Catalytic Synthesis of DL-Serine and Glycine from Glycerol

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DL-serine (DL-Ser), glycine (Gly), serinol (SerOH) and related compounds were catalytically derived from glycerol (GLY). Catalytic oxidation in the presence of ammonia of GLY, followed by hydrogen treatment over noble metals, to achieve direct synthesis of amino acids is not practical. Reductive amination over an Ru-Pd/C catalyst of glyceric acid, one of the oxidation products of GLY, was effective for DL-Ser synthesis. Gly was catalytically formed from DL-Ser by dehydrogenation and decarbonylation in hydrogen atmosphere. Catalytic oxidation of SerOH prepared by reductive amination over an Rh-Pd/C catalyst of dihydroxyacetone, another oxidation product of GLY, was also effective for DL-Ser synthesis. A new route for DL-Ser and Gly from GLY is presented. DL-alanine and γ-aminobutyric acid also formed, depending on reaction conditions.

KEY WORDS: Amination, dihydroxyacetone, DL-serine, glyceric acid, glycerol, glycine, oxidation, Rh-Pd/C, Ru-Pd/C, serinol.

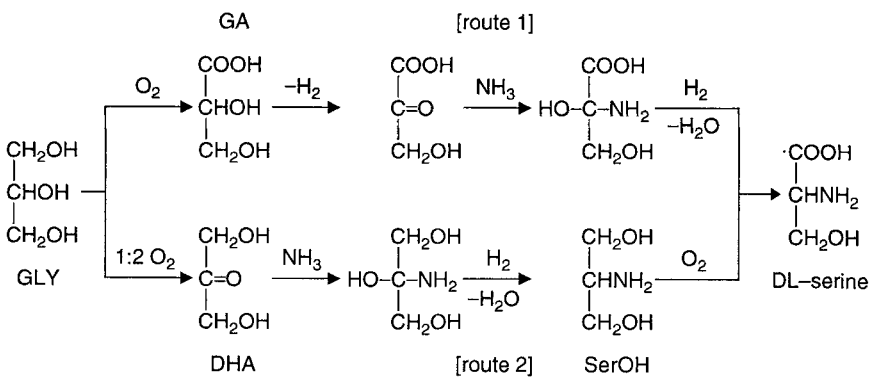
Glycerol (GLY) has a variety of industrial applications. The recent worldwide trend of increasing production of fatty alcohols from natural fats is bringing about excessive production of GLY. Therefore, new applications for consumption of GLY are important. We planned to derive amino acids from GLY by the combination of oxidation and reductive amination reactions. In a preliminary study of the direct oxidation of GLY in the presence of ammonia followed by hydrogenation, only trace amounts (50 ≈ 60 ppm) of amino acids, such as DL-serine (DL-Ser), glycine (Gly), DL-alanine and the related compound serinol (SerOH), were observed. It appeared that the single-step approach was not practical. We shifted to the multistep synthesis of amino acids from GLY. The oxidation products of GLY, glyceric acid (GA, route 1) and dihydroxyacetone (DHA, route 2) could be the starting materials for DL-Ser. Oxidation appears to be a key step to new applications for GLY. If just the DL-Ser synthesis is targeted, route 1 through GA is favored over route 2. However, in route 2, DHA is also synthesized effectively (Scheme 1).

The commercial processes for DL-Ser and our new process are compared in Scheme 2. The "Aziridine Process" (1) is a long one, which results in low yield. The "Glycine Process" is a one-step process (2,3), but is carried out at low concentrations. Our "Glycerol Process" is advantageous because intermediates have uses (4,5). These intermediates and DL-Ser can serve as starting materials for polymers. In the present study, synthesis of DL-Ser from GLY by routes 1 and 2 is examined.

