Asymmetric Hydrogenation with Modified Raney Nickel. I. Studies on Modified Hydrogenation Catalyst. II(1)

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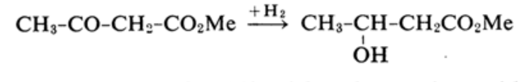
Although a number of methods for asymmetric hydrogenation have been attempted, few reports are available on the asymmetric hydrogenation based on the assymmetric function of catalysts, except enzymatic hydrogenation. Akabori et al.(2-3) reported on asymmetric hydrogenation observed in the experiments using silk-palladium catalyst. However, the efficiency of their asymmetric hydrogenetion was very low and the results were not reproducible. Isoda et al.(4) also reported that asymmetric hydrogenation occurred by the use of silk-palladium catalyst and with R-Ni*, on which optically active amino acid has been adsorbed.

In the previous paper of this series(1) it was reported that the treatment of R-Ni with amino acid solution e. g. Glu* diminished the hydrogenation activity for the carbonyl group without any appreciable effect on the activity toward the C=C double bond.

The present paper deals with the asymmetric hydrogenation of carbonyl compounds carried out with R-Ni modified with optically active amino acid. It has been confirmed that R-Ni treated with L- or D-Glu solution has a definite ability to catalyze the hydrogenation of carbonyl compounds asymmetrically. Ethyl acetoacetate, methyl acetoacetate and acetophenone were asymmetrically hydrogenated with the use of this modified catalyst yielding the corresponding, optically active alcohols. An excellent result was obtained in the hydrogenation of methyl acetoacetate to methyl 2-hydroxybutyrate by the use of R-Ni treated with L- or D-Glu.



$$CH_3\text{-}CO\text{-}CH_2\text{-}CO_2Me \xrightarrow{+H_2} CH_3\text{-}\underset{\substack{|\\ OH}}{CH}\text{-}CH_2CO_2Me$$

The treatment of R-Ni with other amino acids showed the same effect to a lesser extent. R-Ni treated with D-tartaric acid also had the capacity to catalyze asymmetric hydrogenation.

The results of experiments described above were reproducible and products of high optical activity were obtained. R-Ni treated with L- and D-Glu respectively gave levo- and dextrorotatory 2-hydroxybutyrate. When R-Ni treated with DL-Glu the product was fully inactive as could naturally be expected. Hydrogenation of benzalazlactone with R-Ni treated with L-Glu gave, however, optically inactive phenylalanine.

The catalyst modified with Glu had no asymmetric activity for the hydrogenation of benzalazlactone. As reported in the previous paper modification of R-Ni with amino acids had no effect on the hydrogenation activity toward the C=C double bond, while it showed a strong inhibition of the activity toward the carbonyl group. On the other hand, the modified catalysts had asymmetric hydrogenation activity toward the carbonyl group above 60°C.

The results described above and that reported in the previous paper suggest that the hydrogenation of the carbonyl group and C=C double bond may take place at different active centers.

Results and Discussion

Effect of the pH of Modifying Solution.—Asymmetric yields of catalytic hydrogenation by R-Ni treated with 2% L-Glu solution of various pH at 0°C were investigated. The pH of the Glu solution was adjusted with 1 N ($f=0.833$) sodium hydroxide solution according to the titration curve shown in Fig. 1.

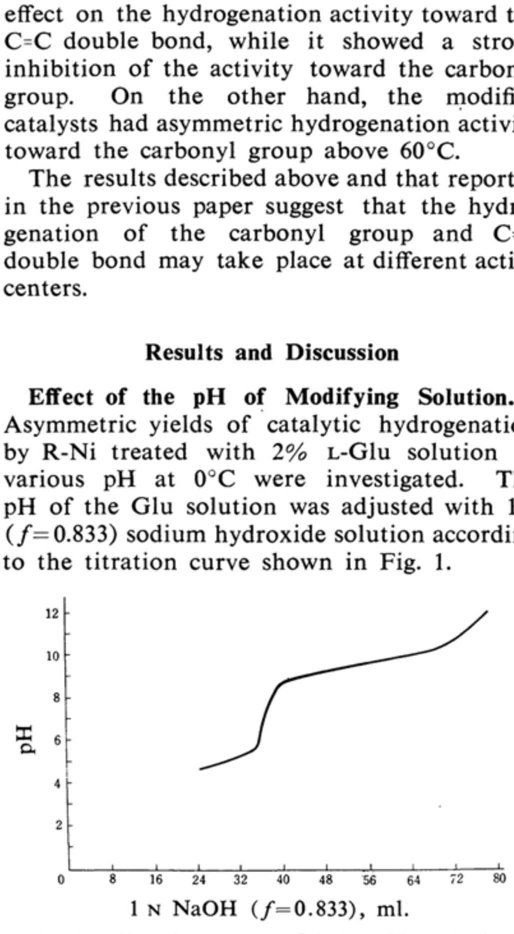


Fig. 1. Titrating curve of 2% L-Glu solution with 1 N NaOH.

