Direct Organocatalytic Ring-Opening Polymerizations of Lactones

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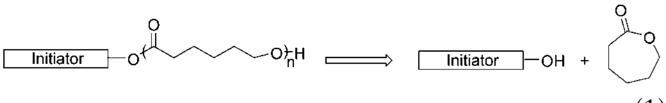
Abstract: We have developed a novel organocatalytic, direct synthesis of aliphatic polyesters. The synthesis was based on a novel direct organic acid-catalyzed living ring-opening polymerization (ROP) of ε-caprolactone and δ-valerolactone with benzyl alcohol as the initiator. The organic acid-catalyzed ROPs were performed without solvent and the catalyst was recovered by precipitation of the polyester products. In addition, they were operationally simple, inexpensive and environmentally benign. Organic acid catalysis provides a new entry for the synthesis of valuable biodegradable materials as well as polyesters for biomedical applications.

Keywords: lactones; organic acids; organic catalysis; polyesters; ring-opening polymerizations

The development of polymeric materials with tailored surface properties plays an important role in today's society. Essentially all devices and carriers contain different materials that have to be compatible with their surroundings. In addition, there is a need to develop chemistry that is based on renewable resources.[1]

Aliphatic polyesters such as poly(ε-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.[2] One of the most commonly used synthetic strategies for preparing these macromolecules is ring-opening polymerization (ROP) of ε-caprolactone (ε-CL) and other cyclic esters. The ROPs can be performed with transition metal initiating compounds with high efficiency.[3] However, removal of the metal contaminant, attached to the chain end, of the polymer products has to be considered prior to application as biomaterials and microelectronics. Another method for the synthesis of aliphatic biodegradable polymers is lipase-catalyzed ROPs.[4] More recently, nucleophilic amines and *N*-heterocyclic carbenes were utilized as catalysts for the ROP of cyclic ester monomers.[5]

Asymmetric reactions that are mediated by small organic molecules have received increasing attention in recent years.[6] The employment of non-toxic small organic molecules has the potential for allowing environmentally benign reaction conditions and sustainable chemistry. Based on our previous investigations of enzyme-catalyzed ROPs and synthetic transformations mediated by metal-free organic catalysts,[7,8] we became interested whether a small organic molecule would be able to catalyze ring-opening polymerizations in a similar fashion as an enzyme. In addition, retrosynthetic analysis suggested that we would be able to prepare end-group functionalized polyesters based on this process [Eq. (1)].



(1)

Hence, we embarked on the quest of developing biomimetic organocatalytic polymerizations. Herein, we report the novel organic acid-catalyzed living ROP of lactones.

In an initial screen of different organic acids, we found that several organic acids and amino acids were able to mediate the ROP of ε-CL with benzyl alcohol as the initiator affording poly(ε-caprolactone) (PCL, **1**) (Table 1).

We found that organic acids with pK_a values between 3 and 5 were able to efficiently mediate the benzyl alcohol-initiated ROPs of ε-CL furnishing PCL with an M_W of up to 2800 Da with a polydispersity index (PDI) of 1.3 as determined by proton NMR and MALDI-TOF analyses. The order of catalytic efficiency of the organic acid catalysts was: tartaric acid > citric acid > lactic acid > proline. For example, the reaction with tartaric acid was almost completed after 4 h (Table 1, Entry 7). The resulting PCL **1** was isolated by precipitation in cold methanol with an M_W of 2730 and a PDI of 1.3 and the tartaric acid catalyst was simply recovered from the filtrate by removal of the methanol under reduced pressure. In fact, the reaction could be recycled

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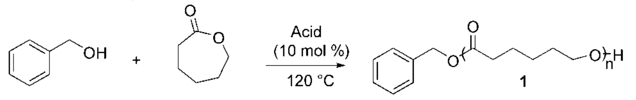
Table 1. Catalyst screen for the ROP of ε-CL.[a]



Entry	Acid	Time [h]	Conv. [%][b]	M_w[c]	PDI[d]
1	L-Lactic acid	2	32	1020	1.3
2	L-Tartaric acid	2	66	1704	1.3
3	Hexanoic acid	2	10	450	n.d.
4	Propionic acid	2	12	450	n.d.
5	L-Lactic acid	4	78	1590	1.3
6	L-Tartaric acid	4	90	2730	1.3
7	Glycine	4	<10	450	1.2
8	L-Proline	4	49	1248	1.2
9	L-Serine	4	<5	n.d.	n.d.
10	Citric acid	4	81	2502	1.3

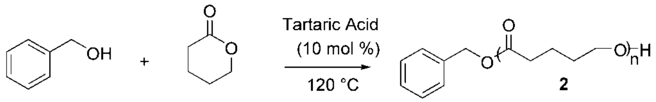
[a] In a typical experiment, the benzyl alcohol (3 mol %) and the corresponding acid (10 mol %) were dissolved in ε-CL at 120 °C. The ROP was quenched by decreasing the temperature to room temperature and precipitation of the crude polymer in cold methanol.

[b] Determined by NMR of the crude PCL product.

[c] Determined by NMR of the isolated PCL **1**.

