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# Asymmetric Transformation of (*RS*)-Cysteine via Formation of (*RS*)-4-Thiazolidinecarboxylic Acids

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Either (*R*)- or (*S*)-cysteine ((*R*)- or (*S*)-Cys) was efficiently obtained from (*RS*)-Cys by the asymmetric transformation via formation of (*RS*)-4-thiazolidinecarboxylic acid ((*RS*)-THC) or (*RS*)-2,2-dimethyl-4-thiazolidinecarboxylic acid ((*RS*)-DMT) and by using (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid ((*R*)- or (*S*)-TA), as a resolving agent, in acetic acid. The asymmetric transformation was carried out by combination of crystallization of less soluble salt of (*S*)-THC or -DMT with (*R*)-TA (or salt of (*R*)-THC or -DMT with (*S*)-TA) and epimerization of soluble diastereomeric salt. The (*R*)- and (*S*)-THCs from the less soluble salts gave approximately optically pure (*R*)- and (*S*)-Cys's, respectively, in 64% yield. The asymmetric transformation via formation of (*RS*)-DMT was more successfully achieved by adding 0.1 molar equivalent of salicylaldehyde; that is, hydrolysis of the obtained less soluble salt gave optically pure (*R*)- and (*S*)-Cys's, respectively, in 80% yield based on the (*RS*)-Cys used as the starting material.

(*RS*)-Cysteine (abbreviated as (*RS*)-Cys) has been optically resolved by preferential crystallization to obtain (*R*)-Cys, a useful material for medicines, food additives, and cosmetics, and (*S*)-Cys, a pharmaceutical material.[1-3] The optical resolution by preferential crystallization is useful for industrial purposes and gives both enantiomers. In many cases, only one enantiomer is demanded in large amounts, but the other is not in so large an amount. Asymmetric transformation has the possibility of converting a racemate solely into the desirable enantiomer. An asymmetric transformation has been carried out for (*RS*)-amino acid derivatives by combination of selective crystallization of a less soluble diastereomeric salt and epimerization of the other soluble one.[4-9] This paper describes an attempt to obtain either (*R*)- or (*S*)-Cys efficiently from (*RS*)-Cys.

(*R*)-4-Thiazolidinecarboxylic acid ((*R*)-THC), a material for antihypertensive agent, has been obtained by reacting (*R*)-Cys with formaldehyde.[10] We reported the asymmetric transformation of (*RS*)-THC via formation of its diastereomeric salts with equimolar (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid ((*R*)- or (*S*)-TA).[11] Although a treatment of (*R*)- or (*S*)-THC with hydroxylamine hydrochloride gives optically active Cys,[2,11] the overall yield based on initial (*RS*)-Cys is estimated to be 50%. It has been reported that optically active amino acids are racemized in the presence of aldehydes in an organic acid such as acetic acid.[12] If formation of (*RS*)-THC from (*RS*)-Cys, epimerization by excess formaldehyde of its soluble diastereomeric salt with TA, and crystallization of its less soluble salt take place simultaneously in one system, it is expectable to obtain optically active Cys in higher yield.

Optically active 2,2-dimethyl-4-thiazolidinecarboxylic acid (DMT) is rapidly formed by reacting optically active Cys with acetone in acetic acid and racemized simultaneously by excess acetone, as described in our previous paper.[13] DMT is more easily hydrolyzed in water to regenerate Cys than THC.[14,15] In addition, DMT seems to form easily the salt with equimolar TA similarly to THC.

On the basis of the above suggestions, the asymmetric transformation of (*RS*)-Cys was tried via formation of (*RS*)-THC and (*RS*)-DMT and by using optically active TA as a resolving agent.

## Experimental

**Materials.** (*R*)- and (*RS*)-Cysteine hydrochloride monohydrates were purchased from Wako Pure Chemicals Ind. and Sigma Chemicals Co., respectively, and recrystallized from water. Aqueous solutions of the hydrochlorides were adjusted with concentrated aqueous ammonia to pH 6 to obtain (*R*)- and (*RS*)-Cys. (*R*)-Cys: $[\alpha]_D^{20}$ +6.5° (*c* 4.00, 5 mol dm$^{-3}$ HCl). (*R*)- and (*S*)-TAs were purchased from Wako Pure Chemicals Ind.

