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# Enantioselective Hydrogenation

## I. Surface Conditions during Methyl Pyruvate Hydrogenation Catalyzed by Cinchonidine-Modified Platinum/Silica (EUROPT-1)

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An investigation has been made of surface conditions during the enantioselective hydrogenation of methyl pyruvate, MeCOCOOMe, to *R*-(+)-methyl lactate, MeCH(OH)COOMe, at 10 bar pressure catalyzed by 6.3% Pt/silica EUROPT-1 modified by cinchonidine. Isotherms for the adsorption of cinchonidine and of methyl pyruvate at 298 K are reported. During modification, cinchonidine adsorbs both on the platinum active phase and on the silica support; co-adsorption of ethanol with cinchonidine on the platinum enhances the effectiveness of the modifier. Methyl pyruvate is strongly chemisorbed and forms physically adsorbed multilayers on EUROPT-1. Cinchonidine promotes the rate of methyl pyruvate hydrogenation at 293 K by a factor of 25. Some characteristics of the reaction of cinchonidine with adsorbed hydrogen are reported. The effectiveness of cinchonidine both as a modifier and as a promoter collapses above 322 K. The kinetics of methyl pyruvate hydrogenation are reported as are the optical yields obtained over the catalyst preconditioned in four ways before modification. The best activity and enantioselectivity were observed over EUROPT-1 reduced at 373 K from which hydrogen had been desorbed before modification. A mechanism is proposed which interprets both the observed enantioselectivity and the promoting effect of cinchonidine on the rate of reaction. 

## INTRODUCTION

Selectivity is an important feature of catalyzed reactions, and an understanding of the factors that influence selectivity is fundamental to the theory and practice of catalysis. In this series of papers we address the subject of metal-catalyzed asymmetric hydrogenation wherein selectivity is evident in the preferential formation of one optical isomer of the product.

The use of heterogeneous catalysts to effect asymmetric hydrogenation is very restricted, only two systems having been described in detail. Izumi has reviewed the very considerable amount of work reported on the hydrogenation of β-ketoesters catalyzed by nickel modified by optically active acids (e.g., tartaric acid) (*1*). Less well known is the enantioselective hydrogenation of α-ketoesters catalyzed by platinum modified by certain cinchona alkaloids, reported by Orito *et al.* over the period 1979 to 1982 (*2–5*) and more recently by Blaser, Baiker, and co-workers (*6, 7*).

We have chosen to study the Orito reaction for two reasons. First, simple α-ketoesters are formally isoelectronic with the alka-1,3-dienes that we have studied extensively from the standpoint of their selectivity in catalytic hydrogenation (*8*). Second, it was considered essential that any such study should involve the use of a well-characterized catalyst, and we had available the standard Pt/silica EUROPT-1, the detailed characterisation of which has been published

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TABLE 1

Pretreatments of the Catalyst EUROPT-1

| | |
|---|---|
| State 1 | No pretreatment (used as received) |
| State 2 | Reduced at 293 K in 1 bar $H_2$ for 1 h |
| State 3 | Reduced at 373 K in 1 bar $H_2$ for 1 h |
| State 4 | As State 3; adsorbed H removed by temperature-programmed desorption to 673 K |

(*9–12*). Catalysis of this reaction by Pt/silica has not previously been studied in detail.

In this paper we describe the conditions prevailing at the catalyst surface during methyl pyruvate hydrogenation catalyzed by cinchonidine-modified Pt/silica. This we have achieved by measurement of adsorption isotherms for the modifier and the reactant, reaction kinetics, and optical yields. In addition catalyst pretreatment has been varied in order to determine the surface conditions that provide the highest optical selectivities.

At present this system appears to be highly specific; for reasons that are not clear, high enantioselectivity can be achieved only with platinum, only with cinchona alkaloid modifiers, and only in $\alpha$-ketoester hydrogenations. It is hoped that our studies will permit us to develop a mechanism which interprets this high specificity and thereby will enable us to diversify the system and to develop new catalysts for asymmetric hydrogenation.

## EXPERIMENTAL

### *Materials*

Experiments involved the use of the EUROPT-1 standard catalyst, a 6.3% Pt/silica of total surface area 185 $m^2\ g^{-1}$ manufactured by Johnson Matthey and characterized by the EUROCAT group (*9–12*). The platinum in EUROPT-1 is substantially oxidised in the as-received material (*9, 13*). In this work, EUROPT-1 was used in four states of pretreatment as set out in Table 1. When reduced at the modest temperatures indicated in Table 1 the mean platinum particle size is about 2 nm and the dispersion of the platinum is 60% (*10*).

