Supporting Information

Cascade synthesis of architecture-transformable thermo-labile multisite multiblock copolymers

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Experimental

Materials

The chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd. unless otherwise stated. Styrene (St, 99%, Meryer) was purified by successive washing with 5% NaOH aqueous solution and water, drying over Na₂SO₄ and distilled under reduced pressure. ε-Caprolactone (CL, 99%, Sigma-Aldrich) was distilled from CaH₂ under reduced pressure, and N-isopropylacrylamide (NIPAM, 97%, Sigma-Aldrich) was recrystallized twice from mixtures of hexane and toluene. Poly(ethylene glycol) methyl ether acrylate (PEGA, $M_n \approx 480$ Da, 98%, Sigma-Aldrich) was passed through a basic alumina column to remove the inhibitor. CuBr (98%) was purified by stirring in glacial acetic acid and washing with acetone for three times. Anthracene-9-carboxylic acid (98%, Macklin), N,N,N',N'',N''pentamethyldiethylenetriamine (PMDETA, 99%, Aladdin), 2-bromoisobutyryl bromide (97%, Aladdin), stannous octoate (Sn(Oct)₂, 97%, Sigma-Aldrich), maleic anhydride (99%, Alfa Aesar), D,Lhomocysteine thiolactone hydrochloride (98%, Aladdin), ethanolamine (EA, Sigma-Aldrich, 99%) and other reagents with analytical grade were used directly. The organic solvents such as toluene, acetone, dichloromethane (DCM), tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were dried and distilled according to standard procedures. N,N-bis(2-(bromoisobutyryloxy)ethyl)-9anthracenemethanamine (BAMA)¹ and 2-maleimidyl-4-thiobutyrolactone (MTL)² were prepared according to reference methods.

One-shot synthesis of multisite multiblock copolymers

To determine the microstructure and composition of the resultant copolymers, atom transfer radical copolymerization of St with MTL was performed. The copolymerization kinetics was monitored to reveal the continuous formation of P(St-co-MTL) (A), PSt-b-P(St-co-MTL)-b-PSt (BAB), (BAB), and thermolyzed copolymers. BAMA (0.890 g, 1.5 mmol), PMDETA (0.520 g, 3.0 mmol), St (12.5 g, 120 mmol) and MTL (1.48 g, 7.5 mmol) were successively added to a Schlenk tube under nitrogen, and dry toluene was added to reach a total volume of 30 mL. After three freeze-pump-thaw cycles, CuBr (0.430 g, 3.0 mmol) was added to the tube under nitrogen, followed by another two freeze-pump-thaw cycles. The reaction mixture was subjected to cascade reactions at 110 °C. At time intervals (t = 0.5, 0.8, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12, 16, 24, 36, 48, 72, 96 and 120 h), about 2.0 mL (t = 4-36 h) or 1.0 mL (for other runs) of polymer solution was carefully drawn under nitrogen. Partial solution was diluted with CDCl₃ and subjected to ¹H NMR analysis, and monomer conversion (C) was deduced by the equations $C_{\text{St}} = (I_{6.10-6.84} - I_{5.76})/(I_{6.10-6.84} + I_{5.76})$ and $C_{\text{MTL}} = 1 - 3I_{4.76}/(3I_{4.26-4.90} - 4I_{8.40})$, in which I denoted the integral area. The residual solution was diluted with excess THF and passed through a short column of neutral alumina, concentrated and precipitated into hexane or methanol to isolate the copolymer. After purification, various copolymers obtained at different times were labelled as P1-P17, in which the sample number increased with prolonging time, and the results were listed in Table 1. The reaction was eventually stopped at 168 h, the polymer solution was immediately cooled down, and the isolated copolymer was denoted as P18. Various copolymers were subjected to ¹H NMR and GPC analyses to determine the chemical composition, molar mass and dispersity.

P1: $C_{St} = 11.6\%$, $C_{MTL} = 93.2\%$, $M_{n,GPC} = 1.92$ kDa, $D_M = 1.25$. ¹H NMR (CDCl₃, ppm): δ 7.3-8.6 (m, ArH of Ant), 6.0-7.2 (m, PhH of St unit), 4.25-5.00 (m, terminal CHBr, AntCH₂N, and CHN of MTL unit), 3.50-4.25 (m, CH₂O), 3.24 (m, CHCON and CH₂CH₂S of MTL unit), 2.2-3.0 (m, CHCON and CH₂S of MTL unit, and NCH₂CH₂O), 1.2-2.2 (m, CH₂CH of St unit), 0.84 (m, C(CH₃)₂).

