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Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel. XII

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The asymmetric hydrogenation of methyl acetoacetate to optically active methyl 3-hydroxybutyrate with a Raney nickel catalyst modified with optically active α-amino or α-hydroxy acid has been reported in previous papers of this series.[1,2] In these previous papers, the correlation between the asymmetric activity of the catalyst and the structure of modifying reagent, and the roles of the substituents at the α-asymmetric carbon of a modifying reagent have been discussed, and it has been found that the direction of the asymmetric activity of the catalyst with respect to the optical rotation of the product is decided by the absolute configuration of α-carbon and by the nature of the α-substituents of the modifying reagent. However, the asymmetric activities of the catalysts modified with α-substituted α-amino acids have not been discussed except with 2-methyl- and 2-benzylglutamic acids.

In the present paper, the asymmetric activities of the catalysts modified with (+)-isovaline and with (−)-2-methylaspartic acid are decribed; the results are compared with those obtained with 2-aminobutyric acid and aspartic acid in Table 1 and Fig. 1 respectively, in order to investigate the effect on the asymmetric activity of the replacement of an α-hydrogen of the modifying reagent with a methyl group. Moreover, as the absolute configuration of (+)-2-benzylglutamic acid was confirmed by means of the X-ray diffraction method by Kakudo *et al.*,[3] the relationship between the direction of the asymmetric activity of the catalyst with respect to the optical rotation of the product and the absolute configuration of the α-substituted amino acid used for modification is discussed in this report.

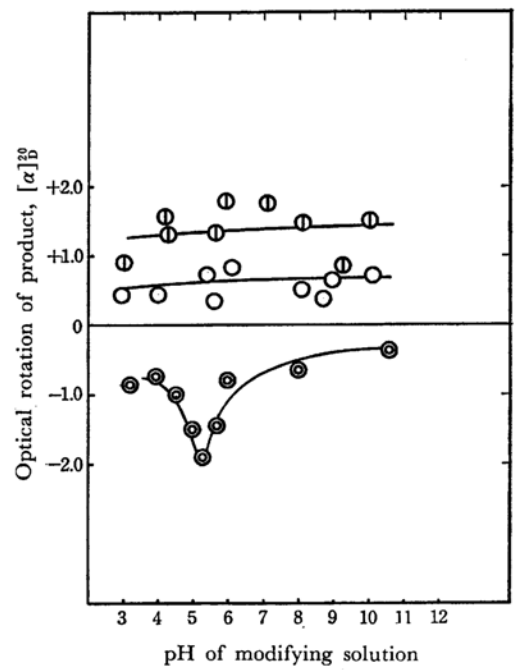


Fig. 1. Modifications with (−)-2-methylaspartic acid and L-aspartic acid.
—◑— (−)-2-Methylaspartic acid (modifying temp.: 100°C)
—○— (−)-2-Methylaspartic acid (modifying temp.: 0°C)
—◎— L-Aspartic acid (modifying temp.: 0°C)

TABLE 1. MODIFICATIONS WITH (+)-ISOVALINE AND L-2-AMINOBUTYRIC ACID

Modifying reagent	Modifying conditions		$[\alpha]_D$ of methyl 3-hydroxybutyrate
	pH	Temp. °C	
(+)-Isovaline	6.0	0	−0.66
	6.0	100	−0.65
L-2-Aminobutyric acid	6.05	0	−1.46
	5.85	100	−1.61

Experimental

Preparation of Catalyst. One and a half grams of Raney nickel alloy (Ni : Al=40 : 60) were added in small portions to 20 m*l* of a 20% sodium hydroxide solution over a 5-min period, and then the solution was allowed to stand for 45 min at 80°C. The nickel catalyst was washed several times with water.

Modification of Catalyst. An aqueous solution of the modifying reagent, the pH and the temperature of

1) Part X: Y. Izumi, K. Matsunaga, S. Tatsumi and M. Imaida, This Bulletin, **41**, 2515 (1968); Part XI: Y. Izumi, M. Imaida, T. Harada, T. Tanabe, S. Yajima and T. Ninomiya, *ibid.*, **42**, 241 (1969).

2) S. Tatsumi, *ibid.*, **41**, 408 (1968).

3) T. Ashida, Y. Sasada and M. Kakudo, This Bulletin, **40**, 476 (1967).

which had been adjusted to specified values, was added to a newly-prepared Raney nickel catalyst, and then the mixture was allowed to stand at the specified temperature, with occasional shaking, for 1.5 hr. After the modifying solution had been removed by decantation, the catalyst was washed once with water and twice with methanol.

Measurement of the Asymmetric Activity of the Catalyst. Redistilled methyl acetoacetate (18 m*l*) was hydrogenated in the presence of a modified Raney nickel catalyst which had been prepared from 1.5 g of an alloy. The reaction was run at 60°C under an initial hydrogen pressure of 80—100 kg/cm² in a shaking autoclave. The reduction product was filtered to remove the catalyst and then distilled under reduced pressure (bp 61—62°C/12 mmHg). The purity of the methyl 3-hydroxybutyrate was tested by gas chromatography. The optical rotatory power of the distilled product was measured by a conventional polarimeter in 1-dm tube at 20°C without dilution; the value was taken as the specific rotation because the density of methyl 3-hydroxybutyrate is nearly 1.0. According to Levene and Haller,[4] the optical rotatory power of methyl D-3-hydroxybutyrate is $[\alpha]_D^{20}$ −20.9.

