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ARTICLE *in* MACROMOLECULES · JULY 2014

Impact Factor: 5.8 · DOI: 10.1021/ma501007j

Macromolecules

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Straightforward ARGET ATRP for the Synthesis of Primary Amine Polymethacrylate with Improved Chain-End Functionality under Mild Reaction Conditions

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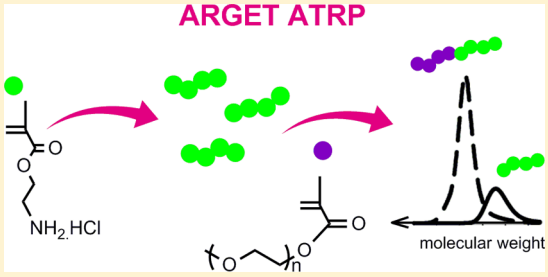
Supporting Information

ABSTRACT: Activators regeneration by electron transfer atom transfer radical polymerization (ARGET ATRP) of 2-aminoethyl methacrylate hydrochloride (AMA) was successfully performed for the first time. The polymerizations were conducted at 35 °C in isopropanol (IPA)/water mixtures or pure water, using $CuBr_2$/TPMA (TPMA: tris(2-pyridylmethyl)amine) as a metal catalyst complex with slow feeding of ascorbic acid (AscA) to allow regeneration of the activator species. The reactions showed first-order kinetics with monomer conversion and high monomer conversion (>90%), and controlled polymers ($Đ \approx 1.3$) were obtained using optimized conditions. For the first time, as a result of the PAMA's high chain-end functionality, it was possible to extend the polymer and synthesize a well-defined block copolymer (PAMA-*b*-POEOMA) (OEOMA: oligo(ethylene oxide) methyl ether methacrylate) by ATRP techniques, using AMA as the first block. PAMA-based nanogels, with potential biomedical applications, were prepared by ARGET ATRP in inverse miniemulsion.



INTRODUCTION

Atom transfer radical polymerization (ATRP) is a popular reversible deactivation radical polymerization (RDRP) technique, which allows the preparation of polymers with controlled molecular weight, low molar mass dispersity ($Đ$), complex architectures, and high chain-end functionality.[1,2] The control of the polymerization is achieved by reversible cycles of activation/deactivation of alkyl halide polymer chains. A transition metal/ligand catalytic complex in a lower oxidation state is responsible for the activation of the dormant alkyl halide chains to generate the corresponding alkyl radical and the catalytic complex in a higher oxidation state. The radical can then propagate by adding a limited number of monomer units before being deactivated by the higher oxidation state catalytic complex to form a dormant alkyl chain.[2−4] Polymers prepared by ATRP have active chain-ends which can be used for chain extension or functionalization, allowing the preparation of copolymers, supramolecular architectures, and bioconjugates.[2,5−7]

ATRP techniques have been used for the controlled polymerization of a wide range of monomers, including functional monomers, such as (meth)acrylates,[3,8−11] (meth)acrylamides,[12] styrene,[13,14] and 4-vinylpyridine.[15,16] However, there are still important challenges associated with the ATRP of functional monomers bearing primary amine groups or free acidic groups. Primary amine groups can participate in side reactions with the growing polymer halide chain-ends, resulting in dead chains.[17,18] Further, a competitive complex formation between the amino groups in the monomer/polymer and the metal catalyst can occur.[19] Finally, the acidic character of some monomers can contribute to catalyst poisoning and loss of activity, resulting in uncontrolled reactions. 2-Aminoethyl methacrylate hydrochloride (AMA) is a synthetically useful monomer due its amine reactive handle which can be used in several postpolymerization reactions, such as Michael addition or ring-opening of epoxy groups, to afford functional materials for different applications. AMA is a challenging monomer to polymerize by ATRP due to the amino functionality and its acidic character, both interfering with catalyst stability. Moreover, it is well-known that both AMA and PAMA are not chemically stable under basic conditions (pH > 9) and undergo rapid rearrangement to give 2-hydroxyethyl methacrylamide and poly(2-hydroxyethyl methacrylamide), respectively.[20,21] PAMA homopolymers and copolymers have been successfully used in the preparation of drug/gene delivery carriers,[22−29] and we expect that the development of activators regenerated by electron transfer atom transfer radical polymerization (ARGET) ATRP conditions for this monomer could lead to widespread utilization of PAMA in new applications. The ARGET ATRP could be advantageous over the normal

Received: May 15, 2014
Revised: June 23, 2014
Published: July 11, 2014

   dx.doi.org/10.1021/ma501007j | *Macromolecules* 2014, 47, 4615−4621

ATRP technique, for instances considering biomedical applications, since it allows the use of lower amount of metal catalyst to achieve control over the polymerization. In this variation, reducing agents such as ascorbic acid are used to (re)generated, *in situ*, Cu(I) activator species from oxidatively stable Cu(II) complexes.[30] In addition, ARGET ATRP was successfully implemented in aqueous medium.[31]

