Asymmetric Hydrogenation with Modified Raney Nickel. III. Studies of the Modified Hydrogenation Catalyst. IV

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The asymmetric hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate has been achieved by the use of a R-Ni* catalyst modified with optically active 2-amino or 2-hydroxycarboxylic acids, and it has been found that the asymmetric activity of the catalyst is much influenced by the pH and by the temperature of the modifying solution.[1,2]

In the present investigation, optically-active 2-hydroxycarboxylic acids prepared from L-valine, L-leucine, L-isoleucine and L-phenylalanine were tested as modifying reagents and compared with the parent amino acids.

The modifying effects of diacetyl-D-tartaric acid and monobenzoyl-D-tartaric acid were also tested to study the mode of asymmetric modification.

Materials

Modifying Reagents. — The L-2-hydroxycarboxylic acids used in this report were prepared from L-2-aminocarboxylic acids by the following common reaction:

$$R\text{-}\underset{NH_2}{\overset{*}{C}}H\text{-}COOH \xrightarrow{HNO_2} R\text{-}\underset{OH}{\overset{*}{C}}H\text{-}COOH$$

The absolute configurations of amino acids are believed to be maintained during this reaction, and the 2-hydroxycarboxylic acids obtained must have the same configurations as the parent amino acids.

Thus, L-2-hydroxyisovaleric, L-2-hydroxyisocaproic, L-2-hydroxy-3-methylvaleric and L-2-hydroxy-3-phenylpropionic acids were prepared as described by Winitz.[3] *O,O'*-Diacetyl-D-tartaric acid and *O*-monobenzoyl-D-tartaric acid were prepared according to the directions

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* Abbreviation: R-Ni, Raney Nickel.

[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] M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S. M. Birnbaum, C. G. Baker and J. P. Greenstein, *J. Am. Chem. Soc.*, 78, 2423 (1956).

TABLE I. MELTING POINT AND OPTICAL ROTATION OF L-2-HYDROXYCARBOXYLIC ACID AND *O*-ACYLATED D-TARTARIC ACID

			Lit. value	
Hydroxycarboxylic acid	M. p., °C	$[\alpha]_D^{20}$	M. p., °C	$[\alpha]_D^{20}$
L-2-Hydroxyisovaleric	71	−1.0°[a]	—	−1.0°[8]
L-2-Hydroxyisocaproic	81∼83	−12.6[a]	80∼82[6]	−13.3[8]
L-2-Hydroxy-3-methylvaleric	49∼50	+4.0[a]	47∼49[7]	+3.9[8]
L-2-Hydroxy-3-phenylpropionic	126	−20.4[a]	124∼126[8]	−20.0[8]
O-Acylated-D-tartaric acid				
O, *O*′-Diacetyl-D-tartaric	117	−23.6[b]	118[4]	−24.57[4]
O-Monobenzoyl-D-tartaric	205∼206	−4.6[c]	202∼203[5]	−4.4[5]

a) One to four per cent aq. solution
b) Ten per cent acetone solution
c) Six per cent ethanol solution

of Austin[4] and Langenbeck[5] respectively.

The melting points and the optical rotations $[\alpha]_D^{20}$ of the L-2-hydroxycarboxylic acids, *O*, *O*′-diacetyl-D-tartaric acid and *O*-monobenzoyl-D-tartaric acid, used in the present work are shown in Table I.

Results and Discussion

The Effect of the pH of the Modifying Solution.—Measurements were made of the asymmetric activities of the catalyst modified at 0°C with solutions of L-2-hydroxyisovaleric acid, L-2-hydroxyisocaproic acid, L-2-hydroxy-3-methylvaleric acid and L-2-hydroxy-3-phenylpropionic acid, the pH of which had been adjusted to specified values; the results are shown in Table II.

