Direct Synthesis of Controlled-Structure Primary Amine-Based Methacrylic Polymers by Living Radical Polymerization

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ABSTRACT: We report the direct homopolymerization and copolymerization of a primary amine-based methacrylic monomer, 2-aminoethyl methacrylate (AMA), in its hydrochloride salt form by living radical polymerization. Linear PAMA homopolymer and AB diblock copolymers (where A = AMA and B = 2-(diisopropylamino)ethyl methacrylate, or DPA) were prepared with reasonably narrow polydispersities ($M_w/M_n \sim 1.2-1.3$) in either DMSO or DMSO/1,4-dioxane mixtures at 70 °C using cumyl dithiobenzoate (CDB) as a reversible addition−fragmentation transfer (RAFT) chain transfer agent. AMA monomer is highly unstable in its nonprotonated form, undergoing rapid internal rearrangement to afford 2-hydroxyethyl methacrylamide. PAMA homopolymer proved to be significantly more stable than AMA monomer, but nevertheless slow chemical degradation occurred over long time scales (days) in alkaline solution. Initial ^{1}H NMR studies confirm that (i) this PAMA degradation involves the elimination of 2-aminoethanol and (ii) at least some of its repeat units are converted into 2-hydroxyethyl methacrylamide units. AMA was also polymerized by atom transfer radical polymerization (ATRP) in methanol, water, and either 95:5 or 80:20 2-propanol/water mixtures. Polymerization was slow and incomplete in methanol at both 20 and 50 °C. Using water gave a fast, poorly controlled polymerization at 50 °C, while the 95:5 2-propanol/water mixture proved to be an inadequate solvent for PAMA at this temperature. However, an 80:20 2-propanol/water mixture gave slower, well-controlled polymerizations at 50 °C with relatively low final polydispersities ($M_w/M_n < 1.25$). Thus, this solvent mixture was used to prepare well-defined AMA-based diblock copolymers using poly(ethylene oxide)-based ATRP macroinitiators. Furthermore, statistical copolymerizations of AMA with either 2-hydroxyethyl methacrylate (HEMA), glycerol monomethacrylate (GMA), 2-hydroxypropyl methacrylate (HPMA), or 2-(dimethylamino)ethyl methacrylate (DMA) were conducted using ATRP in methanol at 20 °C. Selected copolymers were cross-linked in aqueous solution at pH 9 by Michael addition using poly(ethylene glycol) diacrylate (PEGDA), as confirmed by ^{1}H NMR studies. Shell cross-linked micelles with pH-responsive cores were also prepared from a RAFT-synthesized PAMA−PDPA diblock copolymer in water using PEGDA, as confirmed by dynamic light scattering studies.

Introduction

Primary amine-based copolymers have been exploited for numerous applications, including drug carriers,[1−3] functional colloidal particles for biomedical applications,[4−6] the preparation of sterically stabilized polyaniline particles,[7] the synthesis of polypeptide vesicles and micelles,[8] and the localized biomineralization of calcium carbonate and silica.[9,10]

However, the synthesis of well-defined primary amine-based copolymers with controlled architectures and narrow polydispersities has proven to be extremely challenging. Nakahama and co-workers first reported the controlled polymerization of amino-functionalized *N*,*N*-dialkyl-substituted acrylamide monomers and styrene para-substituted with *N*-arylimino groups via anionic polymerization[11−15] in THF at −78 °C to afford polymers with predetermined molecular weights and very narrow polydispersities. Similarly, Yuan and co-workers prepared a range of near-monodisperse linear poly(ethylene imine)s by hydrolysis of a poly(2-alkyl-2-oxazoline) precursor (previously synthesized by cationic ring-opening polymerization) and showed that these cationic polymers were highly effective in promoting the catalytic deposition of silica under biomimetic conditions.[10,16] However, the rigorous purification conditions and mandatory use of protecting group chemistry are two significant disadvantages to such approaches. Deming and co-workers[8,9,17] reported the synthesis of a wide range of controlled-structure primary amine-based polypeptide block copolymers via the ring-opening polymerization of *N*-carboxyanhydrides. These elegant studies have undoubtedly opened up many exciting applications, but *N*-carboxyanhydrides are generally not commercially available and such air-sensitive polymerizations are best conducted in gloveboxes.

The recent development of living radical polymerization techniques such as atom transfer radical polymerization (ATRP)[18−20] and reversible addition−fragmentation chain transfer (RAFT)[21−24] polymerization has resulted in a paradigm shift in synthetic polymer chemistry. Several thousand papers have described facile syntheses of relatively well-defined vinyl polymers, including many examples based on highly functional/hydrophilic monomers.[25−31] Nevertheless, there are still relatively few studies that have exploited ATRP or RAFT for the synthesis of controlled-structure primary amine-based vinyl polymers. Indeed, we are only aware of two such reports. Dufresne and Leroux[32] polymerized t-Boc-protected 2-aminoethyl methacrylate by ATRP using a poly(ethylene oxide)-based macroinitiator and used the resulting deprotected diblock copolymer for drug delivery applications. More recently, Li and co-workers copolymerized a primary amine-based methacrylamide with *N*-isopropylacrylamide to produce thermoresponsive diblock copolymers that self-assembled to form vesicular structures in aqueous media.[33]

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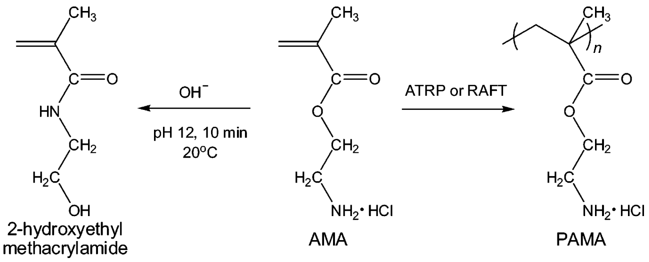
Scheme 1. Internal Rearrangement of AMA Monomer To Give 2-Hydroxyethyl Methacrylamide in Alkaline Media (Left) and the Synthesis of PAMA Homopolymer via Either ATRP or RAFT (Right)



2-Aminoethyl methacrylate hydrochloride (AMA) is a commercially available primary amine-based methacrylic monomer that is readily prepared by reacting methacryloyl chloride with molten 2-aminoethanol hydrochloride at 95 °C.[34] It has been previously used as a comonomer for the preparation of cationic latexes[35] and has also been oligomerized using catalytic chain transfer polymerization to afford polydisperse AMA-based macromonomers.[36] Recently we reported that AMA can be reacted with lactobionolactone in order to prepare a new cyclic sugar methacrylate.[34] In principle, the development of ATRP and RAFT suggests that the direct synthesis of controlled-structure AMA-based copolymers should be both feasible and convenient.

Herein we report the synthesis of well-defined primary amine-based methacrylic copolymers by living radical polymerization techniques. More specifically, AMA monomer is (co)polymerized directly in its hydrochloride salt form via both ATRP and RAFT to produce low-polydispersity homopolymers, statistical copolymers, and diblock copolymers (see Scheme 1). As far as we are aware, this is the first time that AMA monomer has been polymerized with reasonably good control without recourse to protecting group chemistry.[32] The relative merits of ATRP and RAFT for the (co)polymerization of AMA are discussed and the relative stabilities of both AMA monomer and AMA homopolymer with respect to chemical degradation are examined. Since primary amine groups are amenable to a wide range of postpolymerization chemistries (e.g., rapid formation of amides and imines, ring-opening of epoxy groups, Michael addition, etc.), we believe that this synthetic advance opens up new opportunities in several areas, including improved cross-linking strategies for shell cross-linked micelles,[37] novel copolymers for silicification under mild conditions,[8,16,38] and more robust polyelectrolytic macroinitiators for surface polymerizations.[39,40]

