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Calcium methoxide initiated ring-opening polymerization of ε-caprolactone and L-lactide

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Summary

A commercial calcium dimethoxide and an *in-situ* generated calcium methoxide prepared from bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] and methanol, were investigated as initiators for the ring-opening polymerization of ε-caprolactone and L-lactide. Commercial calcium dimethoxide initiated rapid ε-caprolactone polymerization at 120°C in bulk to give quantitatively a polymer with a polydispersity index around 1.3. Significant racemization was observed for L-lactide polymerization. The *In-situ* formed calcium methoxide promoted the solution polymerization of both ε-caprolactone and L-lactide to high conversion at room temperature over a short time period, yielding the corresponding polyesters with narrow molecular weight distribution. NMR spectra showed that the poly(L-lactide) isolated had a purely isotactic microstructure. The initiator efficiency could be tuned by varying the molar ratio of methanol and bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide].

Introduction

Metal alkoxides are very effective initiators for the synthesis of aliphatic polyesters by the ring-opening polymerization of lactones. Sodium and potassium alkoxides are well known to promote an anionic-type polymerization, often plagued by significant side reactions [1-3]. Metal alkoxides containing free *p*-, *d*-, or *f*- orbitals (*e.g.* Mg-, Zn-, Al-, Sn-, Ti-, Zr-, Sm-,Y- alkoxides), on the other hand, bring about lactone polymerizations via a "coordination-insertion" mechanism, commonly referred to as "pseudoanionic" polymerization [4-9]. The metal-oxygen bonds in these catalysts often show sufficient reactivity and an acceptable control in the ring-opening polymerization of lactones could be achieved.

It is highly preferable to use nontoxic catalysts in the synthesis of polyesters intended for biomedical and pharmaceutical applications, since complete removal of

catalyst residues from the polymer is often impossible. Calcium-based catalysts may serve this purpose. However, calcium compounds, such as calcium oxide, carbonate and carboxylate, have a low catalytic activity towards the ring-opening polymerization of L-lactide in bulk at temperatures ranging from 120 to 180°C [10,11]. Calcium hydride appeared more effective and was used to prepare PLA/PEO/PLA triblock copolymers, although racemization was also observed [12,13]. Polyglycolide homopolymers of high molecular weights and random copolymers of glycolide and ε-caprolactone were synthesized using calcium acetylacetonate as a catalyst, but the molecular weight could not be controlled and the end-groups were not identified [14]. Calcium catalysts developed by Union Carbide have long been used for the heterogeneous ring-opening polymerization of oxiranes. The structure of the catalyst, however, is still unclear, owing to the poor solubility in and high reactivity towards most organic solvents [15]. Surprisingly, until now, no calcium alkoxides have been investigated for the ring-opening polymerization of lactides and lactones.

In this paper, the commercial compound calcium dimethoxide and an *in-situ* generated calcium methoxide prepared from bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] and methanol as initiators for the ring-opening polymerization of ε-caprolactone and L-lactide have been described.

Results and discussion

Calcium alkoxides containing sterically compact groups (-OMe, -OEt, etc.) have low solubility in common organic solvents [16,17]. The polymerizations of cyclic esters initiated with commercial calcium dimethoxide (**1**) were therefore examined in bulk at 120°C. The reaction mixture became homogeneous shortly after the polymerization started. For example, when ε-CL and **1** at a mole ratio of 100 reacted at 120°C in an argon atmosphere, complete monomer conversion was achieved within 10 min. Purification by dissolving the polymerization mixture in $CHCl_3$ and precipitation from methanol afforded the polyester with a polydispersity index (PDI) around 1.3. Molecular weights increased with increasing monomer/initiator ratio (no 1-3, Table 1).

Table 1: Bulk polymerization of ε-CL and L-LA initiated with commercial calcium dimethoxide at 120°C.

No	Mono	[M]/[I]	Time (min)	Conv (%)[a]	Mn theo[b]	Mn NMR[c]	Mn GPC[d]	PDI GPC[d]	Eff.[e]
1	ε-CL	20	5	100	1100	5100	7300	1.31	0.45
2	ε-CL	45	8	100	2600	11400	13000	1.55	0.45
3	ε-CL	100	10	100	5700	21000	22200	1.25	0.54
4	L-LA	100	90	66	4800	23300	16300	1.43	0.41

a) Determined from ^{1}H NMR spectra of crude polymerization mixtures.
b) Calculated assuming all methoxide groups take part in initiation.
c) Calculated by ^{1}H NMR end-group analysis (methyl ester end group).
d) Determined by GPC analysis.
e) Initiator efficiency of calcium dimethoxide defined as polymer chains produced per calcium atom based on the experimental molecular weight from ^{1}H NMR end-group analysis.

