Supplementary Information

Aqueous RAFT at pH zero: Enabling controlled polymerization of unprotected acyl hydrazide methacrylamides

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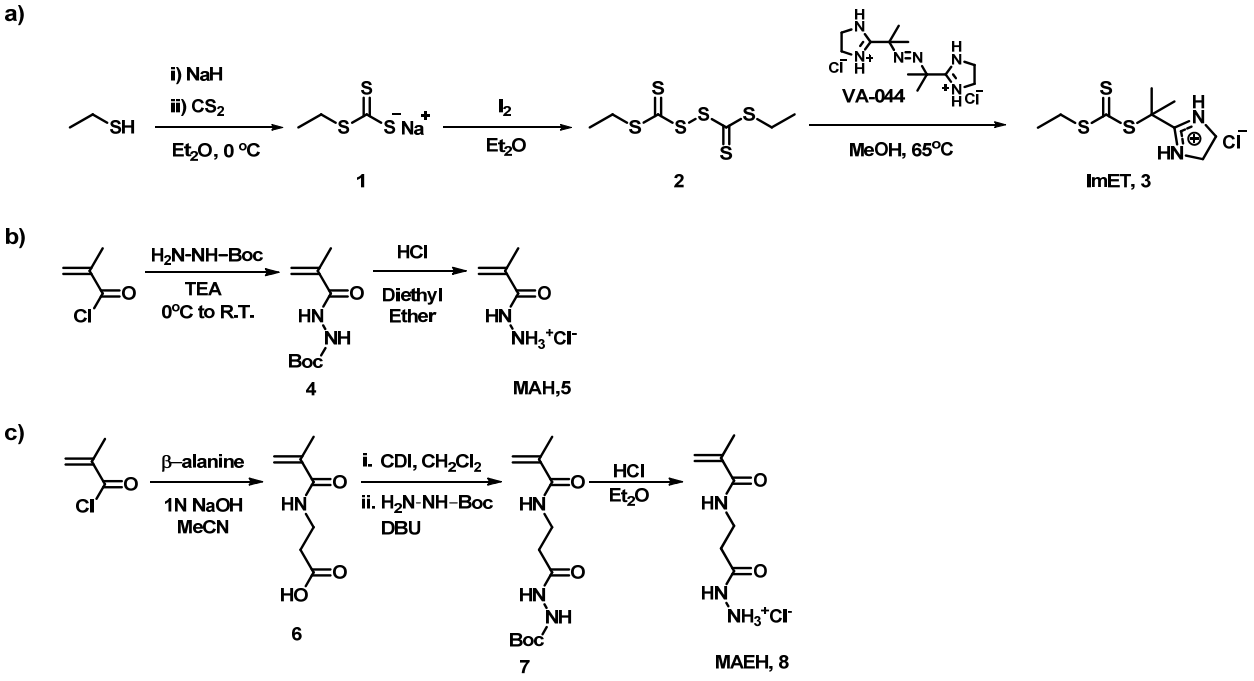
Experimental

Materials. Methacryloyl chloride (Aldrich, 97%) was distilled under vacuum and stored under N_2 prior to use. VA-044 (Wako) was recrystallized from MeOH and stored at -10 °C. Dichloromethane (Fisher, ≥ 99.5%) was dried over $CaCl_2$ and distilled prior to use in reactions. Ethanethiol (Aldich, 97%), hydrochloric acid solution (1 N and 2 N, Fisher), aminopropionic acid (Aldrich, 99%), *tert*-butyl carbazate (Aldrich, 98%), 1,1'-carbonyldiimidazole (Aldrich, ≥ 90%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Acros, 98%), carbon disulfide (Aldrich, ≥ 99.9%), sodium hydride (Aldrich, 95%), anhydrous THF (inhibitor free, Aldrich, ≥ 99.9%), iodine (Aldrich, 99.8%), potassium iodide (Aldrich, ≥ 99%), anhydrous methanol (Aldrich, 99.8%), triethylamine (Aldrich, ≥ 99.5%), and hydrogen chloride solution (2 M in diethyl ether, Aldrich) were used as received.

Characterization. NMR studies were conducted using a Varian INOVA 300 MHz NMR spectrometer. Polymer molecular weights and dispersities ($Đ_M$) were determined by aqueous

size exclusion chromatography (ASEC) with an eluent of 0.4% (v/v) trifluoroacetic acid and 0.1 M $NaNO_3$ (aq) at a flow rate of 0.25 mL/min, Eprogen Inc. CATSEC columns (100, 300, and 1000 Å) connected in series with a Wyatt Optilab DSP interferometric refractometer (λ = 690 nm) and Wyatt DAWN EOS multiangle laser light scattering (MALLS) detector (λ = 633 nm). Absolute molecular weights and $Đ_M$ were calculated using a Wyatt ASTRA SEC/LS software package. d*n*/d*c* values were determined offline utilizing a Wyatt Optilab DSP interferometric refractometer (λ = 690 nm) at 25 °C and Wyatt ASTRA d*n*/d*c* software.