Experimental Section

Materials. 2-Hydroxyethyl methacrylate (HEMA, >99%), 2-hydroxypropyl methacrylate (HPMA, >97%), and glycerol monomethacrylate (GMA) were kindly donated by Cognis UK Ltd. (Hythe, UK). These three monomers were used without further purification. 2-(Dimethylamino)ethyl methacrylate (DMA) was purchased from Aldrich, and 2-(diisopropylamino)ethyl methacrylate (DPA) was purchased from Scientific Polymer Products; in each case inhibitor was removed by passing through a basic alumina column prior to use. Methacryloyl chloride (>97%), ethanolamine hydrochloride (>98%), hydroquinone (99%), Cu(I)Br (99.999%), Cu(I)Cl (99.995%) 2,2′-bipyridine (bpy, 99%), poly(ethylene glycol) diacrylate (PEGDA, $M_n = 575$, 99%), dimethyl sulfoxide (DMSO, 99.8%), and 1,4-dioxane (>99%) were all purchased from Aldrich and were used as received. 2,2′-Azobis(2-methylpropionitrile) (AIBN) was purchased from Fluka and recrystallized from ethanol prior to use. Methanol and 2-propanol (IPA) were purchased from Fisher and were used as received. Deionized water was used in all experiments. Silica gel 60 (0.0632−0.2 mm) was obtained from Merck (Darmstadt, Germany). NMR solvents (D_2O, CD_3OD, $CDCl_3$, MeOD, and NaOD) were purchased from Fisher. Regenerated cellulose dialysis membrane (Spectra/Por 6, molecular weight cutoff 1000 and 2000 Da) was purchased from Fisher. The 2-(4-morpholino)ethyl 2-bromoisobutyrate (ME-Br) ATRP initiator and several poly(ethylene oxide)-based macroinitiators (PEO$_n$-Br) were synthesized according to the literature.[41,42]

Synthesis of AMA Monomer. AMA monomer was synthesized using a previously reported protocol.[34] 2-Aminoethanol hydrochloride (65 g, 0.67 mol), methacryloyl chloride (100 mL, 0.96 mol), and hydroquinone (0.50 g) were added to a three-necked round-bottomed flask fitted with a condenser. The 2-aminoethanol hydrochloride salt was esterified in the melt at 90−95 °C under a nitrogen atmosphere for 1 h, and the reaction was maintained at 70−75 °C for a further 2 h. The HCl gas evolved during this reaction was neutralized using an aqueous NaOH solution connected to the reaction vessel. The crude product was cooled to 40 °C, diluted with THF (50 mL), and precipitated into excess *n*-pentane (500 mL). The resulting creamy white precipitate was isolated by filtration, washed thoroughly with *n*-pentane (500 mL), and dried under vacuum. It was then recrystallized twice using a 7:3 ethyl acetate/2-propanol mixture at −25 °C. The final product was dried under vacuum to produce an overall yield of 64% (>98% purity as judged by ^{1}H NMR).

Synthesis of Cumyl Dithiobenzoate (CDB) RAFT Agent. The synthesis of CDB was carried out according to the literature (see Supporting Information).[43]

RAFT Synthesis of PAMA Homopolymer. RAFT polymerizations of AMA were conducted at 70 °C, employing AIBN as the radical initiator and CDB as the RAFT chain transfer agent. A typical protocol was as follows. In a 25 mL Schlenk flask, AMA (3.31 g, 20 mmol) was first dissolved in anhydrous DMSO (6 mL) before the addition of AIBN (7.0 mg, 0.04 mmol) and CDB (54.0 mg, 0.2 mmol, target $DP_n = 100$). After degassing via three freeze−thaw cycles, the flask was placed in an oil bath within 24 h at 70 °C with continuous stirring. The crude product was purified by dialysis against water to remove unreacted AMA monomer and DMSO and then freeze-dried overnight from water. The monomer conversion was almost 100% as estimated from the ^{1}H NMR spectrum, and the polydispersity obtained from aqueous GPC was 1.28.

RAFT Synthesis of PAMA−PDPA Diblock Copolymer. A RAFT-synthesized PAMA homopolymer (3.0 g, 0.18 mmol, DP = 100) in DMSO (5 mL) was chain-extended directly after polymerization of the AMA monomer. Thus, the viscous reaction solution was diluted with 3 mL of anhydrous DMSO and then mixed with DPA (1.55 g, 7.3 mmol) and AIBN (6 mg, 0.04 mmol) in a 50 mL flask which was subsequently degassed by three freeze−thaw cycles. The DPA polymerization was carried out at 70 °C in an oil bath with continuous stirring for 24 h. Typical DPA conversions ranged from 90 to 99%. AMA-rich diblock copolymers were prepared and purified by dialysis against water to remove DMSO and traces of unreacted monomer. The final copolymer was obtained as a white powder after freeze-drying overnight. Diblock copolymers were also prepared by transferring a degassed solution of DPA in DMSO into the stirred PAMA reaction solution at 70 °C directly, without adding further AIBN initiator. The polymerization was typically terminated after 24 h by exposure to air.

RAFT Synthesis of PDPA Homopolymer and PDPA−PAMA Diblock Copolymer. The protocol for the RAFT homopolymerization of DPA was essentially the same as that used for AMA. DPA (3.0 g, 14.0 mmol) and anhydrous 1,4-dioxane (3 mL) were added to a 25 mL Schlenk flask prior to the addition of AIBN (12 mg, 0.07 mmol) and CDB (96 mg, 0.35 mmol). After degassing via three freeze−thaw cycles, the flask was placed in an oil bath for 24 h at 70 °C with continuous stirring. The crude product was purified by precipitating into excess methanol twice, followed by vacuum-drying. The $PDPA_{162}-PAMA_{30}$ diblock copolymer was prepared from a PDPA macro-RAFT agent using the same procedures described above. The monomer conversion was 90%

for the DPA block and almost 100% for the AMA block, as estimated from ^{1}H NMR spectra.

ATRP Synthesis of AMA-Based Statistical Copolymers. Statistical copolymerizations of AMA with various other methacrylic monomers were conducted by ATRP in methanol at 20 °C. The preparation of a P($HEMA_{45}-AMA_5$) statistical copolymer is typical and was carried out as follows. In a 25 mL Schlenk flask, CuBr (143.5 mg, 1.00 mmol) and bpy (312 mg, 2.00 mmol) were added under a nitrogen atmosphere before a deoxygenated solution of AMA (0.83 g, 5.00 mmol) and HEMA (5.85 g, 45.0 mmol) was added. Afterward, a solution of ME-Br (280 mg, 1.00 mmol) in methanol (6.0 mL) was transferred to the flask, and the polymerization was conducted at 20 °C with continuous stirring. The crude product was diluted with methanol and filtered through a silica column to remove the spent copper catalyst. Finally, the solvent was removed via rotary evaporation, and the copolymer was dried under vacuum to a constant mass. The overall comonomer conversion was determined by ^{1}H NMR in each case.

ATRP Synthesis of PAMA Homopolymers and Diblock Copolymers. The homopolymerization of AMA was performed in turn using three ATRP initiators (ME-Br, PEO_{45}-Br, and PEO_{113}-Br) in either 95:5 IPA/H_2O or 80:20 IPA/H_2O mixtures. The protocol for each AMA polymerization was essentially the same, apart from the choice of initiator and solvent. In a typical ATRP synthesis, AMA (1.47 g, 9.0 mmol), ME-Br (50 mg, 0.18 mmol, target $DP_n = 50$), and bpy (56 mg, 0.36 mmol) were added to a flask under a nitrogen atmosphere. Degassed IPA/H_2O 80:20 (3.1 mL, 33% w/v) was added, and the solution was stirred at 50 °C. On addition of Cu(I)Cl catalyst (18 mg, 0.18 mmol) the reaction solution turned dark brown, indicating the onset of polymerization. After 6 h, the polymerizing solution was diluted with water and dialyzed against water (Spectrapor 6, molecular weight cutoff 1000 Da) for 3 days to remove the Cu(II) catalyst. During dialysis, the blue/green polymer solution gradually became colorless. The aqueous solution was then freeze-dried from water overnight.

Preparation of $PAMA_{100}-PDPA_{40}$ Diblock Copolymer Micelles. Aqueous PDPA-core micelles were prepared by direct dissolution in aqueous solution at neutral pH. The micelle hydrodynamic diameter was determined by dynamic light scattering studies on a 0.50 wt % copolymer solution.

