Kinetic Studies of Enantioselective Hydrogenation of Methyl Acetoacetate on Modified Ni–SiO$_2$ Catalyst

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Enantioselective hydrogenation of methyl acetoacetate (MAA) to methyl 3-hydroxybutyrate (MHB) on tartaric acid-modified Ni–SiO$_2$ catalyst was studied under H$_2$ pressures from 1 to 130 kg/cm^2 in order to examine the effects of reaction conditions on optical purity of the product. Three kinds of autoclaves equipped with different stirring systems were used. Under the condition where the rate is controlled by surface reaction, the optical yield of MHB decreased with increasing H$_2$ pressure, and, at constant H$_2$ pressure, increased with increasing concentration of MAA. This behavior of optical yield was satisfactorily explained by assuming the Langmuir–Hinshelwood-type rate equations for the reactions on both (i.e., selective and nonselective) sites where MAA and H$_2$ are adsorbed competitively on each site and where the adsorption equilibrium constant of MAA on nonselective sites is larger than that on selective sites. Some unsaturated compounds added to the reaction mixture considerably increased the optical yield of MHB. This effect is attributable to the decrease of reaction rate on nonselective sites due to the competitive adsorption of reactants and the added compound.

INTRODUCTION

In the enantioselective hydrogenation of methyl acetoacetate (MAA) to methyl 3-hydroxybutyrate (MHB) on tartaric acid-modified nickel catalysts, preparation of a catalyst having a high ratio of selective (i.e., modified) sites to nonselective (i.e., unmodified) sites is essential to obtain a high optical purity of the product. We have reported that the enantioselectivity of modified nickel catalysts increases with the crystallite sizes of nickel, and described a preparation method for a highly enantioselective and active Ni–SiO$_2$ catalyst having a narrow crystallite size distribution of nickel (*1*). Harada *et al.* (*2*) proposed that the positive effect of addition of NaBr to the modifying solution is caused by the decrease in the fraction of nonselective sites in the total amount of active sites.

On the other hand, if we can suppress the reaction rate on only nonselective sites by changing the reaction conditions, optical purity of the product will increase even when the catalysts with the same surface

properties are used. In fact, it is known that optical purity of the product is affected by reaction conditions, such as hydrogen pressure, amount of catalyst, and reaction temperature (*3, 4*). In most cases reactions were carried out under relatively severe conditions because the modified catalysts had usually low hydrogenation activity; furthermore, higher hydrogen pressure seemed to be favorable for obtaining higher optical purity of the product. However, only in a few cases has the dependence of the enantioselective hydrogenation on the reaction conditions been investigated (*5*). Systematic studies of the effects of reaction conditions upon the optical purity of the product are necessary for obtaining a high optical yield of MHB and also for the study of the mechanism of this hydrogenation reaction.

In a previous paper (*6*) we have shown that (i) the optical purity of the product decreases linearly with increasing hydrogen pressure up to 10 kg/cm^2 and that (ii) it increases with increasing concentration of MAA. This paper presents results of more

detailed studies of the effects of reaction conditions (i.e., hydrogen pressure, concentration of MAA, the kind of solvent or additives, etc.) on the optical yield of (−)-MHB by using a Ni–SiO$_2$ catalyst modified with (R,R)-tartaric acid. The experiments were carried out under a wide range of hydrogen pressures (1 to 130 kg/cm^2) using three kinds of autoclaves equipped with different stirring systems. In order to explain the dependence of the optical yield of (−)-MHB on the concentrations of the reactants, the rate equations for the reactions on selective and nonselective sites are proposed.

EXPERIMENTAL

Catalyst preparation and modification. Ni–SiO$_2$(1 : 1) catalyst was prepared by the precipitation method, as described previously (*1, 7*), and then reduced at 500°C for 1 h in a hydrogen stream of 8 liters/h. The modification of a catalyst with (R,R)-tartaric acid was carried out at 83°C for 1 h in the same way as described previously (*1*). The NaBr-treated catalyst was prepared by modifying the Ni–SiO$_2$ catalyst with 100 ml of aqueous solution (pH = 3.2) containing 1 g of (R,R)-tartaric acid and 10 g of NaBr, according to the method described by Harada *et al.* (*8*). After modification, the catalyst was rinsed once with distilled water, twice with methanol, and then once with the solvent used for the reaction (10 ml portion of each). When the effect of additives was examined, the catalyst was rinsed once with distilled water and three times with methanol.

