Water-Soluble Polymers. 81. Direct Synthesis of Hydrophilic Styrenic-Based Homopolymers and Block Copolymers in Aqueous Solution via RAFT

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ABSTRACT: Homopolymers of sodium 4-styrenesulfonate have been synthesized directly in aqueous media by reversible addition−fragmentation chain transfer polymerization (RAFT). The resulting homopolymers have narrow molecular weight distributions, with polydispersity indices in the range 1.12−1.25, as determined by aqueous size exclusion chromatography. Using a dithioester-capped sodium 4-styrenesulfonate homopolymer as a macro chain transfer agent, a block copolymer with sodium 4-vinylbenzoate has been prepared in aqueous media. Additionally, a block copolymer of (*ar*-vinylbenzyl)trimethylammonium chloride with *N*,*N*-dimethylvinylbenzylamine has been synthesized, using the same methodology. We believe these represent the first examples of AB diblock copolymers prepared directly in aqueous media via the RAFT process. Both block copolymers are stimuli-responsive and undergo reversible pH-induced micellization in aqueous solution. Micelles with hydrodynamic diameters in the range 18−38 nm were observed by dynamic light scattering.

Introduction

In recent years, much effort has focused on the synthesis of water-soluble (co)polymers that undergo a conformational change, or phase transition, in response to external stimuli. The external stimulus may be, but is not limited to, temperature, added electrolyte, changes in pH, light, other molecules, or a combination of these.[1] Only a few stimuli-responsive, hydrophilic block copolymers have been reported in the literature. For example, Forder et al. reported the synthesis of dihydrophilic block copolymers, synthesized by living cationic polymerization, of methyl vinyl ether with methyl triethylene glycol vinyl ether.[2] More recently, Armes and co-workers synthesized two series of diamine block copolymers utilizing group transfer polymerization (GTP). The first comprised 2-(dimethylamino)ethyl methacrylate (DMAEMA) with 2-(diethylamino)ethyl methacrylate (DEAEMA)[3] and the second of DEAEMA with 2-(*N*-morpholino)ethyl methacrylate.[4] All of these show stimuli-induced micelle formation as a function of temperature,[2] pH,[3] or salt.[4] Simmons and Patrickios likewise have used GTP to synthesize block copolymers in which both blocks are polybases. Block copolymers of 2-(1-imidazolyl)ethyl methacrylate with DMAEMA were prepared and evaluated as catalytically active species in the hydrolysis of *p*-nitrophenyl acetate.[5] Kent et al. have reported a third example of a dibasic hydrophilic−hydrophilic block copolymer.[6] Living ring-opening metathesis polymerization was used to prepare norbornene-based block copolymers containing imidazole and a secondary amine functional species. Gabaston et al.[7] recently reported the synthesis of diacid block copolymers comprised of sodium 4-styrenesulfonate and sodium 4-vinylbenzoate. These were synthesized by 2,2,-6,6-tetramethyl-1-piperidinyloxyl (TEMPO) mediated polymerization in an ethylene glycol/water (3:1) mixture, where a poly(sodium 4-styrenesulfonate) homopolymer was used as a macroinitiator for the polymerization of sodium 4-vinylbenzoate. These block copolymers also exhibited reversible, pH-induced aggregation.

To date, the majority of these examples have taken advantage of living polymerization techniques. However, in recent years much effort has been focused on the development of pseudo-living free radical polymerization methods. In particular, nitroxide mediated or stable free radical polymerization (SFRP) was first reported in the late 1980s and has been shown to be particularly effective in the synthesis of controlled styrenic-based (co)polymers.[8,9] Subsequently, Sawamoto and co-workers[10] and Matyjaszewski and co-workers[11] independently developed atom transfer radical polymerization (ATRP). This technique has been exploited and advanced by numerous groups.[12] Like SFRP, ATRP has been shown to work well for styrenic and (meth)acrylate-based monomers. For example, Armes and co-workers demonstrated the ability to conduct ATRP in aqueous solution.[13] More recently, Rizzardo and co-workers reported a third pseudo-living polymerization technique they have termed reversible addition−fragmentation chain transfer polymerization (RAFT).[14] RAFT appears to offer advantages to SFRP or ATRP since it is applicable to a wide range of monomers and can be performed in a wide variety of solvents (including water) under a broad range of experimental conditions. The key to successful RAFT polymerizations is the presence of a highly efficient dithioester chain transfer agent (CTA). The CTA reacts with either the primary radical (derived from the initiator, AIBN for example) or a propagating polymer chain, forming a new CTA and eliminating R$^\bullet$, which reinitiates polymerization. “Living” characteristics are conferred via the reversible addition−fragmentation reactions between active and dormant polymer chains and the S=C(Z)S− species (where Z is Ph for example) (Scheme 1).

