ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 11695–11697

www.rsc.org/chemcomm

**COMMUNICATION**

# An imidazole-based organocatalyst designed for bulk polymerization of lactide isomers: inspiration from Nature†

**Olivier Coulembier,*[a] Thomas Josse,[ab] Brieuc Guillerm,[a] Pascal Gerbaux[b] and Philippe Dubois[a]**

***Received 28th September 2012, Accepted 19th October 2012***
**DOI: 10.1039/c2cc37061a**



**The design of an imidazole-based salt by enzyme-mimicking allowed controlling the ring-opening polymerization of L- and D-LA monomers in bulk. Kinetic study supports a bifunctional activation process only slightly different from the one occurring in Nature.**

Since its first report in 1930,[1] the *in vitro* enzymatic catalysis using lipases has been extensively used for the preparation of various classes of polyesters. Regardless of its numerous advantages including a high turnover number and an excellent reaction control over enantio-, chemo-, regio-, stereo- and choroselectivities,[2] the enzymatic ring-opening polymerization (eROP) applied to the preparation of poly(lactide)s (PLAs) still presents some controversies.[3] While the eROP of L-, D- and D,L-LA has been reported to be successful when using lipase from *Pseudomonas fluorescens* (lipase PS),[4] *Candida antarctica* lipase B (CALB)-catalysed eROP has resulted in no polymer when using L-LA opposite to its D-isomer.[5]

The design of an enzyme-mimicking compound represents to date one of the most exciting subjects but also an important challenging problem in organic chemistry. In the frame of a general LA polymerization, we have chosen to study serine protease mimics since their mechanism of action has been thoroughly studied.[6] The active site of a lipase is generally formed by a catalytic triad consisting of electronically stabilized histidine, serine and aspartate (Fig. 1). Their active sites gather an acyl-receiving and -releasing hydroxymethylene group, and a proton-transfer system in a complexing cavity.[6] If the triad is of importance in the opening step of cyclic monomers, the cavity of the lipase dictates the rate of reaction and the enantioselectivity.[7]

One of the notable advances in lipase catalysis was the discovery that some of them exhibit a high catalytic activity at temperatures as high as 100 °C.[8] For that reason and to minimize the amount of hazardous substances, L-LA ROPs have been conducted in bulk. First a structure has been designed to combine an imidazole and a carboxyl group in a cooperative arrangement similar to that of the lipase (Chart 1). The imidazolium salt (**1**) was first studied and prepared by simple addition of trifluoroacetic acid to 1 eq. of neat imidazole initially dissolved in chloroform (see ESI†). Trifluoroacetic acid was deliberately chosen due to its incapacity to catalyse the ROP of L-LA even at 150 °C.[9]

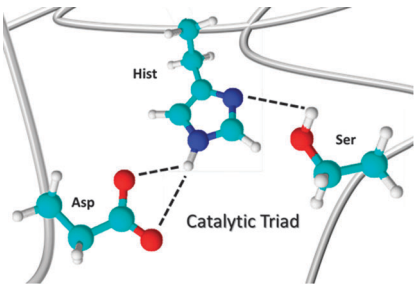


**Fig. 1** Catalytic triad in a lipase complexing cavity.

To mimic the catalytic triad, the primary hydroxyl group is part of the process as the exogenous alcohol (I) is incorporated to control the targeted degree of polymerization ($DP_{th} = [LA]_0/[I]_0$).

Since organocatalysts are generally used in a 5-to-20 molar excess regarding the initiating alcohol,[10] all polymerizations were performed by using a $[(\mathbf{1})]_0$-to-$[I]_0$ molar ratio of 5. Table 1 gathers molecular characteristics of P(L-LA)s obtained

