Synthesis of Biocompatible Polymers. 1. Homopolymerization of 2-Methacryloyloxyethyl Phosphorylcholine via ATRP in Protic Solvents: An Optimization Study

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ABSTRACT: Biocompatible polymers based on 2-methacryloyloxyethyl phosphorylcholine (MPC) have delivered clinically proven benefits in various biomedical applications. In a recent communication [Lobb, E. J.; et al. *J. Am. Chem. Soc.* **2001**, *123*, 7913−7914], we reported that MPC can be polymerized to high conversions in both water and methanol at ambient temperature via atom transfer radical polymerization (ATRP). Low polydispersities were obtained, but the living character of this polymerization was not thoroughly explored. In the present paper we report a more detailed optimization study of the ATRP of MPC. Excellent yields, first-order monomer kinetics, linear M_n vs conversion plots, and relatively narrow polydispersities (M_w/M_n = 1.15−1.35) were obtained in both aqueous and alcoholic media at 20 °C. However, slower polymerizations and narrower polydispersities were always obtained in alcoholic solution, and chain extension experiments indicated significantly greater living character (i.e., greater self-blocking efficiency) under these conditions. The rate of ATRP was significantly slower in 2-propanol (IPA) than methanol due to the reduced polarity of the former solvent. However, acceptable rates of polymerization and reasonable control were obtained at elevated temperature in IPA. Alternatively, the addition of a relatively small amount of water to the IPA led to a significantly faster polymerization at ambient temperature. The effect of varying the ligand type and target DP_n was also investigated. The best results were obtained using 2,2′-bipyridine for target DP_n's of 20−200, with two alternative ligands giving either inferior control or slower rates of polymerization. Higher target DP_n's resulted in significantly higher polydispersities even when using the 2,2′-bipyridine ligand. The spent ATRP catalyst was conveniently removed by treating aqueous solutions of MPC homopolymer with silica. This produced residual catalyst levels of less than 2 ppm, as measured by inductively coupled plasma atomic emission spectrometry, which may be sufficiently low for some biomedical applications. This synthetic advance is expected to allow the preparation of a wide range of novel biocompatible diblock and triblock copolymers for various biomedical applications.

Introduction

The phosphorylcholine (PC) moiety is an important component of cell membranes. The use of PC for modifying surfaces in order to improve their biocompatibility was recognized by Chapman and co-workers in a series of studies conducted in the 1980s.[1] This pioneering work led to the development of a surface treatment based on diacetylenic-functionalized phospholipids, which could be cross-linked to enhance the long-term stability and mechanical integrity of this coating.[2] While the biocompatibility of these materials was excellent, significant difficulties in the synthesis and handling made this particular system unattractive for commercialization. A rather more attractive approach, based on the methacrylic PC monomer, 2-methacryloyloxyethyl phosphorylcholine (MPC), arose from the pioneering work of two independent groups in Japan. In 1982, Nakaya et al. reported[3] the first synthesis of MPC monomer; this synthetic route was elaborated and subsequently exploited by Nakabayashi and co-workers to prepare a range of MPC-based copolymers for biocompatibility studies.[4] Further refinement and optimization by Biocompatibles in the UK[5] led to commercialization of a range of PC-based medical devices including soft contact lenses,[6] haemocompatible coatings on coronary guidewires, stents[7] and extracorporeal circuits,[8] and low biofouling coatings on urological devices[9] and tympanostomy tube implants.[10] The broad applicability of this technology for a wide range of biomedical applications is due to the clinically proven resistance of PC-based polymeric coatings to protein adsorption, which is the crucial first step in the biofouling process (e.g., thrombus formation when in contact with blood or bacterial biofilm formation in urine). The precise mode of action of PC has been a matter of debate for some years. However, recent differential scanning calorimetry and Raman spectroscopy studies by Ishihara et al. on water binding and also protein conformational analysis using circular dichroism spectroscopy suggest that the highly hydrated PC headgroups act as a buffer to prevent protein adsorption and unfolding on a surface treated with an MPC copolymer.[11]

The main focus for PC-based materials has been improvement of the interface between tissue and medical device, and there has been relatively little innovation in the development of improved polymerization chemistry. MPC copolymers with desirable coating characteristics can be readily synthesized using conventional free-radical polymerization, which produces high mo-

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lecular weight statistical architectures. Although conceptually simple, this approach allows only very limited control over the target molecular weight and the molecular weight distribution; in particular, the synthesis of well-defined block architectures is not possible. There have been a few reports of graft and block polymers incorporating MPC, but the synthetic methods employed have been generally crude, leading to ill-defined materials in poor yield.[12,13] The field of phospholipid polymers has been extensively reviewed recently,[14] but we are not aware of any reports of the *controlled* polymerization of MPC.

When considering the use of MPC-based polymers for applications other than coatings on medical prostheses, the ability to control the polymer architecture becomes important. In this context Ishihara and co-workers reported the synthesis of statistical copolymers of MPC with *n*-butyl methacrylate using conventional free radical chemistry.[15] Although heterogeneous in composition and highly polydisperse, these copolymers form water-dispersible aggregates with hydrophobic domains and have been claimed to have potential for drug delivery. In contrast, *well-defined* amphiphilic di- or triblock copolymers have been investigated for many years as carriers for hydrophobic drugs.[16] In particular, these have been modified with poly(ethylene glycol) in order to improve their biocompatibility and hence increase plasma half-life.[17] It would be highly desirable if robust synthetic routes to the analogous MPC-based block architectures could be developed.

