Asymmetric Transformations of Proline and 2-Piperidinecarboxylic Acid via Formation of Salts with Optically Active Tartaric Acid

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The rates of racemization of optically active proline [Pro] and 2-piperidinecarboxylic acid [Pia] by using aldehydes as a catalyst tended to increase with a decrease in the acidity of the carboxylic acid used as solvent. Based on these results, the asymmetric transformations of DL-Pro and (RS)-Pia were carried out via formation of salts with (2R, 3R)-tartaric acid to give optically pure L-Pro in over 80% yield and (R)-Pia in 70% yield. The asymmetric transformation of L-Pro was more successfully achieved by using (2S, 3S)-tartaric acid to give optically pure D-Pro in 85% yield based on the starting L-Pro.

L-Proline [abbreviated as L-Pro] as an important amino acid in vivo is a cyclic amino acid with a five-membered ring and is obtained by fermentation or by isolation from protein hydrolysates. D-Pro is difficult to obtain from natural products in large quantities and has been obtained by synthetic transformations from D-glutamic acid.[1] L-Pro, therefore, is inexpensive, whereas D-Pro is significantly costly. Both D- and L-Pro are useful as chiral reagents and catalysts in asymmetric syntheses. (S)-2-Piperidinecarboxylic acid [(S)-Pia] with a six-membered ring has been synthesized from L-lysine,[2] (R)-Pia also from L-lysine by the Walden inversion,[3] and (RS)-Pia by reduction of 2-pyridinecarboxylic acid[4,5] and from N-benzoyl-1,2,3,6-tetrahydropyridine through cobalt-catalyzed isomerization-carboxylation.[6] (R)- and (S)-Pia, however, are extremely expensive and only (RS)-Pia is readily available. This paper describes easier preparations of optically active Pro and Pia.

An asymmetric transformation has a possibility of converting efficiently a racemate into a desired enantiomer and has been carried out by combination of selective crystallization of a less soluble diastereomeric salt with epimerization of the more soluble one in a solution.[7-10] Although an asymmetric transformation of N-butyryl-DL-proline gives L-Pro by combination of preferential crystallization with racemization,[7] such has not been reported for (RS)-Pia. Then the asymmetric transformation were attempted without converting Pro and Pia into their derivatives, such as N-acyl amino acids. Optically active amino acids are easily racemized by using aldehydes as catalyst in carboxylic acid.[11,12] In addition, optical resolutions of DL-Pro[13] and (RS)-Pia[14] by using (2R,3R)-tartaric acid [(R)-TA] as a resolving agent give the salt of L-Pro with (R)-TA and that of (R)-Pia with (R)-TA as a less soluble diastereomeric salt. The asymmetric transformations of DL-Pro and (RS)-Pia, therefore, were tried by using butanal and salicylaldehyde as the catalyst via formation of a salt with (R)-TA in carboxylic acids. The asymmetric trans-

formation of L-Pro to D-Pro was also examined by using (S)-TA.

Experimental

Materials. DL-Pro and (RS)-Pia were purchased from Tokyo Kasei Kogyo Co., Ltd., L-Pro from Kokusan Chemical Works Ltd., and (R)- and (S)-TA from Wako Pure Chemicals Ind. (R)-Pia was obtained by asymmetric transformation.

Asymmetric Transformation. Proline: A mixture of 20.0 mmol (2.30 g) of L-Pro, 20.0 mmol (3.00 g) of (S)-TA, and 2.00 mmol of butanal in 30 cm³ of butanoic acid was stirred for 1—6 h at 80 °C and subsequently for 0.5 h in an ice bath. The formed D-Pro·(S)-TA salt was collected by filtration, washed thoroughly with diethyl ether, and dried. After adding concentrated aqueous ammonia (0.55 cm³ g⁻¹) to a solution of the salt in 200 cm³ of methanol, followed by stirring the mixture for 0.5 h in an ice bath, the precipitated diammonium (2S, 3S)-tartarate was removed by filtration; the (S)-TA used as the resolving agent was recovered in over 90% yield as the diammonium salt; $[\alpha]_D^{20}$ −33——32° (c 1.00, water): lit,[15] of diammonium (2R, 3R)-tartarate, $[\alpha]_D$ +34.0° (water). Drying of the filtrate gave D-Pro as the residue.

