Ring-Opening Polymerization of L-Lactide Initiated by (2-Methacryloxy)ethyloxy−Aluminum Trialkoxides. 1. Kinetics

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ABSTRACT: Kinetic aspects of the synthesis of (2-methacryloxy)ethyloxy functionalized poly(L-lactide) macromonomers using aluminum mono- and trialkoxides carrying this functionality are presented. The results show the living character of the ring-opening polymerization independently of the reaction temperature, but there are some deviations of the classical first order with respect to the monomer concentration, particularly at 60 °C and for low monomer/aluminum catalyst ratios. The comparative study of aluminum trialkoxides with respect to the corresponding monoalkoxides makes clear that the polymerization initiated by trialkoxides is at least five times faster than that initiated by the monoalkoxide. This behavior is explained by taking into consideration semiempirical calculations based on the PM-protocol, which gives an idea of the reactivity of mono- and trialkoxides with good agreement between theoretical and experimental results.

Introduction

During the last two decades, the advances in modern technologies have required the development of new polymeric materials with highly specific properties, materials where the consumption volume is not the driving force of their development but the specific function for which they have been designed.

In the biomedical field, polyesters and copolyesters of several α-, *β*-, and *ω*-hydroxyacids have been found as a versatile family of materials with interesting applications in surgery and pharmacology due to their biocompatibility and biodegradation into nontoxic byproducts under the conditions of the living organism's physiological medium.[1−4] Thus, polymers and copolymers of *ϵ*-caprolactone, lactides, and glycolide have been used in medicine as biodegradable sutures, artificial skins, and resorbable prostheses. They have also contributed to the design of galenic formulations that provide the controlled release of drugs the ability of and targeting into solid tumors.[5,6]

The biodegradation rate of these systems and, therefore, their physicomechanical properties in a physiological medium, are strongly dependent on factors such as chemical structure, molecular weight, or crystallinity.[7] Thus, even though they fulfill most of the requirements for their application in medicine, they do not always allow, for instance, the maintenance of mechanical properties for long enough, nor do they have an optimal hydrophilic/hydrophobic balance.[8] The use of graft copolymers that combine these polyesters with other biocompatible polymer segments is expected to open an interesting way to new versatile original materials whose specific properties can be modulated by the correct choice of these second components, the average composition of the copolymer, and the length of the graft polymers. Free radical copolymerization of end-functionalized biodegradable grafts ("macromonomers") with acrylic or vinylic monomers is a straightforward and interesting way to prepare these composite polymeric systems.

To produce well-defined graft copolymers, the macromonomers must be synthesized in a controlled way. It has been well-established that the ring-opening polymerization of lactones and lactides using aluminum alkoxides allows the synthesis of polyester chains with predictable molecular weights and well-characterized chain end groups as a result of the polymerization mechanism.[9,10] The preparation of biodegradable macromonomers using this synthetic route was first applied to the synthesis of *ϵ*-caprolactone oligomers functionalized with amino, bromine, allylic groups or even a methacrylic double bond using aluminum alkoxides carrying this functionality.[11,12] More recently, the use of such initiators was extended to the ring-opening polymerization of lactides.[13,14] In this sense, we reported the synthesis of poly(L-lactide) macromonomers using mono- and tri(2-methacryloxy)ethyloxy−aluminum alkoxides as initiators;[15] however, some kinetic data were not presented. A thorough kinetic study of this polymerization with various functional aluminum alkoxide initiators revealed some different reaction behaviors that derive from the particular chemical nature of the functional group anchored to the aluminum atom. This paper deals with the kinetic aspects of the synthesis of (2-methacryloxy)ethyloxy-functionalized poly(L-lactide) macromonomers using aluminum trialkoxides carrying this functionality. In addition, semiempirical calculations about the activity of these alkoxides have been carried out, and the results agree with the observed experimental behavior.

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Experimental Section

The L- and DL-lactides were prepared by catalytic thermolysis of poly(L-lactic acid) or poly(DL-lactic acid) oligomers in the presence of zinc oxide. They were purified by recrystallization (three times) from dry ethyl acetate and dried for 24 h at 25 °C under reduced pressure before polymerization.

Triethyl aluminum, a 1 M solution in hexane (Aldrich), was diluted in dry toluene. Aluminum isopropoxide (Fluka) was distilled under vacuum and dissolved in dry toluene. The solution concentration of both aluminum derivatives was determined by complexometric titration of Al by EDTA.

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 distilled before use. Triethylene glycol dimethacrylate (Fluka) was treated in the same manner.

Toluene and ethyl acetate were dried by refluxing over CaH_2 and $CaCl_2$, respectively, and distilled under nitrogen atmosphere just before use.

