Macromolecular Engineering of Polylactones and Polylactides. XV. Poly(D,L)-lactide Macromonomers as Precursors of Biocompatible Graft Copolymers and Bioerodible Gels

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SYNOPSIS

The functional aluminum alkoxide, $Et_2Al-O-(CH_2)_2-O-C(O)-C(CH_3)=CH_2$, is a very effective initiator for the (D,L)-lactide (LA) polymerization in toluene at 70°C. The coordination-insertion type of polymerization is living and exclusively yields linear P(D,L)-lactide macromonomers of a predictable molecular weight and a narrow molecular weight distribution. IR and ^{1}H-NMR studies show that the methacryloyl group of the initiator is selectively and quantitatively attached to one chain end, whereas the second extremity is systematically a hydroxyl function resulting from the hydrolysis of the living growing site. α,ω-Dimethacryloyl–P(D,L)-lactides, i.e., α, ω-macromonomers, have also been successfully synthesized by the additional control of the termination step, i.e., by reaction of Al alkoxide end groups with methacryloyl chloride. α-Macromonomer and α,ω-macromonomer P(D,L)-lactides are easily free-radical copolymerized with 2-hydroxyethyl methacrylate (HEMA), resulting in a hydrophilic poly (HEMA) backbone grafted with hydrophobic P(D,L)-lactide subchains and a biodegradable amphiphilic network, respectively. © 1994 John Wiley & Sons, Inc.

Keywords: polylactide • macromonomer • ring-opening polymerization • graft copolymers • amphiphilic gel • biocompatible

INTRODUCTION

During the last decade, special attention has been paid to the well-controlled synthesis and through characterization of macromonomers and to their ability to undergo copolymerization with acrylic and vinyl comonomers. Actually, a large variety of macromonomers has been prepared as precursors of graft copolymers of great potential as coatings, adhesives, compatibilizers, emulsifiers, biomaterials, etc.[1,2] Polylactide macromonomers are expected to play an increasingly important role in the biomedical field. Indeed, polylactides (PLA), polyglycolide (PGA), and their copolymers form a family of biodegradable and biocompatible polymers that are widely used in biomedical applications, such as absorbable sutures,[3,4] biomaterials,[5] sustained drug delivery systems,[6] and absorbable fibers.[7,8] These linear aliphatic polyesters are mainly synthesized by ring-opening polymerization of the corresponding cyclic diesters, i.e., lactides (LA) and glycolide (GA).

It has been reported elsewhere that aluminum alkoxides are effective initiators for the controlled polymerization of lactones,[9,10] lactides,[11,12] and cyclic anhydrides[13] with formation of polyesters and polyanhydrides of a very narrow molecular weight distribution. For example, lactides can be polymerized by $Al(O^iPr)_3$ in toluene, at 70°C, according to a "coordination-insertion" mechanism which involves the insertion of the lactide into the "Al—O" bond

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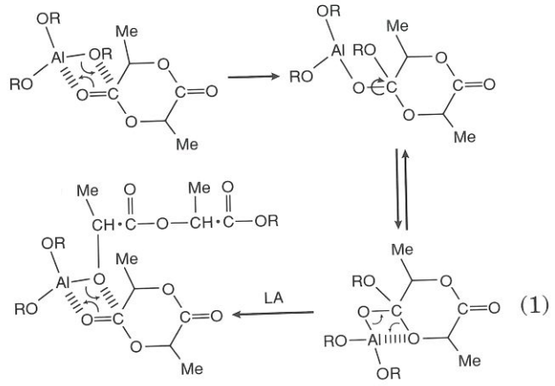
of the initiator and the selective acyl-oxygen cleavage of the monomer [eq. (1), R = *i*Pr]:



(1)

Furthermore, functional aluminum alkoxides, such as $(C_2H_5)_{3-p}Al(ORX)_p$ where X is a functional group, have proven to be very successful in the synthesis of end-reactive polycaprolactone (PCL)[9] and PLA.[14] One end-group of the polyester is systematically an alkoxide and thus an alcohol after hydrolysis of the growing species [see eq. (1)] and the second extremity is quantitatively capped with an ester, the alkoxy radical of which is nothing but the "ORX" alkoxy group of the initiator (X : halogen, tertiary amine, unsaturation, etc.).

This article deals with the synthesis of well-defined α-methacryloyl PLA and α,ω-dimethacryloyl PLA (di)macromonomers from functional diethylaluminum alkoxides. Unsaturated alkoxides have been synthesized on purpose from the equimolar reaction of triethylaluminum with 2-hydroxyethyl methacrylate (HEMA). The discussion will mainly focus on synthetic problem, polymerization kinetics, and control of the end groups. Potentialities of these (di)macromonomers in copolymerization with unsaturated comonomers, such as 2-hydroxyethyl methacrylate (HEMA) will be considered as an access to biodegradable amphiphilic graft copolymers and gels. The use of a (di)macromonomer for the synthesis of polymer networks with tailored properties has recently been described by one of us.[15]

EXPERIMENTAL

Materials

(D,L)-lactide (LA) was purchased from Boehringer and recrystallized three times from dried ethyl acetate at 60°C. The monomer was dried for 24 h, at 35°C, under reduced pressure (10^{-2} mm Hg) before polymerization. The resulting purity of (D,L)LA (mp 127°C) was higher than 99.9% as shown by gasous chromatography and nonaqueous titration revealed a residual acid content lower than 10^{-3} mol %. Triethylaluminum (Fluka) was purified by distillation under reduced pressure and dissolved in dry toluene. Solution concentration was determined by complexometric titration of Al by EDTA. 2-Hydroxyethyl methacrylate (HEMA, Janssen Chimica) was dried over molecular sieves (4 Å) at room temperature and distilled under reduced pressure just before use. The ethylene dimethacrylate (EGDMA) content of purified HEMA was estimated to be lower than 0.02 mol %. Since unreactive in polymerization, this by-product was eliminated in the precipitation step of the final polyester.[9] Methacryloyl chloride (Janssen Chimica) and pyridine (Aldrich) were dried over CaH_2 and KOH, respectively, for 48 h and freshly distilled under reduced pressure. Toluene, ethyl acetate, and tetrahydrofuran (THF) were dried by refluxing over CaH_2, $CaCl_2$ and a benzophenone–sodium complex, respectively.

Polymerization Procedure

Homopolymerization of (D,L)LA

Synthesis and characterization of initiator **1** was reported elsewhere.[9] Polymerization took place under stirring, in toluene, at 70°C; (D,L)-lactide was insoluble in toluene. The monomer was added into the reactor in a glove box under a nitrogen atmosphere. Solvent and initiator were then successively added with a syringe or a stainless-steel capillary through a rubber septum. The reaction was stopped by adding an excess (relative to the initiator) of 1*N* HCl solution. P(D,L)LA being known to be hydrolytically sensitive, the polyester stability under the final hydrolysis conditions has been tested. SEC, ^{1}H-NMR, and nonaqueous titration clearly demonstrated the absence of side reactions preserving the P(D,L)LA integrity.

