BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1792—1795 (1970)

Asymmetric Hydrogenation of C=N Double Bond with Modified Raney Nickel 1.*1 New Determination Method for the Reaction Mechanism Using Asymmetric Catalyst

Yoshiharu IZUMI, Hidemitsu TAKIZAWA,*2 Kunio NAKAGAWA,*3 Ryushichi IMAMURA,*4 Masami IMAIDA,*5 Toshio NINOMIYA and Shinichi YAJIMA*2

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

(Received November 8, 1969)

The hydrogenation process of ethyl 2-acetoximinopropionate was investigated by means of a novel technique using asymmetric hydrogenation with an asymmetrically modified R–Ni catalyst. It was found that the hydrogenation of ethyl 2-acetoximinopropionate to ethyl alaninate proceeded in two steps through ethyl acetoxyalaninate, and that the asymmetric hydrogenation was performed in the step of the formation of ethyl acetoxyalaninate from ethyl 2-acetoximinopropionate. Besides, the asymmetric reductive amination of ethyl pyruvate was tested with an asymmetrically modified R–Ni catalyst.

The most impressive characteristics of the enzyme reactions are their high catalytic reactivities and their substrate- and stereo-specificities. The catalytic reactivities of the enzyme are promoted by the extreme approach of the reacting molecules to the enzyme, due to the binding of the reacting molecule with the active site of the enzyme. The substrate- and stereo-specificities are performed by the steric interaction between the protein molecule surrounding the active site and the substrate molecule. In the earlier works on catalytic asymmetric hydrogenation done by our research group, silk-palladium was used as the asymmetric catalyst; it had been prepared by the dispersion of palladium metal on silk fibroin.[1] It was expected in the investigation of the silk-palladium catalyst that the palladium and the silk fibroin molecule would act as the active site and the protein molecule surrounding the active site of the enzyme respectively. After the fundamental investigation of the silk-noble metal-type catalyst, we intended to substitute the metal catalyst surface for the active site and most of the protein molecule, which takes part in hardening the environment around the active site of the enzyme, and to give the substrate-specificity and the stereospecific environment to the catalyst by means of the adsorption of the optically active molecule on the catalyst surface.

On the basis of the fundamental considerations mentioned above, the asymmetrically-modified Raney nickel (R–Ni) catalyst was prepared by the treatment of R–Ni catalyst with an aqueous solution of the optically active α-amino or α-hydroxy acid, or other compounds. On the surface of the R–Ni catalyst, the reacting molecules, active hydrogen and the substrate, are placed in close contact, as in the enzyme reaction. As, according to the established theory, the hydrogen attacks the double bond to form a *cis*-addition product, the catalyst modified with an optically active compound would have an asymmetric hydrogenation ability if the catalyst surface could control the adsorption style of the substrate molecule. That is, the asymmetric site of the modified R–Ni catalyst would act as the protein molecule surrounding the active site of the enzyme.

The fundamental investigation of the asymmetric hydrogenation of the C=O double bond with a modified R–Ni catalyst, using methyl acetoacetate as the substrate, has been previously reported in a series of reports by our research group.[2] The experimental rules of the relation between the asymmetric hydrogenation activity of the modified R–Ni catalyst for methyl acetoacetate and the structure of the modifying reagent have been made clear.

The asymmetric hydrogenation of the C=N double bond is very useful and important in the syntheses

*1 Presented at the 24th Meeting on Catalysis, Tokyo, March, 1964.

*2 Present address: Kawaken Fine Chemical Co., Ltd., Kawagoe, Saitama.

*3 Present address: Central Research Laboratory of Nisshin Flour Milling Co., Ltd., Fukuoka, Saitama.

*4 Present address: Saito Shozo Co., Ltd., Chiba.

*5 Present address: The Osaka Prefectural Institute of Public Health, Osaka.

1) S. Akabori, Y. Izumi and Y. Fujii, *Nature*, **178**, 323 (1956). S. Akabori, Y. Izumi, Y. Fujii and S. Sakurai, *Nippon Kagaku Zasshi*, **77**, 1374 (1956). S. Akabori, Y. Izumi and Y. Fujii, *ibid.*, **78**, 886 (1957).