Polymerizations were carried out with stirring, in toluene solution, in an exhaustively nitrogen-purged, flame-sealed glass reactor. The monomer was first charged into the reactor in a glovebox under nitrogen atmosphere. Then, solvent was added through rubber septa with syringes and stainless steel capillaries. The initiator was synthesized in situ, adding the required amounts of triethyl aluminum and HEMA. The reaction mixture was kept at room temperature for 3 h and at 40 °C for 30 min. The temperature was then raised to the desired polymerization temperature. At various time intervals, several samples were taken out via syringe. These aliquots were treated with dilute HCl in order to stop the reaction and extract the initiator residues. The reaction mixture was washed with water to neutral pH, dried with anhydrous $MgSO_4$, and finally concentrated for NMR and GPC analyses.

^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform solution with a Varian VXR-300 spectrometer at 25 °C.

Molecular weight and molecular weight distribution were determined by using a gel permeation chromatograph (Waters 150-C ALC/GPC) operating at 25 or 30 °C in chloroform or THF and calibrated with polystyrene standards. The universal calibration method was applied for poly(L-lactide) on the basis of the following viscosimetric relationships, valid in chloroform at 25 °C:

$$[\mu] = 11.2 \times 10^{-5} M_n^{0.73} \text{ (PS)}$$

$$\text{and } [\mu] = 7.4 \times 10^{-5} M_n^{0.87} \text{ (PLLA)}$$

For poly(DL-lactide), the following viscosimetric relationships, valid in THF at 30 °C, were used:

$$[\mu] = 1.25 \times 10^{-2} M_n^{0.717} \text{ (PS)}$$

$$\text{and } [\mu] = 5.49 \times 10^{-2} M_n^{0.639} \text{ (PDLA)}$$

Computational Methods. Given the size of the computed structures, the PM3 semiempirical Hamiltonian[15] was used at the Hartree−Fock (HF) level, because this method has been proven to yield quite accurate geometries in esters and tri- and tetracoordinated aluminum compounds.[16] The energies were recalculated using a hybrid density functional developed by Becke and denoted as B3LYP.[17,18] This three-parameter functional combines the Becke gradient-corrected exchange functional and the Lee−Yang−Parr and Vosko−Wilk−Nusair correlation functionals[19] with part of the exact HF exchange energy. In these latter calculations, the 6-31G* basis set[20] was used. These calculations were performed on the Gaussian 94 suite of programs.[21] All of the stationary points were characterized by harmonic analysis.[22]

Results and Discussion

As it has already been demonstrated[9,13] the ring-opening polymerization of lactides initiated by aluminum alkoxides, functionalized or not, 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-aluminum bond of the initiator (Scheme 1, where R is an alkyl group, functionalized or not). End group analysis of final polymerization products allows this conclusion. In our previous paper,[23] we compared the ^{1}H NMR spectra of the final poly(L-lactide) macromonomer with that of a simple model compound that reproduced the methacrylic unit attached to the polylactide chain. To complete this, we would like to show here the chemical shift data of the ^{13}C NMR spectra of both the macromonomer and the model compound. Once again, as shown in Table 1, which summarizes the chemical shifts of both products, the comparison of both spectra proves the presence of the methacrylic unit in the polylactide chain.

Scheme 1

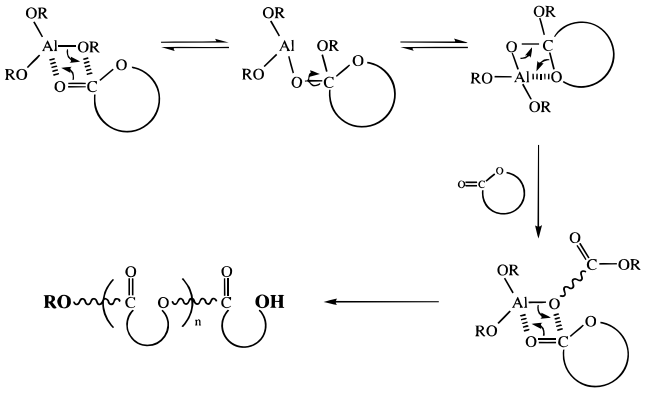

Table 1. Macromonomer and Model Compound ^{13}C NMR Chemical Shifts

macromonomer		2-acetoxyethyl methacrylate	
shift (ppm)	carbon	shift (ppm)	carbon
175.0	C_{10}		
171.0	C_7	170.8	C_7
169.5	C_4	167.1	C_4
135.7	C_2	136.0	C_2
126.2	C_1	126.0	C_1
68.9	C_8		
66.6	C_{11}		
63.0 and 62.0	C_5 and C_6	62.5 and 62.2	C_5 and C_6
20.4	C_{12}	20.8	C_8
18.2	C_3	18.3	C_3
16.6	C_9		

