Direct Synthesis of Thermally Responsive DMA/NIPAM Diblock and DMA/NIPAM/DMA Triblock Copolymers via Aqueous, Room Temperature RAFT Polymerization[†]

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ABSTRACT: We report aqueous, room temperature RAFT polymerization of *N*-isopropylacrylamide (NIPAM) and, subsequently, its block copolymerization utilizing a poly(*N*,*N*-dimethylacrylamide) macro-CTA. A series of thermally responsive AB diblock and ABA triblock copolymers have been prepared. These polymers contain hydrophilic *N*,*N*-dimethylacrylamide (DMA) A blocks of fixed molecular weight and temperature-responsive NIPAM B blocks of varied chain length. Using a combination of ^{1}H NMR spectroscopy, T_2 relaxation measurements, dynamic light scattering (DLS), and static light scattering (SLS), we demonstrate that these block copolymers are indeed capable of reversibly forming micelles in response to changes in solution temperature and that the micellar size and transition temperature are dependent on both the NIPAM block length and the polymer architecture (diblock vs triblock).

Introduction

Recently, a great deal of interest has been focused on the synthesis of water-soluble block copolymers that demonstrate responsive behavior, i.e. those materials capable of undergoing a conformational change or phase transition upon the application of an external stimulus such as a change in solution pH, electrolyte concentration, or temperature.[1−8] These materials typically contain both a permanently hydrophilic block and a "smart" block which is tunably hydrophilic/hydrophobic. Traditionally, these materials have been prepared using living polymerization methods including anionic, cationic, and group transfer polymerization.[9,10] These techniques, however often require stringent reaction conditions and are restricted to a limited number of relatively nonfunctional monomers.

The desire to prepare advanced polymer architectures (e.g., blocks, combs, and stars) with predetermined molecular weights and low polydispersities, while maintaining the robust reaction conditions and wide monomer selection available to radical polymerization, has spurred the development of the controlled radical polymerization (CRP) techniques. These techniques include nitroxide-mediated polymerization (NMP),[11] atom transfer radical polymerization (ATRP),[12] and reversible addition−fragmentation chain transfer (RAFT) polymerization.[13] First introduced by Rizzardo and Moad in 1998, RAFT is arguably the most versatile living radical polymerization technique in terms of monomer selection and reaction conditions.[14,15] The polymerization can be performed in a variety of solvents, including water, simply by adding the appropriate quantity of a suitable RAFT agent to a standard free radical polymerization.

The synthesis of functional block copolymers directly in aqueous media under mild conditions not requiring protection/deprotection chemistry is a major goal in developing stimuli-responsive delivery systems such as micelles and vesicles. Major advances toward this goal have been realized in RAFT polymerization yielding water-soluble polymers with well-controlled structures. For example, homopolymers and block copolymers with anionic,[7,16] cationic,[17] zwitterionic,[18,19] and neutral[20−23] functionality have been synthesized directly in water without postreaction chemistry. Challenges to successful structural control of aqueous RAFT include maintaining a sufficient reaction rate relative to competing CTA hydrolysis and aminolysis and selection of appropriate CTA/initiator/monomer combinations to preclude undesirable termination events.[24,25]

To date, the controlled polymerization of neutral acrylamido monomers has proved to be challenging. While initial studies with *N*,*N*-dimethylacrylamide (DMA) bore many of the characteristics of controlled polymerization, experimental molecular weights were 30−50% higher than those predicted by theory.[20,21] Attempts at RAFT polymerization of acrylamide (AM) resulted in a complete lack of control; however, subsequent experiments conducted in acidic buffers yielded better results.[26] Although these polymerizations exhibited many of the characteristics of controlled "living" systems, the disparity between the experimental and theoretically determined molecular weights remained substantial. Additionally, significant rate retardation under these conditions limited conversions to <28%.[26] To better understand these deviations from ideal behavior and increase the attainable conversion, AM was polymerized in the presence of several dithioester and trithiocarbonate RAFT agents in both water and dimethyl sulfoxide (DMSO).[24] Significant rate enhancements were achieved by employing CTAs (i.e., trithiocarbonates) with higher intermediate fragmentation rates, allowing near quantitative conversions to be reached while still maintaining overall control. Building on these studies, the RAFT polymerizations of AM and DMA mediated by a trithiocarbonate RAFT agent were conducted directly in water at 25 and 50 °C.[27] These polymerizations demonstrated all the characteristics of controlled/"living" systems while eliminating the need for organic solvents or aqueous buffers.

Another technologically important acrylamido monomer, *N*-isopropylacrylamide (NIPAM), is a target for aqueous, room temperature polymerization. Because PNIPAM has a lower

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critical solution temperature (LCST) near human body temperature, it has been cited for a number of biological applications including drug delivery.[28−30] To date, there have been numerous reports detailing the successful RAFT polymerization of NIPAM in organic solvents.[13] For example, Ganachaud et al. reported the AIBN initiated solution polymerization of NIPAM employing both benzyl dithiobenzoate (in benzene) and cumyl dithiobenzoate (in 1,4-dioxane) at 60 °C.[31] Subsequently, Schilli et al. disclosed the benzyl and cumyl dithiocarbamate mediated polymerization of NIPAM, also in 1,4-dioxane at 60 °C.[32] More recently, Ray and co-workers demonstrated the ability to control the tacticity in RAFT polymerizations of NIPAM via the addition of a suitable Lewis acid such as $Sc(OTf)_3$ or $Y(OTf)_3$.[33,34] The successful ATRP polymerization of NIPAM in organic alcohols at room temperature has also recently been reported by Xia and co-workers.[35] In a previous article, we demonstrated controlled RAFT polymerization of NIPAM at room temperature in dimethylformamide, employing a trithiocarbonate RAFT agent in conjunction with an azo initiator.[36]

