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Racemic Structures and Optical Resolution by Preferential Crystallization of Organic Ammonium Salts of (±)-Mandelic Acid

Tadashi Shiraiwa,* Mitsuhiro Nakamura, Masanobu Nobeoka, and Hidemoto Kurokawa
Faculty of Engineering, Kansai University, Yamate-cho, Suita, Osaka 564

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Synopsis. According to a thermodynamic analysis the 4-methylpiperidinium salt of (±)-mandelic acid is a conglomerate around room temperature, though the salt forms a racemic compound in the vicinity of the melting point. A successive preferential crystallization in ethanol at 10 °C yields both the (+)- and (−)-salts with optical purities of over 95%.

Mandelic acid (abbreviated as MAN) is very useful as medicines and intermediate materials, such as phenyramidol, a centrally axting muscle relaxant.[1] Optically active MAN has also been used as a resolving agent in optical resolution of racemic organic bases.[2] (±)-MAN has been optically resolved by the diastereomeric procedure using L-phenylalanine[3] and cinchonine[4] as resolving agents. However, the diastereomeric procedure requires a relatively large quantity of resolving agents. On the other hand, the preferential crystallization procedure is more useful on the industrial scale than the diastereomeric one, since optical resolution can easily be achieved by providing a small amount of one enantiomer as seed crystals in a supersaturated racemic solution. However, the optical resolution by this procedure has scarcely been reported on (±)-MAN.[5] This note describes an attempt to resolve optically organic ammonium salts of (±)-MAN by preferential crystallization.

Racemic structures of propylammonium salt ((±)-PA salt), isopropylammonium salt ((±)-IPA salt), isobutylammonium salt ((±)-IBA salt), benzylammonium salt ((±)-BZA salt), and 4-methylpiperidinium salt ((±)-4-MP salt) of (±)-MAN were determined on the basis of thermodynamic analysis,[6,7] with the results that all of these (±)-salts form racemic compounds in the vicinity of their melting points and that (±)-4-MP salt exists in a conglomerate around room temperature. An optical resolution of (±)-4-MP salt has been achieved by successive preferential crystallization in ethanol at 10 °C.

Experimental

Materials. (±)- and (+)-MAN were purchased from Sigma Chemicals Co., and amines from Wako Pure Chemicals Ind.

Preparation of Organic Ammonium Salts. (±)- or (+)-MAN (0.01 mol) was dissolved in diethyl ether. After adding 0.01 mol of amine and stirring for 10 min in an ice bath, the salt formed was collected by filtration, washed with a small amount of diethyl ether, and dried. The salts obtained were recrystallized from an appropriate solvent.

(±)- and (+)-4-MP salts were recrystallized from ethanol. Elemental analysis, specific rotation, and solubility of (±)-4-MP salt: C, 66.73; H, 8.42; N, 5.56% (calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57%); $[\alpha]_D^{20}$ +56.0° (*c* 0.50, ethanol); 4.470 g/(100 cm^3 ethanol). (±)-4-MP salt: C, 66.73; H, 8.42; N, 5.57%; 11.578 g/(100 cm^3 ethanol). (−)-4-MP salt was obtained from mother liquor in the optical resolution by preferential crystallization and was recrystallized twice from ethanol: Mp 136 °C; $[\alpha]_D^{20}$ −56.0° (*c* 0.50, ethanol).

Optical Resolution. (±)-4-MP salt (3.184 g) was dissolved in 25 cm^3 of ethanol around 40 °C to give a racemic solution with a degree of supersaturation of 110% at 10 °C. The solution was slowly cooled to 10 °C and seeded with 0.010 g of (+)-salt. After stirring for 20 min at 10 °C, the salt precipitated was collected by filtration and washed with a small amount of diethyl ether. (±)-4-MP salt (0.112 g) was dissolved in the filtrate around 40 °C. The solution was cooled to 10 °C and seeded with 0.010 g of (−)-salt. After stirring for 30 min, the salt precipitated was collected by filtration. The filtrate was treated in a similar manner as above. The degrees of resolution of (+)- and (−)-salts were calculated by

$$\text{Degree of resolution}/\% = [\text{YOPM/g} \times 100]/[(\text{Operation amount of (+)- or (−)-salt/g}) - 1.447], \quad (1)$$

where YOPM is the yield of optically pure modification.[8]

Preparation of Optically Pure Mandelic Acid. The (+)- and (−)-4-MP salts (about 0.85 g) obtained in the successive resolution were treated as aqueous solutions through a 1×10 cm column of Amberlite IR-120 in the H$^+$ form by eluting with water; the initial (+)-salt had an optical purity of 96.5% and the (−)-salt that of 98.2%. The eluents were evaporated to dryness under reduced pressure around 40 °C to give (+)- and (−)-MAN. (+)-MAN: yield 95.8%; $[\alpha]_D^{20}$ +154° (*c* 1.00, ethanol). (−)-MAN: yield 94.6%; $[\alpha]_D^{20}$ −157° (*c* 1.00, ethanol) (lit,[9] $[\alpha]_D^{20}$ −159.7° (ethanol)).

