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Hydrogen Pressure Dependence in Enantioselective Hydrogenation of *α*,*β*-Unsaturated Acids with Cinchonidine-Modified Pd/TiO_2 Catalyst

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The enantioselectivity in the hydrogenation of (*E*)-2,3-diphenyl-2-propenoic acid with a cinchonidine-modified 5wt%Pd/TiO_2 catalyst decreases with increasing pressure of hydrogen up to 5 MPa contrary to the tendency observed in the hydrogenation of aliphatic acids, probably because of the difference in the adsorption strength of the substrates on both modified and unmodified sites.

Enantioselective hydrogenation of the C=C double bonds in *α*, *β*-unsaturated acids is known to be catalyzed by palladium catalysts modified with cinchona and vinca-type alkaloids.[1,2] The best enantiomeric excesses (ee) of the products reported to date are 72% and 66% for aromatic and aliphatic acids, respectively.[3,4] These ee values are still moderate, and the influence of many factors, both in the catalyst preparation and reaction conditions, remains to be clarified to give a satisfactory improvement of this catalytic system.

After studying the influence of the reaction medium, we have reported that polar solvents are preferable for the hydrogenation of (*E*)-2,3-diphenyl-2-propenoic acid ((*E*)-*α*-phenylcinnamic acid, **1**),[5,6] while Baiker et al. have found that nonpolar solvents provide higher selectivities in the hydrogenation of (*E*)-2-methyl-2-pentenoic acid (**2**).[7] They have proposed that the high hydrogen solubility in nonpolar solvents is advantageous for enantiodifferentiation, based on the result that ee in the hydrogenation of **2** in cyclohexane increases considerably with ascending pressure of hydrogen up to about 6 MPa.[7] However, no explanation has so far been given for the hydrogen pressure dependence. In the enantioselective hydrogenation of **1**, the highest ee was obtained in polar solvents, such as *N*,*N*-dimethylformamide and 1,4-dioxane containing 2.5 vol% of water, under an atmospheric pressure of hydrogen; a change in the hydrogen pressure from 0.1 to 0.5 MPa resulted in a slight decrease in ee.[3] Therefore, it is necessary to confirm that the two systems, i.e., aliphatic acid in nonpolar solvents and aromatic acid in polar solvents, exhibit opposite tendencies in the hydrogen pressure dependence, before discussing the mechanism for this interesting reaction. Here we report on the effects of hydrogen pressure, over a wider range, on the enantioselective hydrogenation of **1** as well as on the hydrogenation of (*E*)-2-methyl-2-butenoic acid (tiglic acid, **3**) as another aliphatic acid, by using a 5wt%Pd/TiO_2 catalyst modified with cinchonidine (**CD**).

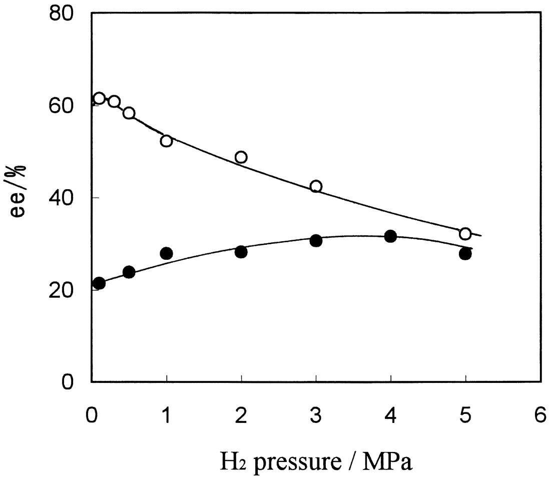

Fig. 1. Hydrogen pressure dependence of the enantioselectivity in the hydrogenations of (*E*)-2,3-diphenyl-2-propenoic acid (○) and (*E*)-2-methyl-2-butenoic acid (●).

As shown in Fig. 1, the enantioselectivity obtained in the hydrogenation of **1** decreased monotonously with an increase in the hydrogen pressure from 0.1 to 5 MPa, while the reactions under lower partial pressures of hydrogen (0.02 and 0.035 MPa in helium) provided slightly lower selectivities (54–56%ee). On the other hand, ee for the hydrogenation of **3** increased with increasing pressure of hydrogen up to 4 MPa, similarly to the tendency reported for **2**,[7] although a slight decline of ee was observed under higher H_2 pressures. The positive hydrogen pressure dependence of ee, as observed for the hydrogenations of **2** and **3**, does not support our previous presumption[3] that the competitive adsorption of hydrogen and **CD** on the catalyst surface leads to the decrease in ee under a high pressure of hydrogen. It is well known that the enantioselective hydrogenation of *α*, *β*-unsaturated acids with modified Pd catalysts is much slower than the reactions with the unmodified catalysts, in contrast to the hydrogenation of *α*-ketoesters with cinchona-modified Pt catalysts.[1,2] Actually, the reaction rates under an atmospheric pressure of hydrogen were decreased by the introduction of **CD** about one and two orders of magnitude for the hydrogenations of **1** and **3**, respectively. Therefore, a slight change in the ratio of the modified and unmodified sites will exert a considerable influence not only on the product ee but also on the overall reaction rate. If the ratio of the modified sites increased with increasing pressure of hydrogen, the overall reaction rates with the modified catalyst must have decreased. This is in conflict with the observation that the reaction rates with the modified catalyst, estimated from the pressure change during the reaction, increased with increasing initial pressure of hydrogen for both systems. These findings indicate that the ratio of the selective sites to all the reaction sites on the modified catalyst is kept constant under different hydrogen pressures. Thus, the observed hydrogen pressure dependence of the product ee should be explained by the change in the relative reaction rates on modified and unmodified sites.

