ELSEVIER

Journal of Molecular Catalysis A: Chemical 146 (1999) 159–166

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

www.elsevier.com/locate/molcata

# Chiral environments at alkaloid-modified platinum surfaces

P.B. Wells [a,*], K.E. Simons [b], J.A. Slipszenko [a], S.P. Griffiths [a], D.F. Ewing [a]

[a] *Department of Chemistry, University of Hull, Hull, HU6 7RX, UK*
[b] *Johnson Matthey, Orchard Road, Royston, SG8 5HE, UK*

**Abstract**

Molecular environments at enantioselective sites are considered with reference to the adsorption of cinchonidine, epiquinidine, brucine, and oxycodone onto 6.3% Pt/silica (EUROPT-1), using the hydrogenation of methyl pyruvate and of butane-2,3-dione as molecular probes. The mode of action of cinchonidine is briefly reviewed, and the ineffectiveness of epiquinidine is interpreted. Pt modified by the strychnos alkaloid brucine is active for the hydrogenation of methyl pyruvate at 10 bar pressure and 293 K giving an enantiomeric excess of up to 20% in favour of *S*-lactate, but is not enantioselective for butane-2,3-dione hydrogenation. Modelling shows that brucine adsorbed at a step at a Pt surface forms a cavity which provides for the selective enantioface adsorption of methyl pyruvate, but not of butane-2,3-dione. The model locates the site for alkaloid adsorption and the site for enantioselective hydrogenation on the same terrace of metal atoms. Pt modified by the morphine alkaloid oxycodone is enantioselective for the hydrogenation of both methyl pyruvate and butane-2,3-dione at 10 bar pressure and 293 K, the enantiomeric excess being typically 15% with respect to R-product in each case. Oxycodone, like brucine, appears to require a step site for adsorption but in this case modelling indicates that sites for alkaloid adsorption and for hydrogenation are on different terraces. The activity and enantioselectivity exhibited by cinchonidine-modified Pt is inhibited when modification and reaction are conducted under anaerobic conditions. The hypothesis that co-adsorption of alkaloid and oxygen limits the coverage of the former and that access to enantioselective sites becomes possible only after removal of adsorbed-oxygen in the early stages of reaction is tested. Modification has been carried out under atmospheres of propyne or of buta-1,3-diene as co-adsorbent; the resulting catalysts show high activity and enantioselectivity after removal of the co-adsorbent in the early stages of pyruvate hydrogenation. Thus, optimisation of Pt catalysts for enantioselective reaction should take into account both metal particle geometry and alkaloid concentration. 

*Keywords:* Enantioselective hydrogenation; Alkaloid modifier; Pt/silica; Catalyst particle morphology; Cinchonidine; Epiquinidine; Brucine; Codeine; Oxycodone; Molecular modelling; Aerobic modification; Anaerobic modification

## 1. Introduction

It is now well established that supported Pt catalysts can be rendered enantioselective by the adsorption of certain alkaloids onto their surfaces [1]. Some other noble Group 8 metals, e.g., Ir, follow Pt in their behaviour whereas others, e.g., Pd, may provide enantioselectivity by different mechanisms [2]. The most studied alkaloids are those of the cinchona family and synthetic variants [3,4], but certain strychnos

* Corresponding author

1381-1169/99/$ - see front matter 
PII: S1381-1169(99)00117-X

and morphine alkaloids are also effective catalyst modifiers [5]. Generally, we have used kinetic and isotope-tracer methods, supported by molecular modelling, to provide information concerning molecular behaviour as reactants are converted to products, and thereby to adduce the features of the alkaloid-modified surface which are responsible for enantioselectivity. This paper provides a different perspective by recognising that various types of alkaloid may differ in the sites that they require for adsorption, and hence that surface morphology and surface concentration of alkaloid may each play a crucial role in the achievement of highly active enantioselective catalysts.

