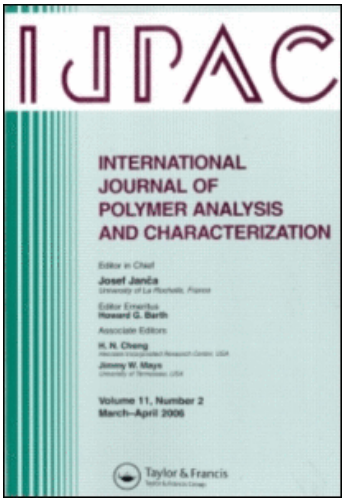

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Abstract: Short 2-hydroxyethylmethacrylate (HEMA)-oligocaprolactone macromonomers were synthesized at different temperatures from 100° to 190°C by bulk ring opening polymerization using HEMA as initiator and stannous octoate as catalyst. The crude products were analysed by MALDI-TOF and NMR and the influence of the temperature on the reaction was studied. In addition to transesterification (found at temperatures of 130°C and higher), other secondary reactions involving HEMA breakdown were also identified at these temperatures. In these processes, difunctional acrylic compounds may be formed.

Keywords: Macromonomers; MALDI-TOF analysis; Ring opening polymerization (ROP); Transesterification

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INTRODUCTION

Ring opening polymerization (ROP) of ε-caprolactone (CL) in the presence of 2-hydroxyethylmethacrylate (HEMA) as initiator and stannous octoate ($SnOct_2$) as catalyst to obtain macromonomers was first reported by Albertsson and coworkers in 1998.[1] These macromonomers are very interesting from a biomedical point of view since they combine a biocompatible polymerizable unit (e.g., HEMA) and a biocompatible biodegradable block (e.g., poly-CL, PCL). Different hybrid graft copolymers may be prepared using pure HEMA or poly-HEMA derivatives as initiators.[2–7] The procedures reported to perform the ROP of caprolactone using both the monomer or some (co)polymers as initiators are very similar. Albertsson and coworkers carried out a bulk polymerization at 120°C and 24 h.[1] Tarabic and Ranucci[2] used the same procedure but a reaction temperature of 110°C. Cretu et al.[3] tested other catalysts—lanthanide derivatives—and increased the reaction temperature to 150°C. Xu and Huang[4] used the hydroxyl groups of the monomeric units in a copolymer poly-(HEMA-co-styrene) as initiators to directly obtain the graft copolymer, and the procedure was very similar: bulk reaction, $SnOct_2$ as catalyst, and 130°C. In another article, the same authors used the identical copolymer as initiator and the same catalyst, toluene as solvent, at 100°C and 24 h.[5] The same strategy—the use of an already polymerized HEMA as initiator—was applied by Penzcek and coworkers[6] with poly-(methylmethacrylate-co-HEMA) as initiator, $SnOct_2$ as catalyst, THF as solvent, and at 80°C.

It is well known that transesterification may be a competitive reaction in ring opening polymerizations[8–13] and that temperature plays an important role in this context because the occurrence of ester interchange reactions will increase with temperature. In addition, this polymerization may even be more complex, as was shown by Eguiburu et al.[10] using HEMA-aluminium alcoxide derivative as initiator. According to these authors, who used nuclear magnetic resonance (NMR) for their studies, HEMA structure may be involved in unwanted side reactions leading to the formation of other methacrylates, different from the macromonomer. This side reaction is also temperature dependent.

In spite of these possible secondary processes, the ROP of caprolactone initiated by HEMA has been performed at many different conditions and temperatures (even at high temperatures, 130°–150°C), as summarized above. In this work, it is shown that MALDI-TOF (itself or in combination with NMR) is a powerful tool for structural identification of the products and processes occurring in the ROP reactions initiated by HEMA and therefore for an optimal selection of the reaction conditions. The ROP of CL initiated by HEMA and using $SnOct_2$ as catalyst has been analyzed by both techniques. Reactions were performed

at 100°, 130°, 160°, and 190°C over 20 h, and the crude products were analyzed by NMR and MALDI-TOF.

