Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

NOTE: Polymerization of Cyclic Esters Using Aminoacid Initiators

Marcin Sobczak[a]; Ewa Oledzka[a]; Wacław L. Kołodziejski[a]
[a] Faculty of Pharmacy, Department of Inorganic and Analytical Chemistry, Medical University of Warsaw, Warsaw, Poland

To cite this Article Sobczak, Marcin , Oledzka, Ewa and Kołodziejski, Wacław L.(2008) 'NOTE: Polymerization of Cyclic Esters Using Aminoacid Initiators', Journal of Macromolecular Science, Part A, 45: 10, 872 — 877
To link to this Article: DOI: 10.1080/10601320802300925
URL: http://dx.doi.org/10.1080/10601320802300925

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2008) **45**, 872–877

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320802300925

Taylor & Francis
Taylor & Francis Group

NOTE: Polymerization of Cyclic Esters Using Aminoacid Initiators

MARCIN SOBCZAK, EWA OLĘDZKA and WACŁAW L. KOŁODZIEJSKI

Medical University of Warsaw, Faculty of Pharmacy, Department of Inorganic and Analytical Chemistry, ul. Banacha 1, 02-097 Warsaw, Poland

Received February 2008 and accepted May 2008

The low-molecular weight poly(ε-caprolactone) and polylactide were obtained by the polymerization of cyclic esters in the presence of amino acid initiators. The polymer structures were elucidated by means of MALDI TOF, NMR and IR studies. Effects of temperature, reaction time and initiator dosage on the polymerization process were examined.

Keywords: Polycaprolactone, polylactide, ring-opening polymerization, amino acid

1. Introduction

Degradable polymeric biomaterials play a key role in tissue engineering and drug delivery systems. Such polymers are currently used in many biomedical applications, such as prosthetic and dental materials, artificial organs, sutures and disposable hygiene products. Polymer based delivery systems are capable of controlled release of drugs into body.

Aliphatic polyesters are typical biodegradable materials, commonly used in medicine and pharmacy because of their good biodegradability, biocompatibility and lack of toxicity. The majority of polyester products are composed of homo- and copolymers of polylactide (PLA) and poly(ε-caprolactone) (PCL) (1–4).For example, poly(L-lactide) (PLLA) is a biodegradable and bioabsorbable polymer, which is degraded *in vivo* by hydrolytic deesterification into lactic acid monomers. The latter species become involved in the carboxylic acid cycle and are subsequently excreted as carbon dioxide and water.

Aliphatic polyesters are usually prepared by ring-opening polymerization (ROP) of the relevant cyclic monomers (e.g. D,L-, L,L-lactide, ε-caprolactone; abbreviations: D,L-LA, L,L-LA, CL, respectively). PLA and PCL have been successfully synthesized by ring opening polymerization in the presence of cationic or anionic initiators, as well as coordinating and enzymatic catalysts (5–25).The ROP reaction of CL, initiated with four natural amino acids (L-alanine, L-proline, L-phenylalanine, L-leucine) has already been examined by Liu et al. (26).

We have decided to carry out more detailed investigation of that reaction by extending the range of amino acids used as initiators. The work deals also with the synthesis of aliphatic polyesters from lactide in the presence amino acids. We believe that the obtained polymers can find practical applications as effective drug delivery systems to specific locations and at the required rate (27).

2. Experimental

2.1. *Materials*

ε-Caprolactone (2-Oxepanone, 99%, CL) was purchased from Aldrich. Before use, it was dried and distilled over CaH_2 at reduced pressure. 3,6-Dimethyl-1,4-dioxane-2,5-dione, (rac-lactide, 98%, LA) (Aldrich) was crystallized from a mixture of dry toluene with hexane and dried at room temperature under vacuum. Amino acids (99%, Aldrich) (L-alanine, L-cysteine, L-leucine, L-methionine, L-phenylalanine, L-proline, L-threonine, L-aspartic acid, L-glutamic acid, L-histidine, L-lysine), dichloromethane (POCh), methanol (POCh) were used as received.

