Catalytic Activity of a Titanium(IV)/Iron(II) Heterometallic Alkoxide in the Ring-Opening Polymerization of ε-Caprolactone and rac-Lactide

Siddhartha O. K. Giese, Cristiano Egevardt, André Luis Rüdiger, Eduardo L. Sá, Thiago Alessandre Silva, Sônia F. Zawadzki, Jaísa F. Soares and Giovana G. Nunes*

Departamento de Química, Universidade Federal do Paraná (UFPR), 81530-900 Curitiba-PR, Brazil

The activity of the heterometallic alkoxide [FeCl[Ti(3-OiPr)3]] (I) towards polymerization of rac-lactide (rac-LA) and ε-caprolactone (ε-CL) was investigated in toluene solution and in bulk at various temperatures, monomer/heterometallic alkoxide molar ratio and reaction times. The alkoxide I was active in solution for ε-CL and in bulk for both monomers. Polymers were obtained in good yields with molecular weights ranging from 3890 to 15000 g mol⁻¹ and polydispersity indexes (PDI) values varying from 1.3 to 2.5. Based on the 1H nuclear magnetic resonance (NMR) end-group analysis of polymers, a coordination-insertion mechanism was suggested for both monomers. The average number of growing chains per molecule of initiator (4 to 5 for rac-LA and 7 to 8 for ε-CL) indicates that both bridging and terminal isopropoxides are active initiating groups. Kinetic studies with ε-CL indicated that the polymerization rate is first order with respect to monomer concentration. The catalytic properties of I were compared to those found for other titanium(IV) and iron(II) complexes using ε-CL as a model monomer.

Keywords: heterometal alkoxide, ring opening polymerization, ε-caprolactone, rac-lactide, iron(II), titanium(IV)

Introduction

Biodegradable and biocompatible polyesters such as poly(ε-caprolactone) (PCL), poly(rac-lactide) (PLA) and their copolymers have been extensively employed in the biomedical field.¹ ² The synthesis of these polymers requires the use of an initiator, usually a metal alkoxide or carboxylate, based on a choice of different metals.³ The most commonly used initiator has undoubtedly been stannous(II) octoanote, due to its easy handling and solubility in several organic solvents. Main inconveniences, on the other hand, lie on its relatively low polymerization activity and the occurrence of a large degree of intermolecular and intramolecular transesterification reactions when this initiator is employed.⁴ ⁵

As an alternative, the use of initiators based on biocompatible metals, such as zinc, calcium, magnesium,⁶ iron and titanium has been studied.⁷ The complex [Ca[N(SiMe₃)₂]₂(thf)₁]₂ for example, requires an in situ formation of isopropoxide groups to show good control over polymerization.⁸ ⁹ On the other hand, [ZnCl₂(OEt)L] (L = 2,6-bis{N-(2-dimethylaminoethyl)-N-methyl}-4-methylphenol) produces poly-(rac-lactide) with low polydispersity index (PDI) values (ca. 1.1) and high molar mass.¹⁰ Simple titanium(IV) alkoxides or aryloxides such as [Ti(OBu)₃], [Ti(OiPr)₃] and [Ti(OPh)₃] have also been tested and have shown good activity towards ring-opening polymerization (ROP) of cyclic esters.¹¹ Despite these promising results, lack of control upon the reaction pathway has been observed in most cases, evidencing the need to develop new initiators with ancillary bulky ligands in order to restrict chain growth to few catalytic sites.¹²

More complex, polynuclear titanium(IV) alkoxides have also been employed in bulk polymerization of cyclic esters in a reasonably well-controlled processes.¹³ ¹⁴ In this context, our group has successfully employed the ionic [Ti₅(µ₃-OiPr)₅(µ-OiPr)₃(0iPr)₉][FeCl₄]¹⁵ halo-alkoxide in the bulk polymerization of lactides and ε-caprolactone, producing polysteres with Mₙ values ranging from 6350 to 13750 g mol⁻¹ and PDI varying from 1.2 to 1.5.¹⁶ Despite the heterometallic nature of the initiator, our work revealed that its activity could be assigned mainly to the trinuclear cation [Ti₃(OiPr)₁₁]⁺.

*e-mail: nunesgg@ufpr.br
A catalytic alternative towards the ROP of cyclic esters that has shown promising results is the use of bimetallic initiators containing the transition metal together with Zn, Mg or Al. These compounds apparently owe their activities to the cooperative effect of the different metal ions, which leads to higher catalytic activities than those from the corresponding mononuclear complexes.\textsuperscript{7,10,17-19} In this context, heterometallic alkoxides of titanium(IV) with alkali metals, magnesium or zinc improved the catalytic activity for ε-caprolactone (ε-CL) and L-lactide polymerization, probably due to the withdrawal of electron density from titanium by the second metal through the bridging alkoxide ligands.\textsuperscript{20} Bimetallic alkoxides based on titanium(IV) and lanthanide(III) centers have also shown cooperative activity of the two metal centers in this type of polymerization.\textsuperscript{21}

