

## Synthesis of Well-Defined Pyrrolidone-Based Homopolymers and Stimulus-Responsive Diblock Copolymers via RAFT Aqueous Solution Polymerization of 2-(*N*-Acryloyloxy)ethylpyrrolidone

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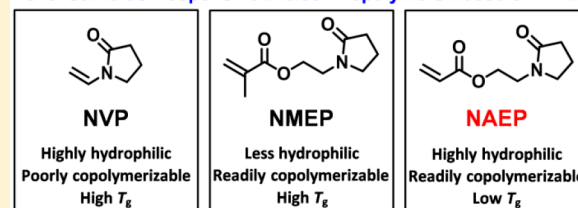
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### Supporting Information

**ABSTRACT:** Poly(*N*-vinylpyrrolidone) (PNVP) is a well-known, highly polar, nonionic water-soluble polymer. However, *N*-vinylpyrrolidone (NVP) usually exhibits strongly non-ideal behavior when copolymerized with methacrylic or styrenic monomers. Moreover, NVP is not particularly well-controlled under living radical polymerization conditions. For these reasons, alternative pyrrolidone-based monomers have been investigated. For example, the reversible addition–fragmentation chain transfer (RAFT) polymerization of 2-(*N*-methacryloyloxy)ethylpyrrolidone (NMEP) has been recently investigated using various polymerization formulations. However, PNMEP homopolymers are significantly less hydrophilic than PNVP and exhibit inverse temperature solubility in aqueous solution. In the present work, we studied the RAFT aqueous solution polymerization of 2-(*N*-acryloyloxy)ethylpyrrolidone (NAEP) using either AIBN at 70 °C or a low-temperature redox initiator at 30 °C. PNAEP homopolymers are obtained in high yield (>99%) with good control ( $M_w/M_n < 1.20$ ) for target degrees of polymerization (DP) of up to 400 using the latter initiator, which produced relatively fast rates of polymerization. However, targeting DPs above 400 led to lower NAEP conversions and broader molecular weight distributions. 2-Hydroxyethyl acrylate (HEA) and oligo(ethylene glycol) methyl ether acrylate (OEGA) were chain-extended using a PNAEP<sub>x</sub> macro-CTA via RAFT aqueous solution polymerization, yielding double-hydrophilic acrylic diblock copolymers with high conversions (>99%) and good control ( $M_w/M_n < 1.31$ ). In addition, a PNAEP<sub>95</sub> macro-CTA was chain-extended via RAFT aqueous solution polymerization of *N*-isopropylacrylamide (NIPAM) at 22 °C. Dynamic light scattering (DLS) analysis indicated that heating above the lower critical solution temperature of PNIPAM led to so-called “anomalous micellization” at 35 °C and the formation of near-monodisperse spherical micelles at 40 °C. Finally, 2-(diethylamino)ethyl methacrylate (DEA) was polymerized using an *N*-morpholine-functionalized trithiocarbonate-based RAFT chain transfer agent and subsequently chain-extended using NAEP to form a novel pH-responsive diblock copolymer. Above the p*K*<sub>a</sub> of PDEA (~7.3), DLS and <sup>1</sup>H NMR studies indicated the formation of well-defined PDEA-core spherical micelles.

### Novel Stimulus-Responsive Diblock Copolymers Based on NAEP



## INTRODUCTION

Poly(*N*-vinylpyrrolidone) (PNVP) is a commercially important nonionic water-soluble polymer with a wide range of commercial applications.<sup>1,2</sup> Its high dipole moment (4.06 D)<sup>3</sup> enables the efficient sequestration of many fugitive dyes and hence its widespread use as an anti-dye transfer agent in laundry formulations.<sup>4,5</sup> PNVP can also be utilized as a film-forming agent in hair sprays<sup>6</sup> and various cosmetics, and its excellent biocompatibility and relatively low cost account for its use as an excipient in drug formulations.<sup>6,7</sup> Bulk copolymerization with other vinyl monomers enables the production of soft contact lenses<sup>8</sup> while so-called “popcorn” polymerization of *N*-vinylpyrrolidone (NVP) produces cross-linked particles that can be used to clarify alcoholic beverages such as beer and wine.<sup>9</sup> PNVP can also be used as an emulsifier,<sup>10</sup> a dispersant for  $\beta$ -carotene,<sup>11</sup> or a steric stabilizer for the preparation of conducting polymer nanoparticles.<sup>12</sup>

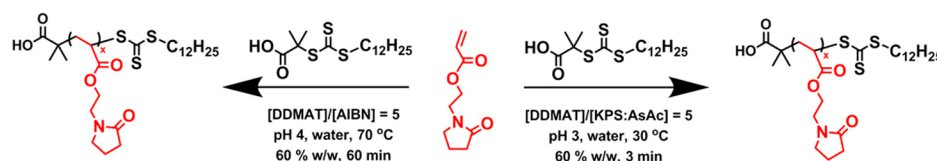
NVP is an example of a less activated monomer (LAM). As such, it can be readily statistically copolymerized with comonomers such as vinyl acetate or acrylics. However, its copolymerization with methacrylics or styrene is more problematic, with strongly non-ideal behavior typically being observed.<sup>13–15</sup> There are a number of literature reports of the reversible addition–fragmentation chain transfer (RAFT) polymerization of NVP using xanthates or dithiocarbamates.<sup>16–18</sup> However, control is usually inferior to that achieved for (meth)acrylic monomers under optimized conditions, particularly for polymerizations performed in aqueous solution.<sup>19–25</sup> For example, Guinaudeau et al. reported the successful RAFT/MADIX aqueous polymer-

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**Scheme 1. Synthesis of PNAEP Homopolymers by RAFT Aqueous Solution Polymerization of 2-(*N*-Acryloyloxy)ethylpyrrolidone (NAEP) Utilizing a Trithiocarbonate-Based RAFT Agent (DDMAT) and Either  $\alpha,\alpha'$ -Azobisisobutyronitrile (AIBN) or a Low-Temperature Redox Initiator System Based on a 1:1 Molar Ratio of Potassium Persulfate (KPS) and Ascorbic Acid (AsAc)**



ization of PNVP-based double-hydrophilic diblock copolymers by employing redox initiation at ambient temperature.<sup>26,27</sup> Using ascorbic acid led to the formation of *N*-( $\alpha$ -hydroxyethyl)pyrrolidone in acidic solution, but switching to sodium sulfite under mildly alkaline conditions (pH 9) prevented generation of this unwanted side product. Under the latter optimized conditions, relatively good control was achieved for the RAFT homopolymerization of NVP ( $M_w/M_n < 1.20$ ). However, a self-blocking chain extension experiment led to a final  $M_w/M_n$  of 1.72, which suggests imperfect control. Nevertheless, the synthesis of PNVP-based double-hydrophilic diblock copolymers was achieved by preparing the other hydrophilic block first, followed by NVP polymerization.

Notwithstanding these advances in the controlled polymerization of NVP, a methacrylic analogue (2-(*N*-methacryloyloxy)ethylpyrrolidone, NMEP) has been recently examined to address the copolymerizability problem. The latter monomer has been polymerized with good control using RAFT polymerization by Cunningham and co-workers.<sup>28–30</sup> Poly(2-(*N*-methacryloyloxy)ethylpyrrolidone (PNMEP) was subsequently used as a steric stabilizer block for the synthesis of diblock copolymer nano-objects via RAFT dispersion polymerization of benzyl methacrylate in ethanol<sup>28</sup> and also employed as a core-forming block for RAFT dispersion polymerization formulations conducted in *n*-dodecane.<sup>30</sup> However, PNMEP is significantly less hydrophilic than PNVP, exhibiting inverse temperature solubility in aqueous solution at around 55 °C in the high molecular weight limit.<sup>31,32</sup> Indeed, this property was exploited by Cunningham and co-workers to devise a RAFT aqueous dispersion polymerization formulation in which the growing PNMEP chains formed the hydrated cores of sterically stabilized nanoparticles at 70 °C.<sup>29</sup> In view of such observations, PNMEP was considered to be unsuitable for use as a *stabilizer* block for either RAFT aqueous emulsion polymerization or RAFT aqueous dispersion polymerization because it did not confer sufficient steric stabilization. Given this restriction, a more hydrophilic analogue of NVP was sought, with one obvious candidate being 2-(*N*-acryloyloxy)ethylpyrrolidone (NAEP).