From the analysis of polylactide end groups, the living character of the polymerization was anticipated. The propagation of the L-lactide polymerization is, in fact, perfectly living when it is initiated by this functionalized trialkoxide: as shown in Figure 1, the molecular weight of the poly(L-lactide) macromonomer increases linearly with monomer conversion during L-lactide polymerization at 60 °C. A living propagation is also proved by the linear dependence of the mean degree of polymerization (DP) at total conversion on [monomer]/[initiator] molar ratio (Figure 2). It must be pointed out that the same behavior is observed at 80 °C; even at this temperature, the reaction parameters are under control if the time required to reach high conversions is not exceeded. Under these conditions, the molecular weight distribution remains lower than 1.3 in all cases. This confirms

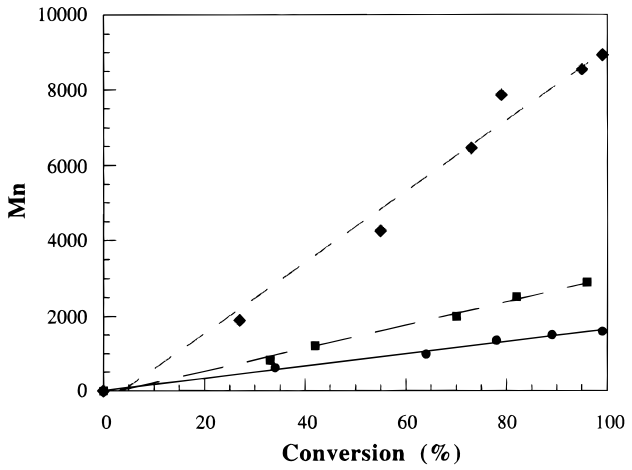

Figure 1. Relationship between M_n (GPC) and monomer conversion (%) for the polymerization of L-lactide in toluene at 60 °C initiated by HEMA-functionalized aluminum trialkoxides. $[LA]_0 = 0.5$ mol/L. $[LA]_0/[Al] = 31.2$; $M_{n\ theor.} = 1630$ (●). $[LA]_0/[Al] = 62.4$; $M_{n\ theor.} = 3130$ (■). $[LA]_0/[Al] = 187.2$; $M_{n\ theor.} = 9130$ (◆).

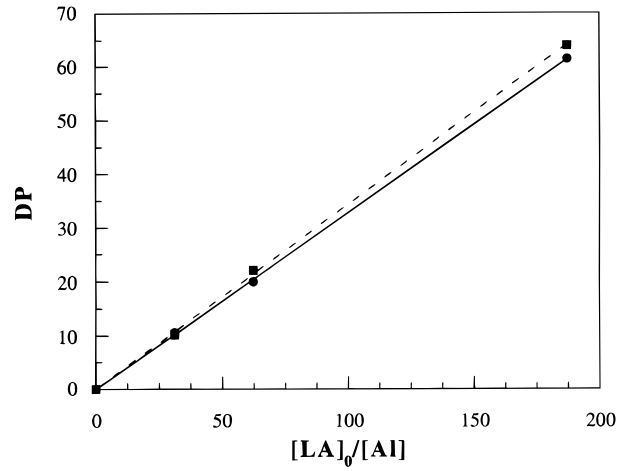

Figure 2. Dependence of DP on monomer/initiator molar ratio at 98−99% conversion for the polymerization of L-lactide in toluene initiated by HEMA-functionalized aluminum trialkoxides. $[LA]_0 = 0.5$ mol/L. $T = 60$ °C (●). $T = 80$ °C (■).

the absence of termination or transfer reactions under the polymerization conditions used.

The slope of the linear dependence of DP versus the [monomer]/[initiator] molar ratio is $^1/_3$, which means that each alkoxide group of the initiator is active on the initiation step in agreement with the results obtained for the polymerization of DL-lactide initiated by other aluminum trialkoxides. Thus, the molecular weight of a PLLA macromonomer can be predicted on the basis of eq 1, where M_{LA} is the molecular weight of L-lactide (144 g/mol), $[LA]_0$ is the initial monomer concentration, [Al] is the initiator concentration, and *x is* the conversion; *n* represents the number of active alkoxy groups per aluminum atom, which takes the value 3 for this system.

$$\mathrm{Mn} = \frac{[\mathrm{LA}]_0}{n[\mathrm{Al}]} M_{\mathrm{LA}} \frac{x}{100} \qquad (1)$$

Kinetics of L-lactide polymerization initiated by (2-methacryloxy)ethyloxy-functionalized aluminum trialkoxides was investigated in toluene at several reaction conditions. Kinetics were followed by ^{1}H NMR: samples