The initiator residues were extracted four times with a dilute HCl solution. The reaction mixture was then washed with water to a neutral pH and the polymer was precipitated into an excess of cold methanol, filtered, and dried under vacuum to a constant weight.

Except for the termination reaction, the PLA α,ω-macromonomer **4** was synthesized according to the homopolymerization recipe. Initiator **1** was used and the aluminum alkoxide end groups were reacted with methacryloyl chloride instead of being hydrolyzed. When the monomer conversion was complete, toluene was distilled off and substituted by the same volume of dried THF. An excess of 10 equiv of methacryloyl chloride and pyridine in THF was slowly added to the PLA solution at 50°C. After 30 h, the polymerization medium was hydrolyzed, filtered, and the PLA α,ω-macromonomer **4** was recovered by repeated precipitation in cold methanol. The α,ω-macromonomer **4** was purified as previously described.

Copolymerization of HEMA with P(D,L)LA Macromonomer 3

α-Methacryloyl, ω-hydroxy-PLA macromonomer **3** ($\bar{M}_n$ = 4300, 0.5 g, 0.12 mmol), freshly distilled HEMA (0.9 g, 6.9 mmol), and AIBN (50 mg) were dissolved in DMF and stirred for 24 h at 60°C. DMF was distilled off and the crude copolymerization product was redissolved in THF, and precipitated in heptane. It was filtered, dried overnight under reduced pressure, and analyzed by IR, ^{1}H-NMR, and DSC. It will be designated as "graft" copolymer **5**.

Copolymerization of HEMA with α,ω-Methacryloyl-P(D,L)LA Dimacromonomer 4

α,ω-Dimethacryloyl-PLA dimacromonomer **4** ($\bar{M}_n$ = 2150, 0.9 g, 0.42 mmol) and AIBN (75 mg) were dissolved in freshly distilled HEMA (3.0 g, 23.1 mmol) under stirring. This solution was poured into a teflon mold, and kept at 60°C for 30 h. The disk-shaped gels were removed, dried under vaccuum at 40°C for 1 day, and weighed (w_1). They were then stepwise extracted with THF (50 mL) and methanol (50 mL), respectively. They were finally dried and weighed (w_2). The gel fraction was calculated as w_2/w_1 = 0.78. Swelling was measured at room temperature by plunging cubic-shaped samples (w_2 = 0.3 g) into 50 cc of buffered-water (pH 7.15), and chloroform, respectively. After various periods of time, gels were weighed (w_3) and the solvent content was calculated as $w = (w_3 - w_2)/w_3 \times 100\%$.

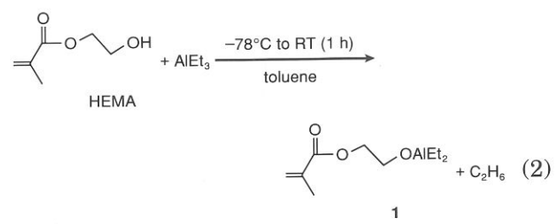
Measurements

IR spectra were recorded with a Perkin-Elmer IR 197. ^{1}H-NMR spectra of PLA were recorded in $CDCl_3$ with a Bruker AM 400 apparatus at 25°C. Molecular weight and molecular weight distribution were determined by size exclusion chromatography. GPC Hewlett-Packard 1090 chromatograph was used in THF and calibrated with polystyrene standards. Calibration for P(D,L)LA was set up from the appropriate viscometric relationships in THF at 30°C.[11,14] Molecular weights of oligomers were also calculated by ^{1}H-NMR from the relative intensity of the signals of the methacryloyl end group and the methine ester groups of the polyester chain. A good agreement was usually observed between M_ns obtained by SEC and NMR.

RESULTS AND DISCUSSIONS

Synthesis of PLA Macromonomers

Diethylaluminum 2-hydroxyethyl methacrylate **1** is prepared by substitution of one ethyl group of $AlEt_3$ by freshly distilled 2-hydroxyethyl methacrylate (HEMA) [eq. (2)]:



(2)

The structure of resulting compound **1** is confirmed by ^{1}H NMR spectroscopy as previously reported.[9]

The (D,L)-lactide polymerization is initiated by the Al alkoxide **1**, used in various molar ratios with respect to the monomer. Polymerization is carried out in toluene solution at 70°C. After hydrolysis of the reaction medium, the final polymer is recovered by precipitation in cold methanol and analyzed by SEC, ^{1}H-NMR, and IR spectroscopy.

A typical size exclusion chromatogram of a P(D,L)LA macromonomer is shown in Figure 1. This particular sample corresponds to a monomer to **1** molar ratio of 14 and to monomer conversion of 96% (96 h at 70°C). The molecular weight distribution is relatively narrow ($\bar{M}_w/\bar{M}_n \leq 1.2$, $\bar{M}_n$ = 1950). No peak due to cyclic oligomers can be detected in the low molecular weight region.

As shown in Figure 2, the number-average molecular weight ($\bar{M}_n$) of the polymer increases linearly with monomer conversion, although the polymolecularity is nearly constant at 1.1–1.25. This observation is in favor of a living polymerization, which is convincingly assessed by the linear dependence of $\overline{DP}$ versus [monomer]/[initiator] molar ratio (Fig. 3): since the slope of this plot is close to 1, it is obvious that each of the alkoxide group initiates the lactide polymerization at 70°C. Molecular weight

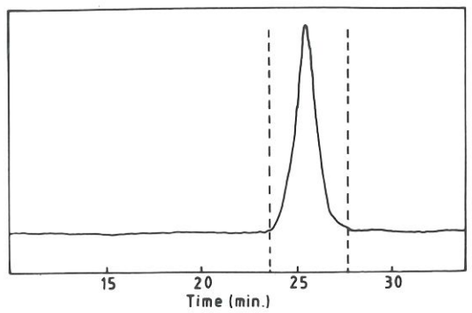


Figure 1. GPC curve of the polymerization product of (D,L)LA initiated with Al monoalkoxide **1.** Reaction conditions: toluene at 70°C for 96 h, conversion 96%, $\bar{M}_w/\bar{M}_n \leq 1.2$ ([LA]/[Al] = 14).

of PLA macromonomers can thus be predicted from the eq. (3):

$$\bar{M}_{n\,(\text{theoretical})} = \frac{[\text{LA}]_0 \cdot \text{MM}_{\text{LA}} \cdot x}{[\text{Al}]} \qquad (3)$$

where MM_{LA} and x are the molecular mass of lactide (LA) (144 g mol^{-1}) and the monomer conversion, respectively.

