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Preparation of Nanoparticles of Well-Controlled Water-Soluble Homopolymers and Block Copolymers Using an Inverse Miniemulsion ATRP

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ABSTRACT: Stable colloidal nanoparticles of well-controlled water-soluble poly(oligo(ethylene glycol) monomethyl ether methacrylate) (P(OEOMA)) homo- and copolymers were successfully synthesized by inverse miniemulsion atom transfer radical polymerization using activators generated by electron transfer (AGET ATRP) at ambient temperature (30 °C). Oil-soluble sorbitan monooleate (Span 80) surfactant, ascorbic acid as a reducing agent, oxidatively stable $CuBr_2$/tris[(2-pyridyl)methyl]amine (TPMA) catalyst complex, and $[\text{initiator}]_0/[CuBr_2/\text{TPMA}]_0 = 1/0.5$ were selected for the controlled AGET ATRP inverse miniemulsion. The effect of reaction parameters on control over AGET ATRP and colloidal stability were explored. It was found that the use of water-soluble poly(ethylene oxide)-based bromoisobutyrate macroinitiators (PEO-Br) with long chain EO units, up to 90% ascorbic acid of Cu(II) complex, and appropriate amount of water resulted in the formation of stable colloidal particles with less than 200 nm diameter and well-controlled P(OEOMA) with $M_w/M_n < 1.3$. The addition of a long chain poly(ethylene glycol) monomethyl ether (PEOH) as a costabilizer improved colloidal stability without interfering the polymerization. A water-soluble $CuBr_2$/bipyridine catalyst complex was also suitable for AGET ATRP of OEOMA in inverse miniemulsion. Finally, colloidal particles of well-controlled block copolymers of OEOMA with different sizes of OEO side chains (degree of polymerization of EO = 5 and 9) were produced with relatively low $M_w/M_n = 1.3$ at 85% conversion.

Introduction

Atom transfer radical polymerization (ATRP) enables the synthesis of a wide range of (co)polymers with controlled molecular weight, narrow molecular weight distribution, and range of architectures and functionalities.[1−9] Many ATRP reactions have been conducted in heterogeneous media, mostly in oil-in-water (o/w) heterogeneous systems.[10−13] Typical processes include emulsion,[14−17] miniemulsion,[18−24] microemulsion,[25] and suspension[26−28] polymerization. These methods have produced stable particles of well-defined hydrophobic polymers. Polymers that have been successfully synthesized by ATRP in aqueous dispersion include homopolymers of poly(methyl methacrylate), poly(butyl methacrylate), poly(butyl acrylate), and polystyrene. These methods have also been extended to the preparation of well-defined gradient, block, and multiarmed copolymers in stable latex particles. However, only a few reports described the preparation of hydrophilic and water-soluble particles using ATRP in water[29] and inverse miniemulsion.[30]

An inverse miniemulsion is a water-in-oil (w/o) heterogeneous system where water-soluble species are stably dispersed in organic media with the aid of oil-soluble surfactants.[31] Conventional free radical polymerization of water-soluble and hydrophilic monomers in inverse miniemulsion has been applied to the synthesis of stable colloidal particles of poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(acrylic acid).[32] Temperature-sensitive hollow microspheres of poly(*N*-isopropylacrylamide),[33] core−shell nanocapsules with hydrophobic acrylic shell and hydrophilic interior,[34] and polyaniline particles[35] were also synthesized. Moreover, this method has been utilized to prepare stable organic−inorganic hybrid particles containing magnetic iron oxide nanoparticles[36,37] and clays[38] in cyclohexane-based inverse miniemulsions. However, all of these procedures have resulted in the preparation of polymers with broad molecular weight distribution (i.e., $M_w/M_n > 2.0$) due to the use of an uncontrolled polymerization process.

Recently, we reported the first successful controlled/living radical polymerization (CRP) using the ATRP process in a cyclohexane inverse miniemulsion.[30] A new initiation process for ATRP named activators generated by electron transfer (i.e., AGET ATRP)[18,39−41] was utilized for the synthesis of stable nanometer-sized colloidal particles of water-soluble polymers with narrow molecular weight distribution ($M_w/M_n < 1.3$). The additional introduction of a disulfide-functionalized dimethacrylate cross-linker into an inverse miniemulsion ATRP allowed for the synthesis of cross-linked nanogel particles. Application of this methodology resulted in the preparation of materials with many useful features: (1) preservation of a high degree of halide end-functionality to enable further chain extension and formation of block copolymers and/or functionalization with biorelated molecules, (2) formation of a uniformly cross-linked network in an individual nanogel particle, and (3) degradation of the nanogels in a reducing environment to individual polymeric chains with relatively narrow molecular weight distribution ($M_w/M_n < 1.5$). These unique properties suggest that the well-defined functional nanogels hold great potential as controlled drug delivery scaffolds to target specific cells.

This paper describes our systematic investigation of inverse miniemulsion AGET ATRP for the synthesis of stable colloidal particles of well-controlled polymers (Scheme 1). Oligo(ethylene glycol) monomethyl ether methacrylates with different molecular weights, OEOMA300 ($M = 300$ g/mol and pendent EO units DP ≈ 5) and OEOMA475 ($M = 475$ g/mol, pendent EO units DP ≈ 9), were used. The effect of several important parameters on the degree of control over polymerization and the colloidal

