Enantioselective hydrogenation using cinchona-modified Pt/γ-Al_2O_3 catalysts: comparison of the reaction of ethyl pyruvate and buta-2,3-dione

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The enantioselective hydrogenation of buta-2,3-dione to 3-hydroxy-buta-2-one and ethyl pyruvate to ethyl lactate are compared using cinchona-modified Pt/γ-Al_2O_3 catalysts. The reactions were carried out in a range of solvents and both reactants gave the same linear relationship between enantiomeric excess (e.e.) and the dielectric constant of the solvent. The e.e. for the 3-hydroxy-buta-2-one is lower than that for ethyl pyruvate. For both reactants there is an optimal concentration of the cinchona modifier but the optimal concentration required for the hydrogenation of buta-2,3-dione is approximately an order of magnitude higher than that required for the hydrogenation of ethyl pyruvate. The hydrogenation of buta-2,3-dione in acetic acid as solvent leads to a suppression in the e.e. with an enhancement in rate, whereas the reaction of ethyl pyruvate in acetic acid leads to an enhancement in e.e. The e.e. for 3-hydroxy-buta-2-one formation is independent of conversion in the initial period of the reaction which contrasts markedly with the observed initial induction period for ethyl lactate formation. The results are discussed in terms of the interaction of the reactants with the cinchona alkaloid adsorbed on the Pt surface.

KEY WORDS: enantioselective hydrogenation; ethyl pyruvate; buta-2,3-dione; cinchonidine-modified Pt catalyst; cinchonine-modified Pt catalyst.

1. Introduction

Heterogeneous enantioselective hydrogenation of prochiral ketones has been extensively studied using cinchona-modified supported Pt catalysts [1–4] and tartrate modified supported Ni catalysts [5–7]. However, the hydrogenation of pyruvate esters using cinchonidine-modified Pt/SiO_2 and Pt/γ-Al_2O_3 represent the most well investigated reactions and these are often studied as a model system. For this reaction the enantioselectivity can be high and enantiomeric excess (e.e.) in excess of 90% has been reported in many studies [1–4,8–10]. The structure of the cinchona alkaloids has been extensively studied [11–15] and in general cinchonidine produces a higher *R*-excess than cinchonine produces an *S*-excess. The solvent has also been found to be important since it affects the proportions of the different conformers of cinchonidine present in solution [16] and the highest e.e. are observed when the proportion of the open 3 conformer is maximised, typically using acetic acid as solvent.

Cinchona-modified Pt catalysts are highly specific for particular substrates, and only a few types of substrate can be hydrogenated with high enantioselectivity. Recent studies have extended the use of these catalysts to other activated ketones. Vermeer *et al.* [17] have described the enantioselective hydrogenation of buta-2,3-dione to 3-hydroxy-buta-2-one with e.e. in the range 20–40% (*R*) using cinchonidine-Pt/SiO_2. Baiker and co-workers [8,16,18] reported that e.e. of 79% (*R*) and 92% (*R*) for the hydrogenation of ketopantolactone and methylketopantolactone, respectively under optimised conditions using cinchonidine-modified Pt/γ-Al_2O_3. Blaser and co-workers [19] and Baiker and co-workers [20] have shown that α-keto acetals can be readily hydrogenated to the corresponding α-hydroxy acetals with e.e. up to 97% indicating that these substrates are particularly well suited to the cinchona-modified Pt catalysts with respect to both enantioselectivity as well as activity. Baiker and co-workers [21,22] have also shown that cinchona-modified Pt can be used for the enantioselective hydrogenation of 1,1,1-trifluoroacetophenone to (*R*)-1-phenyl-1,1,1-trifluoroethanol and 1- and 4-substituted-2,3,5-triones to the corresponding 3-hydroxy derivatives. Although many reactants have been studied using cinchona-modified supported Pt catalysts, to date there have been few comparative studies. In this paper we present a comparative study of the enantioselective hydrogenation of ethyl pyruvate and buta-2,3-dione and in particular compare and discuss the similarities and differences that are observed with these reactants.

