

Bulk Polymerization of (L,L)-Lactide Using Non-Organometallic Triazolium Carbene: Limited Advantages

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Abstract: The ring-opening polymerization (ROP) of L,L-lactide (L-LA) has been studied in bulk using alcohol (either methanol or benzyl alcohol) and 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene carbene, **1**, respectively as initiator and non-organometallic catalyst, over a range of temperature and alcohol-to-**1** molar ratios. Although **1** is known to perfectly control the polymerization of L-LA in solution at 90°C, its efficiency in bulk is drastically decreased since its thermal instability limits the possibility to reach high molecular weight poly(L-lactide) (PL-LA). Under optimum conditions, PL-LA chains with average molecular weight up to 10,000 g.mol⁻¹ have been obtained within 15 minutes and interestingly characterized by very narrow polydispersity indices. Compared to PL-LA conventionally prepared with stannous octoate as catalyst, the thermal stability proved remarkably enhanced when the ROP was promoted by **1**.

INTRODUCTION

The development of biodegradable polymers as resorbable biomaterials and, more recently, as commodity thermoplastics from renewable resources has received significant attention. Poly(lactides) (PLAs), have been the preferential candidates for such (bio)materials design [1-4] and are prepared most of the time by ring-opening polymerization (ROP) of lactides (L-LA, D,L-LA) using metal-based catalysts (Sn, Al, Ti,...) [5,6]. However, as far as biomedical applications are concerned, it is recommended to avoid organic solvent as well as most of commonly used organometallic catalysts, which in some cases can trigger cytotoxicity and reduce down the biocompatibility of the resulting PLA-based biomaterials [7]. Accordingly, there has been a recent resurgence of interest in organocatalytic methods as an alternative to more conventionally used organometallic reagents. These metal-free catalytic methods also prove particularly useful in situations where residual metals can compromise the purity of the product, an important consideration for instance when thermal stability is looked for microelectronic applications. Interestingly enough, various nucleophilic catalysts such as tertiary amines, phosphines, and, in particular, stabilized singlet carbenes, have recently displayed remarkable efficiency in controlled ROP of cyclic esters [8]. More particularly we recently demonstrated the unique behavior of the commercially available 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, **1**, *N*-heterocyclic carbene (NHC) towards the ROP of L-LA when conducted in solution [9,10]. Indeed, in presence of alcohols, triazole carbene **1** efficiently catalyzed the ROP of lactide in solution at 90°C, [10] affording extremely well-controlled poly(lactide) chains with molecular weights close to those predicted from the monomer-to-initiator (alcohol) molar ratio, low polydispersity (<1.2) and end-group fidelity. Furthermore in presence of **1**, primary amines were found to function as bifunctional initiators

for the ROP of lactides leading to the formation of an imide function within the polyester chain actually terminated by two secondary hydroxyl functions [9].

As bulk polymerization of lactide exhibits certain advantages over solution polymerization, i.e. (i) no solvent required, (ii) less vulnerable to impurities and generally unwanted side reactions, (iii) often useful for the large-scale production of PLAs, [11] our attention has been drawn towards the utilization of the thermally activated **1** NHC for the bulk polymerization of L-LA.

EXPERIMENTAL PART

Materials

L-Lactide (Boehringer-Ingelheim, 99+%) was recrystallized three times in dried toluene (20% wt/vol) at 70°C and then dried under vacuum overnight. 5-Methoxy-1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (Acros, 98%) was purified and degassed at r.t. by three nitrogen/vacuum treatments prior to any polymerization reaction. 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene was obtained after thermal treatment of 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (Acros, 98%) under vacuum at 100°C for 12 hours. Benzyl alcohol (Acros, 99%) was dried over CaH₂ for 48 hours prior to its distillation. Carbonyl disulfide (Riedel-de Haën, p.a.), methanol (Acros) and CDCl₃ (Cortec) were used as received.