**Synthesis of 4-Thiazolidinecarboxylic Acid and 2,2-Dimethyl-4-thiazolidinecarboxylic Acid.** (*RS*)- or (*R*)-Cys (0.0200 mol, 2.42 g) was dissolved in the presence of 1.62 g of 37% aqueous formaldehyde (0.0200 mol of formaldehyde) in 40 cm$^3$ of acetic acid at 50 °C, and the solution was cooled immediately to 30 °C. After stirring for 1 h at 30 °C, the solution was dried under reduced pressure at 40 °C. The THC obtained as the residue was washed thoroughly with methanol and dried. (*RS*)-THC: Yield 2.49 g (93.5%); mp 188—191 °C (decomp) (lit,[16] 183—184 °C, 195 °C (decomp)). (*R*)-THC: Yield 2.48 g (93.1%); mp 200—202 °C (decomp) (lit,[16] 196—197 °C, 205—209 °C (decomp); $[\alpha]_D^{20}$ −141° (*c* 0.500, water) (lit,[16] $[\alpha]_D$ −141° (water)).

(*R*)-DMT was obtained by reacting (*R*)-Cys with acetone in acetic acid and (*RS*)-DMT by racemization of (*R*)-DMT, as described in our previous paper.[13] (*R*)-DMT: Mp 144—145 °C (lit,[14] 138—140 °C); $[\alpha]_D^{20}$ −188° (*c* 0.100, acetone) (lit,[14] $[\alpha]_D$ −183° (acetone)). (*RS*)-DMT: Mp 150—152 °C.

**Preparation of Standard Salts.** A mixture of 0.0200 mol of (*R*)-Cys, 0.0200 mol of (*S*)-TA, and 0.0500 mol (2.90 g) of acetone in 10 cm$^3$ of acetic acid was refluxed for 30 min. After stirring the mixture for 30 min at room temperature, the formed salt of (*R*)-DMT with (*S*)-TA ((*R*)-DMT·(*S*)-TA salt) was collected by filtration, washed thoroughly with diethyl ether, and dried. The salt of (*R*)-DMT with (*R*)-TA

could not be obtained because the formed salt was strongly hygroscopic. The (*R*)-DMT·(*S*)-TA salt: Yield 5.95 g (95.6%); mp 172—174 °C (decomp); $[\alpha]_D^{20}$ −81.8° (*c* 0.500, methanol); Found C, 38.44; H, 5.47; N, 4.48% (Calcd for $C_{10}H_{17}NO_8S$: C, 38.58; H, 5.50; N, 4.50%).

The salt of (*R*)-THC with (*S*)-TA ((*R*)-THC·(*S*)-TA salt) and that of (*R*)-THC with (*R*)-TA ((*R*)-THC·(*R*)-TA salt) were prepared by the method described in our previous paper.[17] The (*R*)-THC·(*S*)-TA salt: Mp 171—173 °C (decomp); $[\alpha]_D^{20}$ −74.0° (*c* 0.500, water). The (*R*)-THC·(*R*)-TA salt: Mp 149—150 °C (decomp); $[\alpha]_D^{20}$ −55.8° (*c* 0.500, water).

**Asymmetric Transformation. Procedure I:** A mixture of 0.0200 mol of (*RS*)-Cys, 0.0200 mol of (*R*)- or (*S*)-TA, and 1.95 g of 37% aqueous formaldehyde (0.0240 mol of formaldehyde) in 40 cm³ of acetic acid was stirred for 0.5—2 h at 80 °C. After stirring the mixture for 15 min in an ice bath, the formed salt was collected by filtration, washed with diethyl ether, and dried. The salt was washed by stirring in 250 cm³ of ethanol for 1 h at 20 °C and then in 50 cm³ of methanol for 1 h to give (*R*)- or (*S*)-THC. The obtained (*R*)- and (*S*)-THCs (2.04 g) were treated with 1.5 molar equivalents of hydroxylamine hydrochloride in methanol to give 1.54 g of (*R*)- and (*S*)-Cys's, as described in our previous paper;[2] the yield based on 0.0200 mol of (*RS*)-Cys was 63.6%.

