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Asymmetric Hydrogenation with Modified Raney Nickel. VIII

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Asymmetric hydrogenation catalysts were prepared by modifying Raney nickel with aqueous solutions of D-tartaric acid, monomethyl D-tartrate, L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid, L-malic acid, (+)-*erythro*- and (−)-*threo*-3-methylmalic acid, L-citramalic acid and L-methylsuccinic acid. Their asymmetric activities in the hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate were compared with each other in order to study the effect of the chemical structure of the modifying reagent on the activity. Monomethyl D-tartrate, L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid are less effective in asymmetric activity than D-tartaric acid. On modification with these three reagents, optimum asymmetric activities were obtained under acidic conditions. With D-tartaric acid, however, while high asymmetric activities were obtained at pH 5—9, there was a considerable decrease in activity at lower pH values. This suggests that the β-carboxyl group of tartaric acid plays an important role in the modification. (−)-*threo*-3-Methylmalic acid is more effective in asymmetric activity than L-malic acid, while (+)-*erythro*-3-methylmalic acid and L-citramalic acid are less effective. It has been suggested that these differences are related to hindrances due to the methyl groups on the α- or β-asymmetric centers, and also related to the correlations of the configurations of the asymmetric centers of 3-methylmalic acids. L-Methylsuccinic acid has little asymmetric effect on Raney nickel.

Previous papers in this series[1-7] have reported on the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate using Raney nickel catalysts modified with various optically active 2-amino acids and 2-hydroxy acids. High asymmetric activities were generally observed when Raney nickel was modified with such optically active dihydroxy dicarboxylic acids as D-tartaric acid, (+)-*threo*-2-methyltartaric acid and (+)-*threo*-2, 3-dimethyltartaric acid.[6] An especially high asymmetric activity was obtained by modification with (+)-*threo*-2-methyltartaric acid. On the contrary, optically active hydroxy monocarboxylic acids had rather low asymmetric effects upon Raney nickel.[3]

In the present work, the asymmetric activities of Raney nickel catalysts modified with monomethyl D-tartrate, L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid were tested and compared with that of the catalyst modified with D-tartaric acid; this was done in order to study the role of the β-carboxyl group of D-tartaric acid and in order to elucidate the difference in the asymmetric effects

1) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, This Bulletin, **36**, 21 (1963).
2) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, ibid., **36**, 155 (1963).
3) S. Tatsumi, M. Imaida, Y. Fukuda, Y. Izumi and S. Akabori, ibid., **37**, 846 (1964).
4) Y. Izumi, S. Akabori, H. Fukawa, S. Tatsumi, M. Imaida, Y. Fukuda and S. Komatsu, *Proceedings of the 3rd International Congress on Catalysis*, **2**, 1364 (1964).
5) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, This Bulletin, **38**, 1206 (1965).
6) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, ibid., in press.
7) Y. Izumi, S. Tatsumi and M. Imaida, ibid., to be published.

Table I. The optical rotation of modifying reagent

Modifying reagent	Optical rotation, $[\alpha]_D^{20}$	Value in literature
(+)-*erythro*-3-Methylmalic	+9.1° (*c* 3.7, H_2O)	—
(−)-*threo*-3-Methylmalic acid	−5.3° (*c* 3.2, H_2O)	—
L-Citramalic acid	+23.2° (*c* 3, H_2O)	+23.2° (*c* 4.4, H_2O)[8]
L-Methylsuccinic acid	−11.5° (*c* 5, H_2O)	−11.7° (*c* 3, H_2O)[12]
Monomethyl D-tartrate monohydrate	+18.1° (*c* 3, H_2O)	+18.4° (*c* 10, H_2O)[10]
L-*erythro*-2, 3-Dihydroxybutyric acid	+10.3° (*c* 3.2, H_2O)	+8.8° (—, H_2O)[13]
D-*threo*-2, 3-Dihydroxybutyric acid	+15.9°(*c* 2.1, H_2O)	+15.5° (—, —)[14]

of a hydroxy dicarboxylic acid and a hydroxy monocarboxylic acid.

