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Solvent Dependence of Optical Resolution of α−Methylbenzylamine Using *N*–Tosyl–(*S*)–phenylalanine

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Abstract

The optical resolution system of racemic (*RS*)–*α*–methylbenzylamine (MBA) **1** with naturally–based and commercially available reagent *N*–tosyl–(*S*)–phenylalanine (TPA) **2** via diastereomeric salt formation has been investigated. A significant role of the dielectric constant (ε) of solvent used in this resolution process also reported here. Highly optically pure (*S*)–**1** was obtained as the less–soluble diastereomeric salt using 2–PrOH as a resolving solvent (68.4% ee, *E* 47.7%). The enantiomeric excess of **1** in the less–soluble diastereomeric salt was found to vary depending on the solvent used; the enantiomeric excess of **1** in the salt was controlled by adjusting the solvent dielectric constant (ε)

Introduction

The reliable preparation of enantiomerically pure compounds is important in such areas as the pharmaceutical and food industries. To date, amongst the various new and attractive techniques for the preparation of enantiomerically pure compounds, optical resolution via diastereomeric salt formation is still a useful technique on an industrial scale, since it is generally simple, clean, and easy to reproduce the laboratory-scale data on an industrial–scale.[1] Estimation assessed that more than half of the chiral drugs on the pharmaceutical market are produced by the diastereomeric salt formation method using enantiomerically pure resolving agents.[2]

The general importance of chiral amines is well recognized and *α*–methylbenzylamine (MBA) **1** is well known as a simple, yet powerful, chiral reagent.[3] Enantiomerically pure MBA and its derivatives have important applications as effective chiral adjuvants in the resolution of racemates, as ligands in asymmetric (or disymmetric) catalysts.[4] Nowadays it's being used as a chiral auxiliary and as a chiral base.

It's notable that several stereoselective syntheses for *α*–MBA have been reported.[5,6] Stereoselective synthesis would be a course of action to get enantiopure *α*–MBA, but high cost, multiple steps, low chemical yields, or low diastereoselectivity are the disadvantageous causes to be considered. The direct resolution is the most convenient method to produce a pure enantiomer, although tedious separation processes of the corresponding salts are sometimes required. The resolutions of racemic **1** with tartaric acid,[7] (*S*)–carbamalactic acid,[8] and mandelic acid[9] seem to be the efficient systems.

Recent papers by Sakai *et al.* show that solvent dependence of the diasetereomeric salt formation method allow efficient resolution of both enantiomers using a *single* resolving

agent.[10-12] This technique is apparently very effective for the use of natural resolving agents, which are usually available as a single enantiomer.[13] Herein we report the solvent dependence of optical resolution (*RS*)–*α*–methylbenzylamine (MBA) 1 using *N*–tosyl–(*S*)–phenylalanine (TPA) 2.

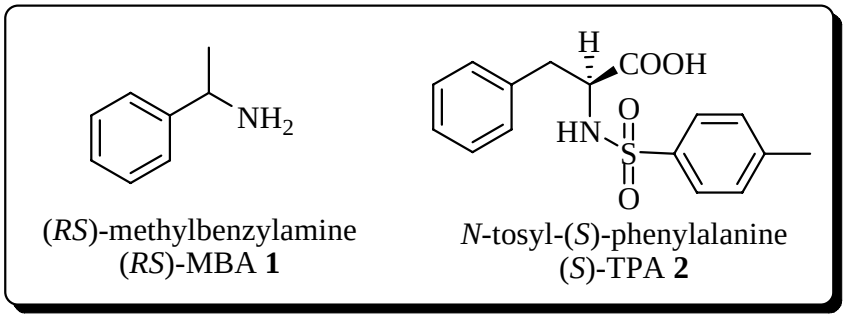


Figure 1. Chemical structures of MBA and TPA

Results and Discussion

To resolve (*RS*)–*α*–methylbenzylamine (MBA) 1, recrystallizable resolving agent *N*–tosyl–(*S*)–phenylalanine (TPA) **2** was selected rather than a number of other commercially available acidic resolving agents.[7–9] From a known concept, '*a resolving agent should have similar or longer molecular length than the racemic target compound*',[9] and no resolution work on MBA with TPA has been reported so far, so that we were interested to choose 2 as a resolving agent for the present cumbersome works. It was also found from our efforts that TPA could be recovered easily.

