Organic Acids Catalyzed Polymerization of ε-Caprolactone: Synthesis and Characterization

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ABSTRACT: Environmentally friendly organocatalytic synthesis of aliphatic polyesters was studied. The catalysis investigated is novel, and lends itself well to the potential production of valuable biodegradable products. The reactions were based on an organic acids-catalyzed ring-opening polymerization of ε-caprolactone with fatty acid derivatives as the initiator and were performed in the absence of solvents. The chemical structures of the functionalized polymers were confirmed by ^{1}H and ^{13}C-NMR spectra. Polymers with different molecular weights, in the range 10,900–15,200 were obtained in the presence of fumaric acid as catalyst. The thermal properties of the functionalized PCLs were determined by modulated differential scanning calorimetry and thermogravimetric analysis. The MDSC results verified that the crystallinity and the melting point of the lipid-functionalized polymers were lower than that of the unfunctionalized poly(ε-caprolactone). The hydrolytic degradation of the functionalized polymer was also investigated. The result shows the degradation rate was affected by the presence of oleic acid derivatives in the polymer molecule. The lipid-functionalized polymers synthesized by the metal-free polymerization systems seem to be suitable biodegradable polyesters for use in biomedical and pharmacological applications. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 1873–1882, 2011

Key words: polyesters; biodegradable; degradation; polymer synthesis and characterization; thermal properties; lipids

INTRODUCTION

Aliphatic polyesters, such as poly(ε-caprolactone) (PCL), have attracted much interest because of their biodegradability, biocompatibility and high drug permeability. Moreover PCL is nontoxic to living organisms.[1,2] These properties qualify PCL as a good candidate for biomedical and environmentally friendly applications (drug delivery systems, tissue engineering, surgical sutures, packing materials, etc.).[3–12] PCL has been widely synthesized from ε-caprolactone (CL) by cationic,[13,14] anionic,[15,16] free-radical,[17] and coordination polymerization.[18–20] Among the four kinds of polymerization listed above, the use of metal catalysts, including compounds containing aluminum[18] and tin[18,19] have been intensively investigated and effectively applied. Other metals such as lanthanide, ruthenium, zirconium, and titanium compounds have been used as well.[21–33] The complete removal of the catalyst residue from the polymerization product is difficult but necessary as the residue can be harmful to human bodies. It is therefore of some importance to develop methods which avoid the use of metal catalysts in the synthesis of PCL, especially for biomedical and pharmaceutical applications.

Ring-opening polymerization (ROP) of CL can also proceed by a combination of alcohol as initiator and acid as activator or catalyst.[34] Shibasaki et al.[34] synthesized homo- and copolymers of CL and δ-valerolactone (VL) by controlled ROP initiated with *n*-butyl alcohol/HCl Et_2O and H_2O/HCl Et_2O systems. Similar synthesis of the homo- and copolymers of CL and L,L-lactide (LA) were conducted by Basko and Kubisa[35,36] Three different alcohols (2-propanol, 1.4-butanediol, and ethylene glycol) and trifluoromethanesulfonic acid were used as polymerization systems. An analysis of the ^{13}C-NMR spectra of the copolymers indicated that the transestrification reaction was slow and that the microstructure of the copolymers was governed by the relative reactivity of the comonomers.[36,37] On the other hand, Biler et al.[37] recorded the polymerization of CL in the presence of carboxylic acids alone at high temperatures. Even if Biler et al.[37] proved that carboxylic acids can initiate the polymerization of CL, the molecular weight of the resulting polymers was low ($M_w < 10{,}000$). Moreover, polymerization of CL in

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the presence of succinic acid resulted in a polymer with two terminal carboxylic groups with a low average molecular weight, below 3000.[38] Star-shaped PCLs with three or four arms and controlled molecular weights were synthesized by ROP of CL with trimethylolpropane and pentaerythritol as the initiators, using fumaric and other organic acids as catalysts.[39] By varying the molar ratio of the initiator to catalyst, polymers with different molecular weights were obtained. The melting point values of the resulting polymers were directly related to the degree of branching within each molecule. Room-temperature studies in tetrahydrofuran or dichloromethane using the HCl Et_2O catalyst proved relatively unsuccessful, likely due to the low solubility of the initiator.[39] Star-shaped polymers of VL with average-molecular weights up to 99,000 were similarly produced by the bulk polymerization of VL at 100°C in the presence of fumaric acid, as the catalyst, and dipentaerythritol as the multifunctional initiator.[40]

Given that fatty acids are found naturally in the human body they are considered biologically safe and are generally considered suitable candidates for the preparation of biodegradable polymers.[41–44] The incorporation of fatty acid terminals into polymer molecules can improve biocompatibility, lower crystallinity and melting point, and contributes to the flexibility and pliability of the resulting material. Moreover, drug release from these polymers might be dependent on the fatty acid chain length and content.[42]

Oxalic, succinic, and fumaric acids are natural and environmentally friendly compounds. Moreover, they are nontoxic. They are plentiful in many plants, roots, and leaves. Succinic acid plays a biochemical role in the citric acid cycle and is capable of donating electrons to the electron transfer chain. Fumaric acid is a food acidulant used since 1946 because it is nontoxic. In addition, it is generally present in beverages and baking powders.[45–47]

In a previous work,[48] we reported on the synthesis (using $Sn(Oct)_2$ as the catalyst) and characterization of novel lipid functionalized PCLs. This study provided a systematic investigation of the synthesis, characterization, and enzymatic degradation of lipid functionalized PCLs.[48]

This study presents ROP of CL utilizing hydroxylated oleic acid derivatives and fumaric, oxalic, and succinic acids. The generalized synthetic process itself has the potential to be very useful in biopolymer field as it can be repeated to prepare biodegradable polymers with good biocompatibility without toxic impurities.

