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A new rigid cinchona modified (α-IQ) platinum catalyst for the enantioselective hydrogenation of activated ketones: Data to the origin of enantioselection

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Abstract

The enantioselective hydrogenations of ethyl pyruvate (EP), methyl benzoylformate (MBF), ketopantolactone (KPL) and pyruvaldehyde dimethylacetal (PADA) were studied on Pt–alumina catalyst modified by a new modifier namely α-isoquinine (α-IQ) with rigid conformation and for comparison by quinine (Q) in toluene and in acetic acid. The effects of modifier concentration, mixtures of modifiers, hydrogenation of α-IQ and theoretical calculations were examined on the interpretation of features of reactions. Using the Engelhard 4759 catalyst under mild experimental conditions (room temperature, 1 bar hydrogen pressure) the ees were lower in the case of α-IQ than for Q. The inversion of enantioselectivity observed in the case of the previously studied β-isocinchonine (β-ICN) containing C8(*R*) and C9(*S*) atoms in toluene as solvent failed to occur in the presence of α-IQ containing C8(*S*) and C9(*R*) atoms. Indirect experimental evidence for structure of adsorbed chiral modifier was supported by studies on hydrogenation and relative adsorption strength of α-IQ as well as by theoretical calculations. The significant enantioselectivity changes along the series of otherwise structurally related modifiers (Q, α-IQ and β-ICN) were compared with the *ab initio* computed geometrical features. The results revealed that besides the effects disclosed up to now in the literature, the orientational angle of the N-lone pair in the quinuclidine moiety relative to the quinoline also influences the structure and the adsorption mode of the intermediate responsible for the enantioselection.

Keywords: Chiral hydrogenation; Pt–alumina; α-Isoquinine; Activated ketones; Intermediate; Rigid conformation; Inversion of enantioselectivity; Origin of enantioselection

1. Introduction

Methods of choice for the preparation of chiral compounds are asymmetric syntheses of various types [1–4]. An important representative of asymmetric syntheses is heterogeneous catalytic enantioselective hydrogenation of activated ketones (Orito reaction [5,6], Scheme 1), a method that allows the realization of enantiomeric excesses (ee) as high as 96–98% for certain compounds [7–11]. Owing to the outstandingly high enantioselectivity, important chiral building blocks can be synthesized that serve as starting material for the synthesis of compounds of important practical applications [12].

The Orito reaction has been the subject of about 400 studies, including numerous reviews (since 2003 [13–16]). Recently research has been focused on a more detailed study of the reaction mechanism. The main objective is the interpretation of the origin of chiral induction. It has by now become generally accepted that the intermediate complex (IC) responsible for enantioselection is the 1:1 complex of the cinchona alkaloid and the substrate, as suggested in 1994 by Augustine, Baiker, Wells and coworkers [17–19]. No consensus has been reached, however, concerning the structure of the IC. As for the conformation of the cinchonas, most researchers assumed the determinant

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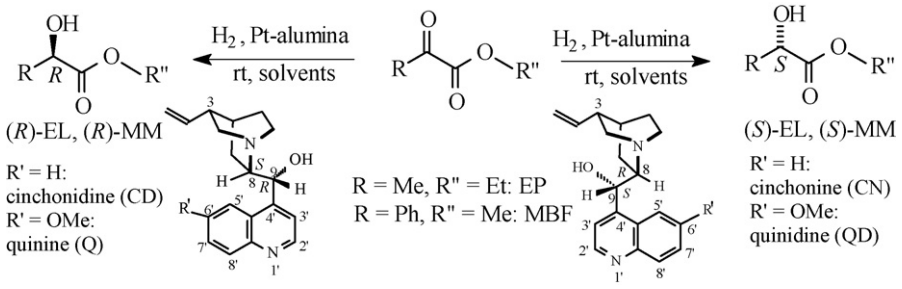


Scheme 1.

role of the anti-open (open-3) conformation in chiral induction [13–16] that could later be experimentally confirmed in the case of rigid isocinchona alkaloids (α-ICN, β-ICN) [20–25]. These cinchona alkaloids, due to inhibition of rotation along the C8–C9 bond (Figs. 1 and 2) can exist only in anti-open conformation.

It was established already by Orito et al. [5,6] that, during hydrogenation of EP, in the presence of parent cinchona alkaloids containing C atoms of C8(*S*) and C9(*R*) (CD, Q) an excess of (*R*)-EL is formed, whereas in the presence of C8(*R*) and C9(*S*) cinchona alkaloids (CN, QD) (*S*)-EL is formed in excess (Scheme 1). According to the unexpected inversion [23] of sense in enantioselective hydrogenation (Table 1), it appears that in certain cases the principal factor responsible for enantioselection and its direction is not only the configuration of the C8 and C9 atoms, but other circumstances may also play an important role. It was assumed for the interpretation of the inversion [24,25] that in the IC the spatial position of the N atom of the quinuclidine skeleton relative to the electrophilic carbonyl C atom of adsorbed substrates is determinant. Similar conclusions were arrived in a study on enantioselective hydrogenation on the chiral catalyst Pt–O–phenyl cinchonidine [36].

