Palladium-catalysed enantioselective hydrogenation of alkenoic acids. Role of isomerization

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The enantioselective hydrogenation of 2-ethyl-propenoic acid over Pd/alumina modified with cinchonidine has been studied. The reaction, carried out in a batch reactor at 1 bar hydrogen pressure and room temperature, revealed that the isomerization of the C=C double bond is a competing side reaction. Double-bond migration and the subsequent hydrogenation of the two isomer alkenoic acids lowered the enantioselectivity drastically due to the formation of opposite enantiomers.

Keywords: enantioselective, hydrogenation, isomerization, cinchonidine, Pd/alumina, alkenoic acid

1. Introduction

Although homogeneous metal complexes with chiral ligands are still the most versatile catalysts for enantioselective hydrogenation [1], heterogeneous catalysts would be preferable due to their inherent practical advantages [2]. Until now only carbonyl compounds could be hydrogenated with more than 95% ee over chirally modified Pt and Ni catalysts [3–5]. Hydrogenation of C=C double bonds with cinchona-modified Pd has been far less successful [6–8]. The best enantioselectivities are 72 and 53% for aromatic and aliphatic α,β-unsaturated acids, respectively [7,9]. There is a remarkable variation in the efficiency of the Pd–cinchonidine system, depending on the substituents of the C=C bond in the alkenoic acid substrate [10].

We propose that in many instances the poor enantiodifferentiation is not an intrinsic characteristic of this catalyst system, rather the result of a competing side reaction. Double-bond migration in the substrate and the subsequent hydrogenation of the two isomer alkenoic acids seems to be a major reason for the observed low enantioselectivities. To demonstrate the role of isomerization as a competing side reaction during the enantioselective hydrogenation of alkenoic acids, 2-ethyl-propenoic acid (**1**) was chosen as a model substrate (scheme 1).

2. Experimental

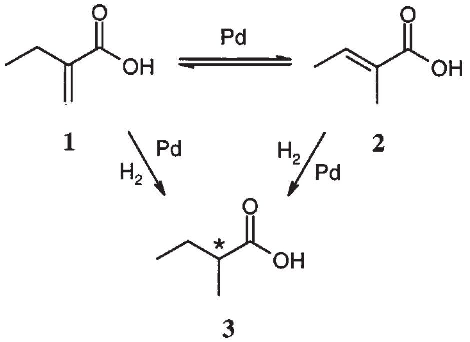
Synthesis of 2-ethyl-propenoic acid and related compounds has been described previously [10]. Cinchonidine (CD, Fluka) was used as received.

Isomerization of 2-ethyl-propenoic acid to 2-methyl-2-butenoic acid (tiglic acid) (**2**) was investigated in a nitrogen atmosphere, in the absence of CD. The reactions were carried out in a magnetically stirred 100 ml glass reactor. 10 mg 5 wt% Pd/Al_2O_3 (Engelhard 40692, $D = 0.21$ as determined by TEM) in 10 ml solvent was pretreated with H_2 at 1 bar for 10 min, at room temperature. Catalyst prereduction was necessary to reduce the surface oxides (PdO_x) to metallic active sites (Pd^0). Excess hydrogen was carefully removed by nitrogen, then 100 mg **1** in 2 ml solvent was injected into the reactor and the transformation followed by GC analysis (CP-cyclodextrin-2,3,6-M-19 column, Chrompack).

Hydrogenation reactions were carried out under conditions similar to the isomerization experiments (1 bar, room temperature). The catalyst was reduced in the presence of 2 mg CD, resulting in the formation of 10,11-dihydrocinchonidine (HCD). Enantiomeric excess is expressed as ee (%) $= 100 \times |(R - S)|/(R + S)$, with a reproducibility of $\pm 0.5\%$.

3. Results and discussion

The influence of the reaction medium on the rate of isomerization is shown in figure 1. The thermodynamically



Scheme 1. Isomerization of 2-ethyl-propenoic acid (**1**) to 2-methyl-2-butenoic acid (**2**), and hydrogenation of both isomers over Pd/Al_2O_3.

