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Role of acetic acid added to the reaction media for the enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid-modified nickel catalyst

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The role of acetic acid added to the reaction media for the enantio-differentiating hydrogenation of methyl acetoacetate over a (*R,R*)-tartaric acid-in-situ-modified nickel catalyst was studied from the viewpoint of the hydrogenation rate during repeated runs. The hydrogenation of methyl acetoacetate on the "enantio-differentiating sites" of a tartaric acid-modified nickel catalyst was specifically accelerated by the acetic acid added to the reaction media to increase the enantio-differentiating ability of the catalyst. In order to increase the enantio-differentiating ability, the addition of acetic acid to the reaction media was required in each run during the repeated use of the catalyst.

KEY WORDS: tartaric acid-modified nickel; enantio-differentiating; hydrogenation rate; acetic acid; site specific acceleration; repeated uses.

1. Introduction

The production of optically active compounds is an important issue for the pharmaceutical and agrochemical industries [1]. Many feasible strategies for designing the catalysts for this purpose have been proposed [2–4]. Enantio-differentiating solid catalysts, which are prepared by the modification of the solid with an intrinsic catalytic activity, have attracted much attention because of their easy handling, that is, easy preparation, easy separation, easy recovery and reuse, and ease scale up. Of the enantio-differentiating solid catalyst, a few systems have been intensively studied. Those are a tartaric acid modified nickel catalyst and a cinchona modified platinum group metal catalyst. The tartaric acid-modified nickel catalyst produces optically active alcohols for the enantio-differentiating hydrogenation of various β-functionalized ketones and 2-alkanones. The enantio-differentiating ability (e.d.a.) of this catalyst has reached 80–98% [5–6] for β-ketoesters and 72–85% for 2-alkanones [7]. The modified nickel catalyst can be prepared by two methods; a pre-modification and an in-situ-modification. The pre-modification has been conventionally studied for many years [8]. The activated nickel catalyst is soaked in an aqueous solution of tartaric acid (and if necessary, NaBr) at pH 3.2 and 373 K. The pre-modified nickel catalyst was prepared in a different vessel from the reactor before the hydrogenation of the substrate. On the other hand, the in-situ-modification is carried out in the reactor during the initial stage of the hydrogenation [9]. In this case, tartaric acid (and if necessary, NaBr) is added to the reaction mixture.

In order to determine the mechanism of the enantio-differentiation over a tartaric acid-modified nickel catalyst, kinetic studies have been studied using pre-modified catalysts [10–15]. However, it is difficult to evaluate the effect of the adsorption of the modifier on the hydrogenation activity over a pre-modified catalyst, because pre-modification in an aqueous solution at pH 3.2 and 373 K is a corrosive procedure that changes the nickel surface conditions and the surface area during the modification. On the other hand, by the in-situ-modification, tartaric acid was adsorbed on a nickel surface without such corrosion of the surface. Therefore, the in-situ-modification is suitable for comparing the hydrogenation activity over the modified catalyst with that over the unmodified one. This is a significant advantage regarding the in-situ-modification.

Concerning the additives to the reaction media for the enantio-differentiating hydrogenation of methyl acetoacetate, it was reported that the addition of a small amount of acetic acid increased the e.d.a. [5,16]. However, only a few studies on the mechanism of its effect have been reported. Harada *et al.* demonstrated that the added acetic acid converted sodium nickel tartrate to nickel hydrogen tartrate and that this increased the e.d.a. of the tartaric acid–NaBr-pre-modified nickel catalyst [17]. From a kinetic viewpoint, we briefly communicated that the addition of acetic acid accelerated the hydrogenation rate over the tartaric acid-in-situ-modified nickel catalyst compared with that over the unmodified one in the 1st run [18].

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For the characteristics of the in-situ-modification, the added tartaric acid would partly remain in the reaction media during the 1st run. In order to avoid the effect of the remaining tartaric acid in the reaction media for evaluating the intrinsic effect of acetic acid, the hydrogenation was carried out without the addition of tartaric acid to the reaction media during the reuse of the recovered catalyst in the present study. It can be presumed that the amount of tartaric acid in the reaction media is negligible in the subsequent runs. Whether or not the addition of acetic acid to the reaction media was required in each run was also examined.

2. Experimental

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

2.1. Reduced nickel catalyst

Nickel oxide (Wako Pure Chemical Industries, Ltd., lot LDQ3413) was calcined in air at 1373 K for 6 h. The resultant nickel oxide was reduced at 623 K in a hydrogen stream (40 cm^3 min^{-1}) for 1 h to produce the reduced nickel catalyst.

