Optical Resolution of (±)-Phenylsuccinic Acid by Using (−)-Proline as Resolving Agent

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Synopsis. A solution of equimolar mixture of (±)-phenylsuccinic acid ((±)-PSA) and (−)-proline ((−)-Pro) in ethanol or its suspension in 2-propanol selectively gave a salt composed of 1-molar amount of PSA and 2-molar amount of (−)-Pro. The salt purified gave (+)-PSA with an optical purity of about 100%. A salt composed of equimolar amounts of PSA and (−)-Pro was obtained from the ethanolic mother liquor, and gave (−)-PSA with an optical purity of 98%.

(±)-Phenylsuccinic acid (abbreviated as (±)-PSA) has been used as an intermediate material for phensuximide.[1,2] (±)-PSA has been optically resolved by the diastereomeric procedure using brucine.[3] However, it is not easy to obtain PSA with high optical purity in high yield, since it is difficult to purify the diastereomeric salts separated by repetition of recrystallization. (±)-Proline ((±)-Pro) has been optically resolved through its diastereomeric salts with an optically active dibasic acid, (+)-tartaric acid.[4] This suggests that (−)-Pro would easily form a salt with a dibasic acid such as PSA. Thus, optical resolution of (±)-PSA was attempted by using (−)-Pro as a resolving agent to find out a more practical procedure. In this note, 1-1 and 1-2 salts represent a salt composed of equimolar amounts of PSA and (−)-Pro and one composed of 1-molar amount of PSA and 2-molar amount of (−)-Pro, respectively; salts which contain the PSA rich in the (+)-enantiomer are represented as (+)-1-1 and (+)-1-2 salts, and those rich in (−)-PSA as (−)-1-1 and (−)-1-2 salts.

Experimental

Materials. (±)-PSA was obtained from Aldrich Chemical Co., Inc., (+)-PSA ($[\alpha]_D^{20}$ +168° (*c* 2.00, acetone); lit,[3] $[\alpha]_D^{20}$ +173.3° (*c* 1.8235, acetone)) from Kanto Chemical Co., Ltd., and (−)-Pro ($[\alpha]_D^{20}$ −84.7° (*c* 1.00, water)) from Wako Pure Chemical Ind., Ltd. (−)-PSA was obtained by optical resolution; $[\alpha]_D^{20}$ −170° (*c* 2.00, acetone).

Preparation of Standard Salts. 1-2 Salts: (+)-PSA (0.01 mol, 1.942 g) and 0.02 mol (2.302 g) of (−)-Pro were dissolved in 80 cm^3 of ethanol. After stirring for 1 h at room temperature, the (+)-1-2 salt formed was collected by filtration and recrystallized from ethanol: yield 3.53 g; mp 160 °C; $[\alpha]_D^{20}$ +13.5° (*c* 1.00, methanol); solubility at 30 °C 1.04 g/(100 cm^3 ethanol).

Found: C, 56.49; H, 6.60; N, 6.57%. Calcd for $C_{20}H_{28}N_2O_8$: C, 56,60; H, 6.65; N, 6.60%.

In the case of (−)-1-2 salt, after stirring a similar initial solution for 30 min at 15 °C, the crude (−)-1-2 salt formed was removed by filtration and the filtrate was stirred for 30 min in an ice bath. The (−)-1-2 salt crystallized was collected by filtration and washed thoroughly with diethyl ether: yield 1.70 g; mp 130 °C; $[\alpha]_D^{20}$ −107°(*c* 1.00, methanol); solubility at 30 °C 3.12 g/(100 cm^3 ethanol).

Found: C, 56.78; H, 6.70; N, 6.62%

1-1 Salts: After dissolving 0.02 mol of (+)- or (−)-PSA and 0.01 mol of (−)-Pro in ethanol, the solution was evaporated to dryness under reduced pressure around 50 °C. The residue was stirred in 200 cm^3 of diethyl ether for 1 h. The salt was collected by filtration and washed with diethyl ether.

(+)-1-1 Salt: Yield 2.92 g; mp 141 °C; $[\alpha]_D^{20}$ +51.4° (*c* 1.00, methanol).

Found: C, 58.09; H, 6.14; N, 4.50%. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53%

(−)-1-1 Salt: Yield 2.90 g; mp 136 °C; $[\alpha]_D^{20}$ −117° (*c* 1.00 methanol).

