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Well-controlled, zinc-catalyzed synthesis of low molecular weight oligolactides by ring opening reaction

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ABSTRACT

The paper describes a comparative study on a precise synthesis of short oligomers by ring opening polymerization of L-lactide (L-LA) with ZnL_2 (L = aminophenolate) or $Sn(Oct)_2$ (Oct = bis(2-ethylhexanoate)) as initiators and propargyl alcohol as a co-initiator. The oligolactide synthesis is much more efficacious in the presence of zinc initiator than in the case of tin compound. Moreover, under an appropriate molar ratio of zinc complex/LA/alcohol, the catalytic reaction can yield either oligomers or alkyl lactyllactates or alkyl lactates. DFT calculations concerning the 1:1 or 1:2 complexes of methyl lactyllactate with methanol reveals a selectivity mechanism of zinc complex towards one of these processes. As for the tin compound, it appears not selective towards alcoholysis and hence oligolactide must always be accompanied by the formation of alkyl lactyllactate. Hence, when a low-molecular-weight oligomer constitutes a synthetic priority, quenching the reaction with hexanes or heptane is much more effective.

1. Introduction

Over the last few years, we have been able to observe the growing interest in biodegradable and biocompatible polyesters, such as polylactide (PLA) and poly(lactide-co-glicolide) (PLGA), mostly due to their pharmaceutical and biomedical applications [1–6]. High-molecular-weight PLA is required for most applications and is of great significance in commercial production. Usually, PLA is prepared industrially via the ring opening polymerization (ROP) of lactide (LA) with the use of bis(2-ethylhexanoate)tin(II) ($Sn(Oct)_2$) [5], although, for biomedical applications and green packages, ROP catalysts tailored around environmentally friendly, non-toxic metal complexes are regarded as more favorable. Such "single-site", well-defined initiators for the controlled ROP of cyclic esters have played a preponderant role in academic and industrial studies over the last decade [7–13].

Recently, the low-molecular-weight PLAs have received special attention in the field of medical application and as materials for molecular engineering. In particular, nanomedicine has provided a crucial impulse to the development of various types of drug-loaded carriers, based on biodegradable polymers. In these type of applications, a target material's biodegradation profile has to meet exactly the needs of the application [14–20]. Because active modifiers of polymers matrices need to be released before or during degradation of the carrier, a comprehensive study of the whole process has to take into account formation of oligomers. Furthermore, flexibility in the design of functionalized oligomers allows for the synthesis of a wide range of polymers with varying mechanical, biological and degradable properties to suit various applications. PLA-based biomedical materials present many advantages for drug delivery, but also some disadvantages like high cost of production and scaling-up difficulty.

Current methods to synthesize low-molecular-weight oligolactides mostly include iterative, direct condensation of lactic acid as shown in Scheme 1 [21].

Although short oligomers can be obtained by catalytic ROP of lactides, nevertheless, the use of these methods is relatively limited [22,23]. The alternative synthetic strategy to provide well-defined oligomers is for instance segmer-assembly polymerization (SAP) approach (or geometrical growth) but it is less efficient than ROP [24–26].

Our previous investigations concerning ROP of LA in the presence of inexpensive commercial catalyst $Sn(Oct)_2$ and hydroxyacetylene or alcohol derivatives of oxanorbornene as co-initiator revealed, that in the case of low-molecular-weight PLA, ROP could not be precisely controlled [27,28]. Alternative binary catalytic systems based on L_2M/ROH combination have been neglected in the

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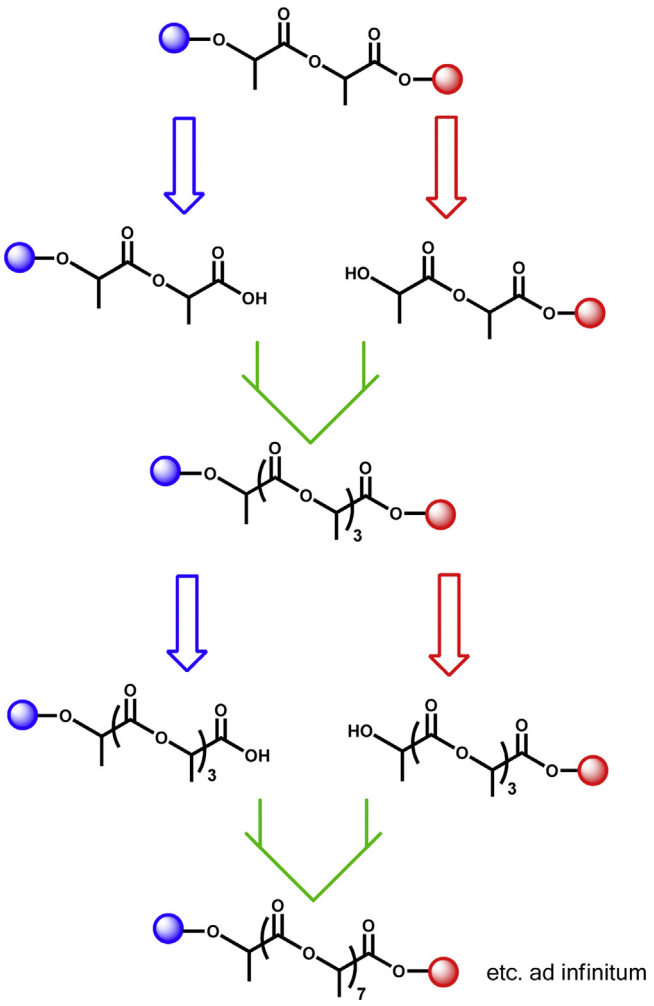

Scheme 1. Oligolactide formation from double protected lactid acid dimer.

field of ROP catalysts, but some of them might have the tendency to indicate selectivity towards polymerization or alcoholysis of lactides depending on reaction conditions. This dual display of ROP reaction has been observed for homoleptic metal complexes with N,O-donor ancillary ligands [29–31]. Such complexes, based on biologically benign metals as for instance magnesium and zinc could constitute a versatile class of catalytic systems well suited for the synthesis of polymers from high to ultra-low-molecular-weight and new macromonomers for classical ROP and SAP processes.