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* Abbreviation: R-Ni, Raney nickel; Glu, Glutamic acid.

1) H. Fukawa, Y. Izumi, S. Komatsu and S. Akabori, This Bulletin, **35**, 1703 (1962).

2) S. Akabori, Y. Izumi, Y. Fujii and S. Sakurai, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 1374 (1956); S. Akabori, Y. Izumi and Y. Fujii, ibid., **78**, 886 (1957).

3) Y. Izumi, This Bulletin, **32**, 932 (1959).

4) T. Isoda, A. Ichikawa and T. Shimamoto, *J. Sci. Res. Inst.* (*Rikenhokoku*), **34**, 134 (1958); **34**, 143 (1958).

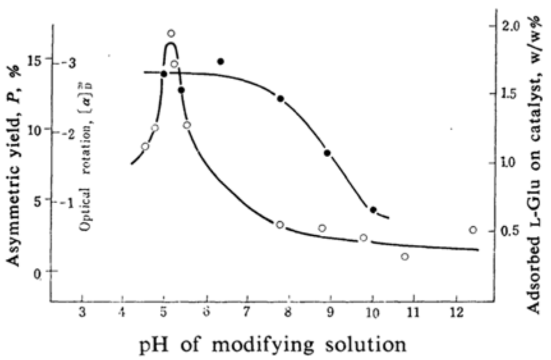

Fig. 2. Effect of pH of modifying solution.

○ Optical rotatory power of reduction product

● Adsorbed L-Glu on R-Ni

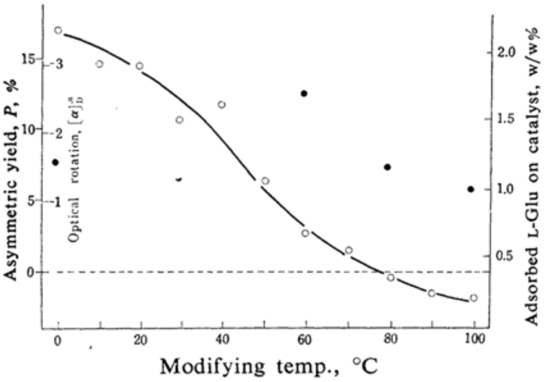

Fig. 3. Effect of modifying temperature.

○ Optical rotatory power of reduction product

● Adsorbed L-Glu on R-Ni

As shown in Fig. 2, the pH of the Glu solution greatly influenced the capacity of the catalyst for asymmetric hydrogenation and adsorbed L-Glu. There was a distinct optimum capacity at pH 5.1 with considerable diminution observed both at higher and lower pH values. It is interesting that the modifying solution turned green on treating R-Ni below pH 5 and blue above pH 5.

Effect of Modifying Temperature.—The relationship between the asymmetric capacity and the temperature of modifying solution was studied using R-Ni immersed in 2% L-Glu at pH 5.0∼5.2. The highest asymmetric yield was obtained with R-Ni modified at 0∼20°C, and the asymmetric yield was decreased at higher temperatures as shown in Fig. 3. If R-Ni was treated with the same modifying solution at temperatures higher than 80°C the product showed reverse optical rotation. Reaction velocity of hydrogenation decreased as the modifying temperature was increased. However, no relationship between the quantity of adsorbed amino acid and catalytic activity could be established, because exact determination of adsorbed Glu was impossible. The facts mentioned above might sugget that the mode of modification of the catalyst at higher temperature is different from that at lower temperature.

Effect of Concentration of Modifying Solution.—The asymmetric capacity of the modified R-Ni was independent of the concentration of L-Glu within the range of 6 to 0.0625% as can be seen in Fig. 4. This result shows that adsorption of Glu on R-Ni reaches saturation at the lower concentration.

