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Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel. XX. The Effect of Additives on the Asymmetric Activity

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The effects of various additives in methyl acetoacetate were tested in the asymmetric hydrogenation reaction. Among them, water has a particular effect on the asymmetric activities of the catalysts; in the presence of a certain amount of water, the catalysts modified with L-Glu, L-Val, and L-Ala hydrogenated methyl acetoacetate to methyl $L_s(+)$3-hydroxybutyrate, while, without the addition of water, the catalysts promoted the hydrogenation to yield methyl $D_s(-)$3-hydroxybutyrate. The catalyst modified with L-Ala at pH 6.0 and the catalyst modified with L-Glu at pH 5.0 and 100°C were especially sensitive to water, and both catalysts showed (+) asymmetric activity when a trace of water was also present. Even in the hydrogenation without the addition of water, the recovered catalysts modified with L-Glu, L-Val, and L-Ala from the hydrogenation in the presence of water gave results similar to those in the hydrogenation in the presence of water. The effect of water as an additive was discussed, and it was concluded that the water affects the asymmetric site of the catalyst rather than the keto-enol equilibrium of the substrate.

In the previous reports of this series on asymmetric hydrogenation with a Raney nickel catalyst modified with optically active amino acid or hydroxy acid, the asymmetric activity of the catalyst has been demonstrated to be affected by the structure of the modifying reagent, and by the pH and temperature in the modifying procedures.[1]

The present paper will report on the effects of various additives in the hydrogenation system on the asymmetric activity of the catalyst modified with L-amino acid. As modifying reagents, L-glutamic acid (L-Glu), L-valine (L-Val), and L-alanine (L-Ala) were used because the effect of the modifying temperature on the asymmetric activity of the catalyst is quite different in each case, as was shown in a previous paper.[2]

The present paper will also discuss the particular effect of water on the asymmetric activity of the catalyst modified with L-amino acid and will refer to the irregular asymmetric activity of the catalyst modified with L-Ala at pH 6.0 and 0°C reported in the previous paper.[2]

Experimental

The preparation and modification of the Raney nickel catalyst, the hydrogenation of methyl acetoacetate, and the measurement of the asymmetric activity of the catalyst were carried out in the manner described in a previous paper.[3]

The Addition of the Additives. The additive was introduced into the autoclave with methyl acetoacetate and the catalyst at the same time.

Recovery of the Catalyst and the Recovered Catalyst. After the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate, the hydrogenation product was removed by decantation; then the catalyst was washed three times with a small amount of methanol. The catalyst thus obtained, served as the recovered catalyst in the hydrogenation of methyl acetoacetate.

Results and Discussion

Table 1 shows the asymmetric activity of the catalyst modified with L-Glu in the hydrogenation of methyl acetoacetate (MAA) in the presence of various additives. As Table 1 shows, water caused a (+) asymmetric activity of the catalyst, while other additives caused a (−) asymmetric activity of the catalyst. A similar tendency

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[1] Part XV: T. Tanabe, T. Ninomiya, and Y. Izumi, This Bulletin, **43**, 2276 (1970).

[2] Y. Izumi, M. Imaida, H. Fukawa, and S. Akabori, *ibid.*, **36**, 155 (1963).

[3] Y. Izumi, T. Harada, T. Tanabe, and K. Okuda, This Bulletin, **44**, 1418 (1971).

Table 1. The effect of additives on the asymmetric activity of the catalyst modified with L-Glu (pH 5.0) at 0°C

Additive	m*l*	[α]$^{20}_{D}$ of Methyl 3-hydroxybutyrate
n-hexane	18	−3.90
EtOEt	18	−3.44
MAA	18	−3.35
AcOH	18	−1.65
H_2O	18	+0.80

Table 2. The effect of additives on the asymmetric activity of the catalyst modified with L-Val(pH 6.0) at 0°C

Additive	m*l*	[α]$^{20}_{D}$ of Methyl 3-hydroxybutyrate
n-hexane	18	−2.25
EtOH	18	−2.01
MAA	18	−2.55
AcOH	18	−1.90
H_2O	18	+0.48