Measurements. Specific rotations were measured with a Union Giken high sensitivity PM-101 digital polarimeter using a 0.5 dm path length quarz cell. 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 DSC-8230. The solubilities of (±)- and (+)-4-MP salts and the ternary phase diagram were obtained in a similar manner as described in our previous paper.[10]

Results and Discussion

Racemic Structures. Racemic Structures at Melting Point: Free energies of formation of racemates at melting point, ΔG^F_{mp}, were calculated on the basis of

Table 1. Thermodynamic Data for Organic Ammonium Salts of Mandelic Acid

Salts	Mp/K		ΔH^{f}[a]/kJ mol^{-1}		$\Delta G^{\mathrm{F}}_{\mathrm{mp}}$[b]	Eutectic point		
	(±)	(+)	(±)	(+)	kJ mol^{-1}	Mole fraction of (+)-salt[c]	Temperature	
							Found	Calcd[c]
PA[d]	374	373	35.9	26.6	−2.28	0.83	364	365
IPA[e]	435	431	43.1	38.5	−2.88	0.84	426	424
IBA[f]	404	399	32.6	27.4	−2.77	0.85	390	391
BZA[g]	472	449	54.0	48.6	−5.18	0.94	448	447
4-MP[h]	394	409	31.8	33.5	−1.01	0.65	393	392

a) ΔH^{f}; Enthalpy of fusion. b) $\Delta G^{\mathrm{F}}_{\mathrm{mp}}$: Free energy of formation of racemate at melting point. c) These values were calculated by the Schröder-Van Laar and Prigogine–Defay equations. d) PA: Propylammonium salt. e) IPA: Isopropylammonium salt. f) IBA: Isobutylammonium salt. g) BZA: Benzylammonium salt. h) 4-MP: 4-Methylpiperidinium salt.

the enthalpies of fusion, ΔH^{f}, and melting points of (±)- and (+)-salts.[6,7] The thermodynamic data are given in Table 1.

The $\Delta G^{\mathrm{F}}_{\mathrm{mp}}$ values suggest that these (±)-salts are racemic compounds or racemic solid solutions in the vicinity of their melting points, since the values are negative.[6,7,10] The mole fractions and temperatures at the eutectic points were calculated from the Schröder-Van Laar and Prigogine-Defay equations.[11] Mixtures with mole fractions calculated were prepared and their melting points were compared with the eutectic temperatures calculated (Table 1). The melting points obtained agreed closely with the eutectic temperatures calculated. The mixtures melted at their respective temperatures and not over wide ranges. It is concluded from the above results that these (±)-salts form racemic compounds in the vicinity of their melting points.

The mole fractions of (+)-PA, -IPA, -IBA, and -BZA salts at their eutectic points (0.83—0.94) are close to 1, and the absolute values of $\Delta G^{\mathrm{F}}_{\mathrm{mp}}$ are more than 2 kJ mol^{-1}. Therefore, the above (±)-salts form stable racemic compounds.[6,7] However, (±)-4-MP salt may be an unstable racemic compound, since the mole fraction (0.65) is relatively close to 0.5 and the $\Delta G^{\mathrm{F}}_{\mathrm{mp}}$ is −1.01 kJ mol^{-1}.[6,7]

Racemic Structures Around Room Temperature: Unstable racemic compounds such as 4-MP salt have a possibility of transformation to conglomerate at a lower temperature.[6,7] The $\Delta G^{\mathrm{F}}_{283}$ at 283 K of (±)-4-MP salt was calculated to examine this possibility,[6,7] a positive value (+0.26 kJ mole^{-1}) being obtained. This value indicates that (±)-4-MP salt will form no racemic compounds at 283 K. (±)-4-MP salt shows a infrared spectrum identical with that of its (+)-salt and is more soluble than the (+)-salt at 10 °C. The ternary phase diagram of solubility of 4-MP salt at 10 °C displays the pattern of a conglomerate as shown in Fig. 1.[12] The above results clearly indicated that (±)-4-MP salt exists in a conglomerate around room temperature.

The infrared spectra of (±)-PA, -IPA, -IBA, and -BZA salts are different from those of respective (+)-salts, and the $\Delta G^{\mathrm{F}}_{283}$ values are negative. Therefore, these (±)-salts also form racemic compounds around room temperature.

