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Optical Resolution by Preferential Crystallization of (*RS*)-Bromosuccinic Acid

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The racemic structure of (*RS*)-bromosuccinic acid [(*RS*)-BSA] was examined based on the melting-point, solubility, infrared spectrum, and binary and ternary phase diagrams. The results indicated that (*RS*)-BSA exists as a conglomerate at room temperature, although it forms a racemic compound at the melting point. The optical resolution by preferential crystallization of (*RS*)-BSA yielded (*R*)- and (*S*)-BSA with optical purities of 81—93%. In addition, (*RS*)-BSA was optically resolved using (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol as a resolving agent, to yield (*R*)- and (*S*)-BSA with optical purities of 99 and 83%, respectively. The obtained (*R*)- and (*S*)-BSA were recrystallized from water to obtain optically pure BSA enantiomers.

Of the many methods available for obtaining optically active compounds, the optical resolution can be rapidly achieved without special techniques to give relatively large amounts of enantiomers from racemates. Preferential crystallization and diastereomeric methods have been employed for optical resolution.[1—6] Racemates exist in the form of racemic compounds, racemic solid solutions, and conglomerates. Although optical resolution by the diastereomeric method requires another optically active compound as a resolving agent, all racemates can in principle be optically resolved by such a method. On the other hand, preferential crystallization is achieved by seeding a small amount of one enantiomer into a racemic supersaturated solution. Only conglomerates can be optically resolved by preferential crystallization. Conglomerates which are defined as mechanical mixtures of crystals of both enantiomers are much less common than racemic compounds in which both enantiomers form a molecular compound with each other.[1,6] However, optical resolution is a simple and useful method for the large-scale separation of enantiomers from racemates. Therefore, we have been engaged in screening for conglomerates.

Optically active bromosuccinic acid (BSA) is a useful chiral material for asymmetric syntheses, since it contains one bromine atom and two carboxy groups. For example, potent penem antibacterials, CP-70429 and CP-81054, have been synthesized starting with (*S*)-BSA.[7] We first attempted to optically resolve (*RS*)-BSA using (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol [(*S*)-APP], as a resolving agent. Further, (*RS*)-BSA was concluded to exist as a conglomerate at room temperature from the results of examination of the infrared spectrum, melting point, solubility, and binary and ternary phase diagrams.[1,2,6] Therefore, we attempted to optically resolve (*RS*)-BSA by preferential crystallization.

Results and Discussion

Optical Resolution of (*RS*)-Bromosuccinic Acid by Diastereomeric Method. The optical resolution by diastereomeric method of (*RS*)-BSA was attempted using various optically active amines as basic resolving agents. Of the organic amines used, only (*S*)-APP formed a good crystalline salt with BSA. A salt of (*R*)-BSA with (*S*)-APP [(*R*)-BSA·(*S*)-APP salt] was crystallized as a less soluble diastereomeric salt from a methanol solution containing equimolar amount of (*RS*)-BSA and (*S*)-APP. (*RS*)-BSA showed an infrared absorption band at 1709 cm^{-1} due to a free carboxy group. Although the (*R*)-BSA·(*S*)-APP salt showed a band at 1559 cm^{-1} due to a COO^{-} group, no band was observed at around 1700 cm^{-}. Therefore, the IR spectra and elemental analysis demonstrated that the salt was composed of 1-molar amount of BSA and 2-molar amount of (*S*)-APP. An aqueous solution of the salt was passed through a column on a cation-exchange resin without recrystallization to give (*R*)-BSA of 89% optical purity in 47% yield, based on half of the starting amount of (*RS*)-BSA. After collecting the (*R*)-BSA·(*S*)-APP salt by filtration, (*S*)-BSA of 18% optical purity was obtained from the filtrate. When the molar amount of (*S*)-APP was twice that of (*RS*)-BSA, optical resolution gave (*R*)-BSA of 99% optical purity in 90% yield and (*S*)-BSA of 83% optical purity in 92% yield.