The first controlled ATRP synthesis of PAMA was reported by Leroux's research group who employed CuBr/PMDETA (PMDETA: pentamethyldiethylenetriamine) as a catalytic system in tetrahydrofuran (THF) at 65 °C.[26] *t*-Boc-protected AMA was used in order to avoid side reactions with the amino groups.[26,28] The Armes group reported the direct polymerization of AMA in its hydrochloride salt form by normal ATRP in isopropanol (IPA)/water mixtures at 50 °C, using CuBr/bpy (bpy: 2,2′-bipyridyl) as a catalyst.[20,21] This strategy presented a significant improvement since it allowed the direct polymerization of AMA, avoiding troublesome protection/deprotection procedures. However, a critical issue related with the lack of chain-end functionality of the PAMA-Br synthesized by normal ATRP remained to be addressed. Therefore, the preparation of well-defined block copolymers, using AMA as the monomer of the first block, was not possible.[32] Controlled polymerization of AMA has been also achieved by reversible addition−fragmentation chain transfer (RAFT) to produce both well-defined homopolymers and copolymers.[20,33−35] In opposition to ATRP, the Armes group was able to prepare primary amine-based block copolymers, with reasonable dispersity ($Đ \approx 1.4$), by RAFT with AMA as the first building block.[20] However, the RAFT polymerization required the use of organic solvents (dimethyl sulfoxide/1,4-dioxane mixture) at a relatively high temperature (70 °C). Therefore, considering the utility of primary amines in preparing functional polymers, the development of new ATRP systems which allow the controlled synthesis of these polymers with high chain-end functionality under aqueous conditions is desirable.

Herein, the controlled synthesis of PAMA was accomplished using ARGET ATRP in IPA/water mixtures or aqueous medium, near room temperature (35 °C), using slow feeding of ascorbic acid (AscA) for the regeneration of the activator (Scheme 1). In addition, AMA was successfully copolymerized

Scheme 1. Polymerization of AMA in Its Hydrochloride Salt Form by ARGET ATRP

with the water-soluble oligo(ethylene oxide) methyl ether methacrylate (OEOMA) monomer. To the best of our knowledge, this was the first time that PAMA-Br, synthesized by ATRP techniques, was used as the first block of a well-defined block copolymer. Finally, the application of the ARGET ATRP system was expanded to the preparation of PAMA-based nanogels, which could be used as responsive nanomaterials for biomedical applications.

EXPERIMENTAL SECTION

Materials. Acetone (Fisher Scientific), 2-aminoethyl methacrylate hydrochloride (≥95%, Polysciences), AscA (Sigma-Aldrich), bpy (≥99%, Sigma-Aldrich), copper(II) bromide (99.999%, Aldrich), deuterium oxide (99.9%, Cambridge Isotope Laboratories), ethyl α-bromoisobutyrate (EBiB, 98%, Sigma-Aldrich), ethyl α-bromophenyl acetate (EBPA, Alfa Aesar), glacial acetic acid (Fisher Chemical), hydrochloric acid (Fisher Scientific), 2-hydroxyethyl α-bromoisobutyrate (HBiB, 95%, Aldrich), isopropanol (Fisher Scientific), sodium bromide (≥99%, Sigma-Aldrich), Span-80 (Sigma-Aldrich), and water (HPLC grade, Fisher Scientific) were used as received.

Inhibitor was removed from oligo(ethylene oxide) monomethyl ether methacrylate ($OEOMA_{300}$, average molecular weight ≈300, Aldrich) and $OEOMA_{475}$ (99%, average molecular weight 475, Aldrich) by passing through a basic alumina column.[36]

Poly(ethylene oxide) monomethyl ether 2-bromoisobutyrate ester (PEO_{2K}iBBr, M_n = 2000) and poly(ethylene oxide) dimethacrylate (PEO_{4K}DM, M_n = 4000) were prepared as previously described in the literature.[37]

CuCl (97%, Aldrich) was washed with glacial acetic acid, followed by 1% aqueous HCl solution. Finally, it was washed with acetone and dried under nitrogen to give a white powder.

Tris(pyridin-2-ylmethyl)amine (TPMA) was synthesized as reported in the literature.[38,39]

Instrumentation. A syringe pump (KDS Scientific, Legato 101) was used for the continuous feeding of the reducing agent at the rate of 1 μL/min.

Monomer conversion was measured using ^{1}H NMR spectroscopy in D_2O using a Bruker Avance 500 MHz spectrometer at 27 °C.

Polymers number-average molecular weights (M_n^{SEC}) and dispersity ($Đ$) were determined by using a size exclusion chromatography (SEC) Water 2695 Series with a data processor (Empower Pro), equipped with three columns (Waters Ultrahydrogel Linier, 500 and 250), using 100 mM sodium phosphate buffer with 0.2 vol % trifluoroacetic acid (pH = 2) as an eluent at a flow rate 1.0 mL/min, with detection by a refractive index (RI) detector. Before the injection (100 μL), the samples were filtered through a hydrophilic poly(ether sulfone) (PES) membrane with 0.2 μm pore. The system was calibrated with six narrow poly(ethylene glycol) standards, and the molecular weights were determined by conventional calibration.

