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Ring-opening copolymerization of α-chloromethyl-α-methyl-β-propiolactone with 1,3-trimethylene carbonate

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Summary

α-Chloromethyl-α-methyl-β-propiolactone (CMMPL) has been copolymerized with 1,3-trimethylene carbonate (TMC) using a wide range of feed composition and 1,3-dichlorotetrabutyl-distannoxane as a catalyst. Random copolymer, P(CMMPL-co-TMC), was obtained and characterized by ^{1}H NMR and DSC. The pendant chloromethyl groups of the copolymers are expected to be further modified by reaction with a tertiary amine containing compounds to increase the hydrophilicity of the copolymer or to conjugate bio-active residues onto the copolymer.

Introduction

Aliphatic polyesters have been widely used as biomedical materials and environmentally degradable thermoplastics (1-3). The homo- and copolymers of lactides and lactones such as polylactide, poly(lactide-co-glycolide), poly(ε-caprolactone-co-lactide) and poly(1,3-trimethylene carbonate-co-lactide) are among the well known biodegradable synthetic polymers which have long been studied (4). Since aliphatic polyesters normally do not have many pendant functional groups (other than end groups) to allow chemical modification altering their properties or to conjugate with drugs and bio-active residues, the application of these polyesters is limited. Novel aliphatic polyesters containing functional pendant groups, mainly derived from malic acid or trifunctional amino acids, have been studied continuously in the recent past (5-10). It has also long been known that random copolymerization is a useful method to prepare new materials, whose properties are different from those of the parent homopolymers, and sometimes are the average of them. Poly(1,3-trimethylene carbonate) (PTMC) is an amorphous polymer and shows slow degradable rates (11). Copolymerization of 1,3-trimethylene carbonate (TMC) with LA, GL, CL or other cyclic esters yields biodegradable and biocompatible polyesters with a large range of chemical and physical properties (12-14). Therefore, copolymerization of functional monomers with TMC is expected to provide a way to obtain new functional biodegradable materials. We have reported on the synthesis and ring-opening polymerization of a new kind of modifiable

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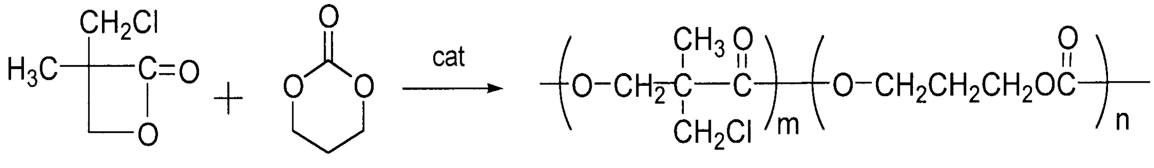
propiolactone, α-chloromethyl-α-methy-β-propiolactone (CMMPL) (15). However, the resulting polymer P(CMMPL) was found to possess very high crystallinity and low solubility in common organic solvents, which makes it difficult to modify the polymer. In this article, we have tried the ring-opening copolymerization of CMMPL with TMC to afford a new kind of random copolymer containing pendant functional groups. These copolymers may be used to conjugate drugs or bio-active residues, they can also be quaternized to increase the hydrophilicity of the copolymers.



Scheme 1 Copolymerization of CMMPL with TMC

Experimental

Materials

α-Chloromethyl-α-methyl-β-propiolactone (CMMPL) was prepared as reported in our previous paper (15), it was dried over CaH_2, and freshly distilled under reduced pressure prior to use. TMC was synthesized according to the published procedure (11) and distilled over CaH_2 under reduced pressure. Titanium (IV) butoxide [$Ti(OBu)_4$], dibutyltin dimethoxide [$Bu_2Sn(OMe)_2$] and stannous octoate [$Sn(Oct)_2$] were purchased from Aldrich and distilled under reduced pressure. 1,3-dichlorotetrabutyl-distannoxane (DCTBD) and 1-ethoxyl-3-chlorotetrabutyl-distannoxane (ECTBD) were prepared according to literature (16). *o*-Dichlorobenzene was distilled under nitrogen over 4Å molecular sieve. All other chemicals were commercial products of Beijing Chemical Reagent Co. and used without further purification.

Copolymerization

Bulk copolymerization was carried out with 0.05 mol% of catalyst relative to monomer. A mixture of a certain amount of CMMPL, TMC and catalyst in *o*-dichlorobenzene was put into a previously flamed and dry argon-purged glass tube. The tube was degassed for 10 min and sealed under vacuum. After a pre-determined reaction time, the tube was allowed to cool down to room temperature. The reaction mixture was dissolved in chloroform, then a mixture of diethyl ether and hexane (1/3, v/v) was added to precipitate the copolymer as a white solid. The copolymer was further purified by reprecipitation and dried in vacuo at 50°C for 48 h.

