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Studies of the effects of the modification conditions on the hydrogenation rate for the enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid–NaBr-modified nickel catalyst

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The effects of the modification conditions on the hydrogenation rate and the enantio-differentiating ability (e.d.a.) for the enantio-differentiating hydrogenation of methyl acetoacetate were studied over an (*R*, *R*)-tartaric acid–NaBr-*in-situ*-modified nickel catalyst. It was revealed that a tartaric acid modification increased the hydrogenation rate irrespective of the presence of the auxiliary modifier, NaBr. In the presence of the tartaric acid, NaBr would have two roles, i.e., Na^+ activates the enantio-differentiating sites through the interaction with tartaric acid, and Br^- deactivates both the enantio-differentiating sites and non-enantio-differentiating sites. The e.d.a. values and the hydrogenation rate would be determined by the combination of these effects of Na^+ and Br^-.

KEY WORDS: enantio-differentiating; enantio-differentiating ability; hydrogenation rate; modification; nickel catalyst; tartaric acid.

1. Introduction

Many feasible strategies for producing optically active compounds have been widely studied. Successful and commonly applied strategies use enantio-selective homogeneous catalysts such as organometallic complexes or enzymes [1–3], enantio-selective heterogenized catalysts [4,5], and enantio-selective solid catalysts [6–8]. Among them, the enantio-selective solid catalysts are most promising solutions in this century for saving energy and resources, because solid catalysts have several advantages, that is, (i) easy preparation, (ii) easy separation from the reaction mixture, and (iii) easy reuse. A tartaric acid–NaBr-modified nickel catalyst is one of the successful enantio-differentiating solid catalysts. This catalyst produces optically active alcohols for the hydrogenation of various β-functionalized ketones and 2-alkanones. The enantio-differentiating ability (e.d.a.) of this catalyst reaches 80–98% for the hydrogenation of β-ketoesters [9], and 72–85% for the hydrogenation of 2-alkanones [8]. The optimization of the parameters affecting the e.d.a. and hydrogenation activity has been widely studied [8–10]. In order to understand the features of the modified catalyst, which is necessary for the development of a more efficient enantio-differentiating catalyst (having a higher e.d.a. and a higher hydrogenation activity) for various substrates, the kinetic studies of unmodified and modified catalysts have been carried out [11–16]. However, even for the effect of the tartaric acid modification on the hydrogenation rate, the experimental results were quite diverse. Yasumori *et al.* [12] and Woerde *et al.* [13] reported that the hydrogenation rate decreased after the modification of the tartaric acid. In contrast, Sachtler [15] and Keane [16] showed that the hydrogenation rate increased after the modification. One of the reasons for this divergence would be the difference of the modification conditions. The tartaric acid–NaBr-modified nickel catalyst is conventionally prepared by immersing a nickel catalyst in an aqueous solution of tartaric acid and NaBr (pre-modification method) [10]. By using this method, corrosion of the surface of the nickel catalyst occurred. Therefore, both the adsorption of the modifiers on the nickel surface and the change in the nickel surface affected the hydrogenation rate. Overlapped effects would cause confusion when interpreting the experimental results. We reported an alternative modification method, that is, an *in-situ*-modification method [17]. The *in-situ*-modification is very simple, i.e., tartaric acid and NaBr are added to the reaction media and then the mixture of a substrate and the modification reagents are subjected to hydrogenation. By this method, the adsorption of the modifiers is carried out in the reactor

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during the initial stage of the hydrogenation without corrosion of the nickel surface by the modification solution (reaction mixture). Therefore, the *in-situ*-modification is suitable for comparing the hydrogenation rate over the modified catalyst to that over the unmodified one. This is a significant advantage regarding the *in-situ*-modification. By using the *in-situ*-modification, we investigated the effect of the amount of acetic acid added to the reaction media on the hydrogenation rate of methyl acetoacetate over the tartaric acid-modified nickel catalyst and that over the unmodified nickel catalyst [18]. It is known that the addition of acetic acid increases the e.d.a. for the hydrogenation of methyl acetoacetate [19–20]. The results indicated that the hydrogenation rate is higher over the tartaric acid modified catalyst than over the unmodified one in the presence of acetic acid in the reaction media. This would be interpreted as the acetic acid increasing the e.d.a., because the hydrogenation rate of the enantio-differentiating site (e.d.-site), in which optically active compounds are produced with the aid of the tartaric acid, was specifically accelerated by the addition of acetic acid.

