Electronic Supplementary Information

Facile one-pot/one-step synthesis of hetero-telechelic *N*-acylated poly(aminoester) macromonomers for carboxylic acid decorated comb polymers

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Experimental details

Materials

Acrylic acid (AA, 99%, anhydrous, Sigma Aldrich), acetonitrile (ACN, 99.8%, Sigma Aldrich), 4-methoxyphenyl (MEHQ, 99%, Sigma Aldrich), diethyl ether (DEE, >98%, Sigma Aldrich), methanol (MeOH, 98%, Sigma Aldrich), 1,4-dioxane (>99%, Sigma Aldrich), Luperox® TBH70X *tert*-butylhydroperoxide solution (tBuOOH, 70 wt.% in H_2O, Sigma Aldrich), L-ascorbic acid (AsAc, 99%, Sigma Aldrich), sodium hydroxide standard solution (NaOH, 0.1001 M, Sigma Aldrich), hydrochloric acid (HCl, 37%, Fisher Scientific), benzyl amine (99%, Sigma Aldrich), α-methoxy-ω-aminopoly(ethylene glycol) (PEG-amine, MW = 750 Da, 99%, Rapp Polymere), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 98%, Alfa Aesar), *N,N*-diisopropylethylamine (DIPEA, 99%, Sigma Aldrich), phenylalanine methylester hydrochloride (PME, 98%, Sigma Aldrich) and *N,N*-dimethylformamide (DMF, 99%, Fisher Scientific) were used as received. 2-Methyl-2-oxazoline (MeOx, 99% Sigma Aldrich) and 2-ethyl-2-oxazoline (EtOx, 99%, Sigma Aldrich) were distilled to dryness over barium oxide (BaO) and stored in a nitrogen atmosphere. The chain transfer agent (CTA), 2-(((butylthio)-carbonothionyl)thio)propanoic acid was prepared according to a literature procedure.[1]

Instrument and analysis

^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer using deuterated solvents obtained from Sigma Aldrich. Size exclusion chromatography (SEC) measurements were conducted using an Agilent 390-LC MDS fitted with differential refractive index (DRI), light scattering (LS) and viscometry (VS) detectors equipped with 2 x PLgel 5 mm mixed-D columns (300 x 7.5 mm), 1 x PLgel 5 mm guard column (50 x 7.5 mm) and autosampler. All samples were passed through 0.2 µm nylon filter before analysis. The mobile phase was DMF containing 5 mM NH_4BF_4 with a flow rate of 1 ml min^{-1} at 50 °C. SEC data was analysed using Agilent Technologies SEC Software. Calibration curves were produced using Agilent Easi-Vials linear poly(methyl methacrylate) standards (200 – 4.7 x 10^5 g mol^{-1}). MALDI-ToF MS spectra were recorded in reflection mode on a Bruker Daltonics Autoflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix solution was prepared by dissolving the matrix (super DHB; 2,5-dihydroxybenzoic acid and 2-hydroxy-5-methoxyben-

zoic acid) in MeOH (200 mg mL^{-1}). Sodium iodide was dissolved in MeOH (4 mg mL^{-1}). Polymer samples were dissolved in MeOH (1 to 5 mg mL^{-1}). Samples were prepared by mixing 5 µL of polymer solution, 5 µL of salt solution and 20 µL of matrix solution. Calibration was performed with a poly(ethylene glycol) methyl ether methacrylate M_w 1100 g mol^{-1} standard. Cloud point measurements were recorded on an Agilent Technologies Cary 60 UV-Vis spectrometer at a wavelength of 500 nm using a cuvette with a 1 cm path length. The solutions (5 mg mL^{-1}, pH 4) were heated and cooled (temperature range: 10-70 °C) at a rate of 1 °C min^{-1} while stirring at 1200 rpm. The cloud point was determined as the temperature were the transmittance decreased to 50 % in the third heating run. Acid-base titrations were performed on the macromonomers by dissolving them in water (9.5 mg mL^{-1}). To protonate the carboxylic acid groups 0.1 M HCl solution was added. Subsequently, titration was run against 0.1001 M aqueous NaOH solution. Molecular weights determined by ^{1}H NMR spectroscopy were used to calculate the amount of ω-carboxylic acid end groups. DSC spectra were recorded on a Mettler Toledo DSC1. Samples were measured from -50 to 150 °C at 20 °C min^{-1}. Glass transition temperatures were recorded on the second heating cycle. TGA spectra were recorded on a Mettler Toledo TGA/DSC1. Samples were measured from 25 to 600 °C at 10 °C min^{-1}.

General procedure for the synthesis of macromonomers by spontaneous zwitterionic copolymerisation of Ox with AA

In a dried Schlenk flask equipped with a magnetic stirrer bar, MEHQ (1 mg, 8.06 x 10^{-6} mol) was dissolved in ACN, and Ox and AA were subsequently added under nitrogen (see Table S1 for exact amounts per reaction). The mixture was placed in an oil bath (70 °C) for 24 h. Subsequently, the polymer solution was cooled down to room temperature and precipitated in DEE. The precipitated polymer was isolated by centrifugation. The purification method was repeated two more times. To remove the DEE, the polymer was placed under vacuum to give the products as yellowish oils. The repeating units and molar mass of the oligomers were calculated by ^{1}H NMR, by comparing the ratio of the integrals of the vinyl end group and the ring-opened Ox and AA repeating unit signals. Summary of the characterisation data is provided in Table S2.

General procedure for the synthesis of comb polymers by redox-initiated RAFT

CTA, macromonomer and ascorbic acid were added to a sample vial equipped with a magnetic stirrer bar and dissolved in deionised H_2O and 1,4-dioxane. The mixture was deoxygenated for 15 min. In parallel, an aqueous stock solution of tBuOOH was deoxygenated. An aliquot of

the latter was added to the sample vial via a nitrogen-purged syringe. The sample vial was placed in a thermostated water bath set at 25 °C for 24 h. Subsequently, ^{1}H NMR and SEC samples were taken to determine the conversion of the polymerisation. The comb polymers were purified by dialysis (MWCO = 1000 g mol^{-1} for DP 10, MWCO = 3500 g mol^{-1} for DP 100) against deionised water for two days. Amounts and concentrations of the individual RRAFT polymerisations are provided in Table S3. Summary of the characterisation data is provided in Table S4.

