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A model for the enantioselective hydrogenation of pyruvate catalysed by alkaloid-modified platinum [a]

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Abstract. A LEED and XPS study of the adsorption of naphthalene, quinoline, and 10,11-dihydrocinchonidine on Pt(111) at 300K has shown that only naphthalene forms an ordered ad-layer, and that quinoline and the alkaloid adsorb in a disordered state and without decomposition. These experiments do not support the hypothesis of ordered adsorption of alkaloid that forms the basis of the template model for the interpretation of enantioselectivity in Pt-catalysed pyruvate hydrogenation. The model is accordingly reviewed. Molecular modelling studies show that a highly specific 1 : 1 interaction between cinchonidine (or cinchonine) and pyruvate interprets the observed sense of the enantioselectivity, provided relative energy relationships derived for purely intermolecular interactions are valid for the same molecules in the adsorbed state. Moreover, the 'product' of this 1 : 1 interaction is a satisfactory precursor to the H-bonded state considered responsible for the greatly enhanced rate that always accompanies enantioselective reaction over cinchona-modified Pt. The previously published dependencies of optical yield on (*a*) surface concentration of adsorbed cinchonidine modifier, and (*b*) modifier composition for mixtures of quinine and quinidine, are shown to be in quantitative agreement with the proposed 1 : 1 interaction model and at variance with the ordered adsorption model. Catalysts modified and used under strictly anaerobic conditions show negligible activity and enantioselectivity demonstrating that oxygen plays a crucial role in successful catalyst preparation. XPS experiments confirm that adsorption of cinchonidine from air-saturated ethanolic solution on Pt(111) provides an adlayer containing both alkaloid and adsorbed oxygen. (*S*)-(−)-1-benzyl-pyrrolidine-2-methanol, various configurations of ephedrine, D-and L-histidine and the methyl esters of D- and L-tryptophan have been examined as modifiers for supported Pt. Although there is evidence that these compounds can provide chiral direction to pyruvate hydrogenation, rate enhancement is slight and enantioselectivity is correspondingly low.

Introduction

Catalyst selectivity is a subject of very considerable importance both in respect of the practical economics of catalyst applications and from the academic standpoint of understanding the mechanism of catalytic action. The need for heterogeneous enantioselective catalysts has become evident as the chemicals industry responds to pressures to provide optically pure products (*e.g.* for pharmaceuticals, herbicides, pesticides) and society generally demands the adoption of cleaner technologies.

The achievement of chiral selectivity in heterogeneous catalysis by metals presents a special challenge because metal surfaces as normally prepared possess no inherent chiral quality. Chiral properties may be induced, in principal, by adsorbing a chiral substance, known as a *modifier*, onto the active phase of a conventional supported metal catalyst. The first steps in this direction were taken over half a century ago by *Lipkin* and *Stewart* who treated nickel catalysts with glucose and platinum catalysts with cinchonine[1]. Since that time, many modified metal catalysts have been examined for a variety of reactions[2] but very few have shown high enantioselectivities, and only the hydrogenations of β-keto esters (first reported in 1956[3] and reviewed in 1983[4] and 1992[5]) and of α-keto esters (first reported in 1978[6] and reviewed in 1992[5]) have been the subject of detailed mechanistic studies.

Chiral organic compounds suitable for the modification of Ni for the achievement of the enantioselective hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate include a variety of α-hydroxy acids, such as tartaric acid, and α-amino acids. Enantioselectivity is dependent on virtually every parameter related to catalyst preparation and modification[7]. Consequently, the attainment of reproducible reaction rates and optical yields has proved difficult, not least because the modification procedure in-

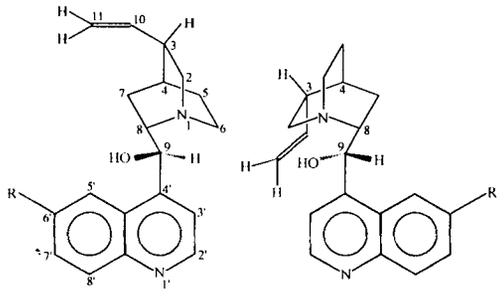
[a] Dedicated to Professor *W.M.H. Sachtler* on the occasion of his 70th birthday.

volves, or leads to processes involving a corrosive interaction of the modifier with the catalyst surface[5]. Much of the original work was carried out using Raney Ni. However, the Dutch group under *Sachtler* also examined conventional supported nickel catalysts paying particular attention to the mode of modifier adsorption on both metal and support as determined by infrared spectroscopy[8-14]. The outcome was a model involving the perpendicular chelation of modifier molecules to surface Ni sites which successfully interpreted the chiral sense of the observed enantioselectivity.

The enantioselective Pt-catalysed hydrogenation of α-keto esters in the liquid phase at elevated pressures is a less difficult reaction to conduct reproducibly in the laboratory. The cinchona alkaloids, which include cinchonidine, cinchonine, quinidine, quinine, (Figure 1) and their 10,11-dihydro derivates, are suitable modifiers. The effect of modification of the Pt catalyst by cinchonidine or quinine is to provide for the selective production of (*R*)-(+)-methyl lactate MeCH(OH)COOMe by hydrogenation of methyl pyruvate (MeCOCOOMe), whereas modification using cinchonine or quinidine provides enantioselectivity in favour of (*S*)-(-)-methyl lactate. A remarkable feature of this reaction is that the rate of enantioselective hydrogenation in the presence of the modifier is greatly enhanced over that of the racemic hydrogenation in the absence of the modifier[15,16]; rate enhancements in the range 25 to 60 are normally observed.

Reaction proceeds smoothly in solution at room temperature, under elevated hydrogen pressure (10 bar is sufficient[16]) over any supported Pt catalyst containing Pt particles about 2 nm or larger in diameter[15,17]. The procedure for catalyst modification as described by *Orito* et al.[6] involves: (*i*) catalyst reduction, (*ii*) adsorption of the modifier from solution, (*iii*) stirring the catalyst and modifier solution in air for a period, (*iv*) separation of the modified catalyst and (*v*) its transfer to a high pressure reactor, with subsequent addition of solvent, pyruvate, and hydrogen. Highly reproducible reaction rates and enantioselectivities are obtained by this method[17]. Comparable enantioselectivities have been achieved by conducting the modification *in situ* in the high-pressure reactor and omitting the step involving digestion in air[18,19]. However, intentional exclusion of air impairs enantioselectivity and greatly reduces the rate[16].

Enantioselective excesses of 75% can be achieved without difficulty[16], values of nearly 90% have been obtained in the authors' laboratory after optimisation of catalyst preparation and the modification procedure, and *Blaser* and co-workers[20] have achieved 95%.



R = H	Cinchonidine	Cinchonine
R = OMe	Quinine	Quinidine

Atom	C3	C4	C8	C9		C3	C4	C8	C9
Configuration	*R*	*S*	*S*	*R*		*R*	*S*	*R*	*S*

Figure 1. Structures and configurations of some cinchona alkaloids.

