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Journal of Catalysis 239 (2006) 74–82
JOURNAL OF CATALYSIS
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Inversion of enantioselectivity in the hydrogenation of ketopantolactone on a Pt-β-ICN chiral catalyst

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Received 22 November 2005; revised 10 January 2006; accepted 11 January 2006

Available online 10 February 2006

Abstract

The enantioselective hydrogenation of ketopantolactone (KPL) both in AcOH and in toluene was studied on a Pt-alumina catalyst modified by α-isocinchonine (α-ICN) and β-isocinchonine (β-ICN). The effects of the modifier concentration, temperature, solvents, and mixtures of modifiers on the reaction rate and enantioselectivity were examined under mild experimental conditions (253–298 K, 1 bar H_2 pressure, 0.001–0.1 mM/L modifier concentration). Formation of excess (*S*)-PL was observed in the presence of α-ICN in both solvents (ee_{max}, 37%). In the enantioselective hydrogenation of KPL over a Pt-alumina-β-ICN chiral catalyst, the major enantiomer was (*R*)-PL (ee_{max}, 60%) in toluene, whereas in AcOH, (*S*)-PL (*ee*, 5%) was formed. The (*R*) configuration was opposite to what was expected from the absolute configuration of the cinchonine backbone; namely, inversion of enantioselectivity occurred. The conformational rigidity of both chiral modifier and reactant provides new insight into the possible structure of intermediate complexes in the enantioselective hydrogenation of activated ketones. The proposed structure of the intermediate responsible for the inversion of enantioselectivity is an adsorbed 1:1 β-ICN-KPL surface complex [**C1** pro(*R*) and **C2** pro(*R*)] in which the β-ICN acts as a nucleophile and binds KPL.

Keywords: Chiral hydrogenation; Pt-alumina; α- and β-isocinchonine; Ketopantolactone; Intermediate; Conformation; Inversion of enantioselectivity; Sense of enantioselection

1. Introduction

The synthesis of optically active compounds has become one of the most important fields of organic chemical research [1–5]. Its well-known advantages make the preparation of chiral compounds using enantioselective heterogeneous catalytic hydrogenation an extremely significant synthetic method. Two of these preparation procedures, the hydrogenation of some 1,3-dioxo compounds and β-oxo-carboxylic acid esters on tartrate-modified Raney–Ni [6,7] and the hydrogenation of certain activated ketones on cinchona-modified Pt (Orito reaction, Scheme 1) [8], are currently done on an industrial scale [9]. The common feature of both procedures is chiral modification of the surface of the metals by an appropriate chiral compound, which makes chiral hydrogenation possible.

The state of research on the enantioselective hydrogenation of activated ketones has been the subject of numerous reviews since 2000 [10–15]. The main objectives of recent studies on the Orito reaction have been to expand its field of utilization, elucidate the reaction mechanism, and interpret the origin of chiral induction in this context. Various research strategies and methods have been used to study the reaction mechanism. Because these studies have concluded that the structure of the chiral modifier plays a decisive role in enantioselection, many experiments have been and are currently being conducted to gain better insight into the relationship between ee and the structure of the chiral modifier.

It was established as early as in 1979 that the two pseudoenantiomers (CD and CN) induce the formation of ethyl lactates of opposite configurations during EtPy hydrogenation [8] (Scheme 1). Further studies proved this phenomenon to be generally valid; of the parent alkaloids, those with the C8(*S*) C9(*R*) configuration (i.e., CD and Q) induce the formation of (*R*)-α-

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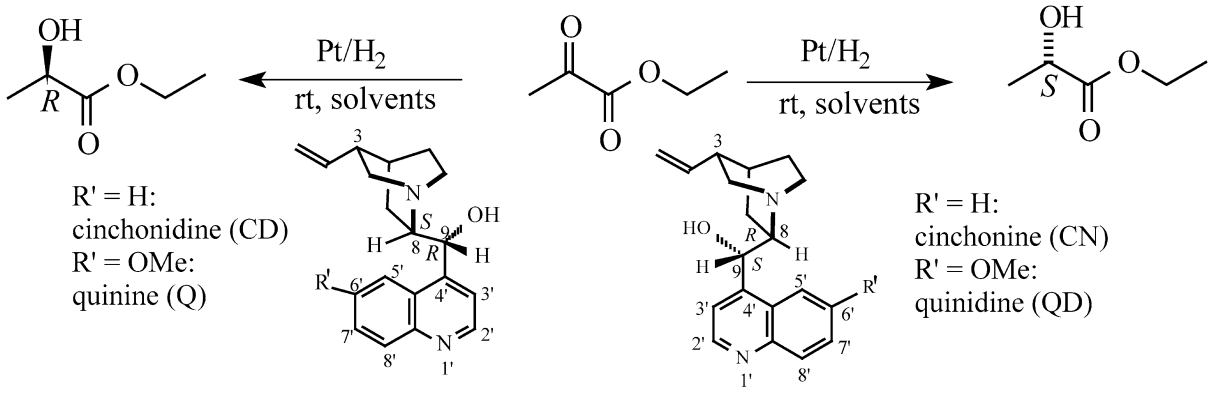
0021-9517/$ – see front matter
doi:10.1016/j.jcat.2006.01.016



Scheme 1.