2.2. Fine nickel powder catalyst

Commercially available fine nickel powder (Vacuum Metallurgical Co., Ltd., Chiba, Japan, mean particle diameter: 20 nm, specific surface area: 43.8 m^2 g^{-1}, bulk density: 0.19 g cm^{-3}) was treated with a hydrogen stream (40 cm^3 min^{-1}) for 0.5 h at 553 K before the hydrogenation.

2.3. 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 a mixture of THF (10 cm^3) and acetic acid. For the hydrogenation over an in-situ-modified catalyst, (*R,R*)-tartaric acid (1.7 mg) was added to the reaction mixture. The hydrogenation was carried out in a stirred autoclave at the 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 automatically recorded every minute by a PC. The hydrogenation rate 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 cm^3 of THF and then used for the 2nd run under the same reaction conditions except for the absence of tartaric acid.

2.4. Enantio-differentiating hydrogenation of methyl acetoacetate over a fine nickel powder

Methyl acetoacetate (5 g) was hydrogenated with a fine nickel powder catalyst (0.5 g) in a mixture of THF (10 cm^3) and acetic acid (0.1 g). (*R,R*)-tartaric acid (0.1 g) and NaBr (2 mg in 50 mm^3 water) were added to the reaction media only in the 1st run. Hydrogenation was carried out in a reciprocal shaking autoclave at the initial hydrogen pressure of 9 MPa and at 373 K. For the repeated use of the catalyst, the used catalyst was recovered and washed three times with 10 cm^3 of THF and then used for the next run under the same reaction conditions except for the absence of the tartaric acid and NaBr. Post-treatment of the hydrogenated product was the same as that with the reduced nickel catalyst.

2.5. 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.

$$\text{Optical purity}\,/\% = ([\alpha]_D^{20} \text{ of methyl 3-hydroxybutyrate} \,/[\alpha]_D^{20} \text{ of pure enantiomer}) \times 100$$

The specific optical rotation $[\alpha]_D{}^{20}$ of the optically pure (*R*)-methyl 3-hydroxybutyrate is $[\alpha]_D{}^{20} = -22.95°$ (neat) [8].

3. Results and discussion

Figure 1 shows the effect of the addition of acetic acid to the reaction media on the hydrogenation rate over a tartaric acid-in-situ-modified reduced nickel and an unmodified reduced nickel catalyst. For the hydrogenation of 2-octanone over an in-situ-modified reduced nickel, it was reported that all the tartaric acid added to the reaction media was not adsorbed on the nickel surface and that the rest remained in the reaction media [19]. In the present study on the hydrogenation of methyl acetoacetate, in order to examine the effect of the remaining tartaric acid in the reaction media in the 1st run, the hydrogenation was carried out over the recovered catalyst with the freshly prepared reaction mixture in the absence of tartaric acid (the 2nd run). When the

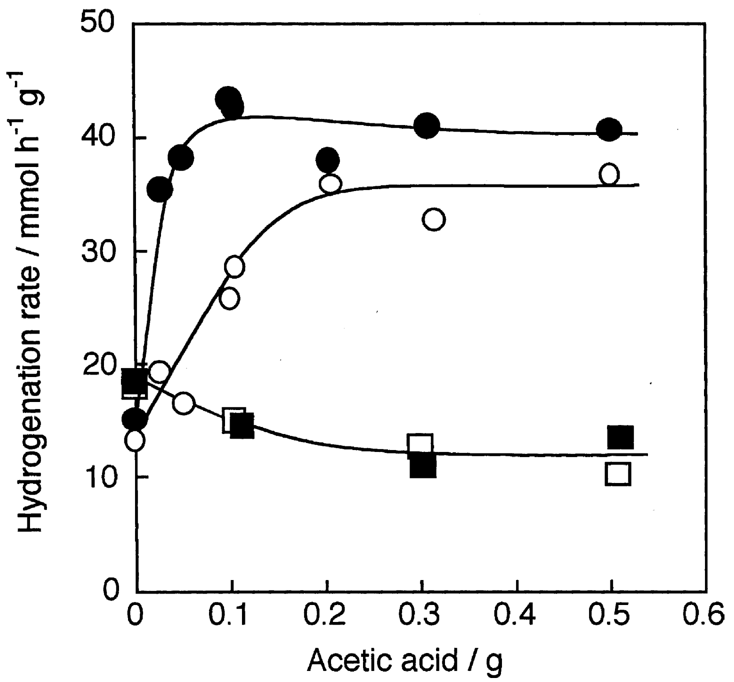

Figure 1. Effect of the addition of acetic acid on the hydrogenation rate over a reduced nickel ○: Tartaric acid-modified nickel (1st run) [18], ●: Tartaric acid-modified nickel (2nd run), □: Unmodified nickel (1st run) [18], ■: Unmodified nickel (2nd run).

