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Single-Site Calcium Initiators for the Controlled Ring-Opening Polymerization of Lactides and Lactones

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Summary

Single-site calcium initiators containing chelating tmhd (H-tmhd = 2,2,6,6-tetramethylheptane-3,5-dione) ligands $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$ (**2**) and $[(THF)Ca(tmhd)]_2[\mu\text{-}OCH(Me)Ph](\mu\text{-tmhd})$ (**3**) have been synthesized and applied for the ring-opening polymerization of L-lactide and ε-caprolactone. Both **2** and **3** were highly reactive and promoted a fast polymerization of L-lactide and ε-caprolactone to high monomer conversions under mild conditions (THF as a solvent, room temperature). More importantly, results showed that the ring-opening polymerizations of lactides and lactones initiated by either **3** or **2** in the presence of equivalent 2-propanol are living, to provide polymers and block copolymers of controlled molecular weights and tailored end-groups. The polymerizations were first-order in monomer up to high conversions, in which the *in situ* initiating system **2**/2-propanol revealed no induction period and much faster polymerization kinetics as compared to **3**.

Introduction

Catalysis in the ring-opening polymerization of lactides and lactones has gained increasing interest in the past decade, driven by the fact that aliphatic polyesters and their copolymers are one of the few materials featuring biocompatibility, biodegradability and nontoxicity [1]. These polymers are used for various biomedical and pharmaceutical applications *e.g.* as resorbable sutures, carriers for controlled release systems and scaffolds for tissue engineering [2, 3]. Many metal alkoxides such as aluminum alkoxides [4], tin alkoxides [5, 6], and yttrium alkoxides [7] have shown capable of initiating a living polymerization of lactides and lactones, to furnish pre-designed polyesters with defined molecular weights and end-groups.
Materials applied in medicine and pharmacy should be exempted from any potentially toxic contaminants. Because in general the catalyst/initiator residues cannot be

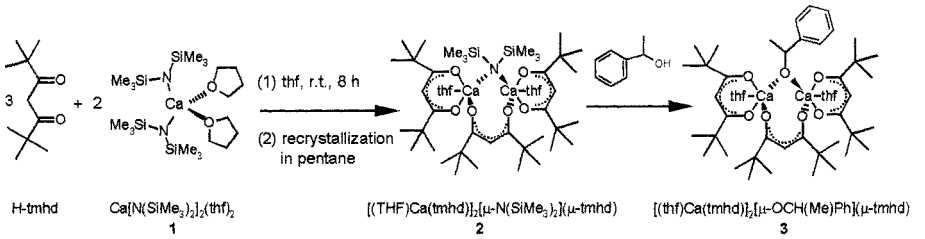
thoroughly removed, it is essential to use biologically compatible catalyst/initiator systems. To this end, carboxylates and/or alkoxides of metals like Fe [8, 9] and Ca [10-12] have been surveyed. However, most of these catalysts/initiators are aggregates and/or insoluble in common organic solvents, resulting in poor control over polymerization processes. Previously we have demonstrated that bis(tetrahydrofuran-*O*)calcium bis[bis(trimethylsilyl)amide], which is soluble in common organic solvents, can be used for fast polymerization of L-lactide and ε-caprolactone [13, 14]. Especially interesting is that the generation of calcium alkoxides *in situ* from bis(tetrahydrofuran-*O*)calcium bis[bis(trimethylsilyl)amide] and an alcohol under mild conditions circumvents the formation of multinuclear structures and brings about living lactide polymerization to give aliphatic polyesters of defined macromolecular architecture, low polydispersity and predetermined molecular weight [13, 15].
In this paper, we report single-site calcium-based initiators, which contains sterically hindering tmhd ligands (H-tmhd: 2,2,6,6-tetramethylheptane-3,5-dione), for the ring-opening polymerization of ε-caprolactone and L-lactide. Single-site initiators are of interest since the bulky chelating ligand might suppress side reactions *e.g.* inter- and intra-transesterifications [16] and some of these initiators could even bring about a stereoselective polymerization of lactides [17, 18]. The tmhd ligand was chosen because it is simple while capable of imparting stability and solubility to many metal complexes. In this study, we have combined two conceptually important approaches, single-site catalyst and *in situ* generation of initiating species. These *in situ* generated single-site calcium initiators have the advantage of controlled kinetics and no gelation when di- or multi-hydroxyl molecules are used as coinitiators. Therefore, using these catalysts/initiators, various types of block, graft and star copolymers can be designed and synthesized.

