Racemic Structures of Organic Ammonium Salts of *N*-Acetyl-DL-2-aminobutyric Acid and *N*-Acetyl-DL-norvaline and Optical Resolution by Preferential Crystallization of DL-Ammonium Salts

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The racemic structures of the ammonium salts (AM salts) and seven organic ammonium salts of *N*-acetyl-DL-2-aminobutyric acid (DL-AcAbu) and *N*-acetyl-DL-norvaline (DL-AcNva) were studied on the basis of thermodynamic analyses to explore the possibility of optical resolution by preferential crystallization. An empirical equation has been derived from thermodynamic data at melting points of ammonium and organic ammonium salts of *N*-acyl-DL-amino acids to predict racemic structures around room temperature. The AM salts of DL-AcAbu and -AcNva exist in conglomerate around room temperature. It is possible to resolve optically these DL-AM salts by preferential crystallization in ethanol at 10 °C, and the successive preferential crystallization followed by purification gave D- and L-2-aminobutyric acids and -norvalines with optical purities close to 100%.

DL-2-Aminobutyric acid[1] (abbreviated as DL-Abu) and DL-norvaline[2] (DL-Nva) have been optically resolved in the form of the *N*-acetyl derivatives by using the optically active α-methylbenzylamine as a resolving agent. However, no optical resolution by preferential crystallization of DL-Abu or -Nva has been reported though this procedure is considered to be useful for industrial operation. This paper describes an attempt to resolve optically the ammonium salts and organic ammonium salts of *N*-acetyl-DL-2-aminobutyric acid (DL-AcAbu) and *N*-acetyl-DL-norvaline (DL-AcNva) by preferential crystallization. The DL-salts employed are the ammonium (AM), *t*-butylammonium (TBA), pentylammonium (PTA), hexylammonium (HA), and 1,1,3,3-tetramethylbutylammonium (TMB) salts of DL-AcAbu and the AM, ethylammonium (EA), butylammonium (BA), and propylammonium (PA) salts of DL-AcNva.

The racemic structures of these DL-salts were examined, since optical resolution by preferential crystallization requires that a racemic modification exists in conglomerate. A racemic modification existing in conglomerate has a positive free energy of formation of racemate,[3-5] shows an infrared spectrum identical with that of the corresponding optically active one,[6] and is more soluble than the optically active one.[6] In this paper, an empirical equation is also derived on the basis of thermodynamic data at melting points of ammonium and organic ammonium salts of *N*-acyl-DL-amino acids[5,7-11] to predict racemic structures around room temperature. Since it was found that the AM salts of DL-AcAbu and -AcNva exist in conglomerate around room temperature, optical resolution by preferential crystallization of these DL-salts were attempted at 10 °C in ethanol.

Experimental

Materials. DL-Abu and -Nva were purchased from Sigma Chemicals, and (−)-α-methylbenzylamine and amines from Wako Pure Chemicals Ind.

***N*-Acetylation.** DL-AcAbu[12] and -AcNva[2] were obtained, respectively, by acetylating DL-Abu and -Nva in the usual way. The DL-AcAbu obtained was recrystallized from ethanol, and the DL-AcNva from water. DL-AcAbu: Mp 134 °C (lit,[12] 128—130 °C); yield 82.0%. DL-AcNva: Mp 117 °C (lit,[2] 118—119 °C); yield 81.7%.

Preparation of Optically Active *N*-Acetylamino Acids. D- and L-AcAbu's[1] and -AcNva's[2] were obtained, respectively, by optical resolution of DL-AcAbu and -AcNva by using (−)-α-methylbenzylamine as a resolving agent. D-AcAbu: Mp 135 °C (lit,[1] 135 °C); $[\alpha]_D^{20}$ +43.3° (*c* 2.00, water) (lit,[1] $[\alpha]_D^{20}$ +43.6° (*c* 2, water)). L-AcAbu: Mp 135 °C (lit,[1] 135 °C); $[\alpha]_D^{20}$ −43.3° (*c* 2.00, water) (lit,[1] $[\alpha]_D^{20}$ −43.5° (*c* 2, water)). D-AcNva: Mp 105 °C (lit,[12] 100 °C); $[\alpha]_D^{20}$ +34.7° (*c* 2.00, water) (lit,[12] $[\alpha]_D^{25}$ +35.0° (*c* 1—2, water)). L-AcNva: Mp 105 °C; $[\alpha]_D^{20}$ −34.3° (*c* 2.00, water).

