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Polymerization Catalysis

Replacing Tin in Lactide Polymerization: Design of Highly Active Germanium-Based Catalysts**

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Biodegradable polymers have recently gained much interest as a replacement for conventional oil-based materials.[1] Among the most promising candidates in this class of materials are aliphatic polyesters, and in particular polylactide (PLA).[2,3] Polylactide is produced from renewable resources and is biodegradable, biocompatible and nontoxic. In addition, PLA has unique physical properties that make it useful in a wide range of commodity applications and also in life science.[4] In this context, there is increasing interest in methods that allow for the preparation of PLAs in a reproducible and controlled fashion. Current methods to synthesize PLA include direct condensation from lactic acid or ring-opening polymerization (ROP) of the related cyclic dimer, namely lactide (LA).[5,6] A large number of investigations have been directed towards synthesizing efficient metal-based initiators and studying their reactivities.[7] The most employed initiators are simple homoleptic metal complexes,[8] principally the industrially relevant tin(II) bis(2-ethylhexanoate).[4] However, the toxicity associated with most tin compounds is a considerable drawback in the case of biomedical applications.[9] In addition, tin(II) bis(2-ethylhexanoate) does not afford high activities or good control over the ROP parameters. It is therefore essential to search for active initiators containing metals, which are not harmful for the human organism.[10]

The past few years have witnessed a renaissance in main-group-element research. Their abundance, availability, and diversity make them useful for a variety of applications of industrial, economic, and environmental importance. Their chemistry turns out to be highly interesting and differs in important aspects from that of their carbon analogues. Notably, small energy separations between the frontier orbitals can lead to properties and reactivities (e.g., the activation of small molecules) which were previously thought possible only for transition-metal complexes.[11] Although germanium compounds are advocated as non-toxic alternatives[12] to many toxic tin-based reagents, researchers have long neglected the full range of possibilities in harnessing germanium complexes for the design of efficient catalysts. In particular, examples of germanium complexes for the synthesis of PLA remain rare. In the past decade, Albertsson and Davidson have published the use of germanium compounds as initiators for lactide polymerization.[13,14] However, these germanium-based systems exhibit quite modest catalytic activities and productivities and proceed only at high temperatures. As a consequence, their direct use in ROP reactions is energy intensive and requires drastic conditions to drive the reaction towards high conversion and to obtain high-molecular-weight products. In this context, the overall production cost of PLA still needs to be decreased to be competitive with petrochemical-derived chemicals. This change could be achieved by using more active and productive catalysts.

Amide derivatives are among the most studied and used compounds in catalysis and new materials preparation.[15] In particular, the heavier elements of Group 14 metal amides with the metal atom in a lower oxidation state are widely accepted as carbene [$M(NR_2)$], or radical [$M(NR_2)_3$] analogues.[16,17] Special attention has been paid to the reactivity of $M(NR_2)_2$ compounds in oxidative addition reactions or in the activation of small molecules.[18,19] Although the first work on these groups of metal species was reported by Lappert in 1974[16] and the coordination chemistry of tin(IV)[20] is among the most extensive of the *p*-block elements, the coordination chemistry of the lighter Ge^{IV} amides remain rather uncommon.[21] In addition, the use of metal amides as catalyst components in polymerization reactions is a recent development and has only been explored by a few research groups in both academia and industry.[22] Herein, we describe the synthesis of new germanium(IV) complexes and their catalytic activities for the polymerization of lactide. The germanium complexes exhibit unprecedented activity yet controlled behavior for the polymerization of LA.

To develop a straightforward methodology to prepare amido germanium complexes on a large synthetic scale, we chose to target our efforts on the commercially available $GeCl_4$ complex. The amido germanium complex **1** was synthesized by reaction of $GeCl_4$ with 10 equivalents of $NaN(SiMe_3)_2$ and was isolated in good yield (65%) as a white solid (Scheme 1). The Ge complex **1** is stable at room temperature, is sparingly soluble in toluene and THF, but insoluble in hydrocarbon solvents, such as pentane. The ^1H NMR spectrum of **1** contains one set of $Si(CH_3)_3$ resonances and exhibits two distinct multiplets indicating that two THF moieties are coordinated to the metal center. Elemental analysis also confirmed the composition of the complex.

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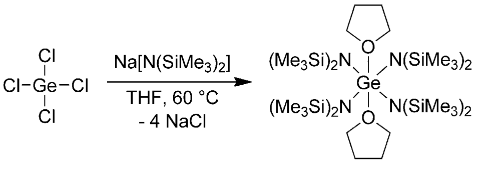

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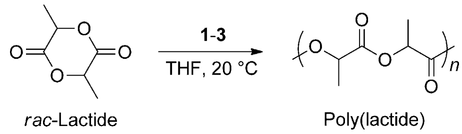
Scheme 1. Synthesis of Ge complex **1**.



Scheme 2. Synthesis of PLA.