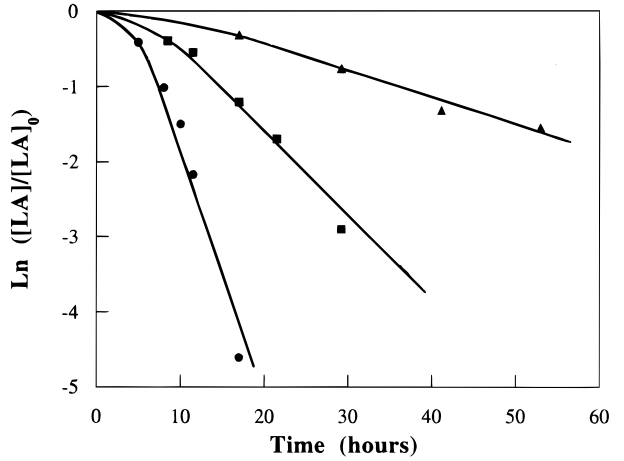

Figure 3. Determination of the reaction order with respect to the monomer concentration for the polymerization of L-lactide in toluene at 60 °C initiated by HEMA-functionalized aluminum trialkoxides. $[LA]_0 = 0.5$ mol/L. $[LA]_0/[Al] = 31.2$; $M_{n\ theor.} = 1630$ (●). $[LA]_0/[Al] = 62.4$; $M_{n\ theor.} = 3130$ (■). $[LA]_0/[Al] = 187.2$; $M_{n\ theor.} = 9130$ (▲).

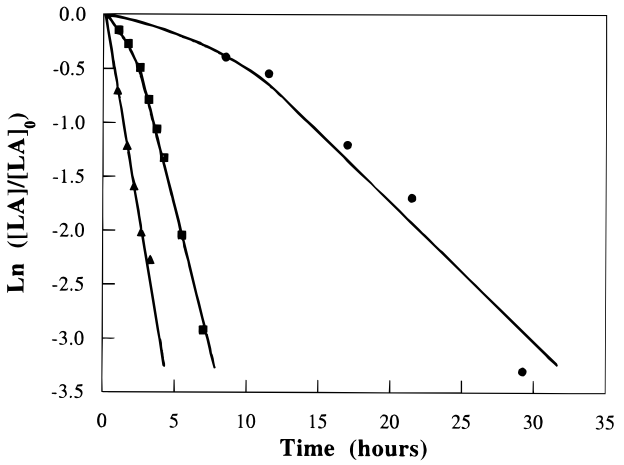

Figure 4. Variation of the kinetic parameter $\ln([LA]/[LA]_0)$ with the polymerization time for the polymerization of L-lactide in toluene initiated by HEMA-functionalized aluminum trialkoxides at several temperatures: $[LA]_0 = 0.5$ mol/L. $[LA]_0/[Al] = 62.4$; $M_{n\ theor.} = 3130$. $T = 60$ °C (●). $T = 80$ °C (■). $T = 100$ °C (▲).

were withdrawn from the reaction medium after different periods of time, hydrolyzed, and concentrated. Monomer conversion was determined by measurement of the signal of the methine or methyl group in the monomer in relation to that in the macromonomer.

Figures 3 and 4 show the logarithmic plots $\ln([LA]/[LA]_0)$ versus time for several initial $[LA]_0/[Al]$ molar ratios (Figure 3) or temperature (Figure 4). It can be considered that after a variable induction period polymerization is first-order in monomer, as demonstrated by the linear relationship between monomer conversion and polymerization time for most of the polymerization conditions. However, it must be pointed out that when polymerizations are carried out at 60 °C, especially at low $[LA]_0/[Al]$ molar ratios, some degree of curvature is observed.

As demonstrated by Duda,[24] low-molecular-weight alcohols or diols, introduced purposely into the polymerization of ϵ-caprolactone initiated by aluminum isopropoxide, operate not only as chain-transfer agents but also as either inhibitors or accelerators depending on the initial ratio of trimeric/tetrameric species of the

initiator. Thus, at the early stages of polymerization, the relative polymerization rate increases and at higher conversions, after the complete consumption of the starting alcohol or diol, the polymerization rate becomes constant.

In the results found in this work, the observed process cannot be attributed to the presence of any free molecule that could interfere with the active species in the initiation step. As we showed by ^{1}H NMR in our previous work,[23] the reaction of triethyl aluminum with HEMA to obtain the functionalized aluminum trialkoxides used in the synthesis of PLA macromonomers was complete after 4 h at room temperature. This means that no significant amount of free HEMA could be found in the polymerization medium in the experimental conditions; so, the hypothesis of the presence of any free HEMA molecule to explain the induction process can be discarded. The reason is more likely to rely on the degree of association of the functionalized initiator molecules in toluene solution.

It is well-known that in nonpolar solvents aluminum alkoxides exist as di-, tri-, and tetramers.[25−28] Thus, for example, it has been shown[29] that aluminum triisopropoxide is coordinatively aggregated in toluene in such a way that tetra- and trimeric species are in equilibrium; upon addition of γ-butyrolactone (BL), a nonpolymerizable model, this equilibrium is shifted toward the formation of an octahedric $[Al(O^iPr)_3\ BL_3]$ mixed tetramer coexisting with $[Al(O^iPr)_3]_4$ tetramers, being the external tetrahedric Al atoms coordinated with extra monomer molecules. This equilibrium is totally shifted to the formation of the mixed tetramer in the presence of a large excess of BL, suggesting that these are the real initiator species for the ring-opening polymerization of lactones and lactides.

