Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel. XXI. The Effect of Water on the Asymmetric Activity of the Catalyst

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The effect of water added to the hydrogenation system of methyl acetoacetate was investigated on catalysts modified with L-amino acids, their derivatives, and D- or L-hydroxy acids. In the absence of water, catalysts modified with all L-amino acids except L-serine and L-proline gave methyl $D_s(-)$-3-hydroxybutyrate, and in the presence of water all the catalysts modified with L-amino acids gave methyl $L_s(+)$-3-hydroxybutyrate. On the other hand, the catalysts modified with L- or D-hydroxy acids were not affected by the addition of water and gave an $L_s(+)$ or $D_s(-)$ hydrogenation product respectively. In the presence of water, the catalyst modified with the L-valine methyl ester gave an $L_s(+)$ product, while the catalysts modified with *N*-acetyl L-amino acids were not affected by water. As a whole, it was concluded that water added to the hydrogenation system affected the amino group of the modifying reagent on the catalyst surface, which might play an important role in the asymmetric control of the substrate approaching the catalyst surface. The water in the hydrogenation system also promoted the hydrogenation rate, regardless of the modifying reagents.

In a previous report on the investigation of asymmetric hydrogenation with Raney nickel catalysts modified with optically-active amino acids or hydroxy acids,[1] the catalysts modified with L-glutamic acid, L-valine, and L-alanine were demonstrated to show (+) asymmetric activities upon the addition of water, and it was concluded that water affected the asymmetric site of the catalyst rather than the position of the keto-enol equilibrium of the substrate, methyl acetoacetate.[2]

It seemed that an investigation of the effect of water on the asymmetric site of the catalyst would be important and informative in connection with the clarification of the asymmetric hydrogenation mechanism. The present work is intended to make clear the effect of the water.

The present paper will report on the effect of water on the asymmetric activities of the catalysts modified with L-amino acids, *N*-acetyl L-amino acids, L-amino acid methyl ester, L-amino acid nickel chelate, and L- or D-hydroxy acids. Also, the role of the amino group of the modifying reagent, L-amino acid, will be discussed in connection with the effect of water.

As as whole, it can be deduced that the amino group of L-amino acid plays an important role in the asymmetric control of the substrate approaching the catalyst surface.

The influence of water on the hydrogenation rate will also be referred to.

Experimental

The preparation and the modification of the Raney nickel catalyst, the hydrogenation of methyl acetoacetate, the addition of water to the hydrogenation system, and the measurement of the asymmetric activity of the catalyst were performed in the manner described in the previous paper.[1]

As the Raney nickel alloy, 1.5 g of R-Ni ND (from Kawaken Fine Chemicals Co., Ltd., lot 1949) was used, and as the substrate for hydrogenation was used 0.15 mol of methyl acetoacetate (from the Nippon Synthetic Chemical Industry Co., Ltd., lot 70).

Results and Discussion

Figures 1–1 and 1–2 shows the asymmetric activities of the catalysts modified with L-leucine (L-Leu), L-phenylalanine (L-Phe), L-tryptophan (L-Try), L-methionine (L-Met), L-threonine (L-Thr), L-serine

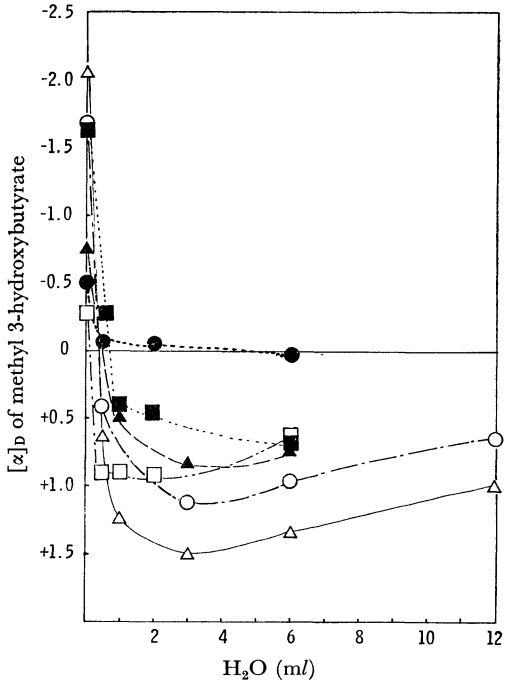

Fig. 1–1. Effect of added water on asymmetric activity of catalyst modified with L-amino acids at 0°C.
○: L-leucine △: L-methionine
△: L-phenylalanine ■: L-tryptophan
□: L-threonine ●: L-histidine

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1) Part XX: F. Higashi, T. Ninomiya, and Y. Izumi, This Bulletin, **44**, 1333 (1971).

