The Effect of Sodium Hydroxide on the Stereoselectivity of Hydrogenolytic Asymmetric Transaminations between (*R*)-2-Amino-2-phenylethanol and 2-Keto Acids†

Minoru TAMURA,†† Shozo SHIONO,††† and Kaoru HARADA*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305
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Hydrogenolytic asymmetric transaminations between (*R*)-2-amino-2-phenylethanol and 2-keto acids were carried out over Pd catalyst in the absence or presence of various amount of sodium hydroxide in water or alcohols. The stereoselectivity of the reaction was significantly influenced by the amount of sodium hydroxide in the reaction mixture. When pyruvic acid was used in water the optical purity of alanine was 22% ee (*R*) and in 1 M (1 M=1 mol dm^{-3}) sodium hydroxide solution it was 62% ee (*S*). When 2-oxobutyric acid was used in ethanol in the absence and presence of sodium hydroxide (1M), the optical yields of 2-aminobutyric acid were 2% ee (*R*) and 81% ee (*S*), respectively. In contrast, the addition of sodium hydroxide had little or no effect on the stereochemistry of the reaction using (*S*)-α-methylbenzylamine as a chiral source in aqueous or ethanolic solution. The substituent, additive, temperature, and solvent effects on the asymmetric reactions were examined in aqueous or ethanolic alkaline solution. Based on these experimental results, a possible explanation for the change in stereoselectivity by using sodium hydroxide is discussed.

There have been many studies on the hydrogenolytic asymmetric transamination between chiral amines or amino acid derivatives and 2-keto acids or their esters, and some of them have been explained by the chelation mechanism.[1-6]

In the previous study,[6] a hydrogenolytic asymmetric transamination between pyruvate and (*R*)-2-amino-2-phenylethanol (**1a**) in organic solvent was carried out. The configuration of the resulting amino acid was (*S*), and its optical purity increased with the decrease of the polarity of the solvent used. Such an effect and also substituent effect on the stereoselectivity were explained by the chelation mechanism.

In the present study, hydrogenolytic asymmetric transaminations between 2-keto acids and **1a** were carried out in aqueous and alcoholic alkaline solutions (Scheme 1). As a result, we found that (*S*)-selectivity increased by the addition of sodium hydroxide. This result could not be explained by the chelation mechanism, because (*S*)-selectivity should be decreased with the increase of the solvent polarity.

Figure 1 shows the results of the preliminary experiments of hydrogenolytic asymmetric transamination between pyruvic acid and **1a** in the mixtures of methanol or ethanol and 1 M of aqueous NaOH (1 M=1 mol dm^{-3}). With the increase of the content of 1 M NaON, the optical purites of the products (52, 57%) decreased and reached a minimum (8,13%) with a 33% content of 1 M NaOH and then increased (61, 62%).

Figure 2 shows the result of the experiments carried out in the mixtures of water and methanol in various ratios at certain alkali concentrations. It was found that the addition of sodium hydroxide increased the optical yeild of the product, while an increase of water content decreased the optical purity. It was therefore concluded that the increase of (*S*)-selectivity in the reaction was mainly due to sodium hydroxide.

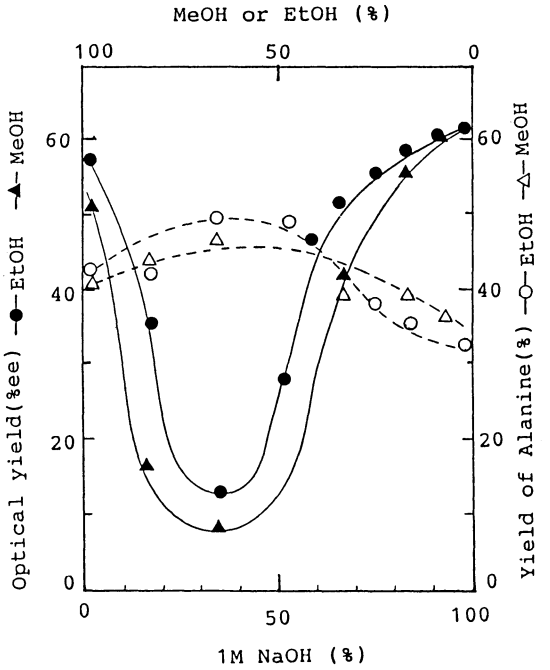

Fig. 1. Asymmetric hydrogenation in a mixture of alcohol and 1M NaOH aq.

