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RAFT Synthesis and Aqueous Solution Behavior of Novel pH- and Thermo-Responsive (Co)Polymers Derived from Reactive Poly(2-vinyl-4,4-dimethylazlactone) Scaffolds

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Ⓢ Supporting Information

ABSTRACT: Well-defined homopolymers of 2-vinyl-4,4-dimethylazlactone (VDA) and AB diblock copolymers of VDA with N,N-dimethylacrylamide (DMA) and N-isopropylacrylamide (NIPAM) prepared by reversible addition–fragmentation chain transfer (RAFT) radical polymerization are reported. VDA homopolymers reacted with N,N-dimethylethylenediamine (DMEDA), N,N-diethylethylenediamine (DEEDA), and picoylamine (PA) give novel tertiary amine functional polymers that exhibit inverse temperature aqueous solution characteristics in the case of the DMEDA and DEEDA derivatives (provided they are not protonated) and a pH-dependent solubility for the PA species—it is soluble at low solution pH but becomes hydrophobic at ca. pH 4.0. VDA-DMA/NIPAM AB diblock copolymers are also readily modified with DMEDA, DEEDA, and PA to give a novel series of stimulus responsive block copolymers including tunably amphiphilic and schizophrenic species. DMEDA-DMA and DEEDA-DMA/NIPAM block copolymer derivatives undergo reversible temperature induced self-assembly in aqueous media by virtue of the inverse temperature solubility characteristics associated with these tertiary amino species. The aggregation behavior of these species is characterized using a combination of dynamic light scattering (DLS), ^{1}H NMR spectroscopy and transmission electron microscopy (TEM). For the PA derivatives, schizophrenic behavior is demonstrated in AB block copolymers with NIPAM with normal and inverse micelles being readily accessible simply by controlling the solution pH or temperature. Self-assembled species derived from a DMEDA-DMA block copolymer, containing tertiary amino functionality in the core, can be readily core cross-linked, locking the self-assembled structure, using 1,10-dibromodecane as evidenced by DLS. The ability of examples of the 'smart' block copolymers to sequester hydrophobic Nile Red upon application of a pH or temperature stimulus from an aqueous environment is also demonstrated. Finally, we show how, if desired, the DMEDA homopolymers can be further modified via the facile reaction with 1,3-propanesultone yielding the sulfopropylbetaine analogous materials.
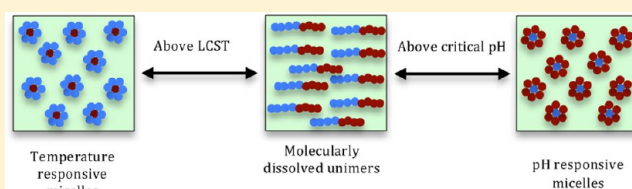
INTRODUCTION

Stimuli-responsive (co)polymers are macromolecules that undergo a conformational change or phase transition in response to an applied external stimuli. The triggers, or stimuli, include changes in solution pH, temperature, the addition or removal of electrolyte, electromagnetism, and other molecules.[1–5] Such stimuli may be applied alone or in combination depending on the chemical structure of the parent (co)polymer. Of these possible triggers, the uses of temperature or pH are the most widely employed. For example, acrylamido (co)polymers based on poly(N-isopropylacrylamide) (PNIPAM) or poly(N,N-diethylacrylamide) (PDEA) are widely exploited as temperature responsive based materials given their readily accessible lower critical solution temperature (LCST) in water of ca. 32 °C,[6–10] although a range of alkylacrylamido-based (co)polymers exhibit such behavior. Indeed, exploiting the inverse temperature-dependent aqueous solubility characteristics of (co)polymers is by far the most commonly employed thermal trigger. However, and in a similar vein,

there has recently been increasing interest in exploiting the upper critical solution temperature (UCST) as a trigger for inducing phase transitions in block copolymers, although this is less common.[11–16]

One of the most thoroughly studied group of (co)polymers, with respect to various stimulus-induced behaviors in aqueous media, are those based on the methacrylic family of polymers containing tertiary amino functionality in the side chains. This includes species such as poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA), poly(2-(diisopropylamino)ethyl methacrylate) (PDPAEMA), poly(2-morpholinoethyl methacrylate) (PMEMA), and various copolymers thereof.[17–23] Briefly, PDMAEMA has a well-documented LCST in the range of ca. 32–47 °C in its nonionized form, the exact value being

dependent on the molecular weight of the polymer; PDEAEMA and PDPAEMA are only soluble in water in their protonated, cationic polyelectrolyte forms and thus solution pH can be employed as a trigger to control their solubilities, and PMEMA exhibits rich solution behavior possessing an LCST of 34−53 °C (again depending on molecular weight) and is also readily salted out of aqueous solution with certain divalent salts such as Na_2SO_4.[17] Such triggers have been employed alone, or in combination, in multiply responsive copolymers to induce the self-assembly of multiblock copolymers in aqueous media giving a wide range of functional micelles and/or vesicles.

Recently there has been renewed interest in reactive (co)polymers as precursors to novel functional materials,[24] with significant interest being given to (co)polymers containing activated esters (pentafluorophenyl esters for example)[12,25−29] as well as (co)polymers containing 2-vinyl-4,4-dimethylazlactone (VDA).[30−38] Both of these species exhibit an extremely high reactivity toward primary amines, reacting rapidly and quantitatively at ambient or slightly elevated temperatures yielding amide derivatives in the case of activated esters via simple acyl substitution and bisamides via ring-opening in the case of VDA derivatives. For example, Sun et al.[37] described the facile synthesis of a library of tertiary amine functional homopolymers from a parent VDA homopolymer ($\bar{M}_n$ = 74,000, $Đ_M = \bar{M}_w\bar{M}_n$ = 2.65). The precursor homopolymer was reacted with a series of 12 primary amines (also containing tertiary amine functional groups), with ring-opened products being obtained in near quantitative yields. The authors demonstrated that the resulting tertiary amino functional polymers were effective in the delivery of DNA to cells although the efficacy was found to be structure dependent. This work did, however, very nicely demonstrate how (co)polymers containing VDA can serve as very efficient reactive scaffolds facilitating the straightforward preparation of a library of novel materials with targeted applications. More recently, Zhu and co-workers[39] reported the reversible addition−fragmentation chain transfer (RAFT) homopolymerization of VDA to give well-defined polymers with $\bar{M}_n$ values in the range 46,000−75,000 with corresponding $Đ_M$ values <1.21. These homopolymers were modified with a large library of 1° and 2° amines as well as with examples of alcohols. In the case of polymers modified with N-ethylamine, N-isopropylamine, N,N-dimethylamine, N,N-diethylamine, N,N-diethylaminoethylamine, Jeffamine M-600, and tetrahydrofurfurylamine, the resulting water-soluble homopolymers were shown to possess lower critical solution temperatures spanning the range 17.3−70.8 °C, demonstrating how VDA can likewise serve as a suitable precursor species for the preparation of stimulus-responsive (co)polymers.

We have a long-standing interest in the synthesis and evaluation of well-defined stimulus responsive (co)-polymers.[25,28,40,41] Recognizing that (co)polymers containing VDA offered the opportunity to prepare novel (co)polymers that were structurally similar to materials with well-established, rich, aqueous solution properties (such as the tertiary amino methacrylate family of materials), here we describe our initial studies on the synthesis and aqueous solution properties of examples of well-defined tertiary amine-containing (co)-polymers obtained from precursor VDA (co)polymers prepared via RAFT[42−45] radical polymerization. This work extends the known family of pH and temperature responsive (co)polymers and demonstrates how a range of novel parent (co)polymers give facile access to an even larger group of functional macromolecules with interesting and varied aqueous solution properties.

■ EXPERIMENTAL SECTION

All reagents were purchased from the Sigma-Aldrich Chemical Co. at the highest available purity and used as received unless noted otherwise. Benzyl propyl trithiocarbonate (BPTC) was prepared following a literature procedure.[25] 2,2′-Azobis(2-methylpropionitrile) (AIBN) was recrystallized twice from methanol and stored at −24 °C until needed. N-Isopropylacrylamide (NIPAM) was recrystallized twice from hexane and stored at 5 °C until needed. N,N-Dimethylacrylamide (DMA) was purified by passage over a column of basic alumina to remove inhibitor and then stored at 5 °C until needed. 2-Vinyl-4,4-dimethylazlactone (VDA) was prepared according to a literature procedure.[34]

RAFT Homopolymerization of 2-Vinyl-4,4-dimethylazlactone (VDA). Below is a typical procedure for the RAFT polymerization of VDA.

VDA (1.0 g, 7.19 mmol), BPTC (17.4 mg, 0.0719 mmol), AIBN (1.2 mg, 0.00719 mmol), and acetonitrile (3.0 mL) were combined in a glass vial equipped with a magnetic stir bar. The vial was sealed with a rubber septum and the homogeneous solution purged with nitrogen for ca. 30 min. The vial was subsequently immersed in a preheated oil bath set to 70 °C. Polymerization was allowed to proceed for 6 h. After the polymerization was terminated by cooling and exposure to air, the resulting polyVDA was isolated by precipitation into diethyl ether. After filtration the polymer was dried in vacuo.

