Continuous enantioselective hydrogenation of ethylbenzoylformate over Pt/Al_2O_3 catalyst: bed dilution effects and cinchonidine adsorption study

E. Toukoniitty, P. Mäki-Arvela, N. Kumar, T. Salmi, and D. Yu. Murzin*

Laboratory of Industrial Chemistry, Process Chemistry Centre, Åbo Akademi University, FIN-20500 Turku-Åbo, Finland

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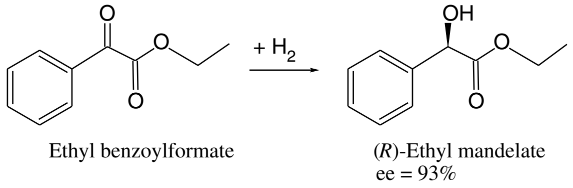
Depending on the reaction medium (toluene or acetic acid) striking differences were observed in the development of enantiomeric excess with time-on-stream in continuous enantioselective hydrogenation of ethylbenzoylformate on cinchonidine-modified Pt/Al_2O_3, which correlated well with the amount of adsorbed cinchonidine on alumina and silica from acetic acid and toluene solutions. Maximally 93% enantiometric excess (ee) of (*R*)-ethyl mandelate was obtained.

KEY WORDS: bed dilution; adsorption of cinchonidine; continuous hydrogenation.

1. Introduction

Continuous enantioselective hydrogenation of ethyl pyruvate [1,2], ketopan to lactone [1], 1-phenyl-1,2-propanedione [3,4], ethyl-2-oxo-4-phenylbutyrate [5] and isopropyl-4,4,4-trifluoroacetate [6] have been studied in a fixed bed reactor over cinchona-modified Pt catalysts. The catalyst bed is typically diluted by an inert material to either provide more favorable hydrodynamic conditions, improve the heat transfer or to diminish the mass transfer effects. In α- keto ester hydrogenation, the common diluent has been Al_2O_3 [2,6], which as such is inert toward the hydrogenation. However, the effect of the diluting material has not been studied. The ζ potential of alumina and silica vary as a function of pH, which implies that the surface charge changes from positive towards negative with increasing pH [7]. The influence of it on cinchonidine (CD) adsorption can be considerable as CD is protonated in acidic media. In acidic media, the positively charged alumina and silica effectively repel protonated cinchonidine.

Adsorption of CD on Pt catalysts has been investigated by UV spectroscopy [8,9]. The solvent selection affects on the amount of CD needed for modifying the Pt surface. A larger amount of CD is adsorbed on Pt/Al_2O_3 catalyst in toluene compared to methanol [8], because methanol interacts stronger with the catalyst surface. Moreover, different supports adsorb different amounts of modifier, for instance, Pt/C catalyst adsorbs 10 times more cinchonidine than Pt/Al_2O_3. A weak correlation between the specific surface area and the amount of adsorbed cinchonidine has been observed [8]. Sutherland et al. [9] have concluded based on CD adsorption measurement on 5wt% Pt/SiO_2 (EUROPT-1) that CD adsorbed both on the support and on the Pt metal in ethanol solvent.



Scheme 1. EBF and the main product (*R*)-ethyl mandelate (the maximum ee obtained in continuous hydrogenation).

Ethylbenzoylformate has previously been hydrogenated in a batch reactor [10] with a high enantiomeric excess (ee) (98%) by using acetic acid as a solvent. In the present study, the enantioselective hydrogenation of ethylbenzoylformate (EBF) (Scheme 1) was carried out in a continuous fixed bed reactor, where the catalytic performance and catalyst deactivation can be studied in solvents with different protonation properties, e.g., acetic acid and toluene. In the present work the dilution of the Pt/Al_2O_3 powder catalyst either with silica or with alumina was demonstrated to affect the reactor performance. Moreover, separate adsorption studies of CD on the both supports were performed in order to explain the catalytic results.