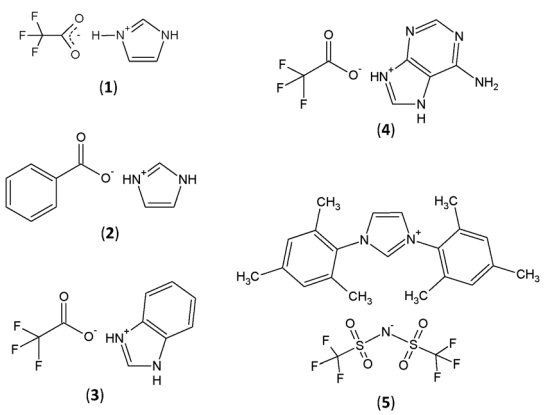


**Chart 1**

[a] *Center of Innovation and Research in Materials and Polymers (CIRMAP), Laboratory of Polymeric and Composite Materials, University of Mons, 23 Place du Parc, B-7000, Mons, Belgium. E-mail: olivier.coulembier@umons.ac.be; Fax: +32 (0)65 373484; Tel: +32 (0)65 373480*
[b] *Interdisciplinary Center for Mass Spectrometry (CISMa), Mass Spectrometry Research Group, University of Mons, 23 Place du Parc, B-7000 Mons, Belgium*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc37061a

**Table 1** Molecular characteristics of P(L-LA)s obtained at 140 °C[a]

| Entry | Activator | Pol. time (h) | Conv. (%) | $M_{n,th}$ (g mol$^{-1}$) | $M_{n,GPC}$[c,d] (g mol$^{-1}$) | $Đ_M$[c] |
|---|---|---|---|---|---|---|
| 1 | Imidazole | 1 | 39 | 4000 | 3400 | 1.33 |
| 2 | Imidazole | 2 | 70 | 7100 | 7100 | 1.78 |
| 3 | (**1**) | 2 | 60 | 6100 | 6600 | 1.14 |
| 4 | (**1**) | 3.7 | 84 | 8500 | 8700 | 1.28 |
| 5[b] | Imidazole | 0.3 | 44 | — | 11 000 | 3.14 |
| 6[b] | Imidazole | 3.3 | 77 | — | 18 000 | 2.18 |
| 7[b] | (**1**) | 48 | 0 | — | — | — |

[a] [L-LA]$_0$/[Activator]$_0$/[BzOH]$_0$ = 70/5/1. [b] No alcohol used: [L-LA]$_0$/[Activator]$_0$ = 100/10. [c] As determined by GPC in THF/$NEt_3$ (2 wt%) in reference to PS standards. [d] Molar mass obtained after application of a correction value of 0.58 reported by Duda *et al.*;[12] "Imidazole" refers to pristine imidazole.

at 140 °C by using benzyl alcohol ($DP_{th}$ = 70) and either pristine imidazole or (**1**) as initiator and activator, respectively (entries 1–4). For the sake of comparison and to evaluate the impact of all three components of the catalytic triad on the L-LA ROP, the process has also been carried out without exogenous alcohol (entries 5–7). Clearly, a total absence of control characterizes the polymerizations led only using the imidazole base (entries 5 and 6). Gel permeation chromatography (GPC) and electrospray ionization-mass spectrometry (ESI) confirm that the bulk polymerization of L-LA at 140 °C leads to a mixture of high molar mass linear P(L-LA)s and low molar mass cyclic structures with unpredictable molecular parameters (experimental details in ESI†, Fig. S1). Note that the generation of small cyclic PLA chains was also observed by Kricheldorf *et al.* under the same conditions of polymerization.[11]

In agreement with a strong influence of the hydroxymethylene group, the presence of the exogenous benzyl alcohol significantly improves the control over the reaction for which the P(L-LA) average molar masses depend on the [L-LA]$_t$/[I]$_0$ (with [L-LA]$_t$ = [L-LA]$_0$ × conv.) (entries 1 and 2). By assessing the capacity of the imidazole–alcohol mixture to polymerize L-LA in bulk deprived of any acid, it was found that the system is unable to provide a narrow molar mass distribution. In contrast when (**1**) is used as activator, the catalytic triad formed with the exogenous/propagating alcohol gives access to P(L-LA)s mirroring the theoretical targeted molar mass (Fig. S2, ESI†) but also significantly reduces the dispersity values ($Đ_M = M_w/M_n \leq 1.28$).

