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Unexpected change of the sense of the enantioselective hydrogenation of ethyl pyruvate catalyzed by a Pt–alumina-cinchona alkaloid system

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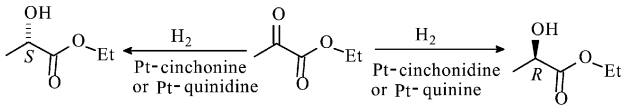
In the enantioselective hydrogenation of ethyl pyruvate (EtPy) over β-isocinchonine (β-ICN) modified Pt–alumina catalysts, the major enantiomer was (*R*)-ethyl lactate ((*R*)-EtLt (ee 50%)) in toluene, while in AcOH (*S*)-EtLt (ee 60%) was formed; the (*R*) configuration is opposite to what is expected from the absolute configuration of the cinchonine backbone.

Despite its twenty-two year old history,[1] the research activity in the asymmetric hydrogenation of activated ketones over cinchona-alkaloid-modified platinum catalysts still increases.[2–4] A model compound of the most wide-ranging studies is ethyl pyruvate (EtPy), which can be converted to (*R*)- and (*S*)-ethyl lactate (EtLt) with an extremely high enantioselectivity (96–97%).



Besides improving the cinchonidine (CD)–platinum catalyst system, extensive efforts have been made in developing a reliable mechanistic interpretation. The most important parameters for the efficiency of the Pt–cinchona system are: i) the structure and concentration of the modifier, ii) the platinum particle size, morphology and support, and iii) the solvent. According to systematic studies[3–5] three structural elements are crucial for the functioning of the cinchona alkaloids as chiral modifiers: (i) an anchoring part, represented by the flat extended aromatic ring system, (ii) the absolute configuration at C(8) which controls the sense of chirality, (iii) a basic nitrogen which is able to interact with EtPy resulting in 1 : 1 interaction.

Numerous mechanistic details, among others the conformation of cinchona alkaloids and other modifiers[5–7] and the structure of the intermediate responsible for chirality[3–5,8–10] have been described. There is no consensus concerning the structure of the intermediate (CD–pyruvate 1 : 1 complex) responsible for chiral induction. For this reason different structural elements of cinchonas were studied.[5] The modifiers derived from CD and quinine (Q) lead to an excess of (*R*)-ethyl lactate (EtLt) whereas cinchonine (CN) and quinidine (QD) derivatives preferentially lead to the *S* enantiomer.

According to the evidence supplied by NMR and XRD studies on parent cinchona alkaloids as well as molecular mechanical calculations,[6,7] the alkaloids are present predominantly in the so-called anti-open (open 3) conformation in solution. Indirect experimental results and calculations[3–5] suggest that the conformation of cinchona alkaloids on the surface of the catalyst is also anti-open. Our earlier results[10,11] support this finding too, since isocinchona alkaloids with rigid structures exist only in the open conformation[12,13] (Fig. 1).

This manuscript contains new experimental results concerning the effect of the structure of cinchona alkaloid modifiers on enantioselectivity. Hydrogenation of EtPy was performed in an atmospheric batch reactor at room temperature (298 K). The catalytic system including Engelhard 4759 catalyst (E 4759: 25 mg) and 2 mL of solvent was purged three times with hydrogen and after prehydrogenation (30 min), the calculated amount of modifier and 0.12 mL of EtPy were introduced and stirred (1200 rpm) in the presence of hydrogen for the required reaction time (usually 10–50 min). The product was identified by GC and the enantiomeric excess [ee% = ([*R*] − [*S*]) × 100/([*S*] + [*R*])] was monitored by GC (HP 5890 GC-FID, 30 m long Cyclodex-B capillary column, uncertainty ±2%). α-ICN and β-ICN were synthesized according to the literature.[14] The crude product was purified by column chromatography. According to HPLC and ESI-MS, the purity of both products was 100%. The ^{1}H NMR and ^{13}C NMR spectra were identical to the literature data.[12,13]

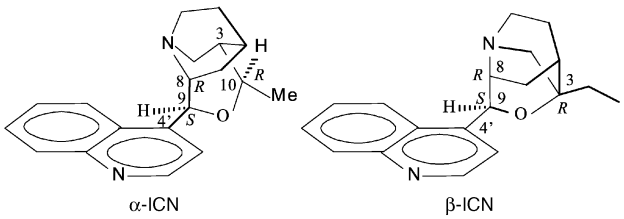


Fig. 1 Structures and stereogenic centers of α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN).

According to Blaser *et al*.[5] the absolute configuration at C(8) of the quinuclidine controls the absolute configuration of the product. In spite of the fact that systems composed of Pd–EtPy-CN[15] and Pt–EtPy–cinchona alkaloids with large substituents[5] show slightly different behavior, the above conclusion was unchanged. After such preliminaries our new experimental results, shown in Fig. 2 appeared to be surprising.

Our experimental data can be summarized as follows: (i) in the presence of β-ICN and AcOH an excess of (*S*)-EtLt was formed as expected, whereas in toluene, surprisingly, (*R*)-EtLt was produced (ee = 50%); (ii) by increasing the conversion the absolute configuration of EtLt did not change either in toluene or AcOH, there is always *R* and *S*; (iii) there is a linear

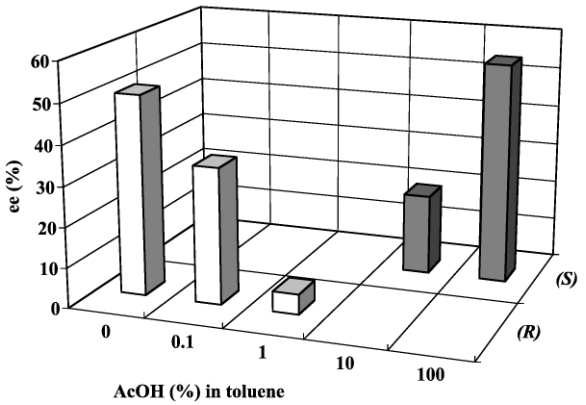


Fig. 2 Hydrogenation of EtPy to (*R*)- and (*S*)-EtLt on β-ICN modified platinum in toluene and AcOH mixtures (25 mg E 4759, 0.1 mM L^{-1} β-ICN, 1 bar H_2, 2 mL solvents, 0.12 mL EtPy, 296 K, 1200 rpm, conversion: 100%, time of hydrogenation: 25 min, for abbreviations, see Fig. 1): change of absolute configuration of EtLt.

