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Electronic supplementary information (ESI) for

Contrasting thermoresponsiveness of stereoisomers of a dense 1,2,3-triazole polymer carrying amide side chains

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Experimental

Measurements

^1H and ^{13}C NMR measurements were carried out on a JEOL JNM ECS400 or ECA500 spectrometer at 25 °C using chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) as a solvent. Chemical shifts were referenced to the signal due to tetramethylsilane (TMS) (0 ppm) in ^1H NMR and to the solvent signals in ^{13}C NMR (77.0 and 39.5 ppm for $CDCl_3$ and DMSO-d_6, respectively). ^1H NMR spectra were also obtained on a JEOL JNM ECS400 spectrometer at varying temperatures using D_2O containing 0.05 wt % 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid (TMSP-d_4), sodium salt as an internal standard (0 ppm). High-resolution mass spectra (HRMS) were measured on a Thermo Fisher Scientific Orbitrap XL using an electrospray ionization (ESI) source. Methanol was used as a solvent. Internal calibration of ESI-MS was carried out using the monoisotopic peaks of sodium adduct ion of diethyl phthalate (*m*/*z* 314.1410), protonated ion of di-2-ethylhexyl phthalate (*m*/*z* 391.2843), and sodium adduct ion of di-2-ethylhexyl phthalate (*m*/*z* 413.2662). Size exclusion chromatography (SEC) measurements were carried out on a JASCO LC-2000 Plus system equipped with a JASCO PU-2086 pump, a JASCO UV-2075 detector, and two TOSOH TSKgel SuperAWM-H columns using dimethyl sulfoxide (DMSO) containing lithium bromide ($1.05\ g\ L^{-1}$) as the eluent at a flow rate of 0.5 or $1.0\ mL\ min^{-1}$. The preset temperature of column oven was 40 °C. The molecular weights were calibrated with standard samples of poly(ethylene glycol) (PEG) and poly(ethylene oxide) (PEO) (Scientific Polymer Products, Inc. (Ontario, NY)). Sample solutions were filtrated with a DISMIC-13JP PTFE 0.50 μm filter (ADVANTEC Toyo Kaisha, Ltd., (Tokyo, Japan)) just prior to injection. The values of enantiomeric excess (ee) were determined by high performance liquid chromatography (HPLC) using a JASCO LC-200 Plus system equipped with a JASCO PU-2080 pump, UV-2075 and CD-4095 detectors, and a DAICEL CHIRALPAK® AD-H (250 mm × φ 4.6 mm) column. A mixed solvent of hexane and 2-propanol (99/1, v/v) was used as an eluent with a flow rate of 1.0 mL min^{-1}. The preset temperature of column oven was 40 °C and the UV and CD signals were detected at 210 nm. Ultraviolet (UV) absorption spectra were collected on a JASCO V-650 spectrophotometer using a 1.0 cm path length quartz cuvette at 25 °C. Circular dichroism (CD) spectra were recorded on a JASCO J-720W spectropolarimeter using a 1.0 cm path length quartz cuvette at 25 °C. Acetonitrile was used as a solvent for UV and CD measurements. Powder X-ray diffraction (PXRD) patterns were taken using nickel-filtered Cu Kα radiation (λ = 0.15418 nm) with a Rigaku RINT 2000 diffractometer. The transmittance data of aqueous polymer solutions were recorded at 510 nm using a JASCO V500 UV-visible spectrometer equipped with a Peltier-type thermostatic cell holder, model ETC-505, increasing and decreasing temperature at a preset speed. Differential scanning calorimetry (DSC) measurements were performed on a CSC Nano-DSC microcalorimeter equipped with a 0.245 mL cell with heating and cooling at 1.0 °C min^{-1} in the range of 20 – 60 °C under elevated pressure. Water was used as a reference.

Materials

Tetrahydrofuran (THF), ethyl acetate, hexane, pyridine, ethanol, 2-propanol, acetone, and diethyl ether were purchased from FUJIFILM Wako Pure Chemical Corp. (Osaka, Japan). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), a solution of tetrabutylammonium fluoride (TBAF) in THF (1 M), *N*-methylethylamine, and 3-mercaptopyropyl silica gel were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). 1-Hydroxybenzotriazole (HOBt), trifluoroacetic acid (TFA), copper(I) bromide (CuBr), dichloromethane (DCM), *N*,*N*-dimethylformamide (DMF), acetic acid (AcOH), toluene, dimethyl sulfoxide (DMSO), chloroform, acetonitrile, and methanol were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Water was purified with a Millipore Milli-Q system. If necessary, solvents were dried with flame-dried molecular sieves 4A or 5A (Nacalai Tesque). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 F254) were used. The products were purified by column chromatography using silica gel 60 (Nacalai Tesque, spherical, neutrality). Other reagents were used without further purification.