According to the investigations on ethereal isomers of CN and QD with C8(*R*) and C9(*S*) configuration of carbon atoms yielded new information for a better understanding of the structure of the IC responsible for enantioselection by verifying the role of the anti-open conformation [20,21]and by the recognition of the inversion of enantioselectivity [23]. The necessity of performing experiments using ethereal isomers of cinchona alkaloids with C8(*S*), C9(*R*) was already proposed at this early time. These compounds, however, were unknown at that time, since in the case of CD and Q the two reactive groups serving for their synthesis (C=C and OH) were not spatially close to each other unlike in the case of CN and QD (Scheme 1). According to experiments reported in the past few years, however, Q can be converted to the oxazacycloalkane by superacid treatment [37] (Scheme 2). The structure of the resulting compound (designated α-isoquinine [α-IQ] based on the nomenclature of isocinchonines) was verified by NMR and X-ray analysis. This opened the possibility of studies of enantioselective hydrogenation of activated ketones using a Pt–α-IQ chiral catalyst. As a superacid trifluorometanesulfonic acid was used for the synthesis of α-IQ [38]. This manuscript summarizes the results of investigations on the Pt–α-IQ catalyst in the enantioselective hydrogenation of EP, MBF, KPL and PADA (Schemes 1, 3 and 4).

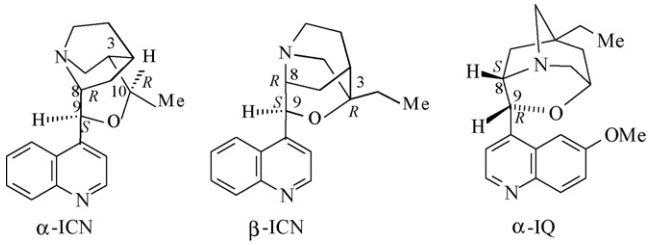


Fig. 1. The structures of iso-cinchona alkaloids (α-ICN, β-ICN, α-IQ).

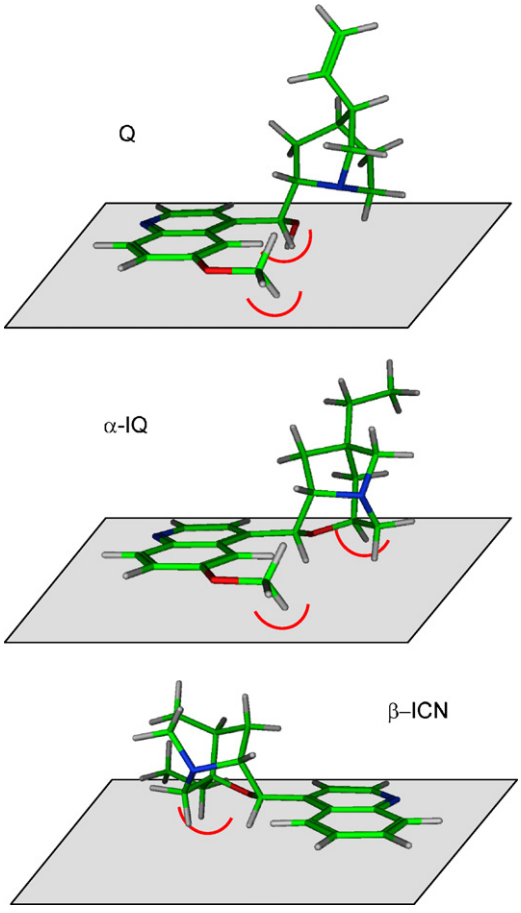
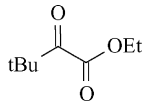
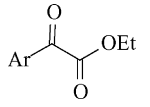
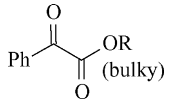
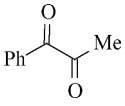
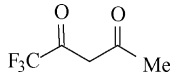
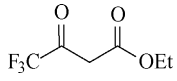
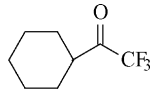
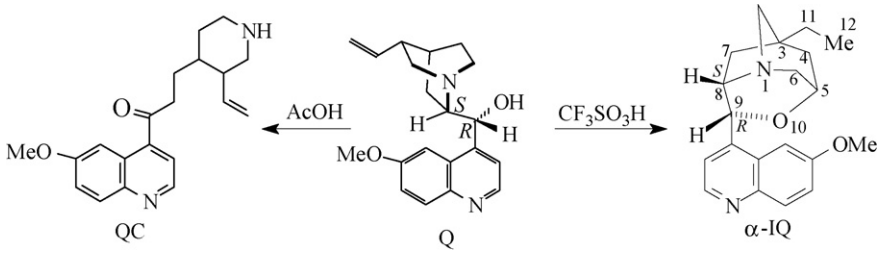