Cross-Linking of $PAMA_{100}-PDPA_{40}$ Diblock Copolymer Micelles Using PEGDA. Poly(ethylene glycol) diacrylate PEGDA, 28 mg, 0.10 mmol of acrylate groups) was added to an aqueous solution of $PAMA_{100}-PDPA_{40}$ copolymer micelles (0.50 wt %, 12.5 mL, 0.25 mmol of amine units) at pH 9. Cross-linking of the PAMA chains via Michael addition resulting was monitored by ^{1}H NMR for 162 h at 20 °C. DLS studies of the resulting shell cross-linked micelles were also conducted.

Characterization Techniques. *^{1}H NMR Spectroscopy.* All ^{1}H NMR spectra were recorded in either DMSO, $CDCl_3$, D_2O, CD_3OD, or d_5-pyridine using a 250 MHz Bruker ACF-250 spectrometer.

Dynamic Light Scattering (DLS). DLS studies were conducted at 25 °C using a Brookhaven BI-200SM instrument equipped with a 9000AT correlator and a solid-state laser (50 mW, $\lambda = 532$ nm) at a fixed scattering angle of 90°. Data were analyzed using Contin software, and hydrodynamic diameters were calculated from diffusion coefficients using the Stokes–Einstein equation, which is valid for isolated, noninteracting, monodisperse spheres.

THF GPC. The molecular weights (M_n) and polydispersities (M_w/M_n) of P(DMA–AMA) and P(HPMA–AMA) statistical copolymers were assessed by THF GPC. The GPC setup comprised two Polymer Laboratories PL gel 5 μm MIXED-C columns. The GPC eluent was HPLC grade THF containing 2.0% (v/v) TEA and 0.05% (w/v) BHT at a flow rate of 1.0 mL min^{-1}. The column temperature was set at 30 °C. Ten near-monodisperse PMMA standards ($M_p = 2000-300\,000$ g mol^{-1}) were used for calibration. The data were analyzed using PL Cirrus GPC software (version 2.0) supplied by Polymer Laboratories.

DMF GPC. The molecular weights and polydispersities of the P(HEMA–AMA) and P(GMA–AMA) statistical copolymers were determined by DMF GPC at 70 °C. The GPC setup comprised three Polymer Laboratories PL gel 10 μm MIXED-B columns in series with a Viscotek TriSEC model 302 refractive detector. The flow rate was 1.0 mL min^{-1}, and the mobile phase contained 10 mmol of LiBr. Ten near-monodisperse PMMA homopolymer standards ($M_p = 2000-300\,000$ g mol^{-1}) were used for calibration. The data were analyzed using Viscotek TriSEC 3.0 software.

Aqueous GPC. The molecular weights and polydispersities of all the PAMA homopolymers, the PDPA–PAMA diblock copolymers, and various PEO–PAMA diblock copolymers were determined by aqueous GPC at 35 °C using a PL Aquagel-OH 40 and a Aquagel-OH 30 column connected in series to a Polymer LabsERC-7517A refractive index detector. The eluent was a pH 3.3 buffer solution comprising 0.30 M NaH_2PO_4 and 1.0 M acetic acid at a flow rate of 1.0 mL min^{-1}. Eight near-monodisperse poly(2-vinylpyridine) standards ($M_p = 1480-117\,000$ g mol^{-1}) were used for calibration. The data were analyzed using PL Cirrus GPC software (version 2.0) supplied by Polymer Laboratories.

Results and Discussion

Monomer Synthesis. AMA is commercially available as a "technical" grade. However, its purity is only around 90%, so we elected to synthesize this monomer on a 50 g scale using a literature protocol.[34] AMA monomer is highly unstable in its free amine form, since it undergoes internal rearrangement to generate the thermodynamically more stable isomer, 2-hydroxyethyl methacrylamide (see Scheme 1). However, AMA is indefinitely stable in its as-synthesized hydrochloride salt form (see below).[44] The assigned ^{1}H NMR spectrum of AMA monomer, as recorded in its hydrochloride salt form in $CDCl_3$, is shown in Figure 1S (see Supporting Information) and confirms its high purity (>99%). Acid titration of this monomer indicated a pK_a of around 8.8 (see Figure 2S in the Supporting Information), as expected for a typical primary amine.[45] The chemical stability of AMA monomer was studied by ^{1}H NMR spectroscopy in D_2O, with the solution pH being adjusted using NaOD. At pH 12, AMA was rapidly converted to 2-hydroxyethyl methacrylamide within 10 min at 20 °C (see Figure 1S in the Supporting Information), whereas AMA monomer remained stable in its hydrochloride salt form in D_2O (i.e., around pH 7) for at least 14 days at 20 °C.

ATRP Homopolymerization of AMA. Initially, we examined the ATRP of AMA using a ME-Br initiator and CuBr/bpy catalyst in methanol at 20 °C for a target DP of 50. This protocol was selected since it had previously proved useful for a range of other hydrophilic methacrylic monomers such as MPC,[46] HEMA,[27] HPMA,[26] and GMA.[26] However, AMA polymerization was rather slow under these conditions: conversions of only 33% were achieved as judged by ^{1}H NMR. Moreover, the ATRP catalyst generally became inactive overnight (as judged by a color change from dark brown to bright green).

In contrast, AMA homopolymerization in DMSO using RAFT chemistry[22] was successful when using CDB as a chain transfer agent[43] and AIBN as a radical source (at a molar ratio of CDB/AIBN of 5.0). Kinetic studies conducted at 70 °C using an initial $[AMA]_0/[CDB]_0$ molar ratio (or target degree of polymerization, DP) of 50 afforded a linear semilogarithmic plot indicating first-order kinetics with respect to monomer (see Figure 1). Monomer conversions were calculated by ^{1}H NMR spectroscopy by comparing the integrated vinyl resonances at δ 5.4–6.3 to the integrated methylene signals at δ 0.5–1.0. Aqueous GPC analyses of aliquots taken from the AMA homopolymerization indicated a series of unimodal curves and a monotonic increase in molecular weight with conversion (see Figure 2). Further analysis confirmed a linear evolution in molecular weight with conversion, and polydispersities remained relatively narrow throughout the polymerization (see Figure 3).

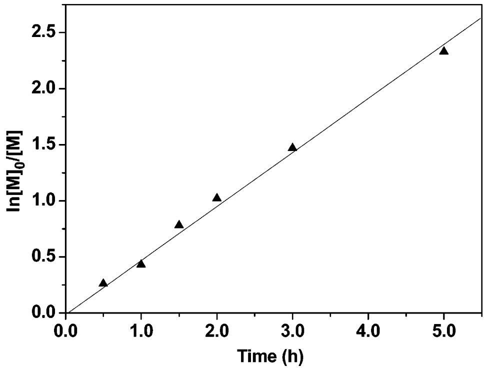


Figure 1. Semilogarithmic plot for the RAFT homopolymerization of AMA at 70 °C using CDB as a chain transfer agent in DMSO at a relative molar ratio of [AMA]:[CDB]:[AIBN] = 50:1.0:0.2.

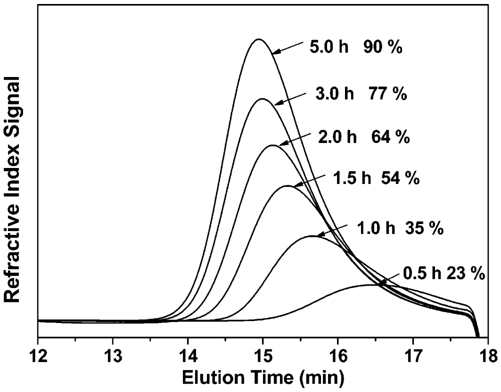


Figure 2. Aqueous GPC curves showing the evolution of molecular weight with elution time for the homopolymerization of AMA by RAFT at 70 °C using CDB in DMSO at a relative molar ratio of [AMA]:[CDB]:[AIBN] = 50:1.0:0.2.