Results and Discussion

Synthesis of Calcium β-Diketonate Complexes

The treatment of $(THF)_2Ca[N(SiMe_3)_2]_2$ (**1**) with 2,2,6,6-tetramethylheptane-3,5-dione (H-tmhd) in a stoichiometric ratio of 2:3 in THF gave a dinuclear complex $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$ (**2**) (scheme 1) [19]. The molecular structure of complex **2** and the numbering scheme are represented in Figure 1, in which the methyl groups are neglected for clarity reasons. Here, the bis(trimethylsilyl)amide ligand is in a bridging position with extremely large Ca1-N1 and Ca2-N1 distances of 246.5 and 251.2 pm, respectively. In a substituted and crowded cyclopentadienyl calcium bis(trialkylsilyl)amide, Ca-N distances of 241 and 248 pm were found [20]. One of the tmhd substituents occupies a bridging position whereas the other chelating tmhd substituents are located terminally. The structure can be described as two distorted octahedra interconnected *via* a common face. This leads to a rather short distance between the calcium atoms of 337.5 pm. The lengths of the Ca-O bonds of the terminally bound tmhd ligands are much smaller than that of the bridging tmhd ligands.
The bis(trimethylsilyl)amide ligand in complex **2** can be replaced readily by an alcohol to afford the corresponding alkoxide derivative. For instance, the reaction of complex **2** with one equivalent of 1-phenylethanol in THF at 0 °C yielded

[(THF)Ca(tmhd)]$_2$[μ-OCH(Me)Ph](μ-tmhd) (**3**) (Scheme 1). NMR shows that complex **3** was contaminated by free HN(SiMe$_3$)$_3$ residues. Previously, we have shown that HN(SiMe$_3$)$_3$ molecules have no influence on the polymerization [13, 14], therefore the mixture was used as initiator without further purification.



Scheme 1. Synthesis of [(THF)Ca(tmhd)]$_2$[μ-N(SiMe$_3$)$_2$](μ-tmhd) (**2**) and [(THF)Ca(tmhd)]$_2$[μ-OCH(Me)Ph](μ-tmhd) (**3**).

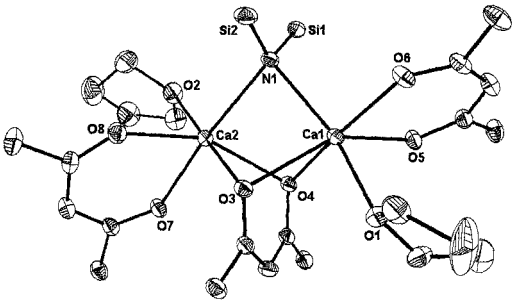


Figure 1. Molecular structure of **2**. The ellipsoids represent a probability of 30%. All H atoms as well as methyl groups are omitted for clarity reasons. Selected bond lengths [pm]: Ca1-N1 246.5(2), Ca1-O1243.7(2), Ca1-O3 248.1(2), Ca1-O4 243.7(2), Ca1-O5 226.4(2), Ca1-O6 229.2(2), Ca2-N1 251.2(2), Ca2-O2 241.8(2), Ca2-O3 244.8(2), Ca2-O4 239.7(2), Ca2-O7 231.5(2), Ca2-O8 225.9(2), N1-Si1 172.2(2), N1-Si2 171.3(2).

