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Sterically Controlled Syntheses of Optically Active Organic Compounds. XXI. The Temperature Dependence of Hydrogenolytic Asymmetric Transamination between Optically Active Phenylglycine and α-Keto Acids*

Kaoru HARADA, Tameo IWASAKI, and Tadashi OKAWARA

Institute for Molecular and Cellular Evolution, Department of Chemistry, University of Miami, 521 Anastasia Avenue, Coral Gables, Florida 33134, U.S.A.

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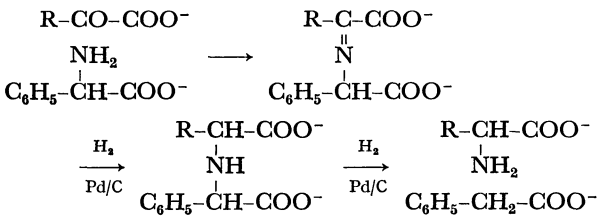
Generally, temperature is one of the most important factors in determining the molecular conformation in asymmetric syntheses. Several studies of the effect of temperature on asymmetric syntheses have been recorded in the literature.[1-7]

A temperature dependent asymmetric synthesis by hydrogenolytic asymmetric transamination between ethyl pyruvate and optically active benzylic amines was reported from this laboratory.[8,9] It was found that the difference of entropy of activation ($\Delta\Delta S^{\ddagger}$) for the diastereomeric transition states was the important factor in the asymmetric synthesis. These facts agreed with the previously proposed explanation (chelation hypothesis) for the steric course of the sterically controlled reaction.[10-12]

In the previous study from this laboratory, the hydrogenolytic asymmetric transamination between α-keto acids and optically active α-phenylglycine in aqueous alkaline solution was examined.[13,14] The possible steric course of this asymmetric synthesis was discussed.[14] The chelated intermediate formed between the substrate and the catalyst would not be expected to be as important in this reaction as in similar asymmetric reactions using organic solvents[10-12] because of the high dielectric constant of the solvent used.



This investigation examines the temperature dependence of the hydrogenolytic asymmetric transamination between (*R*)-α-phenylglycine and (A) pyruvic acid or (B) α-ketoglutaric acid. The reaction temperatures used ranged from 0 to 70°C. The hydrogenation reactions were carried out at 1 atmosphere of hydrogen using palladium on charcoal (5%) in an aqueous solution that contained an equimolar amount of sodium hydroxide to the carboxyl groups in the substrate. The reaction procedures are similar to those described in an earlier paper.[13,14] The results are summarized in Table 1. When (*R*)-phenylglycine was used, (*R*)-alanine and (*R*)-glutamic acid were synthesized. The optical purities ranged from 31 to 57% for alanine and from 4 to 46% for glutamic acid. At 0°C, the optical purities of amino acids were the highest and the optical purities decreased as the reaction temperature was increased.

Formation of optically active amino acids in the asymmetric synthesis is due to the difference between the rates of formation of the two diastereomers from the starting material (substrate*). The rates of formation of the diastereomeric activated complexes are determined by the difference of the free energies of activation ($\Delta G^{\ddagger}$) for two diastereomeric transition states. According to the transition state theory, the rate of formation of an activated complex [(*R*)-substrate* complex]‡ in the transition state is expressed as follows:[2,15-18]

$$k_R = \kappa_R \frac{kt}{h} e^{-\Delta G_R^{\ddagger}/RT}$$

If we assume that the transmission coefficient κ_R is equal to κ_S, the *R*-product*/*S*-product* is expressed as shown below:

$$\frac{R\text{-product*}}{S\text{-product*}} = \frac{R}{S} = \frac{k_R}{k_S} = \exp\frac{\Delta S_R^{\ddagger} - \Delta S_S^{\ddagger}}{R} \exp\frac{-(\Delta H_R^{\ddagger} - \Delta H_S^{\ddagger})}{RT}$$

$$= \exp\frac{\Delta\Delta S_{R-S}^{\ddagger}}{R} \exp\frac{-\Delta\Delta H_{R-S}^{\ddagger}}{RT}$$

$$\log\frac{R}{S} = \log\frac{k_R}{k_S} = \frac{\Delta\Delta S_{R-S}^{\ddagger}}{2.3R} - \frac{\Delta\Delta H_{R-S}^{\ddagger}}{2.3RT}$$

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18) The $\Delta G^{\ddagger}$ of the equation includes external factors such as solvents and catalysts, which cause to change the free energy of activation of the reactions, *Cf.* Chapters 4 and 8 of literature 15.

