

Supporting Information

Watching Polymers Grow: Real Time Monitoring of Polymerizations via an On-line ESI-MS/Microreactor Coupling

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In addition to this supporting information document, a video is provided that shows the evolution of the ESI-MS spectra during a RAFT polymerization (see reaction conditions below) in real time as in principle observed during measurement.

1. Materials

The monomers *n*-butyl acrylate (*n*BA, Acros, 99%) and 2-ethylhexyl acrylate (EHA, Acros, 99%) were deinhibited over a column of activated basic alumina prior to use. 1,1'-azobis(isobutyronitrile) (AIBN, Sigma-Aldrich, 98%) was recrystallized twice from ethanol prior to use. 2-cyano-2-propyl dodecyl trithiocarbonate (CPD-TTC, Sigma-Aldrich, 97%) and 2-(dodecylthiocarbonothioylthio)propionic acid (DoPAT, Sigma-Aldrich, 97%) were used as received. All solvents used are obtained from commercial sources (Acros and Sigma-Aldrich) and used without further purification.

2. Characterization

Purification of products was performed on a **recycling preparative HPLC** LC-9210 NEXT system operated by prepure V1.0 software in the manual injection mode (3 mL) comprising a JAIGEL-1H and JAIGEL-2H column and a NEXT series UV detector using CHCl_3 as the eluent with a flow rate of $3.5 \text{ mL} \cdot \text{min}^{-1}$. Fractions were collected manually.

NMR spectra were recorded in deuterated chloroform with a Varian Inova 300 spectrometer at 300 MHz for ^1H NMR and at 75 MHz for ^{13}C NMR using a Varian probe (5 mm-4-nucleus AutoSWPFG) and a pulse delay of 12 s. NMR spectra were analyzed in MestReNova software.

Analysis of the MWDs of the polymer samples were performed on a Tosoh **EcoSEC** operated by PSS WinGPC software, equipped with a PLgel 5.0 μm guard column ($50 \times 8 \text{ mm}$), followed by three PLgel 5 μm Mixed-C columns ($300 \times 8 \text{ mm}$) and a differential refractive index detector using THF as the eluent at 40°C with a flow rate of $1 \text{ mL} \cdot \text{min}^{-1}$. The SEC system was calibrated using linear narrow polystyrene standards ranging from 474 to $7.5 \times 10^6 \text{ g} \cdot \text{mol}^{-1}$ PS ($K = 14.1 \times 10^{-5} \text{ dL} \cdot \text{g}^{-1}$ and $\alpha = 0.70$), and toluene as a flow marker.

ESI-MS was performed using an LTQ orbitrap velos pro mass spectrometer (ThermoFischer Scientific) equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electro spray mode. The instrument was calibrated in the m/z range 220-2000 using a standard solution containing caffeine, MRFA and Ultramark 1621. A constant spray voltage of 5 kV was used and nitrogen at a dimensionless sheath gas flow-rate of 7 was applied. capillary temperature was set to 275°C . A mixture of THF and methanol (THF:MeOH = 3:2), all HPLC grade, were used as solvent. Spectra were analyzed in Thermo Xcalibur Qual Browser software.

3. Microreactor Setup

Microreactions were performed in the Labtrix Start R2.2 system (Chemtrix BV, NL), fitted with a glass microreactor chip (3227, reactor volume = 19.5 μL) containing an SOR-2 static micromixer. Reactant solutions were introduced into the reactor through two 1 mL gas-tight syringes (SGE) capable of delivering two solutions at flow rates between 0.1 and 40 $\mu\text{L}\cdot\text{min}^{-1}$. The system was maintained at 20 bar of back pressure by means of a pre-set ultralow dead-volume (6 μL) back-pressure regulator (Upchurch Scientific, USA), in order to prevent boiling of the reactants and solvent system when temperatures above the atmospheric boiling point were employed. The flow rates were controlled via syringe pumps (Chemyx) and the reactor temperature was controlled via a thermoelectric cooler temperature controller MTTC1410 (Melcor Thermal Solutions, temperature range -15 $^{\circ}\text{C}$ to 195 $^{\circ}\text{C}$). The 3227 microreactor chip has two main reagent inlets and one quench inlet at the end.

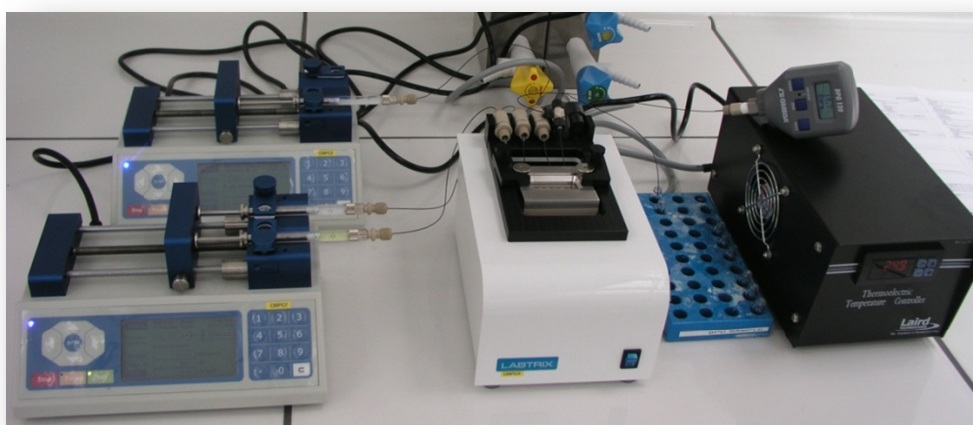


Figure S3.1 Microreactor setup for production of material under optimized conditions.

4. ESI-MS/Microreactor Coupling

Details of the microreactor setup are described in section 3. A flow chart and photo of the on-line ESI-MS microreactor setup is shown in Figure S4.1. Reagent solutions are injected via syringe pumps (**A**) directly into the microreactor (**D**). Reaction temperature is regulated by a temperature controller (**C**) and reactor heating unit (**B**). An in-line back-pressure regulator (**E**) (20 bar) increases the flow stability and allows for operation above ambient pressure boiling points of reactants and creates overpressure which contains the microreactor oxygen free if necessary. Reaction mixtures that exit the microreactor and pass through the back-pressure regulator are diluted with ESI-MS solvent mixtures by implementation of a T-splitter (Valco VICI stainless steel Tee) (**F**). Suitable ESI-MS solvent mixtures are introduced by a Knauer HPLC pump (**G**) and provided from the solvent reservoir (**H**). One dilution factor can be chosen for a certain concentration in the microreactor since the dimensions of the microreactor are very small. The quench line present in a 3227 microreactor chip can be utilized as a pre-dilution channel and can speed up the flow that exits the microreactor to have less dead time before injection into the ESI-MS. The diluted reaction mixture is splitted by a second T-splitter (Valco VICI stainless steel Tee) (**I**) to meet the flow requirements of the probe. Approximately, a 400:1 fixed split is obtained by 45 cm polyether ether ketone (PEEK) tubing (1/32" O.D. and 90 μ m I.D.) and 340 cm perfluoroalkoxy alkane (PFA) tubing (1/16" O.D. and 1/32" I.D.). The PFA split flow is drained or collected (**J**) while the PEEK split flow is directly injected into the ESI-MS (**K**). A fixed split can be applied that serves a large range of dilution factors due to the relatively broad ESI-MS window. Data are continuously collected by a central computer (**L**) and analyzed by Thermo Scientific

Xcalibur software. The dead volume in between the microreactor exit and the ESI chamber is 305 μL , calculated by considering the tubing lengths, tubing internal diameters and swept volumes of T-splitters and back-pressure regulator. The corresponding dead time that correlates with the dead volume depends on the flow rate of the reaction mixture in the microreactor (residence time), the dilution factor and the fixed split flow to the ESI-MS. Here, a 2 mL/min dilution flow, 4 $\mu\text{L}/\text{min}$ reaction flow and 5 $\mu\text{L}/\text{min}$ fixed split flow were applied. This results in 3.13 min dead time. The dead time between the microreactor and the ESI-MS is mainly due to the unavoidable dead swept volume (6 μL) of the in-line back-pressure regulator (BPR). The dead time can be reduced by decreasing the PEEK tubing length between the microreactor and the first T-split (dilution), although it was chosen in the described way due to practical reasons. After the first T-split it is only a matter of 10^{th} seconds before injection into the MS since the flow rate is increased by dilution with proper MS solvent mixtures.

