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Priority Communication

New insights into the relationship between conversion and enantioselectivity for the asymmetric hydrogenation of alkyl pyruvate

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Abstract

The initial transient period in the enantioselective hydrogenation of alkyl pyruvate esters is probed using the sequential reactions of ethyl and methyl pyruvate. The reaction of methyl pyruvate, subsequent to the hydrogenation of ethyl pyruvate, led to a higher e.e. when compared to the coreaction of these reactants, or prehydrogenation with methyl pyruvate followed by reaction of ethyl pyruvate. The initial transient effect, in which e.e. increases with conversion, is observed in both periods of the sequential reaction and the origin of this effect is discussed.

Keywords: Enantioselective hydrogenation of alkyl pyruvates; Cinchonidine-modified Pt/Al_2O_3 catalysts

1. Introduction

The study of enantioselective catalysts continues to receive significant attention due to the importance of pure enantiomers in the manufacture of pharmaceuticals and agrochemicals. Much progress has been achieved with homogeneous catalysts [1–3], but significant attention remains focused on heterogeneous asymmetric catalysts where a number of catalysts have been identified that give very high enantioselection, e.g., the hydrogenation of ethyl pyruvate using cinchona-modified supported Pt catalysts [4,5] and the aziridination of alkenes using (bis)oxazoline-modified Cu^{2+}-exchanged zeolite Y [6] and the subject of immobilised homogeneous catalysts has recently been reviewed by Sing and Lee [7]. One intriguing observation with some heterogeneous asymmetric catalysts is that the enantioselection is enhanced during the initial period of conversion; whereas, typically, the reverse is observed in many systems. The effect of this initial transient period has been well studied for the cinchona-modified Pt catalysts [8–11]. However, the origin of the enhanced enantioselection during the initial reaction remains a matter of considerable debate [12,13].

Herein, we deal with the origin of the increase in enantioselection with conversion for cinchona-modified Pt/Al_2O_3 catalysts for the hydrogenation of alkyl pyruvates. At present, two schools of thought exist concerning the origin of this effect. Baiker and co-workers [11,13] consider that the enhancement in e.e. is caused by removal of impurities present on the catalyst surface at the start of the reaction, for example, oxygen or the degradation products of dissociative chemisorption of the substrate. During the initial reaction in the presence of hydrogen, these impurities are removed. In contrast, Blackmond and co-workers [9,12] consider the effect to be due to a “reaction-driven equilibration” of the catalyst surface and have shown that the effect of rising rate and enantioselection in the initial reaction period was linked solely to substrate conversion and was independent of reaction conditions. To aid our understanding of this intriguing process, we have designed a sequential experiment that adds new insight into this fascinating problem.

2. Experimental

A 5% Pt/Al_2O_3 (Johnson Matthey, type SR94B) was pretreated with hydrogen at 400 °C prior to use. Cinchonidine (Fluka, 98%) was used as received. Ethyl pyruvate (Fluka, $> 97\%$) and methyl pyruvate (Fluka, $> 97\%$) were purified with great care prior to use. The pyruvate (50 ml) was mixed with CH_2Cl_2 (50 ml) and 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

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and the purified pyruvate was used immediately. Each pyruvate ester contained no detectable impurities; in particular, they contained no lactate, for example, racemic lactates. CH_2Cl_2 was purified by distillation over anhydrous $CaCl_2$ and stirred over a 4A molecular sieve. Toluene was purified by distillation over a 4A molecular sieve and stored over a 4A molecular sieve.

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: pyruvate substrate (66 mmol), CH_2Cl_2 solvent (12.5 ml), cinchonidine (2.5 mg), and 5% Pt/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 commenced (1200 rpm) to start the reaction and the reaction was stopped by turning off the stirrer, removing the hydrogen atmosphere, and filtering off the catalyst, 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. Methyl pyruvate (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 depressure the vessel subsequently. The small pressure vessel containing the methyl pyruvate/CH_2Cl_2 was then filled with H_2 (50 bar). Following reaction of ethyl pyruvate at 30 bar, the methyl pyruvate/CH_2Cl_2 solution was added to the autoclave reactor under the increased H_2 pressure without admission of air.