## 2. Experimental

The catalyst used in this investigation was the reference material EUROPT-1, a 6.3% Pt/silica which has been well characterised [6]. Pt particle size ranged from 0.9 to 3.5 nm with a maximum in the distribution at 1.8 nm (dispersion ca. 60%). Samples were re-reduced before use in hydrogen at 393 K for 0.5 h. Reduced under these conditions the Pt particles may be raft-like with preferential (111) orientation [7]. The alkaloids cinchonidine (Aldrich), epiquinidine (Aldrich), brucine (Fluka), and oxycodone (gift from MacFarlan Smith) were used as received; their structures are shown in Fig. 1. Ethanol (BDH), methyl pyruvate and butane-2,3-dione (Fluka) were used as received or after distillation as appropriate.

Reactions were conducted in a stirred high-pressure glass reactor (Fischer Porter). Procedures for catalyst reduction and modification (both normal (aerobic) and anaerobic), for the conduct of reactions, and for the analysis of products by chiral gas chromatography have been described elsewhere [8,9]. 2-D NOE spectra were obtained by use of a LAMBDA 400 instrument using a standard pulse sequence with a mixing time of 500 ms. The F1 dimension was 256 points filled to 512 points. Sixteen

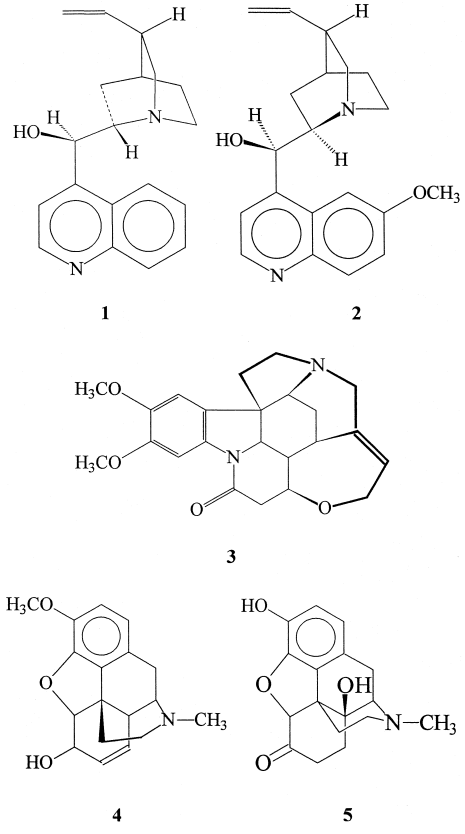


Fig. 1. Structures of cinchonidine (**1**), epiquinidine (**2**), brucine (**3**), codeine (**4**) and oxycodone (**5**).

scans were obtained for each point. The F2 dimension was 512 points for a frequency range of 3800 Hz. Probe temperature was 24.5°C.

Molecular-mechanics calculations have been performed using the Cerius 2 Silicon Graphics modelling package. Representations of molecules have been constructed using default values of bond lengths and angles and then optimised with MOPAC (semi-empirical) forcefield calculations using the AM1 Hamiltonian.

## 3. Results and discussion

### *3.1. Cinchona-modified Pt*

Cinchona-modified Pt catalysts have been studied in detail and there is considerable agree-