Reaction of polyVDA Homopolymer with Primary Amines in the Presence of S-Methyl Methanethiosulfonate. Poly(2-vinyl-4,4-dimethylazlactone) (PVDA) homopolymer was reacted with three different primary amines, namely N,N-dimethylethylenediamine (DMEDA), N,N-diethylethylenediamine (DEEDA), and 2-picolyl-amine (PA) in the presence of S-methyl methanethiosulfonate (MMTS). The example below gives the procedure for the reaction of PVDA with PA.

To a glass vial equipped with a magnetic stir bar was added PVDA (0.2 g, 1.44 mmol, 1.0 equiv of repeat units), MMTS (18.9 μL, 10.0 equiv with respect to polymer end-groups) and DMF (2.0 mL). To a separate glass vial was added PA (0.467 g, 4.31 mmol, 3.0 equiv) and DMF (2.0 mL). After complete dissolution, the two solutions were combined and the reaction left to stir overnight at 50 °C. The same equivalent of reagents were used in the case of reactions with DMEDA and DEEDA.

DEEDA and PA-modified PVDA were purified by dialysis against MeOH using regenerated cellulose membrane with a molecular weight cut off of 3500 g/mol. Dialysis was performed for three days with solvent changes three times daily. After removal of MeOH via rotary evaporation the modified polymers were dried in vacuo at 40 °C. In the case of the DMEMA modified homopolymer, the polymer was purified and isolated by precipitation in diethyl ether followed by centrifugation at 8000 rpm for 10 min followed by drying in vacuo at 40 °C.

RAFT Block Polymerizations of PVDA with N,N-Dimethylacrylamide. Below is given a typical procedure for the preparation of AB diblock copolymers of VDA with DMA.

To a glass vial equipped with a magnetic stir bar were added macroRAFT VDM (1 g, 7.186 mmol of VDA units), DMA (0.997 g, 10 mmol), AIBN (2.35 mg, 0.0143 mmol), and acetonitrile (5 mL). The vial was sealed with a rubber septum and nitrogen was bubbled through the solution for 20 min. The reaction vessel was subsequently immersed in a preheated oil bath set to 70 °C and the polymerization was allowed to proceed for 1 h. Purification was carried out by a series of precipitations in diethyl ether before the copolymer was filtered and dried in a vacuum oven at 40 °C.

RAFT Block Polymerizations of PVDA with N-Isopropylacrylamide. Below is given a typical procedure for the preparation of AB diblock copolymers of VDA with NIPAM.

To a glass vial equipped with a magnetic stir bar were added macroRAFT PVDA (1.5 g, 10.8 mmol of VDA), NIPAM (1.83 g, 16.2 mmol), AIBN (3.52 mg, 0.0214 mmol), and acetonitrile (8 mL). The

Scheme 1. Conditions Employed for the Synthesis of polyVDA Homopolymers and AB Diblock Copolymers of VDA with *N,N*-Dimethylacrylamide or *N*-Isopropylacrylamide
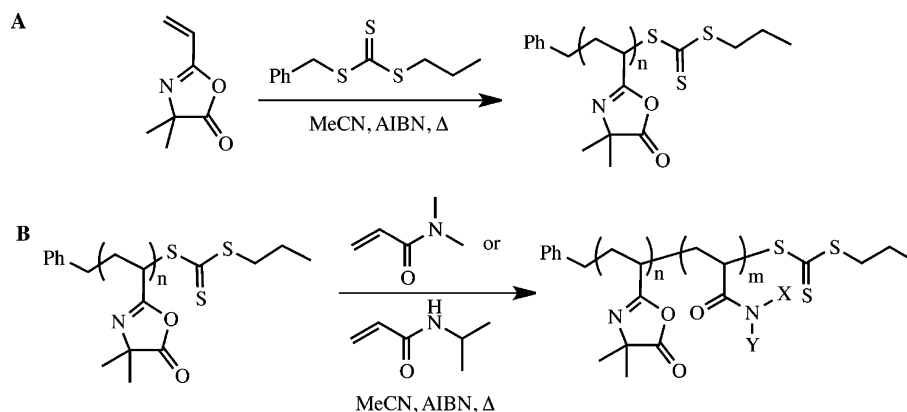
vial was sealed with a rubber septum and nitrogen was bubbled through the solution for 20 min. The reaction vessel was subsequently immersed in a preheated oil bath set to 70 °C and the reaction was allowed to proceed for 2 h. Purification was carried out by a series of precipitations in diethyl ether before the copolymer was filtered and dried in a vacuum oven at 40 °C.

Reaction of VDA-DMA and VDA-NIPAM AB Diblock Copolymers with Primary Amines in the Presence of *S*-Methyl Methanethiosulfonate. VDA-DMA/VDA-NIPAM diblock copolymers were reacted with three different primary amines, namely *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA), and 2-picolyamine (PA), in the presence of *S*-methyl methanethiosulfonate (MMTS). The example below gives the general procedure.

To a glass vial equipped with a magnetic stir bar was added VDA-DMA copolymer (0.25 g, 0.898 mmol, 1.0 equiv), MMTS (12.0 μL, 10.0 equiv with respect to polymer thiocarbonylthio end-groups) and DMF (2.0 mL). To a separate glass vial was added PA (0.291 g, 2.69 mmol, 3.0 equiv based on VDA residues) and DMF (2.0 mL). After complete dissolution, the two solutions were combined, and the reaction was left to stir overnight at 50 °C. The same equivalent of reagents were used in the case of reactions with DMEDA and DEEDA as well as for the VDA-NIPAM AB diblock copolymers.

All the modified VDA-DMA and VDA-NIPAM AB diblock copolymer were purified by dialysis against MeOH using regenerated cellulose membrane with a molecular weight cut off of 3500 g/mol. Dialysis was performed for 3 days with solvent changes three times daily.

Core-Cross-Linking of P(DMEDA₅₄-*b*-DMA₄₆) with 1,10-Dibromodecane. 1,10-Dibromodecane (1.84 mg, 6.12 × 10⁻³ mmol, 10 mol % based on DMEDA residues) was added to a solution of P(DMEDA₅₄-*b*-DMA₄₆) (10.0 mg, 6.12 × 10⁻² mmol of DMEDA units) in 1.0 mL of 0.1 M NaOH. The solution was heated to 85 °C and allowed to stir overnight. After cooling to room temperature the solution was dialyzed against slightly acidic water for 2 days with the water being changed twice daily. The core cross-linked aggregates were isolated by lyophilization.

Betainization of PDMEDA and PDEEDA Homopolymers. Betainization of PDMEDA and PDEEDA homopolymers was performed according to the general method of Lowe, Billingham, and Armes,[46] with a slight modification.

1,3-Propanesultone (76.2 mg, 0.624 mmol, 10 mol % excess based on DMEDA or DEEDA residues) was added to the parent polyDMEDA (PDMEDA) or polyDEEDA (PDEEDA) homopolymers (50.0 mg, 0.567 mmol of amine groups) dissolved in CHCl₃ (2.0 mL) at room temperature. The solutions were subsequently immersed in a preheated oil bath set to 40 °C. For the PDMEDA homopolymer, gelation/precipitation occurred within 6 h of reaction but the reaction was left overnight prior to work-up. The precipitates were filtered, and unreacted 1,3-propane sultone was removed by excess washing of the polymer with CHCl₃. In the case of the

PDEEDA homopolymer, the polymer was reacted for 72 h after which the formed precipitate was filtered and washed with CHCl₃.

Instrumentation. Size exclusion chromatography (SEC) was performed on a Shimadzu system with four phenogel columns in dimethylacetamide (DMAc) (0.03% w/v LiBr, 0.05% BHT stabilizer) as eluent at a flow rate of 1.0 mL/min at 50 °C. A Shimadzu modular system was employed comprising a DGC-12A solvent degasser, an LC-10AT pump, a CTO 10A column oven and a RID-10A refractive index detector. The system was equipped with a Polymer Laboratories 5.0 mm bead-size guard column (50 × 7.8 mm²) followed by four 300 × 7.8 mm² linear PL columns (10⁵, 10⁴, 10³ and 500 Å). Chromatograms were analyzed using Cirrus SEC software (version 3.0) and the system was calibrated with a series of narrow molecular weight distribution polystyrene (PS) standards with molecular weights ranging from 580–1,820 000 g/mol.

Dynamic light scattering (DLS) measurements were performed on a Malvern Zetasizer Nano ZS at a scattering angle of 173 °C and analyzed by Malvern Zetasizer Software version 6.20. Samples were concentrated in a solution of 10 g/L for analysis. All samples were filtered through 0.45-μm filters prior to analysis.

Transmission electron microscopy (TEM) was conducted on a Jeol 1400 instrument with an accelerating voltage of 100 kV. Samples were dissolved in 0.1 M HCl after which 0.1 M NaOH was added dropwise until the pH reached 7.0. Two drops of the solution were dropped onto a carbon-coated TEM grid on a tissue and dried overnight.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 300 spectrometer at 300 MHz for hydrogen nuclei. Chemical shifts are reported in parts per million (ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constants in Hertz, integration]. Measurements were performed in CDCl₃, D₂O or CD₃OD with the internal solvent signal being used as the reference signal (7.26 ppm for CDCl₃ solutions, 4.79 ppm in D₂O solution and 3.31 ppm for CD₃OD). NMR data were evaluated using iNMR 4.0.4 Mestrelab Research software. In cases where DCl was employed as an NMR solvent, it was initially diluted with D₂O to give a 0.1 M DCl solution.

