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A dual organic/organometallic approach for catalytic ring-opening polymerization[†]

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A dual catalytic system combining an original cationic zinc complex and a tertiary amine is shown to promote efficiently the polymerization of lactide under mild conditions.

Over the last two decades, considerable achievements have been reported on the development and application of metal complexes and organic compounds to the ring-opening polymerization (ROP) of cyclic esters and carbonates.^{1,2} In this area, metal-alkoxide based initiators have attracted major interest for the preparation of biodegradable polymers, and impressive levels of activity and control have been achieved.¹ In parallel, a variety of organic compounds have been shown to catalyze efficiently ROP, providing a valuable metal-free approach to well-controlled polyesters and polycarbonates.² Noticeably, metal-alkoxides typically promote ROP via a coordination-insertion mechanism, while a variety of mechanistic pathways are encountered in organo-catalyzed ROP (*i.e.*, nucleophilic/electrophilic activation of the monomer, basic activation of the initiating/propagating alcohol, or bifunctional activation of the monomer and alcohol).

The organometallic and organic approaches of ROP are complementary and feature different advantages. Metal complexes generally display higher activities and better (stereo)selectivities, whereas organocatalysts exhibit higher functional group tolerance³ and inherently allow one to work under catalytic conditions. With the aim of combining the respective advantages of these two strategies and of exploring new mechanistic pathways, we recently became interested in investigating dual organometallic/organic systems for ROP catalysis. The association of transition metal and organic catalysis has recently emerged as a powerful approach in organic synthesis,⁴ but to the best of our knowledge, the feasibility of such a dual catalytic approach has not been substantiated so far in ROP. Herein we report that the ROP of lactide can indeed be promoted efficiently and in a controlled manner upon combining an original cationic zinc complex (a Lewis acidic metal fragment activating the monomer) and a tertiary amine (activating the initiating/propagating alcohol).

The new discrete cationic complex $[{NNO}Zn]^+[B(C_6F_5)_4)]^-$ (2) was prepared by treatment of the previously reported ${NNO}ZnEt$ complex $({NNO} = 2,4-di$ -*tert*-butyl-6- $\{[(2'-di-methylaminoethyl])methylamino]methyl}phenolate) (1)^5 with 1 equiv. of <math>[HNMe_2Ph]^+[B(C_6F_5)_4]^-$ in THF (Scheme 1).† Turner's reagent, $[HNMe_2Ph]^+[B(C_6F_5)_4]^-$, was selected for this protonolysis, based on the non-coordinative nature of the borate anion that should make the resulting cationic species quite electrophilic toward the monomer. The identity of **2** was established on the basis of ${}^{1}H$, ${}^{13}C$, ${}^{19}F$, ${}^{11}B$ NMR spectroscopy, including 2D experiments (${}^{1}H-{}^{1}H$ COSY, ${}^{1}H-{}^{13}C$ HMBC and HMQC)†, and elemental analysis. The presence of a single set of sharp ${}^{1}H$ and ${}^{13}C$ NMR resonances (THF- d_8 , 25 °C) supports a monomeric structure for complex **2** in solution.

The combination of **2** with pentamethylpiperidine (PMP) as a base was examined for the ROP of *rac*-lactide (LA) in the presence of *neo*-pentanol (*neo*-PentOH) as an initiator. We found that, under optimized conditions, complete conversion of the monomer can be achieved within 3 h at room temperature to give PLAs in up to 98% yield with M_n values up to 14 500 g mol⁻¹ and M_w/M_n values ranging between 1.2 and 1.4.⁶ Representative polymerization results are summarized in Table 1. In order to probe the cooperativity of the dual organometallic/organic catalytic system, we carried out the ROP of LA in the presence of *neo*-PentOH with only **2** or PMP (entries 1 and 2). In both cases, no polymerization



Scheme 1 Synthesis of cationic zinc complex $[\{NNO\}Zn]^+ - [B(C_6F_5)_4)]^-$ (2).

