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Rapid Conversion of Glycerol to Lactic Acid under Alkaline Hydrothermal Conditions, by Using a Continuous Flow Reaction System

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A rapid conversion of glycerol to lactic acid (lactate) could be successfully achieved under alkaline hydrothermal conditions, by using a continuous flow reaction system. A rapid conversion by a continuous flow-type reaction system made it possible to achieve the reaction under high-temperature conditions without side reactions. The rapid conversion and high reaction yield (reaction: 2 min; yield: 90%) resulted from the rapid temperature-shift advantageous for the inhibition of side reactions.

Glycerol is a main candidate to be used as a building block especially in chemical synthesis using a C3 backbone. As a biomass derivative, glycerol is currently produced in a large amount as a by-product in manufacturing biodiesel by transesterification of vegetable oils, in such a way that its annual production from biodiesel has tripled, from 1995 to 2006, from 200000 to 600000 tons.¹ Thus, methods for effective utilization of glycerol to produce value-added chemicals have been investigated.¹⁻¹¹

Conversion of glycerol to lactic acid has attracted attention because the lactic acid is a useful compound to obtain valueadded materials such as lactide and poly(lactic acid).^{2–6} The clarification of reaction mechanisms is required to establish the industrial chemistry with respect to lactic acid. At the present, there are two different reaction mechanisms: (i) glycelaldehyde-routed reaction mechanism^{2–5} and (ii) acetol-routed reaction mechanism.⁶

Lactic acid has been generated by batch reaction under alkaline hydrothermal conditions.^{3,4} This method is a *green* process for production of lactic acid, because water is used as a reaction medium. It has been reported that a continuous degradation of carbohydrates using a capillary reactor is possible.¹² Furthermore, such reactors have recently been used successfully in various reaction and flow-multistep reactions.^{13–15} It is therefore expected that capillary reactions will be applied to conversion of glycerol to lactic acid.

In this study, it was demonstrated that an alkaline hydrothermal reaction of glycerol to lactic acid could be rapidly achieved and the reaction time could be hastened by 30-fold over previous reports, which is the fastest example to the best of our knowledge. We discuss the mechanism of the rapid conversion of glycerol based on kinetic study, NMR, and operational aspects.

Glycerol solution mixed with NaOH was prepared and injected by pump (LC-20AD, Shimadzu Co., Ltd.), into a SUS316 reactor incubated at 573–623 K, followed by the termination of reaction by cooling solution at the cooling bath (293 K) (Figure 1). The reaction time was set as the residence time in the reactor (column length: 2 m) by varying the flow rate (approximately 0.0033–0.033 mL s⁻¹). To maintain the reaction



Figure 1. Experimental set up of continuous flow reaction system.

solution in the liquid state, the pressure was set to 20 MPa by the back-pressure valve. The samples obtained were recovered and the yields of both lactate and other compounds were estimated by high-performance liquid chromatography (HPLC): UV detector UV SPD-6A (Shimadzu, Kyoto, Japan), column COSMOSIL 5C18-AR-II ODS column (4.6×150 mm) (Nakalai tesque), and the column oven (CTO-10ASVP). 10 mM phosphate buffer (pH 2.6) was used as a mobile phase. The optical density at 215 nm was monitored. Prior to the experiment, no significant change in yield of lactic acid was observed in the case of SUS316 alone, indicating that the materials of the reactor wall have no obvious catalytic role.

In the continuous flow reaction system presented here, lactic acid, formic acid, acrylic acid, and other compounds were detected for 2 min (Figure S1a).¹⁶ By varying the alkaline hydrothermal conditions as shown in Table S1,¹⁶ the best yield was 90% (Entry 1), as shown in Table 1. The performance of catalysts for glycerol conversion is summarized in Table 1, together with representative results previously reported. However, these previous reports were conducted in a batch reaction, and at least 60-min was required to achieve 90% yield (Entry 2). Metal-supported catalysts have recently been applied for the conversion of glycerol to lactic acid. In the case of catalysts such as Cu₂O/NaOH, Au–Pt/TiO₂, and Ru/C, the yield of lactic acid was reported that the rapid conversion of glycerol to lactic acid could be achieved by using the continuous flow reaction system.

