# Direct Organocatalytic Chemoselective Synthesis of a Dendrimer-like Star Polyester

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ABSTRACT: We have developed a direct organocatalytic synthesis of a dendrimer-like star polyester. The synthesis was based on lactic acid-catalyzed bulk ring-opening polymerization (ROP) of $\epsilon$-caprolactone ($\epsilon$-CL) with the hexahydroxy-functional dendrimer 2,2-bis(hydroxymethyl)propanoic acid as the initiator. The polymerization was highly chemoselective, and the catalyst was readily recovered by precipitation of the polyester products. The reaction was performed without solvent and without the need of an inert atmosphere. In addition, the ROPs are operationally simple, inexpensive, and environmentally benign. Organic acid catalysis provides a new entry for the synthesis of valuable dendritic materials as well as polyesters for biomedical applications.

## Introduction

Aliphatic polyesters such as poly($\epsilon$-caprolactone) (PCL) and its copolymers are part of an important class of macromolecules for applications in biological and biomedical areas due to their desirable properties of biodegradability, biocompatibility, and permeability.[1] One commonly used synthetic strategy for preparing these macromolecules is ring-opening polymerization (ROP) of $\epsilon$-caprolactone ($\epsilon$-CL) and other cyclic esters. The ROPs can be performed with transition-metal-initiating compounds with high efficiency.[2] Another method for the synthesis of aliphatic biodegradable polymers is lipase-catalyzed ROPs.[3] More recently, methods based on metal-free organic catalysis for the ROP of cyclic ester monomers have been developed.[4−7]

Dendrimers are macromolecules characterized by a well-defined and highly branched layered structure with a multitude of chain ends.[8] Aliphatic polyester dendrimers based on 2,2-bis(hydroxymethyl)propanoic acid (bis-MPA)[9] are interesting as scaffolds for ferroelectric dendrimers,[10] may be used for biomedical applications, and work as initiators for valuable dendritic macromolecules.[11]

Asymmetric reactions that are catalyzed by small organic molecules have received increased attention in recent years.[12] In particular, the employment of nontoxic small organic molecules has the potential for allowing environmentally benign reaction conditions. Our previous investigations of enzyme-catalyzed ROPs[13] and synthetic transformations mediated by metal-free organic catalysts[14] intrigued us to more closely investigate the capability of small organic compounds to catalyze selective polymerizations. A previous study has shown that carbohydrate-functionalized PCL with high regioselectivity could be synthesized using L-lactic acid as catalyst.[15] A screening of different organic acids revealed that also citric acid and tartaric acid were efficient catalysts for homogeneous and heterogeneous ROPs.[1] On the basis of our previous experience in organic acid catalysis, we became interested in whether an organic acid could catalyze ROP with high chemoselectivity. Herein, we report the first organic acid-catalyzed chemoselective ROPs and synthesis of a dendrimer-like polyester. The reaction is outlined in Scheme 1.

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## Materials and Methods

**General.** Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques and dried either over $P_2O_5$ in a desiccator or over activated molecular sieves prior to use. The reactions were performed in dried glass tubes sealed with plugs containing activated drying agent. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040−0.063 mm); $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian AS 400. Chemical shifts are given in $\delta$ relative to tetramethylsilane (TMS), and the coupling constants $J$ are given in hertz. The spectra were recorded in $CDCl_3$ or $CD_3OD$ as solvent at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for $^1$H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for $^{13}$C NMR.

**GPC.** Samples were diluted in tetrahydrofuran to a concentration of 2 mg/mL and filtered through a 0.45 $\mu$m PTFE membrane prior to injection into the GPC system (Rheodyne 7125 injector, 20 $\mu$L sample loop, Waters HPLC pump 510, and a Waters 410 differential refractometer). The separation was accomplished by three columns connected in series (50, 100, and 500 Å, Ultrastyragel, Waters). Tetrahydrofuran was used as eluent at a flow rate of 1 mL/min. The GPC system was calibrated using polystyrene standards, 266−34500 Da (Machery Nagel). All GPC measurements were performed in duplicates.

