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L-Lactide polymerization by calix[4]arene-titanium (IV) complex using conventional heating and microwave irradiation

Marco Frediani,[1] David Sémeril,[2] Dominique Matt,[2] Fabio Rizzolo,[1 3] Anna Maria Papini,[1 3] Piero Frediani,[1] Luca Rosi,[1] Marco Santella,[1] Guido Giachi[1]*

[1*]Department of Organic Chemistry, University of Florence, Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy; fax: +39 (0)55 4573531; e-mail: marco.frediani@unifi.it.
[2] Laboratoire de Chimie Inorganique Moléculaire et Catalyse, Institut de Chimie UMR 7177 CNRS, Université de Strasbourg, 1 rue Blaise Pascal, F-67008 Strasbourg cedex, France.
[3]Laboratory of Peptide & Protein Chemistry & Biology, Polo Scientifico e Tecnologico, University of Florence, 50019 Sesto Fiorentino, Italy.

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Abstract: Since the first contributions by Gedye and Giguere in 1986, growing attention has been registered on the use of microwave heating in organic synthesis. However still many aspects need to be clarified especially about the so called “microwave effect” and the possible degradation phenomena that may be recognized during polymer synthesis. In this work the complex *cone*-25,27-dipropyloxy-26,28-dioxo-calix[4]arene titanium (IV) dichloride (**1**) has been tested for the ring opening polymerization of *L*-lactide, comparing the effect of conventional heating with a possible microwave assisted strategy. The polymers obtained were fully characterized (NMR, IR, HPLC-SEC, DSC, MALDI-TOF and WAXD analysis). As expected the use of microwave irradiation induced an increase of the polymerization rate. On the other side the use of microwaves resulted in a slight loss of the control over molecular weight and molecular weight distribution if compared with a conventional thermal treatment.

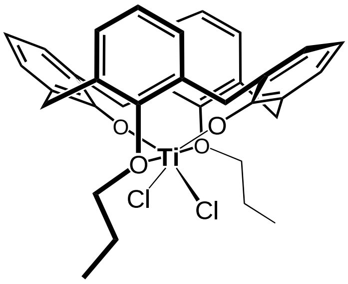
Introduction

Ring opening polymerization (ROP) of optically active cyclic monomers is the method of choice for the synthesis of polymers with high control on molecular weight and low racemization level. The efficiency of tin compounds (*i.e.* $Sn(Oct)_2$) in the ROP of *L*-lactide (LLA) is well documented in the literature [1]. However, due to the toxicity of organotin derivatives, such complexes cannot be used for the synthesis of polylactides finding medical applications. In this context, the development of new catalysts based on non toxic oxophilic metals still represents an important objective [2]. In particular, the development of catalytic systems involving group IV metal complexes is currently attracting much attention. Due to the variety of structures available with these metals, it may be anticipated that fine-tuning of the corresponding complexes will allow elaboration of new polymers with well-defined properties [3].

Generic calix[4]arenes are readily available macrocyclic molecules made of four phenol units linked via methylene bridges. The presence of four oxygen atoms at the lower rim of these conical molecules provides an interesting platform for the synthesis of poly(phenoxy) metal complexes. Recently we have reported on a calix[4]arene titanium complex that was found active in the ROP of lactides [4]. As a matter of fact calix[4]arene-derived ligands not only display a high structural versatility, but may also confer a high thermal stability to the corresponding complexes. Furthermore, some of them possess high human compatibility [5].

Since the first contributions by Gedye [6] and Giguere [7] in 1986, a growing attention has been registered on the use of microwave heating in organic synthesis. However still many aspects need to be clarified especially about the so called “microwave effect” and the possible degradation phenomena that may be recognized during polymer synthesis [8, 9]. Recently much attention has been focused on the synthesis of poly(lactide) [10].

In the present work we describe for the first time the use of *cone*-25,27-dipropyloxy-26,28-dioxo-calix[4]arene titanium (IV) dichloride (**1**) (Scheme 1) in the ROP of *L*-lactide as a comparison between the effects on the polymerization under standard thermal treatment and *microwave* irradiation.



