Asymmetric Transformation of (*RS*)-2-Phenylglycine via Formation of Salt with (1*S*)-10-Camphorsulfonic Acid

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An asymmetric transformation of (*RS*)-2-phenylglycine [(*RS*)-Phg] was carried out via formation of a salt with (1*S*)-10-camphorsulfonic acid [(*S*)-CS] in acetic acid, propanoic acid, or butanoic acid by heating at 100 °C without using any catalysts such as aldehydes. The rate of epimerization of a more soluble salt of (*S*)-Phg with (*S*)-CS was estimated to be lowest in acetic acid and highest in butanoic acid. The asymmetric transformation in propanoic acid, however, was achieved successfully to give the salt of (*R*)-Phg with (*S*)-CS with 100% optical purity in 82% yield. Optically pure (*R*)-Phg was obtained from the salt in 80% yield based on the (*RS*)-Phg used as the starting material.

(*R*)-2-Phenylglycine [abbreviated as (*R*)-Phg] as a useful material for ampicillin has been obtained from synthetic (*RS*)-Phg by optical resolution[1-6] because (*R*)-Phg is not found in natural amino acids. (*S*)-Phg, however, is also given by optical resolution but is not of value as a material for ampicillin. Asymmetric transformation is carried out by combination of selective crystallization of a less soluble diastereomeric salt with epimerization of a more soluble salt, and has a possibility of converting a racemate solely into a desirable enantiomer. (1*S*)-10-Camphorsulfonic acid [(*S*)-CS] is a good resolving agent for the optical resolution of (*RS*)-Phg because (*S*)-CS is easily available and forms a salt with (*R*)-Phg as a less soluble diastereomeric salt without coverting (*RS*)-Phg into any derivatives such as ester. The asymmetric transformation of (*RS*)-Phg has been attempted via formation of the salt with (*S*)-CS in acetic acid in the presence of salicylaldehyde as a catalyst for epimerization.[7] Since the presence of aldehyde, such as salicylaldehyde, in the reaction system raises the solubility of the less soluble salt, the yield of the salt of (*R*)-Phg with (*S*)-CS [(*R*)·(S) salt] seems not to be so high.[7]

Optically active (*R*)- and (*S*)-Phg were apt to racemize on heating in carboxylic acid. We, therefore, tried asymmetric transformations of (*RS*)-Phg by heating in acetic acid, propanoic acid, or butanoic acid without using any catalyst, such as aldehyde, to establish a more efficient method for obtaining (*R*)-Phg. In addition, rates of racemization of (*R*)-Phg and (*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-Hpg] were examined in these carboxylic acids to estimate the rate of epimerization of the more soluble salt of (*S*)-Phg with (*S*)-CS [(*S*)·(S) salt].

Experimental

Materials. (*RS*)- and (*R*)-Phg, (*R*)-Hpg, and (*RS*)- and (*S*)-CS were purchased from Wako Pure Chemicals Ind.

Asymmetric Transformation. A mixture of 20.0 mmol (3.02 g) of (*RS*)-Phg and 18.0 (4.18 g), 19.0 (4.41 g), or 20.0 (4.64 g) mmol of (*S*)-CS in 10 cm³ of acetic acid, propanoic acid, or butanoic acid was stirred for 1—10 h at 100 °C. After further adding 1.00 mmol (0.232 g) and 2.00 mmol (0.464 g) of (*S*)-CS to the mixture at 60 °C in the reaction consuming 19.0 and 18.0 mmol of (*S*)-CS, respectively, the mixture was stirred for 5 min at 60 °C and successively for 20 min in an ice bath. The formed (*R*)·(*S*) salt was filtered off, washed with diethyl ether, and dried. The optical purity of the obtained salt was determined on the basis of the specific rotations of the salts of Phg with (*S*)-CS: (*R*)·(S) salt, $[\alpha]_D^{25}$ −49.7° (*c* 2, 1 mol dm⁻³ HCl);[7] the salt of (*RS*)-Phg with (*S*)-CS, $[\alpha]_D^{25}$ +13.6° (*c* 2, 1 mol dm⁻³ HCl).[7] The degrees of crystallization of the (*R*)·(*S*) and (*S*)·(*S*) salts ($DC_{(R)}$ and $DC_{(S)}$/%) were calculated by

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

$$DC_{(R)}/\% = [\text{Yield}/\% \times \text{Optical purity}/\%] + DC_{(S)}/\%. \quad (2)$$

The obtained salt was dissolved in methanol (10 cm³ g⁻¹) at room temperature. After adding an equivalent of triethylamine to the solution, the mixture was stirred for 0.5 h in an ice bath. The precipitated (*R*)-Phg was filtered off, washed with methanol, and dried. The optical purity of the obtained (*R*)-Phg was determined on the basis of the specific rotation ($[\alpha]_D^{20}$ −157.8° (dil HCl))[8] of authentic (*R*)-Phg.