Fig. 2. *Ab initio* geometries of the studied cinchona modifiers and the potential steric clash between the Pt surface and the modifiers (red arches). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Table 1
Unexpected inversion of enantioselectivity in the Orito reaction using CD, CD derivatives and β-ICN as chiral modifiers

Entry	Substrate	Modifier	Solvent	ee (%)	Ref.
1	EP	CD	EtOH	15(*S*)	[26]
2	EP	9-PhnOQD	EtOH	18(*R*)	[27]
3	EP	β-ICN	T	48(*R*)	[24,23]
4	EP	β-ICN	T	29–34(*R*)	[28]
5	EP	9-PhOCD	T	21(*S*)	[29]
6	EP	9-Me_3SiOCD	THF	28(*S*)	[30]
7	EP	9-Bn_3SiOCD	THF	19(*S*)	[30]
8		9-PhOCD	T	41(*S*)	[29]
9	KPL	9-Me_3SiOCD	THF	35(*S*)	[31]
10	KPL	9-PhOCD	T	21(*S*)	[32]
11	KPL	β-ICN	T	46(*R*)	[25]
12	MBF	β-ICN	T	50(*R*)	[33]
13		9-PhOCD	T	31–78(*S*)	[29]
14		β-ICN	T	8–54(*R*)	[33]
15		CD	T	38(1*R*2*S*)	[34]
16		CD	AcOH	67(1*S*2*R*)	[34]
17		9-XylOCD	T	14(*R*)	[32]
18		9-XylOCD	$PhCF_3$	36(*R*)	[32]
19		CD	EtOH	16(*S*)	[35]



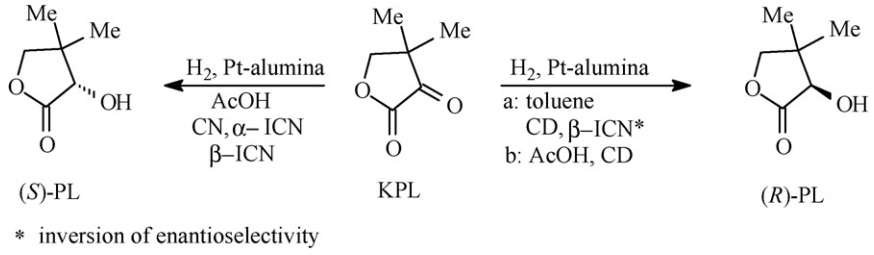
Scheme 2.

2. Experimental

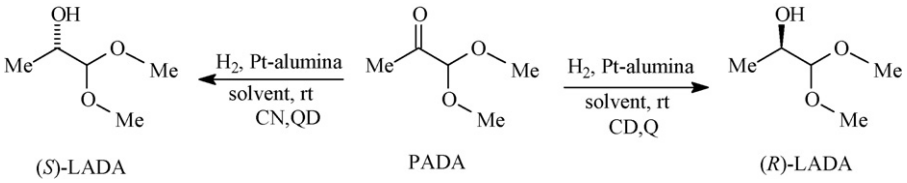
2.1. Materials

EP, MBF, KPL, PADA, solvents and reactants for synthesis of α-IQ were from Fluka or Aldrich, and used as received. EP, PADA and MBF were distilled in vacuum using Vigreaux-column.

Synthesis of ethereal isomer of quinine (α-IQ): 0.2 g quinine was added to 15 mL CF_3SO_3H at 273 K. The reaction mixture was magnetically stirred at 323 K for 6 h. The reaction mixture was then neutralized with water/ice and sodium carbonate



Scheme 3.



Scheme 4.

and followed by usual work-up. 70% yield was achieved after column chromatography over Al_2O_3 eluated with the mixture of CH_2Cl_2/MeOH/7N MeOH/NH_3: 95/2/3 (v/v/v). These NMR data are identical with the published data [37].

Based on the data in the literature [13–16], 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 [39].

