Stereochemical Studies of the Hydrogenation with Asymmetrically Modified Nickel Catalysts; The Hydrogenation of Methyl 2-Alkyl-3-oxobutyrate

Akira TAI,* Hiroshi WATANABE, and Tadao HARADA

Institute for Protein Research, Osaka University, Yamada-kami, Suita, Osaka 565

(Received September 25, 1978)

The hydrogenation of methyl 2-methyl-3-oxobutyrate (I) to methyl 3-hydroxy-2-methylbutyrate (III) was carried out with various types of asymmetrically modified nickel catalysts (MNi). The use of MNi always resulted in the deviation of the ratio, **2S/2R**=((2*S*,3*R*)-III+(2*S*,3*S*)-III)/((2*R*,3*R*)-III+(2*R*,3*S*)-III), from 1/1, in spite of the use of racemic I. A catalyst giving a larger **2S/2R** value always gave a larger **3R/3S** value. These results led to the conclusion that the configurations at the C-2 and C-3 positions of the product were determined in the process of the formation of the complex between the substrate and the modifying reagent (the absorption step), not at the step of the hydrogen addition to the adsorbed substrate (the rate-determining step). The best optical yield and the highest ratio of *erythro*-III/*threo*-III were obtained when (*R*,*R*)-tartaric acid–MNi was used as a catalyst. The amounts of the isomers produced were in the following order: 2*S*,3*R*≫2*R*,3*R*≈2*R*,3*S*>2*S*,3*S*. Stereochemical models are proposed to account for the formation of the 2*S*,3*R*-isomer in a large excess.

The comparative study of the rate and the optical yield of methyl acetoacetate (MAA) over an asymmetrically modified Raney nickel catalyst has revealed that the enantioface-differentiating step of the substrate took place elsewhere than in the step of the hydrogen addition to the adsorbed substrate (the rate-determining step).[1] Although the kinetic study has suggested that the modifying reagent differentiated the enantioface of the substrate by making a complex with the substrate at the adsorption step, the mode of the differentiation has not yet been made clear.

In the hydrogenation of methyl 2-methyl-3-oxobutyrate (I) to *threo*- and *erythro*-methyl 3-hydroxy-2-methylbutyrate (III) over a modified nickel catalyst (MNi), it has been noticed that the function of the modifying reagent is not only to differentiate the enantioface of the substrate, but also to determine the ratio of the diastereomers produced.[2]

The readily interconvertible chiral center at the C-2 position of I may serve as an internal probe for the detection of the substrate-modifying reagent interaction. In this respect, the stereochemical investigation of the hydrogenation of I was expected to give useful information about the mode of the enantio-differentiation.

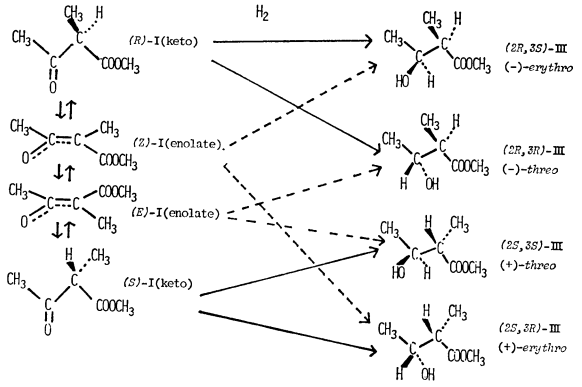
In this paper, we will present an account of the mode of the enantio-differentiation and evidence which may support the conclusion of our kinetic study with respect to the enantio-differentiating step.

Results and Discussion

The stereochemical relationship between the substrate and the products in the hydrogenation of I is shown in Scheme 1.

The results of the hydrogenations of I as well as of methyl 2-ethyl-3-oxobutyrate (II) and MAA over various sorts of modified nickel catalysts are summarized in Table 1.

