Optical Resolution by Preferential Crystallization of (RS)-α-Amino-γ-butyrolactone Hydrochloride

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(RS)-α-Amino-γ-butyrolactone hydrochloride [(RS)-ABL·HCl] was found to exist as a conglomerate based on the infrared spectrum, solubility, and melting point. Optical resolution by preferential crystallization of (RS)-ABL·HCl was achieved to yield (R)- and (S)-ABL·HCl. The obtained (R)- and (S)-ABL·HCl were recrystallized, taking into account the solubility of (RS)-ABL·HCl to give optically pure (R)- and (S)-ABL·HCl.

Key words   α-amino-γ-butyrolactone; conglomerate; optical resolution; preferential crystallization

Optically active α-amino-γ-butyrolactone (ABL) is a key compound for syntheses of various biologically active compounds and non-proteinogenic α-amino acids. For example, N-(3-hydroxybutanoyl)-α-amino-γ-butyrolactone, which is obtained by N-acylation of ABL, functions as an inducer of luminescence.[1,2] (S)-ABL hydrobromide yields (S)-2-amino-4-hydroxybutanoic acid [(S)-AHB; L-homoserine] by ring cleavage under basic conditions.[3] (S)-2-Azetidinecarboxylic acid can be synthesized starting with N-tosyl-(S)-ABL.[4] Optically active 2-amino-4-halobutanoic acids, which are obtained by reactions of ABL with hydroiodic acid and hydrogen bromide,[5,6] have been reported to afford α-amino acids with a long alkyl side chain by reaction with alkyl cuprates.[6,7] However, optically active ABL is not readily available. Therefore, N-tert-butoxycarbonyl-(S)-ABL is usually synthesized starting with L-methionine (L-Met) via (S)-(3-amino-3-carboxypropyl)dimethylsulfonium halide and (S)-AHB as the intermediates.[8] (RS)-ABL hydroiodide has also been obtained by ammonolysis of (RS)-2-bromo-4-butanolide [(RS)-BBL].[5] We attempted to obtain optically active ABL by optical resolution, because optical resolution is a rapid and convenient method for obtaining relatively large amounts of enantiomers from racemates.

Preferential crystallization and diastereomeric methods have been satisfactorily employed in the optical resolution of racemates. Racemates exist in the forms of racemic compounds, racemic solid solutions, and conglomerates. Although all racemates can in principle be resolved by the diastereomeric method, this method requires other optically active compounds as resolving agents. For example, (RS)-ABL has been optically resolved using O,O-dibenzoyl-(2S,3S)-tartaric acid as the resolving agent.[9] On the other hand, preferential crystallization is a simpler method for large-scale separation of enantiomers than the diastereomeric method, though this method requires that the racemate exists as a conglomerate whose incidence is much smaller than that of the racemic compound. The optical resolution of (RS)-ABL by preferential crystallization has not been reported. Therefore, the racemic structure of (RS)-ABL hydrochloride [(RS)-ABL·HCl] was examined through studies of the infrared spectrum, solubility, and melting point.[10] Since (RS)-

ABL·HCl was concluded to exist as a conglomerate, optical resolution by preferential crystallization of (RS)-ABL·HCl was attempted to obtain both (R)- and (S)-ABL·HCl.

Results and Discussion

Racemic Structure   First we synthesized (S)-ABL·HCl starting with L-Met by a modification of the literature procedure.[8] However, the (S)-AHB obtained as the intermediate had been undergone partial racemization. Although (S)-ABL·HCl of 69.5% optical purity was obtained from (S)-AHB of 52% optical purity, this (S)-ABL·HCl could be recrystallized from methanol to give optically pure (S)-ABL·HCl. This result suggests that (RS)-ABL·HCl exists as a conglomerate. Therefore, we examined the racemic structure of (RS)-ABL·HCl. (RS)-ABL·HCl decomposed on heating at a lower temperature than (S)-ABL·HCl and is more soluble, as described in the experimental section. In addition, (RS)-ABL·HCl shows an infrared spectrum identical with that of (S)-ABL·HCl. Therefore, (RS)-ABL·HCl is either a racemic solid solution or a conglomerate.[10] The ternary solubility diagram of ABL·HCl shows a simple mixed pattern, namely, that of a conglomerate, as shown in Fig. 1. The above results indicate that (RS)-ABL·HCl exists as a conglomerate.
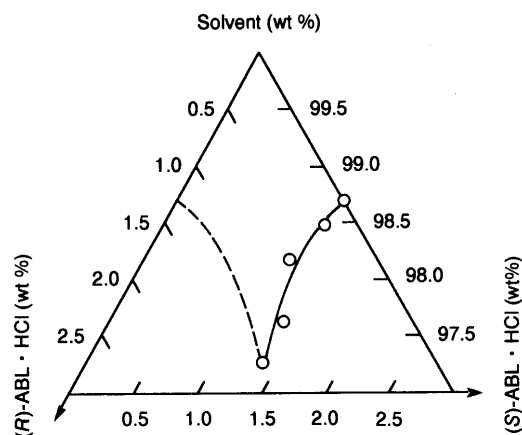