Particle size of the nanogels was measured using a Zetasizer Nano from Malvern Instruments.

Procedures. *Typical Procedure for the ARGET ATRP of AMA.* AMA (0.6 g, 3 mmol), $CuBr_2$ (3.8 mg, 17 μmol), TPMA (20 mg, 69 μmol), and EBPA (8.4 mg, 84 μmol) were dissolved in water (1.2 mL)/IPA (0.52 mL). The mixture was added to a 10 mL Schlenk flask, equipped with a magnetic stirrer bar, and purged with nitrogen for 30 min. The flask was placed in an oil bath at 35 °C, and a deoxygenated ascorbic acid solution (10 mM) was continuously injected into the reaction medium using a syringe pump at the rate of 1 μL/min. Different reaction mixture samples were collected during the polymerization. The samples were analyzed by ^{1}H NMR spectroscopy in order to determine the monomer conversion and by aqueous SEC to determine the molecular weights and dispersity of the polymers. The final reaction mixture was dialyzed against deionized water and the polymer was obtained after freeze-drying.

Typical Procedure for the Normal ATRP of AMA. Normal ATRP of AMA was performed following a procedure reported elsewhere.[20] CuCl (13.2 mg, 014 mmol) was placed in a Schlenk flask, equipped with a magnetic stirrer bar, deoxygenated with three freeze−vacuum−thaw cycles, and purged with nitrogen. AMA (0.7 g, 4.02 mmol), bpy (42 mg, 0.27 mmol), and EBiB (26.1 mg, 0.14 mmol) were dissolved in water (400 μL)/IPA (1.61 mL) and purged with nitrogen for 30 min. The mixture was added to the Schlenk flask, containing the CuCl, under nitrogen. The flask was placed in an oil bath at 50 °C, and the reaction was allowed to proceed for 2.5 h. At the end, water was added to the flask in order to dissolve the precipitated polymer. A sample was collected and analyzed by both ^{1}H NMR spectroscopy and SEC to determine the monomer conversion and the molecular weight and dispersity of the polymer, respectively.

Typical "One-Pot" Chain Extension of PAMA-Br with $OEOMA_{475}$. AMA (0.3 g, 1.72 mmol), $CuBr_2$ (6.4 mg, 29 μmol), TPMA (33 mg, 115 μmol), and EBPA (14 mg, 57 μmol) were dissolved in water (600

dx.doi.org/10.1021/ma501007j | Macromolecules 2014, 47, 4615−4621

μL)/IPA (60 μL). The mixture was added to a 10 mL Schlenk flask, equipped with a magnetic stirrer bar, and purged with nitrogen for 30 min. The flask was placed in an oil bath at 35 °C, and a deoxygenated ascorbic acid solution (10 mM) was continuously injected into the reaction medium using a syringe pump at the rate of 1 μL/min. When the monomer conversion reached more than 90%, a degassed mixture of $OEOMA_{475}$ (2 mL, 4.0 mmol), water (2.2 mL), and IPA (0.9 mL) was added to the Schlenk flask under nitrogen. The monomer conversion was determined by ^{1}H NMR spectroscopy, and the molecular weights and dispersities were determined by aqueous SEC.

Typical Procedure for the Preparation of the PAMA-Based Nanogels. Amine nanogels were prepared through a water-in-oil inverse miniemulsion using ARGET ATRP. The inverse miniemulsion was composed of a water phase consisting of $CuBr_2$ (1.9 mg, 0.0085 mmol)/TPMA (2.9 mg, 0.01 mmol), PEO_{2K}iBBr (33.4 mg, 0.017 mmol, M_n = 2000), $OEOMA_{300}$ (1450 mg, 4.8 mmol, M_n = 300), AMA (88 mg, 0.53 mmol), PEO_{4K}DM (226 mg, 0.56 mmol), and 66 mg of PEO-OH (as a stabilizer) dissolved in 1.4 mL of ultrapure water and emulsified with 20 g of a 0.05% (w/w) of Span-80 in cyclohexane using ultrasonication (3 min) to form stable droplets. After degassing, 100 μL of ascorbic acid (100 mg/mL degassed) was injected to initiate the ARGET ATRP, which was stopped after 24 h at 30 °C. The nanogels were purified by precipitation into THF followed by dialysis (50 000 MWCO membrane) into THF and then into water to remove unreacted reagents.

