

New data on enantiomeric excess versus conversion during enantioselective hydrogenation of activated ketones on a platinum catalyst

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Abstract

The initial transient period (ITP) was studied in the enantioselective hydrogenation of activated ketones (ethyl pyruvate, pyruvaldehyde dimethyl acetal, methyl benzoyl formate) on Pt-alumina (E4759) catalyst modified by cinchonidine (CD) or dihydrocinchonidine (DHCD) under mild experimental conditions in toluene (hydrogen pressure: 1 bar, temperature: 253–298 K, modifier concentration: 0.001–1 mmol/L). The effects of temperature, modifier concentration, different pretreatments of the catalyst, and structure of the reactants on the relationship of the enantiomeric excess (ee) and conversion were studied. Our results suggest that the ITP is affected not only by impurities/contaminants present in the catalytic system but also by the competitive adsorption of reactants, modifier, and solvent. Consequently it may not be excluded that the ITP can be considered an intrinsic feature of this type of enantioselective hydrogenation reaction.

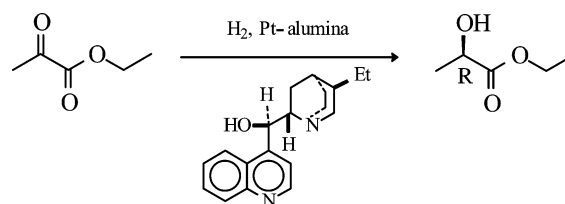
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Keywords: Hydrogenation; Enantioselective; Pt-alumina; Cinchonidine; Activated ketones; Enantiomeric excess versus conversion; Initial transient period

1. Introduction

The theoretical and practical importance of the heterogeneous catalytic enantioselective hydrogenation of activated ketones has been demonstrated by widely known experimental results. These results have been summarized and reviewed continuously: the first detailed overview was published in 1997 [1] and the most recent one in 2003 [2]. The most extensively studied reaction is the hydrogenation of ethyl pyruvate (EtPy) to ethyl lactate (EtLt) on Pt-alumina catalyst modified by cinchona alkaloids (Scheme 1).

Despite the diverse research done over the years in this field, numerous tasks await solution before satisfactory answers can be given to the questions that have arisen. One such problem is the reason for the rapid increase in enantioselectivity (ee) in the initial transient period (ITP) of the conversion. Details of previous studies in this field (Table 1 [3–17]) are reviewed in the Discussion of the present work.



Scheme 1.

Experimental data prove that in the course of the hydrogenation of EtPy, maximal ee can be attained only after a certain extent of conversion, i.e., in the initial period ee is low. The following statements were made about this phenomenon in the two reviews cited above [1,2]: “At the moment it is not clear why the catalyst is less selective at the very beginning of the reaction” (1997) and “maximum enantioselectivity and rate are reached only after a certain period of time. Despite a spirited debate, the reasons for this effect are still controversial” (2003).

It was established at an early stage of research that the efficiency of chiral hydrogenation is significantly affected not only by the experimental parameters, which play a decisive role, but also by the methods of execution [6–21]. In general, four different methods and their variants [1,2] have

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Table 1

Published experimental data on enantiomeric excess versus conversion during enantioselective hydrogenation of EtPy on Pt-alumina catalysts

| Entry | Substrate (S) | Modifier (M) | Solvent | Temp. (K) | H ₂ pressure (bar) | ee _{max} | Pt _s /M | S/M | Conclusion ^a | Ref. |
|-------|--------------------------|--------------|---------------------------------|-----------|-------------------------------|-------------------|--------------------|--------|-------------------------|--------|
| 1 | EtPy | CD | EtOH | 343 | 20 | 77 | 100 | 1210 | A | [3] |
| 2 | EtPBA | DHCD | Tol. | 363 | 20 | 85 | 380 | 3500 | A | [3] |
| 3 | MePy | DHCD | MeOH | 343 | 20 | 77 | 100 | 400 | A | [3] |
| 4 | MePy ^b | CD | EtOH | 293 | 10 | 77 | 30 | 77 | E | [4] |
| 5 | EtPy | CD, DHCD | EtOH | 296 | 70 | 80 | 34 | 400 | E | [5] |
| 6 | MePy ^b | DHCD | EtOH | 293 | 10 | 60 | 15 | 77 | A | [6] |
| 7 | EtPy | CD | EtOH | 343 | 70 | 73 | 100 | 5880 | C | [7] |
| 8 | EtPy | DHCD | Tol. | 293 | 20 | 85 | 1000 | 15,200 | E | [8] |
| 9 | EtPy | DHCD | EtOH | 293 | 20 | 75 | 1000 | 15,200 | E | [8] |
| 10 | EtPy | DHCD | PrOH | 263–323 | 5 | 60 | 800 | 2900 | C | [9,10] |
| 11 | EtPy ^c | DHCD | MA | 298 | 1, 10 | 58 | 300 | 380 | E | [11] |
| 12 | EtPy | CD | Tol., EtOH | 296 | 50 | 76 | 43 | 5000 | C | [12] |
| 13 | EtPy | CD | AcOH, EtOH | 295 | 1 | 80 | 480 | 1800 | B | [13] |
| 14 | TFAP | CD | DCB | 295 | 1 | 50 | 620 | 770 | B | [13] |
| 15 | EtPy | DHCD | Tol. | 293 | 100 | 84 | 230 | 6700 | E | [14] |
| 16 | EtPy | CD | PrOH | 283 | 7 | 60 | 130 | 10,000 | C | [15] |
| 17 | No new experimental data | | | | | | | | B,D | [16] |
| 18 | EtPy | CD | CH ₂ Cl ₂ | 293 | 50 | 80 | 2050 | 8000 | E | [17] |

Abbreviation used: MePy, methyl pyruvate; EtPy, ethyl pyruvate; TFAP, trifluoroacetophenone; EtPBA, 2-oxo-4-phenylbutyric acid ethyl ester; DCB, 1,2-dichlorobenzene; MA, methyl acetate; CD, cinchonidine; DHCD, dihydrocinchonidine.

^a (A) ITP was not observed. (B) Emphasize role of impurities/contaminants. (C) Intrinsic feature of catalytic system is stressed. (D) Results of several superimposed effects. (E) There is no definite conclusion.

