

Supporting information to

Use of a Continuous-Flow Microreactor for Thiol-Ene Functionalization of RAFT-Derived Poly(Butyl Acrylate)

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Experimental Section

Materials. *n*-Butyl acrylate (*n*-BuA, Acros, 99%), isobornyl acrylate (iBoA, Acros, 99%), propargyl acrylate (Sigma-Aldrich, 98%), poly(ethylene glycol) methyl ether acrylate (Sigma-Aldrich, $M_n \approx 480$ g/mol) and pentaerythritol tetraacrylate (Sigma-Aldrich, 10–40% tri-ester) were deinhibited over a column of activated basic alumina, prior to use. The initiator 1,1'-azobis(isobutyronitrile) (AIBN, Sigma-Aldrich, 98%) was recrystallized twice from ethanol prior to use. 2-cyano-2-propyldodecyltrithiocarbonate (Sigma-Aldrich, 97%) and hexylamine (Sigma-Aldrich, 99%) were used as received. THF was obtained from commercial sources (Acros and Sigma-Aldrich) and used without further purification.

Microreactor setup. Microreactions were performed in the Labtrix[®] Start R2.2 system (Chemtrix BV, NL), fitted with a glass microreactor (3227, reactor volume = 19.5 μ L) containing an SOR-2 static micromixer. Reactant solutions were introduced into the reactor through three 1 mL gas-tight syringes (SGE) capable of delivering three solutions at flow rates between 0.1 and 25 μ L \cdot min⁻¹. The system was maintained at 20 bar of back pressure by means of a preset ultralow dead-volume 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 2 syringe pumps (Chemyx) and the reactor temperature was controlled via a thermoelectric cooler temperature controller MTTC1410 (Melcor Thermal Solutions, temperature range -15 °C to 195 °C).

Characterization. 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 μ m guard column (50 \times 8 mm), followed by three PLgel 5 μ m Mixed-C columns (300 \times 8 mm) and a differential refractive index detector using THF as the eluent at 40 °C with a flow rate of 1 mL min⁻¹. The SEC system was calibrated using linear narrow polystyrene standards ranging from 474 to 7.5 $\times 10^6$ gmol⁻¹ (PS ($K = 14.1 \times 10^{-5}$ dLg⁻¹ and $\alpha = 0.70$), and toluene as a flow

marker. ESI-MS was performed using an LCQ Fleet 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 auxiliary gas flow-rate of 3 and a dimensionless sheath gas flow-rate of 3 were applied. The capillary voltage, the tube lens offset voltage and the capillary temperature were set to 25 V, 120 V, and 275°C respectively. A 250 μL aliquot of a polymer solution with concentration of 20 $\mu\text{g mL}^{-1}$ was injected. A mixture of THF and methanol (THF:MeOH = 3:2), all HPLC grade, were used as solvent. UV-Vis spectroscopy was performed on a VARIAN CARY 500 UV-Vis-NIR spectrophotometer (scan rate: 600 nm/min).

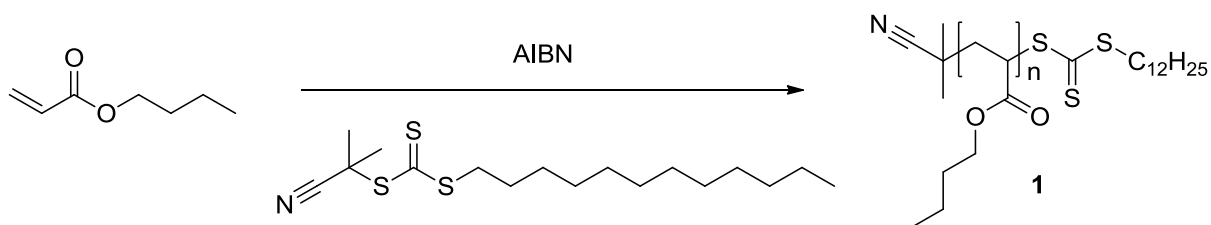
General RAFT polymerization of *n*-BuA. 0.039 mol (5 g, 80 equiv) of the monomer *n*-BuA, 0.049 mmol (0.008 g, 0.1 equiv) of AIBN and 0.488 mmol (0.169 g, 1 equiv) of 2-cyano-2-propyldodecyltrithiocarbonate RAFT agent were added into a sealed Schlenk tube. The schlenk tube was subjected to 3 freeze-pump-thaw cycles, after which the mixture was polymerized inside a glove-box for 1.75 h at 60 °C. Subsequently, the reaction mixture was poured into an aluminium pan and quenched with Hydroquinone/MeOH. Afterwards the residual monomer was evaporated, yielding 1.37 g of P(*n*-BuA) (**1**) polymer with $M_n = 4100 \text{ g mol}^{-1}$ and PDI = 1.1 (by THF-SEC).

General Aminolysis and Thiol-ene click reaction in bulk. P(*n*-BuA) (**1**) RAFT polymer (27 μmol , 100 mg, 1 equiv) was dissolved in 2 mL of THF in a Schlenk tube. Subsequently, the ene-compound (iBoA, propargyl acrylate, PEG methyl ether acrylate or pentaerythritol tetraacrylate) (270 μmol , 10 equiv) was added and the tube was sealed. The mixture was degassed by 3 freeze-pump-thaw cycles. Afterwards, a degassed mixture of hexylamine (270 μmol , 27 mg, 10 equiv) in THF (0.4 mL, 0.68M) was added and the mixture was reacted for 3 hours at room temperature, by which it turned colourless. Subsequently, the reaction mixture

was poured into an aluminium pan and the excess of solvent was evaporated, yielding 0.1 g of functionalized P(*n*-BuA) (**2**, **3**, **4** or **5**) polymer. The dried product was analyzed with ESI-MS to determine the conversion of the initial RAFT endgroups into the different thiol-ene click end-group functionalities.

General Aminolysis and Thiol-ene click reaction in continuous-flow microreactor.

By using the Labtrix[®] Start R2.2 system, fitted with a glass microreactor (3227, reactor volume = 19.5 μ L) and a back-pressure regulator set to 20 bar, a degassed THF solution of *p*(*n*-BuA) RAFT polymer (**1**) (0.027 M) and acrylate compound (0.27 M respectively) was pumped into the reactor from inlet 1 and a degassed THF solution of hexylamine (0.27 M) was introduced from inlet 2. After a reactant residence time of 5, 10 or 20 min at a reaction temperature of 25 $^{\circ}$ C, a 45 μ L aliquot of the reaction product was collected in a SEC vial and diluted with THF in order to take a UV-Vis spectrum, a second sample was diluted with THF:MEOH 3:2 and measured directly after collecting with ESI-MS.



Scheme 1. RAFT polymerization of *n*-butyl acrylate.

Product Characterization

Full characterization of starting polymer **1**

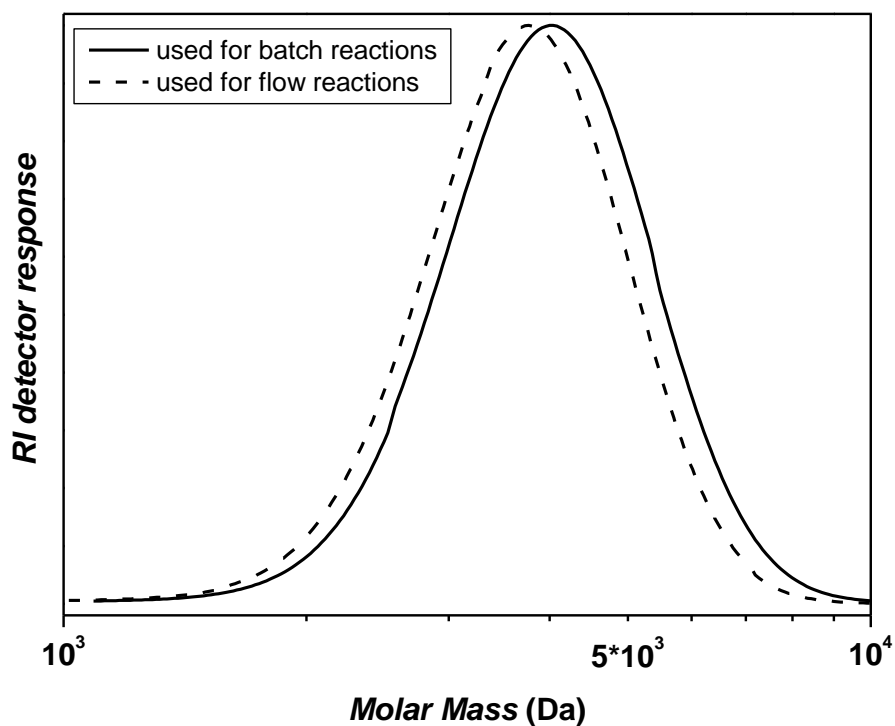


Fig. 1: SEC chromatogram of RAFT P(*n*-BuA) **1**. Used for batch reactions: $M_n = 4100$ g/mol, PDI = 1.10. Used for flow reactions: $M_n = 3800$ g/mol, PDI = 1.10.

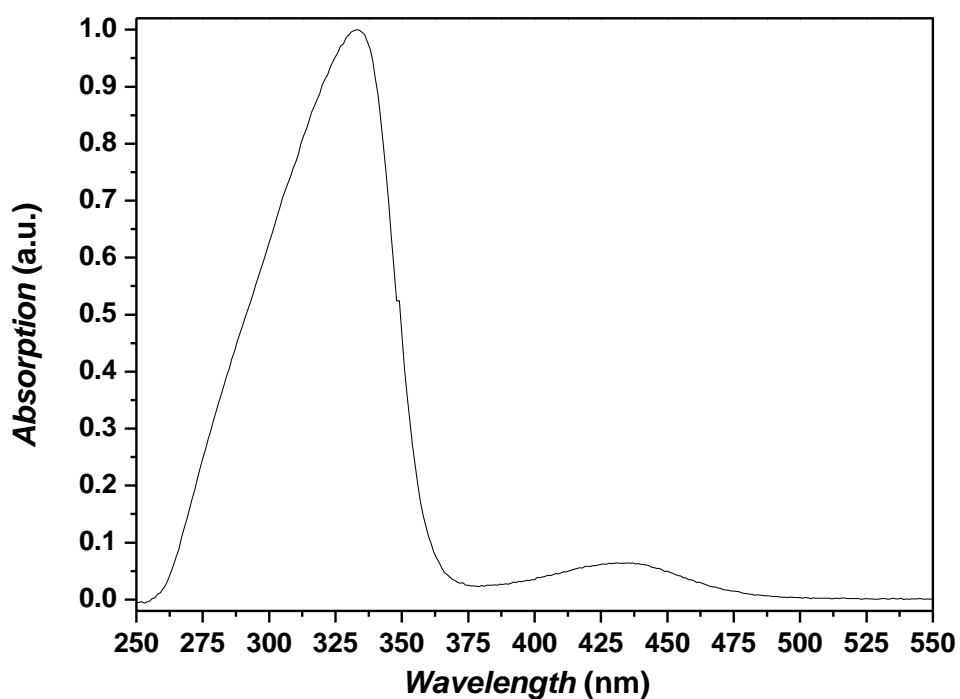


Fig. 2: UV-Vis absorption spectrum of starting polymer **1**.

