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# Communications to the Editor

## Thiol End-Functionalization of Poly(ϵ-caprolactone), Catalyzed by *Candida antarctica* Lipase B

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Polymers with thiol functionalities are of interest because of the special properties that the thiol group presents. Applications are found in many areas, such as microelectronics, biotechnology, and material science, where the thiol group for instance can self-assemble into monolayers on gold substrates.[1−5] To date, polymers with thiol functionalities are accomplished by tedious chemical routes.[6,7] Thiols have been introduced into polyesters by the use of the protection−deprotecting approach. A variety of functional groups have been introduced into polyesters by using *Candida antarctica* lipase B (CALB), for example, fatty acids, aromatic compounds, unsaturated compounds, and glycosides.[8−10] Earlier studies have shown that various lipases show chemoselectivity between alcohols and thiols.[11,12] In this paper we present direct routes to thiol-functionalized polymers by using the properties of CALB as a chemoselective catalyst. The benefit of using a chemoselective enzyme as catalyst was that protecting and deprotecting steps were unnecessary.

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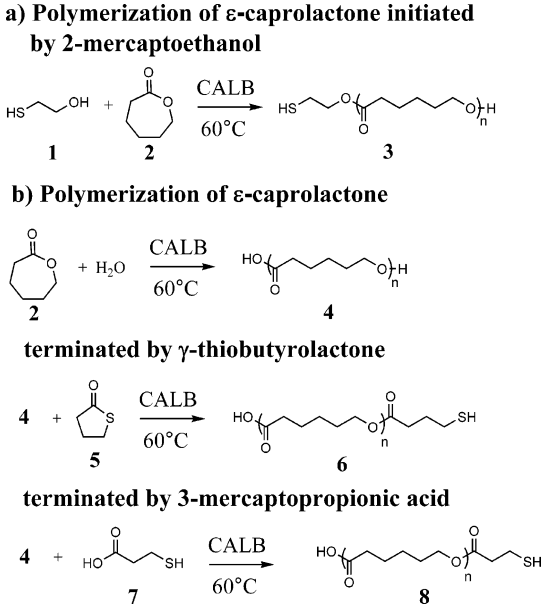
**Scheme 1. Thiol End-Functionalization of PCL**




**Results.** Thiol-functionalization of poly(ϵ-caprolactone) (PCL) was made by an initiation reaction catalyzed by *Candida antarctica* lipase B in bulk. 2-Mercaptoethanol (**1**) was used to initiate the enzyme-assisted ring-opening polymerization of ϵ-caprolactone (**2**) to give the desired thiol-functionalized polymer **3** (Scheme 1). The polymer was characterized by $^{1}$H and $^{13}$C NMR, IR, and GPC. The characteristic $^{1}$H NMR peaks of the repeating unit of PCL can be seen in Figure 1. The resonance for the methylene protons adjacent to the oxygen of 2-mercaptoethanol shifted from 3.71 ppm ($HSCH_2CH_2OH$) **1** to 4.20 ppm ($-CH_2OCO-$, i in Figure 1a) **3** upon incorporation. The proton from the free thiol group at the chain end of the polymer was observed in the NMR spectrum (g, Figure 1a), and the methylene protons closest to the thiol group (h, Figure 1a) were split into a doublet of triplets appearing as a quartet. The presence of the initiator in PCL was also confirmed

