Supplementary Information

POT-PISA: Core-degradable particles via aqueous radical ring-opening polymerization-induced self-assembly using 7-phenyloxepane-2-thione

Thomas J. Neal,[a] Jingming Cao,[a] Bastien Luzel,[b] Yohann Guillaneuf,[b] Julien Nicolas[a]*

[a] Universite Paris-Saclay, CNRS, Insitut Galien Paris-Saclay, 17 avenue des Sciences 91400 Orsay, France.

[b] Aix-Marseille Université, CNRS, Institut de Chimie Radicalaire, UMR 7273, F-13397 Marseille, France.

*To whom correspondence should be addressed.

Email: julien.nicolas@universite-paris-saclay.fr

Tel.: +33 (0)1 80 00 60 81

Table of content

Experimental

Materials

Dimethylacrylamide (DMA, 99%), *n*-butyl acrylate (BA, 99%), styrene (St, 99%), 4,4′-azobis(4-cyanovaleric acid) (ACVA, 98%), 2,2′-azobis(2-methylpropionamidine) dihydrochloride (V-50, 97%), 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanol (97%) dioxane (anhydrous, 99.8%), acetic acid (99%), NaOH, and isopropylamine (≥99%), butylamine (99.5%), ethanolamine (98%) were purchased from Sigma-Aldrich. DMSO (HPLC grade) and acetone were obtained from VWR Chemicals. Hydrochloric acid (HCl, 37%) was supplied by Carlo-Erba. DMSO-d_6 and $CDCl_3$ were purchased from Eurisotop. 7-Phenyloxepane-2-thione (POT) was prepared as reported previously.[1]

Methods

Synthesis of PDMA macro-CTA

ACVA (7.1 mg, 25 µmol), 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanol (98 mg, 0.25 mmol), and DMA (1 g, 10 mmol), were added to sample vial and dissolved in dioxane (2.6 mL). The reaction was sealed then degassed by bubbling argon through the solution for 30 min. The vial was then placed in an oil bath at 73 °C and left to react for 4 h. The polymerisation was terminated by exposure to air and cooling to ambient temperature. The copolymer was isolated by precipitation (two times) in diethyl ether and dried under vacuum.

PISA synthesis of PDMA-P(BA-co-POT) nanoparticles

In a typical procedure (copolymer 2), PDMA macro-CTA (17 mg, 4 mmol) was dissolved in 0.9 mL of deionised water. To this solution 0.1 mL of an aqueous V-50 stock solution (2 mg/mL) was added. In a separate vial, POT (18 mg, 0.078 mmol) was dissolved in BA (200 mg, 1.5 mmol) and added to the polymerisation vial. The reaction was sealed then degassed by bubbling argon through the solution for 20 min. The vial was then placed in an oil bath at 55 °C and left to react for 4 h. The polymerisation was terminated by exposure to air and cooling to ambient temperature.

PISA synthesis of PDMA-P(St-co-POT) nanoparticles

In a typical procedure (copolymer 10), PDMA macro-CTA (21 mg, 5 mmol) was dissolved in 0.9 mL of deionised water. To this solution 0.1 mL of an aqueous V-50 stock solution (13 mg/mL) was added. In a separate vial, POT (22 mg, 0.096 mmol) was dissolved in St (200 mg, 1.9 mmol) and added to the polymerisation vial. The reaction was sealed then degassed

by bubbling argon through the solution for 20 min. The vial was then placed in an oil bath at 55 °C and left to react for 4 h. The polymerisation was terminated by exposure to air and cooling to ambient temperature.

Monomer-starved PISA synthesis of PDMA-P(St-co-POT) nanoparticles

In a typical procedure (copolymer 11), PDMA macro-CTA (21 mg, 5 mmol) was dissolved in 1.3 mL of deionised water. To this solution 0.1 mL of an aqueous V-50 stock solution (13 mg/mL) was added. In a separate vial, POT (22 mg, 0.096 mmol) was dissolved in St (200 mg, 1.9 mmol). Both vials were sealed with rubber septa and purged with argon gas for 20 min. The degassed comonomer mixture was drawn into a degassed 2.0 mL plastic syringe, which was carefully placed within a motorized syringe pump. The reaction vial containing the aqueous solution of PDMA macro-CTA and V-50 initiator was placed in an oil bath at 55 °C. Then a comonomer mixture was added dropwise over 4 h a with continuous stirring of the reaction. After complete addition of the two comonomers, the copolymerization was allowed to proceed at 55 °C. After 2 h, the polymerization was terminated by exposure to air and cooling to ambient temperature.

