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Some Aspects on the Optical Resolution by Preferential Crystallization based on Phase Equilibrium

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The relationship of racemic structure to resolution by preferential crystallization was discussed on the ternary phase diagrams of systems containing optical isomers and a solvent. From these discussions, it was concluded that the resolution by this method is applicable only to racemic mixtures, and that racemic compounds and also racemic solid solutions can not be resolved. In addition, we reexamined the resolution of 3,3-diethyl-5-methyl-2,4-dioxopiperidine reported to be resolved by this method in spite of the formation of a racemic solid solution, and found it impossible to resolve this compound by preferential crystallization.

Keywords——resolution; preferential crystallization; ternary phase diagram; racemic modification; racemic mixture; racemic compound; racemic solid solution; optical isomer; 3,3-diethyl-5-methyl-2,4-dioxopiperidine

Resolution by preferential crystallization may be an industrially convenient and practical separation procedure of optical isomers from a racemic modification, and many chemical compounds have been resolved by this method.[2]

However, there appeared no established theories on the clarification of this kind or racemic structure to which this resolution is applicable and hence various opinions concerning this problem have been described.[3]

In the present paper, the relationship of racemic structure to resolution by preferential crystallization was discussed based on the ternary phase diagram of a system containing optical isomers and solvent, and the racemic structure resolved by this method was theoretically revealed to be only racemic mixtures. In addition, the resolution of 3,3-diethyl-5-methyl-2,4-dioxopiperidine which was reported to be resolved by this method in spite of the formation of a racemic solid solution[4] was reexamined. Consequently, it was found that these phenomena were not the case for the definition of resolution generally used by preferential crystallization.

General Concepts

Resolution is defined as a separation of optical isomers from a racemic modification. The definition of resolution has been discussed in more detail by various authors.[2a,b,3a] In this paper, resolution is defined as the process whereby an optical isomer is separated from a

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[2] *a*) R.M. Secor, *Chem. Rev.*, 63, 297 (1963); *b*) I. Chibata, K. Toi, and S. Yamada, "Kagaku Sōsetsu No. 4: Fusei Hannō no Kagaku," ed. by Chemical Society of Japan, Tokyo Daigaku Shuppankai, Tokyo, 1974.

[3] *a*) E.L. Eliel, "Stereochemistry of Carbon Compounds," Mcgraw-Hill Book Company. Inc., New York, 1962; *b*) T. Shiba, "Kagaku Monogurafu 21: Rittai Kagaku" Kagakudōjin, Tokyo, 1971; *c*) T. Taguchi, "Rittai Kagaku Nyumon," Nanzando, Tokyo, 1969; *d*) P.L. Shriner, R. Adams, and C.S. Marvel, "Organic Chemistry an Advanced Treatise: Stereoisomerism," Vol. I, ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1969; *e*) T. Watanabe and G. Noyori, *Kogyo Kagaku Zasshi*, 71, 676 (1968); T. Watanabe and G. Noyori, *Kogyo Kagaku Zasshi*, 72, 1080 (1969).

[4] K. Vogler and M. Kofler, *Helv. Chim. Acta*, 34, 1387 (1956).

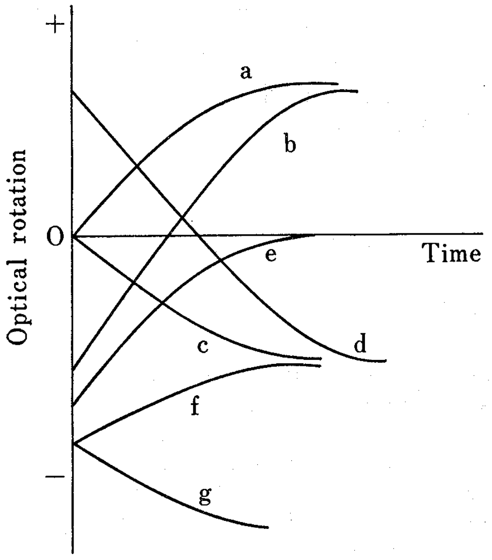

Fig. 1. Optical Rotational Changes of Solutions

racemic modification or from a non-racemic starting material containing an excess of the isomer, while the material containing an excess of the opposite isomer is left in a solution. This definition is generally used for resolution by preferential crystallization.[2a,5] According to this definition, the optical rotation in the solution changes as shown in Fig. 1-a, b, c or d by resolution, and the changes shown in Fig. 1-e, f and g are not caused by resolution. The concrete examples of these optical rotational curves have been already reported in the studies on the resolution of DL-O-acetylpantolactone.[6,7]

