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Experimental and theoretical investigation of the enantioselective hydrogenation of ethyl pyruvate with a Pt catalyst with new non-cinchona chiral modifiers

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ABSTRACT

The enantioselective hydrogenation of ethyl pyruvate using a Pt/SiO_2 catalyst modified with six different chiral modifiers was studied. The chiral modifiers chosen were: (*S*)-(+)-1-aminoindan, (*R*)-(−)-1-aminoindan, (1R,2S)-(+)-*cis*-1- amino-2-indanol, (1S,2R)-(−)-*cis*-1-amino-2-indanol, (*S*)-(+)-1-indanol and (*R*)-(−)-1-indanol.An excess of the (R) enantiomer of the product of 63% and 45% with (*S*)-(+)-1-aminoindan and (*R*)-(−)-1-aminoindan modifiers, respectively was obtained. When using (1S,2R)-(−)-*cis*-1-amino-2-indanol and (1R,2S)-(+)-*cis*-1-amino-2-indanol, the enantiomeric excess (*ee%*) obtained was 30% and 5%, respectively, while with both indanols *ee%* did not exceed 8%. Molecular modeling of the complex formed between the chiral modifier and ethyl pyruvate performed by DFT calculations allowed predicting the values of *ee%* obtained experimentally. The low *ee%* value obtained both aminoindanol chiral modifiers were used, could be explained by the analysis of non-covalent interactions (NCI) method. These calculations demonstrated the presence of an intramolecular hydrogen bond in the structure of these modifiers.

1. Introduction

The growing demand for enantiomerically pure compounds in the field of pharmaceutical and agrochemical industries has increased the importance of optically active compounds synthesis [1–3].

In this sense, asymmetric catalysis has become a challenging subject in the field of catalysis over the last years. One of the very interesting heterogeneous catalytic processes, named *"classical approach"*, is enantioselective hydrogenation using metallic catalysts modified with chiral compounds [4,5]. This methodology allowed the development of the most widely employed heterogeneous chiral catalysts: Ni catalyst modified with sodium tartrate/NaBr [6,7] and Pt(Pd) catalyst modified with alkaloids of the cinchona group used to hydrogenate α-ketoesters ([8] and references therein). The enantioselective hydrogenation of α-ketoesters constitutes a useful reaction at industrial level since the reaction products, α-hydroxyesters, are key intermediates in the synthesis of biologically active compounds [9]. Japanese researchers were the first ones to perform studies in the field of asymmetric catalysis using Pt/C catalysts modified with cinchonidine for the hydrogenation of ethyl pyruvate, obtaining high optical yields [10]. In the last three decades, these reactions have been studied for the enantioselective hydrogenation of a large number of α-ketoesters and α-diketones [11–16].

With respect to the nature of the chiral modifier, when analyzing the performance of Pt-based catalysts modified with cinchonidine, the effectiveness in obtaining a high enantiomeric excess is assigned to the structure of this modifier. Three factors are crucial: a group capable of anchoring the molecule onto the surface of the metallic catalyst, the presence of a basic nitrogen atom near the stereogenic center, and a chiral center [10].

There is clear evidence that cinchonidine adsorbs on the metal surface via the aromatic quinoline π-system [17–20] forming the chiral site. Methyl pyruvate, one of the most widely molecules used as substrate in hydrogenation reactions, adsorbs on these modified chiral sites either by the oxygen lone pairs [21,22] or the π-bonding of the C=O groups [23]. Hydrogen bond and donor–acceptor inter-

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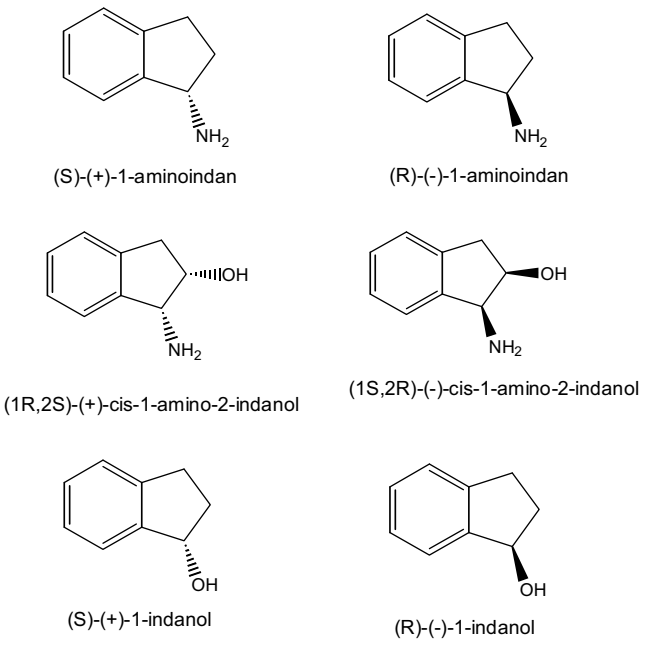

Scheme 1. Chemical structures of the chiral modifiers studied.