General procedure for the functionalisation of DP 10 MeOx/AA comb polymers P1 and P2 with selected amines

Approximately 30 mg of comb polymer was dissolved in 400 µL DMF. 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 12.1 equiv.) and *N,N*-diisopropylethylamine (DIPEA, 24.2 equiv.*) were added and the mixture was stirred for 10 min to activate the carboxylic acids. Next, the amine (16.5 equiv.) was added and the reaction mixture was stirred for 24 h at room temperature. The product was purified by dialysis for 2 days against deionised water (MWCO = 1000 g mol^{-1}, for PEG-amine) or MeOH (MWCO = 500 g mol^{-1}, for benzyl amine and PME) and freeze dried from water to yield the product. Amounts and concentrations of the individual amidation reactions are provided in Table S5. Summary of the characterisation data is provided in Table S6.

*For phenylalanine methyl ester, which is a hydrochloride salt, 40 equiv. of DIPEA were used.

Table S1 Conditions used to prepare macromonomers **M1** – **M4**.

Code	Ox	Ox : AA	[Ox] [mol L^{-1}]	[AA] [mol L^{-1}]
M1	MeOx	1 : 1	9.92	9.92
M2	MeOx	1 : 2	4.94	9.92
M3	EtOx	1 : 1	9.91	9.92
M4	EtOx	1 : 2	6.60	13.2

Table S2 Characterisation data for macromonomers **M1** – **M4**.

Code	DP[a] (M_N/AA)	$M_{n,NMR}$[a] [g mol^{-1}]	$M_{n,SEC}$[b] [g mol^{-1}]	$M_{w,SEC}$[b] [g mol^{-1}]	Đ[b]
M1	3/3	543	1500	1900	1.27
M2	2.5/2.5	465	1300	1500	1.18
M3	3/3	585	1600	1900	1.22
M4	2/2	414	1300	1500	1.16

[a] Determined from ^{1}H NMR from peak area of vinyl groups and methylene group of Ox and AA repeating units. [b] Determined by SEC.

Table S3 Typical RRAFT conditions used to prepare comb polymers **P1** – **P4** from macromonomers **M1** – **M4** (H_2O/dioxane (v/v 75%/25%), 25 °C, and redox initiator pair: tBuOOH/AsAc). All reactions were performed at approximately 280 mg macromonomer scale.

Code	Macro-monomer	DP	$[M_0]$ [mol L^{-1}]	[CTA] [mol L^{-1}]	[AsAc] [mmol L^{-1}]	[tBuOOH] [mmol L^{-1}]
P1	M1	10	1.01	0.10	9.3	18.4
P2	M2	10	1.13	0.11	13.9	27.5
P3	M3	100	0.93	9.2×10^{-3}	1.2	2.3
P4	M4	100	0.86	8.6×10^{-3}	1.1	2.1

Table S4 Characterisation data for comb polymers **P1** – **P4**.

Code	DP[a] back-bone	$M_{n,NMR}$[b] [g mol^{-1}]	$M_{n,SEC}$[c] [g mol^{-1}]	$M_{w,SEC}$[c] [g mol^{-1}]	Đ[c]
P1	10	5670	9100	9800	1.07
P2	10	4890	8800	9900	1.12
P3	100	58700	36500	45300	1.24
P4	100	41600	24900	29600	1.19

[a] Calculated from conversion (quantitative in each case). [b] Calculated by ^{1}H NMR from DP and molar mass of the macromonomer. [c] Determined by SEC.

Table S5 Conditions used to functionalise comb polymers **P1** and **P2** with selected amines

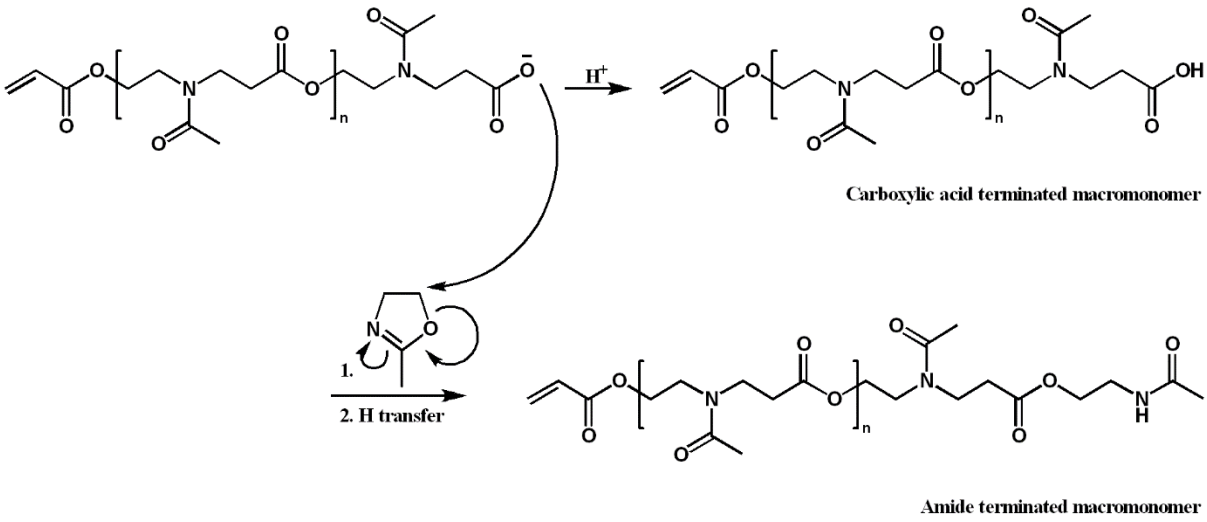
Code[a]	Comb polymer [mg]	HATU [mg]	DIPEA [µl]	Amine
P1a	29.4	24.6	22	10 µL
P1b	31.3	30.1	26	11 µL
P1c	20.1	18.4	15	47.8 mg
P2a	31.5	29.6	26	76.1 mg
P2b	32.6	26.4	37	21.3 mg
P2c	32.1	32.9	43	27.8 mg

[a] The last letter indicates the amine used to modify the comb polymer: benzyl amine (a), α-methoxy-ω-aminopoly(ethylene glycol) (b) or phenylalanine methyl ester (c).

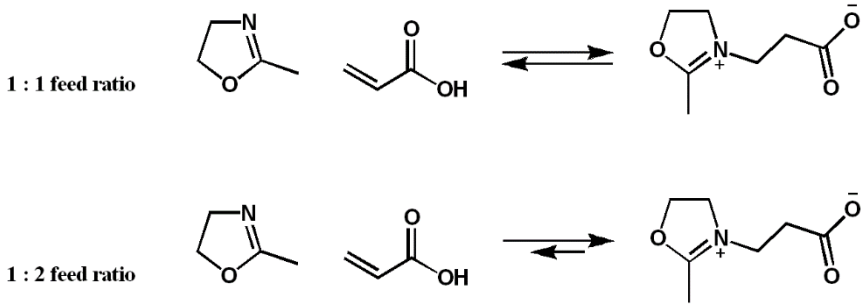
Table S6 Characterisation data for the functionalised comb polymers **P1** and **P2**.

