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Preparation of block copolymer of ε-caprolactone and 2-methyl-2-carboxyl-propylene carbonate

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Abstract

A block copolymer PCL-*b*-PMBC of ε-caprolactone (ε-CL) and 2-methyl-2-benzyloxycarbonyl-propylene carbonate (MBC) was synthesized by sequential ring-opening polymerization of the ε-CL and MBC monomers with amino isopropoxyl strontium (Sr-PO) as an initiator. It was debenzylated by catalytic hydrogenation to obtain a linear block copolymer PCL-*b*-PMCC with pendant carboxyl groups. WAXD showed that the presence of PMBC segment in PCL-*b*-PMBC influenced obviously the crystallizability of PCL block, in agreement with the DSC results. Diffraction peak of PCL-*b*-PMCC after debenzylation was hardly observed and moreover, melting enthalpy ΔHm of PCL-*b*-PMCC was 10.9 J/g compared to 68.0 J/g of PCL-*b*-PMBC, due to the replacement of the benzyl ester by the carboxyl group. The presence of carboxyl groups is expected to enhance the biodegradability of the copolymer and to facilitate a variety of medical applications.

Keywords: Biodegradable; Block polyesters; Functional polymers

1. Introduction

Poly(ε-caprolactone) (PCL) has received steadily increasing attention for medical applications over the past 20 years, because of its unique properties such as biodegradability, biocompatibility, miscibility with other polymers, permeability to a wide range of drugs, and so forth [1–3]. However, its high hydrophobicity, high crystallinity, slow biodegradation rate and, especially, lack of chemical reactivity have considerably limited its medical applications. Therefore, its modification is necessary. Poly(ethylene oxide-*b*-ε-caprolactone) has attracted much attention, because this kind of polyester-polyether-type block copolymer has a superior amphiphilic property as compared with the parent PCL homopolymer [4–10]. Block copolymer of ε-caprolactone with vinyl pyrrolidone also exhibits amphiphilic property by forming micelles of 30–80 nm [11]. Copolymerization of ε-caprolactone with other cyclic ester monomer [12–17], such as lactide, carbonate et al., improves the crystallinity and biodegradation of PCL. Recently, functionalized cyclic monomers such as NCA's of amino acids [18], (3 s)-[(benzoxylcarbonyl) methyl]-morpholine-2, 5-dione [19] and ε-caprolactones bearing carboxyl [20] or hydroxyl [21] groups have been used as the comonomers to prepare functionalized poly(ε-caprolactone)s. They are expected to have enhanced chemical reactivity and to facilitate further modifications to improve the bio-compatibility and bio-affinity. But some of these monomers are difficult to synthesize such as functionalized ε-caprolactones, some are difficult to copolymerize with ε-caprolactone so that the copolymers with high molecular weights are hardly obtained.

On the other hand, aliphatic polycarbonate is a well-known biodegradable polymer [22–25], and 1, 3-propylene carbonate was found to be polymerized and copolymerized with cyclic ester monomers easily [26,27]. Therefore, we tried to take this advantage to prepare functionalized PCL. The strategy was first to prepare a functionalized cyclic carbonate and then to copolymerize it with ε-caprolactone. To our knowledge, block copolymers of carboxyl-bearing cyclic carbonates with ε-caprolactone have never been reported.

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The homopolymer and copolymers of ε-caprolactone are usually synthesized by ring-opening polymerization (ROP) of cyclic ester monomers with anionic, cationic, or coordination initiators [28–33] as well as enzymatic catalysts [11,34]. However, anionic initiators such as alkali metal alkoxides lead to significant side reactions, and cationic initiators (such as triethyloxonium tetrafluoroborate and trifluoroacetic acid) or enzymatic catalysts (such as lipases) do not have sufficient efficiency [28,35]. Many coordination initiators for ROP of cyclic esters have been developed such as zinc, iron, titanium, lanthanon, stannous and aluminum etc. But less attention was paid to catalysts or initiators based on group II metals. In our previous papers [36,37], calcium and strontium complexes were successfully applied to the ROP of ε-caprolactone and L-lactide. They exhibited high catalytic activity, low reaction temperature, and high conversion. Especially, they can initiate the block copolymerization of ε-caprolactone with L-lactide, or these two monomers with other cyclic monomers such as ethylene oxide, because the ROP they initiated is a quasi-living polymerization.

Therefore in this paper, 2-methyl-2-benzyloxycarbonyl-propylene carbonate (MBC) was synthesized and its homopolymer (PMBC) and block copolymers with ε-caprolactone (PCL-*b*-PMBC) were prepared via the ring-opening polymerization in the presence of the amino isopropoxyl strontium (Sr-PO) as an initiator. After catalytic hydrogenation, the pendant ester groups were converted to carboxyl groups. They are expected to react with related chemical or bioactive reagents to impart hydrophilicity and bio-affinity, and to facilitate a variety of potential applications in controlled drug delivery, surgery, and tissue engineering.

