Electronic Supplementary Information (ESI) for Polymer Chemistry.

Supplementary Information

Ring-Opening Copolymerization of Hydroxyproline-Derived Thiolactones and Lipoic Acid Derivatives

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MATERIALS AND METHODS

Materials

All commercially obtained reagents were used as received unless otherwise specified. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzyl mercaptan (BnSH), and 1,2-dithioethane (EDT) were purchased from J&K (Beijing, China). Diisopropyl azodicarboxylate (DIAD) was purchased from Energy Chemical (Shanghai, China). $(2S,4R)$-1-cabobenzoxy-4-hydroxypyrrolidine-2-carboxylic acid (N^Z-HYP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide ($\times$ hydrochloride) (EDC) and lipoic acid (Lp) were purchased from Macklin Inc. (Shanghai, China). Triethylamine (Et_3N), benzylamine ($BnNH_2$), 4-dimethylaminopyridine (DMAP) and ε-caprolactone (CL) were purchased from Aladdin Reagent Co. Ltd. (Shanghai, China). Aniline ($PhNH_2$) was purchased from Xilong Scientific Co., Ltd. (Sichuan, China). Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained by passing HPLC-grade solvents through columns packed with activated 4 Å molecular sieves.

Equipments for characterizations

^1H NMR spectra were recorded on 400 MHz Bruker ARX400 FT-NMR spectrometer. Differential scanning calorimetry (DSC) analyses were performed on a TA Instrument Q2000 calorimeter with a heating or cooling rate of 10 °C/min. T_g was obtained from the second heating scan after the thermal history was removed from the first heating scan. Size exclusion chromatography (SEC) experiments in THF were performed on the equipment consisting of a Waters 1525 binary HPLC pump, a Waters 2414 refractive index detector, and three Waters Styragel columns (HT2, HT3, and HT4) at a flow rate of 1.0 mL · min^{-1} and 30 °C; the temperature of the refractive index detector was 25 °C and polystyrene standards were used for calibration. Molecular weight and dispersity ($Đ$) were calculated using Millennium 32 software. Stress-strain tensile tests were performed on an INSTRON single column bench type test system, data collected by Bluehill 2.0 software.

Synthesis of lipoic acid-derived monomers

N-benzyl-6-hydroxyhexanamide (BnNHCL)
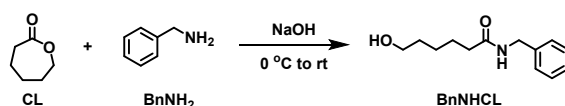
Benzylamine (BnNH$_2$, 4.50 g, 42.0 mmol, 1.2 equiv.) was dissolved in 200 mL THF in a round-bottom flask with a stir bar. The system was cooled in ice bath to 0 °C，then sodium hydroxide (NaOH, 1.68 g, 42.0 mmol, 1.2 equiv.) was added into the system. ε-Caprolactone (CL, 4.00 g, 35 mmol. 1.0 equiv.) was dissolved in 50 mL THF, then the solution was added dropwise into the mixture. The system was slowly warmed up to room temperature, and stirred for another 16 h. 100 mL ammonium chloride solution (sat. aq.) was used to quench the system, the aqueous phase washed by DCM (100 mL × 3 times) and then organic phase washed by 100 mL brine. All the organic phase was collected and dried by Na$_2$SO$_4$, then evaporated to remove the solvent. Then the crude residue was purified by silica gel with the eluent DCM/MeOH = 20/1 (v/v). Finally white and waxy solid was obtained. (5.89 g, yield 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.11 (m, 5H), 6.60 (t, J = 5.8 Hz, 1H), 4.34 (d, J = 5.8 Hz, 2H), 3.54 (q, J = 5.5 Hz, 2H), 3.10 (d, J = 4.6 Hz, 1H), 2.17 (t, J = 7.5 Hz, 2H), 1.62 (p, J = 7.6 Hz, 2H), 1.51 (p, J = 6.8 Hz, 2H), 1.34 (qd, J = 9.5, 8.9, 5.9 Hz, 2H).

Synthesis of lipoic amide derivatives[1]
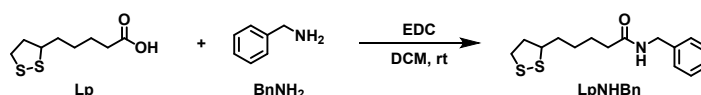
Taking the synthesis of thiooctyl benzylamine (LpNHBn) as an example:

Benzylamine (BnNH$_2$, 1.07 g, 10.0 mmol, 1.0 equiv.) and lipoic acid (Lp, 3.09 g, 15.0 mmol. 1.5 equiv.) were dissolved in 100 mL DCM in a round-bottom flask with a stir bar. EDC (2.16 g, 11.3 mmol, 1.13 equiv.) was dissolved in 50 mL DCM, then the solution was added dropwise into the mixture, and stirred for another 16 h. Then the system was washed with 100 mL NaHCO$_3$ (sat. aq.) and 100 mL brine subsequently, and Na$_2$SO$_4$ was used to dry the collected organic phase. Then the crude product after evaporation was purified by silica gel with the eluent DCM/MeOH = 30/1 (v/v). The final product was a yellow solid (2.60 g, yield 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.29 (m, 2H), 7.26 (td, J = 6.1, 1.4 Hz, 3H), 6.07 (t, J = 5.7 Hz, 1H), 4.40 (d, J = 5.7 Hz, 2H), 3.54 (dq, J = 8.3, 6.4 Hz, 1H), 3.21 – 3.04 (m,

2H), 2.43 (dtd, J = 13.0, 6.6, 5.4 Hz, 1H), 2.20 (t, J = 7.5 Hz, 2H), 1.88 (dq, J = 12.6, 6.9 Hz, 1H), 1.76 – 1.57 (m, 4H), 1.55 – 1.35 (m, 2H).

Thiooctyl aniline (LpNHPh) was acquired in the same method as a yellow solid (yield 82%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (d, J = 7.9 Hz, 2H), 7.39 (s, 1H), 7.30 (t, J = 7.7 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 3.57 (dq, J = 8.4, 6.4 Hz, 1H), 3.25 – 3.05 (m, 2H), 2.54 – 2.40 (m, 1H), 2.36 (t, J = 7.4 Hz, 2H), 1.90 (dq, J = 13.6, 6.9 Hz, 1H), 1.83 – 1.60 (m, 4H), 1.50 (ddt, J = 16.0, 8.5, 6.2 Hz, 2H).

Synthesis of 6-(benzylamino)-6-oxohexyl 5-(1,2-dithiolan-3-yl)pentanoate (LpOCLNHBn)
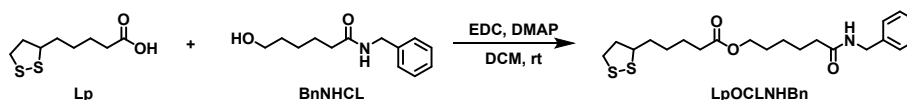
Lipoic acid (Lp, 2.00 g, 9.7 mmol, 1.0 equiv., EDC (2.23 g, 11.6 mmol, 1.2 equiv.), and 4-dimethylaminopyridine (DMAP, 0.59 g, 4.8 mmol, 0.5 equiv.) was dissolved in 100 mL DCM in a round-bottom flask with a stir bar, N-benzyl-6-hydroxyhexanamide (BnNHCL, 2.45 g, 9.7 mmol, 1.0 equiv.) was added into the system. The system was stirred at room temperature for another 16 h, and then washed with 100 mL NaHCO$_3$ (sat. aq.) and 100 mL brine subsequently, and Na$_2$SO$_4$ was used to dry the collected organic phase. Then the crude product after evaporation was purified by silica gel with the eluent DCM/MeOH = 30/1 (v/v). The final product was a sticky yellow liquid (2.58 g, yield 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.30 (m, 2H), 7.27 (q, J = 4.2 Hz, 3H), 5.85 (t, J = 5.3 Hz, 1H), 4.43 (d, J = 5.6 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 3.56 (dq, J = 8.5, 6.4 Hz, 1H), 3.22 – 3.04 (m, 2H), 2.45 (dtd, J = 12.9, 6.6, 5.3 Hz, 1H), 2.30 (t, J = 7.4 Hz, 2H), 2.22 (t, J = 7.5 Hz, 2H), 1.90 (dq, J = 12.6, 7.0 Hz, 1H), 1.75 – 1.60 (m, 7H), 1.55 – 1.33 (m, 4H).

Synthesis of poly(thioester-*r*-disulfide)s (PTE-*r*-PDS)

N^Z- HPTL (N^Z-HPTL, 566 mg, 2.15 mmol, 100 equiv.) and thiooctyl benzylamine (LpNHBn, 635 mg, 2.15 mmol, 100 equiv.) were dissolved in dichloromethane (DCM, 1000 μL) in a 5-mL bottle. To the monomer mixture was added initiator benzylmercaptan (BnSH in DCM, 21 μL × 1 mol/L, 1 equiv.) and catalyst Et$_3$N (21 μL× 1 mol/L in DCM, 1 equiv.) successively. The system was mixed well and placed in a -10 °C refrigerator for 24 h. To quench the

polymerization, DCM solution of acetic acid (AcOH, 39 mg, 10 equiv.) was added into the system, mixed well and incubated at -10 °C for another 2 hours. Then the reaction was added dropwise into 30 mL Et$_2$O for precipitation. The mixture was centrifuged to discard the supernatant, and pumped dry to obtain the final material. All the products with different monomer ratios were all obtained in the same method to obtain yellow solids, and all the yields are higher than 75%.

Synthesis of quasi-block poly(disulfide-*b*-thioester)s (PDS-*b*-PTE)

Thiooctyl benzylamine (LpNHBn, 635 mg, 2.15 mmol, 100 equiv.) was dissolved in 1000 μL DCM in a 5-mL bottle. To the thiolactone solution, was added initiator benzylmercaptan (BnSH in DCM, 21 μL × 1 mol/L, 1 equiv.) and catalyst Et$_3$N (21 μL× 1 mol/L in DCM, 1 equiv.) successively. The system was mixed well and placed in a -10 °C refrigerator for 16 h. Then N^Z-HPTL (566 mg, 2.15 mmol, 100 equiv. in 600 μL DCM) was added into the system, mixed well and placed in the -10 °C refrigerator for another 8 h. Then DCM solution of acetic acid (AcOH, 39 mg, 10 equiv.) was added into the system, mixed well and incubated at -10 °C for 2 h. Them the system was added dropwise into 30 mL Et$_2$O for precipitation. The mixture was centrifuged to discard the supernatant, and pumped dry to obtain the final material. All the products with different monomer ratios were all obtained in the same method to obtain yellow solids, and all the yields are higher than 75%.

Preparation of splines and characterization of mechanical properties of materials

A bench type powder tablet press (Sichuang Jingshi Company) was used to prepare for the splines. After the temperature of both the upper and lower heating plates of the press was stabilized at 120 ° C for 15 min, 600 mg polymer sample was put into a 30 × 30 × 0.5 mm mold, and pressurized to 10 MPa. Maintaining the temperature for 30 minutes, then heating was stopped, and the samples were naturally cooled to room temperature within about 5 hours to obtain transparent film materials ranging from amber to light yellow.