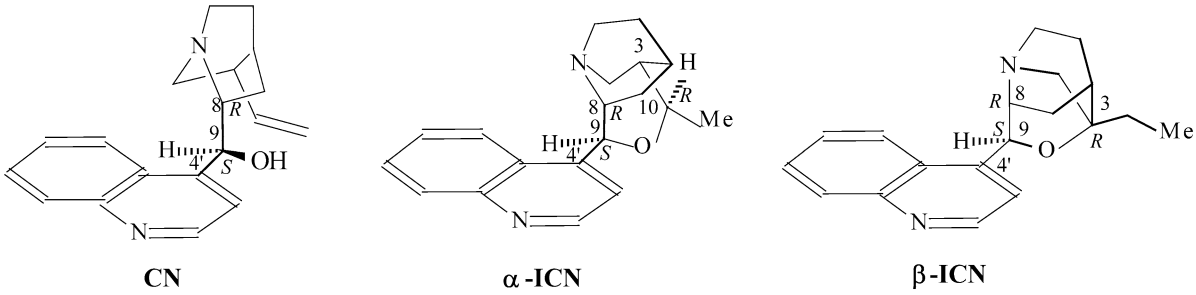


Fig. 1. The structure of ethereal derivatives (α-ICN, β-ICN) of cinchonine (CN).

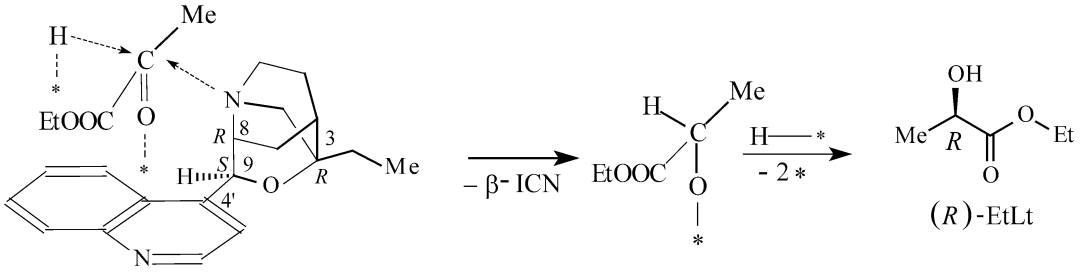


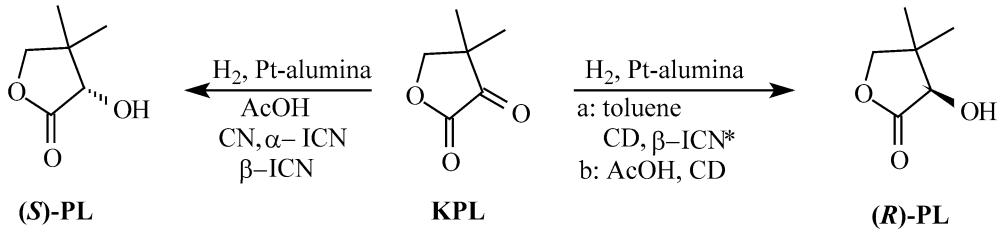
Fig. 2. The inversion of enantioselectivity in the hydrogenation of EtPy catalyzed by β-ICN modified Pt-alumina in toluene.

hydroxy esters, whereas those with the C8(R) C9(S) configuration (i.e., CN and QD) promote the formation of (S)-α-hydroxy esters [10–15]. It has been shown that among the five stereogenic centers of cinchona alkaloids, only the one at C8 determines the sense of enantioselection [10,12,13]. Along with the configuration of carbon atoms, these studies also stressed the importance of the conformation of chiral modifiers [16]. According to nuclear magnetic resonance and X-ray diffraction measurements on the parent cinchona alkaloids, as well as molecular mechanical calculations, of the four stable conformations possible, alkaloids are present in solution mostly in the so-called "open-3" or "anti-open" conformation [17] (Fig. 1).

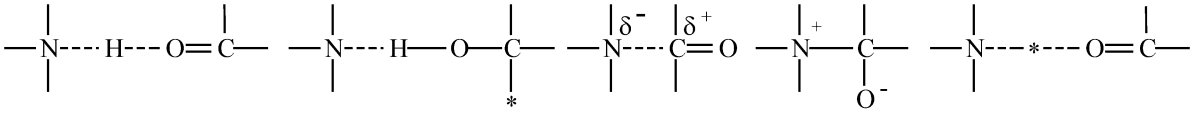
Most researchers have assumed a determining role of the open-3 conformation in chiral induction [10–15] that could later be experimentally confirmed in the case of rigid isocinchona alkaloids (e.g., α- and β-ICN) [18]. Because of inhibition of rotation along the C8–C9 bond (Fig. 1), these cinchona alkaloids can exist only in open conformation [19–21].