As attested by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF) carried out on P(L-LA) obtained after 2 h (entry 3, Fig. 2), the control of the reaction is lauded by a good matching of the $M_{n,MALDI}$ (~5600 g mol$^{-1}$) to both theoretical and the corrected experimental GPC values. It is important to note that the relative abundance, observed in the mass spectrum, does not reveal the sample composition due to an overestimation of the low mass ions compared to the high mass ions caused by a huge difference in the efficiency of the processes involved during the MALDI-ToF analysis.[13] Importantly, Fig. 2 reveals that the control over the ROP is well evidenced by (i) a 144 u (atomic mass unit) major separation between successive peaks, *i.e.* the molecular weight of the lactide unit, attesting to a low level of the transesterification process[14] and (ii) the fidelity of the expected benzyl alcohol end-groups. While also visible in

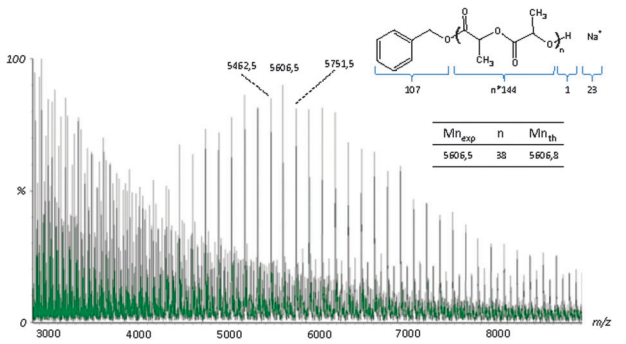


**Fig. 2** P(L-LA) MALDI spectrum recorded after 2 h of polymerization (entry 3, Table 1).

the low molar masses population, controlled polymer chains are accompanied by transesterified PLAs end-capped by water and cationized by either sodium or an imidazolium cation.

Quite recently, Hedrick *et al.* also reported that the addition of one equivalent of acid to the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) base yields a salt capable of controlled polymerization of lactide allowing for targeted molecular masses and narrow dispersities (in the presence of an alcohol initiator).[15] Even if used in solution at rt, their system unfortunately suffers from a very low kinetics in comparison to the one rendered by the DBU alone. From our data, the comparison between semilogarithmic *vs.* time plots allows concluding that the apparent rate of polymerization dictated by the triad is only 1.2 slower than the one obtained without complexing acid (Fig. S3, ESI†).

The exogenous alcohol is necessary in the L-LA ROP activated by (**1**) since no conversion into the polymer is observed without it (entry 7). In comparison to a few organocatalysts,[16] nucleophilic activation of the monomer by the imidazolium salt (**1**) leading to a zwitterionic process is then precluded here. To decide in favour of a bifunctional catalytic mechanism or nucleophilic activation of the initiating/propagating alcohol, the nature of the imidazole-based catalyst has been modified (structures 2–5 in Chart 1). Table 2 gathers their thermal properties.

Since the degradation temperature ($T_d$) of the imidazolium salt (**2**) is too close to the reaction temperature, the L-LA ROP was characterized by a total loss of control (results not shown here). In contrast, salt (**4**) is by far too stable and did not yield any reaction even at 180 °C. Salt (**5**) revealed a very low activity (5% of conversion after 2 hours), and the benzimidazolium salt (**3**) showed more interesting results, *i.e.* 16% conversion after 2 hours ($M_{n,GPC}$ = 2140 g mol$^{-1}$; $Đ_M$ = 1.31), indicating the polymerization process. The state-of-the-art instructs us that, during cationic ROP of lactones carried out in the presence of an acid catalyst (or simple organic reactions for some),

**Table 2** Thermal properties of imidazole-based salts

| Salt | $T_m$[a] (°C) | $T_d$[b] (°C) |
|---|---|---|
| (**1**) | 127.2 | 170 |
| (**2**) | 99.5 | 142 |
| (**3**) | 176 | 195 |
| (**4**) | 229.5 | 264.5 |
| (**5**) | 135.4 | —[c] |

[a] Melting point. [b] Onset of the degradation signal measured by DSC from rt to 300 °C. [c] Not observed in the temperature range.