One problem is that betaine monomers such as MPC are normally insoluble in the organic solvents (e.g., toluene, THF, dichloromethane) typically used for conventional ionic living polymerization, which is the traditional method for producing controlled-structure, near-monodisperse copolymers. However, in 1995 atom transfer radical polymerization (ATRP) was developed independently by Wang and Matyjaszewski[18,19] at Carnegie Mellon University and Sawamoto's group in Kyoto.[20] Reversible chain-end capping using halogen atoms ensures that the instantaneous polymer radical concentration is lower than in conventional radical polymerization, which suppresses termination relative to propagation and hence leads to relatively narrow molecular weight distributions. Efficient block copolymer syntheses can be achieved under optimized conditions, and this pseudo-living free radical chemistry[21−23] has gained a deserved reputation for its excellent tolerance of both monomer functionality and protic solvents.[24−28]

We recently reported that ATRP is particularly effective for a wide range of hydrophilic monomers in protic media such as water and/or lower alcohols under mild conditions.[29−38] In view of these results, and given that MPC is insoluble in many organic solvents, we investigated the feasibility of polymerizing MPC via aqueous or alcoholic ATRP (see Figure 1). Our initial results were reported in a recent communication;[39] herein, we describe the homopolymerization of MPC in more detail. In particular, we have attempted to optimize the ATRP formulation in order to obtain good living character, which is essential if well-defined block architectures are desired.

Experimental Section

Materials. MPC monomer (99.9% purity) was kindly donated by Biocompatibles, UK. Copper(I) bromide (Cu(I)Br), 2,2′-bipyridine (bpy), and 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) were all purchased from Aldrich. The oligo(ethylene glycol)-based water-soluble initiator (OEGBr) was synthesized by reacting monohydroxy-capped oligo(ethylene glycol) with 2-bromoisobutyryl bromide and purified as described previously.[23] The 3-(*N*-morpholino)propylpyridinyl-2-methanimine (MPMA) ligand was synthesized by reacting 2-pyridinecarbaldehyde and 3-(*N*-morpholino)propylamine in ether at 20 °C, as described previously.[40] 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).

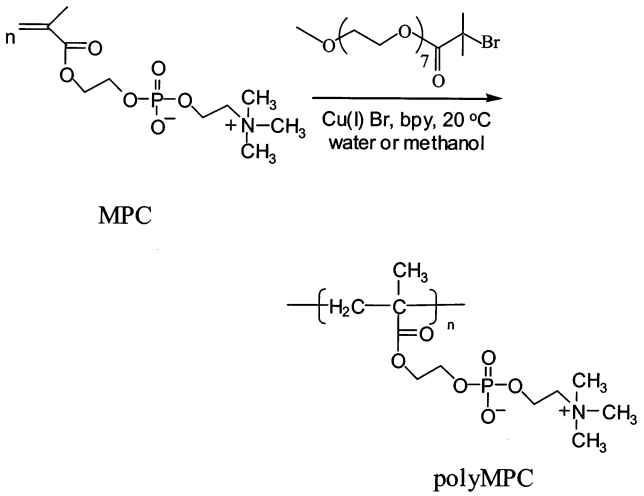

Figure 1. Reaction scheme for the atom transfer radical polymerization of 2-methacryloyloxyethyl phosphorylcholine (MPC) in protic media at 20 °C.

Homopolymerization of MPC in Aqueous Solution. A typical protocol for the controlled polymerization of MPC by aqueous ATRP is as follows. The water-soluble ATRP initiator (OEGBr, 67.0 mg, 0.135 mmol, 1 equiv) was dissolved in doubly distilled, deionized water (10 mL). After purging with nitrogen for 30 min, Cu(I)Br catalyst (19.0 mg, 0.135 mmol, 1 equiv) and bpy ligand (42.0 mg, 0.27 mmol, 2 equiv) were added to the stirred solution under nitrogen. MPC (2.00 g, 6.73 mmol, 50 equiv, target M_n = 15 000) was then added as a solid to the reaction mixture under nitrogen. The reaction mixture immediately became dark green and progressively more viscous. Exotherms of 2−4 °C were typically observed, indicating that polymerization was occurring. After approximately 1 h, ^{1}H NMR analysis indicated that 99% of the MPC had been polymerized. The MPC homopolymer was precipitated into THF, then redissolved in water, and passed through a silica gel column to remove residual ATRP catalyst. This purification protocol resulted in the loss of up to 20% MPC homopolymer due to adsorption. Aqueous GPC analysis indicated an M_n of 12 000 (vs poly(ethylene oxide) standards) and an M_w/M_n of 1.24. Polymerizations in methanol (or IPA) were carried out using essentially the same protocol. In these syntheses the reaction turned dark brown, and no exotherms were observed, which reflects the slower rates of polymerization in the absence of water. For MPC polymerizations carried out using either HMTETA (31.0 mg, 0.135 mmol, 1 equiv based on Cu(I)Br) or MPMA (63.2 mg, 0.27 mmol, 2 equiv based on Cu(I)Br) as the ligand, the reaction solution turned either blue or brown, respectively. In all of these latter alcoholic syntheses the spent ATRP catalyst was removed by treating methanolic solutions of MPC homopolymer with silica gel.

Polymerizations were carried out at different temperatures by immersing the reaction flasks into an oil bath equipped with a thermostat. Target degrees of polymerization (DP_n) were adjusted by varying either the initiator or the monomer concentrations. In the majority of syntheses the initiator/catalyst molar ratio was unity, but other molar ratios were explored for two entries in Table 1.

Table 1. Summary of Conversion and Molecular Weight Data for 2-Methacryloyloxyethyl Phosphorylcholine (MPC) Homopolymers Prepared with Varying Target DP_n's Synthesized via Either Aqueous or Methanolic ATRP at 20 °C[a]

expt. no.	solvent (10 mL)	target DP_n	target M_n	[MPC] (g)	[OEGBr] (mg)	reaction time (min)	conv (%) by ^{1}H NMR	M_n	M_w/M_n	residual Cu in MPC homopolymer (ppm)
1	H_2O	50	15 000	4.0	134	60	98	12 000	1.24	1.4
2	H_2O	70	21 000	4.0	94	90	99	19 000	1.24	1.2
3	H_2O	100	30 000	4.0	67	90	95	22 000	1.26	1.6
4	MeOH	20	6 000	0.8	67	420	100	5 300	1.18	1.1
5	MeOH	50	15 000	2.0	67	380	100	12 000	1.16	1.3
6	MeOH	100	30 000	4.0	67	300	100	24 000	1.21	1.2
7	MeOH	150	45 000	4.0	47	360	96	42 000	1.26	1.4
8	MeOH	200	60 000	8.0	67	150	93	46 000	1.28	1.5
9	MeOH	250	75 000	4.0	28	360	86	61 000	1.32	1.2
10	MeOH	300	90 000	4.0	24	360	82	74 000	1.48	1.3

[a] The molar ratio of initiator:Cu(I)Br:bpy was 1:1:2 for all entries except 1 and 2, for which the molar ratios were 2:1:2 and 1.43:1:2, respectively. Aqueous GPC data are expressed as poly(ethylene oxide) equivalent molecular weights. The Cu contents of the MPC homopolymers were determined using ICP−AES (see main text for further details).

