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Enantioselective Hydrogenation

V. Hydrogenation of Butane-2,3-dione and of 3-Hydroxybutan-2-one Catalysed by Cinchona-Modified Platinum

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Pt/silica modified by cinchonidine and cinchonine is active for the enantioselective hydrogenation of butane-2,3-dione to butane-2,3-diol in dichloromethane at 268–298 K and 10 bar pressure. Reaction proceeds in three stages. In the first, about 85% of the butane-2,3-dione is converted to 3-hydroxybutan-2-one and 15% to three higher molecular weight products by hydrodimerisation. The initial enantiomeric excess in the hydroxybutanone is modest (20 to 40%(R) with cinchonidine as modifier, 10%(S) with cinchonine as modifier) and dependent on the amount of alkaloid used in catalyst preparation. In the second stage, 3-hydroxybutan-2-one is converted to butane-2,3-diol; a marked kinetic effect is observed whereby the minority enantiomer is converted preferentially to butanediol and the enantiomeric excess in the remaining hydroxybutanone increases dramatically to values in the range 62 to 89%(R) and to 30%(S). Under all conditions, the most abundant stereochemical form of the final product is meso-butane-2,3-dione. In the third stage the three dimers are slowly converted by hydrogenation, dissociation, and further hydrogenation to butane-2,3-diol. In the absence of alkaloid, butane-2,3-dione hydrogenation to racemic products in dichloromethane solution proceeds in two distinct stages with no dimer formation. Butane-2,3-dione hydrogenation has also been studied over Pt/silica modified anaerobically by exposure to cinchonidine in ethanol under propyne at 2 bar. This catalyst is remarkably active for the conversion of diketone to diol in ethanol at 293 K and 10 bar and kinetic selection in the second stage of reaction is again observed. The hydrogenation of racemic 3-hydroxybutan-2-one in dichloromethane over cinchonine-modified Pt/silica at 273 K and 10 to 40 bar pressure also showed kinetic selection, an enantiomeric excess of up to 70%(S) appearing in the reactant as it was consumed. Mechanisms which account for these hydrogenations and dimerisations and for the enantioselectivities observed and their variation are presented. This diketone hydrogenation provides an example of consecutive thermodynamic and kinetic control of enantioselectivity in a multistage catalytic reaction.

Key Words: **Butane-2,3-dione hydrogenation; 3-hydroxybutan-2-one hydrogenation; enantioselective hydrogenation; enantiomeric excess; cinchona alkaloids; cinchonidine; cinchonine; platinum; EUROPT-1; modification (of catalysts by alkaloids); kinetic selection; selective enantioface adsorption; diol formation; hydrodimerisation of diones.**

INTRODUCTION

The enantioselective hydrogenation of butane-2,3-dione to 3-hydroxybutan-2-one is catalysed by Pt/silica modified by adsorption of cinchona alkaloids onto its surface (1). Cinchonidine and cinchonine (Figs. 1a and 1b) facilitate the preferential formation of R-product and S-product, respectively, and in this respect the reaction resembles the much-studied enantioselective hydrogenation of methyl pyruvate over the same cinchona-modified Pt/silica catalysts (2–6).

Preliminary communications have recorded that reaction occurs in dicholoromethane, toluene, acetone, and ethanol as solvent, the enantiomeric excess at 10 bar pressure and 273–293 K decreasing from 38% in dichloromethane to 8% in ethanol (1) and that the conversion of 3-hydroxybutan-2-one to butane-2,3-diol occurs readily in dichloromethane, the enantiomeric excess in the remaining hydroxyketone increasing dramatically to 89% at high conversion (7). This paper describes (i) the three-stage hydrogenation of butane-2,3-dione to butane-2,3-diol over cinchona-modified Pt/silica in dichloromethane solution, (ii) the hydrogenation of racemic 3-hydroxybutan-2-one under the same conditions, (iii) the stereochemistry of the first stage of the hydrogenation of hexane-2,3-dione and of hexane-3,4-dione, and (iv) a novel preparation technique which provides a catalyst capable of fast continuous hydrogenation of butane-2,3-dione to butane-2,3-diol.

Modification by the strychnos alkaloid brucine and the morphine alkaloid codeine is ineffective in inducing enantioselectivity in butane-2,3-dione hydrogenation, although

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these alkaloids each induce enantioselectivity in methyl pyruvate hydrogenation (8,9).

EXPERIMENTAL

Materials

Experiments were conducted using 0.1-g samples of 6.3% Pt/silica (EUROPT-1) for which a detailed characterisation has been reported (10,11). As-received catalyst, reduced by the manufacturer (Johnson Matthey) but subsequently oxidised by the action of air, was evacuated at 293 K for 0.5 h, reduced at 403 K for 0.5 h in two changes of hydrogen (1 bar) and cooled to ambient temperature in hydrogen before modification by alkaloid.

Butane-2,3-dione, 3-hydroxybutan-2-one (acetoin), and butane-2,3-diol (all Fluka), cinchonidine and cinchonine (Aldrich, Figs. 1a and 1b), dichloromethane and ethanol were used as received. Reference materials 3-quinuclidinol, and RR- and SS-butane-2,3-diol were obtained from Aldrich and 2,3,5,6-tetramethyl-1,4-dioxan-2,5-diol (acetoin dimer, Fig.1c) from Lancaster.

In this paper, the terms butanedione and diketone always refer to butane-2,3-dione, hydroxybutanone and hydroxyketone always refer to 3-hydroxybutan-2-one, and butanediol and diol always refer to butane-2,3-diol.

