Optical Resolution by Replacing Crystallization of Ammonium Salts of *N*-Acetyl-DL-2-aminobutanoic Acid, *N*-Acetyl-DL-norvaline, and *N*-Acetyl-DL-norleucine

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Synopsis. Ammonium salts of *N*-acetyl-DL-2-aminobutanoic acid, *N*-acetyl-DL-norvaline (DL-AcNva·AM salt), and *N*-acetyl-DL-norleucine were optically resolved by replacing crystallization in the presence of the ammonium salt of *N*-acetyl-L-alanine to give their salts with L-configuration. The optical resolution of the DL-AcNva·AM salt, espcially, gave the optically pure L-AcNva·AM salt by purification in 80% yield based on the half amount of the DL-salt used as the starting material.

Ammonium salts of *N*-acetyl-DL-2-aminobutanoic acid (denoted by DL-AcAbu·AM salt), *N*-acetyl-DL-norvaline (DL-AcNva·AM salt), and *N*-acetyl-DL-norleucine (DL-AcNle·AM salt) exist in conglomerates at room temperature and have been optically resolved by preferential crystallization.[1,2] Optical resolution by replacing crystallization is another procedure for obtaining one enantiomer from a conglomerate. Since this optical resolution is based on interactions between each of the enantiomers and an optically active cosolute,[3] it may give a clue to elucidate the chiral interaction in a solution. We, therefore, have been engaged in studying the optical resolution by replacing crystallization.[4] Optical resolutions by replacing crystallization of the DL-AcAbu·AM, DL-AcNva·AM, and DL-AcNle·AM salts were attempted as a part of our study program. This optical resolution seems to give a good result when we employ an optically active cosolute whose structure is similar to that of the racemate. In addition, the cosolute must be more soluble in the solvent than the racemate because crystallization of the cosolute makes it difficult to separate the crystallized mixture into the cosolute and the enantiomer. The ammonium salt of *N*-acetyl-L-alanine (L-AcAla·AM salt) is readily available and seems to be more soluble in ethanol than the DL-AcAbu·AM, DL-AcNva·AM, and DL-AcNle·AM salts. Hence we have been chosen the L-AcAla·AM salt as a cosolute and optically resolved the DL-AcAbu·AM, DL-AcNva·AM, and DL-AcNle·AM salts by replacing crystallization in ethanol.

Experimental

Materials. DL-2-Aminobutanoic acid, DL-norvaline, and DL-norleucine were purchased from Sigma Chemicals, and L-alanine from Wako Pure Chemicals, Ind. DL-AcAbu, DL-AcNva, DL-AcNle, and L-AcAla were obtained, respectively, by acetylating the corresponding compounds in a usual manner.[1,2,5,6] These were then converted to the DL-AcAbu·AM, DL-AcNva·AM, and DL-AcNle·AM, and L-AcAla·AM salts by the procedure described in previous papers.[1,2] L-AcAla·AM salt: Found: C, 40.70; H, 8.24; N, 18.77% (Calcd for $C_5H_{12}N_2O_3$: C, 40.53; H, 8.16; N, 18.91%); mp 161—162 °C; $[\alpha]_D^{20}$ +11.6° (*c* 1.00, ethanol).

Optical Resolution. The DL-AcAbu·AM salt 10.00 mmol (1.622 g), the DL-AcNva·AM salt 10.00 mmol (1.762 g), or the DL-AcNle·AM salt 10.00 mmol (1.902 g) and the L-AcAla·AM salt were dissolved in ethanol at 40 °C; the amounts of the L-AcAla·AM salt and ethanol used were 10.00 mmol (1.482 g) and 100 cm³, 2.00—10.00 mmol (0.296—1.482 g) and 40 cm³, and 8.000 mmol (1.185 g) and 55 cm³, respectively, for the optical resolution of the DL-AcAbu·AM, DL-AcNva·AM, and DL-AcNle·AM salts. The solution was slowly cooled to 5 °C and then stirred for 10—60 min. The precipitated L-salt was collected by filtration, washed with a small amount of cold ethanol, and dried. The optical purities were estimated on the basis of the specific rotations of the L-AcAbu·AM salt ($[\alpha]_D^{20}$ +20.7° (*c* 1.00, ethanol)),[2] L-AcNva·AM salt ($[\alpha]_D^{20}$ +19.7° (*c* 1.00, ethanol)),[2] and L-AcNle·AM salt ($[\alpha]_D^{20}$ +22.8° (*c* 1.00, methanol)),[1] respectively. The degree of resolution was calculated from the equation.