In spite of the high asymmetric effect with (+)-*threo*-2-methyltartaric acid, only a very low effect was observed on modification with (−)-*erythro*-2-methyltartaric acid.[6] It was suggested that the difference in the effects of these two reagents on Raney nickel is related to the erythro-threo isomerism, that is, that it results from the configurational difference between the two diasymmetric centers in these molecules.

In the present work, the asymmetric activities of catalysts modified with (+)-*erthro*- and (−)-*threo*-3-methylmalic acid were also compared with each other, and with that of a catalyst modified with L-malic acid, in order to study the effect of the configuration of the modifying reagent upon the catalyst. Raney nickel was also modified with L-citramalic acid, in which the hydrogen atom on the asymmetric α-carbon of malic acid is replaced by a methyl group, in order to study the role of an α-substituted group in the formation of an asymmetric catalyst. L-Methylsuccinic acid was also tested as a modifying reagent.

The optical purities of the modifying reagents used in the present study are listed in Table I.

Experimental

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

Modifying Reagents. — (+)-*erythro*-3-Methylmalic acid,* (−)-*threo*-3-methylmalic acid,* L-citramalic acid[8] and L-methylsuccinic acid[9] were prepared from the corresponding racemic acids. Monomethyl D-tartrate monohydrate was prepared by a slight modification of Markward's procedure.[10] L-*erythro*-2, 3-Dihydroxybutyric acid and D-*threo*-2, 3-dihydroxybutyric acid were prepared from L-allothreonine and D-threonine respectively.[11]

Results and Discussion

Modifications with Monomethyl D-Tartrate Monohydrate, L-*erythro*- and D-*threo*-2, 3-Dihydroxybutyric Acid.—Measurements were made of the asymmetric activities of catalysts modified at 0°C with aqueous solutions of monomethyl D-tartrate monohydrate, L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid, the pH values of which had been adjusted to specified values with a sodium hydroxide solution.

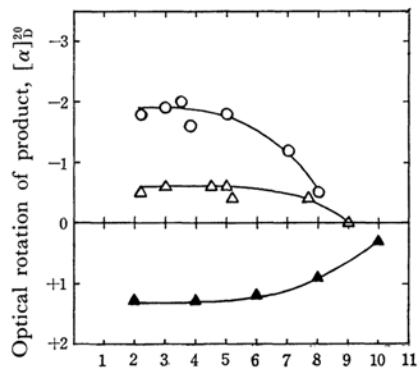

Fig. 1. Modifications with monomethyl D-tartrate, L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid. (Modified at 0°C for 15 min.)

○ Monomethyl D-tartrate
△ D-*threo*-2, 3-Dihydroxybutyric acid
▲ L-*erythro*-2, 3-Dihydroxybutyric acid

As is shown in Fig. 1, the catalysts modified with monomethyl D-tartrate monohydrate and D-*threo*-2, 3-dihydroxybutyric acid gave levorotatory products predominantly, while that modified with L-*erythro*-2, 3-dihydroxybutyric acid gave dextrorotatory products. In all cases, the optimum asymmetric activity was observed under acidic condi-

* Details of the preparation of the racemic acid, its separation into the two isomeric forms, the optical resolutions of the isomers, and the determination of their configurations have recently been reported by the present authors. This Bulletin, in press.

8) M. J. Coon, "Biochemical Preparations," Vol. IX, John Wiley & Sons, New York (1962), p. 21.

9) A. Ladenberg, *Ber.*, **28**, 1170 (1895).

10) W. Markward and L. Karczag, ibid., **42**, 1518 (1909).

11) C. E. Meyer and W. C. Rose, *J. Biol. Chem.*, **115**, 721 (1936).

tions, and there was a considerable decrease in activity under alkaline conditions. These asymmetric activity curves were similar in character to those obtained on modifications with optically active monohydroxy monocarboxylic acids[3]; however, they were quite different from that obtained with D-tartaric acid.**

On modification with D-tartaric acid, optimum asymmetric activities were observed at pH 5—9; there was a considerable decrease in activity at both lower and higher pH values, as is shown in Fig. 2.