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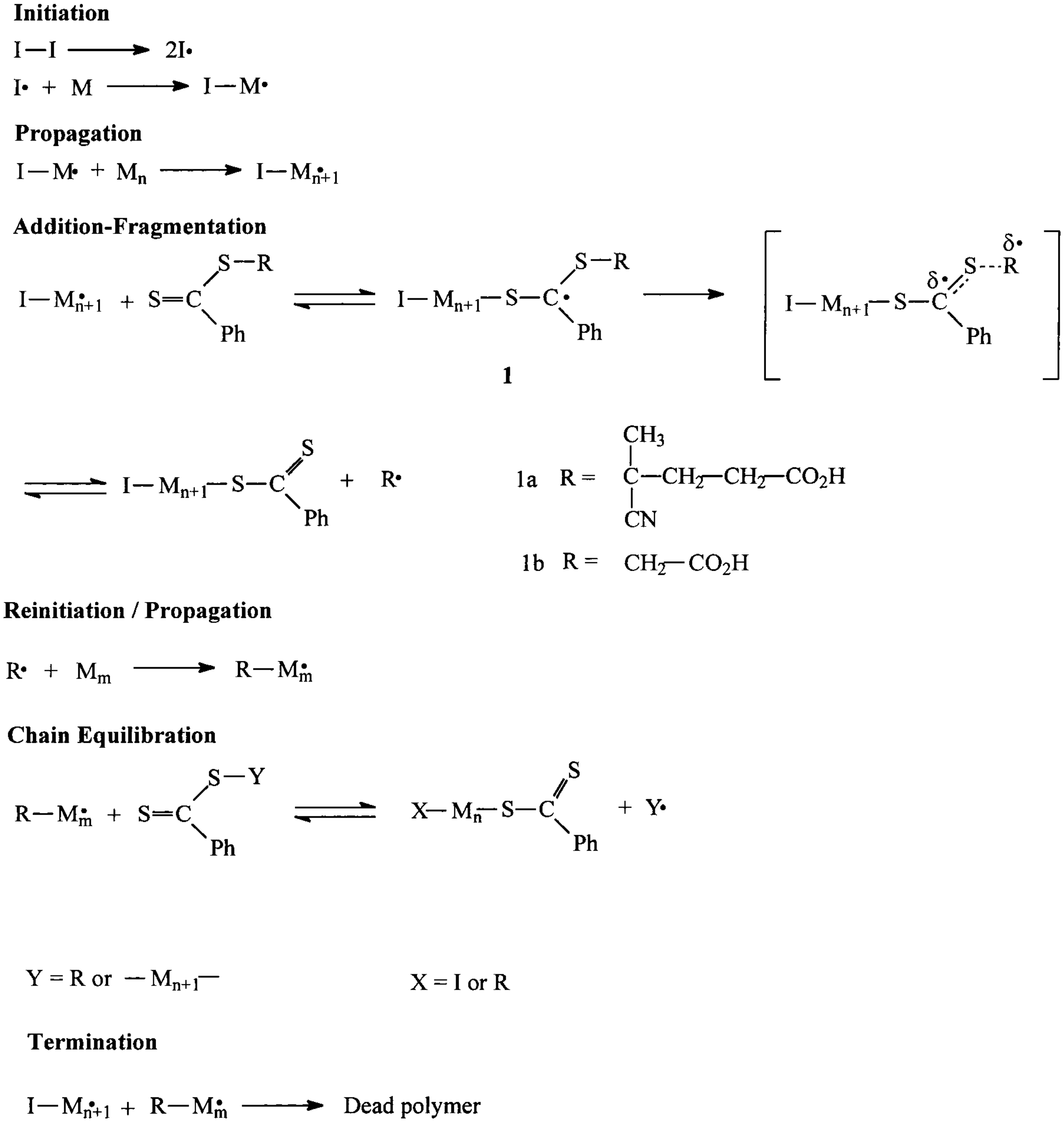
Scheme 1. Pathway for Reversible Addition−Fragmentation Chain Transfer Polymerization



In the present work we demonstrate the controlled synthesis of sodium 4-styrenesulfonate homopolymers directly in aqueous media using 4-cyanopentanoic acid dithiobenzoate as the RAFT CTA and 4,4′-azobis(4-cyanopentanoic acid) as the free radical initiator. This particular combination ensures that the initiating species for each polymer chain is identical. We have subsequently used near-monodisperse sodium 4-styrenesulfonate homopolymer as a macro-CTA for the aqueous block copolymerization with sodium 4-vinylbenzoate. Using the same methodology, a block copolymer of (*ar*-vinylbenzyl)trimethylammonium chloride and *N*,*N*-dimethylvinylbenzylamine has also been prepared. These block copolymers exhibit interesting aqueous solution properties such as reversible, pH-induced aggregation. We believe this represents the first report concerning the synthesis of controlled AB diblock copolymers in aqueous solution utilizing RAFT.

Experimental Section

All reagents were purchased from either Fischer or Aldrich Chemical Companies, unless stated otherwise. 4,4′-Azobis(4-cyanopentanoic acid) was donated by Wako Chemicals USA. 4,4′-Azobis(4-cyanopentanoic acid) and carboxymethyl dithiobenzoate were purified by recrystallization from methanol and benzene, respectively. *N*,*N*-Dimethylvinylbenzylamine was purified by vacuum distillation to remove inhibitor. 4-Vinylbenzoic acid was synthesized from 4-carboxybenzyltriphenylphosphonium bromide via the Wittig reaction.

Synthesis of Dithiobenzoic Acid (DTBA). DTBA was prepared by a modification of the method of Becke and Hagen.[15]

To a thoroughly dried 1 L, three-necked round-bottomed flask equipped with a magnetic stir bar, addition funnel (250.0 mL), thermometer, and rubber septum for liquid transfers was added sodium methoxide (30% solution in methanol, 180.0 g, 1.0 mol). Anhydrous methanol (250.0 g) was added to the flask via cannula, followed by rapid addition of elememtal sulfur (32.0 g, 1.0 mol). Benzyl chloride (63.0 g, 0.5 mol) was then added dropwise via the addition funnel over a period of 1 h, at room temperature under a dry nitrogen atmosphere. The reaction mixture was heated in an oil bath at 67 °C for 10 h. After this time, the reaction mixture was cooled to 7 °C using an ice bath. The precipitated salt was removed by filtration and the solvent removed in vacuo. To the residue was added deionized water (500.0 mL). The solution was filtered a second time and then transferred to a 2 L separatory funnel. The crude sodium dithiobenzoate solution was washed with diethyl ether (3 × 200.0 mL). Diethyl ether (200.0 mL) and 1.0 N HCl (500.0 mL) were added, and dithiobenzoic acid was extracted into the ethereal layer. Deionized water (300.0 mL) and 1.0 N NaOH (600.0 mL) were added, and sodium dithiobenzoate was extracted to the aqueous layer. This washing process was repeated two more times to finally yield a solution of sodium dithiobenzoate.

Synthesis of Di(thiobenzoyl) Disulfide. Potassium ferricyanide(III) (32.93 g, 0.1 mol) was dissolved in deionized water (500.0 mL). Sodium dithiobenzoate solution (350.0 mL) was transferred to a 1 L conical flask equipped with a magnetic stir bar. Potassium ferricyanide solution was added dropwise to the sodium dithiobenzoate via an addition funnel over a period of 1 h under vigorous stirring. The red precipitate was filtered and washed with deionized water until the washings became colorless. The solid was dried in vacuo at room temperature overnight. The product was recrystallized from ethanol.

Synthesis of 4-Cyanopentanoic Acid Dithiobenzoate. The target compound was prepared by the method of Thang et al.[14g]

To a 250 mL round-bottomed flask was added distilled ethyl acetate (80.0 mL). To the flask was added dry 4,4′-azobis(4-cyanopentanoic acid) (5.84 g, 21.0 mmol) and di(thiobenzoyl) disulfide (4.25 g, 14.0 mmol). The reaction solution was heated at reflux for 18 h. The ethyl acetate was removed in vacuo. The crude product was isolated by column chromatography (silicagel 60 Å, 70−230 mesh) using ethyl acetate:hexane (2:3) as eluent. Fractions that were red in color were combined and dried over anhydrous sodium sulfate overnight. The solvent mixture was removed in vacuo, and the red oily residue placed in a freezer at −20 °C, whereupon it crystallized. The target compound was recrystallized from benzene.