2. Experimental

2.1. Hydrogenation experiments

Hydrogenation of EBF (Aldrich, 95%, 25,891-1) was carried out in a fixed-bed reactor (10 cm length and 0.9 cm internal diameter) at 25 °C and 5 bar hydrogen. The fixed bed composed of 25 mg 5% Pt/Al_2O_3 (Strem Chemicals 78-1660) catalyst diluted with 400 mg of Al_2O_3 (JM, EN AL4174P) or 700 mg SiO_2 (Merck 7734) resulting in the bed thickness of 2.0 cm. The larger amount of SiO_2 was used to maintain the bed dimensions constant. Both the catalyst and the diluting

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*To whom correspondence should be addressed.
E-mail: dmurzin@abo.fi

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material consisted of 90–125 μm particles. The catalyst was reduced *ex situ* under flowing hydrogen at 400 °C and 1 bar for 2 h and cooled down to room temperature in hydrogen followed by flushing with Ar for 30 min. Preliminary test showed that catalyst could be stored at least 3 days in air without any loss of activity or selectivity. The pre-reduced catalyst and the diluting material were mechanically mixed and loaded into the reactor tube followed by activation under hydrogen flow at 5 bar for 20 min. The liquid phase containing the modifier, the solvent and the reactant, was bubbled with hydrogen for 20 min before commencing the reaction. Typically the experiments were carried out with co-current downward gas (50 cm^3 min^{-1}) and liquid flows (2.8 cm^3 min^{-1}). The concentrations of the reactant and the catalyst modifier were 0.025 mol dm^{-3} and 8.5 or 17 $\times 10^{-4}$ mmol dm^{-3}, respectively.

2.2. Cinchonidine adsorption measurements

The CD adsorption on the diluting materials SiO_2 and Al_2O_3 was studied at atmospheric pressure by UV spectroscopy. Four hundred milligrams of Al_2O_3 or SiO_2 (particle size 90–125 μm), 12.3 mg of CD and 50 ml of solvent (toluene or acetic acid) was stirred in a closed vessel for 2h at 25 °C. The solid material was removed in a centrifuge and from the remaining liquid phase, the amount of CD was determined. The amount of CD was measured with Varian DMS90 double beam UV–Vis spectrometer from the absorbance at λ (25 °C) = 308 nm using toluene or acetic acid in a reference cell.

2.3. Characterization of solids

Detailed characterization of 5% Pt/Al_2O_3 (Strem Chemicals 78-1660) catalyst has been described previously [11]. The catalyst has the mean Pt particle size 2.5 nm and dispersion 40% after reduction in hydrogen for 2 h at 400 °C, the BET specific surface area of the catalyst was 95 m^2 g$_{cat}^{-1}$ and the surface area of Pt 5.5 m^2 g$_{cat}^{-1}$. The catalyst has relatively large pores; 57% of pore volume was in pores between 10–100 nm.

The BET surface area and pore size distribution were determined by nitrogen physisorption using Sorptomatic 1900 (Carlo Erba). The Al_2O_3 and SiO_2 samples were outgassed at 200° C for 4 and 3 h, respectively, prior to the measurements.

3. Results and discussion

3.1. Hydrogenation experiments

EBF was hydrogenated in the continuous fixed bed reactor with a high enantiomeric excess ee. Maximally 93% ee of (*R*)-ethylmandelate was obtained in toluene. The production rate of ethylmandelate was 1.7 mmol min^{-1} g$^{-1}_{cat}$ (60% conversion of EBF and ee = 90%) corresponding to TOF of 1000 h^{-1} (Figure. 1). The TOF value is similar to those reported for ethylpyruvate and ketopantolactone in [1] 370 and 1420 h^{-1}, respectively. Calculation based on reported experimental data [10] for a platinum catalyst with somewhat lower dispersion than in the present study gives a value of 520 h^{-1} , which is in rather good correspondence with the value reported here. The conversion of EBF exhibited a maximum, after which the conversion decreased indicating catalyst deactivation (figure 1). In the enantioselective hydrogenation, i.e., in the presence of CD, the activity decreased more rapidly than in racemic hydrogenation. No rate acceleration was observed in enantioselective hydrogenation. The slight initial increase in the activity observed both in enantioselective and racemic hydrogenations cannot be taken as rate acceleration as such but more as the dynamic bed behavior. The activity decreased after the maximum almost linearly in racemic hydrogenation. The catalyst deactivation in the absence of CD is