Reactors and Procedures

Liquid-phase hydrogenations were mostly conducted at 273 K and 10 bar pressure in a glass Fischer–Porter reactor of volume 200 ml fitted with a magnetic stirrer. Hydrogen pressure was maintained at 10 bar and hydrogen uptake recorded by computer control. Reactions at 293 K involving cinchonine as modifier and described in Tables 1 and 5 were carried out at pressures in the range 10 to 40 bar in a Baskerville stirred stainless steel reactor of volume 80 ml.

Procedure I involving ex-situ aerobic modification. This procedure follows the original Orito methodology (12) and the "normal modification" described in Part II (13). 50 mg alkaloid dissolved in 5-ml dichloromethane was injected via a septum onto 0.1 g reduced catalyst under hydrogen. Catalyst and modifier solution were then transferred to an open beaker which contained a further 35 ml of the modifier solution and stirred in air for 1 h, after which the solution was decanted and discarded and the wet catalyst washed into the Fischer–Porter reactor with a further 20-ml solvent. 10-ml (115-mmol) butanedione was added to the vessel, the reactor was flushed first with nitrogen and then with hydrogen, and subsequently pressurised to 10 bar. Stirring was commenced immediately.

Procedure II involving in-situ aerobic modification. Alkaloid (50 mg) was dissolved in 5-ml solvent in the Fischer–Porter reactor. To this was added 0.1-g reduced catalyst in 5-ml solvent, 6-ml (69 mmol) butanedione, and a further 24-ml solvent. The reactor was then flushed with hydrogen, pressurised to 10 bar, and the stirring commenced. The above procedure was followed for reactions in the Baskerville reactor, except that the quantity of butanedione was 3 ml (34.5 mmol) and the total volume of solvent 27 ml. This procedure was also used for studies of hydroxybutanone hydrogenation.

Procedure III involving in-situ anaerobic modification under hydrogen. This procedure has been described previously (13). Solvent (ethanol), reactant, and modifier solution were each rigorously degassed by the successive freeze–thaw method. 0.1-g catalyst was reduced in the Fischer–Porter reactor under the conditions described above. Modifier solution containing 50-mg alkaloid in 20-ml ethanol was injected via a septum onto the reduced catalyst under hydrogen and the mixture stirred for 1 h; 10-ml (115 mmol) butanedione was then added. Hydrogen pressure raised to 10 bar and the stirrer started.

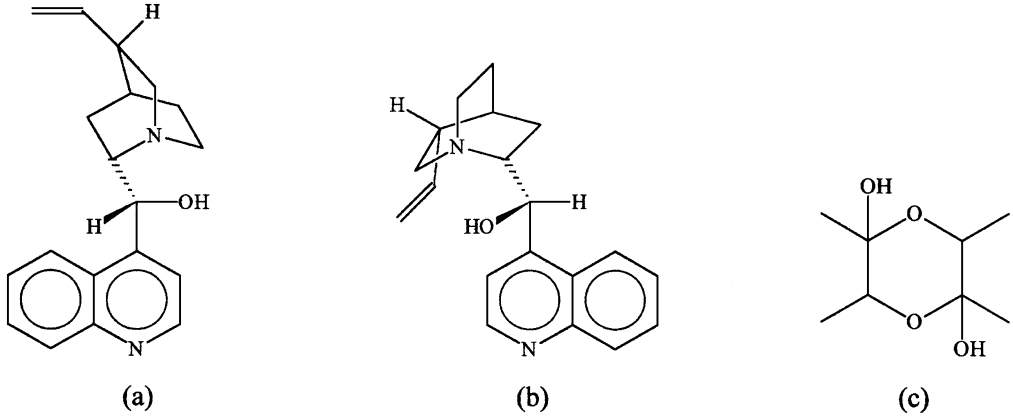

FIG. 1. Structures of the modifiers cinchonidine (a), cinchonine (b), and of the reference compound acetoin dimer (c).

Procedure IV involving in-situ anaerobic modification under hydrocarbon. Procedure III was followed except that, after catalyst reduction, hydrogen was removed and immediately replaced by 2 bar propyne or buta-1,3-diene (ca 17 mmol). When the slurry had been stirred for 1 h in this hydrocarbon atmosphere, hydrogen was admitted to 10-bar pressure and the stirrer started.

Analysis

After filtration to remove catalyst, 0.1 μl aliquots of reaction mixture were analysed by chiral gas–liquid chromatography using a 50-m permethylated beta-cyclodextrin (Cydex B) column. Separation of reactant and all products was achieved; components were eluted in the order: solvent, diketone, hydroxyketone, diol, dimers. Complete separation of R- and S-hydroxybutanone was obtained. Two of the dimers were eluted in rapid succession with baseline separation as peaks of identical size; the third dimer in comparable yield was eluted later. The enantiomers of butanediol were eluted in the order SS-, RR-, meso-, as determined by use of the first two compounds as reference materials. The meso-form was separated from the SS- and RR-forms but baseline separation between RR- and SS- was not achieved. Values of the yield of meso-butanediol were determined from the chromatograms on the assumption that the response factors for the enantiomers were equal. Values of the ratio [RR-] : [SS-] were determined by comparison of gc traces with those of known calibration mixtures.

Analysis by gas chromatography mass spectrometry (GCMS) was achieved by use of a conventional gc (no chiral separation) and a Finnegan GCQ quadrupole mass spectrometer.

Rate Measurements

Hydrogen uptake against time curves for reactions in dichloromethane were similar to those reported for pyruvate ester hydrogenation in ethanol in Part I (14); i.e., there was a short period during which the rate accelerated followed by a sustained period at a constant maximum rate, R_m/mmol h^{-1} (g catalyst)$^{-1}$. The period of acceleration was less pronounced than with pyruvate ester, so that values of R_m did not differ greatly from the initial rates for most reactions.

