

Ultraproductive, Zinc-Mediated, Immortal Ring-Opening Polymerization of Trimethylene Carbonate

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In the general context of the depletion of fossil feedstocks, use of monomers derived from renewable resources nowadays appears as a priority for sustainable synthesis of polymers. Thus, cheap glycerol originating from biomass can be converted into valuable chemicals, for example, 1,3-propanediol readily affords trimethylene carbonate (TMC).^[1] Poly(trimethylene carbonate) (PTMC) is a synthetic polymer, best obtained by ring-opening polymerization (ROP) of TMC, which shows good promise for various applications, in particular in the biomedical field as diagnostic and therapeutic tools, including controlled and sustained drug or gene delivery vehicles, or tissue engineering and tissue repair systems.^[2] Therefore, efficient synthetic procedures for the formation of PTMC with reagents/solvents that are as nontoxic as possible are highly desirable.

To that end, the concept of “immortal” polymerization appears as an extremely worthy approach, since it allows the growth of many—that is, more than one as in “conventional” living mechanisms—polymer chains per metal center while maintaining the control of the reaction, thanks to the presence of protic sources acting as chain-transfer agents. First pioneered by Inoue for the ROP of epoxides by an Al-porphyrin/alcohol system,^[3a-c] this approach has been further extended to other less reactive heterocyclic monomers.^[3d-g] Yet, the productivity of these immortal catalytic systems (monomer-to-metal ratios <2000) does not compare to those achieved for the polymerization of olefins, for which

truly minute amounts of metallic species are used, and never has it been applied to the ROP of cyclic carbonates.

ROP of six-membered carbonates has been investigated through cationic, anionic and insertion-coordination pathways, including nontoxic initiating systems.^[4] Among these, zinc-based initiators are particularly attractive given that this metal participates to the human metabolism.^[5] However, the use of Zn^{II} complexes remains quite limited in the ROP of carbonates,^[6] relative to that of other cyclic esters^[2c,7] for which discrete Zn^{II} complexes supported by a variety of ancillary ligands have emerged as highly performant initiators.^[8-13]

Herein, we report the “immortal” solvent-free polymerization of TMC by using a simple binary catalyst system based on Coates’ zinc complex supported by a β -diiminate ligand, and benzyl alcohol as a transfer agent (Scheme 1). The “immortal” approach is applied here for the first time to a carbonate monomer and is shown to be extremely effective: huge amounts of TMC can be fully converted into PTMC in a highly controlled manner from minute catalytic amounts of zinc combined with large quantities of benzyl alcohol under mild reaction conditions.

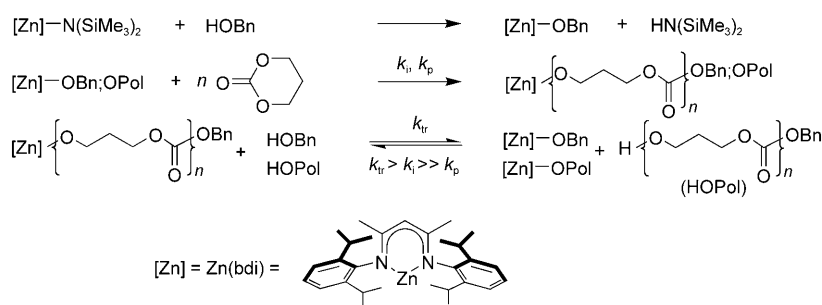
The results summarized in Table 1 show that TMC is efficiently polymerized in bulk at 60–110 °C in the presence of [Zn(bdi){N(SiMe₃)₂}] (bdi = CH(CMeNC₆H₃-2,6-*i*Pr₂)₂)^[9] as the catalyst precursor and benzyl alcohol (BnOH) as the transfer agent, with an initial alcohol/zinc ratio varying from 0 to 50 and a monomer/zinc loading ranging from 500 up to 50 000. Implementation of this binary catalyst system to generate in situ, within 15 min, the active alkoxide species [Zn(bdi)(OBn)] is straightforward (Scheme 1, top) and does not require the prior synthesis of this derivative, which is a significant advantage. The reaction mixtures and final polymers were analyzed by NMR spectroscopy and size exclusion chromatography (SEC) to determine the monomer conversion, the total number of chains, and the chain-end structure (see Supporting Information).

