Supporting information

Inverse miniemulsion ATRP. A new method for synthesis and functionalization of well-defined water-soluble/crosslinked polymeric particles

Jung Kwon Oh, Chuanbing Tang, Haifeng Gao, Nicolay V. Tsarevsky, Krzysztof Matyjaszewski*

Center for Macromolecular Engineering, Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213

Materials

Oligo(ethylene glycol) monomethyl ether methacrylate (OEOMA) with different molecular weights was purchased from Aldrich. OEOMA300 with M = 300 g/mol, pendent EO units DP ≈ 7, was purified by passing it through a column filled with basic alumina to remove inhibitor. OEOMA1100 with M = 1100 g/mol, pendent EO units DP ≈ 23, was dissolved in tetrahydrofuran (THF) before passing through the column. Copper(II) bromide ($CuBr_2$, 99%), 1,3-dicyclohexylcarbodiimide (DCC, 99%), and Bu_3P (95%) were used as received from Acros. 4-Dimethylaminopyridine (DMAP, 99+%), 3,3'-dithiopropionic acid (**3**), L-ascorbic acid (99+%), sorbitan monooleate (Span 80), N,N,N',N",N"-pentamethyldiethylenetriamine (PMDETA, 99%), and cyclohexane (HPLC grade) were used as received from Aldrich. Copper(I) bromide (CuBr, 99%, Acros) was purified[1] and tris[(2-pyridyl)methyl]amine (TPMA) was prepared according to literature procedures.[2]

Synthesis of poly(ethylene glycol)-functionalized bromoisobutyrate (PEO5000-Br) macroinitiator

A water-soluble macroinitiator, poly(ethylene glycol) (PEO)-functionalized bromoisobutyrate (PEO5000-Br, EO units DP ≈ 113), was synthesized using a reported procedure.[3] Poly(ethylene glycol) monomethyl ether (PEO5000-OH, M = 5000 g/mol, Fisher Scientific, 20 g, 4 mmol) was reacted with 2-bromo-2-methylpropionic acid (98%, Acros, 0.74 g, 4.4 mmol) in the presence of

DCC (0.9 g, 4.4 mmol), and a catalytic amount of DMAP (0.5 g), in CH_2Cl_2 (150 mL). The product was mixed with THF, isolated from dispersion by vacuum filtration, and then dried in a vacuum oven at 30 °C for 12 h. In this way, residues such as excess DCC, DMAP, and dicyclohexyl urea could be removed from the final product.

Synthesis of dithiopropionyl poly(ethylene glycol) dimethacrylate (1, DMA-PEOSS)

Poly(ethylene glycol) methacrylate (**2**, PEOMA526, M = 526 g/mol, Aldrich) was purified using the solvent extraction method as described elsewhere.[4] THF was distilled over metallic sodium and benzophenone. A solution consisting of **3** (2.3 g, 10 mmol) in dried THF (30 mL) was added dropwise to a solution consisting of the purified **2** (10 g, 19 mmol), DCC (3.9 g, 19 mmol), and a catalytic amount of DMAP (0.5 g), in CH_2Cl_2 (60 mL) in an ice bath at 0 °C over 20 min. The resulting mixture was allowed to stir at room temperature for 12 h. The formed solids were removed by vacuum filtration and the combined solvents were removed by rotary evaporation. The resulting oily residue was dissolved in CH_2Cl_2 (100 mL), and was washed with aqueous $NaHCO_3$ solution three times to remove excess diacid. After CH_2Cl_2 was removed, the resulting yellow oily residue was dissolved in a minimum amount of THF (5 mL), and put in refrigerator at – 5 °C for 12 h. The insoluble solids were removed by vacuum filtration, THF was removed by rotary evaporation, and then the product was dried in a vacuum oven at 35 °C for 12 h to form a yellow oily residue, yield 6.8 g, 50 %. ^{1}H-NMR (DMSO-d_6, ppm) 1.9 (s, 6H, CH_3-), 2.7 (t, 4H, -C(O)-$\underline{CH_2}$-CH_2-SS-), 2.9 (t, 4H, -O(O)C-CH_2-$\underline{CH_2}$-SS-), 3.3-3.7 (m, 72H, -$(CH_2CH_2O)_n$-), 4.0-4.3 (m, 8H, -C(O)O-CH_2- and -CH_2-O(O)C-), 5.7 (s, 2H, CH=), 6.0 (s, 2H, CH=).

