September, 1987] *Bull. Chem. Soc. Jpn.*, **60**, *3277—3283 (1987)* 3277

Optical Resolution by Preferential Crystallization of DL-Thiazolidine-4-carboxylic Acid

Tadashi SHIRAIWA,* Yujin SADO, Masamitsu KOMURE, and Hidemoto KUROKAWA
Faculty of Engineering, Kansai University, Yamate-cho, Suita, Osaka 564
(Received March 19, 1987)

Infrared spectrum, solubility, and ternary solubility diagram indicated that DL-thiazolidine-4-carboxylic acid (DL-THC) is a conglomerate at room temperature. The free energy of critical nucleation in supersaturated solutions for the crystallization of D- and L-THC was examined to resolve DL-THC efficiently by preferential crystallization. Successive preferential crystallization of DL-THC was experimented at 20 °C for an aqueous racemic solution with a supersaturation of 150%, and D- and L-THC with optical purity of 96—100% were obtained in the range of resolution of 58—76%. The optical resolution was more successfully done in 1 mol dm^{-3} aqueous glycine to give D- and L-THC with optical purity of 93—99% in the degree of resolution of 77—87%. Recrystallization of D- and L-THC obtained with a succeeding treatment with hydroxylamine hydrochloride gave D- and L-cysteine with 100% optical purity.

L-Cysteine (abbreviated as L-Cys) as a useful material for medicines, food additives, and cosmetics has been obtained mainly from hair. Although D-Cys was also noted, recently, as a pharmaceutical material,[1] it is difficult to find D-Cys in natural products. An efficient synthesis of DL-Cys has been known,[2] and DL-Cys can be optically resolved by the diastereomeric procedure.[3,4] The optical resolution by a preferential crystallization seems to be more useful for an industrial purpose than the diastereomeric procedure. However, the optical resolution by preferential crystallization of DL-Cys was tried only for DL-cysteine hydrochloride monohydrate.[1] This paper describes an attempt to obtain D- and L-Cys efficiently by the preferential crystallization.

DL-Thiazolidine-4-carboxylic acid (DL-THC) was easily obtained by the reaction of DL-cysteine hydrochloride monohydrate with formaldehyde.[5] By infrared spectrum, solubility, and ternary solubility diagram, DL-THC seemed to be a conglomerate. DL-THC was subjected to optical resolution in water at 20 °C. The free energy of critical nucleation in supersaturated solutions of D- and L-THC was examined to find the appropriate conditions for optical resolution by preferential crystallization of DL-THC.[6—8] The optical resolution in 1 mol dm^{-3} aqueous glycine was also examined to obtain D- and L-THC more efficiently than in water.

Experimental

Materials. DL- and L-Cysteine hydrochloride monohydrate were purchased from Sigma Chemicals Co. and Wako Pure Chemicals Ind., respectively, and formaldehyde, hydroxylamine hydrochloride, and triethylamine from Wako Pure Chemicals Ind.

Synthesis of Thiazolidine-4-carboxylic Acid. DL- and L-Thiazolidine-4-carboxylic acid were prepared by the reaction of each cysteine hydrochloride monohydrate with formaldehyde.[5] DL-THC: Mp 195—198 °C (decomp) (lit,[9] mp 183—184 °C, 195 °C (decomp)). L-THC: Mp 202—204 °C (decomp) (lit,[9] mp 196—197 °C, 205—209 °C (decomp)); $[\alpha]_D^{20}$ −141° (*c* 1.00, water) (lit,[9] $[\alpha]_D^{20}$ −141° (water)).

D-THC of 37.5% optical purity was obtained from the mother liquor in optical resolution of DL-THC. After dissolving 26.64 g of D-THC in 280 cm^3 of water at an elevated temperature, and the solution was stirred for 1 h at 20 °C. The precipitated D-THC was collected by filtration, washed with a small amount of cold water and ethanol successively, and dried to give 9.88 g of optically pure D-THC; mp 202—204 °C (decomp); $[\alpha]_D^{20}$ +141° (*c* 1.00, water).