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more stable *trans* isomer, tiglic acid was the main product formed. The *cis* isomer angelic acid could be detected only in ethanol (*trans*/*cis* ratio: 10). Excluding ethanol, there is a clear negative correlation between solvent polarity and the rate of isomerization. The diminished rate of isomerization in polar solvents may be explained by the competing adsorption of solvent molecules on Pd [11]. The exceptionally fast isomerization of **1**, and the formation of *cis*-**2**, in ethanol may be attributed to a special solvent–substrate interaction.

Time-resolved formation of **2** and **3** in toluene, and the remarkable drop in ee during the enantioselective hydrogenation of **1** is shown in figure 2. Apparently, tiglic acid (*trans*-**2**) adsorbed weaker on Pd than **1** and was (partially) replaced by **1**. As a result, the amount of **2** in solution increased monotonously till about 70% conversion of **1** (dotted line at ca. 400 s). With increasing concentration of **2** and decreasing concentration of **1** the situation changed and the hydrogenation of **2** gradually diminished the ee. Similar behaviour was observed in other solvents, such as ethanol and hexane.

In a previous report [10], we have shown that in the hydrogenation of **1** the Pd–CD system favours the formation of R-**3**, while in the reduction of **2** the S-**3** enantiomer is produced in excess. It was proposed that *trans* alkenoic acid dimers interact with CD via H bonding on the Pd surface. The dimer adopts an adsorption geometry in which one of the C=C double bonds points towards the quinoline ring of CD. On the basis of this model the major enantiomer of alkenoic acid hydrogenation could be predicted. A general consequence of the proposed alkenoic acid–CD interaction is that after double-bond migration the hydrogenation of the isomer α,β-unsaturated acid affords the opposite enantiomer in excess.

There are two possible mechanisms for double-bond migration in the chemisorbed reactant: (a) interconversion between the alkenoic acid and the half-hydrogenated intermediate [12], (b) interconversion between olefinic and π-allylic complexes [13] (scheme 2). In the former case the formation of a σ-bonded intermediate requires the addition of a preadsorbed H atom (associative mechanism). In the latter, formation of a π-allylic complex occurs by abstraction of a hydrogen atom from the molecule (dissociative mechanism).

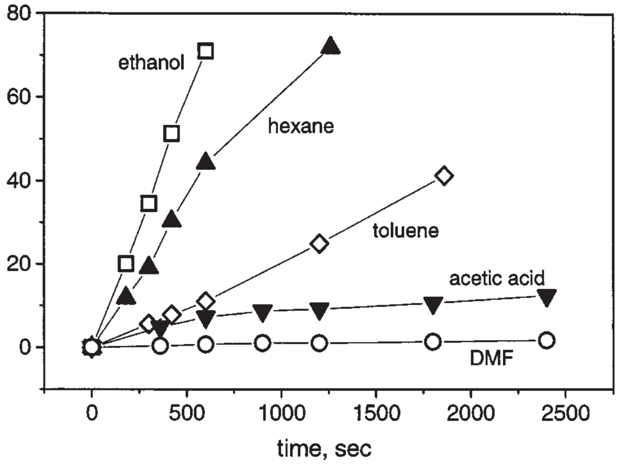


Figure 1. Isomerization of **1** to **2** in various solvents.

During the isomerization experiments in a nitrogen atmosphere (figure 1) the surface hydrogen concentration was very low; minor hydrogenation of **1** to **3** could be observed only in the early stage of the reaction. It is reasonable to assume that under these conditions double-bond migration occurs mainly by the dissociative mechanism. At medium surface hydrogen concentration both mechanisms may be operative. At high pressure (30–100 bar) isomerization via the π-allylic complex (dissociative mechanism) is suppressed due to the high surface hydrogen concentration. Besides, further hydrogenation of the half-hydrogenated intermediate is much faster than the formation of alkenoic acid (**1** or **2**) by hydrogen abstraction (associative mechanism). Accordingly, high surface concentration of hydrogen suppresses the double-bond migration by both mechanisms, providing an explanation for the beneficial effect of high hydrogen pressure on the ee in the hydrogenation of various alkenoic acids [7]. Competing isomerization can explain the low ee observed in the enantioselective hydrogenation of α,β-unsaturated acids possessing a terminal C=C bond [10]: transformation of the reactant to the thermodynamically more stable isomer is expected to be very fast.

