Synthesis of a Poly(ϵ-caprolactone) Monosubstituted First Generation Dendrimer by Lipase Catalysis

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Received June 29, 1998

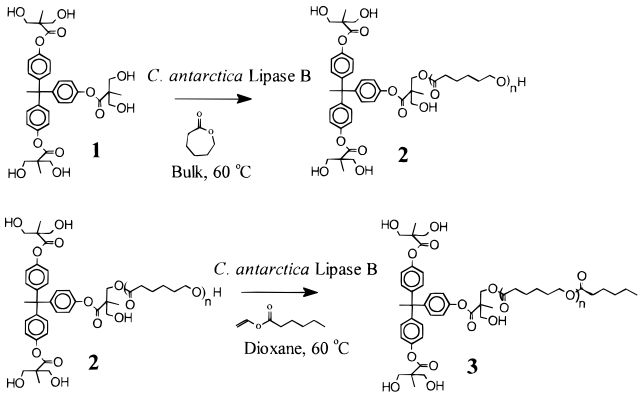
We report the synthesis of a poly(ϵ-caprolactone) (PCL) monosubstituted first generation dendrimer and the selective acylation of the hydroxyl end-group of the PCL chain by lipase catalysis.

Dendrimers are a new type of macromolecules characterized by a well-defined and highly branched layered structure with a multitude of chain ends.[1] Aliphatic polyester dendrimers based on 2,2-bis(hydroxymethyl)propanoic acid (bis-MPA)[2] are, for example, used as scaffolds in the synthesis of ferroelectric dendrimers[3] and as multifunctional initiators for stannous-2-ethylhexanoate ($Sn(Oct)_2$)-catalyzed ring-opening polymerization (ROP) of ϵ-caprolactone (ϵ-CL) to give controlled synthesis of branched macromolecules.[4]

The aliphatic polyester PCL and its copolymers are of great interest for applications in biological and biomedical areas due to their desirable properties of biodegradability, biocompatibility, and permeability.[5]

Lipase-catalyzed ROP of lactones is a special type of transesterification where no leaving group is released as a separate molecule. It has received increased attention over the past few years, and various polyesters can be produced by the choice of lactone and lipase.[6] *Candida antarctica* lipase B (CALB) is an efficient catalyst in the ROP of lactones[7] and regioselective in the acylation of carbohydrates.[8] Using glycosides as initiators for the ROP of ϵ-CL, CALB regiospecifically acylates the primary hydroxyl group.[9] CALB is also efficient in catalyzing the end-group functionalization of PCL.[10]

Scheme 1. ROP and Selective Acylation of the PCL End-Group



Our aim was to obtain a PCL monosubstituted first generation bis-MPA dendrimer using the hexahydroxy-functional dendrimer **1** (Scheme 1) as an initiator for the ROP of ϵ-CL. The high selectivity of lipase catalysis, in combination with lipase-catalyzed polyester synthesis, is an attractive alternative to poorly selective chemical catalysts.

The hexahydroxy-functional dendrimer **1**, with six equivalent hydroxyl groups, was synthesized according to a procedure developed by Hult et al.[2b,4a] The dendrimer-initiated ROP of ϵ-CL was performed according to Córdova et al.[9a,10] The ROP mechanism occurs in two steps. In the nonregioselective initial step, the Ser105[11] of the lipase will make a nucleophilic attack on ϵ-CL, and formation of an acyl-enzyme intermediate is achieved.[6a,7,9] The acyl-enzyme intermediate can then be deacylated by any of the six equivalent hydroxyl groups of **1** to form **2** ($n = 0$) (this deacylation could be stereoselective[12]). The second step, propagation step, was regioselective since the selectivity of the enzyme will decide whether the 6-hydroxy group or the bis-MPA hydroxyl groups of **2** ($n = 0$) will deacylate the acyl-enzyme intermediate. CALB was regioselective for the less sterically hindered 6-hydroxy group of **2**, and hence, a selective chain propagation occurred. The ROP in dioxane gave a low conversion of the dendrimer (20%) and cyclic PCL byproducts. Therefore, ROP was conducted in bulk (Scheme 1). Figure 1 shows a MALDI-TOF MS spectrum from a 24 h ROP of ϵ-CL (200 mg, 1.75 mmol), initiated by **1** (30 mg, 0.05 mmol) and catalyzed by CALB (10 mg).[13] The average M_w of the PCL substituted products was 2573 Da, with a polydispersity of 1.2 as determined by MALDI-TOF MS. 98% of **1** was converted to PCL substituted products[14] and >99% of the ϵ-CL was consumed.[15] There was a small amount of water initiated PCL, <5% of the consumed ϵ-CL, that

