Supplementary Information

Four Component Passerini Polymerization of Bulky Monomers under High Shear Flow

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Materials

Unless otherwise noted, all reagents were used without further purification.

Solvents: Acetone (AR grade, AIM Scientific), chloroform, dichloromethane (DCM, analytical reagent, Fisher), acetonitrile (can, HPLC Grade, Fisher), diethyl ether (Et_2O, anhydrous, Ajax-Finechem), N, N-dimethylacetamide (DMAc, 00%, Fisher), dimethyl sulfoxide, deuterated chloroform ($CDCl_3$, 99.9%D, Cambridge Isotope Laboratories), tetrahydrofuran (THF, HPLC Grade, Fisher),

Reagents*:* *tert*-butyl isocyanide (98% Sigma), cyclohexyl isocyanide (98% Merck), 3-hydroxybenzaldehyde (99% Sigma), 4-hydroxybenzaldehyde (99% Sigma), succinic anhydride (99% Sigma), maleic anhydride (99% Sigma, glutaric anhydride (99% Sigma), itaconic acid (99% Sigma), bromoethanol (95% Sigma), di-*tert*-butyl dicarbonate (98% Sigma), potassium carbonate (anhydrous, Chem Supply Australia Pty. Ltd.), triethylamine (99%, Thermo-Fisher), poly(ethylene glycol) monomethyl ether (M_n = 2000 g·mol^{-1}, Thermo-Fisher)

Characterization

^{1}H Nuclear Magnetic Resonance (NMR) Spectroscopy: ^{1}H NMR spectra were recorded on a Bruker System 600 Ascend LH, equipped with a BBO-Probe (5 mm) with z-gradient (1 H: 600.13 MHz, 13C 150.90 MHz). Resonances are reported in parts per million (ppm) relative to tetramethylsilane (TMS).

The δ-scale was calibrated to the respective solvent signal of $CHCl_3$ DMSO-d_6 or acetonitrile-d_3 for ^1H spectra. To analyse the spectra, the software MESTRENOVA 11.0 was used. The resonances are quoted as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, s = sextet, h = septet, dd = doublet of doublets and m = multiplet.

Size Exclusion Chromatography (Tetrahydrofuran, SEC-THF): SEC measurements were conducted on a PSS SECurity2 system consisting of a PSS SECurity Degasser, PSS SECurity TCC6000 Column Oven (35 °C), PSS SDV Column Set (8x150 mm 5 µm Precolumn, 8x300 mm 5 µm Analytical Columns, 100000 Å, 1000 Å and 100 Å) and an Agilent 1260 Infinity Isocratic Pump, Agilent 1260 Infinity Standard Autosampler, Agilent 1260 Infinity Diode Array and Multiple Wavelength Detector (A: 254 nm, B: 360 nm), Agilent 1260 Infinity Refractive Index Detector (35 °C). HPLC grade THF, stabilized with BHT, is used as eluent at a flow rate of 1 $mL{\cdot}min^{-1}$. S-4 Narrow disperse linear poly(styrene) (M_n: 266 $g{\cdot}mol^{-1}$ to $2.52x10^6$ $g{\cdot}mol^{-1}$) and poly(methyl methacrylate) (M_n: 202 $g{\cdot}mol^{-1}$ to $2.2x10^6$ $g{\cdot}mol^{-1}$) standards (PSS ReadyCal) were used as calibrants. All samples were passed over 0.22 µm PTFE membrane filters. Molecular weight and dispersity analysis was performed in PSS WinGPC UniChrom software (version 8.2).

Size Exclusion Chromatography (Dimethylacetamide, SEC-DMAc): SEC measurements were conducted on a PSS SECurity2 system consisting of a PSS SECurity Degasser, PSS SECurity TCC6000 Column Oven (60 °C), PSS GRAM Column Set (8x150 mm 10 µm Precolumn, 8x300 mm 10 µm Analytical Columns, 1000 Å, 1000 Å and 30 Å) and an Agilent 1260 Infinity Isocratic Pump, Agilent 1260 Infinity Standard Autosampler, Agilent 1260 Infinity Diode Array and Multiple Wavelength Detector (A: 254 nm, B: 360 nm), Agilent 1260 Infinity Refractive Index Detector (35 °C). HPLC grade DMAc, 0.01 M LiBr, is used as eluent at a flow rate of 1 $mL{\cdot}\ min^{-1}$. Narrow disperse linear poly(styrene) (M_n: 266 $g{\cdot}mol^{-1}$ to $2.52x10^6$ $g{\cdot}mol^{-1}$) and poly(methyl methacrylate) (M_n: 202 $g{\cdot}mol^{-1}$ to $2.2x10^6$ $g{\cdot}mol^{-1}$) standards (PSS ReadyCal) were used as calibrants. All samples were passed over 0.22 µm PTFE membrane filters. Molecular weight and dispersity analysis was performed in PSS WinGPC UniChrom software (version 8.2).

Synthesis

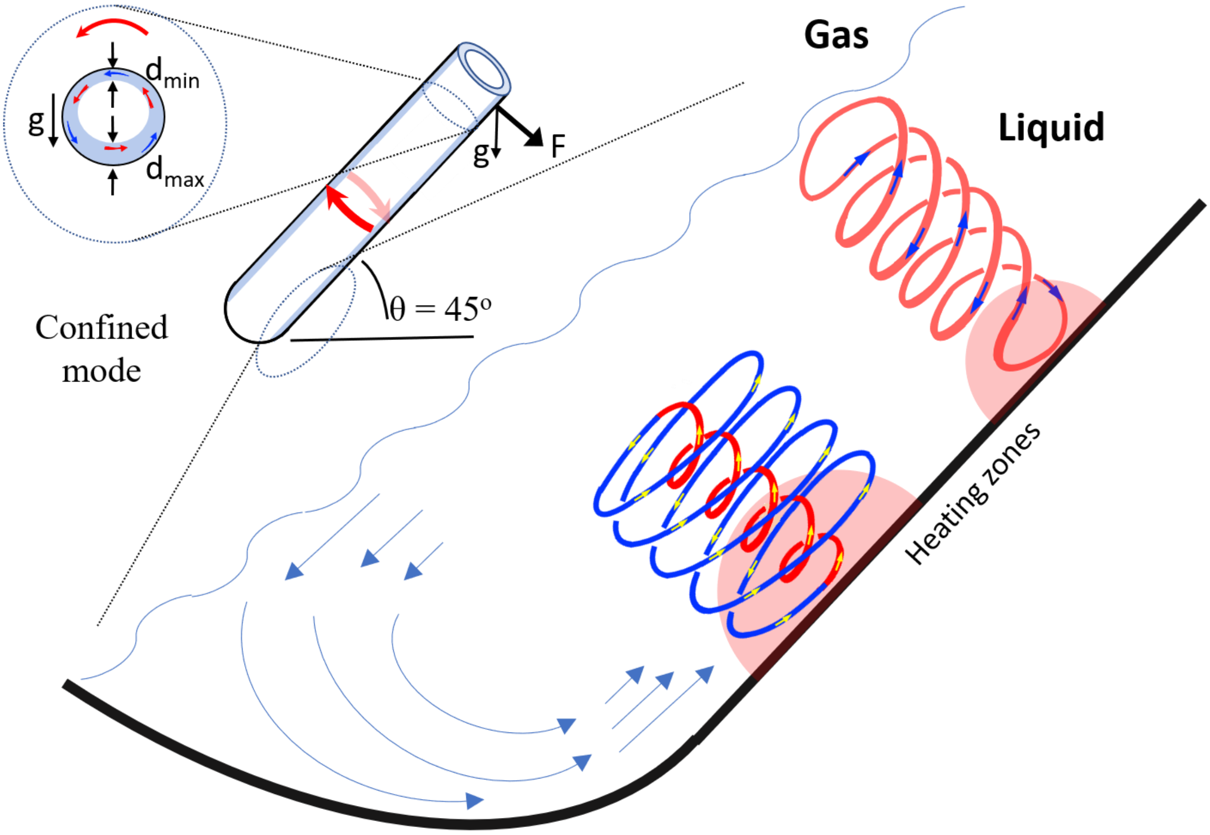
General Passerini polymerization procedure for control reactions

Representative procedure: To a small 1.2 mL vial 50 mg (0.4 mmol) of 3-hydroxybenzaldehyde, 43 mg of succinic anhydride (0.42 mmol), and 47 mg (0.42 mmol) of cyclohexylisocyanide were added. Subsequently, 0.2 mL of acetonitrile as solvent was added. The mixture was allowed to stand for 18 h at ambient conditions and was then precipitated into 0 ˚C diethyl ether to afford 33.8 mg of a white solid.

Note: When the exact same conditions were applied using tert-butyl isocyanide, there was no reaction in any attempt

General Passerini polymerization procedure using the Vortex Fluidic Device

Representative procedure: To a 20 mm diameter (17.5 mm internal diameter) hemispherical base quartz tube, 18.5 cm in length, 50 mg (0.4 mmol) of 3-hydroxybenzaldehyde, 43 mg of succinic anhydride (0.42 mmol), and 34.9 mg (0.42 mmol) of *tert*-butyl isocyanide were added. Subsequently, 0.2 mL of acetonitrile as solvent was added. The quartz tube was tightly capped with a rubber septum, and loaded into the VFD apparatus. The VFD was set at 45˚ and rotated at 7000 rpm for 2 h. After 2 h of rotation in the VFD the sample was allowed to stand for 2 additional h and was then precipitated into 0 ˚C diethyl ether to afford 76.8 mg of a white solid.



Scheme S1. Schematic diagram of the thin-film fluid dynamics in a hemispherical tube in confined mode. At 7000 rpms in a hemispherical tube both twisted eddies (due to Faraday waves, red vortex), as well as "spinning top" vortices (due to the Coriolis effect, blue vortex) are formed causing intense micro-mixing under localized high-shear and high-temperature conditions.[1]

Synthesis of itaconic anhydride

The procedure was adapted directly from the literature. [2] To a round bottom flask was added 1.0 g (7.7 mmol) of itaconic acid, 1.68 g (7.7 mmol), and 15 mg (0.15 mmol) $MgCl_2$ and 10 mL of THF. The reaction was heated to 40 ˚C and stirred open to atmosphere for 2.5 hours. Volatiles were evaporated then placed in a vacuum oven at 40 ˚C overnight. Itaconic anhydride was separated from $MgCl_2$ via sublimation yielding 0.72 g (83% yield) of pure itaconic anhydride. ^{1}H NMR ($CDCl_3$): 6.55 (m, 1H), 5.90 (m, 1H), 3.60 (m, 2H).

Synthesis of 4-(2-hydroxyethoxy)benzaldehyde

Procedure was modified from the literature.[3] A suspension of 1.70 g (12.3 mmol) of potassium carbonate, 0.5 g (4.1 mmol) of 4-hydroxybenzaldehyde, and 0.537 g (0.304 mL, 4.3 mmol) of bromoethanol was added to DMSO and heated at 100 ˚C for 5.5 hours. After filtration and evaporation, the crude product was redissolved in chloroform (5 mL) and washed twice with 1.0 M HCl (2 x 10 mL), twice with deionized water (2 x 10 mL), and finally once with saturated sodium chloride solution (10 mL). Organic layer was dried with $MgSO_4$, filtered and evaporated to yield 0.443 g (65% yield) of a yellow oil. Compound was used without further purification. ^{1}H NMR ($CDCl_3$): 9.79 (s, 1H), 7.75 (d, 2H), 6.95 (d, 2H), 4.10 (t, 2H), 3.94 (t, 2H).

Thiol-PEG synthesis

Monomethoxy-polyethylene glycol (M_n = 2000 g·mol^{-1}, 4.0 g, 2 mmol), 3-mercaptopropionic acid (1.7 g, 16 mmol), pTsOH (0.1 g, catalytic amount) were mixed with the cyclohexane (100 mL) in a round bottom flask fitted with a Dean-Stark condenser. The mixture was heated to reflux (90 o C) for 20 h. Cyclohexane was evaporated in vacuo, and the mixture was taken up in the CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL), and dried $MgSO_4$). The solution was concentrated to ca. 5 mL and precipitated by dropwise addition into ice cold diethyl ether (200 mL) to give product as a white powder (yield 4.27 g, 95%).