Catalytic Hydrogenation in Aqueuous Solution. Asymmetric transaminations between **1a** and pyruvic acid or 2-oxobutyric acid were carried out in aqueous solution containing various amounts of sodium hydroxide (Fig. 3). The optical yield of the products increased considerably by the addition of sodium

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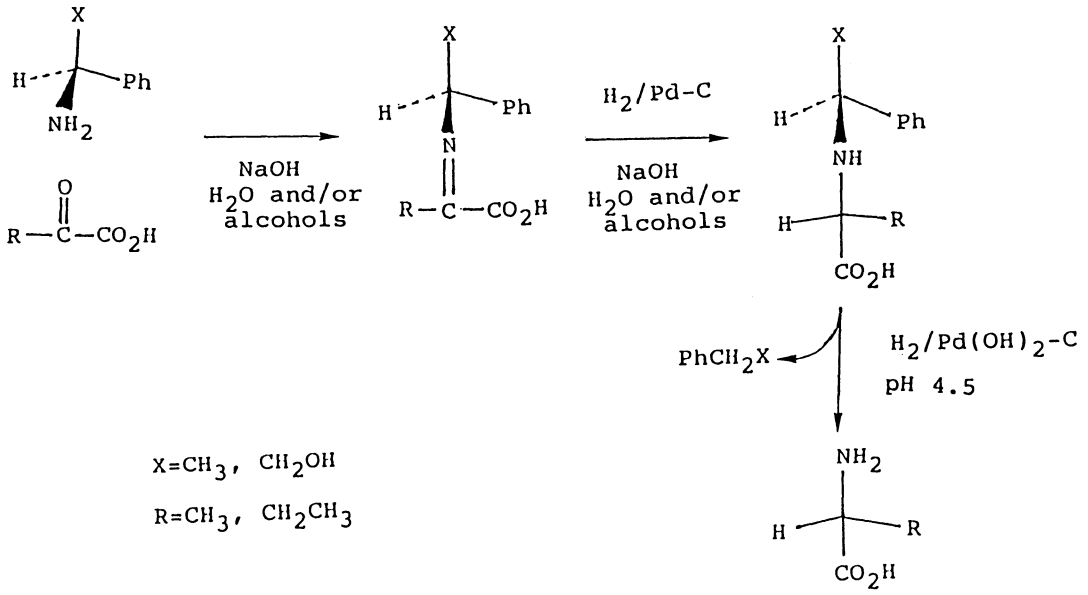
†† Present address: Department of Biochemistry, Medical College of Oita, Hazama-cho, Oita 879-56.

††† Present address: Research Laboratory, Shionogi Pharmaceutical Co., Osaka.



Scheme 1. Hydrogenolytic asymmetric transamination in aqueous and alcoholic alkaline solutions.

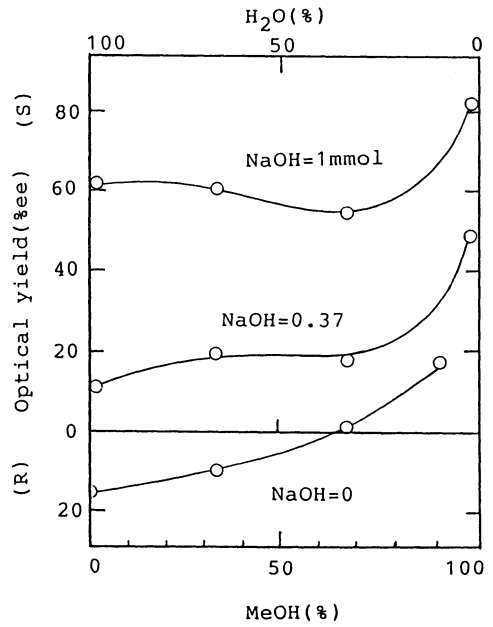


Fig. 2. Asymmetric hydrogenation in a mixture of MeOH and water in the presence of different amount of NaOH.