Optical Resolution. Preferential Crystallization: DL-THC was dissolved in 50 cm^3 of water at 40 °C to give racemic solutions with different degrees of supersaturation from 120 to 170% (20 °C) as shown in Table 1. The solution was slowly cooled to 20 °C and seeded with 0.050 g of L-THC. After stirring the mixture at 100 rpm and 20 °C, the precipitated L-THC was collected by filtration, washed with a small amount of ethanol, and dried. The optical purity, yield of optically pure modification (YOPM/g), degree of resolution of L-THC, and amounts of crystallization of D- and L-THC (W_D and W_L/g) were determined by

$$\text{Optical purity}/\% = (\text{Specific rotation of obtained THC}/^\circ \times 100)/(-141), \quad (1)$$

$$\text{YOPM/g} = (\text{Yield/g} \times \text{Optical purity}/\%)/100 - 0.050, \quad (2)$$

Table 1. Preparation of Supersaturated Solution in Water[a]

Degree of supersaturation[b]/%	Amount of DL-THC[c]/g
120	3.586
130	3.885
140	4.184
145	4.333
150	4.483
155	4.632
160	4.782
170	5.080

a) Water: 50 cm^3. b) Temperature: 20 °C. c) DL-THC: DL-Thiazolidine-4-carboxylic acid.

$$\text{Degree of resolution}/\% = (\text{YOPM/g}\times 100)/(1/2)(\text{Amount of consumed DL-THC/g} - 2.989), \tag{3}$$

$$W_{\mathrm{D}}/\mathrm{g} = (1/2)(\text{Yield/g} - \text{YOPM/g} - 0.050), \tag{4}$$

$$W_{\mathrm{L}}/\mathrm{g} = \text{YOPM/g} + W_{\mathrm{D}}/\mathrm{g}. \tag{5}$$

Successive Preferential Crystallization: DL-THC was dissolved in 50 cm^3 of water or 1 mol dm^{-3} aqueous glycine at 40 °C; 4.483 g in water (150% supersaturation) and 4.710 g in 1 mol dm^{-3} aqueous glycine (155% supersaturation). The solution was cooled to 20 °C and seeded with 0.050 g of L-THC. After stirring the mixture at 100 rpm and 20 °C, the precipitated L-THC was collected by filtration. DL-THC was dissolved in the filtrate at 40 °C; the amount was equal to that of crystallized THC. After seeding the solution with 0.050 g of D-THC at 20 °C, the mixture was treated similarly as above. The degree of resolution of D- and L-THC was calculated by

$$\text{Degree of resolution}/\% = (\text{YOPM/g}\times 100)/(\text{Operation amount of D- or L-THC/g} - M), \tag{6}$$

where M is 1.494 g in water, and 1.520 g in 1 mol dm^{-3} aqueous glycine.

The optical resolution was also performed for a solution containing 26.892 g of DL-THC in 300 cm^3 of water using 0.300 g of D- or L-THC as seed crystals; the supersaturation of the initial solution was 150%.

Preparation of Optically Active Cysteine. A mixture of D- or L-THC recrystallized from water (1.332 g, 0.010 mol) and 0.732 g (0.010 mol) of hydroxylamine hydrochloride in 50 cm^3 of methanol was refluxed for 60 min. After adding 0.366 g (0.005 mol) of hydroxylamine hydrochloride to the mixture and refluxing for 60 min, the solution was stirred in an ice bath for 60 min. The formed formaldehyde oxime was removed by filtration, and pH of the filtrate was adjusted to 5—6 with triethylamine. Precipitated crude Cys (0.02 g) was filtered out; $[\alpha]_{\mathrm{D}}^{20}$ +18.7 or −18.0° (water). After drying the filtrate under reduced pressure at 30 °C, the residue was added to 50 cm^3 of methanol. The mixture was stirred for 1 h at 40 °C and insoluble Cys was filtered, washed with methanol, and dried. D-Cys: Yield 0.989 g; $[\alpha]_{\mathrm{D}}^{20}$ +16.5° (*c* 2.00, water). L-Cys: Yield 0.995 g; $[\alpha]_{\mathrm{D}}^{20}$ −16.5° (*c* 2.00, water) (lit,[10] $[\alpha]_{\mathrm{D}}$ −16.5° (water)).

