Synthesis of acrylate functional telechelic poly(lactic acid) oligomer by transesterification

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The controlled synthesis of low molecular weight (Mn from 700 to 10 000 g/mol) poly(lactic acid) (PLA) telechelic oligomers end-capped with acrylate groups by a one-step reaction was investigated. A transesterification reaction was carried out in solution with a Lewis acid titanium catalyst using a high molecular weight PLA and a low molar mass diacrylate. End-functionalization was demonstrated by proton NMR spectroscopy which was also used for quantitative analysis and number average molecular weight determination using the ratio between the acrylic chain ends to the main groups of poly(D,L-lactic acid). The formation of low molar mass oligomers from high molecular weight poly(lactic acid) was verified by gel permeation chromatography. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry showed that the above oligomerization was accompanied by the formation of cyclic compounds. By these means the feasability of a simple transesterification for a controlled synthesis of telechelic oligomers with molecular mass being a function of the added amount of diacrylate has been demonstrated. The glass transition temperatures of the elaborated oligomers varied from -35 to $-5\,^{\circ}$C. Subsequent thermal crosslinking was performed using benzoyl peroxide which enabled the formation of amorphous networks with Tg's close to the body temperature of 40 °C. Upon storage in a humid atmosphere the initially fairly hard and brittle networks became, due to hydrolysis, progressively more flexible thus demonstrating the potential biodegradability of these materials.

1. Introduction

Over the last decade, biocompatible and biodegradable polymers have become widely employed for medical applications such as sutures, tissue scaffolds or drug delivery [1, 2]. The bioabsorbable devices present clear advantages compared with non-degradable polymers. No additional operation is necessary to remove the implant and hence postoperative complications are eliminated. The most commonly used synthetic biodegradable polymers for surgery and pharmaceutical applications are the polyesters. Polyesters of glycolic, lactic, hydroxybutyric acid (PGA, PLA and PHB, respectively) and their copolyesters represent the main groups of interest due to their favorable mechanical properties in combination with low toxicity of the degradation products [3] which are easily metabolized. The *in vivo* degradation and tissue tolerance of these matrix materials have been extensively studied demonstrating their biocompatibility [4, 5]. Manipulation of their physical properties and chemical composition may be employed to achieve the desired rate of degradation and the desired physico-chemical properties *in vivo*. These properties are indeed strongly dependent on the chemical structure, molecular weight and crystallinity of the polymer considered.

However, for many biomedical applications, these polymers exhibit limitations. Since these are saturated polyesters they do not submit with ease to crosslinking, rendering impossible any *in-situ* modifications and control of their shapes or properties [6]. Moreover, in semi-crystalline high molecular weight polymers, small crystalline domains are undigestable residues for the macrophages affecting their biocompatibility in a fashion that may hinder their employment [7]. In order to control the physico-mechanical properties of the biodegradable materials, a modification of the molecular structure and chain length is a possible means to obtain new building blocks for the production of segmented copolymers and polymer networks with improved and tailored characteristics.

Among several approaches, the intentional synthesis of end functional prepolymers is a valuable method for the elaboration of new materials [8]. Concerning the poly(lactic acid), the most efficient way of synthesis is living ring-opening polymerization of the lactic acid cyclic dimer usually initiated by coordination initiator

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such as metal alkoxides leading polymer with narrow molecular weight distribution [9, 10]. The synthesis of low molecular weight oligomers has also been described earlier either by polycondensation of lactic acid [11] or by hydrolytic degradation of the high molecular weight PLA [12]. In addition, the use of functional initiators of the living polyaddition reaction have proved to be very successful [13–17] for the synthesis of end-reactive telechelic oligomers or macromonomers. The chemical structure and molecular weights of the polymers obtained are highly influenced by the occurrence of interchange reactions at the ester bonds [18] leading to a random cleavage of the main chain [19] and even rearrangements of chiral units. Hiltunen *et al*. [20] have recently reported on the preparation of lactic acid based telechelic prepolymers and the mechanisms of the reactions. They did also examine the effect of acid catalysts and polymerization conditions on the resulting molecular weight, physical properties and ester exchange reactions. Several types of catalysts, acidic, basic or organometallic compounds can favor these reactions [21].