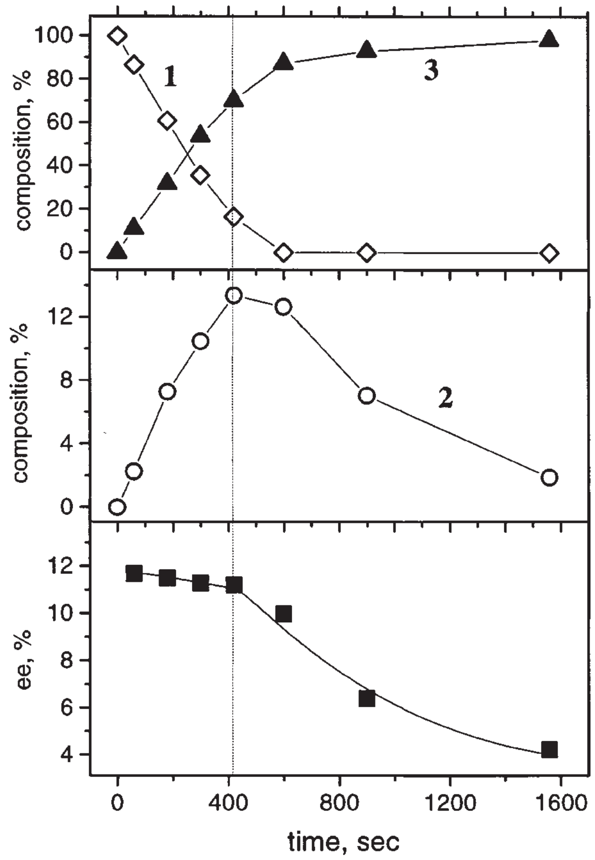
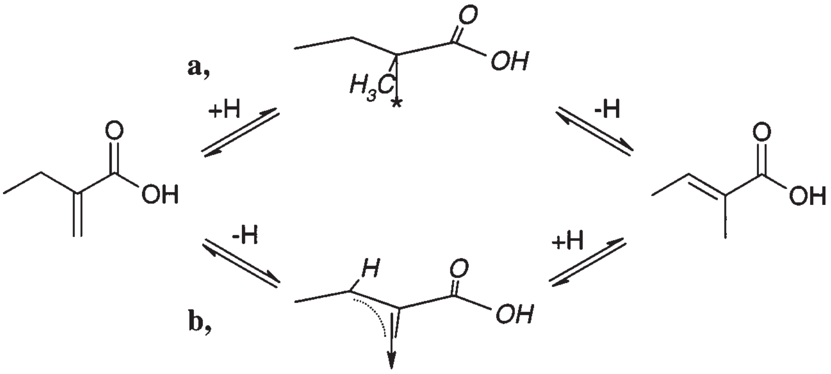


Figure 2. Hydrogenation of **1**, according to scheme 1.



Scheme 2. Associative (**a**) and dissociative (**b**) pathway for the isomerization of 1 (side top-view, ⋆ denotes an adsorption site on the Pd surface).

4. Conclusion

The present findings indicate that chirally modified Pd can afford good ee only if double-bond migration in the reactant is slow relative to the hydrogenation reaction, or this side reaction can completely be ruled out (e.g., (E)-α-phenylcinnamic acid [9]). Similar limitations of chirally modified Pd catalysts can be expected in the hydrogenation of other unsaturated compounds possessing a C=C or C=N bond, due to the generally high activity of Pd for double-bond migration [14]. Another obvious consequence of competing substrate isomerization is that due care is required in the analysis of parameter effects in Pd-catalysed asymmetric hydrogenation reactions.

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