General procedure for AGET ATRP of OEOMA in inverse cyclohexane miniemulsion

A series of AGET ATRP reactions in inverse miniemulsion, using OEOMA300 and OEOMA1100, were carried out at 30 °C. An example detailing a typical procedure for the synthesis of P(OEOMA1100) colloidal particles follows: OEOMA1100 (1.4 g, 1.27 mmol), PEO5000-Br (93.3 mg, 0.018 mmol), TPMA (2.6 mg, 0.009 mmol), $CuBr_2$ (2.0 mg, 0.009 mmol), and water (1.4 mL) were mixed in a 50 mL round bottom flask at room temperature. The resulting clear solution was mixed with a solution of Span 80 (1.0 g) in cyclohexane (20 g), and

the mixture was sonicated for 2 min in an ice bath at 0 °C to form a stable inverse miniemulsion. The dispersion was transferred into a 50 mL Schlenk flask, and then bubbled with nitrogen for 30 min. The flask was immersed in an oil bath preheated to 30 °C, and then an argon-purged aqueous solution of ascorbic acid (0.028 mmol/mL, 0.006 mmol, 224 μL) was added via syringe to start the polymerization. Samples were removed periodically from the reaction to determine conversion and molar mass by GPC. The polymerization was stopped by exposing the reaction mixture to air.

A similar procedure was used for the inverse miniemulsion AGET ATRP of OEOMA300, except that OEOMA300 (1.4 g, 4.67 mmol), PEO5000-Br (79.8 mg, 0.016 mmol), TPMA (2.3 mg, 0.008 mmol), $CuBr_2$ (1.7 mg, 0.008 mmol), water (1.4 mL), and aqueous ascorbic acid solution (0.005 mmol, 192 μL) were used.

Synthesis of P(OEOMA300) nanogels by AGET ATRP

A procedure similar to that used for the AGET ATRP of OEOMA300 in inverse miniemulsion at 30 °C was employed except that 1.5 mol% crosslinker (**1**) was introduced into aqueous solution. Ascorbic acid was added to start polymerization. The polymerization was stopped at 2 h by exposing the reaction mixture to air. The resulting nanogels were purified by removal of the cyclohexane, addition of THF, and then the resulting heterogeneous mixture was stirred at room temperature for 5 h. The gels were separated by centrifugation (15,000 rpm x 20 min) and decantation of the supernatant. THF was added and the same procedure was repeated twice to remove THF-soluble species such as unreacted monomers and Span 80 (surfactant). After the final wash the precipitate was dried in a vacuum oven at 30 °C for 2 h to yield nanogels.

Chain extension of styrene from P(OEOMA300) nanogels for synthesis of nanogel-ce-PS copolymers by ATRP

A normal ATRP of styrene was carried out in the presence of the nanogels in anisole at 90 °C. Dried, purified nanogels (0.7 g) were swollen by suspending the nanogels in styrene (3 mL, 26.2 mmol) at room temperature overnight. PMDETA (3.1 μL, 14.3 x 10^{-3} mmol) and anisole (3 mL) were added to a 25 mL Schlenk flask. The resulting mixture was deoxygenated by five freeze-pump-thaw cycles. The reaction flask was filled with nitrogen and then CuBr (2.0 mg,

14.3 x 10^{-3} mmol) was added to the frozen solution. The flask was closed, evacuated with vacuum, and backfilled with nitrogen three times. The mixture was thawed and an initial sample was taken via syringe. The flask was then immersed in an oil bath preheated to 90 °C to start the polymerization. Aliquots were withdrawn at different time intervals during the polymerization to monitor conversion by GC. The polymerization was stopped by exposing the reaction mixture to air.

