ENANTIOSELECTIVE HYDROGENATION OF ETHYL PYRUVATE IN FLOW REACTOR OVER Pt-CD/SiO₂ CATALYSTS.

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ABSTRACT

The continuous enantioselective hydrogenation of ethyl pyruvate (EP) in a continuous flow reactor at 25°C on 1%Pt-CD/SiO₂ catalysts has been studied. The catalytic study included the analysis of variables such as: particle size, feed flow, H₂ pressure and the addition of chiral modifier to the reactor feed.

The catalysts were prepared using impregnation of Pt colloids which are stabilized with different quantities of cinchonidine (CD) on SiO₂. This process gives chiral properties to the catalyst and allows changing the particle size for the reaction of interest.

The catalysts were characterized by adsorption/desorption isotherms of N₂ at 77 K, TEM, XPS and the analysis of products by GC-MS. The monitoring of the reaction indicates a significant increase in the conversion when decreasing the contact time and a maximum in the enantiomeric excess (ee) of 63 % to the (R)-ethyl lactate which is obtained after using 200mg of 1%Pt/SiO₂ catalyst (1.6nm) at 10 bar of H₂ and a flow of 0.3 mL/min of a mixture EP (0.01M) and CD (0.034M) in cyclohexane.

Keywords: Continuous hydrogenation, Nanoparticles, Platinum, Ethyl Pyruvate, Cinchonidine.

INTRODUCTION

In the last few years fine chemical products obtained either selective hydrogenation or enantioselective hydrogenation to obtain chiral product has reached importance especially in the pharmaceutical industry¹⁻⁶. The heterogeneous catalysis starts to develop in this area when Orito and coworkers reported the enantioselective hydrogenation of ethyl pyruvate to (R)-lactate on modified Pt with cinchonidine with an ee >95%⁷. Since then, many researchers have focused their studies on optimizing these systems mainly for α, β-ketoesters and ketones hydrogenation⁸⁻¹⁰.

Usually, these reactions have been studied in *batch* reactors. The first researches that used heterogeneous catalysis in enantioselective synthesis in continuous reactors were done recently¹¹⁻¹⁹. The hydrogenation of citral²⁰, ethyl pyruvate²¹ and 1-phenyl-1,2-propanedione^{22,23} have been significant impact on the perfume and pharmacy industry.

Current researches have also shown that it is important the size of the metallic particle for the catalysts used in this kind of reactions²⁴, suggesting that metal particle size near to the 3 nm can produce ideal levels of ee, in studies carried out on metallic catalysts obtained by traditional methods. In this work colloidal Pt was synthesized by a chemical method which allows to control the metallic particle size by adding different quantities of a stabilizer (CD), this process avoids the excessive growth of the metallic agglomerates and it may increase the ee in the hydrogenation of ethyl pyruvate (Scheme 1).

Scheme 1. Enantioselective hydrogenation of ethyl pyruvate

EXPERIMENTAL

The Pt colloids were prepared by a similar procedure to the one used by Bönemann²⁴ in which 160 mL of an aqueous solution of H₂PtCl₆ (0.2460g, 0.6mmol, Aldrich) was refluxed at 100°C prior the addition of (-)-cinchonidine, CD (Aldrich) in 15 mL 0.1M de HCOOH (MERCK). Once the colloid was formed the dispersion was cooled down up to room temperature, and the colloid was washed with an aqueous solution of NaHCO₃ (200 mL, 100g/L) to eliminate the acidity.

The colloidal dispersion was impregnated on silica (BASF D-11-11, 142 (m²/g) by B.E.T and pore average diameter of 15.9 nm by B.J.H) in appropriate amount to obtain a Pt loading of 1.0wt. %. In order to obtain different metallic particle sizes the CD concentrations which were added in the colloid formation varies from 2,2 to 9,8 x 10⁻³ M^{25,26}. The 1%Pt-CD/SiO₂ catalysts were labeled

as marked (a), (b) and (c) corresponding to catalysts with Pt particle size of 3.4, 2.4 and 1.6 nm respectively (table 1).

Nitrogen adsorption isotherms at 77 K was carried out in a Micromeritics ASAP 2010 apparatus. TEM micrographs were obtained in a Jeol Model JEM-1200 EXII System and X-ray photoelectron spectra (XPS) were recorded using an Escalab 200R spectrometer provided with a hemispherical analyzer operated in a constant pass energy mode and Mg Kα X-ray radiation (hν = 1253.6 eV) operated at 10 mA and 12 kV.

The catalytic behavior was evaluated by studying the ethyl pyruvate hydrogenation (Aldrich) at 25 °C and the pressure was changed from 3 to 30 bar of H₂ (AGA) in a stainless steel continuous flow reactor (Scheme 2) with a feed of a mixture of EP (0.01M) in cyclohexane (MERCK) which varies from 0.3 to 1.5 mL/min. When the conditions were improved, it was added CD (0.034M) to the feed with a flow pump Lab Alliance Series I-110SFN01 and 200mg of (c) catalyst. The stainless steel reactor is 23 cm long and 10 mm internal diameter, the catalytic bed is located in the middle of the reactor, the volume left was filled with glass fiber. The analysis of reactants and products was followed by a GC-MS device (Shimadzu GCMS-QP5050), using a chiral β-dex 225, 30 m column (SUPELCO) and helium as carrier gas.