Alternatively, the transesterification can be a useful reaction for the chemical modification of high molecular weight polyesters. Although this reaction is generally described in polymer chemistry as a secondary reaction occurring during polyester synthesis, in recent publications it appears as the main reaction. A statistical method for the prediction of molecular weight and molecular weight distribution for PLA transesterified by poly-(ethylene glycol) has been developed by Gallardo *et al*. [22]. Hirt *et al*. [23] have studied the chemical modification of high molecular weight polyhydroxybutyrate (PHB) and the synthesis of telechelic macrodiols by transesterification. They have developed a procedure using an excess of ethylene glycol as diol and dibutyltin dilaurate as catalyst. Other examples include the transesterification for the elaboration of PHB macrodiols with 1,10-decanediol or 2,2-dimethyl-1,3-propanediol and p-toluenesulfonate or dibutyltin oxide as transesterification agent and as catalysts [24, 25]. Unfortunately, in both approaches, large excess of catalyst and coreactants has been found necessary to push the conversion to a desired molecular weight of the polyester.

The aim of this work is to prepare controlled molecular weight telechelic oligomers. Specifically, acrylic end groups are intended to be introduced in a one step procedure by a transesterification reaction starting from a high molecular weight polyester and a low molecular weight diacrylate. Such telechelic oligomers should be susceptible to radical crosslinking to form potentially biodegradable networks.

2. Experimental section

2.1. Materials

The PLA sample Resomer 207 ($Mn = 128\,900$, $I = 2.09$) was supplied by Boerhinger Ingelheim (Germany). The transesterification agents, ethylene diacrylate (I) and tetra(ethylene glycol)diacrylate (II), were purchased from Aldrich. Ethylene diacrylate was used after vacuum distillation while tetra(ethylene glycol)diacrylate was used as received.

The highly reactive titanium isopropoxide (Aldrich) was used in a glove box under nitrogen. Toluene used for the synthesis was dried by stirring with CaH_2 for 15 h and distilled under dry Ar atmosphere. The other solvents (p.a.) where purchased from Fluka and used as received.

2.2. Characterizations – measurements – methods

The molecular weights (Mn and Mw) and molecular weight distributions (Mw/Mn) were determinated by gel permeation chromatography (GPC) using a Waters 150 CV System equipped with differential refractometer and viscosimeter detectors. For the separation of the low molecular weight oligomers ($Mw < 30\,000$ g/mol) two columns Plgel mixed-E (Polymer Laboratories) connected in series were applied (length 300 mm, diameter 7.5 mm, pore width 3 μm). For the PLA characterization a series of Waters Ultrastyragel columns 10^3, 10^2, and 10^1 nm were used. Calibration was performed using polystyrene standards. Methylene chloride was used as the eluting solvent with a flow rate of 1.0 ml/min at 30 °C using a polymer concentration of 1 mg/ml. The injection volume was 200 μl.

Matrix-assisted laser desorption ionization (MALDI) was performed using 3,5-dimethoxy-4-hydroxycinnamic (DHBA) acid as matrix on a Perseptive Biosystems Voyager RP mass spectrometer using a 337 nm nitrogen laser, a 25 kV accelerating potential and a delayed extraction of 300 ns. To 1 μl of the sample solution was added 9 μl of the matrix solution and 1 μl thereof was deposited on a gold-plated target and air-dried prior to transfer into the mass spectrometer. The matrix solution of DHBA was prepared with 10 mg/ml in H_2O/0.1% trifluoroacetic acid : acetonitrile (2 : 1).

The chemical structure of the compounds was determined by proton nuclear magnetic resonance (NMR) spectroscopy on a Bruker AC–P200 spectrometer at 200 MHz using deuteriochloroform as solvent and tetramethylsilane as internal standard with a sample concentration of 20 mg/ml.

Differential scanning calorimetry (DSC) was performed on a DSC 7 Perkin Elmer apparatus from -50 to 100 °C at a heating rate of 10 °C/min. The glass transition was determined from the second heating period as the midpoint of the slope.