Table 1. Asymmetric synthesis of amino acids at varying temperatures

Reaction		Reaction temp. (°C)	Phegly config.	Synthesized amino acid		DNP-Amino acid	
				Config. of amino acid	Yield[a] (%)	$[\alpha]_D^{25}$[b]	Optical purity[c] (%)
A	Ala	10	*R*	*R*	—[d]	−82.0	57
		20	*R*	*R*	33	−74.5	52
		30	*R*	*R*	29	−66.0	46
		40	*R*	*R*	26	−59.8	42
		50	*R*	*R*	46	−56.2	39
		60	*R*	*R*	44	−44.8	31
		70	*R*	*R*	40	−50.8	35
B	Glu	10	*R*	*R*	30	+37.4	46
		20	*R*	*R*	24	+31.0	38
		30	*R*	*R*	29	+21.8	27
		40	*R*	*R*	27	+16.6	20
		50	*R*	*R*	36	+10.8	13
		60	*R*	*R*	34	+ 9.8	12
		70	*R*	*R*	35	+ 3.2	4

a) Yields were calculated from phenylglycine.
b) Specific rotation of DNP-alanine was measured in 1M NaOH. Specific rotation of DNP-glutamic acid was measured in glacial acetic acid.
c) Optical purity was defined as $[\alpha]_D$ obsed/$[\alpha]_D$ of the compound ×100; DNP-(*R*)-(−)-alanine, $[\alpha]_D^{25}$ −143.9° (1M NaOH), DNP-(*R*)-(+)-glutamic acid, $[\alpha]_D^{25}$ +80.8° (AcOH).
d) A part of the sample was lost.

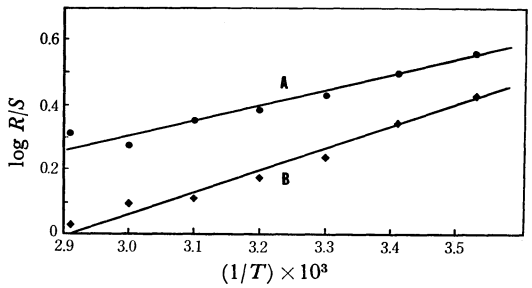

Fig. 1. Temperature dependence of hydrogenolytic asymmetric transamination. Reaction A, alanine: Reaction B, glutamic acid.

Figure 1 shows the plot of log R/S against $1/T$ from the results obtained in the asymmetric transamination reactions. In both reactions A and B, the plots are almost linear in the range from 10 to 70°C. From this plot, $\Delta\Delta H^{\ddagger}_{R-S}$ and $\Delta\Delta S^{\ddagger}_{R-S}$ of reactions A and B were calculated.

reaction A $\Delta\Delta H^{\ddagger}_{R-S} = -5.0$ kcal mol^{-1}

$\Delta\Delta S^{\ddagger}_{R-S} = -11.8$ cal mol^{-1} deg^{-1}

reaction B $\Delta\Delta H^{\ddagger}_{R-S} = -7.5$ kcal mol^{-1}

$\Delta\Delta S^{\ddagger}_{R-S} = -22.0$ cal mol^{-1} deg^{-1}

These results indicate that the free energy of activation ($\Delta G^{\ddagger}$) is independent of the reaction temperature and that the asymmetric hydrogenation reaction proceeds by a single mechanism in this temperature range.

Experimental

All the asymmetric transamination reactions were carried out as described in reference 14, except for the reaction temperature and the apparatus. Hydrogenation and hydrogenolysis were carried out in a three neck flask (100 ml) at one atmosphere with magnetic stirring at varying temperatures. The accuracy of the reaction temperature is about ±1°C. (*R*)-Phenylglycine (1.5 g, 0.001 mol, $[\alpha]_D^{25}$ −168.0°, *c* 1.11, 5M HCl) and 0.01 mol of α-keto acids were dissolved in 20 ml (30 ml in the case of α-ketoglutaric acid) fo aqueous sodium hydroxide (1M). Palladium on charcoal (5%, 2.5 g) was added to the solution and hydrogenation and hydrogenolysis were carried out. The hydrogenation and hydrogenolysis reactions proceeded at different rates depending on the temperature used. At 70°C, 20 min was sufficient to complete the reaction; however, at 10°C, more than 100 hr was necessary. After hydrogenolysis, the resulting amino acids were isolated by the use of a Dowex 50 column. A part of the amino acid was converted to DNP-amino acid by the use of 2,4-dinitrofluorobenzene. The resulting amino acids were purified by the use of Celite column chromatography in the usual manner[19] without fractionation of optical isomers. The DNP-amino acids were used for measurement of optical purity of amino acid. The dinitrophenylation was especially necessary in these asymmetric syntheses because the resulting crude amino acids contained impurities which had amphoteric properties. Therefore, the yield of alanine and glutamic acid was determined by the use of an automatic amino acid analyzer after appropriate dilution. The elution pattern of alanine in the amino acid analyzer showed 4—7 peaks other than alanine. However, the elution pattern of glutamic acid showed a single peak.

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