A Facile Method for the Production of D-*p*-Hydroxyphenylglycine. Asymmetric Transformation of DL-*p*-Hydroxyphenylglycine Using (+)-1-Phenylethanesulfonic Acid

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A practical method for the production of D-*p*-hydroxyphenylglycine, useful as a starting material for preparing semisynthetic penicillins or cephalosporins, has been developed. The diastereomeric salts of DL-*p*-hydroxyphenylglycine with (+)-1-phenylethanesulfonic acid as a resolving agent, were efficiently resolved into less soluble D-*p*-hydroxyphenylglycine (+)-1-phenylethanesulfonate [D-HPG·(+)-PES] and soluble L-HPG·(+)-PES by the fractional crystallization of its salts in aqueous solution. The soluble L-HPG·(+)-PES could be easily epimerized into DL-HPG·(+)-PES by heating it with water containing a 0.1 molar equivalent of free DL-HPG in an autoclave. When the fractional crystallization of DL-HPG with (+)-PES was simultaneously carried out under the epimerizing conditions, the DL-HPG·(+)-PES was transformed into D-HPG·(+)-PES in up to 90% yield. The present asymmetric transformation should be a suitable method for preparing D-HPG in a large scale.

It is well-known that D-*p*-hydroxyphenylglycine is useful as a side chain of semisynthetic penicillins or cephalosporins.[1] Thus far, we have presented several methods for the production of D-*p*-hydroxyphenylglycine.[2-5] Our previous paper[5] showed that (+)-1-phenylethanesulfonic acid [(+)-PES] was a favorable resolving agent for the diastereomeric resolution of DL-*p*-hydroxyphenylglycine (DL-HPG) and, for the asymmetric transformation of DL-HPG: a combination of the fractional crystallization of the less soluble D-*p*-hydroxyphenylglycine (+)-1-phenylethanesulfonate [D-HPG·(+)-PES] and the epimerization of the soluble L-*p*-hydroxyphenylglycine (+)-1-phenylethanesulfonate [L-HPG·(+)-PES] in a system. In the previous work, the asymmetric transformation of DL-HPG·(+)-PES was performed in acetic acid in the presence of salicylaldehyde. In the course of our further studies, it has been found that the asymmetric transformation of DL-HPG·(+)-PES could be achieved merely by heating a mixture of DL-HPG, (+)-PES, and water in an autoclave. The present paper describes a simple method for the asymmetric transformation of DL-HPG by the use of (+)-PES as a resolving agent.

The advantages of asymmetric transformation have been described in our previous reports[4-6] and the literature.[7-9] An asymmetric transformation between two diastereomers by a combination of fractional crystallization of the less soluble diastereomer and the epimerization of the soluble diastereomer is known as a second-order asymmetric transformation. In order to perform such an asymmetric transformation, we must search for the conditions under which both fractional crystallization and epimerization can be carried out simultaneously, and for which the resolving agent is chemically and optically stable.

The solubility of L-HPG·(+)-PES in water at 20 °C is about 80 times greater than that of D-HPG·(+)-PES as was noted in our previous paper.[5] Consequently, the fractional crystallization of the less soluble D-HPG·(+)-PES from the solution consisting DL-HPG, (+)-PES, and water occurred efficiently. On the other hand, we previously reported that the salt of L-HPG with achiral sulfonic acid (*o*-toluenesulfonic acid) was readily racemized by heating it in water at 140 °C.[2] To combine this racemization method and the optical resolution method of DL-HPG with (+)-PES, we have studied the epimerization of the soluble L-HPG·(+)-PES in water; this study was carried out by using

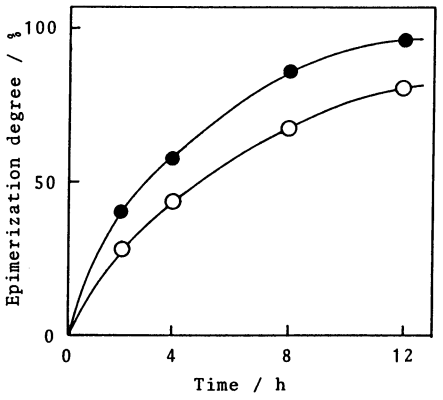

Fig. 1. Time course on epimerization of L-HPG·(±)-PES. The reactions were carried out at 140 °C in aqueous solution containing L-HPG·(±)-PES in a sealed tube. Additives: none (○), a 0.1 molar equivalent of DL-HPG (●).

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L-HPG·(±)-PES instead of L-HPG·(+)-PES to aim at accurately determining the racemization degree of the L-HPG moiety.

When L-HPG·(±)-PES was heated in water at 140 °C in a sealed tube, the epimerization of L-HPG·(±)-PES occurred as well as the racemization of L-HPG *o*-toluenesulfonate.[2] In Fig. 1, the time course of the epimerization of L-HPG·(±)-PES is shown together with that of adding a 0.1 molar equivalent of free DL-HPG. The presence of free DL-HPG considerably accelerated the rate of the epimerization. Under such epimerizing conditions, (+)-PES was confirmed to be chemically and optically stable in the manner described in our previous report.[5] Furthermore, the crystals of D-HPG·(+)-PES precipitated from the epimerizing solution were also detected to accumulate without redissolving into its solution. Thus the essential requirements for the intended asymmetric transformation were fulfilled.