For the sake of comparison, the amido precursor [Zn(bdi){N(SiMe₃)₂}] was first evaluated without any added

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Scheme 1. [Zn/alcohol]-mediated "immortal" ROP of TMC.

 Table 1. Bulk polymerization of TMC initiated by the [(bdi)Zn(N(SiMe₃)₂)/BnOH system.

	[TMC] ₀ :[ROH] ₀ ^[a]	T [°C]	t [min] ^[b]	Monomer conv. ^[c] [mol %]	$\bar{M}_{n,theory}$ ^[d] [g mol ⁻¹]	$\bar{M}_{n,SEC}$ ^[e] [g mol ⁻¹]	\bar{M}_w/\bar{M}_n ^[f]	TOF [mol(TMC)mol(Zn) ⁻¹ h ⁻¹]
1	500:0	60	8	34	17 450	102 600	1.91	1275
2	500:1	60	8	95	48 600	42 000	1.70	3560
3	500:2	60	8	100	25 600	27 700	1.65	3750
4	500:5	60	7	99	10 200	12 400	1.55	4240
5	500:10	60	30	100	5200	7300	1.38	1000
6	500:20	60	60	99	2600	3500	1.35	495
7	500:50	60	120	100	1150	1600	1.10	250
8	1000:5	60	10	100	20 500	25 900	1.60	6000
9	1000:50	60	20	89	1900	2200	1.17	2670
10	2000:5	60	15	79	32 350	35 700	1.90	6320
11	2000:20	60	30	95	9800	13 100	1.38	3800
12	5000:20	60	75	90	23 100	28 760	1.70	3600
13	10000:20	60	180	89	45 500	43 290	1.90	2967
14	25000:10	110	40	83	211 750	185 200	1.68	31 125
15	25000:20	110	50	96	122 500	110 230	1.84	28 800
16	25000:50	110	40	80	40 900	49 300	1.90	30 000
17	50000:20	110	120	93	237 250	160 600	1.68	23 250

[a] Monomer and alcohol equivalents relative to [Zn]₀; See the Supporting Information for experimental details. [b] Reaction time was not necessarily optimized. [c] Determined by ¹H NMR. [d] Calculated from [TMC]₀/[ROH]₀ × monomer conversion × MTMC + MROH, with MTMC = 102 g mol⁻¹ and MBnOH = 108 g mol⁻¹. [e] Determined by SEC and corrected by 0.73.^[17] [f] Molar mass distribution calculated from SEC traces.

alcohol (Table 1, entry 1). Although this complex shows a moderate activity (170 turnovers in 8 min), the polymerization is not controlled, as evidenced by the molar mass value, which is much higher than the calculated one, and by the broad molar mass distribution value. This result falls within the trend of observations made upon polymerizing lactones with homoleptic metal amide derivatives.^[14]

Addition of BnOH (1–50 equiv vs. Zn) generates a more active species and allows the controlled polymerization of TMC at various monomer/alcohol ratios with high to quantitative monomer conversions within 0.1–3 h (entries 2–17). The SEC traces of the polymers all exhibit a unimodal and symmetrical peak.^[15] The molar mass values determined by SEC ($\bar{M}_{n,SEC}$) are in quite good agreement with the calculated ones ($\bar{M}_{n,theory}$), assuming that all the added alcohol molecules contribute to the immortal polymerization.^[16] As further documented hereafter, these observations suggest that 1) benzyl alcohol is the actual initiator of the ROP and 2) a fast, reversible exchange takes place between the growing polymer chains and the free alcohol moieties (Scheme 1).

The polymerization of up to 10000 equivalents of TMC proceeds readily at 60 °C. Raising the temperature to 110 °C allows high conversions to be reached within similar short periods of time (<2 h) for significantly larger amounts of TMC, up to 50000 equivalents. Remarkably, turnover numbers (TONs) and turnover frequencies (TOFs) reach 46500 mol(TMC)mol(Zn)⁻¹ (entry 17) and 31000 mol(TMC)mol(Zn)⁻¹h⁻¹ (entry 14), respectively, under such conditions. These productivity and activity data range much higher than the maximum values (TON = 1293 in 1 h; TOF = 970–1290 h⁻¹ at 110 °C) reported for the TMC/Zn(acac)₂ system^[6c] and are, to the best of our knowledge, unprecedented for a carbonate, or even a lactone, polymerization initiated by a zinc derivative.^[18,19]

