# Communications to the Editor

## Ring-Opening Polymerization of ϵ-Caprolactone Initiated by Natural Amino Acids

**Jiyan Liu and Lijian Liu***

*Department of Polymer Science, College of Chemistry and Molecular Science, Wuhan University, Key Laboratory of Biomedical Polymers (Wuhan University), Ministry of Education, Wuhan 430072, China*

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**Introduction.** Poly(ϵ-caprolactone) (PCL) is currently being investigated for use in medical devices and pharmaceutical controlled release systems because of its biocompatibility, biodegradability, and good drug penetrability.[1−3] PCL is usually synthesized by ring-opening polymerization (ROP) of ϵ-caprolactone (ϵ-CL), which is carried out in the presence of metal-contained[4−8] or metal-free compounds.[9−13] The ROP can be initiated by active hydrogen of amine and alcohol,[14−16] and the effect of active hydrogen on the polymerization is enhanced by an organic acid. Rozenberg obtained PCL with molecular weight over 8000 g/mol from the polymerization of ϵ-CL initiated by aniline in the presence of a protonic acid.[17] Xie et al. revealed that the polymerization of ϵ-CL in the presence of hydroxyl acid was a hydroxyl-initiated reaction, and the carboxyl group did not initiate but accelerated the polymerization.[18] Sanda et al. carried out the polymerization of ϵ-CL with alcohols as initiators and fumaric acid as an activator of the monomer.[19]

Recently, we investigated the ROP of ϵ-CL in the presence of natural amino acids considering that they are essential components in human nutrition, and the biocompatibility and in vivo safety of thus-obtained PCL must be satisfying for medical and pharmaceutical purpose. The results, which are presented in this paper, indicate that polymerization of ϵ-CL was initiated by the amino group of amino acid (Scheme 1).

**Experimental Section.** ϵ-CL (Aldrich) was dried over calcium hydride for 48 h and distilled under reduced pressure. 1,4-Dioxane was purified by distillation after drying with sodium. All other materials were analytical grade and used as received.

$^1$H NMR spectra of PCL were recorded on a Mercury VX-300 (300 Hz) apparatus with tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. Number-average molecular weight by GPC ($M_{n,GPC}$) and polydispersity index ($M_w/M_n$) of PCL were measured with a Waters high-performance liquid chromatography system equipped with a model 2690D separation module, a model 2410 refractive index detector, and Shodex K802.5 (pore size 60 Å) and Shodex K805 (pore size 500 Å) columns in series. The measurements were performed in $CHCl_3$ at 35 °C and calibrated with polystyrene standards, and the value of $M_{n,GPC}$ was determined by the well-known universal calibration method using a viscosity detector.

*Ring-Opening Polymerization of ϵ-CL.* ϵ-CL was mixed with a certain amount of amino acid, and the mixture in a vacuum-sealed ampule (40 Pa) was stirred at 160 °C for the appointed time. A part of the reaction mixture was taken out for direct analysis, and the residue was purified by dissolving it in tetrahydrofuran (THF) and then being precipitated with a mixture of $CH_3OH$ and $H_2O$ (v/v = 4:1) at room temperature. The precipitate was filtrated and dried in a vacuum at 30 °C for 24 h.

*Determination of Unreacted Amino Acid in Reaction Mixture.* 1 g of reaction mixture was dissolved in 50 mL of chloroform, and then 10 mL of water was added to extract the unreacted amino acid, which was analyzed by the method of ninhydrin−ascorbic acid with a Shimadzu 2401 ultraviolet−visible spectrometer.[20]

*Titration of Carboxyl End Group in PCL.* Purified PCL was dissolved in a mixture solvent of isopropyl alcohol:1,4-dioxane = 1:4 (v/v), and the solution was titrated with 0.008 mol/L potassium hydroxide/isopropyl alcohol:1,4-dioxane = 1:4 (v/v) using 1% phenolphthalein/ pyridine as indicator.

**Results and Discussion.** The ROP of ϵ-CL in the presence of L-alanine, L-proline, L-phenylalanine, and L-leucine was investigated with a molar ratio of ϵ-CL to amino acid ([ϵ-CL]/[amino acid]) ranging from 30 to 200, and the temperature of the polymerization reaction was 160 °C. The reaction time for molar ratio 30, 50, and 100 was 24 h, but for 200 it was 48 h. The results are summarized in Table 1.

The ROP could take place with molar ratio 30, but $M_{n,GPC}$ of PCL was below 4000 g/mol with $M_w/M_n$ from 1.67 to 1.85 for the four amino acids, which was improved at larger molar ratio. $M_{n,GPC}$ by L-phenylalanine increased from 3900 to 6800, 13 300, and 25 200 g/mol when the molar ratio enlarged from 30 to 50, 100, and 200, and that by L-leucine was 6300, 12 500, and 26 800 g/mol, respectively. However, $M_w/M_n$ decreased to 1.69, 1.67, and 1.54 for L-phenylalanine and 1.61, 1.56, and 1.50 for L-leucine.