Measurements. The specific rotation was measured by a Union Giken PM-101 digital polarimeter with a quartz cell of 0.5 dm path length. The infrared spectra were obtained in the range 4000—400 cm^{-1} by a JASCO A-102 infrared spectrophotometer using the KBr disk method.

Results and Discussion

Racemic Structure. DL-THC shows identical infrared spectrum with that of L-THC and is more soluble than L-THC as described in Table 2. The ternary solubility diagram is shown in Fig. 1.

The above results infer that DL-THC is a conglomerate at room temperature.[11]

Preferential Crystallization. Since DL-THC was optically resolved by preferential crystallization in 50 cm^3 of water at 20 °C in the presence of 0.050 g of L-THC seed crystals, as shown in Table 3, DL-THC was confirmed to be a conglomerate at room temperature. Relationships between the amounts of crystallization of D- and L-THC and the resolution

Table 2. Solubility of DL- and L-Thiazolidine-4-carboxylic Acid[a)]

Solvent	Solubility/g/(100 cm^3 solvent)	
	DL-THC	L-THC
Water	5.977	3.193
Gly[b)]	6.078	3.314

a) Temperature: 20 °C. b) Gly: 1 mol dm^{-3} aqueous glycine.

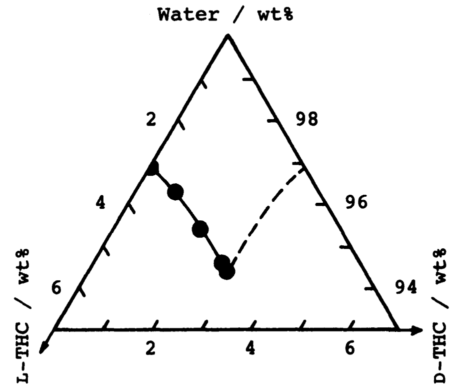

Fig. 1. Ternary solubility diagram of thiazolidine-4-calboxylic acid.
Temperature: 20 °C. Solvent: Water.

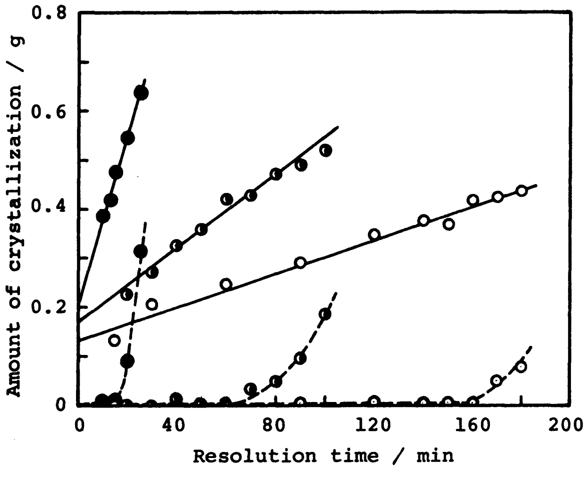

Fig. 2. Relationship between amounts of crystallization and resolution time.
Solvent: 50 cm^3 of water. Seed crystals: 0.050 g of L-THC. Temperature: 20 °C. ——: L-THC. – – –: D-THC. ○: 130% degree of supersaturation. ◑: 140% degree of supersaturation. ●: 160% degree of supersaturation.

time are shown in Fig. 2 for the solutions of supersaturation of 130, 140, and 160%, where the solvent is 50 cm^3 of water.