2.3. Synthesis of telechelic PLA oligomers

For the preparation of the telechelic PLA oligomers, a solution of high molecular weight PLA was transesterified with a diacrylate in presence of a catalyst. All reactions were carried out in solution under a positive argon pressure. A specific example of an oligomer with a degree of polymerization (DP) of 105 is given below. Into a two-necked, flame-dried 500-ml flask equipped with a magnetical stirrer, a Dean-Stark separator, a reflux condenser and an argon inlet, PLA (10 g, 139 mmol of lactic acid repeating units (LA r.u.)) are dissolved in a freshly distilled toluene ($\sim$160 ml) to give a $\sim$6 wt % solution. The toluene was partly removed ($\sim$80 ml) by azeotropic distillation, the residue was left to reflux (130 °C in oil bath) for 12 h and an additional 20 ml of toluene was distilled out. After cooling under dry argon a

calculated amount of diacrylate (0.96 mol % with respect to the LA r.u.) and the titanium isopropoxide catalyst (~ 10 mol % with respect to the diacrylate) was added. Then, the flask was connected to a flamed condenser and submerged into an oil bath thermostated at 115 °C. A continuous flow of dried argon gas was maintained under the surface during the reaction. After 15 h the solution was cooled to room temperature. In order to isolate the reaction products, the solvent was evaporated by bubbling air into the solution at 45 °C. The viscous solution obtained was then subjected to purification by flash chromatography.

2.4. Purification procedure of the oligomers

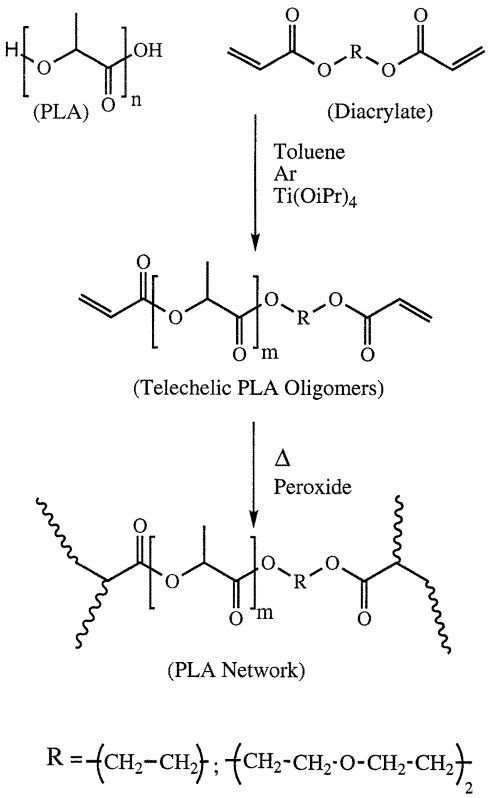
In order to purify the functionalized oligomers, to eliminate residual solvent, any eventual unreacted ethylene diacrylate and the catalyst, flash chromatography was chosen [26]. The viscous solution was mixed with silicagel (Kieselgel 40) and placed on top of a layer of 15 cm of silicagel. A gradient of hexane to ethylacetate was passed through the column using a gas flow of 5 cm^3/min. All fractions collected were first dried under mild vacuum at 30 °C with a rotary evaporator and subsequently in a dessicator under vacuum.

2.5. Thermal crosslinking

Benzoyl peroxide (4 mg) was dissolved in 0.1 ml of acetone and mixed into 400 mg of functionalized oligomer. This mixture was placed on a Mylar® foil and subjected to vacuum for 10 min at room temperature to evaporate the solvent and finally heated to 100 °C for 2 h under nitrogen to complete the crosslinking. The gel content was determined by extraction with dry toluene until constant weight (24 h).

3. Results and discussion

To synthesize biodegradable crosslinked networks composed of polylactide suitable for new biomedical applications, acrylated telechelic oligomers of poly(-lactic acid) were synthesized by a transesterification reaction according to Scheme 1. A one-step procedure allows for the reaction between high molecular weight poly(D,L-lactic acid) and a diacrylate by presence of an organometallic catalyst i.e. titanium (IV) isopropoxide or butoxide. Such reactions can be catalyzed by a variety of acids or bases, particularly the titanates are known to be extremely powerful for the ester-exchange reaction [20, 27, 28]. The mechanism recognized in organic chemistry is rearrangement between esters and can be described by a temporary complex between the oxygen of an ester group and the metal of the organometallic compound. It is followed by a successive ligant exchange on catalyst with one of the esters in the reaction mixture and finally the modified catalyst reacts with a second ester. The transesterification proceeds by a continuous random cleavage and the recombination of the polylactide chains. In this work, we have decided to carry out the transesterification to give acrylate end-groups functionalization which should enable a subsequent radical reaction with the build-up of crosslinked networks. A series of transesterifications of polylactide with ethylene diacrylate or tetra(ethylene glycol)diacrylate were carried out in solution at 100 °C. The various oligomers prepared with molecular weights defined between 700 to 7800 g/mol are presented in Table I. The DP was controlled by the molar ratio between the lactic acid monomeric units (PLA r.u.) and the diacrylate and could be calculated from the Carother equation and concidering a total conversion of diacrylate. It was shown that the catalyst concentrations of 10 mol % to diacrylate was necessary for reasonable reaction times. Irrespective of diacrylate used, the same visible evolution of reaction mixtures were noted. At first the solutions were water white but became slightly orange and opalescent after some hours of reaction. This is probably caused by deactivation of the catalyst by hydrolysis [29]. Indeed, the initial attempts to perform this reaction showed its extreme sensitivity to any traces of water. For reproductible results, it is absolutely essential to carry out the reaction under very dry conditions. Therefore, an azeotropic distillation with dried and deoxygenated toluene was applied to remove all residual traces of water in the solvent, absorbed in the polyester by hydrogen bonding or on the glassware.