Self-Blocking (Chain Extension) Experiments. MPC (3.0 g, 10.1 mmol) was polymerized in 10.0 mL of a doubly distilled water such that the relative molar ratios of [MPC]:[OEGBr]:[Cu(I)Br]:[bpy] were 50:1:1:2. After 25 min the monomer conversion was more than 95%, as judged by ^{1}H NMR spectroscopy. At this point a second batch of MPC (3.00 g, 10.1 mmol) was added to the polymerizing solution. After 2 h, a chain-extended MPC homopolymer was obtained with essentially 100% monomer conversion. For the self-blocking experiments conducted in methanol, a period of 2 h was required for more than 95% conversion of the first batch of MPC, as judged by ^{1}H NMR spectroscopy. After addition of the second batch of MPC, the polymerizing solution was left for at least 20 h. Subsequent NMR analysis indicated that residual vinyl signals (formerly at δ 5.6 and 6.1 ppm) were now absent, suggesting that the overall conversion was approximately 100%.

Polymer Characterization. ^{1}H NMR spectra were recorded in either D_2O or CD_3OD using a 300 MHz Bruker Avance DPX300 spectrometer in order to monitor the polymerization kinetics. The molecular weight and molecular weight distributions of the MPC homopolymers were determined by aqueous gel permeation chromatography (GPC), using a Pharmacia Biotech "Superose 6" column (upper limit molecular weight was $\sim 4 \times 10^7$ g mol^{-1}, the flow rate was 0.50 mL min^{-1}, and the column temperature was 20 °C) connected to a Polymer Labs ERC-7517A RI detector. The eluent was 0.20 M $NaNO_3$ solution with a 50 μM Trizma buffer solution comprising equimolar amounts of tris(hydroxymethyl)aminomethane and tris(hydroxymethyl)aminomethane hydrochloride (both purchased from Aldrich). Calibration was based on 14 poly(ethylene oxide) standards ranging from 440 to 288 000 g mol^{-1}.

Determination of the Residual ATRP Catalyst Level. After silica treatment to remove the ATRP catalyst, aqueous solutions of selected, purified MPC homopolymers were analyzed for their Cu contents using a Perkin-Elmer Plasma 400 inductively coupled plasma atomic emission spectrometer (ICP-AES) using the following protocol. Approximately 50 mg of polymer was accurately weighed, dissolved in distilled water containing 5% v/v "trace analysis" grade nitric acid, and made up to 5.00 mL. The unknown aqueous polymer solution was introduced into the argon plasma, and the Cu emission at 327.396 nm was measured and compared to that found for stock solutions containing 0.100, 0.050, and 0.020 ppm of Cu; a blank solution containing 5% v/v nitric acid in distilled water was used as a fourth calibration solution. For sample solutions that exceeded 0.100 ppm of Cu, a second analysis was performed using calibration solutions containing 1.000 and 0.100 ppm, together with the blank solution. The manufacturer's estimated detection limit is around 0.0097 ppm of Cu for the above emission wavelength. This ICP-AES technique indicated residual Cu levels in the range of 1−2 ppm for the purified MPC homopolymers.

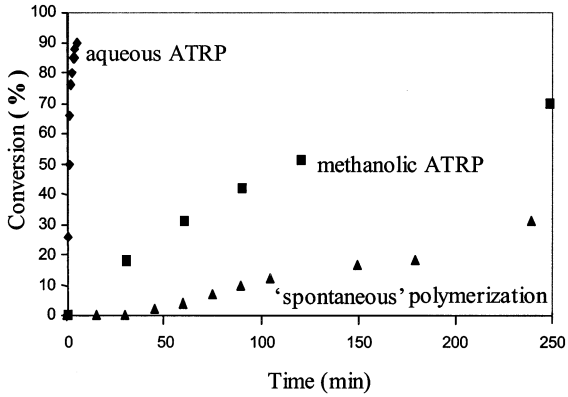

Figure 2. Comparison of the conversion vs time curves for the homopolymerization of MPC at 20 °C: (a) under aqueous ATRP conditions (17 wt % MPC, pH 7, target $DP_n = 10$; see text for further synthesis details); (b) under identical ATRP conditions but in methanol rather than water; (c) "spontaneous" polymerization in the absence of ATRP initiator or catalyst (conditions: 17 wt % MPC at pH 7).

Results and Discussion

An unexpected problem was encountered in our preliminary experiments, since the MPC monomer polymerized in the absence of any ATRP initiator[41] in aqueous solution at 20 °C. In initial syntheses this problem was exacerbated because we had elected to add the ATRP initiator last to an aqueous (and already polymerizing!) solution of MPC. GPC analysis of the resulting polymer indicated a bimodal molecular weight distribution, with the higher mass peak corresponding to the uncontrolled spontaneous polymerization of MPC. Fortunately, later experiments confirmed that adding solid MPC monomer to an aqueous solution containing the ATRP initiator and catalyst produced a very fast rate of ATRP, with over 90% conversion achieved within 5 min at 20 °C (see Figure 2). Since the rate for the auto-polymerization of MPC is much slower (conversions of 50% required 5 h for a 17 wt % solution of MPC at 20 °C), essentially only ATRP occurred, and polymers with unimodal distributions were readily obtained. In methanol the rate of ATRP is much slower, but fortunately auto-polymerization of MPC does not occur in this solvent. Thus, for both water and methanol it is possible to find conditions under which the polymerization of MPC occurs exclusively via an ATRP mechanism.

