Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supplementary Information

Synthesis of Peptide–Vinyl Polymer Multiblock Hybrids by Nitroxide-mediated Polymerization: Breaking the Limitations of Monomer Compatibility

Shin-nosuke Nishimura, Nobuyuki Higashi* and Tomoyuki Koga*

Department of Molecular Chemistry & Biochemistry, Faculaty of Science & Engineering, Doshisha University, Kyotanabe, Kyoto 610-0321, Japan

Table of Contents

Experimental Procedures

Materials

Solvents of analytical grade were used unless otherwise stated. *N*,*N*-Dimethlylformamide (DMF), *N*-methyl-2-pyrrolidone, methanol, trifluoroacetic acid (TFA), tetrahydrofuran (THF), dichloromethane, diethyl ether, hexane, cyclohexane, ethyl acetate, triethylamine (TEA), piperidine, styrene (St), *N*-isopropylacrylamide (NIPAM), acryloylchloride, 2-bromo-2-methylpropanoyl bromide, sodium hydroxide (NaOH), 12 M-hydrochloric acid, 25%-ammonia water, copper(II) acetate ($Cu(OAc)_2$), hydroquinone, 2,2'-azobisisobutylonitrile (AIBN), sodium sulfate anhydrous (anhydrous Na_2SO_4), magnesium sulfate anhydrous (anhydrous $MgSO_4$), DMSO-d_6, acetone-d_6 and chloroform-*d* were purchased from Nacalai Tesque. DMF was used after purification with distillation. Tetrakis(triphenylphosphine)palladium(0), phenylsilane, triisopropylsilane (TIS), *N*-Boc-ethylenediamine (*N*-Boc-*EDA*), copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$), 2-methyl-2-nitropropane, isobutylaldehyde, ammonium chloride (NH_4Cl), 4-iodobenzoic acid, potassium *tert*-butoxide, chloroform and acrylonitrile (AN) were purchased from Tokyo Chemical Industry. LiBr, Cu(0) powder (99.9%, ϕ=75 μm), zinc powder (99.9%, ϕ=75-150 μm), thionyl chloride, *N*,*N*'-diisopropyl carbodiimide (DIPC), super dehydrated THF, stabilizer free (THF_{SD}), 1 M-*i*PrMgBr THF solution, ethyl acrylate (EA), *tert*-butyl acrylate (*t*BuA), ethylenediaminetetraacetic acid disodium dihydrate (EDTA) and *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) were purchased from Wako Pure Chemical. Fmoc-L-Leu, Fmoc-L-Asp-β-allyl ester (Fmoc-L-Asp(OAll)), Fmoc-NH-SAL MBHA resin (resin loading 0.67 mmol/g), 1-hydroxybenzotriazole anhydrous (HOBt) and H-Ala-OMe hydrochloride were purchased from Watanabe Chemical Industries. 2,5-Dihydroxybenzoic acid (DHBA), 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (Me_4Cyclam) and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, free radical (TIPNO) were purchased from Sigma Aldrich. Fmoc-8-amino-3,6-dioxaoctanoic acid (Fmoc-*deg*-COOH) was purchased from Combi-Blocks. St, NIPAM, EA and *t*BuA were purified by being passed through activated alumina prior to use. AN was distilled in the presence of hydroquinone to remove inhibitors prior to use. The others were used as received.

Measurements

^{1}H NMR spectra were acquired using a JEOL JNM-ECA500 (JEOL Resonance) spectrometer (500 MHz). ESR spectrum was obtained using a JEOL JET-TE200 spectrometer in $CHCl_3$ at -196˚C. The values of M_n and $Đ$ (M_w/M_n) of the block copolymers were determined by size exclusion chromatography (SEC) on a JASCO LC-net II/AD (JASCO Ltd.) equipped with a refractive index (RI) detector. Block copolymers **P1**-**P8**, **P10** were analyzed in THF (flow rate: 1 mL/min, temperature: 40 ˚C, column: GF-710F), and **P9** was analysed in DMF (containing 10 mM LiBr) (flow rate: 0.6 mL/min, temperature: 40 ˚C, column: TSKgel α-4000). Polystyrenes and poly(methyl methacrylate)s were purchased from GL Sciences Inc. and used as the calibration standards. Direct analysis in real-time MS (DART MS) analysis was carried out on a DART-SVP (Ionsense Inc.). Matrix-assisted laser desorption ionization-time-of-flight MS (MALDI-TOF MS) analyses were carried out on an Autoflex speed (Bluker Daltonics) using DHBA as a matrix. Transmission-FTIR spectra were measured with a FT/IR-4600 (JASCO Ltd.) using a deuterated L-alanine triglycine sulphate (DLATGS) detector (resolution: 4 cm^{-1}, number of scan: 8). CD spectra were recorded on a J-820 spectropolarimeter (JASCO Ltd.) under N_2 atmosphere. Experiments were performed in a quartz cell with a 1 mm path length over the range of 190-250 nm at 25˚C (sample concentration: 0.01 wt%).

Synthesis of (9*H*-fluoren-9-yl)methyl *tert*-butyl ethane-1,2-diyldicarbamate (*N*-Fmoc-*N*'-Boc-*EDA*)

N-Boc-*EDA* 10.0 g (62.4 mmol), Fmoc-OSu 23.16 g (68.4 mmol) and TEA 9.56 mL (68.4 mmol) were dissolved in 500 mL chloroform and stirred for 24 h at room temperature. The reaction mixture was washed three times with 0.1 M HCl_{aq} (100 mL), 0.1 M $NaOH_{aq}$ (100 mL) and distilled water (100 mL), respectively. The organic layer was collected and dried over anhydrous Na_2SO_4. The mixture was concentrated in *vacuo* to give a crude. The crude was washed with cyclohexane/methanol (v/v=4/1) (100 mL) and dried to give pure *N*-Fmoc-*N*'-Boc-*EDA* as a white-colored solid.
Yield: 18.95 g (79.4 %)
^{1}H NMR (acetone-d_6, TMS) (Figure S1): 1.46 ppm (-OC(CH_3)$_3$, 9H), 3.25 ppm (-NH(CH_2)$_2$NH-, 4H), 4.25 ppm (-OCH$_2$C*H*<, 1H), 4.38 ppm (-OCH_2CH<, 2H), 7.35-7.90 ppm (Fmoc, 8H, aromatic ring; -N*H*(CH$_2$)$_2$N*H*-, 2H).

Synthesis of 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)ethan-1-aminium chloride (*N*-Fmoc-*EDA*•HCl (1))

N-Fmoc-*N*'-Boc-*EDA* 18. 95 g (49.5 mmol) was dissolved in 12 M HCl_{aq}/methanol (v/v=1/2) mixed solution (300 mL) and stirred for overnight at room temperature. The reaction solution was concentrated and filtrated. The residue was washed with acetone to give pure *N*-Fmoc-*EDA*•HCl (**1**) as a white-colored solid.
Yield: 13.63 g (86.3 %)
^{1}H NMR (DMSO-d_6, TMS) (Figure S2): 2.83 ppm (-C$H_2$$NH_3^+$, 2H), 3.26 ppm (-NHC$H_2CH_2$$NH_3^+$, 2H), 4.29 ppm (-OCH$_2$C*H*<, 1H), 4.38 ppm (-OCH_2CH<, 2H), 7.37-8.06 ppm (Fmoc, 8H, aromatic ring; -N*H*(CH$_2$)$_2$$NH_3^+$, 1H; -NH(CH$_2$)$_2NH_3^+$, 3H).

Synthesis of (9*H*-fluoren-9-yl)methyl (2-(2-bromo-2-methylpropanamido)ethyl)carbamate (Fmoc-*EDA*-Br (2))

Compound **1** 13.63 g (42.7 mmol) and TEA 13.15 mL (94.0 mmol) were dissolved in 300 mL chloroform. 2-Bromo-2-methylpropanoyl bromide 6.33 mL (51.2 mmol) was added to the **1**-solution and stirred for 6 h over an ice bath. The reaction mixture was concentrated in *vacuo,* and ethyl acetate (200 mL) was added. The solution was washed three times with 1M HCl_{aq} (100 mL), 1 M $NaOH_{aq}$ (100 mL) and distilled water (100 mL), respectively. The organic layer was collected and dried over anhydrous Na_2SO_4. The solution was concentrated to give pure Fmoc-*EDA*-Br (**2**) as a white-colored solid.
Yield: 14.83 g (80.5%)
^{1}H NMR ($CDCl_3$, TMS) (Figure S3): 1.93 ppm (-C(=O)C(CH_3)$_2$Br, 6H), 3.40 ppm (-NH(CH_2)$_2$NH-, 4H), 4.22 ppm (-OCH$_2$C*H*<, 1H), 4.41 ppm (-OCH_2CH<, 2H), 7.08-7.80 ppm (Fmoc, 8H, aromatic ring; -N*H*(CH_2)$_2$N*H*-, 2H).

Synthesis of *N*-*tert*-butyl-α-isopropylnitrone (3)

2-Methyl-2-nitropropane 10 g (97.0 mmol), isobutylaldehyde 8.81 mL (97.0 mmol), and ammonium chloride 5.71 g (106.8 mmol) were dissolved in 200 mL water and 100 mL diethyl ether over an ice bath. Then, zinc powder 25.37 g (388 mmol) was added to the solution in small portions over 1 h with stirring. After the addition, the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was filtered through a sintered glass filter, and the residue was washed with methanol (100 mL). The organic solvent in the filtrate was removed *in vacuo*. The objective nitrone was extracted three times with dichloromethane (50 mL) from a water solution. The organic solution was dried over anhydrous Na_2SO_4. The mixture was concentrated *in vacuo* to give pure *N*-*tert*-butyl-α-isopropylnitrone (**3**) as a colorless liquid.
Yield: 10.05 g (72.3%)
^{1}H NMR ($CDCl_3$, TMS) (Figure S4): 1.11 ppm (-CH(CH_3)$_2$, 6H), 1.48 ppm (-C(CH_3)$_3$, 9H), 3.16 ppm (-C*H*(CH_3)$_2$, 1H), 6.61 ppm (-N^+(-O^-)=C*H*-, 1H).

Synthesis of *tert*-butyl 4-iodobenzoate (4)

4-Iodobenzoic acid 25.0 g (100.8 mmol) and thionyl chloride 21.4 mL (302.4 mmol) were dissolved in ethyl acetate/toluene (v/v=1/1) mixed solution (40 mL) and reacted for 4 h under reflux condition. The excess thionyl chloride and solvent were removed from the reaction solution in *vacuo* to give 4-iodobenzoyl chloride as a pale yellow-colored solid. The resulting product was used in the next step without purification. The 4-iodobenzoyl chloride was dissolved in 50 mL THF. Potassium *tert*-butoxide 12.5 g (111.6 mmol) was dissolved in 350 mL THF and added dropwise to the THF solution of 4-iodobenzoyl chloride over an ice bath, and then the reaction mixture was stirred for 1h. A cooled pure water (65 mL) was slowly added to the reaction solution to quench excess potassium *tert*-butoxide. The mixture was concentrated in *vacuo,* and a pure water (200 mL) was added. The crude product was extracted from the water solution with diethylether (200 mL). The organic solution was dried over anhydrous Na_2SO_4 and concentrated to give a crude. The crude was passed through a silica gel column using hexane/diethylether mixture solution (v/v=20/1) as an eluent (R_f = 0.61). The obtained solution was concentrated to give pure *tert*-butyl 4-iodobenzoate (**4**) as a pale yellow-colored oil.
Yield: 19.7 g (64.1%)
^{1}H NMR ($CDCl_3$, TMS) (Figure S5): 1.58 ppm (*tert*-butyl, 9H), 7.70 and 7.84 ppm (phenyl, 4H).

Synthesis of 2,2,5-trimethyl-4-*p*-*tert*-butyl-benzoate-3-azahexane-3-nitroxide, free radical (TIPNO-COO*t*Bu, free radical (5))

All glassware was well dried in a drying machine at 70°C prior to use. THF_{SD} (200 mL) was added to a two-neck flask and cooled to −30°C with stirring. Next, a 1 M-*i*PrMgBr THF solution 76 mL (76.0 mmol *i*PrMgBr) was added. Subsequently, **4** 15.41 g (50.7 mmol) was dissolved in THF_{SD} (50 mL) and added drop-wise to the Grignard solution over 10 min. After stirring for 1 h at −30°C, a THF_{SD} solution (30 mL) of **3** (10.16 g (71.0 mmol)) was added drop-wise to the Grignard solution over 10 min and reacted for 12 h at −30°C. Saturated NH_4Cl_{aq} (22.5 mL) and pure water (150 mL) were added slowly to the reaction mixture to quench the excess Grignard agent and form two clear layers. The organic layer containing a precursor of the objective molecule was collected. The remaining precursor was extracted from the aqueous layer three times with diethyl ether (50 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The mixture was concentrated *in vacuo* and dissolved in methanol (150 mL) and 25%-ammonia water (22.5 mL). $Cu(OAc)_2$ 135 mg (0.74 mmol) was added to the mixture and stirred for 2 h at room temperature with air bubbling. The reaction mixture was concentrated *in vacuo*, dissolved in a hexane/ethyl acetate (v/v=1/2) solution (100 mL), and washed three times with 0.1 M $EDTA_{aq}$ (100 mL, pH 8.0) and pure water, respectively. The organic layer was collected and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give an orange crude product. The crude product was passed through a silica gel column using hexane / ethyl acetate / dichloromethane (v/v/v=10/1/1) solution as an eluent (R_f = 0.47). The obtained solution was concentrated to give the pure TIPNO-COO*t*Bu, free radical (**5**) as an orange-colored low-melting solid.
Yield: 10.29 g (63.3%)
DART-MS (Figure S6A): found $[M+H]^+$ (calcd. $[M+H]^+$); *m*/*z* 321.2 (321.5).
ESR ($CHCl_3$, -196˚C, Freq.: 9.148 GHz) (Figure S6B): *g* value=2.011.

Synthesis of *tert*-butyl 4-(11-(*tert*-butyl)-1-(9*H*-fluoren-9-yl)-9,9,13-trimethyl-3,8-dioxo-2,10-dioxa-4,7,11-triazatetradecan-12-yl)benzoate (Fmoc-NH-TIPNO-COO*t*Bu (6))

Compound **2** 2.00 g (4.64 mmol), **5** 1.49 g (4.64 mmol), Cu(0) powder 0.296 g (4.64 mmol), $Cu(OTf)_2$ 33.7 mg (0.112 mmol), Me_4Cyclam 72.3 mg (0.376 mmol) and methanol (50 mL) were mixed together in a test glass tube. The solution was

deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixture was placed in a preheated oil bath at 60 °C for 24 h. After the reaction, the reaction mixture was added to ethyl acetate (200 mL) and washed three times with 0.1 M $EDTA_{aq}$ (100 mL, pH 8.0), 0.1 M HCl_{aq} and distilled water (100 mL), respectively. The collected organic layer was dried with anhydrous Na_2SO_4. After evaporation of the solvent, a crude objective was obtained. The crude was purified by a silica gel column chromatography using hexane/diethylether/dichloromethane (v/v/v=2/1/1) as an eluent (R_f=0.32). Finally, the objective Fmoc-NH-TEMPO-COO*t*Bu (**6**) was obtained after removal of the solvent as a white-colored solid.
Yield: 1.97 g (63.2 %).
^{1}H NMR (acetone-d_6, TMS) (Figure S7): 0.45 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.98 ppm (>NC(CH_3)$_3$, 9H), 1.23 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 1.58 ppm (-OC(CH_3)$_3$, 9H), 1.65 ppm (>C(CH_3)$_2$, 6H), 2.14 ppm (>CHC*H*(CH$_3$)$_2$, 1H), 3.22 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H), 3.34 ppm (-OC(=O)NHCH$_2$CH_2NH-, 2H), 3.68 ppm (>C*H*CH(CH$_3$)$_2$, 1H), 4.20 ppm (-OCH$_2$C*H*<, 1H), 4.32 ppm (-OCH_2CH<, 2H), 6.42 ppm (-OC(O)N*H*(CH$_2$)$_2$NHC(O)-, 1H), 7.17-7.95 ppm (Fmoc, 8H, aromatic ring; TIPNO, 4H, aromatic ring; -NH(CH$_2$)$_2$N*H*-, 1H).