The starting materials in this study, i.e., *t*-butyldimethylsilyl(TBDMS)-protected stereoregular dimers of *t*-butyl 4-azido-5-hexynoate (tBuAH) (**1RR** and **1RS**), were prepared according to the procedure reported previously.[75]

Synthesis of stereoregular dimers of *N*-ethyl-*N*-methyl-4-azido-5-hexynamide (ME)

The monomers for stereoregular poly(**ME**), i.e., the RR and RS dimers of **ME**, were synthesized from **1RR** and **1RS**, respectively, according to Scheme 1.

Synthesis of 2RR and 2RS. TFA (2.00 mL, 26.1 mmol) was added into a flask containing a solution of **1RR** (832 mg, 1.56 mmol) in DCM (30 mL) at room temperature, and the reaction mixture was stirred at room temperature for 11 h. Then, TFA (1.00 mL, 13.1 mmol) was further added to the reaction mixture, and stirring was continued at room temperature for another 19 h. Volatile fractions were removed under reduced pressure. The product was purified by column chromatography using a mixed solvent of hexane and ethyl acetate (1/1, v/v) as an eluent. After evaporation of the solvent, **2RR** was obtained as a yellow oil (504 mg, 76.7 %). δ_H (500 MHz; $CDCl_3$; Me_4Si) δ 7.79 (1H, s, triazole CH), 5.59 (1H, t, J = 6.5 Hz, CH), 4.84 (1H, t, J = 6.9 Hz, CH), 2.57 – 2.23 (8H, m, CH_2), 0.95 (9H, s, t-C_4H_9), 0.16 (6H, s, CH_3). δ_C (126 MHz; $CDCl_3$) 177.64, 176.66, 146.25, 120.38, 99.26, 92.81, 56.99, 53.05, 31.90, 30.00, 29.72, 29.41, 26.01, 16.48, –4.88. m/z 443.1833 ($[M + Na]^+$).

2RS was synthesized by deprotection of *t*-butyl ester side chains of **1RS** (2.56 g, 4.81 mmol) using TFA (2 × 2.00 mL, 2 × 26.1 mmol) in the same procedure as that for **2RR**. The product (**2RS**) was obtained as a yellow oil (1.58 g, 77.9 %). δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.79 (1H, s, triazole CH), 5.60 (1H, t, J = 6.8 Hz, CH), 4.81 (1H, m, CH), 2.58 – 2.21 (8H, m, CH_2), 0.95 (9H, s, t-C_4H_9), 0.16 (6H, s, CH_3). δ_C (126 MHz; $CDCl_3$) 178.00, 177.12, 146.03, 120.47, 99.24, 92.76, 56.60, 52.84, 31.79, 30.12, 29.70, 29.15, 25.96, 16.43, –4.93. m/z 443.1832 ($[M + Na]^+$).

Synthesis of 3RR and 3RS. EDC (3.81 g, 19.9 mmol), HOBt (3.01 g, 22.3 mmol), and DIPEA (4.00 mL, 23.2 mmol) were added to a two-neck flask containing a solution of **2RR** (3.07 g, 7.30 mmol) in dry DCM (50 mL), and the reaction mixture was stirred at room temperature for 30 min. Then, *N*-methylethylamine (2.55 mL, 29.8 mmol) was added to the reaction mixture, and stirring was continued for 39 h. Volatile fractions were removed under reduced pressure. The product was purified by column chromatography using a mixed solvent of ethyl acetate and methanol (1/0 − 40/1, v/v) as an eluent. After evaporation of the solvent, **3RR** was obtained as a yellow oil (3.25 g, 88.5%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.75 (1H, s, triazole CH), 5.62 (1H, q, J = 6.1 Hz, CH), 4.80 (1H, t, J = 7.1 Hz, CH), 3.42, 3.40, 3.33, 3.26 (4H, q, J = 7.1 or 7.2 Hz, NCH_2), 2.96, 2.92, 2.90, 2.89 (6H, s, NCH_3), 2.52 – 2.23 (8H, m, CH_2), 1.18 – 1.07 (6H, m, CH_3), 0.94 (9H, s, t-C_4H_9), 0.14 (6H, s, CH_3). δ_C (100 MHz; $CDCl_3$) 171.1, 171.0, 170.2_0, 170.1_7, 146.4, 120.2, 100.4, 91.6, 57.0, 53.0, 44.4, 44.3, 42.5_3, 42.4_6, 34.6, 34.5, 32.8, 32.7, 29.7, 29.6, 29.0, 28.8, 28.3, 26.0, 16.5, 13.5, 13.4, 12.4, 12.3, –4.82. *m*/*z* 525.3090 ($[M + Na]^+$).