5. Tracing AIBN-derived endgroups in RAFT polymerization

Figure S5.1 shows the percentage of CIP-initiated polymer against the recorded time. The conditions applied to the microreactor were changed from 1 min to 5 min residence time, from that point on the ESI-MS spectra were recorded (time zero). The dead volume of the on-line setup, in between the microreactor exit and injection into ESI probe, was calculated to be 305 μL which corresponds to 190 s dead time; taking into account tubing lengths, tubing internal diameters, swept volumes and flow rates (see SI section 4). After increasing the residence time, an increase in the CIP-initiated polymer chains was observed after approximately 190 s recorded time which correlates with the dead volume/time of the on-line setup and the conditions applied. Figure S5.1 was constructed by analysing the corresponding CIP-initiated polymer peak of the most intense polymer peak in the ESI-MS spectrum. Spectra were analysed every 3 seconds during the 600 seconds recorded time, in total 200 data points were analysed. Figure 2 in the main paper represents the residence time of the reaction mixture in the microreactor, not to be confused with the recorded time in Figure S5.1. The conversion of the time axis is carried out as follows:

From the time given in Figure S5.1, the dead volume time of 190 seconds is subtracted, then referred to as t_m . Important is to define which time a certain volume increment had already been in the reactor at the time that the flow rate was changed (start of measurement). This specific residence time t_1 is given by:

$$t_1 = (1 - x_v) \cdot \frac{V_{\text{reactor}}}{f_1}$$

Whereby x_v represents the volume fraction that the volume increment has passed at t_1 , V_{reactor} the total volume of the reactor and f_1 the flow rate before start of the measurement. The remaining residence time t_2 until exit from the reactor after switching flow rates is then consequently defined as:

$$t_2 = x_v \cdot \frac{V_{\text{reactor}}}{f_2} \quad \text{and} \quad x_v = t_2 \cdot \frac{f_2}{V_{\text{reactor}}}$$

With f_2 being the flow rate after start of measurement. The total residence time of any volume increment in the reactor is thus:

$$t_{res} = t_1 + t_2 = (1 - x_v) \cdot \frac{V_{reactor}}{f_1} + x_v \cdot \frac{V_{reactor}}{f_2}$$

Since $t_2 = t_m$, x_v can be inserted and the above equation can be rearranged to correlate t_m with the reactor residence time t_{res} :

$$\begin{aligned} t_{res} = t_1 + t_m &= \left(1 - t_m \cdot \frac{f_2}{V_{reactor}}\right) \cdot \frac{V_{reactor}}{f_1} + t_m \\ \Leftrightarrow t_{res} &= \frac{V_{reactor}}{f_1} - t_m \cdot \frac{f_2}{f_1} + t_m \\ \Leftrightarrow t_{res} &= \frac{V_{reactor}}{f_1} + t_m \left(1 - \frac{f_2}{f_1}\right) \end{aligned}$$

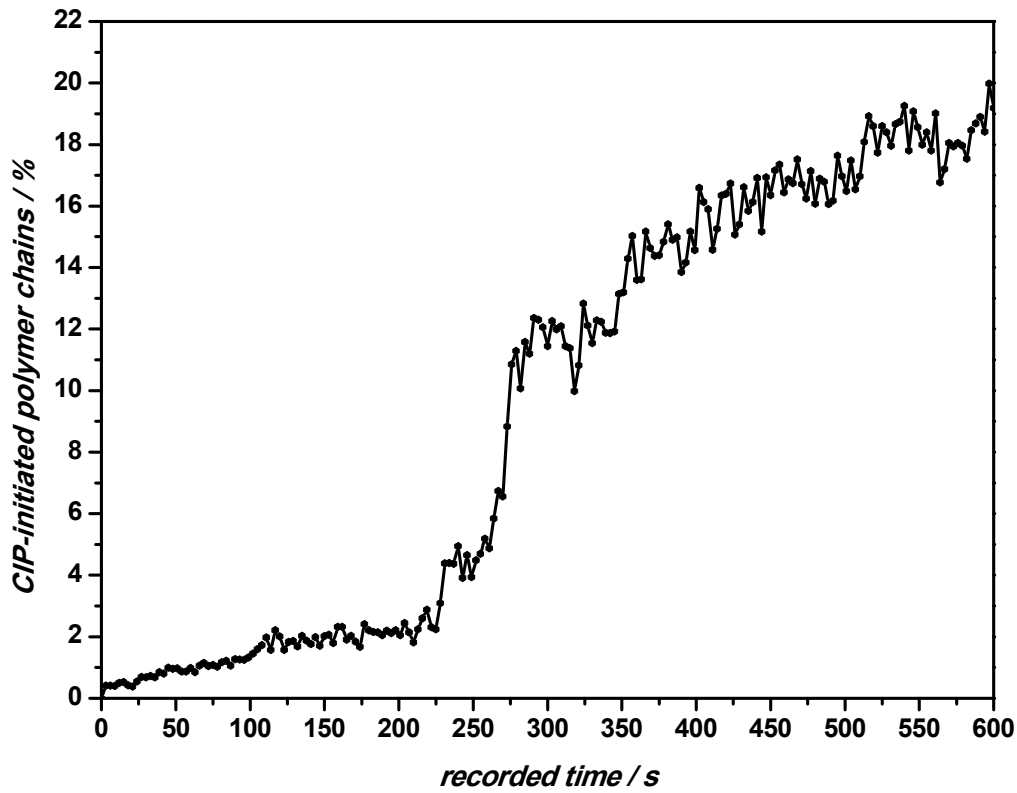


Figure S5.1. CIP-initiated polymer chains against recorded time in ESI-MS.

6. ESI-MS Calibration Curves

Fig. S6.1 and S6.2 show the ESI-MS calibration curves for the reaction products **A**, **B** and **C**. Calibration curves were established to correlate measured ESI-MS peak abundances (Table S7.1) with obtained product yields (Main text, Table 1) since the peak abundances measured in ESI-MS are not quantitative due to mass-bias effects. Higher insertion products are ionizing more facile relative to lower insertions, typically observed for single unit monomer insertion (SUMI) reactions of acrylates. Fig. S6.1 represents the mole fraction of **A** and **B** against the peak abundance measured in ESI-MS. As expected, **A** is highly underestimated relative to **B**. To establish the calibration curves a polynomial fit was applied and utilized to correlate the measured peak abundances and the obtained yields after applying the optimal conditions to the microreactor. Fig. S6.2 represents mole fractions of **A**, **B** and **C** against ESI-MS peak abundances where one out of the three products was varied while the other two were equimolar. Product **C** was overestimated relative to **A** and **B** but the ionization effect was less relative to the observations in Fig. S6.1. Fig. S6.3 represents the **A:B** peak abundance in ESI-MS for a constant **A:B** ratio (50:50) in the calibration mixture while **C** was varied. The **A:B** ESI-MS peak abundance remains relatively constant for different values of **C** in the calibration mixture. Optimal reaction conditions for the synthesis of **B** were chosen in Table 1 (main text).

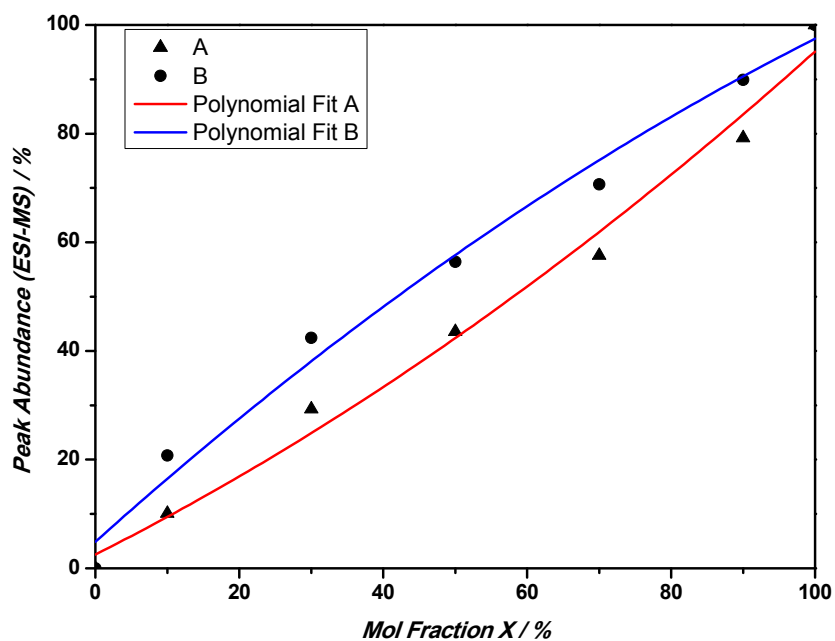


Fig. S6.1 ESI-MS calibration curve for reaction products **A** and **B**.

