Supporting Information

Synthesis of Multiple Stimuli-Responsive Degradable Block Copolymers via Facile Carbonyl Imidazole-Induced Postpolymerization Modification

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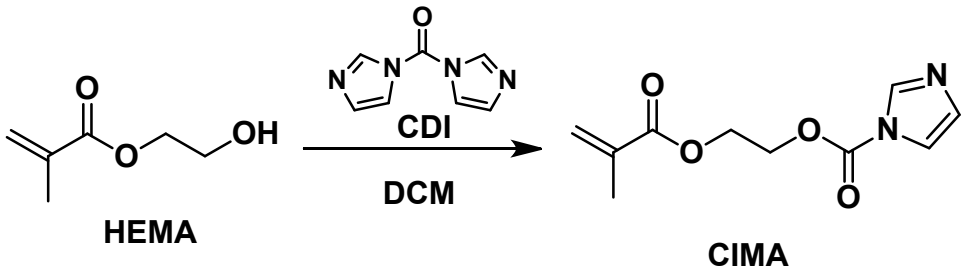
I) Synthesis and characterization of triple stimuli responsive TrSP degradable block copolymer

Synthesis of *o*-nitrobenzylamine (ONB). 2-nitrobenzyl bromide (4.1 g, 19.0 mmol) was added dropwise to a clear suspension containing cystamine hydrochloride (1.46 g, 19.0 mmol), LiOH (0.91 g, 38.0 mmol), in distilled water (25 mL) and ethanol (EtOH, 100 mL). The reaction mixture was stirred vigorously for 1 hr at room temperature, evaporated, and then extracted with dichloromethane (DCM, 250 mL) two times. Solvents were removed by rotary evaporation and the product was purified by silica gel column chromatography using dichloromethane (DCM)/methanol (MeOH) (4/1 v/v). The product, yellow oil, was collected as the second of the total two bands off a silica gel column. $R_f = 0.45$ on silica (4/1 v/v DCM/MeOH).

Scheme S1. Reaction scheme to synthesize CIMA.



Scheme S2. Reaction scheme to synthesize ONB.

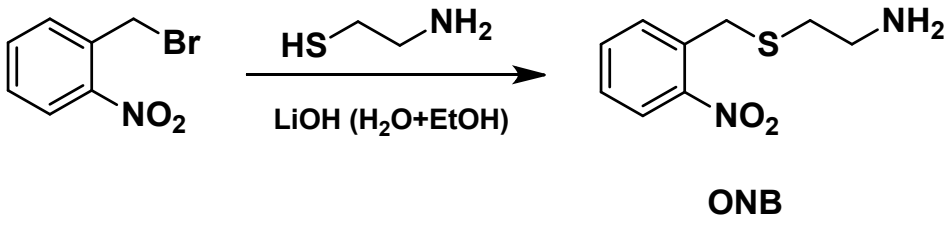


Figure S1. ^{1}H-NMR spectrum of A2 in $CDCl_3$.

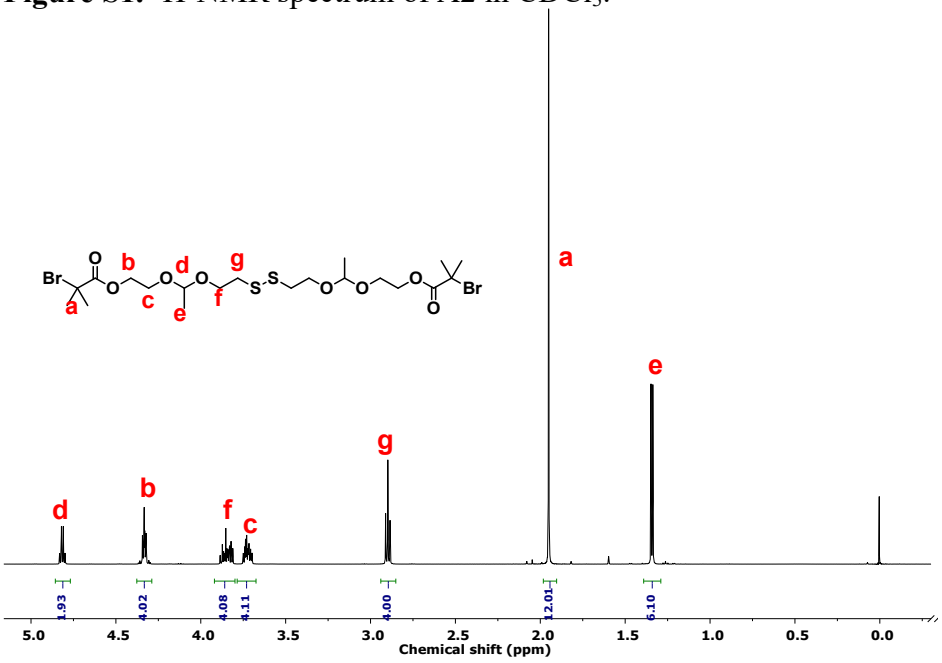


Figure S2. ^{13}C-NMR spectrum of A2 in $CDCl_3$.