Turbidity measurements were performed on a Varian Cary 300 Scan spectrophotometer equipped with a Cary temperature controller and a Peltier heating element in quartz cuvettes of 10 mm path length at a wavelength of 520 nm. In all cases, a polymer concentration of 10 mg/mL was employed. Heating rates were 1 °C/min for all measurements. For all clear solutions, the baseline was corrected to zero absorbance, *A*. Transmittance, $T = 10^{-A}$, was plotted against temperature, and cloud points were determined at 50% transmittance. The maximum temperature evaluated for all solutions was 80.0 °C. In the case of buffer solutions, a citrate-phosphate buffer was employed. Citric acid (6.5 mL of a 0.1 M solution) and dibasic sodium phosphate (43.6 mL of a 0.2 M solution) were mixed to form the buffer solution.

Scheme 2. Reaction of a VDA Homopolymer with Primary Amines in the Presence of MMTS
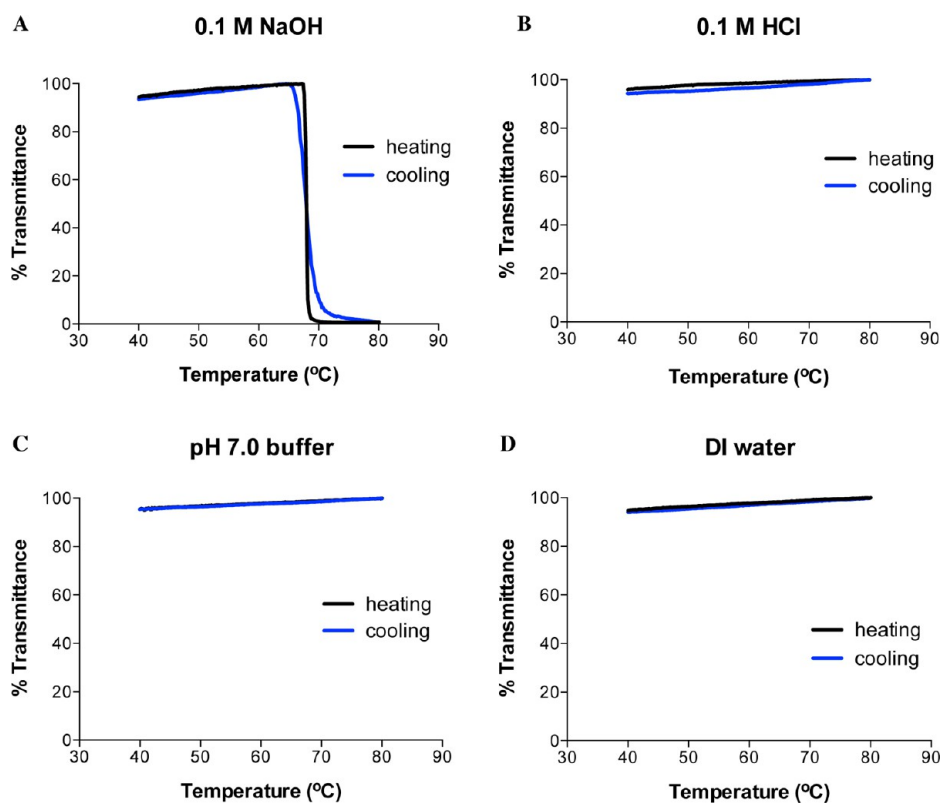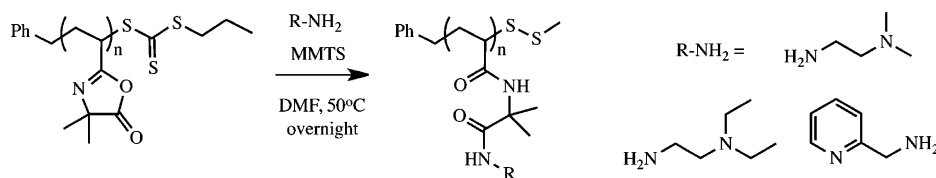

Figure 1. Heating and cooling turbidity curves for a PDMEDA homopolymer at a concentration of 1 wt % in (A) 0.1 M NaOH, (B) 0.1 M HCl, (C) pH 7.0 buffer, and (D) deionized water.

Fourier transform infrared spectroscopy (FTIR) measurements were performed on a Bruker IFS 66/S instrument under attenuated total reflectance (ATR). Data was analyzed with OPUS software version 4.0.

RESULTS AND DISCUSSION

Synthesis of 2-Vinyl-4,4-dimethylazlactone Homopolymers and Their Subsequent Modification with Primary Amines. A series of homo- and AB diblock copolymers containing a common building block, namely 2-vinyl-4,4-dimethylazlactone (VDA), were prepared by RAFT radical polymerization mediated by a trithiocarbonate chain transfer agent (CTA), according to Scheme 1, parts A and B.

Consider first the homopolymers. VDA was homopolymerized with benzyl propyl trithiocarbonate (BPT) to give two well-defined reactive species with SEC measured $\bar{M}_n$'s of 35 160 (PVDA1) and 45 700 (PVDA2) and corresponding dispersities ($Đ_M$) of 1.19 and 1.15. In addition to SEC, the homopolymers were characterized via ^{1}H NMR and FTIR spectroscopies (see Supporting Information).

As noted in the introduction, VDA-based (co)polymers serve as convenient reactive scaffolds with the dimethylazlactone rings being readily opened by nucleophiles.[37,39] Specifically, primary amines are extremely efficient in such ring-opening

reactions although both alcohols and thiols can also be employed. With VDA homopolymers in hand we treated PVDA1 with three small molecule amines, namely *N,N*-dimethylethylenediamine (DMEDA), *N,N*-diethylethylenediamine (DEEDA), and picolylamine (PA), Scheme 2. These amines were chosen based on the hypothesis that the resulting tertiary amino polymers would exhibit interesting aqueous solution behavior in a fashion analogous to that exhibited by tertiary-amino-containing (meth)acrylic species. It is noted that the ring-opening reactions were performed in the presence of *S*-methyl methanethiosulfonate (MMTS). Primary amines, while readily opening the azlactone heterocycle, are also capable of reacting with the trithiocarbonate end-group, cleaving it to give the corresponding macromolecular thiol; indeed, such aminolysis reactions represent the most common method for removing thiocarbonylthio end-groups in RAFT-prepared (co)polymers.[6,11,47−50] To prevent thiol−thiol coupling reactions between the macromolecular thiols following aminolysis, MMTS was used as a trapping agent. This has previously been demonstrated to be an effective method for trapping such polymeric thiols.[25,51−54]

Successful conversion of the parent PVDA1 homopolymer to the various bisamide-derivatives was quantitatively confirmed using ^{1}H NMR spectroscopy, and qualitatively by FTIR
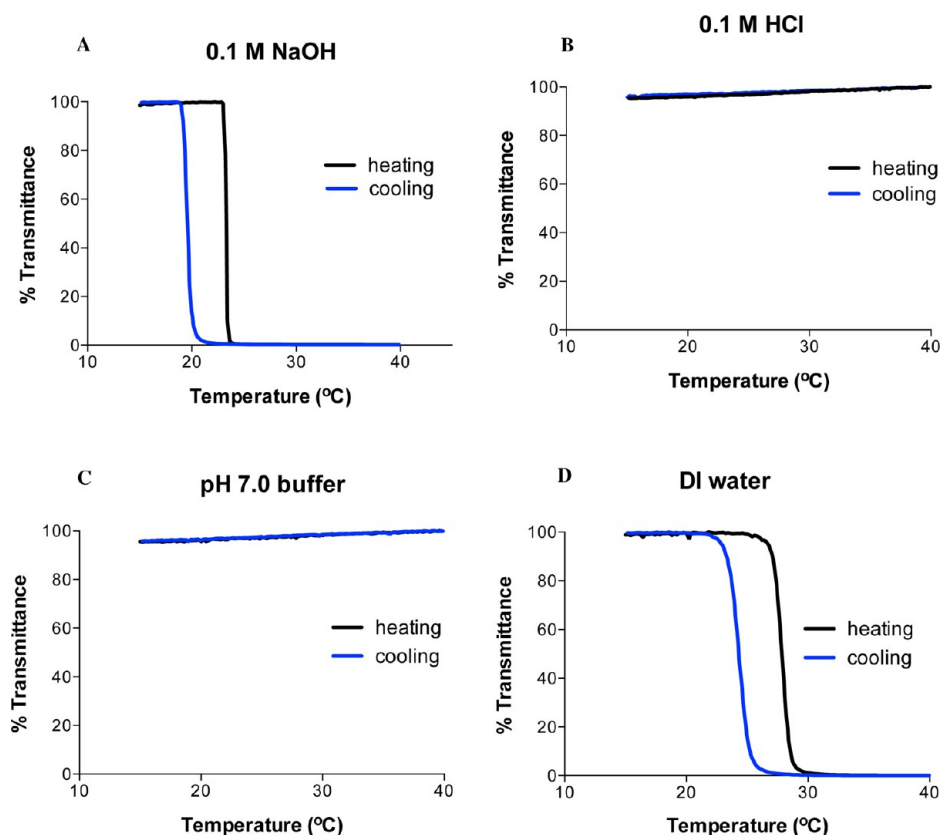
Figure 2. Heating and cooling turbidity curves for a PDEEDA homopolymer at a concentration of 1 wt % in (A) 0.1 M NaOH, (B) 0.1 M HCl, (C) pH 7.0 buffer, and (D) deionized water.

