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Enantioselective Hydrogenation

IV. Hydrogen Isotope Exchange in 10,11-Dihydrocinchonidine and in Quinoline Catalyzed by Platinum Group Metals

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Hydrogen isotope (H/D) exchange in the alkaloid 10,11-dihydrocinchonidine has been studied over 6.3% Pt/silica (EUROPT-1), 5% Ru/alumina, 5% Rh/alumina, and 5% Pd/alumina at 293 K using C_2H_5OD and D_2 as solvent and deuterium source. Exchange was accompanied by hydrogenation. Over Pt, fast exchange occurred in the hydroxyl group followed by multiple exchange in which alkaloid molecules containing 2, 3, 4 and 5 deuterium atoms were formed simultaneously. Mass spectrometry and ^1H NMR showed that this multiple exchange occurred in the quinoline ring system and at C_9, but not in the quinuclidine ring system. The pattern of exchange in Ru was similar. Over Rh extensive hydrogenolysis of the quinuclidine ring system occurred, and over Pd the quinoline ring system was rapidly hydrogenated. Quinoline exchange and hydrogenation were also studied at 293 K; relatively rapid exchange occurred over Pt, Ru, and Rh, particularly at the 2- and 8-positions, whereas hydrogenation without significant exchange occurred over Pd. 10,11-Dihydrocinchonidine is adsorbed on Pt and Ru via the quinoline ring system and the multiple nature of the exchange indicates that the quinoline moiety is adsorbed approximately parallel to the metal surface by multicenter π-bonding. An additional interaction of the alkaloid molecule with the surface occurs at carbon atom C_9, which may interpret the slower exchange in the alkaloid by comparison with that in quinoline. This study supports and enhances the model proposed to interpret the origin of enantioselectivity in pyruvate hydrogenation over Pt and Ir modified by cinchona alkaloids. The similarities of exchange over Pt and Ru suggest that enantioselective catalysis should be achievable over Ru. The failure of 10,11-dihydrocinchonidine to retain molecular integrity on adsorption on these particular Rh and Pd surfaces interprets our failure so far to achieve enantioselective pyruvate hydrogenation over these catalysts.

INTRODUCTION

Enantioselective hydrogenation of methyl pyruvate to methyl lactate is achievable over Pt catalysts at room temperature when a cinchona alkaloid is preadsorbed onto the surface (*1–6*). The alkaloid is termed a modifier, and the process in which it is adsorbed onto the catalyst is termed modification. The absolute configuration of the modifier determines the sense of the observed enantioselectivity. Thus, modification by cinchonidine (Fig. 1) or quinine causes the preferential formation of R-lactate, whereas modification by the near enantiomers cinchonine or quinidine provides preferential formation of S-lactate. Values of the enantiomeric excess of 70% (i.e., 85% R-, 15% S-) can be obtained easily without the adoption of special procedures (4, 5), and 95% has been recorded for an optimized system (6).

The origin of enantioselectivity was considered in Part I (4) and was attributed to a template effect arising from a proposed ordered adsorption of alkaloid molecules at the Pt surface. Enantioselective reaction occurs more rapidly than racemic reaction (4, 5) and this has been attributed to the effect of a proposed H-bonding interaction between the quinuclidine–N atom in the alkaloid and the half-hydrogenated state derived from pyruvate (7). Recognition of this spatial relationship between modifier and reactant made necessary a revision of the first model, but the concept of an ordered array of alkaloid molecules at the Pt surface was retained (3).

In parallel with this study, surface science experiments have been conducted to search for ordered adsorption of 10,11-dihydrocinchonidine on Pt(111) by LEED and to examine the adsorbed state of the alkaloid by X-ray photoelectron (XPS) spectroscopy (8). The ability of naphthalene to undergo ordered adsorption on Pt(111), previously reported by Gland and Somorjai (9) and by Dahlgren and Heminger (10), has been confirmed, but no evidence has been obtained for ordered adsorption of quinoline or of 10,11-dihydrocinchonidine. In view of (i) this failure to detect ordered adsorption of alkaloid, (ii) further consideration of our experiments involving low coverages of alkaloid and involving mixtures of modifiers, and (iii) molecu-