2.2. Hydrogenation

Hydrogenations were performed in an atmospheric batch reactor. The catalytic system including catalyst (12.5 mg) and 2.5 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 0.5 mmol of substrate was added and stirred in the presence of hydrogen for the required reaction time. Standard conditions were: 12.5 mg E4759, 2.5 mL solvent, 1 bar hydrogen pressure, 294–297 K, 900–1000 rpm (no diffusion control is operating), 0.5 mmol of substrate. The product identification and the enantiomeric excess [ee% = ([*R*] − [*S*]) × 100/([*R*]+[*S*])] were monitored by gas chromatography (HP 6890 N GC-FID (21.65 psi He), 30 m long Cyclodex-B capillary column. Retention times (min): EP 343 K: 6.6 of (*R*)-EL, 7.3 of (*S*)-EL; KPL 398 K: 10.6 of (*S*)-PL, 11.2 of (*R*)-PL; MBF 393 K: 22.5 of (*R*)-MM, 23 of (*S*)-MM; PADA 338 K: 9.4 of (*R*)-LADA, 9.9 of (*S*)-LADA. Reproductibility is ±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 mode using 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*, max. accumulation time = 300 ms, fragmentation amplitude = 1.5 V, fragmentation time = 40 ms. Solvent: MeOH/0.1% AcOH; flow rate: 0.5 mL/min; concentration of sample: 0.1 μmol/L; injected volume 1.5 μL.

2.4. Measurements using mixtures of modifiers

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. ee was measured as described above.

2.5. Molecular modeling

For the force field calculations (MMFF94) and input generation, the Chemical Computing Group's Molecular Operating Environment was utilized. In *ab initio* quantum chemical calculations, the molecular structure, the stereochemistry and the geometry were exclusively defined in terms of their z-matrix internal coordinate system. The optimizations were achieved with the Gaussian03 program. The optimizations were performed in a cascade manner: force field - HF/3-21G - B3LYP/6-31G*. All the other parameters were set as default in Gaussian03.

3. Results and discussion

In order to study the effect of the novel chiral catalyst Pt–α-IQ on the enantioselective hydrogenation of activated ketones,

the following experimental parameters and research tasks were selected on the basis of earlier experimental experience:

(i) constant parameters: r.t., hydrogen pressure 1 bar, E4759 Pt–alumina catalyst; (ii) variable parameters: solvents (toluene and AcOH, two solvents allowing the highest ee values according to earlier studies), substrates, α-IQ concentration; (iii) of the four compounds to be studied, high ee could be achieved on Pt–CD catalyst in the case of EP [22,24,39–42] and KPL [25] in a fast reaction, whereas in the case of MBF [9,33] and PADA [10,41,43] hydrogenation was slow (Schemes 1, 3 and 4); (iv) for the sake of comparison, hydrogenation of the four substrates was also studied on Pt–Q chiral catalyst; (v) changes in hydrogenation rate with increasing α-IQ concentration are usually described by a saturation curve or a curve with a maximum, similarly to the thoroughly examined CD [13,39–41]; (vi) the stability of the Pt–α-IQ catalyst was also investigated under the conditions of hydrogenation; (vii) modifier mixture experiments were also conducted with the aim of determining the relative adsorption strength of the α-IQ modifier; (viii) molecular modeling was used to examine the structural features of IC.

3.1. Catalytical hydrogenation measurements

As shown by the results in Table 1, inversion was mostly observed in the case of the C9-ethers of the cinchona alkaloid. On this ground it was to be expected that enantioselective hydrogenation on a Pt-catalyst modified with α-IQ might also be accompanied by the inversion of enantioselection. The experimental data obtained in the hydrogenation of EP, MBF, KPL and PADA using both Pt–α-IQ and Pt–Q chiral catalysts are summarised in Table 2 which lead to the following main conclusions: (i) inversion of ee was not observed in the case of Pt–α-IQ chiral catalyst, i.e. compounds of (*R*)-configuration were formed in excess, just like in the case of Pt–Q catalyst; (ii) α-IQ induced lower ee values as compared to Q in the hydrogenation of all four compounds studied; (iii) values of ee attained in hydrogenation of EP and PADA using the chiral catalyst Pt–α-IQ are lower than those obtained using Pt–Q and significantly lower than those obtained in the case of KPL and MBF; (iv) higher ee values could be attained in AcOH as compared to toluene, in agreement with studies on the parent cinchonas; (v) changes in hydrogenation rate induced by increasing α-IQ concentration are usually described by a saturation curve or a curve with a maximum, similarly to the thoroughly examined CD [13,39–41].