Synthesis of 4-(11-(*tert*-butyl)-1-(9*H*-fluoren-9-yl)-9,9,13-trimethyl-3,8-dioxo-2,10-dioxa-4,7,11-triazatetradecan-12-yl)benzoic acid (Fmoc-NH-TIPNO-COOH (7))

Compound **6** 1.20 g (1.79 mmol) was dissolved in TFA/dichloromethane/TIS (v/v/v=8.5/1/0.5) (30 mL) and stirred at room temperature for 12 h. After the reaction, the solvent was removed in *vacuo* to give a crude. Finally, the objective Fmoc-NH-TIPNO-COOH (**7**) was obtained by reprecipitation from acetone/hexane system as a white-colored solid.
Yield: 1.05 g (95.2 %).
^{1}H NMR (DMSO-d_6, TMS) (Figure S8): 0.36 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.88 ppm (>NC(CH_3)$_3$, 9H), 1.14 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 1.44 and 1.51 ppm (>C(CH_3)$_2$, 6H), 1.98 ppm (>CHC*H*(CH$_3$)$_2$, 1H), 3.00 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H), 3.17 ppm (-OC(=O)NHCH$_2$CH_2NH-, 2H), 3.60 ppm (>C*H*CH(CH$_3$)$_2$, 1H), 4.19 ppm (-OCH$_2$C*H*<, 1H), 4.28 ppm (-OCH_2CH<, 2H), 7.16-7.94 ppm (Fmoc, 8H, aromatic ring; TIPNO, 4H, aromatic ring; -N*H*(CH$_2$)$_2$N*H*-, 2H), 12.75 ppm (-COOH, 1H).

Synthesis of cyclic tetraleucine NMP initiator

Cyclic tetraleucine peptide initiator was prepared by SPPS using Fmoc chemistry. The target sequence (linear peptide) was constructed on Fmoc-NH-SAL MBHA resin by using Fmoc-L-Leu, Fmoc-L-Asp(OAll), Fmoc-8-amino-3,6-dioxaoctanoic acid (Fmoc-*deg*-COOH), Fmoc-NH-TIPNO-COOH (3 equiv), 1-hydroxybenzotriazole anhydrous (HOBt) (3 equiv) and 1,3-diisopropylcarbodiimide (DIPC) (3 equiv) in DMF for coupling, and piperidine(20 vol%)/DMF for Fmoc removal. Deprotection of the allyl group of the Asp residue was carried out on resin through treatment with tetrakis(triphenylphosphine)palladium(0) (0.1 equiv) and phenylsilane (10 equiv) in dichloromethane for 3 h at room temperature under a N_2 atmosphere. Cyclization reaction was then carried out on the resin in DMF for 6 h together with HOBt (3 euqiv) and DIPC (3 equiv). After cyclization, a resultant peptide was cleaved from the resin by treatment with TFA/dichloromethane/TIS (v/v/v=8.5/1/0.5) for 4 h. The obtained cyclic peptide (white-colored solid) was purified by repeated precipitation from a DMF/diethyl ether system, and subsequently identified by MALDI-TOF MS and ^{1}H NMR analyses.
MALDI-TOF MS (Figure 1A): found $[M+H]^+$ (calcd. $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$); **1**: 1233.68 (1233.57, 1255.56, 1271.67).
^{1}H NMR (DMSO-d_6, TMS) (Figure 1B): 0.32 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.75-0.92 ppm (>NC(CH_3)$_3$, 9H; Leu, δ-CH_3, 24H), 1.11 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 1.34-1.61 ppm (>C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H), 1.95 ppm (>CHC*H*(CH$_3$)$_2$, 1H), 2.46 ppm (Asp, β-CH_2, overlapped with DMSO), 3.05 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H), 3.11-3.28 ppm (-OC(=O)NHCH$_2$CH_2NH-, 2H; -NHCH_2CH$_2$O-, 4H), 3.34-3.64 ppm (-O(CH_2)$_2$O-, 8H; >C*H*CH(CH$_3$)$_2$, 1H), 3.88 ppm (-NHCH$_2$CH_2O-, 4H), 4.20-4.54 ppm (-OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H; Leu, α-C*H*, 4H), 7.00-8.48 ppm (TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of cyclic peptide, 9H).

Synthesis of *N*-acryloylalanine-*O*-methyl ester (NAAMe)

H-Ala-OMe hydrochloride 5.00 g (35.8 mmol) and TEA 11.0 mL (78.9 mmol) were dissolved in chloroform (200 mL) and cooled over an ice bath. Acryloyl chloride 3.48 mL (43.0 mmol) was diluted with chloroform (15 mL) and added dropwise to the amino acid solution. After the addition, the reaction solution was stirred for overnight at room temperature. The reaction mixture was washed five times with 1.5 M $MgSO_{4\,aq}$ (100 mL×5). The organic layer was collected and dried over anhydrous $NaSO_4$. The solution was concentrated in *vacuo* and then passed through a silica gel column using diethylether as an eluent (R_f=0.48). The resultant solution was concentrated in *vacuo* to give a crude NAAMe as a pale yellow colored liquid. To improve purity of the monomer, the pale yellow-colored NAAMe was passed through a basic alumina short column using diethyl ether as an eluent. A solvent was removed from the obtained solution to give pure NAAMe as a white-colored solid.
Yield: 3.32 g (58.9 %).
^{1}H NMR (DMSO-d_6, TMS) (Figure S21): 1.30 ppm (-NHCH(CH_3)C(O)O-, 3H), 3.62 ppm (-C(O)OCH_3, 3H), 4.33 ppm (-NHC*H*(CH$_3$)C(O)O-, 1H), 5.62 and 6.10ppm (-CH=C$H_a$$H_{a'}$, 2H), 6.27 ppm (-C*H*=CH$_a$H$_{a'}$, 1H), 8.51 ppm (-CON*H*-, 1H).

.

Synthesis of multiblock copolymers P1-P5, [Leu$_4$-*b*-PNIPAM]$_m$

N-isopropylacrylamide (NIPAM) 113.16 mg (1.0 mmol), cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol) and DMF (41.2 μL) were mixed together in a glass test tube (5 sets, monomer concentration: ca. 6 M). Note that the mixture could not form a homogeneous solution below the melting point of NIPAM. The heterogeneous mixtures were

deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixtures were placed in a preheated oil bath at 120 °C to initiate polymerization. At this temperature, the mixture could form a homogeneous solution. After polymerization (1-24 h), the reaction tubes were removed from the oil bath, rapidly cooled in liquid N_2 and exposed to ambient air to stop the polymerization. The resulting polymers **P1**-**P5** were precipitated by dropping the polymer solutions into a large excess of diethyl ether. After centrifugation, the obtained multiblock copolymers were further purified by a reprecipitation method from a DMF/diethylether system. The chemical structure and molecular weight of the multiblock copolymers (white-colored solid) were evaluated by ^{1}H NMR, FTIR, CD and SEC analyses.

SEC (THF, 40 °C, PMMA standard): **P1** (Figure S11A, blue line): M_n=7000, M_p=10300, $Đ$=1.77. **P2** (Figure 3A, blue line): M_n=11200, M_p=17800, $Đ$=1.67. **P3** (Figure S12A, blue line): M_n=19700, M_p=30600, $Đ$=1.87. **P4** (Figure S13A, blue line): M_n=24500, M_p=36100, $Đ$=1.67. **P5** (Figure S14A, blue line): M_n=38600, M_p=64300, $Đ$=2.12.

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2): **P1** (Figure S11B, blue line): 3432 cm^{-1} (ν_s: CON-H), 3301 cm^{-1} (ν_s: CON-H), 3078 cm^{-1} (ν_s: C-H (methylene)), 2973 cm^{-1} (ν_s: C-H (methyl)), 2936 cm^{-1} (ν_s: C-H (methine)), 2877 cm^{-1} (ν_s: C-H (methyl)), 1650 cm^{-1} (ν_s: C(=O)NH), 1545 cm^{-1} (δ: CON-H), 1460 cm^{-1} (δ: C-H (methylene)), 1388 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P2** (Figure S10, blue line): 3429 cm^{-1} (ν_s: CON-H), 3300 cm^{-1} (ν_s: CON-H), 3071 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2935 cm^{-1} (ν_s: C-H (methine)), 2876 cm^{-1} (ν_s: C-H (methyl)), 1645 cm^{-1} (ν_s: C(=O)NH), 1538 cm^{-1} (δ: CON-H), 1476 cm^{-1} (δ: C-H (methylene)), 1368 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P3** (Figure S12B, blue line): 3431 cm^{-1} (ν_s: CON-H), 3301 cm^{-1} (ν_s: CON-H), 3073 cm^{-1} (ν_s: C-H (methylene)), 2969 cm^{-1} (ν_s: C-H (methyl)), 2935 cm^{-1} (ν_s: C-H (methine)), 2878 cm^{-1} (ν_s: C-H (methyl)), 1646 cm^{-1} (ν_s: C(=O)NH), 1539 cm^{-1} (δ: CON-H), 1459 cm^{-1} (δ: C-H (methylene)), 1376 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P4** (Figure S13B, blue line): 3429 cm^{-1} (ν_s: CON-H), 3306 cm^{-1} (ν_s: CON-H), 3068 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2934 cm^{-1} (ν_s: C-H (methine)), 2878 cm^{-1} (ν_s: C-H (methyl)), 1648 cm^{-1} (ν_s: C(=O)NH), 1535 cm^{-1} (δ: CON-H), 1458 cm^{-1} (δ: C-H (methylene)), 1376 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P5** (Figure S14B, blue line): 3433 cm^{-1} (ν_s: CON-H), 3303 cm^{-1} (ν_s: CON-H), 3068 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2932 cm^{-1} (ν_s: C-H (methine)), 2876 cm^{-1} (ν_s: C-H (methyl)), 1646 cm^{-1} (ν_s: C(=O)NH), 1536 cm^{-1} (δ: CON-H), 1457 cm^{-1} (δ: C-H (methylene)), 1373 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group).

^{1}H NMR ($CDCl_3$, TMS): **P1** (Figure S11C, blue line): 0.50 ppm (>CHCH(C*H*$_3$)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-C*H*$_3$, 24H; >NC(C*H*$_3$)$_3$, 9H), 1.05-2.30 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(C*H*$_3$)$_2$, 3H, enantiomer; >C(C*H*$_3$)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-C*H*$_2$, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-C*H*$_2$, 2H), 3.80 ppm (-O(C*H*$_2$)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHC*H*$_2$CH$_2$NH-, 2H; -OC(=O)NHCH$_2$C*H*$_2$NH-, 2H; -NHC*H*$_2$CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$C*H*$_2$O-, 4H; -OC*H*$_2$C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CON*H*$_2$, 2H; amide bonds of peptide, 9H). **P2** (Figure 3C, blue line): 0.50 ppm (>CHCH(C*H*$_3$)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-C*H*$_3$, 24H; >NC(C*H*$_3$)$_3$, 9H), 1.05-2.40 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(C*H*$_3$)$_2$, 3H, enantiomer; >C(C*H*$_3$)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-C*H*$_2$, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-C*H*$_2$, 2H), 3.80 ppm (-O(C*H*$_2$)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHC*H*$_2$CH$_2$NH-, 2H; -OC(=O)NHCH$_2$C*H*$_2$NH-, 2H; -NHC*H*$_2$CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$C*H*$_2$O-, 4H; -OC*H*$_2$C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CON*H*$_2$, 2H; amide bonds of peptide, 9H). **P3** (Figure S12C, blue line): 0.50 ppm (>CHCH(C*H*$_3$)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-C*H*$_3$, 24H; >NC(C*H*$_3$)$_3$, 9H), 1.05-2.90 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(C*H*$_3$)$_2$, 3H, enantiomer; >C(C*H*$_3$)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-C*H*$_2$, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-C*H*$_2$, 2H), 3.80 ppm (-O(C*H*$_2$)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHC*H*$_2$CH$_2$NH-, 2H; -OC(=O)NHCH$_2$C*H*$_2$NH-, 2H; -NHC*H*$_2$CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$C*H*$_2$O-, 4H; -OC*H*$_2$C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CON*H*$_2$, 2H; amide bonds of peptide, 9H). **P4** (Figure S13C, blue line): 0.50 ppm (>CHCH(C*H*$_3$)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-C*H*$_3$, 24H; >NC(C*H*$_3$)$_3$, 9H), 1.05-2.70 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(C*H*$_3$)$_2$, 3H, enantiomer; >C(C*H*$_3$)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-C*H*$_2$, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-C*H*$_2$, 2H), 3.80 ppm (-O(C*H*$_2$)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHC*H*$_2$CH$_2$NH-, 2H; -OC(=O)NHCH$_2$C*H*$_2$NH-, 2H; -NHC*H*$_2$CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$C*H*$_2$O-, 4H; -OC*H*$_2$C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CON*H*$_2$, 2H, 2H; amide bonds of peptide, 9H). **P5** (Figure S14C, blue line): 0.50 ppm (>CHCH(C*H*$_3$)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-C*H*$_3$, 24H; >NC(C*H*$_3$)$_3$, 9H), 1.05-2.60 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(C*H*$_3$)$_2$, 3H, enantiomer; >C(C*H*$_3$)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-C*H*$_2$, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-C*H*$_2$, 2H), 3.80 ppm (-O(C*H*$_2$)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHC*H*$_2$CH$_2$NH-, 2H; -OC(=O)NHCH$_2$C*H*$_2$NH-, 2H; -NHC*H*$_2$CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$C*H*$_2$O-, 4H; -OC*H*$_2$C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CON*H*$_2$, 2H; amide bonds of peptide, 9H).

Fragmentation of multiblock copolymers P1-P5

The multiblock copolymer **P1**, **P2**, **P3, P4** or **P5**, [(Leu)$_4$-*b*-PNIPAM]$_m$, (10.0 mg, 1.43 μmol (**P1**), 0.89 μmol (**P2**), 0.51 μmol (**P3**), 0.41 μmol (**P4**), 0.26 μmol (**P5**)) and TIPNO (22.0 mg, 100 μmol) were initially dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a glass test tube. The solution was deoxygenated using three freeze-

pump-thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 120 ˚C for 12 h. The fragmented polymer was purified by repeated precipitation in diethyl ether and dried to give a pale orange-colored powder. The molecular weight and $Đ$ were evaluated by SEC analysis, while the structure was analyzed by FTIR, CD and ^{1}H NMR spectroscopies.

