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Journal of Catalysis 231 (2005) 33–40
JOURNAL OF CATALYSIS
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Enantioselective hydrogenation of ethyl pyruvate catalyzed by α- and β-isocinchonine-modified Pt/Al_2O_3 in toluene: inversion of enantioselectivity

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Abstract

The enantioselective hydrogenation of ethyl pyruvate (EtPy) in toluene was studied on a Pt-alumina catalyst modified with α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN). The effects of the modifier concentration, temperature, and hydrogen pressure on the reaction rate and the enantioselectivity were examined. Using the Engelhard 4759 catalyst under mild experimental conditions, we observed the formation of an excess of (*S*)-ethyl lactate (EtLt) in the presence of α-ICN formed (ee_{max}: 27%). In the case of β-ICN, an inversion of enantioselectivity was observed and (*R*)-EtLt formed in excess (ee_{max}: 50%). α-ICN mainly undergoes hydrogenation during the reaction, followed by desorption, whereas β-ICN works as a chiral modifier, and the hydrogenation of EtPy is the main transformation. The results of ESI-MS-MS, HPLC-ESI-ion-trap-MS, NMR, UV–vis measurements, and experiments with modifier mixtures strongly suggest that β-ICN, with a rigid, open conformation, is responsible for enantioselection and inversion. The proposed structure of the intermediate responsible for the inversion of enantioselectivity is a 1:1 β-ICN–EtPy surface complex in which the β-ICN acts as a nucleophile and binds EtPy.

Keywords: Chiral hydrogenation; Pt-alumina; α- and β-Isocinchonine; Ethyl pyruvate; ESI-MS-MS; Intermediate; Conformation; Inversion enantioselectivity

1. Introduction

The results described in this study represent the continuation of our previous work [1] in which we addressed the chiral hydrogenation of ethyl pyruvate (EtPy) in the presence of the chiral modifiers α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN) (Fig. 1), and in the presence of acetic acid (Ref. [1]) and toluene (this work) as solvents. To avoid repetition, we simply refer to the Introduction of Ref. [1], where the significance of this research, its status, and future research objectives were discussed in detail. Here we only outline recent results disclosed during the last year with respect to the Orito reaction (Scheme 1), to demonstrate the present state of this important area. Moreover, we only mention new developments that are closely related to the problems of the present study. Recent research has mainly focused on gaining a better understanding of the reaction mechanism. These studies span the role and importance of catalyst pretreatment [2–4], the interpretation of the effect of solvents [2,5–8], and the application of various instrumental techniques [3,4,7,9,10] and quantum chemical calculations [5,11,12]. New information has been presented on the relationship between modifier structure and enantioselectivity [6,8,13,14]. Recent studies have focused on the elucidation of the relationships between the enantiomeric excess (ee) and conversion (and in this context, the initial transient period) [2,15,16] and between the rates of enantioselective and racemic hydrogenation [9,13]. Addressing the structure of the intermediate responsible for chiral induction [10,11,17,

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0021-9517/$ – see front matter
doi:10.1016/j.jcat.2004.11.013

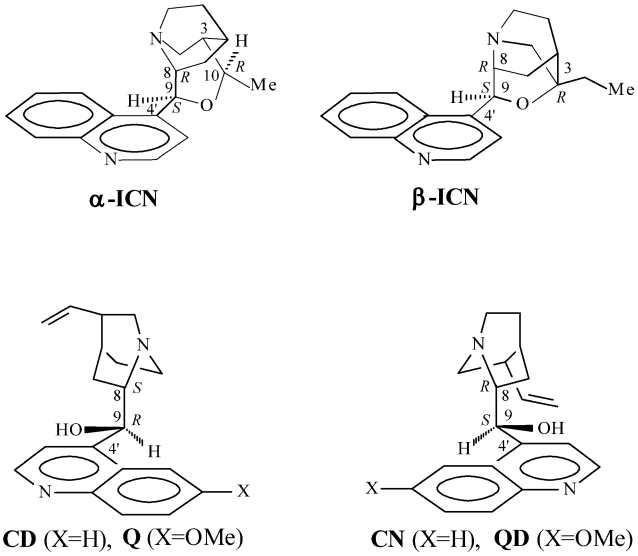
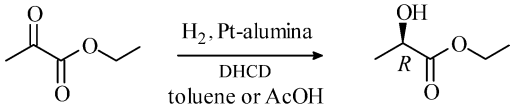


Fig. 1. The structures of ethereal derivatives of cinchonine (α-ICN, β-ICN) and parent cinchona alkaloids (CD, CN, Q, QD).



Scheme 1.