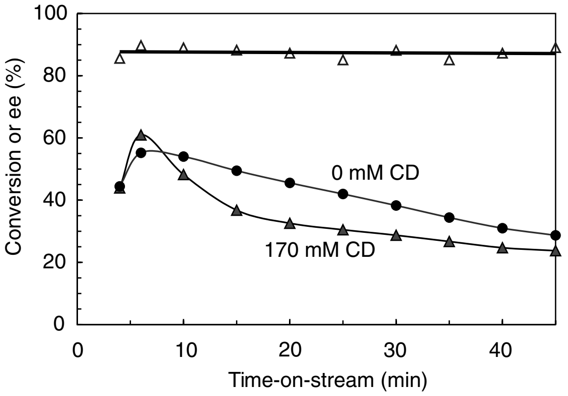

Figure 1. Enantiomeric excess (8) and conversion of EBF in (●) racemic and (▲) enantioselective hydrogenation with Al_2O_3 as catalyst dilutant. $C_{EBF} = 0.025$ mol dm^{-3}. Solvent was toluene.

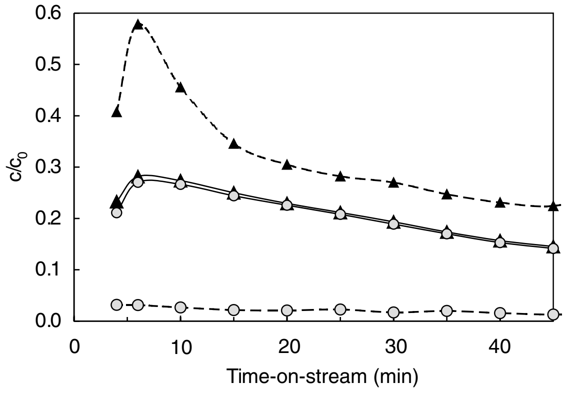

Figure 2. The dimensionless concentrations of (*R*)- and (*S*)-ethyl mandelate during enantioselective and racemic hydrogenation of EBF over Pt/Al_2O_3; $C_{EBF} = 0.025$ mol dm^{-3}. Symbols: (▲) (*R*)- and (○) (*S*)-ethyl mandelate. Dashed line: enantioselective hydrogenation, solid line: racemic hydrogenation.

probably due to decomposition of EBF, which produces CO and strongly adsorbing $C_xH_yO_z$ [12].

As the formation rates of the reaction products (*R*)- and (*S*)-ethyl mandelate were investigated (figure 2), it became clear that the enantioselectivity is obtained by the considerably decreased rate of (*S*)-enantiomer and the increased rate of (*R*)-enantiomer with respect to racemic hydrogenation. Similar behavior has been previously observed by us in case of 1-phenyl-1,2-propanedione hydrogenation [13]. The ee exceeding 90% has been obtained without any rate acceleration, in fact the presence of CD decreased the activity. These results confirm the previous finding [10] which indicate that EBF can be hydrogenated with a high ee = 98%, but without a considerable rate acceleration.

The diluting material, although it is inert with respect to hydrogenation, has a significant influence on the development of the enantioselectivity. In toluene, with silica as diluent, the ee increased linearly and after 55 min time-on-stream just 40% ee was attained (Figure 3). The reproducibilities of ee and rate were excellent. As the catalyst bed was diluted with alumina, ee increased linearly up to 80% ee (attained after 25 min time-on-stream) after which the increase was marginal.

