Extending the Scope of Benign and Thermally Stable Organocatalysts: Application of Dibenzoylmethane for the Bulk Copolymerization of L-Lactide and ε-Caprolactone

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Due to the complementary properties of polylactide (PLA) and poly(ε-caprolactone) (PCL) in terms of biocompatibility, permeability, and biodegradability, random copolymers based on PLA and PCL, P(LA-*co*-CL), have received a significant attention for their applications in both medical and pharmaceutical fields.[1–5] Their thermal and mechanical properties, which can be tuned by varying the copolymer composition, make them also suitable for industrial applications, such as compatibilizing and plasticizing agents.[6] Their general attractiveness is reflected by their industrial production and both P(LA-*co*-CL) and P(LA-*co*-CL)-*b*-PEG are commercially available with average molecular weights (M_w), ranging from 1700 to 800,000 g mol^{-1}.

Over the last two decades, various metallic initiating/catalytic systems enabling the ring-opening copolymerization (RO*c*P) of lactide (LA) and ε-caprolactone (CL) have been developed.[1,7–10] Aluminum[7,11–14] and stannous (Sn)-based[1,2,5,6,15] complexes are among the most widely studied catalysts to produce P(LA-*co*-CL) with high molecular weights and/or controlled structures. To date, only bulky aluminum complexes are efficient for a true random distribution of both monomer units, without any detectable "type II" transesterification reactions.[7,12–14] Despite their undisputable performances, those complexes are not environmentally friendly and their inherent toxicity on humans and animals is a subject of controversy.[16,17] Those issues still limit the applications of the resulting materials and are, to our own opinion, detrimental for their large-scale production for both biomedical and electronic fields.

In that context, organocatalysts[18] with low toxicity[19] are of interest to achieve P(LA-*co*-CL)-based materials. Attempts to use typical basic organocatalysts, such as phosphazenes,[20] *N*-heterocycliccarbenes,[21] or guanidine "superbases", such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene[22] did not enable to control the copolymerization of the two monomers. Acidic organocatalysts such as trifluoromethane sulfonic acid (TfOH) and (R)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BPA) have also been used for this purpose.[23–25] When using TfOH in solution at low temperatures, a random distribution of LA and CL units has been evidenced.[23,24] LA is consumed in the early stage of the RO*c*P process—due to a higher reactivity ratio (r) as compared to CL– and the random character of the final copolymer is achieved owing to the occurrence of transesterification reactions. Although such backbiting reactions are not detrimental in a sense, the control of the general chemical route cannot be claimed either. Note here that such a behavior follows the same trend than the one observed from most of the organometallic catalysts, that is, a CL reactivity ratio (r_{CL}) far lower than the LA one (r_{LA}) ($r_{CL} \ll r_{LA}$; Supporting Information Table S2 for numerical values).[8,15] In contrast, attempt at copolymerizing LA and CL by BPA has led to the incorporation of a limited fraction of LA (8 mol %) into the final copolymer,[25] suggesting a r_{CL} higher than r_{LA} in these peculiar conditions. Importantly, it has to be noticed that one other major drawback of the organocatalysts used in the ROP of L-LA is their poor thermostability.[26]

In this communication, we wish to report on the RO*c*P of L-LA and CL in presence of a minor constituent of licorice,

Additional Supporting Information may be found in the online version of this article.

TABLE 1 Results and Conditions of LA and CL Copolymerization in Bulk

Entry	Time (h)	$[M]_0/[DBM]_0/[I]_0$[a]	C_{CL}, C_{LA}[b] (%)	$M_{n,SEC}$[c] (g mol^{-1})	$Đ$[c]
0	41	30/0/0	0,0	/	/
1	24	30/1.5/1	14, 36	1000	1.3
2	48	30/1.5/1	52, 72	2200	1.36
3	51	30/1.5/1	65, 78	2750	1.32
4	68	30/1.5/1	90, 91	3450	1.4
5	70	30/1.5/1	93, 94	3600	1.48
6	72	30/1.5/1	99, 96	3300	1.72
7	48	30/1.5/1	54,70	3850	1.34
8	38	30/1.5/1	86, 92	4100	1.55