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(14) Determined by MALDI-TOF MS and TLC, as described in refs 7a and 10.

(15) Determined by GC as described in ref 9a.

10.1021/ja982252u CCC: $15.00
Published on Web 12/30/1998

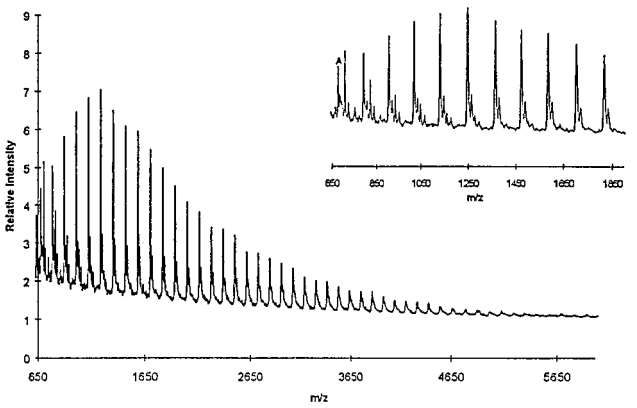

Figure 1. MALDI-TOF MS spectrum of the products from a 24 h bulk polymerization with a DHB matrix. The inset shows an expanded view of the 650−1860 Da region of the spectrum. **A** = remaining initiator **1**.

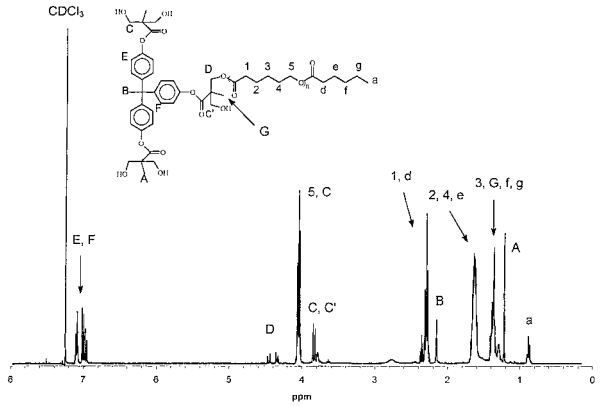

Figure 2. ^{1}H NMR (400 MHz) of a pure fraction of **3** (Scheme 1) in $CDCl_3$.

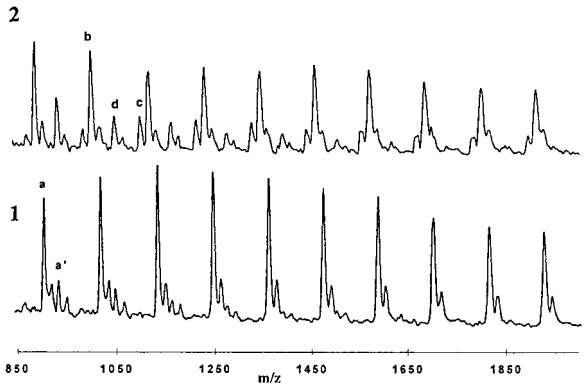

Figure 3. Spectra of the selective acylation of the products obtained in the bulk polymerization, catalyzed by *C. antarctica* lipase B. Spectrum 1 = 0 h. Spectrum 2 = 24 h. **a** = Na^+-cationized PCL substituted **1**. **a′** = Na^+-cationized linear PCL, **b** = Na^+-cationized monohexanoyl acylated **2** (Scheme 1), **c** = Na^+-cationized dihexanoyl acylated **2**, **d** = Na^+-cationized hexanoate terminated linear PCL.