(*R*)-Cys (0.0200 mol) and 0.0200 mol of (*R*)-TA were dissolved in the presence of 1.62—2.44 g of 37% aqueous formaldehyde (0.0200—0.0300 mol of formaldehyde) in 40 cm³ of acetic acid at 70 °C. After stirring the mixture for 30 min at 30 °C and then for 1 h at 80 °C, the formed salt was filtered off and treated similarly to above.

**Procedure II:** A mixture of 0.0400 mol of (*RS*)-Cys, 0.0400 mol of (*R*)- or (*S*)-TA, and 0.200 mol of acetone in 15 cm³ of acetic acid was refluxed (approximately at 83 °C) for 2—10 h. The formed salt was filtered off, washed with diethyl ether, and dissolved in 80 cm³ of water. After refluxing for 2 h, the solution was dried under reduced pressure at 40 °C. The residue was stirred for 2 h in 100 cm³ of methanol to give (*R*)- or (*S*)-Cys.

**Procedure III:** After refluxing a mixture of 0.0400 mol of (*RS*)-Cys, 0.0400 mol of (*R*)- or (*S*)-TA, and 0.200 mol of acetone in 10 cm³ of acetic acid, 0.0040 mol of salicylaldehyde was added to the mixture. The mixture was refluxed (approximately at 77 °C) for 2—7 h and successively stirred for 30 min in an ice bath. The formed salt was filtered off, washed thoroughly with diethyl ether, and dried. The obtained salt was hydrolyzed to give (*R*)- or (*S*)-Cys and to recover TA. For example, 10.38 g of optically pure (*R*)-DMT·(*S*)-TA salt was added to a mixture of 10 cm³ of water and 100 cm³ of ethanol. After stirring the mixture for 1 h at 60 °C, crude (*R*)-Cys was filtered off: yield 5.61 g; $[\alpha]_D^{20}$ +4.7° (*c* 4.00, 5 mol dm⁻³ HCl). The (*R*)-Cys was washed by stirring for 30 min in 50 cm³ of methanol to give 3.88 g (80.1% yield) of optically pure (*R*)-Cys: $[\alpha]_D^{20}$ +6.5° (*c* 4.00, 5 mol dm⁻³ HCl) (lit,[18] $[\alpha]_D$ +6.5° (5 mol dm⁻³ HCl)). The $^1$H NMR spectrum of the (*R*)-Cys in deuterium oxide showed no methyl protons. Drying of the above ethanol and methanol washings gave 4.96 g (82.6% recovery) of (*S*)-TA: $[\alpha]_D^{20}$ −12.1° (*c* 20.0, water) (lit,[19] (*R*)-TA $[\alpha]_D^{20}$ +11.98° (*c* 20%, water)).

**Racemization Rate of (*R*)-2,2-Dimethyl-4-thiazolidinecarboxylic Acid.** A mixture of 0.0200 mol of (*R*)-Cys and 30 cm³ of acetic acid was heated to 80 °C. After adding 0.100 mol of acetone and 0.0020 mol of acetaldehyde, benzaldehyde, 2-chlorobenzaldehyde, or salicylaldehyde, the resulting solution was stirred at 80 °C; (*R*)-Cys was dissolved completely by stirring for several minutes at 80 °C. One cm³ portions of the solution were pipetted out at 30 min intervals and diluted rapidly to 10 cm³ with acetic acid. The optical rotation at 589 nm was measured. The rate constant ($k_R$/h⁻¹) was calculated by the least-squares method from

$$\ln \alpha_0/\alpha_t = k_R t, \quad (1)$$

where $\alpha_t$ is the optical rotation at time *t* h and $\alpha_0$ that extrapolated to zero time. The half-life period ($t_{1/2}$/h) was calculated on the basis of $k_R$ values obtained by Eq. 1. The above solution was dried under reduced pressure after stirring for 3 h at 80 °C and the residue was washed thoroughly with diethyl ether. The $^1$H NMR spectrum showed that the residue was DMT and not any 4-thiazolidinecarboxylic acid derivatives.