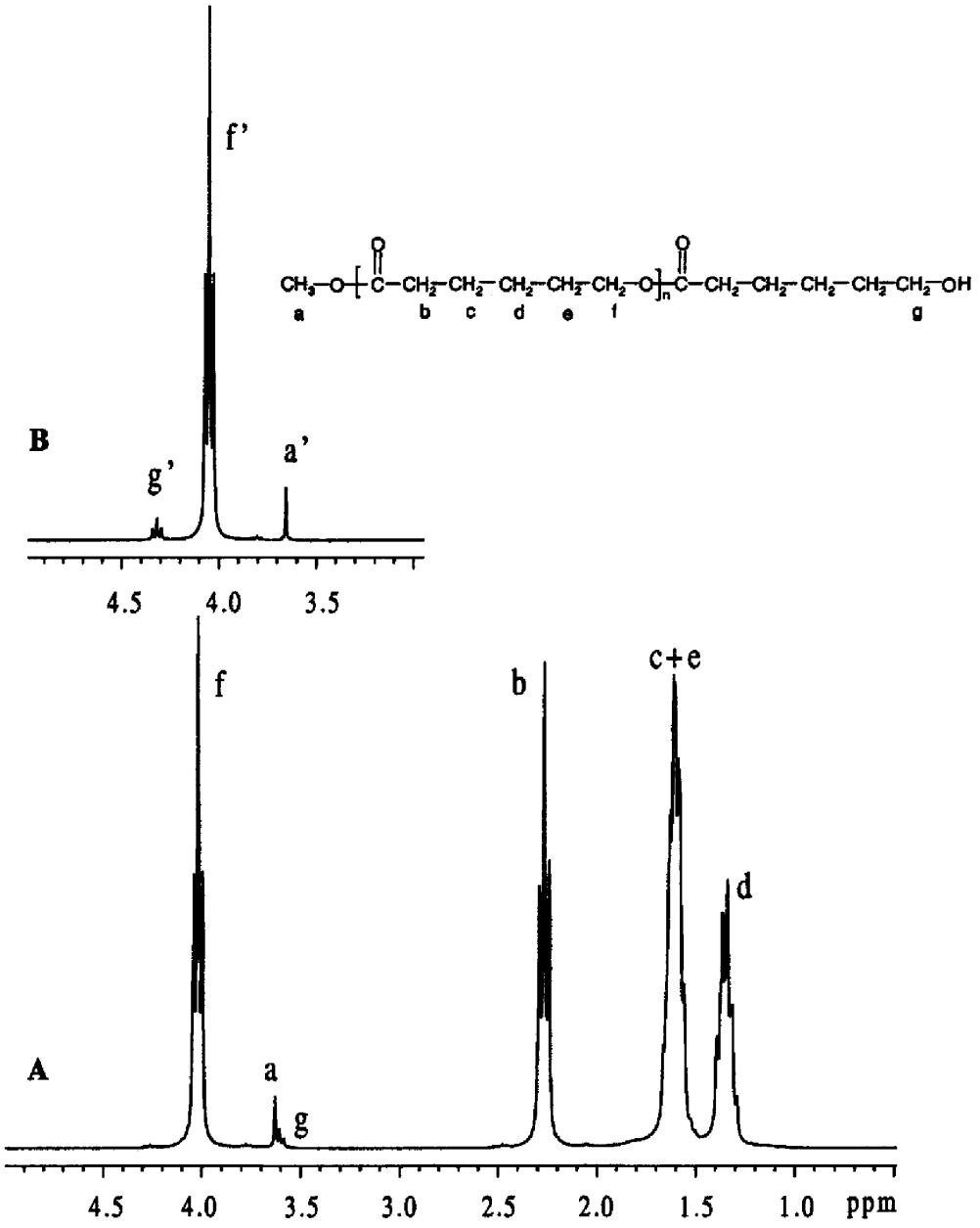
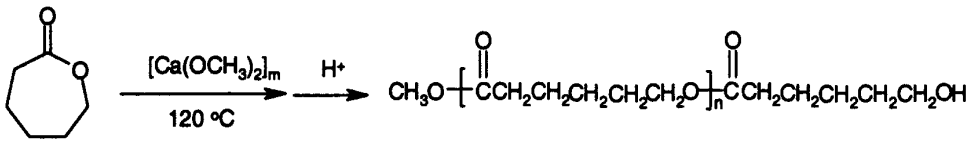


Figure 1. ^{1}H NMR spectra of poly(ε-caprolactone) ($CDCl_3$) before (A) and after (B) addition of excess trifluoroacetic anhydride (no 1, Table 1).

