Asymmetric Transformation of *N*-Acyl-DL-amino Acids

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The asymmetric transformation which converted *N*-acyl-DL-amino acids to the desired optically active isomers was studied. *N*-Acylamino acids such as *N*-butyrylproline, *N*-acetylleucine, and *N*-benzoylphenylglycine were easily racemized in the presence of a catalytic amount of acetic anhydride in melted states or in acetic acid or chloroform solutions. The racemic modification of these *N*-acylamino acids crystallized as a true racemic mixture suitable for optical resolution by a preferential crystallization procedure under the conditions of racemization. By combining preferential crystallization of the desired enantiomer by seeding from a supercooled melt or a supersaturated solution of a racemic modification and simultaneous racemization of the opposite isomer, *N*-acyl-DL-amino acid was partially converted to an optically active isomer and the whole reaction mixture became optically active (10—40% enantiomeric excess).

The optical resolution of DL-amino acids by a preferential crystallization procedure has been extensively investigated in our laboratory.[1–7] This procedure is considered to be one of the most useful methods for practical and industrial purposes since it enables the desired optical isomer to crystallize preferentially from a supersaturated solution of the racemic modification by simple inoculation of the same isomer.

Our previous report[6] showed that some *N*-acyl-DL-prolines were resolvable by the preferential crystallization procedure and that the undesired optically active isomer recovered from the mother liquor was completely racemized by heating at a temperature above its melting point in the presence of a catalytic amount of acetic anhydride and could be reused as the starting material. In the course of further studies, a large single crystal of almost optically pure *N*-butyryl-L-proline (*N*-Bu-L-Pro) was found to deposit in the reaction vessel when *N*-butyryl-D-proline (*N*-Bu-D-Pro) was completely racemized by heating with acetic anhydride and allowing the racemized melt to stand for 2 d at room temperature. This fact indicated that one of the optically active isomers preferentially crystallized from the super-cooled melt of *N*-butyryl-DL-proline (*N*-Bu-DL-Pro) by spontaneous crystallization of the isomer. If such optical resolution by preferential crystallization can be achieved at a high temperature, which enables the opposite isomer in the melt to racemize at a high rate, all of the racemic modification will be theoretically transformed to the optically active crystals. We were interested in the asymmetric transformation of *N*-Bu-DL-Pro by the combination of the preferential solidification from a melted racemic modification and simultaneous racemization of the opposite isomer in the melt. Besides *N*-Bu-DL-Pro, some *N*-acyl-DL-amino acids such as *N*-acetyl-DL-leucine[8] (*N*-Ac-DL-Leu) and *N*-benzoyl-DL-phenylglycine[9] (*N*-Bz-DL-PG) are known to form a true racemic mixture suitable for the optical resolution by a preferential crystallization procedure. These optically active isomers are expected to be readily racemized. Therefore, these substances were also chosen as test compounds; we sought the systems in which the asymmetric transformation took place by preferential crystallization under conditions of simultaneous racemization. The screening was carried out with combinations of the racemization process and two kinds of resolution procedures, *i.e.*, solidification from a melted racemic modification and the usual preferential crystallization from a supersaturated solution dissolving a racemic modification. In the former case, *N*-Bu-DL-Pro and *N*-Ac-DL-Leu were found to be partially converted to the respective optically active isomers and to become optically active as a whole. In the latter case, the asymmetric transformation was observed with *N*-Bu-DL-Pro, *N*-Ac-DL-Leu, and *N*-Bz-DL-PG. We wish to report here these results. A preliminary account of this work has been already published.[10]

Racemic and optically active *N*-Bu-Pro, *N*-Ac-Leu, and *N*-Bz-PG were prepared by the usual acylation of the respective amino acids. The physical properties are shown in Table 1; these indicate that these racemic modifications crystallize as a true racemic mixture suitable for the preferential crystallization procedure in the appropriate solvent. As shown in Table 2, these optically active isomers could be racemized at a very high rate by melting at a temperature near each one's melting point in the presence of a catalytic amount of acetic anhydride. Furthermore, as shown in Table 3, they could be easily racemized by heating at a relatively low temperature in acetic acid (for *N*-Ac-Leu and *N*-Bz-PG) or chloroform (for *N*-Bu-Pro) solution containing a small amount of acetic anhydride. In both cases, no racemization occurred without acetic anhydride, which was essential for the racemization process. Thus, the two important requirements for the intended asymmetric transformation were fulfilled.

