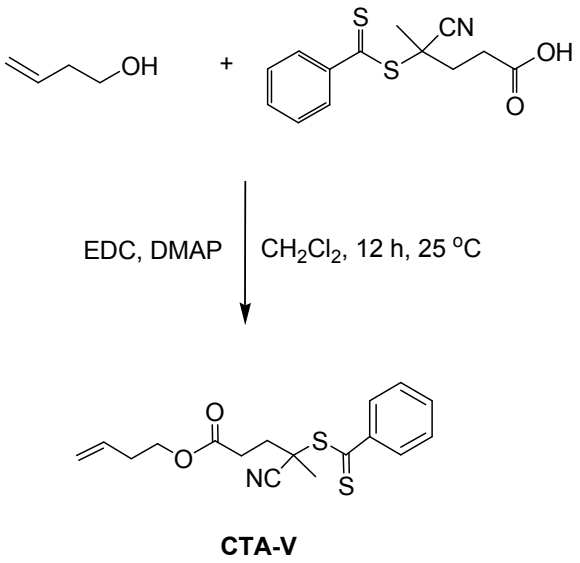


Figure S3. Synthesis of vinyl-functionalized CTA (CTA-V).

In a 10 mL round-bottom flask equipped with a stir bar, a solution of 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (200.0 mg, 0.72 mmol), 3-buten-1-ol (68.0 mg, 0.94 mmol), and DMAP (18.0 mg, 0.15 mmol) in 4 mL of CH_2Cl_2 was cooled to 0 °C under N_2. EDC (150.0 mg, 0.78 mmol) was dissolved in 2 mL of CH_2Cl_2 and added dropwise to the reaction flask. The reaction was stirred at 0 °C for one hour and then allowed to warm to room temperature overnight. The reaction medium was then washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated to give viscous oil. The crude product was purified by column chromatography on silica with hexane and EtOAc (4:1) to give final product as a red oil (206.0 mg, 86 %). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.87-7.95 (m, 2H); 7.53-7.60 (m, 1H); 7.35-7.45 (m, 2H); 5.72-5.88 (m, 1H); 5.08-5.14 (m, 2H); 4.17 (t, 2H, J = 8.0 Hz); 2.38-2.73 (m, 6H); 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 222.2, 171.5, 144.5, 133.7, 133.0, 128.5, 126.6, 118.5, 117.5, 64.0, 45.7, 33.4, 33.0, 29.8, 29.7, 24.1. Anal. Calcd. [$C_{17}H_{19}NO_2S_2$]: C, 61.23; H, 5.74; N, 4.20; S, 19.23. Found: C, 60.76; H, 6.04; N, 4.46; S, 20.08.