1-Point degradation analysis of the copolymers with amines

In a typical procedure, 32 µL of isopropylamine (35 eq.) was added to 0.5 mL of a 5% w/w nanoparticle dispersion (copolymer 2). The solution was left to stir at ambient temperature for 24 h at which point the solution was quenched and neutralised by the dropwise addition of acetic acid (10%). The water was removed from the sample *via* lyophilization and the sample analysed by SEC in chloroform.

1-Point degradation analysis of the copolymers with isopropylamine in THF

Nanoparticle dispersion 9 was dried by lyophilization and dissolved with 0.5 mL THF to create 5% w/w solution. 16 µL of isopropylamine (35 eq.) was added to the solution and left to stir at ambient temperature for 24 h at which point the solvent was removed under vacuum and the sample was analysed by SEC in chloroform.

1-Point degradation analysis of the copolymers with NaOH(aq)

20% w/w dispersion 10 was diluted to 5% w/w using 5 % NaOH aqueous solution. The solution was left to stir at ambient temperature for 24 h at which point the solution was quenched and neutralised by the dropwise addition of 5% HCl soluton. The water was removed from the sample *via* lyophilization and the sample was analysed by SEC in chloroform.

Dynamic Light Scattering (DLS)

Measurements were performed using a Malvern Zetasizer Nano ZS instrument equipped with a 4 mW He–Ne 633 nm laser and an avalanche photodiode detector. Back-scattered light was detected at an angle of 173° and data were recorded at a copolymer concentration of 0.2 % w/w at 25 °C. Malvern Zetasizer Software v7.11 was used to calculate z-average hydrodynamic diameters (D_z) via the Stokes-Einstein equation, which assumes perfectly monodisperse, non-interacting spherical particles. Data were averaged over at least three consecutive runs with at least ten measurements being recorded for each run.

Size Exclusion Chromatography (SEC) - DMSO

SEC was performed at 60 °C using two columns in series from Agilent Technologies (PL PolarGel-M, 300 × 7.5 mm; bead diameter 8 µm; molar mass range 1000–5,00,000 g mol^{-1}) preceded by a guard column from Agilent Technologies (PL PolarGel-M, 7.5 × 50 mm; bead diameter 8 µm) and a triple detection system (Viscotek TDA/GPCmax from Malvern) with a differential refractive index detector, low and right-angle light scattering detectors, a differential viscometer detector, and an additional UV detector. The eluent was DMSO with 0.1% w/v LiBr and 0.36 wt.% of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a marker at a flow rate of 0.7 mL min^{-1}. The system was calibrated using pullulan standards (peak molar masses, M_p = 504–739,000 g mol^{-1}) from Agilent Technologies. This allowed the determination of the number-average molar mass (M_n), the weight-average molar mass (M_w) and the dispersity ($Đ = M_w/M_n$). All samples were filtered over 0.22 µm PTFE filters prior to injection. Data were collected and processed with OmniSEC 5.12 software.

Size Exclusion Chromatography (SEC) – Chloroform

SEC measurements were performed at 35 °C with two columns from Polymer Laboratories (PL-gel MIXED-D; 300 × 7.5 mm; bead diameter, 5 µm; linear part, 400–400 000 g mol^{-1}) and a differential refractive index detector (Spectrasystem RI-150 from Thermo Electron Corp.). Chloroform was used as the eluent at a flow rate of 1 mL min^{-1} and toluene (0.5% v/v) was added as a flow-rate marker. A conventional calibration curve was based on poly(methyl methacrylate) (PMMA) standards (peak molar masses, M_p = 625–625 500 g mol^{-1}) from Polymer Laboratories. This technique allowed for the determination of Mn (number-average molar mass), M_w (weight-average molar mass), and M_w/M_n (dispersity, Đ).

Nuclear Magnetic Resonance (NMR)

NMR spectroscopy was performed in 5 mm diameter tubes in deuterated chloroform at 25 °C. ^{1}H-NMR spectroscopy was performed on a Bruker Avance 300 spectrometer at 300 MHz. The

chemical shift scale was calibrated based on the internal solvent signals ($\delta = 7.26$ ppm for $CDCl_3$). Data were processed with MestReNova 11.0.4 software.