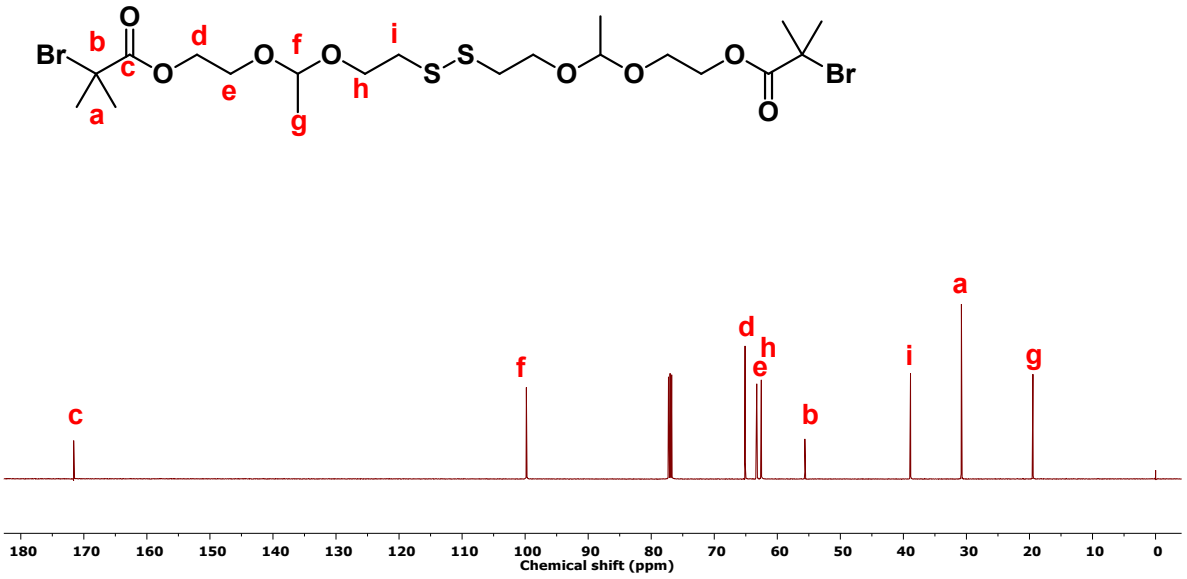


Figure S3. ^{1}H-NMR spectrum of CIMA in $CDCl_3$.

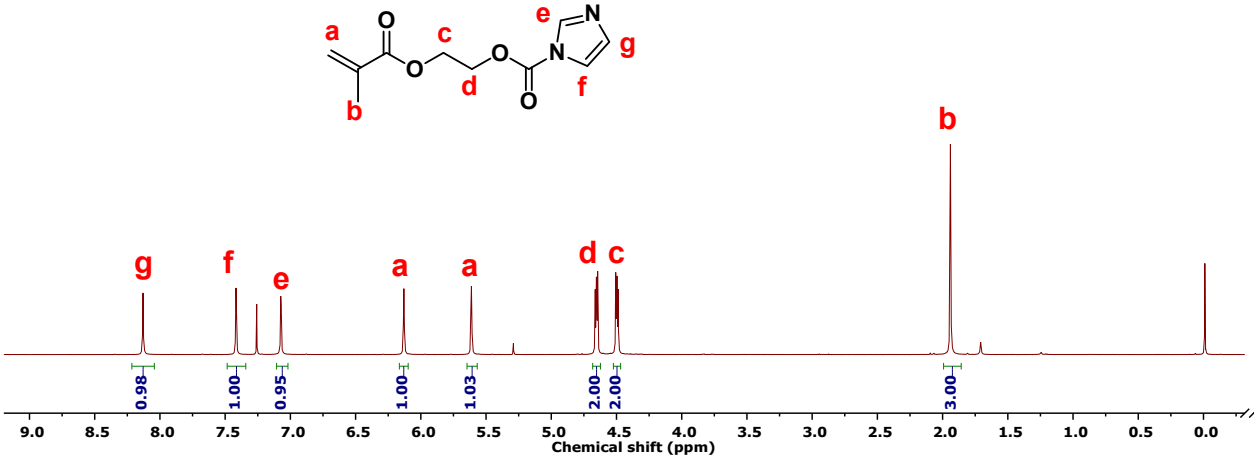


Figure S4. ^{1}H-NMR spectrum of ONB in $CDCl_3$.

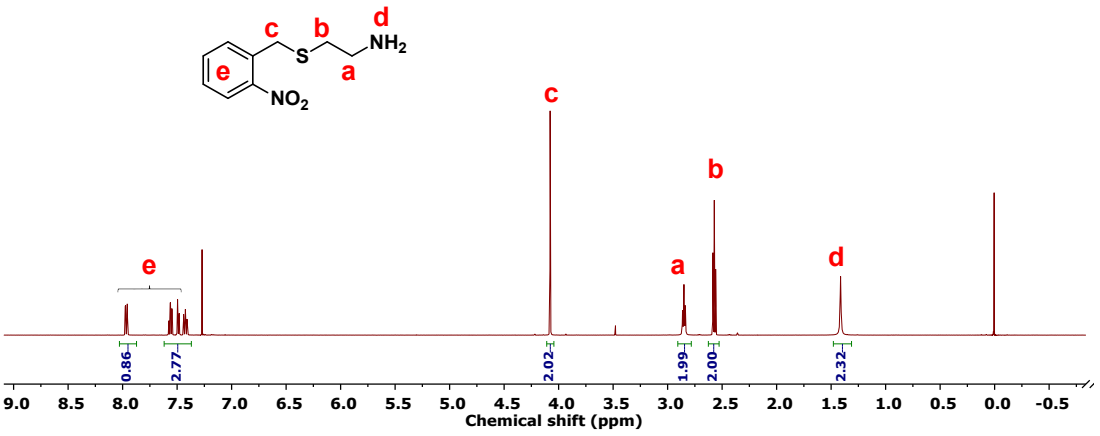
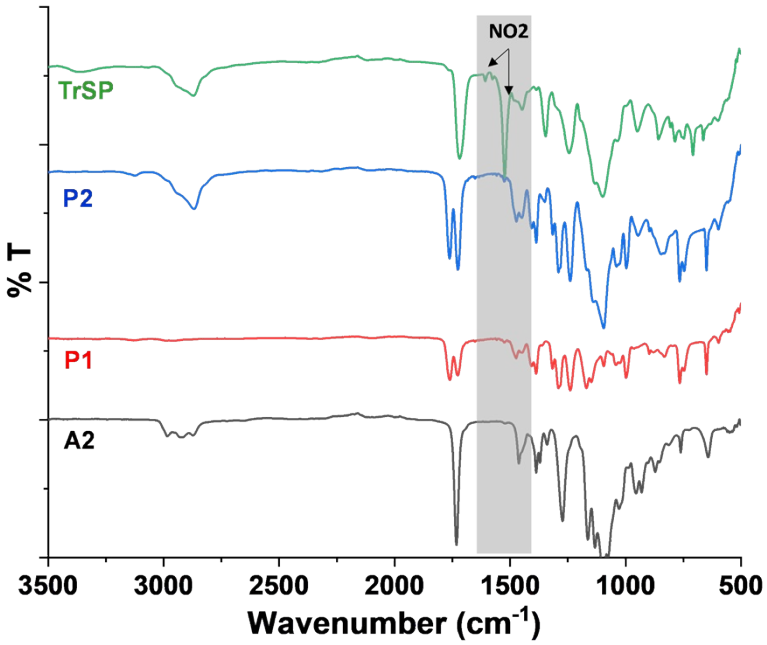


