

Racemic Structure and Optical Resolution by Preferential Crystallization of DL-Cysteine Salts of Substituted Benzenesulfonic Acids

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Infrared absorption spectrum, solubility, and thermodynamic analysis indicated that DL-cysteine salts of benzenesulfonic acid (DL-BA salt) and 4-ethylbenzenesulfonic acid (DL-4-EB salt) are conglomerates at room temperature, but DL-BA salt forms a racemic compound at the melting point. These DL-salts were optically resolved by the preferential crystallization. As for DL-4-EB salt, suitable conditions were estimated by the free energy of critical nucleation in supersaturated solutions. The successive preferential crystallization in ethanol at 20 °C was found to give D- and L-4-EB salts with optical purity of 97—100% in the resolution yield of 83—90%. Purification and following treatment with triethylamine gave optically pure D- and L-Cys's.

L-Cysteine (abbreviated as L-Cys) is a useful material for medicines, food additives, and cosmetics, and D-Cys is also noted to be useful for medicines.¹⁾ Since L-Cys has been obtained from hair, optical resolution by preferential crystallization of DL-Cys has been reported only for DL-cysteine hydrochloride monohydrate¹⁾ and DL-4-thiazolidinecarboxylic acid.^{2,3)} This paper describes a possibility of optical resolution by the preferential crystallization of DL-cysteine salts of substituted benzenesulfonic acids. These DL-salts include benzenesulfonate (DL-BA salt), 4-methylbenzenesulfonate (DL-4-MB salt), 4-ethylbenzenesulfonate (DL-4-EB salt), 3-aminobenzenesulfonate, 4-amino-3-methylbenzenesulfonate, and 2-hydroxy-5-sulfobenzoate.

Since only DL-BA salt has the melting point, its racemic structure was examined by the thermodynamic analysis.^{4,5)} As for other DL-salts that decompose on heating, the racemic structures were estimated by comparing infrared absorption spectra or solubility values of the DL-salts with those of the corresponding L-salts. The DL-BA and -4-EB salts seemed to be conglomerate at room temperature, but DL-BA salt appeared to form a racemic compound at the melting point. These DL-salts were subjected to optical resolution by preferential crystallization. As for DL-4-EB salt, suitable conditions were examined by the free energy of critical nucleation in supersaturated solutions,^{3,6-8)} and the successive preferential crystallization was tried in ethanol at 20 °C.

Experimental

Materials. DL- and L-Cysteines were purchased from Sigma Chemicals Co. and Wako Pure Chemicals Ind., respectively, and substituted benzenesulfonic acids and triethylamine from Wako Pure Chemicals Ind. and Kanto Chemical Co. Ltd., respectively.

Preparation of Salts. A mixture of 0.005 mol of DL- or L-Cys and equimolar substituted benzenesulfonic acid in 15 cm³ of methanol was stirred for 30 min at 40 °C. After addition of 30 cm³ of diethyl ether, the solution was stirred

for 30 min in an ice bath. The salt formed was filtered and recrystallized from ethanol. In the cases of DL- and L-BA salts, the initial mixture was allowed to stand for 1 d at 5 °C, and the salts formed were recrystallized from 1-propanol.

DL-BA salt: Mp 179 °C; Found: C, 38.62; H, 4.66; N, 5.04% (Calcd for C₆H₁₃O₅NS₂: C, 38.70; H, 4.69; N, 5.01%). L-BA salt: Mp 205 °C; Found: C, 38.63; H, 4.69; N, 5.03%; [α]_D²⁰ +9.23° (c 1.00, 5 mol dm⁻³ HCl).

DL-4-MB salt: Mp 212—215 °C (decomp); Found: C, 40.76; H, 5.10; N, 4.66% (Calcd for C₁₀H₁₅O₅NS₂: C, 40.94; H, 5.15; N, 4.77%). L-4-MB salt: Mp 225—227 °C (decomp); Found: C, 40.91; H, 5.11; N, 4.74%; [α]_D²⁰ +8.08° (c 1.00, 5 mol dm⁻³ HCl).

