Direct Synthesis of Well-Defined Quaternized Homopolymers and Diblock Copolymers via ATRP in Protic Media

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ABSTRACT: The direct synthesis of well-defined cationic homopolymers and block copolymers based on methyl chloride-quaternized 2-(dimethylamino)ethyl methacrylate [MeDMA] by ATRP in protic media at 20 °C is described. Homopolymerization of MeDMA in purely aqueous media was fast and poorly controlled, leading to a relatively high polydispersity of 1.37 and low initiation efficiency. Addition of $Cu(II)Br_2$ led to slower polymerizations but only slightly lower polydispersities. Addition of methanol also reduced the rate of polymerization and produced narrower molecular weight distributions. Unfortunately, ^1H NMR studies indicated that transesterification of MeDMA with methanol produced significant quantities of methyl methacrylate (MMA) on the time scale of the polymerization; this side reaction led to the unwanted production of MeDMA−MMA statistical copolymers. This problem was alleviated by replacing the methanol cosolvent with 2-propanol, since the secondary alcohol was much less prone to transesterification. High conversions were obtained with a 1:1 2-propanol/water composition within a few hours at 20 °C, but partial phase separation occurred toward the end of the polymerization, particularly at higher monomer concentration. Although nonlinear kinetic plots were observed, final polydispersities were relatively low (ranging from 1.19 to 1.27, according to aqueous GPC studies), and good self-blocking efficiencies were demonstrated in chain extension experiments. A range of new cationic diblock copolymers were prepared either by using a poly(ethylene oxide)-based macroinitiator or via sequential monomer addition with various hydrophilic methacrylates such as glycerol monomethacrylate, [2-(methacryloyloxy)ethyl]phosphorylcholine, the benzyl chloride-quaternized analogue of MeDMA, and the sulfobetaine adduct of the reaction of 2-(dimethylamino)ethyl methacrylate with 1,3-propane sultone, [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide. Potential applications for these cationic diblock copolymers include novel gene/oligonucleotide transfer agents and also polymeric templates for the catalytic formation of silica in aqueous solution under mild conditions.

Introduction

Cationic water-soluble polymers find widespread use in many commercial applications and processes.[1] These include high molecular weight bridging flocculants for industrial wastewater purification, solid/liquid separation, papermaking, and sewage treatment. Cationic polyelectrolytes are also important components of certain cosmetic formulations and various home and personal care products, including shaving gels and shampoos.[2,3] Cationic comonomers are often incorporated into latex formulations to enhance adhesion to textile fibers.[4] Creutz and co-workers recently reported that zwitterionic diblock copolymers are promising pigment dispersants of wide applicability.[5] In most of the above cases, the cationic nature of the polymer chains ensures strong electrostatic binding to either planar or colloidal substrates, which usually carry an anionic surface charge.

Biomedical applications for cationic polymers include hydrogels[6] and humidity sensors.[7] Various research groups have shown that cationic polymers, particularly diblock copolymers, can act as efficient synthetic vectors for DNA condensation.[8−13] This is potentially important in the context of gene therapy applications, although in practice transfection efficiencies for the genetic material after transport across the cell membrane remain relatively low. A number of synthetic cationic polymers can act as templates for the catalytic formation of silica in aqueous solution under mild conditions.[14−16] Various cationic diblock copolymer surfactants have also been shown to exhibit interesting pH-modulated surface activity.[17−19]

2-(Dimethylamino)ethyl methacrylate (DMA) has no labile protons and hence can be polymerized directly under anhydrous conditions by either classical anionic polymerization, group transfer polymerization, oxyanion-initiated polymerization, or nitranion-initiated polymerization.[20−23] Good control over the target number-average molecular weight (M_n) can be achieved, and a range of near-monodisperse homopolymers and block copolymers have been reported. In addition, several research groups have reported the polymerization of DMA by atom transfer radical polymerization (ATRP), a form of living radical polymerization.[24−29] In principle, well-defined cationic (co)polymers can be prepared by the postpolymerization quaternization of DMA (co)-polymers using various alkyl halides such as methyl iodide, benzyl chloride, or dimethyl sulfate.[23b,30] However, methyl iodide and dimethyl sulfate are highly mutagenic and toxic, while benzyl chloride requires elevated temperature and long reaction times for high degrees of quaternization. In view of these problems, it is worth considering whether ATRP (or other living radical polymerization chemistries) can be used to polymerize the methyl chloride-quaternized analogue of DMA, 2-[(methacryloyloxy)ethyl]trimethylammonium

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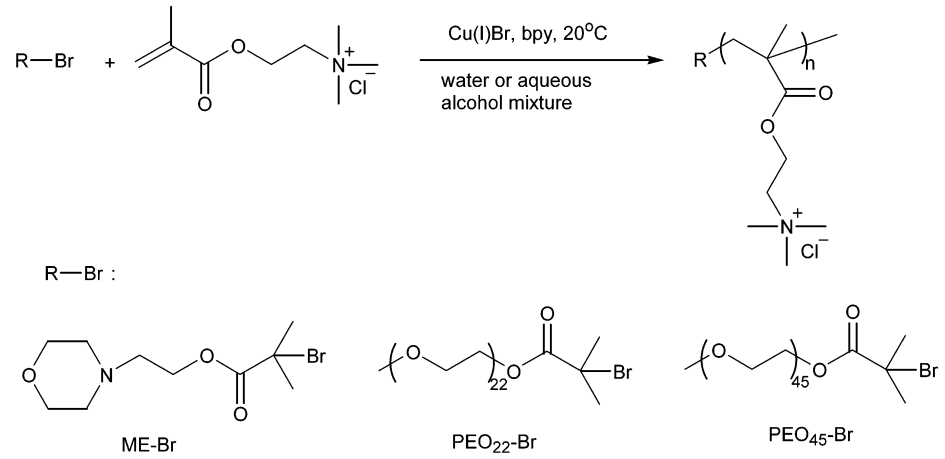

Figure 1. Reaction scheme for the synthesis of well-defined, MeDMA-based cationic homopolymers and diblock copolymers by ATRP in protic media at 20 °C.

chloride (MeDMA), *directly* to form well-defined cationic (co)polymers from the quaternized monomer. This cationic monomer is commercially available, and its (co)-polymerization by conventional free radical chemistry has been extensively studied.[31,32]

As far as we are aware, there have been no reports of the polymerization of MeDMA by living radical polymerization, although at least one quaternized monomer has been polymerized using RAFT.[33] Herein we describe the first direct homopolymerization and block copolymerization of MeDMA via ATRP (see Figure 1). In view of the ionic nature of this monomer, such syntheses require protic media to ensure reasonable monomer/polymer solubility. Accordingly, we examined the use of purely aqueous media, methanol/water mixtures, and 2-propanol/water mixtures. Various problems were encountered, but ultimately we were able to synthesize a range of new, well-defined cationic diblock copolymers with relatively low polydispersities at ambient temperature.