Figure S5. FT-IR spectrum of TrSP, compared with P2, P1 and A2.



II) Investigation of self-assembly and polymers degradation in homogenous and heterogenous media

Figure S6. DLS diagram of aqueous micelles self-assembled from TrSP at 1 mg/mL.

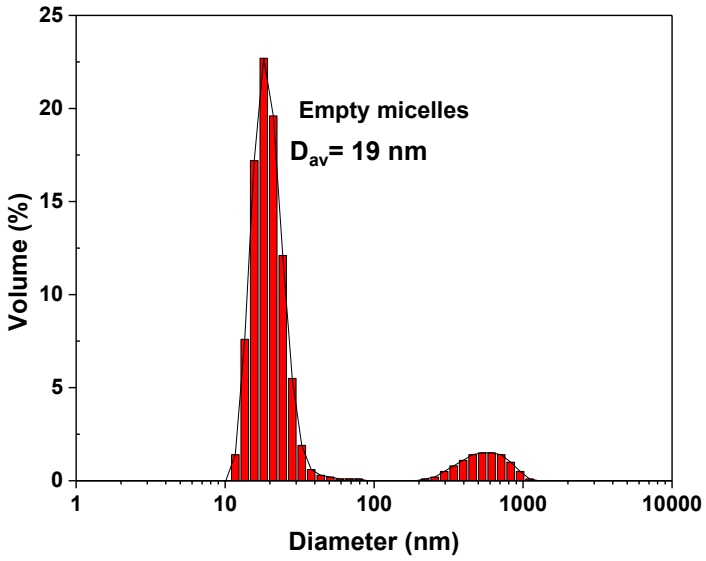


Figure S7. Overlaid fluorescence spectra of NR-loaded TrSP micelles at pH = 7.4 (control) (a), 10 mM GSH (b), pH = 5.4 (c), 10 mM GSH&pH = 5.4 (d), and 10 mM GSH&pH = 4.2 (e).

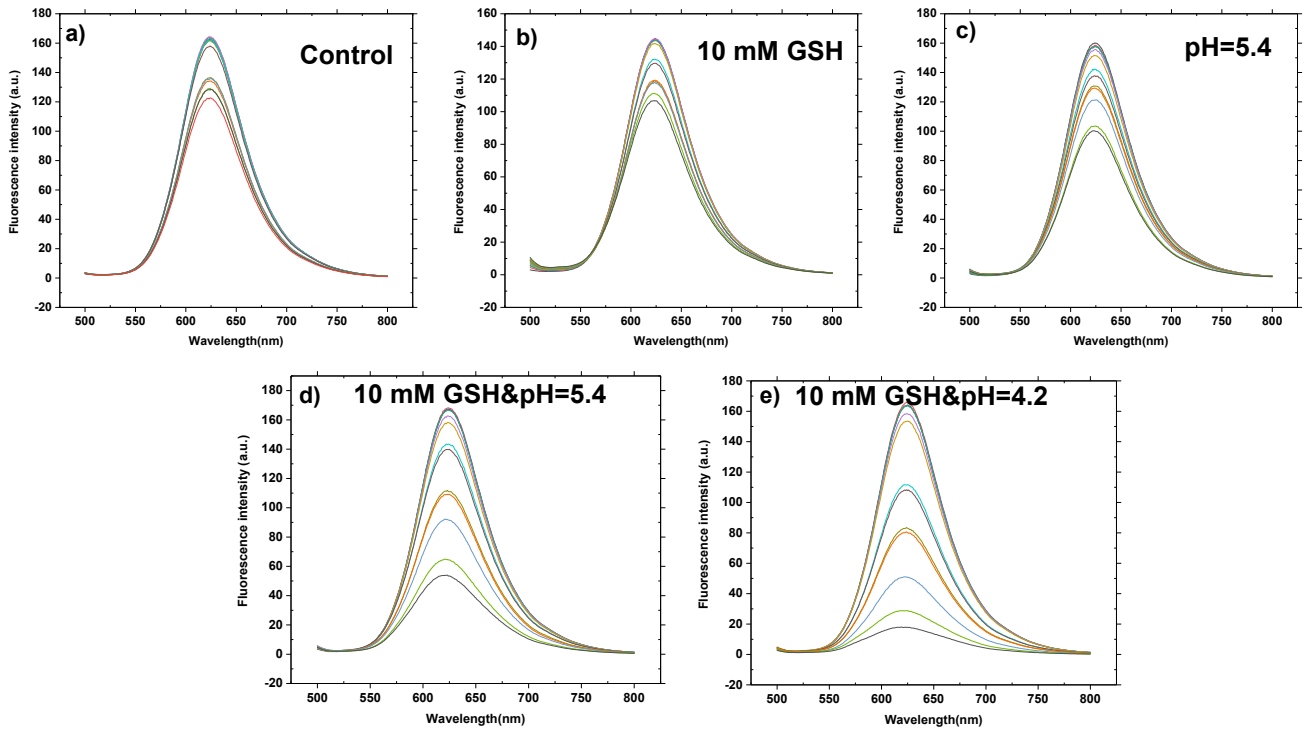


Figure S8. Overlaid DLS diagram of NR-loaded micelles before and after treatment with 10 mM GSH and pH= 5.3.