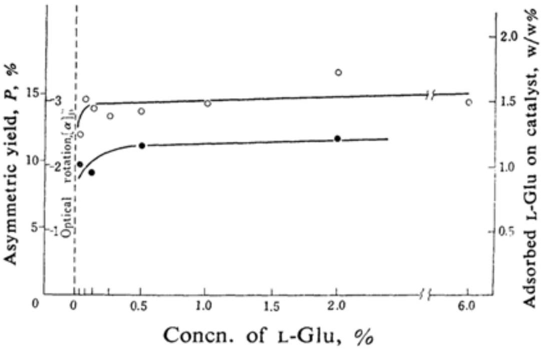

Fig. 4. Effect of concentration of modifying solution.

○ Optical rotatory power

● Adsorbed L-Glu on R-Ni

Effect of Immersion Time for Modification.—The effect of immersion time of R-Ni in Glu solution upon the asymmetric hydrogenation is shown in Table I. The adsorption equilibrium appears to be attained within 15 min.

Table I. Effect of immersion time for modification

Immertion time	Optical rotation $[\alpha]^{20}_{D}$	Asymmetric yield P, %
2 min.	−2.56	12.2
10 min.	−3.51	16.8
1.5 hr.	−3.46	16.5
19 hr.	−3.30	15.8
47 hr.	−2.98	14.3

Table II. Effect of mixture D- and L-Glu in different ratio upon the asymmetric yield

Mixing ratio		Optical rotation $[\alpha]^{20}_{D}$	Asymmetric yield P, %
L-Glu	D-Glu		
10	0	−2.86	13.7
9	1	−1.90	9.1
6	4	−0.45	2.2
0	10	+2.95	14.1

Effect of Mixing L- and D-Glutamic Acid.—The effect of mixtures D- and L-Glu in different ratios upon the asymmetric yield has been measured and has been compared with the effects of pure D- and L-Glu. A nearly linear relationship between the activity of the reaction products and the mixing ratio was observed as shown in Table II.

TABLE III. EFFECT OF DOUBLE MODIFICATION

Exp. No.	Modifying agent 1st	Modifying agent 2nd	Optical rotation $[\alpha]_D^{20}$
1	L-Glu	L-Glu	−3.14
2	L-Glu	D-Glu	+4.84
3	D-Glu	L-Glu	−3.58
4	D-Glu	D-Glu	+4.89

Effect of Double Modification.—When R-Ni was first treated with L- or D-Glu, and then D- or L-Glu, the capacity of asymmetric hydrogenation was determined by the configuration of the second modifying agents as shown in Table III.

Effect of Relative Amount of Catalyst.—The effect of varying the proportion of catalyst to substrate was investigated. Seventeen grams of methyl acetoacetate were reduced completely to methyl 2-hydroxybutyrate in the presence of modified catalyst which prepared from 1∼7 g. of R-Ni alloy and modified with 225 ml. of 2% Glu solution.

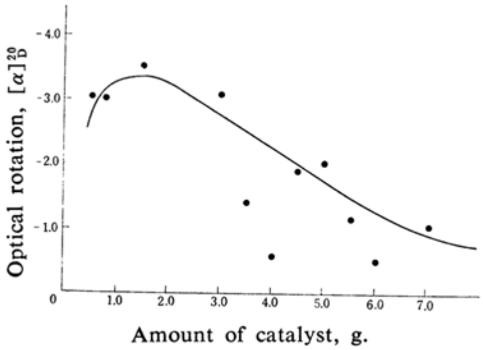

Fig. 5. Effect of the amount of catalyst prepared at 0°C.

When the catalyst was prepared at 0°C, increasing of the amount of catalyst decreased the asymmetric yield (Fig. 5). Catalyst prepared from 1.5 g. of alloy yielded a product with optical rotation $[\alpha]_D^{20}$, of −3.5. A product with the small rotation value, α −0.5, was obtained when a catalyst prepared from 6 g. of alloy was used; however, when the latter catalyst was recovered and one-fourth of it was used, the product showed an optical rotation of α −3.5.

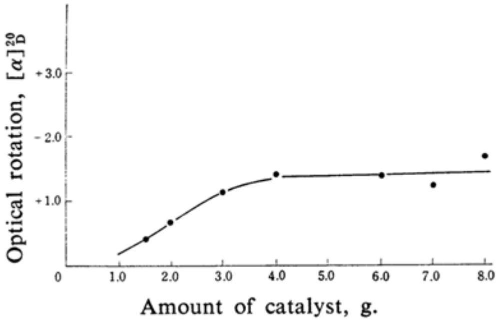

Fig. 6. Effect of the amount of catalyst prepared at 100°C.

