Phenylphosphinic Acid Initiated Ring Opening Insertion Polymerization of ε-Caprolactone

Shaojun Cai\textsuperscript{a,b}, Lijian Liu\textsuperscript{b}, Xueqing Liu\textsuperscript{c}, and Jiyan Liu\textsuperscript{a}

Abstract — Phenylphosphinic acid (Ph(O)P(H)OH) initiated ring opening insertion polymerization (ROIP) of ε-caprolactone (ε-CL) was investigated. The metal-free ROIP occurred through a monomer-activated mechanism without any catalyst. The activated-monomer was traced by \textsuperscript{31}P NMR and GPC spectra and the structure of resultant PCL was confirmed by \textsuperscript{1}H NMR and MALDI-TOF analysis. PCL with $M_n$ of 8000 g/mol and polydispersity index of 1.45 was obtained after 60 min conventional heating whereas that of microwave heating was 6230 g/mol and 1.99.

Keywords — ε-caprolactone, metal-free, phenylphosphinic acid, ring opening insertion polymerization.

Cite this article as: Cai SJ, Liu LJ, Liu XQ and Liu JY. Phenylphosphinic Acid Initiated Ring Opening Insertion Polymerization of ε-Caprolactone CRC 2014. In press

I. INTRODUCTION

POLY(ε-caprolactone) (PCL) is one of the biodegradable polyesters that provides many potential biomedical applications because of its good biodegradability and biocompatibility. PCL is generally synthesized by the ring-opening polymerization (ROP) of ε-caprolactone (ε-CL) in the presence of catalyst containing aluminum, tin, zinc, and rare-earth metals. Metal alkoxides, especially aluminum alkoxides, are known as the effective initiators of the polymerization of lactones.\textsuperscript{1,16} When metal alkoxides are used as initiators, a two-step “coordination-insertion” mechanism which consists of lactone complexation to the initiator followed by monomer insertion into the metal-oxygen bond, is proposed.

In addition, each molecule of R\textsubscript{2}AlOR’ initiates one macromolecule and only R’O- groups are involved in initiation and transferred to the polymer chain quantitatively as the head end groups.\textsuperscript{2}

However, there are some problems in the polymers obtained by ROP using organometallic catalysts, including incomplete catalyst removal because of the difficulty in removing the metal contaminant from the resultant polymers. Hence, the use of metal catalyst conflicted with extending the practical biomedical applications of PCL, and the metal-free organocatalytic ROPs of cyclic esters\textsuperscript{7,14} attracted much more interest. Nucleophilic phosphines have been used as transesterification catalysts for the controlled ROP of lactide and a phosphorus-activated lactide complex was formed during the reaction.\textsuperscript{7} These organic catalysts must be used in combination with an initiator, such as an alcohol, to generate an alkalolate ester α-end group upon ROP. Recently, we investigated a hydrogen-phosphonate (diisopropyl hydrogen phosphonate, diiPro-HP) initiated ring opening insertion polymerization (ROIP) of ε-CL without any catalyst.\textsuperscript{15,16} It was revealed that the diiPro-HP initiated ROIP of ε-CL occurred by a coordination-insertion mechanism, in which an intermediate was formed through the cleavage of acyl-oxygen bond and the coordination of carbonyl carbon and acyl oxygen of ε-CL to phosphorus atom. DiiPro-HP incorporated into the product to form a diiPro-HP-incorporated product, which could further initiate the ROP of ε-CL with the unchanged nucleophilic center (O=P-H). The mechanism is similar with that of aluminum alkoxides mentioned above. However, in the ROIP of ε-CL initiated by H-phosphonate, whether P-R groups of H-phosphonate could also be involved in initiation and transferred to the polymer chain as end groups just like P-OR groups, has not been discussed. Furthermore, after finding that CL segments could insert into the P-O bond of hydrogen-phosphonate with alkoxy (P-OR) as end group, we wonder if CL segments could also insert into the P-O bond of hydrogen-phosphonate with hydroxy (P-OH) as end group. In this work, we chose phenylphosphinic acid (PPA, Ph(O)P(H)OH), a hydrogen-phosphonate which contains both P-alkyl and P-OH as end groups as initiator for the ROP of ε-CL.

Microwave synthesis has attracted a considerable amount of attentions as a newly developed green method in contemporary chemistry\textsuperscript{17} and the reaction time could be dramatically reduced by microwave. The application of microwave energy to the
ring-opening polymerization of \( \varepsilon \)-CL \cite{18-22} has also attracted much interest for the greatly enhancement of \( \varepsilon \)-CL ROP by microwave irradiation \cite{19-21}. For further investigation into the new metal-free approach to the ROP of \( \varepsilon \)-CL initiated by hydrogen phosphonates, we described the microwave-assisted ROIP of \( \varepsilon \)-CL initiated by PPA with different molar ratios in detail and compared the results with those obtained for the reaction conducted by conventional heating.

