

SYNTHESIS OF NOVEL BLOCK COPOLYMERS OF POLY(3-HYDROXYBUTYRIC ACID) WITH POLY(ETHYLENE GLYCOL) THROUGH ANIONIC POLYMERISATION

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Abstract A novel kind of copolymer with ABA-type block structure was synthesized by anionic ring-opening polymerization of β -butyrolactone (β -BL) in the presence of a PEG-based dicarboxylates as macroinitiators which were prepared by the esterification of aliphatic cyclic anhydride and poly(ethylene glycol) (PEG) oligomers ($M_n = 2000, 4000$ and 6000) and conversion of potassium dicarboxylates. The resultant copolymers as well as the intermediates were characterized by IR, $^1\text{H-NMR}$ and GPC.

Keywords Block copolymer, Poly(ethylene glycol), Poly(3-hydroxybutyric acid)

INTRODUCTION

Over the past decades, synthetic biodegradable polymers have increasingly attracted research interest due to their potential applications in medicine, agriculture and the commercial packaging field^[1]. Some the most attractive biodegradable polyesters suitable for drug-delivery systems are poly(hydroxy acid)s, which have proved to be biocompatible, completely biodegradable and non-toxic^[2, 3].

Admittedly, the biocompatibility and the biodegradability of aliphatic polyesters are relevant to their hydrophilicity which on the other hand depends on polymer microstructure and composition. Generally, the hydrophilicity of these polymers to some extent is a prerequisite for medicinal use^[4, 5]. Much work has been done in synthesizing novel copolymers of aliphatic polyester with hydrophilic PEG to increase the hydrophilicity of the product^[6-10]. Unfortunately, chemically synthesized copolymers based on the most attractive PHB have been scarcely reported.

Previously we reported the synthesis of biodegradable polymers through polycondensation^[11, 12], anionic or coordination polymerization of lactone or lactide^[5, 13], enzyme-catalyzed polymerization^[14, 15]. Block copolymers of PHB and poly(pivalolactone)^[16] as well as PEG-based copolyanhydrides were synthesized. In this paper, novel PHB-PEG-PHB block copolymers were synthesized through anionic polymerisation.

EXPERIMENTAL

Material

Racemic β -butyrolactone and 18-crown-6 ether from Aldrich were purified as described previously^[18]. Maleic anhydride and succinic anhydride were used as received. Poly(ethylene glycol) was purified by precipitation into dry hexane from dry tetrahydrofuran (THF) solution, the precipitate was then dried at room temperature under

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vacuum for one week. Pyridine was dried by potassium hydroxide.

All solvents are analytical reagent grade. Pre-treated THF^[19] was distilled over sodium-potassium alloy in a dry argon atmosphere. Toluene and hexane were dried over metallic sodium before distillation under dry argon. Methanol and chloroform were used as received.

Preparation of PEG-Based Dicarboxylate Macroinitiator

Hydroxyl-terminated PEG was converted to carboxy-terminated intermediate by esterification with cyclic aliphatic anhydride according to the method reported before^[11, 17].

Typically, into an oven-dried glass vial under argon were introduced 6.2×10^{-3} mol PEG, 1.25 g maleic anhydride (12.5×10^{-3} mol), 1.5 mL pyridine and 80 mL toluene. The reaction mixture was magnetically stirred at 70°C for 48 h. During the reaction process, small aliquot portions of the reaction mixture were withdrawn periodically for characterization and determination of the PEG esterification number which is defined as the average molecular carboxylic number (AMCN)^[17].

The reaction mixture was washed several times with aqueous hydrochloric acid. The toluene phase separated was then dried by anhydrous MgSO_4 . Intermediate diacid was obtained by precipitating into hexane and drying under vacuum.

The target macroinitiators were prepared by neutralization with 0.1 mol/L KOH methanol solution in THF, followed by precipitation into hexane.

Synthesis of PHB-PEG-PHB Triblock Copolymers

Polymerization was conducted at 20°C in a THF solution. The PEG-based macroinitiator (5×10^{-4} mol) as well as pre-dried solvent THF (10 mL) was introduced under argon into a previously flamed glass reactor. 18-Crown-6 ether, with twice molar amount of the macroinitiator, was introduced quickly by injection with a syringe. Then a desired amount of β -BL was added. The reaction vessel filled with dry argon was sealed and the reaction mixture was stirred with magnetic bar. Small aliquot portions were periodically withdrawn via syringe for performing IR, NMR and GPC measurements and to monitor the polymerization process. Copolymers were obtained by precipitation into hexane followed by drying under vacuum.