Conventional free radical polymerization (RP) of OEOMA300 in inverse miniemulsion

For the synthesis of uncrosslinked P(OEOMA300) particles by inverse miniemulsion RP, 2,2-azobis(4-methoxy-2,4-dimethl valeronitrile) (V-70, Wako Chemie) and Span 80 (1.0 g) were dissolved in cyclohexane (20 g) at room temperature in 50 mL beaker. A small amount of undissolved V-70 was observed. The resulting mixture was combined with a clear solution of OEOMA300 (1.4 g, 4.7 mmol) in water (1.4 mL), and sonicated for 2 min in an ice bath at 0 °C to form a stable inverse miniemulsion. The dispersion was transferred into a 50 mL Schlenk flask, and then bubbled with nitrogen for 30 min. The flask was immersed in an oil bath preheated at 40 °C to start the polymerization. Samples were removed periodically from the reaction at different time intervals to determine conversion and molar mass by GPC. The polymerization was stopped after 4 h by lowering the temperature to room temperature. Conversion = 89%, M_n = 61,400 g/mol and M_w/M_n = 2.2.

For the synthesis of crosslinked P(OEOMA300) particles by inverse miniemulsion RP, a similar procedure was used except that 1.5 mol% crosslinker (**1**) was introduced into the aqueous solution. The polymerization was stopped after 2 h. A significant amount of coagulum was observed. An aliquot of the dispersion was dried at room temperature and the dried particles were not dissolved in THF.

Degradation of nanogels

Crosslinked nanogels and nanogel-*ce*-PS particles were degraded into the corresponding linear polymers in the presence of Bu_3P in THF at room temperature. In a typical procedure, dried, purified P(OEOMA300) gels (0.9 g, 0.08 mmol - disulfide) were stirred in THF (5 mL) at room temperature for 24 h to allow the nanogels to be fully swollen. Excess Bu_3P (0.06 mL, 0.25

mmol) was added and the reaction mixture was stirred for 3 days. An aliquot of the mixture was taken and analyzed by GPC.

Micellization of degraded P(OEOMA300)-block-PS copolymers in water

Degraded P(OEOMA300)-b-PS copolymers as described above were purified by precipitation into hexane and dried in a vacuum oven at 30 °C overnight to form white solids. An aliquot of the purified solids (3.3 mg) was dissolved in THF (3 mL). Water (15 mL) was added into the resulting clear solution at a rate of 0.5 mL/min for 30 min under stirring, and then the resulting dispersion was stirred to allow for evaporation of THF for 24 h.

Instrumentation and analyses

Molecular weights were determined by gel permeation chromatography (GPC), with a Waters 515 pump and Waters 410 differential refractometer using PSS columns (Styrogel 105, 103, 102 Å) and THF as eluent at 35 °C at a flow rate of 1 mL/min. Linear poly(methyl methacrylate) (PMMA) standards were used for calibration. For synthesis of uncrosslinked P(OEOMA) latex particles, conversion was also determined using GPC by following the decrease of the macromonomer peak area relative to the increase of polymer peak area. For synthesis of nanogel-ce-PS copolymers, conversion was determined on a Shimadzu GC-17A gas chromatograph equipped with a flame ionization detector using a capillary column (CEC-Wax, 30 m x 0.53 mm x1.0 μm, Chrom Expert Co.). The initial temperature was 80 °C (2 min hold), and the final temperature of 180 °C (2 min hold) was reached at a heating rate of 20 °C/min.

Particle size and size distribution were measured by dynamic light scattering (DLS) on High Performance Particle Sizer, Model HP5001 from Malvern Instruments, Ltd. DLS measurement provides average diameter, D_{av}, and size distribution index, CV (coefficient of variation), which is defined as follows, $D_{av} = \sum_{i=1}^{n} D_i / n$; $S = \left[\sum_{i=1}^{n} (D_i - D_{av})^2 / (n-1)\right]^{1/2}$; $CV = S/D_{av}$, where D_i is the diameter of the particle i, n is the total number counted, and S is the size standard deviation.