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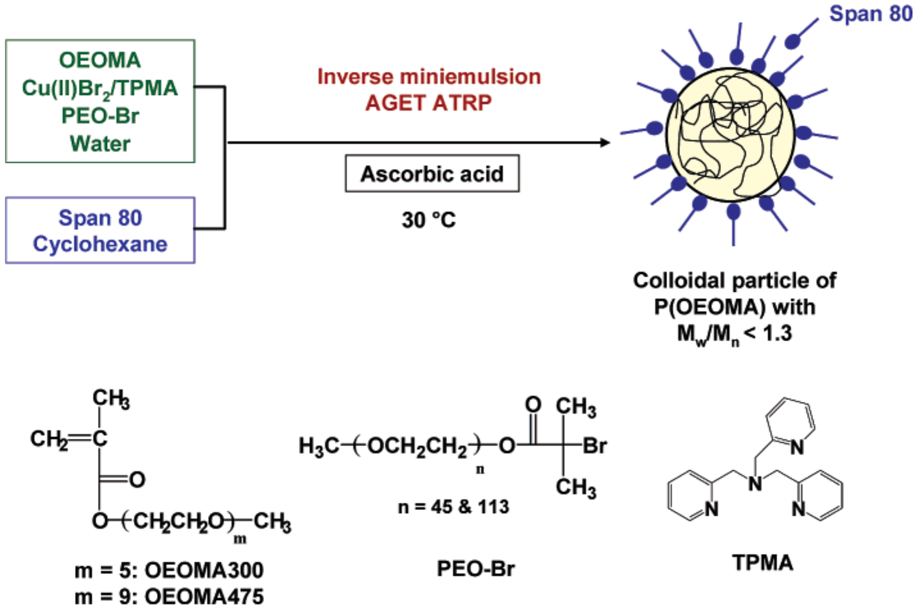
Scheme 1. Illustration of Inverse Miniemulsion AGET ATRP



stability of the resulting particles was examined. These include variation of initiators, addition of poly(ethylene glycol) monomethyl ether (PEOH) as a costabilizer, variation of the amounts of ascorbic acid and water, and use of a bipyridine ligand. Colloidal particles of well-defined P(OEOMA300)-*b*-P(OEOMA475) block copolymers were also successfully synthesized using inverse miniemulsion AGET ATRP of OEOMA475 from P(OEOMA300)-Br macroinitiators, which was also prepared by inverse miniemulsion ATRP.

Experimental Section

Materials. OEOMA300 and OEOMA475 were purchased from Aldrich and purified by passing them through a column filled with basic alumina to remove inhibitor. Copper(II) bromide ($CuBr_2$, 99%), 2,2′-bipyridine (bpy, 99+%), ethyl 2-bromoisobutyrate (EBiB, 98%), and L-ascorbic acid (AscA, 99+%) from Acros, sorbitan monooleate (Span 80) and cyclohexane (HPLC grade) from Aldrich, and 2,2-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) from Wako Chemie were used as received without purification. Tris[(2-pyridyl)methyl]amine (TPMA) was prepared according to literature procedures.[42,43]

Various poly(ethylene glycol)-functionalized bromoisobutyrate (PEO-Br) macroinitiators with different molecular weight (or EO chain lengths) were synthesized by the reaction of PEOH with 2-bromo-2-methylpropionic acid in the presence of dicyclohexyl carbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) in methylene chloride (CH_2Cl_2). Our notation of the macroinitiators is PEO750-Br, PEO2000-Br, and PEO5000-Br, where the numbers indicate the molecular weight of each PEOH segment. PEO750-Br was purified as described elsewhere.[44] PEO2000-Br and PEO5000-Br were purified as follows: the product was dissolved in water, and then undissolved solids (dicyclohexylurea byproducts) were removed by vacuum filtration. The product was extracted with CH_2Cl_2, isolated by evaporation of CH_2Cl_2, and further dried in a vacuum oven at 30 °C for 12 h.

General Procedure for AGET ATRP of OEOMA in Cyclohexane Inverse Miniemulsion. A series of AGET ATRP of OEOMA was conducted in inverse miniemulsion of cyclohexane under different conditions. A typical procedure for the synthesis of stable colloidal particles of well-controlled P(OEOMA300) is described below. OEOMA300 (1.4 g, 4.67 mmol), PEO2000-Br (33.4 mg, 0.016 mmol), TPMA (2.3 mg, 0.008 mmol), $CuBr_2$ (1.7 mg, 0.008 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 argon for 30 min. The flask was immersed in an oil bath preheated to 30 °C, and then an argon-purged aqueous solution of AscA (0.094 mmol/mL, 0.007 mmol, 74 μL) was added via syringe to activate the catalyst and start the polymerization. Samples were withdrawn periodically from the reaction to determine conversion and molar mass by GPC. The polymerization was stopped by exposing the reaction mixture to air.

The synthesis of colloidal particles of well-controlled P(OEOMA475) was carried out using the following amounts of reagents: OEOMA475 (1.4 g, 2.95 mmol), PEO2000-Br (21 mg, 0.009 mmol), PEO2000-OH (50 mg, 3.5 wt % of OEOMA475), TPMA (1.5 mg, 0.005 mmol), $CuBr_2$ (1.1 mg, 0.005 mmol), water (1.4 mL), Span 80 (1.0 g), cyclohexane (20 g), and an argon-purged aqueous solution of AscA (0.028 mmol/mL, 0.0034 mmol, 120 μL).

Synthesis of P(OEOMA300)-*b*-P(OEOMA475) Block Copolymers by AGET ATRP in Cyclohexane Inverse Miniemulsion. A stable inverse miniemulsion of P(OEOMA300) was prepared as described above and purified as follows: solvents were removed by rotary evaporation, and the remaining residues were dissolved in a minimum amount of THF. The resulting THF solution was added dropwise into cyclohexane, precipitating the polymers which were isolated by decantation, and then dried in a vacuum oven at 30 °C for 12 h. In this way, unreacted OEOMA300 and Span 80 can be removed from reaction mixture, since they are miscible with cyclohexane. The purified P(OEOMA300) macroinitiators had M_n = 22 300 g/mol and M_w/M_n = 1.27.

For the synthesis of well-defined P(OEOMA300)-*b*-P(OEOMA475) block copolymer, an AGET ATRP of OEOMA475 was conducted from the P(OEOMA300) macroinitiator in cyclohexane inverse miniemulsion under similar conditions to those described above: OEOMA475 (1.4 g, 2.95 mmol), P(OEOMA300) macroinitiator (294.7 mg, 0.013 mmol), PEO2000-OH (56 mg, 4 wt % of OEOMA475) as a costabilizer, TPMA (1.9 mg, 0.007 mmol), $CuBr_2$ (1.5 mg, 0.007 mmol), water (1.4 mL), Span 80 (1.0 g), cyclohexane (20 g), and an argon-purged aqueous solution of AscA (0.094 mmol/mL, 0.007 mmol, 74 μL) were used.

