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Enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester using cinchonine-modified Pd/TiO_2 catalysts

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Abstract

The enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester is investigated using cinchonine-modified Pd/TiO_2 catalysts. The catalysts were prepared using deposition–reduction and wet impregnation methods and were evaluated for reaction using methanol as solvent with various cinchonine/NADPME molar ratios. Enantioselectivity was sensitive to this ratio and comparison with $Pd/\gamma\text{-}Al_2O_3$ showed that the Pd/TiO_2 gave marginally higher enantioselectivity when tested under comparable conditions. The effect of Pd loading and dispersion was investigated and the maximum enantiomeric excess observed was dependent on the dispersion; the role of the Pd particle size is discussed in the context of cinchonine adsorption. The reactions were carried out in solvents (methanol and dimethyl formamide) and mixed solvents (methanol–water and dimethyl formamide–water); the enantiomeric excess was significantly enhanced using dimethyl formamide. The addition of water does not have a significant effect for the Pd/TiO_2 catalysts. In this paper we report the highest enantiomeric excess for the hydrogenation of a prochiral ester using an immobilised catalyst.

Keywords: Enantioselective hydrogenation; *N*-acetyl dehydrophenylalanine methyl ester; Pd/TiO_2; Cinchonine-modified Pd catalyst

1. Introduction

Enantioselective hydrogenation remains one of the most intensely studied fields of research in catalysis, particularly for the synthesis of pharmaceuticals and agrochemicals. Considerable progress has been achieved with homogeneous catalysts where the design of ligands has led to the achievement of high enantioselection in many reactions. However, for practical utilisation heterogeneous catalysts are preferred, but in this respect there has been significantly less progress [1–4]. To date there have been three different approaches that dominate the design of enantioselective heterogeneous catalysts, namely (a) tethering an active homogeneous catalyst on a solid matrix which can either be a polymer or an inorganic solid, (b) electrostatic immobilisation of an active homogeneous catalyst onto a suitable matrix and (c) chiral modification of achiral catalyst surfaces. All tend to be specific for various classes of reaction, and all demonstrate a number of advantages and disadvantages that currently limit their commercialisation.

One reaction for which homogeneous catalysts are very effective but, to date, there has been no success with the identification of a heterogeneous counterpart is the hydrogenation of prochiral carbon carbon double bonds in esters. An example of this class of reactions is the enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester. Many pharmaceutical substances, such as L-DOPA, are amino acids. Synthesising homochiral natural and non-natural amino acids in high purity represents a challenging problem for modern chemistry. The enantioselective hydrogenation of enamides, such as NADPME, is often a crucial step in these syntheses. At present, the enantioselective hydrogenation of NADPME and related prochiral molecules has been achieved homogeneously using chiral rhodium complexes [5–8], most notably using BINAP as the ligand [4]. The immobilisation of chiral rhodium diphosphine complexes has been intensely studied. Hölderich and coworkers [9], de Rege et al. [10] and Augustine et al. [11] have shown that chiral Rh disphosphine complexes can be immobilised on MCM-41 or heteropolyacids. However, these

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catalysts, although initially effective, tend to give lower enantioselection compared with their homogenous counterparts and also typically required long reaction times. In addition for many complex reactants, such as enamides, these immobilised catalysts tend to be unstable and leach rhodium rapidly during reaction. For this reason we have investigated the modification of nanocrystalline palladium catalysts using chiral alkaloids to determine if enantioselectivity can be induced in this reaction. The approach has been well studied for heterogeneous enantioselective hydrogenation of prochiral ketones particularly using cinchona-modified supported Pt catalysts [12–15] and tartrate-modified Ni catalysts [16–18]. To date there has been significant progress in the use of alkaloid-modified supported palladium catalysts for the hydrogenation of prochiral carbon–carbon double bonds in acids [5,19–25]; for example, the hydrogenation of 4-hydroxy-6-methyl-2-pyrone has been achieved with an ee of 85%. However, enantioselective hydrogenation of the corresponding methyl esters has not met with success. In this paper we present our initial results for the enantioselective hydrogenation of NADPME using cinchonine-modified Pd/TiO_2 catalysts and report promising enantioselection (ee ca. 30%) which is the first example of enantioselectivity for these substrates with a heterogeneous catalyst.

