BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 408—418 (1968)

Asymmetric Hydrogenating Activity of Modified Raney Nickel Catalyst

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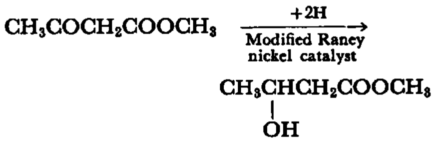
(Received July 22, 1967)

In the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate using Raney nickel catalysts modified with optically active hydroxy dicarboxylic acids and related compounds (for example, Y. Izumi, S. Tatsumi and M. Imaida, *Bull. Chem. Soc. Japan*, **39**, 2223 (1966)), the relationship between the asymmetric activities of the catalysts and the chemical or stereochemical structures of modifying reagents was discussed on the basis of data obtained previously. The effects of the conditions used for modification upon the asymmetric activity were also discussed inclusively. Moreover, the stability of asymmetric activity in the modified catalysts has been found to be very excellent.

Only a few attempts to obtain asymmetric hydrogenation using asymmetric catalysts have been recorded during the past ten years. In 1956, Akabori *et al.*[1-3] first reported on the asymmetric hydrogenation observed in experiments using silk-palladium catalysts. Subsequently, Isoda *et al.*[4] also reported the occurrence of asymmetric hydrogenation using an amino acid-palladium catalyst following a similar principle. The efficiencies of these catalysts, however, were rather low and the results were inconsistent because of the complexity of the conditions used.

Recently, Izumi and coworkers[5-6] obtained an excellent asymmetric hydrogenation catalyst. They reported that a Raney nickel catalyst treated with aqueous solutions of optically active amino acids has an asymmetric activity in the hydrogenation of carbonyl compounds to the corresponding alcohols. The author[7] also reported that in the hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate similar asymmetric activities are observed on the modifications[*2] of a Raney nickel catalyst with optically active hydroxy acids, and that the hydroxy acids derived from the corresponding amino acids retaining their absolute configurations have reverse asymmetric effects in the direction of their optical rotation upon a Raney nickel catalyst to the parent amino acids. Subsequently, several reports on the asymmetric hydrogenation of methyl acetoacetate by catalysts modified with various optically active amino acids, hydroxy acids and their derivatives have appeared from our laboratory.[8-12]



$$CH_3COCH_2COOCH_3 \xrightarrow[\text{Modified Raney nickel catalyst}]{+2H} CH_3\underset{\displaystyle OH}{\underset{|}{CH}}CH_2COOCH_3$$

Thus, high asymmetric activities were obtained by modifications with optically active hydroxy dicarboxylic acids, such as D- or L-tartaric acid, L-malic acid and their *C*-alkyl or *C, C'*-dialkyl derivatives. An especially high asymmetric effect was observed on modification with optically active 2-methyltartaric acid,[10,13] the configuration of which has recently been assigned the threo form by the author.[14] However, there are no reports on the relationship between the chemical or stereochemical structures of modifying reagents and the

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1) S. Akabori, Y. Izumi, S. Sakurai and Y. Fujii, *Nature*, **178**, 323 (1956).

2) S. Akabori, Y. Izumi, Y. Fujii and S. Sakurai, *Nippon Kagaku Zassi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **77**, 1374 (1956).

3) S. Akabori, Y. Izumi and Y. Fujii, *ibid.*, **78**, 886 (1957).

4) T. Isoda, A. Ichikawa and T. Shimamoto, *Riken Hokoku (J. Sci. Res. Inst.)*, **34**, 134 (1958).

5) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, This Bulletin, **36**, 21 (1963).

6) Y. Izumi, M. Imaida, H. Fukawa and S. Akabori, *ibid.*, **36**, 155 (1963).

7) S. Tatsumi, M. Imaida, Y. Fukuda, Y. Izumi and S. Akabori, *ibid.*, **37**, 846 (1964).

[*2] Modification refers to the altering of the behavior of the catalyst by treatment with certain reagents. The reagent used for the modification is called the modifying reagent in this paper.

8) Y. Izumi, S. Akabori, H. Fukawa, S. Tatsumi, M. Imaida, Y. Fukuda and S. Komatsu, "Proceedings of the 3rd International Congress on Catalysis," North-Holland Publishing Co., Amsterdam (1964), p. 1364.

9) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, This Bulletin, **38**, 1206 (1965).

10) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, *ibid.*, **39**, 361 (1966).

11) Y. Izumi, S. Tatsumi and M. Imaida, *ibid.*, **39**, 1087 (1966).

12) Y. Izumi, S. Tatsumi and M. Imaida, *ibid.*, **39**, 2223 (1966).

13) S. Tatsumi, Y. Izumi, M. Imaida, Y. Fukuda and S. Akabori, *ibid.*, **39**, 602 (1966).

14) S. Tatsumi, *ibid.*, **39**, 2202 (1966).

asymmetric activities of the catalysts. It is very important to find this relationship in order to obtain an effective asymmetric catalyst and elucidate the mechanism of this asymmetric hydrogenation.

In this paper, the relationship between the asymmetric activities of the catalysts in the hydrogenation of methyl acetoacetate to optically active methyl 3-hydroxybutyrate and the chemical or stereochemical structures of modifying reagents, such as optically active hydroxy dicarboxylic acids and related compounds, is discussed on the basis of the data obtained previously. The relation between the asymmetric activities and the conditions used for the modification of Raney nickel catalyst is also discussed. Moreover, the stability of asymmetric activity in the catalyst is studied.

The Occurrence of Asymmetric Activity[*3]

When a Raney nickel catalyst was modified with aqueous solutions of D- or L-tartaric acid[12] adjusted to pH 3—11, it had a high asymmetric hydrogenating activity, as shown in Fig. 1. On the contrary, under the same conditions the catalyst modified with optically inactive meso or racemic tartaric acid[12] did not.

Similar differences were observed on modifications with DL- and L-malic acid[12] and with DL- and L-citramalic acid (*α*-*C*-methylmalic acid),[12] as shown in Fig. 2.