The amido Ge complex **1** is an active initiator for the controlled ROP of *rac*-lactide under mild conditions (Scheme 2). Representative polymerization data are summarized in Table 1. High polymerization activity was observed at room temperature. Homopolymerization of *rac*-lactide with the prepared germanium metal complex proceeds very rapidly at 20 °C, equally in toluene and THF in terms of activity. In all cases, complete conversions of the monomer to PLA are achieved for monomer-to-initiator ratios up to 400. In marked contrast with what is observed for most homoleptic initiators, there is no induction time and complete conversions are achieved in about 5 min at room temperature for a lactide to $[\mathrm{Ge\{N(SiMe_3)_2\}_4(THF)_2}]$ ratio of 200:1 and an initial monomer concentration of 1 M. As the reactive site for ring-opening is not sufficiently crowded to avoid unwanted side reactions, such as undesirable transesterifications, it is not surprising to observe relatively broad molecular weight distributions, especially at high conversions. This situation is in agreement with previous studies with homoleptic initiators and in particular with tin(II) bis(2-ethylhexanoate) or other systems bearing bulky initiating groups.[4,6]

Kinetic monitoring by ^{1}H NMR spectroscopy of experiments conducted at high monomer-to-initiator ratios ([*rac*-LA]/[Ge] $\geq$ 200) indicated turnover frequencies (TOFs) in the range 5000–5200 $\mathrm{h^{-1}}$, which remain constant up to 95 % conversion; at higher conversions, a progressive decrease in activity is observed, concomitant with the increase of viscosity. Remarkably, the rate of polymerization with the amido initiator **1** is several orders of magnitude higher than that observed with the most active homoleptic germanium complex reported.[13] As opposed to the homoleptic metal complexes that were previously evaluated in similar conditions, the germanium complex $[\mathrm{Ge\{N(SiMe_3)_2\}_4(THF)_2}]$ is significantly more efficient.[4] Indeed, these data lie in the same range as the highest activity obtained with the oxophilic $[\mathrm{Ca\{N(SiMe_3)_2\}_2}]$-ROH catalytic system, the major difference being that our germanium catalytic system is even more reactive in the absence of an alcohol.[4] To confirm the influence of the amido ligand on the activity, a control experiment was carried out with the commercially available $\mathrm{Ge(O}i\mathrm{Pr)_4}$ as initiator. Most interestingly, the results show that no polymer was formed, even after prolonged reaction times when the polymerization is carried out at room temperature.[23] Also germanium-based system **1** proved to be active in the presence of a transfer agent, offering polymers with a linear relationship between M_n and the number of 2-propanol added (M_n values proportional to the number of 2-propanol added; Table 1, entry 2).[24] Therefore we were able to obtain PLA by converting catalytically *rac*-LA in the presence of 3 equivalents of 2-propanol; the excess of free alcohol yields polymer chains with reduced molecular weights and a narrower molar mass polydispersity. Since $\mathrm{Ge(O}i\mathrm{Pr)_4}$ is inactive at room temperature, no alkoxide germanium species is involved before complexing and ring-opening of the monomer. As proposed by Kricheldorf for tin(II) bis(2-ethylhexanoate),[25] this reaction suggests a monomer-activated mechanism where the co-initiating alcohol functionality and the monomer are both coordinated to the Ge complex during propagation. Moreover, the productivity of the system **1** was further evidenced by the polymerization of 400 equivalents of lactide, for which complete conversion was observed in 10 min (entry 3).

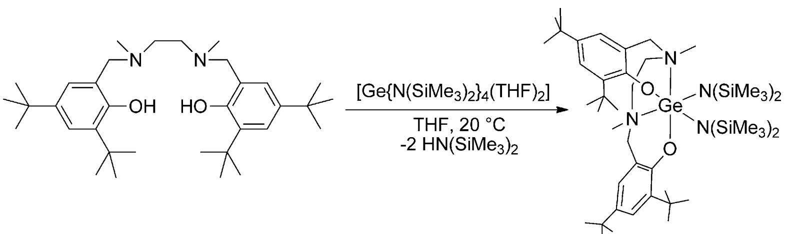
Table 1: Ring-opening polymerization of LA promoted by **1–3**.[a]

Entry	Initiator [I]	[LA]/[I]	[*i*PrOH]/[I]	*t* [min][a]	Conv.[b]	M_n ($\mathrm{kg\,mol^{-1}}$)[c]	M_w/M_n[c]
1	**1**	200	–	5	95	35.2	1.9
2	**1**	200	3	120	97	10.0	1.3
3	**1**	400	–	10	83	98.1	1.6
4	**2**	200	–	5	98	44.0	1.6
5	**2**	200	–	2	96	45.9	1.6
6	**2**	200	2	30	98	10.3	1.4
7	**2**	400	–	10	98	133.8	1.5
8	**3**	200	–	5	97	46.5	1.6
9	**2**	100+150	–	5+5	98	47.5	1.6

[a] All reactions performed with [*rac*-LA] = 1 M at 20 °C in THF until completion as determined by integration of the ^{1}H NMR resonance signals of the methyl groups in LA and PLA. Time was not necessarily optimized. [b] Calculated by ^{1}H NMR spectroscopy. [c] M_n and M_w/M_n of PLA determined by size-exclusion chromatography with refractive index detector (SEC-RI) using polystyrene standards. M_n values were not corrected by a Mark–Houwink factor.