In spite of the growing interest in the application of heterometallic alkoxide complexes as catalytic tools in polymer chemistry,\textsuperscript{22,23} this line of research has not yet been completely established. Environmental and biomedical challenges, for example, point to the application of low toxicity metal ions such as iron(II) and iron(III) in the catalysts. Despite this, iron alkoxides are still barely reported and only few of them have been assessed for their activity towards ROP.\textsuperscript{24-26} Promising examples come from bimetallic iron(II) and sodium complexes with alkoxide and aryloxide ligands that were able to promote ring-opening polymerization of rac-lactide efficiently at room temperature and afforded good control of the molecular weight.\textsuperscript{27}

In the present work, the activity of the neutral, iron(II)/titanium(IV) alkoxide [FeCl{Ti(PrO)\textsubscript{3}}\textsubscript{3}]\textsuperscript{28} (1, Figure 1) as initiator of ring-opening polymerization was investigated both in bulk (for rac-lactide and ε-CL) and in solution (for ε-CL). This complex is one of the few examples of heterometallic alkoxides that contain biocompatible metals (iron and titanium) in the same molecular framework. Its synthesis and characterization, both structural and spectroscopic, have been described earlier by our research group.\textsuperscript{23} In the attempt to elucidate the role of the different metal ions present in 1 in the polymerization reaction, results obtained with this complex were compared with those given by [Ti(O\textsubscript{2}Pr)\textsubscript{3}] \textsuperscript{29} (2), [Fe\textsubscript{2}Cl\textsubscript{4}(thf)\textsubscript{4}]\textsuperscript{30} (3) and [FeCl\textsubscript{2}(PrOH)\textsubscript{3}]\textsuperscript{10} (4) as ROP initiators in the same experimental conditions.

**Experimental**

**General considerations**

The synthesis and manipulation of the initiators and the polymerization essays were carried out under nitrogen or under vacuum using either standard Schlenk techniques or a VAC/NEXUS 2000 glove-box. The complexes [FeCl{Ti(PrO)\textsubscript{3}}]\textsubscript{32}, [Fe\textsubscript{2}Cl\textsubscript{4}(thf)\textsubscript{4}]\textsuperscript{30,31} and [FeCl\textsubscript{2}(PrOH)\textsubscript{3}]\textsuperscript{11} were prepared according to earlier literature reports. Toluene was refluxed over sodium benzophenone and freshly distilled prior to use. The compound ε-caprolactone (ε-CL, Aldrich, 97\%) was distilled under vacuum over calcium hydride. The compound rac-lactide (rac-LA, Alfa Aesar, 99\%) was dried under vacuum in the presence of phosphorus pentoxide. Both monomers were stored under N\textsubscript{2}. Polymeric products were precipitated in air using dichloromethane ( Vetec, 99.5\%) and methanol ( Vetec, 99.9\%).

**Instruments**

Molecular weights (M\textsubscript{n} and M\textsubscript{w}) and polydispersity indexes (PDI) of the polymers were determined by gel permeation chromatography (GPC) using a HPLC Waters 1515 equipment with a isocratic pump, two columns (Progel g 1000 HXL and Progel g 2000 HXL of 30 cm × 7.8 mm) and two detectors, namely a refraction index Waters 2414 (40 °C) and an ultraviolet (λ = 210 nm e 254 nm) Waters 2487 cell. Tetrahydrofuran (thf) (Baker) was used as mobile phase at 40 °C. Calibration curves were obtained with polystyrene (PS) standards and correction values of 0.56 and 0.58 were used to calculate the PCL and PLA molecular weights, respectively.\textsuperscript{25} Electron paramagnetic resonance (EPR) data (X-band, 9.5 GHz) were recorded on an X-band Bruker EMX-MICRO spectrometer from solid samples at 77 K. Melting temperatures (T\textsubscript{m}) of the polymers were determined by differential scanning calorimetry (DSC) using a Netzsch DSC 204 F1 MAIA calorimeter under continuous nitrogen purge and heating and cooling rates of 10 °C min\textsuperscript{-1}. Poly(ε-caprolactone) samples were analyzed sequentially from ambient temperature to 150 °C, with 5 min in isotherm, cooling to 120 °C, 5 min in isotherm and up to 150 °C, while poly(rac-lactide) samples were analyzed from 20 to 200 °C, 5 min in isotherm, cooling to –20 °C, 5 min in isotherm and up to 200 °C. Sample amounts ranged between 4 and 8 mg and indium was used to perform instrument calibration. Powder X-ray diffractograms were recorded with a Shimadzu XRD-600

