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Strontium Isopropoxide: A Highly Active Catalyst for the Ring-Opening Polymerization of Lactide and Various Lactones

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Commercially available strontium isopropoxide represents a suitable catalyst/initiator for the ring-opening polymerization (ROP) of lactide (LA), ε–caprolactone, δ–valerolactone, δ–caprolactone, and δ–decalactone. Well-defined polyesters are accessible via the solution polymerization of lactide in toluene with a [LA]:[Sr] ratio of 100:1 at room temperature with or without the addition of dodecanol as coinitiator. Kinetic studies and detailed analysis by means of matrix-assisted laser desorption ionization mass spectrometry reveal pseudo-first-order kinetics of the ROP as well as excellent endgroup fidelity of the polylactide (PLA) with isopropyl and dodecyl α-endgroups. Both isopropanolate moieties as well as the coinitiator each initiate PLA chains, enabling the synthesis of PLA with tailored molar mass. The polymerization of ε–caprolactone and δ–valerolactone confirms the high catalyst activity, which causes quantitative monomer conversion after 1 min polymerization time but broad molar mass distributions. In contrast, the catalyst is well suited for the ROP of the less reactive δ–caprolactone and δ–decalactone. Although kinetic studies reveal initially bimodal molar mass distributions, polyesters with dispersity values $Đ < 1.2$ and unimodal molar mass distributions can be obtained at moderate to high monomer conversions.

In the last decades, polyesters have been subject to extensive investigation in the field of biomedicine due to their high tissue compatibility and biodegradability.[1–3] Applications range from the formulation of well-defined micro- and nanomaterials for drug delivery to tissue engineering or implant materials.[2,4] As materials approved by the U.S. Food and Drug Administration, polylactide (PLA), poly(lactide-*co*-glycolide) (PLGA), and poly(ε-caprolactone) (PεCL) represent the most commonly used polyesters for this purpose and are commercially available under the trade name Resomer. However, a range of alternative polyesters are accessible from various lactones that are commercially available and can be used to tailor, for example, the thermal or mechanical material properties.[5] In particular, δ-lactones such as δ–valerolactone (δVL), δ–caprolactone (δCL), and δ–decalactone (δDL) are naturally occurring and/or used as food additives.[6] Differing in reactivity compared to the standard monomers lactide, glycolide, and ε-caprolactone (εCL), many of these monomers cannot be efficiently polymerized using the standard catalyst tin octanoate ($Sn(Oct)_2$), although alternative catalysts such as organic acids or bases have been successfully applied.[5,7–10] Long reaction times or high catalyst loadings are usually required for their polymerization.[5,7,8,11]

During selection of an appropriate ring-opening polymerization (ROP) catalyst, one has to consider that, besides influencing the ROP performance, the catalyst can be retained in the final material.[12] Besides influencing the material properties, in particular trace amounts of toxic catalysts based on, for example, tin or aluminum, represent a major concern if biomedical applications are intended. In contrast, catalyst residues could be advantageous, if the catalyst is based on elements that are beneficial at the site of action of the final polyester material.

Alkaline earth metal compounds based on calcium and strontium are well known as active agents for bone remineralization.[13–16] In particular, strontium salts can prevent osteoporosis.[17,18] Moreover, a range of magnesium, zinc, and calcium complexes are known to represent efficient ROP catalysts.[19–21] Although extensive ligand design enables stereo-controlled ROP, the utmost majority of these complexes is not commercially available. The very few strontium-based ROP catalysts reported in the literature are all noncommercial compounds as well.[22–26] On the other hand, the well-known ROP catalyst aluminum isopropoxide features a comparably simple structure, and other alkoxides have been utilized for the same purpose.[27] Despite being commercially available, strontium isopropoxide ($Sr(OiPr)_2$) has, to the best of our knowledge, not been studied in detail, although strontium amino isopropoxide (Sr-PO) has been applied for the ROP of lactide and εCL by Tang et al. in 2003.[28]

We hence explored the potential of $Sr(OiPr)_2$ as initiator/catalyst for the polymerization of L-lactide (LLA) and a series of lactones (**Scheme 1**).