ment as to their general mode of action, although interpretations of detail differ [10,11]. The following is a brief summary. Pyruvate ester hydrogenations occur rapidly at modestly elevated pressures and room temperature; values of the enantiomeric excess of 70% can be achieved without optimisation [12,13]. Calculations indicate that cinchonidine and cinchonine may, in principle, exist in three conformations of approximately equal energy, two of which (A and B) are separated from the third (C) by a high energy barrier and from each other by a relatively low energy barrier [12]. For cinchonidine the 2-D NOE spectra indicate that the major conformation in solution is conformation A; this is close to that adopted by the molecules in the solid state [14]. The assumption is made that these conformations remain the lowest energy states when the alkaloids are adsorbed onto a Pt surface; D-tracer studies show that adsorption occurs via the quinoline ring system [15]. Conformation A adsorbed on a (111) terrace of Pt atoms presents a 'pocket' at which *selective enantioface adsorption* of pyruvate ester can occur, and at which subsequent hydrogenation provides an enantiomeric excess in the product. Our molecular representations of this selective enantioface adsorption have been published [12], and the selective formation of R-lactate ester over cinchonidine-modified catalysts and of *S*-lactate ester over cinchonine-modified catalyst is thereby interpreted [2]. Experimentally, the gross rate of lactate formation in the presence of alkaloid is greatly enhanced over that observed in the absence of alkaloid; this enhanced rate has its origin in H-bonding involving the quinuclidine-N atom of the adsorbed alkaloid and the carbonyl function of the ester which is undergoing hydrogenation [4,12,13]. Rate and enantioselectivity are lost when these alkaloids are quaternised at the quinuclidine-N atom, which is consistent with the mechanisms proposed [13].

### *3.1.1. Epiquinidine*

In 1992 we published, without detailed interpretation, the result of an experiment in which the synthetic alkaloid epiquinidine was investigated as a catalyst modifier [13]. The natural alkaloids cinchonidine and quinine have the *S*-configuration at C8 and the *R*-configuration at C9, whereas cinchonine and quinidine have the *R*-configuration at C8 and the *S*-configuration at C9. By contrast, epiquinidine has the *R*-configuration at both C8 and C9. Pt/silica modified by epiquinidine gave an optical yield of 1% in favour of *R*-lactate in methyl pyruvate hydrogenation in ethanol at 10 bar pressure and 293 K; the rate enhancement was by a factor of 2 compared with a typical value of 25 for the natural alkaloids. Thus, neither substantial enhanced rate nor enantioselectivity are imparted by use of this modifier. Molecular mechanics energy calculations have been carried out for full rotations in the epiquinidine molecule around the C4′–C9 bond, the C8–C9 bond, the C9–O bond, the C3–C10 bond, and the C6′–O bond [16]. Again, three minimum energy conformations are observed (Fig. 2) two of which (A and B) are separated from the third (C) by a high energy barrier and from each other by a low energy barrier. For these three conformations adsorbed on a Pt terrace, only C provides *both* a 'pocket' capable of permitting the selective enantioface adsorption of pyruvate *and* the quinuclidine-N atom in a position to form a H-bond with the half-hydrogenated state. In

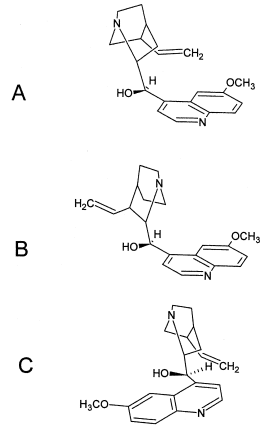


Fig. 2. Minimum energy conformations of epiquinidine (for A, B, C see text).

conformation A the quinuclidine-N atom is directed away from the quinoline ring and in conformation B it is positioned over the quinoline ring; in neither case does the geometry permit of H-bond formation with the half-hydrogenated state of the reactant. The 2-D NOE spectrum of epiquinidine in solution is consistent with conformation A being the major conformer present (at least 90%). The spectrum indicated that the epiquinidine supplied contained a minor impurity. Any relationship between the structure of this alkaloid in solution and in the solid state cannot be established because the crystal structure has not been reported. Thus, it appears that the requirements for enantioselective reaction are not achieved, this interesting negative result is interpreted, and the behaviour of a further novel alkaloid becomes incorporated into our general understanding of this reaction.