Conventional Free Radical Polymerization (FRP) of OEOMA300 in Inverse Miniemulsion. Inverse miniemulsion FRP of OEMA300 was conducted in cyclohexane in the absence and presence of PEO2000-OH. A typical procedure for the synthesis of P(OEOMA300) particles in the presence of PEO2000-OH was as follows: V-70 (0.04 g) 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) and PEO2000-OH (50 mg, 3.5 wt % of OEOMA300) 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. The polymerization was stopped after 2.5 h by lowering the temperature to room temperature. Conversion = 87%, $M_n = 80\,400$ g/mol, and $M_w/M_n = 2.6$.

In the absence of PEO2000-OH, polymerization was proceeded to 87% conversion, producing P(OEOMA300) particles with $M_n = 61\,400$ g/mol and $M_w/M_n = 2.2$.

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 an eluent at 35 °C at a flow rate of 1 mL/min. Linear poly(methyl methacrylate) (PMMA) standards were used for calibration. For GPC measurements, an aliquot of the polymer samples was dried in air, dissolved in THF, containing a small amount of toluene as internal standard, and then filtered through a column filled with alumina to remove Cu species. Conversion was also determined using GPC by following the decrease of the macromonomer peak area relative to the increase in the polymer peak area. Particle size and size distribution were measured by dynamic light scattering (DLS) on a 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: $D_{av} = \sum_{i=1}^{n} D_i/n$; $S = [\sum_{i=1}^{n}(D_i - D_{av})^2/(n - 1)]^{1/2}$; 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. In this paper, particle sizes are expressed as $D_{av} \pm S$ nm.

Results and Discussion

Selection of Surfactant and Concentration of Cu(II) Complex. To conduct an inverse miniemulsion polymerization, aqueous droplets containing water-soluble monomers should form stable dispersion with the aid of surfactants in continuous oil phase such as cyclohexane. Consequently, the correct selection of surfactants is important to ensure colloidal stability of monomer droplets and the resulting polymeric particles. The use of oil-soluble nonionic surfactants with hydrophilic–lipophilic balance (HLB) value around 4.0 is recommended for conventional inverse miniemulsion polymerization.[32] Span 80 is a commercially available surfactant and has HLB = 4.3. Its critical micellar concentration (cmc) is 1.25–1.5 vol % in cyclohexane.[45] Recently, we as well as others have used Span 80 with cyclohexane,[30] and its mixture with *n*-hexane,[46–48] for the successful synthesis of stable colloidal particles of hydrophilic and water-soluble polymers. Consequently, Span 80 was selected in all experiments described in this paper.

A complex of TPMA with $CuBr_2$ was selected as the catalyst precursor in the experiments. The use of TPMA as ligand leads to formation of an active water-soluble catalyst complex, with relatively low tendency toward dissociation in water.[49] Since AGET ATRP processes use oxidatively stable Cu(II) complexes that can be reduced to active Cu(I) complexes in the presence of reducing agents such as AscA, the amount of added Cu(II) complex is important for control over AGET ATRP. It was found that in aqueous AGET ATRP of OEOMA the use of high concentrations of Cu(II)/TPMA complex resulted in P(OEOMA) with bimodal molecular weight distribution, while smaller amounts of Cu(II) complex resulted in limited conversion.[50] When the ratio of initiator to $CuBr_2$/TPMA complex was 1/0.5, well-defined polymers with narrow molecular weight distribution ($M_w/M_n < 1.3$) at over 80% conversion were produced in water. Similar results were also observed for the AGET ATRP of OEOMA in inverse miniemulsion.[30] Therefore, the ratio of initiator/Cu complex = 1/0.5 was used in all experiments described in this paper.

Table 1. Conversion and Molecular Weight Data for P(OEOMA300) Prepared by AGET ATRP of OEOMA300 in Inverse Miniemulsion with EBiB at 30 °C[a]

time (min)	conv (%)	$M_{n,theo}$ [b]	$M_{n,GPC}$	M_w/M_n
20	0.30	26 800	113 100	1.56
45	0.55	49 300	118 700	1.82
120	0.69	62 400	129 700	2.02

[a] $[OEOMA300]_0/[EBiB]_0/[CuBr_2/TPMA]_0/[AscA]_0 = 300/1/0.5/0.35$. [b] $M_{n,theo}$ = MW(OEOMA300) × ($[OEOMA300]_0/[EBiB]_0$) × conversion.

A series of AGET ATRP of OEOMA300 in cyclohexane inverse miniemulsion were conducted under similar conditions. The effect of the variation of initiators, addition of PEOH, variation of amounts of AscA and water, and use of a bipyridine ligand on control over polymerization and the colloidal stability of the resulting particles were studied.

Variation of Water-Soluble ATRP Initiators. Various water-soluble, PEO-Br with different EO chain lengths were synthesized and examined as ATRP initiators for the preparation of PEO-*b*-P(OEOMA) block copolymers. These include PEO750-Br (EO units ≈ 16), PEO2000-Br (EO units ≈ 45), and PEO5000-Br (EO units ≈ 113). For comparison, ethyl 2-bromoisobutyrate (EBiB), an ATRP initiator commonly used for methacrylates, was also examined.

EBiB was the first initiator examined in an inverse miniemulsion AGET ATRP. Since EBiB is miscible with OEOMA300, an aqueous mixture consisting of EBiB, OEOMA300, water, and $CuBr_2$/TPMA formed a homogeneous solution. As presented in Table 1, polymerization proceeded, reaching 70% conversion within 120 min. Molecular weight increased with conversion; however, the values were much larger than those predicted for quantitative initiation. In addition, molecular weight distribution was quite broad, $M_w/M_n = 1.5–2.1$. These results indicate that the polymerization initiated with EBiB was not well controlled. This is presumably due to the limited solubility of EBiB in a 1/1 w/w mixture of OEOMA300/water. Consequently, the dispersion was not stable, showing phase separation through a whole polymerization period.