SEC (THF, 40°C, PMMA standard): **P1**(fragment) (Figure S11A, red line): M_n=2400, M_p=3400, $Đ$=1.20. **P2**(fragment) (Figure 3A, red line): M_n=3800, M_p=4800, $Đ$=1.25. **P3**(fragment) (Figure S12A, red line): M_n=7500, M_p=9600, $Đ$=1.19. **P4**(fragment) (Figure S13A, red line): M_n=8300, M_p=12900, $Đ$=1.21. **P5**(fragment) (Figure S14A, red line): M_n=12400, M_p=21800, $Đ$=1.28.

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2): **P1**(fragment) (Figure S11B, red line): 3432 cm^{-1} (ν_s: CON-H), 3301 cm^{-1} (ν_s: CON-H), 3078 cm^{-1} (ν_s: C-H (methylene)), 2973 cm^{-1} (ν_s: C-H (methyl)), 2936 cm^{-1} (ν_s: C-H (methine)), 2877 cm^{-1} (ν_s: C-H (methyl)), 1650 cm^{-1} (ν_s: C(=O)NH), 1545 cm^{-1} (δ: CON-H), 1460 cm^{-1} (δ: C-H (methylene)), 1388 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P2**(fragment) (Figure S10, red line): 3429 cm^{-1} (ν_s: CON-H), 3300 cm^{-1} (ν_s: CON-H), 3071 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2935 cm^{-1} (ν_s: C-H (methine)), 2876 cm^{-1} (ν_s: C-H (methyl)), 1645 cm^{-1} (ν_s: C(=O)NH), 1538 cm^{-1} (δ: CON-H), 1476 cm^{-1} (δ: C-H (methylene)), 1368 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P3**(fragment) (Figure S12B, red line): 3431 cm^{-1} (ν_s: CON-H), 3301 cm^{-1} (ν_s: CON-H), 3073 cm^{-1} (ν_s: C-H (methylene)), 2969 cm^{-1} (ν_s: C-H (methyl)), 2935 cm^{-1} (ν_s: C-H (methine)), 2878 cm^{-1} (ν_s: C-H (methyl)), 1646 cm^{-1} (ν_s: C(=O)NH), 1539 cm^{-1} (δ: CON-H), 1459 cm^{-1} (δ: C-H (methylene)), 1376 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P4**(fragment) (Figure S13B, red line): 3429 cm^{-1} (ν_s: CON-H), 3306 cm^{-1} (ν_s: CON-H), 3068 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2934 cm^{-1} (ν_s: C-H (methine)), 2878 cm^{-1} (ν_s: C-H (methyl)), 1648 cm^{-1} (ν_s: C(=O)NH), 1535 cm^{-1} (δ: CON-H), 1458 cm^{-1} (δ: C-H (methylene)), 1376 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group). **P5**(fragment) (Figure S14B, red line): 3433 cm^{-1} (ν_s: CON-H), 3303 cm^{-1} (ν_s: CON-H), 3068 cm^{-1} (ν_s: C-H (methylene)), 2970 cm^{-1} (ν_s: C-H (methyl)), 2932 cm^{-1} (ν_s: C-H (methine)), 2876 cm^{-1} (ν_s: C-H (methyl)), 1646 cm^{-1} (ν_s: C(=O)NH), 1536 cm^{-1} (δ: CON-H), 1457 cm^{-1} (δ: C-H (methylene)), 1373 cm^{-1} (δ: C-H (methyl), δ: *i*Pr group).

^{1}H NMR ($CDCl_3$, TMS): **P1**(fragment) (Figure S11C, red line): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.50 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CH*CH*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H). **P2**(fragment) (Figure 3C, red line): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.50 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CH*CH*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H). **P3**(fragment) (Figure S12C, red line): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.90 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CH*CH*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H). **P4**(fragment) (Figure S13C, red line): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.85 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.40 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CH*CH*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H). **P5**(fragment) (Figure S14C, red line): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.50 ppm (PNIPAM, 2*n*H, methylene of main chain; PNIPAM, *n*H, methine of main chain; PNIPAM, 6*n*H, methyl of side chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CH*CH*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.70 ppm (-O(CH_2)$_2$O-, 8H), 4.02 ppm (Leu, α-C*H*, 4H; PNIPAM, *n*H, methine of side chain), 3.20-4.50 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.00-7.80 ppm (PNIPAM, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Synthesis and fragmentation of P6, [(Leu)$_4$-*b*-PNAAMe]$_m$

N-acryloylalanine-*O*-methyl ester (NAAMe) 157.17 mg (1.0 mmol), cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol), and DMF (41.2 μL) were mixed together in a glass test tube (monomer concentration: ca. 5 M). Note that the mixture could not form a homogeneous solution below the melting point of NAAMe. The heterogeneous mixture was

deoxygenated using three freeze–pump–thaw cycles under dry N_2. The reaction mixture was placed in a preheated oil bath at 120°C for 18 h. At this temperature, the mixture could form a homogeneous solution. After polymerization, the reaction tube was removed from the oil bath, rapidly cooled in liquid N_2, and exposed to ambient air to stop the polymerization reaction. The resulting polymer **P6** was precipitated by dropping the polymer solutions into a large excess of diethyl ether. After centrifugation, the obtained multiblock copolymer was further purified using a reprecipitation method from a DMF/diethyl ether system. Fragmentation of **P6** was carried out as follows: **P6** (10.0 mg, 0.31 μmol) and TIPNO (22.0 mg, 100 μmol) were dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a glass test tube. The solution was deoxygenated using three freeze–pump–thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 120°C for 12 h. The fragmented polymer was purified by repeated precipitation in diethyl ether and dried to give a pale brown-colored powder. The chemical structure and molecular weight of the original and fragmented **P6** were evaluated by ^{1}H NMR, FTIR and SEC analyses.

SEC (THF, 40°C, PMMA standard): **P6** M_n=32300, M_p=53000, $Đ$=1.46, **P6**(fragment) M_n=12700, M_p=19800, $Đ$=1.23 (Figure S15A).

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2) (Figure S15B): **P6** & **P6**(fragment) 3343 cm^{-1} (ν_s: CON-H), 3211 cm^{-1} (ν_s: CON-H), 3070 cm^{-1} (ν_s: C-H (methylene)), 2986 cm^{-1} (ν_s: C-H (methyl)), 2955 cm^{-1} (ν_s: C-H (methine)), 2883 cm^{-1} (ν_s: C-H (methine)), 2855 cm^{-1} (ν_s: C-H (methyl)), 1730 cm^{-1} (ν_s: C(=O)O), 1661 cm^{-1} (ν_s: C(=O)NH), 1544 cm^{-1} (δ: CON-H), 1440 cm^{-1} (δ: C-H (methylene), δ: COO-CH_3), 1381 cm^{-1} (δ: C-H (methyl), δ: COO-CH_3).

^{1}H NMR ($CDCl_3$, TMS) (Figure S15C): **P6** & **P6**(fragment) 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.70 ppm (PNAAMe, 3*n*H, methyl of side chain; PNAAMe, 2*n*H, methylene of main chain; PNAAMe, *n*H, methine of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), , 3.65 ppm (PNAAMe, 3*n*H, methyl ester), 3.25-3.95 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; -O(CH_2)$_2$O-, 8H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 4.00-4.70 ppm (Leu, α-C*H*, 4H; PNAAMe, *n*H, α-methine), 6.80-8.40 ppm (PNAAMe, *n*H, amide; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Synthesis and fragmentation of P7, [(Leu)$_4$-*b*-P*t*BuA]$_m$

Tert-butyl acrylate (*t*BuA) 144.5 μL (1.0 mmol) and cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol) were dissolved in DMF (41.2 μL), and the mixture was poured into a glass test tube (monomer concentration: 5 M). The solution was deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixture was placed in a preheated oil bath at 120 °C for 17 h. After polymerization, the reaction tube was removed from the oil bath, rapidly cooled in liquid N_2 and exposed to ambient air to stop the polymerization. The resulting polymer **P7** was precipitated by dropping the polymer solutions into a large excess of water/methanol (v/v=1/4). After centrifugation, the obtained multiblock copolymer was further purified by a reprecipitation method from DMF/(water/methanol) system. Fragmentation of **P7** was carried out as follows, **P7** (10.0 mg, 0.38 μmol) and TIPNO (22.0 mg, 100 μmol) were dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a test glass tube. The solution was deoxygenated by three freeze-pump-thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 120 ˚C for 12 h. The fragmented polymer was purified by repeated precipitation in water/methanol (v/v=1/4) and dried to give a pale brown-colored powder. The chemical structure and molecular weight of the original and fragmented **P7** were evaluated by ^{1}H NMR, FTIR and SEC analyses.

SEC (THF, 40°C, PMMA standard): **P7** M_n=26300, M_p=42800, $Đ$=1.89, **P7**(fragment) M_n=9500, M_p=13100, $Đ$=1.18 (Figure S16A).

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2) (Figure S16B): **P7** & **P7**(fragment) 3430 cm^{-1} (ν_s: CON-H), 3282 cm^{-1} (ν_s: CON-H), 2979 cm^{-1} (ν_s: C-H (methylene)), 2934 cm^{-1} (ν_s: C-H (methyl)), 2918 cm^{-1} (ν_s: C-H (methine)), 2873 cm^{-1} (ν_s: C-H (methyl)), 2851 cm^{-1} (ν_s: C-H (methylene)), 1727 cm^{-1} (ν_s: C(=O)O), 1641 cm^{-1} (ν_s: C(=O)NH), 1541 cm^{-1} (δ: CON-H), 1479 cm^{-1} (δ: C-H (methylene)), 1452 cm^{-1} (δ: C-H (methyl)), 1393 cm^{-1} (δ: *t*Bu group), 1368 cm^{-1} (δ: *t*Bu group).

^{1}H NMR ($CDCl_3$, TMS) (Figure S16C): **P7** & **P7**(fragment) 0.45 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.40 ppm (P*t*BuA, 9*n*H, *tert*-butyl of side chain; P*t*BuA, 2*n*H, methylene of main chain; P*t*BuA, *n*H, methine of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H)3.20-4.40 ppm (-OC(=O)NHCH_2CH_2NH-, 2H; -OC(=O)NHCH_2CH_2NH-, 2H; -NHCH_2CH_2O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH_2CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.80-7.80 ppm (TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Deprotection of *tert*-butyl group of P7

P7 20 mg (0.76 μmol) was dissolved in TFA/dichloromethane/TIS (v/v/v=8.5/1/0.5) (30 mL) and stirred at room temperature for 12 h. After the reaction, the solvent was removed in *vacuo* to give a crude. Finally, objective deprotected **P7**, which composed of tetraleucine and poly(acrylic acid) (PAA), ([Leu$_4$-*b*-PAA]$_m$), was obtained by reprecipitation from a methanol/diethylether system as a pale yellow-colored solid.

Transmission-FTIR (cast film from methanol onto CaF_2) (Figure S17A): 3429 cm^{-1} (ν_s: COO-H, ν_s: CON-H), 3131 cm^{-1} (ν_s: CON-H), 2949 cm^{-1} (ν_s: C-H (methylene)), 2879 cm^{-1} (ν_s: C-H (methine)), 2623 cm^{-1} (ν_s: COO-H), 1708 cm^{-1} (ν_s: C(=O)OH), 1632 cm^{-1} (ν_s: C(=O)NH), 1564 cm^{-1} (δ: CON-H), 1455 cm^{-1} (δ: C-H (methylene)).

^{1}H NMR (CD_3OD, TMS) (Figure S17B): 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.60 ppm (PAA, 2*n*H, methylene of main chain; PAA, *n*H, methine of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.40-4.70 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H; -OC(=O)NHCH$_2$CH_2NH-, 2H -NHCH_2CH$_2$O-, 4H; -O(CH_2)$_2$O-, 8H; >C*H*CH(CH_3)$_2$, 1H; -NHCH$_2$CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H; Leu, α-C*H*, 4H), 6.80-7.80 ppm (TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Synthesis and fragmentation of P8, [(Leu)$_4$-*b*-PEA]$_m$

Ethyl acrylate (EA) 108.4 μL (1.0 mmol) and cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol) dissolved in DMF (41.2 μL), and the mixture was poured into a glass test tube (monomer concentration: 6.2 M). The solution was deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixture was placed in a preheated oil bath at 120 °C for 25 h. After polymerization, the reaction tube was removed from the oil bath, rapidly cooled in liquid N_2 and exposed to ambient air to stop the polymerization. The resulting polymer **P8** was precipitated by dropping the polymer solutions into a large excess of petroleum ether/diethylether (v/v=1/4). After centrifugation, the obtained multiblock copolymer was further purified by a reprecipitation method from a DMF/(petroleum ether/diethyl ether) system. Fragmentation of **P8** was carried out as follows, **P8** (10.0 mg, 1.05 μmol) and TIPNO (22.0 mg, 100 μmol) were dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a test glass tube. The solution was deoxygenated by three freeze-pump-thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 120 ˚C for 12 h. The fragmented polymer was purified by repeated precipitation in a petroleum ether/diethyl ether (v/v=1/4) and dried to give a pale brown-colored powder. The chemical structure and molecular weight of the original and fragmented **P8** were evaluated by ^{1}H NMR, FTIR and SEC analyses.

SEC (THF, 40°C, PMMA standard): **P8** M_n=9500, M_p=18400, $Đ$=1.63, **P8**(fragment) M_n=3700, M_p=6200, $Đ$=1.22 (Figure S18A).

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2) (Figure S18B): **P8** & **P8**(fragment) 3278 cm^{-1} (ν_s: CON-H), 3080 cm^{-1} (ν_s: CON-H), 2982 cm^{-1} (ν_s: C-H (methylene)), 2958 cm^{-1} (ν_s: C-H (methyl)), 2874 cm^{-1} (ν_s: C-H (methine)), 1732 cm^{-1} (ν_s: C(=O)O), 1639 cm^{-1} (ν_s: C(=O)NH), 1543 cm^{-1} (δ: CON-H), 1434 cm^{-1} (δ: C-H (methylene)), 1380 cm^{-1} (δ: C-H (methyl)).

^{1}H NMR ($CDCl_3$, TMS) (Figure S18C): **P8** & **P8**(fragment) 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.90 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.05-2.40 ppm (PEA, 3*n*H, methyl of side chain; PEA, 2*n*H, methylene of main chain; PEA, *n*H, methine of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.80 ppm (-O(CH_2)$_2$O-, 8H), 4.00 ppm (Leu, α-C*H*, 4H), 4.05 ppm (PEA, 2*n*H, methylene of side chain), 3.20-4.10 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H; -OC(=O)NHCH$_2$CH_2NH-, 2H; -NHCH_2CH$_2$O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH$_2$CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.80-7.80 ppm (TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Synthesis and fragmentation of P9, [(Leu)$_4$-*b*-PAN]$_m$

Acrylonitrile (AN) 65.6 μL (1.0 mmol) and cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol) were dissolved in DMF (88.8 μL), and the mixture was poured into a glass test tube (monomer concentration: 6 M). The solution was deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixture was placed in a preheated oil bath at 120 °C for 16 h. After polymerization, the reaction tube was removed from the oil bath, rapidly cooled in liquid N_2 and exposed to ambient air to stop the polymerization. The resulting polymer **P9** was precipitated by dropping the polymer solutions into a large excess of diethyl ether. After centrifugation, the obtained multiblock copolymer was further purified by a reprecipitation method from a DMF/dithylether system. Fragmentation of **P9** was carried out as follows, **P9** (10.0 mg, 0.29 μmol) and TIPNO (22.0 mg, 100 μmol) were dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a test glass tube. The solution was deoxygenated by three freeze-pump-thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 120 ˚C for 12 h. The fragmented polymer was purified by repeated precipitation in a diethyl ether and dried to give a pale brown-colored powder. The chemical structure and molecular weight of the original and fragmented **P9** were evaluated by ^{1}H NMR, FTIR and SEC analyses.