To confirm unambiguously that P(D,L)LA is selectively and quantitatively capped by the methacryloyl radical of the initiator **1** the recovered polyester has been characterized by ^{1}H-NMR (Fig. 4) and IR (Fig. 5) spectroscopies. The absorption at 1638 cm^{-1} is consistent with the presence of a carbon–carbon double bond (Fig. 5). The same quantitative conclusion is supported by the ^{1}H-NMR signals and their relative intensity at 5.60 (I_b = 0.55) and 6.12 ppm (I_a = 0.57) consistent with the α-hydroxymethine protons at δ = 4.35 ppm ($I_{g+d}/5$ = 0.56) (Fig. 4).

From the nature of the end groups, i.e., a methacryloyl group and a hydroxyl function, respectively, it must be concluded that the lactide is inserted into the Al—O bond of the initiator through the selective cleavage of the acyl-oxygen bond of the monomer:

$$\mathbf{1} \xrightarrow[\text{Toluene, 70°C}]{\text{(D,L)LA}} H_2C{=}C(CH_3){-}C(O){-}O{-}(CH_2)_2{-}O{-}[C(O){-}CH(CH_3){-}O]_n{-}AlEt_2$$

$$\mathbf{2} \xrightarrow{HCl/H_2O} H_2C{=}C(CH_3){-}C(O){-}O{-}(CH_2)_2{-}O{-}[C(O){-}CH(CH_3){-}O]_n{-}H \qquad (4)$$

At our best knowledge, it is the first time that polylactide macromonomers **3** have been proposed

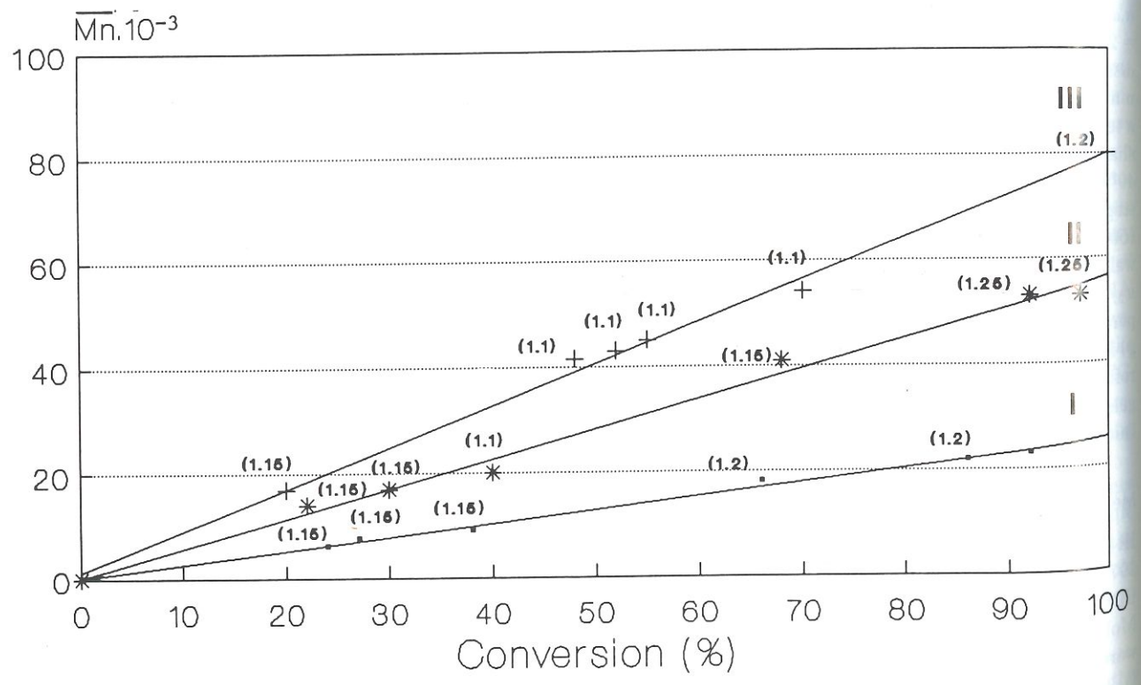


Figure 2. Polymerization of (D,L)LA initiated by Al alkoxide **1;** relationship between $\bar{M}_n$ or $\bar{M}_w/\bar{M}_n$ (determined by SEC) and time; toluene at 70°C, $[\text{LA}]_0$ = 0.655 mol L^{-1} and $[\mathbf{1}]_0 = 3.17 \times 10^{-2}$ mol L^{-1} (**I**), 1.57×10^{-2} mol L^{-1} (**II**), 1.20×10^{-2} mol L^{-1} (**III**).

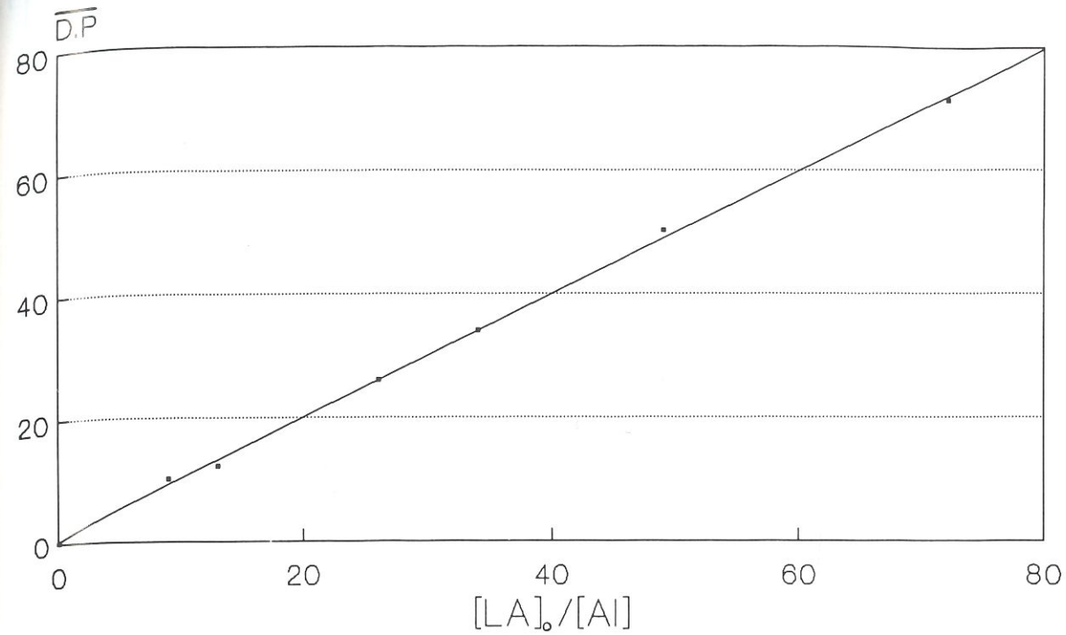


Figure 3. Dependence of $\overline{\text{DP}}$ at quantitative conversion of monomer on the [monomer]/[initiator **1**] molar ratio for the polymerization of (D,L)LA ($[\text{LA}]_0$ = 0,655 mol L^{-1}) in toluene at 70°C.