Racemic Mixture

Fig. 2 shows the ternary phase diagram in which the optical isomers exist as a racemic mixture in a solid state. The triangular area *l*N*d* represents three-phase compositions consisting of *d*-isomer crystals, *l*-isomer crystals and a saturated solution of composition N. The fan-shaped area *l*MN represents two-phase equilibria in which the solid phase is *l*-isomer and similarly the fan-shaped area *d*NO represents two-phase equilibria in which the solid phase is *d*-isomer.

When *l*-isomer is seeded into the supersaturated solution of composition A (*l*-isomer=*d*-isomer) or composition A′ (*l*-isomer>*d*-isomer) in the triangular area *l*N*d*, *l*-isomer crystallizes selectively from the solution, if the supersaturated solution of *d*-isomer is stable. During the crystallization of *l*-isomer the composition of the solution changes away from the *l*-isomer apex of the phase diagram along line AB or A′B′. After the solution reaches the composition represented by point B or B′, *d*-isomer crystallizes from the solution, to move the composition of the solution along the straight line from B or B′ to N. In these cases, the optical rotations

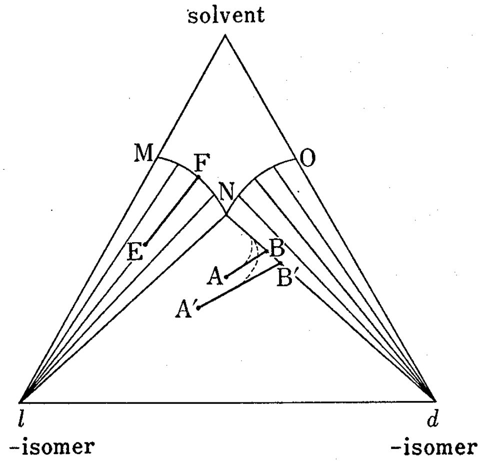

Fig. 2. Ternary Phagram Phase Diagram for Optical Isomers Forming a Racemic Mixture and Changes in Solution Composition

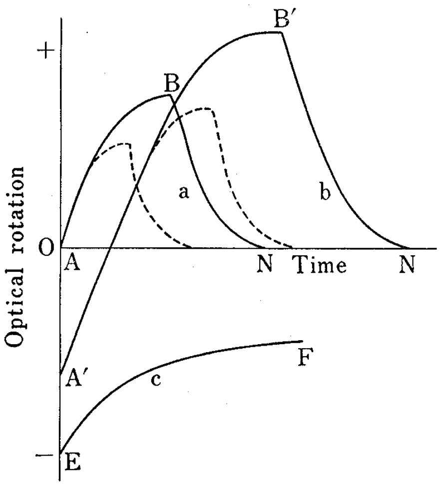

Fig. 3. Optical Rotational Changes of Solutions in the Case of Optical Isomers Forming a Racemic Mixture

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5) T. Watanabe and G. Noyori, *Kogyo Kagaku Zasshi*, **70**, 2174 (1967).
6) M. Inagaki, I. Kuniyoshi, and S. Nabeta, *Yakugaku Zasshi*, **96**, 71 (1976).
7) M. Inagaki, K. Yamamoto, K. Kataoka, and O. Akazawa, *Yakugaku Zasshi*, **97**, 151 (1977).

of the solution change as illustrated in Fig. 3-a and b. Therefore, *l*-isomer with high optical purity is obtained by filtration before the solution reaches the composition represented by point B or B′. In many practical resolutions, *d*-isomer crystallizes before the solution reaches the composition represented by point B or B′, and hence the compositions and the optical rotations of the solutions change along the dotted lines.

