

# Solvent effect on the structure sensitivity in enantioselective hydrogenation of $\alpha$ , $\beta$ -unsaturated acids with modified palladium catalysts

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## Abstract

The solvent effect on the enantioselective hydrogenation of  $\alpha$ ,  $\beta$ -unsaturated carboxylic acids has been studied using cinchonidine-modified Pd/TiO<sub>2</sub> catalysts with different Pd dispersions. The structure sensitivity observed in the hydrogenation of (*E*)-2,3-diphenyl-2-propenoic acid was found to depend on the property of the solvent used, especially in the dispersion range lower than 0.2. In the solvents with low polarity, the optimal Pd dispersions are much lower than those observed in polar and protic solvents. The catalysts with the lowest dispersions, however, exhibit unexpectedly poor selectivities irrespective of the solvent employed. With the reactions of smaller aliphatic acids: (*E*)-2-methyl-2-pentenoic acid and (*E*)-2-methyl-2-butenic acid, the Pd dispersion dependencies are much milder and independent of the solvents. These variations of the structure sensitivity could be explained by the difference in the steric interference of the metal surface with the modifier–substrate adduct in different solvents.

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## 1. Introduction

Enantioselective hydrogenation of the C=C double bonds in  $\alpha$ ,  $\beta$ -unsaturated carboxylic acids is known to be catalyzed by palladium catalysts modified with cinchona alkaloids [1,2]. Enantiomeric excesses (ee) of up to 72, 66, and 47% have been reported for the hydrogenations of (*E*)-2,3-diphenyl-2-propenoic acid ((*E*)- $\alpha$ -phenylcinnamic acid (**1**)) with a Pd/TiO<sub>2</sub> catalyst [3], (*E*)-2-methyl-2-pentenoic acid (**2**) with a Pd/Al<sub>2</sub>O<sub>3</sub> catalyst [4], and (*E*)-2-methyl-2-butenic acid (tiglic acid (**3**)) also with a Pd/Al<sub>2</sub>O<sub>3</sub> catalyst [5], respectively, all modified with cinchonidine (**CD**). However, these enantioselectivities are still moderate and not satisfactory for practical use. The influence of many factors remains to be clarified, in contrast to the hydrogenations of the C=O double bonds in  $\alpha$ - and  $\beta$ -keto esters with modified Pt and Ni catalysts, respectively [1,2,6]. Little has been known about the suitable surface of Pd metal, although the metal-particle morphology is thought to be of greater

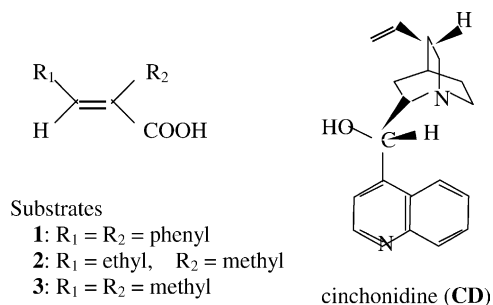
importance for these reactions with large spatial demands than for simpler reactions [2].

As for the catalyst preparation, we have reported on the effects of preparation parameters such as support materials and texture, Pd loadings, precipitation procedures, and the activation method of the catalyst precursors [7–9]. In the course of the studies to optimize the catalyst preparation conditions, we have found that the selectivity, obtained for the reaction of **1** in a mixed solvent of *N,N*-dimethylformamide (DMF) and water (10 vol.%), varies depending on the degree of Pd dispersion ( $D_M$ ) with a maximum at  $D_M$  of around 0.2 and with a sudden decrease of ee at lower  $D_M$  [9,10]. In order to explain this peculiar dispersion dependence, we have suggested that the substrate structure would exert considerable influence on the adsorption mode and strength of the modifier–substrate adduct; the phenyl groups around the C=C bond in **1** would cause a difficulty in the tight adsorption of the adduct on a flat Pd surface with an efficient orientation (Scheme 1).