3RS was synthesized by amide coupling of **2RS** (947 mg, 2.25 mmol) with *N*-methylethylamine (0.77 mL, 9.0 mmol) using EDC (1.13 g, 5.91 mmol), HOBt (808 mg, 5.98 mmol), and DIPEA (1.20 mL,6.90 mmol) in the same procedure as that for **3RR**. The product (**3RS**) was obtained as a yellow oil (660 mg, 58.3%). δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.76 (1H, s, triazole CH), 5.63 (1H, q, *J* = 6.5 Hz, CH), 4.80 (1H, dt, *J* = 1.7 and 7.1 Hz, CH), 3.42, 3.40, 3.33, 3.26 (4H, q, *J* = 7.1 or 7.2 Hz, NCH_2), 2.96, 2.92, 2.90, 2.89 (6H, s, NCH_3), 2.51 – 2.26 (8H, m, CH_2), 1.18 – 1.08 (6H, m, CH_3), 0.94 (9H, s, *t*-C_4H_9), 0.14 (6H, s, CH_3). δ_C (126 MHz; $CDCl_3$) 171.0, 170.9, 170.2, 170.1, 146.4, 120.1, 100.4, 91.5, 57.1, 57.0, 53.0, 52.9, 44.3, 44.2, 42.5, 42.4, 34.5, 34.4, 32.7, 32.6, 29.7, 29.6, 29.5, 29.0, 28.7, 28.2, 26.0, 16.4, 13.4, 13.3, 12.3_0, 12.2_7, –4.89. *m*/*z* 525.3096 ($[M + Na]^+$).

Synthesis of the RR and RS dimers of ME. AcOH (750 μL, 13.1 mmol) was added to a solution of **3RR** (3.24 g, 6.44 mmol) in dry THF (50 mL) under a nitrogen atmosphere cooling with an ice-salt-water bath, and the solution was stirred for 20 min. Then, a solution of TBAF in THF (1 M, 13.5 mL, 13.5 mmol) was added dropwise to the solution cooling with an ice-salt-water bath. After 30 min, the reaction was allowed to run with stirring at room temperature for 12 h. The volatile fractions were removed under reduced pressure. The product was purified by column chromatography using a mixed solvent of ethyl acetate and methanol (1/0 − 10/1, v/v) as an eluent. The RS dimer was obtained as a yellow oil (2.36 g, 94.4%). δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.78 (1H, s, triazole CH), 5.65 (1H, dt, *J* = 6.9 and 2.3 Hz, CH), 4.80 (1H, t, *J* = 7.2 Hz, CH), 3.44 – 3.38

(2H, m, NCH_2), 3.33, 3.26 (2H, q, *J* = 7.2 Hz, NCH_2), 2.97, 2.92, 2.91, 2.90 (6H, s, NCH_3), 2.64 (1H, d, *J* = 2.4 Hz, CH≡C), 2.52 – 2.22 (8H , m), 1.18 – 1.08 (6H, m, CH_3). δ_C (126 MHz; $CDCl_3$) 171.1, 171.0, 170.1_1, 170.0_8, 146.6, 120.5, 100.4, 78.8, 75.8, 57.0, 52.1, 44.3_5, 44.2_7, 42.6, 42.5, 34.6, 34.5, 32.8, 32.5, 32.4, 29.8, 29.6_2, 29.5_6, 28.8, 28.7, 28.1, 13.5, 13.4, 12.4, 12.3. *m*/*z* 411.2227 ($[M + Na]^+$).

The TBDMS protecting group of **3RS** (1.01 g, 2.01 mmol) was removed using AcOH (240 μL, 4.20 mmol) and TBAF (1 M, 4.40 mL, 4.40 mmol) to obtain the RS dimer as a yellow oil (691 mg, 88.5%). δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.78 (1H, s, triazole CH), 5.65 (1H, dt, *J* = 6.9 and 2.3 Hz, CH), 4.80 (1H, t, *J* = 7.2 Hz, CH), 3.44 – 3.38 (2H, m, NCH_2), 3.33, 3.26 (2H, q, *J* = 7.2 Hz, NCH_2), 2.96, 2.92, 2.91, 2.90 (6H, s, NCH_3), 2.64 (1H, d, *J* = 2.5 Hz, CH≡C), 2.54 – 2.25 (8H, m), 1.16, 1.13, 1.09_9, 1.09_5 (6H, t, *J* = 7.2 or 7.3 Hz, CH_3). δ_C (126 MHz; $CDCl_3$) 171.1, 171.0, 170.1_1, 170.0_9, 146.7, 120.4, 78.8, 75.8, 57.1, 52.1, 44.4, 44.3, 42.6, 42.5, 34.6, 34.5, 32.8, 32.5, 32.4, 29.9, 29.7, 29.6, 28.8, 28.7, 28.0, 13.5, 13.4, 12.4, 12.3. *m*/*z* 411.2226 ($[M + Na]^+$).