2) Part XII of the series; Y. Izumi, S. Tatsumi and M. Imaida, This Bulletin, **42**, 2373 (1969).

of the natural products, especially in the syntheses of amino acids and alkaloids. To date, however, only three reports on the asymmetric hydrogenation of the C=N double bond in the presence of an asymmetric catalyst have been published.[1,3,4] The first success was accomplished by our research group using the silk-palladium catalyst on the hydrogenation of ethyl 2-acetoximino-3-phenylpropionate, benzil dioxime, and diethyl 2-acetoximinoglutarate.[1] Subsequently, Isoda *et al.* performed the asymmetric hydrogenation of diethyl 2-oximinoglutarate and 2-acetoximinoglutaric acid with a palladium catalyst and a R–Ni catalyst which had been treated with optically-active amino acids.[3] Recently, acetophenone oxime was asymmetrically hydrogenated with a modified R–Ni catalyst by Petrov *et al.*[4] However, no systematic investigation of the asymmetric hydrogenation of the C=N double bond has been done, in spite of its scientific and economical importance.

New efforts to obtain an effective asymmetric hydrogenation catalyst, one which has an asymmetric hydrogenation activity for the C=N double bond to the optically-active amine, have been made by the present authors. The present paper will deal with our preliminary and basic research into the asymmetric hydrogenation of the C=N double bond.

Acetoximino compounds may be suitable as a substrate for the asymmetric hydrogenation of the C=N double bond. However, three hydrogenation route for acetoximino compounds to amino compounds can be expected when two moles of hydrogen are taken up in two steps during the hydrogenation. The supposed hydrogenation routes of ethyl 2-acetoximinopropionate (I) are shown schematically in Fig. 1. Ethyl alaninate (IV) can be obtained through three pathways; I-II-IV, I-III-IV, and I-II-III-IV; the A and D processes give a chance of asymmetric hydrogenation. Consequently, for the investigation of asymmetric hydrogenation, it is very important to elucidate the main route of the hydrogenation.

An asymmetrically-modified R–Ni catalyst was used in the present work in order to elucidate the reaction path of the hydrogenation of I; this is a novel technique for the investigation of the reaction mechanism. The authors proved that I-II-IV is the main route of the hydrogenation of an acetoximino compound and that the asymmetric hydrogenation occurs in the A process.

Independently of the investigation described above, the asymmetric reductive amination of ethyl pyruvate was performed.

Results and Discussion

Hydrogenation of Ethyl 2-Acetoximinopropionate (I). The hydrogenation of I was performed in alcohol and in ethyl acetate; the results are shown in Fig. 2. Depending on the solvent used for the hydrogenation, different hydrogenation products were obtained.

In methanol, ethyl alaninate (IV) was obtained by the hydrogenation with a hydrogen uptake of two moles. On the other hand, in ethyl acetate I took up only one mole hydrogen to give ethyl acetoxyalaninate (II), and at this point the hydrogen uptake was over; II was identified by elemental analysis and by gas chromatography.

The results of the gas chromatography of the hydrogenation products in methanol are shown in Fig. 3. Figure 3-a and 3-b show the analytical results for the partial hydrogenation products,

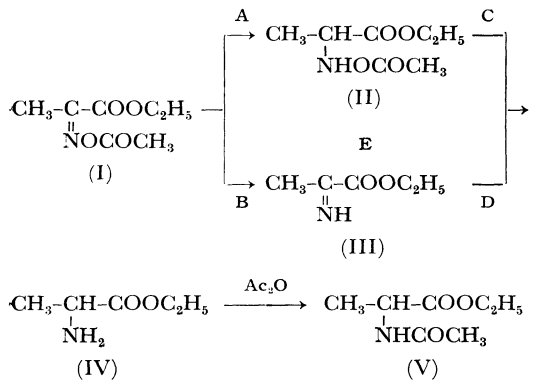

Fig. 1. Hydrogenation routes of ethyl 2-acetoximinopropionate.

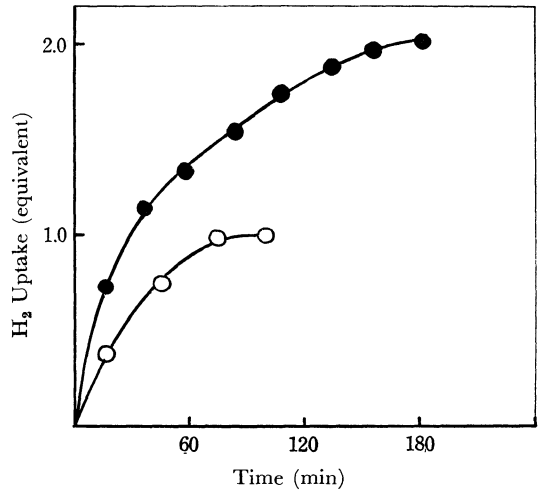

Fig. 2. Effect of solvent on the hydrogenation of I.
—○— In ethyl acetate or ether
—●— In methyl alcohol or ethyl alcohol

3) T. Isoda, A. Ichikawa and T. Shimamoto, *Riken Hokoku*, **34**, 134, 143 (1958).