Scheme 1 Reaction scheme for the synthesis of crosslinkable acrylated telechelic oligomers of poly(lactic acid).

The reaction was monitored by regularly taking out all aliquots for GPC analysis. A complete disappearance of the high molecular weight PLA and the appearance of a single peak low molecular weight product indicated the completion of the reaction. Usual reaction times were 24 h. GPC of the starting high molecular weight PLA is shown in Fig. 1a together with an oligomer as produced by the reaction (Fig. 1b) (Mn = 11 630g/mol) and with a fraction of this oligomer purified on a silica column (Fig. 1c). After 24 h of reaction, the GPC traces show a

TABLE I Synthesis conditions, molecular weight determinations and thermal characterizations of the oligomers prepared

Polymer	Diacrylate [a]% mol	Time (h)	Temp. (°C)	Mn theory [b] g/mol	Mn GPC g/mol	I GPC g/mol	Mn NMR g/mol	Tg (°C)
1	–	–	–	–	128 900	2.09	128 900	55
2	12.0	24	115	770	1217	1.42	602	– 34.5
3	4.78	24	115	1846	1468	1.65	1827	– 12.6
4	0.96	24	120	7818	11 630	1.68	7096	– 5*

[a]Amount in mol% of diacrylate transesterification agent.
[b]Estimated number average molecular weight considering a total conversion of diacrylate. *Purified.

monomodal peak distribution of low molecular weight oligomers. The polydispersity of the oligomer in Fig. 1b is by GPC 1.42. Most likely this is caused by the inability of GPC to determine Mw correctly. Somewhat surprising was the polydispersity of only 1.15 of the sample purified on silica, since a part of the chain ends probably contained titanium which is known to be toxic and hence unusable for *in vivo* use.

The investigation of the chemical structure and in particular the end functionalization of the oligomers was done by ^{1}H-NMR spectroscopy. Deuterated chloroform ($CDCl_3$) was the selected solvent as generally reported in the literature for NMR analysis of PLA polymers and copolymers [30], although some of the results have demonstrated that a better resolution and identification of resonance positions can be improved considerably by using DMSO-d_6 [31]. In the present study, however, the PLA repetitive units and the chain ends gave distinct signal of resonance as shown by Fig. 2. After transesterification with the diacrylate, the resonance peaks of the polymer backbone were clearly identified. Compared to a pure poly(lactic acid) showing multiplets at $\delta = 1.6$ ppm (d, H_d) and $\delta = 5.2$ ppm (m, H_e) assigned to the protons of the methyl $(-CH_3)$ and methine (–CH–) groups respectively of the lactic acid unit, the characteristic signals of the acrylate appeared in the range 5.9 to 6.5 ppm which showed that the chemical modification and the intended functionalization was achieved. The peaks H_i (m, 5.2 ppm) and H_{ii} (d, 1.7 ppm) revealed the formation of a cyclic lactide. This is due to the randomness of the ester exchange reaction and the formation of cyclic derivatives along with linear chains [32].

Moreover, in each spectra a H_{iii} doublet (1.2 ppm) is present corresponding to the methyl group of the isopropoxide deriving from the ligand of titanium isopropoxide catalyst now showing up as the terminal group in some polymer chains. For biomedical and pharmacological applications, a catalyst based on tin would be preferable due to lower toxicity [33].