Molecular Modelling

The procedures used for molecular modelling were exactly as described elsewhere (15).

RESULTS

A. Reactions in Dichloromethane Solution under Aerobic Conditions

(a) Butanedione hydrogenation. Enantioselective hydrogenation of butanedione in dichloromethane over cinchonidine-modified Pt/silica at 268 to 298 K and 10-bar pressure occurred in three stages (Fig. 2a). A fast first stage (typically $R_m = 275$ mmol h^{-1} g^{-1} at 273 K) was followed by a less rapid second stage ($R_m = 30$ mmol h^{-1} g^{-1}) and a very slow third stage. Maximum rates at 273 K for the first stage were first order in hydrogen pressure (3 to 10 bar), approximately zero order in diketone, and of 0.6 order in catalyst mass (0.025 to 0.100 g). Such rates obeyed the Arrhenius equation over the range 268 to 298 K, giving a value of 30 ± 5 kJ mol^{-1} for the apparent activation energy, E_a. The order in catalyst mass suggests a measure of diffusion control but the value of E_a confirms that rate was largely controlled by chemical processes at the catalyst surface. Above 298 K rates and values of the enantiomeric excess declined in a manner similar to that previously described for pyruvate hydrogenation (13).

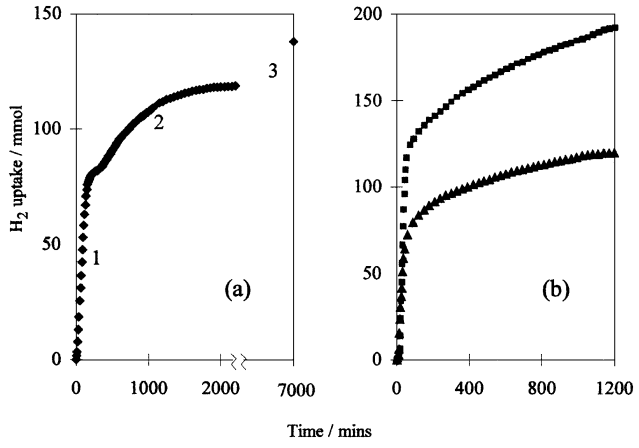

FIG. 2. Variations of hydrogen uptake with time. (a) Butane-2,3-dione hydrogenation in dichloromethane at 273 K and 10 bar over cinchonidine-modified Pt/silica (aerobic modification, Procedure II) showing the three stages of reaction. (b) Butane-2,3-dione hydrogenation in ethanol at 293 K and 10 bar over cinchonidine-modified Pt/silica (upper curve) and unmodified Pt/silica (lower curve) (anaerobic modification, Procedure IV, 2 bar propyne).

3-Hydroxybutan-2-one (acetoin) was formed as major product in the first stage, together with three minor products in comparable yields which accounted for about 15% of reactant consumption. No butanediol was formed in the first stage. GCMS showed the minor products to be of mass 174 and of related structure. Parent ions were present at m/z = 175 (due to proton addition in the source) and the major fragment ions were at m/z = 131, 88 and 89, 71, and 43. Interpretation of the spectra of these products was assisted by comparison with that of the reference compound acetoin dimer to which they showed a family resemblance. Accordingly these products were assigned structures proposed in the Discussion and contained in Fig. 6; they were partially hydrogenated dimers of butanedione.

The second stage of reaction commenced when most of the butanedione had reacted, hydroxybutanone being converted to butanediol.

TABLE 1

Enantiomeric Compositions of the Products during Butanedione Hydrogenation in Dichloromethane at 10 bar Pressure over Pt/silica Modified by Cinchonidine (CD) and Cinchonine (CN)

			H_2 uptake[b]	Hydroxybutanone			Butanediol	
Entry	Modifier	Temp/K	$[Dione]_i$	R/%	S/%	ee/%	meso/%	[RR-] : [SS-]
1	CD	273	0.12	60	40	20	—[c]	
2	CD	273	0.18	60	40	20	—[c]	
3	CD	273	0.50	61	39	22	—[c]	
4	CD	273	0.95	62	38	24	—[d]	
5	CD	273	1.58	81	19	62	63	2 : 1
6	CD	273	1.63	77	23	54	60	2 : 1
7	CN	293	0.17	44	56	12	—[c]	
8	CN	293	1.13	39	61	22	62	1 : 1.5
9	CN	293	1.53	35	65	30	68	1 : 1.5

[a] Modification: Procedure II (50 mg alkaloid). Reactions at 273 K conducted in the Fischer–Porter reactor, reactions at 293 K conducted in the Baskerville reactor.
[b] Units: H_2 uptake = mmol; $[Dione]_i$ = mmol dione originally present (69 mmol, entries 1–6; 34.5 mmol, entries 7–9).
[c] Butanediol yield = zero.
[d] Butanediol yield <1%.

The third stage corresponded to the last 15% or so of hydrogen uptake and involved mostly the conversion of the dimers to butanediol which was the only product at the end of the reaction.

Hydrogenation of butanedione to racemic product in dichloromethane over unmodified catalyst (Procedure II, no alkaloid added) at 293 K and 10 bar provided a hydrogen uptake curve similar to that shown in Fig. 2a over the first stage; i.e., modified and unmodified catalysts showed similar values of R_m. Over an unmodified catalyst, no higher molecular weight products were formed, the second stage of the hydrogenation was slow and no third stage was evident. However, formation of the same dimers accompanied the reaction to racemic product when 3-quinuclidinol was present in the reaction mixture (Procedure II, 50-mg N-base added in place of cinchona alkaloid).

