



Preparation of pendant group-functionalized amphiphilic diblock copolymers in the presence of a monomer activator and evaluation as temperature-responsive hydrogels

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ABSTRACT

Temperature-responsive hydrogels have been widely developed for biomedical applications. In this study, 4-benzyloxy- ϵ -caprolactone (CL-OBn) was synthesized and the subsequent ring opening polymerization (ROP) of ϵ -caprolactone (CL) and CL-OBn monomers was performed by using the hydroxyl group of methoxy polyethylene glycol (MPEG) in the presence of HCl·Et₂O as a monomer activator. MPEG-*b*-poly(ϵ -caprolactone) (MC) with benzyl pendant groups (MC-OBn) was successfully obtained in almost quantitative yield and the segment ratios and molecular weights were close to the theoretical values. Deprotection of the benzyl pendant groups successfully provided MC with hydroxyl pendant groups (MC-OH). Suspensions of MC-OBn and MC-OH exhibited distinct sol-to-gel phase transitions as a function of the temperature. The sol-to-gel phase transition of the MC-OBn and MC-OH diblock copolymers depended on the type (benzyl or hydroxyl) and amount of pendant groups in the diblock copolymer structure. The pendant group on the MC-OBn and MC-OH diblock copolymers either stabilized and/or destabilized hydrophobic aggregation between the MC segments. The hydrophobic aggregation was confirmed by the detection of crystallinity in the MC-OBn and MC-OH diblock copolymer suspensions. In conclusion, MC-OBn and MC-OH diblock copolymers were successfully prepared and served as temperature-responsive hydrogels.

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1. Introduction

Temperature-responsive hydrogels exhibit sol-to-gel phase transitions between room temperature and body temperature [1,2]. Such temperature-responsive hydrogels have attracted great attention in the past few decades for application in injectable biomedical systems. Several cells and/or bioactive molecules can easily be entrapped in a formulation that is an injectable solution at room temperature solution, where the solution can be easily injected into the body by using a syringe and becomes a hydrogel at the injected site [3–6].

Several kinds of amphiphilic block copolymers consisting of hydrophobic biodegradable aliphatic polyesters, poly(L-lactic acid) (PLLA), poly(glycolic acid), or poly(ϵ -caprolactone) (PCL) and their

copolyesters, and hydrophilic poly(ethylene glycol) (PEG) have been reported as typical examples of temperature-responsive injectable hydrogels [7–9]. The driving force for temperature-responsive hydrogels of amphiphilic block copolymers consisting of PEG and polyesters is the formation of a structured network via hydrophobic aggregation between the hydrophobic polyester blocks.

It is well known that the ring opening polymerization (ROP) of ester monomers [such as L-lactic acid (LA), glycolic acid (GA), and ϵ -caprolactone (CL)] leads to the formation of amphiphilic block copolymers in the presence of stannous octoate or organometallics as a monomer activator or catalyst at comparatively high temperatures [10,11]. Metal catalyst should be one of the concerns for the use of temperature-responsive hydrogels of amphiphilic block copolymers for biomedical application.

Thus, it is necessary to develop a metal-free ROP to copolymerize LA, GA or CL. Even though some efforts were devoted to polymerize LA, GA or CL by using organic catalysts or without

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catalyst for long polymerization time [12–15], there are a limited studies of the polymerization as the metal-free method.

Recently, Endo et al. reported successful ROP of CL with alcohol initiator in the presence of HCl·Et₂O as the metal-free method [16,17]. Some researchers have also studied the feasibility of the ROP of CL and LA ester monomers using the polymers with hydroxyl group as the initiator at room temperature in the presence of HCl·Et₂O [18–20] or trifluoromethanesulfonic acid [21–23] as a monomer activator to prepare amphiphilic block copolymers. In this polymerization process, the monomer activator could be easily removed from the amphiphilic block copolymers after ROP. Additionally, ROP could be performed at room temperature. Thus, ROP in the presence of HCl·Et₂O or trifluoromethanesulfonic acid is one of the most powerful as the metal-free method of preparing amphiphilic block copolymers.

More recently, we prepared amphiphilic diblock copolymers such as MPEG-*b*-PCL (MC), MPEG-*b*-polyester, MPEG-*b*-(PCL-*ran*-poly (trimethylene carbonate)), and MPEG-*b*-(PCL-*ran*-poly (1,4-dioxan-2-one)) through ROP in the presence of HCl·Et₂O and reported the formation of temperature-responsive hydrogels [24–26].

Generally, mechanism of the hydrogel formation of amphiphilic block copolymers can be proposed by the micelle percolation. The amphiphilic block copolymers in aqueous solution were firstly formed into micelles, then aggregation of micelles and finally hydrophobic aggregated domains.

If amphiphilic block copolymers have functional group at the chain end or pendant-position, the functional groups on amphiphilic block copolymers can alter the packing or aggregation in the micelle formation and then affect the occurrence of the macroscopic gelation through stabilization or destabilization of intra- and inter-molecular hydrophobic aggregation.

Several amphiphilic block copolymers with various functional groups in the chain end- or pendant-position have also been prepared [27–33]. The prepared amphiphilic block copolymers with various functional groups were utilized as the temperature-responsive hydrogel or micelles for preparation of nanoparticles, or drug and gene delivery carriers [34–37].

