BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 39 361—364 (1966)

Asymmetric Hydrogenation with Modified Raney Nickel. VI

By Yoshiharu IZUMI, Susumu TATSUMI, Masami IMAIDA
Yoshio FUKUDA and Shiro AKABORI

Division of Organic Chemistry, Institute for Protein Research, Osaka University, Kita-ku, Osaka

(Received June 26, 1965)

The asymmetric hydrogenation catalyst has been prepared by the modification of Raney nickel with solutions of (−)-2-methyltartaric acid (A), (+)-2-methyltartaric acid (B) and (+)-2, 3-dimethyltartaric acid, and its asymmetric hydrogenation activity has been measured by the hydrogenation of methyl acetoacetate to optically active methyl 3-hydroxybutyrate. The asymmetric activity of the catalyst is much influenced by the pH and the temperature of the modifying solution. Generally, (+)-2-methyltartaric acid (B) and (+)-2, 3-dimethyltartaric acid have a high asymmetric activity in reaction to Raney nickel. The highest asymmetric activity has been obtained by modification with (+)-2-methyltartaric acid (B) and with it the specific rotation of the hydrogenation product has been found to be $[\alpha]_D^{20}$ +11.72° (without a solvent) under the optimum conditions. This value means that the product is 78% composed of the dextro- and 22% of the levorotatory form. On the other hand, the asymmetric activity of the catalyst modified with (−)-2-methyltartaric acid (A) is very low and quite different from that of the catalyst modified with (+)-2-methyltartaric acid (B). It has been supposed that this difference depends on the stereoisomerism of the threo-erythro form of the 2-methyltartaric acid molecule.

The previous papers of this series[1-5] reported the asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate using Raney nickel catalysts modified with optically active 2-amino and 2-hydroxy carboxylic acids. It was found that the asymmetric activity of the catalysts is much influenced by the pH and temperature of the modifying solution. An especially high asymmetic activity was obtained when the catalyst was modified at 100°C with a D-tartaric acid solution, the pH of which had been adjusted to 5.1—5.2.[2]

In the present work, optically active 2-methyltartaric and 2, 3-dimethyltartaric acid will be tested as modifying reagents in an attempt to study the role of substituents on asymmetric carbon atoms of tartaric acid in the modification of the Raney nickel catalyst.

Materials

Modifying Reagents.*—2-Methyltartaric acid has two racemic forms, the melting points of which are 146°C and 161°C. Both racemic substances were synthesized from ethyl acetoacetate and resolved with brucine by the fractional crystallization of the diastereomers in water. The optical rotation values of the four isomers were as follows;

(A) From the racemic form with the lower melting point (2-methyltartaric acid A):

(+)-isomer $[\alpha]^{20}_{\text{D}}$ +8.90° (*c* 3.7, water) (I)

(−)-isomer $[\alpha]^{20}_{\text{D}}$ −8.94° (*c* 3.7, water) (II)

(B) From the racemic form with the higher melting point (2-methyltartaric acid B);

(+)-isomer $[\alpha]^{20}_{\text{D}}$ +5.88° (*c* 3.2, water) (III)

(−)-isomer $[\alpha]^{20}_{\text{D}}$ −5.60° (*c* 3.2, water) (IV)

2, 3-Dimethyltartaric acid has two optically inactive modifications; the one is the racemic (m. p. 187°C), and the other is the meso form (m. p. 180°C). Both substances were prepared from diacetyl, while the optical resolution of the racemic form was performed with brucine. The optical rotation values of the two optical isomers of this hydroxy carboxylic acid were as follows:

(+)-isomer $[\alpha]^{20}_{\text{D}}$ +13.4° (*c* 4.0, water) (V)

(−)-isomer $[\alpha]^{20}_{\text{D}}$ −13.4° (*c* 4.0, water) (VI)

In the present asymmetric hydrogenation experiments, optically active (−)-2-methyltartaric acid (A) (II), derived from the racemate with the lower melting point; (+)-2-methyltartaric acid (B) (III), derived from the racemate with the higher melting point, and (+)-2, 3-dimethyltartaric acid (V) were used as the modifying reagents.