The amounts of the four stereoisomers, calculated from the data of Table 1, are listed in Table 2, together with following values: **2R**=(2*R*,3*R*)-III+(2*R*,3*S*)-III, **2S**=(2*S*,3*R*)-III+(2*S*,3*S*)-III, **3R**=(2*R*,3*R*)-III+(2*S*,3*R*)-III, **3S**=(2*R*,3*S*)-III+(2*S*,3*S*)-III, configuration excess at the C-2 position: |**2R**−**2S**|/(**2R**+**2S**), and configuration excess at the C-3 position: |**3R**−**3S**|/(**3R**+**3S**).



Scheme 1.

The activated nickel powders prepared either by the thermal decomposition of nickel formate (DNi) or by the hydrogenolysis of nickel oxide (HNi), gave better optical yields than did Raney nickel (RNi). As for modifying reagents, the enantio-differentiating abilities were in the order of tartaric acid≫valine≈glutamic acid. These greneal features were the same as those found in the hydrogenation of MAA[3].

Enantio-differentiating Step. The preliminary experiment indicated that an authentic IIIe or IIIt was not epimerized nor racemized under the conditions used for the hydrogenation of I to III.

Therefore, in the course of the reaction, the configuration of the product is determined before the addition of hydrogen to the substrate. Thus, the distribution of stereoisomers in the product directly reflects the equilibrium situation of the substrate, as is shown in Scheme 1.

If the distribution of stereoisomers is different between the modified and unmodified catalysts, the difference indicates the interaction between the substrate and the modifying reagent prior to the step of the hydrogen addition.

As may be seen in Tables 1 and 2, with asymmetrically modified catalysts the values of |**2R**−**2S**|/(**2R**+**2S**) always deviated from zero despite the use of racemic

Table 1. Hydrogenation of the β-keto ester with a modified nickel catalyst

	Catalyst	Modifying reagent	Substrate	Products: Diastereomers ratio (*erythro*/*threo*)	Products: Optical purity(%) *erythro*[d]	Products: Optical purity(%) *threo*[e]
1	MRNi[a]	(*R*,*R*)-Tartaric acid	I	65.1/39.4	24.0	17.3
2	MDNi[b]	(*R*,*R*)-Tartaric acid	I	77.9/22.1	55.8	41.2
3	MHNi[c]	(*R*,*R*)-Tartaric acid	I	78.4/21.6	56.7	64.4
4	MHNi	(2*S*,3*S*)-2-Methyltartaric acid	I	72.0/28.0	46.2[f]	20.5[g]
5	MDNi	(*S*)-Valine	I	62.3/37.7	5.5	0.5
6	MDNi	(*S*)-Glutamic acid	I	67.6/32.4	0.6	0
7	HNi	None	I	62.6/37.4	—	—
8	MHNi	(*R*,*R*)-Tartaric acid	II	70.7/29.3	79.9[h]	71.3[h]
9	NHNi	(*R*,*R*)-Tartaric acid	MAA	—	83.0[i]	

a) RNi: Raney nickel. b) DNi: Activated Ni catalyst prepared by the thermal decomposition of nickel formate. c) HNi: Activated Ni catalyst prepared by the hydrogenolysis of nickel(II) oxide. d) (2*S*,3*R*)-isomer in excess, e) (2*R*,3*R*)-isomer in excess. f) (2*R*,3*S*)-isomer in excess. g) (2*S*,3*S*)-isomer in excess. h) Enantiomer excess was determined by NMR. i) (*R*)-isomer in excess.