To test the tensile properties of the materials, the films obtained above were cut into 30 × 4.0 × 0.5 mm splines, and then tested by the INSTRON 5943 single column bench type test system (INSTRON Company) at room temperature (25 °C). The length between the tensile clamps was 10.00 mm, and the tensile rate of different samples was fixed at 10 mm/min.
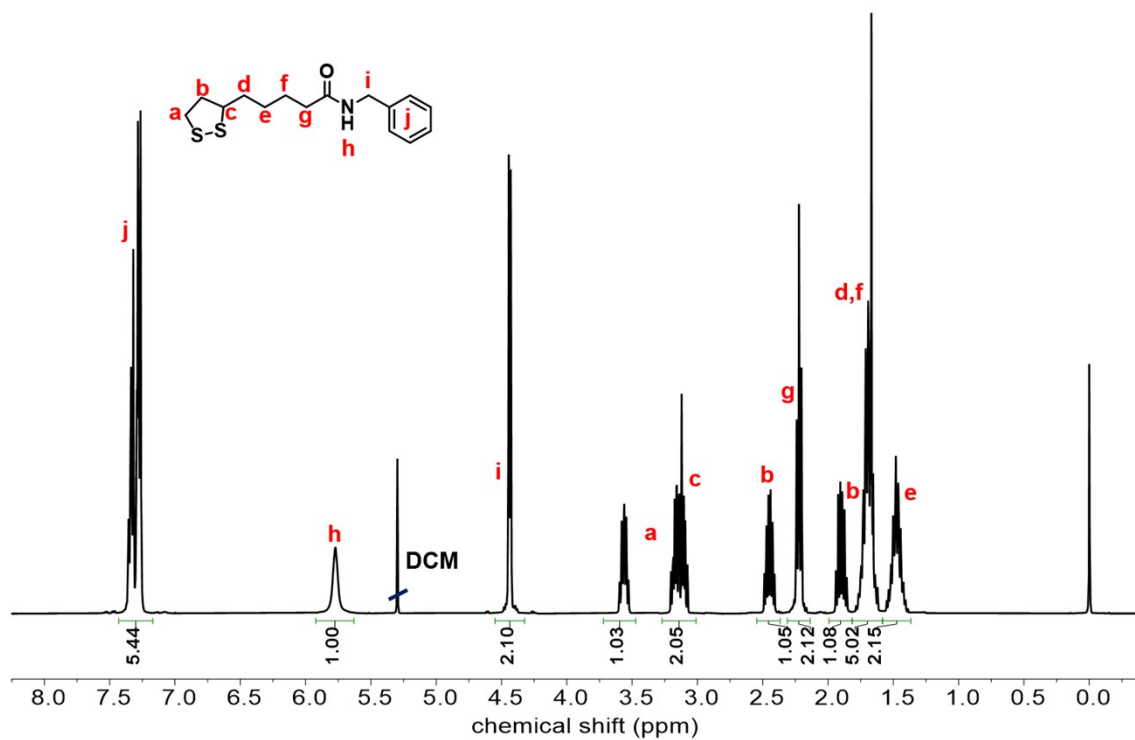
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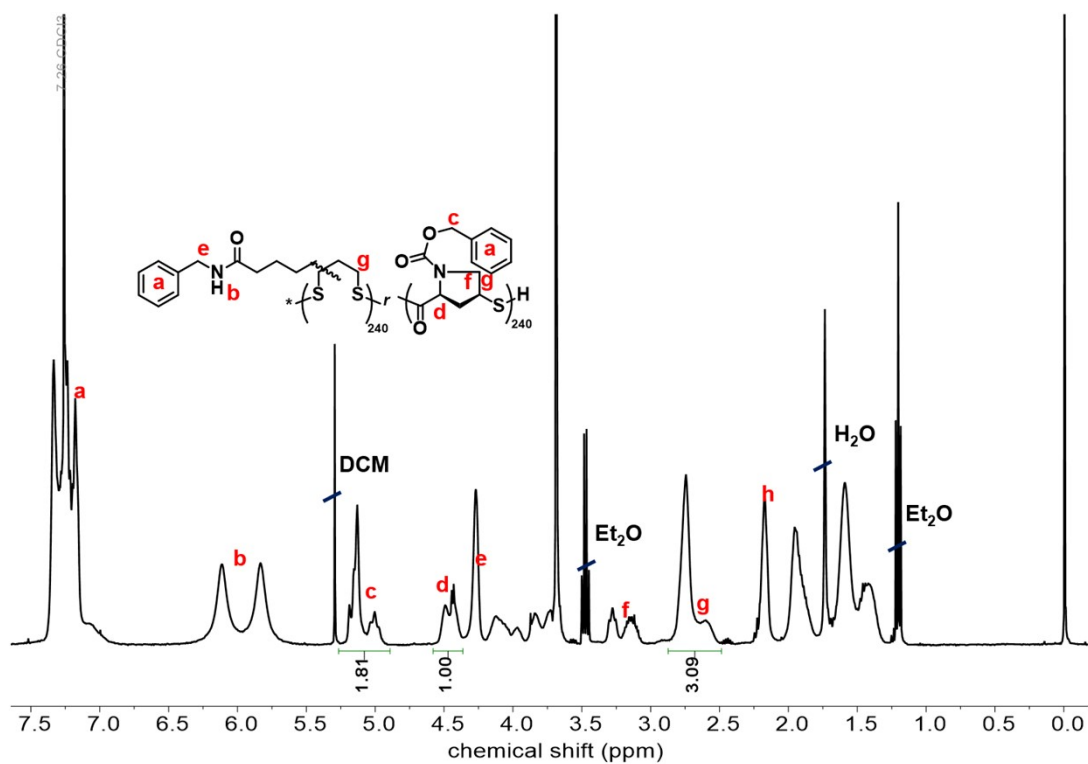

Figure S1. ^{1}H NMR spectrum of LpNHBn (solvent: CDCl$_3$)