Thiol-Michael addition post-polymerization modification

To a round bottom flask was added 21 mg (M_n = 4000 g·mol^{-1}) of p(A-2-β), (0.063 mmol of olefin moiety), 0.126 g of PEG-SH (M_n = 2000 g·mol^{-1}, 0.063 mmol), and 0.05 mL of triethylamine dissolved in 0.5 mL of THF. The solution was refluxed for 18 hours then precipitated into 0 ˚C diethyl ether to afford 94.1 mg of an off-white solid.

Table S1. Summary of number average molecular weight of all polymer samples measured in the VFD

Sample	M_n [Da]	*Đ*
p(A-1-α)	2510	1.7
p(A-2-α)	2220	1.8
p(A-3-α)	3900	3.6
p(A-4-α)	1620	1.5
p(B-1-α)	1030	1.5
p(B-2-α)	915	1.5
p(B-3-α)	1830	1.9
p(B-4-α)	1020	1.6
p(A-1-β)	1920	1.9
p(A-2-β)	1160	1.6
p(A-3-β)	2150	2.2
p(A-4-β)	880	1.6
p(B-1-β)	1210	2.7
p(B-2-β)	1240	1.6
p(B-3-β)	1360	2.2
p(B-4-β)	800	1.3

Supporting Figures

Size-Exclusion Chromatographs

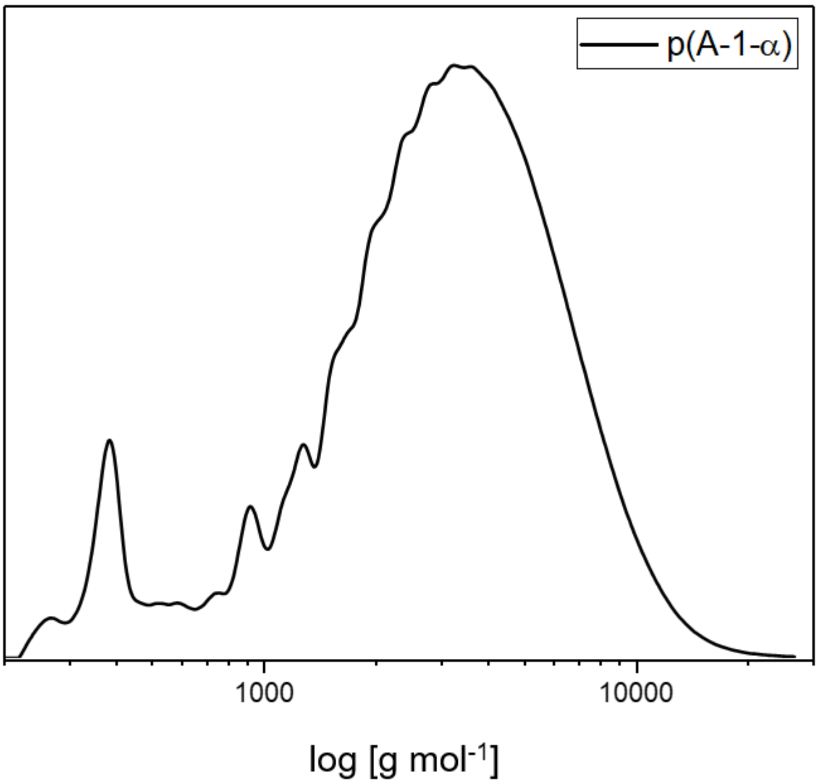


Figure S1. Molar mass distribution (RI) of sample p(A-1-α) measured in THF.

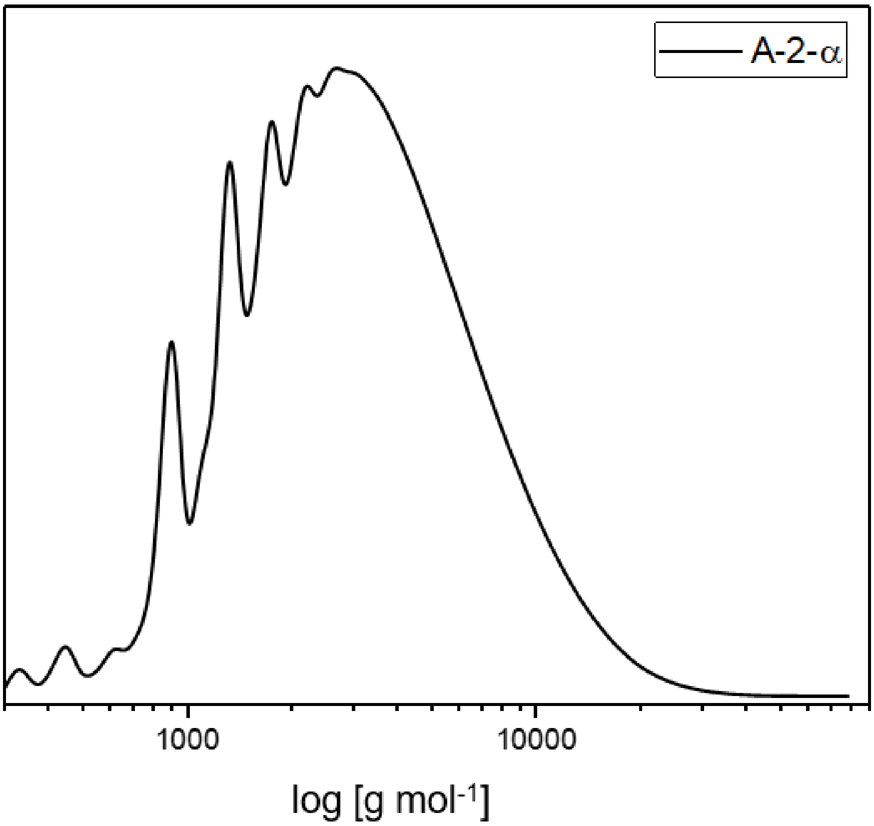


Figure S2. Molar mass distribution (RI) of sample p(A-2-α) measured in THF.

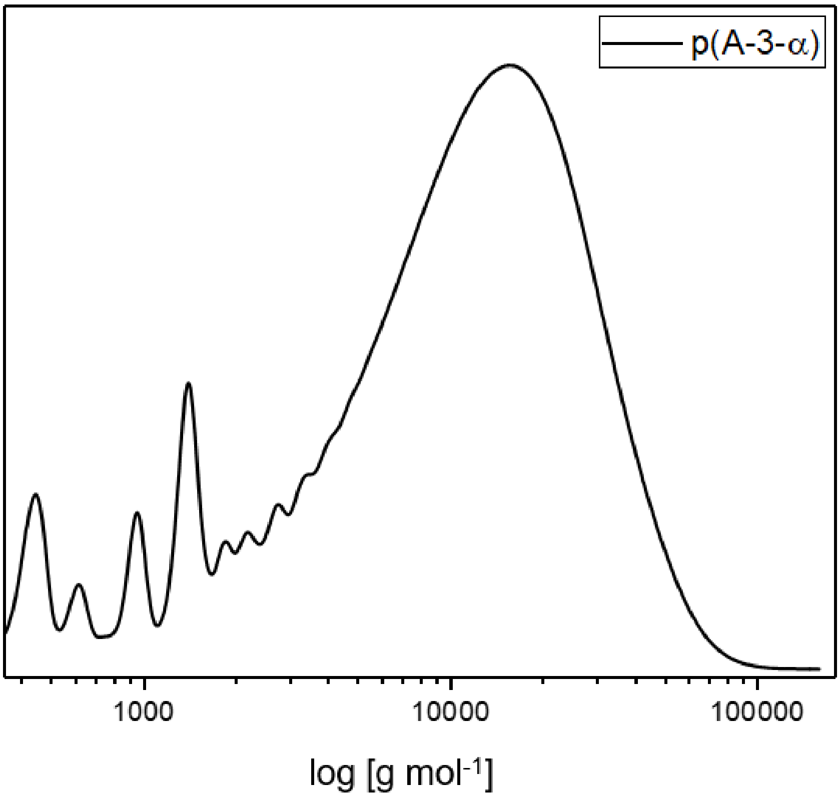


Figure S3. Molar mass distribution (RI) of sample p(A-3-α) measured in THF.

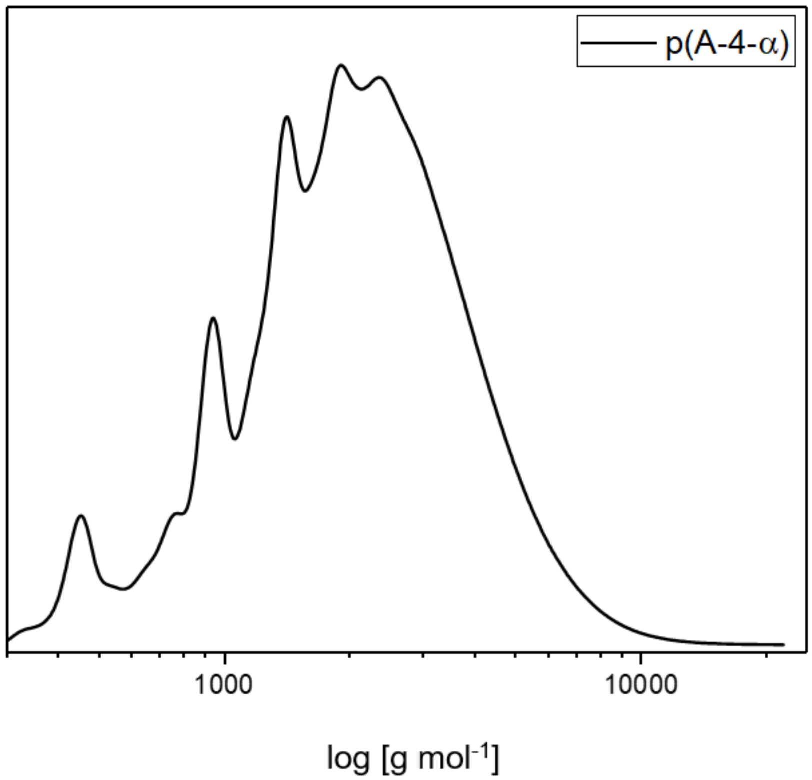


Figure S4. Molar mass distribution (RI) of sample p(A-4-α) measured in THF.

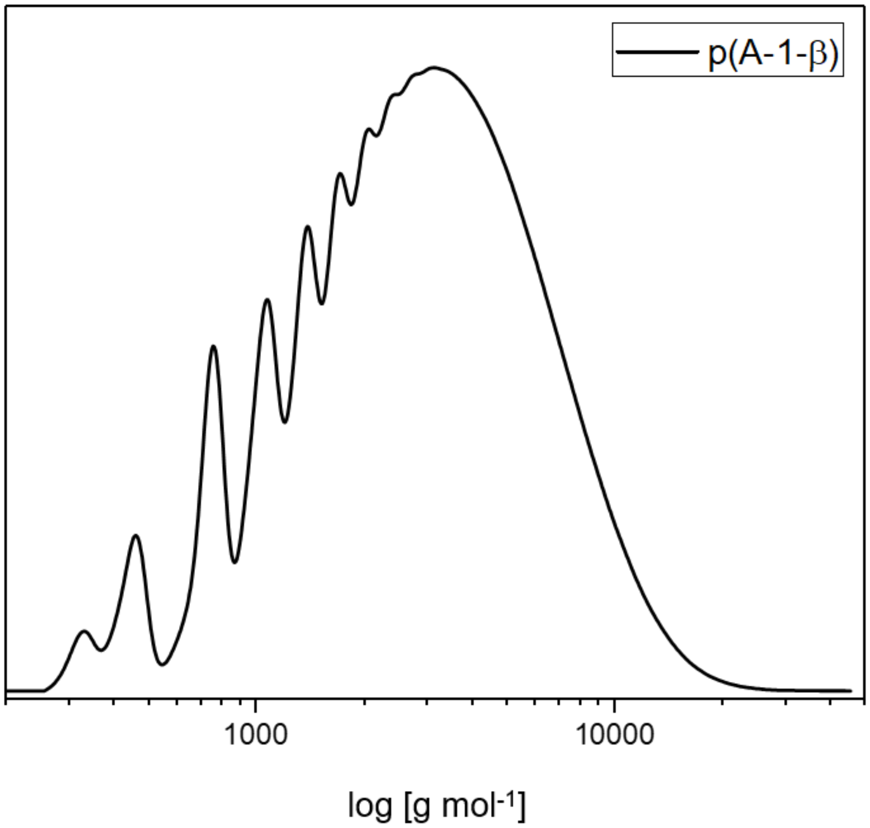


Figure S5. Molar mass distribution (RI) of sample p(A-1-β) measured in THF.