CuAAC polymerization of the RR and RS dimers of ME

A typical example of CuAAC polymerization of the RR and RS dimers is described below.

CuBr (4 mg, 28 μmol) was added to a solution of the RS dimer (120 mg, 309 μmol) in DMF (618 μL) under a nitrogen atmosphere. The reaction solution was warmed using an oil bath thermostated at 60 °C with stirring for 48 h. Then, the reaction mixture was cooled down to room temperature. The polymer obtained was purified by reprecipitation using DMF and diethyl ether (1/20, v/v), followed by extraction with water. The polymer (*syndio*-poly(**ME**)-1) was recovered by lyophilization as a light green powder (92 mg, 77 %). Anal. calcd for

$(C_9H_{14}N_4O)(H_2O)_{1.1}(CuO)_{0.042}$: C, 49.72; H, 7.51; N, 25.77; O, 15.76. Found: C, 50.48; H, 6.99; N, 25.16 (ash 1.55%).

Elemental analysis data for the poly(ME) samples

syndio-Poly(**ME**)-3; Anal. calcd for $(C_9H_{14}N_4O)(H_2O)_{1.25}(CuO)_{0.11}$: C, 47.94; H, 7.37; N, 24.85; O, 16.74. Found: C, 47.95; H, 6.62; N, 24.56 (ash 3.87%). *iso*-Poly(**ME**)-1; Anal. calcd for $(C_9H_{14}N_4O)(H_2O)_{0.67}(CuO)_{0.082}$: C, 50.79; H, 7.26; N, 26.32; O, 13.17. Found: C, 51.32; H, 7.28; N, 25.91 (ash 3.08%). *iso*-Poly(**ME**)-2; Anal. calcd for $(C_9H_{14}N_4O)(H_2O)_{1.5}(CuO)_{0.152}$: C, 46.32; H, 7.34; N, 24.01; O, 18.18. Found: C, 47.75; H, 6.90; N, 22.29 (ash 5.19%).

Treatment of the *syndio*-poly(ME)-1 sample with 3-mercaptopropyl silica gel

3-Mercaptopropyl silica gel (50.0 mg) was added to a solution of *syndio*-poly(**ME**)-1 (30.0 mg) in DMF (1.0 mL). The mixture was stirred at room temperature for 4 h, and then the insoluble fractions were removed by passing through a short silica gel column. The polymer sample was recovered by reprecipitation using a pair of DMF and diethyl ether as good and poor solvents. After drying under reduced pressure, the polymer sample was obtained as a colorless powder (27.7 mg, 96%). Anal. calcd for $(C_9H_{14}N_4O)(H_2O)_{1.0}(CuO)_{0.032}$: C, 50.33; H, 7.51; N, 26.08; O, 15.14. Found: C, 51.18; H, 7.02; N, 25.28 (ash 1.18%).

Reference

S1. Y. Kamon, J. Miura, K. Okuno, M. Nakahata and A. Hashidzume, *Macromolecules*, 2023, 56, 292-304.

Table S1. Synthesis of *iso*-poly(**ME**) and *syndio*-poly(**ME**) samples by CuAAC polymerization of the RR and RS dimers [a]

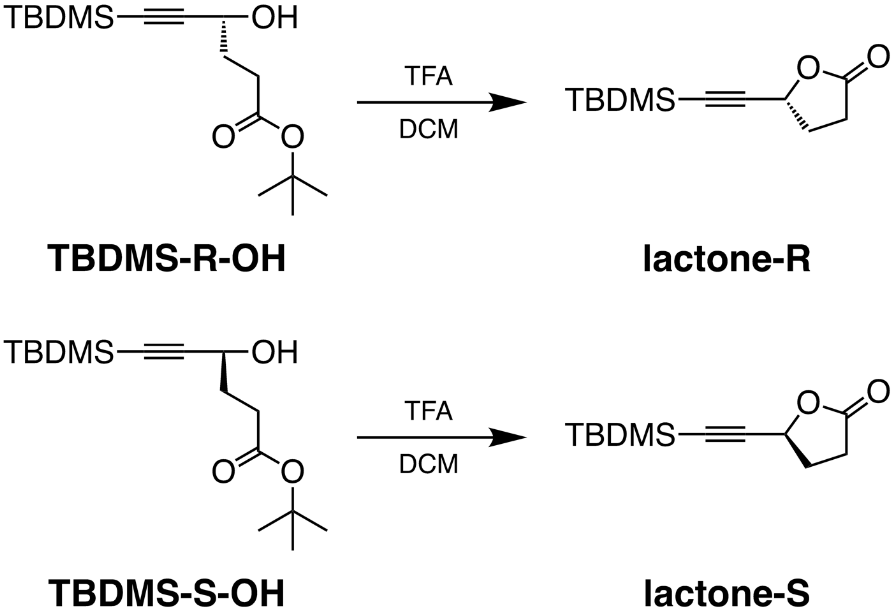
polymer code	monomer	CuBr / mol%	yield / %	M_w [b] / 10^3	M_w/M_n [b]
iso-poly(**ME**)-1 [c]	RR dimer	10	53	18	7.8
iso-poly(**ME**)-2 [d]			14	1.8	1.1
syndio-poly(**ME**)-1	RS dimer	10	77	9.1	2.7
syndio-poly(**ME**)-2	RS dimer	10	71	6.6	2.8
syndio-poly(**ME**)-3	RS dimer	7.5	52	2.5	1.4