![Figure 1. Schematic view of the molecular structure of [FeCl{Ti(PrO)\textsubscript{3}}\textsubscript{3}](1).\textsuperscript{28}](image-url)
equipment at 40 kV and 40 mA, using Cu-K\textsubscript{α} radiation ($\lambda = 1.5418$ Å) and scanning rates between 0.02° s\textsuperscript{-1} and 6° s\textsuperscript{-1} in 2θ. Samples were spread on a conventional glass sample holder. Powder silicon reflections were used for 2θ calibrations. The products of the rac-lactide and ε-caprolactone polymerization reactions were analyzed by \textsuperscript{1}H nuclear magnetic resonance (RMN) spectroscopy on a Bruker AVANCE 400 spectrometer. Polymers (10 mg) were dissolved in CDCl\textsubscript{3} (0.1% tetramethylsilane, tms) and the percentage of conversion ($\alpha$) was calculated from the integration of the polymer and monomer signals. Homodecoupled \textsuperscript{1}H NMR spectra were acquired for poly(rac-lactide) by selective irradiation of the signal at 1.56 ppm employing the Bruker zgbd pulse sequence. The probability of racemic linkages between monomeric units ($P_\text{r}$) was determined as described by Ovitt and Coates\textsuperscript{31} from the equation $P_\text{r} = 2I_\text{r}/(I_1 + I_2)$, in which $I_1$ = intensity of the tetrad signals at 0.520-0.525 ppm (sis, siliis) and $I_2$ = intensity of the signals at 0.513-0.520 ppm (iiisii, iisi, isi).\textsuperscript{31} \textsuperscript{1}H NMR spectroscopy was also employed to determine molecular weights of PCL for comparison with size exclusion chromatography data. Experiments were carried out according to previous literature reports.\textsuperscript{34}

Polymerization procedure and kinetic studies

Polymerization reactions of ε-caprolactone and rac-lactide were carried out varying temperature, reaction time and catalyst/monomer rate. Yields were calculated from the expected mass of products considering 100% of conversion. All experiments were performed at least in duplicate.

Polymerization of ε-caprolactone in solution

In a 10 mL Schlenk flask containing a magnetic stirring bar, 1.0 mL of toluene and the desired amount of the initiators were introduced. The resulting solution received the addition of ε-caprolactone (1.00 g, 8.76 mmol) and the system was heated to the appropriate temperature for the desired time, after which the solvent was removed under vacuum. The reaction media was then allowed to cool down to room temperature and the product was redissolved in dichloromethane (1 mL) and precipitated with cold methanol (10:1 v/v). The polymeric material was then filtered and dried under vacuum to constant weight.

Polymerization of ε-caprolactone and rac-lactide in bulk

In an ampoule-type vial, rac-LA (1.0 g, 6.94 mmol) and the desired amount of 1 were mixed under N\textsubscript{2} in a small volume of toluene (3 mL). After the complete evaporation of the solvent, the ampoule was sealed under vacuum and immersed in an oil bath at the required temperatures. For ε-CL, 1.0 g (8.76 mmol) of monomer was introduced in a similar tube with the required amount of each initiator (1 to 4); the reaction mixture was then heated to the appropriate temperature for the required time. After reaction, the polymers were cooled to room temperature and exposed to the air. The solids were dissolved in dichloromethane, precipitated with methanol (1:10 v/v) and dried under vacuum to constant weight.

Kinetic studies of ε-caprolactone in bulk polymerization

Kinetic studies of the bulk polymerization of ε-CL were performed by \textsuperscript{1}H NMR spectroscopy by quantifying the conversion of monomer to polymers at different reaction times. Reactions were conducted as described above, with 1.0 g (8.76 mmol) of ε-CL mixed with [FeCl\{Ti\textsubscript{2}(OPPr\textsubscript{3})\}] (1) in ε-CL/I\textsubscript{1} ratios ranging from 500 to 1000. After the pre-established time under the desired temperature, an aliquot of the reaction mixture was taken, cooled to 0 °C and dissolved in CDCl\textsubscript{3} to be analyzed. The monitored signals of PCL and ε-CL were those at 2.31 ppm and 2.64 ppm, respectively, assigned to –CH\textsubscript{2} groups. For comparison, kinetic studies with titanium(IV) isopropoxide ([Ti(OPr\textsubscript{3})\textsubscript{4}] 2) in ε-CL/I\textsubscript{2} ratios of 250 and 500 were also conducted. These amounts were chosen because they correspond to the same amount of titanium(IV) present in an ε-CL/I\textsubscript{1} ratio of 500.