P18: $C_{\text{St}} > 99\%$, $C_{\text{MTL}} > 99\%$, $M_{n,\text{GPC}} = 19.3$ kDa, $D_{\text{M}} = 1.71$. ¹H NMR (CDCl₃, ppm): δ 7.3-8.6 (m, Ar*H* of Ant), 6.0-7.2 (m, Ph*H* of St unit), 4.25-5.00 (m, terminal C*H*Br, AntC*H*₂N, and C*H*N of MTL unit), 3.50-4.25 (m, C*H*₂O), 3.23 (m, C*H*CON and C*H*₂CH₂S of MTL unit), 0.5-3.0 (m, other C*H* and C*H*₂ of St and MTL units, NC*H*₂CH₂O, and C(C*H*₃)₂ of linking group).

Fractionation of P10

P10 ($M_{n,GPC}$ = 31.2 kDa, D_M = 2.42) was chosen for fractional precipitation to obtain MMBPs with relatively low dispersity. As P10 (0.70 g) was subjected to the fractionation using mixtures of THF and methanol, centrifugation of the resultant turbid solution was performed to isolate the higher molar mass fraction. After purification, two major fractionated copolymers F1 (0.14 g, $M_{n,GPC}$ = 78.9 kDa, $D_{\rm M}$ = 1.24) and F2 (0.32 g, $M_{\rm n,GPC}$ = 37.0 kDa, $D_{\rm M}$ = 1.45) were obtained. Based on ¹H NMR analysis, no pronounced change of chemical composition of copolymers occurred after fractionation.

Formation of single-chain folding MMBPs via UV-induced anthracene dimerization

Linear MMBPs Px (x = 8-12) were chosen to synthesize single-chain folding copolymers Sx. Px was dissolved in THF to form polymer solution ($c_p = 2.0 \text{ mg mL}^{-1}$), followed by bubbling with nitrogen for 10 min. The polymer solution was then subjected to 365 nm UV irradiation (with the irradiation intensity of 150 mW cm⁻²) at ambient temperature for 3 h. After purification, Sx was isolated in high yield (> 95%).

S10: $M_{n,GPC} = 19.6$ kDa, $D_M = 1.90$. ¹H NMR (CDCl₃): δ 6.0-7.7 (m, Ph*H* of St unit and Ar*H* of AntD), 4.3-4.9 (m, ArC*H* of AntD, terminal C*H*Br and C*H*N of MTL unit), 3.9-4.3 (m, C*H*₂O), 3.82 (m, ArCC*H*₂N), 3.60 (m, NC*H*₂CH₂O), 3.21 (m, C*H*CON and C*H*₂CH₂S of MTL unit), 2.2-3.0 (m, C*H*CON and C*H*₂S of MTL unit), 0.7-2.2 (m, C*H*₂C*H* of St unit and C(C*H*₃)₂).

Synthesis of multiblock homografted copolymer G1

Starting from a linear MMBP F1 ($M_{n,GPC} = 78.9$ kDa, $D_M = 1.24$, $F_{n,Ant} = 6.7$), tandem amine-thiol-ene reactions were performed to synthesize (PSt-*b*-P(St-*co*-MTL)-*b*-PSt)_{*n*}-*g*-EA/PEG (denoted as G1). F1 (0.120 g, with 0.063 mmol of MTL unit), ethanolamine (7.7 mg, 0.126 mmol), triethylamine (6.4 mg, 0.063 mmol) and DMF (1.2 mL) were added to a glass tube under nitrogen. The mixture was heated at 50 °C for 24 h to perform aminolysis of thiolactone groups, followed by addition of PEGA (0.121 g, 0.252 mmol) under nitrogen. The Michael addition between thiol and acrylate moieties was conducted at 25 °C for 24 h. The mixture was transferred into a dialysis membrane tubing (MWCO 1000), followed by dialysis against deionized water for 48 h to remove the impurities. After freeze-drying, G1 (153 mg, 99% yield) was isolated.