Characterization

^{1}H-NMR spectra were recorded on a Bruker ARX-400 spectrometer operated at 400 MHz. Composition of copolymers were determined either by elemental analysis of the chlorine content of the copolymers or by ^{1}H-NMR analysis based on the relative intensity of the methylene signal of P(CMMPL) at 3.7 ppm and the methylene signal of PTMC at 2.0 ppm. $CDCl_3$ was used as a solvent and tetramethylsilane was used as an internal standard. The number and weight average molecular weights of copolymers were determined by gel permeation chromatography (GPC). The GPC measurements were carried out with THF as an eluent (1.0 mL/min) using a Waters 510 pump, three Waters μStyragel columns (10^5, 10^4, 500 Å) in series, and a Waters 401 differential refractometer. The columns were calibrated with polystyrene standards having a narrow molecular weight distribution. Differential scanning calorimetry (DSC) measurements were performed on a Shimadzu DSC-50 at a heating rate of 10°C/min. The melting temperature (T_m) was taken as the peak temperature of the melting endotherm. The glass transition temperature (T_g) was taken as the inflection point of the specific heat increment at the glass transition.

Results and Discussion

In general, it is difficult to get random copolymers of 4-numbered ring lactones such as β-butyrolactone and larger numbered ring esters such as CL, TMC, LA and GL due to the large difference in monomer reactivity (17,18). It is well-known that in the case of ring-opening polymerization, different catalysts may result in different propagation mechanisms, and in turn alter the monomer reactivity. Therefore, the selection of a suitable catalyst is crucial to obtain random copolymers of CMMPL and TMC. Hori et al. has reported that distannoxane compounds can effectively catalyze the copolymerization of β-butyrolactone with TMC and CL to afford random copolymers (13, 19, and 20). In this article, five catalysts, namely $Bu_2Sn(OMe)_2$, DCTBD, ECTBD as well as $Ti(OBu)_4$ were evaluated for the copolymerization of TMC and CMMPL. Since P(CMMPL) itself is a high crystalline polyester with low solubility in common organic solvents, the low comonomer feed ratio ([CMMPL]=20 mol%) was used in order to obtain soluble copolymers for composition determination. The results are summarized in Tab. 1. The composition of the copolymer was determined by ^1H NMR spectra. Fig. 1 shows a representative ^1H-NMR spectrum of P(CMMPL-co-TMC), together with the assignments of peaks from both TMC and CMMPL units. The peaks at 3.7 ppm ($-CH_2Cl$ of CMMPL) and 2.0 ppm ($-C-CH_2-C-$ of TMC) were used for the calculation. It can be seen from Tab. 1 that among the five catalysts used, the compositions of copolymers obtained by using ECTBD and DCTBD as catalysts are close to the feed ratios, indicating that random copolymerization of TMC and CMMPL might have taken place by using these two catalysts. It seems that ECTBD may be much more preferable than DCTBD due to the shorter polymerization time and the higher polymer yield.

Tab.1 Copolymerization of CMMPL and TMC using different catalysts*

No.	Cat.	Yield (%)	CMMPL(mol%)[a] in copolymer	T_g (°C)
A-1[b]	ECTBD	67	21.2	-17.9
A-2[c]	DCTBD	39	19.7	-18.6
A-3	$Sn(Oct)_2$	47	14.8	-17.7
A-4	$Bu_2Sn(OMe)_2$	24	23.6	-15.3
A-5	$Ti(OBu)_4$	36	7.8	-18.2

* [CMMPL] = 20.0 mol%, [M]/[cat.] =2000 (molar ratio), 130 ℃, 4h.

[a] Calculated from ^1H NMR spectra. [b] The polymerization time was 10min.

[c] The polymerization time was 30min.

