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Functionalization of poly(L-lactide) macromonomers by ring-opening polymerization of L-lactide initiated with hydroxyethyl methacrylate–aluminium alkoxides

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End-functionalized hydroxyethyl methacrylate macromonomers of poly(L-lactide) (HEMA–PLA) were synthesized by the ring-opening polymerization of L-lactide (LA), using mono- and trihydroxyethyl methacrylate–aluminium alkoxides as initiators. The polymerization carried out in toluene at high vacuum and 60°C presented a living character, giving rise to the formation of a linear polymer without cyclization side reactions. After hydrolysis of the active growing centres with dilute HCl, one hydroxyl group was formed at the end of the polymeric chains. To study the structural characteristics of the end-groups, macromonomers of relatively low molecular weight were obtained by using the mono- and tri-HEMA–aluminium alkoxides at a low ratio of [LA]/[Al]. The polymers obtained were analysed by Fourier-transform infra-red and ^{1}H nuclear magnetic resonance spectroscopies, taking into consideration the signals of a low-molecular-weight model compound, 2-acetyloxyethyl methacrylate, which reproduces the structure of the HEMA functional end-group of the PLA macromonomer.

(Keywords: poly(L-lactide); functionalization; hydroxyethyl methacrylate)

INTRODUCTION

Polyesters and copolyesters of several α-, β- and ω-hydroxy acids have been used widely during the past 20 years for the preparation of biodegradable materials with interesting applications in surgery and pharmacology[1–5]. Although these polymeric systems constitute the most important group of biodegradable materials because of the non-toxicity of the degradation products for living organisms[6], the biodegradation rate and therefore their physico-mechanical properties in a physiological medium are strongly dependent on factors related to the chemical structure, molecular weight, molecular-weight distribution and crystallinity[7]. In this way, crystalline domains are more resistant than amorphous to biodegradation in physiological conditions, and the hydrophobic or hydrophilic character of the polymeric chains noticeably affects the biodegradation process[8]. The rather low hydrophilicity of poly(L-lactide), as a consequence of its non-polar methyl side substituents, decreases its rate of biodegradation in such a way that it can affect the long-term biocompatibility of surgical implants if a hard fibrous capsule around the implant is formed[9]. This means that a change in the molecular structure of polymeric chains (by modification of the side substituents or by copolymerization) provides biodegradable systems with mechanical properties and biodegradation behaviour controlled mainly by the chemical composition. In this sense, Cohn *et al.*[10] have reported the excellent properties in physiological medium of poly(ethylene glycol)–poly(L-lactide) block copolymers obtained by polycondensation of L-lactic acid in the presence of poly(ethylene glycol). More recently, Jedlínski *et al.*[11] have reported the synthesis of ABA triblock copolymers by anionic polymerization of L-lactide in the presence of the sodium salt of poly(ethylene glycol).

The present paper deals with the preparation of acrylic macromonomers of poly(L-lactide) by the ring-opening polymerization of L-lactide, initiated by functionalized aluminium alkoxides. The poly(L-lactide)s prepared can be copolymerized with other vinyl or acrylic monomers to obtain graft copolymers with physical and mechanical properties controlled by the average composition and sequence distribution of the graft copolymer chains.

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EXPERIMENTAL

Reagents

L-Lactide was prepared by catalytic thermolysis of poly(L-lactic acid) oligomers in the presence of Mn(II) catalyst, according to the treatment reported by Dahlman *et al.*[12]. The L-lactide was purified by recrystallization from dry ethyl acetate and stored under vacuum over P_2O_5; m.p. = 97°C.

Triethyl aluminium, 1 M solution in hexane (Aldrich), was used as received.

2-Hydroxyethyl methacrylate (HEMA) of high purity, containing less than 0.5% of ethylene glycol dimethacrylate (Scientific Polymer Products Inc.), was dried over molecular sieves (4 Å) and freshly distilled before use.

The solvents toluene, ethyl acetate and benzene-d_6 were dried by treatment with CaH_2 and $CaCl_2$ for 24 h and distilled under dry N_2 atmosphere.