Even if the supersaturated solution of composition E in the fan-shaped area *l*MN is seeded with any isomers or is self-seeded, the deposited crystals are only *l*-isomer and the composition of the solution changes along the tie line from E to F. In this case, the optical rotation of the solution changes as illustrated in Fig. 3-c. It can be seen from Fig. 2 and Fig. 3-c that this phenomenon is caused only from the crystallization of *l*-isomer, not from the resolution of *l*-isomer.

These facts indicate that resolution by preferential crystallization is applicable to racemic mixtures, provided that the composition of the supersaturated solution is in the region of the triangular *l*N*d* of the phase diagram.

Racemic Compound

Eliel3a) and Shiba3b) described that the resolution by this method is applicable to racemic compounds, provided that the compound was more soluble than either of the optical isomers. Taguchi3c) stated that this method was applicable to the racemic compounds separated into two optical isomers in the solution. Shriner, *et al.*3d) also described that this resolution could occur even if the racemic modification was a compound more soluble than its component isomers. On the other hand, Watanabe, *et al.*3e,f) reexamined the possibility of the resolution on such racemic compounds as glutamic acid,8) aspartic acid9) and histidine monohydrochloride10) and concluded that these resolutions were applicable not to racemic compounds but to racemic mixtures because the racemic compounds can not be resolved.

Fig. 4 shows the ternary phase diagram in which the optical isomers form a racemic compound. The triangular area *l*NQ is a three-phase region in which the equilibrium phases are solid *l*-isomer, solid racemic compound and a saturated solution of composition N, while the triangular area *d*OQ is a three-phase region in which the equilibrium phases are solid *d*-isomer, solid racemic compound and a saturated solution of composition O. Each fan-shaped area *l*MN, QNO or *d*OP represents two-phase equilibria in which the solid phase is *l*-isomer, racemic compound or *d*-isomer, respectively.

From the supersaturated solution in the fan-shaped area QNO, no *l*-isomer or *d*-isomer can crystallize, no matter how *l*-isomer or *d*-isomer is seeded. In this region, only the racemic compound can crystallize from the solution. Therefore, in a case of composition A (*l*-isomer >*d*-isomer), the composition of the solution changes along the tie line from A to B and the optical rotation of the solution changes as illustrated in Fig. 5-a because the relative composition of *l*-isomer in the solution increases depending on the crystallization of racemic compound.

When *l*-isomer is seeded into the supersaturated solution of composition E in the triangular area *l*NQ, *l*-isomer crystallizes selectively from the solution, if the supersaturated solution of the racemic compound is stable. During the crystallization of *l*-isomer the composition of the solution changes away from the *l*-isomer apex of the phase diagram along the line EF. After the solution reaches the composition represented by point F, the racemic compound crystallizes from the solution, to move the composition of the solution along the line from F to N. In this case, the optical rotation of the solution changes as illustrated in Fig. 5-b.

As described above, the optical rotation of the solution changes from zero or plus to minus, or from zero or minus to plus by resolution. Fig. 5 shows apparently that racemic com-

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8) T. Akashi, *Nippon Kagaku Zasshi*, **83**, 528 (1962).
9) K. Harada, *Bull. Chem. Soc. Japan*, **38**, 1552 (1965).
10) R. Duschinsky, *Chem. Ind.* (London), **1934**, 10.

pounds, though its solubility is greater or less than that of the isomers, can not be resolved by preferential crystallization.

Three types of racemic forms, mixture, compound and solid solution, exist in the solid state and their properties disappear on dissolution or fusion of the solid. Therefore, it is not the resolution of a racemic compound but the resolution of a racemic mixture to resolve the supersaturated solution obtained by the dissolution of crystalline racemic compound under the same crystallized conditions as racemic mixture when both crystalline forms of racemic compound and racemic mixture exist.