The amount of alcohol added to the zinc amide complex has been increased, in the present work, up to 50 equivalents, still with a good control of the polymerization in terms of the agreement between the experimental molar mass values ($\bar{M}_{n,SEC}$) and monomer/alcohol ratios (Table 1, entries 7, 9, and 16). The dependence of the experimental molar mass ($\bar{M}_{n,SEC}$) on the amount of added BnOH, for a given TMC/Zn ratio of 500 (Figure 1), eviden-

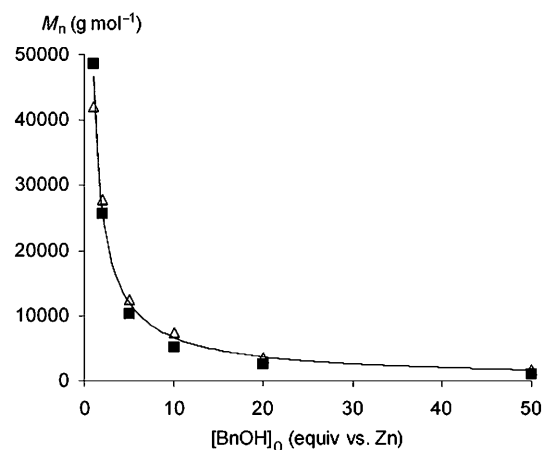


Figure 1. Dependence of the molar mass \bar{M}_n on the alcohol concentration at [TMC]₀/[Zn]₀ = 500. Δ : experimental values determined by SEC; \blacksquare : theoretical values.

ces that the $[\text{Zn}(\text{bdi})(\text{OBn})]/\text{BnOH}$ transfer efficiently takes place, since the molar mass of the resulting polymer decreases with increasing quantity of alcohol. This means that the number of polymer molecules becomes larger, proportionally to the number of added BnOH molecules.

The dependence of molar masses of PTMCs on the monomer/alcohol ratio for 1) 20 equivalents of BnOH versus Zn and 2) a TMC/Zn ratio of 500, is presented Figure 2. The

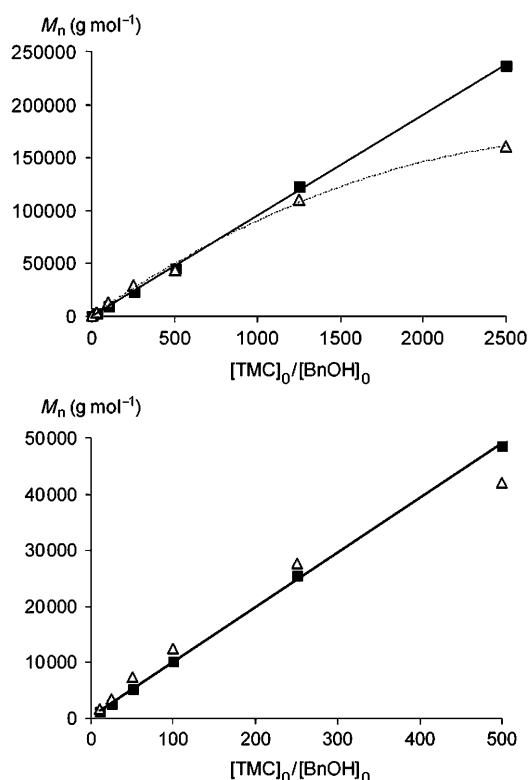


Figure 2. Dependence of the molar mass \bar{M}_n on the $[\text{TMC}]_0/[\text{BnOH}]_0$ ratio for $[\text{Zn}]_0/[\text{BnOH}]_0 = 1:20$ (top) and $[\text{TMC}]_0/[\text{Zn}]_0 = 500:1$ (bottom). Δ : experimental values determined by SEC; \blacksquare : theoretical values.