To provide steric and electronic control at the germanium center, we investigated the reactivity of the amido complex **1** with a tetradentate phenoxyamine (salan-type)[26] ligand to prepare an active initiator directly by amine elimination. Our attention was drawn to the tetradentate ligand $\mathbf{[L^1]H}$ (Scheme 3), which has given interesting performances in aluminum-catalyzed ROP of lactide and yttrium-catalyzed ROP of β-butyrolactone.[27,28] Thus, protonolysis of the homoleptic amide $[\mathrm{Ge\{N(SiMe_3)_2\}_4(THF)_2}]$ precursor leads to the heteroleptic amido complex by a σ-bond metathesis. We observed that the reaction of **1** with the *salan* ligand $\mathbf{[L^1]H}$ produces the germanium complex $[(\mathbf{L^1})\mathrm{Ge\{N(SiMe_3)_2\}_2}]$ (**2**), isolated in 90 % yield following crystallization from pentane (Scheme 3).

The polymerization of lactide using complex **2** was then investi-



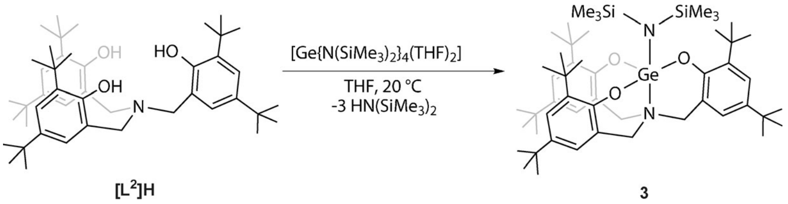
[L^1]H **2**

Scheme 3. Synthesis of Ge complex **2**.

gated. The results are summarized in Table 1. The (salan)Ge^{IV} complex **2** proved to be highly active under mild conditions, allowing high conversion of 100–400 equivalents of lactide in 2–10 min (reaction times not optimized) at 20 °C in THF solutions (entries 4, 5, and 7). Compared to complex **1**, the polymerization reactions initiated by the more sterically hindered amido derivative **2** resulted in narrower polydispersities. The resulting polymers have number-average molecular masses values close to the theoretical ones (calculated on the assumption that one silylamide group initiates the polymerization). Our studies also showed that **2** polymerizes lactide at a rate faster than any other reported germanium-containing system (TOFs up to 5800 h^{-1}). In particular, these activity data compare favorably with the tris(phenolate) germanium complex reported by Davidson, that affords (at 130 °C) TOFs two orders of magnitude lower than **2** at room temperature.[14] Also complex **2** proved to be efficient in the presence of 2-propanol (Table 1, entry 6). The polymerization of *rac*-LA afforded PLA with a M_n value proportional to the number of 2-propanol added and a narrower molar mass polydispersity. In addition, the controlled character of the polymerizations initiated by **2** was further evidenced by the sequential polymerization of 100 equivalents of lactide plus an additional 150 equivalents of lactide, for which complete conversion was observed together with monomodal molecular weight distribution (entry 9).

The amide complex [(**L^2**)GeN(SiMe$_3$)$_2$] (**3**) can be obtained from the corresponding trisphenoxide ligand **[L^2]H** by direct protonolysis of the amido precursor [Ge{N(SiMe$_3$)$_2$}$_4$(THF)$_2$] **1** by amine elimination (Scheme 4). This system was also found to be active for the polymerization reaction of LA to afford polylactide with high number-average molecular masses (M_n = 46.5 Kg mol^{-1}; entry 8).

In summary, germanium metal complexes are efficient initiators in the ROP of *rac*-lactide to form poly(lactide) polymers. This finding foreshadows new vistas in germanium-based reactions and catalysis. The most notable feature of the amido initiators described in this study is their high polymerization activity and productivity for polymer formation. It can be anticipated that this class of germanium complexes will continue to provide new and interesting results. Future work will explore the mechanism and modification of the current system to develop new initiators that exhibit high stereochemical control during the polymerization reaction.



[L^2]H **3**

Scheme 4. Synthesis of Ge complex **3**.

Experimental Section

All reactions were performed under an inert atmosphere using dry solvents in anhydrous conditions, unless otherwise noted. Full experimental details and characterization data for all new compounds are included in the Supporting Information.

Typical polymerization procedure: All polymerizations were performed under argon in a 15 mL flame-dried Schlenk tube equipped with a Teflon coated stirring bar. In a glove box, a Schlenk tube was charged with Ge catalyst **1** (17 mg, 0.02 mmol) in THF (2 mL), *rac*-lactide (293 mg; 2 mmol) was then added to the solution. The reaction mixture was vigorously stirred for the desired time. Conversion was determined by ^{1}H NMR spectroscopic analysis of the crude mixture (integrating the methyl region in the spectrum). The polymer was precipitated from 400 mL of a mixture of diethyl ether and pentane. The resulted polymer was dried under vacuum until constant weight.

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