In our earlier communication,[39] we reported that the aqueous ATRP of MPC was very rapid at 20 °C: high yields (>96%) were obtained within 10 min at MPC concentrations of 17% w/v, with polydispersities of 1.12−1.28 being obtained. At 40% w/v MPC, conversions of

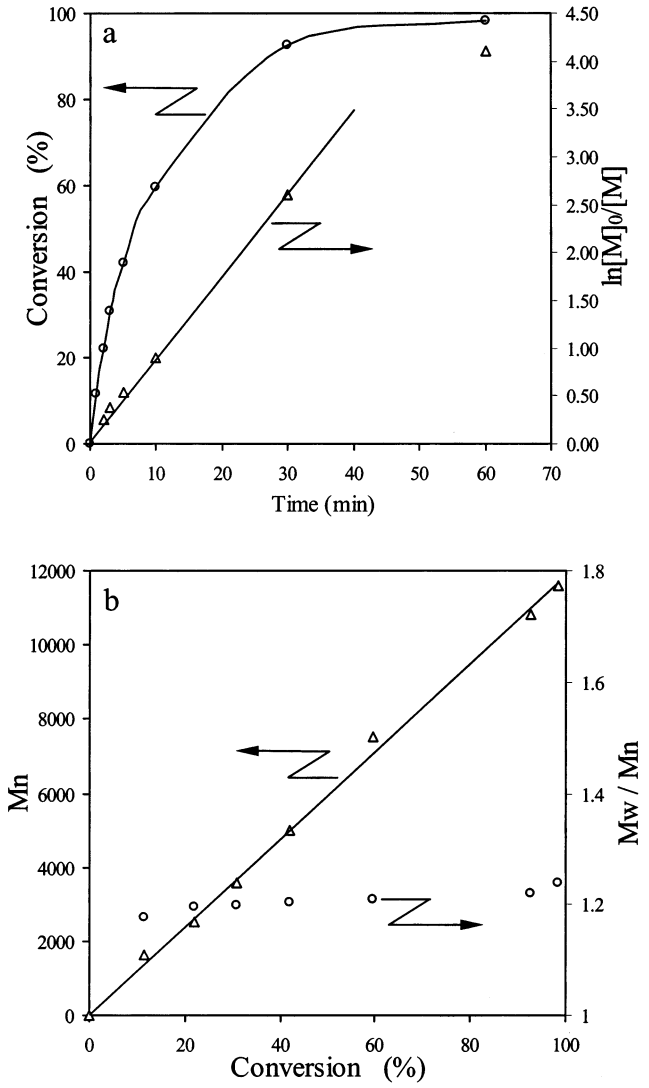

Figure 3. Homopolymerization of MPC via aqueous ATRP at 20 °C: (a) Conversion vs time data and semilogarithmic plot of monomer concentration vs time. Conditions: MPC (2.0 g, 6.73 mmol), OEGBr initiator (67.0 mg, 0.135 mmol, 1 equiv), Cu(I)Br (19.0 mg, 0.135 mmol, 1 equiv), and bpy ligand (42.0 mg, 0.27 mmol, 2 equiv); 10 mL of double-distilled water, target $DP_n = 50$. (b) Evolution of molecular weight vs conversion; conditions as stated in (a).

more than 96% were obtained within 3 min. However, polydispersities were somewhat higher at 1.23−1.45, indicating reduced control at this higher monomer concentration. The semilogarithmic plot of monomer concentration vs time for the homopolymerization of MPC was linear up to around 75% conversion. At higher conversions, nonlinear behavior was observed, which indicated that the polymer radical concentration was no longer constant, probably due to some premature chain termination. On the other hand, the molecular weight vs conversion plot was linear up to 95%. Similar results for the aqueous ATRP of MPC are reported in the first three entries in Table 1 and also in Figure 3. These polymerizations were somewhat slower than those reported earlier,[39] because the target DP_n's were 50−100, rather than ranging from 10 to 30 in the previous study. Nevertheless, very high conversions were obtained within 60−90 min, and final polydispersities ranged from 1.24 to 1.26. Target DP_n's were adjusted by varying the initiator concentration at a fixed monomer concentration. However, aqueous GPC analyses indicated only relatively small increases in M_n as the target DP_n was doubled from 50 to 100 (see entries 1−3).

"Living" polymerizations are characterized by the linear evolution of M_n with conversion and, if the rate of initiation is fast relative to that of propagation, relatively low polydispersities. However, probably the most discriminating test of the "livingness" of a polymerization is efficient chain extension. In this study we have performed a number of "self-blocking" experiments. MPC was homopolymerized to very high conversion (>95%), and then a second batch of MPC was added to this polymerizing solution. Provided that the polymer chain ends were still capped with halogen atoms, chain extension should occur, which can be readily monitored using GPC. The results obtained in our first set of chain extension experiments are depicted in Table 2. In this case the MPC was polymerized in aqueous solution at 20 °C, with an initial target DP_n of 10, 50, or 100, and then further MPC was added to double the initial polymer molecular weight. The data presented in Table 2 show that chain extension occurred, but the final M_n values were somewhat higher than expected. Moreover, the final polydispersity indices are significantly higher, especially for higher target DP_n's (see Figure 4). These data indicate that a significant proportion of the polymer chain ends became deactivated toward the end of the first-stage polymerization and suggest that the aqueous ATRP of MPC has less than ideal living character. We have recently obtained similar results with other hydrophilic methacrylates,[31,36] and contrary to our earlier claims,[29,30,32,33] we now believe that aqueous ATRP is not well-suited for the synthesis of controlled-structure block copolymers. There are two plausible explanations for the reduced living character encountered in aqueous ATRP syntheses. First, the copper−halogen bond of the Cu(II) complex is likely to be less covalent (more ionic) in aqueous media, which could reduce the efficiency of polymer radical deactivation. Second, the terminal halogen atom on the polymer chain ends may be prone to hydrolysis.

