Effect of Palladium Dispersion on the Enantioselective Hydrogenation of α,β-Unsaturated Acids with Modified Pd/TiO_2 Catalysts

Yuriko Nitta,* Takeshi Kubota ,† and Yasuaki Okamoto†

Niihama National College of Technology, Yagumo-cho, Niihama, Ehime 792-8580

†Department of Materials Science, Shimane University, Matsue, Shimane 690-8504

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The enantioselective hydrogenation of the C=C double bonds in (*E*)-2-methyl-2-butenoic acid, (*E*)-2-methyl-2-pentenoic acid, and (*E*)-2,3-diphenyl-2-propenoic acid has been studied using cinchonidine-modified Pd/TiO_2 catalysts with different metal loadings of between 0.5 to 30 wt%. For all of the substrates examined, those catalysts with degrees of Pd dispersion lower than 0.2 have been shown to be rather detrimental for obtaining a high enantioselectivity, as opposed to the tendencies reported for the hydrogenations of keto esters with modified Pt and Ni systems. The hydrogenations of the aliphatic acids are almost structure insensitive with a slight decrease in the enantioselectivity at Pd dispersions lower than 0.2, which is in great contrast to the hydrogenation of the aromatic acid. A similar difference in the structure sensitivity has been observed with catalysts modified by a larger modifier, (−)-dihydroapovincaminic acid ethyl ester. The influence of the substrate structure on the adsorption mode and the strength of the modifier-substrate complex is discussed in relation to the size of the Pd ensemble on the catalyst surface.

The enantioselective hydrogenation of the C=C double bonds in α, β-unsaturated acids and ketones is catalyzed by palladium catalysts modified with cinchona and vinca-type 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*)-α-phenylcinnamic acid, **1**) with a Pd/TiO_2 catalyst,[3] (*E*)-2-methyl-2-pentenoic acid (**2**) with a Pd/Al_2O_3 catalyst,[4] and (*E*)-2-methyl-2-butenoic acid (tiglic acid, **3**) also with a Pd/Al_2O_3 catalyst,[5] respectively, all modified with cinchonidine (**CD**). Isophorone, an α, β-unsaturated ketone, has been hydrogenated to give 55% ee by using a Pd black catalyst modified with (−)-dihydroapovincaminic acid ethyl ester (**DHVIN**).[6] However, these ee values are still not satisfactory for practical use and the influence of many factors remains to be clarified, in contrast to the hydrogenations of the C=O double bonds in α- and β-keto esters with modified Pt and Ni catalysts, respectively, where enantioselectivities close to 99% ee have been achieved as a result of extensive studies.[1,2,7–10]

Especially, little has been known about the effect of the structural properties of the Pd catalysts, 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 influence of the metal dispersion on the hydrogenations of C=O double bonds in α- and β-keto esters, it has been reported that, in general, high metal dispersions are detrimental for obtaining high enantioselectivities.[10,11] In the hydrogenation of methyl acetoacetate with tartaric acid-modified Ni catalysts, the enantioselectivity increases monotonously with increasing crystallite size of Ni under otherwise fixed conditions.[12–15] Maximum optical yields of 87–91% were achieved on Ni catalysts with very low Ni dispersions.[16,17] With the hydrogenation of α-keto esters, a similar tendency was reported for the hydrogenation of ethyl pyruvate with **CD**-modified Pt/Al_2O_3 catalysts.[18–20] Blaser et al.[20] concluded that the Pt dispersion is the most important catalyst parameter; in order to obtain high optical yields the Pt dispersion should be lower than 0.2. From these effects of the metal dispersion, it has been speculated that a flat arrangement of the metal atoms is favorable for the adsorption of a modifier and a substrate interacting with each other in a proper conformation.[1] Recently, Zuo et al.[9,21] have reported that the reaction with Pt catalysts is less structure sensitive; better enantioselectivity was achieved over polymer-stabilized small Pt clusters. They have suggested a possibility of enantioface recognition even working for the limited surface of the smaller Pt particles. Under these situations, studies on the correlation between the enantioselectivity and the metal dispersion will contribute to an understanding of the enantioface-differentiation mechanism, also in the hydrogenation of C=C double bonds with **CD**-modified Pd catalyst, and to improving these catalytic systems.

