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Enantioselective hydrogenation of ethyl pyruvate catalyzed by α- and β-isocinchonine-modified Pt/Al_2O_3 in acetic acid

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Abstract

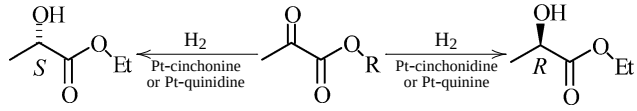
The enantioselective hydrogenation of ethyl pyruvate (EtPy) was studied on Pt-alumina catalysts modified by high-purity α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN) in AcOH. The effect of the modifier concentration, temperature, and hydrogen pressure on the reaction rate and the enantioselectivity was examined. Using the Engelhard 4759 catalyst under medium experimental conditions (273 K, hydrogen pressure of 25 bar, α-ICN concentration of 1 mmol/L) an optical yield of 93–94% can be achieved. In the case of β-ICN, maximum *ee* is 70–72% (297 K, 20 bar, β-ICN concentration of 1 mmol/L); at the same time, the rate of EtPy hydrogenation is higher than in the case of dihydrocinchonine (DHCN) or α-ICN. Chiral modifiers themselves are converted under the conditions of hydrogenation. The results of ESI-MS, ESI-MS-MS, HPLC-MS, and desorption measurements strongly suggest that α-ICN and β-ICN compounds with a rigid structure are responsible for chiral induction, since DHCN and hydrogenated products of DHCN were not identifiable among the reaction products. These experimental results support the earlier assumption that it is cinchona alkaloids in the "open 3" (in another terminology "antiopen") conformation that participate in enantioselection. However, based on other experimental observations of this work, the participation of other, so far unknown factors in enantioselection may not be excluded either.

Keywords: Hydrogenation; Enantioselective; Pt/Al_2O_3; α- and β-isocinchonine; Ethyl pyruvate; ESI-MS; Intermediate; Conformation

1. Introduction

The significance of asymmetric syntheses, and especially of heterogeneous catalytic reactions [1–3], has gained wide recognition. In this field, the enantioselective hydrogenation of activated ketones has received special attention [3,4]. Compounds most widely used for chiral transfer in asymmetric syntheses are cinchona alkaloids [5,6] (Fig. 1).

Despite its 22-year-old history [7], the intensity of research on the asymmetric hydrogenation of α-ketoesters over cinchona–alkaloid-modified platinum catalysts still keeps increasing. The preferred model compound of these elaborate studies is ethyl pyruvate (EtPy), which could be hydrogenated to ethyl lactate (EtLt) with an extremely high enantioselectivity (96–97%) [8,9].



Successful applications with *ee* values usually higher than 95% *ee* were recently reported including a cyclic ketoester, α-ketoesters, α-ketoacetals, α-ketodicarboxylic acid esters, and 2,4-diketoesters [9–14]. Besides improving the dihydrocinchonidine (DHCD)–platinum catalyst system, extensive efforts have been made in developing a reliable mechanistic interpretation. Although this topic was extensively reviewed in recent years [2–4], no significant new details concerning the reaction mechanism have been published since. The most important task in this respect would be the elucidation of the origin of chiral induction, i.e., the verification of the structure of the intermediate responsible for chiral induction. Numerous mechanistic details have been described, including data (i) on the conformation of cinchona alkaloids and other chiral modifiers [15–18], (ii) how DHCD and EtPy are adsorbed and on which surface site [8,19–29], and (iii) the structure of the intermediate

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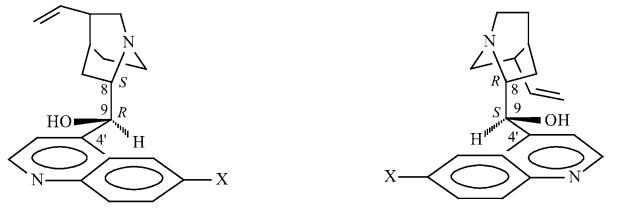

Fig. 1. The structure of the parent cinchona alkaloids (CD, cinchonidine; CN, cinchonine; Q, quinine, QD, quinidine).

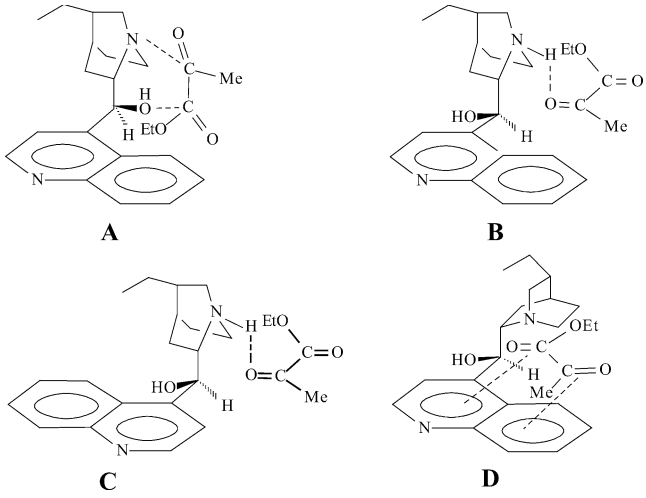

Fig. 2. The structure of the DHCD–EtPy intermediate complexes (**A** and **B**, DHCD "antiopen;" **C**, "syn open;" **D**, "closed" conformation; DHCD, dihydrocinchonidine; EtPy, ethyl pyruvate).

responsible for chirality [3,4,16,19,20,22,24,30–32]. However, no consensus has been reached over the structure of the intermediate (a 1:1 complex of DHCD and pyruvate) responsible for chiral induction.