Concerning the modifier structure, it has been shown that the most stable conformation of **CD** depends on the solvent polarity [11]. Therefore, the modifier–substrate interaction,

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Scheme 1. Structures of the substrates and the modifier.

and hence the adsorption mode of the adduct on Pd surface, may be influenced by the solvent employed, which could lead to a different dispersion dependence of the enantioselectivity. Here we describe some new observations about the Pd dispersion dependencies of the hydrogenation of **1**, carried out in various solvents with different polarity or in those containing water. The hydrogenation of small aliphatic acids, **2** and **3**, was also examined for comparison.

## 2. Experimental

### 2.1. Materials

Supported Pd catalysts (0.5–50 wt.%Pd/TiO<sub>2</sub>) were prepared by a precipitation-deposition method with PdCl<sub>2</sub> and a non-porous titania (JRC-TIO-3, Catalysis Society of Japan) according to the procedure described in our previous paper [9], and reduced at 473 K for 1 h in a hydrogen flow immediately before use. A Pd black catalyst (Wako Pure Chemical, 9.3 m<sup>2</sup>/g) was used for comparison without the heat treatment. The degree of Pd dispersion ( $D_M$ ) was estimated from the surface area of Pd metal determined by a CO chemisorption measurement at 323 K, assuming the CO/Pd ratio of 1:2. Most of the solvents (Wako Pure Chemical, special grade), CD (Wako Pure Chemical, 99%), and the substrates, **1** (Aldrich, 98%) and **3** (Tokyo Kasei, >98%), were used as received. Ethyl acetate and tetrahydrofuran (THF) were dehydrated overnight with molecular sieve 4 Å.

### 2.2. Enantioselective hydrogenation

#### 2.2.1. Hydrogenation of **1**

The freshly reduced catalyst (0.02 g) was modified with CD (0.02 mmol) by stirring for 20 min in 10 cm<sup>3</sup> of solvent under hydrogen atmosphere. One millimole of **1** was introduced to the mixture and hydrogenated at 298 K under an atmospheric pressure of hydrogen and an agitation speed of 1200 rpm. After the hydrogen uptake finished, the hydrogenation products were isolated from the reaction mixture, esterified to the methyl ester by the reaction with CH<sub>3</sub>OH/BF<sub>3</sub>·CH<sub>3</sub>OH, and analyzed by HPLC on a chiral column (CHIRACEL OJ-R, DAICEL). The enantioselectivity is expressed as the enantiomeric excess (ee)

of (*S*)-(+)-2,3-diphenylpropionic acid at full conversion: ee (%) =  $(S - R) \times 100 / (S + R)$ .

#### 2.2.2. Hydrogenations of **2** and **3**

Since high H<sub>2</sub> pressures were found to be favorable for the hydrogenation of **2** [12] and **3** [13], the reactions were performed in a 30 ml stainless steel autoclave equipped with a magnetic mixing system (1000 rpm). The freshly reduced catalyst (0.02 g) was transferred to a glass inlet with 10 cm<sup>3</sup> of a solvent, and CD (0.02 mmol) and a substrate (1 mmol) were added successively. The hydrogenations were carried out under 4 MPa of hydrogen at ca. 288 and 303 K for **2** and **3**, respectively. The products were analyzed by GLC using a chiral capillary column (Cyclodextrine-β-236M-19, Chrompack). The enantioselectivity is expressed as ee of *S*-isomer at 80–100% conversion.

## 3. Results and discussion

In our previous study on the enantioselective hydrogenation of **1** [10], the Pd dispersion dependence was examined only in a polar solvent, because the highest ee was obtained for the reactions carried out in polar solvents containing water, and also because the use of a non-polar solvent, hexane, brought about very low activities [14]. However, the reactions in solvents with low polarity, such as THF and ethyl acetate, have been found to exhibit different structure sensitivity from that observed in 90% DMF. In Fig. 1, the ee values, obtained for the hydrogenation of **1** in different solvents, are plotted against the degree of Pd dispersion ( $D_M$ ). In the range of  $D_M > 0.2$ , ee mildly decreased with increasing dispersion in all the solvents examined, similarly to the typical dependency reported in enantioselective hydrogenations of α- and β-keto esters with modified Pt and Ni