3. Results and discussion

The observation of the initial transient period is shown in Fig. 1 for the hydrogenation of ethyl pyruvate in an autoclave reactor using cinchona-modified $Pt/\gamma\text{-}Al_2O_3$. For each data point in Fig. 1, a separate experiment was carried out in duplicate. At the designated time, the reaction was stopped by release of the hydrogen reactant pressure and the product isolated. The observed enhancement in enantioselection is apparent in both the overall enantiomeric excess (e.e.) determined at the specified reaction times, and the differential e.e. (Δe.e.) determined from the increase in e.e. over that of the previous data point, which shows a more significant increase in e.e. at the low reaction times.[1] In our experiments, we added the solvent, catalyst, cinchona alkaloid, and ethyl pyruvate to the reactor in that order and purged the system with hydrogen several times to remove residual oxygen. Following this, the hydrogen was introduced and the stirrer started. Experiments showed that, under our conditions, the e.e. was independent of stirring speed above 800 rpm and it took 10 s to achieve the optimal stirring rate of 1200 rpm. During this time, only 1% substrate conversion was observed (Fig. 1) and, since the significant enhancement in e.e. is observed up to ca. 20% conversion, we do not consider that the e.e. enhancement is due to initial diffusion effects. In addition, experiments using different amounts of cinchona modifier and substrate concentrations did not affect the nature of the initial transient period. However, in carrying out these experiments, it is clear that the initial transient period could be influenced by factors that are difficult to control, since the reactor stirring and addition of hydrogen are requisites to start the reaction, but they take a finite time to reach optimal levels. To overcome these problems, we devised the following set of experiments using the sequential hydrogenation of ethyl pyruvate and of methyl pyruvate.

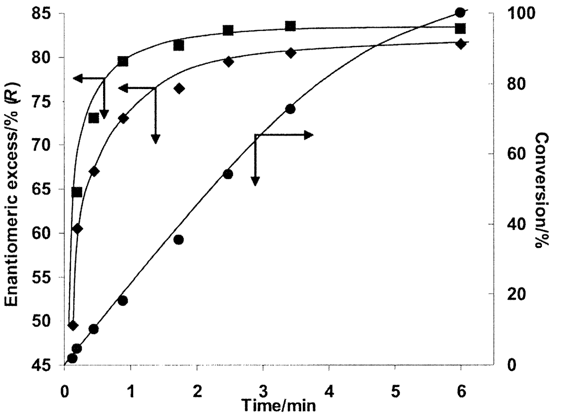

Fig. 1. Dependence of enantiomeric excess and conversion of ethyl pyruvate hydrogenation. Key: ●, ethyl pyruvate conversion; ◆, (*R*)-ethyl lactate; ■, Δe.e. Conditions: 5% Pt/Al_2O_3 (0.25 g), CH_2Cl_2 (12.5 ml), cinchonidine (2.5 mg), ethyl pyruvate (66 mmol), $P_{H_2} = 50$ bar, 20 °C, 1200 rpm stirring speed.

First, the enantioselective hydrogenation of the two alkyl pyruvates was investigated separately; both gave the expected initial transient effect and the final e.e.s observed at 100% substrate conversion are given in Table 1. Significantly, when reacted separately, the pyruvate esters give almost identical e.e.s for the lactates, and the increase in e.e. with conversion was also indistinguishable. Second, the hydrogenation of the ethyl pyruvate and methyl pyruvate was investigated simultaneously using half the normal concentrations of each substrate, both being added at the beginning

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[1] Δe.e. is the mean value of the e.e. provided by the reaction between data points. As the e.e. is increasing with conversion and the initial turnovers have the lowest e.e., there is a cumulative effect for the e.e. at any time, which is the sum of all the earlier less enantioselective reactions. Δe.e. gives the e.e. for the conversion between the reaction time, at which it is recorded, and the preceding reaction time. This provides a better representation of the enantioselection achieved at the catalyst surface.

Table 1
Comparison of the enantiomeric excess for the hydrogenation of alkyl pyruvates using Procedures I and II

Experimental procedure[a]	Substrate	e.e.[b] (%)	
		R-Ethyl lactate	*R*-Methyl lactate
I	Ethyl pyruvate[c]	80.5 ± 0.5	–
I	Methyl pyruvate[c]	–	79.0 ± 0.5
I	Ethyl and methyl pyruvate simultaneous[d]	74.0 ± 0.5	75.0 ± 0.5
II	Sequential: ethyl pyruvate followed by methyl pyruvate[d]	81.0 ± 0.5	91.0 ± 0.5

[a] See experimental, CH_2Cl_2 (12.5 ml), cinchonidine (2.5 mg), 5% Pt/Al_2O_3 catalyst (0.25 g), 20 °C, 1200 rpm stirring speed.

[b] At end of the reaction.

[c] Pyruvate (66 mmol).