EtPy hydrogenations in the presence of β-ICN have led to completely unexpected results, however. In the enantioselective hydrogenation of EtPy over a Pt-alumina-β-ICN chiral catalyst, the major enantiomers were (S)-EtLt (*ee* 60%) in AcOH and (R)-EtLt (*ee* 50%) in toluene; the (R) configuration is opposite to that expected from the absolute configuration of the β-ICN backbone [22,23]. According to our interpretation [23], inversion of enantioselectivity relative to CN is a consequence of the change of the adsorption mode of the β-ICN + EtPy intermediate complex. The surface complex responsible for the inversion was assumed to be 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 [23] (Fig. 2). Experimental verification of the inversion of enantioselectivity allows to conclude that the determinant role of the configuration of carbon atom C8 cannot be universally valid.

Unexpected inversion of enantioselectivity under conditions similar to those of the Orito reaction had been reported earlier, but, due to the low ee values involved, these results received little attention [24–26]. Since the publication of the study by [22], however, the inversion of enantioselection has become a popular research objective, because it yields important new



Scheme 2.



Scheme 3. Proposed intermediate complexes in Orito reaction: **A** [10,12,39–44], **B** [10,11,39,41], **C** [22,45,46], **D** [47], **E** [24,48,49].

information regarding the characteristics of the reaction mechanism [27–35]. Inversion of enantioselectivity was also observed in the conversion of 4,4,4-trifluoroacetoacetate under the conditions of the Orito reaction; however, this case involved enantioselective hydrogenolysis of a geminal diol rather than hydrogenation [36].

In the studies carried out to date, inversion in the enantioselective hydrogenation of activated ketones was observed when the structure of the chiral modifier or the reaction conditions were altered [26–34]. More recently, it has been recognized that inversion of enantioselection in the case of the prochiral C=C bond hydrogenation on a Pd-cinchona chiral catalyst occurs when chiral modifier concentration is altered [35].

Because we observed an unusual new phenomenon [22] in the case of the hydrogenation in toluene of EtPy on Pt-alumina-β-ICN chiral catalyst, we proceeded to study the dependence of inversion on substrate structure to obtain further information on the Orito reaction. We first chose to examine the rigid dihydro-4,4-dimethyl-2,3-furanedione [ketopantolactone (KPL)] studied by Baiker et al. [37,38], whose hydrogenation on Pt-alumina catalyst modified by CD yielded (*R*)-pantolactone (PL) (Scheme 2) in high enantioselectivity. Studies of the two rigid compounds (modifier and reactant), which have not yet been studied together, are expected to yield new information regarding the structure of the proposed intermediate complexes responsible for enantioselective hydrogenation of activated ketones (Scheme 3).

2. Experimental

2.1. Materials

KPL (Aldrich) and solvents (Fluka) were used as received. α- and β-ICN (100% purity) were synthesized as described previously [19–21]. Based on data in the literature, the most commonly used catalyst 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 stored under air before use.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric batch reactor. The catalytic system including catalyst (25 mg) and 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 injected, and after 0.5–1 min, 128 mg of KPL in 1 mL of toluene was injected and stirred in the presence of hydrogen for the required reaction time. Standard conditions were 25 mg of E4759, 5 mL of solvent, 1 bar hydrogen pressure, 294–297 K, 900–1000 rpm (no diffusion control operating), and 128 mg of KPL. The product identification and enantiomeric excess [ee (%) $= ([R] - [S]) \times 100/([R] + [S])$] were monitored by gas chromatography [HP 6890 N GC-FID (398 K, 21.65 psi He), with a 30-m-long Cyclodex-B capillary column; retention times: 10.6 min of (*S*)-PL, 11.2 min of (*R*)-PL; reproductibility, ±2%].

2.3. ESI ion trap MS measurements

The ESI-MSD ion trap (AGILENT 1100 LC-MSD TRAP SL ion trap MS) was operated under positive-ion and auto MS-MS modes using 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; maximum accumulation time, 300 ms; fragmentation amplitude, 1.5 V; fragmentation time, 40 ms.
Solvent MeOH/0.1% AcOH.
Flow rate 0.5 mL/min.
Sample concentration 0.1 μmol/L.
Injected volume 1.5 μL.