Supplementary Figures

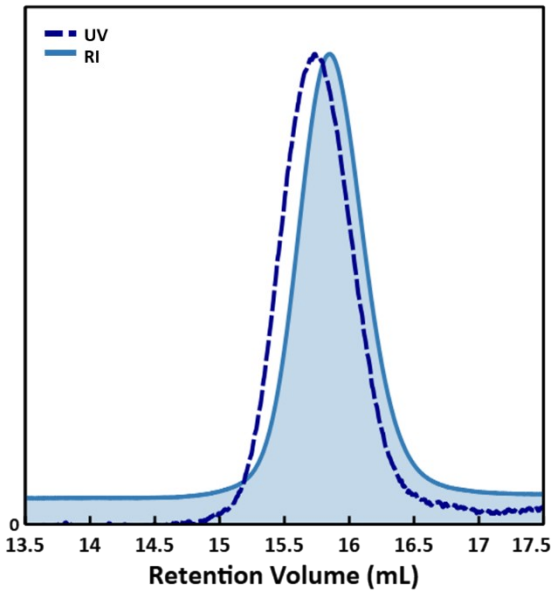

Figure S1. SEC chromatograms of PDMA macro-CTA

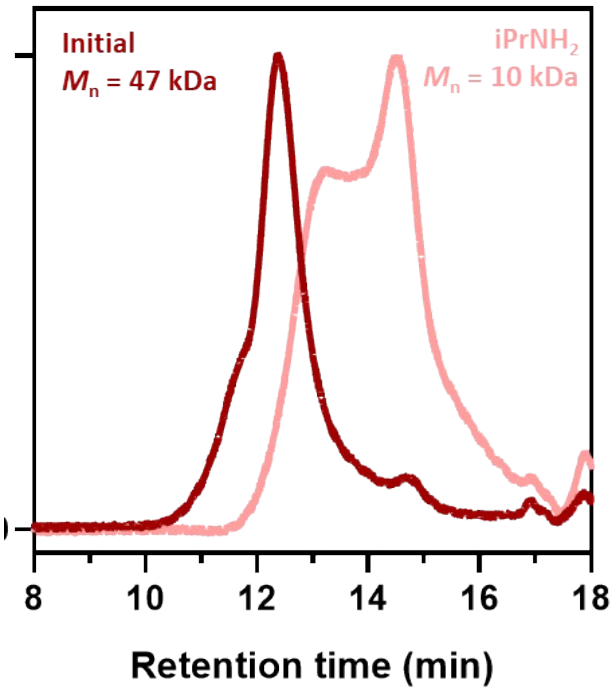

Figure S2. Evolution of the SEC RI-chromatograms of PDMA-b-P(BA-co-POT) copolymers **5**,