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Table 1 Dual ROP catalyzed by the combination of 2 and amines in the presence of *neo*-PentOH as an initiator^a



Entry	[LA] ₀ :[<i>neo</i> -PentOH] ₀ :[2] ₀ :[amine] ₀	Amine	Solvent	Temp./°C	Time/h	Conv. ^b (%)	${M_{ m n,theo}}^c_{ m /}$ g mol $^{-1}$	$M_{ m n,NMR}/$ g mol ⁻¹	$M_{ m n,SEC}^{}_{d/}$ g mol $^{-1}$	$M_{ m w}/M_{ m n}^{a}$
1	100:1:1:0	_	Tol	50	24	0	_		_	
2	100:1:0:1	PMP	Tol	50	24	0	_	_		_
3	100:1:0.5:0.5	PMP	Tol	50	3	98	14 200	14 500	11 700	1.34
4	100:1:0.2:0.2	PMP	Tol	50	3	95	13 768	14 500	12 600	1.32
5	100:1:0.5:0.5	PMP	THF	50	24	94	13 600	12 500	8700	1.70
6	100:1:0.5:0.5	PMP	DCM	25	3	92	13 336	13900	12 700	1.34
7	100:1:0.5:0.5	Et ₃ N	DCM	25	8	90	12904	13900	13100	1.33
8	100:1:0.5:0.5	Collidine	DCM	25	168	56	8152	8000		_
9	100:1:0.5:0.5	PhNMe ₂	DCM	25	144	3				
10	50:1:0.2:0.2	PMP	DCM	25	3	96	7000	7300	7100	1.22
11	70:1:0.2:0.5	PMP	DCM	25	2.1	98	9965	10 200	10 300	1.21
12	50:1:0.5:0.5	PMP	DCM	25	2.5	97	7072	6300	6800	1.22
13	100:2:0.5:0.5	PMP	DCM	25	5	87	6496	6100	5700	1.17
14	100:4:0.5:0.5	PMP	DCM	25	5	95	3688	4400	4300	1.30
15	100:6:0.5:0.5	PMP	DCM	25	5.5	90	2488	3100	3000	1.30
⁴ nos DentOU = nos pontonol DMD = 12266 contemptivizionidina ^b Manamar conversion una determinad hu ¹ U NMD ^c Calculated from										

^{*a*} *neo*-PentOH = *neo*-pentanol, PMP = 1,2,2,6,6-pentamethylpiperidine. ^{*b*} Monomer conversion was determined by ¹H NMR. ^{*c*} Calculated from $[LA]_0/[neo-PentOH]_0 \times LA$ conversion $\times M_{LA} + M_{neo-PentOH}$, with $M_{LA} = 144 \text{ g mol}^{-1}$ and $M_{neo-PentOH} = 88 \text{ g mol}^{-1}$. ^{*d*} Determined by SEC using a viscosimeter or a RI detector *vs.* PS standards.

occurred after 24 h at 50 °C, indicating that the combination of the two components (*i.e.*, **2** and PMP) is essential.^{7–9}

By analogy with the mode of action of bifunctional organocatalysts,^{2,10} we postulate that the electrophilic zinc cation activates the monomer by coordination to the carbonyl moiety while the amine activates the initiating/propagating alcohol through hydrogen bonding (Scheme 2). Noteworthily, Tolman *et al.*⁵ have shown that zinc-alkoxides derived from **1** are active towards ROP of lactide, and the *in situ* formation of such species might be considered as an alternative pathway. However, ¹H NMR monitoring of a 1:1:1 mixture of **2**/PMP/*neo*-PentOH showed no sign of reaction under the polymerization conditions, ruling out this hypothesis.

In accordance with the electrophilic activation of LA upon coordination to 2, we observed a solvent effect on the activity of the dual catalyst 2/PMP/neo-PentOH. Indeed, polymerizations proceed equally in toluene and dichloromethane (DCM), in terms of activity (95% and 97% conversion in 3 h, respectively) and polymerization control, but a much lower polymerization rate is observed in THF (94% yield in 24 h) with a lower degree of polymerization control (entries 4–6). THF is likely competing with LA for coordination to 2, and thereby



Scheme 2 Bifunctional activation of the monomer (by the Lewis acidic zinc complex 2) and initiating/propagating alcohol (by the amine) proposed to account for the dual ROP of lactide.

