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Practical resolution of 1-phenyl-2-(4-methylphenyl)ethylamine using a single resolving agent controlled by the dielectric constant of the solvent

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Abstract—A practical resolution of 1-phenyl-2-(4-methylphenyl)ethylamine 1 for obtaining (*R*)- and (*S*)-enantiomers by a dielectrically controlled resolution (DCR) method using a single resolving agent, (*S*)-mandelic acid 2, has been studied. The configuration of the excess enantiomer 1 in the less-soluble diastereomeric salt was found to vary depending on the solvent controlled by adjusting the solvent dielectric constant ε and the water content of the alcohol solvent. It was found that the presence of water molecules and the solvent molecular structures was key to controlling the configurational change phenomenon in the chiral discrimination between molecules 1 and 2. Moreover, the reaction environment controlled by the solvent dielectric constant plays a very distinct role in utilizing water molecules for crystallizing the less-soluble diastereomeric salt during the resolution. Based on the results, a practical resolution process for (*R*)-1 and (*S*)-1 production has been developed involving a simple solvent switch method; the (*S*)-1·(*S*)-2·H₂O salt (33% yield, 96% de, *E* 64%) was obtained by the crystallization from 74% (w/w) aqueous ethanol in the first resolution, while the (*R*)-1·(*S*)-2 salt (23% yield, 98% de, *E* 46%) was crystallized from 100% ethanol of the condensate of the mother liquor after the first resolution.

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1. Introduction

It has been estimated that more than half of chiral drugs in the pharmaceutical market are produced by the diastereomeric salt formation method using enantiopure resolving agents because of the ease of operation and wide applicability.¹ Currently, chiral intermediates for important chiral drugs such as indinavir (anti-viral),² sertraline (anti-depressant),³ orlistat (anti-obsessional),⁴ and duloxetine (anti-depressant)⁵ are widely known to be efficiently produced by this method on an industrial scale. It is generally understood that one of the chiral species of the resolving agent only acts on one stereoisomer of the target substrate to crystallize the less-soluble diastereomeric salt.⁶ Therefore, it is common to apply the other enantiomer of the resolving agent to obtain the opposite stereoisomer of the target substrate. If both enantiomers can be resolved as the less-soluble salts by a single enantiomer of the resolving agent, the resolution process would become much more costeffective.

Recently we have found a quite unusual but useful phenomenon; a single resolving agent can recognize both stereoisomers of the target substrate and give the corresponding less-soluble diastereomeric salts by simply adjusting the dielectric constants (ε) of the solvent. The first example that we discovered was the resolution system of (*RS*)- α -amino- ε -caprolactam **3** as a target substrate to be resolved and *N*-tosyl-(*S*)-phenylalanine **4** as the resolving agent.⁷ Based on this finding, we successfully developed a practical continuous resolution for (*R*)-**3** and (*S*)-**3** production by diastereomeric salt formation using one naturally-based resolving agent (*S*)-**4**^{8,9} (Fig. 1). We designated this procedure as a simple solvent switch method.

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Figure 1. Resolution of α -amino- ε -caprolactam 3 with *N*-tosyl-(*S*)-phenylalanine 4.

The crystal structures of the less-soluble salts, (R)-3·(S)-4 and (S)-3·(S)-4·H₂O, showed that the molecular recognition between the resolving agent and the target substrate is governed by a specific hydrogen-bonding network due to the difference of the solvent dielectric constant. If this phenomenon is general, namely if the hydrogen-bonding system can be controlled by adjusting the solvent's ε value, this dielectrically controlled resolution (DCR) method could be quite promising to a variety of resolution systems.

Nohira et al. reported¹¹ that the chirality of the resolution product in the system of (RS)-1-phenyl-2-(4-methylphenyl)ethylamine 1 and (S)-mandelic acid 2 changes and it depends on the solvent used (Fig. 2). It is interesting to examine whether this system is dielectrically controlled or not and therefore we investigated the effect of the solvent on this resolution. Herein we report that this resolution system can be controlled by the dielectric constant of the solvent. We also report that the molecular structure of the solvent can have significant influence on the resolution.