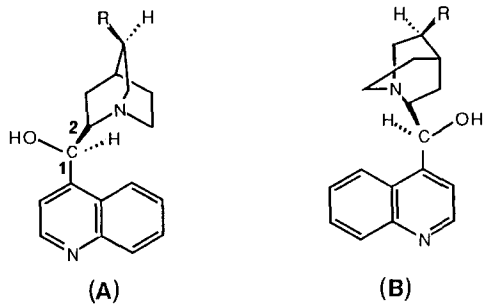
Methyl pyruvate and methyl lactate (Fluka), cinchonidine and cinchonine (Aldrich), ethanol (AnalaR grade), and hydrogen were used as received.

### *Measurement of Adsorption Isotherms*

Isotherms were measured for the adsorption of cinchonidine and of methyl pyruvate from ethanolic solution onto reduced EUROPT-1 at 298 K. Adsorptive at various concentrations in 10 ml solvent was allowed to equilibrate with the catalyst with periodic shaking. Initial cinchonidine concentrations were in the range 0.001 to 0.040 *M* (0.040 *M* was the concentration under modification conditions). Concentrations in the solvent at equilibrium were determined spectrophotometrically by use of bands at 283 and 315 nm. Initial methyl pyruvate concentrations were in the range 0.001 to 3.8 *M* (3.8 *M* was the concentration under reaction conditions). Concentrations were determined by differential pulsed polarography.

### *Catalyst Modification*

The preparation of a surface capable of achieving enantioselective hydrogenation is effected by the process of *modification* in which a chiral substance (the modifier) is adsorbed onto the catalyst surface. The modifier used most extensively was cinchonidine(A) but a few experiments were also performed with cinchonine(B). Modification was achieved by immersion of the




(A) (B)

SCHEME 1

freshly reduced catalyst in 40 ml of a 1% wt/vol solution of the modifier in ethanol for 1 h at 293 K. The solution of the modifier was introduced via a septum into the vessel containing the reduced catalyst under hydrogen. Once the catalyst was thoroughly wetted, the vessel was opened to air, and the catalyst and modifier solution were transferred to an open beaker and stirred at ambient temperature for 1 h. Finally, the modifier solution was decanted and the wet catalyst was transferred to the high-pressure reactor. This procedure follows that described by Orito *et al.* except that, in this work, the period of digestion of the catalyst with the modifier was reduced from the literature value of 20 h (*3, 4*) to 1 h.

*Reaction Procedure*

Methyl pyruvate hydrogenations were carried out in a Fischer–Porter static reactor constructed in glass of volume 200 ml, fitted with a magnetic stirrer, and capable of sustaining pressures of >10 bar. Reactions described below as having been carried out under standard conditions were conducted as follows. Catalyst (0.2 g) pretreated and modified as described, was used together with 20 ml ethanol solvent, 10 ml methyl pyruvate, and 10 bar hydrogen at 293 K. Any variation or departure from these standard conditions is specified in the text. The hydrogen pressure, once set, was maintained by microcomputer control to within ±0.1 bar and the reaction was followed as a recording of hydrogen consumption as a function of time, which was displayed on the data processor. When the desired extent of reaction had been achieved the catalyst was recovered by filtration and conversion was determined by GLC (10% 20 *M* Carbowax on 40/60 mesh Celite). The solution was then vacuum distilled to remove solvent and traces of modifier. The optical rotation of the resultant mixture of methyl lactate and methyl pyruvate was measured (ambient temperature, sodium *D*-line) and a second GLC analysis carried out to determine accurately the concentration of methyl lactate. Cinchonidine in chloroform solutions was hydrogenated over EUROPT-1 at 10 bar in the same static reactor.

*Measurements of Optical Yield*

Optical yields were determined from measurements of optical rotation by use of Eq. (1), where $[\alpha]_D^T$ is the specific rotation of the product solution,

$$\text{optical yield} = [\alpha]_D^T/[\alpha]_0^T = 100\alpha/[\alpha]_0^T lc, \quad (1)$$

measured at the sodium *D*-line and temperature $T$, $[\alpha]_0^T$ is the specific rotation of the pure enantiomer under the same conditions (8.25° for *R*-(+)-methyl lactate), $\alpha$ is the measured optical rotation, $l$ is the path length of the cell, and $c$ the solute concentration. We have made the normal assumption that there is a direct relationship between the ratio of the concentrations of the enantiomers and the magnitude of the optical rotation, so that the optical yield as determined experimentally from Eq. (1) can also be expressed thus:

$$\text{optical yield} = |x_R - x_S|/(x_R + x_S). \quad (2)$$

This will be true provided the contribution to the optical rotation from each enantiomer is independent of the relative concentrations of the enantiomers. Furthermore, since optical rotation is concentration-, solvent-, and temperature-dependent, $[\alpha]_D^T$ and $[\alpha]_0^T$ should both be determined under identical conditions. Since this is difficult to achieve, the common practice is to use the literature value for $[\alpha]_0^T$.