^b EuPt1.

^c Pt-silica.

been adopted for performing liquid-phase chiral hydrogenation:

- (i) The catalyst is previously modified with the cinchona in the appropriate solvent;
- (ii) All the necessary reaction components (catalyst, solvent, modifier, reactant) are added to the reactor and hydrogenation is started after setting the appropriate hydrogen pressure and temperature;
- (iii) The reaction is performed in fixed-bed reactors with continuous feeding of reactant stream with and without modifier;
- (iv) To the mixture of the catalyst and solvent present in the reactor, a solution of the modifier is introduced in the presence of hydrogen under constant stirring, and a solution of the material to be hydrogenated is next added within a very short time (a few minutes).

In the case of academic research, the last of these methods has proven to be the most practicable. The measurements described in this article also followed this method (see Section 2).

The majority of the experiments addressing ITP were conducted at hydrogen pressures exceeding 1 bar in various solvents (Table 1), whereas those described in this article were carried out at 1 bar hydrogen pressure in toluene. Here we present our new results concerning the hydrogenation of mainly EtPy and also pyruvaldehyde dimethyl acetal (PADA) and methyl benzoylformate (MBF) on Pt-alumina (E4759) catalyst modified by CD or DHCD.

2. Experimental

2.1. Materials

Cinchonidine (CD), toluene, EtPy, and PADA were purchased from Fluka, and EtPy and MBF from Aldrich. EtPy (Fluka), PADA, and MBF were distilled before use and were 98% pure. In the case of EtPy the impurities are ~ 1% racemic EtLt, and ~ 1% unknown. EtPy distilled on a Vigreux column was used in the majority of the experiments. At later stages of the work, measurements were also made with EtPy purchased from Aldrich and distilled before use to a purity of 99.9% (0.1% EtOH). As evidenced by GC and HPLC analysis, this EtPy contained no EtLt.

The impurities in CD as determined by HPLC are 1.1% quinine and 2.6% quinidine. DHCD was prepared by hydrogenation of CD (Pd/C, 1 N H₂SO₄/H₂O, 1 bar, 298 K) and used after crystallization. A 1 mmol/L DHCD solution was prepared in toluene and the required volume was added to the reactor. (The 1 mmol/L DHCD solution contained ~ 1% AcOH, because the solubility of DHCD in toluene is limited.) Because of the good solubility of CD in toluene, solutions containing 1 mmol/L CD can be made up without difficulty.

Based on data in the literature [1], among several catalysts the one most often used is Engelhard 4759 (E4759). E4759 was pretreated before use in a fixed-bed reactor by flushing with 30 mL min⁻¹ helium at 300–680 K for 30 min and 30 mL min⁻¹ hydrogen at 680 K for 100 min. After being cooled to room temperature in hydrogen, the catalyst was

flushed with helium for 30 min and stored under air before use.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric batch glass reactor with a volume of 10 mL [22]. The agitator speed was 1200 rpm to avoid the diffusion range. The catalytic system including catalyst and 2 or 5 mL toluene was purged three times with hydrogen, and after re-reduction (30 min), the calculated amount of modifier, and after 1 min 0.1 mL of reactants, was introduced and stirred in the presence of hydrogen for the required reaction time. Standard conditions and standard abbreviations are: 25 mg E4759, 2 or 5 mL solvent, 1 bar hydrogen, 297–298 K, 1200 rpm, 0.1 mL reactant, ee = cumulative enantiomeric excess, Δee (dashed lines) = actual ee. The quantification of conversion and ee is based on GC data [22]. The actual (or incremental) ee was calculated as $\Delta ee = (ee_2 y_2 - ee_1 y_1) / (y_2 - y_1)$, where y = the yield to EtLt, index 2 = sample subsequent to sample 1. The measurements were reproduced several times (an effect was accepted as significant only after several convincing reproductions).

In the case of pretreatment in helium, the following changes were made. After re-reduction, the catalytic system (i.e., catalyst + toluene) was purged without mixing twice with helium (99.996%, < 5 ppm oxygen) and after mixing in helium (4 min) the calculated amount of modifier was introduced and the system was stirred in the presence of helium (1 min). The catalytic system was next purged with hydrogen three times without stirring, 0.1 mL of reactant was added, and the system was stirred in the presence of hydrogen for the required reaction time.

ESI-MS and ESI-MS/MS measurements were as described in an earlier publication [22].

3. Results and discussion

The first experimental observations regarding the relationship between ee and conversion in the hydrogenation of EtPy were published by Blaser and co-workers in 1989 [3]. As these authors had not studied the conversion range 0–20%, they could not observe any changes. The phenomenon was later investigated by several research groups and diverse conclusions were drawn depending on the experimental conditions (Table 1). After reviewing the experimental results and completing various novel experiments, Blackmond and co-workers [9,10] and Margitfalvi et al. [12], on the one hand, and Baiker and co-workers [13] on the other, proposed explanations for the ITP. According to the former authors [9,10,12], a change in ee versus conversion is an intrinsic feature of the catalytic system, whereas in the opinion of the latter authors [13], the phenomenon is caused mainly by impurities. Publication of the different interpretations was

followed by a dispute [15,16]; however, it has not been decided to date [17] whether the initial increase in ee with conversion is a “reaction-driven” phenomenon or is due to the presence of impurities in the system.

Consequently it seemed promising to initiate serial measurements under well-defined mild experimental conditions (as this complicated system behaves with extreme sensitivity, even to nearly imperceptible changes in experimental conditions). In general, it is not easy to participate in a debate and to take sides. It is new experimental data that inspire the formulation of a clearly defined opinion. In fact, it is the recently published statement of Studer et al. cited above [2] that encourages scientists in this field to publish their observations, even though there has been little progress in interpreting their results.

Variable parameters in our experiments were: catalyst pretreatment, the method of introducing the reaction partners, the temperature of hydrogenation, the concentrations of CD and DHCD, the purity of EtPy, modifications in hydrogenation conditions and the structures of activated ketones (different reactants). We tried to set up experimental conditions that minimize the role of impurities (toluene as selected solvent, various pretreatments, fresh catalyst, addition of reactant to reaction mixture as the last component, use of EtPy free of EtLt).