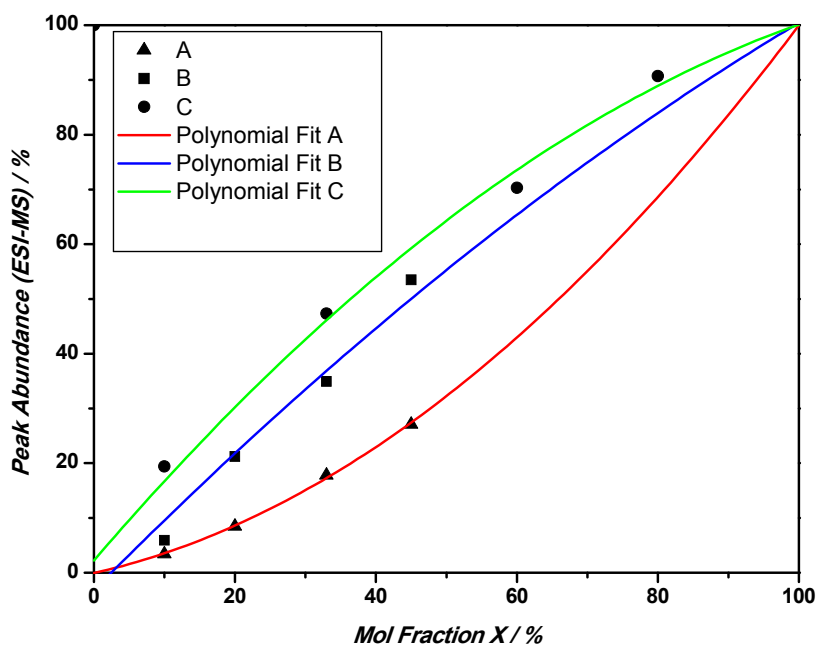


Fig. S6.2 ESI-MS calibration curve for reaction products **A**, **B** and **C**.

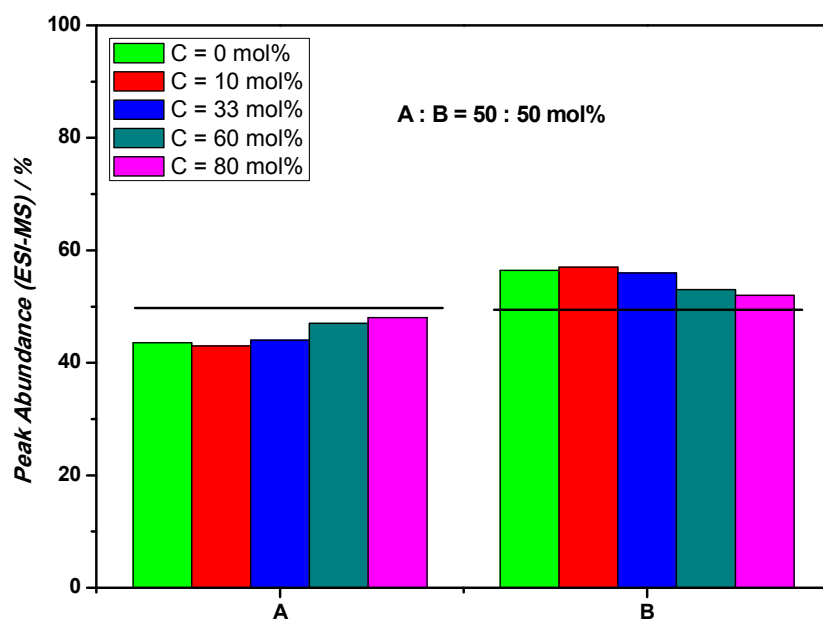


Fig. S6.3 ESI-MS peak abundance of **A** and **B** for a constant **A:B** molar ratio in the calibration mixture while **C** is varied.

7. ESI-MS Screening

Tables S7.1 and S7.2 show the screening conditions and results for the synthesis of insertion product **B**. Table S7.1 represents the peak abundances measured in ESI-MS for the insertion products **A**, **B**, **C** and **D** which can be misleading due to the mass-bias effect described in the main text. Table S7.2 represents the relative peak abundances for **A** and **B** while **C** and **D** are left out of consideration. Conditions can be chosen based on the **A** and **B** calibration curve since the **A:B** ratio remains relatively constant for different values of **C** according to the calibration table shown in the main text. Product **D** is only observed in small amounts (< 4%).

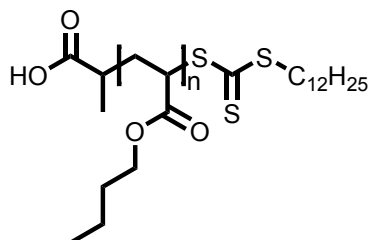
Table S7.1 Screening conditions and results for the synthesis of insertion product **B**.

Condition	Temperature (°C)	[EHA] : [1]	Residence Time (min)	A (%)	B (%)	C (%)	D (%)
1	95	5:1	10	50	38	10	2
2	95	10:1	5	41	50	9	0
3	95	10:1	7,5	11	58	27	4
4	100	1:1	5	70	30	0	0
5	100	2:1	5	47	49	4	0
6	100	2:1	10	22	62	16	0
7	100	3:1	8	9	61	27	3
8	100	4:1	6	12	60	25	3
9	100	5:1	2,5	40	54	6	0
10	100	5:1	4	16	62	20	2
11	100	5:1	5	9	60	26	4
12	110	3:1	2,5	19	65	16	0
13	110	3:1	4	9	68	19	4
14	110	2:1	4	28	61	11	0
15	110	2:1	5	20	64	16	0

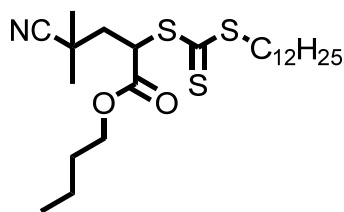
Table S7.2 Screening conditions and results for the synthesis of insertion product **B**. Product **C** and **D** are left out of consideration.

Condition	Temperature (°C)	[EHA] : [A]	Residence Time (min)	[A] : [B]
1	95	5:1	10	57 : 43
2	95	10:1	5	45 : 55
3	95	10:1	7,5	16 : 84
4	100	1:1	5	70 : 30
5	100	2:1	5	49 : 51
6	100	2:1	10	26 : 74
7	100	3:1	8	13 : 87
8	100	4:1	6	15 : 85
9	100	5:1	2,5	43 : 57
10	100	5:1	4	21 : 79
11	100	5:1	5	13 : 87
12	110	3:1	2,5	23 : 77
13	110	3:1	4	12 : 88
14	110	2:1	4	32 : 68
15	110	2:1	5	24 : 76

8. Synthetic Procedures

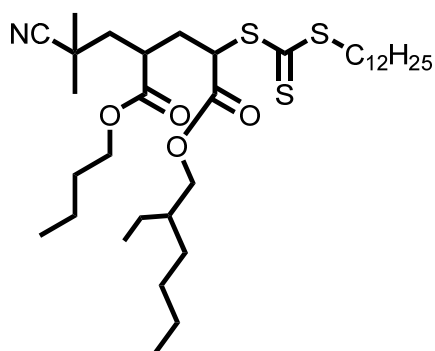


Poly(*n*-butyl acrylate). In a typical procedure, 17.577 mmol (2.25 g, 30 equiv) of the monomer *n*BA, 0.059 mmol (9.69 g, 0.1 equiv) of 2-2'-Azoisobutyronitrile (AIBN), 0.585 mmol (0.205 g, 1 equiv) of (dodecylthiocarbonothioylthio)propionic acid (DoPAT) and 1.5 mL of butyl acetate were added into a glass vial. The glass vial was sealed by a rubber septa. The solution was degassed for 15 min by N₂ purging, and subsequently inserted into the glovebox. The glass vial was opened and the solution was transferred to two gas-tight 1 mL syringes (SGE). The syringes were employed to the ESI-MS microreactor setup. Number molecular weights and polydispersities of the polymer were measured by SEC for 1 minute (1100 g.mol⁻¹, 1.16) and 5 minutes (2700 g.mol⁻¹, 1.11) residence time in the microreactor. ESI-MS spectra are included in section 9.