Scheme S1. Synthetic routes to (a) 2-(ethylthiocarbonothioylthio) 2-(2-imidazolin-2-yl)propane hydrochloride (ImET), (b) methacryloyl hydrazide hydrochloride (MAH), and (c) (2-methacrylamidoethyl) carbohydrazide hydrochloride (MAEH).

Sodium Ethyl Trithiocarbonate (1). A suspension of NaH (2.11 g, 83.5 mmol) in anhydrous diethyl ether (150 mL) was cooled to 0 °C using an ice bath, upon which ethanethiol (5.73 g, 92.3 mmol) was added over 15 min accompanied by vigorous evolution of hydrogen gas. The reaction was stirred for an additional 15 min at 0 °C followed by dropwise addition of CS_2 (7.03g, 92.3 mmol) over 5 min and the reaction stirred for an additional 60 min at room

temperature. The reaction was diluted with pentane (100 mL) and the yellow precipitate isolated by vacuum filtration before drying *in-vacuo* yielding **1** (12.07 g, 90%) as a hygroscopic yellow powder. ^{1}H NMR (300 MHz, D_2O) δ 3.16 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).

Bis(ethylsulfanylthiocarbonyl) Disulfide (2). Solid I_2 (8.63g, 34.0 mmol) was added to a suspension of sodium ethyl trithiocarbonate (9.89g, 61.7 mmol) in diethyl ether (200 mL) at room temperature over 5 min. The reaction was stirred for 60 min at room temperature and the precipitated NaI salts removed by vacuum filtration and washed with 50 mL diethyl ether. The filtrate was transferred to a separatory funnel and washed with 5% $Na_2S_2O_4$ (2 x 150 mL), H_2O (1 x 150 mL), and brine (1 x 150 mL) before drying over $MgSO_4$. The solvent was removed via rotary evaporation followed by drying *in-vacuo* to yield **2** (8.13 g, 96%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (q, J = 7.4 Hz, 4H), 1.35 (t, J = 7.4 Hz, 6H).

2-(Ethylthiocarbonothioylthio) 2-(2-Imidazolin-2-yl)propane Hydrochloride (ImET, 3). Bis(ethylsulfanylthiocarbonyl) disulfide (3.00 g, 11.0 mmol) and VA-044 (5.30 g, 16.3 mmol) were combined in anhydrous MeOH (250 mL) and heated at 65 °C for 18 h. The reaction was quenched by cooling to room temperature and exposing to air followed by removal of the solvent via rotary evaporation. CH_2Cl_2 (75 mL) was added to the crude solid, inducing precipitation of residual VA-044, which was then removed via vacuum filtration. The filtrate was isolated and the solvent removed by rotary evaporation and the crude product dissolved in acetonitrile (35-40 °C) followed by recrystallization at 0 °C to give **3** (ImET) (4.65 g, 75%) as orange needle-like crystals. ^{1}H NMR (300 MHz, D2O) δ 3.38 (s, 1H), 2.77 (q, J = 7.3 Hz, 1H), 1.25 (s, 6H), 0.75 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, D_2O) δ 221.09, 173.63, 49.18, 44.78, 31.73, 24.94, 12.21.

***tert*-Butyl 2-Methacryloylhydrazinecarboxylate (4).** *tert*-Butyl carbazate (8.72g, 66.0 mmol) and triethylamine (6.68g, 66.0 mmol) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0ºC in an ice bath. Methacryloyl chloride (6.27g, 60.0 mmol) was added to the solution dropwise over 15 min and the reaction was allowed to warm to room temperature. The reaction was stirred for 2 h under N_2 and then washed with 0.5 M HCl in 50% brine (3 x 100 mL), saturated $NaHCO_3$ (1 x 100 mL), and brine (1 x 100 mL). The organic layer was dried over Na_2SO_4 before the solvent was removed via rotary evaporation to yield **4** (9.04g, 75%) as a white crystalline solid. ^{1}H NMR (300 MHz, CDCl3) δ 8.69 (s, 1H), 7.08 (s, 1H), 5.80 (s, 1H), 5.34 (s, 1H), 1.90 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.96, 156.06, 137.48, 121.61, 81.57, 28.11, 18.39.