spectroscopy (see Supporting Information, Figures S3 and S4). The ^{1}H NMR spectrum of the PVDA1 parent polymer is entirely consistent with previous reports,[35] while integration of relevant signals in the three amine modified samples indicate successful and quantitative conversion to the tertiary-amino bisamide derivatives. The key diagnostic absorptions in the FTIR spectra include the total disappearance of the band centered at ~1818 cm^{-1} (C=O of azlactone ring), the disappearance of the band at ca. 1670 cm^{-1} (the imine C=N absorption band associated with the azlactone precursor), the appearance of new C=O bands at ~1640 cm^{-1} (amide absorption) in the products and the clear appearance of N−H stretching absorption bands at ~3280 cm^{-1}. SEC analysis of the modified homopolymers proved problematic due to solubility issues associated with the SEC eluent and analysis of the DMEDA and DEEDA derivatives could not be performed. However, analysis of the PA derivative was possible and gave a narrow, symmetrical, unimodal SEC trace with a measured polystyrene equivalent $\overline{M}_n$ of 50 400 and $Đ_M$ of 1.25. This indicates that in addition to retaining the well-defined features of the parent VDA1 homopolymer that trapping of the intermediate polymeric thiol with MMTS was successful given the absence of any detectable coupled polymeric species in the SEC traces.

Aqueous Solution Characteristics of Modified Homopolymers. While the DMEDA and DEEDA derivatives of PVDA have been previously reported and evaluated as cellular delivery vehicles for DNA,[37] their potential stimulus responsive behavior in aqueous media has never been examined, with the exception of our recent report of a DEEDA-modified VDA homopolymer ($\overline{M}_n$ = 53 600, $Đ_M$ = 1.16) exhibiting a cloud

point (CP) in aqueous media.[39] Given their structural similarity to well-known "smart" (co)polymers, especially those of the tertiary-amine containing (meth)acrylate and (meth)-acrylamido family of (co)polymers, we examined their potential thermoresponsive characteristics via turbidity measurements. Consider first the DMEDA derivative. Initially, solutions of the polyDMEDA (PDMEDA) derivative were prepared in 0.1 M NaOH, 0.1 M HCl, pH 7.0 buffer, and deionized (DI) water at a concentration of 1 wt %. The % transmittance was subsequently monitored as a function of increasing temperature, and where a clear change in the transmittance was observed the CP was taken as the temperature at which the transmittance dropped to 50%. Figure 1A−D shows the experimentally determined CP curves for the PDMEDA homopolymer under the four different solution conditions noted above. In 0.1 M NaOH (Figure 1A), when the tertiary amine residues are expected to be deprotonated (note the measured pH of this solution was 12.4), we observe a very sharp transition with a corresponding CP of 68.0 °C. This is substantially higher than the measured CP of structurally similar species PDMAEMA whose CP spans the range 32−47 °C, the precise value depending on the average degree of polymerization,[17] and poly[N-(3-(dimethylamino)propyl) acrylamide] which has a reported CP of ~35 °C.[55] However, this is consistent with our recent findings regarding the difference in measured CPs for poly[oligo(ethylene glycol) (meth)acrylamide]s versus the more common (meth)acrylic derivatives in which the (meth)acrylamido species were found to be significantly more hydrophilic.[56] This difference was attributed to the presence of the N−H functional species and its ability to serve as an H-bond donor. It is possible that the

bisamide derivatives reported here, such as PDMEDA, with two H-bond donor groups have a similarly enhanced relative hydrophilicity. The corresponding cooling curve in Figure 1A mirrors, almost exactly, the heating curve, and the DMEDA homopolymer redissolves giving an optically transparent solution. Such behavior is not uncommon and the heating/cooling curves for a given polymer sample may or may not exhibit some hysteresis.[57] In contrast, in 0.1 M HCl (Figure 1B), where the tertiary amine residues are expected to be fully protonated (measured solution pH = 1.44), we observe no change in the transmittance up to 80 °C, and the heating and cooling curves are simply superimposable straight lines, consistent with the polyelectrolyte nature of the polymer under these conditions. Identical behavior was observed for the PDMEDA homopolymer in pH 7.0 buffer (measured solution pH = 8.14) and in deionized water (measured solution pH = 8.30) with the polymer remaining soluble up to temperatures of 80 °C. This is in contrast to the aqueous phase behavior of PDMAEMA at intermediate pH values but mirrors the behavior described for poly[N-(3-(dimethylamino)propyl) (meth)-acrylamide]s[55] that were reported to have CP's only at pH 14.0. In the case of such (meth)acrylamido derivatives, the absence of phase behavior at lower pH values was attributed to partial ionization of the amino residues, even at pH 13.0, to an extent sufficient to eliminate any inverse temperature dependent solubility behavior. The fact that the PDMEDA homopolymer exhibited a CP in aqueous media obviously suggests that it can be employed as a "smart" building block in more advanced (co)polymer architectures which require an in-built thermal trigger, *vide infra*. However, it is noted that its relatively high CP coupled with its accessibility only at highly elevated pH may limit its use, especially in biomedical applications.

Given the pH dependent phase behavior of the DMEDA derivative a similar series of experiments were performed for the polyDEEDA (PDEEDA) homopolymer, Figure 2. Consider first the 0.1 M NaOH solution (measured solution pH = 12.4, polymer expected to be fully deprotonated). As with PDMEDA, PDEEDA did exhibit inverse temperature solubility behavior under these conditions with a measured CP of 23.4 °C, some 45 °C lower than the PDMEDA analogue.

Such a large difference in solubility behavior between the dimethyl vs diethyl derivatives is consistent with the significant differences in aqueous solution properties of PDMAEMA vs PDEAEMA. For example, while PDMAEMA does exhibit inverse temperature dependent solution properties, PDEAEMA does not and is only water-soluble in its protonated (or quaternized) state. Importantly, this much lower CP at elevated pH does make PDEEDA a more attractive "smart" building block in advanced applications and represents a new chemical species with a thermal trigger at a more practically accessible temperature. Unlike PDMEDA, PDEEDA does exhibit some hysteresis upon cooling under these conditions, redissolving at 19.7 °C. In 0.1 M HCl (measured solution pH = 1.37), the PDEEDA homopolymer does not exhibit any inverse temperature solubility characteristics, again due to the cationic polyelectrolyte nature of the polymer under these conditions. In pH 7.0 buffer (measured pH = 8.30) the PDEEDA homopolymer also behaves in a manner identical to that of PDMEDA with no observable phase transition over the temperature range analyzed. Apparently, at this pH there is still a sufficient degree of ionization of the tertiary amino residues to eliminate any temperature induced phase behavior.

In contrast to PDMEDA, the PDEEDA homopolymer (measured solution pH = 9.59) does exhibit a CP in DI water, with a sharp transition occurring at 27.9 °C some 4.5 °C higher than for the same polymer at pH 14.0, indicating that the polymer is slightly more hydrophilic under these conditions. As with the buffer solution this difference suggests that at pH 9.59 a small fraction of the tertiary amino residues are still ionized although we have not, at this point, attempted to determine the actual degree of ionization under these conditions. However, such an effect on the CP of water-soluble polymers is known. For example, 5% quaternization, with methyl iodide, of the tertiary amine residues in a PDMAEMA homopolymer has been reported to raise the CP from 39.3 to 52.8 °C,[58] highlighting how even fractional degrees of ionization (whether it be protonation or quaternization) can have a significant effect on the aqueous solution behavior. However, the fact that the CP of PDEEDA is so readily accessible, occurring above ambient temperature but below normothermia (37.0 °C), makes it an attractive building block for the formation of polymeric micelles and vesicles under facile conditions with potential bio/nanomedicine related applications. Finally, we note that the solution exhibits some hysteresis upon cooling with the redissolution temperature being 24.3 °C, a few degrees lower than the measured CP.

While both the DMEDA and DEEDA homopolymers exhibit thermoresponsiveness in aqueous media, albeit under fairly specific conditions, the picolylamine (PA)-modified homopolymer did not exhibit any thermal response in water. However, the PA homopolymer did exhibit a pH dependent solubility. As with other pyridine-containing homopolymers,[59−62] the PA-modified species was only soluble at low pH when the N atom in the pendent pyridyl rings was protonated. During a base titration of the PA homopolymer, the polymer began to phase separate when the solution pH reached ca. 4.0, a value that is close to the literature value for the pK_a of poly(2-vinylpyridine) or poly(4-vinylpyridine) which are typically reported to be in the range of 3.0−5.0 although these values can vary considerably depending on the presence/absence of low molecular weight electrolytes or water-miscible cosolvents for example.[63] This data indicates that the PA modified homopolymer can be employed in advanced synthesis as a pH-responsive building block exhibiting tunable solubility in water.