Fig. 1.   Ternary Solubility Diagram of α-Amino-γ-butyrolactone Hydrochloride

Solvent: mixture of ethanol and $5 \, mol \, dm^{-3}$ hydrochloric acid in a volume ratio of 9:1. Temperature: 10 °C.

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Optical Resolution by Preferential Crystallization of (RS)-α-Amino-γ-butyrolactone Hydrochloride To optimize the degree of supersaturation, the optical resolution by preferential crystallization of (RS)-ABL·HCl was conducted by stirring solutions with 120, 130, and 140% degrees of supersaturation for 30 min at 10 °C and employing 0.020 g of (S)-ABL·HCl as seed crystals. The employed solvent was a mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1. The results are shown in Fig. 2.

The amount of crystallization on the seeded (S)-ABL·HCl gradually increased with increasing degree of supersaturation. When the solution with 140% supersaturation was employed, rapid crystallization of the unseeded (R)-ABL·HCl was observed and the obtained (S)-ABL·HCl had 25.5% optical purity. However, optical resolution employing the solution with 130% supersaturation gave (S)-ABL·HCl of 68% optical purity with 33% degree of resolution. Therefore, the solution with 130% degree of supersaturation was stirred for 10—70 min, as shown in Fig. 3.

Figure 3 shows that the amount of crystallization on the seeded (S)-ABL·HCl increased with resolution time and that the unseeded (R)-ABL·HCl began to crystallize

rapidly at 50 min. Therefore, the optical resolution at 40 min gave (S)-ABL·HCl of 71.5% optical purity with the highest degree of resolution (51%). Based on these results, successive optical resolution was attempted to obtain both (R)- and (S)-ABL·HCl. A solution of (RS)-ABL·HCl with 130% supersaturation was employed as the initial solution and was stirred for 40 min. The result is summarized in Table 1.

The successive optical resolution yielded (R)- and (S)-ABL·HCl of 71—88% optical purities with 50—68% degrees of resolution. Although the obtained (R)- and (S)-ABL·HCl did not have very high optical purities, they could be efficiently recrystallized from a mixture of ethanol and hydrochloric acid by taking into account the solubility of (RS)-ABL·HCl, as described in the experimental section. Further, the purified (R)- and (S)-ABL·HCl were transformed into (R)- and (S)-AHB by treatment of their aqueous solutions with triethylamine, respectively. Since the specific rotations of the (R)- and (S)-AHB agreed with the reported values,[11,12] it was confirmed that optically pure (R)- and (S)-ABL·HCl had been obtained.

Experimental

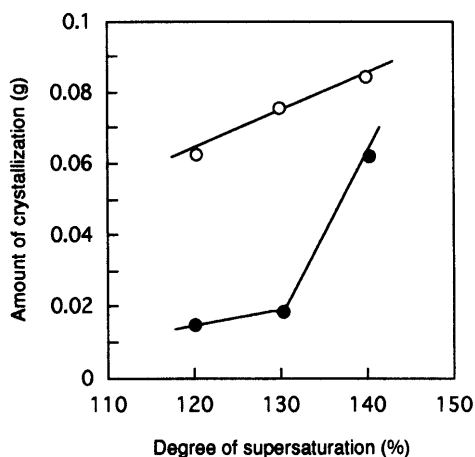Specific rotations were measured at 589 nm with a Horiba Seisakusho

Fig. 2. Relationship between Amount of Crystallization and Degree of Supersaturation in Optical Resolution of (RS)-α-Amino-γ-butyrolactone Hydrochloride

Conditions: (RS)-ABL·HCl 1.380, 1.495, and 1.610 g; seed crystals 0.020 g of (S)-ABL·HCl; solvent 50 cm³ (mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1); stirring time 30 min; temperature 10 °C. Amount of crystallization: O, (S)-ABL·HCl; ●, (R)-ABL·HCl.

