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Thermally Responsive P(M(EO)$_2$MA-*co*-OEOMA) Copolymers via AGET ATRP in Miniemulsion

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ABSTRACT: Thermally responsive random copolymers of di(ethylene glycol) methyl ether methacrylate (M(EO)$_2$MA) and oligo(ethylene glycol) methyl ether methacrylate (OEOMA) ($M_n \sim 300$ or 475) with varied compositions were successfully synthesized via activators generated by electron transfer for atom transfer radical polymerization (AGET ATRP) in miniemulsion at 65 °C. The copolymerizations were controlled, generating well-defined copolymers with relatively narrow molecular weight distribution ($M_w/M_n \sim 1.3-1.5$). Because of the relatively high reaction temperature (65 °C), OEOMA was confined into oil phase, although OEOMA was miscible with water in all proportions at room temperature. The compositional study proved that the composition of the copolymers reflected the comonomer feed ratio. The cloud point of the resulting copolymer increased proportionally with the OEOMA molar content. Microgels of P(M(EO)$_2$MA-*co*-OEOMA) were also prepared by addition of ethylene glycol dimethacrylate (EGDMA) cross-linker. Similar to their linear analogues, the phase transition temperature of the copolymer microgels can be tuned by changing OEOMA content in the microgels.

Introduction

Atom transfer radical polymerization (ATRP) is one of the most robust and efficient controlled/living radical polymerizations, yielding well-defined (co)polymers with precisely controlled topology, composition, and functionality.[1−7] It is attractive to extend ATRP to aqueous dispersed media due to environmental benefits, good process control, and feasibility of commercial production of latex particles, although it is more complicated and challenging than in homogeneous bulk or solution system.[8−15] Development of a new efficient initiation system, activators generated by electron transfer (AGET), significantly facilitated ATRP in heterogeneous systems.[15−20] Instead of using activating Cu(I) catalyst which is sensitive to air, a higher oxidation state catalyst derived from a Cu(II) complex is added to the reaction mixture so that a stable dispersed medium is formed without initiation of polymerization. A reducing agent is used to react with the Cu(II) complex and to generate the activator without involvement of organic radicals or formation of reaction products that could initiate new chains. AGET has been successfully extended to activators regenerated by electron transfer (ARGET) and initiators for continuous activator regeneration (ICAR) processes with a very low concentration of Cu catalyst.[21−27] In recent years, our group has successfully conducted AGET ATRP in various heterogeneous systems, including emulsion, suspension, (inverse) miniemulsion, microemulsion, and dispersion.[15,28−30] A variety of well-defined functional nanomaterials have been prepared, such as gradient and block copolymers, molecular bottle brushes, star polymers, microgels, hairy nanoparticles, nanocapsules, and polymer-modified inorganic nanoparticles.[31−39]

Temperature-sensitive polymers exhibiting a lower critical solution temperature (LCST) in water have been extensively investigated for the development of smart materials in biomedical applications, such as bioseparation and hyperthermia-induced drug delivery.[40−46] Below the LCST, such polymers are soluble in water but precipitate at temperatures exceeding LCST. However, there are only a few papers that report synthesis of thermally responsive polymers via ATRP technique in suspension and precipitation polymerizations, in which the formation of water-soluble macroinitiators before polymerization was required in order to achieve stable dispersed systems.[47−49]

Recently, our group reported the first preparation of a thermally responsive polymer, poly(di(ethylene glycol) methyl ether methacrylate) (PM(EO)$_2$MA), via AGET ATRP in miniemulsion.[50] The monomer M(EO)$_2$MA is not soluble in water, while the polymer PM(EO)$_2$MA becomes water-soluble below 25 °C. Therefore, at a reaction temperature of 65 °C, the miniemulsion polymerization of M(EO)$_2$MA was stable without diffusion of monomer and polymer into aqueous phase. Using this technique, well-defined PM(EO)$_2$MA microgels with entrapped magnetic nanoparticles were prepared and exhibited well-controlled drug-releasing properties as well as excellent biocompatible behavior. However, the PM(EO)$_2$MA microgels began shrinking at around 19 °C. Such a low transition temperature limits their practical application in drug delivery systems.