3.1. Enantioselective hydrogenation of EtPy: effect of temperature and DHCD concentration on the relationship between ee and conversion

To study the ITP, of the two solvents (toluene, AcOH) ensuring the highest ee (90–97%) in EtPy hydrogenation, the practical choice was toluene because, on the one hand, the ITP was less observable in AcOH [13] and, on the other hand, our studies have suggested [23] that there is a far larger difference between the hydrogenation mechanisms in the two solvents than was initially supposed [1,2]. Toluene was also expected to serve as a more favorable solvent for these studies because it allows experiments on the ee/conversion relationship under milder conditions (in AcOH, the mixture freezes by 280–285 K, AcOH reacts with alumina). At a hydrogen pressure of 1 bar the reaction proceeds so fast that the stage of 0–10% conversion is hardly measurable. Considering that ee is strongly dependent on the rate of hydrogen transport [9,13], conditions and measurement techniques excluding the effect of mass transport processes on changes in ee must be selected.

Earlier investigations have already demonstrated the effect of stirring rate, DHCD concentration, and solvent volume on conversion, which has been known to be closely correlated with ee [24]: “a linear relationship should exist between the observed ee and the reciprocal observed rate.” According to our preliminary experiments, measurements within the kinetic range may be carried out under the following experimental conditions: E4759 25 mg, hydrogen 1 bar, [DHCD] 0.001–0.1 mmol/L, EtPy ~ 1 mM,

Table 2
Experimental data on enantioselective hydrogenation of EtPy on Pt-alumina catalyst^a

| Entry | Modifier (mmol/L) | Temp. (K) | Pretreatment | Time (min) | Conv. (%) | Rate | ee (%) |
|-------|-------------------|-----------|------------------------|------------|-----------|------|--------|
| 1 | 0.01 | 298 | Hydrogen + DHCD 0 min | 16 | 99 | 3.6 | 66 |
| 2 | 0.01 | 298 | Hydrogen + DHCD 10 min | 20 | 99 | 3 | 40 |
| 3 | 0.01 | 298 | Hydrogen + DHCD 30 min | 25 | 99 | 2.4 | 31 |
| 4 | 0.01 | 298 | Hydrogen + DHCD 60 min | 25 | 98 | 2.4 | 24 |
| 5 | 0.001 | 298 | Hydrogen | 20 | 98 | 3 | 9 |
| 6 | 0.001 | 273 | Hydrogen | 50 | 97 | 1.2 | 18 |
| 7 | 0.001 | 263 | Hydrogen | 60 | 51 | 0.4 | 28 |
| 8 | 0.1 | 263 | Hydrogen | 30 | 98 | 1.8 | 85 |
| 9 | 0.01 | 263 | Hydrogen | 31 | 97 | 1.6 | 86 |
| 10 | 0.01 | 253 | Hydrogen | 75 | 100 | 0.5 | 86 |
| 11 | 0.001 | 263 | Hydrogen | 60 | 51 | 0.4 | 29 |

^a Standard conditions, 5 mL toluene, Entries 1–4: 2 mL toluene, EtPy 98% purity, rate: mmol/(min g).

263–298 K, toluene 5 mL, mixing efficiency level 7–9 (level 9 = 1300 min⁻¹). In this case ([DHCD] = 0.01 mmol/L, Pt_s/DHCD = 35 and EtPy/DHCD = 20000.

Before discussion of the results it is necessary to mention that in studies on the reaction mechanism it was found that the modifier is also converted in the course of hydrogenation [21,25–28], in the presence of EtPy, however, this hydrogenation can be suppressed. The slowdown of hydrogenation and the decrease in ee as a function of the duration of catalyst pretreatment in the presence of DHCD are well demonstrated in Table 2 (entries 1–4).

To our best knowledge, the relationship between ee and conversion has been studied mainly in alcohols, at relatively high pressures and within a narrow range of modifier concentrations (Table 1). Studies have also been conducted in toluene and recently in dichloromethane; even in this case, however, conditions were quite severe (relatively high modifier concentration, temperatures: room temperature and above, hydrogen pressures of 20–100 bar). We have found no published results obtained under mild experimental conditions (modifier concentrations 0.001–0.1 mmol/L, hydrogen pressure 1 bar, room temperature and below). Because of the high hydrogenation rate, in some measurements the concentration of DHCD was kept low (0.001 mmol/L) to study the relationship between ee and conversion. According to the evidence presented in Table 2 (entries 5–11) and Figs. 1 and 2, the ITP depends both on the temperature and on the initial concentration of DHCD, namely, the lower the initial concentration of DHCD, the more pronounced the increase in ee. This is especially well shown by the change in Δee.

The data in Table 2 illustrate the well-known fact that the reaction rate increases with increasing temperature. Fig. 1 not only verifies the existence of the ITP, but also demonstrates that, in the case of hydrogenation in toluene at a DHCD concentration of 0.001 mmol/L, ee and Δee also increase continuously above 20% conversion, except for hydrogenation at 296 K. At 296 K, over ~10% conversion (time of reaction is 2–3 min) Δee decreases, probably because—due to hydrogenation of the quinoline skeleton of DHCD [21,25–28]; the concentration of DHCD responsi-

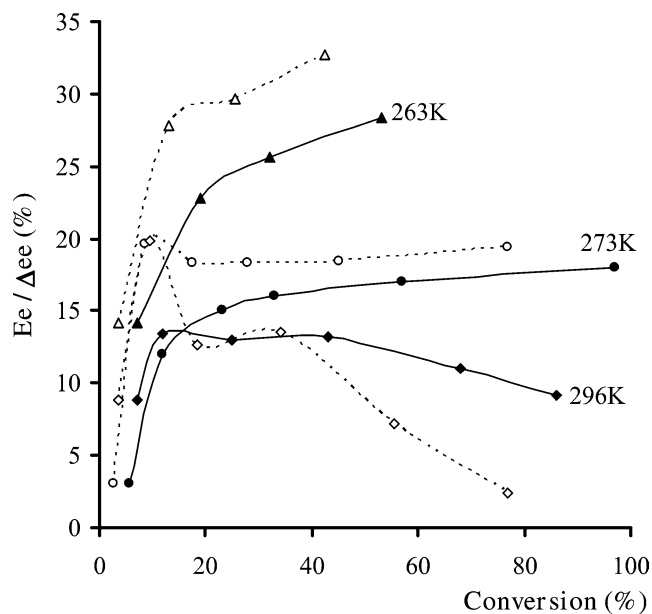


Fig. 1. Enantioselective hydrogenation of EtPy (98% purity): effect of temperature and conversion on ee and Δee (dashed lines). Standard conditions, [DHCD] = 0.001 mmol/L, toluene = 5 mL.