**MALDI-TOF MS.** 10 $\mu$L of samples diluted to 10 mg/mL with THF were mixed with 40 $\mu$L of a matrix solution (50 mg/mL 2,5-dihydroxybenzoic acid dissolved in a one-to-one mixture of methanol and water). 0.5 $\mu$L of this solution was applied to the sample probe and inserted to the spectrometer (Hewlett-Packard G20205A LD-TOF) after removal of the solvent under reduced pressure.

*Preparation of Dendrimer* ***1***. The dendrimer was synthesized according to literature procedures.[9b,c] $^1$H NMR ($CD_3OD$): $\delta = 1.29$ (s, 9H), 2.14 (s, 3H), 3.71 (dd, $J = 10.5$, 5.4 Hz, 6H), 3.83 (dd, $J = 10.5$, 5.4 Hz, 6H), 7.02 (d, $J = 10.8$ Hz, 6H), 7.14 (d, $J = 8.4$ Hz, 6H). $^{13}$C NMR: $\delta = 16.9$, 30.4, 50.9, 51.3, 64.0, 121.3, 129.2, 145.8, 149.0, 173.6. MALDI-TOF MS: ($M + Na^+$): 677.43.

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**Scheme 1. Use of Hexahydroxy-Functional Compound 1 in the Synthesis of Dendrimer-like PCL 2 Catalyzed by L-Lactic Acid at 120 °C**

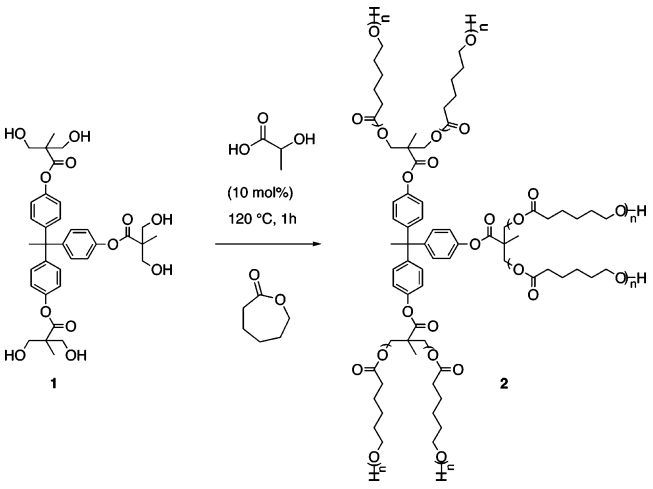



**Table 1. Catalyst Recycling of the L-Lactic Acid-Catalyzed ROP of ϵ-CL with 1 as the Initiator[a]**

| entry | recycle | yield (%)[b] | $M_w$[c] | PDI[c] |
|---|---|---|---|---|
| 1 | | 90 | 12 550 | 1.4 |
| 2 | 1st | 92 | 12 440 | 1.5 |
| 3 | 2nd | 96 | 10 800 | 2.1 |

[a] In a typical experiment, dendrimer **1** (0.05 mmol) and a catalytic amount of L-lactic acid (10 mol %) were dissolved in ϵ-CL (3.7 mmol) at 120 °C. After 1 h the reaction temperature was decreased to room temperature, and the polymer precipitated in cold MeOH to afford **2**. Next, the MeOH filtrate containing the L-lactic acid was removed under reduced pressure, and the ROP was repeated by addition of **1** and ϵ-CL. [b] Isolated yield of **2**. [c] Determined by GPC.