Methacryloyl Hydrazide Hydrochloride (MAH, 5). *tert*-Butyl 2-methacryloylhydrazinecarboxylate (7.97g, 39.8 mmol) was dissolved in anhydrous THF (10 mL) under a N_2 atmosphere. To this solution, 2M HCl in diethyl ether (200 mL, 0.4 mol HCl) was transferred via cannula and stirred at room temperature for 24 h. The precipitate was isolated by vacuum filtration, rinsed with diethyl ether, and dried *in-vacuo* to give **5** (4.31g, 79%) as a white solid. ^{1}H NMR (300 MHz, D_2O) δ 5.79 (s, 1H), 5.59 (s, 1H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ 169.33, 135.49, 124.16, 16.96.

Carboxyethyl Methacrylamide (6). Methacryloyl chloride (9.39 g, 90 mmol) in acetonitrile (30 mL) was added dropwise over 30 min to a solution of β-alanine (8.00 g, 90 mmol) and BHT (100 mg, inhibitor) in 1 N NaOH (180 mL) and acetonitrile (80 mL) at 0 °C. The reaction was then stirred for 60 min at room temperature upon which NaCl (25 g) was added to the reaction mixture followed removal of acetonitrile by rotary evaporation. The aqueous solution was then cooled using an ice bath and the solution acidified to pH = 2 using 12 N HCl. The acidified solution was transferred to a separatory funnel and extracted with EtOAc (4 x 100 mL) followed

by washing the combined EtOAc extracts with brine (1 x 200 mL). The organic layer was isolated, dried over Na_2SO_4, and the solvent removed by rotary evaporation to yield **6** (11.94 g, 85%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (s, 1H), 6.81 (s, 1H), 5.67 (s, 1H), 5.29 (s, 1H), 3.53 (q, *J* = 3.5 Hz, 2H), 2.56 (t, *J* = 5.1 Hz, 2H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.27, 169.12, 139.08, 120.81, 35.14, 33.55, 18.43.

***tert*-Butyl 2-(3-Methacrylamidopropanoyl)Hydrazinecarboxylate (7).** A solution of carboxyethyl methacrylamide (11.73 g, 75 mmol) and BHT (100 mg, inhibitor) in anhydrous CH_2Cl_2 (300 mL) was added via cannula over 15 min to a suspension of 1,1'-carbonyldiimidazole (12.10 g, 75 mmol) in anhydrous CH_2Cl_2 (250 mL) and the resulting homogenous solution stirred at room temperature for an additional 90 min. *tert*-Butyl carbazate (10.85 g, 82 mmol) was then added as a solid followed by DBU (0.52 mL, 3.5 mmol) and the reaction stirred at room temperature for 4 h. The reaction mixture was then filtered of any solids and the filtrate transferred to a separatory funnel and washed with a 4:1 (v:v) mixture of brine and 4N HCl (2 x 200 mL), brine (1 x 200 mL), and dried over Na_2SO_4 before removing the solvent via rotary evaporation to yield **7** (17.03g, 84%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 6.92 (s, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 5.75 (s, 1H), 5.30 (s, 1H), 3.67 – 3.54 (m, 2H), 2.47 (t, *J* = 5.8 Hz, 2H), 1.92 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.12, 168.79, 155.63, 139.30, 120.40, 81.62, 35.87, 33.56, 28.10, 18.46.

(2-Methacrylamidoethyl) Carbohydrazide Hydrochloride (MAEH, 8). A suspension of *tert*-butyl 2-(3-methacrylamidopropanoyl)hydrazinecarboxylate (10.00 g, 37 mmol) in anhydrous diethyl ether (150 mL) was cooled to 0 °C followed by the addition 2.0 M HCl in diethyl ether (130 mL, 260 mmol) via cannula over 30 min. The reaction was stirred overnight (18 h) at room temperature upon which the precipitated product was briefly isolated by vacuum filtration. The

hygroscopic white solid was then triturated with a 1:1 (v:v) mixture of anhydrous diethyl ether and cyclohexane (3 x 50 mL) followed by trituration with cyclohexane (1 x 50 mL) and dried overnight *in-vacuo* to yield **8** (7.65 g, 82%) as a hygroscopic solid that was stored under nitrogen at -10 °C. ^{1}H NMR (300 MHz, D_2O) δ 5.62 (s, 1H), 5.39 (s, 1H), 3.50 (t, *J* = 6.3 Hz, 2H), 2.54 (t, *J* = 6.3 Hz, 2H), 1.85 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ 171.83, 171.73, 138.72, 121.14, 35.23, 32.78, 17.48.

