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Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel Catalyst. XXV. Contributions of pH-Adjusting Reagents in the Asymmetric Hydrogenation

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In the asymmetric hydrogenation of methyl acetoacetate with modified Raney nickel catalysts, the effects of pH-adjusting reagents were studied using $\mathrm{D_s}$-tartaric acid, $\mathrm{L_s}$-2-hydroxyisovaleric acid, L-glutamic acid, and L-aspartic acid as the modifying reagents. The effects of various metal ions and ammonium ions were investigated at pH 5.0. The asymmetric activity of the catalyst modified with the 2-hydroxy monocarboxylic acid or 2-amino dicarboxylic acid was not affected by the pH-adjusting reagents. However, 2-hydroxy dicarboxylic acid was markedly influenced by the reagents. The univalent metal ion was more effective than divalent or ammonium ions. Sodium hydroxide was the best pH-adjusting reagent. The adsorption state of the modifying reagent was discussed on the basis of the effects of the pH-adjusting reagent.

In the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate, the pH of a modifying solution has been found to affect the asymmetric activity of the catalyst.[1,2] All the modifying reagents which have been tested, except neutral amino acids,[3] can be classified into two groups according to the effects of the modifying pH, as is shown in Fig. 1.

Group A: The hydroxy dicarboxylic acids. The asymmetric activity of catalyst modified with an acid of this group is at its maximum at about pH 5 and decreases on both the acidic and alkaline sides.

Group B: The hydroxy monocarboxylic acids and most monoamino dicarboxylic acids. The asymmetric activity of a catalyst treated with this group of acids is not influenced by the modifying pH on the acidic side and decreases with an increase in the modifying pH.

It was suggested by Tatsumi[4] that the pH-dependency of the asymmetric activity of the catalyst modified with the 2-hydroxy carboxylic acid might be brought about by the neutralization of the carboxyl groups. However, the case of the pH-dependency and the factors producing the two different kinds of effects of the modifying pH was not clear. The in-

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[1] Y. Izumi, M. Imaida, H. Fukawa, and S. Akabori, This Bulletin, **36**, 21 (1963).

[2] Y. Izumi, T. Harada, T. Tanabe, and K. Okuda, *ibid.*, **44**, 1418 (1971).

[3] The effect of the modifying pH was not reported because of the lack of any investigation into the proper pH-adjusting reagent.

[4] S. Tatsumi, This Bulletin, **41**, 408 (1968).

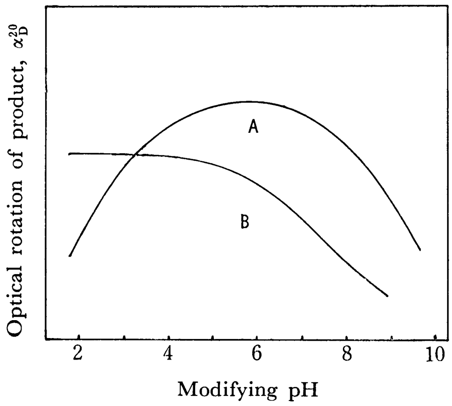

Fig. 1. Effect of modifying pH on modification at 0°C.

fluences of the various pH-adjusting ions were studied, and the adsorption state of the modifying reagent and the pH-dependency of the asymmetric activity are discussed.

Experimental

L-2-Hydroxyisovaleric Acid (HIV). The HIV was prepared by the method of Winitz *et al.*[5]

Divalent Metel D-Tartarates. Divalent metal D-tartarates were prepared from the metal chlorides and sodium tartarate.[6]

Preparation of Raney Nickel Catalyst. Raney nickel alloy (40% of nickel, 1.5 g) was developed with a 20% aqueous sodium hydroxide solution (20 ml) and the suspension was allowed to stand for 1 hr at 100°C. Then the catalyst was washed with total 500 ml of deionized water.

Preparation of the Modifying Solution and the Modification of the Catalyst. The pH of a 1—2% aqueous solution (100—200 ml) of a modifying reagent was adjusted to 5.0 with a diluted aqueous solution of the metal hydroxide or a solid metal oxide, except for the study of the effect of the divalent metal ion on the asymmetric activity of the catalyst modified with D-tartaric acid. As, with the divalent transition metal oxide or the hydroxide, the pH-adjustment of a D-tartaric acid solution was difficult, metal D-tartarate prepared from the corresponding metal chloride and sodium D-tartarate was saturated in 0.2—1 l of water and the resulting solution was adjusted to pH 5.0 with D-tartaric acid. The modifying solution thus prepared was brought to the specified temperature and poured onto the catalyst; the suspension was then kept, with occasional shaking, at the specified temperature for 1.5 hr. After the removal of the modifying solution by decantation, the catalyst was washed once with water and three times with methanol.