The intermediate complexes published recently are summarized in Fig. 2. DHCD in **A** (Augustine's model [22]), **B** (Wells' and Baiker's models [2,20]), and **C** (Blaser's model [32]) is in "open," while in **D** (Margitfalvi's model [30]) is in "closed" conformation. The intermediates **A**–**C** are anchored on the surface of the platinum by a multicenter π-bond of the quinoline skeleton and the conjugated $\delta\pi$ systems of pyruvate. In contrast, structure **D** is already formed in solution and this complex is hydrogenated.

According to NMR and XRD measurements on the parent cinchona alkaloids as well as molecular mechanical calculations [15,17], from the four stable conformations possible, alkaloids are present in solution mostly in the so-called "open 3" or "antiopen" conformation (**B**) (in "anti" conformation, the benzene ring is turned away from the C9–OH whereas "syn" denotes the conformation in which the benzene ring is turned toward the C9–OH (**C**)). No direct experimental evidence is available to prove whether, in the course of chiral hydrogenation, the cinchona alkaloid engaged in the 1:1 intermediate on the surface of the catalyst is in the open or in the closed conformation, as the intermediate has not been isolated. Indirect experimental observations

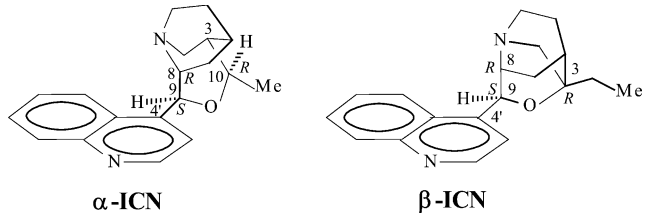

Fig. 3. The structure of α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN).

and calculations [3,4,8,18,20] indicate that it might be in the antiopen conformation. Our own studies on isocinchona alkaloids [which, due to their rigid structure, may only exist in the open conformation [33,34] (Fig. 3)] support the presence of the open conformation [31].

The reader may ask why, and with reason, further studies on isocinchona alkaloids were necessary. The most important motive is a result we obtained in our latest experiments [35], namely that DHCD is capable of ensuring enantioselectivities over 90% under mild experimental conditions (room temperature, hydrogen pressure of 1 bar) even at a concentration as low as 0.004 mmol/L. More over *ee* is 80% even at 0.001 mmol/L DHCD. Considering that the α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN) modifiers contained 3% impurities [including dihydrocinchonine (DHCN)], the question arose whether the enantioselectivities attained [31,36] could be due to the DHCN present.

It was therefore necessary to purify isocinchona alkaloids and the experiments had to be repeated with 100% pure modifiers. By the evidence of ESI-MS measurements carried out to date [31,36], the ion with maximal abundance in the solution is the one with $m/z = 299$, an ion attributed to the protonated form of tetrahydro-α-ICN (TH-α-ICN) and tetrahydro-β-ICN (TH-β-ICN). In addition, optimization measurements in order to determine maximal *ee* (α-ICN and β-ICN concentration, temperature, pressure) as well as further studies to elucidate the effect of experimental conditions on the conversion of α-ICN and β-ICN in the course of the hydrogenation were also necessary. These experiments were also justified by our new observations demonstrating an unexpected change in the sense of enantioselection with β-ICN as modifier [37].

2. Experimental

2.1. Materials

Cinchonine (CN), AcOH, and solvents were purchased from Fluka. EtPy (Fluka) was distilled before use to attain 99.5% purity. DHCN was prepared by hydrogenation of CN (Pd/C, 1 N H_2SO_4/H_2O, 1 bar H_2, 298 K) and used after crystallization. For the preparation of α- and β-ICN, 5 g (17 mM) of CN (Fluka 27370) was dissolved in 30 ml of 70% H_2SO_4. The solution was stirred at 343–348 K for 24 h. The solution was next cooled and alkalized using ammonium