***n*BA oligo-RAFT agent (A).** In a typical procedure, 15.604 mmol (2.00 g, 10 equiv) of the monomer *n*BA, 0.078 mmol (0.013 g, 0.05 equiv) of AIBN, 1.560 mmol (0.540 g, 1 equiv) of 2-cyano-2-propyl dodecyl trithiocarbonate (CPD-TTC) RAFT agent and 2 mL of butyl acetate were added into a sealed Schlenk tube. The schlenk tube was subjected to 3 freeze-pump-thaw cycles, and subsequently inserted into the glovebox. The schlenk tube was opened and the mixture was transferred into a glass vial with a stirring bar inside. The glass vial was placed in a copper heat-block of 100 °C. The mixture was reacted for 10 min at 100 °C and subsequently quenched by cooling the vial in liquid nitrogen and subjecting to ambient atmosphere. Subsequently the mixture was transferred into an aluminium pan to evaporate excess of solvent and monomer, yielding 0.690 g of crude product mixture. The mixture was purified via recycling SEC to yield 0.347 g (48%) of pure *n*BA macro-RAFT agent (**1**). ¹H NMR (300 MHz, CDCl₃, δ): 4.99 (dd, *J* = 9.7 and 4.5 Hz, 1H, CHCOO, backbone), 4.17 (t, *J* = 6.6 Hz, 2H, CH₂OC=O, side chain), 3.36 (t, *J* = 7.5 Hz, 2H, CH₂SC=S, chain end), 2.45 (dd, *J* = 14.4 and 9.7 Hz, 1H, CH₂CH, backbone), 2.02 (dd, *J* = 14.4 and 4.5 Hz, 1H, CH₂CH, backbone), 1.79–1.57 (m, 2H, CH₂, side chain + 2H, CH₂, chain end), 1.47 (s, 3H, CN-C-CH₃), 1.44–1.32 (br, 2H, CH₂, side chain + 2H, CH₂, chain end + 3H, CN-C-CH₃), 1.30–1.18 (br, 16H, CH₂, chain end), 0.97–0.90 (t, *J* = 7.4 Hz, 3H, CH₃, side chain), 0.90–0.83 (t, *J* = 6.8 Hz, 3H, CH₃, chain end). ¹³C NMR (75 MHz, CDCl₃, δ): 220.85, 169.91, 123.77, 66.31, 49.16, 42.25, 37.61, 32.04, 31.78, 30.42, 29.74, 29.67, 29.55, 29.47, 29.20,

29.02, 27.96, 27.56, 26.40, 23.39, 22.82, 19.20, 14.26, 13.81. ESI-MS (m/z): 496.24 (M+Na⁺).



***n*BA-EHA oligo-RAFT agent (B).** A 2 mL solution of 0.711 mmol (0.131 g, 5 equiv) of the monomer 2-ethylhexylacrylate (EHA), 0.158 mmol (0.069 g, 1 equiv) of oligo-RAFT agent **A**, 0.006 mmol (0.00098 g, 0.04 equiv) of AIBN was prepared with butyl acetate as reaction solvent. Chemicals were weighted in a glass vial with stirring bar and inserted into the glovebox where butyl acetate was added. The solution was stirred for 15 min to remove the residual oxygen. The solution was transferred to two gas-tight 1 mL syringes (SGE) and subsequently employed to the microreactor setup. The conditions applied to the microreactor were 100 °C and 5 min residence time. After 7.4 h reaction time the reaction mixture was transferred into an aluminum pan to evaporate excess of solvent and monomer. The crude product mixture was purified via recycling SEC to obtain oligo-RAFT agent **B** as a yellowish oil in 43% yield (35 mg). ¹H NMR (300 MHz, CDCl₃, δ): 4.98–4.82 (m, 1H, CHCOO, backbone, EHA unit), 4.20–3.94 (br, 4H, CH₂OC=O, side chains), 3.35 (t, *J* = 7.5 Hz, 2H, CH₂SC=S, chain end), 2.82–2.66 (br, 1H, CHCOO, backbone, *n*BuA unit), 2.50–1.82 (br, 4H, CH₂CHCH₂CH, backbone), 1.75–1.50 (m, 2H, CH₂, *n*BuA side chain + 1H, CH, EHA side chain + 2H, CH₂, chain end), 1.46–1.15 (br, 10H, CH₂, side chains + 18H, CH₂, chain end + 6H, CN-C-(CH₃)₂), 0.94 (t, *J* = 7.4 Hz, 3H, CH₃, *n*BuA side chain), 0.91–0.80 (br, 3H, CH₃, chain end + 6H, CH₃, EHA side chain). ¹³C NMR (75 MHz, CDCl₃, δ): 221.27, 221.02, 174.30, 170.30,

170.17, 124.18, 68.37, 65.43, 50.55, 49.79, 42.66, 40.63, 40.29, 38.77, 37.62, 35.22, 34.71, 32.02, 31.74, 31.67, 30.59, 30.53, 30.40, 30.37, 29.74, 29.67, 29.55, 29.46, 29.21, 29.01, 27.98, 27.00, 26.96, 26.87, 26.75, 24.97, 23.83, 23.78, 23.09, 22.81, 19.31, 14.25, 14.19, 13.88, 11.10. ESI-MS (m/z): 680.38 (M+Na⁺).

9. Polymer Characterization

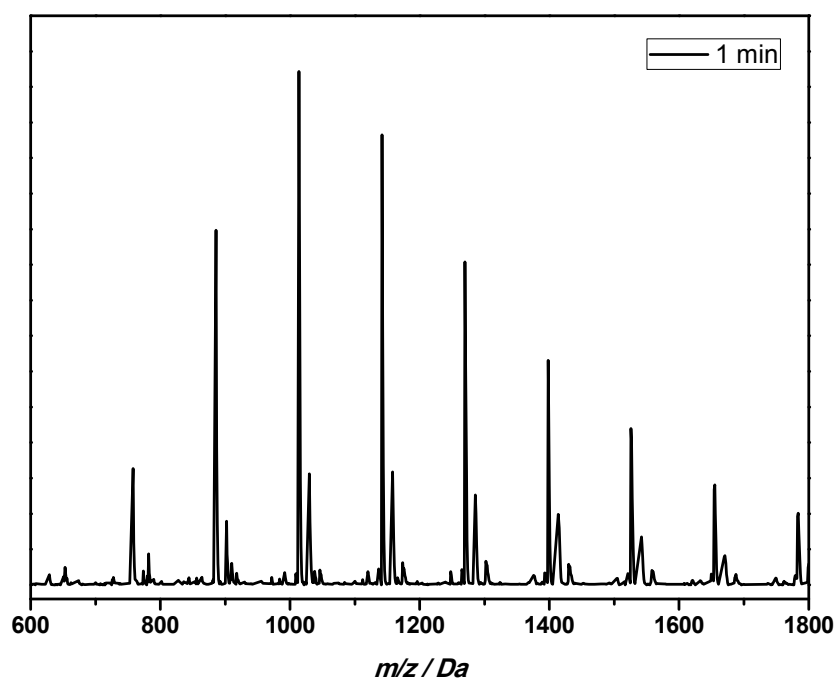


Figure S9.1. ESI-MS spectrum of PnBA after 1 min residence time in the microreactor.