In this study, in order to investigate the clear-cut effect of the tartaric acid adsorption on the nickel surface on the hydrogenation rate, the hydrogenation of methyl acetoacetate was carried out without acetic acid in the reaction media. The effects of the adsorption of NaBr on the hydrogenation rate and the e.d.a. were also studied.

2. Experimental

The GLC measurement for determining the conversion was carried out using a Hitachi 263–30 gas chromatograph. The measurement of the optical rotations was carried out using a JASCO DIP-1000 polarimeter.

2.1. Reduced nickel catalyst

Nickel oxide (Wako Pure Chemical Industries, Ltd., lot LDQ3413) was reduced at 623 K in a hydrogen stream (40 $\mathrm{cm^3\ min^{-1}}$) for 1 h to produce the reduced nickel catalyst.

2.2. Enantio-differentiating hydrogenation of methyl acetoacetate over a reduced nickel

Methyl acetoacetate (5 g) was hydrogenated with the reduced nickel catalyst (0.33 g) in THF (10 $\mathrm{cm^3}$). The modification was carried out using an in-situ-modification method. (*R*,*R*)-tartaric acid and NaBr (the amounts were stated in the text) were added to the reaction mixture. As the solubility of the NaBr in the reaction mixture was low, NaBr was dissolved in 50 $\mathrm{mm^3}$ of distilled water. The hydrogenation was carried out in a stirred autoclave at an initial hydrogen pressure of 9 MPa and at 373 K. For measuring the hydrogenation rate, the stirring rate and the amount of the catalyst were examined in order to avoid the mass diffusion control. A stirring rate of 1370 r.p.m. and a catalyst amount of less than 0.5 g were the optimum conditions, where the mass diffusion control was avoided and the apparent hydrogenation rate would represent the intrinsic rate of hydrogenation. The hydrogen pressure in the reactor was recorded by a PC every one minute. The hydrogenation rate or the rate of alcohol production was expressed by the amount of hydrogen consumption during the reaction after the temperature of the autoclave reached the reaction temperature (373 K). After the reaction was completed, the reaction solution was separated by decantation from the catalyst, and then subjected to distillation. Conversion was determined by GLC analyses (5% Thermon 1000 on Chromosorb W at 383 K). For the repeated use of the catalyst, the used catalyst was recovered and washed three times with 10 $\mathrm{cm^3}$ of THF and then used for the 2nd run under the same reaction conditions except for the absence of tartaric acid and NaBr.

2.3. Determination of e.d.a

The e.d.a. of the modified catalyst was expressed using the optical purity of the hydrogenated product determined by polarimetry.

$$\text{Optical purity}/\% = ([\alpha]_{\mathrm{D}}^{20}\text{ of methyl3-hydroxybutyrate}/[\alpha]_{\mathrm{D}}^{20}\text{ of pure enantiomer}) \times 100$$

The $[\alpha]_{\mathrm{D}}{}^{20}$ of methyl 3-hydroxybutyrate was calculated using its specific gravity; $d_{20} = 1.058$. The specific optical rotation $[\alpha]_{\mathrm{D}}{}^{20}$ of the optically pure (*R*)-methyl 3-hydroxybutyrate is $[\alpha]_{\mathrm{D}}{}^{20} = -22.95°$ (neat) [10].

3. Results and discussion

In this study, as the modification was carried out by the *in-situ*-modification method, modifiers (tartaric acid and/or NaBr), which were not adsorbed on the nickel surface, remained in the reaction media during the 1st run and would cause a decrease in the hydrogenation rate and e.d.a. [18]. Therefore, the hydrogenation without the addition of modifiers to the reaction media over a recovered catalyst was carried out (the 2nd run). The results of the hydrogenation rate and the e.d.a. in the 2nd run are shown and used for the discussion in this paper.