2. Experimental

2.1. Preparation of materials

2.1.1. Preparation of dehydrophenylalanine azlactone

Benzaldehyde (55 g), *N*-acetylglycine (61 g) and sodium acetate (43 g) were suspended in ethyl acetate (125 ml), acetic anhydride (36 g) was added and the mixture was heated (85–90 °C) with stirring for 20 h. The resultant solution was cooled to 50 °C and deionised water (382 ml) was added to precipitate the product. The mobile slurry was stirred at 30–35 °C for 0.5 h and then cooled to 0–5 °C for 1 h. The product was recovered by vacuum filtration and washed with deionised water. The product was characterised by ^1H NMR (CD_3OD, 400 MHz), δ: 2.2 (singlet, 3H), 6.9 (singlet, 1H), 7.3 (multiplet, 3H), 7.9 (multiplet, 2H).

2.1.2. Preparation of (E)-N-acetyl dehydrophenylalanine methyl ester

Dehydrophenylalanine azlactone (15 g) was slurried in methanol (50 ml) at 25 °C for 1 h, 25% sodium methoxide in methanol was slowly added to form a brown solution which was stirred for 1 h. The product was recovered by vacuum filtration and dried (50 °C, 16 h) and characterised by ^1H NMR (CD_3OD, 400 MHz), δ: 2.2 (singlet, 3H), 3.9 (singlet, 3H), 7.0 (singlet, 1H), 7.5 (multiplet, 6H).

2.1.3. Catalyst preparation

Palladium catalysts were prepared using two methods, the deposition–reduction method (A) and wet impregnation method (B).

2.1.3.1. Method A. Titanium dioxide (2 g, anatase, Degussa, 50 $m^2\ g^{-1}$) was added to distilled water (30 ml). An appropriate amount of potassium tetrachloropallidite (K_2PdCl_4, Johnson Matthey) was added to this suspension and was maintained at pH 11 by the addition of solid KOH. The suspension was refluxed for 1 h, and sodium borohydride (ca. three times the stoichiometric requirement) was added. After 0.5 h the mixture was cooled and the catalyst recovered by filtration. A 5% Pd/Al_2O_3 catalyst was also prepared using this method (γ-Al_2O_3, Sasol, 148 $m^2\ g^{-1}$).

2.1.3.2. Method B. Five percent Pd/TiO_2 catalyst was prepared as follows. Titanium dioxide (2 g, anatase, Degussa, 50 $m^2\ g^{-1}$) and sodium hydroxide (4 ml, 0.14 mol l^{-1}) were added to distilled water (30 ml) at 25 °C. Palladium nitrate solution (10 ml, 0.28 mol l^{-1}) was added dropwise whilst maintaining the temperature at 25 °C, and the mixture was stirred for 0.5 h following complete addition. The materials were then recovered by vacuum filtration, washed with deionised water and dried (110 °C, 16 h). Before use the catalyst was reduced in a tube furnace at 250 °C in 5% H_2 in He for 10 h.

The catalysts were characterised using powder X-ray diffraction, Pd content was determined using atomic absorption and the Pd dispersion was determined using CO chemisorption. Some samples were analyzed using transmission electron microscopy (TEM).

2.2. Hydrogenation reactions

A standard procedure was adopted for the hydrogenation of NADPME as follows. NADPME (100 mg, 0.46 mol) and cinchonine (Fluka) were dissolved in methanol (10 ml) and added to the catalyst (50 mg) in a Parr autoclave (50 ml reactor volume) and the reactor was closed. Various amounts of cinchonine were used to investigate the effect of the cinchonine:NADPME molar ratio on enantioselectivity. The reactor was purged twice with He and then twice with H_2 (3 bar) to remove residual air from the reactor. The reactor was pressurized to 10 bar and stirring started (1000 rpm) and maintained at 25 °C for 3 h to achieve complete conversion; all results are quoted at 100% conversion. Products were analyzed using chiral gas chromatography after the catalyst was removed by filtration. Experiments were carried out in triplicate and the average results are presented in this study. Detailed calibration of the GC method showed that the ee could be determined with an accuracy of ±0.7%.

3. Results and discussion

3.1. Effect of catalyst support and preparation method

Five percent Pd/TiO_2 and 5% Pd/Al_2O_3 catalysts were investigated for the enantioselective hydrogenation of NADPME and the results are shown in Table 1. Using cinchonine as modifier leads to the formation of a small ee to *S*-*N*-acetyl phenylalanine methyl ester. Experiments were also

Table 1
Effect of support and preparation method on the hydrogenation of NADPME using 5% Pd/TiO_2 and 5% $Pd/\gamma\text{-}Al_2O_3$