SEC (DMF, 40°C, PMMA standard): **P9** M_n=34200, M_p=43500, $Đ$=1.54, **P9**(fragment) M_n=13400, M_p=15200, $Đ$=1.38 (Figure S19A).

Transmission-FTIR (cast film from DMSO onto CaF_2) (Figure S19B): **P9** & **P9**(fragment): 3283 cm^{-1} (ν_s: CON-H), 3069 cm^{-1} (ν_s: CON-H), 2947 cm^{-1} (ν_s: C-H (methylene)), 2872 cm^{-1} (ν_s: C-H (methine)), 2242 cm^{-1} (ν_s: C≡H), 1644 cm^{-1} (ν_s: C(=O)NH), 1537 cm^{-1} (δ: CON-H), 1453 cm^{-1} (δ: C-H (methylene)), 1366 cm^{-1} (δ: C-H (methyl)).

^{1}H NMR (DMSO-d_6, TMS) (Figure S19C): **P9** & **P9**(fragment) 0.45 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.85 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 0.79-2.40 ppm (PAN, 2*n*H, methylene of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6HLeu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH_3)$_2$, 1H; Asp, β-CH_2, 2H), 3.20 ppm (PAN, *n*H, methine of main chain), 3.60 ppm (-O(CH_2)$_2$O-, 8H), 3.85 ppm (Leu, α-C*H*, 4H), 3.00-4.70 ppm (>-OC(=O)NHCH_2CH$_2$NH-, 2H; -OC(=O)NHCH$_2$CH_2NH-, 2H; -NHCH_2CH$_2$O-, 4H; >C*H*CH(CH_3)$_2$, 1H; -NHCH$_2$CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 7.00-8.70 ppm (TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

Synthesis and fragmentation of P10, $[(Leu)_4$-*b*-PSt$]_m$

Styrene (St) 115 μL (1.0 mmol) and cyclic tetraleucine peptide initiator 12.3 mg (0.010 mmol) were dissolved in DMF (41.2 μL), and the mixture was poured into glass test tube (monomer concentration: 6 M). The solution was deoxygenated using three freeze-pump-thaw cycles under dry N_2. Then the reaction mixture was placed in a preheated oil bath at 110 °C for 72 h. After polymerization, the reaction tube was removed from the oil bath, rapidly cooled in liquid N_2 and exposed to ambient air to stop the polymerization. The resulting polymer **P10** was precipitated by dropping the polymer solutions into a large excess of methanol. After centrifugation, the obtained multiblock copolymer was further purified by a reprecipitation method from a DMF/methanol system. Fragmentation of **P10** was carried out as follows, **P10** (10.0 mg, 0.26 μmol) and TIPNO (22.0 mg, 100 μmol) were dissolved in *N*-methyl-2-pyrrolidone (100 μL), and the solution was poured into a test glass tube. The solution was deoxygenated by three freeze-pump-thaw cycles under dry N_2. The fragmentation reaction was then performed in a preheated oil bath at 110 ˚C for 12 h. The fragmented polymer was purified by repeated precipitation in methanol and dried to give a pale brown-colored powder. The chemical structure and molecular weight of the original and fragmented **P10** were evaluated by ^{1}H NMR, FTIR and SEC analyses.

SEC (THF, 40°C, PSt standard): **P10** M_n=38800, M_p=55000, $Đ$=1.77, **P10**(fragment) M_n=8400, M_p=9100, $Đ$=1.10 (Figure S20A).

Transmission-FTIR (cast film from $CHCl_3$ onto CaF_2) (Figure S20B): **P10** & **P10**(fragment) 3274 cm^{-1} (ν_s: CON-H), 3101 cm^{-1} (ν_s: CON-H), 3083 cm^{-1} (ν_s: C-H (phenyl)), 3061 cm^{-1} (ν_s: C-H (phenyl)), 3026 cm^{-1} (ν_s: C-H (methylene)), 3001 cm^{-1} (ν_s: C-H (methyl)), 2925 cm^{-1} (ν_s: C-H (methylene)), 2851 cm^{-1} (ν_s: C-H (methine)), 1944 cm^{-1} (δ: C-H (phenyl)), 1873 cm^{-1} (δ: C-H (phenyl)), 1803 cm^{-1} (δ: C-H (phenyl)), 1745 cm^{-1} (δ: C-H (phenyl)), 1633 cm^{-1} (ν_s: C(=O)NH), 1600 cm^{-1} (ν_s: C=C (phenyl)), 1539 cm^{-1} (δ: CON-H), 1493 cm^{-1} (δ: C-H (methylene)).

^{1}H NMR ($CDCl_3$, TMS) (Figure S20C): **P10** & **P10**(fragment) 0.50 ppm (>CHCH(CH_3)$_2$, 3H, enantiomer), 0.85 ppm (Leu, δ-CH_3, 24H; >NC(CH_3)$_3$, 9H), 1.10-2.40 ppm (PSt, 2*n*H, methylene of main chain; PSt, *n*H, methine of main chain; >CHCH(CH_3)$_2$, 3H, enantiomer; >C(CH_3)$_2$, 6H; Leu, γ-C*H*, 4H; Leu, β-CH_2, 8H; >CHC*H*(CH$_3$)$_2$, 1H; Asp, β-CH_2, 2H), 3.70 ppm (-O(CH_2)$_2$O-, 8H), 3.95 ppm (Leu, α-C*H*, 4H), 2.80-4.10 ppm (-OC(=O)NHCH_2CH$_2$NH-, 2H; -OC(=O)NHCH$_2$CH_2NH-, 2H; -NHCH_2CH$_2$O-, 4H; >C*H*CH(CH$_3$)$_2$, 1H; -NHCH$_2$CH_2O-, 4H; -OCH_2C(=O)-, 4H; Asp, α-C*H*, 1H), 6.30-7.80 ppm (PSt, 5*n*H, phenyl; TIPNO, 4H, aromatic ring; -CONH_2, 2H; amide bonds of peptide, 9H).

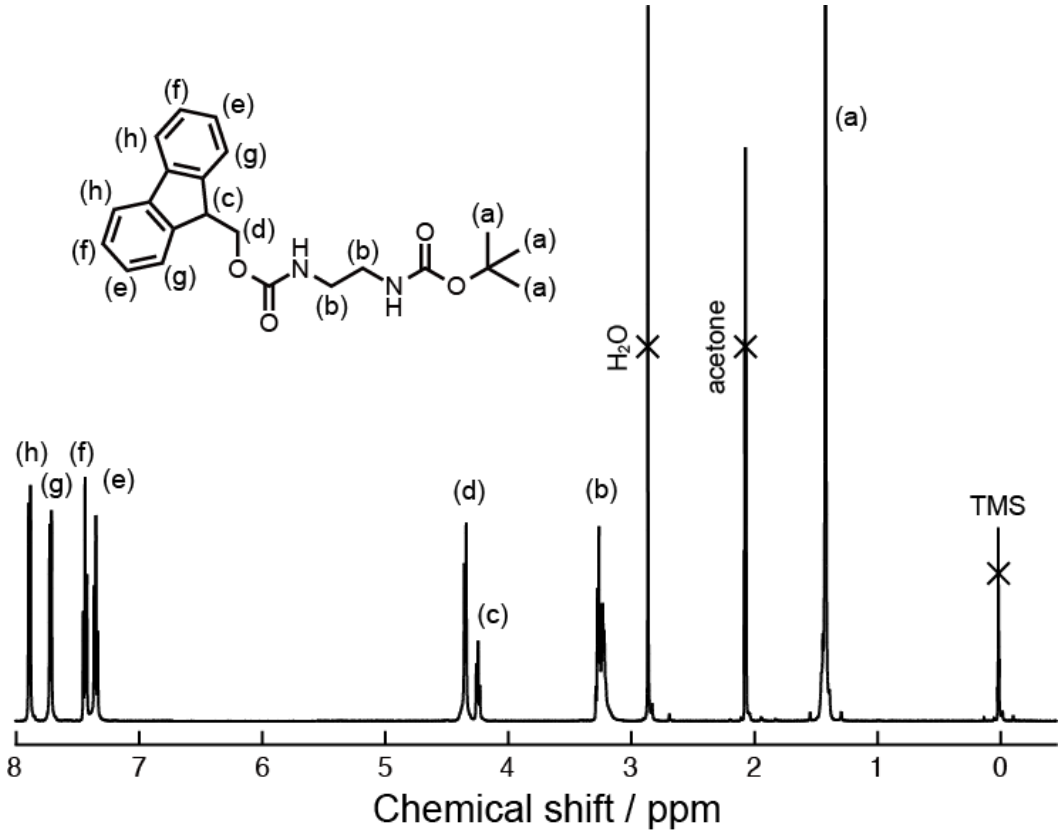

Figure S1. ^{1}H NMR spectrum of *N*-Fmoc-*N*'-Boc-*EDA* in acetone-d_6 at 25˚C.

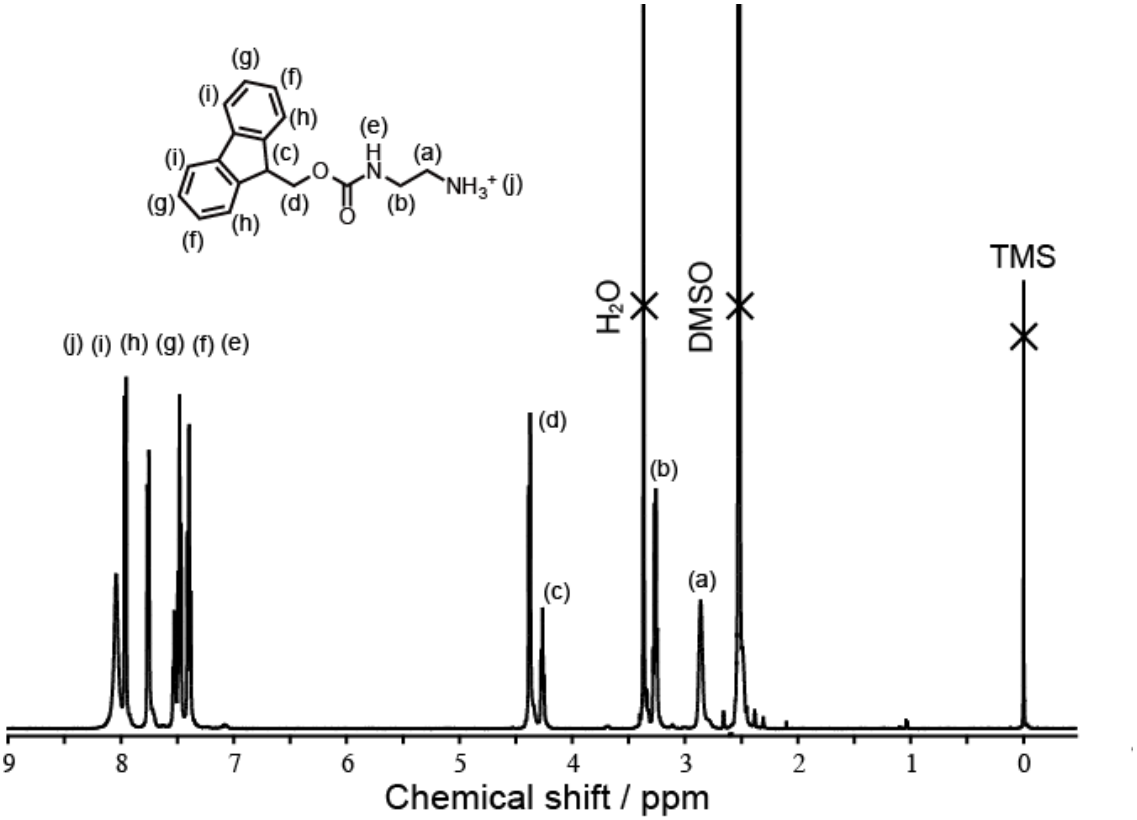

Figure S2. ^{1}H NMR spectrum of *N*-Fmoc-*EDA*•HCl (**1**) in DMSO-d_6 at 25°C.

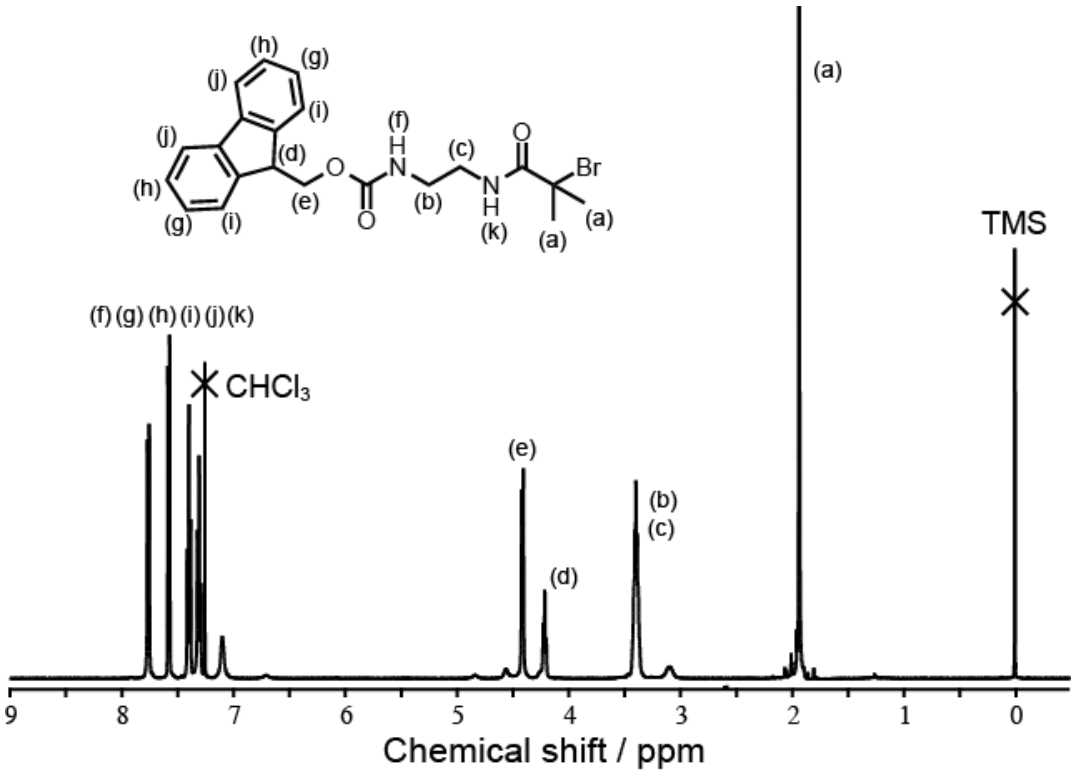

Figure S3. ^{1}H NMR spectrum of Fmoc-*EDA*-Br (**2**) in $CDCl_3$ at 25°C.