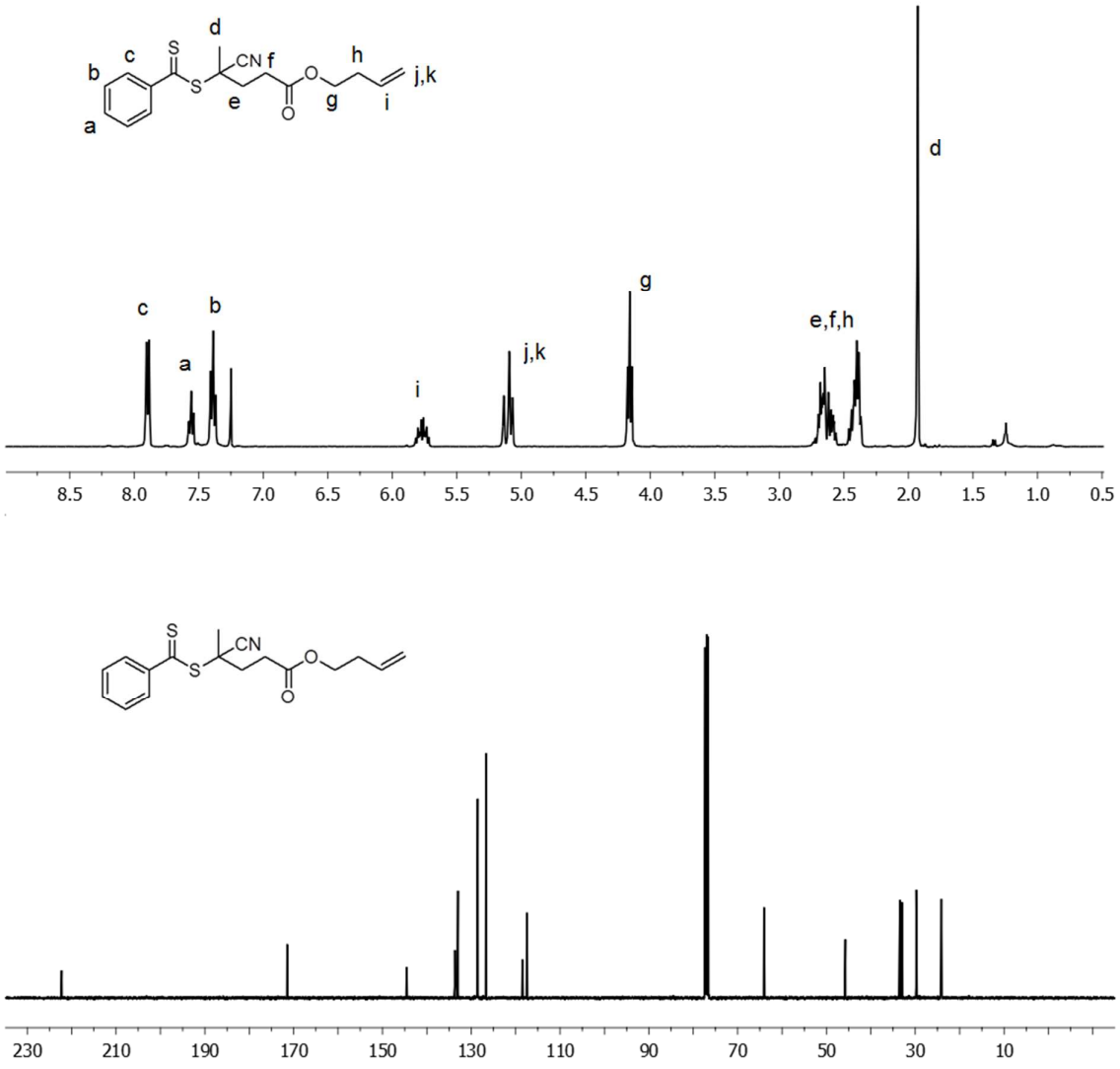


Figure S4. ^{1}H and ^{13}C NMR spectra of CTA-V.

Synthesis of Bisvinyl-Functionalized Azo Initiator (Azo-V):

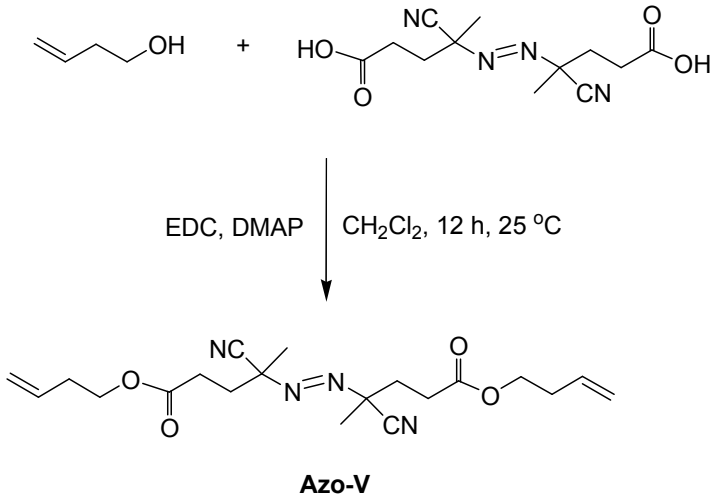


Figure S5. Synthesis of bisvinyl-functionalized azo initiator (Azo-V).