$M_{n,GPC}$ was very close to the calculated value ($M_{n,calcd}$) from the initial $[\epsilon\text{-CL}]_0$/[amino acid], which confirmed that most amino acid incorporated into the polymer. The deduction was supported by the determination of residue of amino acid in the reaction mixture after polymerization finished. No amino acid was detected for the reaction mixture with molar ratio 50, 100, and 200. For molar ratio 30, only 0.9−2.7% amino acid was left. The results indicate that the polymerization was initiated by the four amino acids.

The same conclusion comes from the structure data of obtained PCL by $^1$H NMR spectroscopy. Figure 1 illustrates the $^1$H NMR spectrum of PCL initiated by

* Corresponding author: e-mail liulj@chem.whu.edu.cn.

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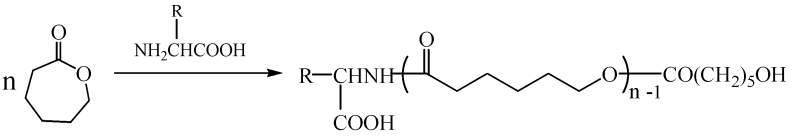
**Scheme 1**




R
NH$_2$CHCOOH = L-alanine, L-leucine, L-phenylalanine, L-proline

**Table 1. Results of the Polymerization of ϵ-CL Initiated by Natural Amino Acid (160 °C)**

| entry | amino acid | [ϵ-CL]/[amino acid] | reaction time (h) | conv[a] (%) | α[b] (%) | $M_{n,calcd}$[c] ($\times10^{-3}$ g/mol) | $M_{n,NMR}$[d] ($\times10^{-3}$ g/mol) | $M_{n,GPC}$ ($\times10^{-3}$ g/mol) | $M_w/M_n$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | L-alanine | 30 | 24 | 96 | 2.7 | 3.4 | 3.6 | 3.7 | 1.85 |
| 2 | L-proline | 30 | 24 | 97 | 1.4 | 3.4 | | 3.6 | 1.67 |
| 3 | L-phenylalanine | 30 | 24 | 100 | 0.6 | 3.4 | 3.5 | 3.9 | 1.73 |
| | | | | | | | | 3.8[e] | 1.89[e] |
| 4 | L-phenylalanine | 50 | 24 | 100 | 0 | 5.7 | 5.5 | 6.8 | 1.69 |
| | | | | | | | | 6.7[e] | 1.85[e] |
| 5 | L-phenylalanine | 100 | 24 | 97 | 0 | 11.1 | | 13.3 | 1.67 |
| 6 | L-phenylalanine | 200 | 48 | 98 | 0 | 22.4 | | 25.2 | 1.54 |
| 7 | L-leucine | 30 | 24 | 99 | 0.9 | 3.4 | 3.4 | 3.9 | 1.68 |
| 8 | L-leucine | 50 | 24 | 100 | 0 | 5.7 | 5.9 | 6.3 | 1.61 |
| 9 | L-leucine | 100 | 24 | 99 | 0 | 11.3 | | 12.5 | 1.56 |
| 10 | L-leucine | 200 | 48 | 100 | 0 | 22.8 | | 26.8 | 1.50 |

[a] Monomer conversion determined by $^1$H NMR. [b] Unreacted amino acid measured by the method of ninhydrin−ascorbic acid. [c] $M_{n,calcd} = [\epsilon\text{-CL}]_0/[\text{amino acid}] \times \text{conv} \times 114.14$ (molecular weight of ϵ-CL) /(1 − α%). [d] Estimated from the integration of proton signal in terminal methyl (L-alanine and L-leucine) or methylene (L-phenylalanine) group of amino acid and the methylene proton signal of the main chain. [e] The reaction mixture without purifying.