Characterization

FTIR spectra were recorded on a FTS 40A BIO-RAD spectrometer at room temperature; solid samples were pressed into KBr pellets or were analyzed in solution (THF or methanol as solvents).

¹H-NMR spectra were recorded on a Varian VXR-300 or a Varian Unity Inova 300 multinuclear spectrometer using CDCl_3 and TMS as solvent and internal standard, respectively.

GPC measurements were conducted at 35°C using THF as an eluent at a flow rate of 1 mL/min, a Spectra-Physics 8800 solvent delivery system with two mixed Styragel columns in series and a Shodex SE 61 refractive index detector was employed. Polystyrene standards with low poly-dispersity were used to generate the calibration curve. A volume of 10 μL of sample solution in THF (concentration 2 % *W/V*) was injected.

RESULTS AND DISCUSSION

In the previous work^[11, 17], we have demonstrated that the hydroxyl end-groups of PEG oligomers can almost be completely converted to carboxylic end-groups through esterification of PEG with succinic anhydride in organic solvent at 55°C using an organic base, pyridine, as the catalyst and proton adopter.

In this research, maleic anhydride was also selected as a reagent for PEG esterification. This anticipates introduction of a carbon double bond into the molecular chain, which could provide a possibility of improving the product's properties by crosslinking. Further corresponding research results will be published later.

Likewise, esterification of PEG with maleic anhydride in toluene at 70°C catalyzed by pyridine proved to be an effective way to prepare the PEG-based intermediate diacids. After the reaction proceeded for several hours, two distinct characteristic peaks at 1735 cm^{-1} (s, $\nu_{\text{C=O}}$ of ester) and 1715 cm^{-1} (s, $\nu_{\text{C=O}}$ of carboxylic acid, sample was washed with aqueous HCl) as well as a characteristic peak at 1648 cm^{-1} (s, $\nu_{\text{C=C}}$) appeared in IR spectra.

Table 1 lists the average molecular carboxylic numbers (AMCN) of resultant intermediate diacids.

Table 1. The AMCN of PEG-based intermediate diacids ^{a)}

Reactant	PEG-2000	PEG-4000	PEG-6000
AMCN ^{b)}	1.98	1.97	1.98
AMCN ^{c)}	1.52	0.93	0.70
AMCN ^{d)}	0.89	0.55	0.57

a) reaction proceeded for 48 h, and see previous report ^[17] about the AMCN determination;

b) pyridine as catalyst and proton adopter, maleic anhydride as esterification reagent;

c) without pyridine, maleic anhydride as esterification reagent;

d) without pyridine, succinic anhydride as esterification reagent

Table 1 shows that with pyridine as a catalyst the hydroxyl groups of PEG irrespective of its molecular weight were almost wholly esterified by maleic anhydride within 48 h. Pyridine is an effective esterification-promoting catalyst for this reaction, however PEG esterification with maleic anhydride can attain a relatively high esterification degree even without pyridine, especially when the number-average molar mass of PEG is not high. In this respect, maleic anhydride turned out to be a more desirable reagent for PEG esterification than succinic anhydride.

A typical ¹H-NMR spectrum of intermediate diacids based on PEG-2000 is shown in Fig. 1. The characteristic peaks accord well with the structure of intermediate diacid.

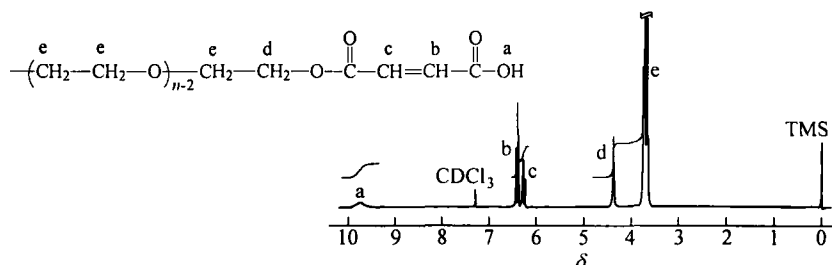


Fig. 1 A typical ¹H-NMR spectrum of PEG-2000-based intermediate diacids

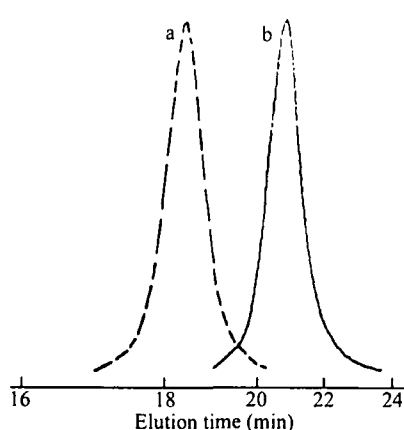


Fig. 2 Typical GPC traces of a) the block copolymer and b) corresponding intermediate macroinitiator based on PEG-2000