In order to evaluate the catalytic performance of $Sr(OiPr)_2$, preliminary tests on the ROP of LLA were conducted at room

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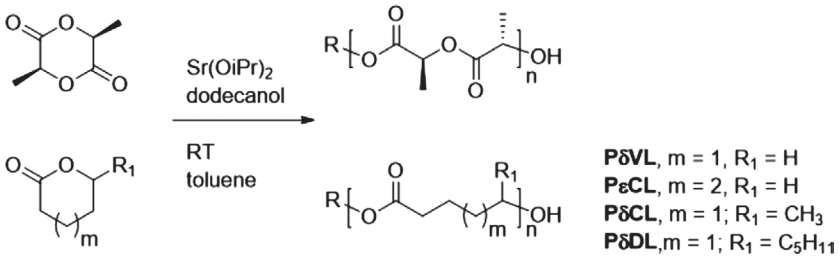

Scheme 1. Schematic representation of the ring-opening polymerization of L-lactide (top) and various lactones (bottom).

temperature (23 °C) in anhydrous toluene under inert atmosphere (**Table 1**). Keeping a constant monomer concentration of 0.5 mol L^{-1}, a first test screening was performed varying the monomer to catalyst ratio. All reactions were conducted with as well as without addition of an equimolar amount of dodecanol as coinitiator. For a [LLA]:[Sr] ratio of 20:1, quantitative monomer conversions were observed even at reaction times below 1 min, irrespective of the presence or absence of dodecanol. Size exclusion chromatography (SEC) indicated monomodal molar mass distributions of the obtained PLA. The same held true for an [LLA]:[Sr] ratio of 100:1 and a reaction time of 15 min, hinting toward a high activity of the catalyst for comparably low [LLA]:[Sr] ratios. Further increase of the [LLA]:[Sr] ratio to 200:1 resulted in moderate monomer conversions and bimodal molar mass distributions, even after comparably long polymerization times of 90 min. In these cases, the LLA conversion was increased when dodecanol was added, although SEC analysis revealed similar molar masses for both PLA samples. In contrast, the molar mass of PLA obtained with the lower [LLA]:[Sr] ratio was found to be lower when dodecanol was added.

We hence assumed that isopropanolate as well as dodecanol served as initiating species for PLA chains. To verify this assumption, detailed kinetic studies were performed at a [LLA]:[Sr] ratio of 100:1. Samples were taken periodically, quenched with a fourfold excess of benzoic acid and analyzed by means of ^{1}H nuclear magnetic resonance (NMR) spectroscopy, SEC, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF-MS) in order to determine conversions, molar masses, dispersities as well as endgroup identities.

Figure 1 shows a zoom into the MALDI-ToF mass spectra measured from the kinetic sample taken after 2 min reaction time. For the ROP conducted without dodecanol, a single m/z distribution was observed, corresponding to PLA chains bearing an isopropanolate α-endgroup, as was clearly evident from the isotopic pattern overlay. The spacing between two neighboring peaks ($\Delta m/z = 72$) corresponded to single lactate repeating units, as reported for various ROP catalyzed by metal complexes.[22,24] In contrast to most reports, cyclic species were not observed in any of our mass spectra, hinting toward the fact that the m/z difference might be caused by the catalytic mechanism rather than by chain transfer reactions.[25] This was confirmed by the MALDI-ToF mass spectrum of a purified PLA sample with lower molar mass (entry 2 in Table 1). Although the ROP was driven to high conversion, cyclic species were still not found in the spectrum.

In contrast, two m/z series were evident from the mass spectra of the PLA obtained from the ROP with dodecanol addition. While the most abundant m/z series still corresponded to isopropanolate initiated chains, the additional m/z (labelled with 'B' in Figure 1B) was assigned to dodecanol initiated macromolecules, thereby confirming our assumption.

Table 1. Characterization data of the synthesized polyesters.

Entry	Monomer	[M]:[C]:[I][a)]	[M] [mol L^{-1}]	t [min]	Conversion [%][b)]	$M_{n,\,theo}$ [kg mol^{-1}]	M_n[c)] [kg mol^{-1}]	$Đ$[c)]
1	LLA	20:1:1	0.5	0.17	>99	1.0	1.0	1.41
2	LLA	20:1:0	0.5	1	96	1.5	3.2	1.21
3	LLA	100:1:1	0.5	15	>99	4.9	13	1.16
4	LLA	100:1:0	0.5	15	>99	7.3	16	1.16
5	LLA	200:1:1	0.5	90	72	6.9	20	1.29
6	LLA	200:1:0	0.5	90	52	7.5	19	1.27
7	εCL	100:1:1	0.5	1	>99	3.9	1.5	5.10
8	εCL	100:1:0	0.5	1	>99	5.8	3.0	6.56
9	δVL	100:1:1	0.5	1	>99	3.4	n.a.	n.a.
10	δVL	100:1:0	0.5	1	>99	5.1	4.0	3.80
11	δCL	110:1:1	4.0	15	82	3.2	5.0	1.16
12	δCL	110:1:0	4.0	15	6	0.4	1.2	1.49
13	δDL	110:1:1	4.0	15	52	3.0	5.0	1.16
14	δDL	110:1:0	4.0	15	32	2.8	5.0	1.19