## RESULTS

*Adsorption of Cinchonidine on EUROPT-1*

An isotherm for cinchonidine adsorption at 298 K from ethanolic solution on EUROPT-1 previously reduced at 373 K (State 3) is shown in Fig. 1. The highest values recorded for the extent of cinchonidine adsorption correspond to the uptake of about $1.8 \times 10^{20}$ molecules per gram of catalyst. One gram of catalyst contains $1.1 \times 10^{20}$

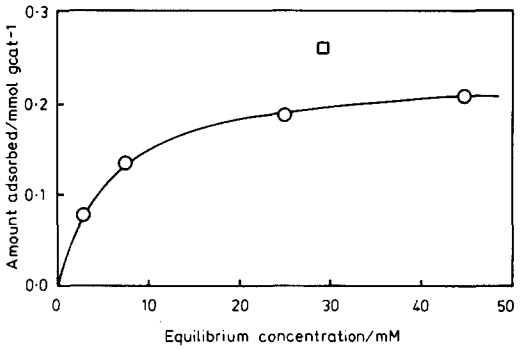



FIG. 1. Isotherm for the adsorption of cinchonidine at 298 K onto 0.2-g samples of State 3 EUROPT-1. Equilibration time: 45 h (circles) or 163 h (square).

surface Pt atoms, and hence adsorption of cinchonidine occurs on the surface of the support in addition to the surface of the Pt crystallites. Supposing the surface area obscured on adsorption of one cinchonidine molecule to be about 0.7 $nm^2$ then the total area covered by $1.8 \times 10^{20}$ cinchonidine molecules, assuming monolayer adsorption, is 125 $m^2$. The BET surface area of EUROPT-1 by nitrogen adsorption is 185 $m^2 g^{-1}$ (*9*) and the material has a porous structure such that not all pores may be penetrable by cinchonidine. It thus seems reasonable to suppose that cinchonidine adsorbs in a monolayer fashion over most of the accessible surface of EUROPT-1, both on the active phase and on the support.

Modified EUROPT-1 (State 3) was examined by infrared spectroscopy in the diffuse reflectance mode (Fig. 2). Only the aliphatic C–H region was visible above the broad absorption band due to hydroxyl groups of the support. The bands for adsorbed cinchonidine were shifted by comparison with their positions in the pure compound. Spectra for catalysts that had been modified for 1 h (the standard modification time), 3 h, and 4 h showed a progressive strengthening of the spectrum.

*Adsorption of Ethanol on EUROPT-1*

The addition of ethanol or of ethanolic solutions of cinchonidine to State 4 EUROPT-1 resulted in the evolution of gaseous hydrogen. These surfaces, which had been depleted of adsorbed H by temperature-programmed desorption, were apparently repopulated via the dissociation of ethanol (Eq. (3)) even in the presence of cinchonidine:

$$C_2H_5OH(l) \rightarrow C_2H_5O(ads) + H(ads) \quad (3)$$

$$2H(ads) \rightarrow H_2(g). \quad (4)$$

This was confirmed by reacting 2 ml $C_2H_5OH$ with 1 bar $D_2$ over State 4 EUROPT-1 at 298 K; the product was ethanol exchanged in the hydroxyl group but not in the alkyl group.

No hydrogen evolution occurred in com-

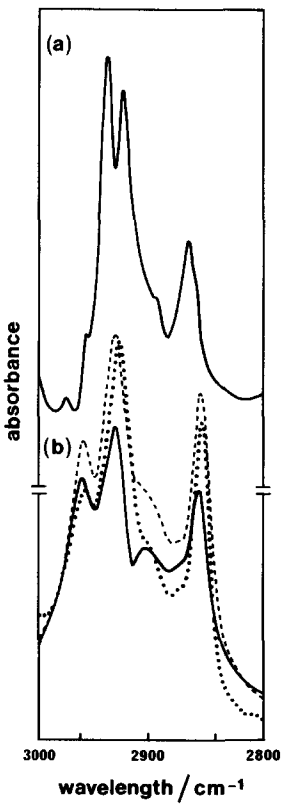



FIG. 2. (a) Transmission infrared spectrum of cinchonidine in the C–H stretching region. (b) DRIFT spectra in the same region of cinchonidine adsorbed on EUROPT-1 after modification times of 1 h (solid line), 3 h (dotted line), and 4 h (dashed line).

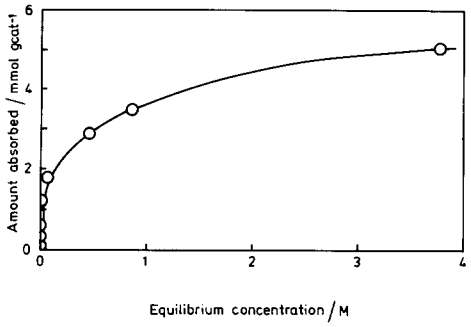



FIG. 3. Isotherm for the adsorption of methyl pyruvate at 298 K onto 0.2-g samples of State 3 EUROPT-1. Equilibration time, 60 h.

parable experiments with States 1, 2, or 3 EUROPT-1, from which it is assumed that co-adsorption of ethanol with cinchonidine during the modification of these catalysts was minimal.

