

Observation of high enantioselectivity for the gas phase hydrogenation of methyl pyruvate using supported Pt catalysts pre-modified with cinchonidine†

Matthias von Arx,^{ab} Nicholas Dummer,^a David J. Willock,^a Stuart H. Taylor,^a Richard P. K. Wells,^c Peter B. Wells^a and Graham J. Hutchings^{*a}

^a Department of Chemistry, Cardiff University, PO Box 912, Cardiff, UK CF10 3TB. E-mail: hutch@cf.ac.uk

^b University of Basel, Institut für Physik, Klingelbergstrasse 82, CH-4056, Basel, Switzerland

^c Department of Chemistry, University of Aberdeen, Aberdeen, UK AB24 3UE

Received (in Cambridge, UK) 2nd May 2003, Accepted 27th May 2003

First published as an Advance Article on the web 27th June 2003

Pt supported on α -Al₂O₃, γ -Al₂O₃ and SiO₂ pre-modified with cinchonidine gives over 50% ee in the hydrogenation of methyl pyruvate to methyl lactate using gas phase reactants at 40 °C giving the first clear observation of high enantioselectivity at the gas/solid interface.

In recent years extensive efforts have been made to expand the scope of cinchona alkaloid-modified Pt catalysts.^{1,2} To date, there have been no reports of asymmetric hydrogenation using cinchonidine-modified supported metal catalysts using gas phase reactants. We have now successfully addressed this aspect of the reaction and report, for the first time, clear evidence for an asymmetric reaction occurring at the gas/solid interface.

Our initial experiments were carried out using a cinchonidine pre-modified Pt/ γ -Al₂O₃ catalyst³ for the hydrogenation of methyl pyruvate using a fixed bed plug flow reactor.⁴ Significant ee for the formation of *R*-methyl lactate was observed and the results are shown in Table 1. Comparable experiments, with 2 bar hydrogen pressure, were carried out using the same pre-modified catalysts in a batch autoclave reactor⁵ and the results are also shown in Table 1. At high hydrogen concentration (25%) close to 50% ee was obtained in the gas phase reaction. In the batch liquid phase reaction up to 70% ee was attained with toluene as solvent at 25 °C and 2 bar hydrogen pressure. Valuable information on the modifier, adsorbed on the metal surface, was obtained by following the ee with reaction time, with respect to the reaction temperature,

hydrogen and modifier concentration. At elevated temperature or hydrogen concentration and at low modifier concentration the ee started to decrease after less than 2 hours. This effect was cumulative. If several factors were changed according to these findings, the enantioselectivity decreased from the start of the reaction using gas phase reactants. This indicates that, very similar to the situation in liquid phase batch reactions, adsorption of cinchonidine by the aromatic ring system is crucial for enantioselection. If the ring system is (partially) hydrogenated (a process favourable at elevated temperature and hydrogen concentration) enantioselectivity is lost.⁶

The influence of hydrogen concentration on ee is observed to be significant (Table 1). Under most conditions, the ee was almost doubled by increasing the hydrogen concentration in the gas stream from 2.5 to 50%.^{6,7} This observation is of special interest with respect to some recent spectroscopic investigations dealing with the adsorption geometry of reactants and modifiers. For both it has been found that the adsorption geometry is changing from a tilted to a more flat adsorption mode in the presence of hydrogen.^{6,7} Using gas phase reactants this effect seems to be particularly marked, increasing enantioselection.

The behaviour of the reaction with increasing temperature was different in the liquid and gas phase (Table 1). While in the liquid phase ee decreased with increasing temperature, as expected from previous studies, in the gas phase, ee increased from room temperature to 40 °C and decreased only slightly when the temperature was raised to 60 °C. As a result, at 60 °C, the enantioselectivity in the gas phase reaction using pre-modified 5% Pt/ γ -Al₂O₃ was higher than that in the corresponding liquid phase experiment. For the gas phase reactants, the ee was observed to be 42%, whereas for liquid phase reactants the ee was observed to be 35%. Finally, upon addition of small amounts of acetic acid during the pre-modification step the ee could be increased above 50%. Addition of acids seems to have a positive effect on enantioselectivity, both in liquid and in gas phase reactions. To our knowledge, the value of 51% ee is the highest reported for any enantioselective reaction using gas phase reactants.