Rate Constant for Racemization. (*R*)-Phg (0.151 g, 1.00 mmol) or (*R*)-Hpg (0.167 g, 1.00 mmol) and (*RS*)-CS (0.220 g, 0.950 mmol or 0.232 g, 1.00 mmol) were immediately dissolved in 30 cm³ of acetic acid, propanoic acid, or butanoic acid or in a mixture of 30 cm³ of the carboxylic acid and 3 cm³ of water at 100 °C, respectively. Portions of the solution were pipetted out at appropriate time intervals and the optical rotation was measured. The rate constant (k_R/s⁻¹) for racemization was calculated by the least-squares method from

$$\ln \alpha_0/\alpha_t = k_R \cdot t, \quad (3)$$

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time. The half-life period ($t_{1/2}$/s) was calculated on the basis of the obtained k_R value.

Measurement. Optical and specific rotations at 589 nm were measured with a Union Giken PM-101 digital

polarimeter equipped with a quartz cell of 0.100 or 0.500 dm path length.

A mixture of (*RS*)-Phg (20.0 mmol) and (*RS*)-CS (20.0 mmol) in 20 cm^3 of acetic acid, propanoic acid, or butanoic acid was stirred for 2 h at 100 °C and successively for 5 h at 10 °C. The formed salt of (*RS*)-Phg with (*RS*)-CS [(*RS*)·(*RS*) salt] was rapidly filtered off, washed with diethyl ether, and thoroughly dried. The solubilities of the (*RS*)·(*RS*) salt in acetic acid, propanoic acid, or butanoic acid at 10 °C were estimated on the basis of the weight of the (*RS*)·(*RS*) salt and those of the (*RS*)-Phg and (*RS*)-CS used as the starting materials.

Results and Discussion

Racemization of (*R*)-2-Phenylglycine and (*R*)-2-(4-Hydroxyphenyl)glycine. One of the major problems in asymmetric transformation is the rate of epimerization of a more soluble diastereomeric salt, that is, the racemization of optically active substances. (*R*)-Phg was racemized by heating in carboxylic acid; for example, (*R*)-Phg (20.0 mmol) was stirred for 3 h at 100 °C in 10 cm^3 of acetic acid and successively for 20 min in an ice bath to give approximately racemic Phg ($[\alpha]_D^{20}$ −3.6° (*c* 1.00, 1 mol dm^{-3} HCl)) in 97.7% (2.95 g) yield. The rates of racemization of (*R*)-Phg and (*R*)-Hpg, therefore, were measured in acetic acid, propanoic acid, or butanoic acid in the presence of (*RS*)-CS at 100 °C, as described in the experimental section. The rates of (*R*)-Hpg in propanoic acid or butanoic acid were measured in mixtures of 30 cm^3 of the carboxylic acid and 3 cm^3 of water because (*R*)-Hpg did not dissolve completely in these carboxylic acids. Since the racemization of (*R*)-Phg and (*R*)-Hpg in the carboxylic acids is an acid-catalyzed reaction, the rates depend upon the concentration of (*R*)-Phg or (*R*)-Hpg and the carboxylic acid. The racemization, however, could be regarded as a pseudo first-order reaction because the carboxylic acids existed in large excess in the reaction system and linear relationships were found between $\ln \alpha_0/\alpha_t$ and time *t*. The rate constant of racemization (k_R/s^{-1}) and the half-life period ($t_{1/2}/s$) are listed in Table 1.