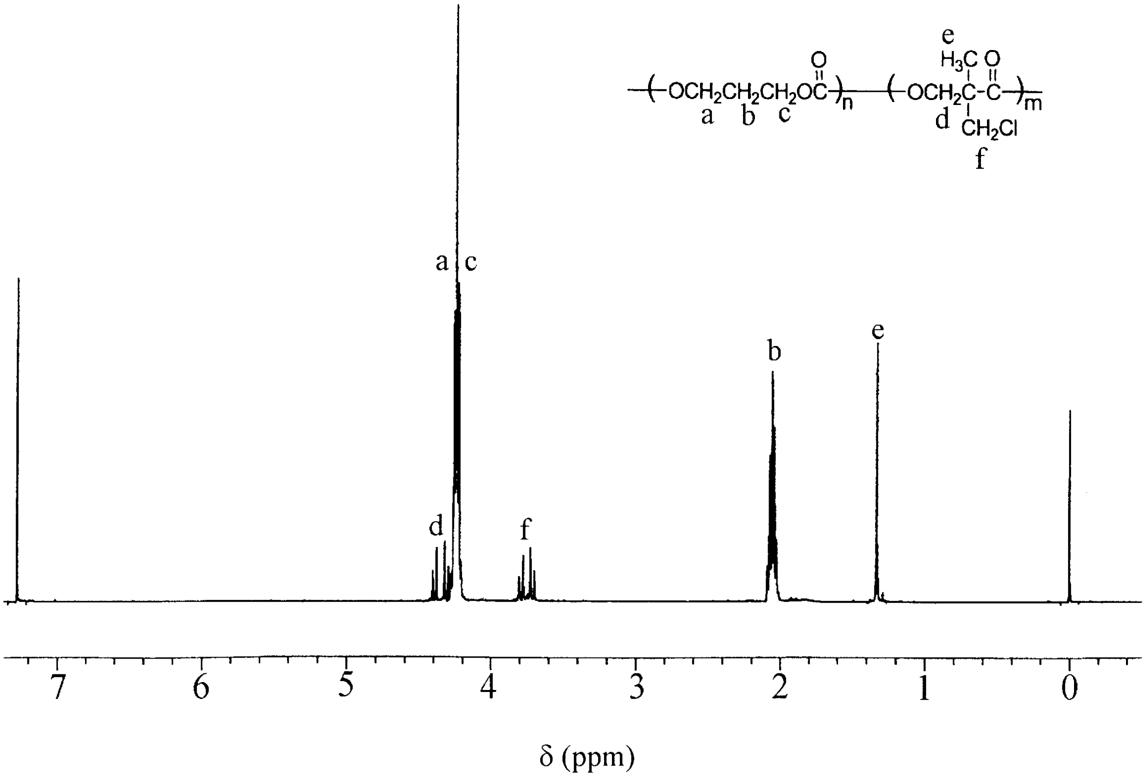


Fig. 1 ^{1}H-NMR spectrum of P(CMMPL-co-TMC) (No. A-1 in Tab. 1)

Subsequently, the copolymerization of CMMPL and TMC was carried out at different temperatures by using ECTBD and DCTBD as catalysts. The results are listed in Tab. 2, from which it can be seen that the polymerization temperature does not influence the compositions of copolymers obviously. The compositions are all similar and close to the feed ratios for the two catalysts. However, higher temperature tends to increase the copolymerization rates and the copolymer yields.

Based on the above results, the bulk copolymerization of CMMPL and TMC was conducted under the following conditions: [M]/[cat.] = 2000 (in molar ratio), 130°C, 18 h. The results are summarized in Tab. 3. It can be seen very clearly from Tab. 3 that when the feed CMMPL ratio was higher than 60 mol%, the CMMPL contents in the resulting copolymers were larger than the feed ratios; below this feed ratio, the compositions of the copolymers were close to their corresponding feed ratios. Meanwhile, It seems that the

Tab. 2 Copolymerization of CMMPL and TMC at different temperatures*

No.	Cat.	Temp. (°C)	Time (min)	Yield (%)	CMMPL(mol%)^a in copolymer	T_g (°C)
B-1	ECTBD	80	90	32	19.8	-19.2
B-2	ECTBD	100	40	31	20.5	-17.7
B-3	ECTBD	130	10	67	21.2	-17.9
B-4	DCTBD	80	90	33	21.2	-16.1
B-5	DCTBD	100	40	31	19.8	-17.3
B-6	DCTBD	130	30	39	19.7	-18.6

* [CMMPL] = 20.0 mol%, [M]/[cat.] =2000 (molar ratio).

[a] Calculated from ^{1}H NMR spectra.

Tab. 3 Copolymerization of CMMPL and TMC using DCTBD as a catalyst*

No.	CMMPL (mol%) in feed	Yield (%)	CMMPL (mol%)[a] in copolymer	T_g (°C)	T_m (°C)	ΔH_f (J/g)	T_c (°C)	$\overline{M}_n$[c] (10^4)	$\overline{M}_w$[c] (10^4)
C-0	100	87	100	-8.0[b]	230.2	27.1	19.6	-[d]	-
C-1	90	84	97	-9.1[b]	236.0	35.8	25.5	-	-
C-2	80	83	94	-10.4[b]	235.4	50.1	24.9	-	-
C-3	70	70	89	-13.8[b]	233.5	51.6	24.7	-	-
C-4	60	68	78	-14.0	229.0	43.0	20.8	-	-
C-5	50	78	55	-14.5	224.5	35.9	-	-	-
C-6	40	63	47	-13.5	203.1	16.5	-	-	-
C-7	30	76	23	-13.0	-	-	-	-	-
C-8	20	79	19	-12.9	-	-	-	0.68	1.32
C-9	10	71	13	-15.1	-	-	-	0.82	2.86
C-10	0	85	0	-19.3	-	-	-	0.91	2.48