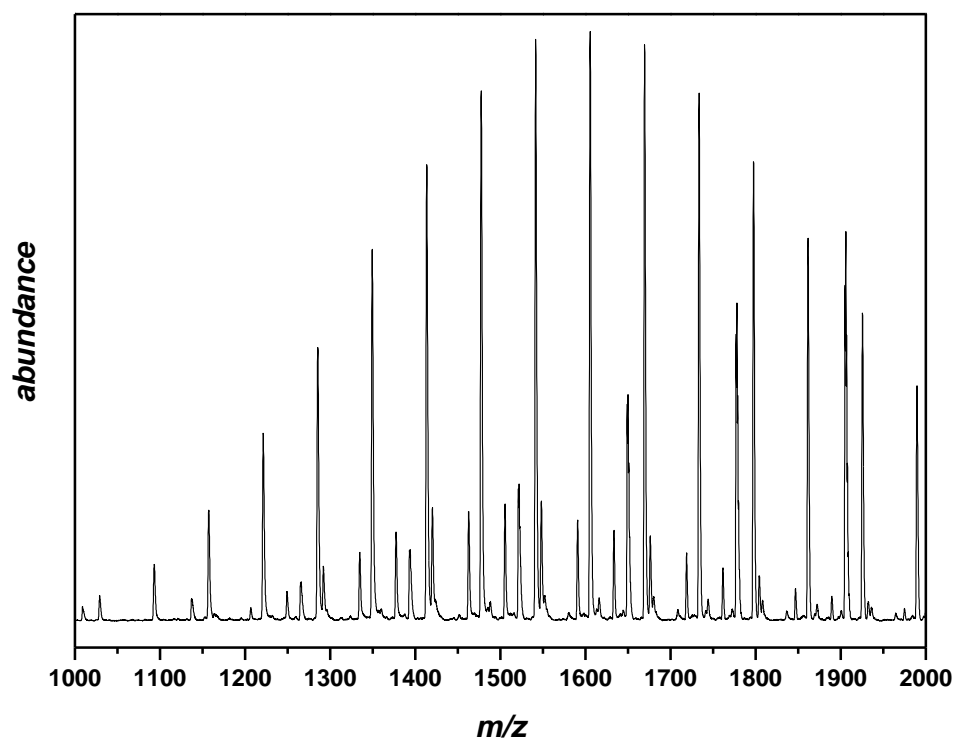


Fig. 3: Full ESI-MS spectrum of starting polymer **1**.

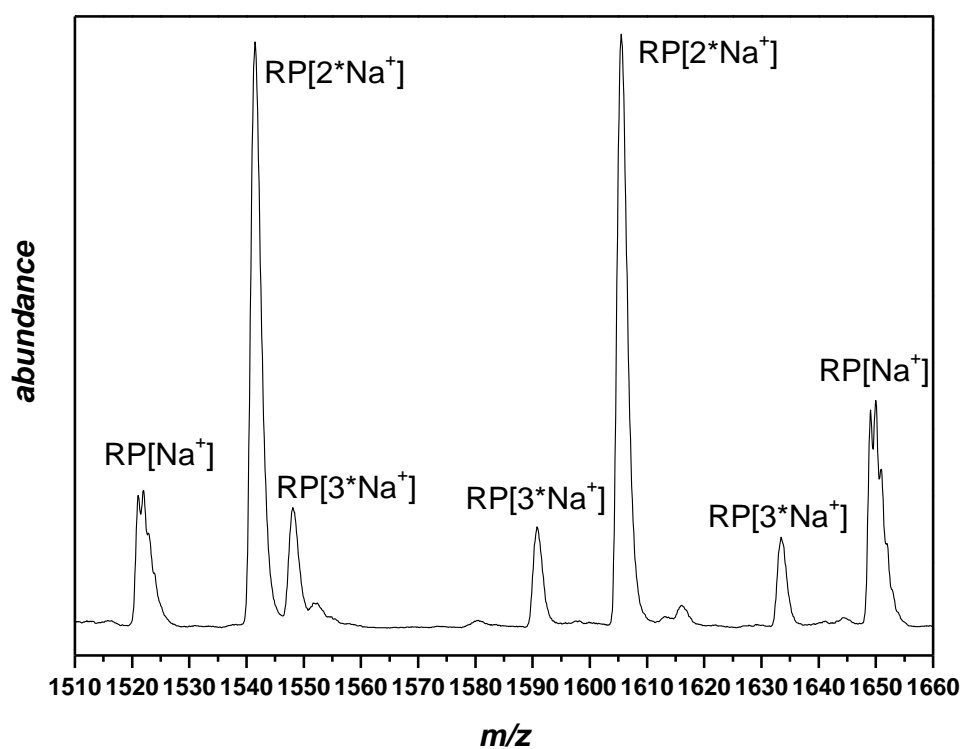


Fig. 4: ESI-MS spectrum of single monomer repeat unit of starting polymer **1**.

Full characterization of thiolene polymer 2, prepared in batch.

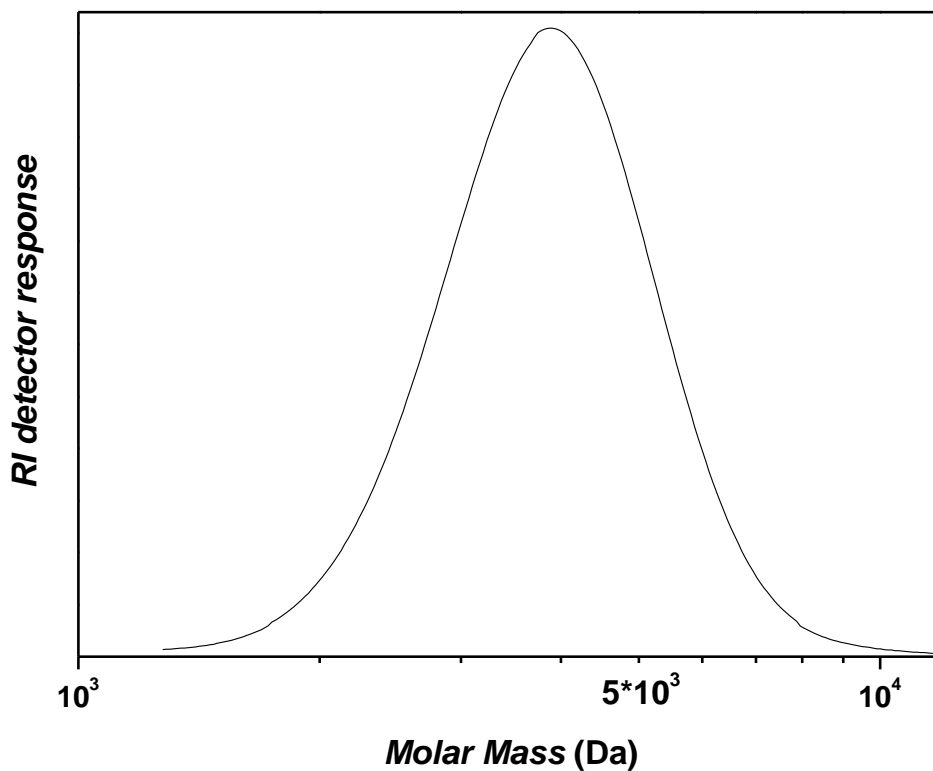


Fig. 5: SEC chromatogram of batch thiol-ene polymer 2. $M_n = 3900$ g/mol, PDI = 1.10.

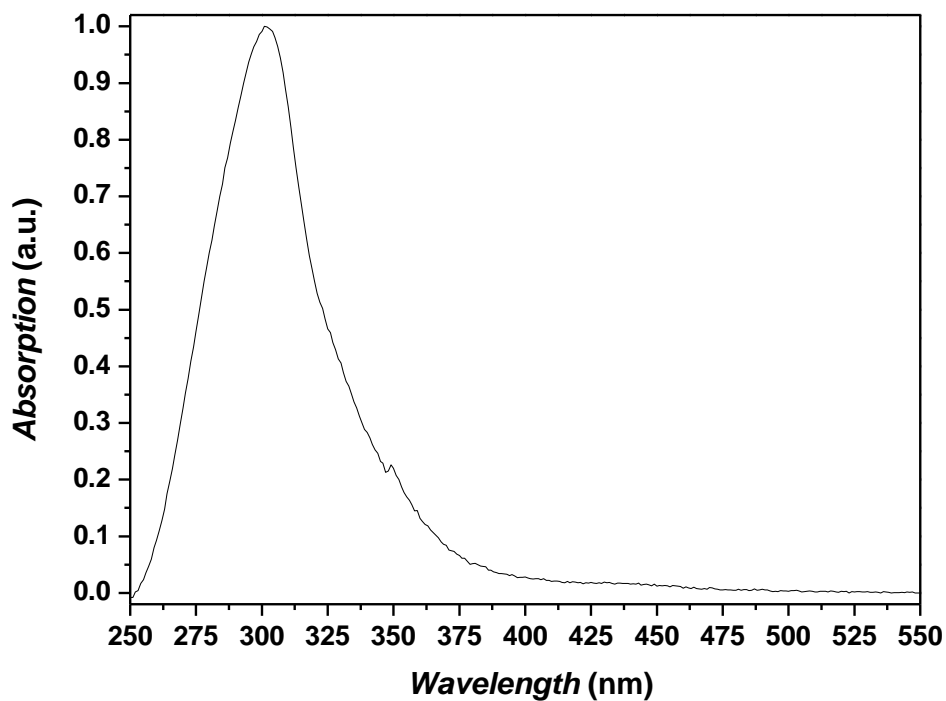


Fig. 6: UV-Vis absorption spectrum of batch thiol-ene polymer 2.