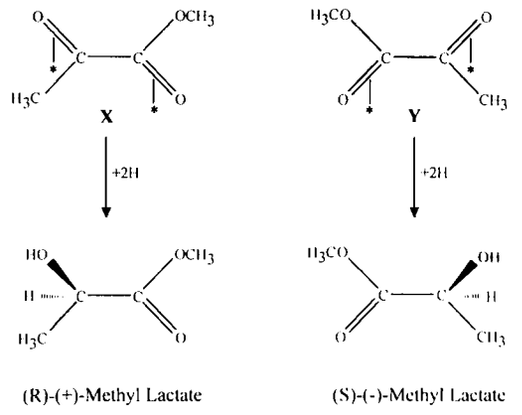


Figure 2. Configurations of adsorbed methyl pyruvate, X and Y, and of their hydrogenation products.

In the early phase of our work it appeared that the reaction as described by *Orito* was very specific in that catalysis by Group 8 metals other than Pt was difficult or impossible to achieve, enantioselectivity was restricted to α-keto ester hydrogenation, and the cinchona alkaloids were the only effective modifiers. There was thus every incentive to develop a mechanism for the reaction and a model for the role of the modifier which interpreted (*i*) the sense of the observed enantioselectivity and (*ii*) the origin of the enhanced rate. The purpose of this paper is briefly to review the development of our model, to reassess it in the light of recent work including the application of surface sensitive spectroscopies, and to examine the extent to which it has proved possible to apply the principles so revealed to diversify the reaction (*i.e.* to achieve enantioselectivity in different reactions, using metals other than Pt, and modifiers other than cinchona alkaloids).

Development of a mechanism

It is helpful, for philosophical purposes, to distinguish between those aspects of reaction mechanism which describe the conversion of pyruvate to lactate (which may, but need not involve the participation of the modifier), and those aspects which induce enantioselectivity (to which the mode of action of the modifier is crucial).

Pyruvate hydrogenation is, in principle, a simple process. Adsorption of MeCOCOOMe may occur in two mirror-image configurations (**X** and **Y**, Figure 2); the molecule before adsorption and in its lowest energy state has the two carbonyl groups in a *trans* configuration and it is assumed that this is retained on adsorption. Interaction of both carbonyls with surface sites is expected (*e.g.* by analogy with buta-1,3-diene adsorption[21]) so that the adsorbed molecule lies in a plane parallel with that of the surface. No enolisation of **X** or **Y** occurs as judged by D-tracer studies[16]. Hydrogenation is assumed to take place by the consecutive addition of two hydrogen atoms to the α-keto group, addition to the pro-chiral carbon atom being from below the plane of the adsorbed pyruvate molecule. On the basis of these assumptions, **X** gives (*R*)-methyl lactate on hydrogenation and **Y** gives (*S*)-methyl lactate.

In our early studies, priority was given to interpreting the sense of the observed enantioselectivity [cinchonidine providing the (*R*)-lactate in excess, and cinchonine the (*S*)-lactate]. These alkaloids, in their lowest energy configurations, are L-shaped but in opposite senses. A 'template model' was developed which provided a simple geometrical interpretation of the chiral selectivity[15]. It was supposed that the L-shaped alkaloid was adsorbed in a non-

close-packed ordered array so as to leave exposed shaped ensembles of Pt atoms that would be available as sites for pyruvate adsorption. The geometry was such that the shaped ensembles remaining after cinchonidine adsorption admitted pyruvate adsorption as **X** but not **Y**, whereas the ensembles remaining after cinchonine adsorption permitted **Y** but not **X**. An interpretation of the sense of the enantioselectivity was thereby achieved. The crucial feature of this model is the proposed ordered adsorption of the alkaloid. The surface-science literature at the time contained evidence for the occurrence of ordered naphthalene adsorption on Pt[22,23], and for ordered co-adsorption of benzene and CO[24]. Steps were therefore taken to search for ordered adsorbed states of quinoline and a cinchona alkaloid on Pt(111) and for ordered co-adsorption of these molecules with O_2 (*vide* the modification procedure) using the techniques of LEED and XPS. That co-adsorbed oxygen at metal surfaces can have a pronounced influence on chemical reactivity is well established and one of us drew attention to this in the context of enantioselectivity at nickel surfaces[25].

Enantioselectivity in this system goes hand in hand with the enhanced rate, as a Pt surface is progressively covered with adsorbed cinchonidine so the enantiomeric excess and the enhanced rate develop in tandem and reach maximum values at a loading of alkaloid on the surface that approximates well to that required by the template model[26]. However, the rate of racemic hydrogenation of pyruvate over (unmodified) Pt was accelerated by organic nitrogen-containing bases, of which quinuclidine and quinuclidinol were especially potent[27]. From these observations it was deduced (*i*) that a hydrogen-bond interaction was established between the quinuclidine-N of the adsorbed alkaloid and the half-hydrogenated state derived from pyruvate [MeC(OH)COOMe], and (*ii*) that this interaction stabilised the half-hydrogenated state against H-atom loss, thus increasing its steady-state concentration and thereby its rate of conversion to product in the rate-determining step[27].

This development made necessary a re-examination of the template model. First, the location of pyruvate with respect to alkaloid, as originally proposed, was not such as to permit the interaction now proposed for the interpretation of the enhanced rate[5]. Second, the H-bonding interaction between modifier and reactant brought a further consideration into the model, that of an important 1:1 interaction between these two components; such an interaction had previously been proposed, on different grounds, by *Blaser* and *Baiker*[28–30]. In Ref. 5, the representation of the templated surface was revised to allow for this 1:1 interaction between alkaloid and reactant, while not abandoning the representation of alkaloid adsorption as involving a non-close-packed ordered array.

Subsequent studies concerning the shape of the optical yield *versus* alkaloid loading curve[19], and the effect of using mixtures of modifiers (*e.g.* quinine and quinidine) have provided further evidence for the importance of the 1:1 interaction[31]. The time is now ripe for a reappraisal of our model[5].

Experimental

XPS and LEED experiments were carried out in an updated VG ESCA3 spectrometer fitted with a VG Microtech LEED facility. The Pt(111) single crystal was polished to a mirror finish using diamond paste (0.25 μ) and was spot-welded on a stainless-steel stub using tantalum foil. The crystal was cleaned using cycles of Ar-ion sputtering and electron bombardment heating in 10^{-7} Torr oxygen at 1300K until all contaminants disappeared. Finally the crystal was flashed at 1300K in vacuum to generate an atomically clean surface. The clean crystal gave a sharp hexagonal LEED pattern corresponding to the (111) surface (Figure 3a).

Exposure of the surface to vapours of thoroughly degassed naphthalene and quinoline was achieved via a stainless-steel tube directed on to the crystal face. An ethanolic solution of 10,11-dihydrocinchonidine was pipetted directly onto the crystal surface *in situ* in a flowing-helium atmosphere. XPS measurements were carried out using AlKα radiation, and spectral binding energies were calibrated against the Pt($4f_{7/2}$) peak at 71.0 eV. Data were acquired using commercial software (SPECTRA) and analysed using software developed in-house[32]. Surface coverages were determined from the integrated intensities of the adsorbate and substrate core-level peaks[33]. The supported metal catalyst used in this work was EUROPT-1, the 6.3% Pt/silica reference catalyst the full characterisation of which has been published[34]. The platinum active phase has a particle size distribution centred at 1.8 nm and a dispersion of about 60%. Reduced under certain conditions the Pt particles have a preferential (111)-orientation and a raft-like morphology[17].