The ^{1}H NMR spectrum of low molecular weight poly(ε-CL) (Fig. 1) clearly shows, besides the signals characteristic of the polymer chains, overlapping resonances assignable to the methyl ester end group (s, δ 3.66) and the -$CH_2C\underline{H}_2OH$ end group (t, δ 3.63). The peak assignment was ascertained by the downfield shift of the triplet from δ 3.63 to δ 4.32 after reacting the polymer with an excess of trifluoroacetic anhydride, where the relative integral ratio of the singlet at δ 3.66 and the triplet at δ 4.32 was close to 3:2 within the NMR experimental errors. ^{13}C NMR end-group analysis also clearly showed the resonances corresponding to both terminal groups, δ

62.07 ($HOCH_2$-) and δ 50.98 ($CH_3OC(O)$-). The molecular weight determined from GPC was in close agreement with the experimental value from the ^1H NMR end group analysis (methyl ester end group), implying that only methoxide groups took part in the initiation and polymerization proceeded via selective acyl-oxygen cleavage of the monomer (Scheme 1). Molecular weights of the polymers were substantially higher than the expected values. This suggests that not all the methoxide groups are active in the polymerization.



Scheme 1. Bulk ring-opening polymerization of ε-caprolactone initiated with commercial calcium dimethoxide (1).

The initiator efficiency, defined as the number of polymer chains produced per calcium atom, was used here in order to compare the results of different polymerizations. If all methoxide groups were active in the polymerization, an initiation efficiency of 2 is expected. However, an initiator efficiency of ~0.45 was obtained in **1** mediated ε-CL polymerization. The low efficiency could be attributed to aggregation (multi-nuclear structures) of **1** and/or polymer growing species, since it is known that calcium dimethoxide is a cluster compound [16]. This is similar to polymerizations promoted by easily aggregating metal alkoxides such as aluminum alkoxides where only part of the potentially active ligands participate in the polymerization process [18]. The L-LA bulk polymerization under similar conditions only resulted in 66% conversion after 90 min reaction (no 4, Table 1), and significant racemization was discerned (^1H and ^{13}C NMR), which might be due to the high ionic character of the Ca-O bond.

Application of an *in-situ* formed initiating system for lactone polymerization may afford an opportunity to avoid the poor solubility and even oligomerization of the initiator, thereby leading to a high initiator efficiency and good control over the polymerization process [19,20]. The quantitative alcoholysis of homoleptic calcium bisamides provides a facile access to various calcium alcoholates (so-called amide route). The $N(SiMe_3)_2$ ligands are particularly attractive as a leaving group since $HN(SiMe_3)_2$ is a volatile byproduct having very low Lewis basicity due to the bulky $SiMe_3$ groups [21]. In this study, bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] (**2**) and methanol were used to generate an *in-situ* calcium methoxide. Previous results have shown that in the presence of two or more equiv. alcohol, not calcium bis[bis(trimethylsilyl)amides] but calcium alcoholate initiates the polymerization [22]. Two different approaches were adopted. In the first approach, a THF solution of ε-CL was added to a mixture of **2** and methanol in THF. Mixing **2** and 2 equiv. methanol instantaneously resulted in a viscous or turbid solution depending on the concentration, indicative of the formation of an oligo- and/or polynuclear complex. A similar example was reported for yttrium isopropoxide, where the pentanuclear oxoaggregate $Y_5O(O^iPr)_{13}$ is produced upon treatment of $Y[N(SiMe_3)_2]_3$ with 2-PrOH in toluene at –78°C [23]. After 6 min. polymerization of ε-CL ([ε-CL]/[methanol]/[**2**] = 100/2/1, [ε-CL] = 0.8 mol/L) at room temperature in THF gave at 81% conversion a polymer with molecular weight and PDI of 12600 and 1.15, respectively (no 1, Table 2). The molecular weight is

much higher than predicted from the initial monomer-initiator molar ratio and monomer conversion (Mn, theory = 4600), in line with the assumption that the *in-situ* formed calcium methoxide and/or polymer growing species has a multi-nuclear structure. In the second approach, a THF solution of **2** was added to a mixture of monomer and methanol. Polymerization of ε-CL proceeded smoothly to afford a polymer with molecular weight of 9000 (no 2, Table 2). L-LA polymerization under similar conditions (([L-LA]/[methanol]/[**2**] = 100/2/1, r.t., THF) reached 97% conversion within 18 min. GPC data showed a molecular weight of 12700 and a low polydispersity (1.07) (entry 5, Table 2). More significantly, NMR (^{1}H and ^{13}C) experiments revealed that poly(L-LA) isolated has a purely isotactic microstructure, revealing no base-promoted epimerization of the L-LA monomer or poly(L-LA) polymer chains.