Figure S2. ^{1}H NMR spectrum of P(LpNHBn$_{240}$-r-N^Z-PTE$_{240}$) (solvent: CDCl$_3$)
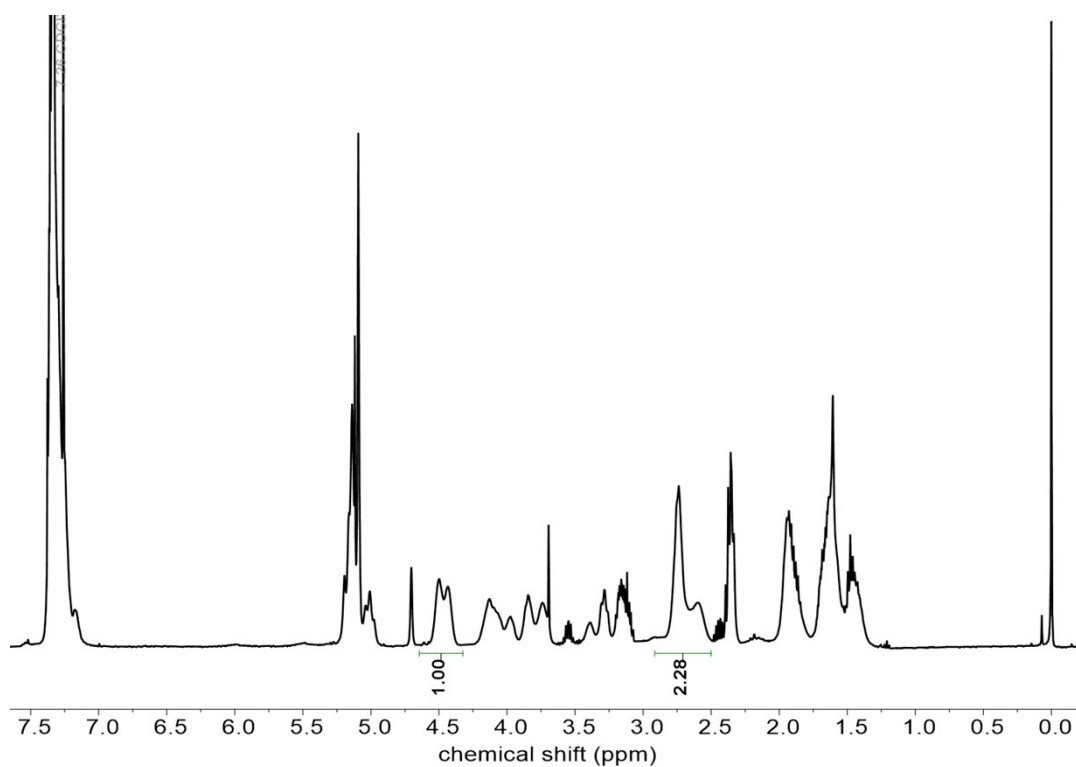
Figure S3. ^{1}H NMR spectrum of P(LpNHBn$_{240}$-*r*-N^Z-PTE$_{180}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with differences only in the integrated areas)
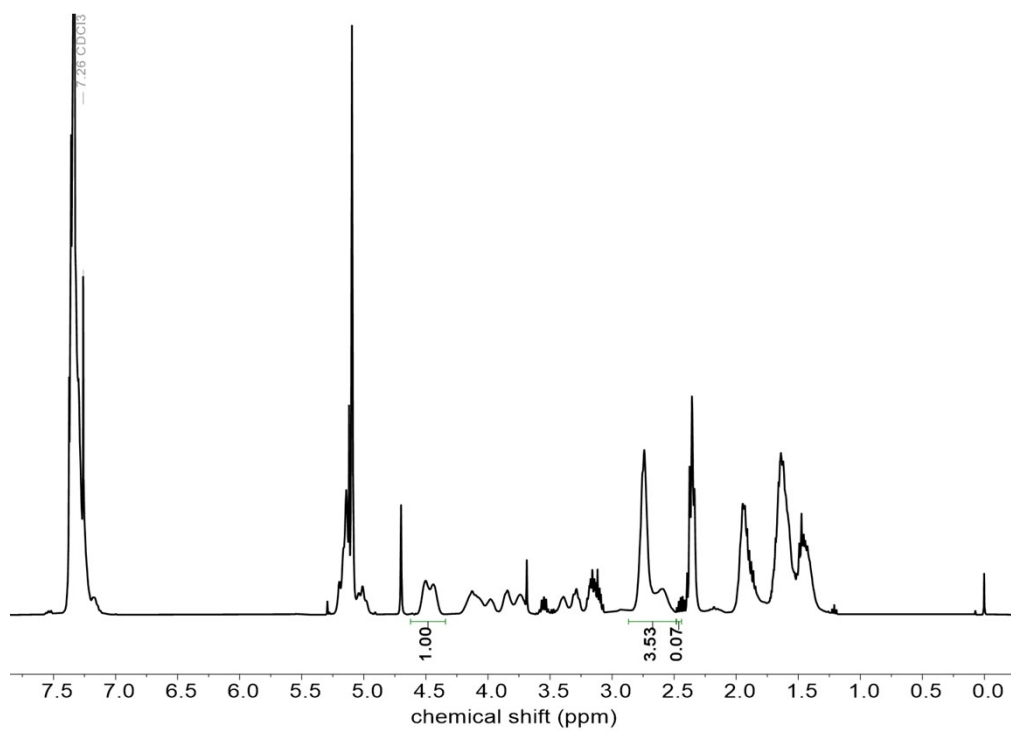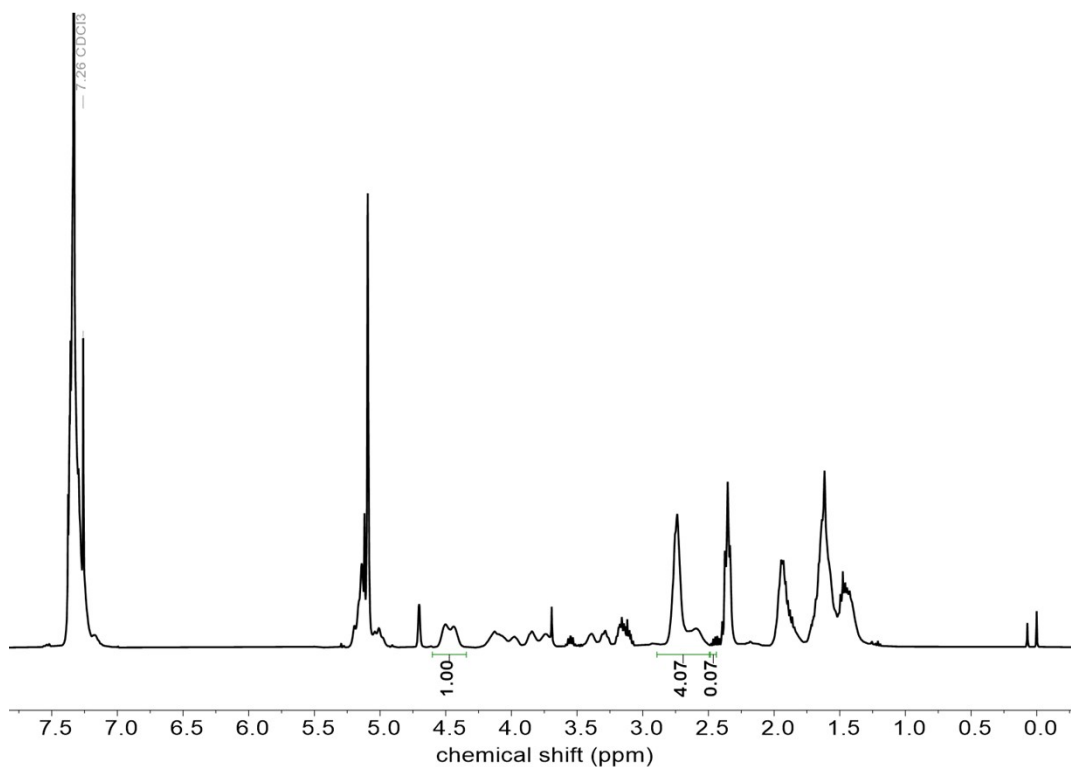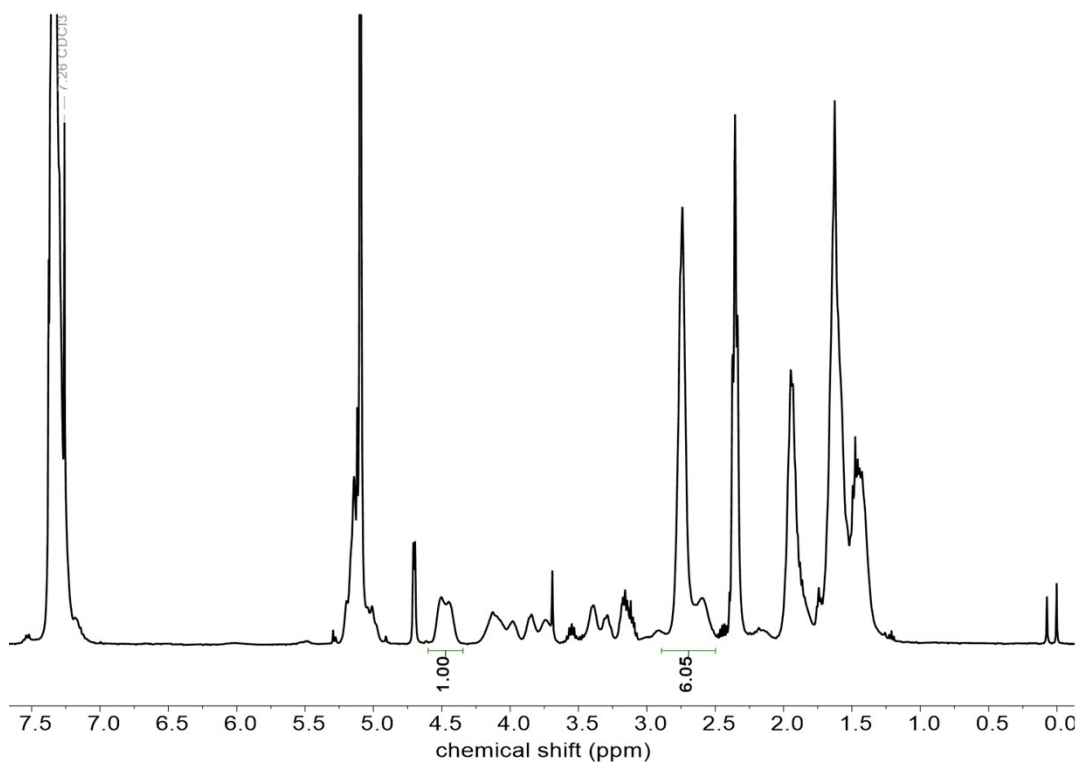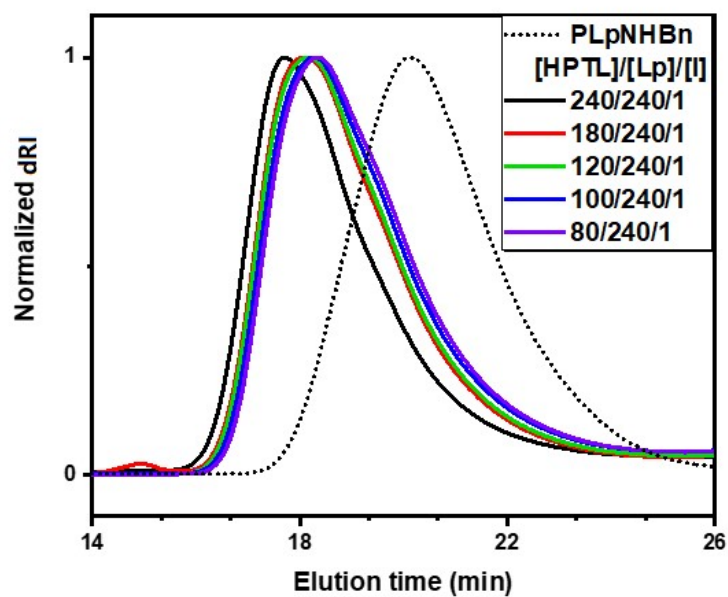

Figure S4. ^{1}H NMR spectrum of P(LpNHBn$_{240}$-*r*-N^Z-PTE$_{120}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)

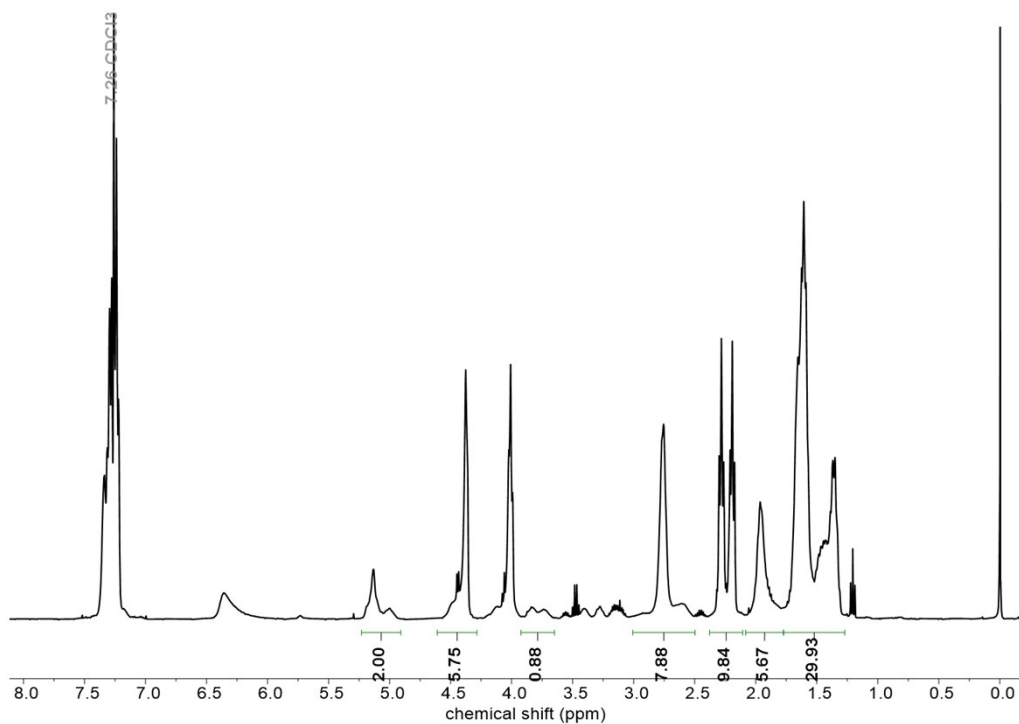Figure S5. ^{1}H NMR spectrum of P(LpNHBn$_{240}$-r-N^Z-PTE$_{100}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)


Figure S6. ^{1}H NMR spectrum of P(LpNHBn$_{240}$-r-N^Z-PTE$_{80}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)