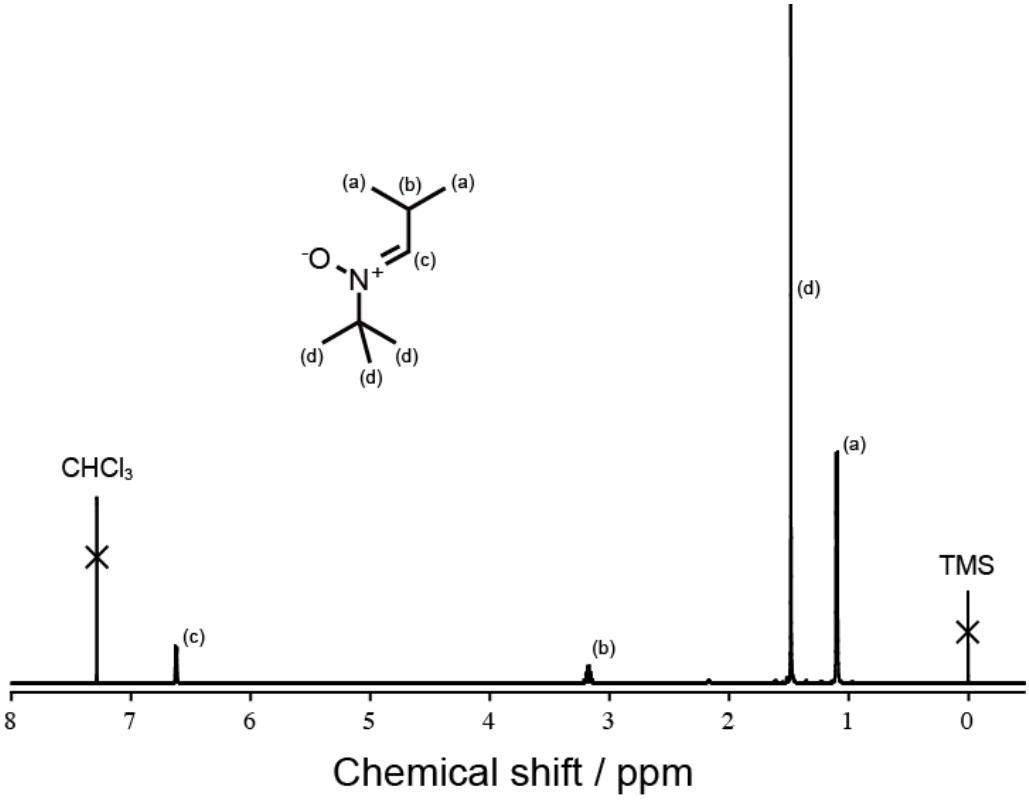

Figure S4. ^{1}H NMR spectrum of *N-tert*-butyl-α-isopropylnitrone (**3**) in $CDCl_3$ at 25°C

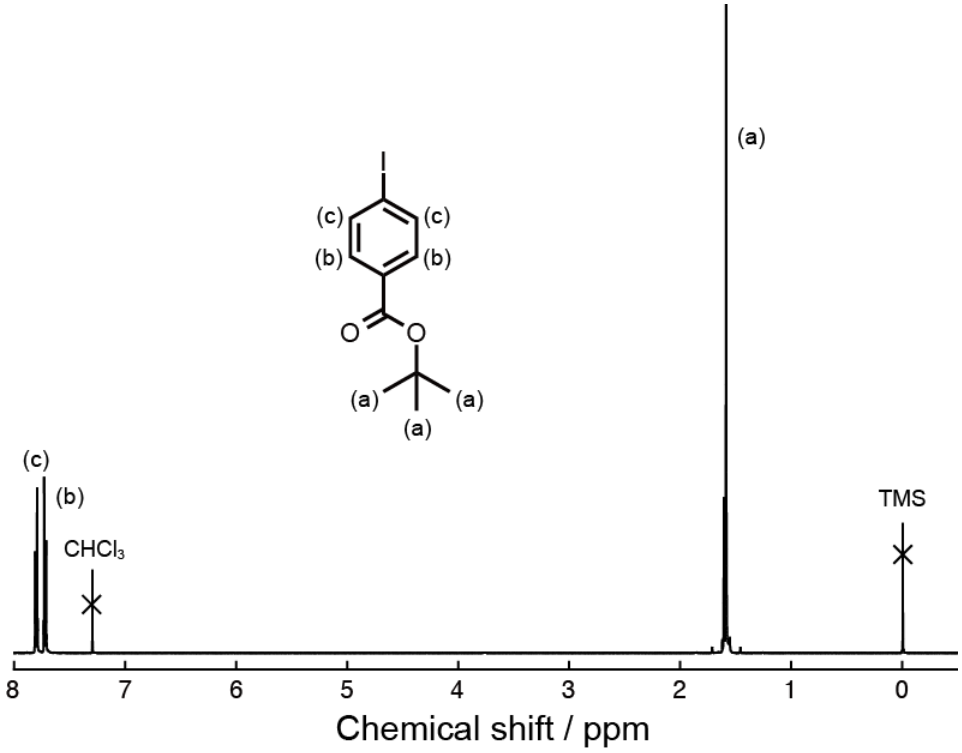

Figure S5. ^{1}H NMR spectrum of *tert*-butyl 4-iodobenzoate (**4**) in $CDCl_3$ at 25°C.

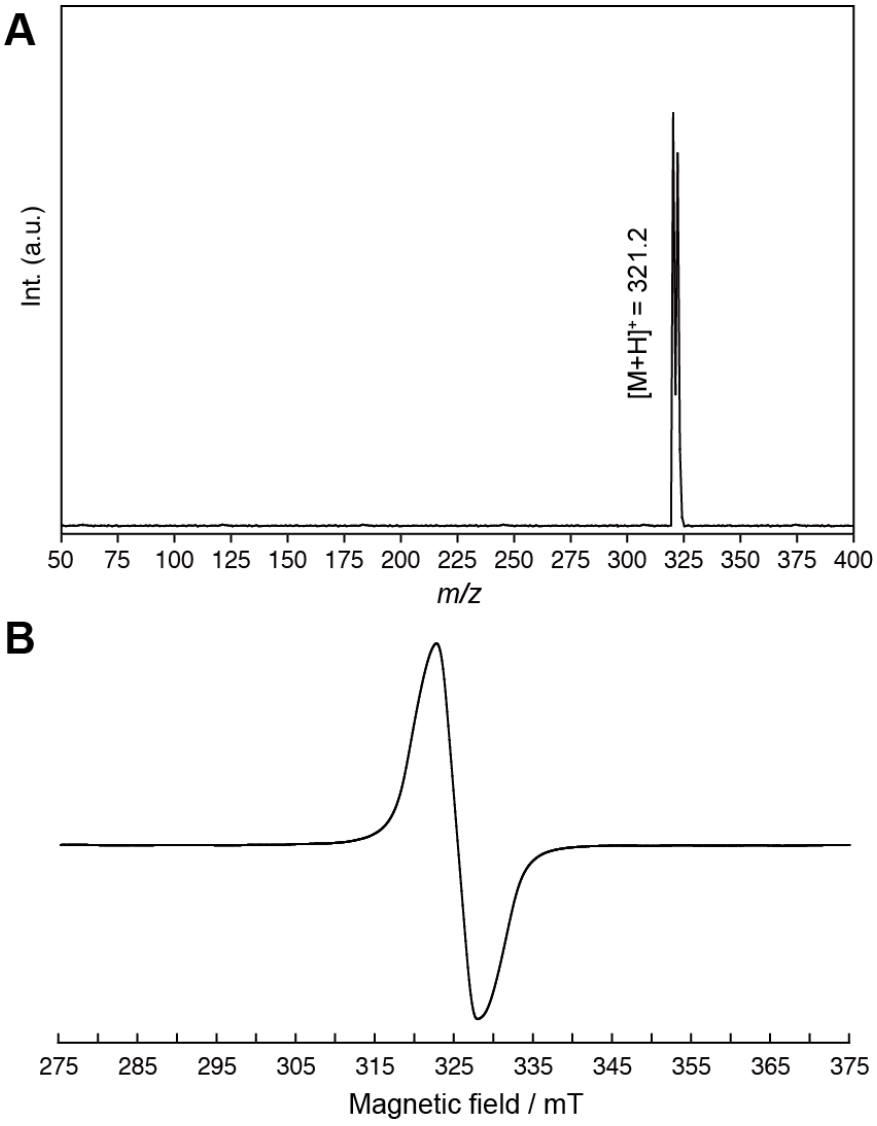

Figure S6. A. DART MS spectrum of TIPNO-COO*t*Bu, free radical (**5**). Ionization temperature: 300˚C. **B.** ESR spectrum of **5** in $CHCl_3$ at -196˚C.

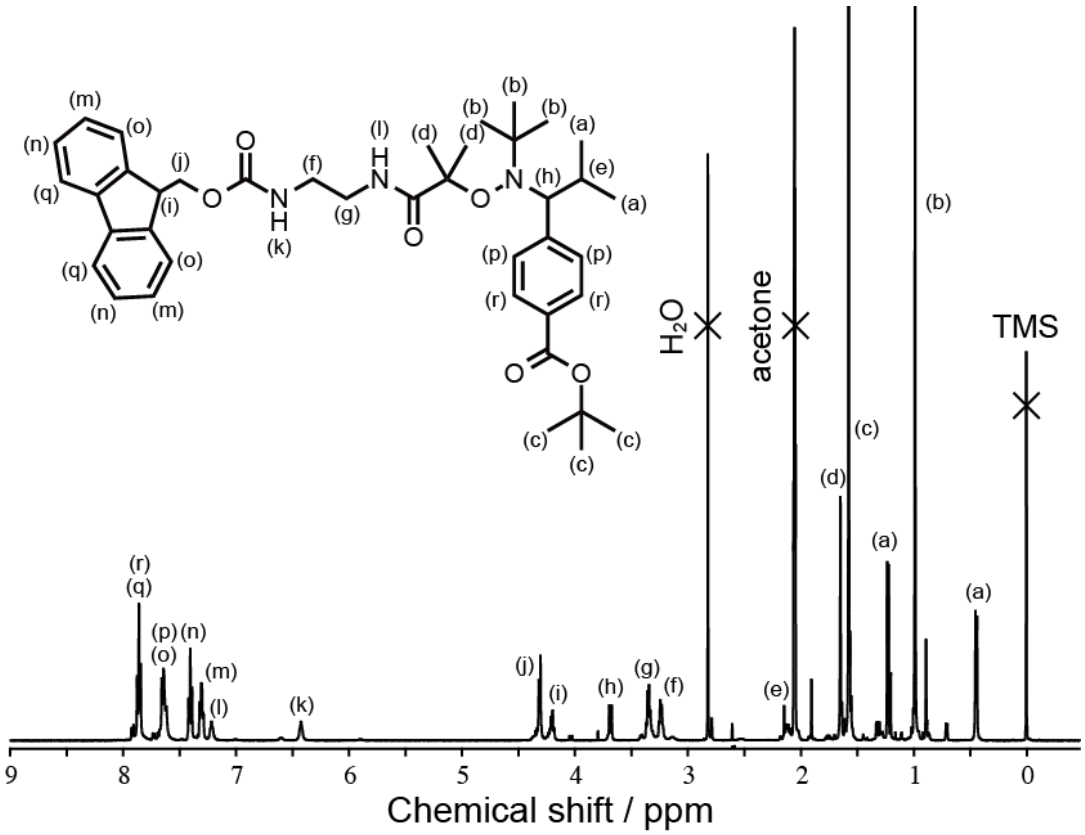

Figure S7. ^{1}H NMR spectrum of Fmoc-NH-TIPNO-COO*t*Bu (**6**) in acetone-d_6 at 25°C.

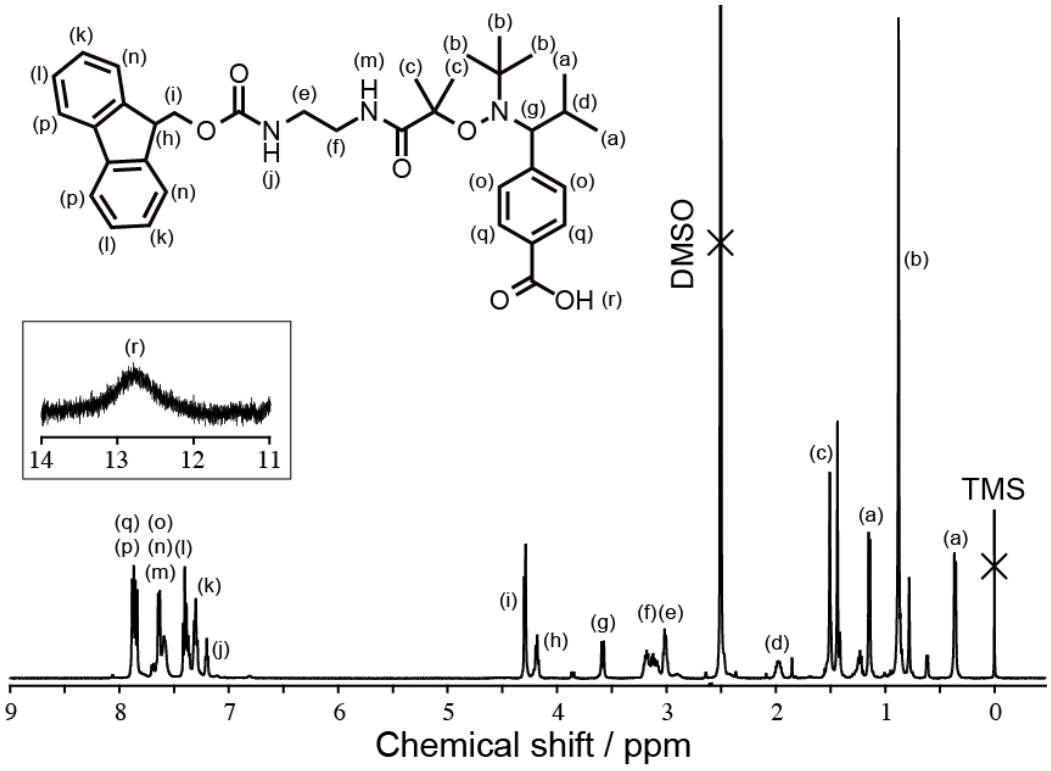

Figure S8. ^{1}H NMR spectrum of Fmoc-NH-TIPNO-COOH (**7**) in DMSO-d_6 at 25°C.

