

Enantioselective hydrogenation of α,β -unsaturated carboxylic acids over cinchonidine-modified Pd catalysts: effect of substrate structure on the adsorption mode

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Abstract

Systematic variation of the substrate structure in the enantioselective hydrogenation of α,β -unsaturated carboxylic acids over cinchonidine-modified Pd catalysts indicated that aryl substituents in β position changed the adsorption mode of the substrates on the metal surface and eventually the configuration of the products formed in excess as compared to aliphatic substrates. The configuration of the products formed in excess by hydrogenation of eight α,β -unsaturated carboxylic acids, of which two have not been described yet, indicated that the substrates bearing aromatic ring in β position were adsorbed on the opposite face of the C=C group compared to acids having aliphatic group in β position.

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1. Introduction

The enantioselective catalytic hydrogenation of prochiral α,β -unsaturated carboxylic acids has attracted much attention. The reaction is among the most convenient methods for obtaining optically pure carboxylic acids used in the production of pharmaceuticals, flavors and fragrances [1–3]. Recently, much effort has been devoted to find heterogeneous catalytic systems for this purpose. Such catalytic systems, affording high enantioselectivities are the well-known tartaric acid-modified Ni catalysts in the hydrogenation of β -keto esters [4,5] and the cinchona alkaloid-modified Pt catalysts in that of α -keto esters [5,6]. In spite of many attempts, earlier over Raney-Ni catalyst [7], no such heterogeneous catalytic system has been found for the hydrogenation of

α,β -unsaturated carboxylic acids yet. However, good enantioselectivities were obtained by using cinchona alkaloid-modified Pd catalysts (see Fig. 1) [8,9]. In order to increase the enantioselectivity in this reaction, the effect of several reaction parameters has been investigated, using some test molecules, such as (*E*)-2,3-diphenyl propenoic acid, (*E*)-2-methyl-2-butenoic acid and (*E*)-2-methyl-2-pentenoic acid [8–24]. Other substrates have scarcely been studied, although remarkable variations in enantiomeric excess (ee) values depending on the structure of the substrate have been observed [25,26]. Moreover, changing some reaction parameters, i.e. hydrogen pressure and solvent polarity, had opposite effect on the ee in the hydrogenation of the above-mentioned aliphatic acids compared to what was obtained for (*E*)-2,3-diphenyl propenoic acid. Therefore, we have decided to study the effect of systematic variation in the structure of α,β -unsaturated carboxylic acids on the ee. Results of this study are reported in the following sections.

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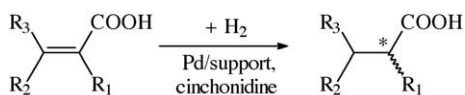


Fig. 1. Scheme of catalytic hydrogenation of α,β -unsaturated carboxylic acids over cinchonidine-modified supported Pd catalysts.

2. Experimental

Cinchonidine (CD, $\geq 98\%$) was purchased from Nacalai Tesque Inc. and was used as received. The substrates, 2-ethyl propenoic acid (**1**, Aldrich), (*E*)-2-methyl-2-butenoic acid (**2**, Wako Pure Chem. Ind.), (*Z*)-2-methyl-2-butenoic acid (**3**, Tokyo Kasei Kogyo Co.), (*E*)-2-methyl-2-pentenoic acid (**4**, Tokyo Kasei Kogyo Co.), (*E*)-2-methyl-2-hexenoic acid (**5**, Tokyo Kasei Kogyo Co.), (*E*)-2-ethyl-2-hexenoic acid (**6**, Aldrich), (*E*)-2-methyl-3-phenyl propenoic acid (**7**, Aldrich) and (*E*)-2,3-diphenyl propenoic acid (**8**, Tokyo Kasei Kogyo Co.), were used as received. High purity, dehydrated organic solvents were purchased from Wako Pure Chem. Ind.

Commercial alumina supported Pd catalysts were used as received: 5% Pd/ Al_2O_3 Engelhard 40692 (Pd/ Al_2O_3 -E) and 5% Pd/ Al_2O_3 Wako Pure Chem. Ind. 163-13871 (Pd/ Al_2O_3 -W). The 5% Pd/ TiO_2 catalyst was prepared by precipitation following a published procedure [27,28] using TiO_2 anatase (Wako Pure Chem. Ind., particle diameter $< 5 \mu\text{m}$).