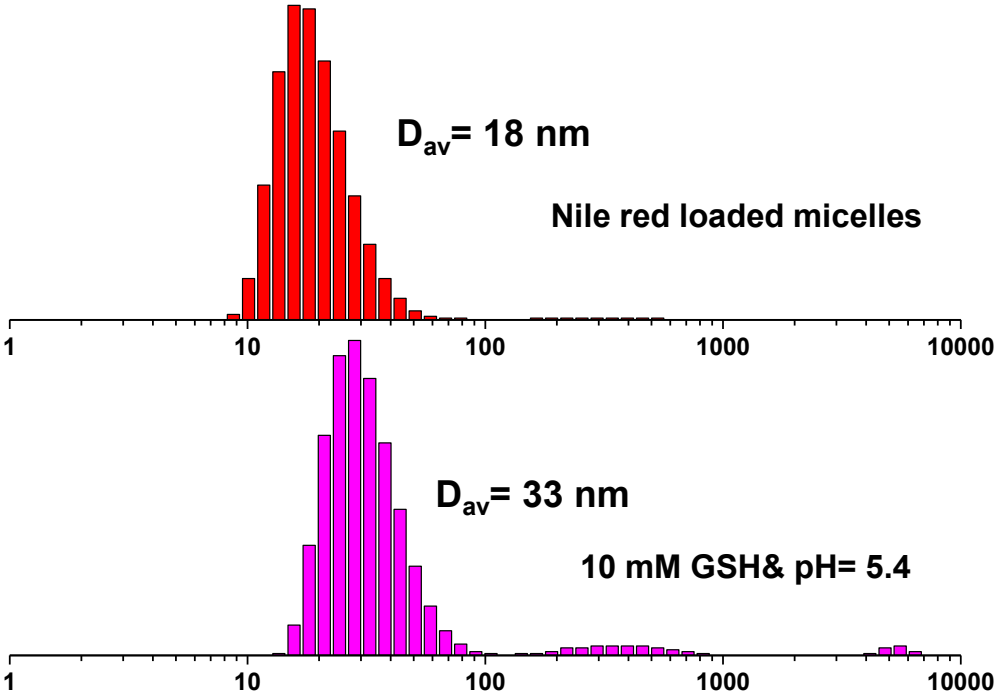
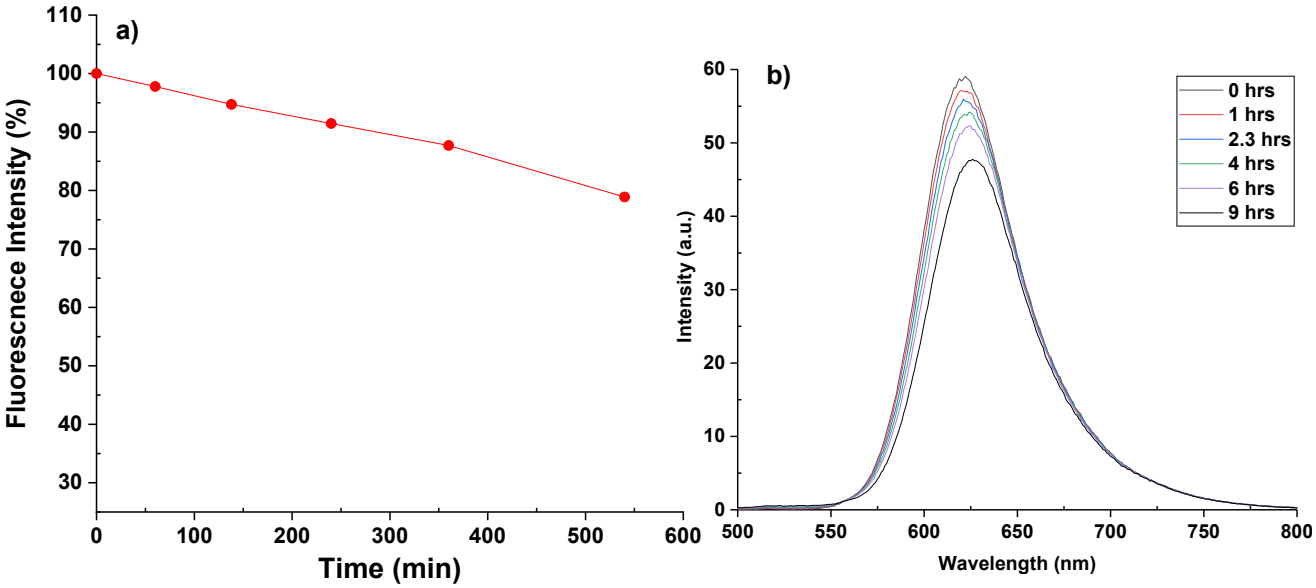
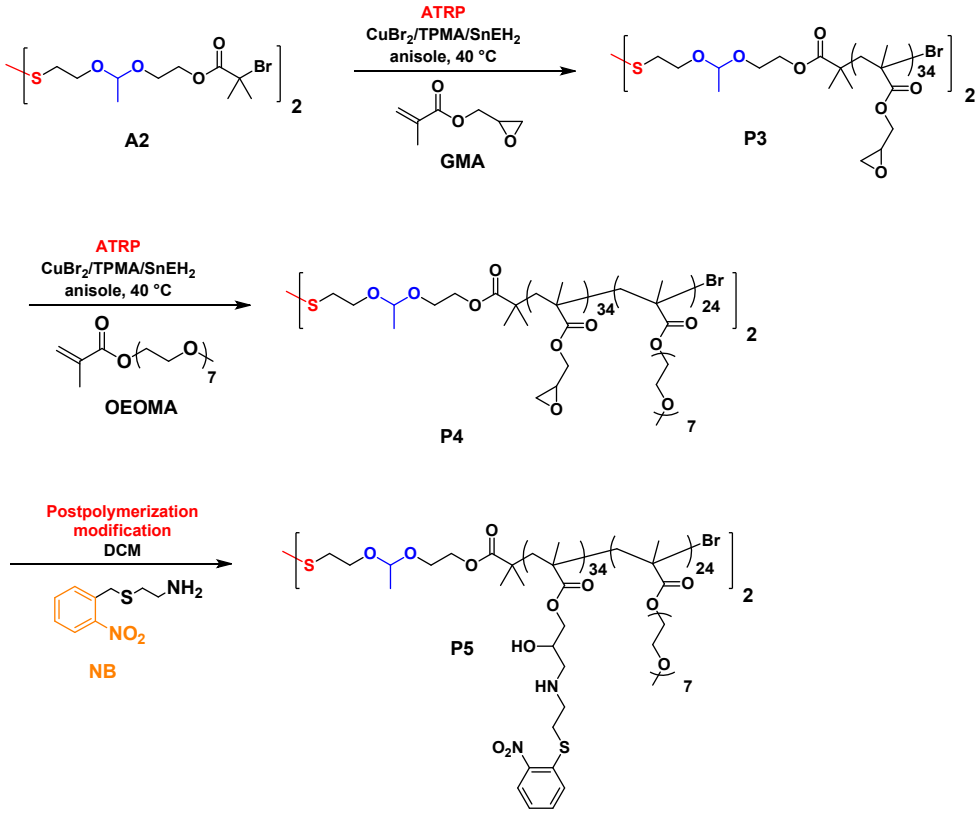