18] has greatly contributed to the clarification of the mechanism of enantioselective hydrogenation and the origin of chiral induction. The extension by Baiker et al. [7,20,21] of the so-called nonlinear effect (NLE) [19] (recognized by Kagan in the context of homogeneous catalytic reactions) to the Orito reaction is of great significance, because this makes it possible to draw conclusions regarding a very important phenomenon, the relative adsorption strengths of modifiers. It should be noted that the adsorption of chiral modifiers has recently been studied by instrumental techniques [17,18, 22]. Observations of the inversion of enantioselection [6,8, 21,23], which may be the key to the origin of chiral induction, also require interpretation.

The new results summarized above confirm our previous suggestions regarding the interpretation of the sonochemical pretreatment of catalysts [24], the effect of solvents on the hydrogenation mechanism [25,26], the effect of the structure of chiral modifiers and substrates on the proposed structure of the intermediate responsible for enantioselection [23,27], and our reservations [27–29] about the significance of ligand acceleration [30]. Results from the application of cinchona alkaloids of rigid structure (Fig. 1, α-ICN, β-ICN) as chiral modifiers in the hydrogenation of EtPy on Pt-alumina catalyst in AcOH are summarized in Ref. [1]. These results prove the earlier assumption (summarized in Ref. [31, 32]) that, in the case of hydrogenations in AcOH, it is the open-3 conformation of the cinchona alkaloid that is present in the intermediate responsible for enantioselection in the Orito reaction. Preliminary experiments in toluene, one of the two solvents (AcOH and toluene) permitting outstanding ee for EtPy hydrogenation, however, gave surprising results. Addition of the chiral modifier β-ICN led to the formation of ethyl lactate of opposite configuration [(R)-EtLt] instead of the expected (S)-EtLt [23]. This new observation encouraged us to perform more detailed studies in toluene of enantioselective hydrogenations on Pt-alumina catalysts modified by high-purity α-ICN and β-ICN.

2. Experimental

2.1. Catalysis

EtPy (Aldrich) was distilled before use to attain 99.5% purity. α- and β-ICN (100% purity) were synthesized according to the methods described in Ref. [1]. Pretreated Engelhard Pt-alumina (E4759) was used as a catalyst [1]. Hydrogenations were performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave. The catalytic system including catalyst (25 mg) and 2 mL of toluene 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 minutes 0.12 mL of EtPy was injected and stirred in the presence of hydrogen for the required reaction time. Standard conditions were 25 mg E4759, 2 mL toluene, 1 bar hydrogen pressure, 294–297 K, 1200 rpm (no diffusion control operating), 0.12 mL EtPy. The product identification and the enantiomeric excess $[\text{ee}\% = ([S] - [R]) \times 100/([S] + [R])]$ were monitored by gas chromatography (HP 5890 GC-FID, 30-m-long Cyclodex-B capillary column, uncertainty ±2%).

The mass spectrometric measurements were performed with an AGILENT 1100 LC-MSD TRAP SL ion-trap mass spectrometer equipped with an ESI source. The LC separations were carried out on a Zorbax Eclipse XDB-C18 column (4.6 mm i.d. × 250 mm) at 313 K, under the following step-gradient elution conditions: mobile phase A: 5 mmol/L ammonium formate in water; mobile phase B: 0.1% formic acid in methanol; time program: 0 min, 75% A/25% B; 13 min, 20% A/80% B; 15 min, 0% A/100% B; 18 min, 0% A/100% B; 20 min, 75% A/25% B. The program ended with a 4-min reequilibration. UV detection was performed at 301 nm. The ESI-MSD trap was operated under positive ion and auto MS-MS mode with the following parameters: ESI: capillary (needle) voltage = 3.5 kV, capillary exit voltage = 136 V, drying gas (N_2) = 9 L/min, drying gas temperature = 623 K, nebulizer gas = 40 psi; ion trap: scan range = 80–350 m/z, trap drive = 60, max. accumulation time = 300 ms, resonance excitation = 1.5 V, fragmentation time = 40 ms. The composition of the product mixture (%) was determined on the basis of the area of the MS spectrum of the chromatogram.

Hydrogenation with mixtures of modifiers was carried out in toluene as described above for a single modifier, with the exception that hydrogenation was continued after the addition of the second modifier to the hydrogenation mixture

containing the first modifier. The procedure was as follows. Hydrogenation was performed at a modifier concentration of 0.05 mmol/L until 10–20% conversion was achieved; at this point stirring was stopped and after 1 min a sample was taken. The second modifier was added next and hydrogenation and sampling were continued. Enantiomeric excess was measured as described above.

2.2. Characterization

^{1}H NMR spectra were recorded with a Bruker DRX-500 instrument at 500 MHz in $CDCl_3$ solution, with Me_4Si as an internal standard. In the proton spectra of the crude hydrogenated product of α- and β-ICN (m/z 299), there are only four aromatic proton signals and there are no benzylic proton signals at $\sim$ 6 ppm. On the other hand, there are seven new proton signals in the aliphatic proton region (0.8–4.2 ppm).

