Preferential Crystallization of 2-Amino-2-phenylethanol and Its Application as a Resolving Agent

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(±)-2-Amino-2-phenylethanol (phenylglycinol) prepared from (±)-2-amino-2-phenylacetic acid (DL-phenylglycine) by lithium aluminium hydride reduction was efficiently resolved into a pair of optically active forms by preferential crystallization. The optically active amino alcohol was successfully applied as a basic resolving agent to the resolution of tartaric acid, 2-hydroxy-2-phenylpropionic acid, 2-hydroxy-3-phenylpropionic acid, 2-phenylpropionic acid, and 2-phenyl-2-ureidoacetic acid.

In the fractional crystallization of diastereomers, which is as useful for getting chiral compounds as biological method and asymmetric induction, a natural product or its derivative is widely used as a resolving agent.[1] But, only one of a pair of the enantiomers can be employed as a resolving agent since the other is frequently commercially unavailable. The restriction in utilization of a natural product or its derivative as a resolving agent often becomes to be disadvantageous for fractional crystallization because the desired enantiomer of a chiral compound does not always form the less soluble diastereomer, which is able to be purified by recrystallization, with the resolving agent.[2]

The synthesis of new resolving agents and their optical resolutions by preferential crystallization are tried in our laboratory based on the considerations that preferential crystallization would improve the problem, giving both enantiomers of a resolving agent in preparative quantities and that the desired enantiomer of a chiral compound whould be resolvable as the less soluble diastereomer with either of the enantiomers. The preceding papers presented that 3-*endo*-benzamido-5-norbornene-2-*endo*-carboxylic acid,[3] α-methylbenzylamine,[4] and 1-phenyl-2-(*p*-tolyl)ethylamine[4] were satisfactorily resolved into pairs of enantiomers by preferential crystallization of their achiral amine or carboxylic acid salts. As a part of our further studies along the line concerning the preferential crystallization, the resolution of 2-amino-2-phenylethanol (phenylglycinol) was examined with expectation that it would be useful as a basic resolving agent in the optical resolution of carboxylic acids.

(±)- And (−)-2-amino-2-phenylethanol ((±)-**1** and (−)-**1**) were easily prepared by the lithium aluminium hydride reduction of (±)- and (*R*)-(−)-2-amino-2-phenylacetic acid (DL- and D-phenylglycine), respectively.[5] The optically active **1** has higher melting point and is less soluble in benzene. The physical properties

$C_6H_5CHCH_2OH$
$\quad\quad|$
$\quad\quad NH_2$ **1**

	Mp θ_m/°C	Solubility (g/100 ml C_6H_6 at 20 °C)
(±)-**1**	47—49.5	10.5
(−)-**1**	75—76	1.3

indicate the posibility that crystals of **1** itself are deposited from a supersaturated benzene solution as a conglomerate, which is resolvable by preferential crystallization. Actually, (−)-**1** was obtained from a supersaturated solution of (±)-**1** when (−)-**1** was seeded to the solution and the solution was stood overnight at around 6 °C. Alternate seeding of (+)- and (−)-**1** to the solution supersaturated in a similar magnitude gave (+)- and (−)-**1**, respectively, as shown in Table 1.

Table 1. Preferential crystallization of **1** from benzene solution

Run	(±)-**1** (mg)[a]	Seed	Yield mg	$[\alpha]_{435}$/° (*c* 1.00, MeOH)	Optical purity/%[b]
1	—	(−)-**1**	199	−46.8	90
2	375	(+)-**1**	209	+47.3	91
3	254	(−)-**1**	292	−47.7	92
4	232	(+)-**1**	169	+48.2	93

The initial composition of the mother liquor: (±)-**1** (4.00 g) in benzene (100 ml). In all runs, 20—25 mg of seed were added. a) Ammount of (±)-**1** supplied for each run. b) Based on $[\alpha]_{435}^{29.5}$ + and −52.0°(*c* 1.00, MeOH).

The procedure is inapplicable to the optical resolution of (±)-**1** in a preparative scale because only 170—290 mg of optically active **1** is obtainable from 100 ml of benzene solution containing 4.0 g of (±)-**1**. After several examinations on the crystallization conditions such as concentration, cooling temperature, cooling time, and solvent system, it was found that the mixed solvent of benzene and ethanol was more suitable for the preferential crystallization in a preparative scale (see Table 2). Moreover, gentle stirring of the supersaturated solution during crystallization was found to be effective to shorten the cooling time as shown in Table 3. Stirring made the solution uniform and accelerated the crystal growth from seed surface. But, the nucleation of the unseeded antipode crystals of **1** occured when the solution was stirred too vigorously.

