Supporting Information

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Hyperbranched Bisphosphonate-Functional Polymers via Self-Condensing Vinyl Polymerization and Postpolymerization Multicomponent Reactions

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Experimental Section

Materials and Measurements

All reagents were obtained from commercial sources and used as received, with the exception of 1,4-dioxane, which was purified by passing through a basic alumina plug, and 2,2´-azobisisobutyronitrile (AIBN), which was recrystallized from methanol. Anhydrous solvents were obtained from an anhydrous solvent system and used immediately. All ^{1}H NMR (300 MHz, 500 MHz) spectra were recorded on a Varian Mercury 300 or Varian Mercury 500 spectrometer with chemical shifts referenced to residual signals from $CDCl_3$ (7.27 ppm). Elemental Analysis was performed by Midwest Laboratories. HRMS (ESI) was conducted by the UF Mass Spectrometry Laboratories. Gel permeation chromatography (GPC) was conducted in *N*,*N*-dimethylacetamide (DMAc) (with 0.05 M LiCl) at 50 °C with a flow rate of 1.0 mL/min (Pump: Agilent 1260 Infinity Isocratic Pump G1310B, Columns: Guard + two ViscoGel I-series G3078 mixed bed columns, molecular weight range 0–20 × 10^3 and 0–100 × 10^5 g mol^{-1}). Detection consisted of a Wyatt Optilab T-rEX refractive index detector operating at 658 nm and a Wyatt miniDAWN TREOS laser light scattering detector (operating at 50 mW, 658 nm with detection angles of 49°, 90°, and 131°). Molecular weights were calculated using measured d*n*/dc values determined by assuming 100% recovery during GPC analysis.

Synthesis of *tert*-butyl-*N*-(2-aminoethyl)carbonate

A solution of 1,2-diaminoethane (162 g, 2.67 mol, 9 equiv.) was prepared in 1,4-dioxane (300 mL) and stirred. A second solution of di-*tert*-butyldicarbonate (65.6 g, 0.298 mol, 1 equiv.) in 1,4-dioxane (400 mL) was added to the first solution over a 2 h period. The reaction was stirred for 22 h. The solvent (1,4-dioxane) was evaporated, and H_2O (500 mL) was added to the crude reaction mixture to precipitate bis(*N*,*N*′-*t*-butyloxycarbonyl)-1,2-diaminoethane, which was removed by gravity filtration. The filtrate was saturated with NaCl and then extracted with CH_2Cl_2 (4× 200 mL) and dried over $MgSO_4$. After removing $MgSO_4$ by filtration, the remaining solvent was removed by rotary evaporation. A colorless oil was obtained in 70% yield (32.96 g). ^{1}H NMR: ($CDCl_3$, 300MHz, ppm): 5.22 (s, 1H, NHBoc), 3.06-3.07 (m, 2H, CH_2NH), 2.67-2.70 (m, 2H, CH_2NH_2), 1.34 (s, 9H, $3CH_3$), 1.18 (s, 2H, NH_2); ^{13} C NMR: ($CDCl_3$, 125 MHz, ppm): 156 (C=O), 78.5 ($OCMe_3$), 43 (CH_2NH), 41.6 (CH_2NH_2), 28 (CH_3).

Synthesis of *N*-*tert*-butyloxycarbonyl-*N*′-acryl-1,2-diaminoethane.

A 3-neck round bottom flask was placed under argon with an attached addition funnel. *Tert*-butyl-*N*-(2-aminoethyl)carbonate (33.0 g, 0.206 mol, 1 equiv.), triethylamine (100. mL), and anhydrous CH_2Cl_2 (350 mL) were added to the flask. The flask was cooled to -20 °C with an ice-salt bath. CH_2Cl_2 (200 mL) and acryloyl chloride (185 mL, 0.227 mol, 1.1 equiv.) were transferred to the addition funnel, added drop-wise over a 2 h period, and the mixture was left stirring for 16 h. The solution was extracted with four portions of H_2O (250 mL), and the organic layer was dried with $MgSO_4$. After removing $MgSO_4$ by filtration, CH_2Cl_2 was removed by rotary evaporation. A solid white product was obtained in 86% (38.02 g) yield. The product was dissolved in ethyl acetate and passed though a silica plug for further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): 6.62 (s, 1H, CONH), 5.1 (s, 1H, NHBoc),