ble for enantioselection also decreases (Fig. 1). The same is shown by the data in Fig. 2. The data obtained at 253 K using EtPy of 99.9% purity are especially noteworthy. At this temperature, 100% conversion can be attained only in 75 min. Despite this, ee and Δee did not decrease, because hydrogenation of the quinoline skeleton does not take place at 253 K. Within the ITP, the change in Δee is somewhat faster in the case of 98% EtPy than when EtPy of 99.9% purity is used.

Changes in the composition of the hydrogenated cinchona derivatives desorbed from the catalyst are summarized in Table 3. The relative abundances of hydrogenated cinchonas increase with increasing conversion of EtPy. Because the adsorption strength of hydrogenated cinchonas is considerably lower than that of DHCD, they are easily desorbed at high DHCD concentrations, whereas at low DHCD concentrations (below 0.01 mmol/L) Δee will decrease, be-

Table 3
Relative abundances of $[M + H]^+$ ions in the ESI mass spectra of cinchonas formed from DHCD in the enantioselective hydrogenation of EtPy^a

| DHCD (mmol/L) | Time (min) | Conv. (%) | m/z values (relative peak intensity, %) | | | | ee (%) |
|------------------|---------------|--------------|---|---------------|---------------|---------------|--------|
| | | | $[296 + H]^+$ | $[298 + H]^+$ | $[300 + H]^+$ | $[306 + H]^+$ | |
| 0.001 | 15 | 30 | 100 | — | — | — | 14 |
| 0.001 | 30 | 60 | 100 | — | — | — | 10 |
| 0.01 | 10 | 43 | 43 | 37 | 100 | — | 52 |
| 0.1 | 9 | 77 | 47 | 100 | 18 | — | 79 |
| 0.1 | 15 | 99 | 8 | 100 | 35 | 28 | 79 |
| 1 | 10 | 65 | 100 | 24 | 34 | — | 79 |
| 1 | 25 | 100 | 100 | 40 | 70 | — | 69 |

^a Standard conditions, 2 mL toluene. $m/z = 296$ (DHCD: dihydrocinchonidine). $m/z = 298$ (THCD: tetrahydrocinchonidine). $m/z = 300$ (HHCD: hexahydrocinchonidine). $m/z = 306$ (DDHCD: dodecahydrocinchonidine).

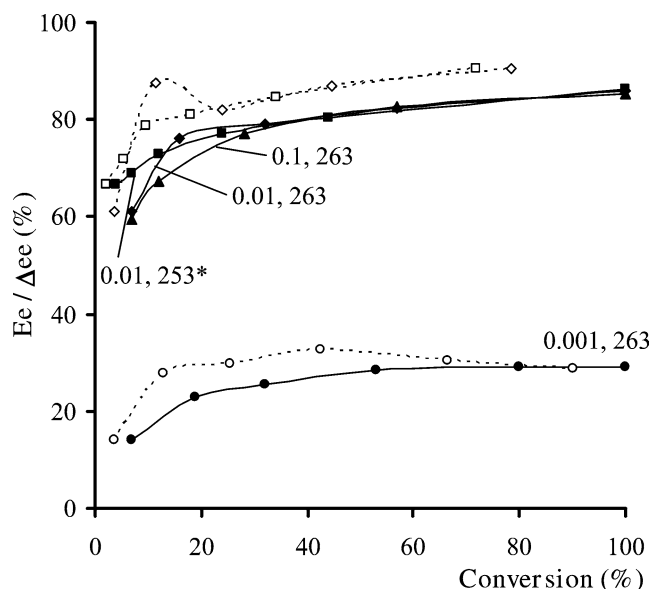


Fig. 2. Enantioselective hydrogenation of EtPy (98% purity): effect of DHCD concentrations (0.001–0.1 mmol/L) and conversion on ee and Δee . Standard conditions, toluene = 5 mL. *EtPy 99.9% purity.

cause there is insufficient DHCD present to produce optimal surface coverage [23]. At 0.001 mmol/L DHCD, when the amount of DHCD present is sufficient to cover only 10% of the Pt surface [22], hydrogenated cinchonas do not appear in the solution, probably due to the detection limit of the analytical method used and irreversible adsorption [29,30]. At DHCD concentrations above 0.01 mmol/L, desorbing hydrogenation products of the quinoline skeleton of DHCD (THCD, HHCD, DDHCD) are readily identified in the liquid phase.

3.2. Enantioselective hydrogenation of EtPy: effect of catalyst pretreatment on the relationship between ee and conversion

The studies described above verified that despite a great variation in experimental conditions, the ITP was detectable in every case. These studies, however, cannot explain the cause of this transient stage. Although the role of impuri-

ties was verified by the experimental data obtained by Baiker and co-workers [13,31], it cannot be excluded that the phenomenon is an intrinsic feature of the system [9,10,12]. To elucidate this problem and also to obtain more information for our suggestion [23] on the chemisorption mechanism of the hydrogenation of EtPy in toluene, the methods of pretreatment of catalyst E4759 were studied. As attention had earlier been called to the effect of purity [2,20] and origin [32] of EtPy on ee, it also seemed practicable to study EtPy of different purities. The results obtained are summarized in Figs. 3–5 and Table 4.

Fig. 3 and Table 4 (entries 1–4) demonstrate the effect of the pretreatment conditions of the re-reduced catalyst on the rate of enantioselective hydrogenation of EtPy (purity: 98%) and on the relationship between ee/ Δee and conversion. In these experiments the catalyst was pretreated in toluene with hydrogen or helium, as described under Section 2. The experimental data allow the following direct conclusions to be drawn.