Various techniques have been applied to the physicochemical characterization of the prepared polymers. Namely, proton and carbon nuclear magnetic resonance (NMR), gel permeation chromatography (GPC), modulated differential scanning calorimetry (MDSC), and thermal degradation analysis (TGA).

EXPERIMENTAL

Materials

ε-Caprolactone (2-Oxepanone, >99.0%, Sigma-Aldrich, USA) was dried and distilled over CaH_2 at reduced pressure before use. Formic acid (purity > 96.0%, Sigma-Aldrich, USA), oxalic acid (purity = 97.0%, Sigma-Aldrich, USA), succinic acid (purity = 99.0%, Fluka, USA), and fumaric acid (purity = 99.0%, Fluka, USA) were dried under vacuum prior to being used. Phosphate buffer solution 0.05*M*, pH = 7.0 (Fischer Chemicals, USA), (composed of water (98% of the weight), sodium phosphate dibasic (1.47% of the weight), and dihydrogen potassium phosphate (0.35% of the weight)), oleic acid (>90.0%, Sigma-Aldrich, USA), hydrogen peroxide solution (35 wt % in water, Fischer Chemicals, USA), dichloromethane (>99.0%, Fischer Chemicals, USA), and methanol (>99.0%, Fischer Chemicals, USA) were used as received.

Synthesis of the initiator; *threo*-9,10-dihydroxyoctadecanoic acid

The synthesis of *threo*-9,10-dihydroxyoctadecanoic acid was performed according to literature.[48,49] To a solution of oleic acid (10.0 g, 0.035 mol) and formic acid (29.5 mL, 0.035 mol), approximately 3.4 mL of 34% hydrogen peroxide was added gradually while stirring. After 5–10 min, the reaction became slightly exothermic. In the following 20–30 min, a homogeneous mixture was obtained. The temperature was maintained at 40°C with a cold water bath at the beginning of the reaction, and with warm water at the end. After approximately 3 h, the formic acid was removed by distillation under reduced pressure. The residue in the flask was heated for 1 h at 100°C with an excess of 3*N* aqueous sodium hydroxide, and the hot solution was cautiously poured into an excess of 3*N* hydrochloric acid with stirring. The oil phase was allowed to solidify, and the aqueous layer was discarded. The solid was remelted in a steam bath, and hot water was added and stirred to dissolve any remaining residual salts and water-soluble acids. The solution was again cooled, the oil solidified and the aqueous layer was again discarded, and the solid was broken up and dissolved in 350 mL of 95% ethanol by heating in the steam bath. After crystallization at 0°C for several hours, the product was collected on a filter paper (Whatman, Grade 5, 9 cm, Fischer Chemicals, USA) and dried under vacuum. The product yield was 9.0 g (90%) (m.p. 93°C,

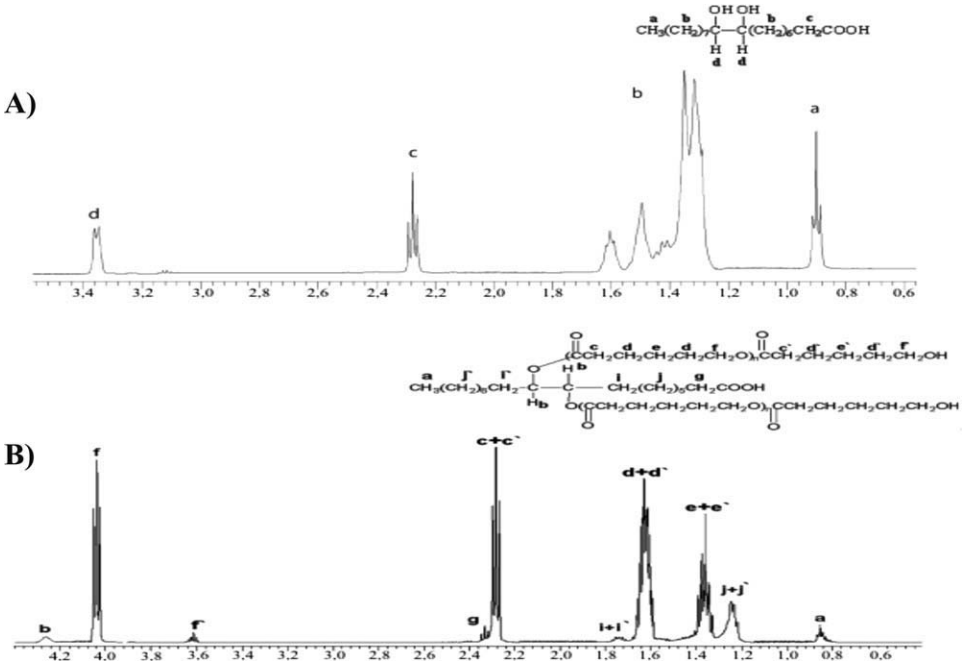


Figure 1 (A) ^{1}H-NMR spectra of *threo*-9,10-dihydroxyoctadecanoic acid, (B) ^{1}H-NMR spectra of functionalized PCLs.

