Catalysis Letters Vol. 110, Nos. 1–2, August 2006 (© 2006)
DOI: 10.1007/s10562-006-0096-9

Unexpected inversion of enantioselectivity during the hydrogenation of ethyl pyruvate using hydroquinine and hydroquinidine modified Pt/Al_2O_3

Robert L. Jenkins,[a] Nicholas Dummer,[a] Xiabao Li,[a] Salem M. Bawaked,[a] Paul McMorn,[a] Richard P. K. Wells,[a] Andrew Burrows,[b] Christopher J. Kiely,[b] and Graham J. Hutchings[a,*]

[a]*Department of Chemistry, Cardiff University, Cardiff CF10 3AT, UK*
[b]*Center for Advanced Materials and Nanotechnology, Lehigh University, Bethlehem, PA 18015-3195, USA*

Received 28 March 2006; accepted 11 April 2006

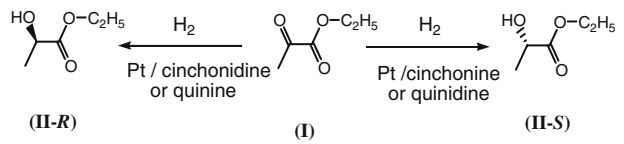
In the enantioselective hydrogenation of ethyl pyruvate using hydroquinidine 4-chlorobenzoate modified Pt/γ-Al_2O_3 catalyst, the sense of the enantioselectivity is a function of the modifier concentration. At low concentration (*S*)-ethyl lactate is preferred and at higher concentration (*R*)-ethyl lactate is formed; the opposite trend is observed with hydroquinine 4-chlorobenzoate. This is the first example where enantio-inversion is induced solely as a function of the chiral modifier concentration.

KEY WORDS: enantioselective hydrogenation; enantio-inversion; ethyl pyruvate hydrogenation.

1. Introduction

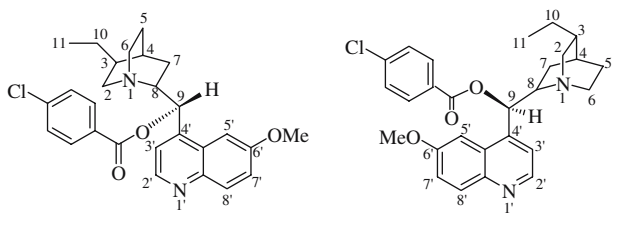
Heterogeneous asymmetric catalysis has become an increasingly researched topic and in particular enantioselective hydrogenation remains a very active area of research. A number of approaches have been adopted which have been reviewed by Davis [1,2]. In general, the chirality required within the transition state to achieve enantioselectivity in the reaction can be supplied by a chiral surface [2], by a chiral solvent [3] or by a chiral modifier associated with either an immobilised metal centre [4] or a metal surface [5,6]. For many studies it is the latter approach that has been adopted, and of the relatively few systems capable of high levels of enantioselection, the asymmetric hydrogenation of α-ketoesters using supported Pt nanoparticles modified with cinchona alkaloids has been studied extensively and is considered to be a model system [5,6].

In earlier studies [5] of the enantioselective hydrogenation of ethyl pyruvate (I), it has been well established that with cinchonidine- and quinine- modified platinum catalysts the reaction proceeds to form (*R*)-ethyl lactate (II-*R*) predominantly, whereas with cinchonine- and quinidine- modified platinum catalysts the reaction forms (*S*)-ethyl lactate (II-*S*) preferentially (Scheme 1). Considerable effort has been focussed on understanding the mechanism of these reactions, and three structural features of the cinchona and related modifiers that ensure they are effective in enantio-direction have been identified, namely (a) an aromatic moiety that enables adsorption on the platinum surface (b) the absolute configuration at C(9) which controls the sense of the enantioselectivity, and (c) a basic nitrogen which is considered to interact with the substrate resulting in a 1:1 complex that is hydrogenated enantioselectively [5]. The reaction is, however, complicated by effects observed in the early part of the reaction where enantioselection increases with conversion [7–10]. Consequently, there has been limited progress in gaining an understanding of this fascinating reaction at the molecular level.



Scheme 1. The possible products of ethyl pyruvate (I) hydrogenation over cinchona modified platinum catalysts.