DL-4-EB salt: Mp 176—179 °C (decomp); Found: C, 42.83; H, 5.58; N, 4.59% (Calcd for C₁₁H₁₇O₅NS₂: C, 42.98; H, 5.58; N, 4.59%). L-4-EB salt: Mp 199—200 °C (decomp); Found: C, 42.87; H, 5.56; N, 4.55%; [α]_D²⁰ +7.15° (c 1.00, 5 mol dm⁻³ HCl).

D-4-EB salt with 89% optical purity was obtained from the mother liquor in the optical resolution of the corresponding DL-salt. After refluxing a mixture of 1.76 g of the D-salt and 5 cm³ of ethanol for 20 min, the mixture was stirred for 30 min at 20 °C. The precipitated salt was collected by filtration to give optically pure D-salt in 1.43 g yield; mp 199—201 °C (decomp); [α]_D²⁰ -7.15° (c 1.00, 5 mol dm⁻³ HCl).

Table 1. Preparation of Supersaturated Solutions

DL-Salt	Solvent ^{a)}	Degree of supersaturation ^{b)}	Mass of DL-salt
		%	g
BA ^{c)}	Ethanol	118	8.485
	1-Propanol	149	2.887
	1-Butanol	215	1.534
4-EB ^{d)}	Ethanol	143	3.084
		153	3.299
		160	3.450
		165	3.558
		170	3.666
		188	4.054

a) Solvent: 50 cm³. b) Temperature: 20 °C. c) BA: Benzenesulfonate. d) 4-EB: 4-Ethylbenzenesulfonate.

Optical Resolution. Preferential Crystallization: DL-BA or -4-EB salt was dissolved in 50 cm³ of ethanol, 1-propanol, or 1-butanol at 40 °C to give racemic solutions with the degree of supersaturation of 118–215% at 20 °C; results of preparation of these supersaturated solutions were summarized in Table 1. The solution was slowly cooled to 20 °C and seeded with 0.050 g of the L-salt. After the solution was stirred at 120 rpm by a 1.5 cm×4.0 cm stirrer at 20 °C, the precipitated salt was collected by filtration, washed with diethyl ether, and dried. The optical purity, yield of optically pure modification (YOPM), and degree of resolution of the L-salt were determined by the equations described in a previous paper.⁹⁾

Successive Preferential Crystallization: The DL-4-EB salt (3.450 g) was dissolved in 50 cm³ of ethanol at 40 °C. After cooling to 20 °C, the solution was seeded with 0.050 g of the L-salt and stirred for 62 min at 120 rpm and 20 °C. The precipitated salt was collected by filtration, and 0.465 g of the DL-4-EB salt was dissolved in the filtrate at 40 °C. After being seeded with 0.050 g of D-salt at 20 °C, the procedure was followed in a similar way. The optical resolution was performed for the initial solution containing 3.450 g of the DL-4-EB salt and 0.100 g of the L-salt in the same manner as in the single-step resolution. The degree of resolution of the D- and L-4-EB salts was calculated by

$$\text{Degree of resolution/\%} = [\text{YOPM} \times 100/\text{g}] / [(\text{Operation amount of D- or L-salt/g}) - 1.078].$$

Preparation of Optically Active Cysteine. Optically pure D- or L-4-EB salt (1.363 g) was dissolved in 25 cm³ of methanol. After the solution was adjusted at pH 5–6 with triethylamine and stirred for 30 min in an ice bath, the precipitated Cys was collected by filtration to give about 0.51 g each of optically pure D- and L-Cys's. D-Cys: $[\alpha]_D^{20} +16.5^\circ$ (c 1.00, water). L-Cys: $[\alpha]_D^{20} -16.5^\circ$ (c 1.00, water) (lit.¹⁰⁾ $[\alpha]_D^{20} -16.5^\circ$ (water)).

Measurements. The specific rotation was measured by a Union Giken PM-101 digital polarimeter with a quartz cell of 1.0 dm path length. Infrared spectra were obtained in the range 4000–400 cm⁻¹ by a JASCO A-102 infrared spectrophotometer by the KBr disk method. The enthalpy of fusion was determined by a Rigaku Denki differential scanning calorimeter DSC-8230.

