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Racemic Structure and Optical Resolution by Preferential Crystallization of (±)-Organic Ammonium Hydrogen Malates

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Gibbs energies of formation of racemate, binary melting point diagrams, and ternary solubility diagrams indicate that (±)-propylammonium ((±)-PA salt) and (±)-1,1,3,3-tetramethylbutylammonium ((±)-TMB salt) hydrogen malates are conglomerates at room temperature, whereas (±)-TMB salt forms a racemic compound at its melting point. Free energies of critical nucleation in supersaturated solutions were examined to resolve (±)-PA and -TMB salts efficiently by preferential crystallization. Successive preferential crystallization of (±)-PA salt in methanol at 10 °C and that of (±)-TMB salt in water give (+)- and (−)-PA and -TMB salts with about 90% optical purity. Optically pure (+)- and (−)-malic acids are obtained from purified (−)- and (+)-salts.

Optically active malic acid (abbreviated as MAL) is a useful material for food additives and medicines and a resolving agent for racemic organic amines. (±)-MAL has been optically resolved by preferential crystallization in the form of (±)-ammonium[1] and (±)-α-methylbenzylammonium[2] hydrogen malates and by the diastereomeric procedure using (+)-tartaric acid[3] as a resolving agent. This paper describes an attempt to resolve optically (±)-organic ammonium hydrogen malates by preferential crystallization. The examined (±)-salts were methylammonium ((±)-MA salt), ethylammonium ((±)-EA salt), propylammonium ((±)-PA salt), isopropylammonium ((±)-IPA salt), butylammonium ((±)-BA salt), isobutylammonium ((±)-IBA salt), *t*-butylammonium ((±)-TBA salt), pentylammonium ((±)-PTA salt), hexylammonium ((±)-HA salt), octylammonium ((±)-OA salt), 1,1,3,3-tetramethylbutylammonium ((±)-TMB salt), anilinium ((±)-AN salt), diisobutylammonium ((±)-DIB salt), dicyclohexylammonium ((±)-DCH salt), dibenzylammonium ((±)-DBZ salt), and cyclohexylmethylammonium ((±)-CMA salt) salts.

The racemic structure of the (±)-salts was determined by thermodynamic analysis.[4,5] (±)-PA and -TMB salts which seemed to be conglomerates were subjected to a resolution by preferential crystallization. The free energy of critical nucleation in supersaturated solutions of the (+)- and (−)-salts was examined to find the appropriate conditions for the optical resolution.[6–8]

Experimental

Materials. (±)-Malic acid and amines were purchased from Wako Pure Chemicals Ind. and Kanto Chemical Co., Ltd., and (+)- and (−)-MAL were donated from Fuso Chemical Co., Ltd.; (+)-MAL $[\alpha]^{20}_{\mathrm{D}}+2.90°$ (*c* 30.0, methanol); (−)-MAL $[\alpha]^{20}_{\mathrm{D}}-2.92°$ (*c* 30.0, methanol) (lit,[9] $[\alpha]_{\mathrm{D}}-2.92°$ (*c* 30%, methanol)).

Preparation of Organic Ammonium Salt. A solution of 0.01 mol of (±)-, (+)-, or (−)-MAL and equimolar amine in acetone was allowed to stand overnight at 5 °C. The salt formed was filtered and recrystallized from an appropriate solvent; the PA salt was recrystallized from 1-propanol and the TMB salt from ethanol. The (+)-salts were formed from (−)-MAL and amines, and the (−)-salts from (+)-MAL and amines.

(±)-PA salt: Found C, 43.33; H, 7.78; N, 7.13% (calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83; N, 7.25%); solubility 11.593 g/(100 cm³ methanol) at 10 °C. (+)-PA salt: Found C, 43.45; H, 7.82; N, 7.29%; $[\alpha]^{25}_{436}+11.6°$ (*c* 1.00, methanol); solubility 5.135 g/(100 cm³ methanol) at 10 °C.

(±)-TMB salt: Found C, 54.53; H, 9.47; N, 5.35% (calcd for $C_{12}H_{25}NO_5$: C, 54.73; H, 9.57; N, 5.32%); solubility 8.640 g/(100 cm³ water) and 5.644 g/(100 cm³ methanol) at 10 °C. (+)-TMB salt: Found C, 54.56; H, 9.49; N, 5.34%; $[\alpha]^{25}_{436}+11.9°$ (*c* 1.00, methanol); solubility 5.959 g/(100 cm³ water) and 3.320 g/(100 cm³ methanol) at 10 °C.