These results clearly show that the presence or absence of asymmetric activity in the modified catalyst depends on the optical purity of the reagent used for the modification. Moreover, on modification with a reagent of the L-configuration, the catalyst produces the L-hydrogenation product, methyl L-3-hydroxybutyrate; while with a reagent of the D-configuration, the D-hydrogenation product is formed. The asymmetric activities of the catalysts in both cases were the same except for their direction of optical rotation. From these results, it is clear that on modification with a racemic form, two kinds of catalyst are produced in

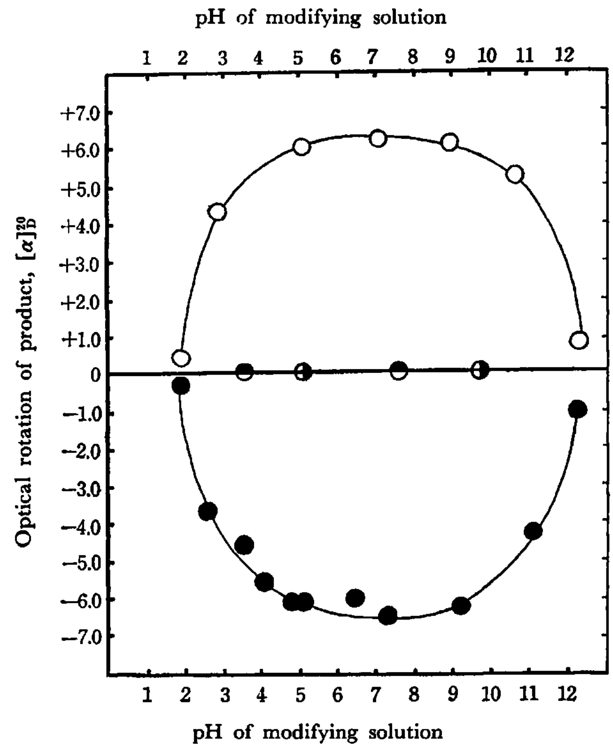

Fig. 1. Modifications with optically active and inactive tartaric acids. (Modified at 0°C)

● D-Tartaric acid ◑ DL-Tartaric acid

○ L-Tartaric acid ◓ *meso* Tartaric acid

[*3] The asymmetric activity is provided by the observed specific rotation value of the hydrogenation product, methyl 3-hydroxybutyrate. According to Levene and Haller (Ref. 15), optically pure methyl 3-hydroxybutyrate has the value, $[\alpha]_D^{20}$ ±20.9° (without a solvent) and the levorotatory and dextrorotatory compounds correspond to the D- and L-series, respectively, in absolute configuration. The symbols, D and L, for the configurations used in this paper are based on the D_g- and L_g-series.

15) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925).

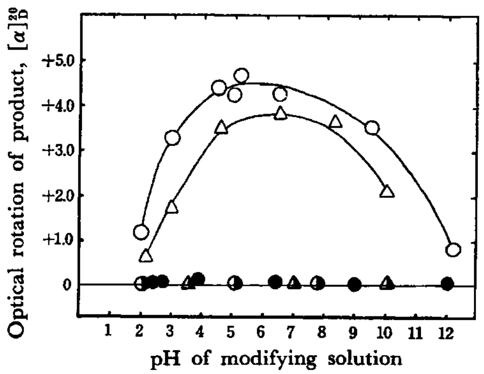

Fig. 2. Modifications with DL- or L-malic acid, DL- or L-citramalic acid and L-methylsuccinic acid. (Modified at 0°C)
○ L-Malic acid ▲ DL-Citramalic acid
△ L-Citramalic acid ● L-Methylsuccinic acid
◑ DL-Malic acid

the same ratio; one has the asymmetric activity to hydrogenate the substrate predominantly to the L-product and the other has the opposite asymmetric activity. As a result of the two activities the product is thus optically inactive and no asymmetric effect of the catalyst on the hydrogenation is observed.

On the other hand, when the modifying reagents loose their ability to be adsorbed on Raney nickel due to acylation of their hydroxyl groups and esterification of their carboxyl groups, the resulting catalysts have only very low asymmetric activities. In spite of the high asymmetric effect with D-tartaric acid, diethyl D-tartrate and *O, O'*-diacetyl D-tartaric acid had only very low or no asymmetric effects upon a Raney nickel catalyst.[6-7] These results show that the free hydroxyl and carboxyl groups of the modifying reagent play important roles in the asymmetric modification.

A similar result was observed on modification with an optically active dicarboxylic acid which has no hydroxyl groups in the molecule, such as L-methylsuccinic acid.[12] Although, like L-malic acid, L-methylsuccinic acid has one asymmetric center on the α-carbon atom, it has little or no asymmetric effect upon a Raney nickel catalyst. This is in marked contrast to the high asymmetric effect obtained on modification with L-malic acid, as shown in Fig. 2.

The difference in the asymmetric effects of these two optically active acids is clearly due to the fact that L-methylsuccinic acid does not contain a hydroxyl group which can be adsorbed or chelated to the nickel metal.

Thus it is concluded that to obtain an effective asymmetric catalyst the modifying reagent must possess at least two functional groups such as a hydroxyl group and a carboxyl group, and the reagent must have a strong ability to be adsorbed or chelated to a Raney nickel catalyst.

The Direction of Optical Rotation of the Asymmetric Activity

Catalysts modified with D-tartaric acid gave methyl D-3-hydroxybutyrate as a hydrogenation product, while those modified with L-tartaric acid gave methyl L-3-hydroxybutyrate, as shown in Fig. 1. Moreover, on modifications with compounds of the D-configuration, such as monomethyl D-tartrate,[12] *O*-monobenzoyl D-tartaric acid,[7] and D-*threo*-2, 3-dihydroxybutyric acid,[12] D-hydrogenation products were obtained. On the contrary, with compounds of the L-configuration, such as L-malic acid,[12] and several L-hydroxy monocarboxylic acids,[7,12] L-products were obtained. The same tendency was also observed on modification with an optically active α-*C*-alkyl-substituted hydroxy carboxylic acid such as L-citramalic acid.[12]

This relationship between the direction of optical rotation of asymmetric activity of the catalyst and the absolute configuration of the modifying reagent was also clearly recognized on modifications with solutions containing various proportions of D- and L-tartaric acid. As shown in Fig. 3, there was a linear relationship between the optical activity of the hydrogenation product and the ratio of modifying reagents in the mixture. An optically inactive product was obtained by catalyst modified with a solution containing equal proportions of D-tartaric acid and L-tartaric acid. These results offer additional evidence in support of the consideration on the occurrence of asymmetric activity mentioned in the preceding chapter.