 

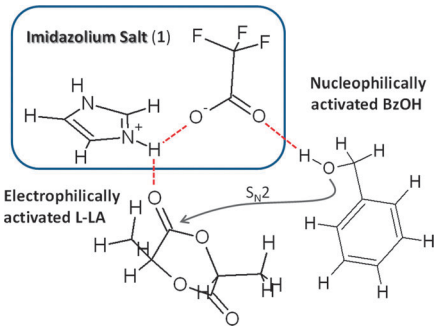


**Fig. 3** Proposed mode of activation of both BzOH and the L-LA monomer by the salt (**1**) leading to an $S_N2$ reaction.

the oxygen atom of the catalyst's carbonyl group mediates the proton shuffling of the initiating alcohol.[17] As demonstrated by Hedrick *et al.* such a phenomenon has also been highlighted in the L-LA ROP catalysed by a DBU–benzoic acid mixture.[15] Because salts (**1**) and (**3**) present the same trifluoroacetate anion and lead to totally different results in terms of polymerization, a "simple" nucleophilic activation of the initiating/propagating alcohol seems to be excluded here. Hydrogen bonding plays an important role in tuning the acidity of (benz)imidazolium salts.[18] Since both salts (**1**) and (**3**) carry the same anion, their intrinsic activity is dictated by their respective p$K_a$ values. Benzimidazolium cations are known to be more acidic than imidazolium cations,[19] and they also suffer from π–π interactions due to their benzene rings.[20] In the case of a bifunctional mechanism such interaction may play an important role regarding their interaction with the L-LA monomer. Indeed, as already observed for protonated DBU,[15] (benz)imidazolium cations are believed to function as L-LA electrophilic activators. The negatively charged carboxylate is then well positioned to foster a bifunctional mode of catalysis by interaction with the initiating/propagating alcohol. Fig. 3 shows the proposed active catalytic complex for the enchainment of the lactide in the presence of salt (**1**) and BzOH.

Despite a slightly higher p$K_a$, the salt (**1**) cation does not suffer from any dimerization and is hence more involved in the electrophilic L-LA activation compared to the salt (**3**) cation. This difference may explain the kinetic variation observed tending then to confirm the bifunctional mechanism.

To provide further support for the controlled nature of this polymerization, two chain-extension experiments were performed from an initial polymerization using L-LA carried out at 140 °C for 2 h to give PLLA of $M_{n,GPC}$ = 6600 g mol$^{-1}$. Additional L-LA ($1.4 \times 10^{-3}$ mol, 1 eq.) was added to the medium at rt and the mixture was allowed to react at 140 °C. After 2 h, the medium was charged again with $1.4 \times 10^{-3}$ mol (1 eq.) of monomer at rt. After 2 h, the final molecular weight increased to 18 000 g mol$^{-1}$ with a slight change in the dispersity (1.49) but a reasonable accord between theoretical and experimental molar masses (total conv. ~51%, $M_{n,th}$ = 22 000 g mol$^{-1}$) exhibiting the characteristics of a controlled system. The well-defined polymerization behavior of the triad along with the possibility of conducting the ROP of both L- and D-LA isomers is ideally suited for the preparation of complex macromolecular architectures. For that purpose, a monohydroxypoly(ethylene oxide) oligomer, *i.e.* PEO ($M_w$ 2000 g mol$^{-1}$, $Đ_M$ 1.09), was used as initiator for the ROP of the D-LA monomer ($DP_{th}$ = 70, $[PEO]_0/[(1)]_0$ = 1/5, 140 °C). After 2 hours, GPC analysis reveals an increase of molecular weight from 2800 to 8900 g mol$^{-1}$ (GPC *vs.* polystyrene) and a $Đ_M$ of 1.13 (conv. ~ 52% as determined by $^1$H NMR, Fig. S4, ESI†). In conclusion Nature inspired us to produce a stable imidazolium-based catalyst for the controlled ring-opening polymerization of L- and D-lactide in bulk. This catalyst was formed through a simple acid–base reaction between an imidazole base and one equivalent of trifluoroacetic acid. Experimental results support a bifunctional catalytic mechanism where both the monomer carbonyl and nucleophilic hydroxyl groups are activated *via* hydrogen bonding, which is slightly different from the one implied in LA eROP.