[a)][M]:[C]:[I] corresponds to the initial molar ratio of [monomer]:[$Sr(OiPr)_2$]:[dodecanol] used for the polymerization; [b)]Determined by integration of suitable signals in the ^{1}H NMR spectra of the reaction solution; [c)]Eluent $CHCl_3$, RI detection, polystyrene (PS) calibration.

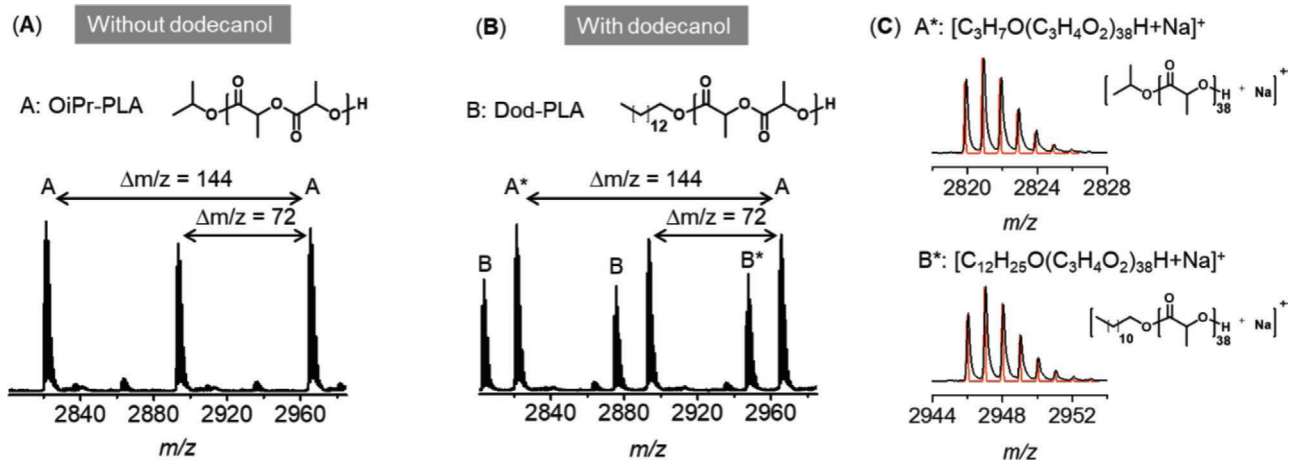

Figure 1. Zoom into the MALDI-ToF mass spectra (DCTB, NaI) of the PLA samples collected after 2 min of the $Sr(OiPr)_2$-mediated ROP of L-lactide and assignment of the peaks to the polymer structure. A) ROP without dodecanol ([LLA]:[$Sr(OiPr)_2$]:[DodOH] = 100:1:0). B) ROP with dodecanol ([LLA]:[$Sr(OiPr)_2$]:[DodOH] = 100:1:1). C) Overlay of experimental and theoretical isotopic patterns of the peaks indicated by an asterisk.

An increase of the molar mass throughout the kinetic studies was already evident from the MALDI-ToF mass spectra (**Figure 2**A). However, mass spectrometry does not represent a quantitative method, and mass discrimination effects were observed in the spectra at higher monomer conversions.

In order to access reliable molar mass values, SEC measurements in THF with PLA calibration were performed. Monomodal molar mass distributions and dispersity values ($Đ$) mostly below 1.2 were detected for all kinetic samples (Figure 2B). The molar mass of the PLA increased in a linear fashion with monomer conversion. As expected from the preliminary test reactions, the molar masses of the PLA samples prepared with dodecanol were consistently lowered in comparison with those obtained without dodecanol. The theoretically expected molar masses were calculated according to $M_n(\text{theo}) = M(\text{LA}) \times [\text{M}]_0/[\text{I}]_0 \times \text{conversion}$ taking into account the fact that two isopropanolate moieties per $Sr(OiPr)_2$ molecule and each dodecanol molecule would initiate a PLA chain, corresponding to an effective [M]/[I] ratio of 50 or 33 for the reaction without or with dodecanol, respectively. The resulting values were in excellent agreement with the molar masses determined by SEC, thereby confirming that a) both isopropanolate moieties of the catalyst are active during polymerization, and b) the molar mass of the PLA could be tailored by the polymerization time as well as by the amount of alcohol to serve as additional initiating species. The theoretical molar mass values provided in Table 1 were hence calculated accordingly.