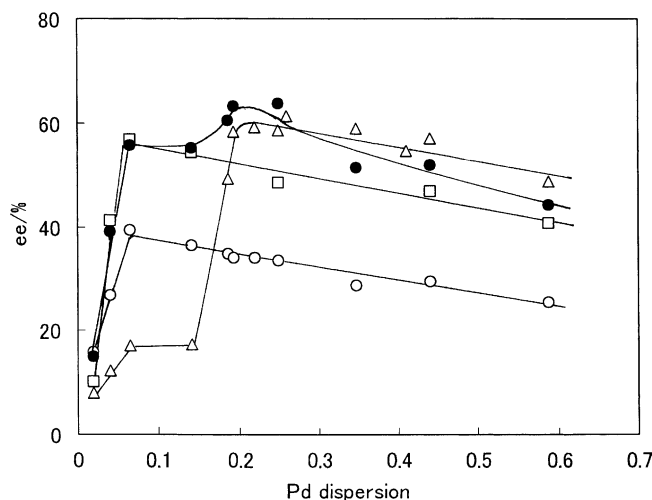


Fig. 1. Pd dispersion dependence of the enantioselective hydrogenation of: (*E*)-2,3-diphenyl-2-propenoic acid (**1**) in different solvents. Solvent: ethyl acetate (○); THF (□); 1,4-dioxane containing 2.5 vol.% water (●); DMF containing 10 vol.% water (△).

catalysts, respectively [1,2,6]. On the other hand, in the range of lower dispersions the feature of the structure sensitivity was different depending on the solvent used; the highest ee was obtained at much lower dispersion in solvents with low polarity than in polar or protic solvents. Although a sudden drop in ee at  $D_M < 0.2$  was also observed in the hydrogenation carried out in 1,4-dioxane containing a small amount of water, it was not as remarkable as observed with the reactions in DMF containing 10 vol.% water [10]. In ethyl acetate and THF, the ee increased smoothly with increasing Pd loading up to 30% ( $D_M > 0.06$ ). It is worthy noting that the catalysts with the lowest dispersions (50%Pd/TiO<sub>2</sub> and Pd black catalysts) exhibited poor selectivities in all the solvents examined, in great contrast to the tendencies reported for the enantioselective hydrogenations of methyl acetoacetate with tartaric acid-modified Ni catalysts [15–17] and of isophorone with Pd catalysts modified by a vinca-type alkaloid [18]. The unexpectedly low selectivity as well as the low activity of the catalysts with poor Pd dispersions can be explained by the steric hindrance between the rigid substrate–modifier adduct and the flat Pd surface; it would be difficult for the C=C bond in **1**, having bulky substituent groups around it, to approach the flat Pd surface with an efficient orientation [10].

Since the significant difference in the dispersion dependences, observed in the range of  $0.06 < D_M < 0.2$ , seemed to be related to the solvent polarity, the ee values obtained in the hydrogenations with 30%Pd/TiO<sub>2</sub> (catalyst A,  $D_M = 0.06$ ) were compared to those with 5%Pd/TiO<sub>2</sub> (catalyst B,  $D_M = 0.25$ ) in various solvents. As listed in Table 1, the relative selectivities ( $ee_A/ee_B$ ) of catalyst A to catalyst B, obtained in ethyl acetate and THF, were slightly higher than those obtained in polar or protic solvents. Addition of water to various solvents, especially to non-polar solvents, always greatly increased the activities of both catalysts as we reported previously [14], but favored the selectivity of 5%Pd/TiO<sub>2</sub> catalyst only. However, no significant tendency was observed between the relative selectivity and the dielec-

tric constant of the polar or protic solvents, including the water-containing solvents.