[d] Ethyl pyruvate (33 mmol) and methyl pyruvate (33 mmol).

of the reaction. Interestingly, the final e.e.s for this simultaneous experiment are significantly lower for both alkyl lactate products when compared to the e.e. achieved for the single substrate (Table 1) and the e.e.s for the two lactate products were identical with respect to their increase with conversion. Third, a sequential experiment was carried out in which the reaction of methyl pyruvate was carried out following the initial hydrogenation of ethyl pyruvate using chinona-modified Pt/Al_2O_3. In these experiments, the initial hydrogenation of ethyl pyruvate was carried out with 30 bar hydrogen pressure. Following this reaction, methyl pyruvate was rapidly added under hydrogen pressure while the stirring was continued in such a way that no oxygen could be admitted to the reaction. The second hydrogenation was consequently conducted at a higher reaction pressure (50 bar), but, as noted previously, the observation of the initial transient effect is independent of the reaction conditions [9,12]. The results of the sequential experiment are shown in Fig. 2a and are most revealing. Most importantly, two effects are apparent; first, the initial transient period is observed for the hydrogenation of methyl pyruvate and, second, the final e.e. observed in *R*-methyl lactate formation (91%) is significantly higher than that observed in the single (79% e.e.) or simultaneous (75% e.e.) experiments. It should be noted that each data point in Fig. 2 is for a separate experiment carried out in duplicate and, therefore, is a composite of 22 separate experiments for Fig. 2a and 16 experiments for Fig. 2b. In addition, the e.e. of the *R*-ethyl lactate remained unchanged during the subsequent formation of *R*-methyl lactate. The observation of enhanced e.e. for the sequential hydrogenation of methyl pyruvate is totally unexpected and represents one of the most highly enantioselective hydrogenations of this substrate recorded.

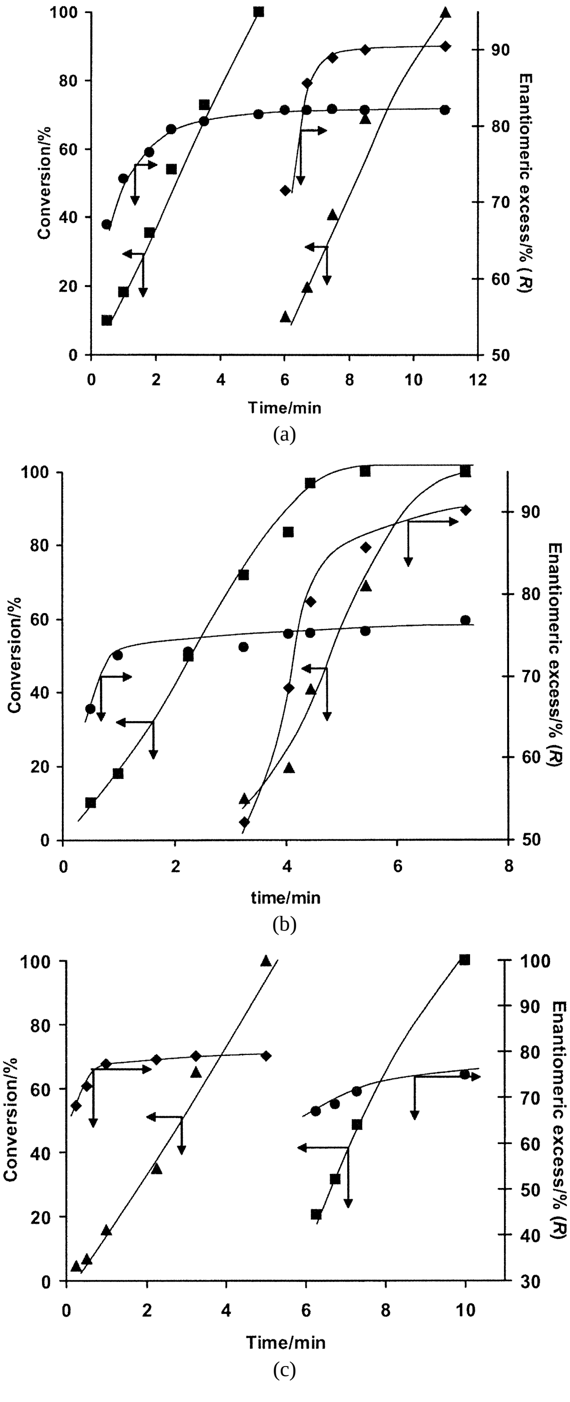

Fig. 2. Sequential hydrogenation experiment using reaction Procedure II. (a) Ethyl pyruvate reacted to 100% conversion prior to addition of methyl pyruvate; (b) ethyl pyruvate reacted to 50% conversion prior to addition of methyl pyruvate. Key: ■, ethyl pyruvate conversion; •, e.e. in (*R*)-ethyl lactate, ▲, methyl pyruvate conversion; ◆, e.e. in (*R*)-methyl lactate. Conditions: 5% Pt/Al_2O_3 (0.25 g), CH_2Cl_2 (12.5 ml), cinchonidine (2.5 mg), ethyl pyruvate (33 mmol), methyl pyruvate (33 mmol), 20 °C, 1200 rpm stirring speed, reaction pressure 30 bar H_2 for ethyl pyruvate hydrogenation, 50 bar H_2 for methyl pyruvate introduction; (c) methyl pyruvate reacted to 100% conversion prior to addition of ethyl pyruvate.