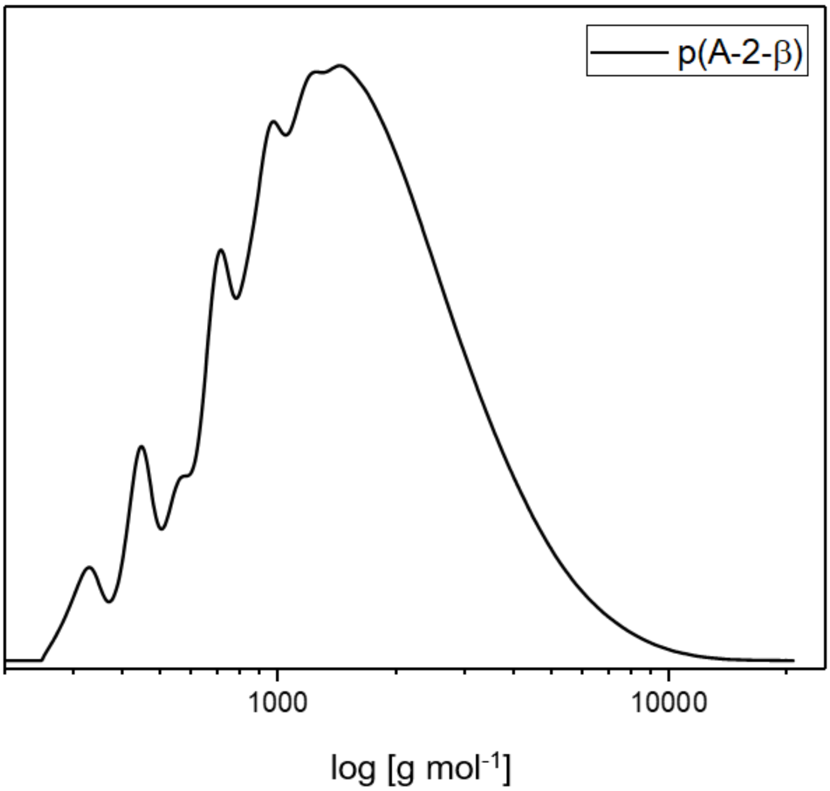


Figure S6. Molar mass distribution (RI) of sample p(A-2-β) measured in THF.

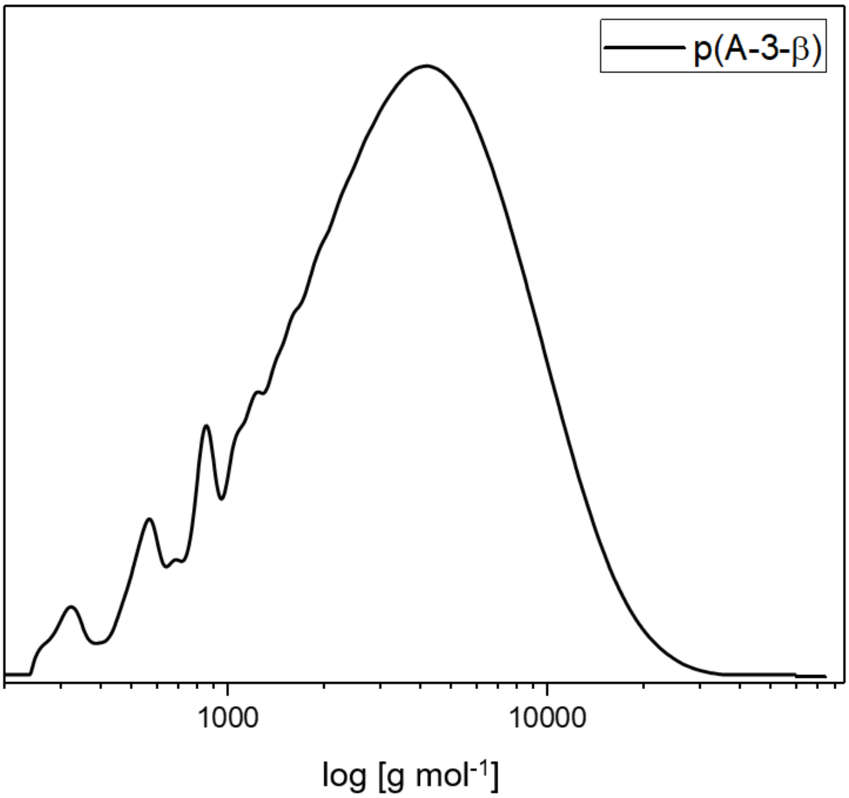


Figure S7. Molar mass distribution (RI) of sample p(A-3-β) measured in THF.

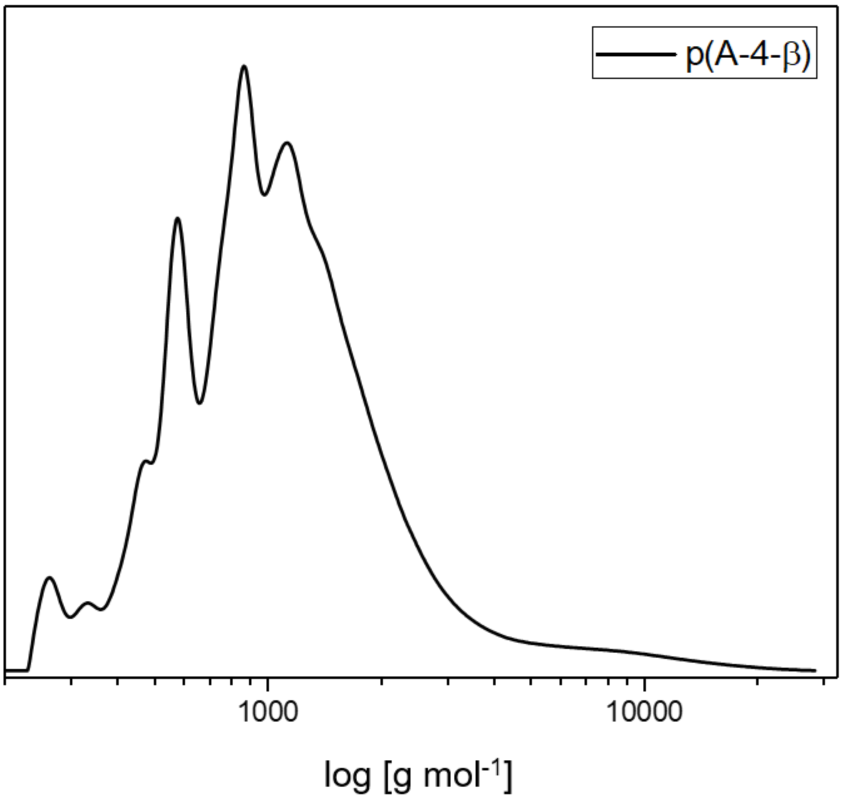


Figure S8. Molar mass distribution (RI) of sample p(A-4-β) measured in THF.

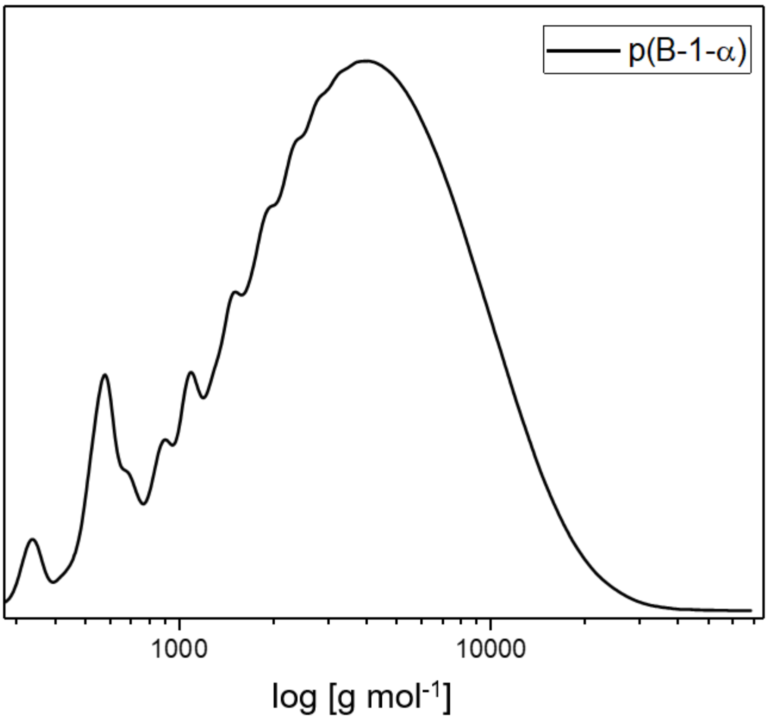


Figure S9. Molar mass distribution (RI) of sample p(B-1-α) measured in THF.

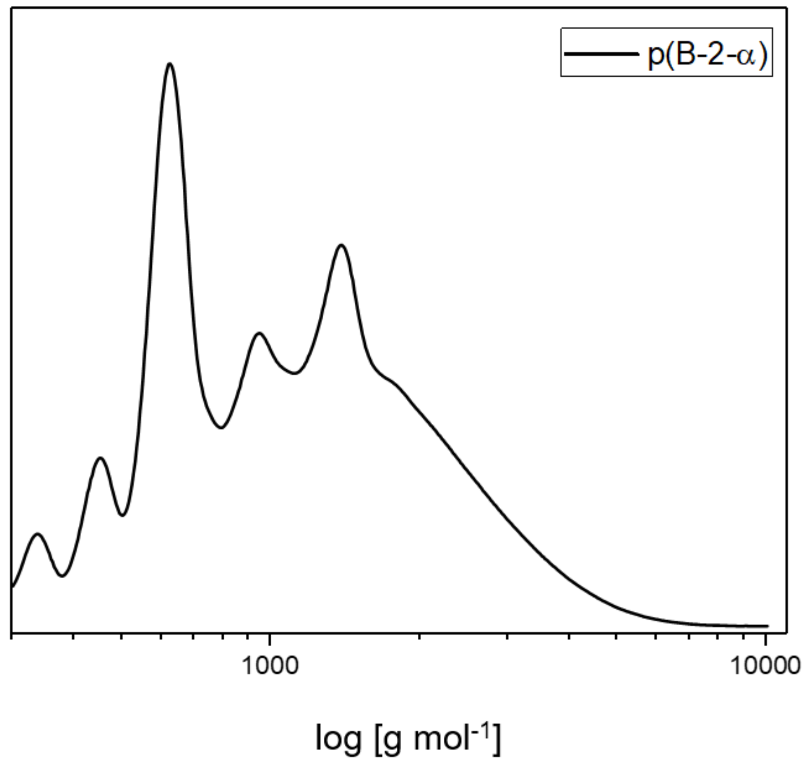


Figure S10. Molar mass distribution (RI) of sample p(B-2-α) measured in THF.