### *3.2. Brucine-modified Pt*

Brucine is a member of the strychnos family of alkaloids. Modification of 6.3% Pt/silica by brucine induces enantioselectivity in methyl pyruvate hydrogenation in favour of *S*-lactate; best values of the enantiomeric excess for reactions in ethanol at 10 bar pressure and room temperature are about 20% and the rate enhancement factor is typically 4. Brucine induces no enantioselectivity in butane-2,3-dione hydrogenation under the same conditions although a rate enhancement of 12 is observed. Brucine in its minimum energy configuration has a structure such that, on adsorption at the edge of a plane of Pt atoms, a 'cavity' is formed as shown in Fig. 3. Modelling suggests that methyl pyruvate may adsorb utilising a Pt atom within this cavity as an adsorption site. Fig. 4 shows the adsorption of pyruvate by each of its enantiofaces at this site. For the enantioface shown in Fig. 4b there is a repulsive interaction between the ester-oxygen atom of the reactant and the ether-oxygen atom of the modifier, whereas this repulsive interaction is absent for the enantioface shown in Fig. 4a. It is therefore proposed that this Pt atom site is one at which selective enantioface adsorption should occur, and that the enantioface shown in Fig. 4a is preferred; hydrogenation of this enantioface would give *S*-methyl lactate as product and the observed sense of the enantioselectivity is thereby interpreted. The observation of an enhanced rate is evidence for H-bonding involving the carbonyl group undergoing hydrogenation and the adja-

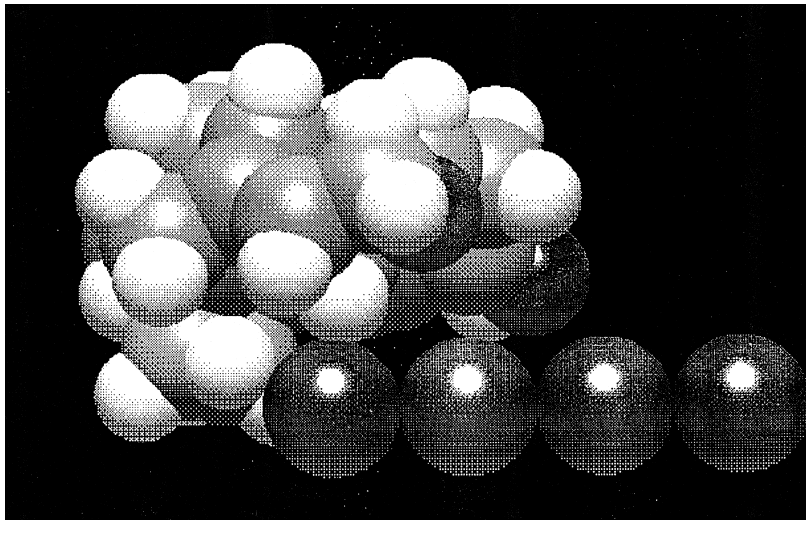

Fig. 3. Representation of the cavity formed by the adsorption of a brucine molecule on a terrace of Pt atoms.

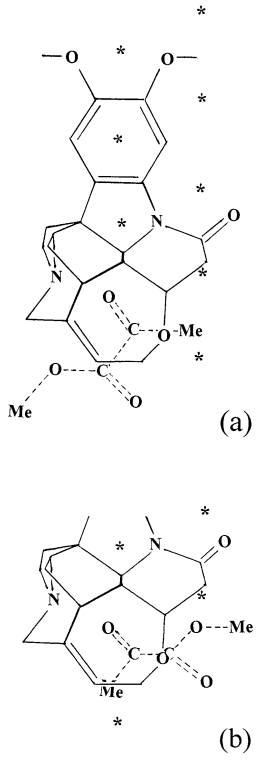


Fig. 4. Representations of methyl pyruvate adsorbed by each enantioface at the proposed enantioselective site at the brucine-modified Pt surface.

cent basic-N atom located in the 'roof' of the cavity. Butane-2,3-dione may be regarded for present purposes as methyl pyruvate from which the ester-oxygen atom has been removed. Thus, when butane-2,3-dione is adsorbed by each of its enantiofaces at the same Pt atom site within the brucine cavity, no selective enantioface adsorption occurs, and no enantioselectivity is to be expected. (That butane-2,3-dione does indeed enter the cavity and adsorb at this site is confirmed by the observation of the enhanced rate.)