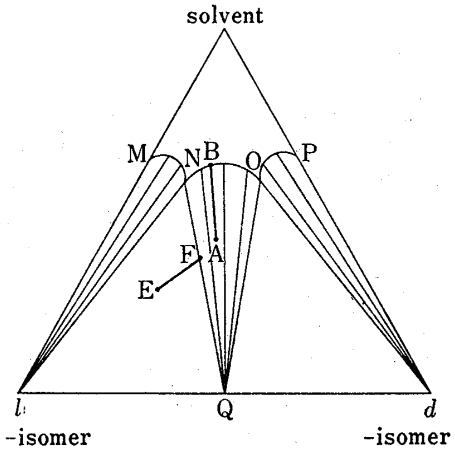

Fig. 4. Ternary Phase Diagram for Optical Isomers Forming a Racemic Compound and Changes in Solution Composition

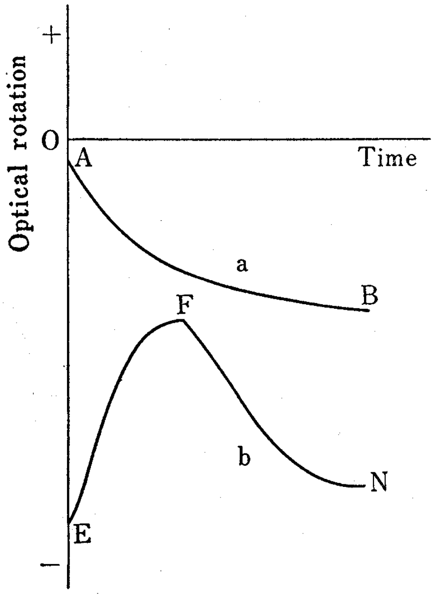

Fig. 5. Optical Rotational Changes of Solutions in the Case of Optical Isomers Forming a Racemic Compound

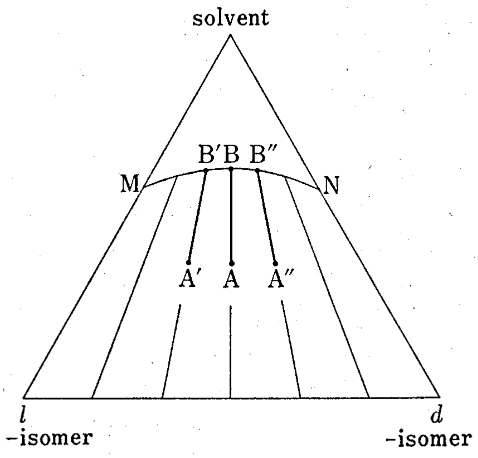

Fig. 6. Ternary Phase Diagram for Optical Isomers Forming a Racemic Solid Solution and Changes in Solution Composition

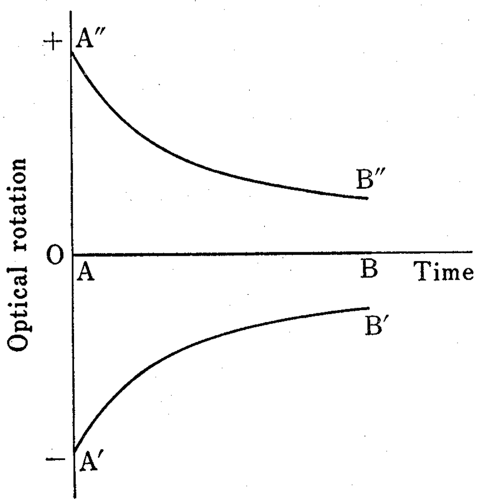

Fig. 7. Optical Rotational Changes of Solutions in the Case of Optical Isomers Forming a Racemic Solid Solution

Racemic Solid Solution

Shiba[3b)] described that this resolution was applicable to racemic solid solution.

Racemic solid solutions show nearly ideal behavior even in the solid state, meaning that there is little difference in affinity between molecules of like or opposite isomer.[3a)] In that case, the arrangement of the molecules in the solid is random and hence the crystallization of racemic solid solutions is not deviations from ideal generally observed.

Fig. 6 shows the ternary phase diagram in which the isomers form a racemic solid solution. The region bounded by the solubility curve MN and the lines *l*M, *d*N and *ld* is a two-phase region containing the tie lines connecting compositions of solid and liquid in equilibrium with one another. Therefore, a optical isomer does not crystallize selectively from the supersaturated solution of the racemic solid solution, no matter how *l*-isomer or *d*-isomer is seeded. In the cases of composition A (*l*-isomer=*d*-isomer), A′ (*l*-isomer>*d*-isomer) or A″ (*l*-isomer<*d*-isomer), the compositions of the solution change along the tie lines from A, A′ or A″ to B, B′ or B″ and the optical rotations of the solution change as illustrated in Fig. 7.