determined by DSC, data not reported).[50] The structure of the product was confirmed by NMR spectra ^{1}H-NMR (500 MHz, CD_3OD-d_4, ppm) δ: 0.91 (t, 3H, —C**H$_3$**), 1.21–1.77 (m, 26H, —C**H$_2$**—), 2.29 (t, 2H, —C**H$_2$**COOH), 3.39 (d, 2H, —C**H**(OH)—C**H**(OH)) [Fig. 1(A)]; and ^{13}C-NMR (125 MHz, CD_3OD-d_4, ppm) δ: 177.72 (COOH), 75.31, 75.29 (CH—OH), 34.97, 33.96, 33.93, 33.06, 30.86, 30.73, 30.66, 30.43, 30.39, 30.21, 27.07, 27.00, 26.10, 23.73, 14.42 (CH_3).[51] No signals derived from impurities were observed in the NMR spectra, indicating that a pure product was obtained [Fig. 1(A)].

Polymerization

PCLs functionalized with oleic acid derivatives were prepared (Tables I and II). For each polymerization, the monomer (CL), initiator (9,10-dihydroxyoctadecanoic acid) and catalyst (oxalic, succinic, or fumaric acid) were placed in 50 mL glass ampoules under nitrogen. The reaction vessel was then maintained at appropriate temperature for 24 h. The cooled product was dissolved in CH_2Cl_2, precipitated in cold methanol, and dried under vacuum for 72 h. The resulting polymers were characterized by ^{1}H and ^{13}C-NMR spectra. NMR data for PCLs: ^{1}H-NMR (500 MHz, $CDCl_3$, ppm) δ 0.87 (t, —C**H$_3$**, initiator), 1.27–1.33 (m, —C**H$_2$**—, initiator), 1.38 (m, —C**H$_2$**—, PCL chain), 1.65 (m, —C**H$_2$**—, PCL chain), 1.74–1.77 (m, —C**H$_2$**—CH—, initiator), 2.30 (t, —C**H$_2$**CO, PCL chain), 2.36 (t, —C**H$_2$**COOH, initiator), 3.65 (t, —C**H$_2$**OH, PCL end group), 4.05 (t, —C**H$_2$**O, PCL chain), 4.25 (*d*, —C**H**—O, initiator) [Fig. 1(B)]. ^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ 173.57, 64.16, 62.44, 34.12, 28.35, 25.53, 24.58. No signals derived from the initiator were observed on ^{13}C-NMR spectra. For comparison, linear PCL was also synthesized utilizing the same reaction conditions for functionalized PCLs but without adding oleic acid derivatives. NMR data for linear PCL: ^{1}H-NMR (500 MHz, $CDCl_3$, ppm) δ 1.34 (m, —C**H$_2$**—, PCL chain), 1.61 (m, —C**H$_2$**—, PCL chain), 2.25 (t, —C**H$_2$**CO, PCL chain), 3.64 (t, —C**H$_2$**OH, PCL end group), 4.05 (t, —C**H$_2$**O, PCL chain). ^{13}C-NMR (125 MHz, $CDCl_3$, ppm) δ 173.77, 64.15, 62.61, 34.12, 28.35, 25.53, 24.58.

In vitro hydrolytic degradation

Polymer films for degradation studies were obtained by compression molding at 80°C, followed by rapid cooling to room temperature. The weight of the square samples was approximately 100 mg, with dimensions of 20 mm × 20 mm and initial thickness about 300 μm. The hydrolytic degradation study was carried out over 16 days,[52] with the samples immersed in 10 mL of buffer solution (0.05*M*, pH = 7.0). The vials were placed in an oven at 37°C. The buffer solution was changed every day to restore the solution to its original level of activity. Each day the specimens were withdrawn from the degradation system and washed with distilled water. They were then vacuum-dried at room temperature for 3 days. All the samples were weighed after drying. For the samples harvested after 8 and 16 days, the surface of each of the films was coated with gold[52] and then

TABLE I
Polymerization of CL with Threo-9.10-dihydroxyoctadecanoic Acid Catalyzed by Organic Acids

Entry[a]	Acid	$[Acid]_{\bigcirc}/[alcohol]_{\bigcirc}$	Yield[b] (%)	M_n[c]	M_w/M_n[c]
1	Oxalic	5	28	8300	1.20
2	Succinic	10	78	10,100	1.40
3	Succinic	5	73	11,500	1.48
4	Succinic	2.5	60	7500	1.43
5	Succinic	1	No polymer	–	–
6	Fumaric	10	95	12,000	1.22
7	Fumaric	5	90	15,200	1.23
8	Fumaric	2.5	85	13,700	1.21
9	Fumaric	1	64	10,100	1.20

[a] $[monomer]_{\bigcirc}/[alcohol]_{\bigcirc}$ molar ratio: 50 : 1.
[b] Methanol-insoluble fraction.
[c] Determined by GPC.

examined by SEM (Philips XL30 ESEM LaB_6, manufactured by FEI Company, OR).

Measurements

The polymerization products were characterized by means of ^1H and ^{13}C-NMR (Varian 500 or 125 MHz, Varian, CA). The NMR spectra of the starting materials and polymers were recorded in $CDCl_3$ or CD_3OD-d_4.

Number-average molecular weights (M_n) and polydispersity index (M_w/M_n) were estimated by GPC and were performed on an Agilent GPC (Agilent series 1200, U.S.A.) equipped with a RI detector. Chloroform ($CHCl_3$) was used as the mobile phase at a flow rate of 1.0 mL/min. A 10-μL amount of 0.4% (w/w) was injected for each analysis. Calibration was performed with polystyrene standards (Polysciences).