Herein we report the synthesis of thermally responsive AB and ABA block copolymers based on DMA and NIPAM directly in water at 25 °C utilizing the RAFT polymerization technique. To our knowledge, this is the first report of room temperature polymerization and block copolymerization of NIPAM in aqueous media. Our recent success with room temperature polymerization of DMA in water and previous literature reports of controlled NIPAM polymerization have allowed us to develop appropriate reaction conditions for this research. To facilitate the synthesis of both AB and ABA block copolymers under these conditions, we have also synthesized a novel trithiocarbonate RAFT agent which is both monofunctional and water-soluble. Using these conditions, we have prepared a series of temperature-responsive AB and ABA block copolymers. These polymers contain a hydrophilic DMA A block of fixed molecular weight while the temperature-responsive NIPAM B block has been systematically varied. Using a combination of ^{1}H NMR spectroscopy, T_2 relaxation measurements, dynamic light scattering (DLS), and static light scattering (SLS), we demonstrate that these block copolymers are indeed capable of reversibly forming micelles in response to changes in solution temperature and that the micellar size and transition temperature are dependent on both the NIPAM block length and the polymer architecture (diblock vs triblock).

Experimental Section

Materials. All reagents were purchased from Aldrich at the highest purity available and used as received unless otherwise stated. 4,4′-Azobis[2-(imidazolin-2-yl)propane] dihydrochloride (VA-044) was donated by Wako Chemicals and was recrystallized twice from methanol prior to use. NIPAM was recrystallized twice from hexanes prior to use (mp 64 °C). 2-(1-Carboxy-1-methylethylsulfanylthiocarbonylsulfanyl)-2-methylpropionic acid (CMP) was donated by Noveon and was recrystallized from hexanes (mp 181 °C).

Synthesis of *S*-Ethyl-*S*′-(α,α′-dimethyl-α″-acetic acid)trithiocarbonate (EMP). Ethanethiol (12.4 g, 0.200 mol), acetone (96.4 g, 1.66 mol), and trioctylmethylammonium chloride (Aliquat 336; 3.23 g, 8.00 mmol) were mixed in a round-bottom flask and cooled to 10 °C under a nitrogen atmosphere. Sodium hydroxide solution (50%) (16.8 g, 0.210 mol) was then added over 20 min. The reaction was stirred for an additional 20 min before carbon disulfide (15.2 g, 0.200 mol) in acetone (20.3 g, 0.350 mol) was added over a 20 min period. After 20 min, chloroform (35.8 g, 0.300 mol) was added in one portion, followed by dropwise addition of 50% sodium hydroxide solution (80.0 g, 1.00 mol) over 30 min. The reaction was then allowed to react overnight, after which time the acetone was removed via rotary evaporation. The residue was then redissolved in 250 mL of water, and concentrated HCl was added while vigorously stirring at 5−10 °C. The aqueous solution was then extracted four times with hexane, concentrated via rotary evaporation, and washed with water three times. The crude product was isolated by column chromatography (silica gel 60 Å, 70−230 mesh) using ethyl acetate:hexane (2:3 v/v) as an eluent. Removal of the solvent by rotary evaporation yielded an orange-brownish oil, which was dissolved in a small amount of hexane and washed three times with water. The hexane solution was placed in a freezer at −20 °C, whereupon the EMP crystallized. The target compound was recrystallized from hexane three more times at 5−10 °C, resulting in large bright yellow crystals (yield 12.44 g, 28%; mp 53−54 °C). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.30$ (q, 2H), 1.73 (s, 6H), 1.34 (t, 3H). ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 220.54$ ($\mathit{C}{=}S$), 179.06 ($\mathit{C}OOH$), 55.53 ($S\mathit{C}CH_3$), 31.28 ($S\mathit{C}H_2$), 25.18 ($C\mathit{C}H_3$), 12.88 ($CH_2\mathit{C}H_3$).

General Procedure for the RAFT Polymerization of NIPAM. Polymerizations were conducted at 25 °C, employing VA-044 as the primary radical source and CMP and EMP as the RAFT CTAs. All the polymerizations were performed directly in deuterium oxide (pD 4.75) with an initial monomer concentration ($[M]_0$) of 0.5 M in individual, septa-sealed vials, which were purged with nitrogen at 5 °C for 25 min prior to the reaction. The initial monomer to CTA ratio ($[M]_0/[CTA]_0$) was held constant at 600:1 with CTA-to-initiator ratios ($[CTA]_0/[I]_0$) of 3:1. The polymerization kinetics and the absolute molecular weights were determined from aliquots (0.5 mL) taken at predetermined time intervals and quenched via immersion in liquid nitrogen.

Monofunctional Macro-CTA of *N*,*N*-Dimethylacrylamide. *N*,*N*-Dimethylacrylamide (41.5 g, 0.418 mol), EMP (0.633 g, 2.82 mmol), and VA-044 (0.450 g, 1.39 mmol) were added to a 250 mL, round-bottom flask equipped with a magnetic stirring bar. Deionized water was added until the total solution volume was 140 mL. The flask was sealed with a rubber septum, and the contents were purged with nitrogen for 90 min at 5 °C. The flask was subsequently immersed in a water bath preheated to 25 °C, and the polymerization was allowed to proceed for 3 h before being quenched by rapid cooling. The monofunctional DMA macro-CTA was then purified by dialysis and subsequent lyophilization at 3 °C.