Polymerization

L-Lactide was polymerized in previously flame-dried and nitrogen purged 25 ml glass ampoules equipped with a stopcock capped with a rubber septum. In a dry box, the dried ampoules were filled with ca. 1 g recrystallized lactide and appropriate amount of catalyst/alcohol. Out of the dry box, the ampoules were finally sealed and thermostated at a well-defined temperature. At predetermined reaction times, the ampoules were rapidly cooled down to room temperature, their content dissolved in a CS₂/THF solution and kept under agitation at 50°C for 2 hours prior to precipitation in cold methanol.

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Characterization

$^1\text{H-NMR}$ spectra were recorded on a 300 MHz spectrometer, with shift reported in parts per million downfield from tetramethylsilane ($^1\text{H-NMR}$) used as internal reference. Gel permeation chromatography was performed in tetrahydrofuran at 35°C on a Waters chromatograph equipped with four 5 μm Waters columns (300 mm x 7.7 mm) connected in series with increasing pore size (10, 100, 1000, 10^5 , 10^6 Å). Polystyrene samples of known molecular weight were used as calibration standards. A Waters 410 differential refractometer and 996 photodiode array detector were employed. Experimental absolute molecular weights (Mn_{exp}) have been determined using the Mark-Houwink correction (see main text). Temperature DSC measurements were performed under nitrogen flow using a DSC Q1000 from TA Instruments (heating rate : 10°C/min). Thermogravimetric analyses were performed on a Hi-ResTM TGA 2950CE from TA Instruments, using helium as purge gas. High resolution analyses were performed with a heating ramp of 30°C/min and by using a resolution parameter of 5, which means that a continuously variable heating rate is applied in response to changes in the sample decomposition rate. This resolution parameter can be tuned within an eight-step scale to maximize weight loss resolution. A $\pm 1^\circ\text{C}$ precision over the degradation temperature has been estimated from the derivative of the temperature dependant weight loss curves (DTGA curves). The analysis of gas evolved all along the thermal degradation was carried out with a Bio-Rad Excalibur FTIR spectrometer with a 0.2 cm^{-1} resolution. Spectra were recorded owing to a gas cell heated at 225°C and an MCT detector cooled down by liquid nitrogen.

RESULTS AND DISCUSSION

In a first series of experiments, the bulk polymerization of L-LA has been catalyzed by **1** in presence of methanol (or benzyl alcohol) as initiator and for an initial monomer-to-alcohol ratio ($[\text{L-LA}]_0/[\text{ROH}]_0$) of 100. The time dependence of the L-LA conversion and the PL-LA molecular weight on the initial **1**-to-alcohol molar ratio ($0.02 \leq R = [\text{1}]_0/[\text{ROH}]_0 \leq 1$) have been studied at 135°C. Experimental results seem to indicate that compound **1** is an efficient catalyst for the bulk

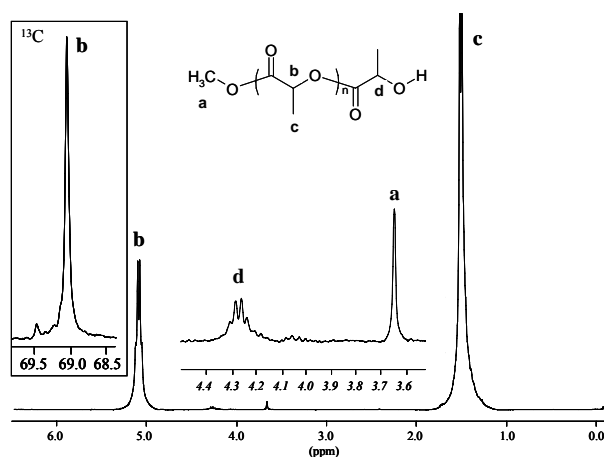


Fig. (1). $^1\text{H-NMR}$ spectrum in CDCl_3 of PL-LA as obtained by ROP of L-LA initiated from methanol in the presence of carbene **1** at 135°C. Inset: methine region of the $^{13}\text{C-NMR}$ spectrum.