Polymerization

The polymerization reactions were carried out in Pyrex glass ampoules exhaustively flamed under high vacuum (10^{-4} mmHg). The ampoules were equipped with a glass–Teflon stopcock to facilitate the addition of the reactants under high-vacuum conditions. First, 2 g of L-lactide was introduced in a flamed ampoule and exhaustively dried under high vacuum at room temperature for 4 h. Then, 50 ml of dry toluene was distilled into the flask at low temperature through the vacuum line.

The synthesis of mono- and tri-HEMA–aluminium alkoxides was performed *in situ* by the addition of the required amount of triethylaluminium and HEMA (1:1 for mono-HEMA and 1:3 for tri-HEMA). The amount of the initiator was varied in each case as a function of the molecular weight to be obtained. The reaction medium was kept at room temperature for 30 min and then was heated at 40°C for 15 min with vigorous stirring.

The polymerization reaction was carried out at 60°C with stirring for the length of time necessary to reach high conversion. The reaction was stopped by the addition of 10 ml of a 2 N solution of HCl to the reaction medium. After washing with cold water, the polymer was precipitated with an excess of cold methanol. The isolated polymer was washed with methanol and dried under reduced pressure at room temperature over P_2O_5.

Characterization

The purified HEMA-PLA polymers were characterized by *FT*i.r. and n.m.r. spectroscopies. Thin films of the polymers were cast on KBr windows. After most of the solvent (chloroform) was evaporated, the films were dried at 70°C in a vacuum oven for 24 h to remove any residual solvent. Infra-red spectra were taken on a Nicolet 5 DXC *FT*i.r. spectrometer with a resolution of 4 cm^{-1}. Sixty-four scans were signal-averaged and stored on magnetic disks.

^1H n.m.r. spectra were recorded in deuterated chloroform solution with a Varian VXR-300 spectrometer at 25°C.

The molecular weight was determined by viscosimetry, measuring the intrinsic viscosity of poly(L-lactide)s in chloroform solution at 25°C. An Ubbelohde viscosimeter with a calibrated capillary of 0.46 mm was used, giving a flux time for the pure solvent longer than 120 s. For the determination of the average molecular weight, the following equation was applied[13]:

$$[\eta] = 3.25 \times 10^{-4} M_n^{0.77}$$

RESULTS AND DISCUSSION

Jérôme and Teyssie[14–18] have studied intensively the preparation of end-reactive polyesters and copolyesters derived from ε-caprolactone and α-hydroxy acids such as glycolic and lactic acids. In order to obtain macromolecular systems with controlled chemical structure and molecular weight, they suggested in the late 1970s the use of initiators based on aluminium alkoxides bearing functional groups that could be active in a further polymerization process, mainly via polyaddition reactions. In this sense, alkylaluminium alkoxides and aluminium trialkoxides carrying polymerizable functional groups have been used to obtain the selective end functionalization of biodegradable polyesters[14,15,19–21]. The functional group associated with the alkoxy residues of the initiator is, after polymerization, selectively attached to the polyester chain end, whereas the other end is always a hydroxyl group, which results from the hydrolysis of the active growing centre.

It has been demonstrated recently that the ring-opening polymerization of lactones and lactides initiated by aluminium alkoxide catalysts proceeds without cyclization, giving rise to the formation of linear polyester chains with controlled molecular weight and structure of the functional end-groups[19,22,23]. Jérôme and Teyssie have shown that the ring-opening polymerization of these compounds proceeds through a 'coordination–insertion' mechanism that involves the selective rupture of the acyl–oxygen bond of the monomer and the insertion into the alkoxide–aluminium bond of the initiator[14].

These authors have prepared interesting polyester macromonomers with amino, bromine, allylic and methacrylic end-groups, using aluminium alkoxides carrying the corresponding functional groups. Particularly, they have reported the preparation of poly(ε-caprolactone) and poly(δ-valerolactone) macromonomers with HEMA and hydroxyl end-groups. As they indicated in a recent paper[16], these systems provide a good way to synthesize macromonomers of poly(lactide) or poly(glycolide), which can be useful for the preparation of biocompatible block and graft copolymers.