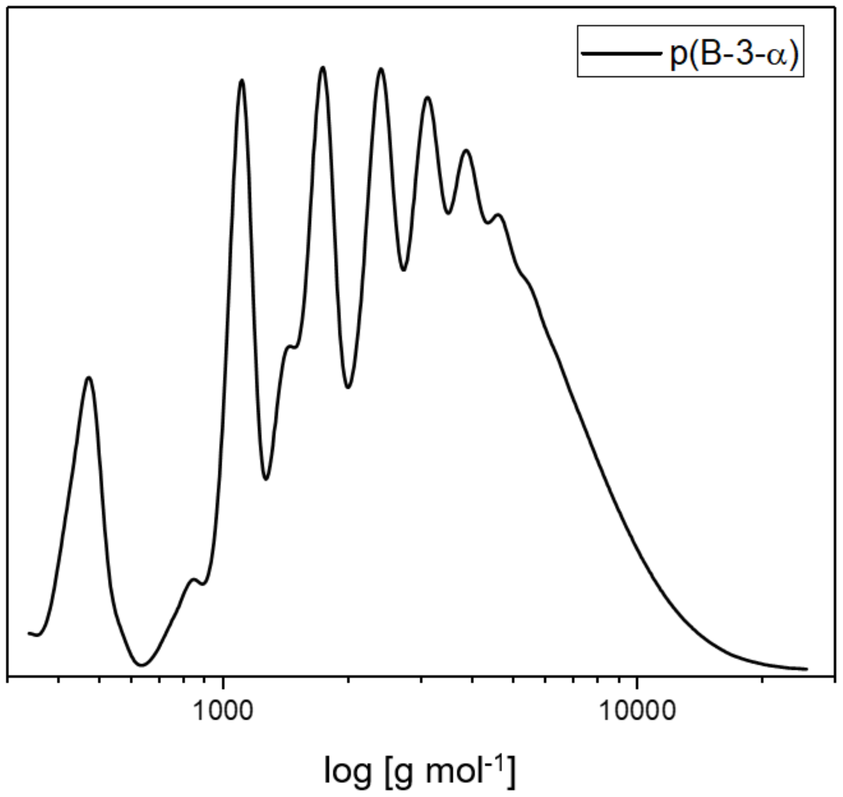


Figure S11. Molar mass distribution (RI) of sample p(B-3-α) measured in THF.

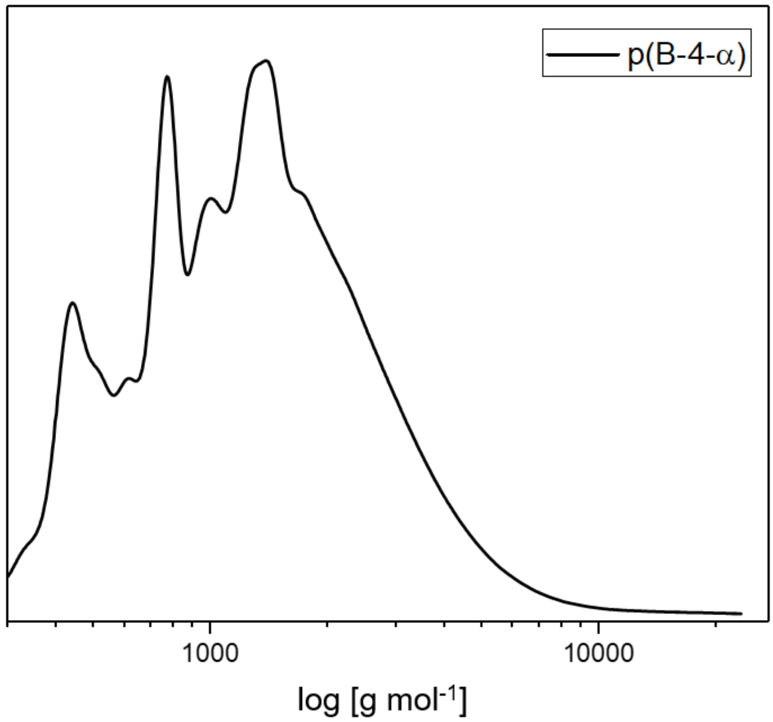


Figure S12. Molar mass distribution (RI) of sample p(B-4-α) measured in THF.

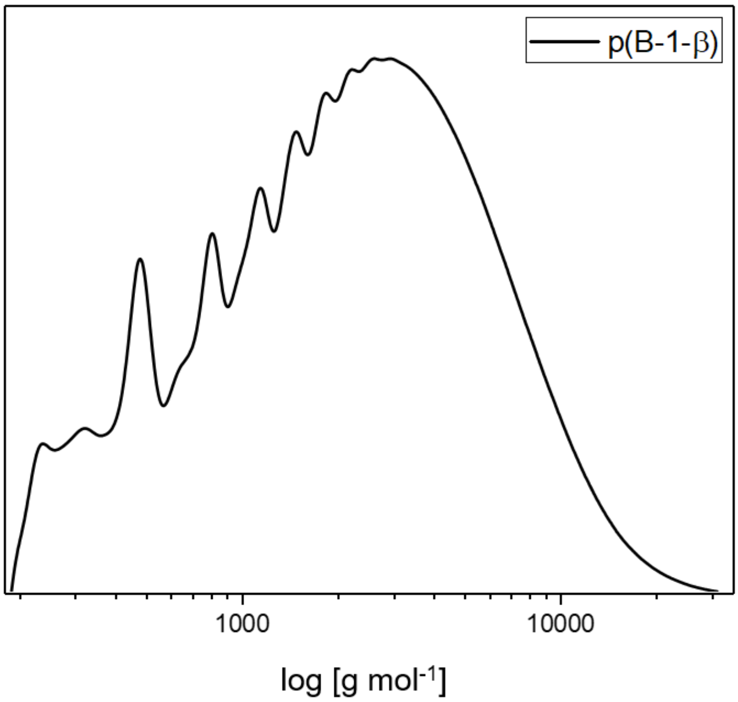


Figure S13. Molar mass distribution (RI) of sample p(B-1-β) measured in THF.

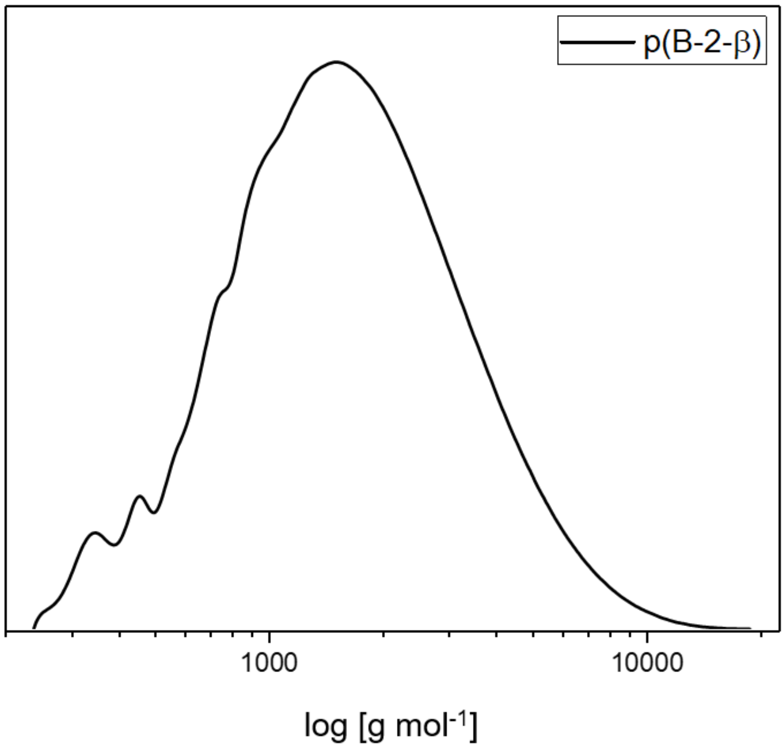


Figure S14. Molar mass distribution (RI) of sample p(B-2-β) measured in THF.

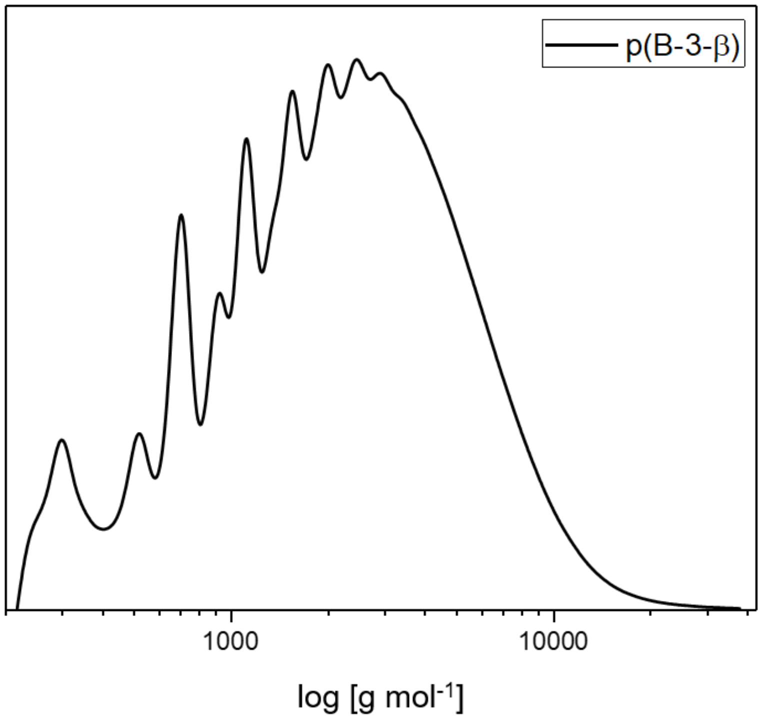


Figure S15. Molar mass distribution (RI) of sample p(B-3-β) measured in THF.

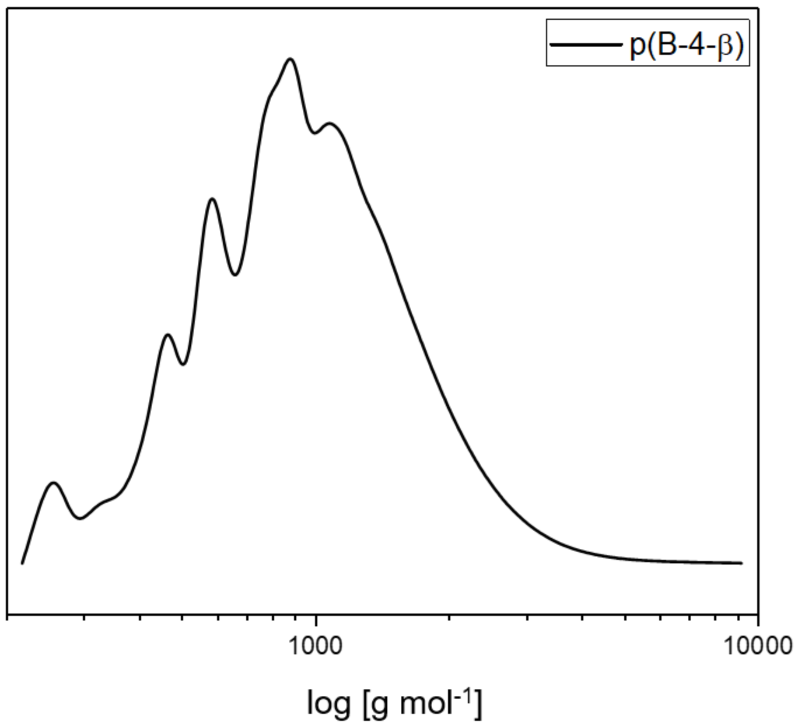


Figure S16. Molar mass distribution (RI) of sample p(B-4-β) measured in THF.