In the next set of experiments, water-soluble PEO-Br macroinitiators were examined: PEO750-Br, PEO2000-Br, and PEO5000-Br. Similar kinetic data were observed for reactions with both PEO5000-Br and PEO2000-Br with relatively long PEO lengths; conversion reached 80% within 120 min (Figure 1a). Molecular weight increased linearly with conversion, and polydispersity was as low as $M_w/M_n < 1.3$ up to 75% conversion and then increased to $M_w/M_n > 1.3$ (Figure 1b). This increase may possibly be due to termination reactions at higher conversion. These results indicate that both polymerization reactions were well-controlled. However, somewhat better control over inverse miniemulsion AGET ATRP of OEOMA300 was achieved with the use of PEO2000-Br macroinitiator, as indicated by lower polydispersity (Figure 1b).

Both reactions produced stable colloidal particles. As an example, Figure 2 illustrates a CONTIN plot for P(OEOMA300) colloidal particles prepared in the presence of PEO2000-Br macroinitiator. The DLS measurements show that the average particle size was 150–174 nm for polymerization with PEO2000-Br and 120–145 nm for the polymerization with PEO5000-Br, with narrow and monomodal size distributions for both cases.

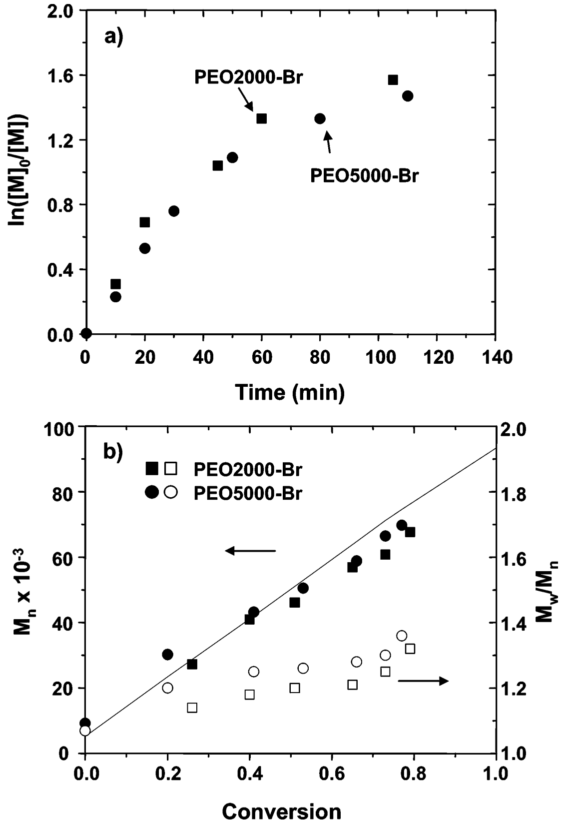


Figure 1. Kinetic plots (a) and evolution of molecular weight (closed symbols) and polydispersity (open symbols) with conversion (b) for AGET ATRP of OEOMA300 in cyclohexane inverse miniemulsion with PEO2000-Br and PEO5000-Br macroinitiators at 30 °C. Conditions: $[\text{OEOMA300}]_0/[\text{PEO-Br}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0 = 300/1/0.5/0.45$; OEOMA300/water = 1/1 v/v; solids content = 10 wt %.

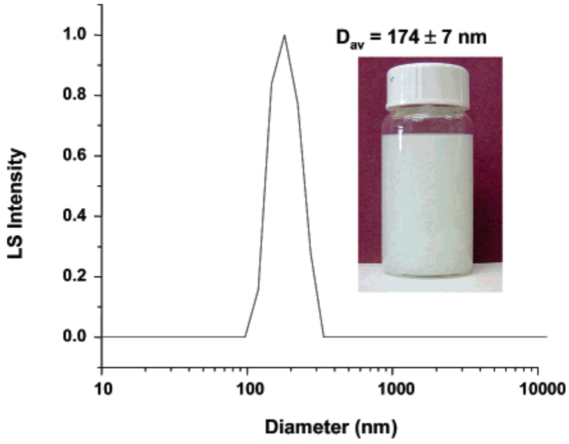


Figure 2. A CONTIN plot of P(OEOMA300) colloidal particles prepared by AGET ATRP in inverse miniemulsion with PEO2000-Br macroinitiator at 30 °C. Conditions are described in Figure 2.

However, interesting results were observed when PEO750-Br, a macroinitiator with a relatively short PEO length, was used for AGET ATRP of OEOMA300 in cyclohexane inverse miniemulsion. Under the similar conditions, conversion reached 65% (Figure 3a), which was lower than that (80%) obtained in the presence of either PEO2000-Br or PEO5000-Br. Molecular weight increased linearly with conversion, and molecular weight distribution was narrow, $M_w/M_n < 1.2$ (Figure 3b). However, the resulting particles precipitated after 3 days storage at room temperature, indicating limited colloidal stability. These results suggest that macroinitiators with long PEO segments could function as a costabilizer, such as high molecular weight polymers in normal miniemulsion polymerization, to enhance colloidal stability. This assumption is confirmed in the next section.