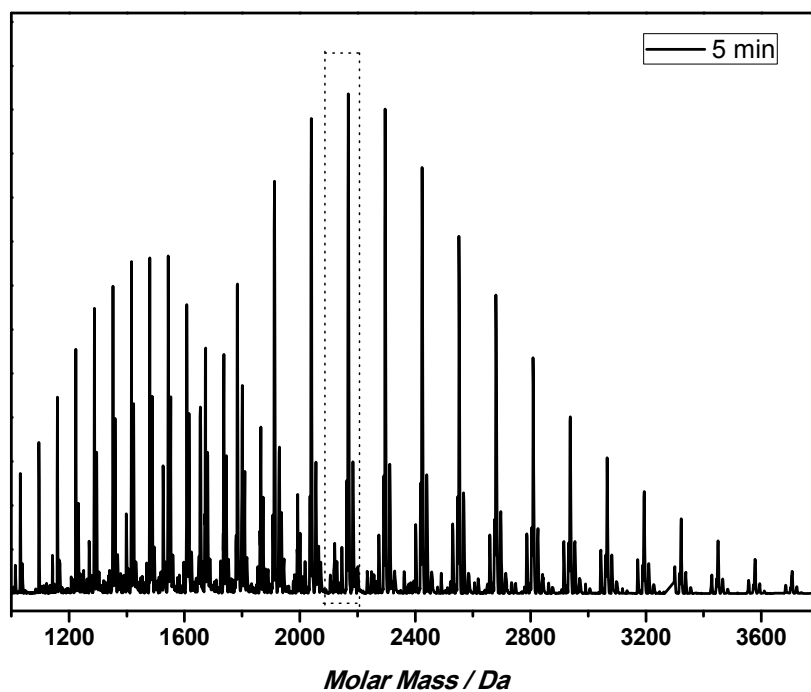


Figure S9.2. ESI-MS spectrum of PnBA after 5 min residence time in the microreactor. Peaks are assigned in S9.3.

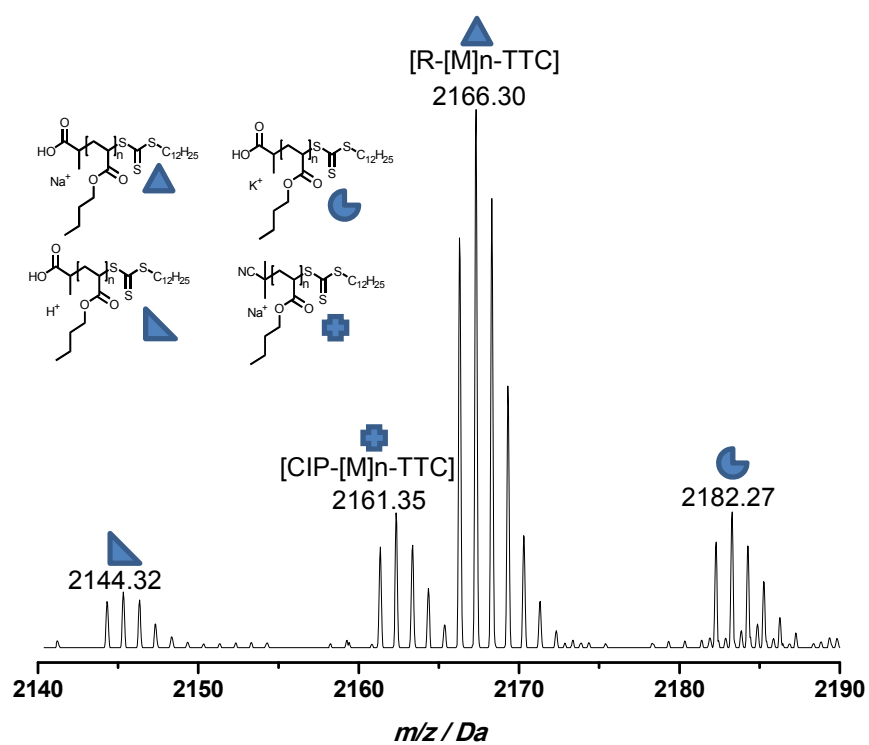


Figure S9.3. Zoomed peak area of S9.2 where peaks are all assigned.

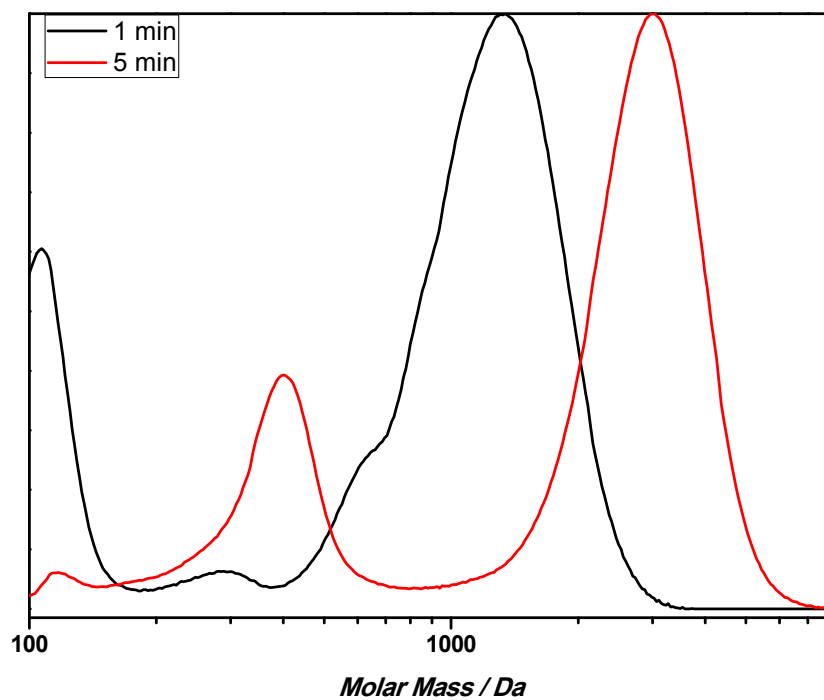


Figure S9.4. SEC chromatograms of PnBA after 1 min and 5 min residence time in the microreactor.

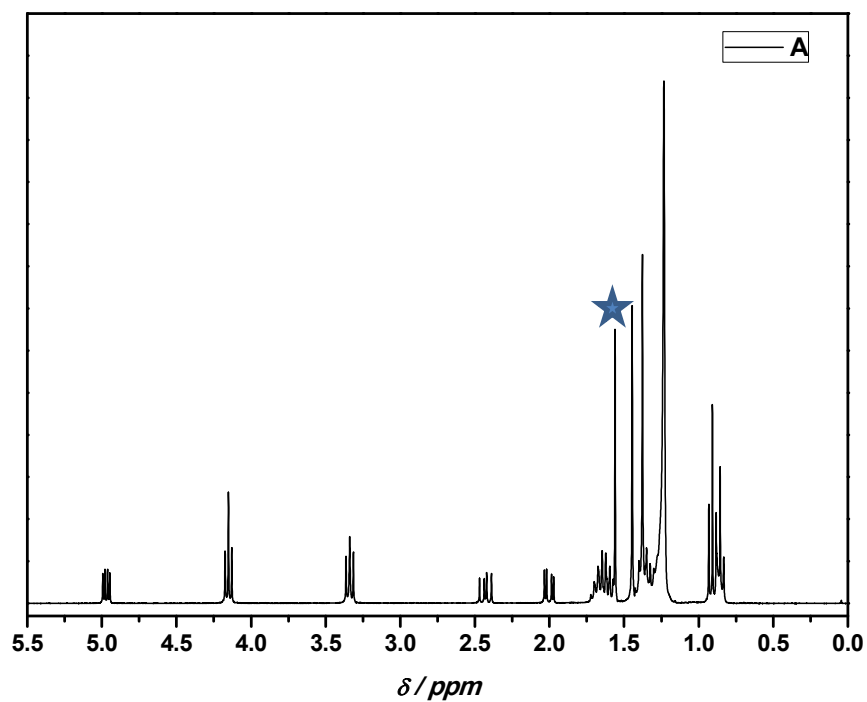


Figure S9.5. ^1H NMR spectrum of *n*BA oligo-RAFT agent **A**. The resonance peak marked with an asterisk results respectively from H_2O traces present in the CDCl_3 solvent bottle.