Preparation of Salts. DL-, D-, or L-AcAbu (0.01 mol) and 0.01 mol of an amine were dissolved in 50 cm³ of acetone. After stirring for 30 min at 5 °C, the salt formed was collected by filtration. The salt obtained was recrystallized from ethanol. The AM salts of DL-, D-, and L-AcNva's were also prepared in a similar manner.

The AM salt of DL-AcAbu: Mp 170 °C; found C, 44.35; H, 8.67; N, 17.43% (calcd for $C_6H_{14}N_2O_3$: C, 44.43; H, 8.70; N, 17.27%); solubility at 10 °C 2.103 g/(100 cm³ ethanol). The D-salt: Mp 188 °C; found C, 44.35; H, 8.66; N, 17.38%; $[\alpha]_D^{20}$ −20.7° (*c* 0.50, ethanol); solubility at 10 °C 1.319 g/(100 cm³ ethanol). The L-salt: Mp 188 °C; $[\alpha]_D^{20}$ +20.7° (*c* 0.50, ethanol).

The AM salt of DL-AcNva: Mp 150 °C; found C, 47.61; H, 9.11; N, 15.99% (calcd for $C_7H_{16}N_2O_3$: C, 47.71; H, 9.15; N, 15.90%); solubility at 10 °C 4.733 g/(100 cm³ ethanol). The D-salt: Mp 181 °C; found C, 47.57; H, 9.11; N, 16.04%; $[\alpha]_D^{20}$ −19.7° (*c* 0.50, ethanol); solubility at 10 °C 2.269 g/(100 cm³ ethanol). The L-salt: Mp 181 °C; $[\alpha]_D^{20}$ +19.7° (*c* 0.50, ethanol).

Optical Resolution by Successive Preferential Crystallization. Ammonium Salt of *N*-Acetyl-DL-norvaline: The AM salt of DL-AcNva (5.208 g) and 0.050 g of the L-salt were dissolved in 100 cm³ of ethanol around 40 °C. The solution was slowly cooled to 10 °C and seeded with 0.010 g of the L-salt. After stirring for 10 min at 10 °C, the salt that

precipitated was collected by filtration, washed with a small amount of diethyl ether, and dried; yield 0.276 g. The DL-salt (0.277 g) was added to the filtrate, and dissolved in ethanol around 40 °C. The solution was cooled to 10 °C and seeded with 0.010 g of the D-salt. After stirring for 11 min at 10 °C, the salt that precipitated was collected by filtration; yield 0.287 g. The filtrate was treated similarly.

Ammonium Salt of *N*-Acetyl-DL-2-aminobutyric Acid: The AM salt of DL-AcAbu (2.103 g) and 0.050 g of the L-salt were dissolved in 50 cm^3 of ethanol and the solution was seeded with 0.020 g of the L-salt at 10 °C. After stirring for 8 min, the salt precipitated was collected by filtration. The DL-salt (0.218 g) was dissolved in the filtrate. After seeding with 0.020 g of the D-salt and stirring for 8 min at 10 °C, the salt precipitated was collected by filtration. The filtrate was treated similarly.

The degree of resolution of the AM salts of D- and L-AcAbu and -AcNva's obtained was calculated by

$$\text{Degree of resolution}/\% = [\text{YOPM}/\text{g} \times 100]/[(\text{Operation amount of D- or L-salt}/\text{g}) - \text{M}],$$

where YOPM is the yield of optically pure modification[7] and M is 0.526 for the AM salts of AcAbu, and 2.367 g for the AM salts of AcNva.

Purification of Partially Resolved Ammonium Salts. The AM salt of D-AcAbu with an optical purity of 52.7% (3.78 g) was added to 85 cm^3 of ethanol. After stirring around 40 °C for 30 min, the suspension was further stirred for 1 h at 10 °C. The D-salt was collected by filtration, washed with a small amount of diethyl ether, and dried; yield 1.94 g; $[\alpha]_D^{20}$ −20.7° (*c* 0.50, ethanol).

The partially resolved AM salts of D-AcNva were purified by using ethanol similarly to the AM salt of D-AcAbu. The D-salt with an optical purity of 74.1% (6.96 g) was treated with 39 cm^3 of ethanol to give the D-salt with an optical purity of 100% in 5.07 g yield.