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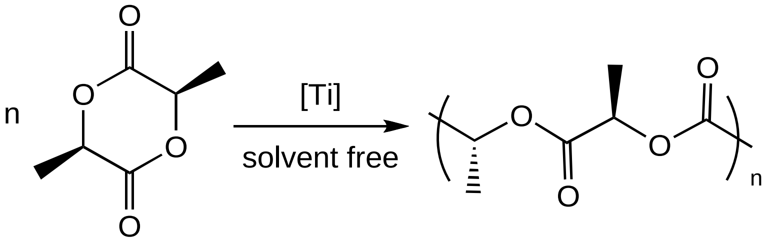
Scheme 1. 25,27-Dipropyloxy-26,28-dioxocalix[4]arene titanium (IV) dichloride.

Results and discussion

First of all the thermal stability of the catalyst was tested with TGA analysis, revealing that no decomposition of **1** occurred at temperatures below 230 °C. The high thermal stability of the complex may be attributed to the presence of the two propyl-substituted oxygen atoms able to stabilize the metal center through coordination [4, 11]. This property combined with the electron-deficient character of the titanium atom, makes **1** a potential precatalyst for ROP of *L*-lactide (Scheme 2). The catalytic runs were carried out under solvent-free conditions either using conventional heating or microwave irradiation. All analytical investigations (HPLC-SEC [12], DSC [13], NMR [14], MALDI-TOF [15] and WAXD [16]) were consistent with the formation of PLLA polymers. The MALDI-TOF spectra revealed the occurrence of transesterification during polymerization.



Scheme 2. Ring opening polymerization (ROP) of *L*-lactide.

Thermal heating

Two series of polymerization reactions using thermal heating were carried out. Both series were performed using an oil bath at 130 °C (Table 1). We first studied the influence of the monomer/catalyst ratio ([LA]/[Ti]) in experiments carried over 3 h (Table 1, entries 1-5 and Figure 1).

Tab. 1. Thermal-assisted polymerization of *L*-lactide using complex **1.**

entry	[LA]/[Ti] ratio	time (min)	conversion[a] (%)	activity[b]	M_w[c] (g·mol^{-1})	M_n[d] (g·mol^{-1})	MWD[e]
1	1995	180	48	45.9	30300	24600	1.2
2	1000	180	74	35.8	26600	21300	1.2
3	498	180	>99	24.9	30000	23800	1.3
4	199	180	97	9.3	29800	25300	1.2
5	100	180	>99	4.8	18800	14000	1.3
6	200	120	93	13.4	28700	22800	1.3
7	199	90	72	13.9	22000	17900	1.2
8	202	60	60	17.2	14200	12000	1.2
9	200	30	12	7.0	n.d.	n.d.	n.d.

[a] determined by ^{1}H NMR
[b] kg(PLLA)·mol(cat)$^{-1}$·h^{-1}
[c] number average molar mass measured by HPLC-SEC
[d] weight average molar mass measured by HPLC-SEC
[e] molecular weight distribution

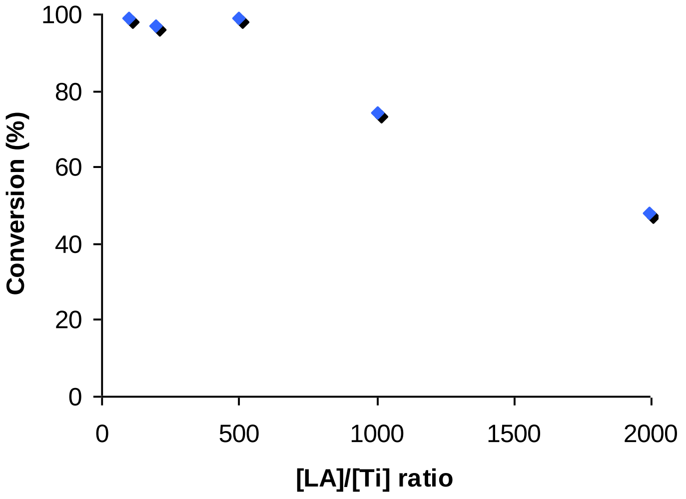


Fig. 1. Variation of the conversion as a function of the monomer/catalyst ratio.

