Racemization of Optically Active Aromatic *N*-Acetylamino Acids and Asymmetric Transformation of *N*-Acetyl-2-(4-hydroxyphenyl)glycine via Salt Formation with Optically Active α-Methylbenzylamine

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The racemization rates of *N*-acetyl-(*S*)-tyrosine, *N*-acetyl-(*S*)-phenylalanine, *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-AcHpg], *N*-acetyl-(*R*)-2-phenylglycine, and *N*-acetyl-(*S*)-alanine were measured by use of (*RS*)-α-methylbenzylamine [(*RS*)-MBA] as a base-catalyst. The first-order rate constant for racemization tended to increase with an increase in the polar substituent constant of the *N*-acetylamino acid side chain. The racemization appeared to be subject to the inductive effect by the side chain. An asymmetric transformation of (*RS*)-AcHpg by using (*R*)-MBA, based on the result of racemization, gave an optically pure salt of (*R*)-AcHpg with (*R*)-MBA by successive use of the filtrate as the solvent. Optically pure (*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-Hpg] was separated from the salt in 87—90% yield based on the starting (*RS*)-AcHpg. In addition, the asymmetric transformation of (*R*)-AcHpg was achieved by using (*S*)-MBA to give optically pure (*S*)-Hpg in 80% yield after purification of the salt of (*S*)-AcHpg with (*S*)-MBA followed by hydrolysis.

Asymmetric transformation is an efficient means to obtain a desired enantiomer from a racemate and is carried out by combination of selective crystallization of a less soluble diastereomeric salt with epimerization of the more soluble one in a solution. (*R*)-2-(4-Hydroxyphenyl)glycine [abbreviated as (*R*)-Hpg], a useful material for antibiotics such as amoxycillin, has been obtained efficiently by asymmetric transformation via salt formation with (+)-1-phenylethanesulfonic acid.[1,2] (+)-1-Phenylethanesulfonic acid as a resolving agent, however, may not be commonly available. Since optically active Hpg was apt to racemize in carboxylic acids on heating,[3] the asymmetric transformation was also attempted via salt formation with optically active 10-camphorsulfonic acid. The asymmetric transformation, however, could not be achieved because the salt obtained was strongly hygroscopic.[3]

We found that a salt of *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-AcHpg] with (*R*)-α-methylbenzylamine [(*R*)-MBA] is less soluble than that of (*S*)-AcHpg with (*R*)-MBA. Asymmetric transformations of *N*-benzoyl-(*RS*)-2-phenylglycine[4] and *N*-acetyl-(*RS*)-2-phenylglycine[5] [(*RS*)-AcPhg] have been carried out by using optically active MBA and seem to proceed via epimerization promoted by MBA as a base-catalyst. The racemization rates of optically active aromatic *N*-acetylamino acids, therefore, were measured by using (*RS*)-MBA as a catalyst to examine an influence of the side chain; the *N*-acetylamino acids chosen were *N*-acetyl-(*S*)-tyrosine [(*S*)-AcTyr], *N*-acetyl-(*S*)-phenylalanine [(*S*)-AcPhe], (*R*)-AcHpg, (*R*)-AcPhg, and *N*-acetyl-(*S*)-alanine [(*S*)-AcAla]. The asymmetric transformation of (*RS*)-AcHpg, based on the result of racemization, was attempted by using (*R*)-MBA as a resolving agent and base-catalyst for epimerization to obtain (*R*)-Hpg effectively.

Although optical resolution of (*RS*)-Hpg may give both (*R*)- and (*S*)-Hpg, (*RS*)- and (*S*)-Hpg are not commercially obtainable and only (*R*)-Hpg is readily available. The asymmetric transformation of (*R*)-AcHpg into (*S*)-AcHpg, therefore, was also attempted by using (*S*)-MBA to obtain (*S*)-Hpg.

In what follows, the (*R*)·(*R*) salt denotes the salt of (*R*)-AcHpg with (*R*)-MBA, the (*S*)·(*S*) salt that of (*S*)-AcHpg with (*S*)-MBA, and the (*RS*)·(*R*) salt that of (*RS*)-AcHpg with (*R*)-MBA.

Experimental

Materials. (*S*)-Phenylalanine [(*S*)-Phe], (*R*)-Hpg, (*R*)-2-phenylglycine [(*R*)-Phg], (*S*)-alanine [(*S*)-Ala], and (*RS*)-, (*R*)-, and (*S*)-MBA were purchased from Wako Pure Chemicals Ind.