Polymerizations. *General Procedure.* All polymerizations were performed in ampules. In all cases, 4-cyanopentanoic acid dithiobenzoate and 4,4′-azobis(4-cyanopentanoic acid) were used as the CTA and initiator, respectively. The monomers, CTA and initiator were solubilized in deionized water at a molar ratio of 5:1. For 4-vinylbenzoic acid and *N*,*N*-dimethylvinylbenzylamine, NaOH and HCl were added respectively to solubilize the monomers. The monomer concentrations were kept constant at 16.7 wt %. Degassing was achieved by three freeze−thaw−pump cycles. After degassing, the ampules were flame-sealed under vacuum and heated in an oil bath at 70 °C. The polymerizations were terminated by rapid cooling and freezing. The homopolymers were purified by dialysis against deionized water for 1 week and recovered by lyophilization before determining conversions gravimetrically.

Block Copolymerizations. 1. Poly(sodium 4-styrenesulfonate-block-sodium 4-vinylbenzoate). To a 100 mL round-bottomed flask equipped with a magnetic stir bar was added poly(sodium 4-styrenesulfonate) (2.09 g, 10.0 mmol), 4-vinylbenzoic acid (1.50 g, 10.0 mmol), 4,4′-azobis(4-cyanopentanoic acid) (11.7 mg, 0.042 mmol), and water (17.5 g, 0.97 mol). Sodium hydroxide (6.0 M) was added to the solution to solubilize the 4-vinylbenzoic acid. The final solution pH was adjusted to 7.5. The mixture was deoxygenated by purging with nitrogen for 20 min. The flask was sealed and immersed in a preheated water bath at 70 °C. The polymerization was allowed to proceed for 24 h. The block copolymer was then isolated by precipitation into acetone, followed by lyophilization from water.

2. Poly((ar-vinylbenzyl)trimethylammonium chloride-block-N,N-dimethylvinylbenzylamine). To a 100 mL round-bottomed flask equipped with a magnetic stir bar was added poly(*ar*-vinylbenzyl)trimethylammonium chloride (1.97 g, 9.30 mmol), *N*,*N*-dimethylvinylbenzylamine (1.50 g, 9.30 mmol), 4,4′-azobis(4-cyanopentanoic acid) (11.0 mg, 0.039 mmol), and water (17.5 g, 0.97 mol). Hydrochloric acid (6.0 M) was added to the solution to solubilize the *N*,*N*-dimethylvinylbenzylamine. The final solution pH was adjusted to 6.95. The mixture was degassed by purging with nitrogen for 20 min. The flask was sealed and immersed in a preheated water bath at 70 °C. The polymerization was allowed to proceed for 24 h. The block copolymer was isolated by precipitation into 2-propanol, followed by lyophilization from water.

Polymerization of Sodium 4-Styrenesulfonate in D_2O. Sodium 4-styrenesulfonate (6.0 g, 29.1 mmol), 4-cyanopentanoic acid dithiobenzoate (55.9 mg, 0.2 mmol), and 4,4′-azobis(4-cyanopentanoic acid) (11.2 mg, 0.04 mmol) were dissolved in D_2O (30.0 g, 1.50 mol). Aliquots of this master solution (5.0 mL) were transferred to five glass ampules. The ampules were degassed by three freeze−pump−thaw cycles and subsequently flame-sealed. The solutions were heated at 70 °C in a preheated oil bath for 1, 2, 4, and 8 h. Polymerizations were terminated by rapid cooling. A sample from each ampule was extracted and analyzed by NMR spectroscopy.

Time−Conversion Studies via ^1H NMR Spectroscopy. Sodium 4-styrenesulfonate (2.0 g, 9.7 mmol), 4-cyanopentanoic acid dithiobenzoate (18.6 mg, 0.067 mmol), carboxymethyl dithiobenzoate (14.2 mg, 0.067 mmol), and 4,4′-azobis(4-cyanopentanoic acid) (3.7 mg, 0.013 mmol) were dissolved in deuterium oxide (10.0 g, 0.5 mol). A small volume of the solution was added to an NMR tube and deoxygenated with nitrogen for approximately 30 s. After deoxygenation, the cap was sealed and the tube placed in the temperature-equilibrated (70 °C) probe of a 300 MHz NMR spectrometer.

Aqueous Size Exclusion Chromatography (ASEC). The molecular weights of the homopolymers and block copolymers were estimated by aqueous size exclusion chromatography (ASEC), using a Viscotek TSK Viscogel column, a Spectra-physics UV2000 detector, and a HP 1047A RI detector. The mobile phase consisted of 80% HPLC grade water, 20% acetonitrile, 0.05 M $NaNO_3$, and 0.01 M Na_2HPO_4, at a flow rate of 0.5 mL min^{-1}. Calibration was with near-monodisperse poly(sodium 4-styrenesulfonate) standards purchased from Polysciences Inc. Molecular weight averages and polydispersity indices were calculated using software written in-house.

Dynamic Light Scattering. Dynamic light scattering experiments were performed using a Brookhaven Instruments 128-channel BI-2030 AT digital correlator equipped with a Spectraphysics He−Ne laser operating at 632.8 nm. Measurements were made at 90°. CONTIN analyses were used to fit the data. The block copolymer samples were prepared as 1 w/v % solutions in water.

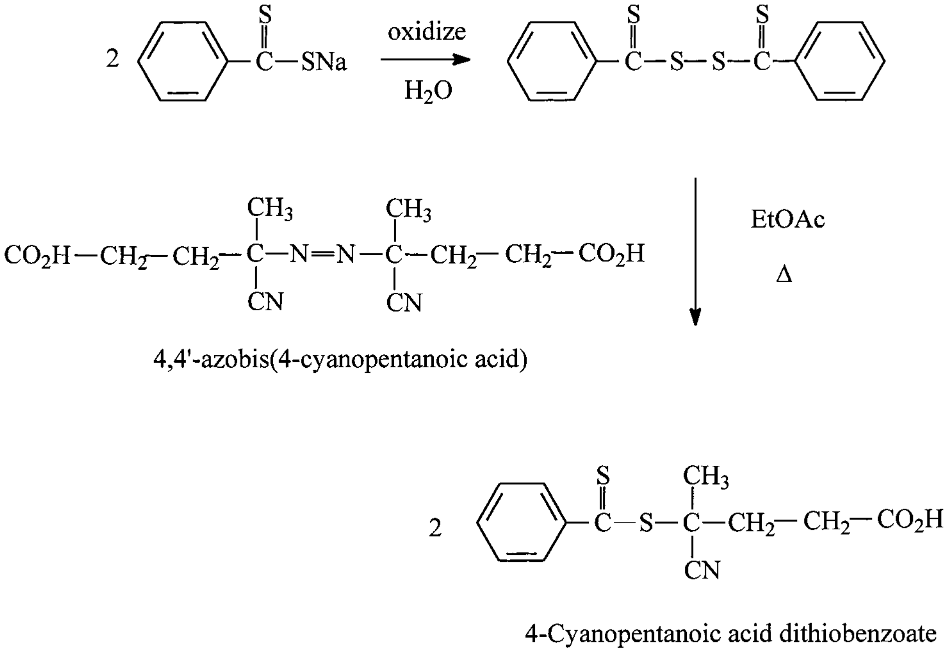
Nuclear Magnetic Resonance Spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC3000 spectrometer in D_2O, with HOD as the internal reference.