In this kind of the asymmetric transformation (the second order), the composition of two diastereomers in the whole system is displaced to the one component by the crystallization. The yield of the desired diastereomer [D-HPG·(+)-PES] therefore is dependent on how much of the precipitate of the diastereomer crystallized in the reaction system. To increase the amount of the precipitate under the above conditions for epimerization, the amount of the solvent (in this case, water) must be minimized.

When the amount of water used as a solvent was almost equal to that of the ammonium (+)-1-phenylethanesulfonate [(+)-PES·NH_4, was used because it was easier to handle than (+)-PES (free acid: syrup or pasty crystals[5])], a good yield was obtained and the stirring state of the reaction mixture was satisfactory. A typical experiment of the resulting asymmetric transformation was performed by heating a slurry consisting of DL-HPG (35.3 g, 0.19 mol×1.1), (+)-PES·NH_4 (39.0 g, 0.19 mol), sulfuric acid (9.4 g, 0.19 mol×0.5), and water (40 ml) with stirring in a glass autoclave. This reaction proceeded in the slurry state of the solid-liquid heterogeneous system. In order to achieve a high yield in the above experiment, the optimal conditions of the reaction were examined in further detail. Figure 2 shows the yield of D-HPG·(+)-PES as a function of the reaction time for three different temperatures. The excessive heating resulted in a lowering of yield of D-HPG·(+)-PES owing to the decomposition of HPG although the (+)-PES was stable. The highest yield (91.2% based on the DL-HPG·(+)-PES) was obtained in the reaction at 125 °C for 20 h. The change in the composition of both diastereomeric salts during the period of the reaction is illustrated in Fig. 3.

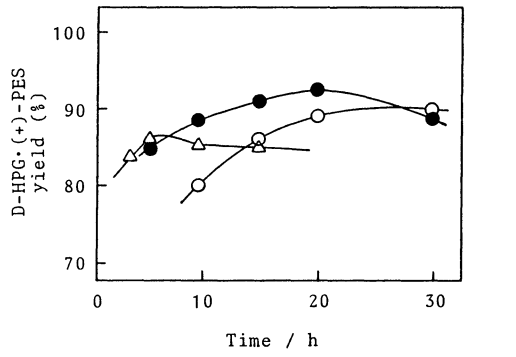


Fig. 2. Effect of temperature and time on asymmetric transformation of DL-HPG·(+)-PES. A mixture of DL-HPG (35.3 g), (+)-PES·NH_4 (39.0 g), sulfuric acid (9.4 g), and water (40 ml) was stirred at a temperature (○; 118 °C, ●; 125 °C, △; 135 °C) in an autoclave.

Since the D-HPG·(+)-PES obtained above was optically pure, it could be decomposed to optically pure D-HPG by neutralization with aqueous ammonia without further purification. The (+)-PES·NH_4 contained in the mother liquor after the separation of D-HPG could be reused as the resolving agent for the

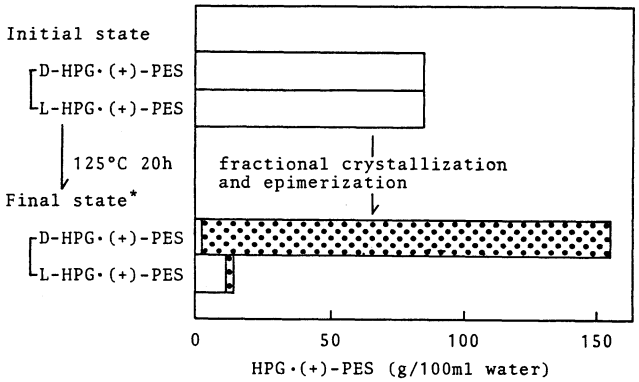
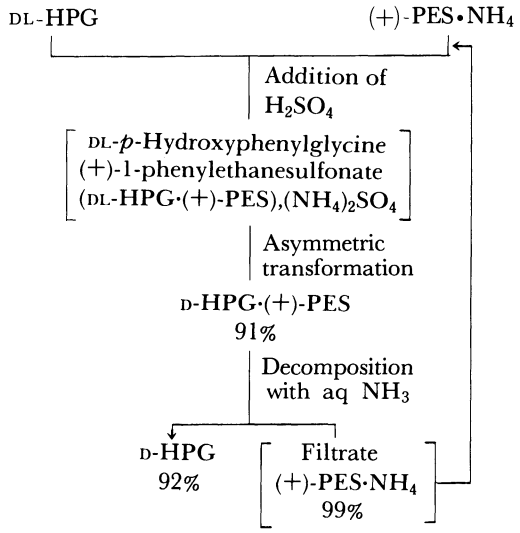


Fig. 3. The change in the composition of diastereomeric salts by asymmetric transformation. *: ▨, crystals of (+)-PES salt; □, (+)-PES salt in solution.