Accordingly, the mechanism of the ring-opening polymerization of L-lactide by means of HEMA–aluminium alkoxides is represented schematically in *Figure 1*. The coordination of the aluminium ligand with the lactide ring through the HEMA–alkoxide residue activates the ring opening of the lactone by the heterolytic rupture of the oxygen–acyl bond, giving rise to the addition of two lactic acid units to the growing chain end, which subsequently is coordinated with a new lactide ring. The addition has a clear living character[24,25], and therefore the deactivation of the active growing end is usually produced by the addition of dilute HCl, which hydrolyses the coordinated Al complex, giving a hydroxyl group at the end of the poly(lactide) chain.

The preparation of the initiator HEMA–aluminium alkoxides involves the treatment in strictly dry conditions of triethylaluminium with HEMA in toluene solution at

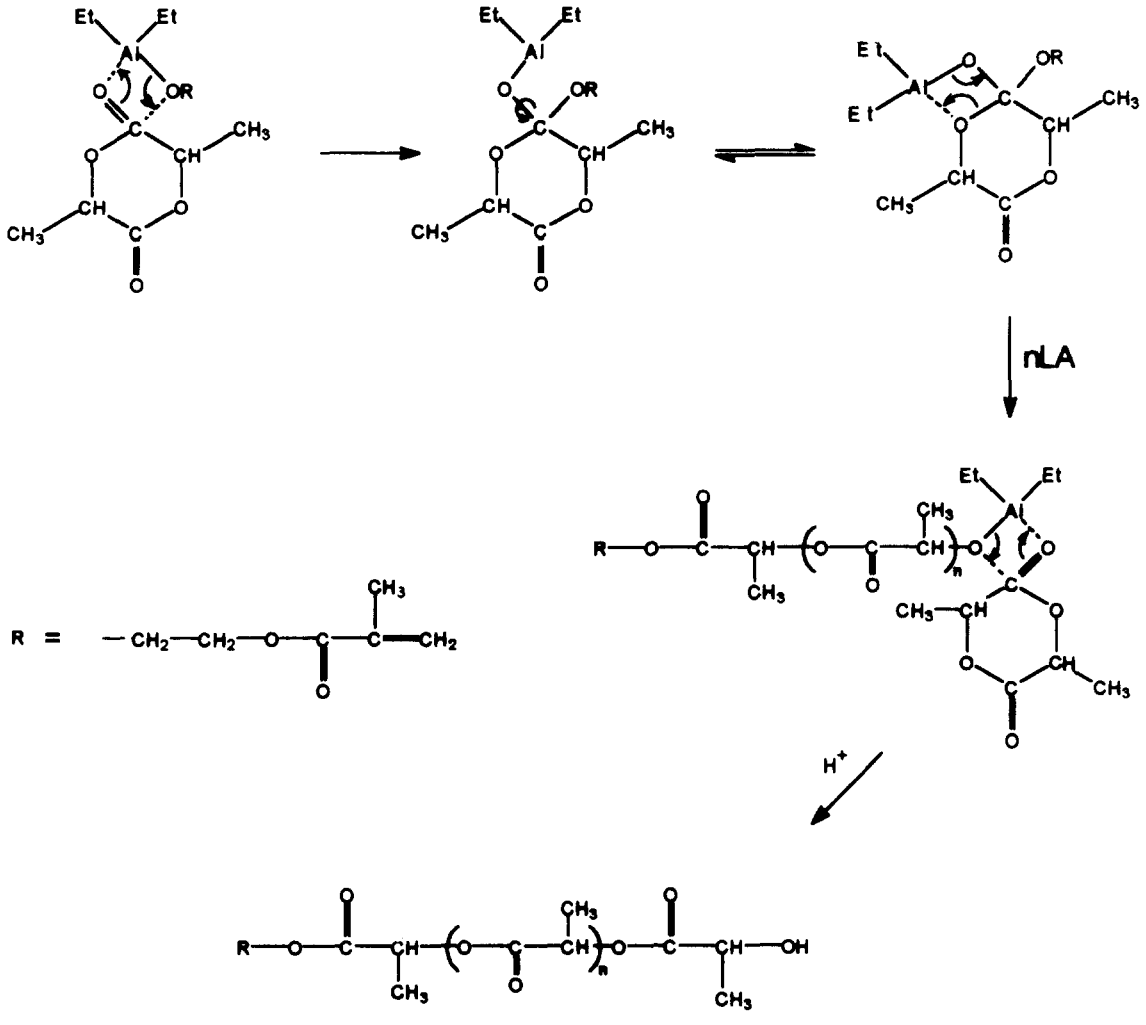

Figure 1 Coordination–insertion mechanism of the ring-opening polymerization of L-lactide promoted by HEMA–$AlEt_3$

moderate temperature. Depending on the stoichiometric ratio of HEMA to Et_3Al, mono- or trialkoxides can be easily prepared because the reaction equilibrium is favourably displaced by the elimination of one ethane molecule per HEMA–alkoxide formed[14]. We have studied the formation of the HEMA–aluminium alkoxide by the analysis of the ^1H n.m.r. spectra of mixtures of HEMA and Et_3Al in solution of deuterated benzene. *Figure 2* shows the resonance signals of the methacrylic double bond and oxymethylene hydrogens of pure HEMA recorded in deuterated benzene at 35°C, and those of a mixture of an equimolecular amount of HEMA and Et_3Al in this solvent. The spectra recorded at different times of treatment show an interesting change of the intensity and the position of the resonance signals with the time of reaction. The spectrum of a mixture just after the addition of the reagents to the tube used to record the