The first approach for asymmetric transformation was carried out by preferential solidification from a super-cooled melt of a racemic modification. In the cases of *N*-Bu-Pro and *N*-Ac-Leu, the whole reaction mixtures became optically active (34% and 10% enantiomeric excess respectively). The second approach was carried out by preferential crystallization from a supersaturated solution of a racemic modification. In this case, two modes of operation were employed to maintain a supersaturation state during the asymmetric transformation, *i.e.*, continuous removal of solvent or addition of an inert solvent effective for reducing the solubility. In both operational modes, the asymmetric transformation of *N*-Bu-Pro, *N*-Ac-Leu, and *N*-Bz-PG was observed and the respective

Table 1. Properties of *N*-acylamino acids

N-Acylamino acid	Form	Mp/°C	$[\alpha]_D^{25}$/°	Solubility g/100 ml (Temp/°C)	Solvent	IR-Spectra[a]
N-Bu-Pro	DL	89— 90		152 (50) 194 (55)	$CHCl_3/Ac_2O$ (6/1)	Identical
				149 (50) 173 (55)	$CHCl_3$	
	L	114—116	−105.4 (*c* 1, H_2O)	—[b]	$CHCl_3/Ac_2O$ (6/1)	
				64 (50) 75 (55)	$CHCl_3$	
N-Ac-Leu	DL	159—160		65 (70) 88 (80)	AcOH/Ac_2O (10/1)	Identical
				55 (70) 75 (80)	AcOH	
	L	187—188	−24.9 (*c* 1, MeOH)	—[b]	AcOH/Ac_2O (10/1)	
				28 (70) 34 (80)	AcOH	
N-Bz-PG	DL	178—180		33 (70) 53 (80)	AcOH/Ac_2O (100/3)	Identical
				24 (70) 37 (80)	AcOH	
	L	195—196	+116.1 (*c* 1, MeOH)	—[b]	AcOH/Ac_2O (100/3)	
				8 (70) 12 (80)	AcOH	

a) The infrared spectra of L- and DL- forms which were crystallized from each solvent were compared. b) The solubility of L-isomer could not be determined because the dissolved L-isomer was readily racemized in the solvent system. L-Isomer was not dissolved in a saturated solution of DL-form.

Table 2. Racemization of *N*-acylamino acids by melting with acetic anhydride

N-Acylamino acid	Conditions: L-Isomer (g)	Ac_2O (ml)	Temp °C	Time h	Initial α_D^{25}/°	Final[a] α_D^{25}/°	Racemization[b] degree %
N-Bu-L-Pro	1.0	—	120	2	−1.713	−1.439	16
	1.0	0.05	97	0.5	−1.713	0.000	100
N-Ac-L-Leu	1.0	—	150[c]	0.5	−0.482	−0.482	0
	1.0	0.05	150	0.5	−0.482	0.000	100
N-Bz-L-PG	1.0	—	160[d]	1	+2.295	+2.295	0
	1.0	0.04	160	1	+2.295	+0.642[e]	72

a) After the reaction, the whole reaction mixture was dissolved in methanol (50 ml) and the optical rotation was measured. b) $\frac{\text{Initial optical rotation} - \text{final optical rotation}}{\text{Initial optical rotation}} \times 100$. c) *N*-Ac-L-Leu remained in solid state because the reaction temperature was lower than the melting point. At 190 °C for 30 min, the racemization was complete, but *N*-Ac-Leu partially decomposed. d) *N*-Bz-L-PG remained in solid state because the reaction temperature was lower than the melting point. At 200 °C for 30 min, the racemization was complete, but *N*-Bz-PG partially decomposed. e) The formation of by-products or decomposition was observed.