$$\text{Degree of resolution/\%} = [\text{Yield/g} \times \text{Optical purify/\%}]/M,$$

where *M* is the half amount (5.00 mmol) of the DL-salt used as the starting material. The ^{1}H NMR spectra of the L-salt obtained were measured without recrystallization and showed that the L-salts were free from the L-AcAla·AM salt. The L-salts were recrystallized from ethanol;[1,2] the L-AcAbu·AM salt (optical purity 73%) 1.50 g, the L-AcNva·AM salt (optical purity 82%) 3.00 g, and the L-AcNle·AM salt (optical purity 50%) 1.30 g yielded, respectively, 1.05, 2.39, and 0.625 g of the optically pure L-salt.

Measurements. Optical rotation was measured with a Union Giken digital polarimeter PM-101 with a quartz cell of 5.00 cm path length. ^{1}H NMR spectra were recorded on a JEOL NMR spectrometer JNM-PMX 60 in deuterium oxide without internal standard.

Results and Discussion

Optical Resolution of Ammonium Salts of *N*-Acetyl-DL-2-aminobutanoic Acid and *N*-Acetyl-DL-norleucine. The results are summarized in Table 1. Optical resolution of the DL-AcAbu·AM salt gave the L-salt with 70—75% optical purity at 50% or higher degree of resolution in 20—40 min. The L-salt was recrystallized from ethanol to give the optically pure L-AcAbu·AM salt. The yield was estimated to be 50%, based on the half amount (5.00 mmol, 0.811 g) of the DL-salt used as the starting material. In contrast, optical resolution by preferential crystallization of the DL-AcAbu·AM salt gave the D- or L-salt only in 10% yield though its enantiomer can easily be obtained from a mother liquor.[2] Replacing crystallization thus appears to be superior to preferential crystallization for optical resolution of the DL-AcAbu·AM salt.

The result of optical resolution of the DL-AcNle·AM

Table 1. Replacing Crystallization of Ammonium Salts of *N*-Acetyl-DL-amino Acids[a]

Ammonium salt[b]	Resolution time	L-Salt		
	min	Yield	Optical purity	Degree of resolution
		g	%	%
AcAbu·AM salt[c]	10	0.500	73.7	45.5
	20	0.582	74.2	53.3
	30	0.611	70.9	53.5
	40	0.612	74.8	56.0
	50	0.654	63.0	50.8
	60	0.707	56.4	49.2
AcNva·AM salt[d]	10	0.433	73.1	35.9
	20	0.736	78.6	65.6
	30	0.881	83.8	83.8
	40	0.886	83.8	84.6
	50	0.919	80.2	83.4
	60	0.920	81.2	84.4
AcNle·AM salt[e]	10	0.232	50.0	12.2
	20	0.507	50.9	27.2
	30	0.528	50.9	28.3
	40	0.592	50.0	31.2
	50	0.611	40.4	26.0
	60	0.620	37.3	24.4

a) Ammonium salt of *N*-acetyl-DL-amino acid 10.00 mmol; temperature 5 °C. b) AcAbu·AM salt=Ammonium salt of *N*-acetyl-2-aminobutanoic acid; AcNva·AM salt=Ammonium salt of *N*-acetylnorvaline; AcNle·AM salt=Ammonium salt of *N*-acetylnorleucine. c) Ammonium salt of *N*-acetyl-L-alanine (L-AcAla·AM salt) 10.00 mmol; ethanol 100 cm³. d) L-AcAla·AM salt 8.000 mmol; ethanol 40 cm³. e) L-AcAla·AM salt 8.000 mmol; ethanol 55 cm³.

salt was not better than that of the DL-AcAbu·AM salt; purification of the L-AcNle·AM salt with 50% optical purity obtained in 20—40 min gave the optically pure L-salt and the yield was estimated to be 25%.

