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COMMUNICATIONS

Published on Web 12/06/2006

An Activated Equivalent of Lactide toward Organocatalytic Ring-Opening Polymerization

Olivier Thillaye du Boullay,[†] Emmanuel Marchal,[†] Blanca Martin-Vaca,[†] Fernando P. Cossío,[§] and Didier Bourissou*,[†]

Laboratoire Hétérochimie Fondamentale et Appliquée du CNRS (UMR 5069), Université Paul Sabatier, 118, route de Narbonne, 31062 Toulouse Cedex 09, France, and Departamento de Química Orgánica I/Kimika Organikoa I Saila, Facultad de Química/Kimika Fakultatea P. K. 1072, 20080 San Sebastián/Donostia, Universidad del País, Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), Spain

Received October 2, 2006; E-mail: dbouriss@chimie.ups-tlse.fr

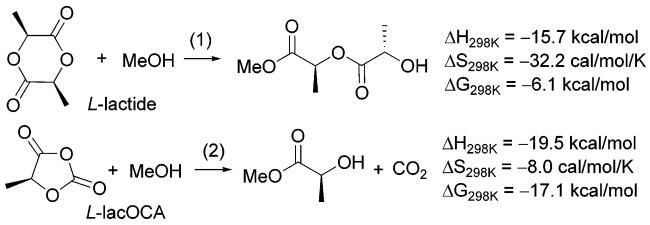
In the last three decades, biodegradable polymers have received increasing attention as resorbable biomaterials as well as commodity thermoplastics. Thanks to their biodegradability, biocompatibility, and ready availability from inexpensive renewable resources, polylactides (PLAs) occupy a forefront position.[1] PLAs can be directly prepared from lactic acid by polycondensation under azeotropic distillation conditions, but ring-opening polymerization (ROP) of lactide is usually preferred since it gives access to higher molecular weights and lower polydispersities and allows for the preparation of block copolymers. In this context, numerous metallic and organic derivatives have been investigated over the last 15 years as promoters for the ROP of lactide, and spectacular improvements have thereby been achieved in terms of activity, productivity, and stereocontrol.[2]

Due to the presence of two planar ester moieties within a skew-boat conformation,[3] lactide is among the rare examples of polymerizable six-membered rings. However, the relief of ring strain, which provides the driving force for the ROP, remains modest so that highly active promoters are required if the ROP of lactide is to be proceeded under mild conditions.[4] Associated drawbacks are the typically high sensitivity of the promoters and significant amounts of undesirable transesterification reactions. In order to circumvent these limitations, activated equivalents of lactide would be highly desirable.[5] Since α-lactones themselves are far too reactive to be used practically as monomers,[6] we turned our attention to synthetic equivalents thereof. In this regard, the readily available[7] 1,3-dioxolane-2,4-diones, so-called *O*-carboxyanhydrides (OCAs), that proved to be rather reactive for the derivatization of alcohols[7e,8] were considered as promising candidates.[9] Here we report that the organocatalyzed ROP of lacOCA is indeed a competitive route, giving access to PLAs of controlled molecular weights and narrow polydispersities under particularly mild conditions.[10]

As a preliminary assessment of the relative reactivity of lactide and lacOCA, the reactions 1 and 2 modeling the propagation step of the ROP were computationally investigated. The polymerization of lacOCA was predicted to be thermodynamically much more favorable than that of lactide, the liberation of a CO_2 molecule being a considerable driving force for both enthalpic and entropic reasons (Scheme 1).

Taking into account the biomedical interest of PLAs, special interest has been devoted over the last 5 years to metal-free synthetic methods using nucleophilic,[11] cationic,[12] or even, more recently, bifunctional[13]organocatalysts as well as enzymatic approaches.[14] In this context, we turned our attention to nucleophilic monomer activation and chose DMAP as a readily available organocatalyst

Scheme 1



that proved to be only moderately active toward lactide.[11a] As a control experiment, polymerization of L-lactide in 0.75 M dichloromethane solution required heating at 35 °C for 4 days to reach 93% monomer conversion for a monomer/initiator(*neo*-pentanol)/catalyst ratio of 10/1/1. In comparison, L-lacOCA[7c] was found to be extremely rapidly polymerized in the presence of *neo*-PentOH/DMAP, complete conversion being achieved in 5 min at room temperature for a related M/I/catalyst ratio of 20/1/1. Having established the much higher polymerizability of L-lacOCA relative to that of L-lactide, we then investigated the controlled character of the polymerization.

The quantitative incorporation of the protic initiator in the resulting PLAs was first demonstrated by ^{1}H NMR spectroscopy and electrospray-ionization mass spectrometry (Figures S1 and S2). Variation of the monomer/initiator ratio from 10 to 600 led to PLAs with molecular weights up to 60 000 g/mol, the degree of polymerization (DP_{NMR} determined by ^{1}H NMR) closely matching the monomer feed (Table 1). The controlled character of these nucleophilic polymerizations was clearly evidenced by the plots of DP_{NMR} versus monomer conversion and monomer to initiator ratio (Figure 1). The polydispersities are fairly low (<1.3) up to high monomer conversion, and even after prolonged reaction time, they demonstrate that undesirable transesterification reactions did not occur to a significant extent.