The UV–vis measurements were performed in transmission mode on a Uvikon 930 spectrophotometer with a 1-cm quartz cuvette. Spectra are given in relative absorbance units, with neat tetrahydrofuran (THF) serving as the reference. The pretreatment of E4759 was the same as described for the hydrogenation of EtPy. After hydrogenation of chiral modifiers on E4759, the samples were filtered through a 0.45-μm PTFE membrane (Cole Parmer).

The conformations of α- and β-ICN were investigated with molecular modeling. The geometries of the quinuclidine fragments (the quinoline ring replaced with a hydrogen atom) were optimized by density functional calculations at B3LYP/6-31G* [33].

3. Results and discussion

The preliminary experiments in toluene with β-ICN of 100% purity gave the already mentioned unexpected result, that because of the inversion of enantioselection, (*R*)-EtLt was formed in excess [23]. We now report our studies aimed at the interpretation of this new phenomenon. To establish the difference between the isocinchona–Pt-alumina–toluene system and the system containing the parent alkaloids (Fig. 1) (cinchonidine—CD, cinchonine—CN, quinine—Q, quinidine—QD), optimization experiments were done. The data obtained at various modifier concentrations and various temperatures are summarized in Tables 1 and 2.

3.1. Effects of reaction conditions

Dihydrocinchonidine (DHCD) concentration has been reported to have a significant influence on reaction rate and ee during hydrogenation of EtPy in toluene, at hydrogen pressures of 1 bar [26] and 20–100 bar [34,35]. The data in Tables 1 and 2 do not show such a tendency, however, mainly because in some cases the reproduction of the results proved to be problematic. In spite of all efforts, the establishment of identical experimental conditions was unsuccessful, which is most probably due to differences in the surface state of the freshly activated catalyst. The measurements were reproduced several times (an effect was accepted as significant only after several convincing reproductions).

Table 1
Experimental data on enantioselective hydrogenation of EtPy on Pt-alumina catalyst modified by α-ICN (standard conditions)

Entry	Modifier (mmol/L)	Temperature (K)	Time (min)	Conversion (%)	Rate (mmol/(min g)) ($r \pm 0.2$)	Ee (*S*%)
1.	0.01	293	45	100	1.1	10
2.	0.1	273	60	100	0.7	22
3	0.1	297	35	100	1.9	22
4.	1	263	60	51	0.3	20
5.	1	273	50	87	0.6	18
6.	1	273	60	85	0.6	14
7.	1	283	50	100	1.0	20
8.	1	293	35	100	1.3	20
9.	1	303	25	100	2.7	19
10.	1	333	15	100	3.5	27
11.	10	273	60	72	0.6	20

Table 2
Experimental data on enantioselective hydrogenation of EtPy on Pt-alumina catalyst modified by β-ICN (standard conditions)

Entry	Modifier (mmol/L)	Temperature (K)	Time (min)	Conversion (%)	Rate (mmol/(min g)) ($r \pm 0.2$)	Ee (*R*%)
1.	0.001	293	30	77	1.5	0
2.	0.002	293	30	88	1.5	0
3.	0.004	293	30	95	1.9	0
4.	0.006	293	30	100	2.2	20
5.	0.01	263	35	100	1.4	45
6.	0.01	273	20	100	2.8	38
7.	0.01	293	20	100	2.8	48
8.	0.01	293	25	100	3.0	40
9.	0.1	297	15	100	3.1	50
10.	0.1	297	15	100	3.3	44
11.	1	283	20	100	2.7	34
12.	1	297	20	100	3.0	42
13.	1	303	10	100	4.5	39
14.	1	333	10	100	6.5	35

The following conclusions can be drawn from the data in Tables 1 and 2: (i) in the presence of α-ICN, (*S*)-EtLt was produced in excess, whereas with β-ICN as a modifier, an excess of (*R*)-EtLt was formed; (ii) with α-ICN the reaction rate did not increase as compared with the rate of racemic hydrogenation, which is an unusual phenomenon; (iii) for β-ICN the modified reaction is significantly faster than the racemic reaction and the reaction rate hardly changes at all in the β-ICN concentration range of 0.01–1 mmol/L; (iv) the apparent activation energies of hydrogenation are $\sim$ 26 and $\sim$ 14 kJ/mol of α- and β-ICN, respectively.[1] Since no diffu-

[1] Referee's suggestion.

Table 3
Effect of hydrogen pressure on enantioselective hydrogenation of EtPy on Pt-alumina catalyst modified by α-ICN in toluene (conditions: 50 mg E4759, 5 mL toluene, 1200 rpm, 0.2 mL EtPy)

Entry	Modifier (mmol/L)	Temperature (K)	H_2 (bar)	Time (min)	Ee (%)
1.	α-ICN (1)	273	10	30	30 *S*
2.	α-ICN (1)	273	20	30	34 *S*
3	α-ICN (1)	273	50	30	20 *S*
4.	α-ICN (1)	338	20	20	16 *S*
5.	α-ICN (1)	338	40	20	10 *S*
6.	α-ICN (1)	338	80	20	7 *S*
7.	β-ICN (0.1)	273	20	30	38 *R*
8.	β-ICN (0.1)	273	50	30	34 *R*

sion control is operating [26], this indicates different hydrogenation mechanisms for α- and β-ICN.