2) The + or − asymmetric activity of the catalyst is represented by the optical rotatory sign (+ or −) of the hydrogenation product, methyl 3-hydroxybutyrate.

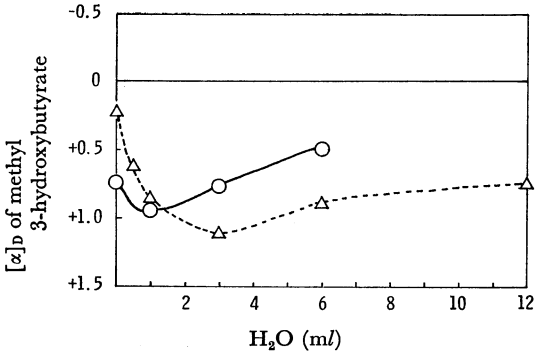

Fig. 1-2. Effect of added water on asymmetric activity of catalyst modified with L-serine and L-proline at 0°C.
—○—: L-serine ---△---: L-proline

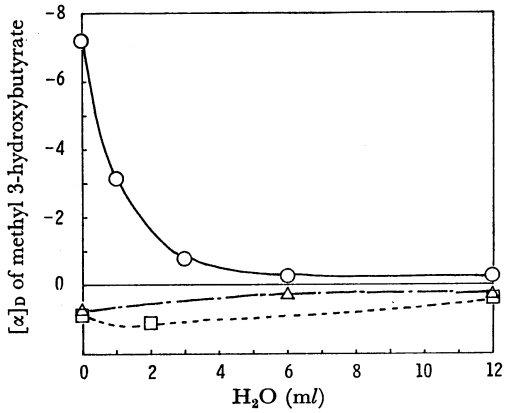

Fig. 2. Effect of added water on asymmetric activity of the catalyst modified with optically active hydroxy acids at 0°C.
—○—: D-tartaric acid
·-△-·: L-2-hydroxy-3-methylbutyric acid
---□---: L-2-hydroxy-3-phenylpropionic acid

(L-Ser), L-proline (L-Pro) and L-histidine (L-His) in the hydrogenation of methyl acetoacetate (MAA) with the addition of water. As is shown in Fig. 1, with the addition of water the catalysts modified with L-Leu, L-Phe, L-Try, L-Met, L-Thr, and L-His showed (+) asymmetric activity, while without any addition of water these catalysts showed (−) asymmetric activity. The catalysts modified with L-Ser and L-Pro, having (+) asymmetric activities in the absence of water, showed higher (+) asymmetric activities in the presence of water. Compared with the catalysts modified with other L-amino acids, the catalyst modified with L-His was little affected by water and showed only (+) asymmetric activity with the addition of 6 m*l* of water.

Figure 2 shows the effect of water on the catalysts modified with D-tartaric acid, L-2-hydroxy-3-methylbutyric acid, and L-2-hydroxy-3-phenylpropionic acid. The added water did not cause the inversion of the asymmetric direction when the catalysts were modified with these hydroxy acids.

As can be seen in Figs. 1 and 2, the catalysts modified with L-amino acids showed (+) asymmetric activities in the presence of water, while the catalysts modified with D- or L-hydroxy acids were not affected by water.

The above facts clearly show that the effect of water is characteristic of the catalysts modified with L-amino

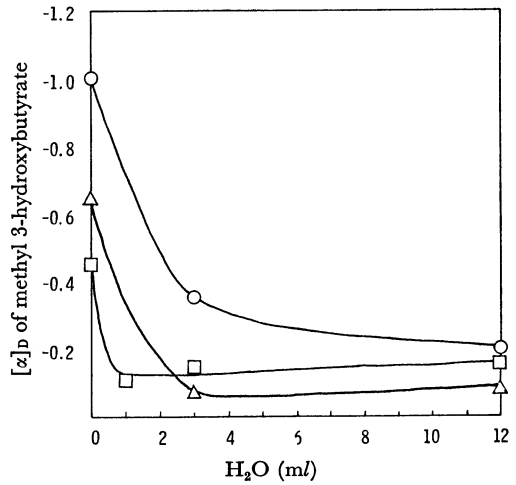

Fig. 3. Effect of additional water on asymmetric activity of catalyst.
—○—: Modification with *N*-acetyl L-isoleucine at 0°C
—△—: Modification with *N*-acetyl L-phenylalanine at 0°C
—□—: Modification with *N*-acetyl L-alanine at 0°C