Atomic Force Microscopy (AFM) studies of distinct colloidal particles were carried out in the Tapping Mode with the aid of a NanoScope III-M system (Digital Instruments, Santa Barbara, CA), equipped with a J-type vertical engage scanner. The AFM observations were performed at

room temperature in air using silicon cantilevers with a nominal spring constant of 40 N/m and nominal resonance frequency of 300 kHz (standard silicon TESP probes). For the AFM measurements, an aliquot of the inverse miniemulsion was diluted to a concentration of 1 mg solids per 1 mL cyclohexane, and was then drop-cast onto freshly cleaved mica followed by allowing the sample to dry in air.

Transmission Electron Microscopy (TEM) analysis of micelles consisting of P(OEOMA300)-block-PS copolymers was conducted using Hitachi H-7100 TEM (Hitachi High Technologies America) operating at 50 kV. For the TEM measurements, a drop of dispersion containing the sample was placed on a formvar-coated copper grid. After several seconds, the drop was removed by blotting with filter paper. The sample that remained on the grid was allowed to dry before inserting the grid into the microscope. Digital images were obtained using an AMT Advantage 10 CCD Camera System (Advanced Microscopy Techniques Corporation) and NIH Image software.

Gradient polymer elution chromatography (GPEC) analysis was carried out on a Waters 600 controller and pump with an evaporative light scattering detector (ELSD) (Polymer Laboratories, PL-ELS 1000, Amherst, MA, nitrogen flow 1.2 L/min, evaporator temperature 90 ^{o}C). A Waters Nova-Pak C18 column (column dimensions 150 × 3.9 mm) was used at 26 ^{o}C for all the GPEC analysis. A binary mobile phase with constant flow rate (0.8 mL/min) was employed, whose composition gradually changed from THF/acetonitrile (MeCN) (40/60 by volume) to THF/ MeCN (100/0 by volume) within 15 min. The column was equilibrated back to initial conditions at the end of each analysis. The Waters 600 controller and pump used in GPEC analysis contains a multi-solvent delivery system, guaranteeing a stable flow rate of the eluents. Dilute polymer solutions were prepared in THF/MeCN (1/1 by volume, 2 mg/mL), and a 20 μL sample was injected for analysis. Data was collected with PSS-WINGPC 7 (Polymer Standards Service, Mainz, Germany).

Figure S1. First-order kinetic plot (a) and evolution of molecular weight and molecular weight distribution (b) for AGET ATRP of OEOMA1100 in inverse miniemulsion of cyclohexane at 30 °C. Conditions: $[OEOMA1100]_0/[PEO5000\text{-}Br]_0/[CuBr_2/TPMA]_0/[\text{ascorbic acid}]_0$ = 70/1/0.5/0.35; OEOMA1100/water = 1/1 v/v; solids content = 10 wt%. The straight line is a linear fit of the data (a) and the theoretically predicted molecular weight over conversion (b). Molecular weights of P(OEOMA1100) were calibrated with PMMA standards. An induction period was observed at the beginning of polymerization which may be due to the slow partial reduction of the Cu(II) complex to the active Cu(I) catalyst complex. The downward curvature of molecular weight observed at higher monomer conversion over 80% is presumably due to transfer.