In view of the fact that the α-ICN modifier affected neither the hydrogenation rate nor the ee significantly, the role of other experimental conditions (hydrogen pressure, temperature) had to be examined (Table 3). α-ICN enabled 34% ee at a hydrogen pressure of 20 bar and a temperature of 273 K. When the modifier was β-ICN, the ee was not affected by hydrogen pressure. In summary, the isocinchona–Pt-alumina–toluene chiral catalytic system is significantly different from the catalytic system containing DHCD studied earlier [31,32].

3.2. Results of HPLC-MS measurements

Optimization of the conditions of the HPLC permitted efficient separation for the identification and quantification of certain cinchona derivatives formed in the course of the hydrogenation of α- and β-ICN (Table 4). The stability of α-ICN under the conditions used is significantly lower than that of β-ICN. The fast hydrogenation of α-ICN under very mild experimental conditions (1 bar H_2, 298 K) in the presence of EtPy is particularly striking. Regarding the composition of the product mixtures, the ions at m/z 295 have been proved by ESI-MS-MS and ^{1}H NMR to be the protonated forms of α- and β-ICN. Compounds 299, formed from α-ICN and β-ICN with relatively high selectivity, were successfully isolated in specifically designed experiments (hydrogenation conditions: 20 mg α-ICN, 313 K, 40 bar hydrogen, 3 h; 20 mg β-ICN, 323 K, 50 bar hydrogen, 6 h). The hydrogenated compounds were identified as 1′,2′,3′,4′-tetrahydro-α-ICN (**A**) and 1′,2′,3′,4′-tetrahydro-β-ICN (**B**) by ^{1}H NMR (Fig. 2). A compound with m/z 305 formed from α-ICN was identified by ESI-MS-MS as decahydro-α-ICN (**C** in Fig. 2).

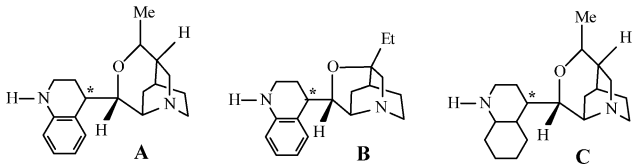


Fig. 2. Cinchona alkaloid derivatives formed by hydrogenation of α-ICN and β-ICN.

When EtPy hydrogenation was carried out in the presence of the chiral modifiers **A** and **B** (Fig. 2, standard conditions, 0.01 mmol/L of **A** or **B**, toluene) the ee-s were 0%. The most important conclusion of these experiments is that the compound responsible for the formation of the product of unexpected configuration [(*R*)-EtLt] is β-ICN. Otherwise **A** and **B** cannot be the initiators of chiral induction, since ee has been proved to decrease in the presence of hydrogenated cinchonas [36]. These conclusions are also supported by the UV spectra of the hydrogenation products of α-ICN and β-ICN (Figs. 3a and 3b). Figs. 3a and 3b clearly demonstrate that α-ICN is significantly less stable than β-ICN under the conditions of hydrogenation.

3.3. Results of modifier mixtures

One of the most important conclusions of these studies is the estimation of the relative adsorption strength of the modifiers. This is a crucial piece of information with respect to the elucidation of the reaction mechanism [7,20,21]. Some of the experimental results (Fig. 4) provide information mainly on the adsorption tendency of β-ICN. It is highly probable that the adsorption strength of β-ICN is higher than that of QD and Q and very similar to that of CN. This indicates that the quinoline skeleton of adsorbed β-ICN is approximately parallel to the Pt surface. In contrast, the quinoline plane of adsorbed Q and QD is tilted relative to the Pt surface. Data in Fig. 4 (see α-ICN–β-ICN) clearly show

Table 4
Hydrogenation of α-ICN and β-ICN on Pt-alumina in toluene in the absence and in the presence of EtPy[a]

Substrate (M)		M = α-ICN			M = β-ICN	
m/z values of $[M+H]^+$		295 $[M+H]^+$	299 $[A+H]^+$	305 $[C+H]^+$	295 $[M+H]^+$	299 $[B+H]^+$
Temperature (K)	H_2 (bar)	Composition (%) of cinchona derivatives				
263	1	91	9	–	98	2
298	1	79	21	–	97	3
298[a]	1	10	60	30	93	7
323	40	14	80	6	94	6
Retention time (min)		7.3	9.6	2.3–2.8	8.3	10.5

[a] Standard conditions, 5 mL toluene, [modifier] = 1 mmol/L, time 30 min, **A**, **B** and **C** see in Fig. 2.