Monomer Titrations. Monomer stock solutions of MAH or MAEH (1 mM) were first prepared by weighing each monomer (0.1 mmol) into separate 100 mL volumetric flasks, followed by the addition of 2.00 mL of 0.05 N HCl (0.1 mmol) to each flask. Once the monomers were completely dissolved, DI H_2O (18.2 MΩ) was added to each volumetric flask to achieve a final volume of 100 mL. Twenty-five mL of each stock solution was transferred to a 100 mL beaker containing a stir bar and titrated against 0.05 N NaOH in volume increments of 5 µL at 25 °C using a Metrohm 848 Titrino Plus autotitrator. All titrations were performed in triplicate. Monomer pK_a values were determined using eq 1, where $pH_{EP1/2}$ is the pH corresponding to the half equivalence point ($EP_{1/2}$) of the titration curve. The volume of NaOH titrant required to reach $EP_{1/2}$ ($Vol_{EP1/2}$) was determined by eq 2, where Vol_{EP} is the volume of NaOH titrant required to reach the equivalence of the titration curve, [monomer] is the concentration of monomer being titrated, [NaOH] is the concentration of titrant used, and Vol_{sol} is the initial volume of the monomer solution being titrated. Figure S1 of the supporting information shows the positions of EP and $EP_{1/2}$ on the titration curve obtained for MAEH.

$$pK_a = pH_{EP_{1/2}} \quad (1)$$

$$Vol_{EP_{1/2}} = Vol_{EP} - \frac{1}{2}\frac{[monomer]}{[NaOH]}Vol_{sol} \quad (2)$$

Trithiocarbonate Degradation Analysis by UV−Vis. Reactions (final volume = 2500 μL) were performed using $[ImET]_0 = 5 \times 10^{-3}$ M and $[M]_0$:$[ImET]_0$:$[VA\text{-}044]_0$ = 10:1:0.2 in 1 N HCl. A typical procedure was as follows: MAEH (250 μL of an 103.8 mg/mL stock solution in 1 M HCl, 10 equiv), ImET (250 μL of a 14.2 mg/mL stock soln. in 1 M HCl, 1 equiv), VA-044 (25 μL of a 32.3 mg/mL stock solution in 1 N HCl, 0.2 equiv), and 1 M HCl (1975 μL) were combined in a 4 mL test tube equipped with magnetic stir bar and rubber septum. The reaction was then degassed via three freeze-pump-thaw cycles and backfilled with argon. An initial aliquot (50 μL) was taken using an argon-purged gastight syringe and subsequently diluted into a quartz cuvette containing 2500 μL of DI water (18.2 M) before measuring the absorbance at λ = 315 nm using a Lambda 35 UV-vis spectrometer. Subsequent aliquots (50 μL) were taken and analyzed in the same manner.

General Procedure for RAFT Polymerization of MAH and MAEH. An acyl hydrazide-containing monomer, MAH or MAEH, (4.8×10^{-3} mol) was added to a vial containing a magnetic stir bar and dissolved in a solution of RAFT agent, 2-(ethylthiocarbonothioylthio) 2-(2-imidazolin-2-yl)propane hydrochloride (ImET) (1.93×10^{-5} mol) in 1.0 M HCl. Initiator (VA-044) (4.8×10^{-6} mol) and benzene sulfonic acid (70 mg, ^{1}H NMR internal standard) were then combined in the vial with monomer and RAFT agent and 1.0 M HCl was added to achieve a final solution volume of 4.8 mL ($[M]_0$= 1 M). The vial containing the polymerization solution was then capped with a rubber septum and purged with argon for 40 min. before placing the reaction vessel in an oil bath preheated to 40 ºC. To monitor polymerization kinetics, an initial aliquot (200 μL) was taken after degassing, but prior to placing reaction vessel in an oil bath. After initiating the polymerization, additional aliquots for kinetic measurements were taken at timed intervals. Aliquots were analyzed by ^{1}H NMR (D_2O) to determine monomer conversion

and SEC-MALLS to determine molecular weights and dispersities. Polymers derived from monomers MAH and MAEH are denoted pMAH and pMAEH, respectively, and were purified via precipitation in 10-fold excess isopropanol followed by lyophilization from 1 M HCl.