In order to alleviate this problem, in this study, oligo(ethylene glycol) ethyl ether methacrylate (OEOMA) including OEOMA300 (M_n = 300, number of pendent EO units ~4−5) and OEOMA475 (M_n = 475, number of pendent EO units ~9) randomly copolymerized with M(EO)$_2$MA in varied compositions via AGET ATRP in miniemulsion. Lutz et al. and other groups have reported that copolymerization of M(EO)$_2$MA and OEOMA macromonomers yielded thermosensitive statistical copolymers with a tunable LCST between 25 and 90 °C.[51−60] The thermally responsive behavior was demonstrated to be directly linked to the M(EO)$_2$MA/OEOMA composition of the formed copolymers.[55,58−60]

Copolymerization of OEOMA and M(EO)$_2$MA in miniemulsion reported here significantly differs from the earlier

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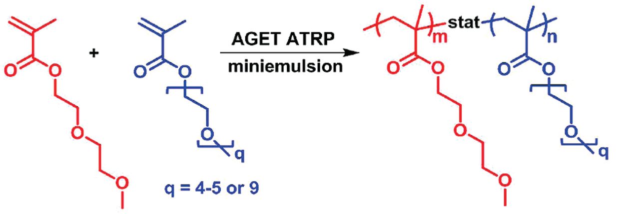
homopolymerization of $M(EO)_2MA$, in that polar OEOMA is soluble in water and may partition in aqueous phase, whereas $M(EO)_2MA$ is not soluble in water. In this work, partition of OEOMA in oil and water phases during copolymerization in miniemulsion was evaluated through compositional study and LCST of the resulting copolymers. Copolymer-based microgels were also prepared by addition of dimethacrylate cross-linker. The thermally responsive behavior of linear copolymers and cross-linked microgels was investigated.

Experimental Section

Materials. Di(ethylene glycol) methyl ether methacrylate ($M(EO)_2MA$) (95%, Aldrich) was purified by vacuum distillation before use. Oligo(ethylene glycol) methyl ether methacrylate (OEOMA300 and OEOMA475, average $M_n \sim 300$ and 475, respectively; Aldrich) were purified by passing through a column filled with basic alumina. Bis(2-pyridylmethyl)octadecylamine (BPMODA) was synthesized according to the procedures previously published.[61,62] Ethyl 2-bromoisobutyrate (EBiB, 98%, Aldrich), ethylene glycol dimethacrylate (EGDMA, 98%, Aldrich), $CuBr_2$ (99.999%, Aldrich), polyoxyethylene(20) oleyl ether (Brij 98, Aldrich), hexadecane (Aldrich), and hydrazine solution (35 wt % in H_2O, Aldrich) were used as received.

Synthesis of Linear P(M(EO)$_2$MA-*co*-OEOMA300) via AGET ATRP in Miniemulsion. In a typical AGET ATRP of $M(EO)_2MA$ and OEOMA in miniemulsion (Table 1, entry 1), a 50 mL round-bottom flask was charged with $CuBr_2$ (3.0 mg, 0.013 mmol), BPMODA (6.1 mg, 0.013 mmol), $M(EO)_2MA$ (2.0 g, 10.6 mmol), OEOMA300 (0.325 g, 1.06 mmol), and anisole (0.60 mL). The resulting mixture was stirred at 65 °C for about 2 h to dissolve the copper complex and then cooled to room temperature. The EBiB initiator (8.0 μL, 0.054 mmol) and hexadecane (139 μL) were added into the cold solution. Aqueous Brij 98 solution (11.9 mL, 5 mmol/L) was added to the organic solution before the mixture was subjected to sonication (Heat Systems Ultrasonics W-385 sonicator; duty cycle at 70% for 2.5 min). The resulting homogenized miniemulsion was transferred to a Schlenk flask and purged with nitrogen for 1 h. The flask was then immersed in an oil bath thermostated at 65 °C. A bubbled aqueous solution of hydrazine (0.5 mL, 8.1 μmol/mL) was injected into the reaction to initiate the polymerization. Aliquots were taken at periodic intervals to measure the conversion by ^{1}H NMR and to examine the evolution of molecular weight.