Hydrogenation. Twenty milliliters of a mixture of MAA and a solvent (usually ethyl acetate) or an added compound was hydrogenated with 1.4 g of the catalyst at 60°C under various hydrogen pressures. Three kinds of autoclaves, Nos. 1, 2, and 3, were used. No. 1 autoclave is a 50-ml glass autoclave (TEM-U-50, Taiatsu Glass Industry Co.) equipped with a vigorous stir-

ring system with a magnetic bar. The glass vessel is coated by an electric heater and therefore can be directly heated. This autoclave was used for the reactions carried out under hydrogen pressures ranging from 1.5 to 10 kg/cm^2. No. 2 autoclave is a 100-ml stainless-steel autoclave (NAC-5, Nitto Autoclave Co.) equipped with a vigorous stirring system (up to 1000 rpm) with a magnetic shaft and a screw blade. No. 3 autoclave is a 300-ml stainless-steel autoclave (Nitto Autoclave Co.) attached to a shaking apparatus of 65 times per minute. Nos. 2 and 3 were used for the reaction carried out under hydrogen pressures ranging from 5 to 130 kg/cm^2. Reactions under atmospheric hydrogen pressure were carried out at 20°C using an apparatus connected with a manometer and a vigorous stirring system (*9*). All reactants and solvents were dried and distilled before use.

Analysis. The reaction mixture, which reached about 15 or 100% conversion (usually 100% unless otherwise stated), was filtered and distilled under reduced pressure. The conversion of the reaction and purity of the distilled product were determined with GLC with a 2-m column of 20% PEG 20M on Celite 545. The optical rotation (α_D) of the distilled product was determined with a Union PM-101 automatic digital polarimeter at 20°C in a 0.1-dm cell. The α_D values for the products obtained from the reactions with lower conversions were corrected on the basis of separately determined dependence of α_D on the concentration of MHB in MAA. The optical yield of (−)-MHB was calculated from the α_D value according to the equation OY = (α_D/22.95) × 100 (*8*).

In the case of reactions carried out under atmospheric hydrogen pressure, the initial overall hydrogenation rate (r_t) was determined on the basis of measurement of hydrogen uptake at 17–18% conversion of the reaction. When autoclaves were used for the reaction, r_t was determined from pressure decrease during the initial 3–5 min of the reaction (up to ca. 10% conversion).
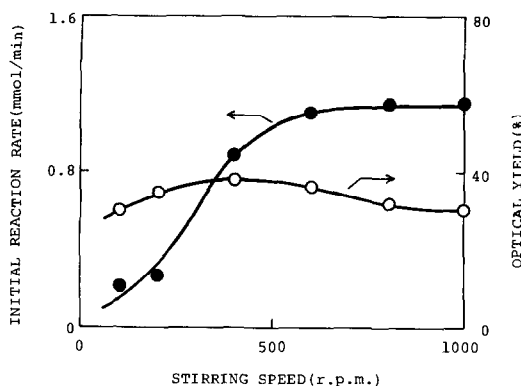
FIG. 1. Effect of stirring speed on initial reaction rate (●) and optical yield (○) of the reaction carried out under H_2 pressure of 60 kg/cm^2 with the use of autoclave No. 2 (MAA: 50% in ethyl acetate).
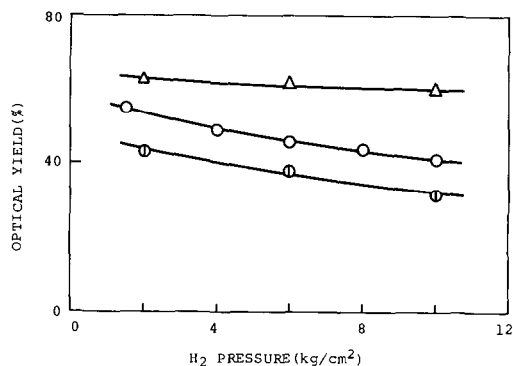

FIG. 2. Effect of H_2 pressure on optical yield of (−)-MHB obtained in the reaction in autoclave No. 1 (solvent: ethyl acetate). ○: 50% MAA; ⏀: 5% MAA: △: initial optical yield at conversion of ca. 15% (50% MAA).