EXPERIMENTAL SECTION

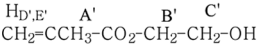
Materials

2-Hydroxyethyl methacrylate (HEMA, Fluka) was distilled before use. Stannous octoate ($SnOct_2$, Aldrich), caprolactone (CL, Aldrich), and hydroquinone (from Analar) were used as received.

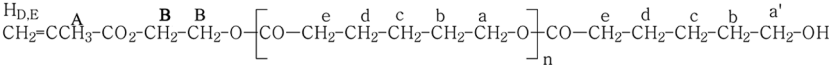
Ring Opening Mass Polymerization of CL Initiated by HEMA

A feed molar ratio HEMA/CL of 1/10 was used in all reactions. First, 0.5 mL of HEMA, 4.70 g of CL, and 30 μL of $SnOct_2$ were mixed in a laboratory threaded tube. A spatula tip of hydroquinone was added to avoid premature polymerization of the acrylic functionality. The mixture was bubbled with N_2 for 15 min. After that, the tube was closed and kept for 20 h at the required temperature (i.e., 100°, 130°, 160°, or 190°C) in an oven. Then, the tube was cooled and the crude sample collected. Characteristics of the product obtained at 100°C: ^{1}HNMR (CDCl3): $\delta = 1.373$ (*m*, c), 1.643 (*m*, b, d), 1.934 (*q*, A), 1.953 (*q*, A′), 2.294 (*t*, e), 3.633 (*t*, a′), 3.832 (*t*, C′), 4.049 (*t*, a), 4.327 (*m*, B), 5.580 (*m*, H_D, $H_{D'}$), 6.109 (*m*, H_E), 6.136 (*m*, $H_{E'}$). Assignments are described in the following scheme:

HEMA



HEMA-CL_n-OH



The percentage of residual unreacted HEMA was calculated from the areas of the acrylic signals at 6.109 and 6.136, according to the following expression:

$$residual\ HEMA = \frac{A_{6.136}}{A_{6.136} + A_{6.109}} 100 \quad (1)$$

In the reaction at 100°C, there is 4% of residual HEMA. The average length of the oligo-CL chains can be calculated from the integrals of $CH_2{-}O{-}$ (a) and $CH_2{-}OH$ (a′) of the CL units at 4.049 and

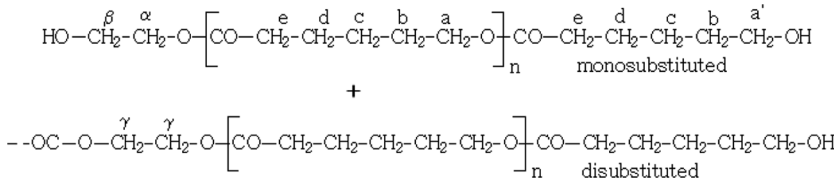
3.633 ppm respectively.

$$\overline{DP}_n = \frac{A_{4.049} + A_{3.633}}{A_{3.633}} \quad (2)$$

which is in this case 10.2, very close to the theoretical value, 10.4, obtained from the initial feed ratio (10) and the residual HEMA (4%). Residual unreacted CL has never been detected. The products obtained at higher temperatures exhibit complex spectra that will be analyzed in the discussion section below.

Ring Opening Polymerization of CL Initiated by Ethylene Glycol

CL was polymerized with ethylenglycol (EG) as initiator and $SnOct_2$ as catalyst as described in the literature.[14] CL/EG feed ratio was adjusted to obtain dihydroxy oligomers with low nominal Mn (approximately 500 Da). It has already been shown for diethylenglycol (DEG)-initiated PCL diols that three species are formed after complete CL polymerization: free DEG, monosubstituted DEG, and disubstituted DEG.[15] For our EG-initiated PCL diol, after complete CL polymerization, vacuum was applied when the reaction was at high temperature (130°C) to eliminate free EG. The remaining polymerized mass consisted of mono and disubstituted species. ^{1}H NMR ($CDCl_3$): $\delta = 1.386$ (*m*, c), 1.635 and 1.571 (*m*, b, d), 2.295 (*m*, e), 3.631 (*t*, a′), 3.812 (*t*, β), 4.048 (*t*, a), 4.199 (*t*, α), 4.263 (*t*, γ). Assignments are described in the following scheme:



NMR Characterization

Products were characterized by ^{1}H-NMR in a Varian VNMRS-500 at 500 MHz, using $CDCl_3$ as solvent, 5% W/v, and the relaxation time between pulses of 5 s. The residual signal of the deuterated solvent was used as the internal reference (7.24 ppm).