RESULTS AND DISCUSSION

ARGET ATRP of AMA. The first report on the normal ATRP of AMA in its hydrochloride salt form reported in the literature required high concentration of CuCl catalyst coordinated with bpy (see Table 1).[20] In order to overcome such issues, a new ARGET ATRP system was tested for the polymerization of the primary amine monomer. The polymerization was performed in IPA/water mixtures at 35 °C, using ascorbic acid as reducing agent and catalyst $CuBr_2$/TPMA. Ligand selection was based on the stability of $CuBr_2$/TPMA in water,[31] even at low pH. In addition it was experimentally determined that TPMA complexes proved to better control the ARGET polymerization of AMA than bpy complexes (see Figure S1). Initial attempts of the ARGET ATRP of AMA were done by adding the total amount of ascorbic acid (molar ratio of 0.3 in comparison to the initiator) at the beginning of the polymerization. However, a fast reduction of Cu(II) species was observed by the disappearance of the green color, characteristic of $CuBr_2$/TPMA complexes, after approximately 1 h of reaction. This resulted in an uncontrolled polymerization ($Đ$ > 1.5) with limited monomer conversion of 60%. Alternatively, ascorbic acid was fed to the reaction via a syringe pump to regenerate the Cu(I) activator species in a slow and controlled manner. Using this strategy, it was possible to achieve high monomer conversion (>90%) and controlled polymerizations ($Đ \approx 1.3$). The level of control obtained by the new ARGET ATRP was comparable to that of normal ATRP for different targeted degree of polymerization (DP) values (Table 1). In addition, ^{1}H NMR spectra of samples collected during the ARGET ATRP showed no sign of the formation of methacrylamide derivatives resultant from the AMA/PAMA rearrangement (Figure 1), which is known to happen under basic conditions.[20,21]

Our initial experiments (Table 1) indicated that the reaction conditions required optimization to achieve control over the ARGET ATRP of AMA. Therefore, a range of polymerization conditions were studied to understand their influence on AMA's polymerization.

Influence of the Reaction Temperature. The reports on the controlled polymerization of AMA, either in its *t*-Boc-protected or hydrochloride salt form, employ reaction temperatures of 50 °C[20,21,29,32,40] or higher.[25,26] To understand the influence of the temperature on the ARGET ATRP of AMA, three different temperatures were studied to find a balance between lowest polymerization temperature while still retaining good control over PAMA molecular weight at a reasonable polymerization rate. Table 2 shows that the polymerization rate was similar for 44 and 35 °C. However, at 25 °C the reaction was much slower, and after 5 h, the mixture lost its green color, indicating that $CuBr_2$ was completely reduced. Therefore, based on a compromise between the rate of reaction and temperature, 35 °C was determined as the optimal value for this study.

In aqueous ICAR,[41] ARGET,[31] or SARA[42] ATRP systems of neutral monomers, the addition of halide salts (e.g., NaCl and NaBr) enhanced the control over the polymerization. The halide salt helps to maintain the sufficiently high concentration of the deactivator complex, which can partially dissociate and loose activity in water during the polymerization. In our initial experiments (Table 1 and Figure 2) 30 mM of NaBr was added. However, as shown in Figure S2, the use of extra halide salt revealed no improvement in the control over the polymerization, since AMA monomer provides intrinsically enough halide anions (Cl^-). Therefore, in the remaining experiments no additional halide salts were added.

Influence of the Copper Concentration. Typically, ARGET ATRP systems use a lower concentration of catalyst compared to normal ATRP. However, for some challenging monomers (e.g., primary amines), higher catalyst loadings may be required to effectively control the polymerization. The influence of copper concentration on the control of the ARGET ATRP of AMA was evaluated from 10 000 to 3000 ppm (Figure 2). The three amounts of deactivator complex studied afforded reactions with similar rate of polymerization (Figure 2a). When the higher amount of $CuBr_2$ was used, the reaction was slightly faster, most probably due to a higher rate of reduction and no induction period was observed. As expected, the increase of the deactivator concentration led to better control over the polymerization (Figure 2b). However, there was a slight increase of the PAMA $Đ$ during the polymerization, especially for monomer conversions above ≈60%. The deviation of the observed molecular weights from theoretical molecular weights (Figure 2b) can be attributed to the use of conventional calibration using poly(ethylene glycol)

Table 1. Molecular Weight Parameters of PAMA Obtained by Both Normal ATRP and ARGET ATRP

entry	method	DP	time (h)	conv (%)	$M_n^{th} \times 10^{-3}$	$M_n^{SEC} \times 10^{-3}$	$Đ$
1	normal ATRP[a]	100	2.4	63	10.5	9.9	1.36
2	ARGET ATRP[b]	100	2.8	79	12.8	7.6	1.35
3	normal ATRP[a]	30	2.3	91	4.8	6.3	1.33
4	ARGET ATRP[c]	30	4.5	93	4.8	4.4	1.30

[a]Reaction conditions: $[AMA]_0/[EBiB]_0/[CuCl]_0/[bpy]_0$ = DP/1/2; IPA/H_2O = 80/20 (v/v); T = 50 °C; $[AMA]_0$ = 2 M. [b]Reaction conditions: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0$ = DP/0.5/2; FR_{AscA} = 43 nmol/min; IPA/H_2O = 30/70 (v/v); T = 35 °C; $[AMA]_0$ = 2 M. [c]Same reaction conditions as those mentioned in entry 2, but with FR_{AscA} = 10 nmol/min.

