Efficient Synthesis and RAFT Polymerization of the Previously Elusive *N*-[(Cycloalkylamino)methyl]Acrylamide Monomer Class

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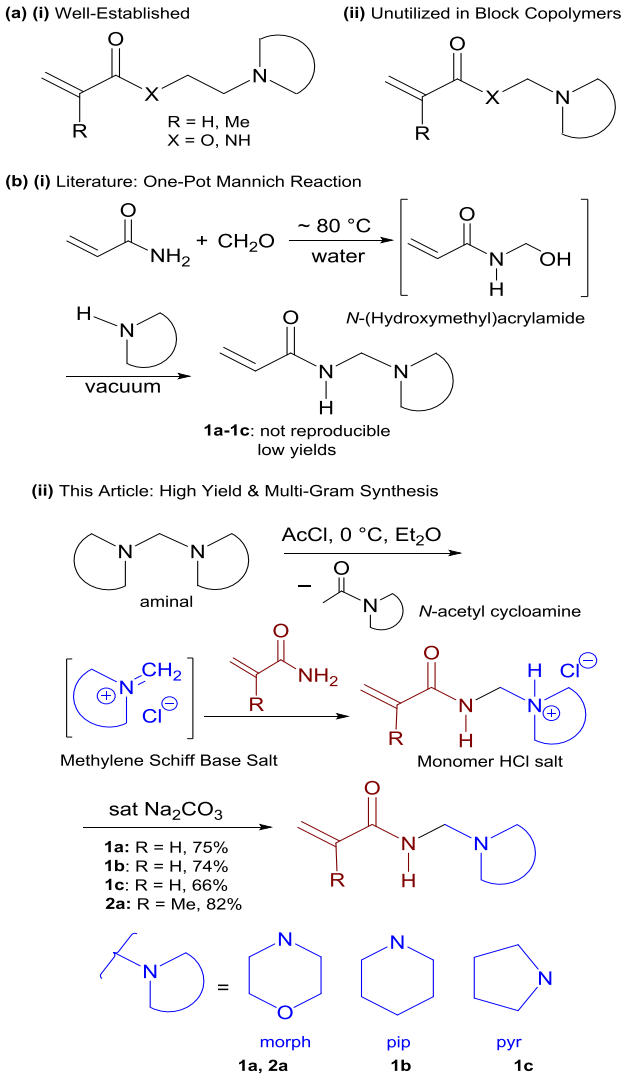
(Additional Supporting Information may be found in the online version of this article.)

Saturated nitrogen heterocycles (SNHs) have recently been utilised as ionisable tertiary amino groups in amphiphilic block copolymers allowing rapid switching between a hydrophobic and hydrophilic state. Gao et al reported copolymers consisting of poly(ethylene oxide) (PEO) and methacrylate blocks containing SNH substituents, which self-assembled into micelles before lowered pH caused dissociation and increased fluorescence emission.[1] Efficient penetration of dendrimers incorporating platinum prodrugs was facilitated by analogous amphiphilic block copolymers with pH-sensitive azepane substituents enabling nanoparticle collapse in the acidic environments of tumour cells.[2] The pH-responsive SNH was incorporated using reversible deactivation radical polymerizations[3] of 2-(cycloalkylamino)ethyl (meth)acrylates or 2-(cycloalkylamino)ethyl (meth)acrylamides (Scheme 1a(i)) with nitroxide mediated radical polymerization (NMP),[4] atom transfer radical polymerization (ATRP),[1,5] and reversible addition fragmentation chain transfer radical polymerization (RAFT)[2,6,7] of these monomers reported. There are, however, scarce reports of polymerizations (including no controlled/living polymerizations) of *N*-[(cycloalkylamino)methyl](meth)acrylamides containing a methylene amine (e.g. cycloalkylamino = SNH) rather than an ethyl amine pendent, presumably due to difficulties in their synthesis (Scheme 1a(ii)).[9-11]



SCHEME 1 *N*-[(Cycloalkylamino)methyl]Acrylamides**: (a)** Preponderance **(b)** Synthesis.