with a predictable molecular weight and a narrow molecular weight distribution. Moreover, these results are in a perfect agreement with the ε-CL polymerization initiated with the same functional diethylaluminum alkoxide **1.**[9] As a result, the sequential addition of ε-CL and (D,L)LA to initiator **1** in toluene at 25 and 70°C, respectively, successfully leads to the expected diblock P(CL-b-LA) macromonomers where, once again, the molecular parameters are perfectly controlled.[16]

It is known that, when the polymerization medium is kept at 70°C beyond the time required for the complete lactide conversion, the molecular weight distribution starts to broaden. This effect is more likely due to side transesterification reactions.[11,14] Any increase in the polymerization time enhances the deleterious effect of transesterification and the loss of control on the molecular characteristics of PLA chains. Accordingly, kinetics of (D,L)LA polymerization has been investigated by a gravimetric method as described elsewhere.[14]

After a typical induction period (ca. 1 h), the polymerization is first order in monomer as shown by a linear relationship between monomer conversion ($\ln[\text{LA}]/[\text{LA}]_0$) and polymerization time (Fig. 6). The induction period is systematically observed when the polymerization of ε-CL and (D,L or L)LA is promoted by Al alkoxides.[9,11,14] A recent study of the "coordination-insertion" mechanism using ^{13}C- and ^{27}Al-NMR spectroscopy, cryoscopy, and viscosimetry,[17] has shown that this initial period has to be attributed to a complete deassociation of the coordinative aggregates of the initiator in toluene upon addition of the monomer. Polymerization of (D,L)LA is also first order in initiator **1** as shown in Figure 7. Except for the induction period, kinetics of (D,L)LA polymerization obeys as simple kinetic law:

$$\frac{-d[\text{LA}]}{dt} = k[\text{LA}][\text{Al}] \qquad (5)$$

where k, the kinetic constant is 1.58×10^{-2} L mol^{-1} min^{-1} in toluene at 70°C. The same kinetic behavior has been observed for the lactide polymerization initiated by $Br{-}(CH_2)_2{-}OAlEt_2$ and $H_2C{=}CH{-}(CH_2)_3{-}OAlEt_2$, under the same experimental conditions.[14] Using these two initiators, the kinetic constants k are 1.1×10^{-2} and 1.0×10^{-2} L mol^{-1} min^{-1}, respectively, supporting that the functional groups under consideration are of a very limited effect on the "$Et_2Al{-}O$-" active species.

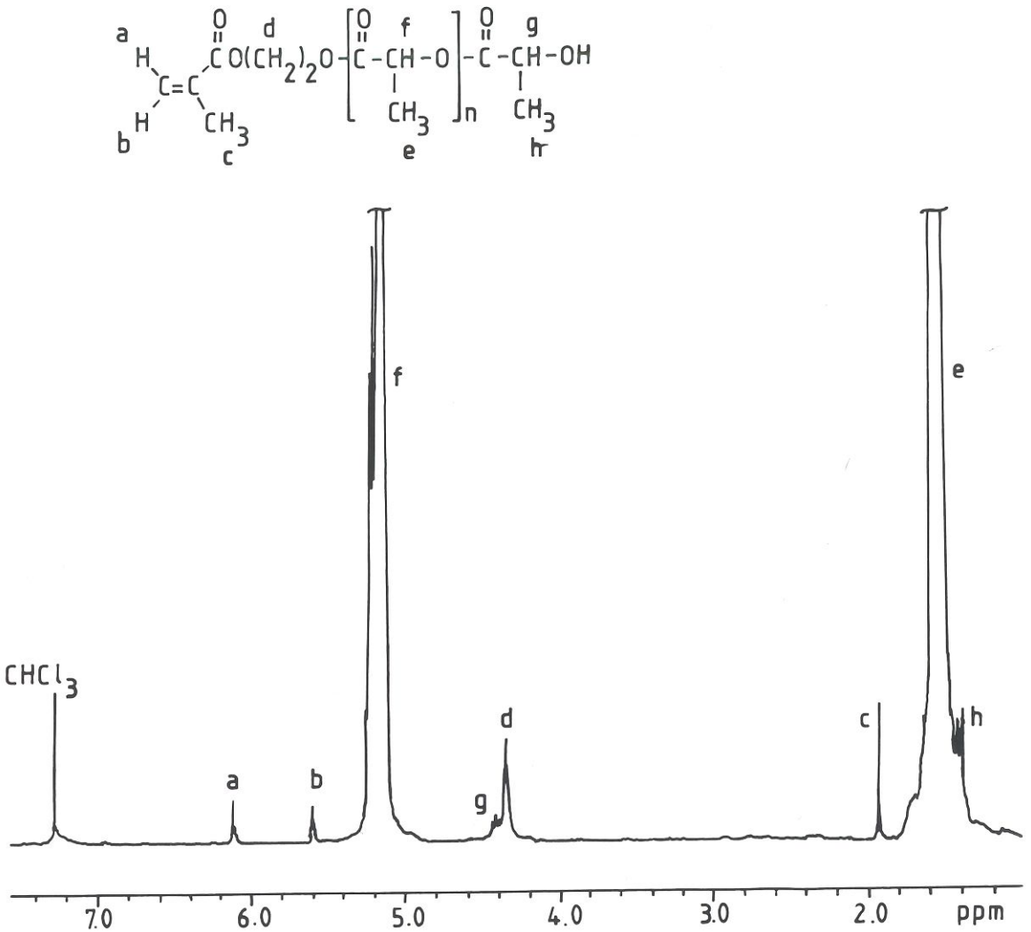


Figure 4. ^{1}H NMR spectrum of P(D,L)LA ($\bar{M}_n$ = 3700) as recovered after hydrolysis of P(D,L)LA initiated by diethylaluminum alkoxide **1** (solvent : $CDCl_3$):

Protons	δ (ppm)	Intensity
a	6.12	0.57
b	5.60	0.55
c	1.94	1.42
d	4.35	2.78
g	4.38	2.78
e	1.56	90.50
h	1.47	90.50
f	5.20	28.31