Hydrogenation of Methyl Acetoacetate and Measurement of the Optical Rotation of the Product. Methyl acetoacetate (17.5 ml) was hydrogenated with a modified catalyst obtained by the procedure described in the previous section, under an initial pressure of 90 kg/cm^2 at 60°C in a shaking autoclave. The catalyst was then removed by filtration and the filtrate was distilled under reduced pressure (bp 61—62°C/12 mmHg). The optical rotation of the methyl 3-hydroxybutyrate thus produced was measured without dilution in a 1-dm tube.

Results and Discussion

The Influence of the Remaining Developing Reagent. Though the Raney nickel catalyst was washed with a sufficient amount of water (500 ml of water/600 mg of catalyst) after development with a 20% sodium hydroxide solution, a small smount of the remaining sodium ion could interchange with the metal ions used for the pH-adjustment and influence the asymmetric activity of the catalyst. For the study of the effect of the metal ions remaining in the catalysts, the two kinds of catalysts, those developed with sodium hydroxide and with potassium hydroxide, were modified with D-tartaric acid, and the their asymmetric activities were compared each other. The results are shown in Table 1.

Table 1. Effect of residual developing reagent in Raney nickel catalyst

Mod. reagent	Develop. reagent	pH-Adjusting reageat	Optical rotation of product α_D^{40}
D-Tartaric acid	NaOH	NaOH	−7.73
D-Tartaric acid	KOH	NaOH	−7.32
D-Tartaric acid	NaOH	KOH	−3.70

The asymmetric activity of the catalyst developed with sodium hydroxide and modified with potassium tartarate is considerably lower than that of the catalyst modified with sodium tartarate. However, the asymmetric activity of the catalyst developed with potassium hydroxide and modified with sodium tartarate hardly differed from that of the catalyst developed with sodium hydroxide and modified with sodium tartarate. Accordingly, the exchange of the ions used for the pH-adjustment with the sodium ion remaining on the catalyst surface seems to be negligible, judging from the above results.

The Effect of the pH-Adjusting Reagents on the Asym-

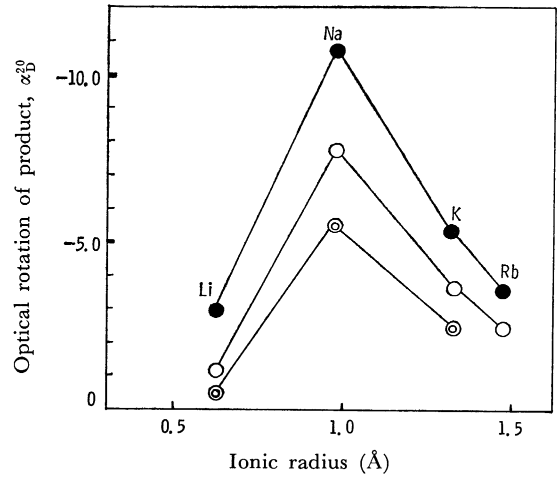

Fig. 2. Effect of pH-adjusting reagent. Catalysts were modified with D-tartaric acid, and D-malic acid at pH 5.0, 0°C and 100°C.
○: modified with D-tartaric acid at 0°C, ●: modified with D-tartaric acid at 100°C, ◎: modified with D-malic acid at 0°C.

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5) M. Winitz, L. Bloch Frankental, N. Izumiya, S. M. Birnbaum, C. G. Baker, and J. P. Greenstein, *J. Amer. Chem. Soc.*, **78**, 2423 (1956).

6) S. Hakomori, *Sci. Rep. Tohoku Univ.*, **16**, 841 (1927).

metric Activity of the Catalyst Modified with the Hydroxy Dicarboxylic Acid. The Effect of the Univalent Alkaline Ion: On the modification with the acid belonging to Group A, the asymmetric activity of the catalyst increased with the elevation of the modifying pH in the acidic region and reached a maximum between pH 5 and 8. In the alkaline region, the asymmetric activity of the catalyst gently decreased with the elevation of the modifying pH. In the present investigation, the modifying solutions of D-tartaric acid and D-malic acid were adjusted to pH 5.0, and the effect the univalent metal ion was studied. The results are shown in Fig. 2.