modified nickel catalyst was used, the hydrogenation rate was significantly increased with the addition of a small amount of acetic acid to the reaction media and reached a plateau. In the absence of acetic acid, the hydrogenation rate in the 2nd run was almost the same as that in the 1st run. However, when acetic acid was added to the reaction media, the rate was higher in the 2nd run than in the 1st run. The large effect of the acetic-acid addition in the 2nd run would be attributed to the fact that no tartaric acid was added during the 2nd run. The dissolved tartaric acid in the 1st-run reaction media may inhibit the acceleration of the hydrogenation rate, which is induced by the addition of acetic acid. More acetic acid was required for reaching a plateau in the 1st run than in the 2nd run. This suggests that, in the 1st run, the added acetic acid interacts with the tartaric acid

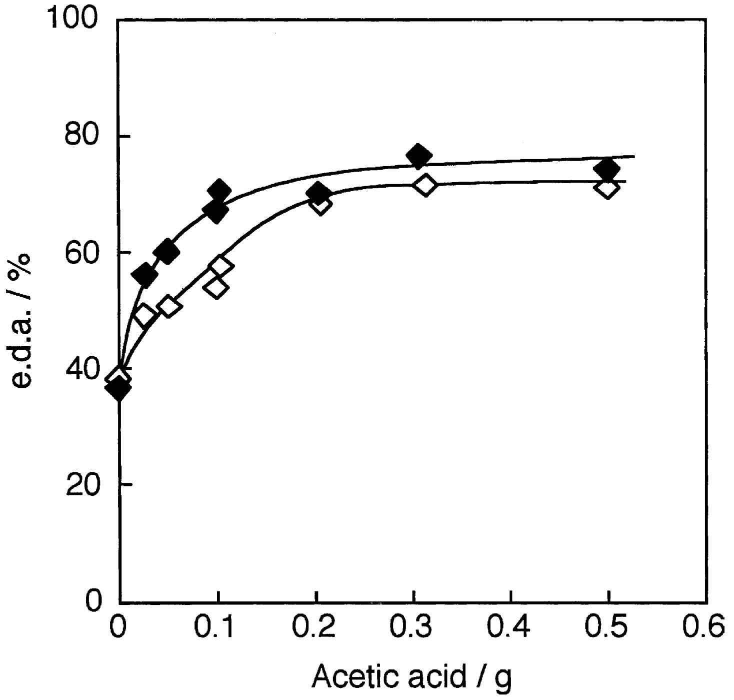

Figure 2. Effect of the addition of acetic acid on e.d.a. ◇: 1st run [18], ◆: 2nd run, Catalyst: tartaric acid-in-situ-modified reduced nickel.

Table 1
Effect of the repeated use of the catalyst on the hydrogenation rate and the e.d.a. in the presence or absence of acetic acid

Addition of acetic acid (0.1 g)		Hydrogenation rate/ mmol h^{-1} g^{-1}		e.d.a. / %	
1st run	2nd run	1st run	2nd run	1st run	2nd run
No	No	13	15	38	37
Yes	Yes	29	43	61	71
Yes	No	29	32	61	56

Catalyst: Tartaric acid-in-situ-modified reduced nickel.

in the reaction media as well as that adsorbed on the catalyst surface. For the hydrogenation over the unmodified catalyst, the hydrogenation rate gradually decreased with the increase in the added acetic acid. The acetic acid would be competitively adsorbed against the substrate on the nickel surface. The hydrogenation rates of the 1st and 2nd runs were almost the same, regardless of the acetic acid addition.

The effect of the addition of acetic acid on the e.d.a. is shown in figure 2. As was reported in the literature [5,16], the addition of acetic acid increased the e.d.a. which eventually reached a plateau. The e.d.a. values in the 2nd run were higher than those in the 1st run in the presence of acetic acid. The required amount of acetic acid for reaching a plateau was more in the 1st run than in the 2nd run. This tendency was the same as the effect on the hydrogenation rate shown in figure 1.

It has been reported that there are two types of active sites on the tartaric acid-modified nickel catalyst, that is, the "enantio-differentiating site" and the "non-enantio-differentiating site" [5]. The active site where tartaric acid is adsorbed is called the "enantio-differentiating site" and optically active compounds are produced there. The "non-enantio-differentiating site" is where tartaric acid is not adsorbed and racemic compounds are produced.