Difunctional Macro-CTA of *N*,*N*-Dimethylacrylamide. *N*,*N*-Dimethylacrylamide (41.5 g, 0.418 mol), CMP (1.18 g, 4.18 mmol), and VA-044 (0.270 g, 0.836 mmol) were added to a 250 mL, round-bottom flask equipped with a magnetic stir bar. The solution was cooled via an ice bath, and deionized water was added until the total solution volume was 140 mL. The flask was sealed with a rubber septum, and the contents were purged with nitrogen for 90 min at 5 °C. The flask was subsequently immersed in a water bath preheated to 25 °C, and the polymerization was allowed to proceed for 3 h before being quenched by rapid cooling. The difunctional DMA macro-CTA was then purified by dialysis against deionized water and subsequent lyophilization (see above).

Block Copolymer Synthesis. Mono- and difunctional DMA macro-CTAs were used for preparing DMA/NIPAM block copolymers. All polymerizations were conducted directly in water (pH 5.0) with an initial monomer concentration of 0.5 M at 25 °C with VA-044 as the initiator. The $[PDMA]_0$:$[VA\text{-}044]_0$ ratio was maintained at 1:1 (mole basis) while the $[NIPAM]_0$:$[PDMA]_0$ ratio was varied in order to prepare block copolymers with a range of compositions. The polymerizations were conducted under a nitrogen atmosphere in round-bottomed flasks equipped with magnetic stir bars and sealed with rubber septa. The products were purified by dialysis against deionized water and isolated by lyophilization.

Aqueous Size Exclusion Chromatography. The polymerization mixtures were analyzed directly by aqueous size exclusion chromatography (ASEC) using an eluent of 0.1 M $NaNO_3$ (aqueous) at a flow rate of 0.5 mL/min at 25 °C, Viscotek TSK Viscogel columns [G3000 PWXL (<50 000 g mol^{-1}, 200 Å) and G4000 PWXL (2000−300 000 g mol^{-1}, 500 Å), a Polymer Labs LC 1200 UV/

vis, Wyatt Optilab DSP interferometric refractometer, and Wyatt DAWN EOS multiangle laser light scattering detectors (690 nm)].

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were recorded with a Bruker AC-200 spectrometer using a 2 s recycle time. Samples were prepared as 1% w/v solutions in D_2O (HOD internal standard). Block copolymer compositions were determined by a comparison of resonances associated with the two comonomers. NIPAM monomer conversion was determined by comparing the area of the vinyl protons ($\delta \sim 5.4-6.3$ 3H/mol NIPAM monomer) to the total isopropyl methyne area ($\delta \sim 3.6-3.85$ 1H/mol NIPAM).

T_2 NMR Measurements. T_2 NMR measurements were performed in deuterium oxide using a standard Carr−Purcell/Meiboom−Gill (CPMG) pulse sequence ($90°_x-\tau-180°_y-\tau-$acq) with a temperature-controlled Mercury Innova 500 MHz spectrometer. At least 50 measurements were obtained for each sample using the following parameters: 90° pulse width (8.7 μs), echo delay (0−1.576 s), recycle delay (10 s), acquisition time (2 s). Between 16 and 64 transients were signal-averaged at each echo delay. The NIPAM methyne and DMA methyl signals were used for T_2 calculations at a polymer concentration of 5 mg/mL and a heating rate of 0.066 °C min^{-1}.

Light Scattering Measurements. Static light scattering measurements were performed on a Malvern Instruments Zetasizer at a constant scattering angle of 173°. The micellar molecular weight (M_w) and second virial coefficient (A_2) were estimated from the relationship

$$KC_p/R_\theta = 1/M_w + 2A_2C_p$$

where K, C_p, M_W, R_θ, and A_2 are the optical constant, polymer concentration, molecular weight, Rayleigh ratio, and second virial coefficient, respectively. Specific refractive index increments (dn/dc) for the block copolymers in water were calculated using the equation[37−39]

$$\mathrm{d}n/\mathrm{d}c = w_A(\mathrm{d}n/\mathrm{d}c)_A + w_B(\mathrm{d}n/\mathrm{d}c)_B$$

in which w_A and w_B are the mass fractions of pure polymers PNIPAM and PDMA and (dn/dc)$_A$ and (dn/dc)$_B$ their refractive index increments, respectively.

By measuring R_θ at a series of C_p values between 2.0 and 0.20 mg/mL, M_w and A_2 were estimated from Debye plots.

Dynamic Light Scattering. Dynamic light scattering studies of the block copolymers at concentrations of 1.00 g/L in aqueous solution were conducted using an Malvern Instruments Zetasizer Nano series instrument equipped with a 22 mW He−Ne laser operating at $\lambda = 632.8$ nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE-5003 multiple tau digital correlator electronics system.

Results and Discussion

Synthesis of *S*-Ethyl-*S′*-(α,α′-dimethyl-α″-acetic acid)-trithiocarbonate. The key to successful RAFT polymerizations is the use of a suitable chain transfer agent (CTA), which is typically a dithioester or trithiocarbonate. Trithiocarbonates have the added versatility in that they may contain either one or two homolytic leaving groups, allowing for the convenient synthesis of di- or triblock copolymers in only two synthetic steps.[40] Given our desire to prepare both AB and ABA block copolymers directly in aqueous media at room temperature and the limited number of monofunctional trithiocarbonates that are also water-soluble, we chose to synthesize *S*-ethyl-*S′*-(α,α′-dimethyl-α″-acetic acid)trithiocarbonate (EMP) in this study. It is prepared via a one-pot procedure using synthetic methodology described by Lai and co-workers[41] in which 1 equiv of ethanethiol and carbon disulfide are reacted with sodium hydroxide in the presence of a phase transfer catalyst, followed by the addition of chloroform and acetone. Subsequent acidification and purification yields EMP as a crystalline solid (mp 53−54 °C).