In order to examine (*S*)-TPA 2 as a resolving agent of (*RS*)–1, at first the effects of four alcohols (ε = 17–33) [14] and water (ε = 78) [14] on the resolution were studied as a resolving solvent. All solvent systems gave crystalline precipitates and the results of a single crystallization in each solvent are summarized in Table 1. The optical purity was determined by chiral HPLC analysis after acetylation of (*S*)–1 liberated from the precipitated salt. As seen in Table 1, only (*S*)–1·(*S*)–2 was obtained as the less–soluble diastereomeric salt and highly optically pure (*S*)–1 was obtained using EtOH and 2–PrOH solvents.

Table 1 Resolution of (*RS*)–**1** with (*S*)–**2** in some alcohols and water[a]

Entry	Solvent	Dielectric constant[b] (*ε*)	Solvent / (*RS*)–**1** (v / w)	Yield[c] %	Optical Purity[d] %ee	Resolution Efficiency[e] (*E*) %	Absolute configuration
1	MeOH	33.0	10	50.5	17.9	9.04	*S*
2	EtOH	24.0	28	45.7	59.8	27.3	*S*
3	2–PrOH	18.0	35	69.8	68.4	47.7	*S*
4	*n*–BuOH	17.0	40	61.6	48.3	29.8	*S*
5	H_2O	78.0	5.4	50.7	1.93	0.98	*S*

a) Resolving agent (*S*)–2 / (*RS*)–1 = 1.0 (molar ratio).
b) Dielectric constant (*ε*) for a mixed solvent is the weighted average value calculated from those of pure solvents.
c) Yield calculated based on half the amount of racemic MBA.
d) Determined by chiral HPLC analysis (HPLC Conditions–Column: Chiralpak AD–H (Daicel Chemical Ind. Ltd.), Eluent: 10% 2–propanol in hexane, Flow rate : 0.5 mL/min).
e) Resolution efficiency (*E*: %) = yield (%) x optical purity (% ee) / 100

The results summarized in Table 1 also indicate that the enantiomeric excess of (*S*)–1 in the less–soluble diastereomeric salt would vary depending on the solvent polarity. Therefore the optical purity and even the configuration of resolved 1 could be controlled by using a mixed solvent of alcohols and water as shown by Sakai *et al.*[10–12] The effects of various mixed solvents of alcohol and water (ε = 18–78)[14] on the resolution were examined as shown in Table 2.

Table 2 Resolution of (*RS*)–1 with (*S*)–2 in various alcoholic solvents[a]

Entry	Solvent[b]	Dielectric constant[c] (ε)	Solvent / (*RS*)–**1** (v / w)	Yield[c] %	Optical Purity[d] %ee	Resolution Efficiency[e] (*E*) %	Absolute configuration
1	100%MeOH	33.0	10	50.5	17.9	9.04	*S*
2	90% MeOH	36.9	8	45.3	17.5	7.93	*S*
3	80% MeOH	41.5	7.5	45.8	13.2	6.05	*S*
4	70% MeOH	47.0	6	52.1	11.3	5.89	*S*
5	60% MeOH	51.0	5	50.6	2.70	1.37	*S*
6	100% EtOH	24.0	28	45.7	59.8	27.3	*S*
7	90% EtOH	29.0	17	54.2	44.9	24.3	*S*
8	80% EtOH	33.9	9	44.0	15.7	6.91	*S*
9	70% EtOH	39.1	6	48.5	8.58	4.16	*S*
10	60% EtOH	46.0	5	52.6	4.45	2.34	*S*
11	100% 2–PrOH	18.0	45	69.8	68.4	47.7	*S*
12	90% 2–PrOH	25.7	25	64.4	48.3	31.1	*S*
13	80% 2–PrOH	31.5	13	49.3	32.4	16.0	*S*
14	70% 2–PrOH	36.0	7.5	46.8	17.5	8.20	*S*
15	60% 2–PrOH	42.0	6.5	47.7	12.6	6.01	*S*
16	H_2O	78.0	5.4	50.7	1.93	0.98	*S*

a) Resolving agent (*S*)–2 / (*RS*)–1 = 1.0 (molar ratio).
b) Dielectric constant (ε) for a mixed solvent is the weighted average value calculated from those of pure solvents.
c) Yield calculated based on half the amount of racemic MBA.
d) Determined by chiral HPLC analysis (HPLC Conditions–Column: Chiralpak AD–H (Daicel Chemical Ind. Ltd.), Eluent: 10% 2–propanol in hexane, Flow rate : 0.5 mL/min).
e) Resolution efficiency (*E*: %) = yield (%) x optical purity (% ee) / 100

The results in Table 2 show that the enantiomeric excess of (*S*)–1 in the less–soluble diastereomeric salt was largely affected by the solvent polarity, that is, the enantiomeric excess of 1 in the salt was controlled by adjusting the water content in an alcohol. The trends of the optical purity changes are illustrated in Figure 2 as the dielectric constant (ε) as an index. The lower the solvent ε is, the higher the optical purity of (*S*)–1 becomes. This phenomenon demonstrates that the solvent composition or polarity plays an important role during chiral discrimination process.