polymerization of L-LA. As an example, examination of the $^1\text{H-NMR}$ spectrum of a PL-LA obtained after 15 minutes of L-LA polymerization from MeOH/**1** ($[\text{MeOH}]_0/[\text{1}]_0 = 1$) at 135°C shows resonance signals attributed to an α -methoxycarbonyl at $\delta = 3.65$ ppm (Fig. 1, H_a) as well as the methine ω -hydroxyl chain ends at $\delta = 4.3$ ppm (H_d). Examination of the microstructure of the PL-LA by $^{13}\text{C-NMR}$ spectroscopy reveals a high isotactic polymer with very low levels of stereoirregularity (Fig. 1, inset).

As determined by gel permeation chromatography (GPC) by reference to polystyrene standard calibration and using the Mark-Houwink relationship ($Mn_{exp}(\text{PL-LA}) = 0.4055 \times Mn(\text{PS})^{1.0486}$)^[12], the efficiency of polymerization, whatever the R value, is demonstrated by the good linear relationship between Mn_{th} and Mn_{exp} even if some deviations might not be completely excluded (Fig. 2).

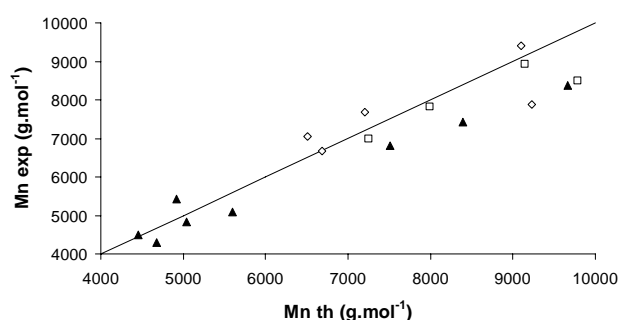


Fig. (2). Dependence of molar mass (Mn_{exp}) of poly(L-lactide) measured by GPC on Mn_{th} calculated (Mn_{th}) from the feed composition; $Mn_{th} = 144.13 ([\text{LA}]_0 - [\text{LA}])/[\text{ROH}]_0$. Conditions of polymerization : $[\text{L-LA}]_0/[\text{ROH}]_0 = 100$, 135°C; (\blacktriangle) $R = 0.02$, ROH = MeOH; (\square) $R = 0.05$, ROH = BzOH and (\diamond) $R = 1$, ROH = BzOH.

Expectedly, polymerization rates decrease with the R ratio, as observed from time-evolution of both monomer conversion and experimental molecular weight, while polydispersity indices (PDIs) slightly increase from 1.15 to 1.33 when R increases from 0.02 to 1 (Figs. 3A and B).

The polymerization kinetics have also been studied at different temperatures, ranging from 110°C to 155°C, for a constant monomer-to-methanol-to-**1** molar ratio ($[\text{L-LA}]_0/[\text{MeOH}]_0 = 100$; $[\text{MeOH}]_0/[\text{1}]_0 = 1$). As shown by (Fig. 4A), the polymerization rate is increased when reactions are conducted at low temperature (110°C) while conversions already start to level off at 155°C after 3 hours of polymerization. Interestingly, higher molecular weights could be obtained more rapidly when the polymerization was conducted at 110°C yielding PL-LA samples characterized by lower PDIs (Fig. 4B). It is also worth noting that experimental PL-LA molecular weights pass through a maximum and decrease slightly beyond the time required to reach the maximum monomer conversion whatever the temperature of polymerization. All these observations might be explained by appearance of subsequent phenomena during the L-LA bulk ROP: (i) the thermal decomposition of the triazolium carbene catalyst during the polymerization process and especially at elevated temperature, (ii) the occurrence of transesterification reactions perturbing the chain propagation and, in case of intramolecular transesterification, decreasing the polyester molecular weights.

