Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supplementary information

Looped flow polymerization for multiblock copolymer synthesis

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Experimental methods

Materials. 1, 4 dioxane (Sigma-Aldrich), *N*-Hydroxyethyl Acrylamide (HEAm, Sigma-Aldrich), *N*-Isopropylacrylamide (NIPAm, Sigma-Aldrich) and 2,2'-Azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044, Wako) were used without further purification. 4-Acryloylmorpholine (NAM), Dimethylacrylamide (DMAm) and Diethylacrylamide (DEAm) were purchased from Sigma-Aldrich and used after removing the inhibitor by passing through a column of aluminium oxide. Mili-Q water was directly used as a solvent for polymerizations. All polymerizations were carried out under a nitrogen atmosphere. The RAFT agent 3-((((1-carboxyethyl)thio)carbonothioyl)thio)propanoic acid (BM1429) was obtained from Boron Molecular and used as received.

Methods.

Nuclear Magnetic Resonance (NMR) Spectroscopy. ^{1}H NMR spectra were recorded on a Bruker Advance 300 spectrometer (300 MHz) at 27 °C in deuterated DMSO or acetone. For ^{1}H NMR, the delay time (dl) was 2 s. Chemical shift values (δ) are reported in ppm. The residual proton signal of the solvent was used as internal standard.

Size exclusion chromatography (SEC). SEC was conducted using an Agilent 390-LC MDS instrument equipped with differential refractive index (DRI), viscometry (VS), dual angle light scatter (LS) and dual wavelength UV detectors. The system was equipped with 2 x PLgel Mixed D columns (300 x 7.5 mm) and a PLgel 5 µm guard column. The eluent is DMF with 5 mmol NH_4BF_4 additive. Samples were run at 1 ml min^{-1} at 50 °C. Poly(methyl methacrylate) standards (Agilent EasyVials) were used for calibration. Analyte samples were filtered through a nylon membrane with 0.22 µm pore size before injection. Experimental molecular weight ($M_{n,SEC}$) and dispersity ($Đ$) values of synthesized polymers were determined by conventional calibration using Agilent GPC/SEC software.

The loop set-up used is based on a commercially available Vapourtec R2/R4TM flow reactor. Two standard Vapourtec pumps were used. The loop was comprised of a standard Vapourtec stainless steel reactor coil module (10 mL volume, 1.0 mm ID) connected to stainless steel tubing (1 m length, 1.0 mm ID), two Omnifit® three-way-valve connectors (PTFE, 0.8 mm bore), Upchurch Scientific® tees, and unions (PEEK, 1.25 mm thru hole), and a Swagelok® back pressure regulator (stainless steel, spring-loaded, 3.4-24.1 bar).

Synthesis of block copolymers in a looped flow process

Typical synthesis of the initial block. The set-up was thoroughly flushed with a solution of dioxane/water (2:8) degassed with nitrogen. Monomer, initiator and CTA were introduced in a test tube equipped with a mechanical stirrer and a rubber septum (Tables 1, S1 and S2) for the quantity of reagents needed for the multiblock copolymers). The solution was degassed with nitrogen for ca. 20 min. The monomer solution was then introduced in the reactor coil at 5 mL min^{-1} with the set-up at RT. The loop was closed and the stock solution was circulated in the loop using pump B for 5 minutes (at up to 8 mL min^{-1}). The heating was then set to 70 °C and the timer was reset when the temperature reached 69 °C. After 1 h 50 min at 70 °C with a flow rate of 5 mL min^{-1}, the heating was turned off, resulting in 2 hours.

Typical synthesis of subsequent blocks. The line for pump A was purged with the new monomer stock solution, then, the solution was loaded in the reactor using pump A at 0.5 mL min^{-1} and pump B at 1.17 mL min^{-1}) for 6 min at RT (T = 23 °C). Sample from the previous block was collected for ^{1}H NMR and SEC analysis after loading the stock solution for 2 min. The loop was closed and the solution was circulated using pump B for 5 min at 8 mL min^{-1} at RT. The heating was then set to 70 °C and the timer was reset when the temperature reached 69 °C. After 1h 50 min at 70 °C the heating was turned off.