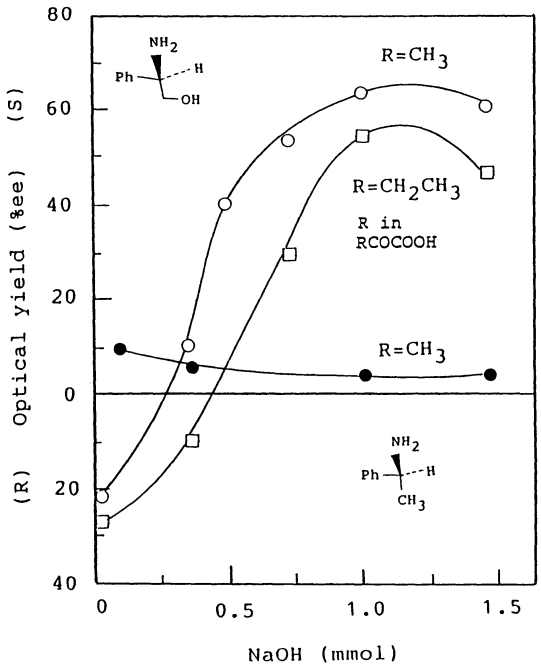


Fig. 3. Effect of NaOH on the optical yield of the asymmetric transamination in aqueous solution.

hydroxide. When the amount of sodium hydroxide was zero or small, (*R*)-product was obtained in excess. With an increase of sodium hydroxide, the configuration of the product inverted from (*R*) to (*S*), and the optical purity of the product increased to 62% ee (alanine) or 54% ee (2-aminobutyric acid) at 1 mmol of sodium hydroxide. By further increasing the amount of sodium hydroxide, the optical yield decreased slightly.

In order to examine whether the hydroxyl group of the chiral source was involved or not in the improvement of the optical yield in alkaline solution, (*S*)-α-methylbenzylamine (**1b**) was used as a chiral source, in which the hydroxymethyl group of **1a** is replaced with a methyl group. The addition of sodium hydroxide had no significant effect on the stereochemistry of the catalytic hydrogenation with **1b** (Table 1, Fig. 3). This result suggested that the hydroxyl group plays an important role in determining the steric course of the reaction in the presence of sodium hydroxide.

Table 2 shows the effect of various additives on the optical purity of the product obtained in aqueous

Table 1. Effect of NaOH on Asymmetric Hydrogenation in Aqueous Solution

R in RCOCOOH	Asymmetric moiety	NaOH (mmol)	Amino acid formed	Chem.y. (%)	Opt.y. (% ee)
R=CH_3	**1a**	0	Ala	41	22 (*R*)
		0[a]		35	33 (*R*)
		0.37		36	11 (*S*)
		0.5		37	40 (*S*)
		0.73		35	54 (*S*)
		1.0		34	62 (*S*)
		1.46		27	61 (*S*)
		1.0[b]		29	61 (*S*)
	1b	0.1	Ala	49	11 (*S*)
		0.37		43	9 (*S*)
		1.0		47	3 (*S*)
R=CH_2CH_3	**1a**	0	But	54	28 (*R*)
		0.37		48	10 (*R*)
		0.73		34	29 (*R*)
		1.0		34	54 (*S*)
		1.46		29	47 (*S*)

a) Pd-C was washed well with water before use. b) The starting mixture was stirred without NaOH, and NaOH was added just before hydrogenation reaction.

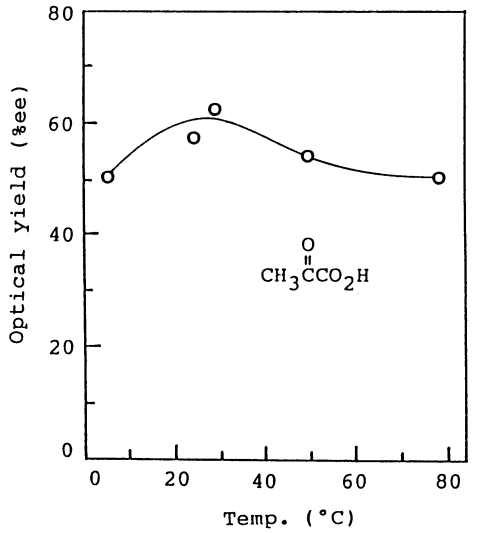


Fig. 4. Temperature effect on the optical yield of asymmetric transamination in aqueous alkaline solution.

solution. When alkali halides or triethylamine were added to the reaction mixture, the (*S*)-product was obtained in a small excess. The effects of potassium hydroxide and lithium hydroxide were similar to that of sodium hydroxide. When NaCl or urea was added together with sodium hydroxide, the optical yield was lower than that with sodium hydroxide alone. These results indicated that the effect of sodium hydroxide on optical yield is mainly caused by hydroxide ion.