The high-pressure reactors, computerised hydrogen-admission systems, methods of catalyst reduction, modification, and use and the preparation of 10,11-dihydrocinchonidine are described elsewhere[15,16]. Where enantioselectivity is presented as optical yield the measurement has been made by polarimetry; where it is presented as enantiomeric excess the measurement has been made by chiral gas chromatography backed up as necessary by polarimetric measurements. Each is defined as $\%(R-S)/(R+S)$.

Most pyruvate hydrogenations were conducted under 'standard conditions' *i.e.* reactions were carried out at ambient temperature in glass or glass-lined stirred autoclaves utilising 0.1 g modified catalyst, 40 ml solvent, 10 ml methyl pyruvate (113 millimoles), and 10 bar hydrogen. Reaction mixtures were analysed at high conversions (> 90% unless otherwise specified); enantioselectivity decreases only slowly with increasing conversion[16].

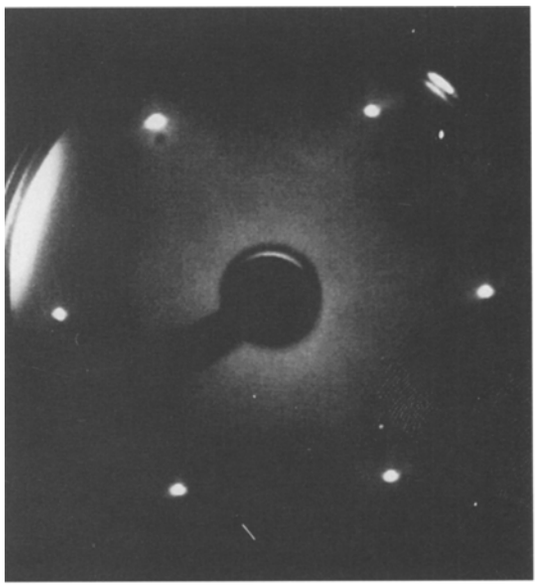
Results and discussion

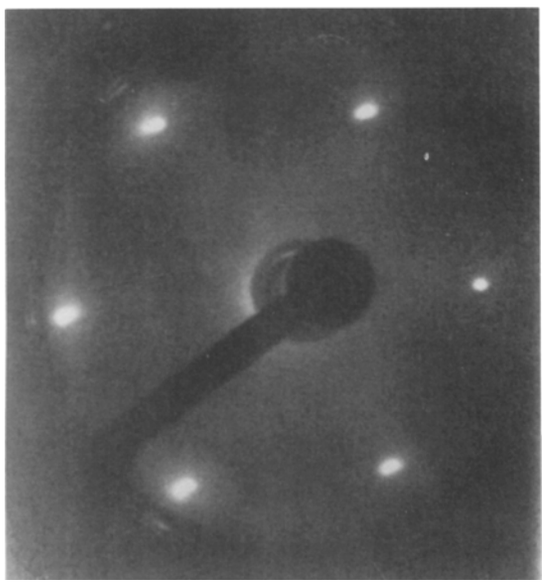
1. Search for ordered adsorbed states

(a) Naphthalene. C(1s) XP spectra for the saturation coverage of naphthalene at room temperature, are shown in Figure 4a. A single C(1s) peak is observed centred at a binding energy of 284.2 eV (FWHM = 2.2 eV). Heating the overlayer to temperatures up to 700K resulted in a shift in the peak maximum to lower binding energy (283.8 eV) and an increase in the FWHM to 2.5 eV, consistent with dehydrogenation and partial dissociation of the molecule. A clear (3 × 3) LEED pattern is obtained at 300K temperature for the saturation coverage of naphthalene on Pt(111) indicative of ordered chemisorption (Figure 3b). Previous LEED studies had found only very poorly ordered structures at room temperature, which became more ordered on heating to 373 or 423K[22,23].

(b). Quinoline. Unlike naphthalene, the adsorption of quinoline on Pt(111) does not result in ordered structures at 300K (Figure 3c) or at higher temperatures. For a saturation coverage of quinoline at 300K the N(1s) and C(1s) peaks are at binding energies of 398.9 eV and 284.4 eV respectively (Figures 4b and 4c). The value for the N(1s) peak is higher than that expected (397.3 eV) for atomic nitrogen on Pt(111)[35]. Quantitative analysis of these C(1s) and N(1s) spectra for the overlayer gives a value for the C/N ratio of about 9 which is consistent with the quinoline ring remaining intact on the surface. *Kishi* et al.[36] have reported similar N(1s) binding energy values for the molecular adsorption of pyridine at 300K on evaporated surfaces of Ni (398.8 eV) and Fe (398.9 eV) and suggested that pyridine is adsorbed with the plane of the ring parallel with the metal surface, bonding being via the π orbitals of the ring and the lone-pair on the N atom.

O(1s) spectra for the adsorption of quinoline on an atomic oxygen pre-covered Pt(111) surface (Figure 4d) show that atomic oxygen readily reacts and desorbs or is displaced by quinoline. The O(1s) difference spectrum in this figure represents the amount of atomic oxygen (529.6 eV peak) removed by reaction with the quinoline.





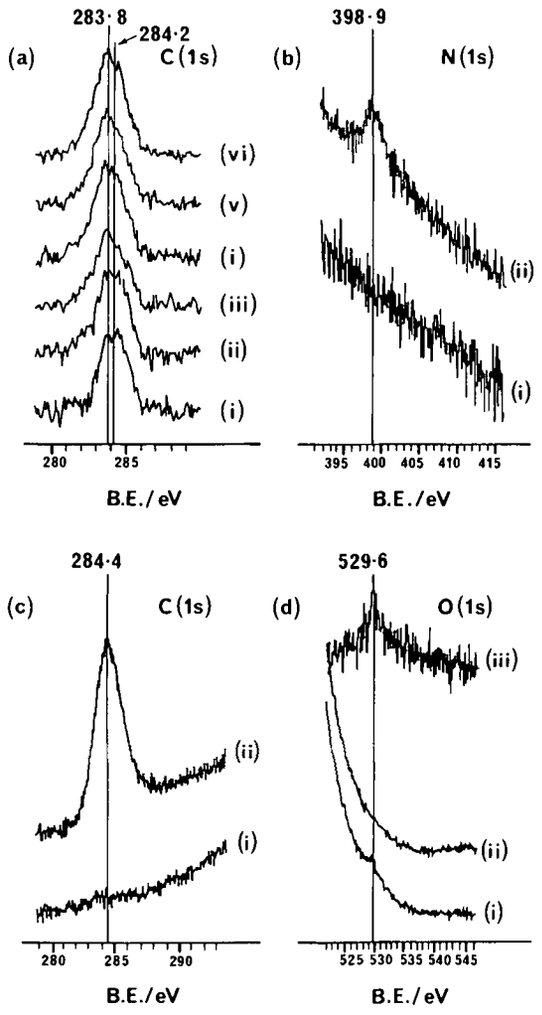


Figure 4. (a) C(1s) spectra for the adsorption of naphthalene at 300K on a Pt(111) surface followed by annealing to the indicated temperatures: (i) 300K (C/Pt = 0.8); (ii) 423K; (iii) 473K; *(iv)* 527K; *(v)* 600K; *(vi)* 700K. (b) N(1s) spectra for quinoline adsorbed at 300K on a Pt(111) surface. *(i)* Clean Pt; *(ii)* after quinoline adsorption. (c) C(1s) spectra for quinoline adsorbed at 300K on a Pt(111) surface. *(i)* Clean Pt; *(ii)* after quinoline adsorption (C/N = ~ 9)($\sigma_C = 1.56 \cdot 10^{15}$ atoms/cm^2). (d) O(1s) spectra for quinoline adsorption at 300K on atomic oxygen pre-covered Pt(111). *(i)* Atomic oxygen on Pt; *(ii)* after quinoline adsorption, *(iii)* difference spectrum representing the atomic oxygen removed by reaction with quinoline.