Results and Discussion

Synthesis of 4-Cyanopentanoic Acid Dithiobenzoate. RAFT is a newly reported “pseudo-living” free radical polymerization technique that operates by an addition−fragmentation mechanism. The key to successful RAFT polymerizations is the presence of a suitable chain transfer agent (CTA), which is typically a dithioester. These CTAs, with the exception of carboxymethyl dithiobenzoate, are not commercially available. Given the desire to conduct the polymerizations directly in aqueous media, we chose to use 4-cyanopentanoic acid dithiobenzoate in this study. It is prepared via a multistep procedure involving the synthesis of DTBA, which is subsequently oxidized to di(thiobenzoyl) disulfide, before final reaction with 4,4′-azobis(4-cyanopentanoic acid) to yield the target compound (Scheme 2).

There are numerous synthetic routes to DTBA: (1) reaction of phenylmagnesium bromide with carbon disulfide, followed by acidification;[16] (2) reaction of trichlorophenylmethane, potassium hydrogen sulfide, and potassium hydroxide;[17] (3) reaction of trichlorophenylmethane with sodium sulfide;[18] or (4) reaction of benzyl chloride, elemental sulfur, and sodium methoxide.[15]

Scheme 2. Synthetic outline for the Synthesis of 4-Cyanopentanoic Acid Dithiobenzoate



In our hands, route 4 gave the best yields and purity of DTBA, as determined by thin-layer chromatography. Given the oxidative instability of DTBA, it is used immediately in the next step—the synthesis of di(thiobenzoyl) disulfide (DTBDS). Rizzardo and co-workers originally reported using KI/I_2 as the oxidizing species for the synthesis of DTBDS from DTBA. However, we obtained significantly better yields using an alternative oxidizing agent, potassium ferricyanide(III) ($K_3Fe(CN)_6$). The target CTA, 4-cyanopentanoic acid dithiobenzoate, is subsequently synthesized from the reaction of DTBDS with 4,4′-azobis(4-cyanopentanoic acid) as described by Thang et al.[14g] Figure 1a,b shows the ^1H and ^{13}C NMR spectra, recorded in $CDCl_3$, of 4-cyanopentanoic acid dithiobenzoate.

In the ^1H NMR spectrum, the resonances labeled 1, 2, and 3 ($\delta \sim 7.4-8.0$ ppm) represent the aromatic hydrogens of the phenyl group, those labeled 4 and 5 ($\delta \sim 2.5-3.0$ ppm) represent the methylene hydrogens of the cyanopentanoic acid fragment, and that labeled 6 ($\delta \sim 2.0$ ppm) represents the hydrogens of the methyl group on the same fragment. Similarly, the peaks are assigned and labeled in the ^{13}C NMR spectrum.

Shown in Figure 2 is the FTIR spectrum of 4-cyanopentanoic acid dithiobenzoate. The spectrum confirms the formation of the target CTA, with the key bands at ~3100 (COO−H), 2200 (−CN), 1700 (C=O), and 1050 (C=S) wavenumbers.

RAFT Polymerization of Sodium 4-Styrenesulfonate in D_2O. Sodium 4-styrenesulfonate was polymerized in D_2O for varying lengths of time using 4,4′-azobis(4-cyanopentanoic acid) as the free radical initiator and 4-cyanopentanoic acid dithiobenzoate as the CTA as described by Rizzardo et al.[14b] The initiator: CTA molar ratio was maintained at 1:5. The monomer: CTA ratio was such that a theoretical molecular weight of 30 000 at 100% conversion was expected. Table 1 gives a summary of the molecular weights, polydispersities, and percent conversions for the polymerizations.

Table 1. Molecular Weight, Polydispersity, and Conversion Data for Poly(sodium 4-styrenesulfonate) Homopolymers

polymerization time (h)	M_n[a]	M_w[a]	M_w/M_n[a]	conv (%)[b]	conv (%)[c]	theor M_n[b]
1	19 800	22 200	1.12	70	61	21 000
2	25 500	29 700	1.16	94	81	28 200
4	24 800	29 300	1.18	95	86	28 500
8	25 300	31 600	1.25	100	86	30 000

[a] As determined by aqueous size exclusion chromatography, calibrated with poly(sodium 4-styrenesulfonate) standards with a mobile phase of 20% acetonitrile/80% 0.05 M $NaNO_3$ + 0.01 M Na_2HPO_4. [b] As determined by ^1H NMR spectroscopy. [c] As determined gravimetrically.

It is clear that the polymerization of sodium 4-styrenesulfonate, in aqueous media, by RAFT occurs fairly rapidly. Near-quantitative conversion is obtained within 1−2 h, as determined by ^1H NMR spectroscopy and evidenced by the close similarity in the molecular weights as determined by ASEC. The homopolymers produced are near-monodisperse, with polydispersity indices in the range 1.12−1.25, well below the theoretical lower limit of 1.5 for classical free-radical polymerization. However, the polydispersity does increase with conversion, indicating that it may be affected by the increase in solution viscosity as conversion proceeds. These results are comparable to those reported by Chiefari et al.[14b] These authors reported a single example of poly(sodium 4-styrenesulfonate), synthesized in aqueous media using the same initiator and CTA as reported here. The homopolymer had an M_n (as determined by ASEC) of 8000 and a polydispersity index of 1.13, with 73% conversion being achieved after 4 h at 70 °C. The ASEC traces are all unimodal with no evidence of high molecular weight species that may be indicative of uncontrolled polymerization and/or termination by coupling of poly(sodium 4-styrenesulfonate) propagating radicals (Figure 3).