*Procedure for the* L*-Lactic Acid-Catalyzed Synthesis of* ***2***. Hexahydroxy-functional dendrimer **1** (30 mg, 0.046 mmol), L-lactic acid (33 mg, 0.37 mmol), and ϵ-CL (420 mg, 3.7 mmol) were mixed and heated to 120 °C under stirring. After 1 h reaction, all monomer had been consumed according to GPC. The polymer was purified by dilution with THF followed by precipitation in methanol to give a white powder. All spectroscopic data of **2** were identical to those previously reported.[11a,b] $^1$H NMR ($CDCl_3$): $\delta = 1.34$ (m, C$H_2$, PCL chain), 1.61 (m, C$H_2$, PCL chain), 2.26 (t, $J = 6.0$ Hz, C$H_2$CO, PCL chain), 2.21 (s, 3H, C$H_3$, dendrimer), 3.64 (t, $J = 5.0$ Hz, 12H, C$H_2$OH, PCL end group), 4.05 (t, $J = 5.2$ Hz, C$H_2$OR), 4.36 (bs, 12H, C$H_2$OR, dendrimer), 6.88 (d, $J = 6.9$ Hz, 6H, Ar*H*, dendrimer), 7.07 (d, $J = 6.9$ Hz, 6H, Ar*H*, dendrimer). $^{13}$C NMR: $\delta = 17.7$, 24.4, 25.4, 28.2, 32.2, 34.0, 46.6, 51.5, 62.2, 64.0, 65.1, 120.6, 129.6, 146.2, 148.6, 171.3, 172.7, 173.4.

*Chemoselectivity Test: Procedure for the Synthesis of PCL in the Presence of 2-(4-Hydroxyphenyl)ethanol.* 3.5 mmol of ϵ-CL, 0.1 mmol of 2-(4-hydroxyphenyl)ethanol, and tartaric acid (0.07 mmol, 2 mol % based on α-CL) were mixed and heated to 120 °C. The reaction was terminated after 24 h, and the crude was analyzed by NMR and GPC. $^1$H NMR ($CDCl_3$): $\delta = 1.38$ (m, C$H_2$, PCL chain), 1.69 (m, C$H_2$, PCL chain), 2.26 (t, $J = 6.0$ Hz, C$H_2$CO, PCL chain), 2.85 (t, $J = 7.2$ Hz, 2H, C$H_2$, initiator), 3.65 (t, $J = 6.6$ Hz, 2H, C$H_2$OH, PCL end group), 4.06 (t, $J = 6.6$ Hz, C$H_2$OR, PCL chain), 4.25 (t, $J = 6.9$ Hz, 2H, C$H_2$OR, initiator), 6.77 (d, $J = 8.5$ Hz, 2H), 7.06 (d, $J = 8.5$ Hz, 2H). $^{13}$C NMR: $\delta = 24.2$, 24.4, 25.2, 25.3, 27.9, 28.1, 32.1, 33.9, 34.0, 62.3, 64.0, 64.9, 115.2, 129.0, 129.7, 154.9, 173.3, 173.4.[17]

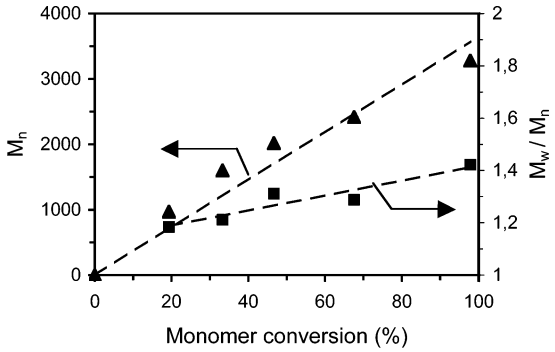



**Figure 1.** Bulk polymerization of ϵ-CL at 120 °C catalyzed and initiated by L-lactic acid. The molar ratio of ϵ-CL to L-lactic acid is 10 to 1.