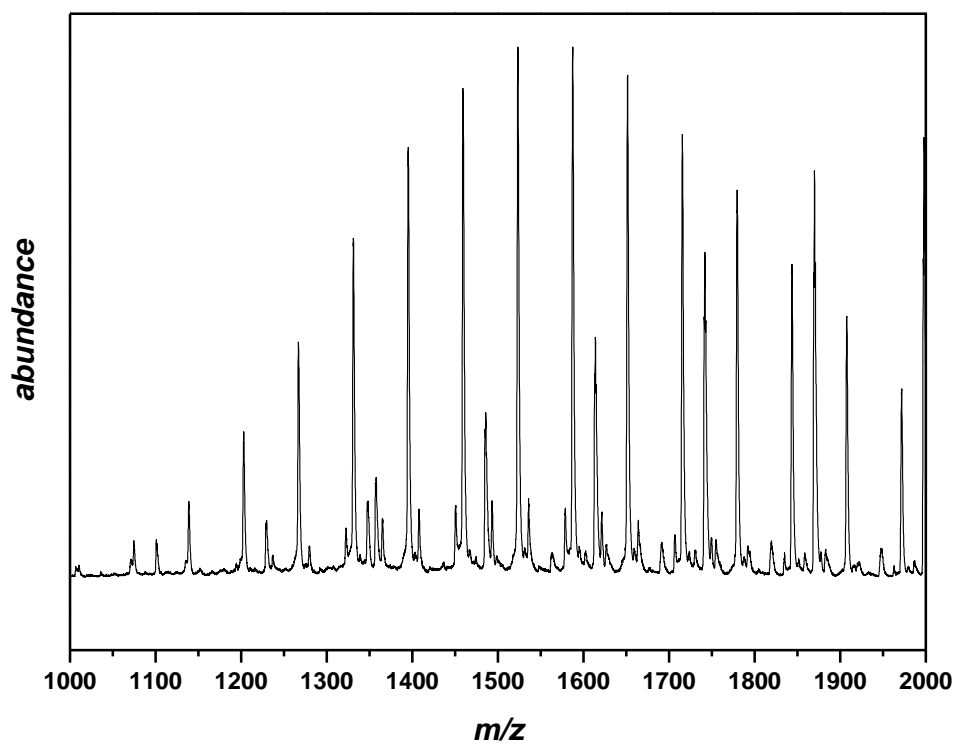


Fig. 7: Full ESI-MS spectrum of batch thiol-ene polymer **2**.

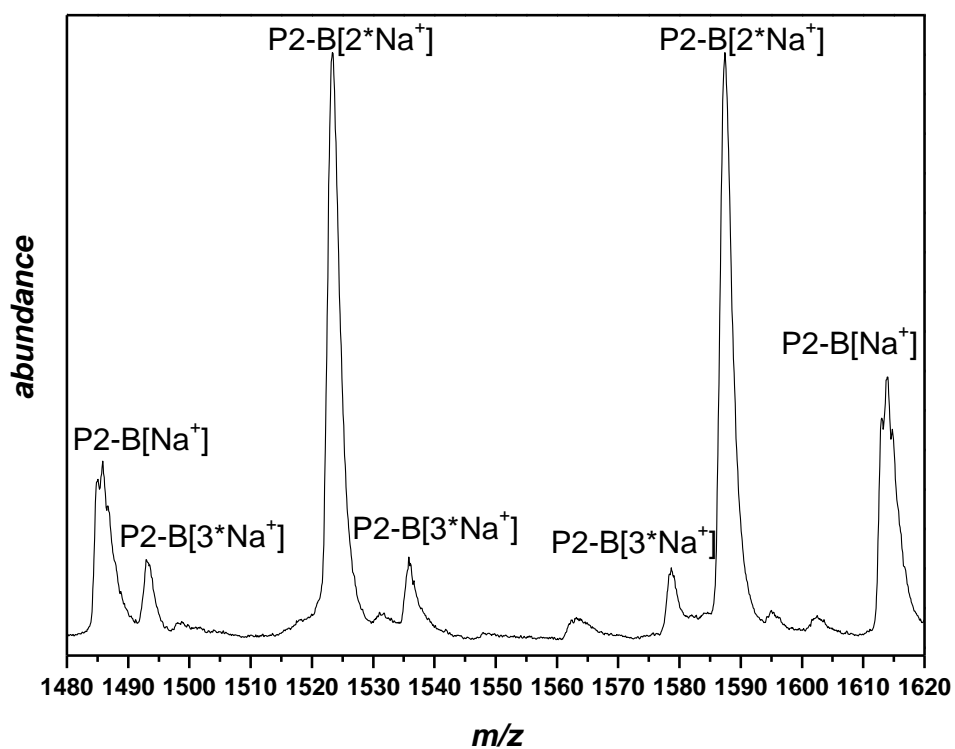


Fig. 8: ESI-MS spectrum of single monomer repeat unit of batch thiol-ene polymer **2**.

Full characterization of thiolene polymer 2, prepared in flowreactor.

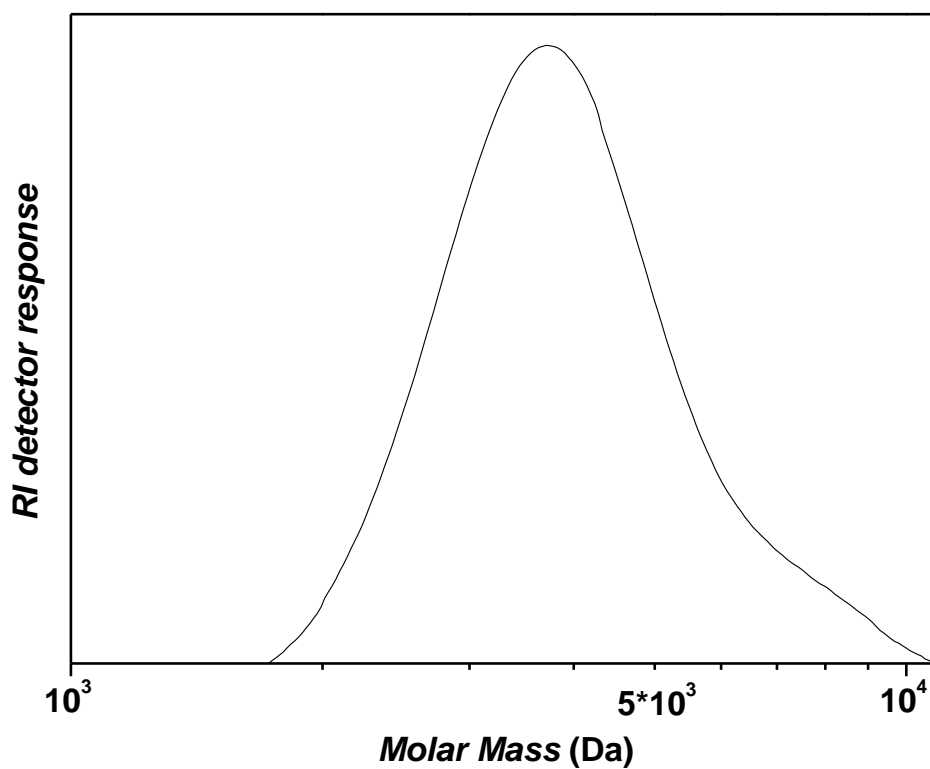


Fig. 9: SEC chromatogram of thiol-ene polymer 2. $M_n = 4000$ g/mol, PDI = 1.12.

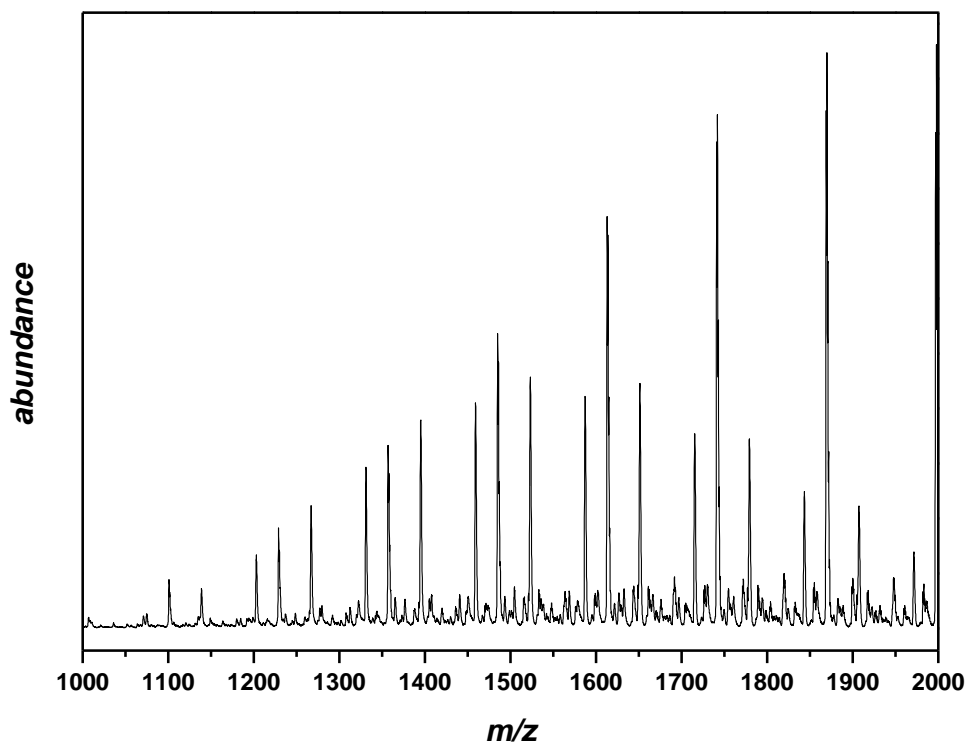


Fig. 10: Full ESI-MS spectrum of thiol-ene polymer 2.

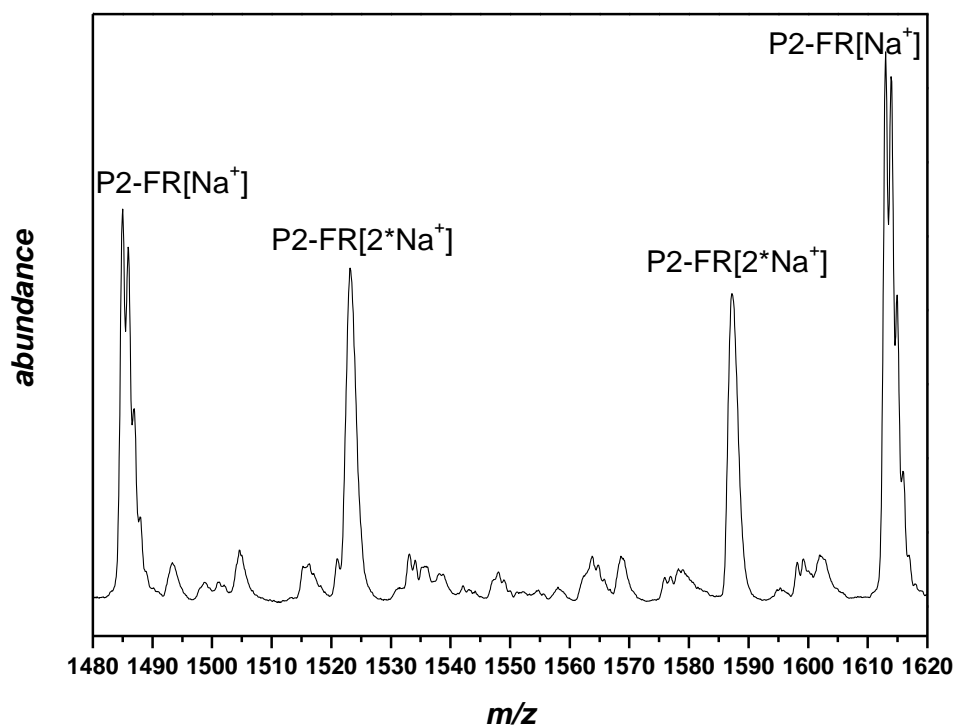


Fig. 11: ESI-MS spectrum of single monomer repeat unit of thiol-ene polymer **2**.