In view of the poor self-blocking efficiencies obtained for MPC in aqueous media, we decided to examine the feasibility of polymerizing MPCin methanol (see entries 4−7 in Table 1). The polymerizations in methanol were significantly slower than the equivalent syntheses in aqueous media (for example, compare entries 3 and 6, which have the same target DP_n): up to 7 h was required for complete conversion at 20 °C, as judged by the disappearance of the ^{1}H NMR vinyl signals at 5.6 and 6.1 ppm. Target DP_n's were adjusted from 20 to 200 by varying the monomer/initiator molar ratio, typically by increasing the monomer concentration at a fixed initiator concentration. In these syntheses, unlike those conducted in water, aqueous GPC analysis indicated the approximate expected increase in M_n, within experimental error (see Table 1). The conversion vs time data for a typical MPC homopolymerization in methanol at 20 °C with a target DP_n of 100 is shown in Figure 5. Approximately 6 h was required for 90% conversion, and the semilogarithmic plot was linear, suggesting that a constant polymer radical concentration was maintained during polymerization. Aqueous GPC analysis confirmed a linear increase in M_n with conversion. Moreover, the polydispersity indices remained below 1.20 and decreased throughout the polymerization.

Table 2. Self-Blocking Experiments (Chain Extension) for the Homopolymerization of MPC via Aqueous ATRP at 20 °C[a]

target composition of MPC homopolymer	M_n (theory)		M_n (aqueous GPC)		M_w/M_n	
	initial MPC homopolymer	chain-extended polymer	initial MPC homopolymer	chain-extended polymer	initial MPC homopolymer	chain-extended polymer
$MPC_{10}-MPC_{10}$	3 000	6 000	4 400	8 300	1.15	1.27
$MPC_{50}-MPC_{50}$	15 000	30 000	20 000	44 000	1.16	1.41
$MPC_{100}-MPC_{100}$	30 000	60 000	50 000	90 000	1.25	1.45

[a] The initiator:Cu(I)Br:bpy molar ratio was 1:1:2; for further experimental details see main text.

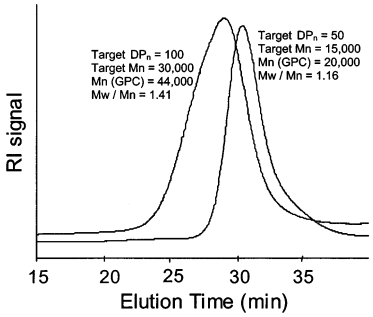

Figure 4. Self-blocking experiments in water at 20 °C. Aqueous GPC curves for an MPC homopolymer precursor (M_n = 20 000; M_w/M_n = 1.16) prepared via aqueous ATRP and the corresponding chain-extended MPC homopolymer (M_n = 44 000; M_w/M_n = 1.41) obtained after the addition of a second batch of MPC monomer to the polymerizing solution. Conversion of the first batch of MPC prior to chain extension was 95%. Overall final MPC conversion was 100%. Conditions: first batch of MPC (3.00 g, 10.1 mmol), 10 mL of water, target DP_n = 50, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2; second batch of MPC (3.00 g, 10.1 mmol).

Chain extension experiments were also conducted in methanol in order to assess the living character of the polymerization in this medium. Again, three different target DP_n's were selected, and the second batch of MPC monomer was chosen to be sufficient to double the initial molecular weight, assuming living character. Typical aqueous GPC data are depicted in Figure 6, for which the target DP_n was 50 for the first batch of MPC and 100 for the final chain-extended MPC homopolymer. An M_n of 12 000 (vs PEO standards) and a polydispersity of 1.17 were achieved for the first-stage polymerization. After the second-stage polymerization the final M_n was 24 000, which is precisely double the initial molecular weight, and the final polydispersity index was 1.22. These data indicate excellent blocking efficiencies, and hence good living character, for the homopolymerization of MPC in methanol, which is in striking contrast to the results obtained from aqueous ATRP for the same target DP_n's (see second entry in Table 2).

The effect of varying the nature of the solvent on the rate of polymerization of MPC was also studied; the results are depicted in Figure 7. For a fixed target DP_n of 100, the apparent rate constant for aqueous ATRP is about 5 times higher than that for methanolic ATRP, which is in turn around 50% more than that for IPA. This order of reactivity is consistent with an earlier report by Matyjaszewski and co-workers,[42] who found a correlation between the dielectric constant of the solvent and the rate of ATRP of *n*-butyl acrylate. IPA is of particular interest because it is much more environmentally friendly than methanol, which is toxic. There is a second advantage in using IPA as an ATRP solvent. With certain hydrophilic methacrylates we have observed some degree of transesterification occurring during methanolic ATRP, even for polymerizations conducted at ambient temperature. Fortunately, this