Only (*S*)–1 was obtained by the solvent systems used in the wide dielectric constant range, 18 < ε < 78. In order to observe the solvent effect at lower ε range, it is necessary to use less polar alcoholic and other solvents as a resolving solvent.

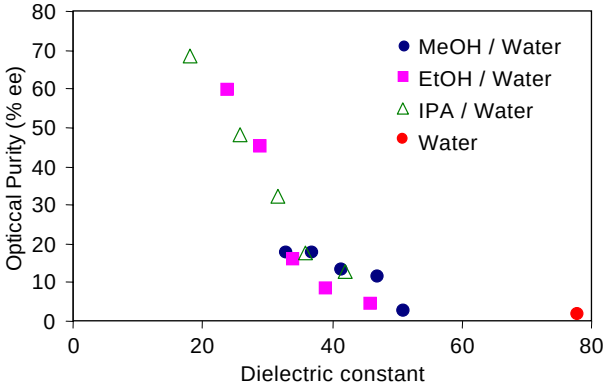


Figure 2. Relationship between the optical purity and the solvent.

Conclusion

N-Tosyl–(*S*)–phenylalanine was found to effectively serve as a new resolving agent for racemic (*RS*)–*α*–methylbenzylamine (1) to give (*S*)–1 using an alcohol (MeOH, EtOH, 2–PrOH, *n*–BuOH) and the alcohol-water mixtures. Moreover, it was found that the optical purity of 1 in the diastereomeric salt largely varied depending on the composition or polarity of the solvent used.

Experimental

The measurement of ^{1}H NMR spectra was performed on Brucker AC300P and AC200 spectrometers (Molecular Analysis and Life Science (MALS) Center, Saitama University). Infrared spectra were recorded on a JASCO FT/IR 400 spectrometer. Melting temperatures were determined on Mel–Temp melting point apparatus (Laboratory Devices, MA) and were reported uncorrected. Optical rotation was measured on a JASCO DIP–370 polarimeter. High performance liquid chromatography was performed by a JASCO Intelligent HPLC system 900 equipped with a JASCO CD–1594 detector.

Resolution procedure:

A general experimental procedure (i.e. preparation of the diastereomeric salt) is as follows: A mixture of (*RS*)–*α*–methylbenzylamine 1 (121 mg, 1.0 mmol), *N*–tosyl–(*S*)–phenylalanine 2 (319 mg, 1.0 mmol) and solvent (required amount as table) was heated to give a clear solution. The solution was then cooled to room temperature or lower (corresponding to the crystallization temperature) to give a suspension. The crystals were filtered off and washed with respective solvent to afford crude less-soluble diastereomeric salt (*S*)–1·(*S*)–2.

(*S*)–1/(*S*)–2: Pure (*S*)–1·(*S*)–2 was prepared to determine it's properties as follows: In MeOH (10 mL), (*S*)–1 (121 mg, 1.0 mmol) and (*S*)–2 (319 mg, 1.0 mmol) were dissolved, and the solvent was removed under reduced pressure to afford the salt. $[\alpha]_D^{27}$ = +50.5 (*c*

0.107, MeOH, T=27 °C); mp 156–158 °C; IR (KBr) cm^{-1}: 3300–2400, 1566, 1446, 1404, 1373, 1330, 1171, 1153, 1088, 949, 868, 816, 768, 752, 700, 660, 567, 547; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47–6.99 (m, 14H), 5.66 (br s, 4H), 4.16 (m, 1H), 3.79 (m, 1H), 2.96 (dd, J = 13.6, 5.2 Hz, 1H), 2.68 (dd, J = 13.6, 7.3 Hz, 1H), 2.34 (s, 3H), 1.42 (d, J = 6.6 Hz, 3H).

