BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 941—943 (1968)

Asymmetric Hydrogenation with Modified Raney Nickel.*1 IX

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(Received July 8, 1967)

The asymmetric hydrogenation catalysts were prepared from the Raney nickel catalyst by modifying it with L_s-3,3-dimethyl-2-hydroxybutyric acid and the corresponding amino acid, L-*t*-leucine, which have most methyl groups at the β-position. The asymmetric activities of the catalysts were measured by the hydrogenation of the methyl acetoacetate to methyl 3-hydroxybutyrate. The asymmetric activity of the catalyst modified with an aqueous solution of L_s-3,3-dimethyl-2-hydroxybutyric acid was very low, and the direction of asymmetric activity at pH 5.0 was inverted by the temperature of the modifying solution. However, there was a high asymmetric activity in the catalyst modified with L-*t*-leucine, and this activity was not so influenced by the temperature of the modifying solution. The aysmmetric activities of catalysts modified with α-hydroxy acids and the corresponding amino acids reported in this paper and the previous papers are compared, and the effect of the bulk of the α-alkyl substituent of the modifying reagent upon the asymmetric activity of the catalyst is discussed.

The asymmetric activities of Raney nickel catalysts, modified with various optically active amino acids or hydroxy acids, in the hydrogenation of methyl acetoacetate to methyl 3-hydroxy butyrate have previously been reported on by the present authors.1-8)

The asymmetric activity of a modified Raney nickel catalyst was found to be influenced not only by the pH and temperature of the modifying solution,1) but also by the structure of the modifying reagent. The "asymmetric activity" of a catalyst involves two factors. One is the direction of the asymmetric activity, which is expressed as the direction of the specific rotation, (+) or (−), of the hydrogenated product. The other is the degree of asymmetric activity, which is usually presented as the asymmetric yield. On modification at 0°C, the direction of the asymmetric activity of a catalyst is mainly controlled by the absolute configuration of the α-carbon of the modifying reagent. Catalysts modified with L-α-amino acids other than alanine, serine, proline, and cystine produce methyl D_s-3-hydroxybutyrate predominantly. However, on modification with L_s-2-hydroxy acids, methyl L_s-3-hydroxybutyrate is produced predominantly. However, the factor controlling the asymmetric yield has not been discussed. In the present work, *t*-leucine and 3,3-dimethyl-2-hydroxybutyric acid, which have a bulky *t*-butyl substituent on the α-carbon, were investigated as asymmetric modifying reagents, and the role of the alkyl group of the modifying reagent discussed in

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[*1] Presented in part at the 19th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1966.

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

2) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, *ibid.*, **36**, 21 (1963).

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TABLE 1. OPTICAL ROTATION OF MODIFYING REAGENTS

Modifying reagent	Optical rotation, $[\alpha]^{20}_{D}$	Value in literature
L-(+)-3,3-Dimethyl-2-hydroxybutyric acid	+4.5 (*c* 4, water)	—
L-(−)-*t*-Leucine	−9.5 (*c* 2, water)	−10.2 (*c* 4.3, water)[9]

comparison with the results reported in a previous paper.

Materials

Modifying Reagents.*2 The optical rotations of the L$_S$(+)-3,3-dimethyl-2-hydroxybutyric acid and L-(−)-*t*-leucine used in this work are listed in Table 1.

Experimental

The preparation of the Raney nickel catalyst, the hydrogenation of methyl acetoacetate, and the measurement of the asymmetric activity of the catalyst were performed as has been described in a previous paper.[3]

Results and Discussion

Modification with L$_S$-3,3-Dimethyl-2-hydroxybutyric Acid (I). The Raney nickel catalyst was modified at 0°C or 100°C with an aqueous solution of L$_S$-3,3-dimethyl-2-hydroxybutyric acid (1) which had been adjusted to a specified pH with 1 N sodium hydroxide. The asymmetric activity of the catalyst modified at pH 3—12 and the neutralization curve of the 2% aqueous solution of 1 with 1 N sodium hydroxide (f=0.996) are shown in Fig. 1.

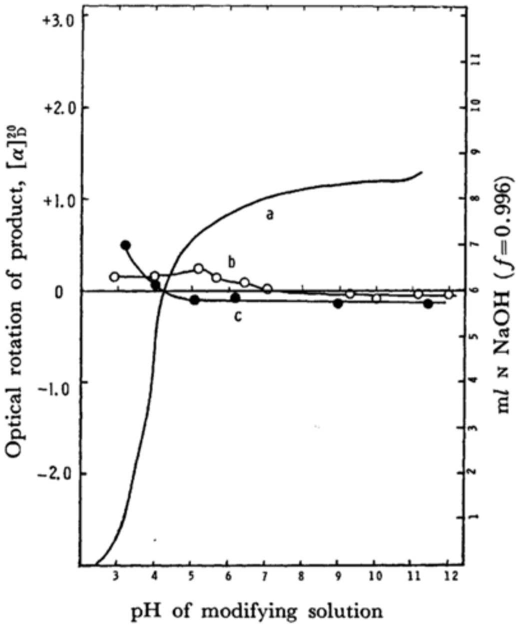

Fig. 1. Neutralization curve of 2% solution of (1) with N NaOH and effects of pH in modifications with (1) at 0°C and 100°C.
a Neutralization curve
b Modified at 0°C
c Modified at 100°C

The optimum asymmetric activity of catalysts modified with 1 at 0°C was observed at pH 5.0. This pH value corresponds to the pH-jumping region of the neutralization curve of 1 observed with other hydroxy acids. The direction of asymmetric activity of the catalyst changed at the complete neutralization point.