Similarly, the asymmetric transformation of DL-Pro was carried out by using (R)-TA and 0.1 mol equivalent of salicylaldehyde and butanal in butanoic acid at 90 °C. The optical purities of the obtained D-Pro·(S)-TA and L-Pro·(R)-TA salts were estimated on the basis of the specific rotations of the L-Pro·(R)-TA salt ($[\alpha]_D^{25}$ −24.2° (c 1, water)[13] and the D-Pro· (R)-TA salt ($[\alpha]_D^{25}$ +44.4° (c 1, water))[13] and those of D- and L-Pro from the specific rotation of L-Pro ($[\alpha]_D^{20}$ −86.2° (c 1.00, water)).[16]

To a solution of the D-Pro·(S)-TA or L-Pro·(R)-TA salt with over 90% optical purity in water (1 cm³ g⁻¹) was added ethanol (20 cm³ g⁻¹). After stirring the mixture for 1 h in an ice bath, the purified salt was collected by filtration, washed with diethyl ether, and dried. The salt was treated with concentrated aqueous ammonia similarly to the above to obtain optically pure D- and L-Pro.

(RS)-2-Piperidinecarboxylic Acid: A mixture of 10.0 mmol (1.29 g) of (RS)-Pia, 10.0 mmol (1.50 g) of (R)-TA, and 5.00 mmol of salicylaldehyde in 50 cm³ of butanoic acid, pentanoic acid, or hexanoic acid was stirred for 2—10 h at 110 °C and then for 0.5 h in an ice bath. The formed (R)-Pia·

(R)-TA salt was treated with concentrated aqueous ammonia to give (R)-Pia.

A suspension of the (R)-Pia·(R)-TA salt with 80% optical purity in methanol (3.3 cm³ g⁻¹) was stirred for 0.5 h at 50 °C and then for 2 h at 20 °C. The purified (R)-Pia·(R)-TA salt was collected by filtration, washed with diethyl ether, and dried. Treatment of the salt with concentrated aqueous ammonia gave optically pure (R)-Pia; lit,[2] of (S)-Pia, $[\alpha]_D^{20}$ −30.6° (c 1, water).

Rate Constant of Racemization. After adding 4.00 mmol of butanal or salicylaldehyde to a solution of 40.0 mmol of L-Pro in 100 cm³ of formic acid, acetic acid, propanoic acid, or butanoic acid at 80 °C, the solution was stirred at 80 °C. Two cubic centimeter portions of the solution were pipetted out at appropriate time intervals, cooled rapidly, and diluted to 10 cm³ with acetic acid. The optical rotation at 589 nm was measured with a Union Giken PM-101 digital polarimeter equipped with a quartz cell of 5.00 cm path length. The rate constant of racemization ($k_R/$s⁻¹) was calculated by the least-squares method from the equation

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

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time. The half-conversion period ($t_{1/2}/$s) was calculated by using the k_R value from Eq. 1.

The rate of racemization of (R)-Pia was measured at 110 °C for solutions of (R)-Pia (20.0 mmol) and butanal or salicylaldehyde (2.00 mmol) in 100 cm³ of formic acid, acetic acid, and propanoic acid.

Results and Discussion

Racemization of L-Proline and (R)-2-Piperidinecarboxylic Acid. One of the major problems in an asymmetric transformation is the rate of epimerization, that is, that of racemization of an optically active substance. The rates of racemization of L-Pro and (R)-Pia, therefore, were measured by using butanal or salicylaldehyde in formic acid, acetic acid, propanoic acid, and butanoic acid. The rate of racemization of (R)-Pia in butanoic acid and those of L-Pro and (R)-Pia in higher carboxylic acids could not be measured because

L-Pro and (R)-Pia did not completely dissolve in these carboxylic acids even at 110 °C. These racemizations were regarded as a first-order reaction because a linear relationship was found between $\ln \alpha_0/\alpha_t$ and time t. The rate constant for racemization ($k_R/$s⁻¹) and the half-life conversion ($t_{1/2}/$s) are summarized in Table 1.

In these racemizations, the first step is the formation of the Schiff base.[11,12] This dehydration-condensation of a cyclic amino acid with the aldehyde proceeds by protonation from the carboxylic acid used as solvent, and hence the Schiff base formed has a positive charge on the nitrogen atom.[11] The second step is proton abstraction from the α-carbon atom by the resulting carboxylate anion.[11,12]

The rate of racemization of (R)-Pia was extremely lower than that of L-Pro, as seen in Table 1. The four carbon and one nitrogen atoms in the five-membered ring on L-Pro lie on the approximately same plane,[17] whereas the six-membered ring on (R)-Pia exists in a chair form.[18] Such steric bulkiness of the ring on (R)-Pia may hinder the formation of the Schiff base, and hence slow down the rate of racemization compared with the pseudo-planar ring on L-Pro.