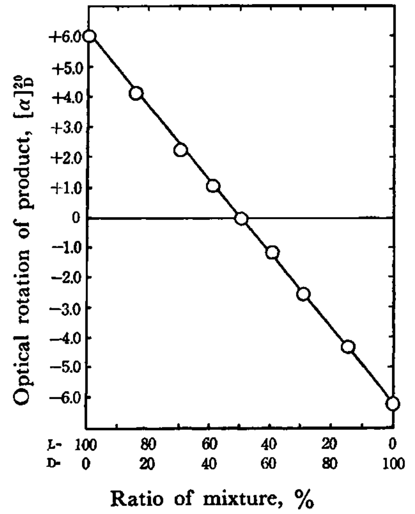

Fig. 3. Effect of ratio of mixture of D- and L-tartaric acid.
(Modified at 0°C and at pH 5.0)

Thus, on modifications with hydroxy carboxylic acids containing one asymmetric center or containing two asymmetric centers of identical absolute

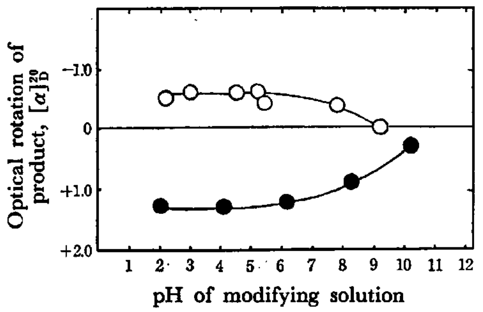

Fig. 4. Modifications with L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid.
(Modified at 0°C)
○ D-*threo*-2, 3-Dihydroxybutyric acid
● L-*erythro*-2, 3-Dihydroxybutyric acid

configuration, it is concluded that catalysts modified with D-hydroxy carboxylic acids produce methyl D-3-hydroxybutyrate in the hydrogenation of methyl acetoacetate, while those modified with L-hydroxy carboxylic acids give methyl L-3-hydroxybutyrate.

Modifications with L-*erythro*- and D-*threo*-2, 3-dihydroxybutyric acid were also studied.12) Since both the α- and β-asymmetric centers of L-*erythro*-2, 3-dihydroxybutyric acid are assigned the L-configuration,16) the catalyst modified with this compound evidently gave the product of the L-configuration, as shown in Fig. 4.

With D-*threo*-2, 3-dihydroxybutyric acid, however, although the α- and β-asymmetric centers are opposite in configuration and belong to the D- and L-series respectively,16) the product was predominantly of the D-configuration. This shows that, when a hydroxy monocarboxylic acid used for modification has two asymmetric centers of opposite configuration in its α- and β-carbon atoms, the direction of optical rotation of the asymmetric activity of the catalyst is decided by the configuration of the α-asymmetric center carrying the functional groups which have the highest affinity for the Raney nickel catalyst.

This conclusion will hold good for catalysts modified with optically active polyhydroxy monocarboxylic acids which have asymmetric centers of different configuration.

The Effect of the Modifying Conditions on the Asymmetric Activity

The Effect of the pH of the Modifying Solution. The asymmetric activities of catalysts modified with hydroxy dicarboxylic acids were influenced more by the pH of the modifying solution than those of catalysts obtained on modifications with hydroxy monocarboxylic acids.7,10-12) Maximal asymmetric activities were observed at pH 5—9 on modifications with hydroxy dicarboxylic acids and there was considerable diminution in activity at both higher and lower pH values, as shown in Figs. 1 and 2. This optimum pH range approximately corresponded to the pH-jumping region of the neutralization curves of these acids.10) However on modifications with hydroxy monocarboxylic acids,7) a similar decrease in activity was observed only when the pH value was increased, as shown in Fig. 5.

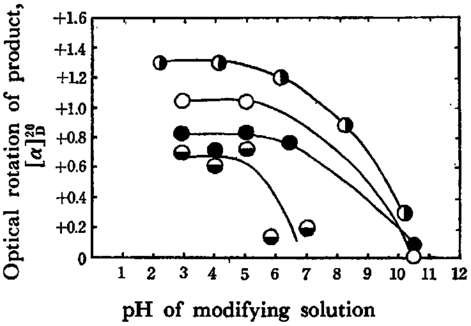

Fig. 5. Modifications with L-hydroxy monocarboxylic acids.
(Modified at 0°C)
◑ L-*erythro*-2, 3-Dihydroxybutyric acid
○ L-2-Hydroxyisovaleric acid
● L-2-Hydroxyisocaproic acid
◒ L-2-Hydroxy-3-phenylpropionic acid

Izumi *et al.*5) reported that optically active α-amino acids have very small asymmetric effects on a Raney nickel catalyst under alkaline conditions. These workers determined the amount of amino acid adsorbed on the catalyst and concluded that the weak asymmetric effects of amino acids under alkaline conditions are caused by desorption of amino acids from the catalyst. On the other hand, it was reported from the Accumulatoren-Fabrik17) that a Raney nickel catalyst maintains its original properties for a long time under strongly alkaline conditions, even if it is treated with solutions containing substances with which it can form complexes, such as tartaric acid and amino aliphatic compounds. This indicates that under strongly alkaline conditions a Raney nickel catalyst can hardly be affected by these substances.

In connection with these observations, the amount of hydroxy carboxylic acid adsorbed on the catalyst in the asymmetric modification was determined. The results18-19) obtained with D-tartaric acid are

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16) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley & Sons, Inc., New York (1961), p. 178.

17) Accumulatoren-Fabrik A. G., Berg. Pat. 613541 (1962).

18) The preparation and modification of Raney nickel catalyst were performed as described in a previous paper.7)

19) D-Tartaric acid adsorbed on the catalyst was eluted by treatment with N sodium hydroxide at 90—95°C for one hour. The acid eluted was determined by the method of Sharma with a slight modification. N. N. Sharma and R. C. Mehrotra, *Anal. Chim. Acta*, **11**, 414 (1954).