Figure S9. Photobleaching experiment of NR in tetrahydrofuran irradiated with UV light (365 nm) for 540 mins.



III) Synthesis of triple stimuli responsive degradable block copolymer via ATRP of glycidyl methacrylate (GMA) and postmodification

Scheme S3. Reaction scheme to synthesize P5 block copolymer by ATRP of GMA and OEOMA, and postpolymerization modification by amine-epoxide reaction.



Synthesis of P5 triblock copolymer by a consecutive ATRP and postpolymerization modification. In the first step, A2 (118 mg, 0.21 mmol), GMA (1.8 g, 12.6 mmol), [Cu(II)TPMABr]Br complex (5.61 mg, 10.9 µmol), TPMA (9.51 mg, 32.7 µmol), and anisole (7.5 g) were mixed in a 25 mL Schlenk flask. In the second step, macroinitiator (P3, 0.31 g, 57.9 µmol), monomer (OEOMA, 1.1 g, 2.31 mmol), [Cu(II)TPMABr]Br complex (1.49 mg, 2.89 µmol), TPMA (2.52 µg, 8.68 µmol), and anisole (4.6 g) were mixed in a 25 mL Schlenk flask. The mixtures were deoxygenated by purging under nitrogen for 1 hr and then placed in an oil bath pre-heated at 40 °C. A nitrogen pre-purged solution of $Sn(II)(EH)_2$ dissolved in anisole (0.5 g, 87.3 µmol for P3 and 23.2 µmol for P4) were injected to initiate polymerization. Polymerization was stopped by cooling the reaction mixture in an ice-bath and exposing it to air. For purification, the as-prepared polymer solution was diluted with acetone and passed through a basic alumina column to remove residual

copper species. The solvent was removed under rotary evaporation at room temperature. The polymer was isolated by precipitation from hexane, and dried in a vacuum oven at room temperature for 15 hrs.

In the third step, A solution of ONB (0.5 g, 2.38 mmol) dissolved in DCM (20 mL) was added dropwise to a solution containing the purified P4 (0.12 g, 7.2 μmol) and DCM. After being stirred for 24 hrs at room temperature, the resulting mixture was precipitated from cold diethyl ether/hexane (8/2 v/v), and dried in vacuum oven at room temperature for 12 hrs, yielding a yellow residue.

Note: ARGET ATRP using A2 initiator and GMA and OEOMA was carried out for the synthesis of P3 and P4 block copolymer. The DP was determined to be 34 for GMA and 24 for OEOMA block from ^{1}H-NMR (Figure S10). Successful conjugation of ONB to GMA via epoxide ring opening was demonstrated with both ^{1}H-NMR and GPC (Figure S10 and S11). The acid pH and reduction stimuli responsive degradation were demonstrated by GPC where shift to lower molecular weight region were detected (Figure S12) and UV-VIS spectroscopy for UV light degradation (Figure S13). Further characterization of P5 block copolymer and self-assembly studies were not possible due to the crosslinking of polymers during storage and insolubility in water.

Figure S10. ^{1}H-NMR spectra of P3 (a), P4 (b) in $CDCl_3$ and P5 (c) in DMSO-d_6.

