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Comparison of chiral modifiers in the Pd catalysed hydrogenation of phenylcinnamic acid and isophorone

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Abstract

The asymmetric induction of (−)-dihydroapovincaminic acid ethyl ester [(−)-DHVIN] and cinchonidine employed as chiral modifiers was compared in the Pd catalysed hydrogenation of the C=C double bonds of phenylcinnamic acid and isophorone. The differences in their effect and behaviour were attributed to the difference in the interaction between the modifier and the reactant and to their different basicity.

Keywords: Chiral modifier; Dihydroapovincaminic acid ethyl ester; Enantioselectivity; Hydrogenation; Isophorone; Phenylcinnamic acid

1. Introduction

The most efficient enantioselective heterogeneous catalytic systems, to date, are the platinum catalysts modified with cinchona alkaloids in the hydrogenation of α-keto esters and the Raney-Ni catalyst modified with tartaric acid in the hydrogenation of β-keto esters, providing up to 95% ee and 98% ee, respectively [1,2]. As a result of the intensive research work, new chiral modifiers, chiral amines and amino alcohols [3–8], were synthesised; and apart from α- and β-keto esters, some other carbonyl compounds, such as α-keto acids [9], α-diketones [10], ketopantolactone [11], trifluoroacetophenone [12], α-keto amides [13] were hydrogenated in considerable enantioselectivities. Moreover, besides platinum, dihydrocinchonidine (DHCND) modifies palladium in the hydrogenation of the C=C double bond of phenylcinnamic acid affording 72% ee [14–18], and that of an α,β-unsaturated ketone, isophorone, giving 20% ee [19].

A vinca-type alkaloid, (−)-dihydroapovincaminic acid ethyl ester [(−)-DHVIN] (Fig. 1), also proved to be an efficient chiral modifier for the hydrogenation of isophorone over palladium catalysts, where up to 55% ee was achieved under optimised reaction conditions [19,20]. On the other hand, (−)-DHVIN induces enantioselectivity, but to a smaller extent (ca. 30% ee), in the hydrogenation of ethyl pyruvate over platinum catalysts. None of the systems mentioned above surpass the effectiveness of the cinchona alkaloid–platinum–pyruvate system. However,

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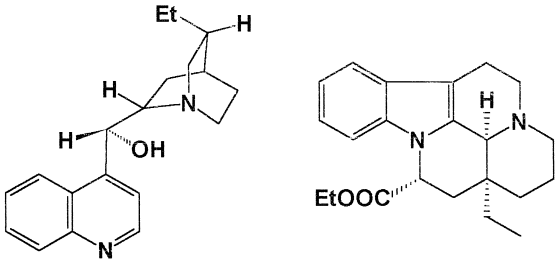

Fig. 1. Structures of dihydrocinchonidine and (−)-DHVIN.

their investigation reveals that this enantioselective system, previously considered to be very specific, is not exclusive and makes it possible to learn the principles of operation of enantioselective heterogeneous catalysts.

Here we report the results on the hydrogenation of (*E*)-α-phenylcinnamic acid in the presence of (−)-DHVIN as a chiral modifier. Furthermore, we have compared the effects of the catalysts and solvents in the enantioselective hydrogenation of (*E*)-α-phenylcinnamic acid and isophorone (Fig. 2).

2. Experimental

Two types of Pd/TiO_2 catalysts were used. Type A 10 wt.% Pd/TiO_2 catalyst was prepared as follows: the calculated amount of the catalyst precursor (K_2PdCl_4) was added to the aqueous suspension of the support (nonporous TiO_2). The pH value of the solution was adjusted to 10–11 by addition of KOH. The suspension was boiled for 1 h, and then Na(HCOO) was added to the boiling mixture. After half an hour, the suspension was cooled, the catalyst was filtered and washed with distilled water.

Type B Pd/TiO_2 catalysts with Pd contents ranging from 0.5 to 10 wt.% were prepared according to the following procedure. An aqueous suspension of $PdCl_2$ and support (nonporous TiO_2, 40 m^2/g) was gently stirred for 15 min at 348 K. A Na_2CO_3 solution was added dropwise to the suspension under vigorous stirring. The final pH value of the solution was adjusted to 10–11. After gentle stirring for 15 min at the same temperature, the precipitate was filtered, washed three times with distilled water, and dried in air at 383 K for 20 h. A portion of the catalyst precursor (0.02 g) was reduced immediately before use by heating at 473 K for 1 h in a hydrogen flow of 8 dm^3/h.