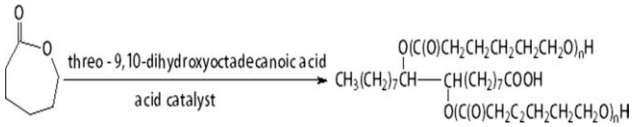
A TA Q-100 modulated DSC (MDSC) system from TA Instruments (New Castle, USA) was used to analyze the thermal transitions of the polymers. The sample was held at 20°C for 3 min to reach its equilibrium state and then was heated to 130°C at a rate of 20°C/min to erase thermal history. For the crystallization curve, the sample was cooled down to −80°C at a constant rate of 5°C/min and kept at this temperature for 3 min to allow for the completion of crystallization. The sample was then heated to 130°C at a constant rate of 3°C/min to obtain the melting curve. All the procedures were performed in a dry nitrogen gas atmosphere. The thermal property measurements were performed in duplicate.

Thermal Gravimetric Analysis was carried out on a TGA Q50 (TA Instruments, New Castle, USA) following the ASTM D3850-94 standard. Approximately 12 mg of sample was loaded in the open platinum pan. The samples were heated from 25 to 600°C under dry nitrogen at constant heating rates of 10°C/min. All the samples were run in duplicate for thermal property measurements.

TABLE II
Polymerization of CL with Threo-9.10-dihydroxyoctadecanoic Acid Catalyzed by Fumaric Acid

Entry[a]	Temperature (°C)	Yield (%)[b]	$M_{n(calc.)}$[c]	$M_{n(NMR)}$[d]	M_n[e]	M_w/M_n[e]
1	70	–	–	–	–	–
2	90	85	4800	4900	10,900	1.25
3	105	90	5100	6500	15,200	1.23
4	120	97	5500	6300	14,100	1.22
5	150	88	5000	6200	13,800	1.46
6[f]	105	83	–	–	13,000	1.11

The molecular characterization of functionalized and unfunctionalized PCLs.
[a] A monomer (CL)/initiator (threo-9.10-dihydroxyoctadecanoic acid) ratio was 50 : 1, A initiator/acid catalyst (fumaric acid) molar ratio was 1 : 5. Polymerizations were carried out for 24 h.
[b] Isolated yield.
[c] The number-average molecular weight was calculated from [CL]/[initiator] and polymer yield.
[d] Obtained from the equation $M_{n(NMR)} = (M_w(M))(DP_{(NMR)}) + M_w(initiator)$; $DP_{(NMR)} = I_{pol}/I_{ter} + 1$, where M_w is the molecular weight of ε-caprolactone monomer or threo-9.10-dihydroxyoctadecanoic acid; I_{pol} and I_{ter}. respesent the integrals obtained by ^1H-NMR from the polymer (4.0 ppm {—CH_2O—] and hydroxyl end group (3.6 ppm [—CH_2OH] peaks, respectively.
[e] The number-average molecular weight was determined by GPC analysis using a polystyrene standard, CH_2Cl_2.
[f] Linear PCL was synthesized using a monomer/catalyst molar ratio 10/1 without adding oleic acid derivatives, polymerization was carried out for 24 h.



Scheme 1 Synthesis of lipid functionalized PCLs.

RESULTS AND DISCUSSION

Synthesis and characterization of lipid functionalized polymers

The effect of acid catalyst on the ROP of CL

ROP is an efficient method for the production of high molecular weight aliphatic polyesters. Using initiators bearing hydroxyl groups and organic acid catalysts, well-defined polymers with controlled architecture can be produced.[53–55] To achieve the required control over molecular weight and polydispersity index, the reactivity of the monomers and/or catalyst-initiator system should be high and well-defined.

Scheme 1 and Table I summarize the results of the polymerization of CL with *threo*-9.10-dihydroxyocadecanoic acid in the presence of fumaric, succinic, or oxalic acids. All are examples of naturally occurring organic acid catalysts, friendly for the environment, human bodies, and biomedical applications. Initially the polymerization was attempted using oxalic acid (ethanedioic acid, $pK_{a1} = 1.27$) as the catalyst for ROP of CL (Entry 1). To the authors' knowledge this is the first example of using of oxalic acid as a catalyst in ROP of CL. In this study, polymers with an average molecular weight $M_n = 8300$, and polydispersity index 1.20 (Table I) were obtained but the yield of the resulting product was very low (28%). For a better understanding of this reaction, we collected the methanol-soluble fraction of the polymerization products and examined its contents via flash chromatography (silica gel; hexane/EtOAc 1 : 1, 1 : 2, 1 : 3, 1 : 4). It was determined that a fraction of unreacted oxalic acid and a fraction of low molecular oligo(ε-caprolactone)s remained. In addition, as the degradation temperature of oxalic acid is relatviely low, 101–102°C, partial decomposition was expected. As previously observed by Korshak and Rogozhin,[56] 25% of oxalic acid is decomposed when heated with ethylene glycol for 5 h at 110°C.