Full characterization of thiolene polymer 3, prepared in batch.

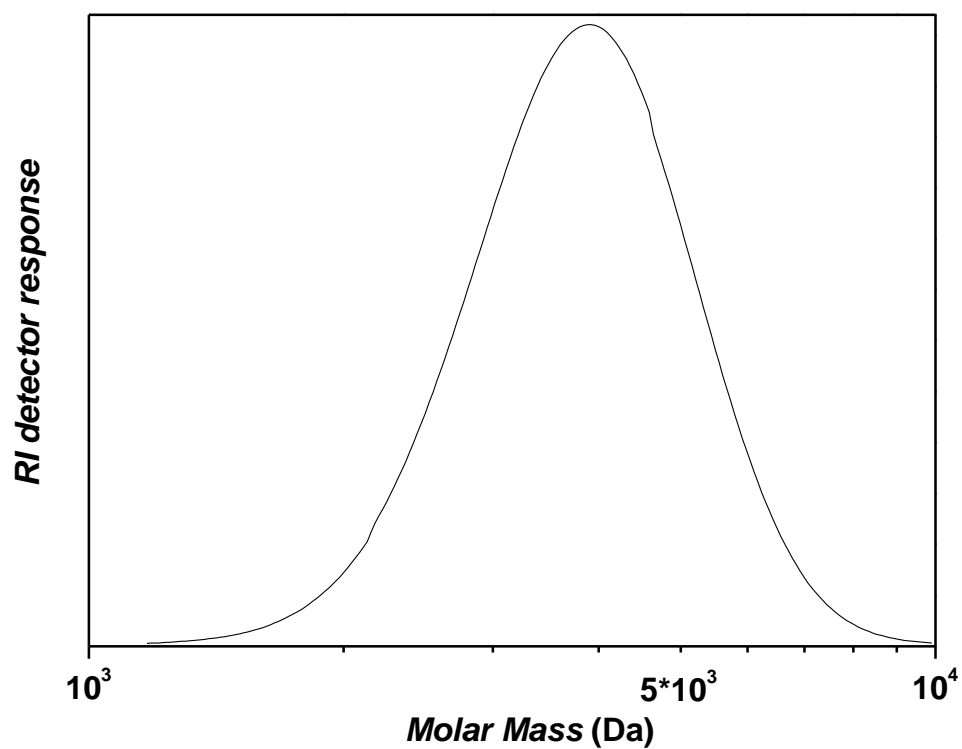


Fig. 12: SEC chromatogram of batch thiol-ene polymer **3**. $M_n = 3900$ g/mol, PDI = 1.10.

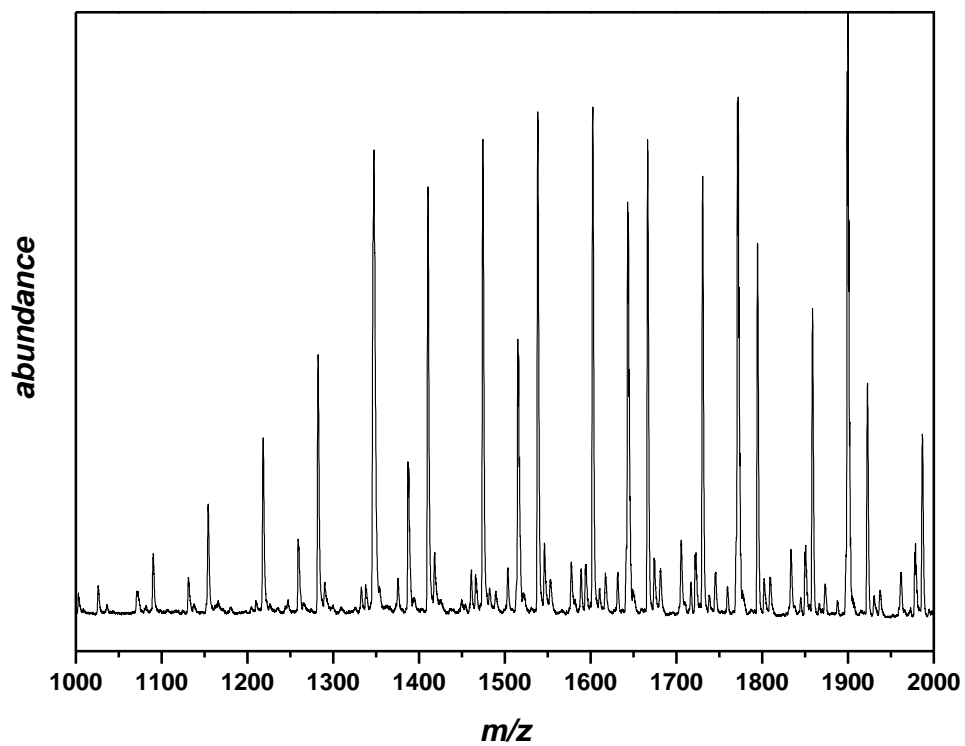


Fig. 13: Full ESI-MS spectrum of batch thiol-ene polymer **3**.

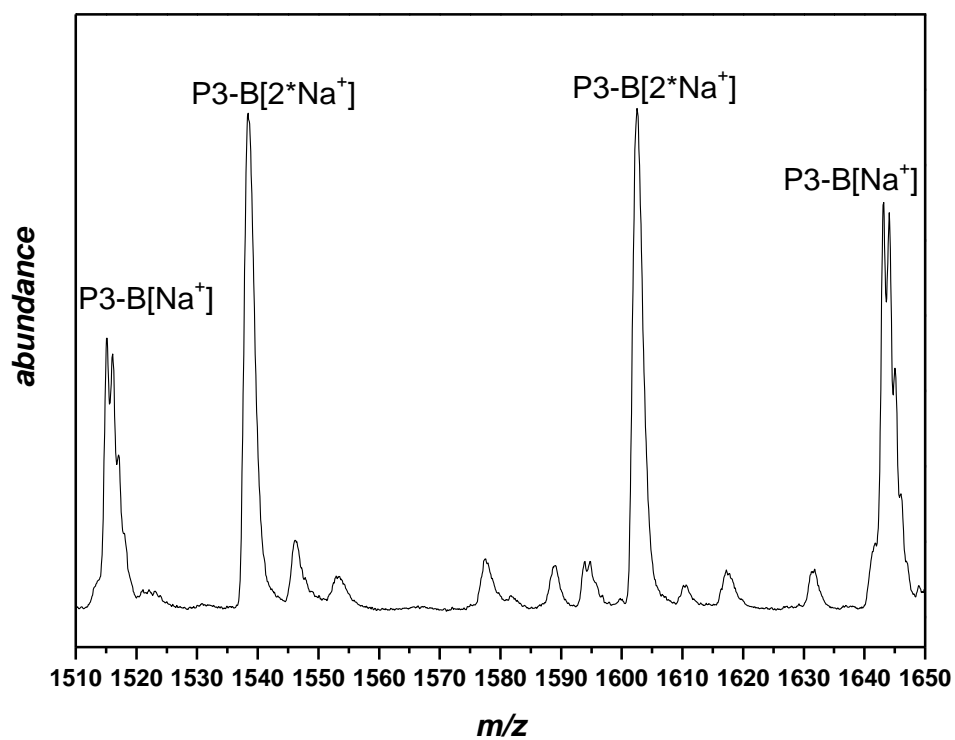


Fig. 14: ESI-MS spectrum of single monomer repeat unit of batch thiol-ene polymer **3**.

Full characterization of thiolene polymer 3, prepared in flow reactor.