Scheme 1. Synthetic Pathway for the Aqueous Room Temperature RAFT Polymerization of NIPAM

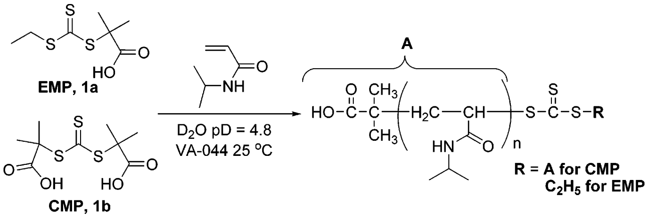


Table 1. Conversion, Molar Mass, and Polydispersity Data for the Aqueous RAFT Polymerization of *N*-Isopropylacrylamide (NIPAM) at 25 °C Mediated by CMP and EMP with Initial CTA:Initiator and Monomer:CTA Ratios of 3:1 and 600:1, Respectively

sample no.	CTA[a]	time (min)	% conv[b]	M_n[b] (g/mol)	M_n theory (g/mol)	M_w/M_n[b]
1	CMP	90	22	22 600	15 200	1.32
2	CMP	180	55	45 800	37 600	1.09
3	CMP	300	75	61 600	51 200	1.07
4	CMP	525	89	73 000	60 700	1.06
5	EMP	90	25	21 200	17 300	1.15
6	EMP	210	54	44 500	37 000	1.05
7	EMP	360	72	59 400	49 200	1.05
8	EMP	720	88	76 200	60 000	1.03

[a] Polymers synthesized at 25 °C at 0.5 M monomer in D_2O ([CTA]$_0$/[M]$_0$: 1/600) under a nitrogen atmosphere with VA-044 as the initiator. [b] Conversions were determined using ^{1}H NMR spectroscopy by comparing the area of the vinyl proton resonances to the total methyne signal. [c] As determined by ASEC [0.5 mL min^{-1}, 25 °C, Viscotek TSK Viscogel columns G3000 PWXL (50 000 g mol^{-1} , 200 Å) and G4000 PWXL (2000−300 000 g mol^{-1}, 500 Å), 0.1 M $NaNO_3$ (aqueous) eluent].

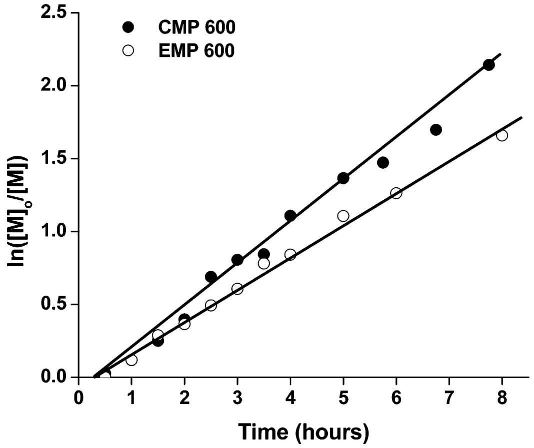


Figure 1. Pseudo-first-order kinetic plot for the CMP/EMP mediated hompolymerizations of NIPAM at 25 °C.

Aqueous Room Temperature RAFT Polymerization of NIPAM. NIPAM was polymerized in D_2O over selected time intervals using VA-044 as the free radical initiator and CMP or EMP as the RAFT CTA (Scheme 1). Monomer conversions were monitored as a function of time by a comparison of the vinyl resonances ($\delta \sim 5.4$ and 6.3 ppm) and the total methyne proton resonance ($\delta \sim 3.6$ and 3.85 ppm). For polymerizations mediated by both CTAs, the initial [M]$_0$/[CTA]$_0$ was maintained at 600/1. Because of the relatively long half-life of VA-044 at 25 °C, a [CTA]$_0$/[I]$_0$ of 3/1 was employed for these polymerizations. Experimental data for the homopolymerizations of NIPAM are summarized in Table 1.

Shown in Figure 1 are the pseudo-first-order kinetic plots for the CMP/EMP mediated hompolymerizations of NIPAM at 25 °C. Following a short induction period (∼30 min) at 25 °C, linear pseudo-first-order kinetics are observed for both CTAs, even at high monomer conversions. The apparent rate of