Optical Resolution. Preferential Crystallization: (±)-PA or -TMB salt was dissolved in 50 cm³ of methanol or water, respectively, at 40 °C to give racemic solutions with different degrees of supersaturation of 120—200%. The solution was slowly cooled to 10 °C and seeded with 0.050 g of the (+)-salt. After stirring the mixture at 10 °C, the precipitated salt was collected by filtration, washed with a small amount of diethyl ether, and dried.

Successive Preferential Crystallization: A methanol solution of (±)-PA salt with 180% supersaturation was seeded with 0.050 g of the (+)-salt at 10 °C. After stirring the mixture for 30 min at 10 °C, the precipitated salt was filtered. (±)-PA salt (0.918 g) was dissolved in the filtrate at 40 °C; the amount was equal to that of the crystallized salt. After seeding the solution with 0.050 g of the (−)-salt at 10 °C, the mixture was treated similarly to above.

An optical resolution of (±)-TMB salt was performed on an aqueous solution with 155% supersaturation, similarly to (±)-PA salt.

The degree of resolution of the (+)- and (−)-salts was calculated by

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

where M is 2.898 g for the PA salt and 2.160 g for the TMB salt, and YOPM is the yield of optically pure modification.[10]

Preparation of Optically Active Malic Acid. The purified (+)- or (−)-PA salt (1.93 g) or -TMB salt (2.63 g) with 100% optical purity was treated as aqueous solutions through a 1.3×17.8 cm column of Amberlite IR-120 of H^+ form by eluting with water. The eluent was evaporated to dryness under reduced pressure at 40 °C; optically pure (+)-MAL was obtained in 1.12 g yield from the (−)-PA salt and in 1.29 g yield from the (−)-TMB salt, and optically pure (−)-MAL was obtained in 1.20 g yield from the (+)-PA salt and in 1.31 g yield from the (+)-TMB salt.

Measurements. Specific rotation was measured by a Union Giken PM-101 digital polarimeter with a quartz cell of 1.0 dm path length. Infrared spectra were obtained in the range 4000—400 $\mathrm{cm^{-1}}$ 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.

Saturated solutions of (±)- and (+)-PA and -TMB salts were prepared at 10 °C; methanol was employed as a solvent for PA salt and water for TMB salt. Refractive index was measured with a Shimadzu refractometer Abbe 3L. Solubility was determined by using the refractive index from calibration curves.

Results and Discussion

Racemic Structure. Racemic Structure at Melting Point: The Gibbs energy of formation of racemate ($\Delta G_T^F/\mathrm{kJ\,mol^{-1}}$) is calculated from enthalpies of fusion ($\Delta H^f/\mathrm{kJ\,mol^{-1}}$) and melting points.[4,5] These values are listed in Table 1; the ΔG_T^F value of (±)-TBA salt could not be calculated because (+)-TBA salt decomposed on heating.

All the (±)-salts give negative values of ΔG_{mp}^F at their melting points except (±)-PA salt. Eutectic temperatures and compositions calculated on the basis of ΔH^f and melting point[11] are listed in Table 1, together with observed melting points of mixtures with eutectic compositions. The melting points agree well with the calculated eutectic temperatures. Only PA salt shows a composition of 0.5 and the other salts those of 0.60—0.93; the binary melting point diagrams of PA and TMB salts are shown in Figs. 1 and 2, respectively. These results have led us to infer that only (±)-PA salt is a conglomerate at the melting point and that the other (±)-salts form racemic compounds.

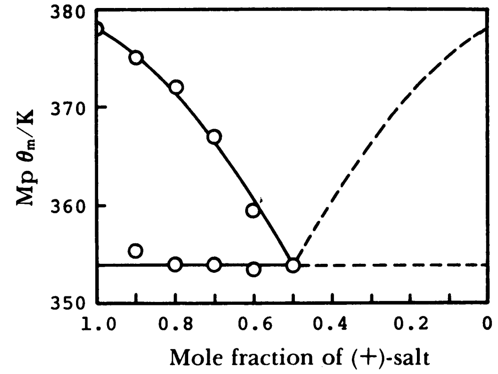

Fig. 1. Binary melting point diagram of propylammonium hydrogen malate.