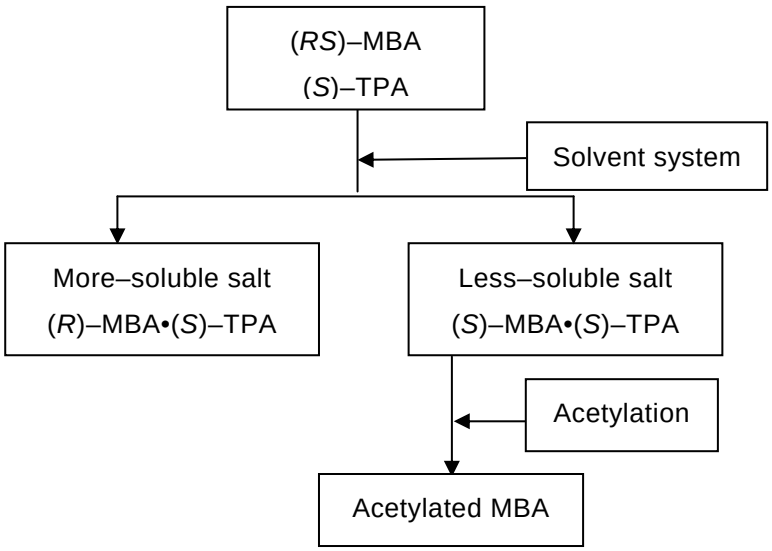
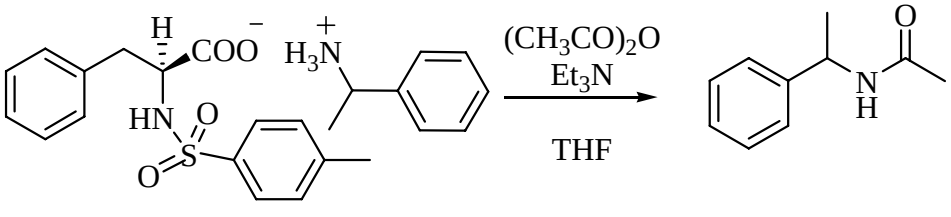


Figure 3. Flow chart of the resolution system of (*RS*)–MBA 1 with (*S*)–TPA 2.

Optical Purity Determination

The less–soluble diastereomeric salt (*S*)–1·(*S*)–2 was acetylated to determine the optical purity of 1. A typical experimental procedure is as follows: To a stirred solution of the salt (94 mg, 0.21 mmol) in dry THF was added Et_3N (54 mg, 0.53 mmol) in dry THF at room temperature under a nitrogen atmosphere. Acetic anhydride (26 mg, 0.26 mmol) in dry THF was added dropwise to the mixture, which was stirred for 10 h at the same temperature. The reaction mixture solvent was removed under reduced pressure. The residue was dissolved in EtOAc and was washed with saturated aqueous $NaHCO_3$, brine, dried with anhydroud Na_2SO_4. After concentration under reduced pressure, the residue was purified by preparative silica gel TLC (EtOAc) to give (31 mg, 0.19 mmol, 89.7%) as a white solid.

The optical purity of α-methylbenzylamine 1 was determined on its acetylated derivative by chiral HPLC analysis. Chiral HPLC analysis was performed using CHIRALCEL AD–H (Daicel Chemical Ind. Ltd., ϕ 4.6 mm × 250 mm, detection: UV 254 nm, flow rate: 0.5 mL/min, eluent: 10% 2–propanol in hexane).



(*S*)-MBA•(*S*)-TPA

Figure 4. Acetylation reation of less soluble diasteomeric salt

Acetylated (*S*)–1 [*N*–(1–phenylethyl)acetamide]: $[\alpha]_D^{24} = -170.0$ (*c* 0.106, MeOH, T=24 °C); mp 102–104 °C; IR (KBr) cm^{-1}: 3265, 3070, 2980, 1643, 1556, 1491, 1450, 1375, 1302, 1286, 756, 742, 704, 621, 534; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.23 (m, 5H), 5.76 (s, 1H), 5.13 (m, 1H), 1.98 (s, 3H), 1.49 (d, *J* = 6.6 Hz, 3H).

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14. 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 & literatures; $\varepsilon_{(mix)} = (wt\%_{(alcohol)} \times \varepsilon_{(alcohol)}) + (wt\%_{(water)} \times \varepsilon_{(water)})$, where $\varepsilon_{(alcohol)}$ & $\varepsilon_{(water)}$ are the dielectric constants at 20 °C of pure alcohol and water, respectively. (a) Jouyban, A.; Soltanpour, S.; Chan, H.-K. *Int. J. Pharm.*, **2004**, *269*, 353–360; (b) Prakongpan, S.; Nagai, T. *Chem. Pharm. Bull.*, **1984**, *32*, 340–343.