The observed molecular weights, as determined by ASEC, correspond very closely to the theoretical molecular weights, based on conversion, as determined by ^1H NMR spectroscopy, and indicate that the polymerizations occurred in a controlled fashion. The percent conversion as determined by ^1H NMR spectroscopy is considered more reliable than that determined gravi-

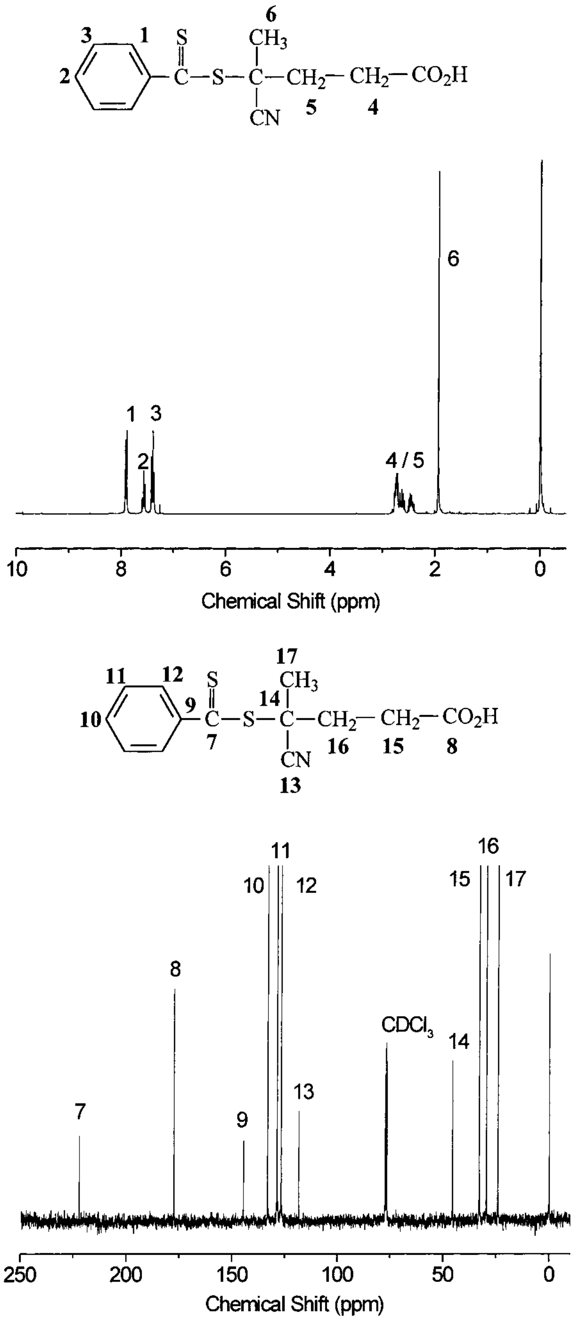


Figure 1. (a, upper) ^1H NMR spectrum recorded in $CDCl_3$ for 4-cyanopentanoic acid dithiobenzoate. (b, lower) ^{13}C NMR spectrum recorded in $CDCl_3$ for 4-cyanopentanoic acid dithiobenzoate.

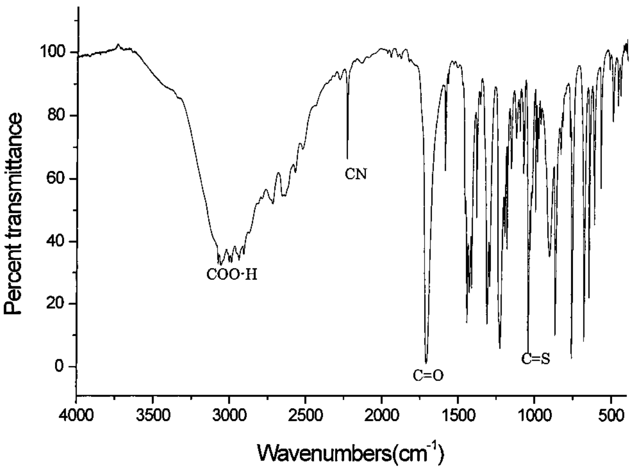


Figure 2. FTIR spectrum of 4-cyanopentanoic acid dithiobenzoate.

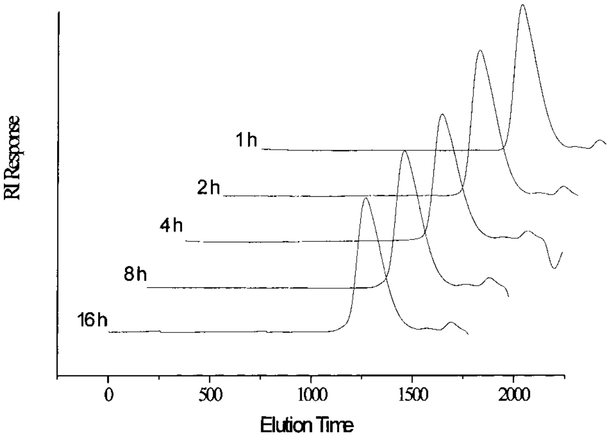


Figure 3. Aqueous size exclusion chromatograms for a poly(sodium 4-styrenesulfonate) homopolymer evolution as a function of time.

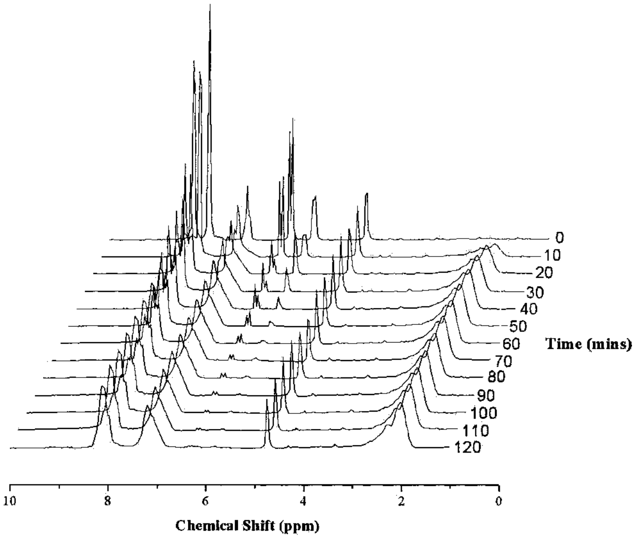


Figure 4. ^1H NMR spectra recorded in D_2O as a function of time for the polymerization of a poly(sodium 4-styrenesulfonate) homopolymer.

metrically. The percent conversions determined gravimetrically are based on the final weight of polymer isolated after dialysis and lyophilization. It is highly probable that low molecular weight homopolymer species were lost during the dialysis step.