hydroxide and the solid material precipitated was dissolved in absolute EtOH. Insoluble inorganic salts were removed by filtration, the filtrate was evaporated and the residue was again dissolved in EtOH, filtrated, and evaporated. The procedure was repeated two more times in order to remove inorganic salts. The complex reaction mixture was purified by repeated column chromatography (Fluka 60741 silica gel 60; eluent: toluene/EtOAc/diethylamine 7/2/1). The fraction composition was analyzed by thin-layer chromatography (Fluka 60778 silica gel/TLC cards; eluent composition, see above). α-ICN obtained were 0.7 g, m.p. = 398–400 K, $[\alpha]_D{}^{20} = +63^\circ$ ($c = 0.5$; EtOH), $R_F = 0.54$; β-ICN, 0.4 g, m.p. = 401–402 K, $[\alpha]_D{}^{20} = -60^\circ$ ($c = 0.5$; EtOH), $R_F = 0.43$. By the evidence of HPLC, the compounds are 100% pure. The ^{1}H NMR and ^{13}C NMR spectra of the compound (Bruker DRX 500, $CDCl_3$, 500 and 125.8 MHz) are identical with the published data [33,34].

2.2. Catalyst

Based on the data in the literature, from 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 300–673 K for 30 min and 30 mL min^{-1} hydrogen at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min and was stored under air before use.

2.3. Hydrogenation

Hydrogenation was performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave. The catalytic system including catalyst (25 or 50 mg) and 2 or 4 mL of solvent was purged three times with hydrogen. The catalyst was stirred and prehydrogenated for 30 min. The calculated amount of modifier was introduced and after several min 0.12–0.5 mL of EtPy was injected and stirred in the presence of hydrogen for the required reaction time (usually 10–50 min). Standard conditions are 25 mg E4759, 2 mL AcOH, 0.1 mmol/L modifier, 1 bar H_2, 293 K, 1200 rpm, 0.12 mL EtPy. The product identification and the enantiomeric excess [$ee\% = ([S] - [R]) \times 100/([S] + [R])$] were monitored by gas chromatography (HP 5890 GC-FID, 30-m long Cyclodex-B capillary column, uncertainty ±2%).

ESI-MS and ESI-MS/MS measurement methods were described in an earlier publication [35].

2.4. Desorption studies

After enantioselective hydrogenation, the catalyst was separated from the solution by centrifugation. The ratio of hydrogenated cinchona alkaloids in the solution was determined by ESI-MS. The catalyst was washed with various solutions under constant stirring (1200 rpm) and centrifuged several times, alkaloids were isolated from the washing solutions by the usual procedures, and their composition was determined. The catalyst was finally kept at 473 K, 20 Hg mm for 2 h, the escaping product was recovered at the temperature of liquid nitrogen, and its composition was determined.

2.5. HPLC and HPLC-MS measurements

The HPLC/ESI-MS measurements were run on a Finnigan TSQ 7000 tandem mass spectrometer (Finnigan Ltd., San Jose, CA). An Applied Biosystems ABI 140C syringe pump was used for HPLC separations using a 30-min linear gradient from 5 to 95% solvent **B** (0.04% TFA in 80% aqueous acetonitrile) in solvent **A** (0.05% TFA in water). The flow rate in the experiments was 150 µL/min. The injected volume was 10 µL of sample. A Hypersil column (PEP 300 C18 5 µm, length 150 mm, i.d. 2.1 mm) was used for separation.

3. Results and discussion

In order to achieve the aim described in the Introduction, the effect of the experimental parameters (α-ICN, β-ICN, DHCN concentration, temperature, and pressure) on the rate of the hydrogenation and on enantioselectivity was studied. The conversion of the chiral modifiers in the course of the hydrogenation reaction was followed by ESI-MS, ESI-MS-MS, and HPLC-MS measurements. ESI-MS was also used to determine the composition after desorption of cinchona alkaloids adsorbed on the catalyst.

3.1. Effects of α- and β-ICN concentration

The relevant experimental results are summarized in Figs. 4–6. Data measured at 293 and 273 K over a wide range of modifier concentrations are presented in Figs. 4 and 5 and those obtained in the narrow concentration range of 0.001–0.01 mmol/L at 273 K are summarized in Fig. 6. The aim of the latter measurements was (just like in the study on DHCD [35]) to determine the minimal modifier concentration necessary for maximal enantioselectivity under mild experimental conditions (low temperature, 1 bar hydrogen pressure): this piece of information may contribute significantly to the interpretation of the reaction mechanism which, although intensively studied, still raises many unanswered questions. These experimental results and their comparison to the data obtained with DHCD allow the following important conclusions to be drawn.

