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Lipase-catalyzed synthesis of glycerol carbonate from renewable glycerol and dimethyl carbonate through transesterification

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Abstract

Glycerol carbonate is a key multifunctional compound employed as solvent, additive, monomer, and chemical intermediate. Enzymatic synthesis of glycerol carbonate from renewable starting materials (glycerol and dimethyl carbonate) was successfully achieved by immobilized lipase from *Candida antarctica* (CALB, Novozym 435). Addition of molecular sieves as scavenger for the removal of methanol, which was generated from dimethyl carbonate during the reaction, accelerated a reaction rate. After the optimization, the equimolar use of glycerol and dimethyl carbonate in the Novozym 435-catalyzed reaction yielded a glycerol carbonate with almost quantitative yield. The resulting glycerol carbonate from 60 °C reaction has shown the low enantiomeric excess (13% ee) as configuration of (*R*)-enantiomer.

Keywords: Glycerol; Glycerol carbonate; Lipase; *Candida antarctica*

1. Introduction

The utilization of glycerol has a significant role on biodiesel production since large amount of glycerol is obtained as a by-product of the plant oil methanolysis [1]. As a renewable and cheap raw chemical, the conversion processes of glycerol to useful materials have received increasing attentions, and recently several examples have been reported: acid-induced dehydration of glycerol to acrolein in supercritical water [2], glycerol oxidation to dihydroxyacetone and glyceric acid using carbon-supported gold catalysts [3], and 1,3-propanediol production by metabolic engineering approach [4].

Glycerol carbonate is a stable and colorless liquid that offers useful applications as a novel component of gas separation membranes, a surfactant component, a new solvent for several types of materials or a nonvolatile solvent in the paint industry, a component in coatings, and a component of detergents [5,6]. Also glycerol carbonate can be utilized as a source of new polymeric materials [7].

Only a few synthetic routes for glycerol carbonate have been described in literatures. The carboxylation of glycerol with carbon dioxide resulted in glycerol carbonate by Sn-catalyst [8], zeolites or ion exchange resins [9]. Although those catalytic conversions to glycerol carbonate need harsh reaction conditions, moderate yield of targeted product was obtained and another purification step using distillation was required.

In this study, we report the lipase-catalyzed synthesis of glycerol carbonate from glycerol and dimethyl carbonate in THF. Enzymatic synthesis in organic media has gained increasing attention due to the mild reaction conditions and high selectivity [10]. Dimethyl carbonate is being positioned as a green replacement for phosgene in the production of polycarbonates and polyurethanes. Up to our best knowledge, it is the first enzymatic example to synthesize glycerol carbonate. Immobilized lipase B from *Candida antarctica* (Novozym 435) was selected from various lipases through the screening of various commercially available lipases. Novozym 435-catalyzed synthesis provided quantitative yield of glycerol carbonate selectively under mild reaction conditions when equimolar amount of glycerol and dimethyl carbonate was used. In addition, the low enantiomeric

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excess of resulting glycerol carbonate was observed during this enzymatic reaction.

2. Materials and methods

2.1. Materials

Immobilized lipase B from *C. antarctica* (Novozym 435) was purchased from Novozymes (Denmark) and all other reagents and solvents were purchased from Sigma–Aldrich (USA) and used without further purification.

2.2. Instrumental methods

The ratio of glycerol, glycerol carbonate, dimethyl carbonate, methanol and other by-products in reaction mixture was determined by gas chromatography (DS6200, Donam Instrument, Korea) equipped with a flame ionization detector (FID) and a capillary column (Supelco 5, 30 m × 0.25 mm). The ee was determined by gas chromatography (M600D, Younglin, Korea) equipped with a flame ionization detector (FID) and a capillary column (Rt-βDEXsp^{TM}, 30 m × 0.25 mm, Restek). Diphenyl ether was added in the reaction mixture as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer FT-IR 2000. ^{1}H NMR spectra were recorded on a Bruker AMX-500 FT-NMR Spectrometer (Bruker Co., Germany) and ^{13}C NMR spectra were recorded on a Varian System 300 NMR Spectrometer.