To a stirred solution of 4,4'-azobis(4-cyanovaleric acid) (1.0 g, 3.57 mmol), 3-buten-1-ol (670.0 mg, 9.27 mmol) and DMAP (175.0 mg, 1.43 mmol) in 20 mL of dry CH_2Cl_2 at 0 °C, a 10 mL solution of EDC (1.50 g, 7.85mmol) was added dropwise. The reaction was stirred at 0 °C for one hour and then allowed to warm to room temperature overnight. The reaction medium was then washed with saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated to give a white solid. The crude product was purified by column chromatography on silica with hexane and EtOAc (1:1) to give final product as white solid. (1.05 g, 76 %). ^{1}H NMR ($CDCl_3$) δ (ppm): 5.71-5.82 (m, 2H); 5.06-5.13 (m, 4H); 4.16 (t, 4H, *J* = 7.9 Hz); 2.29-2.60 (m, 12H); 1.72 (s, 3H); 1.67 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.2, 125.9, 117.4, 71.8, 64.0, 33.1, 32.9, 29.0, 23.7. Anal. Calcd. [$C_{20}H_{28}N_4O_4$]: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.14; H, 7.94; N, 13.77.

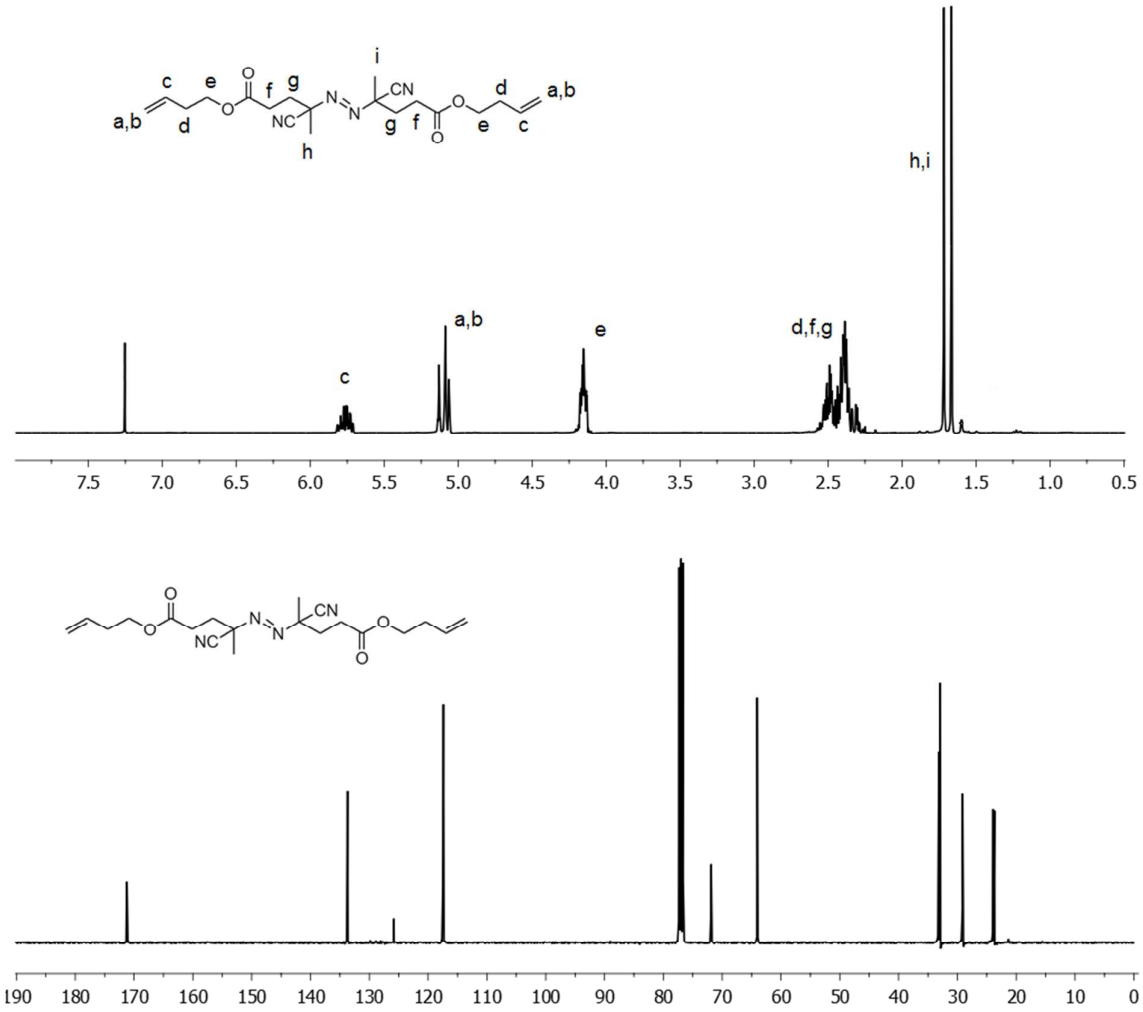


Figure S6. ^{1}H and ^{13}C NMR spectra of Azo-V.