Scheme 1. Copolymerization of M(EO)$_2$MA and OEOMA via AGET ATRP in Miniemulsion



Synthesis of P(M(EO)$_2$MA-*co*-OEOMA300) Microgels via AGET ATRP in Miniemulsion. Stable cross-linked P(M(EO)$_2$MA-*co*-OEOMA) microgels were prepared in the presence of EGDMA. In a typical reaction (Table 2, entry 1), $CuBr_2$ (3.0 mg, 0.013 mmol), BPMODA (6.1 mg, 0.013 mmol), $M(EO)_2MA$ (2.0 g, 10.6 mmol), OEOMA300 (0.325 g, 1.06 mmol), and anisole (0.60 mL) were charged in to a round-bottom flask. The resulting mixture was stirred at 65 °C for about 2 h to dissolve the copper complex and then cooled to room temperature. The EBiB initiator (4.0 μL, 0.027 mmol), EGDMA cross-linker (20.1 μL, 0.106 mmol), and hexadecane (139 μL) were added into the cold solution. Aqueous Brij 98 solution (11.9 mL, 5 mmol/L) was added to the organic solution before the mixture was subjected to sonication (Heat Systems Ultrasonics W-385 sonicator; duty cycle at 70% for 2.5 min). The resulting homogenized miniemulsion was transferred to a Schlenk flask and purged with nitrogen for 1 h. The flask was then immersed in an oil bath thermostated at 65 °C. An aqueous solution of hydrazine (0.5 mL, 8.13 μmol/mL) was injected into the reaction to initiate the polymerization. After 6.0 h, the reaction was stopped by opening the flask and exposing the catalyst to air. The monomer conversion was 49.9%, as determined by ^{1}H NMR. The cross-linked microgels were purified using dialysis tubing (MWCO = 25 000) against methanol and water for at least 1 week.

Analyses. Molecular weight and molecular weight distribution were determined by gel permeation chromatography (GPC)

Table 1. Copolymerization of M(EO)$_2$MA and OEOMA via AGET ATRP in Miniemulsion[a]

entry	comonomer	OEOMA feed (mol %)	[hydrazine]$_0$:[CuBr$_2$]$_0$	time (h)	conv[b] (%)	M_n[c] (theo)	M_n[d]	M_w/M_n[d]
1	OEOMA300	9.1	0.3	7.0	33.2	14 490	25 230	1.34
2	OEOMA300	9.1	0.4	7.0	57.0	24 880	49 720	1.91
3	OEOMA300	9.1	0.6	7.0	74.5	32 520	64 290	5.67
4	OEOMA300	22.7	0.4	7.0	40.0	18 800	34 930	1.45
5	OEOMA300	31.8	0.3	3.0	42.8	21 070	40 200	1.50
6	OEOMA300	50.0	0.2	2.5	35.9	19 280	33 170	1.50
7	OEOMA475	9.1	0.3	6.0	51.9	24 470	33 730	1.52
8	OEOMA475	22.7	0.2	8.0	37.7	21 020	33 020	1.42

[a] $(M(EO)_2MA + OEOMA):EBiB:CuBr_2:BPMODA = 220:1:0.25:0.25$ in miniemulsion at 65 °C. Monomers/anisole = 4/1 v/v. Solid content = 20 wt %; Brij98 = 2.3 wt % of solid content; hexadecane = 3.6 wt % of solid content. [b] Measured by ^{1}H NMR. [c] $M_n(\text{theo}) = ([M(EO)_2MA]_0 + [OEOMA]_0)/[EBiB]_0 \times$ conversion. [d] Determined by GPC with THF as eluent, based on poly(methyl methacrylate) standards.