6.19 (d, 1H, CH_2=), 5.56 (d, 1H, CH_2=), 6.05 (dd, CH=), 3.34-3.39 (m, 2H, $CONHCH_2$), 3.23-3.26 (m, 2H, CH_2NHBoc), 1.36 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4 (C=O), 157.1 (C=O, Boc), 130.9 (=CH), 126.3 (CH_2=), 79.74 (t-C), 40.85 ($CONHCH_2$), 40.08 (CH_2NHBoc), 28.35 ($3CH_3$). FTIR: 3312 cm (CON-H), 1650 cm (NC=O), 1711 (Boc C=O).

Synthesis of (S)-1-Doceyl-(S)-(α,α′-dimethyl-α′′-acetic acid) Trithiocarbonate, DDMAT

DDMAT was prepared according to a previously reported procedure.[39] Dodecanethiol (40.48 g, 0.20 mol, 1 equiv.), acetone (96.12 g, 1.655 mol, 8.275 equiv.) and tricaprylylmethyl ammonium chloride (3.23 g, 0.008 mol, 0.04 equiv.) were combined in a three neck round bottom flask and cooled to 10 °C under argon. A solution of 50% NaOH (16.77 g, 0.21mol, 1.05 equiv.) was added over a 20 min period and stirred for an additional 15 min. A white precipitate formed. Carbon disulfide (15.21 g, 0.2mol, 1 equiv.) was added to acetone (20.18 g, 0.34 mol, 1.7 equiv.), and the resulting solution was added to the reaction over a 20 min period. The previously formed precipitate dissolved, and the solution turned a red-orange color. After 10 min, chloroform (35.6 g, 0.3 mol, 1.5 equiv.) was added. 50% NaOH (80 g, 1 mol, 5 equiv.) was added dropwise over a 30 min period. The solution was stirred overnight, and a heavy orange precipitate was formed. The next day, water (300 mL) was added along with concentrated HCl (50 mL). The flask was purged with argon and stirred vigorously to evaporate acetone. The solid was collected by filtration, stirred into 2-propanol (0.5 L), and the remaining undissolved solid was removed by filtration. The filtrate was concentrated to dryness and recrystallized from hexanes to provide 27.78 g of yellow solid. ^1H NMR (300 MHz, $CDCl_3$): 3.32−3.26 (t,2H, CH_2CH_2S), 1.72 (s, 6H, $COC(CH_3)_2S$), 1.64−1.70 (m, 2H, $CH_2CH_2CH_2S$), 1.25−1.45 (m, 20H, $CH_3(CH_2)10CH_2$), 0.85−0.90 (t, 3H, CH_3CH_2).

Synthesis of 2-((2-(((Dodecylthio)carbonothioyl)thio)-2-methylpropanoyl)oxy)ethyl Acrylamide, AmCDT

DDMAT (2.00 g, 5.49 mmol, 1.00 equiv.) was dissolved in dry chloroform (50 mL) in a round bottom flask. EDC (1.58 g, 8.23 mmol, 1.50 equiv.) was added, and the solution was cooled to 0 °C in an ice bath and stirred. After 15 min, *N*,*N*-dimethylaminopyridine (DMAP) (0.10 g, 0.82 mmol, 0.15 equiv.) was added to the solution, followed by 2-hydroxyethylacrylamide (0.76g, 6.58 mmol, 1.2 equiv.). The solution was allowed to stir after warming to room temperature. After 5 days, the solution was washed with 1 M HCl (2 x 50mL) and brine (2 x 50mL) and dried over anhydrous $MgSO_4$. The remaining solvent was removed by rotary evaporation. The crude product was purified using column chromatography with a mobile phase starting from a 10:1 hexane: ethyl acetate mixture and increasing the polarity to a 1:1 hexane: ethyl acetate mixture to yield 2.04 g of a viscous orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 6.37−6.44, 6.06−6.16, and 5.81−5.86 (m, 3H, CH_2CHCN), 4.39 (t, 2H, $COO(CH_2)$, 3.61 (t, 2H, CH_2NHCO)m 3.25 (t, 2H, $SCH_2(CH_2)_{10}CH_3$), 1.69 (s, 6H, $COC(CH_3)_2S$), 1.20−1.41 (m, 20H, $CH_3(CH_2)_{10}CH_2$), 0.88 (t, 3H, CH_3CH_2). ^{13}C NMR (500 MHz, $CDCl_3$, ppm) 222.3, 173.6, 166.2, 131.1, 128.4, 63.9, 58.1, 39.5, 39.0, 31.2, 28.3, 25.4, 22.1, 12.6. Elemental Analysis calculated: 57.2 % C, 8.5 % H, 3.0% N, found: 57.2% C, 8.5% H, 3.0 %H, ESI-MS calculated: 484.198 g/mol, found: 484.199 g/mol.