The enantiomeric compositions of the C_4-products during the first and second stages of reaction over alkaloid-modified catalysts are shown in Table 1. In the first stage, cinchonidine induced enantioselectivity in favour of R-hydroxybutanone, whereas cinchonine directed reaction towards S-product. The enantiomeric excess was independent of conversion in the early stages of reaction, independent of hydrogen pressure (3 to 10 bar), fairly independent of diketone concentration (Table 2), and increased slightly as temperature was lowered (295 to 268 K). The enantiomeric excess was, however, dependent on the quantity of cinchonidine used in catalyst modification; the value at low conversion rose from 20% (Table 1) to 38% (Table 2, entry 6) as the mass of cinchonidine used in modification was increased from 50 to 200 mg.

In the second stage of reaction the enantiomeric excess in the remaining hydroxybutanone rose dramatically as the minor enantiomer was preferentially hydrogenated to butanediol. All three stereochemical forms of butanediol were produced; the yield of meso-diol exceeded 50% and the concentrations of RR- and SS-diol were comparable whichever alkaloid was adsorbed at the catalyst surface.

The high values of the enantiomeric excess in the remaining hydroxyketone during stage two of the reaction recorded in Table 1 were further raised by increasing both the amount of modifier used in catalyst preparation from 50 to 200 mg and the amount of catalyst from 0.1 to 0.6 g (Table 3).

Towards the end of stage three, when the reaction was virtually complete, analysis showed the dimers to be absent (i.e., they had been consumed) but very small quantities of both butanedione and hydroxybutanone were present. The latter was almost racemic (ee = 2%).

TABLE 2

Variation of Maximum Rate, R_m, and Enantiomeric Excess, ee, with Reactant Concentration during Butanedione Hydrogenation over Cinchonidine-Modified Pt/Silica in Dichloromethane at 273 K and 10 bar Pressure

[Dione]/M	R_m/mmol h^{-1} g^{-1}	ee/%(R)[b]
11.4[c]	1225	36
11.1	1375	36
10.2	1350	33
8.5	1000	38
5.7	1200	42
2.8	1100	38

[a] Modification: Procedure I (200 mg modifier).
[b] Measured during the first stage of reaction.
[c] Pure reactant (no solvent).

TABLE 3

Values of the Enantiomeric Excess in the Remaining Hydroxybutanone at High Conversion Observed during Butanedione Hydrogenation to Diol over Cinchonidine-Modified Pt/silica in Dichloromethane at 10 bar Pressure

Mass of catalyst/g	[Dione]/M	Temp/K	ee/%
0.1	1.7	273	62
0.6	0.6	273	63
0.6	1.3	273	75
0.6	0.9	283	85
0.6	0.9	273	89

Hydrogenation of the symmetrical hexane-3,4-dione to 4-hydroxyhexan-3-one over cinchonidine-modified catalyst at 293 K and 10 bar pressure gave an enantiomeric excess of 33%(R) in the first stage of reaction. Reaction of the unsymmetrical hexane-2,3-dione at 273 K gave equal yields of 3-hydroxyhexan-2-one and 2-hydroxyhexan-3-one showing values of the ee of 35%(R) and 29%(R), respectively. Comparable reactions of hexane-2,3-dione over cinchonine-modified catalyst provided values of the ee of 20%(S) and 11%(S), respectively.

The competitive hydrogenation of butanedione and methyl pyruvate in dichloromethane and in ethanol over cinchonidine-modified catalyst at 273 K and 10 bar pressure was investigated (Table 4). The reactants competed effectively with each other for the surface. The enantiomeric excess in the hydroxyketone was not affected by the presence of methyl pyruvate, but that in methyl lactate was depressed by 10 to 15% by the presence of the diketone.

(b) Hydrogenation of 3-hydroxybutan-2-one. Hydrogenation of racemic 3-hydroxybutan-2-one in dichloromethane over modified and unmodified Pt/silica was investigated under a range of conditions. Reactions at 273 K and 10 bar over unmodified and modified catalyst proceeded at comparable rates; i.e., as with the dione, there was no rate enhancement over the modified catalyst. Instantaneous reaction rate was strictly first order in the remaining hydroxyketone. As reaction over modified catalyst progressed an enantiomeric excess appeared in the reactant; the effect was favoured by an increase in temperature but not by an increase in pressure (Table 5). No dimers were formed. All three enantiomers of butanediol were again formed with the yield of the meso-form exceeding 50% but with [RR-] > [SS-] when cinchonidine was modifier and [SS-] > [RR-] when cinchonine was the modifier.

TABLE 4

Competitive Hydrogenation of Butane-2,3-dione to 3-Hydroxybutan-2-one and of Methyl Pyruvate to Methyl Lactate in Dichloromethane (DCM) and in Ethanol at 273 K and 10 bar over Cinchonidine-Modified Pt/silica[a]

			Enantiomeric excess/%(R)	
Solvent	Reactant(s)	Conversion/%	Single reactant reaction	Competitive reaction
DCM	Butanedione	95	38	
DCM	Pyruvate ester	95	86	
DCM	Diketone + ester	95		40, 75
Ethanol	Butanedione	60	22	
Ethanol	Pyruvate ester	60	75	
Ethanol	Diketone + ester	60		26, 60

[a] Modification: Procedure I (200-mg modifier).