Code[a]	Functionalisation (%)[b]	$M_{n,SEC}$[c] [g mol^{-1}]	$M_{w,SEC}$[c] [g mol^{-1}]	Đ[c]
P1a	54	8200	9300	1.14
P1b	45	12600	14600	1.16
P1c	51	9100	10100	1.10
P2a	quant.	9200	11300	1.22
P2b	80	17200	19900	1.16
P2c	95	9900	10900	1.09

[a] The last letter indicates the amine used to modify the comb polymer: benzyl amine (a), α-methoxy-ω-aminopoly(ethylene glycol) (b) or phenylalanine methyl ester (c). [b] Calculated from ^{1}H NMR, theoretical maximum based on DP 10 comb polymers and one RRAFT CTA carboxylic acid end group. [c] Determined by SEC.



Scheme S1 Mechanism for the introduction of a ω-carboxylic acid and group or a ω-amide end group in the spontaneous zwitterionic copolymerisation.



Scheme S2 Relative equilibria during the reversible formation of the initial zwitterion between MeOx (or EtOx) and AA for different feed ratios.

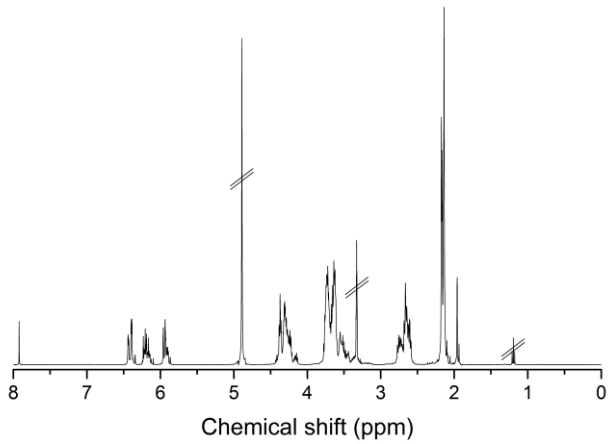


Fig. S1 ^{1}H NMR (400 MHz, MeOD) of **M2** (oligo(MeOx-*alt*-AA)$_{2.5}$A).

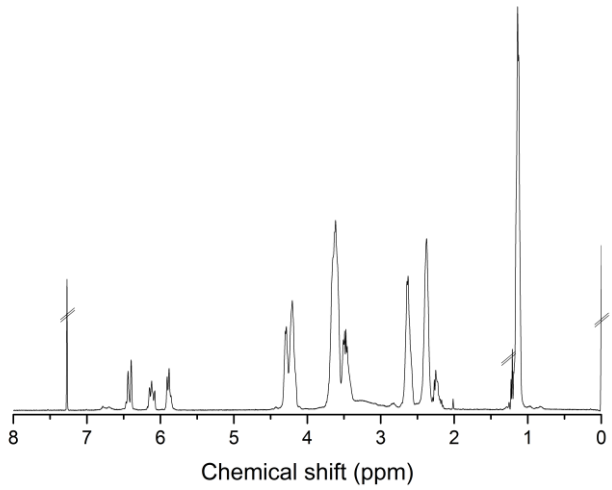


Fig. S2 ^{1}H NMR (400 MHz, $CDCl_3$) of **M3** (oligo(EtOx-*alt*-AA)$_3$A).

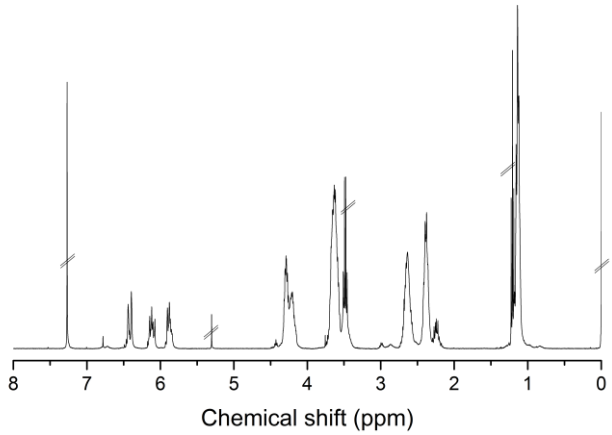


Fig. S3 ^{1}H NMR (400 MHz, $CDCl_3$) of **M4** (oligo(EtOx-*alt*-AA)$_2$A).

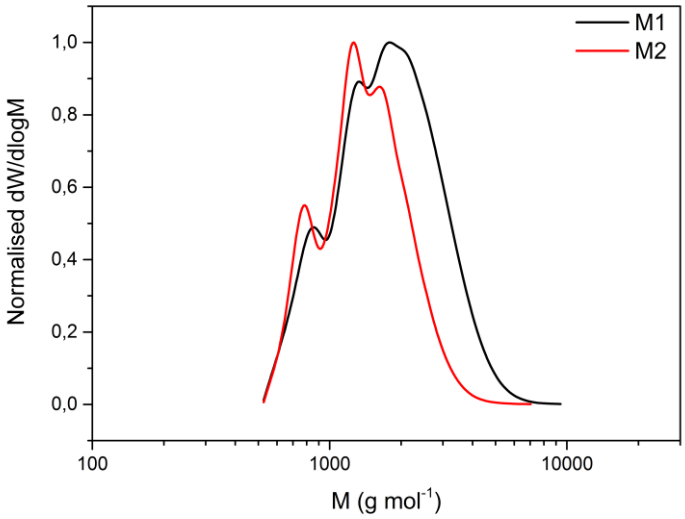


Fig. S4 SEC traces for macromonomers **M1** and **M2** (oligo(MeOx-*alt*-AA)$_n$A).