Titration Data:

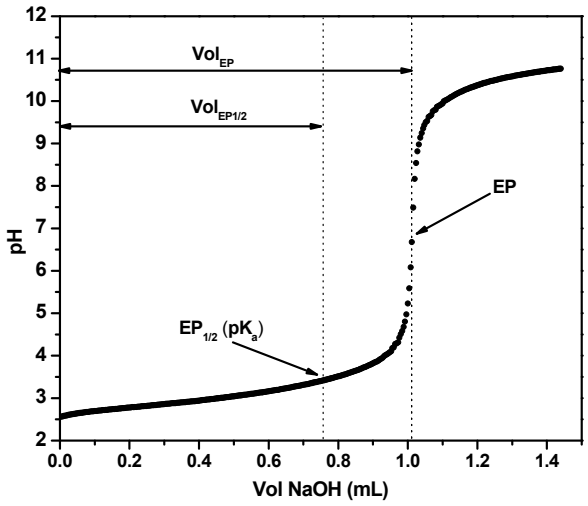


Figure S1. EP and $EP_{1/2}$ locations on the titration curve of MAEH (1 mM) titrated against NaOH (0.05 N) at 25 °C using a Metrohm 848 Titrino Plus autotitrator.

Table S1. pKa values determined for MAH and MAEH and control pKa determination for imidazole via titration.

	EP run 1	EP run 2	EP run 3	Summary	
Monomer	pK_a	pK_a	pK_a	Avg. pK_a	STD Dev.
MAH	**3.68**	**3.72**	**3.70**	**3.70**	**0.02**
MAEH	**3.42**	**3.43**	**3.43**	**3.43**	**0.01**