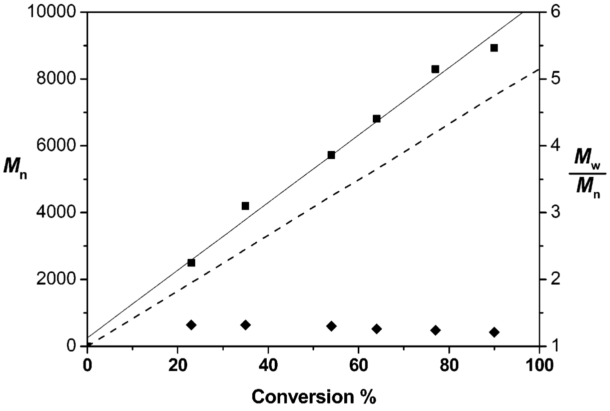


Figure 3. Evolution of M_n and polydispersity vs conversion for the homopolymerization of AMA mediated by CDB at 70 °C in DMSO at a relative molar ratio of [AMA]:[CDB]:[AIBN] = 50:1.0:0.2. Experimental M_n obtained from aqueous GPC (solid squares) and theoretical M_n calculated from the monomer conversion (dashed line).

This suggests that good living character was achieved under these conditions. However, the aqueous GPC data indicate somewhat higher M_n values than those expected from the AMA/CDB molar ratio (dashed line) throughout the polymerization. This is presumably because the poly(2-vinylpyridine) calibration standards are not ideal for the analysis of PAMA homopolymers. Similar molecular weight errors have also been observed for the polymerization of other hydrophilic monomers reported by McCormick's group and others.[47,48]

As shown in Table 1, a series of PAMA homopolymers were prepared with mean DP ranging from 40 to 200 by adjusting the AMA/CDB molar ratio; in each case reasonably high conversions were attained within 24 h. Aqueous GPC analysis indicated that each of these homopolymers had a relatively narrow, unimodal molecular weight distribution (M_w/M_n = 1.24−1.29, see Figure 4). These data confirm that RAFT syntheses allow the preparation of a series of near-monodisperse PAMA homopolymers by systematic variation of the reaction conditions.

Table 1. Summary of AMA Homopolymerizations by RAFT in DMSO at 70 °C

actual degree of polymerization	initial molar ratio[a]	conv (^{1}H NMR), %	time (h)	M_n[b]	M_w/M_n[b]
$PAMA_{40}$	50:1:0.2	80	5	8 400	1.27
$PAMA_{65}$	100:1:0.2	65	4	11 000	1.25
$PAMA_{100}$	100:1:0.2	100	24	15 500	1.28
$PAMA_{168}$	300:1:0.3	56	6	20 500	1.24
$PAMA_{200}$	200:1:0.2	100	24	25 700	1.29

[a] [Monomer]:[RAFT agent]:[AIBN]. [b] Determined by aqueous GPC via poly(2-vinylpyridine) standards using a NaH_2PO_4/CH_3COOH eluent at pH 2.5.

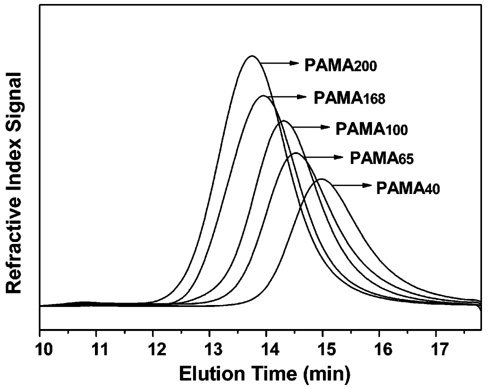


Figure 4. Aqueous GPC traces obtained for a series of PAMA homopolymers prepared by RAFT using CDB in DMSO at 70 °C.

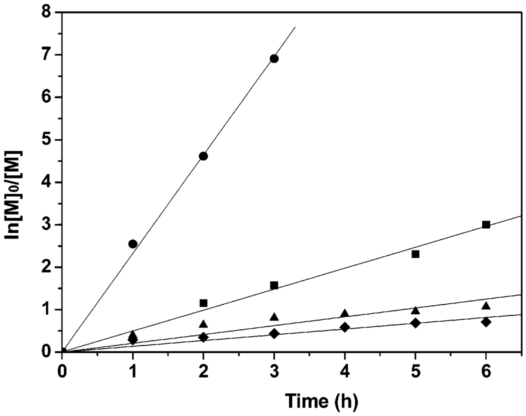


Figure 5. Semilogarithmic plots for the homopolymerization of AMA by ATRP at 50 °C in methanol (diamonds), 95:5 methanol/H_2O (triangles), 95:5 IPA/H_2O (squares), and 80:20 IPA/H_2O (circles) under the following conditions: [AMA]:[ME-Br]:[CuCl]:[bpy] = 50:1:1:2.

Given the sluggish rate of ATRP observed in our initial experiments at 20 °C, we studied the ATRP kinetics for $PAMA_{50}$ at 50 °C over a range of solvent conditions (methanol, 95:5 methanol/H_2O, 95:5 IPA/H_2O and 80:20 IPA/H_2O) (see Figure 5). In all cases linear semilogarithmic plots were obtained, indicating first-order kinetics with respect to monomer. Monomer conversions were calculated by ^{1}H NMR spectroscopy by comparing the integrated intensity of the vinyl signals at δ 5.4−6.3 to the methacrylic backbone signals at δ 0.5−1.0. For polymerizations conducted in methanol, 95:5 methanol/H_2O, and H_2O (see Table 2), complete conversions could not be achieved

Table 2. Conversion, Molecular Weight, and Polydispersity Data for the Homopolymerization of AMA by ATRP at 50 °C Using ME-Br Initiator in Various Solvents and [AMA]:[MEBr]:[CuCl]:[bpy] Relative Molar Ratios of m:1:1:2, Where $m = 10-50$

target polymer composition	solvent	time (h)	conv (%)[a]	M_n (g/mol)[b]	M_w/M_n[b]
$PAMA_{50}$	H_2O	1	62	7800	1.41
$PAMA_{50}$	methanol	6	66	7900	1.20
$PAMA_{50}$	95:5 methanol/H_2O	6	91	8800	1.16
$PAMA_{50}$	95:5 IPA/H_2O	6	92	9300	1.41
$PAMA_{50}$	80:20 IPA/H_2O	3	99	9500	1.24
$PAMA_{40}$	80:20 IPA/H_2O	3	97	8200	1.15
$PAMA_{30}$	80:20 IPA/H_2O	3	98	6300	1.21
$PAMA_{20}$	80:20 IPA/H_2O	3	97	5400	1.12
$PAMA_{10}$	80:20 IPA/H_2O	3	100	4500	1.09

[a] Conversions were determined using ^1H NMR spectroscopy by comparing the area of the vinyl proton resonances to the total methyl signal. [b] As determined by aqueous GPC at pH 2.5

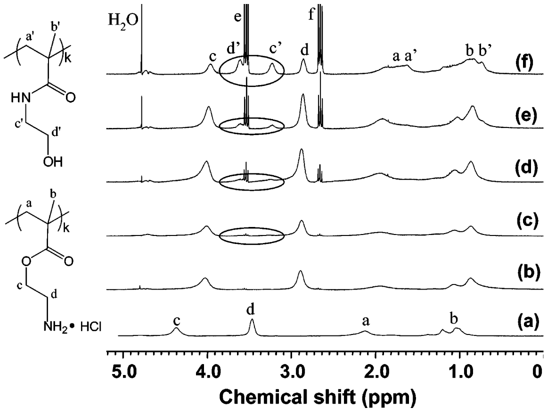


Figure 6. ^1H NMR spectra recorded at 20 °C for $PAMA_{65}$ in D_2O initially at (a) pH 7 and then at pH 12 after (b) 0, (c) 7, (d) 24, (e) 72, and (f) 656 h.

because the ATRP catalyst became inactive during these syntheses (as judged by its change in color from dark brown to bright green). For example, only 66% conversion was obtained in methanol after 6 h at 50 °C. Under purely aqueous conditions, the reaction solution turned green almost immediately, and the polymerization was poorly controlled ($M_w/M_n = 1.41$). The best results were obtained using 95:5 or 80:20 IPA/H_2O mixtures. Relatively high conversions (91−100%) were obtained within 3−6 h while maintaining good control, particularly for the 80:20 IPA/water composition ($M_w/M_n < 1.24$). Increasing the proportion of water from 5% to 20% enabled the reaction time to be reduced from 6 to 3 h (see entries 4 and 5 in Table 2). As the polymerization proceeded, the growing PAMA chains became increasingly insoluble in 95:5 IPA/H_2O. This did not adversely affect the polymerization kinetics, but may be responsible for the higher polydispersity observed for this sample (entry 4 in Table 2). Using an 80:20 IPA/H_2O mixture improved the PAMA solubility significantly, and a highly viscous solution was obtained at the end of the reaction with little sign of precipitation. Thus, this latter composition gave short reaction times, high conversions, and low final polydispersities and was therefore considered to be optimal for the ATRP synthesis of PAMA homopolymers.

