Ring Opening Polymerization of Aliphatic Cyclic Carbonates in the Presence of Natural Amino Acids

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Received 9 November 2007; accepted 14 September 2007
DOI 10.1002/app.27440
Published online 27 November 2007 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Poly(dimethyl trimethylene carbonate) (PDTC) and poly(trimethylene carbonate) (PTMC) were synthesized by ring-opening polymerization (ROP) of dimethly trimethylene carbonate (DTC) and trimethylene carbonate (TMC) in the presence of five kinds of natural amino acids (L-alanine, L-valine, L-leucine, L-proline, and L-phenylalanine). PDTCs with number-average molecular weight (M_n) from 6700 to 18,900 g/mol and PTMCs with M_n from 7200 to 17,800 g/mol were obtained at a feed ratio of [monomer]/[L-phenylalanine] ranging from 50 to 200. The results of ^{1}H nuclear magnetic resonance and titration proved amino acid connecting onto the polymer backbone. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 3275–3279, 2008

Key words: dimethyl trimethylene carbonate; trimethylene carbonate; natural amino acid; initiator; ring-opening polymerization

INTRODUCTION

Ring-opening polymerization (ROP) of aliphatic cyclic carbonates has attracted much attention because the resulting polymers are biodegradable and applicable to biomedical material. The reaction is often carried out by using tin, aluminum, titanium, or rare-earth metals compounds as the catalysts.[1–4] However, the difficulty of removing these metal residues completely from the polymerization products will cause potential toxicity problems for biomedical application. To overcome the disadvantage of the metallic catalysts, except for the enzyme-catalyzed method,[5,6] a metal free method was developed. This method includes two approaches. One is the using of organic compound as the initiator without any metallic catalyst. For example, Kricheldorf[7] reported the cationic ROP of trimethylene carbonate (TMC) initiated by $CF_3SO_3CH_3$. Ariga[8,9] showed that alkyl halide such as methyl iodide and benzyl bromide initiate the cyclic carbonates to produce corresponding oligomer having a molecular weight of about 3000–5000 g/mol. Murayama[10] demonstrated that amine such as 1,8-diazabicyclo diazabicyclo-[5,4,0]-undec-7-ene, 1,4-diazabicyclo-[2.2.2]-octane and 4-(dimethylamino) pyridine initiate the anionic ROP of cyclic carbonates to obtain the corresponding polycarbonates. In the other approach, both the initiator and the catalyst are metal free compounds. For example, Shibasaki[11,12] reported using alcohol and water as the initiator, and the $HCl \cdot Et_2O$ as the catalysts for the ROP of a seven-memebered cyclic carbonate (1,3-dioxepan-2-one) to obtain the corresponding polycarbonate with a controlled molecular weight and narrow polydispersity under mild conditions.

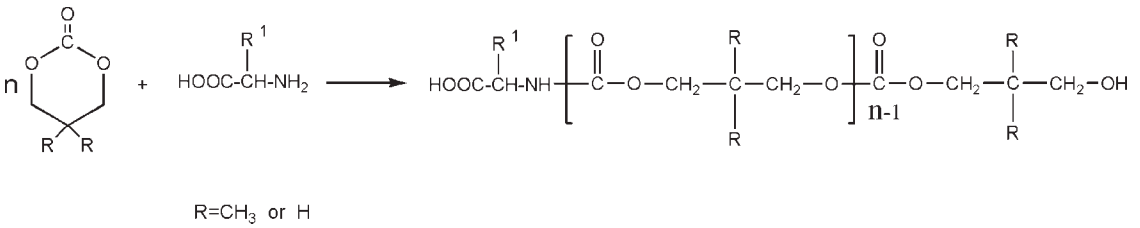
The natural amino acid is the nutrition supplement of human body; so it has an excellent safety for synthesizing biomedical polymers.[13–15] In this article the ROPs of dimethly trimethylene carbonate (DTC) and TMC in the presence of some natural amino acids including L-alanine, L-valine, L-leucine, L-proline, and L-phenylalanine were studied (Scheme 1). Polymers with different molecular weights were obtained by varying the molar ratio of the [monomer]/[amino acid]. ^{1}H nuclear magnetic resonance (^{1}H NMR) and titration analysis proved amino acid was incorporating into the polymer end.