The results of hydrogenations can be interpreted on the basis of experience obtained in studies on the chiral modifiers CD, CN (summarized in [16]) and the isocinchonas [21,24,25], thanks to the previously performed extensive and complex studies. In 1999 the following conclusion was drawn when interpreting results obtained with chiral modifiers of the isocinchonas [21]: "All factors stereochemically hindering the formation of the 1:1 surface

Table 2
Experimental data on enantioselective hydrogenation of EP, MBF, KPL and PADA on Pt–alumina catalyst modified by Q and α-IQ (standard conditions)

Substrates	Modifier (mmol/L)	Solvent	Time (min)	Conv. (%)	Rate (mmol/min*g)	Ee (%)
EP	Q (1)	Toluene	7	100	7.0	80
EP	Q (1)	AcOH	8	100	6.4	92
EP	α-IQ (0.01)	Toluene	22	98	2.9	26
EP	α-IQ (0.01)	AcOH	12	100	4.8	60
EP	α-IQ (0.1)	Toluene	18	100	3.9	44
EP	α-IQ (0.1)	AcOH	12	100	5.6	68
EP	α-IQ (1)	Toluene	30	91	1.6	46
EP	α-IQ (1)	AcOH	25	98	2.1	65
MBF	Q (1)	Toluene	60	67	0.52	64
MBF	Q (1)	AcOH	45	75	0.83	35
MBF	α-IQ (0.1)	Toluene	60	56	0.41	21
MBF	α-IQ (0.1)	AcOH	60	77	0.55	11
MBF	α-IQ (1)	Toluene	60	52	0.38	33
MBF	α-IQ (1)	AcOH	60	60	0.52	22
KPL	Q (1)	Toluene	8	100	8.9	55
KPL	Q (1)	AcOH	7	100	8.8	54
KPL	α-IQ (0.01)	Toluene	8	100	6.4	9
KPL	α-IQ (0.01)	AcOH	13	100	3.0	10
KPL	α-IQ (0.1)	Toluene	6	100	8.9	10
KPL	α-IQ (0.1)	AcOH	7	100	10.3	14
KPL	α-IQ (1)	Toluene	10	100	5.2	0
KPL	α-IQ (1)	AcOH	13	95	3.9	15
PADA	Q (1)	Toluene	60	43	0.3	61
PADA	Q (1)	AcOH	45	47	0.5	96
PADA	α-IQ (0.01)	Toluene	60	13	0.08	3
PADA	α-IQ (0.01)	AcOH	60	16	0.17	68
PADA	α-IQ (0.1)	Toluene	60	14	0.11	58
PADA	α-IQ (0.1)	AcOH	60	20	0.17	74
PADA	α-IQ (1)	Toluene	60	8	0.05	66
PADA	α-IQ (1)	AcOH	60	9	0.09	73

complex [17–19] of cinchona alkaloid and reactant do not favor high optical yields either". It was later experimentally verified by in situ ATR-IR- [44,45] and RAIRS spectroscopy measurements [46,47] that three adsorption modes can be distinguished in the adsorption of CD, of which it is presumably the strongly anchored flat adsorption mode that is responsible for high optical yields. The same conception is adopted by the latest review [15]. According to this concept, in the case of α-IQ the rigid conformation inhibits the formation of the 1:1 surface complex in a substrate-dependent fashion. The inhibition is more intensive in the case of KPL and MBF, because the advantageous sterical arrangement necessary for the formation of a 1:1 surface complex is made impossible by conformational rigidity (KPL) or the adsorption of the phenyl group (MBF). We presume that in the case of α-IQ, just like in the case of other modifiers, the difference between ee values realizable in the two different solvents can be interpreted by surface complexes of different structures [22,24,39,40]. The modifier concentration required for the achievement of high ee values is higher in toluene than in AcOH [40,48].

3.2. Catalytic hydrogenation of α-IQ on Pt–alumina catalyst

It was revealed in the course of studies on the Orito reaction that cinchona alkaloids added as chiral modifiers are themselves hydrogenated (mostly on the quinoline skeleton), resulting in a decrease in catalyst activity and ultimately in the deactivation of the catalyst [39,49–52]. When studying the hydrogenation reaction, special attention should be paid to the hydrogenolysis of ethereal derivatives of cinchona alkaloids (as cyclic ethers [53]). Hydrogenolysis of the C–O bonds of increased reactivity (benzyl C–O, tertiary C–O) of isocinchonas may lead to the loss of chirality of C9. The formation of DHCN and DHQ in the case of β-ICN and α-IQ, respectively, as a consequence of which the cause of enantioselectivity can no more be identified.

Hydrogenation of α-IQ had therefore to be examined under the conditions of enantioselective hydrogenation. The results of the experiments, shown in Table 3 allow the following direct conclusions to be drawn:

(i) in the case of short hydrogenations (<10 min), no significant alterations affecting ee occur in α-IQ; (ii) when reaction time is increased, α-IQ is hydrogenated to a significant extent; (iii) hydrogen uptake is faster in toluene than in AcOH; (iv) hydrogenolysis of the cyclic ether structure that would be associated with the formation of the ions *m*/*z* 297 (DHCN + H⁺) and *m*/*z* 327 (DHQ + H⁺) is not observed; (v) although in some cases the amount of certain ions formed barely approaches the noise level of *m*/*z* measurement, characteristic differences are observable in the ratio of the main hydrogenation products formed in the two solvents; (vi) the most significant reaction routes are the following: reactions resulting in the formation of the products *m*/*z* 299, 305, 329 in toluene and the products *m*/*z* 333, 353 in AcOH.