This observation is only valid when diethylaluminum alkoxides are considered. Indeed, rate constants of the ε-CL and LA polymerization as initiated by Al trialkoxides, are directly affected by the nature of the alkoxide group (functional or not). This kinetic behavior, which is at least partly con-

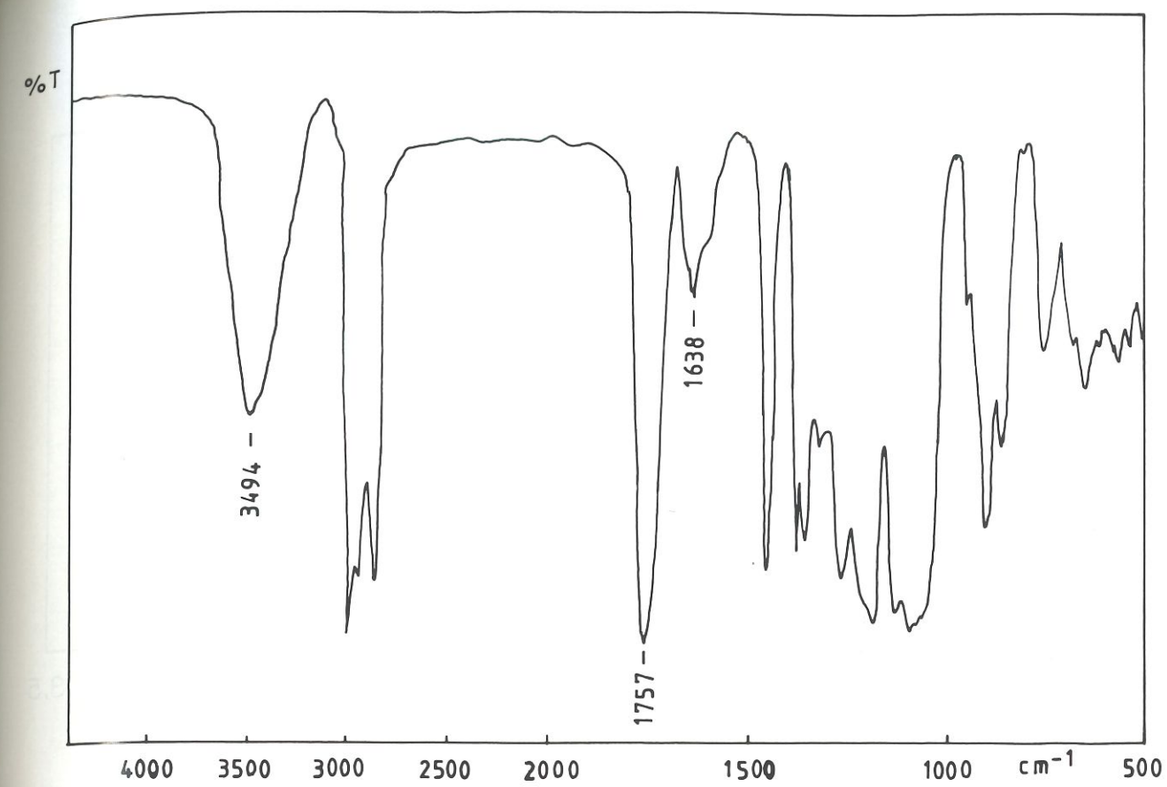


Figure 5. IR spectrum of P(D,L)LA ($\bar{M}_n$ = 1950) as recovered after hydrolysis of P(D,L)LA initiated by diethylaluminum alkoxide **1**.

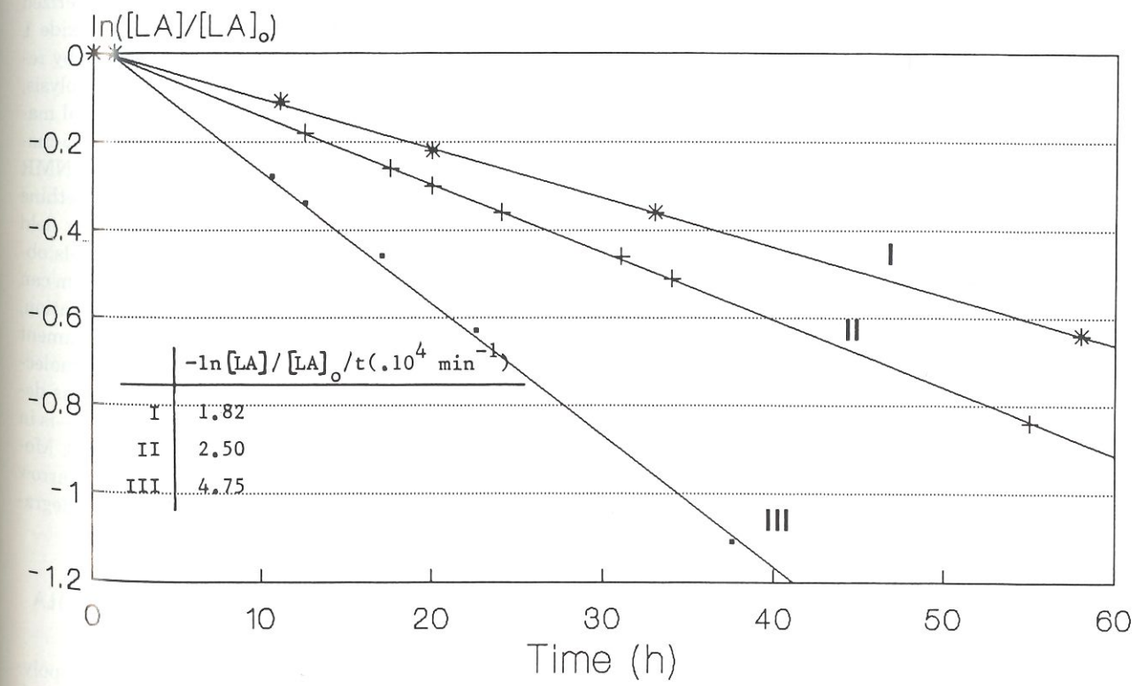


Figure 6. Order in monomer for the polymerization of (D,L)LA initiated by diethylaluminum alkoxide **1** in toluene at 70°C. $[LA]_0$ = 0.65 mol L^{-1}; [Al] = 1.15×10^{-2} mol L^{-1} (**I**), 1.58×10^{-2} mol L^{-1} (**II**), and 3.0×10^{-2} mol L^{-1} (**III**).