EXPERIMENTAL

Materials

L-alanine, L-valine, L-proline, L-leucine, and L-phenylalanine (Bioreagent Limited Company, Shanghai,

Correspondence to: J. Liu (liujiyan918@163.com).
Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 20274032.
Contract grant sponsor: Natural Science Foundation of Hubei province, China; contract grant number: 2005ABA068.



Scheme 1 ROP of DTC and TMC in the presence of natural amino acid.

China) were of analytical grade and used as received. DTC and TMC were synthesized according to reference.[14] The product was recrystallized five times from a mixed solvent of diethyl ether and tetrahydrofuran (THF) (v/v = 4/1). Melting point of obtained DTC is 106.5°C, TMC is 44.5°C. The ^{1}H NMR spectrum of DTC (6H, 4.08 ppm; 4H, 1.13 ppm) TMC (4H, 4.47 ppm; 2H, 2.17 ppm) was in accordance with that reported previously.[16] All other materials were of analytical grade and used as received.

ROPs of the DTC and TMC in the presence of natural amino acid

About 1.5 g DTC or TMC, certain amount of amino acid, and a mini electromagnetic stirrer in a vacuum-sealed ampoule (40 Pa) were polymerized in an oil bath at a predetermined temperature (110°C for DTC; 80°C for TMC). The ampoules were taken out of the oil bath at given time and cooled in ice water to stop the polymerization. Part of the reaction mixture was analyzed immediately by ^{1}H NMR and the residue was dissolved in THF and precipitated by a mixture of methanol and distilled water (v/v = 4/1) at room temperature. The precipitate was filtrated and dried in vacuum at 30°C for 24 h.

Characterizations

^{1}H NMR spectra of poly(dimethly trimethylene carbonate) (PDTC) and poly(trimethylene carbonate) (PTMC) were recorded on a Mercury VX-300 (300 Hz) apparatus with tetramethylsilane as internal standard and deuterated chloroform as the solvent. Number average molecular weight (M_n) and polydispersity index (M_w/M_n) of the polymerization product were measured with a Waters gel permeation chromatography (GPC) system equipped with a model 2690D separation module, a model 2410 refractive-index detector, and Shodex K802.5 (pore size 60Å) and Shodex K805 (pore size 500 Å) columns with Shodex K-G Guard column. The measurements were performed in chloroform at 35°C and calibrated with polystyrene standards, and the universal calibration of the M_n obtained by GPC was performed using a viscosity detector.

Determination of unreacted free amino acid in the polymerization system: 1 g of the reaction mixture was dissolved in 50 mL chloroform; then 10 mL of water was added to extract the amino acid. The pregnant water phase was analyzed by the Ninhydrin-Ascorbic acid method using a Shimadzu 2401 ultraviolet-visible spectrometer.[15]

TABLE I
The ROP of DTC in the Presence of Natural Amino Acid

Amino acid	[DTC]/[amino acid][a]	Time (h)	Convn.[b] (%)	M_n[c]	M_w/M_n[c]
None	DTC 1g	72	33.5	–	–
L-alanine	100	24	92.6	10,400	1.59
				11,000[d]	1.63[d]
L-valine	100	24	97.3	10,800	1.58
L-proline	100	24	93.4	14,300	1.59
L-leucine	100	24	100	12,500	1.52
L-phenylalanine	50	16	100	6700	1.51
L-phenylalanine	100	24	98.7	11,700	1.55
				10,900[d]	1.60[d]
L-phenylalanine	150	36	93.6	15,800	1.60
L-phenylalanine	200	48	92.5	18,900	1.67
L-phenylalanine	300	72	68.7	13,200	1.75

[a] Molar ratio.
[b] DTC conversion determined by ^{1}H NMR of the reaction mixture without purification.
[c] Determined by GPC of the purification production.
[d] Reaction mixture without purification.

