  Bull. Chem. Soc. Jpn., 60, 649—652 (1987)

The Optical Resolution and Asymmetric Transformation of DL-*p*-Hydroxyphenylglycine with (+)-1-Phenylethanesulfonic Acid

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(Received July 18, 1986)

Optically active 1-phenylethanesulfonic acid was found to be an efficient resolving agent for the optical resolution and asymmetric transformation of DL-*p*-hydroxyphenylglycine. When DL-*p*-hydroxyphenylglycine was resolved by the fractional crystallization of its diastereomeric salt with (+)-1-phenylethanesulfonic acid, less soluble D-*p*-hydroxyphenylglycine (+)-1-phenylethanesulfonate [D-HPG·(+)-PES] was obtained in a good yield. Soluble L-HPG·(+)-PES was easily epimerized into DL-HPG·(+)-PES by heating it at 100 °C in glacial acetic acid in the presence of a small amount of salicylaldehyde. Under such epimerizing conditions, the asymmetric transformation of DL-HPG·(+)-PES was attempted by simultaneously combining the fractional crystallization of the less soluble D-HPG·(+)-PES and the epimerization of the soluble L-HPG·(+)-PES. This asymmetric transformation was achieved successfully; that is, 80% of the DL-HPG used as the starting material was converted into D-HPG.

D-*p*-Hydroxyphenylglycine is a starting material in the production of β-lactam antibiotics, such as semi-synthetic penicillins or cephalosporins. In order to develop a practical method for the production of this D-*p*-hydroxyphenylglycine (D-HPG), we have been studying the optical resolution of synthetic DL-HPG[1,2] by several techniques, for instance, preferential crystallization,[3] diastereomer salt formation,[4] and asymmetric transformation.

In our recent studies of asymmetric transformation,[5-8] it was reported that D-HPG was successfully prepared by asymmetric transformation combined with preferential crystallization and simultaneous racemization.[8] Besides this convenient procedure, if a suitable resolving agent of DL-HPG through diastereomer salt formation can be found, it will also provide an advantageous resolution method (i.e., asymmetric transformation) for the preparation of D-HPG. In the present work, we could find that optically active 1-phenylethanesulfonic acid was a favorable resolving agent for this purpose. In this paper, we wish to describe particularly a unique method for the preparation of D-HPG by asymmetric transformation between two diastereomeric salts of DL-HPG with (+)-1-phenylethanesulfonic acid.

In general, free neutral amino acids can not form diastereomeric salts directly with ordinary weak basic or weak acidic resolving agents. For the formation of these diastereomeric salts, it has usually employed such strongly acidic resolving agents[9,13] as the camphorsulfonic acids and also, rarely, the terpenesulfonic acids or cholestenonesulfonic acid. However, these chiral sulfonic acids derived from naturally occurring products are not necessarily satisfactory for practical production because they are expensive, are somewhat optically or chemically labile, and are not available in large amounts. Therefore, we have carried out the screening of resolving agents aimed at discovering one without these disadvantages; this led to the finding of 1-phenylethanesulfonic acid.

The synthesis and optical resolution of racemic 1-phenylethanesulfonic acid [(±)-PES] has been fairly well described in the literature.[10] According to the previously reported synthetic method, however, (±)-PES could not be easily prepared.[11] In the course of our further researches, it was found that (±)-PES synthesized by sulfonating (±)-1-phenylethyl bromide[11] could be resolved into the (+)-isomer through its diastereomeric salt with D-HPG in an aqueous solvent. On the contrary, DL-HPG could be easily resolved in the same manner into the D-isomer by using the (+)-PES as the resolving agent. In Table 1, the physical properties of D-*p*-hydroxyphenylglycine (+)-1-phenylethanesulfonate (D-HPG·(+)-PES) and L-HPG·(+)-PES are shown. Since the difference in solubility between the two diastereomeric salts in water (20 °C) was very large, the fractional crystallization of DL-HPG with less than an equivalent amount of (+)-PES in water afforded almost optically pure D-HPG·(+)-PES in a good yield (43.8% based on DL-HPG·(+)-PES).