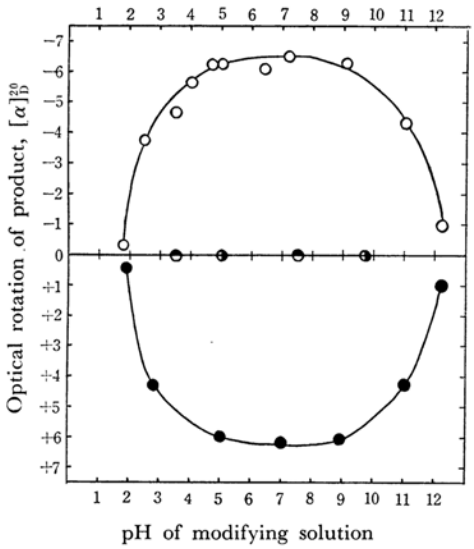

Fig. 2. Modifications with optically active and inactive tartaric acid. (Modified at 0°C)

○ D-Tartaric acid ◑ DL-Tartaric acid
● L-Tartaric acid ◓ *meso*-Tartaric acid

Both monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid are characterized by the lack of the free β-carboxyl group of D-tartaric acid. Therefore, in the modification with D-tartaric acid, the diminution of asymmetric activity under acidic conditions is clearly due to the free β-carboxyl group of the reagent. It is likely that both carboxyl groups of D-tartaric acid are adsorbed freely on the surface of nickel metal in the absence of alkali, and that with a decrease in acidity one is desorbed from the nickel metal and then produces a massive steric hindrance which regulates the approach of the hydrogenation substrate to the catalyst. On the other hand, in modifications with monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid, their adsorption forms on the surface of the metal similarly under all acidic conditions, since the ester and methyl groups are less affected by the modifying conditions.

Modifications with L-Malic Acid, (+)-*erythro*- and (−)-*threo*-3-Methylmalic Acid.— Raney nickel was modified with L-malic acid, (+)-*erythro*- and (−)-*threo*-3-methylmalic acid in order to study the role of a β-substituted methyl group and the effect of the configuration at the β-carbon of the modifying reagent upon asymmetric hydrogenation. The asymmetric activities of the resulting catalysts were then compared. The results are shown in Fig. 3.

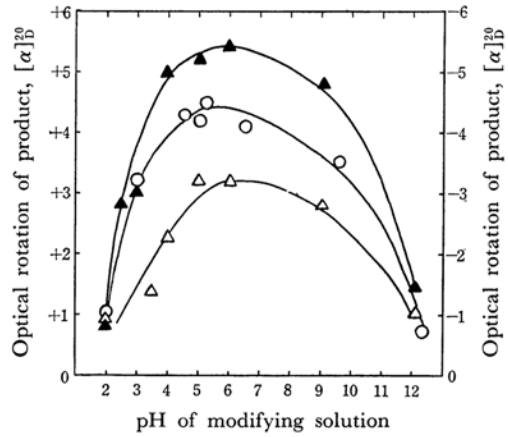

Fig. 3. Modifications with L-malic acid, (+)-*erythro*- and (−)-*threo*-3-methylmalic acid. (Modified at 0°C)

The left scale is used for L-malic acid, and the right scale for (+)-*erythro*- and (−)-*threo*-3-methylmalic acid.