Since an optical yield of 30.5% was reported in the hydrogenation of **1** with a **CD**-modified 5 wt% Pd/C catalyst,[22] we have investigated the influence of process variables to optimize the catalyst preparation and reaction conditions for this reaction.[3,23–30] In preparing Pd catalysts, we have found that the use of a nonporous titania with a moderate specific surface area is preferable as the support material; the presence of Pd metal particles in micropores of the supports exerts a detrimental effect on the enantioselectivity of the modified catalysts.[27] For studies on the effect of metal dispersion, surface contaminants, which may affect the adsorption of **CD**, must also be eliminated as thoroughly as possible. Using a series of Pd/TiO_2 catalysts prepared with a nonporous titania under optimum conditions, the influence of Pd loading has been studied on the enantioselective hydrogenation of **1**.[29] It was found that the enantioselectivity (ee) depends on the degree of Pd dispersion (D_M) with a maximum at D_M of around 0.2–0.3 and with a sudden decrease at D_M lower than 0.2. In order to explain this peculiar dispersion dependence, we have suggested that the substrate structure would exert some influence on the adsorption mode of the modifier-substrate complex; phenyl groups around the C=C bond in **1** would cause a difficulty in the tight adsorption of the complex on a flat Pd surface with an efficient orientation. Here, we report on the dispersion dependencies observed in the hydrogenations of smaller aliphatic acids, **2** and **3**, with a series of **CD**- and **DHVIN**-modified Pd/TiO$_2$ catalysts, comparing them with the previous results obtained for **1**.

Experimental

Supported Pd catalysts (0.5–30 wt% Pd/TiO$_2$) were prepared by a precipitation–deposition method with PdCl$_2$ and a nonporous titania (JRC-TIO-3, Catalysis Society of Japan) according to the procedure described in our previous paper.[29] A portion of the dried catalyst was reduced by heating at 473 K for 1 h in a hydrogen flow of 8 dm^3/h immediately before use. A commercial Pd black catalyst (Wako Pure Chemical, 9.3 m^2/g) was used without a heat treatment in hydrogen. 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. **CD** (Wako Pure Chemical, 99%), **1** (Aldrich, 98%), **2** (Aldrich, 99%), **3** (Tokyo Kasei, > 98%), and the solvents (Wako Pure Chemical, Special grade) were used as received. **DHVIN**, prepared by the catalytic hydrogenation of vinpocetine,[31] was supplied from Tungler's laboratory.

Hydrogenation of 1. The freshly reduced catalyst (0.02 g) was modified with **CD** or **DHVIN** (0.02 mmol) by stirring for 20 min in 10 cm^3 of *N*,*N*-dimethylformamide (DMF), containing 10 vol% of water, or methanol, respectively, under a hydrogen atmosphere. One mmol 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 a reaction with CH$_3$OH/BF$_3$·CH$_3$OH, and analyzed by HPLC on a chiral column (CHIRACEL OJ-R, DAICEL).[29] The enantioselectivity is expressed as the enantiomeric excess (ee) at full conversion: ee (%) = 100 × $|S-R|/(S + R)$.

Hydrogenations of 2 and 3. 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^3 of hexane, and the modifier (0.02 mmol) and the substrate (1 mmol) were added successively. The hydrogenations were carried out at 288 K and 303 K for **2** and **3**, respectively, under 4 MPa of hydrogen. The products were analyzed by GLC using a chiral capillary column (Cyclodextrine-*β*-236M-19, Chrompack). The enantioselectivity is expressed as the enantiomeric excess (ee) at 80–100% conversion.

Results and Discussion

With an increase in Pd loading on TiO$_2$ from 0.5 to 30 wt%, the degree of Pd dispersion smoothly decreased from 0.72 to 0.06, as expected. In Fig. 1, the ee values for the predominant *S*-products, attained in the hydrogenations of **2** and **3** with the **CD**-modified Pd/TiO$_2$ catalysts, are plotted against the degrees of Pd dispersion, together with the results for the bulky substrate **1**.[29] The data obtained with a Pd black catalyst (D_M = 0.02) are also included for a comparison. For all of the substrates examined here, the catalysts with fairly low Pd dispersions ($D_M < 0.2$) are rather detrimental for obtaining high enantioselectivities, contrary to the positive effect of lower metal dispersion reported for the Pt and Ni systems,[10,11] as mentioned above.