As found in racemization by using butanal, the rates of racemization of L-Pro and (R)-Pia were dependent on the nature of the carboxylic acid used as solvent, that is, acidity of the carboxylic acid or basicity of its carboxylate anion. The acidity constants (pK_a), estimated from the data at 0—60 °C,[19] at 80 and 110 °C tend to suggest that an order of protonation is formic acid> acetic acid>propanoic acid>butanoic acid and that of proton abstraction is butanoate anion>propanoate anion>acetate anion>formate anion. A relationship between the k_R and pK_a values is shown in Fig. 1.

The k_R value tended to increase with an increase in the pK_a value, as seen in Fig. 1. It has been reported that the rate of racemization of optically active amino acids may be most rapid in acetic acid.[11] The above result,

Table 1. Rate Constants and Half-Conversion Periods for the Racemization of
L-Proline and (R)-2-Piperidinecarboxylic Acid

| Amino acid | Aldehyde | Carboxylic acid | k_R[a] | $t_{1/2}$[b] |
			10^{-4} s⁻¹	10^2 s
L-Pro[c]	Butanal	FrA[f]	0.101	686
		AcA[g]	15.3	4.53
		PrA[h]	25.6	2.71
		BuA[i]	26.2	2.65
	SA[e]	AcA[g]	3.10	22.4
(R)-Pia[d]	Butanal	FrA[f]	ca. 0	—
		AcA[g]	0.845	82.0
		PrA[h]	5.28	13.1
	SA[e]	AcA[g]	0.741	93.5

a) k_R: Rate constant for racemization. b) $t_{1/2}$: Half-conversion period. c) L-Proline [L-Pro] 40.0 mmol; aldehyde 4.00 mmol; carboxylic acid 100 cm³;temperature 80°C. d) (R)-2-Piperidinecarboxylic acid [(R)-Pia] 20.0 mmol; aldehyde 2.00 mmol; carboxylic acid 100 cm³; temperature 110°C. e) SA: Salicylaldehyde. f) FrA: Formic acid. g) AcA: Acetic acid. h) PrA: Propanoic acid. i) BuA: Butanoic acid.

Table 2. Asymmetric Transformation of Proline[a]

Starting proline	Aldehyde	Reaction time h	Salt Configuration	Salt Yield g [%b]	Salt Optical purity %	Proline Configuration	Proline Yield[c] %	Proline Optical purity %
DL-Pro[d]	SA[f]	1	L·(R)[h]	4.89 [90.9]	58.5	L	90.0	57.7
		2		5.08 [95.8]	78.7		94.4	77.4
		3		5.10 [96.2]	84.0		95.2	82.5
		4		5.07 [95.7]	88.4		94.7	87.1
		5		5.08 [95.8]	90.4		93.0	88.5
		5[g]		4.41 [83.2]	100		80.9	100
		6		5.06 [95.5]	89.2		93.2	87.9
DL-Pro[d]	Butanal	1	L·(R)[h]	4.98 [93.8]	73.5	L	92.1	72.0
		2		5.04 [95.0]	90.1		93.1	89.7
		3		5.03 [94.8]	90.8		94.1	91.0
		3[g]		4.49 [84.7]	100		83.3	100
L-Pro[e]	Butanal	1	D·(S)[i]	5.21 [98.3]	15.1	D	97.0	15.1
		2		5.15 [97.2]	82.8		96.1	84.2
		3		5.16 [97.4]	93.3		94.8	92.9
		3[g]		4.67 [88.1]	100		85.2	100
		4		5.15 [97.2]	93.3		93.2	92.5
		4[g]		4.62 [87.2]	100		84.8	100
		5		5.16 [97.4]	93.6		93.9	93.2
		6		5.18 [97.7]	94.5		95.2	93.6