Table 2. Synthesis of Thermally Responsive P(M(EO)$_2$MA-*co*-OEOMA) Microgels[a]

entry	comonomer	OEOMA feed (mol %)	time (h)	conv[b] (%)	LCST[c] (°C)	LCST of linear analogue (°C)[d]
1	OEOMA300	9.1	6.0	49.9	22.7	29.3
2	OEOMA300	31.8	6.8	75.7	32.9	40.9
3	OEOMA300	50.0	5.0	56.3	39.0	47.4
4	OEOMA475	9.1	5.0	67.0	26.2	35.8

[a] $(M(EO)_2MA + OEOMA):EGDMA:EBiB:CuBr_2:BPMODA:hydrazine = 220:2:1:0.25:0.25:0.10$ in miniemulsion at 65 °C. Monomers/anisole = 4/1 v/v. Solid content = 20 wt %; Brij98 = 2.3 wt % of solid content; hexadecane = 3.6 wt % of solid content. [b] Measured by ^{1}H NMR. [c] Determined from the minimum of the first derivative of microgel hydrodynamic diameter vs temperature in aqueous solution (0.1 wt %). [d] Based on the results in Figure 4.

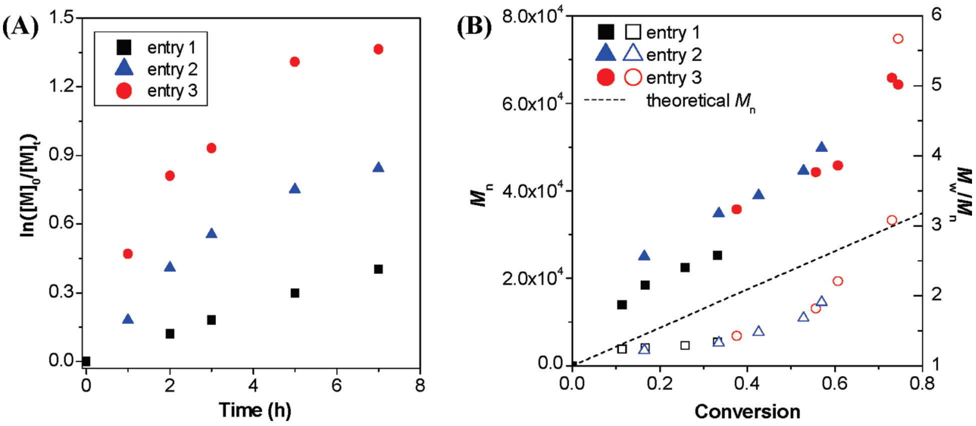


Figure 1. Kinetics (A) and evolution of molecular weights and M_w/M_n (B) with monomer conversion in AGET ATRP of M(EO)$_2$MA and OEOMA300 in miniemulsion (Table 1, entries 1−3).

conducted with a Waters 515 pump and Waters 2414 differential refractometer using PSS columns (Styrogel 10^5, 10^3, and 10^2 Å) in THF as an eluent (35 °C, flow rate of 1 mL/min). Toluene was used as an internal standard. Linear poly(methyl methacrylate) standards were used for calibration. ^{1}H NMR spectra of copolymers were examined in CDCl$_3$ at 30 °C using a Bruker Advance 300 MHz spectrometer. The cloud point of the copolymer solution in deionized water was measured using a Varian Cary 7 Bio UV−vis spectrophotometer equipped with a digital temperature controller. Transmittance of the copolymer aqueous solution at 600 nm was monitored as a function of temperature. The range of temperatures was from 17 to 60 °C, and heating and cooling rates were 1 °C/min. Particle size and size distribution were measured by dynamic light scattering (DLS) on a zetasizer, model MAL060045 from Malvern Instruments, Ltd. The sizes are expressed as $D_{av} \pm S$ (volume-average diameter ± standard deviation). Measurements were run with a heating or cooling program at 1 °C intervals. The solution was equilibrated for at least 5 min at each temperature.