HEMA-functionalized trialkoxides are also expected to form aggregates as other aluminum alkoxides do, but in this case, it must be taken into account that the nature of the carbonyl in the methacrylic residue can give rise to interactions between free d-orbitals of the aluminum atom and the carbonyl double bond (or the whole methacrylic-conjugated system) stronger than those that would be established between the same d-orbitals and free electron pairs of a simple alkoxide. This means that the monomer is involved in a competitive process in which the methacrylic group prevents its complete coordination with the aluminum atom, making the polymerization rate slower than expected during the induction step. As long as several lactide units are inserted between the active chain end and the methacrylic unit, these end groups move away from each other, making more difficult the coordination between them. As a result of all these phenomena, the interaction with lactide becomes favored as the polymerization proceeds, which is detected as an increase of the polymerization rate. Relatively low temperatures and low $[LA]_0/[Al]$ ratios would favor the association of the initiator, making this effect more evident, as shown in Figures 4 and 3 where the effect of temperature for a fixed $[LA]_0/[Al]$ ratio and the effect of the molecular weight ($[LA]_0/[Al]$ ratio) for a given temperature are represented, respectively. Finally, there is other experimental evidence that could support this hypothesis: if we compare the behavior of the trialkoxide with that of the monoalkoxide bearing the same functional group (Figure 5), it can be seen that there is a clear linear relationship between the monomer conversion and the polymerization time in the case of the polymerization

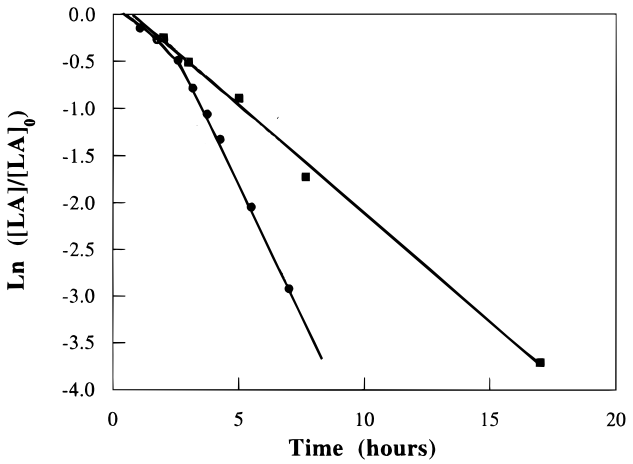

Figure 5. Comparative kinetic behavior of the polymerization of L-lactide in toluene at 80 °C initiated by HEMA-functionalized aluminum alkoxides with different stoichiometry. $[LA]_0 = 0.5$ mol/L. $[LA]_0/[Al] = 62.4$; $M_{n\ theor.} = 3130$. Trialkoxide (●). Monoalkoxide (■).

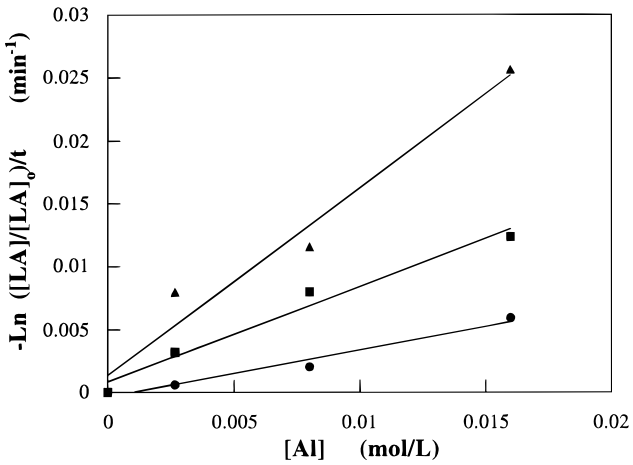

Figure 6. Dependence of $\ln([LA]/[LA]_0)/t$ vs [Al] for the polymerization of L-lactide in toluene initiated by HEMA-functionalized aluminum trialkoxides at several temperatures: $[LA]_0 = 0.5$ mol/L. $T = 60$ °C (●). $T = 80$ °C (■). $T = 100$ °C (▲).

initiated by the monoalkoxide. Because the monoalkoxide has only one methacrylic unit attached to the aluminum atom, it is expected to have less difficulty in coordinating lactide and thus showing a different kinetic behavior.

The polymerization of L-lactide initiated by these functionalized trialkoxides is also first-order in initiator, according to the linear relationship found between $-\ln([LA]/[LA]_0)/t$ and initiator concentration (Figure 6).

