Synthesis of Polymorpholine-2,5-dione-*block*-polylactide by Two-Step Anionic Ring-Opening Polymerization

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ABSTRACT: Polymorpholine-2,5-dione-*block*-polylactide (PMD-*b*-PLA) was synthesized via two-step anionic ring-opening polymerization at room temperature. First step of ring-opening polymerization was the ring-opening of morpholine-2,5-dione (MD). It was carried out in an airtight and dry polymerization tube using potassium ethoxide/THF (0.2*M*/L) as an initiator for 90 min. Then lactide was ring-opened in THF solution by the potassium alcoholate of PMD. From the FTIR of the copolymer, we can find all the peaks in PLA and PMD. The ^{1}H-NMR of copolymer gave us a proof to the principle of the anionic ring-opening polymerization and the fraction of PMD in the copolymer was calculated as 86.3%. DSC analysis of copolymer indicated that it was a copolymer with one T_g (63.6°C) and two T_ms (155.6 and 171.4°C) instead of a mixture of PMD and PLA. The yields of the PMD and the copolymer were 32 and 26%, respectively.
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Key words: polymorpholine-2,5-dione; polylactide; anionic ring-opening polymerization

INTRODUCTION

Biodegradable polydepsipeptide, copolymer of α-hydroxy acids and α-amino acids, are widely used in medical applications, such as drug carrier for release and tissue engineering.[1–3] Ring-opening polymerization of morpholine-2,5-dione (MD) and its derivatives is an excellent way to prepare polydepsipeptide. In 1985, Feijen et al. synthesized a polydepsipeptide by ring-opening method at 130°C using stannous octoate as a catalyst for the first time.[4] Then various of morpholine- 2,5-dione derivatives were ring-opened to synthesize polydepsipeptide.[5–10] But most of them were in bulk initiated by stannous octoate. Copolymerization of MD derivatives with lactide (LA) can bring amino acid segment into polylactide (PLA) and produce lots of copolymers with a variety of properties. Höcker et al. synthesized several kinds of copolymers of MD derivatives and lactones by ring-opening polymerization using stannous octoate[11–13] and enzyme[14] as catalysts. Ouchi and coworkers reported block copolymers prepared via anionic ring-opening polymerization.[15–17] However, they only used some of MD derivatives containing amino acids with pendant groups. The preparation of poly(morpholine-2,5-dione) (PMD) by anionic ring-opening polymerization has not been reported yet.

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First, we describe the preparation of PMD with THF solution of potassium ethoxide as an initiator. Then an AB-type block copolymer of PMD and PLA was synthesized by anionic ring-opening polymerization of LA using alcoholates of PMD as macroinitiator.

EXPERIMENTAL

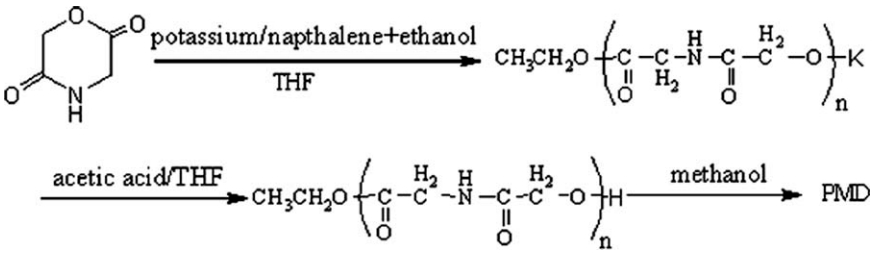
Materials

LA was synthesized from lactic acid with stannous octanoate as a catalyzer, then the crude was recrystallized four times from ethyl acetate. MD was synthesized from the cyclization of chloroacetyl glycine, which was made from chloroacetyl chloride and glycine in the basic condition. Then the crude was recrystallized from acetonitrile three times.[18] THF solution of potassium ethoxide was prepared according to the method reported by Ouchi et al.[14] The organic solvents used in the experiment were purified by the usual distillation methods. The other reagents were commercial grade and used without purified.

Methods

Preparation for macroinitiator

A polymerization tube was airproofed by a rubber plug. It was roasted and vacuumed at the same time for more than 1 hour to clean the hydrosphere. Then it was cooled to room temperature in vacuo and refilled with dry high purity nitrogen. 1.15 g (0.01*M*) MD was taken in the tube. The required amount of initiator (THF solution of potassium ethoxide, 0.2*M*/L)



Scheme 1 Synthetic route of polymorpholine-2,5-dione.

was injected into the tube after a second hydrosphere removing operation. The polymerization was carried out at room temperature for 90 min. It was terminated by adding trace of acetic acid. The mixture was poured into a mass of methanol to precipitate PMD. The product was white powder and dried in vacuo overnight. The process can be described as in Scheme 1. The required amount of THF solution of potassium /naphthalene was injected into PMD to prepare a macroinitiator.