2. Experimental section

2.1. Materials

Dimethylolpropionic acid (DMPA) and strontium were purchased from Aldrich. Ten percent Palladium on charcoal (10% Pd/C) and benzyl bromide were obtained from corporations in China. ε-Caprolactone (ε-CL, Acros), isopropanol and propylene oxide were dried over calcium hydride. Toluene and tetrahydrofuran (THF) were purified by refluxing over calcium hydride and sodium with the indicator benzophenone complex. Ammonia was dried by a sodium hydroxide column. Amino isopropoxyl strontium (Sr-PO) was prepared according to reference [37].

2.2. Measurements

FT-IR spectra were recorded on a Bio-Rad Win-IR instrument. NMR spectra were recorded on a Bruker AV 300 MHz or a Bruker AV 400 MHz in $CDCl_3$ or DMSO at 25 °C. Chemical shifts were given in parts per million from that of tetramethylsilane as internal reference. The GPC measurements were conducted at 35 °C with a Waters 410 GPC instrument equipped with two Waters Styragel columns (HT6E, HT3) and a differential refractometer detector. $CHCl_3$ was used as eluent at a flow rate of 1.0 mL/min. The molecular weights were calibrated against polystyrene standards. X-ray diffractometric analysis was carried out on a Philips apparatus with a Cu Kα (λ = 0.154 nm) source. Thermal analysis was performed using a Perkin–Elmer DSC-7 under N_2 atmosphere at a heating rate of 10 °C/min.

2.3. Synthesis of benzyl 2, 2-bis(hydroxymethyl)propionate (BHP)

Fifty grams (372.8 mmol) of DMPA and 14.9 g (373.0 mmol) of sodium hydroxide were dissolved in 40 mL of water, and the mixture was poured into a large amount of acetone to precipitate the salt formed as a white solid (54.2 g). This product (347.2 mmol) and 41.5 mL (348.3 mmol) of benzyl bromide were added to dioxane (250 mL) as solvent. After 20 h of vigorous stirring at 165 °C, the solvent was removed under reduced pressure and the residue was dissolved in 350 mL of ethyl acetate and extracted with three portions (160×3 mL) of saturated sodium chloride aqueous solution. The combined organic phase was dried with $MgSO_4$ and evaporated to give the diol product as white crystals, 69.4 g, yield: 93.4%; ^{1}H NMR ($CDCl_3$, TMS): δ = 1.10 (s, 3H, –CH_3), 3.52 (d, 4H, –CH_2OH), 5.09 (s, 2H, –CH_2Ar), 7.33 (m, 5H, C$_6H_5$); ^{13}C NMR ($CDCl_3$, TMS): δ = 175.56 (–*C*OO–), 142.65–128.94 (*C*$_6$H$_5$), 68.47 (–*C*H$_2$Ar), 64.69 (–*C*H$_2$OH), 48.17 (*C*–COO), 14.22 (–*C*H$_3$); Elemental Anal. Calcd. for $C_{12}H_{16}O_4$: C 64.3 H 7.19 O 28.5; Found: C 64.1 H 7.29 O 28.6.

2.4. Synthesis of 2-methyl-2-benzyloxycarbonyl-propylene carbonate (MBC)

MBC was prepared by reacting ethyl chloroformate with BHP (Scheme 1) [38]. Firstly, BHP (10.1 g, 40.4 mmol) and ethyl chloroformate (26.0 mL, 0.272 mmol) were dissolved in 250 mL of THF and then, with vigorous stirring, triethylamine (38.0 mL, 0.273 mol) dissolved in THF (70 mL) was added dropwise to the above mixture at 0 °C over a period of 30 min and the reaction was continued at room temperature for another 2 h. Finally, the precipitated triethylamine hydrochloride was filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from THF/ether. White crystals were obtained (yield: 88%). mp: 72–74 °C. ^{1}H NMR ($CDCl_3$ TMS): δ = 1.34 (s, 3H, –CH_3), 4.20 (d, J = 10.8 Hz, 2H, –CH_2O–, 4.71 (d, J = 10.8 Hz, 2H, –CH_2O–), 5.22 (s, 2H, –COOCH_2Ar), and 7.34 ppm (m, 5H, *Ar*). ^{13}C NMR ($CDCl_3$): δ = 17.39 (*C*H$_3$), 40.13 (*C*(CH$_3$)), 67.76 (Ar*C*H$_2$OOC–), 72.84 (–*C*H$_2$OH), 128.45 (ArC), 128.71 (ArC), 134.71 (ArC), 147.36 (*C*COO), 170.88 (O*C*=O). Elemental Anal. Calcd.