2. Experimental

Five percent Pt/γ-Al_2O_3 was obtained from Johnson Matthey and was pre-treated with hydrogen (5% H_2 in

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Ar) for 2 h at 300 °C prior to use. Cinchonidine (Fluka, 98%) and cinchonine (Fluka, 98%) were used as received. Ethyl pyruvate (Fluka, >97%) and methyl pyruvate (Fluka, >97%) were purified prior to use. The pyruvate (50 mL) was mixed with CH_2Cl_2 (50 mL) and was treated with $KHCO_3$ (0.1 mol/L, 50 mL). The organic layer was collected and distilled under reduced pressure over $MgSO_4$ to remove CH_2Cl_2. The residue was distilled over anhydrous $CaCl_2$ under vacuum and the purified pyruvate was used immediately. Detailed analysis showed that no impurities, such as racemic lactates, were present in the purified reactant. Buta-2,3-dione (Aldrich, >97%) was used as received. Considerable care was adopted in the purification and drying of the solvents used in this study. Halogenated solvents were purified by distillation over anhydrous $CaCl_2$ and stored over 4A molecular sieve. Alcohols were distilled over CaO and stored over 4A molecular sieve. Aromatic solvents were dried by storage over 4A molecular sieve.

Pt catalysts were modified using an *in situ* procedure in which the cinchona modifier was added to the autoclave reactor immediately prior to H_2 addition. The enantioselective hydrogenation reactions were carried out using a Parr 50 mL stirred autoclave reactor. Two experimental procedures were used and all experiments were conducted at 20 °C in duplicate. Procedure I: reactant (66 mmol), solvent (12.5 mL), cinchona modifier (2.5 mg) and 5% Pt/γ-Al_2O_3 catalyst (0.25 g) were sealed into the autoclave. The autoclave was purged three times with hydrogen or argon to a pressure of 30 bar to remove residual air. Hydrogen was then admitted to the required reaction pressure (30 or 50 bar). At the same time, stirring was commence (1200 rpm) to start the reaction and the reaction was stopped by stopping the stirring and decreasing the hydrogen pressure and the product was isolated and analysed by gc and chiral gc. Procedure II: this was adopted for the sequential experiments. The initial reaction of ethyl pyruvate was carried out as described in procedure I, except that a decreased amount of ethyl pyruvate (33 mmol) was used and a small pressure vessel (10 mL volume) was connected to the autoclave. The small pressure vessel was initially filled with hydrogen (50 bar) using three purge cycles. Buat-2,3-dione (33 mmol) in CH_2Cl_2 (5 mL) was added to the hydrogen-filled small pressure vessel carefully via a syringe and this was purged by three successive additions of hydrogen (50 bar) using switching valves to add the hydrogen and to depressurise the vessel subsequently. The small pressure vessel containing the buta-2,3-dione/CH_2Cl_2 was then filled with H_2 (50 bar). Following reaction of ethyl pyruvate at 30 bar, the buta-2,3,-dione/CH_2Cl_2 solution was added to the autoclave reactor under the increased H_2 pressure (50 bar) without admission of air. Products were analysed using a chiral gas chromatograph and initial rates (mmol/min/g) were determined from hydrogen uptake.

3. Results

3.1. Effect of concentration of cinchonidine

The concentration of modifier in solution is an important parameter controlling both the rate of hydrogenation and the e.e. observed. The enantioselective hydrogenation of ethyl pyruvate and buta-2,3-dione were investigated using a very broad range of cinchonidine concentrations and the results are shown in figure 1. It is apparent that for both substrates the initial rate, determined from the rate of hydrogen uptake, and

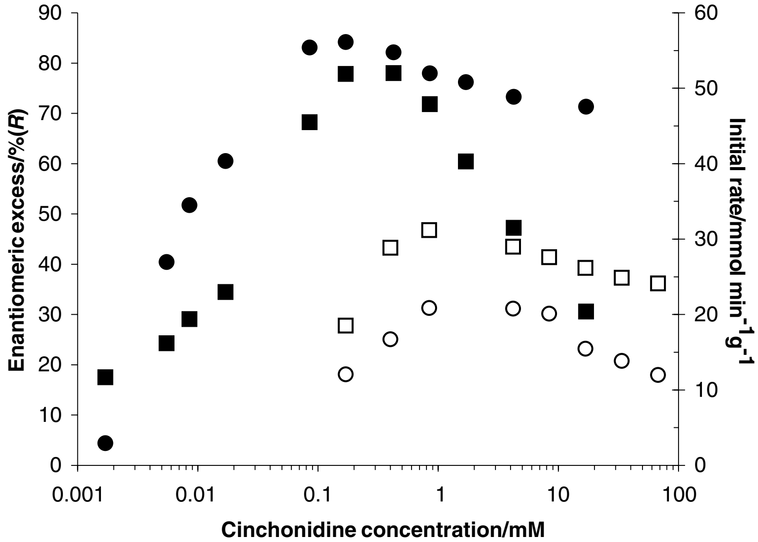

Figure 1. Effect of cinchonidine concentration on the e.e. and the initial rate of hydrogenation, (■) e.e. ethyl pyruvate, (●) initial rate ethyl pyruvate, (□) e.e. buta-2,3-dione, (○) initial rate buta-2,3-dione. Reaction conditions: dichloromethane (12.5 mL), reactant (66 mmol) catalyst (0.25 g), 50 bar H_2, 20 °C, 1200 rpm stirring.

