



Photoinduced atom transfer radical polymerization in a polar solvent to synthesize a water-soluble poly(2-methacryloyloxyethyl phosphorylcholine) and its block-type copolymers



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ABSTRACT

Photoinduced atom transfer radical polymerization (ATRP) has promising applications because it requires small amounts of transition metal catalysts and low temperatures, and can be extended to numerous monomers. We investigated the photoinduced ATRP of 2-methacryloyloxyethyl phosphorylcholine (MPC) in a polar medium and prepared block-type copolymers with a poly(MPC) segment. Polymerizations in methanol at room temperature were rapid and well-controlled under photoirradiation, with a linear relationship between monomer conversion and actual exposure time. Extension of polymer chains to prepare ABA triblock-type copolymers composed of poly(MPC) and poly(glycidyl methacrylate (GMA)), which possesses a reactive epoxy group in the side chain, was achieved by one-pot photoinduced ATRP in a shorter time and under milder reaction conditions than those in conventional ATRP. The synthesized poly(MPC) and its ABA triblock-type copolymers had sufficiently narrow molecular weight distributions. These results endorse photoinduced ATRP as an attractive technique to obtain water-soluble polymers with a poly(MPC) segment.

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1. Introduction

One of the essential aims of synthetic polymer chemistry is the production of well-defined polymers with the desired macromolecular architecture, adequately low polydispersity, predictable molecular weight, and precisely engineered functionality [1,2]. Reversible deactivation radical polymerization (RDRP), in which the equilibrium of an active propagating chain and a deactivated dormant species is well established, can lead to continuous polymeric chain growth without significant irreversible chain transfer and chain termination [3,4]. Atom transfer radical polymerization (ATRP) is one of the most employed RDRP methods. ATRP techniques make use of an exchange of a halide via a transition metal (e.g., copper) complex to achieve the interchange between active and dormant states [3,5]. Recently, there has been significant progress in advanced approaches to achieve uncomplicated, cleaner, and more preferable polymerization conditions. These

approaches can be listed as initiators for continuous activator regeneration (ICAR) [6], simultaneous reverse and normal initiated (SR&NI) [7], activators generated by electron transfer (AGET) [8], and activators regenerated by electron transfer (ARGET) ATRP [9,10]. Among them, photoinduced ATRP has become widely attractive as it allows polymerization under mild conditions while being suitable for a broad range of monomers. In the direct photoinduced ATRP, the application of photoirradiation promotes photoredox reactions that the reaction undergoes radical formation and activator (re)generation in the presence of light and produce activated copper catalysts and induce polymerization [11–15]. However, the actual phenomena of activation of photoinduced ATRP is under investigation with various pathway have been proposed [15]. The light-induced controlled living polymerizations were also studied using other light sources, as reported elsewhere [14–18].

Polymers bearing phosphorylcholine groups, i.e., phospholipid polymers, are one of the potential materials for medical, pharmaceutical, and bioengineered applications [19,20]. 2-Methacryloyloxyethyl phosphorylcholine (MPC) is usually employed in the preparation of phospholipid polymers as it shows excellent polymerization ability via radical polymerization and is easily

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copolymerizable with other monomers [21]. MPC polymers express high cytocompatibility and the ability to resist protein adsorption and cell adhesion [19,20,22]. Various MPC polymers with specialized functionality have been prepared, e.g., copolymers with hydrophobic moiety for use as drug solubilizers [23], antibody-conjugating copolymers for surface modifications to improve the sensitivity of immunoassays [24], and reversible cross-linkable polymer for formations of cell encapsulating hydrogels [25].

Recent advances in RDRP have led to the formation of tailored MPC polymers with various structures, such as polymer brushes and block-type copolymers, with well-defined chain lengths [26–29]. In the sequence of the first publication, by Lobb et al. in 2001 [30], detailing the application of ATRP in the preparation of MPC polymers, a broad range of MPC polymers with well-defined chains and manipulated molecular structures have been successively developed [29,31–33].

In this study, we investigated the potential of photoinduced ATRP for synthesizing poly(MPC) in a polar solvent, under the assumption that photoirradiation can be used to synthesize well-defined MPC polymers under mild conditions. We also demonstrated that the application of photoinduced ATRP allows chain-extension polymerization to obtain triblock-type copolymers composed of poly(MPC) and reactive poly(glycidyl methacrylate (GMA)) segments in a one-pot reaction within a shorter time and with smaller amounts of by-products.

2. Experimental

2.1. Materials

MPC purchased from NOF Co., Ltd. (Tokyo, Japan) was synthesized by a previously reported procedure [19]. Ethylene bis(2-bromoisobutyrate) (EBBiB), tris(2-pyridylmethyl)amine (TPMA), GMA, and copper (II) bromide ($\text{Cu}^{\text{II}}\text{Br}_2$) were purchased from Sigma–Aldrich (St. Louis, Missouri, USA). All solvents and reagents were extra pure grade and were used as received, without further purification.