RESULTS

Preliminary experiments carried out under 10 kg/cm^2 of hydrogen pressure with the use of autoclave No. 1 showed that increase in substrate-to-catalyst molar ratio (MAA/Ni) from 4 to 10 scarcely affects the optical activity of the product, in agreement with a previous report (10). The increase in the ratio from 10 to 20 resulted in about 5% decrease in the optical yield (OY) of (−)-MHB. Therefore, in this work, hydrogenations were carried out usually at MAA/Ni =

8. The hydrogenation rate was proportional to the catalyst concentration in the reactions in autoclaves No. 1 and No. 2.

Effect of stirring speed. When autoclave No. 2 was used, both OY of (−)-MHB and the hydrogenation rate were independent of the stirring speed in the range higher than 800 rpm, as shown in Fig. 1. Therefore, hydrogenations with autoclave No. 2 were carried out at 800 rpm. In the case of autoclave No. 1, the stirring speed was ca. 400–500 rpm; the results of preliminary experiments have shown that in this range OY
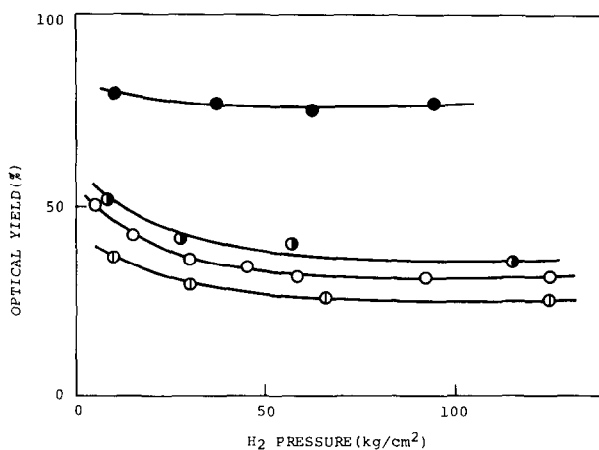

FIG. 3. Effect of H_2 pressure on optical yield of (−)-MHB obtained in the reaction in autoclave No. 2 (solvent: ethyl acetate), ⏀: 10% MAA; ○: 50% MAA; ◑: 100% MAA; ●: initial optical yield obtained in the presence of NaBr-treated catalyst (50% MAA).
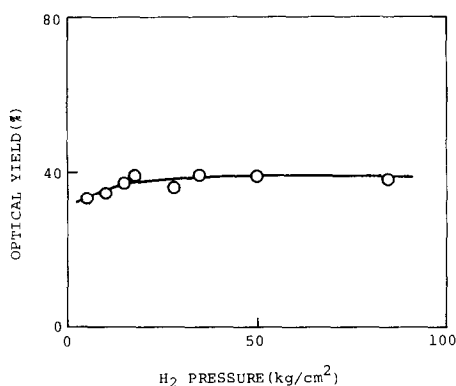
FIG. 4. Effect of H_2 pressure on optical yield on (−)-MHB obtained in the reaction in autoclave No. 3 (50% MAA in ethyl acetate).

and the hydrogenation rate were independent of the stirring speed.

Effect of hydrogen pressure. Figures 2, 3, and 4 show the effect of hydrogen pressure on OY of (−)-MHB produced in autoclaves Nos. 1, 2, and 3, respectively. When the stirring was vigorous, OY decreased with increasing hydrogen pressure up to about 70 kg/cm² and then became constant in all the examined cases (Figs. 2 and 3). On the other hand, it was almost independent of hydrogen pressure when the stirring was not so vigorous (Fig. 4). Similar observation was reported for the enantioselective hydrogenation of ethyl acetoacetate on modified Raney-Ni catalyst (*3a*).

Effect of MAA concentration. As shown in Fig. 5, an increase in the initial concentration of MAA in ethyl acetate resulted in an increase in OY of (−)-MHB produced in the reactions carried out under vigorous stirring and under various hydrogen pressures. Similar tendency was observed in the presence of other solvents (i.e., methanol as a protic solvent and tetrahydrofuran as an aprotic solvent), though slight variations in OY at given concentrations of MAA were noticed (Fig. 6).