Found: C, 57.99; H, 6.18; N, 4.56%

Optical Resolution. Procedure I: (−)-Pro (0.02 mol) was dissolved in 80 cm^3 of ethanol. After cooling to 40 °C, 20 cm^3 of an ethanolic solution of 0.02 mol of (±)-PSA was added, and the solution was stirred for 30 min at 40 °C. The (+)-1-2 salt formed was collected by filtration: yield 2.88 g; $[\alpha]_D^{20}$ +3.8° (*c* 1.00, methanol). After evaporating the filtrate to dryness under reduced pressure around 50 °C, the residure was stirred in 200 cm^3 of diethyl ether for 1 h at room temperature. Then, the (−)-1-1 salt formed was collected by filtration: yield 1.98 g; $[\alpha]_D^{20}$ −115° (*c* 1.00, methanol). PSA (1.23 g, $[\alpha]_D^{20}$ +10.5° (*c* 2.00, acetone)) was recovered from the filtrate and resolved similarly to above. (+)-1-2 Salt ($[\alpha]_D^{20}$ +4.0° (*c* 1.00, methanol)) and (−)-1-1 salt ($[\alpha]_D^{20}$ −115° (*c* 1.00, methanol)) were obtained in 0.91 and 0.66 g yields, respectively, and 0.39 g of PSA was recovered.

Procedure II: (±)-PSA (0.02 mol) was dissolved in 100 cm^3 of 2-propanol, and 0.02 mol of (−)-Pro was added. After refluxing for 30 min followed by stirring for 30 min at 25°C, the (+)-1-2 salt formed was collected by filtration and washed with diethyl ether: yield 4.00 g; $[\alpha]_D^{20}$ +4.0° (*c* 1.00, methanol). After evaporating the filtrate to dryness, the residue and 0.780 g of (−)-Pro were dissolved in ethanol, and the solution was again evaporated to dryness under reduced pressure around 50 °C. After stirring the residue in 200 cm^3 of diethyl ether for 1 h at room temperature, (−)-1-1 salt was collected by filtration and washed with diethyl ether: yield 2.37 g; $[\alpha]_D^{20}$ −114° (*c* 1.00, methanol). PSA (0.35 g) was recovered from the filtrate.

The optical purities of the salts obtained by the procedures I and II were calculated on the basis of the specific rotations of the standard salts.

Preparation of (+)- and (−)-Phenylsuccinic Acids: (+)-1-2 Salt with an optical purity of around 80% was added to ethanol (6 cm^3 g^{-1}). After refluxing for 30 min followed by stirring for 30 min at 30 °C, the (+)-1-2 salt purified was collected by filtration. The (+)-1-2 salt purified or the (−)-1-1 salt obtained was added to concentrated hydrochloric acid (5 cm^3 g^{-1}). After stirring for 1 h in an ice bath, PSA was collected by filtration, washed with a small amount of cooled water, and dried. The PSA was dissolved in diethyl ether, and the solution was filtered. The filtrate was evaporated to dryness to obtain (+)- and (−)-PSAs. For example, 3.23 g of (+)-1-2 salt with an optical purity of 98% gave 1.39 g of (+)-PSA with that of 99.1%; the yields of (+)- and (−)-PSAs were calculated on the basis of the half amount of (±)-PSA consumed by reaction (1.942 g). It is confirmed by ^{1}H NMR spectra in acetone-d_6 that the (+)-and (+)-PSAs obtained are free from (−)-Pro.

Measurements. Specific rotations were measured with a

Table 1. Influence of Temperature on Formation of Diastereomeric Salts[a)]

Temperature °C	Salt or PSA[b)]	Yield g	Specific rotation[c)] ·	Optical purity[d)] %
5	(+)-1-2	1.76	−10.8	56
	(−)-1-1	0.43	−116	99
	PSA	0.74	−42.7	25
20	(+)-1-2	1.61	−2.6	73
	(−)-1-1	0.67	−117	100
	PSA	0.71	−19.9	12
30	(+)-1-2	1.50	+1.5	80
	(−)-1-1	0.76	−115	99
	PSA	0.64	−9.4	5
35	(+)-1-2	1.41	+3.2	83
	(−)-1-1	0.87	−114	97
	PSA	0.61	+2.0	1
40	(+)-1-2	1.36	+3.9	84
	(−)-1-1	0.99	−114	98
	PSA	0.58	+8.1	5

a) (±)-PSA and (−)-Pro: 0.01 mol. Total amount of ethanol: 50 cm³. Stirring time: 30 min. b) PSA: Phenylsuccinic acid. c) (+)-1-2 and (−)-1-1 salts: $[\alpha]_D^{20}$ (*c* 1.00, methanol). PSA: $[\alpha]_D^{20}$ (*c* 2.00, acetone). d) The optical purities of the salts were calculated on the basis of the specific rotations of standard (+)- and (−)-1-1 salts, 1-2 salt, and (+)-PSA ($[\alpha]_D$ +173.3° (*c* 1.8235, acetone)).