MALDI-TOF Characterization

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) spectra were recorded by using a Voyager DE-PRO time-of-flight mass spectrometer (Applied Biosystems) equipped with a nitrogen laser emitting at $\lambda = 337$ nm with a 3 ns pulse width and working in positive ion mode and delayed extraction. A high acceleration voltage of 20 kV was employed, and 2,5-dihydroxybenzoic acid (DHB) at a concentration of 10 mg/mL in acetonitrile was used as a matrix. Samples were dissolved in acetonitrile and mixed with the matrix at a molar ratio of approximately 1:100.

RESULTS AND DISCUSSION

In Figure 1, the main reactions related to the competition between ring opening and transesterification are depicted. There are several distinctive issues that must be addressed. Transesterification broadens the size distribution, as has been extensively reported for similar polymerizations.[8,10,11,13] It is also well known that the higher the temperature, the higher the weight of transesterification. Moreover, intramolecular ester interchange reactions will lead to cyclic compounds. If we initially discard these intramolecular reactions, which are expected to occur in

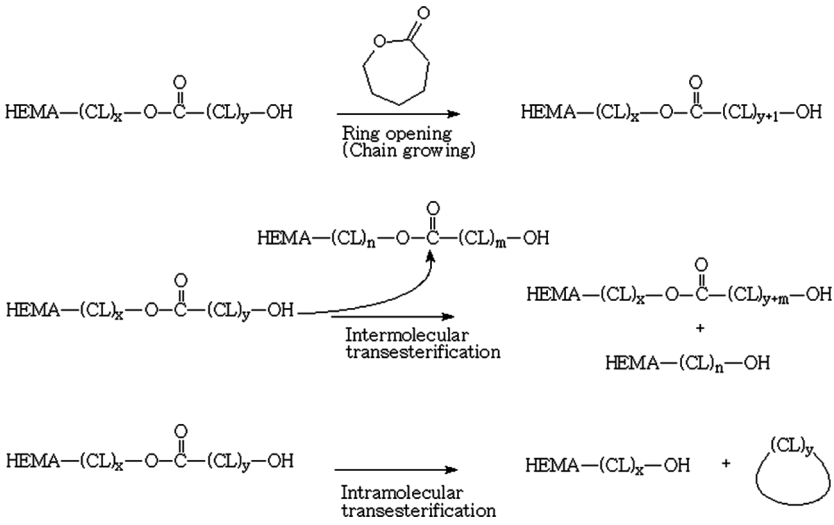


Figure 1. Competition between ring opening and transesterification in the reaction of HEMA and CL in the presence of $SnOct_2$.

low extension in oligocompounds such as those prepared in this work, the transesterification does not affect the total number of active OH end groups or the number-average molecular weight unless the first ester group is attacked, the ester that links the oligo-CL to HEMA. In this case, free HEMA is formed and if we exclude this HEMA fraction, the average M_n of the macromonomers will increase compared with the case of no free HEMA formation.

In Figure 2, the mass spectra of the reactions carried out (as described in the experimental section) at 100° and 130°C are shown. The spectra of the products obtained at higher temperatures were very similar to these obtained at 130°C but are not shown here. The mass spectra present complex patterns, the most populated signals corresponding to the macromonomers HEMA-CL_n-OH with different lengths. For the shake of simplicity, the signals of the macromonomers with 10, 20, 30, and 40 units are indicated in the spectra. If we focus initially on the shape of the distribution of the macromonomers (the main peaks), we see clear differences. Transesterification takes place at higher extension in the reaction performed at 130°C, as would be expected, because there is a broadening in the distribution and the spectra exhibit higher population of high molecular weight species. Further increase in temperature does not seem to increase much the influence of transesterification, as the spectra are very similar to the spectrum at 130°C.

