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

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The state of the amino acid molecule used as a modifying reagent on a catalyst surface was investigated. From the relationship between the asymmetric activities of the catalysts modified with L-valine and its derivatives and the stability constants of the nickel chelates of L-valine and its derivatives, it was concluded that L-valine adsorbs like a ligand of the chelate on the catalyst surface. This conclusion was also supported by the finding that the asymmetric activity of the catalyst modified with the nickel L-valine chelate was higher than those of the catalysts modified with L-valine and its derivatives. Also, the asymmetric activities of the catalysts modified with L-histidine, L-serine, and L-proline, and with the nickel chelates of the above three L-amino acids were discussed on the basis of the stability constants of the nickel chelates of the above three L-amino acids, it was concluded that two conditions at least are necessary for the modifying reagent to be effective; it must adsorb stably on the catalyst surface, and it must have a structure affording effective asymmetric control of the substrate.

In a series of investigations of asymmetric hydrogenation by our research group, it has been reported that the catalysts modified with *O*-acetyl D-tartaric acid, *O*-benzoyl D-tartaric acid, and the D-tartaric acid diethyl ester show lower (−) asymmetric activities than the catalyst modified with D-tartaric acid, and also that the catalysts modified with *N,N*-dimethyl-L-glutamic acid and *N*-cyanoethyl-L-glutamic acid have lower (−) asymmetric activities than the catalyst modified with L-glutamic acid.[1] From the above results, it was conclusively inferred that a hydroxyl group or an amino group and a carboxyl group are desirable modifying reagents to produce the high asymmetric activity of the catalyst.

However, no systematic information about the adsorption state of the modifying reagent on the catalyst surface has been obtained. The present work was undertaken in order to elucidate the adsorption state of the modifying reagent, L-amino acid, on the catalyst surface. As the modifying reagents, monoamino monocarboxylic acids were mainly used by virtue of the ease of analysis of the state of the modifying reagent on the catalyst surface.

The adsorption form of amino acid formed by the chelation on the catalyst surface is discussed on the correlation between the asymmetric activity of the catalyst and the stability constant of the nickel chelate of the modifying reagent. Furthermore, the essential chemical character of the modifying reagent in the asymmetric hydrogenation is discussed.

Experimental

The preparation of the modified Raney nickel catalyst, the hydrogenation of methyl acetoacetate, and the measurement of the asymmetric activity of the catalyst were done as described in a previous paper.[2]

Results and Discussion

Table 1 indicates the asymmetric activities of the catalysts modified with L-valine and its derivatives. As Table 1 indicates, the catalyst modified with L-valine showed a higher (−) asymmetric activity than the

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1) S. Tatsumi, M. Imaida, Y. Fukuda, Y. Izumi, and S. Akabori, This Bulletin, **37**, 846 (1964).

2) Y. Izumi, T. Harada, T. Tanabe, and K. Okuda, This Bulletin, **44**, 1418 (1971).

Table 1. The asymmetric activities of the catalysts modified with L-valine and L-valine derivatives

Modifying reagent	Solvent	concn. %	Modifying condition Temp. (°C)	Time (min)	$[\alpha]_D$ of Methyl 3-hydroxybutyrate
L-Valine	H_2O	2	0	90	−2.47
L-Valine·Na	H_2O	2	0	90	−0.33
L-Valine·HCl	H_2O	2	0	90	−1.79
N-Acetyl L-Valine	H_2O	1	0	90	−0.79
N-Benzoyl-L-valine	MeOH	1	0	90	−0.27
L-Valine methyl ester	H_2O	1	0	90	−0.20
L-Valinol	H_2O	1	0	90	−0.15
trans-Ni[L-Val]$_2$ ·H_2O	MeOH	1	0	90	−3.42
trans-Cu[L-Val]$_2$	MeOH	0.2	0	90	−3.10
Zn[L-val]$_2$	MeOH	0.8	0	90	−2.32

R–Ni ND (Kawaken Fine Chemicals Co., Ltd.) lot 1949 1.5 g.
MAA (The Nippon Synthetic Chemical Industry Co., Ltd.) lot 70, 0.15 mol.

catalysts modified with *N*-acetylated L-valine, L-valine methyl ester, and L-valinol.