Scheme 2. Flow reaction system.

RESULTS AND DISCUSSION

Catalysts characterization

Transmission electronic microscopy (TEM)

The average metal particle size of colloidal platinum and Pt-CD/SiO₂ catalysts were evaluated by transmission electronic microscopy and the obtained results are compiled in Table 1. It can be seen that the crystal size decreases as the amount of CD increases, in agreement with results previously reported by Bönemann²⁴. This behavior is explained due to the fact that the CD has a stabilizer role in the colloid formation. For this reason an increase of

the amount of CD inhibits the growth of small metallic crystals. These results are explained through the interactions taking place from the unsaturation of the aromatic ring of the quinoline, the quinuclidinic nitrogen atom and, the stereogenic centre oxygen of the CD with the incomplete orbitals of the metal.

Although the obtained values for the Pt crystals in the dispersions and catalysts are similar for a given concentration of CD, the fact that the three cases are higher for the dispersion can be explained taking into account that the colloids are not thermodynamically stable and they could agglomerate in a small extent before observing them in the microscope. This phenomenon is more restricted when it is deposited in the support. Table 1 also shows the Pt dispersion in the catalysts; this dispersion is estimated taking into account the crystal size and assuming that the particles possess a cubic shape.

Table 1. Average metal particle size of Pt catalysts.

Added CD in the coll synthesis (M)	Particle diameter (nm)		Metallic dispersion for 1%Pt-CD/SiO ₂
	Colloidal Pt	1%Pt-CD/SiO ₂	
0,0022	3,7	3,4 (a)	0,25
0,0074	2,5	2,4 (b)	0,35
0,0098	1,7	1,6 (c)	0,53

X-ray photoelectron spectroscopy (XPS).

The catalysts were pretreated *in situ* with hydrogen at 120°C prior the analyses to remove a possible surface oxidation. The Si 2p of the support displays a binding energy of 103.4 eV whereas the Pt 4d_{5/2} presents a binding energy of 314.9 eV indicative of Pt is in a reduced state (Pt⁰)¹⁶. XPS revealed the presence of two types of N in a different chemical environment placed at 398.0 ± 0.1 eV (non-aromatic) and ~400 ± 0.1 eV (in aromatic ring) belonging to the N of the chiral inducer¹⁶. Additionally, the Pt/Si and Pt/CD surface ratios increases with the amount of CD in the preparation, in line with the previous explanation that the CD limits the growth of metallic crystals.

With regard to the Pt/Si and Pt/N surface atomic ratios of 1wt %Pt/SiO₂ catalysts (table 2) it can be observed that both increases in parallel with an enhancement in the amount of CD used in the synthesis of colloidal Pt. This fact can be explained considering that the addition of CD during the synthesis of the colloids, allow a stabilization of the metal nanoparticles avoiding the growth of them. Thus, the higher the CD concentration, the lower the metal particle size and consequently, the highest the Pt/Si and N/Si atomic surface ratios.

Table 2. Pt/Si and N/Si atomic surface ratios of 1%Pt-CD/SiO₂ catalysts

Catalyst	[CD] M	Pt/Si at	N/Si at
Pt-CD/SiO ₂ (c)	0.0098	0.0193	0.033
Pt-CD/SiO ₂ (b)	0.0074	0.0058	0.026
Pt-CD/SiO ₂ (a)	0.0022	0.0010	0.008

Enantioselective hydrogenation of ethyl pyruvate

The effect of some of the variables which can affect the enantioselectivity of the asymmetric hydrogenation of ethyl pyruvate (Scheme 1) were studied in a continuous flow reactor. Thus, when the catalysts were assayed at 25 °C, an H₂ pressure of 10 bar, 0.200 g of catalyst and EP concentration of 0.01 M in cyclohexane, the catalysts show conversion level which increases from 62 to 72% as Pt particle size decreases. With regard to the enantioselectivity, it was found a preferential formation of the (*R*)-ethyl lactate, being the enantiomeric excess, higher as lower is the Pt particle size, as can be seen in figure 1.

Figure 1. Evolution of the enantiomeric excess of (*R*)-ethyl lactate with time on stream of the different 1%Pt-CD/SiO₂ catalysts at 25°C, 10 bar de H₂ and 0.3 mL/min of EP 0.01M in cyclohexane

This result differs from previous studies in which it has been suggested that metal crystals closed to 3 nm are more appropriate for a higher chiral induction in this reaction^{10, 21}. The observed behavior can be explained on the basis of the difference in the type of metallic cluster. Thus, in the present study the metal crystals obtained from a colloid dispersion were stabilized by the chiral inducer, remaining a significant amount of CD remains linked to the metallic crystals, being higher the coverage of metallic sites as lower is the particle size. Conversely, in the previous studies performed in batch reactors the inducer was supplied with the substrate, and the induction take place in modified sites generated by adsorption of CD on the Pt sites. The decreases of the ee at higher reaction times observed in figure 1, may be attributed to a slight release of the inducer molecules. This phenomenon occurs in a lower extent in the catalyst with smaller metal particle size and may be assigned to a higher unsaturation displayed by the smaller crystals which allow a higher metal-inducer interaction. Additionally, catalytic results obtained on a Pt/SiO₂ system generated in absence of CD showed the formation of the racemic mixture confirming the crucial role of the chiral inducer in asymmetric hydrogenation.

