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

Yoshiharu IZUMI and Kazuo OHKUBO

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

(Received September 7, 1970)

The asymmetric activities of the catalysts modified with L-α-amino and L-α-hydroxy acids, which have two asymmetric centers on α, β and α, γ-carbons were studied, and the participation of the β- and γ-configurations to the asymmmetric activity of the catalyst was made clear. It was found that the S:β-configuration and the S:γ-configuration increase the asymmetric activity of the + and − directions respectively.

The asymmetric hydrogenation with a modified Raney nickel catalyst has been widely studied by our research group on the basis of the relationship between the stereochemical structures of the modifying reagents and the asymmetric activities of the modified catalyst.[1] The studies have mainly been done using α-amino or α-hydroxy acids which have one α-asymmetric carbon; it was found that the catalysts modified with L-α-amino and L-α-hydroxy acids predominantly give (−) and (+)-3-hydroxybutyrate respectively in the asymmetric hydrogenation of methyl acetoacetate.[2,3]

In order to elucidate the participation of the β- or the γ-asymmetric center of the modifying reagents to the asymmetric activities of the catalysts and to make clear the relationship between the diastereoisomeric structures of the modifying reagents and the asymmetric activities of the catalysts, the asymmetric activities of the catalysts modified with α-amino or α-hydroxy acids, which have two asymmetric centers, have been studied in the present investigation.

Moreover, the effect of the configuration of the β-methoxyl group was also investigated using the diastereomers of *O*-methylthreonine and compared with that of the β-ethyl group of the diastereoisomers of isoleucine.

Experimental

Materials. Modifying Reagents: The optical rotations of the modifying reagents used in this study are listed in Table 1.

Preparation, Modification and Measurement of the Asymmetric Activities of the Catalysts. The preparation of the R-Ni catalyst, the hydrogenation of methyl acetoacetate, and the measurement of the asymmetric activities of the catalysts were carried out by the procedures described in the previous paper.

The catalysts were modified with 1% aqueous solutions of modifying reagents at isoelectric points for the amino acids, and at pH 2.9 for the hydroxy acids, by the procedure described in the previous paper.

Results and Discussion

Asymmetric Activity of the Catalyst Modified with Diasymmetric Amino and Hydroxy Acid. The asymmetric activities of the catalysts modified with diastereomers of L-isoleucine, L-β-methylnorleucine and L-β-methylleucine are listed and compared with that of the one modified with valine in Table 2.

As can be seen in Table 2, the asymmetric activities

Table 1. The optical rotation of modifying reagent

Modifying reagent	Optical rotation $[\alpha]_D^{20}$	Value in literature
L-(2S:3S)-β-Methylleucine	+38.6 (*c* 1.2, 6NHCl)	
L-(2S:3R)-β-Methylleucine	+40.6 (*c* 1.0, 6NHCl)	
L-(2S:3S)-β-Methylnorleucine	+30.4 (*c* 1.5, 6NHCl)	
L-(2S:3R)-β-Methylnorleucine	+46.7 (*c* 1.5, 6NHCl)	
L-(2S:4S)-γ-Methylnorleucine	+21.0 (*c* 1.9, 6NHCl)	
L-(2S:4R)-γ-Methylnoreucine	+19.0 (*c* 1.0, 6NHCl)	
L-(2R:3S)-*O*-Methylthreonine	+29.4 (*c* 1.8, 6NHCl)	+30.5 (5NHCl)[a]
L-(2R:3R)-*O*-Methylthreonine	−12.7 (*c* 1.5, 6NHCl)	−13.5 (5NHCl)[a]
L-(2S:3S)-2-Hydroxy-3-methylvaleric acid	+3.9 (*c* 2.5, water)	+3.9 (water)[b]
L-(2S:3R)-2-Hydroxy-3-methylvaleric acid	+3.7 (*c* 2.2, water)	
L-(2S:3S)-2-Hydroxy-3-methylisocaproic acid	+6.44 (*c* 3.3, C_2H_5OH)	
L-(2S:3R)-2-Hydroxy-3-methylisocaproic acid	+11.33 (*c* 3.5, C_2H_5OH)	
L-(2S:3S)-2-Hydroxy-3-methylcaproic acid	+ 8.8 (*c* 5, C_2H_5OH)	
L-(2S:3R)-2-Hydroxy-3-methylcaproic acid	+14.5 (*c* 4.1, C_2H_5OH)	
L-(2S:4S)-2-Hydroxy-4-methylcaproic acid	−10.0 (*c* 5, C_2H_5OH)	
L-(2S:4R)-2-Hydroxy-4-methylcaproic acid	− 9.6 (*c* 5.3, C_2H_2OH)	

a) J. P. Greenstein and M. Winitz, *Chemistry of Amino Acid*, **3**, 2252. (1961).
b) M. Winitz, L. Bloch-Frankental, N. Izumiya, S. M. Birnbaum, C. G. Baker, and J. P. Greenstein, *J. Amer. Chem. Soc.*, **78**, 2433 (1956).