After a rapid crystallization in extremely short time, L-THC appears to crystallize at a constant speed with respect to the increase in resolution time. The speed of crystallization of L-THC (R_L/g min^{-1}) and the amount of crystallization extrapolated to zero resolution time (W_0/g) were calculated from linear plots in Fig. 2 for different degrees of supersaturation; the correlation coefficient of the linear relationships ranges from 0.989 to 0.997. The retardation time for crystallization of D-THC (Θ_D/min), defined as the resolution time until D-THC begins to crystallize rapidly, was estimated from Fig. 2. Although Fig. 2 indicates that D-THC co-exists in L-THC crystallized in shorter resolution time than Θ_D, DL-THC adhered on precipitates should have been considered in the estimation. These factors on crystallization of D- and L-THC are given in Table 4.

Optical Resolution by Preferential Crystallization. Relationship between Factors Controlling Crystallization and Free Energy of Critical Nucleation: In our previous paper,[8] it was reported that the

Table 3. Preferential Crystallization of DL-Thiazolidine-4-carboxylic Acid in Water[a]

Degree of supersaturation %	Resolution time min	Yield g	Optical purity %	YOPM[b] g	Degree of resolution %	Amount of crystallization/g L-THC	D-THC
120	360	0.284	100	0.234	78.4	0.234	0
	490	0.319	94.7	0.252	84.3	0.261	0.009
130	15	0.182	100	0.132	29.5	0.132	0
	30	0.253	100	0.203	45.3	0.203	0
	60	0.293	100	0.243	54.2	0.243	0
	90	0.346	97.1	0.286	63.8	0.291	0.005
	120	0.405	96.4	0.340	75.9	0.348	0.008
	140	0.426	98.7	0.370	82.6	0.373	0.003
	150	0.424	97.5	0.363	81.0	0.369	0.006
	160	0.470	99.0	0.415	92.6	0.418	0.003
	170	0.524	80.9	0.374	83.5	0.424	0.050
	180	0.567	71.8	0.357	79.7	0.437	0.080
140	20	0.274	100	0.224	37.5	0.224	0
	30	0.321	100	0.271	45.3	0.271	0
	40	0.387	93.9	0.313	52.3	0.325	0.012
	50	0.408	100	0.358	59.9	0.358	0
	60	0.474	98.1	0.415	69.4	0.420	0.005
	70	0.509	87.8	0.397	66.4	0.428	0.031
	80	0.572	82.5	0.422	70.6	0.472	0.050
	90	0.633	70.6	0.397	66.4	0.490	0.093
	100	0.758	50.7	0.334	55.9	0.521	0.187
145	40	0.500	97.4	0.437	65.0	0.444	0.007
	50	0.598	82.9	0.446	66.4	0.497	0.051
150	20	0.419	98.3	0.362	48.5	0.366	0.004
	30	0.527	96.3	0.458	61.3	0.468	0.010
	40	0.617	81.8	0.455	60.9	0.511	0.056
	50	0.912	54.2	0.444	59.4	0.653	0.209
155	20	0.510	96.7	0.443	53.9	0.452	0.009
	30	0.711	74.5	0.480	58.4	0.571	0.091
160	10	0.442	96.3	0.376	42.0	0.384	0.008
	13	0.476	97.1	0.412	46.0	0.419	0.007
	15	0.534	96.4	0.465	51.9	0.475	0.010
	20	0.687	73.9	0.458	51.1	0.548	0.090
	25	0.998	37.1	0.320	35.7	0.634	0.314
170	6	0.461	91.5	0.372	35.6	0.392	0.020
	15	0.959	46.1	0.392	37.5	0.651	0.259

a) Water: 50 cm^3. Seed crystals: 0.050 g of L-THC. Temperature: 20 °C. b) YOPM: Yield of optically pure modification.