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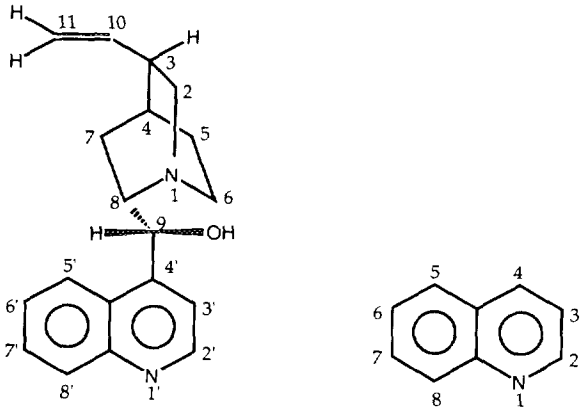

FIG. 1. Structures of cinchonidine (left) and quinoline (right).

lar modeling calculations for the docking of pyruvate with cinchona alkaloids, our model for the interpretation of enantioselectivity has been reassessed (8). All experimental evidence presently available both from our laboratory (8, 11, 12) and elsewhere (13–19) is consistent with the view that the origin of the induced enantioselectivity is a 1 : 1 interaction between adsorbed pyruvate and adsorbed cinchona alkaloid. Most models conceive of the alkaloid as adsorbed to Pt via the π-system of the quinoline moiety, i.e., with the quinoline ring system approximately parallel to the Pt surface.

The present study of the exchange of H for D in 10,11-dihydrocinchonidine was undertaken to provide direct evidence for the reactivity or otherwise of the quinoline and quinuclidine ring systems of the alkaloid at the Pt surface, and thereby to provide by inference evidence for its mode of adsorption as a modifier during enantioselective hydrogenation. The dihydro-derivative was chosen in preference to the naturally occurring cinchonidine because, as exploratory reactions showed, adsorption of the alkaloid by the vinyl group at C_3 in the quinuclidine moiety (Fig. 1) provided an unnecessary complication. Moreover, 10,11-dihydrocinchonidine is a little more effective as a modifier than cinchonidine, and was the alkaloid of choice in our study of the effects of experimental variables on enantioselectivity in pyruvate hydrogenation (5) and for our LEED and XPS studies (8). Because the alkaloid is a substituted quinoline, the exchange of quinoline under comparable conditions was also investigated.

A remarkable feature of this enantioselective reaction is the ease with which it can be achieved over Pt, and the difficulty, indeed failure, normally encountered when other metals are used. Conditions for reproducible enantioselective hydrogenation over various supported Ir catalysts have now been established (20) and isotope exchange in the alkaloid is reported in that context. Other workers have reported enantioselective pyruvate hydrogenation over cinchona-modified Rh (21); in our investigations over both Rh and Ru (22) an enantiomeric excess has been obtained in occasional reactions but is not achieved reproducibly. Catalysis of this reaction by cinchonidine-modified Pd is remarkable in that the sense of the enantioselectivity achieved is the reverse of that described above (21); this will be discussed in a later paper. Against this background, H/D exchange in 10,11-dihydrocinchonidine and in quinoline has been studied over the four metals Ru, Rh, Pd, and Pt.

EXPERIMENTAL

Materials

Pt/silica (EUROPT-1) (6.3%) is a standard reference catalyst having a total surface area of 185 $m^2\ g^{-1}$. The size distribution of the Pt particles is narrow and centered at 1.8 nm, such that the platinum dispersion is about 60% (23, 24). EXAFS spectroscopy has shown the Pt particles to be preferentially oriented as (111)-rafts (25). Ru/alumina (5%), Rh/alumina (5%), and Pd/alumina (5%) were supplied by Johnson Matthey. Cinchonidine (Fig. 1) (Aldrich), quinoline (BDH), C_2H_5OH (AnalaR), C_2H_5OD (Aldrich), and gaseous deuterium (99.8 atom %D, BOC) were used as received. 10,11-Dihydrocinchonidine was prepared and purified as previously described (5).