Since the configuration of carbon atoms C8 and C9, responsible for the direction of the enantiodiscrimination, is opposite to that of the corresponding carbon atoms of DHCD, α-ICN and β-ICN direct the formation of excess (*S*)-EtLt. In agreement with earlier observations [2–4], the hydrogenation is completed faster on the modified catalyst than on the unmodified one. Two explanations have been proposed for this phenomenon in the case of hydrogenation

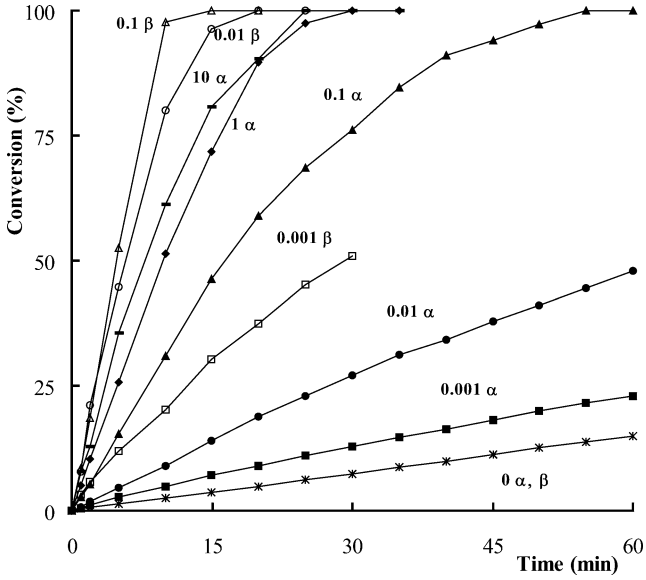

Fig. 4. The effect of α-ICN (α) and β-ICN (β) concentration (mmol/L) in enantioselective hydrogenation of EtPy at 293 K (25 mg E4759, 2 mL AcOH, 1 bar H_2, 1200 rpm, 0.12 mL EtPy).

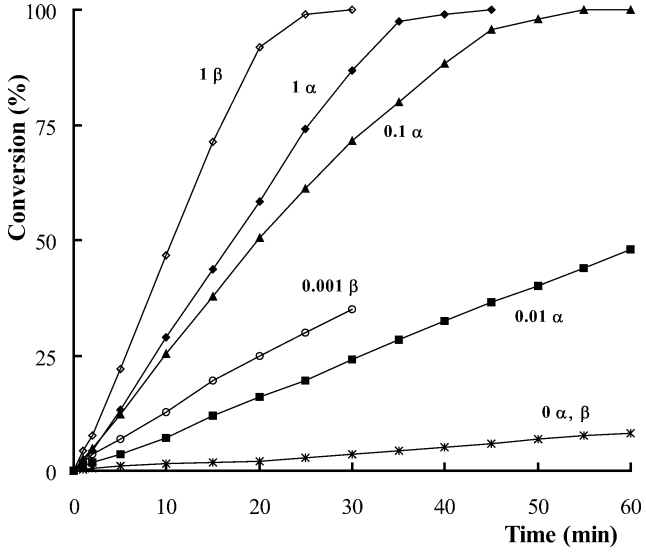

Fig. 5. The effect of α-ICN (α) and β-ICN (β) concentration (mmol/L) in enantioselective hydrogenation of EtPy at 273 K (25 mg E4759, 2 mL AcOH, 1 bar H_2, 1200 rpm, 0.12 mL EtPy).

in AcOH. One of these is the so-called ligand-accelerated mechanism [38], whereas another interpretation emphasizes the role of electrostatic acceleration [35]. At the same time, it should be noted that in nonacidic solvents, when the hydrogenation of EtPy proceeds in the presence of tertiary amines, rate acceleration is observed [39,40]. The effect of cinchona alkaloids, however, is much stronger than that of tertiary amines. Based on theoretical calculations concerning the hydrogenation of acetophenones in toluene, a correlation has been found between the orbital energy of the keto carbonyl groups and hydrogenation rates [41].

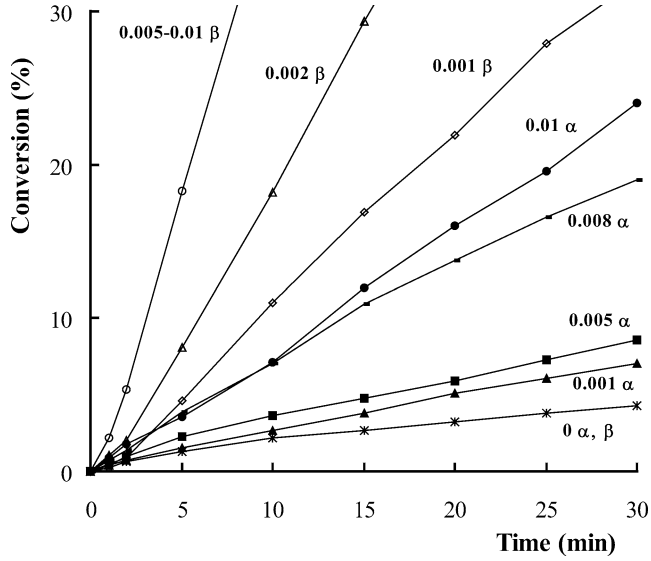

Fig. 6. Enantioselective hydrogenation of EtPy in the narrow range (0.001–0.01 mmol/L) of modifier concentration (25 mg E4759, 2 mL AcOH, 1 bar H_2, 273 K, 1200 rpm, 0.12 mL EtPy).