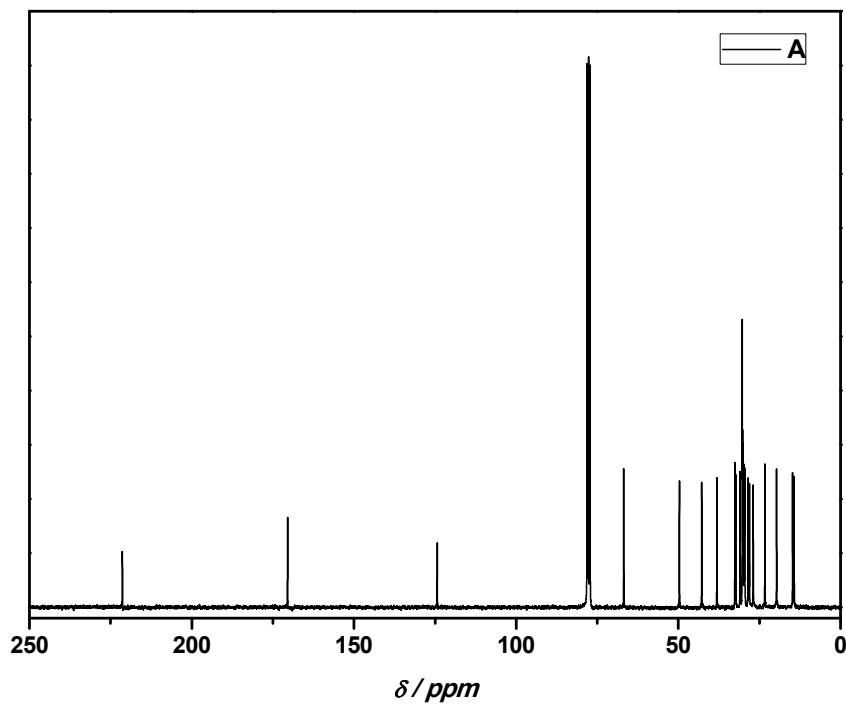


Figure S9.6. ^{13}C NMR spectrum of *n*BA oligo-RAFT agent **A**.

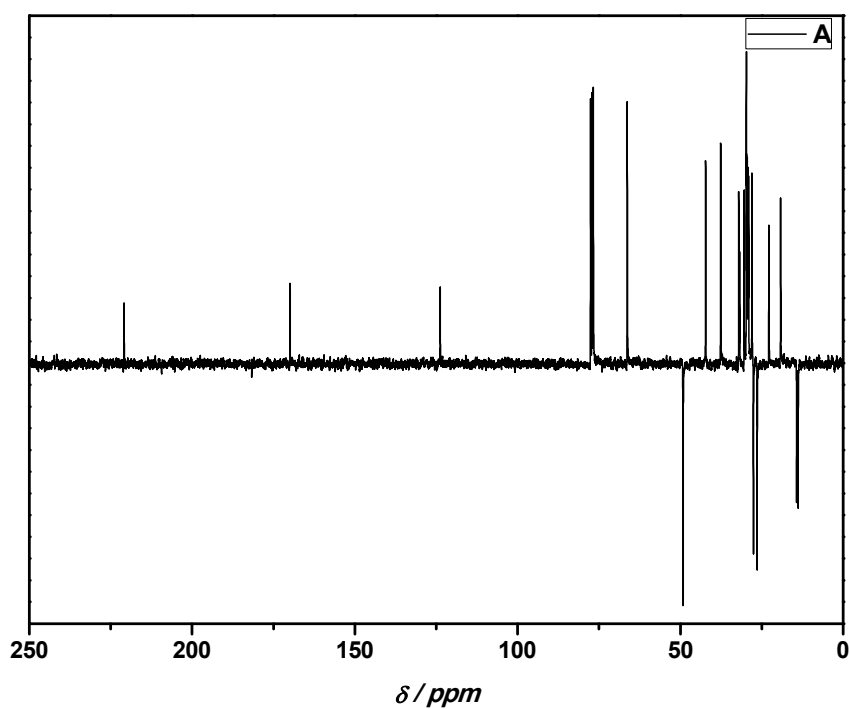


Figure S9.7. ^{13}C NMR APT spectrum of *n*BA oligo-RAFT agent **A**.

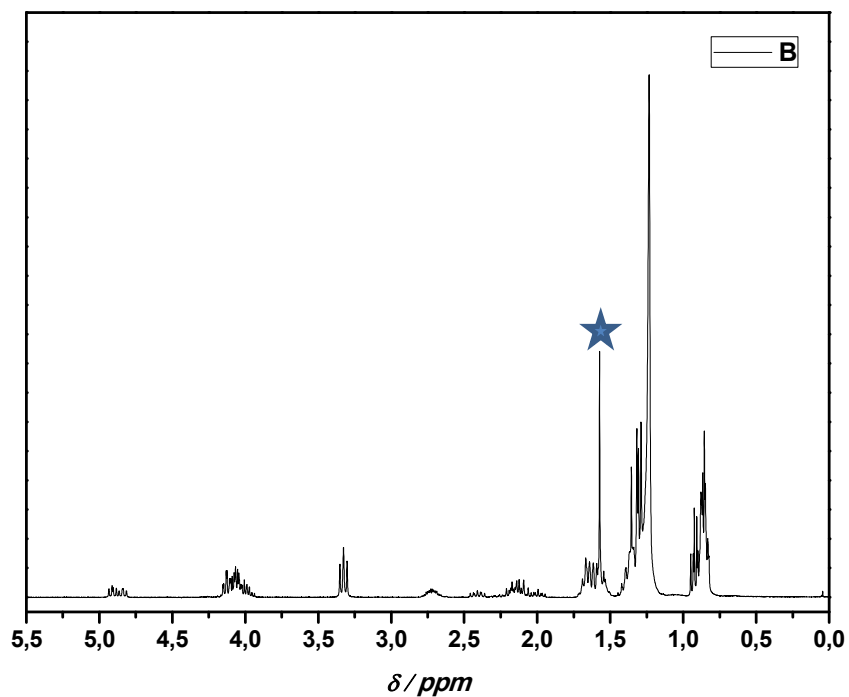


Figure S9.8. ^1H NMR spectrum of *n*BA-EHA oligo-RAFT agent **B**. The resonance peak marked with an asterisk results respectively from H_2O traces present in the CDCl_3 solvent bottle.

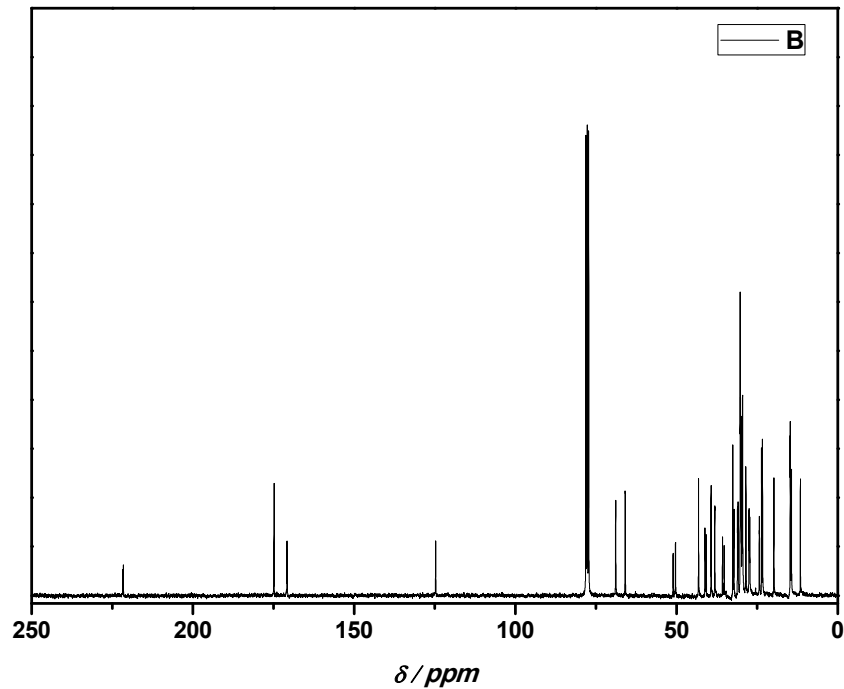


Figure S9.9. ^{13}C NMR spectrum of *n*BA-EHA oligo-RAFT agent **B**.