Figure 4 shows the ^1H NMR spectra of a sodium 4-styrenesulfonate homopolymerization conducted in D_2O in the presence of 4-cyanopentanoic acid dithiobenzoate with 4,4′-azobis(4-cyanopentanoic acid) as the free radical initiator at 70 °C. The polymerization was performed directly in the NMR spectrometer. Spectra were recorded every 10 min.

In all the spectra, the $\delta \sim 4.8$ ppm HOD resonance is used as an internal reference. Conversion was monitored by a comparison of the resonances at $\delta \sim 5.9$ and 6.4 ppm in the pure monomer (spectra recorded at time $= 0$ min) (two of the vinylic hydrogens) to those at the same δ values for spectra recorded at time $= 10 \rightarrow 120$ min. It is apparent that the homopolymerization of sodium 4-styrenesulfonate occurs rapidly under these conditions, with a high degree of conversion being

Table 2. Molecular Weight, Polydispersity, and Conversion Data for Poly(sodium 4-styrenesulfonate) Homopolymers, Synthesized in the Presence of 4-Cyanopentanoic Acid Dithiobenzoate or in the Presence of Carboxymethyl Dithiobenzoate

CTA	M_n[a]	M_w[a]	M_w/M_n[a]	M_n (theory)[b]	conv (%)[b]	conv (%)[c]
4-cyanopentanoic acid dithiobenzoate	16 900	19 800	1.17	19 800	66	51
carboxymethyl dithiobenzoate	507 000	1 520 000	3.00	20 700	69	57

[a] As determined by aqueous size exclusion chromatography, calibrated with poly(sodium 4-styrenesulfonate) standards with a mobile phase of 20% acetonitrile/80% 0.05 M $NaNO_3$ + 0.01 M Na_2HPO_4. [b] As determined by ^1H NMR spectroscopy. [c] As determined gravimetrically.

observed after only 2 h (cf. spectrum at time = 120 min with the spectrum at time = 0 min).

The choice of CTA for any particular monomer is extremely important in controlled polymerization. It is desirable to achieve fast rates for both addition of a given radical species to the C=S double bond and fragmentation of the intermediate radical species (producing R•) relative to the rate of propagation. Fast rates of addition can be achieved when the Z species has a stabilizing effect on the intermediate radical, such as a phenyl group. The R group must be a good free radical leaving group and efficient at reinitiating polymerization. As a comparison, two polymerizations were carried out, in D_2O, using two different water-soluble CTAs. The first employed 4-cyanopentanoic acid dithiobenzoate, which yields a tertiary radical species upon fragmentation. The second used carboxymethyl dithiobenzoate (commercially available CTA) that yields a primary radical species upon fragmentation. Both polymerizations were conducted with 4,4′-azobis(4-cyanopentanoic acid) as the source of initiating radicals. The molecular weights, polydispersities, and conversions are listed in Table 2.

It is apparent that there are significant differences in the efficiency of the two CTAs to mediate the RAFT polymerization of sodium 4-styrenesulfonate in aqueous media. While 4-cyanopentanoic acid dithiobenzoate-mediated RAFT yielded a poly(sodium 4-styrenesulfonate) homopolymer with a narrow molecular weight distribution ($M_w/M_n = 1.17$) and a molecular weight close to the theoretical value, carboxymethyl dithiobenzoate-mediated RAFT yielded a homopolymer with a broad molecular weight distribution and average molecular weight significantly higher than the theoretical value. Interestingly, the conversions are almost identical for the two polymerizations. Figure 5 shows the ASEC traces of the two homopolymers.

Both traces are unimodal, although it is obvious that the carboxymethyl dithiobenzoate-mediated polymerization is considerably less controlled than that utilizing 4-cyanopentanoic acid dithiobenzoate. The differences can be rationalized by considering fragmentation of the intermediate radicals (**1a** and **1b**), Scheme 1, and the activity of the expelled radical species R•, where R = **1a** or **1b**. In the ground state, the S−R bond is weakened for **1a** vs **1b** due to steric factors. Resonance and polar factors also lower the transition state energy in the formation R• from **1a** as compared to **1b**. Thus, kinetically, the rate of fragmentation of **1a** should be faster than **1b**. Additionally, the produced 4-cyanopentanoic acid radical fragment, R•, is less reactive than the carboxymethyl radical due to both resonance stabilization and steric bulk. The former radical should be substantially more selective in adding to CTA and dithioester segments vs monomer and additionally should be less likely to participate in recombination (radical coupling) events. Le et al.[14h] have addressed selectivity in RAFT, indicating that a chain transfer constant > 2 is necessary for optimal control.

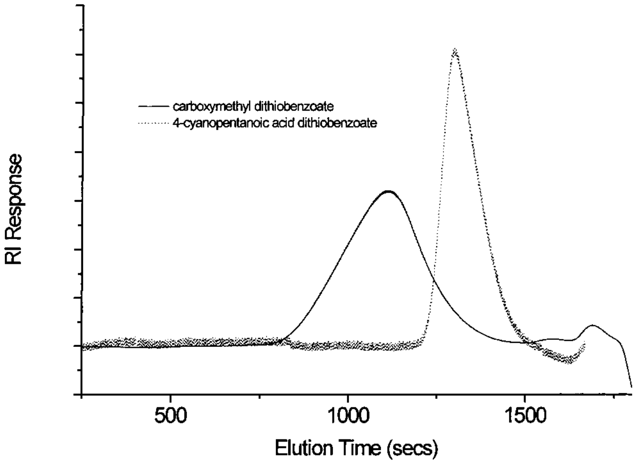


Figure 5. Aqueous size exclusion chromatograms for poly(sodium 4-styrenesulfonate) homopolymers synthesized in the presence of 4-cyanopentanoic acid dithiobenzoate and carboxymethyl dithiobenzoate.

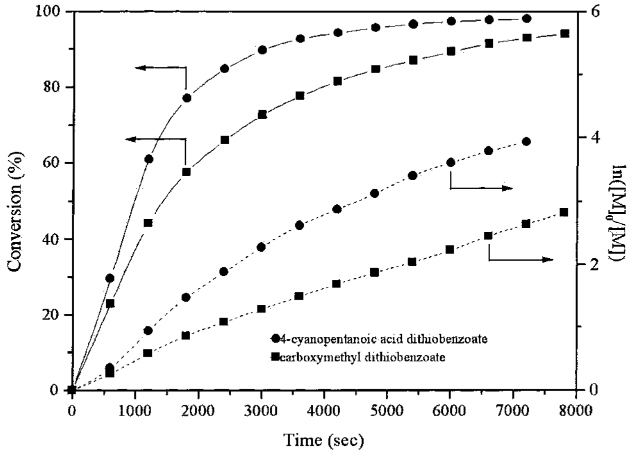


Figure 6. Time−conversion and first-order kinetic plots for the polymerization of sodium 4-styrenesulfonate in the presence of 4-cyanopentanoic acid dithiobenzoate and carboxymethyl dithiobenzoate.