Table 4. Factors on Preferential Crystallization in Water a)

Degree of supersaturation	R_{L} b)/$\times 10^{-3}$ g min^{-1}		W_0 c)/g		θ_{D} d)/min		$W_{(-5)}$ e)/g	
%	Found	Calcd f)	Found	Calcd g)	Found	Calcd h)	Found	Calcd i)
130	1.716	1.593	0.132	0.135	165	174.1	0.418	0.404
140	3.682	4.186	0.169	0.164	65	68.4	0.420	0.430
145	—	6.197	—	0.177	45	46.8	0.444	0.436
150	9.040	8.787	0.183	0.190	35	33.4	0.468	0.444
155	—	12.033	—	0.204	25	24.7	0.452	0.439
160	16.898	16.015	0.212	0.214	18	18.7	0.419	0.434
170	—	26.492	—	0.237	11	11.5	0.392	0.409

a) Water: 50 cm^3. Seed crystals: 0.050 g of L-THC. Temperature: 20 °C. b) R_{L}: Speed of crystallization of L-THC. c) W_0: Amount of crystallization of L-THC extrapolated to zero resolution time. d) θ_{D}: Retardation time for crystallization of D-THC. f) The value was calculated by Eq. 7. g) The value was calculated by Eq. 9. h) The value was calculated by Eq. 8. i) The value was calculated by Eq. 10.

Table 5. Properties of Critical Nucleus in Supersaturated Solution a)

Degree of supersaturation	r_{cr} b)	σ_{cr} c)	Δg_{max} d)
%	$\times 10^{-9}$ m	$\times 10^{-2}$ J m^{-2}	$\times 10^{-18}$ J nucleus^{-1}
120	15.978	4.466	47.758
130	10.911	4.388	21.883
140	8.368	4.317	12.663
145	7.518	4.283	10.140
150	6.837	4.250	8.321
155	6.278	4.218	6.964
160	5.811	4.187	5.924
170	5.075	4.129	4.455

a) Solvent: Water. Temperature: 20 °C. b) r_{cr}: Radius of critical nucleus. c) σ_{cr}: Interfacial energy of critical nucleus. d) Δg_{max}: Free energy of critical nucleation.

appropriate conditions for the optical resolution by preferential crystallization is predictable by the free energy of critical nucleation (Δg_{max}/J nucleus^{-1}) in supersaturated solutions. The values of Δg_{max} were calculated for aqueous solutions of DL-THC with various degrees of supersaturation,[6—8,12] and given in Table 5. The relationship between R_{L} and Δg_{max} for different degrees of supersaturation of 130, 140, and 160% and that between θ_{D} and Δg_{max} were obtained by Eqs. 7 and 8,[8] respectively,

$$\ln R_{\mathrm{L}} = -1.766 \ln \Delta g_{\mathrm{max}} - 74.19, \tag{7}$$

$$\ln \theta_{\mathrm{D}} = 1.707 \ln \Delta g_{\mathrm{max}} + 70.64, \tag{8}$$

where the correlation coefficients for Eqs. 7 and 8 were 0.995 and 0.997, respectively. The relationship between W_0 and Δg_{max} is expressed by Eq. 9

$$\ln W_0 = -0.3543 \ln \Delta g_{\mathrm{max}} - 15.59, \tag{9}$$

where the correlation coefficient was 0.993. The amount of crystallization of L-THC at θ_{D} can be estimated by Eqs. 7—9 for various degrees of supersaturation.

The values of R_{L}, W_0, and θ_{D} for an aqueous solution with 120% supersaturation were calculated to be 4.01×10^{-4} g min^{-1}, 0.102 g, and 660 min, respectively; the solvent was 50 cm^3 of water. The value of θ_{D} suggests that D-THC does not crystallize rapidly within 660 min. The optical resolution at 360 min gave L-THC with 100% optical purity in 0.284 g yield as shown in Table 3. The amount of crystallized L-THC was 0.234 g and agreed well with the calculated value at 360 min by Eqs. 7 and 9 (0.247 g). The calculated values of R_{L} and W_0 suggest that the theoretical amount of L-THC (0.299 g) crystallizes after 490 min. The optical resolution at 490 min gave L-THC with 94.7% optical purity in 0.319 g yield; the amount of crystallization of L-THC was 0.261 g. The relatively large difference between the experimental result and calculated value suggests that the crystallization of L-THC is inhibited after a long resolution time, because the supersaturation of L-THC in the solution decreases considerably with crystallization of L-THC. However, for the solutions with supersaturation of 130—160%, L-THC seems to crystallize at a rate proportional to the resolution time until at least θ_{D} min as demonstrated in Fig. 2 and indicated by Eq. 7.

