

Rapid Communication

SYNTHESIS OF POLY(5,5-DIMETHYL-1,3-DIOXAN-2-ONE) BY
LIPASE-CATALYZED RING-OPENING POLYMERIZATION*

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Abstract Porcine pancreas lipase (PPL) and PPL immobilized on narrow distributed micron-sized glass beads were employed successfully for the ring-opening polymerization of 5,5-dimethyl-1,3-dioxan-2-one (DTC) for the first time. Different polymerization conditions such as enzyme concentration and reaction temperature were studied. Immobilized PPL exhibits higher activity than native PPL. Along with the increasing enzyme concentration, the molecular weight of resulting PDTC decreases. PPL immobilized on narrow distributed micron-sized glass beads has outstanding recyclability. For the third recycle time, immobilized PPL exhibits the highest catalytic activity and with high activity even after the fifth recycle time for the synthesis of PDTC. The $^1\text{H-NMR}$ spectra indicate that decarboxylation does not occur during the ring-opening polymerization.

Keywords Enzymatic polymerization, Immobilized enzyme, Ring-opening polymerization, Polycarbonates

INTRODUCTION

Ring-opening polymerization has been regarded as an efficient process for the synthesis of biodegradable high molecular weight polymers, such as polyesters, polycarbonates and polyphosphates. In view of the biomedical applications of these biodegradable polymers, the catalysts used in ring-opening polymerization are very important. The conventional chemical catalysts, such as organometallic catalysts used in polymerization required the monomer to be extremely pure and anhydrous conditions. Furthermore, the catalysts must be completely removed from the reaction products because of the potential toxicity of the trace remaining compounds. In recent years, enzymatic polymerization has become known as a new methodology of polymer syntheses and has been proven to be an efficient method to avoid the aforementioned restrictions, especially in the synthesis of biomedical polymer materials. Enzymatic ring-opening polymerizations of lactide^[1] and lactones with different ring size^[2] have been studied widely. In our previous papers, we have also reported the enzymatic ring-opening polymerizations of cyclic phosphates^[3,4]. Because the lipase immobilized on porous silica beads exhibits more attractive properties, especially improved thermostability^[4–6], we have been studying the use of immobilized lipase for the synthesis of other biodegradable and biocompatible polymers.

Polycarbonate is a kind of surface erosion biodegradable polymer material and has been used in drug controlled release system and other biomedical applications due to its good biocompatibility, favorable mechanical properties and elasticity^[7]. Up to now, poly(1,3-dioxanone)^[6], poly(5-methyl-5-benzoyloxycarbonyl-1,3-dioxanone)^[8] and their copolymers have been synthesized by enzymatic ring-opening polymerization. In this

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study, we employed PPL as such and PPL immobilized on narrow distributed micron-sized glass beads as the catalyst for the synthesis of poly(5,5-dimethyl-1,3-dioxan-2-one).

EXPERIMENTAL

Materials

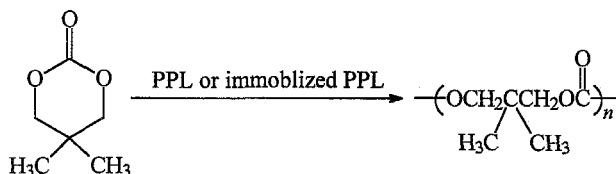
Porcine pancreas lipase (PPL) was purchased from Sigma with an activity of 198.90 units/mg protein (pH = 6.0, using olive oil as substrate) and used without further purification. Glass beads (1 μm , narrow distribution) were obtained from Dupont Co.. Immobilized lipase (IM-PPL) was prepared according to He^[4]. 5,5-Dimethyl-1,3-dioxan-2-one (DTC) was synthesized according to the literature^[9]. All other reagents used in this study were of analytically pure grade.

Measurements

Gel permeation chromatograph (GPC) was carried out on a Waters HPLC system equipped with a Model 2690D separation module, a Model 2410 refractive index detector (RI), and a Shodex K803 column. Chloroform was used as eluent at a flow rate of 1.0 mL/min. Waters Millennium³² module software was used to calculate molecular weights based on a universal calibration curve generated by narrow molecular weight distribution polystyrene standards. ¹H-NMR spectra were recorded on a Varian Mercury-VX 300 apparatus.