B. Reactions in Ethanolic Solution over Catalysts Prepared under Aerobic and Anaerobic Conditions: Butanedione Hydrogenation

Hydrogenation of butanedione in ethanol over Pt modified by cinchonidine according to Procedure II (aerobic modification) gave hydroxyketone as the major product, together with smaller yields of the three dimers than were observed in dichloromethane solution. Activity for the second stage of reaction was minimal. Hydrogenation rates at 293 K were typically 2200 mmol h^{-1} g^{-1} over modified catalyst with ee = 15 to 20%(R) and 550 mmol h^{-1} g^{-1} for reaction over the unmodified catalyst; i.e., a conventional rate enhancement (13) was observed. Anaerobic preparation by Procedure III produced modified catalysts of relatively low activity, 220 mmol h^{-1} g^{-1}, and enantioselectivity, 5 to 8%(R), and unmodified catalysts showed an activity of 40 mmol h^{-1} g^{-1} (the rate enhancement was again observed). Anaerobic preparation under 2-bar propyne (Procedure IV) gave catalysts, both unmodified and modified, of comparable high activity (i.e., no rate enhancement for modified reaction) as shown in Fig. 2b. Reactions showed a very short induction period after which fast reaction in the range R_m = 1300 to 2000 mmol h^{-1} g^{-1} occurred. Reaction over unmodified catalyst ceased after the formation of 3-hydroxybutan-2-one, but over modified catalyst rapid hydrogenation extended to diol formation and complete conversion was achieved. The initial enantiomeric excess in the hydroxyketone was about 10%, lower than the values observed for reactions in dichloromethane over catalysts prepared by Procedure II. During butanediol formation over cinchonidine-modified catalyst the preferential removal of S-hydroxybutanone was again observed. Thus, as butanediol yields progressed from 10, to 30, to 50, to 75%, so the enantiomeric excess in the remaining hydroxyketone rose from 8, to 11, to 26, to 40%(R).

Anaerobic modification with cinchonidine under 2 bar buta-1,3-diene (Procedure IV) gave a fast first stage reaction without an induction period. Catalysts so modified were not active for the conversion of hydroxyketone to diol. The enantiomeric excess in the 3-hydroxybutan-2-one again increased with the amount of the modifier present, the

TABLE 5

Enantiomeric Composition of the Reactant and Product and Values of k_S/k_R Observed during the Hydrogenation of a Racemic Mixture of R- and S-Hydroxybutanone in Dichloromethane over Pt/silica Modified by Cinchonidine (CD) and Cinchonine[a] (CN)

Modifier	H_2 pressure /bar	Temp/K	Conv[b]/%	Enantiomeric composition /% in hydroxybutanone R/%	S/%	ee/%	meso-diol/%	k_S/k_R
None	10	273	30	50	50	0	50[c]	1.0[d]
CD	10	273	50	54	46	8	—[d]	1.3
CN	10	273	90	44	56	12	65[e]	1.1
CN	10	293	80	20	80	60	56	2.2
CN	20	293	90	15	85	70	60	2.0
CN	30	293	90	27	73	46	59	1.8
CN	40	293	95	30	70	40	55	1.3

[a] Modification: Procedure II (50 mg cinchonidine). Reactions at 273 K conducted in the Fischer–Porter reactor, reactions at 293 K conducted in the Baskerville reactor.

[b] (H_2 uptake/mmol)/(mmol 3-hydroxybutan-2-one initially present).

[c] [RR-] : [SS-] = 1 : 1.

[d] [RR-] : [SS-] ≈ 8 : 1, meso-diol not measured.

[e] [SS-] : [RR-] ≈ 8 : 1.

values at 90% conversion, for reactions at 293 K and 10 bar pressure, being 12%, 18% and 35% when the amounts of modifier present were 5 mg, 50 mg, and 100 mg, respectively.

DISCUSSION

A. Reactions in Dichloromethane Solution

The first stage of the reaction, the hydrogenation of butan-2,3-dione to 3-hydroxybutan-2-one, shows many of the characteristics of the more extensively studied hydrogenation of pyruvate to lactate esters (13). Thus, each reaction is zero order in the organic reactant and first order in hydrogen, indicating strong adsorption of the former and relatively weak adsorption of the latter. The apparent activation energy of 30 kJ mol^{-1} for diketone hydrogenation compares with 38 kJ mol^{-1} for pyruvate ester hydrogenation (13). In each system, cinchonidine induces enantioselectivity in favour of R-product, whereas cinchonine favours preferential S-product formation but as temperature is raised above 300 K the activity and enantioselectivity are progressively lost. The reactions show some interesting differences. First, for catalysts capable of providing hydroxyketone hydrogenation, enantioselective diketone hydrogenation is not rate-enhanced; by contrast single-stage pyruvate hydrogenation is normally rate-enhanced over modified catalysts. Second, the enantiomeric excess in diketone hydrogenation is not conversion dependent over the first 20% or so of reaction as is the case in pyruvate hydrogenation (14, 16–18). Third, the initial enantiomeric excess in dione hydrogenation varied with the amount of alkaloid used in the modification step (compare Tables 1 and 2), whereas in pyruvate hydrogenation maximum ee was achieved at very low alkaloid concentrations (19). The second and third features suggest that the diketone is more strongly adsorbed than pyruvate and may displace some alkaloid from the platinum surface. Certainly, butanedione competed effectively for the surface with pyruvate in the competitive reaction (Table 3). Moreover, the distinct transition from stage 1 to stage 2 of the reaction (Fig. 2a and Table 1) shows that the concentration of diketone had to be reduced to a very low level before its surface coverage fell sufficiently for hydroxyketone hydrogenation to diol to become significant.