The most striking observation is that in the course of DHCD treatment of the catalyst in the absence of hydrogen (i.e., in helium), significantly more active chiral surface sites are generated. We consider this to be both a significant and surprising observation. Not only is hydrogenation faster on these more active sites, but they also allow higher ee values to be attained, as has been reported. Reaction rate and ee also increase with increasing DHCD concentration. The initial increase in the ITP is quite conspicuous, especially in Δee , which exceeds 90% despite the fact that the material to be hydrogenated contains EtPy of only 98% purity.

Figs. 4a–c and Table 4 (entries 5–10) represent hydrogenation on catalysts pretreated in the same way, with the significant difference that EtPy of 99.9% purity, containing no EtLt at all, was used. In this case the effect of temperature was also studied under otherwise identical experimental conditions. The data obtained are essentially identical to those in Fig. 3. However, there is a significant difference: the data measured at 298 K show that over a catalyst pretreated in hydrogen, Δee significantly decreases, even after 20 min reaction in the case of 0.01 mmol/L DHCD concentration.

The most important result of the pretreatment studies in helium is that ee values 15–20% higher than those without

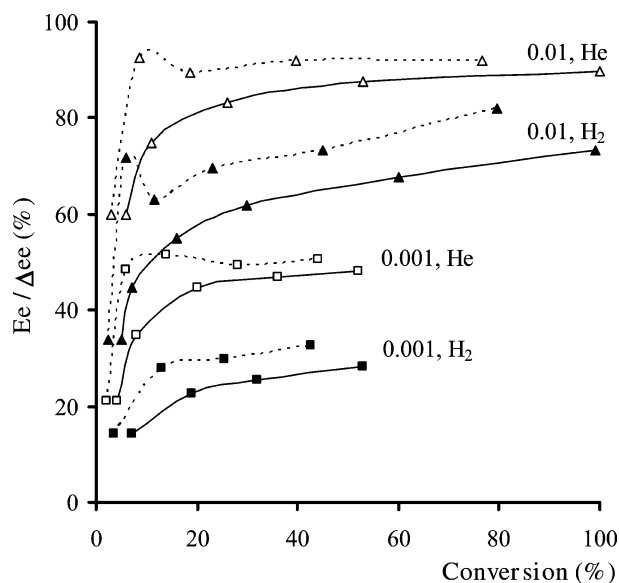


Fig. 3. Enantioselective hydrogenation of EtPy (98% purity): pretreatment of re-reduced catalyst in toluene with hydrogen or helium: effect of pretreatment conditions on relationship between conversion and $ee/\Delta ee$. Standard conditions, $[DHCD] = 0.001$ and 0.01 mmol/L, 263 K, toluene = 5 mL.

Table 4

Experimental data on enantioselective hydrogenation of EtPy on Pt-alumina catalyst^a

| Entry | Modifier (mmol/L) | Temp. (K) | Pretreatment | Time (min) | Conv. (%) | Rate | ee (%) |
|-------|-------------------|-----------|--------------|------------|-----------|------|--------|
| 1 | 0.01 | 263 | Hydrogen | 32 | 99 | 1.4 | 80 |
| 2 | 0.01 | 263 | Helium | 20 | 99 | 2.1 | 90 |
| 3 | 0.001 | 263 | Hydrogen | 90 | 60 | 0.3 | 28 |
| 4 | 0.001 | 263 | Helium | 60 | 50 | 0.4 | 48 |
| 5 | 0.01 | 298 | Hydrogen | 20 | 99 | 4 | 56 |
| 6 | 0.01 | 298 | Helium | 10 | 100 | 6.7 | 89 |
| 7 | 0.01 | 273 | Hydrogen | 30 | 99 | 1.7 | 79 |
| 8 | 0.01 | 273 | Helium | 25 | 99 | 1.9 | 89 |
| 9 | 0.01 | 263 | Hydrogen | 35 | 100 | 1.2 | 88 |
| 10 | 0.01 | 263 | Helium | 22 | 99 | 1.8 | 92 |
| 11 | 0.01 | 298 | Air | 13 | 99 | 4.9 | 75 |
| 12 | 0.01 | 298 | Hydrogen | 16 | 98 | 5.3 | 64 |
| 13 | 0.01 | 298 | Hydrogen | 19 | 97 | 3.4 | 75 |
| 14 | 0.01 | 298 | Hydrogen | 16 | 96 | 4.0 | 82 |

^a Standard conditions, 5 mL toluene, entries 1–4: EtPy 98% purity, entries 5–14: EtPy 99.9% purity, rate: mmol/(min g).

pretreatment in helium can be attained. In our opinion the ~4-min treatment of the catalyst with helium removes the surface impurities (e.g., CO) retained on the catalyst surface during the 30-min re-reduction. On the other hand, it may not be excluded that the oxygen present in helium oxidizes the hydrogen atoms chemisorbed on the Pt surface, thereby generating new Pt clusters, which in turn can form chiral surface sites or complexes of higher activity with DHCD or CD *via* surface interaction or chemisorption and increase hydrogenation rate, ee , and Δee .

Thus, the explanation of the role of helium pretreatment most probably lies in the presence of 5 ppm oxygen in he-