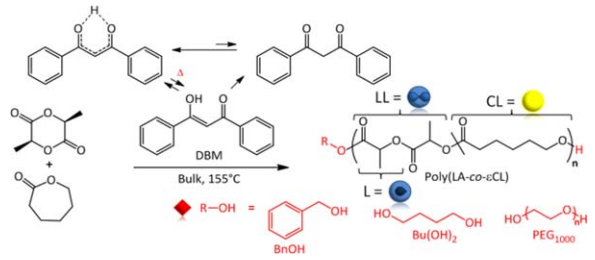
All reactions were carried out in bulk under nitrogen atmosphere at 155 °C with reaction conditions: $n_{CL} = n_{LA} = 1.4$ mmol.
[a] $[I]_0$ initiator: benzyl alcohol (BnOH) for entries 1–6, 1,4-butanediol ($Bu(OH)_2$) (entry 7) and poly(ethylene glycol) (PEG_{1000}, $M_w \approx 1000$ g mol^{-1}) (entry 8).
[b] CL and LA conversions determined by ^{1}H NMR analysis.
[c] Average molar mass and dispersity ($Đ$) of crude copolymers determined by SEC chromatography (polystyrene standards), THF/NEt_3 (2 wt %) as eluent.

namely, dibenzoylmethane (DBM) as new and benign organocatalyst. This β-diketone issued from the flavonoid family is known to exhibit interesting antitumor promoting activities.[27,28] In the context of polymer synthesis, DBM has already been used as efficient ligand of Sn(II)-based complex for the bulk ROP of LA.[29] Here, DBM is evaluated as a true organocatalyst for the preparation of random-like P(LA-*co*-CL) copolyesters under solvent-free conditions at 155 °C.

Under the conditions summarized in Table 1, DBM enables the consumption of both LA and CL comonomers, in presence of benzyl alcohol used as initiator (entries 1–6). Reactions were carried out in bulk at 155 °C, using 5 mol % of DBM and with an initial comonomer-to-initiator ratio of 30 ($[M]_0/[I]_0 = 30$, that is, a $[LA]_0/[I]_0 = [CL]_0/[I]_0 = 15$)). As attested by ^{1}H NMR (Supporting Information Figs. S4 and S5), 93%–94% of both comonomers were polymerized after 70 h of reaction, giving relatively narrowly distributed copolymers at such high temperature ($M_w/M_n = Đ < 1.5$) (Scheme 1).

Despite a discordancy between the experimental molecular weights ($M_{n,exp}$) and the theoretical values ($M_{n,th}$)—ascribed to deleterious (or side) initiation by water—the RO*c*P exhibits an acceptable level of control, as evidenced by the linear correlation between $M_{n,SEC}$ and the total monomer conversion (Fig. 1). When pushed to almost full consumption of both monomers (>98%), the reaction led to a molecular weight lowering and an increase in $Đ$ values up to 1.72 (entry 6).

A discrepancy between the degree of polymerizations (DPs) calculated from the α- and ω-chain ends was found by ^{1}H NMR (Supporting Information Fig. S4) ($DP_{n,NMR\alpha} = 27 > DP_{n,NMR\omega} = 18$) verifying that water really co-initiates the



SCHEME 1 General scheme of LA and CL copolymerization catalyzed by DBM in the presence of alcohol initiator. [Color figure can be viewed at wileyonlinelibrary.com]

polymerization. Since the polymerization required long reaction times, the catalyst activity was further demonstrated by performing a blank experiment without any catalyst or initiator (Entry 0, Table 1; Supporting Information Fig. S3). As expected, no polymerization took place after 41 h; even in the presence of trace amounts of water.

Interestingly, both monomers were effectively copolymerized throughout the DBM-catalyzed RO*c*P process, as evidenced by ^{1}H NMR analyses of the crude mixtures (Supporting Information Fig. S5). Copolymerizations were monitored by the Kelen-Tüdös and Fineman-Ross linear methods, which enabled to determine a r_{LA} of 1.8 and a r_{CL} of 0.1 (Supporting Information p.7).[30,31] Those values indicate that the caproyl chain-end units are 10 times more reactive toward L-LA (than CL), while the lactidyl chain-end units are twice more reactive toward L-LA (than CL monomer). Following the course of the copolymerization, the recorded reactivity ratios explain why at the early first stage of the process (entry 1, Table 1), L-LA monomers are preferably incorporated into the copolymer. The concentration of the more reactive L-LA decreases then more rapidly increasing the probability for the ω-chain end units to come across CL monomers progressively, leading to the formation of a random copolymer from