Results and Discussion

Synthesis of Linear P(M(EO)$_2$MA-*co*-OEOMA) Copolymers. AGET ATRP of M(EO)$_2$MA and OEOMA was carried out in miniemulsion at 65 °C, in the presence of EBiB initiator, BPMODA as a highly hydrophobic ligand, and hydrazine as a mild water-soluble reducing agent.[18,21,50] OEOMA is miscible with water in all proportions at room temperature, and its partitioning between the oil and water phases is governed by the polarity and hydrogen-bonding ability of the oil phase. Therefore, a water-immiscible solvent, anisole, was used to help confine OEOMA in oil phase. Commercially available Brij 98 and hexadecane acted as surfactant and cosurfactant, respectively. A series of copolymerizations were conducted under similar conditions, except for amount of reducing agent and comonomer feed ratio. The results are shown in Table 1.

During all the copolymerizations, the miniemulsion systems remained stable without phase separation or precipitation. Since the reaction temperature (65 °C) is above LCST of the resulting copolymer, there was no diffusion of the copolymer into aqueous phase. Dynamic light scattering (DLS) measurements indicated that the size of monomer droplets was 154 ± 4 nm with narrow distribution (Table 1, entry 1) and did not change much during the reaction. In Table 1, entries 1−3, the molar ratio of M(EO)$_2$MA to OEOMA300 was 10:1, where the amount of hydrazine was adjusted to obtain an appropriate reaction rate. According to Figure 1, the reaction proceeded with a linear increase in M_n vs monomer conversion. The kinetic plots in Figure 1A suggest that the copolymerization became faster with an increase of molar ratio of hydrazine to Cu(II) complex. The small curvature of the kinetic plot could indicate a possible loss of the bromine end groups through termination and side reactions or a progressive migration of the catalyst to the aqueous phase. The molecular weights of the copolymers obtained from GPC were about 1.5−2 times of the theoretical values, and therefore, the initiator efficiency was about 50−70%. The possible reason for the low efficiency could be that at the very beginning of the reaction too many radicals were generated and quickly terminated by radical termination reactions. The GPC traces were symmetric and smoothly shifted to high molecular weight but exhibited a slight shoulder at high molecular weight at above 60% conversion, leading to an increase in molecular weight distribution. Since miniemulsion polymerization is more complicated and challenging than solution polymerization, side reactions such as transesterification and radical transfer processes of ethylene glycol containing monomers can become more significant. In addition, the copper catalyst may slowly migrate into aqueous phase, leading to lower control in polymerization. All of these could contribute to the increase of M_w/M_n of the copolymer.

In Table 1, entries 3−8, M(EO)$_2$MA was copolymerized with OEOMA300 or OEOMA475 under varied feed ratios, in a range from 9.1 to 50.0 mol %. All the reactions were well-controlled, generating the random P(M(EO)$_2$MA-*co*-OEOMA) copolymers with relatively low molecular weight distribution (~1.5).

Compositional Study of Linear P(M(EO)$_2$MA-*co*-OEOMA) Copolymers. Although M(EO)$_2$MA is water-insoluble, OEOMA300 and OEOMA475 are soluble in water and might partition into the aqueous phase in miniemulsion polymerization system. ^{1}H NMR was used to determine compositions of P(M(EO)$_2$MA-*co*-OEOMA) copolymers at different monomer conversions and feed ratios in order to evaluate the potential partition behavior of OEOMA.[63] Figure 2 exhibits a typical ^{1}H NMR spectrum of a purified copolymer P(M(EO)$_2$MA-*co*-OEOMA300) (Table 1, entry 3) in CDCl$_3$. Although peaks originating from M(EO)$_2$MA unit have similar chemical shifts as OEOMA300 unit, the two monomer units have different number of ethylene glycol units. The copolymer composition was evaluated from the ratio of integrals of proton peaks labeled as c−e in Figure 2, representing methylene protons adjacent to the ester groups and protons in ethylene glycol and methyl ether moieties, respectively.