Results and Discussion

Solution polymerization

The initiator [FeCl\{Ti\textsubscript{2}(OPr\textsubscript{3})\}] (1, Figure 1) was initially investigated for its activity in the solution polymerization of rac-LA and ε-CL in toluene, with good yields for ε-CL even at 30 °C. On the other hand, all attempts to run the polymerization of rac-LA in similar conditions were unfruitful. The ε-CL polymerization reactions were performed with a fixed ε-CL/I\textsubscript{1} molar ratio of 500, according to a previous report by our research group\textsuperscript{36} and varying temperature (from 30 to 90 °C) and time (8 to 16 h). Selected reaction results are presented in Table 1 (entries 1 to 9). In the majority of the essays, narrow ranges of molecular weight ($M_\text{w}$) and PDI values were observed; also, $M_\text{w}$ values are in good agreement with those calculated by \textsuperscript{1}H NMR. Optimum reaction conditions for ε-CL polymerizations were found to be 90 °C for 8 h. Reactions carried out for 16 h produced polymers similar to those presented in Table 1 (data not shown).
The increase in the ε-CL/1 ratio from 250 to 3000 showed that this monomer could be quantitatively polymerized even at the lowest concentrations of 1. As expected, the obtained PCL samples present increasing molecular weights as the ε-CL/1 ratio increases from 250 to 1500; this is due to the larger amount of monomer present in the reaction medium, which leads to longer macromolecules (entries 7 to 9). Even for ε-CL/1 ratios of 2000 and 3000, PCL was obtained quantitatively within the same Mₙ range; however, the obtained PDI values were higher than 2 and evidenced poor control over the polymerization process in these conditions (data not shown). At low initiator concentrations, the structure of 1 probably breaks down, generating metal alkoxides of different nuclearities that compete for the monomer molecules. Aggregation equilibria are common in alkoxide chemistry, being highly dependent on the chemical nature of the metal center and on the bulk of the alkoxide group. The composition of the equilibrium mixture may vary with alkoxide concentration, temperature and storage time.35-37

Once the optimized reaction conditions for ε-CL polymerization in solution were established, three more consecutive additions of the monomer to the initial polymerization reaction mixture were made in 8 h intervals (Table S1 of the Supplementary Information). After the first addition, quantitative conversion of the monomer was again observed and, after purification of the product, its average molecular weight (Mₙ) increased from 9080 to 15400 g mol⁻¹ without increasing the PDI value (1.60). After the second and third additions, polymers with similar molecular weights (13,000-15,000) and PDI values (ca. 1.5) were isolated, but in lower yields. In fact, the chromatograms of the raw reaction mixtures obtained after the second and third additions of ε-CL both contain broad peaks assigned to the monomer. These results suggest that 1 achieves its best performance for the production of PCL after the first addition of monomer and that this is a more efficient procedure than the use of diluted conditions.

e-Caprolactone and rac-lactide polymerization in bulk

Polymerizations of ε-CL and rac-LA employing 1 as initiator were successfully performed in bulk without addition of co-initiators. The experiments were performed
from 30 to 120 °C for ε-CL and 130 to 160 °C for rac-LA, by varying time (5 to 60 min) and monomer/initiator molar ratio (Table 1, entries 10 to 17, for ε-CL, and Table 2 for rac-LA). The temperature ranges were established as a function of the melting point of the monomers (−1 °C for ε-CL and 125-127 °C for rac-LA).

Polymerization essays with ε-CL in bulk have demonstrated a more expressive dependence on temperature than in solution. As an example, at 30 °C with an ε-CL/I ratio of 500, an oligomer was the only product obtained, even after 24 h of reaction (Table 1, entry 10). This low activity observed at room temperature could be related to the energy required to the first monomer insertion. Quantitative yields and higher molecular weight polymers were obtained when the reaction was conducted at 90 °C for 30 min (entry 12), suggesting that the higher activity of 1 could be related to its melting point of 68.4 °C as determined by DSC analysis, which favors a homogeneous reaction medium or even some thermal activation of the initiator. Similarly to the observed in solution, the control over the polymerization process in bulk showed to be highly dependent on the concentration of 1, being poor at an ε-CL/I ratio of 1500 (entry 17). In this case, a broad molecular weight distribution indicated that undesired transesterification reactions took place. In contrast to the results obtained in solution, the reactions carried out in bulk showed decreased Mf values for an ε-CL/I ratio of 2000 and no activity was observed at an ε-CL/I ratio equal to 3000 (data not shown).

Reactions of rac-LA conducted with a monomer/initiator ratio of 500 at 130 °C showed that 1 is able to produce PLA with an Mf of ca. 14000 g mol⁻¹ and a PDI value of 1.37; this reaction gives quantitative yield in 2 h. For rac-LA/I ratios of 500 and 1000, the reaction time has a stronger influence in reaction yield than in the final molecular weight or PDI values, evidencing a better controlled polymerization process than the observed with ε-CL. The rac-LA/I ratio of 750 was found to be the best proportion considering reaction time, temperature and final molecular weight. As far as reaction temperature is concerned, essays performed at a higher temperature, for instance 160 °C, produced polymers with similar GPC data as compared with 130 °C. This result is equivalent to those reported for the trinuclear [Ti4(OPr)12]⁺ cation in similar reaction conditions, in which the advantage of the trinuclear species over other polynuclear titanium(IV) alkoxides such as [Ti4(toed)(OPr)10] (toed = tetrapodal N,N,N′,N′-tetrakis(2-hydroxy-ethyl)ethylenediamine) and [(MeC(CH2)₇-O)(CH2-μ-O)₂]₂Ti₂(OPr)₁₀] consists in a lower molecular weight distribution of the PLA product.