2.2. *Polymerization procedure*

Monomers (CL and LA) and amino acids were placed in 10 ml glass ampoules under nitrogen atmosphere. The reaction vessels were then left standing in a thermostated oil bath for the required temperature and time. When the reaction was completed (Table 1), the cold product was dissolved in dichloromethane, precipitated from cold

Address correspondence to Marcin Sobczak, Medical University of Warsaw, Faculty of Pharmacy, Department of Inorganic and Analytical Chemistry, ul. Banacha 1, 02-097 Warsaw, Poland. Tel.: 48 22 572 07 55; Fax: 48 22 572 07 84. E-mail: marcin.sobczak@wp.pl

Table 1. Homopolymerization of ε-caprolactone and rac-lactide initiated by amino acids

Monomer	*Amino acid*	*M/I*	*Time (h)*	*Temp. (°C)*	*Yield (%)*	M_n^{cal}	M_V^a *(Da)*	M_{nL}^b *(Da)*	PD_L^b	M_{nM}^b	PD_M^b	*% MC*^{b}	M_n^c	PD^c
CL	L-Ala	20:1	24	160	96	2200	2100	—	—	—	—	—	—	—
CL	L-Ala	50:1	48	160	92	5200	3300	2900	1.2	2200	1.2	17	3900	1.6
CL	L-Ala	50:1	24	120	48	2700	2100	—	—	—	—	—	—	—
CL	L-Ala	100:1	24	160	78	8900	7300	—	—	—	—	—	—	—
CL	L-Cys	50:1	24	160	83	4700	3900	—	—	—	—	—	—	—
CL	L-Leu	50:1	24	160	95	5400	3700	—	—	—	—	—	—	—
CL	L-Met	50:1	24	160	78	4400	5600	—	—	—	—	—	—	—
CL	L-Phe	50:1	24	160	93	5300	4000	3400	1.1	2200	1.1	18	3600	1.3
CL	L-Pro	50:1	24	160	63	3600	3800	3600	1.2	2500	1.1	15	—	—
CL	L-Thr	50:1	24	160	78	4400	2900	2300	1.1	1800	1.1	11	—	—
CL	L-Asp	50:1	24	160	58	3300	3600	—	—	—	—	—	—	—
CL	L-Glu	50:1	24	160	54	3100	3500	4100	1.2	2800	1.1	18	—	—
CL	L-His	50:1	24	160	42	2400	1000	—	—	—	—	—	—	—
CL	L-Lys	50:1	24	160	88	5000	3200	—	—	—	—	—	—	—
LA	L-Ala	50:1	24	120	87	5000	2400	1800	1.1	1600	1.1	6	2200	1.6
LA	L-Cys	50:1	24	120	64	4600	1400	—	—	—	—	—	—	—
LA	L-Leu	50:1	24	120	82	5900	1400	—	—	—	—	—	—	—
LA	L-Met	50:1	24	120	64	3600	1600	—	—	—	—	—	—	—
LA	L-Phe	20:1	24	120	51	1500	1800	—	—	—	—	—	—	—
LLA	L-Phe	50:1	48	120	75	5400	2500	2200	1.1	1800	1.1	4	2600	1.3
LA	L-Phe	50:1	24	160	89	6400	1900	—	—	—	—	—	—	—
LA	L-Pro	50:1	24	120	69	5000	1300	1100	1.1	1000	1.1	9	—	—
LA	L-Thr	50:1	24	120	68	4900	1500	—	—	—	—	—	—	—
LLA	L-Asp	50:1	24	120	46	3300	1300	—	—	—	—	—	—	—
LA	L-Glu	50:1	24	120	49	3500	1200	—	—	—	—	—	—	—
LA	L-His	50:1	24	120	32	1800	1400	—	—	—	—	—	—	—
LA	L-Lys	50:1	24	120	78	5600	1300	—	—	—	—	—	—	—