Ring-Opening Polymerizations

The β-diketonate calcium complexes **2** and **3** were tested as initiators for the polymerization of ε-caprolactone (ε-CL) and L-lactide (L-LA). Complex **2** displayed extremely high catalytic activity in the ring-opening polymerization of both ε-CL and L-LA in THF at room temperature (No. 1-3, Table 1). However, the isolated polymers had high polydispersity index (PDI) and much higher molecular weights as compared to the calculated values assuming that every catalyst molecule produces one polymer chain. Furthermore, no specific end-group could be detected with ^{1}H NMR spectroscopy. Similar results were observed for other amide catalyst (Y[N(SiMe$_3$)$_2$]$_3$ and (THF)$_2$Ca[N(SiMe$_3$)$_2$]$_2$) mediated ring-opening polymerizations [13, 21]. The trimethylsilylamide ligand is known as a relatively weak non-nucleophilic base due to steric effects. Therefore it can be concluded that complex **2** acts as a catalyst rather

than an initiator in the ring-opening polymerization reactions. Of great interest is that using **2** at high monomer/catalyst ratios high molecular weight poly(ε-CL)s can be readily synthesized. For example, ε-CL polymerization in THF at room temperature at a molar ratio $[\varepsilon\text{-CL}]_0/[\mathbf{2}]_0$ of 750/1 afforded complete monomer conversion after 5 mins to yield a polymer of Mn = 1.67×10^5 (No. 2, Table 1).

Table 1. *Ring-opening polymerization using β-diketonate calcium complexes in THF at room temperature.*

No	mono.	cat.	$[M]_0/[I]_0$ (mol/mol)	time (min)	conv (%)[a]	Mn_{theo}[b] ($\times 10^{-4}$)	Mn_{GPC}[c] ($\times 10^{-4}$)	PDI (GPC)[c]
1	ε-CL	**2**	150/1	1	100	1.7	3.9	3.17
2	ε-CL	**2**	750/1	5	100	8.6	16.7	1.80
3	L-LA	**2**	150/1	30	92	2.0	3.0	2.13
4	ε-CL	**3**	150/1	30	98	1.7	1.5	1.13
5	L-LA	**3**	150/1	120	96	2.1	1.8	1.14
6	L-LA	**3**	75/1	120	94	1.0	0.86	1.19
7	ε-CL	HO^iPr/**2**	150/1	5	100	1.7	1.8	1.67
8	L-LA	HO^iPr/**2**	150/1	23	94	2.0	2.2	1.26

[a] Estimated from ^{1}H NMR spectra (300 MHz, $CDCl_3$) of the crude polymerization mixtures. [b] Calculated based on the following formula: Mn, theory = MW monomer × $[M]_0/[I]_0$ × conversion. [c] Determined by GPC analysis (PS standards, universal calibration, eluent: $CHCl_3$).

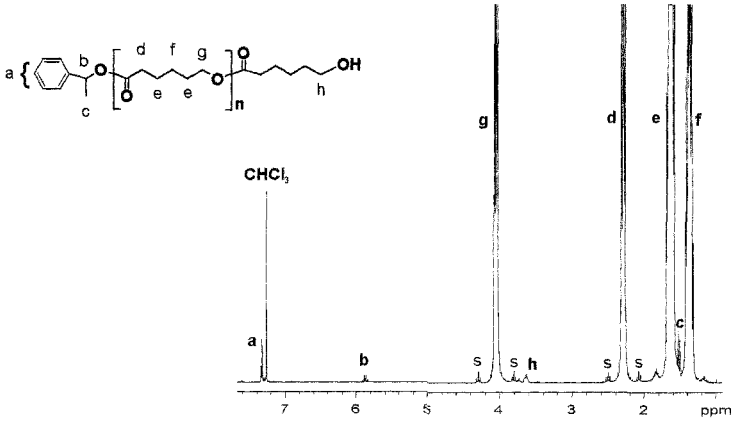


Figure 2. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of poly(ε-CL) (No. 4, table 1). (side bands are indicated by s)