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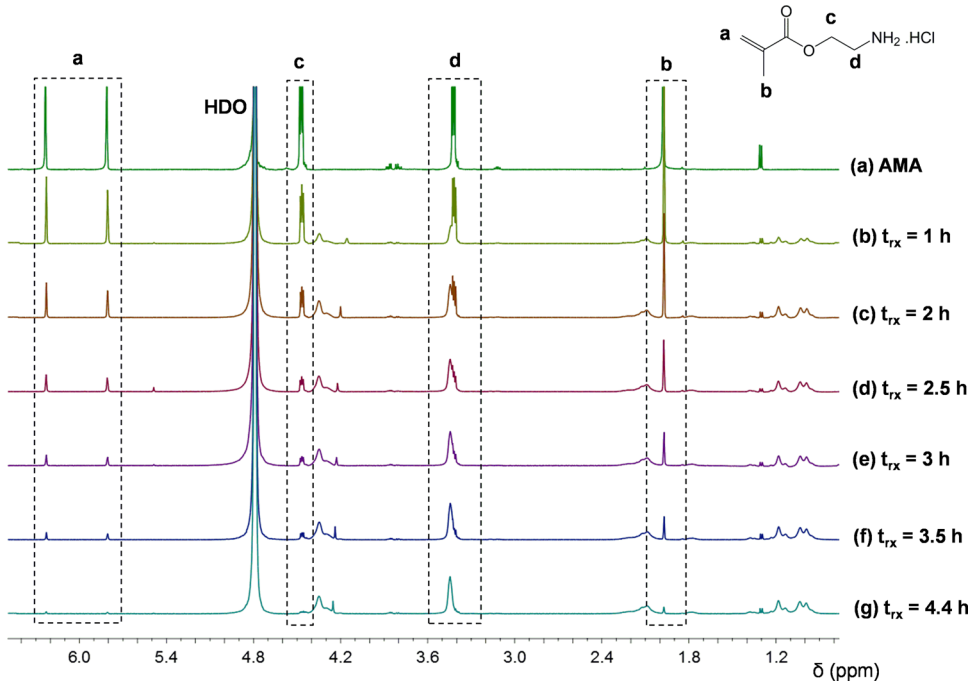

Figure 1. ^{1}H NMR spectra, in D_2O of (a) AMA monomer and (b–g) reaction mixture samples collected during the ARGET ATRP in water at 35 °C. Reaction conditions: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0$ = 100/1/0.5/02.0; FR_{AscA} = 43 nomL/min; $[AMA]_0$ = 2 M.

Table 2. Kinetic Parameters for the ARGET ATRP of AMA at Different Temperatures[a]

entry	T (°C)	k_p^{app} (h^{-1})	time (h)	conv (%)	$M_n^{SEC} \times 10^{-3}$	$Đ$
1	44	0.563	3.3	89	9.1	1.40
2	35	0.545	3.3	77	6.6	1.45
3	25	0.229	4.5	42	5.7	1.41

[a]Conditions: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0$ = 100/1/0.3/1.2, with $[NaBr]_0$ = 30 mM, $[AMA]_0$ = 2 M, FR_{AscA} = 43 nmol/min in IPA/H_2O = 50/50 (v/v).

standards, which have different hydrodynamic volumes than PAMA. Similar limitations have also been reported by other authors in the polymerization of AMA[20] and other hydrophilic monomers.[43−45] Therefore, to confirm the level of control obtained during the ARGET ATRP, one sample of PAMA obtained at 86% conversion (targeted DP of 100) was isolated from the reaction mixture and the molecular weight of the polymer was determined by ^{1}H NMR (see details in Figure S5) as being M_n^{NMR} = 17 × 10^3. This value is much closer to the theoretical molecular weight (M_n^{th} = 15 × 10^3) than the one obtained by SEC, suggesting that the ARGET ATRP is a suitable method for the control polymerization of the primary amine monomer.

Influence of the Solvent Mixture Composition. Prior reports have found that reaction with 20% of water in the IPA/water solvent mixture for the normal ATRP of AMA lead to minimal precipitation during the reaction.[20] However, in this work, these conditions resulted in complete precipitation of the polymer during the reaction, even for targeted DP as low as 30 (see Figure S3). To avoid precipitation of PAMA during polymerization several ratios of IPA to water were used to polymerize AMA (Figure 3). Polymerization of AMA in 50% IPA/water formed minor amounts of precipitate during the