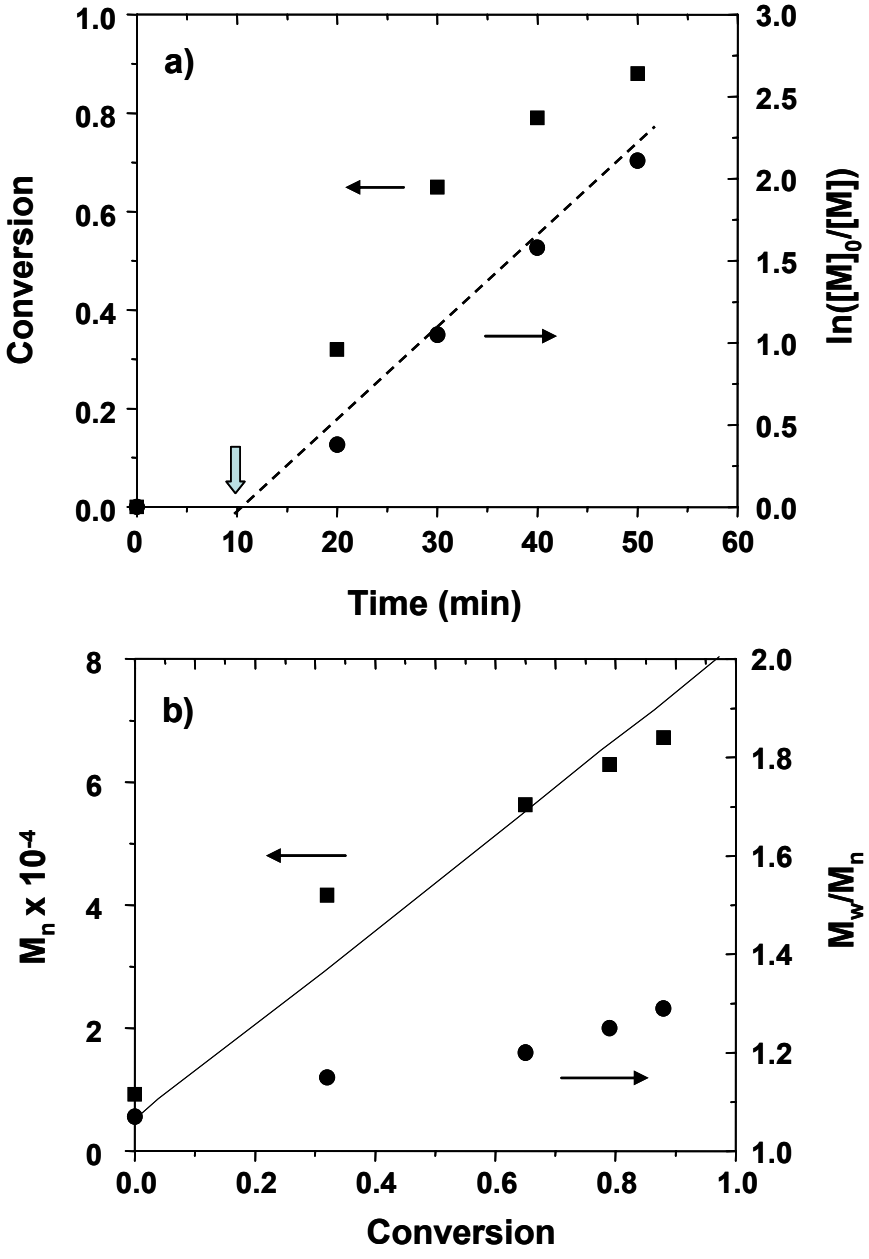


Figure S2. An example of a size distribution diagram of water-soluble P(OEOMA300) colloidal particles prepared by AGET ATRP in inverse miniemulsion at 30 °C. Conditions: $[OEOMA300]_0/[PEO5000\text{-}Br]_0/[CuBr_2/TPMA]_0/[\text{ascorbic acid}]_0 = 300/1/0.5/0.35$; OEOMA300/water = 1/1 v/v; solids content = 10 wt%.

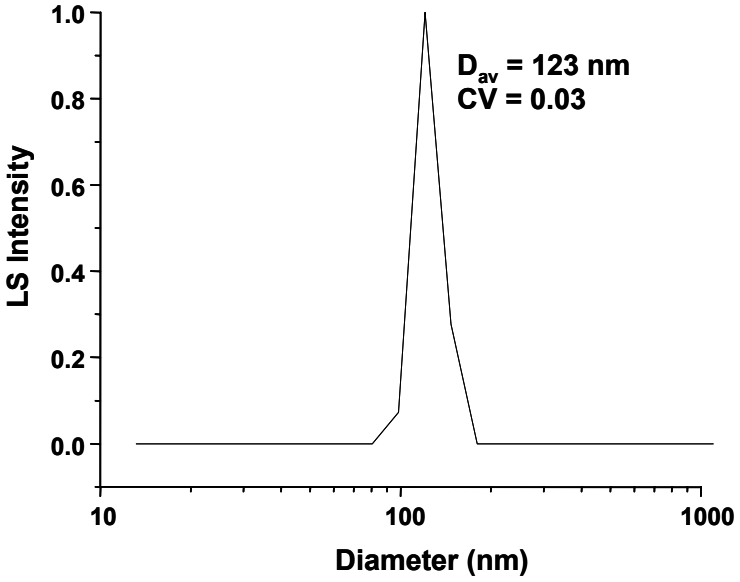


Figure S3. Kinetic plot of conversion with time for inverse miniemulsion RP in cyclohexane, initiated with V-70, at 40 °C. Conditions; $[OEOMA300]_0$ = 4.7 mmol; V70 = 2.9 wt% of OEOMA300; OEOMA300/water = 1/1 v/v; solids content = 10 wt%; Span 80 = 5 wt% of cyclohexane.