The literature NMR data of *N*-[(morpholino-4-yl)methyl]prop-2-enamide **1a**, which is erroneous (due to insufficient signals and incorrect chemical shifts) is evidence of the synthetic challenge posed by these molecules.[10] Müller et al described monomer preparations

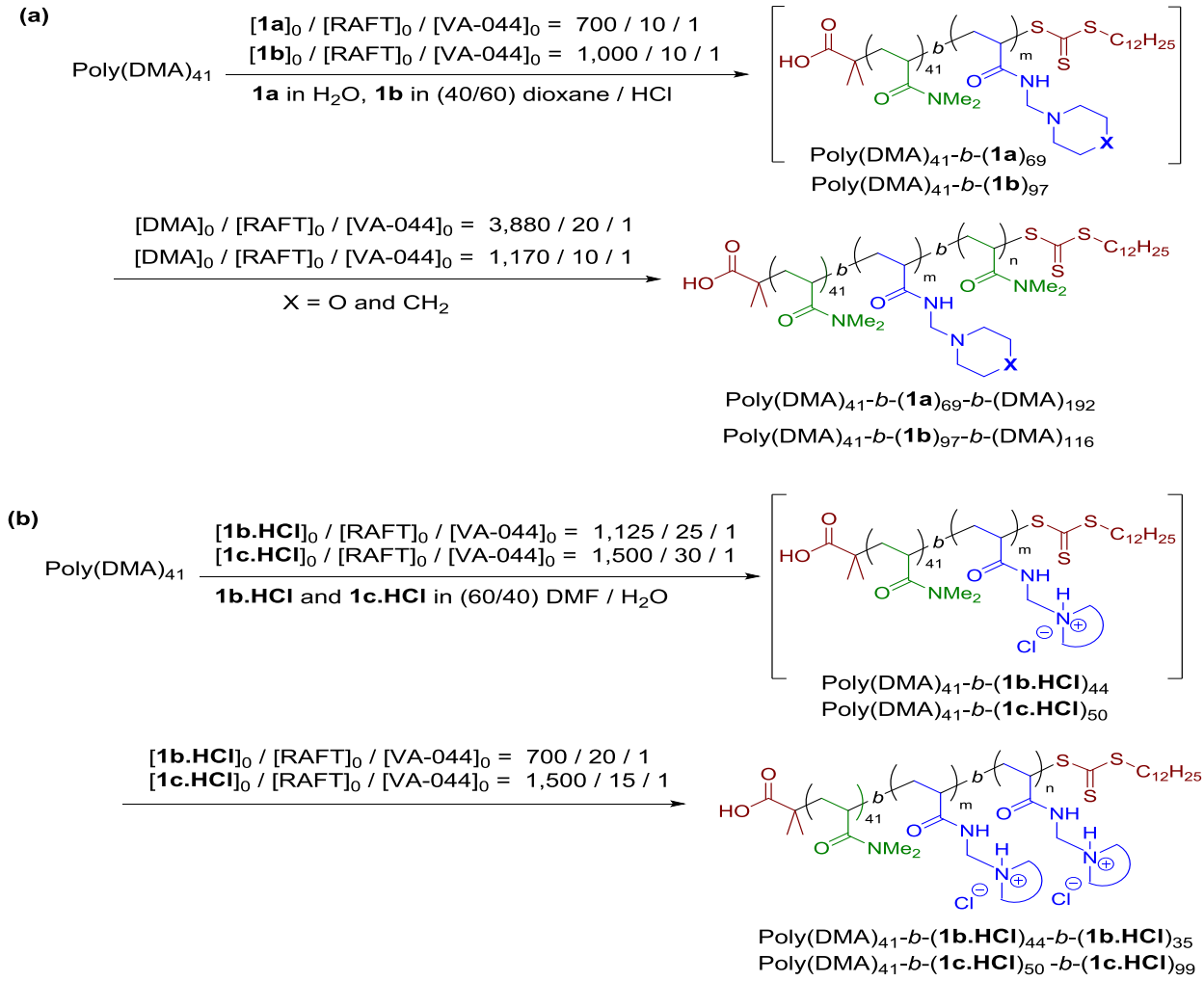
as far back as the early 1960s involving one-pot Mannich reactions of formaldehyde with acrylamide to give *N*-(hydroxymethyl)acrylamide followed by addition of the secondary amine (Scheme 1b(i)).[8,9] The Mannich approaches are however low yielding due to inadvertent thermal polymerization or degradation of the monomer or intermediates at the elevated reaction temperatures (~80 °C) with monomer isolation requiring difficult distillations from the aqueous reaction mix. A new monomer synthesis is now introduced based on the concept of Böhme,[12,13] involving *in situ* generation of the methylene Schiff base salt by convenient quaternization of the readily accessible aminal (Scheme 1b(ii)). Herein our new facile room temperature protocol has allowed the efficient multi-gram preparation of acrylamides **1a-1c** with methylene SNH substituents via basification of the respective heterocyclic monomer hydrochloride salts **1a.HCl-1c.HCl**. The expedient synthesis motivated us to carry out the first controlled/living polymerizations of this previously elusive monomer class, as well as, its hydrochloride salts using the RAFT process. Living polymerization infers the retention of the ω-end (RAFT) group, which we now demonstrate through efficient preparation of block copolymers by rapid sequential monomer addition so, providing a straightforward means of incorporating new acrylamides containing bridged pH-responsive SNHs into intricate well-defined polymer architectures.