Procedure

The reaction vessel consisted of a closed tube of volume ca. 20 ml fitted with a vacuum-tight septum, and a sidearm and tap. Samples of catalyst (0.10 g) were reduced in 760 Torr H_2 (static reduction) for 2 h at 433 K (Ru), 473 K (Rh, Pd), or 393 K (Pt). Ten milliliters of a 1% wt/volume solution of alkaloid or quinoline in C_2H_5OD was introduced into the vessel via the septum and immediately frozen, whereupon the hydrogen was removed and replaced by 300 Torr deuterium. The solution was stirred magnetically. After the desired reaction time, the reactor was opened and the solution separated from the catalyst by filtration. In the case of quinoline exchange, the solution was analyzed by use of a Finnigan 1020 OWA GC/MS which separated quinoline and tetrahydroquinoline and provided a mass spectrum for each product. No detectable hydrogenation occurred during the first 4 h of isotope exchange in dihydrocinchonidine; in this case the spectrum of the exchanged alkaloid was obtained by placing a drop of alkaloid solution on the insertion probe of the mass spectrometer, and by heating the probe until the vapor pressure of alkaloid in the spectrometer was sufficient to provide a spectrum. The spectrum contained a parent ion, $C_{19}N_2OH_{24}^+$, (m/z = 296 and intensity = 20) and fragment ions $C_{10}NOH_9^+$ (m/z = 159, intensity = 40, attributed to scission of the C_8–C_9 bond and reaction of

$C_{10}NOH_8^+$ with a hydrogen atom from the environment of the ion source), and $C_9NH_{16}^+$ (m/z = 138, intensity = 100, the other product of the C_8–C_9 scission). Deuterium distributions in the product were calculated by use of the parent ion spectra; corrections were made for the presence of the natural abundances of ^{13}C and ^{15}N, and for fragmentation of the parent ion by loss of one H or D atom which occurred to the extent of 10%.

The positions of deuterium exchange in 10,11-dihydrocinchonidine and in quinoline were determined by ^1H NMR using a JEOL GX270 spectrometer. The assignments of the protons at the seven positions on the quinoline ring system of 10,11-dihydrocinchonidine were unequivocal. H at 2′, 3′, 5′, and 8′ gave doublets at 9.05, 7.90, 8.15, and 8.35 ppm, respectively; H at 6′ and 7′ gave triplets at 7.50 and 7.70 ppm, respectively. Exchange of H for D resulted in a reduction in intensity at the 2′, 5′, 6′, and 8′ positions. The effect of extensive exchange at positions 2′ and 8′ was to decouple the signals from protons 3′ and 7′, respectively. This resulted in H at 3′ giving a singlet superimposed on the doublet (resulting in a quasi-triplet) and H at 7′ giving a doublet superimposed on a triplet (giving a quasi-multiplet). Products of reactions which had proceeded to high conversions were distilled at room temperature to remove ethanol solvent. In the case of 10,11-dihydrocinchonidine, the peaks at 2.5 and 2.7 ppm relative to TMS, which were of identical area and represent the single protons at C_3 and C_4 in the quinuclidine ring system (Fig. 1), were assumed to contain no deuterium. The integrated areas of the individual peaks corresponding to the H atoms bonded to the quinoline ring and at C_9 were then compared with that of the peak of 2.5 ppm; the resulting ratios correspond to the percentage exchange at each of these positions. The interpretation for quinoline was more difficult because no comparable reference proton was present. Thus it was necessary to assume that the largest peak in the spectrum represented an unexchanged H atom; under conditions where the exchange at two or more positions is minimal, as was the case in the Ru-, Rh-, and Pt-catalyzed reactions, this represented a valid procedure. For the product of the Pd-catalyzed reaction, the peak areas for proton corresponding to all seven H atoms were the same, indicating either that no measurable exchange had occurred or that the same degree of exchange had occurred at each position. The mass spectrum indicated the first of these alternatives to be the case.

The extent of hydrogenation was determined from the NMR spectra by the procedure described above. In the case of quinoline hydrogenation, the extent of hydrogenation was also determined by gas chromatographic analysis.