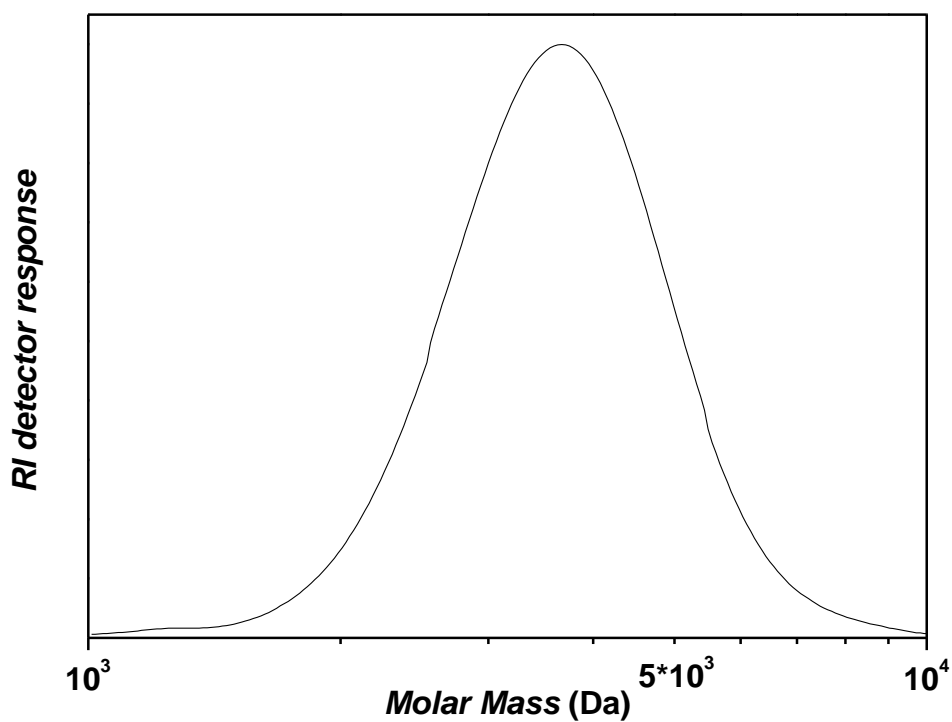


Fig. 15: SEC chromatogram of thiol-ene polymer 3. $M_n = 3700$ g/mol, PDI = 1.12

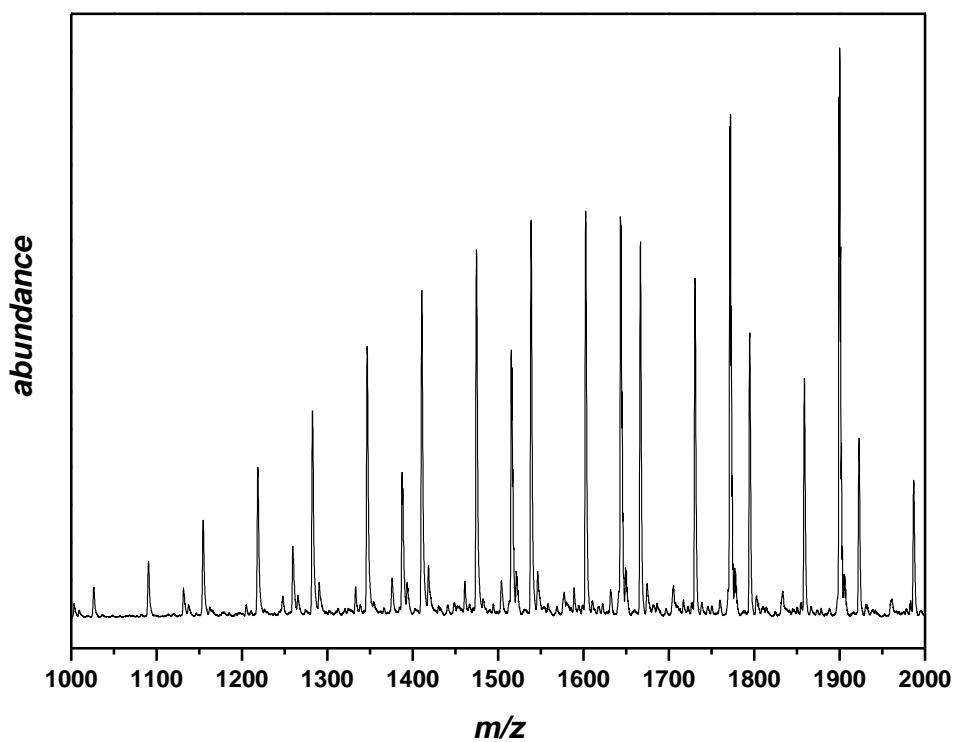


Fig. 16: Full ESI-MS spectrum of thiol-ene polymer 3.

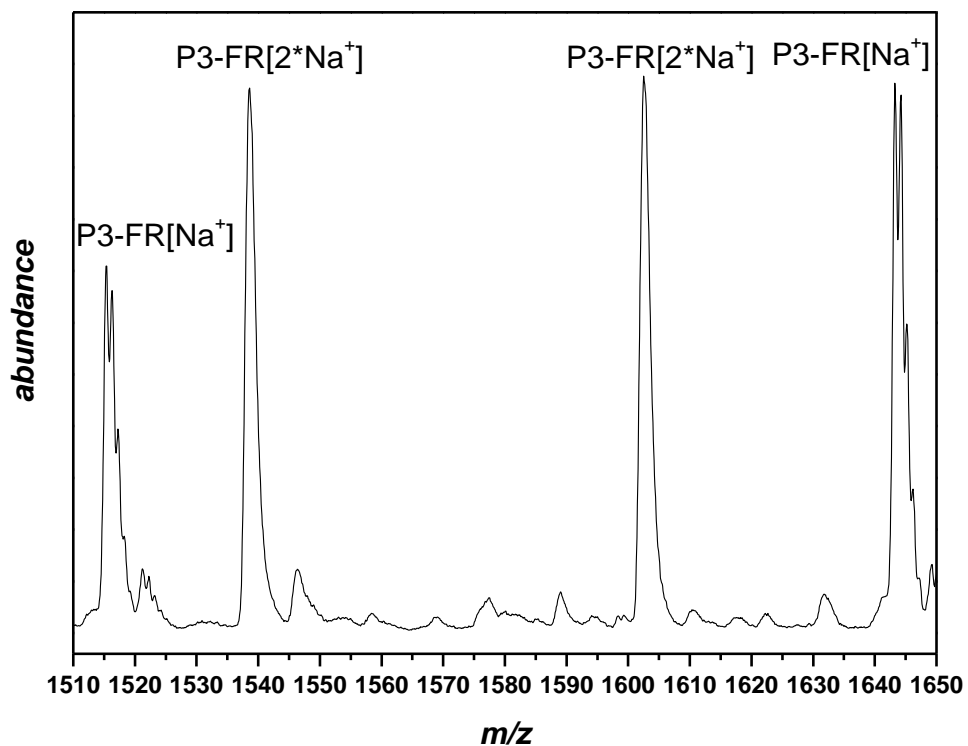


Fig. 17: ESI-MS spectrum of single monomer repeat unit of thiol-ene polymer **3**.

Full characterization of thiolene polymer 4, prepared in batch.

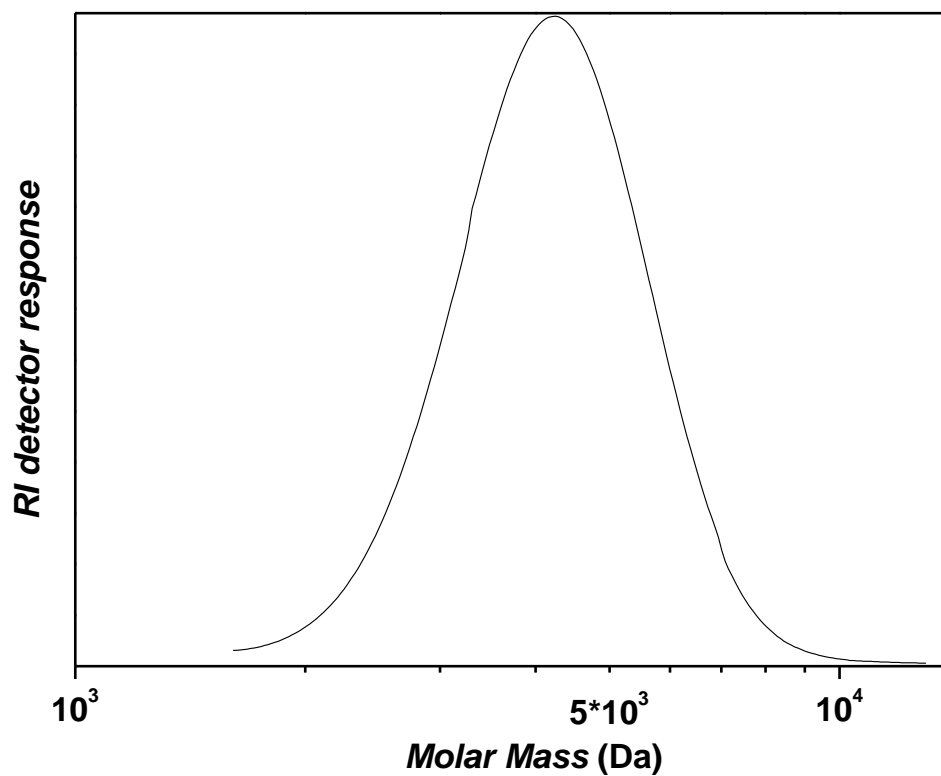


Fig. 18: SEC chromatogram of batch thiol-ene polymer **4**. $M_n = 4300$ g/mol, PDI= 1.09.

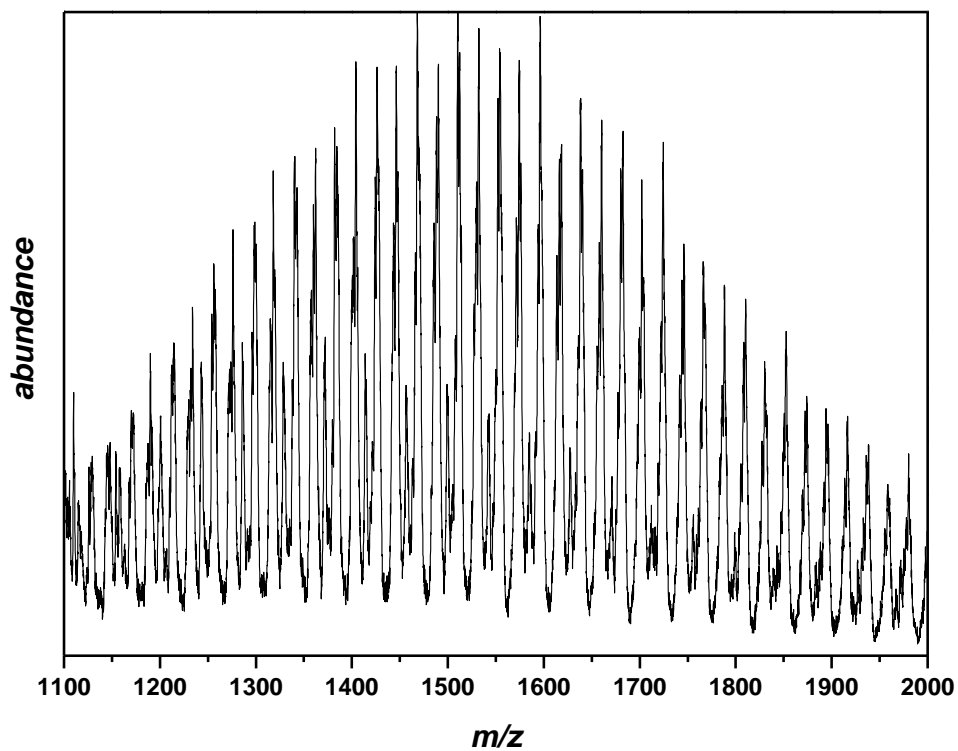


Fig. 19: Full ESI-MS spectrum of batch thiol-ene polymer **4**.

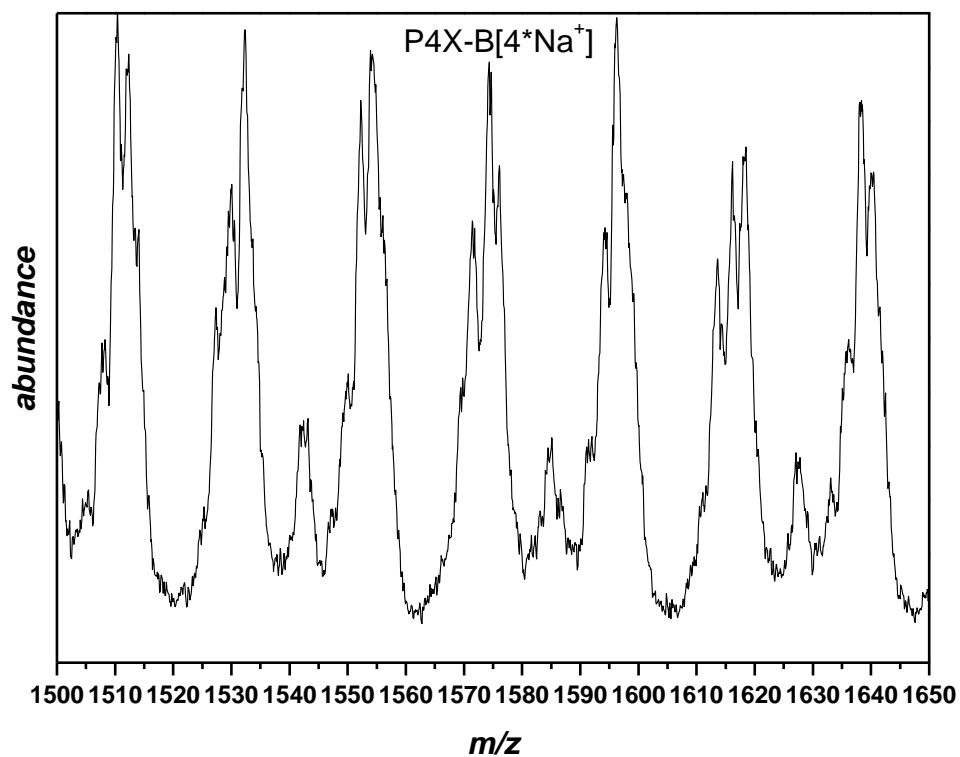


Fig. 20: ESI-MS spectrum of single monomer repeat unit of batch thiol-ene polymer **4**.