Optical Resolution of Ammonium Salts of *N*-Acetyl-DL-norvaline. Optical resolution of the DL-AcNva·AM salt gave a better result than those of the DL-AcAbu·AM and DL-AcNle·AM salts. Optimization regarding the mixing ratio was attempted by stirring 10.00 mmol of the DL-AcNva·AM salt with 2.00—10.00 mmol of the L-AcAla·AM salt in 40 cm³ of ethanol for 20 min at 5 °C. The degrees of crystallization of the D- and L-AcNva·AM salts ($DC_{(D)}$ and $DC_{(L)}$/%) were calculated from the equations

$$DC_{(D)}/\% = (1/2)[\text{Yield/g} \times (100 - \text{Optical purity}/\%)]/0.881,$$

$$DC_{(L)}/\% = \text{Yield/g}/0.881 - DC_{(D)},$$

where 0.881 (g) corresponds to the half amount (5.00 mmol) of the DL-AcNva·AM salt used. The dependencies of the $DC_{(L)}$ and $DC_{(D)}$ values on the amount of the L-AcAla·AM salt are shown in Fig. 1.

The D-AcNva·AM salt did not rapidly crystallize under these conditions, because the $DC_{(D)}$ value ranged from 3 to 10%, and the L-AcNva·AM salt obtained was of 76—83% optical purity. When 2.00—7.00 mmol of the L-AcAla·AM salt was used, the $DC_{(L)}$ value increased with an increase in the amoun of the L-AcAla·AM salt. The $DC_{(L)}$ value, however, was approximately constant (75%) in the range of 7.00—10.00 mmol of the L-AcAla·AM salt. Optical resolution at 10—60 min, therefore, was performed with

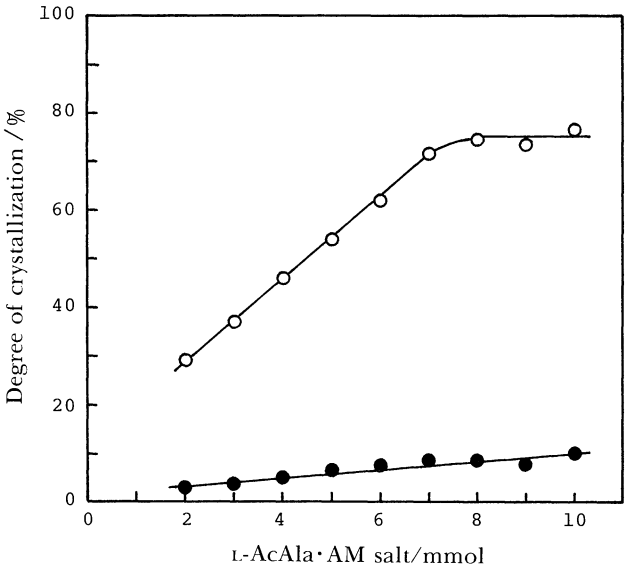

Fig. 1. Influence of the amount of the L-AcAla·AM salt on replacing crystallization of the DL-AcNva·AM salt. Conditions: DL-AcNva·AM salt 10.00 mmol; ethanol 40 cm³; temperature 5 °C; stirring time 20 min. Degree of crystallization: ○ L-AcNva·AM salt; ● D-AcNva·AM salt.

8.00 mmol of the L-AcAla·AM salt for 10.00 mmol of the DL-AcNva·AM salt. The result is listed in Table 1.

The L-AcNva·AM salt rapidly crystallized and the $DC_{(L)}$ value reached 92—94% at 30—60 min, whereas the crystallization of the D-salt was slow at 10—60 min. Optical resolution at 30—60 min gave the L-AcNva·AM salt with 81—84% optical purity at 84% degree of resolution. This L-AcNva·AM salt was recrystallized from ethanol to give the optically pure L-salt. The yield was estimated to be 80%. This result is far better than that by the optical resolution by preferential crystallization[2] and seems to be comparable to that attained by a diastereomeric procedure.

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