Multiblock copolymer synthesis by iterative RAFT batch polymerization.

Typical synthesis of the initial block. Monomer, initiator, CTA and solvents were introduced in a test tube equipped with a mechanical stirrer and a rubber septum (Table 1, S1 and S2 for the quantity of reagents needed for the multiblock copolymers). The solution was degassed with nitrogen for ca. 20 min and the polymerization was then performed in a thermostated oil bath at 70 °C. After 2 hours, the test tube was withdrawn from the oil bath and a sample was taken for ^{1}H NMR and SEC analysis.

Typical synthesis of subsequent blocks. The test tube with the reaction mixture was opened and additional monomer, initiator and solvent were introduced. After the mixture was sealed with a septum, the solution was degassed for ca. 20 min, then placed in an oil bath set at 70 °C for the polymerization to occur. The tube was withdrawn from the oil bath after 2 hours and a sample was taken for ^{1}H NMR and SEC analysis.

Determination of Monomer Conversions. Monomer conversions (p) were calculated from ^{1}H NMR data using the following equation $p = 1 - (\frac{\int I_{5.4-6.4ppm}}{3 \times \int I_a} \times \frac{1}{DPtargeted})$ where $\int I_{5.4-6.4ppm}$ is the integral of the three vinyl protons of the monomer, $\int I_a$ is the integral of HOOC-C**H**(CH$_3$)-TTC (assigned on the ^{1}H NMR of Fig. S1, S3, S4 and Fig. S6) of the CTA and DP$_{\text{targeted}}$ is the average degree of polymerization targeted. This determination of the molecular weight is based on the full consumption of the CTA, which was confirmed by the shift of the proton HOOC-C**H**(CH$_3$)-TTC on Fig. S6.

The theoretical number-average molecular weight ($M_{n,th}$) is calculated using Equation 1.

$$M_{n,th} = \frac{[M]_0 p M_M}{[CTA]_0 + 2f[I]_0(1 - e^{-k_d t})(1 - \frac{f_c}{2})} + M_{CTA}$$

Equation 1. Calculation of $M_{n,th}$.