The mixture of the DL- or L-salt (BA, 4-MB, and 4-EB salts) and solvent (ethanol, 1-propanol, and 1-butanol for the BA salt; ethanol for the 4-MB and 4-EB salts) was stirred at 20 °C, in the presence of the solid salt. A constant volume of the solution was withdrawn from the mixture, avoiding contamination of the solid salt, diluted in an appropriate concentration, and the absorbance was measured at 263 nm

by a Shimadzu double-beam spectrophotometer UV-150-02 with a quartz cell of 0.1 dm path length. After stirring the mixture until the absorbance showed a constant value, the solubility was determined on the basis of the absorbance calibration curves prepared previously.

Results and Discussion

Racemic Structure. In the salts that decompose on heating, infrared spectra of the DL-salts were compared with those of the corresponding L-salt. DL-4-MB and -4-EB salts showed infrared spectra identical with those of L-salts. The solubility of DL-4-EB salt was 2.21 times as large as that of the L-salt. However, the solubility of DL- and L-4-MB salts was approximately equal to each other, as listed in Table 2; the value of α is 1.19 (α =solubility of DL-salt/solubility of L-salt). DL-4-EB salt was optically resolved by preferential crystallization, as will be described in a later section, whereas DL-4-MB salt was unable to resolve by this procedure.

The above results suggest that the DL-4-EB salt is a conglomerate at room temperature, and that the DL-4-MB salt forms a racemic solid solution.^{11–14)}

Other DL-salts form racemic compounds because their infrared spectra are different from those of the corresponding L-salts.¹¹⁾

Racemic Structure of DL-Benzenesulfonate. Only the DL- and L-BA salts show melting points. The mole fraction of the L-salt at the eutectic point was calculated to be 0.61 from the melting point and the

Table 2. Solubility of Cysteine Salt of Substituted Benzenesulfonic Acids^{a)}

Salt	Solvent	Solubility/g/(100 cm ³ solvent)		
		DL-Salt	L-Salt	$\alpha^b)$
BA ^{c)}	Ethanol	14.381	9.305	1.55
	1-Propanol	3.875	2.725	1.42
	1-Butanol	1.427	0.980	1.46
4-MB ^{d)}	Ethanol	2.296	1.932	1.19
4-EB ^{c)}	Ethanol	4.313	1.952	2.21

a) Temperature: 20 °C. b) α =solubility of DL-salt/solubility of L-salt. c) See notes in Table 1. d) 4-MB: 4-Methylbenzenesulfonate.

Table 3. Thermodynamic Data of Cysteine Salt of Benzenesulfonic Acid

Salt	Mp θ_m/K	ΔH^f a) kJ mol^{-1}	ΔG_f° b)/kJ mol ⁻¹		Eutectic point		
			ΔG_{400}°	ΔG_{293}°	Mole fraction ^{c)}	Temperature/K Found	Calcd ^{e)}
DL-BA ^{d)}	452	31.8	-0.91	+0.12	0.61	451	451
L-BA ^{d)}	478	33.9	—	—			

a) ΔH^f : Enthalpy of fusion. b) ΔG_f° : Gibbs energy of formation of racemate at T K. The ΔG_f° 's at the melting point (ΔG_{400}°) and at 293 K (ΔG_{293}°) were calculated from the equations in Refs. 4 and 5. c) These values were calculated from the Schröder-Van Laar and Prigogine-Defay equations. d) See note in Table 1.

enthalpy of fusion (ΔH_f),⁴⁾ and the observed melting point of mixture with the composition agreed with the calculated eutectic temperature (451 K);⁴⁾ these values are listed in Table 3 and the binary melting point diagram is shown in Fig. 1. These results indicated that DL-BA salt forms a racemic compound at the melting point.⁴⁾

The Gibbs energy of formation of the racemate from its antipode at melting point ($\Delta G_{452}^F/\text{kJ mol}^{-1}$) and 293 K (ΔG_{293}^F) was calculated from the melting temperature and ΔH_f ,^{4,5)} and listed in Table 3. The negative ΔG_{452}^F value supports the above result. However, the positive ΔG_{293}^F suggests that DL-BA salt does not form a racemic compound at 293 K, although the absolute value is small (+0.12 kJ mol⁻¹). The DL-BA salt shows infrared spectrum identical with that of the L-salt and is more soluble than the L-salt, as listed in Table 2; the values of α are 1.42–1.55 in ethanol, 1-propanol, and 1-butanol.^{11–14)}

The above results indicate that DL-BA salt is a conglomerate at room temperature though the DL-salt forms a racemic compound at the melting point.