Preparation of Optically Active Amino Acids. The AM salts of D- and L-AcAbu's and -AcNva's obtained by preferential crystallization were purified similarly. The salts purified were treated with hydrochloric acid in the usual way to give the respective optically active amino acids.

The AM salt of D-AcNva with an optical purity of 100% (3.50 g) was dissolved in 4 cm^3 of 6 mol dm^{-3} hydrochloric acid around 50 °C, and the solution was stirred around 5 °C for 1 h. The D-AcNva was collected by filtration, washed with a small amount diethyl ether, and dried; yield 3.03 g; $[\alpha]_D^{20}$ +34.9° (*c* 2.00, water). The D-AcNva (2.90 g) was added to 7 cm^3 of 6 mol dm^{-3} hydrochloric acid. After refluxing for 2.5 h, the solution was evaporated to dryness under reduced pressure around 35 °C and the residue was dissolved in 30 cm^3 of methanol. After adding 2.4 cm^3 of concentrated aqueous ammonia, the solution was stirred for 1 h around 5 °C. The D-Nva that precipitated was collected by filtration, washed with small amounts of cold water and methanol, and dried: yield 1.56 g (total yield 71.1%); $[\alpha]_D^{20}$ −24.0° (*c* 2.00, 5 mol dm^{-3} HCl) (for L-Nva[13] $[\alpha]_D^{20}$ +24.1° (5 mol dm^{-3} HCl)).

The purified AM salts of L-AcNva and D- and D-AcAbu's were treated with hydrochloric acid similarly to the AM salt of D-AcNva. L-Nva: total yield 70.5%; $[\alpha]_D^{20}$ +23.9° (*c* 2.00, 5 mol dm^{-3} HCl). D-Abu: total yield 65.3%; $[\alpha]_D^{20}$ −20.7° (*c* 2.00, 5 mol dm^{-3} HCl). L-Abu: total yield 65.1%; $[\alpha]_D^{20}$ +20.9° (*c* 2.00, 5 mol dm^{-3} HCl) (lit,[13] $[\alpha]_D^{20}$ +20.9° (5 mol dm^{-3}HCl)).

Measurements. Specific rotations were measured with a Union Giken high sensitivity PM-101 digital polarimeter using a quartz cell of 0.5 dm path length. Infrared spectra were obtained in the range 4000—400 cm^{-1} with a JASCO A-102 infrared spectrophotometer by the KBr disk method. Enthalpies of fusion and melting points were determined with a Rigaku Denki differential scanning calorimeter DSC-8230.

Results and Discussion

Racemic Structure. Thermodynamic Data: The formation of a racemate in the solid state corresponds to the reaction between the solid enantiomers. The Gibbs energy of formation at *T* K (ΔG_T^F) is calculated

Table 1. Thermodynamic Data for Ammonium and Organic Ammonium Salts of *N*-Acetyl-2-aminobutyric Acid and *N*-Acetylnorvaline

N-Acetylamino acid	Salt	Mp/K		ΔH^f a)/kJ mol^{-1}		ΔG_T^F b)/kJ mol^{-1}	
		DL-Salt	D-Salt	DL-Salt	D-Salt	ΔG_{mp}^F	ΔG_{283}^F
AcAbu[c]	AM[e]	443	461	33.3	38.7	−1.08	+1.48
	TBA[f]	435	411	38.2	25.2	−4.51	−5.68
	PTA[g]	385	386	33.1	23.1	−2.15	−3.83
	HA[h]	388	388	34.2	25.9	−2.24	−3.43
	TMB[i]	421	434	37.2	37.8	−1.29	−0.43
AcNva[d]	AM[e]	423	454	32.1	36.7	+0.16	+1.15
	EA[j]	397	404	31.9	25.9	−1.84	−2.74
	PA[k]	388	397	28.5	28.1	−0.52	−1.09
	BA[l]	387	398	35.9	28.9	−0.76	−2.82

a) ΔH^f: Enthalpy of fusion. b) ΔG_T^F: Free energy of formation of racemate. The ΔG_T^F's at the melting point (ΔG_{mp}^F) and at 283 K (ΔG_{283}^F) were calculated from equations in Refs. 3—5. c) AcAbu: *N*-Acetyl-2-aminobutyric acid. d) AcNva: *N*-Acetylnorvaline. e) AM: Ammonium salt. f) TBA: *t*-Butylammonium salt. g) PTA: Pentylammonium salt. h) HA: Hexylammonium salt. i) TMB: 1,1,3,3-Tetramethylbutylammonium salt. j) EA: Ethylammonium salt. k) PA: Propylammonium salt. l) BA: Butylammonium salt.