3.1. Effect of the amount of tartaric acid on the rate of alcohol production and e.d.a.

3.1.1. Modification with tartaric acid

For the enantio-differentiating hydrogenation of methyl acetoacetate over a modified nickel catalyst, using tartaric acid and NaBr as modifiers and the addition of acetic acid to the reaction media were necessary to attain a high e.d.a. [21]. In the present study, first of all, in order to reveal whether or not the adsorption of the tartaric acid on the nickel surface increased the hydrogenation rate, the hydrogenation was carried out over the tartaric acid-modified nickel (not over the tartaric acid–NaBr-modified nickel) without the addition of acetic acid to the reaction media. These results are shown in figure 1. When the tartaric acid was added to the reaction media, i.e., the *in-situ* -modification by the tartaric acid was carried out, the hydrogenation rate increased. The maximum hydrogenation rate was attained with the 0.5 mg addition of tartaric acid and then the rate gradually decreased and remained constant. This would be attributed to the interaction between the adsorbed tartaric acid on the nickel surface and methyl acetoacetate, and to the increase in the concentration of methyl acetoacetate on the catalyst surface. However, an excess amount of the adsorbed tartaric acid could hinder the appropriate adsorption of methyl acetoacetate which resulted in the decreased e.d.a. It has been reported that there are two types of areas on the nickel surface; one prefers to adsorb tartaric acid and the other prefers to adsorb Br^- [22]. The area where the tartaric acid is adsorbed becomes the e.d.-site and produces optically active compounds. The area where no modifiers are adsorbed is the non-enantio-differentiating site (non-e.d.-site) where racemic compounds are produced. The present results indicate that the rate on an e.d.-site is higher than that on a non-e.d.-site. The dependence of the e.d.a. on the amount of tartaric acid was similar to that of the hydrogenation rate, i.e., when the hydrogenation rate was high, a high e.d.a. was attained. This would be attributed to the increase in the ratio of the e.d.-sites on the surface.

Figure 1 also shows the rate of the (*R*)-isomer production and that of the (*S*)-isomer production, which were calculated from the alcohol production rate and the e.d.a. values, based on the assumption that the ratio of the (*R*)-isomer production to that of the (*S*)-isomer production would be constant during the reaction. The rate of the (*R*)-isomer production increased with the addition of tartaric acid, while that of the (*S*)-isomer production decreased.

3.1.2. *Modification with tartaric acid and NaBr*

NaBr is known as an auxiliary modifier that increases the e.d.a. [21,23–29]. For the *in-situ*-modification, tartaric acid and NaBr are added to the reaction media.

Figure 2 shows the changes in the rate of the alcohol production and the e.d.a. over the nickel catalyst modified with tartaric acid and 0.4 mg of NaBr. The rate was significantly low without the addition of tartaric acid (modified only by 0.4 mg of NaBr), compared with the results obtained using the unmodified catalyst (0 mg of tartaric acid in figure 1). This low rate would be attributed to the deactivation of the catalyst by Br^-. The amount of Br^- could be greater on the nickel modified only with NaBr than that modified with both NaBr and tartaric acid. When nickel was modified with tartaric acid and NaBr, the rate of the alcohol production increased as in the case of the modification only by tartaric acid. An almost constant rate and e.d.a. (85%) were attained between the additions of 0.5–3.5 mg of tartaric acid. Compared to the results in figure 1, the hydrogenation rate in the presence of tartaric acid was almost the same in spite of the absence or presence of

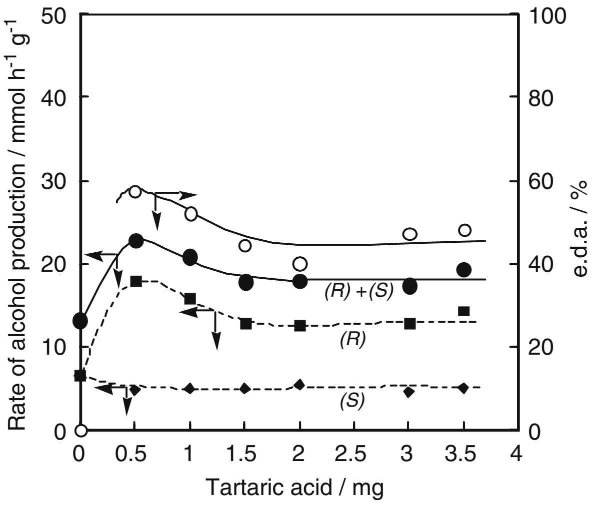

Figure 1. Enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid-modified nickel catalyst. ○: e.d.a., ●: Rate of alcohol production, ■: Rate of (*R*)-isomer production, ♦: Rate of (*S*)-isomer production, Modifying reagent: tartaric acid.