Although the optical resolution using (*S*)-APP as the resolving agent gave good results, (*S*)-APP is not commercially available at present. Therefore, another procedure for the optical resolution of (*RS*)-BSA was necessary.

Racemic Structure of (*RS*)-Bromosuccinic Acid. Since the (*R*)- and (*S*)-BSA partially resolved by the diastereomeric method were recrystallized from water to give optically pure BSA, (*RS*)-BSA was postulated to exist as a conglomerate.

Therefore, the racemic structure of (*RS*)-BSA was examined, aiming at optical resolution by preferential crystallization. (*RS*)-BSA has a lower melting point than (*R*)-BSA. Although racemates that exist as conglomerates have such melting-point characteristics,[1,2)] the melting-point binary phase diagram of BSA suggested that (*RS*)-BSA forms a racemic compound, as shown in Fig. 1.[1,2,6)] However, the binary phase diagram indicated a racemic structure at the melting point, but not necessarily at room temperature. (*RS*)-BSA was assumed to undergo transformation into a conglomerate at a lower temperatures because the mole ratio (0.61) of (*R*)-BSA at the eutectic point was relatively close to that (0.50) of the racemate.[1,8)] We reported an empirical relationship among the Gibbs energy of racemate formation at the melting point ($\Delta G^{F}_{mp}/\mathrm{kJ\,mol^{-1}}$), the difference in melting point ($\Delta T^{f} = T^{f}_{R} - T^{f}_{E}/\mathrm{K}$), and the difference in enthalpy of fusion ($\Delta\Delta H^{f} = \Delta H^{f}_{R} - \Delta H^{f}_{E}/\mathrm{kJ\,mol^{-1}}$) for 41 kinds of racemates (Eqs. 1 and 2):[8)] the subscripts R and E designate racemate and enantiomer, respectively:

$$\Delta G^{F}_{mp} = \Delta E - 2.285, \tag{1}$$

$$\Delta E = -0.0865\Delta T^{f} - 0.0223\Delta\Delta H^{f}. \tag{2}$$

Although the physicochemical significance of ΔE is obscure, we found that racemates having a ΔE larger than +1.17 kJ mol^{-1} exist as conglomerates at room temperature regardless of whether they form racemic compounds at their melting points.[8)] Therefore, the enthalpy of fusion of (*RS*)-BSA ($\Delta H^{f}_{(RS)}/\mathrm{kJ\,mol^{-1}}$) was calculated on the basis of the melting points (T^{f}/K) in the range of 0.500—0.589 mole fraction of (*R*)-BSA in Fig. 1 from Eq. 3[1,6)] and that of (*R*)-BSA ($\Delta H^{f}_{(R)}/\mathrm{kJ\,mol^{-1}}$) on the basis of the melting points in the range of 0.624—1.00 from Eq. 4:[1,6)]

$$\ln 4x(1-x) = (2\Delta H^{f}_{(RS)}/R)(1/T^{f}_{(RS)}) - 1/T^{f}), \tag{3}$$

$$\ln x = (\Delta H^{f}_{(R)}/R)(1/T^{f}_{(R)} - 1/T^{f}), \tag{4}$$

where x is mole fraction of (*R*)-BSA and $T^{f}_{(RS)}$ (437K) and $T^{f}_{(R)}$ (452 K) are melting points of (*RS*)-and (*R*)-BSA, respectively. The values of $\Delta H^{f}_{(RS)}$ and $\Delta H^{f}_{(R)}$ were estimated to be 25.5 and 48.5 kJ mol^{-1}, respectively, and the value of ΔE was calculated to be +1.81 kJ mol^{-1}. In addition, the infrared spectra of (*RS*)- and (*R*)-BSA were identical and the former was more soluble than the latter at 10 °C, as described in the Experimental section. The ternary solubility diagram at 10 °C also showed what is expected for a conglomerate (Fig. 2).[1,2,6)]