spectra (*Figure 2b*) gives a wide signal centred at 3.95δ, which overlaps with that of the hydrogens of the oxymethylene group directly bound to the methacrylic ester function, at 3.92δ; but at the same time, the resonance signals of the methacrylic protons split into two peaks at lower field. This could be explained by the formation of a molecular complex through the interaction of the carbonyl ester group and the aluminium ligand. The deshielding effect would be produced by the partial polarization of the electronic cloud of the C=O group towards the ligand, as represented in the scheme of *Figure 3*. This polarization is transferred to the methacrylic double bond by conjugation.

The spectrum drawn in *Figure 2c* corresponds to the reaction mixture after 30 min of reaction. The modification of the oxyethylene signals, initially at 3.32 and 3.92δ, gives a well resolved multiplet at 4.00δ, whereas the intensity of the signals at 3.32δ, corresponding to the hydrogens of the free hydroxymethylene side group, decreases strongly. After 4 h of reaction, the hydroxymethylene signal at 3.32δ disappeared and a well defined multiplet (which looks like two distorted triplets) appeared at 4.00δ (*Figure 2d*). The two triplets correspond logically to the oxyethylene protons of the mono-HEMA–aluminium alkoxide formed, with a rather similar magnetic character for all the oxyethylene protons of the complex molecule, and is clear evidence of the formation of the monoalkoxide derivative.

It is interesting to stress that the chemical shifts of the hydrogens of the methacrylic double bond are similar to those of pure HEMA, which means that the character of the methacrylic double bond is not drastically changed by the formation of the oxyalkylaluminium derivative. The addition of new amounts of HEMA to the reaction medium gives rise to the formation of the trialkoxide derivative quantitatively, with a spectroscopic behaviour similar to that described above. In a recent article Jérôme