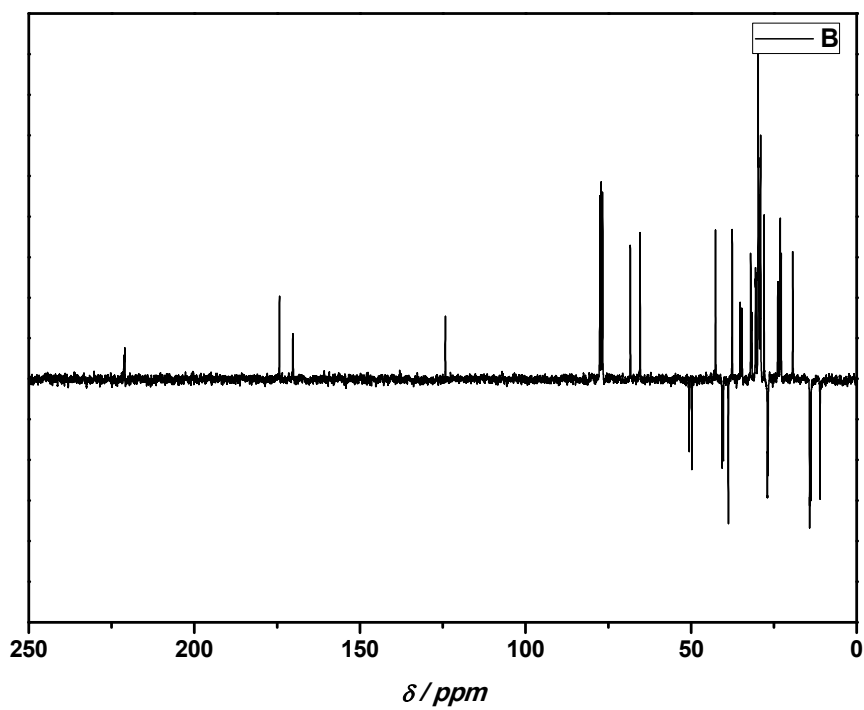


Figure S9.10. ^{13}C NMR APT spectrum of *n*BA-EHA oligo-RAFT agent **B**.

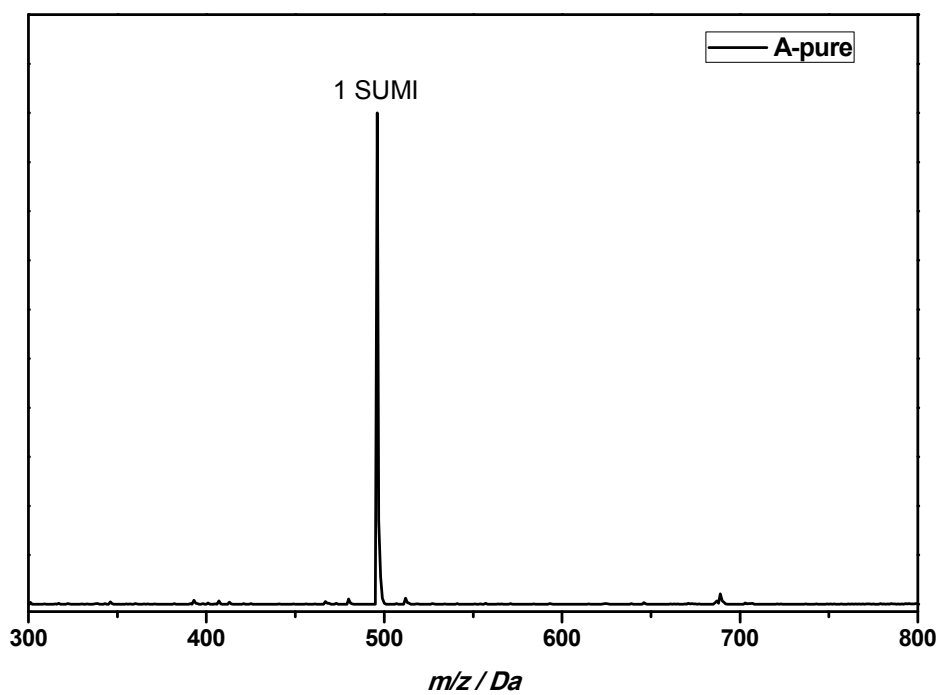
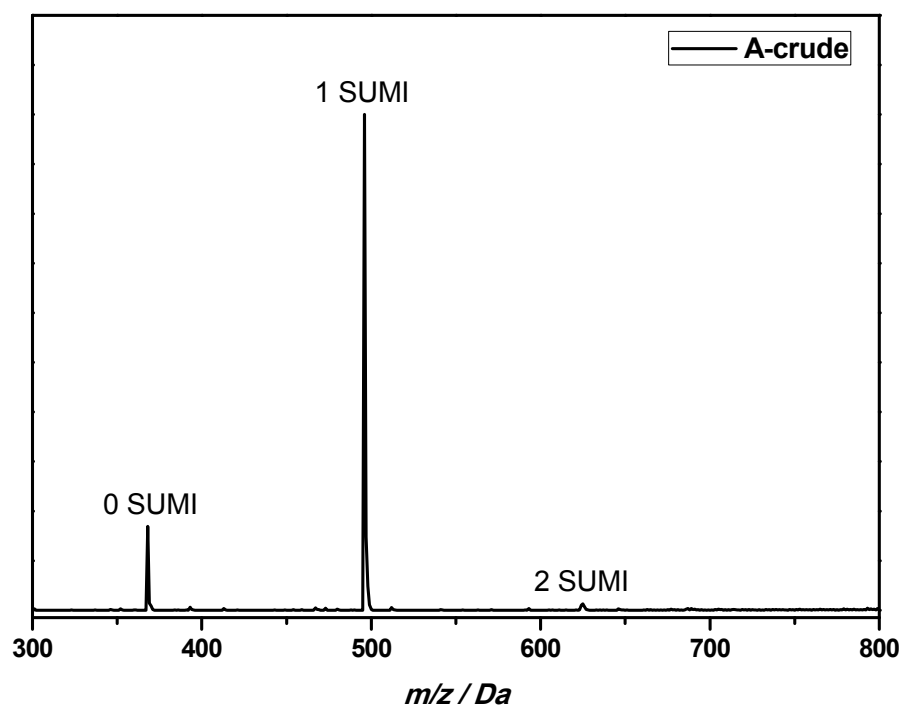


Figure S9.11. ESI-MS spectra of *n*BA oligo-RAFT agent **A**, before and after purification with recycling SEC.