From the information provided by co-ordination chemistry, L-amino acids are well known as usual chelating reagents for transition metals, and it is also known that the stability constants of the metal chelates of L-amino acids are depressed by the chemical derivation of the amino group or carboxyl group.[3)]

On the basis of the above facts, the decrease in the (−) asymmetric activity of the catalyst by the chemical derivation of the amino or carboxyl group of the modifying reagent, as is shown in Table 1 seems to depend on the depression of the stability of the chemical adsorption of the modifying reagent on the catalyst surface by the chemical derivation, and the modifying reagent, L-valine, seems to be adsorbed as a ligand of the chelate on the catalyst surface.

Table 2. The asymmetric activities of the catalysts modified with L-Ileu, L-Phe, L-Met and their metal chelates

Modifying reagent	Solvent	concn. %	Modifying condition Temp. (°C)	Time (min)	$[\alpha]_D$ of Methyl 3-hydroxybutyrate
trans-Ni[L-isoleu]$_2$ ·$2H_2O$	MeOH	1	0	90	−2.98
cis-Cu[L-isoleu]$_2$ ·$2H_2O$	MeOH	1	0	90	−2.44
L-Isoleucine	H_2O	1	0	90	−2.84
Ni[L-Phe]$_2$·$2H_2O$	$PhCH_2OH$	1	0	90	−1.89
L-Phenylalanine	H_2O	1	0	90	−2.11
Ni[L-Met]$_2$·$1/2H_2$	H_2O	0.8	0	90	−0.86
L-Methionine	H_2O	1	0	90	−0.72

R–Ni ND (Kawaken Fine Chemicals Co., Ltd.) lot 1949, 1.5 g.
MAA (The Nippon Synthetic Chemical Industry Co., Ltd.) lot 70, 0.15 mol.

Table 2 lists the asymmetric activities of the catalysts modified with L-isoleucine (L-Ileu). L-phenylalanine (L-Phe), and L-methionine (L-Met) and those nickel chelates. As is listed in Table 2, the asymmetric activities of the catalysts modified with the nickel chelates of the above three L-amino acids were nearly equal to or higher than those of the catalysts modified with the corresponding L-amino acids. The catalysts modified with *N*-acetyl L-isoleucine and *N*-acetyl L-phenylalanine showed far lower (−) asymmetric activities than those modified with L-Ileu and L-Phe respectively. The low (−) asymmetric activities of the catalysts modified with *N*-acetyl L-isoleucine and *N*-acetyl L-phenylalanine probably result from the less stable adsorption of *N*-acetyl L-isoleucine and *N*-acetyl L-phenylalanine on the catalyst surface than that of L-Ileu and L-Phe. These results also support the above-mentioned deduction that the L-amino acid used as the modifying reagent adsorbs like a ligand of the chelate on the catalyst surface.

Table 2 also shows that the catalyst modified with the *trans* nickel L-isoleucine chelate and a higher (−) asymmetric activity, while, the catalyst modified with the *cis* copper L-isoleucine chelate had a lower (−) asymmetric activity, than the catalyst modified with L-Ileu. These results may be interpreted as follows: in the modification of the *trans* nickel L-isoleucine chelate, both secondary butyl groups of the nickel L-Ileu chelate stretch out on the same side from the chelate-ring plane and the chelate adsorbs through the *d*-electron as the less sterically-hindered side on the catalyst surface, as is illustrated in Fig. 1.

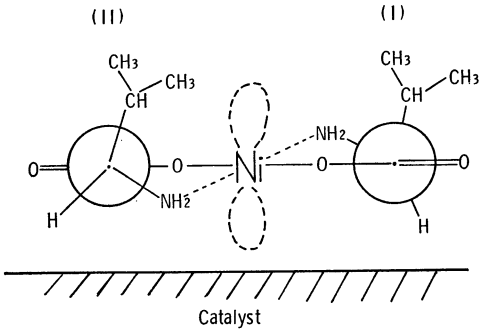

Fig. 1. Proposed adsorption state of *trans* nickel L-isoleucine chelate.

When the substrate, methyl acetoacetate, approaches the catalyst surface, if the interaction of the substrate with the right modifying reagent molecule (I) in Fig. 1, fit for the asymmetric hydrogenation, the left molecule (II) should strongly reject the substrate, and *vice versa*.