EXPERIMENTAL PROCEDURES

Materials. As starting material for amino acid synthesis, we used a 10 wt% aqueous solution of GLY oxidation products, which was composed of GA (≈4 wt%), DHA (≈4 wt%) and unreacted GLY. The method of GLY oxidation has been reported (6–8). Rh-Pd/C and Ru-Pd/C catalysts supported on charcoal with 5% loading for reductive amination of GLY oxidation products were purchased from N. E. Chemcat. Corp. (Tokyo, Japan). These two-component catalysts were used as a mechanical mixture of each single-element catalyst. Granular charcoal WH_2C (BET surface area, 1200 m^2/g; pore volume, 0.8 cc/g; mean pore size, 17–18Å; particle size, 40 ≈ 100 mesh), provided by Takeda Chemical Industries, Ltd. (Osaka, Japan), was the catalyst support for SerOH oxidation.

Reductive amination of GLY oxidation products. Batchwise reductive amination of GLY oxidation products was performed as follows. A 0.5-L autoclave was charged with 300 mL of 10% aqueous solution of GLY oxidation products, 18 g of 35% aqueous solution of ammonia (mole ratio of NH_3 to C_3 compounds = 1.0), 7.5 g of Pd/C and 0.38 g of Ru/C catalysts. Air in the reactor was substituted with hydrogen several times, and then hydrogen pressure was set to 0 kg/cm^2G. The reactor was heated to 50°C, then pressurized with hydrogen to 6 K/cm^2G and maintained



SCHEME 1

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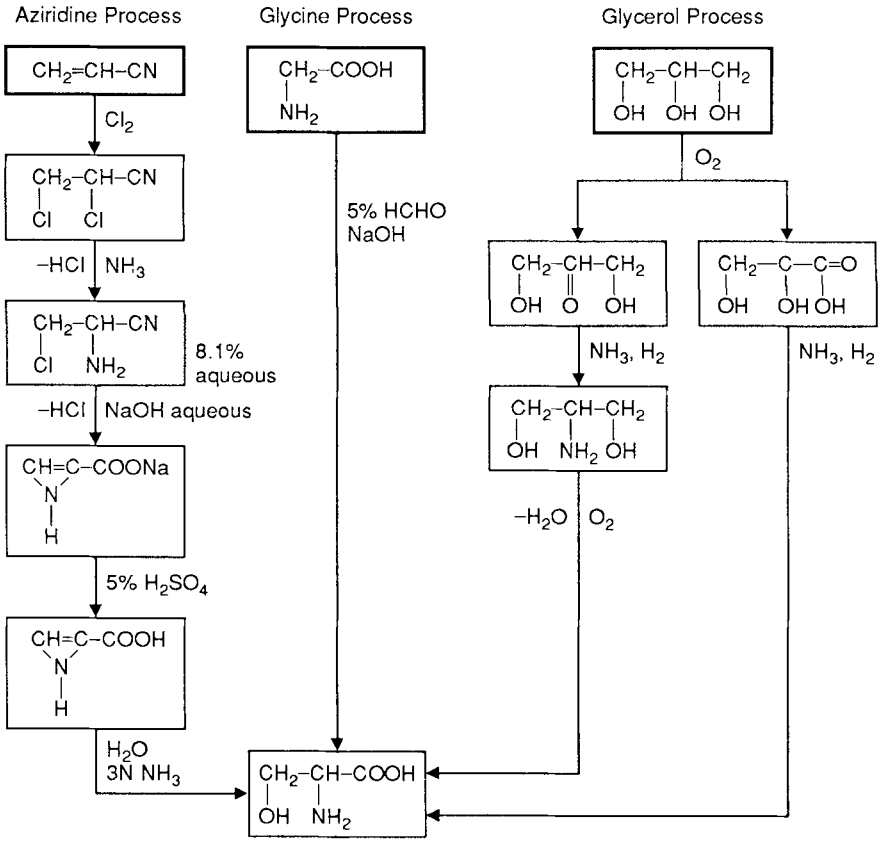

SCHEME 2

at this value by resupplying consumed hydrogen. Vigorous stirring (≈1000 rpm) was performed to avoid the effect of mass transfer. Sampling was carried out every hour, and the catalyst was removed by filtration for quantitative analysis of the aminated products and unreacted materials by amino acid analysis and high-performance liquid chromatography (HPLC).