Union Giken high sensitivity PM-101 digital polarimeter. The solubilities of the standard (+)- and (−)-1-2 salts and the ternary phase diagram were obtained in a similar manner as described in our previous paper;[5)] (+)- and (−)-1-2 salts have maximal absorptions at 259 nm and molar absorptivities are 152 $cm^3\ mol^{-1}\ cm^{-1}$, ^1H NMR spectra were recorded on a JEOL JNM-PMX 60 NMR spectrometer.

Results and Discussion

Influence of Temperature on Formation of Salts. A separation of the diastereomeric salts was attempted for an ethanolic solution containing 0.01 mol of (±)-PSA and (−)-Pro at 5—40 °C similarly to the optical resolution described in the experimental section. The total amount of ethanol was 50 cm^3. The ^1H NMR spectrum in deuterium oxide and the specific rotation indicated that (+)-1-2 salt deposited selectively from the solution. (−)-1-1 Salt and unreacted PSA were obtained by evaporating the mother liquor to dryness around 50 °C, and the (−)-1-1 salt had an optical purity of about 100%. These results are given in Table 1. The relationship between the degrees of resolution of (+)-1-2 and (−)-1-1 salts and temperature was examined to resolve (±)-PSA efficiently, as shown in Fig. 1. The degrees of resolution were calculated by

$$\text{degree of resolution}/\% = (\text{yield of salt}/g \times \text{optical purity}/\% \times f)/0.971/g, \quad (1)$$

where f is 0.458 for (+)-1-2 salt and 0.628 for (−)-1-1 salt.

The degree of resolution of (+)-1-2 salt is scarcely influenced by temperature, since the optical purity increases with increase in temperature though the yield decreases. On the other hand, the degree of resolution of (−)-1-1 salt linearly increases with increase in temperature. Therefore, it is found that, of the temperatures employed, the separation of (+)-1-2 salt at 40 °C yields (−)-1-1 salt with an optical purity of 98% in the highest yield from the mother liquor.

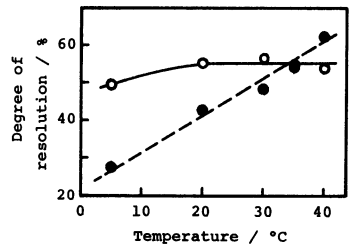

Fig. 1. Relationship between degree of resolution and temperatures. (±)-PSA and (−)-Pro: 0.01 mol. Total amount of ethanol: 50 cm³.
——○——: (+)-1-2salt, ——●——: (−)-1-1 salt.

A separation of (+)-1-2 salt was attempted at 45 °C with the expectation that (−)-1-1 salt with high optical purity would be obtained in higher yield. However, (+)-1-2 salt did not crystallize under this condition. In the preparation of the standard salts, the salt formation using equimolar amounts of (+)-PSA and (−)-Pro gave (+)-1-2 salt and unreacted (+)-PSA, though (+)-1-1 salt was obtained when (+)-PSA and (−)-Pro were used in the molar ratio of 2 : 1. Moreover, after (+)-1-2 salt was filtered off from a solution of equimolar mixture of (±)-PSA and (−)-Pro, a stirring of the mother liquor in an ice bath or a concentration around 40 °C gave 1-2 salt which was a near racemate. The above results suggest that (+)-1-2 salt tends to form from (±)-PSA and (−)-Pro, and that (−)-1-2 salt forms below 40 °C, whereas (−)-1-1 salt forms above 45 °C.