Figure S7. Overlay of SEC curves of random copolymers P(LpNHBn$_{240}$-r-N^{Z}PTE$_x$), corresponding to Figure S2-S6 (THF as the eluent)
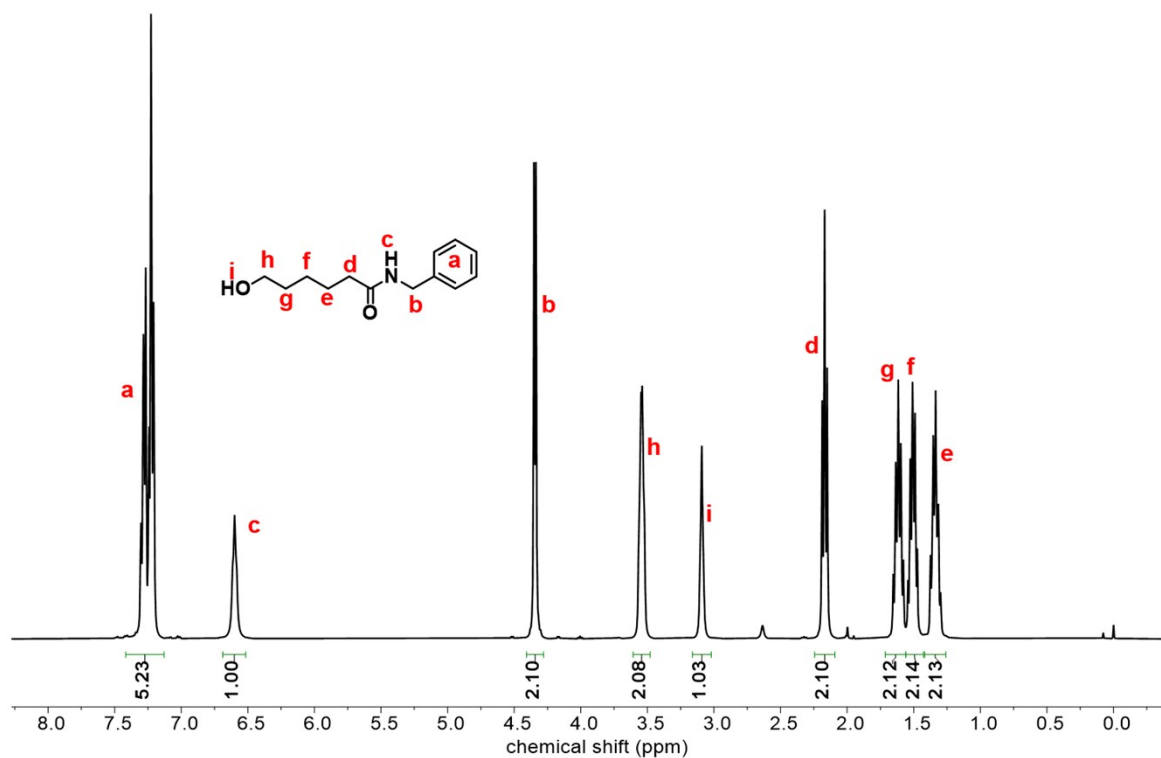
Figure S8. ^{1}H NMR spectrum of BnNHCL (solvent: CDCl$_3$)
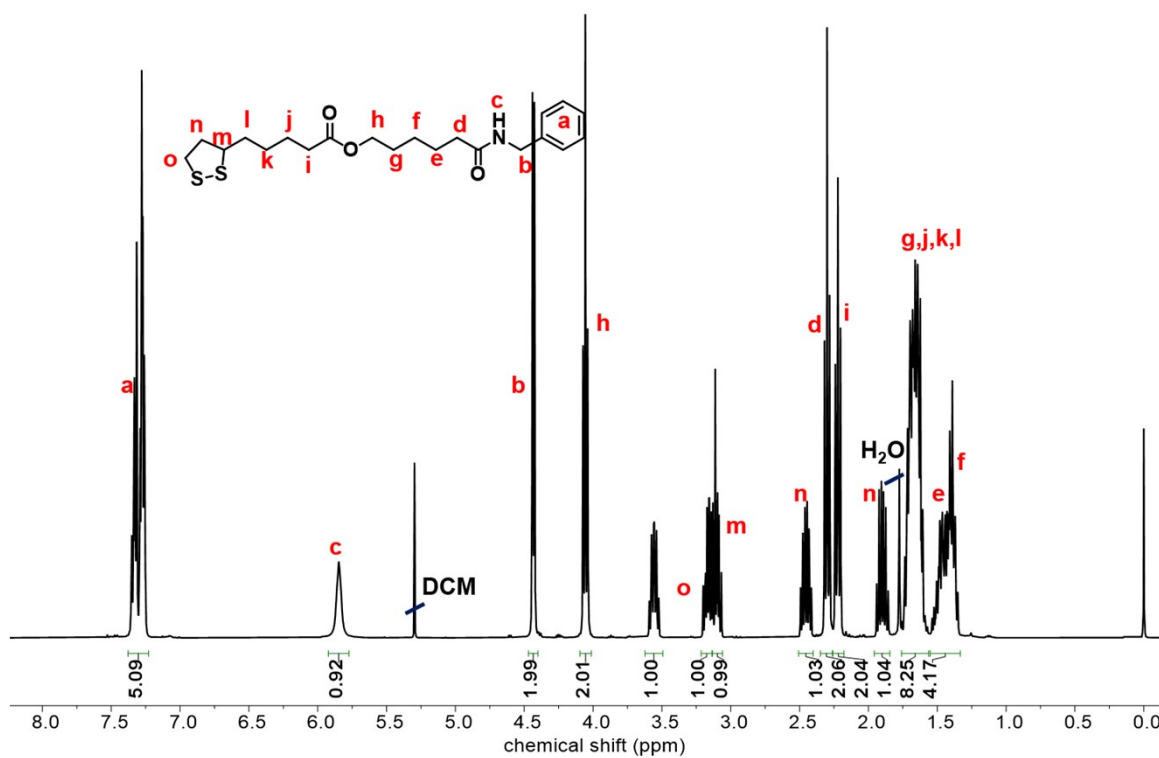
Figure S9. ^{1}H NMR spectrum of LpOCLNHBn (solvent: CDCl$_3$)
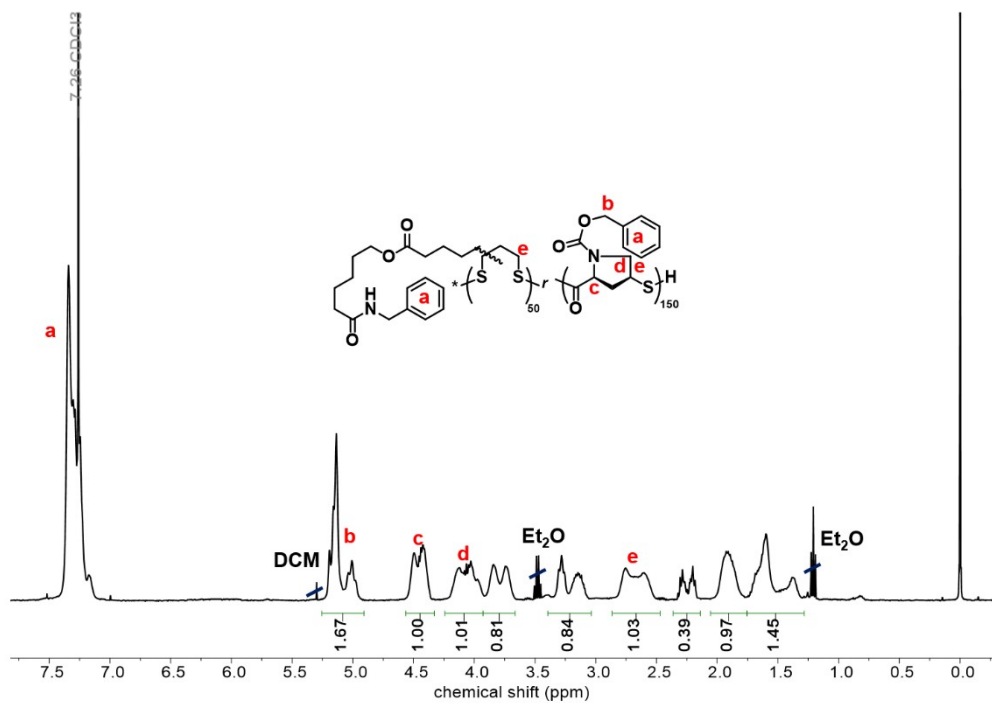
Figure S10. ^{1}H NMR spectrum of P(LpOCLNHBn$_{50}$-r-N^Z-PTE$_{150}$) (solvent: CDCl$_3$)
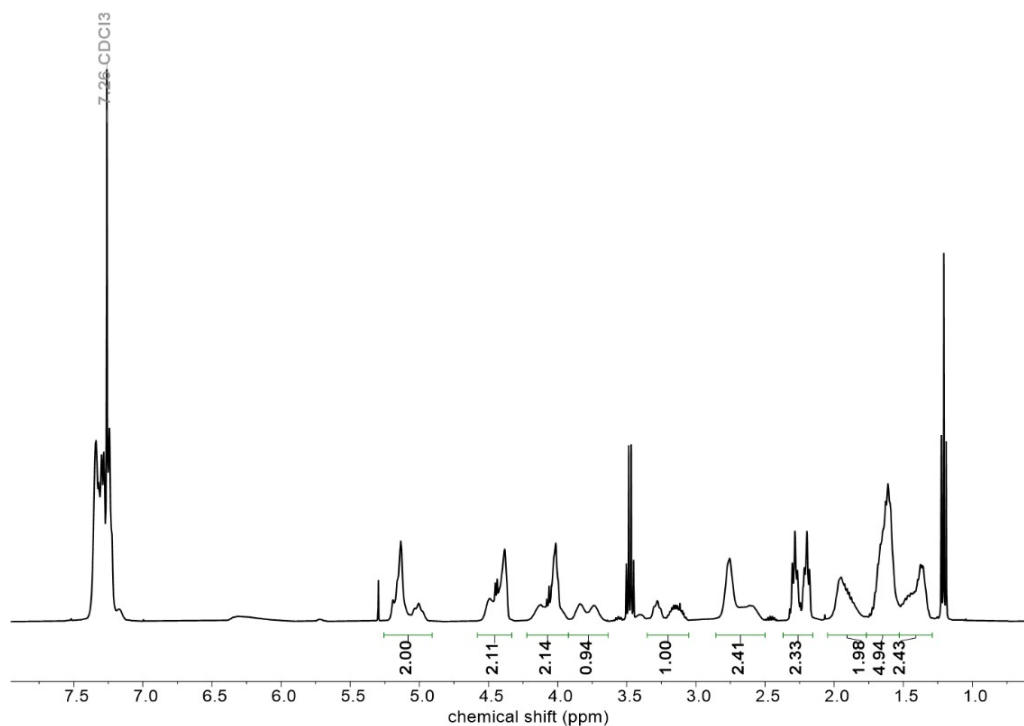
Figure S11. ^{1}H NMR spectrum of P(LpOCLNHBn$_{100}$-r-N^Z-PTE$_{100}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)