3. Synthesis of Maleimide and Vinyl Functionalized Telechelic Polymers.

Typical Procedure for RAFT Homopolymerization / Copolymerization of DEGMA and HEMA Monomers with CTA-FM and CTA-V: Polymerization procedure for copolymers furan-protected maleimide containing copolymer of HEMA and DEGMA (P-FM-HD) and vinyl-terminated copolymer of HEMA and DEGMA (P-V-HD): DEGMA (132.0 mg, 0.70 mmol), HEMA (91.0 mg, 0.70 mmol), CTA (0.047 mmol, 22.90 mg for CTA-FM and 15.70 mg for CTA-V) and AIBN (0.77 mg, 0.0047 mmol) were dissolved in DMF (1.40 mL) and placed in a sealed round-bottom flask equipped with a magnetic stir bar. The reaction mixture was purged with nitrogen for 15 min and stirred at 70 °C for 12 h. After polymerization, the solvent was removed under reduced pressure and the residue was re-dissolved in minimum

amount of methanol before precipitating into the cold ether. The precipitated polymer was dried under vacuum and characterized using SEC and ^{1}H NMR.

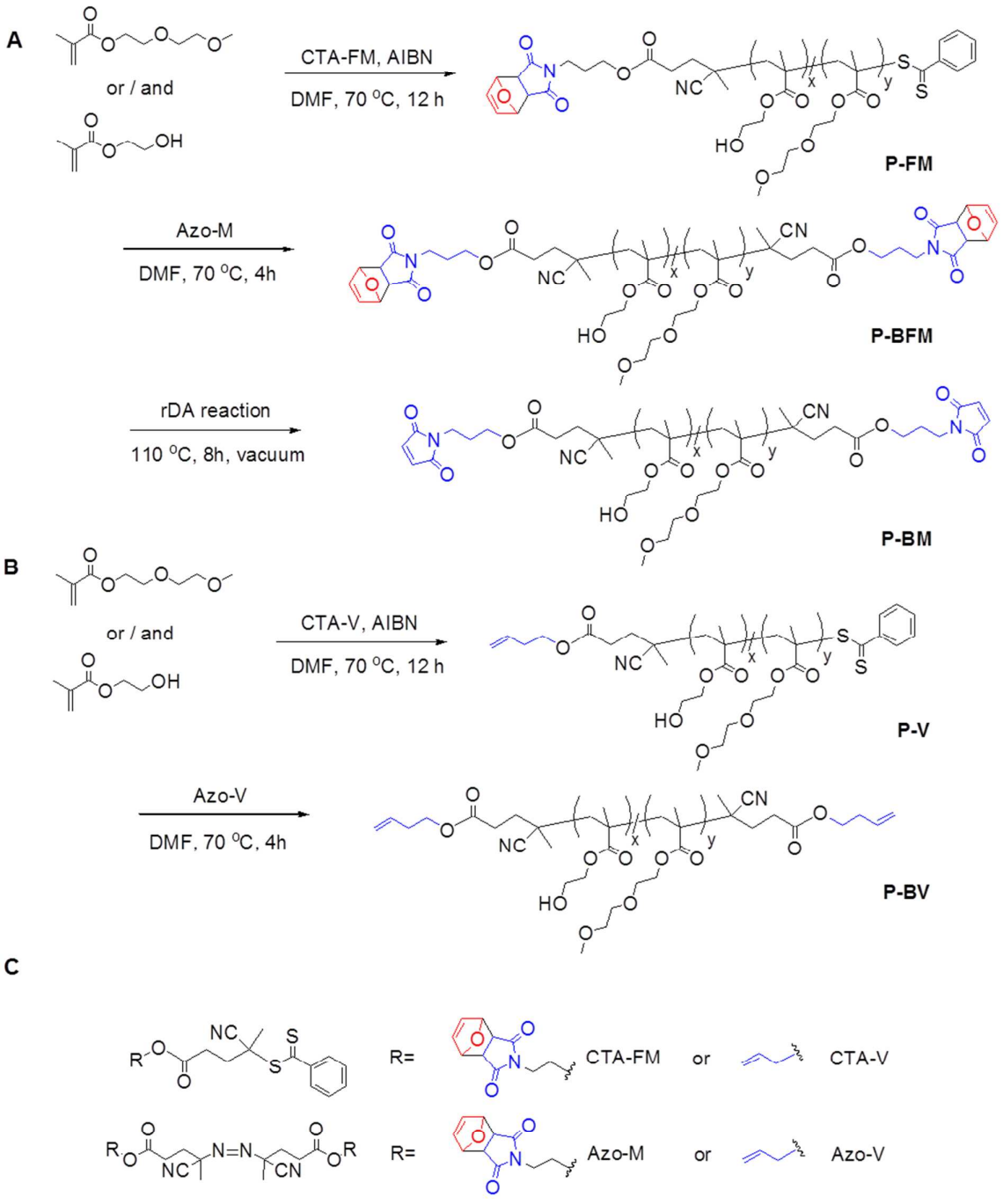
Typical Radical Cross-Coupling of Thiocarbonylthio End-Functional Polymers with Functionalized Azo Initiators:

Synthesis of bis-furan-protected maleimide containing copolymer (P-BFM-HD): Polymer P-FM-HD (100.0 mg, 0.028 mmol) and Azo-M (480.0 mg, 0.70 mmol) were dissolved in DMF (4.0 mL) in a sealed tube. The reaction mixture was purged with nitrogen for 15 min and stirred at 70 °C for 4 h. After the reaction, the solvent was removed in vacuo and the resulting polymer P-BFM-HD was purified by dialysis (1:1 EtOAc:MeOH, MWCO 6-1000 Da), (Yield: 85 %).

Synthesis of bisvinyl containing copolymer (P-BV-HD): Polymer P-V-HD (100.0 mg, 0.026 mmol) and Azo-V (257.0 mg, 0.66 mmol) were dissolved in DMF (4 mL) in a sealed tube. The mixture was purged with nitrogen for 15 min and stirred at 70 °C for 4 h. Then, the solvent was removed in vacuo and the resulting polymer P-BV-HD was purified by precipitating into the cold ether (repeated twice), (Yield: 67 %).

Typical Procedure for Activation of Maleimide Functional Groups:

Polymer P-BFM-HD (50 mg, 0.014 mmol) was dissolved in MeOH (30 mL) in a 100 mL round-bottom flask. The solvent was removed to form a thin film of polymer on the flask surface. The polymer was heated under vacuum at 110 ^{o}C for 8 h to afford telechelic bis-maleimide containing copolymer P-BM-HD, quantitatively.



Scheme S1. Synthesis of (A, B) maleimide and vinyl-functionalized telechelic polymers, (C) Functional group-containing CTAs and azo compounds used in this work.

Table S1. Conversion, molar mass, and polydispersity data for the RAFT mediated polymers.

Entry	Polymer [a]	$F_{theo.}$ [b]	$F_{cal.}$ [c]	% Yield	$M_{n,\ theo.}$	$M_{n,\ NMR}$ [c]	$M_{n,\ GPC}$ [d]	M_w/M_n [d]
1	P-FM-D	1 : 0	-	76.0	4780	4250	3860	1.27
2	P-FM-HD	1 : 1	1 : 1.32	71.0	3870	4015	3590	1.29
3	P-FM-H	0 : 1	-	88.0	3930	3840	3350	1.32
4	P-V-D	1 : 0	-	72.0	4400	3720	3460	1.26
5	P-V-HD	1 : 1	1 : 1.37	77.0	4010	3640	3550	1.31
6	P-V-H	0 : 1	-	85.0	3660	3590	3220	1.32

[a]$[M]_o$ / [CTA] / [AIBN] : 30 / 1 / 0.1; $[M]_o$: 1 M; CTA : CTA-FM for P-FM's and CTA-V for P-V's; Temp. : 70 °C; Time: 12 h; Solvent : DMF. [b]$F_{theo.}$= [DEGMA] : [HEMA]. [c]$F_{cal.}$= [DEGMA] : [HEMA], determined by ^{1}H NMR. [d]Estimated by SEC eluted with DMAc using poly(methyl methacrylate) standards.