Our earlier experience in the mass spectrometry of cinchona alkaloids [54] and the evaluation of ESI-ion-trap MS2 and MS3 spectra [24] led us to propose the reactions represented in Scheme 5. In toluene, on the one hand, hydrogenolysis of the C6′–O bond (Scheme 1) of the quinoline skeleton and, subsequently, hydrogenation of the quinoline skeleton take place. The so far unknown compounds tetrahydro-α-isocinchonidine (TH-α-ICD) and decahydro-α-isocinchonidine (DH-α-ICD) may be formed. On the other hand, hydrogenation of the quinoline skeleton may also take place without hydrogenolysis of the C6′–O bond, resulting in the formation of TH-α-IQ and DH-α-IQ.

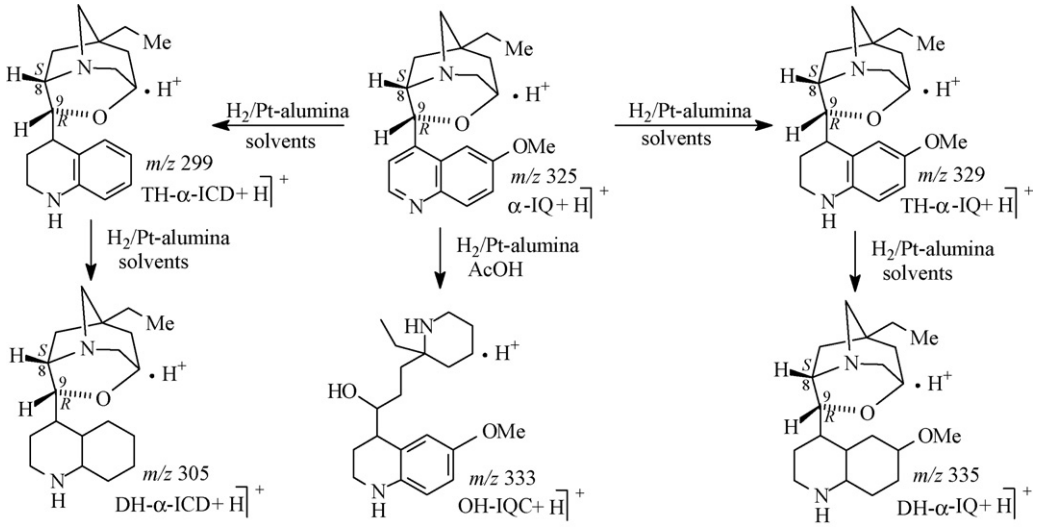
As regards the main hydrogenative conversions taking place in AcOH, these can be traced back to the rearrangement recognized by Pasteur [55]. Accordingly, under acid conditions the α-IQ turns into isoquinicine, which is in turn converted to octahydro-isoquinicine (OH-IQC) via the uptake of 8H (Scheme 5). If, in the future, a better understanding of the structure of the product with *m*/*z* = 353 is required, further investigations need to be performed.

On the basis of experimental data of the hydrogenation of CD and CN [52,56,57] and examination of the hydrogenation α-IQ and β-ICN [24] under identical conditions in toluene (Table 3) can give a conclusion regarding the type of adsorption the later two compounds undergo. Adsorption of β-ICN is presumably slightly tilted towards the surface, which is promoted by the ethyl group close to the surface. Since no similar inhibition may occur in the case of α-IQ because of the presence of the Et group far from the catalyst surface (Fig. 2), α-IQ is hydrogenated faster than is β-ICN.

Table 3
Relative abundances of the ESI-MS spectra of products formed by hydrogenation of α-IQ on Pt–alumina catalyst (12.5 mg E4759, [α-IQ]: 0.1 mM/L, 2.5 mL solvent, 298 K, 1 bar H_2 pressure

Entry	Solvent	Time (min)	*m*/*z* values (relative peak intensity, %)						
			299	305	325	329	333	335	353
1	T	10	8	0	100	13	0	0	0
2[a]	T	30	13	6	100	57	10	7	9
3	T	60	40	9	70	100	18	10	7
4	T	120	27	77	10	87	0	100	12
5	AcOH	10	0	0	100	0	7	0	52
6	AcOH	30	4	0	80	0	20	2	100
7	AcOH	60	6	1	50	3	60	4	100
8	AcOH	120	10	4	40	6	100	2	73

[a] In case on the hydrogenation of β-ICN (*T*, 30 min): *m*/*z* 295: 100%, *m*/*z* 299: 3% [24]).