As stated previously, it is clear that the homopolymerization of sodium 4-styrenesulfonate occurs rapidly in water with either 4-cyanopentanoic acid dithiobenzoate or carboxymethyl dithiobenzoate as the RAFT CTAs. The time−conversion relationships for the two polymerizations as well as the first-order kinetic plots are shown in Figure 6. For the 4-cyanopentanoic acid dithiobenzoate-mediated polymerization, ~90% conversion is achieved after only ~50 min, while ~70% conversion is obtained with carboxymethyl dithiobenzoate after the same period of time. The carboxymethyl dithiobenzoate-mediated polymerization exhibits first-order kinetics, although there does appear to be a slight deviation early

Table 3. Molecular Weight, Polydispersity, and Conversion Data for the Diacid and Diamine Block Copolymers

block copolymer	theor comp	obsd comp[a]	theor MW	M_n[b]	M_w[b]	M_w/M_n[b]
diacid	50:50	46:54	14 000	18 600[c]	21 900[c]	1.18[c]
diamine	50:50	49:51	11 700	51 000[d]	68 600[d]	1.37[d]

[a] As determined by ^{13}C NMR spectroscopy. [b] As determined by aqueous size exclusion chromatography. [c] Calibrated with poly(sodium 4-styrenesulfonate) standards with a mobile phase of 20% acetonitrile/80% 0.05 M $NaNO_3$ + 0.01 M Na_2HPO_4. [d] Calibrated with poly(ethylene oxide) standards with a mobile phase of 0.5 M acetic acid + 0.3 M Na_2SO_4.

on for the 4-cyanopentanoic acid dithiobenzoate-mediated polymerization indicating more complex kinetics.

RAFT Synthesis of Diacid and Diamine AB Block Copolymers. The ability to synthesize controlled architectures, such as AB diblock copolymers, is one of the features that distinguish "pseudo-living" free radical from conventional free radical polymerization. The polymerization of sodium 4-styrenesulfonate, for example, yields a homopolymer with a dithioester chain-end functionality that can be used as a macro-CTA. Poly(sodium 4-styrenesulfonate) and poly(*ar*-vinylbenzyl)trimethylammonium chloride have been prepared in our laboratories and employed as macro-CTAs for the block copolymerizations of sodium 4-vinylbenzoate and *N*,*N*-dimethylvinylbenzylamine, respectively. (Both precursor homopolymers were synthesized using 4-cyanopentanoic acid dithiobenzoate as the RAFT CTA.) A summary of the molecular weights, polydispersities, block copolymer compositions, and yields is given in Table 3. The observed molecular weights for the diamine block copolymer are significantly higher than the theoretical molecular weights due to the lack of suitable standards. Whereas the molecular weight for poly(sodium 4-styrenesulfonate-*block*-sodium 4-vinylbenzoate) is based on near-monodisperse poly(sodium 4-styrenesulfonate) standards, the molecular weight for the cationic diamine block copolymer is based on near-monodisperse, nonionic, linear poly(ethylene oxide) standards.

To our knowledge these are the first examples of AB diblock copolymers synthesized directly in aqueous media via RAFT.

Figure 7 shows the ^{1}H and ^{13}C NMR spectra of the poly(sodium 4-styrenesulfonate-*block*-sodium 4-vinylbenzoate) copolymer, recorded in D_2O, with HOD as the internal reference. It is not possible to determine the block copolymer composition from the ^{1}H NMR spectrum, since all the peaks for both blocks overlap. (The acidic hydrogen from 4-vinylbenzoic acid cannot be seen due to H−D exchange with the solvent.) However, the block copolymer composition can be determined from the ^{13}C NMR spectrum.

The ^{13}C NMR spectrum in Figure 7 is gated-decoupled and can therefore be accurately integrated. According to a previous report,[7] the resonances at δ 136 and 143 ppm are due to the aromatic $\mathbf{C}-CO_2Na$ and $\mathbf{C}-SO_3Na$ carbon atoms in the sodium 4-vinylbenzoate and sodium 4-styrenesulfonate residues, respectively. The ratio of these areas yield a block copolymer composition of 46:54 (mol %), close to the theoretical composition of 50:50. Figure 8 shows the ^{1}H and ^{13}C NMR spectra of the poly((*ar*-vinylbenzyl)trimethylammonium chloride-*block*-*N*,*N*-dimethylvinylbenzylamine) copolymer, recorded in D_2O, with HOD as the internal reference.

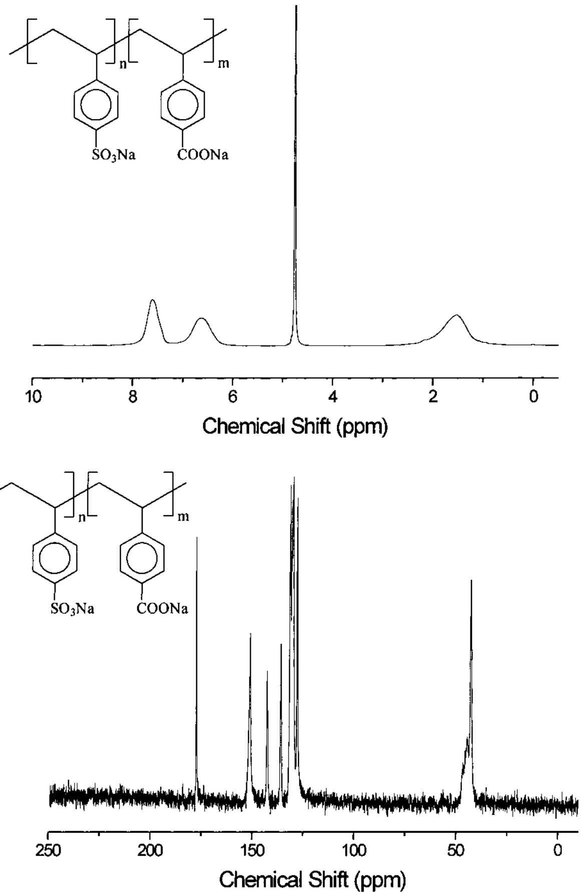


Figure 7. ^{1}H and ^{13}C NMR spectra recorded in D_2O of a poly(sodium 4-styrenesulfonate-*block*-sodium 4-vinylbenzoate) copolymer.