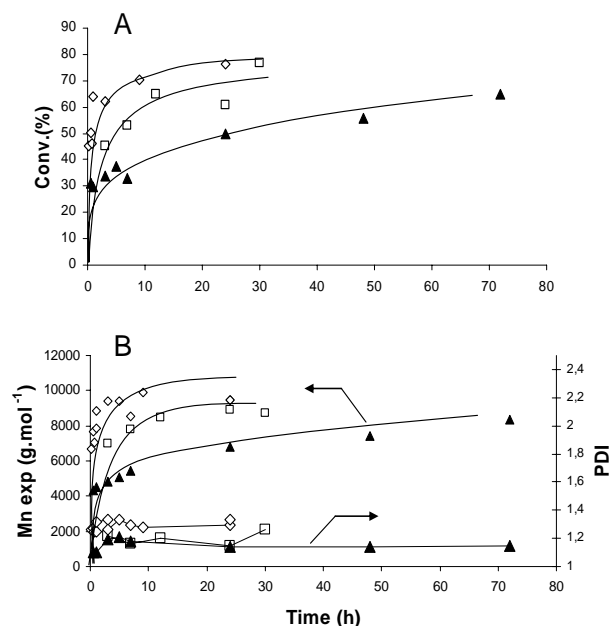


Fig. (3). Time dependence of L-LA conversion (A), PL-LA number average molecular weight and associated PDI (B) as determined by gravimetry and GPC, respectively. Conditions of polymerization : $[\text{L-LA}]_0/[\text{ROH}]_0 = 100$, 135°C with (\blacktriangle) $R = 0.02$, $\text{ROH} = \text{MeOH}$; (\square) $R = 0.05$, $\text{ROH} = \text{BzOH}$ and (\diamond) $R = 1$, $\text{ROH} = \text{BzOH}$.

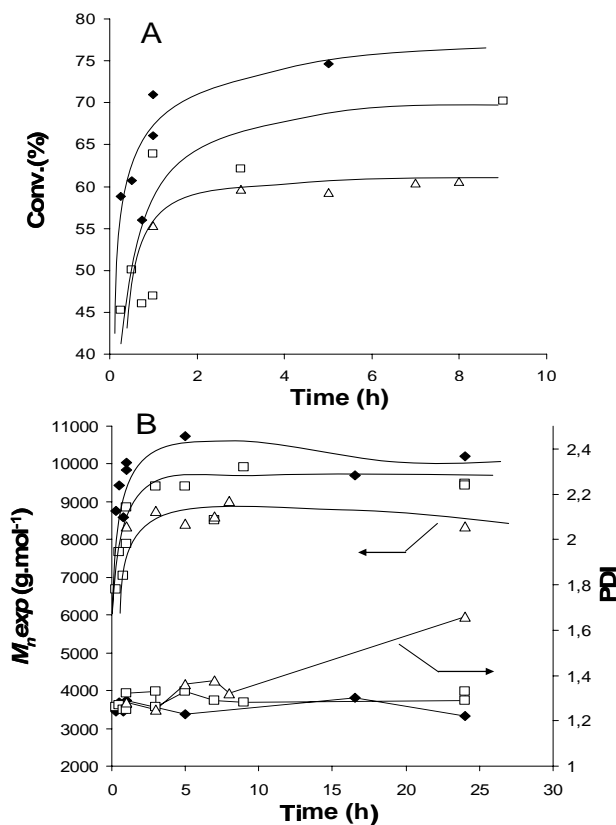


Fig. (4). Time dependence of L-LA conversion on the polymerization temperature at an initial L-LA to MeOH molar ratio of 100 and R of 1 (A) and the number average molecular weight and associated PDI as determined by GPC (B). Conditions of polymerization : (\blacktriangle) 110°C ; (\square) 135°C and (\diamond) 155°C .