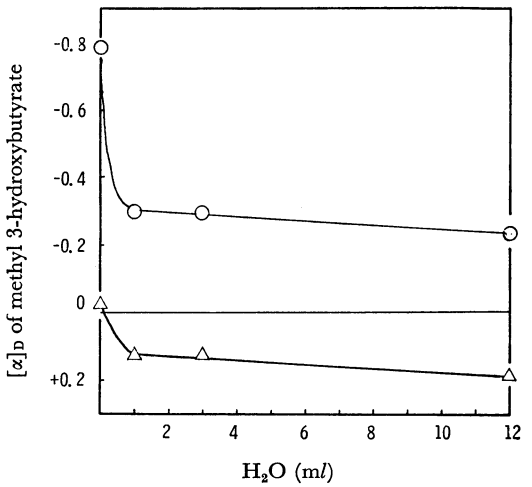

Fig. 4. Effect of additional water on asymmetric activity of catalyst.
—○—: Modification with *N*-acetyl-L-valine at 0°C
—△—: Modification with L-valine methyl ester at 0°C

acids. In the previous paper,[1] the water added to the hydrogenation system was demonstrated to influence the asymmetric sites of the catalysts modified with L-amino acids.

In order to investigate in detail the effect of water on the asymmetric site of the catalyst modified with L-amino acids, the effect of water on the catalysts modified with *N*-acetyl L-amino acids and the L-amino acid methyl ester was examined.

Figure 3 shows the effect of water on the catalysts modified with *N*-acetyl L-isoleucine, *N*-acetyl L-phenylalanine, and *N*-acetyl L-alanine. As may be seen in Fig. 3, even in the presence of water these catalysts showed (−) asymmetric activities and did not show (+) asymmetric activities; this was in striking contrast to the catalysts modified with L-Ileu, L-Phe, and L-Ala. The above facts suggest that the sensitivities of the catalyst to water may be decreased by the acetylation of the amino group.

Figure 4 shows the effect of water on the asymmetric activities of catalysts modified with the L-valine methyl ester and *N*-acetyl L-valine. As may be seen in Fig. 4, in the presence of water the catalyst modified with the L-valine methyl ester showed (+) asymmetric activity, while the catalyst modified with *N*-acetyl L-valine showed (−) asymmetric activity. The above facts make it clear that the free amino group may be affected by water and bring the catalyst (+) asymmetric activity. From the standpoint of the above discussion, the effect of the water on the asymmetric activity of the catalyst modified with L-histidine shown in Figs. 1–1 can be explained as follows; L-histidine, well known as a strong chelating reagent, can be adsorbed as a tridentate on the catalyst surface, and, because of both the steric and electrostatic effects of the imidazole group neighboring the amino group, the amino group may be hardly affected at all by a small amount of water added to the hydrogenation system.

Figure 5 illustrates the effect of water on the catalyst modified with the L-valine nickel chelate. As is illustrated in Fig. 5, the catalyst modified with the L-valine nickel chelate, which showed a much higher (−) asymmetric activity than the catalyst modified with L-valine in the absence of water, also gave (+) asymmetric activity in the presence of water, as did the catalyst modified with L-valine. The amino group of the L-valine nickel chelate is considered to be in a nearly free state, because, as is shown in Fig. 6, the nickel L-valine complex had adsorption bands corresponding to the ν_s and ν_{as} of NH_2 around 3300 cm^{-1}, while crystalline L-valine showed absorption bands around 3000 cm^{-1} assigned to the ν_s and ν_{as} of NH_3^+. Accordingly, the catalyst modified with the L-valine nickel chelate is considered to be easily affected by water to show (+) asymmetric activity.

The above discussion shows that water can affect the free amino group of the L-amino acid used as the modifying reagent and cause the inversion of the asymmetric activity and/or give higher (+) asymmetric activity to the catalyst modified with L-amino acid. From the fact that the catalyst modified with the L-valine methyl ester behaved toward water like that modified with L-valine, as is shown in Fig. 4, but showed a far lower (−) asymmetric activity than that modified with L-valine, it seems that the carboxyl group of the modifying reagent is independent of the effect of water and probably participates in the stable