Scheme 1. Flowsheet for preparation of D-*p*-hydroxyphenylglycine by asymmetric transformation. [ ] were used in the next process without separation.

next asymmetric transformation without isolation. Our proposed repetitive process for preparing D-HPG is shown in Scheme 1. The asymmetric transformation presented here proceeds in a slurry state containing a large amount of solid and gives a high degree of transformation and a high yield of D-HPG·(+)-PES per a unit volume of water solvent (Fig. 3). This method for the preparation of D-HPG, therefore, has a definite advantage and is suitable for industrial application.

Experimental

Materials and Analyses. Optically active and racemic HPG manufactured by our company, Tanabe Seiyaku Co., Ltd., were used. (+)-1-Phenylethanesulfonic acid [(+)-PES] was prepared in a manner described in our previous report.[5] Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. ^{1}H NMR spectra were measured with a Hitachi Perkin-Elmer R-40 spectrometer using tetramethylsilane as an internal standard. A glass autoclave TEM-U300 (Taiatsu Glass Industry Co., Ltd., Japan) was used. The temperature control for asymmetric transformation was carried out by a Thermo-mate oil bath BZ-21 (Yamato Scientific Co., Ltd., Japan).

Epimerization of L-HPG·(+)-PES. The experiments aimed at the epimerization of the diastereomeric salt were carried out using the 1 : 1 molar ratio salt of L-HPG with (±)-PES [L-HPG·(±)-PES]. The epimerization degree, i.e., the racemization degree of the L-HPG moiety was evaluated by measurement of the optical rotation. A mixture of L-HPG·(±)-PES (50 mg), DL-HPG (2.4 mg), and water (0.6 ml) was heated in a sealed tube at 140 °C. After heating for the prescribed time, the reaction mixture was diluted with water (10 ml), and the optical rotation was measured. The epimerization degree was evaluated from the change in the optical rotation. The results together with those without free DL-HPG are shown in Fig. 1.

Preparation of Ammonium (+)-1-Phenylethanesulfonate. A solution of (+)-PES [40.0 g; $[\alpha]_D^{25}$ +20.9 ° (*c* 3, DMSO)] in water was adjusted to pH 7 with 28% aqueous ammonia (14.5 ml). The aqueous solution was concentrated to dryness under reduced pressure. To the residue was added acetone (150 ml), and the resulting crystals were filtered, and dried at 90 °C to give (+)-PES·NH_4 (41.5 g; $[\alpha]_D^{25}$ +15.2 ° (*c* 1, MeOH); mp 208—209 °C; IR (Nujol) 3200, 1600, 1410, 1020, and 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=1.46 (3H, d, *J*=7 Hz, CH_3), 3.67 (1H, q, *J*=7Hz, CH), and 6.9—7.3 (5H, m, aromatic H).

Asymmetric Transformation of DL-HPG. A mixture of DL-HPG (35.3 g), (+)-PES·NH_4 (39.0 g), sulfuric acid (9.4 g), and water (40 ml) was heated at a prescribed temperature (118, 125, and 135 °C) in an autoclave fitted with a mechanical stirrer. The reaction system was a thick slurry during the reaction. After heating for a required time, into the heterogeneous reaction mixture were added water (40 ml) and sulfuric acid (0.9 g). The mixture was cooled to 5 °C and then stirred for 2 h. The crystals which precipitated were collected by filtration, washed with a small amount of cold water, and dried to give almost optically pure D-HPG·(+)-PES (yield, 54.4—61.9 g). The relationships between the yield of D-HPG·(+)-PES and the reaction time at each reaction temperature are shown in Fig. 2. The highest yield was obtained when the reaction mixture was treated at 125 °C for 20 h; yield of D-HPG·(+)-PES 61.9 g (91.2% based on the DL-HPG·(+)-PES); $[\alpha]_D^{25}$ −76.8° (*c* 1, MeOH); optical purity, 97.6%. The change in the composition of both diastereomeric salts during the reaction is shown in Fig. 3.

Preparation of D-HPG. A mixture of D-HPG·(+)-PES (60.0 g; optical purity, 97.6%) and water (60 ml) was heated at 60 °C with stirring. The suspended mixture was adjusted to pH 6.0 with 6 mol dm^{-3} aqueous ammonia. After stirring for 1 h at the same temperature, the mixture was stirred for 2 h at 5 °C. The reaction proceeded in a thick slurry. The crystals which precipitated were collected by filtration, washed with a small amount of cold water, and dried to give D-HPG (26.0 g) in a 91.6% yield; $[\alpha]_D^{25}$ −158.0° (*c* 1, 1 mol dm^{-3} HCl).

Found : C, 57.43 ; H, 5.40 ; N, 8.41%. Calcd for $C_8H_9NO_3$: C, 57.48 ; H, 5.43 ; N, 8.38%.

The mother liquor obtained after the separation of D-HPG was the aqueous solution containing (+)-PES·NH_4, which could be reused for the next asymmetric transformation in the form of the solution without isolating the (+)-PES·NH_4.

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