Table 1
Experimental data on enantioselective hydrogenation of KPL on Pt-alumina catalyst modified by cinchona alkaloids (standard conditions)

Entry	Modifier (mmol/L)	Solvent	Temperature (K)	Time (min)	Conversion (%)	Rate (mmol/(min g))	*ee* (%)
1	CD 0.1	T	283	8	100	5.9	52 *R*
2	CD 0.1	T	298	6	100	7.2	48 *R*
3	CD 0.1	AcOH	283	11	100	4.2	51 *R*
4	CN 0.1	T	298	6	100	8.2	52 *S*
5	CN 0.1	AcOH	298	8	100	5.2	55 *S*
6	α-ICN 0.1	T	298	10	100	5.7	15 *S*
7	α-ICN 0.1	AcOH	298	9	100	5.4	37 *S*
8	β-ICN 0.1	T	298	6	100	8.8	46 *R*
9	β-ICN 0.1	AcOH	298	8	100	6.5	5 *S*
10	β-ICN 0.1	CH_2Cl_2	298	12	100	4.2	27 *R*
11	β-ICN 0.1	THF	298	12	100	4.8	41 *R*
12	β-ICN 0.1	Dioxane	298	40	85	0.9	32 *R*
13	β-ICN 0.1	F_3T	298	9	100	6.5	45 *R*
14	β-ICN 0.1	T	273	9	100	6.1	57 *R*
15	β-ICN 0.1	T	263	12	98	5.1	58 *R*
16	β-ICN 0.1	T	253	1	10	–	55 *R*
17	β-ICN 0.1	T	253	5	30	2.4	57 *R*
18	β-ICN 0.1	T	253	26	96	2.2	60 *R*
19	β-ICN 0.01	T	298	6	100	8.8	45 *R*
20	β-ICN 0.01	T	273	8	100	6.9	58 *R*
21	β-ICN 0.001	T	298	15	99	5.0	27 *R*
22	β-ICN 0.001	T	273	32	100	2.4	33 *R*
23	β-ICN 0.001	T	263	50	100	1.5	43 *R*

2.4. Infrared measurements

The infrared measurements were performed on a BIO-RAD FTS-7 spectrometer using 128 scans at a resolution of 4 cm^{-1}. The spectra were recorded using a liquid cell of 1 mm path length equipped with KBr windows in CCl_4 solution or neat reactant using a thin film placed between KBr plates. Solutions of EtPy, KPL, DABCO, MeOCD, and β-ICN of 20 mM/L were used for comparison. Mixtures of EtPy/MeOCD 1/1, EtPy/β-ICN 1/1, KPL/DABCO 1/1 and 1/5, and KPL/MeOCD 1/1 and 1/5 were prepared using the above solutions. In these experiments, the neat solvent was used as reference for the spectra of the solutions. The spectra of trifluoromethylphenyl ketone and trifluoromethylphenyl ketone/DABCO 1/1 mixture were recorded neat.

3. Results and discussion

KPL is made an excellent model compound for studies on the reaction mechanism due not only to its rigid structure, but also to the cis conformation of this five-membered ring compound containing two oxo groups. Baiker et al. obtained much amount new information in their multifaceted studies on the enantioselective hydrogenation of KPL to enrich the knowledge base on this complicated catalytic system [27,32,50–52]. That is why planning the experimental tasks was done with great expectations that the two rigid systems (β-ICN and KPL) would provide new insights relative to those recognized in experiments using EtPy.

Preliminary experiments on hydrogenation of KPL over Pt-alumina-β-ICN chiral catalyst in toluene showed inversion of enantioselectivity similar to the case of EtPy hydrogenation; that is, (*R*)-PL was formed in higher enantiomeric excess. Our next step was to perform a series of experiments on Pt catalysts modified with α- and β-ICN at a hydrogen pressure of 1 bar, with variations in the individual experimental conditions (i.e., modifier concentrations, hydrogenation temperatures, solvents, mixtures of β-ICN and CN modifiers). For the sake of comparison, we also made some measurements using CD and CN under conditions identical to those used for β-ICN.

3.1. Effects of reaction conditions

The data obtained under various reaction conditions are summarized in Table 1 and can be summarized as follows. In the presence of CD and β-ICN in toluene, (*R*)-PL was produced in excess (entries 1, 2, and 8), whereas with CN and α-ICN as modifiers, an excess of (*S*)-PL was formed (entries 4 and 6). This means that β-ICN and CN, modifiers with stereogenic centers of identical configurations [C8(*R*) and C9(*S*)] showed a divergence in enantioselection. In other words, β-ICN played a role in enantioselection identical to that of CD; that is, β-ICN brought about an inversion of enantioselectivity of such magnitude that CD and β-ICN had nearly identical ee values (Scheme 2). It is quite remarkable that hydrogenation of KPL was faster on Pt-β-ICN chiral catalyst than on Pt-CD chiral catalyst (entries 2 and 8); this may be associated with a more favorable conformation of the intermediate forming on the catalyst surface responsible for enantioselection.