Appropriate Conditions of Optical Resolution: Although the optical resolution at θ_{D} will give the maximum yield of L-THC with high optical purity, the optical resolution at θ_{D}—5 min seems to be more suitable to stable operation than that at θ_{D}, because D-THC begins to crystallize rapidly after θ_{D}. The amount of L-THC produced at θ_{D}—5 min ($W_{(-5)}$/g) is expressed by Eq. 10

$$W_{(-5)} = R_{\mathrm{L}}(\theta_{\mathrm{D}}-5) + W_0. \tag{10}$$

The values of R_{L}, W_0, θ_{D}, and $W_{(-5)}$ for various degrees of supersaturation were calculated by Eqs. 7—10. The relationship between $W_{(-5)}$ and the degree of supersaturation is shown in Fig. 3.

The calculated $W_{(-5)}$ values showed an identical tendency with that of experimental data in supersaturation between 130 and 170%. Figure 3 suggests that the optical resolution at 150% supersaturation gives the muximum amount of L-THC. This optical resolution was performed at resolution time in the range 20—50 min as given in Table 3, because Θ_D is 33.4 min calculated by Eq. 8. The experimental amounts of crystallization of L-THC are compared with those calculated by Eqs. 7 and 9 in Fig. 4.

The value of Θ_D is 35 min in Fig. 4 and agrees well with the calculated value of 33.4 min. The optical resolution at 30 min, namely at Θ_D—5 min, gave L-THC with 96.3% optical purity of 61.3% degree of resolution. The amount of crystallization of L-THC is 0.468 g; the amount calculated is 0.440 g at 28.4 min by

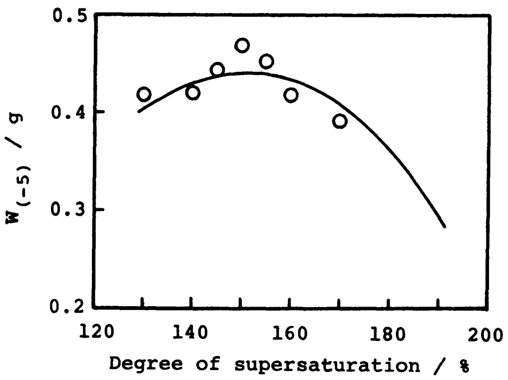

Fig. 3. Relationship between amount of crystallization of L-thiazolidine-4-carboxylic acid at θ_D—5 min and degree of supersaturation.
Conditions: Solvent 50 cm^3 of water; seed crystals 0.050 g of L-THC; temperature 20 °C. $W_{(-5)}$: Amount of crystallization of L-THC at θ_D—5 min; —— calculated amount by Eq. 10; ○ found. θ_D: Retardation time for crystallization of D-THC.

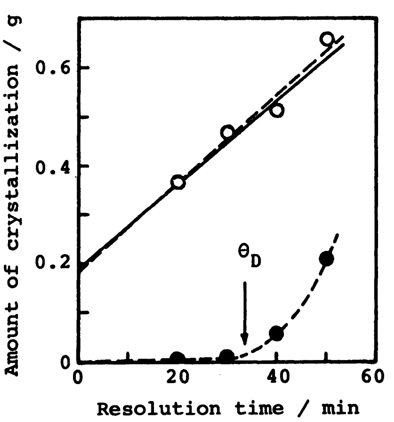

Fig. 4. Preferential crystallization from aqueous solution with 150% degree of supersaturation.
Solvent: 50 cm^3 of water. Seed crystals: 0.050 g of L-THC. Temperature: 20 °C. ——: Calculated amount of crystallization of L-THC. Found: ○ L-THC; ● D-THC. θ_D: Calculated retardation time for crystallization of D-THC (33.4 min).