Preferential Crystallization. Optical resolution of the DL-BA and -4-EB salts was attempted by

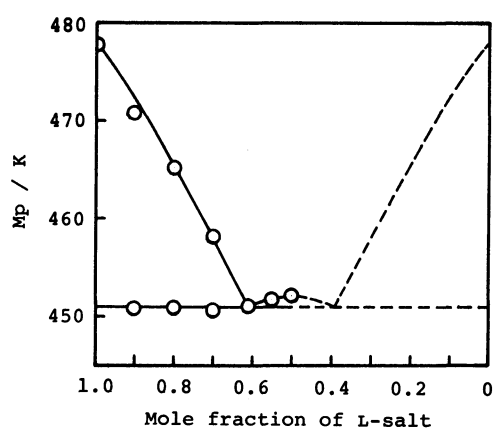


Fig. 1. Binary melting point diagram of cysteine salt of benzenesulfonic acid.

preferential crystallization at 20 °C with the L-salt as seed crystals, and the results are given in Tables 4 and 5, respectively.

Since it was possible to resolve these DL-salts by preferential crystallization, it was confirmed that the DL-BA and -4-EB salts are conglomerates at room temperature. Although the L-BA salt with approximately 90% optical purity is obtained from 1-propanol and 1-butanol solutions, the yield of optically pure modification (about 0.05 g) and degree of resolution (about 12%) are extremely low. The small absolute value of ΔG_{293}^F of DL-BA salt may be the reason why the optical resolution by preferential crystallization is poor.

On the other hand, the optical resolution of the DL-4-EB salt gave better result than that of the DL-BA salt. This result indicates that the use of the DL-4-EB salt is more favorable for obtaining optically pure Cys in a high yield.

Estimation of Suitable Conditions for Optical Resolution. Relationship between Factors for Crystallization and Free Energy of Critical Nucleation: Suitable conditions for optical resolution of the DL-4-EB salt were estimated by free energy of critical nucleation ($\Delta g_{\max}/\text{J nucleus}^{-1}$) and factors of crystallization of the D- and L-salts for different degrees of supersaturation of 143, 153, and 188%;^{3,8)} the values of $\Delta g_{\max}$ were calculated by the equations described in the previous papers.^{8,15)} The amounts of crystallization of the D- and L-salts were calculated from the data in Table 5.¹⁶⁾ The relationship between the amount of crystallization and resolution time is shown in Fig. 2. The speed of crystallization of the L-salt ($R_L/\text{g min}^{-1}$) was calculated from linear plots of Fig. 2; the straight lines had the correlation coefficient of 0.97–0.99. The retardation time for crystallization of the D-salt (θ_D/min) was defined as the time that elapsed before the D-4-EB salt begins to crystallize rapidly and was estimated from Fig. 2. The values of $\Delta g_{\max}$, R_L , and θ_D are listed in Table 6.

Table 4. Preferential Crystallization of DL-Cysteine Salt of Benzenesulfonic Acid^{a)}

Solvent	Degree of supersaturation %	Resolution time min	Yield g	Optical purity %	YOPM ^{b)} g	Degree of resolution %
Ethanol	118	5	0.256	32.7	0.034	5.3
		20	1.281	5.4	0.020	3.1
1-Propanol	149	10	0.120	87.6	0.055	11.6
		20	0.479	30.8	0.098	20.7
1-Butanol	215	10	0.109	93.3	0.052	12.7
		20	0.161	82.5	0.083	20.2
		30	0.195	60.6	0.068	16.6
		40	0.286	34.0	0.047	11.5

a) Solvent: 50 cm³. Seed crystals: 0.050 g of L-salt. Temperature: 20 °C. b) YOPM: Yield of optically pure modification.

