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Challenging activated monomer ring-opening polymerization for direct synthesis of thiol end-functionalized polyesters

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ABSTRACT

A direct, non-enzymatic procedure for the synthesis of thiol-functionalized polylactones was developed and optimized by using 2-mercaptoethanol, the simplest unprotected thiol-containing initiator for cationic ring-opening polymerization, catalyzed by HCl and methanesulfonic acid in dichloromethane solutions. Thiol-functionalized polylactones with a molecular weight of up to approximately 5000 Da were obtained in a controlled manner. It was observed that acid can play the dual role of activator and initiator, and for the first time, it was shown that abundant HCl and/or ambient temperature lead to the formation of undesired α-carboxy-ω-chloro-functionalized polylactones that form in parallel with the targeted thiol-functionalized ones. A plausible pathway towards the formation of chlorinated products is proposed based on an active-chain-end mechanism, and the procedure was optimized to eliminate its contribution to the polymerization process, thus allowing for the activated-monomer mechanism to prevail. Molecular weight characterization was performed using ^{1}H NMR and size-exclusion chromatography. The results indicate that the polymers obtained under optimized conditions possess high SH functionality and moderate polydispersity, and that ring-opening polymerization proceeded in a controlled fashion. The proposed method allows for the preparation of metal free materials readily suitable for biomedical and/or electronic applications.

1. Introduction

Thiol-functionalized polymers are of special interest due to the unique properties of the thiol group, such as the ability to bind to metal substrates in both –SH [1] and –S–S– form [2] or to quantitatively couple with various reactive carbon–carbon double bonds [3], and thus has found applications in many areas of microtechnology, biotechnology and materials science [4,5]. Various indirect approaches have been explored to incorporate thiol functionality into polyesters, such as utilizing hydroxyl initiators bearing a protected thiol moiety. This approach allows for the use of metal catalysts for the ring-opening polymerization (ROP) of cyclic lactides or lactones, thus providing good control over molecular weight and functionality [6]. Alternatively, polyesters can be thiol end-functionalized by coupling with carboxylic acids possessing protected thiol [6,7] or disulfide moieties [8,9], followed by cleavage of the protective moiety. To eliminate the abovementioned multiple protection/deprotection steps, an ROP initiator containing a free thiol group could be used, allowing for thiol-functionalized polyesters to be readily obtained. To the best of our knowledge, attempts to use metal catalysts, namely $Sn(Oct)_2$ [10], $Sn(CF_3SO_3)_2$ [11], Bu_2SnO [12] or $[Bi(SCH_2CH_2OH)_2]^+$ [13,14] together with 2-mercaptoethanol (2-ME), have led to poor control over molecular weight distribution and/or low thiol functionality due to the undesired transesterification reactions involving a free thiol moiety and/or the formation of metal thiolates. Due to the chemoselectivity of lipase towards hydroxyl groups, direct enzymatic ROP provides better control over the thiol functionality in both direct and indirect approaches, with the latter allowing for the use of unprotected ω-mercapto carboxylic acids for end functionalization [15]. Thus, to date, only enzyme-catalyzed ROP has been reported to employ a free thiol-containing initiator for the direct incorporation of SH functionality into polyester chains. However, lipase-mediated polymerizations require the presence of a certain amount of water [16] that inevitably compromises quantitative initiation by mercaptoalcohol. Therefore, it would be interesting to further investigate non-enzymatic catalytic systems that will, on the one hand, be tolerable to SH groups and, on the other hand,

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allow for polymers with quantitative functionality and moderate polydispersity (PDI) to be obtained.

In this paper, we present a direct one-step process for synthesizing thiol-functionalized polyesters using 2-ME as an initiator of activated-monomer ROP [17] catalyzed by anhydrous HCl or methanesulfonic acid (MSA) in dichloromethane at 0 °C or ambient temperature. The drawbacks and peculiarities of the polymerization process are discussed, and a plausible mechanism for undesired parallel polymerization is proposed.