Results and Discussion

The Effect of the pH of the Modifying Solution.—Measurements were made of the asymmetric activities of catalysts modified at 0°C with aqueous solutions of substances II, III and V, the pH of which had been adjusted to specified values with a 1 N (f=0.893) sodium hydroxide solution according to the titration curve shown in Fig. 1. The results are shown in Fig. 2.

The catalysts modified at 0°C with these hydroxy carboxylic acids hydrogenated methyl acetoacetate predominantly to dextrorotatory methyl 3-hydroxybutyrate. Higher asymmetric activities were observed on modification with III and V, when the catalysts were less influenced by the pH of the modifying solutions. In the case of modification

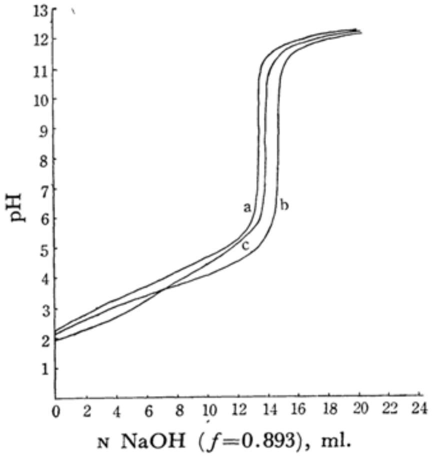

Fig. 1. Titration curve of 1% hydroxy carboxylic acid solution with N NaOH.

a (−)-2-Methyltartaric acid (A)

b (+)-2-Methyltartaric acid (B)

c (+)-2, 3-Dimethyltartaric acid

---

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).

* The preparation of optically active 2-methyltartaric acids and 2, 3-dimethyltartaric acid will be published by the present authors in this Bulletin in the near future.

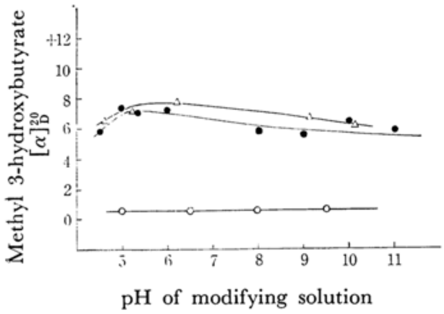

Fig. 2. Effect of pH of modifying solution at 0°C.
—○— (−)-2-Methyltartaric acid (A)
—●— (+)-2-Methyltartaric acid (B)
—△— (+)-2, 3-Dimethyltartaric acid

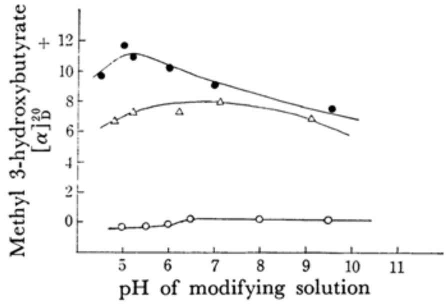

Fig. 3. Effect of pH of modifying solution at 100°C.
—○— (−)-2-Methyltartaric acid (A)
—●— (+)-2-Methyltartaric acid (B)
—△— (+)-2, 3-Dimethyltartaric acid

with II, however, the asymmetric activity was very low and was not at all influenced by the pH of the modifying solution.

The effect of the pH value of the modifying solution at 100°C on the asymmetric activities of the modified catalysts is shown in Fig. 3.

As is shown in Fig. 3, upon modification with III the asymmetric activity was greater and was much influenced by the pH of the modifying solution. The greatest asymmetric activity was obtained at pH 5.0 when the specific rotation value of the hydrogenation product was $[\alpha]^{20}_{D}$ +11.72° (without a solvent). There was a considerable decrease in activity at both lower and higher pH values. Under acidic conditions below pH 4.5, the catalytic activity of the modified catalyst was too low to permit any hydrogenation experiments. On modification with V, although a high asymmetric activity was obtained, it was lower than with III; and the asymmetric activity curve showed a tendency similar to that shown on modification at 0°C. In the case of modification with II, however, the asymmetric activity was very low and the levorotatory product was obtained at pH values below the pH jump of the titration curve of this acid shown in Fig. 1.