4) Yu. I. Petrov, E. I. Klabnovskii and A. A. Balandin, *Kinetika i Kataliz*, **8**, 814 (1967).

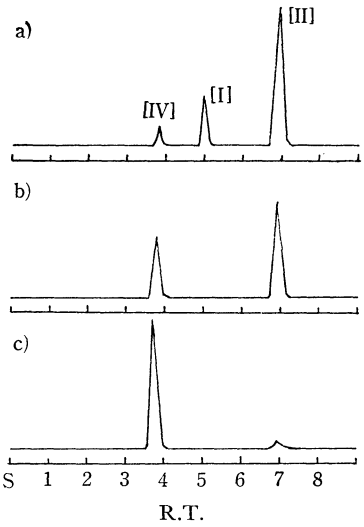

Fig. 3. Relation between products and H_2 uptake of ethyl 2-acetoximinopropionate.
Shimadzu GC-4A P.E.G. 20M 3 m
Column temp. 130°C
a; 28% of theoretical H_2 uptake
b; 68% of theoretical H_2 uptake
c; 98% of theoretical H_2 uptake

which were obtained at 28, 64, and 98% of the theoretical value of the hydrogen uptake.

From the findings that the ratio of II to IV decreases with the increase in the hydrogen uptake, it is clear that II occupies the intermediate position in the hydrogenation of I to IV in methanol.

Asymmetric Hydrogenation of I. The optically-active II and IV were, respectively, obtained by the hydrogenation of I in alcohol and in a nonpolar solvent in the presence of a R–Ni catalyst modified with optically-active histidine, as is shown in Table 1. The asymmetric direction of the product depends on the absolute configuration of the histidine used as a modifying reagent. That is, the catalyst modified with D-histidine gave (−)-II or ethyl (−)-acetylalaninate ((−)-V),*2,*3) and that modified with L-histidine gave (+)-II or (+)-V, while that, with DL-histidine gave (±)-II or (±)-V.

Hydrogenation of II. As is shown in Table 2, the optical purity of the hydrogenation product depends only on the optical purity of the substrate, II, and not on the absolute configuration of the modifying reagent; that is, II with $[\alpha]_D^{20}=-0.25$ gave V with $[\alpha]_D^{20}=-0.25$ upon hydrogenation in the presence of a R–Ni catalyst modified with L-histidine, D-histidine, or DL-histidine and upon N-acetylation with acetic anhydride. From these results, it is clear that the asymmetric hydrogenation does not occur in this process and that the hydrogenation of II to IV does not proceed through ethyl 2-imino-propionate (III).

As is shown in Table 2, by the hydrogenation of (−)-II with the catalyst modified with L-, D-, or DL-histidine, L-IV, which gives (−)-V, was obtained. Since this reaction proceeds with a retention of the configuration of II, (−)-II can be said to have an L-configuration.

Table 2. Hydrogenation of ethyl acetoxyalaninate (II)

$[\alpha]_D^{20}$ of II	Modifying reagent	Solvent	$[\alpha]_D^{20}$ of ethyl acetylalaninate (V)*	Yield (%)
−0.25	DL-His	CH_3OH	−0.25	58
−0.25	L-His	CH_3OH	−0.25	60
−0.25	D-His	CH_3OH	−0.25	60
±0.00	L-His	CH_3OH	±0.00	51

* Ethyl alaninate, the hydrogenation product, was acetylated for the measurement of the optical rotation.

Table 1. Asymmetric hydrogenation of ethyl 2-acetoximinopropionate (I)

	Modifying reagent	Solvent	Product	$[\alpha]_D^{20}$**	Yield (%)
1	L-His	—	Ethyl acetylalaninate (V)*	+0.25	38
2	L-His	CH_3OH	Ethyl acetylalaninate	+0.25	45
3	D-His	CH_3OH	Ethyl acetylalaninate	−0.25	43
4	DL-His	CH_3OH	Ethyl acetylalaninate	±0.00	48
5	L-His	C_2H_5OH	Ethyl acetylalaninate	+0.25	43
6	L-His	$CH_3COOC_2H_5$	Ethyl acetoxyalaninate (II)	+0.25	60
7	D-His	$CH_3COOC_2H_5$	Ethyl acetoxyalaninate	−0.25	57
8	DL-His	$CH_3COOC_2H_5$	Ethyl acetoxyalaninate	±0.00	63
9	L-His	$C_2H_5OC_2H_5$	Ethyl acetoxyalaninate	+0.25	46

* Ethyl alaninate, the hydrogenation product, was acetylated for the measurement of the optical rotation.
** Measured without dilution.

*2 The hydrogenation product is ethyl alaninate, and its optically rotatory power was measured after the acetylation.