[a] Determined by viscosity method.
[b] Determined by MALDI-TOF.
[c] Determined by GPC.
L-Ala: L-alanine, D,L-Cys: D,L-cysteine, L-Leu: L-leucine, L-Met: L-methionine, L-Phe: L-phenylalanine, L-Pro: L-proline, D-Thr: D-threonine, L-Asp: L-aspartic acid, L-Glu: L-glutamic acid, L-His: L-histidine, L-Lys: L-lysine.
M_{nL}^2, PD_L^2—molecular mass and dispersity of linear oligomers.
M_{nM}^2, PD_M^2 molecular mass and dispersity of macrocycles.
% MC—macrocycles content (determined by MALDI-TOF).
M_n^{cal}—the theoretical molecular weight: $M_n = [M]/[I] \times M_m \times X/100$, where [M]/[I] is the monomer to initiator molar ratio in feed, M_m—monomer mass, X—monomer conversion (%).

methanol and dried in vacuo for 72 h to isolate a powdery or oily polymer.

2.3. *Measurements*

The polymerization products were characterized by means of ^{1}H an ^{13}C-NMR (Varian 300 MHz), and FT-IR spectroscopy (Perkin-Elmer). The NMR spectra were recorded in $CDCl_3$. The IR spectra were measured from KBr pellets. Relative molecular mass and molecular mass distributions were determined by MALDI-TOF and gel permeation chromatography (GPC) techniques. MALDI-TOF spectra were measured in the linear mode on a Kompact MALDI 4 Kratos analytical spectrometer using a nitrogen gas laser and 2[(4hydroxyphenyl)diazenyl] benzoic acid (HABA) as a matrix. Molecular weight and molecular weight distributions of polymers were determined at 308 K on Lab Alliance gel permeation chromatography equipped with Jordi Gel DVB Mixed Bed (250 mmA10 mm) columns and refractive detector, and THF or chloroform as eluent (1 cm^3/min). The molecular weights were calibrated with polystyrene standards.

Polymer viscosity was measured in chloroform (at 25°C) and N,N-dimethylformamide (at 30°C) using a Ubbelohde viscometer. Polymer molecular weights were calculated from the Mark-Houwink formula using the following equation constants: $K = 2.21 \cdot 10^{-4}$ ml/g and $\alpha = 0.77$ (for PDLA), $K = 1.94 \cdot 10^{-4}$ and $\alpha = 0.73$ (for PCL) (28–32).

3. Results and discussion

The polymerization reaction of CL and LA were carried out at 120–160°C. The molar ratio of amino acids to a given monomer was 1:20, 1:50 or 1:100. Reaction conditions, yields and average molecular weight of polyesters are summarized in Table 1.

The chemical structures of the obtained polymers were confirmed by ^{13}C,

^{1}H-NMR and IR studies:

3.1. *Poly(ε-caprolactone)*

^{1}*H-NMR (CDCl$_3$, δ, ppm)*: 4.01 (2H, t, -CH_2C**H**$_2$OC(O)-), 3.70 (2H, t, -CH_2C**H**$_2$OH, end group), 2.24 (2H, t, -CH_2C**H**$_2$COO-), 1.58 (4H, m, -C**H**$_2$$CH_2$COO-), 1.33 (2H, m, -$CH_2CH_2$C**H**$_2$$CH_2CH_2$-)

^{13}*C-NMR (CDCl$_3$, δ, ppm):* 173.1 (-**C**(O)O-), 63.7 (-CH_2**C**H_2OC(O)-), 33.6 (-CH_2**C**H_2COO-), 27.9 (-**C**$H_2$$CH_2$OC(O)-), 25.1 (-**C**$H_2$$CH_2$COO-), 24.1 (-$CH_2CH_2$**C**$H_2$$CH_2CH_2$-)

FTIR (KBr, cm^{-1}): 2949 ($\upsilon_{as}CH_2$), 2865 (υ_sCH_2), 1727 (υC=O), 1240 (υ_{as}COC), 1190 (υOC-O), 1170 (υ_sCOC)

Poly(D,L-lactide): ^{1} *H-NMR (CDCl3, δ , ppm)*: 5.17 (1H, q, -C**H**(CH_3)-), 4.36 (1H, q, -C**H**(CH_3)OH, end group), 1.58 (3H, d, -C**H**$_3$)

^{13} C NMR (CDCl3, δ , ppm): 169.80 (-**C**(O)O-), 69.2 (-**C**H(CH_3)-), 16.8 (-**C**H_3).