The racemization involves protonation of the carbonyl oxygen atom in the carboxyl group, followed by the loss of α-hydrogen atom by formation of the enol; these steps are reversible.[9] (*RS*)-CS acts as an extremely stronger proton donor for the amino groups in (*R*)-Phg and (*R*)-Hpg than the carboxylic acids. The presence of the positively charged nitrogen atom resulting from such a protonation hinders the second protonation of the carbonyl oxygen atom.[9] The rate of racemization in the presence of free (*R*)-Phg or (*R*)-Hpg, therefore, is more speeded up than in the presence of equimolar amounts of (*R*)-Phg or (*R*)-Hpg and (*RS*)-CS. The ammonium ion in (*R*)-Hpg is estimated to be more stable by the presence of the hydroxyl group on the aromatic ring than in (*R*)-Phg. The rate of racemization of (*R*)-Hpg, therefore, is slower than that of (*R*)-Phg.

Since the rate-determining step is the formation of

Table 1. Rate Constant and Half-Life Period for Racemization[a]

(*R*)-Amino acid	Conditions			k_R[d]	$t^{1/2}$
	Carboxylic acid[b]	Water / cm^3	(*RS*)-CS[c] / mmol	10^{-4} s^{-1}	10^2 s
(*R*)-Phg	AcA	0	0.95	4.63	15.0
		3	0.95	2.11	32.9
		0	1.00	4.14	16.7
		3	1.00	1.17	59.2
	PrA	0	0.95	14.0	4.95
		3	0.95	3.63	19.1
		0	1.00	8.23	8.42
		3	1.00	2.59	26.8
	BuA	0	0.95	80.0	0.866
		3	0.95	4.23	16.4
		0	1.00	44.7	1.55
		3	1.00	2.77	25.0
(*R*)-Hpg	AcA	0	0.95	1.24	55.9
		3	0.95	0.476	146
		0	1.00	0.508	136
		3	1.00	0.238	291
	PrA	3	0.95	0.810	85.6
		3	1.00	0.486	143
	BuA	3	0.95	0.920	75.3
		3	1.00	0.555	125

a) Conditions: (*R*)-2-phenylglycine [(*R*)-Phg] 1.00 mmol; (*R*)-2-(4-hydroxyphenyl)glycine [(*R*)-Hpg] 1.00 mmol; carboxylic acid 30 cm^3; temperature 100 °C. b) AcA=acetic acid; PrA=propanoic acid; BuA=butanoic acid. c) (*RS*)-CS: (1*RS*,4*SR*)-10-Camphorsulfonic acid. d) k_R: Rate constant for racemization. e) $t_{1/2}$: Half-life period.

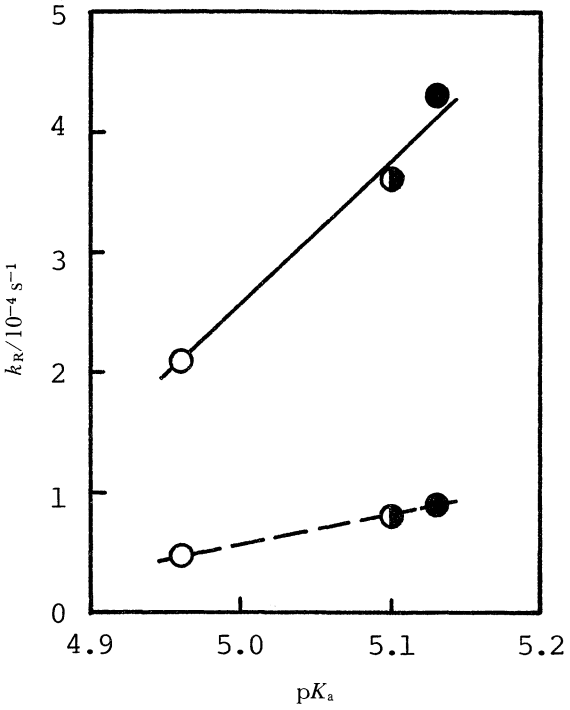

Fig. 1. Rate constant for racemization in carboxylic acids. pK_a: The value at 100 °C was estimated from data 0—60 °C. —: (*R*)-2-Phenylglycine (1.00 mmol). ---: (*R*)-2-(4-Hydroxyphenyl)glycine (1.00 mmol). (1*RS*,4*SR*)-10-Camphorsulfonic acid: 0.95 mmol. Temperature: 100 °C. Solvent: Mixture of 30 cm^3 of carboxylic acid and 3 cm^3 of water. k_R: Rate constant for racemization. Carboxylic acid: ○ Acetic acid; ◑ propanoic acid; ● butanoic acid.

the enol by abstract of the α-hydrogen atom by the carboxylate anion, the rates of racemization of (*R*)-Phg and (*R*)-Hpg seem to be dependent of the basicity of the carboxylate anions, that is, the acidity of the carboxylic acids employed as the solvent. The acidity constants at 100 °C of the carboxylic acids were estimated from data at 0—60 °C;[10] the pK_a values of acetic acid, propanoic acid, and butanoic acid were calculated to be 4.96, 5.10, and 5.13,[10] respectively. The relationship between the k_R and pK_a values is shown in Fig. 1.