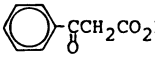
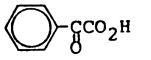
The temperature effect was examined by the use of pyruvic acid (Fig. 4). The temperature dependence on the optical yield was not high. This result was apparently different from that with phenylglycine,[4] in which the optical yield decreased with increase of the temperature.

Table 2. Effect of Additives on Asymmetric Hydrogenation in Aqueous Solution[a]

Additives (1 mmol)	Chem.y.[b] (%)	Opt.y.[c] (% ee)	Confign
—	41	14	(*R*)
NaCl	17	2	(*S*)
KBr	19	19	(*S*)
Triethylamine[d]	46	2	(*S*)
Triethylamine	36	11	(*S*)
NaOH	34	62	(*S*)
LiOH	36	55	(*S*)
KOH	37	63	(*S*)
NaOH+NaCl	22	23	(*S*)
NaOH+Urea[d]	24	29	(*S*)

a) The reaction was carried out with **1a** and pyruvic acid. The asymmetric hydrogenation was performed with various additives. b) Chemical yields of alanine were starting from pyruvic acid. c) Optical yields were determined by GLC-method. d) 0.36 mmol of additives were used.

Table 3. Asymmetric Transamination Using Several α-Keto Acids[a] in Aqueous Alkaline Solution

α-keto acids	Amino acids formed	Chem.y. (%)	Opt.y.[b] (% ee)	Confign
CH_3CCO_2H (O)	Ala	38	64	(*S*)
$CH_3CH_2CCO_2H$ (O)	But	29	54	(*S*)
	Phe[c]	10	10	(*S*)
	Ph-Gly[c]	18	19	(*R*)

a) Asymmetric hydrogenation was carried out in aqueous alkaline solution (NaOH, 1 mmol). b) Optical yields were determined by GLC-method. c) Trace amount of hexahydrophenylalanine or α-cyclohexylglycine was also formed.

Table 4. Effect of NaOH on the Asymmetric Hydrogenation in Ethanolic Solution

R in RCOCOOH	Asymmetric moiety	NaOH (mmol)	Amino acid formed	Chem.y. (%)	Opt.y.(% ee) GLC-method	DNP-method
$R=CH_3$	**1a**	—[a]	Ala	44	48 (*S*)	
		0.37		43	51 (*S*)[b]	49 (*S*)
		0.73		42	76 (*S*)	
		1.0		40	85 (*S*)[b]	82 (*S*)
		1.5		41	84 (*S*)	
$R=CH_2CH_3$	**1a**	—[a]	But	69	2(*R*)	
		0.37		58	6(*R*)[b]	5 (*R*)
		0.73		38	70(*S*)	
		1.0		35	87(*S*)[b]	87 (*S*)
		1.5		30	82(*S*)	
		1.0[c]		19	81(*S*)	
	1b	0.37	But	40	35 (*R*)	
		0.73		31	28 (*R*)	
		1.1		16	21 (*R*)	

a) Et_3N (1 equiv mol, 0.37 mmol) was added to the reaction mixture. b) These values were the averages of the results from independent experiments. c) The reaction was carried out in the presence of NaOH (1 mmol) and NaCl (0.5 mmol).

The substituent effect was examined by the use of several 2-keto acids in the presence of sodium hydroxide (Table 3). When pyruvic acid, 2-oxobutyric acid, and phenylpyruvic acid were used, the optical purities were 62, 54, and 11% ee (*S*), respectively. When benzoylformic acid was used, the configuration of the product was inverted. The selectivity of (*S*)-product decreased in the order of CH_3->CH_3CH_2->$PhCH_2$->Ph-. This order agreed with the effective bulkiness of R group of 2-keto acids.[5]

Catalytic Hydrogenation in Ethanolic Solution. In order to examine the alkali effect in ethanol, the reaction was performed in ethanol containing various amounts of sodium hydroxide using pyruvic acid and 2-oxobutyric acid (Table 4, Fig. 5). When pyruvic acid was used in the absence of sodium hydroxide (1 equiv mol of triethylamine was used in the reaction), the optical yield of alanine was 48% ee (*S*). With the increase of the amount of sodium hydroxide, the optical purity increased to 85% ee (*S*). When 2-oxobutyric acid was used in the absence of sodium hydroxide, (*R*)-2-aminobutyric acid was favored slightly. Addition of sodium hydroxide resulted in the inversion of configuration of the product, and a sudden increase in the selectivity of (*S*)-configuration was observed. When 1 mmol of sodium hydroxide was used, (*S*)-2-aminobutyric acid was obtained in an optical yield of 87% ee. In the reaction with 2-oxobutyric acid, the chemical yields decreased with increasing amount of sodium hydroxide.