(*RS*)-Hpg was obtained by racemization of (*R*)-Hpg. A suspension of 0.626 mol (105 g) of (*R*)-Hpg in 700 cm³ of acetic acid was refluxed under stirring for 4 h and was then stirred for 30 min in an ice bath. The Hpg racemized was collected by filtration, washed thoroughly with 800 cm³ of ethanol, and dried; yield 95.2% (100 g); $[\alpha]_D^{20}$ −1.2° (*c* 1.00, 1 mol dm⁻³ HCl); lit,[6] of (*R*)-Hpg, $[\alpha]_D^{20}$ −160.0° (*c* 1, 1 mol dm⁻³ HCl). The solid was recrystallized from water to give (*RS*)-Hpg.

(*S*)-AcTyr ($[\alpha]_D^{20}$ +47.1° (*c* 0.500, water)) was purchased from Sigma Chemicals Co.; lit,[7] of (*S*)-AcTyr, $[\alpha]_D$ +47.3° (*c* 0.5, water). (*S*)-AcPhe ($[\alpha]_D^{20}$ +51.1° (*c* 1.00, ethanol), mp 170—171 °C), (*R*)-AcPhg ($[\alpha]_D^{20}$ −195° (*c* 0.500, water), mp 188—191 °C), and (*S*)-AcAla ($[\alpha]_D^{20}$ −64.9° (*c* 2.00, water), mp 125—126 °C) were obtained, respectively, by acetylating (*S*)-Phe, (*R*)-Phg, and (*S*)-Ala in the usual manner;[8] lit,[7] of (*S*)-AcPhe, $[\alpha]_D$ +51.4° (*c* 1, ethanol), mp 171 °C; lit,[9] of (*R*)-AcPhg, $[\alpha]_D$ −195.4° (*c* 0.55, water), mp 190—191 °C; lit,[7] of (*S*)-AcAla, $[\alpha]_D$ −66.2° (*c* 2.00, water), mp 125 °C.

Preparation of *N*-Acetyl-(*RS*)- and *N*-Acetyl-(*R*)-2-(4-hydroxyphenyl)glycine. Acetic anhydride (0.400 mol, 40.8 g) was added dropwise for 1 h to a mixture of 0.400 mmol (66.9 g) of (*RS*)- or (*R*)-Hpg in 2 dm^3 of acetic acid. After stirring for 30 h at room temperature, the mixture was dried under reduced pressure at 35 °C. The crude (*RS*)- or (*R*)-AcHpg obtained as the residue was recrystallized from ethanol to give the purified (*RS*)- or (*R*)-AcHpg. (*RS*)-AcHpg: Yield 92.3% (77.3 g); mp 217—220 °C. Found: C, 57.36; H, 5.29; N, 6.66%. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70%. (*R*)-AcHpg: Yield 96.6% (80.9 g); mp 211—213 °C; $[\alpha]_D^{20}$ −209° (*c* 0.500, water). Found: C, 57.62; H, 5.37; N, 6.89%.

Preparation of Standard Salts. To a solution of 10.0 mmol (2.09 g) of (*R*)-AcHpg in 50 cm^3 of ethanol was added 10.0 mmol (1.21 g) of (*R*)-MBA. After stirring the solution for 30 min at 50 °C and then for 30 min in an ice bath, the (*R*)·(*R*) salt precipitated was collected by filtration and recrystallized from ethanol. (*R*)·(*R*) salt: Yield 82.4% (2.72 g); mp 217—220 °C; $[\alpha]_D^{20}$ −126° (*c* 0.500, water). Found: C, 65.39; H, 6.64; N, 8.49%. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48%.

(*RS*)-AcHpg (10.0 mmol) and 10.0 mmol of (*R*)-MBA were dissolved in 170 cm^3 of ethanol. The solution was dried under reduced pressure at 30—35 °C and the (*RS*)·(*R*) salt obtained as the residue was washed thoroughly with diethyl ether and dried. (*RS*)·(*R*) salt: Yield 97.6% (3.22 g); mp 170—172 °C, 223—225 °C; $[\alpha]_D^{20}$ +7.5° (*c* 0.500, water). Found C, 65.29; H, 6.71; N, 8.41%.