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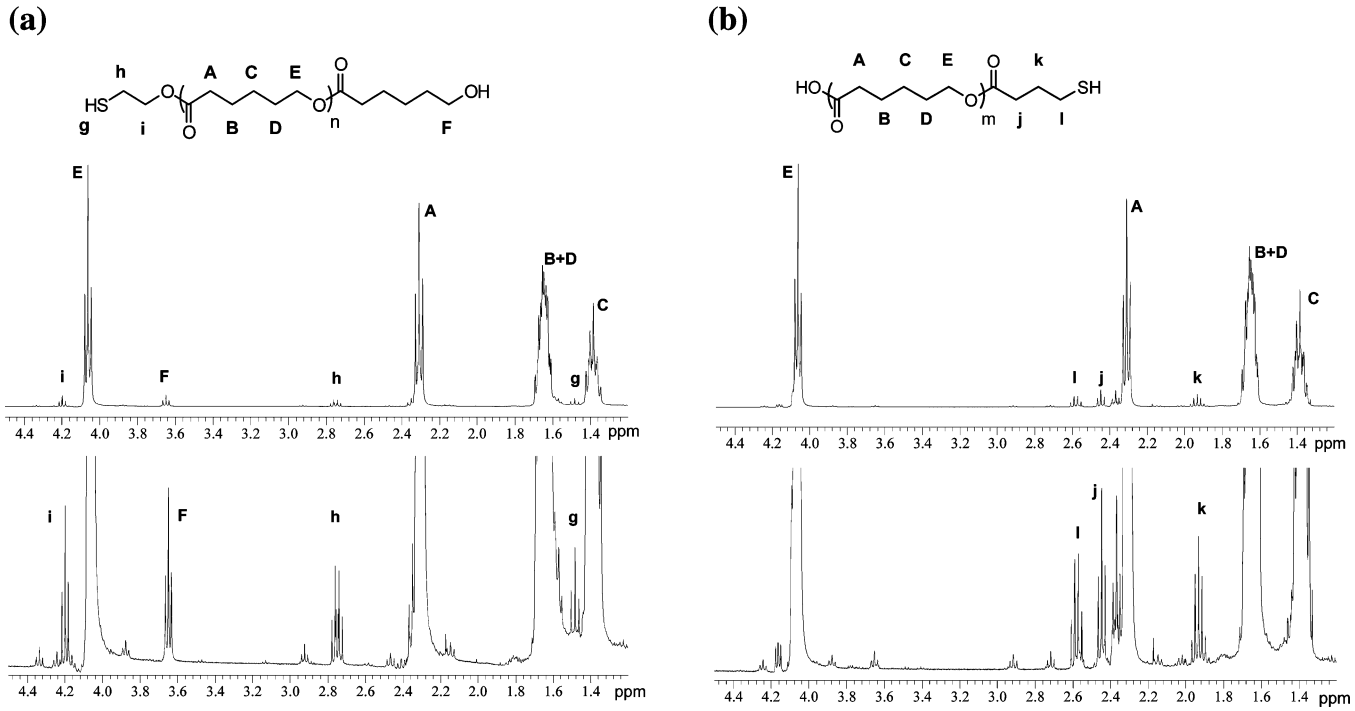


**Figure 1.** $^1$H NMR spectra of (a) 2-mercaptoethanol-initiated PCL and (b) $\gamma$-thiobutyrolactone-terminated PCL in $CDCl_3$. Enlargements of the whole area, 4.5−1.2 ppm, are found just under the main spectra for both (a) and (b).

**Table 1. Thiol End-Functionalization of PCL**

| polymer product | I or T[a] | I:M[a] | T:M | time (h)[b] | solvent[c] | polymers with −SH[d] (%) | $M_n$ (Da) NMR | $M_n$ (Da) GPC | $M_w/M_n$ (Da) GPC |
|---|---|---|---|---|---|---|---|---|---|
| **3** | **1** | 1:30 | | 24 | bulk | 70 | 3100 | 2940 | 1.42 |
| **6** | **5** | | 5:1 | 72 | MTBE | 90 | 2300 | 2070 | 1.82 |
| **8** | **7** | | 1:30 | 24 | bulk | 70 | 6900 | 6740 | 2.73 |

[a] I = initiator, T = terminator, M = monomer. Ratio in mol/mol. [b] Time for the end-functionalization reaction. [c] MTBE = methyl *tert*-butyl ether. [d] Fraction of the polymer that was thiol end-functionalized.

by $^{13}$C NMR (see Supporting Information). The product contained 70% thiol end-functionalized polymers as calculated by comparing the integrals of the peaks from the methylene protons adjacent to the thiol group, h, with the methylene protons at 3.65 ppm, F, next to the hydoxy-functional chain end. The remaining polymers were initiated by the thiol group of mercaptoethanol (10%) (4.34 ppm (t, 2H, $-SCH_2CH_2OH$), 2.92 ppm (t, 2H, $-SCH_2CH_2OH$)) or by water from the reaction system (20%).[13] Less than 1% of the esters in PCL were thioesters according to $^1$H NMR analysis. No thioesters were detectable in $^{13}$C NMR and IR analysis. The polymer product **3** had an average degree of polymerization of 27 repeating units and a $M_n$ of 3000 as detected by GPC and NMR (Table 1).