On the other hand, we previously reported that the racemization of optically active amino acid salts (e.g., achiral sulfonates) was accomplished by heating them in an acetic acid solution in the presence of a catalytic amount of an aldehyde and free DL-amino acid.[6] This racemization method prompted us to study the asymmetric transformation of DL-HPG with (+)-PES.

In order to apply the asymmetric transformation to DL-HPG·(+)-PES, (+)-PES must be chemically and optically stable under the conditions for the above racemization (epimerization for diastereomer). The optical stability of (+)-PES was tested under the pre-

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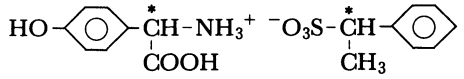
Table 1. Properties of D-HPG·(+)-PES and L-HPG·(+)-PES

		D-HPG·(+)-PES	L-HPG·(+)-PES
Mp (θ_m/°C)		251—252	204—205
$[\alpha]_D^{25}$/° (*c* 1, MeOH)		−78.9	+98.6
Solubility (g/100 ml water)	5°C	0.8	—
	20°C	1.1	77
	40°C	1.7	—
(g/100 ml AcOH)	20°C	0.2	1.0
	70°C	0.2	4.1



D-*p*-Hydroxyphenylglycine (+)-1-Phenylethanesulfonate
[D-HPG·(+)-PES]

Table 2. Optical Stability of (+)-PES in Various Solvents

Solvent	Racemization degree/%		
	2h	5h	10h
Water	0	0	0
1M-H_2SO_4	0	0	0
AcOH	0	0	0
2M-NaOH	8	17	31

The solutions of (+)-PES (0.2 g) dissolved in solv. (6 ml) were stirred at 100°C for 10 h.

sent heating conditions in various solvents. As shown in Table 2, (+)-PES was quite stable at 100 °C for 10 h in water, 1 M H_2SO_4 (1 M=1 mol dm^{-3}) and in acetic acid, but in 2 M NaOH it was gradually racemized. Since (+)-PES was optically stable in acetic acid, it was preferable to accelerate the epimerization of the soluble L-HPG·(+)-PES (i.e., the racemization of the L-HPG moiety). As can be seen in Fig. 1, L-HPG·(±)-PES was easily epimerized into DL-HPG·(±)-PES by heating it at 100 °C for ca. 4 h in acetic acid containing a 0.2 molar equivalent of salicylaldehyde. In addition, the crystals of D-HPG·(+)-PES were also confirmed to be rather insoluble in acetic acid (Table 1) and to precipitate without changing, even under the above epimerizing conditions.

Thus, the characteristics of the foregoing HPG·(+)-PES satisfied the most essential requirement for the intended asymmetric transformation via diastereomer salt formation. Therefore, using the optical resolution and the epimerization method described above, the asymmetric transformation of DL-HPG·(+)-PES was examined in a system. For instance, a mixture of DL-HPG (10.0 g), (+)-PES (11.2 g), glacial acetic acid (200 ml), and salicylaldehyde (0.63 ml) (added for accelerating the epimerization) was stirred at 100 °C for 5 h. The reaction proceeded continuously in a slurry state of the solid-liquid heterogeneous system. After this reaction mixture had then been cooled at 20 °C, precipitated crystals were collected to give D-HPG·(+)-PES

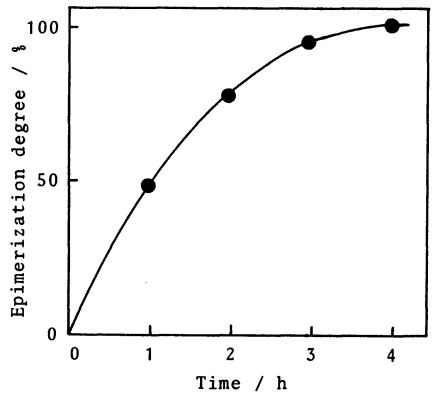


Fig. 1. Time course on epimerization of L-HPG·(±)-PES. The reactions were carried out at 100°C in L-HPG·(±)-PES/AcOH in the presence of salicylaldehyde (0.2 molar equivalent).