In order to determine the average molecular weights (M_n), the quantitative analysis of the NMR spectra was performed. We calculated this using the ratio of the integration values of end group protons to the main chain protons. M_n values are in good agreement to the charged compositions (theoretical values) as can be seen in Table I. The slight lowering might be due to isopropoxide ligands attached to some chain ends.

In order to study each individual species in a mixture of oligomers matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) may be employed, as it possesses unprecedented high sensitivity allowing for desorption and ionization even of very large molecules such as polymer samples [34]. An analysis using MALDI-TOF (Fig. 3) indeed showed the

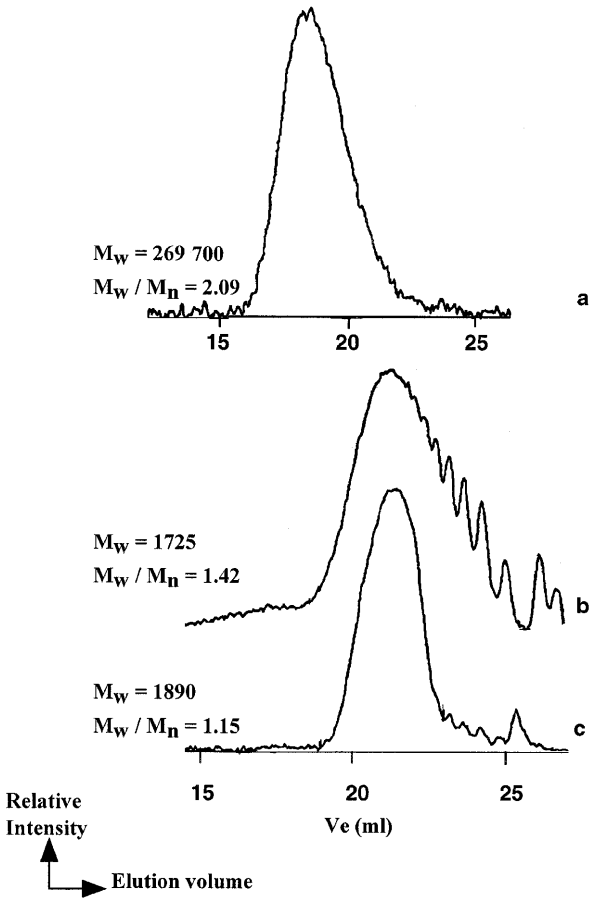


Figure 1 Gel permeation chromatography (GPC) trace of high molecular weight poly(D,L-lactic acid) and the oligomers obtained by its catalytic depolymerization.

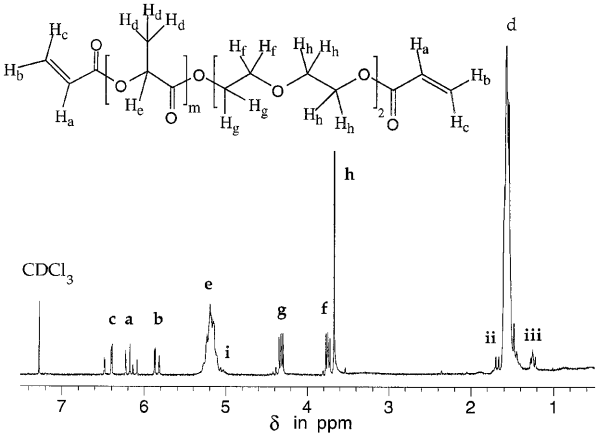


Figure 2 ^{1}H-NMR spectrum of telechelic poly(D,L-lactide acid) (DP = 105) derived from PLA and tetra(ethylene glycol)diacrylate.

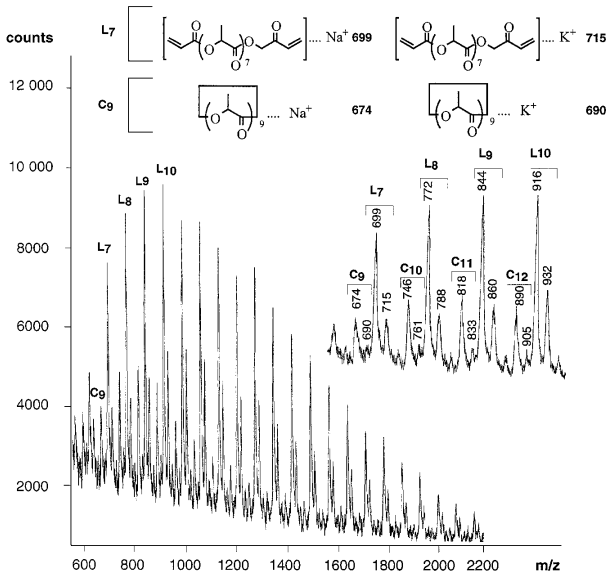


Figure 3 MALDI–TOF mass spectrum of the low molecular weight telechelic poly(D,L-lactide acid) (DP = 8) derived from PLA and ethylene diacrylate.