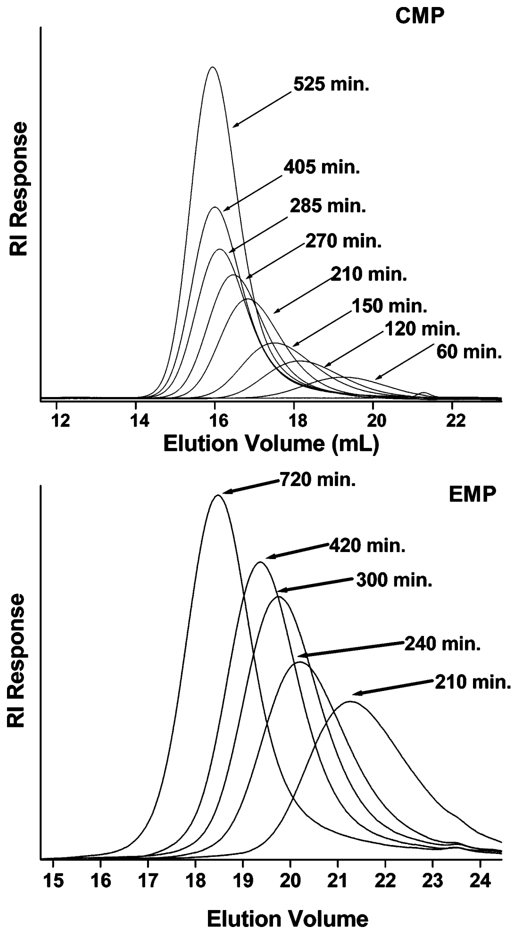


Figure 2. RI traces for the (a) CMP and (b) EMP mediation hompolymerizations of NIPAM showing the evolution of molar mass with time.

polymerization with CMP was observed to be slightly higher than EMP (e.g., 75% conversion after 300 min for CMP vs 72% conversion for EMP after 360 min). Because both CTAs have identical R groups and similar Z groups, the observed differences in the polymerization rates are likely a result of higher fragmentation rates from the adduct radical for CMP.

Shown in Figure 2a,b is the evolution of molecular weight, as determined by ASEC, for aliquots taken from the NIPAM homopolymerizations. The observed increases in the respective molecular weights as the peaks shift toward shorter retention times is consistent with a controlled polymerization process. Significantly, the traces are unimodal and free from both the low molecular weight tailing and the high molecular weight termination products.

Figure 3a,b shows the respective M_w/M_n and M_n values as a function of conversion. Given the low polydispersities and the linear increase in molecular weight with conversion, it is clear that both CTAs allow for the controlled synthesis of PNIPAM in water at 25 °C. Molecular weights, determined by ASEC/MALLS, are somewhat higher than those predicted by theory (solid line). Similar molecular weight overshoots have also been observed for the polymerization of other acrylamido monomers by our group and others.[19,20,42,43] Although a number of explanations for such behavior have been put forward in the literature, no consensus exists at the present time. Accepting the classic RAFT mechanism, one might suggest that the relatively high initiator concentrations employed in the present work (necessitated to obtain reasonable polymerization rates) could lead to irreversible coupling of the intermediate species to the extent observed here.[24] For example, loss of 13% CTA by intermediate coupling prior to reaching the "main" RAFT equilibrium would account for the discrepancy observed in Figure 3b.

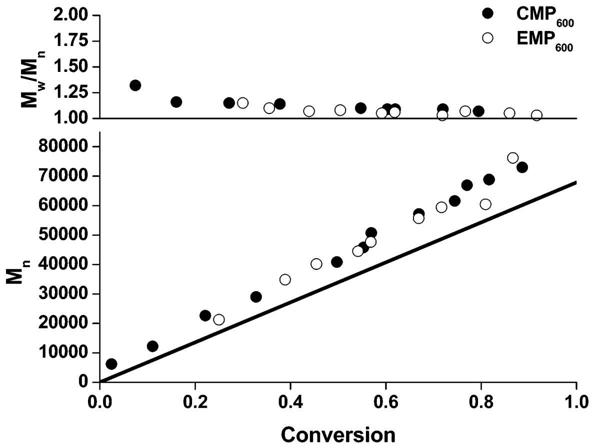
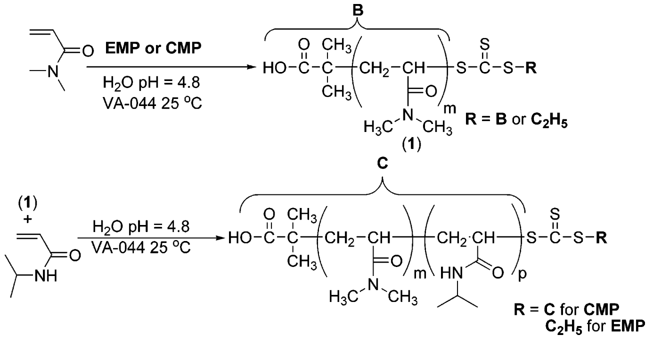


Figure 3. (a) M_n and (b) PDI vs conversion for the aqueous homopolymerizations of NIPAM mediated by CMP and EMP at 25 °C.

Scheme 2. Synthetic Route for Preparation of Di- and Triblock Copolymers of DMA and NIPAM via Aqueous Room Temperature RAFT



Block Copolymer Synthesis and Characterization. Having established conditions for room temperature polymerization of NIPAM in water, we synthesized homopolymers of DMA using EMP and CMP as the RAFT agents to yield the corresponding mono- and difunctional macro-CTAs (Scheme 2). The homopolymerizations were conducted in water at 25 °C with VA-044 as the initiator in the presence of CTA, EMP, and CMP, respectively. Following purification by dialysis and subsequent lyophilization, the resulting monofunctional (M_n = 9900 g/mol; M_w/M_n = 1.07) and difunctional (M_n = 10 500 g/mol; M_w/M_n = 1.04) poly-DMA macro-CTAs were then used for the subsequent RAFT block copolymerization of NIPAM (Scheme 2) to yield a range of di- and triblock copolymers. The molecular weight and polydispersity values are listed in Table 2.

Shown in Figure 4 are the normalized ASEC chromatograms for the difunctional DMA macro-CTA and the resultant DMA-*b*-NIPAM-*b*-DMA triblock copolymers. Under these conditions, high blocking efficiency was observed with the resulting block copolymers having unimodal and narrow molecular weight distributions.