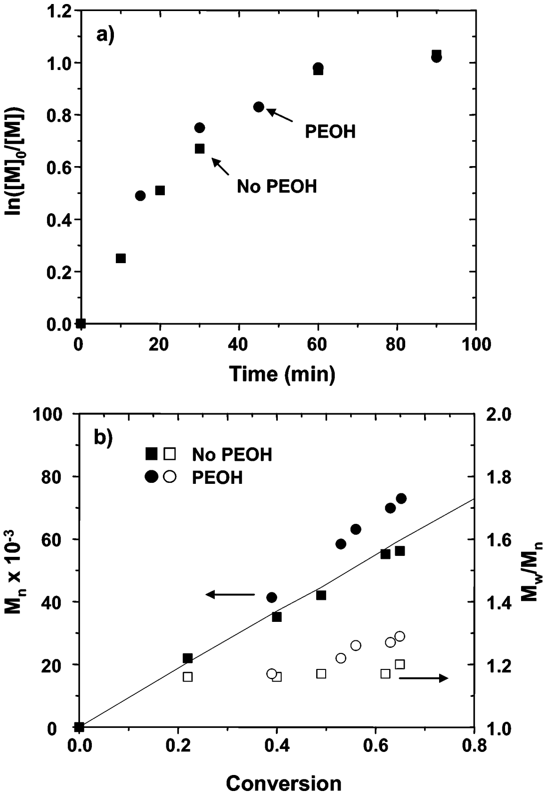


Figure 3. Kinetic plots (a) and evolution of molecular weight (closed symbols) and polydispersity (open symbols) with conversion (b) for AGET ATRP of OEOMA300 in inverse miniemulsion of cyclohexane with PEO750-Br in the absence and presence of PEO2000-OH as a costabilizer at 30 °C. Conditions: $[\text{OEOMA300}]_0/[\text{PEO750-Br}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0 = 300/1/0.5/0.45$; OEOMA300/water = 1/1 v/v; solids content = 10 wt %.

Effect of PEOH as a Costabilizer. 4.4 wt % PEO2000-OH was introduced into an AGET ATRP inverse miniemulsion of OEOMA300 in the presence of PEO750-Br macroinitiator. As shown in Figure 3, kinetic and molecular weight data were similar to those obtained in the absence of PEO2000-OH. However, the presence of PEO2000-OH enhanced the colloidal stability of the resulting dispersion. The DLS measurement indicated that the average particle size was 176 ± 10 nm with narrow size distribution, which is almost the same as that (d = 174 ± 7 nm) for P(OEOMA300) colloidal particles produced in the presence of PEO2000-Br macroinitiator.

The presence of higher molecular weight PEOH as a costabilizer also enhanced the colloidal stability of P(OEOMA300) particles in a conventional free-radical inverse miniemulsion polymerization of OEOMA300. In the absence of PEO2000-OH, the resulting particles precipitated, indicating poor colloidal stability. However, the addition of 3.5 wt % PEO2000-OH of OEOMA300 resulted in the formation of stable P(OEOMA300) colloidal particles. The average particle size was 152 ± 6 nm with monomodal size distribution from the DLS measurements. In addition, high conversion, over 87%, was reached within 2.5 h, similar to the results obtained in the polymerization conducted in the absence of PEO2000-OH. Thus, the long chain PEO-Br macroinitiators can function as costabilizers as well as ATRP macroinitiators in inverse miniemulsion ATRP.

Effect of Concentration of Ascorbic Acid. In an AGET ATRP the added AscA reduces the oxidatively stable Cu(II)/

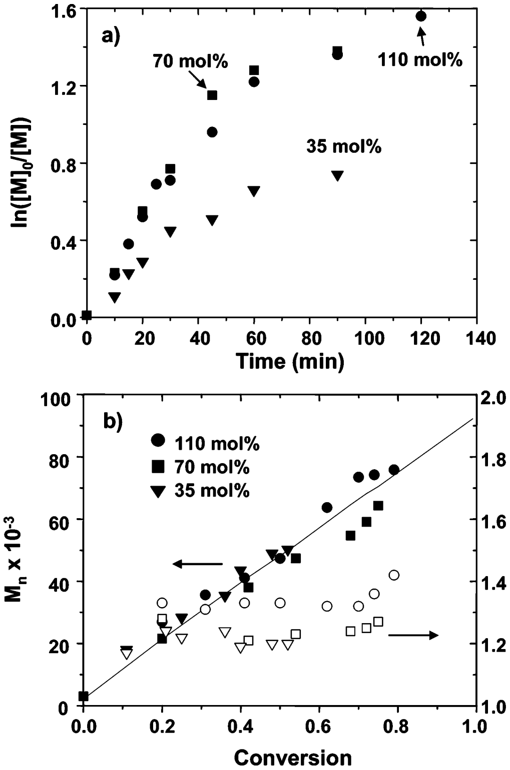


Figure 4. Kinetic plots (a) and molecular weight (closed symbols) and polydispersity (open symbols) with conversion (b) for AGET ATRP of OEOMA300 in inverse miniemulsion of cyclohexane. Different amounts of ascorbic acid were varied at 35 mol % (triangle), 70 mol % (rectangle), and 110 mol % (circle) of Cu(II) complex at 30 °C. Conditions: [OEOMA300]$_0$/[PEO2000-Br]$_0$/[CuBr$_2$]$_0$ = 300/1/0.5; OEOMA300/water = 1/1 v/v; solids content = 10 wt %.

ligand precursor to the active Cu(I)/ligand complex. Consequently, the concentration of AscA added to the reaction mixture directly influences the ratio of Cu(I)/L$_m$ activator to X−Cu(II)/L$_m$ deactivator in the reaction mixture and ultimately the rate of polymerization as well as the molecular weight distribution of the polymer formed in an ATRP.

Amounts of AscA were varied from 35 to 110 mol % of Cu(II) complex for inverse miniemulsion AGET ATRP of OEOMA300. The results are shown in Figure 4 for 35, 70, and 110 mol % AscA and in Figure 1 for 90 mol % AscA. The first-order kinetic plots show that the use of lower concentration of AscA (35 mol % of Cu(II) complex) resulted in slow polymerization and low conversion, reaching only 55%. Increasing the concentration of AscA (70 mol %) resulted in a faster polymerization and higher conversion, reaching 75%. The rate of polymerization remained unchanged with further increases in AscA, up to 110% of initial concentration of the Cu(II) complex. The molecular weight increased linearly with conversion for all the polymerizations. Molecular weight distribution was narrow, $M_w/M_n < 1.3$, except for the use of 110% AscA of Cu(II) complex.