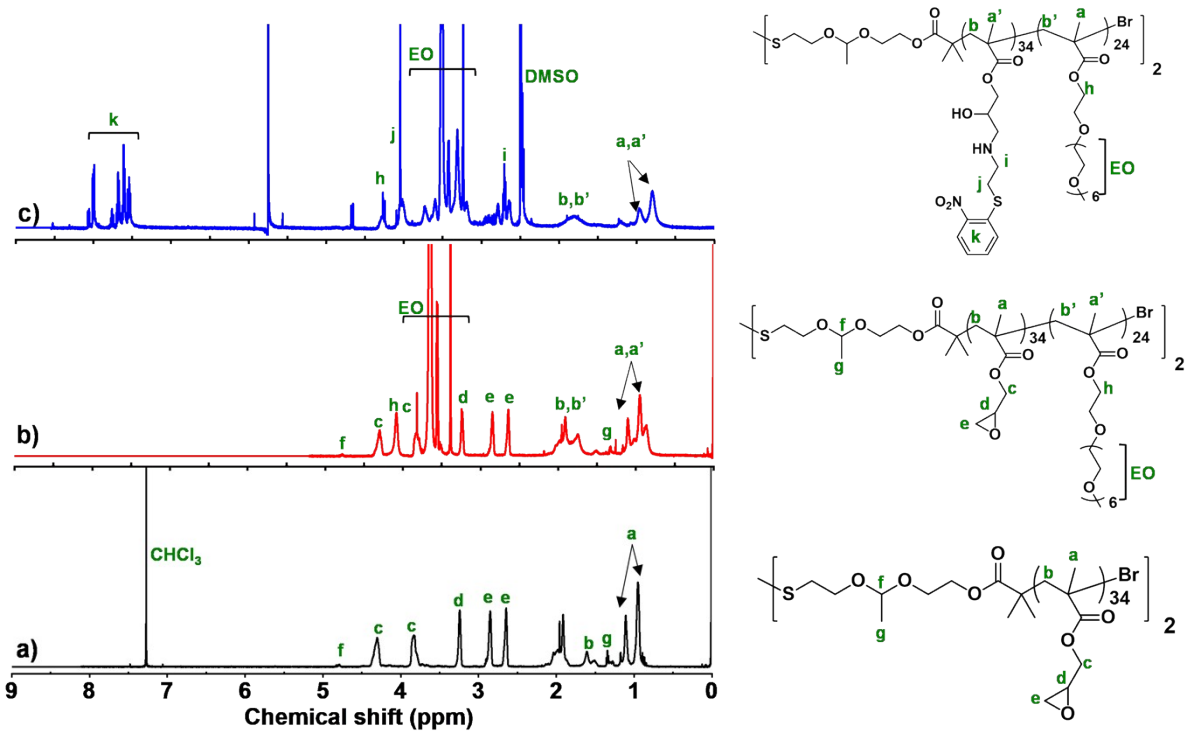


Figure S11. GPC traces of P3 (black) compared with P4 (red) and P5 (blue).

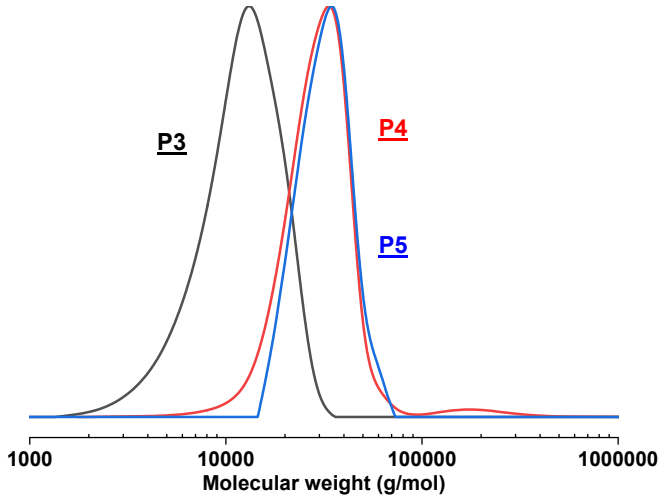


Figure S12. GPC traces of P4 (black) compared with HCl treatment (red) and DTT treatment (blue).

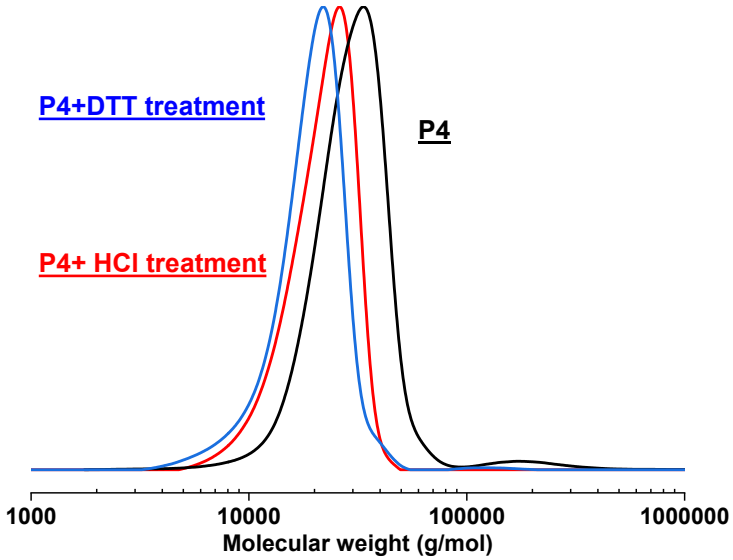
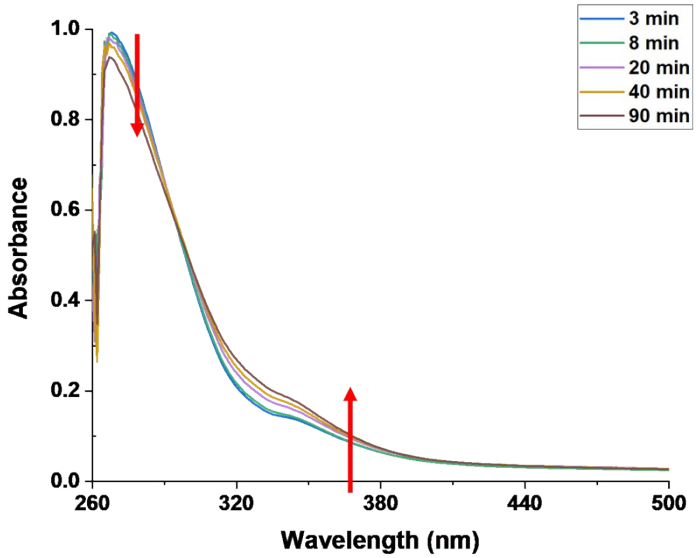


Figure S13. Overlaid UV-VIS spectra (a) of P5 after treatment with UV light (365 nm) for 90 mins.