by the following equation which is derived from the equations reported by Jacques et al.[3] by combination:

$$\Delta G_T^F = (\Delta H_A^f - \Delta H_R^f) - T(\Delta S_A^f - \Delta S_R^f) - RT\ln 2 - \Delta C_p(T_A^f - T_R^f + T\ln T_R^f/T_A^f) + (\alpha/2)(T_{R,A}^f - T)^2, \quad (1)$$

where ΔH^f, ΔS^f, and T^f are the enthalpy of fusion, entropy of fusion, and melting point, respectively, R is the gas constant, and ΔC_p is the difference in heat capacity between the liquid and solid states in the vicinity of melting point; subscripts "A" and "R" represent the optically active and racemic modifications, respectively; $T_{R,A}^f$ represents T_R^f when $T_R^f < T_A^f$ and T_A^f when $T_R^f > T_A^f$; α is calculated from $C_A^s - C_R^s = \alpha T_{R,A}^f$ as a first approximation; C^s is the heat capacity in the solid state.[3] The term containing ΔC_p is negligible for the calculation of ΔG_{mp}^F at the melting point because the contribution is very much smaller than that of the sum of the other terms in the right-hand side of Eq. 1;[3] T is equal to $T_{R,A}^f$ at the melting point and hence the last term is zero. In our calculation, ΔC_p was taken as 105 J mol^{-1} K^{-1} and $C_A^s - C_R^s$ as 31.4 J mol^{-1} K^{-1}.[3-5] The ΔG_T^F's at the melting point (ΔG_{mp}^F) and 283 K (ΔG_{283}^F) are given in Table 1.

As found in Table 1, all salts of DL-AcAbu and -AcNva give negative ΔG_{mp}^F values except the AM salt of DL-AcNva. The eutectic temperatures and compositions calculated on the basis of the ΔH^f and melting points[14] are listed in Table 2, together with the observed melting points of mixtures with eutectic compositions. Only the AM salt of AcNva shows the composition of 0.5. These results indicate that only the AM salt of DL-AcNva exists in conglomerate and that the other DL-salts form racemic compounds in the vicinity of the melting points. The above results are supported by the binary phase diagrams of melting points; the phase diagrams of the AM salts of AcAbu and AcNva are shown in Figs. 1 and 2 as examples.

Table 2. Mole Fractions and Temperatures at Eutectic Points

N-Acetyl-amino acid	Salt	Mole fraction of D-salt[a]	Temperature/K	
			Found	Calcd[a]
AcAbu	AM	0.64	442	441
	TBA	0.94	408	407
	PTA	0.82	377	375
	HA	0.82	378	379
	TMB	0.68	419	418
AcNva	AM	0.50	423	424
	EA	0.76	390	390
	PA	0.73	381	383
	BA	0.72	383	384

a) These values were calculated from the Schröder-Van Laar and Prigogine-Defay equations.

The AM salt of DL-AcNva gives a positive ΔG_{283}^F value, whereas negative ΔG_{283}^F values were obtained for the TBA, PTA, HA, and TMB salts of DL-AcAbu and the EA, BA, and PA salts of DL-AcNva. Therefore, the racemic structures of the latter around room temperature may be identical with those in the vicinity of the melting points, respectively. On the other hand, since the AM salts of DL-AcAbu and DL-AcNva give positive ΔG_{283}^F values, it is inferred that the DL-salts do not form racemic compounds around room temperature.

Racemic Structure Around Room Temperature: The relationship among various thermodynamic data at melting points was examined to predict the racemic structures around room temperature for the 41 kinds of AM and organic ammonium salts of DL-AcAbu, DL-AcNva, and *N*-acyl-DL-amino acids, dealt with in our previous paper.[5,7-11] There is an empirical relationship among their ΔG_{mp}^F, ΔT^f ($=T_R^f - T_A^f$), and $\Delta\Delta H^f$

