Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel. XXIV. The Effect of Unsaturated Compounds on the Asymmetric Activity of the Catalyst

Toshio Ninomiya*

Division of Organic Chemistry, Institute for Protein Research, Osaka University, Kita-ku, Osaka

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Dehydroacetic acid and methyl *cis*-3-acetoxycrotonate were picked out as trace impurities of the substrate, methyl acetoacetate. The effects of dehydroacetic acid, methyl *cis*-3-acetoxycrotonate, and diketene, which is the starting material for the preparation of methyl acetoacetate, on the asymmetric activities of catalysts modified with L-amino acids were examined in the hydrogenation of methyl acetoacetate. The above three compounds, when added to the hydrogenation system, raised the asymmetric activity of the catalyst. Also, simple unsaturated compounds, such as acetone and diethyl maleate, has a similar effect on the catalyst. The effects of the above unsaturated compounds on the asymmetric activities of the catalysts modified with L-amino acids were discussed, and it was suggested that the unsaturated compounds adsorb on the catalyst surface and might scavenge the asymmetrically uncontrolled active hydrogen absorbed on the catalyst surface.

In the course of an investigation of asymmetric hydrogenation with Raney nickel catalysts modified with optically-active amino or hydroxy acids, it was often observed that a difference in the lot number of the substrate, methyl acetoacetate, caused an indefinite asymmetric activity in the catalyst. As one of the reasons for the above phenomenon, the contaminant components in the substrate can be considered to have an influence on the asymmetric activity of the catalyst.1) The present investigation was carried out in order to confirm the trace components in the substrate and in order to clarify the effect of those trace components on the asymmetric activity of the catalyst.

As the trace components in methyl acetoacetate (The Nippon Synthetic Chemical Industry, Co., Ltd., lot 70), dehydroacetic acid (DHA) and methyl *cis*-3-acetoxycrotonate (MAC) were picked out from the substrate, and the effects of DHA, MAC, and diketene, which is the starting material for the preparation of the substrate, on the asymmetric activity of the catalysts modified with L-amino acids were tested.

From the fact that DHA, MAC, and diketene, being unsaturated compounds or hydrogen acceptors, have a great effect on the asymmetric activity of the catalyst, the effect of simple unsaturated compounds, such as acetone and diethyl maleate, on the asymmetric activities of the catalysts modified with L-amino acids was investigated further.

As a whole, the unsaturated compounds, which have ketone groups or C=C double bonds, caused a rise in the asymmetric activities of the catalysts modified with L-amino acids. The effect of unsaturated compounds on the asymmetric activity of the catalyst was discussed on the basis of the above results.

Results and Discussion

The gas chromatograms of three kinds of methyl acetoacetate, lot A, lot B, and lot 70, are shown in Fig. 1. As is indicated in Fig. 1, the contents of the trace components in methyl acetoacetate were different from one another. To confirm the trace component, in methyl acetoacetate (MAA), lot 70, the lot was rectified under reduced pressure and the trace components of the substrate were concentrated. As trace components, DHA and MAC were isolated and identified.

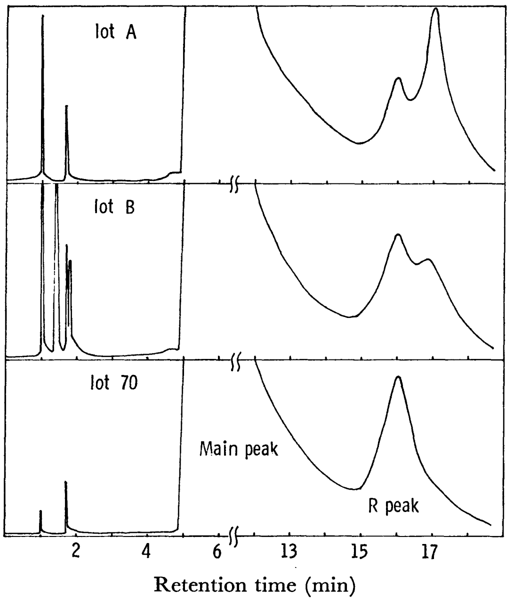

Fig. 1. Gas chromatogram of methyl acetoacetate.
Apparatus: Shimadzu GC-4HPF
Column: PEG 20M 1.5% Chromosorb W 60—80 mesh
Column temperature: 80°C
Injection temperature: 100°C
Sens. 10^4MΩ; Range 1.6 V; Injection 0.2 μ

Figures 2 and 3 show the effect of DHA and MAC, when added to the hydrogenation system, on the assymmetric activities of the catalysts modified with L-glutamic acid and L-valine. The addition of DHA and MAC to the hydrogenation system raises, the (−) asymmetric activities of the catalysts modified with L-glutamic acid and L-valine.