Experimental Section

A. Materials. [2-(Methacryloyloxy)ethyl]trimethylammonium chloride [MeDMA] was supplied as a 75% w/v aqueous solution by Aldrich. The sulfobetaine adduct obtained from the reaction of DMA with 1,3-propane sultone, [2-(methacryloyloxy)ethyl]-dimethyl(3-sulfopropyl)ammonium hydroxide, SBMA], was also obtained from Aldrich. Glycerol monomethacrylate [GMA] was kindly donated by Röhm, Germany, and benzyl[2-(methacryloyloxy)ethyl]dimethylammonium chloride (BzDMA) was kindly provided as a 75% w/v aqueous solution by Elf Atochem, Germany. [2-(Methacryloyloxy)ethyl]phosphorylcholine [MPC] (>99% purity) was a gift from Biocompatibles (Farnham, UK). Cu(I)Br, 2,2′-bipyridine (bpy), methanol, and 2-propanol were purchased from Aldrich and were used as received. The two monohydroxy-capped poly(ethylene oxide) precursors were donated by Cognis Performance Chemicals (Hythe, UK). One sample of poly(ethylene oxide) [PEO_{45}-OH] had an M_n of 2000 and an M_w/M_n of 1.10 (vs PEO calibration standards), and a second sample [PEO_{22}-OH] had an M_n of 1000 and an M_w/M_n of 1.10. These two precursors were each converted into the corresponding ATRP macroinitiators [PEO_{45}-Br and PEO_{22}-Br] by reaction with excess 2-bromoisobutyryl bromide in dry toluene using previously reported protocols.[34,35] The ME-Br initiator was synthesized as described previously.[35] The water used in all experiments was deionized and doubly distilled prior to use. The silica used for removal of the ATRP copper catalyst was column chromatography grade silica gel 60 (0.063−0.200 mm) purchased from E. Merck (Darmstadt, Germany).

B. General Polymerization Protocols. 1. Homopolymerization of MeDMA. A typical protocol for the homopolymerization of MeDMA via aqueous ATRP using the ME-Br initiator was as follows. ME-Br (0.277 g, 1.00 mmol, 1 equiv) and MeDMA (8.3 g aqueous solution, 30 mmol, 30 equiv) were codissolved in water (6.2 mL). After purging with nitrogen for 30 min, the Cu(I)Br catalyst (0.143 g, 1.00 mol, 1 equiv) and bpy ligand (0.390 g, 2.5 mmol, 2.5 equiv) were added to this stirred solution under nitrogen. The reaction mixture immediately became dark brown and progressively more viscous, indicating the onset of polymerization. Exotherms of 5−7 °C were typically observed for polymerizations conducted in purely aqueous media. After approximately 1 h, ^{1}H NMR analysis indicated that more than 99% of the MeDMA had been polymerized (disappearance of vinyl signals between δ 5.5 and 6.0). The above protocol was modified by replacing some of the water with either methanol or 2-propanol (IPA). Little or no exotherm was observed in these alcohol/water reaction mixtures, and the rates of polymerization were significantly slower than that obtained in pure water. In each case the reaction solution turned blue on exposure to air, indicating aerial oxidation of the Cu(I) catalyst. The resulting MeDMA homopolymer was diluted with methanol and passed through a silica column to remove the spent ATRP catalyst. The polymer solution was dried under vacuum to remove the solvent.

2. Self-Blocking (Chain Extension) Experiments. MeDMA (4.98 g aqueous solution, 18.0 mmol) was polymerized in a mixture containing 4.4 mL of IPA and 3.1 mL of doubly distilled water, using a [MeDMA]:[ME-Br]:[Cu(I)Br]:[bpy] relative molar ratio of 30:1:1:2.5. After 1 h the monomer conversion had reached about 90%, as judged by ^{1}H NMR spectroscopy. At this point a 2.1 mL aliquot of the polymerization solution was extracted for subsequent characterization, and a second batch of degassed MeDMA (4.15 g, 0.015 mol; dissolved in 3.6 mL of IPA and 2.6 mL of doubly distilled water) was added to the polymerizing solution. After 20 h, a chain-extended MeDMA homopolymer was obtained with essentially 100% monomer conversion.

3. Block Copolymerization of MeDMA with Other Methacrylic Monomers. The following four examples illustrate the general synthetic protocols employed.

MeDMA−GMA Diblock Copolymer. MeDMA was polymerized first (4.15 g, 0.015 mol; dissolved in 3.6 mL of IPA and 2.6 mL of water) with ME-Br as the initiator, using a [MeDMA]:[ME-Br]:[CuBr]:[bpy] relative molar ratio of 30:1:1:2.5. After 1 h the monomer conversion was about 90%. GMA monomer (2.40 g, 0.015 mol, target Dp = 30) dissolved in 7.2 mL of methanol was then added to this reaction solution. The reaction mixture was maintained under a dry nitrogen purge for the duration of the polymerization. On exposure to air after 24 h, the reaction solution turned blue, indicating aerial oxidation of the ATRP catalyst. ^{1}H NMR studies