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correlation between the composition of the solvent (AcOH + toluene) and the sense of chiral induction; (iv) hydrogenation at β-ICN concentrations higher than 0.01 mM L^{-1} is significantly faster as compared to racemic hydrogenation; (v) according to ESI-MS measurements, enantioselectivity is due to the presence of β-ICN ($[M + H]^+ = 295$) since this compound was proven to be stable under the conditions of hydrogenation at a hydrogen pressure of 1 bar; (vi) the β-ICN is stable heating it at 373 K in AcOH; (vii) another argument supporting the role of β-ICN is that if minimal amounts of dihydrocinchonine were formed in the course of the hydrogenolysis of the six-membered cyclic ether, (*S*)-EtLt should be produced (the formation of dihydrocinchonidine from β-ICN may be excluded).

In our earlier experiments with β-ICN,[16] typical ee values were a few percent in toluene (at 0.01 mM L^{-1}, ee was 2%, same as the margin of error), which is most probably due to impurities present in the β-ICN preparation (the purity of the starting material was only 97%).

In order to adequately interpret these results, several questions need to be answered. Why does β-ICN induce an ee opposite to the one induced by α-ICN, a compound with a nearly identical structure? What is the explanation for the so far unknown solvent effect, *i.e.* why does β-ICN induce the formation of (*S*)-EtLt in AcOH and that of (*R*)-EtLt in toluene? Some structural factors to be taken into consideration for the interpretation of the sense of enantioselection are: the conformation of the cinchona alkaloid present and other stereochemical factors, the configuration of chiral centers and their distance from the site binding the reactant, the proximity of the chiral centers to the surface.

Unlike CN, α-ICN and β-ICN have a rigid structure because the quinuclidine part cannot rotate around the C(8)–C(9) bond (Fig. 1). The oxazatwistane structure in β-ICN is more rigid than α-ICN, in which a certain extent of conformational movement is possible due to the homotwistane structure.[12,13]

Experimental evidence obtained to date demonstrates that the sense of induction is controlled by the absolute configuration at C(8),[3,5] in other words, the configuration of the EtLt produced is opposite to the configuration at C(8) of the modifier. On this basis the most important chiral center may be the one closest to the center binding the reactant (*i.e.* in the α-position relative to N). This really is the case for α-ICN, whereas in the case of β-ICN the configuration of the EtLt product formed is identical with that at C(8). Presumably, the reason why the sense of enantioselection is reversed with β-ICN is that C(3) induces an opposite chirality as compared to C(8), positioned opposite to C(3); furthermore, the fact that C(3) is closer to the surface than C(8) may also be of importance.

On the basis of the literature[2–4] we can assume that the mechanistic interpretation of the enantiodifferentiation is similar using different cinchona alkaloids. Since their structure is basically the same except for the absolute configurations in the stereogenic region, there is no reason to distinguish concerning adsorption properties and complex formation with the ligand (EtPy).

The quinuclidine nitrogen of β-ICN acts either as a nucleophile or as an electrophile (upon protonation) to interact with the α-carbonyl group of the EtPy. Consequently, the structure of the intermediate responsible for chiral induction depends on the solvent applied (AcOH, toluene). The proposed structures of 1 : 1 β-ICN–EtPy intermediate complexes in AcOH and in toluene are shown in ref. 16 and Fig. 3. In AcOH, β-ICN participates in the formation of the 1 : 1 complex as a protonated electrophile, whereas in toluene it binds EtPy as a nucleophile,[17] like in the intermediate complex in Fig. 3.

An unexpected change was observed in the sense of chiral induction in a study on the hydrogenation of EtPy on Pt catalyst modified with β-ICN. The most important result of the manuscript is the experimental verification of a linear relationship between the composition of the solvent mixture (AcOH + toluene) and the production of (*S*)-EtLt–(*R*)-EtLt. A change in solvent composition probably alters the structure of the intermediate responsible for chiral induction. This is the first significant experimental observation indicating that in enantioselective hydrogenation initiated by cinchona alkaloids, it is not the C(8) chiral center of the alkaloid that controls the sense of chiral induction. Since β-ICN exists only in anti-open (open 3) conformation these new data provide additional experimental evidence to support the basic mechanistic model suggested by Baiker, Pfaltz and Wells.

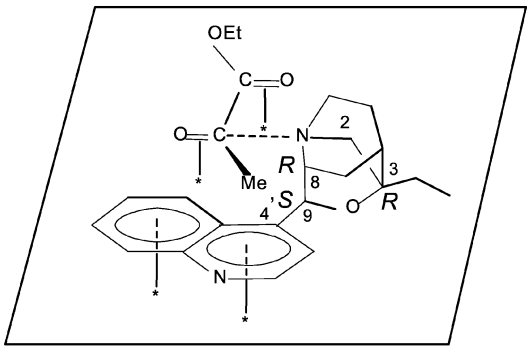

Fig. 3 The proposed structure of the adsorbed 1 : 1 complex between β-ICN and EtPy in toluene.

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