Results and Discussion

Effect of the Modifying Temperature.[*1]

1) Isovaline. The effect of the modifying temperature on the catalyst modified with isovaline is shown in Table 1. No remarkable change in the asymmetric activity of the catalyst with the modifying temperature was found.

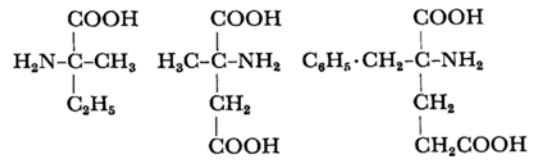
2) 2-Methylaspartic Acid. As is shown in Fig. 1, the asymmetric acitivity of the catalyst increases with the elevation of the modifying temperature, while on modification with aspartic acid it decreases with the elevation of the modifying temperature.[5] The tendency found in the modification with 2-methylaspartic acid was also observed in the cases of modification with 2-methyl- and 2-benzylglutamic acid, as has been reported in a previous paper.[6]

Effect of the Modifying pH.[*2]

The modifying pH does not so strongly affect the asymmetric activity of the catalyst in the case of modification with 2-methylaspartic acid as in the case of modification with 2-methyl- or 2-benzylglutamic acid,[6] as is shown in Fig. 1.

Correlation of the Direction of the Asymmetric Activity of the Catalyst and the Absolute Configuration of α-Substituted α-Amino Acid.

The configurations of (+)-isovaline,[7] (−)-2-methylaspartic acid,[8] and (+)-2-benzylglutamic acid[3] are written in the conventional Fischer diagram as follows:



(+)-isovaline (−)-2-methylaspartic acid (+)-2-benzylglutamic acid

Thus, (+)-isovaline can be assigned either an L- or a D-configuration, depending on whether it is considered as a derivative of L-2-aminobutyric acid or of D-alanine. In a like manner, (+)-2-benzylglutamic acid and (−)-2-methylaspartic acid can be considered as a derivative of L-phenylalanine or of D-glutamic acid and as a derivative of L-alanine or of D-aspartic acid respectively. Moreover, Meister and his co-workers have suggested, after investigations using the biochemical method, that the (+)-isomer of 2-methylglutamic acid can be considered as a derivative of L-glutamic acid.[9] Meanwhile, catalysts modified with (+)-isovaline, with (−)-2-methylaspartic acid, and with (+)-2-benzylglutamic acid at 0°C gave predominantly methyl D-(−)-, L-(+)- and L-(+)-3-hydroxybutyrate respectively as the hydrogenation products.

These facts show that the direction of the asymmetric activity of the catalyst modified with α-substituted α-amino acid conforms to the general rule that the catalyst modified with L (or D)-α-amino acid at 0°C gives methyl D (or L)-3-hydroxybutyrate as the hydrogenation product when the α-substituted α-amino acid is considered as a derivative of the α-amino acid, which is more effective for the preparation of a catalyst with a high asymmetric activity. For example, the catalyst modified with optically active 2-aminobutyric acid at 0°C has a higher asymmetric activity than that modified with optically active alanine, and so in the case of the catalyst modified with (+)-isovaline at 0°C, the direction of the optical rotation of the product conforms to the general rule when the compound is considered as a derivative of L-2-aminobutyric acid.

Effect of the α-Alkyl Substituent of α-Amino Acid on the Formation of the Asymmetrically Active Center. The asymmetric activities of the catalysts modified with isovaline and with 2-methylaspartic acid are increased or

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

*1 "Modifying temperature" means the temperature of the aqueous solution of the modifying reagent.

5) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, This Bulletin, **36**, 155 (1963).

6) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, *ibid.*, **38**, 1206 (1965).

*2 "Modifying pH" means the pH of the aqueous solution of the modifying reagent.

7) S. Yamada and K. Achiwa, *Chem. Pharm. Bull. Tokyo*, **12**, 1525 (1964).

8) S. Terashima, K. Achiwa and S. Yamada, *ibid.*, **14**, 572 (1966).

9) H. M. Kagan, L. R. Manning and A. Meister, *Biochemistry*, **4**, 1063 (1965).

at least not affected with the elevation of the modifying temperature. On the contrary, those with 2-aminobutyric acid and with aspartic acid decrease with the elevation of the modifying temperature. As the same results were obtained with α-substituted amino acids and with β-alkyl substituted amino acids, it can be assumed that the α-substituent has the same effect as the β-alkyl substituent on the formation of an asymmetrically active center on the surface of the catalyst. That is, in the case of modification with α- or β-alkyl substituted α-amino acid, the proportion of the (−)- to the (+)-asymmetrically active centers*3 on the surface of the catalyst does not greatly change with the modifying temperature.

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*3 "(+) (or (−))-asymmetrically active center" means the asymmetric center on the surface of the catalyst in which methyl L-(+) (or D-(−))-3-hydroxybutyrate is preferentially produced in hydrogenation of methyl acetoacetate. For example, on modification with L-glutamic acid, the catalyst modified at 0°C, which produces predominantly methyl D-(−)-3-hydroxybutyrate, contains predominantly (−)-asymmetrically active center, while the catalyst modified at 100°C, which produces predominantly methyl L-(+)-3-hydroxybutrate, contains predominantly (+)-asymmetrically active center.