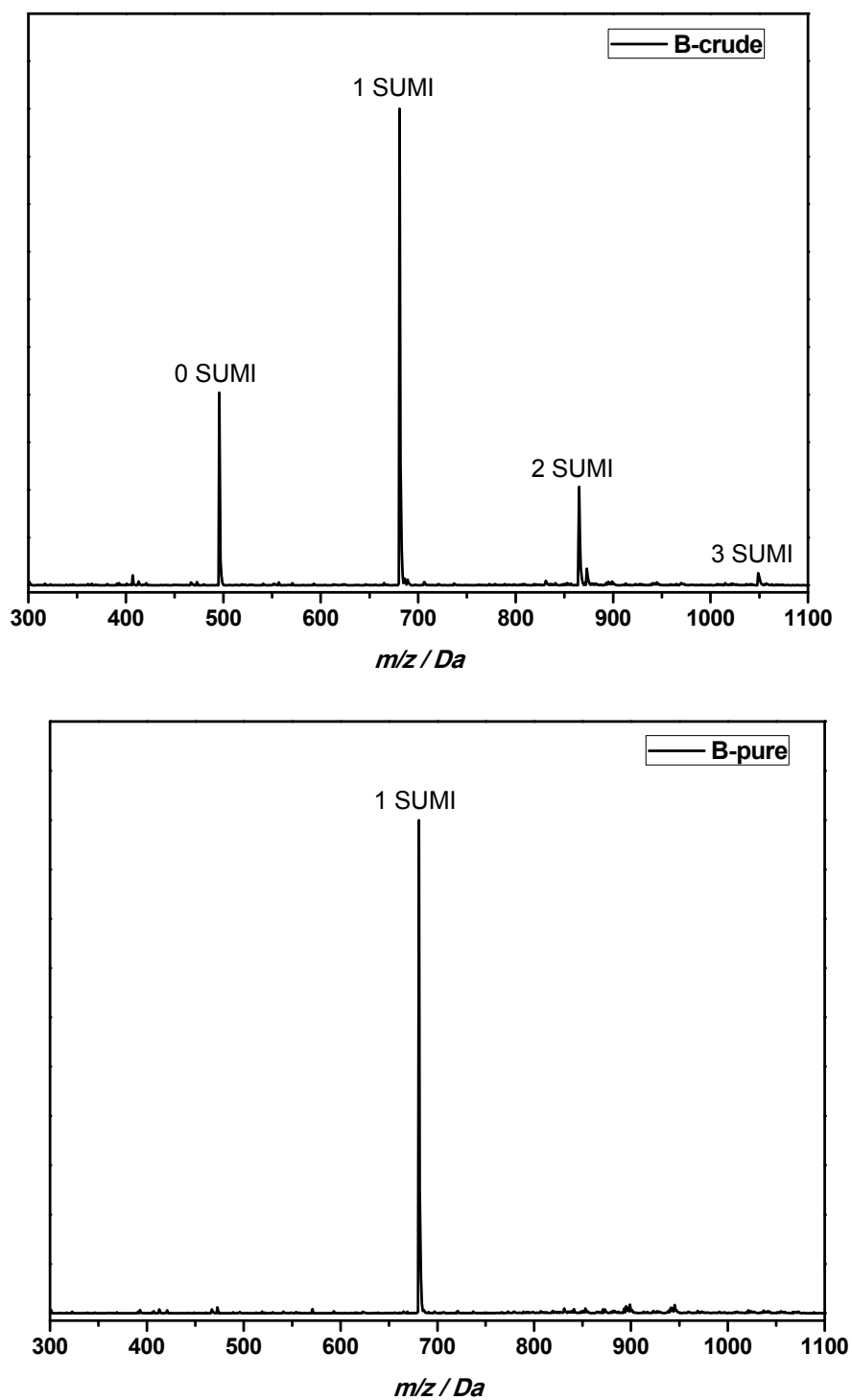


Figure S9.12. ESI-MS spectra of *n*BA-EHA oligo-RAFT agent **B**, before and after purification with recycling SEC.

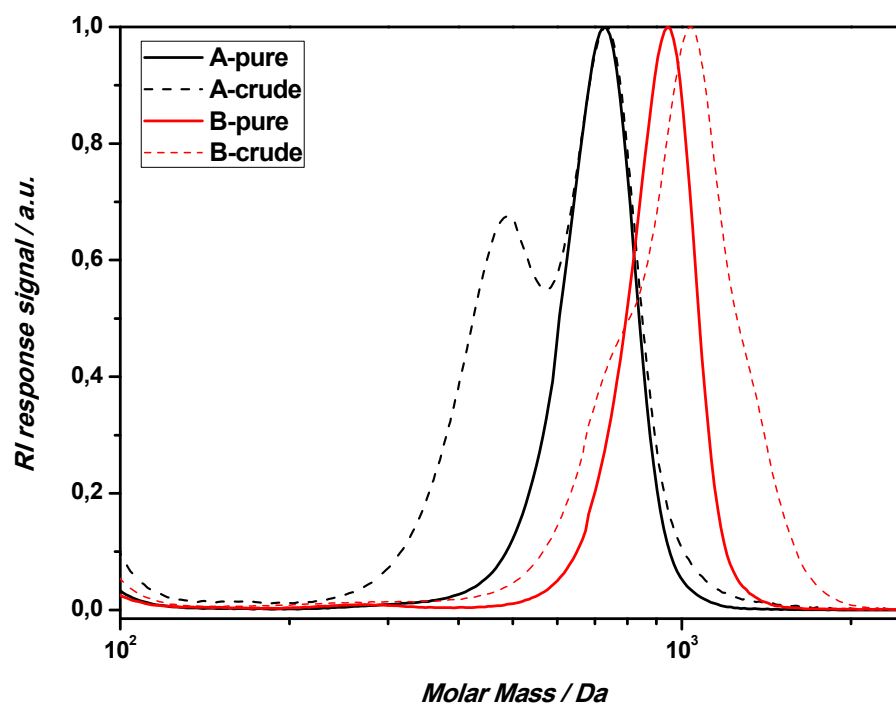


Figure S9.13. SEC chromatograms of oligo-RAFT agents **A** and **B**, before (dashed) and after (solid) purification with recycling SEC.

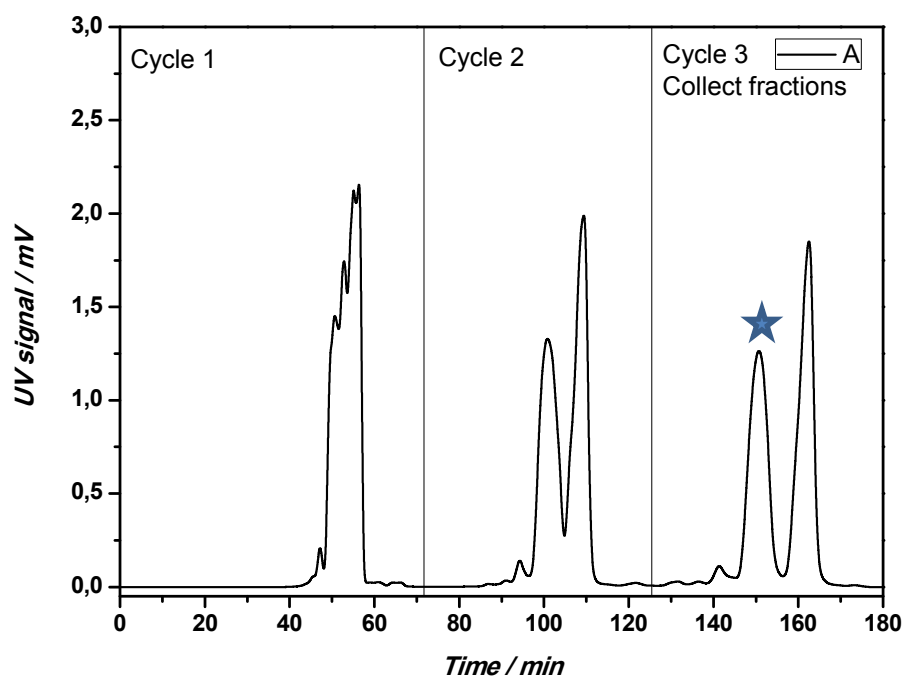


Figure S9.14. Recycling SEC trace recorded during consecutive purification cycles of *n*BA oligo-RAFT **A**. The desired product is marked with an asteriks.

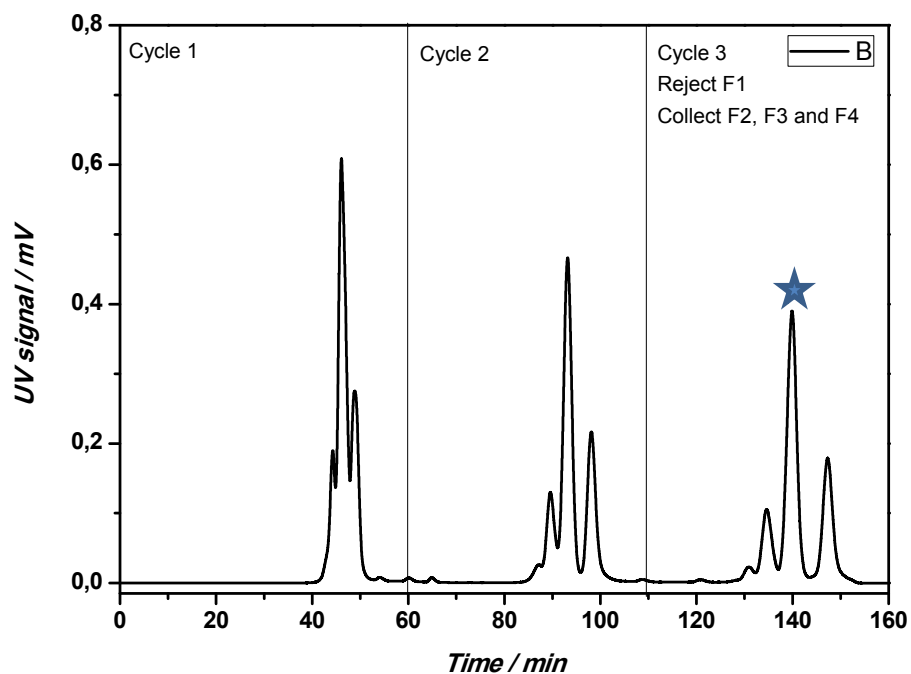


Figure S9.15. Recycling SEC trace recorded during consecutive purification cycles of *n*BA-EHA oligo-RAFT **B**. The desired product is marked with an asteriks.