Hydrogenation rate. Figure 7 shows the effect of hydrogen pressure up to 10 kg/cm² on the initial hydrogenation rates in the reactions where the initial concentration of

MAA is 50% in ethyl acetate. Figure 8 shows the effect of MAA concentration in ethyl acetate on the initial hydrogenation rates in the reactions carried out under atmospheric hydrogen pressure. In these figures the initial reaction rates on selective sites (r_s) and on nonselective sites (r_n) were calculated as follows:

$$r_s = p \cdot r_t, \tag{1}$$

$$r_n = (1 - p) \cdot r_t, \tag{2}$$

where r_t is the overall initial hydrogenation rate and p is OY of (−)-MHB at the stage of the reaction. Here we assumed that on the selective sites only (−)-MHB is produced.

Effect of additives. As shown in Fig. 9, addition of 5 to 10 ml of alkenes such as cyclohexene, cyclooctene, and 2,3-dimethyl-2-butene resulted in a considerable increase in OY of (−)-MHB, produced together with the hydrogenated compounds of additives, in the reaction carried out under initial hydrogen pressure of 10 kg/cm² with the use of autoclave No. 1. Addition of ketones was not so effective. Benzene, when added to the reaction mixture, was not hydrogenated at all but significantly in-
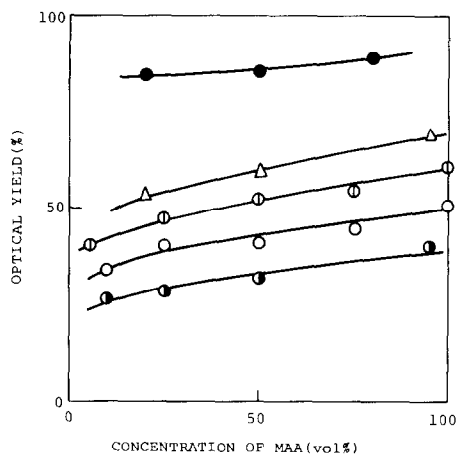

FIG. 5. Effect of MAA concentration in ethyl acetate on optical yield of (−)-MHB obtained in the reaction in autoclaves No. 1 and No. 2. ⊕: 2 kg/cm² H_2; ○: 10 kg/cm² H_2; ◑: 60 kg/cm² H_2; △: initial optical yield at conversion of ca. 15% (10 kg/cm² H_2); ●: initial optical yield obtained in the presence of NaBr-treated catalyst (10 kg/cm² H_2).
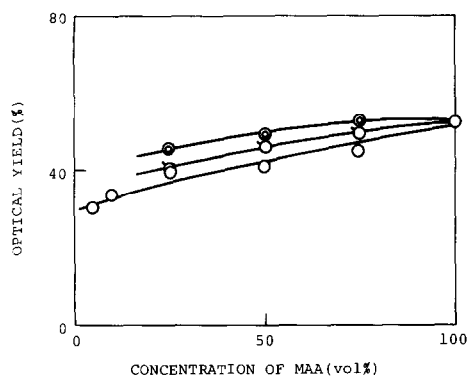
FIG. 6. Effect of MAA concentration in various solvents on the optical yield of (−)-MHB obtained in the reaction in autoclave No. 1 (10 kg/cm²). O: Ethyl acetate; O: methanol; ◉: tetrahydrofuran.

FIG. 8. Effect of MAA concentration on initial reaction rates measured under atmospheric hydrogen pressure. O: Overall reaction rate; ◑: reaction rate on nonselective sites; ⦶: reaction rate on selective sites.

creased OY of (−)-MHB. However, it decreased OY when it was used as a solvent; the adsorption of benzene seems to be strong enough to remove the modifier from the selective sites of the catalyst during washing.