FTIR (KBr, cm^{-1}): 2997 ($\upsilon_{as}CH_3$), 2947 (υ_sCH_3), 2882 (υCH), 1760 (υC=O), 1452 ($\delta_{as}CH_3$), 1348-1388 (δ_sCH_3), 1368–1360 (δ_1CH+δ_sCH_3), 1315–1300 (δ_2CH), 1270 (δCH +υCOC), 1215-1185 (υ_{as}COC + $r_{as}CH_3$), 1130 ($r_{as}CH_3$), 1100–1090 (υ_sCOC), 1045 (υC-CH_3), 960–950 (rCH_3 + υCC), 875-860 (υC-COO), 760–740 (δC=0), 715–695 (γC=O), 515 (δ_1C-CH_3 + δCCO), 415 (δCCO), 350 (δ_2C-CH_3 + δCOC), 300–295 (δCOC +δ_2C-CH_3), 240 (τCC)

The presence of -NHCO- group was confirmed by spectral analysis. The proton NMR peak at 5.8-6.2 ppm was observed in all products, obtained by homopolymerization of CL and LA in the presence amino acids. The formation of the –NHCO- group indicates that the amino group of the amino acids was incorporated into PCL and PDLA chains.

^{1}H-NMR spectra in $CDCl_3$ solutions of the synthesized polymers are presented in Figures 1 and 2.

Figures 3 and 4 show typical MALDI-TOF spectra of the polymeric products.

The MALDI-TOF spectra of PCL comprise three of peaks. The most prominent series of peaks is characterized by a mass increment of 114 Da, which is equal to the mass of the repeating unit in the poly(ε-caprolactone) (Fig. 3). It is assigned to PCL terminated with a hydroxyl group (residual mass: 41 Da, Na^+ adduct) (A). The second series of peaks also corresponded to poly(ε-caprolactone), terminated with a hydroxyl group (residual mass: 57 Da, K^+ adduct) (B). In addition, the mass spectrum contains a low-intensity series of peaks corresponding to cyclic molecules (residual mass: 23 Da, Na^+ adduct) (C). The content of macrocycles was estimated on the basis of the intensity ratio of the peaks for linear and cyclic polymer.

The MALDI-TOF spectra of PDLA comprise three series of peaks (Fig. 4). The main series (A) corresponds to PDLA molecules, terminated with a hydroxyl group (residual mass: 41 Da, Na^+ adduct), and the second series of smaller peaks (B) corresponds also to poly(D,L-lactide) terminated with a hydroxyl group (residual mass: 57 Da, K^+ adduct). The third series of low-intensity peaks (C) corresponds to cyclic molecules (residual mass: 39 Da, K^+ adduct).

In the MALDI-TOF spectrum of PDLA both populations of chains of even and odd number of lactic acid m.u. can be observed. The odd number of acid m.u. shows that under the process conditions the polymer chain undergoes intramolecular transesterification (leading to the formation of macrocycles) and intermolecular transesterification (leading to an exchange of segments), which is a typical phenomenon for the polymerization of lactides (6).

The molecular weight of PCL and PDLA is dependent on the monomer/initiator molar ratio (Table 1). Both, the conversion and molecular weight of the polymers increased, when the temperature was raised from 120 to 160°C.