Table 6. Successive Preferential Crystallization in Water[a)]

Run	Added amount of DL-THC	Operation amount[b)]/g		Resolution time	THC obtained			
	g	D-THC	L-THC	min	Yield g	Optical purity %	YOPM[c)] g	Degree of resolution %
1[d)]	4.482	2.241	2.241	30	L 0.527	96.3	0.458	61.3
2	0.477	2.469	2.011	20	D 0.624	100	0.574	58.9
3	0.574	2.182	2.298	30	L 0.685	97.2	0.619	77.0
4	0.635	2.491	1.988	30	D 0.668	98.8	0.610	61.2
1[e)]	26.892	13.446	13.446	30	L 3.024	80.1	2.122	47.3
2	2.724	14.507	12.385	25	D 3.785	100	3.485	62.9
3	3.485	12.765	14.128	30	L 3.713	100	3.413	66.1
4	3.413	14.472	12.422	30	D 4.168	96.6	3.726	67.6
5	3.865	12.609	14.285	30	L 4.300	98.1	3.918	73.6
6	4.000	14.568	12.326	30	D 4.439	96.8	3.997	71.3
7	4.139	12.570	14.325	30	L 4.509	99.4	4.182	78.0
8	4.209	14.661	12.234	30	D 4.668	98.0	4.275	75.0
9	4.368	12.523	14.371	30	L 4.564	98.0	4.172	77.2
10	4.264	14.609	12.284	30	D 4.839	92.0	4.152	73.6
11	4.539	12.533	14.360	30	L 4.711	96.5	4.246	78.7

a) Temperature: 20 °C. Degree of supersaturation of initial solution: 150%. b) The operation amounts of D- and L-THC in Runs 2—4 or 2—11 were calculated on the basis of the analyses of the obtained THC in Runs 1—3 or 1—10. c) YOPM: See note b) in Table 3. d) Water: 50 cm^3. Seed crystals: 0.050 g of D- or L-THC. e) Water: 300 cm^3. Seed crystals: 0.300 g of D- or L-THC.

Table 7. Successive Preferential Crystallization in Aqueous Glycine[a)]

Run	Added amount of DL-THC	Operation amount[b)]/g		Resolution time	THC obtained			
	g	D-THC	L-THC	min	Yield g	Optical purity %	YOPM[c)] g	Degree of resolution %
1	4.710	2.355	2.355	60	L 0.740	93.6	0.643	77.0
2	0.690	2.676	2.033	50	D 1.024	97.9	0.952	82.4
3	0.974	2.200	2.509	50	L 0.927	98.6	0.864	87.4
4	0.877	2.632	2.077	50	D 1.031	95.0	0.929	83.5

a) Solvent: 50 cm^3 of 1 mol dm^{-3} aqueous glycine. Seed crystals: 0.050 g of D- or L-THC. Temperature: 20 °C. Degree of supersaturation of initial solution: 155%. b) The operation amounts of D- and L-THC in Runs 2—4 were calculated on the basis of the analyses of the obtained THC in Runs 1—3. c) YOPM: See note b) in Table 3.

Eqs. 7 and 9. The maximum yield of optically pure modification (YOPM/g) in Table 3 appears at Θ_D—5 min for each degree of supersaturation (cf. also Table 4). The optical resolution at 30 min with 150% supersaturation is most favorable to obtain efficiently L-THC with high optical purity.

These results revealed that appropriate conditions can be estimated by Δg_{max} in the optical resolution by preferential crystallization.

Successive Preferential Crystallization: Based on the above results, the successive preferential crystallization was carried out in 50 cm^3 of water at 20 °C for 30 min using a solution with 150% initial supersaturation, as listed in Table 6. The procedure gave D- and L-THC with optical purity of 96—100% and resolution of 58—77%.

The optical resolution under the same conditions was scaled up 6 times as described in Table 6. The optical purity of L-THC fell to 80.1%, and hence the degree of resolution was 47.3%. This low optical purity will be due to a change of stirring condition by the scale up. However, the optical resolution in runs 2—11 was satisfactory for producing D- and L-THC with optical purity of 92—100% and resolution of 62—79%.