Effect of Varying the Amount of Water in the Aqueous Phase. It was reported that several side reactions occur in an ATRP conducted in the presence of water; the main side reaction is hydrolysis of the ATRP deactivator (X−Cu(II)/L$_m$), which often leads to loss of control in aqueous ATRP.[51] In the inverse miniemulsion ATRP process, water is used as a solvent to form the aqueous phase as well as a lipophobe to build up an osmotic pressure in the inverse miniemulsion droplets. Since the polymerization occurs in aqueous monomer droplets dispersed in a continuous cyclohexane phase, the effect of varying the amount of water in the aqueous phase on the AGET ATRP of OEOMA300 was examined. The amount of water was expressed as the ratio of water/OEOMA300.

Table 2. Conversion and Molecular Weight Data for P(OEOMA300) Prepared by AGET ATRP of OEOMA300 in Inverse Miniemulsion with Different Amount of Water at 30 °C[a]

entry	water/OEOMA (v/v)	conv (%)	$M_{n,theo}$[b]	$M_{n,GPC}$	M_w/M_n
A	0.5/1	0.40	37 100	36 300	1.30
B	1/1	0.73	68 200	60 700	1.25
C	2/1	0.56	53 100	45 100	1.34

[a] Results are compared for the P(OEOMA300) samples taken at 60 min of polymerizations. Conditions: [OEOMA300]$_0$/[PEO2000-Br]$_0$/[CuBr$_2$/TPMA]$_0$/[AscA]$_0$ = 300/1/0.5/0.45; solids content = 10 wt %. [b] $M_{n,theo}$ = MW(OEOMA300) × ([OEOMA300]$_0$/[PEO2000-Br]$_0$) × conversion + MW(PEO2000-Br).

The water/OEOMA300 ratio was first increased from 1/1 v/v to 2/1 v/v. Table 2 shows that relatively lower conversion (55%) was reached with larger amounts of water (entry C) compared to the ratio of water/OEOMA300 = 1/1 (entry B). Molecular weight increased with conversion; however, bimodal molecular weight distribution with $M_w/M_n = 1.34$ was observed (Figure 5). Furthermore, the resulting particles became unstable, finally precipitating out of dispersion.

When the ratio of water/OEOMA300 was 0.5/1 v/v (entry A), polymerization was also uncontrolled, producing P(OEOMA300) with bimodal molecular weight distribution (M_w/M_n = 1.30). The resulting particles were unstable and had the average size of 378 ± 132 nm with a fairly broad size distribution from DLS measurement. These results suggest that the use of an appropriate amount of water is necessary to achieve control over molecular weight of the resulting polymers as well as colloidal stability of the resulting particles for AGET ATRP in inverse miniemulsion.

Use of 2,2′-Bipyridine Ligand. 2,2′-Bipyridine (bpy), a commercially available ligand, forms a water-soluble Cu(II) complex, which is less active than a TPMA complex.[49] To test feasibility of the use of bpy ligand to prepare stable particles of well-controlled P(OEOMA), AGET ATRP of OEOMA300 was conducted in inverse miniemulsion with CuBr$_2$/bpy complex and PEO2000-Br macroinitiator. The kinetic plot shows that conversion increased with time, reaching 60% in 90 min (Figure 6a). This indicates that polymerization in the presence of the CuBr$_2$/bpy complex was slower than in the presence of the CuBr$_2$/TPMA complex. However, molecular weight increased linearly with conversion, yielding polymers with M_w/M_n = 1.15−1.28 (Figure 6b). In addition, DLS measurement indicates the formation of stable colloidal particles with the average size of 130 ± 7 nm and narrow size distribution.

Synthesis of Colloidal Particles of Well-Defined P(OEOMA475). Polymerization of OEOMA475 macromonomer was also carried out in an inverse miniemulsion AGET ATRP under similar conditions in the presence of PEO2000-Br and PEO5000-Br macroinitiators. The polymerization initiated with PEO2000-Br shows a 10−15 min induction period, and then the reaction followed first-order kinetics, reaching 85% conversion within 60 min (Figure 7a). An induction period was also observed when OEOMA1100 (M = 1100 g/mol, pendent EO units DP ≈ 23) was a macromonomer for AGET ATRP in inverse miniemulsion which is different from AGET ATRP of OEOMA300 in inverse miniemulsion.[30] The occurrence of induction period is presumably due to the slow reduction of the Cu(II) complex to the active Cu(I) complex as well as the greater hydrophilicity of OEOMA475 and OEOMA1100 compared to OEOMA300. Since OEOMA300 is miscible with cyclohexane, there may be

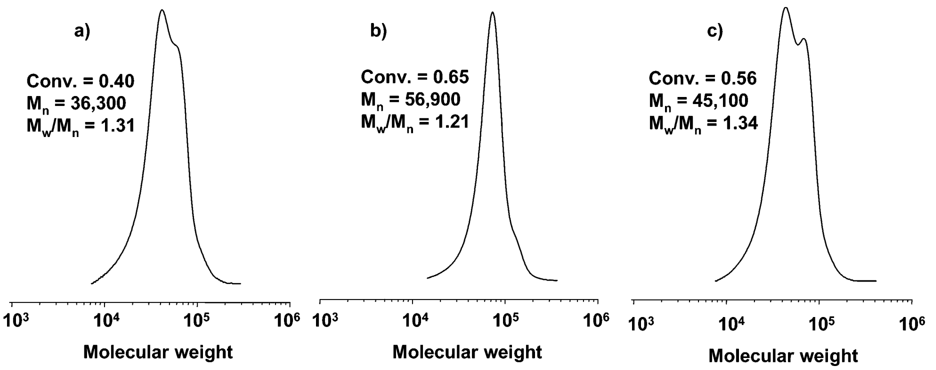


Figure 5. Comparison of GPC traces of P(OEOMA300) prepared by AGET ATRP of OEOMA300 in inverse miniemulsion with the v/v ratio of water/OEOMA = 0.5/1 (a), 1/1 (b), and 2/1 (c) at 30 °C. Conditions: $[\text{OEOMA300}]_0/[\text{PEO2000-Br}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0$ = 300/1/0.5/0.45; solids content = 10 wt %.