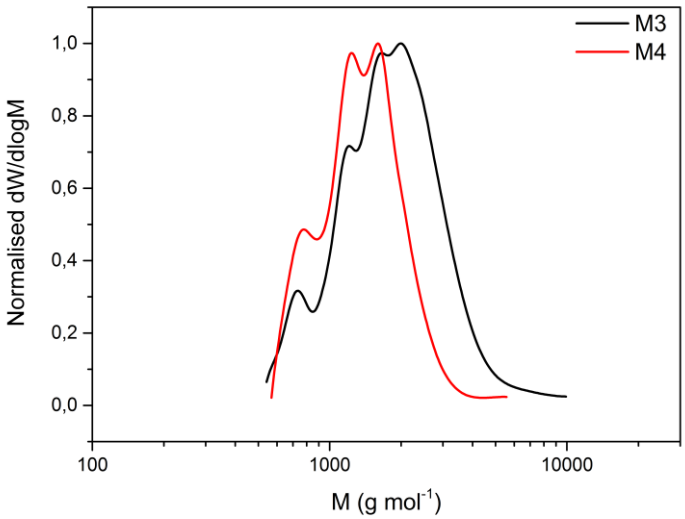


Fig. S5 SEC traces for macromonomers **M3** and **M4** (oligo(EtOx-*alt*-AA)$_n$A).

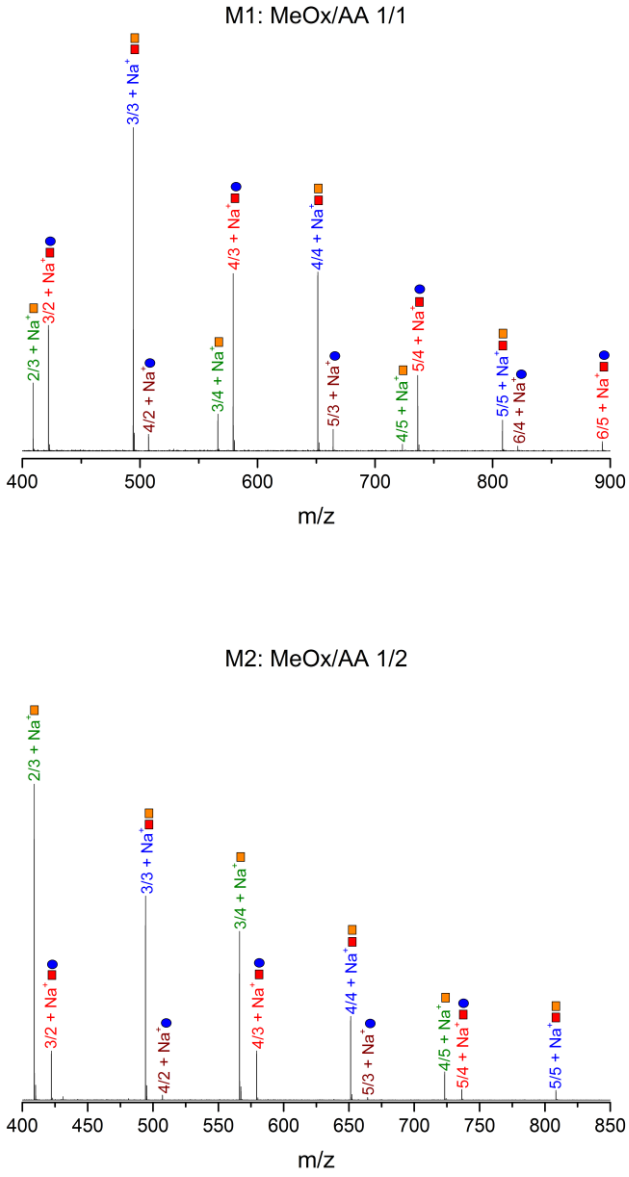


Fig. S6 MALDI-ToF spectra of oligo(MeOx-*alt*-AA)$_n$A macromonomers **M1** (top) and **M2** (bottom). Individual symbols represent different distributions. Rectangular symbols assign distributions with alternating addition of MeOx (85.10 g mol^{-1}) and AA (72.06 g mol^{-1}). Circular symbols demonstrate distributions which deviate from the ideal alternating composition with a higher number of MeOx units incorporated. Distributions with equal numbers suggest the presence of an ω-amido end group and (n/n+1) distributions an ω-carboxylic acid end group.

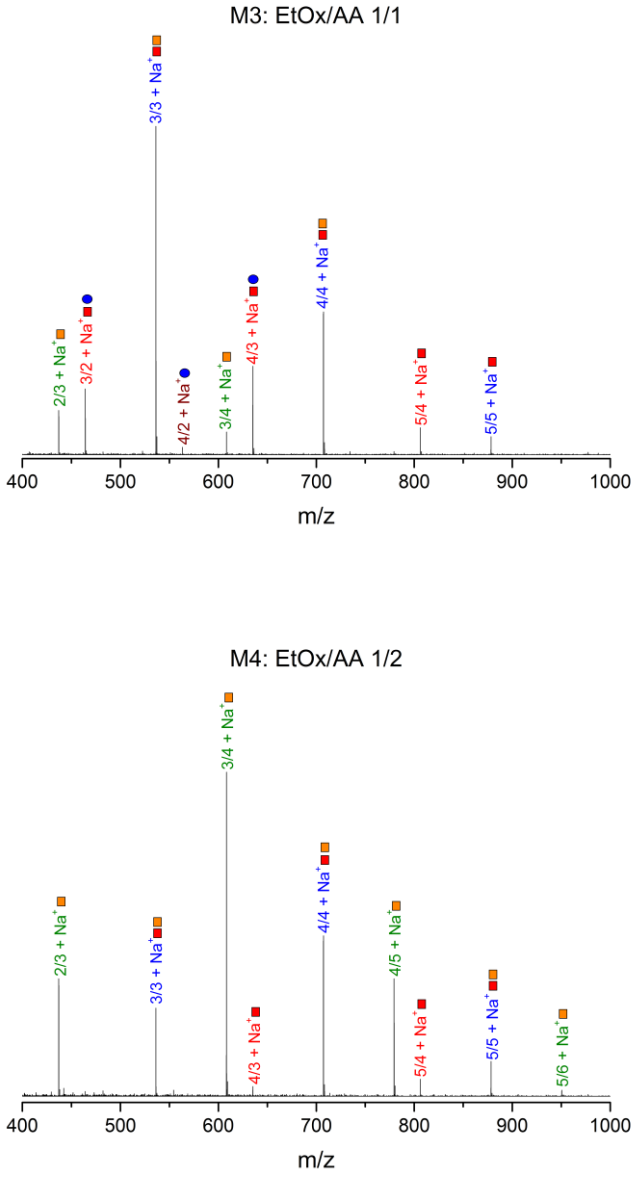


Fig. S7 MALDI-ToF spectra of oligo(EtOx-*alt*-AA)$_n$A macromonomers **M3** (top) and **M4** (bottom). Individual symbols represent different distributions. Rectangular symbols assign distributions with alternating addition of EtOx (99.13 g mol^{-1}) and AA (72.06 g mol^{-1}). Circular symbols demonstrate distributions which deviate from the ideal alternating composition with a higher number of EtOx units incorporated. Distributions with equal numbers suggest the presence of an ω-amido end group and (n/n+1) distributions an ω-carboxylic acid end group.