Hydrogenations were carried out in 100 mL stainless steel Taiatsu Techno autoclaves equipped with Teflon liners and mechanical stirrers. The catalyst (25 mg) was pretreated for 1 h by stirring (1000 rpm) in 10 mL solvent under H_2 atmosphere at 296 K followed by addition of 0.05 mmol CD and 1 mmol substrate. The autoclave was flushed several times and filled with H_2 to the desired pressure and the stirring was started (1000 rpm) at 296 K. After 1 h reaction, the catalyst was filtered and the liquid was washed with HCl solution and analyzed by gas chromatography (GC) on a Shimadzu GC-17A apparatus equipped with flame ionization detector. Products were identified by GC–MS analysis and comparison with authentic samples. Conversion and ee values in the reactions of **1–6** were determined using a HP-Chiral (30 m \times 0.2 mm, J&W Scientific Inc.) chiral capillary column. For **7** and **8** the conversions were determined on a DB-1 (30 m \times 0.2 mm, J&W Scientific Inc.) capillary column. The ee value was determined after transforming the products to methyl esters using a CyclosilB (30 m \times 0.2 mm, J&W Scientific Inc.) chiral capillary column. The enantiomeric excess (ee %) was calculated with the formulae $\text{ee} (\%) = 100 \times |E_1 - E_2| / (E_1 + E_2)$, where E_1 and E_2 are the concentrations of the corresponding saturated carboxylic acid enantiomers. The reactions were repeated three times, the results were reproducible within $\pm 1\%$.

The configuration of the enantiomers formed in excess was determined by GC analysis and comparison with authentic samples (for **1–3**) or according to published data (for **4**, **6**, **8**) [8,9,26]. As the hydrogenation of **5** and **7** over CD-modified Pd catalyst has not been studied yet, the configuration assign-

ments for the excess products were done by measuring the optical rotations. Optical rotations were measured on a Jasco IP-181 Digital Polarimeter.













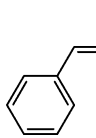
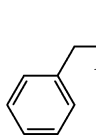
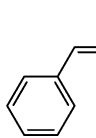
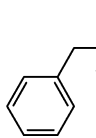
3. Results and discussion

The hydrogenation of **1–8** has been studied over supported Pd catalysts modified by CD. The solvents and the H_2 pressures were chosen following literature data [8,9], except **7**, which has not been studied yet and for this compound the results of preliminary experiments have been used. Accordingly, the hydrogenations of the aliphatic substrates were carried out in toluene under high (5 MPa) H_2 pressure, while methanol and 0.5 MPa H_2 pressure were used in the hydrogenation of **7** and DMF/ H_2O 9/1 mixture and 0.1 MPa H_2 pressure in the hydrogenation of **8**. Selected results are summarized in Table 1.

Hydrogenation of the aliphatic substrates **2–4** and **6** resulted in the formation of the *S* enantiomers **10**, **11** and **13** in excess (see Table 1) in accordance with literature data [9,25,26]. Hydrogenation of **5** afforded the (+) enantiomer in excess, as determined by optical rotation measurement, which, by published data, is also the *S* enantiomer (**12**) [29,30]. The absolute configuration of the chiral center in the 2-methylbutyric acid formed in excess in the hydrogenation of **1** was *R* (**9**). However, this was due to the change in the priority of the substituents on the α -C according to the sequence rule. Accordingly, all the aliphatic substrates were preferentially adsorbed on the same side of the $\text{C}=\text{C}$ group during their hydrogenations. This could be predicted using the empirical rule determined by Baiker and co-workers for aliphatic acids [26]. The preferential adsorption side was not influenced by the orientation of the substituent in β position, both hydrogenation of **2** and **3** afforded **10** in excess. However, the ee value increased significantly with increasing length of this substituent (compare the results obtained in the hydrogenations of **2**, **4** and **5** in Table 1). The highest values were obtained in the hydrogenation of **5**, of which hydrogenation over CD-modified Pd catalyst is reported for the first time. The increase in the length of the substituent in β position was also accompanied by some decrease in the reaction rate, as shown in the conversions obtained over Pd/ TiO_2 . Increasing the length of the substituent in α position did not result in further increase in the ee value and significant rate decrease was obtained, as the comparison of the results obtained in hydrogenations of **5** and **6** reveals.