Therefore, it can be concluded that the polymerization of L-lactide in toluene solution initiated by aluminum trialkoxides functionalized with (2-methacryloxy)ethyloxy units proceeds according to a kinetic law similar to that found for other aluminum trialkoxides[9,13] (eq 2).

$$-\mathrm{d}[LA]/\mathrm{d}t = K_p[LA][Al] \qquad (2)$$

From the slopes of the linear relationships between $-\ln([LA]/[LA]_0)/t$ and [Al] (Figure 6), the values of the polymerization rate constants (K_p) can be calculated as the slope K_p[Al]. The obtained values are collected in Table 2. It must be said that these values are in the range of those found for other trialkoxides in similar reaction conditions.[9,13] Finally, with these three values,

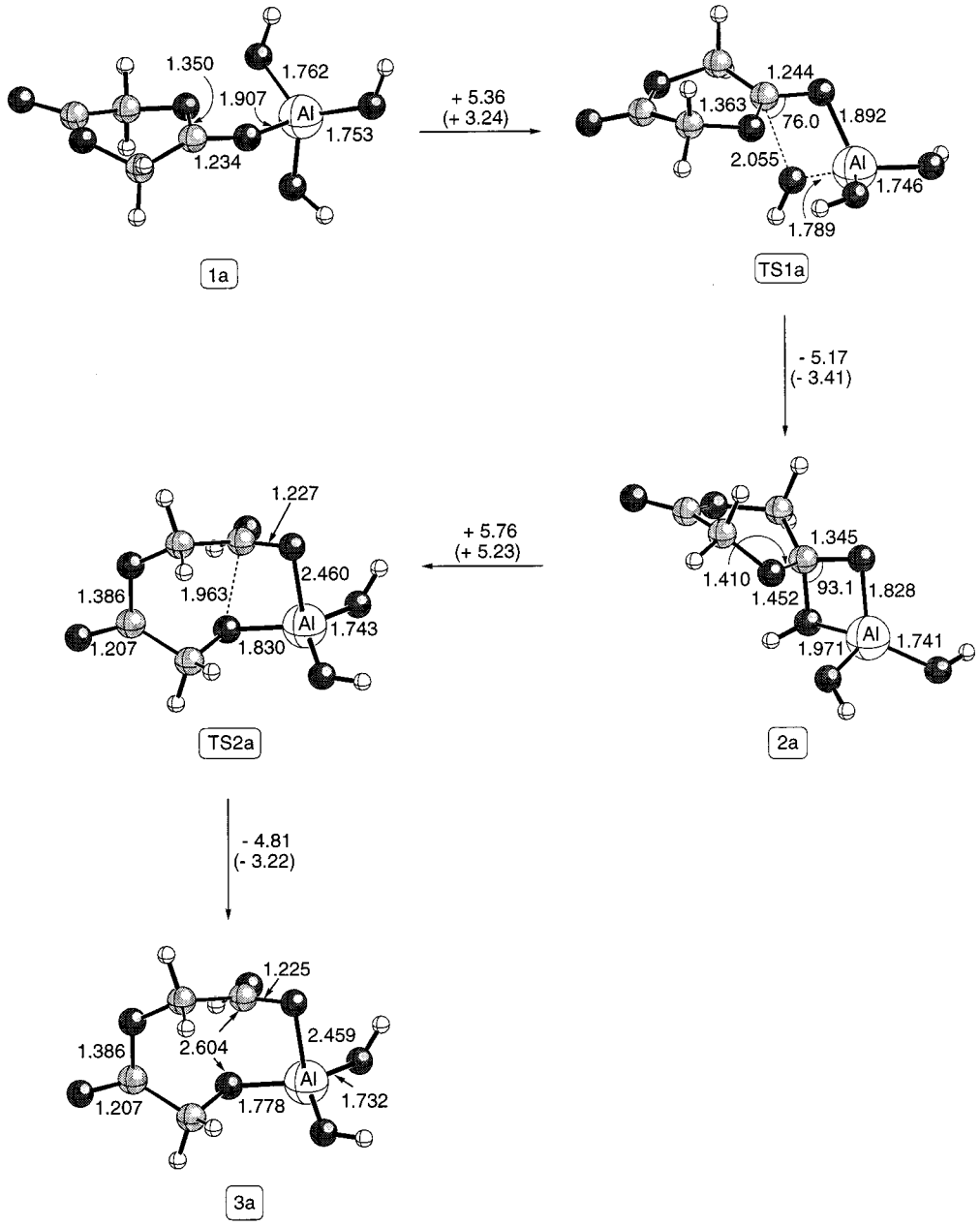

Figure 7. HF/PM3 fully optimized stationary points corresponding to the ring opening of lactide promoted by $Al(OH)_3$. Bond distances are given in angstroms. Numbers over the arrows are the relative energies in kilocalorie per mole between the connected structures, computed at the B3LYP/6-31G*//HF/PM3 and B3LYP(SCIPCM)/6-31G*//HF/PM3 levels (in brackets, see text).