Recently, Baiker and co-workers [11–13] and Bartók *et al.* [14,15] have identified a further intriguing aspect of this reaction, namely that the sense of the enantioselection can be inverted for specific modifiers by changing the extent of reaction [11], the solvent [14] or the substituent at C(9) [12,13]. In all these cases the effect is induced by changes in the reaction conditions. We have now observed, that when hydroquinidine 4-chlorobenzoate **1** and hydroquinine 4-chlorobenzoate **2** (Scheme 2) are used as modifiers,



Scheme 2. Hydroquinidine and hydroquinine modifiers.

*To whom correspondence should be addressed.
E-mail: Hutch@cardiff.ac.uk

the sense of the enantioselectivity can be inverted solely by changing the concentration of the modifier.

2. Experimental

Five percent Pt/Al_2O_3 (Johnson Matthey) and was pre-treated with hydrogen (5% H_2 in Ar, 2 h) at temperatures between 100 and 400°C prior to use. Hydroquinidine 4- chlorobenzoate (Fluka, 98%) and hydroquinine 4-chlorobenzoate (Fluka, 98%) were used as received. Ethyl pyruvate (Fluka, > 97%) and methyl pyruvate (Fluka, > 97%) were purified prior to use. The pyruvate (50 mL) was mixed with CH_2Cl_2 (50 mL) and was treated with $KHCO_3$ (0.1 mol/L, 50 mL). The organic layer was collected and distilled under reduced pressure over $MgSO_4$ to remove CH_2Cl_2. The residue was distilled over anhydrous $CaCl_2$ under vacuum and the purified pyruvate was used immediately. Detailed analysis showed that no impurities, such as racemic lactates, were present in the purified reactant.

Pt catalysts were modified using an *in-situ* procedure in which the modifier [15] was added to the autoclave reactor immediately prior to H_2 addition. The enantioselective hydrogenation reactions were carried out using a stainless steel Parr 50 mL stirred autoclave reactor. Under standard conditions, ethyl pyruvate (66 mmol), solvent (12.5 mL), modifier (1–100 mg) and 5% Pt/Al_2O_3 catalyst (0.25 g) were sealed into the autoclave. The autoclave was purged three times with hydrogen to a pressure of 30 bar to remove residual air. Hydrogen was then admitted to the required reaction pressure (50 bar). At the same time, stirring was commenced (1200 rpm) to start the reaction and the reaction was halted by stopping the stirring and decreasing the hydrogen pressure. The product was isolated and analysed by chiral gas chromatography.

Bright field (BF) and high resolution transmission electron microscopy (HRTEM) was performed at 200 kV using a JEOL 2200FS transmission electron microscope having a point-to-point resolution of 0.19 nm. Samples were prepared for TEM analysis by dry dispersing the catalyst powder on to a holey carbon film supported by a 300 mesh copper TEM grid.

Proton NMR was used to investigate the possible hydrolysis of hydroquinidine 4-chlorobenzoate in the presence of ethyl pyruvate, dichloromethane and water. A series of proton NMR experiments were performed at 1 h intervals over a period of 12 h for a 0.5 mL CD_2Cl_2 solution containing hydroquinidine 4- chlorobenzoate (3.41 mg, 7.3μmol), ethyl pyruvate (2.60 mmol) and an excess of water (1 μL, 55 mmol). The spectra were recorded using a Bruker Avance multinuclear 500 MHz NMR spectrometer. The spectrometer was configured to lock automatically on the deuterium signal of CD_2Cl_2, which also acted as an internal reference.

Table 1
Effect of the solvent on the hydrogenation of ethyl pyruvate

Modifier (mg)	Solvent	Hydroquinidine[a]		Hydroquinine[a]	
		Conv (%)	ee (%)	Conv (%)	ee (%)
79.1	Acetic acid	47	26 S	52	25 R
79.1	Toluene	6	2 R	19	9 R
79.1	Dichloromethane	97	8 R	89	14 S
16.0	Dichloromethane	100	6 S	100	21 R
2.2	Dichloromethane	100	32 S	100	20 R

[a]Modifiers used as 4-chlorobenzoate derivative.

3. Results and discussion

Our initial observations came from experiments using hydroquinidine 4-chlorobenzoate **1** and hydroquinine 4-chlorobenzoate **2** as modifiers. It is known that the conformation of cinchona modifiers can be significantly affected by the nature of the solvent [15] and we investigated this effect for this modifier (Table 1).