the e.e. vary with the cinchonidine concentration in a similar way. However, the maximum e.e. and initial rate observed with ethyl pyruvate are almost twice as high as those observed for the hydrogenation of buta-2,3-dione. In addition, the cinchonidine concentration in solution required to achieve the maximum e.e. and rate was about an order of magnitude higher for buta-2,3-dione as compared with ethyl pyruvate.

3.2. Effect of the solvent on e.e. and initial rate

The enantioselective hydrogenation of ethyl pyruvate and buta-2,3-dione were investigated in a range of solvents and the results are shown in tables 1 and 2 respectively. There are two principle observations from these results. First, solvents have been shown previously [16] to affect the conformation of cinchonidine in solution through a dipolar interaction. The dipole moments for the four lowest energy conformations of cinchonidine decrease in the order closed 2 > closed 1 > open 4 > open 3. Consequently, solvents with high dielectric constants tend to stabilise the closed conformers. However, it has been shown [16] that the highest e.e. is observed when the open 3 conformation is present and this is favoured for solvents with low dielectric constant. The variation of e.e. with the dielectric solvent for both reactants is shown in figure 2 and it is clear that both reactants behave in a similar manner and consequently it can be concluded that the conformation of the cinchonidine required to observe high e.e. is the same for both reactants, i.e. the open 3 conformation. Second, for ethyl pyruvate the highest e.e. and initial rates are observed when acetic acid is used for both cinchonidine and cinchonine (tables 1 and 2). Although the initial rate is enhanced when buta-2,3-dione is reacted in acetic acid, the e.e. is significantly suppressed (tables 1 and 2). The effect is observed in both glacial acetic acid as solvent or when 1 M acetic acid in toluene was used. The effect is surprising since the role of the acid is to protonate the quinulcidine nitrogen thereby enhancing the concentration of the preferred open 3 conformer of cinchonidine.

Table 1
Effect of solvent on the hydrogenation of ethyl pyruvate using Pt/γ-Al_2O_3[a]

Solvent	Cinchonidine		Cinchonine	
	e.e. (*R*)	Initial rate (mmol/min/g)	e.e. (*S*)	Initial rate (mmol/min/g)
Toluene	78.0	33	51.0	17
Chloroform	76.0	14	46.0	10
Dichloromethane	71.5	38	35.0	18
Acetone	65.0	25	65.0	21
Ethanol	52.5	46	31.5	30
Acetic acid (1 M)/ dichloromethane	79.0	52	63.0	46
Acetic acid (glacial)	86.5	53	83.5	49

[a] Reaction conditions: solvent (12.5 mL), reactant (66 mmol) catalyst (0.25 g), 50 bar H_2, 20 °C, 1200 rpm stirring.

Table 2
Effect of solvent on the hydrogenation of buta-2,3-dione using Pt/γ-Al_2O_3[a]

Solvent	Cinchonidine		Cinchonine	
	e.e. (*R*)	Initial rate (mmol/min/g)	e.e. (*S*)	Initial rate (mmol/min/g)
Toluene	47.0	27	26.5	36
Chloroform	44.5	17	22.0	21
Dichloromethane	42.0	35	22.0	35
Butan-1-ol	35.5	38	19.5	33
Ethanol	28.0	40	16.0	34
Acetic acid (glacial)	14.0	42	7.0	46

[a] Reaction conditions: solvent (12.5 mL), reactant (66 mmol) catalyst (0.25 g), 50 bar H_2, 20 °C, 1200 rpm stirring.

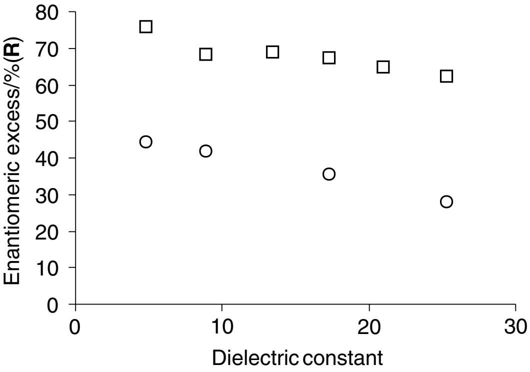

Figure 2. Effect of the dielectric constant of the solvent on e.e. (□) e.e. ethyl pyruvate, (○) e.e. buta-2,3-dione. Reaction conditions: solvent (12.5 mL), reactant (66 mmol) catalyst (0.25 g), 50 bar H_2, 20 °C, 1200 rpm stirring.