Table 2. Kinetic Constants for the Polymerization of L-Lactide in Toluene Solution Initiated by HEMA-Functionalized Aluminum Trialkoxides

temperature (°C)	K_p (L mol^{-1} min^{-1})
60	0.37
80	0.76
100	1.49

the activation energy of the polymerization can be calculated by fitting them to the Arrhenius equation; by means of an adequate representation of ln K_p versus $1/T$ a value of 8.5 kcal mol^{-1} (35.5 KJ mol^{-1}) is deduced for the activation energy, which is in the range of activation energy values for reactions in solution. The resulting preexponential factor is $A = 1.478 \times 10^5$ L mol^{-1} min^{-1}.

In relation to the kinetic behavior shown by the trialkoxides compared with the corresponding monoalkoxides, it must be remarked that the polymerization rate increases when the trialkoxide is used as initiator. It can be verified that the rate constant for the polymerization initiated by the trialkoxide is at least 5 times higher than that corresponding to the same polymerization initiated by the monoalkoxide. This effect has already been found with other aluminum alkoxides[10,13] and has been attributed to a decrease in the electrophilicity of the aluminum atom when it is surrounded by three electron-donating alkoxide groups.

To test this hypothesis, several computational studies were performed on the ring opening of lactide in the presence of $Al(OH)_3$ and $Al(OH)Me_2$, as computational equivalents of an aluminum trialkoxide and a dialkylaluminum monoalkoxide, respectively. Details of the computational methods are given in the Experimental Section. The geometries of the fully optimized stationary points are reported in Figures 7 and 8, and the corresponding energies are shown in Table 3.