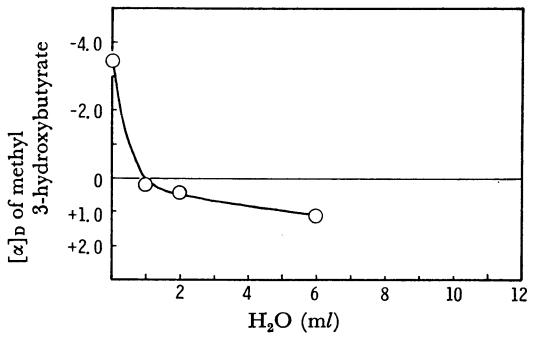

Fig. 5. Effect of additional water on asymmetric activity of catalyst. (Modification with L-valine nickel chelate at 0°C)

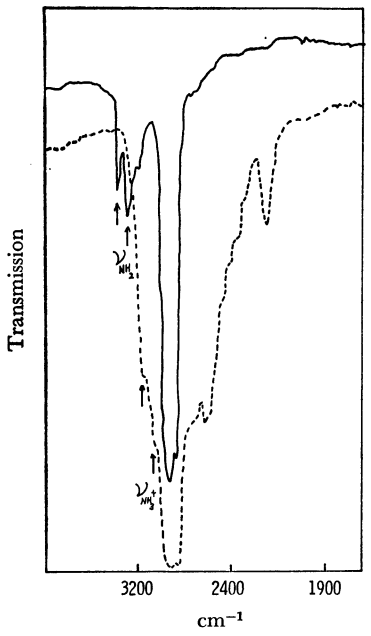

Fig. 6. IR spectra of Ni[L-Val]$_2$ (Nujol, ——) and L-Val (Nujol, -----).

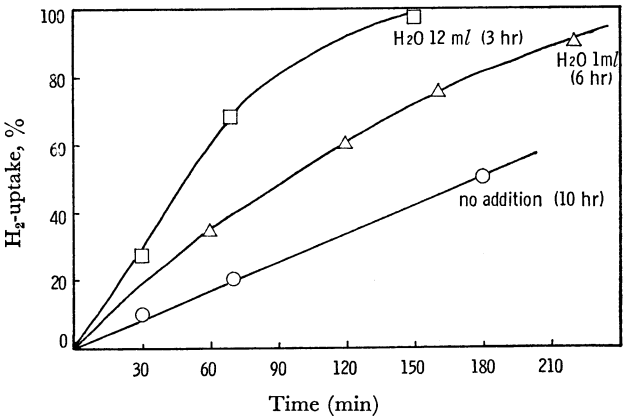

Fig. 7. Effect of additional water on hydrogenation rate. (Modified with D-tartaric acid at 0°C, pH 5.0)

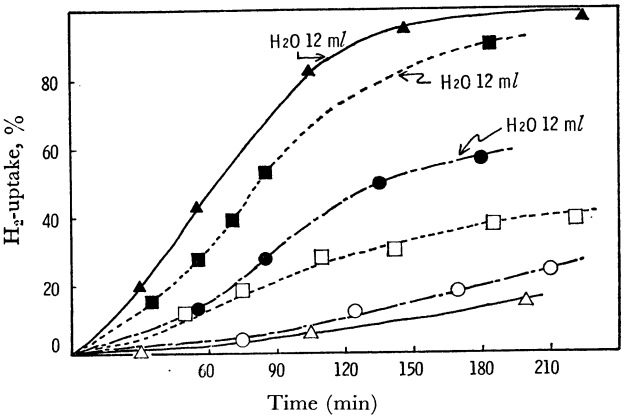

Fig. 8. Effect of additional water on hydrogenation rate.
—△—: Modification with L-valine at 0°C
—○—: Modification with L-3-methyl-2-hydroxybutyric acid at 0°C
—□—: Modification with *N*-acetyl L-isoleucine at 0°C

adsorption of the modifying reagent on the catalyst surface. As a whole, it can be concluded that the amino group of L-amino acid plays an important role in the asymmetric control of the substrate approaching the catalyst surface.

In Fig. 7 the hydrogenation rate is plotted against the amount of water added to the hydrogenation system in the modification with D-tartaric acid. As is illustrated in Fig. 7, the addition of 12 m*l* of water brought about the promotion of the hydrogenation rate and carried the hydrogenation to completion in about 3 hr, while the standard hydrogenation, without any addition of water, took about 10 hr.

A similar promotion of the hydrogenation rate was also observed when the catalysts were modified with L-valine, L-2-hydroxy-3-methylbutyric acid, and *N*-acetyl L-isoleucine, as is shown in Fig. 8.

From the above facts it can be concluded that the water added to the hydrogenation system promotes the hydrogenation rate, independent of the kind of modifying reagent used in the asymmetric hydrogenation of methyl acetoacetate.

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