Synthesis of hyperbranched poly(*N*-*tert*-butyloxycarbonyl-*N′*-acryl-1,2-diaminoethane)

N-*Tert*-butyloxycarbonyl-*N′*-acryl-1,2-diaminoethane was added to an 8 mL vial, which was sealed with a septum and parafilm. Stock solutions of chain transfer monomer (CTM) (AmCDT) and AIBN in 1,4-dioxane were prepared. Appropriate amounts of AIBN and CTM were added to the vials, depending on the intended amount of branching. Solvent

(1,4-dioxane) was added to the vials to achieve an overall monomer concentration of 1.5 M. The vials were purged with argon for 20 min then placed in a silicone oil bath at 70° C for 48 h to ensure high conversions. After removal from the oil bath, additional 1,4-dioxane (1.0 mL) was added to the vials, and the solutions were precipitated into cold hexanes. A fluffy white solid was obtained upon filtration. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): 3.9-4.2 (br s), 2.9-3.6 (br s), 2.0-2.4 (br s), 1.7-1.8 (br s), 1.55-1.65 (br s), 1.2-1.4 (br s), 1.0-1.2 (br s), 0.8-0.9 (t); ^{13}C NMR (500 MHz, $CDCl_3$, ppm): 228.3, 173.6, 166.5, 166.2, 157.4, 79.8, 63.9, 58.1, 40.8, 40.0, 39.5, 39.0, 31.2, 28.3, 25.4, 22.1, 12.6. FTIR: 3312 cm^{-1} (CON-H), 1650 cm^{-1} (NC=O), 1711 cm^{-1} (Boc C=O).

Deprotection of hyperbranched poly(*N*-*tert*-butyloxycarbonyl-*N′*-acryl-1,2-diaminoethane)

Hyperbranched poly(*N*-*tert*-butyloxycarbonyl-*N′*-acryl-1,2-diaminoethane) (0.3g) was added to a 25 mL round bottom flask. Dry DCM (5 mL) and trifluoroacetic acid (5 mL) were added to the flask, and the solution was stirred at room temperature overnight. The solvent was removed by rotary evaporation and the product was used without further purification.

Functionalization of hyperbranched poly(2-aminoethylacrylamide) via a Kabachnik-Fields reaction.

Hyperbranched poly(2-aminoethylacrylamide) from the previous step (1.4 mmol, 1 equiv.) and triethylamine (0.170 g, 1.68 mmol, 1.2 equiv.) were added to a 25 mL round bottom flask and dissolved in a minimal amount of THF (5 mL). Paraformaldehyde (0.126 g, 4.20 mmol, 3.00 equiv.) was added to the solution and the flask was placed in a silicone oil bath at 60 °C with a reflux condenser attached. After 15 min, diethylphosphite (0.580g, 4.20 mmol, 3.00 equiv.) was added and the reaction mixture was stirred under reflux for 48 h. After 48 h the product was dialyzed against deionized water for 3 days, changing the bath

every 12 h. After dialysis the solution was lyophilized to recover the functionalized polymer. The phosphonate ester functionalized polymer was subsequently dealkylated. The polymer was dissolved in dry DCM, and trimethylsilylbromide (TMSBr) (0.96 g, 6.3 mmol, 4.5 equiv.) was added drop-wise to the solution over 3 h. The solvent was removed, and methanol (10 mL) was added. The resulting solution was stirred overnight, and the methanol was evaporated the next day to yield the final phosphonic acid-functional polymer. The polymer was characterized by elemental analysis to determine overall functionalization efficiency (ESI). P^{31} NMR (300 MHz, D_2O, ppm): 17.23

