# Ring-opening copolymerization of α-chloromethyl-α-methyl-β-propionolactone with ε-caprolactone

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SUMMARY: α-Chloromethyl-α-methyl-β-propionolactone (CMMPL) has been copolymerized with ε-caprolactone (CL) using a wide range of feed compositions and aluminium triisopropoxide [$Al(O^iPr)_3$] as an initiator. Random copolymers of CMMPL with CL were obtained. The pendant chloromethyl groups of the copolymer were converted to quaternary ammonium salts by reaction with pyridine, resulting in an increased hydrophilicity of the copolymers.

## Introduction

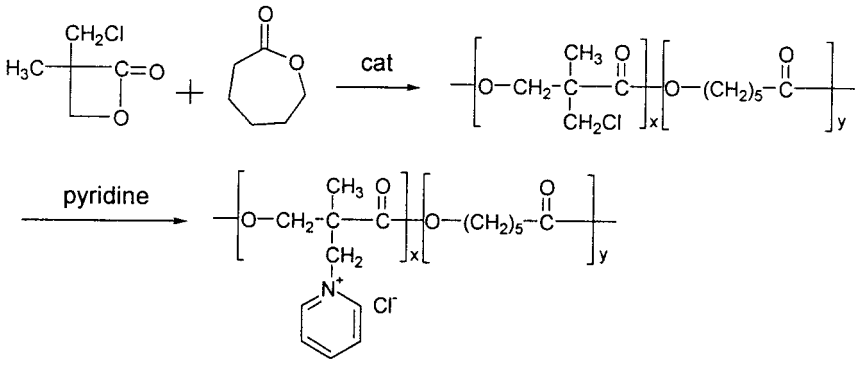
Aliphatic polyesters have been widely used as biomedical materials and environmentally degradable thermoplastics[1–3]. The homo- and copolymers of lactide and other lactones such as polylactide, poly(lactide-*co*-glycolide) and poly(ε-caprolactone-*co*-lactide) are among the well known biodegradable synthetic polymers which have been studied for many years[4]. It has also 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. Copolymerization of ε-caprolactone (CL) with lactide (LA), and/or glycolide (GL) yields biodegradable and biocompatible polyesters with different chemical and physical properties[5–8]. Since aliphatic polyesters generally do not have many pendant functional groups (other than end groups) to allow further chemical modification altering their properties such as hydrophilicity or to conjugate with drugs and bioactive residues, the application of these polyesters is limited. In the recent past, novel aliphatic polyesters containing functional pendant groups have been studied continuously[9–14]. Copolymerization of functional monomers with CL or LA provides a way to obtain functional polyesters. The functional groups of the copolymer usually should be protected, and need to be deprotected after copolymerization. We have reported on a new kind of functional polyester by the ring-opening polymerization of α-chloromethyl-α-methylpropionolactone (CMMPL) using different catalysts[15]. P(CMMPL) has a very high crystallinity and poor solubility in organic solvents, which makes it difficult to modify this polymer. In this article, CMMPL was copolymerized with CL to afford random copolymers, whose pendant chloromethyl groups were allowed to react with pyridine to increase the hydrophilicity of the copolymers (Scheme 1).

## Experimental part

### *Materials*

α-Chloromethyl-α-methyl-β-propionolactone (CMMPL) was prepared as reported in our previous paper[15]. It was dried over $CaH_2$, and freshly distilled under reduced pressure prior to copolymerization. ε-Caprolactone (CL) was purchased from Aldrich, and distilled over $CaH_2$ under reduced pressure

Scheme 1:

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prior to use. Aluminium triisopropoxide [$Al(O^iPr)_3$], 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 before use. 1,3-Dichlorotetrabutyldistannoxane and 1-ethoxy-3-chlorotetrabutyldistannoxane were prepared according to literature[16]. *o*-Dichlorobenzene was distilled under nitrogen over 4 Å molecular sieves and used to dissolve the above catalysts. All other chemicals were purchased from Beijing Chemical Reagent Co. and used without further purification.

*Copolymerization*

Bulk copolymerization was carried out with 0.05 mol-% of catalyst relative to the monomer feed. A mixture of a certain amount of CMMPL, CL and catalyst in *o*-dichlorobenzene was put into a previously flamed and dry argon-purged glass tube. The tubes were degassed for 10 min and sealed in vacuum. After a certain reaction time, the tube was allowed to cool to room temperature and opened. 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 vacuum at 50 °C for 48 h.