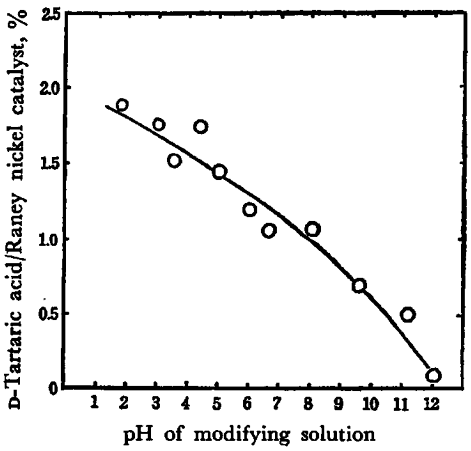

Fig. 6. Adsorption of D-tartaric acid on Raney nickel catalyst.
Raney nickel (0.62 g) was modified with 100 m*l* of a 2% D-tartaric acid solution at 0°C for 1.5 hr.

shown in Fig. 6.

The amount of D-tartaric acid adsorbed on the catalyst was much influenced by the pH of the modifying solution and decreased considerably with increase in the pH value. Under strongly alkaline conditions the reagent is adsorbed very little onto the catalyst. The acid must loose its ability to be adsorbed onto the nickel metal under these conditions because of the conversion to its alkali salt, and so it is desorbed. The weak asymmetric activity observed at high pH values, thus, is evidently caused by desorption of the reagent from the catalyst.

On the other hand, under acidic conditions there is a characteristic difference between the asymmetric activities of catalysts modified with hydroxy dicarboxylic acids and those of catalysts modified with hydroxy monocarboxylic acids. As pointed out at the beginning of this section, on modifications with hydroxy dicarboxylic acids the asymmetric activities decreased remarkably with increase of acidity, while with hydroxy monocarboxylic acids there was no similar decrease. However, as can be seen in Fig. 6, the amount of the hydroxy dicarboxylic acid adsorbed on the nickel metal does not decrease with increase of acidity, but in fact it increases considerably. The above difference in activity, therefore, cannot be explained by the amount of the reagent adsorbed on the catalyst. It is probably related to the presence or absence of the β-carboxyl group in the modifying reagent.[20]

The Effect of the Temperature of the Modifying Solution. On modifications with hydroxy dicarboxylic acids,[10-12] the asymmetric activities of catalysts increased with elevation of the modifying temperature except in the case of (−)-*erythro*-2-methyltartaric acid,[10] as shown in Fig. 7. A similar tendency was observed with several hydroxy monocarboxylic acids.[7]

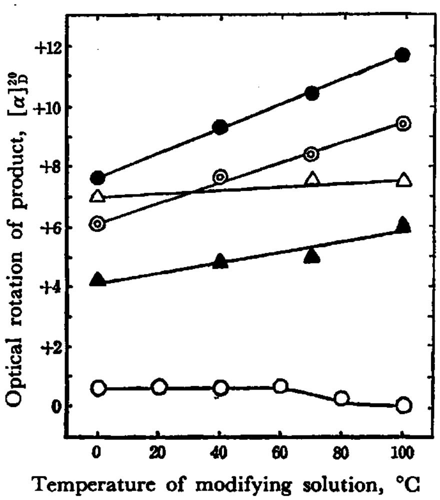

Fig. 7. Effect of temperature on modifications with hydroxy dicarboxylic acids.
(Modified at pH 5.0—5.2)
● (+)-*threo*-2-Methyltartaric acid
○ (−)-*erythro*-2-Methyltartaric acid
△ (+)-2,3-Dimethyltartaric acid
◎ L-Tartaric acid ▲ L-Malic acid

As reported in a previous paper,[7] however, in contrast to the asymmetric activities of the modified catalysts their catalytic hydrogenation activities decreased considerably with elevation of the modifying temperature. It is likely that when a Raney nickel catalyst is modified at a certain pH value, the interaction between the modifying reagent and the nickel metal is intensified by elevation of the temperature, and the reagent spreads itself over the surface of the metal. Consequently a catalyst with many compactly adsorbed asymmetric centers is produced, which thus has a high asymmetric activity in spite of its decreased catalytic hydrogenation activity.

The Effect of the Time of Immersion. To study the effect of the time of immersion of a Raney nickel catalyst upon the asymmetric activity, modifications with a 2% aqueous solution of D-tartaric acid adjusted to pH 5.0 were carried out at 0°C.[18] The asymmetric activities of the resulting catalysts were compared and the results are shown in Fig. 8.

Maximal asymmetric activity was attained when a Raney nickel catalyst was immersed in the solution for 10 min. Immersion for more than 10 min resulted in no further increase in asymmetric activity. It is likely that the adsorption of the modifying reagent on the nickel metal reaches an equilibrium within 10 min at 0°C.

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[20] The role of the β-carboxyl group will be discussed in the subsequent chapter.

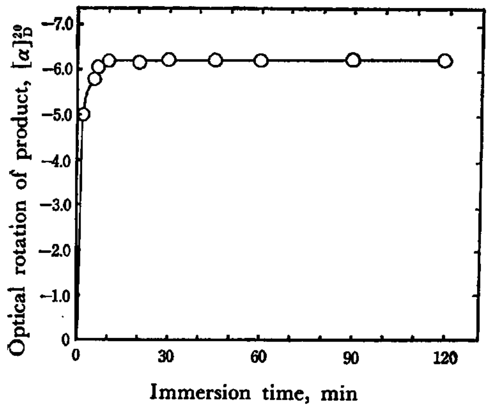

Fig. 8. Effect of time of immersion on modification with D-tartaric acid.
(Modified at pH 5.0 and at 0°C)

Even immersion for 2 or 5 min, however, gives a rather high asymmetric activity to a Raney nickel catalyst. It seems that as soon as Raney nickel is added to the modifying solution, it is strongly adsorbed by the reagent, and the adsorption quickly reaches almost the state of equilibrium.

The Effect of the Concentration of the Modifying Reagent. The effect of the amount of modifying reagent upon the asymmetric activity of the catalyst was studied using aqueous solutions of D-tartaric acid.[18] The results are shown in Fig. 9.

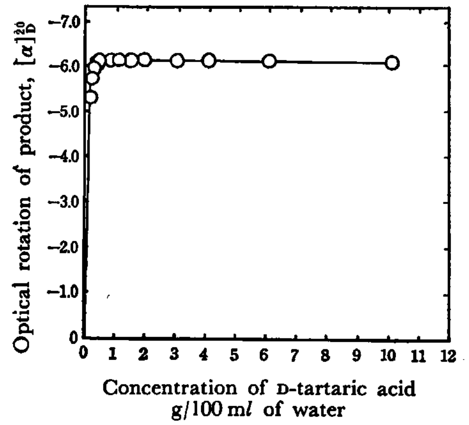

Fig. 9. Effect of concentration of modifying reagent.
(Modified at pH 5.0 and at 0°C)

The asymmetric activity of the catalyst was independent of the concentration of D-tartaric acid in the range of 0.4 to 10%.