Table 1. Thermodynamic Data of Organic Ammonium Hydrogen Malate

Salt	Mp θ_m/K		$\Delta H^{f\,a)}/\mathrm{kJ\,mol^{-1}}$		$\Delta G_T^{F\,b)}/\mathrm{kJ\,mol^{-1}}$		Eutectic point		
	(±)	(+)	(±)	(+)	ΔG_{mp}^F	ΔG_{283}^F	Mole fraction[c]	Temperature/K Calcd[c]	Temperature/K Found
MA[e]	349	361	29.7	31.1	−0.98	−0.59	0.66	347	346
EA[f]	398	410	36.0	35.8	−1.25	−0.80	0.68	395	397
PA[g]	354	378	33.2	36.1	+0.44	+0.44	0.50	356	354
IPA[h]	402	402	40.2	38.8	−2.32	−1.49	0.80	394	393
BA[i]	338	334	20.8	23.4	−2.17	−1.25	0.82	326	328
IBA[j]	371	351	32.8	28.7	−3.79	−3.19	0.93	348	349
TBA[k]	440	450[d]	29.2	—	—	—	—	—	—
PTA[l]	350	346	21.2	20.2	−2.24	−1.75	0.83	337	336
HA[m]	346	343	35.7	36.0	−2.29	−1.61	0.84	338	336
OA[n]	350	349	36.0	35.9	−2.11	−1.52	0.81	343	344
TMB[o]	438	457	33.0	41.8	−0.79	+2.73	0.60	437	436
AN[p]	416	411	40.2	40.5	−2.85	−1.08	0.84	405	405
DIB[q]	414	413	33.9	33.7	−2.46	−1.07	0.80	404	405
DCH[r]	437	441	24.2	23.9	−2.30	−0.89	0.78	425	427
DBZ[s]	435	444	45.4	42.3	−1.65	−1.66	0.71	431	433
CMA[t]	364	377	35.5	33.9	−0.93	−1.12	0.64	362	363

a) ΔH^f: Enthalpy of fusion. b) ΔG_T^F: Gibbs energy of formation of racemate. c) These values were calculated from the Schröder-Van Laar and Prigogine-Defay equations. d) Decomposition. e) MA: Methylammonium salt. f) EA: Ethylammonium salt. g) PA: Propylammonium salt. h) IPA: Isopropylammonium salt. i) BA: Butylammonium salt. j) IBA: Isobuytlammonium salt. k) TBA: *t*-Butylammonium salt. l) PTA: Pentylammonium salt. m) HA: Hexylammonium salt. n) OA: Octylammonium salt. o) TMB: 1,1,3,3-Tetramethylbutylammonium salt. p) AN: Anilinium salt. q) DIB: Diisobutylammonium salt. r) DCH: Dicyclohexylammonium salt. s) DBZ: Dibenzylammonium salt. t) CMA: Cyclohexylmethylammonium salt.

Racemic Structure at Room Temperature: (±)-PA and -TMB salts give positive values of $\Delta G^{\mathrm{F}}_{283}$ at 283 K, whereas the values of the other (±)-salts are negative. (±)-PA and -TMB salts show infrared spectra indentical with those of the corresponding (+)-salts and are more soluble than the (+)-salts as described in the experimental section. The ternary solubility diagram of TMB salt, shown in Fig. 3, illustrates the pattern of a conglomerate.[12] These results indicate that (±)-PA and -TMB salts are conglomerates at room temperature, though (±)-TMB salt forms a racemic compound at its melting point.

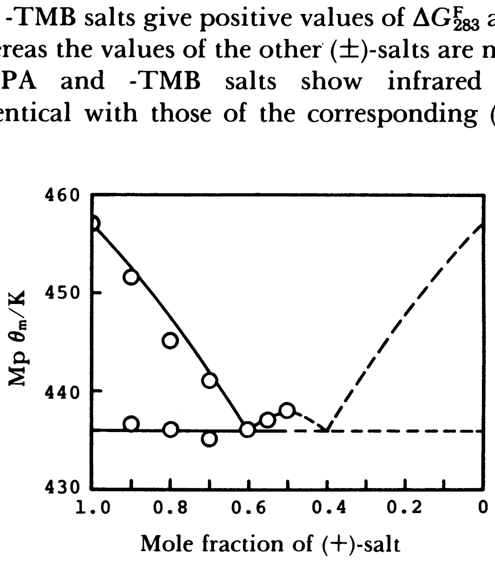

Fig. 2. Binary melting point diagram of 1,1,3,3-tetramethylbutylammonium hydrogen malate.