DISCUSSION

As reported in the preceding paper, the fraction of selective sites on catalyst surface does not change with the progress of the reaction and also is independent of the number of runs (7). In addition, when reac-
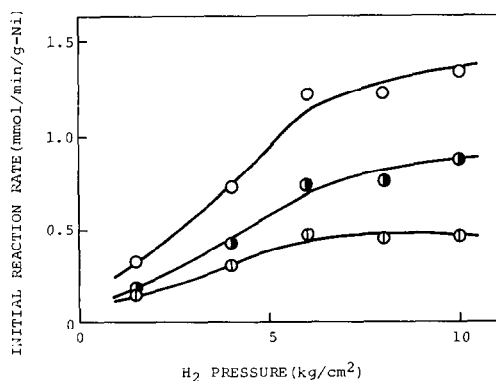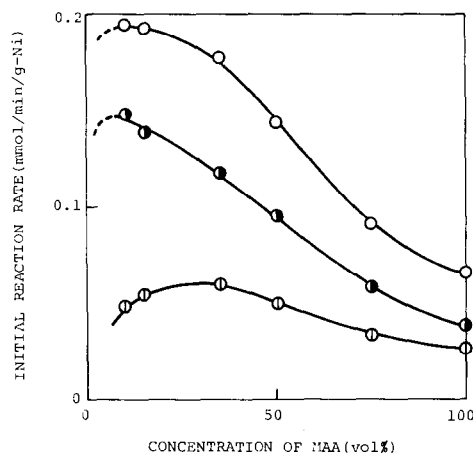
tions were carried out in succession under two different hydrogen pressures, i.e., first at 10 kg/cm² and second at 2 kg/cm², OY of the second reaction with the used catalyst was higher than that of the first reaction with fresh catalyst. This observation denies the possibility of decrease in the number of selective sites with increasing pressure of hydrogen. Therefore, the number of selective sites on the catalyst surface seems to be constant, independent of reaction condi-
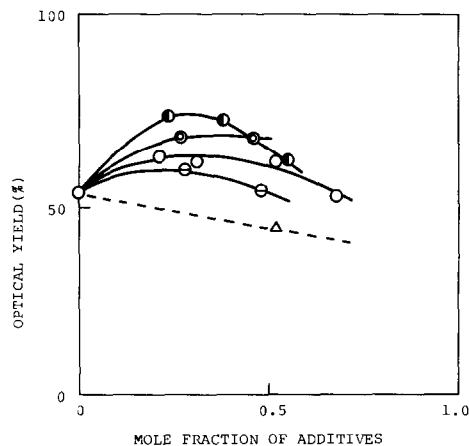

FIG. 7. Effect of H₂ pressure on initial reaction rates measured with the use of autoclave No. 1 (50% MAA in ethyl acetate). O: Overall reaction rate; ◑: reaction rate on nonselective sites; ⦶: reaction rate on selective sites.

FIG. 9. Effect of additives on optical yield of (−)-MHB obtained in the reaction in autoclave No. 1 (initial H₂ pressure: 10 kg/cm²). O: Cyclohexene; ◉: cyclooctene; ⊖: 2,3-dimethyl-2-butene; ◐: benzene; △: ethyl acetate.

tions applied in this work. According to this, the experimental results showing that OY depends on reaction conditions, e.g., on hydrogen pressure and on MAA concentration (Figs. 2 to 6), indicate that the reaction rates on selective sites and on nonselective sites depend in different ways on the reaction conditions.

The rates of the reactions carried out under vigorous stirring (i.e., in autoclaves Nos. 1 and 2) can be regarded as controlled by surface reaction, whereas the diffusion process cannot be neglected in the reactions carried out under mild stirring (i.e., in autoclave No. 3).

The liquid-phase hydrogenation of ketones on Ni catalysts has been explained by the Langmuir–Hinshelwood mechanism where the ketone and hydrogen adsorb competitively on the catalyst surface (9). Since hydrogenation rate, controlled by surface reaction, passes through a maximum (Fig. 8), the enantioselective hydrogenation of MAA on modified Ni catalysts also seems to be expressed by the Langmuir–Hinshelwood-type rate equation. Assuming that (i) MAA and hydrogen molecules adsorb competitively on active sites (both selective and nonselective sites) on the catalyst surface, (ii) the adsorptions of solvent and products on both sites are neglected except for the adsorption of (−)-MHB on selective sites as discussed in a previous report (7), and (iii) the adsorption equilibrium constants of hydrogen on both

sites are equal to each other, the surface reaction rates on selective sites (r_s) and on nonselective sites (r_n) can be expressed by

$$r_s = \frac{\alpha^2 k_s K_H K_{sR} C_H C_R}{(1 + K_H C_H + K_{sR} C_R + K_{sP(-)} C_{P(-)})^2},$$
(3)

$$r_n = \frac{(1 - \alpha)^2 k_n K_H K_{nR} C_H C_R}{(1 + K_H C_H + K_{nR} C_R)^2},$$
(4)

where α is the fraction of selective sites on the catalyst surface, k_s and k_n are rate constants of the surface reactions on selective sites and nonselective sites, respectively, K_H is adsorption equilibrium constant of hydrogen, K_{sR} and K_{nR} are adsorption equilibrium constants of reactant (MAA) on selective sites and nonselective sites, respectively, $K_{sP(-)}$ is adsorption equilibrium constant of (−)-MHB on selective sites, and C_H, C_R, and $C_{P(-)}$ are the liquid-phase concentrations of hydrogen, MAA, and (−)-MHB, respectively.