a In DMF at 60 °C for 48 h. The monomer concentration was 0.50 M.

b Determined by SEC measured using DMSO containing 1.05 g L^{-1} LiBr as eluent. The molecular weights were calibrated with PEG and PEO standards.

c The water-insoluble fraction.

d The water-soluble fraction.



TBDMS-R-OH

lactone-R

TBDMS-S-OH

lactone-S

Scheme S1. Synthesis of the lactone-R and lactone-S for estimation of the values of enantiomer excess (ee).

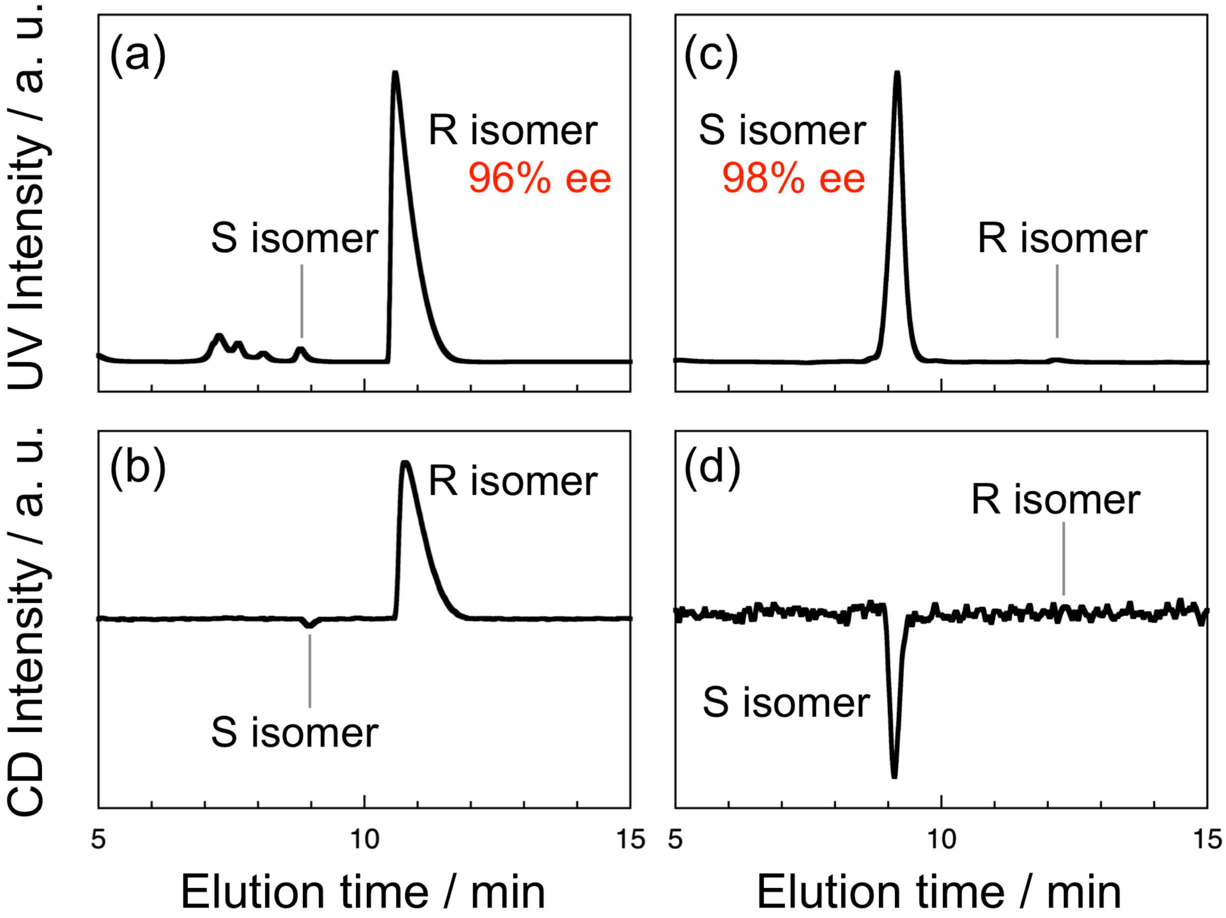


Fig. S1. Chiral HPLC data detected at 210 nm with UV (a and c) and CD detectors (b and d) for lactone-R (a and b) and lactone-S (c and d) using a DAICEL CHIRALPAK® AD-H (250 mm × φ 4.6 mm) column. A mixed solvent of hexane and 2-propanol (99/1, v/v) as eluent with a flow rate of 1.0 mL min^{-1}.

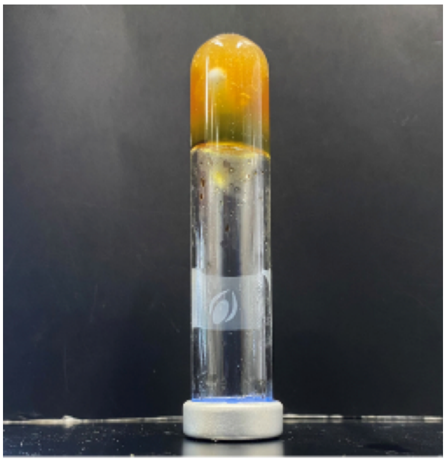


Fig. S2. A photograph of a mixture of CuAAC polymerization of the RR dimer in DMF at 60 °C for 48 h.

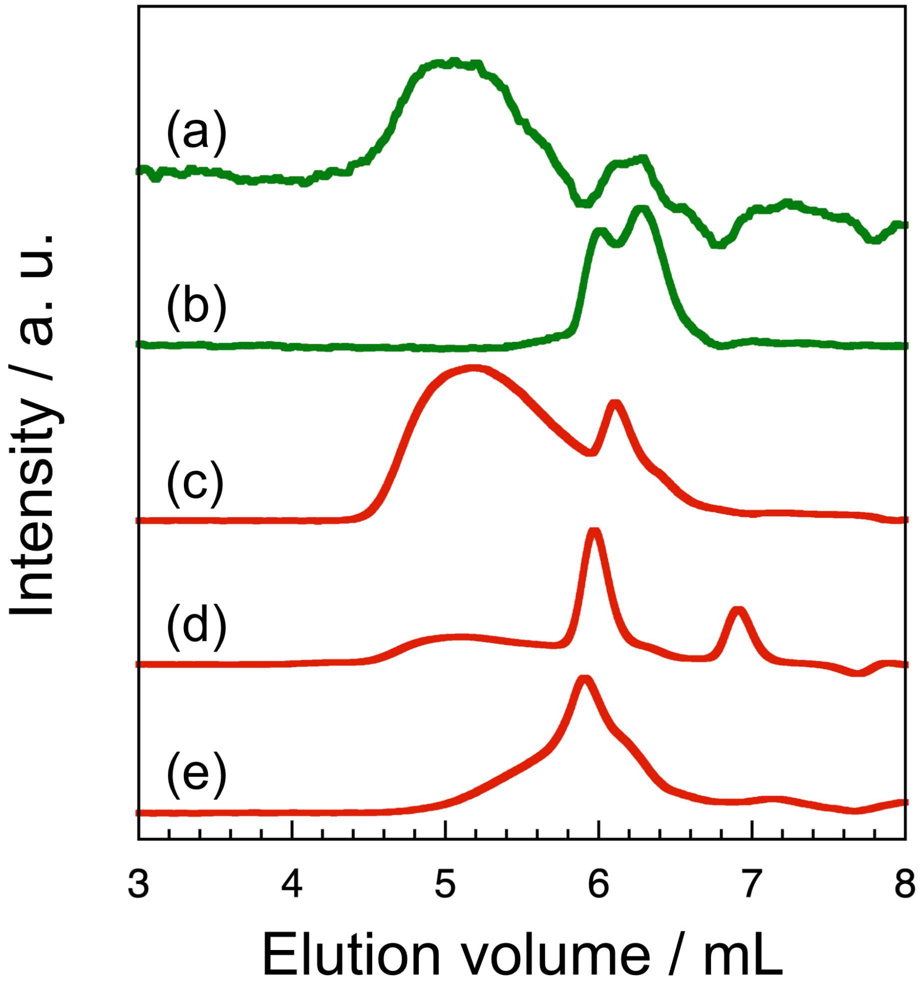


Fig. S3. SEC charts for *iso*-poly(**ME**)-1 (a), *iso*-poly(**ME**)-2 (b), *syndio*-poly(**ME**)-1 (c), *syndio*-poly(**ME**)-2 (d), and *syndio*-poly(**ME**)-3 using DMSO containing lithium bromide (1.05 g L^{-1}) as the eluent at a flow rate of 0.5 or 1.0 mL min^{-1}. The preset temperature of column oven was 40 °C.