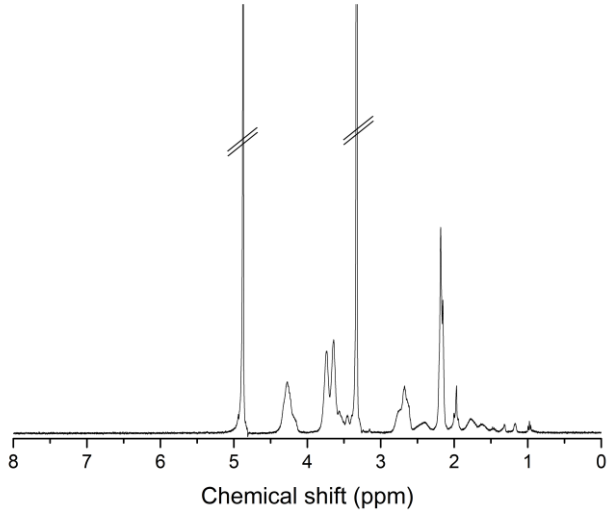


Fig. S8 ^{1}H NMR (400 MHz, MeOD) of **P2** (poly(oligo(MeOx-*alt*-AA)$_{2.5}$A)$_{10}$).

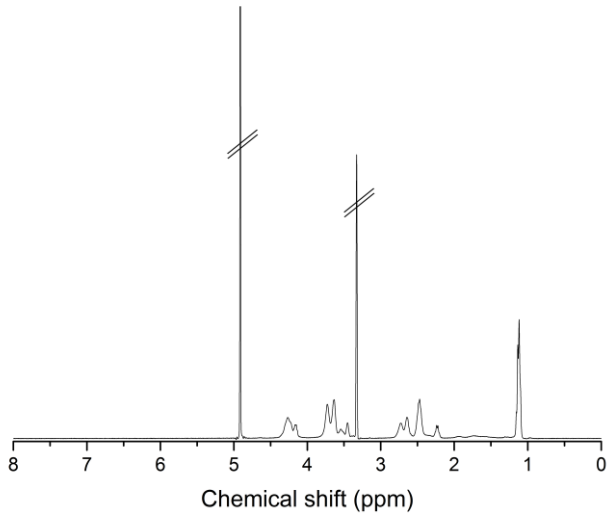


Fig. S9 ^{1}H NMR (400 MHz, MeOD) of **P3** (poly(oligo(EtOx-*alt*-AA)$_{3}$A)$_{100}$).

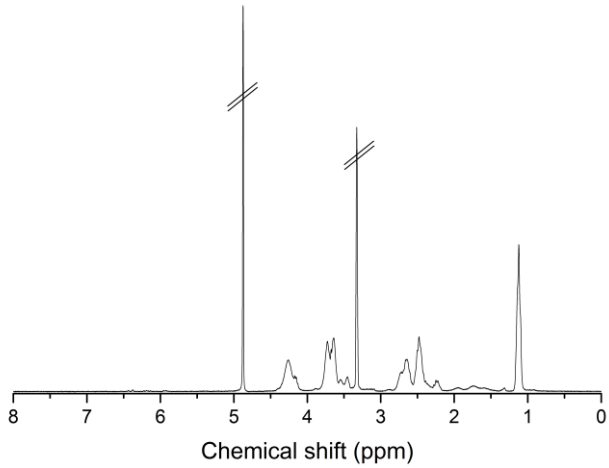


Fig. S10 ^{1}H NMR (400 MHz, MeOD) of **P4** (poly(oligo(EtOx-*alt*-AA)$_2$A)$_{100}$).

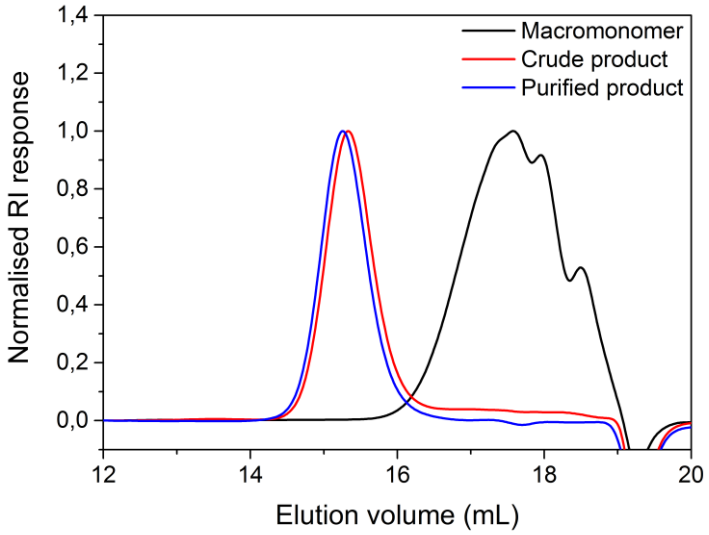


Fig. S11 SEC traces for macromonomer **M1** (oligo(MeOx-*alt*-AA)$_n$A) and comb polymer **P1** (p(oligo(MeOx-*alt*-AA)$_n$A$_{10}$) crude and dialysed.

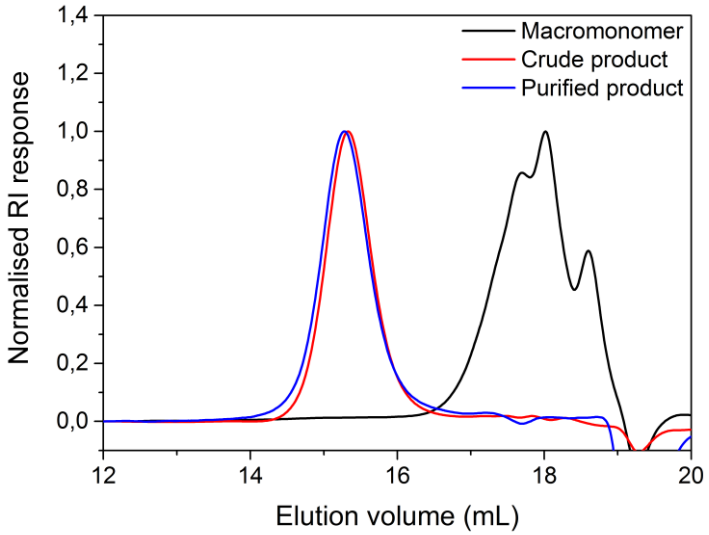


Fig. S12 SEC trace for macromonomer **M2** (oligo(MeOx-*alt*-AA)$_n$A) and comb polymer **P2** (p(oligo(MeOx-*alt*-AA)$_n$A$_{10}$) crude and dialysed.