Full conversion was observed for [LA]/[Ti] ratios lower than 500. For higher [LA]/[Ti] ratios, the conversion decreased with a linear dependence. The conversion reached 48 % when applying a [LA]/[Ti] ratio of 1995. In this latter case the highest activity was observed (45.9 kg(PLLA)·mol(**1**)$^{-1}$·h^{-1}; Table 1, entry 1). As expected, the molecular weight increased when the [LA]/[Ti] ratio increased. For example, M_w passed from 18800 to 30300 g·mol^{-1} when going from a [LA]/[Ti] ratio of 100 to a ratio of 1995 (Table 1, entries 1 and 5). Despite concomitant transesterification during polymerization, the formation of polylactide was well controlled, the molar mass distribution indexes remaining in the restricted range of 1.2-1.3.

For the second series of runs, we studied the influence of the time on the conversion. These experiments were performed using a [LA]/[Ti] ratio of 200 (Table 1, entries 4 and 6-9). Under these conditions full conversion was observed after 3 h. We found that a conversion of 93% required only 2 h of reaction time. This corresponded to an activity of 13.4 kg(PLLA)·mol(cat)$^{-1}$·h^{-1} (Table 1, entry 6). The plot of the conversion as a function of time is shown in Figure 2. The corresponding ^{1}H NMR spectra show in each case two characteristic quartets, one for the monomer (δ = 5.03 ppm), and another for the polymer (ranging from δ = 5.13 to 5.18 ppm) [14].

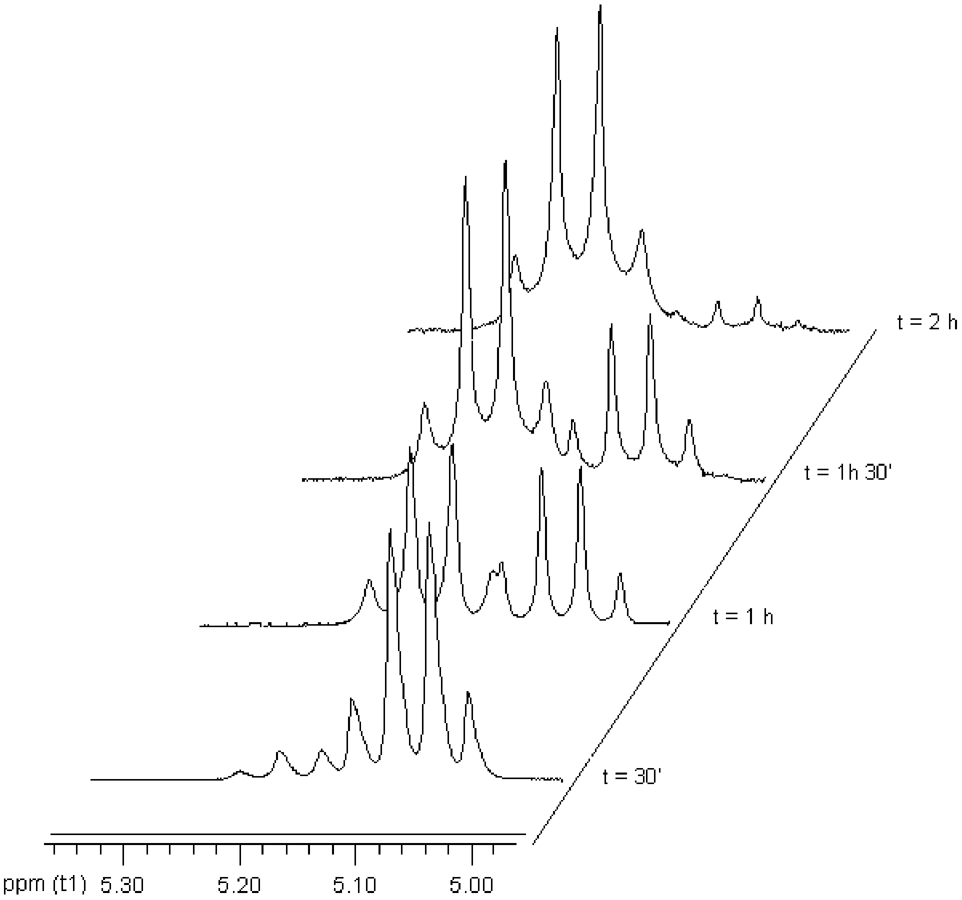


Fig. 2. Variation of the conversion as a function of time.