2.3. Lipase-catalyzed synthesis of glycerol carbonate

In a 100 mL flask equipped with a magnetic stirrer, condenser and thermometer, glycerol (99%) (0.55 g, 6.0 mmol) and dimethyl carbonate (0.54 g, 6.0 mmol) was dissolved in THF (final volume: 12 ml). Into the reaction mixture were added lipase from *C. antarctica* (Novozyme 435 (0.30 g)) as a biocatalyst and molecular sieve 5 Å (2.0 g) as a scavenger of methanol. The reactions were carried out at various temperatures (40–80 °C) for 30 h. The reaction progress was monitored by GC analysis. After a reaction completion, reaction solution was centrifuged at 2000 rpm for 10 min to remove Novozym 435 and molecular sieves. Supernatant was evaporated under reduced pressure, and finally colorless liquid glycerol carbonate was obtained. We examined the enantiopurities of glycerol carbonate obtained from the reaction at 60 °C by GC (Rt-βDEXsp^{TM}). The enantiomeric excess of the resulting glycerol carbonate was observed as configuration of the (*R*)-enantiomer with 13% ee ($[\alpha]^{25}_D$ −7.8 (*c* = 1.0, Dioxane)).

Table 1
Lipase-catalyzed synthesis of glycerol carbonate (**4**) using various lipases[a]

Entry	Lipase	Conversion (%)[b]
1	Novozym 435 (*Candida antarctica* lipase B)	100
2	Novozym 735 (*C. antarctica* lipase A)	0
3[c]	Lipase RM IM (*Mucor miehei* lipase)	0
4[c]	CRL (*Candida rugosa* lipase)	15
5	PFL (*Pseudomonas fluorescence* lipase)	0
6	CCL (*Candida cylindracea* lipase)	0
7	ANL (*Aspergillus niger* lipase)	0
8	PCL (*Pseudomonas cepacia* lipase)	0

[a] Reaction conditions: **1** (6.0 mmol), **2** (6.0 mmol), lipases (0.3 g) and molecular sieves (2.0 g) in THF (12 ml) were shaken at 60 °C for 30 h.
[b] Determined by GC.
[c] Less 1% of unknown product was observed on GC.

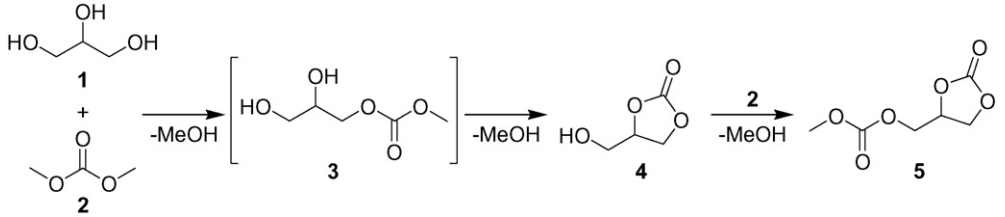
^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 5.29 (t, 1H, O*H*), 4.81–4.76 (m, 1H, C*H*), 4.48 (dd, 1H, OCH_2), 4.28 (dd, 1H, OCH_2CH), 3.65 (ddd, 1H, CH_2OH), 3.50 (ddd, 1H, CH_2OH); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.7, 77.8, 66.6, 61.6; MS (*m*/*z*) 118.4 (M^+).

3. Results and discussion

3.1. Screening of lipase for the synthesis of glycerol carbonate

We have developed a convenient lipase-catalyzed method for the synthesis of glycerol carbonate (**4**) from glycerol (**1**) and dimethyl carbonate (**2**) using Novozym 435. Firstly, all available lipases were screened for investigating the activity for the production of **4**. As shown in Table 1, most of lipases rarely produced the targeted compound **4**, while Novozym 435 showed high catalytic activity (Table 1, entry 1). During the reaction performed by lipase RM IM and CRL, unknown intermediate was observed by GC, but failed to be isolated.

Between two types of hydroxy group in glycerol, two primary alcohols are presumably more reactive than a secondary hydroxy group. Therefore, intermediate **3** might be formed at the first step, and subsequently the formation of product **4** occurs through the intramolecular conversion (Scheme 1). After the 30 h reaction by Novozyme 435, reaction mixture was filtered to remove Novozym 435 and molecular sieves, and evaporated to yield colorless liquid. Since the liquid was shown as an almost single peak on GC, ^{1}H NMR was employed to determine the chemical structure. Fig. 1 shows clear characteristic peaks for **4**. All the protons of **4** were assigned and compared with that of standard glycerol carbonate. In the ^{1}H NMR spectrum of the



Scheme 1. Lipase-catalyzed synthesis of glycerol carbonate (**4**).