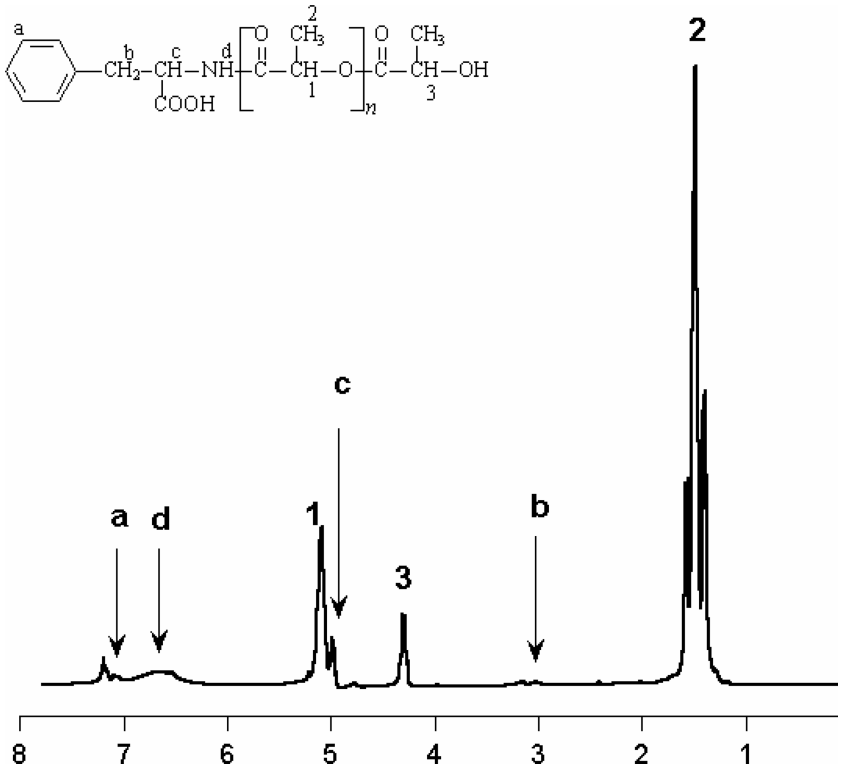

Fig. 1. [1]H-NMR spectra of the LA homopolymer produced in the presence of L-phenyloalanine.

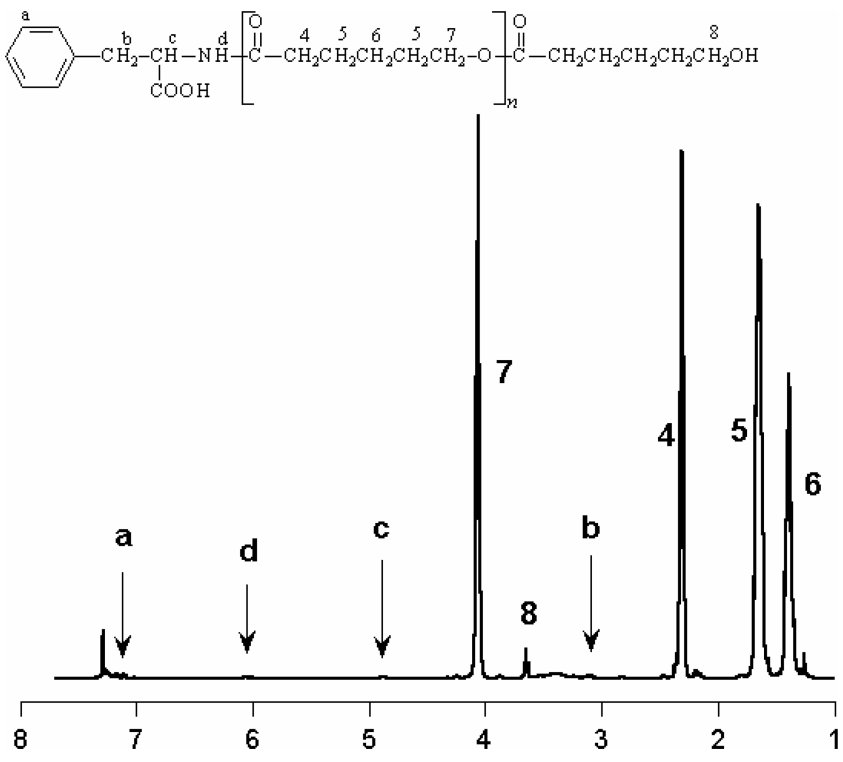

Fig. 2. [1]H-NMR spectra of the CL homopolymer produced in the presence of L-phenyloalanine.