Scheme 5.

The results of the hydrogenation of CD and CN [52,56,57], β-ICN [24] and α-IQ (this work) indicate various adsorption forms of these compounds in which the spatial position of the N atom of the quinuclidine skeleton is not identical. The interpretation of the significantly different selectivities of the hydrogenation of parent pseudo-enantiomeric cinchonas under identical conditions necessitates further investigations.

3.3. Results of modifier mixtures

The significant conclusion of the "nonlinear effect" studies on mixtures of chiral modifiers is the estimation of the relative adsorption strength of the modifiers [19,57-59]. We also found it practicable to use this approach for studying the behaviour of α-IQ in the enantioselective hydrogenation of activated ketones in toluene and in AcOH. Some of the results, allowing conclusions to be drawn concerning the adsorption of the α-IQ on Pt–alumina catalyst are presented in Figs. 3 and 4. It was established earlier that under identical experimental conditions [42] CD has the highest adsorption strength and that of CN is higher than that of QD in both solvents.

According to Fig. 3, in toluene the most probable order of adsorption strengths is CN > Q ≫ QD > α-IQ, because CN replaces α-IQ on the Pt surface more readily than vice versa, α-IQ is replaced by QD more readily than vice versa. According to Fig. 4, in AcOH the probable order of the adsorption strengths is Q > CN ≫ α-IQ > QD because Q replace CN and α-IQ on the Pt surface more readily than vice versa, QD is more easily displaced from the surface by α-IQ than α-IQ by QD.

While summarising the data of Figs. 3 and 4, it is highly probable that the adsorption strength of α-IQ is lower than that of CN and Q and very similar to that of QD in both solvents. Comparison of the experimental data of α-IQ-QD modifier mixtures with those of β-ICN-QD [24] reveals that QD has less effect on the desorption of β-ICN than on that of α-IQ. In other words, the adsorption strength of β-ICN is higher than that of α-IQ. When drawing conclusions from these studies, it has also been taken into account that the structure of the adsorption forms of cinchona alkaloids may be highly dependent on various factors [24,25,45,57–61].

3.4. Molecular modeling

The spatial arrangement of the cinchona modifier might play crucial role in the determination of the sign and extent of the enantioselectivity [24,25,36]. Our modified cinchonas

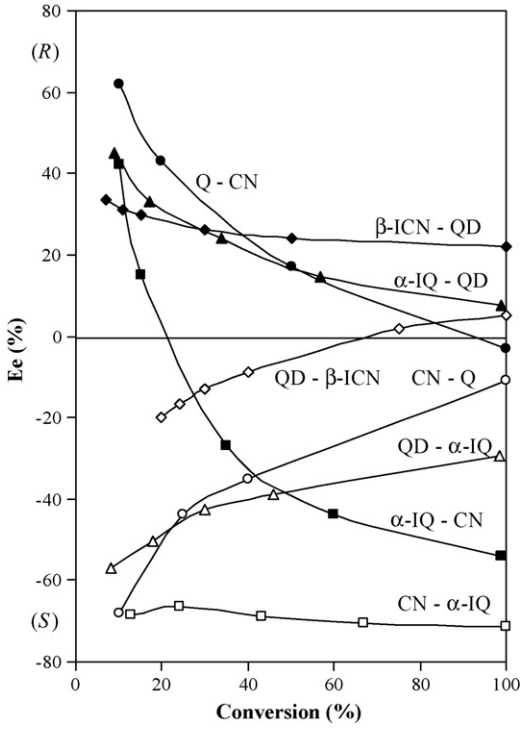


Fig. 3. Enantioselective hydrogenation of EP in toluene: effect of modifier mixtures on ee (standard conditions, 273 K, [modifiers] = 0.05 mmol/L (first abbreviation—modifier used first, second abbreviation—modifier added afterwards)).