2. Results and discussion

The effects of six alcohols $(C1-C4; \varepsilon = 16-33)^{12}$ and water ($\varepsilon = 78$)¹² on the resolution have been examined as the resolution solvent while an equimolar amount of resolving agent (*S*)-**2** to the racemate (*RS*)-**1** was used. Isobutyl alcohol and *tert*-butyl alcohol could not be applied as resolution solvents because of the low water solubility (16%) and the high melting point (25.6 °C), respectively. Resolutions were performed under overhead-stirring without seeding in order to avoid the occurrence of preferential crystallization with specific seed crystals. Components, diastereomeric excesses, and absolute configurations of the salts obtained were determined by elemental, chiral HPLC, and X-ray crystal structure analyses. The results are summarized in Table 1. The (R)-1·(S)-2 salt was crystallized with relatively higher diastereomeric excess (de)¹³ and resolution efficiency $(E)^{14}$ from 1-butanol, 1-propanol and ethanol. The (RS)-1·(S)-2 salt was crystallized from 2-butanol, 2-propanol, and methanol. To our surprise, the (S)- $1 \cdot (S) - 2 \cdot H_2O$ salt crystallized only from water, although the amount of water required is impractical for industrial-scale production. The results indicate that the branched alcohols are not favorable for the chiral discrimination between (S)-2 and 1. The bulky groups in the branched alcohols may disturb the molecular recognition. The exceptional result for methanol may be due to its specific physicochemical properties. (S)-1 was crystallized only from water and reveals that water molecules play a distinctive role in the chiral recognition between (S)-2 and (S)-1 as observed in our previous studies.^{8,10} The results shown in Table 1 suggest that the configuration and enantiomeric excess of 1 could be controlled by using a mixed solvent of non-branched alcohols and water.

Table 1. Resolution of (RS)-1 with (S)-2 in alcohols and water

Entry	Solvent	3	Solvent/ (<i>RS</i>)-1 ^a w/w	De, % ^b	R/S	Yield ^e	E ^d
1	2-BuOH	16	47	1	RS	55	4
2	1-BuOH	17	18	92	R	25	46
3	2-PrOH	18	49	1	RS	54	1
4	1-PrOH	22	21	23	R	23	11
5	EtOH	24	12	96	R	16	31
6	MeOH	33	4	0	RS	27	0
7	Water	78	228	98	S	24	47

(S)-2/(RS)-1 = 1.0 molar ratio.

^a Solvent weight was determined by solubility of the solid substances at 50 °C.

^b Diastereomeric excess (% de) = $[A - B] \times 100/(A + B)$, where A and B are both diastereomers.

^c Calculated based on (RS)-1.

^d Resolution efficiency (*E*, %) = yield (%) × diastereometric excess (% de) × 2/100.

The effects of various mixed solvents of alcohol and water ($\varepsilon = 16-78$)¹⁵ on the resolution were examined as

Entry	Solvent	Alcohol concentration, %	3	Solvent/(RS)-1 ^a w/w	De, % ^b	R/S	Yield ^c	E^{d}
1	2-BuOH	100	16	47	1	RS	55	2
2		92	22	19	96	S	37	71
3		85	25	16	98	S	34	66
4		75	32	11	96	S	37	71
5		65	38	9	97	S	36	69
6	1-BuOH	100	17	18	92	R	25	46
7		99	18	16	19	R	42	16
8	2-PrOH	100	18	49	1	RS	54	1
9		95	21	20	42	S	45	38
10		82	29	12	95	S	38	72
11		70	36	12	97	S	39	76
12		60	42	13	97	S	37	71
13		45	51	16	65	S	48	62
14		15	69	100	48	S	51	48
15	1-PrOH	100	22	21	23	R	23	11
16		92	26	7	48	S	53	51
17		83	32	6	96	S	34	67
18		75	36	6	97	S	37	71
19		50	50	9	98	S	36	70
20		25	64	28	97	S	40	76
21	EtOH	100	24	12	96	R	16	30
22		95	27	10	28	S	38	21
23		90	29	7	35	S	47	33
24		85	32	8	68	S	41	56
25		74	38	10	99	S	34	67
26		60	46	11	66	S	44	58
27		50	51	13	48	S	59	57
28		30	62	39	36	S	65	47
29		16	69	120	98	S	34	67
30	MeOH	100	33	4	0	RS	27	0
31		86	39	3	18	S	56	20
32		70	47	6	39	S	56	43
33		44	58	34	68	S	44	60
34		20	69	100	95	S	34	65
35	Water	0	78	228	98	S	24	47

(S)-2/(RS)-1 = 1.0 molar ratio.