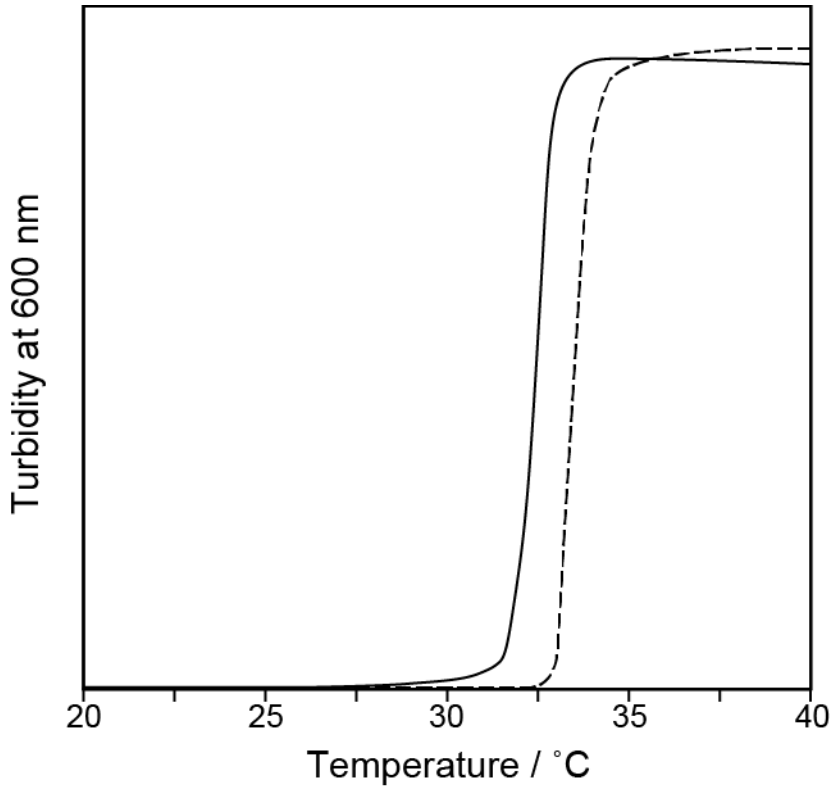

Figure S9. Turbidity measurements of **P5** (solid line) and PNIPAM homopolymer (M_n=74000 g mol^{-1}) (dashed line) in water at 600 nm. [Polymer]=1 wt%.

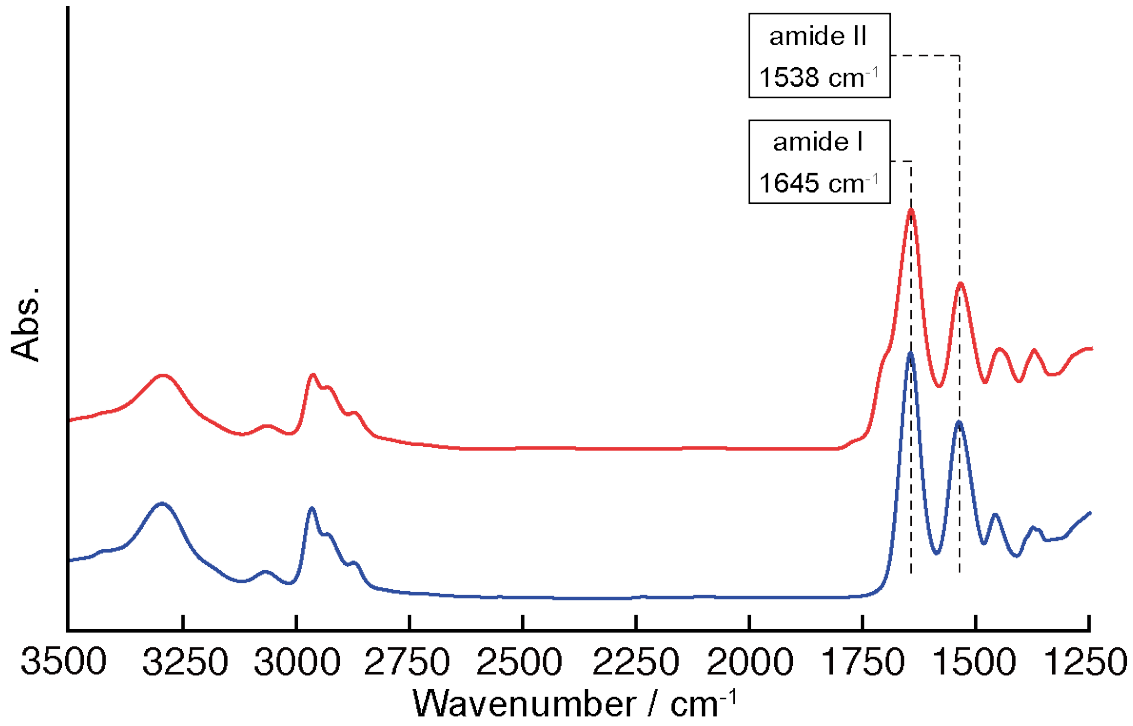

Figure S10. Transmission-FTIR spectra of **P2** (blue) and fragmented **P2** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate.

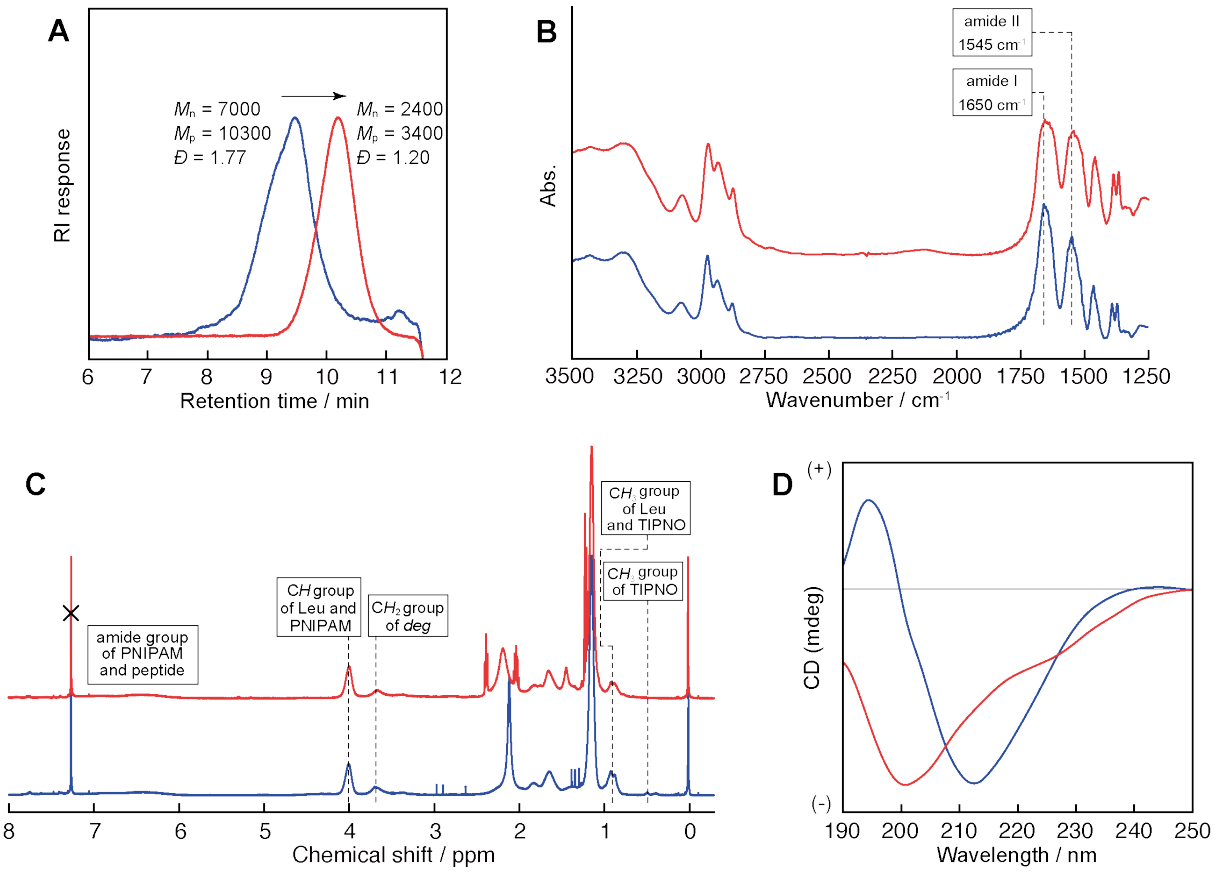

Figure S11. Characterization of the multiblock P1. **A.** SEC traces (THF, 40 °C) of the multiblock **P1** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P1** (blue) and fragmented **P1** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P1** (blue) and fragmented **P1** (red) in $CDCl_3$ at 25°C. **D**. CD spectra of **P1** (blue) and fragmented **P1** (red) in water at 25°C.

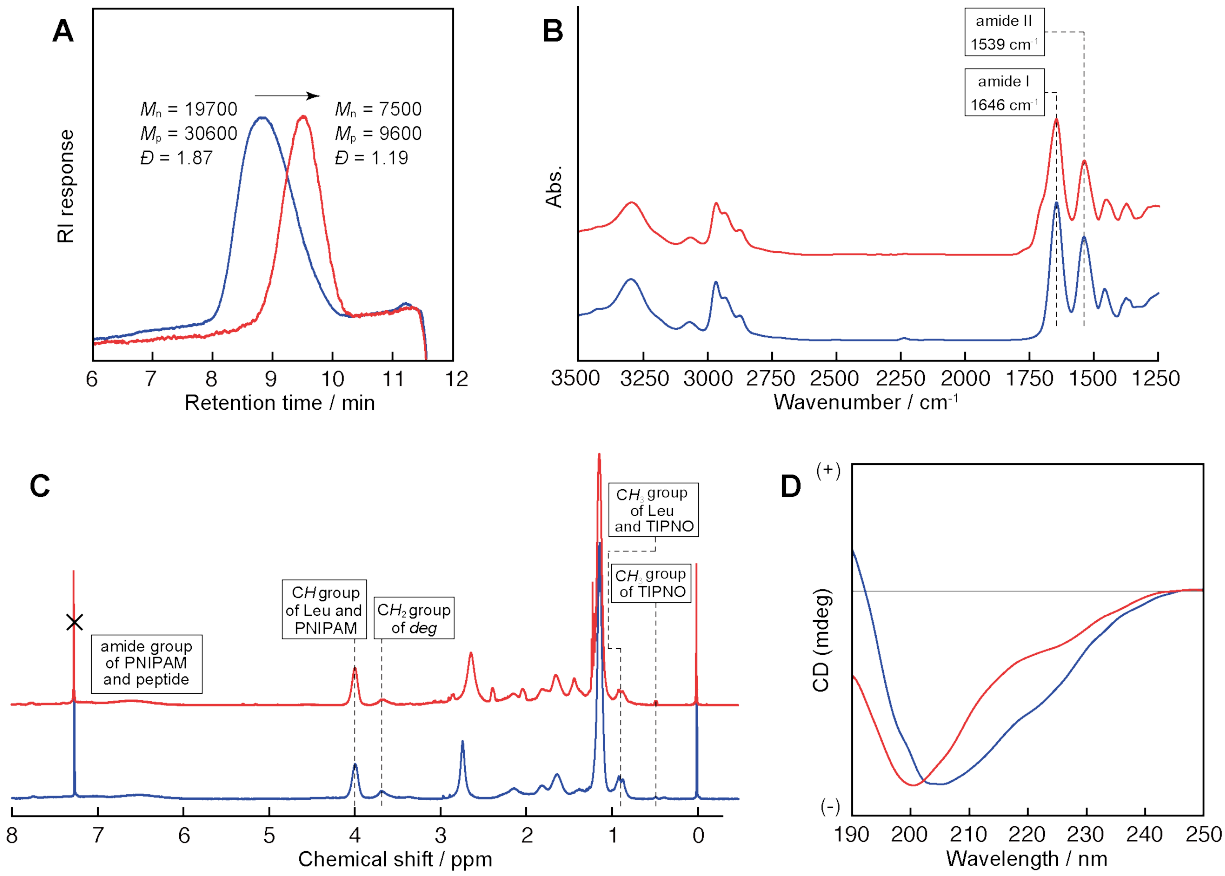

Figure S12. Characterization of the multiblock P3. **A.** SEC traces (THF, 40 °C) of the multiblock **P3** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P3** (blue) and fragmented **P3** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P3** (blue) and fragmented **P3** (red) in $CDCl_3$ at 25°C. **D**. CD spectra of **P3** (blue) and fragmented **P3** (red) in water at 25°C.

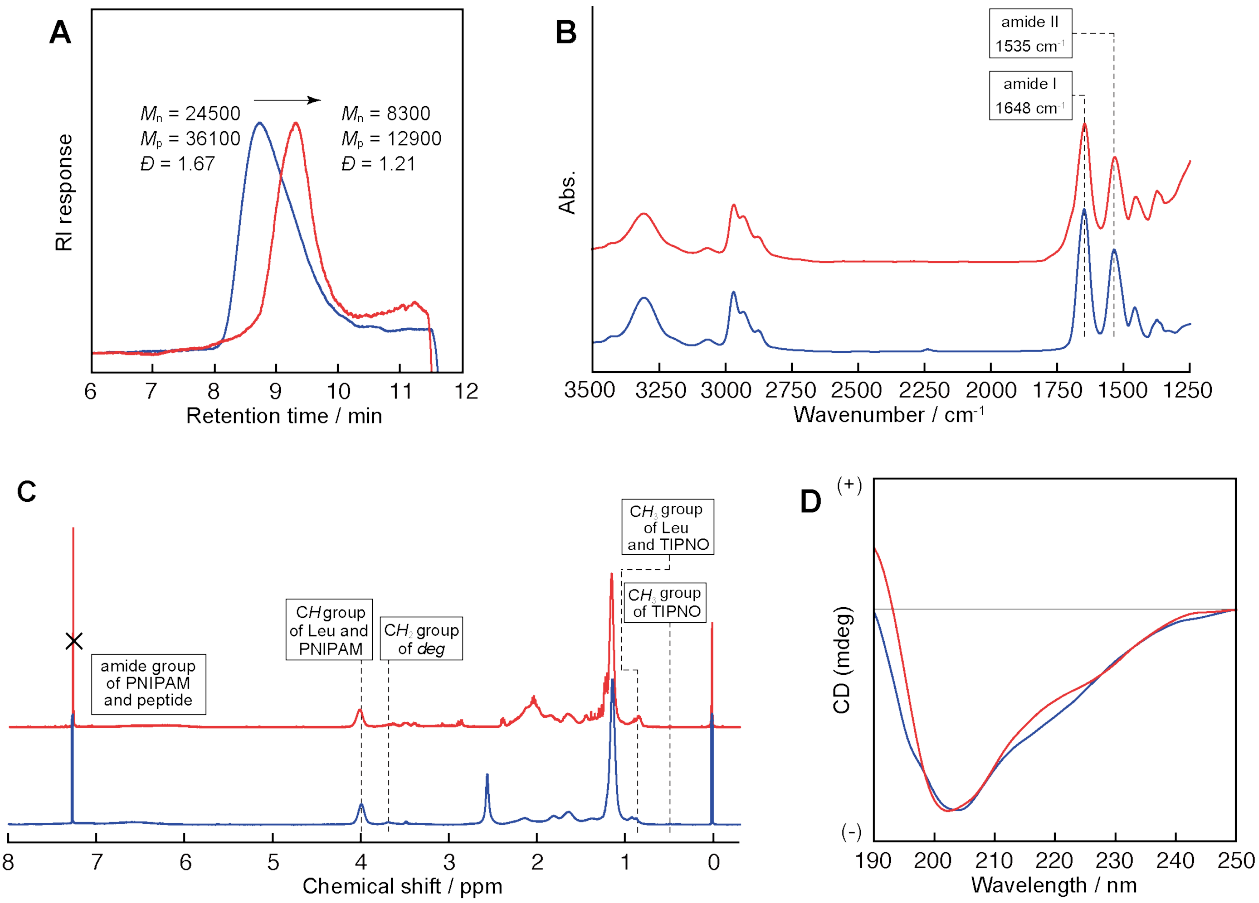

Figure S13. Characterization of the multiblock P4. **A.** SEC traces (THF, 40 °C) of the multiblock **P4** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P4** (blue) and fragmented **P4** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P4** (blue) and fragmented **P4** (red) in $CDCl_3$ at 25°C. **D**. CD spectra of **P4** (blue) and fragmented **P4** (red) in water at 25°C.