*Reaction of pyridine with the pendant chloromethyl groups of the copolymers*

The copolymer (0.5 g) was dissolved in 2 mL of pyridine, and the reaction was carried out at 110 °C for 1 h. The copolymer was recovered by precipitation from a mixture of diethyl ether and hexane (1/4, v/v). The copolymer was further purified by reprecipitation in a mixture of diethyl ether and hexane, and dried in vacuum (0.1 mmmHg) at 50 °C.

*Characterization*

$^1$H NMR spectra were recorded on a Bruker ARX-400 spectrometer operated at 400 MHz. Compositions of copolymers were determined by $^1$H NMR from the relative intensity of the methylene signal of P(CMMPL) at 3.7 ppm and the methylene signal of PCL at 4.0 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 tetrahydrofuran (THF) as an eluent (1.0 mL/min) using a Waters 510 pump, a Waters U6 K injector, 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. Differential scanning calorimetry (DSC) measurements were performed on a Shimadzu DSC-50 at a heating rate of 10 °C/min. Dynamic contact angles (DCA) of the copolymers were determined using distilled water at 25 °C by a Cahn dynamic contact angle analyzer (DCA-322). The samples for the DCA determination were prepared according to the following process. Polymer samples were dissolved in chloroform (0.1 g in 25 mL of $CHCl_3$). A long cover glass was dipped into the solution and lifted at a constant speed to allow a thin film of the copolymer to form evenly on the surface of the glass. The samples were air dried for 1 day and treated in vacuo for another 6 h at room temperature to remove traces of solvent.

## Results and discussion

*Copolymerization of CL and CMMPL*

In general, it is hard to get random copolymers of 4-numbered ring lactones such as β-butyrolactone and six- or larger numbered ring esters such as CL, LA and GL due to their differences in monomer reactivity[17, 18]. In the case of ring-opening polymerization, different catalysts may result in different propagation mechanisms, which changes the reactivity ratios of the cyclic esters. Therefore, for the synthesis of a random copolyester of CMMPL with CL, the selection of a suitable catalyst is crucial. Six catalysts, including $Al(O^iPr)_3$, $Ti(OBu)_4$, $Bu_2Sn(OMe)_2$, $Sn(Oct)_2$, 1,3-dichlorotetrabutyldistannoxane and 1-ethoxy-3-chlorotetrabutyldistannoxane were tested. The experiments were conducted by using these catalysts under the following conditions: [CMMPL]/[CL] = 0.156 (mole ratio), [M]/[Cat] = 2000 (mole ratio), T = 130 °C, time = 4 h. The results revealed that the composition of copolymers obtained by using $Al(O^iPr)_3$ as a catalyst was close to the feed ratio, while its melting temperature ($T_m$) and fusion enthalpy ($\Delta H_f$) were the lowest among the resulting copolymers. This indirectly suggests that random copolymerization might have taken place by using $Al(O^iPr)_3$ as a catalyst.

Subsequently, the copolymerization of CL and CMMPL was carried out at different temperatures using $Al(O^iPr)_3$ as a catalyst. The results indicated that the content of CMMPL units in the copolymers increased with decreasing polymerization temperatures. When the polymerization temperature was raised to 160 °C, the copolymer composition was very close to the feed ratio.

Based on the results above, the bulk copolymerization of CL and CMMPL was conducted under the following conditions: [M]/[$Al(O^iPr)_3$] = 2000 (mole ratio), $T$ = 160 °C, $t$ = 10 h. The results are summarized in Tab. 1. It can be clearly seen that the compositions of the resulting copolymers are close to their corresponding feed ratios over a wide range of feed ratios. Meanwhile, the polymer yields gradually decrease with increasing CL ratio in the feeds. This might be caused by the relatively high polymerization temperature, which favours the chain-transfer reaction of CL-ended chains. As a result, products with a low molecular weight might be lost during the reprecipitation purification process. Moreover, the higher the CL ratio in the feed, the higher the possibility of CL-ended chain-transfer reactions, which in turn results in lower polymer yields and relatively higher molecular weights and lower polydispersities of the purified copolymer.