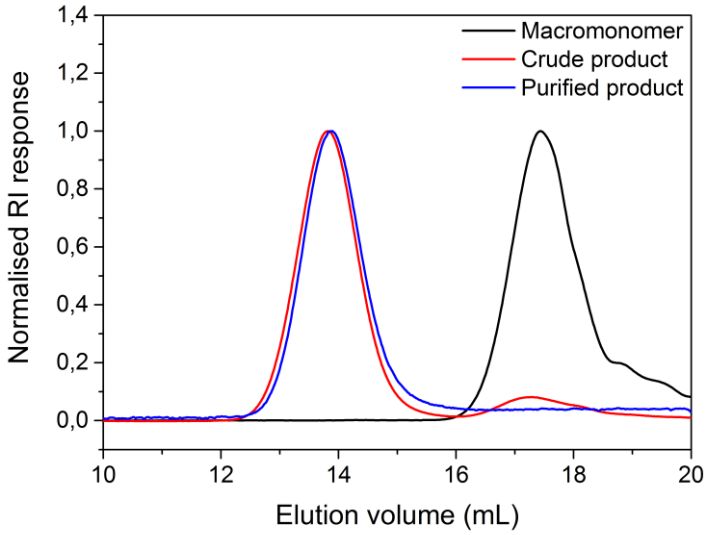


Fig. S13 SEC trace for macromonomer **M3** (oligo(EtOx-*alt*-AA)$_n$A) and comb polymer **P3** (p(oligo(EtOx-*alt*-AA)$_n$A$_{100}$) crude and dialysed.

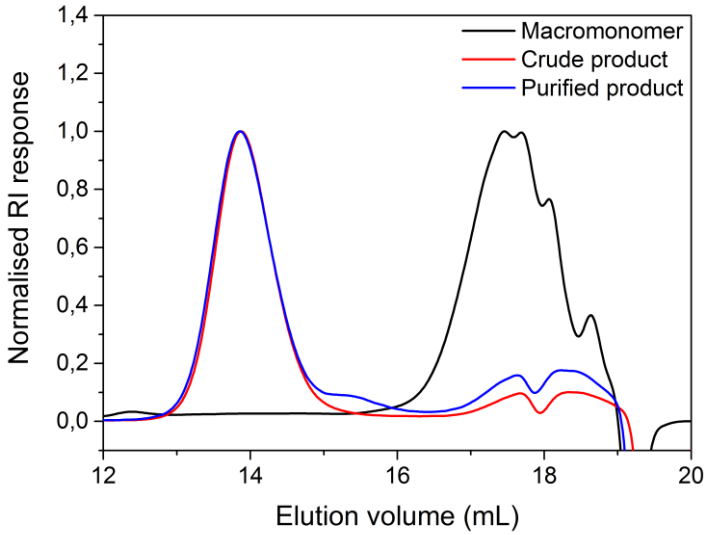


Fig. S14 SEC traces for macromonomer **M4** (oligo(EtOx-*alt*-AA)$_n$A) and comb polymer **P4** (p(oligo(EtOx-*alt*-AA)$_n$A$_{100}$) crude and dialysed.

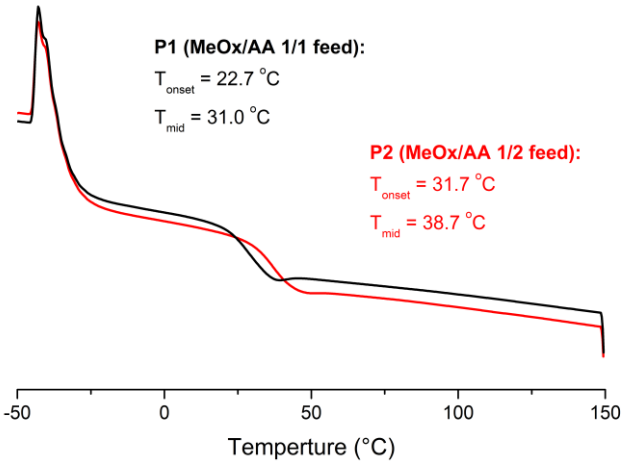


Fig. S15 DSC analysis of DP 10 comb polymers **P1** and **P2** synthesised from oligo(MeOx-*alt*-AA)$_n$A macromonomers **M1** and **M2**, respectively.

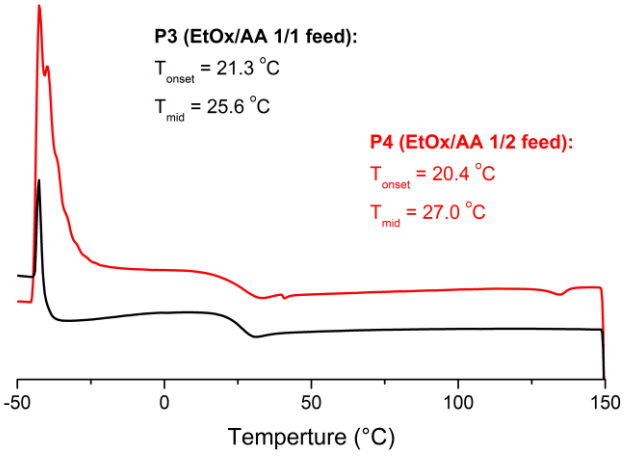


Fig. S16 DSC analysis of DP 100 comb polymers **P3** and **P4** synthesised from oligo(EtOx-*alt*-AA)$_n$A macromonomers **M3** and **M4**, respectively.