Polymerization mechanism

1H NMR analysis of PCL and PLA samples obtained in this work confirmed that the ROP reaction proceeded through the coordination/insertion mechanism for both monomers. The comparison between the 1H NMR spectra of ε-CL and PCL revealed a shift of the resonance peaks assigned to the methylene groups directly bound to the ester carbonyl groups (Figure S2 of the Supplementary Information), which were found at 2.6 and 4.3 ppm for the monomer and 2.3 and 4.1 ppm for the polymers. Low intensity signals at 1.2, 5.0 and 3.7 ppm were assigned to the hydrogen atoms of terminal isopropyl groups, (CH₃)₂CH,
(CH$_3$)$_2$CH and HOCH$_2$, respectively, whose presence is largely accepted as an evidence for the ring opening polymerization mechanism. In turn, the $^1$H NMR spectra of PLA showed signals at 1.56 and 5.17 ppm assigned to the methylic and methinic hydrogens of the polymer (Figure S3 of the Supplementary Information). As observed for PCL, the obtained PLA molecules contain isopropyl ester as end groups, as shown by low intensity signals at 1.25 and 4.36 ppm, attributed to the (CH$_3$)CH– and (CH$_3$)$_2$CH(O) hydrogen.

On the polynuclearity of 1 and the nature of the active species

The molecular weights of PCL and PLA shown in Tables 1 and 2 are not in agreement with the expected theoretical values, $M_n$(theoretical), calculated for an intact molecule of 1 acting as initiator. This suggests the occurrence of transesterification during the polymerization reaction and indicates that the nine alkoxide groups and the terminal chloride present in 1 were not equally able to initiate polymer chains. The literature has demonstrated that terminal and bridging alkoxide have different activities for polymerization of ε-CL and rac-LA, while the activity of halide ligands (chloride, in this case) is not well established. One of the few studies developed applying titanium(IV) complexes with adamantoxo and borneoxo ligands suggest that the reactivity of the ligand groups follow the order alkoxide > alkyl > halide.

The identity of the active species in the reaction mixture was tentatively investigated by the estimation of the $M_n$(theoretical)/$M_n$(GPC) ratio ($N_a$), which accounts for the number of isopropoxide groups available to initiate new chains in the ROP of each monomer. At the most controlled ε-CL polymerization conditions, both in solution and bulk (entries 3 and 12, Table 1), the calculated $N_a$ values are close to seven growing chains of PCL per molecule of 1, which could correspond, in the structure of 1, to four terminal (µ$_3$-OPr) and three bridging (µ$_2$-OPr) active groups (see Figure 1). These results agree with early reports pointing to the following relative order of alkoxide activities in ROP processes: µ$_3$-OPr > µ$_2$-OPr > µ$_1$-OPr. In fact, if seven active isopropoxide groups per molecule of 1 are considered together with the results shown in Table 1 for PCL, the resulting range of calculated $M_n$(theoretical) values, 7890 to 9130 g mol$^{-1}$, is close to the experimental $M_n$ range obtained in this work from both GPC and $^1$H NMR analyses. As far as the concentration of 1 is concerned, in more diluted media $N_a$ values become higher then nine, the total number of alkoxide groups in 1 (entries 8, 9, 16 and 17, Table 1), reflecting a higher number of back-biting reactions for both bulk and solution polymerization of ε-CL. This outcome reinforces the hypothesis that diluted media favors the establishment of an equilibrium between different nuclearity alkoxide species in solution, which are all capable to initiate ε-CL polymerization and give rise to an unknown number of coordinating sites.

This kind of aggregation/disaggregation equilibrium was observed earlier in the polymerization of ε-CL and lactides initiated by Al(OPr)$_3$, La(OPr)$_3$ and, more recently, by the [Ti$_3$(OPr)$_9$]$^+$ cation. For all initiators, the number of active alkoxides capable to initiate ROP process varied with monomer nature and initiator concentration. The dependence on the concentration of 1 was clearly observed in Table 2 and Figure 2, for example, when the rac-LA/1 ratio was gradually increased from 250 to 1000 and supposedly a higher number of catalytic sites was made available to produce growing chains. At a first glance, this monomer shows an opposite tendency to that observed for ε-CL in both bulk and solution polymerizations, that is, $N_a$ varying from 4.3 to 8.1. Despite this, better PLA (higher molecular weight and lower PDI) was obtained exactly in the same $N_a$ range (7 to 8) in which better PCL was also produced in both bulk and solution reactions. As this $N_a$ range can be tentatively associated with the intact molecule of 1 performing as the active polymerization species, this result indicates that the trinuclear structure of 1 resists better to disaggregation in rac-LA than in ε-CL media and suggests that this trinuclear species is indeed the responsible for the best polymerization results obtained in this work.

![Figure 2](image_url)  
**Figure 2.** Variation of $M_n$ and reaction yields for the production of PLA as a function of monomer/I molar ratio at 130 °C. PDI values are presented in brackets.