A fixed-bed reactor for oxidation of SerOH. Two-component catalyst (1% Ce 5% Pd) supported on WH_2C was packed in a reactor to 60-cm height (20-mm i.d.), and aqueous SerOH and air were fed concurrently from the top of the reactor, which was fixed vertically to avoid channeling.

Liquid chromatography-mass spectrometry (LC-MASS) analysis. The reaction mixture from reductive amination was neutralized with 1N HCl to form hydrochlorides of amino acids and amines, which were separated from nonamine materials by extraction with chloroform. After addition of sodium bicarbonate, 5% fluorodinitrobenzene (FDNB) in ethanol was added. After one hour at 40°C, the mixture was acidified to pH 1 with 1N HCl. The products were extracted with ethylacetate and dissolved in methanol for analysis. LC-MASS was performed by the dinitrophenyl (DNP)-amino acid method and liquid chromatography-atmospheric pressure chemical ionization-mass spectroscopy on a Hitachi model M-1000 mass spectrometer (Ibaraki, Japan). LC conditions were as follows: column, GH-C18 (4.0 mm i.d.); column temperature, 40°C; eluent, 1% HCOOH in H_2O/CH_3CN (75:25 or 25:75).

Quantitative analysis of amino acids by amino acid analyzer. Samples were diluted with 3% trichloroacetic acid and injected into the Hitachi L8500 amino acid analyzer, which was operated as follows: column, Li-based cation exchange resin (#2622SC) (6 mm i.d.); ammonia trap column, cation exchange resin (#2650) or resin (#2650L) (4.6 mm i.d.); eluent, L8500 PF-KIT; detection, 570 nm.

Analysis of nonamine materials by HPLC. Analysis of nonamine materials in the reductive amination reactions was performed by HPLC (Hitachi): packing material, C-610S; column, 7.8 mm i.d.; eluent, H_2O; flow rate, 0.5 mL/min; pressure, 15 Kgf/cm^2; column temperature, 60°C; detector, RI).

RESULTS AND DISCUSSION

Identification of formed amino acids by LC-MASS. Amino acids and SerOH, formed by reductive amination of GLY oxidation products, were identified by LC-MASS. Figure 1 shows the comparison of chromatograms of amino acids synthesized in the present study with authentic samples. Amino groups of amino acids and SerOH were identified as FDNB derivatives. The LC chromatogram in Figure 1B shows a mixture of authentic samples of SerOH [1], DL-Ser [2], Gly [3], γ-aminobutyric acid (GABA) [5] and DL-alanine [6]. Peak [4] corresponds to FDNB derivatives of those other than amino acids. The $[M - H]^-$ peak for FDNB derivatives of SerOH, DL-Ser, Gly, GABA and DL-alanine were observed at mass numbers of 256, 270, 240, 268 and 254, respectively. The