Formation of gels from hyperbranched poly(2-aminoethylacrylamide)

Hyperbranched poly(2-aminoethylacrylamide) was dissolved in deionized water to create 1 w/w% solutions of polymer. Glutaraldehyde (0.5 equiv. relative to polymer) was added along with 2 drops of triethylamine. Gel formation was observed within a few minutes.

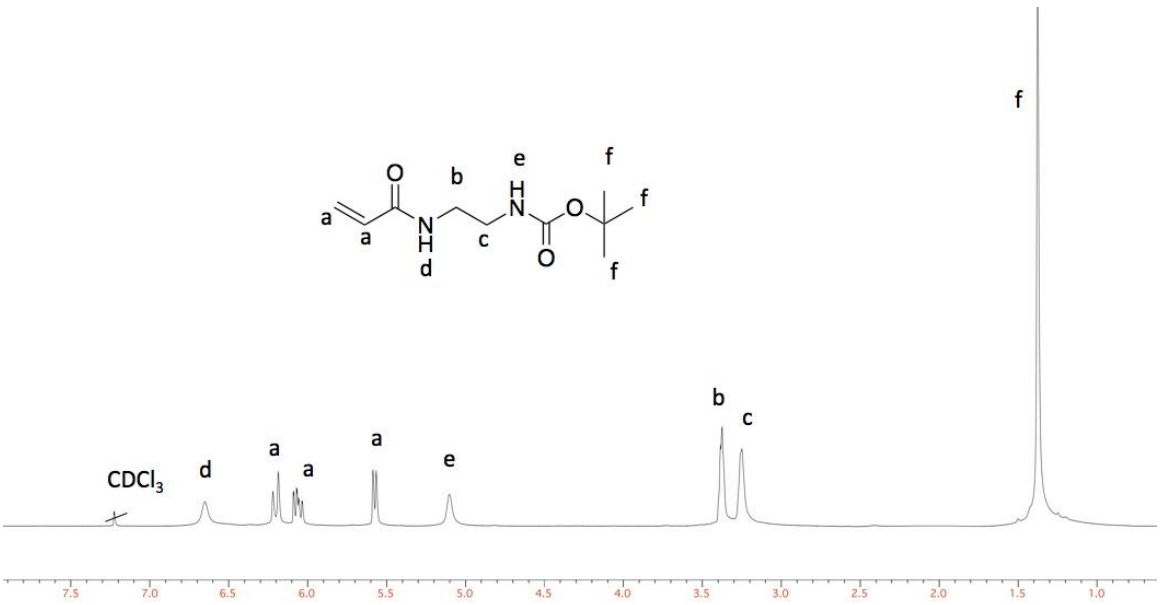


Figure S1. ^{1}H NMR spectrum of *N-tert*-butyloxycarbonyl-*N′* -acryl-1,2-diaminoethane.