Izumi *et al.*[5] observed a similar tendency on modification of a Raney nickel catalyst with an aqueous solution of L-glutamic acid. They reported that the asymmetric activity was not affected by the concentration of the acid in a range of 0.0625 to 6%.

These results clearly show that the adsorption of modifying reagent on Raney nickel readily reaches saturation at a lower concentration.

The Stability of the Asymmetric Activity

To study the stability of the asymmetric activity, a Raney nickel catalyst modified at 0°C with a 2% aqueous solution of D-tartaric acid adjusted to pH 5.0[18] was employed repeatedly in the hydrogenation reaction at 60°C.[21] The results of the stability test are shown in Table 1.

TABLE 1. STABILITY TEST OF ASYMMETRIC ACTIVITY

Catalyst sample	Optical rotation of product, $[\alpha]_D^{20}$
Original modified catalyst	−6.22°
After 1st recovery	−6.30°
After 2nd recovery	−6.09°
After 3rd recovery	−6.01°
After 4th recovery	−6.25°
After 5th recovery	−6.19°

As can be seen in Table 1, the asymmetric activity in the catalyst was very stable. The original asymmetric activity persisted to at least the sixth run. This shows that the modifying reagent is firmly adsorbed on the catalyst and hence the asymmetric centers formed on the surface of the metal are not destroyed during recovery or under the conditions used in the hydrogenation reaction.

The Effect of the Structure of the Modifying Reagent on the Asymmetric Activity

The Effect of the *α*-*C*-Substituted Alkyl Group of the Modifying Reagent. The asymmetric activity of catalyst modified with L-citramalic acid (L-*α*-*C*-methylmalic acid) was lower than that of catalyst modified with L-malic acid, as shown in Fig. 2. This difference is obviously caused by the methyl group on the asymmetric *α*-carbon atom of L-citramalic acid. Similar differences were observed between modifications with glutamic acid and those with *α*-*C*-substituted glutamic acids, such as (+)-2-*C*-methylglutamic acid and (+)-2-*C*-benzylglutamic acid.[9]

These results clearly show that the *α*-*C*-substituted groups play important roles in the formation of an asymmetrically active site of the catalyst, and that to obtain an effective asymmetric catalyst the asymmetric *α*-carbon atom of the modifying reagent should not possess a bulky substituted group in addition to the hydroxyl group, carboxyl

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[21] The hydrogenation reaction and the measurement of the asymmetric activity of the catalyst were performed as described in a previous paper.[7]

group and β-carbon chain. A small group, such as the hydrogen atom in L-malic acid or in L-glutamic acid, seems to be effective for the α-*C*-substituted group. Probably, four groups on the asymmetric α-carbon atom which are rather unbalanced in bulk favor asymmetric hydrogenation.

The Role of the β-Substituted Group of the Modifying Reagent and the Effect of Its Configuration. D-Tartaric acid was more effective for asymmetric activity of a Raney nickel catalyst than L-malic acid, as shown in Figs. 1 and 2. This clearly shows that the β (or α′)-hydroxyl group of tartaric acid and its configuration have a great influence on the formation of an asymmetric catalyst. On the other hand, on modifications with isomeric optically active 3-methylmalic acids, both the (−)-*threo*- and (+)-*erythro*-compounds[12,22] were less effective for asymmetric activity than D-tartaric acid. However, the former was more effective than L-malic acid, while the latter was less effective.[12] The difference in the asymmetric effects of (−)-*threo*-3-methylmalic acid and D-tartaric acid is due entirely to their β-substituted groups, that is, the methyl group of (−)-*threo*-3-methylmalic acid and the hydroxyl group of D-tartaric acid, because *threo*-3-methylmalic acid has the same structure as tartaric acid except that one hydroxyl group is replaced by a methyl group. Moreover, the difference in the asymmetric effects of (+)-*erythro*- and (−)-*threo*-3-methylmalic acid and L-malic acid is also caused by the methyl group attached to the β-carbon atom of malic acid and by its configuration. Thus, like the β-hydroxyl group, the β-methyl group has a great influence on the formation of an asymmetric catalyst though less than the β-hydroxyl group.

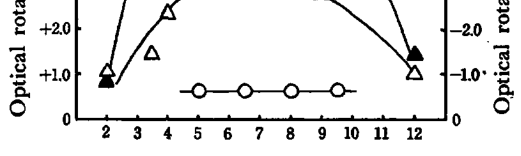

Fig. 10. Modifications with isomeric 3-methylmalic acids and 2-methyltartaric acids.
(Modified at 0°C)
● (+)-*threo*-2-Methyltartaric acid
○ (−)-*erythro*-2-Methyltartaric acid
▲ (−)-*threo*-3-Methylmalic acid
△ (+)-*erythro*-3-Methylmalic acid
The left scale represents (+)-*threo*- and (−)-*erythro*-2-methyltartaric acid, and the right scale represents (−)-*threo*- and (+)-*erythro*-3-methylmalic acid.

To study the effect of the erythro-threo configuration of a modifying reagent on the asymmetric activity, comparisons were made of the asymmetric activities of catalysts modified with optically active α, β-diasymmetric hydroxy dicarboxylic acids, such as (−)-*threo*- and (+)-*erythro*-3-methylmalic acid[12,22] and (+)-*threo*- and (−)-*erythro*-2-methyltartaric acid.[10,13] The results are shown in Fig. 10.

As can be seen in Fig. 10, optically active *threo*-3-methylmalic acid and *threo*-2-methyltartaric acid were more effective for asymmetric activity than the corresponding optically active erythro forms. These results clearly show that the asymmetric activities of catalysts are much influenced by the erythro-threo configuration of the modifying reagents.