The first hypothesis is supported by differential scanning calorimetry (DSC) and thermal gravimetric analysis coupled with infra-red spectroscopy for evolved gas analysis (TGA-FTIR) measurements of the commercially 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene adduct ($[\mathbf{1}]_0/[\text{MeOH}]_0 = 1$). The DSC and TGA-FTIR experiments are shown in (Fig. 5). The DSC chromatogram is characterized by three endotherms centred at 102.6 , 154.2 and 254.7°C in good correlation with the successive weight losses observed in TGA at 102.7 , 174.8 and 268.4°C , respectively. The degradation gases have been analyzed *in situ* by FTIR, the first two degradations observed at 102.7 and 174.8°C are both corresponding to a methanol weight loss, probably physically and chemically bonded to the triazolium carbene $\mathbf{1}$. The most important (73%) weight loss observed in between 200 - 300°C is clearly identified as the complete thermolysis of $\mathbf{1}$ by the appearance of characteristic by-products vibration bands observed by FTIR.

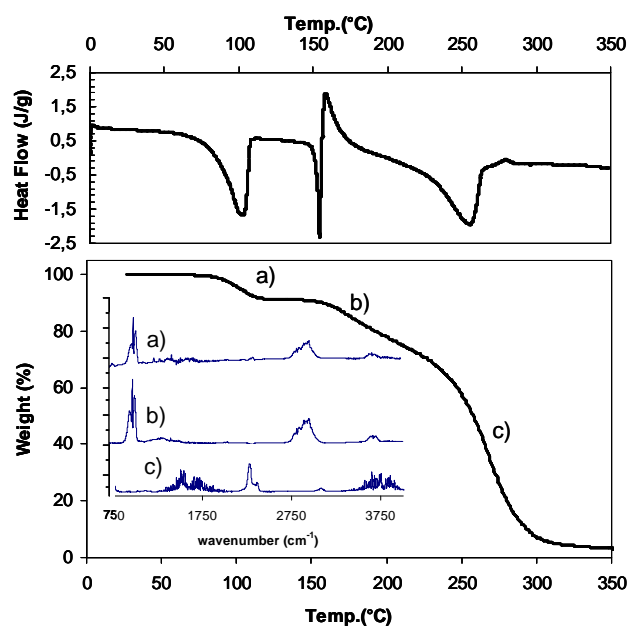


Fig. (5). Thermogravimetric analysis and heat flow of 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene adduct as a function of temperature together with FTIR spectra.

Time dependence of the weight loss under isothermal conditions, i.e., at 110°C and 135°C has also been realized on carbene $\mathbf{1}$ after complete elimination of methanol. The degradation rates calculated from the slopes of the linear dependences of weight loss are equal to 1.46 and $37.06 \times 10^{-3} \text{ \%}\cdot\text{min}^{-1}$ at 110 and 135°C , respectively (Fig. 6).

Such degradation rates thus convincingly indicate that carbene $\mathbf{1}$ is an efficient catalyst for the bulk polymerization of L-LA as soon as temperature reaction is kept under 135°C . Such an inherent thermal instability triggers its degradation at more elevated temperature and its disability to play its catalytic role during the ROP process. Such behavior implies faster formation of higher molecular weight PL-LA samples at low temperature (110°C) and the stagnation of monomer conversion evolutions at temperature as high as 155°C . Moreover experimental data indicate that polymerization of L-LA in bulk at 110°C using $\mathbf{1}$ and MeOH as catalyst and initiator, respectively ($[\text{L-LA}]_0/[\text{MeOH}]_0 = 100$;