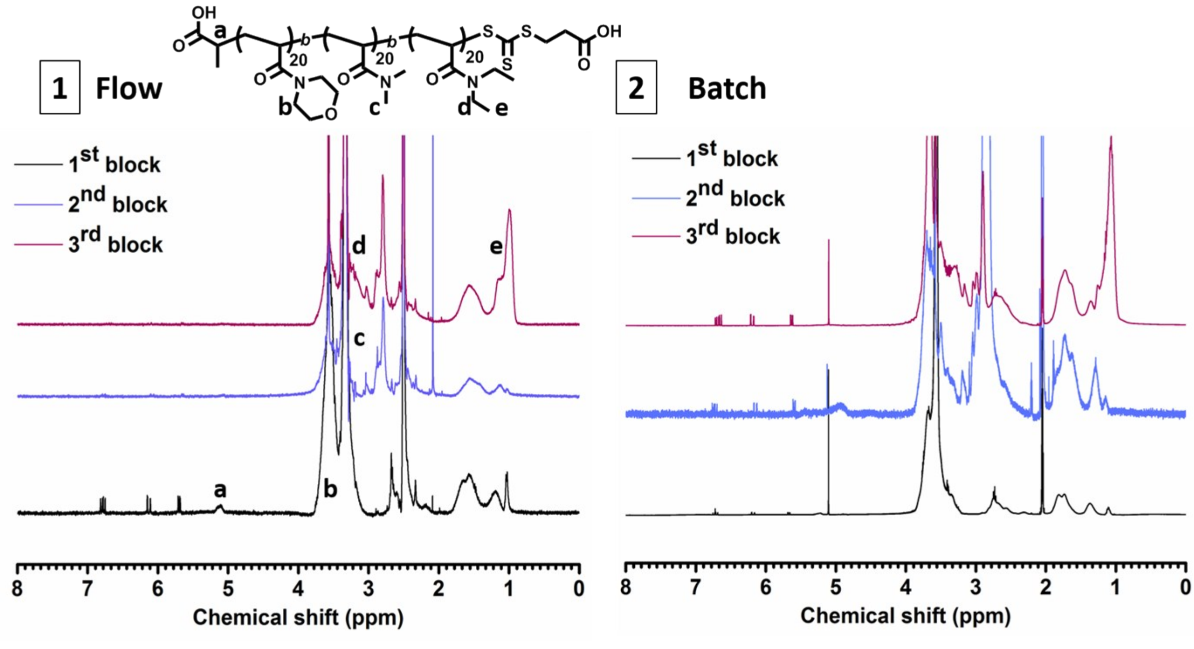
Where $[M]_0$, $[CTA]_0$, $[I]_0$ are the initial concentrations (in mol.L-1) of the monomer, CTA and the initiator respectively; p is the monomer conversion as determined by ^{1}H NMR; M_M and M_{CTA} are the molar masses (in g.mol^{-1}) of the monomer and the CTA, respectively; k_d is the decomposition rate constant (in s^{-1}) of the azo-initiator; and t represents the polymerization time (in seconds). The factor “2” accounts for the fact that one molecule of initiator yields two primary radicals with the efficiency f (assumed to be equal to 0.5 in this study). The decomposition rate constant for VA-044 at the temperature T ($k_{d,\text{VA-044(T)}}$) was determined from the values obtained from Wako ($k_{d,\text{VA-044(44 °C)}}$) = 1.92 X 10-4 s^{-1} and E$_a$ = 108000 J.mol^{-1}) using the Arrhenius equation ($k_{d,\text{VA-044(70 °C)}}$) = 4.30 X 10-4 s^{-1}). The term 1 – (f_c /2) represents the number of chains produced in a radical-radical termination event with fc representing the coupling factor. An f_c value of 1 means that 100 % of bimolecular terminations occur by combination, whereas a value of 0 indicates that 100 % of bimolecular terminations result in disproportionation. In this study, 100 % terminations y disproportionation are assumed (fc = 0).

Determination of the Livingness. The fraction of living chains can be calculated using Equation 1, the parameters being $[CTA]_0$ and $[I]_0$ initial CTA and initiator concentration, whereas k_d, f and $1\text{-}f_c/2$ are related to the thermal decomposition of the initiator.

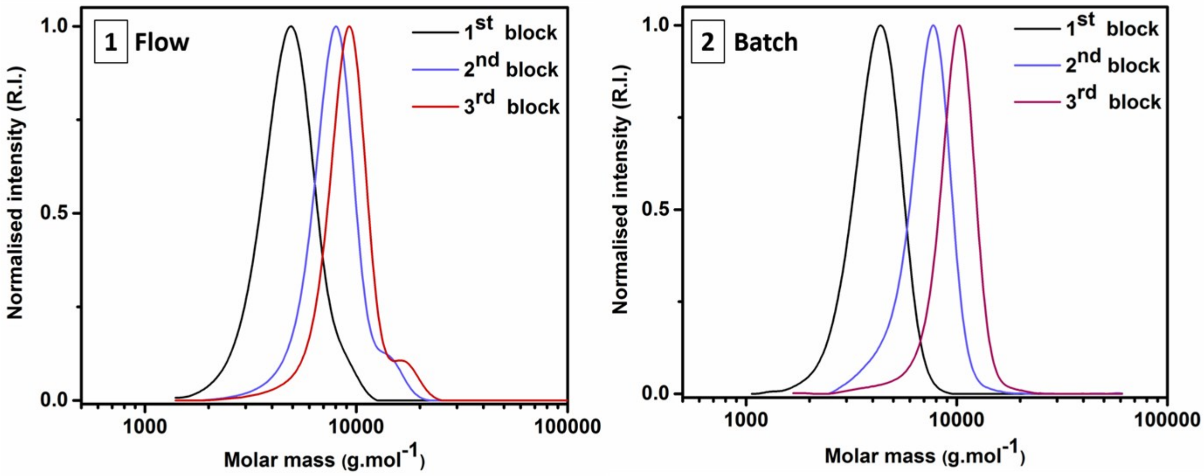
$$L_{th}\,(\%) = \frac{[CTA]_0}{[CTA]_0 + 2f[I]_0(1 - e^{-k_d t})(\frac{1 - f_c}{2})}$$