Hydrogenation of aromatic substrates **7** and **8** resulted in the formation of excess (*R*)-2-methyl-3-phenyl propionic acid (**14**) and (*S*)-2,3-diphenyl propionic acid (**15**), respectively. The product mixture resulted from the reactions of compound **7** and its methyl ester contained the (–) enantiomer in excess having *R* absolute configuration (**14**) according to literature data [31–33]. The low ee value obtained in the hydrogenation of **7** may be explained by the isomerisation of this compound, similarly to other α -alkyl- α,β -unsaturated

Table 1
Hydrogenation of α,β -unsaturated carboxylic acids over CD-modified Pd catalysts

Substrate	Catalyst	ee (%) / conv ^a (%)	Excess enantiomer
1^b 	Pd/Al ₂ O ₃ -E	19	9 
2^b 	Pd/Al ₂ O ₃ -E	46	10 
	Pd/Al ₂ O ₃ -W	46	
	Pd/TiO ₂	44/88	
3^b 	Pd/Al ₂ O ₃ -E	32	10 
	Pd/Al ₂ O ₃ -W	32	
	Pd/TiO ₂	30/95	
4^b 	Pd/Al ₂ O ₃ -E	52	11 
	Pd/Al ₂ O ₃ -W	53	
	Pd/TiO ₂	49/82	
5^b 	Pd/Al ₂ O ₃ -E	54	12 
	Pd/Al ₂ O ₃ -W	56	
	Pd/TiO ₂	51/72	
6^b 	Pd/Al ₂ O ₃ -E	53/99	13 
	Pd/Al ₂ O ₃ -W	55/70	
	Pd/TiO ₂	51/40	
7^c 	Pd/Al ₂ O ₃ -E	23	14 
	Pd/Al ₂ O ₃ -W	15	
	Pd/TiO ₂	15/45	
8^d 	Pd/Al ₂ O ₃ -E	52/60	15 
	Pd/Al ₂ O ₃ -W	40/30	
	Pd/TiO ₂	57/40	

Reaction conditions: 25 mg catalyst, 10 mL solvent, 0.05 mmol CD, 1 mmol substrate, 1000 rpm, 296 K, 1 h.

^a Conversion if the reaction was not complete in 1 h.

^b Solvent: toluene, 5 MPa H₂ pressure.

^c Solvent: methanol, 0.5 MPa H₂ pressure.

^d Solvent: DMF/H₂O 9/1, 0.1 MPa H₂ pressure.

acids [34,35] and the decreased steric hindrance of the methyl group relative to the α -phenyl group in **8**. Although different configurations of the chiral center were obtained for the latter two compounds, this was only due to the change in the order of the priority of the substituents and both aromatic unsaturated acids adsorbed on the same side of the C=C group over the surface. However, their adsorption mode was opposite to that of the aliphatic substrates (illustrated by the structures presented in Table 1).

Variations in reaction conditions, i.e. H₂ pressure and solvent, did not change the adsorption mode of the substrates of different structures. This is indicated by the results obtained in the hydrogenation of **7** in toluene and different H₂ pressures and the results in the hydrogenation of the aliphatic substrates in the polar solvents used. Thus, hydrogenation of **2** in methanol or in DMF/H₂O 9/1 also afforded the *S* product **10** (ee 24 and 9%) and that of **5** in the same sol-

vents afforded the *S* product **12** (ee 25 and 24%) in excess. Furthermore, in the hydrogenation of **7** the *R* enantiomer **14** was always obtained in excess; in toluene, the ee was 13%, while in methanol under 0.1 or 5 MPa H₂ pressures ee of 18 and 16% were measured. Although depending on the solvent used, the substrates may be interacting with CD as dimer (in apolar solvents) or as monomer [21–23], the above results reveal that it has no influence on the sense of the enantioselectivity, it influences only the obtained ee values.