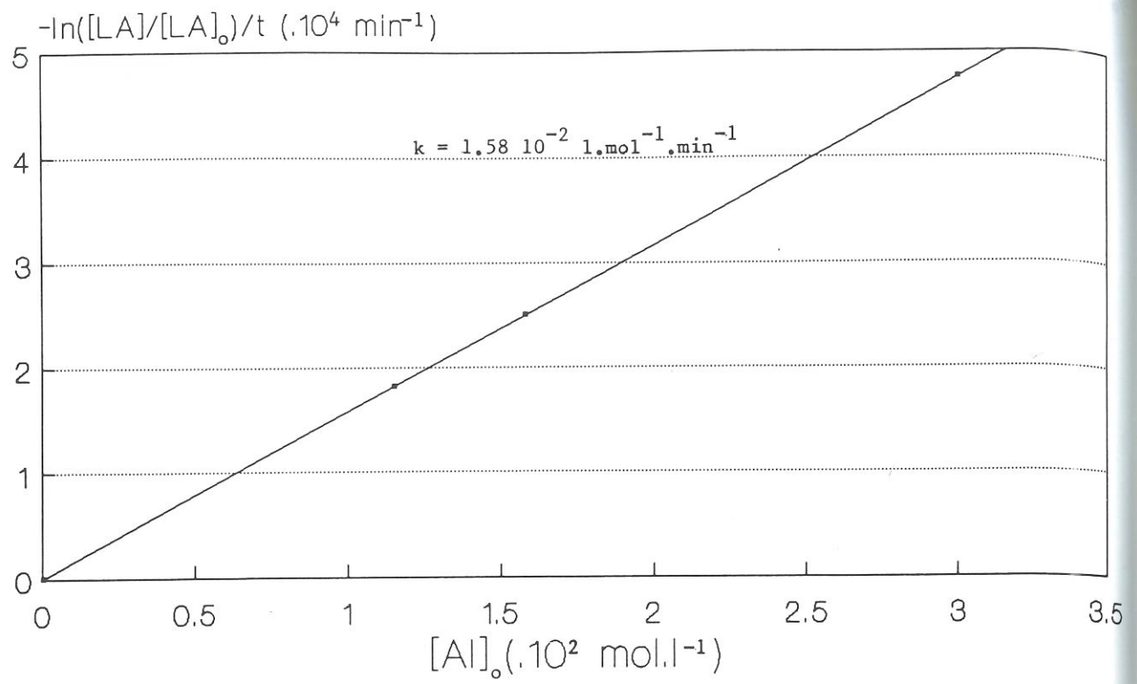
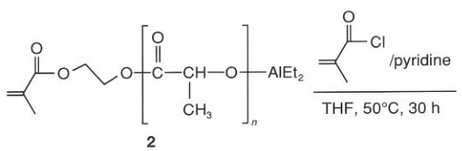


Figure 7. Order in initiator **1** for the polymerization of (D,L)LA ($[LA]_0$ = 0.65 mol L^{-1}) in toluene at 70°C.

nected with the mean number of active alkoxide groups per Al atom ($\bar{n} \leq p$), will be discussed in details in a forthcoming study.[18]

Synthesis of P(D,L)LA α,ω-Macromonomer

Control of both the initiation and termination steps allows α,ω-dimethacryloyl polylactides to be synthesized in a one pot technique. The usual acid hydrolysis of the propagating sites have been substituted by a specific reaction of the aluminum alkoxide group with a functional reagent, e.g., methacryloyl chloride:



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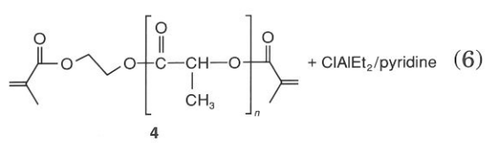

(6)

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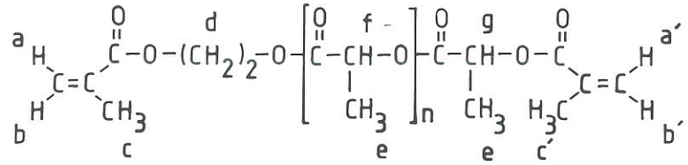
As an example, (D,L)LA has been polymerized in toluene at 70°C by using the Al monoalkoxide **1** as an initiator ($[LA]_0/[Al] = 25$), followed by reaction with methacryloyl chloride. After hydrolysis, the quantitatively recovered PLA difunctional macromonomer (α,ω-dimethacryloyl PLA or α,ω-macromonomer) **4** has been characterized by ^{1}H-NMR (Fig. 8). Signal at 4.35 ppm of the α-hydroxymethine protons (see Fig. 4) has been shifted to lower field (δH_f = 5.20 ppm). Furthermore, extra signals observed at $\delta H_{a''}$ = 6.07 ppm and $\delta H_{b''}$ = 5.56 ppm can be assigned to the second methacrylic unsaturation, which is in a slightly different chemical environment compared to the first one. The experimental molecular weight of PLA chains—3650 and 3800 as determined by ^{1}H-NMR and SEC, respectively—is in a good agreement with theoretical $\bar{M}_n$ = 3600. Molecular weight distribution remains relatively narrow ($\bar{M}_w/\bar{M}_n$ = 1.2), confirming the absence of degradation reactions.

Synthesis of "Graft" Copolymers from P(D,L)LA Macromonomers

P(D,L)LA macromonomers **3** have been copolymerized in a free radical process by HEMA, which