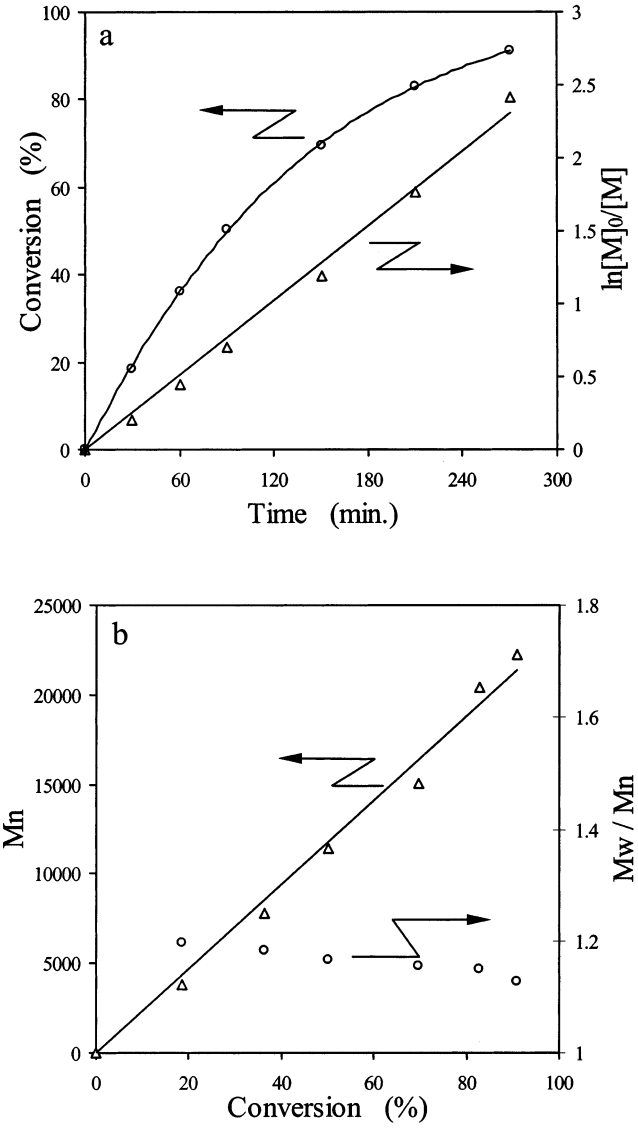

Figure 5. Homopolymerization of MPC in methanol via ATRP at 20 °C: (a) Conversion vs time data and semilogarithmic plot of monomer concentration vs time [conditions: MPC (4.00 g, 13.4 mmol), 10 mL of methanol, target DP_n = 100, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2]. (b) Evolution of molecular weight vs conversion; conditions as stated in (a).

unwanted side reaction is suppressed in IPA, which makes this solvent the preferred choice for the synthesis of certain MPC-based diblock copolymers. More details will be reported in due course.[43]

Relative differences in the living character of these homopolymerizations can be judged by inspecting the evolution of polydispersity with monomer conversion. In the case of aqueous ATRP, the polydispersity *increases* during the polymerization, and the final polydispersity obtained at 95% conversion approaches 1.30. In contrast, polydispersities *decrease* with increasing

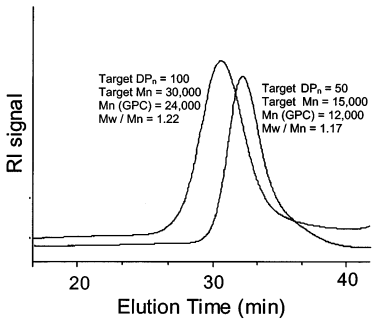

Figure 6. Aqueous GPC curves for an MPC homopolymer precursor (M_n = 12 000, M_w/M_n = 1.17) prepared via methanolic ATRP at 20 °C and the corresponding chain-extended MPC homopolymer (M_n = 24 000, M_w/M_n = 1.22) obtained after the addition of a second batch of MPC monomer to the polymerizing solution. Conversion of MPC prior to chain extension was 96%. The overall MPC conversion was 100%. Conditions: first batch of MPC (3.00 g, 10.1 mmol), 10 mL of methanol, target DP_n = 50, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2; second batch of MPC (3.00 g, 10.1 mmol), and the overall target DP_n of the final chain-extended MPC homopolymer was 100.

conversion for syntheses carried out in alcoholic media, reaching values of around 1.15 in the case of methanol. Clearly, the slower rates of polymerization obtained in alcoholic media lead to better living character, which is consistent with the higher self-blocking efficiencies described earlier.

The effect of varying the temperature of the homopolymerization of MPC in methanol is illustrated in Figure 8. The semilogarithmic plots of monomer conversion vs time were linear for ATRP syntheses conducted at 20 and 40 °C. Some curvature was observed at 60 °C, but only for very high conversions (>95%). As expected, a faster rate of polymerization is obtained at higher temperature. Arrhenius analysis of these data indicated an activation energy of around 29 kJ mol^{-1} for MPC homopolymerization. The evolution of molecular weight vs conversion was reasonably linear at all three temperatures, and the final polydispersities were below 1.20, suggesting good living character.

An alternative approach has been reported by Rannard and McDonald,[44] who have shown that relatively small amounts of water added to alcoholic solutions of *n*-butyl methacrylate have a profound effect on the rate of ATRP. Thus, in the present study we examined the homopolymerization of MPC in a 9:1 IPA:water mixture at 20 °C (target DP_n of 50). The conversion was over 95% after 3 h, and the polydispersity was 1.23. An attempt to chain-extend this homopolymer by adding further solid MPC monomer proved problematic due to the relatively poor solubility of MPC in the IPA-rich solution. As a comparison, the identical reaction (same target DP_n of 50) in pure IPA was rather slow, with 5 h required for 93% conversion at 20 °C. A polydispersity of 1.13 was obtained for this conversion, again indicating good control over the polymerization.

The effect of varying the target DP_n on the ATRP of MPC in methanol at 20 °C was also assessed. Fixed masses of initiator, catalyst, ligand, and methanol were used in these experiments, and the amount of added MPC was systematically increased in order to target higher DP_n's. Under these conditions, the rate of polymerization should *increase* with increasing target DP_n, and this trend was indeed observed (see Figure 9). As the target DP_n was increased from 20 to 200, the time