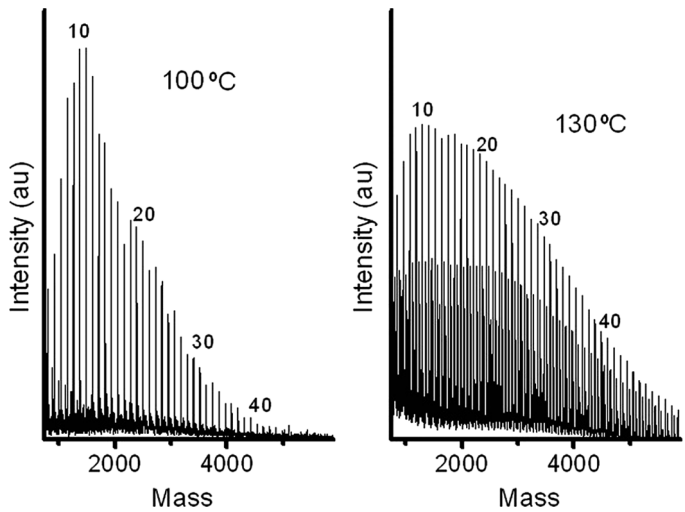


Figure 2. Mass spectra in linear mode of the reactions carried out at 100°C (left) and 130°C (right). Numbers indicate the number of CL units in the chains. Au = arbitrary units.

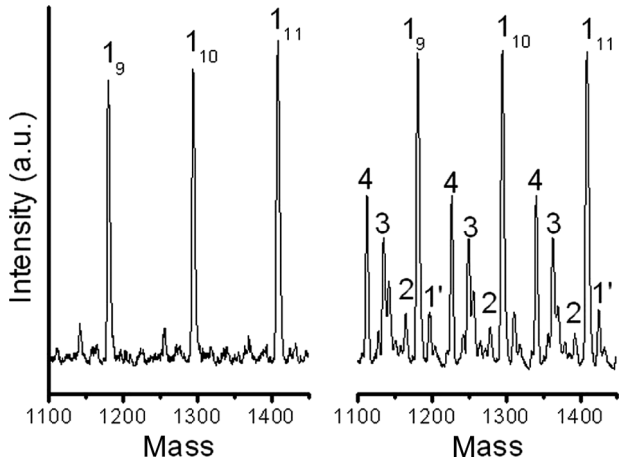


Figure 3. Expanded view for the 1100–1450 m/z fragments (linear mode) of the products in Figure 2. Au = arbitrary units.

The spectrum of the reaction performed at 130°C, however, is quite complex and presents the underlying distributions of other species also separated by a mass of 114 (the mass of the CL unit), which should correspond to polymer or oligomer families with different end groups. In Figure 3, a detailed area of both spectra is shown to analyze them more deeply. The peaks corresponding to the sodiated macromonomers (at masses of $130 + 114 \times n + 23$; in the figure, 1179, 1293, and 1407) have been labeled *1*, the subscript indicating the length of the macromonomer. The potassium cationized species could also be detected, labeled *1′*.

Transesterification is evidenced by the appearance of cycles formed by intramolecular reactions (see Figure 3 at masses 1163, 1277, and 1391), which correspond to the sodiated cycles ($114 \times n + 23$). The peaks are labeled *2*. These cycles are also present in the product at 100°C but only at low molecular weights and with a very low intensity, which is in agreement with the previous discussion: the transesterification takes place (in some degree) at 100°C, but at 130°C, its influence is noticeable.

The other two main species, labeled *3* and *4*, seem to be related with the ester of the HEMA unit itself. As suggested by Eguibiru et al.[10] for L-lactide ROP, HEMA presents an additional ester group that may be sensitive to the ester interchange reactions. If the transesterification takes place at the HEMA ester bond, two new species are formed, as depicted in Figure 4. These two new species *3* and *4* present the masses compatible with the extra peaks of the mass spectrum of the 130°C reaction, at $198 + 114 \times n + 23$ and $62 + 114 \times n + 23$ respectively, in Figure 4 at 1133, 1247, and 1361 for species *3* and 1111, 1225, and 1339 for species *4*.