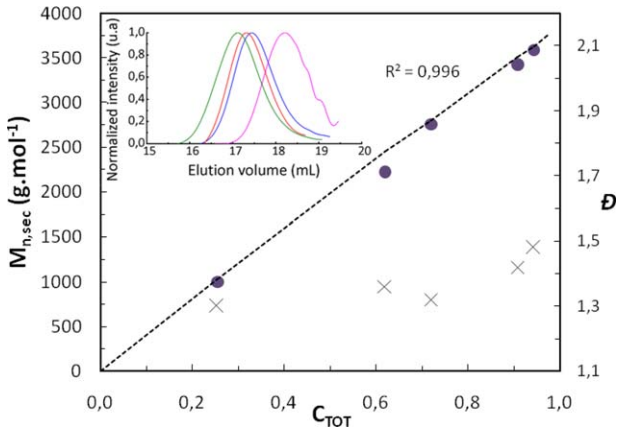


FIGURE 1 Evolution of uncorrected $M_{n,SEC}$ (•) and $Đ$ (*x*) with total monomer conversion for the crude copolymers containing L-LA with CL synthesized using DBM in bulk at 155 °C (entries 1–5). SEC traces of crude copolymers (entries 1–4). [Color figure can be viewed at wileyonlinelibrary.com]

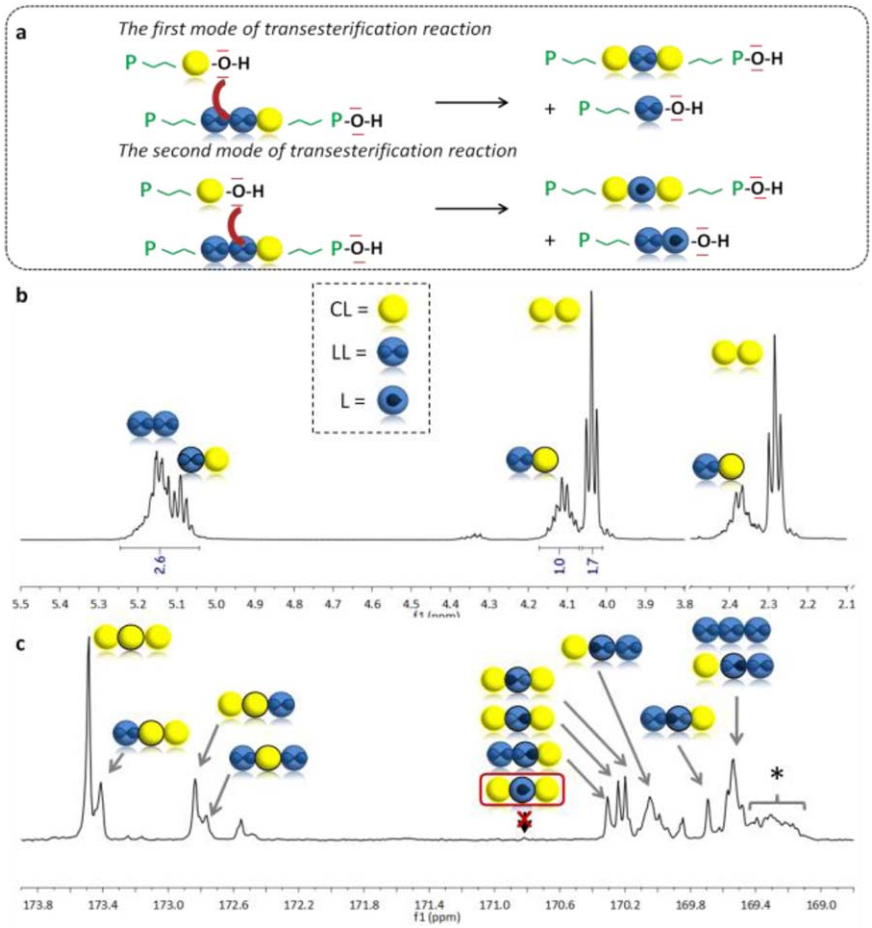


FIGURE 2 The two modes of transesterification reactions (a); ^{1}H (b), and ^{13}C (c) NMR spectra of a P(L-LA-*co*-CL) copolymer (entry 5, Table 1) (LL and L refer to lactidyl and lactoyl units, respectively). $CDCl_3$, 500 MHz, room temperature, * stereoirregular LL-LL-LL.[12] [Color figure can be viewed at wileyonlinelibrary.com]

a gradient one. Such modification of the microstructure also explains why $M_{n,SEC}$ does not evolve linearly with the LA and CL conversions (considered separately).