[d] Determined by MALDI-TOF-MS or GPC of the crude PCL product.

up to two times using this methodology without decreasing the molecular weight of the PCL **1**. Moreover, no polymerization occurred without an organic acid catalyst under the set reaction conditions. We also investigated the possibility of using a six-membered lactone as the monomer, since several synthetically useful cyclic monomers are six-membered rings. Hence, benzyl alcohol (3 mol %) and tartaric acid (10 mol %) was dissolved in δ-valerolactone (δ-VL) at 120 °C [Eq. (2)]. After 7 h almost complete conversion had occurred as determined by NMR and the crude poly(δ-valerolactone) (PVL) was isolated by precipitation in cold methanol with an average M_W of 2608 Da.



(2)

A plot of molecular weight *versus* conversion for the ROP of ε-CL initiated from benzyl alcohol in the presence of tartaric acid is presented in Figure 1. There was a linear relationship between the molecular weight and conversion, which is consistent with a living polymerization. End-group and MALDI-TOF-MS analyses revealed that all the furnished PCL had a benzyl ester group. The PDI was between 1.29 and 1.35 for all points measured as determined by GPC. In addition, no transesterification occurred when PCL was heated together with benzyl alcohol and tartaric acid at 120 °C. Importantly, once quantitative monomer conversion was achieved no undesirable transesterification side reactions were evident. These combined data point to a living polymerization process.

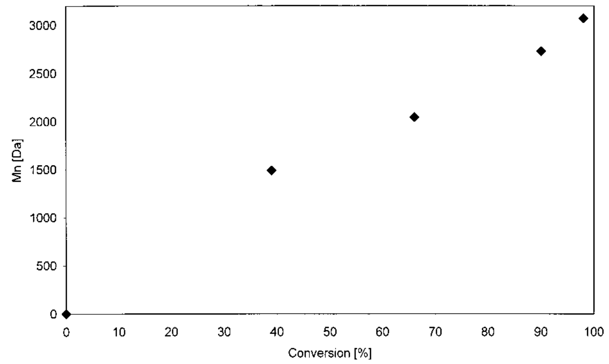


Figure 1. The linear relationship between M_n and conversion ($y=30.2+87$, $R^2=0.992$). The PDI was between 1.29 and 1.35 for all points measured as determined by GPC.

We also found that amino acids as well as tartaric and lactic acids were both the initiator and the catalyst for the ROP of ε-CL in the absence of an alcohol initiator. In this case, the ROP started *via* initiation from the α-amino or hydroxy group of the catalysts. The organic acid-catalyzed ROPs plausibly proceeded *via* a monomer activation mechanism. Initiation occurred when a nucleophile such as an alcohol reacts with the proton activated monomer to form the ring-opened mono ester adduct. The polymerization proceeded when the terminal hydroxy group of the growing polyester acted as a nucleophile towards the activated proton monomer. In fact, proton-activation is employed by several enzymes to mediate their specific transformations.[9] The organic acid-catalyzed ROP exhibited similar performance as the lipase-catalyzed ROPs. Hence, the organic acids may be considered as *micro*-lipases (serine-hydrolases) where the acid moiety together with the α-hydroxy group assisted in the ROP of the lactones.

In conclusion, we have reported the novel organic acid-catalyzed ROP of ε-CL and δ-VL. The living-polymerizations were efficiently mediated by tartaric acid, citric acid and lactic acid. The products were isolated by precipitation of the polyester products in cold methanol and the organocatalyst was 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 is not toxic and therefore the biodegradable polyesters obtained by our synthetic procedure would be suitable as biomaterials as well as for microelectronics. The mechanism of the organic acid-catalyzed ROP and the extension of this concept to asymmetric versions and other cyclic monomers are under current investigation.

Experimental Section

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), $Ce(SO_4)_2.H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ 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.

MALDI-TOF MS Analyses

10 μL of samples diluted to 10 mg/mL with THF were mixed with 40 μL of a matrix solution (50 mg/mL 2,5-dihydroxybenzoic acid dissolved in a one-to-one mixture of methanol and water). 0.5 μL 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.

General Procedure for the Organic Acid-Catalyzed Polymerizations and Synthesis of 1

Benzyl alcohol **1** (0.11 mmol), organic acid (0.37 mmol) and lactone (3.7 mmol) were mixed and heated to 120 °C under stirring. The ROP was quenched by decreasing the temperature to room temperature and the polymer was purified by dilution with THF followed by precipitation in cold methanol to give a white powder. PCL-**1**: ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (m, CH_2, PCL-chain), 1.61 (m, CH_2, PCL-chain), 2.26 (t, $J = 6.0$ Hz, CH_2CO, PCL-chain), 3.64 (t, $J = 5.0$ Hz, 2H, CH_2OH, PCL-end group), 4.05 (t, $J = 5.2$ Hz, CH_2OR), 5.11 (bs, 2H, $ArCH_2$ OR), 7.33 (m, 5H, ArH); ^{13}C NMR: $\delta = 24.7$, 24.8, 25.4, 25.7, 28.3, 28.5, 32.4, 34.3, 62.8, 64.3, 66.3, 128.0, 128.3, 128.7 148.6, 173.7.

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