^a Solvent weight was determined by solubility of the solid substances at 50°C.

^b Diastereomeric excess (% de) = $[A - B] \times 100/(A + B)$, where A and B are both diastereomers.

^c Calculated based on (RS)-1.

^d Resolution efficiency (E, %) = yield $(\%) \times$ diastereometric excess $(\% \text{ de}) \times 2/100$.

shown in Table 2. The mixture, which gives a homogeneous clear solution at ambient temperature, was taken into account. Concentrations of 1-butanol and 2-butanol were limited with the maximum concentrations being 99% and 65%, respectively. The trends of the configuration changes are illustrated in Figure 3. All alcohol solvents, except methanol, behaved similarly in a range of $\varepsilon < ca.$ 40. Their enantiomeric excesses of 1 rapidly shifted to the (S)-enriched state from the (R) or (RS)form state with increase in the solvent dielectric constant. It is noteworthy that the diastereomeric excess of the salt obtained from the aqueous ethanol solution dropped to 36% de at $\varepsilon = 62$ and recovered at $\varepsilon = 69$ (98% de). This phenomenon demonstrates that the solvent dielectric constant seems to be one of the main factors, which govern the chiral discrimination but some other factors may also play influential roles in the discrimination process.



Figure 3. Relation between the diastereomeric excess of the lesssoluble diastereomeric salt and the solvent dielectric constant (ϵ).

From a practical point of view, it is extremely useful that the configuration of the salt was drastically changed from the enantiopure (R)-1 to the enantiopure (S)-1 by adjusting the dielectric constant of the medium by changing the water content. A remarkable resolution efficiency can be achieved when ethanol is used as the solvent. (R)-1 (96% de) was crystallized from 100% ethanol ($\varepsilon = 24$), whereas (S)-1 (99% de) from 74% ethanol $(\varepsilon = 38)$. On the other hand, in the case of branched alcohols such as 2-butanol and 2-propanol, the diastereomeric excesses of the salts crystallized were improved to give the enantiopure (S)-form from the racemic form at $22 < \varepsilon < 38$ and $29 < \varepsilon < 42$, respectively. It is noteworthy that the behavior of methanol was completely different. The diastereomeric excess shifted from the (RS)-form to the (S)-form linearly according to the increase of the solvent dielectric constant, with the maximum (95% de) being obtained at a concentration of 20%.

In order to develop the optimum resolution conditions of (RS)-1 with (S)-2 suitable for an industrial-scale production, 100% ethanol ($\varepsilon = 24$) and 74% ethanol $(\varepsilon = 38)$ was selected as resolution solvents. The resolution was performed in two stages. Since the resolution efficiency of (R)-1 from ethanol was relatively low, the first resolution was designed to produce (S)-1 from 74% ethanol following our strategy of the continuous resolution method described in our previous study.⁷ The second resolution was designed to produce (R)-1 by using ethanol from mother liquor of the first resolution containing the (R)-enriched 1. Resolution experiments were performed under over-head-stirring with seeding in order to effectively enhance the resolution efficiency. The (S)- $1\cdot$ (S)- $2\cdot$ H₂O was obtained in identical efficiency (33% yield, 96% de, E 64%) to the single resolution result shown in Table 2. The result indicates that seeding did not enhance the resolution efficiency. The mother liquor of the first resolution was evaporated to dryness to recover the mixture of the (R)-enriched 1 and the equimolar (S)-2 (49% de), followed by switching the solvent to 100% ethanol for the second resolution. As intended, the resolution efficiency for the (R)-1·(S)-2 salt increased dramatically (23% yield, 98% de, E 46%).