Table 1. Summary of the Molecular Weight and Conversion Data Obtained for MeDMA-Based Homopolymers and Diblock Copolymers Prepared by Either Aqueous or Aqueous Methanolic ATRP at 20 °C[a]

entry no.	target structure	solvent	reaction time (h)	conv (%)	$M_{n,th}$	$M_{n,exp}$	$M_{w,exp}$	M_w/M_n
1	$MeDMA_{60}$	H_2O	0.50	95	12 400	23 000	31 500	1.37
2	$MeDMA_{30}$	H_2O[b]	2.33	93	6 200	13 600	17 900	1.32
3	$MeDMA_{30}$	H_2O[c]	1.5	95	6 200	13 000	16 600	1.28
4	$MeDMA_{30}$	MeOH/H_2O[d]	15	100	6 200	10 100	11 900	1.18
5	$MeDMA_{60}$	MeOH/H_2O[d]	20	99	12 500	12 800	15 700	1.23
6	$MeDMA_{100}$	MeOH/H_2O[d]	17	95	20 800	19 900	24 800	1.25
7	PEO_{22}−$MeDMA_{30}$	MeOH/H_2O[d]	18	100	7 200	9 700	11 700	1.20
8	PEO_{22}−$MeDMA_{60}$	MeOH/H_2O[d]	17	100	13 500	13 400	16 700	1.25
9	PEO_{22}−$MeDMA_{100}$	MeOH/H_2O[d]	24	100	21 800	21 400	26 300	1.23
10	PEO_{45}−$MeDMA_{30}$	MeOH/H_2O[d]	16	100	8 200	10 100	12 300	1.22
11	PEO_{45}−$MeDMA_{60}$	MeOH/H_2O[d]	16	100	14 500	12 500	15 800	1.26
12	PEO_{45}−$MeDMA_{100}$	MeOH/H_2O[d]	16	99	22 800	19 600	14 700	1.26

[a] The relative molar ratios of ME-Br initiator:Cu(I)Br:bpy were 1:1:2.5. [b] This polymerization was carried out in the presence of 5 mol % added Cu(II) and reached 93% conversion within 140 min. [c] This polymerization was carried out in the presence of 30 mol % added Cu(II) and reached 95% conversion within 90 min. [d] MeOH: H_2O = 3:1 v/v.

indicated a GMA monomer conversion of 99%. The reaction solution was passed through a silica gel column to remove the spent catalyst. After solvent evaporation, the copolymer was dried in a vacuum oven at room temperature to yield 5.0 g of a colorless solid.

MeDMA−SBMA Diblock Copolymer. MeDMA was polymerized first (4.15 g, 0.015 mol; dissolved in 3.6 mL of IPA and 2.6 mL of water) with ME-Br as the initiator, using a [MeDMA]:[ME-Br]:[CuBr]:[bpy] relative molar ratio of 30:1:1:2.5. After 1 h the monomer conversion was about 90%. A freshly prepared aqueous solution of SBMA (4.19 g of SBMA, 15.0 mmol; dissolved in 4.2 mL of water) was added to this reaction solution. After 18 h, ^{1}H NMR studies indicated that both monomers had been consumed. The reaction solution was then passed through a silica gel column to remove the spent catalyst. After solvent evaporation, the purified copolymer was dried in a vacuum oven at 20 °C for at least 24 h to yield a colorless solid. This purification protocol resulted in the loss of up to 15% MeDMA−SBMA diblock copolymer due to its adsorption onto the anionic silica gel.

MeDMA−BzDMA Diblock Copolymer. MeDMA was polymerized first (4.15 g, 0.015 mol; dissolved in 3.6 mL of IPA and 2.6 mL of water) with ME-Br as the initiator, using a [MeDMA]:[ME-Br]:[CuBr]:[bpy] relative molar ratio of 30:1:1:2.5. After 1.0 h, the monomer conversion was about 90%. A 75% w/v aqueous solution of BzDMA monomer (5.39 g, 0.015 mol, target Dp = 30) was then added to the polymerizing solution, together with 4.7 mL of degassed IPA and 3.4 mL of degassed water. After 20 h, a MeDMA−BzDMA diblock copolymer was obtained at an overall conversion of about 90%, as indicated by ^{1}H NMR spectroscopy. This reaction solution was passed through a silica gel column to remove the ATRP catalyst. After solvent evaporation, the diblock copolymer was redissolved in water and precipitated into excess IPA to remove any unreacted monomer.

MeDMA−MPC Diblock Copolymer. MeDMA was polymerized first (2.075 g, 0.0075 mol; dissolved in 1.8 mL of IPA and 1.3 mL of water) with ME-Br as the initiator, using a [MeDMA]:[ME-Br]:[CuBr]:[bpy] relative molar ratio of 30:1:1:2.5. After 1.0 h, the monomer conversion was about 90%. MPC (2.21 g, 0.0075 mol, target Dp = 30) was then added to this reaction solution as a solid, along with 2.0 mL of degassed methanol. After 18 h, ^{1}H NMR studies indicated that both monomers had been completely consumed (no detectable vinyl signals). The reaction solution was passed through a silica gel column to remove the spent ATRP catalyst. After solvent evaporation, the purified copolymer was dried in a vacuum oven at 20 °C for at least 24 h to yield a colorless solid. This purification protocol resulted in the loss of up to 20% MeDMA−MPC diblock copolymer due to its adsorption onto the silica gel.

C. Polymer Characterization. ^{1}H NMR Spectroscopy. All ^{1}H NMR spectra were recorded using a 300 MHz Bruker Avance DPX300 spectrometer. The kinetics of polymerization were determined for reactions carried out in either D_2O or $CD_3(CD_3)CDOD$ by comparing the peak integrals due to the monomer vinyl signals at δ 5.5 and 5.9 to those of the methacrylate backbone at δ 0.5−1.1 or at δ 1.5−2.0. If appropriate, the macroinitiator was used as an "end group" to determine the degree of polymerization of the MeDMA block. In these calculations it was assumed that the macroinitiator efficiency was 100%, chain transfer was negligible, and every polymer chain contained a macroinitiator end group.