Table 3. Racemization of *N*-acylamino acids by heating in a solution containing acetic anhydride

N-Acylamino acid	Conditions: L-Isomer (g)	Ac_2O (ml)	Solvent (ml)	Temp °C	Time h	Initial α_D^{25}/°	Final[a] α_D^{25}/°	Racemization[b] degree %
N-Bu-L-Pro	1.0	—	$CHCl_3$, 1.2	50	4	−1.670	−1.670	0
	1.0	0.10	$CHCl_3$, 1.2	50	4	−1.670	−0.033	98
N-Ac-L-Leu	1.0	—	AcOH, 5	75	8	−0.453	−0.435	4
	1.0	0.11	AcOH, 5	75	2	−0.453	−0.009	98
N-Bz-L-PG	1.0	—	AcOH, 10	75	8	+1.955	+1.955	0
	1.0	0.07	AcOH, 10	75	8	+1.955	+0.059	97

a) After the reaction, the whole reaction mixture was diluted in methanol (50 ml) and the optical rotation was measured. b) $\frac{\text{Initial optical rotation} - \text{final optical rotation}}{\text{Initial optical rotation}} \times 100$.

optically active crystals were actually separated from the reaction mixture. From the mother liquor, the racemic modification was recovered. These results are shown in Table 4 and Table 5. In a typical experiment by addition of inert solvent, 4.70 g of *N*-Ac-L-Leu with an optical purity of 89.6% was obtained from 9.5 g of *N*-Ac-DL-Leu. From the mother liquor, 3.53 g of *N*-Ac-DL-Leu was recovered. In the usual optical resolution by the preferential crystallization procedure, the yield of the seeded isomer in one operating cycle is rather low, owing to the limitation of supersaturated state of the opposite isomer; it is usually 5 to 10% based on the original weight of racemic modification. On the other hand, the

Table 4. Asymmetric transformation by preferential crystallization procedure
(Crystallization by continuous removal of solvent)

N-Acyl-amino acid	Composition of solution			Seed crystals (g)	Reaction			Separated crystals		
	DL-Form (g)	Ac_2O (ml)	Solvent (ml)		Temp °C	Time h	Amount of removed solvent ml	Yield g	Optical purity %	Transformed[a] amount g
N-Bu-Pro	10.60	0.8	$CHCl_3$ 5.2	0.20	50	20	4.4	9.38 (—)	41.3 —	3.67 —[b,c]
N-Ac-Leu	10.00	1.1	AcOH 11.0	0.40	75	7	7.2	6.60 (0.40	50.2 0.0	2.91 0.00)[b]
N-Bz-PG	10.00	0.7	AcOH 25.0	0.60	75	7	14.0	7.12 (1.20	43.1 0.0	2.47 0.00)[b]

a) Weight of seed crystals was subtracted from the net weight of the active form obtained. b) The second crop was obtained by cooling the filtrate after the separation of the first crop; the data are shown in parentheses. c) Although a second crop could not be obtained, the filtrate did not show optical rotation.

Table 5. Asymmetric transformation by preferential crystallization procedure
(Crystallization by addition of inert solvent)

N-Acyl-amino acid	Composition of solution			Seed crystals (g)	Reaction			Separated crystals		
	DL-Form (g)	Ac_2O (ml)	Solvent (ml)		Temp °C	Time h	Added solvent (ml)	Yield g	Optical purity %	Transformed[a] amount g
N-Bu-Pro	10.60	0.8	$CHCl_3$ 5.2	0.60	50	7	*i*-Pr_2O 25	5.42 (2.00	60.6 0.0	2.68 0.00)[b]
N-Ac-Leu	9.50	1.0	AcOH 9.0	0.20	75	5	Toluene 50	4.70 (3.53	89.6 0.0	4.01 0.00)[b]
N-Bz-PG	9.00	1.0	AcOH 29.0	0.60	75	5	Xylene 50	3.30 (1.50	67.3 0.0	1.62 0.00)[b]

a) Weight of seed crystals was subtracted from the net weight of the active form obtained. b) The second crop was obtained by cooling the filtrate after the separation of the first crop; the data are shown in parentheses.

asymmetric transformation proposed here can give a high yield, since the concentration of the opposite isomer is decreased by the racemization and the total extent of supersaturation of the desired isomer can be increased by using the continuous operation methods described above.