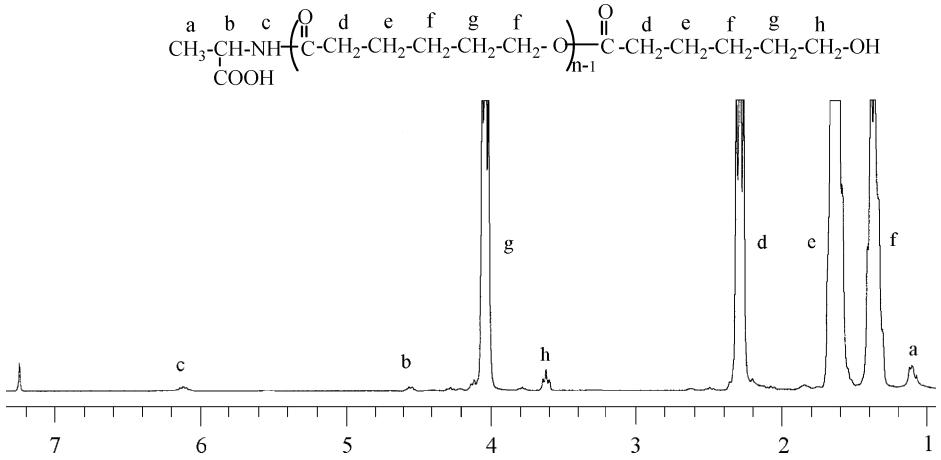



**Figure 1.** $^1$H NMR spectrum of PCL initiated by L-alanine (Table 1, entry 1).

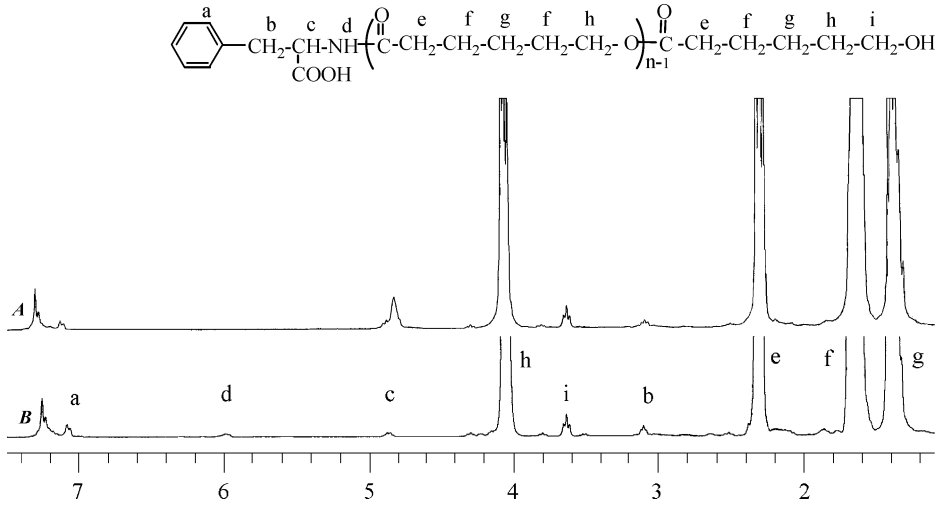



**Figure 2.** (A) $^1$H NMR spectrum of PCL by L-phenylalanine after $D_2O$ exchange. **(**B) $^1$H NMR spectrum of PCL by L-phenylalanine (Table 1, entry 3).

**Table 2. Content of Carboxyl Side Group of PCL Analyzed by Titration**

| item | L-alanine[a] | L-leucine[b] | L-proline[c] | L-phenylalanine[d] |
|---|---|---|---|---|
| KOH (mL) | 14.8 | 12.9 | 12.7 | 13.5 |
| no. of carboxyl group[e] | 1.12 | 1.08 | 1.10 | 1.03 |

[a] Table 1, entry 1. [b] Table 1, entry 7. [c] Table 1, entry 2. [d] Table 1, entry 3. [e] Number of carboxyl group = the amount of KOH (mol) consumed /(mass of PCL/$M_{n,calcd}$ from Table 1).

L-alanine. The peaks at $\delta = 1.1$, 4.5, and 6.1 ppm are assigned to the protons of $CH_3-$ and $-CH-$ in alanine and the newly formed $-NHCO-$ group, respectively. The triplet at $\delta = 3.7$ ppm arises from the protons of methylene in the $-CH_2OH$ end group. All other peaks are due to the backbone chain of PCL.

Figure 2 shows the $^1H$ NMR spectra of PCL by L-phenylalanine. The spectrum after $D_2O$ exchange is marked as Figure 2A. As expected, no signal of proton in the $-NHCO-$ group is observed from Figure 2A, which should appear at $\delta = 6.0$ ppm as shown in Figure 2B. But the peak of $H_2O$ appears at $\delta = 4.8$ ppm, which overlaps the signal of the $-CH-$ group in phenylalanine. The results depict the existence of the $-NHCO-$ group in PCL obtained. In Figure 2A,B, the peaks at $\delta = 3.1$ and 7.18 ppm are attributed to the protons of methylene and phenyl in the $PhCH_2-$ end group, respectively. The formation of the $-NHCO-$ group suggests the amino group of amino acid incorporating into the PCL chain by its addition to $\epsilon$-CL and the rupture of acyloxygen linkage in $\epsilon$-CL during polymerization.

Another evidence of amino acid incorporating into the polymer chain by the amino group is titration of the carboxyl group (cf. structure formula in Figures 1 and 2), and the results are listed in Table 2.

On the basis of the data of $M_{n,calcd}$ and consumption of KOH in titration, PCL by L-alanine, L-leucine, L-proline, or L-phenylalanine each contained one carboxyl side group. The result strongly supports the structure of PCL by $^1H$ NMR.

In conclusion, the polymerization of $\epsilon$-CL was initiated efficiently by some natural amino acids via the rupture of an acyloxygen bond in $\epsilon$-CL and the addition of an amino group in amino acid to form the $-NHCO-$ linkage, and the amino acid was incorporated into the polymer chain. The molecular weight of PCL depended on the molar ratio of [$\epsilon$-CL]/[amino acid] in feed.

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