Increasing solvent polarity in the hydrogenation of KPL on Pt-β-ICN catalyst reduced the formation of (*R*)-PL; moreover, in AcOH, (*S*)-PL was formed in excess (entries 8–13). It is

mainly the latter observation that allows to conclude [22] that the mechanisms of enantioselection in the two solvents found to be the best for enantioselective hydrogenation of EtPy (T and AcOH) should be basically different. In our opinion, the structures of the intermediates formed in the two solvents are different. In case of CD and β-ICN chiral modifiers, the hydrogenation rate was faster in toluene than in acetic acid. In contrast, CN and α-ICN provided a higher hydrogenation rate in acetic acid than in toluene.

The hydrogenation rate on catalysts modified by β-ICN increased as a function of temperature similar to that for the other chiral modifiers. The *ee* did not change significantly (55–60 *R*%) within the range of 253–297 K and was not altered markedly by variations in β-ICN concentration within the range of 0.01–0.1 mmol/L. A significant change was observed at a β-ICN concentration of 0.001 mmol/L (entries 21–23), however; as the temperature was reduced, *ee* increased from 27% (*R*) to 43% (*R*), indicating hydrogenation of the quinoline skeleton of β-ICN at room temperature [23].

The properties of the Pt-α-ICN chiral catalyst in KPL hydrogenation were found to be similar to those in EtPy hydrogenation [23,53]. In both solvents (AcOH and T), the preferential formation of (*S*)-PL was observed, similar to that in the Pt-CN catalyst (entries 4–7). The difference between the behavior of α- and β-ICN can be ascribed to the different conformations of the two chiral modifiers, as has been described in detail previously [23,53].

3.2. Results of modifier mixtures

Studies of this type provide important information on the adsorption strengths of chiral modifiers if the chiral modifier under study does not contain strongly adsorbing impurities [39,54–56]. The presence of a compound with higher adsorbability may falsify the conclusions of mechanistic studies. In the present case, β-ICN of 100% purity and DHCN free of highly adsorbable impurities (the starting material, CN, is rapidly converted to DHCN under the conditions of hydrogenation) were used for the experiments. As demonstrated by the data in Table 1, β-ICN at a concentration of 0.001 mmol/L (entries 21–23) already provides chiral induction by adsorption on the Pt surface.

Based on data reported in a previous study [54], in which hydrogenation of EtPy on modified Pt by α-ICN-β-ICN was done to ca. 10–15% conversion and, after sampling, the second modifier was injected and hydrogenation and sampling were continued to 100% conversion [23], the adsorption strength of β-ICN greatly exceeds that of α-ICN and is very similar to that of CN. Experimental results of enantioselective hydrogenations of KPL on Pt modified by β-ICN–CN mixtures of different compositions are shown in Fig. 3. Nearly linear behavior was observed, with β-ICN having a somewhat greater adsorption strength than DHCN. This slight difference cannot account for the opposite sense of enantioselectivity provided by the two chiral modifiers equipped with identical stereogenic centers, however.

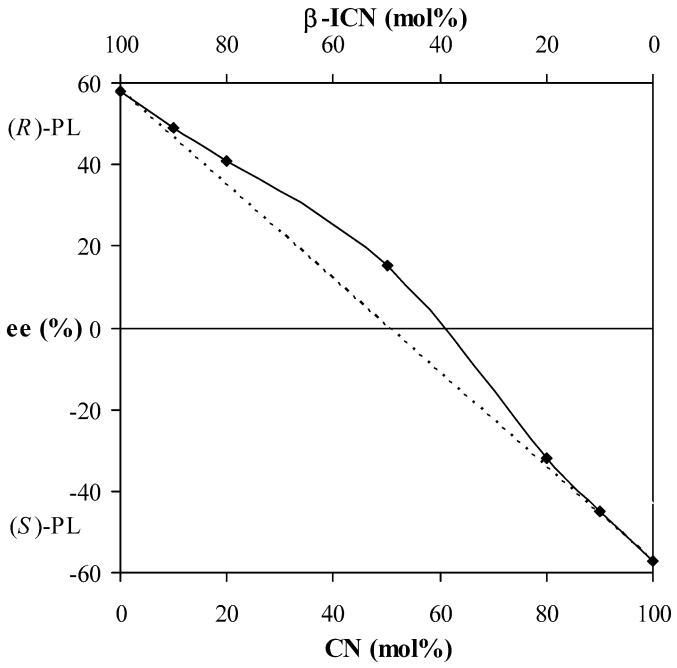


Fig. 3. Hydrogenation of KPL over Pt-alumina modified by β-ICN–CN mixtures (standard conditions: temperature 273 K; [modifiers] 0.1 mmol/L; toluene; dashed line indicates calculated *ee*).

3.3. Results of ESI-MS and IR measurements

Because the ESI-MS technique has provided valuable results in the course of EtPy hydrogenation [57–59], it has also been applied to the chiral hydrogenation of KPL. In the case of EtPy and CD, an $[EtPy + CD + H]^+$ adduct was identified in solution [59]. The formation of several adducts can be observed in the raw product of KPL hydrogenation in the presence of the two solvents most commonly used in the hydrogenation of activated ketones (T and AcOH). In addition to those already known [49,57], to date only three of these have been identified ($PL + H]^+$, $PL + Na]^+$, and $2\,PL + Na]^+$). Unfortunately, no adduct of KPL + β-ICN + $X]^+$ of any sort has yet been identified. Because identification of this type of adduct necessitates measurements under various conditions, further experiments have been initiated.