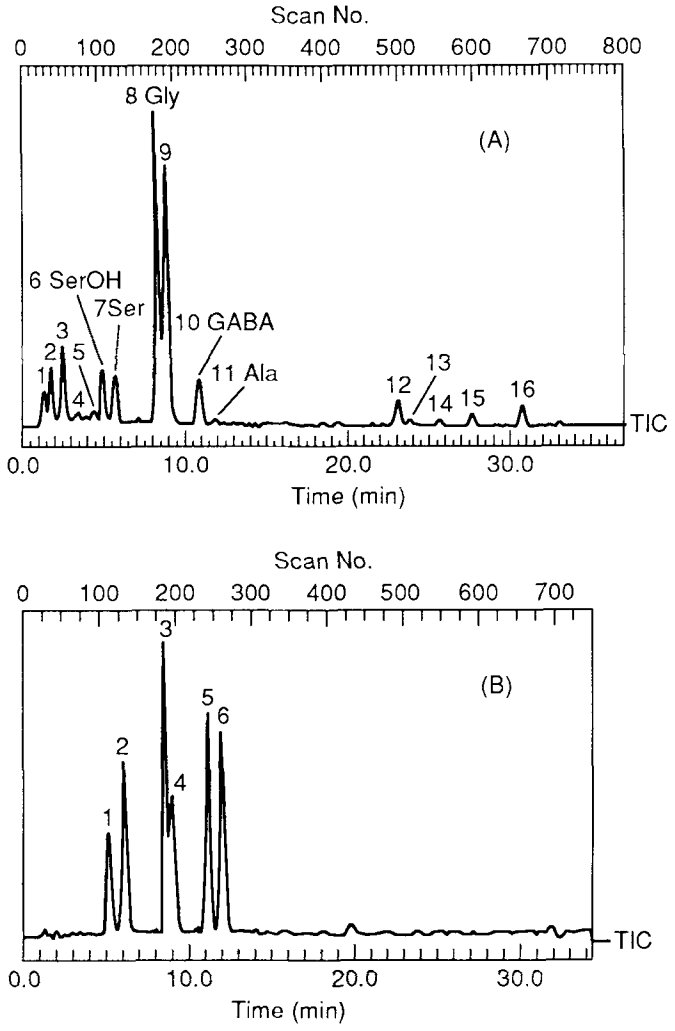

FIG. 1. Identification of amino acids and serinol formed by reductive amination of glycerol oxidation products, glyceric acid and dihydroxyacetone. Peak numbers are described in text. A, Liquid chromatography (LC) chromatogram of fluorodinitrobenzene (FDNB) derivatives of reductive amination products of glycerol oxidation products. B, LC chromatogram of FDNB derivatives of the standard amino acids, DL-serine, glycine (Gly), DL-alanine (Ala), γ-aminobutyric acid (GABA) and serinol (SerOH.

LC chromatogram of the reaction products from the present study is shown in Figure 1A. The main peak [8] corresponds to Gly. Peaks [6], [7], [10] and [11] correspond to FDNB derivatives of SerOH, DL-Ser, GABA and DL-alanine. Peak [9] corresponds to FDNB derivatives of those other than amino acids. Small peaks [1]-[5] and [12]-[16] are not discussed in the present study. The $[M - H]^-$ peaks for FDNB derivatives of SerOH, DL-Ser, Gly, GABA and DL-alanine occurred at mass numbers of 256, 270, 240, 268 and 254, respectively. The same fragmentation patterns were observed as for authentic samples. The peak at 481 in the mass spectum of Gly corresponds to $[2\ M - H]^-$. Therefore, the peak at 240 in the spectrum corresponds to the pseudo-molecular ion $[M - H]$. Peaks at 186 in GABA and at 447 in Ala correspond to impurities having the same retention time. It is concluded from these observations that DL-Ser, Gly, DL-alanine, GABA and SerOH were derived catalytically from GLY.

Identification of amino acids by amino acid analyzer. Reductive amination of GLY oxidation products over Rh-Pd/C (Rh/Pd atomic ratio, 1:20) was performed at 40°C for 6 h. Analysis of the reaction products was performed by amino acid analyzer. DL-Ser, Gly and SerOH were identified, and each peak was composed of a single component. Analysis of the reaction products, formed over an Ru-Pd/C catalyst at 60°C for 2 h, showed that the selectivity for DL-Ser was much higher. These results are summarized in Table 1, which indicates that the Ru-Pd/C catalyst was much better than the Rh-Pd/C catalyst.

Stability of amino acids formed by reductive amination. After reductive amination was performed, catalysts had to be removed immediately. Otherwise, decomposition of amino acids and SerOH proceeded. When the reaction mixture was stored without removing the catalyst, about 50% of the amino acids and SerOH decomposed within a week.

The mechanism for Gly formation. Dehydrogenation of the primary hydroxy group of DL-Ser during amination was followed by decarbonylation, resulting in the formation of Gly. The decomposition rate greatly depended on reaction temperature as well as catalyst composition. SerOH decomposed to monoethanolamine, but the rate was much lower than that of DL-Ser. The formation of DL-alanine was determined by amino acid analysis. The formation was due to reductive amination of lactic acid, which was formed by isomerization of DHA under alkaline conditions (9).