Optical Resolution in Aqueous Glycine Solution. D- and L-THC with high optical purity were efficiently obtained by the successive preferential crystallization in water under appropriate conditions estimated by Δg_{max}, but the values of YOPM were only 10—14% of the amount of DL-THC dissolved in the initial solution; YOPM denotes the theoretical amount of optically pure THC obtained by recrystallization.

Since the solubility of DL- and L-THC is slightly higher in 1 mol dm^{-3} aqueous glycine than in water, as shown in Table 2, an attractive interaction may exist between glycine and THC molecules. This suggests that the value of Θ_D is larger in the glycine solution than in water, because the growth of critical nuclei of THC is inhibited by glycine molecules.[7)] Since the crystallization of L-THC will also be inhibited by glycine, the successive preferential crystallization was attempted in 1 mol dm^{-3} aqueous glycine for a solution with 155% supersaturation. This result was listed in Table 7.

L-THC with 93.6% optical purity was obtained in degree of resolution of 77.0% by the procedure for 60 min; YOPM was 13.7% of the amount of DL-THC dissolved in the initial solution. THC in aqueous glycine may crystallize as a molecular compound with glycine,[13)] but the elemental analyses show that only L-THC crystallizes.[14)] This result is supported by the fact that D-THC does not crystallize for at least 60 min.

The D- and L-THC with optical purity of 95—99% were obtained in degree of resolution of 82—87% in runs 2—4, and YOPM were approxymately 20% of the amount of DL-THC dissolved in the initial solution.

The recrystallization of obtained D- and L-THC from water, followed by treatment with hydroxylamine hydrochloride, gave optically pure D- and L-Cys in 82% yield.

References

1) C. Inoue, Y. Kurima, and S. Moriguchi, Jpn. Patent, 70859 (1982); *Chem. Abstr.*, **97**, 163490 (1982).

2) J. Martens, H. Offermans, and P. Scherberich, *Angew. Chem., Int. Ed. Engl.*, **20**, 668 (1981).

3) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **130**, 109 (1939).

4) H. Nohira, Jpn. Patent, 51239 (1984); *Chem. Abstr.*, **101**, 131104 p (1984).

5) S. Ratner and T. Clarke, *J. Am. Chem. Soc.*, **59**, 200 (1937).

6) T. Nakai, *Bull. Chem. Soc. Jpn.*, **42**, 2143 (1969).

7) T. Nakai, "Shoseki Kogaku," Baifukan, Tokyo (1986), Section 2.

8) T. Shiraiwa, H. Miyazaki, T. Imai, M. Sunami, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **60**, 661 (1987).

9) J. S. Davies, "Amino Acids and Peptides," Chapman and Hall, London, New York (1985), p. 302.

10) Ref. 9, p. 130.

11) H. Nohira, "Shizen Bunsho no Joken to Jitsuyo Rei," in "Fusei Gosei to Kogaku Bunkatsu no Shinpo," ed by S. Ohtsuka and T. Mukaiyama, Kagaku Dojin, Kyoto

(1982), p. 165.

12) In order to calculate Δg_{max}, the molecular volume of THC (1.320×10^{-28} m^3) was measured in water at 20 °C. The molecular radius was calculated to be 3.159×10^{-10} m on the assumption of spherical molecule. The average values of the radius (4.027×10^{-10} m) and interfacial energy (1.807 J m^{-2}) of embryo in the saturated aqueous solution at 20 °C were calculated on the basis of the solubility of DL-THC according to the procedure reported in Ref. 6; the average number of THC molecule forming the embryo in the solution was 2.072.

13) T. Shiraiwa, A. Ikawa, K. Sakaguchi, and H. Kurokawa, *Bull. Chem. Soc. Jpn.*, **57**, 2234 (1984).

14) Elemental analyses of the L-THC crystallized from 1 mol dm^{-3} aqueous glycine: Found C, 36.18; H, 5.30; N, 10.52% (Calcd for $C_4H_7NO_2S$: C, 36.08; H, 5.30; N, 10.52%).