Pd black catalyst was prepared according to the following procedure: 18 mmol (6.0 g) K_2PdCl_4 was dissolved in 50 ml water and reduced at boiling point with 74 mmol (5.0 g) Na(HCOO) dissolved in 20 ml water. When the reduction was complete the pH of the suspension was basic (pH = 11). The catalyst was filtered and washed several times with distilled water.

(*E*)-α-phenylcinnamic acid was supplied by Aldrich. Isophorone and cinchonidine were supplied by Merck. Vinpocetine® (apovincaminic acid ethyl esther) was supplied by Richter Gedeon Co. (−)-DHVIN was prepared by catalytic hydrogenation of vinpocetine followed by the separation of the epimers [20]. (−)-Dihydroapovincaminic acid was prepared from apovincaminic acid ethyl ester by hydrolysis and hydrogenation followed by separation of epimers [21].

2.1. Hydrogenation

The hydrogenation of isophorone (100 mg Pd/TiO_2 or 500 mg Pd black catalyst, 7 g reactant, 20 mg modifier, 200 mg acetic acid, 50 ml methanol) and (*E*)-α-phenylcinnamic acid (20 mg Pd/TiO_2 catalyst, 7–100 mg modifier,

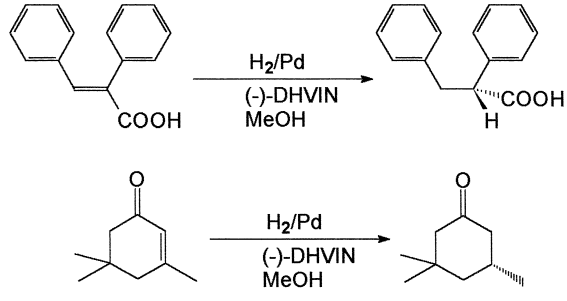

Fig. 2. Hydrogenation of (*E*)-α-phenylcinnamic acid and isophorone.

0.224 g reactant, 10 ml methanol) was carried out in a solution at 298 K and 1–50 bar hydrogen pressure in a conventional apparatus or in a Büchi BEP 280 autoclave equipped with a magnetically driven turbine stirrer and a gas-flow controlling and measuring unit. Prior to the hydrogenation the reaction mixtures were stirred in the reaction vessel under nitrogen for 10 min in the case of isophorone and under hydrogen for 20 min in the case of (*E*)-α-phenylcinnamic acid. The products of the hydrogenation of isophorone were analysed with GC on a β-cyclodextrin capillary column at 383 K. In the hydrogenation of (*E*)-α-phenylcinnamic acid, the products were isolated from the reaction mixture according to the procedure described before [14], esterified to the methyl ester by the reaction with $CH_3OH/BF_3 \cdot CH_3OH$, and analysed by HPLC on a chiral column (DAICEL, CHIRACEL OJ-R). Enantiomeric excess values were calculated from the peak areas of the enantiomers with the usual method: $ee = ([R] - [S])100/([R] + [S])$. The initial reaction rate was measured at 20% conversion based on the hydrogen uptake.

3. Results and discussion

In the hydrogenation of (*E*)-α-phenylcinnamic acid, (−)-DHVIN gives the (*R*)-2,3-diphenylpropionic acid with 28% ee in the best case (the reaction conditions have not been optimised yet). Fig. 3 depicts the dependence of enantioselectivity and reaction rate of the hydrogenation of phenylcinnamic acid on the amount of (−)-DHVIN. Small concentration of the modifier (approx. 6×10^{-3} (−)-DHVIN/reactant molar ratio) is sufficient to induce its maximum effect. Neither ee nor reaction rate changes considerably upon adding further amount of (−)-DHVIN. The reaction rate decreases about an order of magnitude in the presence of (−)-DHVIN like in the case of DHCND [16]. Similar decrease of the reaction rate was observed in the hydrogenation of the