*Adsorption of Methyl Pyruvate*

An isotherm for methyl pyruvate adsorption at 298 K from ethanolic solution on State 3 EUROPT-1 is shown in Fig. 3. The extent of adsorption greatly exceeds that of cinchonidine. At the concentrations at which hydrogenations were conducted (typically, 3.8 *M*) the number of molecules of methyl pyruvate adsorbed exceeded the total number of platinum atoms present in the catalyst by more than an order of magnitude. Clearly, extensive multilayer adsorption of methyl pyruvate occurred under these conditions over the whole of the catalyst surface.

*Hydrogenation of Cinchonidine*

Since the modifier cinchonidine is a highly unsaturated compound it was considered necessary to investigate its interaction with adsorbed hydrogen at the EUROPT-1 surface in the absence of methyl pyruvate. Experiments were conducted (a) at low concentrations of cinchonidine, as employed in some of the isotherm measurements, and (b) at high concentrations of cinchonidine, corresponding to the conditions pertaining during modification. Hydrogenation of cinchonidine using molecular hydrogen was also examined.

Reaction of cinchonidine at low concentrations ($10^{-5}$ to $10^{-4}$ *M* in ethanol) with adsorbed hydrogen on States 2 and 3 EUROPT-1 was complex. UV spectra of solutions altered significantly over 15 min, the changes being such as to suggest a loss of aromaticity in the quinoline system. Mass and $^1$H NMR spectra of such solutions indicated a complete loss of aromaticity and of unsaturation represented by the vinyl group, together with the presence of terminal methyl groups, of long polymethylene chains, and of high mass fragments beyond $m/e$ = 400 ($m/e$ for cinchonidine parent ion = 294). Thus, at very low concentrations, cinchonidine undergoes complex and extensive reaction at the EUROPT-1 surface. This reaction was not greatly reduced when cinchonidine solutions were added to State 4 EUROPT-1 (i.e., to State 3 catalysts having adsorbed hydrogen removed by temperature-programmed desorption). Thus, either this reactivity may be associated with the support or adsorbed hydrogen required for reaction at platinum sites may be transferred from the support in the presence of cinchonidine.

In contrast, no reaction was detectable by UV, NMR, or mass spectrometry when cinchonidine at typical modification concentrations in ethanol (ca. 0.04 *M*) was admitted to EUROPT-1 in State 3.

Cinchonidine was hydrogenated over EUROPT-1 in State 3 at 293 K under 10 bar hydrogen pressure using chloroform as solvent. The dark brown solid from this reaction contained three products and residual cinchonidine (thin layer chromatography), one of the products being in excess. Interpretation of IR, $^1$H NMR, and mass spectra indicated that all components of the mixture contained an ethyl group in place of the vinyl group in cinchonidine and that various degrees of reduction of the aromatic system had occurred.

When 0.1 g cinchonidine was added to

a standard methyl pyruvate hydrogenation over modified EUROPT-1, the residue obtained after distillation of products was mostly dihydrocinchonidine. This observation has also been made by Blaser *et al.* (*6*). There was no evidence for the presence of the products of higher molecular mass ($m/e > 400$) observed when dilute solutions of cinchonidine were contacted with the catalyst in the absence of molecular hydrogen.

*Methyl Pyruvate Hydrogenation: Kinetics*

The dependence of hydrogen consumption on time for reactions over cinchonidine-modified EUROPT-1 in States 1, 3, and 4 under standard conditions is shown in Fig. 4. Reaction always showed a short acceleration region (up to ca. 10% conversion), a substantial region of constant rate (from about 10 to 70% conversion), and a region of slower rate as complete reaction was approached. The constant rates achieved varied considerably with the manner in which the catalyst was pretreated (Table 2), the sequence being

State 4 > State 1 > State 2 ≈ State 3.

Values of the constant rates were used to determine the formal kinetics. At 293 K over EUROPT-1 (State 2) the orders of reaction

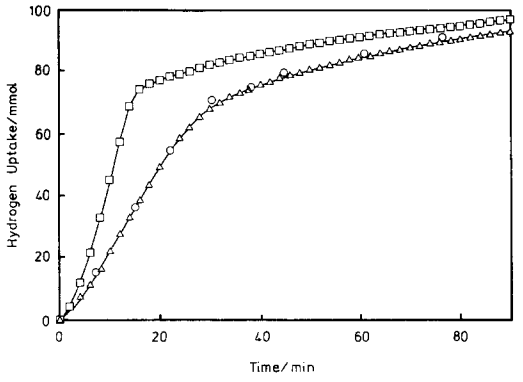



FIG. 4. Typical hydrogen consumption versus time curves for methyl pyruvate hydrogenation catalyzed by cinchonidine-modified EUROPT-1 under standard conditions (see text). 100% conversion corresponds to a hydrogen uptake of 113 mmol. Squares, State 1 of the catalyst; circles, State 2; triangles, State 3.