Since DBM was still present in the crude medium at the end of the ROcP (compare Supporting Information Figs. S4 and S5), copolymers were purified by precipitation in cold methanol. The ^{1}H NMR spectrum of a typical copolymer (entry 5) allows determining an overall composition in good agreement to the one engaged in the feed (LA:CL = 49:51) and the absence of remaining organocatalyst [Fig. 2(b)]. While homo- and heterodiads are clearly identified, the amount of CL-CL homosequences was estimated to be 1.7 times higher than the CL-LA heterosequences [Fig. 2(b)]. The microstructure of the copolymer was also assessed by ^{13}C NMR analysis [Fig. 2(c)], attesting to the presence of all expected triads, as already reported in the literature.[32]

As detailed by Kasperczyk and Bero, because LA is composed by two lactoyl units, two possible modes of transesterification reactions may happen during a LA-based copolymerization [Fig. 2(a)].[33] The second mode of transesterification, which gives rise to "anomalous" CL-L-CL sequences (L, representing one lactoyl unit), was not observed here, as attested by the absence of a peak at 170.8 ppm in the ^{13}C NMR analysis [Fig. 2(c)]. Thus, only the first mode of transesterification occurred, which is mirrored by the slight increase in the dispersity during the copolymerization process (Đ from 1.3 to 1.48).

Finally, in agreement with reported results,[12] thermal analysis carried out by differential scanning calorimetry (DSC) revealed a single glass transition temperature (T_g) at around −19 °C confirming the random nature of this copolymer (Supporting Information Fig. S6).

To get some insight into the reaction mechanism, kinetic analyses are essential. As also reported by Kubisa and Baśko for the TfOH-catalyzed ROP of CL,[23] the recorded semi-log plot versus time curve exhibited an upward curvature (Supporting Information Fig. S7). This might reflect the involvement of a monomer activated mechanism for which the deviation from the first order kinetic is due to a rate of polymerization not related to the monomer concentration ($[M]_t$) but to the protonated monomer concentration, $[MH^+]$. Susperregui et al.[34] have evidenced that TfOH eventually behaves as a bifunctional organocatalyst, that is, acting as a

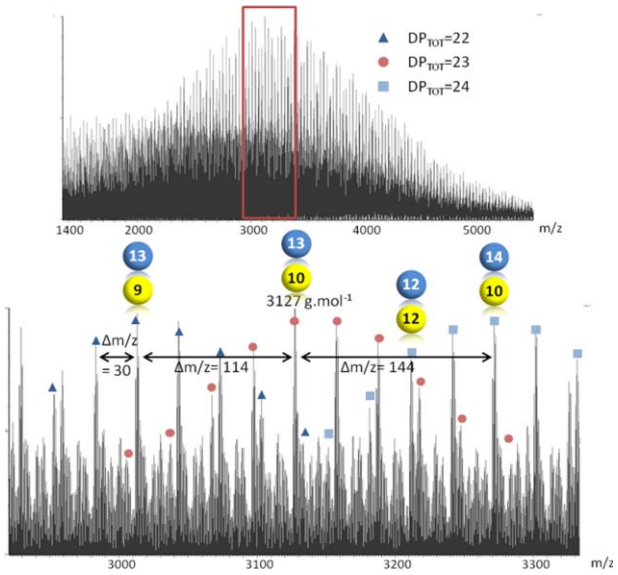


FIGURE 3 MALDI-MS spectrum of pure copolymer initiated by $Bu(OH)_2$ (entry 7). With $M_{LA} = 144.13$ g mol^{-1}; $M_{CL} = 114.14$ g mol^{-1}; M_{LA}-$M_{CL} = 30$ g mol^{-1}. [Color figure can be viewed at wileyonlinelibrary.com]