Figure 3 also shows that, in the presence of the catalyst modified with L-valine, a more purified sub-

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* Present address: Dai Nippon Toryo, Co., Ltd., 38 Nishinoshimonocho, Konohana-ku, Osaka.

1) The report about the impurities contained in methyl acetoacetate was published by Motoda and Yoshie. [T. Motoda and Y. Yoshie, *Kogyo Kagaku Zasshi*, **68**, 41 (1965)].

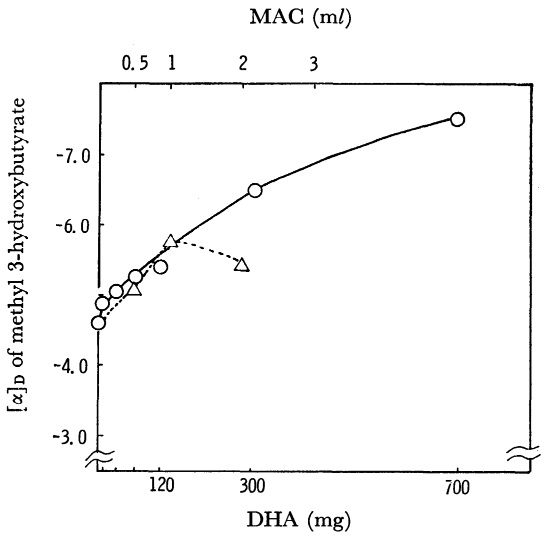

Fig. 2. Effect of added methyl 3-acetoxycrotonate and dehydroacetic acid on asymmetric activity of catalyst. (modified with L-glutamic acid at 0°C, pH 5.0)
—○—: Dehydroacetic acid (DHA)
---△---: Methyl 3-acetoxycrotonate (MAC)

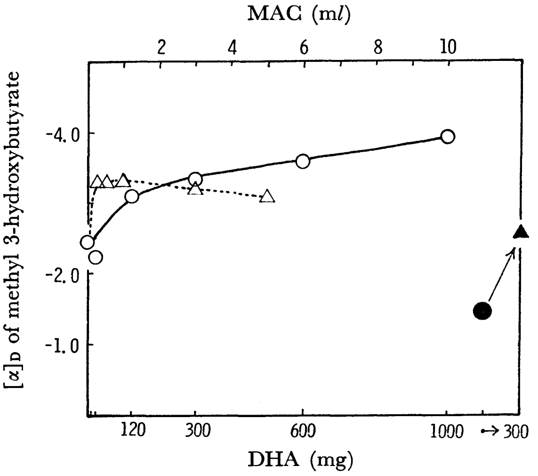

Fig. 3. Effect of added methyl 3-acetoxycrotonate and dehydroacetic acid on asymmetric activity of catalyst. (modified with L-valine at 0°C)
—○—: Dehydroacetic acid (DHA)
—△—: Methyl 3-acetoxycrotonate (MAC)
—●—: Without addition, redistilled MAA being used
—▲—: DHA, redistilled MAA being used

strate, one which had been obtained by the rectification of MAA lot 70, was hydrogenated in a lower asymmetric yield ($[\alpha]_D = -1.48$), while the addition of 300 mg of DHA to the above purified substrate caused a high asymmetric activity ($[\alpha]_D = -2.56$).

The above facts clearly indicate that the asymmetric activity of the catalyst shown in the hydrogenation of MAA lot 70 was intrinsically affected by the trace components of MAA lot 70, DHA, or MAC.

Furthermore, the possibility that MAA includes a small amount of diketene, because diketene is the starting material of MAA, led us to examine the effect of diketene on the asymmetric activity of the catalyst.