TABLE II. EFFECT OF pH OF MODIFYING SOLUTION (AT 0°C)

Modifying reagent	pH of modifying solution	$[\alpha]_D^{20}$ of methyl 3-hydroxy-butyrate
L-2-Hydroxyisovaleric acid	2.9	+1.05°
	5.0	+1.09
	10.5	−0.08
L-2-Hydroxyisocaproic acid	2.9	+1.26
	4.0	+0.71
	5.0	+0.82
	6.4	+0.76
	10.5	+0.07
L-2-Hydroxy-3-methylvaleric acid	2.9	+1.48
	5.0	+1.14
	7.4	−0.06
	10.5	−0.08
L-2-Hydroxy-3-phenylpropionic acid	2.9	+0.70
	4.0	+0.62
	5.0	+0.75
	5.8	+0.13
	7.0	+0.19
	10.5	0

The neutralization curve of L-2-hydroxy-3-phenylpropionic acid, and the asymmetric activities of the catalysts modified at 0°C with solutions of L-2-hydroxy-3-phenylpropionic acid, are shown in Fig. 1.

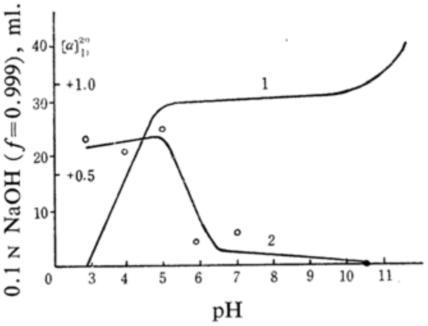

Fig. 1. Effect of pH of L-2-hydroxy-3-phenylpropionic acid solution.
Curve 1, titration curve
Curve 2, asymmetric activity of modified catalyst

With other L-2-hydroxycarboxylic acids, figures similar to those in Fig. 1 are obtained.

Greater asymmetric activities were observed when R-Ni catalysts were treated at pH values below the pH jump of the titration curves of the hydroxycarboxylic acids, as the figure and Table II show. Table II shows that the catalysts modified with L-2-hydroxycarboxylic acids at pH 2.9∼10.5, at 0°C, produced dextrorotatory methyl 3-hydroxybutyrate, except for those modified with L-2-hydroxyisovaleric acid at pH 10.5 and with L-2-hydroxy-3-methylvaleric acid above pH 7.4.

The results described above show that L-2-hydroxycarboxylic acids have an asymmetric

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[4] P. C. Austin and J. R. Park, *J. Chem. Soc.*, **127**, 1933 (1925).

[5] W. Langenbeck and O. Herbst, *Chem. Ber.*, **86**, 1524 (1953).

[6] C. G. Baker and A. Meister, *J. Am. Chem. Soc.*, **73**, 1336 (1951).

[7] O. Lutz and B. Jirgensons, *Ber.*, **65**, 784 (1932).

[8] H. A. Dakin and H. W. Dudley, *J. Biol. Chem.*, **18**, 29 (1914).

effect upon the R-Ni catalyst the reverse of that of the corresponding 2-aminocarboxylic acids. The same relationship has been observed between L-aspartic acid and L-malic acid, as was reported in a previous paper[2].

The difference between 2-amino and 2-hydroxycarboxylic acid can be explained by the difference in the coordination form at the active metallic center of these two series of compounds. Probably the former is tetrahedral and the latter planar, so that stereochemically-different active centers are produced.

The Effect of the Modifying Temperature.—The effect of the temperature of the modifying solution was studied at pH values of 2.9 and 5.0, at 0°C and 70°C. The results are shown in Table III. The catalytic activity of the R-Ni catalyst modified at 100°C was too low to permit any hydrogenation experiments.

Under the conditions shown in Table III, dextrorotatory methyl 3-hydroxybutyrate was formed predominantly on the hydrogenation of methyl acetoacetate.

The catalysts modified at pH 2.9 always showed an increase in their asymmetric activities with an elevation of the modifying temperature. On the other hand, the asymmetric activities of the catalysts modified at pH 5.0 were not always increased by an elevation of the modifying temperature.

TABLE III. EFFECT OF TEMPERATURE OF MODIFYING SOLUTION

Modifying reagent	Modifying conditions pH	Temp., °C	$[\alpha]^{20}_{D}$ of methyl 3-hydroxy-butyrate
L-2-Hydroxyisovaleric acid	2.9	0	+1.05°
	2.9	40	+1.45
	2.9	70	+1.48
	5.0	0	+1.09
	5.0	40	+1.17
	5.0	70	+1.31
L-2-Hydroxyisocaproic acid	2.9	0	+1.26
	2.9	40	+1.27
	2.9	70	+1.54
	5.0	0	+0.82
	5.0	40	+1.12
	5.0	70	+1.01
L-2-Hydroxy-3-methyl-valeric acid	2.9	0	+1.48
	2.9	40	+2.18
	2.9	70	+2.60
	5.0	0	+1.14
	5.0	40	+1.62
	5.0	70	+1.71
L-2-Hydroxy-3-phenyl-propionic acid	2.9	0	+0.70
	2.9	40	+1.03
	2.9	70	+1.08
	5.0	0	+0.75
	5.0	40	+0.86
	5.0	70	+0.47