II. METHODS

A. Materials

Commercial \( \varepsilon \)-CL (99.91%, Solvay) was dried over CaH\(_2\) for 72 hours at room temperature and distilled under reduced pressure prior to use. All the other reagents were of analytical grade and used as received.

B. Microwave equipment

A multimode microwave oven (Whirlpool-VIP273F, 2.45 GHz, 850 W) was used in the study, which was equipped with a carefully shielded thermocouple and a data collector for the temperature recording.

C. Measurements

1) NMR experiments

Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were obtained on Mercury VX-300 (Varian, 300 MHz) apparatus using CDCl\(_3\) as solvent and TMS as the internal standard. \(^3\)P NMR spectra were detected on Inova-600 (Varian, 600 MHz) apparatus using CDCl\(_3\) as solvent and 85\% H\(_3\)PO\(_4\) as the internal standard.

2) GPC experiments

Number-average molecular weight (\(M_n\)) and polydispersity index (PDI, \(M_n/M_w\)) of the product was determined by gel permeation chromatography (GPC) calibrated by polystyrene standards. The GPC system was equipped with a Waters 717 plus autosampler, a Waters 1515 isocratic HPLC pump, a Waters 2414 refractive index detector, and Shodex columns. Chloroform was used as eluent at a flow rate of 1.0 mL/min. The temperatures of the columns and detector were both 30 °C. The experimental molar mass was converted following the equation of \(M_n (PCL) = 0.68 \times M_n (PS)\) \cite{23}.

3) MALDI-TOF experiments

Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS) analyses were performed on a Voyager-DE STR time-of-flight mass spectrometer (Applied Biosystems) equipped with a nitrogen laser (337 nm, 3 ns pulse width). All mass spectra were acquired in the positive reflectron mode using delayed extraction at an acceleration voltage of 20 kV. The delay time used was 500 ns and each mass spectrum consists of 200 laser shots. External mass calibration was performed by using protein standards from a Peptide Mass Standard Kit (Applied Biosystems) and a three-point calibration method, using Angiotension I (m=1296.69 Da), ACTH (clip 1-17) (m=2093.09 Da), and ACTH (clip 18-39) (m=2465.20 Da). Equal volumes of saturated solutions of CHCA matrix prepared in 70% ACN/ 0.1% TFA/5mM ammonium dihydrogen phosphate were used and mixed with each sample solution (1:1 by volume). Finally, 1 \(\mu\)L of the mixture was deposited onto a stainless steel MALDI target plate and air-dried.

D. Microwave-Assisted Ring Opening Insertion Polymerization of \( \varepsilon \)-CL

A mixture of \( \varepsilon \)-CL and PPA was added into an ampoule and sealed after three dry-argon/exhaust cycles in vacuum (<50Pa). The ampoule was irradiated by microwaves for predetermined time. The temperature of the reaction mixture was measured by a thermocouple, regulated by a digital temperature-controlled instrument and recorded by a computer.

E. Conventional Heated Ring Opening Insertion Polymerization of \( \varepsilon \)-CL

The sealed ampoule with a mixture of \( \varepsilon \)-CL and PPA was immersed in a salt bath for predetermined time. The temperature was recorded with the same instruments in the ROIP by microwave irradiation.

III. RESULTS AND DISCUSSION

A. Microwave-Assisted ROIP of \( \varepsilon \)-CL

1) Characterization and Reaction Mechanism

PPA was an effective initiator for the ROP of \( \varepsilon \)-CL, after 10 min microwave heating (MH), PCL with \(M_n\) of 3640 g/mol and monomer conversion of 32.75\% was obtained (molar ratio of PPA to \( \varepsilon \)-CL: 1:25). The structure of the product of ROIP was confirmed by \(^1\)H NMR. As shown in Fig. 1a, the proton signals of P-H in Ph(O)P(H)OH site at 6.69 and 8.59 ppm. The chemical shift changes of P-H in Ph(O)P(H)OH (B and B', from 6.69 and 8.59 ppm to 6.65 and 8.54 ppm) during the ROIP of \( \varepsilon \)-CL indicated the structurally change of Ph(O)P(H)OH and the insertion of \( \varepsilon \)-CL into Ph(O)P(H)OH. It was obvious that there was no shift of the proton signals of P-Phenyl in Ph(O)P(H)OH (Fig. 1b, A and A'), which meant that the P-Phenyl bond was stable in the reaction.