Optical Resolution by Procedure I. In view of the results in the preceding section, an optical resolution of (±)-PSA was carried out at 40 °C as specified in Table 2. A (+)-1-2 salt with an optical purity of 84% crystallized from the initial solution. A (−)-1-1 salt with an optical purity of 98% and PSA were obtained from the mother liquor. Since the PSA was a near racemate and the yield was about one third of (±)-PSA consumed by reaction, the PSA was again allowed to

Table 2. Optical Resolution of (±)-Phenylsuccinic Acid by Using (−)-Proline[a)]

Procedure	Salts purified				Phenylsuccinic acid		
	Salt	Yield	Specific rotation[b)]	Optical purity[c)]	Yield[d)]	Specific rotation[e)]	Optical purity[f)]
		g	·	%	%	·	%
I[g)]	(+)-1-2	3.23	+12.4	98	71.7	+172	99.1
	(−)-1-1[i)]	2.64	−115	98	80.3	−170	98.1
II[h)]	(+)-1-2	3.58	+12.0	98	83.0	+171	98.7
	(−)-1-1[i)]	2.37	−114	96	70.5	−167	96.6

a) (±)-PSA: 0.02 mol. b) $[\alpha]_D^{20}$ (*c* 1.00, methanol). c) The optical purities were calculated on the basis of the specific rotations of standard (+)- and (−)-1-1 salts and 1-2 salt. d) The yields were calculated on the basis of 1.942 g. e) $[\alpha]_D^{20}$ (*c* 2.00, acetone). f) The optical purities were calculated on the basis of the specific rotation of (+)-PSA: $[\alpha]_D$ +173.3° (*c* 1.8235, acetone). g) PSA (0.39 g) was recovered; $[\alpha]_D^{20}$ +17.1°. (*c* 2.00, acetone). h) PSA (0.35 g) was recovered; $[\alpha]_D^{20}$ +17.8° (*c* 2.00, acetone). i) The salt was not purified.

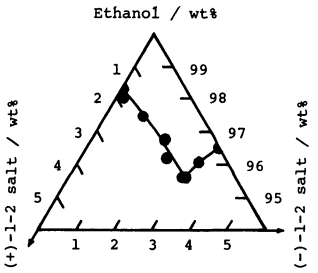

Fig. 2. Ternary phase diagram of solubility of 1-2 salt
Solvent: Ethanol. Temperature: 30°C.

react with an equimolar amount of (−)-Pro. The (±)-1-2 and (−)-1-1 salts obtained in the second run had the same optical purities as the salts obtained in the first run, so that both the salts obtained in the first and second runs were combined. The (−)-1-1 salt was treated with hydrochloric acid without recrystallization, since the salt had an optical purity of about 100%. The salt gave (−)-PSA with an optical purity of 98.1% in 80.3% yield.

For purification of the (+)-1-2 salt, the optimum amount of ethanol was calculated on the basis of the ternary phase diagram of solubility at 30 °C in ethanol shown in Fig. 2;[6)] at the eutectic point, the amount of (+)-1-2 salt is 1.34 wt%, that of (−)-1-2 salt 3.07 wt%, and that of ethanol 95.59 wt%. For 1 g of the (+)-1-2 salt with an optical purity of 80%, the optimum amount of ethanol calculated is 3.99 cm^3. However, 6 cm^3 of ethanol was employed, since 3.99 cm^3 of ethanol was too small to handle. The purification of the crude gave (+)-PSA with an optical purity of 99.1% in 71.7% yield.

Optical Resolution by Procedure II. A suspension of equimolar mixture of (±)-PSA and (−)-Pro in 2-propanol selectively gave (+)-1-2 salt with an optical purity of 84%. The (+)-1-2 salt purified gave (+)-PSA with an optical purity of 98.7% in 83.0% yield. This result is given in Table 2.

It is estimated from the results in ethanol that although equimolar amounts of (+)- and (−)-PSAs in the mother liquor form a racemic compound with each other, the excess of (−)-PSA forms (−)-1-1 salt with an equimolar amount of (−)-Pro. The amounts of (±)-PSA, (−)-PSA, and (−)-Pro in the mother liquor were calculated on the basis of the yield and optical purity of the (+)-1-2 salt obtained: (±)-PSA 0.514 g (0.0026 mol), (−)-PSA 1.540 g (0.0079 mol), and (−)-Pro 0.133 g (0.0011 mol). Therefore, after evaporating the mother liquor to dryness, the residue obtained was allowed to react with 0.780 g (0.0068 mol) of (−)-Pro in ethanol to give (−)-1-1 salt with an optical purity of 96% in 2.37 g yield; the theoretical yield is 2.45 g. (−)-PSA with an optical purity of 96.6% was obtained in 70.5% yield from the (−)-1-1 salt.

The above results indicate that it is possible to resolve (±)-PSA optically by using (−)-Pro as a resolving agent and to obtain (+)- and (−)-PSAs with optical purities of about 100% in 70—83% yield.

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