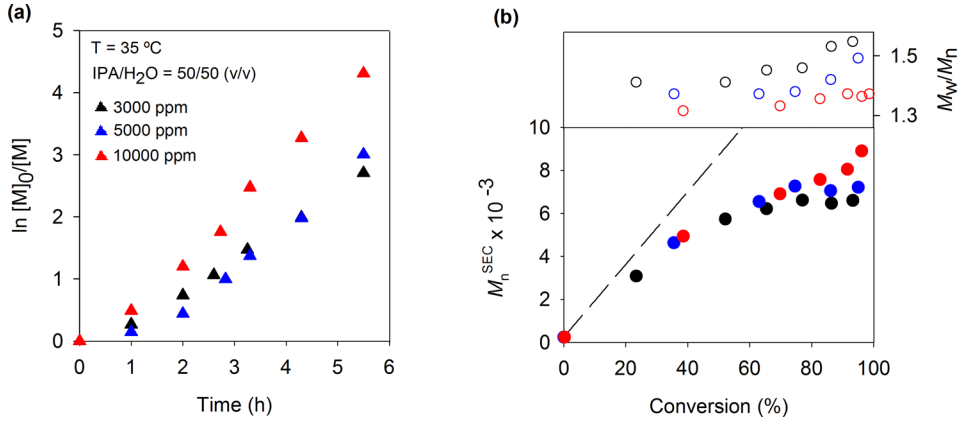

Figure 2. (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ vs time and (b) plot of number-average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) vs monomer conversion for the ARGET ATRP of AMA in IPA/H_2O = 50/50 (v/v) at 35 °C, using different amounts of deactivator complex. Reaction conditions: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0$ = 100/1/$[CuBr_2]_0/[TPMA]_0$; FR_{AscA} = 43 nmol/min; [NaBr] = 30 mM; $[AMA]_0$ = 2 M.

dx.doi.org/10.1021/ma501007j | Macromolecules 2014, 47, 4615−4621

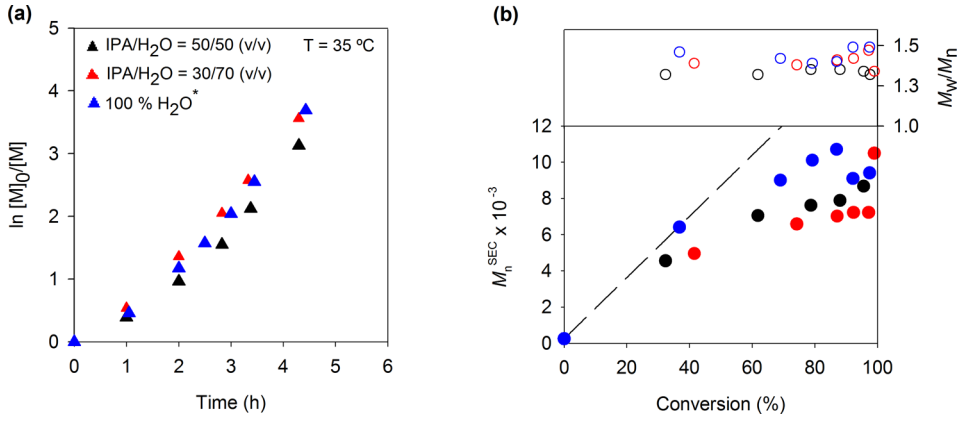

Figure 3. (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ vs time and (b) plot of number-average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) vs monomer conversion for the ARGET ATRP of AMA at 35 °C, using different amounts water in the solvent mixture. Reaction conditions: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0$ = 100/1/0.5/2.0; FR_{AscA} = 43 nomL/min; $[AMA]_0$ = 2 M.

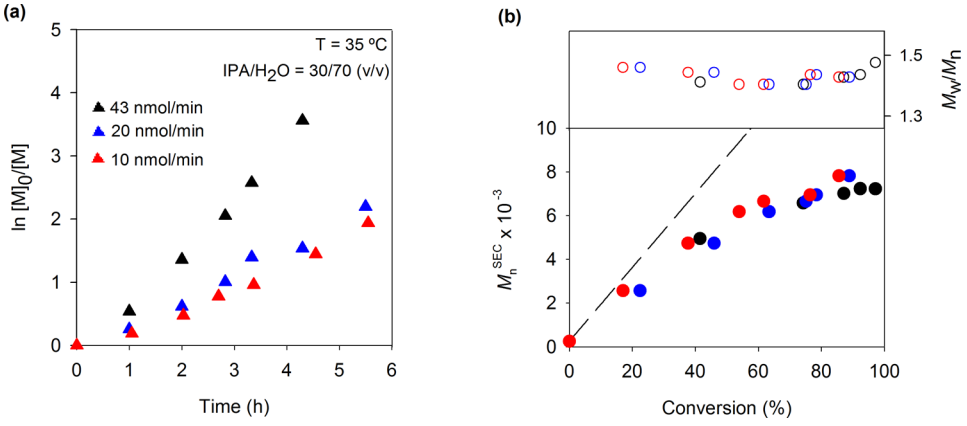

Figure 4. (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ vs time and (b) plot of number-average molecular weights (M_n^{SEC}) and $Đ$ (M_w/M_n) vs monomer conversion for the ARGET ATRP of AMA in IPA/H_2O = 30/70 (v/v) at 35 °C, using different feeding rates of the ascorbic acid. Reaction conditions: $[AMA]_0/[EBPA]_0/[AscA]/[CuBr_2]_0/[TPMA]_0$ = 100/1/FR_{AscA}/0.5/2.0; $[AMA]_0$ = 2 M.