(c). 10,11-Dihydrocinchonidine. This alkaloid was adsorbed on the Pt(111) surface from ethanolic solution. Monolayer coverage was ensured by rinsing with ethanol the multilayer deposit resulting from the evaporation of solvent from the saturated Pt surface. As with quinoline, no adsorbate-induced LEED pattern was obtained for this overlayer at either room temperature or at higher temperatures, suggesting that the adsorbed molecules are randomly adsorbed on the surface. The N(1s) peak position for this overlayer appears at 398.8 eV (Figure 5), similar to that obtained for quinoline adsorbed on the Pt surface. It is interesting to note that even after several cycles of rinsing with the solvent the nitrogen concentration on the surface is $0.28 \cdot 10^{15}$ atoms/cm^2. According to the proposed model for alkaloid adsorption on supported

Figure 3. (a) LEED pattern observed for the clean Pt(111) surface (E = 51 eV); (b) (3 × 3) LEED pattern observed for a monolayer of naphthalene adsorbed on Pt(111) at 300K (E = 51 eV); (c) LEED pattern for a monolayer of quinoline on Pt(111). No discrete diffraction spots were observed, only an increase in the background intensity compared with the pattern for the clean surface (E = 70 eV).

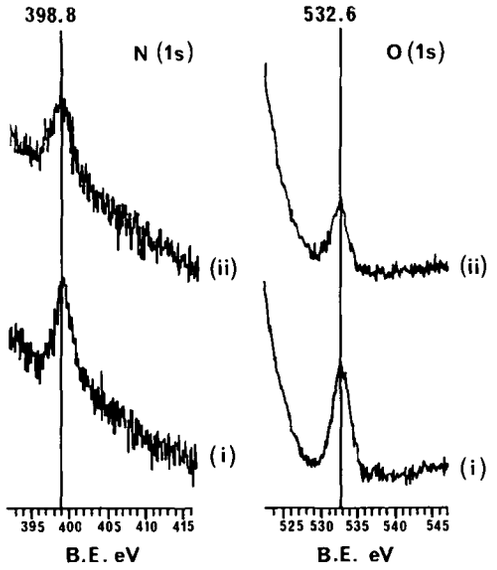


Figure 5. N(1s) and O(1s) spectra for a monolayer of 10,11-dihydrocinchonidine adsorbed on Pt(111). (i) 300K; (ii) after heating to 550K; (σ_N / (atoms / cm^2) = 0.27 · 10^{15} at 300K and 0.28 · 10^{15} at 550K; σ_O / (atoms / cm^2) = 0.49 · 10^{15} at 300K and 0.28 · 10^{15} at 550K).

Pt[15], this nitrogen concentration corresponds to approximately a monolayer of the alkaloid on the Pt surface.

Surface concentrations calculated from the N(1s) and O(1s) spectra (Figure 5) and from the C(1s) spectra (Figure 6) indicate a substantial excess of oxygen on the surface (N/O = 0.6) compared with that observed for multilayers of dihydrocinchonidine (N/O = 1.9) and the actual stoichiometry of the molecule (N/O = 2). However, the C/N ratio is very similar to that observed for multilayers. A likely interpretation is that oxygen originally dissolved in the solvent has co-adsorbed with the alkaloid onto the Pt surface. This oxygen excess diminished as temperature was raised to 550K but the adlayer of dihydrocinchonidine persisted. These and related spectra obtained under a wide variety of conditions will be considered in greater detail in a future publication.

These experiments show no evidence for ordered adsorption of quinoline on Pt(111), either in the absence or presence of oxygen, or for the ordered adsorption of alkaloid. It is thus likely that the adsorption of dihydrocinchonidine and related alkaloids onto reduced EUROPT-1 [which exposes (111)-faces[17]] and other supported platinum catalysts[37] is not ordered, as previously supposed.

2. *Molecular modelling of the alkaloid / pyruvate interaction*

Molecular-mechanics and molecular-dynamics calculations have been performed using HyperChem II. Representations of molecules have been constructed using default values of bond lengths and angles, and then optimised with MM + forcefield calculations using the Polak-Ribiere algorithm. No attempt has been made to take account of the interaction of alkaloid or pyruvate with the Pt surface. In Figures 7 and 8 the surface atoms have been introduced manually as a backdrop, choosing to locate Pt atoms in situations where they could function as adsorption sites.

The minimum-energy conformation of methyl pyruvate has been determined using both molecular mechanics and molecular dynamics. As expected, the molecule is planar with the carbonyl groups disposed in an *anti* conformation. The plot of potential energy *versus* torsion angle for rotation about the internal carbon–carbon bond exhibits a barrier of about 21 kJ/mol for rotation from the *anti* to the *syn* conformation, there being a shallow minimum for the *syn* form.

Molecular mechanics energy calculations were carried out for full rotations in the cinchonidine molecule around the C4′–C9 bond, the C8–C9 bond, the C9–O bond, and the C3–C10 bond (*i.e* the torsion angles of the atoms C3′–C4′–C9–C8, C7–C8–C9–C4′, C4′–C9–O–H and C2–C3–C10–C11 respectively). This calculation (details of which will be published elsewhere) revealed the presence of three minimum-energy conformations; the dihedral angles for these conformations are shown in Table I together with the values reported for the crystal structure.

Values for all three minimum-energy configurations are within 6 kJ/mol of each other, and are to be regarded as identical within the accuracy of the calculation. Conformation A is close to that observed for the material in the solid state[38]. The energy barrier between conformations A and B is small (20 kJ/mol) by comparison with that between A and C (125 kJ/mol).

Conformation A, if adsorbed at a Pt surface with the quinoline ring system parallel with the metal surface, would give the L-shaped adsorption shadow previously adduced and utilised in the template model[15]. Conformation B would have a similar adsorption shadow but with the N atom of the quinuclidine ring oriented over the quinoline ring. Conformation C would have an L-shaped adsorption in the sense opposite to that possessed by conformation A.

Analogous calculations for cinchonine also show the existence of three low-energy conformations (A′, B′, and C′), one of which, A′, is close in configuration to that found in the crystalline state[39].

For present purposes the representation of cinchonidine in Figures 7 and 8 is that of conformation A.