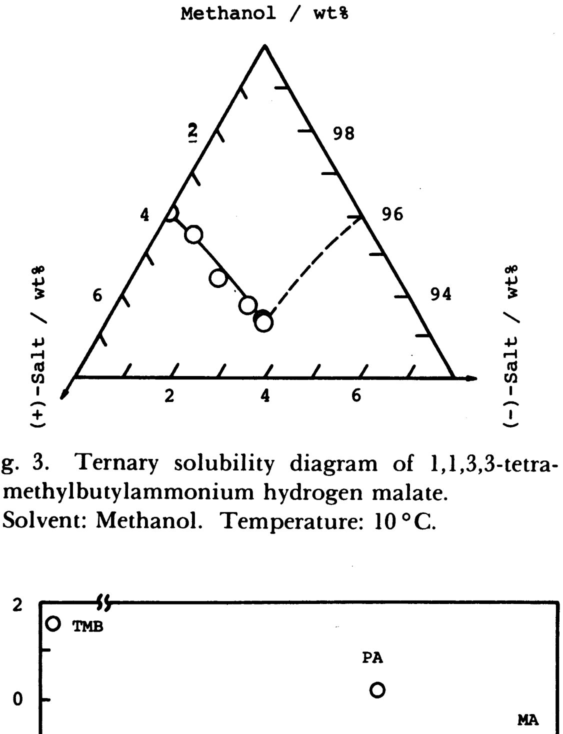

Fig. 3. Ternary solubility diagram of 1,1,3,3-tetramethylbutylammonium hydrogen malate.
Solvent: Methanol. Temperature: 10 °C.

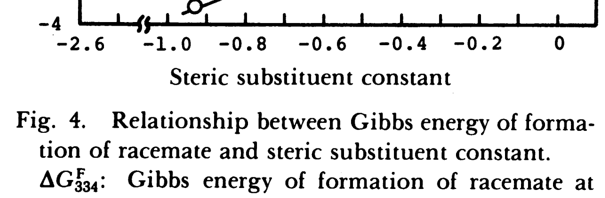

Fig. 4. Relationship between Gibbs energy of formation of racemate and steric substituent constant.
$\Delta G^{\mathrm{F}}_{334}$: Gibbs energy of formation of racemate at 334 K. E_s: Steric substituent constant; see Ref. 13.

Since the infrared spectra of the other (±)-salts and (±)-TBA salt, of which the corresponding (+)-salt decomposes on heating, are different from those of the corresponding (+)-salts, these (±)-salts may be concluded to form racemic compounds at room temperature.

Substituent Effect on the Gibbs Energy of Formation of Racemic Compound: The formation of racemic compounds of the salts of (±)-MAL with primary amines having an alkyl side chain was examined from the relationship between steric substituent constant (E_S)[13] and $\Delta G^{\mathrm{F}}_{334}$ value, shown in Fig. 4; the $\Delta G^{\mathrm{F}}_{334}$ values at 334 K were calculated for comparison at the same temperature.[4,5]

(±)-PA and -TMB salts show positive $\Delta G^{\mathrm{F}}_{334}$ values, whereas the $\Delta G^{\mathrm{F}}_{334}$ values of the other (±)-salts are negative. The absolute value of $\Delta G^{\mathrm{F}}_{334}$ tends to increase with an increase in the absolute value of E_S. Since (±)-PA and -TMB salts and (±)-salts with aromatic amines or secondary amines are out of this relationship, it is impossible to draw any conclusion on conglomerate formation from this relationship. However, Fig. 4 suggests that racemic compounds with smaller alkyl side chains become less stable. This may be related to the fact that the (±)-ammonium hydrogen malate with "the smallest side chain" has been optically resolved by preferential crystallization.[1]

Appropriate Conditions for Preferential Crystallization. (±)-PA salt was optically resolved by preferential crystallization in 50 cm^3 of methanol at 10 °C with 0.050 g of the (+)-salt as seed crystals, and (±)-TMB salt in 50 cm^3 of water. The amount of crystallization of the (+)- and (−)-salts calculated from results of optical resolution[10] and the relationship between the amount and resolution time are shown in Figs. 5 and 6, respectively. (±)-PA and -TMB salts have been confirmed from these results to be conglomerates at 10 °C.