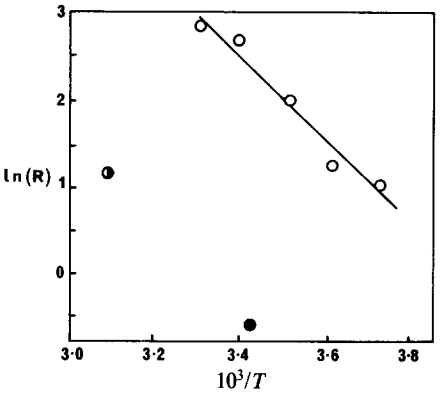



FIG. 5. Dependence of the constant rate, $R$, on temperature, $T$, for unmodified EUROPT-1 (solid circle), modified EUROPT-1 giving a high optical yield (open circles), modified EUROPT-1 giving a depressed optical yield (half-solid circle).

were $0.9 \pm 0.4$ in hydrogen (5–11 bar, 3.8 $M$ methyl pyruvate) and $-0.1 \pm 0.3$ in methyl pyruvate (1.9–7.5 $M$, 10 bar hydrogen pressure). Figure 5 shows the temperature dependence of the constant rate; the apparent activation energy is $38 \pm 6$ kJ mol$^{-1}$ over the range 267 to 302 K (10 bar hydrogen pressure, 3.8 $M$ methyl pyruvate). The reaction failed to obey the Arrhenius equation above 302 K; at 322 K the rate (and the enantioselectivity) collapsed.

The addition of methyl lactate to these hydrogenations reduced the rate, indicating strong product adsorption. For example, when 20 ml of racemic methyl lactate was added initially to a standard reaction mixture over State 3 EUROPT-1 a decrease of 50% in the constant rate was observed.

Rates of methyl pyruvate hydrogenation over unmodified EUROPT-1 were only 4% of the value over modified catalyst under comparable conditions (Fig. 5). Thus, the presence of the cinchonidine modifier greatly promotes the rate as well as inducing optical selectivity in the product.

*Methyl Pyruvate Hydrogenation: Optical Yield and Its Dependence on Experimental Variables*

*(i) Catalyst pretreatment.* Optical yields from experiments at 293 K sampled once at

TABLE 2

Variation of Constant Rate, $R$, and of Optical Yield, OY, with Catalyst Pretreatment

| State of EUROPT-1 | $R^a$ (mmol $h^{-1}$ $g^{-1}$) | Conversion (%) | Products | | OY (%) |
|---|---|---|---|---|---|
| | | | $R$(%) | $S$(%) | |
| 1 | 1680 | 98 | 82.0 | 18.0 | 64 |
| 1 | — | 100 | 82.0 | 18.0 | 64 |
| 2 | 710 | 94 | 86.5 | 13.5 | 73 |
| 2 | 960 | 99 | 85.0 | 15.0 | 70 |
| 3 | 830 | 91 | 87.5 | 12.5 | 75 |
| 3 | 820 | 96 | 87.5 | 12.5 | 75 |
| 4 | 1980 | 94 | 87.0 | 13.0 | 74 |
| 4 | 1840 | 96 | 88.5 | 11.5 | 77 |

[a] Initial conditions: 10 ml methyl pyruvate, 20 ml ethanol, 10 bar hydrogen, 293 K, 0.2 g catalyst.

high conversion are presented in Table 2. The order of optical selectivity is

State 4 ≥ State 3 > State 2 > State 1.

Optical yields were sensitive to the evacuation and hydrogen flushing conditions adopted before catalyst reduction. Failure to conduct these procedures rigorously reduced the optical yields from those given in Table 2 as follows: State 4 catalyst by 4%, State 3 catalyst by 9%, and State 2 catalyst by 20%.

*(ii) Conversion.* Optical yield increased with increasing conversion during the initial stages of reaction, achieving a maximum at about 25% conversion. For example, for a State 2 catalyst (not rigorously evacuated before reduction), opitcal yields of 42, 56, 59, 58, 57, and 50% were recorded at 5, 17, 25, 30, 39, and 99% conversion, respectively.

*(iii) Pressure.* Optical yield was insensitive to hydrogen pressure over the range 3 to 10 bar over a State 3 catalyst under standard conditions.

*(iv) Temperature.* Optical yield showed no temperature dependence over the range 267 to 302 K. A drastic reduction in optical yield to about 30% occurred at 322 K and this was accompanied by a collapse in rate at this temperature (Fig. 5).