Figure S12. ^{1}H NMR spectrum of P(LpOCLNHBn$_{150}$-r-N^Z-PTE$_{50}$) (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)
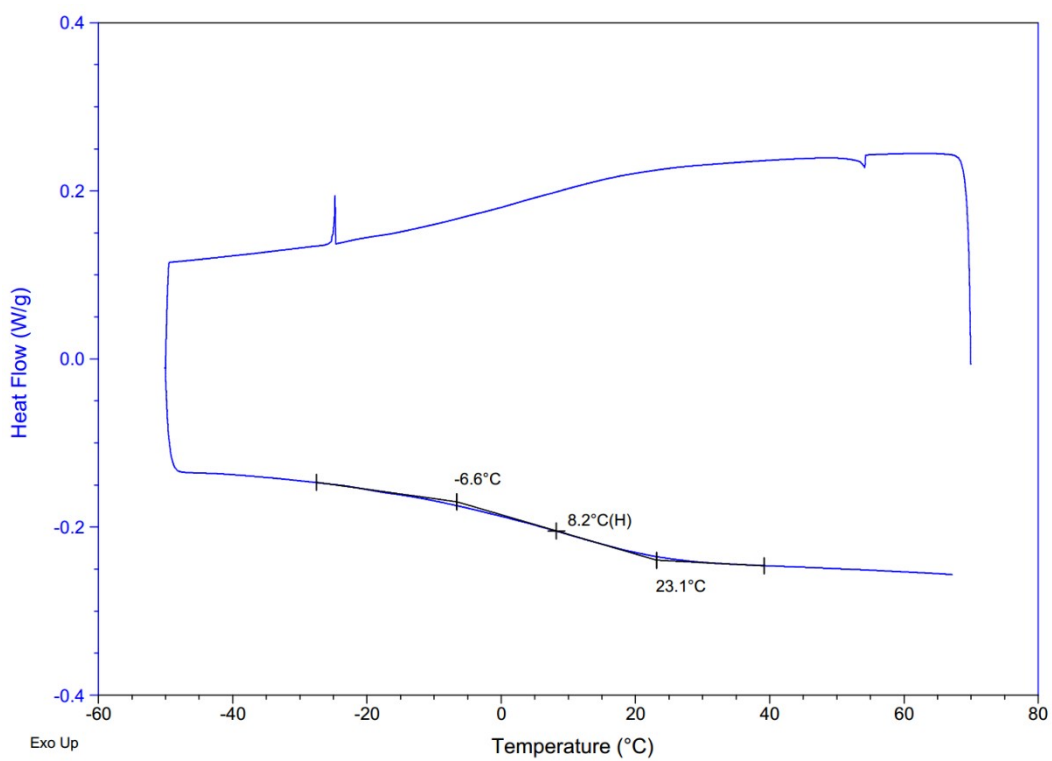
Figure S13. DSC curve of P(LpNHBn$_{240}$-*r*-N^{Z}-PTE$_{240}$)
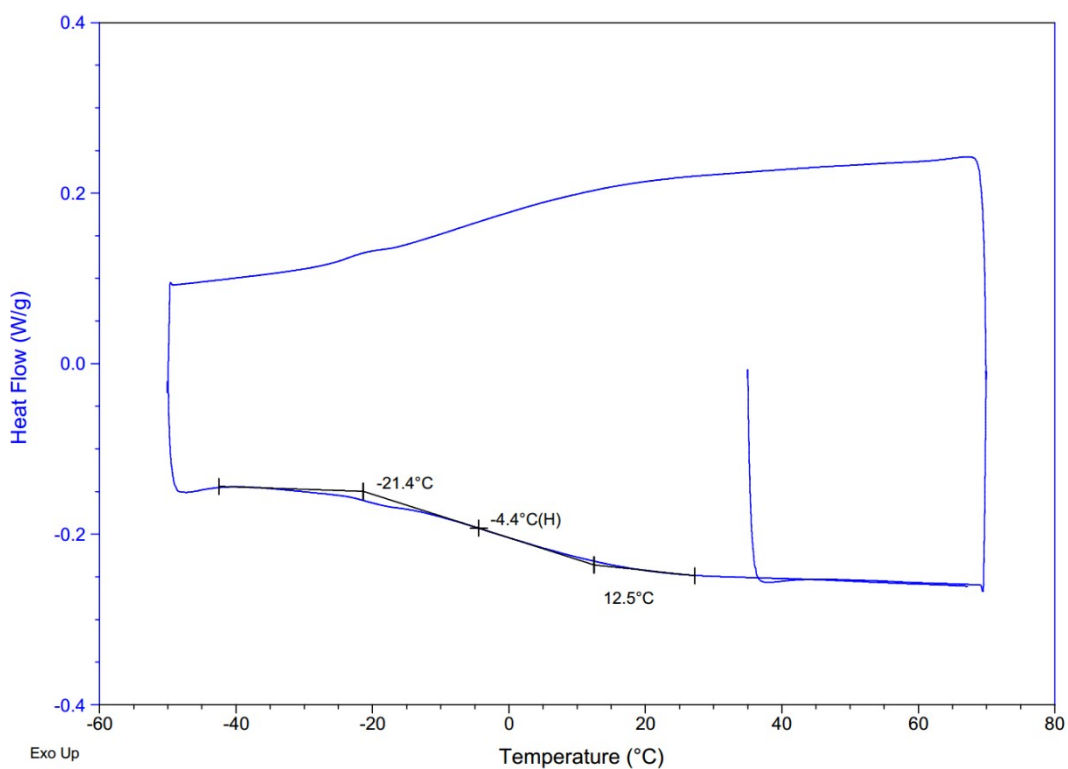
Figure S14. DSC curve of P(LpNHBn$_{240}$-*r*-N^{Z}-PTE$_{180}$)
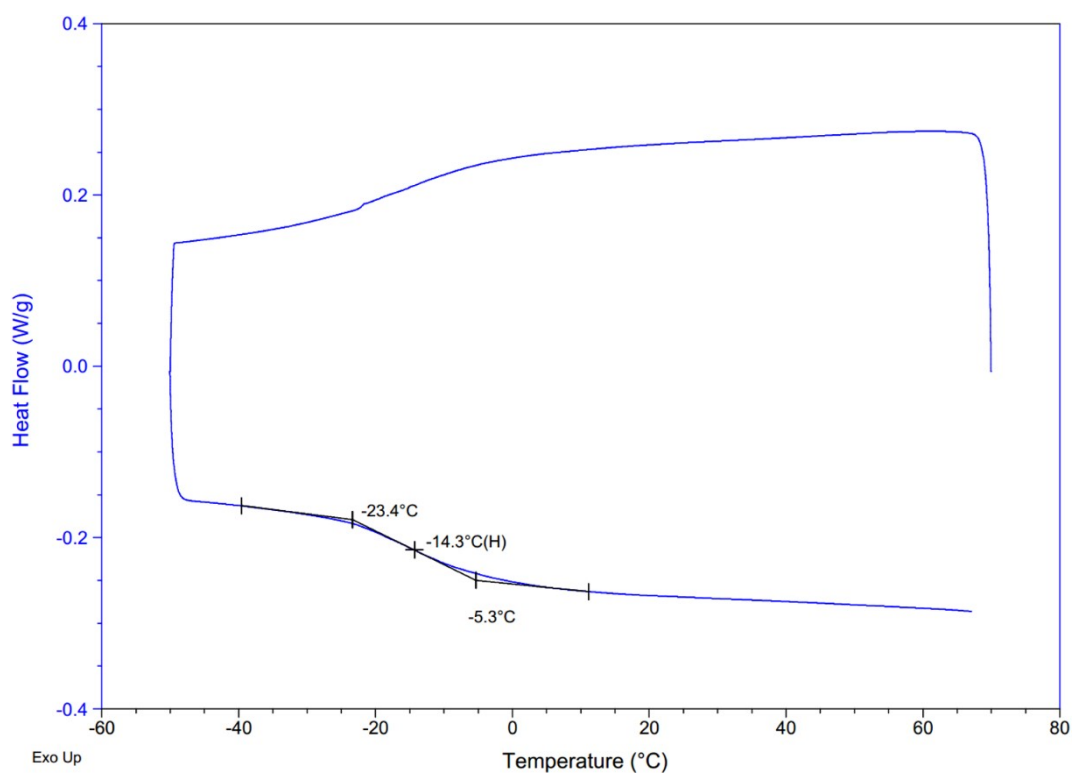
Figure S15. DSC curve of P(LpNHBn$_{240}$-r-N^Z-PTE$_{120}$)
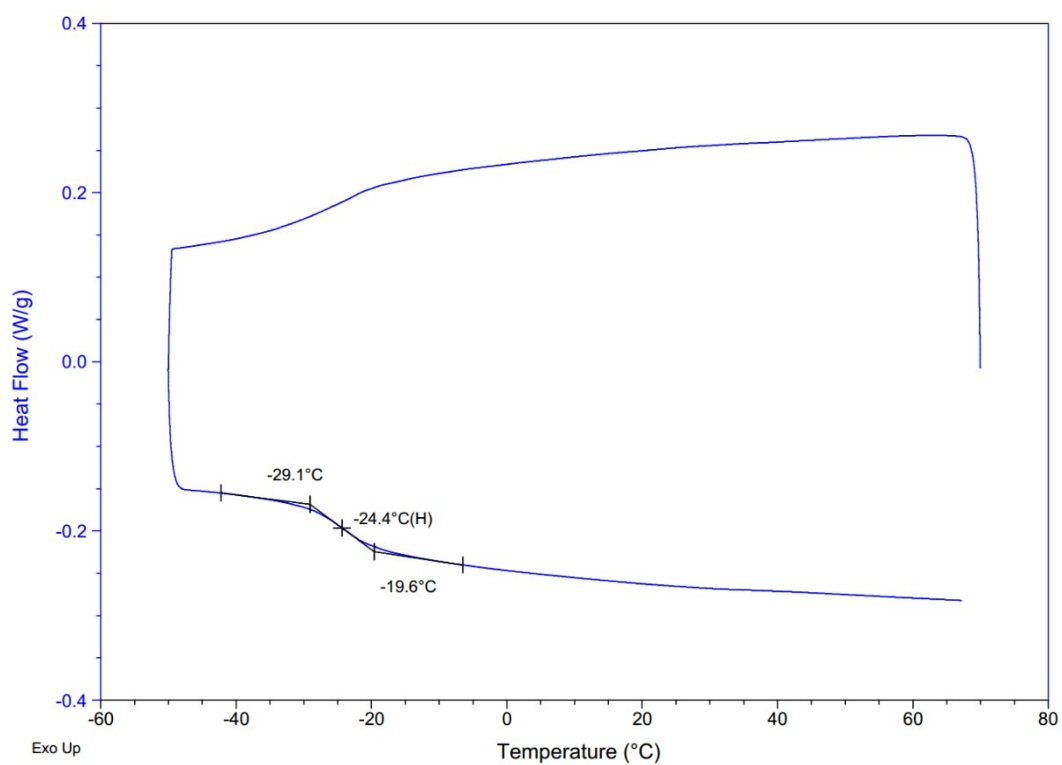
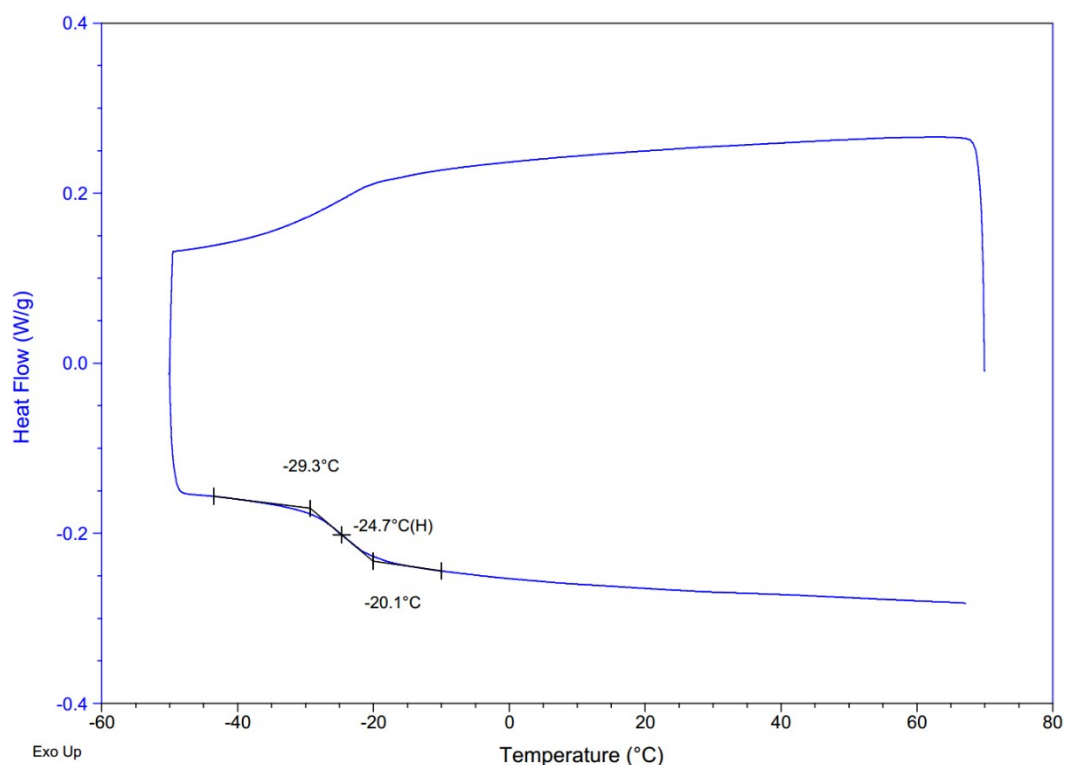Figure S16. DSC curve of P(LpNHBn$_{240}$-r-N^Z-PTE$_{100}$)