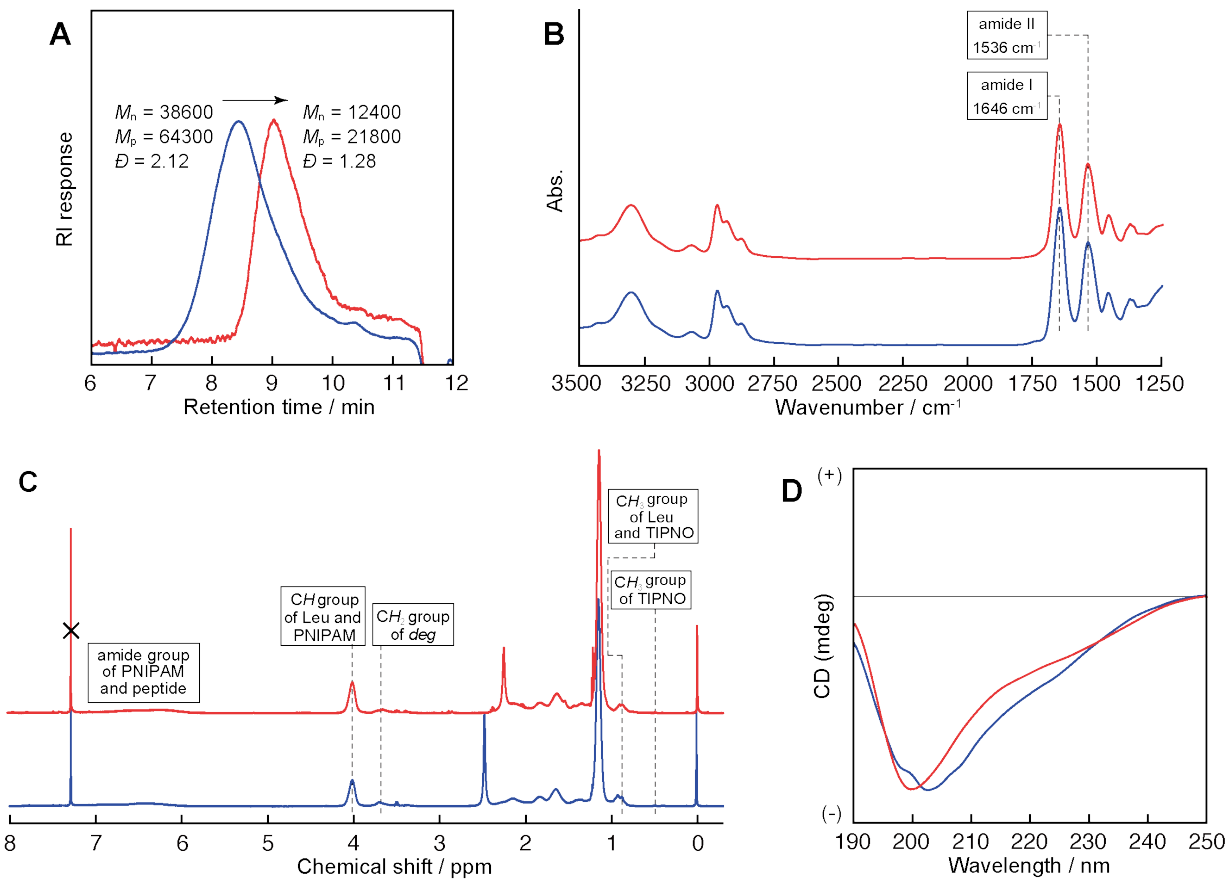

Figure S14. Characterization of the multiblock P5. **A.** SEC traces (THF, 40 °C) of the multiblock **P5** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P5** (blue) and fragmented **P5** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P5** (blue) and fragmented **P5** (red) in $CDCl_3$ at 25°C. **D**. CD spectra of **P5** (blue) and fragmented **P5** (red) in water at 25°C.

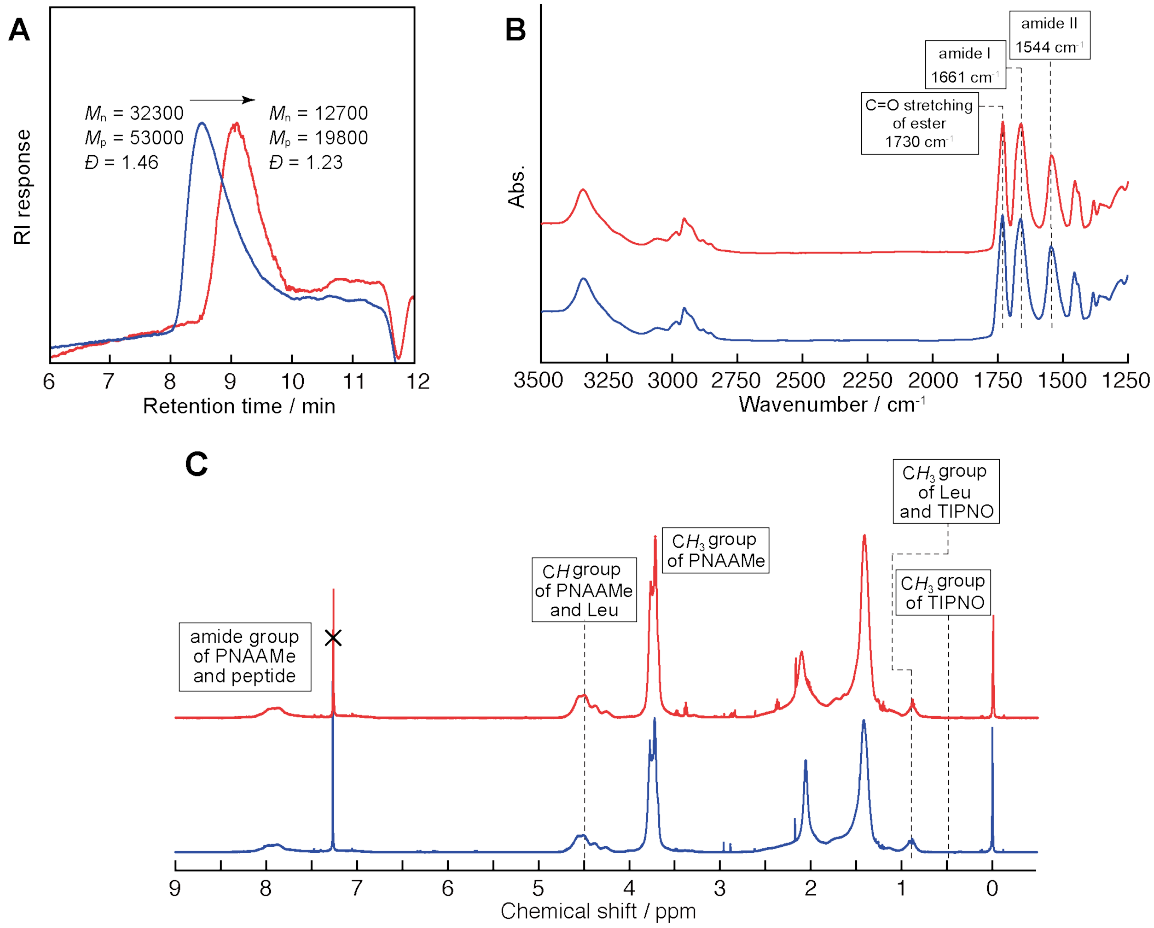

Figure S15. Characterization of the multiblock P6. **A.** SEC traces (THF, 40 °C) of the multiblock **P6** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P6** (blue) and fragmented **P6** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P6** (blue) and fragmented **P6** (red) in $CDCl_3$ at 25°C.

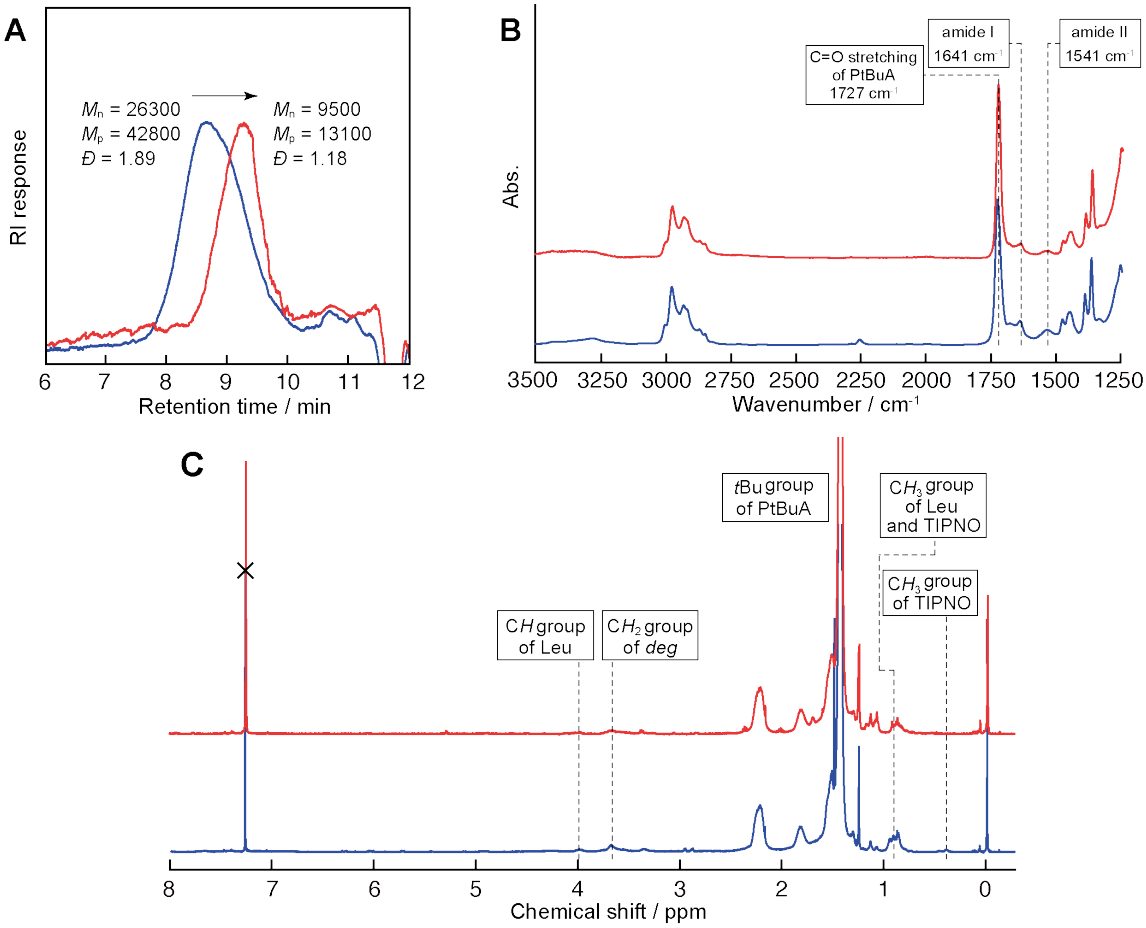

Figure S16. Characterization of the multiblock P7. **A.** SEC traces (THF, 40 °C) of the multiblock **P7** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P7** (blue) and fragmented **P7** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P7** (blue) and fragmented **P7** (red) in $CDCl_3$ at 25°C.

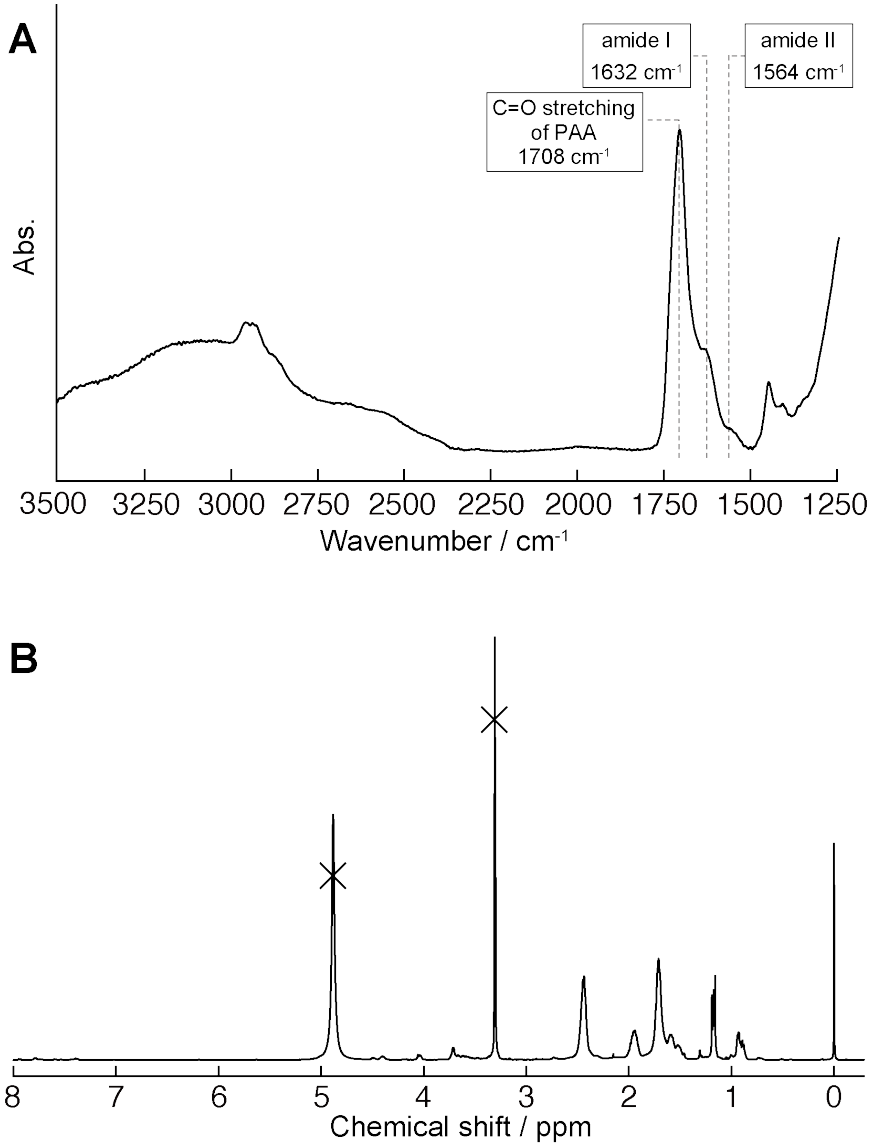

Figure S17. A. Transmission-FTIR spectrum of **P7** obtained after treatment with TFA casted from the MeOH solution onto a CaF_2 plate. **B.** ^1H NMR spectra of **P7** obtained after treatment TFA in CD_3OD at 25°C.