The chemical stability of a RAFT-synthesized $PAMA_{65}$ homopolymer was examined under similar conditions as that used for the AMA monomer (i.e., 3.0% w/w in D_2O at 20 °C). Slow base-catalyzed degradation and partial rearrangement of the PAMA were monitored by ^1H NMR at pH 12 (see Figure 6). Under these conditions, the primary amine groups on the PAMA chains are fully deprotonated (compare spectrum a with spectrum b; the δ shifts observed for peaks c and d are consistent with deprotonation).

There are at least four possible degradation pathways for PAMA under these conditions (see Scheme 2). First, an ester carbonyl group can react intramolecularly with its own primary amine to form an amide (see route A). This is the polymer-analogous reaction to the monomer degradation route shown in Scheme 1, and no small molecule byproduct is produced. Alternatively, a similar intramolecular reaction could occur between an ester and an adjacent primary amine (see route B). In this case, a cyclic species is formed and 2-aminoethanol is eliminated. A third possibility involves intermolecular amidation and is shown in route C. Here a primary amine group on a PAMA chain reacts with an ester carbonyl on another PAMA chain; this also leads to the elimination of 2-aminoethanol. Finally, in more alkaline media (pH > 11) the PAMA ester groups may become susceptible to base hydrolysis by hydroxide anion, producing anionic carboxylate groups and 2-aminoethanol (see route D).

The elimination of 2-aminoethanol (via routes B, C, or D) is indicated by the appearance of two new signals "e" and "f" at δ 3.5 and δ 2.7 after 24 h (see spectra d−f in Figure 6). This assignment was verified by adding 2-aminoethanol (purchased from Aldrich) to a fresh solution of $PAMA_{65}$ homopolymer at pH 12. Thus, the degradation mechanism for PAMA certainly differs from that of AMA, since elimination of 2-aminoethanol was not observed for the monomer (see Figure 1S in the Supporting Information).

The appearance of two new peaks assigned to $HN-CH_2$ and $HO-CH_2$ protons (see signals c′ and d′ in Figure 6) after 72 h is consistent with the formation of 2-hydroxyethyl methacrylamide units within the degraded polymer chains (see route A in Scheme 2). In contrast, the other two amidation mechanisms (routes B and C) lead to retention of the original oxyethylene protons, so only one new signal (due to the two $HN-CH_2$ protons) would be expected in this case. Thus, it appears that PAMA degradation occurs by both route A and at least one of routes B, C, and/or D. Moreover, close inspection of Figure 6 suggests that the kinetics of degradation via route A are relatively slow, since 2-aminoethanol is observed before the appearance of peaks c′ and d′.

The intermolecular degradation pathway shown in route C should lead to either branched or cross-linked PAMA chains of higher molecular weight. Accordingly, aqueous GPC studies of the degraded PAMA were undertaken. An increase in polydispersity from 1.24 to 1.71 was observed for a 10% solution of $PAMA_{168}$ homopolymer stored at pH 12 for 14 days (data not shown). However, the M_n of this degraded homopolymer unexpectedly decreased, rather than increased. This anomaly may indicate polymer adsorption onto the aqueous GPC column rather than actual chain scission, since the C−C bonds in the methacrylic PAMA backbones are unlikely to be cleaved under these relatively mild conditions. This hypothesis is not unreasonable, since such degradation would reduce the cationic charge density on this polymer substantially and our aqueous GPC protocol was optimized for the analysis of cationic polymers. Further ^1H NMR, FT-IR, and GPC studies are clearly required to shed further light on the complex degradation mechanism(s) of PAMA in alkaline media.

Although the relative importance of the various degradation mechanisms remains unclear, the overall extent of degradation of the $PAMA_{65}$ homopolymer was estimated from ^1H NMR studies to be around 27% within 72 h at pH 12, and this increased monotonically up to 51% after 656 h (see Figure 6).

Scheme 2. Possible Degradation Mechanisms for PAMA in Aqueous Alkaline Solution at 20 °C: Intramolecular Amidation (Routes A and B), Intermolecular Amidation (Route C), and Ester Hydrolysis (Route D)

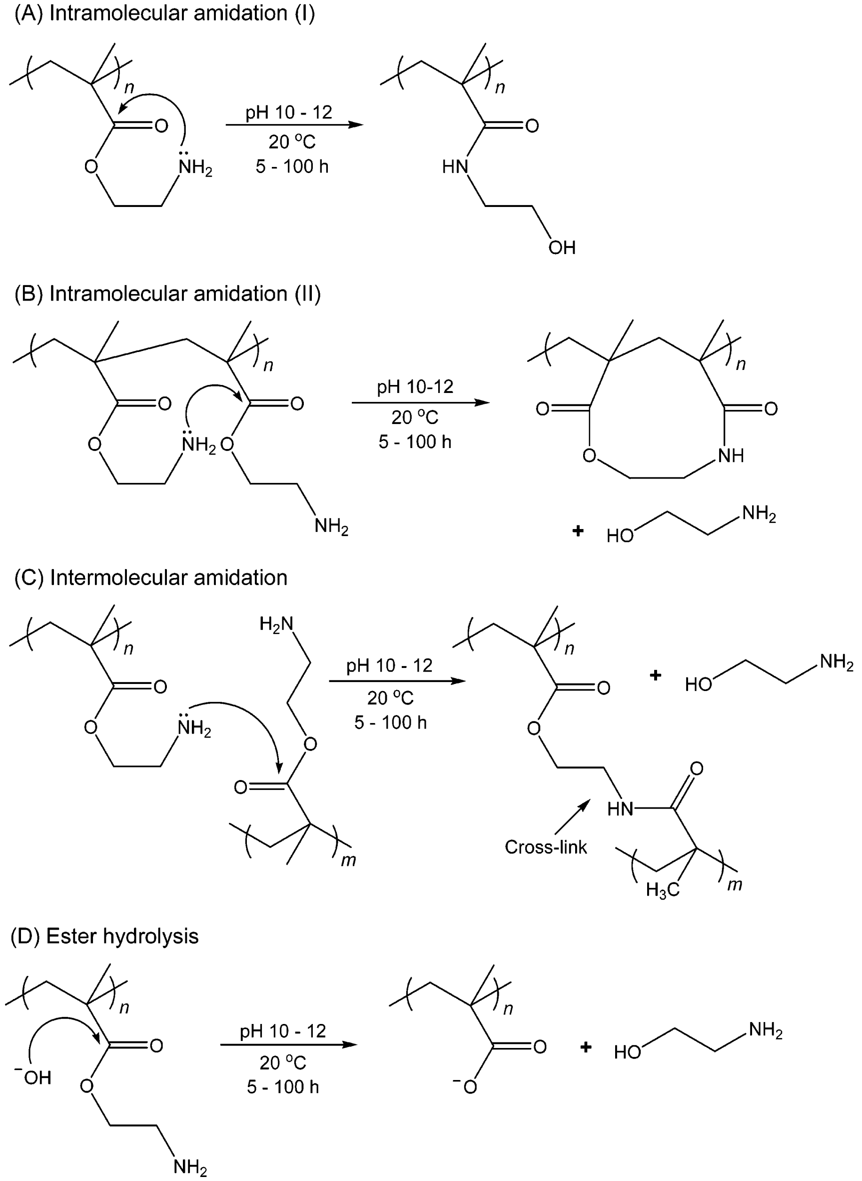


Table 3. Chemical Degradation of a 2.0% w/w Aqueous Solution of $PAMA_{65}$ as a Function of pH and Degradation Time in D_2O/NaOD at 20 °C

	extent of degradation (%)			
time (h)	pH 9.0	pH 10.0	pH 10.5	pH 11.0
5	0.0	0.6	2.0	3.8
24	0.0	1.0	4.0	4.2
49	0.0	2.0	4.9	4.6
73	0.0	2.3	6.6	4.9
100	0.0	3.7	7.2	8.7