Full characterization of thiolene polymer 4, prepared in flow reactor.

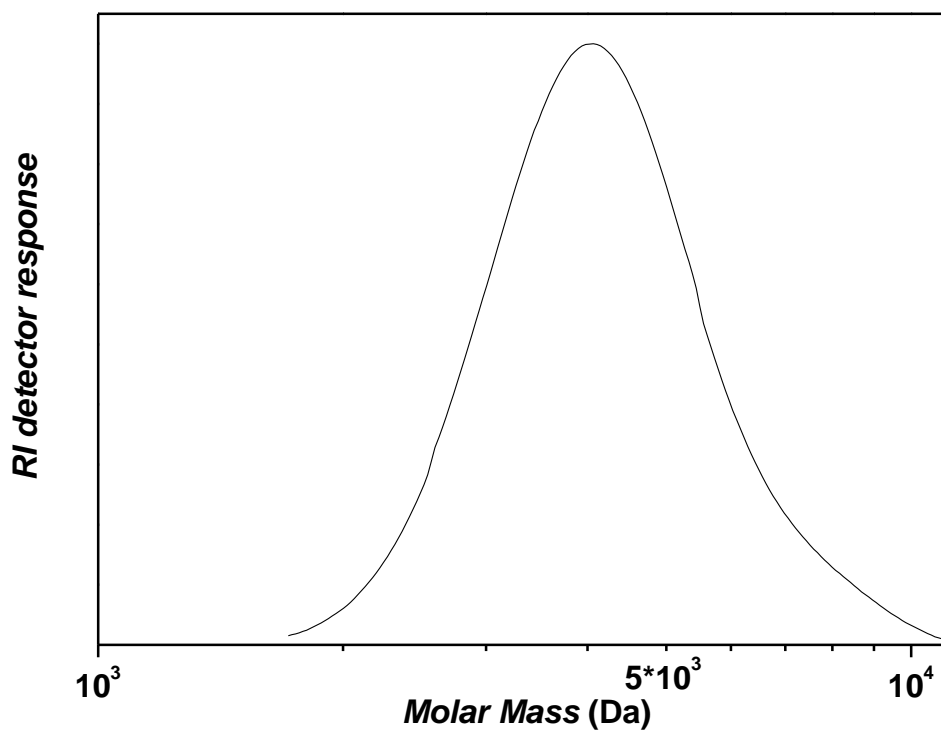


Fig. 21: SEC chromatogram of thiol-ene polymer 4. $M_n = 4300$ g/mol, PDI = 1.11.

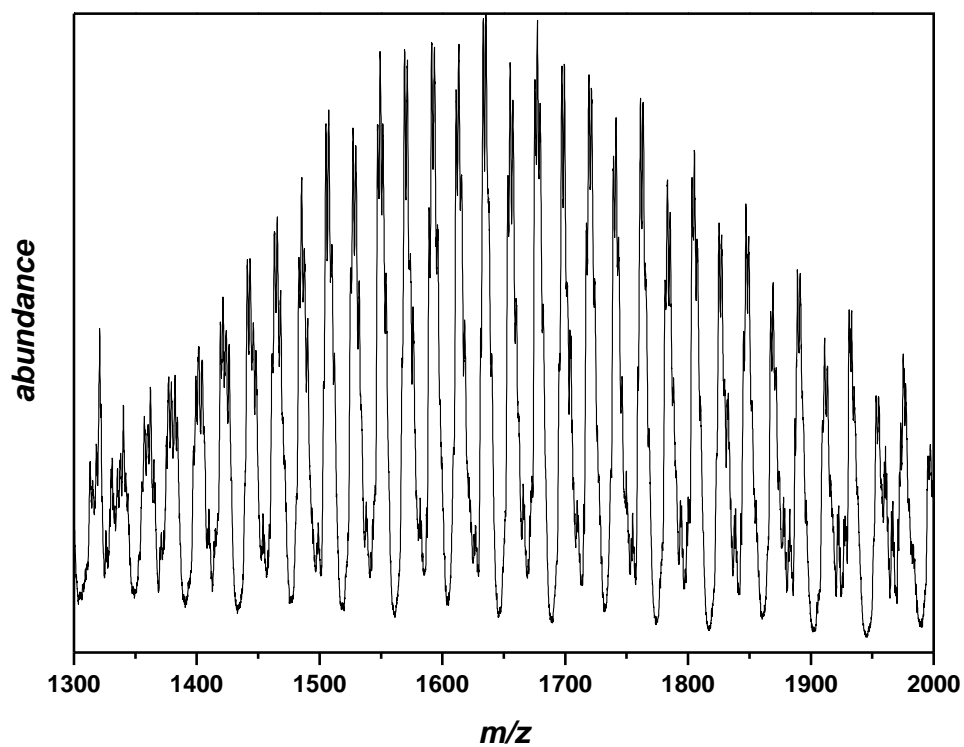


Fig. 22: Full ESI-MS spectrum of thiol-ene polymer 4.

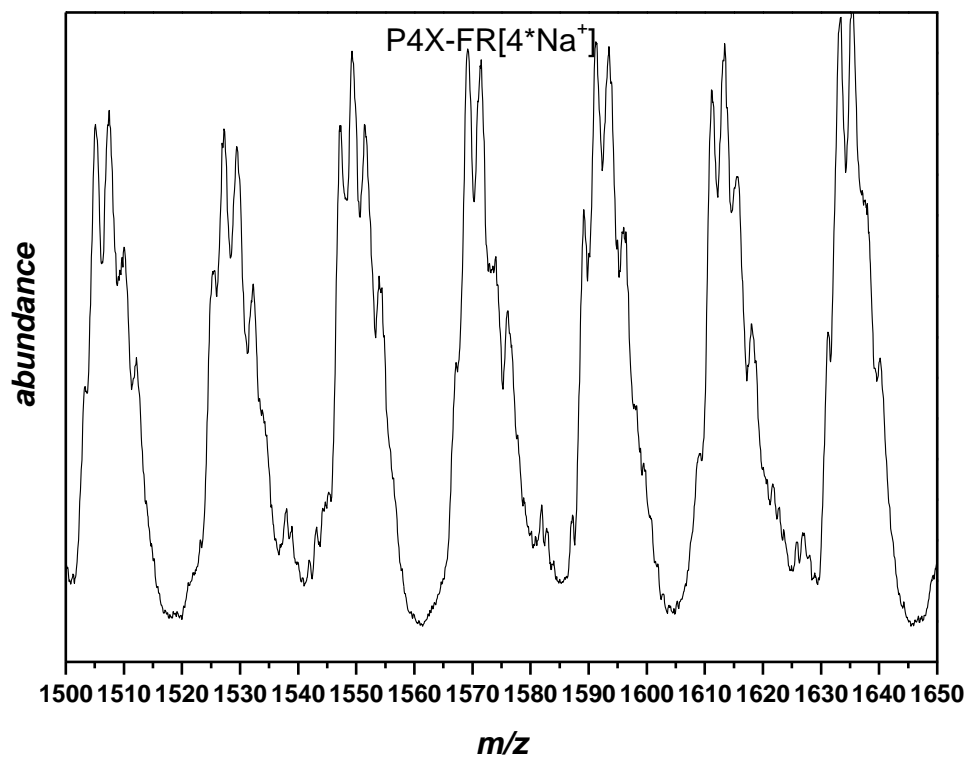


Fig. 23: ESI-MS spectrum of single monomer repeat unit of thiol-ene polymer 4.

Full characterization of thiolene polymer 5, prepared in batch.

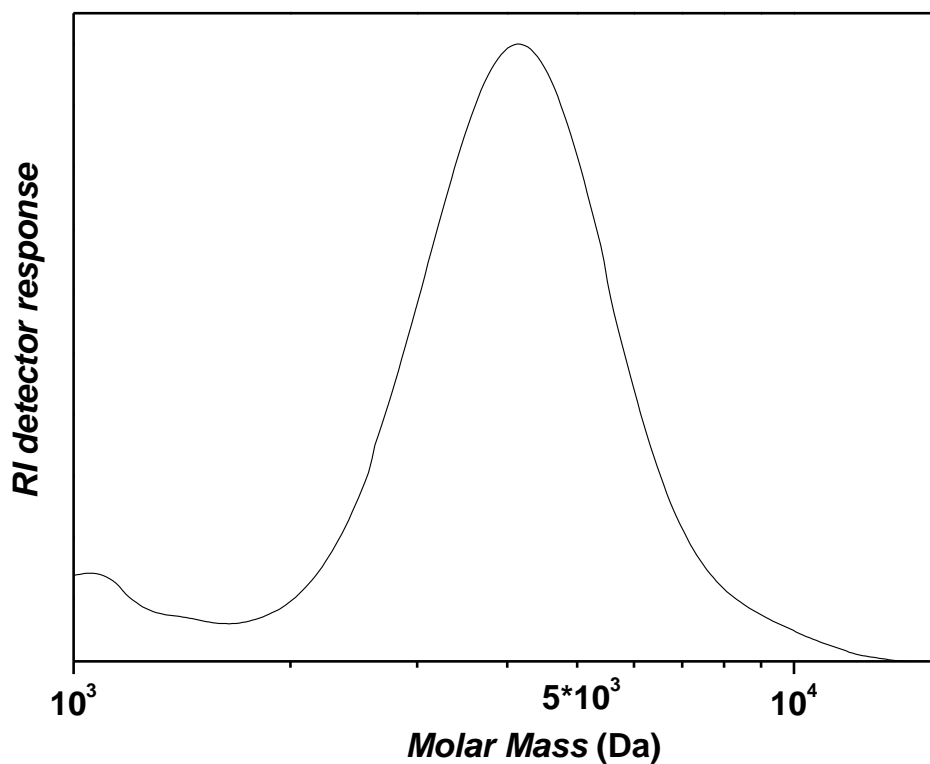


Fig. 24: SEC chromatogram of batch thiol-ene polymer 5. $M_n = 4200$ g/mol, PDI = 1.12.