IR measurements in solution and without solvent have not demonstrated any shift in the carbonyl peak to a lower frequency, such as that observed in the case of alkaloids with intramolecular N···C=O interactions [60]. Based on these experimental observations, we can conclude that only a very weak interaction may exist between the tertiary nitrogen and the carbonyl group. Even if this weak interaction exists, a stronger interactions in the platinum–modifier–reactant system play a decisive role in the enantiomeric discrimination process [47,61,62].

Table 2
Comparison of enantioselective hydrogenation of EtPy and KPL on Pt-alumina modified by α- and β-ICN in toluene (standard conditions; 1 mmol reactant)

Entry	Modifier (mmol/L)	Reactant	Temperature (K)	Rate (±0.2)	*ee* (%)
1	α-ICN 0.01	EtPy	293	1.5	10 *S*
2	α-ICN 0.01	KPL	295	2.7	8 *S*
3	β-ICN 0.01	EtPy	293	4.9	40 *R*
4	β-ICN 0.01	KPL	298	8.8	45 *R*
5	α-ICN 0.1	EtPy	297	3.1	22 *S*
6	α-ICN 0.1	KPL	298	5.7	15 *S*
7	β-ICN 0.1	EtPy	297	4.8	48 *R*
8	β-ICN 0.1	KPL	298	8.8	46 *R*

3.4. Comparison of enantioselective hydrogenation of EtPy and KPL on Pt-alumina modified by α- and β-ICN in toluene (standard conditions; 1 mmol reactant)

Enantioselective hydrogenations of EtPy and KPL on a Pt-alumina-α-ICN chiral catalyst promoted the formation of products of (*S*)-configuration in excess, whereas in the presence of a Pt-alumina-β-ICN chiral catalyst, the products of (*R*)-configuration were formed in excess, due to the inversion of enantioselectivity. These results indicate the similarity of the enantioselective hydrogenations of EtPy and KPL.

The *ee* values for the two rigid compounds (β-ICN + KPL) are somewhat different than those for EtPy + β-ICN, because rigidity may inhibit the geometrical fit of the three components (modifier, reactant, and Pt); that is, the formation of the adsorbed intermediate responsible for enantioselection is hindered. In other words, the stereochemical conditions of the formation of the intermediate are significantly influenced by rigidity. This inhibitory effect is well illustrated by the data in Table 2, showing that, despite the faster hydrogenation of KPL, *ee* values are not higher in the presence of the modifiers α- and β-ICN. At the same time, it is known that *ee* values are higher in EtPy hydrogenation than in KPL hydrogenation when CD is used as a modifier [32].

The different rates of enantioselective hydrogenation are clearly shown in Fig. 4. A further conspicuous difference between the two reactants is that enantioselective hydrogenation already occurs at a lower β-ICN concentration [i.e., at lower surface coverage (β-ICN/Pt_{surf})] in the case of KPL [32]. The difference between hydrogenation rates is presumably explained by the different adsorption mode of the two reactants, which favors KPL, a compound of cis configuration with a rigid structure, containing two oxo groups.

4. Interpretation of enantioselective hydrogenation of KPL on the Pt-alumina-β-ICN chiral catalyst

Based on our experimental data and on the verified open-3 conformation of β-ICN [20,21], as well as on the widely accepted adsorption model [10–15], the proposed structure of the intermediates responsible for the enantioselectivity is outlined in Fig. 5. Considering that in AcOH, (*S*)-PL was formed in excess with both α- and β-ICN used as modifiers, it may

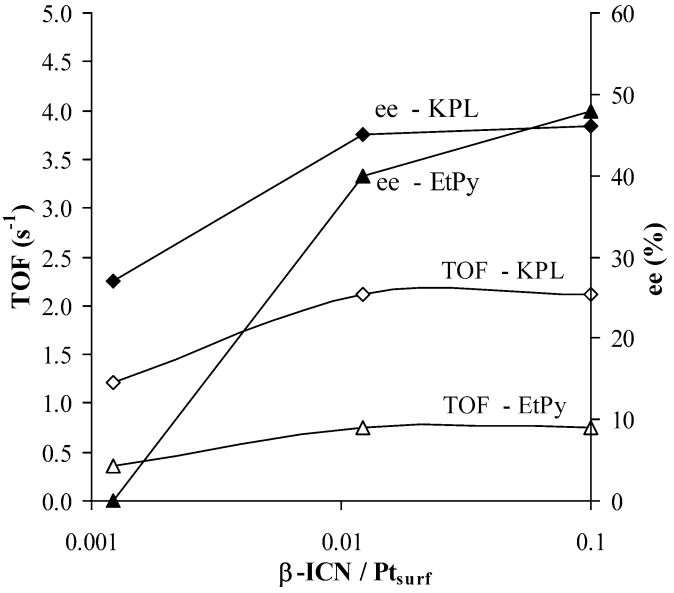


Fig. 4. Initial rate and enantioselectivity as functions of β-ICN/$Pt_{surface}$ (defined in Ref. [57]) for hydrogenation of EtPy and KPL in toluene (standard conditions, rate = $mmol_{reactant}$/(min $g_{catalyst}$); TOF = $mmol_{reactant}$/(mmol $Pt_{surface}$ s).