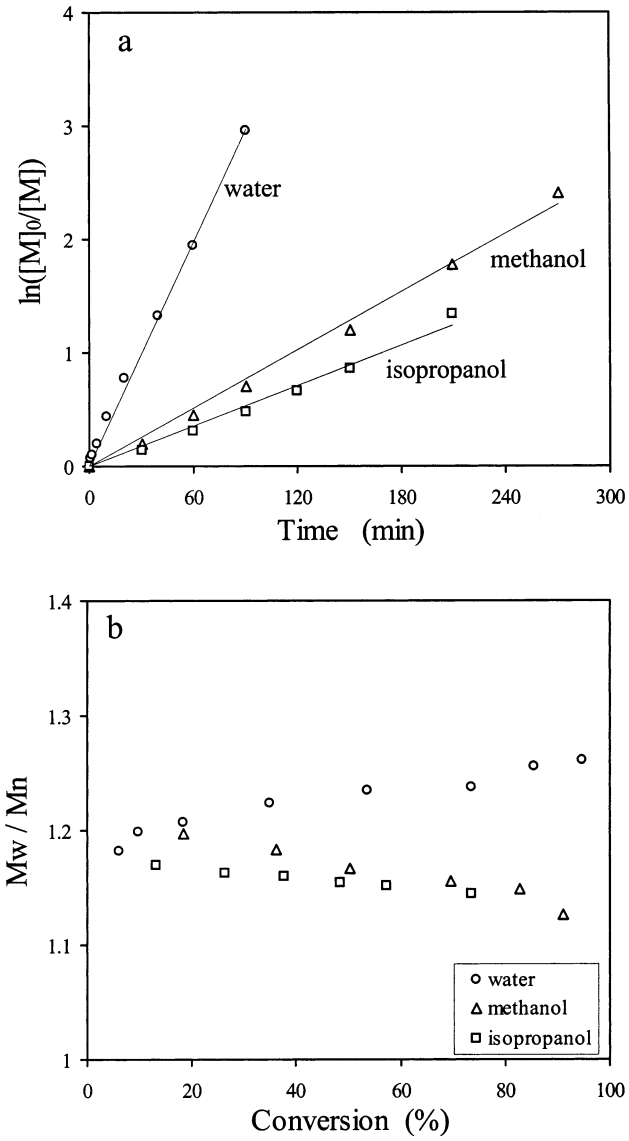

Figure 7. Effect of varying the solvent type on the homopolymerization of MPC at 20 °C: (a) Semilogarithmic plot of monomer concentration vs time [conditions: MPC (4.00 g, 13.4 mmol), 10 mL of water, methanol or 2-propanol, target DP_n = 100, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2]. (b) Polydispersity vs conversion data; conditions as stated in (a).

required for 98% conversion was reduced from 6-7 h to approximately 2.5 h. The evolution of polydispersity with conversion data indicated that higher polydispersities (around 1.28) were obtained at a target DP_n of 200. This probably indicates some reduction in living character. This trend is also seen in Table 1, where there is a clear correlation between target DP_n and final polydispersity: the highest targeted DP_n of 300 produced a final polydispersity of 1.48, which indicates significant loss of control over the polymerization under these conditions.

The nature of the ATRP ligand can have a profound effect on the rate of polymerization and also on its living character.[21−23,33] Three ligand types were examined in the present study: bpy, HMTETA, and MPMA (see Figure 10). Matyjaszewski's group have previously reported the use of bpy and HMTETA,[24,45] and MPMA is a water-soluble version of the Schiff base ligands favored by Haddleton and co-workers.[40] Under the same reaction conditions (see Figure 10 caption for details),

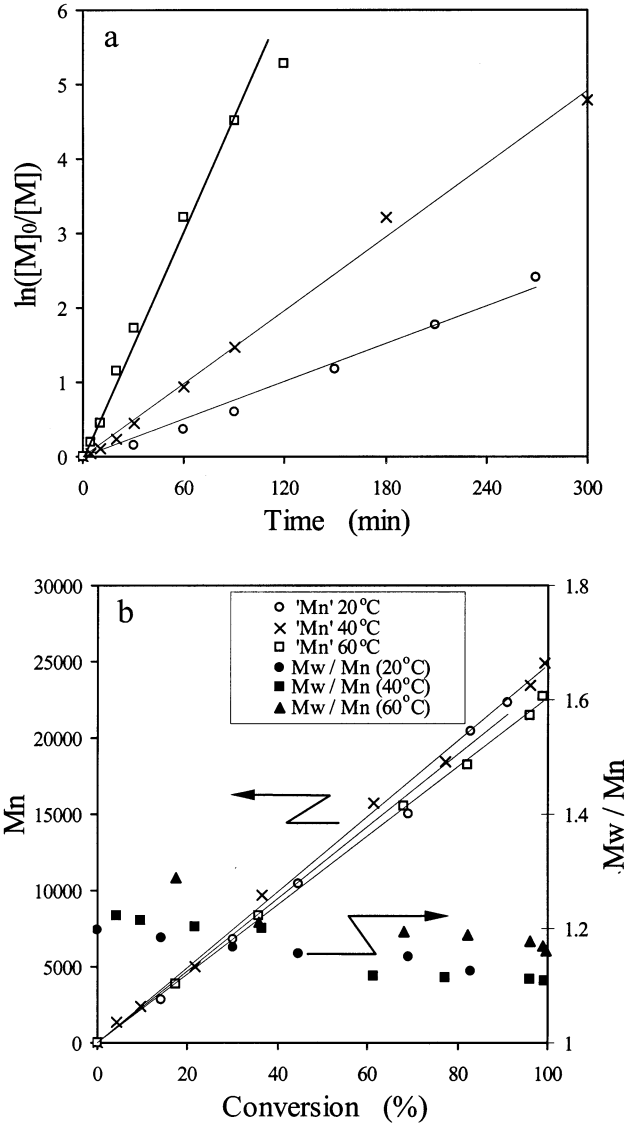

Figure 8. Effect of temperature on the homopolymerization of MPC via methanolic ATRP: (a) Semilogarithmic plot of monomer concentration vs time [conditions: 4.00 g MPC (13.4 mmol), 10 mL of methanol, target $DP_n = 100$, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2]. (b) Molecular weight and polydispersity vs conversion data; conditions as stated in (a).