2.2. Polymerizations

The synthesis of poly(MPC) for polymerization by photoinduced ATRP is similar to the conventional ATRP procedure. A stock solution of $\text{Cu}^{\text{II}}\text{Br}_2/\text{TPMA}$ was prepared by dissolving TPMA (29 mg) and $\text{Cu}^{\text{II}}\text{Br}_2$ (2.0 mg) in degassed methanol (5.0 mL). As the photoinduced ATRP allows polymerization even with some air, the prepared stock solution could be stored for months before use, without adverse effect. The polymerization of MPC, with a targeted number-average degree of polymerization (DP_n) = 100, was conducted as follows. MPC (1.5 g), EBBiB (18 mg), and methanol were placed in a Schlenk tube (i.d = 15 mm) and stirred until complete dissolution. 0.50 mL of $\text{Cu}^{\text{II}}\text{Br}_2/\text{TPMA}$ stock solution was injected into the tube, followed by bubbling argon for degassing before sealing the tube. The mixture was irradiated by a multipurpose uniform radiation unit equipped with a super-high pressure mercury lamp (Multilight, Ushio Inc., Tokyo, Japan) with a glass filter that emits UV light at a maximum wavelength of 365 nm. The irradiation intensity was 25 mW/cm², as measured by an industrial UV checker (Topcon Co., Ltd., Tokyo, Japan). The polymerization was allowed to proceed for a given time (4 h) at room temperature (approx. 25 °C); small aliquots of the reaction mixture were periodically withdrawn to check for monomer conversion by ¹H NMR spectroscopy. The polymerized poly(MPC) was precipitated in acetone/tetrahydrofuran (THF) (80/20 v/v), dried in a desiccator, and kept *in vacuo*. Other

poly(MPC) samples with different targeted DP_n were produced under the aforementioned conditions by changing the feeding composition of polymerization in order to achieve an MPC/EBBiB/ $\text{Cu}^{\text{II}}\text{Br}_2/\text{TPMA}$ ratio of X/1.0/0.020/0.20 (X equals the targeted DP_n). The results are summarized in Table 1.

Chain extension to synthesize ABA triblock copolymers of poly(GMA) and poly(MPC) was conducted in one-pot by a “sequential addition” method. After the ¹H NMR results confirmed that the photoinduced ATRP of poly(MPC) prepolymer (PMPC100 in Table 1: DP_n = 100) reached >99% conversion (approx., 4.0 h), degassed GMA (0.28 g; with final targeted DP_n of 40 GMA units-per-chain) was injected into the reaction tube under a continuous flow of argon. The reaction mixture continued to be irradiated, and secondary polymerization was allowed to take place at room temperature. After 4.0 h, polymerization was stopped by opening the tube, and subsequently, air was bubbled into the tube. The chain extension of the others poly(GMA)-block-poly(MPC)-block-poly(GMA) with different PMPC chain-length were conducted with the same targeted DP_n of GMA (i.e., 40 GMA units-per-chain). The polymerization product was precipitated in acetone/THF (80/20 v/v) and dried under reduced pressure. The results are summarized in Table 2.

2.3. Characterizations

In order to characterize the polymers, their compositions in terms of monomer units were investigated by nuclear magnetic resonance (¹H NMR) spectroscopy (400 MHz NMR spectrometer; JEOL Ltd., Tokyo, Japan). Time-lapse percentages and kinetics of monomer conversion were examined by sampling 0.10 mL of the polymerizing mixture and diluting it to the desired concentration by methanol-*d*₄. The disappearance of the characteristic vinyl peaks of MPC at δ 5.5 ppm and 6.0 ppm in ¹H NMR spectra was recorded. In order to examine the composition in terms of GMA and MPC units of the block copolymer, the solid product was dissolved in methanol-*d*₄. The characteristic peaks attributed to the poly(MPC) and poly(GMA) segments in poly(GMA)-*b*-poly(MPC)-*b*-poly(GMA) were observed (δ in ppm: 2.56–2.70, 2.76–2.93, 3.15–3.32), and the integrals were used to calculate the unit composition of the block copolymer.

The molecular weights and polydispersity were evaluated by gel permeation chromatography (GPC; Jasco system equipped with OHpak SB-803 HQ column, Shodex, Tokyo, Japan) using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) containing 10 mmol/L of sodium trifluoroacetate (TFA-Na) as the eluent (flow rate of 0.50 mL/min at 40 °C). The GPC standard curve was prepared by using poly(methyl methacrylate) with known molecular weight as the standard sample.

Table 1
Photoinduced ATRP of MPC.

Entry	Polymer	[M]/[I] ^a	Yield (%)	M_n^b (kDa/mol)	M_w/M_n (D)
1	PMPC50	50/1	93	37.0	1.14
2	PMPC100	100/1	90	55.1	1.17
3	PMPC200	200/1	94	85.7	1.18
5	PMPC100 (no irradiation) ^c	100/1	–	–	–
5	Poly(MPC) (without ATRP)	100/0	98	105	1.71

^a Ratio of monomer ([M]) and initiator ([I]) for photoinduced ATRP of MPC.

^b Examined by GPC using HFIP containing 10 mM TFA-Na as the eluent.

^c The reaction tube was covered with an aluminum foil and stirred under the same conditions as for the other entries. Polymerization conditions: [MPC]/[EBBiB]/ $[\text{Cu}^{\text{II}}\text{Br}_2]/[\text{TPMA}]$ = targeted $\text{DP}_n/1.0/0.020/0.20$ with feeding concentration of 0.50 M, at room temperature, over 4.0 h.

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