As far as we are aware, there has only been one report of the controlled polymerization of NAEP.<sup>33</sup> In 2009, Shi et al. reported the RAFT aqueous solution homopolymerization of NAEP using visible light irradiation at 25 °C. Good control over the molecular weight distribution was demonstrated ( $M_w/M_n < 1.10$ ), but apparently NAEP conversions did not exceed 77%. Herein we report the efficient synthesis of a series of near-monodisperse homopolymers via RAFT aqueous solution polymerization of NAEP using either a persulfate initiator at 30 °C or an azo initiator at 70 °C (see Scheme 1). Optimized reaction conditions were then employed to prepare a series of new low-dispersity PNAEP-based diblock copolymers in excellent yield and with high blocking efficiencies. The

aqueous solution properties of some of these copolymers have been briefly explored.

## EXPERIMENTAL SECTION

**Materials.** 2-(*N*-Acryloyloxy)ethylpyrrolidone (NAEP; 95% purity) was kindly provided by Ashland Specialty Ingredients (Cherry Hill, NJ, USA) and was further purified through dilution with chloroform followed by sequential washes with 5% Na<sub>2</sub>CO<sub>3</sub> solution, saturated NaCl solution, and finally deionized water. Repeated washes with water were performed until the NAEP solution was neutralized. This solution was then dried over anhydrous MgSO<sub>4</sub>. All chemicals used for NAEP purification were purchased from Sigma-Aldrich (Dorset, UK) and were used as received. 2-Hydroxyethyl acrylate (HEA) was purchased from Sigma-Aldrich (Dorset, UK) and purified via 20 washes with *n*-hexane. Oligo(ethylene glycol) methyl ether acrylate (OEGA,  $M_n \approx 454 \text{ g mol}^{-1}$ ), 2-(diethylamino)ethyl methacrylate (DEA), ascorbic acid (AsAc), potassium persulfate (KPS),  $\alpha,\alpha'$ -azobisisobutyronitrile (AIBN), 4,4'-azobis(4-cyanopentanoic acid) (ACVA; 99%), and 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT; 98%) were purchased from Sigma-Aldrich (Dorset, UK) and used as received. *N*-Isopropylacrylamide (NIPAM; 97%) was purchased from Sigma-Aldrich (Dorset, UK) and recrystallized from *n*-hexane twice before use. 4-Cyano-4-(2-phenylethanesulfanylthiocarbonyl)sulfanylpentanoic acid (PETTC) was prepared and purified as reported elsewhere.<sup>34</sup> MPETTC was then prepared from PETTC using a literature protocol.<sup>35</sup> *d*<sub>4</sub>-Methanol and D<sub>2</sub>O were purchased from Goss Scientific Instruments Ltd. (Cheshire, UK). All other solvents were purchased from Fisher Scientific (Loughborough, UK) and used as received. Deionized water was used for all experiments.

**RAFT Solution Homopolymerization of NAEP in Water at 70 °C.** A typical protocol for the synthesis of a PNAEP<sub>80</sub> homopolymer was as follows: NAEP (1.00 g, 5.46 mmol), DDMAT RAFT agent (24.9 mg, 68.2  $\mu\text{mol}$ ; target DP = 80), deionized water (0.6847 g, corresponding to a 60% w/w solution), and AIBN (2.2 mg, 13.6  $\mu\text{mol}$ ; DDMAT/AIBN molar ratio = 5.0) were weighed into a 14 mL vial charged with a magnetic flea. This reaction vial was then placed in an ice bath and degassed with nitrogen for 30 min. Following this, the vial was then immersed in an oil bath set at 70 °C, and the reaction solution was stirred for 50 min, resulting in a final monomer conversion of 99% as judged by <sup>1</sup>H NMR spectroscopy. DMF GPC analysis indicated an  $M_n$  of 13300 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.14.

**RAFT Solution Homopolymerization of NAEP in Water at 30 °C.** A typical protocol for the synthesis of a PNAEP<sub>80</sub> homopolymer was as follows: NAEP (1.00 g, 5.46 mmol), DDMAT RAFT agent (24.9 mg, 68.2  $\mu\text{mol}$ ; target DP = 80), and AsAc (2.4 mg, 13.6  $\mu\text{mol}$ ) were weighed into a 14 mL vial charged with a magnetic flea and degassed with nitrogen in an ice bath for 30 min (reaction solution 1). Deionized water (0.6873 g, corresponding to a 60% w/w solution) and KPS (3.7 mg, 13.6  $\mu\text{mol}$ ; DDMAT/KPS molar ratio = 5.0) were weighed into a separate 14 mL vial (reaction solution 2), sealed using a rubber septum and degassed with nitrogen in an ice bath for 30 min. After 30 min, the vial containing reaction solution 1 was immersed in an oil bath set at 30 °C. Following this, reaction solution 2 was added to this vial via a degassed syringe and needle to reaction solution 1 under nitrogen. The polymerization was monitored for 5 min, resulting in a final monomer conversion of 99% as judged by <sup>1</sup>H NMR

spectroscopy. DMF GPC analysis indicated an  $M_n$  of 12300 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.15. Targeting mean DPs above 150 required reaction times of up to 60 min for high conversion.

**Preparation of PNAEP<sub>x</sub> Macro-CTA.** The typical protocol for the synthesis of a PNAEP<sub>62</sub> macro-CTA by RAFT aqueous solution polymerization was as follows: NAEP (10.00 g, 54.6 mmol), DDMAT RAFT agent (199.0 mg, 0.5458 mmol; target DP = 100), and AsAc (1.0 mg, 5.5 μmol) were weighed into a 14 mL vial charged with a magnetic flea (reaction solution 1). This reaction solution was then placed in an ice bath and degassed with nitrogen for 30 min. Deionized water (6.8010 g, 60% w/w) and KPS (1.5 mg, 5.5 μmol; DDMAT/KPS molar ratio = 100) were weighed into a second 14 mL vial (reaction solution 2) and degassed with nitrogen in an ice bath for 30 min. After 30 min, the vial containing reaction solution 1 was immersed in an oil bath set at 30 °C. Reaction solution 2 was then added via a degassed syringe and needle to reaction solution 1 under nitrogen. The polymerization was allowed to proceed for 8 min before being quenched via exposure to air and immersed in an ice bath. <sup>1</sup>H NMR analysis of the disappearance of vinyl signals at 5.9 and 6.4 ppm relative to the integrated four ethyl protons at 3.4–3.8 ppm assigned to PNAEP indicated a monomer conversion of 60%. The crude homopolymer was purified by precipitating into a 10-fold excess of diethyl ether. This purification protocol was repeated twice to give a PNAEP macro-CTA containing <1% residual monomer. Its mean degree of polymerization was calculated to be 62 as judged by <sup>1</sup>H NMR spectroscopy (comparison of the integral at 3.4–3.8 ppm (m, 4H) with that assigned to the methyl RAFT chain end at 0.86–0.96 ppm (t, 3H)). DMF GPC analysis indicated an  $M_n$  of 9800 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.25. Other PNAEP<sub>x</sub> homopolymers were obtained by adjusting the NAEP/DDMAT molar ratio.

**Synthesis of PNAEP<sub>62</sub>-PHEA<sub>x</sub> Diblock Copolymers via RAFT Aqueous Solution Polymerization of HEA at 30 °C.** A typical protocol used for the synthesis of the PNAEP<sub>62</sub>-PHEA<sub>100</sub> diblock copolymer was as follows: PNAEP<sub>62</sub> macro-CTA (0.250 g, 21.3 μmol), HEA (0.2476 g, 2.1324 mmol; target DP = 100), and AsAc (0.8 mg, 4.3 μmol) were weighed into a 14 mL vial charged with a magnetic flea (reaction solution 1). This vial was immersed in an ice bath, and the solution was degassed with nitrogen for 30 min. Deionized water (2.2306 g, corresponding to a 15% w/w solution) and KPS (1.2 mg, 4.3 μmol; PNAEP<sub>62</sub> macro-CTA/KPS molar ratio = 5.0) were weighed into a separate 14 mL vial (reaction solution 2) and degassed with nitrogen in an ice bath for 30 min. Reaction solution 1 was then immersed in an oil bath set at 30 °C. Reaction solution 2 was added to this vial via a degassed syringe and needle under nitrogen. The polymerization was allowed to proceed for 18 h before being quenched by exposing the reaction solution to air and immersing the reaction vial in an ice bath. <sup>1</sup>H NMR studies indicated more than 99% conversion while DMF GPC analysis indicated a  $M_n$  of 29400 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.22. Other diblock copolymer compositions were obtained by adjusting the HEA/PNAEP<sub>62</sub> molar ratio to target PHEA DPs of 50 to 400.