^{1}H NMR Spectra

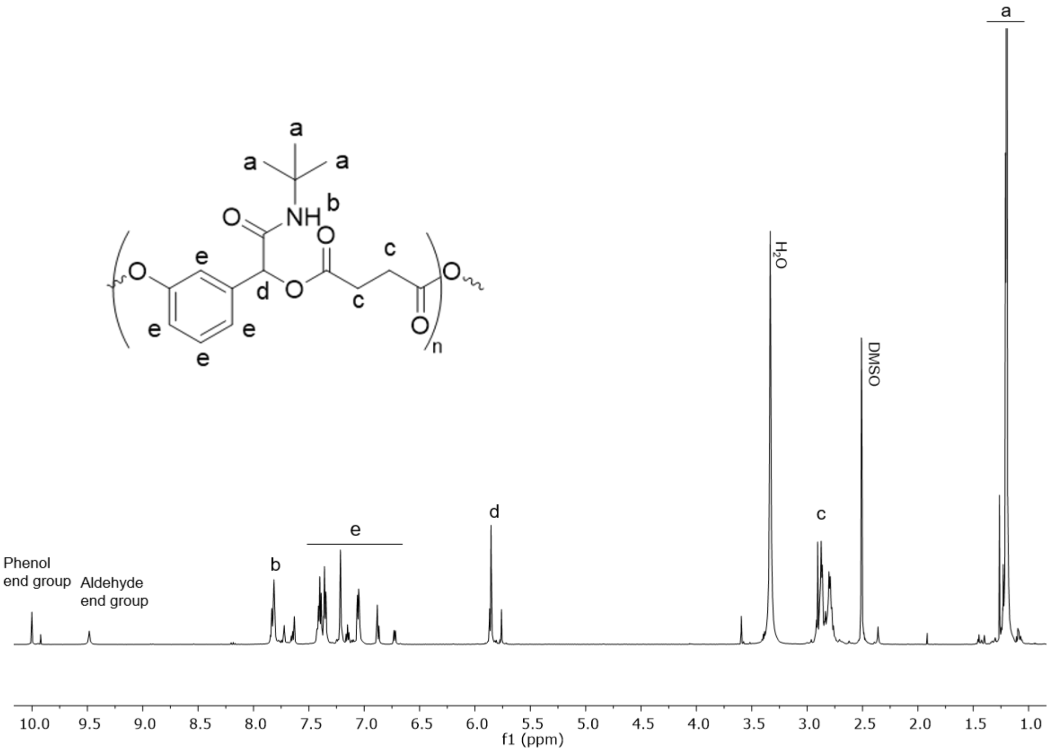


Figure S17. ^{1}H NMR spectrum of p(A-1-α) (600 MHz, DMSO-*d*$_6$).

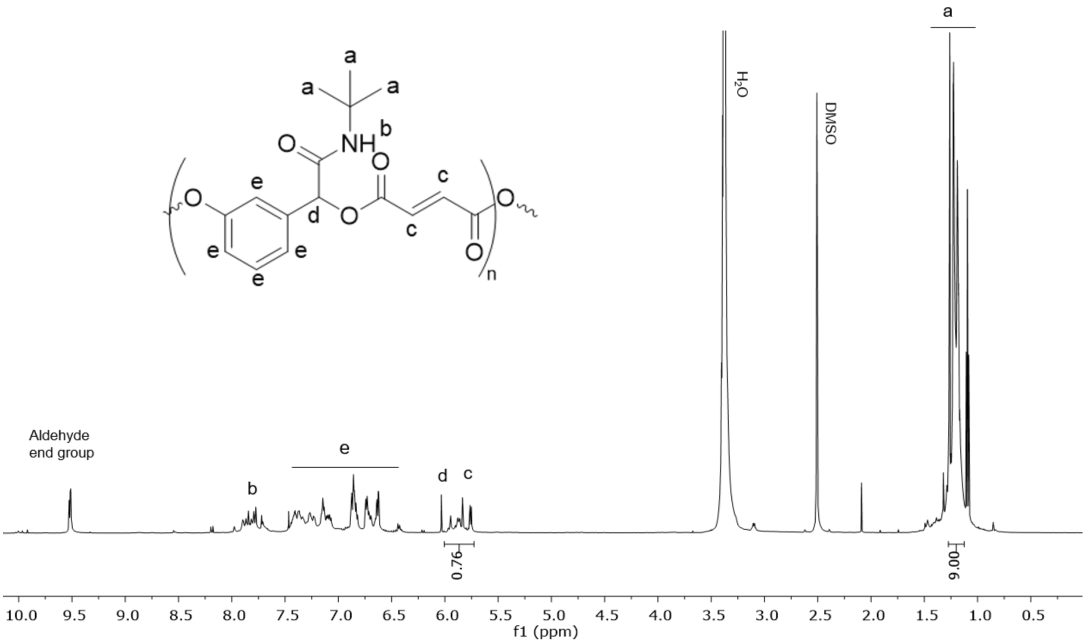


Figure S18. ^{1}H NMR spectrum of p(A-2-α) (600 MHz, DMSO-*d*$_6$).

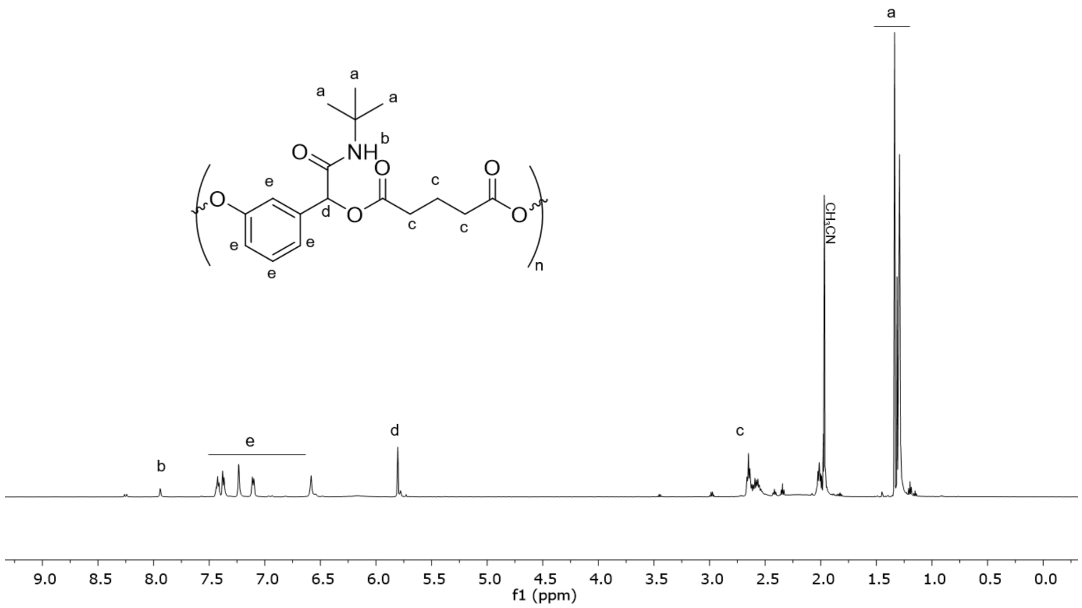


Figure S19. ^{1}H NMR spectrum of p(A-3-α) (600 MHz, CD_3CN).

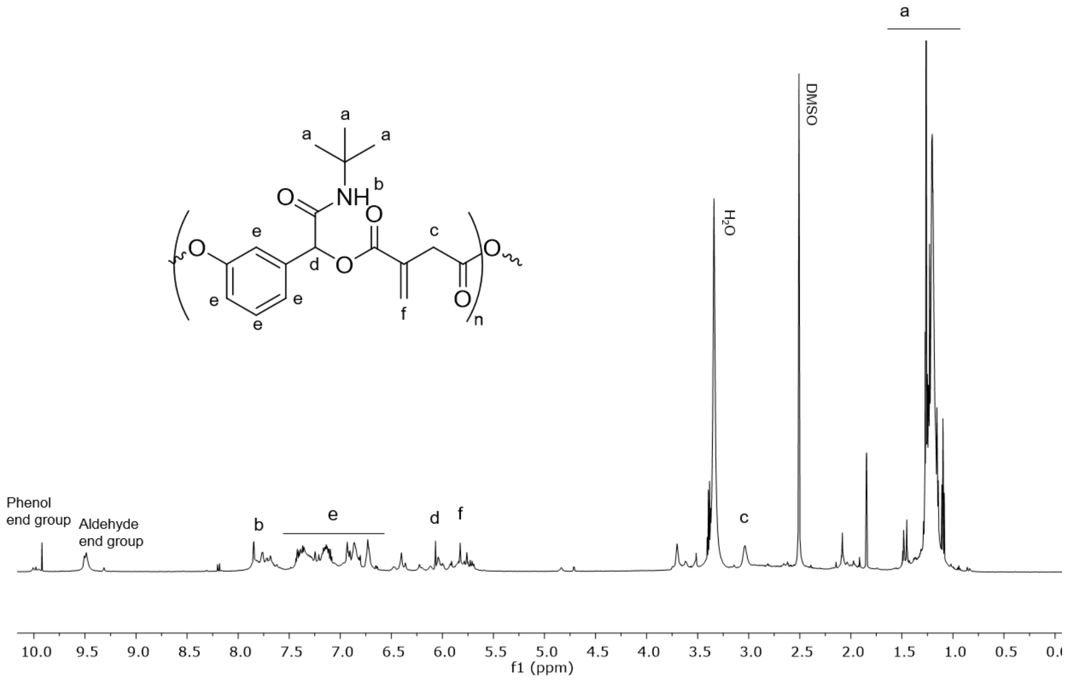


Figure S20. ^{1}H NMR spectrum of p(A-4-α) (600 MHz, DMSO-*d*$_6$).

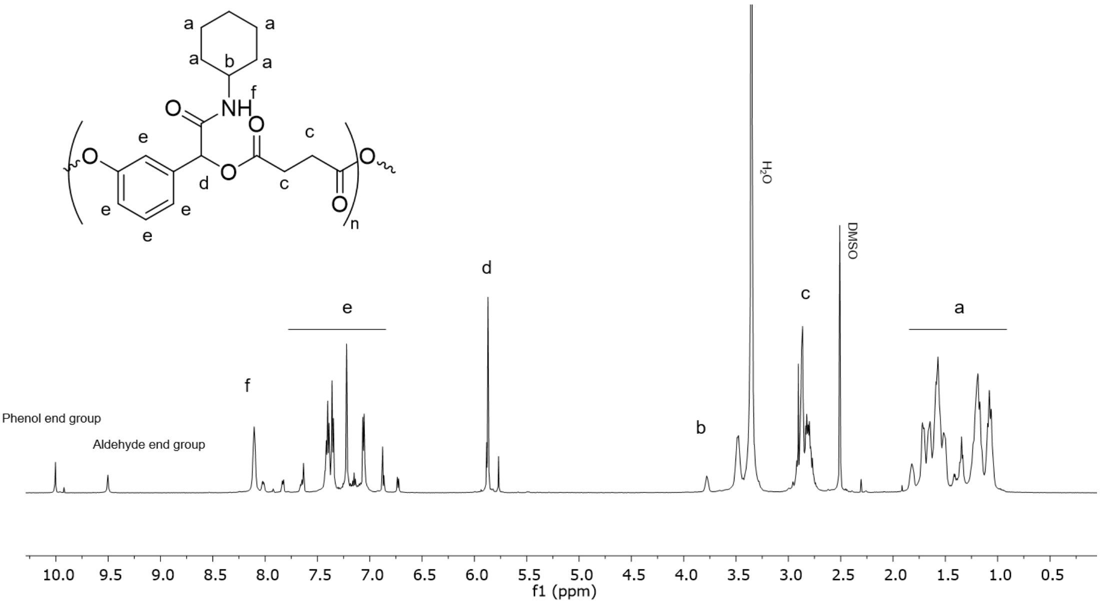


Figure S21. ^{1}H NMR spectrum of p(A-1-β) (600 MHz, DMSO-*d*$_6$).