Aqueous GPC Protocol. The aqueous GPC setup comprised a Waters 2690 liquid chromatograph equipped with four Waters Ultrahydrogel linear 6−13 μm columns in series and a 2410 refractive index detector. The operating temperature was 30 °C, and the eluent consisted of 0.30 M Na_2SO_4 at pH 7 with 0.1% w/v added NaN_3 at a flow rate of 1.0 mL min^{-1}. All GPC data were recorded and processed using a Windows-based Millenium 2.0 software package. A series of near-monodisperse DMA homopolymers ranging from 4000 to 45 000 were synthesized by living anionic polymerization, as reported previously.[23b] These precursors were quaternized using dimethyl sulfate and employed as calibration standards for the aqueous GPC analyses reported in the present work. The difference in hydrodynamic volumes between dimethyl sulfate-quaternized and methyl iodide-quatenized DMA homopolymer was shown to be negligible.[36] Assuming that there are no significant counterion effects, the dimethyl sulfate-quaternized DMA homopolymers are expected to be reliable calibration standards for the methyl chloride-quaternized DMA homopolymers prepared in this study.

Results and Discussion

ATRP of MeDMA in Aqueous Solution. ATRP can be carried out either in the bulk, in solution, or in heterogeneous media (e.g., emulsion, suspension, solid-supported catalyst, etc.). A wide range of solvents, such as benzene, toluene, anisole, diphenyl ether, ethyl acetate, acetone, DMF, ethylene carbonate, alcohol, water, and carbon dioxide, have been used for the controlled polymerization of various monomers.[37]

The cationic MeDMA monomer was supplied as a 75% aqueous solution; it is soluble in water and lower alcohols but insoluble in most other solvents. Initially, we tried to homopolymerize MeDMA in aqueous solution using the ME-Br initiator, which had been previously used for the ATRP of other hydrophilic monomers.[34,38] The aqueous ATRP of MeDMA was very rapid at 20 °C: over 95% conversion was obtained within 30 min at a MeDMA concentration of 42% w/v and a target Dp of 60 (see entry 1 in Table 1). However, the final polydispersity was relatively high at 1.37, indicating reduced control. Moreover, the M_n indicated by aqueous GPC analysis was approximately twice as high as that targeted. Given that near-monodisperse quaternized

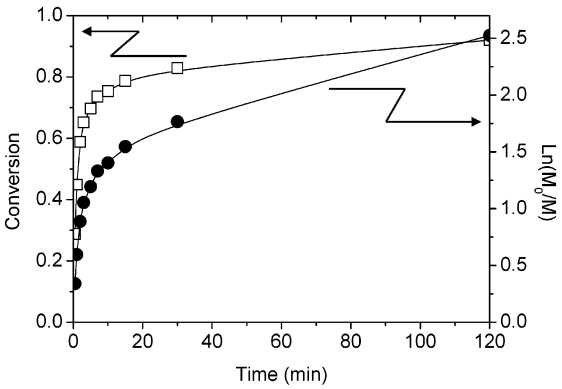

Figure 2. Conversion vs time data and semilogarithmic plot of monomer concentration vs time for the homopolymerization of MeDMA in aqueous solution at 20 °C. Conditions: 30% w/v; target Dp = 30; ME-Br:CuBr:bpy = 1:1:2.5.

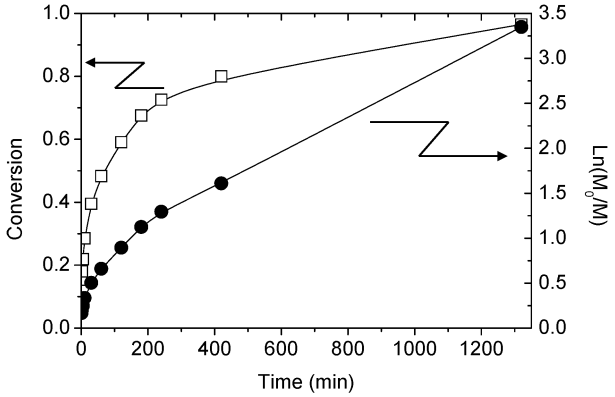

Figure 3. Conversion vs time data and semilogarithmic plot for the homopolymerization of MeDMA in a 85:15 methanol/water mixture at 20 °C. Conditions: 30% w/v; target Dp = 30; ME-Br:CuBr:bpy = 1:1:2.5.

DMA homopolymers were used as calibration standards, this suggests poor initiator efficiency. The semilogarithmic plot of monomer concentration vs time for the homopolymerization of MeDMA is shown in Figure 2. Pronounced curvature was observed, which suggests that the polymer radical concentration did not remain constant during the polymerization. Similar results have been reported by Matyjaszewski and co-workers,[39] who have suggested that the fast rates of polymerization and poor control usually encountered in the aqueous ATRP of hydrophilic methacrylates are due to side reactions in this highly polar medium. Water is a coordinating solvent that may displace halide ligands from the copper-based ATRP catalyst, especially when the latter is in its higher oxidation state (i.e., the deactivating Cu(II) species). Another plausible side reaction in aqueous media is the disproportionation of the Cu(I)-based catalyst to give Cu(II) and Cu(0). The possibility of partial hydrolysis of bromine atoms from the polymer termini also cannot be discounted. These problems are not usually encountered in low-polarity solvents or for syntheses conducted in the bulk. One method that is commonly used to retard the rate of ATRP is to deliberately add a Cu(II) salt to the formulation, which enhances the rate of radical deactivation and often leads to improved control.[40,41] Thus, two further aqueous polymerizations were attempted in the presence of either 5 or 30 mol % added Cu(II)Br_2; see entries 2 and 3 in Table 1. This approach gave much slower polymerizations (with 30 mol % added Cu(II) being more effective, as expected) and some improvement in control. However, the initiator efficiencies were still relatively low and the final polydispersities were around 1.30.