## DISCUSSION

The results presented here establish for the first time some details concerning the surface conditions prevailing during catalyst modification and during enantioselective hydrogenation.

During the modification procedure cinchonidine adsorbs both on the platinum active phase and on the catalyst support (Fig. 1). Reduction of the modification time from 20 h (as recommended by Orito *et al.* (*3, 4*) to 1 h resulted in no loss of optical yield. However, the strengthening of the DRIFT spectrum of cinchonidine adsorbed on EUROPT-1 over a 4-h period (Fig. 2) indicates that the surface concentration of adsorbed cinchonidine increased further after 1 h. We infer that adsorption of cinchonidine occurs rapidly on the platinum active phase and is complete within 1 h, and that further adsorption occurs more slowly over the support extending eventually to the majority of the silica surface. After the modification of State 4 EUROPT-1, in which cinchonidine was adsorbed on EUROPT-1 in competition with ethanol, the resulting catalyst showed

by far the highest activity that we recorded and by a small margin the best optical selectivity. Thus, the presence of $C_2H_5O$(ads) was beneficial to the modification process. In this connection, we note that modification is conducted in air and in Part II we shall report that anaerobic modification is less effective than the standard procedure. Thus, the co-adsorption of oxygen-containing substances with cinchonidine provides the best modified catalyst for enantioselective hydrogenation that we have examined so far.

Orders of reaction were approximately zero in methyl pyruvate and unity in hydrogen, indicating strong adsorption of the ester and weak adsorption of hydrogen. Such orders are commonly encountered in the hydrogenation of unsaturated organic compounds, and the apparent activation energy is that expected for the hydrogenation of a keto group (*14*). However, modified catalysts were more active than an unmodified catalyst at 293 K by a factor of 25, notwithstanding the occupation of a fraction of the surface by alkaloid molecules. The promoting effect of cinchonidine on the rate probably arises because an array of adsorbed cinchonidine molecules (see below) obscures some surface platinum atoms in such a way that they are inaccessible to methyl pyruvate, but accessible to hydrogen molecules. Thus we propose that the greatly enhanced ester hydrogenation rate at the modified surface is attributable to a higher steady-state concentration of adsorbed hydrogen at the surface.

The form of the isotherm for methyl pyruvate indicates that adsorption of this reactant was both strong and extensive. On the assumption that one methyl pyruvate molecule occupies an area of surface of, say, 0.4 $nm^2$, then one monolayer on EUROPT-1 (185 $m^2 g^{-1}$) consists of 0.8 mmol ester. This extent of adsorption was achieved at very low equilibrium concentrations, and thus, at the 3.8 *M* concentration used in hydrogenations, the whole catalyst surface (active phase and support) was covered by five or six monolayers of ester. Hence, transport of hydrogen to the active site and that of methyl lactate away from the active sites was achieved via these multilayers of methyl pyruvate.

The hydrogen consumption versus time curves (Fig. 4) show three distinct regions. Initially, the rate accelerates and this is accompanied by an improvement in optical selectivity. It would appear that the modified catalyst, prepared as described, is not ideally suited for enantioselective hydrogenation, but that in the early stages of reaction some rearrangement within the first adsorbed layer occurs, with the result that the catalyst becomes more efficient. Two interpretations present themselves. The first possibility is that cinchonidine may not be the optimum surface modifier and it may undergo change. It is reported above that hydrogenation to dihydrocinchonidine occurs during methyl pyruvate hydrogenation. On this basis it may be supposed that, initially, some cinchonidine molecules are adsorbed at the quinoline nucleus and some by the vinyl group and that the initial behaviour is attributable to the occurrence of cinchonidine hydrogenation and the establishment of a more regular adlayer of dihydrocinchonidine. A second possibility is that the acceleration phase is attributable to the removal of oxygen-containing adsorbates (O(ads), $C_2H_5O$ (ads)) formed during catalyst modification. If this is the case then the situation is complex since, as mentioned above, anaerobic modification is less effective than the standard method. However, it is known that benzene forms a disordered monolayer on Pt(111), but that ordered coadsorption occurs when benzene and CO are adsorbed together on this surface (*15*); by analogy, it may be that ordered co-adsorption of oxygen with cinchonidine occurs during modification and provides a superior geometrical distribution of the alkaloid at the platinum surface. Maximum rate and selectivity may then be achieved when that oxygen is removed from the surface by hydrogen in the initial phase of reaction. We

are not able to choose between these alternatives at the present time, but this matter will be addressed again in Part II.

The period of acceleration was followed by one of constant rate (Fig. 4) and almost constant optical selectivity. This is to be expected since the order in methyl pyruvate is zero and the hydrogen pressure was maintained constant at 10 bar throughout reaction.

The period of constant rate was followed by a deceleration that was, for some catalysts, both sudden and severe. The deceleration is quantitatively attributable to poisoning by methyl lactate product. For example, the severe retardation at 65% conversion for reaction over State 1 EUROPT-1 shown in Fig. 4 is accurately described by one of the rate equations proposed by Hinshelwood for product-inhibited reaction (*16*).