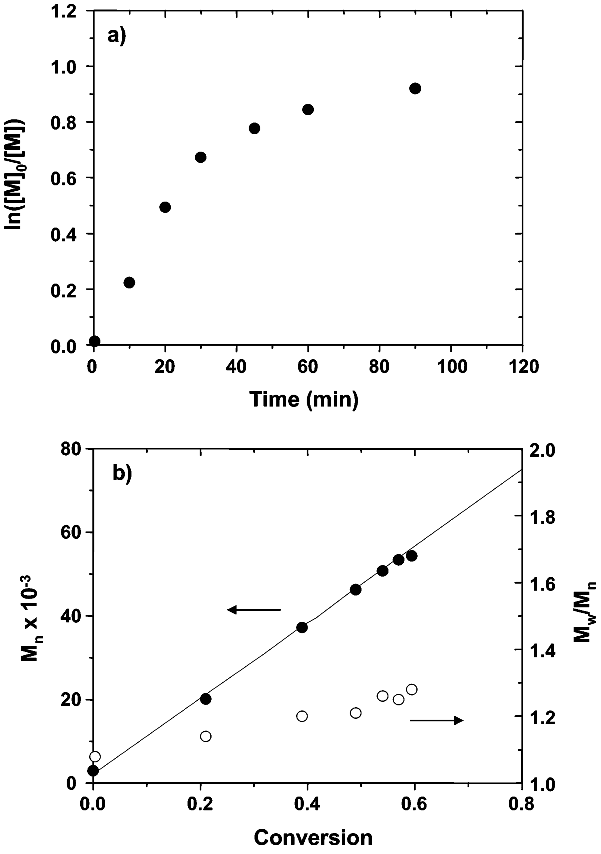


Figure 6. Kinetic plot (a) and molecular weight (closed symbols) and polydispersity (open symbols) with conversion (b) for AGET ATRP of OEOMA300 in inverse miniemulsion of cyclohexane with PEO2000-Br and CuBr_2/2bpy complex at 30 °C. Conditions: $[\text{OEOMA300}]_0/[\text{PEO2000-Br}]_0/[\text{CuBr}_2]_0/[\text{bpy}]_0/[\text{AscA}]_0$ = 300/1/0.5/1/0.45; OEOMA300/water = 1/1 v/v; solids content = 10 wt %.

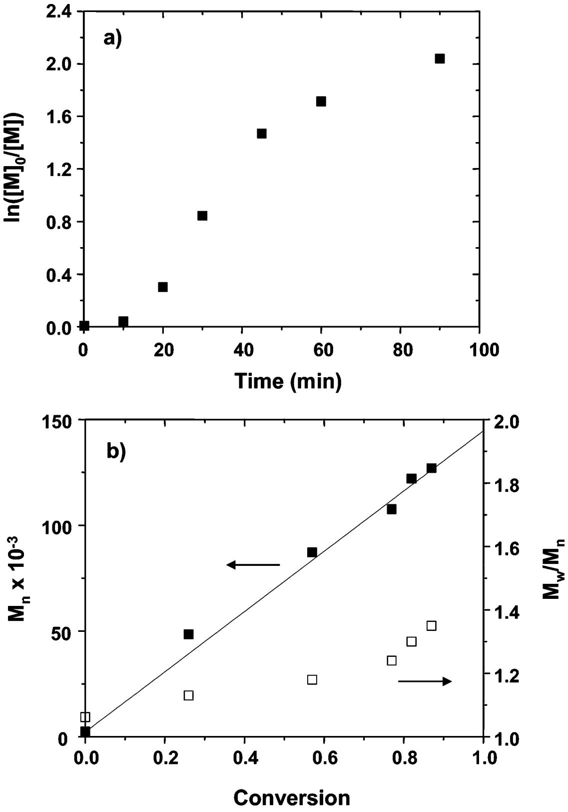


Figure 7. Kinetic plot (a) and molecular weight (closed symbols) and polydispersity (open symbols) with conversion (b) for AGET ATRP of OEOMA475 in inverse miniemulsion of cyclohexane with PEO2000-Br at 30 °C. Conditions: $[\text{OEOMA475}]_0/[\text{PEO2000-Br}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0$ = 300/1/0.5/0.35; OEOMA475/water = 1/1 v/v; solids content = 10 wt %.

Table 3. Conversion and Molecular Weight Data for the Final P(OEOMA475) Prepared by AGET ATRP of OEOMA475 in Inverse Miniemulsion at 30 °C[a]

entry	I	time (min)	conv (%)	$M_{n,\text{theo}}$[b]	$M_{n,\text{GPC}}$	M_w/M_n	*d* (nm)
D	PEO2000-Br	60	0.88	119 500	127 500	1.35	212 ± 33
E	PEO5000-Br	90	0.71	106 300	71 700	1.20	148 ± 11

[a] $[\text{OEOMA475}]_0/[\text{I}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0$ = 300/1/0.5/0.35; solids content = 10 wt %. [b] $M_{n,\text{theo}}$ = MW(OEOMA475) × ($[\text{OEOMA475}]_0/[\text{I}]_0$) × conversion + MW(I).

a significant amount of polymerization of OEOMA300 in the continuous cyclohexane phase, which presumably contributes to earlier initiation for AGET ATRP of OEOMA300. Molecular weight increased linearly with conversion, and molecular weight distribution was narrow, $M_w/M_n < 1.3$ up to 88% conversion (Figure 7b). Polymerization initiated with PEO5000-Br also shows a short induction period at the beginning of polymerization, and then the reaction reached 71% conversion within 90 min, producing well-controlled P(OEOMA475) with M_w/M_n = 1.22 (Table 3).

The resulting dispersions of P(OEOMA475) particles showed some phase separation within a week. However, the addition of extra PEO2000-OH (3.5 wt % of OEOMA475) as a costabilizer enhanced colloidal stability of the resulting dispersion.