Quaternisation of brucine with methyl iodide destroys the rates of both pyruvate and butanedione hydrogenations and the enantioselectivity of the former, as would be expected from the mechanisms just discussed.

If, as proposed, brucine requires an edge or step site in the Pt surface for adsorption, then enantioselectivity should be dependent on metal particle size. Pt atom sites distant from the edges and corners of Pt microcrystallites would not be modified but would be available to catalyse reaction to racemic products. Thus, enantioselectivity should increase with decreasing Pt particle size until the particles become too small to adsorb both modifier and reactants.

### 3.3. Oxycodone-modified Pt

Oxycodone, like codeine is a member of the morphine family of alkaloids. Codeine modifies Pt/silica so as to produce a weak enantioselectivity in methyl pyruvate hydrogenation towards *S*-lactate formation which, exceptionally, is not poisoned by quaternisation of the alkaloid. No enantioselectivity is observed in butane-2,3-dione hydrogenation. These reactions have been discussed recently [17]. By contrast, oxycodone provides a modest enantioselectivity in methyl pyruvate and butane-2,3-dione hydrogenations in favour of *R*-product (ee = 15%) which is poisoned by quaternisation of the alkaloid. Oxycodone (like codeine) is a T-shaped molecule which again appears to require an edge- or step-site for adsorption by the aromatic moiety. In this configuration, the basic-N atom is directed away from the Pt terrace on which the alkaloid is adsorbed, and hence it has been proposed that the enantioselective site is located on a second terrace as shown in Fig. 5 [17]. In this model, the observed sense of the enantioselectivity is interpreted if the pyruvate ester chelates in the *syn*-conformation with the basic-N and OH-group of the alkaloid. (Following Baiker [4] the basic-N atom is shown protonated.) Calculations have been performed to compare the stabilities of (i) pyruvate ester in the *syn*-conformation chelated to the alkaloid by two H-bonds (Fig. 5) and (ii) pyruvate ester in the *anti*-conformation bonded at the ≡NH site by one H-bond. These show that the increase in energy that accompanies rotation of pyruvate from the normal *anti*-conformation into the *syn*-conformation is more than compensated by the stability conferred by the formation of the

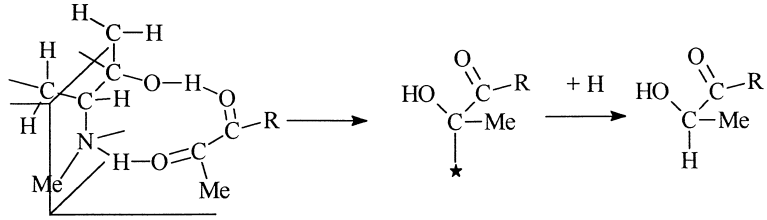

Fig. 5. Proposed interaction of methyl pyruvate in the *syn*-configuration with adsorbed oxycodone, and its conversion via a half-hydrogenated state to *R*-methyl lactate.

second H-bond. The sense of the observed enantioselectivity in pyruvate hydrogenation, its sensitivity to quaternisation of the alkaloid, and the enantioselective hydrogenation of butane-2,3-dione under the same conditions are thus simultaneously interpreted by this mechanism which requires the adsorption of the alkaloid on one terrace and enantioselective reaction on another.