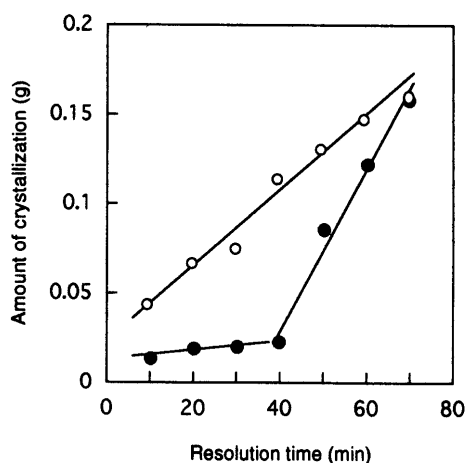
Fig. 3. Relationship between Amount of Crystallization and Resolution Time in Optical Resolution of (RS)-α-Amino-γ-butyrolactone Hydrochloride

Conditions: (RS)-ABL·HCl 1.495 g; seed crystals 0.020 g of (S)-ABL·HCl; solvent 50 cm³ (mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1); temperature 10 °C. Amount of crystallization: O, (S)-ABL·HCl; ●, (R)-ABL·HCl.

Table 1. Successive Optical Resolution by Preferential Crystallization of (RS)-α-Amino-γ-butyrolactone Hydrochloride[a]

Run	Added amount of (RS)-ABL·HCl (g)	Operation amounts of (R)- and (S)-ABL·HCl[b] (g)		ABL·HCl obtained		
		(R)-ABL·HCl	(S)-ABL·HCl	Yield[c] (g)	OP[d] (%)	DR[e] (%)
1	1.495	0.748	0.748	(S) 0.151	71.5	50.9
2	0.131	0.792	0.704	(R) 0.174	83.4	57.9
3	0.154	0.729	0.766	(S) 0.176	85.2	68.1
4	0.156	0.794	0.701	(R) 0.192	80.5	54.3
5	0.164	0.734	0.760	(S) 0.159	87.9	64.9
6	0.139	0.734	0.700	(R) 0.192	80.5	61.6

a) Conditions: seed crystals 0.020 g of (R)- or (S)-ABL·HCl; solvent 50 cm³ (mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1); temperature 10 °C; the optical resolution in runs 1—6 was carried out by stirring for 40 min. b) The operation amounts in runs 2—6 were calculated from the results in runs 1—5. c) The Yield is the sum of the amounts of the crystallized ABL·HCl and seed crystals. d) OP: Optical purity. e) DR: Degree of resolution.

SEPA-200 auto polarimeter equipped with a quartz cell of 5.00 cm path length. Infrared spectra were obtained in the range of 4000—400 cm^{-1} with a Perkin-Elmer Model 1600 FT-IR spectrometer by the KBr disk method. Refractive index values were measured with a Shimadzu refractometer Abbe 3L at 25 °C.

L-Met was purchased from Kokusan Chemical Works, Ltd., and (RS)-BBL from Wako Pure Chemicals Ind. L-Met; $[\alpha]_D^{20}$ +22.4° (c = 1.00, 1 mol dm^{-3} HCl) (lit.[13] $[\alpha]_D^{25}$ +22.5° (1 mol dm^{-3} HCl)).

(RS)-α-Amino-γ-butyrolactone Hydrochloride A solution of 95 wt% (RS)-BBL (34.7 g, 0.20 mol) in 220 cm^3 of 25 wt% aqueous ammonia was allowed to stand in the dark for 2 d at room temperature, then evaporated to dryness under reduced pressure at 60 °C. The oily residue was taken up in 18 cm^3 of concentrated hydrochloric acid, and the solution was refluxed for 30 min (110 °C), then evaporated to dryness under reduced pressure at 60 °C. The crude (RS)-ABL·HCl obtained as the residue was recrystallized from methanol to give pure (RS)-ABL·HCl; yield 16.7 g (60.7%); mp 201—203 °C (dec.) (lit.[14] 203 °C (dec.)). Found: C, 34.76; H, 5.85; N, 10.22. Calcd for C$_4$H$_8$NO$_2$Cl: C, 34.92; H, 5.86; N, 10.18.