Temperature-Induced Micellization. The next objective of our study was to systematically vary the length of the NIPAM blocks in order to study the effect of copolymer composition on the temperature-induced micellization for AB and ABA DMA/NIPAM block copolymers (Scheme 3).

Dynamic Light Scattering. Temperature induced micellization can be followed by monitoring changes in polymer

Table 2. Molecular Weight, Composition, and Polydispersity Data for Di- and Triblock Copolymers DMA (A Block) and NIPAM (B Block) Synthesized in the Presence of EMP and CMP

sample no.	polymer type	polym time (min)	DP DMA[a]	DP NIPAM[b]	molar % NIPAM	MW[b] (g/mol)	M_w/M_n[a]
1	ABA	45	106	77	42	19 200	1.13
2	ABA	120	106	197	65	32 800	1.04
3	ABA	180	106	273	72	41 300	1.03
4	ABA	300	106	376	78	53 000	1.14
5	AB	45	100	71	42	17 900	1.11
6	AB	120	100	174	64	29 600	1.15
7	AB	240	100	254	71	38 600	1.12
8	AB	360	100	460	82	61 900	1.21

[a] As determined by ASEC [0.5 mL min^{-1}, 25 °C, Viscotek TSK Viscogel columns G3000 PWXL (50 000 g mol^{-1} , 200 Å) and G4000 PWXL (2000−300 000 g mol^{-1}, 500 Å), 0.1 M $NaNO_3$ (aqueous) eluent]. [b] Determined by ^1H NMR spectroscopy in D_2O.

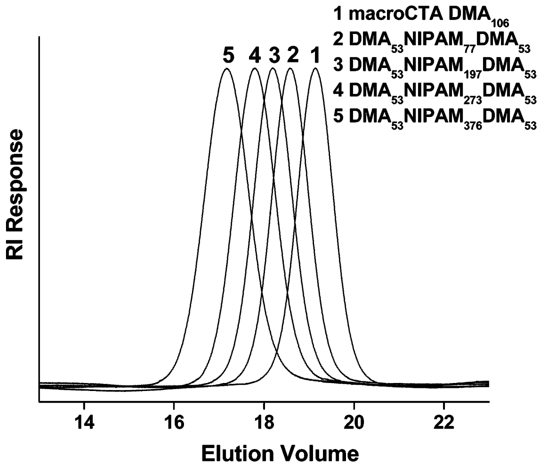
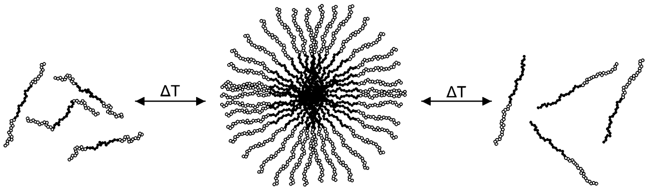


Figure 4. RI traces for triblock copolymers of DMA and NIPAM and the corresponding DMA homopolymer macro-CTA.

Scheme 3. Temperature-Responsive Reversible Micellization of Block Copolymers Comprised of DMA and NIPAM



hydrodynamic volume using dynamic light scattering. Above the LCST, PNIPAM chains become dehydrated due to an entropy gain resulting from the release of water molecules upon association of the isopropyl groups.[44,45] The change in hydrodynamic volume with temperature is depicted in Figure 5a,b. Diblock copolymer solutions (Figure 5a) show the expected transition from molecularly dissolved unimers at low temperatures to aggregated micelles above a critical micelle temperature (cmt). As the solution temperature is raised above the cmt, micelle hydrodynamic diameters begin to decrease. Similar observations by Yusa and co-workers were attributed to either a decrease in the aggregation number of the polymeric micelles or further dehydration of the NIPAM blocks with increasing temperature.[1]

The triblock polymer solutions (Figure 5b), by contrast, exhibit temperature induced association to form micelles only at longer NIPAM block lengths; the smaller triblock polymers remain molecularly dissolved as unimers. Both the di- and triblock copolymer micelles do, however, show increasing sizes along with decreasing cmt's as the NIPAM block length increases. These results are consistent with a recent report by Liu and co-workers.[4] The observed block-length-dependent cmt's are also in agreement with results from the T_2 experiments (vide infra) and are consistent with recent work by Xia and co-workers, who observed a strong decrease in the phase transition temperature with increasing molecular weight for a series of monodisperse PNIPAMs.[35] Figure 6 shows the heat induced changes in the hydrodynamic diameter for an aqueous solution of poly(DMA$_{100}$-*b*-NIPAM$_{460}$) cycled between 25 and 45 °C at 30 min intervals. The temperature induced association/dissociation process is reversible over numerous heating and cooling cycles with both unimer and micelle sizes remaining approximately constant.