On modification at 100°C, the catalyst showed its highest asymmetric activity at pH 3.2. The direction of the asymmetric activity of the catalyst modified at 100°C changed at a low pH value than in the case of modification at 0°C, this pH corresponded to the pH-jumping region in the titration curve. The values of the asymmetric activities of catalysts modified at 0°C and 100°C were both very low over the whole range of modifying pH values.

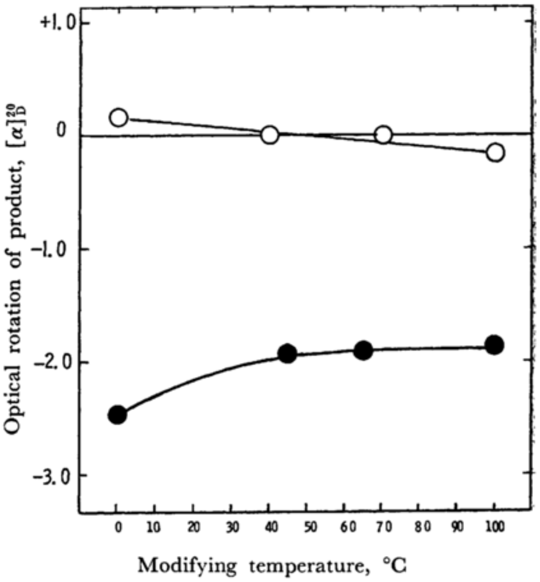

Fig. 2. Effect of modifying temperature.
○ Modified with L-3,3-dimethyl-2-hydroxybutyric acid (1) at pH 5.0
● Modified with L-*t*-leucine (II) at the isoelectric point

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*2 The details of the preparation of these compounds will be reported in this Bulletin later.

9) N. Izumiya, S.-C. J. Fu, S. M. Birnbaum and J. P. Greenstein, *J. Biol. Chem.*, **205**, 221 (1953).

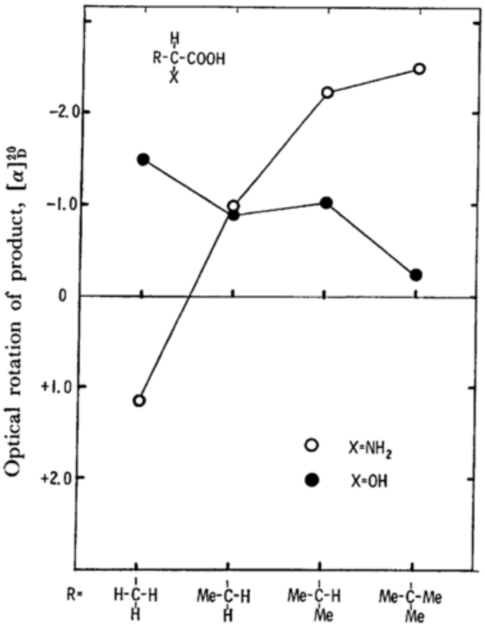

Fig. 3. Effect of substituent.

○ Modified at 0°C, isoelectric point
● Modified at 0°C, pH 5.0

The effect of the temperature of the modifying solution of 1 was studied at pH 5.0; the results are shown in Fig. 2. As is shown in Fig. 2, the asymmetric activity decreased with an increase in the modifying temperature, and the direction of asymmetric activity changed at about 50°C. Such an inversion of the direction of asymmetric activity by the modifying temperature has not been found in the modifications with β-substituted α-hydroxy acids reported in previous papers.²⁾

Modification with L-*t*-Leucine (II). The asymmetric activity of the catalyst modified with an aqueous solution of L-*t*-leucine (2) at the isoelectric point (pH 6.2) was measured at various temperatures. The results are shown in Fig. 2. The asymmetric activity was fairly high, and the activity of the catalyst modified at 0°C was intermediate between the activities of the catalysts modified with L-valine and with L-alloisoleucine*³ at 0°C. The rough linear relation shown in Fig. 2 was also found between the asymmetric activity and the modifying temperature in catalysts modified with other α-amino acids, such as valine and isoleucine.

Effect of α-Alkyl Substituent on Asymmetric Activity of Catalyst. In order to make clear effect of the bulk of α-alkyl substituents in asymmetric modifying reagents on the asymmetric activities of catalysts, the asymmetric activities of the catalysts modified with α-hydroxy acids and the corresponding α-amino acids, reported in this paper and in previous papers,²,³⁾ are compared in Fig. 3. Figure 3 shows the asymmetric activities of the catalysts when the hydrogen atoms on the β-carbon of lactic acid or alanine are replaced with methyl groups, one by one. The catalysts were modified at 0°C, at the isoelectric point with amino acids, and at pH 5.0 with hydroxy acids. The asymmetric activity of the catalyst modified with amino acid increases with the increase in the bulk of the α-alkyl substituent, while, with hydroxy acids, the influence of the bulk of alkyl substituents is smaller than in the case in modifications with amino acids; asymmetric activity is the lowest with the acid having the most bulky alkyl substituent.

This research was supported by the Kawaken Fine Chemicals Co., Ltd., Tokyo.

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*3 The asymmetric activity of this catalyst will be reported on later by the present authors.