Recently, Hedrick et al. reported the amphiphilic block copolymers with various functional groups by ROP of several cyclic ester monomers containing benzyl, hydroxyl, amino and carboxyl groups in the presence of stannous octoate [38–40]. More recently, Lee et al. reported the preparation of MPEG-*b*-PCL (MC) with benzyl carboxylate, carboxylic or hydroxyl groups by ROP using stannous octoate at comparatively high temperature and then examined only micellar characteristics [41–44].

Meanwhile, we also prepared MC with a carboxylic acid group, an amine group, and a zwitterionic group at the chain end-position of the MC chain and examined the temperature-responsive properties [45,46]. Additionally, we reported temperature-responsive injectable hydrogels of MPEG-*b*-(PCL-*ran*-PLLA) [MCL] amphiphilic diblock copolymers modified with benzyl, hydroxyl, or carboxylic acid groups at the chain pendant-position of MCL [47]. The preparation of MCL functionalized at the chain pendant-position was achieved by ROP of the 3-benzylloxymethyl- 6-methyl-1,4-dioxane-2,5-dione (fLA) monomer with a benzylloxymethyl group at the 3-position of the lactide, with subsequent derivatization. However, the total yield of fLA was quite low, being below 20%. In addition, ROP of fLA proceeded at comparatively high temperature with stannous octoate.

Although some studies have been reported the preparation of amphiphilic block copolymers with various functional groups in the chain end- or pendant-position, in this work our interest has focused on two aims. Firstly, we was tried to prepare pendant group-functionalized amphiphilic diblock copolymers in the room

temperature by the use of metal-free method. Secondly, we examined the behavior as temperature-responsive injectable hydrogels of the prepared pendant group-functionalized amphiphilic diblock copolymers.

Hence, we considered 4-benzyloxy- ϵ -caprolactone (CL-OBn) as a candidate for achieving facile ROP in the presence of HCl·Et₂O as a monomer activator. Accordingly, in this study, we address the following questions: 1) Can ROP of CL and CL-OBn in the presence of HCl·Et₂O using the hydroxyl group of MPEG as an initiator at room temperature (as the metal-free method) provide MPEG-*b*-[poly (ϵ -caprolactone)-*ran*-poly (4-benzyloxy- ϵ -caprolactone) (M-CL-*ran*-CL-OBn)] (MC-OBn) amphiphilic diblock copolymers and then can MPEG-*b*-[poly (ϵ -caprolactone)-*ran*-poly (4-hydroxyl- ϵ -caprolactone) (M-CL-*ran*-CL-OH)] (MC-OH) be prepared by subsequent deprotection reaction of benzyl group? 2) Can the prepared MC-OBn and MC-OH be used as temperature-responsive hydrogels? Elucidation of these issues will have a basic understanding on the effects by the type and content of pendant groups on amphiphilic block copolymers.

2. Experimental

2.1. Materials

Sodium borohydride (NaBH₄), sodium hydride (NaH), benzyl bromide (BnBr), 4-chloroperbenzoic acid (mCPBA), 10 wt% palladium on carbon (Pd/C), triethylamine (TEA), and 4-(dimethylamino)pyridine (DMAP) were used as received from Aldrich (MO, USA). Methanol and 1,4-dioxane were used as received from J.T. Baker (PA, USA). Tetrahydrofuran (THF), ethyl acetate (EA), magnesium sulfate (MgSO₄), dichloromethane (CH₂Cl₂), *n*-hexane, ethyl ether and hydrochloric acid (HCl; 35.0–37.0% in DW) were used as received from Samchun (Gyeonggi, Korea). HCl (Aldrich; 1.0 M solution in diethyl ether, MO, USA), 1,4-cyclohexanedione monoethyleneketal (TCI, Tokyo, Japan) and MPEG (number-average molecular weight $M_n \approx 750$, Aldrich, Milwaukee, WI, USA) were used as received. ϵ -Caprolactone (CL; Aldrich, Milwaukee, WI, USA) was repeatedly distilled over calcium chloride (CaCl₂; Aldrich, MO, USA) under nitrogen before use.

2.2. Characterization

For analysis of the MC, MC-OBn, and MC-OH diblock copolymers, ¹H-NMR and ¹³C-NMR spectra were acquired on a Varian Mercury Plus 400 (Varian) instrument using (CD₃)₂CO or CDCl₃ in the presence of TMS as an internal standard. A YL-Clarity GPC system (YL instruments, Gyeonggi, Korea) equipped with YL 9170 RI detector and three columns (Shodex K-802, K-803, and K-804 polystyrene gel columns) at 40 °C was used to determine the molecular-weight distributions of the diblock copolymers. In the measurement, the flow rate of the CHCl₃ eluent was 1.0 mL/min. Differential scanning calorimetry (DSC; Q1000, TA Instruments, Germany) was used to determine the melting temperature (T_m) and the heat of fusion (ΔH_m) of the MC, MC-OBn, and MC-OH diblock copolymer solutions. DSC analysis of the MC, MC-OBn, and MC-OH diblock copolymers in aqueous solutions was performed from 10 to 60 °C at a heating rate of 5 °C/min under nitrogen atmosphere. The heat of fusion per gram of diblock copolymer was determined from the area under the peak.

2.3. Preparation of 4-benzyloxy- ϵ -caprolactone (CL-OBn)

2.3.1. Preparation of 1,4-cyclohexanedione monoethyleneketal

All glasses were heated under vacuum and then flushed with a dry nitrogen stream. All reactions were conducted under a dry

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