proton shuttle both via its acidic hydrogen and its basic oxygen atoms. Analogously, DBM could also act as a bifunctional organocatalyst. Veierov et al.[35] have reported that DBM can exist in three different forms, depending on the analytical conditions: a chelated enol form, a short-lived non-chelated enol form and a diketone form in tautomeric equilibrium. The possible co-existence of those isomers and their different behavior during the initial step of the ROcP may explain the inhibition period observed during the first hours of the reaction. Indeed, the chelated enol form, predominant at room temperature in several solvents[36] ($11 < K_e = [enol]/[keto] < 98$, Supporting Information Fig. S1), is expected to be relatively inert toward its environment due to a strong stabilization by intramolecular hydrogen bonds. This was confirmed by attempting to (co)polymerize both LA and CL in THF, in CH_2Cl_2 (room temperature) and in toluene (90 °C), which did not lead to any (co)polymer, even after 4 days. DBM is thus a thermally activated catalyst and this could be explained by the disruption of the intramolecular hydrogen bonds of the chelated enol form at high temperature. The non-chelated intermediate, which can interact more strongly with proton acceptors and/or donors, is known to be generated under UV stimulation reverting to the original chelated form or tautomerizing to the diketone form.[35] Furthermore, Folkendt et al. have indeed evidenced, based on NMR investigations, an increase in the diketone form of acetylacetone when increasing the temperature.[37] Assumption of the generation of a small amount of the non-chelated enol and diketone isomers can be made when the temperature was increased up to 155 °C. On theses bases, a bifunctional mechanism which involves the three co-existing isomers acting as proton shuttles—without any hydrogen bond formation—between the initiator and the monomers can be proposed here.

To demonstrate the versatility of DBM as organocatalyst for the ROcP, other initiators, that is, 1,4-butanediol ($Bu(OH)_2$) and poly(ethylene glycol) (PEG), were evaluated. Initiation by $Bu(OH)_2$ led to a well-defined copolymer, as attested by combined analytical techniques (entry 7, Table 1). While the ^{1}H NMR spectrum showed the presence of both homo- and heterodiads (Supporting Information Fig. S8), the MALDI-ToF mass spectrum of the copolymer exhibited a Gaussian-like distribution, as illustrated in Figure 3, where a difference of 30 mass units (u) is clearly visible. This value corresponds to the difference of mass between both LA and CL monomers (mass difference: 144 g mol^{-1} to 114 g mol^{-1} = 30 u). The exact mass and isotope pattern of the m/z 3127 signal reveals that the observed cations are likely to correspond to Na^+-cationized copolymer structures that incorporate both CL and LA monomer units [$m/z = 90$ ($M_{Bu(OH)2}$) + $m \times 144$ ($M_{L\text{-}LA}$) + $n \times 114$ (M_{CL}) + 23 (M_{Na+})].

As compared to $Bu(OH)_2$, initiating the copolymerization with an oligoPEG induced a synergetic effect since 90% of both comonomers were converted in only 38 h of reaction (entry 8, Table 1). The effect of PEG on the ROcP kinetic, being out of the scope of the present article, is not explained. As for the other initiators, the copolymerization from the PEG proved also to be efficient, as attested by SEC analysis (Supporting Information Fig. S10) while ^{1}H and ^{13}C NMR again confirmed the formation of a copolymer (Supporting Information Fig. S9).

In summary, DBM, a cheap and commercially available compound, proves efficient to catalyze the ROcP of L-LA and CL under solvent-free conditions at high temperature (155 °C). An acceptable level of control, as attested by a relatively low dispersity and a linear correlation between the SEC molecular weights versus monomer conversion, characterizes these copolymerization reactions. In contrary to basic catalysts, DBM offers new opportunities for synthesizing random-like P(LA-*co*-CL) copolyester from different alcohol-containing initiators, including BnOH, $Bu(OH)_2$, and PEG_{1000}. A bifunctional cooperative mechanism is proposed to operate, and computational studies are undergoing. Full study with optimized reaction conditions are in progress to diminish the relatively high reaction times by modifying the structure of that β-diketone new catalyst.

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