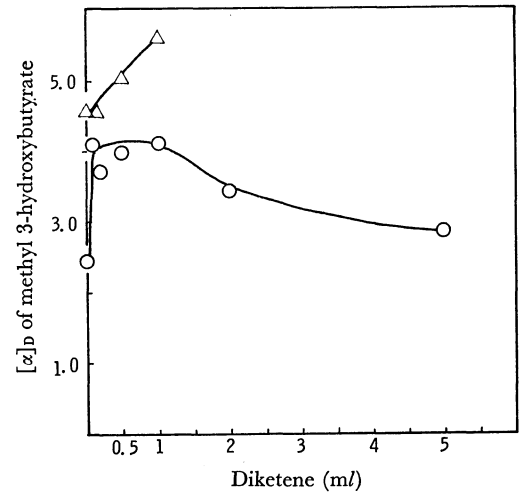

Fig. 4. Effect of added diketene on asymmetric activity of catalyst.
—△—: Modification with L-glutamic acid at 0°C, pH 5.0
—○—: Modification with L-valine at 0°C

Figure 4 indicates the effect of diketene on the asymmetric activities of the catalysts modified with L-glutamic acid and L-valine. As is illustrated in Fig. 4, diketene, when added to the hydrogenation system, raised the asymmetric activities of the catalysts modified with L-glutamic acid and L-valine.

From the results shown in Figs. 2, 3, and 4, it is clear that DHA, MAC, and diketene affect the asymmetric activities of the catalysts modified with L-amino acids in a similar manner. The above three substances have reducible groups, C=O and/or C=C in commons and it can be supposed that the treatment of the catalyst with simple unsaturated compounds, containing ketone groups or C=C double bonds may raise the asymmetric activities of the catalysts modified with L-amino acids.

The effect of simple unsaturated compounds on the asymmetric activities was examined with the catalysts modified with L-valine and L-alanine.

TABLE 1. EFFECT OF VARIOUS REDUCIBLE REAGENTS ON THE ASYMMETRIC ACTIVITIES OF THE CATALYSTS

Reagent (m*l*)	Immersion time (sec)	$[\alpha]_D$ of methyl 3-hydroxybutyrate	
		Modification with L-val at 0°C	Modification with L-ala at 0°C
No treatment	—	−2.47	+0.04
Acetone (18)	90	−3.06	−0.03
Methylethylketone (18)	90	−3.63	−0.18
Cyclohexanone (18)	90	−2.46 −2.47	—
Methylacetoacetate (lot 70) (18)	90	−4.15	−0.32 −0.30
Cyclohexene (18)	90	−3.75	+0.53
Diethyl maleate (18)	90	−4.14	−0.56
Diethyl fumarate (18)	90	no H uptake	no H uptake
Acrylonitrile (18)	90	—	−0.19
Nitromethane (18)	90	—	±0.00

R–NiND (Kawaken Fine Chemical Co., Ltd.) lot 1949, 1.5 g. Substrate; Methyl acetoacetate (The Nippon Synthetic Chemical Industry Co. Ltd.) lot 70 0.15 mol.

Table 1 shows the effect of various reducible compounds on the asymmetric activities of the catalysts modified with L-valine and L-alanine. As is shown in Table 1, the treatment with various ketones and olefins raised the asymmetric activities of the catalysts in most cases. An interesting, remarkable difference was observed between the cases of diethyl maleate and diethyl fumarate; that is, the treatment of the catalyst with diethyl maleate gave a high asymmetric activity to the catalyst, while the treatment of the catalyst with diethyl fumarate lowered and strongly inhibited the hydrogenation.

On the basis of the above results it is clear that unsaturated compounds with ketone groups or C=C double bonds played an important role in raising the asymmetric activities of the catalysts modified with L-amino acids. Then, the unsaturated compounds which gave a high asymmetric activity to the catalyst were hydrogenated under asymmetric hydrogenation conditions.