The same absolute configuration is assigned to the α- and β-asymmetric centers of optically active *threo*-3-methylmalic acid,[23] and the β-methyl group is situated in the same position relative to the α-hydroxyl group as one hydroxyl group of optically active tartaric acid is to the other. However, the β-methyl group of optically active *erythro*-3-methylmalic acid is situated in the same position, relative to the α-hydroxyl group as the one hydroxyl group of meso tartaric acid is to the other, since the α- and β-asymmetric centers of this compound have the opposite absolute configuration to each other.[23]

Moreover, in these two acids the functional groups to be adsorbed predominantly upon the nickel metal are similar; these are the α-hydroxyl group and the α-carboxyl group which have higher affinities for the metal than the other groups. Therefore, it is clearly conceivable that the difference in the asymmetric activities of catalysts modified with these two acids is caused by this difference in configuration of the asymmetric centers.

A similar difference can be seen between modifications with (−)-*erythro*-2-methyltartaric acid and

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[22] S. Tatsumi, M. Imaida and Y. Izumi, This Bulletin, **39**, 1818 (1966).

[23] The threo isomer of 3-methylmalic acid was identified by deamination of *threo*-3-methylaspartic acid with nitrous acid. Since this deamination of an α-amino acid does not affect the configuration, the resulting α-hydroxy acid is identical in configuration with the parent amino acid. On the other hand, from the investigation of Baker *et al.* (H. A. Baker, R. D. Smyth, E. J. Wawszkiewicz, M. N. Lee and R. M. Wilson, *Arch. Biochem. Biophys.*, **78**, 468 (1958).) the α- and β-asymmetric centers of optically active *threo*-3-methylaspartic acid are assigned the same absolute configuration, while those of optically active *erythro*-3-methylaspartic acid are opposite in absolute configuration to each other. Therefore the configurations of *erythro*- and *threo*-3-methylmalic acid can easily be correlated.

(+)-*threo*-2-methyltartaric acid. The catalyst modified with the erythro form has only a very low asymmetric activity, while that modified with the threo form has a very high one. This difference in asymmetric activity can best be explained in a similar way to the difference between modifications with the optically active 3-methylmalic acids described above. As previously reported by the author,[14] the two hydroxyl groups of *threo*-2-methyltartaric acid are situated in the same position relative to each other as those of tartaric acid; while in *erythro*-2-methyltartaric acid the situation of the two hydroxyl groups corresponds to that of the two hydroxyl groups of meso tartaric acid. It thus appears that the α- and β-asymmetric centers of the threo form have the same absolute configuration and those of the erythro form have the opposite configuration to each other.

However, the difference between the asymmetric effects of these two reagents was greater than that between the effects of isomeric 3-methylmalic acids. This result is probably related to the fact that each of the two asymmetric carbon atoms of 2-methyltartaric acid, unlike those of 3-methylmalic acid, has a hydroxyl group. As has been pointed out above, the asymmetric activity of the catalyst is much influenced by a hydroxyl group located on an asymmetric carbon atom, this influence being greater than that of the corresponding methyl group, and also two hydroxyl groups which are identical in configuration cause an increase in the asymmetric activity, while two with the opposite configuration to each other decrease the activity. Therefore, the low asymmetric effect of (−)-*erythro*-2-methyltartaric acid and the high effect of (+)-*threo*-2-methyltartaric acid must be related to the roles of their hydroxyl groups and to their configurations.[24]

The Effect of the *C*, *C*′-Dialkyl Groups of Tartaric Acids. To study the effects of two alkyl groups attached to the asymmetric carbon atoms of tartaric acid upon the asymmetric activity, measurements were made of the asymmetric activities of catalysts modified with (+)-2, 3-dimethyltartaric acid[10,13] and (+)-1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid.[11,25] The results are shown in Fig. 11.

On modification with (+)-2, 3-dimethyltartaric acid the asymmetric activity shows a tendency similar to that obtained on modification with D-tartaric acid, except for the direction of optical rotation.

(+)-2, 3-Dimethyltartaric acid has the same chemical or stereochemical structure as optically active tartaric acid except that both hydrogens on the asymmetric carbon atoms are replaced by methyl groups. The two methyl groups, therefore, are situated in the same threo position relative to each other as the two hydroxyl groups.[14] The two asymmetric centers of this compound are assigned the same absolute configuration and contribute equally to the optical direction of the asymmetric activity of the catalyst. The resemblance in the asymmetric effects of (+)-2, 3-dimethyltartaric acid and D-tartaric acid is due entirely to the above similarity in configuration. In this respect, these reagents are quite different from (−)-*erythro*-2-methyltartaric acid and (+)-*erythro*-3-methylmalic acid.

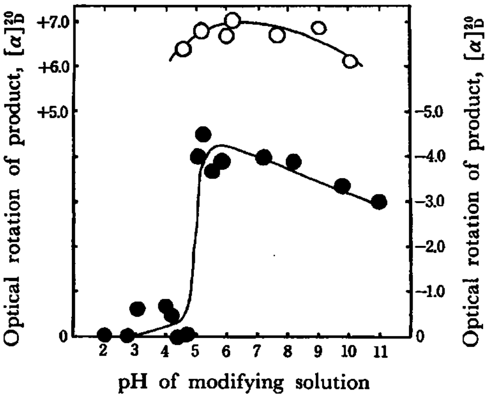

Fig. 11. Modifications with (+)-2, 3-dimethyltartaric acid and (+)-1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid. (Modified at 0°C)

○ (+)-2, 3-Dimethyltartaric acid

● (+)-1, 2-Dihydroxycyclohexane-1, 2-dicarboxylic acid

The left scale represents (+)-2, 3-dimethyltartaric acid and the right scale represents (+)-1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid.

On the other hand, it seems probable that, like meso tartaric acid, 2, 3-dimethyltartaric acid which is assigned the meso form, has no asymmetric effect upon a Raney nickel catalyst.

As shown in Fig. 7, (+)-2, 3-dimethyltartaric acid is less effective for asymmetric activity, particularly at high modifying temperatures, than (+)-*threo*-2-methyltartaric acid. This difference is considered to be due to the presence or absence of an α-*C*-methyl group in the modifying reagents. As can be seen from the difference in the asymmetric effects of L-malic acid and L-citramalic acid, the α-*C*-methyl group is unfavorable for asymmetric activity. In (+)-2, 3-dimethyltartaric acid the group is present, while in (+)-*threo*-2-methyltartaric acid it is not because this compound is preferentially adsorbed with its 3-hydroxyl group and 3-carboxyl group (C_4-carboxyl group) upon the nickel metal[26] and hence its C_2-asymmetric carbon atom, on which the methyl group is located, acts as a

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24) Further discussion of this will be given in the subsequent section.