Evidences were also showed by \(^3\)P NMR and MALDI-TOF MASS measurements results. The \(^3\)P signals of the crude product (Fig. 1c) are at 25.4 and 26.5 ppm, which are different from that of Ph(O)P(H)OH (23.6 ppm) and di-PCL-inserted hydrogen phosphate (8.9 ppm).\(^{18}\) The MALDI-TOF result (Fig. 2) shows that the [m+23 (Na\(^+\))/z for the crude product ranges from 735 to 849, 963, …, and 1875, the interval between the adjacent values (114) is equal to the molar mass of a CL monomer unit. The results indicate that the crude product is a mixture of PCL segments with various chain lengths. The value of each detected [m+23 (Na\(^+\))/z follows the equation below:

\[
[m+23 (Na^+)/z = 1/\varepsilon-CL + n + 142 (Ph(O)P(H)OH)+23 (Na^+)]
\]

This matches well with that of the theoretic calculation from the structure of Ph(O)P(H)\(-[O(CH_2)\_3C(O)\_]-n\)-OH (\(n\) is the number of CL units in a PCL segment). For example, the \([m+23 (Na^+)/z of 735, 849, and 963 presents that PCL segments with \(n\) of 5, 6, and 7, respectively. The results
indicated that one CL monomer molecule inserted into the linkage between the phosphorous atom and hydroxyl group of Ph(O)P(H)OH at first and then the CL molecules inserted into the mono-CL-inserted Ph(O)P(H)OH one by one, which makes the PCL chain propagated via the ring opening insertion mechanism as shown in Scheme 1.

In our research, PCL-inserted-Ph(O)P(H)OH, which was formed through the incorporation of Ph(O)P(H)OH and e-CL by a monomer-activated mechanism, could further initiate the ROIP with the same nucleophilic center (O=P-H) (Scheme 1b). This could be explained by the tautomerization of hydrogen phosphonate that gave a phosphine-like structure (Scheme 1a). The initiator in the reaction was a general designation of a series of analogues containing the identical nucleophilic center that were produced as the PCL-inserted-Ph(O)P(H)OH. The activated-CL is identified by $^{31}$P NMR spectra of the crude product obtained from the ROIP of e-CL by MH with the molar ratio of 1:50 (Ph(O)P(H)OH to e-CL) (Fig. 3). There are two $^{31}$P signals in the spectra (between 23.0 and 27.0 ppm) which are both different from that of Ph(O)P(H)OH (23.6 ppm). The $^{31}$P signal sited at 26.5 ppm with increasing relative intensity as the reaction proceeding, corresponded to the linear PCL-inserted-Ph(O)P(H)OH with the molecular structure of Ph(O)P(H)-\[O(CH_{2})_{5}C(O)_{n}-OH. The other signals ranged from 23.9 to 25.5 ppm, with relative intensity decreasing in the process, could be assigned to the activated-CL formed through the coordination of CL and Ph(O)P(H)OH. The mechanism was further confirmed by GPC traces (Fig. 3). PCL-inserted-Ph(O)P(H)OH (peaks appeared before 29 min) formed via the intermediate of activated-CL (29 to 32 min). As the reaction proceeded, the signal intensities of monomer CL (32 to 33 min) and activated-CL both decreased whereas that of PCL increased. The change trends were the same with that showed by $^{31}$P NMR spectra. After 10 min MH, Ph(O)P(H)OH was consumed out and transformed to phosphorus-activated-CL. Then the activated-CL converted to product PCL (PCL-inserted-Ph(O)P(H)OH) with the consuming of monomer CL via the ROIP mechanism.
2) Microwave-Assisted ROIP of ε-CL with different molar ratios of PPA

Fig. 4 showed the monomer conversion-time curve of PPA-initiated ROIP of ε-CL under microwave irradiation. With the molar ratio of initiator to monomer (I/M) of 1:25 and 1:50, monomer conversions were 32.75% and 25.52% (10 min); 49.09% and 51.76% (30 min); 54.12% and 63.97% (40 min); 67.41% and 84.05% (60 min), respectively. At the early stage of the reaction (before 20 min), higher initiator concentration benefited the formation of active centers, which caused a higher monomer conversion. After 20 min, monomer conversions increased linearly with reaction time, but the system with lower initiator concentration (1:50) had a higher growth rate. Furthermore, the $M_n$ of resultant PCL (Fig. 5) of I/M=1:50 had a sustainable growth with the monomer consumption (3060 g/mol to 7330 g/mol) and that of I/M=1:25 basically remained level (3640 g/mol to 3210 g/mol to 3740 g/mol). These could be explained by the formation of higher concentrations of the monoester of phosphinic acid which may hamper the high-molecular-weight polymer formation and catalyze the side reactions.\(^{25}\)

![Molar ratio of Ph(O)P(H)OH to ε-CL](image1)

**Fig. 4.** Monomer conversion-time curve of Ph(O)P(H)OH-initiated ROIP of ε-CL under microwave irradiation.

![Molar ratio of Ph(O)P(H)OH to ε-CL](image2)

**Fig. 5.** $M_n$-time curve of Ph(O)P(H)OH-initiated ROIP of ε-CL under microwave irradiation.

B. Conventional Heating ROIP of ε-CL

The ROIP of ε-CL initiated by PPA under conventional heating (CH) at the same temperature with that of MH was conducted and compared with the microwave ROIP. The reaction mixture could be heated to a high temperature by CH as fast as that by MH (Fig. 6). The resultant PCL $M_n$ of the ROIP by CH increased from 4730 g/mol to 8000 g/mol with the monomer conversion increased from 45.31% to 81.93% (Fig. 7).