The rate of hydrogenation is lower in the case of the modifier α-ICN than in the presence of the DHCD. We have explained this phenomenon for CN with the vicinity of the Me group on C10 to the surface which inhibits rotation along the C8–C9 axis. Due to this effect, the development of the advantageous conformation of the 1:1 intermediate responsible for enantioselection becomes somewhat inhibited.

There is a remarkable difference between the effects of the chiral modifiers α-ICN and β-ICN on the rate of EtPy hydrogenation and on enantioselectivity (Figs. 4–6). Hydrogenation is faster in the presence of β-ICN and, at a concentration as low as 0.001 mmol/L, high *ee* is obtained as compared not only to α-ICN but also to DHCD [35]. The large difference in reaction rate between α- and β-ICN prompted us to perform the experiments under identical conditions with DHCN (Fig. 7). The order of reaction rates obtained is β-ICN > DHCN > α-ICN.

In contrast to DHCN, the reaction rate is increased in proportion to increasing α-ICN and β-ICN concentrations, while enantioselectivity already reaches its maximum at 0.1 mmol/L α-ICN (*ee* 82%) and at 0.01 mmol/L β-ICN (*ee* 62%) (Table 1). In the case of isocinchonas, however, this maximum does not reach the value of that obtained with DHCN as modifier, which is 90–92% under identical conditions. In the case of β-ICN it is quite striking that increasing modifier concentration has an opposite effect on reaction rate and *ee*: the former increases, whereas the latter decreases with increasing concentration of the modifier. It is well known that the hydrogenation rate of ketones may be increased by bases [42,43]. For this reason the basicities of α- and β-ICN were determined by potentiometric titration: for α-ICN, $pK_1 = 8.23 \pm 0.02$, $pK_2 = 2.96 \pm 0.04$; and for β-ICN, $pK_1 = 7.88 \pm 0.02$, $pK_2 = 2.72 \pm 0.04$ were obtained. These data demonstrate that, from the two tertiary bases,

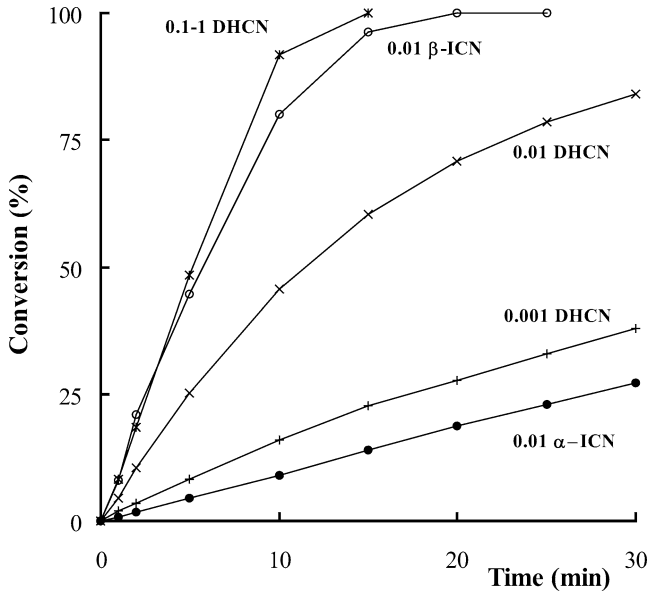

Fig. 7. The effect of dihydrocinchonine (DHCN) concentration (mmol/L) in enantioselective hydrogenation of EtPy (25 mg E4759, 2 mL AcOH, 1 bar H_2, 293 K, 1200 rpm, 0.12 mL EtPy).

β-ICN may be converted to a stronger base. The stronger base formed from β-ICN increases the hydrogenation rate whereas it is less effective in chiral induction, in the development of chiral catalytic centers or in the formation of the intermediate responsible for enantioselectivity.

In the case of DHCD the curve describing the dependence of reaction rate on DHCD concentration has a maximum. There are two interpretations for this maximum in the literature [44,45]. Based on their kinetic study, Blaser et al. explained the phenomenon by the so-called "three-site model" [44], whereas LeBlond et al. [45] attributed it to the change in optimal adsorption geometry of DHCD at higher modifier concentrations in AcOH. The latter was verified by attenuated total infrared spectroscopy [27,46]. Given the absence of conclusive experimental evidence, the reason why no maximum appears in the case of α-ICN and β-ICN can only be guessed (rigid conformation, development of chiral surface sites in a way different from that in the presence of DHCD, possible gradual hydrogenative ring opening of isocinchonas, etc.). It may be established, however, that the modifier concentration necessary for maximal *ee* is higher for α-ICN than for DHCN and β-ICN.

3.2. The effect of temperature

In the enantioselective hydrogenation of the EtPy the role of temperature was first studied [47] under relatively severe experimental conditions (high hydrogen pressure and DHCD concentration). The results obtained under the mild experimental conditions applied by us (hydrogen pressure 1 bar, DHCD concentration 0.001–1 mmol/L, temperature 263–293 K) in AcOH have been published recently [35]. Similar experiments in the case of α- and β-ICN have not been reported. Our new experimental results obtained in the presence of α- and β-ICN are summarized in Figs. 5, 6, and 8 and Table 1.