Our interpretation of the observed sense of the enantioselectivity in the conversion of butanedione to hydroxybutanone during the first stage of reaction follows that published for the hydrogenation of pyruvate to lactate (15) and is therefore presented here in summary only. H/D exchange in cinchona alkaloid over Pt/silica has shown that adsorption occurs via the quinoline moiety (20). The minimum energy conformations of cinchonine and cinchonidine that are involved in the creation of enantioselective sites on their adsorption at the Pt surface have been identified (15). The 1 : 1-interaction between cinchona alkaloid and pyruvate ester that results in (i) selective enantioface adsorption of reactant and (ii) conversion to enantiomerically enriched product has been modelled and visual representations of the proposed molecular arrangements presented (15). An analogous modelling study for the 1 : 1-interaction of butanedione with these alkaloids in their appropriate lowest energy states has been undertaken (21) and again the interaction energies reveal that selective enantioface adsorption

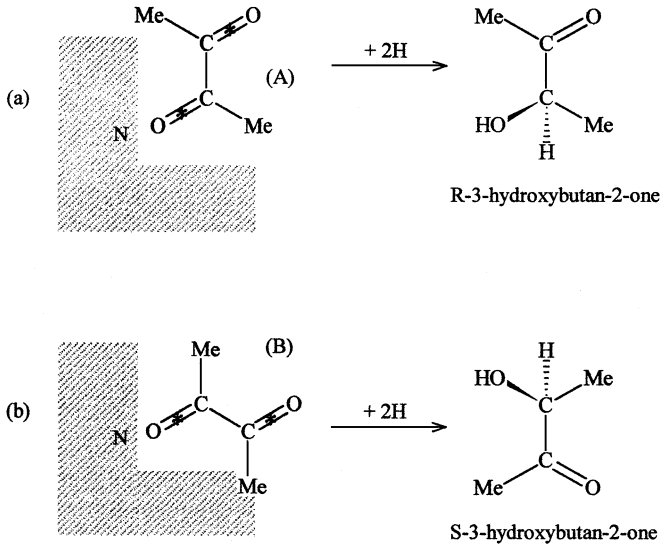

FIG. 3. Schematic representation of the adsorption of butane-2,3-dione as its enantiofaces (A) and (B) on the enantioselective site adjacent to an L-shaped adsorbed cinchonidine molecule. N represents the quinuclidine-N atom. The greater steric interaction between enantioface (B) and the alkaloid disfavours this adsorbed state, and hence the formation of S-product. The diketone is adsorbed by both carbonyl groups; adsorption sites are envisaged as Pt atoms in a (111)-surface and are represented by asterisks.

of the reactant is expected to occur in the vicinity of adsorbed cinchonidine and cinchonine. A schematic representation in Fig. 3 shows that adsorption by enantioface A at the site adjacent to the quinuclidine-N atom of L-shaped adsorbed cinchonidine involves less steric repulsion than that by enantioface B. Adsorption by enantioface A is therefore preferred over that by enantioface B on energetic grounds, but not to the exclusion of B. The reverse situation applies to the cinchonine-modified surface, where the alkaloid is L-shaped in the opposite sense (not shown). On hydrogenation at the cinchonidine-modified surface, enantioface A provides R-hydroxybutanone and enantioface B provides the S-enantiomer; the observed sense of the enantioselectivity is thereby interpreted. Any kinetic distinction in the rates of H-atom addition to enantiofaces A and B is insufficient to invalidate thermodynamic control of the enantioselective outcome of this first stage of reaction.

The enantioselective hydrogenation of hexane-2,3-dione and hexane-3,4-dione provided values of the enantiomeric excess that concurred with those obtained for butane-2,3-dione under comparable conditions. The mechanism presented in Fig. 3 accommodates these observations since the 1 : 1-interaction is only mildly sensitive to a lengthening of the linear hydrocarbon chain.

The most novel features of this reaction reside in the second and third stages of the hydrogenation. First, significant hydrogenation of hydroxybutanone to butanediol occurred in reactions conducted in dichloromethane, whereas diol production was much slower in reactions in alkanols, acetone, toluene, and chlorobenzene (1,21). Second, kinetic selection was observed whereby, with cinchonidine as modifier, S-hydroxyketone was preferentially hydrogenated to diol, whereas with cinchonine the R-hydroxyketone was selectively removed. Thus, the kinetic selection was also manifested in the appearance of an enantiomeric excess in 3-hydroxybutan-2-one when a racemic mixture was hydrogenated over modified catalyst. Third, dimers formed in stage 1 of diketone hydrogenation were consumed in stage 3. These characteristics are discussed in detail.

Choice of solvent. Hydroxybutanone was weakly adsorbed by comparison with butanedione, as evidenced by the fact that its hydrogenation occurred only after near-complete removal of the diketone. In principle, the adsorption of reactant and all intermediates occurs in competition with solvent, and the failure to obtain useful rates of diol formation in other solvents may signify ineffective readsorption of hydroxybutanone onto the catalyst surface under those conditions. At the commencement of this work there was no evidence in the literature for the dissociative adsorption of dichloromethane on Pt; it was considered inert and a good solvent for the purpose (1). More recently, reports have appeared of the dissociative adsorption of haloethanes on copper (22,23) but to our knowledge there are still no reported investigations of dichloromethane adsorption on Pt. It remains our view that the effectiveness of dichloromethane as a solvent for this reaction is related to the ease with which hydroxybutanone can readsorb from this solvent onto the Pt surface after the removal of butanedione.

Kinetic selection. Dynamic kinetic resolution of racemic mixtures has been discussed widely in the literature (24–26).

(a) Kinetic selection in hydroxybutanone hydrogenation. An enantiomeric excess, modest at 273 K but substantial at 293 K, appeared in the hydroxybutanone as it was hydrogenated (Table 5). On the assumption that the usual integrated first-order rate equations apply, the ratio of the rate coefficients for the removal of R- and S-hydroxybutanone is given by Eq. [1], where $[R]_0$ and $[S]_0$ are the

$$\ln\{[R]_0/[R]_t\}/\ln\{[S]_0/[S]_t\} = k_R/k_S \qquad [1]$$

concentrations of R- and S-hydroxybutanone at time zero and $[R]_t$ and $[S]_t$ are the values at a later time t. Substitution of values from Table 5 into Eq. [1] gives $k_S = 1.3k_R$ at 273 K for cinchonidine as modifier and $k_R = 1.1k_S$ for cinchonine as modifier. The higher value of k_S/k_R observed for cinchonine at 293 K (Table 5) diminished with increasing pressure (and with the accompanying increasing reaction rate).