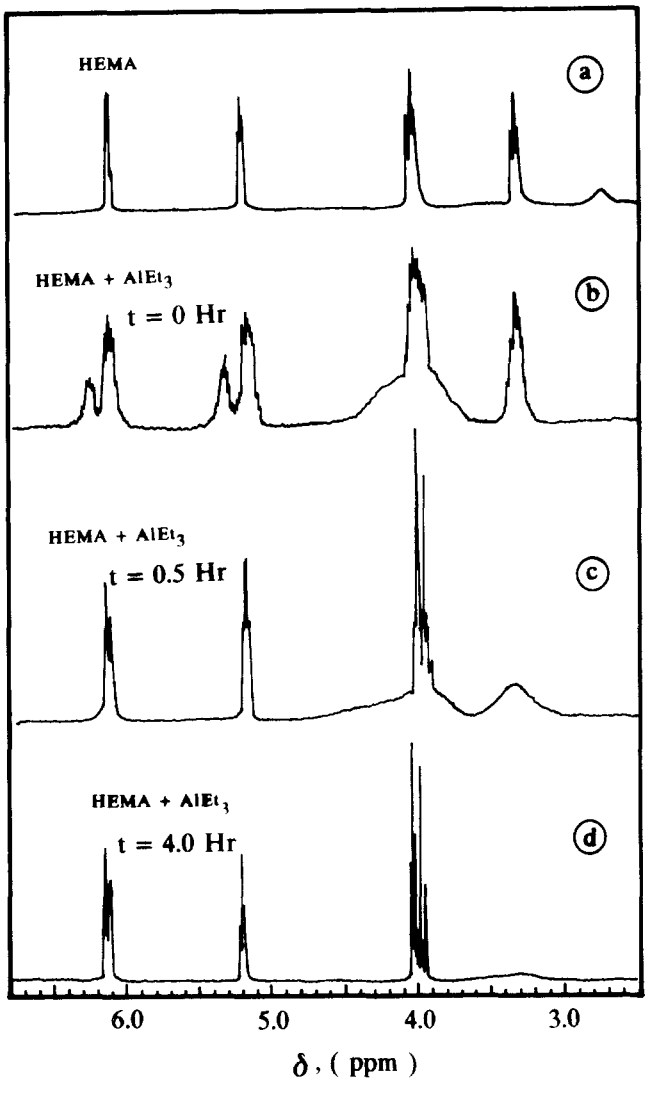

Figure 2 Analysis of the formation of HEMA–aluminium alkoxides by ^{1}H n.m.r. spectroscopy. Signals of the oxyethylene and methacrylic hydrogens of: (a) HEMA; (b) a mixture of HEMA and $AlEt_3$ in benzene-d_6 immediately after preparation; (c) the same mixture after 0.5 h; (d) the mixture after 4 h

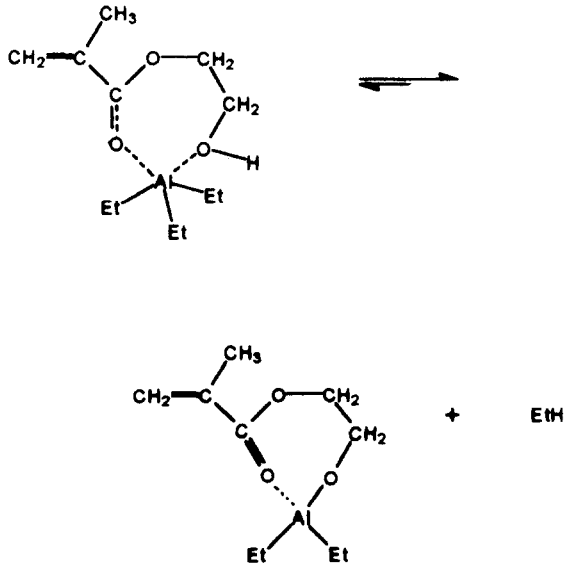

Figure 3 Formation of a molecular donor–acceptor complex between HEMA and $AlEt_3$, previous to the HEMA–aluminium alkoxide

et al.[24] have reported the ^{1}H n.m.r. spectrum of the mono-HEMA–aluminium alkoxide, registered in toluene-d_8. Apart from the signals at 6.17 and 5.45δ of the methacrylic double-bond hydrogens, the spectrum presents two rather distorted and relatively wide triplets centred at 4.11 and 3.76δ, which were assigned to the four hydrogens of the oxyethylene group of the HEMA complexed unit. This result is in agreement with the spectrum obtained in this work, if the possible influence of the solvent in the corresponding spectra is considered. Moreover, in the same report[24], these authors assigned the sharp singlet at 4.35δ (solvent, $CDCl_3$) to the four oxyethylene hydrogens of the HEMA end residue of poly(ε-caprolactone) macromonomers.