As was reported in a previous paper,[2] saturated compounds, for example, ethanol and *n*-hexane, are known not to cause a rise in the asymmetric activities of the catalysts modified with L-amino acids. As a result, the effect of the hydrogenated products of the above unsaturated compounds can be disregarded. Moreover, as is shown in Table 1, the 90-sec pretreatment of the catalyst with the substrate, MAA iteself, as an unsaturated compound brought a higher asymmetric activity to the catalyst than no pretreatment, which is the standard asymmetric hydrogenation procedure. On the other hand, the present author has previously made it clear that MAA adsorbs with a pseudo aromatic ring on the catalyst surface.[3]

Therefore, the effect of unsaturated compounds might be associated with the absorbed hydrogen on the catalyst surface. On the whole, it can be concluded that the unsaturated compounds adsorb on the catalyst surface and that, at that stage, they might scavenge asymmetrically uncontrolled active hydrogen absorbed on the catalyst surface. Therefore, with regard to the above phenomenon, Izumi, one of our research group, has attempted to explain it by the hypothesis of a "Quasi liquid hydrogen layer."[4]

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 performed in the manner described in a previous paper.[5]

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

Isolation and Identification of DHA and MAC. MAA, lot 70 (600 m*l*), was rectified under reduced pressure (15 mmHg) with a Podbielniak 13-mm Heli-Grid column and was then concentrated to 30 m*l*. The yellowish brown residue was cooled overnight in a refrigerator, and the yellowish precipitate was separated by filtration. The precipitate was recrystallized from an ethanol solution. Yield, 0.3 g; mp 105—110°C (capillary).

NMR: δ (10%, $CDCl_3$) 2.26 (3H, s, $CH_3\cdot\underset{\underset{\textstyle O}{|}}{C}{=}C$), 2.62 (3H, s, $CH_3\cdot\underset{\underset{\textstyle O}{|}}{C}-$), 5.93 (1H, s, C=CH–C), and 16.84 (1H, s, $\underset{\underset{\textstyle O}{\|}}{C}-\underset{\underset{\textstyle C=O}{|}}{CH}-C{=}O$). IR: (KBr) 1720 (ketone), 1620—1640 and 1550 cm^{-1} (pyrone ring).

Found: C, 56.41; H, 4.83; N, 1.16%. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80; N, 0.00%.

From the above physicochemical data, the crystals were identified as dehydroacetic acid.

The filtrate was suspended in a nickel chloride aqueous solution ($NiCl_2\cdot6H_2O$ (24 g) in H_2O (50 m*l*)). To the above suspension solution, we slowly added a caustic soda solution (NaOH (8 g) in H_2O (50 m*l*)) under ice-water cooling, and the pH was adjusted about 7.

After the mixture had been stirred for 2 hr, the nickel methyl acetoacetate was filtered off and the filtrate was introduced into a gas-chromatogram apparatus, Varian 90-P3; the peak, R, shown in Fig. 1 was separately collected.

NMR: δ (1%, CCl_4) 2.04 (3H, s, CH_3–C), 2.21 (3H, s, $CH_3-\underset{\underset{\textstyle O}{\|}}{C}-$), 3.57 (3H, s, O–$CH_3$), 6.49 (1H, s, C=CH–C). IR: (liquid film) 1710 and 1760 (esters) and 1660 cm^{-1} (C=C).

From the IR and NMR data and by identification[6] with synthetic *cis*-3-acetoxycrotonate, the R peak was identified as methyl *cis*-3-acetoxycrotonate (MAC).[1] Gas-chromatographic calculation showed the MAA lot 70 to contain 0.3% MAC.

Addition of DHA, MAC, and Diketone. A chemically pure grades of DHA and diketene (Wako Pure Chemical Industries, Ltd.) were used. The MAC was prepared by the method of Claisen.[6] DHA, MAC and diketene were all added to the substrate, MAA, which was then introduced into autoclave, and the reduction product, methyl 3-hydroxybutyrate, was fractionally distilled.

Treatment of the Catalyst with Simple Ketones or Olefins. The catalyst modified with an L-amino acid was immersed for 90 sec in 18 m*l* of a ketone or an olefin; by decantation the catalyst was separated from the ketone or the olefin with the aid of a magnet to retain the catalyst, and the catalyst was introduced with the substrate into the autoclave.

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

[3] T. Ninomiya, *ibid.*, to be published.

[4] Y. Izumi, *Shokubai (Catalyst)*, **12**, 201 (1970).

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

[6] L. Claisen and E. Haase, *Ber.*, **33**, 3778 (1900).