Table 3. The effect of additives on the asymmetric activity of the catalyst modified with L-Ala (pH 6.0) at 0°C

Additive	m*l*	[α]$^{20}_{D}$ of Methyl 3-hydroxybutyrate
MAA	18	−0.08
AcOH	10	−0.14
H_2O	18	+0.34

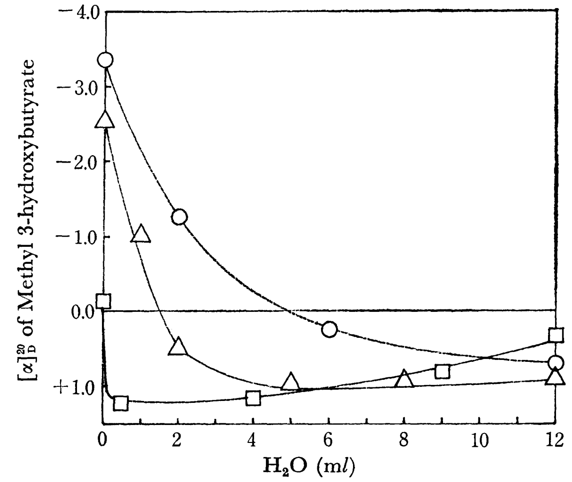

Fig. 1. Effect of water on the asymmetric activities of the catalysts modified at 0°C.
○ L-Glu (at pH 5.0)
△ L-Val (at pH 6.0)
□ L-Ala (at pH 6.0)

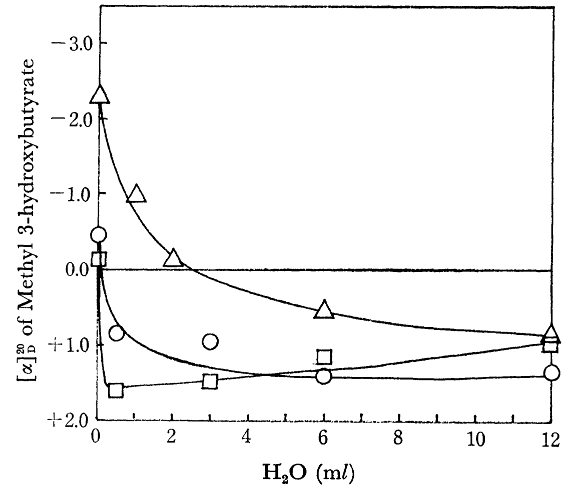

Fig. 2. Effect of water on the asymmetric activities of the catalysts modified at 100°C.
○ L-Glu (at pH 5.0)
△ L-Val (at pH 6.0)
□ L-Ala (at pH 6.0)

was also observed with the catalysts modified with L-Val and L-Ala (Tables 2 and 3).

It is well known that the acetoacetic ester exists in the keto-enol mixture and that the proportion of the keto form of ethyl acetoacetate increases in the following order of the solvents: *n*-hexane (enol form 46.4%) < diethyl ether (27.1%) < ethanol (12%) < ethyl acetoacetate (7.7%) < methanol (6.9%) < acetic acid (5.7%) < water (0.4%).[4]

Therefore, in the case of MAA (94% keto form in the pure state), the proportion of the keto form of MAA in the above solvents can be considered to increase in the same order.

However, the asymmetric activity of each catalyst does not change regularly with the increase in the proportion of the keto form of the substrate, as is shown in Tables 1,2, and 3. Thus the change in the asymmetric activity of the catalyst in the presence of additives can not be explained only by the shift of the keto-enol equilibrium of MAA from the one side to the other.

On the basis of the above discussion, water seems to have a specific effect on the catalyst. Hence, the effect of water was examined in detail. The effect of water on the asymmetric activities of the catalysts modified with L-Glu, L-Val, and L-Ala at 0°C and 100°C was studied; the results are summarized in Figs. 1 and 2.