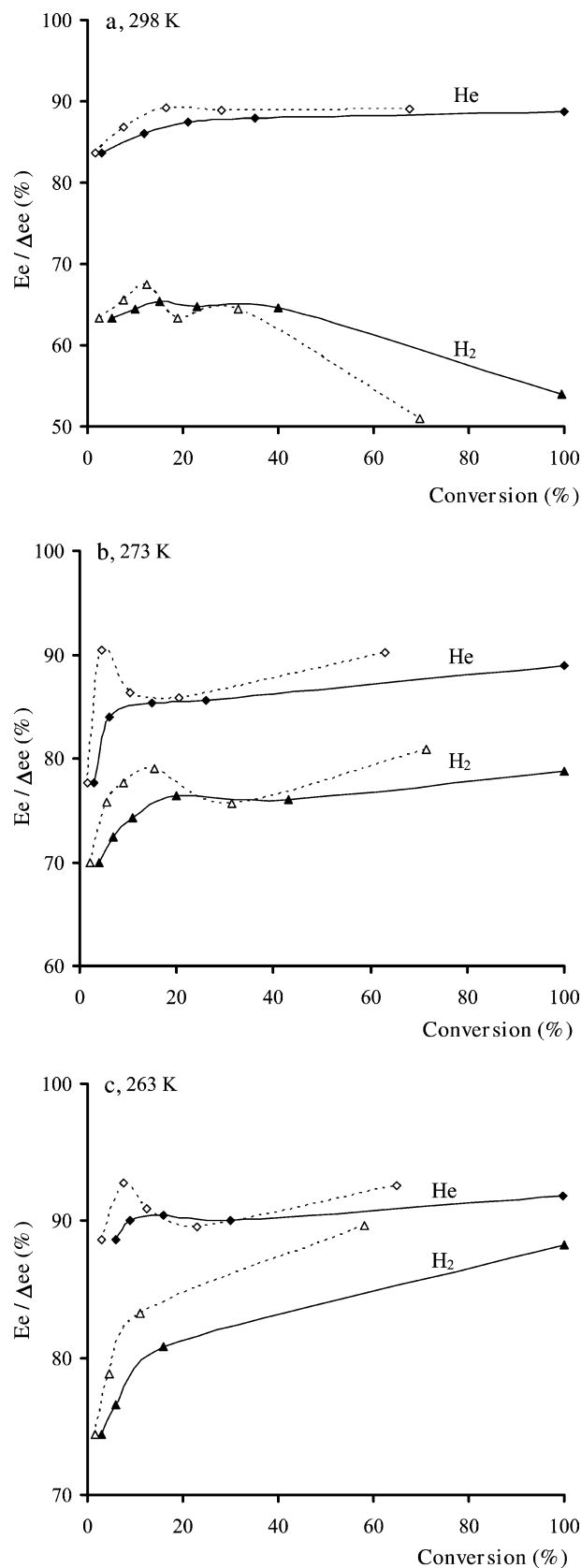


Fig. 4. Enantioselective hydrogenation of EtPy (99.9% purity): effects of pretreated conditions of catalyst and temperature on $ee/\Delta ee$ versus conversion. Standard conditions, $[CD] = 0.01$ mmol/L, toluene = 5 mL: (a) 298 K, (b) 273 K, (c) 263 K.

lium. When helium was replaced by air, pretreatment gave results similar to those obtained with helium (Table 4, entry 11). The effect of oxygen on the adsorption of CD and DHCD and on ee was studied in several laboratories under various conditions [17,33–39]. When interpreting the effect, opposite conclusions were drawn, probably due to differences in experimental conditions and measurement techniques. As the measurement procedures described are not available to us, we had no opportunity to analyze their main conclusions.

Further experimental results yielding new information about the ITP are presented in Fig. 5 and Table 4 (entries 12–14). If the intrinsic feature of the catalytic system, or, in other words, the “reaction-driven equilibration” [9,10], had no effect on the ITP, there should be no great difference between the results obtained on catalysts on which racemic hydrogenation of EtPy and, after removal of the reaction mixtures, chiral hydrogenation of EtPy (Fig. 5b) have been performed, on the one hand, and the results of the original chiral hydrogenation (Fig. 5a), on the other hand. In a similar fashion, a large difference cannot be expected in hydrogenation over a catalyst that was previously used in the enantioselective hydrogenation of another substrate (e.g., PADA) (Fig. 5c). The data in Fig. 5, however, call attention to significant differences exceeding experimental error, especially in the case of curves representing the $e/\Delta ee$, i.e., chiral hydrogenations following racemic hydrogenation (Fig. 5b) and PADA hydrogenation (Fig. 5c): (i) the ITP is clearly recorded in all three cases; (ii) ee and Δee increased considerably in both cases (b,c) as compared with the control (a). In the case of (c), the decrease in Δee with progressing conversion may be explained by deactivation of the catalyst during the prolonged reaction (90 min).

Considering that, on reuse of the catalyst, ee increased significantly despite the increase in contamination, the ITP cannot be accounted for solely by the effect of various impurities/contaminants. Consequently, in the case of the enantioselective hydrogenation of EtPy in toluene, the ITP of the ee/conversion relationship can also be considered an intrinsic feature of the catalytic system. As the above-described results concerning the ee/conversion relationship (Fig. 5) strongly support the effect of modified catalyst, they serve as further evidence for the so-called adsorption model of chiral induction (reviewed in Refs. [1,2,29]).

3.3. Relationship between ee and conversion: effect of the structure of reactants

To test whether the phenomenon observed during chiral hydrogenation of EtPy (i.e., the significant increase in ee with increasing conversion during the ITP) is also detectable in the case of other activated ketones, serial measurements were carried out using PADA and MBF. Enantioselective hydrogenation of PADA and ethyl benzoyl formate under identical conditions gave outstandingly high ee (96–98%) [40,41]. MBF was selected as model compound for the

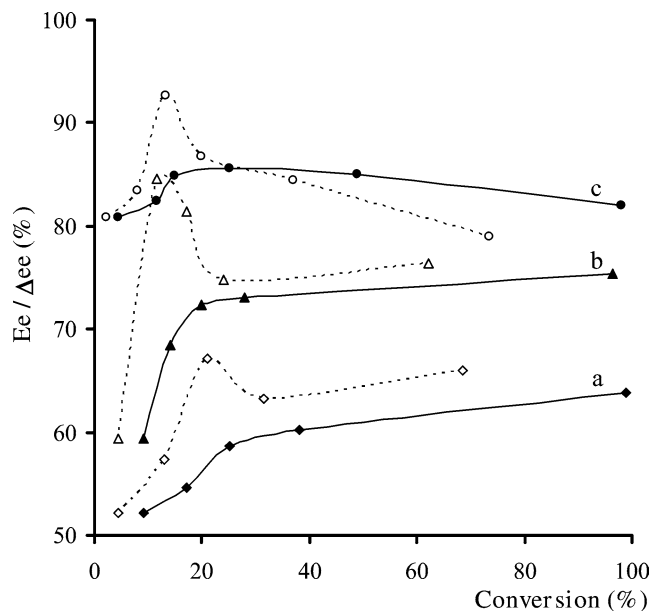


Fig. 5. Enantioselective hydrogenation of EtPy (99.9% purity) over catalyst under standard conditions (a), after racemic hydrogenation of EtPy (b), and after enantioselective hydrogenation of PADA (c): effect of conversion on ee/ Δee . Standard conditions, [CD] = 0.01 mmol/L, toluene 5 mL, PADA = 0.1 mL.