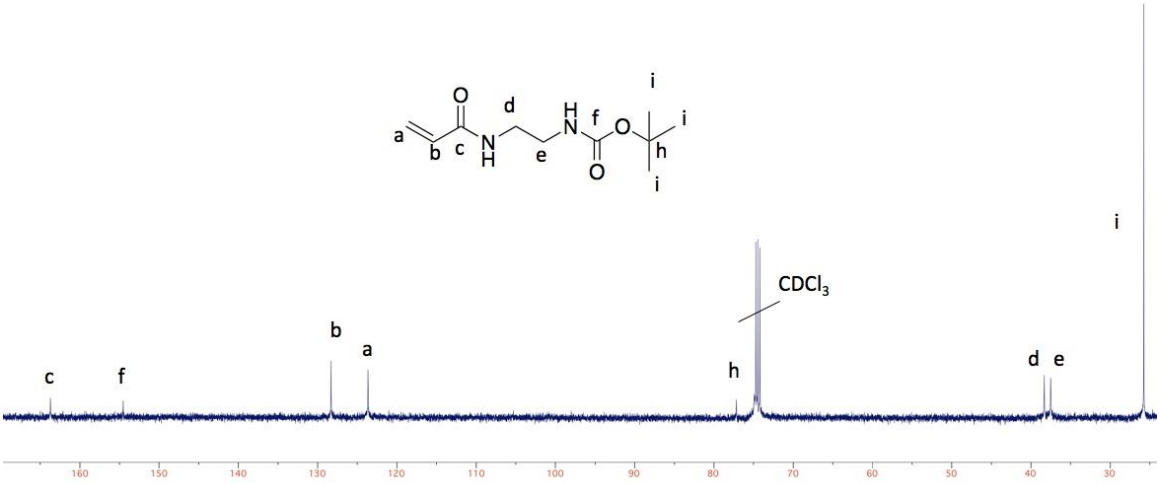
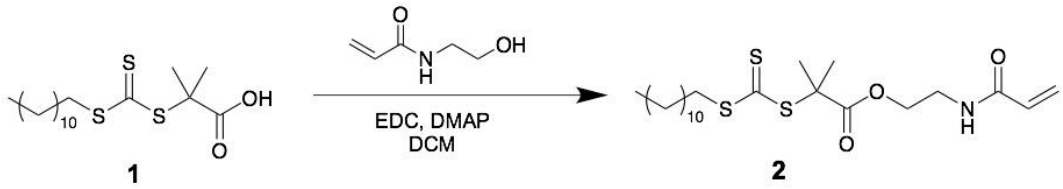


Figure S2. ^{13}C NMR spectrum of *N-tert*-butyloxycarbonyl-*N*′ -acryl-1,2-diaminoethane.



*Scheme S1***.** Synthesis of acrylamide chain transfer monomer (CTM) (**2**) from the RAFT agent **1**