The Effect of the Modifying Temperature.—The effect of the temperature of the modifying solution was studied at pH 5.0—5.2; the results are shown in Fig. 4.

As is shown in Fig. 4, the asymmetric activity of the catalyst modified with III was greater than that of the catalyst modified with V, and it clearly increased with elevation of the modifying temperature. On modification with V, however, the activity was hardly influenced at all by the temperature. In the case of modification with II, the asymmetric activity was very low and the hydrogenation product was dextrorotatory below 70°C, although it showed the opposite optical rotation above this temperature.

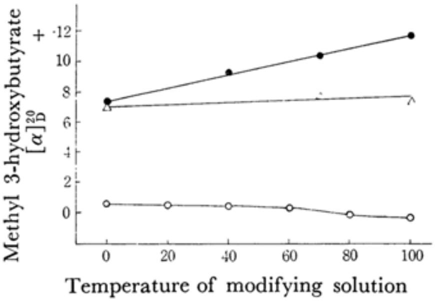

Fig. 4. Effect of temperature of modifying solution.
—○— (−)-2-Methyltartaric acid (A) (pH 5.0)
—●— (+)-2-Methyltartaric acid (B) (pH 5.0)
—△— (+)-2, 3-Dimethyltartaric acid (pH 5.1—5.2)

As is shown in Figs. 2, 3 and 4, on modification with (+)-2-methyltartaric acid (B) (III), the catalyst had a higher asymmetric activity than tartaric acid[2] and gave the dextrorotatory product. Under optimum conditions the specific rotation value of the product was $[\alpha]^{20}_{D}$ +11.72°; this means that the product was 78% composed of the dextro- and 22% of the levorotatory form. On the other hand, (−)-2-methyltartaric acid (A) (II) has only a small asymmetric effect upon Raney nickel.

2-Methyltartaric acid has a structure in which a methyl group is introduced into one of the asymmetric carbons of tartaric acid in place of a hydrogen atom. Thus it is characterized by the existence of two types, the threo and erythro form, which are 2-methyltartaric acid (A) and (B). Although it is unknown at the present time which steric isomer is threo and which is erythro, it is conceivable that the difference in the asymmetric effects of (−)-2-methyltartaric acid (A) and (+)-2-methyltartaric acid (B) depends on their threo-erythro isomerism. On modification with (+)-2, 3-dimethyltartaric acid, however, the asymmetric activity shows a tendency similar to that shown on modification with tartaric acid, except for the difference in the asymmetric direction.

The relationship between the asymmetric activity of the catalyst and the stereoisomerism of the modifying reagent will be discussed after the steric configurations of (−)-2-methyltartaric acid (A), (+)-2-methyltartaric acid (B) and (+)-2, 3-dimethyltartaric acid have been confirmed.

Experimental

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

Summary

1) The asymmetric activities of Raney nickel catalysts modified with (−)-2-methyltartaric acid (A), (+)-2-methyltartaric acid (B) and (+)-2, 3-dimethyltartaric acid have been measured by the hydrogenation of methyl acetoacetate.

2) The highest asymmetric acitivity has been obtained by modification with (+)-2-methyltartaric acid; with it the specific rotation of the hydrogenation product was $[\alpha]_D^{20}$ +11.72° under optimum conditions.

3) The asymmetric activity of the catalyst modified with (−)-2-methyltartaric acid (A) was very low and quite different from that of the catalyst modified with (+)-2-methyltartaric acid (B). This difference depends on the stereoisomerism of the threo-erythro form. On modification with (+)-2, 3-dimethyltartaric acid, the asymmetric activity showed a tendency similar to that shown on modification with D-tartaric acid, except for the difference in the asymmetric direction.

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