**Measurements.** Optical and specific rotations were measured by a Union Giken PM-101 digital polarimeter with a quartz cell of 0.50 dm path length. $^1$H NMR spectra were recorded on a JEOL JNM—PMX 60 NMR spectrometer in deuterium oxide with no internal standard substance.

## Results and Discussion

**Asymmetric Transformation by Procedure I.** (*RS*)-THC was easily formed by reacting (*RS*)-Cys with formaldehyde in acetic acid, as described in the experimental section. The diastereomeric salts of (*RS*)-THC with equimolar (*R*)-TA were separated into the less soluble (*S*)-THC·(*R*)-TA salt and the soluble (*R*)-THC·(*R*)-TA salt.[17] These results indicate a possibility that formation of (*RS*)-THC, selective crystallization of the (*S*)-THC·(*R*)-TA salt, and epimerization by excess formaldehyde of the (*R*)-THC·(*R*)-TA salt take place simultaneously in one system. The epimerization seems to be accelerated with an increase in amount of excess formaldehyde. However, the increase may result in dissolution of a part of the less soluble salt because 37% aqueous formaldehyde (37% FA) is employed. Optimization of the amount of 37% FA was conducted by stirring a mixture of 0.0200 mol of (*R*)-Cys, 0.0200 mol of (*R*)-TA, and 1.62—2.44 g of 37% FA (0.0200—0.0300 mol of formaldehyde) in acetic acid. These results are given in Table 1 and Fig. 1. The degree of transformation into the (*S*)-THC·(*R*)-TA salt in Fig. 1 was calculated by

$$\text{Degree of transformation}/\% = (\text{Yield}/\% \times \text{Optical purity}/\%)/100. \quad (2)$$

Although the use of 1.62 g of 37% FA (0.0200 mol of formaldehyde) gave the (*R*)-THC·(*R*)-TA salt, the salt was partially epimerized even by using equimole of formaldehyde to (*R*)-Cys, as indicated by its having 59.5% optical purity. The (*S*)-THC·(*R*)-TA salts with

Table 1. Asymmetric Transformation by Procedure I[a]

| Conditions | | | | Salt | | | | THC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time h | Amount of formaldehyde[b] mol | Configuration Cys | Configuration TA | Configuration[c] | Yield g[%][d] | Specific rotation[e] ° | Optical purity[f] % | Configuration | Yield g[%][g] | Optical purity[h] % |
| 1 | 0.020 | (*R*) | (*R*) | (*R*·*R*) | 3.35[59.1] | −29.3 | 59.5 | (*R*) | 1.43[53.7] | 65.2 |
| 1 | 0.022 | (*R*) | (*R*) | (*S*·*R*) | 3.66[64.6] | +59.3 | 77.3 | (*S*) | 1.59[59.7] | 82.4 |
| 1 | 0.024 | (*R*) | (*R*) | (*S*·*R*) | 3.83[67.6] | +73.2 | 98.8 | (*S*) | 1.68[63.1] | 99.3 |
| 1 | 0.026 | (*R*) | (*R*) | (*S*·*R*) | 3.57[63.0] | +72.4 | 97.5 | (*S*) | 1.56[58.6] | 97.2 |
| 1 | 0.028 | (*R*) | (*R*) | (*S*·*R*) | 3.33[58.8] | +72.8 | 98.2 | (*S*) | 1.45[54.4] | 98.6 |
| 1 | 0.030 | (*R*) | (*R*) | (*S*·*R*) | 3.08[54.4] | +72.1 | 97.1 | (*S*) | 1.33[49.9] | 97.9 |
| 0.5 | 0.024 | (*RS*) | (*R*) | (*S*·*R*) | 3.46[61.1] | +67.0 | 89.2 | (*S*) | 1.47[55.2] | 92.2 |
| 1 | 0.024 | (*RS*) | (*S*) | (*R*·*S*) | 4.56[80.5] | −73.8 | 99.7 | (*R*) | 1.98[74.4] | 100 |
| 1.5 | 0.024 | (*RS*) | (*R*) | (*S*·*R*) | 4.68[82.6] | +73.2 | 98.8 | (*S*) | 2.04[76.6] | 99.3 |
| 2 | 0.024 | (*RS*) | (*S*) | (*R*·*S*) | 4.68[82.6] | −73.7 | 99.5 | (*R*) | 2.04[76.6] | 100 |