The use of increased amounts of catalyst prepared at 100°C increased the asymmetric yield, as shown in Fig. 6. For example a catalyst prepared from 1.5 g. R-Ni alloy yielded a product with an optical rotation, α +0.4, while a catalyst prepared from 6 g. of alloy yielded a product with optical rotation, α +1.65. Recovery of the latter catalyst and the use of about a half and a third of the recovered material for reduction, yield products with rotation, α +0.60 and +0.41, respectively.

These results show that catalyst prepared in small or large amounts have the same activity when used under the same conditions. Therefore the effects shown in Figs. 5 and 6 resulted from the ratio of catalyst to substrate and not from the quantity in which the catalyst was prepared.

Desorption of Glutamic Acid from Asymmetric Catalyst. — The asymmetric catalyst prepared by contact with L-Glu solution of pH 5.2 at 0°C or 100°C was used for study. When this preparation was treated with N sodium hydroxide solution in boiling water for 1 hr., adsorbed Glu on R-Ni was removed from it, and the catalyst lost the adsorbed Glu and the asymmetric activity.

These results show that the presence of glutamic acid absorbed on the R-Ni was necessary for its asymmetric activity.

The results described above suggest that the asymmetric hydrogenation by the modified R-Ni was affected by many factors, particularly by pH and temperature of the modifying solution.

TABLE IV. ASYMMETRIC ACTIVITY OF DIFFERENT LOT OF R-Ni ALLOY

Lot	Optical rotation $[\alpha]_D^{20}$	Asymmetric yield *P*, %
A	−3.02	14.4
B	−3.30	15.8
C	−3.51	16.8

Catalysts were modified with 2% L-Glu solution at 0°C in pH 5.0.

However, so far as the authors experienced with the hydrogenation of methyl acetoacetate by the modified R-Ni prepared from different lots of R-Ni alloy of the same metal composition (Ni : Al=4 : 6) gave 2-hydroxybutyrate of almost the same optical activity as shown in Table IV.

Further experiments on the asymmetric modification of hydrogenation catalysts are going on in the authors' laboratory.

Experimenal

Preparation of Catalyst.—R-Ni Catalyst used in the present work was prepared by a method similar to that described in the previous paper[4]. One and a half grams of powdered R-Ni alloy (Ni : Al= 40 : 60) was added to 20 ml. of 20% sodium hydroxide solution in small portions during 5 min. and was allowed to stand for 45 min. at 80°C. The nickel catalyst was washed several times with water. All of the hydrogenation experiments were carried out with this quantity of R-Ni catalyst.

Modification of Catalyst. — Two hundred and twenty-five milliliters of 2% L-Glu solution, the pH of which had been adjusted to a specified value, was added to newly prepared R-Ni and was allowed to stand with occasional shaking at 0°C for 1.5 hr. After the modifying solution was removed by decantation the catalyst was washed once with distilled water and twice with methanol, and was then separated by centrifugation.

Hydrogenation of Methyl Acetoacetate.—Commercial methyl acetoacetate was purified by washing with saturated sodium bicarbonate solution and then distilling under reduced pressure. Redistilled methyl acetoacetate (17.0 g.) was hydrogenated in the presence of modified R-Ni which was prepared from 1.5 g. of alloy. The reaction was run at 60°C under initial hydrogen pressure of 90 kg./cm^2 in a shaking autoclave. Hydrogen uptake was almost complete in about 12 hr. Reaction velocity was calculated as per cent hydrogen uptake during the first 3 hr. The reduction product was filtered off from R-Ni and distilled under reduced pressure. The main fraction boiling at 61～62°C/12 mmHg was identified as methyl 2-hydroxybutyrate by an elemental analysis of its hydrazide. The purity of methyl 2-hydroxybutyrate was tested by gas chromatography.

Asymmetric Yield. — Optical rotatory power of the distilled product was measured by a conventional polarimeter at 20°C without dilution in 1 dm. tube and the value was taken as the specific rotation because the density of methyl acetoacetate is nearly 1.0. According to Levene and Haller[5] the optical rotatory power of methyl-L-2-hydroxybutyrate is $[\alpha]^{20}_{\mathrm{D}}$ -20.9, and therefore the percentage asymmetric yield, P, was calculated by the equation $P=([\alpha]^{20}_{\mathrm{D}}/20.9)\times 100$.