The living character of the polymerization was further supported by a second-feed experiment. A PLA with $M_n = 5125$ g/mol and $M_w/M_n = 1.13$ was first prepared by complete polymerization of 50 equiv of L-lacOCA with *neo*-PentOH/DMAP (1/1). Polymerization was then restarted by subsequent addition of 50 equiv of L-lacOCA to afford a PLA with $M_n = 10\,400$ g/mol and $M_w/M_n = 1.14$ (Figure S4).

From a mechanistic viewpoint, the rather acidic character of the α-proton of OCAs[7e] suggests that DMAP may act as a base rather than a nucleophile. However, no detectable amount of epimerization of the stereogenic carbon atom could be observed by homonuclear decoupled ^{1}H NMR spectroscopy (Figure S5). We therefore postulate that the polymerization of lacOCA proceeds via monomer activation by nucleophilic attack of DMAP at the more electrophilic

[†] Université Paul Sabatier.
[§] Universidad del País.

10.1021/ja067046y CCC: $33.50

Table 1. DMAP-Catalyzed Polymerization of L-lacOCA[a]

run	initiator	$[M]_0/[I]_0$	time[b]	DP_{NMR}[c]	M_{nSEC}[d]	M_w/M_n[d]
1	*neo*-PentOH	11	<5	10	1220	1.22
2	*neo*-PentOH	20	5	20	2110	1.20
3	*neo*-PentOH	100	90	97	11980	1.16
4	*neo*-PentOH	600	1140	592	62290	1.18
5	*i*-PrOH	20	5	21	2510	1.34
6	cholesterol	20	5	20	2610	1.21
7	2-BrEtOH	20	5	18	1870	1.17

[a] Polymerizations carried out with [L-lacOCA] = 0.9 M in CH_2Cl_2 at 25 °C with I/Cat = 1/1. Conversion >96% in all cases. [b] In minutes. [c] Measured by ^1H NMR. [d] Measured by GPC in THF using polystyrene standards.

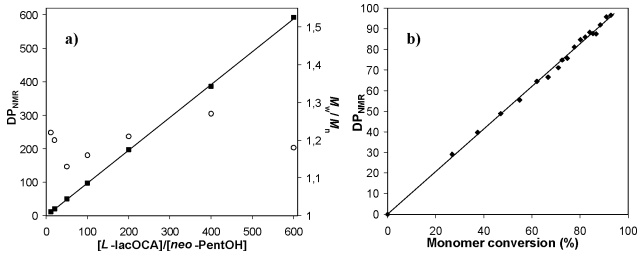
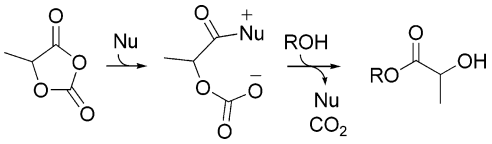


Figure 1. (a) DP_{NMR} (■) and M_w/M_n (○) versus $[L\text{-lacOCA}]_0/[neo\text{-PentOH}]_0$ ratio (CH_2Cl_2, 25 °C, $[I]_0/[Cat]_0 = 1$, $[M]_0 = 0.9$M). (b) DP_{NMR} versus L-lacOCA conversion (measured by ^1H NMR) ($CDCl_3$, 25 °C, $[M]_0/[I]_0/[Cat]_0$ 100/1/1, $[M]_0 = 0.9$ M).

Scheme 2



carbonyl group of lacOCA, followed by an exchange reaction with either the initiating alcohol or the growing polymer chain, and decarboxylation (Scheme 2).[15,16]

Notably, primary as well as secondary alcohols were shown to be convenient initiators without noticeable variations in the polymerization time and control (Table 1). The much higher reactivity of L-lacOCA compared to that of L-lactide and the ensuing milder polymerization conditions should broaden the scope of compatible initiators to include functionalized ones. As a representative example, a PLA oligomer featuring a β-brominated ester end group was efficiently prepared initiating the polymerization of 20 equiv of L-lacOCA with 2-bromoethanol (entry 7). In marked contrast, the related DMAP-catalyzed polymerization of L-lactide required 5 days at 35 °C to reach 93% monomer conversion and was contaminated with a significant amount of pyridinium salt formation (up to 30%) (Figure S6).

In conclusion, the α-lactone equivalent lacOCA exhibits remarkable reactivity compared with lactide in nucleophile-catalyzed ROP. PLAs of controlled molecular weights and narrow polydispersities are typically obtained under mild conditions using DMAP and various protic initiators.[17] Due to their readily availability and high polymerizability, *O*-carboxyanhydrides are promising monomers for the preparation of tailored architectures derived from well-defined polyhydroxyacids.

Acknowledgment. Thanks are due to the CNRS, UPS, and ISOCHEM for financial support of this work. J. P. Senet and Y. Robin are warmly acknowledged for helpful discussions, as well as C. Claparols and E. Leroy for their assistance in MS analyses.

Supporting Information Available: Full computational and experimental details, Figures S1−S6, and Tables S1−S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA067046Y