The catalytic effects of succinic acid (butanedioic acid) ($pK_{a1} = 4.19$) and fumaric acid (*trans*-1,2-ethylenedicarboxylic acid) ($pK_{a1} = 3.03$) were next examined, with varying ratios of acids to alcohol (Table I). The polymerization with succinic acid, for the molar ratios of acid to alcohol 5 and 10 (Entries 2 and 3, Table I), resulted in polymers with an average high yield 73–78% and with the M_w/M_n being relatively large (1.40–1.48). When the molar ratio of acid to alcohol was decreased to 2.5 and 1, the effect was not significant (Entries 4 and 5, Table I). In the first case, a polymer with an average low molecular weight (7500) and relatively large polydispersity index of 1.43 (Entry 4) was obtained, whereas in the second case no polymer was observed (Entry 5). From this data, we can deduce that, in general, increasing the molar ratio of succinic acid to alcohol (*threo*-9,10-dihydroxyoctadecanoic acid) increases the yield of the resulting polymer, except for the case when an equimolar ratio of these compounds are used where no polymeric product is obtained. On the contrary, the same equimolar ratio of alcohol to acid catalyst using fumaric acid, produced polymers with an average high molecular weight (10,100) and a relatively low M_w/M_n (1.20, Entry 9). For the other molar ratios (10 and 2.5) the use of fumaric acid also resulted in satisfactory results (Entries 6, 8). However, the optimal run conditions were a 1 : 5*M* ratio of the alcohol to the acid (Entry 7), with a polymer yield of 90%. Consequently, this reaction condition was used for the synthesis of functionalized PCLs and, by varying polymerization temperature, production of PCLs with a desired range of molecular weights were obtained.

Given that the pK_a of the carboxyl acids plays an important role in the catalysis of the ROP of CL,[57] this study tested acids with different pK_a values in the range of 1.20–4.20. It is hypothesized that the carboxyl acids act as a Brönsted acid; activating the CL monomer by protonation of the carbonyl group. Next, the activated monomer is ring-opened in a nucleophilic attack by the aliphatic alcohol moiety of the initiator. The chain propagation of the growing PCL proceeds via the proton-activated monomer.[58] In this study, the use of fumaric acid ($pK_a = 3.03$) resulted in a high polymer yield, low polydispersity index, and high average molecular weight (Table I) when it was applied as an catalyst in the ROP of CL. For succinic ($pK_a = 4.19$) and oxalic acids ($pK_a = 1.29$) less satisfactory results were obtained, as they had lower average-molecular weights (for example oxalic acid $M_n = 8300$, Table I) and broader polydispersity indices (M_w/M_n for succinic acid 1.43–1.48, Table I). From these results, it is suggested that the optimized pK_a value for the ROP of CL is around 3. Song et al.[59] found that suitable pK_a range for the acid-catalyzed polymerization of CL was from 2 to 4. When a stronger acid was used, the polymerization proceeded faster and significant transesterification occurred. Conversely, when a weaker acid was engaged, the weaker nucleophilic ability of catalyst hindered the ROP.[59] Moreover, Casas et al.[60] found that the order of catalytic efficiency of the organic acid catalysts in ROP of CL and VL, was as follows: tartaric acid ($pK_a = 2.98$) > citric acid ($pK_a = 3.08$) > lactic acid ($pK_a = 3.14$) > proline ($pK_a = 1.95$). These results are in the good agreement with those found in this study.

Oleic acid derivatives used as the initiator in this work can also potentially play a catalytic role in the ROP of CL, by virtue of being a carboxylic acid. To demonstrate that the *threo*-9,10-dihydroxyoctadecanoic acid used did not in fact act as a catalyst, we carried out the reaction between it and CL at 105°C. No polymeric product was observed and the reaction mixture consisted only of unreacted starting materials. Moreover, the literature pK_a value for oleic acid is 9.85.[61] This suggests that the oleic acid derivative used here should not act as a catalyst in this reaction

The effect of the reaction temperature on the ROP of CL

Lipid-functionalized PCL samples were synthesized by ROP of CL in the presence of *threo*-9.10-dihydroxyoctadecanoic acid and fumaric acid catalyst at different temperatures. The number-average molecular weight M_n and polydispersity M_w/M_n of the obtained PCLs samples were determined by GPC measurements (Table II). The M_n values of PCLs samples ranged from 10,900 to 15,200 depending on the polymer yield, as the monomer/initiator/catalyst ratio was the same in all cases (50/1/5). The calculated molecular weight ($M_{n(\text{calc.})}$) of the obtained samples was estimated from the monomer/initiator ($[CL]_0/[$*threo*-9.10-dihydroxyoctadecanoic acid$]_0$) ratio and the polymer yield.[62] These values differ from that obtained by GPC and from calculated by ^{1}H-NMR spectra (Table II). Number-average molecular weight obtained by ^{1}H-NMR spectra is close to the theoretical ($M_{n(\text{calc.})}$) and lower (by a (factor $\sim$ 0.45) than the values obtained by GPC. MacLain and Drysdale[63] proposed the factor of 0.45 to convert M_n(GPC) values into the actual number-average molecular weight of PCL. This factor accounts for the difference in hydrodynamic volume between polystyrene and aliphatic polyesters derived from lactones.[64] Other authors have proposed that M_n (GPC) values are larger than the M_n values obtained from ^{1}H-NMR spectra by 15–25% for PCL.[65] In this study, the ratio was ranged from 0.44 to 0.45 and was therefore consistent with the reported correction factor.