Synthesis of Novel 2-Vinyl-4,4-dimethylazlactone-Based AB Diblock Copolymers. Having demonstrated that a well-defined VDA homopolymer can be readily converted to materials that exhibit rich and varied "smart" solution behavior in water we expanded our library of reactive parent scaffolds to include AB diblock copolymers in which the comonomers were either *N,N*-dimethylacrylamide (DMA) or *N*-isopropyl-acrylamide (NIPAM). The AB diblock copolymers were prepared as outlined in Scheme 1B in which polyVDA (PVDA) homopolymers were employed as macro-CTAs for the subsequent polymerization of DMA or NIPAM. Four examples were prepared—two with NIPAM as a comonomer and two with DMA, with varying final compositions—in two instances near-equimolar compositions were targeted while in the other two asymmetric block compositions were targeted. In all instances block copolymerization proceeded smoothly with the resulting SEC traces being both unimodal and narrow (see Supporting Information, Figure S10). Table 1 gives a summary of the measured number-average molecular weights ($\bar{M}_n$), dispersities ($Đ_M$) and ^{1}H NMR-determined block copolymer

Table 1. Summary of the SEC-Determined Number Average Molecular Weights ($\bar{M}_n$) and Dispersities ($Đ_M$) and NMR-Determined Copolymer Compositions for the VDA Homopolymers and AB Diblock Copolymers with DMA and NIPAM

entry	sample	$\bar{M}_n{}^a$	$Đ_M{}^a$	composition[b]
1	PVDA1	35 160	1.19	—
2	PVDA1-b-DMA	41 890	1.19	70:30
3	PVDA1-b-NIPAM	54 860	1.13	62:38
4	PVDA2	45 700	1.15	—
5	PVDA2-b-DMA	52 480	1.12	54:46
6	PVDA2-b-NIPAM	73 770	1.11	50:50

[a]As determined by size exclusion chromatography. Molecular weights are reported as polystyrene equivalents. [b]As determined by ^{1}H NMR spectroscopy.

compositions for VDA homopolymers and the series of VDA-DMA and VDA-NIPAM AB diblock copolymers.

Modification and Aqueous Solution Properties of DMA and NIPAM-Based AB Diblock Copolymers. The VDA residues in each of the four AB diblock copolymers were reacted with DMEDA, DEEDA and PA in the presence of MMTS to give a new series of 12 functional AB diblock copolymers, Table 2. Successful conversion of the precursors to the target functional block copolymers was confirmed using a combination of FTIR and NMR spectroscopies (see Supporting Information, Figures S11−S21). In the case of DMA-based block copolymers the new series (formally DMEDA$_x$-b-DMA$_y$, DEEDA$_x$-b-DMA$_y$ and PA$_x$-b-DMA$_y$ where x and y are the molar fractional incorporation of each block) represent amphiphilic block copolymers in which the permanently hydrophilic DMA block is bound to tunably hydrophilic/hydrophobic species. As such they have the potential to

undergo temperature and pH induced assembly in aqueous media giving nanoparticles with stabilizing hydrophilic DMA coronas and tunable hydrophobic cores containing DMEDA, DEEDA, or PA units. In the case of the DMEDA$_x$-b-NIPAM$_y$, DEEDA$_x$-b-NIPAM$_y$, and PA$_x$-b-NIPAM$_y$ materials there is an added level of complexity with the potential for some materials to exhibit "schizophrenic" behavior. In aqueous media such materials have the potential to form normal and inverse self-assembled nanostructures in the same environment simply by tuning the applied stimulus. While such species are known,[41,64−67] they are far less documented than the more traditional amphiphilic or tunably amphiphilic species.

Consider first the AB diblock copolymers containing DMA as a permanently hydrophilic block with a near-equimolar ratio of comonomers (functional DMEDA, DEEDA, and PA derivatives derived from PVDA2, entries 7−9, Table 2). Since DMA is permanently hydrophilic, self-assembly in aqueous media can be induced by exploiting the thermal responsive properties of the DMEDA- and DEEDA-functional blocks and the pH-responsive nature of the PA building block. Block copolymers were first analyzed by DLS. Figure 3 shows the number-average DLS size distributions for the DMA$_{46}$-DMEDA/DEEDA/PA$_{54}$ AB diblock copolymers under conditions where unimers are expected (all block species are hydrophilic) and under conditions where aggregation is expected. Each of the three AB diblock copolymers was initially dissolved in aqueous media under slightly different conditions—those conditions being determined by the earlier thermo- and pH-responsive studies for the functional homopolymers. Under the specified conditions all the block copolymers exist as single molecularly dissolved chains (unimers), with measured hydrodynamic diameters (D_h) in the range 5.9−10.4 nm and corresponding polydispersity values (μ_2/Γ^2) in the range 0.218−0.767.

Table 2. Summary of the Number Average Molecular Weights ($\bar{M}_n$) and Dispersities ($Đ_M$), As Determined by SEC, for the Series of NIPAM, DMA, and PA-Based Stimulus Responsive AB Diblock Copolymers and the Unimer and Aggregate Hydrodynamic Diameters (D_h) As Determined by DLS

entry	sample	$\bar{M}_n{}^a$	$Đ_M{}^a$	solution conditions, unimer hydrodynamic diameter and polydispersity (μ_2/Γ^2)[b]	solution conditions, aggregate hydrodynamic diameter and polydispersity (μ_2/Γ^2)[b]
1	P(DMEDA1$_{70}$-b-DMA$_{30}$)			0.1 M NaOH 10 °C, 8.9 nm, 0.162	0.1 M NaOH 85 °C, 85.6 nm, 0.181
2	P(DEEDA1$_{70}$-b-DMA$_{30}$)	13 280	1.07	0.1 M NaOH 10 °C, 10.3 nm, 0.097	0.1 M NaOH 30 °C, 58.4 nm, 0.0006
				DI water, 10 °C, 4.7 nm, 0.529	DI water 30 °C, 220.0 nm, 0.096
3	P(PA1$_{60}$-b-DMA$_{40}$)	61 200	1.06	0.1 M HCl 25 °C, 6.4 nm, 0.140	pH 7.0 solution 25 °C, 72.5 nm, 0.118
4	P(DMEDA1$_{62}$-b-NIPAM$_{38}$)	30 000	1.06	0.1 M HCl 10 °C, 7.9 nm, 0.373	0.1 M HCl 40 °C, 225.8 nm, 0.140
				DI water, 10 °C, 5.2 nm, 0.157	DI water 50 °C, 149.6 nm, 0.099
5	P(DEEDA1$_{62}$-b-NIPAM$_{38}$)	30 950	1.04	0.1 M HCl 10 °C, 7.6 nm, 0.419	0.1 M HCl 40 °C, 201.9 nm, 0.146
				0.1 M NaOH 10 °C, 10.8 nm, 0.091	0.1 M NaOH 30 °C, 2270 nm, 0.024
6	P(PA1$_{62}$-b-NIPAM$_{38}$)	69 580	1.13	0.1 M HCl 10 °C, 7.0 nm, 0.217	0.1 M HCl 50 °C, 41.6 nm, 0.191
					pH 7.0 solution 25 °C, 57.2 nm, 0.037
7	P(DMEDA2$_{54}$-b-DMA$_{46}$)	27 330	1.19	0.1 M NaOH 10 °C, 10.4 nm, 0.767	0.1 M NaOH 85 °C, 66.5 nm, 0.002
8	P(DEEDA2$_{54}$-b-DMA$_{46}$)	37 060	1.12	0.1 M NaOH 10 °C, 9.3 nm, 0.217	0.1 M NaOH 30 °C, 55.4 nm, 0.028
				DI water, 10 °C, 5.9 nm, 0.582	DI water, 50 °C, 79.8 nm, 0.147
9	P(PA2$_{54}$-b-DMA$_{46}$)	80 150	1.16	0.1 M HCl 25 °C, 8.5 nm, 0.218	pH 7.0 solution 25 °C, 45.2 nm, 0.068
10	P(DMEDA2$_{50}$-b-NIPAM$_{50}$)	58 340	1.11	0.1 M HCl 10 °C, 9.5 nm, 0.245	0.1 M HCl 60 °C, 48.3 nm, 0.239
				DI water, 10 °C, 8.2 nm, 0.446	DI water, 60 °C, 51.3 nm, 0.128
11	P(DEEDA2$_{50}$-b-NIPAM$_{50}$)	68 490	1.14	0.1 M HCl 25 °C, 8.6 nm, 0.286	0.1 M HCl 60 °C, 54.0 nm, 0.233
				0.1 M NaOH 10 °C, 11.6 nm, 0.330	0.1 M NaOH 30 °C, 2840 nm, 0.102
12	P(PA2$_{50}$-b-NIPAM$_{50}$)	96 490	1.20	0.1 M HCl 25 °C, 9.9 nm, 0.296	0.1 M HCl 60 °C, 49.8 nm 0.243
					pH 7.0 solution 25 °C, 58.5 nm, 0.015