Table 2: Polymerization of ε-CL and L-LA using *in-situ* generated calcium methoxide conducted at room temperature (~18°C) in THF ([monomer]/[2]=100/1).[a]

No	Mono	[MeOH]/[2] (mol/mol)	Time (min)	Conv (%)	Mn NMR	Mn GPC	PDI GPC	Eff.
1	ε-CL	2/1	6	81	12800	12600	1.15	0.72
2	ε-CL	2/1	10	100	8500	9000	1.29	1.34
3	ε-CL	4/1	6	100	7000	6700	1.12	1.63
4	ε-CL	8/1	6	100	3100	2600	1.16	3.68
5	L-LA	2/1	18	97	10300	12700	1.07	1.36

[a] No 1: Polymerization was conducted by adding a THF solution of ε-CL into the mixture of methanol and 2 in THF; Others: A THF solution of 2 was introduced into the mixture of methanol and monomer.

The addition of excess protic compounds such as alcohols and amines has been proposed to effectively avoid aggregated structures, *e.g.* for aluminum alkoxides [24-26]. In this study, ε-CL polymerizations in the presence of excess methanol with regard to **2** were examined. The polymerization of ε-CL with [ε-CL]/[methanol]/[**2**] of 100/4/1 gave a polymer at complete conversion after 6 min polymerization with a molecular weight of 6700, corresponding to an initiator efficiency of 1.63 (no 3, Table 2). The initiator efficiency increases significantly with increasing methanol/**2** ratio. In case [ε-CL]/[methanol]/[**2**] molar ratio of 100/8/1, an initiator efficiency as high as 3.68 was observed (no 4, Table 2).

Based on these observations, we propose the following reaction mechanisms. Mixing methanol and **2** instantaneously results in an aggregated calcium methoxide, which simultaneously initiates the ring-opening polymerization of cyclic esters via a coordination-insertion mechanism. Both alcoholysis reaction and initiation are much faster than propagation. In the presence of excess methanol, rapid and reversible site exchange occurs between methanol and coordinated methoxide ligands.

In conclusion, this study has demonstrated that calcium methoxide, *in-situ* generated by **2** and methanol, is very active for the ring-opening polymerization of ε-CL and L-LA. This catalyst system is promising in the synthesis of polymers intended for biomedical and pharmaceutical applications.

Experimental part

Materials

ε-Caprolactone (Merck-Schuchardt, Darmstadt, Germany) and methanol were dried over CaH_2 and distilled prior to use. L-Lactide (Purac Biochem b.v., the Netherlands) was recrystallized from dried toluene. Calcium dimethoxide (Aldrich, Brussels, Belgium) was used as received. Bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] was prepared according to a reported procedure [27]. Tetrahydrofuran was dried by refluxing over sodium. All glassware for the polymerization was dried in an oven at 130°C before use.

Polymerization

All operations were carried out under a nitrogen or argon atmosphere by using a glove box or Schlenk techniques. (1) Polymerization with commercial calcium dimethoxide: A representative polymerization was performed as follows. To an ampoule equipped with a magnetic stirrer were added ε-CL (27.1 mmol) and calcium dimethoxide (0.271 mmol) in a glovebox. The ampoule was sealed with a glass stopper and connected to a Schlenk line. The ampoule was placed into an oil bath thermostated at 120°C for a period of 10 min, whereafter the reaction was stopped by rapid cooling in a cold water bath. A sample of the crude product was taken for ^{1}H-NMR analysis. The polymer was dissolved in $CHCl_3$, precipitated from an excess of methanol, washed with methanol for 3 times and then dried at 40°C in vacuo. Complete monomer conversions and quantitative yields (>96%) were obtained in almost all the experiments. (2) Polymerization with *in-situ* calcium methoxide generated from **2** and methanol: Polymerization was carried out under nitrogen at room temperature (~18°C) in THF with methanol/**2** molar ratios ranging from 2 to 8. After predetermined periods of time, polymerizations were terminated by adding acetic acid. The polymer was isolated by pouring the reaction mixture into excess methanol followed by filtration and drying at 40°C in vacuo.

Measurements

^{1}H and ^{13}C NMR spectra using $CDCl_3$ as a solvent were recorded on a Varian Inova spectrometer operating at 300 MHz and 75.26 MHz, respectively. Monomer conversion and the degree of polymerization (DP) were determined by integration of the relevant signals. The GPC measurements were conducted with a Waters 6000A GPC apparatus equipped with four standard Waters Styragel HR columns and a H502 viscometer detector (Viscotek Corp.) for absolute molecular weight determinations. Polymers were dissolved in chloroform (1.0 wt.-%) and elution was performed at 25°C at a flow rate of 1.5 mL/min using chloroform as eluent.

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