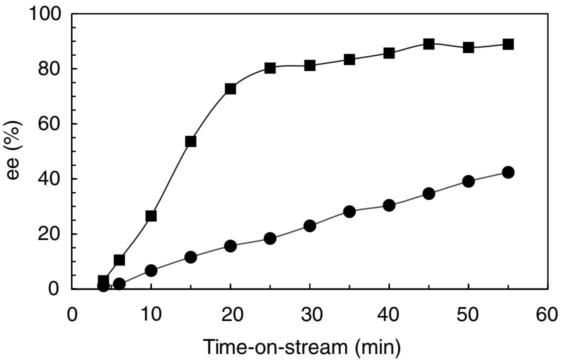

Figure 3. Development of ee in EBF hydrogenation with time-on-stream with (■) Al_2O_3 and (●) SiO_2 as dilutant. $C_{EBF} = 0.025$ mol dm^{-3} and $C_{CD} = 8.5 \times 10^{-4}$ mol dm^{-3}. Solvent was toluene solvent.

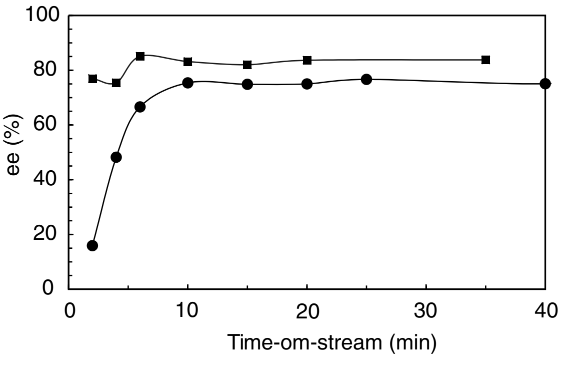

Figure 4. Development of ee in EBF hydrogenation with time-on-stream with (■) Al_2O_3 and (●) SiO_2 as dilutant. $C_{EBF} = 0.025$ mol dm^{-3} and $C_{CD} = 8.5 \times 10^{-4}$ mol dm^{-3}. The solvent was acetic acid.

As acetic acid was utilized as a solvent, the results were very different indicating that the solvent affects the system considerably. In acetic acid the maximum ee was obtained almost instantaneously with alumina diluted bed and with silica diluted bed the steady-state ee was obtained just after 10 min time-on-stream (figure 4). These experiments indicate that the steady-state ee in acidic solvent is obtained almost immediately, regardless on the diluting material.

3.2. Cinchonidine adsorption results

The CD adsorption measurements provided a plausible explanation for the observed solvent effects on the development of ee more specifically. Almost all dissolved CD (12.3 mg corresponds to the same liquid-phase concentration as in the hydrogenation experiments) was adsorbed from toluene on 400 mg of alumina and just about 10% of CD remained in a liquid-phase (table 1). The same amount of silica, however, adsorbed extremely effectively CD so that no characteristic CD UV-spectrum was detected. In acetic acid, the CD adsorption was much more modest. Al_2O_3 adsorbed a negligible amount of CD and SiO_2 adsorbed just about 20% (table 1).

These observations can be understood in terms of surface charge of alumina and silica in different solvents. The surface tends to adsorb cations (i.e., protonated cinchonidine CDH^+) as it carries a negative charge and *vice versa*. The isoelectric point of alumina and silica are around 7–9 and 1.5–3 pH [14], respectively, i.e., both silica and alumina have a positive surface charge in acidic media, although alumina has clearly higher positive ζ potential [14]. It has been previously reported that CD is protonated in acidic solution [15]. Therefore, as CDH^+ and alumina and silica have a positive charge in acidic media, they repel each other and only some adsorption takes place, which correlates well with experimental observations. In neutral media (e.g. toluene) the surface of silica is slightly negatively charged which explains why silica extremely well adsorbs CD. Alumina also tends to get negative charge but at slightly higher pH, and therefore, the adsorption of CD form toluene on alumina is not that pronounced as on silica.