Table 1 Influence of reaction parameters on enantioselectivity^a

H ₂ -concentration (%)	Amount of modifier ^b	Temperature/°C	AcOH additive ^c	<i>R</i> -methyl lactate ee (%)
2.5	0.5	40	—	25
5	0.5	40	—	31
10	0.5	40	—	37
25	0.5	40	—	42 ^{*d}
50	0.5	40	—	43 [*]
25	1	40	—	46 (54) ^e
25	2	40	—	47
25	1	25	—	29 (70) ^e
25	1	60	—	40 [*] (35) ^e
25	2	40	5	48
25	2	40	20	51 [*]

^a Standard reaction conditions as specified in notes 10 and 11. ^b Molar ratio of: Modifier/Ms (metal surface atoms) at a metal dispersion of 0.25. ^c Added during premodification (molar equiv. to CD). ^d Values designated with * are initial values. ee decreases during time on line. ^e Values in parentheses are the corresponding values from liquid phase batch reaction at 2 bar H₂-pressure using toluene as solvent.

† Electronic supplementary information (ESI) available: use of the Kelvin equation and reactant partial pressure to estimate the effective partial pressure for condensation as a function of pore radius. See <http://www.rsc.org/suppdata/cc/b3/b304976k/>

Table 2 Comparison of the reaction rates using premodified catalysts in liquid and gas phases^a

Experimental number	H ₂ -Concentration (bar)/(%)	Amount of CD ^b	Reaction rate relative to unmodified catalyst ^c	
			Liquid	Gas
1	10/5	0.5	3.8	0.48
2	10/5	0.5 ^d	3.9	—
3	10/5	1	2.8	0.27
4	2/25	1	2.9	0.7

^a reaction carried out using standard conditions in ref. 4,5. ^b molar ratio of: Modifier/Ms (metal surface atoms) at a metal dispersion of 0.25. ^c reaction rate based on the H₂-uptake for the liquid phase reaction and on pyruvate conversion for the gas phase reaction ^d standard modification procedure for liquid phase hydrogenation reaction.

Table 3 Hydrogenation of ethyl pyruvate using Pt/SiO₂ and Pt/ α -Al₂O₃ catalysts

Catalyst g	Reactant	Vaporiser temperature/°C	Reactor temperature/°C	Max conv. (%)	Max ee at max conv. (%)
2.5% Pt/Silica (25 mg)	Methyl pyruvate	0	40	100	38
2.5% Pt/Silica (25 mg)	Methyl pyruvate	20	40	100	43
2.5% Pt/Silica (25 mg)	Ethyl pyruvate	20	40	100	35
2.5% Pt/Silica (25 mg)	But-2,3-dione	0	35	75	20
1% Pt/ α -Al ₂ O ₃ (50 mg)	Methyl pyruvate	20	40	78	25

To our surprise the pre-modified catalysts showed a decrease in reaction rate compared to the unmodified reference catalyst, independent of the reaction conditions (H₂-partial pressure, T, modifier concentration, see Table 2). This is in contrast to the well reported rate enhancement observed when cinchonidine catalysts are used with liquid phase reactants.^{1,2} However, using the identical catalyst under liquid phase (batch) conditions, the rate enhancement was observed when the standard *in situ* modification in solution was used (see Table 2, experiments 1 and 2 for liquid phase reactions). Hence, the different behaviour must, therefore, be due to the absence of solvent and cannot be the result of the pre-modification procedure. In the liquid phase the rate enhancement was more pronounced at low modifier loading, while in gas phase reactions the decrease in reaction rate is increased at the higher modifier concentration. Changing the hydrogen pressure in the batch liquid phase reaction had no significant influence on the degree of the rate enhancement. On the other hand, the decrease in conversion observed for the gas phase reaction, relative to the unmodified catalyst, was less when the reaction was carried out at higher hydrogen concentration.

To show that the observation of high enantioselectivity for the gas phase reaction was not solely related to the Pt/ γ -Al₂O₃ catalyst,⁸ a series of experiments were conducted under similar conditions with Pt/SiO₂⁸ and Pt/ α -Al₂O₃ catalysts,⁸ using methyl pyruvate, ethyl pyruvate and butane-2,3-dione. The results, shown in Table 3, clearly demonstrate that a significant ee was observed for the two pyruvate reactants and, to a lesser extent, with butane-2,3-dione. These results are in line with the relative enantioselectivity for these reactants using liquid phase reactants.