IV) Attempts to synthesize triple stimuli responsive degradable block copolymer via ATRP of N-hydroxysuccinimide (NHS) functionalized monomer

Synthesis of NHS-MA. A clear solution containing NHS (5 g, 43.4 mmol), Et_3N (5.3 g, 52.1 mmol) and anhydrous DCM (100 mL) was made and stirred in an ice-bath for 20 min. After addition of methacryloylchloride (5 g, 47.8 mmol), the reaction mixture was stirred vigorously for 2 hrs at room temperature. The mixture was filtered and washed with PBS (pH = 7.4, 200 mL) three times for removing Et_3N-HBr adduct, passed through Na_2SO_3 to eliminate water, and precipitated in mixture of hexane and ethyl acetate (1/1 v/v). The product was collected by vacuum filtration.

Synthesis of DSC-HEMA. HEMA (2 g, 15.4 mmol) was added dropwise to a clear solution containing DSC (9.9 g, 16.9 mmol), Et_3N (1.56 g, 15.4 mmol) and anhydrous DCM (100 mL). The reaction mixture was stirred for 4 hrs at room temperature, and then passed through silica column. After removing DCM by rotary evaporation, the product was collected as colorless oil.

Attempts to polymerize NHS-MA by ARGET ATRP (P6). A2 (43.1 mg, 79.7 μmol), NHS-MA (0.73 g, 3.98 mmol), [Cu(II)TPMABr]Br complex (2.05 mg, 3.98 μmol), TPMA (3.47 mg, 11.6 μmol), and anisole (4.1 g) were mixed in a 25 mL Schlenk flask. The mixture was deoxygenated by purging under nitrogen for 1 hr and then placed in an oil bath pre-heated at 40 °C. A nitrogen pre-purged solution of $Sn(II)(EH)_2$ dissolved in anisole or DMF (0.012 g, 31.9 μmol) was injected to initiate polymerization. Polymerization was stopped after insoluble precipitates were observed.

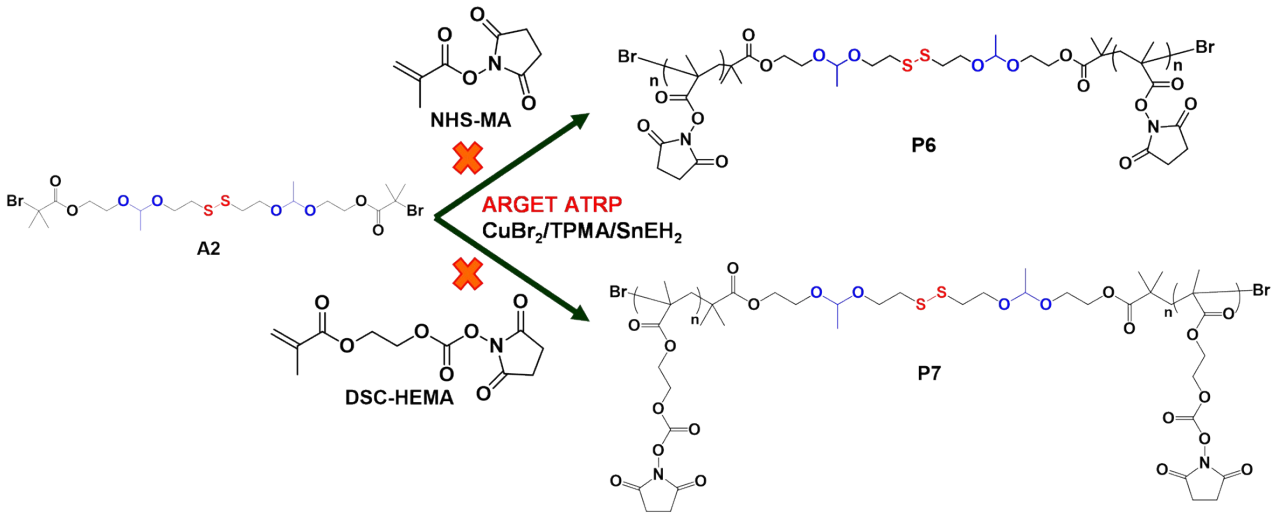
Note: The polymerization of NHS-MA was attempted with ARGET ATRP in both anisole and DMF. Insoluble species were observed during the polymerization which was attributed to crosslinking reaction. The GPC trace of these polymers showed bimodal traces (Figure S16) which suggests formation of ill-defined NHSMA homopolymers by ARGET ATRP.

Attempts to polymerize of DSC-HEMA by ARGET ATRP (P7). A2 (25.8 mg, 0.047 mmol), DSC-HEMA (0.75 g, 2.76 mmol), [Cu(II)TPMABr]Br complex (1.22 mg, 2.33 μmol), TPMA (2.08 mg, 7.15 μmol), and anisole or DMF (3.1 g) were mixed in a 25 mL Schlenk flask. The mixture was deoxygenated by purging under nitrogen for 1 hr and then placed in an oil bath pre-heated at 40 °C. A nitrogen pre-purged solution of $Sn(II)(EH)_2$ dissolved in anisole (7.73 g, 19.1 μmol) was injected to initiate polymerization. Polymerization was stopped after insoluble precipitate was observed.

