

Well-Defined Thermoresponsive Copolymers with Tunable LCST and UCST in Water

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A thermoresponsive polymer, poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), was successfully synthesized by atom transfer radical polymerization (ATRP). Different amounts of 1,3-propanesultone were used as quaternization agent to transit the PDMAEMA into partially modified poly(zwitterions), resulting in p[DMAEMA-co-3-dimethyl(methacryloyloxyethyl)ammonium propanesulfonate] (PDMAEMA-co-PDMAPS). Molecular weight, molecular weight distribution, and degree of quaternization were determined by gel permeation chromatography (GPC) and ¹H NMR spectroscopy. The transmission spectra of the 1.0 wt % aqueous solutions of the resulting polymers at 650 nm were measured as a function of temperature. Results showed that the lower critical solution temperature (LCST) and the upper critical solution temperature (UCST) could be easily controlled by the different composition of dimethylamino and zwitterion groups. The effect of partial quaternization on thermoresponsive properties was also studied by dynamic light scattering (DLS) with the same aqueous concentration (1.0 wt %) as employed for turbidimetry studies. The LCST and UCST values measured by DLS correlated well with those determined by turbidimetry.

Key Words : ATRP, UCST, LCST, PDMAEMA, Zwitterions

Introduction

Stimuli-responsive polymers have attracted great interest in academic and applied science recently.¹⁻⁸ They exhibit structural and property changes to external changes such as pH, temperature, and light. The increasing demand for “smartness” in biomedical and material devices has generated an increasing interest for synthetic polymers that can serve as an ideal platform for locating stimuli-responsive molecular elements. While various stimuli-responsive polymers have been developed, thermoresponsive polymers are among the most widely studied due to relatively easy introduction of desired sensitivity. For thermoresponsive polymers, approaches take advantage of thermally induced, reversible phase transitions.⁹⁻¹¹ Polymers that exhibit lower critical solution temperature (LCST) behavior become less hydrophilic above their LCST because the elongated polymer chains shrink into an insoluble bead. On the contrary, polymers that exhibit upper critical solution temperature (UCST) behavior become more hydrophilic in water with increasing temperature.¹²⁻¹⁵ Such thermoresponsive polymers featuring a LCST and a UCST in water are expected to find applications in nanotechnology and biotechnology.^{16,17}

Poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA),¹⁸ which displays a LCST in water around 40 °C, has been the most studied thermoresponsive polymer targeting biological applications. Interestingly, slight modification of PDMAEMA to p[3-dimethyl(methacryloyloxyethyl)ammonium propanesulfonate] (PDMAPS) with betaine-type structures leads to property conversion from LCST to UCST behaviors. Despite recent progress in the field, few polymers that can switch responsiveness between LCST and UCST easily have been

reported.

Herein, we report the synthesis of a series of PDMAEMA-co-PDMAPS by atom transfer radical polymerization (ATRP)^{19,20} of DMAEMA, followed by partial quaternization of amino groups with 1,3-propanesultone. The cloud points of these copolymers were strongly dependent on the composition of dimethyl amino and zwitterions groups.

Experimental

Material. 2,2-(Dimethylamino)ethyl methacrylate (DMAEMA, 98%, Aldrich) were purified by passing the monomers through a column filled with basic alumina to remove the inhibitor. CuBr (98%), ethyl 2-bromoisobutyrate (EBiB, 98%), 2-2'-bipyridyl (bpy 98%) were purchased from Aldrich. Anisole (99.0%) and 1,3-propanesultone (99%) were purchased from Tokyo chemical industry (TCI) and used as received.

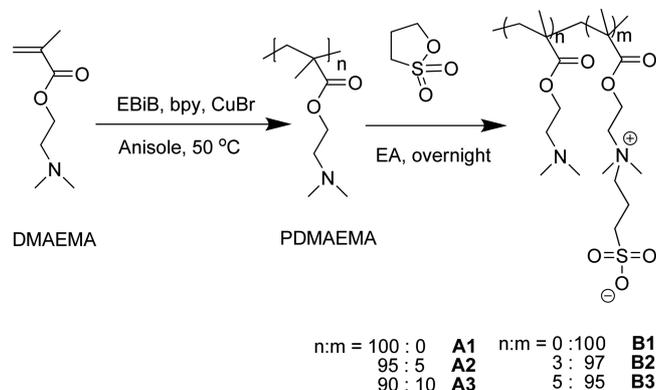
Instrumentation. ¹H NMR spectra were collected in D₂O on a Bruker avance 300 MHz NMR spectrometer. The apparent molecular weights and molecular weight distributions were measured by gel permeation chromatography (GPC) (Agilent technologies 1200 series) using a polystyrene (PS) standard, with dimethyl formamide (DMF) as the eluent at 30 °C and a flow rate of 1.00 mL/min. UV-vis spectra were recorded using an OPTIZEN 3220 UV-vis spectrophotometer equipped with a digital temperature controller. The wavelength of 650 nm was used for the determination of the LCST and UCST. The temperature range was from 10 to 80 °C, and heating and cooling rate were 1 °C/min. Hydrodynamic diameters were measured using dynamic light scattering (DLS, Nano ZS 90, Malvern, UK).