Optical Resolution of (±)-4-Methylpiperidinium Salt. The optical resolution of (±)-4-MP salt by successive preferential crystallization has been carried out for a racemic solution with a degree of supersaturation of 110% in ethanol at 10 °C. The result is given in Table 2.

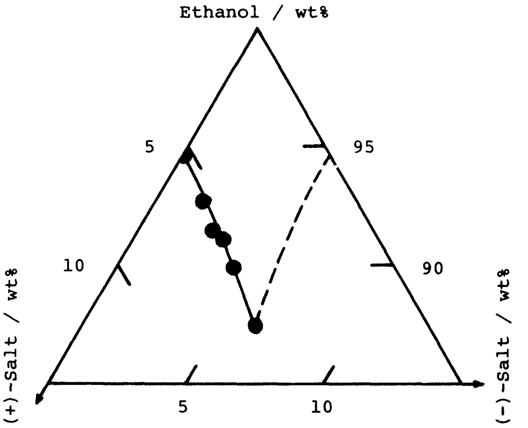

Fig. 1. Ternary phase diagram of solubility of 4-methylpiperidinium salt of mandelic acid. Solvent: Ethanol. Temperature: 10 °C.

It was possible to obtain the (+)- and (−)-salts with an optical purity of 95—100% in a degree of resolution of 62—81%. The (+)- and (−)-salts obtained gave (+)-MAN with an optical purity of 96.4% and (−)-MAN with that of 98.3%, respectively.

The optical resolution has also been carried out for a racemic solution with a degree of supersaturation of 138% to give the (+)-salt with an optical purity of around 90% at a resolution time of 5—10 min. However, the optical purity of the (+)-salt obtained at a resolution time beyond 10 min rapidly decreased with resolution time. The salt with a low optical purity is easily purified by recrystallization. The phase diagram of solubility or the solubility of the (±)-salt gives the optimum amount of ethanol which permits one to obtain the maximum yield of the optically pure salt.[13] The amount of ethanol W_s/wt% is expressed by

$$W_{\mathrm{s}} = 100\, W_{\mathrm{E}} \cdot W / [5000 - W_{\mathrm{E}} \cdot (50 - W)], \tag{2}$$

where W_{E}/wt% is the amount of ethanol at the eutectic point at 10° ((+)-4-MP salt, 6.34; (−)-salt, 6.34; ethanol, 87.33 wt%) and W/wt% is the amount of the (−)-salt contained in the crystalline salt having an abundance

Table 2. Successive Preferential Crystallization of 4-Methylpiperidinium Salt of (±)-Mandelic Acid[a]

Run	Added amount of (±)-salt	Operation amount[b]/g		Resolution time	Salt obtained			
	g	(+)-Salt	(−)-Salt	min	Yield	Optical purity	YOPM[c]	Degree of resolution[d]
					g	%	g	%
1	3.184	1.592	1.592	20	0.122	(+) 95.7	0.107	73.8
2	0.112	1.538	1.645	30	0.168	(−)100	0.158	79.8
3	0.158	1.617	1.566	40	0.151	(+) 96.8	0.137	80.6
4	0.141	1.549	1.634	40	0.132	(−) 95.5	0.116	62.0

a) Solvent: 25 cm^3 of ethanol. Degree of supersaturation of initial racemic solution: 110%. Seed crystals: 0.010 g of (+)- or (−)-salt. Temperature: 10°C. b) The operation amounts of the (+)- and (−)-salts in solutions were calculated on the basis of the analyses of the salts obtained in Run 1—3. c) YOPM: Yield of optically pure modification. d) Degree of resolution/%=[YOPM/g×100]/[(Operation amount of (+)- or (−)-salt/g)−1.447/g].

of the (+)-salt.

A (+)-4-MP salt with an optical purity of 28.0% (4.00 g) was recrystallized from 25 cm^3 of ethanol; the amount calculated is 25.07 cm^3. After dissolving the salt at an elevated temperature, the solution was stirred for 30 min at 10°C to crystallize 1.05 g of the (+)-salt with an optical purity of 99.6%; the theoretical yield of the optically pure (+)-salt is 1.12 g. An approximate (±)-salt ($[\alpha]^{20}_{D}$ +0.7°) was recovered in 2.89 g from the filtrate. (+)-MAN with an optical purity of 99.6% was obtained from the (+)-salt recrystallized.

The above result indicates that (±)-4-MP salt exists in a conglomerate around room temperature, though the (±)-salt forms a racemic compound in the vicinity of the melting point. It was possible to obtain the (+)- and (−)-MAN with a high optical purity by successive preferential crystallization of the (±)-4-MP salt.

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