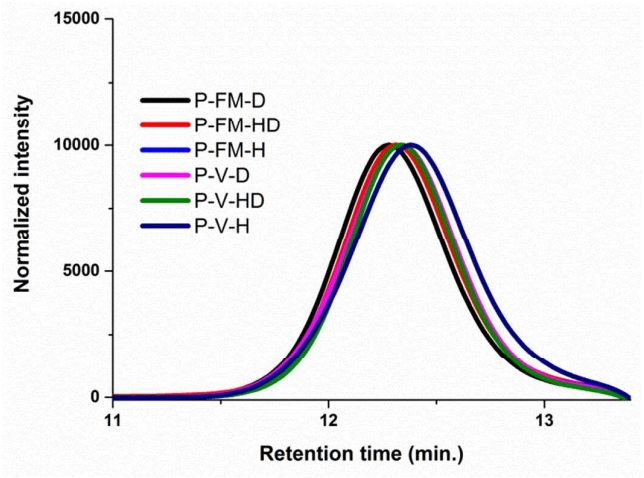


Figure S7. SEC traces of RAFT polymers.

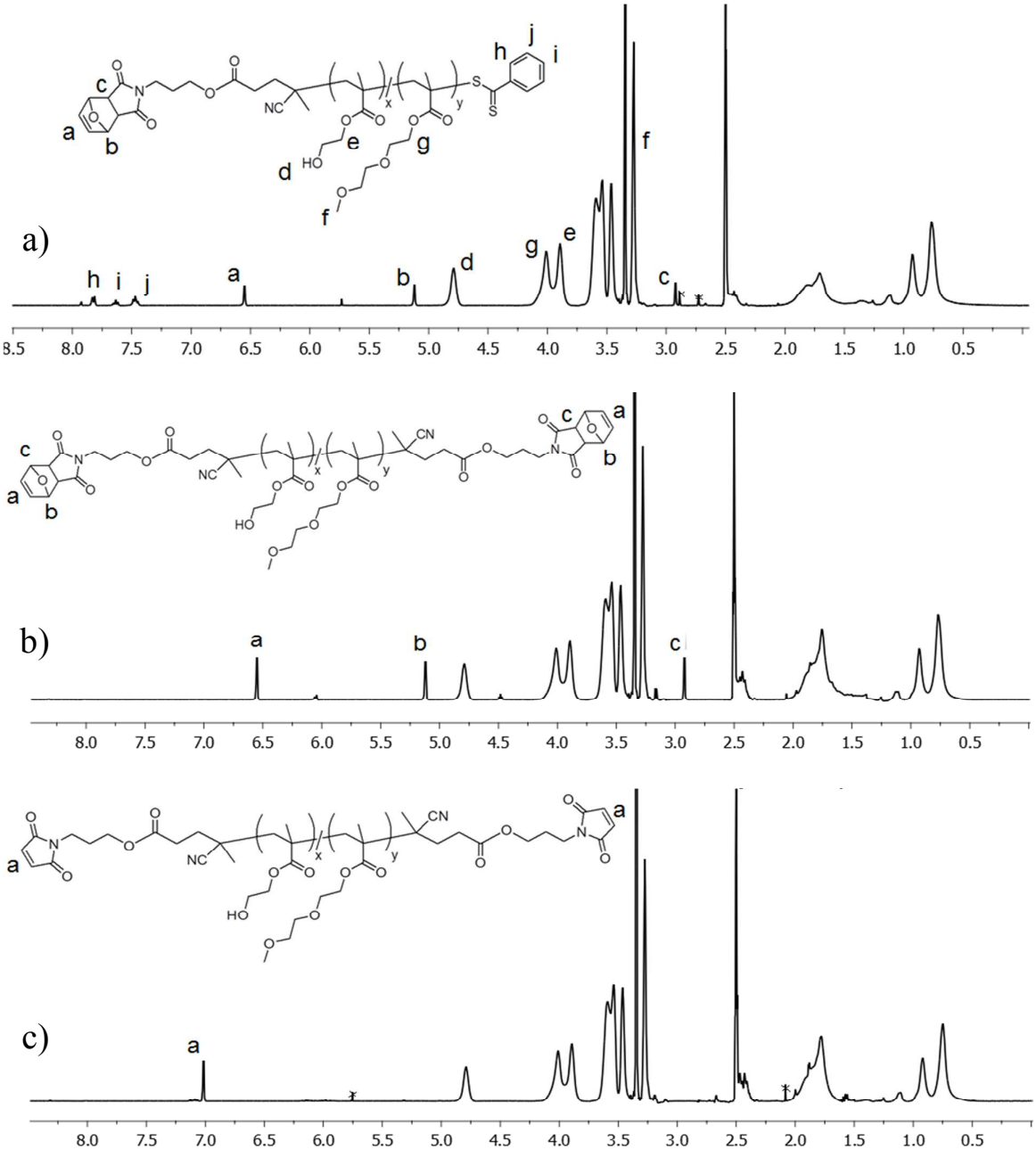


Figure S8. ^{1}H NMR spectra of polymers