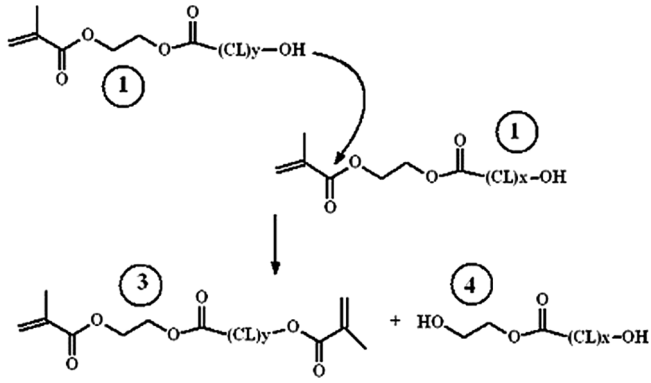


Figure 4. Possible tansesterification of the acrylic ester of HEMA with the formation of species *3* and *4*.

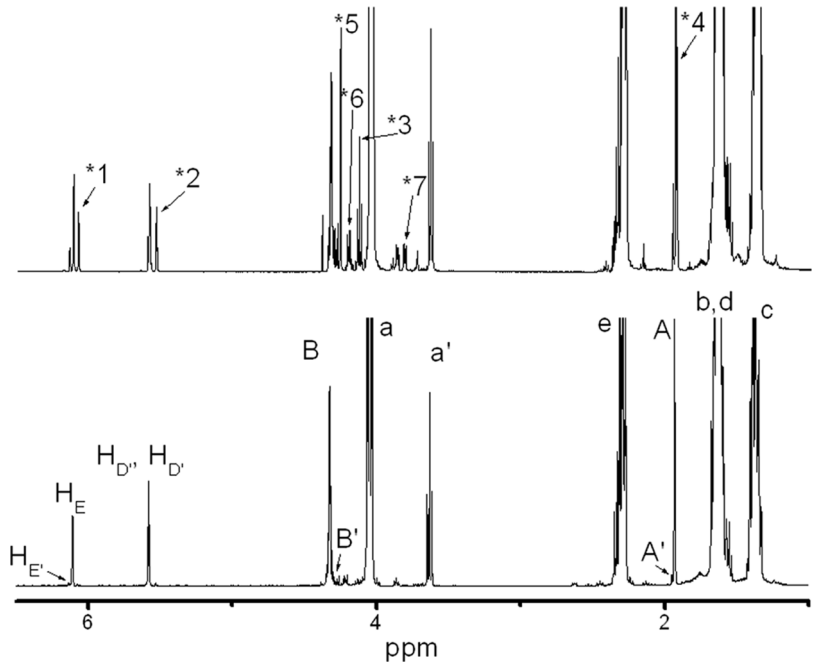
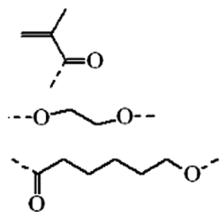


Figure 5. ^{1}H-NMR of the reactions carried out at 100°C (lower spectrum) and 130°C (upper spectrum). Labels of the lower spectrum according to the scheme presented in the experimental section. Labels of the upper spectrum are explained in the text.

This transesterification reaction has been confirmed by ^{1}H-NMR analysis of the reaction performed at 130°C, shown in Figure 5 together with the spectrum of the reaction at 100°C used as reference of low transesterification.