reaction, and decreasing the amount of IPA to 30% and 0% led to homogeneous and precipitate-free polymerization (see Figure S4). Overall, our results indicate that both control over the molecular weight distribution and the rate of polymerization are not influenced by increased water content in the reaction media.[46]

Influence of the Ascorbic Acid Feeding Rate. It has been reported that the feeding rate of the ascorbic acid (FR_{AscA}) influences both polymerization rate and control over the polymers molecular weight.[31] Usually, higher feeding rates provide faster reactions but poorer control. The FR_{AscA} acid was studied from 10 to 43 nmol/min in the ARGET ATRP of AMA (Figure 4). As expected, the lowest rate of polymerization was obtained for FR_{AscA} of 10 nmol/min (Figure 4a), whereas 20 and 43 nmol/min gave faster polymerization rates. Despite the difference in polymerization rates, there was no significant improvement of the control over the PAMA molecular weight during the polymerization in the range of FR_{AscA} studied (Figure 4b).

Evaluation of the PAMA "Livingness". A PAMA-Br macroinitiator obtained at high conversion (>90%) by ARGET ATRP was extended with the water-soluble $OEOMA_{475}$ monomer. The complete shift of the SEC trace confirmed the formation of a well-defined block copolymer with $Đ$ = 1.25 (Figure 5). No tailing was observed in the block copolymer molecular weight distribution, which suggests that the PAMA-Br prepared by ARGET ATRP retains high chain-end functionality. These results present a significant improvement

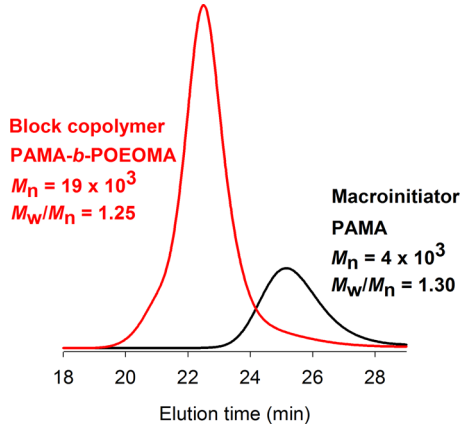

Figure 5. SEC traces of PAMA before and after extension with $OEOMA_{475}$: macroinitiator obtained at 93% of monomer conversion (black line) and block copolymer at 90% of OEOMA conversion (red line). First block: $[AMA]_0/[EBPA]_0/[CuBr_2]_0/[TPMA]_0/[AscA]$ = 30/1/0.5/2.0/10 nmol/min; second block: $[OEOMA_{475}]_0$ = 1 M; $[OEOMA_{475}]_0/[EBPA]_0$ = 70. Chain extension was done by "one-pot ARGET ATRP in IPA/H_2O = 30/70 (v/v) at 35 °C; $[AMA]_0$ = 2M; $V_{solvent}$ (first block) = 860 μL.

dx.doi.org/10.1021/ma501007j | Macromolecules 2014, 47, 4615−4621

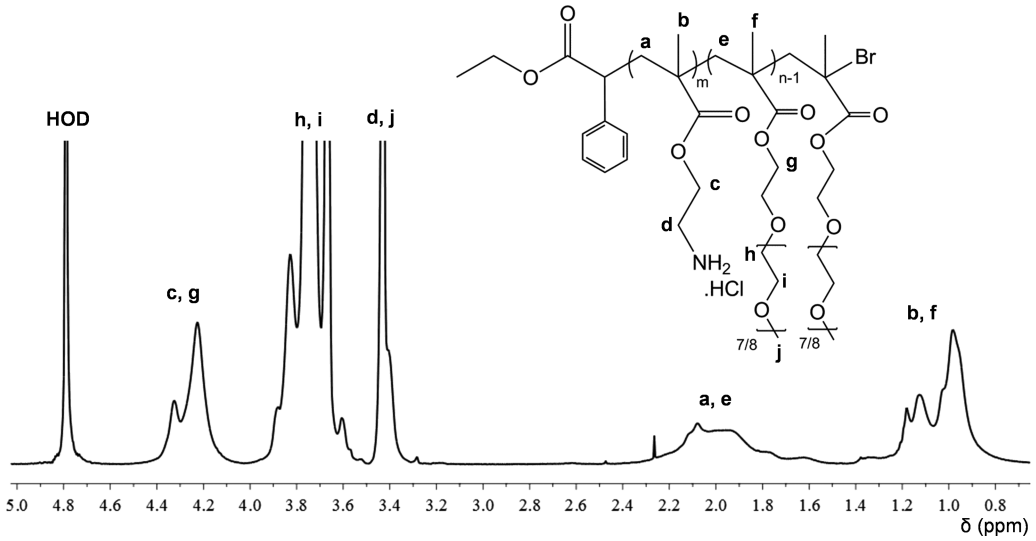

Figure 6. 400 MHz ^{1}H NMR spectrum, in D_2O, of the PAMA-*b*-POEOMA block copolymer obtained by "one-pot" ARGET ATRP.