**Synthesis of PNAEP<sub>71</sub>-POEGA<sub>x</sub> Diblock Copolymers via RAFT Aqueous Solution Polymerization of OEGA at 30 °C.** A typical protocol used for the synthesis of the PNAEP<sub>71</sub>-POEGA<sub>40</sub> diblock copolymer was as follows: PNAEP<sub>71</sub> macro-CTA (0.250 g, 21.3 μmol), OEGA (0.3872 g, 853 μmol; target DP = 40), and AsAc (0.8 mg, 4.3 μmol) were weighed into a 14 mL vial charged with a magnetic flea (reaction solution 1). This vial was placed in an ice bath, and the solution was degassed with nitrogen for 30 min. Deionized water (2.3066 g, corresponding to a 20% w/w solution) and KPS (1.2 mg, 4.3 μmol; PNAEP<sub>71</sub> macro-CTA/KPS molar ratio = 5.0) were weighed into a separate 14 mL vial (reaction solution 2) and degassed with nitrogen using an ice bath for 30 min. Reaction solution 1 was immersed in an oil bath set at 30 °C. Reaction solution 2 was then added to this vial via a degassed syringe and needle under nitrogen. <sup>1</sup>H NMR studies indicated more than 99% conversion while DMF GPC analysis indicated an  $M_n$  of 20400 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.27. Other diblock copolymer compositions were obtained by adjusting the OEGA/PNAEP<sub>71</sub> macro-CTA molar ratio to give target POEGA DPs ranging from 50 to 400.

**Synthesis of PNAEP<sub>95</sub>-PNIPAM<sub>x</sub> Diblock Copolymers via RAFT Aqueous Solution Polymerization of NIPAM at 22 °C Using a PNEAP<sub>95</sub> Macro-CTA.** A typical protocol used for the synthesis of the PNAEP<sub>95</sub>-PNIPAM<sub>100</sub> diblock copolymer was as follows: PNAEP<sub>95</sub> macro-CTA (0.250 g, 14.1 μmol), NIPAM (0.159 g, 141 μmol; target DP = 100), and AsAc (0.50 mg, 2.8 μmol) were weighed into a 14 mL vial charged with a magnetic flea (reaction solution 1). This vial was placed in an ice bath, and the solution was degassed with nitrogen for 30 min. Deionized water (1.6393 g, corresponding to a 20% w/w solution) and KPS (0.76 mg, 2.8 μmol; PNAEP<sub>95</sub> macro-CTA/KPS molar ratio = 5.0) were weighed into a separate 14 mL vial (reaction solution 2) and degassed with nitrogen using an ice bath for 30 min. Reaction solution 1 was immersed in an oil bath set at 22 °C. Reaction solution 2 was then added to this vial via a degassed syringe and needle under nitrogen. <sup>1</sup>H NMR studies indicated more than 99% conversion while DMF GPC analysis yielded an  $M_n$  of 20400 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.21. Other diblock copolymer compositions were obtained by adjusting the NIPAM/PNAEP<sub>95</sub> macro-CTA molar ratio to give target PNIPAM DPs ranging from 100 to 300.

**Preparation of PDEA<sub>x</sub> Macro-CTA.** A typical protocol used for the synthesis of the PDEA<sub>x</sub> homopolymer was as follows: DEA (10.00 g, 54.0 mmol), MPETTC RAFT agent (244.1 mg, 0.540 mmol; target DP = 100), ACVA (50.4 mg, 180 μmol; MPETTC/ACVA molar ratio = 3.0), and THF (6.86 g, corresponding to a 60% w/w solution) were weighed into a 50 mL round-bottom flask charged with a magnetic flea. This flask was placed in an ice bath and degassed with nitrogen for 30 min before being immersed in an oil bath set at 70 °C. The polymerization was allowed to proceed for 190 min, affording a monomer conversion of 95% as judged by <sup>1</sup>H NMR. The crude homopolymer was purified by precipitation into a 10-fold excess of mildly alkaline water (pH 10). This neutral PDEA homopolymer was then dried under vacuum before being protonated using an aqueous solution of 1.0 M HCl. The fully protonated PDEA homopolymer was isolated in its HCl salt via precipitation into a 10-fold excess of acetone. This homopolymer was then dried in a vacuum oven to afford a PDEA macro-CTA containing <1% residual monomer. Its mean degree of polymerization was determined to be 99 by <sup>1</sup>H NMR spectroscopy (integral at 3.90–4.14 ppm (t, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>N) was compared to that assigned to the aromatic RAFT chain-end protons at 7.2–7.3 ppm (m, 5H)). Chloroform GPC analysis indicated an  $M_n$  of 10800 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.24.

**Synthesis of PDEA<sub>100</sub>-PNAEP<sub>y</sub> Diblock Copolymers via RAFT Aqueous Solution Polymerization of NAEP at 30% w/w Solids Using a PDEA<sub>100</sub> Macro-CTA at pH 2.** A typical protocol used for the synthesis of the PDEA<sub>100</sub>-PNAEP<sub>100</sub> diblock copolymer via RAFT aqueous solution polymerization of NAEP was as follows: PDEA<sub>100</sub> macro-CTA (200 mg, 10.5 μmol), NAEP (190 mg, 1.054 mmol; target DP = 100), and AsAc (0.37 mg, 2.1 μmol) were weighed into a 14 mL vial charged with a magnetic flea (reaction solution 1). This vial was immersed in an ice bath and degassed with nitrogen for 30 min. Dilute aqueous HCl (0.001 M, 1.12 g) and KPS (57 mg, 2.1 μmol; PDEA<sub>100</sub> macro-CTA/KPS molar ratio = 5.0) were weighed into a separate 14 mL vial (reaction solution 2; final pH 2), which was immersed in an ice bath and degassed with nitrogen for 30 min. The vial containing reaction solution 1 was then immersed in an oil bath set at 30 °C. Reaction solution 2 was added to this vial using a degassed syringe/needle under nitrogen to afford a final solution at pH 2 targeting 30% w/w solids. <sup>1</sup>H NMR studies indicated that an NAEP conversion of 99% was achieved after 120 min. DMF GPC analysis indicated an  $M_n$  of 39500 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.27. Other diblock copolymer compositions were obtained by adjusting the NAEP/PDEA<sub>100</sub> macro-CTA molar ratio to give target PNAEP DPs ranging from 50 to 100.

**Copolymer Characterization. <sup>1</sup>H NMR Spectroscopy.** <sup>1</sup>H NMR spectra were recorded at 25 °C in d<sub>4</sub>-methanol and D<sub>2</sub>O using a 400 MHz Bruker Avance-400 spectrometer (64 scans averaged per spectrum).

**Gel Permeation Chromatography (GPC).** The molecular weights and dispersities of the homopolymers series and diblock copolymers were determined by using an Agilent 1260 Infinity setup comprising

two Polymer Laboratories PL gel 5  $\mu\text{m}$  Mixed-C columns and a refractive index detector operating at 60  $^{\circ}\text{C}$ . The mobile phase was HPLC-grade DMF containing 10 mmol LiBr at a flow rate of 1.0 mL  $\text{min}^{-1}$ . Ten near-monodisperse poly(methyl methacrylate) standards (PMMA;  $M_n = 625$  to 618000  $\text{g mol}^{-1}$ ) were used for calibration. The molecular weight and dispersity of the PDEA<sub>99</sub> homopolymer was determined by using an Agilent 1260 Infinity setup comprising two Polymer Laboratories PL gel 5  $\mu\text{m}$  Mixed-C columns and a refractive index detector operating at 35  $^{\circ}\text{C}$ . The mobile phase was HPLC-grade chloroform containing 0.25% v/v TEA at a flow rate of 1.0 mL  $\text{min}^{-1}$ . Ten near-monodisperse poly(methyl methacrylate) standards (PMMA;  $M_n = 625$  to 618000  $\text{g mol}^{-1}$ ) were used for calibration. The molecular weights and dispersities of the PDEA<sub>100</sub>-PNAEP<sub>y</sub> diblock copolymers were determined by using an Agilent 1260 Infinity setup comprising two Polymer Laboratories PL gel 5  $\mu\text{m}$  Mixed-C columns and a refractive index detector operating at 60  $^{\circ}\text{C}$ . The mobile phase was HPLC-grade DMF containing 0.25% v/v TEA and 10 mmol LiBr at a flow rate of 1.0 mL  $\text{min}^{-1}$ . Ten near-monodisperse poly(methyl methacrylate) standards (PMMA;  $M_n = 625$  to 618000  $\text{g mol}^{-1}$ ) were used for calibration.