In the ^{1}H-NMR spectrum for functionalized PCLs [Fig. 1(B)], signals from methylene end group *g* [$-CH_2COOH$, initiator, $\delta = 2.36$ ppm], *f*′[$-CH_2OH$, PCL end group, $\delta = 3.64$ ppm] and *a* [$-CH_3$, initiator, $\delta = 0.87$ ppm) are evident (^{1}H-NMR spectrum of the initiator, *threo*-9,10-dihydroxyoctadecanoic acid [Fig. 1(A) as the comparison]. The intensity ratio of the signals are *a*: *f*: *g* is 3 : 4 : 2. Thus, the obtained polymers functionalized with oleic acid derivatives possessed two hydroxyl end groups, indicating that *threo*-9.10-dihydroxyoctadecanoic acid acts as effective initiator in the polymerization of CL.

The effect of reaction temperature on fumaric acid catalyzed polymerization of CL was investigated (Table II). At 70°C (Entry 1, Table II) no polymerization process occurred. Zeng et al.[66] found that rate of polymerization of VL in the presence of dipentaerythriol as the initiator and fumaric acid as catalyst was relatively slow at 60 and 70°C. By using 1 : 10 *M* ratio of the initiator to catalyst, they obtained a polymer with $M_{n(\text{calc.})}$ in the range from 7000 to 7250, after 2 and 3 days, respectively. In our study the different molar ratio of the initiator to the organic acid catalyst was probably responsible for this unsatisfactory result. An increase in the reaction temperature (from 90 to 120°C) resulted in an increase of the reaction efficiency (Entries 2–4, Table II). The resulting polymers were found to have relatively high molecular weights (10,900–15,200), low polydispersity indices ranging from 1.22 to 1.25, and high yields (Table II). The monomer conversion and molecular weights of the polymers reached maximum values around 120°C. Conversely, increasing the reaction temperature to 150°C, caused a decrease in the molecular weight of the polymer, suggesting the possible occurrence of transesterification, which is known to increase with an increase of reaction time and temperature.[67] Moreover, it is also known, that the ionic chains ends may undergo transesterification even at moderate temperatures.[68] Therefore, it is suggested that at 150°C, the decrease in molecular weight and broadening polydispersity (M_w/M_n) occurs due to the side transesterification reaction. This data is consistent with that found in the literature.[64,69]

Because the functionalized PCL obtained at 120°C possessed suitable number-average molecular weight, polydispersity index, and sufficient polymer yield (Entry 4, Table II), this procedure was selected for use in further studies.

Thermal properties of the lipid functionalized PCLs

Thermal properties of functionalized PCL and linear PCL were characterized using both MDSC and TGA. The glass-transition temperature (T_g), melting temperature (T_m), enthalpy of fusion (ΔH_m), and degree of crystallinity (X_c) are listed in Table III [Fig. 2(A)].

As evidenced, the functionalized PCL has a lower melting point than that of the linear PCL (52.3°C $\pm$ 0.4°C), which makes it suitable for drug incorporation by the melt molding process (the molecular weights were quite similar for both samples). This suggests that the main influence on melting point is the presence of lipid compound in the macromolecule and the branched structure of functionalized PCL. In addition, the ΔH_m value of functionalized

TABLE III
Thermal Properties of Functionalized and Unfunctionalized PCLs

Sample	T_g[a] (°C)	T_m[a] (°C)	ΔH_m[a] (J/g)	X_c (%)
1[b]	−59.6 ± 0.3	52.3 ± 0.4	71.1 ± 0.5	52.2 ± 0.5
2[c]	−61.1 ± 0.1	54.6 ± 0.3	80.7 ± 0.5	59.3 ± 0.5

[a] Glass-transition temperature, melting temperature, enthalpy of fusion were measured by MDSC (second heating scan).
[b] functionalized PCL − M_n=14100, M_w/M_n=1.22 (run 4, table 2).
[c] linear PCL − M_n = 13000, M_w/M_n = 1.11 (run 6, table 2).

PCL was also smaller that that of the unfunctionalized compound.

The degree of crystallinity (X_c) of functionalized and unfunctionalized polymer was determined from MDSC analysis (Table III), using the enthalpy of fusion (136 [J/g]) for perfectly crystalline PCL.[48,70] X_c of the functionalized PCL was smaller than that of unfunctionalized PCL. Teomin and Domb[41] found that the ΔH_m values for the nonlinear fatty acid terminated poly(sebacic anhydride) were lower to that of unfunctionalized polymer. They explained this occurrence to the presence of the ricinoleic acid-based nonlinear terminals, suggesting therefore that fatty acid terminated polymers are less crystalline relative to poly(sebacic acid).[41] Moreover, Slivniak and Domb[71] detected that increasing of ricinoleic acid content in lactic acid and ricinolic acid based copolyesters, decreased the melting point and the crystallinity of the polymers. Therefore, the content of fatty acid derivatives in the macromolecule and crystalline imperfections caused by the branched structure of the polymer are both responsible for the lower values of T_m, ΔH_m, and X_c of functionalized PCLs. This is in accordance with previous studies.[48,72]

The glass transition temperature for lipid-functionalized PCL was −59.6°C ± 0.3°C, while for unfunctionalized polymer it was −61°C ± 1°C, implying that the fatty acid derivatives had little influence on the glass-transition temperature of the functionalized PCL (Table III).