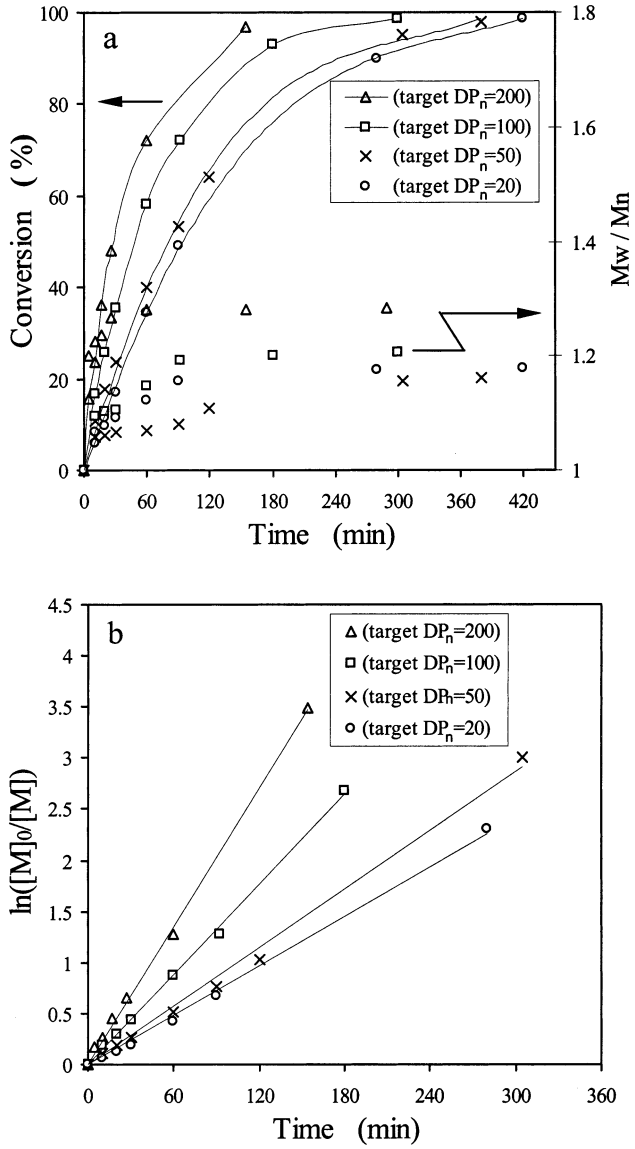

Figure 9. Effect of varying the target DP_n from 20 to 200 on the homopolymerization of MPC via methanolic ATRP at 20 °C: (a) Conversion and polydispersity vs time data [conditions: OEGBr initiator (659 mg, 0.135 mmol), 10 mL of methanol, molar ratio of [I]:[Cu(I)]:[L] = 1:1:2. (b) Semilogarithmic plots of monomer concentration vs time under identical conditions.

HMTETA gave a significantly faster rate of polymerization but a higher polydispersity ($M_w/M_n = 1.35$) than bpy. On the other hand, the rate of polymerization obtained using the MPMA ligand was very low, with less than 10% polymer produced after 4 h at 20 °C. Rather better conversions (approximately 80% within 5 h) were obtained at 60 °C with this latter ligand, but the final polydispersity was relatively broad at 1.38. In a self-blocking experiment using the HMTETA ligand, an initial MPC charge (corresponding to a target DP_n of 50) yielded a unimodal GPC trace with a polydispersity of 1.35, but addition of a second batch of MPC led to a bimodal GPC trace with a polydispersity of 1.68. Thus, the ATRP of MPC in methanol using HMTETA apparently has rather poor living character; this is consistent with the observation by Müller and coworkers[46] of loss of terminal halogen atoms in the ATRP of other methacrylic monomers using a related multidendate amine ligand. This indicates premature termination of the propagating chains, which accounts for the relatively poor living character achieved with such multidentate ligands. Overall, these data clearly indicate that bpy is the preferred ligand for the ATRP of MPC in alcoholic media.

The ICP−AES technique indicated residual Cu levels of only 1−2 ppm in the purified MPC homopolymers (see final column of Table 1). Obviously, even lower Cu levels would be desirable for biomedical applications, but these relatively low levels were readily achieved using just one treatment with silica gel. In our experience removal of residual ATRP catalyst from MPC homopolymer is particularly easy compared to other hydrophilic (co)polymers. Additional treatments and/or exhaustive dialysis is expected to produce final Cu levels below 1 ppm.

Conclusions

The homopolymerization of MPC via ATRP in protic media has been studied in some detail. In water, the polymerization is very fast at ambient temperature but has poor living character, as judged by self-blocking

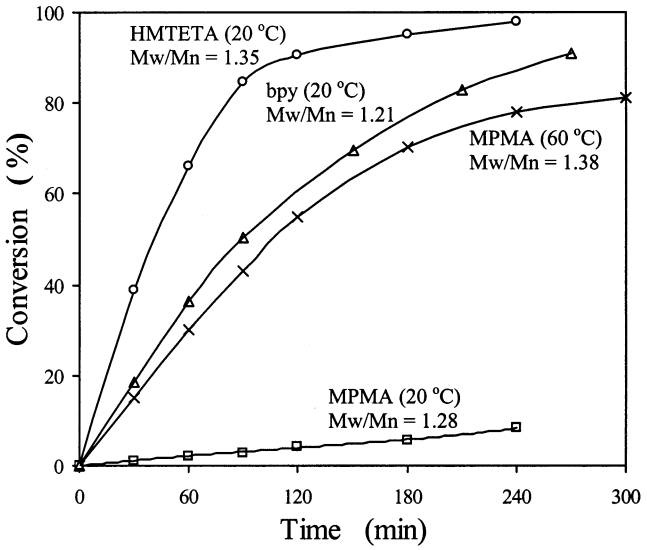

Figure 10. Conversion vs time data for the homopolymerization of MPC via methanolic ATRP using three different ligands. Conditions: MPC (4.00 g, 13.4 mmol), 10 mL of methanol, target DP_n = 100, molar ratio of [I]:[Cu(I)]:[HMTETA] = 1:1:1; molar ratio of [I]:[Cu(I)]:[bpy (or MPMA)] = 1:1:2 ; see text for further details. The stated polydispersities refer to the final polymer isolated after 4−5 h.

(chain extension) experiments. In contrast, polymerization in methanol is slower but much better controlled: excellent self-blocking efficiencies can be achieved under optimized conditions. In addition to solvent effects, a number of other synthesis parameters have been investigated, including the effect of varying the ligand type, target DP_n, and reaction temperature. The preferred ligand for the copper catalyst is bpy, and there is a progressive reduction in living character as higher DP_n's were targeted, as expected. Higher rates of polymerization were obtained at higher temperature, but faster rates could also be achieved at ambient temperature by the addition of a relatively small amount of water. Treating aqueous or alcoholic solutions of MPC homopolymer with silica gel readily enables the levels of residual ATRP catalyst in the final purified polymer to be reduced to below 2 ppm. This synthetic advance is expected to allow the preparation of a wide range of novel biocompatible diblock and triblock copolymers for various biomedical applications.

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