3. Conclusion

In the resolution process development of (RS)-1-phenyl-2-(4-methylphenyl)ethylamine 1 with (S)-mandelic acid 2 using various alcohol solvents, it was found that the configuration of the excess enantiomer 1 in the less-soluble diastereomeric salt varies depending on the solvent used; the configuration and enantiomeric excess of 1 in the salt were controlled by adjusting the solvent dielectric constant ε while controlling water content in the alcohol solvent. Moreover, it was also found that the solvent's molecular structure affects the chiral recognition ability of the resolving agent (S)-2 during the resolution; the (S)-1·(S)-2·H₂O salt was obtained by the crystallization from water or water-contained alcohols, while the (R)-1·(S)-2 salt was crystallized from nonbranched alcohols such as ethanol, 1-propanol, and 1butanol. These results clearly indicate that not only the presence of water but also the solvent's molecular structure plays a very distinctive role in the chiral molecular recognition between molecules 1 and 2. Based on these findings, we could develop a practical resolution process for obtaining (R)-1 and (S)-1 using only one enantiomer of the resolving agent, together with a simple solvent switch method. In addition to the practical significance, the solvent dielectric constant ε was found to be a good measure for comparing the resolution results obtained from different sorts of solvents in the resolution process development.

4. Experimental

4.1. General

(*RS*)-1 (CP 98.7%) and (*S*)-mandelic acid 2 (>99.5% ee)¹⁶ were made of Yamakawa Chemical (Tokyo). Other reagents were purchased from Junsei Chemical, unless otherwise indicated. ¹H NMR spectra were recorded on a JEOL JNM-ECP400 spectrometer in DMSO- d_6 with Me₄Si as an internal reference. IR spectra were measured on a JASCO IR-700 spectrometer using KBr pellets. Optical rotations were measured on a JASCO P-1020 polarimeter with a circular temperature control unit. High-performance liquid chromatography was performed by a JASCO Intelligent HPLC system equipped with a UV-970 detector. Melting points were determined with a YAMATO MP-21 instrument and are uncorrected.

4.2. Determination of diastereomeric purity

The diastereomeric purity of the salts, (R)-1·(S)-2 and (S)-1·(S)-2·H₂O, were directly determined by HPLC using a Shiseido Chiral CD-Ph column (ID 4.6 mm × 250 mm). Analytical conditions for the HPLC were as follows: 0.5 M NaClO₄/CH₃CN (50/50 v/v), 0.5 mL/min, 35 °C, detected at 254 nm; injection sample 10 µL (10 mg/10 mL); retention times: (S)-1 13.6 min, (R)-1 20.7 min, (S)-2 5.5 min.

4.3. Strategic continuous resolution: resolution starting from (*S*)-1 separation

In order to obtain (R)-1 more efficiently, the resolution was started from (S)-1 resolution. A typical experimental procedure is as follows: to a 50 mL flask were added (RS)-1 (3.00 g, 14.2 mmol), (S)-2 (2.16 g, 14.2 mmol) and 74% ethanol (28.7g), and the mixture was stirred and heated up to about 50 °C to give a clear solution. The solution was then gradually cooled, seeded (2mg) at 26 °C, kept for 1h at around the crystallization temperature, and then cooled again to 20 °C. After aging the suspension at the temperature for 1 h, the crystals were filtered off and washed twice with 74% ethanol to afford the crude (S)-1·(S)-2·H₂O salt (1.74g, 4.6 mmol, 33% yield, 96% de, E 64%). Analytical data for the recrystallized salt are as follows: $(S)-1\cdot(S)-2$ salt·H₂O: 99.6% de; mp 149.5–52.0°C; $[\alpha]_{D}^{20} = +126.5$ (c 1.04, EtOH); IR (KBr) cm⁻¹: 3634, 3324, 2944, 2734, 2590, 2178, 1640, 1574, 1545, 1514, 1450, 1401, 1375, 1348, 1328, 1194, 1084, 1060, 933, 811, 778, 740, 702, 618; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.16–7.40 (m, 10H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 4.65 (s, 1H), 4.28 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.11 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.95 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.21 (s, 3H). Anal. Calcd for C₂₃H₂₅NO₃·H₂O: C, 72.42; H, 7.13; N, 3.67. Found C, 73.32; H, 7.08; N, 3.70.

The mother liquor obtained after the first resolution described above was evaporated to dryness to give a condensate [3.17 g; (*R*)-enantiomer rich 49% de; water contents 0.14% measured by KF method]. To the condensate was added ethanol (21.3 g), the slurry was transferred to a 50 mL flask. The mixture was stirred and heated up to about 60 °C to give a clear solution. The solution was then gradually cooled, seeded (2mg) at 25 °C, kept for 1 h at around the crystallization temperature and then cooled again to 20 °C. After aging the suspension at the temperature for 1 h, the crystals were filtered off and washed twice with ethanol to afford the crude (*R*)-1·(*S*)-2 salt (1.20 g, 3.3 mmol, 23% yield, 98% de, *E* 46%). Analytical data for the recrystallized salt are as follows.