Bürgi and Baiker investigated the conformational behavior of **CD** in different solvents and reported that a conformer called Open(3) is stable in non-polar solvent while the stability of the closed conformers, Closed(1) and Closed(2), relative to the Open(3) increases with solvent polarity [11]. They showed that the ee, obtained in the enantioselective hydrogenation of ketopantolactone with a **CD**-modified Pt catalyst, exhibits the same solvent dependence as the fraction of conformer Open(3) in solution, and suggested that this conformer plays a crucial role for the enantio-differentiation. Although it is difficult to estimate the adsorbed structure of the **CD**-substrate complex from the stable conformer in solution, the solvent effect on the Pd dispersion dependence of ee, shown above in the range of  $0.2 > D_M > 0.06$ , could also be attributed to the difference in the most stable **CD** conformation in different solvents. The interaction between **CD** and the substrate, and accordingly, the adsorption mode and strength of the **CD**-substrate adduct on the Pd surface will be strongly influenced by the **CD** conformation. The steric interference of the **CD**-**1** adduct with the flat Pd surface seems to be less dominant in the solvents with low polarity than in polar or protic solvents; the **CD** conformer Open(3) could interact with **1** keeping the C=C bond close to the Pd surface. However, it has been shown by spectroscopic experiments that **CD** adopts Open(3) conformation in the presence of acids, and that alkenoic acids are present as dimers in non-polar solvents [5,11,19]. The adsorption of a **CD**:acid 1:2 adduct on the Pd surface will be sterically less hindered than that of a 1:1 adduct. Therefore, another possible explanation of our experimental results is the variation of the nature of modifier–substrate interaction from 1:1 to 1:2 adduct with decreasing polarity of the solvent. The sudden drop in ee observed at  $D_M < 0.2$  for the reactions in polar solvents can be caused by the steric hindrance to the adsorption of the 1:1 adduct on the flat Pd surface. Even for the reactions in non-polar solvents, flat Pd surface

Table 1  
Solvent effect on enantioselective hydrogenation<sup>a</sup> of (*E*)-2,3-diphenyl-2-propenoic acid (**1**)

Solvent	Dielectric constant	ee <sub>A</sub> (%) <sup>b</sup> ( $D_M = 0.06$ )	ee <sub>B</sub> (%) <sup>c</sup> ( $D_M = 0.25$ )	ee <sub>A</sub> /ee <sub>B</sub>
Ethyl acetate	6.0	39	34	1.15
THF	7.6	57	49	1.16
3-Methyl-1-butanol	15.2	30	33	0.91
2-Propanol	19.9	34	44	0.77
Ethanol	24.6	42	45	0.93
Methanol	32.7	38	49	0.78
Acetonitrile	35.9	50	55	0.91
DMF	36.7	41	53	0.77
1,4-Dioxane + water (9:1)	–	49	58	0.84
THF + water (9:1)	–	39	52	0.75
Acetonitrile + water (9:1)	–	51	55	0.93
DMF + water (9:1)	–	17	59	0.29

<sup>a</sup> Reaction conditions: catalyst, 20 mg; **CD**, 0.02 mmol; substrate, 1 mmol; solvent, 10 ml; 298 K; H<sub>2</sub>, 0.1 MPa.

<sup>b</sup> ee obtained with 30%Pd/TiO<sub>2</sub> catalyst.

<sup>c</sup> ee obtained with 5%Pd/TiO<sub>2</sub> catalyst.

larger than ca. 20 nm, corresponding to  $D_M < 0.06$ , would be disadvantageous for the adsorption of the rigid acid–base complex between the bulky substrate **1** and the CD conformer Open(3); a somewhat curved structure with terraces and steps seems to be indispensable to the catalysts for this reaction. Further research is required for detailed discussion on the interaction mode of modifier–substrate adduct and the optimal structure of Pd surface where the adduct can be adsorbed effectively.

In the case of Pd catalysts with higher dispersions, other factors such as the solvating ability have been considered to interpret the favorable effect of polar solvents [14]. Since the contribution of unmodified sites to the overall reaction will increase in the hydrogenations with highly dispersed catalysts, the kinetic effects of solvent on the reactions over modified and unmodified sites will become more important. Furthermore, a highly dispersed catalyst affords various types of Pd surface where the CD–**1** adduct could be adsorbed in a manner keeping the C=C bond close to the surface irrespective of the geometry of the adducts.