An intimate relation between the asymmetric activities of the catalyst and the bulk of the ions used for the pH-adjustment of the modifying solutions was found in the cases of modifications with D-malic acid and D-tartaric acid at 0°C and 100°C. That is, bulkier or smaller ions than sodium decreased the asymmetric activity; an optimum value was observed with sodium. The facts suggest that metal ions contribute to the enantiotopic selection of the substrate and that at least one carboxyl group of the hydroxy dicarboxylic acid forms salt with the metal ion on the catalyst surface.

The Effect of the Mixed Univalent Ions: The modifying pH was adjusted with equal amounts of two kinds of cations and the asymmetric activities were compared with the calculated values, which were given as a mean of the values obtained with the catalysts treated with the solutions adjusted with the cations separately. As is shown in Table 2, the observed activities were not proportional to the concentrations of ions, and stronger bases predominantly controlled the asymmetric activity.

The Effect of the Divalent Metal Ions: The effect of the divalent metal ion was examined using divalent metal D-tartarate; the results are shown in Table 3. The calcium ion gave the catalyst a slightly higher symmetric activity than the zinc, cupric, ferrous, nickel, and cobaltous ions. These divalent ions gave much lower asymmetric activities than the monovalent ions. These facts suggest that the divalent cations, which can form intermolecular or intramolecular salts with the dicarboxylic acids, contribute to the adsorption of a modifying reagent in a different manner from the univalent cations.

Table 2. Effect of mixed univalent metal ions on asymmetric activity of catalyst modified with D-tartaric acid

pH-Adjusting reagent	Optical rotation of product, α_D^{20}	Calcd.[a] Optical rotation, α_D^{20}
LiOH	-1.13	—
NaOH	-7.73	—
KOH	-3.70	—
NH_4OH	-0.62	—
NaOH+LiOH (1 : 1)	-6.09	-4.03
NaOH+KOH (1 : 1)	-4.40	-5.71
$NaOH+NH_4OH$ (1 : 1)	-6.53	-3.18

a) The calcd. optical rotation: The average value of the two asymmetric activities of the catalysts pH-adjusted with NaOH and KOH separately.

Table 3. Effect of divalent metal ion on asymmetric activity of catalyst modified with D-tartaric acid

Modifying reagent	Optical rotation of product, α_D^{20}
Calcium D-tartarate·$4H_2O$	-1.71
Zinc D-tartarate	-0.63
Cupric D-tartarate[a]	-0.19
Ferrous D-tartarate·$2H_2O$	-0.37
Nickel D-tartarate·$2H_2O$	-0.40
Cobaltous D-tartarate	-0.66

a) The modifying pH was 4.8.

Table 4. Effect of amine on asymmetric activity of catalyst modified with D-tartaric acid

pH-Adjusting reagent	Optical rotation of product, α_D^{20}
NH_3	-0.62
NH_2CH_3	-0.88
$NH(CH_3)_2$	-0.59
$N(CH_3)_3$	-0.84
$N(C_2H_5)_4OH$	-0.45
Pyridine	$+0.47$
Piperidine	$+0.19$
Ethylenediamine	$+0.11$
α-Picolione	-0.07
Aniline[a]	-0.72
Imidazole	-0.22
Hydrazine	-0.96
Ethanolamine	-0.27

a) The modifying pH was 4.8.

Table 5. Effect of pH-adjusting reagent on asymmetric activity of catalyst modified with L-2-hydroxy-isovaleric acid

pH-Adjusting reagent	Optical rotation of product, α_D^{20}
LiOH	$+0.32$
NaOH	$+0.31$
KOH	$+0.31$
NH_4OH	$+0.31$

The Effect of the Amines: The influence of the bulk of the alkyl substituent of ammonia was also studied; the results are shown in Table 4. The asymmetric activity of a catalyst was lower when modified with a solution adjusted with the amines than when modified with a solution adjusted with the sodium ion. No effect of the bulk of the alkyl substituents was observed.

The Effect of the Metal Ions on the Asymmetric Activity of the Catalyst Modified with Hydroxy Monocarboxylic Acid: As has already been reported in a previous paper,[7] the 2-hydroxy monocarboxylic acid differed

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[7] Y. Izumi, S. Tatsumi, and M. Imaida, This Bulletin, **39**, 2223 (1966).

from the 2-hydroxy dicarboxylic acid in that it gave the catalyst a constant asymmetric activity independently of the modifying pH in the acidic region.