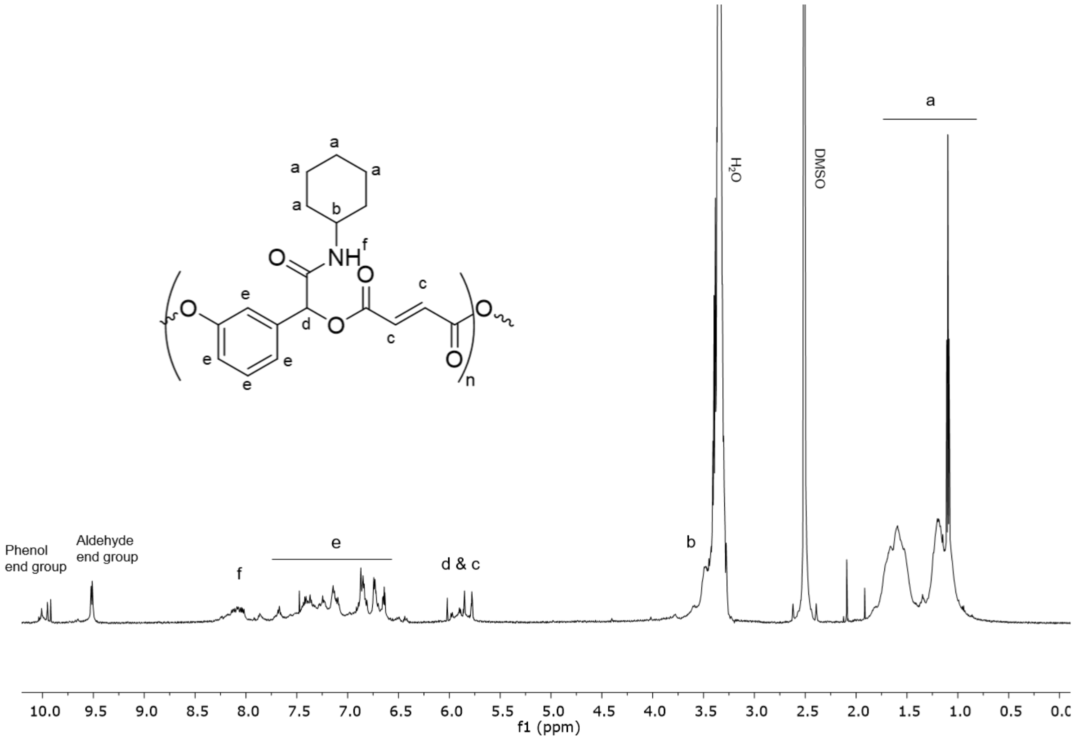


Figure S22. ^{1}H NMR spectrum of p(A-2-β) (600 MHz, DMSO-*d*$_6$).

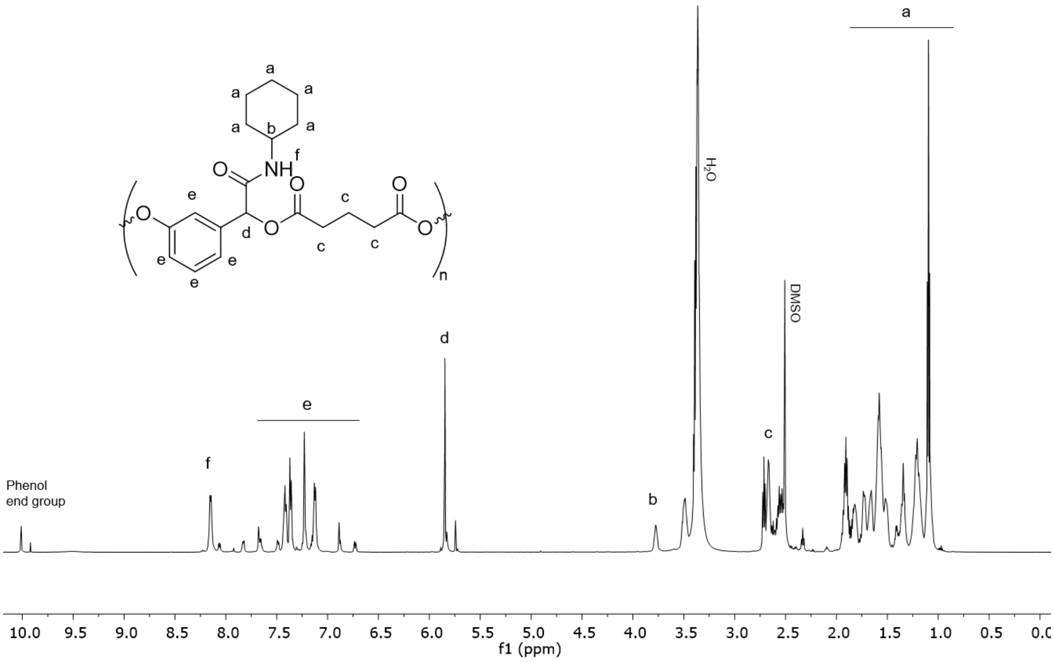


Figure S23. ^{1}H NMR spectrum of p(A-3-β) (600 MHz, DMSO-d_6).

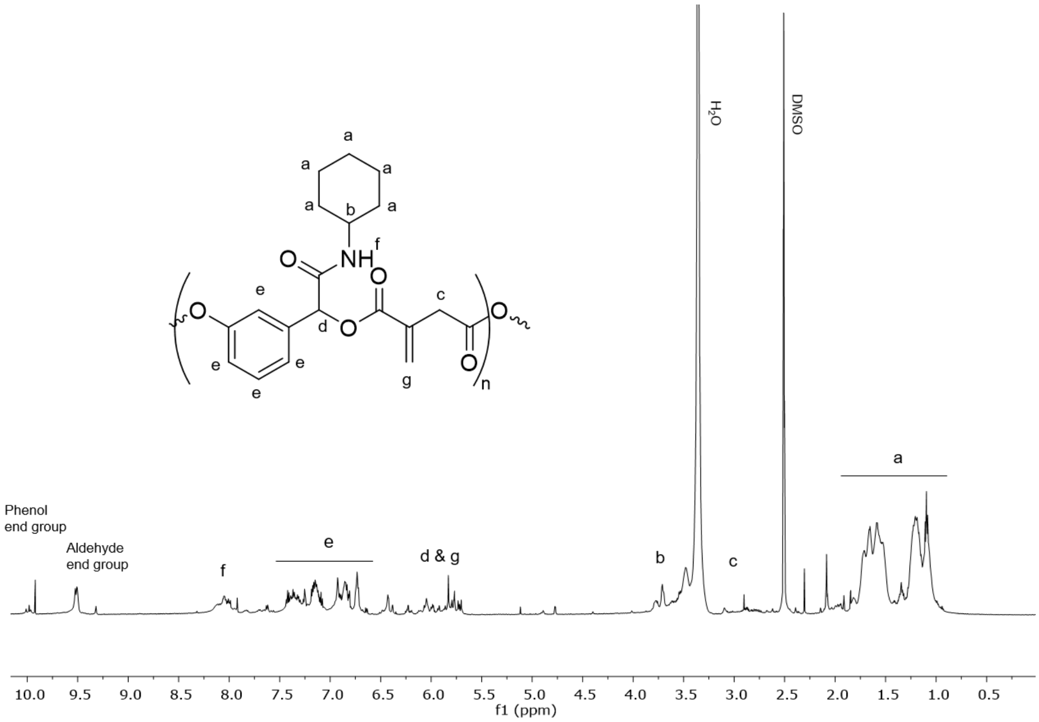


Figure S24. ^{1}H NMR spectrum of p(A-4-β) (600 MHz, DMSO-d_6).

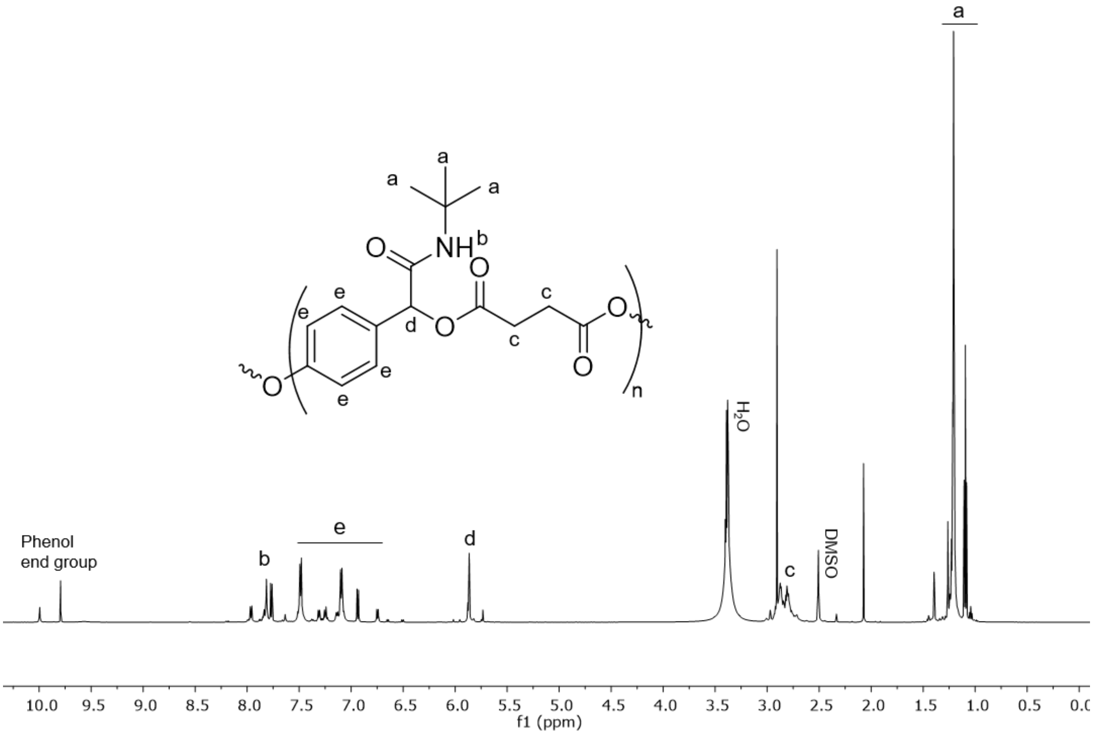


Figure S25. ^{1}H NMR spectrum of p(B-1-α) (600 MHz, DMSO-*d$_6$*).

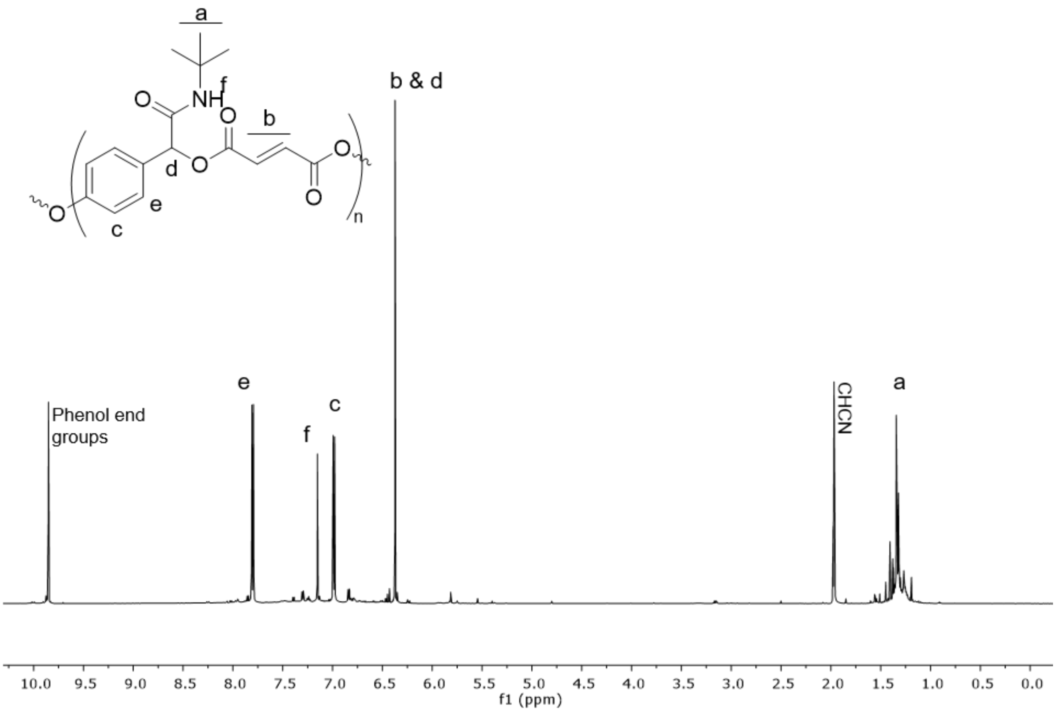


Figure S26. ^{1}H NMR spectrum of p(B-2-α) (600 MHz, CD_3CN).