Catalyst	ee (%) (*S*) Cinchonine:NADPME molar ratio					
	0.006	0.01	0.02	0.04	0.07	0.1
5% Pd/TiO_2 (A)	8.0	8.5	12.0	16.5	17.0	13.0
5% Pd/TiO_2 (B)	9.0	13.0	16.0	17.0	17.0	14.0
5% $Pd/\gamma\text{-}Al_2O_3$ (A)	9.0	13.0	14.5	14.0	14.0	13.5

conducted with cinchonidine as modifier under similar conditions for the 5% Pd/Al_2O_3 catalyst and similar ee to the *R*-*N*-acetyl phenylalanine methyl ester was observed. Pd/TiO_2 catalysts prepared using the two methods (A and B) gave very similar results within experimental error, showing that the catalyst preparation method is not significant for this reaction. The ee is clearly sensitive to the cinchonine:NADPME molar ratio, and this has been observed in numerous previous studies of other reactants with cinchona-modified catalysts [14,15,20]. The Pd/Al_2O_3 catalyst gives very similar enantioselection, although the ee is slightly lower than that for Pd/TiO_2. Previous studies for the hydrogenation of prochiral carbon–carbon double bonds in acids have also shown that titania is the preferred support. For example, Nitta et al. [26] have reported an increase of ca. 20–30% in ee for the hydrogenation of phenylcinnamic acid when titania is used as support instead of alumina. The effect is not so marked in our initial studies. We analyzed the 5% Pd/TiO_2 and 5% Pd/Al_2O_3 catalysts prepared by method A using TEM and the average Pd particle size was found to be ca. 4 nm for the titania supported sample and ca. 7 nm for the alumina supported sample. This indicates that Pd dispersion and particle size are potentially important rather than the nature of the surface of the support.

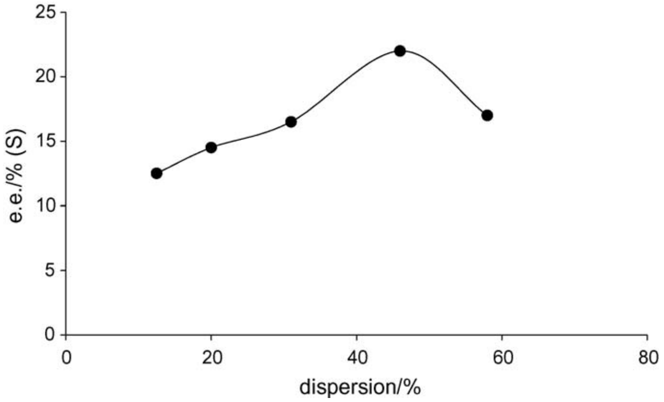

Fig. 1. Effect of Pd dispersion on the maximum ee observed for the enantioselective hydrogenation of NADPME using Pd/TiO_2 catalysts (cinchonine:-NADPME ratio, see Table 2).

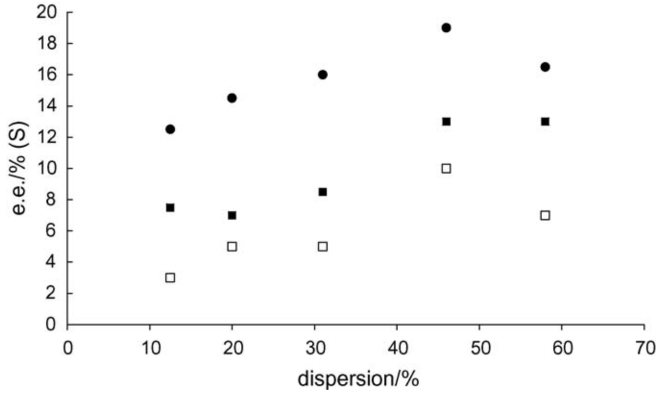

Fig. 2. Effect of Pd dispersion on the ee observed for the enantioselective hydrogenation of NADPME using Pd/TiO_2 catalysts at a fixed cinchonine:-NADPME ratio. *Key*—cinchonine:NADPME ratio: (■) 0.01, (●) 0.08 and (□) 0.40.