The effects of univalent metal ions and ammonium ions were studied using a catalyst modified with L-2-hydroxyisovaleric acid (HIV). The results are shown in Table 5. The asymmetric activities of the catalysts modified with HIV were not affected by the pH-adjusting reagent and had values similar to that of the catalyst modified with a pH-adjusted solution containing the sodium ion. These results are quite different from the results obtained in the case of tartaric acid and show that the cation used for pH-adjustment does not take part in the adsorption of the hydroxy mono-carboxylic acid.

The Effect of Metal Ions and Ammonium Ions on the Asymmetric Activity of the Catalyst Modified with the Amino Acid: Most amino acids, except for α-alkyl substituted amino acids, are classified in Group A on the basis of their pH-dependency, and the asymmetric activities of the catalyst treated with those amino acids were not affected by the modifying pH in the acidic region.

The effects of metal and ammonium ions on the asymmetric activities of the catalysts treated with L-aspartic acid and L-glutamic acid were also studied; the results are shown in Tables 6 and 7.

The bulk of the univalent metal ions and ammonium ions, all except ethylenediamine and pyridine, did not affect the asymmetric activities; this is different from the results with D-malic acid and D-tartaric acid. Ethylenediamine and pyridine decreased the asymmetric activities of the catalysts. The divalent metal ions and the ammonium ions did not so decrease the asymmetric activities of the catalysts as was found on the modification with HIV, and the asymmetric activities of the catalysts were nearly the same when the pH of the modifying solution was adjusted, either with the amines or with the univalent cation, to that of the one modified with the solution pH-adjusted with the univalent cation.

Table 6. Effects of univalent and divalent metal ions on asymmetric activity of catalyst modified with amino acids

Modifying reagent	pH-Adjusting reagent	Optical rotation of product, α_D^{20}
L-Aspartic acid	LiOH	−1.28
	NaOH	−1.19
	KOH	−1.30
L-Glutamic acid	LiOH	−5.20
	NaOH	−5.03
	KOH	−5.21
	$Ca(OH)_2$	−3.51
	$Ba(OH)_2$	−3.44
	MgO	−4.13
Ni(L-Glu)$_2$·2H$_2$O		−4.00[a]

a) Y. Izumi and T. Ninomiya, This Bulletin, **43**, 579 (1970).

Table 7. Effect of amines on asymmetric activity modified with amino acid

Modifying reagent	pH-Adjusting reagent	Optical rotation of product, α_D^{20}
L-Aspartic acid	NH_3	−1.14
	$N(CH_3)_3$	−1.12
	NaOH	−1.19
L-Glutamic acid	NH_3	−4.55
	NH_2CH_3	−4.76
	$NH(CH_3)_2$	−4.56
	$N(CH_3)_3$	−4.60
	Pyridine	−1.50
	Hydrazine	−4.13
	Ethylenediamine	−3.13
	Ethanolamine	−4.39
	NaOH	−5.03

Judging from these facts, the amino dicarboxylic acid seems to be adsorbed on the catalyst surface in a state which is not influenced by the ion used for the pH-adjustment, unlike the case of hydroxy dicarboxylic acid. That is, both the two carboxyl groups of the amino dicarboxylic acid may be used for the adsorption on the catalyst surface and may not form an ionic bond with the cation used for the pH-adjustment. Ethylenediamine and pyridine, which have a strong affinity for nickel, seem to be adsorbed competitively well onto the catalyst and inhibit the adsorption of the amino acid, thus decreasing the asymmetric activity of the catalyst.

The Adsorption State of the Modifying Reagent. It can be concluded, from the effects of the cations used for the pH-adjustment on the asymmetric activities of the catalysts modified with the hydroxy mono- and dicarboxylic acids at pH 5, that the α-carboxyl group of the hydroxy carboxylic acid contributes to the adsorption onto the catalyst surface and that the remaining ω-carboxyl group of the hydroxy dicarboxylic acid forms an ionic bond with the cation used for the pH-adjustment. The cation bound to the ω-carboxyl group takes part in the enantiotopic selection of the substrate as a substituent of the modifying reagent.

The α- and ω-carboxyl groups of an amino dicarboxylic acid chemically bind with the nickel catalyst, and the cations and amines used for the pH-adjustment of the modifying solution do not affect the asymmetric activities of the catalysts modified with amino acids. These facts are also supported by the findings by Ninomiya of our research group[8] that the absorption spectrum of the glutamic acid on the evaporated nickel film on quartz very similar to that of nickel chelate.

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[8] Part XXIII of this series: T. Ninomiya, This Bulletin, to be published.