Likewise, the block copolymer composition was determined using the ^{13}C NMR spectrum. The resonances at $\delta \sim 71.0$ and 62.0 ppm correspond to the C atoms of the methylene groups attached to nitrogen in (*ar*-vinylbenzyl)trimethylammonium chloride and *N*,*N*-dimethylvinylbenzylamine, respectively. The relative ratios yield a block copolymer composition of 51:49, again close to the theoretical value of 50:50 (mol %).

Gabaston et al. previously reported the synthesis of poly(4-sodium styrenesulfonate-*block*-sodium 4-vinylbenzoate) copolymers, although these were synthesized via TEMPO-mediated SFRP.[7] The authors reported difficulties in obtaining reliable molecular weight data by ASEC due to the different eluent conditions required for the two blocks. This is a problem we have not encountered. Using TSK gel columns, both sodium 4-styrenesulfonate and sodium 4-vinylbenzoate homopolymers eluted well (using 20% acetonitrile, 80% water, 0.05 M $NaNO_3$, and 0.01 M Na_2HPO_4), with no evidence of secondary effects such as ion-exclusion or hydrophobic column interactions. Gabaston et al. demonstrated the ability of these block copolymers to undergo reversible micellization as a function of solution pH. Both of the block copolymers reported here exhibit similar reversible, pH-induced aggregation in aqueous media. Poly(sodium 4-styrenesulfonate-*block*-sodium 4-vinylbenzoate) is readily water-soluble and exists as unimers at intermediate and high pHs. Lowering of the solution pH results in the selective protonation of the carboxylate residues forming poly(4-vinylbenzoic acid) which is hydrophobic. Block copolymers in selective solvents are well-known to associate to form spherical

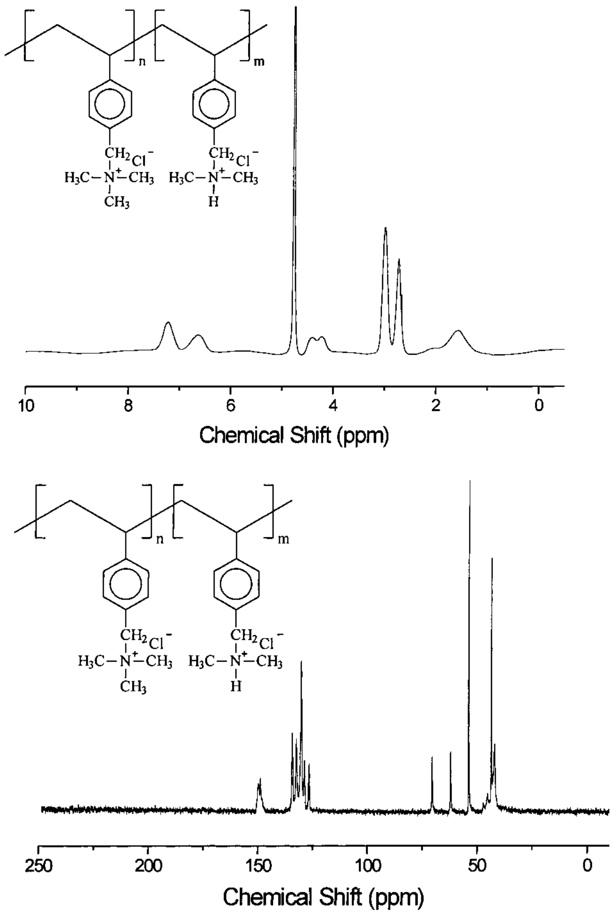


Figure 8. ^{1}H and ^{13}C NMR spectra recorded in D_2O of a poly((*ar*-vinylbenzyl) trimethylammonium chloride-*block*-*N*,*N*-dimethylvinylbenzylamine) copolymer.

micelles that are generally in dynamic equilibrium with unimers in solution.[19] One w/w % solutions of both block copolymers were prepared. Aliquots were taken from each sample, and the solution pH was adjusted by the addition of 6.0 M NaOH and 6.0 M HCl. The samples were subsequently analyzed by dynamic light scattering (using CONTIN analysis). As expected, the poly(sodium 4-styrenesulfonate-*block*-4-vinylbenzoic acid) copolymer formed multimolecular aggregates at low pH, with an observed intensity-average hydrodynamic diameter of 19.0 nm (unimodal distribution). At high pH, where both the blocks are ionized and thus solvated, unimers were observed with an intensity-average hydrodynamic diameter of 8.0 nm (unimodal distribution). The opposite trend was observed for the diamine block copolymer. The poly(*ar*-vinylbenzyl)trimethylammonium chloride block is permanently charged, whereas the poly(*N*,*N*-dimethylvinylbenzylamine) can be selectively protonated. At high pH, in its nonionized form, poly(*N*,*N*-dimethylvinylbenzylamine) is hydrophobic, and therefore the formation of micelles is expected. Indeed, at high pH, aggregates with an intensity-average hydrodynamic diameter of 38.0 nm were observed (unimodal distribution). Lowering of the solution pH results in protonation of the *N*,*N*-dimethylvinylbenzylamine residues, rendering the block copolymer hydrophilic–hydrophilic. Under these conditions, species with an intensity-average hydrodynamic diameter of 8.0 nm were observed (unimodal distribution). The effect of block copolymer composition and molecular weight on the aggregation behavior in aqueous media of these stimuli-responsive block copolymers will be discussed in a forthcoming publication.[20]

Conclusions

We have reported the synthesis of near-monodisperse poly(sodium 4-styrenesulfonate) homopolymers synthesized directly in aqueous solution via the RAFT process. We have demonstrated the need for a suitably active RAFT CTA in order to obtain near-monodisperse (co)polymers. Dithioester end-capped poly(sodium 4-styrenesulfonate) has been employed as a macro-CTA for the synthesis of poly(sodium 4-styrenesulfonate-*block*-sodium 4-vinylbenzoate) copolymers. Using a similar methodology, a block copolymer of (*ar*-vinylbenzyl)trimethylammonium chloride and *N*,*N*-dimethylvinylbenzylamine has also been prepared. Preliminary aqueous solution studies show that both these block copolymers undergo reversible pH-induced micellization in aqueous solution. We believe this represents the first report concerning the synthesis of controlled AB diblock copolymers in aqueous solution utilizing RAFT.

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