Complex **3** on the other hand initiated fast and controlled polymerizations of ε-CL and L-LA in THF at room temperature (No. 4-6, Table 1). Gel permeation chromatography (GPC) revealed that all polymers have low polydispersity indexes and the molecular weights agree well with those calculated based on monomer/initiator ratios. In line with our expectations, both poly(ε-CL) and poly(L-LA) were systematically end-capped with a 1-phenylethyl-ester group and a hydroxyl group. A representative ^{1}H NMR spectrum of isolated poly(ε-CL) as well as the resonance assignments is given in Figure 2. The signals at δ 7.26-7.34 and at δ 1.52

are attributable to the phenyl protons and methyl protons of the 1-phenylethyl ester end group. The quartet appearing at δ 5.87 and the triplet at δ 3.63 with an integral ratio very close to 1:2 are assignable to the methine protons of the 1-phenylethyl ester and the methylene neighboring the hydroxyl end group, respectively. No signals attributable to tmhd ligands were detected. Hence, it is clear that only calcium 1-phenylethoxide bonds are reactive and that the ring-opening polymerization involves acyl-oxygen cleavage of the monomer and insertion into the calcium-alkoxide bonds. The degree of polymerization (DP) of poly(L-LA) determined by ^{1}H NMR end-group analysis followed a linear relationship with monomer conversion and were close to the expected values (Figure 3).

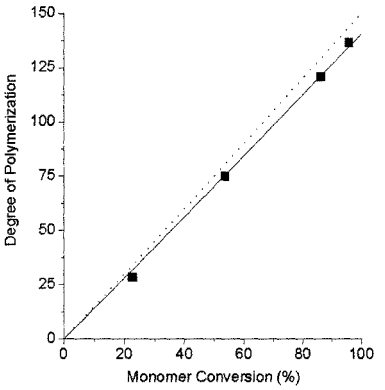


Figure 3. DP of poly(L-LA) versus monomer conversion using **3** in THF at room temperature. $[M]_0$ = 1.5 mol/L, $[M]_0/[I]_0$ = 150/1 (mol/mol). Dotted line: theoretical values. (■) Data determined by ^{1}H NMR end-group analysis.

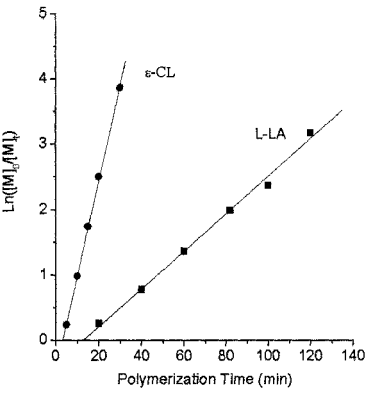


Figure 4. Kinetics of ε-CL and L-LA polymerization initiated with **3** in THF at room temperature. $[M]_0$ = 1.5 mol/L, $[M]_0/[I]_0$ = 150/1 mol/mol.

Kinetic studies revealed a first-order propagation in monomer throughout the whole polymerization course with first-order rate constants of 0.146 and 0.0285 min^{-1}, for ε-CL and L-LA, respectively (Figure 4), suggesting a constant concentration of active species and the absence of termination reactions in the polymerization process. Induction periods were observed for both ε-CL and L-LA polymerizations, which could possibly be due to the presence of **3** in an aggregated form rather than as a simple dinuclear complex as is the case for many other isolated metal alkoxides e.g. yttrium isopropoxide [22] and aluminum alkoxides [23, 24]. An alternative explanation may be that complex **3** has a relatively rigid structure in THF and is sterically hindered which requires rearrangement of the active center before initiation can take place. However, the observations that all the potentially active alkoxide ligands are incorporated in the polymer chains and that the isolated polymers have a low polydispersity suggest that a single active species is operative in the polymerization reactions. Controlled macromolecular parameters and first-order kinetics also indicate that the polymerizations are living. A sequential polymerization of ε-CL and L-LA comonomers was performed. Firstly ε-CL at a molar ratio [ε-CL]/[3] of 70/1 over 20 mins was polymerized to complete monomer conversion to

afford poly(ε-CL) with Mn = 7500 g/mol and PDI = 1.21. A second monomer L-LA (98 equiv relative to **3**) was then added. The polymerization continued up to 95 % L-LA conversion after 2.5 h resulting in a copolymer with Mn = 17 900 g/mol and PDI = 1.10. The ^{1}H NMR analysis has further confirmed that all the poly(ε-CL) prepolymers have initiated L-LA polymerization. Therefore, it is clear that the polymerization of lactones and lactides using complex **3** has a living character.