Table 2. Isomer distribution of the hydrogenation product of the β-keto ester

	Stereoisomer distribution(%) 2*R*3*R*	2*S*3*R*	2*R*3*S*	2*S*3*S*	**2R** isomers (2*R*3*R*+2*R*3*S*)	**2S** isomers (2*S*3*R*+2*S*3*S*)	**3R** isomers (2*R*3*R*+2*S*3*R*)	**3S** isomers (2*R*3*S*+2*S*3*S*)	$\frlvert{2R-2S}{2R+2S}\times100$	$\frlvert{3R-3S}{3R+3S}\times100$
1	20.5	40.5	24.6	14.4	45.1	54.9	61.0	39.0	8.3	22.0
2	15.6	60.7	17.2	6.5	32.8	67.2	76.3	23.7	34.4	52.6
3	17.8	61.4	17.0	3.8	34.8	65.2	79.2	20.8	30.4	58.4
4	11.2	19.3	52.7	16.8	63.9	36.1	30.5	69.5	27.8	39.0
5	19.0	32.8	29.4	18.8	48.4	51.6	51.8	48.2	3.2	3.6
6	16.2	34.0	33.6	16.2	49.8	50.2	50.2	49.8	0.4	0.4
7	18.7	31.3	31.3	18.7	50.0	50.0	50.0	50.0	0	0
8	25.1	63.6	7.1	4.2	32.2	67.8	88.7	11.3	35.6	77.4
9	91.5		8.5		—	—	91.5	8.5	—	83.0

I, and the ratio of *erthro*-III/*threo*-III was also changed from the value obtained with an unmodified catalyst.

Thus, it is evident that the relative amounts of (*S*)-I (keto) and (*R*)-I(keto), or of (*Z*)-I (enolate) and (*E*)-I (enolate), are changed by the modifying reagent. The present results clearly show the existence of an interaction between the substrate and the modifying reagent before the hydrogenation of the adsorbed substrate took place. In Tables 1 and 2 it can also be seen that the catalyst giving a larger $|\mathbf{2S}-\mathbf{2R}|/(\mathbf{2S}+\mathbf{2R})$ value always gave a larger $|\mathbf{3R}-\mathbf{3S}|/(\mathbf{3R}+\mathbf{3S})$ value. In connection with this relation, the increase in *erythro*-III resulted in an increase in the optical purity of both *erythro*- and *threo*-III. These facts strongly suggest that the configurations at both the C-2 and C-3 positions of III were determined by the same process involving the formation of a substrate-modifying reagent complex. Therefore, the stereochemistry of the product is considered to be fixed at the adsorption step of the substrate.

This conclusion is very compatible with that obtained from our kinetic study.[1]

Mode of Enantio-differentiation. The use of (*R*,*R*)-tartaric acid–MHNi gave the best results with respect to the optical yield and the diastereomer excess. The amounts of stereoisomers produced were in the order of 2*S*,3*R*≫2*R*,3*R*≈2*R*,3*S*>2*S*,3*S*. According to the physicochemical studies, tartaric acid is adsorbed on the catalyst with one of its carboxyl groups; the other carboxyl group and two hydroxyl groups are essentially free from the catalyst surface.[4] The two hydroxyl groups of tartaric acid are expected to play an important role in interacting with the substrate.[5] The excellent enantio-differentiation obtained in the combination of tartaric acid and I as well as MAA can be attributed to the two-point interaction with hydrogen bondings between the modifying reagent and the substrate.

When the substrate takes a keto form, the co-adsorbed species with the best-fitting interaction between I and tartaric acid on the catalyst surface gives the complex shown in Fig. 1, in which the carbonyl group to be hydrogenated faces the catalyst with its *si*-face and the configuration at the C-2 position is *S*, so that the methyl group at the C-2 position is remote from the catalyst. The large deviation of the $|\mathbf{2R}-\mathbf{2S}|/(\mathbf{2R}+\mathbf{2S})$ value from zero indicates that the substrate originally having the 2*R* configuration is converted to the 2*S* configuration in order to make this favorable complex. The addition of hydrogen to this complex gives (2*S*,3*R*)-III.

When the substrate takes an enolate form, the complex of (*Z*)-enolate with (*R*,*R*)-tartaric acid shown in Fig. 2 is the best fitting one. This complex also gives (2*S*,3*R*)-III.