DTGA curves of the functionalized with oleic acid derivatives PCL and the unfunctionalized PCL are shown in Figure 2(B). The thermal decompositions started at approximately 350°C and ended at 470°C for both, the functionalized and unfunctionalized PCL. DTGA data revealed one main degradation process with an inflection point at 410°C ± 1°C for functionalized PCL and at 417°C ± 1°C for unfunctionalized PCL. However, minor peaks at higher temperatures suggest a thermal degradation involving two consecutive mechanisms. Recent studies have revealed[73,74] that the first main stage of the decomposition involves a consistent rupture of the polyester chain via a pyrolysis reaction and secondly, production of monomers (CL) as result of an unzipping, depolymerization process. Previous work,[48] on functionalized with oleic acid derivatives PCL, found that the thermal degradation of the polymers proceeded by one main degradation mechanism, but the results do not preclude the possibility of a two-stage degradation. The same occurrence was discovered by Su et al.[75] In this study, the minor peak around 450°C provides strong evidence for a two-stage degradation process. The details of the mechanism of the thermal degradation of the functionalized PCL are under current investigation.

Finally, this result suggests that the thermal degradation of the polymer is significantly affected by the presence of the lipid compounds in the macromolecule (the average-number molecular weights of the polymers was approximately the same), resulting in lower stability of the polymer and degradation at lower temperatures compared to the unfunctionalized polymer.

Hydrolytic degradation

Hydrolysis of the functionalized PCL was studied in comparison with unfunctionalized PCL by monitoring the weight loss of the samples over sixteen days (Fig. 3). The weight loss of both samples after one day of hydrolytic degradation was unchanged.

Unfunctionalized PCL started decreasing in weight after 2 days of hydrolytic degradation (0.1 wt %, Fig. 3) and after 8 days the weight loss reached a

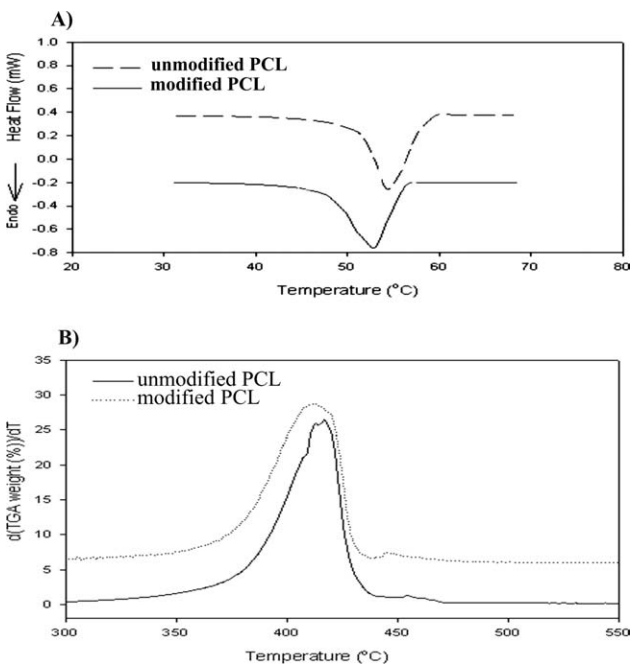


Figure 2 (A) DSC thermograms of functionalized and unfunctionalized PCLs: cooling at the constant rate 5°C/min; (B) DTGA curves of thermal degradation of functionalized and unfunctionalized PCLs.

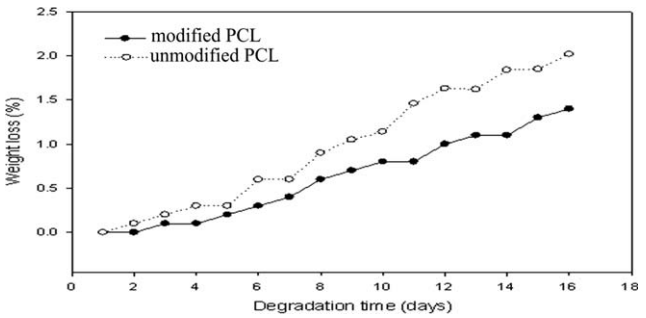


Figure 3 The weight loss of functionalized and unfunctionalized PCLs during the course of hydrolytic degradation.

value of 0.9 wt %. In comparison, the functionalized polymer presented no weight loss after 2 days and a weight loss of only 0.6 wt % after 8 days. After 16 days of hydrolytic degradation the unfunctionalized PCL recorded a weight loss of 2.0 wt % while a significantly lower weight loss (1.4 wt %) was observed for the sample of functionalized PCL. This may be due to the presence of lipid fatty acid derivatives in the polymer molecule.

The surfaces of all samples were examined by SEM; before and after 8 and 16 days of hydrolytic degradation (Fig. 4).

Before degradation, the unfunctionalized PCL exhibited a very flat surface unlike the functionalized PCL, which displayed a rough and porous surface. This initial difference in surface texture could be attributed to the presence of the lipid compound in the macromolecule and its influence on the surface morphology of the polymer. Similarly, a porous surface of a polymer functionalized with hydroxyl fatty acid derivatives, was observed by Kumar and coworkers.[76] After 8 days of degradation, erosion at the surface of the samples was observed by SEM. In the micrographs, rough and porous structures were observed on the surface of the functionalized polymer, whereas minimal pores and roughness were observed on the surface of unfunctionalized PCL [Fig. 4(B) I, II]. After 16 days of degradation, the functionalized PCL exhibited uniformly rough and porous surfaces, while only small holes were observed on the surface of unfunctionalized PCL [Fig. 4(C) I, II].