Inexpensive aminals were first prepared in high yields (80-99%) by condensing formaldehyde (37% formalin) with secondary cyclic amines using well-established literature procedures.[14,15] Aminals were quaternized using acetyl chloride in dry acetonitrile, which formed *in situ* the methylene Schiff base salts, along with the *N*-acetyl cycloamine. Nucleophilic addition of acrylamide onto the Schiff base salts gave the hydrochloride monomer salts (**1a.HCl**, **1b.HCl**, **1c.HCl**) after precipitation from diethyl ether, which also served to separate the *N*-acetyl cycloamine since the latter remained in solution. The HCl salts were suspended in dichloromethane, and basified to give the SNH containing acrylamide monomers **1a**-**1c**. The entire synthesis was conducted at 0 °C to room temperature, thus circumventing potential thermal side-reactions giving at any one time 20-25 g of each of the three monomers **1a-1c**. Overall monomer yields were ~75% for the morpholine **1a** and piperidine **1b** with a lower yield of 66% obtained for the pyrrolidine monomer **1c** due to its inherent hygroscopic nature and low melting point. The scope of the monomer synthesis is demonstrated by the easy preparation of methacrylamide analogues with over 30 g of morpholine analogue **2a** prepared in 82% yield.

Our polymerization strategy is based upon that of Zetterlund and Perrier et al, who demonstrated the use of the RAFT process in yielding well-defined multi-component polyacrylamide block copolymers in one pot without intermittent purification by use of the water soluble azo-initiator, VA-044, where each block was prepared in ~99% conversion in 2 h at 70 °C.[16] Although evidence for living/controlled homopolymerization of **1a** was obtained through efficient chain extension of poly(**1a**)$_{60}$ to give poly(**1a**)$_{130}$ (Figure S1), one-pot block copolymer synthesis (without intermediate polymer isolation) was hampered by the inability to achieve full conversion for the RAFT of **1a** using both 2 h polymerizations with VA-044 and longer polymerization times with AIBN. Consequently, polymerizations employed water-soluble poly(*N*,*N*-dimethylacrylamide, DMA)$_{41}$ as the macroRAFT agent, since this could be prepared in high conversion and theoretical livingness (both 99%, see Supporting Information) so providing the ideal start for two sequential 2 h one-pot chain extensions at 70 °C (Scheme 2).[16,17] Under these conditions, VA-044 undergoes near-complete homolytic decomposition (~95%) into radicals, and an almost quantitative fraction of living chains is maintained by use of high $[RAFT]_0/[VA\text{-}044]_0$ ratios (e.g. $[RAFT]_0/[VA\text{-}044]_0$ = 10-100 provides 91-99% livingness, according to eq. 1).

$$L = \frac{[RAFT]_0}{[RAFT]_0 + 2f[I]_0\left(1-e^{-k_d t}\right)\left(1-\frac{f_c}{2}\right)} \qquad (1)$$

Eq. 1 estimates the theoretical fraction of living chains (L). The factor "2" accounts for one molecule of azo-initiator yielding two primary radicals with the efficiency f (assumed to be equal to 0.5). The decomposition rate constant is k_d is taken as 4.30 x 10^{-4} s^{-1} for VA-044 at 70 °C in water/dioxane (80:20).[17] The quantity represents the number of chains produced in a radical–radical termination event with the coupling factor f_c assumed to be zero.[16,17]



SCHEME 2 One-pot 2 hour sequential RAFT polymerizations at 70°C without intermediate purifications of **(a)** acrylamide monomers and DMA **(b)** monomer hydrochloride salts. All conversions were 99% except for the chain extension with **1b**, which was 97%.