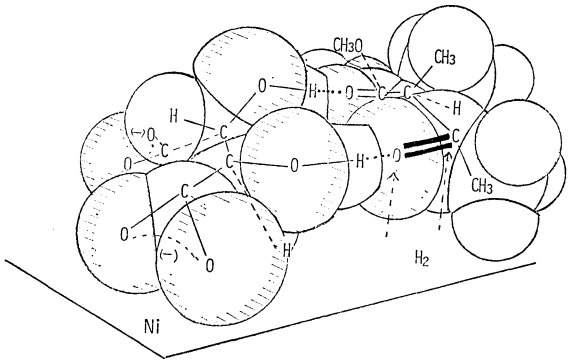


Fig. 1. Schematic representation of the complex between I(keto form) and (*R*,*R*)-tartaric acid on the MNi catalyst. The complex gives (2*S*,3*R*)-III by the attack of hydrogen from the catalyst-side (*si*-face attack)

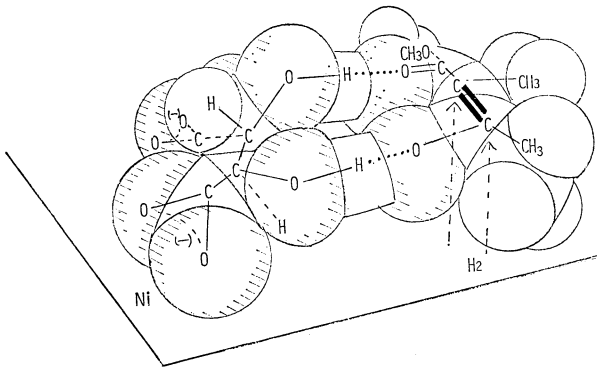


Fig. 2. Schematic representation of the complex between I(enolate) and (*R*,*R*)-tartaric acid on the MNi catalyst. The complex gives (2*S*,3*R*)-III by the attack of hydrogen from the catalyst-side (*si*-face attack).

Thus, the predominant formation of (2*S*,3*R*)-III may be well explained by both of the models. Although it is not clear whether the substrate is hydrogenated in a keto or an enolate form, the mode of the differentiation was found to be well understood without specifying the form of the substrate to be hydrogenated.

The quantitative discussion of the amounts of minor isomers is difficult at present, since the distribution of stereoisomers depends on the relative amount of the unmodified part of the catalyst.[1b] The difference in the results with MRNi and MHNi may be expected to arise in part from the difference in the unmodified part of the catalyst.

The use of (*R*,*R*)-tartaric acid–MNi always gave the 3*R*-isomer in a large excess in the hydrogenation of I as well as those of II and MAA (entries 8 and 9 in Table 2). Thus, it seems that the same mode of interaction between the substrates and the modifying reagent is involved in the enantio-differentiating hydrogenation of β-keto esters with tartaric acid–MNi.

Experimental

The analytical GLC was carried out with a Shimadzu GC-4A-PF gas chromatograph using a 3 m, 5 mm o.d. glass column packed with 15% Ucon 50-HB-2000 on Chromosorb W at the stated temperature. The preparative GLC was carried out with a Shimadzu GC-3HA instrument using a 6 m, 8 mm o.d. stainless column packed with the same packing.

The ^{1}H-NMR spectra were taken with a JEOL-FX-100 spectrometer.

The optical rotations were measured with a Perkin Elmer 241 polarimeter.

Substrate. Methyl 2-methyl-3-oxobutyrate (I) was prepared from methyl acetoacetate and methyl iodide in the presence of sodium methoxide. A slight excess of methyl acetoacetate was used in order to minimize the formation of methyl 2,2-dimethyl-3-oxobutyrate. From 850 g of methyl acetoacetate and 993 g of methyl iodide, 752 g of crude I containing 8% of methyl acetoacetate and 5% of methyl 2,2-dimethyl-3-oxobutyrate was obtained. To 750 g of crude I, 50 g of freshly prepared $Ni(OH)_2$ was added, after which the mixture was stirred for 5 days at room temperature. After removing the insoluble matter by filtration, the filtrate was mixed with 10 g of Raney nickel and allowed to stand overnight at room temperature. After the solid had been removed, the resulting liquid was dried over magnesium sulfate and then distilled under reduced pressure to give 680 g of purified I; bp 88—90 °C/20 mmHg. A GLC (at 90 °C) analysis indicated 95% purity. Also, there were 4% of methyl 2,2-dimethyl-3-oxobutyrate and 1% of methyl acetoacetate.