Synthesis of Well-Defined Block Copolymers in Colloidal Particles. An advantage of an ATRP is the production of well-defined polymers with halogen end functionality, which enables

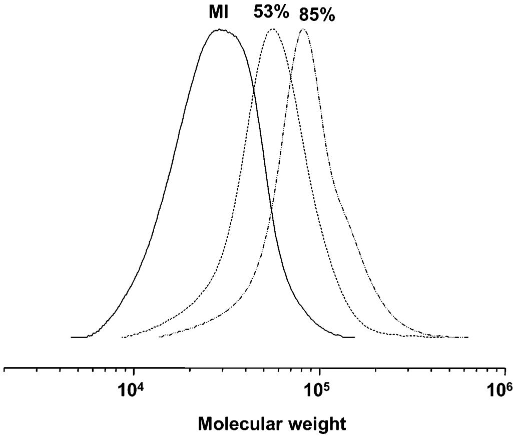


Figure 8. Evolution of GPC traces of P(OEOMA300)-Br macroinitiator (MI) and P(OEOMA300)-*b*-P(OEOMA475) block copolymers at 53 and 85% conversions. Molecular weight data: $M_n = 22\,300$ g/mol ($M_w/M_n = 1.28$) for MI; $M_n = 45\,700$ g/mol ($M_w/M_n = 1.28$) and 68 500 g/mol ($M_w/M_n = 1.30$) for block copolymers at 55 and 85%, respectively. Conditions: $[\text{OEOMA475}]_0/[\text{P(OEOMA300)-Br}]_0/[\text{CuBr}_2/\text{TPMA}]_0/[\text{AscA}]_0 = 223/1/0.6/0.53$. PEO2000-OH = 4 wt % of OEOMA475; OEOMA475/water = 1/1 v/v; solids content = 10 wt %. P(OEOMA300)-Br MI was prepared by AGET ATRP of OEOMA300 in inverse miniemulsion and then purified by precipitation into cyclohexane.

formation of amphiphilic block copolymers[8,9] and further functionalization with biorelated molecules, including using a facile click reaction.[52−56] We previously reported the successful chain extension of P(OEOMA300) nanogels with polystyrene using ATRP in toluene, demonstrating the preservation of bromine end functionality of the polymers in the nanogels.[30] This demonstrates the applicability of inverse miniemulsion ATRP for the synthesis of well-defined block copolymers in colloidal particles. The synthesis of a P(OEOMA300)-*b*-P(OEOMA475) block copolymer was carried out by an AGET ATRP of OEOMA475 from P(OEOMA300)-Br macroinitiator in an inverse miniemulsion. The P(OEOMA300)-Br was first synthesized by inverse miniemulsion AGET ATRP and purified by precipitation into cyclohexane (as described in the Experimental Section). The purified P(OEOMA300)-Br was completely dissolved in a 1:1 v/v mixture of water and OEOMA475. The resulting transparent aqueous solution also contained 4 wt % PEO2000−OH as a costabilizer. Figure 8 shows the GPC traces of P(OEOMA300)-Br macroinitiator and the resulting P(OEOMA300)-*b*-P(OEOMA475) block copolymers at different conversions of 53 and 85%. The polymerization was well-controlled, showing increase in molecular weight with conversion, monomodal molecular weight distributions of both macroinitiator and block copolymers, and low polydispersity with $M_w/M_n < 1.3$. DLS measurement shows that the particle size distribution was monomodal with the average size 226 ± 27 nm in diameter. These results indicate a successful synthesis of well-defined block copolymers by inverse miniemulsion ATRP.

Conclusions

A cyclohexane inverse miniemulsion AGET ATRP of OEOMA was systematically investigated at ambient temperature (30 °C) for the synthesis of stable nanometer-sized colloidal particles of well-defined, water-soluble P(OEOMA) homopolymers and block copolymers. An oil-soluble Span 80 surfactant, oxidatively stable CuBr_2/TPMA complex, and $[\text{initiator}]_0/[\text{CuBr}_2/\text{TPMA}]_0 = 1/0.5$ were selected for the controlled AGET ATRP inverse miniemulsion. Several reaction parameters were varied to understand the effect of these variables on the reaction and achieve better control over the polymerization and the colloidal stability of the resulting particles.

The use of water-soluble PEO-Br macroinitiators with long chain EO units (PEO2000-Br and PEO5000-Br) produced stable colloidal particles of well-controlled P(OEOMA300) with $M_w/M_n < 1.3$. The use of a PEO750-Br macroinitiator with relatively shorter segment of EO units and low molecular weight EBiB resulted in the formation of either unstable colloidal particles or uncontrolled polymers with broad molecular weight distribution ($M_w/M_n > 1.5$) in an inverse miniemulsion polymerization system. The addition of a long chain PEOH improved colloidal stability in both AGET ATRP and conventional FRP inverse miniemulsion systems. In addition, the presence of PEOH did not interfere with the polymerization. These results indicate that PEO2000-Br and PEO5000-Br macroinitiators, with long PEO chains, function as a costabilizer as well as an ATRP macroinitiator in an inverse miniemulsion ATRP.

Higher concentrations of AscA increased the rate of polymerization. Up to 90 mol % AscA of Cu(II), AGET ATRP was well-controlled, producing P(OEOMA300) with narrow molecular weight distribution ($M_w/M_n < 1.3$). However, further increases in the amount of AscA resulted in the formation of polymers with relatively high polydispersity. The use of appropriate amount of water is necessary for good control over polymerization and colloidal stability of the resulting particles. When the ratio of water/OEOMA (v/v) was either larger or smaller than 1/1, lower conversion and bimodal molecular weight distribution were observed. Inverse miniemulsion AGET ATRP of OEOMA475 was also well controlled at conversions as high as 90%. The use of a CuBr_2/bipyridine complex resulted in slower polymerization but yielded stable colloidal particles of well-controlled P(OEOMA300).

In addition, well-controlled P(OEOMA300)-*b*-P(OEOMA475) block copolymers, with relatively low polydispersity ($M_w/M_n = 1.3$) at 85% conversion, were prepared in stable colloidal particles, using AGET ATRP of OEOMA475 from P(OEOMA300)-Br macroinitiator. This successful block copolymerization demonstrates the applicability of the inverse miniemulsion ATRP for the synthesis of amphiphilic block copolymers that can be used, for example, as drug delivery scaffolds for biomedical applications.[57−62]

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