a) (*R*)- or (*RS*)-Cysteine (Cys) 0.0200 mol; (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid (TA) 0.0200 mol; acetic acid 40 cm³; temperature 80 °C; THC 4-thiazolidinecarboxylic acid. b) 37% aqueous formaldehyde (1.62 g) corresponds to 0.0200 mol of formaldehyde. (c) (*R*·*R*) represented the salt composed of equimolar amounts of (*R*)-THC and (*R*)-TA (*S*·*R*) the salt of (*S*)-THC and (*R*)-TA, and (*R*·*S*) the salt of (*R*)-THC and (*S*)-TA. d) The yield was calculated on the basis of 0.0200 ml (5.67 g) of the salt. e) $[\alpha]_D^{20}$ (*c* 0.500, water). f) The optical purity was determined on the basis of the specific rotation of the (*S*·*R*)-salt ($[\alpha]_D^{20}$ +74.0° (*c* 0.500, water)) and that of the (*R*·*R*)-salt ($[\alpha]_D^{20}$ −55.8° (*c* 0.500, water)). g) The yield was calculated on the basis of 0.0200 mol (2.66 g) of Cys. h) The optical purity was determined on the basis of the specific rotation of (*R*)-THC ($[\alpha]_D^{20}$ −141 ° (*c* 0.500, water)).

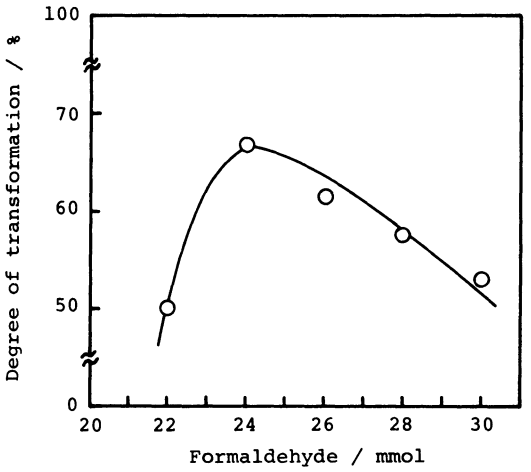


Fig. 1. Relationship between degree of transformation into salt of (*S*)-4-thiazolidinecarboxylic acid with (2*R*,3*R*)-tartaric acid and amount of formaldehyde. Conditions: (*R*)-Cysteine 0.0200 mol; (2*R*,3*R*)-tartaric acid 0.0200 mol; acetic acid 40 cm³; stirring time 1 h; temperature 80 °C; 1.62 g of 37% aqueous formaldehyde corresponds to 0.0200 mol of formaldehyde.

77—99% optical purity were obtained by using 1.79—2.44 g of 37% FA (0.0220—0.0300 mol of formaldehyde). As seen in Fig. 1, the (*S*)-THC·(*R*)-TA salt with 98.8% optical purity was obtained by using 1.95 g of 37% FA (0.0240 mol of formaldehyde) in the highest degree of transformation (66.7%). This salt gave (*S*)-THC with 99.3% optical purity in 63% yield based on the (*R*)-Cys used as the starting material.

Based on the above results, the asymmetric transformation was carried out by reaction of 0.0200 mol of (*RS*)-Cys, 0.0200 mol of (*R*)- or (*S*)-TA, and 1.95 g of 37% FA in 40 cm³ of acetic acid at 80 °C, as shown in Table 1. Although the asymmetric transformation was also attempted at 90 °C, the salt formed at lower temperature was dissolved on heating to 90 °C.