G1: $M_{n,GPC}$ = 83.0 kDa, D_M = 1.31. ¹H NMR (CDCl₃, ppm): δ 7.3-8.6 (m, Ar*H* of Ant), 6.0-7.2 (m, Ph*H* of St unit), 4.3-4.9 (m, AntC*H*₂N, terminal C*H*Br, and C*H*N originating from MTL unit), 4.26 (m, C*H*₂O of linking group and COOC*H*₂ connecting with PEG), 3.65 (m, C*H*₂C*H*₂O of PEG and CONHCH₂C*H*₂OH), 3.38 (s, terminal C*H*₃O and CONHCH₂CH₂OH), 0.5-3.3 (m, other C*H*, C*H*₂ and C*H*₃ of St unit, maleimide-based unit, PCL, and linking group).

Synthesis of multiblock heterografted copolymer G2 by ROP

Hydroxyl bearing G1 was used as a macroinitiator to initiate CL polymerization, and (PSt-*b*-P(St-*co*-MTL)-*b*-PSt)_{*n*}-*g*-PCL/PEG (denoted as G2) was obtained by "grafting from" approach. To a Schlenk tube was added G1 (50 mg, with 0.021 mmol of –OH group), CL (60 mg, 0.525 mmol) and Sn(Oct)₂ (4.3 mg, 0.011 mmol) under nitrogen, and then dry toluene was added to reach a total volume of 0.53 mL. After three freeze-pump-thaw cycles, the mixture was subjected to polymerization at 110 °C for

24 h. The crude product was purified by repeatedly precipitation from the THF solution into excess methanol. After vacuum drying, G2 (97 mg) was isolated as white solid powders, and the monomer conversion was determined as 78% by gravimetry.

G2: $M_{n,GPC} = 121$ kDa, $\mathcal{D}_{M} = 1.34$. ¹H NMR (CDCl₃, ppm): δ 7.3-8.6 (m, Ar*H* of Ant), 6.0-7.2 (m, Ph*H* of St unit), 4.41 (m, AntC*H*₂N, terminal C*H*Br, and C*H*N originating from MTL unit), 3.9-4.3 (m, C*H*₂O of PCL and linking group, CONHCH₂C*H*₂O, and COOC*H*₂ connecting with PEG), 3.65 (m, C*H*₂C*H*₂O of PEG and terminal C*H*₂OH of PCL), 3.49 (m, CONHC*H*₂CH₂O), 3.38 (s, terminal C*H*₃O), 0.5-3.3 (m, other C*H*, C*H*₂ and C*H*₃ of St unit, maleimide-based unit, PCL, and linking group).

Synthesis of multiblock heterografted copolymer G3 by UV-induced concurrent polymerization and intrachain cross-linking

In the presence of type II photoinitiator benzophenone, hydroxyethyl group remaining in G1 upon UV irradiation served as the initiating site to perform radical polymerization to grow pendant chains. Meanwhile, anthryl groups were subjected to intramolecular cross-linking, leading to the formation of AntD-bearing single-chain folding of the multiblock backbone. G1 (50 mg, with 0.021 mmol of –OH group), NIPAM (143 mg, 1.26 mmol) and about 0.1 mL of DCM solution containing benzophenone (0.80 mg, 4.4 µmol) were added to a Schlenk tube, and then dry DCM was added to reach a total volume of 1.3 mL. After three freeze-pump-thaw cycles, the mixture was subjected to reaction upon 365 nm UV irradiation (with the irradiation intensity of 3.0 mW cm⁻²) at ambient temperature for 5 h. The crude product was purified by repeatedly precipitation from the THF solution into excess diethyl ether. After vacuum drying, G3 (133 mg) was isolated as white solid powders, and the monomer conversion was determined as 58% by gravimetry.

G3: $M_{n,GPC} = 136$ kDa, $D_M = 1.59$. ¹H NMR (CDCl₃, ppm): δ 5.8-7.7 (m, Ar*H* of AntD, Ph*H* of St unit and CON*H* of PNIPAM), 3.9-4.8 (m, ArC*H* of AntD, terminal C*H*Br, C*H*N originating from MTL unit, C*H*NH of PNIPAM, C*H*₂O of linking group, and COOC*H*₂ connecting with PEG), 3.69 (m, CONHC*H*₂CHOH), 3.65 (m, C*H*₂C*H*₂O of PEG), 3.52-3.58 (m, CONHCH₂C*H*OH), 3.38 (s, terminal C*H*₃O), 0.5-3.3 (m, other C*H*, C*H*₂ and C*H*₃ of St unit, maleimide-based unit, PNIPAM, and linking group).