### *3.4. Optimum surface coverage of adsorbed alkaloid*

N-containing compounds are well known catalyst poisons and it is remarkable that enantioselective α-ketoester and alkanedione hydrogenations over alkaloid-modified catalysts occur as rapidly as is commonly observed. In 1991 we reported that pyruvate hydrogenations over cinchonidine-modified Pt/silica conducted under anaerobic conditions proceeded with no enhancement of rate and with a 20% reduction in optical yield [8], i.e., reactions appeared to be poisoned by the alkaloid. When catalysts are modified normally by the Orito method [18–20], the slurry of reduced catalyst in the modifier solution is stirred in air; alternatively in *in situ* modification the reactant and solvent normally contain dissolved air. Thus, the collapse in rate and the drop in enantioselectivity appeared to be attributable to an absence of oxygen in the system. Repetition of this work, in which even greater care has been taken to exclude air from reactant and solvent, and modification was carried out under 1 bar nitrogen, has resulted in the behaviour shown in Fig. 6. Under these strictly anaerobic conditions, using the usual excess of alkaloid, the rate was very slow indeed and enantioselectivity was almost entirely lost. These observations led to the hypothesis that, under normal conditions, oxygen dissolved in reactant and solvent adsorbed in competition with alkaloid so as to reduce the fractional surface coverage of alkaloid, and that this adsorbed oxygen is removed by hydrogen in the early stages of reaction leaving an ‘open arrangement’ of adsorbed alkaloid molecules such that pyruvate ester can gain access to the enantioselective sites and be hydrogenated. This hypothesis has been tested by conducting the adsorption of cinchonidine or of cinchonine onto Pt/silica in the presence of various potential co-adsorbents, including propyne and buta-1,3-diene. Fig. 7 shows the uptake-time curve obtained when Pt/silica was modified by the adsorption of cinchonidine under 2 bar butadiene; a comparable curve was obtained when the catalyst was modified under 3 bar propyne except that a substantial initial period of acceleration was observed. Values of the enantiomeric excess in the range 50 to 70% were obtained in these reactions in which the maximum rates were typically 400 to 1000 mmol $h^{-1}$ $g^{-1}$ (modification under propyne) or 1000 to 1900 mmol $h^{-1}$ $g^{-1}$ (modification under butadiene). Analysis of the gas phase showed that propene and propane (or butene and butane) were formed in the early stage of reaction in the proportions expected for propyne hydrogenation over Pt at room temperature [21]. There is thus no reasonable doubt that propyne (or butadiene) and cinchonidine were co-adsorbed during modification and that reactivity for enantioselective hydrogenation of

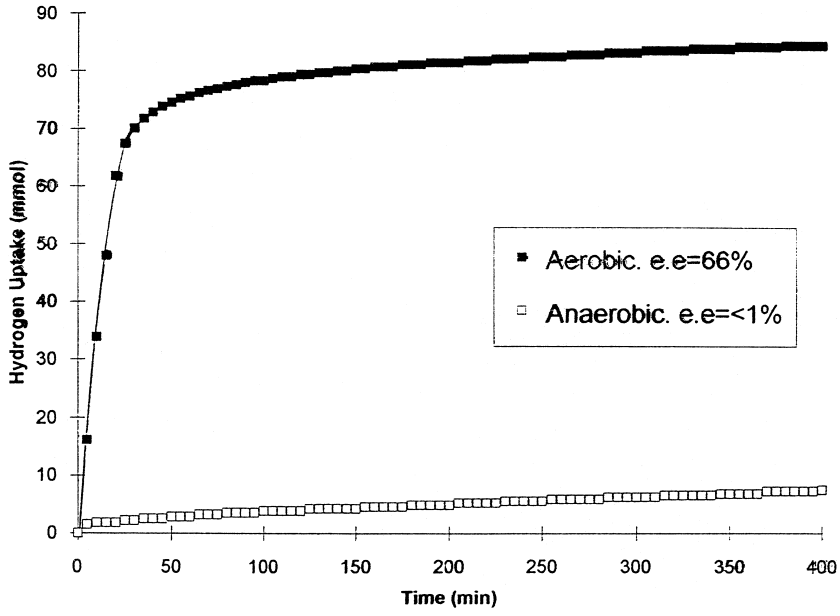


Fig. 6. Hydrogen uptake vs. time curves for methyl pyruvate hydrogenation in ethanol at 10 bar pressure and 293 K for catalysts modified by the normal aerobic procedure (upper curve) and by an anaerobic procedure under 1 bar nitrogen (lower curve).