Mono- and tri-HEMA–aluminium alkoxide derivatives were used as initiators for the ring-opening polymerization of L-lactide at high vacuum in toluene solution. Conversion data after the reaction time considered in both cases, as well as average molecular weight determined by viscosimetry, are collected in *Table 1*. In order to analyse end-groups by n.m.r. spectroscopy, relatively low ratios of [LA]/[Al] were used in the experiments with the mono- and trialkoxides. Conversion degrees very close to 100 wt% were reached after the reaction time of each experiment, which is in good agreement with the living character of the ring-opening polymerization. An interesting result reflected in the data collected in *Table 1* is that it seems to be clear that each HEMA–alkoxide residue of the HEMA–Al complex molecule participates actively in the polymerization of the lactide, independently of the mono- or trialkoxide nature of the initiating species, as indicated by the viscosimetric data and average molecular weight collected in columns five and six of *Table 1*. Moreover, the experimental average molecular weight $\bar{M}_n$(exp) is rather close to the theoretical $\bar{M}_n$(t), according to the ratio [LA]/[Al], in both cases. The ratio $\bar{M}_n$(t)/$\bar{M}_n$(exp) is very close to unity, which means that the effectiveness of the initiating system is independent of the stoichiometry of the HEMA–Al derivative. The conversion–time data collected in the

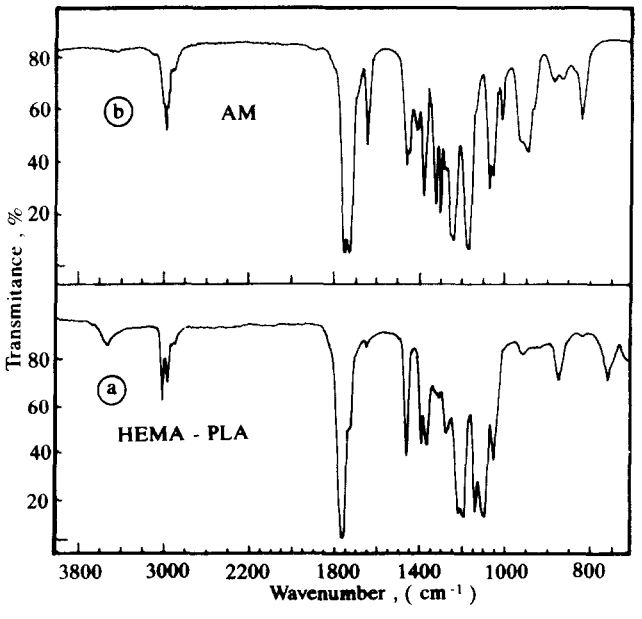

Figure 4 *FT*i.r. spectra of (a) the end-functionalized macromonomer HEMA–PLA and (b) the low-molecular-weight model compound AM

Table 1 Experimental data on the ring-opening polymerization of L-lactide initiated by mono- and tri-HEMA–aluminium alkoxides: $\bar{M}_n$(exp) = experimental; $\bar{M}_n$(t) = theoretical

Sample	[LA]/[Al]	Time (h)	Conversion (wt%)	$[\eta]$ (dl g^{-1})	$\bar{M}_n$(exp)	$\bar{M}_n$(t)
Mono-HEMA	19.84	100	94	0.1397	2600 (2500)[a]	2860
Tri-HEMA	34.72	50	96	0.0946	1600 (1500)[a]	1670

[a] Average molecular weight determined from end-group analysis by ^{1}H n.m.r. spectroscopy