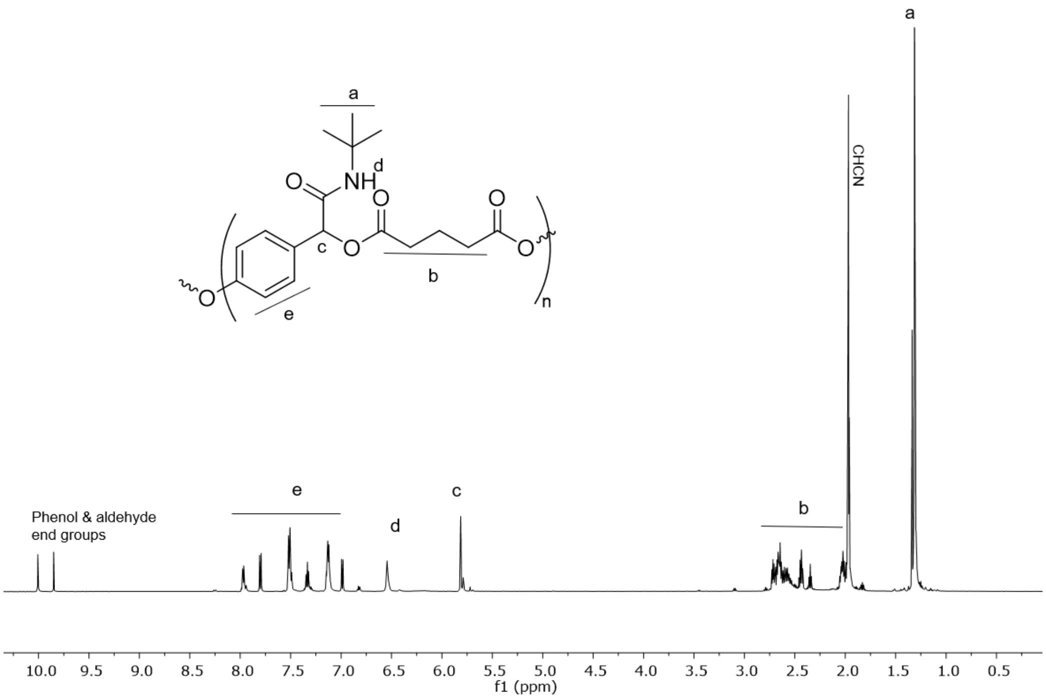


Figure S27. ^{1}H NMR spectrum of p(B-3-α) (600 MHz, CD_3CN).

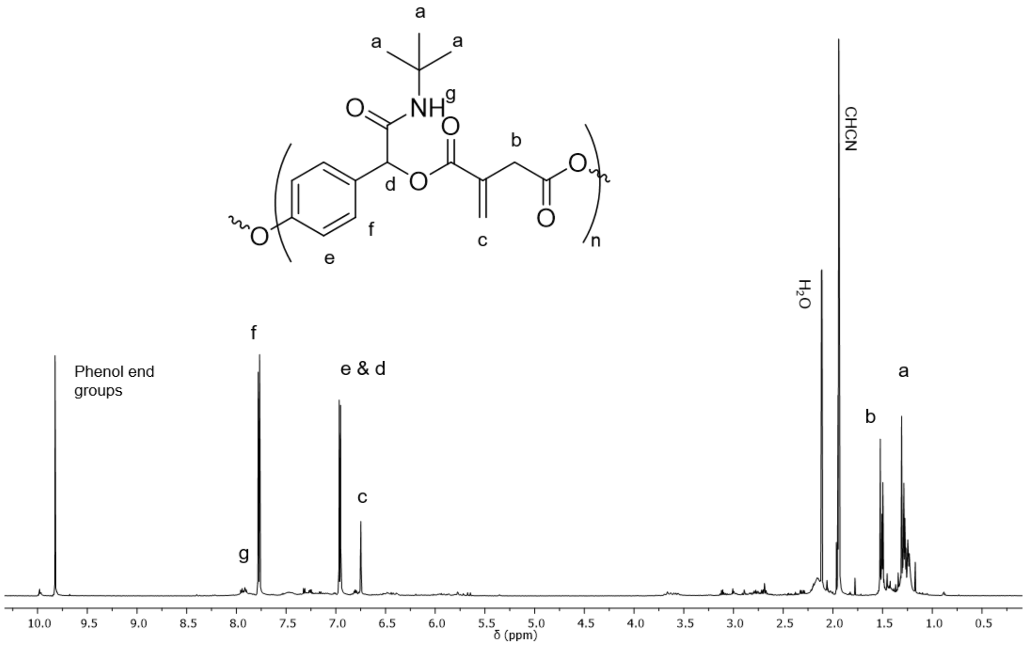


Figure S28. ^{1}H NMR spectrum of p(B-4-α) (600 MHz, CD_3CN).

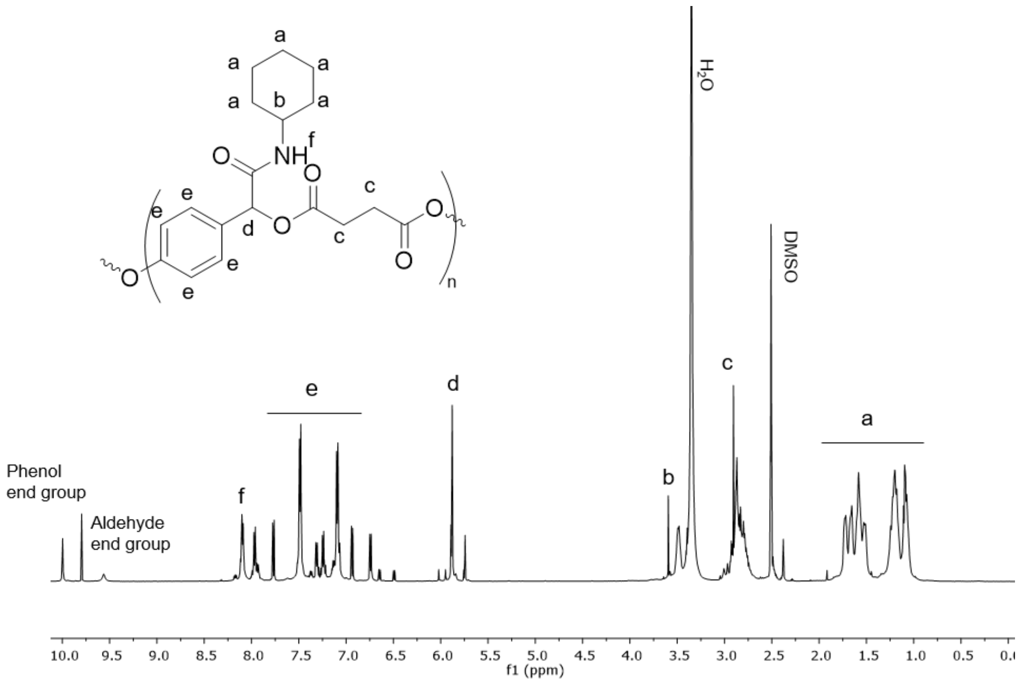


Figure S29. ^{1}H NMR spectrum of p(B-1-β) (600 MHz, DMSO-*d$_6$*).

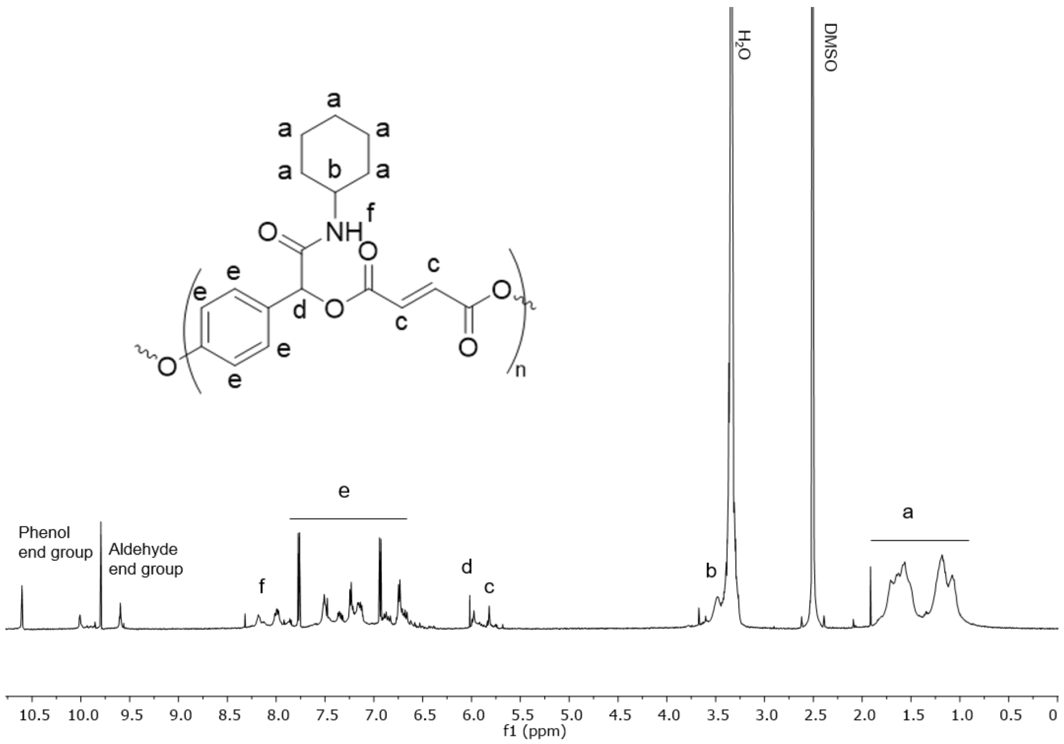


Figure S30. ^{1}H NMR spectrum of p(B-2-β) (600 MHz, DMSO-*d$_6$*).

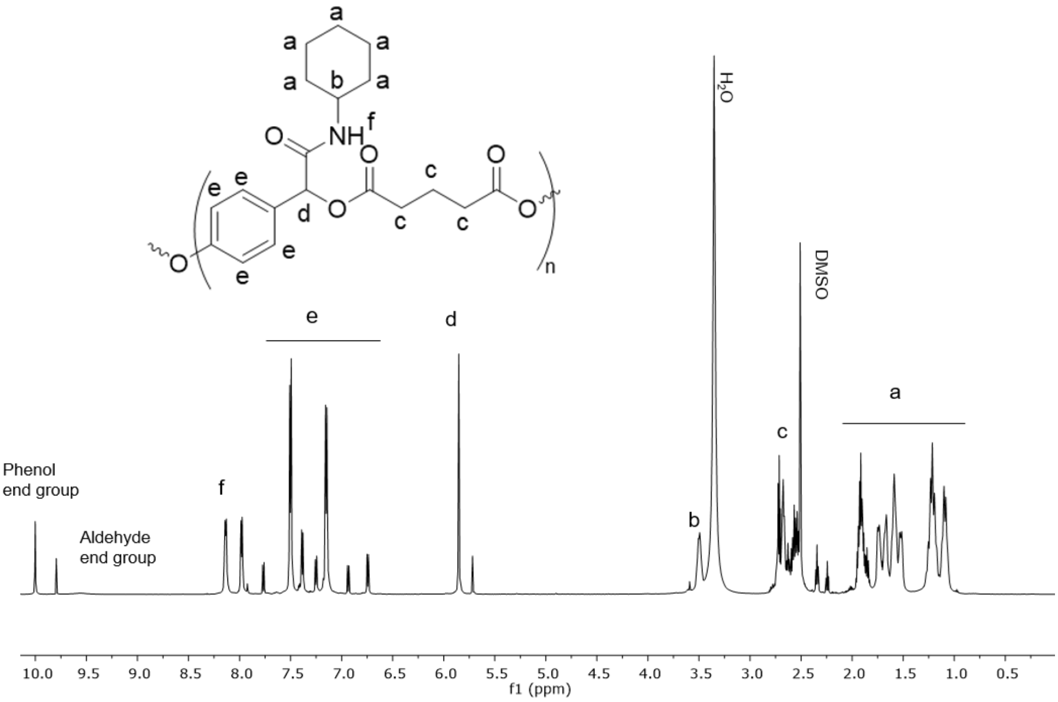


Figure S31. ^{1}H NMR spectrum of p(B-3-β) (600 MHz, DMSO-*d$_6$*).