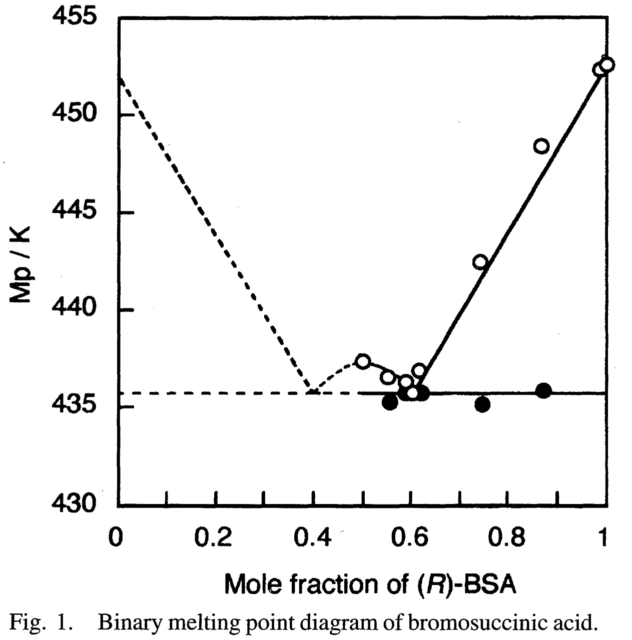

Fig. 1. Binary melting point diagram of bromosuccinic acid. ○: Temperature of termination of melting. ●: Temperature of bigining of melting.

The above results suggest that (*RS*)-BSA exists as a conglomerate at room temperature and forms a racemic compound at the melting point.

Optical Resolution by Preferential Crystallization of (*RS*)-Bromosuccinic Acid. (*RS*)-BSA was optically resolved by preferential crystallization in water at 10 °C. To optimize the conditions, the optical resolution was conducted by stirring aqueous solutions at 113, 126, 140, and 150% supersaturation for 60 min; (*S*)-BSA (0.050 g; ca. 1 wt%) was employed as seed crystals. The yield of the enantiomer (*YE*/g), degree of resolution (*DR*/%) of the obtained (*S*)-BSA, and the amount of crystallization ($AC_{(R)}$ and $AC_{(S)}$/g) were calculated from

$$YE/\mathrm{g} = (Yield/\mathrm{g} \times OP/\%)/100 - 0.050, \tag{5}$$

$$DR/\% = YE/\mathrm{g} \times 100/(1/2)$$
$$(\text{Amount of }(RS)\text{-BSA/g} - 1.980), \tag{6}$$

$$AC_{(R)}/\mathrm{g} = (1/2)\ (Yield/\mathrm{g} - YE/\mathrm{g} - 0.050), \tag{7}$$

$$AC_{(S)}/\mathrm{g} = Yield/\mathrm{g} - AC_{(R)}/\mathrm{g} - 0.050, \tag{8}$$

where *OP* was the optical purity of the obtained (*S*)-BSA and the solubility of (*RS*)-BSA was 1.980 g in 20 cm^3 of water at 10 °C. *Yield* indicates the sum of the amounts of the

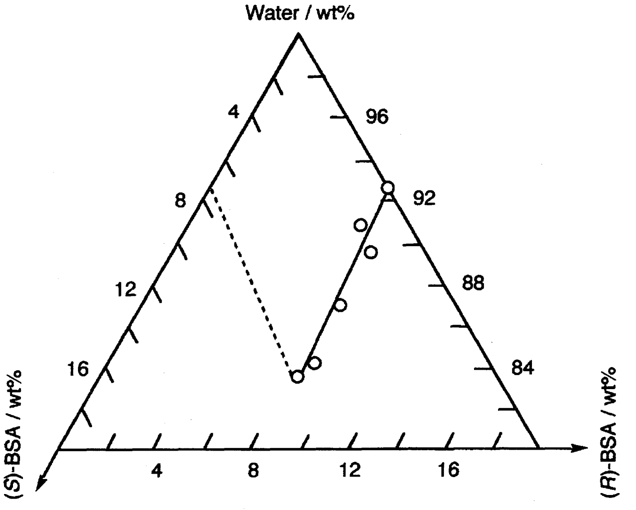

Fig. 2. Ternary solubility diagram of bromosuccinic acid. Conditions: Temperature, 10 °C; solvent, water.

crystallized BSA and seed crystals. The results are shown in Fig. 3.