pyruvate to lactate developed as an 'open arrangement' of adsorbed alkaloid was achieved following the removal of adsorbed propyne (or butadiene) by hydrogenation. We have reported elsewhere the use of Pt/silica modified by cinchonidine under propyne and butadiene atmospheres for enantioselective butane-2,3-dione hydrogenation [9].

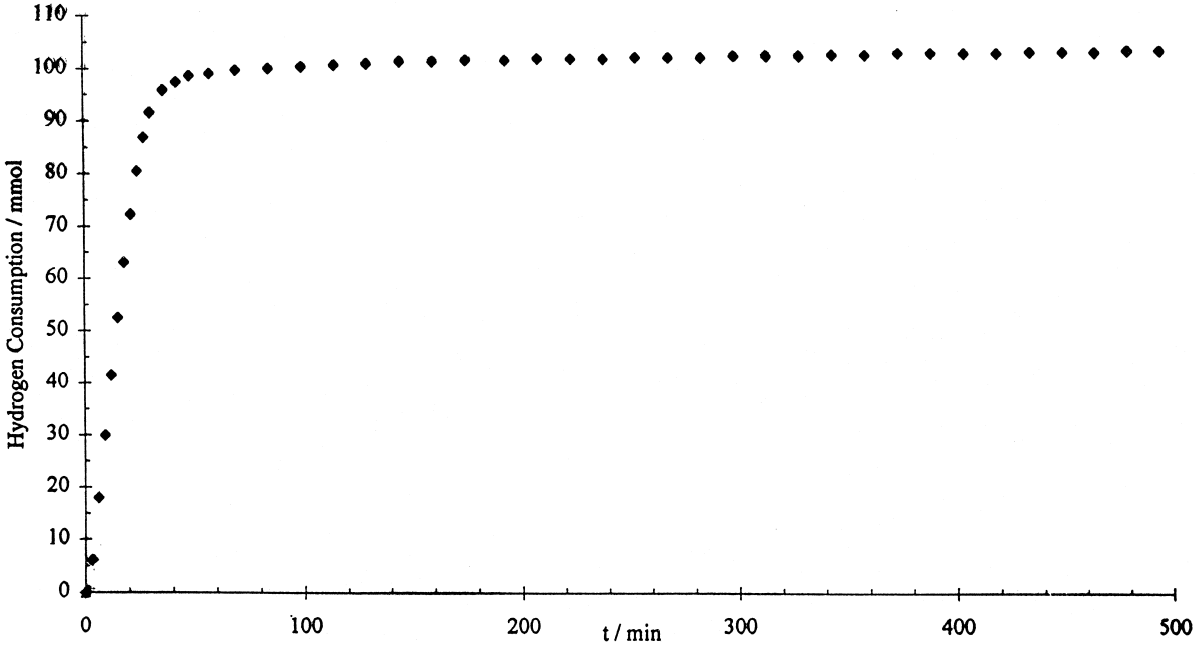


Fig. 7. Hydrogen uptake vs. time curves for methyl pyruvate hydrogenation in ethanol at 10 bar pressure and 293 K for a catalyst modified by an anerobic procedure under 2 bar buta-1,3-diene.

The alkaloid-modified Pt surface is a very complex environment at which modifier, reactant and hydrogen adsorb, probably in competition. It now appears that the alkaloid coverage at the surface has to be controlled and that that control may have been achieved in the past by the presence of adventitious oxygen. Moreover, a new factor has emerged which influences the rate of enantioselective reaction.