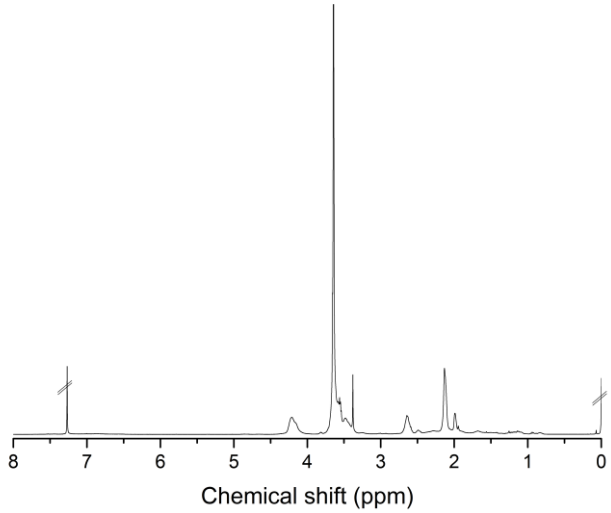


Fig. S17 ^{1}H NMR (400 MHz, $CDCl_3$) of **P1b**: **P1** (poly(oligo(MeOx-*alt*-AA)$_3$A)$_{10}$ functionalised with PEG-amine.

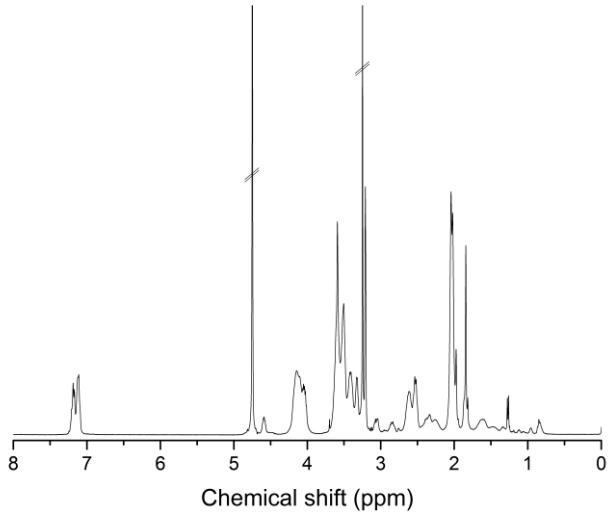


Fig. S18 ^{1}H NMR (400 MHz, MeOD) of **P1c**: **P1** (poly(oligo(MeOx-*alt*-AA)$_3$A)$_{10}$) functionalised with phenylalanine methyl ester.

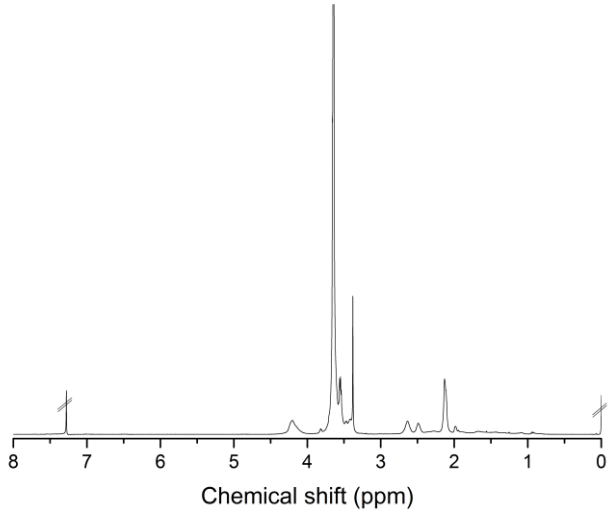


Fig. S19 ^{1}H NMR (400 MHz, $CDCl_3$) of **P2b**: **P2** (poly(oligo(MeOx-*alt*-AA)$_{2.5}$A)$_{10}$) functionalised with PEG-amine.

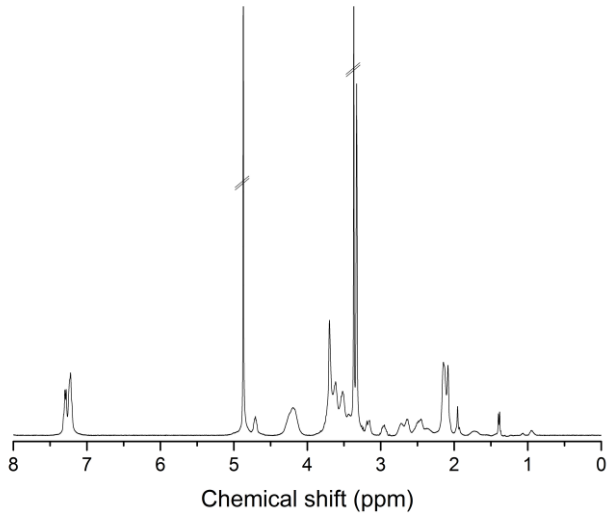


Fig. S20 ^{1}H NMR (400 MHz, MeOD) of **P2c**: **P2** (poly(oligo(MeOx-*alt*-AA)$_{2.5}$A)$_{10}$) functionalised with phenylalanine methyl ester.

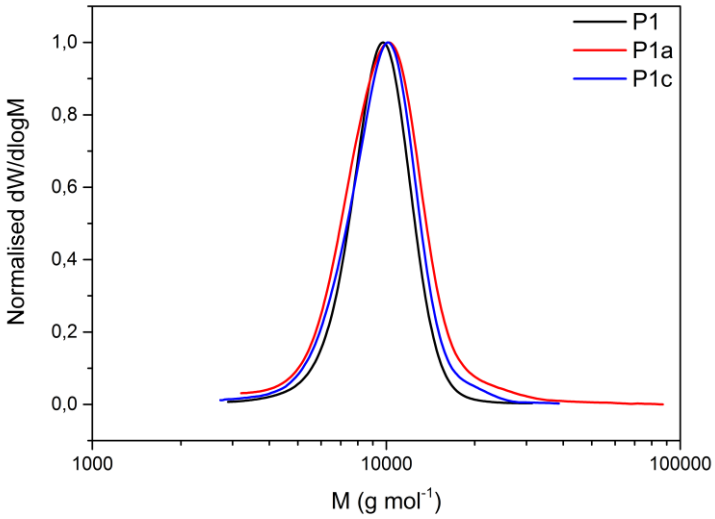


Fig. S21 SEC traces for comb polymer **P1** (poly(oligo(MeOx-*alt*-AA)$_3$)A$_{10}$) before and after functionalisation with benzylamine (**P1a**) and phenylalanine methyl ester (**P1c**).