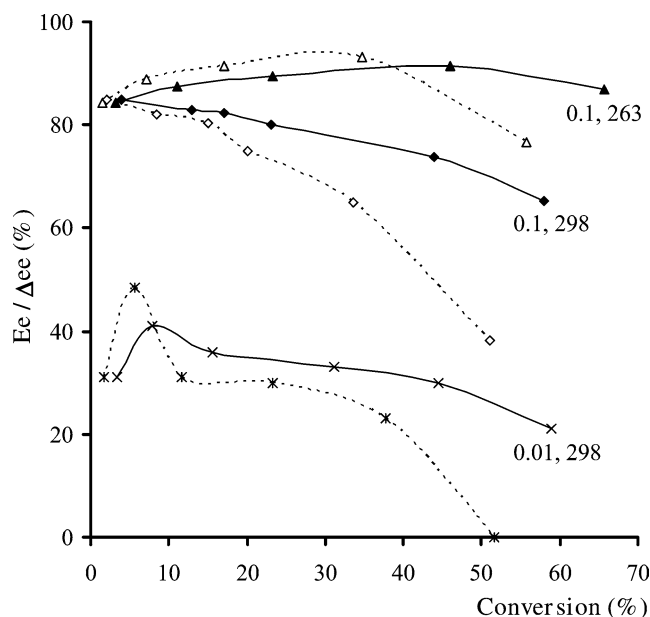


Fig. 6. Enantioselective hydrogenation of PADA: effects of temperature and CD concentrations (0.01 and 0.1 mmol/L) on relationship between conversion and ee/ Δee . Standard conditions, 2 mL toluene.

experiments presented here, because it can be prepared at higher purity than the ethyl ester. The reaction rate increases in the order PADA < MBF < EtPy. The results are summarized in Figs. 6 and 7 and Table 5. The main conclusions are as follows.

Chiral hydrogenation of PADA (Fig. 6; Table 5, entries 1–3) proceeds considerably more slowly than that of EtPy and MBF [41]. Sixty to seventy percent conversion of PADA

Table 5
Experimental data on enantioselective hydrogenation of PADA and MBF on Pt-alumina catalyst^a

| Entry | Modifier (mmol/L) | Temp. (K) | Pretreatment | Time (min) | Conv. (%) | Rate | ee (%) |
|-------|-------------------|-----------|--------------|------------|-----------|------|--------|
| 1 | 0.1 | 298 | Hydrogen | 120 | 84 | 0.7 | 21 |
| 2 | 0.1 | 298 | Hydrogen | 90 | 76 | 1.2 | 65 |
| 3 | 0.1 | 263 | Hydrogen | 90 | 66 | 0.4 | 87 |
| 4 | 0.1 | 298 | Hydrogen | 12 | 100 | 3.3 | 80 |
| 5 | 1 | 298 | Hydrogen | 12 | 92 | 2.9 | 89 |
| 6 | 1 | 263 | Hydrogen | 30 | 74 | 1.1 | 90 |

^a Standard conditions, entries 1–3 (PADA): 2 mL toluene, entries 4–6 (MBF): 5 mL toluene, rate: mmol/(min g).

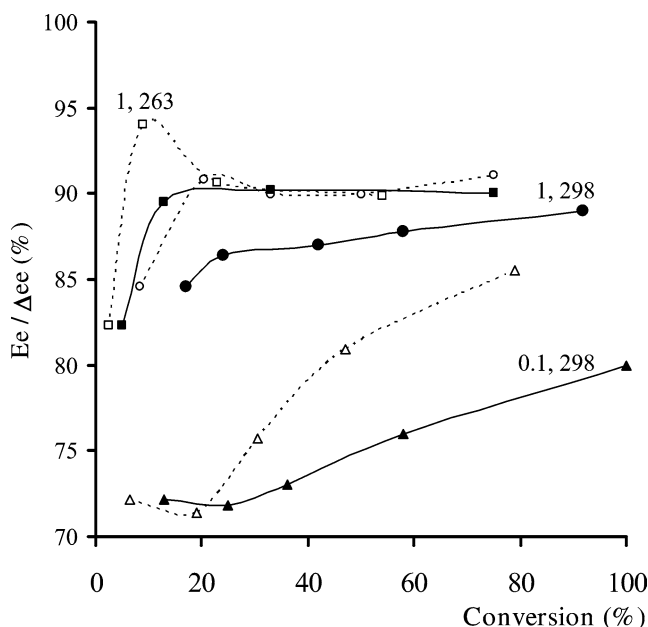


Fig. 7. Enantioselective hydrogenation of MBF: effects of temperature and CD concentrations (0.1 and 1 mmol/L) on relationship between conversion and $ee/\Delta ee$. Standard conditions, 5 mL toluene.

takes nearly 90 min, whereas hydrogenation of EtPy or MBF is completed within 15–30 min, depending on the temperature. In the case of this slow hydrogenation the ITP is essentially nondetectable; Δee slowly increases at a rate depending on modifier concentration and temperature and later slowly decreases due to hydrogenation of the modifier. When PADA is hydrogenated at a CD concentration of 0.01 mmol/L—a value below the optimal modifier concentration necessary for chiral hydrogenation—a slight ITP is already observed: Δee continuously increases up to 10% conversion (Fig. 6). A similar phenomenon can be detected in the case of hydrogenation at 263 K. The probable reason for the latter two phenomena is a slower development of the optimal chiral environment on the Pt surface.

The hydrogenation of MBF (Fig. 7; Table 5, entries 4–6) is a fast reaction, and there is strong competition between CD and MBF. The ITP can therefore be studied only at higher modifier concentrations. The increase in Δee up to ~10% conversion can also be observed in these cases.

Based on the above results, it appears that an ITP with a rapid increase in ee up to ca. 20% conversion cannot be observed in the case of slow chiral hydrogenations probably because of various competitions and strong adsorption of reactant.