The k_R value increased with increase in the pK_a value; k_R values obtained under other conditions, in Table 1, had a tendency to change similar to that shown in Fig. 1. The acidity constant suggests that the order of proton abstraction at 100 °C should be butanoate anion>propanoate anion>acetate anion, and hence the racemization of (*R*)-Phg and (*R*)-Hpg are speeded up in this order. The epimerization of the more soluble (*S*)·(*S*) salt, therefore, is estimated to be most rapid in butanoic acid and to be slowest in acetic acid.

Asymmetric Transformation of (*RS*)-2-Phenylglycine. Influence of Reaction Amount of (1*S*)-10-Camphorsulfonic Acid: The preceding result suggests that

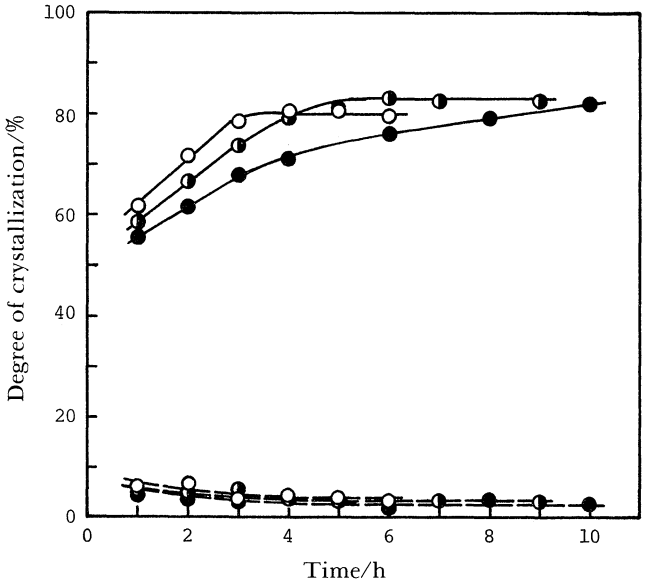

Fig. 2. Influence of amount of (1*S*)-10-camphorsulfonic acid on asymmetric transformation. (*RS*)-2-Phenylglycine [(*RS*)-Phg]: 20.0 mmol. (1*S*)-10-Camphorsulfonic acid [(*S*)-CS]: ○ 18.0 mmol; ◑ 19.0 mmol; ● 20.0 mmol. Solvent: 10 cm^3 of butanoic acid. Temperature: 100 °C. —: Salt of (*R*)-Phg with (*S*)-CS. ---: Salt of (*S*)-Phg with (*S*)-CS.

the rate of epimerization of the more soluble (*S*)·(*S*) salt is most rapid in butanoic acid and is increased in the presence of free (*RS*)-Phg. The asymmetric transformation of (*RS*)-Phg was tried in butanoic acid by consuming 20.0 mmol of (*RS*)-Phg and 18.0, 19.0, or 20.0 mmol of (*S*)-CS. The relationship between the degree of crystallization of the (*R*)·(*S*) and (*S*)·(*S*) salts and reaction time is shown in Fig. 2. Although the asymmetric transformation of (*RS*)-Hpg was attempted similarly to that of (*RS*)-Phg, the formed salt could not be obtained because the salt was strongly hygroscopic.