**Differential Scanning Calorimetry (DSC).** Glass transition temperatures for four PNAEP homopolymers were determined using a Pyris 1 Perkin-Elmer differential scanning calorimeter operating over a temperature range from  $-30$  to  $70$   $^{\circ}\text{C}$  at a rate of  $10$   $^{\circ}\text{C min}^{-1}$ . Each 10 mg sample was freeze-dried and subsequently dried for 24 h in a vacuum oven prior to analysis. Dried samples were hermetically sealed in a vented aluminum pan, and the instrument was calibrated for heat flow and temperature using both indium and zinc standards. Two heating-cooling cycles were performed: the first cycle ensured removal of residual water, and the glass transition temperature was determined during the second cycle.

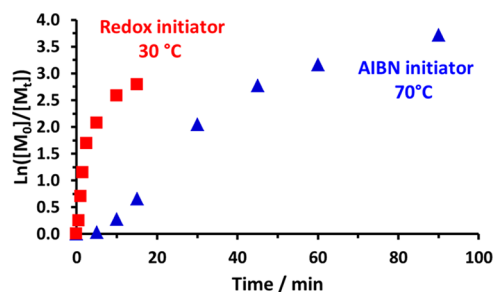
**Visible Absorption Spectroscopy.** Spectra were recorded from 400 to 800 nm for 1.0% w/w aqueous solutions of various PNAEP and PNMEP homopolymers between 20 and  $80$   $^{\circ}\text{C}$  at  $5$   $^{\circ}\text{C}$  increments using a Shimadzu UV-1800 spectrometer. An increase in turbidity at 600 nm indicated the lower critical solution temperature (LCST) of the polymer, if applicable.

**Dynamic Light Scattering (DLS).** DLS studies were conducted using a Malvern Instruments Zetasizer Nano series instrument equipped with a 4 mW He-Ne laser ( $\lambda = 633$  nm) and an avalanche photodiode detector. Scattered light was detected at  $173^{\circ}$ . Intensity-average hydrodynamic diameters were calculated via the Stokes-Einstein equation.

## RESULTS AND DISCUSSION

RAFT polymerizations of methacrylic monomers are often more well-controlled compared to their acrylic counterparts, since the latter tend to undergo chain transfer to polymer.<sup>36,37</sup> In an attempt to optimize the RAFT homopolymerization of NAEP in water, kinetic studies were conducted using a low-temperature redox initiator at  $30$   $^{\circ}\text{C}$  or AIBN initiator at  $70$   $^{\circ}\text{C}$  (see Scheme 1 and Figure 1). In both cases, DDMAT was chosen as the trithiocarbonate-based chain transfer agent (CTA), and a degree of polymerization (DP) of 200 was targeted. Furthermore, a relatively high NAEP concentration of 60% w/w was selected to solubilize the hydrophobic DDMAT. It was envisaged that the low-temperature redox initiator system would confer various benefits, including fewer side reactions, minimal induction periods, and greater RAFT control.<sup>38</sup>

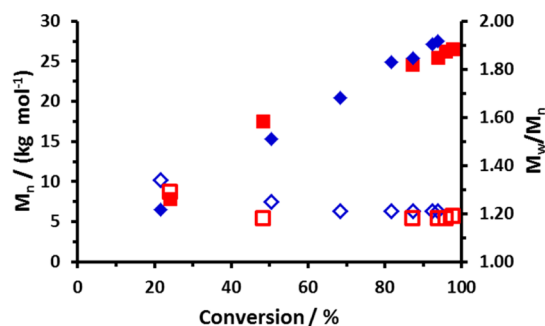
Aliquots of each reaction mixture were taken at regular intervals, and monomer conversions were determined by  $^1\text{H}$  NMR analysis. When using AIBN at  $70$   $^{\circ}\text{C}$ , more than 95% NAEP conversion was achieved within 60 min, despite a brief induction period. Remarkably, NAEP polymerizations conducted using the redox initiator at  $30$   $^{\circ}\text{C}$  proceeded to more than 90% conversion within just 5 min with no discernible



**Figure 1.** Semilogarithmic plots obtained for the RAFT aqueous solution polymerization of NAEP using a DDMAT/initiator molar ratio of 5.0 where the initiator is either AIBN (triangles) at  $70$   $^{\circ}\text{C}$  or KPS/AsAc (squares) at  $30$   $^{\circ}\text{C}$ . Target degree of polymerization = 200 at 60% w/w solids.

induction period. Moreover, comparing the initial gradients of the linear regions of the respective semilogarithmic plots (Figure 1) indicated that the rate of polymerization at  $30$   $^{\circ}\text{C}$  was an order of magnitude faster than that at  $70$   $^{\circ}\text{C}$  (see Figure S1).

DMF GPC was used to monitor the evolution of molecular weight during the RAFT aqueous solution polymerization of NAEP at  $30$  or  $70$   $^{\circ}\text{C}$  (Figure 2). In both cases, relatively high



**Figure 2.** Evolution of  $M_n$  (filled symbols) and  $M_w/M_n$  (open symbols) vs conversion for the RAFT aqueous solution polymerization of PNAEP<sub>200</sub> homopolymer at either  $30$   $^{\circ}\text{C}$  (diamonds) or  $70$   $^{\circ}\text{C}$  (squares). In both cases, the DDMAT/initiator molar ratio was 5.0 (GPC protocol: DMF eluent; refractive index detector; calibration against a series of near-monodisperse PMMA standards).

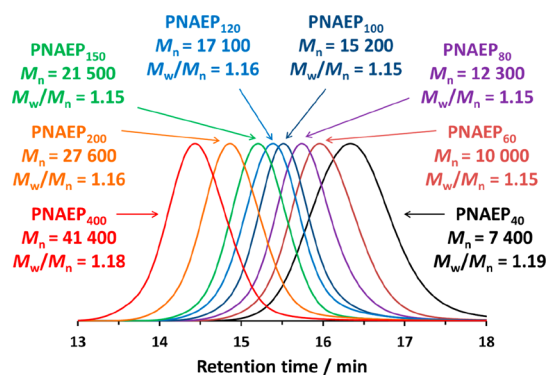
dispersities ( $M_w/M_n > 1.30$ ) were observed during the initial stages (below 40% conversion). Exotherms of up to  $25$   $^{\circ}\text{C}$  were observed during RAFT syntheses conducted at  $30$   $^{\circ}\text{C}$  (see Figure S2), and the polymerizing solutions became highly viscous, with transparent yellow gels being obtained at high conversions when performing such syntheses at 60% w/w. Perhaps surprisingly, relatively low final dispersities ( $M_w/M_n < 1.20$ ) were observed for both PNAEP<sub>200</sub> homopolymers, despite the much faster rate of polymerization achieved at  $30$   $^{\circ}\text{C}$ . To examine whether the RAFT polymerization of NAEP was well-controlled, a series of PNAEP homopolymers were prepared targeting a range of DPs using either AIBN or the low-temperature redox initiator (see Table 1). A DDMAT/initiator molar ratio of 5.0 was used for all these homopolymerizations. DMF GPC analysis was used to determine the  $M_n$  and  $M_w/M_n$  values in each case.

$^1\text{H}$  NMR analysis indicated that high NAEP conversions ( $\geq 98\%$ ) were achieved using either AIBN at  $70$   $^{\circ}\text{C}$  or the redox initiator at  $30$   $^{\circ}\text{C}$  when targeting PNAEP DPs of up to 120 or 400, respectively. These results represent a substantial

**Table 1. Summary of Target PNAEP DP, Conversions, Molecular Weights ( $M_n$ ), and Dispersities ( $M_w/M_n$ ) Obtained for PNAEP Homopolymers Prepared by RAFT Aqueous Solution Polymerization of NAEP at Either 30 °C (Low-Temperature Redox Initiator) or 70 °C (AIBN) at 60% w/w Solids**

target PNAEP DP	conv (%)	temp (°C)	$M_n$ (g mol <sup>-1</sup> )	$M_w/M_n$
PNAEP <sub>40</sub>	99	70	7600	1.13
PNAEP <sub>60</sub>	99	70	11200	1.13
PNAEP <sub>80</sub>	99	70	13300	1.14
PNAEP <sub>100</sub>	99	70	15700	1.19
PNAEP <sub>120</sub>	99	70	19300	1.15
PNAEP <sub>40</sub>	99	30	7400	1.19
PNAEP <sub>60</sub>	99	30	10000	1.15
PNAEP <sub>80</sub>	99	30	12300	1.15
PNAEP <sub>100</sub>	98	30	15200	1.15
PNAEP <sub>120</sub>	98	30	17100	1.16
PNAEP <sub>150</sub>	99	30	21500	1.15
PNAEP <sub>200</sub>	99	30	27600	1.16
PNAEP <sub>400</sub>	99	30	41400	1.18
PNAEP <sub>750</sub>	75	30	74600	1.26
PNAEP <sub>1000</sub>	70	30	115400	1.28

improvement over the data previously reported by Shi et al., who reported 77% conversion within 35 min at 25 °C for the visible light-mediated RAFT aqueous solution polymerization of NAEP at 50% w/w at pH 2.6.<sup>33</sup> DMF GPC analysis indicated that the  $M_n$  values for the final PNAEP<sub>x</sub> homopolymers increased linearly with target DP, as expected. Moreover, monomodal GPC traces and narrow molecular weight distributions ( $M_w/M_n < 1.20$ ) were observed in all cases (see Figure 3). As discussed above for PNAEP syntheses