Table 5. Preferential Crystallization of DL-Cysteine Salt of 4-Ethylbenzenesulfonic Acid^{a)}

Degree of supersaturation %	Resolution time min	Yield g	Optical purity %	YOPM ^{b)} g	Degree of resolution %
143	30	0.074	100	0.024	5.2
	90	0.241	100	0.191	41.2
	120	0.270	100	0.220	47.4
	150	0.393	100	0.343	73.9
	170	0.426	95.8	0.358	77.2
	180	0.467	88.9	0.365	78.8
	190	0.582	59.8	0.298	64.2
	210	0.730	41.8	0.255	55.0
153	60	0.319	99.0	0.266	46.6
	90	0.477	100	0.427	74.8
	100	0.560	83.6	0.418	73.2
	110	0.589	76.5	0.401	70.2
	120	0.882	31.9	0.231	40.5
160	62	0.515	98.2	0.456	70.5
	70	0.601	82.7	0.447	69.1
165	50	0.524	92.5	0.435	62.1
	60	0.656	77.0	0.455	64.9
170	40	0.485	96.1	0.416	55.1
	50	0.684	71.2	0.437	57.9
188	5	0.111	100	0.061	6.4
	15	0.245	92.2	0.176	18.5
	18	0.325	94.2	0.256	27.0
	20	0.412	91.7	0.328	34.6
	25	0.653	79.2	0.467	49.2
	35	1.241	12.5	0.105	11.1

a) Solvent: 50 cm³ of ethanol. Seed crystals: 0.050 g of L-salt. Temperature: 20 °C. b) YOPM: See note in Table 4.

The relationship between R_L and $\Delta g_{\max}$ for the degree of supersaturation of 143, 153, and 188% and that between θ_D and $\Delta g_{\max}$ are then obtained as

$$\ln R_L = -1.660 \ln \Delta g_{\max} - 70.92, \quad (1)$$

$$\ln \theta_D = 1.526 \ln \Delta g_{\max} + 64.76, \quad (2)$$

where the correlation coefficients are higher than 0.999.

Suitable Conditions for Optical Resolution: The optical resolution at θ_D-5 min seems to be a better criterion for evaluating the results of optical resolution than that at θ_D min, because the unseeded D-salt begins to crystallize rapidly after θ_D min. The amount of crystallization of L-salt at θ_D-5 min ($W_{(-5)}^c/g=R_L(\theta_D-5)$) is derived from Eqs. 1 and 2 and expressed by

$$W_{(-5)}^c = 2.120 \times 10^{-3} \Delta g_{\max}^{-0.1344} - 7.950 \times 10^{-31} \Delta g_{\max}^{-1.660}. \quad (3)$$

Since the values of R_L for the degree of supersaturation of 143, 153, and 188% are calculated by the least-squares method from linear plots in Fig. 2,

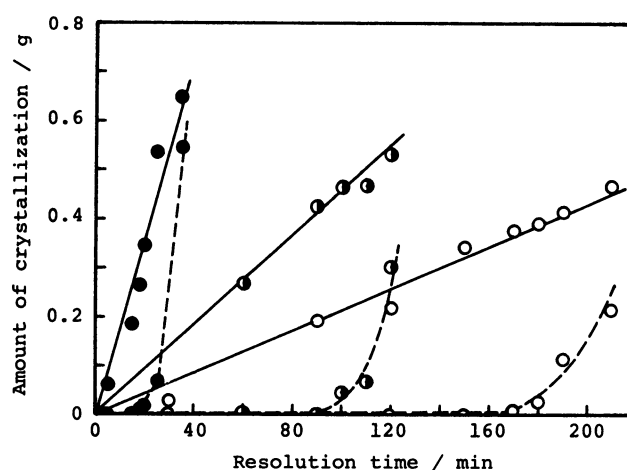


Fig. 2. Relationship between amounts of crystallization of D- and L-cysteine salts of 4-ethylbenzenesulfonic acid and resolution time.

Conditions: Solvent 50 cm³ of ethanol; seed crystals 0.050 g of L-salt; temperature 20 °C. Degree of supersaturation: ○ 143%; ● 153%; ● 188%. —: L-Salt. - - -: D-Salt.