Accordingly, it is reasonable to assume that the presence of the phenyl group in β position directs the adsorption of the aromatic substrates on the opposite side of the C=C group relative to the aliphatic acids, irrespective of the substituent bonded to the α -C. Nevertheless, both substituents in α and β positions had significant effect on the ee values. The surprising directing effect of the β phenyl substituent, unreported

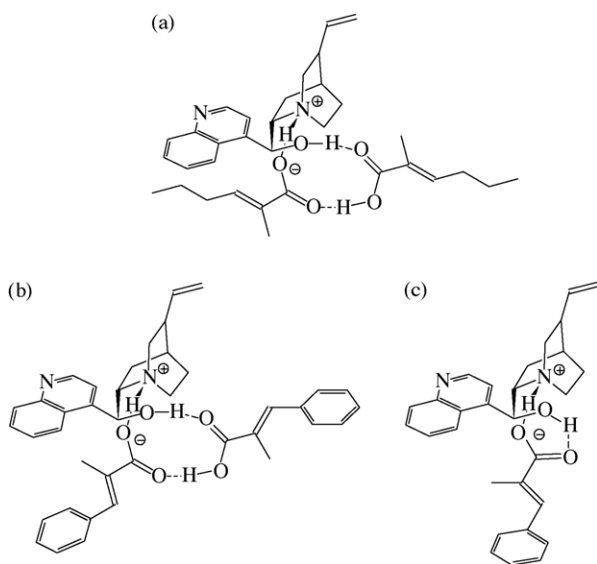


Fig. 2. Proposed hypothetical structures for the (a) CD–(*E*)-2-methyl-2-hexenoic acid 1:2 complex; (b) CD–(*E*)-2-methyl-3-phenyl propenoic acid 1:2 complex and (c) CD–(*E*)-2-methyl-3-phenyl propenoic acid 1:1 complex.

until now, must be due to the steric effect of this group. Thus, the presence of the aromatic ring in β position may favour the formation of CD–acid complexes, which will be adsorbed on the metal surface preferentially on the opposite side of the prochiral C=C group compared to the CD–aliphatic acid complexes. Thus, in accordance with the structures of the CD–acid complexes reported in the literature [13,21,36], we propose the structures presented in Fig. 2 for the complexes of aliphatic and aromatic carboxylic acids. The structures presented for the CD–aromatic acid complexes are hypothetical (for aliphatic acids the structure has been verified by FTIR spectroscopy and *ab initio* calculations [21,22]) and should be verified experimentally. The formation of these complexes may be explained by the steric hindrance of the β phenyl group. However, the low ee values obtained in the hydrogenation of **7** shows that the stability of the complexes, in which the substrates are adsorbed on the opposite side are close to those presented in Fig. 2. For aromatic acids, a bulky substituent in α position is also needed to obtain high ee values. Determining the preferred structures of the CD–acid complexes (1:1 or 1:2 complex, see Fig. 2b and c) for aromatic acids requires further studies as well.

Finally, let us note that only very few examples are known, in which inversion of enantioselectivity had been reported in the heterogeneous catalytic hydrogenation of activated ketones over CD-modified Pt catalyst. In these cases, the inversion was induced by change in the nature of solvents or derivatisation of CD [37–39]. Our report is the first to show that change in the structure of the α,β -unsaturated carboxylic acids, i.e. the presence of aliphatic or aromatic substituent in β position, leads to opposite adsorption mode of the substrates and eventually to inversion of the enantioselectivity in their hydrogenation over CD-modified Pd catalyst.

4. Conclusions

Our systematic study on the effect of the substrate structure in the heterogeneous enantioselective hydrogenation of α,β -unsaturated carboxylic acids over cinchonidine-modified Pd catalysts included two compounds, which have not been reported previously: (*E*)-2-methyl-2-hexenoic acid and (*E*)-2-methyl-3-phenyl propenoic acid. The ee value of the reaction was further increased by increasing the length of the aliphatic chain of the substrates, while the aliphatic or aromatic nature of the β substituents determined the adsorption mode of these compounds and eventually the sense of the enantioselectivity.

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