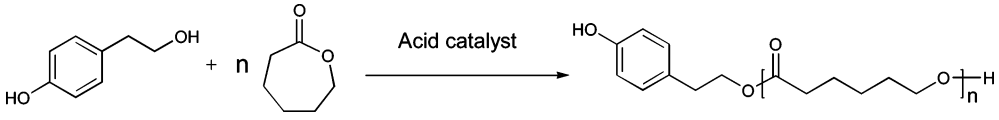
## Results and Discussion

**Preparation of Dendrimer-like PCL.** Having performed the screening of different organic acids (Table 1),[16] we decided to go forth with L-lactic acid as catalyst for the polymerization. The aryl ester function of **1** is, like any other ester, susceptible to hydrolysis or transesterification. L-Lactic acid has a higher p$K_a$ than the other promising candidates of the screening (citric acid and tartaric acid) and can therefore be expected to be less prone to mediate degradation at the aryl position during the course of the polymerization. In addition, L-lactic acid has demonstrated regioselective behavior toward multifunctional initiators like carbohydrates.[15] To demonstrate the versatile potential of this reaction system, the first-generation bis-MPA dendrimer **1** was employed as the initiator in the polymerization of ϵ-CL at 120 °C. After 1 h, complete monomer conversion had occurred as determined by GPC. After precipitation in cold methanol, the dendrimer-like polymer **2** was afforded in 90% yield. NMR analysis of **2** revealed that all of the hydroxyl groups of **1** had initiated the ROP of ϵ-CL. The polymer **2** had an average DP of 13 monomer units on each polymer arm as determined by NMR with a polydispersity index (PDI) of 1.48 and an average $M_w$ of 12 400 Da as determined by GPC. The GPC gave a slightly higher value than the NMR with respect to the polymer weight. Notably, no polymerization occurred at 120 °C, and **2** was not formed without the organic acid catalyst present.

In Figure 1, the dependence of monomer conversion on $M_n$ and PDI in a L-lactic acid-catalyzed ROP of neat ϵ-CL is shown. The relationship between $M_n$ and the monomer conversion is roughly linear, which could indicate a "living" polymerization mechanism. However, the PDI increases slowly as the reaction proceeds. Thus, transesterification reactions may occur.

**Chemoselective Polymerization.** We polymerized ϵ-CL in the presence of 2-(4-hydroxyphenyl)ethanol with tartaric acid as catalyst (Scheme 2). Tartaric acid is a more efficient catalyst, however, with a lower p$K_a$ and was chosen since no detrimental transesterification could occur. After 24 h, the $M_w$ and PDI of the 2-(4-hydroxyphenyl)ethanol initiated PCL was 10 300 Da and 1.49, respectively, according to GPC using 2 mol % catalyst. In comparison, a catalyst loading of 10 mol % furnished the corresponding PCL with a $M_w$ of 8900 Da. Thus, increased catalyst loading results in a decrease of the molecular weight

**Scheme 2. Polymerization of ϵ-CL Initiated with 2-(4-Hydroxyphenyl)ethanol Catalyzed by Tartaric Acid at 120 °C**



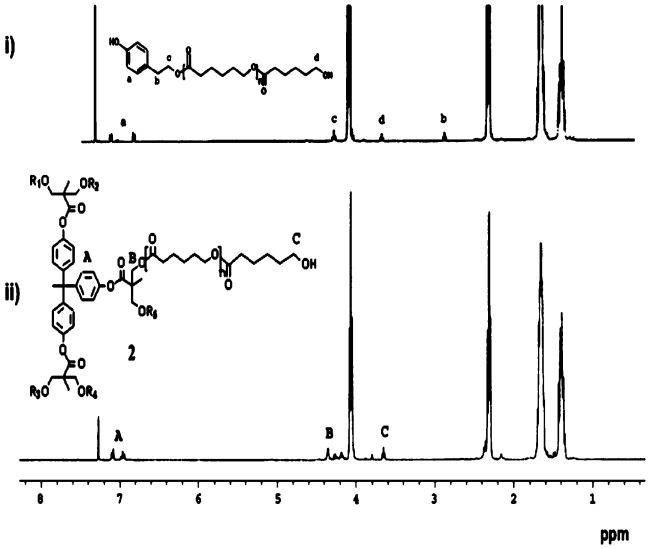



**Figure 2.** $^1$H NMR spectra of PCL initiated with (i) 2-(4-hydroxyphenyl)ethanol and (ii) bis-MPA. $R_n$ = PCL chains.

of the PCL. Notably, the polymers equipped with a free phenol group can be employed as macromonomers in polymerization reactions catalyzed by a peroxidase or some other oxidoreductase.[3] Hence, tailored three-dimensional macromolecules can be synthesized using this approach.