Table 6. Free Energy of Critical Nucleation and Factors for Preferential Crystallization of Cysteine Salt of 4-Ethylbenzenesulfonic Acid^{a)}

Degree of supersaturation %	$\Delta g_{\max}^b)$ $\times 10^{-18} \text{ J nucleus}^{-1}$	$R_L^c)$ $\times 10^{-3} \text{ g min}^{-1}$	$\theta_D^d)$ min	$W_{(-5)}^e)/g$		
				Found	Calcd I ^{f)}	Calcd II ^{g)}
143	10.95	2.387	175	0.367	0.391	0.361
153	7.393	4.242	95	0.427	0.402	0.430
160	5.868	6.512 ^{h)}	66	0.461	0.405	0.449
165	5.059	8.331 ^{h)}	55	0.455	0.405	0.447
170	4.412	10.46 ^{h)}	45	0.426	0.403	0.433
188	2.901	21.25	23	0.266	0.377	0.269

a) Conditions of crystallization: Solvent 50 cm³ of ethanol; seed crystals 0.050 g of L-salt; temperature 20 °C.

b) $\Delta g_{\max}$: Free energy of critical nucleation at 20 °C in ethanol. c) R_L : Speed of crystallization of L-salt. d)

θ_D : Retardation time for crystallization of D-salt. e) $W_{(-5)}$: Amount of crystallization of L-salt at $\theta_D - 5$ min. f)

These values of $W_{(-5)}$ were calculated from Eq. 3. g) These values of $W_{(-5)}$ were calculated from Eq. 5. h)

These values of R_L were calculated from Eq. 1.

the straight lines obtained do not always pass through the origin. Therefore, the calculated values of $W_{(-5)}$ from Eq. 3 show relatively large deviation from experimental values at $\theta_D - 5$ min ($W_{(-5)}/g$); the values of $W_{(-5)}$ are listed under "Calcd I" in Table 6 and those of $W_{(-5)}$ are also listed under "Found" in Table 6. On the other hand, the linear relationship between $W_{(-5)}$ and $W_{(-5)}$ for the degree of supersaturation of 143, 153, and 188% is expressed by

$$W_{(-5)} = 6.249W_{(-5)} - 2.084, \quad (4)$$

where the correlation coefficient is 0.998. Eliminating $W_{(-5)}$ in Eqs. 3 and 4, we have

$$W_{(-5)} = 1.325 \times 10^{-2} \Delta g_{\max}^{-0.1344} - 4.969 \times 10^{-30} \Delta g_{\max}^{-1.660} - 2.084. \quad (5)$$

In order to test Eq. 5, the values of $W_{(-5)}$ for the degree of supersaturation of 160, 165, and 170% calculated from Eq. 5 are listed in Table 6 as Calcd II. The optical resolution for these degrees of supersaturation was carried out at the resolution time approximately equal to the calculated value of $\theta_D - 5$ from Eq. 2. The resulting data are listed in Table 5. The amounts of crystallization of the L-salt obtained from the data agree well with the calculated values of $W_{(-5)}$ from Eq. 5, as shown in Table 6. The values of $W_{(-5)}$ for other degree of supersaturation were also calculated from Eq. 5, and the relationship between $W_{(-5)}$ and degree of supersaturation is shown in Fig. 3.

Figure 3 suggests that the maximum amount of the L-4-EB salt with high optical purity can be obtained with degree of supersaturation of 160–165%. When $W_{(-5)}$ in Eq. 5 or $W_{(-5)}$ in Eq. 4 is differentiated with respect to $\Delta g_{\max}$ and the differential coefficient is put equal to zero, the value of $\Delta g_{\max}$ that gives the maximum $W_{(-5)}$ or $W_{(-5)}$ was calculated to be $5.55 \times 10^{-18} \text{ J nucleus}^{-1}$. This value is approximately equal to the value for an ethanol solution with 160% degree of supersaturation ($5.87 \times 10^{-18} \text{ J nucleus}^{-1}$); the