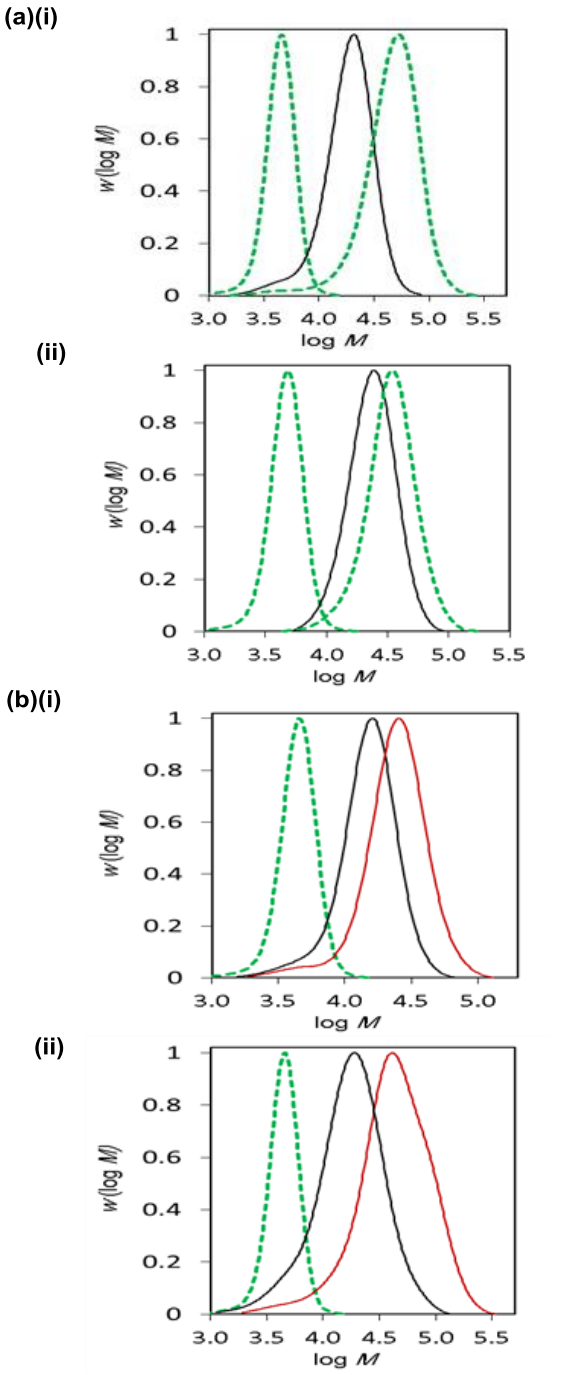


FIGURE 1 MWDs for one-pot RAFT polymerizations of *N*-[(cycloalkylamino)methylene]acrylamides (continuous lines) using poly(DMA) macroRAFT (where DMA polymerizations are dashed lines) to give **(a) (i)** poly(**DMA**)$_{41}$-*b*-(**1a**)$_{69}$-*b*-(**DMA**)$_{192}$; **(ii)** poly(**DMA**)$_{41}$-*b*-(**1b**)$_{97}$-*b*-(**DMA**)$_{116}$; **(b) (i)** poly(**DMA**)$_{41}$-*b*-(**1b.HCl**)$_{44}$-*b*-(**1b.HCl**)$_{35}$; **(ii)** poly(**DMA**)$_{41}$-*b*-(**1c.HCl**)$_{50}$-*b*-(**1c.HCl**)$_{99}$.

Two one-pot chain extensions were carried out to near full conversion (~99%), as monitored by ^{1}H NMR (Figures S2 and S3). The solubility of the macroRAFT agent and initiator allowed chain extensions of poly(DMA)$_{41}$ to give poly(DMA)$_{41}$-*b*-(**1a**)$_{69}$-*b*-(DMA)$_{192}$ to be carried out in water (Scheme 2a). In order to negate purification prior to chain extension with DMA polymerizations to give the intermediate diblock using morpholine **1a** and piperidine **1b** required a relatively high VA-044 concentration ([RAFT]$_0$/[VA-044]$_0$ = 10) for near-complete conversion. For the synthesis of water soluble poly(DMA)$_{41}$-*b*-(**1a**)$_{69}$-*b*-(DMA)$_{192}$, MWDs (molecular weight distributions) remained relatively narrow (M_w/M_n = 1.35-1.50) shifting to higher MW with M_n values close to theoretical ($M_{n,th}$) despite inherent GPC error due to calibration to linear poly(MMA) standards (Table 1). In contrast the polymerization of piperidine **1b** required dioxane due to the formation of a more hydrophobic diblock, however mixtures using varied dioxane/water gave broad MWDs for chain extension of poly(DMA)$_{41}$ with **1b**.

Recent work by Abel and McCormick on the RAFT polymerization of methacrylamides has shown that livingness through preservation of the trithiocarbonate end-group can be achieved by utilizing acidic solutions, which protonate nucleophilic sites (including the *N* atom of the amide).[18,19] This led to the addition of 1.15 equivalents of HCl to the chain extension of poly(DMA)$_{41}$, which gave poly(DMA)$_{41}$-*b*-(**1b**)$_{97}$ in 97% conversion with excellent control/living character as demonstrated by narrow MWD (M_w/M_n = 1.22) with M_n close to $M_{n,th}$ (Figure 1a(ii) and Table 1). It seems that protonation of the piperidine ring of the poly(**1b**) block prevented aminolysis side-reactions that cleave the trithiocarbonate end-group, and that this phenomenon is decreased or is absent for morpholine **1a** due to the electronegative oxygen atom of the heterocycle. Subsequent one-pot chain extension with DMA gave poly(DMA)$_{41}$-*b*-(**1b**)$_{97}$-*b*-(DMA)$_{116}$ with no noticeable loss of control/livingness.