When (*S*)-α-methylbenzylamine was used in the reaction with 2-oxobutyric acid, the configuration of the product was (*R*). The addition of sodium hydroxide had little effect on the optical yield in contrast to the result with **1a**. These results clearly indicate that the hydroxyl group in the substrate is involved in the stereochemistry of the reaction.

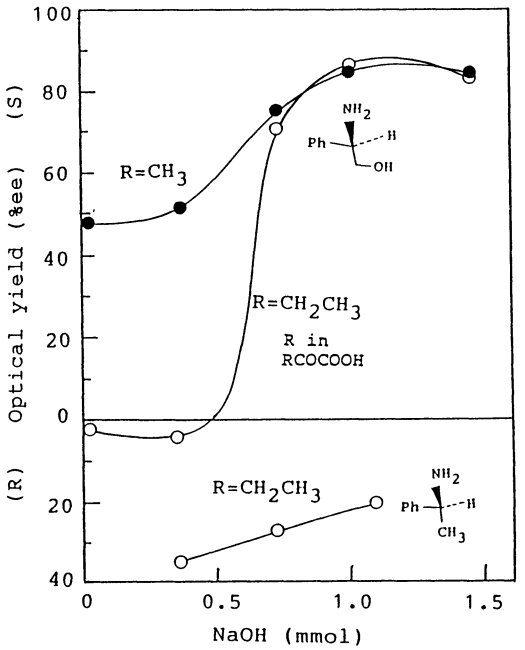
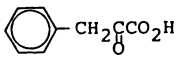
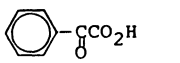


Fig. 5. Effect of NaOH on the optical yield of the asymmetric hydrogenation in ethanolic solution.

In Table 4, the optical yield of the products were further confirmed by DNP method. The optical yields determined by GLC method were in good agreement with those by DNP method.

The effect of substituents in 2-keto acids was examined. The reaction was carried out using several 2-keto acids in the presence of 1 mmol of sodium hydroxide in ethanol. The results are shown in Table 5. When 2-oxobutyric acid was used, the optical yield of the resulting 2-aminobutyric acid was similar to that with pyruvic acid. The selectivity of (*S*)-product was as follows CH_3->C_2H_5->$PhCH_2$->Ph-.

Table 5. Asymmetric Transamination with Several α-Keto Acids in Ethanolic Alkaline Solution[a)]

α-Keto acid	Amino acids formed	Chem.y. (%)	Opt.y.[b)] (% ee)	Confign
$CH_3\overset{\overset{O}{\|}}{C}CO_2H$	Ala	42	85	(*S*)
$CH_3CH_2\overset{\overset{O}{\|}}{C}CO_2H$	But	33	86	(*S*)
	Phe	17	17	(*S*)
	Ph-Gly	21	25	(*R*)

a) The asymmetric hydrogenation was carried out in ethanolic alkaline solution (NaOH, 1 mmol). b) The optical yields were determined by GLC-method.

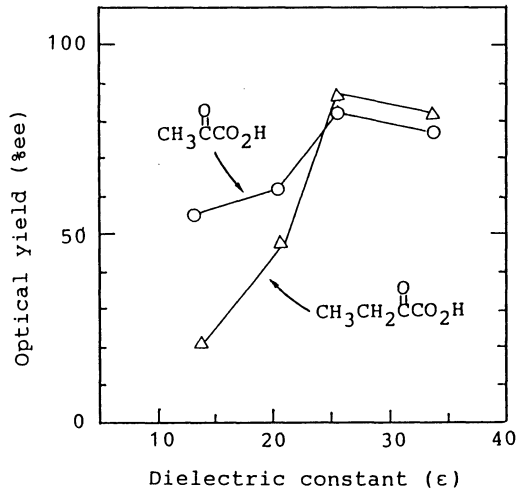


Fig. 6. Effect of solvent on the optical yield of asymmetric hydrogenation in the presence of NaOH.