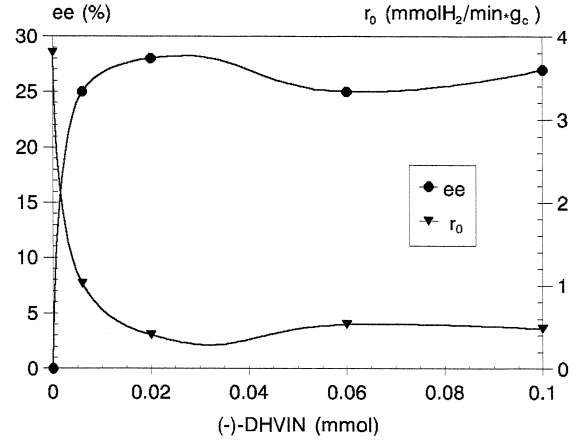

Fig. 3. Effect of (−)-DHVIN concentration on enantioselectivity and reaction rate in the hydrogenation of phenylcinnamic acid. Reaction conditions: 0.02 g 5% Pd/TiO_2, 10 ml methanol, 1 mmol substrate, H_2 1 bar, 25°C, 1200 rpm.

C=C double bond of isophorone over (−)-DHVIN- or DHCND-modified Pd catalysts [22].

On the contrary, in the hydrogenation of the carbonyl group of α-keto compounds the modified catalyst is much more active than the unmodified [23]. This rate-accelerating effect is attributed to the specific interaction between the adsorbed modifier and reactant, i.e., the cinchona alkaloid stabilizes the half-hydrogenated ethyl pyruvate via hydrogen bonding involving the quinuclidine N of the former and the OH group of the latter. It seems that in the hydrogenation of the C=C double bond over Pd, the adsorbed modifier, besides its poisoning effect, interacts in a different way with the adsorbed reactant leading to a rate decrease of the enantioselective reaction. For the hydrogenation of phenylcinnamic acid over DHCND-modified palladium it was assumed that not only the acid–base interaction but also the interaction (via hydrogen bonding) between the C9–OH of DHCND and the carboxyl group of the reactant is crucial to obtain a high selectivity [18]. To this end, (+)-vincamine, which contains a hydroxyl group at C14, and (−)-dihydroapovincaminic acid (Fig. 4) were tested as chiral modifiers in the hydrogenation of both

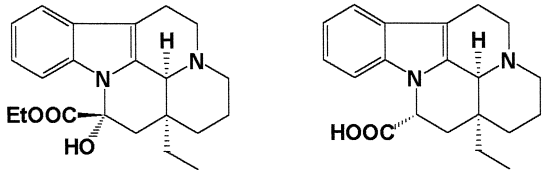

Fig. 4. Structures of (+)-vincamine and (−)-dihydroapovincaminic acid.

isophorone and (*E*)-α-phenylcinnamic acid (Table 1).

(−)-Dihydroapovincaminic acid affords 43% ee in the case of isophorone and 8% ee in the case of phenylcinnamic acid, while (+)-vincamine gave no enantiomeric excess in either hydrogenation. This confirms our previous results [20] that the presence of an OH group instead of H at C14 of the vinca alkaloid and the steric configuration of the COOEt or COOH group considerably affect the enantioselectivity, i.e., these latter groups in an α position are likely to strengthen the adsorption of the alkaloid molecule on the catalyst surface.

Table 2 shows the enantioselectivity and reaction rate values obtained in the hydrogenation of phenylcinnamic acid and isophorone over palladium catalysts of different dispersity modified with (−)-DHVIN. There is an apparent difference between the two reactions: the catalysts with low dispersion, Pd black and 10 wt.% Pd/TiO_2 (A), are almost inactive and nonselective in the hydrogenation of phenylcinnamic acid, whereas in the hydrogenation of isophorone these catalysts are the best ones, giving 55% and 40% ee, respectively. The 5% Pd/TiO_2 (B), which is the best catalyst for the hydrogenation of phenylcinnamic acid (28% ee), results only 14% ee in the case of isophorone. This behaviour can be explained either by the difference in the bulkyness of the reactants or more probably, by the difference in the interaction mode of the transition complex with the Pd surface. It is conceivable that the too tight adsorption of (−)-DHVIN on the large Pd ensembles hinders the C=C double bond of phenylcinnamic acid to approach the Pd surface and to be hydrogenated. Similar tendency was observed for this reaction with the DHCND-modified catalysts [24,25]. In contrast, the hydrogenation of isophorone may be favoured by the strong adsorption of (−)-DHVIN on the large Pd ensembles. The effectiveness of catalysts with very high dispersion is low in both hydrogenations.