One further parameter that requires investigation is the chemical interaction of solvent with the surface. Rates and enantioselectivities vary with the solvent used for modification and for reaction [2]. Common solvents such as ethanol react with Pt surfaces to form hydrocarbonaceous or O-containing adsorbed species that may be reactive or permanent [22,23]. A description of the active enantioselective surface is incomplete without the identification and quantification of these species and a knowledge of their influence on the rates and enantioselectivities of these reactions.

## Acknowledgements

The authors thank Johnson Matthey for financial support and EPSRC for studentships (awarded to KES, JAS and SPG). PBW wishes in particular to acknowledge the contributions of Dr. A. Ibbotson (formerly of ICI FCMO) who suggested the epiquinidine experiment, and of Dr. P. Johnston, formerly of the University of Hull and now with Johnson Matthey.

## References

[1] A. Baiker, H.U. Blaser, in: G. Ertl, H. Knozinger, J. Weitkamp (Eds.), Handbook of Heterogeneous Catalysis, Vol. 5, VCH, Weinheim, 1997, p. 2422.
[2] P.B. Wells, A.G. Wilkinson, Top. Catal. 5 (1998) 39.
[3] A. Pfaltz, T. Heinz, Top. Catal. 4 (1997) 229.
[4] A. Baiker, J. Mol. Catal. A: Chem. 115 (1997) 473.
[5] S.P. Griffiths, P. Johnston, W.A.H. Vermeer, P.B. Wells, J. Chem. Soc. Chem. Commun., 1994, 2431.
[6] J.W. Geus, P.B. Wells, Appl. Catal. 18 (1985) 231 and cognate papers.
[7] S.D. Jackson, M.B.T. Keegan, G.D. McLellan, P.A. Meheux, R.B. Moyes, G. Webb, P.B. Wells, R. Whyman, J. Willis, in: G. Poncelet et al. (Eds.), Preparation of Catalysts V, Elsevier, Amsterdam, 1991, p. 135.
[8] P.A. Meheux, A. Ibbotson, P.B. Wells, J. Catal. 128 (1991) 387.
[9] J.A. Slipszenko, S.P. Griffiths, P. Johnston, K.E. Simons, W.A.H. Vermeer, P.B. Wells, J. Catal. 179 (1998) 267.
[10] D.G. Blackmond, J. Catal. 176 (1998) 267.
[11] T. Mallat, A. Baiker, J. Catal. 176 (1998) 271.
[12] K.E. Simons, P.A. Meheux, S.P. Griffiths, I.M. Sutherland, P. Johnston, P.B. Wells, A.F. Carley, M.K. Rajumon, M.W. Roberts, A. Ibbotson, Recl. Trav. Chim. Pays-Bas 113 (1994) 465.
[13] G. Webb, P.B. Wells, Catal. Today 12 (1992) 319.
[14] B. Oleksyn, Acta Cryst. B 38 (1982) 1832.
[15] G. Bond, P.B. Wells, J. Catal. 150 (1994) 329.
[16] K.E. Simons, PhD thesis, University of Hull, 1994.
[17] S.P. Griffiths, P.B. Wells, K.G. Griffin, P. Johnston, Proc. 17th Conference on Catalysis of Organic Reactions, in: F.E. Herkes (Ed.), Marcel Dekker, New York, 1998, p. 89.
[18] Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn., 1979, 1118.
[19] Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn., 1980, 670.
[20] S. Niwa, S. Imai, Y. Orito, J. Chem. Soc. Jpn., 1982, 137.
[21] S.D. Jackspon, G. Kelly, J. Mol. Catal. 87 (1994) 275.
[22] B.A. Sexton, K.D. Rendulie, A.E. Hughes, Surf. Sci. 121 (1982) 181.
[23] M.K. Rajumon, M.W. Roberts, F. Wang, P.B. Wells, J. Chem. Soc. Faraday Trans. 94 (1998) 3699.