In acetic acid the sense of the enantioselection is inverted when compared with toluene and dichloromethane as solvents and this phenomenon is considered to be related to the conformation of the modifier, which when protonated prefers an *open 3* conformation [16]. However, an interesting effect was observed in dichloromethane, where the sense of enantioselectivity inverted as the concentration of the modifier increased. The opposite effects, with similar magnitude, were also observed with hydroquinine 4-chlorobenzoate, as expected from the absolute configuration at C(9). Since protonation of the modifier can influence the sense and extent of enantioselection, we considered that the effects observed in dichloromethane could have been caused by the instability of the modifier, i.e. during these experiments the modifier is hydrolysed to give 4-chlorobenzoic acid which could protonate the remaining non-hydro-

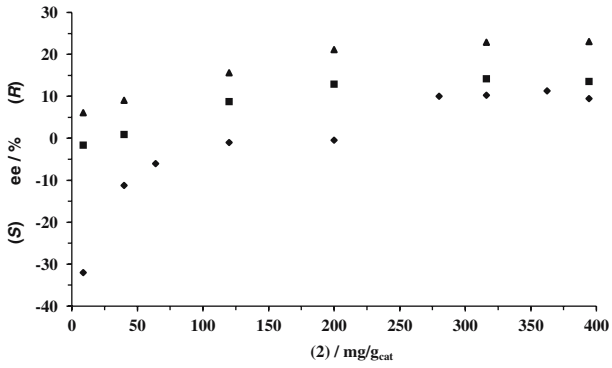


Figure 1. The effect of catalyst reduction temperature on the enantioselective hydrogenation of ethyl pyruvate using hydroquinidine 4-chlorobenzoate as a chiral modifier. ◆400°C, ■200°C, ▲100°C 5% Pt/Al_2O_3.

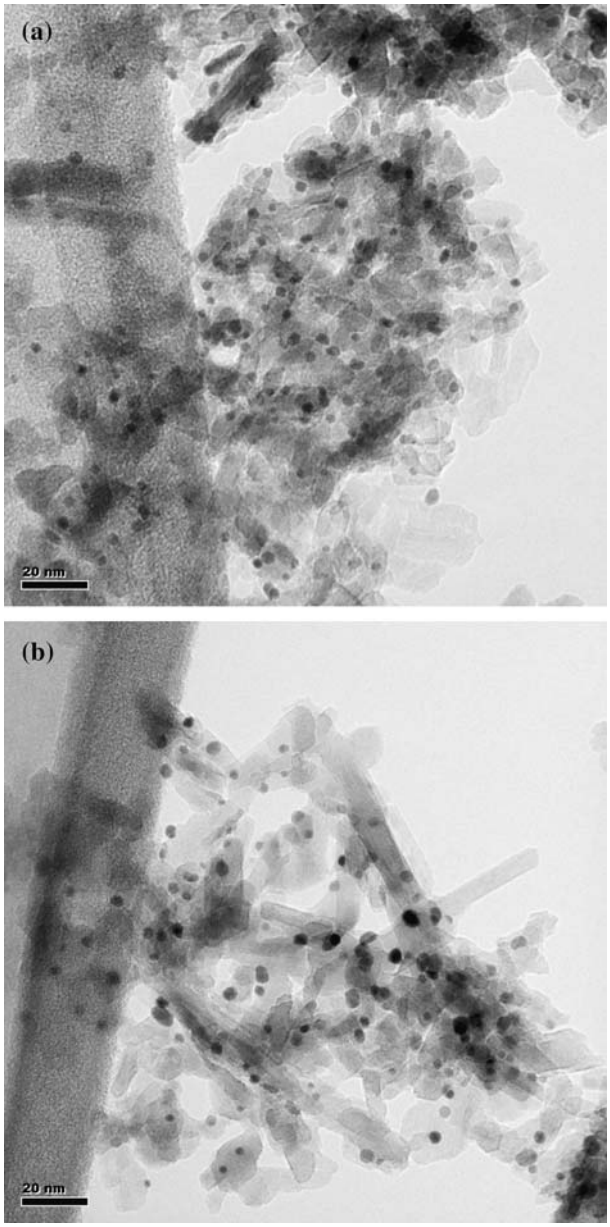


Figure 2. Representative bright field electron micrographs of the Pt/γ-Al_20_3 catalyst materials reduced at (a) 100°C and (b) 400°C respectively.

lysed modifier. Hence, if this hypothesis is correct, the experimental observation of the inversion in enantioselectivity could be explained by structural changes to the modifier. To test this proposition we carried out two further sets of experiments. First, we added 4-chlorobenzoic acid to the reaction mixture and we observed no changes in the sense of the enantioselection. Second, we carried out detailed NMR spectroscopic studies, which showed that the modifier was not prone to hydrolysis when in solution. Specifically, hydroquinidine 4-chlorobenzoate and ethyl pyruvate were stirred with an excess of water under simulated reaction conditions and no hydrolysis of the modifier was observed. Hence, the effect must be related specifically to the way in which the modifier interacts with the Pt nanocrystals.