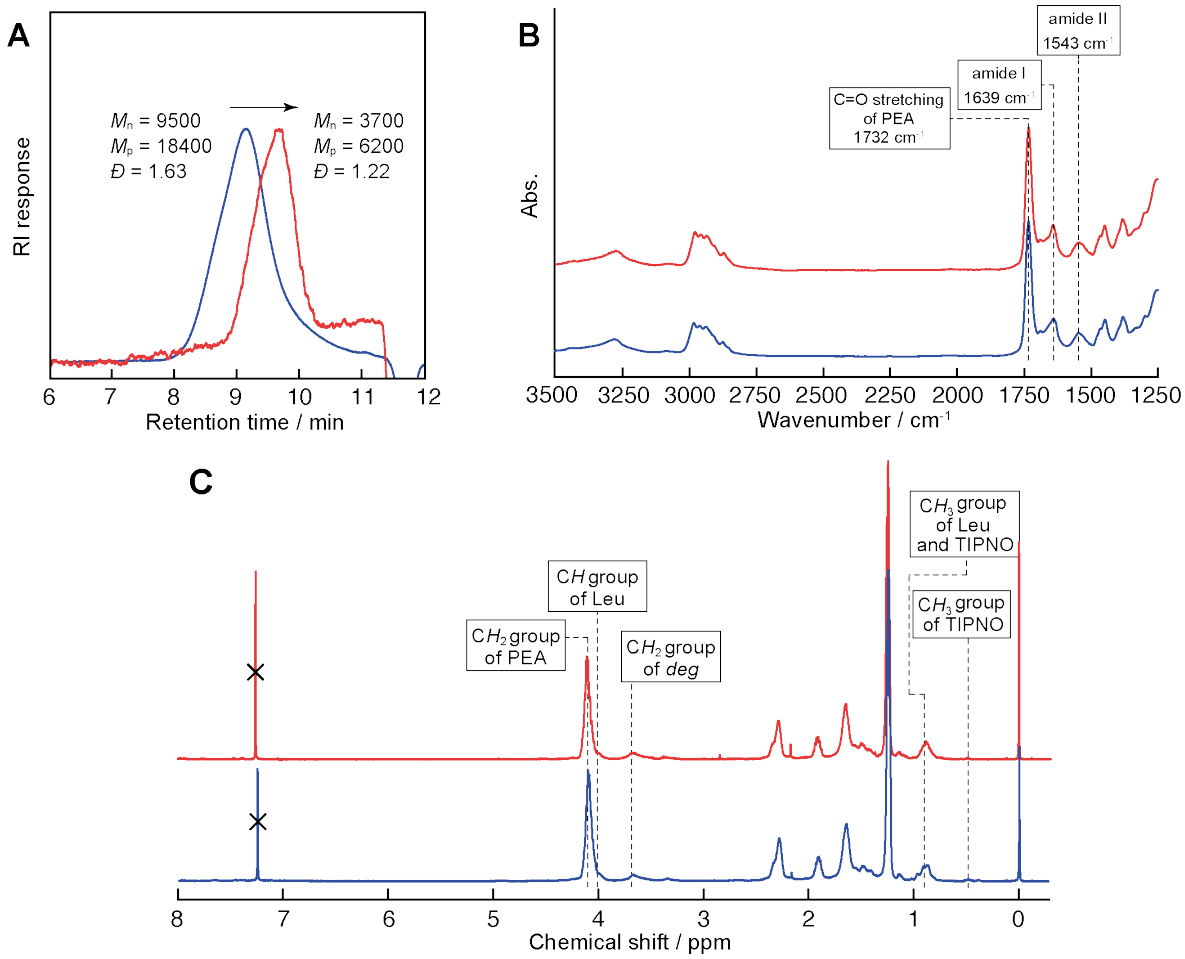

Figure S18. Characterization of the multiblock P8. **A.** SEC traces (THF, 40 °C) of the multiblock **P8** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P8** (blue) and fragmented **P8** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P8** (blue) and fragmented **P8** (red) in $CDCl_3$ at 25°C.

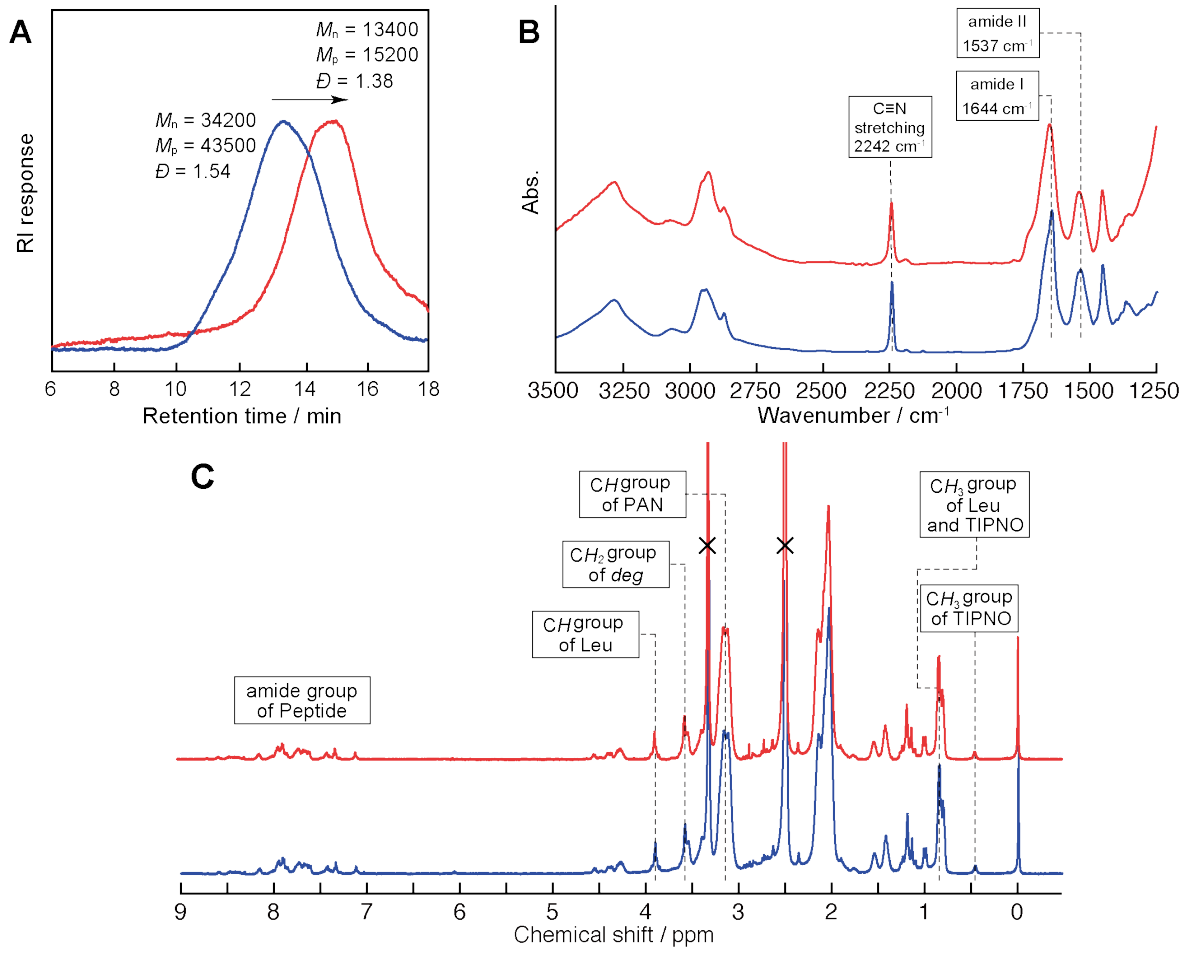

Figure S19. Characterization of the multiblock P9. **A.** SEC traces (DMF, 40 °C) of the multiblock **P9** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P9** (blue) and fragmented **P9** (red) casted from the DMSO solution onto a CaF_2 plate. **C.** ^{1}H NMR spectra of **P9** (blue) and fragmented **P9** (red) in DMSO-d_6 at 25°C.

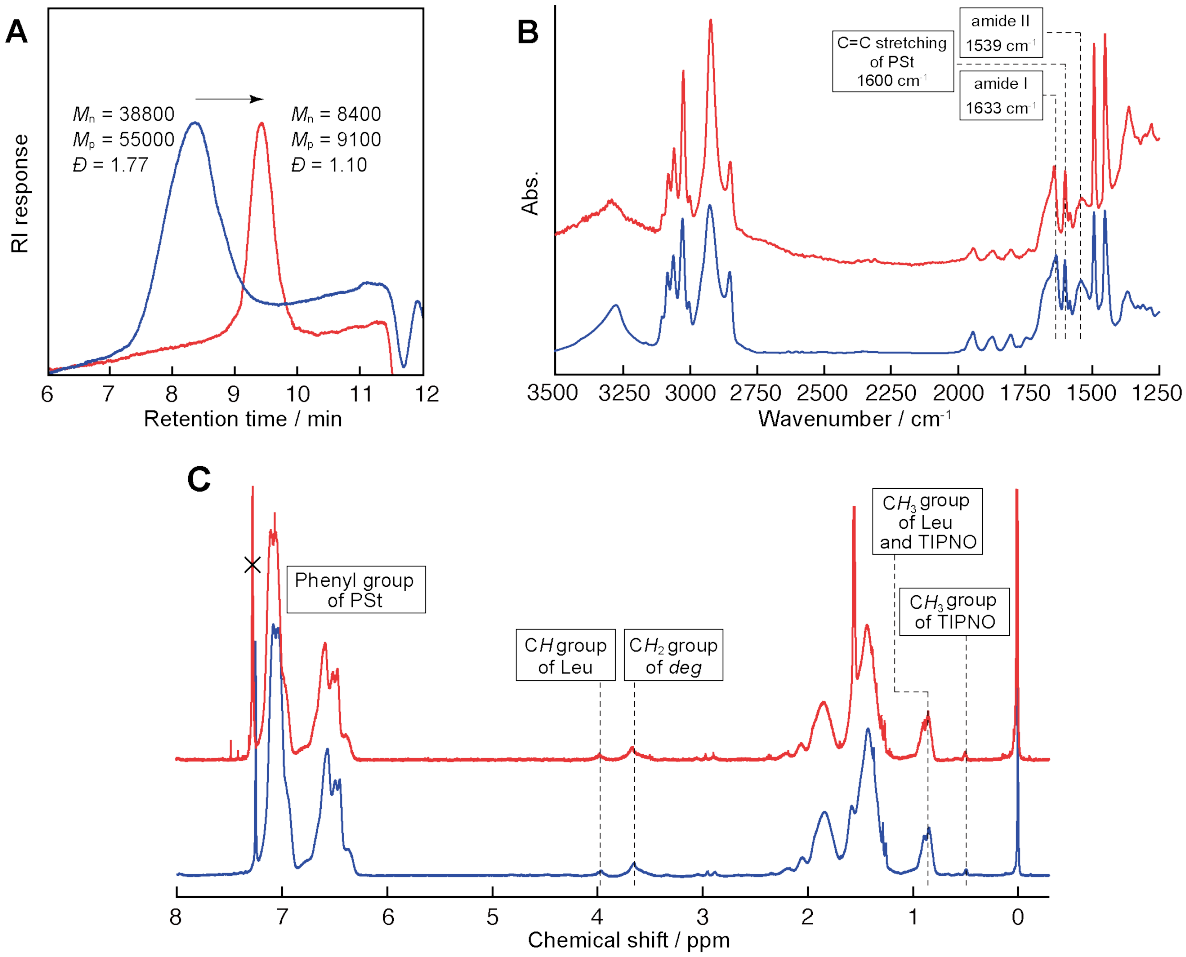

Figure S20. Characterization of the multiblock P10. **A.** SEC traces (THF, 40 °C) of the multiblock **P10** obtained before (blue) and after (red) fragmentation showing a clear shift towards a lower molecular weight. **B.** Transmission-FTIR spectra of **P10** (blue) and fragmented **P10** (red) casted from the $CHCl_3$ solution onto a CaF_2 plate. **C.** ^1H NMR spectra of **P10** (blue) and fragmented **P10** (red) in $CDCl_3$ at 25°C.

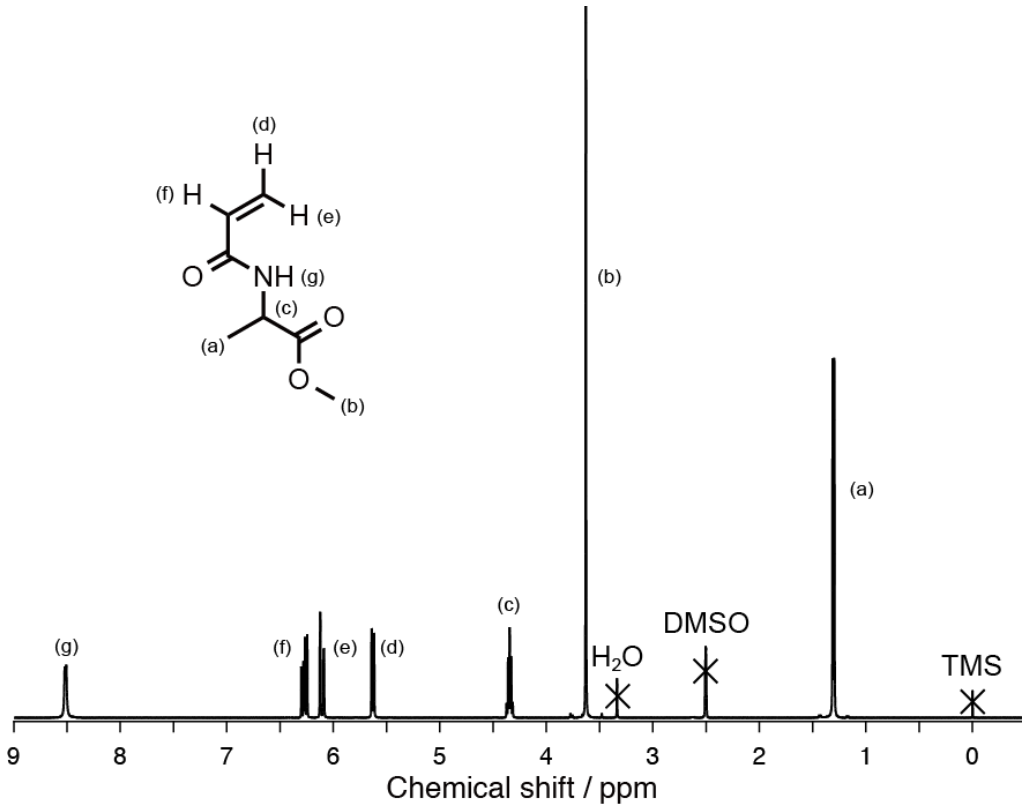

Figure S21. ^{1}H NMR spectrum of NAAMe in DMSO-d_6 at 25°C.