Naturally, it was to be expected that the rate of EtPy hydrogenation would decrease as a consequence of reducing temperature. As temperature is decreased, *ee* increases to 273 K and reaches 86% (0.1 mmol/L α-ICN, 1 bar hydrogen pressure, 100% conversion at 30 min in the case of α-ICN). It seems that the increase in hydrogen concentration due to temperature reduction enhances chiral hydrogenation more than it does racemic hydrogenation. In the presence of β-ICN an unusual effect was observed: reaction rate decreased in parallel with increasing temperature (Fig. 8b), whereas *ee* increased, quite unlike that with α-ICN. According to the experimental data in Table 1, in the case of β-ICN *ee* increases with increasing temperature at all concentrations (0.01, 0.1, 1 mmol/L) with the exception of 0.001 mmol/L, in contrast to α-ICN, in the presence of which *ee* decreases. These results indicate the conversion of isocinchonas during hydrogenation (see below) that brings about a more extensive structural alteration in β-ICN than in α-ICN; alternatively, they may participate in a different way/via a different mechanism in the development of chiral centers responsible for enantioselectivity.

The most important observation is, however, that at 263 K and 0.001 mmol/L α-ICN and β-ICN concentrations (Table 2), the formation of (*S*)-EtLt proceeded 44–53%: this is important because at 263 K, hydrogenolysis of the C–O bond may be excluded. Comparison of the experimental results obtained with DHCD and isocinchonas at a modifier concentration of 0.001 mmol/L reveals a significant difference (Table 2). The higher *ee* may be explained by the higher stability of DHCD under the conditions of hydrogenation.

Table 1
The effect of temperature in enantioselective hydrogenation of EtPy (25 mg E4759, 2 mL AcOH, 1 bar H_2, 1200 rpm, 0.12 mL EtPy)

Temperature (K)	273	293	273	293	273	293	273	293	303	333
Modifier (mmol/L)	0.001	0.001	0.01	0.01	0.1	0.1	1	1	1	1
ee (%)[a]	38	15	68	64	82	74	79	73	73	10
ee (%)[b]	55	44	52	62	20	50	21	52	56	54

[a] In the case of α-ICN.
[b] In the case of β-ICN.

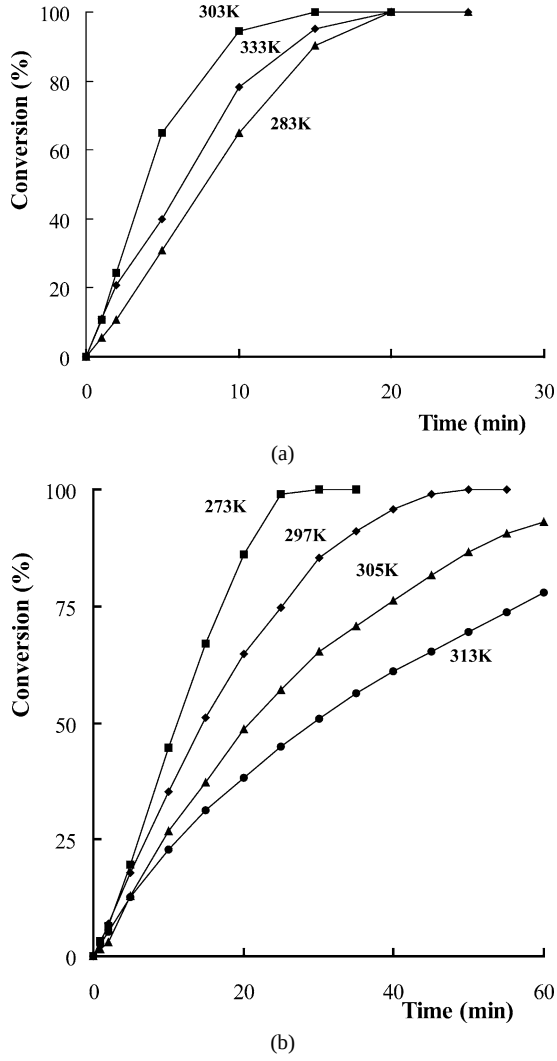

Fig. 8. The effect of temperature in enantioselective hydrogenation of EtPy (25 mg E4759, 2 mL AcOH, 1 bar H_2, 293 K, 1200 rpm, 0.12 mL EtPy, (a) α-ICN concentration 1 mmol/L, (b) β-ICN concentration 0.01 mmol/L).