Subsequently, a series of enantioselective hydrogenations were carried out over 5% Pt/Al_2O_3 reduced at 400 °C (Figure 1, ◆) modified with hydroquinidine 4-chlorobenzoate **1** in which the concentration of the modifier was varied over a range of about two orders of magnitude using dichloromethane as solvent. The results presented in Figure 1 show that the sense of the enantioselection is a function of the modifier concentration and that (*S*)-ethyl lactate is formed (ca. 30% ee) at low concentrations. As the concentration of the modifier is increased, the product becomes racemic and then, subsequently, at higher modifier concentrations (*R*)-ethyl lactate is preferentially formed (ca. 10% ee). Therefore, the modifier concentration has a remarkable effect on the enantiomeric excess of ethyl pyruvate hydrogenation. This is the first observation for any heterogeneously catalysed asymmetric reaction where the sense of the enantioselection is affected solely by changing the concentration of the modifier and is clearly an unprecedented finding given the volume of prior work conducted on this model reaction. Although the absolute change in ee is not particularly high, it is significant and similar in magnitude to the effects observed in previous studies where changes were induced by altering the reaction conditions [11–15].

In a further set of experiments we examined the effect of the reduction temperature of the 5% Pt/Al_2O_3 catalyst on the sense of the enantioselection (Figure 1). When the catalyst is reduced at 200°C (Figure 1, ■) a similar trend was observed with the reaction proceeding racemically at low modifier concentrations and enantioselectively at higher concentrations where (*R*)-ethyl lactate was preferentially formed (ca. 15% ee). At the lower reduction temperature of 100°C (Figure 1,▲) the same trend in enantioselection is observed with increasing alkaloid concentration, but the enantioinversion at low alkaloid is not now observed. It has been well documented that heat treatments can, in some cases, alter the microstructure of supported metal catalysts. Detailed TEM imaging experiments showed that the range of catalyst reduction temperatures (100–400°C) investigated in this study did not significantly affect the platinum particle size distribution. Figure 2(a) and (b) are bright field images of samples reduced at 100 and 400°C respectively, in which the Pt nanoparticles are clearly seen by diffraction contrast to be in the 2–5 nm size range in both cases. Significant sintering of Pt nanoparticles at these relatively low temperatures is not expected since Pt is a fairly refractory metal with a melting point (T_m) of 1772°C. Even taking into account the possibility of a significant melting point depression at the nanoscale, the highest heat treatment temperature (400°C) is still probably less than $0.4T_m$. HREM images of representative metal nanoparticles from the samples reduced at 100 and 400°C are shown in Figure 3(a) and