The modelling programme was further used to simulate the approach of methyl pyruvate as either configuration **X** or configuration **Y** (Figure 2) to conformation A of the alkaloid. Special regard was paid to the potential-energy surface at the point where an underlying (111)-array of Pt atoms provided two metal atoms as sites for adsorption for the quinoline moiety and a further two metal atoms as sites for pyruvate adsorption via the carbonyl groups. This situation is shown in Figures 7 and 8. When the sum of the potential energies of all possible interactions between alkaloid and pyruvate was determined it was found that the interaction of cinchonidine with pyruvate in configuration **Y** exceeded that in configuration **X** by about 50

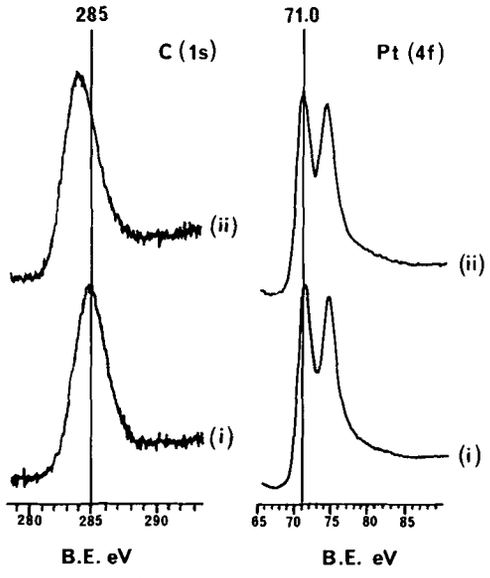


Figure 6. C(1s) and Pt(4f) spectra for a monolayer of 10,11-dihydrocinchonidine adsorbed on Pt(111). (i) 300K; (ii) after heating to 550K; σ_C / (atoms / cm^2) = 3.30 · 10^{15} at 300K and 3.52 · 10^{15} at 550K.

Table I Angles of principal torsion bonds in the three minimum-energy conformations for cinchonidine.

Conformation	C3′–C4′–C9–C8 /degrees	C7–C8–C9–C4′ /degrees	C4′–C9–O–H /degrees	C2–C3–C10–C11 /degrees	Energy /(kJ/mol)
A	97	286	306	141	121
B	63	176	310	144	116
C	255	177	310	145	115
Crystal structure[38]	101	287	299	125	

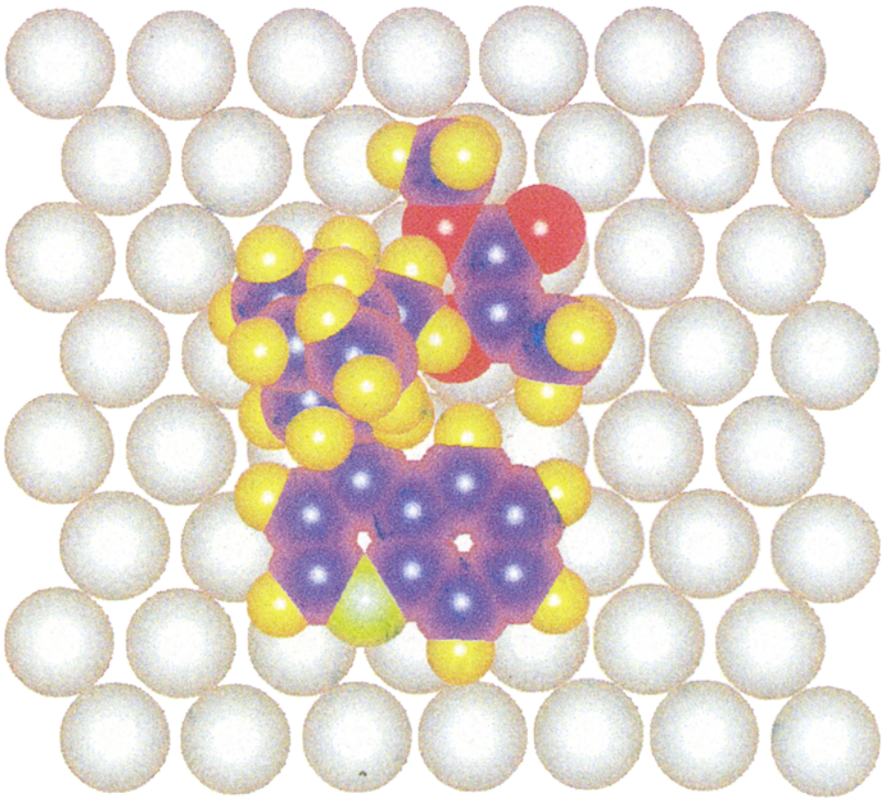


*Figure 7. Representation of methyl pyruvate in configuration **X** adsorbed adjacent to cinchonidine in conformation A.*

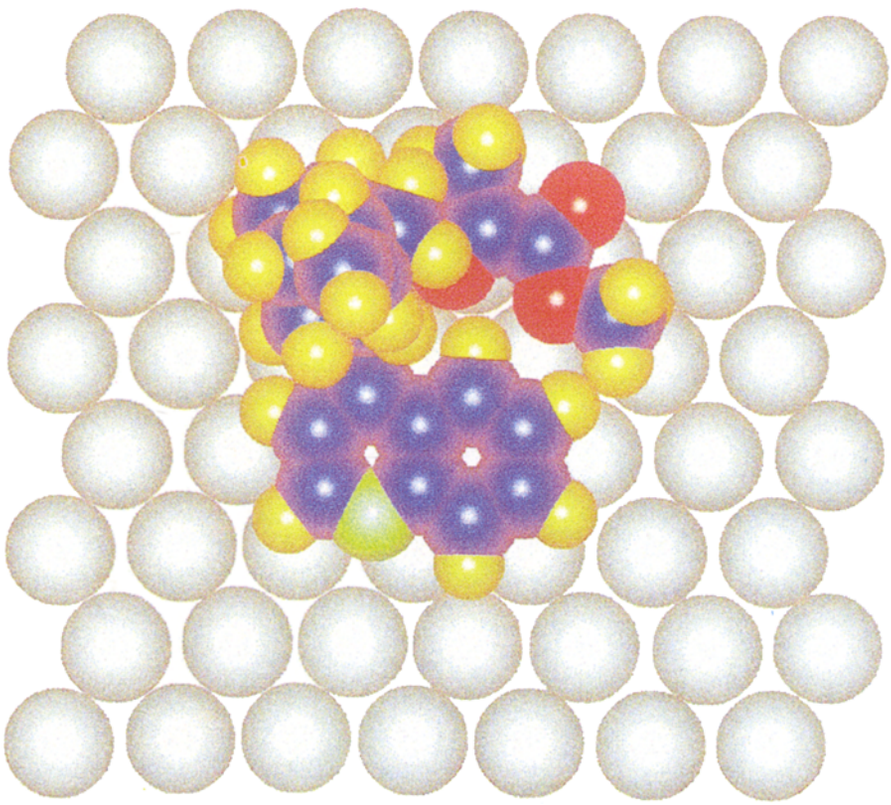


*Figure 8. Representation of methyl pyruvate in configuration **Y** adsorbed adjacent to cinchonidine in conformation A.*

kJ/mol, the precise value depending on the exact positioning of the two molecules relative to one another. Moreover, the modelling programme identified the quinuclidine-N/pyruvate-O environment as being conducive to the formation of a hydrogen bond when a procedure equivalent to forming the half-hydrogenated state was implemented. Indeed when the half-hydrogenated state was rotated about the hydrogen bond (there being no Pt surface present) the orientation appropriate to give (*R*)-lactate was of low energy whereas that to give (*S*)-lactate was of high energy[40].