Synthesis of PDMAEMA by ATRP. A clean and dry schlenk flask was charged with DMAEMA (63.2 mL, 20 mmol), bpy (31.2 mg, 0.1 mmol), EBiB (291 μ L, 0.1 mmol), anisole (31.6 mL), and CuBr (143 mg, 0.05 mmol). The flask was deoxygenated by five freeze-pump-thaw cycles. During the final cycle, the flask was filled with argon before CuBr (143 mg, 0.05 mmol) were quickly added to the frozen mixture. The flask was sealed with a glass stopper then evacuated and back-filled with argon three times before it was immersed in an oil bath at 50 °C. The polymerization was stopped when monomer conversion reached 50%, which was determined by ^1H NMR. The solution was filtered through a column filled with neutral alumina to remove the copper complex before the polymer was precipitated twice in hexane and dried under vacuum at room temperature for a day. $M_n = 18\,500$ g/mol, $M_w/M_n = 1.164$. ^1H NMR (300 MHz, D_2O) δ 4.19 (2H, s, O-CH₂), 2.74 (2H, s, CH₂-CH₂), 2.34 (6H, s, N-(CH₃)₂), 2.0-1.9 (2H, d, CH₂), 1.1-0.94 (3H, d, CH₃).

Representative Example of Partial Quaternization: A2 (Dimethyl Amine Group of PDMAEMA:1,3-propanesultone = 95:5) PDMAEMA (0.2 g, 1.21 mmol) was dissolved in ethyl acetate (EA) in the 20 mL flask with magnetic stirring. 1,3-propanesultone (5.3 μ L, 0.0605 mmol) was added into the flask. The reaction mixture was allowed to stir for overnight at room temperature. After reaction the polymer was precipitated in twice in hexane and dried under vacuum at 40 °C for a day. ^1H NMR (300 MHz, D_2O) δ 4.54 (2H, s, O-CH₂), 4.19 (2H, s, O-CH₂), 3.85 (2H, s, OCH₂-CH₂), 3.65 (2H, s, N-(CH₃)₂-CH₂), 3.28 (6H, s, N-(CH₃)₂), 3.03 (2H, s, CH₂-SO₃), 2.73 (2H, s, OCH₂-CH₂), 2.34 (6H, s, N-(CH₃)₂), 2.32 (CH₃CH₂CH₃), 2.0-1.9 (2H, d, CH₂), 1.1-0.94 (3H, d, CH₃).

Results and Discussion

The strategy employed in this study is schematically illustrated in Scheme 1. ATRP was employed to synthesize PDMAEMA using a CuBr/bpy catalyst system with 2-bromo-isobutyrate (EBiB) as an initiator. The molecular weight and



Scheme 1. Synthesis of zwitterion-functionalized copolymers by ATRP of DMAEMA, followed by quaternization of amino groups with 1,3-propanesultone.

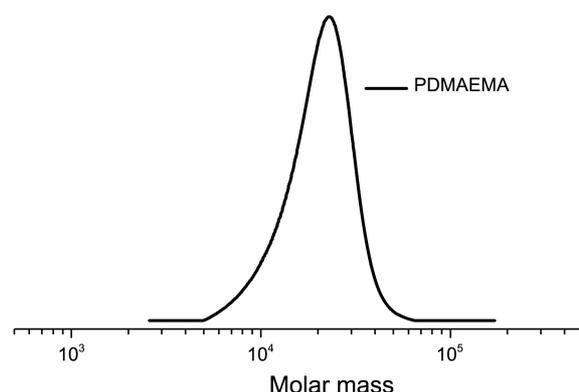


Figure 1. DMF GPC traces of PDMAEMA.