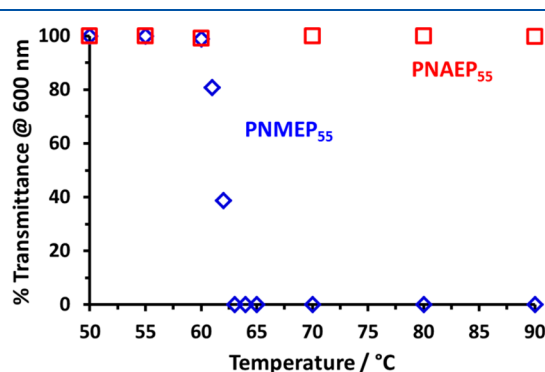


**Figure 3.** DMF GPC curves obtained for a series of PNAEP<sub>x</sub> homopolymers prepared via RAFT solution polymerization of NAEP using KPS/AsAc redox initiator at 30 °C (calibrated against a series of near-monodisperse poly(methyl methacrylate) standards).

targeting a DP of 200, the faster rate of polymerization achieved at 30 °C did not adversely affect RAFT control over these polymerizations, with  $M_w/M_n$  remaining less than 1.20 up to DP 400. Thus, the low-temperature redox initiator route was adopted for all subsequent RAFT syntheses. When targeting DPs above 400, reaction solutions became very viscous when using 60% w/w NAEP, which led to significantly lower conversions (<80%; see Table 1).

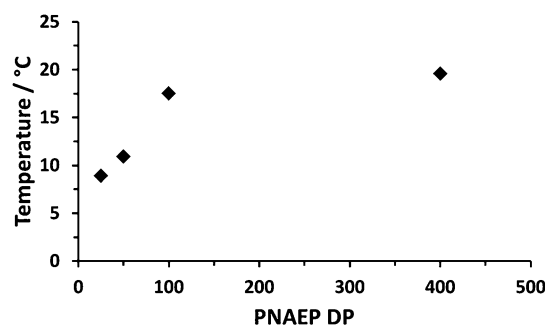
Recently, Cunningham and co-workers reported that PNMEP homopolymers exhibited inverse temperature solubility behavior in aqueous solution.<sup>29</sup> The lower critical

solution temperature (LCST) or cloud point can be monitored by turbidimetry. For example, a 1.0% w/w aqueous solution of PNMEP<sub>55</sub> becomes turbid when heated to 62 °C (see Figure 4).<sup>39</sup> In striking contrast, a 1.0% w/w aqueous solution of PNAEP<sub>55</sub> exhibits no LCST behavior and remains fully water-soluble up to at least 90 °C (see Figure 4). Clearly, the acrylic analogue is significantly more hydrophilic, which is not unexpected. This is important because such PNAEP<sub>x</sub> homopolymers should enable the convenient preparation of a range of new double-hydrophilic pyrrolidone-based diblock copolymers in aqueous solution. This possibility is explored below.



**Figure 4.** % Transmittance (at 600 nm) vs temperature plot recorded for a 1.0% w/w aqueous solution of a PNMEP<sub>55</sub> homopolymer (blue diamonds) compared to that for a 1.0% w/w aqueous solution of a PNAEP<sub>55</sub> homopolymer (red squares). PNMEP<sub>55</sub> has an LCST at 62 °C, whereas the more hydrophilic PNAEP<sub>55</sub> exhibits no discernible LCST behavior over this temperature range.

Glass transition temperatures ( $T_g$ ) for four PNAEP<sub>x</sub> homopolymers prepared via RAFT aqueous solution polymerization of NAEP utilizing the low-temperature redox initiator were determined using differential scanning calorimetry (DSC) for DPs ranging between 50 and 400. This technique indicated  $T_g$  values below room temperature for mean DPs of less than 400 (see Figure 5). A  $T_g$  of ~19.6 °C was obtained for a



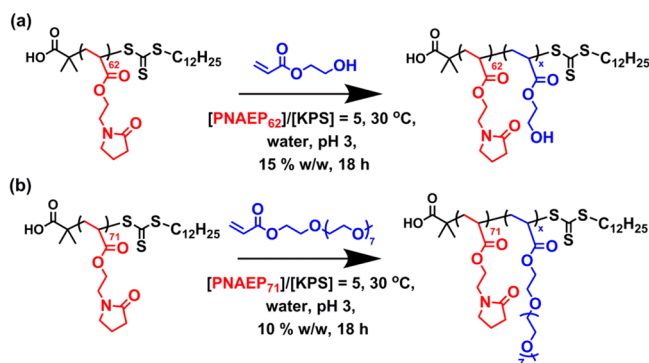
**Figure 5.** Variation of glass transition temperature with PNAEP DP for four PNAEP<sub>x</sub> homopolymers prepared via RAFT aqueous solution polymerization of NAEP at 30 °C.

PNAEP<sub>400</sub> homopolymer, which appears to lie close to the  $T_g$  for the high molecular weight limit.<sup>40</sup> Such  $T_g$  values are significantly lower than those of PNMEP and suggest that the film-forming properties of PNAEP homopolymer at ambient temperature may be of potential commercial interest.

**RAFT Aqueous Solution Polymerization of Either HEA or OEGA at 30 °C Using a PNAEP<sub>x</sub> Macro-CTA. A**

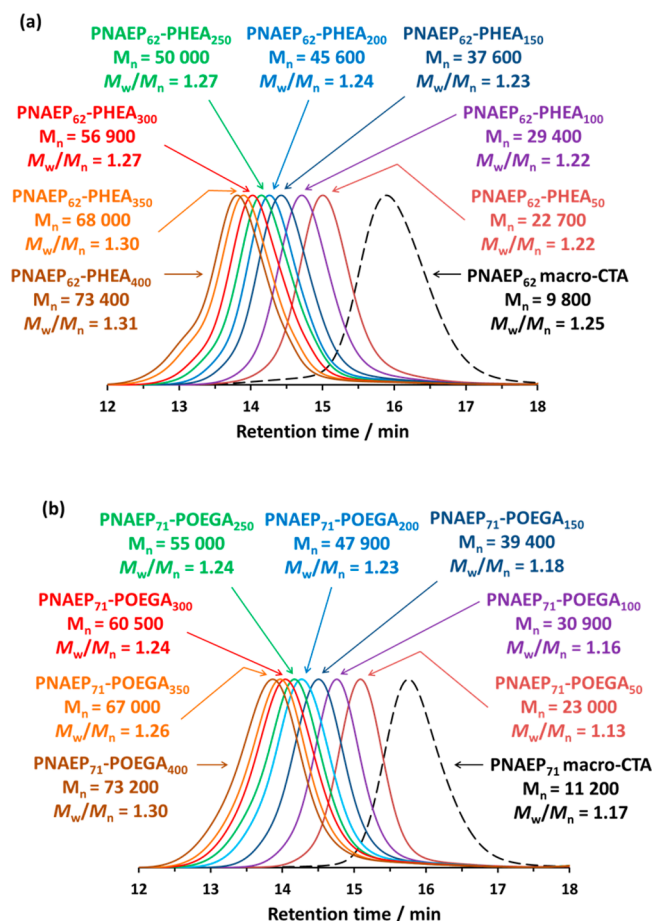
PNAEP<sub>62</sub> macro-CTA was prepared via RAFT aqueous solution polymerization of NAEP at 30 °C using a DDMAT/KPS molar ratio of 100 and targeting a DP of 100. This much higher CTA/initiator molar ratio was selected in view of the relatively fast rate of polymerization observed for a CTA/initiator molar ratio of 5.0 and was designed to ensure maximum RAFT end-group fidelity. The resulting macro-CTA was purified via successive precipitation into excess diethyl ether. <sup>1</sup>H NMR end-group analysis of the methyl proton signals assigned to the RAFT chain-ends indicated a mean DP of 62. Given the final NAEP conversion of 60%, this indicates a RAFT agent efficiency of 97%. DMF GPC analysis indicated an  $M_n$  of 9800 g mol<sup>-1</sup> and a relatively narrow molecular weight distribution ( $M_w/M_n < 1.25$ ). This PNAEP<sub>62</sub> macro-CTA was subsequently used to prepare a series of PNAEP<sub>62</sub>-PHEA<sub>x</sub> diblock copolymers via RAFT aqueous solution polymerization of HEA (see Scheme 2a) targeting PHEA