Yield: 32%, Mn: 1430; IR (KBr, cm^{-1}):3350 (N—H in amide), 2950 (C—H— of CH_2), 1762 (C=O of ester), 1698 (amide I), 1550 (amide II).

^{1}H-NMR (DMSO-d_6, ppm): δ = 1.2 (t, 3H, CH_3—CH_2O—), 2.5 (solvent), 3.3 (solvent), 4.0 (s, 2H, CH_2—NH), 4.1 (m, 2H, CH_3CH_2O—), 4.6 (s, 2H, CH_2—C=O), 8.3 (br2, 1H, CH_2—N*H*).

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The copolymerization was also carried out in a polymerization tube under dry nitrogen atmosphere. 0ne milliliter of THF solution (1*M*/L)of LA was added to the resulting potassium alcoholate of PMD. After 90 min-ultrasonic vibration, the copolymerization was terminated by adding trace of acetic acid. Then the mixture was poured into a mass of methanol. The product was washed for three times with chloroform. Dried in vacuo overnight, a light yellow solid was obtained at last. The route of preparing the copolymer was described as Scheme 2.

Yield: 26%, Mn: 7200, IR(KBr, cm^{-1}): 3353 (NH in amide), 2986 (C—H in CH_3), 1425 (C—H in CH_2), 1353 (C—H in CH_3), 1154 and 1065 (C—O—C—), 1665(amide I), 1535 (amide II), 1754(C=O in ester).

^{1}H-NMR (DMSO-d_6, ppm): δ = 1.2 (t, 3H, CH_3—CH_2O—), 1.5 (d, 3H, CH_3—CH—), 2.5 and 3.3 (solvent), 4.0 (s, 2H, CH_2—NH), 4.1 (m, 2H, CH_3CH_2O—), 4.6(s, 2H, CH_2—C=O), 5.1 (m, 1H, CH_3—C*H*—), 8.5 (br2, 1H, CH_2—N*H*).

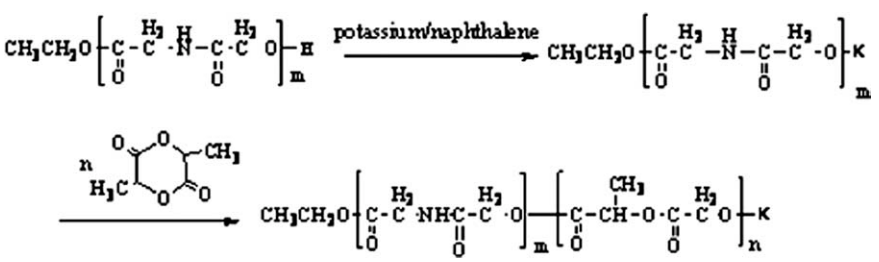
Measurements

^{1}H-NMR spectrum were recorded on an AV500 type. FTIR spectrum were recorded with a TENSOR27 instrument as KBr pellets. Thermal transition data were collected with a DSC204F1-type DSC instrument.

RESULTS AND DISCUSSION

PMD was prepared from the ring-opening polymerization of MD with THF solution of potassium ethoxide as an initiator. Ouchi and coworkers used the derivatives of MD, which were solulble in THF, as monomer. However, MD is not solved in THF. Therefore, the ring-opening polymerization can not be carried out in solution of THF. But it can be solved in DMF, so the polymerization was carried out in the solution of DMF. Red active center can be seen after the initiation for a short time. The yield and polymerization degree of PMD are low. The low yield may be caused by the affection of amido bond to the hydroxyl anion. Although the reason of low polymerization may be that the PMD is not soluble in DMF.

All the solents used in the polymerization must be dried strictly. The amount of ethanol is vital to the preparation of the initiator and the ring-opening



Scheme 2 Synthesis route of PMD-*b*-PLA.