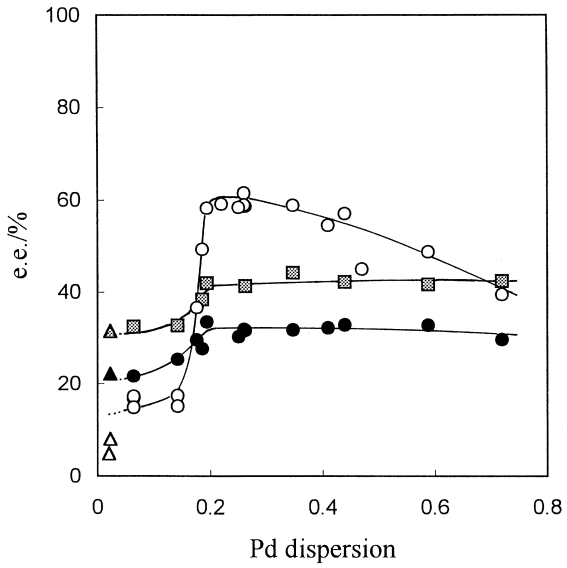


Fig. 1. Correlation between the degree of Pd dispersion and the enantioselectivity of cinchonidine-modified Pd/TiO$_2$ catalysts in the hydrogenations of (*E*)-2,3-diphenyl-2-propenoic acid (○, △), (*E*)-2-methyl-2-pentenoic acid (▨, ◬), and (*E*)-2-methyl-2-butenoic acid (●, ▲). △, ◬, ▲: Data for Pd black catalyst. Reaction conditions: see text.

It is also noted that the dispersion dependences of ee for the hydrogenations of **2** and **3** are quite different from the dependence for **1**. First, the sudden decrease in the ee values observed in the range of $D_M < 0.2$ is much less profound than that observed in the hydrogenation of **1**, and the ee values for **2** and **3** in this range are rather larger than that for **1**. Second, the enantioselective hydrogenations of **2** and **3** are almost structure insensitive, especially in the range of higher dispersion ($D_M > 0.2$). These differences can be explained in terms of the adsorption mode and the strength of the modifier-substrate complex on the surface Pd metal, as already suggested in our previous paper.[29]

It is reasonable to suppose that well-crystallized particles with large ensembles of regularly arranged metal atoms in the surface generally have a better chance to adsorb large molecules of both the modifier and the substrate effectively. Therefore, the higher enantioselectivity is expected on catalysts with lower metal dispersion, especially when the interaction between the adsorbed modifier and the substrate is relatively weak, or flexible, as in the cases of modified Ni and Pt systems.[2,10,20] In the hydrogenation of *α*, *β*-unsaturated acids with **CD**-modified Pd catalysts, the modifier is known to adsorb with the quinoline ring of **CD** parallel to the metal surface, and the basic **CD** molecule is supposed to interact with the acidic substrate molecule via two hydrogen bonds involving the (C-9)–OH group and quinuclidine nitrogen of **CD**.[26,32] Because of the rigid H-bonded structure and the large steric constraint of the modifier-substrate complex in this case, the role which the metal surface plays in the stage of enantio-face differentiation would not be as important as in the cases of Ni and Pt systems. This may explain the relatively mild structure sensitivity observed in the hydrogenation of **1** in a dispersion range higher than 0.2. As for the hydrogenations of smaller substrates, **2** and **3**, with catalysts having higher Pd dispersions, the role of the metal surface played in the enantio-face differentiation becomes less important, because the adsorption mode of the modifier-substrate complex might be dominated by the tight adsorption of **CD** with a sufficiantly controlled orientation. This could lead to the observed structure insensitivity in the range $D_M > 0.2$ for the reactions of **2** and **3**.

On the other hand, when **CD** is adsorbed tightly enough on a flat surface of a much larger Pd ensemble, it could be difficult for **1**, having bulky phenyl groups around the C=C bond, to keep an effective interaction with **CD** and to approach the Pd surface to be hydrogenated enantioselectively. This could lead not only to a sudden decrease in the selectivity, but also to a simultaneous decrease in the activity of the catalyst with a fairly low Pd dispersion. In fact, a drastic decrease in the hydrogenation rate per unit surface area of Pd (r_{Pd}) was observed for the catalysts of $D_M < 0.2$.[29] When the substrate is relatively small and does not have such bulky substituent groups around the C=C bond as **1** has, the low Pd dispersion could cause little problem. This may be the reason for the much smaller extent of the loss of enantioselectivity observed in the hydrogenations of **2** and **3** with catalysts with $D_M < 0.2$. In the hydrogenation of another small substrate, isophorone, with **CD**-modified Pd catalysts, Tungler et al. reported that a Pd black catalyst (D_M = 0.1) gave a higher ee than a Pd/C catalyst (D_M = 0.5).[31]