**Scheme 2. Synthesis of (a) PNAEP<sub>62</sub>-PHEA<sub>x</sub> Diblock Copolymers and (b) PNAEP<sub>71</sub>-POEGA<sub>x</sub> Diblock Copolymers by RAFT Aqueous Solution Polymerization of Either HEA or OEGA at 30 °C**



DPs of between 50 and 400. A DDMAT/KPS molar ratio of 5.0 was used in all cases. <sup>1</sup>H NMR studies indicated that high HEA conversions (>99%) were achieved within 18 h. Furthermore, DMF GPC analysis of the resulting PNAEP<sub>62</sub>-PHEA<sub>x</sub> diblock copolymers indicated a linear increase in  $M_n$  with increasing PHEA DP (Figure 6a). Relatively low dispersities ( $M_w/M_n < 1.35$ ) were obtained for all PNAEP<sub>62</sub>-PHEA<sub>x</sub> diblock copolymers. Moreover, comparison with the GPC trace recorded for the PNAEP<sub>62</sub> macro-CTA confirmed high blocking efficiencies in each case.

A second batch of PNAEP<sub>71</sub> macro-CTA was prepared via RAFT aqueous solution polymerization using a similar protocol to that described above. In this case, <sup>1</sup>H NMR end-group analysis of the three methyl proton signals assigned to the RAFT chain end indicated a mean DP of 71 (69% conversion, CTA efficiency = 97%). DMF GPC analysis indicated an  $M_n$  of 11200 g mol<sup>-1</sup> and a  $M_w/M_n$  of 1.17. This PNAEP<sub>71</sub> macro-CTA was subsequently utilized for the RAFT aqueous solution polymerization of OEGA, targeting POEGA DPs between 50 and 400 and using a DDMAT/KPS molar ratio of 5.0 (see Scheme 2b). OEGA conversions of at least 99% were achieved for all PNAEP<sub>71</sub>-POEGA<sub>x</sub> diblock copolymers within 18 h at 30 °C, as judged by <sup>1</sup>H NMR. DMF GPC analyses of this series of PNAEP<sub>71</sub>-POEGA<sub>x</sub> diblock copolymers indicated a monotonic increase in  $M_n$  with increasing POEGA DP, as expected. However, there is some discrepancy between the experimental and theoretical  $M_n$



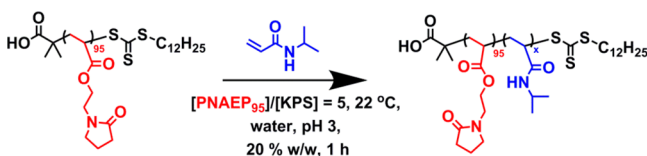
**Figure 6.** DMF GPC curves obtained for (a) a series of PNAEP<sub>62</sub>-PHEA<sub>x</sub> diblock copolymers and the corresponding PNAEP<sub>62</sub> macro-CTA (dashed trace) and (b) a series of PNAEP<sub>71</sub>-POEGA<sub>x</sub> diblock copolymers and the corresponding PNAEP<sub>71</sub> macro-CTA (dashed trace).

values. Bearing in mind the brush-like nature of the POEGA block, this can be attributed to the poly(methyl methacrylate) standards used for GPC calibration. Nevertheless, relatively low dispersities ( $M_w/M_n < 1.30$ ) were achieved for this PNAEP<sub>71</sub>-POEGA<sub>x</sub> diblock copolymer series, which suggests good RAFT control. Moreover, comparison of the GPC traces obtained for these PNAEP<sub>71</sub>-POEGA<sub>x</sub> diblock copolymers with that of the precursor PNAEP<sub>71</sub> macro-CTA indicated high blocking efficiencies (Figure 6b).

**RAFT Aqueous Solution Polymerization of NIPAM at 22 °C Using a PNAEP<sub>95</sub> Macro-CTA.** A third batch of PNAEP<sub>95</sub> macro-CTA was prepared via RAFT aqueous solution polymerization. In this case, <sup>1</sup>H NMR spectroscopy end-group analysis of the three methyl proton signals assigned to the RAFT chain-end indicated a mean DP of 95 (61% conversion, CTA efficiency = 96%). DMF GPC analysis indicated an  $M_n$  of 13800 g mol<sup>-1</sup> and a  $M_w/M_n$  of 1.21.

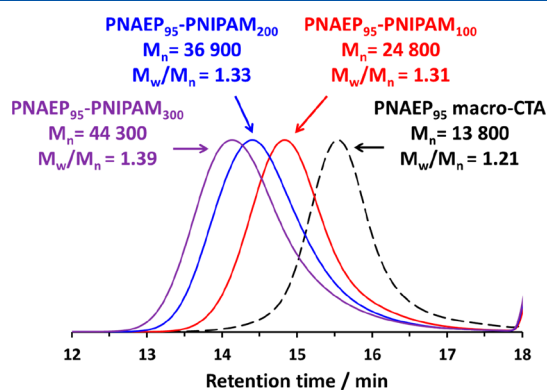
This PNAEP<sub>95</sub> macro-CTA was subsequently utilized for the RAFT aqueous solution polymerization of NIPAM, targeting PNIPAM DPs between 100 and 300 and using a PNAEP<sub>95</sub>/KPS molar ratio of 5.0 (see Scheme 3). The RAFT polymerization of NIPAM was conducted in an oil bath set to 22 °C, which is below the LCST of PNIPAM homopolymer.<sup>41–44</sup> NIPAM conversions of at least 99% were achieved for all PNAEP<sub>95</sub>-PNIPAM<sub>x</sub> diblock copolymers

**Scheme 3. Synthesis of a Series of PNAEP<sub>95</sub>–PNIPAM<sub>x</sub> Diblock Copolymers by RAFT Aqueous Solution Polymerization of NIPAM at 22 °C Using a PNAEP<sub>95</sub> Precursor<sup>a</sup>**



<sup>a</sup>A low-temperature redox initiator (KPS/AsAc molar ratio = 1.0) was utilized, and the macro-CTA/initiator molar ratio was 5.0.

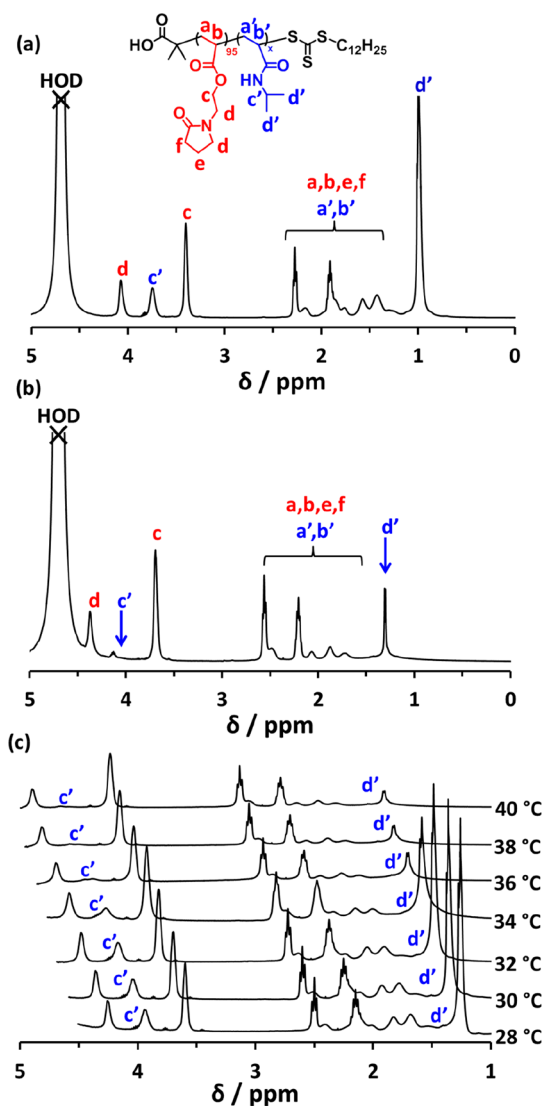
within 1 h at this temperature, as judged by <sup>1</sup>H NMR studies conducted in D<sub>2</sub>O. DMF GPC analysis of this series of PNAEP<sub>95</sub>–PNIPAM<sub>x</sub> diblock copolymers indicated a monotonic increase in  $M_n$  with increasing PNIPAM DP. Relatively low dispersities ( $M_w/M_n < 1.40$ ) were observed in all cases, indicating reasonably good RAFT control. Moreover, comparison of the GPC traces obtained for these PNAEP<sub>95</sub>–PNIPAM<sub>x</sub> diblock copolymers with that of the precursor PNAEP<sub>95</sub> macro-CTA indicated relatively high blocking efficiencies (Figure 7).