To summarise, adsorption of pyruvate as configuration **X** in the vicinity of cinchonidine in conformation A (Figure 7) is energetically favoured and would provide (*R*)-lactate on hydrogenation, whereas adsorption in configuration **Y** (Figure 8) is energetically disfavoured, and would provide (*S*)-lactate on hydrogenation. Adsorption,whether as **X** (favoured) or **Y** (disfavoured) in this environment leads to a hydrogen-bonding interaction with the alkaloid when the half-hydrogenated state is formed, and thereby to an enhancement in the rate of product formation. For this reason, modification of a Pt surface should lead to an increase in the rate of formation of both (*R*)- and (*S*)-lactate (as is observed) but with preferential formation of (*R*)-lactate thereby inducing enantioselectivity. Modelling of the interaction of pyruvate with cinchonine in conformation A' shows, as expected, that configuration **Y** of pyruvate undergoes a lower energy (favoured) interaction with the alkaloid than configuration **X**, leading to preferential formation of (*S*)-lactate. When a 7×7 array of Pt atoms, judged as typical of the crystallite surface in EUROPT-1[17], was populated by four or five cinchonidine molecules (simulating high coverage), it was found that pyruvate in configuration **Y** developed interactions with a second alkaloid molecule whereas that in configuration **X** did not. This recalls the basic premise of the template model, although in the present case the alkaloid molecules are differently disposed. However, such interactions further disfavour the participation of pyruvate as configuration **Y** at the cinchonidine-modified surface, and further enhances enantioselectivity in favour of (*R*)-lactate.

The energetics of the approach of pyruvate to quinine and quinidine were modelled in an analogous manner; the presence in these alkaloids of the methoxy constituent in the quinoline moiety does not affect the favoured alkaloid–pyruvate interactions (configuration **X** with quinine and configuration **Y** with quinidine).

The possibility that pyruvate might interact with cinchonidine in the region near the hydroxy group[37], and that the quinuclidine moiety should rotate to provide the required hydrogen-bonding interaction (participation of conformation C), has been modelled and found to be highly disfavoured on energetic grounds.

It is thus concluded, (*i*) from an absence of evidence for ordered adsorption of quinoline and dihydrocinchonidine on Pt(111) and (*ii*) from the modelling studies of the interaction of methyl pyruvate with the alkaloids, that the origin of enantioselectivity in this reaction is attributable to a 1:1 interaction of modifier and reactant. This being so, it is now necessary to ensure that two pieces of experimental work previously reported are themselves consistent with this 1:1 interaction model; these are discussed in the following two sections.

3. Modelling the variation of optical yield with cinchonidine coverage

Figure 9 shows the experimental variation of optical yield with mass of cinchonidine available for adsorption on 0.1 g EUROPT-1[19,26]. It is assumed that the maximum-achievable surface concentration of cinchonidine is obtained when the optical yield (and the reaction rate) attain their maximum values, *i.e.* at 1.0 mg alkaloid per 100 mg catalyst.

In the model, θ represents the fraction of surface covered by alkaloid together with a small number of Pt atoms that, together with the alkaloid, constitute the enantioselective hydrogenation site, so that $(1-\theta)$ represents the fraction of the surface remaining available for racemic reaction. Enantioselective reaction proceeds with a rate r_{enan} giving products R_{enan} and S_{enan}, and racemic reaction proceeds with a rate r_{rac} giving products $R_{rac} = S_{rac} = 50\%$. Remembering that optical yield is defined as $(R_{total} - S_{total})/(R_{total} + S_{total})$ then, if the enantioselective site is composed of n alkaloid molecules,

$$R_{total} = (1-\theta) \cdot r_{rac} \cdot R_{rac} + \theta^n \cdot r_{enan} \cdot R_{enan}$$

and

$$S_{total} = (1-\theta) \cdot r_{rac} \cdot S_{rac} + \theta^n \cdot r_{enan} \cdot S_{enan}$$

Figure 9 shows the theoretical behaviour for $n = 1$, the 1:1 interaction case, and for $n = 2$ and $n = 3$, which represent variants on the template model. The theoretical curves utilise the values $R_{enan} = 82.5\%$, $S_{enan} = 17.5\%$, $r_{enan} = 1200$ mmol $\cdot$ h^{-1} $\cdot$ g^{-1}, and $r_{rac} = 150$ mmol $\cdot$ h^{-1} $\cdot$ g^{-1}. The experimental behaviour accords with the case of a 1:1 interaction of pyruvate with the modifying alkaloid as envisaged in the foregoing section [b]. The development of optical yield with alkaloid coverage has also been modelled by *Garland* and *Blaser* who took into account adsorption-desorption equilibria in the system[40].

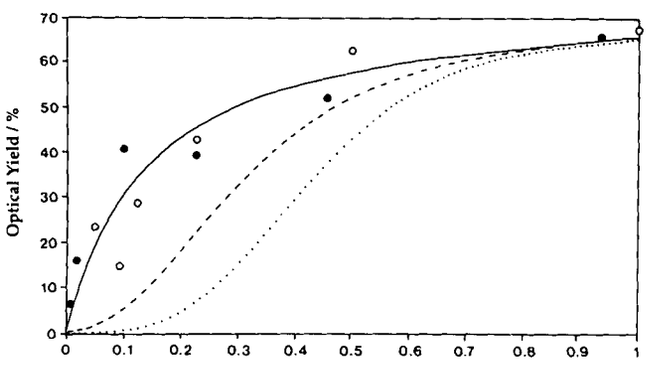


Figure 9. Dependence of optical yield on the mass of cinchonidine (mg) available for adsorption onto 6.3% Pt / silica (EUROPT-1) (100 mg). Open and filled points represent results for catalyst samples re-reduced or not re-reduced before modification. The curves represent the behaviour calculated on the basis of a 1:1 interaction (full curve), the template model requiring 2 alkaloid molecules to compose a site (dashed curve), and the template model requiring 3 alkaloid molecules to compose a site (dotted curve). Reactions were conducted in ethanol solution at 290K and 10 bar pressure; full details are given in Ref. 19.

[b] The model requires a racemic rate of 150 mmol $\cdot$ h^{-1} $\cdot$ g^{-1}, whereas experimental values recorded[15,16] were 30 to 50 mmol $\cdot$ h^{-1} $\cdot$ g^{-1}. We currently believe that racemic hydrogenation in the absence of the modifier is poisoned by a simultaneous catalysed polymerisation of pyruvate, and that in consequence our reported rates of racemic hydrogenation may be underestimated. This matter will be addressed in a subsequent publication. This does not prejudice the reality of the rate enhancement observed in the presence of alkaloid, although the enhancement factor may be in the order of 8 to 16, rather than 25 to 60 as previously recorded.