Crystals obtained by the preferential crystallization were recrystallized from benzene to yield almost optically pure (+)- and (−)-**1**.

The result that both enantiomers of **1** became obtainable preparatively in high optical purities prompted us to examine the ability of optically active **1** as a basic resolving agent. The resolution of mandelic acid is a unique example, which appears in a patent, for the application of **1** as a resolving agent.[6]

Tartaric acid (**2**), 2-hydroxy-2-phenylpropionic acid (**3**), 2-hydroxy-3-phenylpropionic acid (**4**), 2-phenylpropionic acid (**5**), and 2-phenyl-2-ureidoacetic acid (**6**)

Table 2. Preferential crystallization of **1** from benzene–ethanol mixture on standing

Run	(±)-**1**(mg)[a]	Seed	Cooling time / h	Yield / g	$[\alpha]_{435}$/° (*c* 1.00, MeOH)	Optical purity/%[b]
1	—	(+)-**1**	12	1.71	+47.1	91
2	2.01	(−)-**1**	21	2.47	−45.6	88
3	2.25	(+)-**1**	23	3.32	+47.1	91
4	3.85	(−)-**1**	21	3.24	−47.6	92
5	3.27	(+)-**1**	18	2.61	+48.7	94
6	3.61	(−)-**1**	19	2.94	−43.9	84

The initial composition of the mother liquor: (±)-**1** (38.80 g) and (+)-**1** (0.50 g), which was added to facilitate the preferential crystallization from the first stage, in a mixture of benzene (95 ml) and 99% ethanol (10 ml). In all runs, 0.10 g of seed was added. a) Amount of (±)-**1** supplied for each run. b) Based on $[\alpha]_{435}^{29.5}$ + and −52.0° (*c* 1.00, MeOH).

Table 3. Preferential crystallization of **1** under stirring

Run	(±)-**1**(mg)[a]	Seed	Cooling time / min	Yield / g	$[\alpha]_{435}$/° (*c* 1.00, MeOH)	Optical purity/%[b]
1	—	(+)-**1**	65	2.79	+47.6	92
2	3.00	(−)-**1**	65	3.53	−44.4	85
3	3.50	(+)-**1**	65	3.79	+40.0	77
4	3.60	(−)-**1**	70	2.80	−46.1	89
5	3.30	(+)-**1**	65	2.73	+51.3	99

The initial composition of the mother liquor: (±)-**1** (34.30 g) and (+)-**1** (1.30 g), which was added to facilitate the preferential crystallization from the first stage, in a 9: 1 mixture of benzene and 99% ethanol (84 ml). In all runs, 0.20 g of seed was added. a) Amount of (±)-**1** supplied for each run. b) Based on $[\alpha]_{435}^{29.5}$+ and −52.0° (*c* 1.00, MeOH).

Table 4. Resolution of chiral carboxylic acid by fractional crystallization

Salt (Molar ratio)	Recrystallization: Solvent	Recrystallization: Time	Yield[b] / %	Mp θ_m/°C	$[\alpha]_{435}$/°	N(%) Found (Calcd)
A: (+)-**2**(−)-**1** (1:2)	MeOH[a]	1	86	193—194	−15.0[c]	6.54 (6.60)
B: (−)-**2**(+)-**1** (1:2)	MeOH[a]	2	74	192—193	+16.9[c]	—
C: (+)-**3**(−)-**1** (1:1)	EtOAc–C_6H_6 (1:1)	3	44	117—119	+22.4[d]	4.69 (4.62)
D: (−)-**4**(−)-**1** (1:1)	EtOAc–2-Propanol (2:1)	1	71	145—146	−113[d]	4.66 (4.62)
E: (−)-**5**(−)-**1** (1:1)	EtOAc–EtOH (4:1)	4	58	149—150	−52.7[d]	4.96 (4.88)
F: (−)-**6**(−)-**1** (1:1)	75%EtOH	1	76	200—201	−201[c]	12.8 (12.7)

a) Washing. b) Based on half the amount of (±)-carboxylic acid used. c) (*c* 1.00, H_2O). d) (*c* 1.00, MeOH).