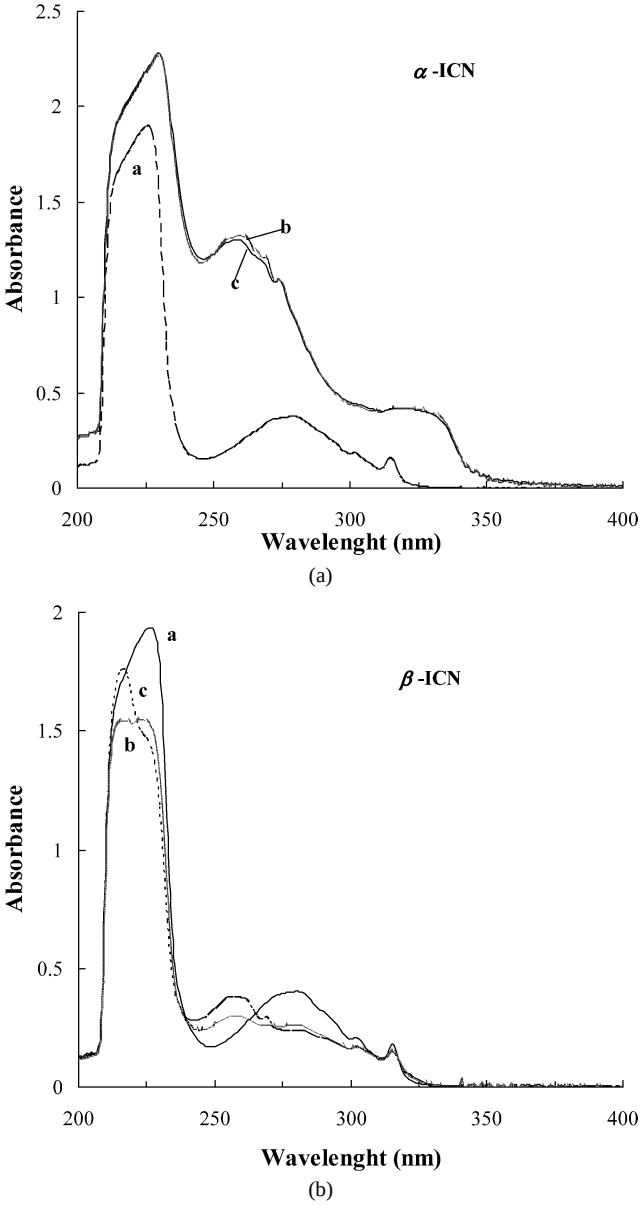


Fig. 3. UV–vis spectra of α-ICN, β-ICN and their hydrogenation products formed over Pt-alumina in tetrahydrofurane (THF) (conditions: 10 mg E4759 pretreated, 5 mL THF, 0.07 mmol/L α-ICN or β-ICN, 1 bar H_2, 293 K, 1200 rpm; a: spectra of initial solutions, b and c: spectra after 5 and 10 min hydrogenation, respectively).

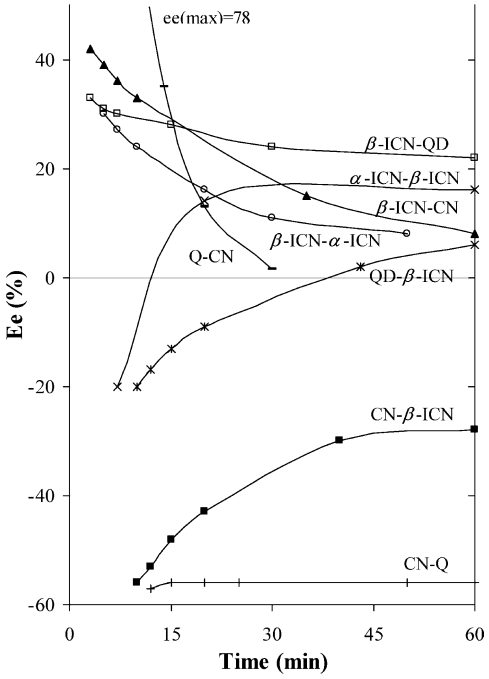


Fig. 4. Enantioselective hydrogenation of EtPy in toluene: effect of modifier mixtures on ee (standard conditions, 273 K, [modifiers] = 0.05 mmol/L, first abbreviation—modifier used first, second abbreviation—modifier added afterwards).