![Temperature vs. Polymerization time](image3)

**Fig. 6.** Thermal behaviors of the ROIP mixtures by CH and MH (molar ratio of Ph(O)P(H)OH to ε-CL: 1:50).

![Conversion vs. Polymerization time](image4)

**Fig. 7.** Monomer conversion-time and $M_n$-time curve of Ph(O)P(H)OH-initiated ROIP of ε-CL by conventional heating.

The monomer conversion of ROIP by CH and MH (molar ratio of Ph(O)P(H)OH to ε-CL: 1:50) was from 45.31% to 81.93% and 25.52% to 84.05% with the $M_n$ ranged from 4730 g/mol to 8000 g/mol and 3060 g/mol to 7330 g/mol, respectively (TABLE I). Schubert and coworkers\(^{26}\) demonstrated that the living cationic ROP of
2-ethyl-2-oxazoline and 2-phenyl-2-oxazoline was accelerated under conventional heating. The conventionally heated pressure polymerizations presented a similar acceleration as microwave-assisted pressure polymerizations did. Li et al. revealed the enhancement of flash conventional heating in the ROP of ε-CL with Sn(Oct)\textsubscript{2} as a catalyst matched well with that by MH. Many reactions were greatly enhanced by microwave irradiation, however, in the majority of the cases reason for the observed rate enhancements is a purely thermal/kinetic effect, that is, a consequence of the high reaction temperatures that can rapidly be attained.\textsuperscript{27-28} In the ROIP of ε-CL initiated by Ph(Ο)P(Ο)H\textsubscript{2}OH under CH, PCL with a higher \textit{M}_\text{n} and narrower PDI (1.36–1.52) was obtained. At 10 min, the monomer conversion of CH (45.31%) was much higher than that by MH (25.52%), which indicated CH was beneficial to the interaction between CL and Ph(Ο)P(Ο)H\textsubscript{2}OH in the initiation period. It agreed well with the heating curves of CH and MH (Fig. 6): the temperature of CH maximized at 6 min, fell back a little and then was close to that of MH, which meant the difference between the two systems mainly focused on the early stage of reaction. This related to the competition between the formation of propagating species and chain propagation. At the early stage of the ROP under CH, monomer was consumed mainly in the resultant PCL with higher PDI (1.37–1.38) after 40 min. Compared with MH, CH was better for chain propagation after 40 min and ROIP under CH resulted in the higher conversion in the initiation stage (25.52% to 32.75%), but also resulted in lower monomer conversion and \textit{M}_\text{n} with broader PDI after 40 min. Compared with MH, CH was better for chain propagation after 40 min and ROIP under CH resulted in the resultant PCL with higher \textit{M}_\text{n} and narrower PDI.

**IV. CONCLUSIONS**

Phenylphosphinic acid initiated ring opening insertion polymerization of ε-CL with different molar ratios under microwave and conventional heating has been demonstrated. The ROIP was conducted efficiently without any catalyst. Only the -OR groups of hydrogen-phosphonate are involved in initiation process and transferred to the polymer chain as end groups in the ROIP and CL segments could also insert into the P-O bond of hydrogen-phosphonate with hydroxy (P-OH) as end group. The higher initiator/monomer ratio could lead to the higher conversion in the initiation stage (25.52% to 32.75%), but also resulted in lower monomer conversion and \textit{M}_\text{n} with broader PDI after 40 min. Compared with MH, CH was better for chain propagation after 40 min and ROIP under CH resulted in the resultant PCL with higher \textit{M}_\text{n} and narrower PDI.

**References**


Shaojun. Cai earned his Bachelor's Degree (applied chemistry) in 2005 and his PhD (polymer chemistry and physics) in 2010, both from the College of Chemistry and Molecular Sciences, Wuhan University, China. Since 2011, he have been a lecturer at the Key Laboratory of Optoelectronic Chemical Materials and Devices of Ministry of Education, School of Chemical and Environmental Engineering, Jianghan University, Wuhan, China. His research interest include the synthesis of biodegradable polymers and flame retardant/heat resistant polymers.