1) Part XV: T. Tanabe, T. Ninomiya, and Y. Izumi, This Bulletin, **43**, 2276 (1970).
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).

Table 2. Modifications with L-α,β-diasymmetric amino acids and L-valine

Modifying conditions: Reagent R–CH(NH_2)–CO_2H R	Configuration	Absolute configuration α-carbon	Absolute configuration β-carbon	pH	Temp. °C	$[\alpha]_D^{25}$ of Methyl 3-hydroxybutyrate
$-CH(C_2H_5)(CH_3)$	Erythro	S	S	5.94	0	−1.95
					100	−2.63
	Threo	S	R	5.94	0	−2.13
					100	−3.04
$-CH(CH_2CH_2CH_3)(CH_3)$	Erythro	S	S	6.12	0	−1.81
					100	−2.66
	Threo	S	R	6.10	0	−2.42
					100	−3.40
$-CH(CH(CH_3)_2)(CH_3)$	Erythro	S	S	5.77	0	−2.18
					100	−2.72
	Threo	S	R	5.97	0	−2.50
					100	−3.30
$-CH(CH_3)_2$	—	S	—	5.96	0	−1.72
					100	−2.30

Table 3. Modifications with L-α,β-diasymmetric hydroxy acids

Modifying conditions: Reagent R-CH(OH)–CO_2H R	Configuration	Absolute configuration α-carbon	Absolute configuration β-carbon	pH	Temp. °C	$[\alpha]_D^{25}$ of Methyl 3-hydroxybutyrate
$-CH(C_2H_5)(CH_3)$	Erythro	S	S	2.9	0	+0.68
					70	+1.07
	Threo	S	R	2.9	0	−0.22
					70	−0.22
$-CH(CH_2CH_2CH_3)(CH_3)$	Erythro	S	S	2.9	0	+0.67
					70	+0.75
	Threo	S	R	2.9	0	+0.22
					70	+0.25
$-CH(CH(CH_3)_2)(CH_3)$	Erythro	S	S	2.9	0	+0.17
					70	+0.24
	Threo	S	R	2.9	0	−0.20
					70	−0.23

of the catalysts modified with these amino acids at 100°C are higher than those of the catalysts modified at 0°C, and the catalysts modified with threo-isomers have higher asymmetric activities than with corresponding erythro-isomers, whether the modifying temperature is 0°C or 100°C.

Furthermore, the asymmetric activity of the catalyst modified with valine was slightly lower than those of the catalysts modified with erythro-isomers, which are less active than the threo-isomers.

In the cases of modifications with diasymmetric L-2-hydroxy-3-methylvaleric acid, L-2-hydroxy-3-methylcaproic acid, and L-2-hydroxy-3-methylisocaproic acid, scarcely no simple correlation was observed between the asymmetric activities of the catalysts and the diastereomeric configurations of the modifying reagents, and, in some cases, the asymmetric direction of the catalysts was inverted, as is shown in Table 3.

As has been mentioned above, a considerably strong effect of the β-configuration of the modifying reagent on the asymmetric activity of the catalyst is observed in the cases of modifications with both amino and hydroxy acids, and the effect of the β-configuration of hydroxy acid often overcomes that of the α-configuration. The mode of the contribution of the β-configuration of the modifying reagent to the asymmetric activity of the catalyst can ben concluded from the results shown in Tables 2 and 3; the S:β-configuration brings the asymmetric activity of the + direction[4] to the catalyst, and the R:β-configuration brings the asymmetric activity of the − direction, without regard to the kind of modifying reagent, whether amino or hydroxy acid.

The effect of the γ-asymmetric center of the modifying reagent on the asymmetric activity of the catalyst was

4) Asymmetric direction of the catalyst. The asymmetric activity consists of two factors; one is presented as the value of the optical purity of the product of the asymmetric hydrogenation, and the other is presented by the sign + or − and correlates with the absolute configuration of the product. In usual discussions, the asymmetric activity of the catalyst is discussed only in connection with the former factor. However, in a special case, the second factor has to be discussed as the problem of the "asymmetric direction of the catalyst."