As shown in Fig. 2, after a rapid crystallization of the (*R*)·(*S*) salt in a short time period, the degree of crystallization of the (*R*)·(*S*) salt reached a maximal value and subsequently became constant in spite of elapse of time; when 20.0 mmol of (*S*)-CS was consumed, the degree of crystallization seemed to increase gradually even at 10 h. The epimerization of the (*S*)·(*S*) salt seems to be most rapid when 18.0 mmol of (*S*)-CS was consumed, as shown in Fig. 2. This result agreed with the estimate from the racemization of (*R*)-Phg. The asymmetric transformation consuming 18.0 mmol of (*S*)-CS, however, requires the addition of 2.00 mmol of (*S*)-CS after reaction at 100 °C and the formed salt should be the salt of (*RS*)-Phg with (*S*)-CS. The optical purity of the obtained (*R*)·(*S*) salt, therefore, was lower than those obtained by consuming 19.0 and 20.0 mmol of (*S*)-CS. Although the asymmetric transformation consuming 20.0 mmol of (*S*)-CS may give the (*R*)·(*S*) salt

with higher optical purity in higher yield, acquisition of such (*R*)·(*S*) salt requires extremely long time. The asymmetric transformation consuming 19.0 mmol of (*S*)-CS gave the (*R*)·(*S*) salt with 92% optical purity in 86% yield after reaction for 6 h. These results suggest that the favorable amount of (*S*)-CS is 19.0 mmol for 20.0 mmol of (*RS*)-Phg.

Influence of Carboxylic Acid Used as Solvent: The asymmetric transformation was carried out by reacting 20.0 mmol of (*RS*)-Phg and 19.0 mmol of (*S*)-CS at 100 °C in acetic acid, propanoic acid, or butanoic acid. These results are listed in Table 2 and shown in Fig. 3.

The solubilities of the salt of (*RS*)-Phg with (*RS*)-CS [(*RS*)·(*RS*) salt] at 10 °C in acetic acid, propanoic acid, and butanoic acid were 6.97, 4.19, and 2.61 g/(100 cm^3 of carboxylic acid), respectively; the (*RS*)·(*RS*) salt is estimated to consist of equimolar amounts of the (*R*)·(*S*) salt and its enantiomer. The order of solubilities of the (*R*)·(*S*) and (*S*)·(*S*) salts are estimated to be equal to that of the (*RS*)·(*RS*) salt. The asymmetric transformation in propanoic acid and butanoic acid gave the (*R*)·(*S*) salt with over 90% optical purity in over 80% yield by reaction for 5—9 h. Although the (*R*)·(*S*) salt obtained by a reaction for 1—5 h in acetic acid had 92—95% optical purity, the yield was low (55—60%) because the (*R*)·(*S*) and (*S*)·(*S*) salts are more soluble in acetic acid than in propanoic acid or butanoic acid. In addition, the epimerization of the (*S*)·(*S*) salt in acetic acid seems to be extremely slower than those in propanoic acid or

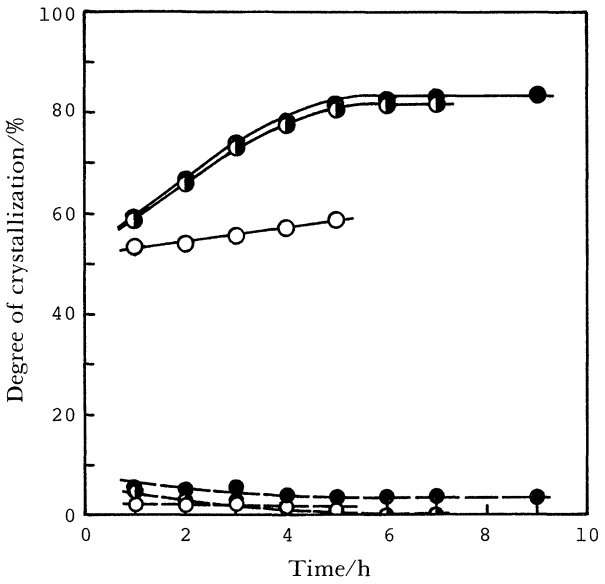

Fig. 3. Influence of carboxylic acid used as solvent on asymmetric transformation. (*RS*)-2-Phenylglycine [(*RS*)-Phg]: 20.0 mmol. (1*S*)-10-Camphorsulfonic acid [(*S*)-CS]: 19.0 mmol. Solvent: ○ Acetic acid; ◑ propanoic acid; ● butanoic acid. Temperature: 100 °C. —: Salt of (*R*)-Phg with (*S*)-CS. ---: Salt of (*S*)-Phg with (*S*)-CS.