distribution of molecular weight centered around 1000 g/mol for polymer 2, but also a second population of molar masses centered at lower molecular weights. A close-up on this spectrum reveals the correspondence in molecular weight to Na^+ complexed linear diacrylate telechelics, with L_7Na^+ to $L_{28}Na^+$. The total molar mass is given by the sum of the individual contributions from ethylene-diacrylate (170.16 g/mol), the multiple n of the PLA repeat unit (72.06 g/mol) and sodium (23.00 g/mol), i.e. for L_nNa^+ with $n = 7$, this becomes $170.16 + 7 \cdot 72.06 + 23.00 = 697.58$ (the small deviation of 2 a.m.u. is within the MALDI accuracy of ± 4 a.m.u. [35]). The small peak, always occurring at 16 g/mol higher molecular weight to the right of each major peak corresponds to the same oligomers but complexed with K^+, i.e. L_7K^+ to $L_{28}K^+$. To the left in Fig. 3 is shown the lower molecular masses where the spectrum is more rich. Along with the linear telechelics an additional mass series is found arising from cyclic oligomers, i.e. C_9Na^+ to $C_{12}Na^+$ with molar mass simply being the sum of multiples of the PLA repeat unit and the sodium ion, also here with smaller C_nK^+ shoulders.

Thermal crosslinking of the oligomers resulted in the formation of fairly hard, colorless, transparent and slightly brittle materials. The Tg value determined by DSC was measured on unreacted oligomers and varied from -34 to $-5\,^\circ$C in correlation with the increase of the molecular weight from preparation. Crosslinking brought about an increase of Tg to approximately 40 °C for oligomers 2 and 3 confirming that a three-dimensional network was formed by the free radical initiator. However the presence of low molar mass cyclic oligomers contributes to plasticize the network giving a Tg that is lower than the high molecular weight linear PLA (50 °C). Extraction of the networks indeed revealed approximately 13 and 18% sol fraction for oligomers 2 and 3 respectively. One month storage in ambient atmosphere decreased Tg to 20 °C demonstrated their latency to hydrolytic degradation.

The residue after complete hydrolysis should, apart from lactic acid, consist of polyacrylic acids which *in vivo* can be removed by the kidneys provided that their molecular weight does not exceed 5000 g/mol [36].

4. Conclusion

We have shown that to elaborate new polymeric bioabsorbable materials, poly(D,L-lactic acid) can be modified by a one-step transesterification procedure to prepare telechelic oligomers with both controlled molecular weight and end functionality. By the amount of the difunctionnal ester compound added, here a diacrylate, the molecular weight of the desired oligomers can be controlled. The end groups of the oligomers were identified by ^{1}H-NMR and the degree of polymerization (DP) was calculated based on the ratio of integration of the acrylic chain ends to the main PLA groups. The formation of low molecular weight oligomers was confirmed by GPC and MALDI which revealed the simultaneous formation of oligomeric cycles.

These acrylated telechelic poly(lactic acid) oligomeric intermediates are not only interesting from the point of view of the macromolecular engineering but also for synthesis of new biodegradable materials with tailored properties.

This procedure of functionalization is easy and time saving compared to the traditional methods using first living polymerization of lactide into PLA of controlled molecular weight followed by functionalization of chain ends. Moreover, it is general for the synthesis of both telechelics and α, ω-macromers simply by the choice of starting low molecular weight ester and one can envisage that this method will be extended to the elaboration of functional oligomers in similarity to the methods using functional initiators and reactive termination.

Acknowledgments

The authors wish to acknowledge the Research Funds UNIL–EPFL 1996 for the financial support, Dr Tuan Nguyen for valuable help and discussion concerning GPC and Dr Torbjörn Mathiesen for encouraging help and Guidor AB for providing the poly(D,L-lactic acid).

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Received 24 December 1998
and accepted 21 June 1999