Table 4. Modifications with L-norvaline, L-leucine, L-norleucine, L-methylnorleucine, and L-2-hydroxy-4-methylcaproic acid

Modifying conditions: R–CH(X)–CO_2H R	X	Absolute configuration α-carbon	Absolute configuration β-carbon	pH	Temp. °C	$[\alpha]_D^{25}$ of Methyl 3-hydroxybutyrate
$-CH_2-CH(C_2H_5)(CH_3)$	NH_2	S	S	5.95	0	−1.08
					100	−1.51
		S	R	5.98	0	−0.73
					100	−0.89
$-CH_2-CH_2-CH_2-CH_3$	NH_2	S	—	6.08	0	−1.14
					100	−1.52
$-CH_2-CH(CH_2)(CH_3)$	NH_2	S	—	5.98	0	−1.08
					100	−1.64
$-CH_2-CH_2-CH_3$	NH_3	S	—	6.04	0	−0.95
					100	−1.62
$-CH_2-CH(C_2H_5)(CH_3)$	OH	S	S	2.9	0	0
					70	+0.03
		S	R	2.9	0	−0.05
					70	−0.08

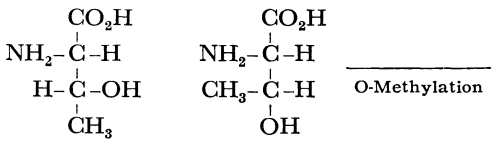
investigated using L-(2S:4S)-γ-methylnorleucine, L-(2S:4R)-γ-methylnorleucine, L-(2S:4S)-2-hydroxy-4-methylcaproic acid, and L-(2S:4R)-2-hydroxy-4-methylcaproic acid as the modifying reagents, while the asymmetric activities of the catalysts modified with these α,γ-diasymmetric amino acids or hydroxy acids were compared with those with norvaline, leucine and norleucine.

The difference between the asymmetric activities of the catalysts modified with L-(2S:4S)-γ-methylnorleucine and those modified with L-norvaline, L-leucine and L-norvaline can be hardly observed in Table 4. However, when the asymmetric activities of the catalysts modified with two diastereoisomers of γ-methylnorleucine were compared, the effect of the γ-asymmetric center was observed; the catalyst modified with L-(2S:4S)-diastereoisomer has a higher asymmetric activity than the one with L-(2S:4R)-diastereoisomer.

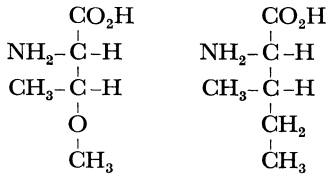
From those results, it seems that the S:γ-methyl group of the amino acid used as a modifying reagent does not increase the asymmetric activity of the catalyst. On the other hand, the R:γ-methyl group of the modifying reagent considerably decreases the asymmetric activity of the catalyst; that is, the R-configuration of γ-carbon brings the asymmetric activity of the + direction and has an effect on the asymmetric activity of the catalyst opposite to that of the R:β-configuration.

On the other hand, in the cases of the modifications of the diastereoisomer of the hydroxy acids, the asymmetric activities of the catalysts modified with these hydroxy acids were too low for us to discuss the exact role of the γ-asymmetric center in the asymmetric activities of the catalysts.

As is shown in Table 5, *threo-O*-methylthreonine has less ability as a modifying reagent than does *erythro-O*-



L-Threonine



L-Isoleucine

L-*threo*-O-Methylthreonine

Fig. 1

Table 5. Modifications of diastereoisomers of L-*O*-methylthreonine

Modifying conditions: Reagent R–CH(NH_2)–CO_2H R	Configuration	Absolute configuration α-carbon	Absolute configuration β-carbon	pH	Temp. °C	$[\alpha]_D^{25}$ of Methyl 3-hydroxybutyrate
$-CH(OCH_3)(CH_3)$	Erythro	S	S	5.90	0	−0.12
					100	−0.38
	Threo	S	R	5.90	0	0
					100	−0.06

methylthreonine, contrary to the results obtained in the cases of the modifications with α,β-diasymmetric amino acids. Furthermore, the asymmetric activities of the catalysts modified with the two diastereoisomers of *O*-methylthreonine are both considerably lower than those of catalysts modified with isoleucine isomers:

These results can be understood as follows. If the CH_3-C-C-COOH structure is replaced by CH_3-O-C-C-COOH as the main chain in *O*-methylthreonine, as is shown by the Fischer diagram in Fig. 1, because the methoxyl group is bulkier than the methyl group, the L-threo-isomer corresponds with L-isoleucine and the L-erythro-isomer corresponds with L-alloisoleucine. Accordingly, the relationship between the asymmetric activities of the catalyst and the configurations of the α,β-diasymmetric amino acid used as the modifying reagent is also established in the case of *O*-methylthreonine.