* [M]/[cat.] =2000 (molar ratio), 130 ℃, 18 h; [a] Determined by elemental analysis;
[b] Obtained from the second scan; [c] Determined by GPC analysis;
[d] These samples were not soluble in THF, the molecular weight were not determined

feed ratio does not influence the copolymer yields significantly, the yields of all the copolymers are high. This was attributed to the relative high polymerization temperature and long polymerization time.

Fig. 2 shows the DSC profiles of the copolymers listed in Tab.3, the related results are summarized in Tab. 3. P(CMMPL) is a high crystalline polymer, which melts at about 230°C under the present polymerization condition. For copolymers obtained from low

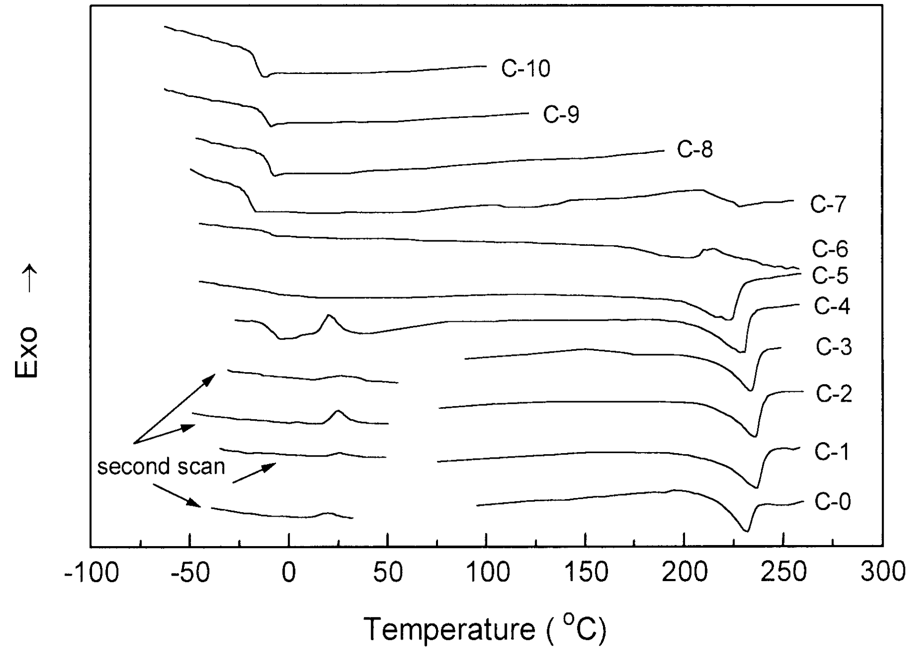


Fig. 2 DSC traces of P(CMMPL-co-TMC) (the numbers correspond to the copolymer numbers in Tab.3. The second scan was done after the melt sample being quenched in liquid nitrogen.)

feed ratio of TMC (sample C-0 to C-3), TMC contents in the copolymers were obviously lower than the TMC feed ratios. The melting temperature and melting enthalpy of these copolymers are higher compared to those of P(CMMPL). This might reflect that the P(CMMPL) crystallization is improved when small amount of TMC unit is present. It is worth mentioning that the T_g of these copolymers could only be observed for the second scan, when the samples were quenched in liquid nitrogen. Meanwhile, crystallization peaks were also detected for these samples. When the molar content of TMC in the copolymer was about 60% (i.e. for sample C-7), the melting process became very broad and the melting enthalpy could not be accurately recorded. This result indicates that an amorphous copolymer was obtained when 60 mol% of TMC units were present. Single T_g values were observed for all the copolymers. The GPC traces of the dissolvable samples were unimodal. Therefore, it can be concluded that copolymerization of CMMPL and TMC can afford random copolymer with low or no crystallinity.

In conclusion, CMMPL and TMC have been successfully copolymerized using 1,3-dichlorotetrabutyl-distannoxane as a catalyst. The DSC results show that when 60 mol% of TMC units is present in the copolymer, an amorphous random copolymer can be obtained. The pendant chloromethyl groups of the copolymers may be converted to quaternary ammonium salts by reaction with a tertiary amine and thus to increase the hydrophilicity of the copolymer or to conjugate bio-active residues onto the copolymer.

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