molecular weight distribution of the resulting PDMAEMA were obtained by GPC with polystyrene (PS) standards ($M_n = 18\,500$ g/mol, $M_w/M_n = 1.16$). As shown in Figure 1, the GPC traces showed monomodal distributions with the relatively low molecular weight distribution, indicating good control over the polymerization. The apparent molecular weight (18 500 g/mol) obtained by GPC was higher than the theoretical molecular weight calculated from the DMAEMA conversion ($M_{n,theory} = \text{conversion} \times \text{MW}_{\text{DMAEMA}} \times [\text{DMAEMA}]_0 / [\text{EBiB}]_0 = 0.5 \times 157 \text{ g/mol} \times 200 = 15\,700 \text{ g/mol}$) due to the differences in hydrodynamic volumes of PDMAEMA and PS standards.^{21,22}

The resulting PDMAEMA was reacted with different amounts of 1,3-propanesultone to yield a series of PDMAEMA-co-PDMAPS copolymers. The reaction was carried out in ethyl acetate (EA) at room temperature. The ^1H NMR spectra provided the evidence of the successful synthesis of PDMAEMA-co-PDMAPS copolymers by partial quaternization (Figure 2). It was monitored that an ester peak (c) of PDMAEMA at 4.1 ppm decreased while peaks (h, i, j, and k) of PDMAPS appeared gradually after partial quaternization. The extent of quaternization was determined by calculating the integral ratio between peak d and g. For example, the integral ratio between peak d and g is 95:5 for **A2** and 3:97 for **B2**, respectively. In a similar way, the extent of quaterni-

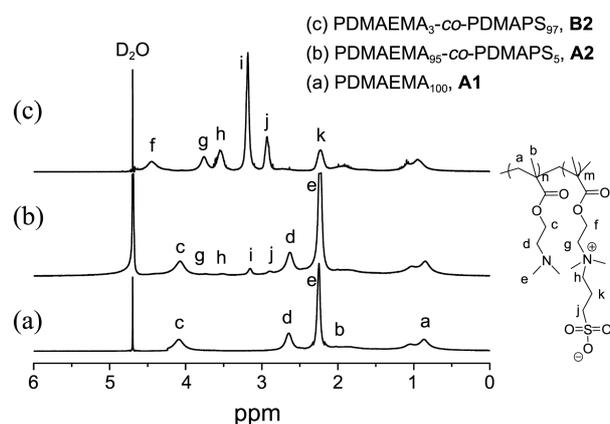


Figure 2. ^1H NMR spectra of PDMAEMA (**A1**), PDMAEMA₉₅-co-PDMAPS₅ (**A2**), and PDMAEMA₃-co-PDMAPS₉₇ (**B2**).

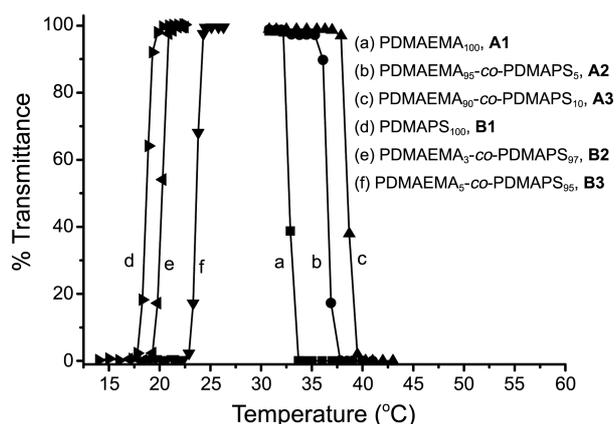


Figure 3. Thermoresponsiveness of 1.0 wt % aqueous solutions of (a) **A1**, (b) **A2**, (c) **A3**, (d) **B1**, (e) **B2**, and (f) **B3** measured by percent transmission at 650 nm. The cloud points of a, b, and c were measured during a heating cycle and those of d, e, and f were measured during a cooling cycle.

zation for **A3** and **B3** was calculated.