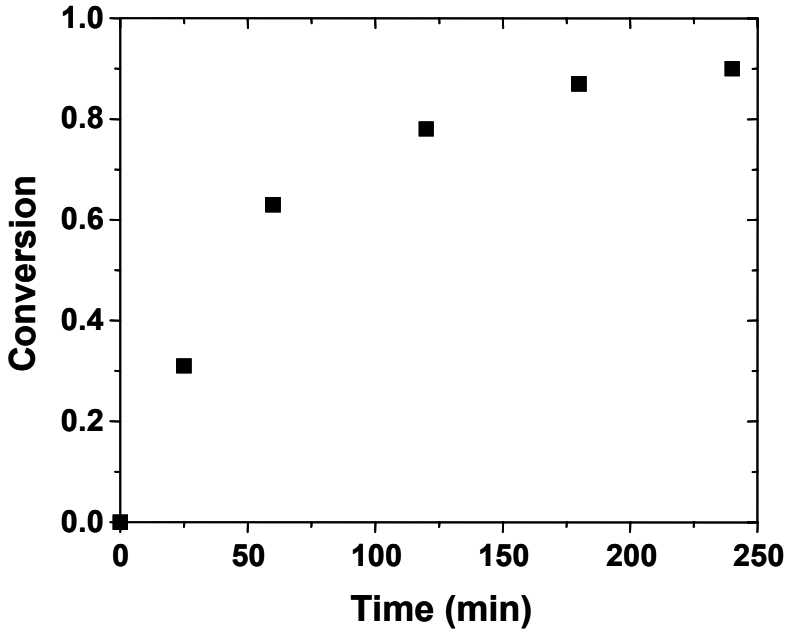


Figure S4. First-order kinetic plot for ATRP of styrene in the presence of purified P(OEOMA300) nanogels in anisole at 90 °C. Conditions: $[styrene]_0/[CuBr]_0/[PMDETA]_0$ = 1605/1/1; ATRP-nanogels as macroinitiators (0.7 g in 3 mL styrene); styrene/anisole = 50/50 v/v.

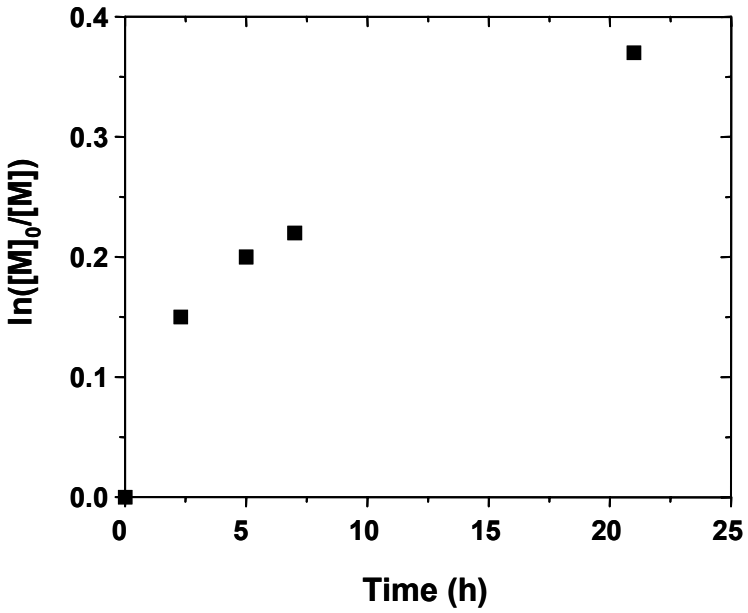


Figure S5. GPC traces of P(OEOMA300) macroinitiator (a) and P(OEOMA300)-block-PS copolymers taken at different time intervals of 7 h (b) and 21 h (c). All samples degraded in the presence of Bu_3P at room temperature for 3 days, and then were injected to GPC without purification. Molecular weight data: (a) M_n = 74.0 K (M_w/M_n = 1.5), (b) M_n = 118.8 K (M_w/M_n = 1.9), and (c) M_n = 156.0 K (M_w/M_n = 2.2).