NMR spectra of copolymers generated during and at the end of copolymerizations in miniemulsion were recorded. The calculated composition results of the copolymers are demonstrated in Figure 3. Although there was some variation in OEOMA contents of the copolymers during the reactions, Figure 3B confirms that the composition of the copolymer corresponds well to the comonomer feed ratio, even for OEOMA475, which is more hydrophilic than OEOMA300. This indicates that there was little OEOMA partitioning into water phase during copolymerization processes in miniemulsion. This conclusion is supported by the observation that OEOMA300 became immiscible with water when temperature was above 60 °C. Similarly, partitioning of OEOMA475 in water should become smaller at reaction temperature (65 °C) than at room temperature. Thus, the relatively high reaction temperature (65 °C) was the key point to keep OEOMA in oil phase without partition in aqueous phase during the copolymerization.

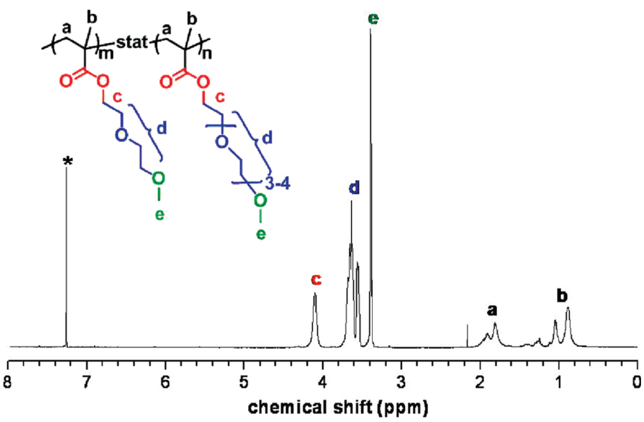


Figure 2. ^{1}H NMR spectrum of a copolymer of M(EO)$_2$MA and OEOMA300 (Table 1, entry 3) in CDCl$_3$.

Thermal Properties of Linear P(M(EO)$_2$MA-*co*-OEOMA) Copolymers. Transmittance of an aqueous copolymer solution was measured by UV−vis to determine the cloud point of the copolymers. Figure 4A shows temperature-induced abrupt phase transition of P(M(EO)$_2$MA-*co*-OEOMA) samples with varied compositions in water. The measured cloud point in Figure 4A is a linear function of OEOMA content in the copolymer, in the studied range of composition (OEOMA300 mol % ≤ 50%; OEOMA475 mol % < 25%). The slope for the OEOMA475 copolymers is higher than that for OEOMA300 due to higher hydrophilicity of OEOMA475 (Figure 4B). Thus, the LCST of the P(M(EO)$_2$MA-*co*-OEOMA)

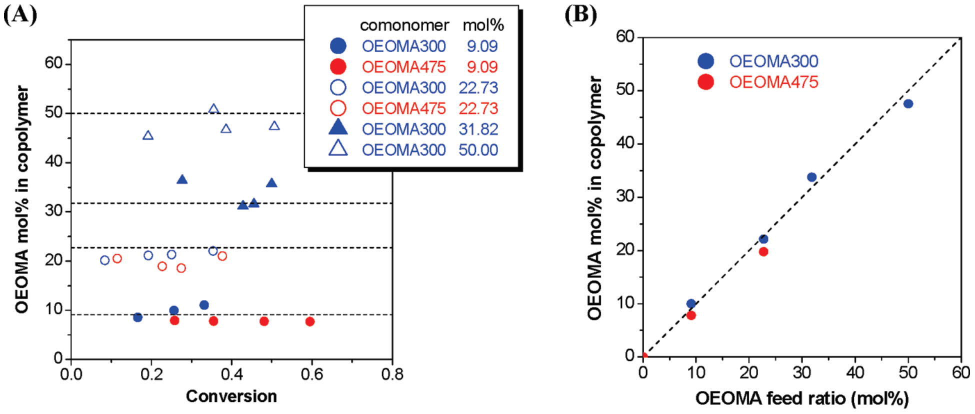


Figure 3. OEOMA content in mole percentage of P(M(EO)$_2$MA-*co*-OEOMA) copolymers vs monomer conversion (A) or OEOMA feed ratio at the beginning of reactions (B). The dashed lines are theoretical values.