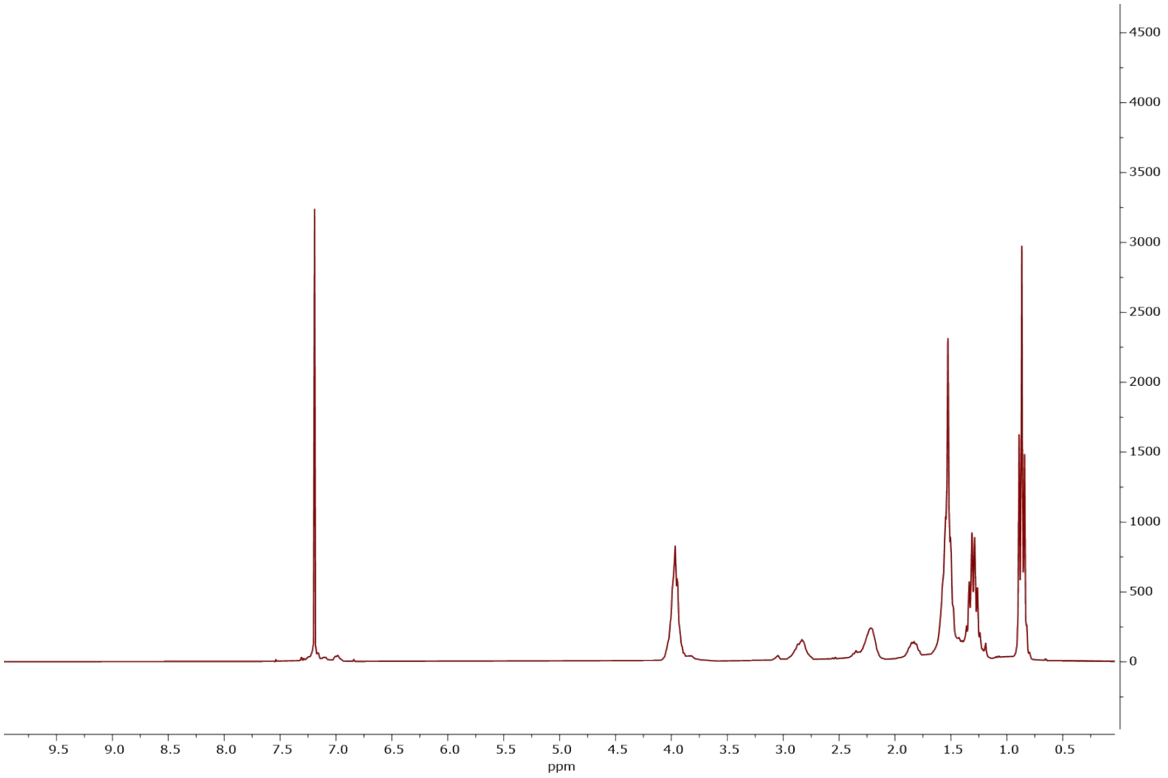

Figure S3. ^{1}H NMR spectrum of copolymer **2** in $CDCl_3$

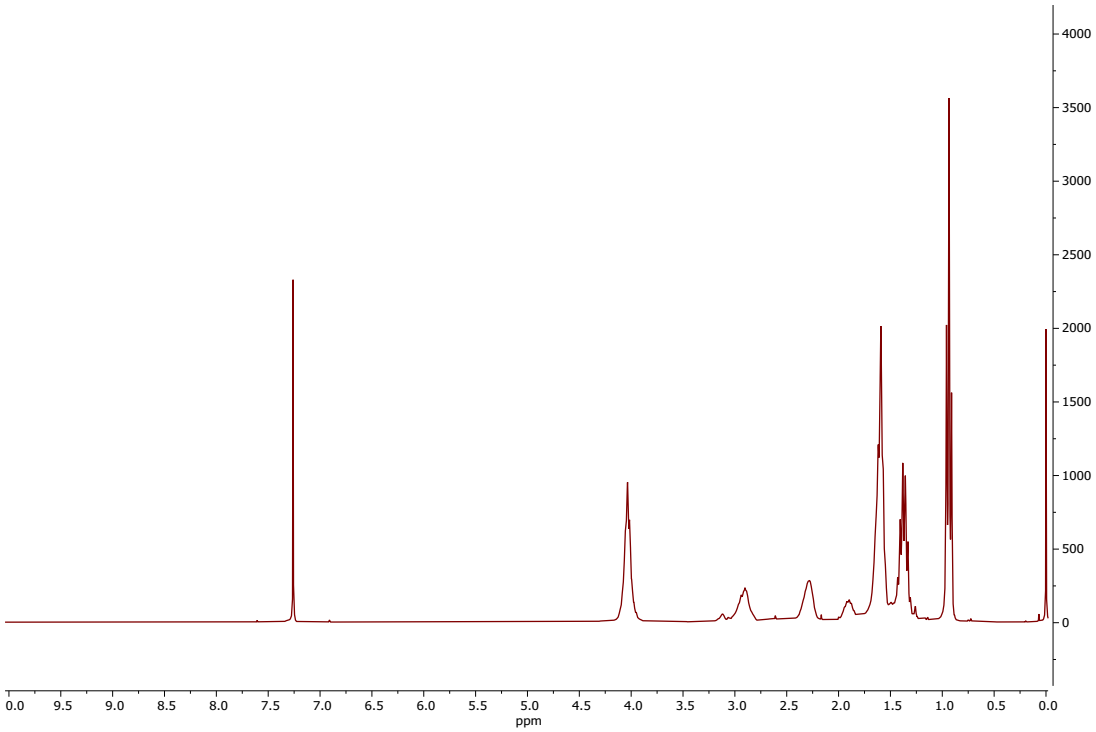

Figure S4. ^{1}H NMR spectrum of copolymer **4** in $CDCl_3$

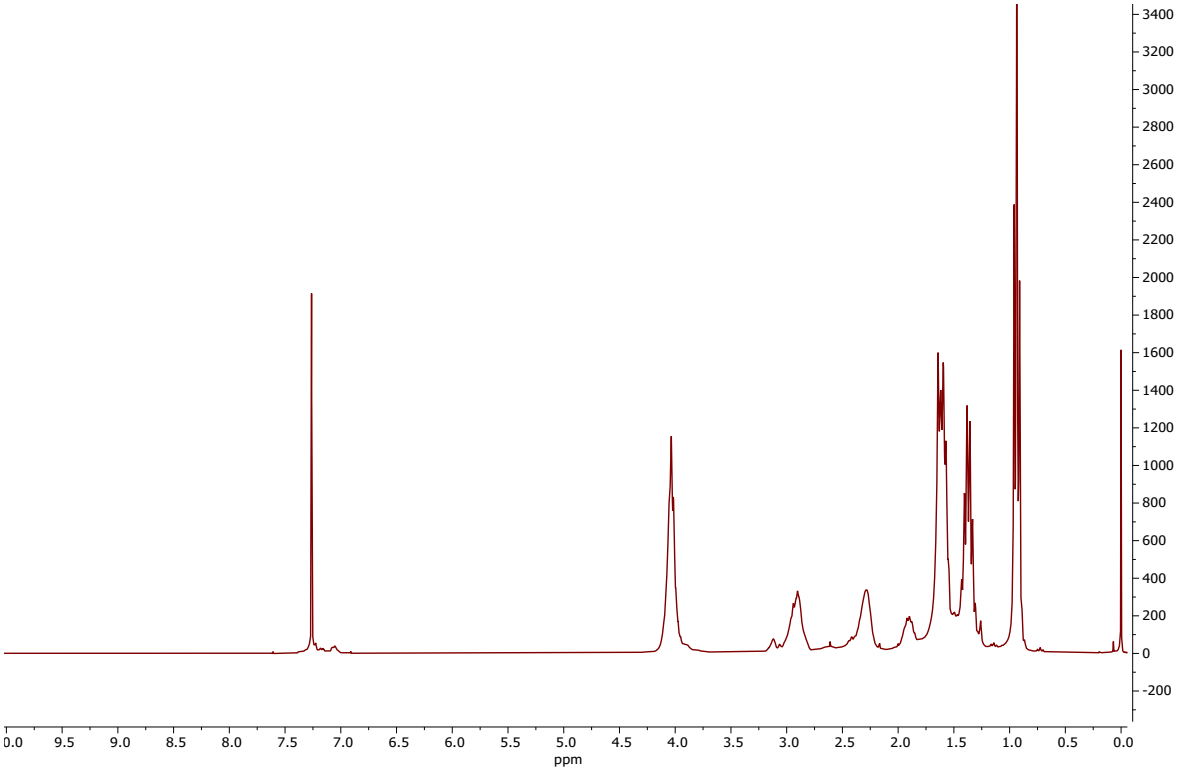

