# 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 monohydrate[1] 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 $C_9H_{13}O_5NS_2$: 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%; $[\alpha]_{436}^{20}$ +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 $C_{10}H_{15}O_5NS_2$: 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%; $[\alpha]_{436}^{20}$ +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 $C_{11}H_{17}O_5NS_2$: 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%; $[\alpha]_{436}^{20}$ +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); $[\alpha]_{436}^{20}$ −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

Degree of resolution/%=[YOPM×100/g]/[(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° (c 1.00, water). L-Cys: $[\alpha]_D^{20}$ −16.5° (c 1.00, water) (lit,[10] $[\alpha]_D^{20}$ −16.5° (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 cm³ solvent) | | |
|------|---------|---------|--------|--------|
| | | DL-Salt | L-Salt | α[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 $\theta_m$/K | $\Delta H^f$ [a] kJ mol⁻¹ | $\Delta G_T^r$ [b]/kJ mol⁻¹ | | Eutectic point | | |
|------|------|------|------|------|------|------|------|
| | | | $\Delta G_{453}^r$ | $\Delta G_{293}^r$ | Mole fraction[c] | Temperature/K | |
| | | | | | | Found | Calcd[c] |
| DL-BA[d] | 452 | 31.8 | −0.91 | +0.12 | 0.61 | 451 | 451 |
| L-BA[d] | 478 | 33.9 | — | — | | | |

a) $\Delta H^f$: Enthalpy of fusion. b) $\Delta G_T^r$: Gibbs energy of formation of racemate at T K. The $\Delta G_T^r$'s at the melting point ($\Delta G_{453}^r$) and at 293 K ($\Delta G_{293}^r$) 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 ($\Delta H^f$),[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 ($\Delta G^F_{452}$/kJ mol$^{-1}$) and 293 K ($\Delta G^F_{293}$) was calculated from the melting temperature and $\Delta H^{f,4,5}$ and listed in Table 3. The negative $\Delta G^F_{452}$ value supports the above result. However, the positive $\Delta G^F_{293}$ 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 $\alpha$ 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
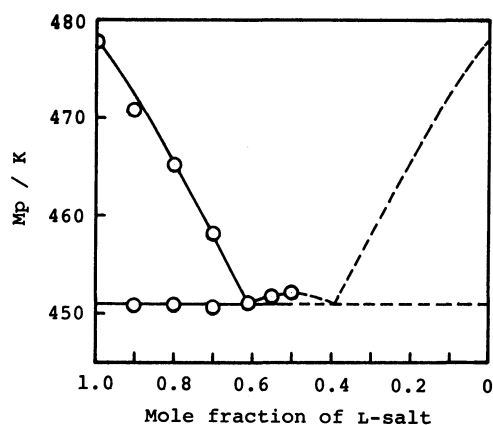


Fig. 1. Binary melting point diagram of cysteine salt of benzenesulfonic acid.

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 $\Delta G^F_{293}$ 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 ($\Delta g_{max}$/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 ($R_L$/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 ($\theta_D$/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 $\theta_D$ are listed in Table 6.

Table 4. Preferential Crystallization of DL-Cysteine Salt of Benzenesulfonic Acid[a]

| Solvent | Degree of supersaturation | Resolution time | Yield | Optical purity | YOPM[b] | Degree of resolution |
|---------|---------------------------|-----------------|-------|----------------|---------|----------------------|
| | % | min | g | % | g | % |
| 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 cm$^3$. 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 | Yield | Optical purity | YOPM[b] | Degree of resolution |
|---|---|---|---|---|---|
| % | min | g | % | g | % |
| 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 $\theta_D$ 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 $\theta_D$—5 min seems to be a better criterion for evaluating the results of optical resolution than that at $\theta_D$ min, because the unseeded D-salt begins to crystallize rapidly after $\theta_D$ min. The amount of crystallization of L-salt at $\theta_D$—5 min $(W^c{}_{(-5)}/g = R_L(\theta_D - 5))$ is derived from Eqs. 1 and 2 and expressed by