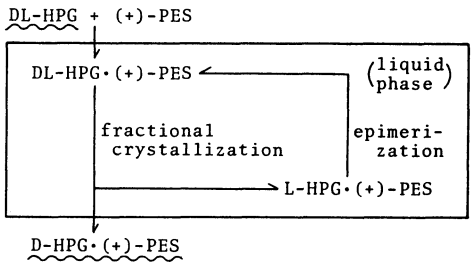


Fig. 2. Asymmetric transformation of DL-HPG with (+)-PES. ~~~, solid state.

(18.0 g); $[\alpha]_D^{25}$ −74.5° (*c* 1, MeOH); optical purity, 95.0%; yield, 85.1% (based on DL-HPG·(+)-PES). The pathway of the asymmetric transformation described here is considered to be that shown in Fig. 2: When the crystals of D-HPG·(+)-PES were fractionally precipitated from a salt solution consisting of DL-HPG and (+)-PES, the epimerization of the soluble L-HPG·(+)-PES proceeded simultaneously in the liquid phase, and D-HPG·(+)-PES was also thereupon immediately precipitated from the epimerizing solution. Since

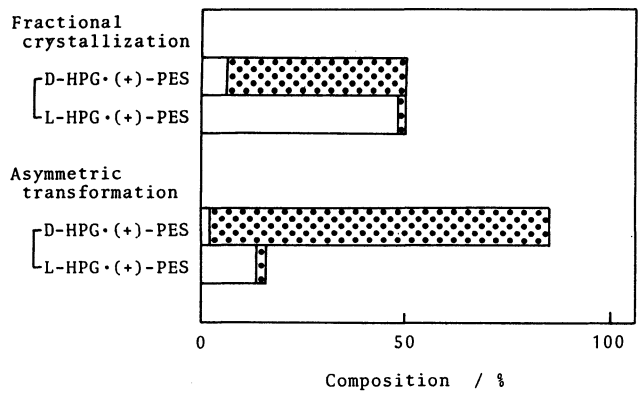


Fig. 3. The change in the composition of D- or L-HPG·(+)-PES by fractional crystallization and asymmetric transformation.
▩: Crystals of (+)-PES salt, □: (+)-PES salt in solution.

these steps were repeated continuously in the reaction system, the equilibrium finally shifted in favor of D-HPG·(+)-PES as a whole. As a result, 80% of the DL-HPG·(+)-PES was transformed into D-HPG·(+)-PES. Figure 3 shows a comparison of the results of the ordinary fractional crystallization and of the asymmetric transformation.

Among the various techniques for optical resolution, the fractional crystallization of the diastereomeric salts with a chiral resolving agent under simultaneous epimerizing conditions is known as an asymmetric transformation of the second order.[12,13] This method is very attractive, particularly when separations for industrial applications are contemplated, because it is possible to transform the racemate to the desired isomer in a nearly quantitative yield through a simple operation. The asymmetric transformation of DL-HPG with (+)-PES is, therefor, expected to be a very promising procedure for the industrial production of D-HPG.

Experimental

Materials and Analyses. D-, L-, and DL-HPG manufactured by our company, Tanabe Seiyaku Co., Ltd. were used. The (±)- and (+)-1-phenylethanesulfonic acids (PES) were prepared by the method shown below. Other chemicals were obtained from Tokyo Kasei Kogyo Co., Ltd. All samples were dried overnight in vacuo at 40 °C. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube; they are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. IR spectra were recorded on a Shimadzu infrared spectrophotometer, Model IR-420. ^{1}H NMR spectra were obtained using a Hitachi Perkin-Elmer R-40 High Resolution ^{1}H NMR spectrometer, with tetramethylsilane as an internal standard. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from both undersaturation and supersaturation. Solute concentration was measured with a Karl Zeiss immersion refractometer.