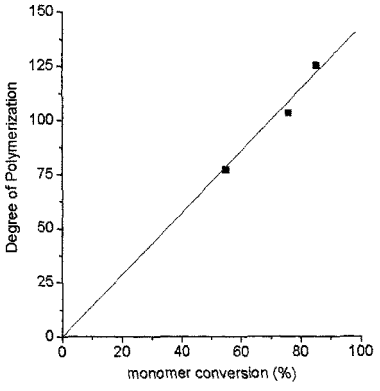


Figure 5. DP of poly(L-LA) versus monomer conversion using 2-propanol/**2** in THF at room temperature. $[M]_0$ = 1.5 mol/L, $[M]_0/[I]_0$ = 150/1 (mol/mol).

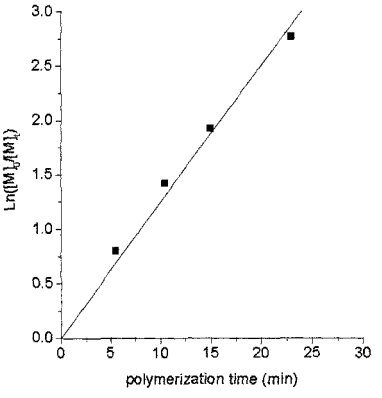


Figure 6. Kinetics of L-LA polymerization initiated with 2-propanol/**2** in THF at room temperature. $[M]_0$ = 1.5 mol/L, $[M]_0/[I]_0$ = 150/1 mol/mol.

We have shown previously that alcohol/$(THF)_2Ca[N(SiMe_3)_2]_2$ initiator systems promote a fast and controlled polymerization of cyclic esters under mild conditions [13]. Similarly, the catalytic behavior of alkoxide derivatives generated *in situ* from equivalent 2-propanol and complex **2** has also been investigated (No. 7-8, Table 1). ^{1}H NMR end group analysis revealed that each polymer chain contains an isopropyl ester and a hydroxyl group, in accordance with calcium isopropoxide initiating units formed from fast and quantitative exchange of the bis(trimethylsilyl)amide ligand with isopropanol. The molecular weights determined by GPC are close to the target values. Besides, a clear correlation exists between the DPs of isolated poly(L-LA)s and monomer conversion (Figure 5). First order kinetics in monomer is observed in L-LA polymerization, as shown in Figure 6. Remarkably, no induction period is present and a very fast propagation with an apparent rate of 0.125 min^{-1}, which is 4.4 fold the rate of **3**-initiated L-LA polymerization under otherwise identical reaction conditions, is observed. Therefore, it is demonstrated that *in situ* generated initiator systems have superior polymerization kinetics with respect to instantaneous initiation upon mixing initiator and monomer and a relatively high polymerization rate [25]. It should be noted that these β-diketonate calcium alkoxides are significantly more active than most reported lactide polymerization initiators *e.g.* aluminum alkoxides [26, 27], yttrium alkoxides [25, 28] and tin alkoxides [5, 6] under similar polymerization conditions. This high reactivity is most probably due to a relatively large ionic radius and high polarisability of calcium ions. The "single" active center nature provides good polymerization control even when di- or multi-hydroxyl molecules are used as

coinitiators. In preliminary experiments, cellulose-*graft*-polyesters were obtained by the ring-opening polymerizaiton of ε-caprolactone or L-lactide using partially protected cellulose and **2**.
In summary, employing a simple bifunctional oxygen-donor ligand (tmhd) dinuclear calcium complexes containing a potentially active amide or alkoxide unit have been isolated. The calcium alkoxide derivatives, preformed compound **3** as well as *in situ* generated from **2** and an equivalent alcohol, initiate fast and living polymerization of lactones and lactides to afford polymers with defined end-groups, predicted molecular weights and low polydispersities.