4. Modelling the effects of modification by mixtures of alkaloids

100-mg samples of EUROPT-1 were modified in ethanolic solutions of quinine (mole fraction n_1) and quinidine (mole fraction n_2). Figure 10 shows the optical yields obtained for reactions under standard conditions. A steady change in optical yield was obtained from −38% (31%*R*-, 69%*S*-) for $n_2 = 1$ to +60% (80%*R*-, 20% *S*-) for $n_1 = 1$. The change was not quite linear, the optical yield being +19% at $n_1 = n_2 = 0.5$. The initial reaction rates were $r_1 = 685$ mmol $h^{-1} \cdot g^{-1}$ for $n_1 = 1$ and $r_2 = 650$ mmol $\cdot h^{-1} \cdot g^{-1}$ for $n_2 = 1$; reactions with mixed modifiers gave reaction rates 10 to 20% lower than expected on the basis of interpolation between these values.

If enantioselectivity results from a 1:1 interaction of modifier and reactant then optical yield is proportional to $n_1 + n_2$ assuming that relative surface concentrations are the same as those in solution. So, if the yields of *R*- and *S*-product are R_1 and S_1 when $n_1 = 1$ and R_2 and S_2 when $n_2 = 1$ then, disregarding any racemic reaction:

$$R_{total} = n_1 \cdot r_1 \cdot R_1 + n_2 \cdot r_2 \cdot R_2$$

$$S_{total} = n_1 \cdot r_1 \cdot S_1 + n_2 \cdot r_2 \cdot S_2$$

The theoretical curve using the values for the parameters stated above is shown in Figure 10 (continuous curve); agreement with experiment is close.

If the asymmetric hydrogenation site involved the participation of two or three alkaloid molecules and if racemic reaction can again be disregarded, then the optical yield should be proportional to $n_1^2 + n_2^2$ or $n_1^3 + n_2^3$ respectively. Curves obtained on this basis are also shown. They have a pronounced S-shape with a point of inflexion near $n_1 = n_2 = 0.5$ because enantiomeric excess would remain high at low values of n_1 or n_2 where there would be insufficient quinidine or quinine, respectively, for a significant number of pairs or triplets of like alkaloid molecules to adsorb in close proximity. If such pairs or triplets promoted racemic reaction at an enhanced rate, the essential S-shape of the curves would be retained but the severity of the change in gradient would be reduced. The experimental results support the 1:1 interaction model.

5. The participation of oxygen in catalyst modification

Conventional modification involves stirring the catalyst in a highly concentrated solution of the modifier in air. *Orito* and co-workers recommended a period of 20 h; our practise is to stir for 1 h which provides a comparable enantioselectivity but the extent of the rate enhancement is slightly reduced. We have reported[16] that for dihydrocinchonidine-modified reaction, omission of the period of stirring in air results in a depressed optical yield (58% compared with 79%) and the virtual elimination of rate enhancement (initial racemic rate = 30 to 50 mmol $\cdot h^{-1} \cdot g^{-1}$, anaerobic rate = 66 mmol $\cdot h^{-1} \cdot g^{-1}$ and normal enhanced rate = 1200 mmol $\cdot h^{-1} g^{-1}$). This result has attracted attention because the procedure of stirring in air is not universally practised[18] (and, indeed, we found it unnecessary when low concentrations of modifier were used[19]). Other workers have recently corroborated our observation[41]. Accordingly, we have again compared the effects of using aerobic and anaerobic conditions of modification using essentially the experimental procedure described in Ref. 16 (high concentrations of modifier solution) but, in addition, taking care in the anaerobic experiments to remove air dissolved in the ethanol solvent and the pyruvate by subjecting these materials to successive freeze/thaw cycles. The results (Table II) clearly demonstrate the important role of air (presumably oxygen) in enabling cinchonidine to act as a modifier, indeed cinchonidine adsorption appears totally to poison pyruvate hydrogenation in the absence of air.

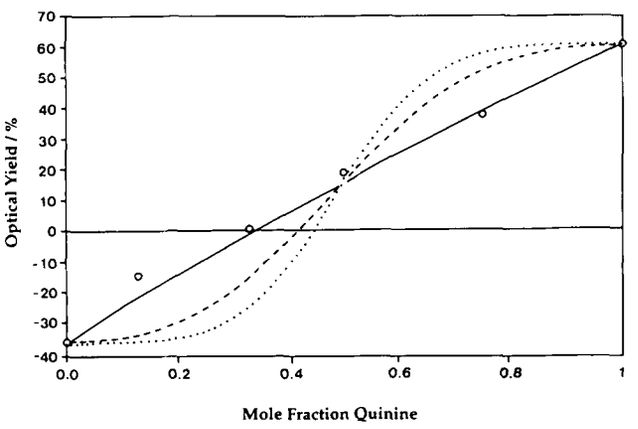


Figure 10. Effects of modification of 6.3% Pt / silica (EUROPT-1) by mixtures of quinine and quinoline in ethanol: variation of optical yield in reactions under standard conditions with mole fraction of quinine. Open points represent experimental results. The curves are as designated in Figure 9. Further details of reaction conditions are given in Ref. 28.

Table II Cinchonidine-modified pyruvate hydrogenation [a] performed under either aerobic or anaerobic conditions.

Conditions	Initial rate / mmol $\cdot h^{-1} \cdot g^{-1}$	Conversion /%	Enantiomeric excess [b] /%
aerobic	2010	66	62
aerobic	1830	55	65
anaerobic	5	<1	0
anaerobic	15	4	3
anaerobic	10	2	5
anaerobic	10	<1	0

[a] Standard conditions: 113 mmol pyruvate, 10 bar pressure, 293K.
[b] ±2%.

Our hypothesis had been that ordered co-adsorption of alkaloid and oxygen was responsible for the ordered distribution of alkaloid required by the template model. The view developed above, that enantioselectivity is the result of a 1:1 interaction of alkaloid and pyruvate, still requires Pt-atom sites to be available adjacent to the alkaloid for adsorption of the ester. Table II suggests that such sites do not exist at the Pt surface modified and used under anaerobic conditions because alkaloid adsorption has achieved too high a coverage. Under standard conditions oxygen adsorption may prevent the alkaloid achieving such a high coverage, and sites for pyruvate adsorption may be generated by reaction of adsorbed oxygen with hydrogen in the initial stage of reaction. This mechanism requires oxygen to be weakly but significantly adsorbed by comparison with the cinchona alkaloids. This is supported by the XPS experiment reported above which shows that an adlayer of dihydrocinchonidine adsorbed from air saturated ethanolic solution contained oxygen in excess of that expected from the formula of the alkaloid and attributable to oxygen originally dissolved in the solvent.

6. Diversification of the reaction

Enantioselective pyruvate hydrogenation over cinchona-modified Pt is easily achieved, but chiral specificity is usually lost if other Group 8 metals are used in place of Pt, or other chiral compounds are used in place of cinchona alkaloids, or if reactions other than α-keto ester hydrogenation are attempted. Diversification of the system is one of our major goals, and a degree of success has been achieved. First, it has been demonstrated that Ir

supported on silica, alumina, or calcium carbonate can be successfully modified by cinchona alkaloids to provide reproducible values of the enantiomeric excess of up to 39% in pyruvate hydrogenation[42]. Enantioselectivities are lower than for Pt because the racemic rate is faster, otherwise the reaction appears to proceed by the same mechanism. Second, cinchona-modified Pt catalyses the enantioselective hydrogenation of diketones such as MeCOCOMe, giving enhanced rates and enantiomeric excesses of up to 38% in dichloromethane solution[43]. The mechanism probably parallels that of pyruvate hydrogenation.