The polymerization of the hydrochloride salts were carried out in 60/40 DMF/water reaction solutions rather than pure water, since the mixed solvent system maintained a homogeneous reaction mixture (Scheme 2(b)). Two sequential chain extensions of poly(DMA)$_{41}$ with the monomer salts were indicative of good control/living character (Figure 1b(i)(ii). Lower initiator concentrations were required for the first chain extension compared to the second for polymerizations with piperidine hydrochloride **1b.HCl** and pyrrolidine hydrochloride **1c.HCl** with high conversion and theoretical livingness (both ~99%) achieved. The successful RAFT polymerization of the ionized monomer salts **1b.HCl** and **1c.HCl**, overcame the lack of chain extension of poly(DMA)$_{41}$ with the free heterocyclic base monomers (Figure S4). Although MWDs shifted to higher MW with M_n close to $M_{n,th}$ (Table 1), the MWDs for **1c.HCl** (M_w/M_n = 1.66-1.80) were noticeably broader than **1b.HCl** (M_w/M_n = 1.31-1.40).

TABLE 1 Characterization of Polyacrylamides

Polymer [a]	$M_{n,th}$ [b]	M_n [d]	M_w/M_n [d]
Poly(DMA)$_{41}$	5300	4450	1.10
Poly(DMA)$_{41}$-*b*-(**1a**)$_{69}$	16250	15280	1.35
Poly(DMA)$_{41}$-*b*-(**1a**)$_{69}$-*b*-(DMA)$_{192}$	34300	34850	1.50
Poly(DMA)$_{41}$-*b*-(**1b**)$_{97}$	20750[c]	20800	1.22
Poly(DMA)$_{41}$-*b*-(**1b**)$_{97}$-*b*-(DMA)$_{116}$	32300[c]	29200	1.25
Poly(DMA)$_{41}$-*b*-(**1b.HCl**)$_{44}$	13550	12750	1.31
Poly(DMA)$_{41}$-*b*-(**1b.HCl**)$_{44}$-*b*-(**1b.HCl**)$_{35}$	19850	19750	1.40
Poly(DMA)$_{41}$-*b*-(**1c.HCl**)$_{50}$	13900	12850	1.66
Poly(DMA)$_{41}$-*b*-(**1c.HCl**)$_{50}$-*b*-(**1c.HCl**)$_{99}$	31750	29800	1.80

[a]The degree of polymerization for poly(DMA)$_{41}$ is calculated using M_n from GPC (deducting the MW of the RAFT end groups), and for all other polymers degree of polymerization is calculated from conversion by ^{1}H NMR (= 99%, except for chain extension with **1b**, which was 97%). In each case the degree of polymerization is obtained by deducting the M_n(GPC) of the extended macroRAFT. [b]$M_{n,th}$ is calculated according to equation 2 (see Supporting Information). [c]$M_{n,th}$ does not take into account the addition of HCl to these polymerizations. [d]Determined by GPC/RI in DMF (0.01 M LiBr) using commercial linear poly(MMA) as molecular weight standards.

In conclusion, *in situ* generated Schiff base salts have allowed the multi-gram preparation of previously difficult to acquire methylene amino substituted monomers opening the way to the facile preparation of related acrylamides and methacrylamides with conceivable acyclic as well as cyclic amine substituents. RAFT polymerization has allowed the preparation of the first well-defined block copolymers, although the close proximity of the trithiocarbonate end-group to the tertiary amino substituent made control/living character for the piperidine and pyrrolidine monomers superior when the heterocyclic pendant was ionized. These new monomers undoubtedly have further synthetic potential and applications, including for the preparation of amphiphilic block copolymers and stimuli-responsive polymersomes for targeted delivery of therapeutics.

EXPERIMENTAL

Monomer synthesis: *N*-[(cycloamino)methyl]-acrylamides and methacrylamide (1a-1c and 2a).
AcCl (14.3 mL, 0.2 mol) was added over 30 min to the aminal (0.2 mol) in MeCN (40 mL) at 0 °C. Acrylamide (14.2 g, 0.2 mol) or methacrylamide (17.0 g, 0.2 mol) in MeCN (40 mL) was added, and stirred at room temperature for 2 h. Et_2O (50 mL) was added and the hydrochloride salt of the monomer precipitated, filtered, and dried under vacuum. The hydrochloride salt **(1a.HCl-1c.HCl and 2a.HCl)** was recrystallized, dried, and characterized. Saturated Na_2CO_3 solution (50 mL) was added to a suspension of hydrochloride salt in CH_2Cl_2 (50 mL) and stirred for 20 min. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to dryness to give the monomer, which was recrystallized.