Equation 2. Theoretical determination of the relative amount of living polymer chains using an azo-initiator compound.

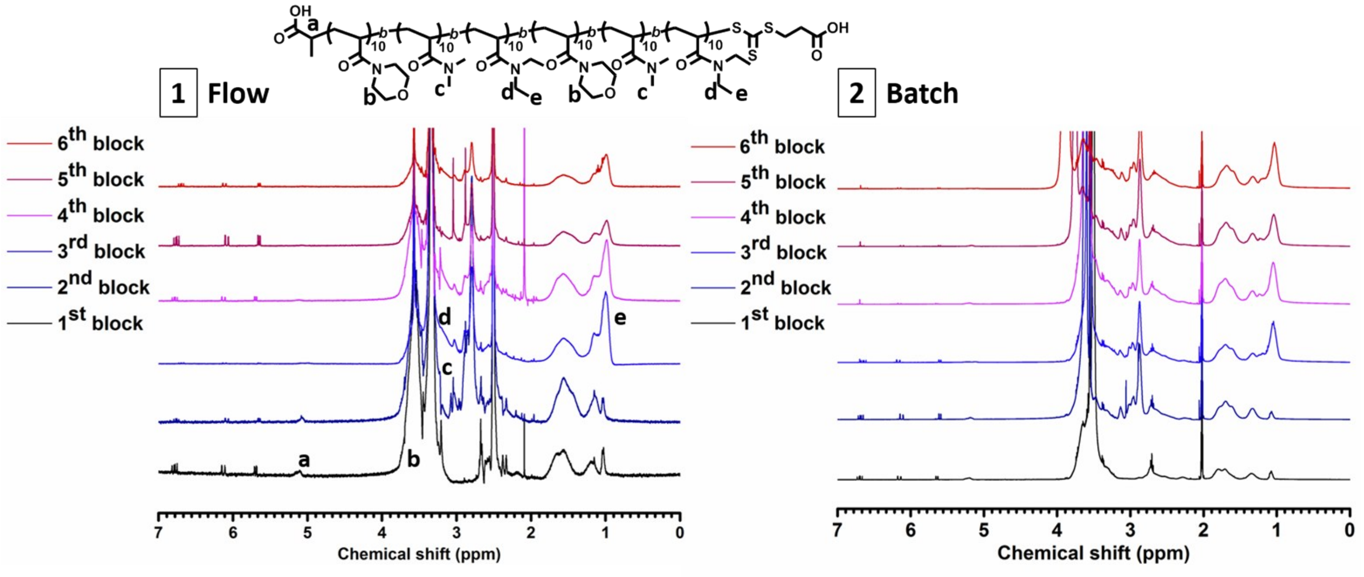
Supplementary Figures



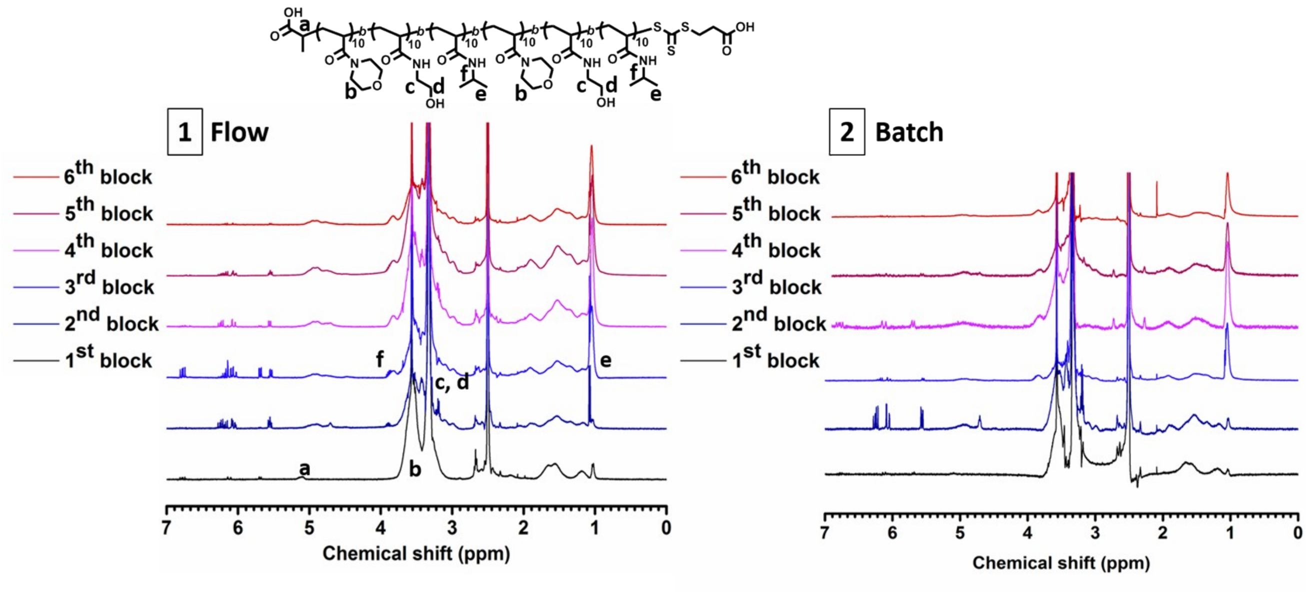
Supplementary Figure S1. ^{1}H NMR spectra in $DMSO_d$ for