A summary of these degradation data at pH 9, 10, 10.5, and 11 is presented in Table 3. It is particularly noteworthy that there are no detectable changes in the ^{1}H NMR spectrum of $PAMA_{65}$ if this homopolymer is stored as a 2.0% w/w solution in D_2O/NaOD (pH 9) for 100 h at 20 °C. Acid titration indicated a pK_a of around 7.6 (see Figure S2 in the Supporting Information), which is reasonably close to the pK_a of 7.1 reported in the literature[25] and is significantly lower than that of AMA monomer (8.8). This difference is expected, since polybases are generally weaker than their corresponding monomers, because the chain connectivity resists the buildup of cationic charge density. Thus, the $PAMA_{65}$ chains are more than 90% deprotonated at pH 9, yet do not undergo significant hydrolytic degradation over time scales of several days at 20 °C. In contrast, a 2.0% w/w solution of AMA *monomer* at pH 9 undergoes at least 95% rearrangement to form 2-hydroxyethyl methacrylamide within 3 h at 20 °C (see Figure 1S in Supporting Information). Thus, the more sterically hindered, less basic PAMA homopolymer is much less susceptible to chemical degradation than AMA *monomer*. Similar results were reported by Hennink and co-workers when comparing the relative hydrolytic stabilities of 2-(dimethylamino)ethyl methacrylate monomer with its corresponding homopolymer.[49]

The chemical stability of a 2.0% w/w solution of $PAMA_{65}$ homopolymer in D_2O (or D_2O/NaOD) was studied as a function of both time and solution pH by ^{1}H NMR (see Table 3). Below pH 10, no spectroscopic changes were observed for at least 100 h. However, detectable degradation commenced at or above pH 10, with greater degradation occurring on longer time scales in more alkaline media, as expected.

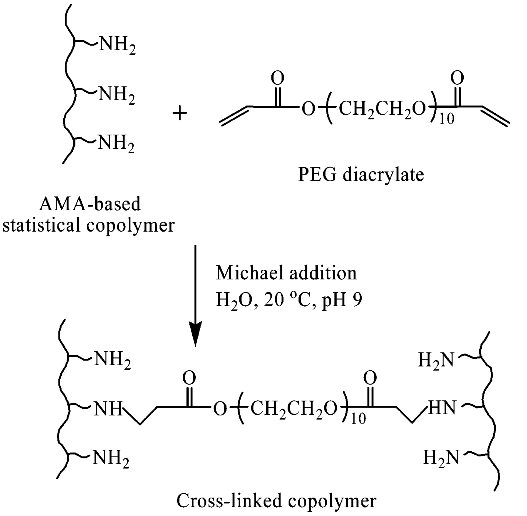
Preparation of AMA-Based Statistical Copolymers. The copolymerization of AMA with three hydrophilic methacrylic

Table 4. Summary of Synthesis Parameters and Molecular Weight Data for AMA-Based Statistical Copolymers Prepared by ATRP in Methanol at 20 °C

target copolymer composition	conv (^{1}H NMR) (%)	actual polymer composition	time (h)	M_n (GPC)^a	M_w/M_n^{a}
P(HEMA$_{90}$−AMA$_{10}$)	100	P(HEMA$_{90}$−AMA$_{10}$)	72	25 100	1.26
P(HEMA$_{70}$−AMA$_{30}$)	100	P(HEMA$_{70}$−AMA$_{30}$)	135	19 100	1.30
P(HEMA$_{50}$−AMA$_{50}$)	98/94^d	P(HEMA$_{49}$−AMA$_{47}$)	159	14 900	1.45
P(HEMA$_{45}$−AMA$_5$)	100	P(HEMA$_{45}$−AMA$_5$)	85	13 300	1.26
P(GMA$_{70}$−AMA$_{30}$)	100/90^d	P(GMA$_{70}$−AMA$_{27}$)	92	14 800	1.43
P(GMA$_{45}$−AMA$_5$)	100/97^d	P(GMA$_{45}$−AMA$_5$)	85	12 400	1.18
P(GMA$_{40}$−AMA$_{10}$)	100	P(GMA$_{40}$−AMA$_{10}$)	72	12 800	1.38
P(HPMA$_{45}$−AMA$_5$)	100	P(HPMA$_{45}$−AMA$_5$)	85	8 300^b	1.13^b

[a] Determined by DMF GPC using near-monodisperse poly(methyl methacrylate) calibration standards. [b] Determined by THF GPC using near-monodisperse poly(methyl methacrylate) calibration standards. [c] ME-Br was used as an ATRP initiator and the CuBr/bpy molar ratio was 1:2. The target DP was 100 for entries 1−3 and entry 5 and 50 for the other entries. [d] The second number is the estimated AMA conversion in each case.

Scheme 3. Cross-Linking of an AMA-Based Statistical Copolymer by Michael Addition in Aqueous Solution at 20 °C Using Poly(ethylene glycol) Diacrylate (PEGDA)



monomers, HEMA, HPMA, and GMA, was investigated by ATRP in methanol at 20 °C using the ME-Br initiator. Inspecting the data shown in Table 4, lower conversions were always obtained at higher AMA comonomer feeds for a fixed target DP. HEMA proved to be the preferred comonomer, since it led to the highest overall conversion and AMA content (around 50 mol %). Higher AMA contents generally led to poorer control, as exemplified by broader molecular weight distributions; for example, the polydispersities of P(HEMA$_{45}$−AMA$_5$) and P(HEMA$_{50}$−AMA$_{50}$) were 1.26 and 1.45, respectively.

We have worked for some years on the synthesis of shell cross-linked micelles.[37,50,51] In principle, the synthesis of controlled-structure primary amine-based block copolymers offers an opportunity to develop improved aqueous cross-linking chemistries, since primary amines react efficiently with a wide range of functional groups under mild conditions. As an initial test of this hypothesis, selected primary amine-functionalized statistical copolymers were cross-linked by Michael addition in dilute aqueous solution at 20 °C using PEGDA, as shown in Scheme 3. Compared to other bifunctional cross-linkers reported previously,[37,50,51] this PEGDA reagent offers several advantages: it is commercially available, cheap, water-soluble, nonvolatile, and relatively nontoxic. Thus, both P(HEMA$_{70}$−AMA$_{30}$) and P(GMA$_{70}$−AMA$_{30}$) copolymers were reacted with PEGDA (acrylate/amine molar ratio = 1.0) at pH 9. Under these mildly alkaline conditions, the AMA units are almost completely deprotonated and hence much more reactive toward Michael addition. Colloidal structures ranging from 200 to 450 nm were formed within 10 min as judged by DLS studies. ^{1}H NMR spectra of a mixture of a P(HEMA$_{70}$−AMA$_{30}$) statistical copolymer and PEGDA are shown in Figure 7a. The extent of cross-linking was estimated from the progressive attenuation of the acrylate signals between δ 5.6 and 6.5 (see Figure 7b). After 27.5 h at 20 °C, the extent of reaction was estimated to be around 51%; this increased only marginally to 54% after 43.5 h. However, our control experiments indicated that a 0.50% w/w PEGDA solution in D_2O/NaOD at pH 9 underwent ~20% ester hydrolysis after 26 h. Thus, slow hydrolytic scission of the PEGDA cross-links is likely to be a competing side reaction during micelle cross-linking in alkaline solution.