Table 5
Experimental data on enantioselective hydrogenation of EtPy in toluene and AcOH on Pt-alumina catalyst modified by α-ICN, β-ICN and DHCD (standard conditions; tw = this work)

Entry	Modifier (mmol/L)	Solvent	Temperature (K)	Rate (mmol/(min g)) ($r \pm 0.2$)	Ee (%)	Ref.
1.	0.01 α-ICN	Toluene	293	1.1	10 *S*	tw
2.	0.01 α-ICN	AcOH	297	0.3	66 *S*	[1]
3.	0.01 β-ICN	Toluene	293	3.1	40 *R*	tw
4.	0.01 β-ICN	AcOH	297	3.3	62 *S*	[1]
5.	0.01 DHCD	Toluene	297	3.4	64 *R*	[26]
6.	0.01 DHCD	AcOH	297	3.3	91 *R*	[26]
7.	0.1 α-ICN	Toluene	297	1.9	22 *S*	tw
8.	0.1 α-ICN	AcOH	297	1.1	66 *S*	[1]
9.	0.1 β-ICN	Toluene	297	3.1	48 *R*	tw
10.	0.1 β-ICN	AcOH	293	3.8	49 *S*	[1]
11.	0.1 DHCD	Toluene	297	5.8	78 *R*	[26]
12.	0.1 DHCD	AcOH	297	5.1	92 *R*	[26]
13.	1 α-ICN	Toluene	303	2.6	18 *S*	tw
14.	1 α-ICN	AcOH	293	1.9	76 *S*	[1]
15.	1 β-ICN	Toluene	297	3.0	42 *R*	tw
16.	1 β-ICN	AcOH	297	2.2	50 *S*	[1]
17.	1 DHCD	Toluene	297	4.3	77 *R*	[26]
18.	1 DHCD	AcOH	297	3.8	92 *R*	[26]

that the adsorption strength of β-ICN significantly exceeds that of α-ICN. The reasons for these assumptions are (i) QD is more easily displaced from the surface by β-ICN than β-ICN is by QD; (ii) β-ICN has a more profound effect on the adsorption of CN than Q has (compare the curves CN–β-ICN and CN–Q); (iii) Q is more easily displaced from the surface by CN than is β-ICN (see Q–CN and β-ICN–CN).

3.4. Comparison of toluene and AcOH as solvents

In the presence of DHCD, enantiomeric excesses are higher in AcOH than in toluene (Table 5). This is in agreement with earlier publications [6,26,31,36], except that these authors did not emphasize the crucial difference between the hydrogenation mechanisms in the two solvents, which is also related to the solubility/solvation of the chiral modifiers [37]. The solubility of the more polar DHCD in toluene is significantly lower than those of the less polar α- and β-ICN. In AcOH the benzene ring of the quinoline skeleton undergoes

hydrogenation, whereas in toluene the pyridine ring of the quinoline skeleton is selectively hydrogenated [7,38].

Regarding the reaction rates, hydrogenation, in general, is faster in toluene than in AcOH with DHCD as a modifier. In the case of α- and β-ICN this tendency is not clear. With DHCD as a modifier, the reaction rate versus modifier concentration function has a maximum in both solvents [26,31,34,39]. Blaser et al. explained this by the so-called three-site model on the basis of their kinetic study [34], whereas LeBlond et al. [39] interpreted it by the change in the optimal adsorption geometry of DHCD at higher concentrations of the modifier in AcOH. The latter was verified by attenuated total infrared spectroscopy [40].

The inversion occurring in the case of EtPy hydrogenation on catalyst E4759 modified with β-ICN prompted us to study changes in ee in AcOH/toluene mixtures [23]. The figure in Ref. [23] demonstrates that there is a linear correlation between the composition of the solvent mixture and the sense of chiral induction, pointing unequivocally to a change in reaction mechanism, that is, a change in the structure of the intermediate responsible for enantioselection.

4. Interpretation of enantioselective hydrogenation on the Pt-alumina–isocinchona–toluene catalyst system

Our experiments on isocinchona alkaloids in toluene suggest that conclusions regarding the mechanism [31,32] of the Orito reaction need further elaboration and probably correction. It appears that in certain cases the principal factors responsible for enantioselection and its direction are not only the configurations of the C8 and C9 atoms; other circumstances may also play an important role. The formation of (*R*)-EtLt instead of the expected (*S*)-EtLt (inversion of enantioselectivity) in the course of EtPy hydrogenation on the Pt-alumina/β-ICN/toluene system seems to support this assumption.

Based on our experimental data, the verified structure and conformation [41,42] of α- and β-ICN (Figs. 5), and the widely accepted adsorption model [31,32,43], the structure of the intermediate responsible for the direction of enantioselectivity must also be different from the one universally accepted (see summaries in Ref. [31,32,43]). In addition, a different structure for the putative intermediate is also indicated by the observation that experimental data obtained in AcOH and toluene with α- and β-ICN as modifiers were entirely different from those for CD and CN under similar experimental conditions. In the latter case, in AcOH the intermediate is generated via the interaction of the protonated cinchona, acting as an electrophilic agent, with the nucleophilic oxygen atom of the keto group of EtPy (Fig. 6**A**). In toluene, an intermediate of similar structure was assumed, with semihydrogenated EtPy (Fig. 6**B**). We have pointed out several times [23,25,26] that the reaction mechanisms of the two solvents must be more different than assumed.