a) Proline [Pro] 20.0 mmol; optically active tartaric acid [TA] 20.0 mmol; aldehyde 2.00 mmol; butanoic acid 30 cm³.   b) The yield was calculated on the basis of 20.0 mmol (5.30 g) of the salt of Pro with TA.   c) The yield was calculated on the basis of 20.0 mmol (2.30 g) of Pro.   d) The asymmetric transformation of DL-Pro was carried out by using (R)-TA as the resolving agent at 90°C.   e) The asymmetric transformation of L-Pro was carried out by using (S)-TA as the resolving agent at 80°C.   f) SA: Salicylaldehyde.   g) The obtained salt was purified by recrystallization.   h) L·(R): Salt of L-Pro with (R)-TA.   i) D·(S): Salt of D-Pro with (S)-TA.
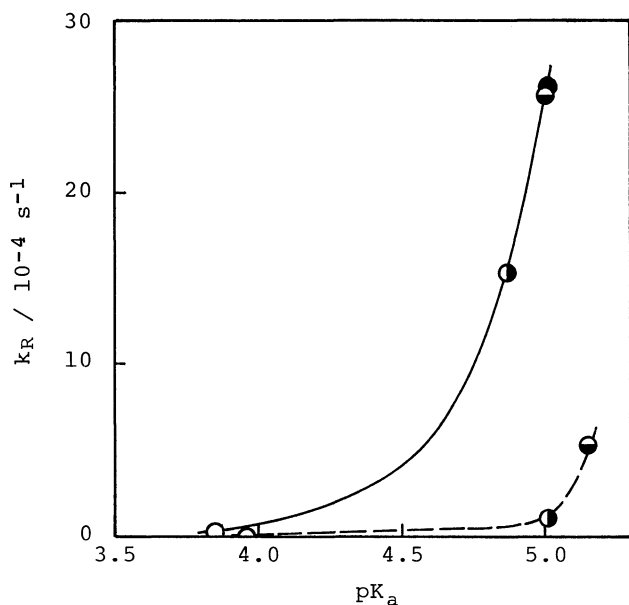
Fig. 1.   Influence of the carboxylic acid used as solvent on the racemization of L-proline and (R)-2-piperidinecarboxylic acid.

Conditions.   See footnote to Table 1. k_R: Rate constant (s^{-1}) for racemization. pK_a: The pK_a values at 80 and 110 °C were calculated by extrapolation from data at 0—60 °C; Ref. 19.   —: Racemization of L-proline at 80 °C.   - - -: Racemization of (R)-2-piperidinecarboxylic acid at 110 °C.   Carboxylic acid: ○ Formic acid; ◐ acetic acid; ◒ propanoic acid; ● butanoic acid.

however, suggests that the rate of racemization of optically active cyclic amino acids, such as L-Pro and (R)-Pia, is accelerated with a decrease in acidity of the carboxylic acid used as solvent, and hence its rate-determining step is the α-proton abstraction by the carboxylate anion.

In addition, the racemizations of L-Pro and (R)-Pia were more accelerated by using butanal as catalyst than salicylaldehyde.

Asymmetric Transformation of Proline.   The asymmetric transformation of DL-Pro was carried out at 90 °C in butanoic acid.   The result is summarized in Table 2.

When butanal was used as catalyst, the L-Pro·(R)-TA salt with 90% optical purity was obtained in 95% yield by allowing to react for 2 and 3 h.   Although the asymmetric transformation by using salicylaldehyde required longer time than that by using butanal, as predicted from the result of racemization, those at 4—6 h gave the L-Pro·(R)-TA salt with 88—90% optical purity in 96% yield.   These salts were purified to give optically pure L-Pro in over 80% yield based on the starting DL-Pro, as summarized in Table 2.

The asymmetric transformation of L-Pro into D-Pro was more successfully achieved by using butanal as catalyst and (S)-TA as the resolving agent, at 80 °C (Table 2).   The D-Pro·(S)-TA salt with 93—95% optical

purity was obtained in 97% yield by a reaction for 3—6 h.   The purified salt gave optically pure D-Pro in 85% yield based on the starting L-Pro.

The rate of racemization of an optically active substance is measured under homogeneous conditions, whereas an asymmetric transformation is carried out under heterogeneous ones.   Optimum conditions for the asymmetric transformation, therefore, may not always be the same as those for the racemization.   However, the asymmetric transformations of DL- and L-Pro gave very good results under the conditions estimated from the result of racemization.

Asymmetric Transformation of (RS)-2-Piperidinecarboxylic Acid.   The optical resolution of (RS)-Pia by using (R)-TA gives the (R)-Pia·(R)-TA salt as a less soluble diastereomeric salt.[14]   The result of racemization of (R)-Pia suggests that the rate of epimerization of the Pia·(R)-TA salt is extremely slower than that of Pro.   In addition, the result of racemization of L-Pro allows to predict that the rate of (R)-Pia is more rapid in butanoic acid than in acetic acid and propanoic acid.   The asymmetric transformation of (RS)-Pia, therefore, was tried by consuming 5.00 mmol of the aldehydes per 10.0 mmol of (RS)-Pia in butanoic acid at 110 °C.   The asymmetric transformation by using butanal, however, could not be carried out because the formed salt became a viscous mass.   The asymmetric transformation of (RS)-Pia, therefore, was carried out by using salicylaldehyde.   The result is summarized in Table 3.