Nomenclature. 10,11-dihydrocinchonidine containing x deuterium atoms in place of protium, $C_{19}N_2OH_{23-x}D_x$, is described by the term "alkaloid-d_x."

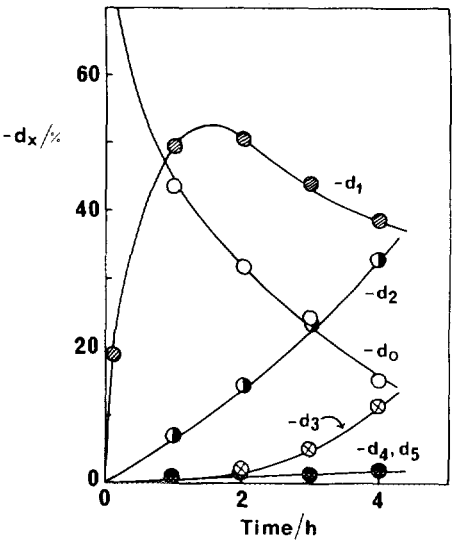

FIG. 2. Progress of exchange of H for D in 10,11-dihydrocinchonidine over 0.10 g 6.3% Pt/silica (EUROPT-1) at 293 K. Solvent = 10 ml C_2H_5OD. Alkaloid concentration = 1% wt/volume. Pressure of gaseous D_2 = 300 Torr.

RESULTS

Attempted Exchange in Cinchonidine

Rapid hydrogenation of cinchonidine to 10,11-dihydrocinchonidine occurred over Pt/silica under the conditions used to attempt exchange. This was not unexpected (26). Remarkably, in the presence of D_2 gas, but with C_2H_5OH as solvent the main addition was of two H atoms to the vinyl group in cinchonidine, indicating either that adsorbed H remained on the catalyst from the reduction or that it was generated by the dissociative adsorption of ethanol. For this and the reasons rehearsed in the Introduction, exchange was investigated in 10,11-dihydrocinchonidine using C_2H_5OD as solvent.

Exchange in 10,11-Dihydrocinchonidine

Exchange of H for D in the alkaloid over Pt/silica at 293 K occurred over a period of 4 h as shown in Fig. 2. Two processes are evident, the very rapid loss of alkaloid-d_0 and formation of alkaloid-d_1, and the slower simultaneous formation of alkaloid-d_2, -d_3, -d_4, and -d_5. The first process is attributed to the exchange of -OH for -OD at C_9 which is expected to be facile. The location of the multiple exchange process is evident from the fragment ions formed. Examination of the spectrum in the region of the fragment ions at m/z = 159 and 139 showed the appearance of new ions in the range 160 to 164 but not in the region above 139. Thus, the multiple exchange occurred in the unsaturated quinoline ring system.

The sites of exchange in the alkaloid were examined

TABLE 1

Location of Exchange of H for D in 10,11-Dihydrocinchonidine Determined by ^{1}H NMR

Catalyst	Pattern of exchange[a](%) Position[b] 2′	3′	5′	6′	7′	8′	9	Extent of hydrogenation(%)
6.3% Pt/silica[c]	94	49	22	51	31	85	31	45
5% Ru/alumina	84	7	18	8	16	50	14	<5
5% Pd/alumina	30	0	0	0	0	0	25	<95

[a] Time = 500 h; temp. = 293 K.
[b] Positions defined in Fig. 1.
[c] EUROPT-1.

by ^{1}H NMR for a sample in which exchange had occurred over Pt/silica at 293 K for 500 h (Table 1). Exchange occurred at all positions in the quinoline ring system, being most rapid at positions 2′ and 8′, and slowest at 5′. In addition exchange also occurred at the H atom bonded at C_9 to the extent of 30%. The mass spectrum of the sample extracted after 500 h again showed no ion intensity at m/z = 140 (after correction for ^{13}C and ^{15}N) confirming that no deuterium had entered the quinuclidine moiety even after this extended period of reaction.