a) P-FM-HD b) P-BFM-HD and c) P-BM-HD (in *d*-DMSO).

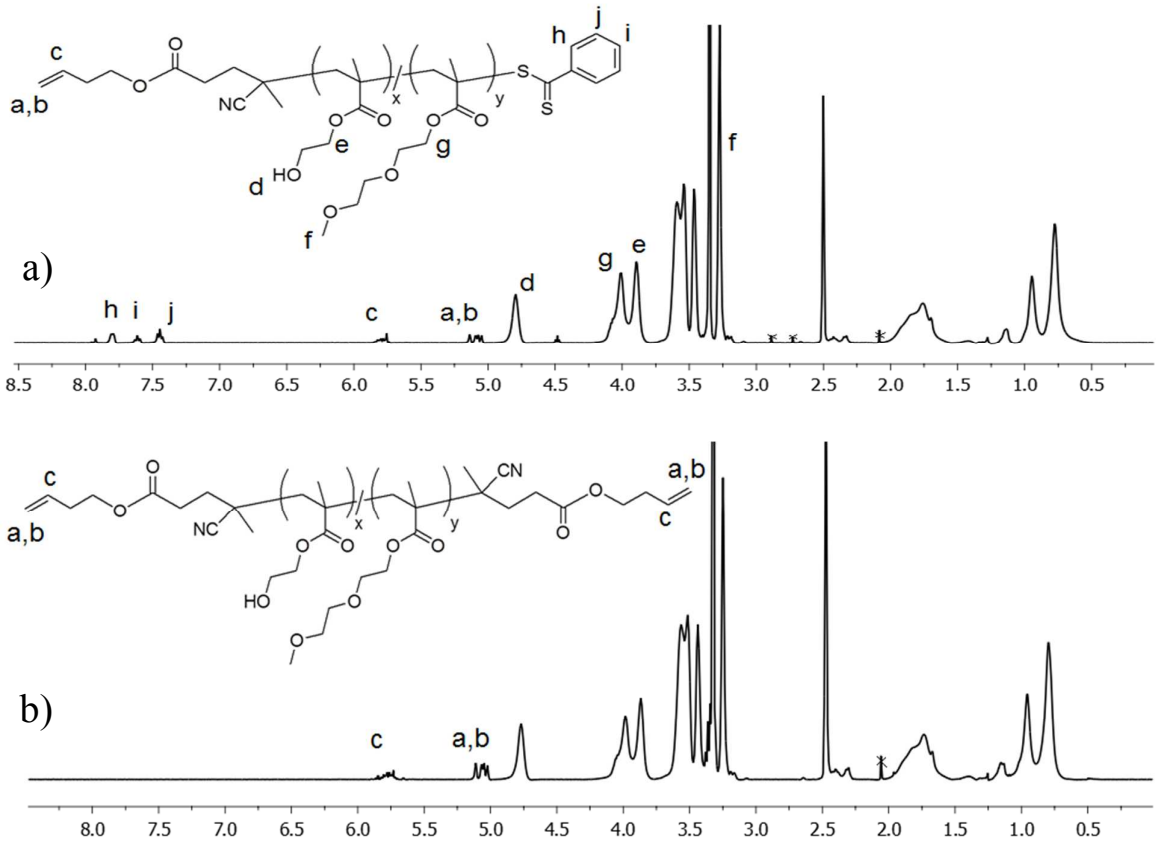


Figure S9. ^{1}H NMR spectra of polymers a) P-V-HD and b) P-BV-HD.