The experimental data presented above demonstrate the decisive role of the conformation and adsorption of modifier molecules (α- and β-ICN) in directing chiral induction. Our reasoning is based on the conformation of α- and β-ICN as described by Thiel et al. [41] and Braje et al. [42]. Although both modifiers have rigid structures due to the hindered rotation along the C8–C9 carbon bond (i.e. they have so-called anti open conformations), there are still large differences between the two modifiers. Regarding the conformations, β-ICN has the more rigid six-membered "oxazatwistane" structure (twist-chair conformation; **A** in Fig. 5) of more ex-

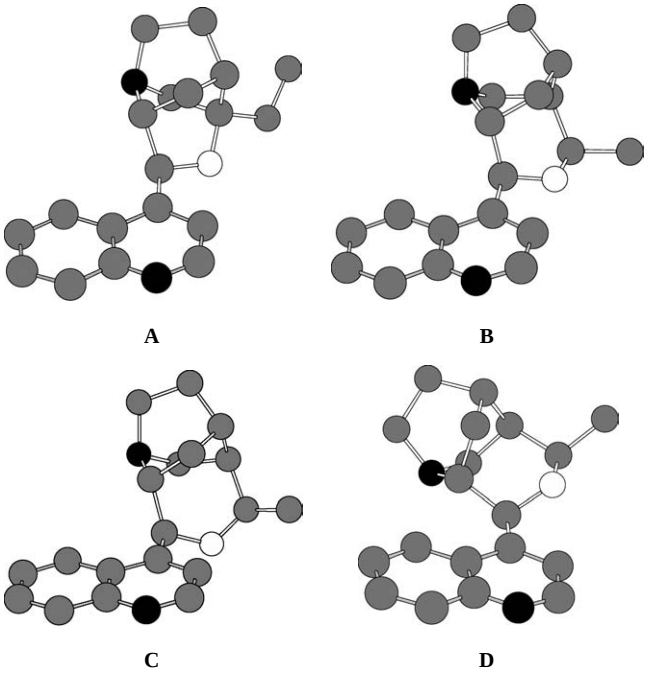


Fig. 5. Conformations of β-ICN (**A** twist-chair) and α-ICN (**B** twist-chair, **C** twist-boat, **D** twist-chair on the surface); (abbreviations: black sphere—N atoms, white sphere—O atoms, grey sphere—C atoms).

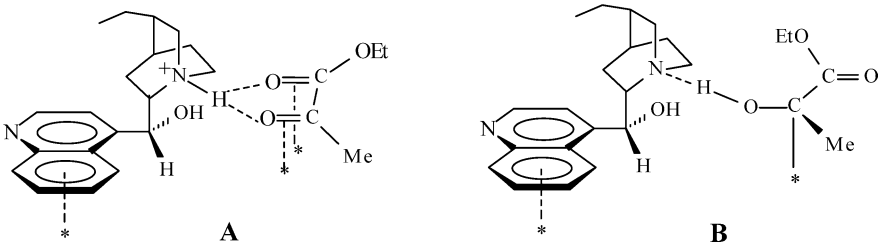


Fig. 6. Proposed adsorbed adduct complexes of DHCD (in anti open conformation) and EtPy.

tensive symmetry. In contrast, α-ICN exists in two stable conformers (Fig. 5): in one conformer the oxazacycloheptane skeleton has twist-chair conformation (**B**), whereas in the other conformer it has the twist-boat conformation (**C**).

On the basis of our calculations the twist-chair conformer **B** has the absolute energy minimum, which is 18 kJ/mol lower than the energy of the twist-boat **C** conformation. The β-quinuclidine fragment is rigid; it has no alternative conformations. The optimized structure of conformer **A** has a total energy 6 kJ/mol higher than that of conformer **B**. In addition, the N atom of the quinuclidine skeleton of conformation **B** may also get close to the surface (Fig. 5**D**). This surface binding allows hydrogenation of α-ICN to TH–α-ICN (Fig. 2**A**), leading to the rapid desorption of the modifier, as verified by our experimental data (Table 4). In any case, surface binding of the quinuclidine skeleton inhibits the formation of the intermediate complex responsible for enantioselection. When β-ICN is adsorbed, the relatively large distance of the N atom of the quinuclidine skeleton from the surface makes the formation of the surface complex possible, because rotation along the C4′–C9 bond, permitted in the case of α-ICN, is inhibited in the case of β-ICN.