The asymmetric transformation by a combination of optical resolution by selective precipitation of the less soluble diastereoisomeric salt and epimerization of the soluble diastereoisomeric salt is well known as an asymmetric transformation of second order.[11] However, the asymmetric transformation by a combination of preferential crystallization of a desired enantiomer by seeding from a supersaturated solution of a racemic modification and simultaneous racemization of the opposite isomer is unique and has not been reported except in the case of α-amino-ε-caprolactam–nickel chloride complex[12] and a few examples of somewhat analogous asymmetric transformations.[13–15] The proposed method is very promising for industrial application because of its operational simplicity. More detailed experiments on the mechanism of this asymmetric transformation and the best conditions for practical application will be described in a subsequent paper.

Experimental

Materials and Analyses. Analytical standard grade amino acids manufactured by our company, Tanabe Seiyaku Co., Ltd., were used. Other chemicals were obtained from Tokyo Kasei Kogyo Co., Ltd. All samples were dried overnight *in vacuo* at room temperature. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube and are uncorrected. Infrared spectra of samples were determined in nujol using a Shimadzu infrared spectrophotometer, Model IR-27G. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from the side of undersaturation. Solute concentration was measured with a Karl Zeiss immersion refractometer. Identification of *N*-acylamino acids was carried out by elemental analysis, IR-spectrum, specific rotation and thin-layer chromatography (solvent system: $CHCl_3$–MeOH–AcOH, 85:15:3, v/v/v) using the ascending technique on Merck's precoated Kieselgel 60 F_{254}. The chromatograms were sprayed with 40% hydrobromic acid, heated at 105 °C for about 5 min, and stained with ninhydrin at 105 °C for 5 min. The stained spots were compared with authentic samples.

Preparation of N-*Acylamino Acids.* *N*-Bu-L- and -DL-Pro were prepared from L- and DL-proline by acylation with *n*-butyryl chloride in chilled aqueous alkali, according to the usual manner described in our previous report.[6]

The racemic modifications and L-isomers of *N*-Ac-Leu and *N*-Bz-PG were similarly prepared from DL- and L-leucine and DL- and L-phenylglycine with acetyl chloride and benzoyl chloride, respectively (yield, 80—95%). The products were used for asymmetric transformation without further purification. The elemental analyses of these *N*-acylamino acids recrystallized from chloroform (for *N*-Bu-Pro) or acetic acid (for *N*-Ac-Leu and *N*-Bz-PG) corresponded to the respective theoretical values. The properties of these *N*-acylamino acids are shown in Table 1.

Racemization of N-*Acyl*-L-*amino Acids. *Racemization by Melting in the Presence of Small Amounts of Acetic Anhydride*: A mixture of *N*-Bu-L-Pro (1.0 g) and 0.1 molar equivalents of acetic anhydride (0.05 ml) was maintained at 97 °C in a sealed tube. The mixture was liquefied with the elapse of time. After 30 min, the liquefied sample was dissolved in methanol (50 ml) and the optical rotation was measured. The initial optical rotation before the reaction was α_D^{25} −1.713°. The reaction mixture did not show any optical rotation. Therefore *N*-Bu-L-Pro seemed to be completely racemized. In the absence of acetic anhydride, the optical rotation was α_D^{25} −1.439° even after heating at 120 °C for 2 h. In this case, the racemization degree was estimated to be 16%, based on α_D^{25} −1.713° of the initial optical rotation. In similar ways, *N*-Ac-L-Leu and *N*-Bz-L-PG were maintained at 150 °C for 30 min and at 160 °C for 1 h respectively in the presence of 0.1 molar equivalents of acetic anhydride. The racemization degrees were estimated as described above. The results were compared with those in the absence of acetic anhydride and are shown in Table 2. The racemization was also confirmed by separation of the reacted *N*-acylamino acids in the following way. After the complete racemization, the mixture was cooled to room temperature and the crystallized *N*-acylamino acid was suspended with a small amount of toluene (for *N*-Bu-Pro) or water/MeOH (2/1, v/v) (for *N*-Ac-Leu and *N*-Bz-PG). The suspended *N*-acylamino acid was collected and dried. The specific rotations, melting points, and IR spectra of these separated *N*-acylamino acids showed that the products were the respective racemic modifications and the true racemic mixtures. In the case of *N*-Bz-PG, however, a slight decomposition and some by-products formation were observed.