Table 6. Effect of Triethylamine on the Asymmetric Hydrogenation in Ethanolic Solution

R in RCOCOOH	Et_3N[a)] (mmol)	Amino acid formed	Chem.y. (%)	Opt.y. (% ee)
R=CH_3	0.37 (1.0)	Ala	44	48 (*S*)
	0.73 (2.0)		40	47 (*S*)
	1.1 (3.0)		38	51 (*S*)
R=CH_2CH_3	0.37 (1.0)	But	69	2 (*R*)
	0.73 (2.0)		50	4 (*R*)
	1.1 (3.0)		49	1 (*R*)

a) The values in parentheses were equivalent mol of triethylamine to starting 2-keto acids.

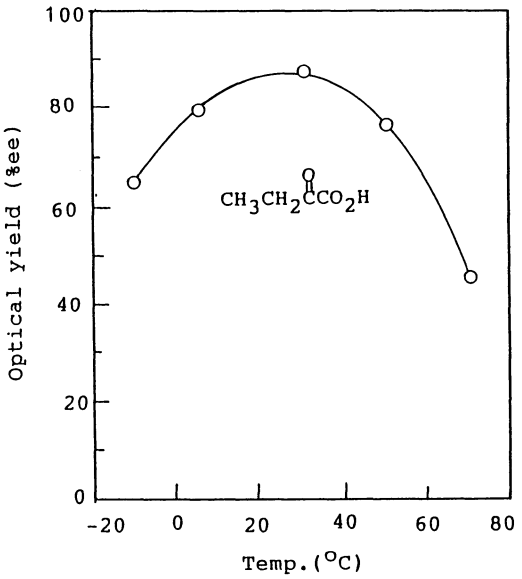


Fig. 7. Temperature effect on the optical yield of the asymmetric hydrogenation in ethanolic alkaline solution.

The solvent effect on the asymmetric transamination in the presence of 1 mmol of sodium hydroxide is shown in Fig. 6. When methanol was used as the solvent, the optical purity of the (*S*)-product was slightly lower than that with ethanol. When isopropyl alcohol or *s*-butyl alcohol was used, the optical yield of the reaction was much lower than that with ethanol. The order of the optical purity with these alcohols is: EtOH>MeOH>*i*-PrOH>*s*-BuOH. And this order was not consistent with the order of the polarity of the solvent.

The temperature effect on the optical yield of the reaction of 2-oxobutyric acid with **1a** is shown in Fig. 7. The plots of the optical yield versus temperature gave a bell-shape profile with a maximum at 30 °C.

In order to examine whether the optical yield was influenced by bases other than sodium hydroxide, the reactions were carried out in the presence of different amounts of triethylamine (Table 6). The change of the amount of triethylamine had no effect on the optical yield with pyruvic acid or 2-oxobutyric acid in the range of 0.37 to 1.1 mmol, although chemical yields decreased with the increase of triethylamine.

Experimental

The amino acid analyses were performed with a Yanagimoto LC-5S and Durrum model 500. The gas chromatographic analyses were carried out with a Hitachi 163 type gas chromatograph. Chirasil-Val glass capillary column was purchased from Applied Science Laboratories, Inc., U.S.A. The specific rotations were measured with a JASCO DIP-181 type polarimeter using a 50 mm cell. (*S*)-Methylbenzylamine (**1b**) was purchased from Aldrich Chemical Co., Inc. and distilled under nitrogen before use (**1b**; $[\alpha]_D$ −42.6, benzene).[7)] (*R*)-2-Amino-2-phenylethanol (**1a**) was synthesized from (*R*)-phenylglycine as described previously[6)] (**1a**; $[\alpha]_D$ −26.4, benzene). Palladium on charcoal (5% Pd-C) was obtained from Nippon Engelhard, Inc. Palladium hydroxide on charcoal was prepared according to the method of Hiskey and Northrop.[8)] Pyruvic acid and 2-oxobutyric acid were distilled before use.