***N*-[(morpholin-4-yl)methyl]prop-2-enamide hydrochloride (1a.HCl):** white solid; mp 146-148 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.84-3.36 (m, 4H), 3.66-4.05 (m, 4H), 4.54 (d, *J* = 6.8 Hz, 2H, 1-CH_2), 5.79 (dd, *J* = 10.2, 1.9 Hz, 1H, *cis*-H), 6.26 (dd, *J* = 17.2, 1.9 Hz, 1H, *trans*-H), 6.43 (dd, *J* = 17.2, 10.2 Hz, 1H), 9.60 (t, *J* = 6.8 Hz, 1H, NH), 11.22-11.42 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 48.6 (CH_2), 58.6 (1-CH_2), 63.0, 128.3 (both CH_2), 130.3 (CH), 166.2 (C=O).
***N*-[(morpholin-4-yl)methyl]prop-2-enamide (1a):** 25.5 g, Yield: 75%, white solid; mp 93-95 °C (recryst. from MeCN); ν_{max} (neat, cm^{-1}) 3254, 2860, 2825, 1669, 1648 (C=O), 1608, 1535, 1228, 1155, 1109; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.57 (t, *J* = 4.7 Hz, 4H), 3.69 (t, *J* = 4.7 Hz, 4H), 4.17 (d, *J* = 6.5 Hz, 2H, 1-CH_2), 5.70 (dd, *J* = 10.3, 1.4 Hz, 1H, *cis*-H), 5.91-6.05 (brs, 1H, NH), 6.10 (dd, *J* = 17.0, 10.3 Hz, 1H), 6.32 (dd, *J* = 17.0, 1.4 Hz, 1H, *trans*-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 50.5 (CH_2), 61.6 (1-CH_2), 66.4, 127.5 (both CH_2), 130.6 (CH), 166.2 (C=O); HRMS (ESI) *m/z* $[M+H]^+$, $C_8H_{15}N_2O_2$, calcd 171.1134, observed 171.1136.

***N*-[(piperidin-1-yl)methyl]prop-2-enamide hydrochloride (1b.HCl):** white solid, mp 143-145 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.27-1.42 (m, 1H), 1.60-1.84 (m, 5H), 2.82 (d, *J* = 11.2 Hz, 2H), 3.30 (d, *J* = 11.2 Hz, 2H), 4.47 (d, *J* = 6.5 Hz, 2H, 1-CH_2), 5.81 (dd , *J* = 10.0, 1.9 Hz, 1H, *cis*-H), 6.27 (dd *J* = 17.1, 1.9 Hz, 1H, *trans*-H), 6.38 (dd, *J* = 17.1, 10.0 Hz, 1H), 9.32-9.43 (brs, 1H, NH), 9.91-10.12 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4, 22.3, 49.8 (all CH_2), 58.7 (1-CH_2), 128.3 (CH_2), 130.6 (CH), 166.4 (C=O).

***N*-[(piperidin-1-yl)methyl]prop-2-enamide (1b):** 24.9 g, Yield: 74%, white solid, mp 55-57 °C (recryst. from Et_2O); ν_{max} (neat, cm^{-1}) 3276, 2936, 2807, 1669, 1650 (C=O), 1611, 1528, 1372, 1227, 1216, 1175, 1027; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.35-1.44 (m, 2H), 1.55 (p, *J* = 5.5 Hz, 4H), 2.49 (t, *J* = 5.5 Hz, 4H), 4.13 (d, *J* = 6.4 Hz, 2H, 1-CH_2), 5.65 (dd, *J* = 10.2, 1.4 Hz, 1H, *cis*-H), 6.10 (dd, *J* = 17.0, 10.2 Hz, 2H, CH, NH), 6.29 (dd, *J* = 17.0, 1.4 Hz, 1H, *trans*-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 24.2, 26.0, 51.5 (all CH_2), 62.2 (1-CH_2) 126.8 (CH_2), 131.2 (CH), 166.6 (C=O); HRMS (ESI) *m/z* $[M+H]^+$, $C_9H_{17}N_2O$, calcd. 169.1341, observed 169.1335.

***N*-[(pyrrolidin-1-yl)methyl]prop-2-enamide hydrochloride (1c.HCl):** white solid, mp 64-66 °C, (recryst. from EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.78-1.97 (m, 4H), 2.91-3.54 (m, 4H), 4.53 (d, *J* = 6.8 Hz, 2H, 1-CH_2), 5.78 (dd, *J* = 10.2, 1.9 Hz, 1H, *cis*-H), 6.24 (dd, *J* = 17.2, 1.9 Hz, 1H, *trans*-H), 6.41 (dd, *J* = 17.2, 10.2 Hz, 1H), 9.72 (t, *J* = 6.8 Hz, 1H, NH), 10.96-11.10 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 23.1, 50.6 (both CH_2), 56.0 (1-CH_2), 128.3 (CH_2), 130.6 (CH), 166.4 (C=O). **1c.HCl** should be stored under vacuum in a desiccator at room temperature.