each block of $pNAM_{20}$-*b*-$pDMAm_{20}$-*b*-$pDEAm_{20}$ in loop (1) and batch (2).



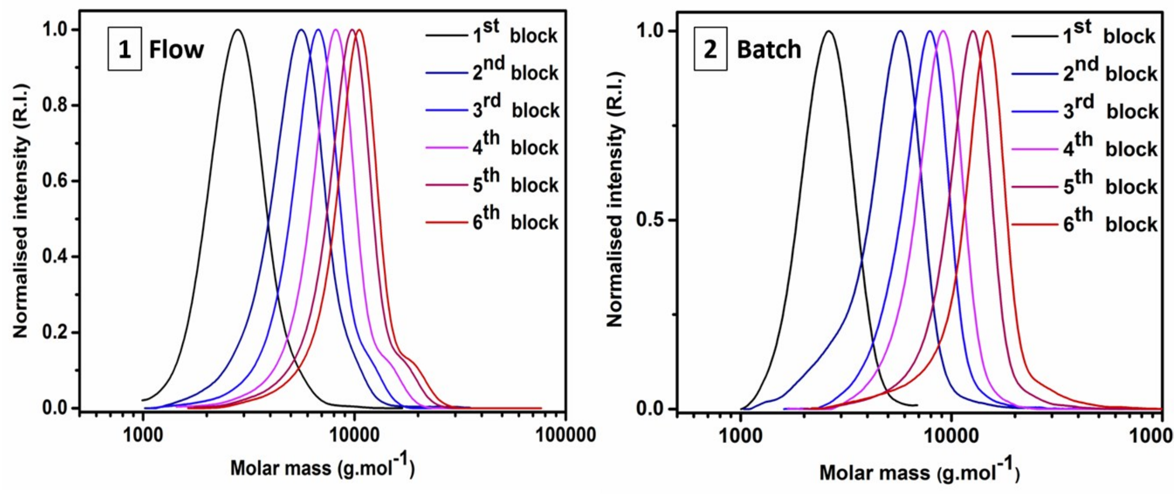
Supplementary Figure S2. DMF-SEC chromatograms for successive chain extensions of $pNAM_{20}$-*b*-$pDMAm_{20}$-*b*-$pDEAm_{20}$ in loop (1) and batch (2).