As previously reported, in the hydrogenation of phenylcinnamic acid DHCND affords the highest ee of 72% in the mixed solvent of *N*,*N*-dimethylformamide–water (DMF–H_2O, 9:1 in volume) and a lower ee of 61% in methanol, while, in the hydrogenation of isophorone, DHCND provides only 10% ee in DMF–H_2O compared with the 20% ee in methanol.

This solvent dependence can also be explained by the different mode of interaction of DHCND with isophorone and phenylcinnamic acid. In contrast, (−)-DHVIN induces much higher enantioselectivity in methanol (28% ee) than in DMF–H_2O (1% ee) in the hydrogenation of phenylcinnamic acid, like in the case of isophorone and ethyl pyruvate.

In the case of phenylcinnamic acid, an acid–base interaction is determining, but the C9–OH group of cinchonidine, forming a H-bridge with the carboxyl group of the reactant, is also crucial. The DMF:water 9:1 mixture, the optimal solvent so far for this reaction, is polar and

Table 1
Enantioselectivities obtained with (−)-DHVIN, (+)-vincamine and (−)-dihydroapovincaminic acid in the hydrogenation of (*E*)-α-phenylcinnamic acid and isophorone

Chiral modifier	(*E*)-α-Phenylcinnamic acid	Isophorone
(−)-DHVIN	28	55
(+)-Vincamine	0	0
(−)-Dihydroapovincaminic acid	8	43

Reaction conditions: 0.05 mol (7.0 g) isophorone, 0.5 g Pd black catalyst, 0.02 g modifier, 0.2 g acetic acid, 50 ml methanol, 50 bar, 25°C.
0.001 mol (0.224 g) (*E*)-α-phenylcinnamic acid, 0.02 g 5% Pd/TiO_2 catalyst, 0.007 g modifier, 10 ml methanol, 1 bar, 25°C.

Table 2
Enantioselectivities in the hydrogenation of (*E*)-α-phenylcinnamic acid and isophorone with different Pd catalysts modified with (−)-DHVIN

Catalyst	Dispersion	(*E*)-α-Phenylcinnamic acid		Isophorone	
		ee (%)	Initial reaction rate (mmol/min g_k)	ee (%)	Initial reaction rate (mmol/min g_k)
Pd black	0.04	< 2	1.3×10^{-2}	55	0.3
10% Pd/TiO_2 (A)	0.02	< 2	1.3×10^{-2}	40	0.5
10% Pd/TiO_2 (B)	0.29	17	0.8	15	2.5
5% Pd/TiO_2 (B)	0.52	28	0.4	20	7.7
2% Pd/TiO_2 (B)	0.41	20	0.3	17	4.7
1% Pd/TiO_2 (B)	0.47	16	0.2	11	2.2
0.5% Pd/TiO_2 (B)	0.86	< 2	1.7×10^{-2}	11	1.3

Reaction conditions: 0.001 mol (0.224 g) (*E*)-α-phenylcinnamic acid, 0.1 g Pd black catalyst, 0.02 g Pd/TiO_2 catalysts, 0.007 g(−)-DHVIN, 10 ml methanol, 1 bar, 25°C.
0.05 mol (7.0 g) isophorone, 0.5 g Pd black catalyst, 0.1 g Pd/TiO_2 catalysts, 0.02 g (−)-DHVIN, 0.2 g acetic acid, 50 ml methanol, 50 bar, 25°C.

protic, which also supports this assumption. The alkaline strength of cinchonidine is higher than that of the (−)-DHVIN, which is higher than that of (−)-dihydroapovincaminic acid. The enantiomeric excesses decrease also in this sequence. On the other hand, for the hydrogenation of isophorone the protic-polar methanol is the best solvent, and addition of a weak acid, such as acetic acid, is advantageous. Together with the results of earlier circular dichroism spectroscopy measurements [20] these experiences support the assumption that the basic tertiary N of the alkaloids is protonated and interacts with the carbonyl oxygen of the reactant. The reactant–modifier complex formed in this way is more stable in methanol than in the more polar DMF:water mixture.

4. Conclusion

Both DHCND and (−)-DHVIN induce enantioselectivity accompanied by moderate decrease of reaction rate in the Pd catalyzed hydrogenation of C=C double bond of phenylcinnamic acid and isophorone. The optimal reaction conditions differ for the two modifiers and the two reactants and depend also on the catalysts used, indicating that the interactions resulting in asymmetric induction are different. The difference in the solvent dependence of the hydrogenation of both reactants can be explained by the different mode of the reactant–modifier interaction.

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