Selected ^{1}H and ^{13}C NMR Spectra

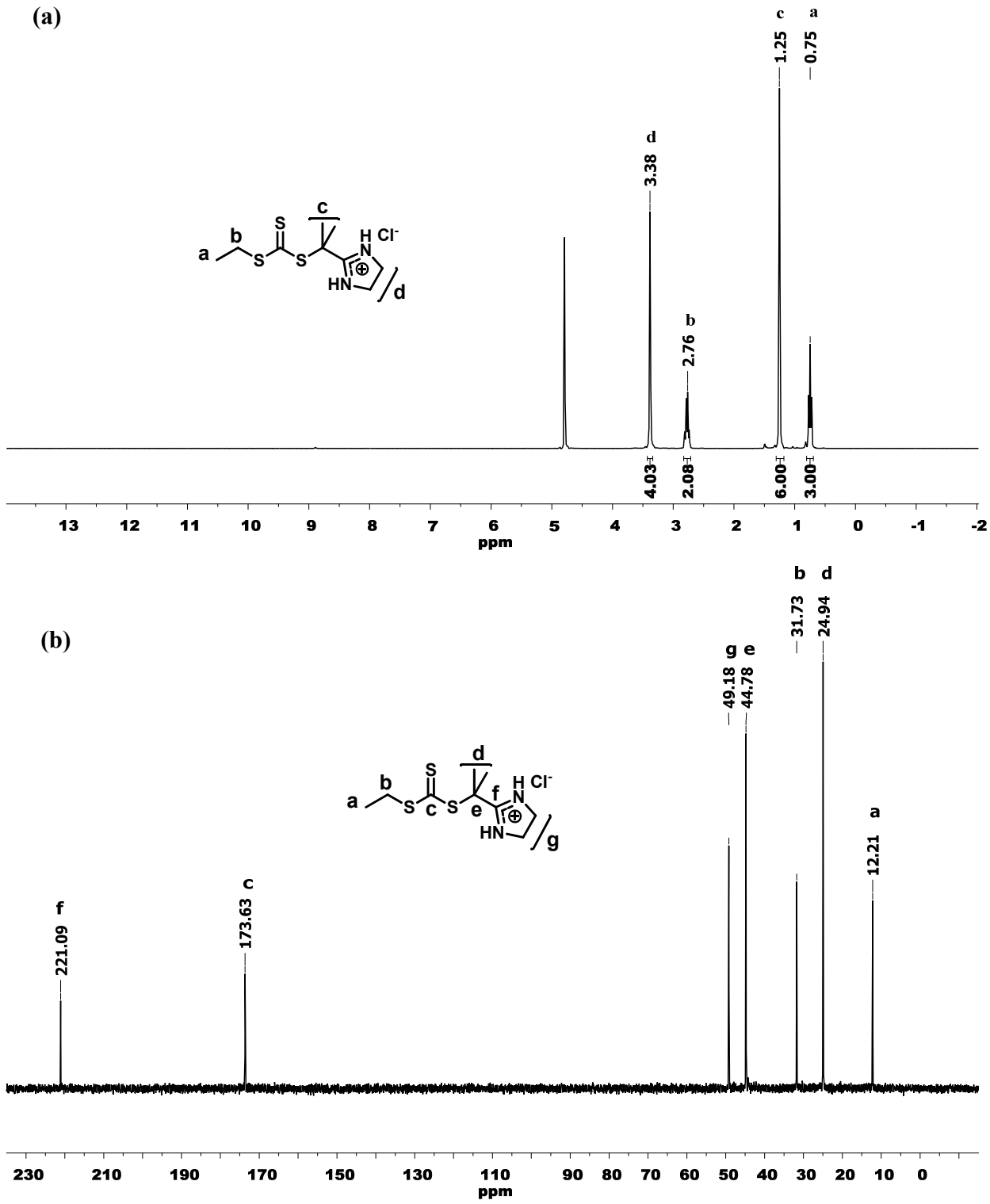


Figure S2. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of 2-(ethylthiocarbonothioylthio) 2-(2-imidazolin-2-yl)propane hydrochloride (ImET, 3).

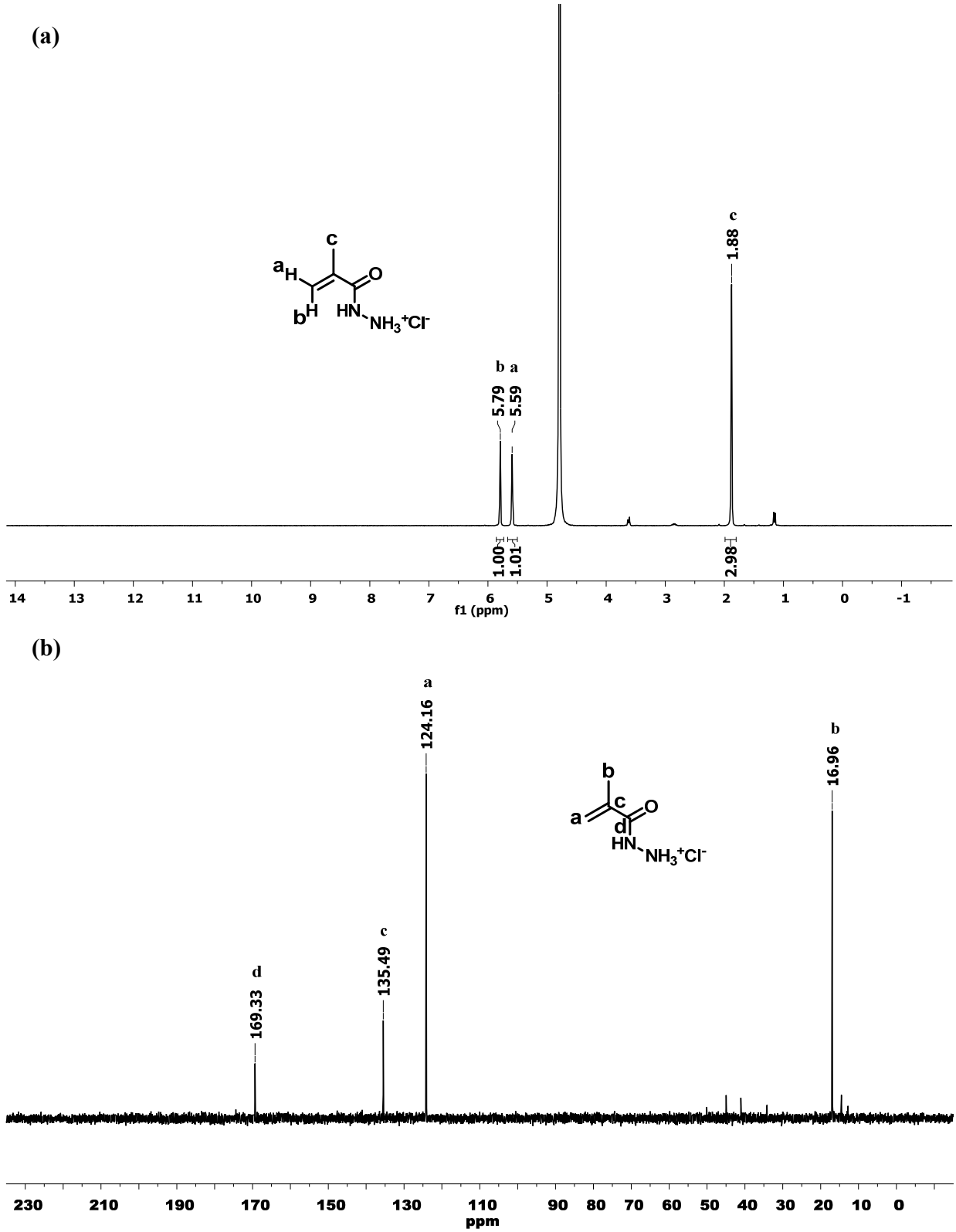


Figure S3. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of methacryloyl hydrazide hydrochloride (MAH, 5).