Tab. 1. Copolymerization of CMMPL and CL using $Al(O^iPr)_3$ as a catalyst. (Copolymerization condition: [M]/[$Al(O^iPr)_3$] = 2000 (mole ratio), 160 °C, 18 h)

| No. | CMMPL (in mol-%) in feed | Yield in % | CMMPL (in mol-%)[a] in copolymer | $T_g$/ °C | $T_m$/ °C | $\Delta H_f$ / J/g | $\overline{M}_n$[c] | $\overline{M}_w$[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $\cdot 10^{-4}$ | |
| C-0 | 100 | 87 | 100 | −17.1[b] | 220.5 | 35.7 | – | – |
| C-1 | 90 | 93 | 80 | −17.8[b] | 217.2 | 30.3 | – | – |
| C-2 | 80 | 80 | 68 | −19.0[b] | 187.3, 150.4 | 45.6 | 0.23 | 0.62 |
| C-3 | 70 | 89 | 62 | −43.4 | 167.2, 134.1 | 35.0 | 0.24 | 1.25 |
| C-4 | 60 | 79 | 53 | −46.8 | 151.8, 116.8 | 15.0 | 0.49 | 1.29 |
| C-5 | 50 | 67 | 49 | −47.0 | 108.6 | 2.4 | 0.39 | 1.59 |
| C-6 | 40 | 66 | 38 | −48.9 | 37.7 | 8.9 | 0.75 | 1.56 |
| C-7 | 30 | 58 | 28 | −49.1 | 40.1 | 14.3 | 0.58 | 2.22 |
| C-8 | 20 | 42 | 20 | −52.7 | 42.1, 46.7 | 35.2 | 1.02 | 1.87 |
| C-9 | 10 | 37 | 13 | −60.2 | 46.6, 49.7 | 56.2 | 0.92 | 1.79 |
| C-10 | 0 | 57 | 0 | −72.5 | 64.3 | 89.6 | 1.54 | 3.11 |

[a] Determined by the peak ratio of 3.7 ppm (PCMMPL) and 4.0 ppm (PCL) in $^1$H NMR spectra.
[b] Obtained from the second scan.
[c] Determined by GPC analysis in THF; for C-2, C-3, only the soluble parts were measured.

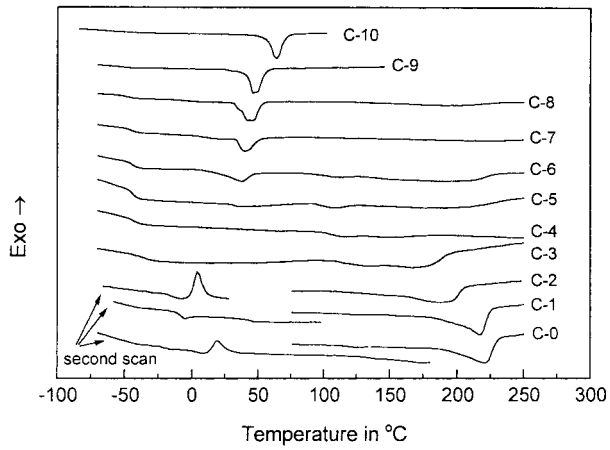


Fig. 1. DSC profiles of P(CMMPL-*co*-CL)s. (The numbers correspond to the copolymer numbers in Tab. 1. The second scan was conducted after the melt sample being quenched in liquid nitrogen)

Fig. 1 shows the DSC profiles of the copolymers listed in Tab. 1, and the related results are also listed in Tab. 1. P(CMMPL) is a highly crystalline polymer, which melts at about 220.5 °C. With increasing CL contents in the copolymers, the melting temperatures of the copolymers decrease, and the melting peaks become broader. When the molar content of CL and CMMPL in the copolymer is almost equal (i.e. for sample C-5), the melting can not be observed clearly, and the melting enthalpy becomes very low. This result shows that an amorphous copolymer was obtained when 50 mol-% CL unit was present. It thus can be concluded that copolymerization of CMMPL with CL affords copolymers with very low or no crystallinity. It is worth mentioning that the $T_g$ of the copolymers with high CMMPL contents (samples C-0, C-1 and C-2) could only be observed from the second scan, when the melt samples were quickly quenched in liquid nitrogen. Single $T_g$ values were observed for all the copolymers, and they are intermediates between that of the parent homopolymers, indicating that random copolymerization might have taken place under the present conditions.