ATRP of MeDMA in Methanol/Water Mixtures. Since the aqueous ATRP of MeDMA was not well controlled, the effect of adding methanol as a cosolvent was examined. This approach has afforded improved control for the ATRP of 2-hydroxyethyl methacrylate.[42] Using pure methanol instead of water usually offers even better control,[42,43] but this approach could not be used in the present study since the MeDMA monomer was supplied as an aqueous solution and MeDMA homopolymer has limited solubility in anhydrous alcohol. For a semilogarithmic plot of monomer concentration vs time for the polymerization of MeDMA in methanol/water mixtures, see Figure 3. This plot is rather less curved than that found for aqueous ATRP, but nevertheless nonlinear behavior is observed. Again, this suggests premature chain termination, which is detrimental to the living character of the polymerization. It is noteworthy that transesterification may also influence the polymerization kinetics, since this side reaction is expected to result in a change in the solvent polarity.[44]

Despite these rather unpromising kinetic results, the molecular weight data presented in Table 1 indicate that the ATRP of MeDMA in a 3:1 methanol/water mixture is much better controlled than that in pure water: for target Dp's of 30, 60, and 100, the polydispersities were 1.18, 1.23, and 1.25, respectively. Higher polydispersities are observed as the target Dp is increased, but these values are nevertheless significantly lower than that obtained in pure water (see entry 1 in Table 1). The GPC molecular weights are somewhat higher than the theoretical molecular weights, which suggests poor initiation efficiency under these conditions. PEO-Br can be employed as an ATRP macroinitiator to prepare a series of apparently well-defined PEO−MeDMA diblock copolymers with relatively narrow molecular weight distributions ($M_w/M_n = 1.20-1.26$). However, Bories-Azeau and Armes reported[45] that the ATRP of several tertiary amine methacrylates in methanol at 20 °C was unexpectedly problematic due to the in situ transesterification of these monomers with the solvent. This side reaction produces methyl methacrylate (MMA), which then copolymerizes with the tertiary amine methacrylate to produce unwanted *statistical* copolymers. A reasonable correlation between the basicity of the monomer and the extent of transesterification was observed, which suggested that the transesterification was base-catalyzed. This hypothesis was supported by the observation that much less transesterification (ca. 1−2%) occurred for other (non-aminated) methacrylic monomers such as GMA, MPC, or 2-hydroxyethyl methacrylate. However, significant degrees of transesterification were also observed in the present work during the homopolymerization of MeDMA in methanol/water mixtures. In Figure 4, the lower ^{1}H NMR spectrum shows a MeDMA homopolymer synthesized by aqueous ATRP, whereas the upper spectrum was recorded for a MeDMA homopolymer synthesized in a 3:1 methanol/water mixture. The latter spectrum has an additional signal at δ 3.55, which is assigned to the methoxy signal of MMA residues. Thus, a MeDMA−MMA statistical copolymer is produced under these conditions, rather than the target MeDMA homopolymer. Since the quaternized MeDMA monomer has no basic character, it seems that transesterification cannot be base-catalyzed

Table 2. Summary of the Molecular Weight Data for MeDMA-Based Homopolymers Prepared by ATRP at 20 °C in Various IPA/Water Mixtures

entry no.	MeDMA (% w/v)	IPA/H_2O composition (v/v)	target Dp	reaction time (h)	conv(%)	GPC M_n	M_w/M_n
1	42	1:3	30	1.33	97	17 000	1.25
2	42	1:1	30	2.33	100	16 100	1.25
3	42	2:3	30	0.5	96	17 100	1.26
4	15	1:2	30	3	90	16 200	1.23
5	20	1:2	30	3	96	17 000	1.27
6	30	2:3	30	2	95	16 900	1.25
7[a]	20	1:2	30	5	95	19 300	1.22
8	30	1:1	30	2	98	16 800	1.23
9[b]	30	1:1	30	16	99	12 800	1.19

[a] The synthesis was carried out in the presence of NaCl at a NaCl/MeDMA molar ratio of unity. [b] The inhibitor was not removed from the monomer prior to polymerization.

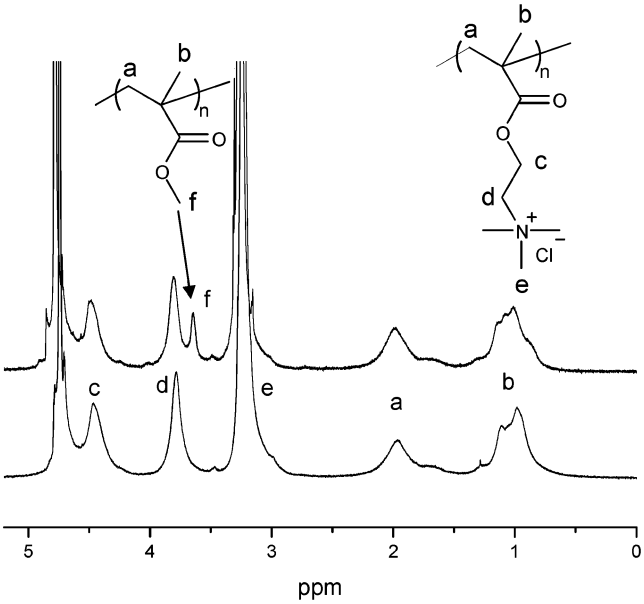

Figure 4. ^{1}H NMR spectra recorded for MeDMA homopolymers synthesized in aqueous solution (lower spectrum) and a 3:1 methanol/water mixture (upper spectrum). Note the additional signal at 3.55 ppm in the latter spectrum, which is assigned to the methoxy protons of methyl methacrylate (MMA). This comonomer is generated in situ by the transesterification of MeDMA with methanol. Hence, in this case a MeDMA−MMA statistical copolymer is formed rather than the desired MeDMA homopolymer.

in this case. However, according to the literature, transesterification can also be catalyzed by copper complexes.[46−48] To investigate whether the Cu(I)Br/bpy ATRP catalyst could promote transesterification, two control experiments were carried out. First, an aqueous solution of degassed MeDMA and degassed methanol were mixed together. After 4 h, only 1% of the monomer was converted to MMA, as judged by ^{1}H NMR. This experiment was then repeated in the presence of the Cu(I)Br/bpy catalyst but with no ATRP initiator (so that no polymerization could occur). After 4 h, 35% of the MeDMA monomer had been converted to MMA. Thus, it appears that the ATRP catalyst promotes significant transesterification on the same time scale as the polymerization. Once polymerized, the MeDMA residues are much less prone to transesterification; presumably this is due to steric hindrance. Nevertheless, the degree of transesterification that occurs during the ATRP of MeDMA under these conditions can be high as 20%. Thus, each of the "PEO−MeDMA" diblock copolymers shown in Table 1 actually contained significant amounts of MMA comonomer, which made these samples unsuitable for their intended applications as well-defined cationic diblock copolymers.