The discovery of new effective modifiers is a difficult task. Cinchona alkaloids are effective because (*i*) they contain a moiety that provides for strong adsorption (the quinoline ring system), (*ii*) the conformation of the modifier has a crucial spatial and energetic relationship with that of the reactant, (*iii*) the enantioselective reaction exhibits an enhanced rate (due to the action of the quinuclidine-N), and (*iv*) rotational flexibility in the modifier permits the 1 : 1 interaction to be achieved to maximum effect. The search for new modifiers is presently concentrated on substances that exhibit some or all of these attributes.

The experiments next to be described were bracketed by a number of reactions conducted under standard conditions but involving no modifier which were required to show no optical yield and a normal racemic rate (30 to 50 mmol · $h^{-1} \cdot g^{-1}$). This blanking procedure was rigorous; the apparent irreproducibility in the results shown in Table III is a measure in part of the difficulty of achieving reproducibility in studies conducted over several years.

On first examination, (S)-(−)-1-benzylpyrrolidine-2-methanol(**1**, Figure 11) performed as a modestly effective modifier, giving a rate enhanced by a factor of 3 and a modest enantioselectivity to (*R*)-product in pyruvate hydrogenation (entry 1, Table III).

However, repetition of the work resulted in no enantioselectivity (entry 2), although the rate was enhanced by a factor of 2.

Ephedrine (**2**, Figure 11) is reported[18] to be a moderately effective modifier (entry 3, Table III) and is available in a number of enantiomeric forms. If it were effective the role of modifier configuration could be investigated. The literature result was reproduced in two separate studies involving the (1*R*,2*S*)-enantiomer (entries 4, 5), in one an enhanced rate was observed and in the other it was not. However, marginal chiral selectivity was achieved at the third attempt (entry 6) which rendered the study of configuration of little value (entries 7,8,9).

Table III Initial rates, R_i, and optical yields observed in pyruvate hydrogenation under standard conditions but using modifiers other than cinchona alkaloids.

Modifier [a]	R_i / (mmol·h^{-1}·g^{-1})	Conversion /%	Optical yield %
1	120	30	12
1	90	27	0
2	–	–	5–25 [b]
(1*R*, 2*S*)-**2**	35	15	7 [c]
(1*R*, 2*S*)-**2**	115	37	13 [d]
(1*R*, 2*S*)-**2**	–	27	2.9
(1*R*, 2*R*)-**2**	80	18	2.2
(1*S*, 2*R*)-**2**	90	11	0.5
(1*S*, 2*R*)-**2**	60	15	0.0
L-**3**	40	16	2.5 [e]
D-**3**	30	17	−1.5
L-**4**	35	20	1.5
D-**4**	40	22	−1.5

[a] Modifiers identified in Figure 11. [b] Ref. 18. [c] Ref. 44. [d] Ref. 37. [e] Similar result for the methyl ester.

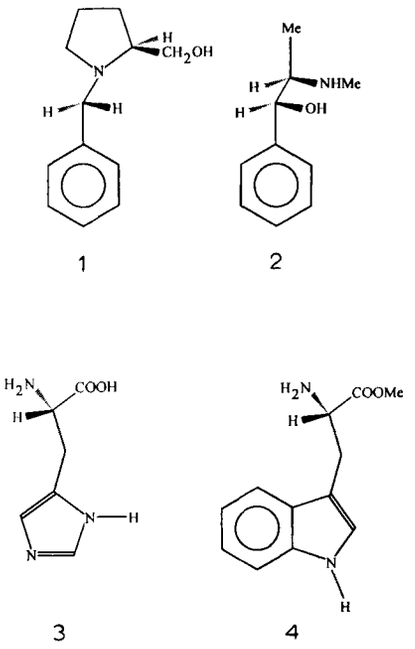


Figure 11. 1, (S)-(−)-1-benzylpyrrolidine-2-methanol. 2, Ephedrine. 3 L*-Histidine. 4,* L*-Tryptophan methyl ester.*

D- and L-histidine (**3**, Figure 11) were examined as modifiers. Only weak modification activity was observed and rate was not enhanced (entries 10, 11, Table III). However, the reversal of the direction of rotation in the product on changing from one enantiomer to the other gives confidence that these modifiers were exerting a genuine directional influence over the reaction. The methyl ester of L-histidine behaved as L-histidine. Finally, the methyl esters of D- and L-tryptophan (**4**, Figure 11) exhibited a similar weak modification activity but again there was apparently no enhanced rate (entries 12, 13).

Statements with regard to enhanced rate must be made with care when marginal enantioselectivity is observed. The adsorption of a potential modifier reduces the fraction of the surface available for both racemic and enantioselective reaction. Thus, where weak modification is observed, an initial rate of, say, 40 mmol · $h^{-1} \cdot g^{-1}$ (which is indistinguishable from a normal racemic rate in the absence of modifier) may be composed of a genuinely reduced racemic rate together with a slightly enhanced enantioselective rate.

To summarise, dramatic modification effects of the cinchona alkaloids at Pt and Ir surfaces is lost when molecular complexity is reduced, even though some formal equivalence of function may be thought to be present in these simpler substances. The molecular modelling described above demonstrates that the energy surface appropriate to the approach of the reactant to the modifier is of crucial importance; moreover, desired high enantioselectivities rely on the reactions showing enhanced enantioselective rates. The latter may require virtually immobile adsorption of the modifier in order that the lifetime of the stabilised half-hydrogenated states can be kinetically significant. Such may not have been the case for the alternative modifiers examined here.

Conclusions

Surface-science, catalysis and molecular-modelling studies have demonstrated that this enantioselective hydrogenation is well interpreted by a model involving a 1 : 1 interaction of cinchona-alkaloid modifier and pyruvate reactant.

The sense of the observed enantioselectivity and the enhanced rate of enantioselective reaction both arise naturally from the proposed model.

Nevertheless, experimental information is required in several further areas before the mechanism of enantioselective action in this system can be said to be adequate. First, acceptance of the 1 : 1 interaction model implies that the minimum necessary Pt-particle size needed to sustain enantioselectivity is smaller than had hitherto been believed, and this should be subjected to experimental test. Second, as the role of oxygen in modification becomes clearer, the question arises as to whether substances other than oxygen might lead to more efficient modification. Third, the role of solvent as a potential adsorbate and as a factor influencing modifier conformation should be explored. With this additional information, the model now proposed and the principles that lie behind it should provide a useful guide to the creation of conditions for the achievement of other chiral reactions on variously modified surfaces involving a variety of catalytically active metals.

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Note added in proof

Following the submission of this paper *Schwalm, Minder, Weber* and *Baiker* (Catal. Letts. **23**, 271 (1994)) have published the results of their theoretical calculations of the interaction of pyruvate with cinchonidine and cinchonine modifiers. There are similarities and differences between their treatments and results and ours; importantly their calculations suggest that protonated cinchonidine (protonated at the quinuclidine-N) is energetically more likely than cinchonidine to interact with pyruvate to give the H-bonding interaction.

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