(R)- and (S)-α-Amino-γ-butyrolactone Hydrochloride A solution of L-Met (20.0 g, 0.134 mol) and iodomethane (28.2 g, 0.199 mol) in 360 cm^3 of water was stirred for 24 h at room temperature, to afford a clear solution, to which sodium hydrogencarbonate (11.3 g, 0.134 mol) was added. The solution was refluxed for 20 h, then evaporated to dryness under reduced pressure at 60 °C. The crude (S)-AHB obtained as the residue was washed thoroughly with methanol; yield 15.1 g; mp 170—182 °C (dec.); $[\alpha]_D^{20}$ −6.14° (c = 1.00, water). The (S)-AHB (13.7 g) was dissolved in 25 cm^3 of water at 70 °C, then 50 cm^3 of methanol was added, and the mixture was allowed to stand overnight at 5 °C. The precipitated (S)-AHB was collected by filtration, washed with methanol, and dried; yield 7.04 g; mp 175—180 °C (dec.); $[\alpha]_D^{20}$ −6.14° (c = 1.00, water). Methanol (25 cm^3) was added to the filtrate, and the mixture was allowed to stand overnight at 5 °C to precipitate further (S)-AHB; yield 2.02 g (12.7% based on the starting L-Met); mp 195—198 °C (lit.[15] 203 °C (dec.)); $[\alpha]_D^{20}$ −8.49° (c = 1.00, water) (lit. $[\alpha]_D^{25}$ −8.8° (c = 5, water)[11,12]; $[\alpha]_D^{23}$ −8.0° (c = 1.00, water)).[15]

A solution of (S)-AHB (29.8 g, 0.250 mol) of 52% optical purity in 22 cm^3 of concentrated hydrochloric acid was refluxed for 1 h. The solution was evaporated to dryness under reduced pressure at 60 °C, then the residue was taken up in 150 cm^3 of ethanol. The mixture was stirred for 1 h at room temperature to precipitate (S)-ABL·HCl. (S)-ABL·HCl was collected by filtration, and the filtrate was evaporated to dryness under reduced pressure at 60 °C to give further (S)-ABL·HCl. The crude (S)-ABL·HCl obtained was combined; yield 22.6 g; $[\alpha]_D^{20}$ −18.9° (c = 1.00, water). This product (15.3 g) was recrystallized from 170 cm^3 of methanol to give (S)-ABL·HCl of 100% optical purity; yield 9.3 g (39.9% based on (S)-AHB); mp 226—228 °C (dec.) (lit.[9] 228 °C (dec.)); $[\alpha]_D^{20}$ −27.2° (c = 1.00, water) (lit.[11] $[\alpha]_D^{26}$ −27.0° (water)). Found: C, 34.70; H, 5.79; N, 10.16.

(R)-ABL·HCl that was partially resolved was obtained from the filtrate after crystallization of (S)-ABL·HCl in the optical resolution. The (R)-ABL·HCl was recrystallized from a mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1; mp 227—229 °C (dec.); $[\alpha]_D^{20}$ +27.2° (c = 1.00, water). Found: C, 34.66; H, 5.83; N, 10.07.

(R)- and (S)-2-Amino-4-hydroxybutanoic Acids The (R)- or (S)-ABL·HCl (1.38 g, 10.0 mmol) obtained by the optical resolution was dissolved in 5 cm^3 of water. Triethylamine (2.02 g, 20.0 mmol) was added to the solution, and the mixture was stirred for 2 h at room temperature, then evaporated to dryness under reduced pressure at 50 °C. The residue was washed by stirring in 30 cm^3 of ethanol for 2 h at room temperature and the suspension was filtered to give (R)- or (S)-AHB. (S)-AHB: Yield 0.977 g (82.1%); mp 202—204 °C (dec.); $[\alpha]_D^{20}$ −8.81° (c = 1.00, water). Found: C, 40.41; H, 7.58; N, 11.77. Calcd for C$_4$H$_9$NO$_3$: C, 40.33; H, 7.62; N, 11.76. (R)-AHB: Yield 0.946 g (79.5%); mp 202—204 °C (dec.); $[\alpha]_D^{20}$ +8.81° (c = 1.00, water). Found: C, 40.42; H, 7.56; N, 11.77.

Optical Resolution by Preferential Crystallization (RS)-ABL·HCl (1.380, 1.495, or 1.610 g) was dissolved in 50 cm^3 of a mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1 at 40 °C. The solution was gradually cooled to 10 °C, (S)-ABL·HCl (0.020 g) was added as seed crystals, and the mixture was stirred for 10—70 min at 10 °C. The crystallized (S)-ABL·HCl was collected by filtration and dried. The optical purity [OP (%)] was calculated on the basis of the specific rotation of (S)-ABL·HCl; $[\alpha]_D^{20}$ −27.2° (c = 1.00, water). The