*3 Ethyl (−)-acetylalaninate has an L-configuration.

Table 3. Reductive amination of ethyl pyruvate

Modifying reagent	Solvent	Product	$[\alpha]_D^{20}$ of V	Yield (%)
L-His	Ammonia-methanol	Ethyl acetyl-alaninate (V)*	+0.09	21

* Ethyl alaninate, the hydrogenation product, was acetylated for the measurement of the optical rotation.

Asymmetric Reductive Amination of Ethyl Pyruvate. The possibility of the asymmetric hydrogenation of III is confirmed by the results of the asymmetric reductive amination of ethyl pyruvate, as is shown in Table 3.

Experimental

1) Preparation of Asymmetric Catalysts. a) Preparation of the R–Ni Catalyst. Into 60 m*l* of 20% aqueous sodium hydroxide solution, 4.5 g of the R–Ni alloy (Ni : Al=40 : 60) were added in small portions without cooling. After the reaction mixture had then been maintained at 100°C for 1 hr, the aqueous solution was removed by decantation and the R–Ni catalyst was washed with deionized water.

b) Modification of the Catalyst. Onto the R–Ni catalyst obtained from 4.5 g of an alloy we poured, as soon as possible 200 m*l* of a 2% aqueous solution of histidine, which had been cooled at 0°C. The mixture was then allowed to stand, with occasional shaking, at 0°C for 1.5 hr. After the removal of the modifying solution by decantation, the catalyst was washed twice with 50-m*l* portions of water and twice with 50-m*l* portions methanol.

2) Hydrogenation of Ethyl 2-Acetoximinopropionate. *a) Hydrogenation to Ethyl Alaninate (IV) in Methanol.* Twenty grams of I in 20 m*l* of methanol were hydrogenated with the R–Ni catalyst, or with the modified R–Ni catalyst obtained from 4.5 g of an alloy, at room temperature under an initial hydrogen pressure of 90 kg/cm² and in shaking 100-m*l* autoclave. After the hydrogen uptake ceased, the reaction product, IV, was separated from the catalyst and treated with 20 m*l* of acetic anhydride at 5°C for 2 hr. The acetylated product, V, was distilled under reduced pressure, and a fraction with a bp of 100—102°C/3 mmHg was collected. The purity of the distillate was checked by means of gas chromatography and the optical rotation measured without dilution.

Found: C, 53.06; H, 8.26; N, 8.41%. Calcd for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8.80%.

b) Hydrogenation to Ethyl Acetoxyalaninate (II) in Ethyl Acetate. The product obtained by the hydrogenation in ethyl acetate was distilled; a distillate boiling at 100—102°C/3 mmHg was thus collected.

Found: C, 48.30; H, 7.96; N, 7.76%. Calcd for $C_7H_{13}O_4N$: C, 47.99; H, 7.48; N, 8.00%.

3) Asymmetric Hydrogenation of II. The optically-active or racemic II prepared by the hydrogenation of I in ethyl acetate was hydrogenated in methanol with a modified R–Ni catalyst under the conditions described above. The hydrogenation product, IV, was acetylated and distilled, and its optical rotation was measured without dilution.

4) Ethyl Acetyl-L-alaninate (L-V). L-IV prepared by the esterification of L-alanine with alcohol and hydrogen chloride, and by subsequent neutralization with triethylamine, was acetylated by acetic anhydride and triethylamine in chloroform.

A fraction of bp 100—102°C/3 mmHg was collected. The optical rotatory power of the product was $[\alpha]_D^{20}$ −56° (without dilution): lit.,[5] $[\alpha]_D^{20}$ −46.4° (without dilution).

5) Reductive Amination of Ethyl Pyruvate. Twenty grams of ethyl pyruvate (0.085 mol) in 50 m*l* of a 5.4N ammonia methanol solution (0.25 mol) were hydrogenated with the modified R–Ni at 60°C under an initial hydrogen pressure of 90 kg/cm² in a shaking 100-m*l* autoclave. When the hydrogenated product was acetylated by the method described above and distilled under reduced pressure, a fraction with a bp of 100—102°/3 mmHg was collected. Yield, 2.1 g. The purity of the distillate was checked by means of gas chromatography and elemental analyses.

Found: C, 52.69; H, 8.45; N, 8.45%. Calcd for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8.80%.

The authors wish to express their thanks to Misses Kiku Koike and Nobuko Ohya for their elemental analyses. This research was supported by the Kawaken Fine Chemicals Co., Ltd., Tokyo. Part of the expenses of this work has also been defrayed by a grant from the Ministry of Education.

5) K. Freunenberg, F. Rhino, *Ber.*, **57**, 1554 (1924).