25) S. Tatsumi, M. Imaida and Y. Izumi, This Bulletin, **39**, 2543 (1966).

26) The form of adsorption of this compound on the nickel metal will be discussed in the next section.

β-carbon atom in the asymmetric modification. However, (+)-2, 3-dimethyltartaric acid is more effective for asymmetric activity than (−)-*erythro*-2-methyltartaric acid. This indicates that the asymmetric activities of catalysts are influenced far more by the configuration of the modifying reagents and orientation of methyl groups and hydroxyl groups in space, than by the hindrance due to the α-*C*-methyl group.

Thus, the asymmetric effects of tartaric acid and its *C*-methyl and *C*, *C*′-dimethyl derivatives assigned the threo form are greater than those of malic acid and its *C*-methyl derivatives. To obtain an especially high asymmetric activity, two hydroxyl groups situated in the threo position relative to each other are indispensable for a modifying reagent.

When a Raney nickel catalyst was modified with (+)-1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid, its asymmetric activity was greatly influenced by the pH of the modifying solution, as shown in Fig. 11, the influence being quite different from those of catalysts obtained on modifications with optically active tartaric acid, malic acid and their *C*-methyl and *C*, *C*′-dimethyl derivatives. Maximal asymmetric activities were observed at pH 5—7; this pH range approximately corresponds to the pH-jumping region of the neutralization curve of this acid.[11] However there was a very great diminution in activity at pH values below pH 5. Under acidic conditions both carboxyl groups of the acid are adsorbed upon the nickel metal and hence the alicyclic ring forms a bulky steric hindrance over the surface of the metal. Therefore it seems that the hydrogenation substrate can hardly be affected by the stereoselectivity of asymmetric centers of the acid.

The Role of the β-Carboxyl Group and the Form of the Modifying Reagent Adsorbed on the Catalyst. To study the role of the β (or α′)-carboxyl group of the modifying reagent, the asymmetric activities of catalysts modified with D-tartaric acid, monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid were compared.[12]

Monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid are characterized by the lack of an acidic property of one of the two carboxyl groups of D-tartaric acid. In the former compound it is lost by esterification and in the latter the carboxyl group is replaced by a methyl group.

As shown in Fig. 12, on modifications with these two reagents, a maximal asymmetric activity is observed under acidic conditions and there is a decrease in activity under alkaline conditions. These curves of asymmetric activity are quite different in character from that obtained on modification with D-tartaric acid but similar to those obtained with several hydroxy monocarboxylic acids. These results evidently show that the considerable decrease of asymmetric activity observed under acidic conditions on modifications with hydroxy dicarboxylic acids depends on the presence of a functional β (or α′)-carboxyl group. It is likely that both carboxyl groups of hydroxy dicarboxylic acids are readily adsorbed on the surface of nickel metal in the absence of alkali. When the acidity of the modifying solution decreases, one carboxyl group is detached from the surface of the metal and the resulting group, carrying a high polarity, produces a massive hindrance, which effectively regulates the form of approach of the hydrogenation substrate to the catalyst and causes an increase in asymmetric activity.

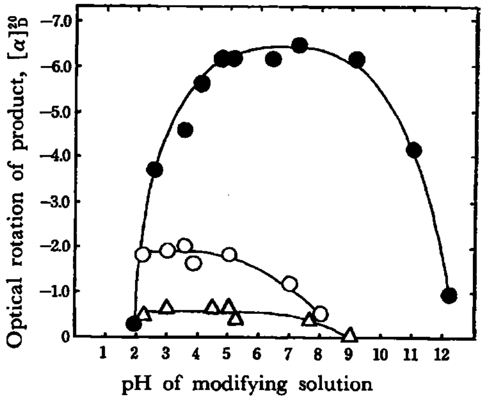

Fig. 12. Modifications with D-tartaric acid, monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid. (Modified at 0°C)
● D-Tartaric acid
○ Monomethyl D-tartrate
△ D-*threo*-2, 3-Dihydroxybutyric acid

On the contrary, since on modifications with monomethyl D-tartrate and D-*threo*-2, 3-dihydroxybutyric acid the ester and methyl groups are less affected by the modifying conditions,[27] the form in which they are adsorbed on the surface of the metal is similar under all acidic conditions. Consequently, under acidic conditions catalysts modified with these two reagents do not show such a great decrease in asymmetric activity as the catalyst modified with D-tartaric acid.

This also holds good for modifications with other hydroxy monocarboxylic acids.

In dihydroxy dicarboxylic acids such as optically active tartaric acid, 2, 3-dimethyltartaric acid and 1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid, the two asymmetric centers are similar in configuration or in the orientation of their groups in space, and hence whether the reagent is adsorbed preferentially by its α-hydroxyl and α-carboxyl groups upon the nickel metal or by its β (or α′)-hydroxyl and β (or α′)-carboxyl groups, the asymmetric

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27) According to Welch, ester and methyl groups are poorly adsorbed upon Raney nickel irrespective of the conditions of treatment. C. M. Welch, H. A. Smith and J. B. Cole, *J. Phys. Chem.*, **65**, 705 (1961).

activity of the resulting catalyst is the same in capacity and in direction of optical rotation.

On the other hand, since the two asymmetric centers of optically active 2-methyltartaric acid are dissimilar, whether the adsorption with the 2-hydroxyl group and the 1-carboxyl group predominates or that with the 3-hydroxyl group and the 4-carboxyl group does, has a great influence on the asymmetric activity of the catalyst.

As can be seen from Figs. 1 and 10, (+)-*threo*-2-methyltartaric acid is more effective for asymmetric activity than D-tartaric acid. This result seems to indicate that this compound is not preferentially adsorbed by its 2-hydroxyl group and 1-carboxyl group on the catalyst, but by its 3-hydroxyl group and 4-carboxyl group. If the adsorption by the 2-hydroxyl group and the 1-carboxyl group were predominant, the 2-methyl group would serve as the α-methyl group in the asymmetric modification and would cause a decrease in the asymmetric effect. Consequently, the asymmetric activity of catalyst modified with this compound would be smaller than that of catalyst modified with D-tartaric acid. However, no such difference in asymmetric activity is observed. Moreover, this compound is more effective for asymmetric activity than (+)-2, 3-dimethyltartaric acid, as shown in Figs. 10 and 11. The difference in the asymmetric effects of these reagents is obviously caused by the α-methyl group of (+)-2, 3-dimethyltartaric acid and then it is nearly equal to the difference in the asymmetric effects of L-malic acid and L-citramalic acid. These results evidently support the above conclusion.