The linearity of the semi-logarithmic plot suggested pseudo-first-order kinetics during both polymerizations (Figure 2A). Already the larger slope of the linear fit according to $\ln([\text{LLA}]_0/[\text{LLA}]_t) = k_{p,app} \times [\text{I}]_0 \times t$ indicated that the apparent polymerization rate was increased if dodecanol was added. It should be noted that the two polymerizations differed with respect to the initiator concentration, as described above ($[\text{I}]_0$ = 15 mmol L^{-1} or $[\text{I}]_0$ = 10 mmol L^{-1} for the ROP conducted with or without dodecanol, respectively). However, the calculated apparent polymerization constant ($k_{p,app}$) should be independent of the initiator concentration. Surprisingly, $k_{p,app}$ was doubled for the ROP conducted with dodecanol (20.8 L mol^{-1} min^{-1} vs 9.6 L mol^{-1} min^{-1}), hinting toward the fact that the addition of alcohol affected the reactivity of the catalyst, that is, the coordination at the metal center during the ROP.

The high reactivity of the catalyst for the synthesis of PLA suggested its applicability for the ROP of different commercially available ε- and δ-lactones. Test reactions conducted on εCL and δVL revealed quantitative conversions already after 1 min reaction time employing a monomer to catalyst ratio of 100:1, regardless of the addition of dodecanol (Table 1, entries 7–10). However multimodal SEC elugrams were obtained from the reaction mixtures with high dispersity ($Đ$ > 3.8) showing that these ROP could not be well controlled in terms of molar mass due to the high activity of the catalyst.[29] Interestingly test reactions conducted on the less reactive δCL and δDL benefitted from the high activity of the catalyst, as the respective PδCL and PδDL could be obtained with low dispersity values in short reaction times (Table 1, entries 11–14). It is to mention that the polymerization of substituted lactones was reported using lanthanum isopropoxide[30] and organic catalysts such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene and diphenyl phosphate.[5,11,31] However, their activity seems to be lower in comparison to the present work.

As particularly the ROP using dodecanol were promising, kinetic studies were performed using an initial monomer concentration of $[\text{M}]_0$ = 4 mol L^{-1} due to the high monomer equilibrium concentration of δCL and δDL (Figure 2).[5] Despite the nonlinearity of the first-order kinetic plot, which is also observed for a range of other catalysts for other substituted lactone monomers,[5,30] the molar mass increased in a linear fashion with monomer conversion, although SEC was used as a relative method here.

Interestingly, SEC analyses revealed bimodal molar mass distributions for samples taken at the beginning of the ROP, which transformed to unimodal signals during the course of the ROP. The dispersity decreased to values below 1.2 for