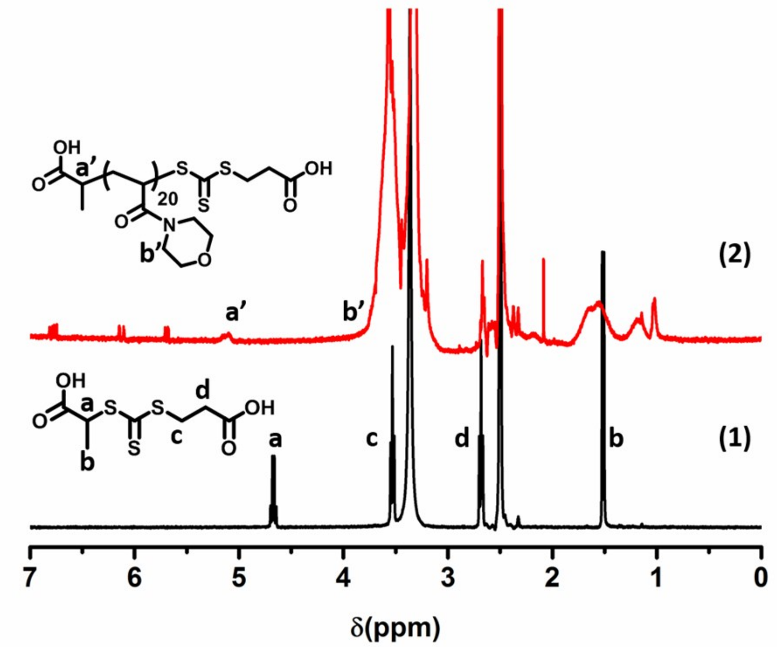
Supplementary Figure S3. ^{1}H NMR spectra in DMSO$_d$ for each block of pNAM$_{10}$-*b*-pDMAm$_{10}$-*b*-pDEAm$_{10}$-*b*-pNAM$_{10}$-*b*-pDMAm$_{10}$-*b*-pDEAm$_{10}$ in loop (1) and batch (2).



Supplementary Figure S4. ^{1}H NMR spectra in DMSO$_d$ for each block of pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$-*b*-pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$ in loop (1) and batch (2).



Supplementary Figure S5. DMF-SEC chromatograms for successive chain extensions of pNAM$_{10}$-*b*-HEAm$_{10}$-*b*-pNIPAm$_{10}$-*b*-pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$ in loop (1) and batch (2).



Supplementary Figure S6. ^{1}H NMR spectra in DMSO$_d$ of the CTA BM1429 (1) and the first block of the triblock pNAM$_{20}$-*b*-pDMAm$_{20}$-*b*-pDEAm$_{20}$ synthesized in the loop (2).

Supplementary Tables

Supplementary Table S1. Experimental conditions and characterisation data for the synthesis of the triblock pNAM$_{20}$-*b*-pDMAm$_{20}$-*b*-pDEAm$_{20}$ in batch and loop.