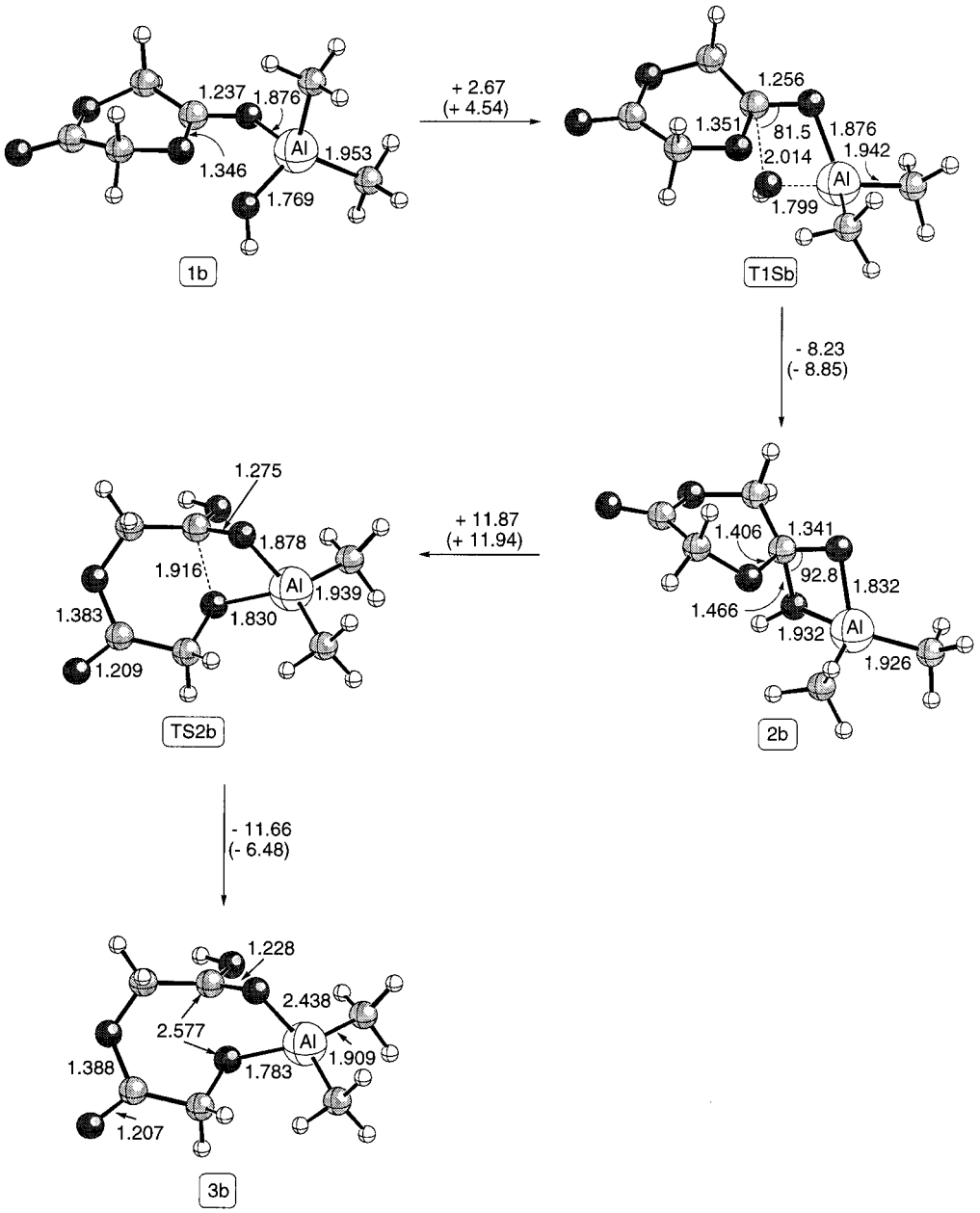

Figure 8. HF/PM3 fully optimized stationary points corresponding to the ring opening of lactide promoted by $AlMe_2OH$. Bond distances are given in angstroms. Numbers over the arrows are the relative energies in kilocalorie per mole between the connected structures, computed at the B3LYP/6-31G*//HF/PM3 and B3LYP(SCIPCM)/6-31G*//HF/PM3 levels (in brackets, see text).

According to our results, the complex **1a** between lactide and $Al(OH)_3$ exhibits a relatively weak interaction between the carbonyl group of lactide and the aluminum atom (Figure 7). In contrast, the same interaction in the analogue complex **1b** between lactide and $AlMe_2OH$ is stronger, as it is shown by the lower O−Al distance (Figure 8). This result can be explained by the donating ability of the oxygen lone pairs on the electron-deficient aluminum atom. From complex **1a**, the intermediate **2a** is obtained via transition structure **TS1a** (Figure 7). This process corresponds to a nucleophilic addition of the hydroxyl on the carbonyl group. The analogue **1b** → **TS1b** → **2b** process is illustrated in Figure 8. Our calculations suggest that this first step has a higher activation barrier if solvent effects are taken into account by means of the self-consistent isodensity polarization continuum model (SCIPCM).[30] Thus, the activation barrier for the **1a** → **TS1a** → **2a**

Table 3. Energies of the Stationary Points Reported in Figures 6 and 7 As Computed at Different Theoretical Levels

station. point	energy		
	HF/PM3[a,b]	B3LYP/6-31G*[b,c]	B3LYP(SCIPCM)/6-31G*[b,c]
1a	−398.77	−925.736 21	−925.746 60
1b	−257.09	−853.816 33	−853.826 69
TS1a	−391.96	−925.727 66	−925.741 44
TS1b	−249.40	−853.812 07	−853.819 46
2a	−406.68	−925.735 90	−925.746 88
2b	−259.97	−853.825 19	−853.833 56
TS2a	−392.75	−925.726 72	−925.738 54
TS2b	−249.64	−853.806 28	−853.814 53
3a	−402.37	−925.734 38	−925.743 68
3b	−256.91	−853.824 87	−853.824 86

[a] Heat of formation in kilocalorie per mole. [b] Energy computed on the fully optimized HF/PM3 geometries. [c] Total energy in atomic units (1 hartree = 627.51 kcal/mol).

process is calculated to be 1.3 kcal/mol lower than the **1b** → **TS1b** → **2b** transformation in simulated toluene solution ($\epsilon = 2.38$),[31] although the reverse relationship between both processes is found in vacuo. This result is due to the higher polarity of **TS1a**, which promotes a larger solvation stabilization energy.

The second step of the ring opening consists of the scission of the O−CO bond of the ester group. The chief geometric features of the transition structures **TS2a** and **b** associated with this step are depicted in Figures 7 and 8. In both cases, the breaking of the O−CO bond takes place together with a new O−Al interaction to yield the aluminum alkoxides **3a** and **b**. We have found that tetrahedral intermediate **2a** is more reactive than **2b**, its O−CO bond distance being shorter. Thus, the second activation barrier for the **2a** → **TS2a** → **3a** process is calculated to be 6.11 kcal/mol lower than that of the analogous **2b** → **TS2b** → **3b** process. Moreover, when this second barrier was calculated in a simulated toluene solution ($\epsilon = 2.38$), this difference is calculated to be 6.71 kcal/mol. Therefore, our calculations indicate that the ring opening of the lactide by an aluminum alkoxide takes place in two steps, the second one being of higher activation energy. The larger polarity of the species involved favors the ring opening when a trialkoxide aluminum compound is used, in good agreement with the experimental evidence available.

Conclusions

The polymerization of L-lactide initiated by HEMA-functionalized aluminum alkoxides (mono- and tri-) has been proved to be first-order in both monomer and initiator. It must be pointed out, however, that compared with other similar systems, the polymerization initiated by the trialkoxide differs from that of the monoalkoxide not only in the polymerization rate but also in the kinetics itself, because of the particular chemical structure of the initiator functionality, which is supposed to lead to associations which interfere with the propagation step.

The higher activity of the trialkoxide, usually attributed to a decrease in the electrophilicity of the aluminum atom when it is surrounded by three electron-donating alkoxide groups, has been supported by a computational study. The ring opening of the lactide can be described as a two-step process where the second one has a lower energy barrier in the case of the trialkoxide compared with the monoalkoxide.

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