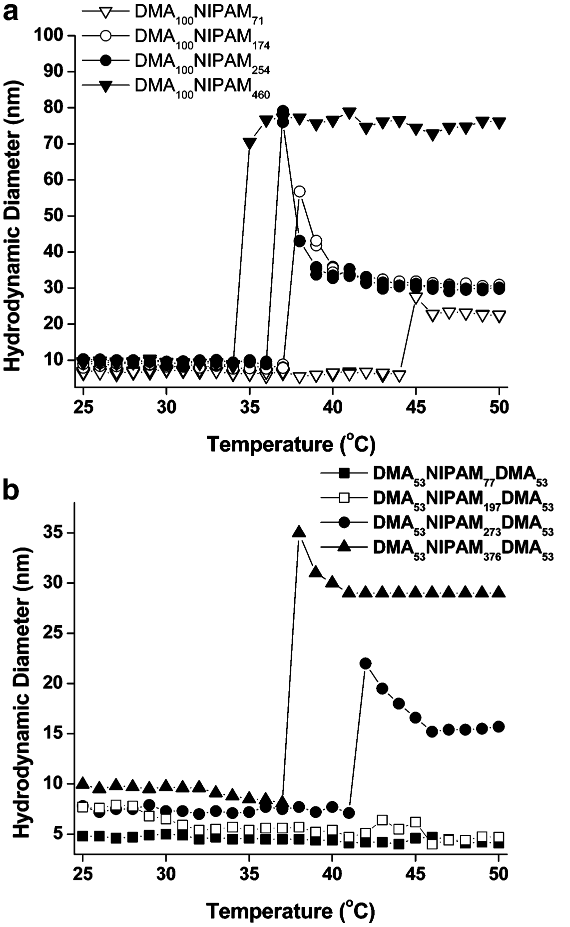


Figure 5. Hydrodynamic diameter (D_h) for a series of (a) di- and (b) triblock copolymers measured by dynamic light scattering as a function of temperature.

NMR Studies of Micellization. The transition from molecularly dissolved unimers to aggregated micelles may also be followed by monitoring changes in peak intensity with temperature.[1,4,8] In Figure 7a, the signals labeled “b” and “c” due to the PNIPAM methyne and methyl protons become broadened and attenuated relative to the PDMA methyl signal “a” at elevated temperatures, indicating reduced mobility and solvation. This transition can be monitored more quantitatively by following changes in proton spin−spin relaxations. The spin−spin relaxation (T_2) for polymers is heavily influenced by local rigidity, with protons in constrained environments exhibiting faster T_2 relaxations than identical protons in less constrained environments. Consequently, T_2 relaxation measurements provide a convenient method to follow the loss of segmental mobility upon micellization. In Figure 7b, T_2 values observed at $\delta \sim 3.9$ ppm corresponding to pendent NIPAM methyne

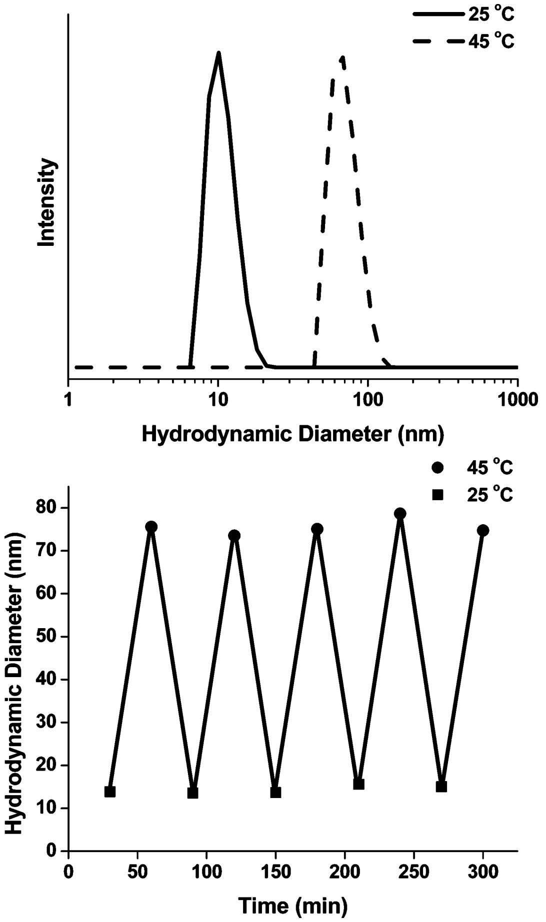


Figure 6. Heat induced reversible association/dissociation of poly(DMA_{100}-*b*-$NIPAM_{460}$) at a polymer concentration of 1.00 g/L in response to temperature changes between 25 and 45 °C at 30 min intervals.

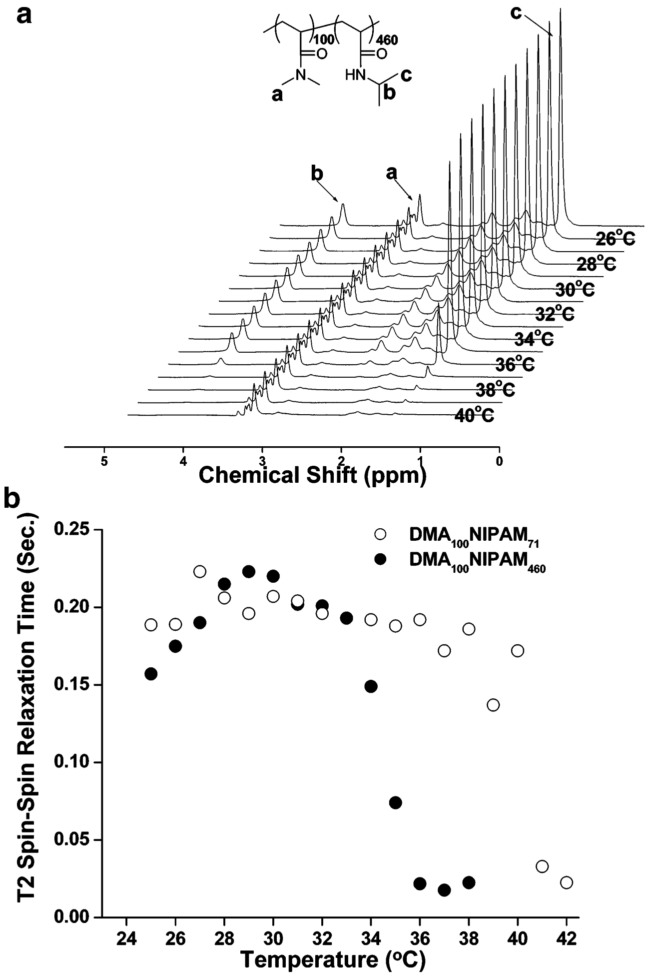


Figure 7. (a) DMA-*b*-NIPAM ^{1}H NMR spectra and (b) spin−spin relaxation times (T_2) as a function of temperature.