Figure 4 shows that the reactions having the rate coefficients k_R and k_S *each* contribute *two* pathways to products, and the fraction of product formed along each pathway, f_1,

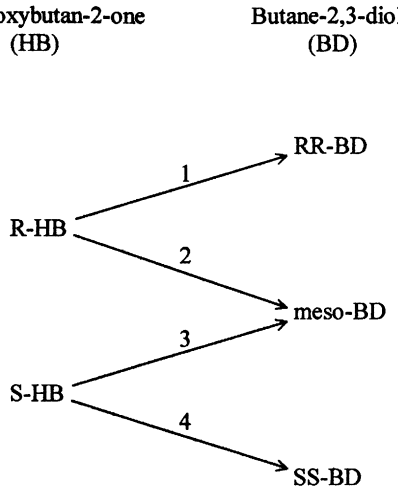

FIG. 4. Processes for the conversion of R- and S-3-hydroxybutan-2-one (HB) to RR-, meso, and SS-butane-2,3-diol.

f_2, f_3, and f_4 can be determined from a knowledge of the enantiomeric composition of the butanediol. Table 6 shows the *f*-values used in these calculations and the calculated and observed values of the yield of meso-butanediol and of the [RR-]:[SS-] ratio. At the enantioselective site adjacent to cinchonidine, R-hydroxybutanone is more likely to undergo the process creating a second chiral centre of R-configuration than one of S-configuration although the distinction is not great, $f_1:f_2 = 3:1$. However, the adsorption of S-hydroxybutanone at the same site adjacent to (R-directing) cinchonidine results in a *very* weak propensity to create a further chiral centre of S-configuration, most of the molecules undergoing the R-directed step to form meso-butanediol, $f_3:f_4 = 14:1$. Remembering that the chiral outcomes are reversed for cinchonine-modified reaction, there is little distinction between paths 3 and 4 with this modifier ($f_4/f_3 = 1.5$) but still the marked preference for path 2 by comparison with path 1 ($f_2/f_1 = 14$).

TABLE 6

Calculated and Observed Values of the [RR-]:[SS-] Ratio and of the Meso-Butanediol Yield Based on the Experimental Values of k_R/k_S and Optimised Values of f_i[a]

Initial reactant[b]	Modifier	f_1 /%	f_2 /%	f_3 /%	f_4 /%	[RR-]:[SS-] Obs	[RR-]:[SS-] Calc	Meso-diol/% Obs	Meso-diol/% Calc
HB	CD	75	25	93	7	8:1	9.6:1	62	62
HB	CN	7	93	40	60	1:8	1:9.1	65	66
BD	CD	50	50	80	20	2:1	2.6:1	63	64
BD	CN	20	80	50	50	1:1.5	1:2.2	68	66

[a] The values f_i represent the fractions of molecules undergoing step *i* in Fig. 4.

[b] HB = hydroxybutanone; BD = butanedione.

(b) Kinetic selection in the second stage of butanedione hydrogenation. The rate at which the enantiomeric excess changed in the second stage of butanedione hydrogenation at 273 K was greater than that observed in the hydrogenation of hydroxybutanone at the same temperature (compare Tables 1 and 5); i.e., the kinetic effect was more pronounced. By use of Eq. [1] and information in Table 1, the values of k_S/k_R for entries 5 and 6 (cinchonidine modification) are 2.5 and 1.9 and the value for k_R/k_S for entry 9 (cinchonine modification) is 1.7. Table 6 shows that the fraction factors that accompany these ratios do not differentiate between f_1 and f_2 for cinchonidine modification but favour f_3 over f_4, and correspondingly do not differentiate between f_3 and f_4 for cinchonine modification but favour f_2 over f_1. It is notable that there is more severe discrimination in hydroxybutanone hydrogenation than in the second stage of butanedione hydrogenation. That is, the adlayer of alkaloid is more discriminating towards hydroxyketone if it has not been previously subject to the effects of the more strongly adsorbed diketone. This suggests that the diketone damaged or disorganised the original alkaloid ad-layer during the first stage of reaction.

Dimer formation and removal. The three partially hydrogenated dimers were initial products of butanedione hydrogenation over cinchona-modified catalysts and were formed in reactions over unmodified catalysts to which the base 3-quinuclidinol had been added. They were not formed in simple solutions of cinchonidine, nor in solutions of butanedione in dichloromethane under hydrogen in the absence of catalyst. Furthermore, they were not formed in butanedione hydrogenation to racemic products over unmodified catalysts or in hydroxybutanone hydrogenation under any conditions. The mechanism set out in Fig. 5 is consistent with these observations. It is proposed that pairs of adsorbed butanedione molecules (I) couple by a base-induced H-transfer involving one molecule in the enol form, to give (II). Repetition of this process would give (III). Addition of one mole of hydrogen to (II) gives two dimers of closely related structure, (IV) and (V). The third dimer, (VI), may be formed by hydrogenation of (III) or, possibly, directly from (V). The C_4- and C_2-ions formed by fragmentation of the dimers in the mass spectrometer are consistent with the structures shown in (IV), (V), and (VI), and the interpretation of the ion fragmentations is consistent with the measured spectrum for acetoin dimer which is the molecule formed by hydrogenation of (VI) (compare Fig. 1c).