**Figure 7.** DMF GPC curves obtained for a series of three PNAEP<sub>95</sub>–PNIPAM<sub>x</sub> diblock copolymers and the corresponding PNAEP<sub>95</sub> macro-CTA (dashed trace). The NIPAM conversion was more than 99% for each of the three diblock copolymers.

PNIPAM is a well-known thermoresponsive polymer that exhibits LCST behavior in aqueous solution at around 32 °C.<sup>41–44</sup> Thus, proton signals assigned to the PNAEP and PNIPAM blocks are observed when inspecting a <sup>1</sup>H NMR spectrum recorded for the PNAEP<sub>95</sub>–PNIPAM<sub>200</sub> diblock copolymer in D<sub>2</sub>O at 20 °C (see Figure 8a). However, on heating this copolymer solution up to 50 °C, the PNIPAM chains become substantially desolvated. This leads to attenuation of all the PNIPAM signals (Figure 8b). On the other hand, all the PNAEP signals remain well-solvated under these conditions. Variable temperature <sup>1</sup>H NMR studies indicated that the two methyl signals assigned to the pendent isopropyl group of PNIPAM (labeled d' in Figure 8) become substantially attenuated between 34 and 36 °C (Figure 8c), suggesting reduced chain mobility owing to dehydration. These spectral changes are consistent with *in situ* self-assembly of the diblock copolymer chains to form PNIPAM-core micelles.

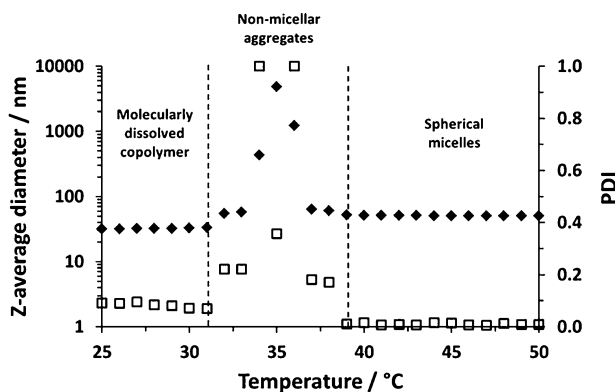
Dynamic light scattering (DLS) was utilized to gain further evidence for such micellar self-assembly. A 0.10% w/w



**Figure 8.** <sup>1</sup>H NMR spectra recorded for a PNAEP<sub>95</sub>–PNIPAM<sub>200</sub> diblock copolymer in D<sub>2</sub>O at (a) 20 °C (upper spectrum), (b) 50 °C (middle spectrum), and (c) between 28 and 40 °C.

PNAEP<sub>95</sub>–PNIPAM<sub>200</sub> solution was monitored between 25 and 50 °C. The weak light scattering and relatively small hydrodynamic diameter observed at 25 °C indicated that this copolymer existed as molecularly dissolved chains at this temperature (see Figure 9). On heating this copolymer solution, relatively large, ill-defined aggregates are obtained at around 35 °C, before well-defined near-monodisperse spherical nanoparticles (*z*-average diameter = 51 nm; PDI = 0.006) are formed above ~40 °C, in good agreement with the variable temperature <sup>1</sup>H NMR spectra shown in Figure 8c. Similar examples of so-called anomalous micellization have been reported in the literature.<sup>44–47</sup> In at least some cases, such observations have been attributed to homopolymer contamination by the more hydrophobic block.<sup>44</sup> At first sight, this hypothesis does not seem to be applicable in the present case because the PNAEP precursor block is more hydrophilic than the PNIPAM block. However, in principle, the RAFT mechanism can generate a low level of PNIPAM homopolymer impurity,<sup>48</sup> so this possible explanation cannot be excluded.

**RAFT Aqueous Solution Polymerization of NAEP at 30 °C Using a PDEA<sub>99</sub> Macro-CTA.** A PDEA macro-CTA



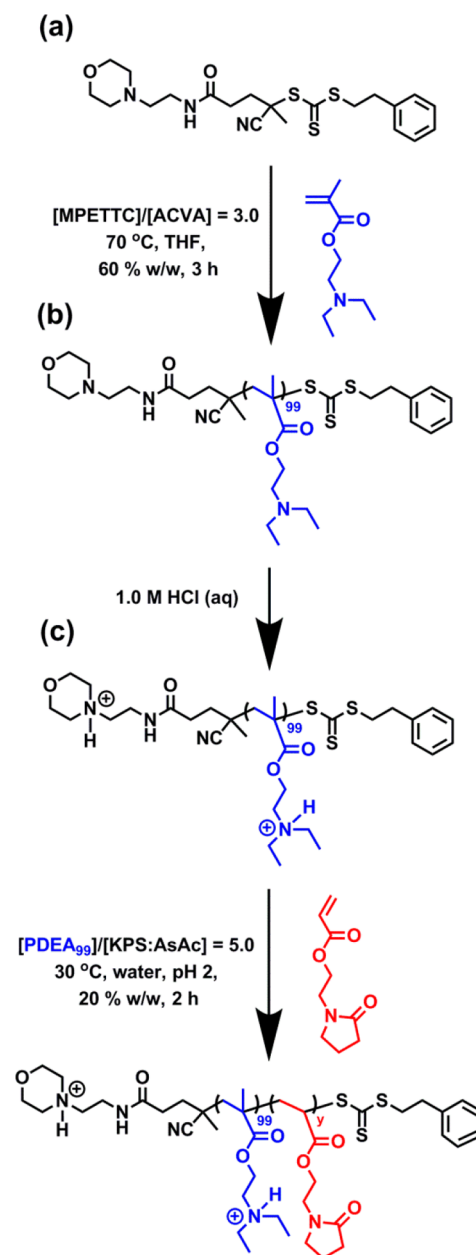
**Figure 9.** Variable temperature DLS studies of a 0.10% w/w aqueous solution of a PNAEP<sub>95</sub>–PNIPAM<sub>200</sub> diblock copolymer at pH 3. Molecularly dissolved copolymer chains are obtained at 25 °C, anomalous micellization occurs at around 35 °C, and well-defined, near-monodisperse micelles are formed above 40 °C. Such self-assembly is driven by the well-known thermoresponsive nature of the PNIPAM block, which exhibits inverse temperature solubility behavior.

(target DP = 100) was prepared via RAFT solution polymerization of DEA in THF at 70 °C using MPETTC (see Scheme 4a). This precursor was purified via successive precipitation into a 10-fold excess of alkaline aqueous solution (pH 10) to afford a yellow gum, which was dried under vacuum before being dissolved in its protonated form using 1.0 M aqueous HCl. The resulting PDEA hydrochloride salt was isolated via precipitation into a 10-fold excess of acetone to yield a yellow powder. <sup>1</sup>H NMR studies indicated negligible residual monomer (<1%), while end-group analysis based on the aromatic proton signals assigned to the MPETTC RAFT chain-ends indicated a mean DP of 99. Chloroform GPC analysis indicated a monomodal trace with an  $M_n$  of 10800 g mol<sup>-1</sup> and an  $M_w/M_n$  of 1.24 (see Table S1).

This PDEA<sub>99</sub> macro-CTA was then utilized for the RAFT aqueous solution polymerization of NAEP targeting a PNAEP DP of 50 to 100, as depicted in Scheme 4b. These syntheses were conducted in acidic aqueous solution to ensure that both blocks were fully water-soluble (with the protonated PDEA block being present in its cationic polyelectrolyte form). <sup>1</sup>H NMR studies confirmed that high NAEP conversions (>99%) were achieved in each case. Inspecting Table S1, DMF GPC analysis of this series of PDEA<sub>99</sub>–PNAEP<sub>y</sub> diblock copolymers confirms that higher  $M_n$  values are obtained on increasing the target PNAEP DP from 50 to 100. A relatively low dispersity ( $M_w/M_n < 1.30$ ) was observed for each PDEA<sub>100</sub>–PNAEP<sub>y</sub> diblock copolymer, as expected.