Figure S17. DSC curve of P(LpNHBn$_{240}$-r-N^Z-PTE$_{80}$)

DATA FOR QUASI-BLOCK COPOLYMERS
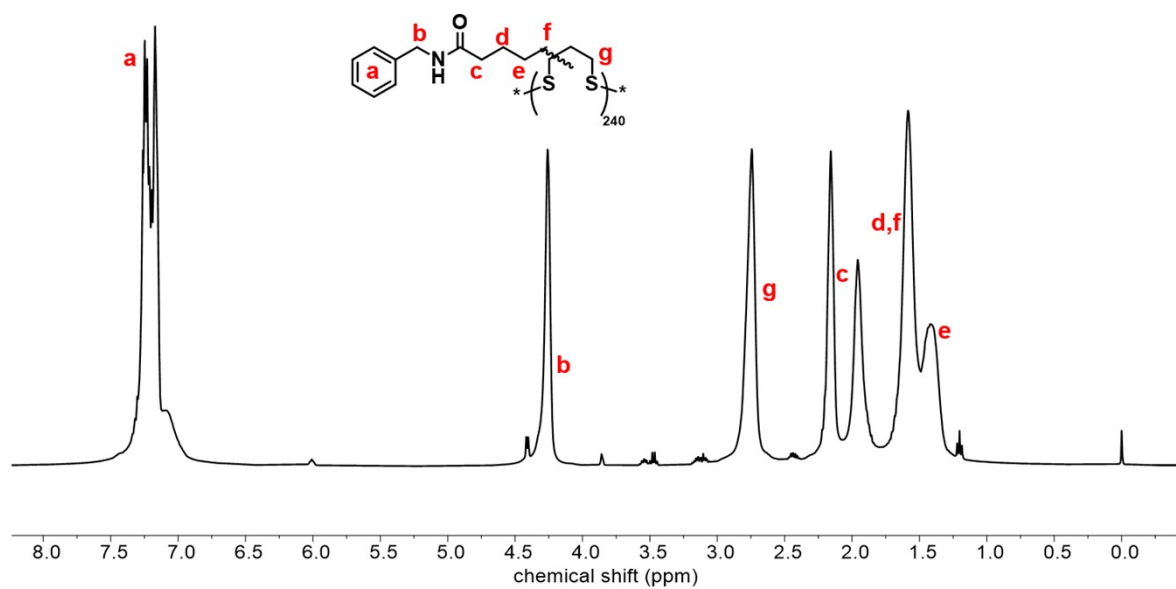
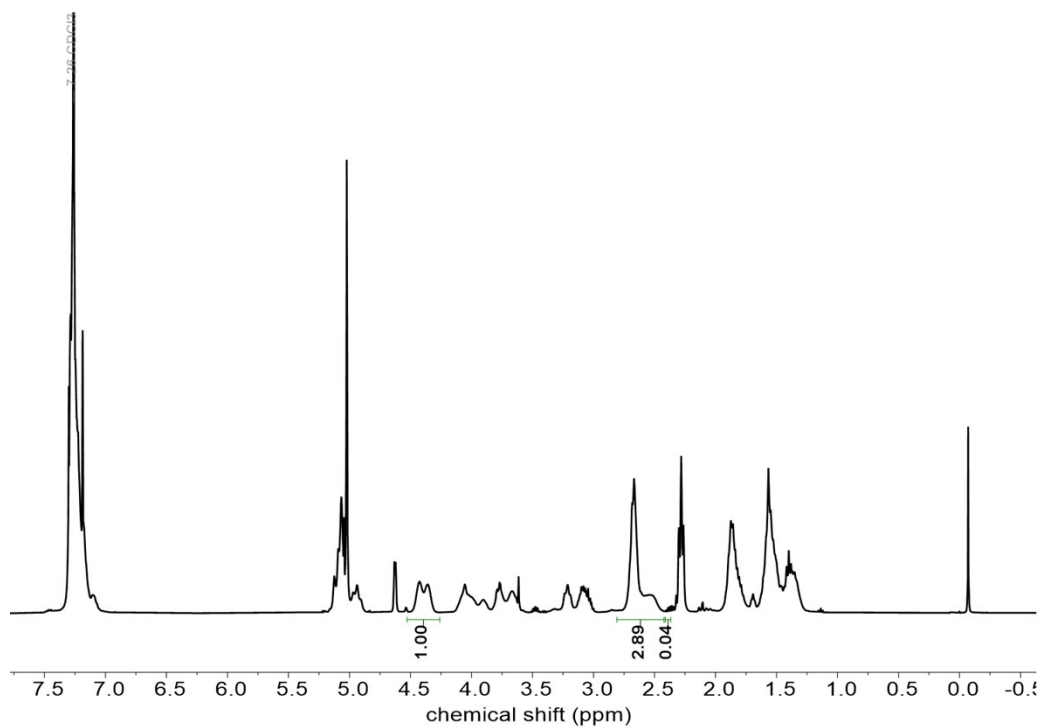Figure S18. ^{1}H NMR spectrum of PLpNHBn$_{240}$ (solvent: CDCl$_3$)

Figure S19. ^{1}H NMR spectrum of PLpNHBn$_{240}$-*b*-N^Z-PTE$_{240}$ (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)
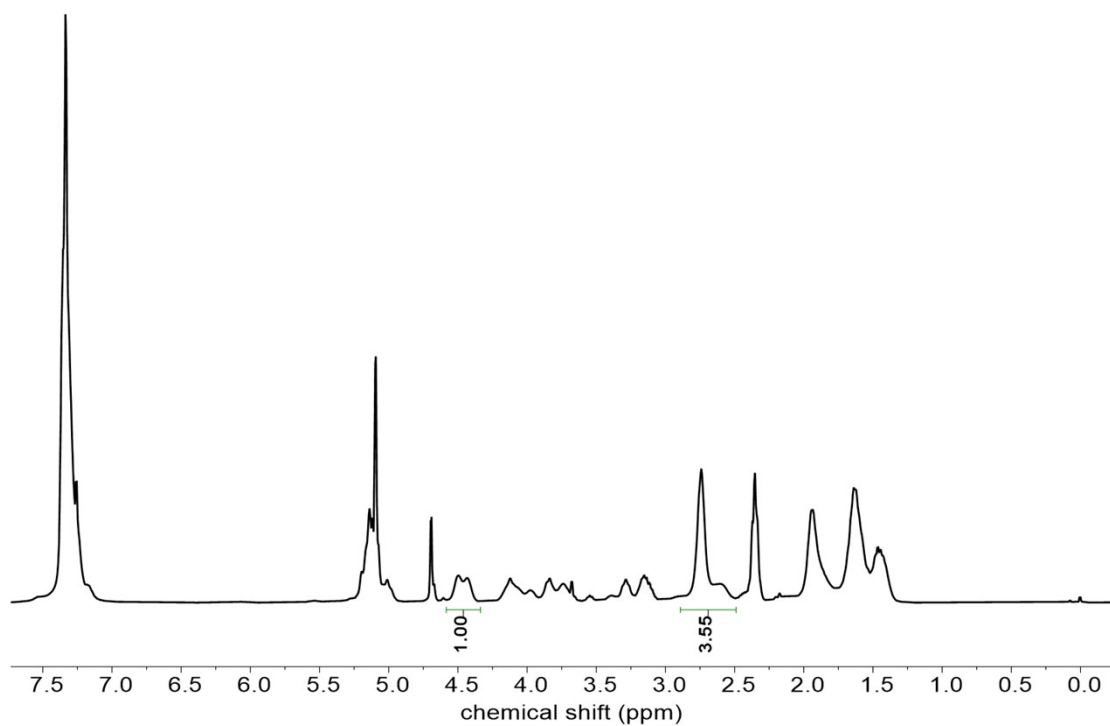
Figure S20. ^{1}H NMR spectrum of PLpNHBn$_{240}$-b-N^Z-PTE$_{180}$ (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)
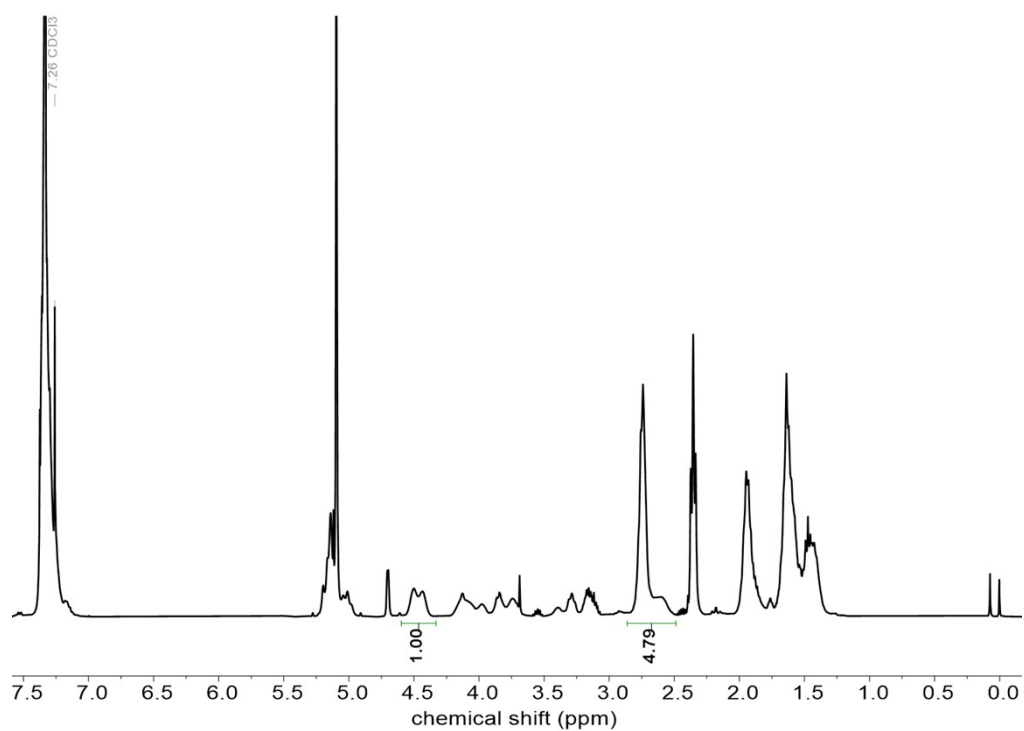

Figure S21. ^{1}H NMR spectrum of PLpNHBn$_{240}$-b-N^Z-PTE$_{120}$ (solvent: CDCl$_3$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)