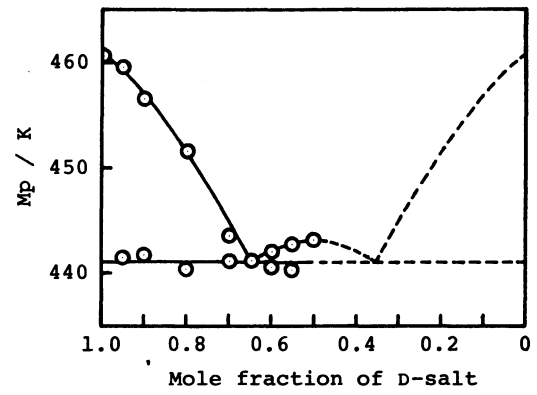

Fig. 1. Binary melting point diagram of ammonium salt of *N*-acetyl-2-aminobutyric acid.

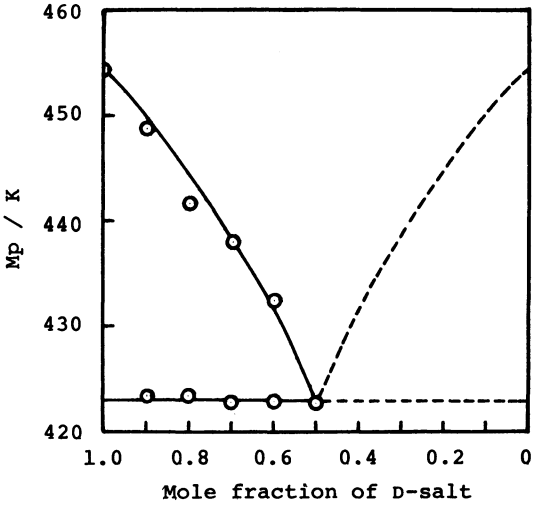

Fig. 2. Binary melting point diagram of ammonium salt of *N*-acetylnorvaline.

$(=H_R^f - \Delta H_A^f)$, which reads

$$\Delta G_{mp}^F = -0.0865\Delta T^f - 0.0223\Delta\Delta H^f - 2.285, \quad (2)$$

where $-0.0865\Delta T^f - 0.0223\Delta\Delta H^f$ $(=\Delta E)$ and 2.285 must be of the same order as ΔG_{mp}^F; the correlation coefficient was 0.958. This empirical equation shows that a DL-salt that exists in conglomerate around room temperature gives ΔE larger than $+1.17\,kJ\,mol^{-1}$, irrespective of whether the DL-salt forms a racemic compound in the vicinity of its melting point, and that a DL-salt forming a racemic compound in the temperature range between room temperature and its melting point gives ΔE smaller than $+1.14\,kJ\,mol^{-1}$. The AM salt of DL-AcAbu gives a ΔE value of +1.68, the AM salt of DL-AcNva +2.87, and the other DL-salts -2.4—$+1.13\,kJ\,mol^{-1}$. Therefore, the ΔE values may be used to determine if the AM salts of DL-AcAbu and -AcNva exist in conglomerate around room temperature. This is consistent with the conclusion derived from their ΔG_{283}^F values, and is also supported by the infrared spectra and solubilities of these DL- and D-salts; the AM salts of DL-AcAbu and -AcNva show infrared spectra identical with those of the corresponding D-salts, they are more soluble than the D-salts, and the ternary solubility diagram of the AM salt of DL-AcAbu shows what is expected for a conglomerate, as shown in Fig. 3.[15] The above results indicate that the AM salts of DL-AcAbu and -AcNva exist in conglomerate around room temperature though the AM salt of DL-AcAbu forms a racemic compound in the vicinity of the melting point.

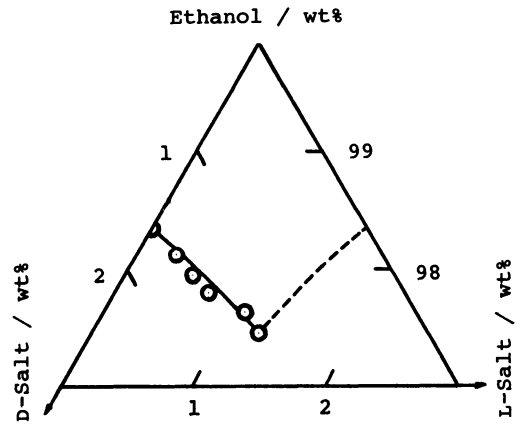

Fig. 3. Ternary solubility diagram of ammonium salt of *N*-acetyl-2-aminobutyric acid.
Solvent: ethanol. Temperature: 10 °C.