Identification of Methyl 2-Hydroxybutyrate.—Forty five grams of the reduction product ($[\alpha]^{20}_{\mathrm{D}}$ -0.8) was boiled with 40 ml. 6 N hydrochloric acid for about 5 hr. and brought to dryness under reduced pressure. The residue was esterified by reacting it with ethanol (30 ml.) in the presence of benzene (20 ml.) and *p*-toluenesulfonic acid (0.5 g.). After the product was cooled, it was extracted with benzene and washed with water. Removal of the solvent followed by distillation gave ethyl 2-hydroxybutyrate (15.6 g.), b. p. 62°C/12 mmHg, $[\alpha]^{20}_{\mathrm{D}}$ -0.7.

To 3.3 g. of ethyl 2-hydroxybutyrate 4.2 ml. of 80% hydrazine hydrate was added, the mixture was refluxed for 1 hr. and allowed to stand overnight. The crystalline product was stirred with 2 ml. ethanol, filtered and washed with a small quantity of ethanol. The yield was 2.6 g. ; m. p. 124～126°C, $[\alpha]^{20}_{\mathrm{D}} < -0.04$.

Found : C, 40.71 ; H, 8.58 ; N, 23.49. Calcd. for $C_4H_{10}O_2N_2$: C, 40.66 ; H, 8.35 ; N, 23.71%.

This first crop is apparently DL-2-hydroxybutyric hydrazide. A second crop was obtained by adding ethanol to the mother liquor and recrystallizing from a mixture of ethyl acetate and ethanol. Yield 0.5 g. m. p. 123～124°C, $[\alpha]^{20}_{\mathrm{D}}$ -5.67 in water.

Found : C, 40.93 ; H, 8.62 ; N, 23.26. Calcd. for $C_4H_{10}O_2N_2$: C, 40.66 ; H, 8.53 ; N, 23.71%.

Determination of Glutamic Acid Adsorbed on R-Ni Catalyst.—The modified catalysts were washed with water two times and were allowed to stand overnight. Then, the catalyst was filtered after the addition of a few drops of 1% methanol solution of lauric acid and dried in a desiccator. Glutamic acid was eluted with 1 N sodium hydroxide solution by heating for 1 hr. in a boiling water bath. The eluted glutamic acid was determined by the ninhydrin-photometric method of Stein and Moore[6].

Effect of Double Modification of L- and D-Glutamic Acid (Treatment of the R-Ni with D- after L- or L- after D-Glu).—R-Ni catalyst used in this cases was treated with 225 ml. of 2% L- or D-Glu solution adjusted to pH 5.0～5.2 at 0°C and washed once with distilled water. Then the catalyst was treated with 100 ml. of D- or L-Glu solution by the usual method as described above.

Hydrogenation of Ethyl Acetoacetate. — The catalyst was prepared by treating 1.5 g. of R-Ni alloy first with alkali and then with 225 ml. of L-Glu solution adjusted to pH 5.0 at 0°C, as described above. This catalyst was used in the hydrogenation of 16 g. of ethylacetoacetate. The reducing product, ethyl 2-hydroxybutyrate was purified by distillation and its optical rotation was measured, as above mentioned, $[\alpha]^{20}_{\mathrm{D}}$ -2.00.

Hydrogenation of Acetophenone.—Sixteen grams of acetophenone was reduced and its optical rotation was measured by a similar method to the above, $[\alpha]^{20}_{\mathrm{D}}$ $+0.90$.

Summary

1. Raney nickel catalyst treated with optically active glutamic acid has the property

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[5] P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 51 (1925).

[6] S. Moore and W. H. Stein *J. Biol. Chem.*, **176**, 367 (1948).

of catalyzing the hydrogenation of carbonyl compounds asymmetrically with high reproducibility and efficiency.

2. Excellent results were obtained in the hydrogenation of methyl acetoacetate to optically active methyl 2-hydroxybutyrate in the presence of Raney nickel catalyst treated with L- or D-glutamic acid.

3. The capacity for asymmetric hydrogenation was strongly dependent upon the pH of the modifying solution. The highest capacity was obtained when modifying solutions were adjusted to pH 4.8～5.5.

4. With elevation of the temperature of the modifying process, the asymmetric capacity of the catalyst decreased markedly, nearly disappearing at 60°C, and yielding products with reverse optical rotation above 80°C.

5. The asymmetric capacity was independent of the concentration of the modifying solution within the range of 6 to 0.0625%.

6. Hydrogenation in the presence of catalyst modified with D-glutamic acid yielded a product with reverse optical rotation to that obtained when L-glutamic acid was used.

7. Asymmetric yield of the reducing product of methyl acetoacetate by the catalyst treated with Glu was varied with the relative amount of the substrate and the catalyst.

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