At the initial stage of the reaction, the inhibitory effect of the product on selective sites can be neglected. Therefore at this stage, r_s is given by Eq. (5) instead of Eq. (3).

$$r_s = \frac{\alpha^2 k_s K_H K_{sR} C_H C_R}{(1 + K_H C_H + K_{sR} C_R)^2}$$
(5)

From Eqs. (1), (4), and (5), OY of (−)-MHB at the initial stage of the reaction, p, is derived as

$$p = \frac{r_s}{r_t} = \frac{r_s}{r_s + r_n} = \frac{1}{1 + r_n/r_s}$$

$$= \frac{1}{1 + \left(\frac{1}{\alpha} - 1\right)^2 \cdot \frac{k_n}{k_s} \cdot \frac{K_{nR}}{K_{sR}} \cdot \frac{(1 + K_H C_H + K_{sR} C_R)^2}{(1 + K_H C_H + K_{nR} C_R)^2}}.$$
(6)

Partial derivative of p with respect to C_H or C_R gives

$$\frac{\partial p}{\partial C_H} = (2A/B) K_H C_R (1 + K_H C_H$$
$$+ K_{sR} C_R)(K_{sR} - K_{nR}),$$
(7)

$$\frac{\partial p}{\partial C_R} = (2A/B)(1 + K_H C_H)$$
$$(1 + K_H C_H + K_{sR} C_R)(K_{nR} - K_{sR}),$$
(8)

where $A = (1/\alpha - 1)^2 \dfrac{k_n}{k_s} \cdot \dfrac{K_{nR}}{K_{sR}}$, and

$$B = \left\{1 + A\left(\frac{1 + K_H C_H + K_{sR} C_R}{1 + K_H C_H + K_{nR} C_R}\right)^2\right\}^2$$

$$\cdot (1 + K_H C_H + K_{nR} C_R)^3.$$

Because $\alpha < 1$, A and B are positive. If $K_{nR} < K_{sR}$, OY increases with increasing hydrogen pressure (i.e., $\partial p/\partial C_H > 0$), and decreases with increasing MAA concentration (i.e., $\partial p/\partial C_R < 0$). If $K_{nR} = K_{sR}$, OY is independent of the changes in hydrogen pressure and in MAA concentration ($\partial p/\partial C_H = 0$, $\partial p/\partial C_R = 0$). As shown in Fig. 8, r_n reaches its maximum at a lower concentration of MAA than does r_s, which indicates that $K_{nR} > K_{sR}$ (9). The adsorption of MAA on selective sites is plausibly more difficult than on nonselective sites because of the steric hindrance of the modifier on selective sites. Thus it seems reasonable to regard $K_{nR} > K_{sR}$. Therefore, OY should decrease with increasing hydrogen pressure and increase with increasing MAA concentration ($\partial p/\partial C_H < 0$ and $\partial p/\partial C_R > 0$).

Figures 10 and 11 show simulated dependence of OY on hydrogen pressure and on MAA concentration, respectively, obtained by using Eq. (6), where $\alpha = 0.5$, $k_n/k_s = 1$, $K_{nR}/K_{sR} = 2.5$, $K_H = 0.2(\text{kg/cm}^2)^{-1}$, and $K_{sR} = 0.07(\text{vol}\%)^{-1}$. For NaBr-treated catalysts α was taken as 0.7. These values of parameters were selected by trial-and-error method so that the simulated curves of OY

and reaction rates could fit the experimental data. Taking into account that OY at the initial stage of the reaction is higher than at the last stage of the reaction (7), and that the dependence of initial OY on hydrogen pressure or MAA concentration is quite similar to that of final OY as shown in Figs. 2 and 5, the simulated curves in Figs. 10 and 11 appear to be in fairly good agreement with the experimental results shown in Figs. 3 and 5. Here the ratio of the rate constants, k_n/k_s, was taken as 1, according to the report of Ozaki et al. (4c). However, concerning the reaction rates, the simulated values of r_n and r_s were not necessarily in good agreement with the observed values shown in Figs. 7 and 8; simulated r_n was a little too small in comparison to r_s. This indicates that k_n should be larger than k_s and that, consequently, α should be larger than 0.5; the product of $(1/\alpha - 1)^2$ and k_n/k_s in Eq. (6) should not be changed in order to retain the simulated curves of OY shown in Figs. 10 and 11.