Modification with *O*-Acylated D-Tatraric Acid.—Catalysts modified with *O*, *O'*-diacetyl-D-tartaric acid and *O*-monobenzoyl-D-tartaric acid were tested for their asymmetric activities in order to study the role of the hydroxy group in the modification of the catalyst.

The effect of the modifying temperature was studied at pH 5.1∼5.2, since the catalyst modified at this pH with tartaric acid showed the greatest asymmetric activity, as was reported in a previous paper.[2] The results are shown in Table IV.

TABLE IV. MODIFICATION WITH *O*-ACYLATED D-TARTARIC ACID AND D-TARTARIC ACID SOLUTION

Modifying reagent	Modifying condition pH	Temp. °C	$[\alpha]^{20}_{D}$ of methyl 3-hydroxy-butyrate
Diacetyl-D-tartaric acid	5.1	0	−0.66°
	5.1	50	−0.41
	5.1	100	−0.18
Monobenzoyl-D-tartaric acid	5.2	0	−2.15
	5.1	50	−2.64
	5.2	100	−2.29
D-Tartaric acid[2]	5.1	0	−5.30
	5.2	40	−5.25
	5.2	70	−7.23
	5.2	100	−8.37

The above results show that *O*, *O'*-diacetyl-D-tartaric acid and *O*-monobenzoyl-D-tartaric acid have smaller asymmetric effects upon the R-Ni catalyst than D-tartaric acid.

It is clearly conceivable that the hydroxy group has a certain important role in the asymmetric modification of the R-Ni catalyst, but no reasonable explanation of the effect of acylation on the mode of asymmetric catalytic activity seems possible at present.

Experimental

The Preparation of the R-Ni Catalyst. — The R-Ni catalyst used in the present work was prepared as described in a previous paper.[1]

The Modification of the Catalyst.—The modification of the catalyst was carried out as described in a previous paper.[1] One hundred milliliters of 1% aqueous solutions of each hydroxycarboxylic acid, the pH of which had been adjusted to a specified value with a N sodium hydroxide solution, were added to the newly-prepared R-Ni catalyst; these mixtures were then allowed to stand, with occasional shakings, at a constant temperature for 1.5 hr. After the modifying solution had been removed by decantation, the catalyst was washed with water and then with methanol, and then it was separated by centrifugation.

The Hydrogenation of Methyl Acetoacetate.—Newly-distilled methyl acetoacetate (17.0 g.) was hydrogenated in the presence of the modified R-Ni catalyst prepared from 1.5 g. of alloy. The reaction was run at 60°C under an initial hydrogen pressure of 80～90 kg./cm^2 in a shaking autoclave. The catalyst was filtered off, and the filtrate was distilled under reduced pressure. The main fraction was collected at 61～62°C/12 mmHg.

The Asymmetric Activity of the Catalyst.—The asymmetric activity of the catalyst was measured as described in a previous paper.[1)]

Summary

1) The asymmetric activities of R-Ni catalysts modified with L-2-hydroxyisovaleric acid, L-2-hydroxyisocaproic acid, L-2-hydroxy-3-methylvaleric acid and L-2-hydroxy-3-phenylpropionic acid have been compared with those of catalysts modified with the corresponding L-amino acids, which had the same stereochemical configurations.

2) On modification with L-2-hydroxycarboxylic acids, the greatest asymmetric activities are obtained when the catalysts are treated at pH values below the pH jump of the titration curves of the acids.

3) Catalysts modified with L-2-hydroxycarboxylic acids have asymmetric activities the reverse of those modified with L-amino acids with the same configurations.

4) The modifying effects of *O,O'*-diacetyl-D-tartaric acid and *O*-monobenzoyl-D-tartaric acid upon the R-Ni catalyst are entirely different from that of D-tartaric acid.

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