[a]As determined by size exclusion chromatography. Molecular weights are reported as polystyrene equivalents. [b]As determined by dynamic light scattering.
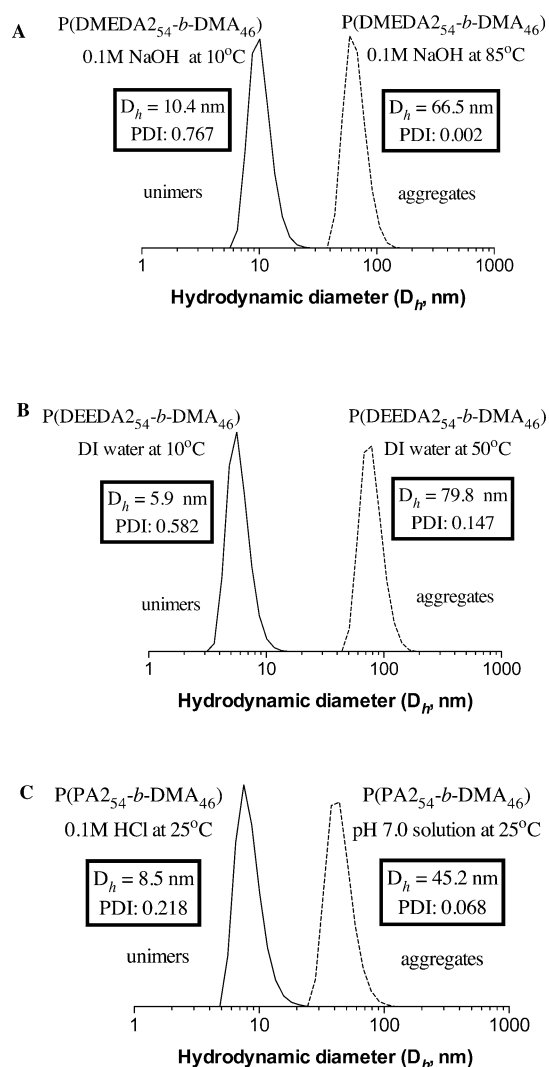
Figure 3. Number-average size distributions for near-equimolar DMA-based copolymers with DMEDA, DEEDA, and PA comonomers. Measurements were made at a concentration of 1 wt % (10 mg/mL) and a scattering angle of 173°. Data was processed via CUMULANTS analysis.

When the P(DMEDA2$_{54}$-b-DMA$_{46}$) copolymer is heated to 85 °C in 0.1 M NaOH, the conditions under which the DMEDA block becomes hydrophobic, we observe a sharp increase in the D_h to 66.5 nm (μ_2/Γ^2 = 0.002), which is indicative of self-assembly (Figure 3A). For P(DEEDA2$_{54}$-b-DMA$_{46}$) there are two different sets of solution conditions that can be exploited to induce self-assembly given the previously established behavior of the DEEDA homopolymer in aqueous media. Figure 3B shows the number-average size distributions for P(DEEDA2$_{54}$-b-DMA$_{46}$) in DI water at 10 and 50 °C. At the lower temperature the block copolymer exists as unimers with a measured D_h of 5.9 nm. In contrast, at 50 °C, above the CP of the DEEDA block in DI water, we observe species with a D_h of 79.8 nm (μ_2/Γ^2 = 0.147). The same block copolymer was also examined in 0.1 M NaOH at 10 and 30 °C, Table 2, entry 8. Consistent with experiments in DI water, at the lower temperature hydrodynamic sizes consistent with unimers, although are somewhat larger than those measured in DI water, are seen while at 30 °C aggregates with a D_h of 55.4 nm (μ_2/Γ^2 of 0.028) are observed. Finally, in the case of the

P(PA2$_{54}$-b-DMA$_{46}$) block copolymer, self-assembly can be induced by taking advantage of the pH-responsive properties of the PA block. Under acidic conditions at 25 °C, the block copolymer is fully hydrophilic and D_h values of 8.5 nm, consistent with unimers, are observed, Table 2, entry 9. Raising the solution pH to 7.0 at 25 °C, conditions under which the PA block becomes deprotonated and hydrophobic, results in self-assembly and the formation of aggregates with a measured D_h of 45.2 nm (μ_2/Γ^2 = 0.068) (Figure 3C). Similar results are observed for the remaining series of AB diblock copolymers and the data is fully summarized in Table 2. However, two additional important features are worth noting about these systems. First, the aggregation behavior for this series of "smart" block copolymers, such as that highlighted above for the DMA-based materials is fully reversible and cyclable. For example, Figure 4 shows the measured change in D_h, as determined by
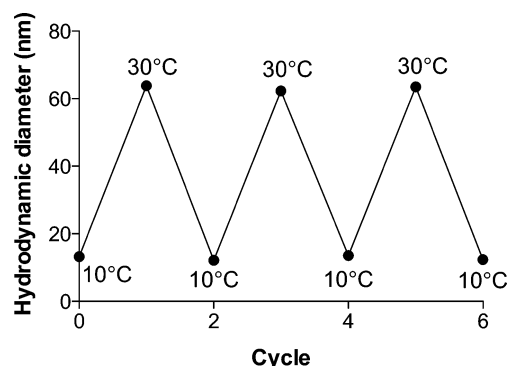

Figure 4. Change in hydrodynamic diameter in aqueous media as a function of heating and cooling cycles for the P(DEEDA2$_{54}$-b-DMA$_{46}$) AB diblock copolymer.

DLS, for the P(DEEDA2$_{54}$-b-DMA$_{46}$) block copolymer dissolved in 0.1 M NaOH when subjected to heating and cooling cycles between 10 and 30 °C. At all measurements at 10 °C the measured D_h values are slightly above 10.0 nm while at 30 °C the D_h vales are consistently measured to be just above 60.0 nm.

As noted above, select examples of these new functional block copolymers are doubly responsive and should be capable of forming normal and inverse micelles in the same solution—which is formed is dictated solely by the nature of the applied stimulus. Of particular importance here are the block copolymers of PA with NIPAM (Table 2 entries 6 and 12). In these AB diblocks the PA residues are pH responsive while the NIPAM repeat units are thermoresponsive. As such, under appropriate conditions it is possible to induce self-assembly with PA *or* NIPAM in the core of the soft nanoparticles stabilized by the other block in the aggregate corona. For example, consider the P(PA2$_{50}$-b-NIPAM$_{50}$) copolymer, Table 2, entry 12. This block copolymer exists as unimers in 0.1 M HCl at 25 °C. Under these conditions the PA residues are protonated rendering the block hydrophilic while the temperature is below the CP of the NIPAM block and as such it is also hydrophilic. Simply heating this solution above the CP of the NIPAM block, to 60 °C in this instance, results in the formation of aggregates with NIPAM in the core stabilized by a protonated PA shell to give species with a DLS-measured D_h of 49.8 nm (μ_2/Γ^2 = 0.243). These can be considered as the "normal" micelles. Alternatively, the pH of the parent AB diblock copolymer solution (0.1 M HCl, 25 °C) can be
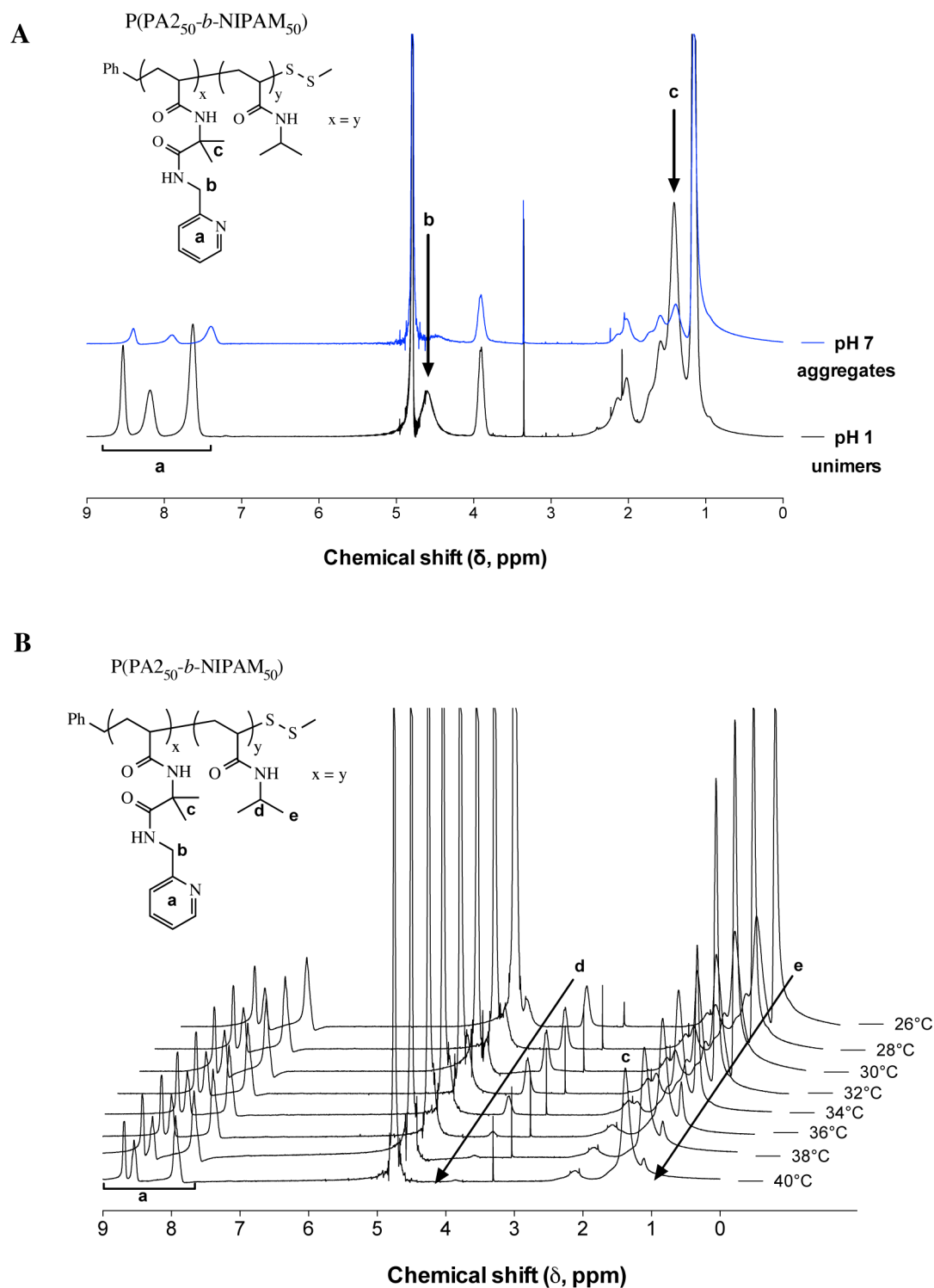
Figure 5. ^{1}H NMR spectra, recorded in D$_2$O, of P(PA2$_{50}$-b-NIPAM$_{50}$) at pH 1 and pH 7 highlighting the desolvation of the PA block upon the change in pH (A) and a series of ^{1}H NMR spectra of the same block copolymer (B), recorded in DCl/D$_2$O, with the sample being heated from 26 to 40 °C highlighting the desolvation of the NIPAM residues.