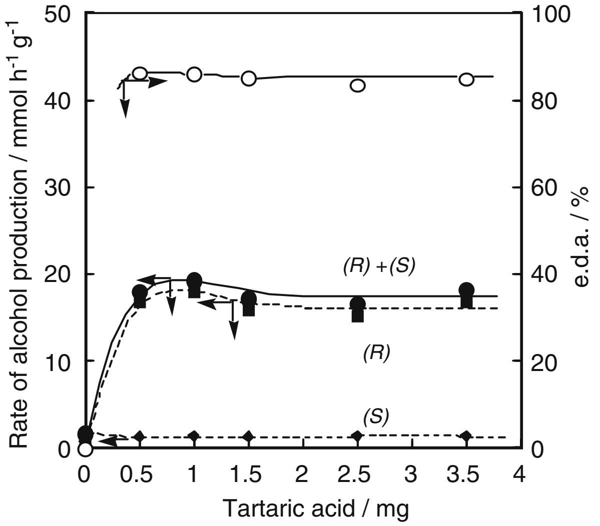

Figure 2. Enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid–NaBr-modified nickel catalyst. ○: e.d.a., ●: Rate of alcohol production, ■: Rate of (*R*)-isomer production, ♦: Rate of (*S*)-isomer production, Modifying reagent: tartaric acid and 0.4 mg of NaBr.

NaBr. On the contrary, the e.d.a. significantly depended on the presence or the absence of NaBr. The production rate of each alcohol isomer is also shown in figure 2. The rate of the (*S*)-isomer production was constantly very low, while the rate of the (*R*)-isomer production significantly increased with the addition of tartaric acid. The modification of tartaric acid and NaBr contributed to the increase in the rate of the (*R*)-isomer production and kept the (*S*)-isomer production as low as possible.

3.2. *Effect of the amount of NaBr on the rate of alcohol production and e.d.a.*

For the *in-situ*-modification method, the effects of the amount of NaBr as the auxiliary modifier on the rate of the alcohol production and e.d.a. were investigated. The results in the absence of tartaric acid in the reaction media (modification only by NaBr) are shown in figure 3. The rate of the alcohol production was very low and monotonously decreased with the increase in the amount of NaBr. By the modification only with NaBr, the catalytic activity would decrease with the increase in the amount of adsorbed Br^- on the surface.

The effect of the amount of NaBr on the rate of the alcohol production and the e.d.a. in the presence of tartaric acid (modification by tartaric acid and NaBr) are shown in figure 4. When nickel was modified by tartaric acid and NaBr, the rate of the alcohol production was much higher compared to the nickel modified only by NaBr (figure 3) in the range of 0–0.4 mg of NaBr. The rate of the alcohol production increased with the addition of up to 0.2 mg of NaBr. Beyond this amount, the rate decreased. The rate of the (*S*)-isomer production monotonously decreased with the increase in the amount of NaBr, while that of the (*R*)-isomer increased and then decreased.

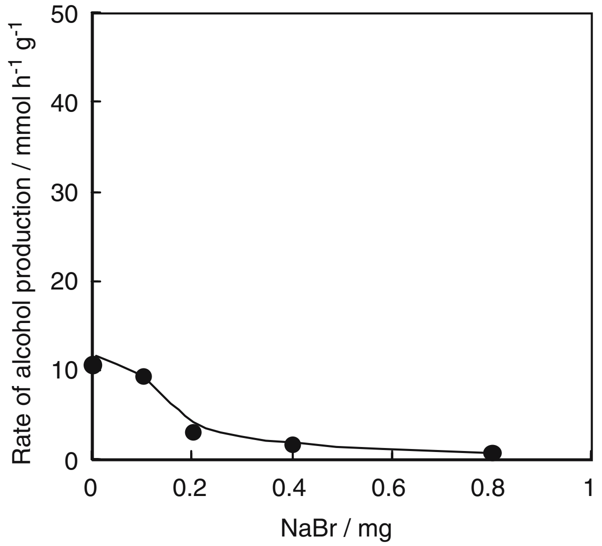

Figure 3. Enantio-differentiating hydrogenation of methyl acetoacetate over a NaBr-modified nickel catalyst. ●: Rate of alcohol production, Modifying reagent: NaBr.