Asymmetric Transformation. A mixture of 10.0 mmol (2.09 g) of (*RS*)-AcHpg and 30.0 (3.63 g) or 50.0 (6.06 g) mmol of (*R*)-MBA in a mixture of cumene (50 cm^3) and 1-hexanol (10 cm^3) was refluxed (approximately 150 °C) for 5 or 3 h, respectively. After stirring the mixture in an ice bath for 20 min, the (*R*)·(*R*) salt precipitated was collected by filtration, washed with a small amount of diethyl ether, and dried. To the filtrate was added 10.0 mmol of (*RS*)-AcHpg and 10.0 mmol of (*R*)-MBA; when 50.0 mmol of (*R*)-MBA was used in the initial asymmetric transformation, 1-hexanol (5 cm^3) was further added to the mixture. The mixture was refluxed for 5 or 3 h and then treated similarly by successively using the filtrate as the solvent. After refluxing a solution of the obtained (*R*)·(*R*) salt in 1 mol dm^{-3} hydrochloric acid (15 $cm^3\,g^{-1}$) for 2 h, the solution was dried under reduced pressure. To the residue obtained was added 20 cm^3 of water and the solution was then dried under reduced pressure; this operation was repeated three times. After dissolving the residue in ethanol (6 $cm^3\,g^{-1}$), an equimolar amount of triethylamine was added to the solution to obtain (*R*)-Hpg.

The asymmetric transformation of (*R*)-AcHpg into (*S*)-AcHpg was carried out similarly by using the initial solution of 10.0 mmol of (*R*)-AcHpg and 50.0 mmol of (*S*)-MBA and by refluxing for 10 h. After stirring a suspension of the obtained (*S*)·(*S*) salt in 1-propanol (4 $cm^3\,g^{-1}$) for 15 min at 40 °C and then for 45 min in an ice bath, the (*S*)·(*S*) salt[10] purified was collected by filtration. The salt purified was hydrolyzed in hydrochloric acid to give optically pure (*S*)-Hpg.

The optical purities of the (*R*)·(*R*) and (*S*)·(*S*) salts were estimated on the basis of the specific rotations of the standard (*R*)·(*R*) and (*RS*)·(*R*) salts and those of the (*R*)- and (*S*)-Hpg on the basis of the specific rotation[6] ($[\alpha]_D^{20}$ −160.0° (*c* 1, 1 mol dm^{-3} HCl)) of (*R*)-Hpg. The yields of the (*R*)·(*R*) or (*S*)·(*S*) salt and (*R*)- or (*S*)-Hpg were calculated on the basis of 10.0 mmol of the salt (3.30 g) and Hpg (1.67 g), respectively.

Rate Constant for Racemization. After dissolving 5.00 mmol of (*S*)-AcTyr, (*S*)-AcPhe, (*R*)-AcHpg, (*R*)-AcPhg, or (*S*)-AcAla in 100 cm^3 of 1-hexanol at 130 °C, followed by addition of 5.00—50.0 mmol of (*RS*)-MBA to the solution, the solution was stirred at 130 °C. A 5-cm^3 aliquot of the solution was pipetted out at appropriate time intervals and was then cooled rapidly; after pipetting out the solution (5 cm^3) of (*S*)-AcAla, 5 cm^3 of methanol and 1 cm^3 of 6 mol dm^{-3} of hydrochloric acid were added to the solution. The optical rotation of the solution was measured at 589 nm with a Union Giken PM-101 digital polarimeter equipped with a quartz cell of 5.00 cm path length. The rate constant for racemization (k_R/s^{-1}) was calculated by the least-squares method from

$$\ln \alpha_0/\alpha_t = k_R \cdot t, \quad (1)$$

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time. The half-life period was calculated by using the k_R value from Eq. 1.

Results and Discussion

Racemization of Optically Active Aromatic *N*-Acetylamino Acids and Substituent Effect. The racemization rates of (*S*)-AcTyr, (*S*)-AcPhe, (*R*)-AcHpg, (*R*)-AcPhg, and (*S*)-AcAla were measured to examine the possibility of asymmetric transformation. The racemization of the *N*-acetylamino acids obeyed the first-order kinetics of Eq. 1. The rate constant (k_R/s^{-1}) and half-life period ($t_{1/2}/s$) are summarized in Table 1 and are shown in Fig. 1.

In the racemization of these optically active *N*-acetylamino acids, the k_R value tended to increase with an increase in the amount of (*RS*)-MBA and, when a 4—10 molar equivalent of (*RS*)-MBA was used per the *N*-acetylamino acid, became approximately constant, as seen in Fig. 1. The racemization rate constants were in the order (*R*)-AcPhg>(*R*)-AcHpg>(*S*)-AcPhe>(*S*)-AcTyr>(*S*)-AcAla.