Microwave assisted strategy (MW)

Although the use of microwaves energy is well documented in the literature, only few examples of ROP using this technique were reported. The use of solvent-free conditions renders the microwave irradiation strategy slightly more delicate, leading to possible degradation. For the following polymerizations, we used a CEM Discover S-Class setting with an output power of 200 W. The reaction temperature was monitored using an IR sensor.

The runs were carried out using a [LA]/[Ti] ratio of 200 (Table 2). All analytical data (HPLC-SEC, NMR, DSC, MALDI-TOF and WAXD) of the polymer formed were typically those of PLLA. Under the experimental conditions used, an increase of the polymerization rate was observed with respect to the previous experiments. Thus, for example, a conversion of 95 % was observed after 80 minutes, which corresponds to an activity of 22.1 kg(PLLA)·mol(cat)$^{-1}$·h^{-1} (Table 2, entry 6). Longer polymerization times led to a partial decomposition of the organic compounds, as revealed by the appearance of a brown color and an acetaldehyde flavor. It is further noteworthy that for the polymers synthesized under microwave irradiation lower molecular weights and slightly higher molecular weight distributions were observed (M_w = 18600 g·mol^{-1}; MWD = 1.4; see Table 2, entry 5) than for those obtained by thermal heating.

Tab. 2. Microwave-assisted polymerization of *L*-lactide using complex **1**.

entry	[LA]/[Ti] ratio	time (min)	convertion[a] (%)	activity[b]	M_w[c] (g·mol^{-1})	M_n[d] (g·mol^{-1})	MWD[e]
1	197	20	39	33.3	8100	5600	1.5
2	200	40	85	36.9	14400	10600	1.4
3	199	60	89	25.6	16400	11700	1.4
4	200	30	74	42.4	13200	8800	1.5
5	202	50	85	29.8	18600	13600	1.4
6	216	80	95	22.1	17400	12000	1.4

a) determined by ^{1}H NMR
b) kg(PLLA)·mol(cat)$^{-1}$·h^{-1}
c) number average molar mass measured by HPLC-SEC
d) weight average molar mass measured by HPLC-SEC
e) molecular weight distribution

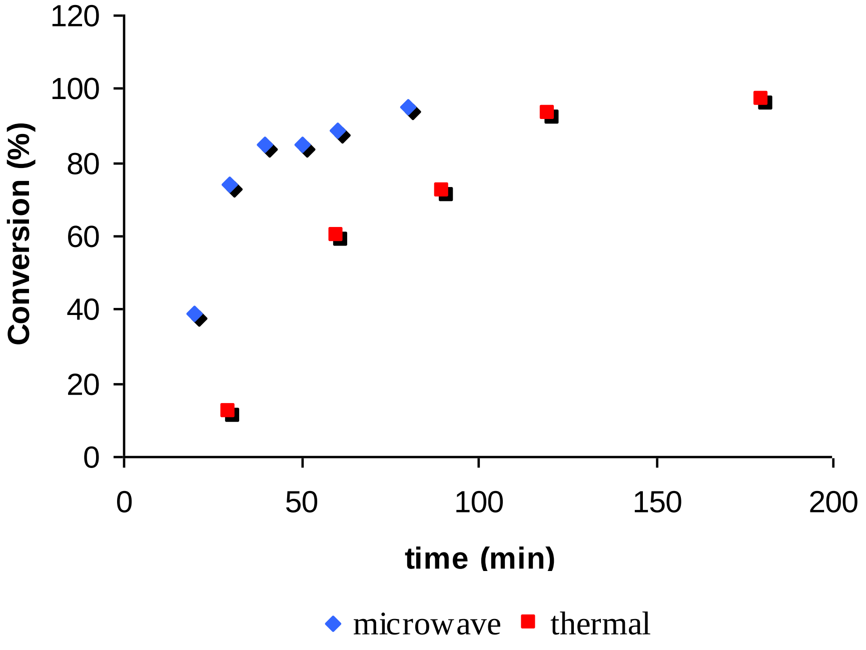


Fig. 3. Variation of the conversion as a function of time: comparison between thermal and microwave activating system.