Methyl 2-ethyl-3-oxobutyrate (III) (bp 75—80 °C/20 mmHg was prepared by the same procedure except for the use of ethyl bromide instead of methyl iodide.

Catalyst. The catalyst from nickel formate (DNi): Well-dried nickel formate prepared from nickel chloride and sodium formate was thermally decomposed at 250—300 °C under a pressure of 20—25 mmHg for 1 h. Reduced nickel oxide (HNi): This was obtained by the reduction of nickel oxide with hydrogen at 350 °C for 1 h. The nickel oxide used for this work was obtained by the dehydration (at 500 °C for 4 h) of nickel hydroxide prepared from nickel nitrate and sodium hydroxide. No active catalyst was obtained from nickel oxide of a commercial grade. Raney nickel (RNi): Raney alloy (Kawaken Fine Chemical Co., Ni 40% Al 60%) was leached with sodium hydroxide in the way previously reported.[1]

Modification of the Catalyst. Each catalyst was soaked in a 1% solution of a modifying reagent adjusted to pH 4.1 with 1 M sodium hydroxide at 85 °C for 1 h. The amount of the modifying solution used was 120 ml per gram of the catalyst.

After the removal of the solution by decantation, the modified catalyst was washed successively with a 60 ml/(g catalyst) portion of water, two 300 ml/(g catalyst) portions of methanol, and a 60 ml/(g catalyst) portion of THF.

Solvent. THF was used as a solvent of the hydrogenation. Commercial THF was dried over NaH overnight and was then distilled under a nitrogen atmosphere.

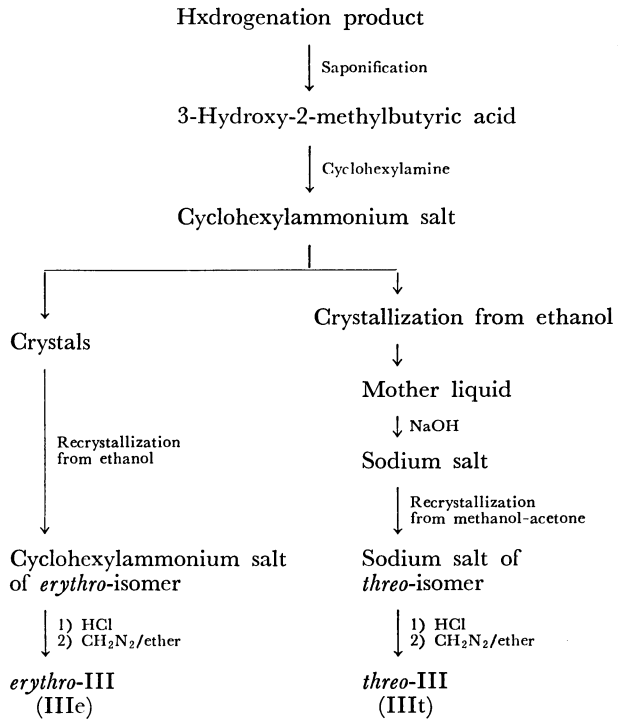
Hydrogenation of I. In an autoclave (1000 ml capacity), I (100 g) in 300 ml of THF with 1.5 g of acetic acid was hydrogenated over 8 g of a modified catalyst under an initial hydrogen pressure of 110 kg/cm^2 at 120 °C until no more consumption of hydrogen was observed. After the removal of the catalyst, the product was subjected to flash distillation under reduced pressure.