3.2. *Effect of Pd loading*

The influence of the Pd loading on the enantioselective hydrogenation was carried out by preparing a set of Pd/TiO_2 catalysts (nominally: 1, 2, 5, 10 and 20% Pd) using method A. The effect of the cinchonine:NADPME molar ratio was also investigated, as it was clear from the initial experiments that this was an important parameter. The results are shown in Table 2, along with the palladium concentrations determined by atomic absorption and the palladium dispersions determined by CO chemisorption and the calculated palladium particle size. It is clear that the ee is a function of both the Pd loading and the cinchonine:NADPME molar ratio. The best results (ee 20–22%) were observed with the 2% Pd/TiO_2 catalyst. Fig. 1 shows the relationship between the Pd dispersion and the maximum ee. The maximum ee is obtained at different cinchonine:-NADPME molar ratios and so the relationship between ee and dispersion at constant cinchonine:NADPME molar ratio is shown in Fig. 2 for low, medium and high ratios. The smooth

Table 2
Effect of Pd loading on the hydrogenation of NADMPE over Pd/TiO_2 catalysts

Pd (%)	Pd_{dis} (%)[a]	Pd (nm)[b]	ee (%) (*S*) Cinchonine:NADPME molar ratio								
			0.01	0.02	0.04	0.08	0.10	0.14	0.16	0.40	0.60
0.94	58	2.1	13.0	16.0	17.0	16.5	14.5	13.0	12.5	7.0	5.0
1.81	46	2.7	13.0	16.0	18.5	19.0	19.0	20.5	22.0	10.0	5.0
4.63	31	4.1	8.5	12.0	16.5	16.0	13.0	–	10.0	5.0	2.0
9.71	20	6.3	7.0	10.0	14.0	14.5	12.5	11.5	12.0	5.0	3.0
19.89	12.5	10.4	7.5	8.0	12.0	12.5	10.0	10.0	9.0	3.0	2.0

[a] Pd dispersion determined by CO chemisorption.
[b] Calculated average Pd particle size.

Table 3
Effect of solvents on the enantioselective hydrogenation of NADPME using Pd/TiO_2 and Pd/γ-Al_2O_3[a]

Solvent	ee (%) (*S*)		
	2% Pd/TiO_2	5% Pd/TiO_2	5% Pd/γ-Al_2O_3
Methanol	22.0	17.0	15.0
Methanol/3% water	18.0	16.0	18.5
DMF	27.0	25.5	20.0
DMF/3% water	24.0	24.5	27.0

[a] All catalysts prepared using method A, optimum cinchonine:NADPME molar ratio used, see Tables 1 and 2.

variation of maximum ee with Pd dispersion suggests the importance of the Pd particle size as a central parameter controlling enantioselectivity. If the Pd dispersion is too high the particle sizes are too small and ineffective interaction with the alkaloid modifier results. Conversely, lower dispersion results in large particles giving lower overall reactivity and not all sites can be effectively modified by the alkaloid. In the present study particles ca. 2.5 nm could be optimal, but further work is required to fully ascertain the optimal Pd particle size. This observation is similar to the relationship observed for ethyl pyruvate hydrogenation over Pt/SiO_2 catalysts with particle size distributions with maxima at 1.8 nm and 0.7 nm. The smaller particle size gave poor enantioselection and it was concluded that such small particles could not interact effectively with the modifier and the reactant [27].

In these initial studies we have explored a range of experimental conditions and although the ee is sensitive to dispersion only relatively limited enantioselection has been observed. Hence a subsequent set of experiments was conducted with both the titania and alumina supported catalysts prepared using method A to determine the effect of water and dimethyl formamide as solvent. The results are shown in Table 3. The use of dimethyformamide as solvent increases the ee significantly, indicating that a more complete investigation of solvent effects could help improve the enantioselection further. The addition of water has different effects for the two supports. For titania the addition of water leads to a small decrease in the ee, whereas with alumina the addition of water increases the ee, and when dimethyl formamide is the solvent the effect is marked. Clearly this indicates that the ee can be manipulated by controlling the nature of the solvent used. The enantioselection observed using dimethyl formamide represent the highest ee's yet observed for the heterogeneous enantioselective hydrogenation of the prochiral carbon–carbon bond in esters. Indeed, this is the first to report that enantioselective hydrogenation can be achieved using this approach.

4. Conclusions

Cinchonine-modified Pd/TiO_2 and Pd/Al_2O_3 catalysts are effective for the enantioselective hydrogenation of NADPME to the *N*-acetyl phenylalanine methyl ester. Neither the support nor the method of preparation appears to be a major factor with respect to enantioselection since similar results can be achieved using titania and alumina as support and with the deposition–reduction and wet impregnation catalyst preparation methods investigated. The Pd dispersion and hence Pd particle size appears to be the dominant factor, in combination with the appropriate selection of the solvent for the reaction. At present the ee obtained can be viewed as promising (ca. 20–30%) and our initial studies can provide a starting point for the design of improved catalysts. However, it should be noted that the enantioselection is the first to be reported for the heterogeneous enantioselective hydrogenation of this class of prochiral reactants.

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