The TBA, PTA, HA, and TMB salts of DL-AcAbu and the EA, BA, and PA salts of DL-AcNva probably form racemic compounds around room temperature because their infrared spectra are different from those of the corresponding D-salts and because their ΔG_{283}^F values are negative.

Optical Resolution by Preferential Crystallization. Results of Optical Resolution and Purification of Salts Partially Resolved: Optical resolutions by preferential crystallization of the AM salts of DL-AcAbu and DL-AcNva were attempted at 10 °C in ethanol using a solution of the AM salt of DL-AcAbu with a degree of supersaturation of 200% and a solution of the AM salt of DL-AcNva with 110%, by a procedure similar to that described in our previous paper;[10] the D-salts were used as seed crystals. The results of the optical resolutions are given in Table 3.

The AM salts of D-AcAbu obtained did not have so high optical purities (41—79%) and the degrees of resolution were also low (10—25%); however it was possible to obtain AM salts of D-AcNva with optical purities of 72—95% and degrees of resolution of 40—78%.

The AM salt of D-AcAbu with a low optical purity was easily purified. The AM salt of D-AcAbu with an optical purity of 71.2% (3.00 g) was dissolved in 110 cm^3 of ethanol around 40 °C, and the solution was

Table 3. Optical Resolutions by Preferential Crystallization of Ammonium Salts of *N*-Acetyl-DL-2-aminobutyric Acid[a] and *N*-Acetyl-DL-norvaline[b]

N-Acetyl-amino acid	Resolution time / min	Yield / g	Optical purity / %	YOPM[c] / g	Degree of resolution / %
AcAbu	5	0.096	79.1	0.056	10.7
	10	0.176	74.0	0.110	20.9
	15	0.233	59.7	0.119	22.6
	20	0.362	41.7	0.131	24.9
AcNva	10	0.113	94.8	0.097	40.9
	15	0.205	94.9	0.184	77.7
	20	0.248	72.5	0.170	71.9

a) Solvent: 50 cm^3 of ethanol. Degree of supersaturation of racemic solution: 200%. Seed crystals: 0.020 g of D-salt. Temperature: 10 °C. b) Solvent: 100 cm^3 of ethanol. Degree of supersaturation of racemic solution: 110%. Seed crystals: 0.010 g of D-salt. Temperature: 10 °C. c) YOPM: Yield of optically pure modification.

allowed to stand for a day around 5 °C to give a D-salt with an optical purity of 100%. However, the yield (1.62 g) was 75.7% of the theoretical (2.14 g) and the recrystallization resulted in a loss of about 24%.

The optimum amount of ethanol was estimated on the basis of the solubility at 10 °C of the DL-salt to obtain the maximum yield of the optically pure salt.[16] The AM salt of D-AcAbu with an optical purity of 52.7% was treated with ethanol. Since 3.78 g of the D-salt was not completely dissolved in 85 cm^3 of ethanol around 40 °C, the suspension was treated by the procedure described in the experimental section; the optimum amount of ethanol calculated was 85.1 cm^3. The purification by this procedure gave the D-salt with an optical purity of 100% in 1.84 g yield; the yield was 92.5% of the theoretical (1.99 g).

The AM salt of D-AcNva partially resolved was also easily purified similarly. The D-salt with an optical purity of 74.1% (6.96 g) was treated with 38 cm^3 of ethanol (the optimum amount 38.0 cm^3) to give the D-salt with an optical purity of 100% in 5.07 g yield; the yield was 98.3% of the theoretical (5.16 g).

Successive Preferential Crystallization: The optical resolution by successive preferential crystallization was carried out to obtain the D- and L-Abu's and -Nva's. The results of such optical resolution are given in Tables 4 and 5.

The AM salts of D- and L-AcAbu obtained had optical purities of 72—81%, and the degrees of resolution were 20—28%. On the other hand, the optical resolution of the AM salt of DL-AcNva was found to give better results; D- and L- salts with optical purities of 90—100% were obtained at degrees of resolution of about 80%. These D- and L-salts purified were treated with hydrochloric acid to give D- and L-Abu's and -Nva's with optical purities of 99—100%.

It was found from the above results that the AM salts of DL-AcAbu and -AcNva exist in conglomerate around room temperature though the AM salt of DL-AcAbu forms a racemic compound in the vicinity of the melting point, and that the optical resolution by preferential crystallization followed by purification gives D- and L-Abu's and -Nva's with optical purities of about 100%.