Appropriate conditions for the optical resolution of (±)-PA and -TMB salts were estimated from the free energy of critical nucleation[6-8,14] ($\Delta g_{\max}$/J nucleus^{-1}), the speed of crystallization of the (+)-salt ($R_{(+)}$/g min^{-1}), and the retardation time of crystallization of the (−)-salt ($\theta_{(-)}$/min);[8] the value of $R_{(+)}$ was calculated from the linear plots of Figs. 5 and 6, with $\theta_{(-)}$ defined as the resolution time before the (−)-salt begins to crystallize rapidly. The value of $\Delta g_{\max}$ and other related factors for crystallization are listed in Table 2.

Table 2. Free Energy of Critical Nucleation and Factors for Crystallization[a]

Salt	Degree of supersaturation	$\Delta g_{\max}$[b]	$R_{(+)}$[c]	$\theta_{(-)}$[d]	$W_{(-5)}$[e]/g	
	%	10^{-18} J nucleus^{-1}	10^{-2} g min^{-1}	min	Found	Calcd[f]
PA[g]	160	2.88	1.25	75	0.879	0.837
	170	2.14	2.03	45	0.851	0.866
	180	1.66	3.00[i]	34[j]	0.897	0.878
	190	1.32	4.41	25	0.871	0.871
	200	1.08	5.72	20	0.852	0.845
TMB[h]	120	59.3	0.116	345	0.380	0.361
	140	15.8	0.501	75	0.336	0.435
	150	10.4	1.17	45	0.434	0.449
	155	8.73	1.36[k]	38[l]	0.447	0.451
	180	4.39	3.53	18	0.415	0.419

a) Conditions of crystallization: 50 cm^3 of solvent (methanol for PA salt; water for TMB salt); seed crystals 0.050 g of (+)-salt; temperature 10 °C. b) $\Delta g_{\max}$: Free energy of critical nucleation at 10 °C. c) $R_{(+)}$: Speed of crystallization of (+)-salt. d) $\theta_{(-)}$: Retardation time for crystallization of (−)-salt. e) $W_{(-5)}$: Amount of crystallization of (+)-salt at $\theta_{(-)}-5$ min. f) The values were calculated from Eq. 5 or 6. g) PA: Propylammonium salt. h) TMB: 1,1,3,3-Tetramethylbutylammonium salt. i) The value was calculated from Eq. 1. j) The value was calculated from Eq. 2. k) The value was calculated from Eq. 3. l) The value was calculated from Eq. 4.

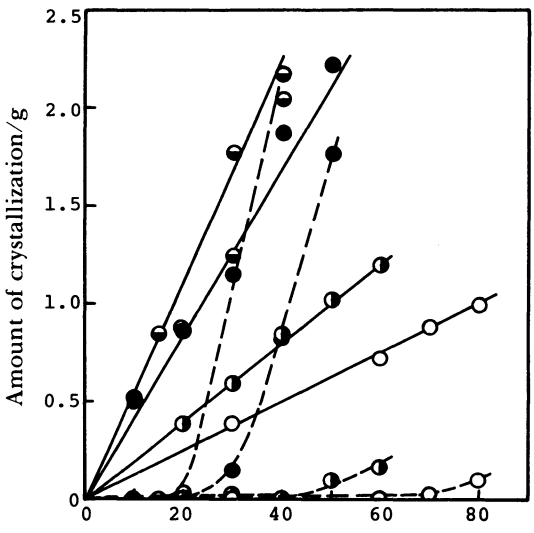

Fig. 5. Relationship between amount of crystallization and resolution time for propylammonium hydrogen malate.
Conditions: Solvent 50 cm^3 of methanol; temperature 10 °C; seed crystals 0.050 g of (+)-salt. Degree of supersaturation: ○ 160%; ◑ 170%; ● 190%; ◒ 200%, ——: (+)-Salt. - - -: (−)-Salt.