adjusted to 7.0 to induce self-assembly giving the "inverse" micelles. Under these conditions, the PA block becomes hydrophobic and is expected to form the aggregate core while the NIPAM block remains hydrophilic and would form the stabilizing corona. Under such conditions, aggregates with a D_h of 58.5 nm ($\mu_2/\Gamma^2 = 0.015$) were observed. Similar behavior was observed for the P(PA1$_{60}$-b-NIPAM$_{40}$) block copolymer

with a slightly asymmetric copolymer composition, Table 2 entry 6.

While DLS is a powerful technique for characterizing polymeric aggregates we assume the formed assemblies have the expected core−shell structure based on our knowledge of the 'smart' aqueous solution properties of the polymeric building blocks. NMR spectroscopy is a convenient technique for verifying which particular block is becoming desolvated/

hydrophobic under a given set of solution conditions and aids in confirming the assumed structure.[68,69] For example, in the $P(PA2_{50}\text{-}b\text{-}NIPAM_{50})$ sample discussed above we noted that at pH 1.0 the block copolymer exists as unimers while raising the aqueous solution pH to 7.0 results in the formation of aggregates and this was attributed to the deprotonation of the PA residues (rendering it hydrophobic) followed by assembly to give aggregates with PA cores and a PNIPAM shell. Figure 5A shows the ^{1}H NMR spectra for the same block copolymer, recorded in D_2O, at pH 1.0 and 7.0. At low pH we observe resonances associated with both building blocks, with those attributed to the PA block being particularly distinct. However, at pH 7.0 these signals (those labeled **a**, **b**, and **c** being the most obvious) decrease significantly in intensity and also broaden (although do not completely disappear) while those associated with the PNIPAM block are unaffected. These features are entirely consistent with the desolvation, and resulting associated restricted mobility, of the PA chains under these conditions leading to self-assembly with the PA blocks in the core of the aggregates.

As highlighted above, this particular AB diblock copolymer has the ability to form normal and inverse aggregates in aqueous media simply by tuning the applied stimulus. Temperature-induced self-assembly (exploiting the CP of the NIPAM block) is also readily monitored by NMR spectroscopy. Figure 7B shows a series of ^{1}H NMR spectra, recorded in DCl, of the same block copolymer over the temperature range 26−40 °C. At 26 °C, below the CP of PNIPAM, we see resonances associated with the PA and NIPAM blocks of the copolymer. At 30−32 °C, we begin to observe a decrease in the intensity of the signals associated with the NIPAM block (labeled **d** (the methine H) and **e** (the dimethyl H's)), a decrease that continues up to 40 °C, 8 °C above the CP of PNIPAM, at which point the PNIPAM signals have essentially vanished. Such observations have been made before such as in the DMA-NIPAM AB diblock copolymers reported by Convertine et al.[70] Importantly, under these conditions the signals associated with the PA block (**a** and **c** being the most obvious) do not change, indicating no change in the solvation state of this block with increasing temperature. This is not surprising since under these conditions the PA block is protonated and exists as a cationic polyelectrolyte. These NMR observations imply that under the specified conditions (low pH and $T > \text{LCST}_{\text{PNIPAM}}$) that block copolymer self-assembly proceeds to give aggregates with a hydrophobic PNIPAM core stabilized by a hydrophilic cationic PA corona.

To confirm the assumed spherical morphology, transmission electron microscopy (TEM) was employed to directly image the self-assembled structures. As a representative example, Figure 6 shows examples of TEM images of the $P(PA2_{54}\text{-}b\text{-}DMA_{46})$ diblock copolymer. Figure 6A clearly demonstrates the spherical morphology of the polymeric aggregates, while Figure 6B shows the same sample at double the magnification. Given the scale bar of 100 nm we can estimate the size of the particles to be ca. 40−50 nm. This is in excellent agreement with the D_h as determined by DLS of 45.2 nm.

Core-Cross-Linking and Sequestration Studies of Block Polymer Self-Assemblies. For the majority of these AB diblock copolymers, stimulus induced self-assembly results in the formation of aggregates in which the core contains a "hydrophobic" tertiary-amine bearing species—DMEDA, DEEDA, or PA. The presence of such functionality in the core facilitates core-cross-linking to lock the aggregates in their
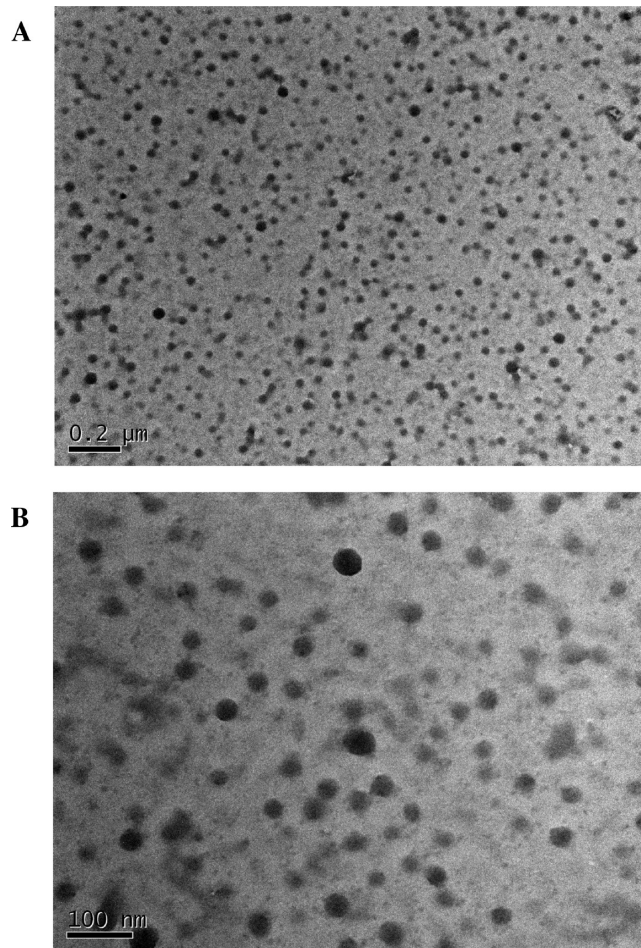
Figure 6. Examples of TEM images for the $P(PA2_{54}\text{-}b\text{-}DMA_{46})$ diblock copolymer demonstrating the spherical morphology of the self-assembled species. Images were taken without prior staining.

self-assembled state. This may be desirable if the aggregates are to be used under highly dilute conditions, i.e., at a concentration below their critical aggregation concentration. The tertiary amine residues allow for core cross-linking via alkylation (quaternization) with a difunctional alkyl halide. To demonstrate that the self-assembled block copolymers described here could likewise be "locked", we conducted a core cross-linking reaction on the $P(DMEDA2_{54}\text{-}b\text{-}DMA_{46})$ copolymer employing 1,10-dibromodecane as a hydrophobic difunctional quaternizing agent at 10 mol % based on tertiary amine residues. Successful core cross-linking was verified via DLS, Figure 7.