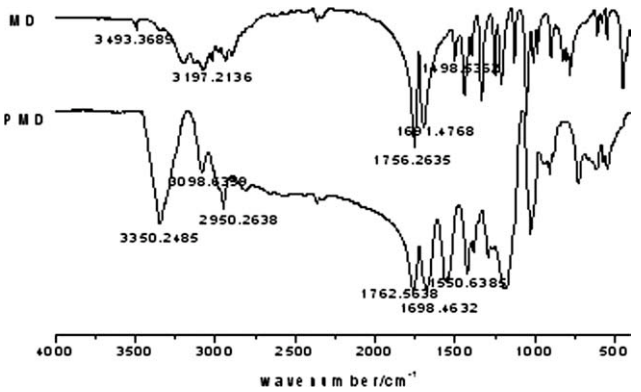


Figure 1 FTIR spectrum of MD and PMD.

polymerization. The color of the solution will be pale green with suitable amount of ethanol. Otherwise, it may be white with excessive of ethanol while green with inadequate amount. The initiator solution and monomer are soluble in methanol, so we can get purified PMD after precipitating the mixture of reaction in methanol.

After adding potassium naphthalene/THF into PMD, the dark blue solution began to fade. The PMD have hydroxyl-terminated H, which can react with the potassium in the solution, so the color of the solution changed. The macroinitiator is not active enough to initiate the ring-opening of all of LA, so the yield is low at about 26%.

Comparing the FTIR of MD with that of PMD (Fig. 1), the wide multiple peaks at 3197 cm^{-1} (association complex in MD) can not be detected in that of PMD. This means that there is no association complex in PMD, which can give a convincing proof to the polymerization. The strong peak at 3350 cm^{-1} in PMD's FTIR spectrum may be from the water.

In the ^{1}H-NMR spectrum of PMD (Fig. 2), the methyl protons at 1.2 and methylene protons at 4.1 correspond to the terminal oxyethyl group. This can support the principle of anionic ring-opening polymerization of MD. From the integral ratio of methyl-

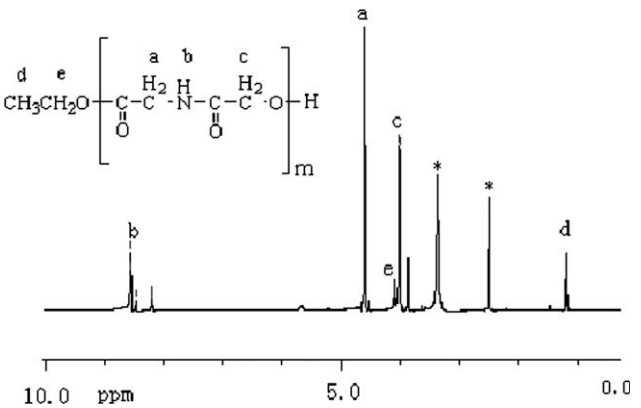


Figure 2 The ^{1}H-NMR spectrum of polymorpholine-2,5-dione (solvent: DMSO-d_6).

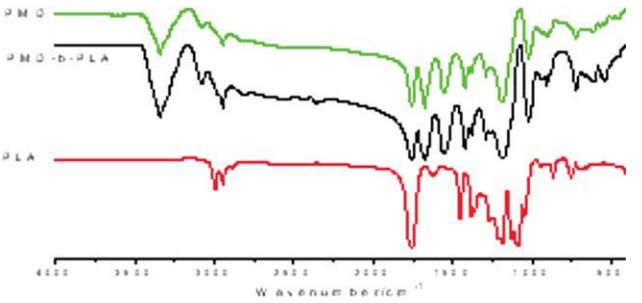


Figure 3 FTIR spectrum of PMD, PMD-*b*-PLA, and PLA. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ene protons at 4.6 (*a* peak) and methylene at 4.1 (*e* peak), we can estimate the M_n value of PMD. The average molecule weight of PMD can not be acquired from GPC test because it is not dissolved in THF.

$$D_p = \frac{l_a}{2l_e} \tag{1}$$

From the ^{1}H-NMR spectrum of PMD (Fig. 2), we can acquire the average polymerization degree, and then we can calculate the Mn of PMD. It can be

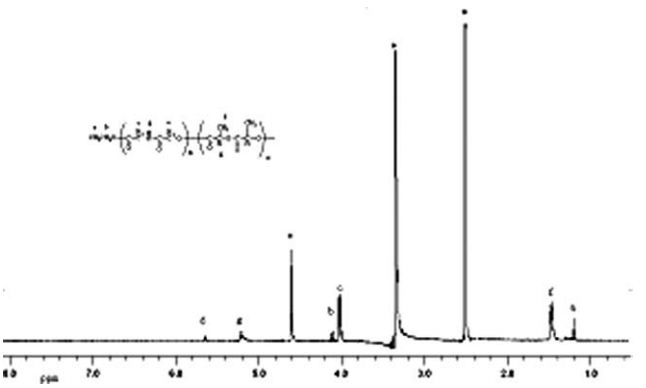


Figure 4 The ^{1}H-NMR spectrum of PMD-*b*-PLA (solvent: DMSO-d_6).