The thiol functionality was also introduced in the termination step. This was conducted by terminating PCL synthesis with $\gamma$-thiobutyrolactone or 3-mercaptopropionic acid using CALB as catalyst which resulted in polymer **6** and **8,** respectively (Scheme 1). The PCL chain was initiated by water from undried $\epsilon$-caprolactone present in the system and was allowed to grow for 24−72 h before addition of the terminator group. When $\gamma$-thiobutyrolactone was incorporated at the end of PCL giving the polymer **6**, the ring was opened and the resonance for the methylene protons closest to the sulfur shifted from 3.41 ppm ($-CH_2SCO-$) **5** to 2.58 ppm ($-CH_2SH$, l in Figure 1b) **6**. Of the product polymers, 90% were terminated by $\gamma$-thiobutyrolactone as calculated by comparing the integrals of the terminator protons (l, Figure 1b) and the methylene protons ($-CH_2OH$) at 3.65 ppm of the end hydroxyl groups of the unterminated polymer. The protons from the thiol were in this case coinciding with the peaks from the polymer chain (B + D, Figure 1b). Comparisons have been made with 3-mercaptopropionic acid where the thiol proton gave a triplet at 1.70 ppm. The doublet of triplets splitting from the adjacent methylene protons (l, Figure 1b) showed that the polymers had free thiol groups at the end. The structure of the terminated PCL was also confirmed by $^{13}$C NMR (see Supporting Information). Of all $\gamma$-thiobutyrolactone incorporated into the polymer, 90% were at the end of the polymer (j, k, and l in Figure 1b), while 10% were copolymerized with PCL as according to NMR, 2.91 ppm ($-CH_2SCO-$), 2.72 ($-CH_2CH_2CH_2SCO-$), and 2.04 ($-CH_2CH_2SCO-$). Less than 1% of the esters in PCL were thioesters according to $^1$H NMR analysis. No thioesters were detectable in $^{13}$C NMR and IR analysis. A high amount of $\gamma$-thiobutyrolactone compared to $\epsilon$-caprolactone monomer (5:1 mol/mol) was required to obtain a high degree of thiol-functionalized polymers. The reason is that CALB displays a lower specificity toward thioesters ($\gamma$-thiobutyrolactone in this case) than esters (PCL).[14] The high concentration of the terminal group and the presence of solvent is probably the cause of the relatively short polymers formed, with a $M_n$ of 2300 Da (Table 1). The reaction with $\gamma$-thiobutyrolactone as terminator was run with MTBE as solvent while the other two reactions were run in bulk $\epsilon$-caprolactone. It was empirically

found that dilution of the polymer increased the yield of the termination reaction. This was the reason why dilactones, visible in the spectra at 2.37 and 4.14 ppm (Figure 1b), were present since the chance of intramolecular deacylation increased.[15,16]

3-Mercaptopropionic acid as terminator resulted in the polymer **8** in a similar manner. The methylene protons adjacent the carbonyl in 3-mercaptopropionic acid shifted from 2.75 to 2.65 ppm when incorporated into the polymer. The quartet splitting of the methylene protons closest to the mercapto group showed that the thiol functionality was intact. 70% of the PCL was thiol end-functionalized (2.77 ppm (2H, q, $-CH_2CH_2SH$), 2.65 ppm (2H, t, $-CH_2CH_2SH$)), while 10% of the 3-mercaptopropionic acid was copolymerized with the PCL (3.11 ppm (2H, t $-CH_2CH_2SCO-$), 2.67 ppm (2H, m, $-CH_2CH_2SCO-$)).[17]

**Conclusions.** We present direct routes to thiol functional polymers by using the chemoselective *Candida antarctica* lipase B as catalyst. CALB easily initiates or terminates ring-opening polymerization of $\epsilon$-caprolactone using various nonprotected thiol compounds. The benefit of using a chemoselective enzyme as catalyst is that protecting and deprotecting steps are unnecessary.

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**Supporting Information Available:** Complete experimental description. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) All chemicals were purchased and of analytical grade. Novozyme 435 (CALB) was purchased from Aldrich. All solvents and chemicals were dried over activated molecular sieves, if not stated otherwise, and Novozyme 435 was equilibrated with saturated LiCl solution prior to use. All reactions were run with molecular sieves at 60 °C and shaking. They were stopped by filtering of the enzyme. The products were precipitated in dry ice cold methanol, and the polymers were filtered off and washed with dry ice cold methanol. The polymers were allowed to dry in a desiccator and analyzed by $^1H$ and $^{13}C$ NMR, IR, and GPC.
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