When the 113 and 126% supersaturated solutions were employed, (*S*)-BSA with an optical purity of over 90% was obtained with 30 and 90% degrees of resolution, respectively. Therefore, (*RS*)-BSA was confirmed to exist as a conglomerate at room temperature. When the solutions with 140 and 150% supersaturation were employed, the optical resolutions gave poor results because of rapid crystallization of the unseeded (*R*)-BSA; (*S*)-BSA of 27 and 10% optical purity was obtained at 31 and 8% degrees of resolution from 140 and 150% supersaturated solutions, respectively. From these results, the optical resolution for the 126% supersaturated solution was determined at resolution times of 20—120 min (Fig. 4). Rapid crystallization of the unseeded (*R*)-BSA was not observed for the first 60 min, but (*R*)-BSA began to crystallize rapidly at 90 min. Based on these results, successive optical resolution was attempted by stirring the 126% supersaturated solution for 60 min (Table 1). The degrees of resolution (*DR*/%) of the obtained (*R*)- and (*S*)-BSA were calculated from

$$DR/\% = YE/\mathrm{g} \times 100/(\text{Operation amount of } (R)\text{- or } (S)\text{-BSA/g} - 1.980), \tag{9}$$

where the operation amount was the amount of (*R*)- or (*S*)-BSA in the solution used in the optical resolution, and those in Runs 2—6 in Table 1 were calculated based on the yields and optical purities of (*R*)- or (*S*)-BSA obtained in Runs 1—5, respectively.

The optical resolution afforded (*R*)- and (*S*)-BSA with optical purities of 81—93% at 50—90% degrees of resolution. Although (*R*)-BSA with 86% optical purity was obtained in Run 2, its amount of crystallization was less than expected. Therefore, the optical resolution in Run 3 was carried out by seeding again with (*R*)-BSA to give (*R*)-BSA of 93% optical purity with 86% degree of resolution. The obtained (*R*)- and (*S*)-BSA were recrystallized from water, as described in the Experimental section, to obtain optically pure (*R*)- and (*S*)-BSA.

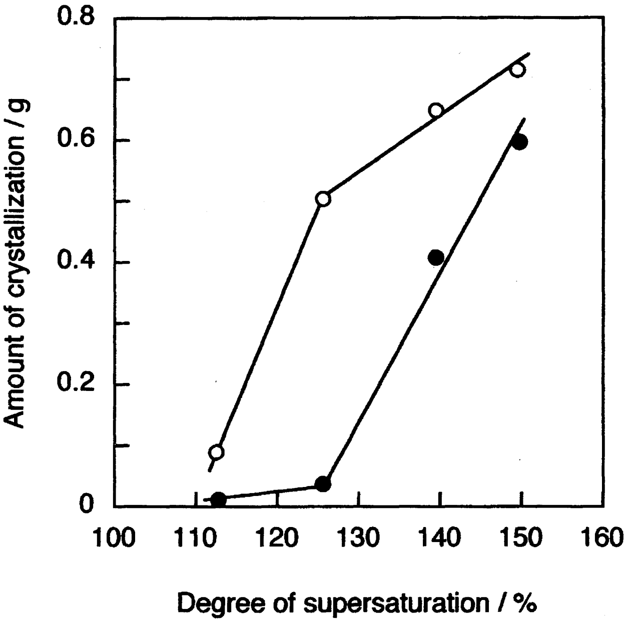

Fig. 3. Relationship between amount of crystallization and degree of supersaturation in optical resolution of (*RS*)-bromosuccinic acid. Conditions: (*RS*)-BSA, 4.475—5.941 g; seed crystals, 0.050 g of (*S*)-BSA; water, 20 cm^3; stirring time, 60 min; temperature, 10 °C. Amount of crystallization: ○ (*S*)-BSA; ● (*R*)-BSA.