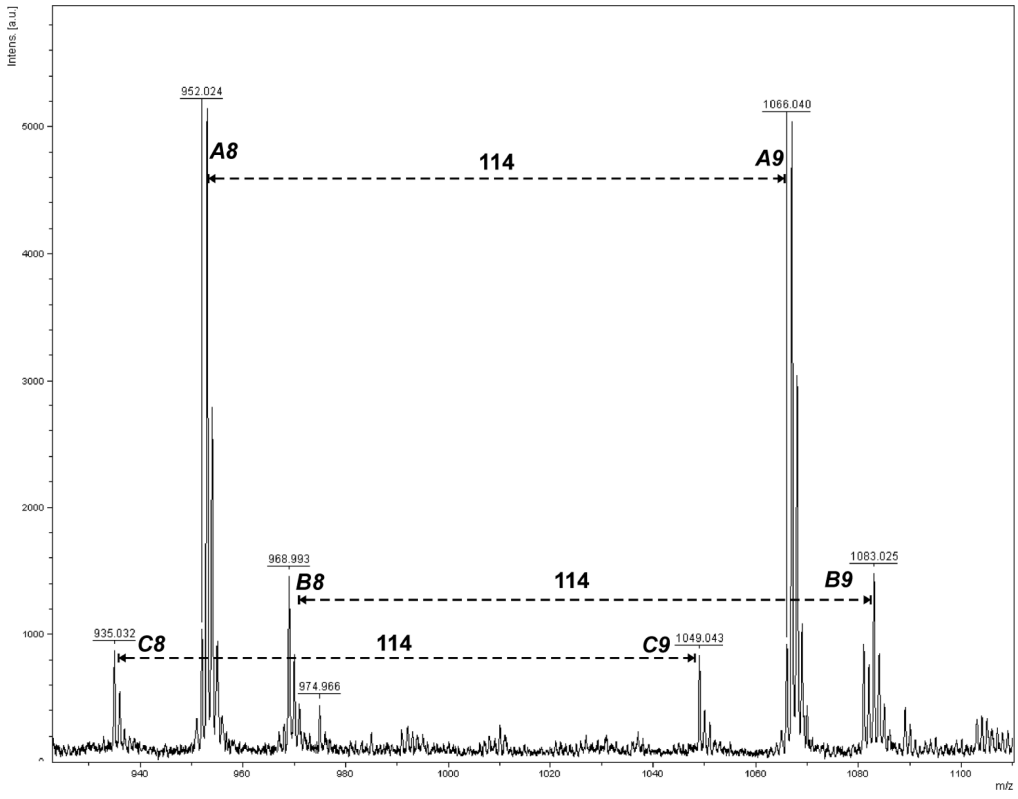

Fig. 3. MALDI TOF spectra of the product of CL polymerization in the presence of L-phenyloalanine, where A8 = -[C(O)$CH_2CH_2CH_2CH_2CH_2O$]$_8$-, etc.