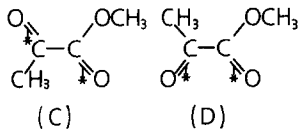
Thus each reaction exhibited three phases. In the first, surface conditions in the adlayer underwent adjustment toward the most appropriate for selective reaction; in the second, activity and selectivity were high; and in the third, reaction was inhibited by product.

*Mechanism of Asymmetric Hydrogenation*

Methyl pyruvate is strongly adsorbed and, by analogy with the alka-1,3-dienes, it is to be expected that interaction of both centres of unsaturation with the platinum surface occurs, giving planar adsorbed states (*8*). These may exhibit an anti-configuration of the carbonyl groups about the $C_2/C_3$ bond, as in Scheme 2C or a syn-configuration as in Scheme 2D.

In the fluid phase, before adsorption, methyl pyruvate molecules undergo rotation about the $C_2/C_3$ bond. However, by far the lowest energy conformation of the free molecule is the anti-form in which the carbonyl–carbonyl repulsion is a minimum and the variable carbonyl–methoxy attraction is at its strongest. Thus the surface concentration of (C) greatly exceeds that of (D).

In principle, both (C) and (D) may be in equilibrium with their corresponding enol



(C) (D)

SCHEME 2

forms. However, reaction of methyl pyruvate with $D_2$ over modified EUROPT-1 at 293 K gives $CH_3CD(OD)COOCH_3$ as the sole product (*17*) (that is, no $CH_2DCD(OH)COOCH_3$ is formed) and thus we discount enolised forms as important chemisorbed species. This concurs with the general observations, recently reviewed by Bartok (*18*), that keto mechanisms predominate at lower temperatures, whereas mechanisms involving enolised intermediates become important above about 423 K. Thus, to a good approximation, (C) represents the adsorbed state of methyl pyruvate.

Methyl pyruvate can adsorb as the planar species (C) in two mirror image forms, depending on its configuration as it approaches the surface. On the assumption that hydrogenation proceeds by the addition of two hydrogen atoms from below the plane of the adsorbed methyl pyruvate, then the lactate enantiomer produced is dependent on which enantioface of the reactant is presented to the surface. Thus, Fig. 6 shows that the two

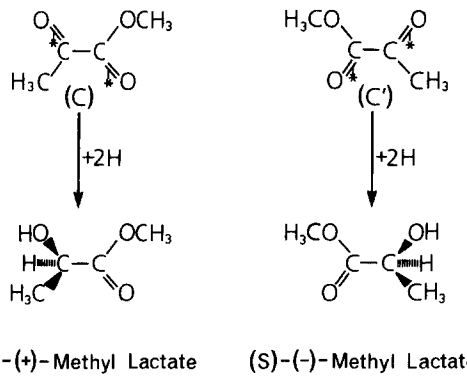



FIG. 6. The conversion of adsorbed methyl pyruvate (structure (C) and its mirror iamge (C')) by hydrogen atom addition to the two enantiomers of methyl lactate.

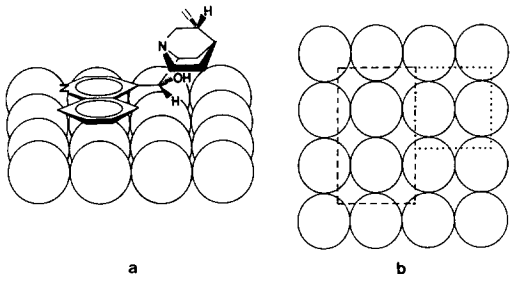



FIG. 7. Schematic representation of the side view (a) and plan (b) of the proposed mode of adsorption of the cinchonidine molecule at the Pt(100) surface. In (b) the dashed line denotes the region of the surface in which the quinoline system is chemisorbed and the dotted line denotes the quinuclidine system overhanging the surface.

enantiofacial variants (C) and (C′) provide *R*-(+)-methyl lactate and *S*-(−)-methyl lactate, respectively, on hydrogenation. Species (C) and (C′) are energentically equivalent when adsorption occurs at a plane surface, and so an unmodified surface provides a racemic mixture as product. However, (C) and (C′) each has a unique geometrical site requirement which becomes important in a translationally restricted environment. The geometrical requirement of (C) is that it requires a pair of adjacent platinum atom sites with the adsorbate oriented so that the sites are located "top left–bottom right" as viewed relative to the $C_2/C_3$ bond, whereas (C′) requires a "top right–bottom left" arrangement. There is thus a certain pair-site requirement for enantioselectivity in favour of the *R*-enantiomer and a different pair-site requirement in favour of the *S*-enantiomer.