Table 5. Liberation of carboxylic acids from salts (**A**—**F**)

Salt	Product	Method[a]	Total yield[b] / %	M_p θ_m(B_p θ_b) / °C	$[\alpha]_{589}$/°	Optical purity/%
A	(+)-**2**	1	77	163—169	+16.1(*c* 1.02,H_2O)	96
B	(−)-**2**	1	63	165—165.5	−15.9(*c* 1.00,H_2O)	95
C	(+)-**3**	2	41	113—114	+34.7(*c* 1.00,EtOH)	92
D	(−)-**4**	2	67	122—123	−17.5(*c* 1.00,EtOH)	94
E	(−)-**5**	2	55	(108—109/267 Pa)	−88.3(*c* 1.30,C_6H_6)	95
F	(−)-**6**	2	72	188—189	−156(*c* 0.50,EtOH)	94

a) Method 1: The salt was decomposed with ion exchange resin, and the product was eluted with water. Method 2: The salt was decomposed with aqueous HCl, and the product was extracted with ether. b) Based on half the amount of (±)-carboxylic acid used.

were chosen as target compounds for optical resolution. The chiral carboxylic acids successfully resolved in high optical purities by fractional crystallization of the diastereomeric salts with the optically active amine **1**. The results are summarized in Tables 4 and 5.

It is especially noteworthy that tartaric acid, which is valuable and widely used as a resolving agent, can be resolved in a high yield and in a high optical purity.

Experimental

The melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The values of specific roration were obtained on JASCO DIP-181 digital polarimeter.

(±)-2-Amino-2-phenylethanol((±)-**1**) was obtained by the reduction of commercially available (±)-2-amino-2-phenylacetic acid (DL-phenylglycine) with lithium aluminium hydride: mp 47—49.5 °C; bp 106—109 °C/133 Pa (lit,[5] mp 47—49 °C; bp 144—147 °C/1866 Pa). Optically active **1**, (−)- and (+)-**1**, used as seeds were prepared in a similar manner from commercially available (*R*)-(−)-2-amino-2-phenylacetic acid (D-phenylglycine), and (*S*)-(+)-2-amino-2-phenylacetic acid obtained by the reciprocal preferential resolution of the salt of (±)-2-amino-2-phenylacetic acid with (±)-10-camphorsulfonic acid,[7] respectively: mp 75—76 °C; $[\alpha]_{589}^{29.5}$ − and +26.7°, $[\alpha]_{435}^{29.5}$ − and +52.0° (*c* 1.00, MeOH) (lit,[8] mp 78—79 °C, 77—78 °C; $[\alpha]_{589}^{17}$ −25.4°, +23.5° in MeOH).

Preferential Crystallization of (±)-2-Amino-2-phenylethanol ((±)-1). A refluxed solution of (±)-**1** (34.30 g) and (+)-**1** (1.30 g), which was added to facilitate the preferential crystallization from the first stage, in a mixture of benzene and 99% ethanol (9 : 1) (84 ml) was cooled at around 13 °C to give a supersaturated solution. The solution was seeded with (+)-**1** (0.20 g) and stirred gently (about 30 min^{-1}) for 65 min at 4—5 °C. The precipitates appeared were collected by filtration, washed with 1 ml of a mixture of benzene and ethanol (9 : 1), and dried over P_2O_5 and solidified paraffin, giving 2.79 g of (+)-**1** ($[\alpha]_{435}^{38}$ +47.6° (*c* 1.00, MeOH)). The optical purity of the product was 92% based on the specific rotation of (−)-**1** prepared from (−)-2-amino-2-phenylacetic acid by the reduction with lithium aluminium hydride ($[\alpha]_{435}^{29.5}$ −52.0° (*c* 1.00, MeOH)). Successively, (±)-**1** (3.00 g) was added to the filtrate and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (−)-**1** (0.20 g), and stirred gently for 65 min at 4—5 °C. Similar treatment of precipitates appeared gave 3.53 g of (−)-**1** ($[\alpha]_{435}^{35.5}$ −44.4° (*c* 1.00, MeOH); 85% optical purity).