polymerization degrees measured by SEC are fully consistent with $[\text{TMC}]_0/[\text{Zn}]_0/[\text{BnOH}]_0$ up to 25 000 monomer units ($[\text{TMC}]_0/[\text{BnOH}]_0 = 25\,000:20 = 1250$; Table 1, entry 15; Figure 2, top); side-reactions^[15] responsible for a decrease of the \bar{M}_n values appear only at higher monomer loadings (50 000 equiv; entry 17). Similarly, for $[\text{TMC}]_0/[\text{Zn}]_0 = 500:1$, $\bar{M}_{n\text{SEC}}$ varies linearly with the $[\text{TMC}]_0/[\text{BnOH}]_0$ ratio (Figure 2, bottom). These observations illustrate the controlled “living” character of the ROP reaction under a broad range of experimental conditions. Indirectly, this hints that the active Zn^{II} species is able to withstand quite large amounts of alcohol,^[19] a good stability most likely provided by the ancillary bdi ligand.^[9,12]

The polycarbonate end-groups have been unambiguously identified by $^1\text{H NMR}$ analyses as a benzyloxy and a hydroxyl function. These groups arise from the initiation by the zinc–benzyloxy species and from the hydrolytic deactivation of the growing species, respectively, thereby support-

ing a coordination–insertion mechanism.^[4] The good agreement of \bar{M}_n values of relatively low-molar-mass macromolecules, as determined from $^1\text{H NMR}$ analysis, with the calculated ones evidences the quantitative chain-end capping at both ends.^[16] Importantly, these analyses also revealed the absence of resonances corresponding to ether units, that is, the absence of decarboxylation of the PTMC, a phenomenon yet often observed in ROP of carbonates.^[4]

On the basis of these data, the “immortal” ROP mechanism depicted in Scheme 1 can be proposed. Addition of the first BnOH molecule onto $[\text{Zn}(\text{bdi})\{\text{N}(\text{SiMe}_3)_2\}]$ leads to the formation of the corresponding zinc alkoxide initiating species $[\text{Zn}(\text{bdi})\text{Zn}(\text{OBn})]$ (Scheme 1, top). Upon subsequent addition of the monomer, a growing zinc alkoxide is formed (Scheme 1, middle). Excess alcohol molecules, being involved in a rapid and reversible exchange with this growing alkoxide, act as chain-transfer agents (CTAs), resulting in the formation of a new growing zinc alkoxide complex along with dormant hydroxy-terminated polymer chains (HOPol) (Scheme 1, bottom). All BnOH/HOPol molecules thus act as a CTA resulting in new growing species from which new PTMCs are formed according to the pendant reaction between the middle and bottom equations shown in Scheme 1. Therefore, the total number of growing macromolecules ($\text{Zn-OPol} + \text{HOPol}$) is greater than the initial number of zinc complex molecules introduced and is directly set by the initial amount of CTA introduced. One of the key points of a successful “immortal” polymerization is the rapidity of the exchange between the metal alkoxide and the CTA (BnOH and resultant HOPol). If the rate of the transfer reaction k_{tr} is rapid enough relative to the rate of the polymerization k_{p} , the molar mass distribution of the macromolecule formed is expected to be narrow, as in the absence of transfer agent. This is actually what is observed in the present work ($\bar{M}_w/\bar{M}_n < 1.90$), keeping in mind that the polymerization reactions are performed in bulk.^[15]

An essential consequence of this process is that polycarbonates prepared accordingly can be directly considered for use as biomaterials. Indeed, when using an initial loading of metal complex as low as 20 ppm to polymerize 50 000 equivalents of monomer (entry 17), the metal recovered in the final polymer is, at most, present in trace amounts. In addition, the appropriate choice of a biometal as the one we picked, that is, zinc, inhibits reservations with regards to toxicity.

In summary, we have shown that the $[\text{Zn}(\text{bdi})\{\text{N}(\text{SiMe}_3)_2\}]/\text{BnOH}$ system features unprecedented, highly efficient, catalytic activities and productivities for the controlled “living” and “immortal” ROP of trimethylene carbonate. This paves the way to the synthesis of as much as 50-fold polymer chains of PTMC in the presence of extremely small amounts of catalyst. This is the first example of an “immortal” polymerization of a carbonate monomer. In addition, the reaction proceeds in bulk, that is, under green and industrially relevant conditions. A further significance of this system lies in the versatility provided by the nature of the alcohol (unsaturated, multifunctional, etc.),

which affords the possibility to eventually tune the end-functionality of the polymers and/or to access telechelic and star polymers. Such metallic complex/protic source chemistry is ripe to be applied for the non-toxic preparation of biocompatible polymers.

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