References

1) D. Pitre and S. Boveri, *Farmaco, Ed. Sci.*, **26**, 733 (1971).
2) P. Alaupovic, *Croat. Chem. Acta*, **29**, 131 (1957).
3) M. Leclercq, A. Collet, and J. Jacques, *Tetrahedron*, **32**, 821 (1976); J. Jacques, A. Collet, and S. H. Wilen,

Table 4. Successive Preferential Crystallization of Ammonium Salt of *N*-Acetyl-DL-2-aminobutyric Acid[a]

Run	Added amount of DL-salt / g	Operation amount[b] / g		Resolution time / min	Salt obtained			
		D-Salt	L-Salt		Yield / g	Optical purity / %	YOPM / g	Degree of resolution[c] / %
1	2.103	1.051	1.101	8	0.217	L 73.9	0.140	24.3
2	0.218	1.131	1.041	8	0.233	D 81.2	0.169	27.9
3	0.233	1.056	1.136	10	0.197	L 72.0	0.122	20.0
4	0.198	1.127	1.086	13	0.230	D 72.0	0.146	24.3

a) Solvent: 50 cm^3 of ethanol. Seed crystals: 0.020 g of D- or L-salt. Temperature: 10 °C. This initial solution contains 2.103 g of DL-salt and 0.050 g of L-salt. b) The operation amounts of D- and L-salts in solutions were calculated on the basis of the analyses of the salt obtained in Runs 1—3. c) Degree of resolution/% = [YOPM/g × 100]/[(Operation amount of D- or L-salt/g) − 0.526].

Table 5. Successive Preferential Crystallization of Ammonium Salt of *N*-Acetyl-DL-norvaline[a]

Run	Added amount of DL-salt / g	Operation amount[b] / g		Resolution time / min	Salt obtained			
		D-Salt	L-Salt		Yield / g	Optical purity / %	YOPM / g	Degree of resolution[c] / %
1	5.208	2.604	2.654	10	0.276	L 90.5	0.240	83.6
2	0.277	2.730	2.540	11	0.287	D 100	0.277	76.3
3	0.288	2.597	2.684	11	0.270	L 92.3	0.239	75.4
4	0.271	2.722	2.570	13	0.305	D 97.5	0.287	80.8

a) Solvent: 100 cm^3 of ethanol. Seed crystals: 0.010 g of D- or L-salt. Temperature: 10 °C. This initial solution contains 5.208 g of DL-salt and 0.050 g of L-salt. b) The operation amounts of D- and L-salts in solutions were calculated on the basis of the analyses of the salt obtained in Runs 1—3. c) Degree of resolution/% = [YOPM/g × 100]/[(Operation amount of D- or L-salt/g) − 2.367].

"Enantiomers, Racemates, and Resolutions," John Wiley and Sons, New York, Chichester, Brisbane, and Toronto (1981), pp. 97—99, 140—142.

4) T. Shiraiwa, A. Ikawa, K. Fujimoto, K. Iwafuji, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1984**, 764.

5) T. Shiraiwa, H. Miyazaki, A. Ikawa, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1984**, 1425.

6) S. Yamada, M. Yamamoto, and I. Chibata, *J. Org. Chem.*, **38**, 4408 (1973).

7) T. Shiraiwa, S. Taniguchi, A. Ikawa, K. Iwafuji, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1983**, 1189.

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

9) H. Miyazaki, T. Shiraiwa, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1986**, 87.

10) T. Shiraiwa, H. Yoshida, K. Mashima, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1986**, 177.

11) T. Shiraiwa, H. Miyazaki, Y. Sakamoto, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **59**, 2331 (1986).

12) R. Marshall, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **78**, 4636 (1956).

13) "Seikagaku Data Bukku," ed by the Japanese Biochemical Society, Tokyo Kagaku Dojin, Tokyo (1982), Vol. I, pp. 36, 48.

14) S. H. Wilen, A. Collet, and J. Jacques, *Tetrahedron*, **33**, 2725 (1977).

15) A. Collet, M. J. Brienne, and J. Jacques, *Chem. Rev.*, **80**, 215 (1980).

16) T. Shiraiwa, M. Nakamura, M. Nobeoka, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **59**, 2669 (1986).