### *Reaction of pyridine with the pendant chloromethyl groups of the copolymers*

In principle, pendant chloromethyl groups on the copolymer chain can react with a tertiary amine to form quaternary ammonium salts and thus the hydrophilicity of the copolymers can be improved. As an example, copolymer C-8 (20 mol-% CMMPL) was reacted with pyridine, resulting in sample MC-8. Fig. 2 and Fig. 3 show the FT-IR and $^1$H NMR spectra of MC-8, respectively, which undoubtedly evidence the formation of the pyridinium salt. This can be seen clearly from the $^1$HNMR spectrum of MC-8 as shown in Fig. 3. After modification of C-8 by pyridine, the characteristic peaks of pyridine in MC-8 appeared at 7.9 ppm, 8.5 ppm and 8.8 ppm, and other peaks of C-8 did not change. From the intensities of the characteristic peaks of pyridine and the methylene protons next to the carbonyl group of CL unit, the content of pyridine in MC-8 was determined to be equal to the amount of CMMPL in the precursor C-8. It is thus concluded that almost all pendant chloromethyl groups of CMMPL in the copolymer can be converted to pyridinium salts under the present condition. Besides, a slight decrease of the molecular weight was observed after reaction, that is, from $1.0 \times 10^4$ ($\overline{M}_n$) and $1.8 \times 10^4$ ($\overline{M}_w$) of sample C-8 to $7.5 \times 10^3$ ($\overline{M}_n$) and $1.7 \times 10^4$ ($\overline{M}_w$) of sample

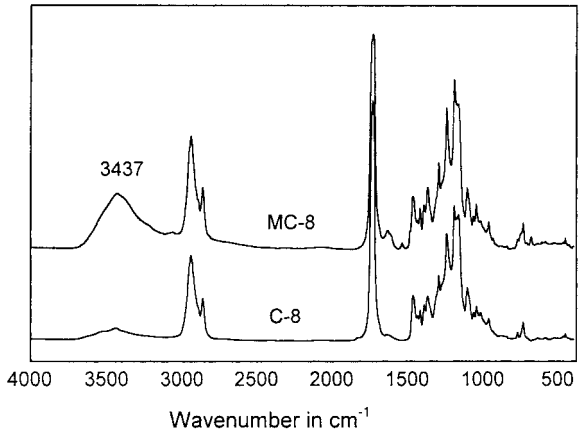


Fig. 2. IR spectra of C-8 and MC-8

MC-8. This may be attributed to a slight degradation of the copolymers during the modification process.

### *Hydrophilicity of the copolymers before and after modification*

In order to explore the hydrophilicity of the resulting modified copolymers, the dynamic contact angle (DCA) of MC-8 was measured using distilled water at 25 °C. The advancing angle ($\theta_a$, contacting angle in immersion) and receding angle ($\theta_r$, contacting angle in emersion), are used to characterize the hydrophilicity of the polymer membrane surface. The advancing and receding angles of C-8, C-10 (PCL) and MC-8 samples are listed in Tab. 2.

Tab. 2. Advancing and receding angles of C-10, C-8 and MC-8 measured by DCA using water at 25 °C

| | C-10 (PCL) | C-8 | MC-8 |
|---|---|---|---|
| $\theta_a$ | 80 ° | 79 ° | 69 ° |
| $\theta_r$ | 62 ° | 50 ° | 41 ° |

It can be seen that both copolymer C-8 and PCL (C-10) had relatively high and similar advancing angles. This indicates that they are both hydrophobic in nature. When the chloromethyl groups in copolymer C-8 were reacted with pyridine to form pyridinium salts, both the advancing and receding angles of the modified copolymer decreased about 10 °. This result indicates that the formation of quaternary ammonium salts on the side chain of P(CMMPL-*co*-CL) increases the hydrophilicity. It also implies that there are possibilities to conjugate bio-active residues via similar quaternisation reactions.

In conclusion, CMMPL has been successfully copolymerized with CL using a wide range of feed ratios and using $Al(O^iPr)_3$ as an initiator. The DSC results show that when equal mole ratios of CMMPL and CL are present in the copolymer, an amorphous random copolymer can be obtained. The pendant chloromethyl groups of the copolymer can be quantitatively converted to quaternary ammonium salts by reaction with pyridine. This provides a new way to increase the hydrophilicity as well as to conjugate bio-active residues on the side chains of the biodegradable polymers.