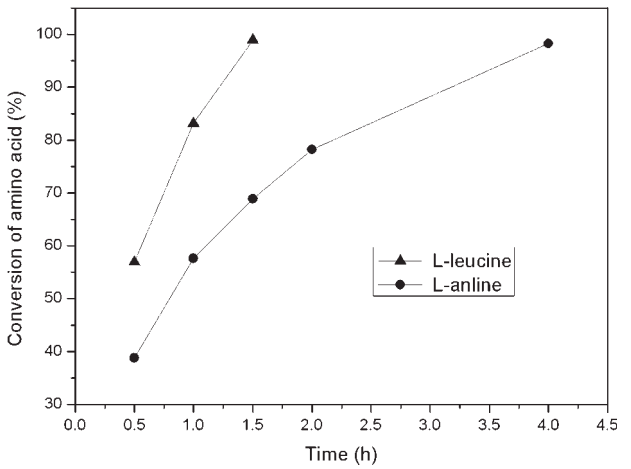


Figure 1 Conversion of amino acid versus time ([DTC]/[amino acid] = 50).

Titration of carboxyl end group in PDTC: Purified PDTC was dissolved in a mixture solvent of isopropyl alcohol and 1, 4-dioxane (v/v = 1/4) and titrated with 0.0078 mol/L potassium hydroxide in the same solvent with 1% phenolphthalein/pyridine as the indicator.

RESULTS AND DISCUSSION

Effect of the amino acids on the ROP of the DTC

The ROP of DTC was studied at 110°C in the presence of L-alanine, L-valine, L-proline, L-leucine, and L-phenylalanine, respectively. The reaction time is set from 18 to 72 h to guarantee high monomer conversion. The results are listed in Table I.

As shown in Table I, in the absence of amino acid, in spite of prolonging the reaction time to 72 h at 110°C, the conversion of DTC only is 33.5%, but no polymer was obtained during the precipitation process. That perhaps is because the thermally oligomerized product has lower molecular weight and cannot be precipitated in the mixture solvent of methanol and water.[16]

In the presence of amino acid, at a [DTC]/[amino acid] molar ratio of 100, the DTC conversions are above 92.6%. The M_n and M_w/M_n values of the PDTC range from 9900 to 12,500 g/mol and 1.52 to 1.67, respectively depending on the type of the amino acids. That shows ROP of DTC proceeded very well in the presence of these amino acids.

For the ROP of DTC in the presence of the L-phenylalanine, the M_n of the polymer increased with the [DTC]/[L-phenylalanine] feed ratio ranging from 30 to 200. At a [DTC]/[L-phenylalanine] feed ratio of 200, the M_n of the PDTC reached the maximum value of 18,900 g/mol, after that it began decreasing gradually with the increasing [DTC]/[L-phenylalanine] feed ratio. At a [DTC]/[L-phenylalanine] feed ratio of 300, the M_n of the resulting polymer and the conversion of the monomer were rather low even after 72 h reaction. This phenomenon may be attributed to the lower rate of the ROP at lower amino acid concentration, which led to lower M_n and conversion.

It was observed that at the initial stage of polymerization the amino acid is partly dissolved in the DTC and the rest exists as white deposition, which disappeared after the reaction proceeded 5–15 min. Then the reaction mixture became colorless and transparent, and it was found that amino acid having longer alkyl side group can be dissolved faster. To determine the role of the amino acids in the polymerization, the conversions of the amino acids were monitored in the polymerization process by the Ninhydrin-Ascorbic acid method. The corresponding conversions were calculated according to the following equation:

$$\text{Conversion } \% = \frac{[A]_0 - [A]_t}{[A]_0} \times 100$$

where $[A]_0$ is initial concentration of free amino acid, $[A]_t$ is the concentration at time t. The results were showed in Figure 1.