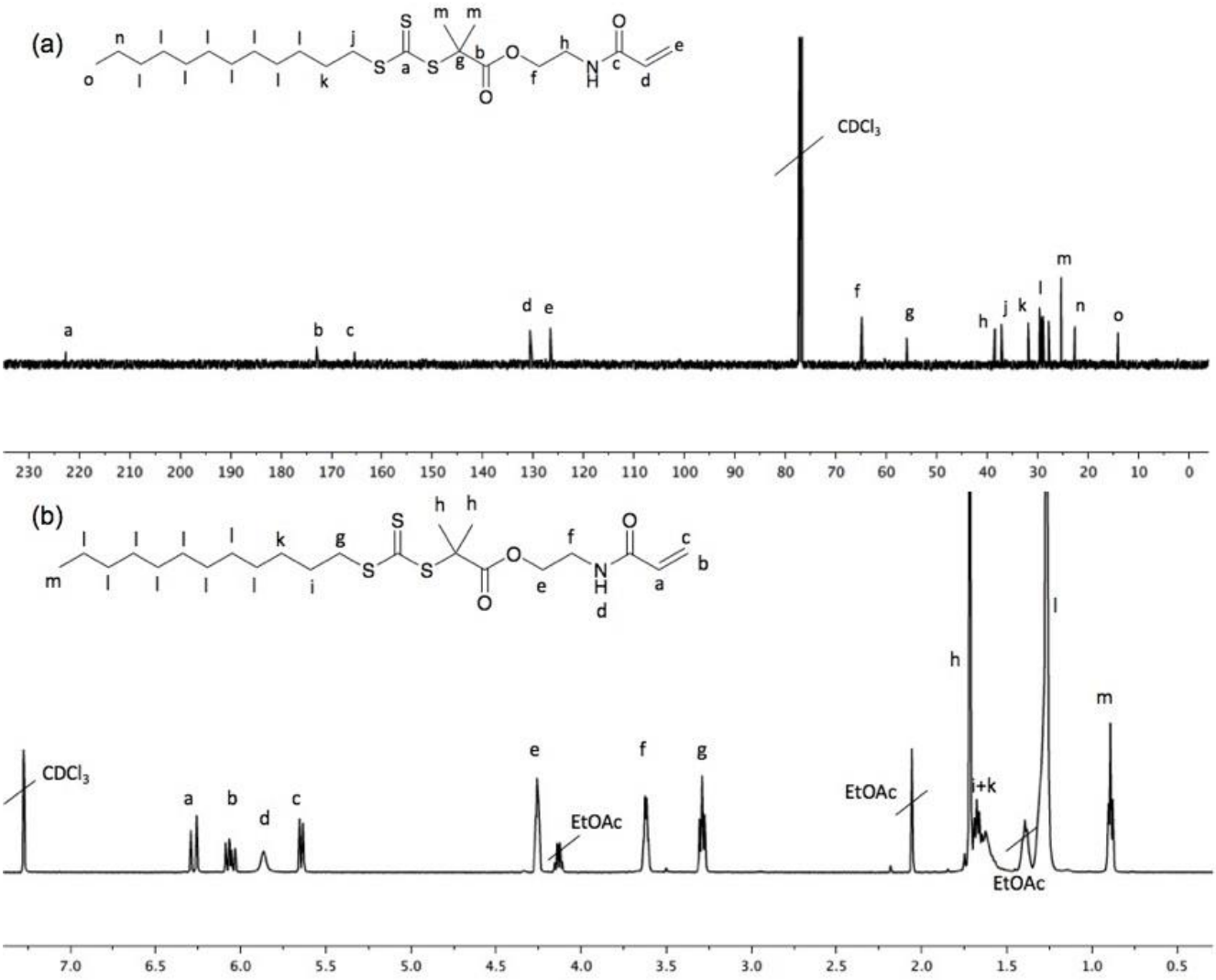


Figure S3. (a) ^{13}C and (b) ^{1}H NMR spectrum of novel acrylamide functional chain transfer monomer.