The active sites of the unmodified catalyst are considered to be "non-enantio-differentiating sites". On the other hand, the modified catalyst has both "enantio-differentiating sites" and "non-enantio-differentiating sites". All of the described results can be explained by the idea that the added acetic acid specifically accelerates the hydrogenation of methyl acetoacetate on the "enantio-differentiating sites". One of the reasons for the increase in the e.d.a. by the addition of acetic acid would be the acceleration of the hydrogenation rate on the "enantio-differentiating site". Since the acceleration of the hydrogenation rate was not observed for the unmodified catalyst, this acceleration would be attributed to the interaction of acetic acid with the tartaric acid on the "enantio-differentiating site".

In order to investigate the addition requirement of the acetic acid in each run for increasing the e.d.a., the effect of the repeated use of the catalyst was examined in the presence or absence of acetic acid. Table 1 shows these results. When acetic acid was not added to the reaction media in the 1st or in the 2nd run, the hydrogenation rate and the e.d.a. were almost the same in both runs. As mentioned in figures 1 and 2, the addition of acetic acid both in the 1st and the 2nd runs increased the hydrogenation rate and the e.d.a. in the 2nd run. When acetic acid was added to the 1st run and not to the 2nd run, the hydrogenation rate was almost the same and the e.d.a. slightly decreased. These results indicate that the addition of acetic acid in each run was required to increase the hydrogenation rate, and hence, the e.d.a.

The effect of the addition of acetic acid on the e.d.a. was also examined over a tartaric acid–NaBr-in-situ-modified fine nickel powder. Figure 3 shows these results. In the presence of acetic acid, the e.d.a. values of 50–70% were attained during the repeated use of the catalyst. In the 4th and 7th runs, the e.d.a.s decreased in the absence of acetic acid compared with that of the preceding run in the presence of acetic acid. However, the e.d.a. recovered in the subsequent run in the presence of acetic acid. These results support the addition requirement of the acetic acid in each run for the repeated use of the catalyst for increasing the e.d.a. Tartaric acid was required to be only added in the 1st run, because it would be firmly adsorbed on the nickel surface. On the other hand, the acetic acid was required to be added to each run for increasing the e.d.a. This suggests that the acetic acid was easily desorbed from the surface during the reuse of the catalyst. This would be attributed to the larger pK_a value of acetic acid ($pK_a = 4.74$) than that of tartaric acid ($pK_{a1} = 2.93$).

4. Conclusion

The role of acetic acid in the reaction media was studied for the enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid–(NaBr)-in-situ-modified nickel during the repeated use of the recovered catalyst. The added acetic acid would specifically accelerate the hydrogenation rate on the "enantio-differentiating site" to increase the e.d.a. of the catalyst. The hydrogenation rate in the 2nd run was greater than that in the 1st run, and hence, the e.d.a. was higher in the 2nd run. This would be attributed to the remaining tartaric acid in the reaction media in the 1st run, which

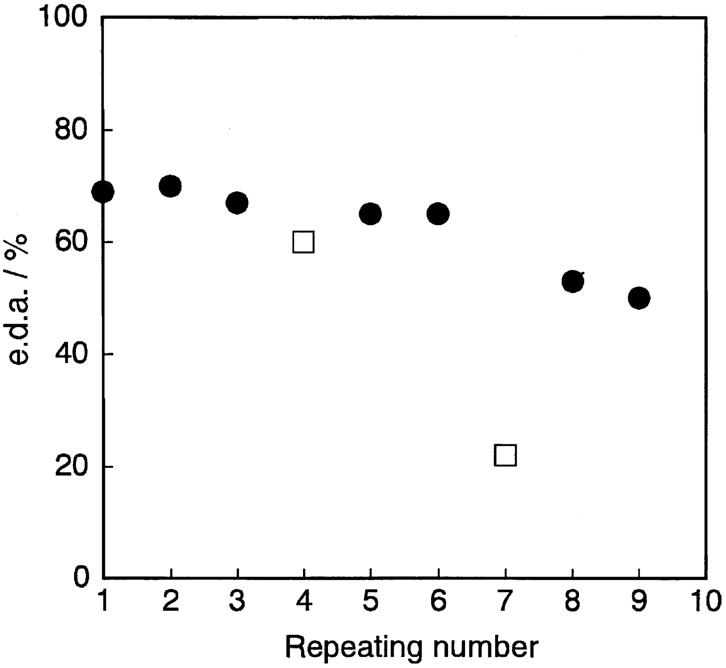

Figure 3. Effect of the presence of acetic acid in the reaction media on e.d.a. during the repeated use of the catalyst ●: In the presence of acetic acid, □: In the absence of acetic acid, Catalyst: tartaric acid–NaBr-in-situ-modified fine nickel powder.

inhibited the acceleration of the hydrogenation rate induced by the acetic acid. Acetic acid was required to be added to the reaction media in each run during the repeated use of the catalyst in order to increase the e.d.a.

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