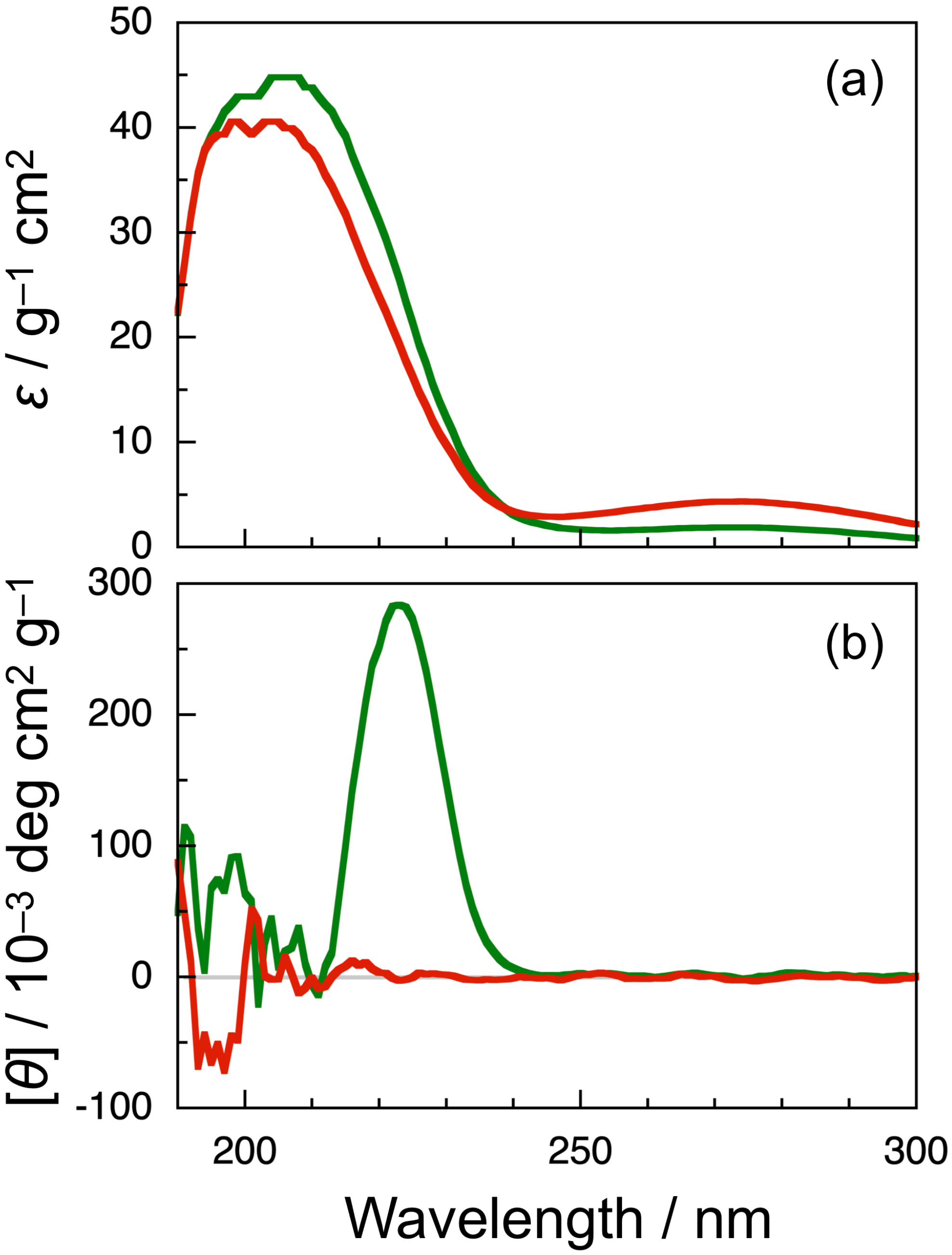


Fig. S4. UV absorption (a) and CD spectra (b) measured for *iso*-poly(**ME**)-2 (green) and *syndio*-poly(**ME**)-2 (red) at 25 °C using acetonitrile as a solvent.