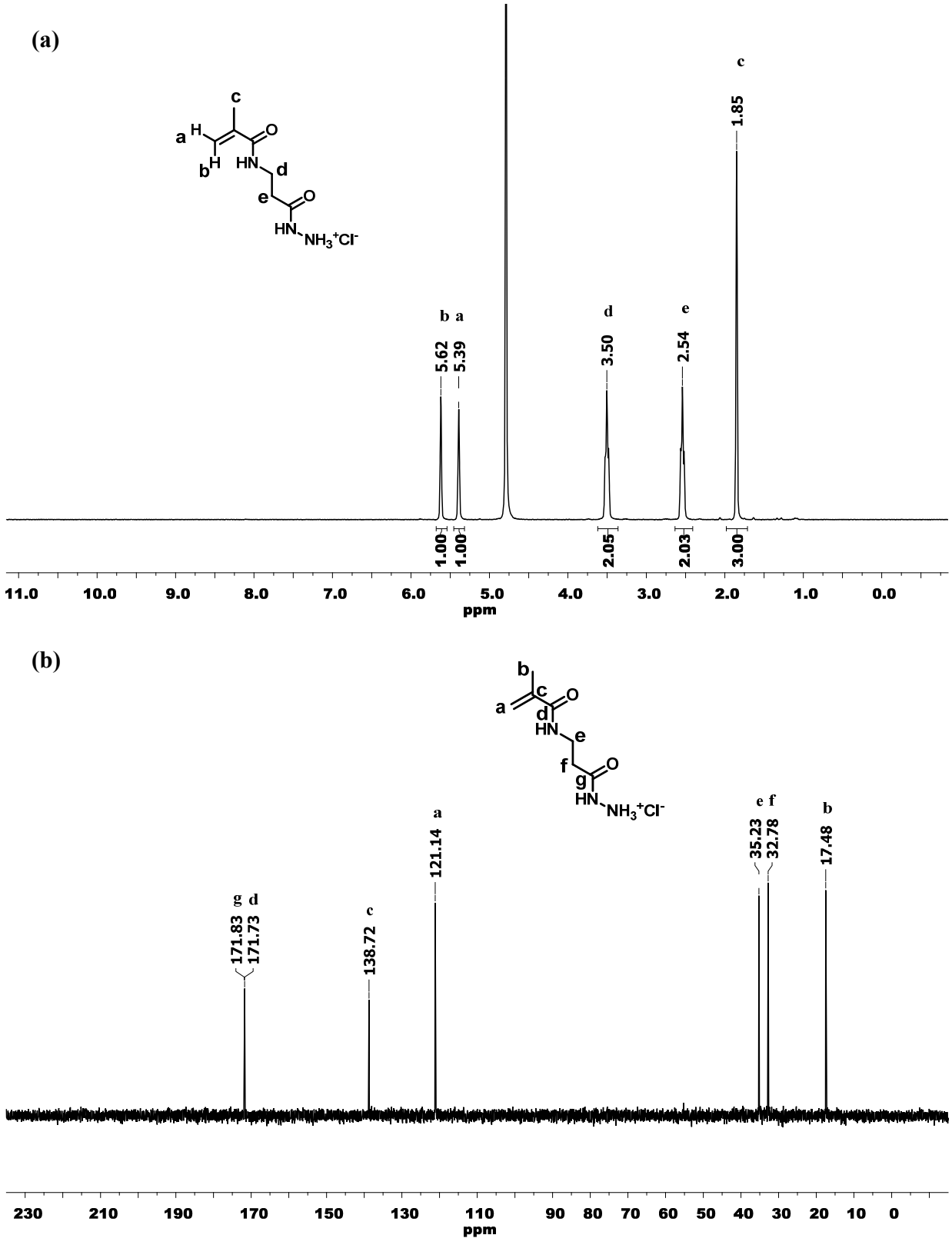


Figure S4. (a) ^{1}H NMR and (b) ^{13}C NMR spectra of (2-methacrylamidoethyl) carbohydrazide hydrochloride (MAEH, 8).