somewhat inhibits the electrophilic activation of the monomer. In addition, a broad range of reactivities was observed depending on the basicity of the amine [PMP ($pK_a = 11.2$) \approx NEt₃ ($pK_a = 10.7$) > collidine ($pK_a = 7.5$) > PhNMe₂ ($pK_a = 5.1$)]. For instance, while a rapid polymerization is observed with PMP (complete conversion of 100 equiv. within 3 h, entry 5), hardly any polymerization occurs with PhNMe₂ (entry 9). Interestingly, with PMP, the catalyst loading can be reduced (from 1 to 0.2 mol% relative to the monomer) without noticeably slowing down the ROP (entry 4), and a faster polymerization rate is observed when the PMP/2 ratio is increased from 1 to 2.5 (entries 10 and 11), in line with the activation of the initiating/propagating alcohol by the amine through hydrogen bonding.

Having established the cooperativity of the zinc cation and amine, the polymerization behavior of the dual catalytic system was explored in more detail. First, end-group analysis by ¹H NMR spectroscopy revealed quantitative initiation by neo-PentOH. In addition, a linear relationship was observed between the initial monomer-to-alcohol ratio (varving from 20 to 150) and the number-average molar mass values (as determined by NMR and SEC analyses), indicating the controlled character of polymerization (Fig. 1). This was further confirmed by a second-feed experiment resulting in a polymer chain extension. A PLA sample with M_n = 8100 g mol⁻¹, $M_{\rm w}/M_{\rm n} = 1.29$ was first prepared by complete ROP of 50 equiv. of LA with neo-PentOH. The polymerization was then restarted by subsequent addition of 100 equiv. of LA to give PLA with $M_{\rm n} = 21\,700 \text{ g mol}^{-1}$, $M_{\rm w}/M_{\rm n} = 1.27.$ † Increasing the monomer-to-initiator feed ratio to 200 enabled to attain higher molar mass, but at the expense of polymerization control ($M_{\rm n} = 28\,000$ g mol⁻¹ and $M_{\rm w}/M_{\rm n} = 1.80$).

According to NMR analysis (homonuclear decoupled ¹H NMR spectrum of the methine region), isotactic PLLA is



Fig. 1 Plot of M_n (as measured by SEC) vs. $[LA]_0/[neo-PentOH]_0$ ratio for the dual ROP of LA with the 2/PMP/neo-PentOH (0.5:0.5:1) system at 25 °C (with M_w/M_n values, left). SEC traces from the successive feed experiments (right).

obtained by ROP of L-lactide, showing that the basic amine does not induce epimerization of the monomer and polymer chain. On the other hand, the PLA samples derived from rac-lactide were found to be essentially atactic, indicating the absence of significant chain-end control. Polymerizations carried out in the presence of an excess of alcohol led to PLAs with molar mass M_n in good agreement with the LA/neo-PentOH ratio and with narrow $M_{\rm w}/M_{\rm n}$ values (entries 13-15). Thus, increasing the amount of alcohol with respect to the catalytic system (2/amine) allows the simultaneous growth of several chains per metal center without affecting either the control or the rate of polymerization. This demonstrates the possibility to carry out lactide ROP with catalytic amounts of the metal. In comparison, the ROP of lactide through a coordination-insertion mechanism offers this opportunity only if the alcohol behaves as a reversible chain transfer agent (i.e., if exchange between the active metal-alkoxide and dormant alcohol species proceeds faster than propagation), as previously observed for "immortal" ROP processes.¹¹

In summary, a dual catalytic system combining an original cationic zinc complex with a tertiary amine is shown to promote efficiently and in a controlled manner the ROP of lactide under mild conditions. The two-component catalyst activates cooperatively the monomer and initiating/propagating alcohol. This illustrates for the first time the possibility to combine the organic and organometallic approaches in ring-opening polymerization catalysis. Such a dual approach bridges the gap between the coordination/insertion and activated-monomer pathways. Future work will seek to generalize this approach to other monomers (lactones, cyclic carbonates...) and to explore other combinations of Lewis acidic metal complexes and organic bases.

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