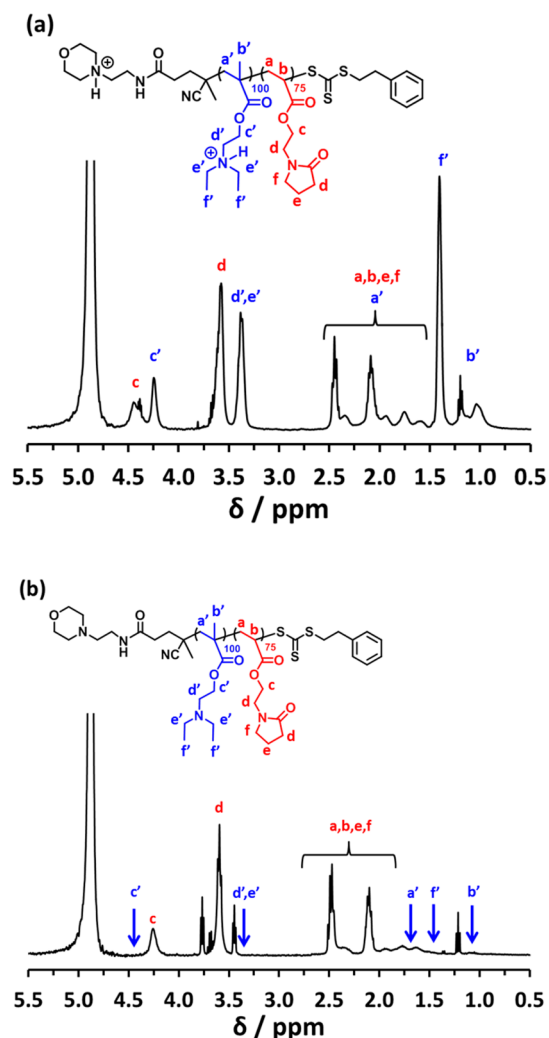
<sup>1</sup>H NMR studies were conducted on a PDEA<sub>99</sub>–PNAEP<sub>75</sub> diblock copolymer in acidic aqueous solution (0.001 M DCl in D<sub>2</sub>O, or pH 3). Under such conditions, all the tertiary amine groups in the PDEA block are protonated, and hence both blocks are fully solvated. Thus, all the expected <sup>1</sup>H NMR signals for both blocks are visible under such conditions (see Figure 10a). In particular, the six pendent methyl protons associated with the PDEA block are prominent between 1.20 and 1.50 ppm. On addition of sufficient NaOD, the PDEA<sub>x</sub> block becomes completely deprotonated ( $pK_a \sim 7.3$ ) and hence hydrophobic.<sup>49</sup> This drives *in situ* self-assembly to form PDEA-core micelles with the PNAEP chains acting as the stabilizer block. Accordingly, the <sup>1</sup>H NMR signals associated with the desolvated PDEA block are no longer visible (Figure

**Scheme 4.** Synthesis of (a) a PDEA<sub>x</sub> Homopolymer by RAFT Aqueous Solution Polymerization of DEA at 70 °C in THF Using a Morpholine-Functionalized RAFT CTA; (b) Protonation of the PDEA<sub>100</sub> Homopolymer Precursor Using 1.0 M HCl; (c) Synthesis of PDEA<sub>100</sub>–PNAEP<sub>y</sub> Diblock Copolymers by RAFT Aqueous Solution Polymerization of NAEP at 30 °C Using a Protonated Water-Soluble PDEA<sub>100</sub> Precursor and a Macro-CTA/Initiator Molar Ratio of 5.0 (KPS/AsAc Molar Ratio = 1.0)

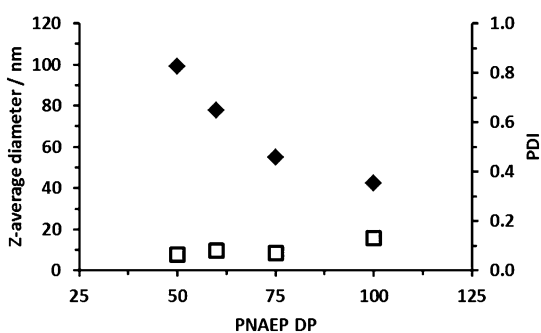


10b). The z-average micelle diameter is reduced from 100 to 40 nm for four PDEA<sub>100</sub>–PNAEP<sub>y</sub> diblock copolymers as the DP ( $y$ ) of the PNAEP block is increased from 50 to 100 (see Figure 11). This indicates lower micelle aggregation numbers when using longer stabilizer blocks, which is consistent with well-known theories of micellization reported in the literature.<sup>50,51</sup>





**Figure 10.**  $^1\text{H}$  NMR spectra recorded for a PDEA<sub>99</sub>–PNAEP<sub>75</sub> diblock copolymer at 25 °C: (a) in DCl/D<sub>2</sub>O at pH 3 (upper spectrum) and (b) in NaOD/D<sub>2</sub>O at pH 10 (lower spectrum).



**Figure 11.** DLS studies for four PDEA<sub>100</sub>–PNAEP<sub>y</sub> diblock copolymers (where  $y = 50$ – $100$ ) in dilute aqueous solution at pH 10.

## CONCLUSIONS

A trithiocarbonate-based CTA (DDMAT) was used for the RAFT aqueous solution polymerization of 2-(*N*-acryloyloxy)-ethylpyrrolidone (NAEP) to prepare a series of PNAEP<sub>x</sub> homopolymers with mean degrees of polymerization varying from 40 to 400. Substituting a typical azo initiator for a low-temperature redox initiator enabled the reaction temperature to be lowered from 70 to 30 °C while also reducing the

reaction time from 60 to 5 min. GPC analyses indicated well-controlled RAFT syntheses under these conditions ( $M_w/M_n \sim 1.20$ ). Unlike the poly(2-(*N*-methacryloyloxy)-ethylpyrrolidone) homopolymers reported previously, these PNAEP<sub>x</sub> homopolymers do not possess LCST behavior as judged by turbidimetry studies, which indicates that they are significantly more hydrophilic. High monomer conversions ( $\geq 99\%$ ) were achieved when targeting mean DPs between 40 and 400 at 60% w/w NAEP. DSC analysis indicated that PNAEP homopolymers with DPs of up to 400 exhibited glass transition temperatures below ambient temperature.

Using such trithiocarbonate-terminated PNAEP homopolymers as precursors, two series of PNAEP<sub>62</sub>–PHEA<sub>x</sub> and PNAEP<sub>71</sub>–POEGA<sub>x</sub> diblock copolymers were prepared via RAFT aqueous solution polymerization of either HEA or OEGA, respectively. High monomer conversions ( $\geq 99\%$ ) were achieved when targeting mean DPs between 50 and 400. DMF GPC analysis confirmed that relatively low dispersities ( $M_w/M_n \leq 1.35$ ) and high blocking efficiencies were obtained for these two all-acrylic formulations, with monomodal GPC traces suggesting reasonably good RAFT control.

Two new classes of stimulus-responsive PNAEP-based diblock copolymers were also prepared. Thus, a series of thermoresponsive PNAEP<sub>95</sub>–PNIPAM<sub>x</sub> diblock copolymers were prepared via RAFT aqueous solution polymerization of NIPAM at 22 °C, which is below the LCST of the PNIPAM block. Variable temperature DLS studies indicated the presence of relatively large, non-micellar aggregates between 32 and 39 °C prior to the formation of well-defined PNIPAM-core spherical micelles above 42 °C (51 nm; PDI = 0.006). Variable temperature  $^1\text{H}$  NMR studies indicated that such self-assembly was accompanied by substantial desolvation of the PNIPAM block, as expected. Finally, a PDEA<sub>100</sub> macro-CTA was chain-extended via RAFT aqueous solution polymerization of NAEP at 30 °C.  $^1\text{H}$  NMR studies confirmed that high conversions ( $\geq 99\%$ ) were achieved when targeting mean DPs of 50–100 and GPC studies indicated good RAFT control and low final dispersities ( $M_w/M_n \leq 1.30$ ) in each case. Such PDEA<sub>99</sub>–PNAEP<sub>y</sub> diblock copolymers exhibited pH-responsive behavior in aqueous solution. Molecular dissolution occurred at low pH, but spherical micelles comprising deprotonated PDEA cores were obtained at pH 10. DLS studies indicated that increasing the PNAEP DP led to a significant reduction in the z-average diameter for this series of PDEA<sub>99</sub>–PNAEP<sub>x</sub> diblock copolymers.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.8b01627.

Figures S1 and S2; Table S1 (PDF)

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### Notes

The authors declare the following competing financial interest(s): A patent application has been filed to protect the results reported in this manuscript.

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