Thus, the striking difference in the dispersion dependence between **1** and the smaller substrates (**2** and **3**) is attributable to the difference in the steric hindrance between the modifier-substrate complex and the flat Pd surface. In other words, it seems likely that the Pd surface should have a curved structure with terraces and steps where the bulky modifier-substrate complex can adsorb in a manner necessary for the efficient enantio-discrimination without any steric hindrance. A rough estimation of the specific hydrogenation rates for **1** on modified and unmodified sites, based on the values of ee and r_{Pd}, indicates that the hydrogenation rate on modified sites reaches a maximum at D_M = 0.2–0.3, and mildly decreases with increasing dispersion, while those on unmodified sites are almost constant in the range of higher Pd dispersions. Assuming that the hydrogenation of **1** on unmodified sites is structure insensitive, as is known for the hydrogenation of ethylene and benzene on Pd catalysts, the fraction of unmodified sites on the Pd surface is speculated to be almost constant. Therefore, not the fraction of modified sites in all the active sites, but the intrinsic activity of the modified sites, which depends on the adsorption mode and strength of the modifier-substrate complex, seems to be more important in determining the enantioselectivity of modified Pd catalysts with different metal dispersions.

Despite the different tendencies in the Pd dispersion dependence, as mentioned above, a distinct change in ee was observed at around D_M = 0.2 for every substrate examined here. This seems to be related to the size of the common modifier **CD**. The degree of Pd dispersion of 0.2 corresponds to the Pd crystallite size of 5 to 6 nm, which is large enough to afford a flat surface for the **CD** molecule to adsorb with the quinoline ring parallel to the metal surface. Based on simple geometric considerations for the cinchona-modified Pt system, Garland and Blaser suggested that a modified ensemble should consist of one adsorbed cinchona molecule and 10–20 platinum atoms.[33] Taking into account the concentration of surface Pd atoms (1.27×10^{19} m^{-2}),[34] the space-demand for the adjacent adsorption of one **CD** molecule and one large substrate molecule in a prescribed configuration is roughly estimated to be up to 30–40 Pd atoms on the catalyst surface, in fair agreement with the crystallite size mentioned above. Molecular modeling and theoretical calculations will be needed for a more quantitative discussion.

A similar difference in the structure sensitivity was observed between the hydrogenations of **1** and **3** with **DHVIN**-modified Pd catalysts, as shown in Fig. 2. In these hydrogenations *R*-enantiomers are predominant in the products. The hydrogenation of **3** is again almost structure insensitive in contrast to the hydrogenation of **1**. On the other hand, the distinct change in ee is not found around D_M = 0.2. Even in the hydrogenation of **1**, a sudden drop in ee was observed only for the Pd black catalyst. This may be attributed to the difference in the structure of the modifiers; **DHVIN** has a much larger and more rigid aromatic ring structure than does **CD**, as shown in Scheme 1. Taking into account the difference in the sizes of **DHVIN** (ca. 1 nm) and the quinoline ring of **CD** (ca. 0.6 nm), the flat Pd surface for the effective adsorption of a **DHVIN** molecule is estimated to be roughly three-times as large as that for a **CD** molecule. Although the **DHVIN**-substrate interac-

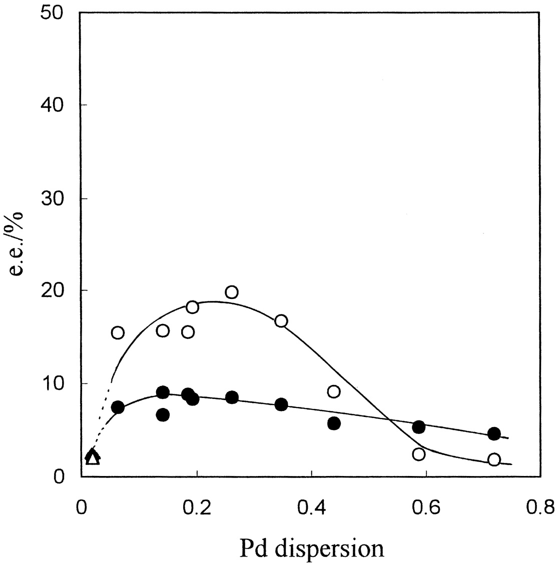
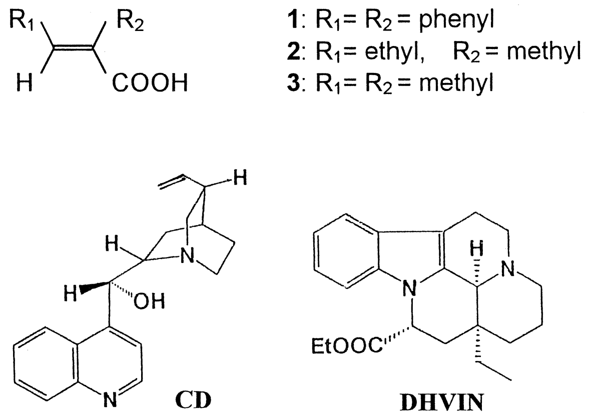