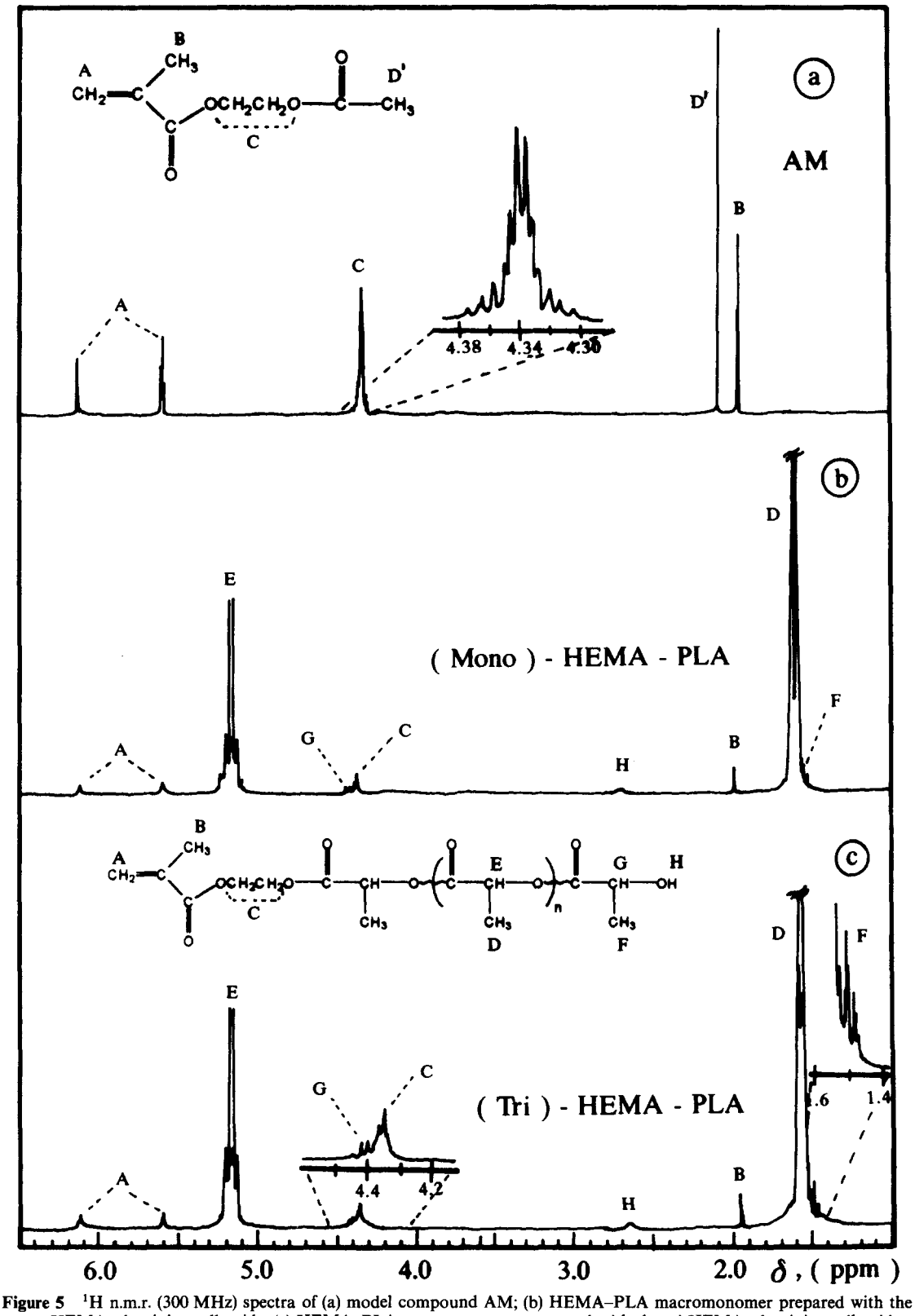

Figure 5 ^{1}H n.m.r. (300 MHz) spectra of (a) model compound AM; (b) HEMA–PLA macromonomer prepared with the mono-HEMA–aluminium alkoxide; (c) HEMA–PLA macromonomer prepared with the tri-HEMA–aluminium alkoxide

third and fourth columns of *Table 1* reveal that the ring-opening polymerization of L-lactide initiated by the tri-HEMA–aluminium alkoxide is at least twice as fast as that initiated by the monoalkoxide. Jérôme and Teyssie[16] have reported recently very similar results for the ring-opening polymerization of D,L-lactide, initiated by mono- and trialuminium alkoxides carrying various functional groups. They concluded that the rate of D,L-lactide polymerization decreases when an aluminium trialkoxide is replaced by the corresponding aluminium monoalkoxide, independently of the functional group attached to the alkoxide residue. According to these authors, the highest polymerization rate constants reported for the trialkoxides could reflect a decrease in the electrophilicity of the Al atom when it is surrounded by three electron-donating alkoxide groups[14,16].