The authors thank the financial support from the Wallonia Region, the European Commission (FSE, FEDER), the National Fund for Scientific Research (F.R.S.-FNRS), and the Belgian Federal Science Policy Office (PAI 6/27). O.C. and P.G. are Research Fellows of the F.R.S.-FNRS.

## Notes and references

1 E. A. Sym, *Biochem. Z.*, 1933, **258**, 304; E. A. Sym, *Enzymologia*, 1936, **1**, 156.
2 S. Kobayashi, *Macromol. Rapid Commun.*, 2009, **30**, 237.
3 M. Takwa, M. Wittrup Larsen, K. Hult and M. Martinelle, *Chem. Commun.*, 2011, **47**, 7392.
4 S. Matsumura, K. Mabuchi and K. Toshima, *Macromol. Rapid Commun.*, 1997, **18**, 477.
5 M. Hans, H. Keul and M. Moeller, *Macromol. Biosci.*, 2009, **9**, 239.
6 D. M. Blow, J. J. Birktoft and B. S. Hartley, *Nature*, 1969, **103**, 337; S. E. Hamilton and B. Zerner, *J. Am. Chem. Soc.*, 1981, **103**, 1827 and references therein.
7 J. van Buijtenen, B. A. C. van As, M. Verbruggen, L. Roumen, J. A. J. M. Vekemans, K. Pieterse, P. A. J. Hilbers, L. A. Hulshof, A. R. A. Palmans and E. W. Meijer, *J. Am. Chem. Soc.*, 2007, **129**, 7393.
8 A. Zaks and A. M. Klibanov, *Science*, 1984, **224**, 1249.
9 H. R. Kricheldorf and R. Dunsing, *Makromol. Chem.*, 1986, **187**, 1611.
10 *Handbook of Ring-Opening Polymerization*, ed. Ph. Dubois, O. Coulembier and J. -M. Raquez, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2009, p. 357.
11 H. R. Kricheldorf, N. Lomadze and G. Schwarz, *Macromolecules*, 2008, **41**, 7812.
12 A. Kowalski, A. Duda and S. Penczek, *Macromolecules*, 1998, **31**, 2114.
13 P. M. Lloyd, K. G. Suddaby, J. E. Varney, E. Scrivener, P. J. Derrick and D. M. Haddelton, *Eur. Mass Spectrom.*, 1995, **1**, 293; J. De Winter, G. Desahayes, F. Boon, O. Coulembier, Ph. Dubois and P. Gerbaux, *J. Mass Spectrom.*, 2011, **46**, 237.
14 *Controlled and Living Polymerizations*, ed. A. H. E. Müller and K. Matyjaszewski, Wiley-VCH Verlag GmbH' Co. KGaA, Weinheim, 2009, p. 241.
15 D. J. Coady, K. Fukushima, H. W. Horn, J. E. Rice and J. L. Hedrick, *Chem. Commun.*, 2011, **47**, 3105.
16 W. Jeong, E. J. Shin, D. A. Culkin, J. L. Hedrick and R. M. Waymouth, *J. Am. Chem. Soc.*, 2009, **131**, 4884.
17 O. J. Jacobsson, C.-O. Abrahamsson, P.-O. Norrby, W. A. Goddard III and U. Ellervik, *Chem.–Eur.J.*, 2008, **14**, 3954; N. Susperregui, D. Delcroix, B. Martin-Vaca, D. Bourissou and L. Maron, *J. Org. Chem.*, 2010, **75**, 6581.
18 R. Kore and R. Srivastava, *J. Mol. Catal. A: Chem.*, 2011, **345**, 117.
19 T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas and K. Toth, *J. Am. Chem. Soc.*, 2004, **126**, 4366.
20 T.-T. Pan, J.-G. Liu and D.-J. Xu, *Acta Crystallogr.*, 2005, **E61**, o3996.