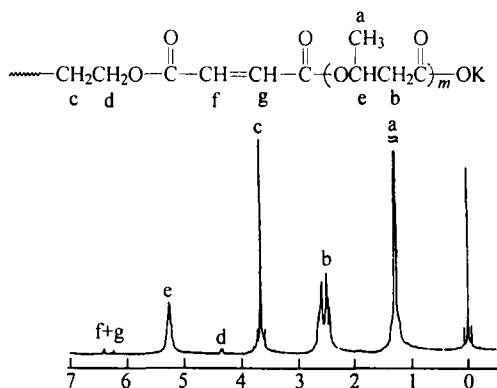


Fig. 3 A typical ¹H-NMR spectrum of the block copolymer based on the macroinitiator from PEG-2000

The course of anionic ring-opening polymerisation of β -butyrolactone was monitored by IR, NMR and GPC measurements. As the reaction time increases, the IR spectrum of the reaction aliquot shows the intensity of the characteristic peak of polyester at 1735 cm^{-1} to increase (s, C=O). On the other hand, the intensity of the

characteristic absorption of β -BL at 1820 cm^{-1} (s, C=O) weakened and finally disappeared as the conversion of β -BL reached 100%.

For the polymerization investigated, the uni-modal molecular mass distribution was revealed in the GPC measurement (Fig. 2), which confirmed the copolymer synthesis as well as no formation of homo-PHB.

The $^1\text{H-NMR}$ spectra of resultant copolymers (Fig. 3) show the signals corresponding to the microstructure of both PEG and PHB blocks, the results further demonstrate the copolymer synthesis.

A series of experiments was carried out to ascertain the effect of reaction conditions. The experimental results are summarized in Table 2. The calculated M_n of copolymer is close to that determined by GPC. Block copolymers with narrow molecular weight distribution were obtained according to the results of GPC measurement.

Table 2. Results of anionic polymerisation of β -BL initiated by the PEG-based macroinitiators^{a)}

Entry	Macroinitiator based on	$[\text{M}]_0/[\text{I}]_0$ ^{b)}	t (h)	Conv. ^{c)} (%)	M_n (calc.) ^{d)}	M_n (GPC)	M_w/M_n (GPC)
A ₁₁	PEG-2000	60	24	38	4240	3650	1.12
A ₁₂	PEG-2000	60	72	64	5580	5230	1.01
A ₁₃	PEG-2000	60	168	100 ^{e)}	7440	7620	1.05
A ₂₁	PEG-2000	200	24	27	6920	6650	1.03
A ₂₂	PEG-2000	200	72	41	9330	10380	1.17
A ₂₃	PEG-2000	200	168	73	14840	13850	1.22
A ₂₄	PEG-2000	200	240	100 ^{e)}	19480	19550	1.13
A ₃₁	PEG-2000	550	24	19	11270	8940	1.14
A ₃₂	PEG-2000	550	168	53	27350	25680	1.10
A ₃₃	PEG-2000	550	312	100 ^{e)}	49580	50120	1.11
B ₂₁	PEG-4000	200	24	30	9440	7560	1.28
B ₂₂	PEG-4000	200	72	39	10980	11820	1.16
B ₂₃	PEG-4000	200	240	100 ^{e)}	21480	19630	1.07
C ₃₁	PEG-6000	550	24	23	17160	15330	1.11
C ₃₂	PEG-6000	550	168	51	30400	31840	1.02
C ₃₃	PEG-6000	550	312	100 ^{e)}	53580	52460	1.22

a) PEG esterified with maleic anhydride; b) $[\text{M}]_0$ and $[\text{I}]_0$ are the initial concentrations of β -BL and macroinitiator, respectively; c) conversion of β -BL; d) number-average molar mass $M_n = [\text{M}]_0/[\text{I}]_0 \times M_{(\beta\text{-BL})} \times \text{Conv.} + M^*$, where M^* is the number-average molar mass of macroinitiator; e) obtained by IR measurement

It can be observed from Table 2 that the anionic polymerisation of β -BL at 20°C initiated by the PEG-based macroinitiator is a slow process. Generally it will take one or more weeks to reach high monomer (β -BL) conversion. The number-average molar mass of macroinitiator does not show a significant effect on the conversion of β -BL. This implies that the length of initiator chain does not affect the initiating and reaction activity of the carboxylate intermediate (comparing series A₃ with C₃, A₂ with B₂).

Investigations on the properties of the obtained block copolymers are under way.

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