Considering the great influences of hydroxyl groups and their configurations upon the asymmetric effect, it seems reasonable that (−)-*erythro*-2-methyltartaric acid has only a very weak asymmetric effect on a Raney nickel catalyst.

Conclusion

The presence or absence of asymmetric activity in the modified Raney nickel catalyst depends on the optical purity of the reagent used for the modification. A racemate and a meso compound have no asymmetric effects upon Raney nickel. Moreover, there is a linear relationship between the capacity of asymmetric activity of the catalyst and the optical purity of the modifying reagent. When a modifying reagent loses its ability to be adsorbed on Raney nickel, the resulting catalyst has little or no asymmetric activity. To obtain an asymmetric catalyst an α-carbon atom of the modifying reagent must have at least two kinds of functional groups such as a hydroxyl group and a carboxyl group which can be adsorbed strongly or chelated to Raney nickel.

On modification with a hydroxy carboxylic acid containing one asymmetric center or containing two asymmetric centers of identical absolute configuration, the catalyst modified with a D-hydroxy acid has an asymmetric activity to produce predominantly the hydrogenation product of the D-configuration; while that modified with an L-hydroxy acid gives a product of the L-configuration. When enantiomeric compounds are used as the modifying reagents, the asymmetric activities of the resulting catalysts are the same except for the direction of optical rotation. On modification with a racemic compound, therefore, two kinds of catalyst are produced in the same ratio; one has the asymmetric activity to hydrogenate the substrate predominantly to the product of the L-configuration and the other has the opposite asymmetric activity. On modification with a hydroxy monocarboxylic acid containing two asymmetric centers of opposite absolute configuration in its α- and β-carbon atoms, the rotatory direction of the asymmetric activity is decided by the configuration of the α-asymmetric center.

The asymmetric activity of catalyst is much influenced by the pH of the modifying solution. On modification with a hydroxy dicarboxylic acid, the maximal asymmetric activity is obtained at pH 5—9 and there is a considerable diminution in activity at both higher and lower pH values; while with a hydroxy monocarboxylic acid a similar decrease is obtained only under alkaline conditions. In both cases, the weak asymmetric activity observed at high pH values is caused by desorption of the reagent from the catalyst. On the other hand, the weak asymmetric effect of a hydroxy dicarboxylic acid observed at low pH values is not related to desorption of the reagent, but to the presence of the β-carboxyl group.

The asymmetric activity of catalyst, in general, increases with elevation of the temperature of the modifying solution.

A maximal asymmetric activity is attained in 10 min when a Raney nickel catalyst is immersed in a modifying solution at 0°C. Immersion for more than 10 min results in no further increase in the activity. It is likely that the adsorption of the reagent on the catalyst reaches an equilibrium within 10 min. Moreover, the asymmetric activity of catalyst is independent of the concentration of reagent in the range of 0.4—10%. It seems that the adsorption of a reagent on Raney nickel readily reaches saturation at a low concentration.

The asymmetric activity in the modified catalyst is very stable. The original activity persisted for at least six runs of the hydrogenation reaction.

An α-*C*-substituted alkyl group in the modifying reagent, such as the methyl group of citramalic acid, reduces the asymmetric activity of the catalyst.

To obtain an effective asymmetric catalyst, an asymmetric α-carbon atom of α-hydroxy carboxylic acid used for the modification should not possess a bulky substituted group in addition to the carboxyl group, hydroxyl group and β-carbon chain.

On modifications with tartaric acid and its derivatives, like their α-hydroxyl groups, the β (or α')-hydroxyl groups play an important role in the formation of an asymmetric catalyst. The methyl group of 3-methylmalic acid also has a great influence on the asymmetric activity of the catalyst though less than the β (or α')-hydroxyl groups of tartaric acid and its derivatives. On modifications with 2-methyltartaric acid and 3-methylmalic acid, the asymmetric activities of the catalysts are greatly influenced by the configurations of the α- and β-asymmetric centers of the reagents. To obtain an effective asymmetric catalyst, the same configuration should be assigned to the α- and β- asymmetric centers. Moreover, the asymmetric activities of catalysts are far more influenced by the configurations of the modifying reagents than by hindrances due to the substituted groups themselves. 2,3-Dimethyltartaric acid has a high asymmetric effect upon the catalyst similar to that of tartaric acid. However, 1,2-dihydroxycyclohexane-1,2-dicarboxylic acid, which is a sort of 2,3-dialkyl tartaric acid, has a quite different asymmetric effect from tartaric acid, malic acid and their *C*-alkyl derivatives. This difference is due to the alicyclic ring of 1,2-dihydroxycyclohexane-1,2-dicarboxylic acid.

The asymmetric effects of tartaric acid and its *C*-methyl and *C*, *C'*-dimethyl derivatives assigned the threo form are greater than those of malic acid and its *C*-methyl derivatives. To obtain an especially high asymmetric activity, two hydroxyl groups situated in the threo position relative to each other are indispensable for a modifying reagent.

On modification with a hydroxy dicarboxylic acid, both the β (or α')-carboxyl group of the reagent and the α-carboxyl group play important roles in the formation of an asymmetric catalyst. It is likely that both carboxyl groups are readily adsorbed on the surface of the catalyst in the absence of alkali. When the acidity of the modifying solution decreases, the β (or α')-carboxyl group is detached from the catalyst and the resulting group, carrying a high polarity, effectively regulates the form of approach of the hydrogenation substrate to the catalyst. On the contrary, on modification with a hydroxy monocarboxylic acid the form of adsorption of the reagent on the surface of the catalyst is similar under all acidic conditions used.

On modification with 2-methyltartaric acid, the 2-methyl group and 1-carboxyl group of this compound serve as a β-methyl group and a β-carboxyl group, respectively, in the formation of an asymmetric catalyst. It is likely that adsorption with the 3-hydroxyl group and 4-carboxyl group is predominant in the asymmetric modification.

The author wishes to express his sincere thanks to Professor Shiro Akabori and Professor Yoshiharu Izumi for their valuable advice and encouragement throughout this work.

This work was made possible by support from the Ajinomoto Co., Inc., Tokyo and the Kawaken Fine Chemicals Co., Ltd., Tokyo.