From the reaction rate theorem, the conversion of glycerol to lactic acid requires one glycerol and one NaOH (Figure S1).¹⁶ The reaction mechanism was also investigated by using ¹H- and ²H NMR. Figure 2 shows the ¹H- and ²H NMR spectra of the solutions after the hydrothermal reactions of glycerol with NaOH or NaOD at 623 K. As described before, it was observed that the gradual consumption of reactant glycerol was accompanied by the production of lactic acid and a small amount of other compounds including formic acid. By comparing spectra (a) and (b) to (c) in Figure 2, it can be observed that the H on the

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Entry	Batch (B) or Flow (F)	Reaction condition and catalyst	Substrate NaOH/Glycerol	Temp. /K	Reaction time/min	Yield /%	Ref.
1	F	Hydrothermal	2 M/0.5 M	623	2	90	This study
2	В	Hydrothermal	1.25 M/0.33 M	573	60	90	4
3	В	Hydrothermal	1.25 M/0.33 M	573	60	75	5
4	В	Cu ₂ O, NaOH/N ₂ -1.4 MPa	1.19 M/1.09 M ^b	513	360	73.1	10
5	В	Au–Pt/TiO ₂ (Au:Pt = 1:1, 2.5 × 10 ⁻³ mmol), 0.1 MPa O ₂	0.88 M/0.22 M	363	—	42	6
6	В	Ru/C, 4 MPa H ₂	0.8 M/1 wt %	473	180	55	9

Table 1. Conversion of glycerol to lactic acid using various catalysts^a

^aReaction conditions: conversion and yield of lacitic acid was determined by HPLC. ^bRecalculated from the ref 10.



Figure 2. ¹H NMR and ²H NMR spectra for solution after the hydrothermal reaction of 0.5 M glycerol at 623 K with 1.5 M NaOD in D₂O for 30 s.

β-C of lactic acid has been almost completely transformed to D when in D₂O, and that any remaining glycerol does not take participate in the H–D exchange reaction. These results are consistent with a previous report.⁶ Furthermore, a ketone carbonyl group such as R¹–CO–R² as an intermediate product might be formed during the production of lactic acid from glycerol because of H–D exchange on the β-C of lactic acid, which was supported by MS observations (Figure S2).¹⁶ It is therefore thought that the reaction in the flow system used herein is the acetol-routed reaction mechanism as reported by Zhang et al.⁶ In this mechanism, glycerol is converted to acetol by dehydration, followed by the elimination of H₂ to induce benzilic acid rearrangement^{4,6,17} (Scheme 1). The obtained lactic acid was racemic (Figure S3),¹⁶ meaning that the conversion of glycerol to lactic acid appeared to be non-enantioselective.

On the other hand, the following experimental results suggest that the glycelaldehyde-routed reaction pathway is unlikely in the present reaction system: 1) high activation energy of conversion from glycerol to 2-hydroxypropenal



Scheme 1. Possible reaction mechanism of glycerol conversion to lactic acid. 6

(Figure S4);¹⁶ 2) no detection of glyceraldehyde as a key intermediate (Figure S1);¹⁶ 3) H_2 gas production late in the reaction process (data not shown).

From the results, we believe that the conversion of glycerol to lactic acid in the present continuous flow reaction system was driven by the acetol-routed reaction mechanism as shown in Scheme 1. In any case, the reaction mechanism in our case was the same as that in the batch reaction system. Therefore, a rapid conversion in the flow system was likely to be caused by other factors different from the reaction mechanism.

Previously, a side reaction resulted in a decreased yield of lactic acid under the alkaline hydrothermal conditions (593 and 613 K).^{3,11} As far as the reaction mechanism was the same as that in the batch reaction, the temperature-shift might be a key factor. We then investigated the influence of temperature-shift on the glycerol conversion. Since a capillary reactor was used in the present study, the rapid elevation and reduction of temperature between 293 and 623 K could be achieved within 15 s whereas 15 min was required in the batch reaction (Figure S5).¹⁶ The influence of rapid temperature-shift on the production of byproduct was then compared between 573 and 623 K (Figure 3). At 573 K, the yield of lactic acid in the batch system was 90%, which was comparable with the previous report (Entry 2 in Table 1). And the yield in the continuous system was at most 35%. By-products including formic acid and acetic acid were not seen. In contrast, a significant production of by-products was observed in the batch system at 623 K, which is in agreement with the previous report.³ Meanwhile, no significant production of by-product was detected in the continuous flow reaction system. These observations indicated that the rapid temperatureshift succeeded in the inhibition of production of by-products.



Figure 3. Temperature effect on the conversion of glycerol and yields of lactate, formic acid, and acetic acid. G: glycerol; L: lactate; F: formic acid; A: acetic acid. In the case of batch system at 623 K, other peaks (not identified) were observed although the data was not involved here. For batch system, 6 mL of solution was loaded into the SUS with 0.013 m in inner diameter (10 mL of volume) to start the reaction.

In conclusion, we succeeded in the rapid conversion of glycerol to lactic acid (reaction time: 2 min; yield: 90%), which is the best performance to the best of our knowledge. This achievement resulted from the rapid temperature-shift rather than the reaction mechanism. Our conditions afforded the racemic lactate, not L- or D-lactic acid, indicating the requirement of both the neutralization after the reaction process and the induction of enantioselectivy. These are under investigation.

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