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

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,
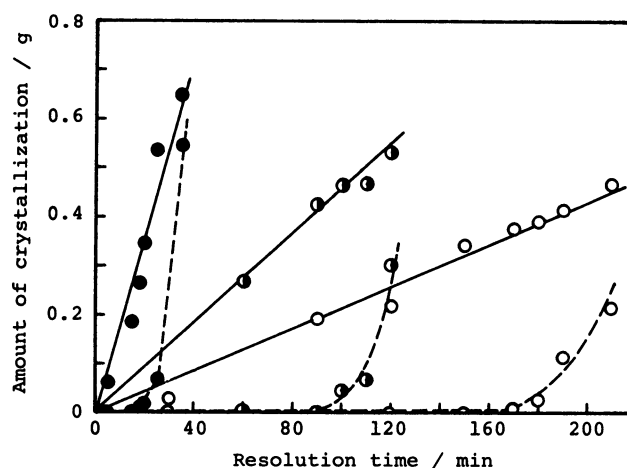


Fig. 2. Relationship between amounts of crystallization of D- and L-cysteine salts of 4-ethylbenzenesulfonic acid and resolution time.

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] | $R_L$[c] | $\theta_D$[d] | $W_{(-5)}$[e]/g | | |
|---|---|---|---|---|---|---|
| % | $\times 10^{-18}$ J nucleus$^{-1}$ | $\times 10^{-3}$ g min$^{-1}$ | min | 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 cm$^3$ 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)
$\theta_D$: 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 $W^c_{(-5)}$ from Eq. 3 show relatively large deviation from experimental values at $\theta_D - 5$ min ($W_{(-5)}/g$); the values of $W^c_{(-5)}$ 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 $W^c_{(-5)}$ and $W_{(-5)}$ for the degree of supersaturation of 143, 153, and 188% is expressed by

$$W_{(-5)} = 6.249 W^c_{(-5)} - 2.084,\qquad(4)$$

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

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

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 $W^c_{(-5)}$ 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 $W^c_{(-5)}$ was calculated to be $5.55 \times 10^{-18}$ J nucleus$^{-1}$. This value is approximately equal to the value for an ethanol solution with 160% degree of supersaturation ($5.87 \times 10^{-18}$ J nucleus$^{-1}$); the
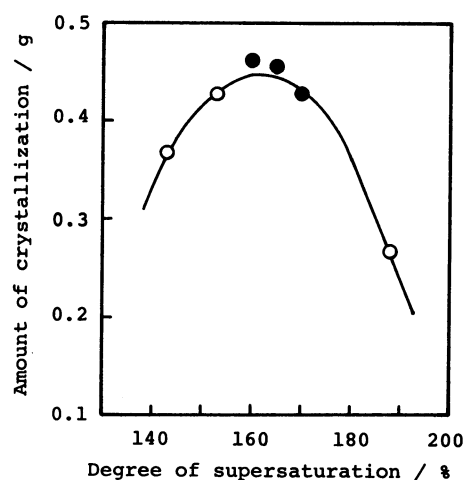


Fig. 3.　Crystallization of L-cysteine salt of 4-ethylbenzenesulfonic acid at $\theta_D - 5$ min.
Conditions: Solvent 50 cm$^3$ of ethanol; seed crystals 0.050 g of L-salt; temperature 20 °C. ——: Calculated amount of crystallization of L-salt at $\theta_D - 5$ min from the data for degree of supersaturation 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 $5.06 \times 10^{-18}$ J nucleus$^{-1}$.

The above result suggests that the optical resolution with 160% degree of supersaturaiton at resolution time of 62 min is the most favorable for obtaining the L-4-EB salt with high optical purity in high yield; $\theta_D$ 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 | Operation amount[b]/g | | Resolution time | Salt obtained | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | g | D-Salt | L-Salt | min | | 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 cm$^3$ 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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