The Taft equation given by Eq. 2[11] expresses a quantitative relationship between the polar substituent constant (σ^*) of the amino acid side chain and the rate constant for racemization in an aqueous solution.[12]

Table 1. Kinetic Data for Racemization[a]

Optically active *N*-acetylamino acid[b]	Rate constant $10^{-4}\,s^{-1}$	Half-life period 10^3 s
(*S*)-AcTyr	0.232	29.9
(*S*)-AcPhe	0.321	21.6
(*R*)-AcHpg	3.17	2.19
(*R*)-AcPhg	8.38	0.821
(*S*)-AcAla	0.0400	173

a) Conditions: Optically active *N*-acetylamino acid 5.00 mmol; (*RS*)-α-methylbenzylamine 25.0 mmol; 1-hexanol 100 cm^3; temperature 130 °C. b) Abbreviations: (*S*)-AcTyr, *N*-acetyl-(*S*)-tyrosine; (*S*)-AcPhe, *N*-acetyl-(*S*)-phenylalanine; (*R*)-AcHpg, *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine; (*R*)-AcPhg, *N*-acetyl-(*R*)-2-phenylglycine; (*S*)-AcAla, *N*-acetyl-(*S*)-alanine.

$$\log k/k_0 = \rho^* \cdot \sigma^*, \quad (2)$$

where k and k_0 are a rate constant and that of a standard substance, respectively, and ρ^* the reaction constant; the σ^* values of 4-hydroxybenzyl,[13] benzyl,[11] 4-hydroxyphenyl,[13] phenyl,[11] and methyl[11] groups are 0.18, 0.215, 0.49, 0.600, and 0, respectively. A relationship between $\log k_R/k_0$ and σ^* is shown in Fig. 2; the rate constant of (*S*)-AcAla was taken as k_0, and the k_R values measured in the presence of 25.0 mmol of (*RS*)-MBA were used because the rate of racemization was not influenced by the amount of (*RS*)-MBA in a range of 20.0—50.0 mmol of (*RS*)-MBA (Fig. 1).

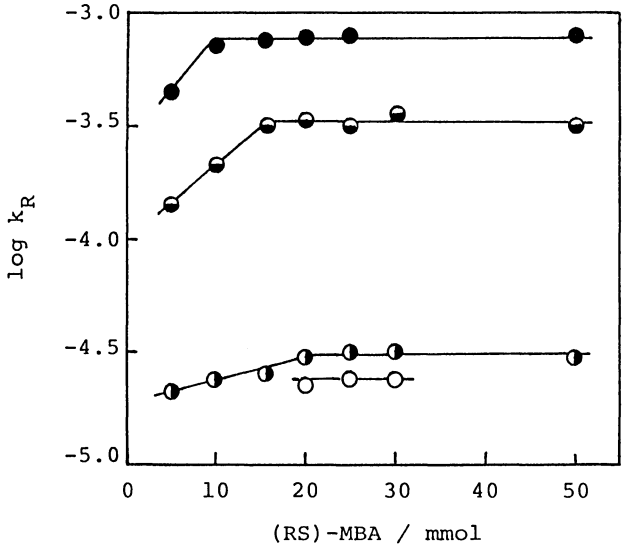

Fig. 1. Rate constant for racemization of optically active aromatic *N*-acetylamino acids.
Conditions: Optically active *N*-acetylamino acid 5.00 mmol; (*RS*)-α-methylbenzylamine 5.00—50.0 mmol; 1-hexanol 100 cm³; temperature 130 °C. ○, *N*-Acetyl-(*S*)-tyrosine; ◑, *N*-acetyl-(*S*)-phenylalanine; ◒, *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine; ●, *N*-acetyl-2-phenylglycine.

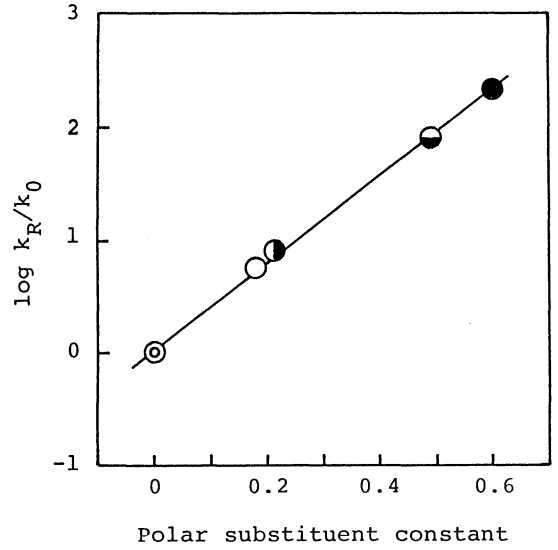

Fig. 2. Influence of side chain of the *N*-acetylamino acids on the rate of racemization.
Conditions: See footnote in Table 1. k_R/s^{-1}: Rate constant for racemization. k_0/s^{-1}: Rate constant for racemization of *N*-acetyl-(*S*)-alanine. ○, *N*-Acetyl-(*S*)-tyrosine; ◑, *N*-acetyl-(*S*)-phenylalanine; ◒, *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine; ●, *N*-acetyl-(*R*)-2-phenylglycine; ◎, *N*-acetyl-(*S*)-alanine.