Preparation of Barium (±)-1-Phenylethanesulfonate. (±)-1-Phenylethanesulfonic acid [(±)-PES] was prepared from commercially available (±)-1-phenylethyl bromide in the manner described by Kharasch et al.[11] That is, a mixture of (±)-1-phenylethyl bromide (70 g), a 50% ammonium hydrogensulfite solution (75 g), and 28% aqueous ammonia (30 ml) was stirred at room temperature overnight. After the oil part of the reaction mixture had been removed, barium hydroxide octahydrate (60 g) was added and the ammonia was boiled out. The aqueous solution was then adjusted to neutrality with sulfuric acid, and the insoluble barium salts were filtered off and washed with water. The filtrates were partly concentrated under reduced pressure, and the precipitated crystals were filtered, washed with cold water, and dried to give (±)-PES·1/2Ba·1/2H_2O (44 g) in a 44% yield; IR (nujol) 3475, 1630, 1185, and 1065 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=1.48 (3H, d, J=7 Hz, CH_3), 3.72 (1H, q, J=7 Hz, CH), and 7.1—7.4 (5H, m, aromatic).

Optical Resolution of (±)-1-Phenylethanesulfonic Acid. To a solution of (±)-PES·1/2Ba·1/2H_2O (42.1 g) in hot 10% HCl (590 ml) was added D-HPG (26.7 g). After it had then been cooled slowly to room temperature, the mixture was stirred at 25 °C for 2 h. The resulting crystals were filtered, washed with a small amount of cold water, and dried to give crude (+)-PES·D-HPG; $[\alpha]_D^{25}$ −79.5° (c 1, MeOH). The crude salt (26.0 g) was recrystallized from 0.1% sulfuric acid (430 ml) to afford the pure (+)-PES·D-HPG (23.0 g); $[\alpha]_D^{25}$ −78.9° (c 1, MeOH); mp 262—263 °C (decomp); IR (nujol) 3050, 1740, 1600, and 1140 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=1.48 (3H, d, J=7 Hz, CH_3), 3.72 (1H, q, J=7 Hz, CH), 4.97 (1H, s, CH), 6.8—7.5 (9H, m, aromatic), and 8.7 (2H, br, NH_2).

Found: C, 54.39; H, 5.51; N, 3.99; S, 8.98%. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38; H, 5.42; N, 3.96; S, 9.07%. This product was optically and chemically pure. The specific rotation of a mixture of (±)-PES and an equivalent amount of D-HPG was $[\alpha]_D^{25}$ −87.1° (c 1, MeOH), and that of an authentic (+)-PES·D-HPG was $[\alpha]_D^{25}$ −78.9° (c 1, MeOH).

The pure (+)-PES·D-HPG (22.0 g) obtained above was suspended in water (22 ml) at 50—60 °C. The solution was adjusted to pH 5.5 with 6M NaOH (ca. 10.4 ml) and then stirred at 20 °C for 2 h. The crystals thus precipitated were filtered, washed with cold water, and dried to obtain D-HPG (9.5 g). The mother liquor filtered was passed through a column of Amberlite IR-120 (100 ml, H^+ form), after which the column was washed with water. The aqueous solution passed through was treated with activated charcoal and concentrated to dryness in vacuo at 40 °C to give (+)-PES (free acid 11.5 g) as pasty crystals; $[\alpha]_D^{25}$ +21.9° (c 3, DMSO); ^{1}H NMR (D_2O) δ=1.71 (3H, d, J=7 Hz, CH_3), 4.24 (1H, q, J=7 Hz, CH), and 7.55 (5H, s, aromatic).