***N*-[(pyrrolidin-1-yl)methyl]prop-2-enamide (1c):** 20.3 g, Yield: 66%, white solid, mp 29-30 °C, (recryst. from EtOAc), ν_{max} (neat, cm^{-1}) 3268, 2964, 1656 (C=O), 1627, 1537, 1232, 1135, 1031; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.69-1.81 (m, 4H), 2.57-2.65 (m, 4H), 4.25 (d, *J* = 6.3 Hz, 1H, 2H, 1-CH_2), 5.65 (dd, *J* = 10.2, 1.4 Hz, 1H, *cis*-H), 6.10 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.28 (dd, *J* = 17.0, 1.4 Hz, 1H, *trans*-H), 6.31-6.37 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 23.7, 50.9 (both CH_2), 58.3 (1-CH_2), 127.0 (CH_2), 130.9 (CH), 165.9 (C=O); HRMS (ESI) *m/z* $[M+H]^+$, $C_8H_{15}N_2O$, calcd 155.1184, observed 155.1176. Monomer **1c** should be stored under vacuum in a desiccator at room temperature.

2-Methyl-*N*-[(morpholin-4-yl)methyl]prop-2-enamide hydrochloride (2a.HCl): white solid, mp 123-125 °C (recryst. from MeCN); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.09 (s, 3H); 2.90-3.30 (m, 4H), 3.70-4.03 (m, 4H), 4.50 (d, *J* = 6.7 Hz, 2H), 5.58 (s, 1H), 5.95 (s, 1H), 9.20-9.22 (brs, 1H), 10.84-11.21 (m, 1H), ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.9 (CH_3). 49.2 (CH_2), 59.7 (1-CH_2), 63.5 (CH_2), 122.5 (CH_2), 138.9 (C), 169.3 (C=O).

2-Methyl-*N*-[(morpholin-4-yl)methyl]prop-2-enamide (2a): 30.2 g, Yield: 82%, white solid, mp 56-58 °C (recryst. from MeCN), ν_{max} (neat, cm^{-1}) 3315, 2960, 2853, 1655 (C=O), 1616, 1523, 1453, 1295, 1216, 1139, 1049, 1014; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.97 (s, 3H), 2.57 (t, *J* = 4.7 Hz, 4H), 3.70 (t, *J* = 4.7 Hz, 4H), 4.15 (d, *J* = 6.4 Hz, 2H), 5.36-5.37 (m, 1H), 5.70-5.71 (m, 1H), 6.15-6.25 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.8 (Me); 50.5 (CH_2), 61.6 (1-CH_2), 66.9, 119.9 (both CH_2), 140.0 (C), 169.0 (C=O); HRMS (ESI) *m/z* $[M+H]^+$, $C_9H_{17}N_2O_2$ calcd 185.1290, observed 185.1371.

General one-pot sequential polymerization procedure

Solutions were heated at 70 °C in an aluminum heating block for 2 h. Polymerizations were stopped by placing test tubes in an ice-water bath. Conversion, $M_{n,}$ and M_w/M_n were measured as described in the Supporting Information. Unless otherwise stated sequential chain extension reactions were performed directly on the macroRAFT reaction solution with the amount of initiator remaining after each cycle taken into account.[16,17]

Preparation of poly(DMA)$_{41}$-*b*-(1a)$_{69}$-*b*-(DMA)$_{192}$ copolymer

Poly(DMA)$_{41}$ (1.43 x 10^{-2} mmol) and **1a** (0.170 g, 1.00 mmol) were added to VA-044 (1.43 x 10^{-3} mmol from a stock solution) in 0.6 mL water and heated as described above. DMA (0.275 g, 2.78 mmol) and VA-044 (6.5 x 10^{-4} mmol from a stock solution) in 0.5 mL water were added to the latter poly(DMA)$_{41}$-*b*-(**1a**)$_{69}$ solution and heated as described above.

Preparation of poly(DMA)$_{41}$-*b*-(1b)$_{97}$-*b*-(DMA)$_{116}$ copolymer

Poly(DMA)$_{41}$ (8.54 x 10^{-3} mmol) and **1b** (0.144 g, 0.854 mmol) were added to VA-044 (8.54 x 10^{-4} mmol from a stock solution) in 0.3 mL HCl (3.28 M, 1.15 eq. HCl:Monomer) solution and 0.2 mL dioxane, and heated as described above. DMA (0.100 g, 1.01 mmol) and VA-044 (8.6 x 10^{-4} mmol from a stock solution) in 0.1 mL water were added to the latter poly(DMA)$_{41}$-*b*-(**1b**)$_{97}$ solution and heated as described above.