In the reaction of **1**, the acid–base interaction between **1** and the adsorbed modifier may be strong enough,[8] and the rate of the selective reaction will hardly be affected by a change in the hydrogen pressure. Based on the effects of solvents and additives, it has been suggested that the rate-determining step for the selective reaction on modified sites is the product desorption step,[6,9] which is in harmony with the idea that hydrogen concentration has little effect on the selective reaction rate of **1**. On the other hand, the nonselective reaction of **1** with unmodified catalysts was accelerated almost in proportion to the hydrogen pressure. Thus, it is clear that the higher hydrogen pressure brings about the larger contribution of the nonselective reaction on unmodified sites to the overall reaction rate, leading to a decrease in the product ee in the hydrogenation of **1**.

Although the hydrogenation rate of **3** with the unmodified catalyst was also increased with increasing pressure of hydrogen, the extent of the acceleration was only one tenth as compared to the case of **1**. The marked difference in the hydrogen pressure dependence of the activities on the unmodified catalyst between the two systems can be explained in terms of the relative concentrations of adsorbed substrates and hydrogen by assuming the Langmuir–Hinshelwood mechanism. The adsorption of **3** on Pd catalyst is expected to be weaker than that of **1**, because **1** has phenyl groups with high affinity to Pd surfaces. In addition, the surface concentration of hydrogen is higher in the nonpolar solvent, used for the reaction of **3**, than in polar solvents. Therefore, the additional increase in the hydrogen pressure will not cause such a remarkable increase in the reaction rate of **3** as observed in the reaction of **1**. On the other hand, when the reaction on modified sites is controlled by the surface reaction, the selective reaction can be directly accelerated by the increase in the surface concentration of hydrogen; the adsorption of **3** on modified sites will be stronger than that on unmodified sites. Preliminary experiments on competitive adsorption of **1** and **3**, carried out with the unmodified catalyst in methanol, indicated that the adsorption of **3** is not as strong as **1**, in agreement with the above expectation. Subsequent introduction of **CD** into the mixture resulted in an immediate adsorption of **CD** and, at the same time, in a complete desorption of **3** once adsorbed on the catalyst surface, indicating that the interaction of **3** with **CD** is much weaker than that of **1**. Furthermore, the selective reaction of **3** was scarcely accelerated at all by the addition of amines or polar solvents,[10] suggesting that the rate-determining step for the selective reaction of **3** is different from that for **1**, i.e., not the product desorption step but perhaps the surface reaction step. Taking into account these observations, we conclude that the reaction on modified sites, rather than the reaction on unmodified sites, is preferentially accelerated by the increase in the surface concentration of hydrogen, which leads to an increase in the product ee in the hydrogenation of **3**.

Thus, the different behavior in the hydrogen pressure dependence of the product ee between the reactions of **1** and **3** is attributed to the fact that the increase in the hydrogen pressure brings about a fair acceleration of the nonselective reaction on the unmodified sites in the hydrogenations of **1**, while the selective reaction on the modified sites is preferentially accelerated in the case of **3**. The different hydrogen pressure dependences of the reaction rates are explained in terms of the relative adsorption strength of these substrates both on the modified and unmodified sites.

Although the use of different solvents in each hydrogenations resulted in similar tendencies in the hydrogen pressure dependence, the use of solvents having different polarity will exert some influence on the adsorption-desorption behavior of the reactants.[6] Furthermore, the amount and the conformation of the adsorbed modifier can be affected by the solvent employed, which also leads to a change in the apparent ratio of the modified sites. Therefore, it seems difficult to explain the solvent effect on the enantioselectivity, as observed for the reaction of **2**,[7] by means of the hydrogen solubility only. The solvent effect on the reaction of **1** was described elsewhere.[6]

Experimental

The 5wt%Pd/TiO_2 catalyst was prepared by a precipitation-deposition method according to the procedure described in our previous paper.[11] The modifier **CD** (Wako Pure Chemical, 99%), the substrates **1** (Aldrich, 98%) and **3** (Tokyo Kasei, $>$ 98%), and the solvents (Wako Pure Chemical, Special grade) were used as received. The solvents employed so as to give reasonable reaction rates and ee values were 1,4-dioxane containing 2.5vol% of water for **1** and hexane for **3**. The reactions were performed at ambient temperatures (ca. 293 K for **1** and ca. 303 K for **3**) in a 30-mL stainless steel autoclave equipped with a magnetic mixing system (1000 rpm), except for the reactions under atmospheric pressure of hydrogen. The freshly reduced catalyst (0.02 g) was transferred to a glass inlet with 10 cm^3 of solvent, and the modifier (0.02 mmol) and the reactant (1 mmol) were added successively. After the hydrogen uptake finished, the catalyst was filtered off and the hydrogenation products were analyzed by HPLC on a chiral column (CHIRACEL OJ-R, DAICEL) and by GLC on a chiral capillary column (Cyclodextrine-β-236M-19, Chrompack) for the hydrogenations of **1** and **3**, respectively. The enantioselectivity is expressed as the enantiomeric excess (ee) at full conversion: ee (%) $= 100 \times (S - R)/(S + R)$. Detailed procedures for the catalyst preparation and the product analyses are described elsewhere.[11]

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