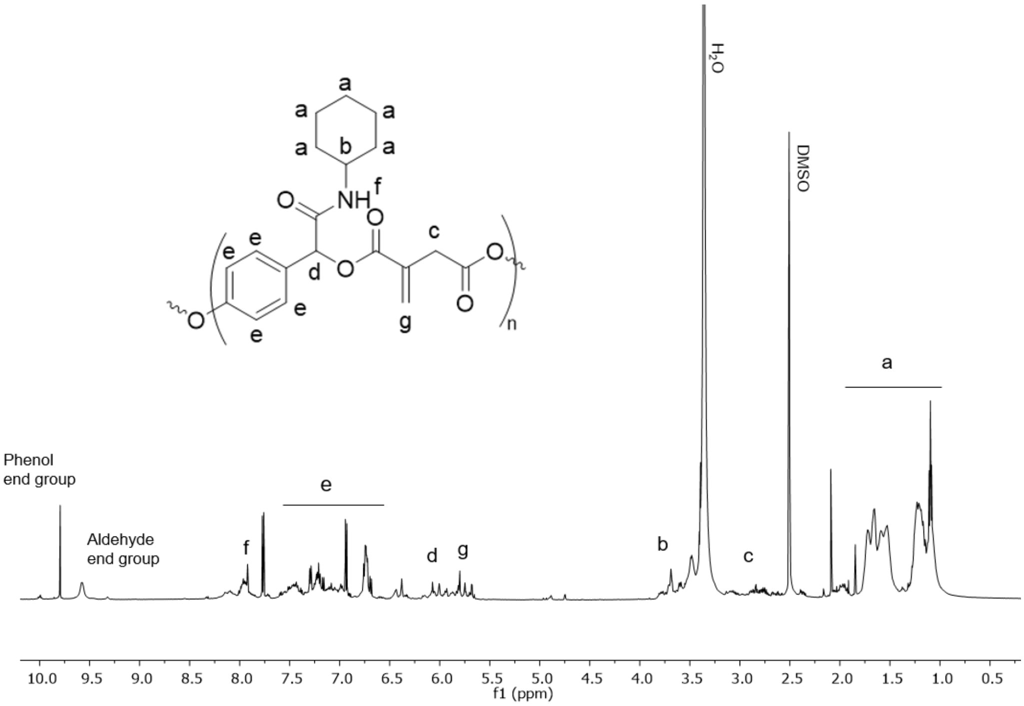


Figure S32. ^{1}H NMR spectrum of p(B-4-β) (600 MHz, DMSO-*d$_6$*).

Post-Polymerization Modification of p(A-2-α) via Thio-Michael Addition

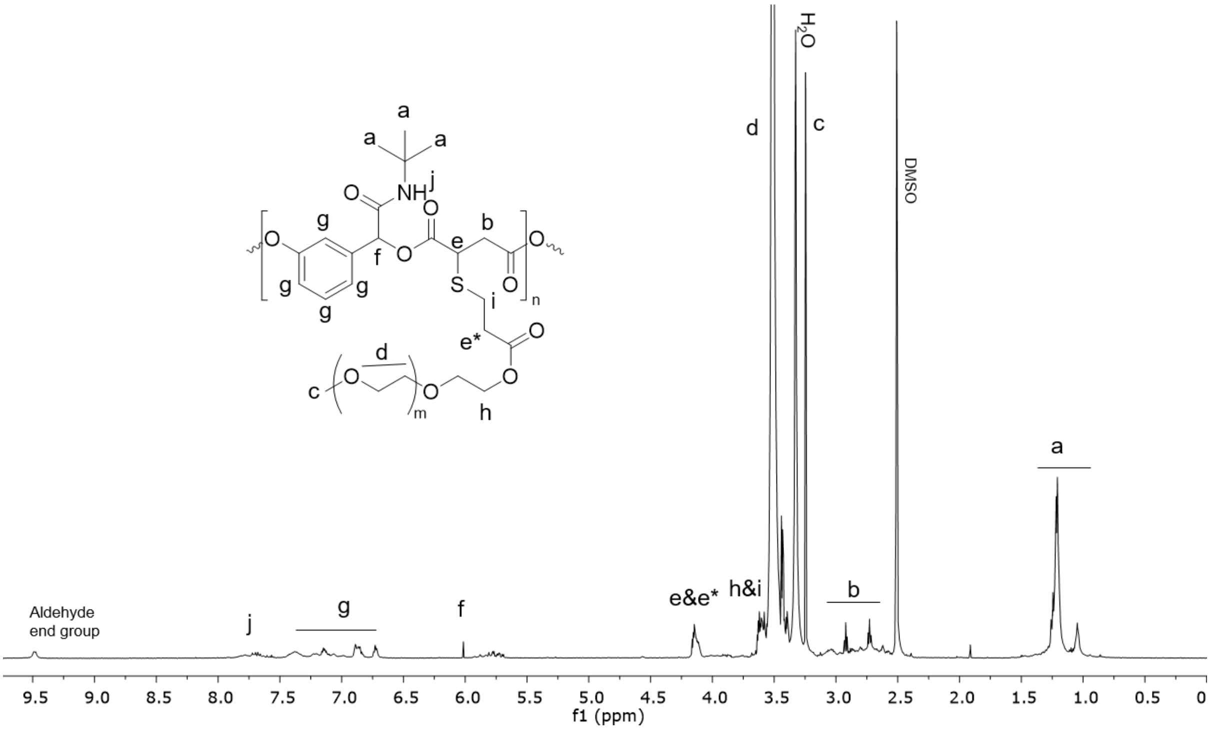


Figure S33. ^{1}H NMR spectrum of post-polymerization modification of p(A-2-α) via thio-Michael Addition (600 MHz, DMSO-*d*$_6$).

Control Test for Passerini-Smiles polymerization

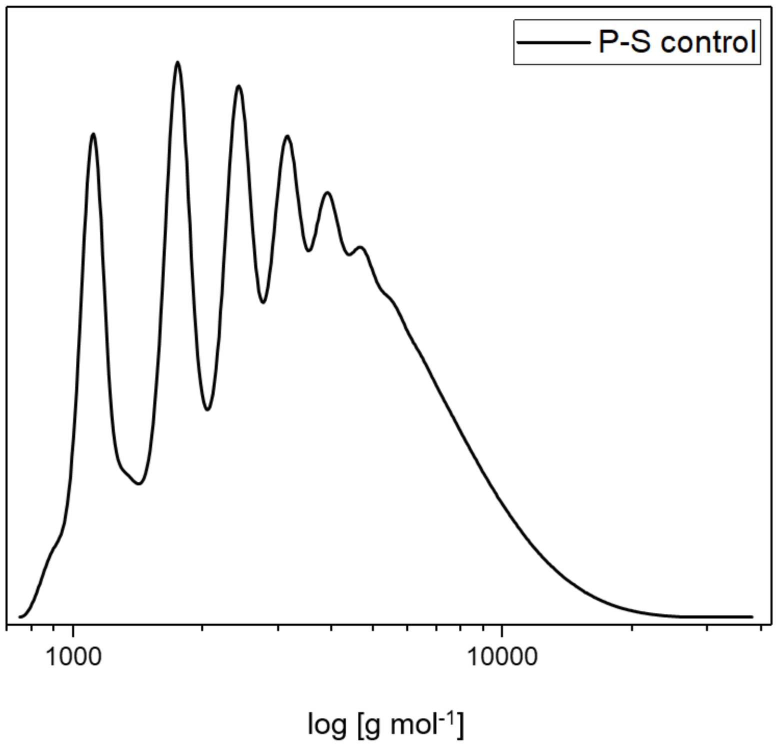


Figure S34. Molar mass distribution (RI) of Passerini-Smiles Control measured in THF.

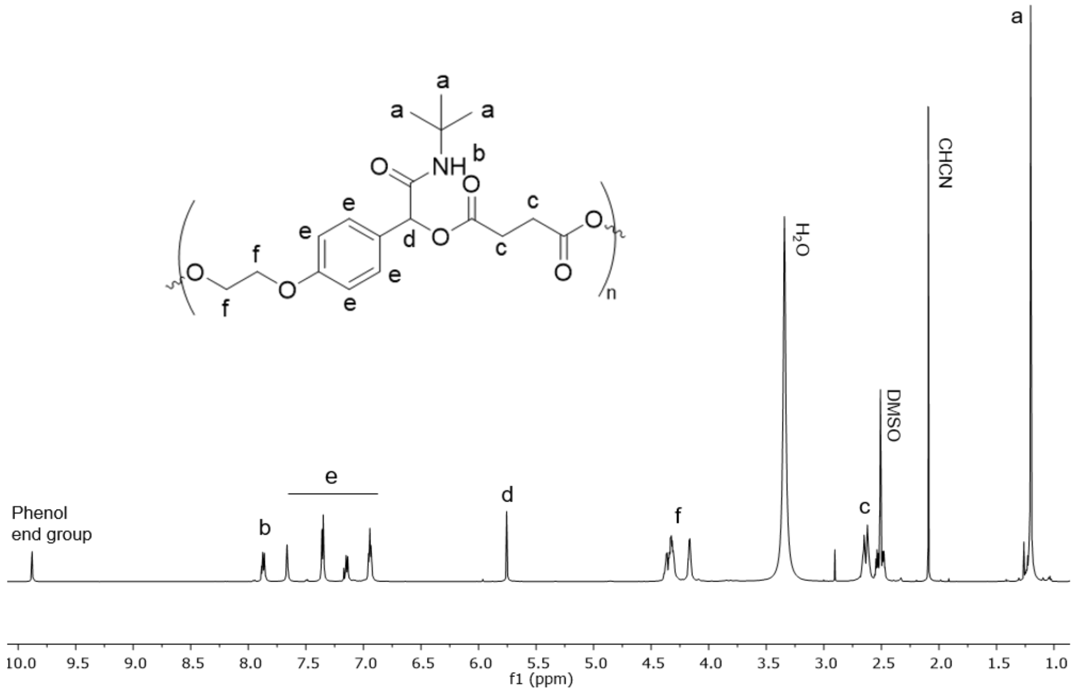


Figure S35. ^{1}H NMR spectrum of Passerini-Smiles Control (600 MHz, DMSO-d_6).

References

[1] T. M. D. Alharbi, M. Jellicoe, X. Luo, K. Vimalanathan, I. K. Alsulami, B. S. Al Harbi, A. Igder, F. A. J. Alrashaidi, X. Chen, K. A. Stubbs, J. M. Chalker, W. Zhang, R. A. Boulos, D. B. Jones, J. S. Quinton, C. L. Raston, *Nanoscale Advances* **2021**.
[2] C. Robert, F. de Montigny, C. M. Thomas, *ACS Catalysis* **2014**, *4*, 3586-3589.
[3] C. Teulère, R. Nicolaÿ, *Polymer Chemistry* **2017**, *8*, 5220-5227.