ATRP of MeDMA in IPA/Water Mixtures. To avoid transesterification, 2-propanol (IPA) was employed as a cosolvent instead of methanol. Since IPA is a secondary alcohol, it is more sterically congested and hence much less prone to transesterification with MeDMA. ^{1}H NMR studies (recorded in CD_3OD; not shown) of MeDMA homopolymers prepared in various IPA/water mixtures showed no evidence for "ghost" vinyl signals or 2-(trimethylammonium)ethanol byproduct, thus confirming that no significant transesterification occurred. It should be noted that, although MeDMA monomer can dissolve in IPA, MeDMA homopolymer is insoluble in this solvent. Thus we elected to explore various IPA/water mixtures for the ATRP of MeDMA at 20 °C.

The polymerization of MeDMA in a 2:3 IPA/water mixture was a little faster (but marginally less controlled) than that in a 1:1 IPA/water mixture, as expected (compare entries 6 and 8 in Table 2). Higher monomer concentrations also led to faster polymerizations, and phase separation often occurred at high conversions. More concentrated reaction mixtures (>30% w/v MeDMA) were particularly prone to becoming heterogeneous. Thus, the preferred polymerization conditions were found to be a 1:1 IPA/water mixture and a MeDMA monomer concentration of around 20−30% w/v; typical kinetic data obtained under conditions are shown in Figure 5a. This protocol produced a MeDMA homopolymer with a polydispersity of 1.23 (see Table 2) with minimal phase separation from solution. A molecular weight vs conversion plot for the ATRP of MeDMA under these optimized conditions is shown in Figure 5b. Control was initially poor, indicating that some nonliving polymerization occurred in the early stages. However, the polymer molecular weight then increased monotonically (and almost linearly) from around 20% up to 95% conversion, which is characteristic of a living polymerization. Polydispersities remained below 1.20 over the same range, but the initiation efficiency was only around 30−48%. The GPC curves obtained for three MeDMA homopolymers synthesized at 20 °C in a 3:1 methanol/water mixture, a 1:1 IPA/water mixture, and water are compared in Figure 6. In each case the target M_n was 12 500 (Dp = 60), and the final conversions were more than 90%. The best results are clearly obtained in the IPA/water mixture, since this reaction mixture suffered from essentially no transesterification, gave reasonable agreement with the target M_n, and had the narrowest polydispersity.

Matyjaszewski et al. attributed the relatively fast polymerization rate of ionic monomers such as sodium 4-styrenesulfonate in aqueous solution to hydrolysis of the Cu−X bonds of the Cu(II) deactivator species.[39] This side reaction leads to inefficient deactivation and there-

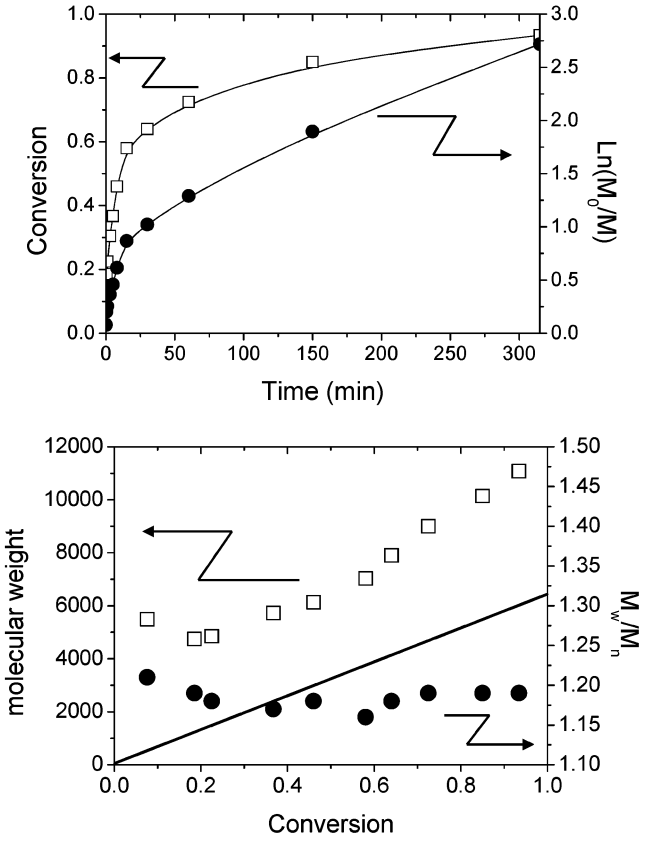

Figure 5. Fractional conversion vs time data and semilogarithmic plot of monomer concentration vs time (upper graph) for the homopolymerization of MeDMA in a 1:1 IPA/water mixture at 20 °C. Evolution of molecular weight and polydispersity with fractional conversion (lower graph) for the same homopolymerization of MeDMA. The solid line represents the theoretical molecular weight at a given conversion. Conditions: 20% w/v MeDMA; target Dp = 30; ME-Br:CuBr:bpy = 1:1:2.5.

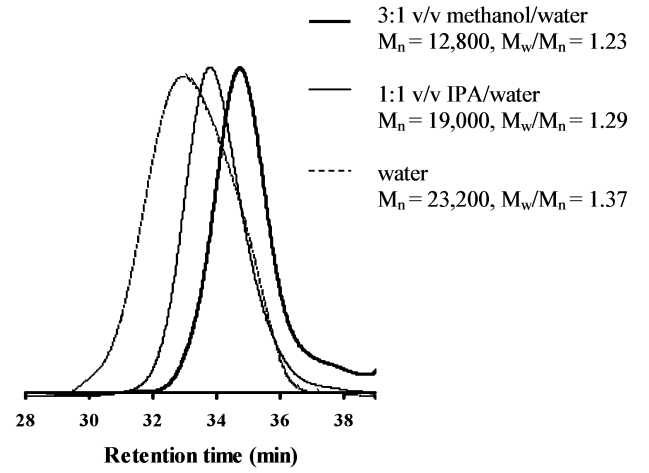

Figure 6. Aqueous GPC curves for the homopolymerization of MeDMA at 20 °C in (a) a 3:1 methanol/water mixture, (b) a 1:1 IPA/water mixture, and (c) water. In each synthesis the target Dp was fixed at 60, the relative molar ratio of [ME-Br]:[Cu(I)]:[L] was 1:1:2.5, and the MeDMA monomer concentration was 30% w/v. Molecular weight data are reported relative to near-monodisperse quaternized DMA homopolymer calibration standards.