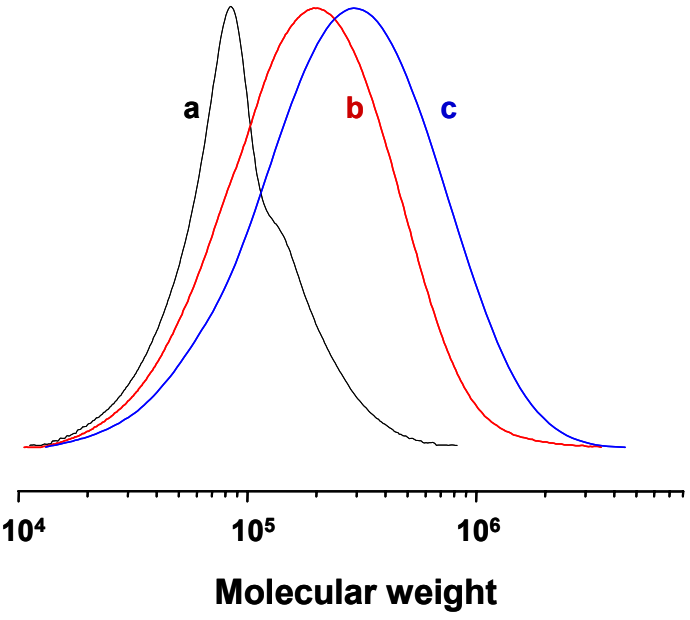
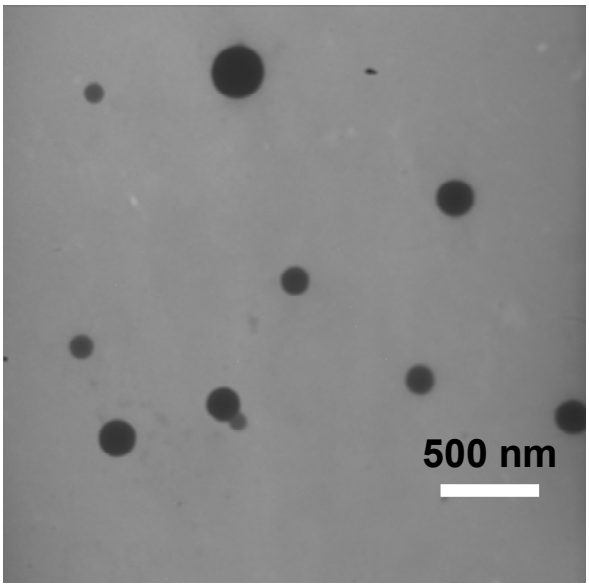


Figure S6. TEM image of spherical micelles consisting of PS core and P(OEOMA300) corona formed from self-assembly of degraded P(OEOMA300)-block-PS in water. For the TEM measurements, a drop of dispersion containing the sample was placed on a formvar-coated copper grid.



References

(1) Matyjaszewski, K.; Patten, T. E.; Xia, J. *J. Am. Chem. Soc.* **1997**, 119, 674-680; Keller, R. N.; Wycoff, H. D. **1946**, 1-4.

(2) Xia, J.; Matyjaszewski, K. *Macromolecules* **1999**, 32, 2434-2437; Tyeklar, Z.; Jacobson, R. R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, 115, 2677-2689.

(3) Tsarevsky, N. V.; Sarbu, T.; Goebelt, B.; Matyjaszewski, K. *Macromolecules* **2002**, 35, 6142-6148.

(4) Ali, M. M.; Stöever, H. D. H. *Macromolecules* **2004**, 37, 5219-5227.