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# Organocatalytic chain scission of poly(lactides): a general route to controlled molecular weight, functionality and macromolecular architecture

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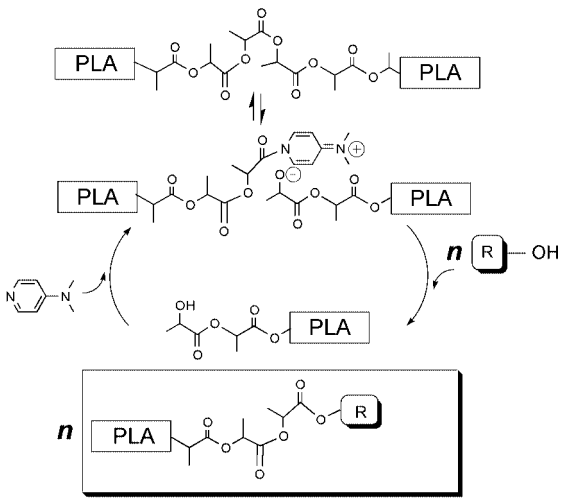
**A facile, single-step transesterification approach to poly(lactides) with controlled molecular weights and end-group functionality, as well as block and star-shaped architectures is described using nucleophilic amine catalysts.**

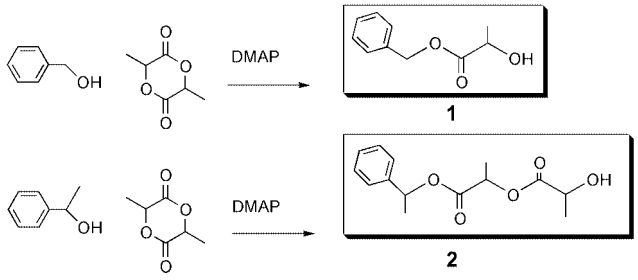
Tailor made bioresorbable polymers, particularly poly(lactide), are needed for a wide variety of biomedical applications and for controlled drug delivery media.[1] For many of these applications, molecular weight modification is accomplished by controlled chain-growth polymerization, *via* ring opening of the cyclic diester in the presence of a suitable organometallic promoter.[2–4] Another recognized procedure for the preparation of defined telechelic polymers involves the depolymerization of a high molecular weight polymer *via* metal catalysis *e.g.* the chain-end functionalization of poly(butadiene) by olefin metathesis.[5,6] Gross *et al.*[7,8] demonstated the versatility of lipase catalyzed transesterification and transacylation chain scission as a route to low molecular weight poly(ε-caprolactone) and block copolymers. In this communication, a new methodology of poly(lactide) (PLA) depolymerization is introduced as a general route to controlled molecular weight, end-group functionality and complex macromolecular architectures in a single step procedure using nucleophilic catalysts (Scheme 1). Nucleophilic catalysts (*i.e.*, tertiary amines, pyridines, imidazoles and tertiary phosphines)[9–12] have been shown to accelerate a wide variety of processes including the 'living' ROP of lactide, initiated from primary alcohols, in the presence of either 4-(dimethylamino)pyridine (DMAP) or 4-pyrrolidinopyridine (PPY).[13] The 'living' character is a manifestation of the rapid initiation and the weakly nucleophilic propagating species (secondary alcohol) that is active only to the cyclic diester monomer, precluding undesirable transesterification reactions. The new depolymerization strategy is based on a single transesterification reaction that should occur between a primary alcohol and poly(lactide), in the presence of DMAP to selectively cleave the PLA chain and produce an α-chain-end bearing the ester of the alcohol and a ω-chain-end having a secondary hydroxy, which is dormant to subsequent reactions (Scheme 1).




**Scheme 1** Depolymerisation cycle.

Model reactions were performed to demonstrate the selectivity of the DMAP catalyzed transesterification of primary alcohols with poly(lactide). Excess of either benzyl alcohol or α-methylbenzyl alcohol were reacted with lactide in the presence of DMAP in $CH_2Cl_2$ at 38 °C (Scheme 2). The lactide was ring-opened by the benzyl alcohol with the formation of the benzyl ester. However, quantitative transesterification of the diester ring-opened product, by the excess benzyl alcohol afforded the monoester, **1**.[14] Conversely, the α-methylbenzyl alcohol ring-opened lactide produced quantitatively the diester product with no evidence of adverse side reactions, **2**.[15] This data clearly demonstrates the susceptability of lactic acid derivatives towards selective transesterification with primary alcohols and confirms that secondary alcohols are dormant towards transesterification with the ring-opened products.