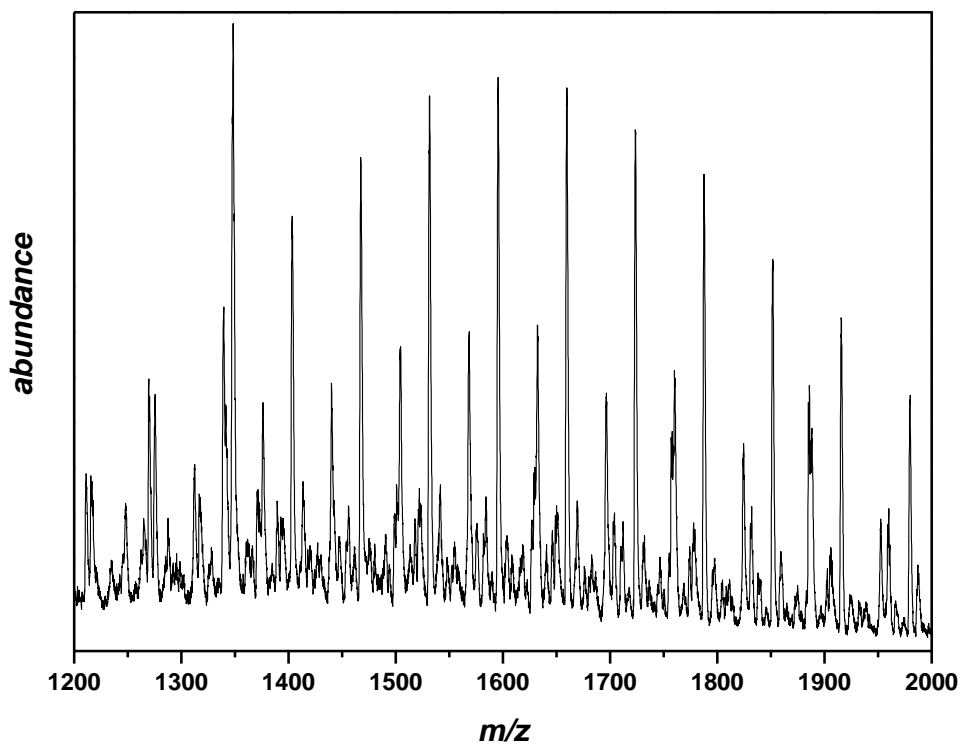


Fig. 25: Full ESI-MS spectrum of batch thiol-ene polymer **5**.

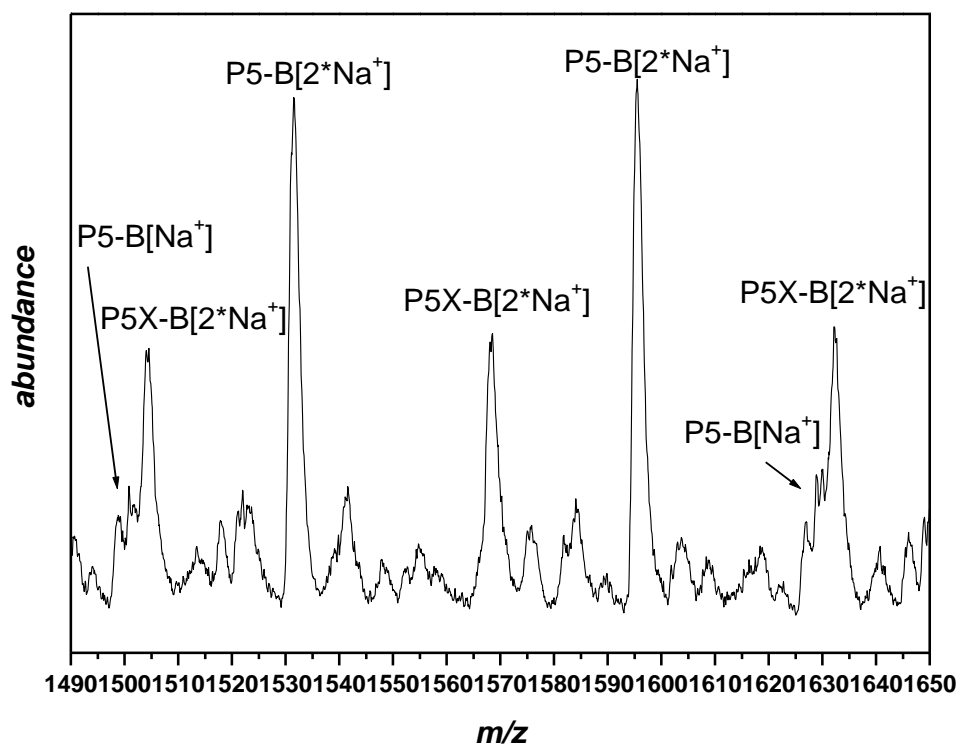


Fig. 26: ESI-MS spectrum of single monomer repeat unit of batch thiol-ene polymer **5**.

Full characterization of thiolene polymer 5, prepared in flowreactor.

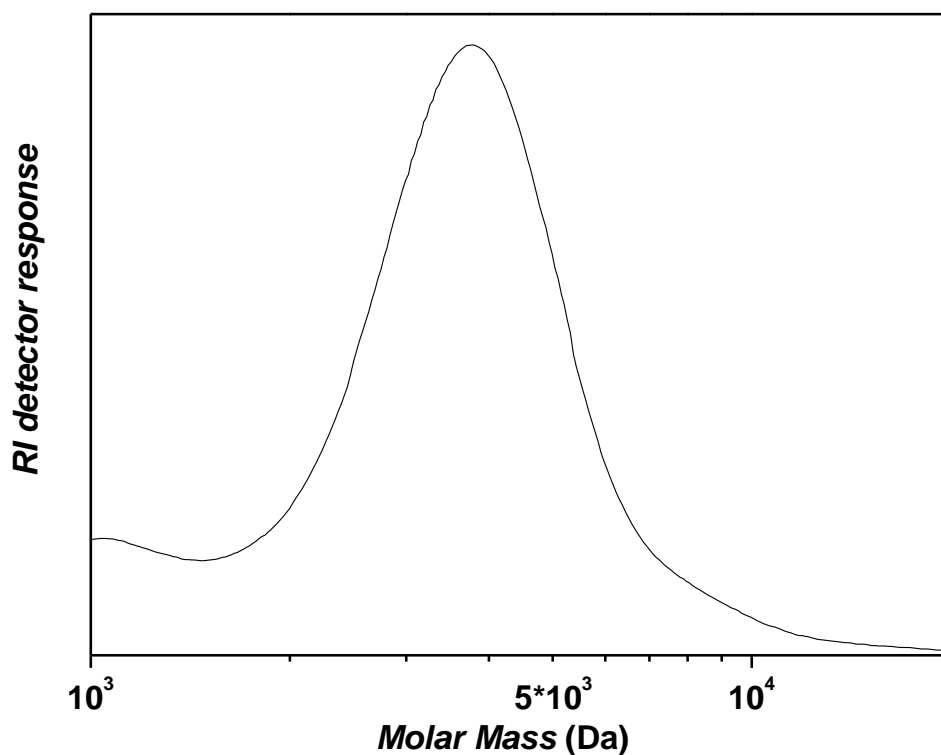


Fig. 27: SEC chromatogram of thiol-ene polymer 5. $M_n = 3900$ g/mol, PDI = 1.20.

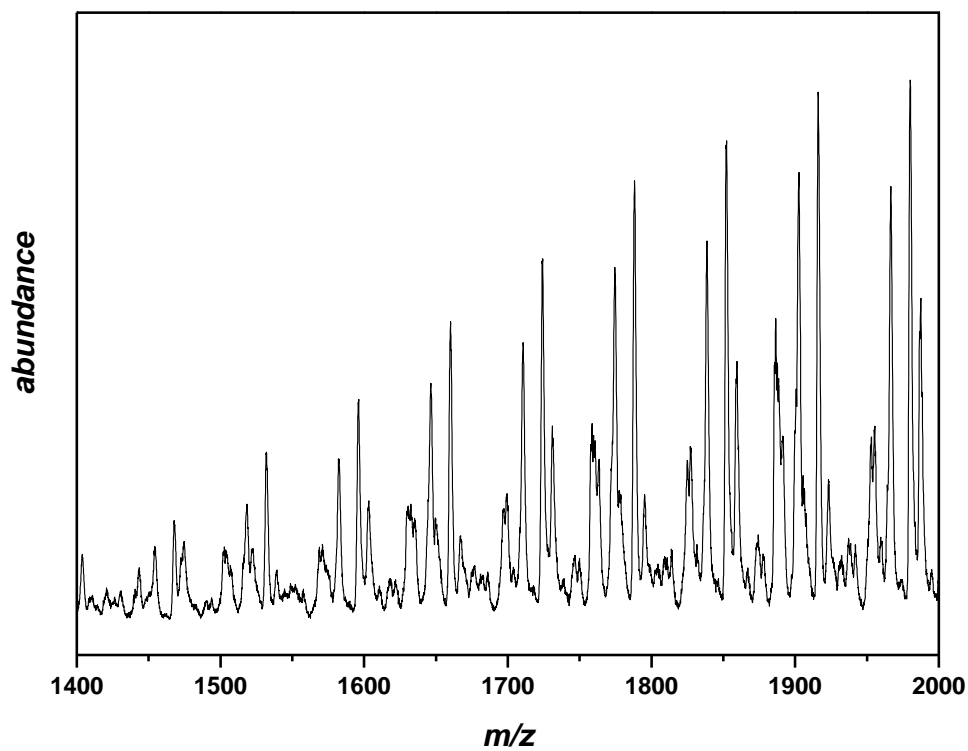


Fig. 28: Full ESI-MS spectrum of thiol-ene polymer 5.