Optical Stability of (+)-1-Phenylethanesulfonic Acid. A solution of (+)-PES (free acid 0.2 g) in various solvents (6 ml) was sealed in a glass tube and shaken at 100 °C for 10 h. After the solution had then been cooled and diluted with water (4 ml), the optical rotation was measured. The racemization degree was calculated from the following formula:

$$\frac{\text{initial optical rotation} - \text{final optical rotation}}{\text{initial optical rotation}} \times 100$$

The optical stability of (+)-PES was judged from the resulting racemization degree in the various solvents shown in Table 2.

Optical Resolution of DL-*p*-Hydroxyphenylglycine. DL-HPG was resolved with (+)-PES in the same manner as in

the optical resolution of (±)-PES described above: A mixture of DL-HPG (10.0 g), (+)-PES (free acid 10.0 g), and water (200 ml) was heated until clear and then allowed to cool to 25 °C with stirring. After 2 h, the product was collected, washed with cold water, and dried to give crude D-HPG·(+)-PES (9.7 g); $[\alpha]_D^{25}$ −74.8° (*c* 1, MeOH); optical purity, 95.4% [based on D-(+) salt $[\alpha]_D^{25}$ −78.9° (*c* 1, MeOH) and DL-(+) salt $[\alpha]_D^{25}$ +9.8° (*c* 1, MeOH)]; yield, 43.8% (based on DL-HPG·(+)-PES). The change in the composition of the diastereomeric salts is shown in Fig. 3.

Epimerization of L-HPG·(+)-PES. The epimerization study of the soluble L-HPG·(+)-PES was carried out by using L-HPG·(±)-PES in order to determine the racemization degree of the L-HPG moiety. A mixture of L-HPG·(±)-PES (0.2 g), a 0.2 molar equivalent of salicylaldehyde (6.8 μl), and glacial acetic acid (6 ml) was heated in a sealed tube at 100 °C for the prescribed time interval. The reaction mixture was then diluted with acetic acid (10 ml), and the optical rotation was measured. The epimerization degree was calculated from the decrease in the optical rotation according to the above-noted formula. The results are shown in Fig. 1.

Asymmetric Transformation of DL-*p*-Hydroxyphenylglycine. A mixture of DL-HPG (10.0 g), (+)-PES (11.2 g), salicylaldehyde (0.63 ml), and glacial acetic acid (200 ml) in a flask fitted with a mechanical stirrer and a condenser was continued at 100 °C for 5 h, during which period the reaction system was heterogeneous. The reaction mixture was cooled to 20 °C, and the precipitated crystals were quickly collected by filtration, washed with a small amount of acetic acid, and dried to give crude D-HPG·(+)-PES (18.0 g); $[\alpha]_D^{25}$ −74.5° (*c* 1, MeOH); optical purity, 95.0%; yield, 85.1% (based on DL-HPG·(+)-PES). This ^{1}H NMR and the IR spectra were in accord with an authentic sample of D-HPG·(+)-PES. The change in the composition of both diastereomeric salts by the present asymmetric transformation is shown in Fig. 3.

Preparation of D-*p*-Hydroxyphenylglycine. The crude D-HPG·(+)-PES (17.0 g) obtained above was recrystallized from hot water (300 ml) to give optically pure D-HPG·(+)-PES (14.5 g); $[\alpha]_D^{25}$ −78.9° (*c* 1, MeOH). The pure salt (14.0 g) was suspended in water (15 ml) at 50—60 °C, and the mixture was adjusted to pH 5.5 by the dropwise addition of 6 M NaOH (ca. 6.6 ml), after which it was stirred at 20 °C for 2 h. The crystals thus precipitated were collected, washed with water, and dried to give D-HPG (6.0 g); $[\alpha]_D^{25}$ −158.4° (*c* 1, 1 mol dm^{-3} HCl).

Found : C, 57.50; H, 5.51; N, 8.33%. Calcd for $C_8H_9NO_3$: 57.48; H, 5.43; N, 8.38%.

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