It is concluded from these facts that racemic solid solutions can not be resolved by preferential crystallization.

From the illustration described above, it was proved that the resolution by preferential crystallization was applicable only to racemic mixtures, and that racemic compounds and racemic solid solutions could not be resolved by this method.

However, the resolutions of racemic compounds by this method have been reported on glutamic acid,[8)] aspartic acid[9)] and histidine monohydrochloride,[10)] and the resolution of racemic solid solution has been reported on 3,3-diethyl-5-methyl-2,4-dioxopiperidine.[4)] As described above, Watanabe, *et al.*[3e,f)] reexamined the resolutions on glutamic acid, aspartic acid and histidine monohydrochloride and concluded that these resolutions were not applicable to the racemic compounds but to the racemic mixtures because these compounds existed in more than one crystalline form and were resolved under the crystallized conditions of the racemic mixtures. Then, the relationship of the racemic structure to the resolution of 3,3-diethyl-5-methyl-2,4-dioxopiperidine was reinvestigated in this paper.

Results and Discussion

The Relationship of the Racemic Structure to the Resolution of 3,3-diethyl-5-methyl-2,4-dioxo piperidine

Vogler, *et al.*[4)] prepared the pure optical isomer ($[\alpha]_D^{20}$ +124°) by repeating the recrystallizations 400 times from methanol, acetone, butanol, water *etc.* From the melting point diagram, they concluded that its racemic structure is a racemic solid solution. Table I sum-

Table I. The Repeated Crystallizations of 3,3-Diethyl-5-methyl-2,4-dioxopiperidine

	The values reported by Vogler, *et al.*[4)]				The values calculated by the author	
Step.	Dissolved material		Crystallized material		Material in filtrate	
	g	$[\alpha]_D^{20}$	g	$[\alpha]_D^{20}$	g	$[\alpha]_D^{20}$
1	600	+ 0.5°	250	+ 7.2°	350	− 4.3°
2	250	+ 7.2°	102	+14.2°	148	+ 2.3°
3	102	+14.2°	40	+22.0°	62	+ 9.2°
4	40	+22.0°	22	+29.5°	18	+12.9°
5	22	+29.5°	10	+38.9°	12	+21.6°
6	10	+38.9°	3.2	+49.0°	6.8	+34.3°
7	3.2	+49.0°	0.4	+60.4°	2.8	+47.4°
8	0.4	+60.4°	0.09	+67.7°	0.31	+56.0°

marized their experimental results obtained by repeated crystallizations from acetone at 0°. From the data on the weights and the specific rotations of dissolved and crystallized materials of Table I, and on the specific rotation of the pure optical isomer, the weights and the specific rotations of the materials in the filtrates were calculated and the results were attached to Table I. It can be seen from the specific rotations of Table I that the phenomenon regarded as the resolution defined above is limited to Step. 1.

In order to reexamine these experimental results obtained by Vogler, *et al.*, the racemic structure of 3,3-diethyl-5-methyl-2,4-dioxo piperidine was examined by DTA (differential thermal analysis) and by solubility determination, and the crystallization was carried out from acetone.

The optical isomers having specific rotations of +60° and −48° were obtained by repeated recrystallizations according to the method of Vogler, *et al.* The solubilities of the crystals having various specific rotations show a similar value of 40±2% for acetone at 0°, and DTA curves of these crystals show an endothermic peak at 77°±1° which is identical with the melting points obtained by Vogler, *et al.* In the cases of racemic mixtures and racemic compounds, the DTA curves for the mixtures of racemic modification with its optical isomers show two endothermic peaks; the first peak corresponds to a thaw point, and the second peak corresponds to a final melting point. From these facts, it was revealed that the racemic structure of 3,3-diethyl-5-methyl-2,4-dioxopiperidine was a racemic solid solution as pointed out by Vogler, *et al.* The various crystals obtained from lower alcohols, acetone, corresponding aqueous solvents, water, *n*-hexane and isopropylether were also examined by DTA and X-ray powder diffraction, and it was found that this racemic modification does not exhibit polymorphism.