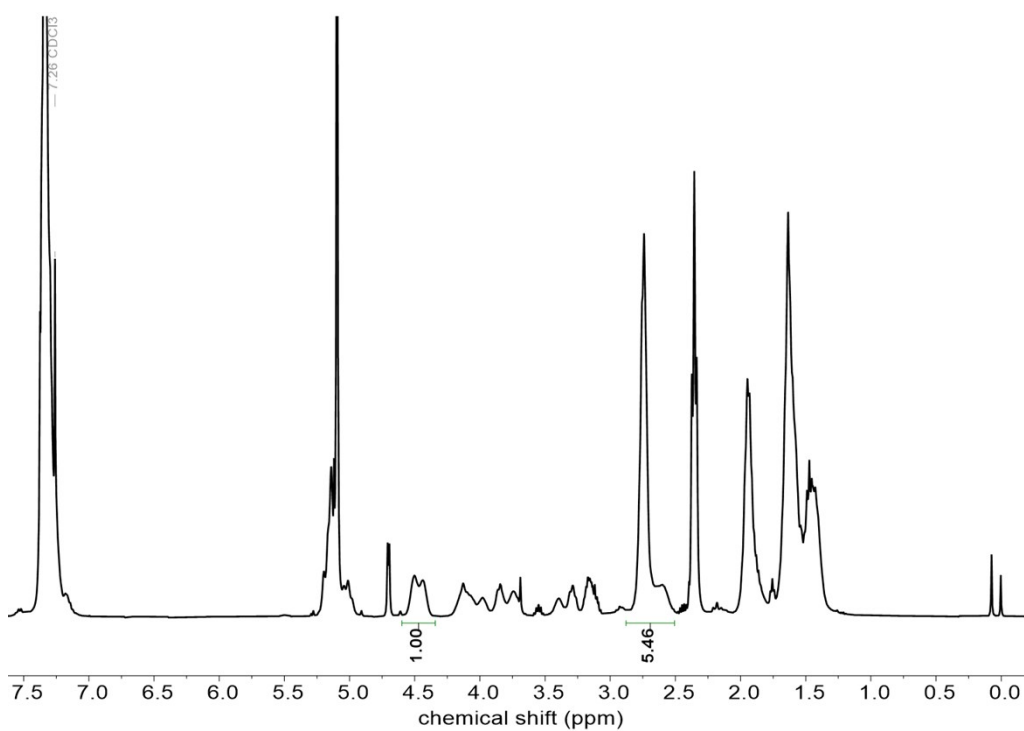Figure S22. ^{1}H NMR spectrum of PLpNHBn$_{240}$-b-N^{Z}-PTE$_{100}$ (solvent: CDCl$_{3}$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)
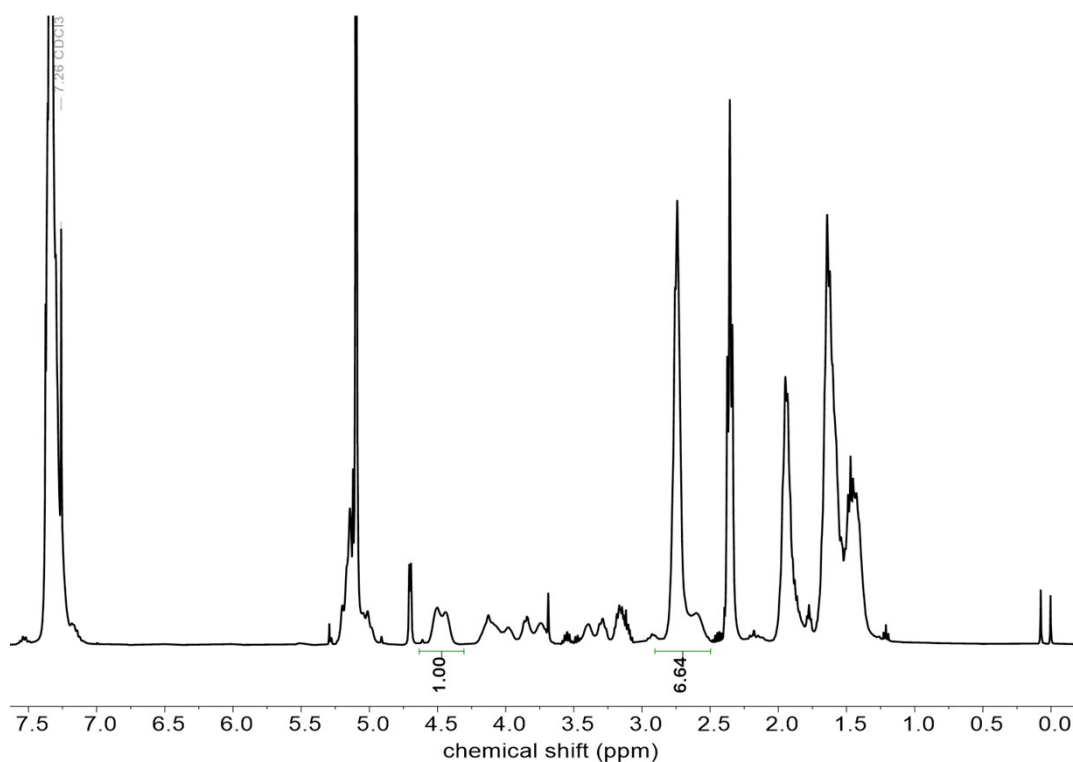

Figure S23. ^{1}H NMR spectrum of PLpNHBn$_{240}$-b-N^{Z}-PTE$_{80}$ (solvent: CDCl$_{3}$, attribution of typical peaks is the same with Figure S2, with only differences in the integrated areas)

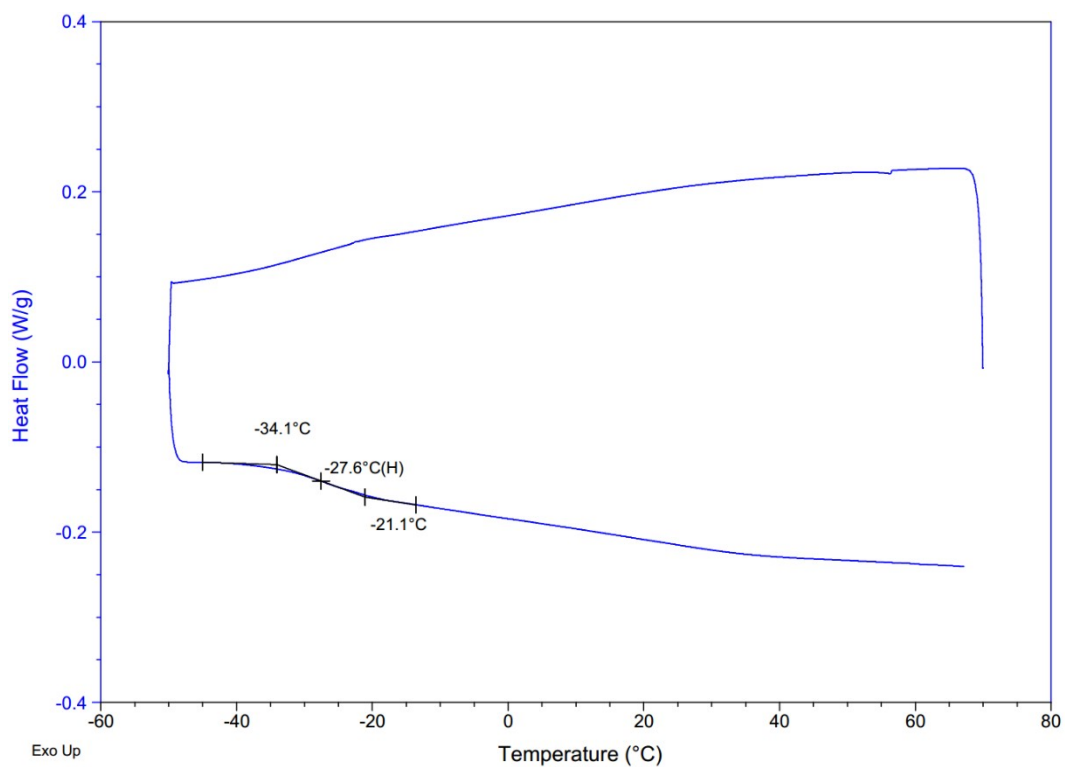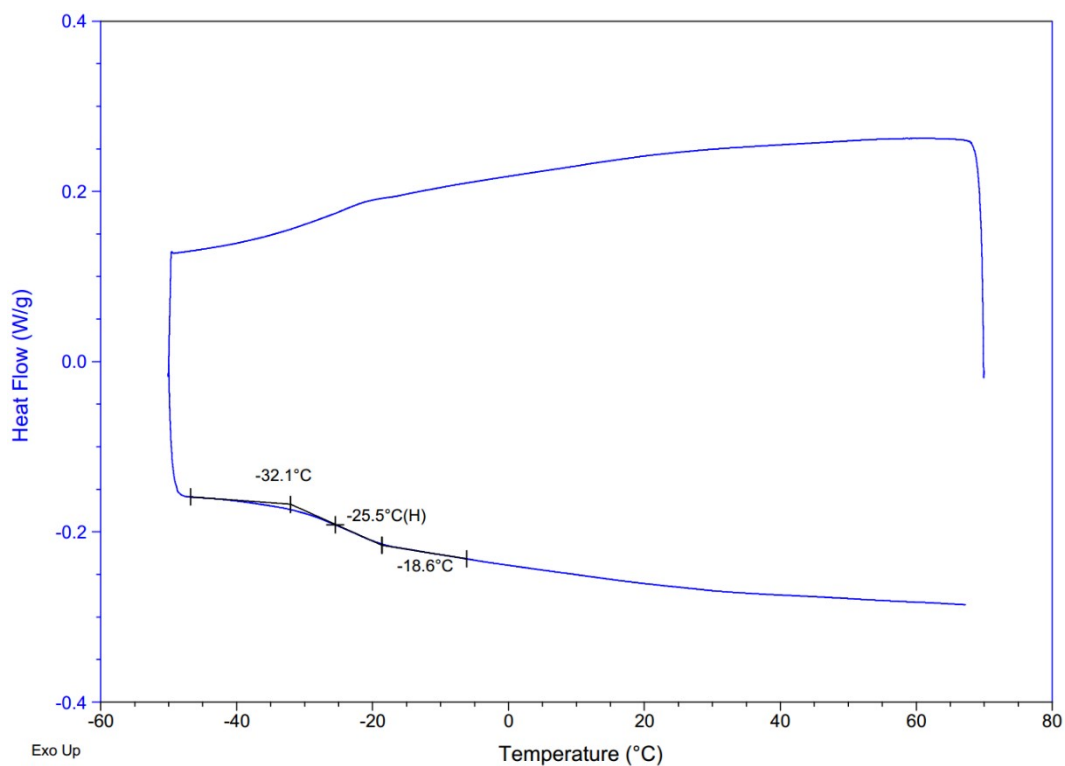Figure S24. DSC curve of PLpNHBn$_{240}$-b-N^Z-PTE$_{240}$