Preparation of poly(DMA)$_{41}$-*b*-(1b.HCl)$_{44}$-*b*-(1b.HCl)$_{35}$ copolymer

Poly(DMA)$_{41}$ (37.1 x 10^{-3} mmol) and **1b.HCl** (0.342 g, 1.67 mmol) were added to VA-044 (1.48 x 10^{-3} mmol from a stock solution) in 0.5 mL DMF/water (60/40) solution, and heated as described above. Monomer **1b.HCl** (0.264 g, 1.29 mmol) and VA-044 (1.84 x 10^{-3} mmol from a stock solution) in 0.5 mL DMF/water (60/40) were added to the latter poly(DMA)$_{41}$-*b*-(**1b.HCl**)$_{44}$ solution and heated as described above.

Preparation of poly(DMA)$_{41}$-*b*-(1c.HCl)$_{50}$-*b*-(1c.HCl)$_{99}$ copolymer

Poly(DMA)$_{41}$ (16.4 x 10^{-3} mmol) and **1c.HCl** (0.156 g, 0.82 mmol) were added to VA-044 (5.46 x 10^{-4} mmol from a stock solution) in 0.5 mL DMF/water (60/40) solution, and heated as described above. Monomer **1c.HCl** (0.313 g, 1.64 mmol) and VA-044 (1.09 x 10^{-3} mmol from a stock solution) in 0.5 mL DMF/water (60/40) were added to the latter poly(DMA)$_{41}$-*b*-(**1c.HCl**)$_{50}$ solution and heated as described above.

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REFERENCES AND NOTES

1 K. Zhou, Y. Wang, X. Huang, K. Luby-Phelps, B. D. Sumer, J. Gao, *Angew. Chem. Int. Ed.* **2011**, *50*, 6109-6114.
2 H. –J. Li, J. –Z. Du, J. Liu, X. –J. Du, S. Shen, Y. –H. Zhu, X. Wang, X. Ye, S. Nie, J. Wang, *ACS Nano.* **2016**, *10*, 6753-6761.
3 A. D. Jenkins, R. G. Jones, G. Moad, *Pure Appl. Chem.* **2010**, *82,* 483-491.
4 C. Magee, Y. Sugihara, P. B. Zetterlund, F. Aldabbagh, *Polym. Chem.* **2014**, *5,* 2259-2265.
5 Y. Li, Z. Wang, Q. Wei, M. Luo, G. Huang, B. D. Sumer, J. Gao, *Polym. Chem.* **2016**, *7,* 5949-5956.
6 L. Zhu, S. Powell, S. G. Boyes, *J. Polym. Sci. Part A: Polym. Chem.* **2015**, *53,* 1010-1022.
7 K. Wang, Z. Song, C. Liu, W. Zhang, *Polym. Chem.* **2016**, *7,* 3423-3433.
8 V. E. Müller, K. Dinges, W. Graulich, *Die Makromol. Chem.* **1962**, *57,* 27-51.
9 V. E. Müller, H. Thomas, *Angew. Makromol. Chem.* ***1*973**, *34,* 111-133.
10 M. L. Eritsyan, Z. B. Barsegyan, R. A. Karamyan, S. M. Manukyan, T. D. Karapetyan, K. A. Martirosyan, *Russ. J. Appl. Chem.* **2011**, *84,* 1257-1260.
11 R. C. Baltieri, L. H. Innocentini-Mei, W. M. S. C. Tamashiro, L. Peres, E. Bittencourt, *Eur. Polym. J.* **2002**, *38,* 57-62.
12 H. Böhme, K. Hartke, *Chem. Ber.* **1960**, *93,* 1305-1309.
13 H. Böhme, P. Backhaus, *Liebigs Ann. Chem.* **1975**, 1790-1796.
14 A. Porzelle, C. M. Williams, *Synthesis* ***2006,*** 3025-3030.
15 H. Heaney, G. Papageorgiou, R. F. Wilkins, *Tetrahedron.* **1997**, *53,* 2941-2958.
16 G. Gody, T. Maschmeyer, P. B. Zetterlund, S. Perrier, *Macromolecules* **2014**, *47,* 3451-3460.
17 G. Gody, T. Maschmeyer, P. B. Zetterlund, S. Perrier, *Macromolecules* **2014**, *47,* 639-649.
18 B. A. Abel, C. L. McCormick, *Macromolecules* **2016**, *49,* 465-474.
19 B. A. Abel, C. L. McCormick, *Macromolecules* **2016**, *49,* 6193-6202.