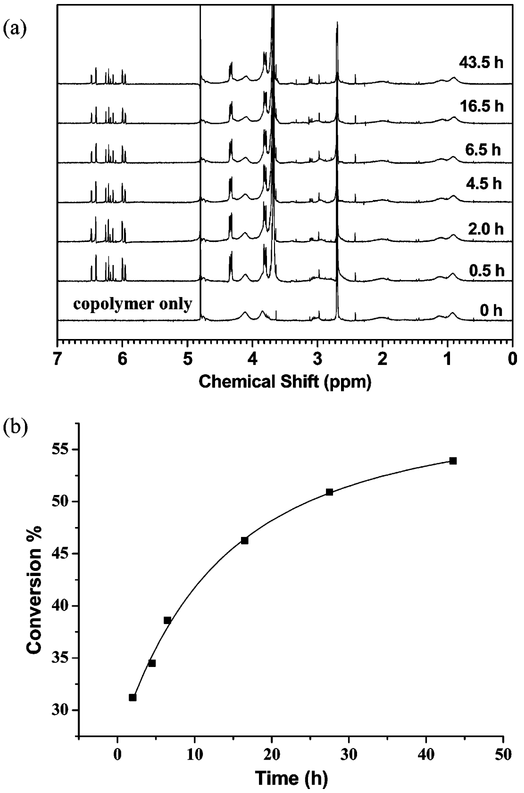


Figure 7. (a) In situ ^{1}H NMR studies of the Michael addition cross-linking of a P(HEMA$_{70}$−AMA$_{30}$) statistical copolymer using PEGDA in D_2O/NaOD at pH 9 at a initial acrylate/amine molar ratio of 1.0. (b) The corresponding acrylate conversion vs time plot for the cross-linked copolymer. The copolymer concentration was fixed at 5.0 g/L.

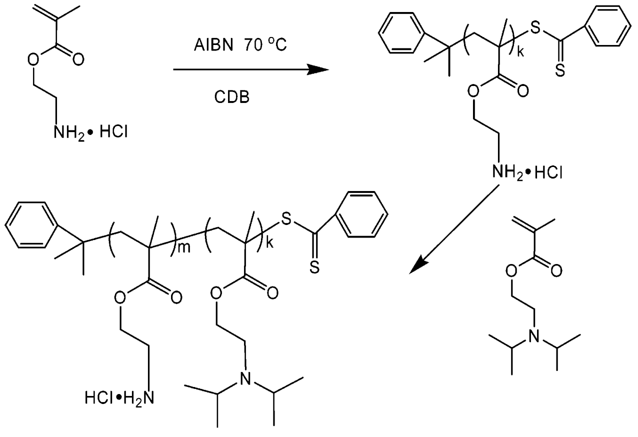
Preparation of AMA-Based Block Copolymers. After establishing appropriate conditions for the homopolymerization of AMA in DMSO at 70 °C, PAMA−PDPA diblock copolymers were prepared by RAFT using the macro-RAFT agent technique, as shown in Scheme 4. The experimental conditions are summarized in Table 5. Bearing in mind the differing solubility requirements for the PDPA and PAMA blocks, these copolymer syntheses were conducted in either DMSO or in a

Table 5. Summary of the Syntheses of AMA-Based Diblock Copolymers by RAFT at 70 °C

			first block				second block			
actual diblock copolymer comp[a]	reaction conditions[b]	solvent	conv (^{1}H NMR) (%)	time (h)	$M_n \times 10^4$ (GPC)[c]	M_w/M_n[c]	conv (^{1}H NMR) (%)	time (h)	$M_n \times 10^4$ (GPC)[c]	M_w/M_n[c]
$PDPA_{162}-PAMA_{30}$	30:1:0.3	1:1 dioxane/DMSO	90	48	21 900	1.26	100	72	25 600	1.45
$PAMA_{100}-PDPA_{40}$	40:1:0.2	DMSO	100	24	15 200	1.27	100	24	20 200	1.41
$PAMA_{200}-PDPA_{60}$	60:1:0.3	3:1 DMSO/dioxane	100	24	25 700	1.29	100	24	30 300	1.43

[a] The first entry was a "macroinitiator"-type synthesis where the $PDPA_{162}$ homopolymer was isolated and purified prior to its redissolution. The other four entries were "one-pot" syntheses. The first named monomer was polymerized first in each case. [b] Reaction conditions are expressed as [monomer]:[RAFT agent]:[AIBN] molar ratios. [c] Determined by aqueous GPC using poly(2-vinylpyridine) standards and NaH_2PO_4/CH_3COOH eluent at pH 2.5

Scheme 4. Synthetic Route for the Preparation of PAMA−PDPA Diblock Copolymer at 70 °C Using CDB as a RAFT Chain Transfer Agent



DMSO/1,4-dioxane solvent mixture at 70 °C. The order of monomer addition was also considered. In initial experiments, DPA was homopolymerized first in 1,4-dioxane at 70 °C using the CDB RAFT agent: high conversions were readily obtained for target DP's of up to 160. Both THF GPC and aqueous GPC chromatograms of the resulting PDPA macro-RAFT agent confirmed its low polydispersity. Following purification by precipitation and subsequent vacuum-drying, this PDPA RAFT macroinitiator was used for the subsequent polymerization of AMA to yield a diblock copolymer (see entry 1 in Table 5). The other two diblock copolymers in Table 5 were prepared using one-pot syntheses by polymerizing the AMA monomer first and then adding degassed DPA/AIBN into the flask at an AMA conversion of 100%. A ^{1}H NMR spectrum of a typical purified $PAMA_{100}-PDPA_{40}$ diblock copolymer is shown in Figure 8. All the signals expected for both blocks are visible at pH 2 (DCl/D_2O), but the signals assigned to the PDPA block disappeared at pH 7 due to selective deprotonation of this block (the pK_a of PDPA is around 6.3[52]). This is consistent with the formation of PDPA-core micelles, and DLS studies confirmed the formation of polydisperse micelles with a mean micelle hydrodynamic diameter of 48 nm in the diluted aqueous copolymer solution at pH 7.

A macroinitiator approach was used to prepare AMA-based diblock copolymers via ATRP. The two macroinitiators were based on poly(ethylene oxide) (PEO) and had mean degrees of polymerization of 45 and 113. Homopolymerization of AMA (DP = 30) with either PEO_{45}-Br or PEO_{113}-Br at 50 °C in 95:5 IPA/H_2O proceeded to high conversion within 6 h, whereas a target DP of 60 required 15 h for complete conversion in an 80:20 IPA/H_2O mixture. After addition of silica to remove the spent ATRP catalyst, these purified diblock copolymers had polydispersities below 1.26 (see Table 6). The final $PEO_{113}-PAMA_{60}$ diblock copolymer remained soluble in 95:5 IPA/H_2O, but using the shorter PEO block led to some precipitation during the AMA polymerization. However, all PEO−PAMA diblock copolymers remained soluble in the 80:20 IPA/H_2O mixture at 50 °C throughout the polymerization. Since this composition