protons for diblock copolymers DMA_{100}-*b*-$NIPAM_{71}$ and DMA_{100}-*b*-$NIPAM_{460}$ are plotted as a function of temperature. Initially, there is a gradual increase in thermal motion, after which time the T_2 values stabilize around 0.20 s. Upon raising the solution temperature, a sharp decrease in the T_2 values from 0.194 s at 35 °C to 0.0213 s at 36 °C is observed for DMA_{100}-*b*-$NIPAM_{460}$. Similarly, DMA_{100}-*b*-$NIPAM_{71}$ also exhibits a sharp decrease in NIPAM T_2 values from 0.172 s at 40 °C to 0.033 s at 41 °C. These results suggest that the onset of micellization occurs at lower temperatures for polymers with longer NIPAM block lengths.

Static Light Scattering. Results from static light scattering experiments along with unimer and micelle sizes are summarized in Table 3. For both the di- and triblock copolymers, there is a clear increase in both micelle size and molecular weight as the NIPAM block length is increased. By comparing unimer molecular weights determined by ASEC-MALLS to micelle molecular weights, it was possible to determine aggregation numbers for the micelles. While both di- and triblock copolymer systems show a general increase in the aggregation number with increasing NIPAM block length, aggregation numbers and sizes for the diblocks are considerably larger than those of triblocks with similar compositions. For example, DMA_{100}-*b*-$NIPAM_{460}$ has hydrodynamic diameter and aggregation number values of 76 nm and 213, respectively, while DMA_{53}-*b*-$NIPAM_{376}$-*b*-DMA_{53} has values of 28 nm and 25. For both the di- and triblock copolymers, a decrease in the A_2 value is observed, which is indicative of a contraction of the micelles

Table 3. Hydrodynamic Diameter (D_h), Critical Micelle Temperatures (cmt), Micelle Molecular Weights (M_w), Aggregation Numbers (N_{agg}), and Second Virial Coefficient (A_2) Determined by Static and Dynamic Light Scattering as a Function of Temperature

sample	D_h(25 °C)^a (nm)	D_h(45 °C)^a (nm)	CMT^a (°C)	$M_w \times 10^{-6}$ ^{b} (g/mol)	$A_2 \times 10^4$ (mL mol/g^2)	N_{agg}^{c}
$DMA_{53}NIPAM_{77}DMA_{53}$	5.0	4.2				
$DMA_{53}NIPAM_{197}$ DMA_{53}	7.3	4.8				
$DMA_{53}NIPAM_{273}$ DMA_{53}	7.5	14.5	41.5	0.59	3.78	14
$DMA_{53}NIPAM_{376}$ DMA_{53}	9.8	28.0	37.5	3.20	2.58	25
$DMA_{100}NIPAM_{71}$	6.3	22.0	44.0	1.36	3.03	68
$DMA_{100}NIPAM_{174}$	7.2	31.0	37.3	3.52	1.11	103
$DMA_{100}NIPAM_{254}$	9.7	31.0	36.4	6.63	1.14	152
$DMA_{100}NIPAM_{460}$	10.5	76.0	34.6	15.94	1.10	213

[a] Dynamic light scattering studies of the block copolymer micelles in aqueous solution were conducted using an Malvern Instruments Zetasizer Nano series instrument equipped with a 22 mW He−Ne laser operating at $\lambda = 632.8$ nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE-5003 multiple tau digital correlator electronics system at a polymer concentration of 1.00 g/L. [b] Static light scattering measurements were performed at 50 °C on a Malvern Instruments Zetasizer at a constant scattering angle to 173°. [c] Determined from the relations $N_{agg} = MW_{micelle}/MW_{unimer}$.

with increasing NIPAM block length. A similar decrease in A_2 values with increasing hydrophobic block length has been observed for poly(sodium 2-(acrylamido)-2-methylpropanesulfonate-*block*-sodium 6-acrylamidohexanoate) and poly(styrene-*block*-sodium acrylate).[46,47] Clearly, block structure has a large influence on the micelle sizes and molecular weights as well as the cmt's.

Conclusions. In this work we have shown that NIPAM can be polymerized in a controlled fashion directly in water at room temperature using the RAFT process. Under these conditions, excellent control of the molecular weight and molecular weight distribution was attained even at high monomer conversion. To facilitate the synthesis of both AB and ABA block copolymers under these conditions, we have synthesized a novel trithiocarbonate which is both monofunctional and water-soluble. A series of di- and triblock copolymers with constant hydrophilic block lengths and variable NIPAM block lengths were then synthesized in order to systematically study the temperature-dependent micellization. Spin−spin relaxation and dynamic light scattering measurements show that cmt is lower for diblock copolymers than triblock copolymers and also decreases as the NIPAM block length is increased. Micelle sizes and molecular weights determined by a combination of dynamic and static light scattering experiments show a general increase with increasing NIPAM block length. This trend is observed for both di- and triblock copolymers; however, micellization in the latter was only observed at longer NIPAM block lengths.

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