be presumed that enantioselection proceeds on the catalyst surface with the participation of **A**-type complexes (in Scheme 3, intermediate **A** type). According to Baiker et al. [34,50], the inversion of enantioselectivity in KPL hydrogenation over Pt-alumina-β-ICN chiral catalyst in toluene likely can be interpreted by the presence of **B** pro(*R*) surface intermediate (in Scheme 3, intermediate **B** type). Nevertheless, in the present case, the probability of **B** pro(*R*) intermediates of the half-hydrogenated type is reduced by the experimental observation that whereas hydrogenation in toluene yields (*R*)-PL in excess, hydrogenation in AcOH produces (*S*)-PL in excess, with no possibility for conformational change in either β-ICN or KPL (due to their rigid structures).

According to our assumption, the hydrogenation of KPL in toluene to (*R*)-PL on a Pt-alumina-β-ICN chiral catalyst is based on the formation of surface intermediate **C1** pro(*R*) or **C2** pro(*R*) in Fig. 5 (in Scheme 3, intermediate **C** type). The surface complex responsible for the enantiodiscrimination 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 KPL, as in EtPy [23] (Fig. 6). In contrast to earlier findings [47], in our opinion an electrostatic interaction of electrophilic and nucleophilic centers occurs; that is, it is not necessary to assume a zwitterion-type structure (**D** in Scheme 3). Based on recent investigations, the existence of such zwitterions is a matter of dispute [63]. Although the N → C=O weak electrostatic interaction between the modifier and reactant cannot be experimentally confirmed, we believe that the role of this interaction cannot be ruled out. Because strong interactions between modifiers and reactants are required for high ee, the **C1** pro(*R*) and **C2** pro(*R*) intermediates may be enhanced by the existence of the H-bonded complexes verified by McBreen [44].