After several stages of the preferential crystallization, the crystals having the same sign of optical rotation were combined and recrystallized. Recrystallization of (+)-**1** (7.24 g; 91% optical purity on the average) from benzene (40 ml) gave 6.32 g (87%) of highly pure (+)-**1** ($[\alpha]_{435}^{29.5}$ +51.6°, $[\alpha]_{589}^{29.5}$ +26.3° (*c* 1.00, MeOH); 99% optical purity). In a similar manner, (−)-**1** (8.22 g; 87% optical purity on the average) was recrystallized from benzene (55 ml), giving 7.15 g (87%) of (−)-**1** ($[\alpha]_{435}^{29.5}$ −50.5°, $[\alpha]_{589}^{29.5}$ −25.9° (*c* 1.00, MeOH); 97% optical purity).

Resolution of (±)-Tartaric Acid (2) with (−)-1. To a solution of (±)-**2** (8.00 g, 53 mmol) in methanol (80 ml) was added a solution of (−)-**1** (14.60 g, 107 mmol) in methanol (20 ml), and the mixture was stood overnight at room temperature. White precipitates appeared were filtered off and dried over P_2O_5 to give crude (+)-**2**·(−)-**1** (1 : 2) salt (10.49 g, 93%): $[\alpha]_{435}^{31.5}$ −19.3° (*c* 1.00, H_2O). The suspension of the salt (10.49 g) in methanol (50 ml) was refluxed for 20 min, and insolubilized crystals and precipitates deposited on cooling at room temperature were collected together by filtration, powdered finely, and dried over P_2O_5 to give 9.70 g (86%) of (+)-**2**·(−)-**1** (1 : 2) salt.

The purified (+)-**2**·(−)-**1** (1 : 2) salt (9.70 g) was dissolved in water (65 ml), and the solution was charged on an ion exchange resin column (Amberlite IR 120B, 77 ml) to decompose the salt. Elution with water (450 ml) gave an aqueous solution of (+)-**2**. After evaporation of the water, white precipitates remained were dried over P_2O_5 to yield (+)-**2** (3.08 g, 77% total yield): mp 163—169 °C; $[\alpha]_{589}^{32}$ +16.1° (*c* 1.02, H_2O); 96% optical purity.

Similarly, (−)-**2** was obtained in 63% total yield by the fractional crystallization of the salt of (±)-**2** with (+)-**1**: mp 165—165.5 °C; $[\alpha]_{589}^{22}$ −15.9° (*c* 1.00, H_2O); 95% optical purity.

The ion exchange resin used for the decomposition of the salt was treated with a large excess of 5 M (1 M=1 mol dm^{-3}) aqueous ammonia solution to recover (−)- or (+)-**1**. The eluate was concentrated under reduced pressure, and slightly yellow oil was treated with 10M NaOH solution and extracted with ether. The ethereal solution was dried with Na_2SO_4 and concentrated under reduced pressure to give (−)- or (+)-**1**. Recovery was over 90% and racemization did not take place.

Resolution of (±)-2-Hydroxy-3-phenylpropionic Acid (4) with (−)-1. A clear solution of (±)-**4** (4.98 g, 30 mmol) and (−)-**1** (4.05 g, 30 mmol) in a mixture of ethyl acetate and 2-propanol (7 : 2) (270 ml) at reflux temperature was cooled with ice bath for 4.5 h to give white precipitates. The precipitates were collected by filtration and dried over P_2O_5, giving crude (−)-**4**·(−)-**1** salt (3.91 g, 87%): $[\alpha]_{435}^{28}$ −74.8° (*c* 1.00, MeOH).

Recrystallization of the salt (3.86 g) from a mixture of ethyl acetate and 2-propanol (2 : 1) (95 ml) gave 3.16 g (71%) of (−)-**4**·(−)-**1** salt: mp 145—146 °C; $[\alpha]_{435}^{25}$ −113° (*c* 1.00, MeOH).

To a solution of purified salt (3.12 g) in water (50 ml) was added 1 M HCl solution (20 ml) to decompose the salt. The liberated acid was extracted with ether (3×40 ml), and the ethereal extracts were combined, dried with Na_2SO_4, and concentrated under reduced pressure to yield (−)-**4** (1.62 g, 67% total yield): mp 122—123 °C; $[\alpha]_{589}^{28}$ −17.5° (*c* 1.00, EtOH); 94% optical purity.

The resolving agent was recovered in 93% yield without racemization by treating the aqueous solution with 1M NaOH solution, followed by extraction with ether.

In a similar fashion, 2-hydroxy-2-phenylpropionic acid (**3**), 2-phenylpropionic acid (**5**), and 2-phenyl-2-ureidoacetic acid (**6**) were resolved in high optical purities (see Tables 4 and 5).

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