Consequently, in the modification of *trans* nickel L-isoleucine chelate, the push-pull effect by both modifying molecules, I and II, on the asymmetric control of the substrate would cause higher (−) asymmetric activity than in the modification with L-Ileu, which produces mixture of *cis* and *trans* forms on the

3) a) R. B. Martin and J. T. Edsall, *J. Amer. Chem. Soc.*, **82**, 1107 (1960); b) J. M. White, R. A. Manning, and N. C. Li, *ibid.*, **78**, 2367 (1956).

catalyst surface. On the other hand, in the case of modification with the *cis* copper L-isoleucine chelate naturally hinders the adsorption of the chelate, so that the *cis* chelate adsorbs less stably than L-Ileu and the *trans* chelate. The catalyst modified with the *cis* chelate would give a lower (−) asymmetric activity than those modified with the *trans* nickel L-isoleucine chelate and L-Ileu.

The above discussion is also supported by the fact that the catalyst modified with the nickel L-valine chelate shows far more (−) asymmetric activity than that catalyst modified with L-valine. The high asymmetric activities of the catalysts modified with the *trans* nickel L-valine chelate and the *trans* copper L-valine chelate, shown in Table 1, seem to be due to stable adsorption by the *d*-electron of nickel or copper metal on the catalyst surface.

TABLE 3. THE ASYMMETRIC ACTIVITIES OF THE CATALYSTS MODIFIED WITH L-Ser, L-Thr, L-Pro, L-His AND THEIR NICKEL CHELATES

Modifying reagent	Solvent	concn. %	Modifying condition Temp. (°C)	Time (min)	$[\alpha]_D$ of Methyl 3-hydroxybutyrate
Ni[L-Ser]$_2$·2H$_2$O	H$_2$O	1	0	90	+0.39
L-Serine	H$_2$O	2	0	90	+0.72
Ni[L-Thr]$_2$·2H$_2$O	H$_2$O	1	0	90	±0.00
L-Threonine	H$_2$O	1	0	90	−0.27
Ni[L-Pro]$_2$·2H$_2$O	H$_2$O	1	0	90	+0.12
L-Proline	H$_2$O	1	0	90	+0.18
Ni[L-His]$_2$·H$_2$O	H$_2$O	1	0	90	±0.00
L-Histidine	H$_2$O	1	0	90	−0.48

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Table 3 lists the asymmetric activities of the catalysts modified with L-serine (L-Ser), L-threonine (L-Thr), L-proline (L-Pro), and L-histidine (L-His) and the nickel chelates of those L-amino acids.

As is listed in Table 3, all the catalysts modified with L-His, L-Ser, L-Thr, and L-Pro showed smaller asymmetric activies than the catalysts modified with L-Val, L-Ileu, and L-Phe, shown in Tables 1 and 2, and they did not always show the (−) asymmetric direction.

The stability constants of nickel chelates of Pro, Ser, and His are known to be equal or greater than that of Val,[3,4] and the above discussion suggests that the stable adsorption of the modifying reagent, *i.e.*, chelation, on the catalyst surface can cause a high asymmetric activity in the catalyst. However, contrary to expectation, the asymmetric activities of the catalysts modified with L-Pro, L-Ser, L-His and L-Thr are less than that of the one modified with Val. The above phenomena can be explained as follows: though Pro, Ser, His and perhaps Thr can adsorb stably on the catalyst surface, their asymmetric control ability to the substrate would be far less effective than that of L-Val, L-Ileu, and L-Phe.

Also, as is shown in Table 3, catalysts modified with nickel chelates of L-His, L-Ser, L-Thr and L-Pro gave lower asymmetric activities than catalysts modified with L-His, L-Ser, L-Thr, and L-Pro respectively. In according for the above fact, it can be considered that all the six bonding electrons of nickel metal are completely occupied by two tridentate-ligand molecules and that the nickel chelate of those ligands will be attached to the catalyst surface only by weak physical adsorption, so that the catalysts modified with these nickel chelates show low asymmetric activities.

On the basis of the above discussion as a whole, it can be concluded that the modifying reagent, L-monoamino monocarboxylic acid, should adsorb like a ligand of the chelate on the catalyst surface and that two conditions at least are necessary in a desirable modifying reagent in the asymmetric hydrogenation; it must adsorb stably on the catalyst surface and it must have a structure affording effective asymmetric control of the substrate.

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4) A. Albert, *Biochem. J.*, **47**, 531 (1950); R. Leberman and B. R. Rabin, *Trans. Faraday Soc.*, **55**, 1660 (1959).