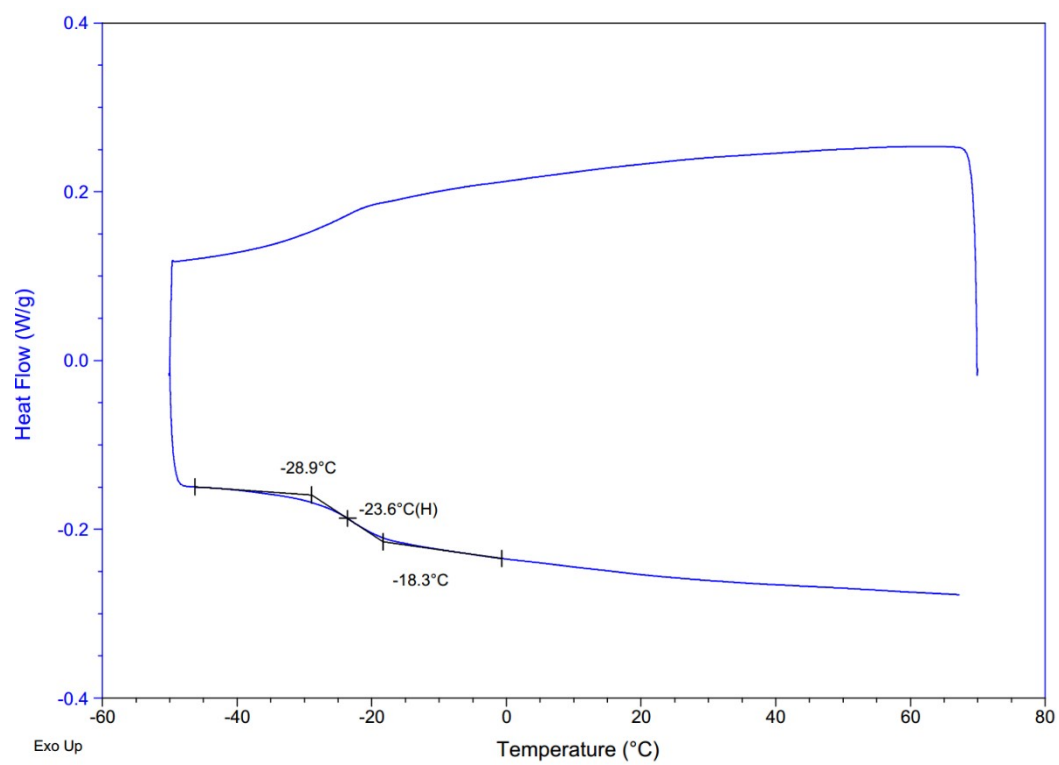Figure S25. DSC curve of PLpNHBn$_{240}$-b-N^Z-PTE$_{180}$

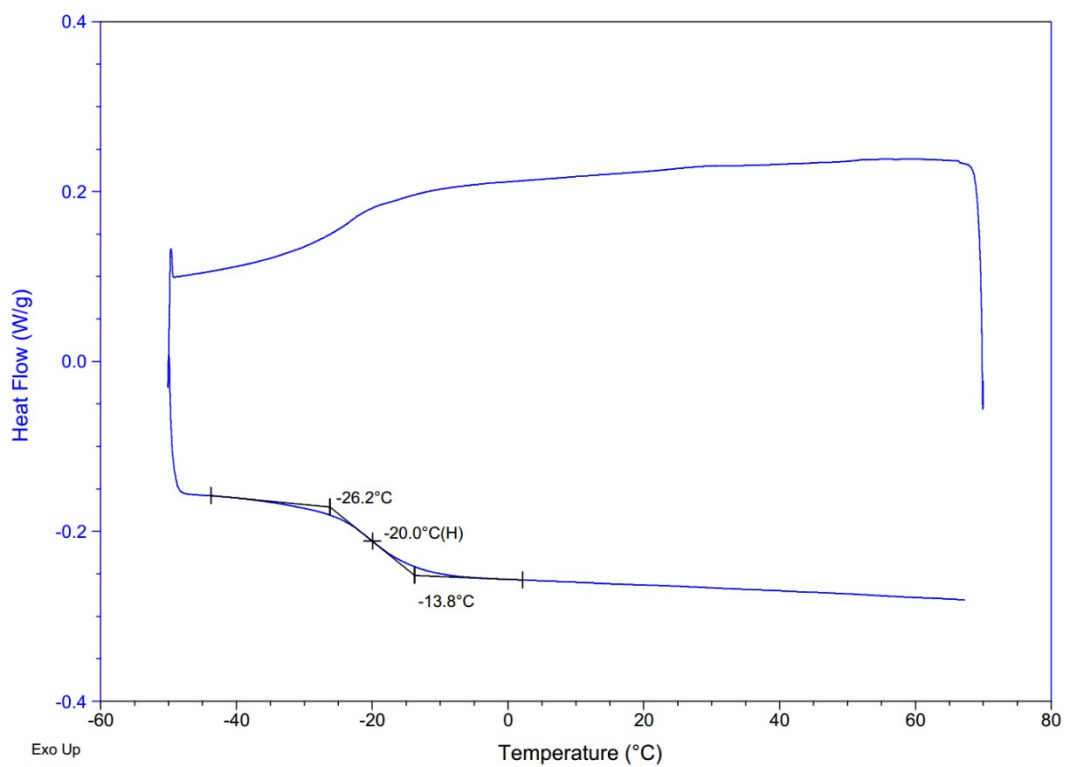Figure S26. DSC curve of PLpNHBn$_{240}$-b-N^Z-PTE$_{120}$
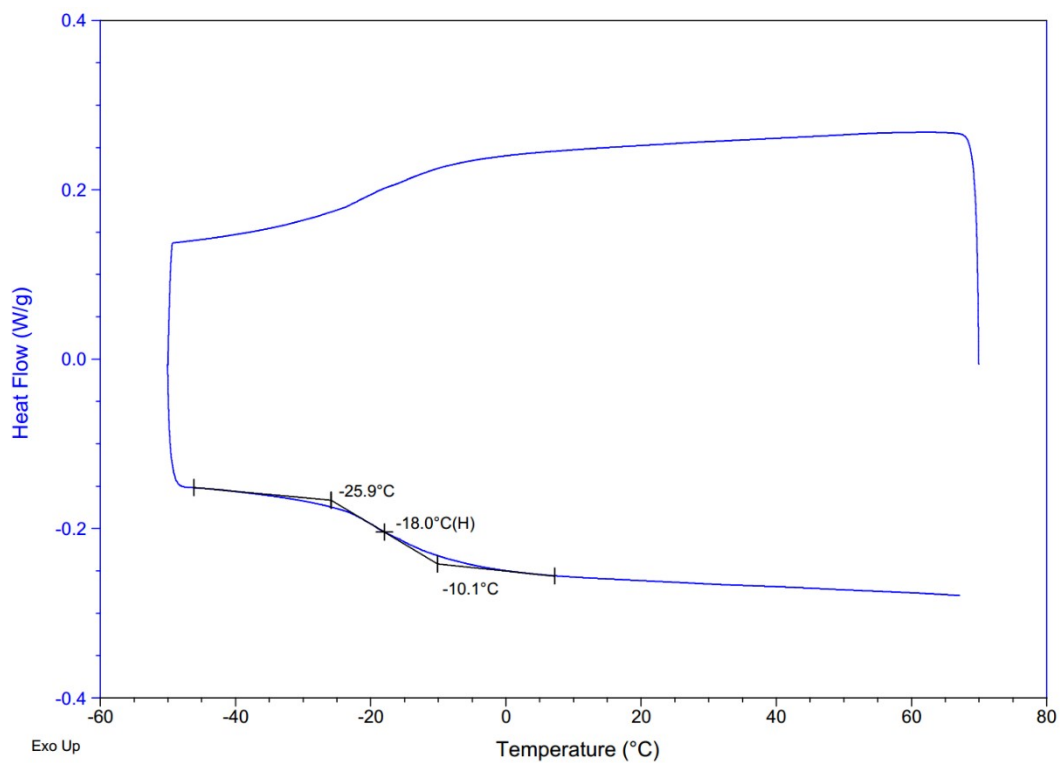
Figure S27. DSC curve of PLpNHBn$_{240}$-b-N^Z-PTE$_{100}$

COPOLYMERIAZTION RESULTS FOR SUPLEMENTARY ENTRIES

Table S1. Supplementary results of random copolymerization of N^Z-HPTL and LpNHBn[a]

Entry	[N^Z-HPTL]$_0$/ [LpNHBn]$_0$/ [BnSH]$_0$	Time/ hrs	$M_{n, SEC}$[b]/ kDa	$Đ$[c]	N^Z-HPTL Conv.[d]/ %	LpNHBn Conv.[d]/ %	T_g/ ^{o}C
1	25/75/1	6	17.0	1.39	89	76	-11.2
2	75/25/1	6	17.2	1.32	>90	68	10.3
3	150/50/1	18	34.8	1.33	>90	70	28.7
4	50/150/1	24	34.6	1.32	80	75	-10.8
5	--/240/1	48	53.7	1.29	--	72	-25.0

[a]All polymerizations were initiated with BnSH in DCM in a refrigerator at -10 ^{o}C, [M]$_0$ = [N^Z-HPTL]$_0$ + [LpNHBn]$_0$ = 2 mol/L, 2 equiv. Et$_3$N (vs. BnSH) was used to catalyze the polymerization; [b]number-average molecular weight, determined by SEC in THF mobile phase calibrated with polystyrene standard; [c]dispersity, determined by SEC; [d]monomer conversion, calculated from the integrations of characteristic peaks in ^{1}H NMR spectra.

Table S2. Quasi-block copolymerization results of N^Z-HPTL and LpNHBn[a]

Entry	[N^Z-HPTL]$_0$/ [LpNHBn]$_0$/ [EDT]$_0$	Time/ hrs	$M_{n, SEC}$[b]/ kDa	$Đ$[c]	N^Z-HPTL Conv.[d]/ %	LpNHBn Conv.[d]/ %	T_g/ ^{o}C
1	240/240/1	24+24	56.0	1.53	89	76	-27.6
2	180/240/1	24+18	46.9	1.54	90	78	-25.5
3	100/240/1	24+10	40.6	1.62	>90	72	-18.0
4[e]	240/240/1	8+24	62.2	2.17	>90	66	16.7
5[e]	180/240/1	8+24	60.0	2.17	>90	55	8.2

[a]All polymerizations were initiated with EDT in DCM in a refrigerator at -10 ^{o}C, [N^Z-HPTL]$_0$ = 2 mol/L, 2 equiv. Et$_3$N (vs. BnSH) was used to catalyze the polymerization; [b]number-average molecular weight, determined by SEC in THF mobile phase calibrated with polystyrene

standard; [c]dispersity, determined by SEC; [d]monomer conversion, calculated from the integrations of characteristic peaks in ^1H NMR spectra; [e]entry with a reversed N^Z-HPTL to LpNHBn feeding sequence, resulting in "soft-hard-soft" structures.
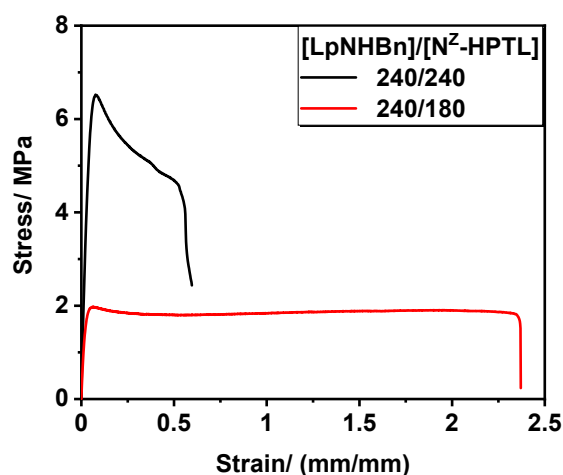

Figure S29. Overlay of stress-strain curves of bulk materials from quasi-block copolymers with varying N^Z-HPTL and LpNHBn ratios (entry 4-5, table S2)

REFERENCE

1   Henderson, L. C.; Altimari, J. M.; Dyson, G.; Servinis, L.; Niranjan, B.; Risbridger, G. P., A Comparative Assessment of alpha-Lipoic acid *N*-Phenylamides as Non-steroidal Androgen Receptor Antagonists both on and off Gold Nanoparticles. *Bioorg. Chem.* **2012,** *40* (1), 1-5.