The (*R*)-THC·(*S*)-TA and (*S*)-THC·(*R*)-TA salts with approximately 100% optical purity were obtained in 83% yield by reaction for 1.5 and 2 h, respectively. These salts gave (*R*)- and (*S*)-THCs, respectively, in 77% yield. The obtained THCs were treated with hydroxylamine hydrochloride to give (*R*)- and (*S*)-Cys's, respectively, in 64% yield based on 0.0200 mol of (*RS*)-Cys.

**Asymmetric Transformation by Procedure II.** The asymmetric transformation by procedure I is more efficient than that described in our previous paper[11] in that it yields optically active Cys in higher yield. However, the treatment of THC with hydroxylamine hydrochloride is tedious and results in lowering of yield of the optically active Cys. Optically active DMT is racemized by acetone in acetic acid and hydrolyzed by adding water to reaction mixture to give (*RS*)-Cys in 97% yield.[13] The asymmetric transformation was tried for a mixture of 0.0400 mol of (*RS*)-Cys, 0.0400 mol of (*R*)-TA, and 0.200 mol of acetone in 15 cm³ of acetic acid under reflux (approximately at 83 °C), as shown in Table 2.

The salt of (*S*)-DMT with equimolar (*R*)-TA ((*S*)-DMT·(*R*)-TA salt) was crystallized as the less soluble diastereomeric salt and obtained in 61—75% yield with approximately 100% optical purity. Although the maximum yield was lower than that (83%) of the salt of THC obtained by procedure I, optically pure (*S*)-Cys was obtained in higher yield (71%) by hydrolysis in water. Therefore, DMT is a more favorable inter-

Table 2. Asymmetric Transformation by Procedure II[a]

| Time | (S)-DMT·(R)-TA salt[b] | | | (S)-Cysteine | |
|---|---|---|---|---|---|
| | Yield | Specific rotation[d] | Optical purity[e] | Yield | Optical purity[g] |
| h | g [%[c]] | ° | % | g [%[f]] | % |
| 2 | 7.63[61.3] | +79.0 | 96.5 | 2.72[56.1] | 92.3 |
| 4 | 8.69[69.8] | +81.2 | 99.2 | 3.15[65.0] | 100 |
| 5 | 9.04[72.6] | +81.4 | 99.5 | 3.35[69.1] | 98.5 |
| 6 | 8.99[72.2] | +81.4 | 99.5 | 3.43[70.8] | 98.5 |
| 8 | 9.19[73.8] | +81.8 | 100 | 3.45[71.2] | 100 |
| 10 | 9.28[74.5] | +81.6 | 99.7 | 3.46[71.4] | 100 |

a) (*RS*)-Cysteine ((*RS*)-Cys) 0.0400 mol; (2*R*,3*R*)-tartaric acid ((*R*)-TA) 0.0400 mol; acetone 0.200 mol; acetic acid 15 cm$^3$; temperature 83 °C; DMT 2,2-dimethyl-4-thiazolidinecarboxylic acid. b) The (*S*)-DMT·(*R*)-TA salt is composed of (*S*)-DMT and (*R*)-TA. (c) The yield was calculated on the basis of 0.0400 ml (12.45 g) of the DMT salt. d) $[\alpha]_D^{20}$ (*c* 0.500, methanol). e) The optical purity was determined on the basis of the specific rotation of the (*R*)-DMT·(*S*)-TA salt ($[\alpha]_D^{20}$ −81.8° (*c* 0.500, methanol)) and that of equimolar mixture of (*RS*)-DMT and (*S*)-TA ($[\alpha]_D^{20}$ −2.9° (*c* 0.500, methanol)). f) The yield was calculated on the basis of 0.0400 mol (4.85 g) of Cys. g) The optical purity was determined on the basis of (*R*)-Cys ($[\alpha]_D^{20}$ +6.5° (*c* 4.00, 5 mol dm$^{-3}$ HCl)).

mediate than THC to obtain optically active Cys by the asymmetric transformation.