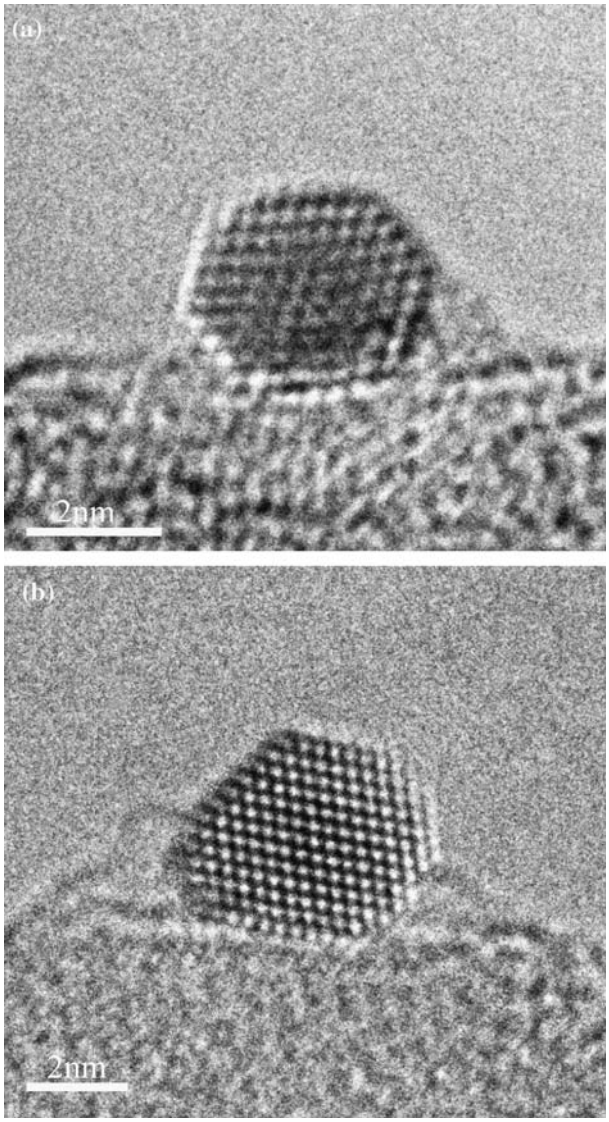


Figure 3. Representative HRTEM images of Pt nanoparticles in the Pt/γ-Al_20_3 catalyst materials reduced at (a) 100°C and (b) 400°C respectively.

(b) respectively. The particles are imaged in profile along the Pt [110] projection and {111} and {002} type lattice fringes are clearly resolved. The particles in both cases have truncated cub-octahedral morphologies and expose low energy {111} and {002} type facet planes. Hence, in summary, our microstructural studies failed to pick up any significant differences in the Pt particle morphology or size distribution between samples reduced at 100, 200 or 400°C that could explain their differing relative behaviour in these enantioselective reactions.

It is possible that the temperature of calcination has an effect on the degree of hydroxylation of the surface of the alumina support and further studies are needed to investigate the origin of this interesting effect. In particular, we have recently shown that enantioselective hydrogenation of alkyl pyruvate esters can be carried out using gas phase reactants [17] thereby avoiding the complicating factor of solvent effects and we plan further studies using this methodology to investigate enantio-inversion.

In conclusion, we have shown that using hydroquinidine 4-chlorobenzoate as a modifier for $Pt/Al_2O_3$the enantioselectivity observed is a function of the modifier concentration, and at low concentrations enantio-inversion is oberved. This is the first time that enantio-inversion is shown to be solely a function of the modifier concentration for the hydrogenation of alkyl pyruvate esters.

Acknowledgments

We thank the Leverhulme Trust, the Commonwealth of Pennsylvania and King Abdul Aziz University (Saudi Arabia Government) for financial support.

References

[1] M.E. Davis, Micropor. Mesopor. Mat. 21 (1998) 173.
[2] M.E. Davis and R.F. Lobo, Chem. Mater. 4 (1992) 756.
[3] W. Adam, A. Corma, A. Martinez, C.M. Mitchell, T.I. Reddy, M. Renz and A.K. Smerz, J. Mol. Catal. A 117 (1997) 357.
[4] S. Feast, D. Bethell, P.C.B. Page, F. King, C. H. Rochester, M. R.H. Siddiqui, D.J. Willock and G.J. Hutchings, J. Chem. Soc. Chem. Commun., (1995) 2409.
[5] M. von Arx, T. Mallat and A. Baiker, Topics Catal. 19 (2002) 75.
[6] H.U. Blaser, Chem. Commun., (2003) 293.
[7] T. Mallat, Z. Bodnar, B. Minder, K. Borszeky and A. Baiker, J. Catal. 168 (1997) 183.
[8] D.G. Blackmond, J. Catal. 176 (1998) 267.
[9] T. Mallat and A. Baiker, J. Catal. 176 (1998) 271.
[10] X. Li, R.P.K. Wells, P.B. Wells and G.J. Hutchings, J. Catal. 221 (2004) 653.
[11] M. von Arx, T. Mallat and A. Baiker, Angew. Chem. Int. Ed. 40 (2001) 2302.
[12] R. Hess, A. Vargas, T. Mallat, T. Bürgi and A. Baiker, J. Catal. 222 (2004) 117.
[13] S. Diezi, A. Szabo, T. Mallat and A. Baiker, Tetrahedron: Asymm. 14 (2003) 2573.
[14] M. Bartók, M. Sutyinski, K. Felföldi and G. Szöllósi, Chem. Commun. (2002) 1130.
[15] S. Cserényi, K. Felföldi, K. Balázsik and G. Szöllök, J. Molec. Catal. A 247 (2006) 108.
[16] T. Bürgi and A. Baiker, J. Am. Chem. Soc. 120 (1998) 12920.
[17] M. von Arx, N. Dummer, D.J. Willock, S. H. Taylor, R.P.K. Wells, P.B. Wells and G.J. Hutchings, Chem. Commun. (2003) 1926.