Figure S5. ^{1}H NMR spectrum of copolymer **5** in $CDCl_3$

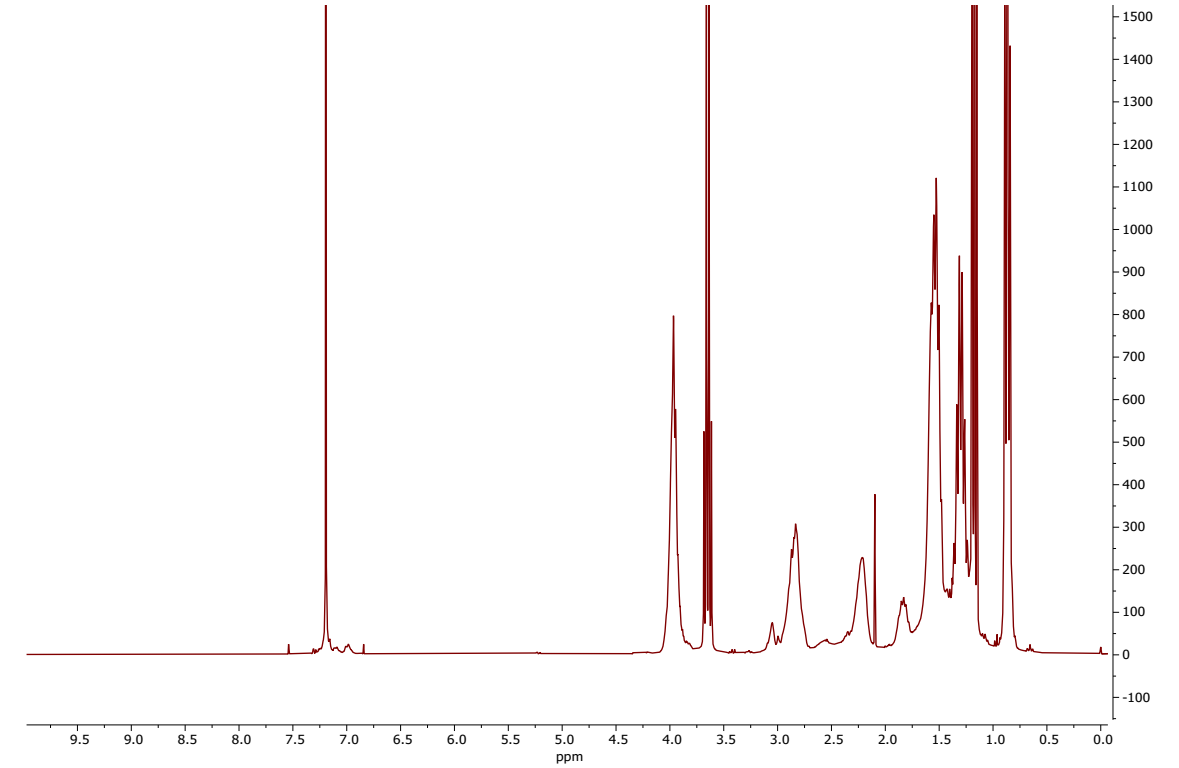

Figure S6. ^{1}H NMR spectrum of copolymer **7** in $CDCl_3$

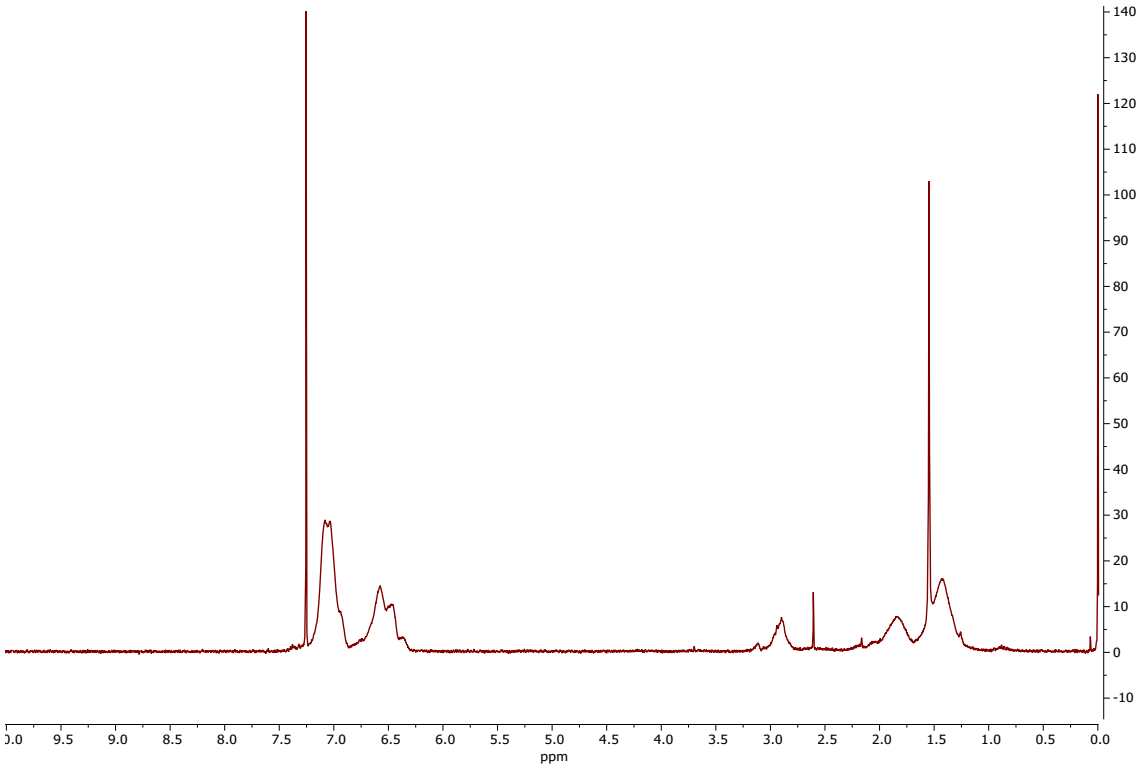

Figure S7. ^{1}H NMR spectrum of copolymer **9** in $CDCl_3$

References

1. B. Luzel, N. Gil, P. Désirée, J. Monot, D. Bourissou, D. Siri, D. Gigmes, B. Martin-Vaca, C. Lefay and Y. Guillaneuf, *J. Am. Chem. Soc.*, 2023, **145**, 27437–27449.