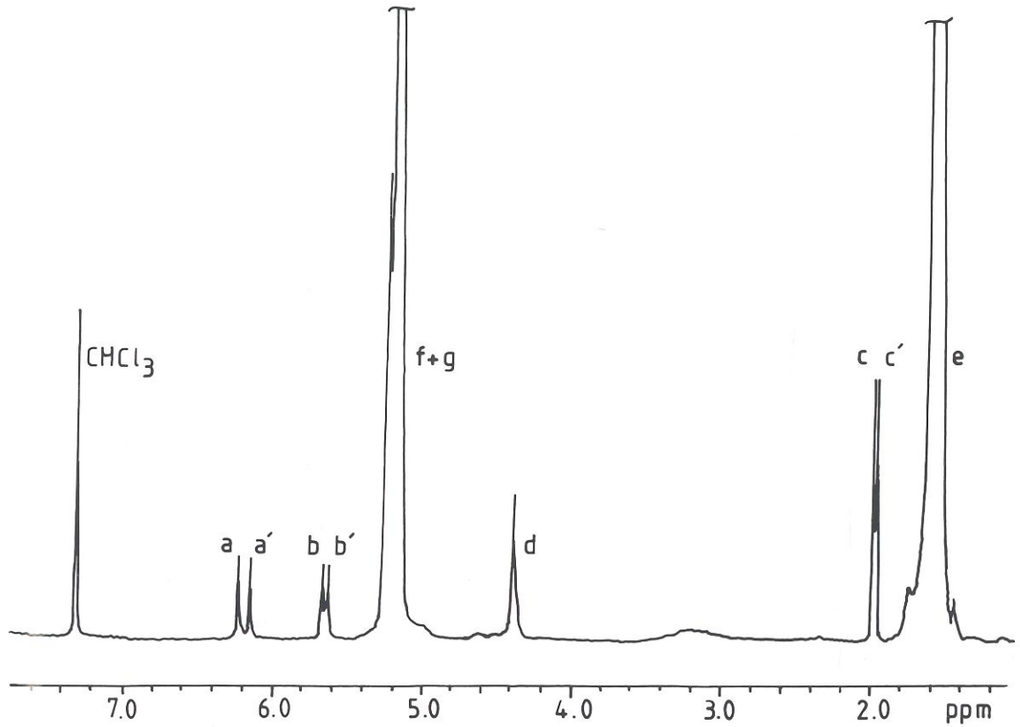
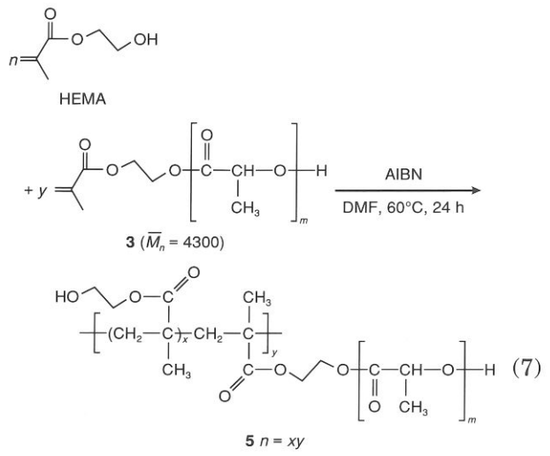


Figure 8. ^{1}H-NMR spectrum of α,ω-dimethacryloyl-PLA **4** ($\bar{M}_n$ = 3650) [see eq. (6)] in $CDCl_3$.

Protons	δ (ppm)	Intensity
a	6.11	0.57
a′	6.07	0.84
b	5.60	0.85
b′	5.56	0.84
f, g	5.20	40.32
d	4.35	3.14
c	1.94	2.24
c′	1.92	2.30
e	1.52	121.52

is the precursor of a biocompatible and hydrophilic polymer.[19]

A ω-methacryloyl-P(D,L)LA macromonomer **3** ($\bar{M}_n$ = 4500, $\bar{M}_w/\bar{M}_n$ = 1.1) has been copolymerized with HEMA in dimethylformamide (DMF) at 60°C for 24 h, by using azo-2,2′-bis (isobutyronitrile) (AIBN) as a free-radical initiator:



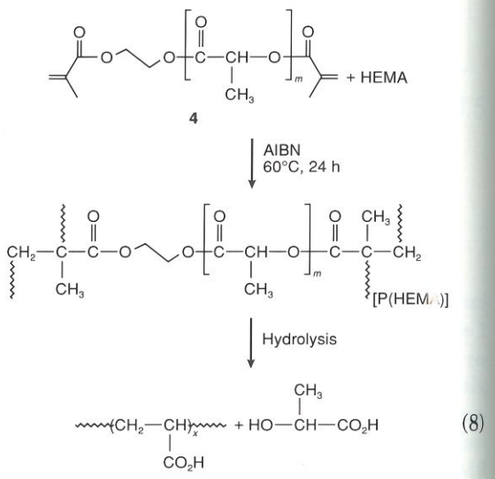
When DMF is replaced by THF, a nonsolvent of poly(HEMA), a clear solution is observed which indicates that no poly(HEMA) is formed, at least at a structural unit ratio [*n*HEMA/(*ym*.) LA units] of 1.95. That the whole P(D,L)LA macromonomer is copolymerized is confirmed by the absence of the unsaturation signals in the IR and ^{1}H-NMR spectra (Figs. 9 and 10).

Composition of the resulting "graft" copolymer **5** has been determined from the polymerization degree of the polylactide macromonomer ($\overline{DP}$ = 30), and the relative intensity of the methine protons (δH_a = 5.25 ppm) in the PLA subchains and the α-hydroxy methylene protons (δH_f = 3.96 ppm) in the polymethacrylate chains (Fig. 10). The experimental final ratio (*n*/*ym*) of 2.05 is in a very good agreement with the initial value (1.95). It may be noted that tacticity of the copolymer backbone is predominantly syndiotactic groups (±65%) ($\delta H_{g,g'}$ = 1.40 ppm and $\delta H_{h,h'}$ = 2.15 ppm) compared to the heterotactic methyl groups (±35%) ($\delta H_{g,g'}$ = 1.46 ppm and $\delta H_{h,h'}$ = 2.25 ppm). A very similar tacticity has previously been reported by De Visser et al. for homopolymerization of HEMA initiated by AIBN in ethanol at 60°C.[20]

As expected, these amphiphilic graft copolymers display interesting surfactant properties. As an example, as small as 1.25 wt % of copolymer *5* ($\bar{M}_{n\,PLA}$ = 4500; HEMA/LA = 2.05) is able to stabilize a toluene/water (1/3) emulsion over a period of at least 10 days. Use of these graft copolymers as surface active agents in emulsions and polyester matrices will be the topic of a forthcoming paper.

Synthesis of Biodegradable and Biocompatible Amphiphilic Networks

Crosslinked hydrophilic polymers or hydrogels are extensively used in the controlled-release of drugs.[21] Most of these hydrogels, however, are nonbiodegradable and the drug release is mainly controlled by diffusion. Interestingly enough, bioerodible and biocompatible hydrogels could be obtained by free-radical copolymerization of P(D,L)LA α,ω-macromonomers (**4**) with HEMA, as shown by eq. (8):



Drug release mechanism, degradation rate and physical properties of these hydrogels can be tailored by the appropriate choice of macromonomer molecular weight and composition of the comonomer feed.

Based on an initial (HEMA/LA) unit ratio of 3.7, the free-radical copolymerization of HEMA and PLA α,ω-macromonomers (**4**) ($\bar{M}_n$ = 2150, $\bar{M}_w/\bar{M}_n$ = 1.15) leads to the formation of a bicomponent network. After 30 h polymerization at 60°C, the crosslinked material has a gel fraction (w_2/w_1) of 0.78 (see Experimental section). Indeed, selective extractions by methanol and THF, respectively, have allowed 8.5 wt % of P(HEMA) and 13.5 wt % of polylactide chains end-capped with a few HEMA units to be isolated.