Process	Blocks	$[I]_{consumed}$ (mol.L^{-1})	[(m)CTA] [a] (mol.L^{-1})	$[M]_0$ (mol.L^{-1})	Monomer conversion[b] (%)	$M_{n,th}$ [c] (g.mol^{-1})	$M_{n,SEC}$ [d] (g.mol^{-1})	Đ[d]	L_{th}[e] *(%)*
Flow	1st	1.9 10^{-3}	0.15	3.0	99	3100	4500	1.11	98.7
	2nd	8.5 10^{-4}	0.09	1.8	> 99	5100	7500	1.10	97.8
	3rd	8.6 10^{-4}	0.08	1.5	93	7600	8700	1.09	96.7
Batch	1st	1.0 10^{-3}	0.15	3.0	98	3080	4000	1.08	99.4
	2nd	0.6 10^{-3}	0.10	2.0	> 99	5060	6900	1.08	98.8
	3rd	0.6 10^{-3}	0.07	1.3	> 99	7600	9400	1.08	97.9

[a] Concentration of CTA for the first block and macroCTA for the following blocks [b] Determined by ^{1}H NMR and is based on the initial ratio of CTA to monomer as detailed in the experimental method; [c] Theoretical molecular weight calculated from equation 1 (SI); [d] Determined by SEC/RI in DMF using PMMA as molecular weight standards; [e] Theoretical estimation of the cumulated fraction of living chains calculated using Equation 2.

Supplementary Table S2. Experimental conditions and characterisation data for the synthesis of the hexablock pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$-*b*-pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$ in batch and loop.

Process	Blocks	$[I]_{consumed}$ (mol.L^{-1})	[(m)CTA] [a] (mol.L^{-1})	$[M]_0$ (mol.L^{-1})	Monomer conversion[b] (%)	$M_{n,th}$ [c] (g.mol^{-1})	$M_{n,SEC}$ [d] (g.mol^{-1})	Đ[d]	L_{th}[e] *(%)*
Flow	1st	2.7 10^{-3}	0.27	3.0	99	1700	2600	1.11	99.0
	2nd	1.1 10^{-3}	0.20	2.1	96	2800	4800	1.15	98.5
	3rd	1.0 10^{-3}	0.15	1.4	94	3900	5900	1.13	98.0
	4th	1.0 10^{-3}	0.11	1.1	97	5400	7300	1.12	97.0
	5th	1.0 10^{-3}	0.08	0.8	97	6500	8600	1.13	95.7
	6th	1.1 10^{-3}	0.06	0.7	98	7600	9400	1.12	94.0
Batch	1st	1.9 10^{-3}	0.30	2.7	>99	1700	2400	1.09	99.4
	2nd	1.0 10^{-3}	0.21	2.0	95	2800	4600	1.17	99.0
	3rd	1.0 10^{-3}	0.14	1.5	99	3900	6900	1.11	98.3
	4th	1.0 10^{-3}	0.11	1.1	99	5400	8100	1.09	97.4
	5th	1.0 10^{-3}	0.08	0.8	99	6500	11000	1.13	96.3
	6th	1.0 10^{-3}	0.07	0.6	99	7600	12500	1.18	95.0

[a] Concentration of CTA for the first block and macroCTA for the following blocks; [b] Determined by ^{1}H NMR and is based on the initial ratio of CTA to monomer as detailed in the experimental method; [c] Theoretical molecular weight calculated from equation 1 (SI); [d] Determined by SEC/RI in DMF using PMMA as molecular weight standards; [e] Theoretical estimation of the cumulated fraction of living chains calculated using Equation 2.

Supplementary Table S3. Concentration for each step for the triblock and both hexablocks calculated using the (m)CTA concentration and the theoretical molecular weight $M_{n,th}$.

Polymer	Block n°	Concentration ($g.L^{-1}$)
pNAM$_{20}$-*b*-pDMAm$_{20}$-*b*-pDEAm$_{20}$	1	462
	2	457
	3	600
pNAM$_{10}$-*b*-pDMAm$_{10}$-*b*-pDEAm$_{10}$-*b*-pNAM$_{10}$-*b*-pDMAm$_{10}$-*b*-pDEAm$_{10}$	1	492
	2	600
	3	663
	4	623
	5	503
	6	517
pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$-*b*-pNAM$_{10}$-*b*-pHEAm$_{10}$-*b*-pNIPAm$_{10}$	1	492
	2	582
	3	578
	4	584
	5	524
	6	470