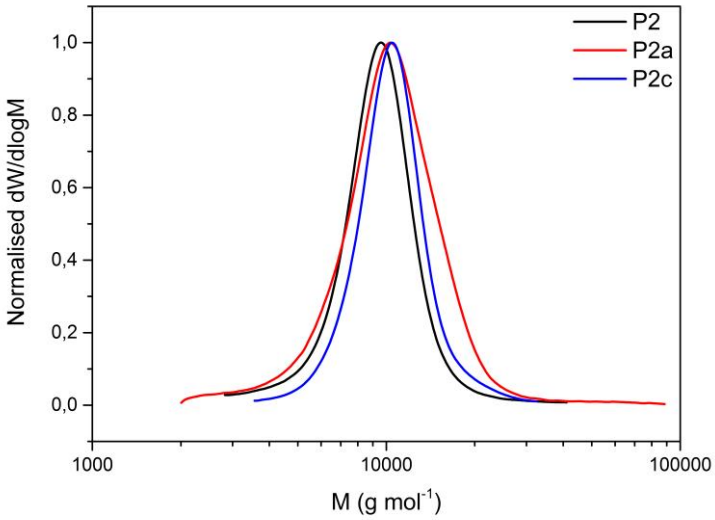


Fig. S22 SEC traces for comb polymer **P2** (poly(oligo(MeOx-*alt*-AA)$_{2.5}$A)$_{10}$) before and after functionalisation with benzylamine (**P2a**) and phenylalanine methyl ester (**P2c**).

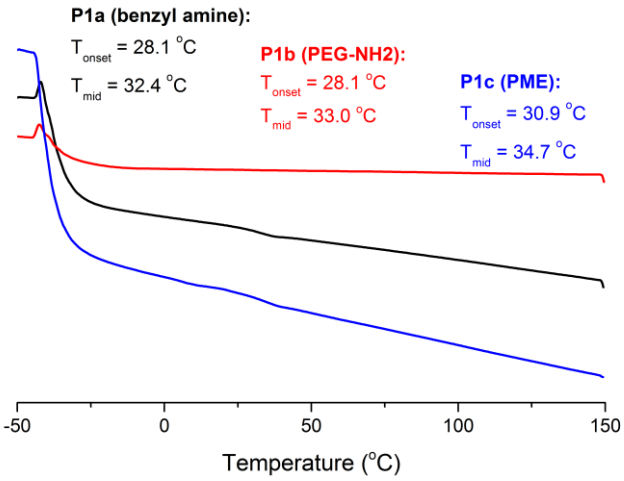


Fig. S23 DSC analysis of comb polymer **P1** modified with benzylamine (**P1a**), PEG-amine (**P1b**) and phenylalanine methyl ester (**P1c**).

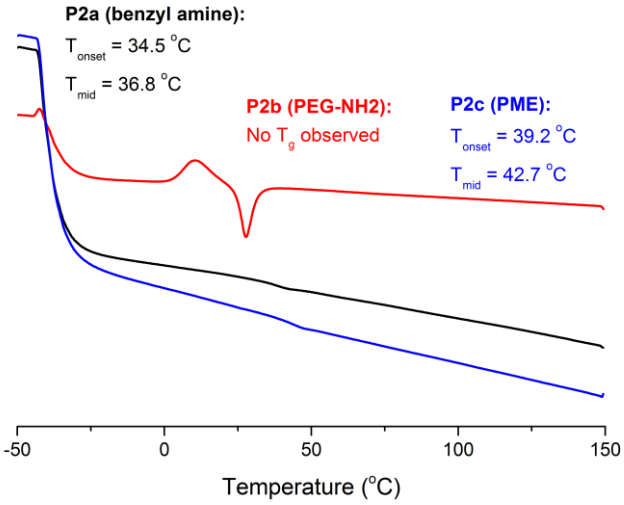


Fig. S24 DSC analysis of comb polymer **P2** modified with benzylamine (**P2a**), PEG-amine (**P2b**) and phenylalanine methyl ester (**P2c**).

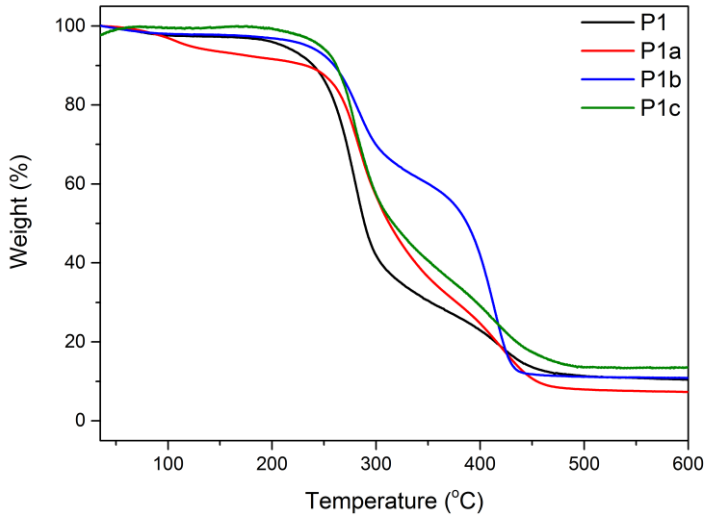


Fig. S25 TGA analysis of comb polymer **P1** before and after modification with benzylamine (**P1a**), PEG-amine (**P1b**) and phenylalanine methyl ester (**P1c**).

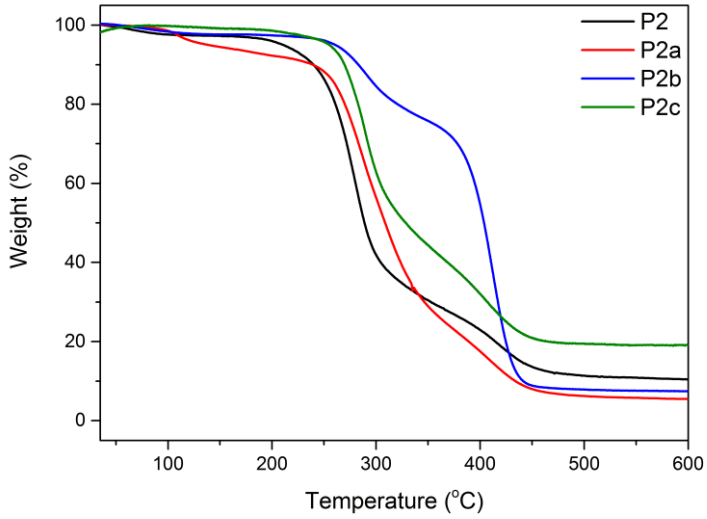


Fig. S26 TGA analysis of comb polymer **P2** before and after modification with benzylamine (**P2a**), PEG-amine (**P2b**) and phenylalanine methyl ester (**P2c**).

References

1 C. J. Ferguson, R. J. Hughes, D. Nguyen, B. T. T. Pham, R. G. Gilbert, A. K. Serelis, C. H. Such and B. S. Hawkett, *Macromolecules*, 2005, **38**, 2191–2204.