The feasibility of the organocatalytic chain scission of poly(lactide) was demonstrated with several modest molecular weight polymers, to discern the end-groups and molecular weight, including; poly(D,L-lactide) having an average DP of 120 and a polydispersity of 1.14 (**3**) and a poly(L-lactide) having an average DP of 88 and a polydispersity index of 1.06, **4**. In addition, two commercially available high molecular weight poly(L-lactides) (*M*n 50 000 g mol$^{-1}$, $M_w/M_n$ = 1.60, **5**, and $M_n$ 100 000, $M_w/M_n$ = 1.61, **6**) were also used to demonstrate the generality of the procedures. Various compositions of benzyl alcohol together with 2.5 equivalents of either PPY or DMAP were allowed to react in solution (36 °C, $CH_2Cl_2$) with **3**.[16] The size exclusion chromatography (SEC) data (Fig. 1) clearly shows a systematic decrease in the hydrodynamic volume with benzyl alcohol content. Consistent with the SEC results, predictable molecular weights, determined from end-group analysis ($^1$H-NMR), were obtained from the alcohol to polymer ratio, further demonstrating the versatility of the transesterification approach (**7–9**, Table 1). The $^1$H-NMR spectra clearly show the presence of the benzyl ester α-chain end and the ω-hydroxy chain-end.[13] The reactions were performed in either solution




**Scheme 2** Model compounds.

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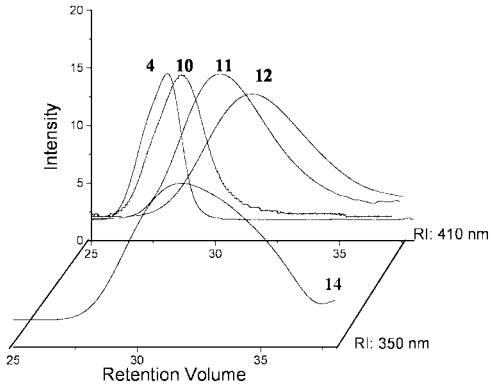


**Fig. 1** SEC chromatography.

(36 °C, $CH_2Cl_2$) or bulk (135 or 185 °C for the D,L- or L-lactide, respectively) in the presence of either PPY or DMAP. The low temperature solution reactions took between 2 and 4 days and were particularly sluggish in the case of DMAP, whereas the bulk reactions took only 15–30 min., irrespective of the catalysts. Notably, these procedures are general and applicable towards high molecular weight commercial poly(lactides) (samples **13**–**14**, Table 1). Pyrenebutanol was used as the nucleophile and the reaction was followed by SEC using a diode array UV detector, **11**, Fig. 1. This data clearly shows that the pyrene is statistically distributed throughout the sample, confirming the utility of the procedure as a general route to functional poly(lactides). The use of α-methylbenzyl alcohol as the nucleophile in the transesterification with poly(lactide) did not result in a molecular weight or end-group change.

The organocatalytic transesterification of poly(lactide) to novel macromolecular architectures and block copolymers is demonstrated by the use of pentaerythritol and monohydroxy functional poly(ethylene oxide) (PEO) oligomers that produced either star-shaped (**15**–**17**) or block polymers (**18**–**21**), respectively. The reactions were performed in bulk and, at these temperatures, the homogeneous mixtures allowed effective transesterification for both of the high molecular weight poly(lactide) samples investigated. In each case, the $^1$H-NMR spectra clearly show the resonances associated with the transesterification alcohol as well as the resonances associated with the hydroxy chain end, allowing molecular weight determination. In each case, the molecular weight of the polylactide was comparable to the alcohol-to-polymer ratio and the polydispersities were monomodal with no evidence of either of the homopolymers. These combined data clearly demonstrate the versitility of the organic catalyzed chain scission approach to functional poly(lactide) block copolymers and architectures in a single-step one-pot aproach.