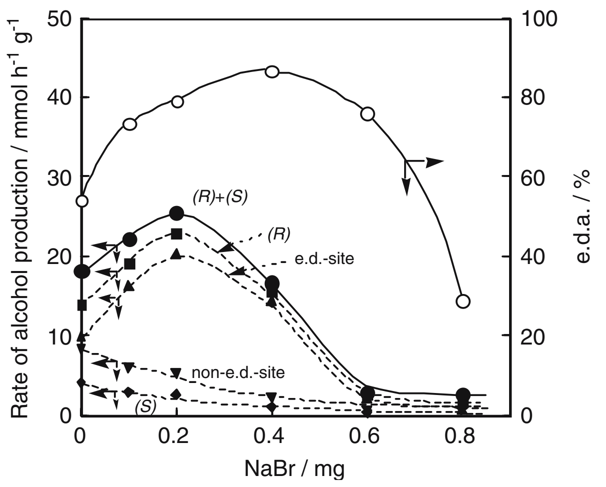

Figure 4. Enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid–NaBr-modified nickel catalyst. ○: e.d.a., ●: Rate of alcohol production, ■: Rate of (*R*)-isomer production : Rate of (*S*)-isomer production, ▲: Rate on the e.d.-site, ▼ : Rate on the non-e.d.-site, Modifying reagent: 2.5 mg of tartaric acid and NaBr.

It has been reported that the role of NaBr is the deactivation of the non-e.d.-site to increase the e.d.a. [22]. From the standpoint of this hypothesis, if the role of NaBr is only the deactivation of the non-e.d.-sites, the rate of the alcohol production should have been decreased by the modification of NaBr. However, based on the results in figure 4, the rate of the alcohol production increased with the addition of NaBr up to 0.2 mg and then decreased. It is known that alkali ions increase [30] and halogen ions decrease [10] the hydrogenation rate for the liquid phase hydrogenation of ketones over nickel catalysts. Based on the present results of the relation between the hydrogenation rate and e.d.a., we propose two roles of NaBr for the *in-situ* -modification, i.e., the deactivation effect by Br^- and the activation effect of Na^+. In order to evaluate this idea, the rate of the alcohol production on the e.d.-site and that on the non-e.d.-site were calculated based on the rate of each isomer production. For this calculation, only the (*R*)-isomer is assumed to be produced on the e.d.-site. These results are also shown in figure 4. The rate of the non-e.d.-site monotonously decreased with the increase in the amount of NaBr. These results would indicate that Br^- deactivated the non-e.d.-site on the nickel surface. On the other hand, the rate on the e.d.-site depended on the amount of NaBr. (i) 0–0.2 mg of NaBr: the combination of tartaric acid and Na^+ would significantly increase the hydrogenation rate on e.d.-site. The increase in the (*R*)-isomer production increased the e.d.a., (ii) 0.2–0.4 mg of NaBr: as the effectiveness of Br^- for decreasing the rate would be more significant than that of Na^+ for increasing the rate, the rate of alcohol production decreased with the increase in the amount of NaBr. However, the e.d.a. increased, because the ratio of the rate on the e.d.-site to that on the non-e.d.-site increased. (iii) 0.4–0.8 mg of NaBr: both the rate of alcohol production and the e.d.a. decreased. As the deactivation effect of Br^- was significant on the e.d.-site, the ratio of the rate on the e.d.-site to that on the non-e.d.-site (e.d.a.) decreased. The values of e.d.a. and the hydrogenation rate would be determined by the combination of the effects of Na^+ and Br^-.

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