Racemization by Heating in a Solution Containing Small Amounts of Acetic Anhydride: *N*-Bu-L-Pro (1.0 g) was dissolved in chloroform (1.2 ml) containing 0.2 molar equivalents of acetic anhydride (0.10 ml). The mixture was maintained at 50 °C for 4 h. The whole reaction mixture was dissolved in methanol (50 ml) and the optical rotation was measured, α_D^{25} −0.033°. The racemization degree was estimated to be 98%, based on the initial optical rotation, α_D^{25} −1.670°. In the absence of acetic anhydride, the racemization did not occur. In similar ways, *N*-Ac-L-Leu and *N*-Bz-L-PG were racemized in acetic acid containing 0.2 molar equivalents of acetic anhydride and the racemization degrees were estimated as described above. The results were compared with those in the absence of acetic anhydride and are shown in Table 3.

The racemization was also confirmed by separation of respective *N*-acylamino acids from the reaction mixture. After the complete racemizations, the reaction mixtures were concentrated to a half volume, and the racemized *N*-acylamino acids were crystallized at room temperature. The precipitated crystals were collected and dried. The specific rotations, melting points, and IR spectra of these separated *N*-acylamino acids showed that the products were the racemic modifications and the true racemic mixtures.

Asymmetric Transformation by Preferential Solidification from Melted Racemic Modification. N-*Bu*-DL-*Pro*: A mixture of *N*-Bu-DL-Pro (10.00 g) and acetic anhydride (0.5 ml) was melted by heating at 100 °C. The complete melt was maintained at 70 °C, seeded with finely pulverized crystals of *N*-Bu-L-Pro (0.50 g), and gently stirred in a sealed flask for 7 h. During the reaction, the crystal growth of seeded L-isomer was observed. After 7 h, toluene (10 ml) was added into the reaction mixture at the same temperature and the precipitated crystals were quickly separated by filtration and dried to give *N*-Bu-L-Pro (6.30 g), $[\alpha]_D^{25}$ −64.7° (*c* 1, water), optical purity 61.4% (3.87 g of *N*-Bu-L-Pro plus 2.43 g of *N*-Bu-DL-Pro). After the separation of the first crop, the second crop was crystallized by cooling the filtrate and was separated by filtration to give *N*-Bu-DL-Pro (3.30 g), $[\alpha]_D^{25}$ 0.0° (*c* 1, water), mp 89—90 °C. The mother liquor did not show any optical rotation. Therefore, we subtract 0.5 g of seeded *N*-Bu-L-Pro from the net weight of *N*-Bu-L-Pro obtained, and find that 3.37 g of *N*-Bu-L-Pro was newly formed from *N*-Bu-DL-Pro. That is, 3.37 g of *N*-Bu-DL-Pro was transformed to *N*-Bu-L-Pro.

N-*Ac*-DL-*Leu*: A mixture of *N*-Ac-DL-Leu (10.00 g) and acetic anhydride (0.6 ml) was melted in a sealed flask by heating at 150 °C. The complete melt was cooled to 117 °C, seeded with finely pulverized crystals of *N*-Ac-L-Leu (0.05 g), and kept at the same temperature for 18 h in a sealed flask to allow the preferential solidification of L-isomer to proceed. Then, water/MeOH (2/1, v/v, 20 ml) was added into the reaction mixture at the same temperature and the precipitated crystals were quickly separated by filtration and dried to give *N*-Ac-L-Leu (1.21 g), $[\alpha]_D^{25}$ −21.4° (*c* 1, MeOH), optical purity 85.9% (1.04 g of *N*-Ac-L-Leu plus 0.17 g of *N*-Ac-DL-Leu). The second crop was crystallized from the filtrate by stirring at a room temperature and separated by filtration to give *N*-Ac-DL-Leu (4.20 g), $[\alpha]_D^{25}$ 0.0° (*c* 1, MeOH), mp 158—159 °C. The mother liquor did not show optical rotation. Therefore, we subtract 0.05 g of seeded *N*-Ac-L-Leu from the net weight of *N*-Ac-L-Leu obtained above, and find that 0.99 g of *N*-Ac-L-Leu was transformed from *N*-Ac-DL-Leu.