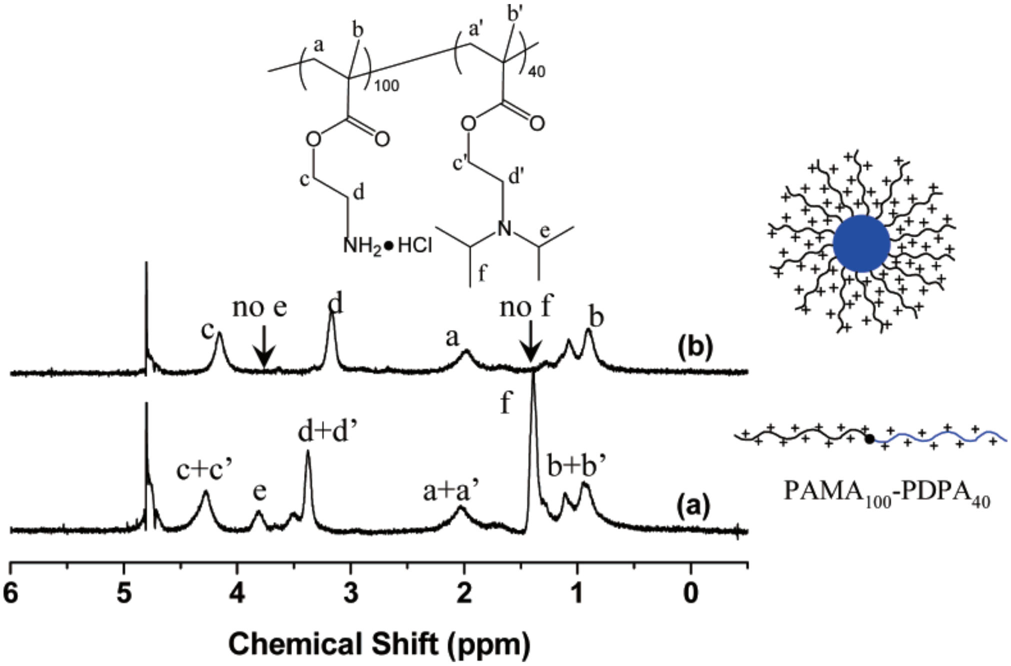


Figure 8. ^{1}H NMR spectra recorded for a 0.50 wt % $PAMA_{100}-PDPA_{40}$ diblock copolymer solution in D_2O at (a) pH 2 and (b) pH 7. Note the disappearance of NMR signals due to the PDPA block in the latter spectrum.

Table 6. Conversion, Molecular Weight, and Polydispersity Data for the Polymerization of AMA at 50 °C in IPA/H_2O Mixtures Using an PEO_nBr Macroinitiator (where $n = 45$ or 113) and [AMA]:[PEO_nBr]:[CuCl]:[bpy] Relative Molar Ratios of Either 30:1:1:2 or 60:1:1:2

target copolymer composition	IPA/H_2O ratio	time (h)	conv (%)[a]	M_n (g/mol)[b]	M_w/M_n[b]
$PEO_{45}-PAMA_{30}$	95:5	6	100	5 300	1.17
$PEO_{45}-PAMA_{60}$	80:20	15	100	10 100	1.20
$PEO_{113}-PAMA_{30}$	95:5	6	94	7 200	1.21
$PEO_{113}-PAMA_{60}$	80:20	15	100	11 100	1.26

[a] Conversions were determined using ^1H NMR spectroscopy. [b] As determined by aqueous GPC.

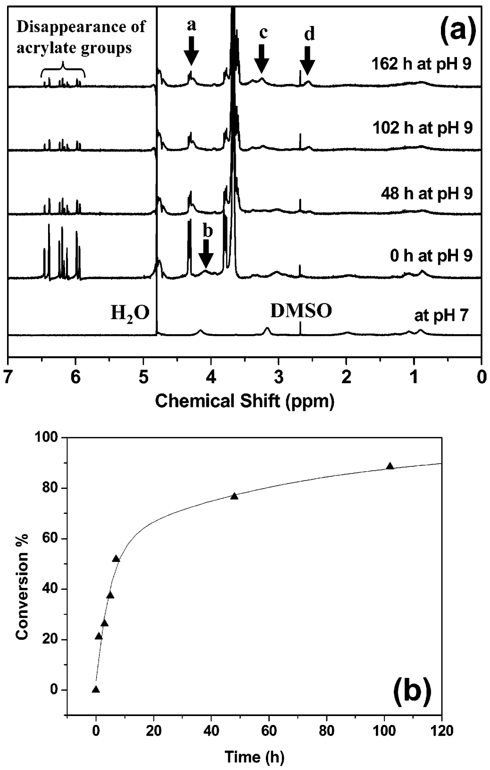


Figure 9. (a) In situ ^1H NMR studies of the shell cross-linking of $PAMA_{100}-PDPA_{40}$ micelles by Michael addition using PEDGA in D_2O/NaOD at pH 9.0 at an initial acrylate/amine molar ratio of 0.40. (b) The corresponding acrylate conversion vs time curve for these shell cross-linked micelles.

also gave good control and high conversions, it appears to be optimal for such syntheses.

Shell Cross-linked Micelles. Our initial results with AMA-based statistical copolymers (see above) suggested that PAMA chains should be readily cross-linkable using PEGDA in aqueous solution. The $PAMA_{100}-PDPA_{40}$ diblock copolymer was first dissolved molecularly at low pH, and then the solution pH was adjusted to pH 7 by the addition of NaOH to form PDPA-core micelles. Shell cross-linking was achieved at pH 9 by the addition of PEGDA (acrylate/amine molar ratio = 0.40) at 20 °C. After 3 h, the mean hydrodynamic diameter had increased to 102 nm, which suggested that some intermicelle fusion had occurred despite the relatively low copolymer concentration. The solution pH also decreased to pH 8.6 during this period. On adjusting the solution pH to 2.6, colloidal aggregates of around 48 nm were obtained. This confirmed successful cross-linking, since rapid micelle dissociation occurred in control experiments conducted in the absence of any PEGDA. The extent of cross-linking was also monitored by ^1H NMR at pH 9.0 under the same conditions (see Figure 9). Successful shell cross-linking was confirmed by the appearance of a new peak at δ 2.6 due to the oxymethylene protons of the PEGDA after Michael addition. The PEGDA conversion was estimated to be 93% after 162 h at 20 °C, which corresponds to around 37% of the amine groups reacted. Further examples of shell cross-linking of PAMA-based block copolymers will be reported in due course.

Conclusions

2-Aminoethyl methacrylate can be polymerized directly in its hydrochloride salt form by living radical polymerization to afford well-defined, low-polydispersity primary amine-functionalized homopolymers, statistical copolymers, and diblock copolymers. RAFT polymerizations were conducted at 70 °C using cumyl dithiobenzoate as a chain transfer agent in either DMSO (for PAMA homopolymer) or a DMSO/1,4-dioxane mixture (for AMA-based diblock copolymers). The evolution of molecular weight was approximately linear with conversion, and final polydispersities were around 1.25. Almost 100% conversion of AMA monomer could be achieved within 24 h for target DP's of up to 200. In contrast, the ATRP of AMA was slow and substantially incomplete (only 33% conversion for a target DP of 50) when conducted in methanol for 168 h at 20 °C. Raising the polymerization temperature to 50 °C and employing a 95:5 IPA/water mixture gave an AMA conversion of 91% within 6 h, albeit with a polydispersity of around 1.41. However, the preferred solvent composition was an 80:20 IPA/water mixture, since this allowed solubility to be maintained during the AMA polymerization, afforded high conversions within short reaction times, and produced final polydispersities of 1.09−1.24, depending on the target DP.

Acid titration studies indicated that AMA monomer has a pK_a of around 8.8. In its nonprotonated form, AMA undergoes rapid internal rearrangement to afford 2-hydroxyethyl methacrylamide. ^1H NMR studies confirmed that PAMA homopolymer ($pK_a \sim 7.6$) is significantly more stable than AMA monomer at pH 9, but slow degradation nevertheless occurred over long time scales (days) in more alkaline solution. Initial results confirm that (i) this PAMA degradation involves the elimination of 2-aminoethanol and (ii) at least some of its repeat units are converted into 2-hydroxyethyl methacrylamide units. At least four possible degradation pathways have been identified, but further spectroscopic studies are required to elucidate the detailed mechanism.

AMA-based statistical copolymers could be readily cross-linked in aqueous solution under mild conditions via Michael addition using a water-soluble diacrylate cross-linker. The same approach allowed shell cross-linked micelles with pH-responsive cores to be prepared from PDPA−PAMA diblock copolymer precursors. Finally, low-polydispersity PEO−PAMA diblock copolymers can be easily synthesized using PEO-based ATRP macroinitiators.

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Supporting Information Available: Synthesis details for the CDB RAFT agent, assigned ^1H NMR spectra for the AMA monomer and its 2-hydroxyethyl methacrylamide degradation product, and acid titration curves for AMA monomer and PAMA homopolymer. This material is available free of charge via the Internet at http://pubs.acs.org.

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