A good linear relationship is noted between $\log k_R/k_0$ and σ^*; the ρ^* value was 3.81 and the correlation coefficient 0.999. The k_R value increased with an increase in the σ^* value, namely, the electron-withdrawing property of the side chain. The racemization seems to be base-catalyzed by (*RS*)-MBA and thus proceed via carbanion formation by α-proton abstraction, followed by enol formation. The above tendency suggests that the electron-withdrawing side chain results in an increase in the stability of the carbanion, and hence the racemization is accelerated. The rate-determining step, therefore, seems to be the α-proton abstraction by (*RS*)-MBA. Since the 4-hydroxyphenyl group on (*R*)-AcHpg seems to be neither electron-donating nor electron-withdrawing, its racemization is extremely faster than (*S*)-AcTyr and (*S*)-AcPhe with a strongly electron-donating side chain though the rate is slower than that of (*R*)-AcPhg with an electron-withdrawing phenyl group, as seen in Fig. 2; the σ^* value of hydrogen

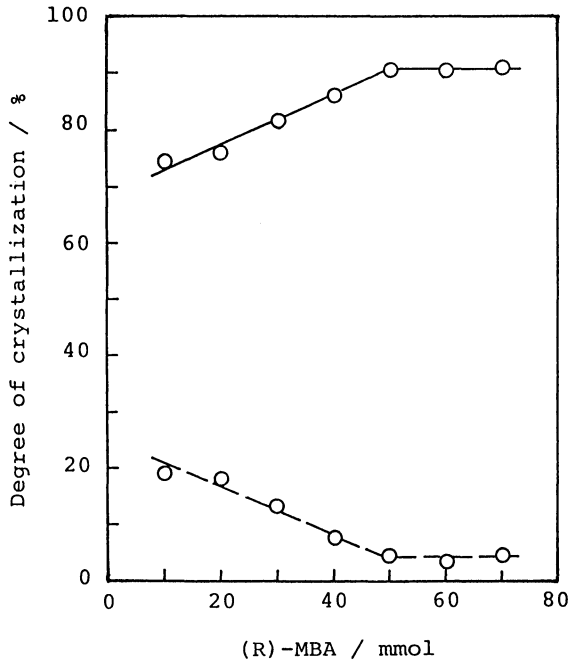

Fig. 3. Influence of amount of (*R*)-α-methylbenzylamine on asymmetric transformation of *N*-acetyl-2-(4-hydroxyphenyl)glycine.
Conditions: *N*-Acetyl-(*RS*)-2-(4-hydroxyphenyl)glycine [(*RS*)-AcHpg] 10.0 mmol; (*R*)-α-methylbenzylamine [(*R*)-MBA] 10.0—70.0 mmol; a mixture of cumene (50 cm³) and 1-hexanol (10 cm³) was used as solvent; temperature 150 °C; stirring time 3 h. Degree of crystallization: —— Salt of (*R*)-AcHpg with (*R*)-MBA; ---- salt of (*S*)-AcHpg with (*R*)-MBA.