The increase in the amount of water added brought about a depression not only in the (−) asymmetric activity, but also in the (+) asymmetric activity relative to the catalysts modified with the above three amino acids, and the amount of water which caused the inversion of the asymmetric direction[5] of the catalyst from (−) to (+) was different in each catalyst.

These facts indicate that the degree of the influence of water on the catalyst is characteristic of the modifying reagent. It may be concluded that water affects the asymmetric site of the catalyst, while it does not affect the keto-enol equilibrium of MAA; if the water affected the equilibrium, the degree of the influence of water on each catalyst would be similar.

Figures 3, 4, and 5 show the symmetric activities of the catalysts modified with L-Glu, L-Val, and L-Ala at 0°C in the hydrogenation with the addition of

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[4] K. H. Meyer, *Ann.*, **380**, 212 (1911).

[5] The asymmetric direction of the catalyst is represented by the optical rotatory sign (+ or −) of the reductive product, methyl 3-hydroxybutyrate.

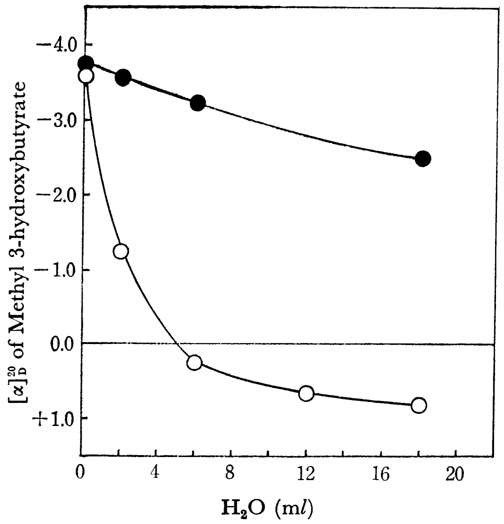

Fig. 3. Asymmetric activities of the catalyst modified with L-Glu at 0°C and of its recovered catalyst.
○ Asymmetric activity of the catalyst in the hydrogenation with addition of water.
● Asymmetric activity of the recovered catalyst under the standard hydrogenation conditions.

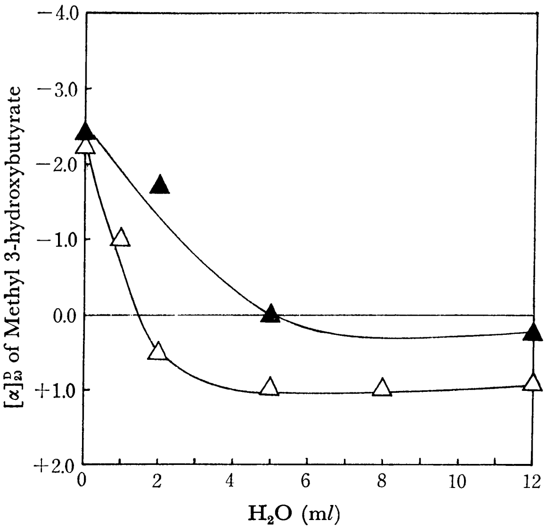

Fig. 4. Asymmetric activities of the catalyst modified with L-Val at 0°C and of its recovered catalyst
△ Asymmetric activity of the catalyst in the hydrogenation with addition of water.
▲ Asymmetric activity of the recovered catalyst under the standard hydrogenation conditions.

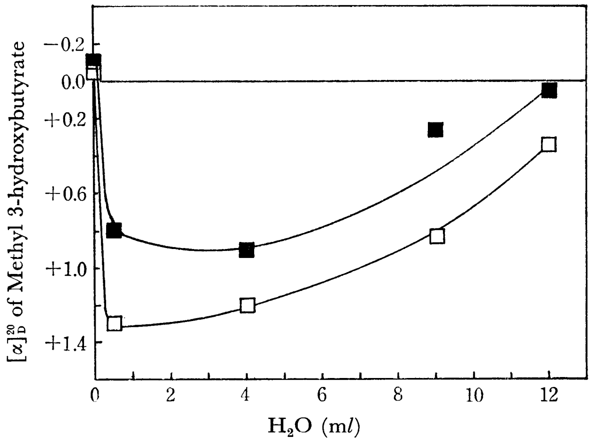

Fig. 5. Asymmetric activityes of the catalyst modified with L-Ala at 0°C and of its recovered catalyst.
□ Asymmetric activity of the catalyst in the hydrogenation with addition of water.
■ Asymmetric activity of the recovered catalyst under the standard hydrogenation conditions.