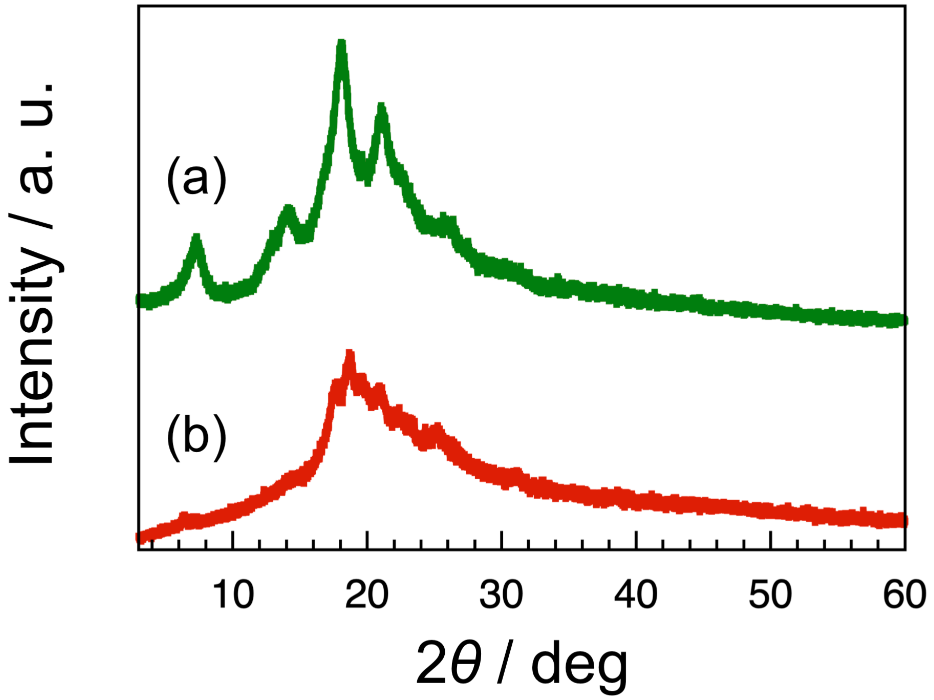


Fig. S5. PXRD patterns for *iso*-poly(**ME**)-1 (a) and *syndio*-poly(**ME**)-2 (b) taken using nickel-filtered Cu Kα radiation ($\lambda = 0.15418$ nm).

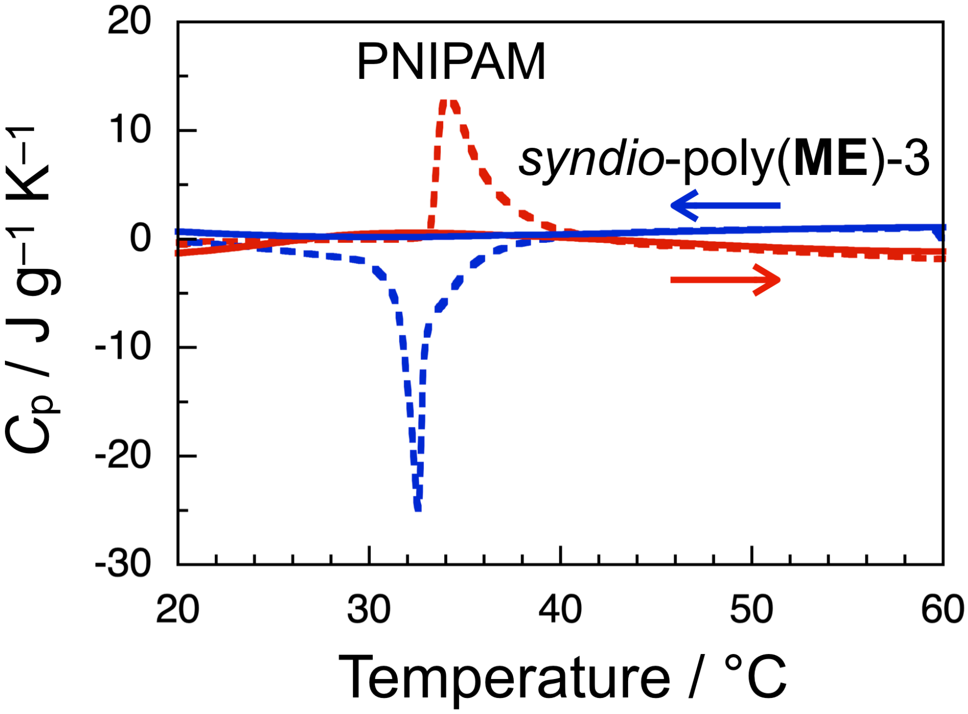


Fig. S6. DSC thermograms for 1.0 wt % aqueous solutions of *syndio*-poly(**ME**)-3 (solid lines) and PNIPAM (broken lines) with heating (red) and cooling (blue) at 1.0 °C min^{-1}.