Conjugation involving the carbon-carbon double bond and the lone pairs on the adjacent O-atom serves to stabilise intermediates (II) to (VI). When (IV), (V), and (VI) undergo saturation of the carbon–carbon double bond conjugative stabilisation is lost and the molecule becomes susceptible to dissociation. As noted above, species (VI), on such hydrogenation becomes "acetoin dimer"; gc and ^{1}NMR experiments with an authentic sample showed that

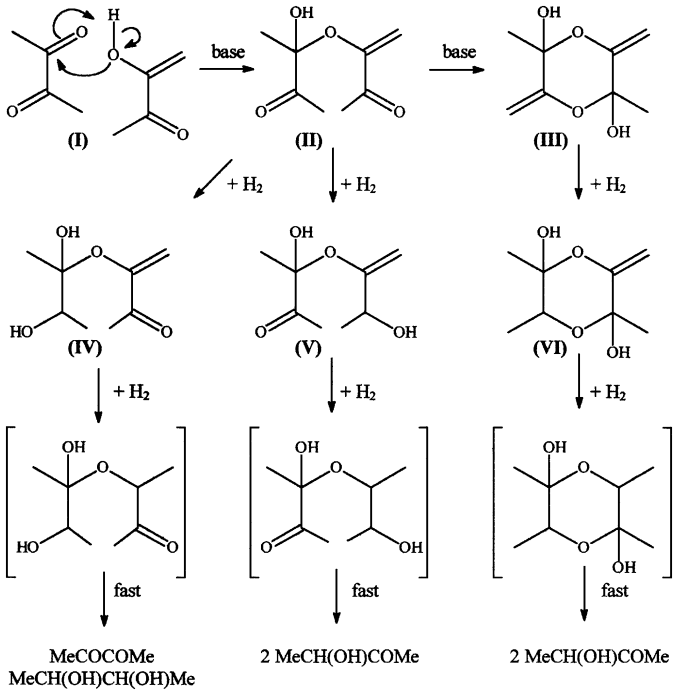

FIG. 5. Proposed mechanism for the dimerisation of butane-2,3-dione and for the subsequent hydrogenation and dissociation of the dimers.

(VI) instantly and completely dissociates to hydroxybutanone in dichloromethane solution at room temperature. Thus, in the third stage of reaction, (V) and (VI) are hydrogenated and dissociate to hydroxybutanone, and (IV) is analogously converted to butanedione and butanediol. The latter accounts for the traces of butanedione present in the very final stages of reaction when the dimers have disappeared. The hydroxybutanone that accompanied this butanedione was racemic which indicates that hydrodimerisation, which involved the creation of various chiral centres, was not directed by the chiral environment of the alkaloid modifier.

B. Reactions in Ethanol Solution

Reactions were fast when catalyst samples were modified under aerobic conditions and when solvent and organic reactant contained normal concentrations of dissolved air. Stringent exclusion of air caused a 90% reduction in rate and a 60% reduction in enantiomeric excess. In this respect, diketone hydrogenation followed pyruvate hydrogenation as reported in Part II (13). As a hypothesis, we suppose that competitive co-adsorption of oxygen and alkaloid prevents alkaloid achieving coverages at which it acts as a poison. Enantioselective sites then become available as adsorbed oxygen is removed by hydrogen in the early stages of reaction. In developing the process of modification under propyne, the objective was to provide an alternative strong co-adsorbent for the alkaloid. The catalysts so obtained were indeed enantioselective and of high activity, from which it is concluded that oxygen and propyne play common roles in these aerobic and anaerobic procedures, respectively. The removal of adsorbed propyne as propene and propane in the early stages of reaction has been confirmed in the context of pyruvate hydrogenation (26) and will be reported in a later paper in this series.

The effects observed are several and inter-related. First, one effect of preconditioning the surface with propyne was to increase the rate of racemic diketone hydrogenation over unmodified catalyst from 40 to 1500 mmol h^{-1} g^{-1}. It is well known that ethyne and propyne adsorb dissociatively on Pt and other Group 8 metals to give permanently retained hydrocarbonaceous residues that promote H-atom transfer between the surface and reactive hydrocarbon intermediates (27–29). This fast hydrogenation to racemic product over propyne-conditioned catalyst is attributable to the effect of such a hydrocarbonaceous ad-layer. Second, catalyst modified under propyne was active for the second stage of butanedione hydrogenation, a feature not shared by unmodified catalyst. Thus, hydroxybutanone hydrogenation required the presence of adsorbed alkaloid and the process was specifically facilitated at the enantioselective site. However, the process was also dependent on conditioning by propyne specifically, because modification under buta-1,3-diene did not provide second stage activity. Third, the two enantioselective catalyst systems reported here that provide rapid second stage activity in diketone hydrogenation do not show the normally observed rate enhancement in respect to activity for the first stage. One factor is that conditions for fast reaction to racemic product have been achieved. However, this feature merits further investigation because the observations and interpretations of enantioselectivity and rate enhancement have, until now, been closely linked, and the reactions described here appear to provide exceptions to a pattern of behaviour that has come to be accepted as the norm.

Note added in proof. After submission of this paper an investigation of butane-2,3-dione hydrogenation in toluene solution at 273–298 K and 25 to 135 bar hydrogen pressure catalysed by Pt/alumina modified by dihydrocinchonidine was reported in *Chemical Communications* by Studer, Okafor, and Blaser (30). The reactions described showed enantioselectivity in the first stage of reaction and similar kinetic resolution in the second stage. However, special procedures had to be adopted to achieve convenient rates and kinetic resolution in the second stage (addition of fresh modifier and catayst) and no dimer formation was observed (31).

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