**Table 1** Depolymerization of polylactide: reactivity of assorted alcohols

| Entry | PLA | Alcohol | Target DP | Exptl DP[e] | PDI[f] |
|---|---|---|---|---|---|
| **7** | **3** | $PhCH_2OH$[a,c] | 56 | 56 | 1.15 |
| **8** | **3** | $PhCH_2OH$[a,c] | 28 | 28 | 1.28 |
| **9** | **3** | $PhCH_2OH$[a,c] | 18 | 16 | 1.38 |
| **10** | **3** | $PhCH_2OH$[a,c] | 18 | 17 | 1.31 |
| **11** | **3** | Pyrenebutanol[b,c] | 18 | 13 | 1.28 |
| **12** | **4** | Pyrenebutanol[a,d] | 22 | 18 | 1.30 |
| **13** | **5** | $PhCH_2OH$[a,d] | 110 | 95 | 1.25 |
| **14** | **5** | $PhCH_2OH$[a,d] | 18 | 10 | 1.35 |
| **15** | **5** | Pentaerythritol[a,d] | 50 | 48 | 1.65 |
| **16** | **5** | Pentaerythritol[a,d] | 25 | 16 | 1.26 |
| **17** | **5** | Pentaerythritol[a,d] | 10 | 6 | 1.21 |
| **18** | **5** | PEO[a,d,g] | 100 | 78 | 1.55 |
| **19** | **5** | PEO[a,d,g] | 40 | 31 | 1.61 |
| **20** | **6** | PEO[a,d,g] | 180 | 160 | 1.67 |
| **21** | **6** | PEO[a,d,g] | 58 | 55 | 1.60 |

[a] PPY. [b] DMAP. [c] $CH_2Cl_2$, 38 °C. [d] Bulk, 135 °C. [e] DP = degree of polymerization, experimentally measured by end group analysis from $^1$H NMR spectroscopy. [f] PDI = polydispersity index, experimentally measured by gel permeation chromatography. [g] $M_w$ = 2000 g mol$^{-1}$, monohydroxy terminated.

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14 In a glove box, DL-lactide (1.0 g, 6.94 mmol) and DMAP (1 eq. to the DL-lactide, 0.848 g, 6.94 mmol) was added to a round bottom flask. An excess of benzyl alcohol (10 eq. to the DL-lactide, (7.18 ml, 0.069 mmol) was charged together with $CH_2Cl_2$ and the reaction flask was slowly heated to 35 °C (5 h). The product was isolated by flash chromatography (90% dichloromethane–10% ethyl acetate). $^1$H-NMR (acetone-$d_6$) $\delta$ = 1.34 (d, 3H, -$CH_3$), 2.05 (s, H, -OH), 4.30 (q, H, -CH-), 5.16 (s, 2H, -$CH_2$-), 7.40–7.30 (m, 5H, $C_6H_5$-). $^{13}$C-NMR (acetone-$d_6$) $\delta$ = 175.4, 137.3, 129.3, 128.9, 128.8, 67.6, 66.8, 20.8.
15 In a glove box, the DL-lactide monomer (1.0 g, 6.94 mmol) and the DMAP (1 eq. to the DL-lactide, 0.848 g, 6.94 mmol) were added into a round bottom flask. An excess of α-methylbenzyl alcohol (10 eq. to the DL-lactide, 8.36 ml, 0.069 mmol) was added under nitrogen and the reaction flask was slowly heated to 35 °C. The reaction was followed by TLC and $^1$H-NMR. After completion the reaction mixture was separated by flash chromatography (80% hexanes–20% ethyl acetate). $^1$H-NMR (acetone-$d_6$) $\delta$ = 1.34 (d, 3H, -$CH_3$), 1.44 (d, 3H, -$CH_3$), 1.54 (d, 3H, -$CH_3$), 4.30 (q, H, -CH-), 5.10 (q, H, -CH-), 5.87 (q, H, -CH), 7.30–7.40 (m, 5H, $C_6H_5$-). $^{13}$C-NMR (acetone-$d_6$) $\delta$ = 175.1, 170.3, 142.3, 129.3, 128.7, 126.7, 73.9, 69.7, 67.2, 22.4, 20.8, 17.1.
16 In a glove box, poly(D,L-lactide) (1.00 g, 0.0009 mol), DMAP (0.082 g, 0.00072 mol) and benzyl alcohol (0.039 g, 0.00036 mol) were charged into a round bottom flask and sealed with a septum. The transesterification reaction was allowed to proceed either in solution ($CH_2Cl_2$ 5 ml, 38 °C, 3–4 days) or in bulk (135 °C, 30 min.). $^1$H-NMR (acetone-$d_6$) $\delta$ = 1.46–1.56 (d, poly -$CH_3$), 4.15–4.29 (q, H, -$CH_2$-), 5.05–5.28 (q, poly -$CH_2$-), 7.3–7.4, (5H, $C_6H_5$).