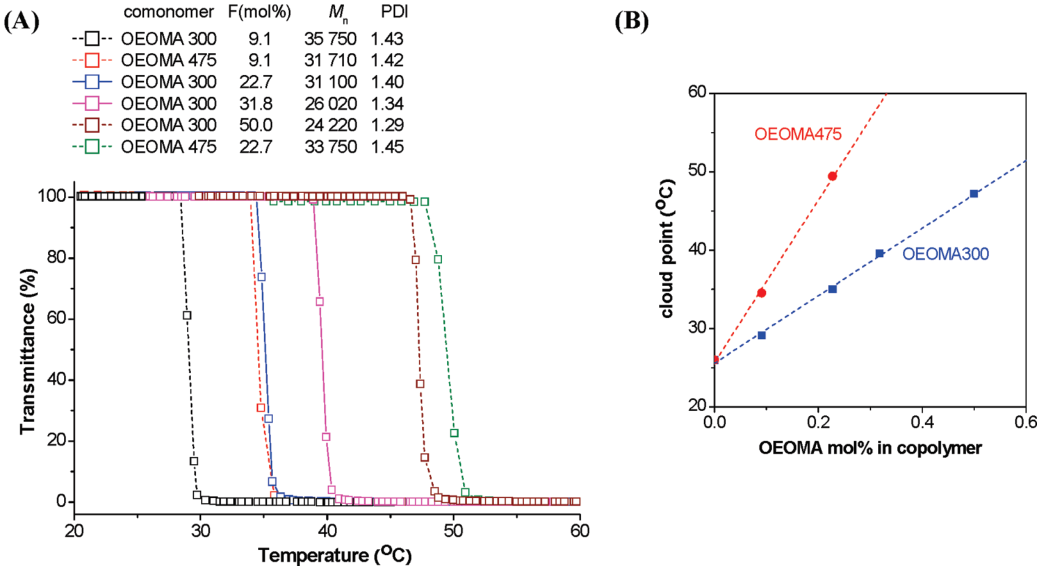


Figure 4. (A) Temperature dependence of transmittance change for 0.3 wt % aqueous solution of P(M(EO)$_2$MA-*co*-OEOMA). (B) Cloud point of the copolymer vs OEOMA content in mole percentage of the copolymer.

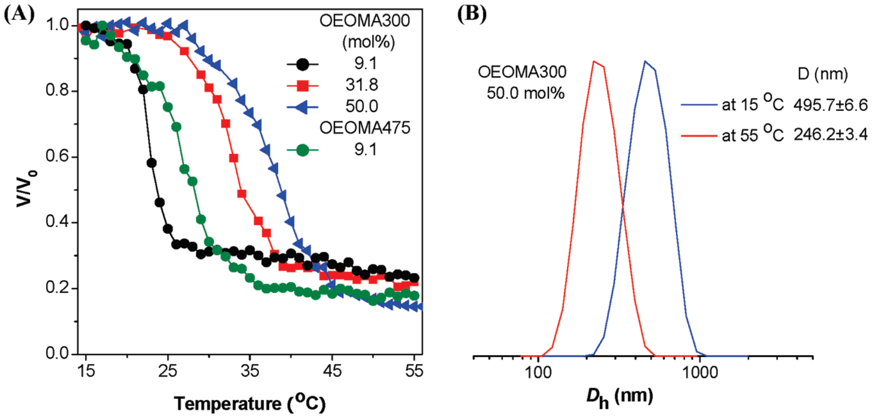


Figure 5. Change of P(M(EO)$_2$MA-*co*-OEOMA300) microgel hydrodynamic volume (a) and diameter (b) vs temperature in aqueous suspension. Concentration of microgels = 1 mg/mL. The volume-average hydrodynamic diameter of the microgels is determined by DLS.

copolymer can be precisely predicted from OEOMA molar ratio in the copolymer.