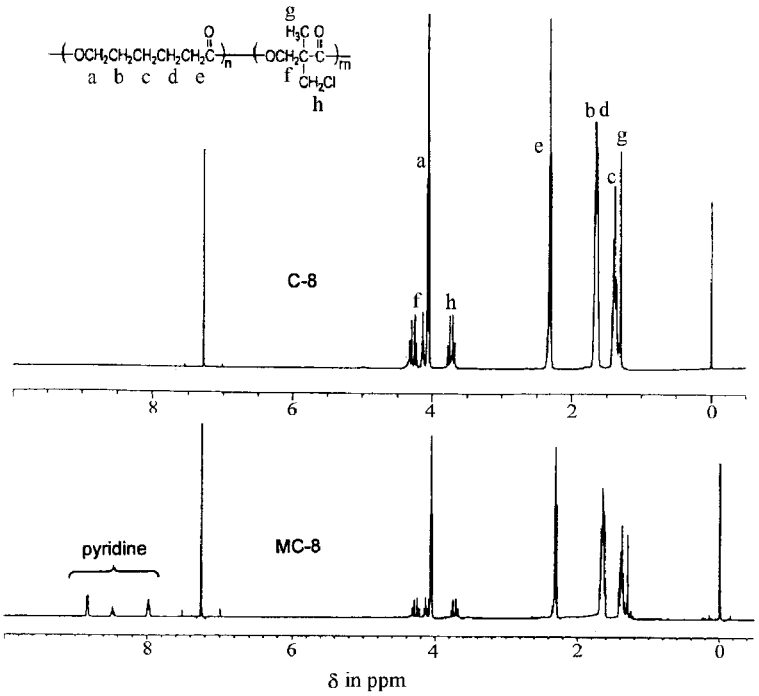


Fig. 3. $^1$H NMR spectra of C-8 and MC-8

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[1] S. Dumitriu, "*Polymeric Biomaterials*", Marcel Dekker Inc., New York 1994
[2] P. J. Hocking, R. H. Marchessault, in "*Chemistry and Technology of Biodegradable Polymers*", G. J. L. Griffin, Ed., Chapman & Hall, London 1994, p. 48
[3] G. Scott, D. Gilead, "*Degradable Polymer Principles and Applications*" Chapman & Hall, London 1995
[4] M.Vert, *Angew. Makromol. Chem.* **166/167**, 155 (1989)
[5] X. D. Feng, C. X. Song, W. Y. Chen, *J. Polym. Sci., Polym. Lett. Ed.* **21**, 593 (1983)
[6] H. R. Kricheldorf, T. Mang, J. M. Jonte, *Macromolecules* **17**, 2173 (1984)
[7] J. M. Vion, R. Jerome, Ph. Tessie, M. Aubin, R. E. Prud'Homme, *Macromolecules* **19**, 18288 (1986)
[8] H. Fukuzaki, M. Yoshida, M. Asano, M. Kamakura, T. Mashimo, H. Yuasa, K. Imai, H. Yamanaka, *Polymer* **31**, 2006 (1990)
[9] J. Kohn, R. Langer, *J. Am. Chem. Soc.* **109**, 817 (1987)
[10] Y. Kimura, K. Shirotani, H. Yamane, T. Kitao, *Macromolecules* **21**, 3388 (1988)
[11] T. Ouchi, A. Fujino, *Makromol. Chem.* **190**, 1523 (1989)
[12] P. J. A. in't Veld, P. J. Dijkstra, J. Feijen, *Makromol Chem.* **193**, 2713 (1992)
[13] J. S. Hrkach, J. Ou, N. Lotan, R. Langer, *Macromolecules* **28**, 4736 (1995)
[14] D. Tian, Ph. Dubois, R. Jerome, *Macromolecules* **30**, 2575 (1997)
[15] X. Q. Liu, M. X. Wang, Z. C. Li, F. M. Li, *Macromol. Chem. Phys.* **200**, 468 (1999)
[16] R. Okawara, M. Wada, *J. Organometal. Chem.* **1**, 81 (1963)
[17] H. R. Kricheldorf, J. M. Jonte, M. Berl, *Macromol. Chem. Suppl.* **12**, 25 (1995)
[18] H. R. Kricheldorf, M. Berl, N. Scharnagl, *Macromolecules* **21**, 286 (1988)