For PA salt, the relationship between $R_{(+)}$ and $\Delta g_{\max}$ for different degrees of supersaturation of 160, 170, 190, and 200% and that between $\theta_{(-)}$ and $\Delta g_{\max}$ were obtained from the following equations:[8)]

$$\ln R_{(+)} = -1.572 \ln \Delta g_{\max} - 67.87, \tag{1}$$

$$\ln \theta_{(-)} = 1.332 \ln \Delta g_{\max} + 58.08, \tag{2}$$

where the correlation coefficients for Eqs. 1 and 2 are 0.999 and 0.996, respectively. For TMB salt, the following equations were obtained for different degrees of supersaturation of 120, 140, 150, and 180%:

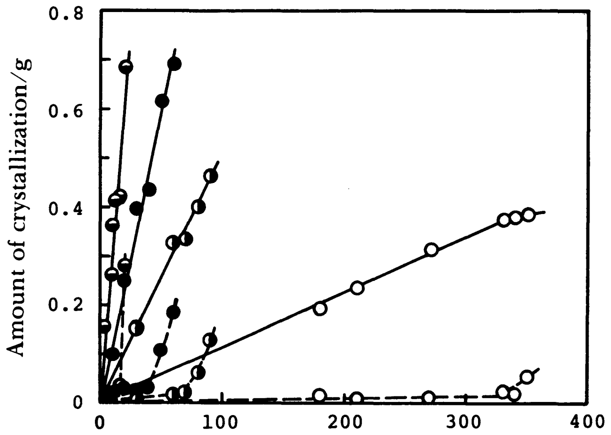

Fig. 6. Relationship between amount of crystallization and resolution time for 1,1,3,3-tetramethylbutylammonium hydrogen malate.
Conditions: Solvent 50 cm^3 of water; temperature 10 °C; seed crystals 0.050 g of (+)-salt. Degree of supersaturation: ○120%; ◑140%; ●150%; ◒180%. ——: (+)-Salt. - - -: (−)-Salt.

$$\ln R_{(+)} = -1.321 \ln \Delta g_{\max} - 56.18, \tag{3}$$

$$\ln \theta_{(-)} = -1.140 \ln \Delta g_{\max} + 48.43, \tag{4}$$

where the correlation coefficients for Eqs. 3 and 4 are 0.995 and 0.999, respectively.

The optical resolution at $\theta_{(-)}-5$ min seems to be a better criterion for evaluating results of optical resolution than that at $\theta_{(-)}$ min because the unseeded (−)-salt begins to crystallize rapidly after $\theta_{(-)}$ min. The amounts of crystallization of (+)-PA and -TMB

Table 3. Successive Preferential Crystallization of (±)-Propylammonium and (±)-1,1,3,3-Tetramethylbutylammonium Hydrogen Malate[a)]

(±)-Salt	Run	Added amount of (±)-salt	Operation amount[b)]/g		Resolution time	Salt obtained				
							Yield	Optical purity	YOPM[c)]	Degree of resolution
		g	(+)	(−)	min		g	%	g	%
PA[d)]	1	10.434	5.217	5.217	30	(+)	0.968	95.6	0.875	37.7
	2	0.918	4.779	5.654	30	(−)	1.634	94.6	1.496	54.3
	3	1.584	5.527	4.906	30	(+)	1.491	93.9	1.350	51.3
	4	1.441	4.852	5.581	30	(−)	1.907	90.1	1.668	62.2
TMB[e)]	1	6.696	3.348	3.348	33	(+)	0.521	90.6	0.422	35.5
	2	0.471	3.137	3.559	40	(−)	0.734	91.7	0.623	44.5
	3	0.684	3.448	3.247	35	(+)	0.606	91.6	0.505	39.2
	4	0.556	3.195	3.499	35	(−)	0.696	88.6	0.567	42.3

a) Solvent: 50 cm³ of methanol for PA salt; 50 cm³ of water for TMB salt. Seed crystals: 0.050 g of (+)- or (−)-salt. Temperature: 10 °C. b) The operation amounts of (+)- and (−)-salts were calculated on the basis of analyses of the salt obtained in Runs 1—3. c) YOPM: Yield of optically pure modification. d) PA: Propylammonium salt. e) TMB: 1,1,3,3-Tetramethylbutylammonium salt.