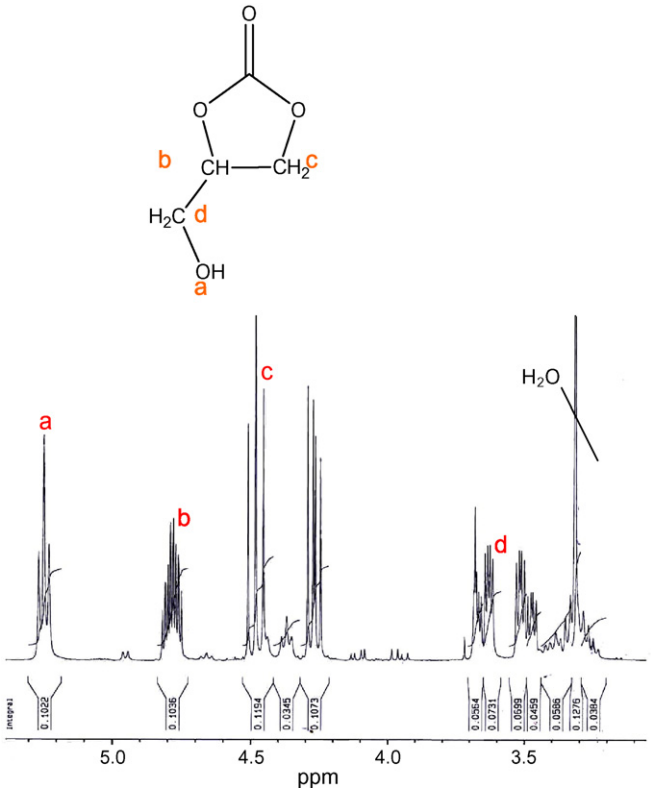
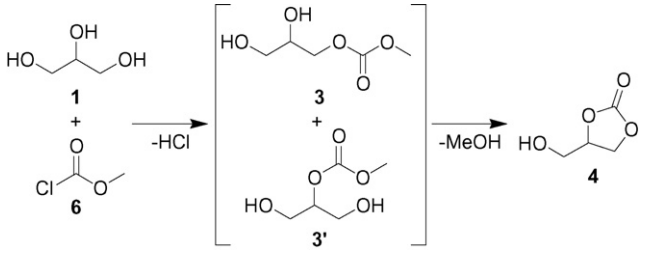


Fig. 1. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of glycerol carbonate.



Scheme 2. Attempt to synthesize the reaction intermediates (**3** and/or **3′**) from glycerol (**1**) and methyl chloroformate (**6**).

product, no signals were present in the range 3.0–3.5 ppm, which was assigned to protons in **1**.

To examine a detailed pathway of this process and identify the unknown product observed in the reaction catalyzed by lipase RM IM or CRL, the preparation of intermediate **3** was attempted through the reaction of **1** and methyl chloroformate (**6**) (Scheme 2). Although the reaction was carried out at −78 °C, glycerol carbonate (**4**) was a major product and the isolation of

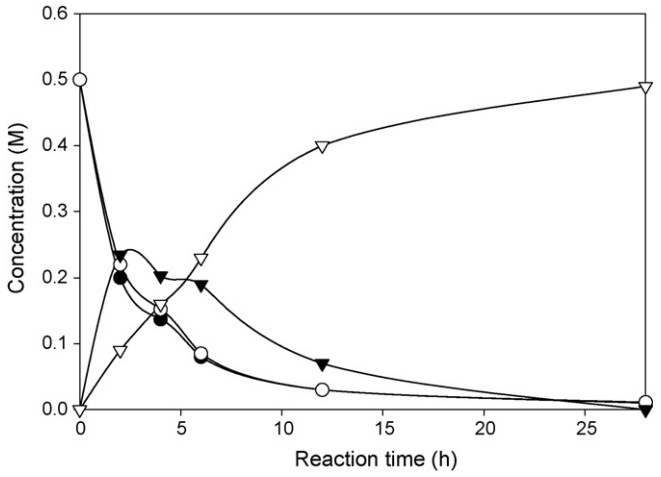


Fig. 2. Time profile of lipase-catalyzed synthesis of **4** in the reaction using equimolar amount of **1** and **2** in THF at 60 °C: (●) glycerol (**1**); (◯) DMC (**2**); (▼) unknown intermediate; (▽) glycerol carbonate (**4**).

3 or **3′** was not successful. This implies the ring cyclization of **3** or **3′** to **4** occurs almost spontaneously.