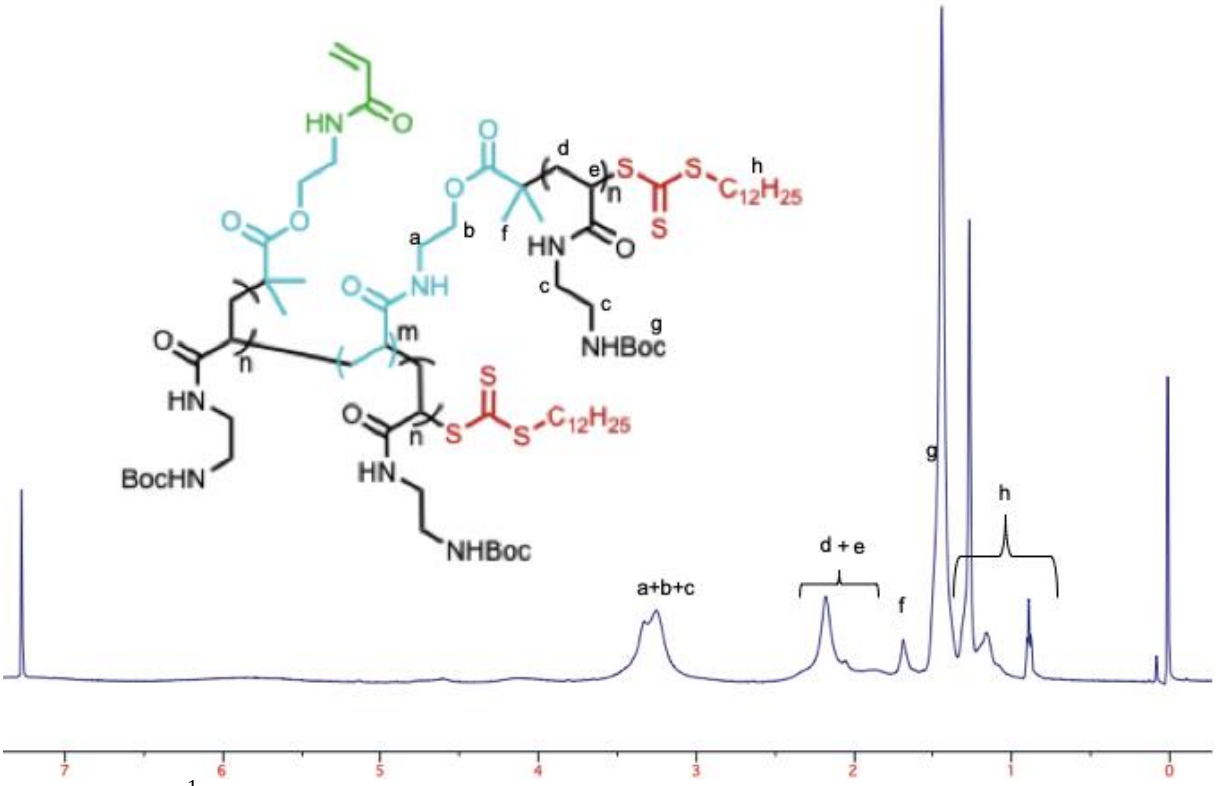


Figure S4. ^{1}H NMR spectrum of hyperbranched Boc-protected amine functional polyacrylamide (P4).

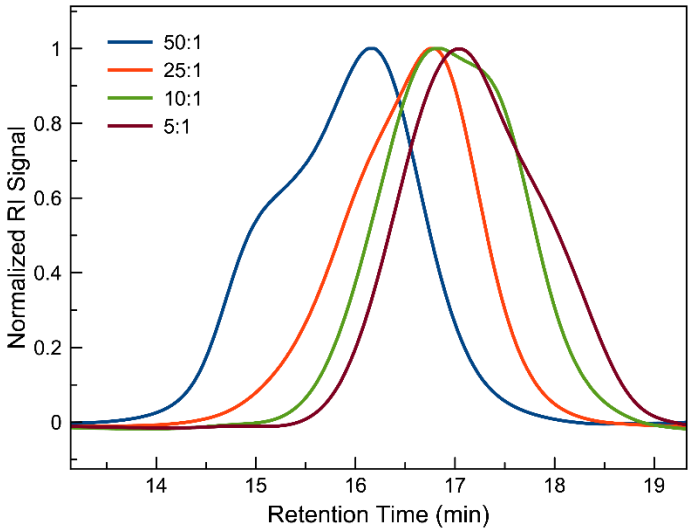


Figure S5. GPC traces of entries P1-4 from Table 1 with different feed ratios of [monomer]:[CTM]

Table S1. Elemental analysis results for polymer P1-P4.

Polymer	C (%)	H (%)	N (%)	P (%)
P1	23.48	5.26	7.50	10.17
P2	20.41	5.56	5.92	10.15
P3	27.00	5.27	6.76	14.30
P4	27.22	5.71	6.97	10.29

Table S2. Elemental analysis results for functionalized polymers 1-4 to calculate percent functionalization.

Entry	Feed Ratio[a]	Theoretical P/N[b]	Actual P/N[c]	Functionalization[d] (%)
P1-a	50:1	2.19	1.36	62
P2-a	25:1	2.18	1.71	78
P3-a	10:1	2.13	2.10	98
P4-a	5:1	2.04	1.46	72

[a] Feed ratio represents initial molar ratio of [monomer]/[CTM]. [b] Determined from elemental composition of polymer, assuming difunctionalization of every repeat unit. [c] Calculated from elemental analysis results. [d] Actual /theoretical P/N ratio.