yield of enantiomer [YE (g)], degree of resolution [DR (%)] of the obtained (S)-ABL·HCl and the amount of crystallization [$AC_{(R)}$ and $AC_{(S)}$ (g)] were calculated from the following equations:

$$YE(g) = [Yield(g) \times OP(\%)]/100 - 0.020 ,$$

$$DR(\%) = YE(g) \times 100/(1/2)[\text{amount of } (RS)\text{-}ABL \cdot HCl(g) - 1.150] ,$$

$$AC_{(R)}(g) = (1/2)[Yield(g) - YE(g) - 0.020] ,$$

$$AC_{(S)}(g) = Yield(g) - AC_{(R)}(g) - 0.020 ,$$

where 0.020 g of (S)-ABL·HCl was employed as seed crystals and the Yield equals the sum of the seed crystals and the crystallized (R)- and (S)-ABL·HCl; solubility of (RS)-ABL·HCl in 50 cm^3 of the mixture of ethanol and hydrochloric acid at 10 °C was 1.150 g.

Successive Optical Resolution by Preferential Crystallization (RS)-ABL·HCl (1.495 g) was dissolved in 50 cm^3 of a mixture of ethanol and hydrochloric acid at 40 °C. The solution was gradually cooled to 10 °C, (S)-ABL·HCl (0.020 g) was added as seed crystals, and the mixture was stirred for 40 min at 10 °C. The crystallized (S)-ABL·HCl was collected by filtration and dried. (RS)-ABL·HCl (0.131 g) was dissolved in the filtrate at 40 °C, and the solution was gradually cooled to 10 °C. (R)-ABL·HCl (0.020 g) was added, and the mixture was stirred for 40 min. The crystallized (R)-ABL·HCl was collected by filtration, washed with a small amount of cold ethanol, and dried. The filtrate was treated in the manner described above to obtain successively (S)- and (R)-ABL·HCl. The degrees of resolution [DR (%)] of the obtained (S)- and (R)-ABL·HCl were calculated from

$$DR(\%) = YE(g) \times 100/[\text{operation amount of } (S)\text{- or}$$
$$(R)\text{-}ABL \cdot HCl(g) - 0.575] ,$$

where the operation amount is the amount of (R)- or (S)-ABL·HCl 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 the (R)- or (S)-ABL·HCl obtained in runs 1—5, respectively.

The (R)- and (S)-ABL·HCl obtained by the optical resolution were recrystallized, taking into consideration the solubility of (RS)-ABL·HCl in a mixture of ethanol and 5 mol dm^{-3} hydrochloric acid. For example, a mixture of ethanol and hydrochloric acid (8 cm^3) was added to 0.997 g of (R)-ABL·HCl of 84% optical purity. The mixture was stirred for 3 h at 10 °C, then the purified (R)-ABL·HCl was collected by filtration and dried; yield 0.801 g; mp 227—229 °C; $[\alpha]_D^{20}$ +27.2° (c = 1.00, water).

(S)-ABL·HCl of 85% optical purity (1.20 g) was purified in 9 cm^3 of a mixture of ethanol and hydrochloric acid; yield 0.950 g; mp 226—228 °C; $[\alpha]_D^{20}$ −27.2° (c = 1.00, water).

Solubility and Ternary Solubility Diagram (RS)-ABL·HCl (0.598 g) or (S)-ABL·HCl (0.298 g) was dissolved in 20 cm^3 of a mixture of ethanol and 5 mol dm^{-3} hydrochloric acid in a volume ratio of 9:1 at 40 °C. The solution was vigorously stirred at 10 °C, then appropriate portion of the solution was pipetted from the mixture, avoiding contamination with solid ABL·HCl, and the refractive index was measured at 25 °C. The mixture was stirred at 10 °C until the refractive index reached a constant value. The solubility was determined on the basis of the calibration curves prepared previously. Solubility of (RS)-ABL·HCl at 10 °C: 2.300 g (100 cm^3 solvent)$^{-1}$. Solubility of (S)-ABL·HCl at 10 °C: 1.169 g (100 cm^3 solvent)$^{-1}$.

To obtain the ternary solubility diagram of ABL·HCl in a mixture of ethanol and hydrochloric acid, the solubilities of mixtures of (RS)- and (S)-ABL·HCl were measured at 10 °C, as described above. After the refractive index value of each solution had become constant, the solid ABL·HCl was removed by filtration and thoroughly dried, and its specific rotation was measured. The amounts of (R)- and (S)-ABL·HCl in the solution were calculated on the basis of the solubility of ABL·HCl and the specific rotation of the solid ABL·HCl.

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