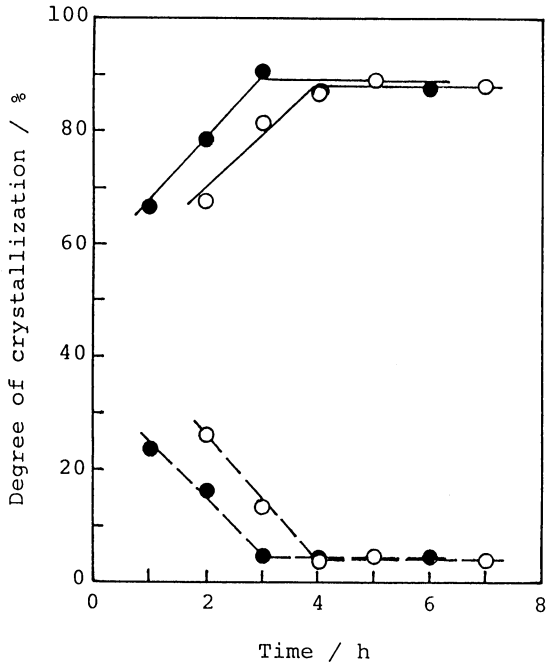

Fig. 4. Asymmetric transformation of *N*-acetyl-(*RS*)-2-(4-hydroxyphenyl)glycine.
Conditions: *N*-Acetyl-(*RS*)-2-(4-hydroxyphenyl)glycine [(*RS*)-AcHpg] 10.0 mmol; (*R*)-α-methylbenzylamine [(*R*)-MBA] 30.0 (○) and 50.0 mmol (●); a mixture of cumene (50 cm³) and 1-hexanol (10 cm³) was used as solvent; temperature 150 °C. Degree of crystallization: —— Salt of (*R*)-AcHpg with (*R*)-MBA; ---- salt of (*S*)-AcHpg with (*R*)-MBA.

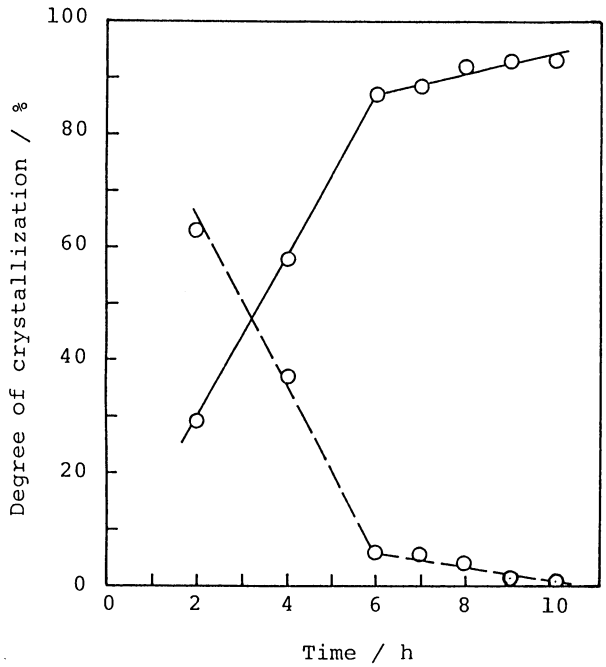

Fig. 5. Asymmetric transformation of *N*-acetyl-(*R*)-2-(4-hydroxyphenyl)glycine into (*S*)-enantiomer.
Conditions: *N*-Acetyl-(*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-AcHpg] 10.0 mmol; (*S*)-α-methylbenzylamine [(*S*)-MBA] 50.0 mmol; a mixture of cumene (50 cm³) and 1-hexanol (10 cm³) was used as solvent; temperature 150 °C. Degree of crystallization: —— Salt of (*S*)-AcHpg with (*S*)-MBA; ---- salt of (*R*)-AcHpg with (*S*)-MBA.

atom is 0.490.[11] The $t_{1/2}$ value of (*R*)-AcHpg, therefore, was 0.6 h and those of (*S*)-AcPhe and (*S*)-AcTyr were extremely large (6 and 8 h).

The above result suggests a possibility of the asymmetric transformation of (*RS*)-AcHpg by use of optically active MBA as base-catalyst for epimerization.

Asymmetric Transformation of *N*-Acetyl-(*RS*)- and *N*-Acetyl-(*R*)-2-(4-hydroxyphenyl)glycine. The asymmetric transformation of (*RS*)-AcPhg was achieved as in a previous work.[5] The results of racemization suggest that the rates of epimerization for the salts of AcTyr and AcPhe are extremely slower than those for the salts of AcHpg and AcPhg. The asymmetric transformation of (*RS*)-AcPhe gave poor results under various conditions; for example, the salt of (*R*)-AcPhe with (*S*)-MBA of 47% optical purity[14] was obtained in 69% yield by refluxing 10.0 mmol of (*RS*)-AcPhe and 50.0 mmol of (*S*)-MBA in 60 cm³ of cumene at 145 °C for 10 h.