From the Figure 1, it can be noted that the conversion of the L-leucine reached 99% at 1.5 h and that of the L-alanine reached 98% at 4.0 h. This demonstrates that amino acids were incorporated into the polymer chains during the reaction. L-leucine was consumed up faster than the L-alanine, this may be attributed to the structural difference between the two amino acids; the L-leucine has longer alkyl side chain, which helps it dissolve in the reaction mixture and makes it easier to react with the monomer and be incorporated into the polymer chain.

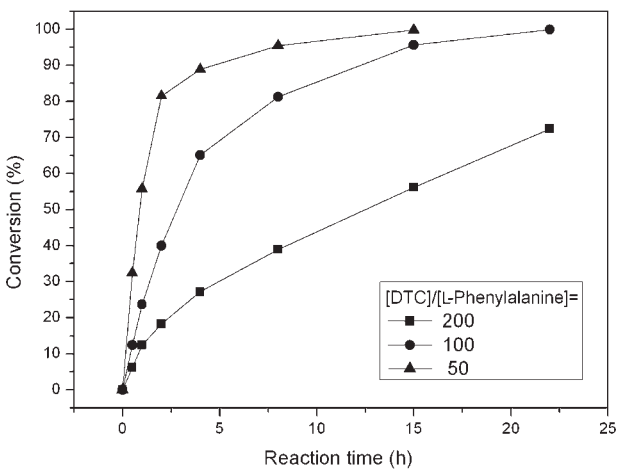


Figure 2 Conversion of DTC versus time in different molar ratio of [DTC]/[L-phenylalanine].

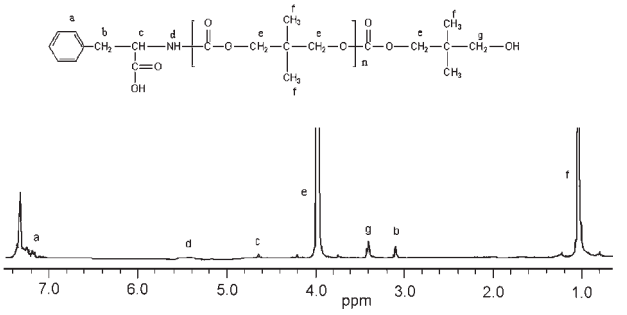


Figure 3 ^{1}H NMR spectrum of PDTC by L-phenylalanine ([DTC]/[L-phenylalanine] = 50).

Relationship of DTC conversion to the concentration of amino acid

Figure 2 shows the dependence of the DTC conversion upon the [DTC]/[L-phenylalanine] feed ratio. The results indicated that the higher conversions are obtained in the faster reactions observed at higher amino acid levels.

Characterization of the polymerization product

^{1}H NMR analysis of PDTC

The resulting product made from ROP of DTC in the presence of the L-phenylalanine was characterized by ^{1}H NMR spectroscopy. Figure 3 shows the ^{1}H NMR spectrum of the polymer. The peaks at 3.1 and 4.6 ppm are assigned to the proton of the methylene and methylidyne groups; the peak at 7.2 ppm is attributed to the phenyl protons in the L-phenylalanine end group; the triplet at 3.7 ppm is due to the methylene proton of —CH_2OH end group. The small and wide signal at 5.3–5.7 ppm is assigned to the proton of newly formed —NHCOO— group, which disappeared after D_2O exchange. All other peaks are due to the backbone chain of PDTC.

TABLE II
Content of Carboxyl End Group of PDTC Analyzed by Titration

Item	L-alanine	L-leucine	L-phenylalanine
M_n of PDTC[a]	5900	6300	6700
KOH (mL)	8.2	7.2	7.0
Mass of PDTC (g)	0.392	0.401	0.398
No. of carboxyl group[b]	0.90	0.88	0.92

[a] Molar ratio of [DTC]/[amino acid] = 50.
[b] Number of carboxyl group = the amount of KOH (mol) consumed/(mass of PDTC/M_n of PDTC).

Determination of carboxyl end groups in the PDTC

The content of carboxyl end groups in the PDTC was determined quantitatively by titration (Table II). The data in Table II demonstrated that the carboxyl group exists in the PDTC chain, which is consistent with the ^{1}H NMR result of the amino acid connecting onto the polymer backbone.