A comparison between thermal heating and microwave assisted process is reported in Figure 3. The plot of the conversion as a function of time clearly illustrates the increase of the polymerization rate when using the microwave irradiation: while full conversion was obtained after 180 minutes under thermal heating, only 80 minutes were needed for quasi full conversion under microwave irradiation. The study also showed that each heating mode required an activation period of a few minutes.

Experimental part

General

Manipulations of air- and/or water-sensitive compounds were performed under a nitrogen atmosphere using either standard Schlenk techniques or a MBraun glove box. *L*-lactide (*L*-LA) was obtained from Aldrich (> 98%), purified by repeated crystallization and dried under vacuum at 70–75 °C for 2–3 h. The *cone*-25,27-dipropyloxy-26,28-dioxo-calix[4]arene titanium (IV) dichloride (**1**) was prepared using a method reported in the literature [11].

Polymerization experiments

L-Lactide (*L*-LA) polymerization was carried out by charging the desired amount of monomer and the appropriate amount of complex **1** into a vial. For these polymerizations, we preferred to carry out the reactions in vials instead of an autoclave, in order to compare directly the two heating systems. The vial was, either immersed into an oil bath at 130 °C or introduced automatically into a microwave oven (Discover S-Class System, CEM). A maximal power of 200 W was applied for the specified time while the temperature was monitored by an IR sensor positioned below the vial. In order to determine the conversion, the polymer was first analyzed by NMR, then recrystallized two or three times in $CHCl_3$-hexane and dried in vacuum at 50 °C for 12 h.

Polymer characterization

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 apparatus using $CDCl_3$ as solvent (solution 0.2 w/w). Melting temperatures (T_m) of the polymers were determined by differential scanning calorimetry (DSC) with a Mettler-Toledo DSC 821e instrument equipped with an intracooler. The temperature scale was calibrated with an indium reference sample (melting transition of indium 156.1°C). Aluminum pans were filled with 0.010 g of the polymer sample. The thermal history of the polymers was eliminated by heating the specimen at a rate of 20 $°C \cdot min^{-1}$ to 200 °C, keeping the sample at this temperature for one minute, then cooled at 20 $°C \cdot min^{-1}$ to 0°C. The second and third scans were then recorded from 0 °C to 200 °C. The molecular weight (M_w) and molecular weight distribution (M_w/M_n) of the polymers were evaluated by size exclusion chromatography (HPLC-SEC) using a Perkin-Elmer type Series 2000 apparatus equipped with a Rheodyne 7010 injector [injection loop 200 μl, refraction index detector type LC-30 with two columns PL GEL (length: 30 cm; diameter: 5 μm; Polymer Labs)]. The analyses were performed at 30 °C using chloroform as solvent, with a flow rate of 1.0 $mL \cdot min^{-1}$ and standard polymethylmetacrylate (PMMA) as reference [12]. The samples were prepared by dissolving 0.005-0.006 g of polymer in 2 mL of chloroform (corresponding to *ca*. 3 $g \cdot L^{-1}$). The WAXD analyses were performed using a D8 Advance (**Bruker**) with a Solx solid state detector, using a Bragg-Brentano Geometry. All the samples were preventively heated at 120-130 °C for three days before analysis. The samples were exposed to a Cu $K\alpha$ X-ray source with a wave length (λ) of 1.541 Å. The angle of incidence was varied from 4° to 50° by steps of 0.02 θ for a period of 1.5 s. The periodical distances (*d*) of the main peaks were calculated according to Bragg's equation ($\lambda = 2d\sin\theta$). MALDI-TOF analyses were carried out on a Ultraflex MALDI TOF/TOF from Bruker, with the following instrumental settings: in linear mode IS1 was set to 25 kV, IS2 to 23.70 kV and delay time to 80 ns. In reflection mode IS1 was set to 25 kV, IS2 to 21.50 and delay time was 20 ns.

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