Table 2
Effect of temperature for the hydrogenation of EtPy on optical yield (25 mg E4759; 0.001 mmol/L modifier; solvent: 1 mL AcOH + 1 mL toluene in order to keep AcOH dissolved; 1 bar H_2; 0.1 mL EtPy for α-ICN and β-ICN; 0.5 mL EtPy for DHCD)

Modifier	Temperature (K)	Time (min)	Conversion (%)	*ee* (%)	Ref.
DHCD	293	150	40	30	[35]
α-ICN	293	60	20	15	This work
β-ICN	293	30	48	44	This work
DHCD	273	150	35	70	[35]
α-ICN	273	30	5	38	This work
β-ICN	273	30	35	55	This work
DHCD	263	150	32	83	[35]
α-ICN	263	30	6	53	This work
β-ICN	263	30	27	44	This work

3.3. Effect of hydrogen pressure

The *ee* value attained in EtPy hydrogenation in the presence of CD and DHCD usually increased with increasing hydrogen pressure, due to increasing hydrogen concentration in the solution, and eventually reached saturation [47, 48]. Similar experiments using α- and β-ICN as modifiers have not been reported. Some characteristic data are presented in Table 3.

In measurements performed at a hydrogen pressure of 25 bar (at the temperature and α-ICN concentration optimized for 1 bar hydrogen pressure) (Table 3) *ee* values exceeding 90% were unexpectedly observed. When hydrogen pressure is further increased under identical conditions, *ee* is reduced, most probably due to hydrogenation of the quinoline skeleton of α-ICN. In contrast to α-ICN, increasing hydrogen pressure had no significant effect on *ee* when a β-ICN modifier was used.

3.4. Desorption studies

The aim of these studies was—using a relatively simple method—to identify hydrogenated cinchonas formed on the catalyst. The target compound was DHCN which might possibly be formed from α-ICN. The results obtained by the method described in the experimental section are summarized in Table 4.

It is demonstrated by the data in Table 4 that DHCN ($[M+H]^+ = 297$) was not formed. Desorbed cinchona alkaloids are α-ICN, TH-α-ICN, and DCH-α-ICN $[M+H]^+ =$ 295, 299, and 305, respectively; for abbreviations, see Fig. 9. Thus, only cinchonas of rigid structure are identified; in other words, cinchona(s) in which rotation along the C8–C9 bond is free could not be identified in the course of desorption either.

Table 3
The effect of hydrogen pressure in enantioselective hydrogenation of EtPy on α-ICN modified catalyst (50 mg E4759, 4 mL AcOH at 297 K, 4 mL AcOH:toluene (3:1) at 273 K, 1200 rpm, 0.24 mL EtPy)

Temperature (K)	273	297	273	297	273	297	273	297
H_2 pressure (bar)	1	1	25	25	1	1	25	25
Modifier (mmol/L)	0.01	0.01	0.01	0.01	0.1	0.1	0.1	0.1
ee (%)	72	64	89	78	86	74	94	88

Table 4
Desorption studies after EtPy hydrogenation on α-ICN-modified catalyst using ESI-MS (100 mg E4759, 1 mg α-ICN, 273 K, 25 bar H_2, 0.4 mL EtPy, 4 mL AcOH: toluene (1:1), reaction time 60 min)

Method	m/z values (relative peak intensity %)			
	295	297	299	305
A	1	0	10	100
B	3	0	5	100
C	13	0	16	100
D[a]	0	0	0	0

A, in the solution after EtPy hydrogenation; B, in the two pooled washes of the catalyst with AcOH + T (1:1); C, in the three pooled washes of the catalyst with concentrated ammonium hydroxide; D, in the distillate of the catalyst after A, B, C at 20 Hg mm, 473 K.

[a] m/z signals of many polycarbonates of unknown structure between 375 and 991 which differ from each other by $m/z = 44$.

3.5. Results of HPLC, HPLC-MS, and ESI-MS

It has been established by HPLC measurements that neither α-ICN nor β-ICN are isomerized to α- and β-ICNN, respectively, at room temperature and below, that is, at a temperature of hydrogenation of EtPy. The minimal temperature at which this isomerization takes place at a measurable rate is 343 K. At 343 K the conversions of β-ICN and α-ICN at 30 min are 5 and 3%, respectively (these conversions at 120 min are 36 and 17%). These experiments make it necessary to correct former conclusions drawn from ESI-MS measurements, i.e., that β-ICN is not converted in glacial acetic acid [37]. The reason why the inconsistency developed is that ring opening of β-ICN in AcOH was not detected by ESI-MS, since the molecular ion $[M + H]^+$ ($m/z = 295$) was not changed. Isomerization under the given experimental conditions was not considered at that time.

HPLC-MS studies were done only in a few cases, because the large number of cinchona alkaloid isomers and diastereoisomers would have made chromatographic separation extremely difficult. It was, however, possible to establish that the hydrogenation products of α-ICN and β-ICN obtained on platinum catalysts in the presence of AcOH, for each m/z value of 295, 299, and 305, two ions are identified by MS. Because of extremely low concentrations, isolation of these isomers and verification of their structure by NMR were not possible. For this reason, the compounds shown in Fig. 9 were identified with the help of characteristic fragment ions of the ESI-MS-MS spectra of the product mixture.