ROP activity of 1 compared to other titanium(IV) and iron(II) complexes, with ε-CL as a model monomer

In an attempt to explain the role of the two metal ions and of the ligands present in 1 in the ROP of ε-CL, three soluble
complexes of titanium(IV) or iron(II) were employed as possible initiators in reaction conditions similar to those applied to 1: (i) the mononuclear [Ti(OiPr)₄] (2), chosen due to its well-known activity towards polymerization of ε-CL and lactides;¹¹ (ii) the tetranuclear complex [Fe₂Clₓ(thf)ₙ]¹⁰ (3), which contains tetrahydrofuran (thf) as neutral ligand, together with terminal and bridging chlorides; and (iii) the mononuclear iron(II) complex trans-[FeCl₄(PrOH)]₁₄ (4), which possesses two chlorides and four isopropanol ligands (Figure S1 of the Supplementary Information). Besides them, anhydrous FeCl₂ was also tested for its activity towards the same reaction. Isopropanol is largely applied as co-initiator of ROP because it potentially produces alkoxide groups in situ to activate the metal site, whereas thf is considered a non-reactive ligand.

Experiments with [Ti(OiPr)₄] (2) were carried out in bulk, for 30 min to 24 h, in the temperature range of 30-120 °C. The ε-CL/2 ratio was fixed at 250 because it corresponds to the same amount of titanium(IV) centers present in the ε-CL/1 ratio of 500 (Table S2 of the Supplementary Information). PCL molecules produced with 2 as initiator had molecular weights ranging from 7210 to 7900 g mol⁻¹ with PDI values from 1.49 to 1.68. The obtained N₄ values, close to 4, were compatible with the mononuclear nature of 2 in the reaction conditions employed in this work. Based on GPC data, alkoxides 1 and 2 showed a similar behavior towards the ROP of ε-CL, as the isolated polyesters were comparable in Mₙ and PDI values, with a small advantage in favor of 1 when the reaction was conducted at 90 °C for 30 min (higher molecular weight and lower PDI). In many systems, polymers obtained with heterometallic initiators usually show a broader molecular weight distribution compared to those produced with homometallic complexes, probably due to the different activities of the distinct metal centers. In this context, our results suggest that both titanium(IV) and iron(II) centers show similar ROP activities towards ε-CL, or alternatively that only one of the metal ions actually contribute to the growth of the polymer chains.

In order to probe the reactivity of iron(II) towards the polymerization of ε-CL and compare the results with those given by 1 in similar reactions conditions, complexes 3 and 4 were tested both in bulk and in toluene solution. They revealed poor activities to promote the ROP reaction in the same ε-CL/initiator ratio employed for 1. Small activity was observed only for complex 4 in toluene solution with an ε-CL/4 ratio of 500 at 90 °C for 20 h, producing an oligomer (Mₙ = 1690 g mol⁻¹) in low yield (20%). Anhydrous FeCl₂ was tested in bulk at 120 °C per 1 h, with an ε-CL/FeCl₂ ratio of 500. However, this reaction did not lead to any monomer consumption. On the other hand, the literature reports the use of FeCl₂·4H₂O as ROP initiator with ε-CL,⁴⁺ in which case an addition of alcohol (co-initiator) is made to allow the in situ formation of an Fe–OH bond that attacks the carbonyl group of ε-CL. This opens the ring and then forms an alkoxide that initiates the polymerization process. Even so, products obtained with this initiator presented low molecular weights and broad PDI ranges from 1.41 to 2.15. In the present work, the addition of isopropanol to 4 (ε-CL/4 ratios of 250 to 2000) produced solids in the low molecular weight range of ca. 1000 g mol⁻¹ (Table S3 of the Supplementary Information). The improvement in yield (85%) and PDI values close to 1.0 obtained with this initiator, as compared to the results given by FeCl₂·4H₂O, is possibly related to the existence of only one active species in the solutions of 4, while a mixture of active Fe(H₂O)₆(OH)₆ species is probably present in hydrated iron(II) chloride solutions.⁴⁺

It has been reported recently that the complex [Fe(bppyH₂)₂Cl₂] (bppyH₂ = 2,6-di(1H-pyrazol-3-yl)pyridine) showed to be completely inactive towards the ROP of ε-CL, even after addition of alcohol, while the correspondent iron(III) complex was a suitable pre-catalyst in the same reaction conditions.⁴⁺ All these reports reinforce the possible low activity of the terminal iron(II)-Cl bond in 1 and suggest that any activity of the iron(II) center in this initiator would only come from the bridging alkoxides.

While the chemistry of iron(III) alkoxides has been more frequently investigated, and the existence of well documented examples of controlled polymerization of cyclic esters by these complexes to produce high molecular weight polymers is long known,²⁵,⁴⁶ investigations with iron(II) compounds are rare and only few of them have been successfully tested in their ability to promote ROP.²⁴,²⁷ High activity of iron(II) homometallic alkoxides for ROP of lactides has been reported only for iron in low coordination environments provided by bulky ligands.²⁸ In the case of the five coordinated iron(II) center in 1, which would present one vacant coordination site for binding the monomer, there is no clear evidence of reactivity or even of the maintenance of this coordination environment in solution. In this context, our polymerization results agree with earlier reports and point to the idea that the iron(II) reactivity in 1 could be due to the presence of the bridging alkoxides.