(*R*)-1·(*S*)-2 salt: >99.9% de; mp 176.5–177.0 °C; $[\alpha]_D^{20} = -45.7$ (*c* 1.03, EtOH); IR (KBr) cm⁻¹: 3454, 2890, 2660, 2120, 1894, 1611, 1566, 1529, 1417, 1366, 1332, 1196, 1080, 1060, 937, 811, 787, 756, 703; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.15–7.40 (m, 10H), 7.00 (d, *J* = 8.0Hz, 2H), 6.92 (d, *J* = 8.0Hz, 2H), 4.65 (s, 1H), 4.28 (dd, *J* = 8.8, 6.0Hz, 1H), 3.07 (dd, *J* = 13.2, 6.0Hz, 1H), 2.94 (dd, *J* = 13.2, 8.8Hz, 1H), 2.21 (s, 3H). Anal. Calcd for C₂₃H₂₅NO₃: C, 76.01; H, 6.93; N, 3.85. Found C, 76.09; H, 6.98; N, 3.85.

4.4. X-ray crystal structure analysis

Crystallographic data for the structures of (R)-1·(S)-2 and (S)-1·(S)-2·H₂O have been deposited with the Cambridge Crystallographic Data Centre as reference numbers CCDC 241593 and 241594, respectively. X-ray diffraction data were measured using the Rigaku RAXIS-RAPID system.

(*R*)-1·(*S*)-2: a colorless platelet single crystal of (*S*)-1· (*S*)-2 salt (0.50 × 0.30 × 0.25 mm) was grown from EtOH using recrystallized salt crystals (>99.9% de). The X-ray intensities were measured up to $2\theta_{\text{max}} = 68.17^{\circ}$ with graphite monochromated CuK_{α} radiation ($\lambda =$ 1.5419Å) at 293 K. C₂₃H₂₅NO₃; formula weight 363.46; orthorhombic, *P*2₁2₁2₁ (# 19), *a* = 6.607(4), *b* = 15.504(1), *c* = 20.243(2)Å, *V* = 2073(1)Å³, *Z* = 4, *D*_{calc} = 1.164 g/cm³, *R* = 0.062; *Rw* = 0.053. Number of reflections measured = total 2085, unique 1387.

(S)-1·(S)-2·H₂O: a colorless platelet single crystal of (S)-1·(S)-2·H₂O salt (0.30 × 0.25 × 0.15 mm) was grown from water using recrystallized salt crystals (>99.9% de). The X-ray intensities were measured up to $2\theta_{\text{max}} = 68.19^{\circ}$ with graphite monochromated Cu K_a radiation ($\lambda = 1.5419$ Å) at 293 K. C₂₃H₂₇NO₄; formula weight 381.47; orthorhombic, P2₁2₁2₁ (# 19),

 $a = 6.135(1), b = 11.901(2), c = 27.907(5) \text{\AA}, V = 2037.5(6) \text{\AA}^3, Z = 4, D_{calc} = 1.243 \text{ g/cm}^3, R = 0.042; Rw = 0.042.$ Number of reflections measured = total 2052, unique 1550.

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- 13. Diastereomeric excess (% de) = $[A B] \times 100/(A + B)$, where A and B are both diastereomers.
- 14. Resolution efficiency (E, %) = yield $(\%) \times$ diastereometric excess $(\% \text{ de}) \times 2/100$, where yield is calculated based on (RS)-1.
- 15. (a) The values of dielectric constants of mixed solvents were calculated as the weighted average of the mixture components, alcohol and water, based on the following

equation and literatures; $\varepsilon_{(mix)} = (wt_{(alcohol)} \times \varepsilon_{(alcohol)}) + (wt_{(water)} \times \varepsilon_{(water)})$, where $\varepsilon_{(alcohol)}$ and $\varepsilon_{(water)}$ are the dielectric constants at 20 °C of pure alcohol and water, respectively. (a) Jouyban, A.; Soltanpour, S.; Chan, H.-K.

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