The mechanism for GABA formation. The presence of GABA acid was identified by amino acid analysis. The combination of DL-Ser and tartronic acid, an oxidation product of GA, was accompanied by the liberation of carbon dioxide from each molecule and hydrogenolysis, resulting in the formation of GABA.

TABLE 1

Reductive Amination of Glycerol Oxidation Products over Noble Metal[a] Catalyst

Run	Catalyst	Promoter	Conversion (%)		Selectivity (%)		
			GA	DHA	DL-serine	Glycine	Serinol
(1)	Pd	—	39.0	79.6	1.3	10.7	5.3
(2)	Pd	Rh	40.7	86.8	14.6	17.1	73.8
(3)	Pd	Ru	75.6	92.5	59.5	14.6	≈100

[a]Support, charcoal; loading, 5%; Rh/Pd or Ru/Pd atomic ratio, 1:20; reaction time, 6 h for runs (1) and (2), 2 h for run (3). GA, glyceric acid; DHA, dihydroxyacetone.

Catalytic oxidation of SerOH to DL-Ser. Catalytic oxidation of SerOH is an alternative route for DL-Ser synthesis. SerOH is an unstable amine, especially in a basic aqueous media; therefore, SerOH is liberated by neutralization of a salt of SerOH (salt of oxalic acid was used as the starting material). Amino acid analysis of the batchwise oxidation of 2.5% aqueous SerOH, prepared over a 5% Pt/C catalyst, showed that DL-Ser was formed. Gly, which was a decomposition product of DL-Ser in the reductive amination of GA, did not form. This is characteristic of the oxidation route to DL-Ser. However, the DL-Ser yield was only 5% over the conventional Pt/C catalyst. This is because Pt easily dissolves under alkaline conditions, resulting in serious loss of catalytic activity. Furthermore, Pt- or Pd-based catalysts are deactivated by the adsorption of amine. Instead of a Pt catalyst, a Pd catalyst incorporated by Ce was selected to improve catalytic activity by promoting oxidation of the primary hydroxy group of SerOH, as well as inhibiting deactivation by amine adsorption. The oxidation reactions were performed in a fixed-bed reactor under the following conditions: SerOH concentration, 2.5%; LHSV (liquid hourly space velocity) of an aqueous solution of SerOH, 0.07 h^{-1}; O_2 feed rate, 0.052 mole/h; SerOH feed rate, 0.0076 mole/h; mole ratio of O_2 to SerOH, 6.6; mole ratio of NaOH to SerOH, 0.50. A higher selectivity of 60% was obtained. Incorporation of Bi in Pd was also performed to inhibit catalyst deactivation by oxygen (self-poisoning), which is usually observed in oxidations over noble metal catalysts. The selectivity over a BiPd catalyst was 24%. The alkaline character by Ce incorporation over the Pd surface inhibits deactivation by amine adsorption, resulting in an increase in DL-Ser yield, and the catalyst was not deactivated by oxygen. Catalytic oxidation of the reductive amination products already containing DL-Ser, Gly and SerOH can be performed in the same way. However, decomposition of DL-Ser and Gly accompanied the oxidation of SerOH, and some catalyst poison, formed in the former step of reductive amination, became a problem.

*Comparison of route 1 (*via *GA) and route 2 (*via *DHA) for DL-Ser synthesis.* Comparison of the two routes, 1 (*via* GA) and 2 (*via* DHA) for DL-Ser synthesis shows that the former route is favorable just for DL-Ser synthesis. However, Gly is produced as a by-product. Reduction of DL-Ser decomposition was attained by catalyst improvement and control of the reaction conditions, especially reaction temperature (the lower the better). Route 2 has the advantage of obtaining DHA. DL-Ser synthesis by catalytic oxidation of SerOH produces no Gly, which is a major problem with route 1. However, route 2 needs improvement to inhibit decomposition of SerOH formed in the reductive amination reaction. Also, catalyst poisons need to be reduced or separated.

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