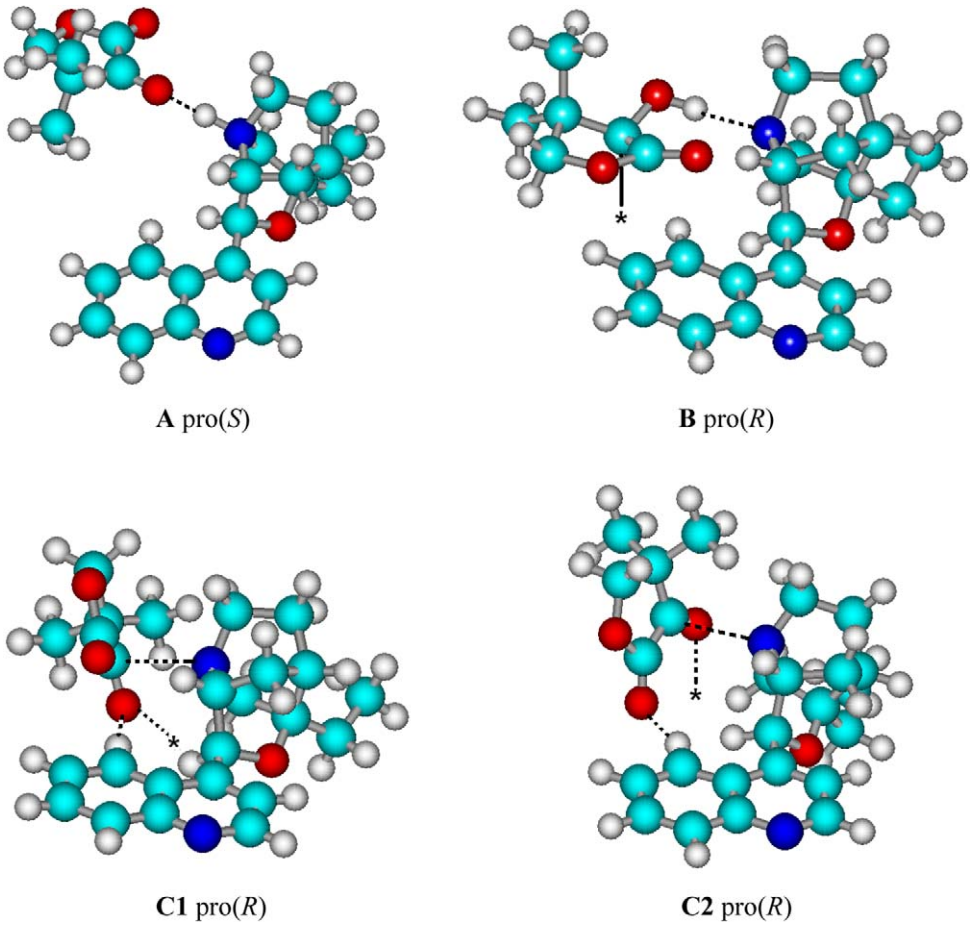


Fig. 5. The proposed structures of the adsorbed adduct complexes of β-ICN and KPL (in AcOH: **A** pro(S); in toluene: **B** pro(R), **C1** pro(R), **C2** pro(R) abbreviations: black sphere, N atoms; dark grey sphere, O atoms; grey sphere, C atoms; white sphere, H atoms).

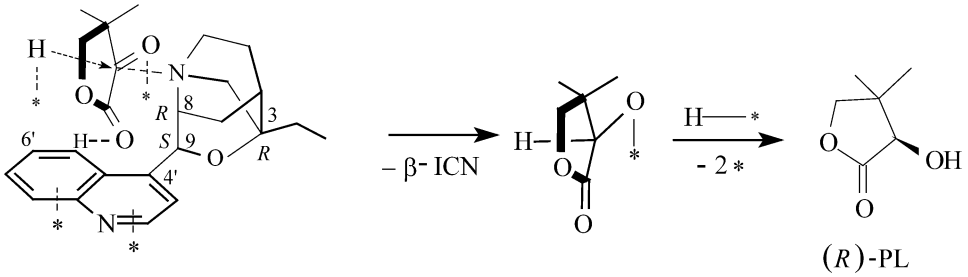


Fig. 6. The inversion of enantioselectivity in the hydrogenation of KPL catalyzed by Pt-alumina-β-ICN chiral catalyst in toluene.

As shown in Fig. 6, the N → C=O interaction can occur only if the nucleophile is positioned perpendicular to the plane of the trigonal carbon atom. To the best of our knowledge, no data on the adsorption of KPL on Pt have been reported to date; however, in view of the results of studies on EtPy [64–67], it seems justified to assume that in the presence of hydrogen, it is mostly lone-pair-bonded KPL that is present on the Pt surface. The H atom attacks the surface complex from the direction opposite to the N atom of quinuclidine (like in S_N2 or push–pull type reactions) [68]; that is, inversion occurs on the carbon atom of the carbonyl group of KPL in the surface-adsorbed state.

In interpretating the inversion of enantioselection in EtPy hydrogenation on Pt-β-ICN chiral catalyst, we have assumed that the spatial position of the N atom of the quinuclidine skeleton relative to the electrophilic carbonyl C atom determines the formation of adsorbed complexes of the **C** pro(R) type [23]. This assumption was confirmed by the inversion in KPL hydrogenation under similar conditions; the formation of the rigid structures **C1** pro(R) or **C2** pro(R) is favored by components with well-defined rigid conformations (reactant–modifier, e.g., KPL-β-ICN). In this case, the KPL may interact with both the modifier and Pt via two attractive sites each. In our opinion, the results of hydrogenation of KPL on a Pt-β-ICN chiral catalyst are in agreement with recently reported results [34], with the exception of the intermediate proposed for the interpretation of enantioselection. Studies on compounds of rigid con-

formation have repeatedly confirmed the conclusion reported in 1985 [69] that the conformation of the reactant molecule helps determine the direction of a heterogeneous catalytic reaction.

5. Conclusion

We have studied the Orito reaction (probably the most intensively researched heterogeneous enantioselective catalytic reaction) using the enantioselective hydrogenation of KPL in the apolar solvent toluene on Pt-alumina-β-ICN chiral catalyst as the model reaction. Enantioselective hydrogenation yielded an excess of (*R*)-PL; that is, inversion of enantioselection occurred, because the (*R*)-configuration was opposite to that expected from the absolute configuration of the cinchonine backbone. Both the reactant and the chiral modifier used in these studies were rigid molecules of well-researched structures. Thus, these studies have yielded new information contributing to a deeper knowledge of the enantioselective hydrogenation of activated ketones. Because of their structural rigidity, conformational movements are excluded. Moreover, these results (after some additions and together with other studies verifying the inversion of enantioselection [27–35]) confirm earlier suggestions regarding the direction of enantioselection [16]. The sense of enantioselection is controlled by the conformation of the adsorbed reactant–chiral modifier (1:1) complex. It was repeatedly verified that solvents may have a profound effect on the reaction mechanism.

Acknowledgments

Financial support was provided by the Hungarian National Science Foundation (OTKA grants TS 044690, T 042466, T 048764, and M 045606). In addition, received a Bolyai János Research grant, and K.B. received a postdoctoral research grant financed by the Hungarian National Science Foundation (OTKA D 048513).

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