water and those of the recovered catalyst in the hydrogenation under the standard conditions.⁶⁾

The catalysts recovered from the hydrogenation of MAA containing water show considerably lower (—) asymmetric activities in the standard hydrogenation of methyl acetoacetate than do the catalysts modified with L-GIu, L-Val, and L-Ala in the hydrogenation under the standard conditions. On the other hand, it has been established that both catalysts modified with these amino acids at 0°C and the recovered catalysts show the same asymmetric activities in the hydrogenation of MAA alone. These facts suggest that the asymmetric site of each catalyst is greatly affected by water and that water affects the recovered catalyst. If the water had no effect on the symmetric site of the catalyst, the recovered catalyst would show the same asymmetric activity as the catalyst used first under the standard conditions.

The Catalyst Modified with L-*Glu.* As has been described previously, the catalyst modified with L-Glu at 0°C shows (—) asymmetric activity, while on the other hand, the one modified at 100°C shows(+) asymmetric activity The catalyst modified with L-Glu at 100°C was studied with the expectation that the (+)asymmetric activity of the catalyst would be produced by the water absorbed during the modification.

In Fig. 6, the asymmetric activities of the catalyst modified at 100°C and those of the recovered catalyst are plotted against the number of repeated recoveries under the standard conditions.

The asymmetric activities of the recovered catalyst

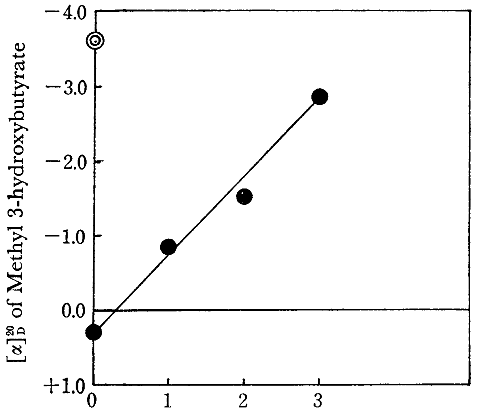

Fig. 6. Asymmetric activity of the catalyst modified with L-Glu at 100°C.
vs. Number of repeating of recovery procedure.

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6) The standard hydrogenation conditions are the conditions of the hydrogenation of methyl acetoacetate alone, without any additives.

modified at 100°C gradually approaches that of the catalyst modified at 0°C. This finding suggests that the asymmetric site of the catalyst modified at 100°C is unstable and that it gradually becomes similar to the state of that modified at 0°C through the recovery procedure.

The Catalyst Modified with L-*Val.* It has been reported in a previous paper$^{1)}$ that (−) asymmetric activity of the catalyst modified with L-Val does not change with the modifying temperature. However, the addition of water causes the (+) asymmetric activity in the catalyst as is shown in Figs. 1 and 2. These facts indicate that the catalyst modified with L-Val, which seems to show only (−) asymmetric activities, also include a factor inducing (+) asymmetric activity.

The Catalyst Modified with L-*Ala.* The catalyst modified with L-Ala is the most sensitive to water among the catalysts modified with the amino acids investigated, as is shown in Fig. 1. From the above fact it can be supposed that the considerably high (+) asymmetric activity of the catalyst modified with L-AIa reported in the previous paper$^{2)}$ is due to the effect of the contaminant water on the catalyst surface.

As it seemed to be difficult to prevent perfectly the inclusion of water in the hydrogenation system in the ordinary modification procedure described above, it seems that the constant values of the asymmetric activities can be obtained only with difficulty with the catalysts modified with L-Ala at 0°C and 100°C, and with L-Glu at 100°C, by the standard method.