Table 2. Asymmetric Transformation of (*RS*)-2-Phenylglycine[a]

Carboxylic acid[b]	Reaction time	(*R*)·(*S*) Salt[c]		(*R*)-Phg	
		Yield	Optical purity	Yield[e]	Optical purity
	h	g [%[d]]	%	%	%
AcA	1	4.22 [55.0]	92.4	54.4	92.1
	2	4.27 [55.7]	93.0	54.6	93.1
	3	4.43 [57.6]	93.0	57.0	92.8
	4	4.50 [58.7]	94.9	57.5	94.7
	5	4.60 [60.0]	94.9	59.1	95.0
PrA	1	4.82 [62.8]	86.3	61.4	86.1
	2	5.28 [68.8]	91.0	67.4	90.5
	3	5.77 [75.2]	93.4	73.5	94.3
	4	6.07 [79.1]	95.9	77.4	94.9
	5	6.22 [81.1]	98.3	79.6	98.2
	6	6.26 [81.6]	100	80.4	100
	7	6.27 [81.8]	100	80.6	100
BuA	1	4.90 [63.9]	83.4	62.8	84.2
	2	5.48 [71.4]	85.9	69.8	86.0
	3	6.05 [78.9]	85.7	77.2	85.7
	4	6.36 [82.9]	90.2	80.1	89.2
	5	6.52 [85.0]	92.0	83.5	91.9
	6	6.63 [86.4]	92.1	84.8	92.0
	7	6.64 [86.6]	92.0	84.9	92.0
	9	6.66 [86.8]	91.8	85.2	91.8

a) Conditions: (*RS*)-2-Phenylglycine [(*RS*)-Phg] 20.0 mmol; (1*S*)-10-(camphorsulfonic acid [(*S*)-CS] 19.0 mmol; carboxylic acid 10 cm^3; temperature 100 °C. b) AcA=Acetic acid; PrA=propanoic acid; BuA=butanoic acid. c) (*R*)·(*S*) Salt: Salt of (*R*)-Phg with (*S*)-CS. d) The yield was calculated on the basis of 20.0 mmol (7.67 g) of the (*R*)·(*S*) salt. The yield was calculated on the basis of 20.0 mmol (3.02 g) of (*R*)-Phg.

butanoic acid, as shown in Fig. 3, and is estimated from the racemization of (*R*)-Phg. Acetic acid, therefore, is not favorable as the solvent for the asymmetric transformation of (*RS*)-Phg.

The epimerization of the (*S*)·(*S*) salt in butanoic acid seems to be a little faster than in propanoic acid. Although the asymmetric transformation in butanoic acid gave the (*R*)·(*S*) salt with 92% optical purity in over 86% yield, recrystallization of the salt from water lowers the yield extremely.[7]

The (*R*)·(*S*) salt with 100% optical purity was obtained in 82% yield by the asymmetric transformation in propanoic acid. Isolation of (*R*)-Phg from the optically pure salt was carried out almost quantitatively by treatment of the methanol solution of the salt with triethylamine to obtain optically pure (*R*)-Phg in 80% yield based on the (*RS*)-Phg used as the starting material.

The above results show that the asymmetric transformation of (*RS*)-Phg is possible by heating in the carboxylic acids without using any catalysts such as aldehydes and gives optically pure (*R*)-Phg efficiently.

References

1) J. Santhanam, British Patent 1210495 (1967); *Chem. Abstr.*, **74**, 42618 (1971).

2) T. Watanabe, S. Hayashi, S. Ouchi, and S. Senoo, Japan Patent 78137 (1973); *Chem. Abstr.*, **80**, 71099 (1974).

3) K. Murakami, N. Katsuta, K. Takano, Y. Yamamoto, T. Kakegawa, K. Saigo, and H. Nohira, *Nippon Kagaku Kaishi*, **1979**, 765.

4) T. Shiraiwa, Y. Ohmichi, K. Iwafuji, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1983**, 1070.

5) T. Shiraiwa, H. Miyazaki, S. Konishi, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1985**, 1577.

6) T. Shiraiwa, H. Miyazaki, T. Imai, M. Sunami, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **60**, 661 (1987).

7) C. Hongo, R. Yoshioka, M. Tohyama, S. Yamada, and I. Chibata, *Bull. Chem. Soc. Jpn.*, **56**, 3744 (1983).

8) J. S. Davies, "Amino Acids and Peptides," Chapman and Hall, London and New York (1985), p. 65.

9) M. Bodanszky, "Peptide Chemistry," Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, and Tokyo (1988), pp. 115—116.

10) H. Ootaki, "Youeki Kagaku," Shoukabou, Tokyo (1985), pp. 184—186.