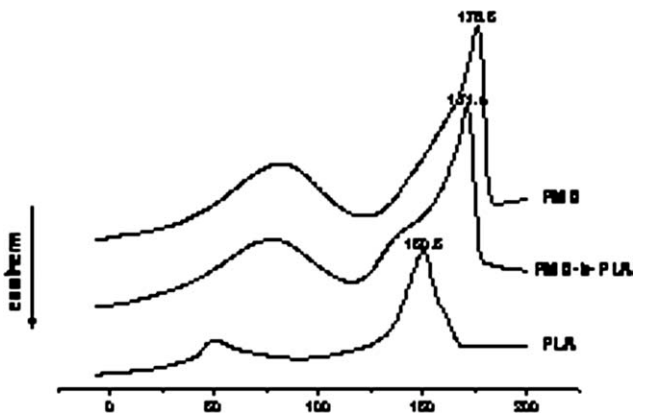


Figure 5 DSC curves of PLA, PMD, and PMD-*b*-PLA.

TABLE I
DSC Results of PLA, PMD, and PMD-*b*-PLA

	T_g (°C)	T_m (°C)	
PLA	46.7	150.5	
PMD	66.7	176.5	
PMD-*b*-PLA	63.6	155.6	171.4

shown as the formula (1). Where D_p is average degree of polymerization, I_a, I_e are the integral areas.

We tried to prepare polymorpholine-2,5-dione-*block*-polylactide (PMD-*b*-PLA) copolymer by ring-opening polymerization of MD initiated by the potassium alcoholate of PLA, but it failed. The most possiblity may be that it is more difficult to be ring-opened for MD than LA. PMD-*b*-PLA was prepared by the ring-opening polymerization of LA, which was initiated by the potassium alcoholate of PMD at room temperature. The initiator was synthesized by the reaction of potassium naphthalene and PMD, so it was difficult to determine the quantity of potassium naphthalene. We used the M_n acquired from the ^{1}H-NMR of PMD spectrum to calculate the amount of THF solution of K/naphthalene. Some of potassium naphthalene may also initiate the LA to produce PLA. The chloroform was used to solve the PLA before the test.

From the FTIR spectrum of PMD-*b*-PLA (Fig. 3), all the special absorbed peaks in PLA and PMD can be found.

According to the ^{1}H-NMR spectrum of PMD-*b*-PLA, the block copolymer has been prepared. It can also convince of the principle of the anionic ring-opening polymerization, because we can find the H signal of terminal group of ethanol.

$$\frac{F_1}{F_m} = \frac{3I_e}{2I_f} \tag{2}$$

From the integral area, we can get the rate of PMD in the copolymer. It can be calculated in formula 2. Where F_l, F_m are the content of monomer in raw material, I_e and I_f are the integral area. From Figure 4 and formula (1 and 2), the calculated fraction of PMD in the copolymer is 86.3%.

In Figure 5 and Table I, the copolymer has one T_g (63.6°C) and two T_ms (155.6°C and 171.4°C). Obviously, the T_ms are between that of PMD (150.5°C) and PLA (176.5°C). The block copolymer should also have two T_gs. But in the DSC curve of copolymer we can only see one T_g peak. This may be because of the content of PLA was much less than that of PMD and their T_gs were close to each other. So, the T_g (63.6°C) peak of PMD is so strong that we can not see the T_g peak of PLA. As calculated from the ^{1}H-NMR spectrum, there were more PMD segment (86.3%) than PLA in the coplymer, which can also be demonstrated from the DSC curves. We can say we get a block copolymer of PMD-*b*-PLA instead of a mixture of PMD and PLA.

CONCLUSIONS

We succeeded in synthesizing an AB-type block copolymer composed of PMD and PLA. The copolymer of PMD-*b*-PLA. was prepare by two-step of anionic ring-opening polymerization. It may have a good hydrophilic property and lipophilicity according to its structure. It will be quite useful for preparing biodegradable and medical materials, such as drug delivery systems and tissue engineering.

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