Under the conditions of EtPy hydrogenation, i.e., at room temperature in the presence of Pt–alumina and hydrogen, however, both isocinchona alkaloids undergo significant conversion, as indicated by the ESI-MS data in Table 5.

In agreement with data of Table 5, hydrogenation of the quinoline skeleton of α- and β-ICN in the absence of EtPy is rapidly completed, yielding tetrahydro- and decahydroderivatives. It is important to note, however, that the formation of $[DHCN + H]^+$ ($m/z = 297$) and $[DDHCN + H]^+$ ($m/z = 307$) is not observed, indicating that under the given mild experimental conditions, hydrogenolysis of the cyclic ether structure fails to occur; i.e., the structure is stable. As shown above (Table 1), in the case of α- and β-ICN ee values of over 80 and 60%, respectively, were attained under these conditions.

Table 5
Relative abundances of the cinchona alkaloids obtained from hydrogenation of α-ICN and β-ICN over Pt catalysts in AcOH (50 mg E4759, 293 K, 2 mg modifier, 5 mL AcOH, 1 bar H_2 pressure)

Modifier	Time hydrogenation	m/z values of $[M + H]^+$ (relative peak intensity %)				
	(min)	295	297	299	305	307
α-ICN	30	3	[a]	63	100	0
α-ICN	60	0	0	30	100	0
α-ICN	120	0	0	[a]	100	0
β-ICN	30	37	[a]	100	6	0
β-ICN	60	0	0	100	18	0
β-ICN	120	0	0	18	100	0

[a] "Noise level" formation.

Since there is no C8–C9 rotation in α- and β-ICN, these cinchonas behave as conformationally rigid chiral ligands on the surface. β-ICN with "oxazatwistane" structures are more rigid than the α-ICN in which a certain extent of conformational movement is possible due to the "homotwistane" structure. The ee expected with β-ICN is therefore lower than with the α-ICN: the more rigid structure is less capable of sterically fitting into the 1:1 intermediate responsible for the induction of chirality.

4. Conclusion

It is assumed highly probable that in the course of EtPy hydrogenation on Pt catalysts modified with high-purity α-ICN and β-ICN, these chiral compounds of rigid structure which have antiopen conformation are responsible for enantioselectivity. Although a portion of α-ICN and β-ICN undergoes conversions during hydrogenation, formation of DHCN could not be verified. Consequently, it may be declare that the "closed" conformation of cinchona alkaloid is not a precondition for chiral induction in enantioselective hydrogenation of EtPy on Pt–alumina–cinchona system.

In order to achieve *ee* values over 90%, higher cinchona alkaloid concentration and hydrogen pressure are needed with α-ICN than with DHCD [35], pointing to the role so

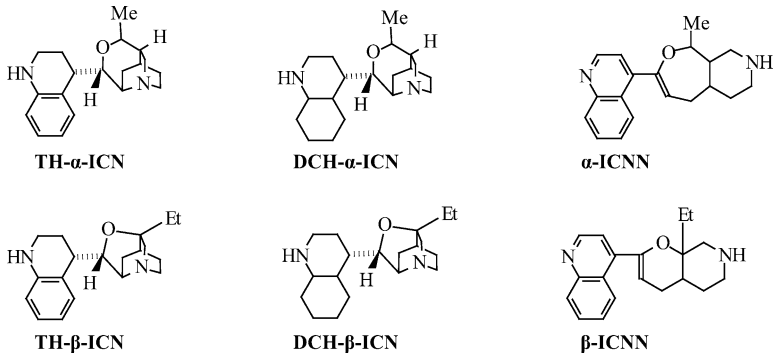

Fig. 9. Isomers and hydrogenated isocinchonas formed from α-ICN and β-ICN.

far of unidentified factor(s). The latter statement is also supported by studies on β-ICN. When using β-ICN, maximal enantioselectivity was only 70–72%, despite the fact that hydrogenation rate exceeded not only that with α-ICN but also that with DHCN.

Since, according to studies published so far, enantioselection happens on the surface of the Pt catalyst (also see in the most recent review [4]), the results presented in this manuscript can offer no answer to the questions raised by the chemistry on the catalyst surface. On the basis of the recent experimental data by in situ STM on Cu(111), an ordered adsorption of CD in "closed 1" conformation was observed [28]. These data, however, do not make it possible to interpret the enantioselection, since the measurements were not performed on Pt(111).

It is to be hoped that further development of IR or other techniques will soon make them applicable to studies on the adsorption of cinchona alkaloids with rigid skeletons on Pt surfaces. Investigations using isocinchona alkaloids and their isomers may also give new information to help understand this complicated process, bringing evidence for the formation of chirally active surface sites of the metal–organic type [49] by irreversible adsorption of cinchonas [29] and the participation of these sites in enantioselection.

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