General procedure of the hydrogenolytic asymmetric transamination was as follows: Compound **1a** (50 mg, 0.365 mmol) and 2-keto acid (0.365 mmol) were dissolved in 1 ml of water or alcohol containing a given amount of sodium

hydroxide. The mixture was stirred under nitrogen for 12 h to form corresponding Schiff base. Asymmetric hydrogenation was carried out by using 5% Pd-C (100 mg) at 30 °C under 1 atm of hydrogen for 3 days. The catalyst was removed by filtration and washed with a small volume of 3 M HCl. The solution was evaporated to dryness, and the residue was dissolved in about 3 ml of water. After the pH of the solution was adjusted to 4.5 with sodium hydrogencarbonate, hydrogenolysis was performed with $Pd(OH)_2$ on charcoal (200 mg) at room temperature under 3 atm of hydrogen for 12 h or under 1 atm for 4 days. The catalyst was removed by filtration and washed with a small volume of 3 M HCl. The solution was evaporated to dryness and a small portion of the aqueous solution was applied to an amino acid analyzer to determine the chemical yield of the resulting amino acid. The optical purities of amino acids were determined by gas chromatographic analysis with a chiral column (GLC-method). Some of the values (Table 4) were confirmed by polarimetry after DNP-ylation.

Determination of Optical Purity. i) GLC-method—The synthesized amino acid, not isolated, was esterified by reflux with isopropyl alcohol saturated with HCl gas and then trifluoroacetylated with trifluoroacetic anhydride in dichloromethane. The derivatives were applied to gas chromatograph equipped with Chirasil-Val,[9] (0.3 mm i.d.×25 m). The column temperature was raised from 90 to 150 °C at a rate of 4 °C min^{-1}. The gas chromatographic analysis was repeated three times each and the peaks were integrated with a Hitachi 834-30 chromato-processor.

ii) DNP-method—The dinitrophenylation of amino acids was carried out as described in the earlier paper. The DNP-derivatives of the amino acids were purified with thin layer chromatography. The specific rotations of the purified DNP-amino acids were measured in 1 M NaOH. The following values were used as the specific rotations of optically pure DNP-amino acids; DNP-(*S*)-alanine, $[\alpha]_D$−143.9 (1 M NaOH); DNP-2-aminobutyric acid, $[\alpha]_D$−98.8 (1 M NaOH).[7] When the DNP-method was used for determining the optical yield, the reaction was carried out in ten-fold scale of the standard procedure described above.

Discussion

There have been many studies on the asymmetric transamination, but few dealing with the effect of alkali.[5] Alkali effects on the stereoselectivity have been studied on the hydrogenation of C=C or C=O double bond over Pd,[10–16] although the mechanism of the effect have not been fully clarified. It was also reported that the hydroxide ion has strong affinity to Pd surface,[17] and that hydroxide ion adsorbed on the Pd catalyst.[11]

Based on the experimental results and the examination with molecular model, a possible steric course for the catalytic hydrogenation in the absence or presence of sodium hydroxide are discussed below. Possible mechanism for the hydrogenation in aqueous and alcoholic solutions.

In the absence of sodium hydroxide, the hydroxyl group of the substrate could have low affinity with the catalyst. Under these conditions, the preferred conformation of the substrate on the catalyst in aqueous solution was thought to be **A**, which would lead to (*R*)-configuration (Fig. 8). In the presence of alkali, the hydroxyl group of the substrate could interact with hydroxide ion adsorbed on the catalyst, presumably by the formation of hydrogen bond. Consequently, the prefered conformation in the adsorption step was assumed to be **B**, in which the carboxyl group would be placed away from hydroxymethyl group owing to steric repulsion. (*S*)-Product is expected to form through structure B. This hypothetical mechanism is supported by the fact that the selectivity of the (*S*)-product of the reaction decreased with the increase of the bulkiness of the alkyl group of 2-keto acids

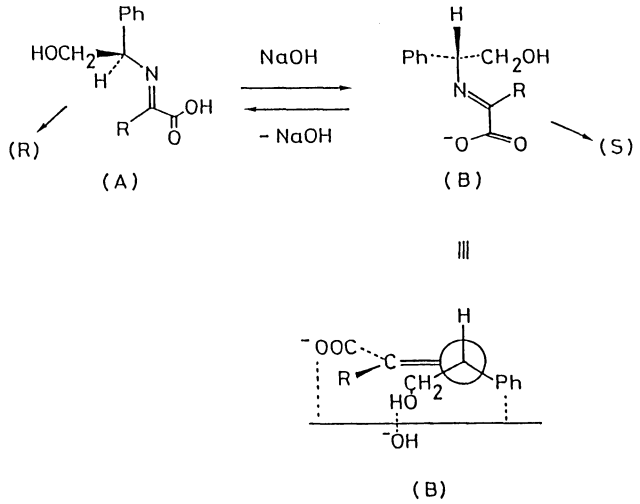


Fig. 8. Possible conformation in the catalytic hydrogenation in aqueous solution in the absence and presence of NaOH.