Thermo-induced self-catalyzed cleavage of various polymers

Upon heating, the cleavage of AntD and ester groups led to "degradation"-type topological transformation. Representative MMBPs P10 and S10 were subjected to thermolysis in DMF at a fixed temperature (T = 120 or 150 °C) for the desired time. In a typical run, P10 (50 mg) was dissolved in DMF under nitrogen, and the polymer solution ($c_p = 50 \text{ mg mL}^{-1}$) was heated at 150 °C. At time intervals (t = 6, 12, 24, 48, 72, 120 and 168 h), about 0.1 mL of polymer solution was drawn. After

cooling down, the polymer solution was subjected to acidification using dilute HCl aqueous solution. Most of solvents were removed by distillation under reduced pressure, followed by addition of methanol to precipitate the thermolyzed polymer. Thermolysis of S10 was performed according to a similar procedure. Thermolyzed polymers obtained at distinct times were subjected to GPC analysis to understand the evolution of $M_{n,GPC}$ and \mathcal{D}_{M} with prolonging time.

Similarly, the graft copolymer G3 ($M_{n,GPC} = 136$ kDa, $D_M = 1.59$) was subjected to thermal treatment in DMF at 150 °C for 96 h. After cooling down to room temperature, a few drops of diluted HCl aqueous solutions were added to the polymer solution, followed by stirring for 2 h. After purification by concentration and precipitation into cold diethyl ether, the thermolyzed polymer G3' was obtained in 90% yield. G3': $M_{n,GPC} = 23.6$ kDa, $D_M = 2.18$. ¹H NMR (CDCl₃, ppm): δ 5.5-7.5 (m, PhH of St unit and CONH of PNIPAM), 3.85-4.60 (m, terminal CHBr, CHN originating from MTL unit, CHNH of PNIPAM, and COOCH₂ connecting with PEG), 3.43-3.85 (m, CH₂CH₂O of PEG and CONHCH₂CHOH), 3.38 (s, terminal CH₃O), 0.5-3.2 (m, other CH, CH₂ and CH₃ of St unit, maleimide-based unit, PNIPAM, and end group).

Self-assembly of P1-P18 in organic solvents

The copolymer (4.0 mg) and THF (2.0 mL) were added to a vial, followed by stirring in a closed system for 4 h. Afterward, methanol (2.0 mL) was carefully added to the polymer solution via a metering pump (with addition rate of around 1.0 mL h⁻¹) under vigorous stirring, followed by stirring overnight to reach an equilibrium. The resultant copolymer assemblies with a concentration of 1.0 mg mL⁻¹ were subjected to DLS and TEM analyses.

Self-assembly of G3 and G3' in aqueous solutions

The solvent switch method was adopted to prepare copolymer assemblies formed in aqueous solutions. In a typical run, 10 mg of the copolymer and 2.0 mL of DMF were stirred to form the solution, followed by slow addition of 6.0 mL of deionized water in 12 h using a metering pump. After further stirring for 5 h, the resultant solution was transferred into a dialysis membrane tubing (MWCO 1000) and dialyzed against deionized water for 24 h to remove the organic solvent. Afterwards, deionized water was carefully added to reach a total volume of 10 mL, followed by stirring for 2 h to form copolymer assemblies with a concentration of 1.0 mg mL⁻¹. On this basis, the thermoresponsive behavior was revealed by turbidity analysis, the apparent hydrodynamic diameter (D_h) and particle size distribution (PD) of copolymer assemblies were analyzed by DLS, and the morphology of nano-objects was determined by TEM.

Characterization

¹H NMR spectra (400 MHz) were recorded in CDCl₃ on a Varian Unity Inova 400 MHz spectrometer

at 25 °C. Apparent molar mass ($M_{n,GPC}$) and dispersity ($D_M = M_w/M_n$) of various polymers were measured on a TOSOH HLC-8320 gel permeation chromatography (GPC) using three TSKgel SuperMultipore HZ-M columns at 40 °C. DMF (for PNIPAM-bearing polymers) or THF (for other polymers) was used as the eluent at a flow rate of 0.35 mL min⁻¹, and the samples were calibrated with PSt standard samples. Differential scanning calorimetry (DSC) was measured on Q200 DSC from TA Instruments using a heating/cooling rate of 10 K min⁻¹. Fourier Transform Infrared (FT-IR) spectra were recorded on a Bruker Vertex 70 spectrometer. UV-vis absorption spectra were recorded using a Shimadzu UV-1800 spectrophotometer. Fluorescence spectra of copolymer solutions were recorded at different temperatures using a Shimadzu RF-5301 fluorescence spectrometer with an excitation wavelength of 365 nm. Turbidity analysis of polymer solutions was performed at 500 nm on a Shimadzu UV-3150 UV-vis spectrophotometer equipped with a thermoregulator, and the cloud point $(T_{\rm c})$ was calculated as the temperature at the half of the maximal and minimal transmittances. To determine apparent hydrodynamic diameter (D_h) and particle size distribution (PD) of copolymer assemblies formed in aqueous solution, dynamic light scattering (DLS) analysis was performed using Zetasizer Nano-ZS from Malvern Instruments equipped with a 633 nm He-Ne laser using backscattering detection. Transmission electron microscopy (TEM) images were measured using a Hitachi HT7700 electron microscope with an acceleration voltage of 120 kV to determine the morphology of nano-objects, in which the freeze-drying technique was used to stabilize the shape of copolymer assemblies formed in aqueous solutions.