A comparative and detailed analysis of the spectra gives us an additional information on the process and confirms the proposed reaction products in Figure 4. The product obtained at 100°C is almost pure macromonomer, with 4% of unreacted HEMA. However, the product obtained at 130°C is a complex mixture of compounds. In addition to the macromonomer, other species are present. New acrylic signals have been detected at 6.082 and 5.541 ppm (labeled **1* and **2*) that have been assigned to the acrylate group of species *3* in Figure 4. The areas of these new acrylic signals are related by a ratio of approximately 2 to the area of a new CH_2-O triplet centered at 4.133 ppm (labeled **3*) that has been assigned to the CH_2-O of the CL end linked to the new acrylic functionality in species *3*. A new α-CH_3 corresponding to this compound is also detected (**4*). In the acrylic region, the increase of the residual HEMA (peaks labeled *H*) in the upper spectrum is also interesting compared with the one of the reaction at 100°C. In this case, by applying Equation (1), we obtain a residual percentage of HEMA of 15%, while in the reaction at 100°C we obtained 4% of residual HEMA. This is also in agreement with a higher transesterification because more free HEMA may be formed.



Possible compounds present in the medium

C01 Acryloyl-OEO-H = HEMA
C02 Acryloyl-OEO-(CL)n-H = HEMA-(CL)n-H (macromonomer, species 1)
C03 Acryloyl-OEO-Acryloyl
C04 Acryloyl-OEO-(CL)n-Acryloyl = species 3
C05 H-OEO-(CL)n-H = species 4
C06 H-(CL)n-OEO-(CL)n-H; mass = mass C05 (species 4)
C07 H-OEO-(CL)n-Acryloyl; mass = mass C02 (species 1)
C08 Acryloyl-(CL)n-OEO-(CL)n-H; mass = mass C02 (species 1)
C09 Acryloyl-(CL)n-OEO-(CL)n-Acryloyl mass = mass C04 (species 3)
C10 H-OEO-H = EG (not found)

Figure 6. Suggested compounds present in the medium if the acrylic ester participates in ester interchange reactions.

The upper spectrum exhibits additional signals in the 3–5 ppm region compared with the lower spectrum, which is the region of the CH_2-O signals. These new peaks are related to the new species *4* and to the further progression of the reaction. This molecule *4* is a diol that may participate in other transesterification reactions, leading to a mixture of mono- and disubstituted ethylene oxide derivatives, which correspond to the new signals at 4.263 (disubstituted compound, labeled **5*) and 4.208 and 3.820 ppm (monosubstituted, labeled **6* and **7*). To confirm these assignments, the ROP of CL initiated by ethylene glycol was carried out as described in the experimental section. This reaction leads to a mixture of mono- and disubstituted compounds, with NMR shifts that are in complete agreement with the scheme described above.

As the acrylic ester participates in the interchange reactions, the process is actually quite complex, and a complete screening of the possible reactions leads to 10 possible compounds that may be present simultaneously in the medium. These 10 compounds, which are depicted in Figure 6, correspond to all possible combinations of the three different blocks: dioxyethylene, acryloyl, and the CL unit.

All these species are compatible with the previous analysis by MALDI-TOF, because, excluding the low molecular weigh compunds C01, C03, and C10 that cannot be analyzed by this technique due to the interference of the matrix signals, the molecules exhibit mass patterns compatible with species *1*, *3*, and *4* described previously, as detailed in Figure 6.

Therefore, the transesterification process may not only affect size distribution, but also the acrylic functionalization itself, leading to alternative acrylic compounds, to difunctional diacrylates, and to diols without polymerizable units.

CONCLUSION

MALDI-TOF and NMR analysis of the ring opening polymerization of CL initiated by HEMA at different temperatures and using $SnOct_2$ as catalyst, evidenced the influence of the transesterification at 130°C and higher temperature on the broadening of the size distribution as well as on the increase in population of longer macromonomers. Moreover, the acrylic ester may also overcome interchange reactions leading to secondary products without acrylic functionality or to difunctional acrylates that may act as cross-linkers. MALDI-TOF discriminates all different end groups (and cycles) formed in the process. If side reactions have to be avoided, the ROP with $SnOct_2$ should be performed at temperatures not exceeding 100°C.

REFERENCES

[1] Lui, Y., M. Schulze, and A. C. Albertsson. (1998). α-Methacryloyl-ω-hydroxyl-poly(ε-caprolactone) macromonomer: Synthesis, characterization, and copolymerization. *J. Macromol. Sci. Pure Appl. Chem.* **A35**, 207–232.