was removed by flash chromatography.[9] MALDI-TOF MS registered detectable peaks from 768 to 6126 Da (corresponding to 1-mer and 48-mer, including the dendrimer end group), with a repeat unit of 114 Da. In this case, MALDI-TOF MS could not determine the degree of substitution of **1**, since the masses will be the same for a PCL hexa- to a PCL monosubstituted dendrimer with the same number of monomer units. Also, ^{1}H NMR analysis of the reaction mixture did not confirm the degree of substitution or whether it was a mixture of PCL mono-, di- or higher substituted dendrimers. However, ^{1}H NMR confirmed that **1** was partially substituted, since the aryl protons of the core molecule did not show two symmetrical doublets (Figure S1 in the Supporting Information.).[2a,4a,c]

^{13}C NMR was used to investigate whether both of the hydroxyl groups of the same bis-MPA unit of **1** had been acylated. The quaternary bis-MPA carbons of **1** in $CDCl_3$ are known to shift if they are di- (46.6 ppm), mono- (48.9 ppm) or nonsubstituted (49.5 ppm).[4a,4c,16] Only two peaks appeared in the spectrum at 48.9 and 49.8 ppm corresponding to PCL monosubstituted and PCL nonsubstituted bis-MPA units, respectively (Figure S2 in the Supporting Information.). This confirms the fact that only PCL monosubstitution of a bis MPA unit of **1** occurred. The selectivity of CALB was used once more to perform a selective acylation of the PCL hydroxyl end-group without further acylation of the bis-MPA hydroxyl groups of **2** (Scheme 1). Figure 3, spectrum 2, shows the result from a 24 h selective acylation of the reaction products from a bulk polymerization (spectrum 1) dissolved in dioxane. The acyl donor was vinyl hexanoate and peaks corresponding to mono- and dihexanoyl acylated products were detected (spectrum 2). The peak area ratio of mono- to diacylated products ($\sum a_{i\ \mathrm{mono}}/\sum a_{i\ \mathrm{di}}$) was 9:1 and 90% **3** (Scheme 1) was obtained.[17] The average M_w of **3** was 2345 Da, with a polydispersity of 1.3. MALDI-TOF MS registered detectable peaks from 888 to 6111 Da (corresponding to the 1-mer and 47-mer, including the dendrimer and hexanoic acid end groups), with a repeat mass of 114 Da. The diacylated products could either have been di-PCL substituted **1** or mono-PCL substituted **1**, where one of its five bis-MPA hydroxyl groups had been further acylated. MALDI-TOF MS confirmed that mono-PCL substitution had occurred, since the mass was different for **3** compared to the dihexanoyl acylated products. Figure 2, shows the ^{1}H NMR spectrum of a pure fraction of **3**. It can be seen that the PCL hydroxyl end group was acylated, since there is no corresponding triplet at 3.65 ppm with the same intensity as protons D.[4c,6c,7a,10] The area ratios of (E + F):D:B:A:a were 12:2:3:6:3 (12Ar*H*, CH_2, CH_3, 2CH_3, CH_3′) confirming the mono-PCL substitution of **1**.

In conclusion, selective monosubstitution of hydroxy-functional dendrimers, in combination with polyester synthesis, could be achieved by lipase catalysis. These products would provide numerous opportunities for further modification. The PCL hydroxyl end-group of **2** was selectively acylated by using *C. antarctica* lipase B as the catalyst and gave **3** in an overall yield of 85% from **1**. This synthetic strategy allows selective functionalization of **2**, and it can be used as a macromonomer to prepare various heteromultiarm block copolymer structures. Further studies in this regard are currently underway in our laboratory.

Acknowledgment. Novozym 435 was generously given by Novo Nordisk A/S, Denmark. Financial support from the Swedish National Board for Industrial and Technical Development is gratefully acknowledged.

Supporting Information Available: Experimental Section, Figures S1−S3 and C−H correlation spectrum of **3** (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA982252U

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(17) Estimated by using the peak area ratio of mono- to diacylated products ($\sum a_{i\ \mathrm{mono}}/\sum a_{i\ \mathrm{di}}$) and extrapolate to calibrated weight ratios, as described in refs 7a and 10.