actions between the modifier and selected functional groups of the substrate molecule control the adsorption mode of methyl pyruvate and facilitate the addition of hydrogen, thereby increasing the reactivity [24,25].The formation of a complex between the modifier and the substrate in a 1:1 stoichiometry is a key feature in this mechanism [26]. In this sense, many studies have been carried out aiming at understanding the role of the chiral modifier structure in the mechanism of Orito's reaction. Tálas and Margitfalvi have written a very complete review article, in which they describe the behavior of natural alkaloids, their synthetic derivatives and analogues as chiral templates in the heterogeneous catalytic asymmetric hydrogenation of activated ketones [27]. The authors demonstrated that different types of activated ketones could be successfully hydrogenated by use of different chiral templates, being cinchonidine the most usable chiral modifier for the asymmetric hydrogenation of a wide variety of activated ketones. Kukula et al. also studied the structural effects in the chiral base employed in the Pd-induced enantioselective deprotection–decarboxylation of β-ketoesters. Various chiral amines and amino alcohols were tested in the reaction, achieving enantioselectivities up to 60% quinine and quinidine [28].

In this work, the enantioselective hydrogenation of ethyl pyruvate using a Pt/SiO_2 catalyst modified with (*S*)-(+)-1-aminoindan, (*R*)-(−)-1-aminoindan, (1R,2S)-(+)-*cis*-1-amino-2-indanol and (1S,2R)-(−)-*cis*-1-amino-2-indanol was studied. The chosen modifiers are simpler and more rigid than cinchonidine, but still present its main structural features. (*S*)-(+)-1-indanol and (*R*)-(−)-1-indanol were also selected as chiral modifiers. All the modifiers employed are represented in Scheme 1. The interaction between the modifiers and the ethyl pyruvate molecule was also modeled using tools from the density functional theory (DFT).

2. Experimental and computational methods

2.1. Catalyst preparation and modification

The monometallic catalyst, Pt/SiO_2, was prepared by ion exchange, using SiO_2 as support (Aerosil Degussa 180 $m^2\,g^{-1}$), previously treated with $NH_4OH_{(aq)}$. The solid obtained was reduced and modified with (*S*)-(+)-1-aminoindan, (*R*)-(−)-1-aminoindan, (1R,2S)-(+)-*cis*-1-amino-2-indanol, (1S,2R)-(−)-*cis*-1-amino-2-indanol, (*S*)-(+)-1-indanol and (*R*)-(−)-1-indanol (Aldrich), according to the previously published procedure [29].

2.2. Catalyst characterization

The platinum content was determined with the aid of an atomic emission spectrometer Perkin Elmer AAnalyst 100 after dissolving the solid. The distribution of metallic particle size was determined by transmission electron microscopy (TEM) using a JEOL 100 CX instrument. To estimate the mean particle size, the particles were considered spherical, and the second moment of the distribution was employed. The expression used for the calculation was:

$$d = \frac{\sum n_i d_i^3}{\sum n_i d_i^2}$$

where n_i is the number of particles with d_i size. Temperature-programmed reduction (TPR) tests were carried out in a conventional reactor with a feeding flow of 20 $cm^3\,min^{-1}$ (10% H_2 in N_2) at a heating rate of 10 K min^{-1}, from room temperature to 1073 K. H_2 consumption during reduction was analyzed on line with a Shimadzu GC-8A gas chromatograph with a thermal conductivity detector (TCD).

2.3. Hydrogenation reactions

The hydrogenation reaction of 1 mL ethyl pyruvate (Aldrich) (Fig. 1) was performed in an autoclave type reactor (Autoclave Engineers), at 1.0 MPa H_2 pressure and at a temperature of 273 K, using 0.25 g catalyst and 60 mL of 2-propanol as solvent.

The reaction advance was followed by gas chromatography in a Varian GC 3800 chromatograph equipped with a capillary column (CP–Chirasil–Dex CB) and a FID detector. The only reaction products obtained, (R) and (*S*)-ethyl lactate, were completely separated under the analysis conditions used. The enantiomeric excess (*ee%*) was calculated using the following expression:

$$ee\% = \frac{([R] - [S])}{([R] + [S])} \times 100 \quad (1)$$

where [R] and [S] are the concentrations of the *R* and *S* enantiomers, respectively.

2.4. Theoretical calculations

The proton affinity (PA) of the chiral modifiers was calculated as:

$$Modifier + H^+ \rightarrow \left(Modifier - H^+\right) \quad (2)$$

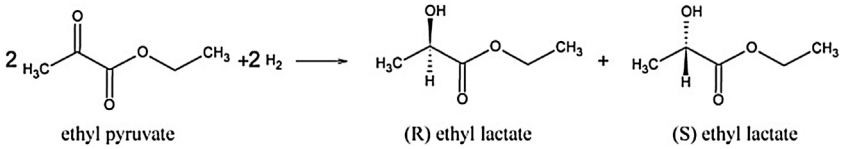

Fig. 1. Enantioselective hydrogenation of ethyl pyruvate to (R) and (*S*)-ethyl lactate.