The crystallizations were performed from the supersaturated acetone solutions of various mixtures of these two isomers. In these several recrystallization procedures, the reproducibility of this method was very poor and the following tendency was confirmed as a common phenomenon in each experiment.

The specific rotations of deposited crystals were within the range of ±10° of that of initially dissolved crystals in spite of the spontaneous or seeded crystallization. Table II

TABLE II. Crystallization of 3,3-Diethyl-5-methy-2,4-dioxopiperidine

Dissolved material $[\alpha]^{20}_{D}$	No.	Crystallized material			
		0.5 hr		1 hr	
		$[\alpha]^{20}_{D}$	Yield (%)	$[\alpha]^{20}_{D}$	Yield (%)
+18°	1	+19°	5	+26°	18
	2	+24°	3	+23°	16
	3	+17°	8	+20°	20
	4	+15°	3	+18°	13
	5	+11°	6	+13°	16
+ 0.5°	1	+ 5°	4	+ 9°	17
	2	+ 1°	3	+ 3°	14
	3	+ 0.4°	4	+ 0.2°	17
	4	− 2°	8	+ 1°	20
	5	− 5°	5	− 8°	18
−11°	1	− 7°	6	− 9°	19
	2	− 9°	6	−10°	17
	3	−13°	8	−14°	18
	4	−12°	7	−15°	18
	5	−18°	3	−20°	15

30 g of 3,3-diethyl-5-methyl-2,4-dioxopiperidine($[\alpha]^{20}_{D}$ +18°, +0.5° or −11°) was dissolved in 30 g of acetone. The crystallizations were accomplished in the solutions at 0°. The samples were withdrawn from the systems at 0.5 and 1 hr after seeding, and the deposited crystals were filtered.

shows an example of the results obtained. When the specific rotation of initially dissolved crystals is more than ±10°, the optical rotation of the mother liquors always changed in plus or minus range. When the specific rotation of initially dissolved crystals is less than ±10°, the optical rotation of the mother liquors sometimes changed from zero or plus to minus or vice versa as shown in Fig. 1-a, b, c and d, but the optical purities of deposited crystals were always low (below 10%) and this phenomenon is different from the selective crystallization of optical isomers and can not be applicable to the definition of resolution.

These facts indicate that the compositions of the solution of 3,3-diethyl-5-methyl-2,4-dioxopiperidine do not always move along the lines AB, A′B′ and A″B″ as shown in Fig. 6, but move within a certain width from the central lines AB, A′B′ and A″B″ because of a slight deviation from ideal behavior.

Experimental

Materials——*dl*-3,3-Diethyl-5-methyl-2,4-dioxopiperidine was purchased from Yamanouchi Pharmaceutical Co., Ltd. The optical isomers were prepared by repeated recrystallizations of racemic modification from acetone, methanol, ethanol, corresponding aqueous solvents or water at 0° or 20°. All solvents used were reagent grade.

DTA——This analysis was carried out with TG-DTA (Rigaku Denki CAT. No. 8021). The samples were crystals having specific rotations of +60°, +42°, +19°, +0.5° and −48° ($c=3$, H_2O).

Determination of Solubility——An excess of crystals having specific rotation of +51°, +19°, +0.5° or −38° ($c=3$, H_2O) was placed in about 20 ml of acetone and stirred at 0°. After 4 hours, about 10 ml aliquots of the solution were withdrawn directly with cotton filter attached pipette. The concentration was determined by weighing the filtrate and the residue after distillating the filtrate at 40° *in vacuo*.

Crystallization Procedure——Thirty grams of crystals having specific rotation of +18°, +0.5° or −11° ($c=3$, H_2O) were dissolved in 30 g of acetone and cooled at 0°. Into these supersaturated solutions 0.1 g of finely-pulverized crystals having specific rotation of +60° or −48° ($c=3$, H_2O) was seeded and mixed. Twenty-thirty ml aliquots were withdrawn from these systems at 0.5 and 1.0 hour after seeding and immediately filtered through glass filter. The optical rotations of these filtrates, and the weights and the specific rotations of the crystals obtained were measured.

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