With the hydrogenation of smaller aliphatic acids **2** and **3**, we have reported that the Pd dispersion dependence of ee, observed in hexane, showed a considerably different tendency as compared to the results with **1** [10]. Although the highest ee was obtained also with the catalyst of  $D_M \sim 0.2$ , the reactions were almost structure insensitive especially in the range of higher dispersions. Concerning the solvent effect on the hydrogenation of aliphatic acids, the use of polar solvents is known to be detrimental to the reaction of **2** [12]. Also, in the hydrogenation of **3**, the use of ethanol as a polar solvent resulted in the considerably low ee's shown in Fig. 2, while the dispersion dependence was similar to that obtained in hexane. A distinct change in ee was observed again at around  $D_M \sim 0.2$ . The significant decrease in the activity and selectivity of the catalysts with the lowest Pd dispersion, shown above for the reaction of **1** (Fig. 1), was not detected

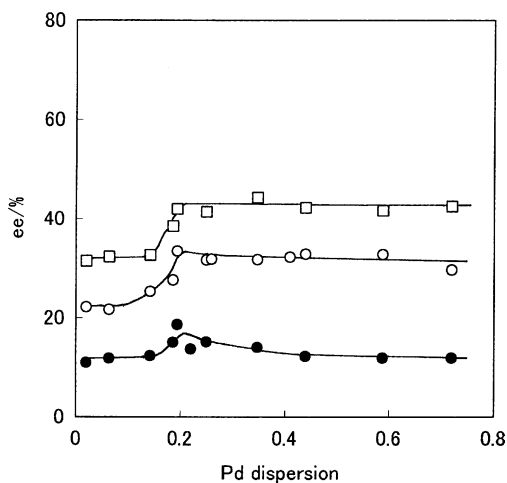


Fig. 2. Pd dispersion dependence of the enantioselective hydrogenation of: (*E*)-2-methyl-2-pentenoic acid (**2**) carried out in hexane (□), and (*E*)-2-methyl-2-butenic acid (**3**) in hexane (○) and in ethanol (●).

in the reactions of **2** and **3**. The remarkable difference in the dispersion dependence between **1** and the smaller substrates (**2** and **3**) can be attributed to the difference in the steric interference of the modifier–substrate adduct with the Pd surface, as discussed above and in our previous paper [10]. Taking into account the strong adsorption of CD on Pd with the quinoline ring parallel to the metal surface and the rigid H-bonded structure of the CD–substrate adduct [19,20], a change in the solvent would not affect the interaction mode and strength between a small substrate and Pd surface so much, as compared to the case of a bulky substrate **1** having large substituent groups around the C=C bond. This would explain the result that the solvent effect on the Pd dispersion dependence of the hydrogenation of **2** or **3** is not as obvious as in the case of **1**.

#### 4. Conclusions

The structure sensitivity observed in the enantioselective hydrogenation of (*E*)-2,3-diphenyl-2-propenoic acid with cinchonidine-modified Pd/TiO<sub>2</sub> catalysts is solvent dependent, especially in the reactions with low dispersion catalysts. The optimal dispersion was around 0.06 for the reactions in THF and ethyl acetate and ca. 0.2 in polar or protic solvents. The activity and selectivity of the catalysts with the lowest dispersion decreased linearly with decreasing Pd dispersion in all the solvents examined. On the other hand, the reactions of smaller aliphatic acids: (*E*)-2-methyl-2-pentenoic acid and (*E*)-2-methyl-2-butenic acid, were much less sensitive to the Pd dispersion, and exhibited similar dispersion dependencies in polar and non-polar solvents. It is suggested that the significant difference in the structure sensitivity could be attributed to the change in the steric effect of the Pd metal surface on the adsorption of the modifier–substrate adduct which depends on the substrate structure and on the most stable modifier conformation in different solvents.

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