**Racemization by Using Aldehydes as Catalyst.** The (*S*)-DMT·(*R*)-TA salt seems to be insoluble in acetone and to be more soluble in acetic acid than the (*S*)-THC·(*R*)-TA and (*R*)-THC·(*S*)-TA salts. Therefore, a relative decrease in amount of acetic acid (or an increase of acetone) may result in an increase in yield of the (*S*)-DMT·(*R*)-TA salt or its enantiomeric salt. However, such a system is refluxed at lower temperature and hence the epimerization rate for the soluble salt is reduced.[12,13] As seen in Tables 1 and 2, procedure I gives the (*S*)-THC·(*R*)-TA or (*R*)-THC·(*S*)-TA salt with high optical purity in 80% yield by reaction for 1 h, whereas procedure II requires long reaction time (over 5 h) to give the (*S*)-DMT·(*R*)-TA salt in over 70% yield. Therefore, aldehydes seem to be more favorable catalysts for epimerization than ketones.

The racemization rate of (*R*)-DMT was measured at 80 °C in the presence of 0.1 molar equivalent of acetaldehyde, benzaldehyde, 2-chlorobenzaldehyde, or salicylaldehyde as the catalyst. Since an addition of a small amount of water to this system resulted in hydrolysis of the formed DMT,[13] 37% FA was not employed as the catalyst. The racemizations using acetaldehyde, salicylaldehyde, or no aldehydes are illustrated in Fig. 2.

Figure 2 shows that linear relationships exist between ln $\alpha_0/\alpha_t$ and time ($t$/h); the correlation coefficients are over 0.99. Therefore, these racemizations can be regarded as first-order reactions. The rate constant ($k_R$/h$^{-1}$) and half-life period ($t_{1/2}$/h) were calculated by Eq. 1 and given in Table 3.

Although the addition of aldehydes tended to accelerate the racemization of (*R*)-DMT, any aldehydes other than salicylaldehyde showed no extremely pronounced catalysis. The $k_R$ value in the case using

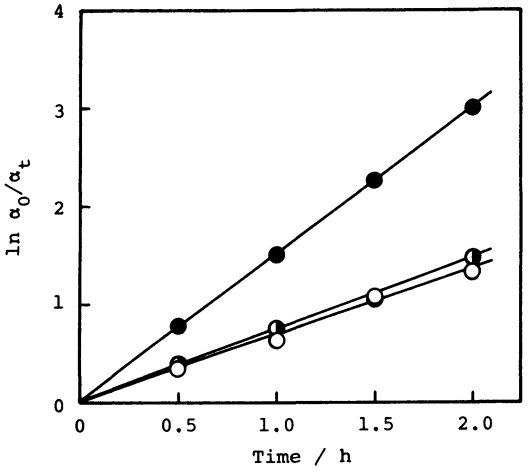


Fig. 2. Racemization of (*R*)-2,2-dimethyl-4-thiazolidinecarboxylic acid.
Conditions: (*R*)-Cysteine 0.0200 mol; aldehyde 0.0020 mol; acetone 0.100 mol; acetic acid 30 cm$^3$; temperature 80 °C. Aldehyde: ○ non; ◑ acetaldehyde; ● salicylaldehyde.

Table 3. Racemization of (*R*)-2,2-Dimethyl-4-thiazolidinecarboxylic Acid by Using Aldehydes as Catalyst[a]

| Aldehyde | Rate constant | Half-life period |
|---|---|---|
| | h$^{-1}$ | h |
| — | 0.675 | 1.03 |
| AA[b] | 0.716 | 0.968 |
| BA[c] | 0.787 | 0.881 |
| 2-CBA[d] | 0.683 | 1.01 |
| SA[e] | 1.51 | 0.459 |

a) (*R*)-Cysteine 0.0200 mol; acetone 0.100 mol; aldehyde 0.0020 mol; acetic acid 30 cm$^3$; temperature 80 °C. b) AA: Acetaldehyde. c) BA: Benzaldehyde. d) 2-CBA: 2-Chlorobenzaldehyde. e) SA: Salicylaldehyde.