Kinect studies of ε-CL bulk polymerization

Lactides and lactones undergo similar ROP processes via coordination-insertion mechanism. Our interest in examining the kinetics of the reaction of 1 with ε-CL comes from the need for additional evidences on the real composition of the reaction mixtures during
polymerization. These studies were not carried out with rac-lactide because of the difficulties created by the high reaction temperature and high viscosity of the reaction medium, as reported earlier by our research group.\textsuperscript{16} Also, our kinetic studies with \(\epsilon\)-CL were performed only in bulk, to avoid misinterpretation of the results caused by the presence of toluene signals in the \(^1\text{H}\) NMR spectra. The reaction conditions employed were an \(\epsilon\)-CL/1 ratio equal to 500 and a temperature range of 90-130 °C, which provided polymers with \(M_n\) values similar to those presented in Table 1.

The polymerization process was very fast, reaching conversions up to 90% in 7 minutes at 110 °C and in only 2 min at higher temperatures (Figure 3a). To bring light into the kinetic behavior of 1 in these reaction conditions, a comparative experiment was carried out with [Ti(OiPr)\textsubscript{4}] (2), employing an \(\epsilon\)-CL/2 ratio of 250 (Figure S4 of the Supplementary Information). Plots of \(\ln(1-\alpha)\) for 1 and 2 as a function of time are shown in Figure 3b and Figure S4b of the Supplementary Information, respectively. In both cases, the polymerization processes were shown to be first-order in monomer concentration, affording the apparent propagation rate constants (\(k_p\)) summarized in Table 3. There is an induction time of about 1 min, probably determined by the time required for coordination of the monomer to the active sites. Comparison of the rate constants obtained for 1 at 90, 120 and 130 °C reveals that the reaction is 17 and 26 times faster, respectively, at the highest two temperatures, while the same comparison involving 90, 100 and 110 °C shows reaction rates that are only 1.8 and 3.1 times higher, respectively (Table 3). Reactions with initiator 2, in turn, gave less abrupted variation of \(k_p\) with temperature, being only 10 times faster at 130 °C than at 90 °C. Additionally, the \(k_p2/k_p1\) ratio changes remarkably above 110 °C. These facts reveal a significant kinetic change in the reaction promoted by 1 above 110 °C, which could be associated to the breakage of the trinuclear structure of 1 to give lower nuclearity species in \(\epsilon\)-CL medium.

Table 3. Apparent propagation rate constants (\(k_p\)) for the ROP of \(\epsilon\)-CL with [FeCl][Ti\textsubscript{2}(OiPr)\textsubscript{9}] (1) or [Ti(OiPr)\textsubscript{4}] (2) as initiators

| Temperature / °C | \(k_p/\text{min}^{-1}\) (\(\epsilon\)-CL/1 = 500) | \(k_p/\text{min}^{-1}\) (\(\epsilon\)-CL/2 = 250) | \(k_p2/k_p1\) |
|------------------|---------------------------------|---------------------------------|----------------|
| 90               | 0.168                           | 0.605                           | 3.6            |
| 100              | 0.304                           | 1.483                           | 4.9            |
| 110              | 0.525                           | 2.177                           | 4.1            |
| 120              | 2.903                           | 3.993                           | 1.4            |
| 130              | 4.463                           | 6.053                           | 1.4            |

The activation energy \(\left(E_a\right)\) required for \(\epsilon\)-CL polymerization with initiator 2 (65.7 kJ mol\textsuperscript{-1}), obtained from a plot of \(\ln(k)\) as a function of \(T^{-1}\) (Figure S4 of the Supplementary Information), is close to values reported for [Ti(OPr\textsubscript{n})\textsubscript{4}] (42.0 kJ mol\textsuperscript{-1}),\textsuperscript{47} Ti[OCH\textsubscript{2}CCl\textsubscript{3}]\textsubscript{4} (70.0 kJ mol\textsuperscript{-1}),\textsuperscript{34} and the trinuclear [Ti\textsubscript{3}(µ\textsubscript{3}OiPr)\textsubscript{2}(µOiPr)\textsubscript{3}(OiPr)\textsubscript{6}][FeCl\textsubscript{4}]\textsubscript{16} (35 kJ mol\textsuperscript{-1}), respectively. Unfortunately, in the case of 1, the kinetic complexity of the system has prevented the determination of a reliable value of \(E_a\) for data in the whole temperature range employed in this work, from 90 to 130 °C. For temperatures below 120 °C, an \(E_a\) value of approximately 100 kJ mol\textsuperscript{-1} was obtained, which lies in the range reported for other titanium(IV) alkoxides in similar reaction conditions.