The asymmetric transformation of (*RS*)-AcHpg was achieved and gave the (*R*)·(*R*) salt as a less soluble diastereomeric salt. The result is shown in Figs. 3 and 4. The degrees of crystallization of the (*R*)·(*R*) and (*S*)·(*R*) salts ($DC_{(R)\cdot(R)}$ and $DC_{(S)\cdot(R)}$/%) were calculated from the formulae

$$DC_{(S)\cdot(R)}/\% = (1/2)[\text{Yield}/\% \times (100 - \text{Optical purity}/\%]/100, \quad (3)$$

$$DC_{(R)\cdot(R)}/\% = \text{Yield}/\% - DC_{(S)\cdot(R)}/\%, \quad (4)$$

The asymmetric transformation was influenced by the amount of (*R*)-MBA, as expected from the result of racemization. Since the racemization rate of (*R*)-AcHpg was measured under homogeneous conditions, whereas the asymmetric transformation was carried out under heterogeneous ones, the optimum conditions for the asymmetric transformation may not always be the same as those for the racemization. Optimization of the amount of (*R*)-MBA, therefore, was conducted by refluxing 10.0 mml of (*RS*)-AcHpg and 10.0—70.0 mmol of (*R*)-MBA in a mixture of cumene (50 cm³) and 1-hexanol (10 cm³) under stirring for 3 h (Fig. 3). When 50.0—70.0 mmol of (*R*)-MBA were used, the $DC_{(R)\cdot(R)}$ and $DC_{(S)\cdot(R)}$ values became approximately constant and the (*R*)·(*R*) salts of 90—93% optical purity were obtained in 95% yield. Even the asymmetric transformation by using 30.0 mmol of (*R*)-MBA gave the (*R*)·(*R*) salt of 73% optical purity in 94% yield. In addition, Figure 4 shows that the asymmetric transformation by using 30.0 mmol of (*R*)-MBA gives the (*R*)·(*R*) salts of 91% optical purity in 92% yield at 5 and 7 h and by 50.0 mmol the salt of 90% optical purity in 87—90% yield at 3—6 h.

The asymmetric transformation of (*R*)-AcHpg, based on the above result, was attempted by using 50.0 mmol

Table 2. Asymmetric Transformation of *N*-Acetyl-(*RS*)- and *N*-Acetyl-(*R*)-2-(4-hydroxyphenyl)glycine[a)]

Starting AcHpg	Run	Reaction time	Added amount of MBA	Salt obtained			Hpg obtained	
				Configuration[b)]	Yield	Optical purity	Yield[c)]	Optical purity
		h	mmol		g[%[c)]]	%	%	%
(*RS*)-AcHpg	1	5	30.0 (*R*)	(*R*)·(*R*)	2.97[90.0]	92.5	(*R*) 81.9	91.0
	2	5	10.0 (*R*)	(*R*)·(*R*)	3.03[91.8]	94.8	(*R*) 82.0	97.2
	3	5	10.0 (*R*)	(*R*)·(*R*)	3.05[92.4]	95.5	(*R*) 82.5	94.0
	4	5	10.0 (*R*)	(*R*)·(*R*)	3.03[91.8]	95.5	(*R*) 81.4	95.9
(*RS*)-AcHpg	1	3	50.0 (*R*)	(*R*)·(*R*)	3.14[95.2]	90.3	(*R*) 85.1	87.5
	2[d)]	3	10.0 (*R*)	(*R*)·(*R*)	3.18[96.4]	100	(*R*) 87.0	100
	3[e)]	3	10.0 (*R*)	(*R*)·(*R*)	3.20[97.0]	100	(*R*) 87.8	100
	4	3	10.0 (*R*)	(*R*)·(*R*)	3.28[99.4]	100	(*R*) 90.3	100
	5	3	10.0 (*R*)	(*R*)·(*R*)	3.21[97.3]	100	(*R*) 87.9	100
(*R*)-AcHpg	1	10	50.0 (*S*)	(*S*)·(*S*)	3.13[94.8]	98.5	(*S*) 85.9	99.2
	2	10	10.0 (*S*)	(*S*)·(*S*)	3.14[95.2]	94.0	(*S*) 85.1	93.4
				(*S*)·(*S*)	2.88[87.3][f)]	100	(*S*) 79.5	100
	3	10	10.0 (*S*)	(*S*)·(*S*)	3.16[95.8]	96.5	(*S*) 87.1	95.7
				(*S*)·(*S*)	2.99[90.6][f)]	100	(*S*) 81.6	100

a) Conditions: *N*-Acetyl-2-(4-hydroxyphenyl)glycine [AcHpg] 10.0 mmol; a mixture of cumene (50 cm³) and 1-hexanol (10 cm³) was used as solvent in Run 1; the asymmetric transformations in Runs 2—5 were carried out by adding 10.0 mmol of (*R*)- or (*RS*)-AcHpg and (*S*)- or (*R*)-α-methylbenzylamine [MBA] to the filtrate in Runs 1—4, respectively; temperature 150 °C. b) (*S*)·(*S*) denotes the salt of (*S*)-AcHpg with (*S*)-MBA, and (*R*)·(*R*) that of (*R*)-AcHpg with (*R*)-MBA. c) Yields of the obtained salt and 2-(4-hydroxyphenyl)glycine [Hpg] were calculated on the basis of 10.0 mmol of the salt (3.30 g) and Hpg (1.67 g), respectively. d) 1-Hexanol (5 cm³) was added to the filtrate in Run 1. e) 1-Hexanol (1 cm³) was added to the filtrate in Run 2. f) The (*S*)·(*S*) salt purified.