fore to fast, uncontrolled polymerizations. This group also suggested that improved control can be achieved in the presence of added halide anions. In the present work we attempted to enhance the living character of

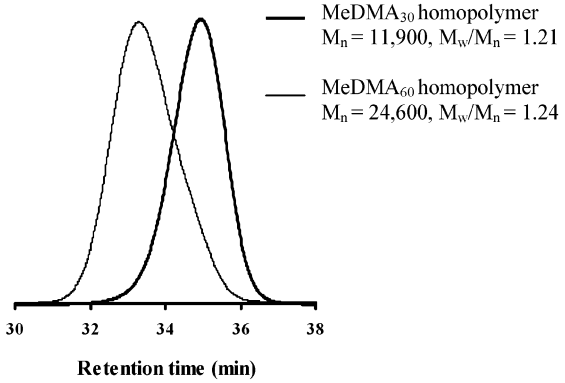

Figure 7. Aqueous GPC curves obtained for an MeDMA homopolymer precursor (M_n = 11 900; M_w/M_n = 1.21) prepared via ATRP in 1:1 IPA/water at 20 °C and the corresponding chain-extended MeDMA homopolymer (M_n = 24 600; M_w/M_n = 1.24) obtained after the addition of a second batch of MeDMA monomer to the polymerizing solution. The initial MeDMA conversion prior to chain extension was 90% and the final conversion was 100%, as judged by ^{1}H NMR. Conditions: first batch of MeDMA (4.15 g, 18 mmol) was dissolved in 4.4 mL of IPA and 3.1 mL of water, target Dp = 30, relative molar ratios of [ME-Br]:[Cu(I)]:[L] = 1:1:2.5; second batch of MeDMA (4.15 g, 18 mmol), overall target Dp of the final chain-extended MeDMA homopolymer was 60.

the homopolymerization of MeDMA in IPA/water solution by adding NaCl, which reduces the rate of polymerization (data not shown). Thus, added chloride appeared to stabilize the Cu(II) halide deactivator complex. Although the semilogarithmic plot remained curved, the polydispersity of the MeDMA homopolymer prepared in the presence of NaCl was 1.22. This is a little lower than that obtained without NaCl (compare entries 5 and 7 in Table 2), which perhaps suggests slightly improved living character. However, this apparent marginal improvement is likely to be within experimental error and batch-to-batch reproducibility.

Chain Extension (Self-Blocking) Experiments. It is well known that living polymerizations usually exhibit certain characteristics, such as the linear evolution of M_n with conversion and relatively narrow molecular weight distributions. However, probably the most useful and discriminating test of the living character of a polymerization is to carry out chain extension experiments.[49] In the present study we performed so-called "self-blocking" experiments in 1:1 IPA/water mixtures at a MeDMA concentration of 30% w/v. Thus, MeDMA was homopolymerized to high conversion (>90%), and then a second batch of MeDMA was added to this polymerizing solution. Provided that most of the polymer chain ends were still capped with halogen atoms, efficient chain extension should occur, which can be readily monitored by aqueous GPC. Typical aqueous GPC curves are depicted in Figure 7, for which the target Dp was 30 for the first batch of MeDMA and 60 for the final chain-extended MeDMA homopolymer. An M_n of 11 900 (vs quaternized DMA homopolymer calibration standards) and a polydispersity of 1.21 were achieved for the first-stage polymerization. The final M_n was 24 600, which is approximately twice the initial molecular weight, and the final polydispersity index was almost unchanged at 1.24. These aqueous GPC data indicate high self-blocking efficiencies, which suggest relatively good living character for the homopolymerization of MeDMA under these conditions.

Diblock Copolymer Syntheses. In view of the encouraging results obtained for the homopolymeriza-

Table 3. Summary of the Molecular Weight Data for Various MeDMA-Based Diblock Copolymers Prepared by ATRP at 20 °C in a 1:1 IPA/Water Mixture[a]

entry no.	target structure	$M_{n,th}$	$M_{n,exp}$	M_w/M_n
1	PEO_{22}−$MeDMA_{30}$	7 200	12 100	1.21
2	PEO_{22}−$MeDMA_{60}$	13 400	18 400	1.28
3	PEO_{22}−$MeDMA_{100}$	21 700	24 900	1.29
4	PEO_{45}−$MeDMA_{30}$	8 200	12 200	1.23
5	PEO_{45}−$MeDMA_{60}$	14 400	18 100	1.30
6	PEO_{45}−$MeDMA_{100}$	22 700	24 400	1.29
7[b]	$MeDMA_{30}$-GMA_{30}	10 500	11 800	1.24
8[b]	$MeDMA_{30}$−$SBMA_{30}$	14 600	13 400	1.29
9[b]	$MeDMA_{30}$-MPC_{30}	15 100	24 300	1.31
10[b]	$MeDMA_{30}$−$BzDMA_{30}$	14 300	10 600	1.19
11[c]	GMA_{30}−$MeDMA_{30}$	10 500	13 400	1.29

[a] The first six entries were prepared using a PEO-based ATRP macroinitiator. The other entries involved sequential monomer addition using the ME-Br initiator; with the exception of the final entry, the MeDMA monomer was polymerized first in each case. [b] The conversion for the first block is 90%. [c] The conversion for the first block is 99%.