The effect of the addition of lower concentrations of acid were consequently investigated in which the reaction was carried in toluene and dichloromethane but with the addition of controlled amounts of pyruvic acid

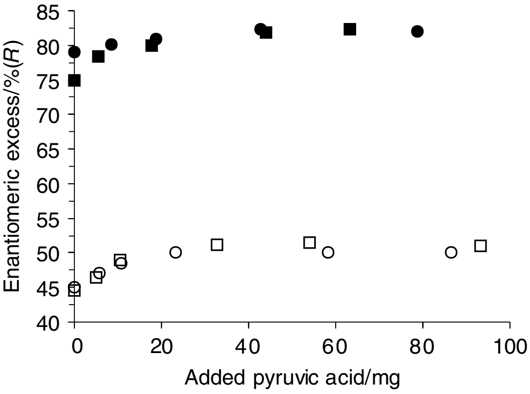

Figure 3. Effect on e.e. of the addition of pyruvic acid to the solvent prior to reaction. (■) e.e. ethyl pyruvate in dichloromethane, (●) e.e. ethyl pyruvate in toluene, (□) e.e. buta-2,3-dione in dichloromethane, (○) e.e. buta-2,3-dione in toluene. Reaction conditions: solvent (12.5 mL), reactant (66 mmol) catalyst (0.25 g), 50 bar H_2, 20 °C, 1200 rpm stirring.

being added at the start. The results (figure 3) show that addition of small amounts of pyruvic acid increase the e.e. for both reactions. The e.e. in both cases reaches a maximum and in the case of ethyl pyruvate this e.e. is ca. 4–5% lower than when the reaction is carried out in glacial acetic acid, whereas for buta-2,3-dione the final e.e. is significantly higher than that observed in glacial acetic acid. The difference in e.e. of 4–5% is considered significant since the e.e. can be determined to ± 0.5% with the methods used. This indicates that acetic acid is clearly acting in different ways for the two reactants.

3.3. Comparison of the initial reaction period

One intriguing observation, that has been well documented for the asymmetric hydrogenation of alkyl pyruvate esters, is that the enantioselection is found to increase with substrate conversion [21–29]. The effect was first observed by Wells and co-workers [21,22], and subsequently it has been shown that, for reactions carried out in an autoclave, the effect is dependent upon conversion but independent of the reaction conditions [25]. We have previously published the data for the initial transient effect with this catalyst for ethyl pyruvate [30] and these data need not be repeated here. We have now studied the initial reaction period with buta-2,3-dione under the reaction conditions used in this study and we have observed that regardless of the concentration of the cinchonidine there is no increase in e.e. with increasing conversion. For example at 50 bar H_2 with a cinchonidine/catalyst ratio of 10 mmol/g, the e.e. of (*R*)-3-hydroxy buta-2-one remained constant at 38% as the conversion of buta-2,3-dione increased. This is a further contrast with the hydrogenation of ethyl pyruvate where the increase in e.e. is observed with increasing conversion.

Subsequently, we carried out a sequential experiment in which the reaction of the buta-2,3-dione was performed following the initial hydrogenation of ethyl pyruvate using cinchonidine-modified Pt/γ-Al_2O_3. These experiments were conducted using experimental procedure II and the initial hydrogenation of ethyl pyruvate was carried out with 30 bar hydrogen pressure. Following reaction for 3 min, the buta-2,3-dione was rapidly added under hydrogen pressure whilst the stirring was continued in such a way that no oxygen could be admitted to the reactor. The second hydrogenation was consequently conducted at a higher reaction pressure (50 bar) and, under these conditions, no initial transient was observed when buta-2,3-dione was reacted by itself without prior reaction of ethyl pyruvate on the catalyst. The results of the sequential experiment are shown in figure 4 and these show that an initial transient is observed for both the initial hydrogenation of ethyl pyruvate, and for the sequential hydrogenation of buta-2,3-dione. This is in agreement with our earlier studies using this sequential methodology [30] using alkyl pyruvate esters where the initial transient is still observed if methyl pyruvate is reacted after the partial or complete reaction of ethyl pyruvate. However, it contrasts with our observations that the initial reaction of buta-2,3-dione alone does not give an initial transient effect. This experiment was conducted at a cinchonidine concentration for the reaction of buta-2,3-dione that is considered non-optimal (figure 1), yet the observed e.e. remains high. However, it is interesting to note that ee observed for the formation of *R*-ethyl lactate is significantly suppressed when co-reacted with buta-2,3-dione. We have previously observed this for the co-reaction of methyl pyruvate and ethyl pyruvate [30].