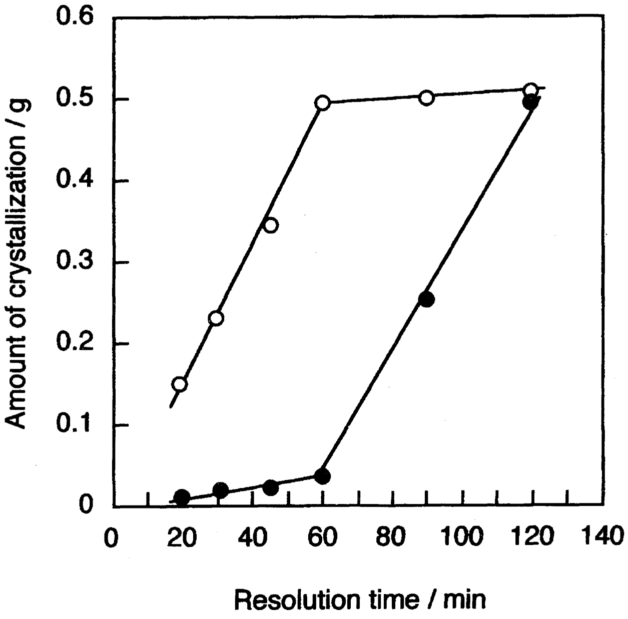

Fig. 4. Relationship between amount of crystallization and resolution time in optical resolution of (*RS*)-bromosuccinic acid. Conditions: (*RS*)-BSA, 4.990 g; seed crystals, 0.050 g of (*S*)-BSA; water, 20 cm^3; temperature, 10 °C. Amount of crystallization: ○ (*S*)-BSA; ● (*R*)-BSA.

Experimental

General. Specific rotation was measured at 589 nm with a Horiba Seisakusho SEPA-200 auto polarimeter equipped with a quartz cell with a 5.00 cm path length. Infrared spectra were obtained in the range of 400—4000 cm^{-1} with a Perkin–Elmer Model 1600 FT-IR spectrometer by the KBr disk method. The refractive indexes were measured with a Shimadzu refractometer Abbe 3L. The melting points were measured with a Yanaco MP-500 D micro melting-point apparatus.

(*RS*)-BSA was purchased from Tokyo Chemical Ind. Co., Ltd. and was recrystallized from water; mp 164 °C. (*S*)-APP was purchased from Tokyo Chemical Ind. Co., Ltd.

Optical Resolution by Diastereomeric Method. (*RS*)-BSA (3.94 g, 20.0 mmol) and (*S*)-App (6.69 g, 40.0 mmol) were dissolved in 50 cm^3 of methanol. The solution was allowed to stand overnight at 20 °C; then, the precipitated (*R*)-BSA·(*S*)-APP salt was collected by filtration, washed with 5 cm^3 of cold methanol, and dried; yield 4.87 g; $[\alpha]_{\mathrm{D}}^{20}$ +36.0° (*c* 1.00, water). Found: C, 48.99; H, 5.92; N, 5.12%. Calcd for $C_{22}H_{31}BrN_2O_8$ with 0.5 H_2O: C, 48.90; H, 5.97; N, 5.18%. The filtrate was evaporated to dryness under reduced pressure at 30 °C to give the (*S*)-BSA·(*S*)-APP salt (5.50 g) as a syrupy residue. The (*R*)-BSA·(*S*)-APP salt (1.29 g) and the (*S*)-BSA·(*S*)-APP salt (1.92 g) were each dissolved in 200 cm^3 of water. The solutions were passed through a 1×45 cm column of Amberlite

Table 1. Successive Optical Resolution by Preferential Crystallization of (*RS*)-Bromosuccinic Acid[a)]