Determination of Stereoisomers in the Hydrogenation Product of I. The flash-distilled hydrogenation product essentially consisted of two components, *erythro*-III (IIIe) and *threo*-III (IIIt), accompanied by less than 5% of an unidentified impurity. The relative amounts of the *erythro* isomer; D_e=

$\frac{\text{IIIe}}{\text{IIIe}+\text{IIIt}}$, and the threo isomer; $D_t=\frac{\text{IIIt}}{\text{IIIe}+\text{IIIt}}$, were determined from the peak area of the analytical GLC (115 °C). The retention times of IIIt and IIIe were 21.6 min and 23.4 min respectively.

The separation of IIIe and IIIt in the reaction product was carried out by the method reported in our previous paper.[6]

The process of separation is illustrated in Scheme 2.



Scheme 2.

The isolated IIIe and IIIt were subjected to the polarimetric determination of their optical purity $(OY)_e=[2S3R-2R3S/(2S3R+2R3S)]\times 100$ and $(OY)_t=[2R3R-2S3S/(2R3R+2S3S)]\times 100$ as a methanol solution (c 5). The values were calculated based on the reported values: $[\alpha]_D^{20}$, (2*S*,3*S*)+36.80° (c 5, methanol) and (2*S*,3*R*), +14.32° (c 5, methanol).[6]

The distribution of each stereoisomer in the reaction product was calculated as follows:

$$2S3R(\%) = D_e \times \left(\frac{100+(OY)_e}{2}\right)$$

$$2R3S(\%) = D_e \times \left(\frac{100-(OY)_e}{2}\right)$$

$$2R3R(\%) = D_t \times \left(\frac{100+(OY)_t}{2}\right)$$

$$2S3S(\%) = D_t \times \left(\frac{100-(OY)_t}{2}\right)$$

The recrystallizations of the authentic sodium *threo*-3-hydroxy-2-methylbutyrate and cyclohexylammonium *erythro*-3-hydroxy-2-methylbutyrate with this separation process under the same conditions resulted in no change in the optical rotations. Thus, the optical purity of diastereomers in the hydrogenation product was proved to be the same as that of the isolated diastereomers.

The Stereochemical Stability of IIIe and IIIt in the Presence of a Catalyst and Hydrogen. An authentic optically active IIIe or IIIt was shaken with MNi under a hydrogen pressure of 100 kg/cm² at 100 °C for one day. The subsequent GLC and polarimetric determination of the recovered IIIe or IIIt indicated that no epimerization and racemization took place on this treatment.

Hydrogenation of II. In an autoclave (100 ml capacity), II (12.5 g) in 25 ml of THF and 1.5 g of acetic acid were hydrogenated over 1 g of the modified catalyst in the way described above.

Determination of Stereoisomers in the Hydrogenation of II. The analytical GLC (140 °C) of the product showed two peaks at the retention times of 7.4 min and 8.8 min.

The two components were isolated by the preparative GLC. The compound with a shorter retention time (7.2 min) in the analytical GLC (140 °C) showed the NMR ($CDCl_3$, TMS) assigned to $\underset{(b)}{CH_3}-\underset{(e)}{\underset{|}{C}}(\underset{|}{\underset{(g)}{H}})(\underset{|}{OH})-\underset{(c)}{\underset{|}{C}}(\underset{|}{\underset{(d)}{H}})(\underset{|}{CH_2CH_3})-\underset{(f)}{COOCH_3}$; δ, 0.93 (3H, t, J=7.1 Hz, (a)), 1.23 (3H, d, J=6.3 Hz, (b)), 1.64 (2H, m, (c)), 2.33 (1H, m, (d)), 2.45 (1H, d (broad), (e)), 3.73 (3H, s, (f)), 3.91 (1H, m, (g)).