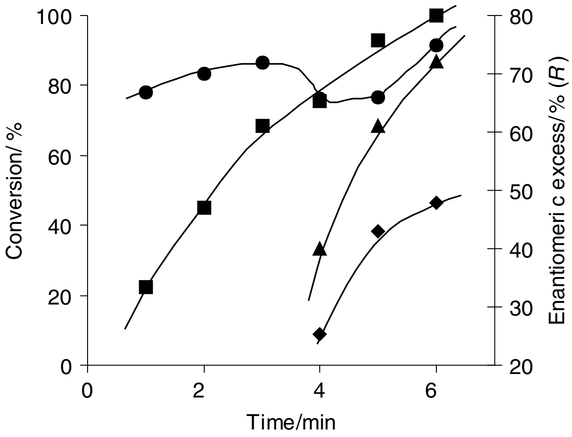

Figure 4. Sequential hydrogenation using reaction procedure II, ethyl pyruvate conversion 100% prior to addition of buta-2,3-dione at 3 min; (■) ethyl pyruvate conversion, (●) e.e. (*R*)-ethyl lactate, (▲) buta-2,3-dione conversion, (◆) e.e. (*R*)-3-hydroxy-buta-2-dione. [ethyl pyruvate (33 mmol), buta-2,3-dione (33 mmol), dichloromethane (12.5 mL), cinchonidine (0.01 g g^{-1}catalyst), 5% Pt/γ-Al_2O_3 (0.25 g), 20 °C, 1200 rpm, H_2 (30 bar, ethyl pyruvate; 50 bar buta-2,3-dione].

4. Discussion

There are three observed differences between the hydrogenation of ethyl pyruvate and buta-2,3-dione using cinchona-modified Pt/γ-Al_2O_3 as catalyst that require further comment, namely: (a) the difference in optimal modifier concentration, (b) the different effects of acetic acid as solvent and (c) the difference in the initial transient period of the reaction.

The difference in the optimal concentration of the modifier for the two reactants may be related to the competitive adsorption of the modifier and the substrate at the Pt surface. In this respect the differences are simply related to the relative adsorption of the two reactants. In a previous study [31] the reaction of buta-2,3-dione together with methyl pyruvate led to a suppression in the rate of hydrogenation of the pyruvate ester without affecting the rate of hydrogenation of the buta-2,3-dione. This suggests that the buta-2,3-dione is more strongly adsorbed and consequently a higher concentration of the cinchona modifier is required in solution to overcome this effect. In the follow on experiment the subsequent reaction of buta-2,3-dione may be more rapid than the desorption of cinchonidine from the surface and hence higher e.e. can be observed with a non-optimal concentration of cinchonidine.

An important difference between the two substrates is the nature of the electron withdrawing group α to the prochiral carbonyl that is hydrogenated. In the buta-2,3-dione the carbonyl group is a weaker electron withdrawing group compared with the carboxyl group. However, the observation that the e.e. for both reactants is correlated with the dielectric constant of the solvent confirms that the prime factor controlling the enantioselection is the conformation of the cinchona modifier. However, the two substrates clearly behave differently in glacial acetic acid although they give similar enhancement in e.e. when lower acid concentrations are present in the solvent. It is possible that under the strong acid conditions the butadione is polymerised and subsequently the reaction via the polymer leads to a lower e.e. It is known that cinchonidine forms 2:1 and 1:1 complexes in glacial acetic acid with the cyclic 2:1 complex being the dominant species [32]. It is possible that these interact differently with the two substrates in the presence of the Pt surface.

The observation that buta-2,3-dione does not exhibit an initial transient indicates that the observed transient with alkyl pyruvate esters may be due to the interaction of the carboxyl functional group with the cinchona–Pt active site. The observation of an initial transient effect following the reaction of ethyl pyruvate may indicate that the cinchonidine modifier interacts differently with the two substrates when in the presence of a Pt-surface. These are factors requiring further investigation.

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