Table 4. Asymmetric Transformation by Procedure III[a]

| Time h | Configuration of TA | Salt | | | | Cysteine | | |
|---|---|---|---|---|---|---|---|---|
| | | Configuration[b] | Yield g [%[c]] | Specific rotation[d] ° | Optical purity[e] % | Configuration | Yield g [%[f]] | Optical purity[g] % |
| 2 | (*R*) | (*S*·*R*) | 9.32[74.9] | +79.1 | 96.6 | (*S*) | 3.47[71.6] | 93.8 |
| 3 | (*R*) | (*S*·*R*) | 9.79[78.6] | +79.8 | 97.5 | (*S*) | 3.68[75.9] | 95.4 |
| 4 | (*S*) | (*R*·*S*) | 10.12[81.3] | −80.5 | 98.4 | (*R*) | 3.79[78.2] | 98.5 |
| 5 | (*R*) | (*S*·*R*) | 10.36[83.2] | +81.8 | 100 | (*S*) | 3.88[80.1] | 100 |
| 6 | (*S*) | (*R*·*S*) | 10.38[83.4] | −81.8 | 100 | (*R*) | 3.88[80.1] | 100 |
| 7 | (*R*) | (*S*·*R*) | 10.38[83.4] | +81.8 | 100 | (*S*) | 3.88[80.1] | 100 |

a) (*RS*)-Cysteine ((*RS*)-Cys) 0.0400 mol; (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid 0.0400 mol; salicylaldehyde 0.0040 mol; acetone 0.200 mol; acetic acid 10 $cm^3$; temperature 77 °C. b) (*S*·*R*) represented the salt composed of equimolar amounts of (*S*)-DMT and (*R*)-TA and (*R*·*S*) the salt of (*R*)-DMT and (*S*)-TA. c) The yield was calculated on the basis of 0.040 mol (12.45 g) of the DMT·TA salt. d) $[\alpha]_D^{20}$ (*c* 0.500, methanol). e) The optical purity was determined on the basis of the specific rotation of the (*R*)-DMT·(*S*)-TA salt ($[\alpha]_D^{20}$ −81.8° (*c* 0.500, methanol)) and that of equimolar mixture of (*RS*)-DMT and (*S*)-TA ($[\alpha]_D^{20}$ −2.9° (*c* 0.500, methanol)). f) The yield was calculated on the basis of 0.0400 mol (4.85 g) of Cys. g) The optical purity was determined on the basis of the specific rotation of (*R*)-Cys ($[\alpha]_D^{20}$ +6.5° (*c* 4.00, 5 mol $dm^{-3}$ HCl)).

salicylaldehyde is 2.2 times that in the absence of aldehyde.

**Asymmetric Transformation by Procedure III.** Based on the above suggestion, the asymmetric transformation of (*RS*)-Cys was achieved in the presence of 0.1 molar equivalent of salicylaldehyde as the catalyst under reflux (approximately at 77 °C), as shown in Table 4. The $^1H$ NMR spectra of the obtained salts showed methyl protons and no aromatic protons.

The (*S*)-DMT·(*R*)-TA salt with 96.6% optical purity was obtained in 75% yield even by reaction for 2 h. This salt gave (*S*)-Cys with 93.8% optical purity in 72% yield. This yield corresponds to that to be obtained at 6 h by procedure II. Therefore, the epimerization was accelerated by adding salicylaldehyde.

The (*S*)-DMT·(*R*)-TA and (*R*)-DMT·(*S*)-TA salts with 98—100% optical purity were obtained in over 80% yield by reaction for 4—7 h. These salts were hydrolyzed in water to give (*R*)- or (*S*)-Cys, respectively, with 98—100% optical purity in 80% yield based on the initial (*RS*)-Cys. Further, (*R*)- and (*S*)-TAs, respectively, were recovered easily from these salts in over 80% recovery.

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