salts ($W_{(-5)}/\mathrm{g}=R_{(+)}(\theta_{(-)}-5)$) are given by the following equations, as derived from Eqs. 1—4:

$$W^{\mathrm{PA}}_{(-5)} = 5.609 \times 10^{-5}\Delta g_{\max}{}^{-0.2398} - 1.676 \times 10^{-29}\Delta g_{\max}{}^{-1.572}, \quad (5)$$

$$W^{\mathrm{TMB}}_{(-5)} = 4.268 \times 10^{-4}\Delta g_{\max}{}^{-0.1807} - 1.992 \times 10^{-24}\Delta g_{\max}{}^{-1.321}. \quad (6)$$

The value of $\Delta g_{\max}$ that gives the maximum $W_{(-5)}$ is calculated from Eqs. 5 and 6 to be 1.60×10^{-18} J nucleus^{-1} for (±)-PA salt and 8.38×10^{-10} J nucleus^{-1} for (±)-TMB salt. This $\Delta g_{\max}$ value for (±)-PA salt is approximately equal to the value for 180% supersaturation, and that for (±)-TMB salt to the value for 155% supersaturation.

The optical resolution of (±)-PA salt for 180% supersaturation and that of (±)-TMB salt for 155% supersaturation were carried out at $\theta_{(-)}-5$ min as calculated from Eqs. 2 and 4, respectively. The amounts of crystallization of the (+)-salts derived from their experimental results agree well with the $W_{(-5)}$ values calculated from Eqs. 5 and 6, as shown in Table 2.

Successive Preferential Crystallization of (±)-Propylammonium and 1,1,3,3-Tetramethylbutylammonium Salts. Based on the above results, the successive preferential crystallization of (±)-PA salt was carried out in 50 cm³ of methanol at 10 °C by using a solution with 180% initial supersaturation, and that of the (±)-TMB salt by using an aqueous solution with 155% initial supersaturation, details being as listed in Table 3. (+)- and (−)-PA and -TMB salts with optical purity of 88—96% were obtained at degree of resolution of 37—62%. The purified (+)- and (−)-salts gave optically pure (−)- and (+)-MAL, respectively.

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References

1) K. Harada, M. Matsuyama, Y. Kataoka, and K. Mizumoto, Japan Patent 156433 (1982); *Chem. Abstr.*, **98**, 142963 p (1983).

2) T. Shiraiwa, M. Morita, K. Iwafuji, and H. Kurokawa, *Nippon Kagaku Kaishi*, **1983**, 1743.

3) V. C. Arsenijevic, *C. R. Acad. Sci.*, **245**, 317 (1957).

4) M. Leclercq, A. Collet, and J. Jacques, *Tetrahedron*, **32**, 821 (1976).

5) T. Shiraiwa, H. Miyazaki, A. Uramoto, M. Sunami, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **60**, 1465 (1987).

6) T. Nakai, *Bull. Chem. Soc. Jpn.*, **42**, 2143 (1969).

7) T. Nakai, "Shoseki Kogaku," Baifukan, Tokyo (1986), Section 2.

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

9) "Kagaku Daijiten," ed by Kagaku Daijiten Henshu Iinkai, Kyoritsu Shuppan, Tokyo (1971), Vol. 9, p. 790.

10) T. Shiraiwa, Y. Sado, M. Komure, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **60**, 3277 (1987).

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

12) A. Collet, M. J. Brienne, *Chem. Rev.*, **80**, 215 (1980).

13) S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, **12**, 91 (1976).

14) In order to calculate the $\Delta g_{\max}$ of PA salt, the value of molecular volume (V_0) was measured at 10 °C in methanol to be 2.21×10^{-28} m³; the molecular radius (r_0) was calculated to be 3.75×10^{-10} m on the assumption of spherical molecule. The values of the radius (r_{sa} 4.83×10^{-10} m) and interfacial energy (σ_{sa} 1.01×10^{-2} J m^{-2}) of the embryo in the saturated methanol solution at 10 °C were calculated on the basis of the solubility of (±)-PA salt according to the procedure described in Refs. 6—8; the average number (j_{sa}) of PA salt molecules forming the embryo in the saturated solution is 2.13. (±)-TMB salt in water at 10 °C: V_0 3.70×10^{-28} m³; r_0 4.45×10^{-10} m; r_{sa} 5.67×10^{-10} m; σ_{sa} 9.25×10^{-3} J m^{-2}; j_{sa} 2.06.