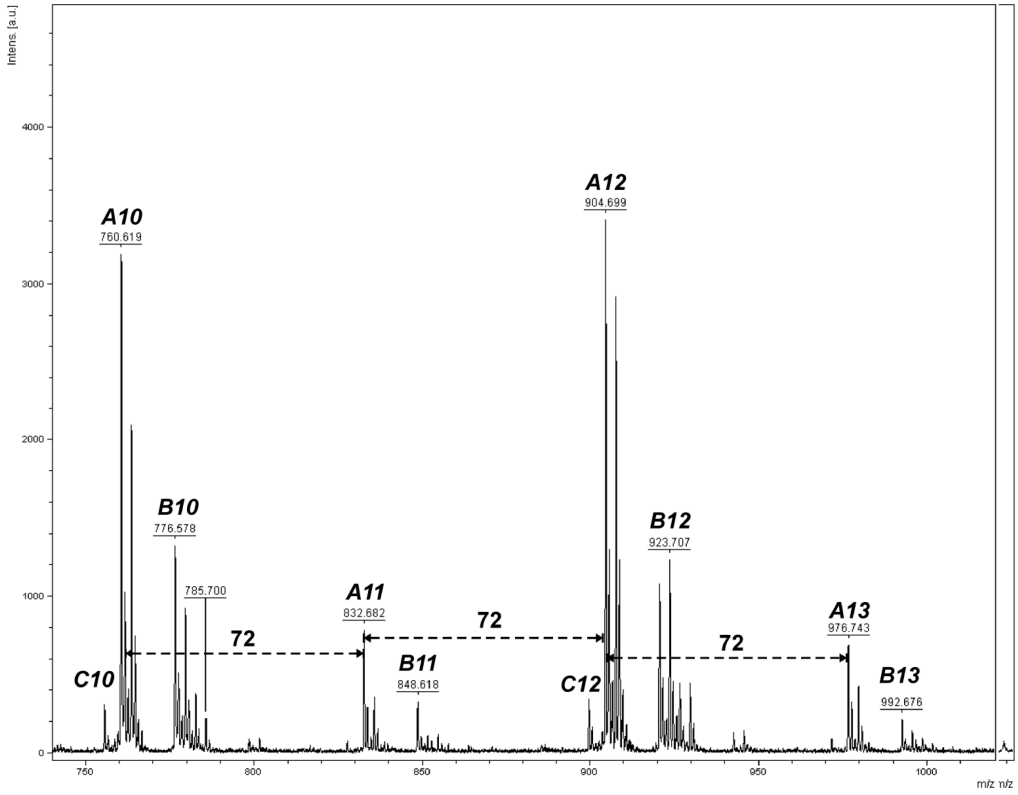

Fig. 4. MALDI TOF spectra of the product of LA polymerization in the presence of L-alanine, where A10 = -[C(O)$CH(CH_3)O$]$_{10}$-, etc.

The average molecular weights of PCL determined by the MALDI-TOF method are in the 2300–4100 Da range and the viscosity method are in the 1000–7300 Da range. For PDLA, the *M*n value determined from MALDI-TOF is 1100–2200 Da and it is comparable to the viscosity measurements. Poly(ε-caprolactone) has higher molecular weights than poly(D,L-lactide). M_n determined from GPC for CL oligomers is in the range of 3600–3900 Da (polydispersity indexes 1.3–1.6). For LA oligomers the *M*n values are 2200–2600 Da and *M*w/ *M*n 1.3–1.6.

Finally, it should be mentioned, that the amino acids initiators were quite effective in the polymerization of ε-caprolactone and rac-lactide. The yield of PCL was in the range of 42–96%, and for PDLA in the range of 32–87%.

Kinetic and mechanistics studies are underway. All this will be presented in the next paper.

4. Conclusions

The ring-opening polymerization of rac-lactide and ε-caprolactone in the presence of amino acids is a very efficient method of the synthesis of low-molecular weight polyesters. Polymerization in bulk at 120–160°C produced polymers with high yield (even ca. 100% in some cases). PCL and PDLA, obtained from such reactions are metal-free materials, thereby highly biosafe and suitable for drug carriers and controlled drug-release devices.

Acknowledgements

The Medical University of Warsaw is acknowledged for the "Young Researcher" grant for FW23/WB3/07.