In this regard, it is crucial to take into consideration the optimum conditions of ROP reaction for polymers/oligomers/esters synthesis, while estimating catalysts. As part of the ongoing efforts aimed at rationalization of this approach and subsequent implementation of aminophenolate zinc complexes for the synthesis of oligolactides, we report here a non-iterative and well-controlled method for the preparation of oligolactide and ester macromonomers by the ZnL_2/ROH catalytic system and a comparison of this with the behavior of commercial $Sn(Oct)_2$.

2. Experimental

2.1. General

All the reactions and operations were performed under an inert atmosphere of N_2 using vacuum/nitrogen line or MBraun glove-box and standard Schlenk techniques unless stated otherwise.

Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX-300 and Avance-500 spectrometers using C_6D_6 or $CDCl_3$ as solvents. Chemical shifts are reported in parts per million and referenced to the residual protons in deuterated solvents. Molecular weights and polydisperisty indexes were determined by Gel Permeation Chromatography (GPC) using a Viscotek GPC max equipped with a refractive index detector Viscotek VE 3580 and 2×300 mm Shodex GPC 6 μm KF-802.5 columns. THF was used as the eluent at a flow rate of 1.0 mL/min at 30 °C. Polystyrene standards were used for calibration. HRMS analyses were conducted on an Apex-Qe Ultra 7 T instrument (Bruker Daltonics, Bremen, Germany) equipped with a dual ESI source and a heated hollow cathode dispenser. The instrument was calibrated with the Tunemix TM mixture (Bruker Daltonics). Analysis of the obtained mass spectra was carried out using a Data Analysis (Bruker Daltonics) software. The instrumental parameters were as follows: scan range, 100–1600 *m/z*; dry gas, nitrogen; temperature, 200 °C; potential between the spray needle and the orifice, 4.2 kV. Compounds dissolved in methanol were analyzed in the positive ion mode as $[M+Na]^+$ and $[M+K]^+$ ions.

2.2. Materials

(3*S*)-*cis*-3,6-dimethyl-1,4-dioxane-2,5-dione (L-LA) (98%; Sigma–Aldrich) was recrystallized twice from toluene, dried and sublimed under vacuum and stored in the fridge under an inert atmosphere of N_2. $Sn(Oct)_2$ and $ZnEt_2$ (1 M solution in hexanes) were purchased from Sigma–Aldrich and used as received. The ligand precursor N-[methyl(2-hydroxy-3,5-di-*tert*-butylphenyl)]-N-methyl-N-cyclohexylamine (L-H) and zinc complex ZnL_2 were prepared according to published procedure [31,32]. Tetrahydrofurane (THF) was distilled from CuCl, predried over NaOH, and then distilled from Na/benzophenone; toluene, benzene-d_6 (C_6D_6), and hexanes were dried under Na; CH_2Cl_2 was dried over P_2O_5; methanol was distilled from Mg; propargyl alcohol (PrgOH) was dried over sieves and distilled prior to use. Heptane (HPLC grade), methanol (HPLC grade), chloroform-*d* ($CDCl_3$) were used without prior purification.

2.3. Solution polymerization procedure

2.3.1. ***Me-5-PLA***

Representative procedure for zinc catalyst. The monomer L-LA (0.53 g, 3.7 mmol) and zinc complex (I) (0.54 g, 0.70 mmol) were dissolved in CH_2Cl_2 (20 mL) in a 50 mL Schlenk flask. Then MeOH (30 μL, 0.70 mmol) was added and the reaction was stirred at room temperature. After the reaction was completed (after ca. 30 min based on the conversion in ^1H NMR), the solution was concentrated in vacuum and an excess of hexanes was added. The white solid was filtered off, dried in vacuo, and dissolved/reprecipitated from CH_2Cl_2/hexanes to give target product which was dried under vacuum. The yield after reprecipitation was generally around 95%.

2.3.2. ***Me-7-PLA***, ***Me-10-PLA***, ***Prg-5-PLA***, ***Prg-7-PLA***, *and* ***Prg-10-PLA***

The syntheses were performed in the way analogous to that for **Me-5-PLA** with the use of L-LA/[I]/ROH in the appropriate ratio, e.g. 1/7/1 for **Me-7-PLA** or **Prg-7-PLA**.

2.3.3. *Me-5-PLA*

Representative procedure for tin catalyst. In a glove-box, $Sn(Oct)_2$ (0.07 g, 0.18 mmol) and 40 μL PrgOH (0.04 g, 0.7 mmol) were added as a toluene solution (1 mL) to a Schlenk flask containing the solution of L-LA (0.50 g, 3.5 mmol) in toluene (4 mL). The solution was removed from the glove-box and stirred at 70 °C under N_2