in the controlled synthesis of PAMA in comparison with the normal ATRP reported in the literature, which have low chain-end functionality preventing the successful extension of the polymer.[32] For the first time, it was possible to prepare a well-defined PAMA-based block copolymer using AMA as the monomer of the first block. Similar increase on the chain-end functionality of polymers prepared by ARGET ATRP was previously reported for the polymerization of styrene.[47] This result was attributed to the lower concentration of metal catalyst/ligand complex used in ARGET ATRP, in comparison with normal ATRP, which decreased the rate of catalyst-induced side reactions.[47,48] The validation of this hypothesis on the ARGET ATRP of AMA requires further investigation. The chemical structure of the PAMA-*b*-POEOMA was confirmed by ^{1}H NMR spectroscopy (Figure 6).

Preparation of PAMA Nanogels by ARGET ATRP. The potential of the ARGET ATRP was explored for the preparation of PAMA-based nanogels. Nanogels are a diverse class of nanosized hydrogels prepared using inverse miniemulsion and have been used in many biomedical applications including drug or gene delivery agents.[49−51] To demonstrate the feasibility of preparing PAMA-based nanogels by ARGET ATRP, an aqueous phase containing AMA and $OEOMA_{300}$ with an organic phase composed of Span-80 in cyclohexane stable and inverse miniemulsion was prepared using ultrasonication. The active catalysis was (re)generated by injection of ascorbic acid. After 24 h the reaction was stopped, precipitated and purified using dialysis. The nanogels were characterized using dynamic light scattering in 10 mM acetate buffer (pH = 4.5), and their diameter was determined to be 290 ± 61 nm (Figure 7). Because of the cationic nature of PAMA at low pH, we anticipate that these nanogels could be promising materials for gene delivery applications.

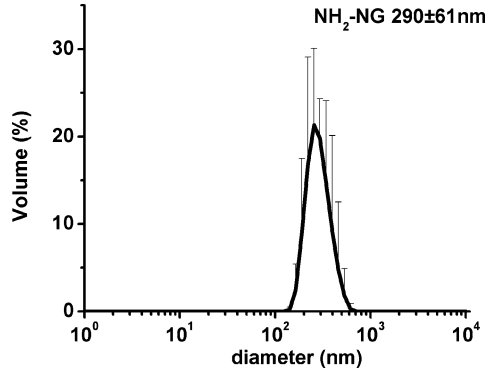

Figure 7. Volume distribution of PAMA-based nanogels (NH_2-NG) prepared by ARGET ATRP in inverse miniemulsion measured using DLS. Samples were measured in 10 mM acetate buffer (pH = 4.5). PAMA-based nanogels prepared from $[PEO_{2K}iBBr]_0/[OEOMA_{300}]_0/[AMA]_0/[PEO_{4K}DM]_0/[CuBr_2]_0/[AscA]_0$ = 1/290/31/3.4/0.5/0.6/3.4, 66 mg of PEG-OH_{2000}, in 5% Span-80 in cyclohexane for 24 h at 30 °C. Size = 290 ± 61 nm.

CONCLUSIONS

An ARGET ATRP system was developed for the preparation of well-defined PAMA in isopropanol/water mixtures or aqueous medium at 35 °C using $CuBr_2$/TPMA as the catalytic complex. Ascorbic acid, which was used as the reducing agent for the regeneration of Cu(I) activator species, had to be slowly feed into the reaction mixture to afford high monomer conversions (>90%) and reasonable control ($Đ \approx 1.3$). For the first time, PAMA prepared by ATRP techniques retained high chain-end functionality, allowing the preparation of a well-defined block copolymer (PAMA-*b*-POEOMA). The ARGET ATRP was also used for the synthesis of PAMA-based nanogels, which can form interesting materials for biomedical applications.

ASSOCIATED CONTENT

Supporting Information

Kinetics, molecular weight, and dispersities evolution plots for different ligands and halide salt concentrations, reaction mixture pictures, and ^{1}H NMR spectrum of PAMA. 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.

■ ACKNOWLEDGMENTS

P.V.M. acknowledges FCT-MCTES for her PhD scholarship (SFRH/BD/69152/2010). The authors thank Hironobu Murata for assistance with the SEC analysis and Joanna Burdynska for the synthesis of TPMA. The work was supported by the NSF (DMR 09-69301), and 500 MHz NMR instrumentation at CMU was partially supported by NSF (CHE-1039870). Part of the work was supported by the Polypulp - QREN 30225 project.

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