○ L-Malic acid
▲ (−)-*threo*-3-Methylmalic acid
△ (+)-*erythro*-3-Methylmalic acid

The catalysts modified with (+)-*erythro*- and (−)-*threo*-3-methylmalic acid produced levorotatory methyl 3-hydroxybutyrate predominantly, while that modified with L-malic acid produced dextrorotatory methyl 3-hydroxybutyrate. Optimum asymmetric activities were obtained under nearly neutral modifying conditions; there was a considerable diminution in activity under both acidic and alkaline conditions, as was observed upon modification with D-tartaric acid. Moreover, (−)-*threo*-3-methylmalic acid was more effective in asymmetric hydrogenation than was L-malic acid, while (+)-*erythro*-3-methylmalic acid was less effective. The difference between these reagents is clearly due to the β-methyl group of the modifying reagent. On the other hand, by

12) M. Naps and I. B. Johns, *J. Am. Chem. Soc.*, **62**, 2450 (1940).
13) E. Hoff-Jörgensen, *Z. physiol. Chem.*, **268**, 194 (1941).
14) I. W. E. Glattfeld and J. W. Chittum, *J. Am. Chem. Soc.*, **55**, 3663 (1933).

** The modification with D-tartaric acid had already been reported on in Part II of this series.[2] Subsequent studies of modifications with optically active and inactive tartaric acid gave the results shown in Fig. 2.

referring to the findings of Baker,[15] the same configuration can evidently be assigned to the α- and β-asymmetric centers of (−)-*threo*-3-methylmalic acid, while those of (+)-*erythro*-3-methylmalic acid are opposite in configuration. Accordingly, it is likely that the difference between (−)-*threo*-3-methylmalic acid and (+)-*erythro*-3-methylmalic acid is related to the above different configurations of the modifying reagents.

Modification with L-Citramalic Acid (L-2-*C*-Methylmalic Acid).—Modification with L-citramalic acid was performed at 0°C; the asymmetric activity of the resulting catalyst was then compared with that of the catalyst modified with L-malic acid in order to study the effect of an α-*C*-substituted group on the asymmetric hydrogenation. The results are shown in Fig. 4.

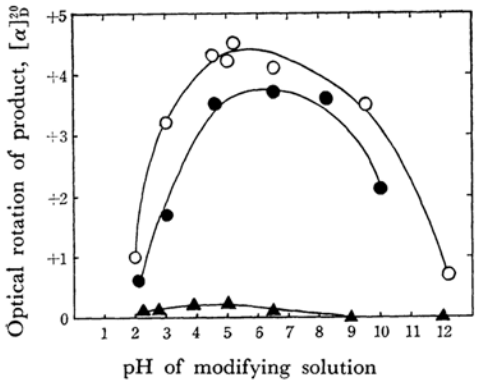

Fig. 4. Modifications with L-malic acid, L-citramalic acid and L-methylsuccinic acid. (Modified at 0°C)
○ L-Malic acid
● L-Citramalic acid
▲ L-Methylsuccinic acid

L-Citramalic acid was less effective in asymmetric hydrogenation than was L-malic acid. The difference is evidently caused by the methyl group on the asymmetric α-carbon atom of L-citramalic acid. Similar differences were observed between the modifications with glutamic acid and α-*C*-substituted glutamic acids.[5] These results clearly show that, to obtain an effective asymmetric catalyst, the α-asymmetric carbon atom of the modifying reagent should not possess a bulky substituted group in addition to the hydroxyl group, carboxyl group and β-carbon chain.

Modification with L-Methylsuccinic Acid.—The asymmetric activity of the catalyst modified with an aqueous solution of L-methylsuccinic acid was also measured.

As is shown in Fig. 4, L-methylsuccinic acid had little or no effect upon Raney nickel under any of the acidic and alkaline conditions tested. These results are in marked contrast to the high asymmetric activities obtained on modification with L-malic acid. Since in L-methylsuccinic acid the hydroxyl group of L-malic acid is replaced by a methyl group, it is clear that the α-hydroxyl group of the modifying reagent plays an important role in the asymmetric modification, and that it is indispensable for the preparation of a catalyst possessing a high asymmetric activity.

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15) H. A. Baker, R. D. Smyth, E. J. Wawszkiewicz, M. N. Lee and R. M. Wilson, *Arch. Biochem. Biophys.*, **78**, 468 (1958).