Enzymatic Ring-Opening Polymerization of DTC

Enzymatic ring-opening polymerization of DTC was carried out in bulk using PPL or immobilized PPL as the catalyst (shown in Scheme 1). A typical polymerization of PDTC with a M_n of 10,800 (entry 5 in Table 1) was carried out as follows. A mixture of DTC (200 mg) and immobilized PPL (7.66 mg, 3.83 wt%) was stirred in a dried and sealed bottle placed in a thermostated oil bath at 120°C for 24 h. The reaction mixture was dissolved in dichloromethane and the insoluble immobilized enzyme was removed by filtration. The dichloromethane was then evaporated under reduced pressure to obtain the polymer. Using dichloromethane as a good solvent and methanol as a poor solvent, the polymer was further purified by reprecipitation to give 188 mg of purified product (94%). The number average molecular weight (M_n) relative to polystyrene and the molecular weight dispersion as measured by GPC were 10800 and 1.61, respectively.



Scheme 1 Ring-opening polymerization of DTC by PPL or immobilized PPL

Enzymatic Ring-Opening Polymerization of DTC by Recycling Immobilized PPL

After thorough washing with dichloromethane and redistilled water in turn, immobilized PPL was dried in vacuo at 25°C for reuse in the following polymerization (shown in Table 2). The recycling polymerization reactions of immobilized PPL having a concentration of 3.83 wt% were carried out at 120°C for 24 h. The resulting polymers were treated as mentioned above.

RESULTS AND DISCUSSION

Enzymatic ring-opening polymerization of DTC was achieved in bulk at 120, 140 and 160°C after 24 h with M_n values ranging from 5,700 to 14,100 g/mol (shown in Table 1 and 2). PPL and PPL immobilized on narrow distributed micron-sized glass beads were both employed as the catalyst for ring-opening polymerization of DTC. The yields of the polymerization are all above 90%.

It was found that DTC was thermally oligomerized on heating to 160°C for 24 h in the absence of catalyst. However, both the MW and yield (< 30%) are much lower than those of the polymers obtained in the presence of PPL or immobilized PPL. This demonstrates that PPL and PPL immobilized on narrow distributed micron-sized glass beads actually catalyze the polymerization.

Table 1. Ring-opening polymerization of DTC with/without enzyme for 24 h

Entry	Enzyme	Enzyme (wt%)	<i>T</i> (°C)	<i>M_n</i>	<i>M_w</i> / <i>M_n</i>	Yield (%)
1	PPL	0.117	120	7000	1.57	90
2	PPL	0.596	120	6600	1.29	91
3	PPL	1.51	120	5700	2.23	90
4	IM-PPL	2.602	120	12300	1.53	92
5	IM-PPL	3.83	120	10800	1.61	94
6	IM-PPL	6.22	120	10100	1.54	90
7	IM-PPL	10.56	120	6200	1.25	91
8	IM-PPL	13.3	120	5800	2.04	90
9	IM-PPL	6.96	140	10400	1.52	90
10	IM-PPL	2.60	160	10500	1.60	91
11	–	–	160	<1500	–	26

Considering the *M_n* of resulting polymers, immobilized PPL has higher activity than that of native PPL. Different polymerization conditions such as enzyme concentration and reaction temperature were studied. Enzyme concentrations play an important role in the enzymatic ring-opening polymerization. Along with the increase of enzyme concentration, the MW of PDTC obtained decreases. In addition, we would emphasize the recyclability of immobilized PPL for the ring-opening polymerization of DTC. In the third recycle time, the immobilized PPL exhibits the highest catalytic activity. Even in the fifth recycle time, the immobilized PPL still has an activity comparable with the original one. The excellent recyclability of immobilized PPL will be very useful for its industrial applications. The molecular structure of polymers was elucidated by ¹H-NMR spectra. No triplet at $\delta = 3.4$ (characteristic peak of an ether group) could be detected, which demonstrates that no decarboxylation occurred during the ring-opening polymerization. Further studies on the enzymatic ring-opening copolymerization of DTC and other cyclic monomers and also their applications in drug controlled release systems are currently underway in our lab.

Table 2. Ring-opening polymerization of DTC by recycling immobilized PPL

Recycle time	IM-PPL(wt%)	<i>t</i> (h)	<i>T</i> (°C)	<i>M_n</i>	<i>M_w</i> / <i>M_n</i>	Yield (%)
1	3.83	24	120	10800	1.61	94
2	3.83	24	120	10400	1.68	90
3	3.83	24	120	14100	1.84	92
4	3.83	24	120	10800	1.66	90
5	3.83	24	120	9800	1.59	91

CONCLUSIONS

Enzymatic ring-opening polymerization of 5,5-dimethyl-1,3-dioxan-2-one by PPL or immobilized PPL is reported. PPL immobilized on narrow distributed micron-sized glass beads not only has higher catalytic activity than native PPL, but also has excellent recyclability. Decarboxylation was not evidenced during propagation.

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