According to our assumption, the hydrogenation of EtPy to (*R*)-EtLt on the Pt-alumina–β-ICN–toluene catalyst system is based on the formation of surface intermediates **A** or **B** (Fig. 7). Thus, the surface complex responsible for inversion is formed as a result of the interaction between the nucleophilic N atom of the quinuclidine skeleton and the electrophilic C atom of the keto group of EtPy. The conformation of β-ICN participating in surface complex **A** is anti open, whereas it is syn open in surface complex **B**. As this interaction appears to be evident in reactions of organic compounds, interactions of this type have occasionally been proposed for heterogeneous catalysis but not accepted for enantioselective heterogeneous catalysis [23,44–46]. The mechanism based on the N → C=O interaction was later verified by quantum chemical calculations [11].

As shown in Fig. 7, the N → C=O interaction can only take place if the nucleophile is positioned perpendicular to the plane of the trigonal carbon atom, in other words when the carbonyl group to be hydrogenated is not parallel with but perpendicular to the Pt surface (end-on fashion or η^1 mode) [47–49]. The H atom attacks the surface complex from the direction opposite the N atom of quinuclidine (as in reactions of the S_N2 type); that is, inversion takes place on the carbon atom of the carbonyl group of EtPy in the surface-adsorbed state (Fig. 8).

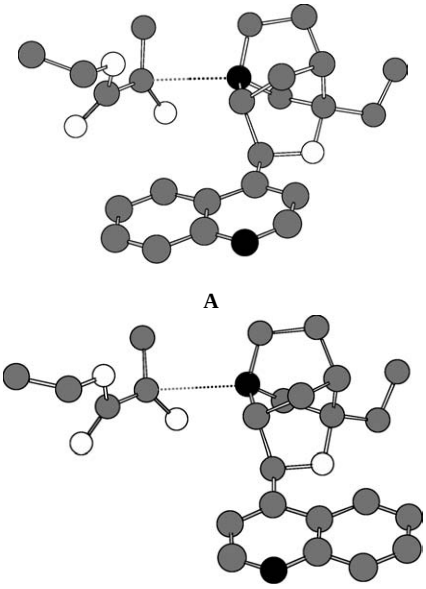


Fig. 7. The proposed structures of the adsorbed adduct complexes of β-ICN and EtPy in toluene (**A** anti open complex, **B** syn open complex; for abbreviations, see Fig. 5).

To interpret the inversion effected by β-ICN, the role of the organometallic type surface complexes may not be excluded either. The formation of this complex was earlier proposed just for the interpretation of hydrogenation in toluene [25,26] and was supported by experimental data in the literature. In accordance with the corresponding C–O bond strengths, β-ICN containing a tertiary C–O bond is less stable than α-ICN, which contains a secondary C–O bond (870 vs. 924 kJ/mol). As a consequence, β-ICN can more readily form a surface complex when interacting with the surface Pt atoms.

It has to be noted that inversion of enantioselectivity has recently been reported [6,8,21,50]. Although the reason for the inversion was not discussed in detail, certain useful suggestions were made, such as "weaker adsorption" of modifiers and the presence of the C9 group, which may alter substrate adsorption. Our observations with α- and β-ICN, however, may not be interpreted along these lines. It is hoped that further development of instrumental techniques will yield further data for the interpretation of chiral induction.

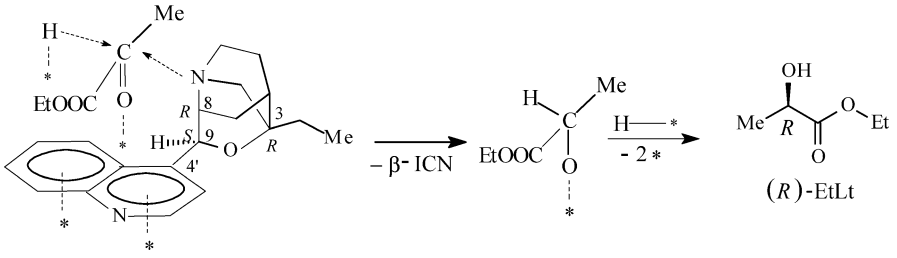


Fig. 8. The inversion of enantioselectivity in the hydrogenation of EtPy catalyzed by β-ICN modified Pt-alumina in toluene.

In some of the methods that have been applied up to now [3,4,10,17,18,22,40,51–56] the concentration of the chiral modifiers is unknown, and in the cases where it is known, the modifier concentration is about 10^{-4} mmol/L, whereas chiral induction proceeds with high ee at a concentration as low as 10^{-6} mmol/L. Our future tasks are to continue these experiments with further substrates to verify the above propositions and to provide experimental proof for the existence of the surface Pt complex formed in the presence of β-ICN.

Acknowledgments

Financial support by the Hungarian National Science Foundation (OTKA Grant TS044690 and T 042466) is highly appreciated. The authors are grateful to Professor Á. Molnár (University of Szeged) for valuable discussions and Dr. P. Forgó and Dr. T. Martinek (University of Szeged) for the NMR measurements.

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