of (*S*)-MBA to obtain (*S*)-Hpg (Fig. 5). The $DC_{(S)\cdot(S)}$ and $DC_{(R)\cdot(S)}$ values were calculated by exchanging the subscripts (*R*) and (*S*) in Eqs. 3 and 4. Although the asymmetric transformation of (*R*)-AcHpg into (*S*)-AcHpg required a longer time than that of (*RS*)-AcHpg, those at 8—10 h gave the (*S*)·(*S*) salts of 92—98% optical purity in 94—96% yield, as seen in Fig. 5.

Asymmetric Transformation by Successive Use of Filtrate as Solvent. The above results suggest that a desired enantiomer of Hpg could be obtained by asymmetric transformation. These asymmetric transformations, however, may be an inefficient procedure because a single asymmetric transformation requires 3 or 5 molar equivalents of optically active MBA per (*RS*)- or (*R*)-AcHpg. The asymmetric transformations of (*RS*)- and (*R*)-AcHpg, therefore, were attempted by using successively the filtrate as a solvent. The results are summarized in Table 2.

The asymmetric transformation by initially using 30.0 mmol of (*R*)-MBA gave the (*R*)·(*R*) salts of 92—96% optical purity in 90—92% yield. The asymmetric transformation by using 50.0 mmol of (*R*)-MBA was more successful and gave optically pure (*R*)·(*R*) salts in 96—99% yield in Runs 2—5. Optically pure (*R*)-Hpg was obtained by hydrolysis of the salts in hydrochloric acid in 87—90% yield based on the starting (*RS*)-AcHpg. In the asymmetric transformation of (*R*)-AcHpg, the (*S*)·(*S*) salts of 94—99% optical purity were obtained in 95 or 96% yield in Runs 1—3. The salts purified were hydrolyzed to give optically pure (*S*)-Hpg in 80% yield based on the starting (*R*)-AcHpg. Further, the yield of (*R*)-Hpg was estimated to be 80% from (*RS*)-Hpg and that of (*S*)-Hpg to be 75% from (*R*)-Hpg.

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10) Optically pure (*S*)·(*S*) salt: $[\alpha]_D^{20}$ +126° (*c* 0.500, water). Found: C, 65.17; H, 6.67; N, 8.45%.
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13) The σ^* value of the 4-hydroxyphenyl group is given from a linear relationship between the σ^* value of 3- and 4-substituted phenyl groups and the normal substituent constant (σ°) of their 3- and 4-substituents; Y. Nagai, H. Matsumoto, T. Nakano, and H. Watanabe, *Bull. Chem. Soc. Jpn.*, **45**, 2560 (1972); Y. Nagai, *Kagaku no Ryoiki*, **27**, 221 (1973). Altough the σ^* value of the phenyl group was estimated from the relationship to be 0.54, the value reported by Taft is 0.600; Ref. 11. The σ^* value of the 4-hydroxyphenyl group, therefore, was estimated from the equation described below in order to match these two values of the phenyl group.

$$\sigma^* = 0.86 \cdot \sigma^\circ + 0.60.$$

The σ^* value of the 4-hydroxyphenyl group was obtained as 0.49 by this equation and that of the 4-hydroxybenzyl group as 0.18 by dividing 0.49 by 2.8; the σ^* values of the 4-hydroxybenzyl and 4-hydroxyphenyl groups were also estimated from the Taft equation based on the k_R values of (*S*)-AcPhe, (*R*)-AcPhg, and (*S*)-AcAla to be 0.191 and 0.486, respectively.

14) The optical purity of the salt obtained was estimated on the basis of the specific rotations of the salt of (*S*)-AcPhe with (*R*)-MBA ($[\alpha]_D^{20}$ +60.5° (*c* 1.00, ethanol)) and the salt of (*RS*)-AcPhe with (*R*)-MBA ($[\alpha]_D^{20}$ +4.6° (*c* 1.00, ethanol)).