Fig. 2. Correlation between the degree of Pd dispersion and the enantioselectivity of **DHVIN**-modified Pd/TiO_2 catalysts in the hydrogenations of (*E*)-2,3-diphenyl-2-propenoic acid (○, △) and (*E*)-2-methyl-2-butenoic acid (●, ▲). △, ▲: Data for Pd black catalyst. Reaction conditions: see text.



Scheme 1. Structure of Substrates and Modifiers.

tion and the adsorption mode of the complex are not well known at present, the rigid structure of **DHVIN** makes it probable that the required size of a flat Pd ensemble for the efficient adsorption of the **DHVIN**-substrate complex is more than twice as large as the size estimated above for the **CD**-substrate complex. Therefore, the critical Pd dispersion in the reaction with **DHVIN** would shift to a dispersion much smaller than $D_M = 0.2$, which seems to be compatible with the result shown in Fig. 2.

Different hydrogen pressures and solvents were employed in this study so as to carry out the reactions under optimal conditions for respective substrates. In order to make sure that the Pd dispersion dependence is not affected by the difference in the hydrogen pressure, the reaction of **1** under 4 MPa (instead of 0.1 MPa) of hydrogen and the reaction of **3** under 0.1 MPa (instead of 4 MPa) of hydrogen were carried out under otherwise constant conditions. As shown in Table 1, these changes in the hydrogen pressure always resulted in considerable decreases in the enantioselectivities, irrespective of the catalyst used, in agreement with the results reported for the standard 5 wt% Pd/TiO_2 catalyst.[35] It is worth noting that similar tendencies in the Pd dispersion dependence of ee are observed for the reactions under both, low and high, hydrogen pressures; the Pd dispersion dependence for **1** is again very characteristic as compared to that for **3**. This seems to be reasonable because the ratio of the selective sites to all the reaction sites on the modified catalyst will not be affected by a change in the hydrogen pressure.[35]

Table 1. Comparison of the Pd Dispersion Dependence in the Enantioselective Hydrogenations of (*E*)-2,3-Diphenyl-2-propenoic acid (**1**) and (*E*)-2-Methyl-2-butenoic acid (**3**) Carried Out with Pd/TiO_2 Catalysts under Different Hydrogen Pressures[a)]

Substrate	Pd loading	D_M[b)]	ee (L)[c)]	ee (H)[d)]
	wt%		%	%
1	1	0.47	57.0	24.9
1	5	0.26	58.6	33.2
1	10	0.19	58.2	29.0
1	20	0.14	17.3	14.6
3	1	0.47	20.8	32.8
3	5	0.26	19.7	31.6
3	10	0.19	20.9	33.4
3	20	0.14	17.1	25.3

a) Reaction conditions; solvent: 10 cm^3 each of DMF containing 10 vol% water for **1** and of hexane for **3**, substrate: 1 mmol, modifier: 0.02 mmol. b) Degree of Pd dispersion estimated from CO uptake. c) Enantiomeric excess obtained in the reaction under an atmospheric pressure of hydrogen. d) Enantiomeric excess obtained in the reaction under 4.0 MPa of hydrogen.

The use of different solvents in these hydrogenations would exert some influence on the adsorption-mode and amount of the modifier-substrate complex on the catalyst surface. Moreover, it has been shown that the most stable conformation of **CD** varies depending on the solvent polarity.[36] Therefore, the modifier-substrate interaction may be influenced by the solvent employed, which could lead to a different dispersion dependence of the enantioselectivity. Because the solubility of **1** in hexane is too low to give a reasonable reaction rate, and the enantioselectivity achieved in the reaction of **3** in polar solvents, such as DMF, is negligibly low, it is difficult to compare the dispersion dependence for both substrates in the reactions using the same solvent. Further studies are needed to clarify the solvent effect on the Pd dispersion dependence of the enantioselectivity in this reaction.

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