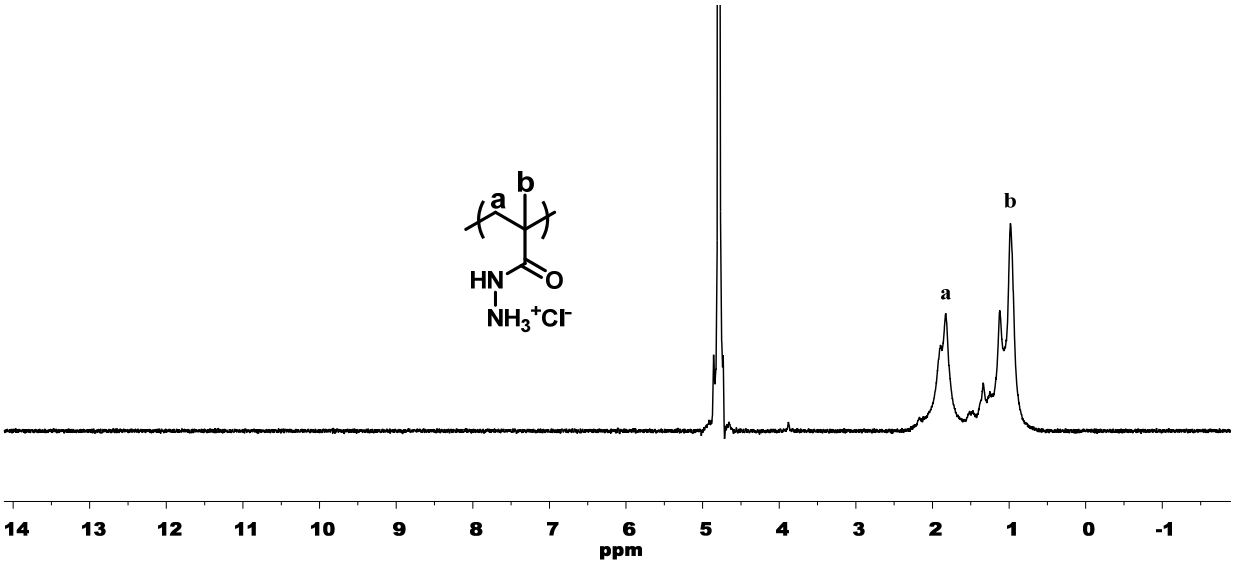


Figure S5. ^{1}H NMR of pMAH.

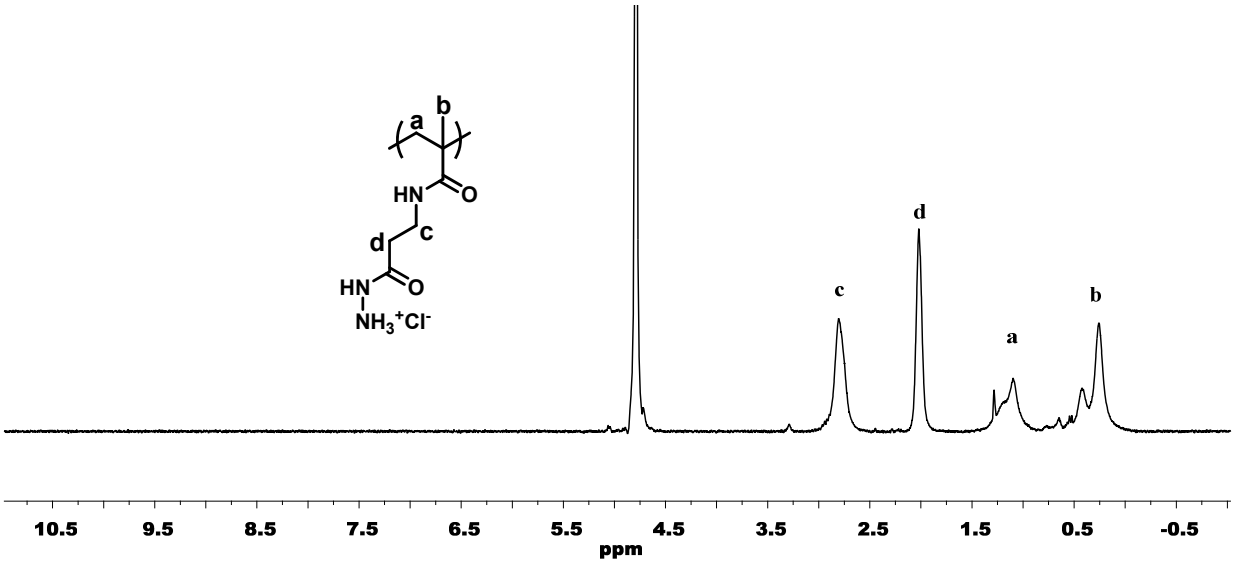


Figure S6. ^{1}H NMR of pMAEH.