There were large differences in the time required to reach steady-state ee during continuous operation (figures. 3 and 4). In acetic acid with alumina diluted

Table 1
The relative amount of adsorbed CD on alumina or on silica (400 mg) from toluene and acetic acid and the BET specific surface area of the diluting material[a]

Support	BET (m^2/g)	Toluene%	Acetic acid%
Al_2O_3	140	91	0
SiO_2	380	100[a]	18

[a]no CD spectra could be recorded from the solution, experimental error in reported values ± 5%.

bed the steady state was attained in less than 2 min time-on-stream whereas in toluene with silica diluted bed the same would take about 100 min (extrapolated from figure. 3). This 50-fold difference can be rationalized based on the cinchonidine adsorption results on the diluting material. The catalyst bed composes of the diluent material (silica 96 wt% or alumina 94 wt%), the active Pt metal and the alumina support of the catalyst. The CD has to adsorb on the Pt metal in order to induce enantioselectivity, while the fraction of unmodified Pt sites produces racemic product mixture. When the steady-state ee is reached the ratio of modified and unmodified Pt sited remains unchanged. Based on adsorption experiments alumina does not adsorb CD in acetic acid, which means that in acetic acid/alumina diluted catalyst bed the catalytically active Pt metal mainly adsorbs CD having a total surface area of 0.007 m^2. In toluene, on the other hand, the silica diluted catalyst bed consists of three components which all adsorb effectively CD, *i.e.*, the silica diluent, the catalyst support and the active Pt metal making a total surface area of about 270 m^2. Not surprisingly it takes much longer (note that CD inlet was same in all cases) to reach steady-state coverage of CD on Pt in silica/toluene bed because the diluting material adsorbs substantial amount of CD. The amount of adsorbed cinchonidine (table 1) silica/toluene 100% > alumina/toluene 91% > silica/AcOH 18% > alumina/AcOH 0% correlates with the time required to attain a steady-state ee in the continuous hydrogenation 100 min > 25 min > 10 min > 0–2 min, respectively. Therefore, one can conclude that the choice of solvent and bed diluting material considerably affects the transient development of ee during a continuous operation due to differences of CD adsorption on the diluting material.

It is well established, especially for the hydrogenation of ethyl pyruvate and 1-phenyl-1,2-propanedione that the concentration of CD affects the enantiomeric excess [13, 16]. Usually a broad maximum as a function of modifier concentration is obtained. The results of the present study indicate that the amount of CD adsorbed on alumina and silica strongly depends on the solvent. In acetic acid, the amount of CD adsorbed on alumina and silica was negligible, whereas in toluene the majority of dissolved CD was adsorbed on silica or alumina. Therefore, in acetic acid, most of the CD is able to adsorb only on Pt metal itself and it is not wasted for covering the inert support. In practice this would mean that a much larger amount of CD is needed in toluene compared to acetic acid to have the maximum ee. Recently Bartók et al. [17] reported for ethyl pyruvate hydrogenation on Pt/Al_2O_3 that the dihydrocinchonidine-to-surface platinum ratio necessary for achieving the maximum enantioselectivity was strongly solvent-dependent, namely 0.007 in acetic acid and 0.12 in toluene, i.e., a 17-fold difference. This implies that about 17 times more dihydrocinchonidine was needed in toluene to obtain the maximum ee. A comparison of the CD adsorption results reveals (table 1) that a 20 times higher amount of CD is adsorbed on alumina from toluene than from acetic acid. Thus the results of this work are in good correlation with the hydrogenation results of Bartók et al. [17] indicating that much more CD is needed in toluene to cover the support surface. On the contrary, in acetic acid the dissolved CD is mainly adsorbed on Pt metal but not on the support material.

4. Conclusions

Continuous hydrogenation of EBF on Pt/Al_2O_3 in fixed bed was carried out with 93% ee of (*R*)-ethyl mandelate. No rate acceleration was visible in enantioselective hydrogenation compared to racemic hydrogenation in the absence of modifier. The CD adsorption measurements demonstrated that CD adsorption on alumina and silica in acidic media is negligible, but from toluene solutions one to two orders of magnitude higher amount of CD was adsorbed on both alumina and silica. The selection of the solvent influences considerably the performance of the system. In acetic acid, the steady-state enantioselectivity is obtained almost instantaneously, because CD adsorbs mainly on the catalyst particles, but not on the bed-diluting material. In toluene, however, considerable CD adsorption on the diluting material takes place, and therefore the attainment of steady-state enantioselectivity takes about 10 times longer time-on-stream.

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