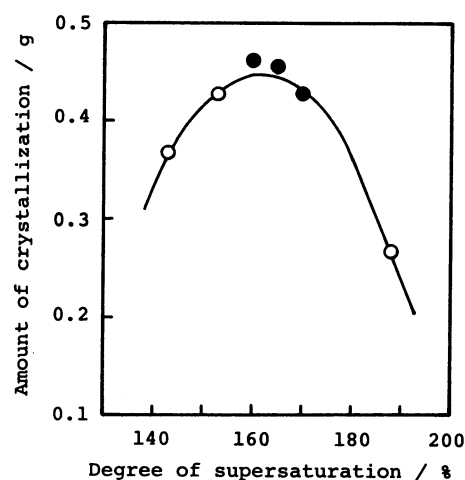


Fig. 3. Crystallization of L-cysteine salt of 4-ethylbenzenesulfonic acid at $\theta_D - 5$ min.

Conditions: Solvent 50 cm³ of ethanol; seed crystals 0.050 g of L-salt; temperature 20 °C. —: Calculated amount of crystallization of L-salt at $\theta_D - 5$ min from the data for degree of supersaturation of 143, 153, and 188% (O). ●: Experimental amount for degree of supersaturation of 160, 165, and 170%.

value of $\Delta g_{\max}$ for 165% degree of supersaturation is $5.06 \times 10^{-18} \text{ J nucleus}^{-1}$.

The above result suggests that the optical resolution with 160% degree of supersaturation at resolution time of 62 min is the most favorable for obtaining the L-4-EB salt with high optical purity in high yield; θ_D calculated from Eq. 2 is 67 min. The results in Table 5 indicate that the optical resolution under these conditions gives the L-4-EB salt with 98.2% optical purity in 70.5% degree of resolution and the yield of optically pure modification (0.456 g) is maximum at $\theta_D - 5$ min. This result supports the above suggestion.

Successive Preferential Crystallization of DL-4-Ethylbenzenesulfonate. In order to obtain the D- and L-4-EB salts with high optical purity, the successive

Table 7. Successive Preferential Crystallization of DL-Cysteine Salt of 4-Ethylbenzenesulfonic Acid^{a)}

Run	Added amount of DL-salt g	Operation amount ^b /g		Resolution time min	Salt obtained				
		D-Salt	L-Salt		Yield g	Optical purity %	YOPM ^c g	Degree of resolution %	
1 ^d	3.450	1.725	1.725	62	L	0.515	98.2	0.456	70.5
2	0.465	1.953	1.497	52	D	0.578	93.0	0.486	55.7
1 ^e	3.450	1.725	1.825	30	L	0.736	98.5	0.675	90.3
2	0.686	2.062	1.488	30	D	0.912	97.3	0.837	85.0
3	0.862	1.643	1.905	40	L	0.782	100	0.732	88.4
4	0.732	2.009	1.539	40	D	0.828	100	0.778	83.4

a) Solvent: 50 cm³ of ethanol. Seed crystals: 0.050 g of D- or L-salt. Temperature: 20 °C. b) The operation amounts of D- and L-salts in solution were calculated on the basis of analyses of the salt obtained in Run 1 or 1—3. c) YOPM: See note in Table 4. d) Degree of supersaturation of the initial solution: 160%. e) DL-Salt (3.450 g) and 0.100 g of L-salt were dissolved in the initial solution.

preferential crystallization was attempted with an initial solution with 160% degree of supersaturation; the result is listed in Table 7. Although it was also possible to obtain the D-4-EB salt with 93.0% optical purity, the degree of resolution (55.7%) was not so high as expected.

The L-4-EB salt (0.100 g) was dissolved in the initial solution to induce more rapid crystallization of the L-salt with high optical purity. This optical resolution was found to give the D- and L-4-EB salts with optical purity of 97–100% in degree of resolution of 83–90%, as shown in Table 7. The yields of optically pure modification of the D- and L-salts obtained also increased to 19–24% of the amounts of the DL- and L-salts contained in the initial solution. The purified D- and L-4-EB salts were treated with triethylamine to give optically pure D- and L-Cys's in 93–94% yield, respectively.

The above results show that suitable conditions are predictable by $\Delta g_{\max}$ and that the optical resolution by preferential crystallization of DL-4-EB salt efficiently gives the optically active Cys.

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