References

1. Ueda, H. and Tabata, Y. (2003) *Adv. Drug Deliver. Rev*., 55, 518.
2. Uhrich, K.E., Cannizzaro, S.M., Langer, R.S. and Shakesheff, K.M. (1999) *Chem. Rev.*, 99, 3181–3198.
3. Jagur-Grodzinski, J. (1999) *React. Funct. Polym*., 39, 99–138.
4. Sobczak, M, Olędzka, E., Kołodziejski, W.L., Kuźmicz, R. (2007) *Polimery*, 52, 411–420.
5. Albertsson, A.C. and Varma, I.K. (2003) *Biomacromolecules*, 4(6), 1466–1486.
6. Florjańczyk, Z., Plichta, A. and Sobczak, M. (2006) *Polymer*, 47, 1081–1090.
7. Marcilla, R., de Geus, M., Mecerreyes, D., Duxbury, Ch.J., Koning, C.E. and Heise, A. (2006) *Eur. Polym. J*., 42, 1215–1221.
8. He, F., Li, S., Garreau, H., Vert, M. and Zhuo, R. (2005) *Polymer*, 46, 12682–12688.
9. Duda, A., Biela, T., Kowalski, A. and Lubiszowski, J**.** (2004) *Polimery*, 50, 501–508.
10. Cai, Q., Zhao, Y., Bei, J., Xi, F. and Wang, S. (2003) *Biomacromolecules*, 4, 828–834.
11. Martin, E., Dubois, P. and Jerome, R. (2003) *Macromolecules*, 36, 5934–5941.
12. Storey, R.F. and Sherman, J.W. (2002) *Macromolecules*, 35, 1504–1512.
13. Sanda, F., Sanada, H., Shibasaki, Y. and Endo, T. (2002) *Macromolecules*, 35, 680–683.
14. Connor, E.F., Nyce, G.W., Myers, M., Moeck, A. and Hedrick, J.L. (2002) *J. Am. Chem. Soc*., 124, 914–915.
15. Okada, M. (2002) *Prog. Polym. Sci*., 27, 87–133.
16. Kobayashi, S., Uyama, H. and Kimura, S. (2001) *Chem. Rev*., 101, 3793–3818.
17. Kowalski, A., Duda, A. and Penczek, S. (2000) *Macromolecules*, 33, 7359–7370.
18. Shibasaki, Y., Sanada, H., Ypkoi, M., Sanda, F. and Endo, T. (2000) *Macromolecules*, 33, 4316–4320.
19. Divakar, S. (2004) *J. Macromol. Sci. Pure and Appl. Chem*., A 41, 537–546.
20. Namekawa, S., Suda, S., Uyama, H. and Kobayashi, S. (1999) *Int. J. Biol. Macromol*., 25, 145–151.
21. Wang, Ch., Li, H. and Zhao, X. (2004) *Biomaterials*, 25, 5797–5801.
22. Duda, A. and Penczek, S. Mechanisms of Aliphatic Polyester Formation, in *Biopolymers*, *Vol. 3b: Polyesters II – Properties and Chemical Synthesis*, ed. by A. Steinbüchel, Y. Doi, Wiley-VCH: Weinheim 2002, Chapter 12, pp. 371–430.
23. Biela, T., Duda, A., Pasch, H. and Rode, K. (2005) *J. Polym. Sci., Part A: Polym. Chem*., 43, 6116–6133.
24. Libiszowski, J., Kowalski, A., Biela, T., Cypryk, M., Duda, A. and Penczek, S. (2005) *Macromolecules*, 38, 8170–8176.
25. Biela, T., Duda, A., Rode, K. and Pasch, H. (2003) *Polymer*, 44, 1851–1860.
26. Liu, J. and Liu, L. (2004) *Macromolecules*, 37, 2674–2676.
27. Sobczak, M., Witkowska, E., Olędzka, E. and Kołodziejski, W. (2008) *Molecules*, 13, 96–106.
28. Mainil-Varlet, P., Rahn, B. and Gogolewski, S. (1997) *Biomaterials*, 18, 257–266.
29. Schindler, A. and Harper, D. (1979) *J. Polym. Sci. Polym. Chem. Edn*., 17, 2593–2599.
30. Channuan, W., Siripitayananon, J., Molloy, R., Sriyai, M., Davis, F.J. and Mitchell, G.R. (2005) *Polymer*, 46, 6411–6428.
31. Nijenhuis, A.J., Grijpma, D.W. and Pennings, A.J. (1992) *Macromolecules,* 25, 6419–6424.
32. Gupta, A.P. and Kumar, V. (2007) *Eur. Polym. J*., 43, 4053–4074.