4. Interpretation of results and conclusion

The role of the presence of contaminants in the ITP is quite obvious and has been convincingly verified by appropriate experiments [13]. It is, however, more difficult to prove that the phenomenon “is an intrinsic feature of the catalytic system.” Based on the results published in the literature concerning the interpretation of the initial transient behavior observed during chiral hydrogenation of EtPy as well as the present results, the cleaning effect of hydrogen cannot be excluded, but neither can the assumption that the ITP is an intrinsic feature of the catalytic system. The dominance of one or the other standpoint is profoundly affected or, in some cases, even determined by the experimental conditions, because the system reacts very sensitively even to minimal, hardly perceivable changes.

The following experimental results described in the present work, concerning the relationship between ee and conversion, indicate the role of factors that play a decisive role in the development and operation of the chiral catalytic system:

- New experimental data on the ITP, obtained in toluene, under mild conditions never studied before;
- The data of experiments using EtPy of 98% purity as well as with 99.9% EtPy containing not even traces of EtLt;
- The increase in reaction rate and ee brought about by the in situ helium pretreatment of the catalyst pretreated at 673 K;
- The results of the second hydrogenation that followed racemic and chiral hydrogenation;
- New data on the ITP of the chiral hydrogenation of other reactants (PADA, MBF).

These results suggest that the ITP is an intrinsic feature of this type of reaction.

In our opinion the assumption that the initial transient behavior of the chiral hydrogenation of EtPy is an intrinsic feature of the system is also supported rather than excluded by the results of several very important studies published recently [17,28,39]: the ITP has been observed with premodified catalysts [17], and, furthermore, the different adsorption strengths of CD and quinidine, which result in enrichment of CD on the Pt surface [28], both prove the development of the chiral environment responsible for enantioselectivity. An intrinsic character may also be attributed to the adsorbate-induced restructuring of the platinum surface [36,39], which was verified at the solid/liquid interface at

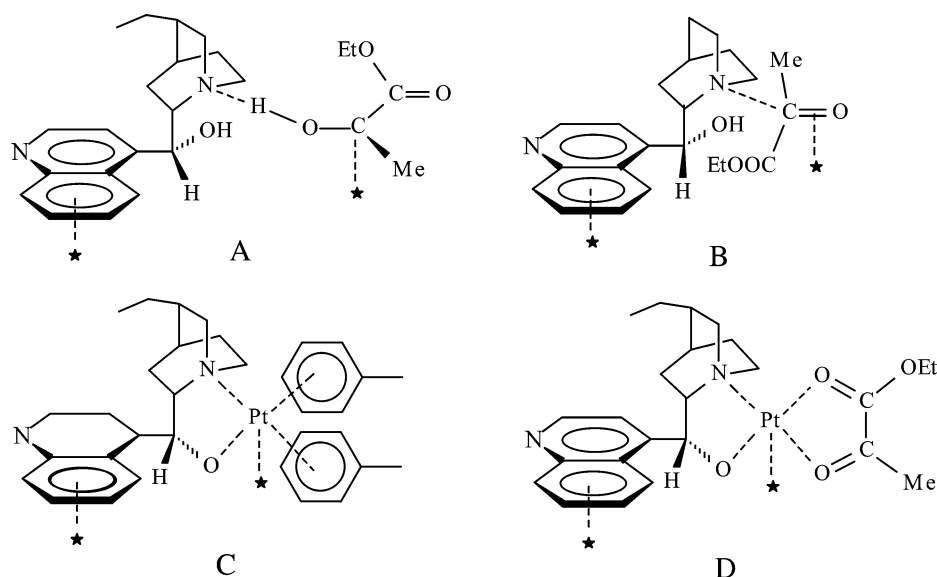


Fig. 8. Proposed adsorbed complexes on platinum.

room temperature [42,43], and the same holds for the results of sonochemical pretreatment of Pt-alumina in the presence of CD [44].

According to the reaction mechanism of enantioselective hydrogenation of activated ketones in toluene [1,2], half-hydrogenated EtPy is bonded to the nitrogen of the quinclidine, also via hydrogen bond (Fig. 8A). The hydrogen source of the latter is the hydrogen dissociatively adsorbed on the platinum. New suggestions have recently been published, which can be supplemented and, as soon as further studies yield new experimental evidence, may modify the presently accepted picture [23,45,46]. According to an assumption DHCD binds the ketone, as a nucleophile (Fig. 8B) [45,46].

We proposed [23] that in toluene the modifier molecules participate in the formation of the surface complex as ligands of the surface Pt atoms (Figs. 8C and 8D). The formation of a surface complex C is supported by the following data:

- (i) Metal complexes containing cinchona ligands of similar structure have been prepared and their structures determined by X-ray diffraction [47];
- (ii) The mechanism of homogeneous catalytic hydrogenation was confirmed with the help of this type of metal complex [48];
- (iii) Extremely high ee values (97%) were achieved using Pt colloid with 1.2-nm particle size [49] that are not accounted for by the intermediates proposed to date;
- (iv) Only the highly reactive and coordinatively unsaturated corner and adatoms participate in chiral induction [20];
- (v) It may be verified by IR [50,51], and by electrochemical [30] and surface science [34] measurements that DHCD is irreversibly adsorbed on platinum.

Of course, it also cannot be excluded that the irreversibly adsorbed modifier does not participate in the enantioselection but acts only as a spectator.

Differences in mechanisms are also indicated by new results [40,52–54] of studies on the widely accepted relationship between chiral hydrogenation rate and enantioselectivity [20]. According to these new results, high ee may also be realized at low reaction rates. This indicates that ligand acceleration is a welcome effect but not a necessary prerequisite for achieving high enantioselectivity.

At the same time, the results presented in this work also indicate that the change in the ee/conversion relationship can be minimized by the appropriate choice of reaction conditions. With respect to the ITP, the role of the competitive adsorption of the chiral modifier, the reactant, the solvent, and hydrogen must naturally also be taken into account. Considering that the chemical system studied is extremely complicated and also that not all the details of the origin of chiral induction are fully known, the observed phenomenon may also be the result of several superimposed effects and its explanation necessitates further studies and new experimental evidence.

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