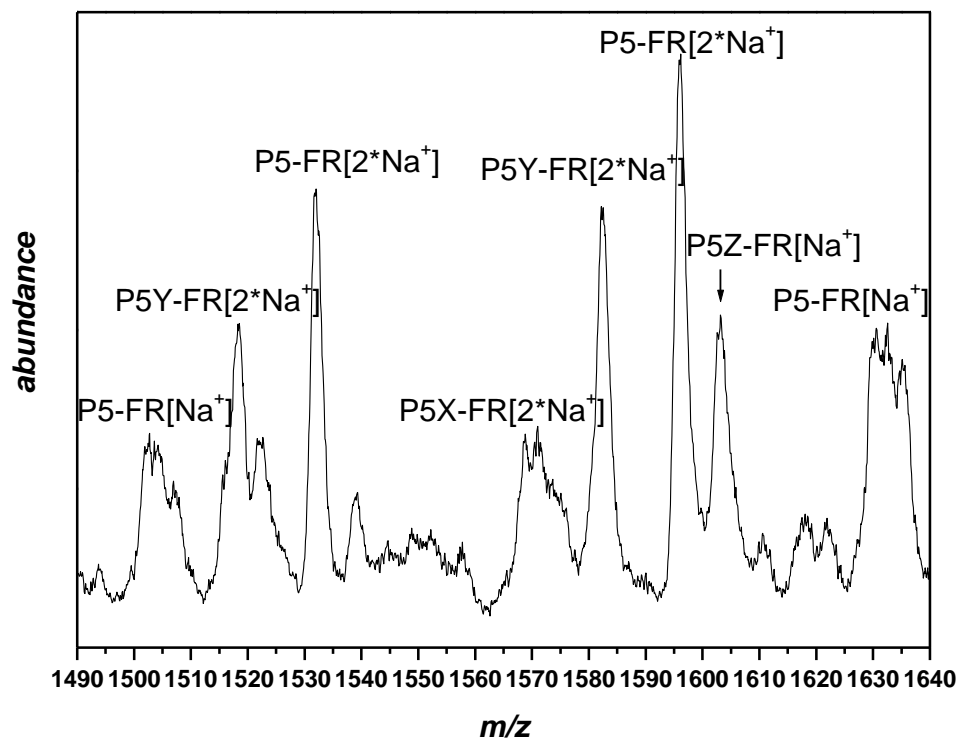


Fig. 29: ESI-MS spectrum of single monomer repeat unit of thiol-ene polymer **5**.

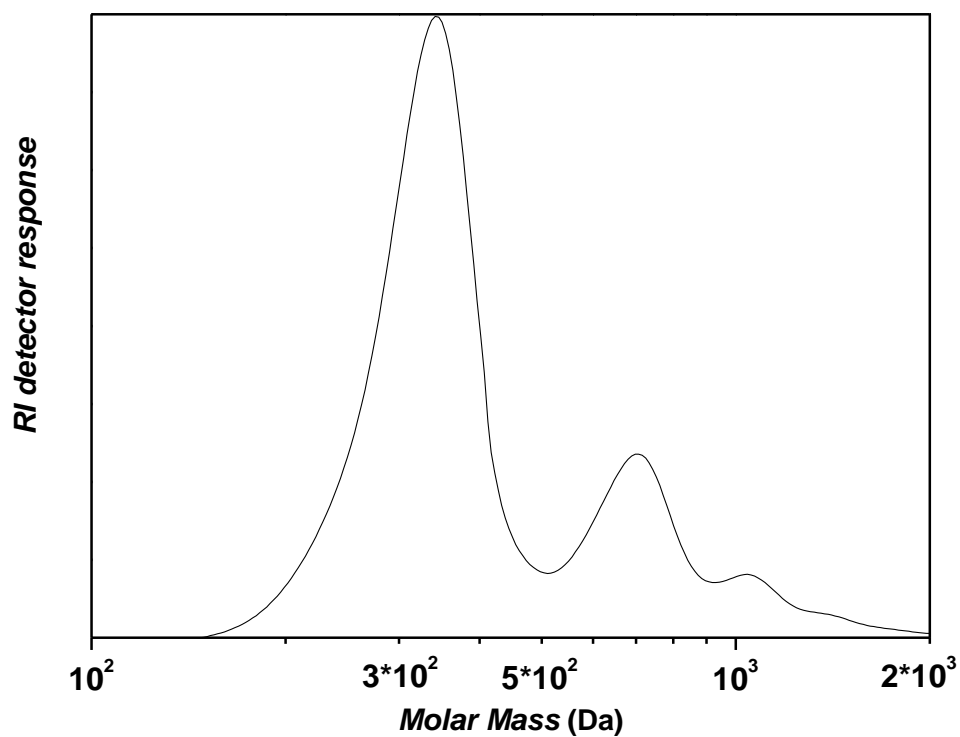


Fig. 30: SEC chromatogram of pentaerythritol tetraacrylate D.

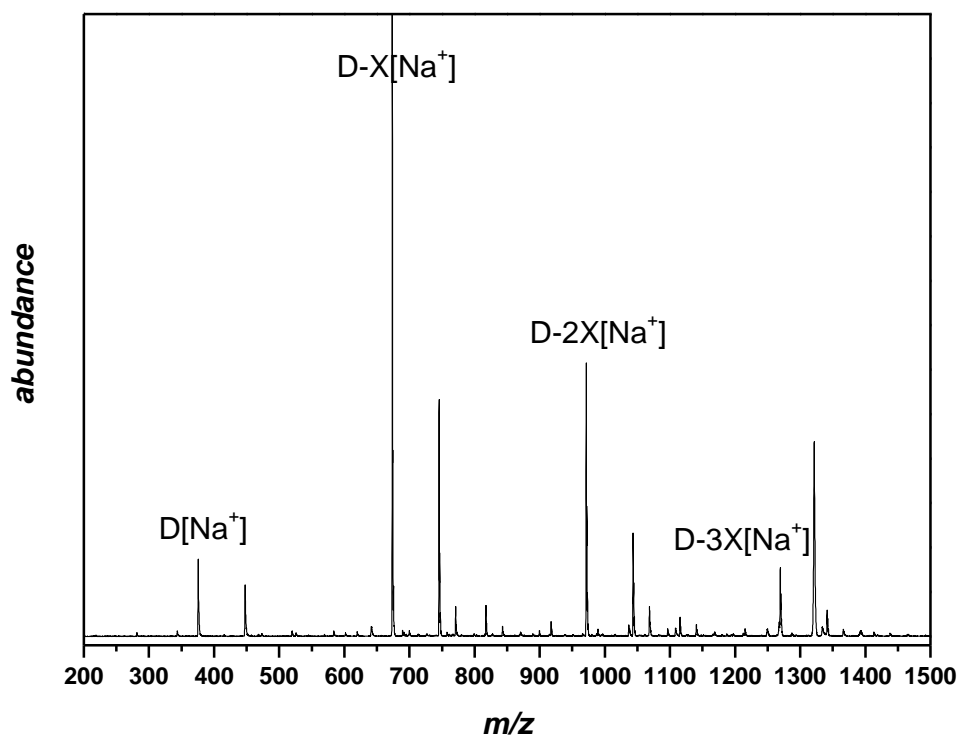


Fig.31: Full ESI-MS spectrum of D. m/z of $D[Na^+]$ = 375.11 Da.

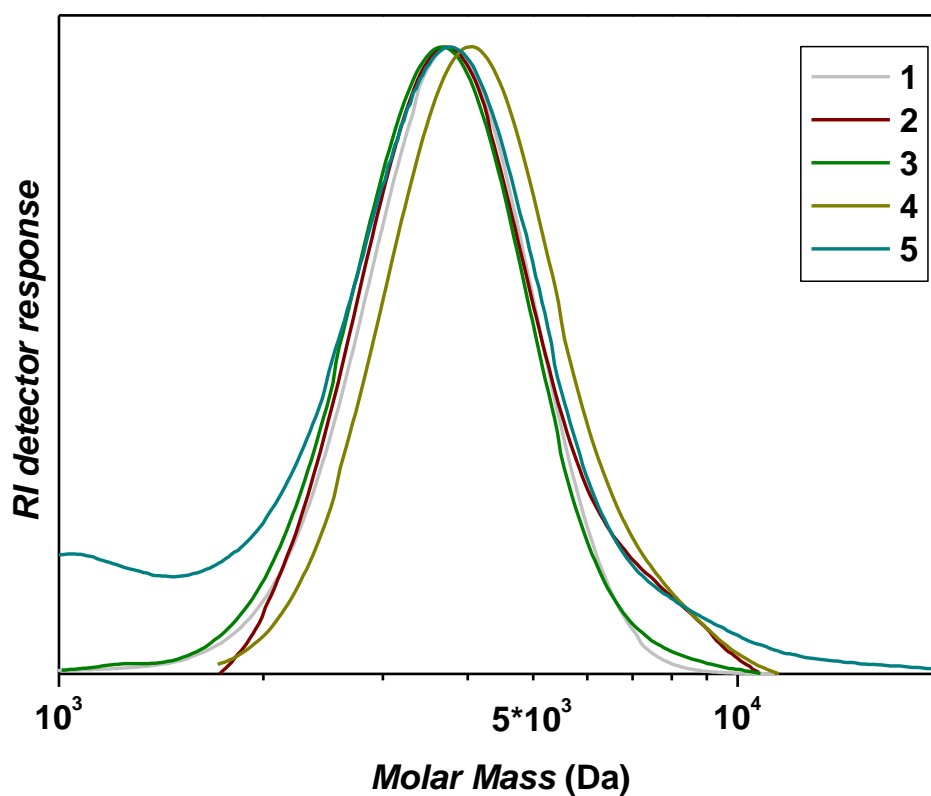


Fig.32: overlay of SEC chromatograms of polymers 1,2,3,4,5, prepared via flow reaction.

Table 1: Table of masses for products identified in the mass spectra.*

Polymer	Species	m/ztheo / Da	m/z/exp / Da	$\Delta m/z$ / Da
1	RP[Na+]	1520,88	1521,08	0,20
	RP[2*Na+]	1541,42	1541,50	0,08
	RP[3*Na+]	1546,93	1548,08	1,15
2-batch	P2-B[Na+]	1613,97	1613,92	0,05
	P2-B[2*Na+]	1650,50	1651,58	1,05
	P2-B[3*Na+]	1663,01	1664,08	1,07
2-flow reactor	P2-FR[Na+]	1612,97	1613,00	0,03
	P2-FR[2*Na+]	1650,50	1651,17	0,67
3-batch	P3-B[Na+]	1642,94	1643,17	0,23
	P3-B[2*Na+]	1601,45	1602,58	1,13
3-flow reactor	P3-FR[Na+]	1642,94	1643,25	0,31
	P3-FR[2*Na+]	1601,45	1602,50	1,05
4-batch	P4X-B[4*Na+]	-	1510,33	-
4-flow reactor	P4X-FR[4*Na+]	-	1507,50	-
5-batch	P5-B[Na+]	1628,86	1628,92	0,06
	P5-B[2*Na+]	1594,41	1595,33	0,92
	P5X-B[2*Na+]	1631,44	1632,17	0,73
5-flow reactor	P5-FR[Na+]	1628,86	1629,08	0,22
	P5-FR[2*Na+]	1594,41	1596,17	1,76
	P5X-FR[2*Na]	1631,44	1632,58	1,14
	P5Y-FR[2*Na+]	-	1646,50	-
	P5Z-FR[Na+]	-	1603,17	-

* m/z values of single charged species are highlighted in grey. The double and triple charged species have highly complicated isotopic patterns that are more difficult to resolve. This explains the higher m/z differences observed for these species.

Chart 1: Chemical structures of products identified in the mass spectra.