[MeOH]₀/[1]₀ = 1) is relatively fast. In such conditions, the half-time of polymerization ($\tau_{1/2}$) is equal to ~ 0.25 h. Comparatively, in the polymerization of L-LA using [3-(*N*-tert-butylacetamido)-1-(2-hydroxycyclohexyl)imidazol-2-ylidene]AuCl or [3-(*N*-tert-butylacetamido)-1-(2-hydroxycyclohexyl)imidazol-2-ylidene]AgCl complexed carbenes, $\tau_{1/2} = 4$ h at comparable conditions [13]. However it is worth noting that attempts of preparation of higher molecular weight PL-LA failed. Increasing the initial [L-LA]₀/[ROH]₀ ratio resulted in significant reduction of molecular weight of PL-LA, compared with these calculated for the living polymerization mechanism. As an example, when bulk polymerization is conducted for an initial [L-LA]₀/[ROH]₀/[1]₀ of 2000/1/1 at 135°C for 120.5 hours (Conv. = 8.3 %, $M_n^{th} = 23,800$ g.mol⁻¹), samples characterized by experimental molecular weights of 3,500 g.mol⁻¹ are obtained.

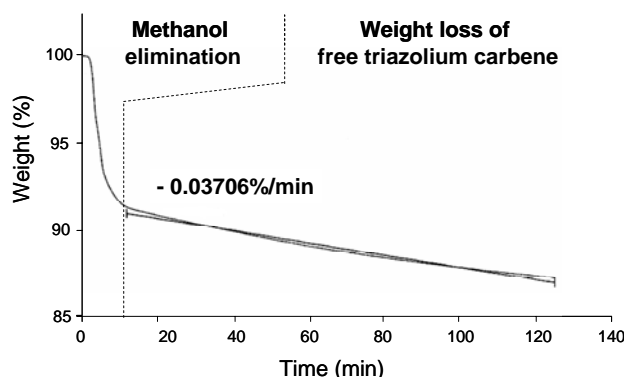


Fig. (6). Time dependence of the triazolium NHC **1** weight loss at 135°C under helium.

The occurrence of transesterification and thus degradation reactions when the bulk polymerization of L-LA is conducted at elevated temperatures, and especially when stannous octoate is used, might be indicative of severe limitations to the use of PL-LA as substitute for commodity thermoplastics [14]. In this respect, it is worth studying the thermal stability of the as-polymerized PL-LA, thus the polyester in presence of the residual catalyst. Table 1 shows the effect of the initial monomer-to-catalyst molar ratio (*N*) when both stannous octoate and **1** are used as catalysts on the PL-LA thermal degradation as measured by TGA.

Table 1. Comparison of Thermogravimetric Data Recorded on PL-LAs Samples as Obtained from Sn(Oct)₂ [14] and **1** Catalysis

Catalyst	<i>N</i> ^a	MDT (°C) ^b	T ₉₅ (°C) ^c
Sn(Oct) ₂	1000	290	246
	5000	314	260
1	100	354	245
	2000	350	260

^a*N* = [L-LA]₀/[Catalyst]₀, ^bMDT = maximum decomposition temperature defined as the inflection point of the sigmoidal temperature dependence of the weight loss, ^cT₉₅ = temperature at which a weight loss of 5% is observed.

While temperatures at which a weight loss of 5% (T₉₅) remain constant whatever the catalyst, the maximum decomposition temperatures (MDTs) are remarkably higher when **1**

is substituted for Sn(Oct)₂ whatever *N* value. It must be stressed out that the thermal stability of the PL-LA obtained from **1** closely follows the thermal degradation value recorded for completely purified PL-LA chains (MDT $\sim 365^\circ\text{C}$) [15].

CONCLUSIONS

Comparatively to the high efficiency of the triazolium carbene **1** to polymerize lactide in solution, such NHC catalyst presents a thermal instability in bulk implying the obtaining of limited molecular weight PL-LAs ($M_n \leq 10,000$) due to their *in-situ* decomposition. However, under optimal conditions, the ring-opening polymerization of L-LA is proceeding more quickly ($\tau_{1/2} \sim 0.25$ h) comparing to the corresponding solution polymerization and, importantly, with obtaining of narrow PDI samples (PDI = 1.15). Such results emphasize the real requirement to fine-tune the molecular structure of NHC catalyst to improve their inherent thermal stability in bulk and to hope their use for the synthesis of elevated molecular weight samples.

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