2. Experimental

2.1. Materials

All chemical materials were obtained from Aldrich unless specified otherwise. Dichloromethane (DCM), ε-caprolactone (CL), δ-valerolactone (VL) and triethylamine (TEA) were distilled over CaH_2 and stored under dry N_2 until use. All other chemicals were used as received. The assembled reaction system (round-bottom flask, three-way adapter and stir bar) was flame-dried under vacuum and refilled with dry Ar by several evacuation/refill cycles. All polymerizations were conducted at a monomer concentration of approximately 2 mol/L unless stated otherwise.

2.2. Techniques of analysis

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker Avance 400 and 500 MHz spectrometers; the solvent residual peak was used as an internal standard. Size exclusion chromatography (SEC) was carried out on a Varian liquid chromatograph equipped with an RI-4 refractive index (RI) detector and three SEC columns from TOSOH Bioscience (G6000H, G4000H, G2000H). THF containing 2–3 vol.% TEA (THF-TEA) was used as a mobile phase at a flow rate of 1 mL/min, and PS standards with molecular weights ranging from 800 to 800,000 g/mol were used for calibration. Differential scanning calorimetry (DSC) measurements were acquired by a TA Instruments Q100 DSC apparatus, using standard aluminum pans and scan rates of 10 °C/min between −80 and 80 °C. An indium standard was used to calibrate the instrument, and nitrogen was used as the purge gas. The melting temperatures (T_ms) were determined by their peak values, and the glass transition temperatures (T_gs) were identified by the peak maxima in the first-derivative curves.

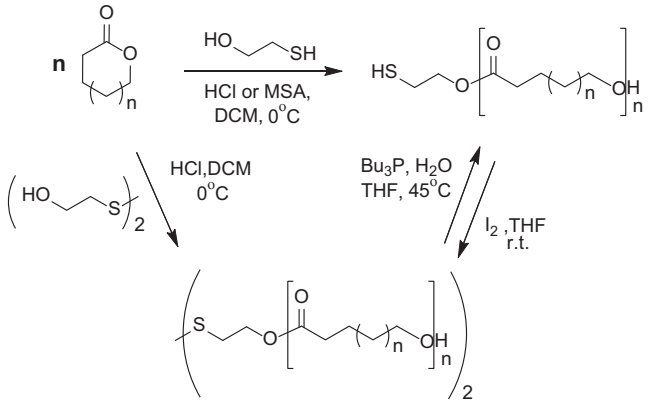
2.3. Synthesis of polymers

2.3.1. Direct synthesis of α-thiol-ω-hydroxy-terminated poly(ε-caprolactone) by $SnOct_2$

Calculated amounts of CL, 2-ME and tin octoate (Section S1) were sealed in a flask under vacuum and left stirring at 100 °C for 4 h. Then, the reaction mixture was slightly diluted with acetone and precipitated into a degassed ethanol/hexane mixture (1:1 v/v). To facilitate precipitation, the mixture was chilled (−20 °C), and the polymer was isolated by filtration, washed with degassed ethanol, and dried at 40 °C under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (*ppm*) 1.31–1.45 (2H, m, $CH_2CH_2CH_2$), 1.55–1.75 (4H, m, $CH_2CH_2CH_2$), 2.29 (2H, t, $CH_2CH_2C(O)O$), 2.70–2.77 (m, $HSCH_2$), 3.11 [t, $OC(O)SCH_2CH_2O$], 3.65 (t, terminal CH_2CH_2OH), 4.05 [2H, t, $CH_2CH_2OC(O)$], 4.16 [t, $OC(O)SCH_2CH_2O$], 4.18 [t, $HSCH_2CH_2OC(O)$].

2.3.2. Direct synthesis of thiol functionalized polylactones catalyzed by HCl or MSA (Scheme 1)

Calculated amounts of monomer, CL and/or VL, and 2-ME (Table 1) were either dissolved in a freshly prepared solution of HCl in DCM (0.16 or 0.04 M, Section S2) at 0 °C or dissolved in DCM, and the required amount of MSA was added. The reaction mixture was stirred at room temperature (r.t.) or at 0 °C for a prescribed time (Table 1), followed by precipitation into degassed ether. The obtained mixture was chilled to −20 °C, and the precipitation was filtered off, washed with degassed ether and dried at r.t. under vacuum.