The 500 h exchange experiment was repeated using Ru/alumina, Rh/alumina, and Pd/alumina (Table 1). Exchange over Ru at 293 K was not dissimilar to that observed over Pt, but was accompanied by much less hydrogenation. Exchange of the H atom at C_9 was again observed. Attempts to achieve exchange over Rh at 293 K failed because of considerable hydrogenolysis of the quinuclidine ring system. Exchange over Pd at 293 K resulted in extensive hydrogenation of the quinoline ring system; the small amount of 10,11-dihydrocinchonidine retrieved was exchanged at the 2′ and 8′ positions. A similar result was observed in a reaction carried out over the Pt/silica catalyst at 333 K.

Exchange in Quinoline

The sites of exchange in quinoline were determined by ^{1}NMR after 24 h reaction at 293 K (Table 2). Exchange was faster than hydrogenation over Pt, Ru, and Rh, but no exchange occurred over Pd. Hydrogenation occurred over each metal and this was accompanied by exchange; for example, over Pt the 17% of hydrogenated product contained tetrahydroquinoline molecules with masses ranging from 133 (C_9NH_{11}) to 142 ($C_9NH_2D_9$). Increasing the temperature to 333 K increased the rates of both exchange and hydrogenation over Pt (Table 2).

DISCUSSION

Reactions Catalyzed by Platinum

The exchange of H for D in 10,11-dihydrocinchonidine over Pt occurred at the hydroxyl group and at the H atoms at positions 2′, 3′, 5′, 6′, 7′, 8′, and 9. Exchange in the quinoline moiety was most rapid at the 2′ and 8′ positions; no exchange occurred in the quinuclidine ring system.

The patterns of exchange in the alkaloid and in quinoline show common features such as preferential exchange at the 2′ and 8′ positions (alkaloid) and the 2 and 8 positions (quinoline). They also show contrasting features in that exchange at the 3′, 6′, and 7′ positions in the alkaloid occurred more readily than at the corresponding positions in quinoline. The exchange pattern in quinoline observed here over 6.3% Pt/silica closely resembles that reported by Garnett and co-workers and reported in the review by Calf and Garnett (27) for reaction catalyzed by Pt powder (compare first and last entries in Table 2). These investigators were the first to deduce that quinoline is adsorbed on Pt by multicenter π-bonds.

Thus, the multiple exchange in the alkaloid (Fig. 2) is consistent with adsorption by the interaction of the π-electrons of the quinoline moiety with the Pt surface. The quinoline system is expected to be oriented approximately parallel with the Pt surface, the influence of the lone pair of electrons on the N atom probably inducing a degree of tilt. The alternative of stepwise exchange via σ-bonded intermediates formed as a result of dissociative adsorption is not consistent with the simultaneous appearance of several D atoms in the alkaloid; moreover, such exchange at the 3′ and 5′ position would involve gross steric hindrance.

The rate of exchange and of hydrogenation in the alkaloid was an order of magnitude slower than that in quinoline (compare exchange times in Tables 1 and 2). Since, in the alkaloid, the quinuclidine group is unlikely to deactivate the quinoline ring system toward exchange by any electronic effect, the origin of the slower exchange is likely to be steric in origin. In this context, exchange of the H atom bonded at C_9 is significant. The dissociation of the H atom at C_9 and the formation of a σ-bond between C_9 and the Pt surface would perturb and possibly disrupt the π-bonding interaction of the quinoline ring with the surface. The slow exchange in the alkaloid by comparison with that in quinoline suggests that this interaction is of importance.

TABLE 2

Location of Exchange of H for D in Quinoline Determined by ^1H NMR

Catalyst	Extent of exchange[a](%)	Pattern of exchange[b](%) Position[c] 2	3	4	5	6	7	8	Extent of hydrogenation(%)
6.3% Pt/silica[d]	22	49	3	7	1	1	0	14	17
6.3% Pt/silica[d]	53	88	28	17	2	14	0	71	28
5% Ru/alumina	85	93	6	0	0	4	2	31	12
5% Rh/alumina	23	78	5	2	0	2	0	11	9
5% Pd/alumina	10	0	0	0	0	0	0	0	9
5% Pt powder[e]	66	56	12			8		18	0

[a] (100 − C_9NH_7/%).
[b] Time = 24 h; temp. = 293 K except entry 2 (333 K).
[c] Positions defined in Fig. 1.
[d] EUROPT-1.
[e] Literature report (27): Catalyst prepared by borohydride reduction of PtO_2; deuterium source = D_2O.