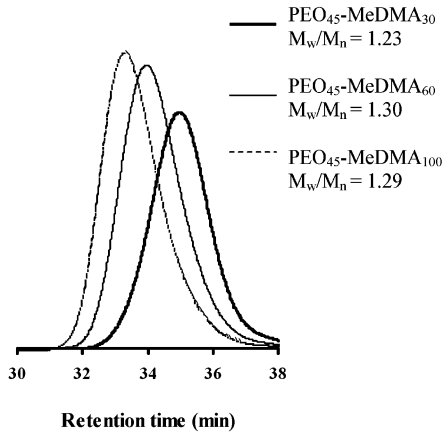

Figure 8. Aqueous GPC curves illustrating the effect of varying the target Dp for the homopolymerization of MeDMA by ATRP using a PEO-based macroinitiator (Dp = 45; M_n = 2000) in a 1:1 IPA/water mixture at 20 °C. Conditions: 30% w/w MeDMA; relative molar ratios of [PEO−Br]:[Cu(I)]:[L] = 1:1:2.5.

tion of MeDMA under the above conditions, a range of novel diblock copolymers were prepared by either the macroinitiator approach or sequential monomer addition (see Table 3 and Figure 9). In the former case two PEO-based macroinitiators were employed, whereas in the latter case the ME-Br initiator was used. The resulting PEO−MeDMA diblock copolymers were obtained in high yield and had relatively narrow molecular weight distributions (M_w/M_n = 1.21−1.30). Bearing in mind the PEO contents of these copolymers, the M_n values indicated by aqueous GPC (vs quaternized DMA homopolymer standards) were consistent with the target block compositions. Overlaid GPC curves obtained for the PEO_{45}−MeDMA diblock copolymer series are shown in Figure 8 with target Dp's of 30, 60, and 100 for the MeDMA block. In each case the chromatograms are unimodal, and the M_n increased from around 12 000 to around 24 000−25 000.

Five MeDMA-based diblock copolymers were prepared by sequential monomer addition, with the second hydrophilic methacrylate being either BzDMA, GMA, MPC, or SBMA (see Figure 9). These comonomers were selected to ensure that the resulting diblock copolymers remained water-soluble and hence amenable to aqueous GPC analysis. BzDMA is a quaternized, cationic monomer that is very similar in structure to MeDMA, GMA is a nonionic hydroxylated monomer for which ATRP protocols in protic media are already established,[40] and both MPC and SBMA are examples of betaine monomers. In most cases the M_n values were similar to the theoretical values, and the polydispersities ranged from 1.19 for the MeDMA−BzDMA diblock to 1.31 for the MeDMA−MPC diblock. This latter diblock also had the biggest discrepancy between the target M_n and the actual M_n, which may be at least partially attributed to the aqueous GPC protocol being nonoptimized for the MPC block. [We have some evidence to support this hypothesis: MPC homopolymer synthesized by ATRP had an M_w/M_n of around 1.20 when assessed using aqueous GPC at *neutral* pH,[49] but the same sample had an M_w/M_n of 1.29 when analyzed using the cationic GPC protocol described in the present paper. We have reported similar GPC problems with MPC-based triblock copolymers.[50]] In most cases the MeDMA was polymerized first, but the effect of changing the order of addition was also explored for the MeDMA−GMA diblock copolymer (compare entries 7 and 11 in Table 3). Similar results were obtained regardless of the order of monomer addition.

Selected PEO−MeDMA diblock copolymers are being examined for their efficacy in the complexation (condensation) of oligonucleotides and subsequent use as synthetic vectors for gene delivery applications. Preliminary results indicate that, compared to MeDMA homopolymers, the quaternized diblock copolymers produce complexes of superior stability. Selected PEO−MeDMA copolymers are also being evaluated as templates for the catalytic formation of silica in aqueous

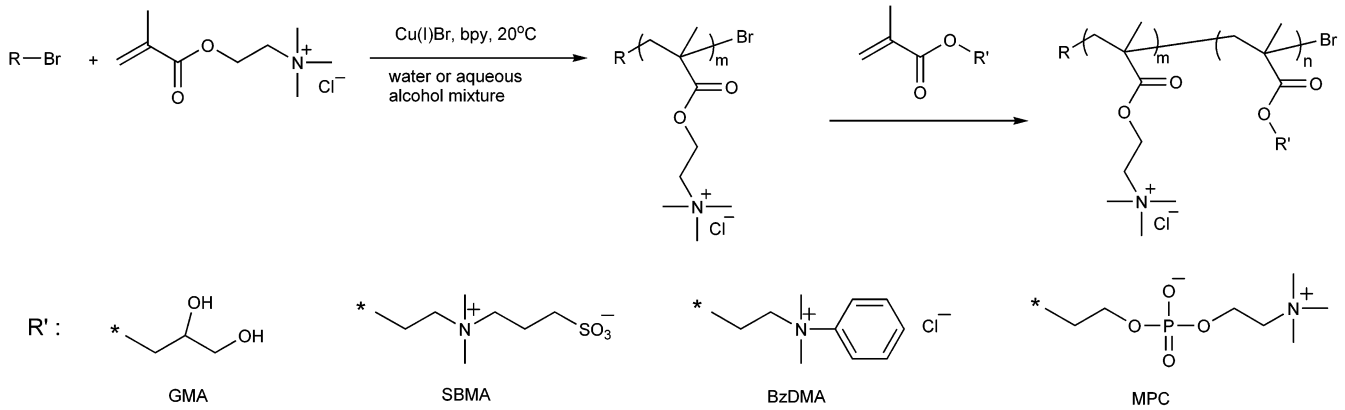

Figure 9. Reaction scheme for the ATRP synthesis of well-defined, MeDMA-based diblock copolymers by sequential monomer addition in protic media at 20 °C.

solution under mild conditions. This application has yielded particularly interesting results with regard to the silica nanomorphology; these will be reported elsewhere in the near future.

Conclusions

In summary, this is the first detailed report of the direct polymerization of a cationic, quaternized monomer via ATRP. The polymerization of MeDMA is only poorly controlled in water and transesterification, apparently catalyzed by the Cu(I) complex, is a significant problem in methanol/water mixtures. The best control was achieved in a 1:1 2-propanol/water mixture at 20 °C at a MeDMA concentration of 20−30% w/v. Although nonlinear kinetic plots were observed even under these optimized conditions, low final polydispersities (M_w/M_n < 1.25) were obtained, and chain extension experiments confirmed good blocking efficiencies. A number of new, well-defined cationic diblock copolymers were readily synthesized using either the macroinitiator approach or sequential monomer addition. Potential applications for selected diblock copolymers are currently being explored.

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