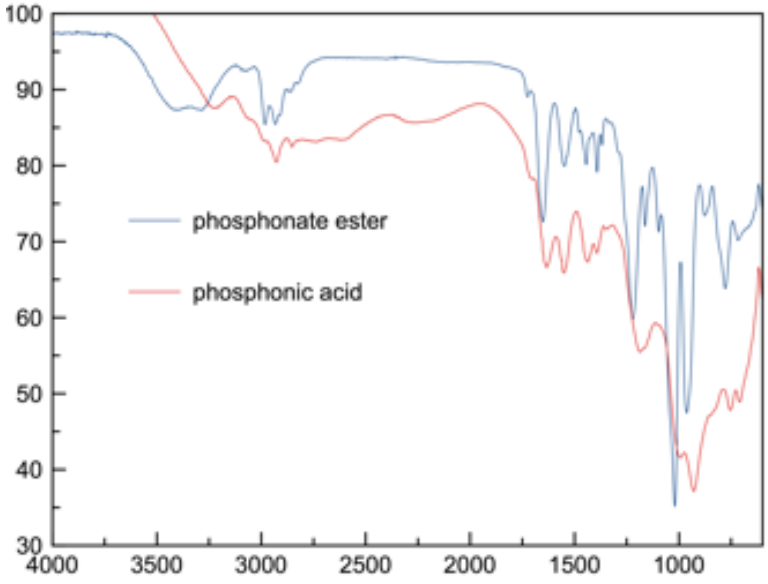


Figure S6. FTIR spectrum of phosphonate ester functionalized polymer and phosphonic acid functionalized polymer (P1-a).

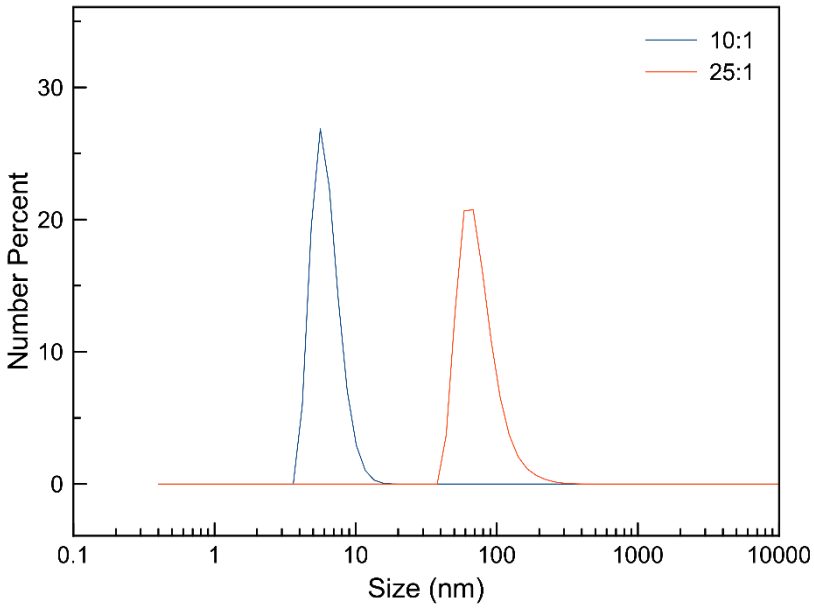


Figure S7. Distribution of hydrodynamic radii in polymers P2-a (25:1) and P3-a (10:1).

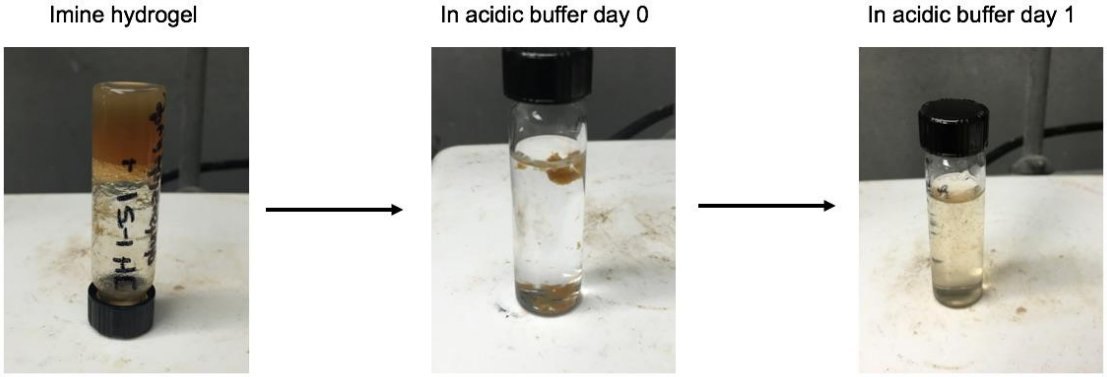


*Figure S8***.** Imine hydrogel from polymer P1 2 h after gel formation, in acidic buffer on day 0, and in acidic buffer on day 1, showing the onset of degradation.