Preparation and Thermal Properties of P(M(EO)$_2$MA-*co*-OEOMA) Microgels. Temperature-sensitive microgels show great potential in biomedical applications, such as controlled drug delivery systems.[14,41−45,64,65] Drug encapsulation and delivery can be efficiently controlled through reversible swelling−deswelling behavior, triggered by changing temperature. It was demonstrated that POEOMA microgels synthesized via AGET ATRP in inverse miniemulsion system exhibited narrow size distribution, a high degree of chain end functionality, a uniform cross-linked network, and properties (ca. swelling ratio, degradation behavior, and colloidal stability) superior to microgels from conventional free radical polymerization.[66−69] These unique features suggest that thermally responsive P(M(EO)$_2$MA-*co*-OEOMA) copolymer microgels prepared by AGET ATRP in miniemulsion have potential in controlled drug delivery application.

The P(M(EO)$_2$MA-*co*-OEOMA) microgels with varied compositions were synthesized in the presence of ethylene glycol dimethacrylate (EGDMA) cross-linker under similar reaction conditions as in Table 1. The molar ratio of [EGDMA]$_0$ to [M(EO)$_2$MA]$_0$ was fixed as 1:110 (Table 2). The cross-linked microgels were purified via dialysis (MWCO ~ 25 000) against methanol and water to remove surfactants, unreacted monomers, and solvents. The temperature dependence of the *Z*-average hydrodynamic diameter of the copolymer microgels with different OEOMA contents was characterized by DLS in aqueous suspensions, as shown in Figure 5A. By slowly increasing temperature from 15 to 55 °C, hydrodynamic volume of the microgels gradually decreased to 15−25 vol % of the original value at 15 °C and then reached plateau. The volume change as a function of temperature was reversible. The transition temperatures of the microgels were about 22.7, 32.9, and 39.0 °C, corresponding to OEOMA300 mol % at 9.1, 31.8, and 50.0%, respectively. The LCST of the microgels containing OEOMA475 was higher than that with OEOMA300, under the same molar ratio of OEOMA to M(EO)$_2$MA. Similar to their linear copolymer analogues, the measured LCST of the microgels increased with OEOMA content. The microgels exhibited lower LCST than the linear copolymer with the same composition due to incorporation of the hydrophobic EGDMA cross-linker. The change of the hydrodynamic diameter distribution of the copolymer microgels (OEOMA-300-50 mol % in the copolymer, entry 3, Table 2) vs temperature is shown in Figure 5B. The volume-average hydrodynamic diameter of the microgels at 15 °C was 2 times that at 55 °C, corresponding to about an 8-fold change in volume. At both temperatures, the size distribution of the microgels was narrow.

Conclusions

Thermally responsive random copolymers of M(EO)$_2$MA and OEOMA ($M_n \sim 300$ or 475 g/mol) with varied compositions were successfully synthesized via AGET ATRP in miniemulsion at 65 °C. The copolymerizations were performed in a controlled way, generating well-defined copolymers with relatively low molecular weight distribution (~1.3−1.5). Compositional study of the formed copolymers revealed that OEOMA content in the copolymer was almost the same as the comonomer feed ratio and did not change much during the reaction, meaning that OEOMA barely partitioned into the water phase in miniemulsion copolymerization due to the relatively high reaction temperature (65 °C). The measured cloud point of the copolymer was proportional to OEOMA mole percentage of the copolymer, and therefore, the LCST could be precisely predicted.

Microgels of P(M(EO)$_2$MA-*co*-OEOMA) were also prepared by addition of EGDMA cross-linker. The thermally responsive behavior of the cross-linked microgels was investigated by DLS. Similar to their linear analogues, the LCST of the copolymer microgels can be tuned by changing OEOMA content of the microgels. The temperature-sensitive microgel with tunable LCST may have potential application in controlled drug delivery systems.

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