Asymmetric Transformation by Preferential Crystallization from Supersaturated Solution of Racemic Modification. Crystallization by Continuous Removal of Solvent: The supersaturation state was kept by continuous removal of solvent during the preferential crystallization of L-isomer and the simultaneous racemization of D-isomer. *N*-Bu-DL-Pro (10.60 g) was dissolved in chloroform (5.2 ml) at 70 °C and maintained at 50 °C. After acetic anhydride (0.8 ml) was added to the solution, the solution was seeded with finely pulverized crystals o *N*-Bu-L-Pro (0.20 g) and stirred for 20 h at the same temperature. Since the reaction was carried out in an open vessel without condenser, the solution was spontaneously concentrated. The amount of removed solvent was calculated to be 4.4 ml from the decrease in the weight of the reaction mixture. The precipitated crystals were quickly collected by filtration, washed with a small amount of cold chloroform, and dried to give *N*-Bu-L-Pro (9.38 g), $[\alpha]_D^{25}$ −43.5° (*c* 1, water), optical purity 41.3% (3.87 g of *N*-Bu-L-Pro plus 5.51 g of *N*-Bu-DL-Pro). Although the second crop was not obtained from the mother liquor, the mother liquor did not show optical rotation. Therefore, we subtract 0.20 g of seeded *N*-Bu-L-Pro from the net weight of *N*-Bu-L-Pro obtained above and find that 3.67 g of *N*-Bu-L-Pro was transformed from *N*-Bu-DL-Pro.

The reactions of *N*-Ac-DL-Leu and *N*-Bz-DL-PG were carried out at 75 °C for 7 h by using acetic acid as a solvent.

During the reaction, the solvent was removed at the rates of 1 ml/h for *N*-Ac-Leu and 2 ml/h for *N*-Bz-PG under a slightly reduced pressure. After 7 h, the precipitated crystals were quickly filtered, washed with a small amount of acetic acid, and dried. The second crops were obtained from the mother liquors which were stirred at room temperature. The results are shown in Table 4.

Crystallization by Addition of an Inert Solvent: During the preferential crystallization of L-isomer and the simultaneous racemization of D-isomer, the supersaturation state was maintained by addition of an inert solvent which was effective for reducing the solubility of racemic modification. *N*-Ac-DL-Leu (9.50 g) was dissolved in acetic acid (10.0 ml) containing acetic anhydride (1.0 ml) at 90 °C. The solution was maintained at 75 °C and seeded with finely pulverized crystals of *N*-Ac-L-Leu (0.20 g). Then toluene (50 ml) was added to the solution over a period of 5 h under stirring at the same temperature. The precipitated crystals were quickly collected by filtration and dried to give *N*-Ac-L-Leu (4.70 g), $[\alpha]_D^{25}$ −22.3° (*c* 1, MeOH), optical purity 89.6%, (4.21 g of *N*-Ac-L-Leu plus 0.49 g of *N*-Ac-DL-Leu). The second crop (3.53 g) was recovered from the mother liquor which was stirred at room temperature, $[\alpha]_D^{25}$ 0.0° (*c* 1, MeOH), mp 158—159 °C. Therefore, we subtract 0.20 g of seeded *N*-Ac-L-Leu from the net weight of *N*-Ac-L-Leu of the first crop and find that 4.01 g of *N*-Ac-L-Leu was transformed from *N*-Ac-DL-Leu. In similar ways, the reactions of *N*-Bu-Pro and *N*-Bz-PG were carried out at 50 °C for 7 h in chloroform solution and at 75 °C for 5 h in acetic acid solution, respectively. In these cases, diisopropyl ether (for *N*-Bu-Pro) or xylene (for *N*-Bz-PG) was added into the respective solutions to reduce the solubility of racemic modification. The results are shown in Table 5.

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