The NMR analyses of the polyester revealed that only the aliphatic hydroxyl of the initiator was involved in the reaction leaving the phenol group unaltered, as seen in Figure 2. The same chemoselectivity was observed when lactic acid was the catalyst. Thus, the organic acid catalyzed ROP reactions were highly chemoselective. In addition, the chemoselectivity in ROP reactions that are catalyzed by organic acids can account for the fact that no transesterification the aryl ester **1** was observed during the preparation of the dendrimer-like star polyester **2**. The NMR spectra of both polymers are shown in Figure 2. A small amount of lactic acid-terminated polyester can be seen in the lower spectra.

**Recycling of Catalyst.** Encouraged by these results, we investigated the sustainability of the catalytic system. Hence, we performed three consecutive reactions with the same lactic acid catalyst (Table 1).

We were able to synthesize the dendrimer-like PCL **2** in >90% yield each time without significantly decreasing the average $M_w$. If wanted, the organic catalysts can hence be reused in subsequent ROPs, making the methodology simple and inexpensive. However, the efficiency and the molecular weight decreased after two cycles due to some loss of catalyst as determined by NMR and MALDI-TOF MS. In Figure 3, a MALDI-TOF spectrum of the dendrimer **1** initiated reaction is depicted.

**Mechanism.** We found that the p$K_a$ of the α-hydroxy acids played an important role for the catalysis of the ROPs to occur, since neither propanoic acid nor hexanoic acid was able to catalyze the ROP and synthesis of **2**. It is suggested that the α-hydroxy acids act as Brønsted acids activating the ϵ-CL monomer by protonation of the carbonyl group. Next, the activated monomer is ring-opened in a nucleophilic attack by the aliphatic alcohol moiety of the initiator. The chain propagation of the growing PCL proceeds via the proton-activated monomer.[18] The seven-membered lactone ϵ-CL is more readily activated for initiation than the linear ester groups and aryl ester groups, explaining the high chemoselectivity and low transesterification of the PCL chain during the ROP. In addition, we found that the α-hydroxy acids

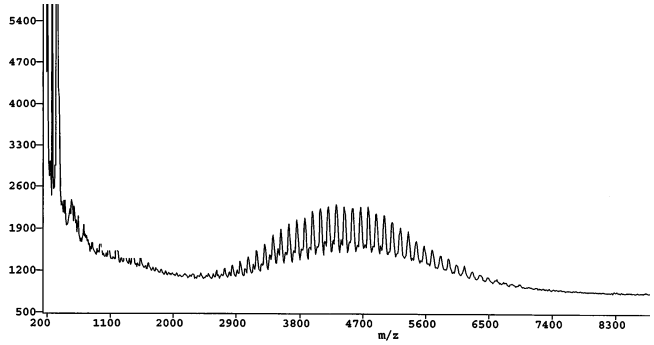



**Figure 3.** MALDI-TOF MS spectra of PCL initiated with dendrimer **1**.

were both the initiators and the catalysts for the ROPs of ϵ-CL in the absence of dendrimer **1** or another alcohol initiator. Thus, the α-hydroxy acid-catalyzed ROP can be autocatalytic by dual activation of the monomer by the hydroxy and acid moiety of the organic catalyst. In fact, dual proton activation is a strategy that is successfully employed in selective catalysis and polymer synthesis.[3,4c,19]

## Conclusion

In conclusion, we have developed a direct organocatalytic synthesis of dendrimer-like star polyester **2**. The synthesis was based on the L-lactic acid-catalyzed bulk ROP of ϵ-CL with dendrimer **1** as the initiator. The organic acid-catalyzed alcohol-initiated ROP of ϵ-CL was chemoselective. The products were isolated by precipitation of the polyester products in cold methanol, and the organocatalyst was readily recovered. In addition, the ROPs were performed without solvent and the need of an inert atmosphere. Furthermore, the organic acid-catalyzed ROPs were operationally simple, inexpensive, and environmentally benign. Importantly, metal-free organic acid catalysis has the potential to produce polymers that are nontoxic, owing to the absence of heavy metals in their synthesis and final product polymers. Hence, the polyesters obtained by our synthetic procedure would be suitable as biomaterials as well as microelectronics. The extension of α-hydroxy acid-catalyzed ROP to asymmetric versions and other cyclic monomers is under current investigation.

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