3.2. Effects of the ratio of glycerol to dimethyl carbonate on the synthesis of glycerol carbonate

Molar ratio of **1** to **2** had a significant influence on the production of **4**. As shown in Table 2, when equimolar amount of **1** and **2** was used, most of **1** was consumed and almost quantitative yield of **4** was obtained (entry 2). However, as the ratio of **2** to **1** becomes higher, the formation of 4-(methoycarbonyloxymethyl)-1,3-dioxolan-2-one (**5**), which was formed from the further alkoxycarbonylation between **4** and **2**, was increased (entry 3). In the K_2CO_3-catalyzed cyclization previously reported by Rokicki, excessive amount (3 equiv.) of **2** was required to convert **1** to **4** [7]. This shows that lipase-catalyzed synthesis of glycerol carbonate was very efficient compared with other catalytic cyclization.

Fig. 2 shows the reaction profile for reactants (**1** and **2**), unknown intermediate, and product **4** when equimolar amount of **1** and **2** was used in THF at 60 °C. Both **1** and **2** were consumed coincidently while the concentration of **4** increased. Interestingly the concentration of unknown intermediate increased steeply at the initial stage and began to decline gradually. Under this reaction profile, the formation of unknown intermediate seemed to be relatively fast compared with that of **4** from unknown intermediate, which might be the second step of this reaction profile. Also lipase-catalyzed reaction must be involved

Table 2
Ratio effects of glycerol (**1**) to dimethyl carbonate (**2**) on the synthesis of glycerol carbonate (**4**)[a]

Entry	Reaction ratio of **1**:**2** (mmol)	Consumed **1** (mmol)	Consumed **2** (mmol)	Produced **4** (mmol)	Produced **5** (mmol)
1	6.0:3.0	2.88	3.0	2.88	Not observed
2	6.0:6.0	5.64	6.0	5.28	0.36
3	6.0:18.0	6.0	9.6	1.68	4.2

[a] Reaction condition: **1**, **2**, Novozym 435 (0.30 g) and molecular sieves (2.0 g) were shaken at 60 °C for 30 h in THF (12 ml).

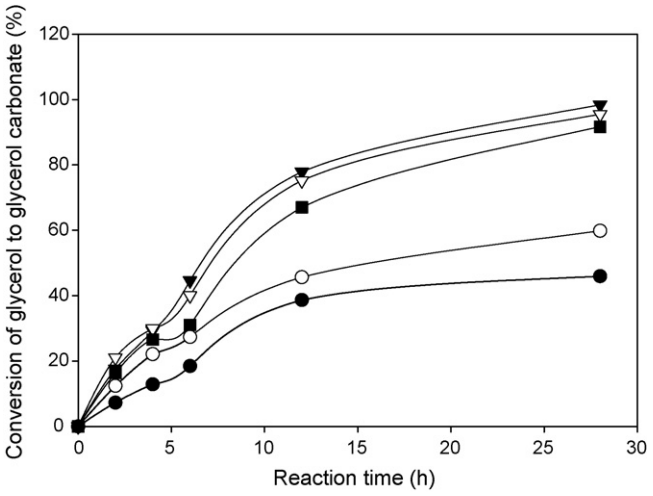


Fig. 3. Time profile on the production of **4** in various temperatures: (●) 40 °C; (◯) 50 °C; (▼) 60 °C; (▽) 70 °C; (■) 80 °C.

at the first step, but further investigation would be required whether next cyclization was accelerated by lipase.

3.3. Effects of temperature on the synthesis of glycerol carbonate

The variation of reaction temperature has a considerable affect on the synthesis of **4**. Up to 60 °C, the rate of conversion to **4** was accelerated and almost quantitative yield was observed within 28 h (Fig. 3). According to Arrhenius equation, reaction rate increases hand-in-hand with temperature. However, this principle was complied up to 60 °C and over 60 °C the conversions decreased slightly. Deactivation of lipase caused by high temperature may be one of the main factors for the drop of conversion. More thermostable lipase tolerant to higher temperature will reduce the overall reaction time. When the enantiomeric excess of the glycerol carbonate obtained from the reaction at 60 °C was examined, the very low ee of **4** (13% ee) was observed as configuration of (*R*)-enantiomer. As a similar case, lipase-catalyzed desymmetrization of glycerol with aliphatic anhydrides has been reported with the low ee of the corresponding product [11].

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