When the stirring speed decreases, the diffusion of reactants will become the main factor determining the reaction rate. In such a case, OY will be not so much affected by the changes in the rate of surface reaction on selective sites or nonselective sites, but will depend directly on α, i.e., on the fraction of selective sites. This seems to
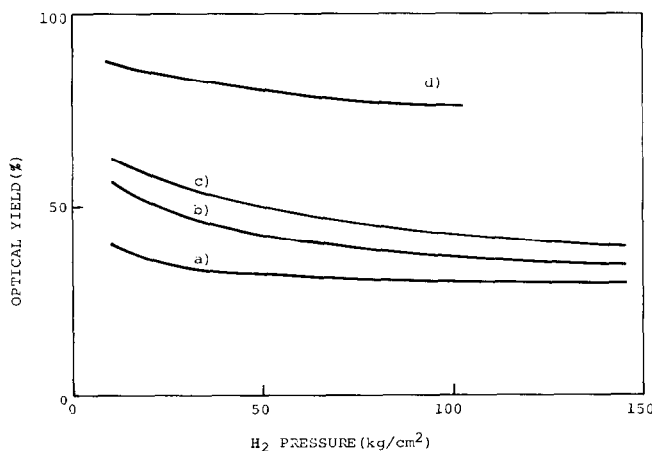

FIG. 10. H_2 pressure dependence of initial optical yield simulated by using Eq. (6). (a): 10% MAA; (b): 50% MAA; (c): 100% MAA; (d): 50% MAA ($\alpha = 0.7$ instead of 0.5).
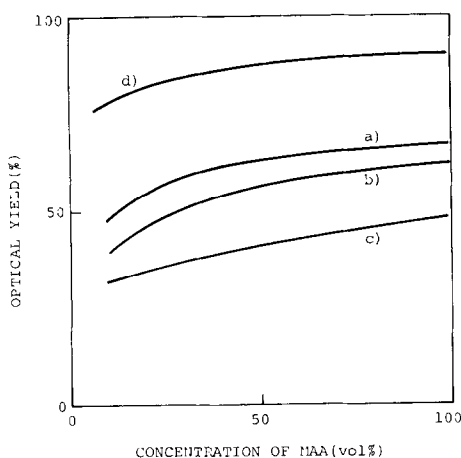
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FIG. 11. MAA concentration dependence of initial optical yield simulated by using Eq. (6). (a): 2 kg/cm² H₂; (b): 10 kg/cm² H₂; (c) 60 kg/cm² H₂; (d): 10 kg/cm² H₂ (α = 0.7 instead of 0.5).
</figure caption>

controlled by diffusion, for increase in OY r_n should decrease to a larger extent than r_s. One possibility to decrease r_n is to increase α. This has been accomplished by poisoning nonselective sites with NaBr added to the modifying solution (2, 8). The values of OY obtained in the presence of NaBr-treated catalyst (Figs. 3 and 5) correspond to the data shown in Figs. 10 and 11, simulated at α = 0.7. When α is constant, r_n can be decreased by addition of some unsaturated compounds which will adsorb on nonselective sites competitively with MAA. This is the case shown in Fig. 9. The added unsaturated compounds are expected to be hydrogenated mainly on nonselective sites because of the steric hindrance of modifier on selective sites.

be the case shown in Fig. 4, especially under higher hydrogen pressures, where the reaction rate is plausibly controlled by the diffusion of MAA. The effect of the stirring speed on OY in hydrogenations carried out under hydrogen pressure of 60 kg/cm² (Fig. 1) also supports this idea; under conditions of slow stirring OY is equal to the value shown in Fig. 4 and under conditions of vigorous stirring it is equal to the value shown in Fig. 3. Low OY in the reaction carried out under a stirring speed slower than 200 rpm can be due to the small amount of catalyst working effectively under such stirring conditions; when the catalyst-to-substrate ratio is very small, OY decreases, as mentioned above and in an earlier report from another laboratory (3a). The effect of the amount of catalyst on OY should be studied further taking into account the diffusion process.

Thus the data showing the relation between OY and hydrogen pressure, previously reported by other investigators (3a), were probably obtained under reaction conditions where contribution of the diffusion of reactants to the reaction rates could not be neglected.

In the case of reactions which are not

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