4. Hydrogel formation by using tetrathiol-functionalized crosslinker PETMP:

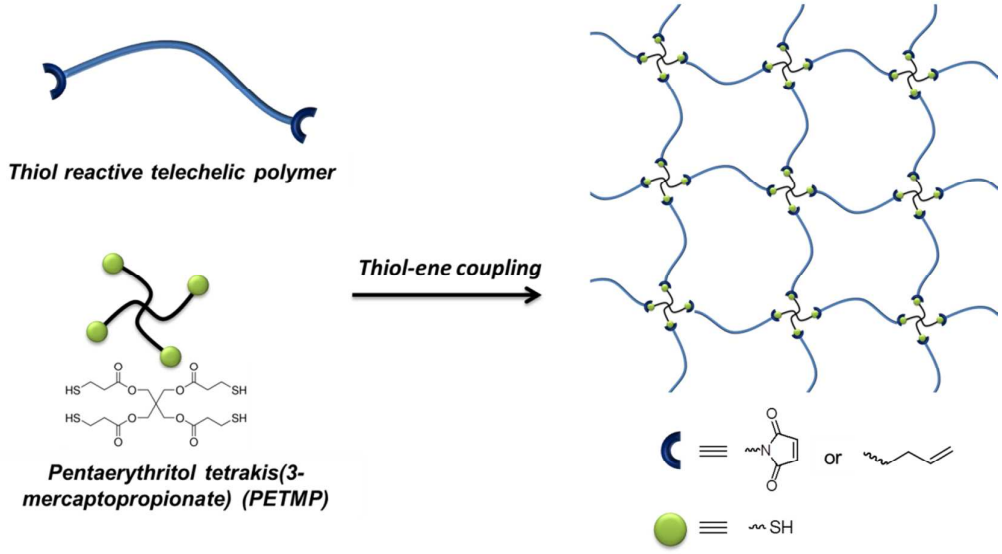


Figure S10. Schematic illustration of hydrogel formation using a tetra-functional crosslinker.

Hydrogel H-PM-H: In a vial, P-BM-H (50.0 mg, 12.5 $x10^{-3}$ mmol) was placed and dissolved in DMF (100 μL). A solution of PETMP (3.07 mg, 6.28 $x10^{-3}$ mmol) and triethylamine (0.010 μL, 2.5 $x10^{-3}$ mmol) in DMF (100 μL) was then added to this solution. The mixture was sonicated briefly. Hydrogel formation was rapid and in about half of a minute there was no flow of sample. Gelation was continued for 12 h to ensure complete conjugation. After hydrogel formation, unreacted reagents were removed by washing the gel with DMF followed by distilled water several times. Obtained gel sample was frozen and lyophilized to yield dried hydrogel.

Hydrogel H-PV-H: P-BV-H (50.0 mg, 13.6 $x10^{-3}$ mmol) was placed in a vial and dissolved in DMF (100 μL). A mixture of PETMP (3.32 mg, 6.8 $x10^{-3}$ mmol) and DMPA (0.2 eq. per thiols) in DMF (100 μL) was then added to this solution. The mixture was irradiated with UV light for 30 minutes at 365 nm. After hydrogel formation, unreacted species were removed by washing the hydrogel with DMF and distilled water several times. Dried hydrogel was obtained by freeze-drying the swollen gel sample.

Table S2. Gel conversions and total thiol contents of hydrogel synthesized by tetrathiol-functionalized crosslinker PETMP.

Entry	Hydrogel	Polymer	Feed Ratio [-SH]:[alkene]	% Gel Conv.	Thiol Content[a] (mmol x 10^{-4})	% Thiol Consumption
1	H-PM-H	P-BM-H	1 : 1	97.0	24.5 / 2.06 (±0.37)	92.0
2	H-PV-H	P-BV-H	1 : 1	91.0	26.0 / 3.56 (±0.44)	86.0

[a] Thiol amount (molar) used for synthesis of hydrogel / thiol amount (molar) determined in hydrogel sample (Data in triplicate).

References:

1. B. J. Neubert and B. B. Snider, *Org. Lett.,* 2003, **5**, 765-768.
2. K. L. Heredia, G. N. Grover, L. Tao and H. D. Maynard, *Macromolecules*, 2009, **42**, 2360-2367.
3. M. T. Rojas, R. Koniger, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.*, 1995, **117**, 336-343.