ROP of TMC in the presence of natural amino acid

The results of the ROP of TMC in the presence of natural amino acid were listed in Table III. In the presence of L-alanine, L-proine, L-leucine, and L-phenylalanine, the ROP of the TMC also proceeded effectively. The M_n of the PTMC increase with the [TMC]/[L-phenylalanine] molar ratio, this was similar to that of the DTC. The PTMC with an M_n of 17,800g/mol and a M_w/M_n of 1.65 was obtained with a [TMC]/[L-phenylalanine] molar ratio of 200 at 80°C for 48 h.

The resulting product made from ROP of TMC in the presence of the L-alanine was characterized by ^{1}H NMR spectroscopy (Fig. 4). The peaks at 1.4 and 4.6 ppm are attributed to the proton of methyl and methylidyne in the L-alanine. The triplet at 3.6 ppm is due to the proton of —CH_2OH end group. The small and wide signal at 5.4–5.8 ppm is assigned to

TABLE III
The ROP of TMC in the Presence of Natural Amino Acid

Amino acid	[TMC]/[amino acid][a]	Reaction time (h)	Convn.[b] (%)	M_n[c]	M_w/M_n[c]
L-alanine	100	24	91.2	12,500	1.63
				10,000[d]	1.70[d]
L-proline	100	24	93.4	14,300	1.59
L-leucine	100	24	99.5	15,000	1.64
L-phenylalanine	50	16	99.5	7200	1.51
L-phenylalanine	100	24	97.8	14,800	1.60
				10,900[d]	1.60[d]
L-phenylalanine	150	36	94.6	15,100	1.61
L-phenylalanine	200	48	95.5	17,800	1.65

[a] Molar ratio.
[b] The TMC conversion determined by ^{1}H NMR of the reaction mixture without purification.
[c] Determined by GPC of the purification production.
[d] Reaction mixture without purification.

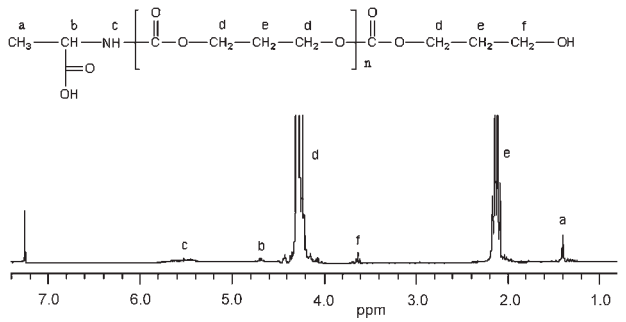


Figure 4 ^{1}H NMR spectrum of PTMC by L-alanine ([TMC]/[L-alanine] = 50).

the newly formed —NHCOO— group, which also disappeared after D_2O exchange. The strong peaks at 2.1 and 4.2 ppm are due to the backbone chain of PTMC. The results of the ^{1}H NMR indicate that L-alanine has incorporated in to the polymer chain, which is similar to the ROP of the DTC.

CONCLUSIONS

The ROP of DTC and TMC were carried out in the presence of L-alanine, L-valine, L-proline, L-leucine, and L-phenylalanine. PDTCs and PTMCs with different M_n were obtained by tuning the mole ratio of [monomer]/[amino acid]. Among these polymers, the maximum values of M_n of the PTDC and PTMC reached 18,900 and 17,800 g/mol and the corresponding M_w/M_n were 1.67 and 1.65, respectively at a [monomer]/[L-phenylalanine] molar ratio of 200. ^{1}H NMR and titration analysis demonstrated that amino acid was incorporated into the polymer chain. In conjunction with facts that M_n of the PDTC increase with the [DTC]/[L-phenylalanine] molar ratio and the conversion rate of the DTC decreases with the [DTC]/[L-phenylalanine] molar ratio. It can be concluded that the amino acid acted as the initiator in the polymerization.

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