Run	Added amount of (*RS*)-BSA	Operation amount[b)]/g		Resolution time	BSA obtained		
		(*R*)-BSA	(*S*)-BSA	min	*Yield*[c)]	*OP*[d)]	*DR*[e)]
	g				g	%	%
1	4.990	2.495	2.495	60	(*S*) 0.570	90.1	90.1
2	0.520	2.727	2.263	40	(*R*) 0.491	86.2	49.9
3	0.441	2.541	2.450	60	(*R*) 0.576	92.7	86.3
4	0.526	2.299	2.692	40	(*S*) 0.551	90.0	62.6
5	0.500	2.521	2.468	40	(*R*) 0.584	80.9	78.0
6	0.534	2.310	2.679	30	(*S*) 0.658	85.4	73.2

a) Conditions: Water, 20 cm^3; seed crystals, 0.050 g of (*R*)- and (*S*)-BSA; temperature, 10 °C. b) The operation amounts in Runs 2—6 were calculated based on the results in Runs 1—5, respectively. c) *Yield* is the sum of the amounts of the crystallized BSA and seed crystals. d) *OP*: Optical purity. e) *DR*: Degree of resolution.

IR-120B in the H$^+$ form by elution with water. The eluents were evaporated to dryness under reduced pressure at 50 °C to give (*R*)- and (*S*)-BSA as residues. (*R*)-BSA: Yield 0.470 g (89.8%, based on a half amount (1.97 g) of the starting (*RS*)-BSA); $[\alpha]_D^{20}$ +73.0° (*c* 1.00, ethyl acetate). (*S*)-BSA: Yield 0.631 g (91.9%); $[\alpha]_D^{20}$ −61.2° (*c* 1.00, ethyl acetate) (lit,[9)] $[\alpha]_D$ −73.5° (*c* 6.0, ethyl acetate)).

Optical resolution was also carried out using equimolar amounts (20.0 mmol) of (*RS*)-BSA and (*S*)-APP in a manner similar to that described above. (*R*)-BSA: Yield 47.4%; $[\alpha]_D^{20}$ +65.1° (*c* 1.00, ethyl acetate). (*S*)-BSA: Yield 112%; $[\alpha]_D^{20}$ −13.4° (*c* 1.00, ethyl acetate).

The obtained (*R*)- and (*S*)-BSA were recrystallized from water. (*R*)-BSA: Mp 178—179 °C (lit,[10)] 176—180 °C); $[\alpha]_D^{20}$ +73.5° (*c* 1.00, ethyl acetate). Found: C, 24.15; H, 2.47%. Calcd for $C_4H_5BrO_4$: C, 24.33; H, 2.55%. (*S*)-BSA: Mp 178—179 °C (lit 185 °C,[7)] 170—171 °C,[9)] 179 °C[10)]); $[\alpha]_D^{20}$ −73.5° (*c* 1.00, ethyl acetate).

Optical Resolution by Preferential Crystallization. (*RS*)-BSA (4.475, 4.990, 5.545, or 5.941 g) was dissolved in 20 cm^3 of water at 40 °C to prepare solutions with 113, 126, 140, or 150% supersaturation at 10 °C, respectively. The solution was cooled to 10 °C over a period of 30 min and then seeded with 0.050 g of (*S*)-BSA. After stirring the mixture for 20—120 min at 10 °C, the crystallized (*S*)-BSA was collected by filtration and dried.

Successive Optical Resolution by Preferential Crystallization. (*RS*)-BSA (4.990 g) was dissolved in 20 cm^3 of water at 40 °C to prepare a solution with 126% supersaturation at 10 °C. The solution was cooled to 10 °C over a period of 30 min and then seeded with 0.050 g of (*S*)-BSA. After stirring the mixture for 60 min at 10 °C, (*S*)-BSA (0.570 g) was collected by filtration and dried (Run 1 in Table 1). (*RS*)-BSA (0.520 g) was dissolved in the filtrate at 40 °C, and the resulting solution was cooled to 10 °C. After adding (*R*)-BSA (0.050 g) as seed crystals to the solution, followed by stirring the mixture for 40 min at 10 °C, (*R*)-BSA (0.491 g) was collected by filtration and dried (Run 2 in Table 1). Optical resolution was carried out at 10 °C by adding further (*RS*)-BSA to the filtrates in a manner similar to that described above; the detailed conditions are given for Runs 3—6 in Table 1.