Scheme 1. Direct and alternative routes towards thiol functionalized polylactones.

HS-PCL-OH, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.31–1.45 (2H, m, $CH_2CH_2CH_2$), 1.55–1.73 (4H, m, $CH_2CH_2CH_2$), 2.30 (2H, t, CH_2CH_2CO), 2.70–2.77 (tt, J = 5.2 Hz, $HSCH_2$), 3.64 (t, CH_2CH_2OH), 4.05 (2H, t, CH_2CH_2OCO), 4.19 (t, $HSCH_2CH_2OCO$).

HOOC-PCL-Cl, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.31–1.45 (2H, m, $CH_2CH_2CH_2$), 1.55–1.73 (4H, m, $CH_2CH_2CH_2$), 2.30 (2H, t, CH_2CH_2CO), 2.35 (t, $HOOCCH_2CH_2$), 3.53 (t, CH_2CH_2Cl), 4.05 (2H, t, CH_2CH_2OCO).

HS-PVL-OH, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.60–1.74 (4H, m, $CH_2CH_2CHCH_2$), 2.33 (2H, t, CH_2CO), 2.70–2.77 (tt, J = 5.2 Hz, $HSCH_2$), 3.64 (t, CH_2CH_2OH), 4.07 (2H, t, CH_2CH_2OCO), 4.19 (t, $HSCH_2CH_2OCO$).

HOOC-PVL-Cl, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.60–1.74 (4H, m, $CH_2CH_2CHCH_2$), 2.33 (2H, t, CH_2CO), 2.38 (t, $HOOCCH_2CH_2$), 3.53 (t, CH_2CH_2Cl), 4.07 (2H, t, CH_2CH_2OCO).

HS-P(CL-co-VL)-OH, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.32–1.43 (2H, m, $CH_2CH_2CH_2$), 1.55–1.75 (4 + 4H, m, $CH_2CH_2CH_2$ + $CH_2CH_2CHCH_2$), 2.23–2.36 (2 + 2H, t, CH_2CH_2CO), 2.70–2.77 (m, $HSCH_2$), 3.64 (t, CH_2CH_2OH), 4.00–4.12 (2 + 2H, t, CH_2CH_2OCO), 4.19 (t, $HSCH_2CH_2OCO$).

2.3.3. Alternative procedure for the synthesis of thiol-functionalized polylactones (Scheme 1)

Calculated amounts of CL and 2-hydroxyethyl disulfide (HEDS) (Table 1) were dissolved in a freshly prepared solution of HCl in DCM (0.04 M, Section S2) at 0 °C. The reaction mixture was stirred at 0 °C for a prescribed time (Table 1), followed by precipitation into degassed ether. The obtained mixture was chilled to −20 °C and the precipitation was filtered off, washed with degassed ether and dried at r.t. under vacuum.

(S-PCL-OH)$_2$, ^{1}H NMR (500 MHz, $CDCl_3$): δ_H (*ppm*) 1.30–1.45 (2H, m, $CH_2CH_2CH_2$), 1.55–1.73 (4H, m, $CH_2CH_2CH_2$), 2.29 (2H, t, CH_2CH_2CO), 2.91 (t, $SSCH_2$), 3.64 (t, CH_2CH_2OH), 4.05 (2H, t, CH_2CH_2OCO), 4.32 (t, $SSCH_2CH_2OCO$).

The abovementioned polymer was dissolved in THF, a threefold excess of tributylphosphine and a twofold excess of water [18], relative to the content of the disulfide moiety, were added, and the obtained solution was stirred at 45 °C for 3 h. The reaction mixture was precipitated into degassed ether and chilled to −20 °C; the precipitate was then filtered off, washed with degassed ether and dried at r.t. under vacuum. The ^{1}H NMR spectrum is identical to that of the product obtained by the direct synthesis route.