These exchange experiments lend general support to the modeling studies (8), which have demonstrated that the adsorption of these alkaloids via the quinoline ring system provides an environment which is suitable for the enantioselective hydrogenation of pyruvate esters. Morevoer, this environment correctly predicts the sense of that enantioselectivity, and allows an intepretation of the greatly enhanced rate of enantioselective reaction. Further modeling is now required to estimate whether 10,11-dihydrocinchonidine adsorbed simply by a σ-bond at C_9 may function as an effective modifier. If not, then interconversion of the molecule between the σ-C_9 and the π-quinoline bonded states may render the molecule ineffective as a modifier for a fraction of its lifetime in the adsorbed state.

As regards the angle between the aromatic ring plane and the surface plane, it should be noted that NEXAFS measurements for pyridine chemisorption at saturation coverage on Pt(111) show an apparent angle of 52° below 200 K and of 74° above this temperature (28). This temperature dependence of the angle is of particular interest in view of our observation that enantioselectivity over Pt collapses *suddenly* above 313 K (5). Exchange in 10,11-dihydrocinchonidine at 333 K occurred only at the 2'- and 8'-positions and was accompanied by extensive hydrogenation. While the collapse of enantioselectivity is undoubtedly the result of the removal of the modifier from the surface by hydrogenation, the sudden intervention of such hydrogenation is unexpected, but it would be understandable if it occurred as a result of a change in the adsorbed state of the alkaloid. An analogous increase in the angle between the aromatic ring plane and the surface plane, as observed for pyridine, would interpret the observed restriction of exchange in the alkaloid to the 2' and 8' positions at 333 K, and provide the most likely interpretation of the collapse of enantioselectivity with increasing temperature.

Reactions Catalyzed by Ruthenium

Exchange of H for D in 10,11-dihydrocinchonidine over Ru is similar to that observed over Pt. Exchange occurred throughout the quinoline ring and at C_9 but not in the quinuclidine system. Extent of hydrogenation was much lower over Ru than over Pt, which is a desirable property in a modifier. Exchange over Ru was intermediate in extent between that observed over Pt (Table 1) and that reported over Ir (20). (Exchange after 9 days over 5% Ir/$CaCO_3$ provided 2' = 45%, 6' = 10%, 8' = 15%, 3' = 5' = 7' = 0%; no exchange in the quinuclidine system.) Both the exchange and hydrogenation of quinoline over Ru was faster than that of the alkaloid, as observed over Pt. The general similarity of these reactions over Pt and Ru suggests that the eventual achievement of reproducible chiral hydrogenation over Ru should be possible. Present studies (22) show that, although enhanced rates are obtained with a cinchonidine-modified Ru catalyst, an enantiomeric excess is obtained only occasionally and irreproducibly. Suitable control over the modification procedure may be lacking and investigations of the chemistry involved continues.

Reactions Catalyzed by Rhodium and Palladium

Exchange in quinoline over Rh was similar to that over Pt but the interaction of the alkaloid was markedly different. The appearance of many products formed by hydrogenolysis of the quinuclidine moiety suggests that 10,11-dihydrocinchonidine is adsorbed on Rh at the aliphatic N atom. The loss of molecular integrity of the alkaloid on adsorption at this particular Rh/alumina surface interprets

our failure to achieve enantioselective hydrogenation over the same catalyst. This mode of adsorption must be inhibited if enantioselective catalysis by Rh is to be achieved.

Pd was unique in this study in its failure to catalyze measurable exchange in quinoline and its exceptional activity for the hydrogenation of the quinoline moiety in the alkaloid (though not in quinoline itself). Clearly, the chemistries of these adsorbates on these Pd/alumina and Pt/silica catalysts were different but it would be unwise to attempt to draw general conclusions from the present work.

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