Figure 3 shows the values of the cloud points measured for aqueous solutions of the series of copolymers with high PDMAEMA contents (**A1**, **A2**, and **A3**) and with high PDMAEMA contents (**B1**, **B2**, and **B3**) (studied reference concentration was 1.0 wt %). For copolymer that are expected to exhibit LCST properties (**A1**, **A2**, and **A3**), the cloud points were measured during a heating cycle and for copolymer that are expected to exhibit UCST properties (**B1**, **B2**, and **B3**), the cloud points were measured during a heating cycle. The LCST of PDMAEMA homopolymer (**A1**) was 33 °C. For a series of copolymer **A**, measured LCST values increased from 33 to 40 °C with the molar fraction of zwitterion groups in the copolymer since sulfobetaine is more hydrophilic than dimethyl amine. Interestingly, copolymers with more than 10% of zwitterions did not show LCST transitions. The UCST of PDMAEMA homopolymer (**B1**) was 17 °C. For a series of copolymer **B**, UCST values increased from 17 to 24 °C with the molar fraction of dimethyl amine groups in the copolymer. Therefore, the LCST and UCST of

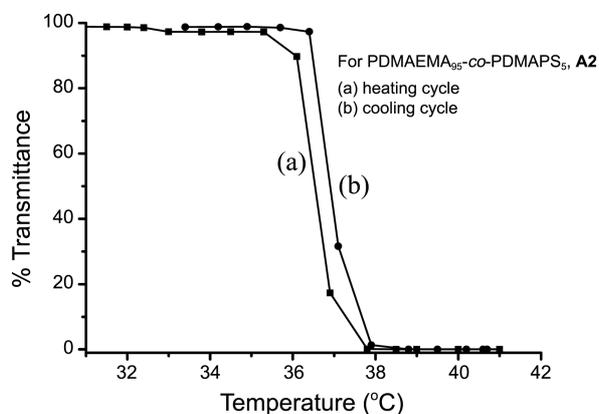


Figure 4. Hysteresis of PDMAEMA₉₅-co-PDMAPS₅ (**A2**) with a 1.0 wt % aqueous solution. The solution was heated and cooled at a rate of 1 °C/min.

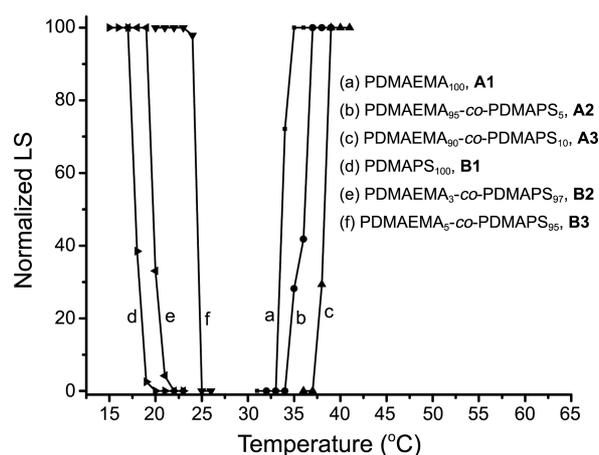


Figure 5. Thermoresponsiveness of 1.0 wt % aqueous solutions of (a) **A1**, (b) **A2**, (c) **A3**, (d) **B1**, (e) **B2**, and (f) **B3** measured by dynamic light scattering (DLS). The normalized light scattering intensities of a, b, and c were measured during a heating cycle and those of d, e, and f were measured during a cooling cycle.

both series of copolymers can be precisely tuned by controlling the fraction of dimethyl amine and sulfobetaine units. Similarly, copolymers with more than 5% of zwitterions did not show UCST transitions. PDMAEMA₉₅-co-PDMAPS₅ (**A2**) was chosen to investigate the hysteresis behavior because it exhibited an LCST transition near physiological temperature; however, we found no significant hysteresis for **A2** (Figure 4).

The effect of quaternization on thermal transitions was also studied by dynamic light scattering (DLS) with the same aqueous concentration (1.0 wt %) as employed for turbidimetry studies. The particle size of the series of copolymers with high PDMAEMA contents (**A1**, **A2**, and **A3**) increased with increasing temperature. On the contrary, the particle size of the series of copolymers with high PDMAEMA contents (**B1**, **B2**, and **B3**) increased with decreasing temperature. The LCST and UCST values measured by DLS correlated well with those determined by turbidimetry.

Conclusions

Thermoresponsive copolymers were successfully synthesized using ATRP and postpolymerization modification process. Well-defined copolymers with predictable molecular weights and low molecular weight distribution were formed. The thermal properties of aqueous solutions of the copolymers were studied by UV-vis. The transmission spectra of an aqueous solution of these polymers as a function of temperature showed that the LCST and UCST of these copolymers were affected by the variation of the composition in the copolymer. In conclusion, we designed a very simple system where the LCST and UCST values can be easily controlled by small change in the composition of the dimethylamine and zwitterion groups.

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