The compound with a longer retention time (8.8 min) in the analytical GLC (140 °C) showed NMR ($CDCl_3$, TMS) δ, 0.91 (3H, t, J=7.1 Hz (a)), 1.19 (3H, d, J=6.4 Hz, (b)), 1.66 (2H, m, (c)), 2.35 (2H, overlapped two signals, (d) and (e)), 3.72 (3H, s, (f)), 3.90 (1H, broad, (g)).

The compound with a shorter retention time was determined to be *threo*-IV (IVt) by the comparisons of its retention time with that of IIIt[6] or ethyl *threo*-3-hydroxy-2-propylbutyrate[7] and of its NMR spectra with those of ethyl *threo*- and *erythro*-3-hydroxy-2-propylbutyrate.[7]

The ratio in the amounts of *threo*-IV: D_t and *erythro*-IV: D_e was determined by the analytical GLC.

The NMR spectra of IVe and IVt taken in the presence of $Eu(hfmc)_3$ showed two signals of H(f), which correspond to those of the enantiomers. Thus, the enantiomer excess (*e.e.*) of each diastereomer was determined from the relative peak area of the H(f) signals of the solution containing 10 mg of IVe or IVt and 25 mg $Eu(hfmc)_3$ in 500 μl of $CDCl_3$.

The absolute configuration at C-3 of IVe with the low-field H(f) signal and that of IVt with the high-field H(f) signal was assigned to the S-configuration by the use of Horeau's method.[6,8]

When the enantiomer excess of each diastereomer is expressed by *e.e.*(%)=[peak area (high-field)−peak area (low-field)]/peak area (high-field+low-field)×100, the distribution of each stereoisomer is calculated as follows:

$$2R3R(\%) = D_t \times \left(\frac{100+(e.e.)_t}{2}\right)$$

$$2S3S(\%) = D_t \times \left(\frac{100-(e.e.)_t}{2}\right)$$

$$2S3R(\%) = D_e \times \left(\frac{100-(e.e.)_e}{2}\right)$$

$$2R3S(\%) = D_e \times \left(\frac{100+(e.e.)_e}{2}\right)$$

The authors wish to express their gratitude to Professor Yoshiharu Izumi, Osaka University, for his many helpful discussions and suggestions in the course of this work. The work was supported partially by a Grant-in-Aid from the Ministry of Education (No. 203522).

References

1) a) T. Harada, Y. Hiraki, Y. Izumi, J. Muraoka, H. Ozaki, and A. Tai, Proc. 6th Int. Congr. Catal., London (1976), pp. 1024—1033; b) H. Ozaki, A. Tai, S. Kobatake, H. Watanabe, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **51**, 3559 (1978).

2) A. Tai, M. Imaida, T. Oda, and H. Watanabe, *Chem. Lett.*, **1978**, 61.

3) a) Y. Izumi, *Angew. Chem. Int. Ed. Engl.*, **10**, 871 (1971); b) T. Harada, S. Onaka, A. Tai, and Y. Izumi, *Chem. Lett.*, **1977**, 1131.

4) a) A. Hatta and W. Suetaka, *Bull. Chem. Soc. Jpn.*, **48**, 3441 (1975); b) J. A. Groenewegen and W. M. H. Sachtler, *J. Catal.*, **33**, 176 (1974); c) T. Tanabe, K. Okuda, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **46**, 514 (1973).

5) a) H. Ozaki, *Bull. Chem. Soc. Jpn.*, **51**, 257 (1978); b) J. A. Groenewegen and W. M. H. Sachtler, *J. Catal.*, **38**, 501 (1975); c) H. Watanabe, T. Harada, A. Tai, and Y. Izumi, 37th National Meeting of the Chemical Society of Japan, April 1978, Abstr. No. 1Q25.

6) A. Tai and M. Imaida, *Bull. Chem. Soc. Jpn.*, **51**, 1114 (1978).

7) K. Masken and N. Polgar, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 109.

8) A. Horeau, *Tetrahedron Lett.*, **1961**, 506.