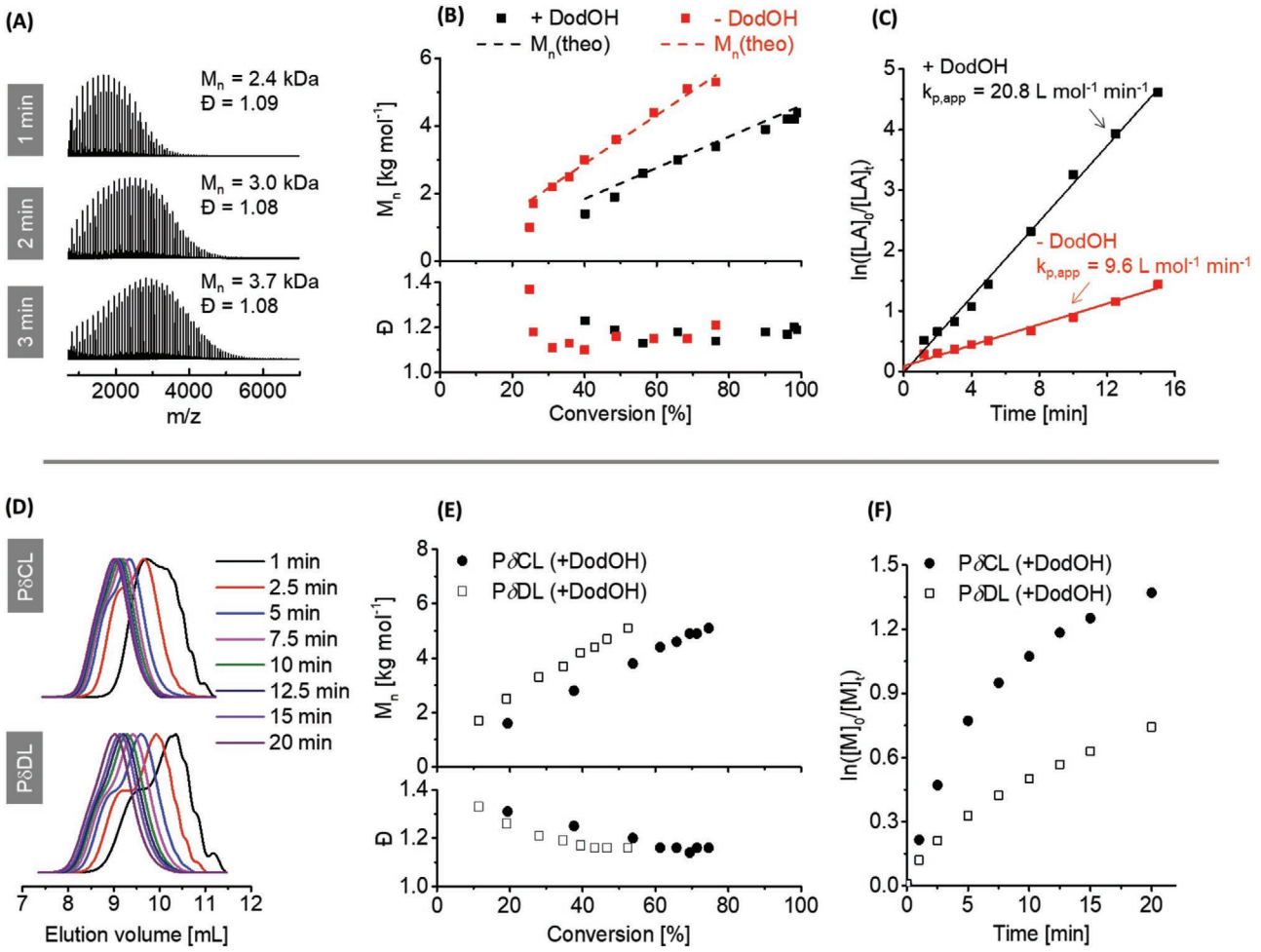

Figure 2. Kinetic studies for the strontium isopropoxide-mediated ROP of LA, δCL, and δDL conducted at room temperature in toluene ([M]:[$Sr(OiPr)_2$] = 100:1). A) Overlay of the MALDI-ToF mass spectra (DCTB, NaI) of the PLA samples collected after 1, 2, and 3 min for the reaction with dodecanol. B) Evolution of the molar mass with LA conversion (dots) (SEC: THF, RI detection, PLA calibration) and $M_{n,theo}$ (dotted lines) according to $M_n(theo) = M(LLA) \times [LLA]_0/[I]_0 \times$ conversion assuming the initiation from all isopropanolate and DodOH moieties ($[I]_0 = 2[Sr(OiPr)_2]_0 + [DodOH]_0$). C) First-order kinetic plots of the ROP of LA with a linear fit according to $\ln([LLA]_0/[LLA]_t) = k_{p,app} \times [I]_0 \times t$. D) Overlay of the SEC elugrams for the ROP of δCL and δDL, respectively ($CHCl_3$, RI detection, PS calibration). E) Evolution of the molar mass with monomer conversion for the ROP of δCL and δDL, respectively ([M]:[$Sr(OiPr)_2$]:[DodOH] = 100:1:1). F) First-order kinetic plots for the polymerization of δCL and δDL, respectively ([M]:[$Sr(OiPr)_2$]:[DodOH] = 100:1:1).

monomer conversions above 50%, ruling out commonly observed transesterification processes as reason for this unusual polymerization behavior. One could speculate that catalyst rearrangements or oligomers[32] with varying activity present in the reaction solution[33] might cause this effect, which clearly requires extensive additional studies.

To summarize, strontium isopropoxide was successfully used for the ROP of lactide and a selection of lactones at room temperature using toluene as solvent. The ROP of lactide proceeded remarkably well controlled, indicating that both isopropanolate moieties initiated a PLA chain. The application of the same experimental settings for lactones revealed a very high activity for the ROP of unsubstituted εCL and δVL resulting in fast but uncontrolled polymerizations. In contrast, the less reactive δCL and δDL could be polymerized in a well-controlled manner, although the exact catalytic mechanism is subject to further investigation during our future research.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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