As discussed, at 10 °C in 0.1 M NaOH this block copolymer is molecularly dissolved while at 85 °C the copolymer self-assembles to give aggregates with a PDMEDA core and a measured D_h of 66.5 nm. 1,10-Dibromodecane was added to the solution of block copolymer aggregates and since it is hydrophobic was expected to partition into the hydrophobic aggregate cores where reaction with the tertiary amine residues could occur. After reaction overnight, cooling and purification by dialysis, the solution conditions were readjusted to those under which unimers would be expected (10 °C). Under these conditions we observed an *increase* in the D_h from 66.5 to 143.7 nm. This qualitatively confirms successful core cross-linking and locking of the aggregate structures. While the aggregates are not able to disassociate due to the inter/intramolecular
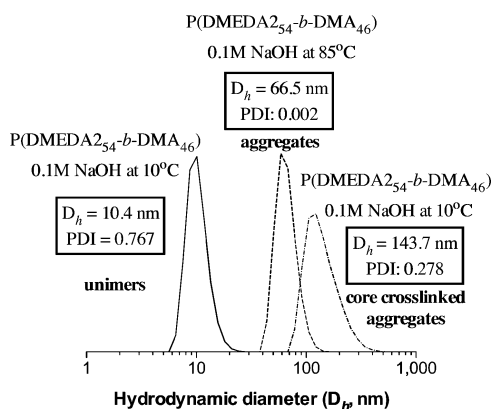
Figure 7. Number-average size distributions for the P(DMEDA2$_{54}$-*b*-DMA$_{46}$) block copolymer in the unimeric and self-assembled states before core cross-linking and the observed increase in D_h after reaction of the DMEDA core repeat units with 1,10-dibromodecane.

quaternization reactions between the DMEDA repeat units, at 10 °C the DMEDA core is hydrophilic (especially since there is now also cationic charge in the core) and becomes solvated. This results in significant swelling of the self-assembled structures and thus the observed increase in D_h.

The ability of AB diblock copolymers to undergo self-assembly in a selective solvent like water is interesting since the resulting aggregates, while dispersed in an aqueous environment, have a hydrophobic core that can be exploited as a "cargo hold" for hydrophobic species such as dyes, fluorescent probes or pharmaceutically active species.[71−73] A straightforward, visual approach for qualitatively demonstrating that sequestration is possible can be accomplished with a hydrophobic stain molecule such as Nile Red as recently demonstrated by Yu and co-workers for poly(ether amine)/POSS hybrid vesicles.[74] We adopted a similar approach here to demonstrate that these stimulus-responsive AB diblock copolymers are likewise able to serve as carriers for potentially interesting hydrophobic small molecules.

Parts A and B of Figures 8 show digital pictures of 2.0 wt % solutions of the P(PA2$_{50}$-*b*-NIPAM$_{50}$) and P(DEEDA2$_{54}$-*b*-DMA$_{46}$) copolymers in the presence of Nile Red, at a concentration of 0.05 mg/mL, under conditions in which the block copolymers exist as unimers (left) and as aggregated species (right). In both instances the sample vials are being irradiated with a light source set at 315 nm. Consider first the P(PA2$_{50}$-*b*-NIPAM$_{50}$) copolymer (Figure 8A). At pH 1.0 the solution is transparent due to the unimeric nature of the copolymer chains with the Nile Red simply dispersed in the aqueous media. In contrast, at pH 7.0 under irradiation, we observe a strong fluorescence with a distinct cyan color. Similar observations are made for the thermoresponsive copolymer P(DEEDA2$_{54}$-*b*-DMA$_{46}$), Figure 8B. In the unimeric state the solution is transparent whereas heating the copolymer/Nile Red solution, followed by irradiation, gives a solution with an intense red color (note—filtering this micellar solution through cotton wool has no effect on the fluorescence whereas filtering of a unimeric solution of the block copolymer/Nile Red removes a substantial amount of the Nile Red). These results qualitatively confirm the successful sequestration of the Nile Red into the hydrophobic interiors of the self-assembled polymeric species. The difference in fluorescence can be attributed to the different core environments within the self-assembled species. Indeed, Nile Red is strongly fluorescent, but
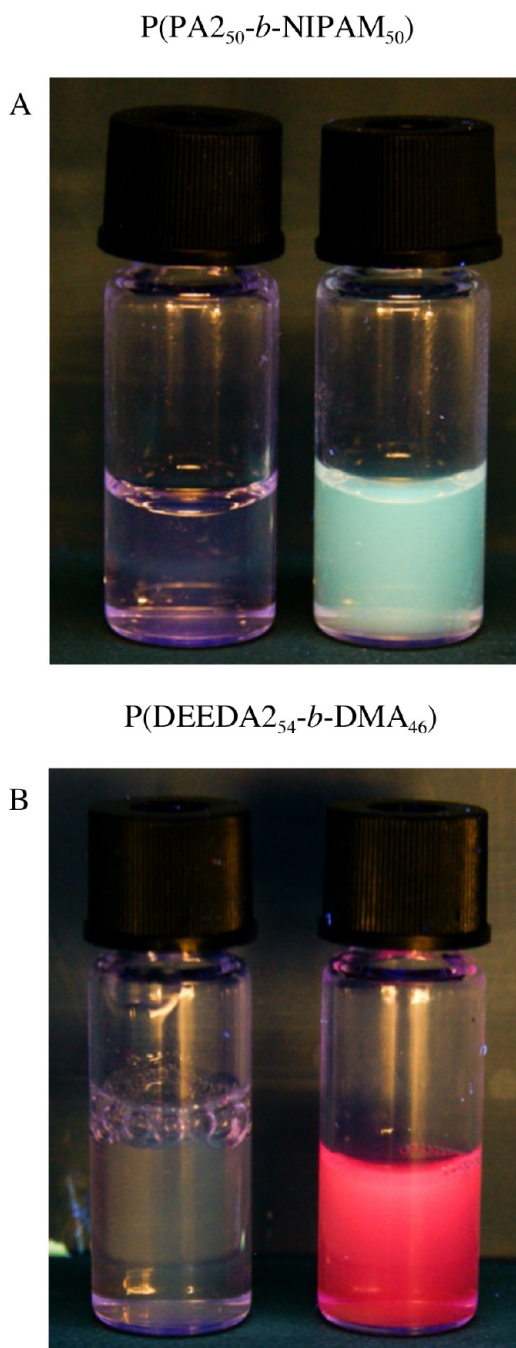
P(PA2$_{50}$-*b*-NIPAM$_{50}$)

P(DEEDA2$_{54}$-*b*-DMA$_{46}$)

Figure 8. Photographs of 2.0 wt % solutions of P(PA2$_{50}$-*b*-NIPAM$_{50}$) (A) and P(DEEDA2$_{54}$-*b*-DMA$_{46}$) (B) in the presence of 0.05 mg/mL Nile Red under conditions where unimers (left) and micelles (right) are expected, qualitatively demonstrating the sequestration of Nile Red. Sample vials are being irradiated with a light source at a wavelength of 315 nm.

very sensitive to its environment, and can emit at a wide variety of wavelengths/colors.

Reaction of Tertiary Amine Containing (Co)Polymers with 1,3-Propanesultone. Finally, we note that it is also possible to further modify DMEDA and DEEDA-based (co)polymers with 1,3-propanesultone to give novel sulfopropylbetaine-based materials.[46,75,76] Such materials are interesting for a variety of reasons including their antipolyelectrolyte behavior in aqueous media, and their established biocompatibility and antifouling properties.[77,78] As an example, the

PDMEDA homopolymer was treated with 1,3-propane sultone to give the corresponding polysulfopropylbetaine (see Supporting Information, Scheme S1). Such ring-opening alkylation (or quaternization) reactions are facile, especially for dimethylamino derivatives,[76] and generally give quantitative formation of the sulfopropylbetaine products. Successful betaine formation was verified by ^{1}H NMR spectroscopy (see Supporting Information, Figure S38, recorded in D_2O for the PDMEDA homopolymer and in D_2O/NaCl for the corresponding sulfopropylbetaine derivative). Such facile functionalization could, of course, be readily extended to DMEDA or DEEDA block copolymers to generate a further series of zwitterionic functional materials.

CONCLUSIONS

Herein we have described the synthesis and aqueous solution properties of novel thermo- and pH-responsive (co)polymers based on the reactive building block 2-vinyl-4,4-dimethylazlactone (VDA). Modification of polyVDA (PVDA) homopolymers with *N,N*-dimethylethylenediamine (DMEDA), and *N,N*-diethylethylenediamine (DEEDA) yields novel functional polymers that exhibit inverse temperature dependent aqueous solubility with measured cloud points in the range ca. 25−85 °C. Modification with picolylamine (PA) gives species with a pH-dependent solubility. The synthesis of VDA-based AB diblock copolymers with *N*-isopropylacrylamide (NIPAM) or *N,N*-dimethylacrylamide (DMA) gives precursor copolymers that when modified with DMEDA, DEEDA or PA yields a new series of "smart" AB diblock copolymers capable of stimulus-induced self-assembly. This includes examples of so-called schizophrenic AB diblocks capable of forming normal and inverse micelles. We have demonstrated, via a combination of ^{1}H NMR spectroscopy, dynamic light scattering and transmission electron microscopy that self-assembly yields spherical micelle-like structures. Cross-linking of the aggregate cores as well as the sequestration abilities of the nanoassemblies was also demonstrated. Finally, we highlighted how the presence of tertiary amine functionality facilitates further chemical modification in a reaction with 1,3-propanesultone to give a sulfopropylbetaine derivative.

ASSOCIATED CONTENT

S Supporting Information

NMR results for a BPTC RAFT agent, a VDA homopolymer and its modified derivatives, DMA/NIPAM to VDA diblock copolymers, and DMA/NIPAM to VDA-modified derivatives, FTIR results for VDA homopolymer and their modified derivatives, and DLS results for DMA/NIPAM to VDA-modified derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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