Experimental part

Materials

L-Lactide (Purac Biochem b.v., the Netherlands) was purified by recrystallization from anhydrous toluene (dried over sodium wire). ε-Caprolactone (Merck-Schuchardt, Darmstadt, Germany) and isopropanol were dried over CaH_2 and distilled prior to use. Tetrahydrofuran (THF) was dried over sodium wire. Bis(tetrahydrofuran-*O*)calcium bis[bis(trimethylsilyl)amide] (**1**) was prepared according to literature [29].

[(THF)Ca(tmhd)]$_2$[μ-N(SiMe$_3$)$_2$](μ-tmhd) (2). To a solution of 4.79 g of **1** (9.48 mmol) in 50 ml of THF at 0°C, 2.97 ml of H-tmhd (14.22 mmol) was added. After warming to room temperature and stirring for 8 h all volatile materials were removed in vacuo. The residue was redissolved in pentane to give a yellow solution. Storage at -32°C afforded 3.44 g of **2** as colorless crystals (78%). ^{1}H NMR (C_6D_6): δ = 0.53 (s, 18 H, $SiMe_3$), 1.26 (s, 54 H, CMe_3), 1.37 (β-THF), 3.63 (α-THF), 5.89 (s, 3H, COCH). ^{13}C NMR (C_6D_6/THF): δ = 5.12, 25.25, 28.63, 41.11, 68.09, 91.24, 200.84. ^{29}Si NMR (C_6D_6/THF): δ = - 7.98. Elemental anal. ($C_{47}H_{91}Ca_2NO_8Si_2$, 934.55): Calcd. C 60.40, H 9.80, N 1.50; Found C 60.38, H 9.81, N 1.41.

[(THF)Ca(tmhd)]$_2$[μ-OCH(Me)Ph](μ-tmhd) (3). To a solution of 320 mg (0.34 mmol) of 2 in THF (6 mL) was added 0.04 mL 1-phenylethanol (0.34 mmol) at 0 °C. After the mixture was stirred for 8 h, the volatile components were removed in vacuo. ^{1}H NMR spectroscopy revealed a complete alcoholysis of **2**. The isolated compound, however, was contaminated by the free $HN(Si(CH_3)_3)_2$. Yield 256 mg (84%). ^{1}H NMR (THF-d_8): δ = 1.09 (s, 36H, CMe_3), 1.10 (s, 18H, CMe_3), 1.76 (β-THF), 1.39 (d, 3H, J = 5.95 Hz, PhCH(Me)O), 3.72 (α-THF), 4.94 (q, 1H, J = 5.95 Hz, PhCH(Me)O-), 5.53 (s, 2H, COCH), 5.58 (s, 1H, COCH), 7.04 (m, 1H, p-Ph), 7.15 (m, 2H, m-Ph), 7.31 (m, 2H, o-Ph).

Polymerizations

All polymerizations were carried out at room temperature with THF as the solvent in a glovebox under a nitrogen atmosphere. In a typical procedure, a solution of **2** (33 mg, 0.035 mmol) in THF (0.5 mL) was added under vigorous stirring to a solution of L-lactide (0.75 g, 5.2 mmol) in THF (3.0 mL) ($[M]_0/[\mathbf{2}]_0$ = 150/1). After the desired reaction time (30 min), polymerization was terminated by introducing acetic acid. A sample was taken for determination of the monomer conversion using ^{1}H NMR

spectroscopy. The polymer was isolated by precipitation from excess methanol followed by filtration and drying at 40°C in vacuo.

Measurements

NMR spectra of catalysts/initiators were recorded on Jeol spectrometers GSX270 and EX400. ^{1}H NMR spectra for polymers were recorded on a Varian Inova spectrometer operating at 300 MHz. GPC measurements were conducted with a Waters 6000A GPC apparatus equipped with a series of 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 eluted with chloroform at 25°C at a flow rate of 1.5 mL/min.

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19. The metalation of H-tmhd with an equimolar amount of **1** in THF yielded the mononuclear calcium complex $(THF)_3Ca[N(SiMe_3)_2](tmhd)$ whereas a molar ratio of 2:1 gave trimeric $Ca(tmhd)_2$. Therefore, the stoichiometry has to be maintained carefully.
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