Due to the amphiplic character of the network, swelling behavior has been studied in water and in an organic medium: chloroform. For a network pre-

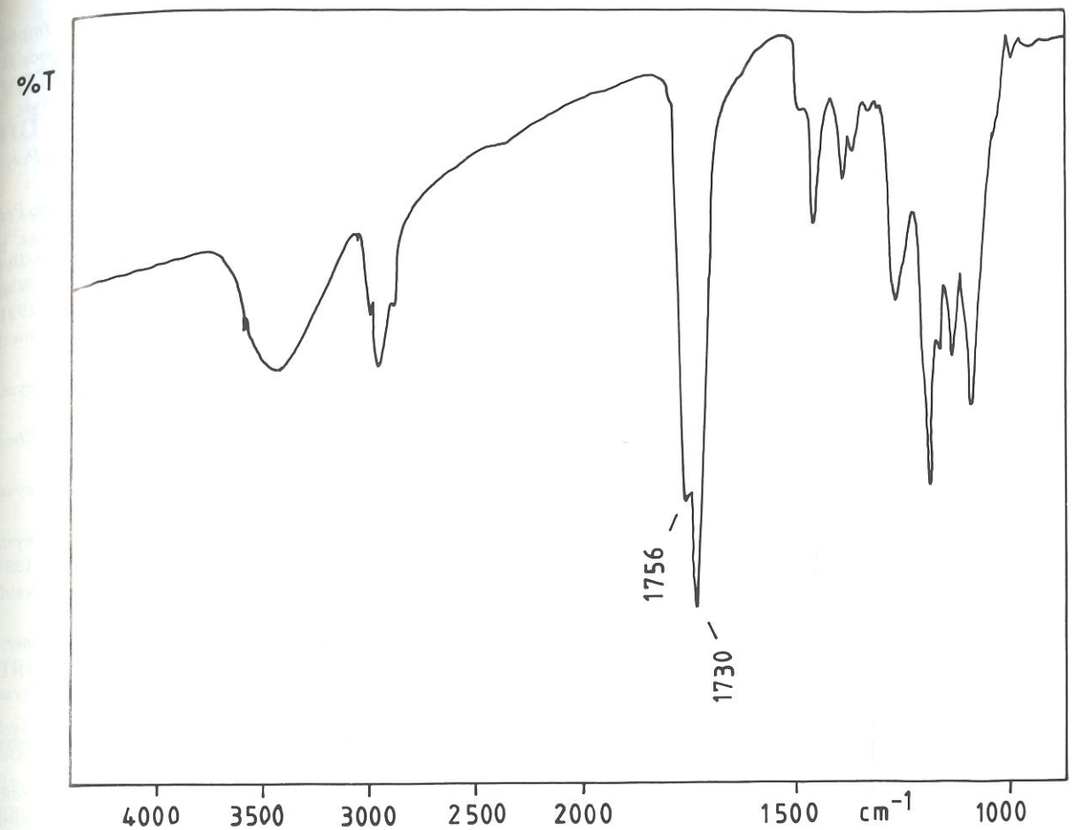


Figure 9. IR spectrum of the P[HEMA-g-(D,L)LA] "graft" copolymer **5** [see eq. (7)].

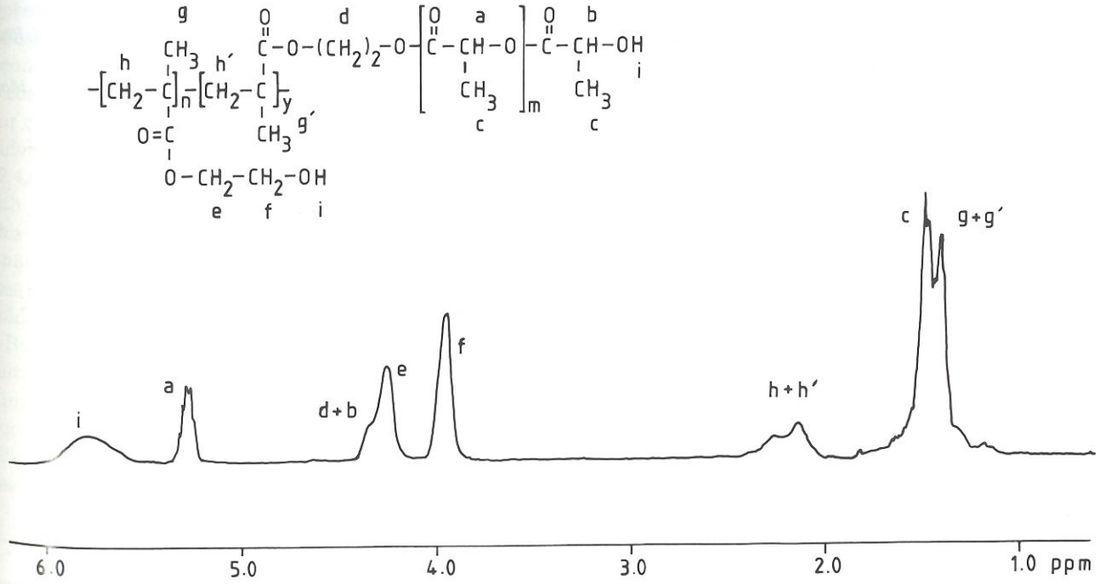


Figure 10. ^{1}H–NMR spectrum of the P[HEMA-g-(D,L)LA] "graft" copolymer **5** [see eq. (7)]. Solvent = pyridine/C_6D_6 (9/1).

pared from an initial (HEMA/LA) unit ratio of 3.7 and $\bar{M}_n$ P(D,L)LA of 2150, the solvent content (w, see Experimental section) is 34.0 ± 2.0%, and 50.0 ± 0.5% in water and in chloroform, respectively. It is clear that these novel amphiphilic networks are suitable for a number of biomedical applications, such as macromolecular drug delivery systems. Indeed, drugs can be easily incorporated either during the free-radical copolymerization or by swelling with an organic solvent. Furthermore, these biocompatible gels are biodegradable. When swelling occurs in distilled water, water pH decreased from neutral to ca. 3.7. This acidity increase might result from the release of lactic acid as a result of the hydrolysis of polylactide chains [see eq. (8)]. Similar observations have been recently reported for bioerodible hydrogels based on poly(ethyleneglycol-co-poly α-hydroxy acid).[22] Extensive study of the ability of poly[HEMA-co-(L or D,L)LA] gels to control drug release is under current investigation. Effect of composition of the comonomer feed, molecular weight of polylactide chains and nature of the hydrophilic comonomer, e.g., HEMA, acrylamide, and *N*-vinyl pyrrolidone, will be related to the degradability and the swelling behavior of the resulting lypo/hydrogels.

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