The asymmetric transformation gave the (R)-Pia·(R)-TA salt with 76—80% optical purity at 3—7 h.   Although the purified salt gave optically pure (R)-Pia in 61% yield based on the starting (RS)-Pia, as summarized in Table 3, the yield was not so high as expected.   Such low yield seems to be due to the relatively high solubility of the salt formed in butanoic acid.   The formed salt seems to be less soluble in pentanoic acid and hexanoic acid than in butanoic acid.   The rates of epimerization in these carboxylic acids are estimated to be approximately equal to that in butanoic acid from the acidity constants of these carboxylic acids at 110 °C.[19,20]   The asymmetric transformation was tried by a reaction for 5 h in pentanoic acid and hexanoic acid (Table 3).   Comparison of the asymmetric transformations in these carboxylic acids indicated that the yield of the obtained (R)-Pia·(R)-TA salt tended to rise with an increase in the carbon number of the carboxylic acids, whereas the optical purity to fall.

One more major problem in the asymmetric transformation is the solubility of the diastereomeric salts in the solvent used.   The solubility influences not only the yield of the less soluble diastereomeric salt, but its optical purity.   If the solubility is too low, the asymmetric transformation in such a solvent may give the salt with low optical purity, and hence require much long time to obtain the salt with high optical purity.   The asymmetric transformation in pentanoic acid, however, gave the (R)-

Table 3. Asymmetric Transformation of (RS)-2-Piperidinecarboxylic Acid[a]

Carboxylic acid	Reaction time h	(R)-Pia·(R)-TA salt		(R)-Pia	
		Yield g [%[b]]	Optical purity %	Yield[c] %	Optical purity %
BuA[d]	3	2.06 [73.8]	75.8	72.4	74.3
	4	2.06 [73.8]	77.3	72.5	76.5
	5	2.04 [73.1]	78.4	71.5	78.0
	6	2.04 [73.1]	78.1	72.1	77.9
	7	2.09 [74.9]	79.8	73.8	78.0
	7[g]	1.76 [63.1]	100	61.4	100
PeA[e]	2	2.41 [86.3]	41.0	84.8	39.6
	3	2.39 [85.7]	52.3	84.8	51.6
	4	2.49 [89.2]	55.5	88.0	53.2
	5	2.27 [81.4]	65.1	80.6	66.2
	6	2.24 [80.3]	73.0	79.8	73.0
	8	2.27 [81.4]	79.8	81.0	78.0
	8[g]	1.94 [69.5]	100	68.5	100
	10	2.30 [82.4]	81.6	81.5	81.2
	10[g]	1.99 [71.3]	100	70.2	100
HxA[f]	5	2.31 [82.8]	52.2	81.9	51.0

a) (RS)-2-Piperidinecarboxylic acid [(RS)-Pia] 10.0 mmol; (2R,3R)-tartaric acid [(R)-TA] 10.0 mmol; salicylaldehyde 5.00 mmol; carboxylic acid 50 cm³; temperature 110°C.   b) The yield was calculated on the basis of 10.0 mmol (2.79 g) of the salt of (R)-Pia with (R)-TA.   c) The yield was calculated on the basis of 10.0 mmol (1.29 g) of (R)-Pia.   d) BuA: Butanoic acid.   e) PeA: Pentanoic acid.   f) HxA: Hexanoic acid.   g) The obtained salt was purified by recrystallization.

Pia·(R)-TA salt with relatively high optical purity (65%) in higher yield (81%) than that (73%) in butanoic acid. The asymmetric transformation, therefore, was carried out by a reaction for 2—10 h in pentanoic acid (Table 3).

As already mentioned, the asymmetric transformation in butanoic acid gave the salt with 76—80% optical purity at 3—7 h. The yields, however, were less than 75%. The asymmetric transformations at 8 and 10 h in pentanoic acid gave the (R)-Pia·(R)-TA salt with 80% optical purity in over 80% yield. These salts recrystallized from methanol gave optically pure (R)-Pia in 70% yield, based on the starting (RS)-Pia, as summarized in Table 3.

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