References

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2 T. Rudolph, P. Espeel, F. E. Du Prez and F. H. Schacher, Polym. Chem., 2015, 6, 4240-4251.



Scheme S1 Synthesis of single-chain folding copolymers Sx (x = 8-12) by UV-induced intrachain cross-linking of anthryl groups of Px, in which only the trans-bis-cycloadduct of anthracene dimer was listed in the chemical structure.



Fig. S1 ¹H NMR spectra of main polymer solutions comprising copolymer, PMDETA, toluene and/or monomers obtained at different times recorded in CDCl₃ (A), and expanded ¹H NMR spectrum (δ = 4-6 ppm) of polymer solution obtained at 0.5 h (B), in which the signals (*) at 6.71, 5.76 and 5.24 ppm denoted the remaining vinyl group of styrene, and the signal of C*H*N (MTL) was noted at 4.76 ppm. See Table 1 for detailed reaction conditions.



Fig. S2 ¹H NMR spectra of typical copolymers obtained at different times (t = 16 (P11), 24 (P12), 48 (P14), 96 (P16), 168 h (P18)) recorded in CDCl₃ (*).



Fig. S3 Influence of reaction time on number-average functionality ratio $(F_n(t)/F_n(16 \text{ h}))$ of anthryl (Ant) and thiolactone (TL) groups of the copolymers obtained at 16 h and a fixed time (*t*).



Fig. S4 UV-vis (A) and fluorescence (B, $\lambda_{ex} = 365 \text{ nm}$) spectra of P10, P11, P12 and P18 in THF ($c_p = 1.0 \text{ mg mL}^{-1}$).



Fig. S5 DSC curves of representative polymers (A), and evolution of $T_g(Px)$ (x = 1-18) with increasing sample number (x) of various polymers (B).



Fig. S6 ¹H NMR spectrum of G1 recorded in CDCl₃ (*), in which f' denoted the signal of $COOCH_2$ connecting with PEG.



Fig. S7 UV-vis spectra of G1, G2 and G3 solutions formed in THF ($c_p = 1.0 \text{ mg mL}^{-1}$).



Fig. S8 GPC traces of copolymers obtained by thermal treatment of P10 in DMF at 120 °C (A) and 150 °C (B) for different times.



Fig. S9 GPC traces of copolymers obtained by thermal treatment of S10 in DMF at 120 °C (A) and 150 °C (B) for different times.



Fig. S10 Proposed chemical structures of P10' and S10' obtained by thermolysis of P10 and S10 at 150 °C for 168 h (A), and ¹H NMR spectra of P10' and S10' recorded in CDCl₃ (B).



Fig. S11 FT-IR spectra of P10, S10 and their thermolyzed polymers P10' and S10'.



Fig. S12 Temperature-dependent transmittances of G3 and G3' aqueous solutions ($c_p = 1.0 \text{ mg mL}^{-1}$).



Fig. S13 DLS plots of copolymer assemblies formed in the mixture of THF and methanol ($v_{\text{MeOH}}/v_{\text{THF}}$ = 1, c_{p} = 1.0 mg mL⁻¹) at 25 °C.



Fig. S14 Representative TEM images of copolymer assemblies formed from P1 (a), P4 (b), P10 (c), P12 (d), P14 (e) and P18 (f) in the mixture of THF and methanol ($v_{\text{MeOH}}/v_{\text{THF}} = 1$, $c_p = 1.0 \text{ mg mL}^{-1}$).



Fig. S15 DLS plots of copolymer assemblies formed from G3 and G3' in aqueous solutions ($c_p = 1.0$ mg mL⁻¹) at 25 °C.