The CD amount in the system strongly affects the level of induced enantioselectivity. Researches performed in batch reactors have reported that in similar reaction conditions the variation of the ee with the CD concentration present a bell type dependence. The ee increases with the CD concentration, they reach a maximum and then decreases. The initial increases is attributed to the coverage of the metallic centers leading to modified sites which are responsible of the chiral induction. The CD linked to the metallic centers increases with the concentration of CD used. Once an optimum coverage has been reached, further increases in surface coverage do not allow an appropriate adsorption of the modifier (planar adsorption) and therefore, both the activity and the enantioselectivity are negatively affected. It has also been suggested the possibility of formation of dimeric species of cinchonidine (CD)₂ which are not able to induce chirality. Taking into account the mentioned reasons, it was decided to add a small amount of CD to the reaction mixture.

Effect of pressure

The enantioselective hydrogenation of ethyl pyruvate was carried out at different pressures using 200 mg of the most selective catalyst found in previous tests; this catalyst (c) displays the lowest metal particle size among the studied catalysts. Figure 2 shows the variation of the enantiomeric excess of (*R*)-lactate at different hydrogen pressures in the range 3 to 30 bar. It was observed that the ee increases significantly (from 15 to 45%) when the pressure increases up to 10 bar, and then it remains constant at higher pressures. The conversion levels also increases from 62 to 72%. This behavior can be understood according to the Langmuir Hinshelwood mechanism. Even though there is an increase of the catalytic activity at higher pressures, it is assumed that at these pressures the H₂ that displaces the substrate or the CD from the active centers. The ee decreases at pressures higher than 20 bar, suggesting the CD displacement from the catalyst surface. Thus, in order to avoid this effect, in the following essays 10 bar was used as hydrogen pressure.

Figure 2. Effect of the H₂ pressure on the enantioselectivity at 25°C, EP Flow (0.01M)/C₆H₁₂: 0.3 mL/min and 200mg of Pt-CD/SiO₂ (c) catalyst.

Effect of reactants flow

The flow of reactants has also an important effect on the catalytic performance. In the present study flow of a 0.01 M ethyl pyruvate solution in cyclohexane ranging from 0.3 mL/min to 1.5 mL/min was used. The results indicate that as the flow increases, or the contact time decreases, there was an important reduction of the conversion level of the substrate and also

a decreases in the ee values to (*R*)-lactate as can be seen in figure 3. The observed decreases in the ee values with time on stream can be attributed to a slight lixiviation of the CD from the metallic crystals. In order to confirm this explanation, the reaction was also performed adding a fixed amount of CD to the reaction mixture, selecting the flow of 0.30 mL/min which was the one that led to the best conversions (~70%). The results revealed that the conversion was not affected by the presence of CD in the feed but the ee excess do not decreases with the time of stream. This may be considered as evidence that the chirally modified centers remain stable under these conditions. Additional studies on this subject suggest that the enantioselectivity can be improved by using other concentration values of modifier, similar to those results obtained in asymmetric hydrogenation reaction carried out in a type batch reactor.

Even though the obtained enantioselectivities are reasonable high for the used experimental conditions, recent researchers performed by Richards²⁷ and Murzin²⁸ have found much higher enantiomeric excess (higher than 80%) for the same reaction performed on Pt catalysts. In the former, the solvent was acetic acid, which is well known lead to higher ee values. In the latter, used a commercial Pt/alumina catalyst with a high metal loading (5 wt%) and toluene as solvent.

Figure 3. Effect of the flow of substrate on the enantioselectivity during ethyl pyruvate hydrogenation on Pt-CD/SiO₂ (a) catalyst. Variation of ee with time on stream (flow (0.01M) in cyclohexane at 25°C, 10 bar H₂ and 200mg of catalyst).

CONCLUSIONS

The results indicate that chiral modified metal supported catalysts can be obtained by the impregnation of a support with a metal colloid dispersion stabilized with a chiral inducer. The amount of modifier used in the synthesis affects both, the metal particle size and the catalytic behavior crystal size result. In a flow reactor it was found that the highest activity and enantioselectivity was displayed by the catalyst with lowest metal particle size which is attributed to a higher proportion of chirally modifies sites. Higher activity and enantioselectivity to the desired enantiomer was obtained using lower reactant flow, and stable ee values may be obtaining adding small amount of the chiral inducer to the flow of the reactants lead to significant increases in the activity and the catalytic behavior in flow reactors is affected by the substrate flow. The best results were reached at lower flows (high contact times) and, the enantioselectivity levels decreases slightly with the reaction time. The addition of CD to the feed mixture allows to get more stable conversion levels and enantiomeric excess.

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