[2] Tarabic, M., and E. Ranucci. (2001). New methacryloxy N-vinyl-2-pyrrolidinone- and lactone-based macromers. *Macromol. Biosci.* **1**, 126–135.

[3] Cretu, A., R. Gattin, L. Brachais, and D. Barbier-Baudry. (2004). Synthesis and degradation of poly (2-hydroxyethyl methacrylate)-graft-poly (ε-caprolactone) copolymers. *Polym. Degradation Stab.* **83**, 399–404.

[4] Xu, X., and J. Huang. (2004). Synthesis and characterization of well-defined poly(2-hydroxyethyl methacrylate-co-styrene)-graft-ε-caprolactone by sequential controlled polymerization. *J. Polym. Sci. Polym. Chem.* **42**, 5523–5529.

[5] Xu, X., and J. Huang. 2006. Synthesis and characterization of amphiphilic copolymer of linear poly(ethylene oxide) linked with [poly(styrene-co-2-hydroxyethyl methacrylate)-graft-poly(ε-caprolactone)] using sequential controlled polymerization. *J. Polym. Sci. Polym. Chem.* **44**, 467–476.

[6] Ydens, I., P. Dubois, J. Libiszowski, A. Duda, and S. Penczek. (2003). Combining ATRP of methacrylates and ROP of L,L-dilactide and ε-caprolactone. *Macromol. Chem. Phys.* **204**, 171–179.

[7] Erdodi, G., and J. P. Kennedy. (2006). Amphiphilic conetworks: Definition, synthesis, applications. *Prog. Polym. Sci.* **31**, 1–18.

[8] Spassky, N., V. Simic, M. S. Montaudo, and L. G. Hubert-Pfalzfraf. (2000). Inter- and intramolecular ester exchange reactions in the ring-opening polymerization of (D,L)-lactide using lanthanide alkoxide initiators. *Macromol. Chem. Phys.* **201**, 2432–2440.

[9] Báez, J. E., A. Martínez-Richa, and A. Marcos-Fernández. (2005). One-step route to α-hydroxyl-ω-(carboxylic acid) polylactones using catalysis by decamolybdate anion. *Macromolecules* **38**, 1599–1608.

[10] Eguiburu, J. L., M. J. Fernandez-Berridi, and J. San Roman. (2000). Ring opening polymerisation of L-lactide initiated by oxyethyl methacrylate-aluminium trialkoxides Part 2: End groups exchange. *Polymer* **41**, 6439–6445.

[11] Dubois, P., C. Jacobs, R. Jerome, and P. Teyssie. (1991). Macromolecular engineering of polylactones and polylactides. 4: Mechanism and kinetics of lactide homopolymerization by aluminum isopropoxide. *Macromolecules* **24**, 2266–2270.

[12] Szymanski, R. (1998). Molecular weight distribution in living polymerization proceeding with reshuffling of polymer segments due to chain transfer to polymer with chain scission. 1. Determination of kp/ktr ratio from DPw = DPn data: Ideal reproduction of polymer chain activities. *Macromol. Theory Simul.* **7**, 27–39.

[13] Isoda, M., H. Sugimoto, T. Aida, and S. Inoue. (1997). Lewis acid-driven accelerated living polymerization of lactones initiated with aluminum porphyrins. Chemoselective activation of ester groups by Lewis acid. *Macromolecules* **30**, 57–62.

[14] Abraham, G. A., A. Marcos-Fernández, and J. San Román. (2006). Bioresorbable poly(ester-ether urethane)s from L-lysine diisocyanate and triblock copolymers with different hydrophilic character. *J. Biomed. Mater. Res.* **76A**, 729–736.
[15] Marcos-Fernández, A., G. A. Abraham, J. L. Valentín, and J. San Román. (2006). Synthesis and characterization of biodegradable non-toxic poly(ester-urethane-urea)s based on poly(ε-caprolactone) and amino acid derivatives. *Polymer* **47**, 785–798.