Purification. The obtained (*R*)- and (*S*)-BSA were recrystallized from water. For example, (*R*)-BSA (10.2 g) of 82% optical purity and (*S*)-BSA (10.7 g) of 86% optical purity were each dissolved in 10 cm^3 of water at 50 °C. After stirring the solutions for 5 h at 10 °C, the crystallized (*R*)- and (*S*)-BSA were collected by filtration. (*R*)-BSA: Yield 7.90 g; $[\alpha]_D^{20}$ +73.5° (*c* 1.00, ethyl acetate). (*S*)-BSA: Yield 8.67 g; $[\alpha]_D^{20}$ −73.5° (*c* 1.00, ethyl acetate).

Solubility and Phase Diagrams. (*RS*)- or (*R*)-BSA (6.00 g) was dissolved in 20 cm^3 of water at 40 °C. After vigorously stirring the solution at 10 °C, an appropriate portion of the solution was pipetted from the mixture, avoiding contamination of the solid BSA, and the refractive index was measured at 25 °C. The mixture was stirred at 10 °C until the refractive index showed a constant value. The solubility was determined based on the calibration curves prepared previously. Solubility of (*RS*)-BSA at 10 °C: 19.802 g (100 cm^3 water)$^{-1}$. Solubility of (*R*)-BSA at 10 °C: 8.163 g (100 cm^3 water)$^{-1}$.

Preparating a ternary solubility diagram, the solubilities of mixtures of (*RS*)- and (*R*)-BSA were measured at 10 °C similarly to the method described above. After the refractive index reached a constant value, the solid BSA was filtered off, thoroughly dried, and the specific rotation was measured. The amounts of (*R*)- and (*S*)-BSA in the solution were calculated based on the solubility of BSA and the specific rotation of the solid BSA.

In preparation of the binary melting point diagram, the melting points of the mixtures composed of (*RS*)- and (*R*)-BSA were measured; after dissolving (*RS*)- and (*R*)-BSA in an appropriate ratio in acetone, the mixtures were obtained by evaporating the solutions to dryness under reduced pressure. The melting point binary phase diagram was prepared from the temperatures at the beginning and end of melting.

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References

1) J. Jacques, A. Collet, and S. H. Wilen, "Enantiomers, Racemates, and Resolutions," John Wiley & Sons, New York, Chichester, Brisbane, and Toronto (1981), pp. 217—368.

2) E. L. Eliel, S. H. Wilen, and L. N. Mander, "Stereochemistry of Organic Compounds," John Wiley & Sons, New York, Chichester, Brisbane, Toronto, and Singapore (1994), pp. 297—464.

3) C. R. Bayler and N. A. Vaidya, "Chirality in Industry," ed by A. N. Collins, G. N. Sheldrake, and J. Crosby, John Wiley & Sons, New York, Chichester, Brisbane, and Toronto (1994), pp. 69—77.

4) A. Bruggink, B. A. Astleford, L. O. Weigel, and W. M. L. Wood, "Chirality in Industry II," ed by A. N. Collins, G.

N. Sheldrake, and J. Crosby, John Wiley & Sons, New York, Chichester, Brisbane, and Toronto (1997), pp. 81—156.

5) S. H. Wilen, A. Collet, and J. Jacques, *Tetrahedron*, **33**, 2725 (1977).

6) A. Collet, M. J. Brienne, and J. Jacques, *Chem. Rev.*, **80**, 215 (1980).

7) R. A. Volkmann, P. R. Kelbaugh, D. M. Nason, and V. J. Jasys, *J. Org. Chem.*, **57**, 4352 (1992).

8) T. Shiraiwa, H. Yoshida, M. Tsuda, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **60**, 947 (1987).

9) J. A. Lawrence and J. E. Hardwicke, *J. Am. Chem. Soc.*, **74**, 3582 (1952).

10) "Dictionary of Organic Compounds," ed by J. Buckingham and F. Macdonald, Chapman & Hall, London, Glasgow, Weinheim, New York, Tokyo, Melbourne, and Madras (1996), Vol. 2, p. 946.