Clearly, from the degradation experiment, the degradation rate is modified by the presence of oleic acid derivatives in the polymer molecule. Unfunctionalized PCL degraded faster than the functionalized PCL, but SEM pictures of degrading functionalized PCL at different time intervals, revealed the increase in porosity over time [Fig. 4(A–C) **I**]. Because of the porous structure of the functionalized polymers, which can gradually widen, a greater amount of water may penetrate into devices produced from functionalized PLC. This occurrence of pores in the samples under hydrolytic degradation may greatly benefit drug release behavior.[76]

Even if PCL-based biomaterials have found broad applications in pharmacological and biomedical fields,

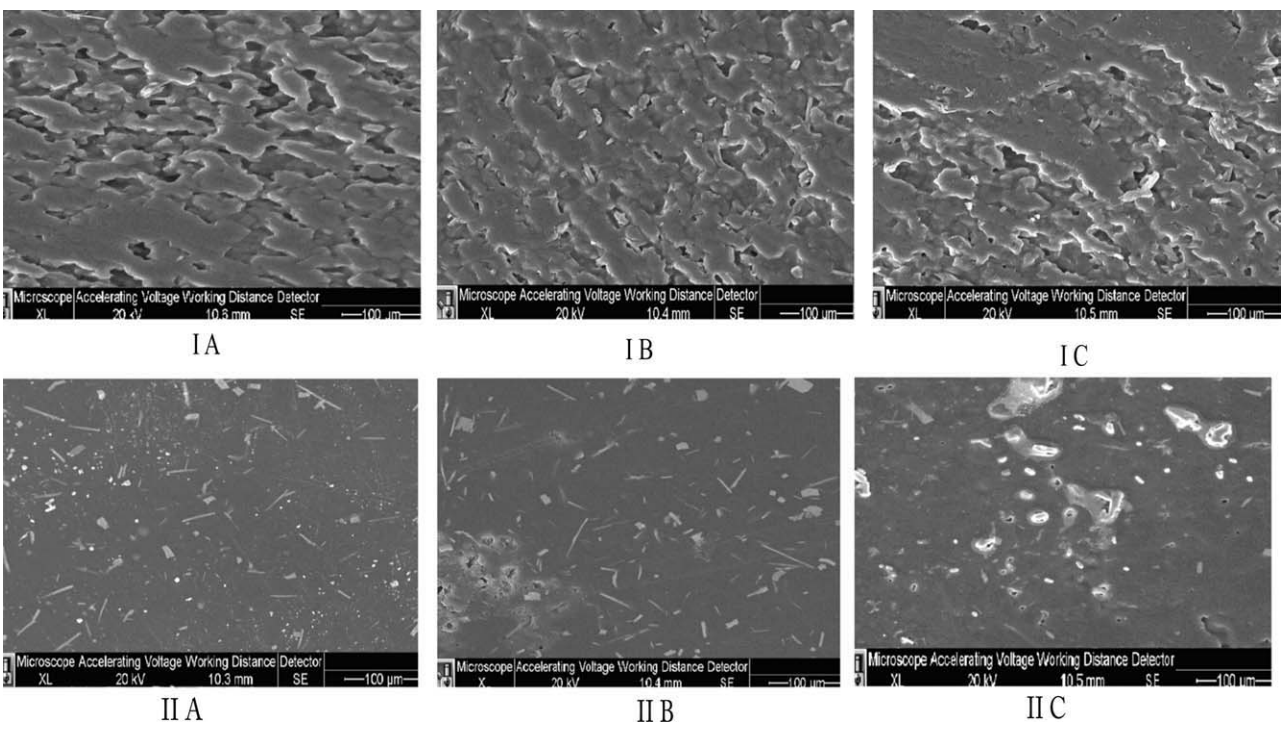


Figure 4 SEM images of functionalized **I** and unfunctionalized **II** polymers: (A) before degradation, (B) after hydrolytic degradation for 8 days, and (C) after hydrolytic degradation for 16 days.

their *in vitro* and *in vivo* degradation rates usually cannot be controlled because of the crystallinity and the hydrophobicity of their polymer backbone. These drawbacks can be overcome through the adjustment of the polymer hydrophilicity-hydrophobicity balance, copolymerization or blending with other polymers, and the control of branched macromolecular architecture.[77,78] Recently, it has been reported that branched copolymers, composed from hydrophobic and hydrophilic parts, exhibited improved properties as drug carriers.[79] In our study, oleic acid derivatives of PCL chains may improve drug encapsulation properties due to the branched structure of the polymer. Although the presence of fatty acid molecule in the polymer molecule increase hydrophobicity, which might limit its application in biomedical field, this problem can be solved by incorporation of some hydrophilic parts into the modified PCLs molecules. This effort is ongoing in our laboratory.

CONCLUSIONS

In this study, the ring-opening polymerization of CL by organic acids catalyst and oleic acid derivatives initiator systems were investigated. The polymerizations were efficiently catalyzed by succinic and fumaric acid. The products were isolated by precipitation of the polyester products in cold methanol. In addition, the ROPs were performed without solvent and the need of an inert atmosphere.

Because of the incorporation of fatty acid molecules, functionalized polymers exhibited less crystallinity and lower melting points relative to the unfunctionazlied PCL. The degradation profile was also affected by the presence of oleic acid derivatives in the polymer molecule. The degradation rate of functionalized PCL was slower when compared to unfunctionalized polymer, but a clear increase in porosity of the functionalized polymers was observed over time. This occurrence might be beneficial in drug release profile.

Finally, the organic acid catalyzed ROPs were operationally simple, inexpensive, and environmentally friendly. More importantly, the metal-free organic acid catalysis used in this study is nontoxic and therefore the biodegradable polyesters obtained by the synthetic procedure are suitable as biomaterials.

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