Evidence of the end functionalization of the macromolecular poly(L-lactide) chains was obtained from the analysis of the polymers by spectroscopic techniques. In order to distinguish the spectroscopic signals of rather similar functional groups associated with structures of the HEMA end-group, we prepared a model compound by direct acetylation of HEMA, giving rise to 2-acetyloxyethyl methacrylate (AM). *Figure 4* shows the *FT*i.r. spectra of AM- and HEMA-functionalized poly(L-lactide) prepared with the monoalkoxide derivative; the polymer prepared with the trialkoxide gives a spectrum similar to that represented in *Figure 4a*.

The *FT*i.r. spectrum of the model compound AM (*Figure 4b*) presents two well resolved bands at 1746.5 and 1723.6 cm^{-1}, which correspond to the carbonyl stretching vibration of the acetate and methacrylate residues, respectively. Also the methacrylic group gives signals at 1638.7, 944.2 and 815.4 cm^{-1}, which are useful for the identification of the HEMA end functionalization of the poly(L-lactide) chains. *Figure 4a* shows the spectrum of the HEMA-functionalized macromonomer. The relatively wide band of the stretching vibration of the –OH end-group is observed clearly at 3460 cm^{-1}, as well as an intense band of the carbonyl lactic ester group of the polymer main chain at 1759.6 cm^{-1}, and a small shoulder at 1725.0 cm^{-1} assigned in the spectrum of the model AM to the methacrylic residue. The C=C band at 1637.2 cm^{-1} can also be distinguished. These spectra show qualitatively that the poly(L-lactide)s prepared by ring-opening polymerization have HEMA and HO– chain ends.

^{1}H n.m.r. spectra of the model compound AM and HEMA–PLA polymers prepared with the mono- and trialkoxides are represented in *Figure 5*. As shown in *Figure 5a*, the chemical structure of AM reproduces that of the HEMA-functionalized poly(L-lactide). It is interesting to stress the fact that, in addition to the resonance signals of the methacrylic double-bond hydrogens at 6.14 and 5.60δ, only one sharp multiplet centred at 4.34δ can be distinguished, and it is assigned to the four hydrogens of the oxyethylene residue. The α-CH_3 protons of the methacrylic HEMA residue give a sharp triplet at 1.95δ. *Figures 5b* and *5c* show the spectra of the HEMA–PLA macromonomers prepared with the mono- and trialuminium alkoxide derivatives, respectively. The spectra are very similar, with the only change being the relative intensities of the signals assigned to the HEMA end, with respect to that of the L-lactic repeat units. The assignment of the resonance signals to the hydrogens indicated in the chemical structures drawn in *Figures 5b* and *5c* is based on the position of the corresponding signals of the model AM, as well as taking into consideration those reported by Jedlinski *et al.*[11] for ethylene glycol–L-lactide block copolymers, by Kricheldorf *et al.*[26] for the ring-opening polymerization of L-lactide initiated by lithium, aluminium, zinc or titanium alkoxides, and by Jérôme *et al.*[16] for end functionalized poly(D,L-lactide). The ^{1}H n.m.r. spectra obtained demonstrate unequivocally that the ring-opening polymerization of L-lactide promoted by mono- or tri-HEMA–aluminium alkoxides provides linear, pure functionalized macromonomers with a hydroxyl end-group, generated by the hydrolytic termination process. The polymerization in the experimental conditions of the present work apparently proceeds without cyclization side reactions.

The use of mono- or trialkoxide initiators only has an influence on the polymerization rate and on the average molecular weight, but does not modify the coordination–insertion mechanism. The macromonomers obtained can be useful for the preparation of biocompatible polymeric systems for surgical and pharmacological applications. In this way, several polyacrylic systems with controlled hydrophilic character are being studied, and their characteristics and hydrolytic behaviour in physiological conditions will be described in a further publication.

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