This series of experiments was also used to investigate the possibility that capillary condensation could occur in the intra-particle pore system of the Pt/ γ -Al₂O₃ catalysts. Using our conditions, in which the reactant vaporiser is maintained at 20 °C, we have estimated that capillary condensation can only occur in pores of <5 Å for reactions at 40 °C.⁹ From N₂ adsorption measurements, the fraction of pores of this dimension are insignificant but, as a further check, Table 3 shows that the results remain consistent when the vaporiser temperature is lowered to 0 °C, for which the reactant partial pressure will be even further from the condensation condition. To provide conclusive evidence that the reaction is occurring at the gas/solid interface, we carried out a final set of experiments using a Pt/ α -Al₂O₃ catalyst for which a substantial ee was still observed (Table 3). α -Al₂O₃ does not contain an intra particle pore structure and, consequently, we consider these results provide the first clear demonstration of an enantioselective reaction occurring at the gas/solid interface. Two previous studies^{10,11} have reported enantioselectivity using gas phase reactants, but both involved the use of microporous zeolites under conditions where capillary condensation was certain to occur.

The decrease in rate observed for the gas phase reaction with the pre-modified catalysts requires further comment. To be sure that the reaction was not being conducted under conditions dominated by diffusion limitations a range of experiments were carried out in which the mass of pre-modified catalysts was increased from 6.25 to 25 mg and these gave similar

conversions of ca. 0.025 mol of pyruvate converted h⁻¹ g⁻¹. Hence, we do not consider the rate decrease observed is due to any diffusion effects in the fixed bed reactor. Earlier studies have shown that an ee can be observed with deactivated catalysts, where the cinchonidine modification is carried out *in situ*. These earlier studies clearly show that the rate can be decoupled from enantioselection. However, we show that the solvent plays a key role in the achievement of the enantioselection since, in our studies, the same catalyst is used in the gas and liquid phase experimentation, yet the rate enhancement is observed only when the solvent is present. From these experimental data, it is clear that there are some substantial differences in the behaviour of this reaction at the gas and liquid/solid and gas/solid interfaces. At the present time we are planning detailed investigations to consider possible differences in the rate determining steps (*e.g.* desorption of the product *vs.* product formation on the catalyst surface) or differences in the molecular interactions on the metal surface and in solution during product formation.

We are convinced that for further mechanistic investigations on the enantioselective hydrogenation over cinchona modified Pt, the observation of enantioselective gas phase hydrogenation is of great interest. In particular the absence of a solvent considerably simplifies the system, allowing the use of various spectroscopic methods under *in situ* conditions to be extended and evaluated.

Notes and references

- 1 M. von Arx, T. Mallat and A. Baiker, *Top. Catal.*, 2002, **19**, 75.
- 2 M. Studer, S. Burkhardt and H.-U. Blaser, *Chem. Commun.*, 1999, 1727.
- 3 Pre-modified catalysts were produced by suspension of catalyst (200 mg) in a solution of cinchonidine in dichloromethane. After stirring for 10 min the modified catalyst was filtered and dried under vacuum before use.
- 4 A flow microreactor (i.d. 3 mm) glass was used. Catalyst samples were pre-conditioned in a He flow (80 ml min⁻¹) for 10 min followed by a 3 : 1 He : H₂ flow (80 ml min⁻¹) for a further 10 min. This He : H₂ mixture was then diverted through the vaporiser at 20 °C to deliver methyl pyruvate vapour to the catalyst. Products were analysed by chiral gc (25 m β -Chirasil-dex).
- 5 Reactions were performed using a stainless steel Baskerville autoclave (100 ml) with a glass liner (volume 80 ml) and the reaction mixture was stirred at 1000 rpm. The catalyst (0.04–0.1 g) was stirred with cinchonidine (13.5 mM) in solvent (20–25 ml) for 10 minutes in air. Methyl pyruvate (0.5 g) was then added along with a further 5 ml of solvent. The vessel was purged with H₂ prior to pressurising to reaction pressure (1 bar).
- 6 H.-U. Blaser, H. P. Jalett, D. M. Monti, A. Baiker and J. T. Wehrli, *Stud. Surf. Sci. Catal.*, 1991, **67**, 147.
- 7 T. Bürgi, F. Atamny, R. Schlögl and A. Baiker, *J. Phys. Chem. B*, 2000, **104**, 5953.
- 8 5 wt% Pt/ γ -Al₂O₃ (Johnson Matthey), 2.5 wt% Pt/silica (Johnson Matthey/Davison catalysts) and 1 wt% Pt/ α -Al₂O₃ (Sasol alumina).
- 9 See ESI for detailed calculations.
- 10 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, 2409–2411.
- 11 A. López-Martínez and M. A. Keane, *J. Mol. Catal. A*, 2000, **153**, 257.