Characterization of the polymers

Powder X-ray diffractograms of the PCL samples produced in this work showed high intensity peaks, typical of the crystalline portion of the polymer chains,\textsuperscript{48} at 2θ values equal to 21.6 and 23.9°, and smaller peaks at 15.8° and in the region ranging from 30 to 50° (Figure S5
of the Supplementary Information). On the other hand, diffractograms of PLA were predominantly amorphous (Figure S6 of the Supplementary Information). All these results are in accordance with data obtained by homonuclear decoupled $^1$H RMN analysis (Figure S7 of the Supplementary Information). The spectra displayed five methyne resonances in the range of 5.10−5.25 ppm, typical of the stereosequences isi, sis, iii, iis and sii, which are known to hamper the orientation of polymer chains in crystalline domains. The probability of occurrence of racemic linkages between rac-LA monomers ($P_r$) was 0.55, which is slightly higher than the commonly accepted value for atactic polymers. It is, however, in the range (0.50 to 0.56) reported for other titanium(IV) alkoxides, including [Ti(OPr)$_3$I and polynuclear complexes containing piperazine and four or more isopropoxide ligands. Stereoselective polymerization of rac-lactide was not observed in this work, reflecting that not only transesterification, but also cyclization and back biting probably occur during polymerization.

Results of DSC analyses were compatible with the expected for PCL polymers (Figure S8 of the Supplementary Information). In DSC curves, all ε-PCL samples showed to be semicrystalline (49 to 58%), presenting a single fusion peak. The melting temperature ($T_m$) in the range of 55.9 to 57.5 °C and a glass transition temperature ($T_g$) of −64.1 °C are in accordance with data reported for polymers of similar molecular weights described in the literature. In turn, DSC analysis performed for products obtained from rac-LA showed similar thermal behavior for all samples. DSC curves confirmed the amorphous nature of PLA by the absence of $T_m$ and $T_g$. The value of $T_m$ increases from 43.3 to 48.2 °C following the increase in $M_v$ values from 7900 to approximately 14000 g mol$^{-1}$; this is in accordance with values reported in the literature.

The molecule of initiator 1 contains metal centers, iron(II) and titanium(IV), that are EPR silent when analysed in the X-band. However, EPR studies of the polymeric products performed at 77 K revealed the presence of residual iron(III) in both polymers, probably formed during the precipitation of the products under air. EPR spectra of PLA and PCL are typical of high spin iron(III) ($S = 5/2$) in rhombic ($g = 4.3$) and axial ($g = 2.0$) environments (Figure 4). This spectral pattern is compatible with those reported for oxides and oxo-hydroxides of iron(III) and can be assigned as follows: the signals at $g = 4.3$ are due to isolated iron(III) species and the peak at $g = 2.0$ arises from oxide-bound or oxo-hydroxo iron(III) in which ions interact magnetically with each other. After one step of purification, the signal at $g = 2$ disappeared from the EPR spectra of PLA, but a weak signal at $g = 4.3$ remained even after two consecutive reprecipitation steps, suggesting that the rhombic iron(III) centres are trapped in the polymeric matrix. From the bulk polymerization of ε-caprolactone, pure PCL, that is, without contamination with iron(III), was obtained after the first purification step, due to an easy leaching of this metal ion from the polymeric matrix (Figure S9 of the Supplementary Information).

![Figure 4. X-Band EPR spectra of PLA at 77 K prepared with 1 as initiator.](image)

**Conclusions**

In the present work, the heterometallic titanium(IV)/iron(II) alkoxide 1 was employed as an initiator in the ROP of ε-CL and rac-lactide, producing polymers within a molecular weight range expected for titanium(IV) alkoxides. In spite of the complexity of titanium(IV) alkoxide chemistry in solution, which often contributes to a substantial degree of uncertainty in identifying the catalytically active species, our results suggest that initiator 1 is the main responsible for the ROP of both monomers at the optimized conditions described in this work.

With ε-CL polymerization as a model, it was possible to identify a small, but systematic, improvement in polymer characterization parameters for 1 in relation to mononuclear [Ti(OPr)$_3$I as initiator, probably due to a small electron-withdrawing effect of the iron(II) ion towards titanium(IV) through the bridging alkoxide ligands. These results are in accordance with the intermediary Pearson hardness of iron(II) centers and suggest that other first-row transition metals harder than iron(II), or even lanthanides, could improve the activity of the [MX$_4$[Ti$_5$(OPr)$_9$I]] trinuclear framework. The poor reactivity of the terminal chloride ligand present in 1 has probably helped in avoiding competition between the two different metal ions for the monomer and also probably improved the activity of the initiator by a cooperative effect of the two metals through the alkoxide bridges.

As for the alkoxide ligands, the estimate of the average number of growing chains per molecule of initiator points
to systematic higher values of $N_n$ for ε-CL (7 to 8) than for rac-LA (4 to 5). Such $N_n$ values are in agreement with the better control over polymerization observed for rac-LA, probably due to a reduced number of active alkoxide sites. On the other hand, for ε-CL, both bridging and terminal alkoxides were active initiating groups, giving a higher number of sites able to grow polymer chains.

Even though I did not promote a living polymerization process, it was possible to increase the $M_n$ of PCL in solution polymerization without increasing PDI values. Also, complex I could be explored as an initiator of block co-polymerization, especially with lactide as comonomer.

### Supplementary Information

Supplementary data associated with this article can be found online at http://jbcs.sbq.org.br.

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