To ensure that the effect was not due to the complete conversion of ethyl pyruvate occurring prior to the addition of the methyl pyruvate, a further experiment was conducted where the ethyl pyruvate reaction was taken to 50% conversion prior to the addition of methyl pyruvate (Fig. 2b). Again, the same initial transient for methyl pyruvate was observed, even though the catalyst was now converting both ethyl and methyl pyruvate. Significantly, the e.e. observed for methyl pyruvate at the end of the reaction (91%) was still significantly higher than that observed if the methyl pyruvate had been added at the start of the reaction (Table 1, 75%).

The experiment was repeated with the order of reagent addition reversed, i.e., methyl pyruvate conversion first, followed by ethyl pyruvate. Again, in this experiment, the initial hydrogenation of methyl pyruvate was carried out with 30 bar pressure and the initial transient effect was observed (Fig. 2c). Following complete conversion of the methyl pyruvate, ethyl pyruvate was added as described previously. An increase in e.e. is observed with increasing conversion but the e.e. is not enhanced. This is an interesting result since it shows that the order of reactant addition is of crucial importance and, although ethyl pyruvate reaction prior to methyl pyruvate leads to a significant enhancement in e.e. of the (R)-methyl lactate, the same is not true for the reverse experiment. Further experiments were carried out using toluene as solvent and similar results were obtained.

As noted previously, Baiker and co-workers [11,13] attribute the observation of the initial transient effect to impurities such as oxygen, or other residues, formed on the surface due to the pyruvate adsorption at the start of the reaction. The reaction has the effect of cleaning the surface of these impurities and it, therefore, takes a significant number of reaction turnovers to achieve the optimal chirally modified surface operating under steady-state conditions. In our experiments, the sequential hydrogenation of ethyl and methyl pyruvates was carried out in such a way that did not expose the catalyst to air or interrupt the reaction progress (Fig. 2). The chiral-active sites at the cinchonidine/Pt surface had been established and were functioning at high enantioselection. The observation that the initial transient effect is still observed with the sequential hydrogenation of ethyl and methyl pyruvates indicates that the increase in e.e. with conversion for this reaction is not attributable to impurity effects, since the optimal chiral-active sites had been achieved from the reaction of ethyl pyruvate. The results support the ideas proposed by Blackmond and co-workers [9,12] concerning the "reaction-driven equilibrium of the chiral surface environment." However, our experiments suggest (Table 1, Fig. 2) that the cinchona modifier adsorbed on the metal surface may interact differently with the two reactants and the active chiral site is dependent upon the nature of the substrate. The different nature of this interaction for the two pyruvate esters is also indicated by the simultaneous reaction data which show identical behaviour, but the e.e. is significantly different from that obtained for the reaction of each alone. However, our observation of markedly enhanced e.e. for the sequential hydrogenation of methyl pyruvate following ethyl pyruvate indicates that there is potential to premodify chiral surfaces to give enhanced enantioselection. This observation could, in effect, be the most significant, since it suggests that surface pretreatment/conditioning could be a fruitful area of investigation in the design of improved heterogeneous asymmetric catalysts. The effect may be caused by selective poisoning of particular surface sites that lead to racemic reaction, and this effect warrants further study. However, our data also show that pretreatment can also give deleterious effects since, when methyl pyruvate is initially reacted prior to ethyl pyruvate, the resulting (R)-ethyl lactate has a significantly lower e.e. than when ethyl pyruvate is reacted with a nonpretreated catalyst. We consider that the steric bulk of the alkyl substitute could have an important role in defining the interaction of the reactant with the cinchona modifier on the surface of the platinum nanocrystals. It is possible that the modifier conformation on the surface, rather than in solution, is affected by the structure of the reactant and this is an effect that warrants further detailed study.

In conclusion, we have described a sequential hydrogenation experiment for the reaction of alkyl pyruvates using cinchona-modified Pt/Al_2O_3 that shows the enhancement in e.e. observed with increasing conversion is related to the interaction of the modifier and the substrate. Furthermore, this effect can be used to provide markedly enhanced enantioselection in specific cases and this could be of importance in the design of enantioselective heterogeneous catalysts.

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