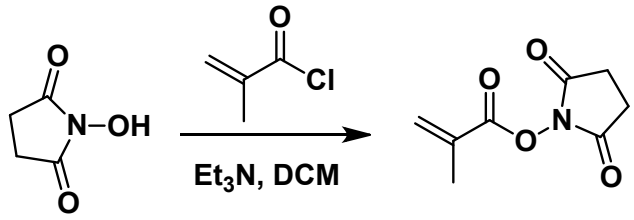
Note: The polymerization of DSC-HEMA was attempted with ARGET ATRP in both anisole and DMF as solvent. The polymerization was stopped at low conversion and GPC trace showed high

molecular weight shoulder (Figure S17) attributed to crosslinking reaction or side reactions that are induced by ARGET ATRP components such as reaction with ligand and Tin.

Scheme S4. Reaction scheme for unsuccessful attempts to synthesize NHS functionalized homopolymers.



Scheme S5. Reaction scheme to synthesize NHS-MA.



Scheme S6. Reaction scheme to synthesize DSC-HEMA.

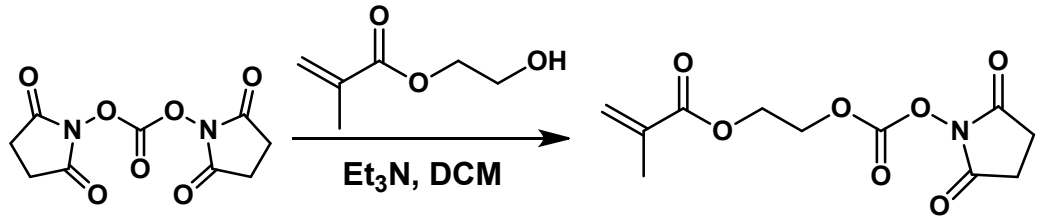


Figure S14. ^{1}H-NMR of NHS-MA in $CDCl_3$.

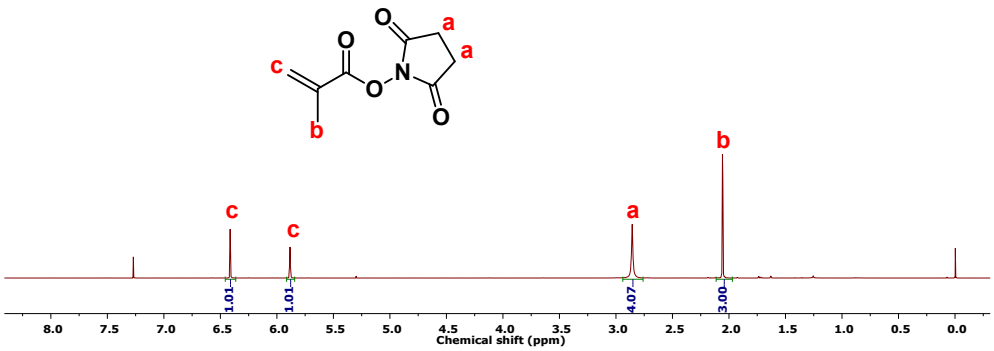


Figure S15. ^{1}H-NMR of DSC-HEMA in $CDCl_3$.

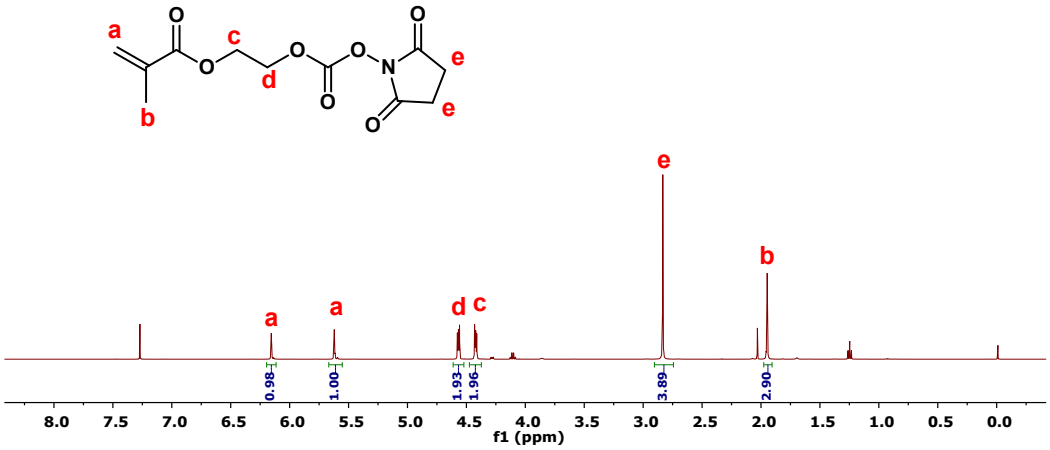


Figure S16. GPC traces for ARGET ATRP of NHS-MA in anisole.

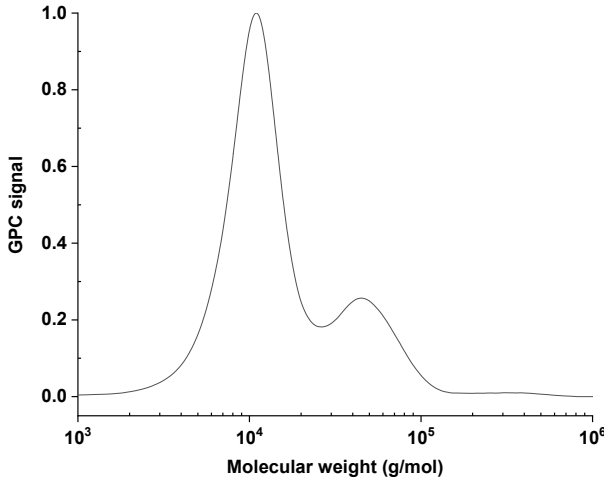


Figure S17. GPC trace (a) and kinetics plot (b) for ARGET ATRP of DSC-HEMA in DMF.