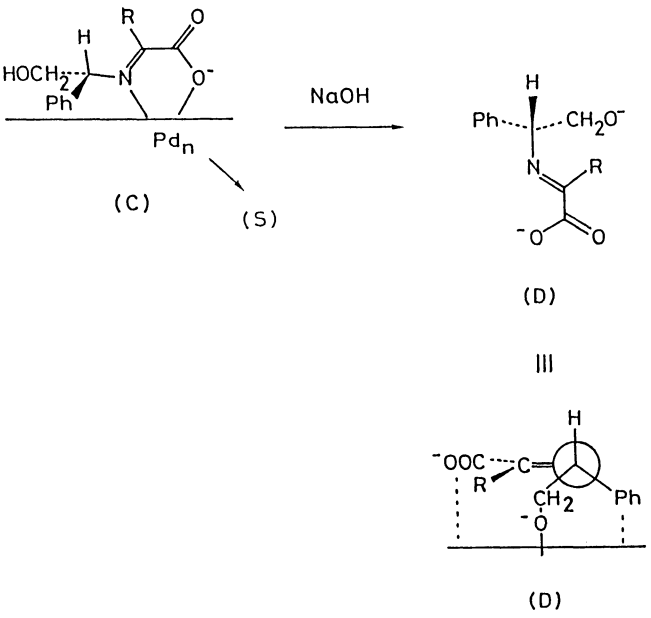


Fig. 9. Possible conformations of the substrate in the absence and presence of NaOH in alcoholic solvent.

(Table 3). The decrease of the optical yield by addition of NaCl together with sodium hydroxide could be caused by the replacement of hydroxide ion with chloride ion on the catalyst surface (Table 2).

When the amount of sodium hydroxide was none or small in alcoholic solution, the experimental results could be interpreted by the chelation mechanism (Fig. 9).[1,2,7] When pyruvic acid was used, conformation **C** was thought to be preferable,[6] which would lead to the (*S*)-product.

In the presence of alkali, the preferred conformation of the substrate was thought to be **D**. This conformation is similar to the conformation **B** except that the proton of hydroxyl group in asymmetric moiety is dissociated and that the distance between the substrate and the catalyst surface is shorter. In this conformation, the carboxyl group is apart from the alkoxide anion by steric and electrostatic repulsion. When 2-oxobutyric acid was used, the relative bulkiness of the R group increase compared with that of pyruvic acid. However, the carboxyl group is thought to be placed away from alkoxide anion as in the conformation **D** owing to the electrostatic repulsion. That may be a reason why the optical yield with 2-oxobutyric acid was similar to that with pyruric acid. When benzoylformic acid was used, the (*R*)-product was preferably obtained. The inversion of the configuration was explained by the dominant steric repulsion between R and alkoxide anion over the electrostatic repulsion between carboxylate and alkoxide anion.

It was also shown that the optical yield was lower in less polar solvent such as *i*-PrOH and *s*-BuOH than that in more polar solvents. This result may be due to the difference of the solvation ability of these alcohols to the alkoxide anion. The stabilization of alkoxide ion by the solvation may not be sufficient in less polar solvents.

The examination of the temperature effect showed that the peak of the optical yield was at around 30 °C. This result might related to the fact that the dissociation is generally accelerated by a rise of the temperature to some extent and decrease at higher temperature.[18]

In summary, it was found that the preferred conformation of the substrate in aqueous or alcoholic solution changed by the modification of the Pd catalyst surface with hydroxide ion. The hydroxyl group of the substrate also played an important role on the adsorbed stage on the catalyst in the hydrogenation process. The alkali concentration effect, additive effect, temperature effect, substituent effect in the hydrogenolytic asymmetric transaminations in both aqueous and alcoholic solutions support the possible mechanism presented for the hydrogenation in the presence of sodium hydroxide.

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