Next, we consider the surface conditions from the standpoint of the modifier. The CHEMMOD molecular modeling system has been used to determine the minimum energy conformation of the free cinchonidine molecule. For this purpose, the rotations about carbon–carbon bonds 1 and 2 in structure (A) were of prime importance, and rotation about each was found to provide a clear minimum with respect to energy. The doubly minimised conformation was identified, from which it was clear that nothing hinders adsorption of cinchonidine molecules either by the aromatic system or by the vinyl group, but that adsorption via both functions simultaneously is not possible.

We propose a mechanism for the action of the modifier based on a consideration of the Pt(100) surface; similar conclusions would have been drawn had we chosen Pt(111) (*19*). Figure 7a shows a schematic representation of a molecule of cinchonidine in the lowest energy conformation adsorbed on Pt(100) via the aromatic system, and Fig. 7b shows the region of the surface that the modifier molecule as a whole obscures. The quinoline system is spatially well suited to lie above two adjacent surface platinum atoms, and the quinuclidine system lies just above the surface forming an overhang. Thus, each adsorbed cinchonidine molecule utilises an L-shaped region of the surface (Fig. 7b).

Molecular graphics indicates (*19*) that cinchonidine molecules should, from a purely geometrical standpoint, be capable of achieving a closely packed arrangement on the Pt(100) surface and that this arrangement leaves unpopulated groups of platinum atoms to which methyl pyruvate may gain access in configuration (C). Thus, enantioselectivity could be attributed to the establishment of a closely packed adlayer of cinchonidine molecules. However, since we have no evidence as to the ordering of the cinchonidine monolayer and since close packing should be regarded as a special case, we present here the mechanistic consequences for a more general situation where adsorption is regular but not close packed. Figure 8a shows the regular disposition of five cinchonidine molecules (represented by their L-shaped "adsorption shadows") on a 7 × 7 grid of Pt atoms (representative of the 2 nm particles most abundant in EUROPT-1; Ref. (*10*)). The adsorption of methyl pyruvate molecules at this surface can occur, but a detailed consideration of the stereochemistry in the neigh-

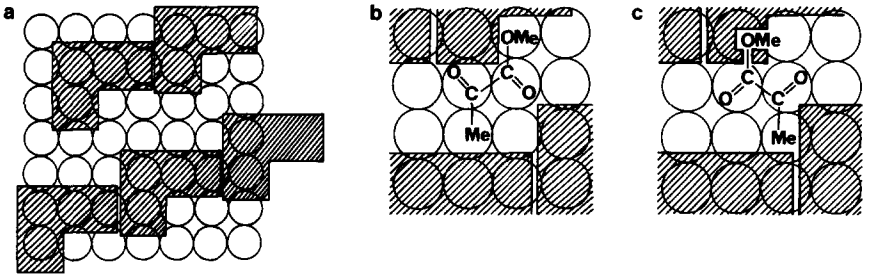



FIG. 8.(a) A representation of a nonclose packed ordered array of five cinchonidine molecules adsorbed on a Pt(100) surface. (b) and (c) The dispositions of adsorbed methyl lactate as structure C and C′, which give respectively the *R*-(+)- and S-(−)-enantiomers of methyl lactate on hydrogenation (see Fig. 6).

bourhood of the exposed Pt atoms shows that the pair-sites proposed above for the production of *R*-(+)-methyl lactate are plentiful (Fig. 8b), whereas those required for the production of *S*-(−)-methyl lactate are virtually nonexistent in that adsorption in the required mode would force the methyl and methoxy groups of the methyl pyruvate into unacceptable steric situations (Fig. 8c). Thus, the majority of the methyl pyruvate molecules present at modified surfaces are adsorbed at pair-sites which, on reaction, produce *R*-(+)-methyl lactate, and the observed enantioselectivity is thereby interpreted.

An experiment involving a differently shaped modifier tests this model. The alkaloid cinchonine (B) is nearly (but not exactly) the mirror image of cinchonidine; certainly it provides an L-shaped adsorption shadow in the mirror image sense to that given by cinchonidine. It is known (*4*) that cinchonine-modified platinum produces *S*-(−)-methyl lactate selectively. This we confirmed by a reaction over EUROPT-1 in State 4 when, under standard conditions, we obtained an optical yield of 71% in favour of the *S*-enantiomer.

We thus propose that the detailed stereochemistry about the pair-sites left accessible to methyl pyruvate by a regular array of adsorbed cinchona alkaloid molecules provides the key to an understanding of enantioselectivity in this reaction. This restriction of the role of cinchonidine to that of a template takes no account of the possibility that an adsorptive interaction of importance might be that of methyl pyruvate with the modifier, particularly involving the oxygen atom and/or the aliphatic nitrogen atom, and that the alkaloid may transfer H-atoms from the Pt surface to the ester. The importance of such processes should become clear when we report reactions involving the use of cinchona alkaloids chemically modified at these centres.

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