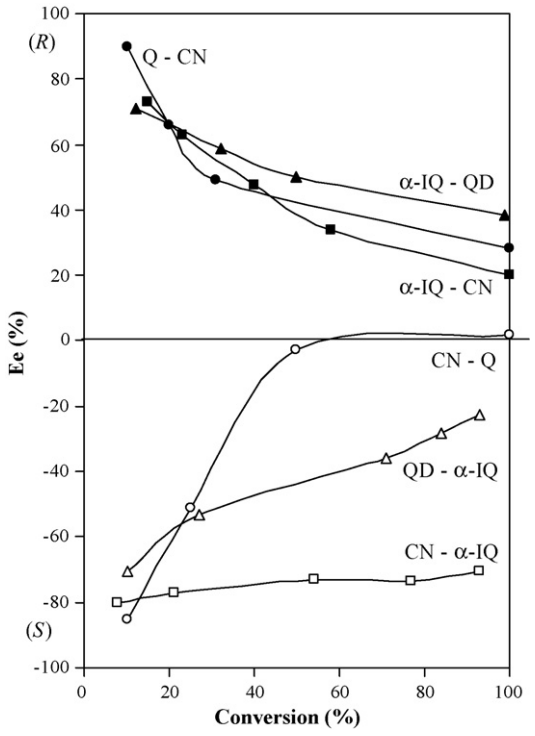


Fig. 4. Enantioselective hydrogenation of EP in AcOH: effect of modifier mixtures on ee (standard conditions, 273 K, [modifiers] = 0.05 mmol/L (first abbreviation—modifier used first, second abbreviation—modifier added afterwards)).

(ethereal isomers of parent cinchona alkaloids: α-IQ and β-ICN) exhibited significant differences in the enantioselection ([20–24] and this work). The comparison of their geometrical features therefore can deliver useful information on the structural requirements on the modifier side to attain either an effective enantioselection or inversion of the enantioselectivity. In order to establish a qualitative structure–enantioselectivity relationship, the *ab initio* optimized geometries (without the Pt surface model) of the studied modifiers were compared with the enantioselectivity data.

There are two important factors to be considered with respect to the formation of the adsorbed intermediate complex. First, the adsorption of the quinoline moiety on the Pt surface can be modified not only by the OMe group, but by the C9-OH, H3 and the CH_2 of the ethyl group for Q, α-IQ and β-ICN, respectively (Fig. 2). To gain a quantitative measure of the steric clash, the distance was measured between the geometric centre of the sagging hydrogens and the best plain of the quinoline moiety. The point-plain distances were of 2.57 Å, 1.70 Å and 2.09 Å for Q, α-IQ and β-ICN, respectively. These data suggest that the sagging can only result in a tilt angle difference of a few degrees, and it can further decrease during the adsorption due to the residual flexibility of the cinchonas. At this point, we cannot conclude that the observed enantioselectivities can be explained exclusively on the basis of the different adsorption geometry of the pure modifiers.

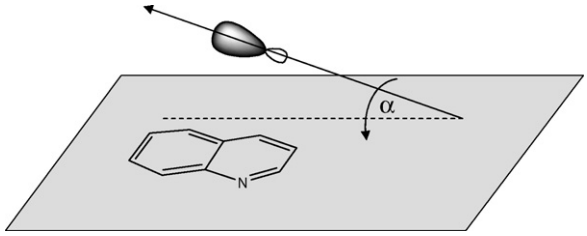


Fig. 5. Definition of the N-lone pair orientation angle.

Second, according the anchor points of the cinchona modifiers responsible for the substrate binding, the activated ketones are attached to the cinchonas through the N-lone pair of the quinuclidine part and the H5' region of the quinoline moiety [13,15,25,62]. Since the stability of the IC is assumedly sensitive to the relative geometrical arrangement of the anchor points, the present models were compared by measuring the distance between H5′ and quinuclidine nitrogen (N) and by calculating the angle between the best plain of the quinoline moiety and the orientation of the N-lone pair (see Fig. 5 for the definition). It is seen from the geometrical data that the almost parallel N-lone pair orientation and the increased H5′-N distance is detrimental to the enantioselectivity for the rigid α-IQ (Table 4). The effective enantioselection can be attributed to the positive orientation angles, that is, the lone pair points toward the quinoline plane and supposedly toward the Pt surface. Shorter H5′-N distances can be observed for Q and β-ICN, the distance differences are however within 0.37 Å. Taking into account the residual flexibility of Q, such a small difference (10%) can easily disappear upon substrate binding. On the other hand, the results reveal large differences in the N-lone pair – quinoline plain angle, and the changes in the experimental enantioselectivity appear to be in connection with the lone pair orientation. It should be noted that the lone pair – quinoline plain angle is smaller for the β-ICN but this does not simply lead to a lower enantioselectivity; the inversion of the enantioselectivity is observed. Although even small variations in the lone pair orientation can lead to strong changes in enantioselection and activity, it is likely that besides the orientation angle other parameters play roles in the reaction mechanism.

Table 4
Geometrical features of the relative arrangement of the substrate binding anchor points of the modifiers and the ees in the hydrogenation in toluene

	Distance (H5′-N) (Å)	N-lone pair orientation (degree)	ee (*R*%)			
			EP	MBF	KPL	PADA
Q	3.27	40.5	80	64	55	61
α-IQ	3.64	−0.2	46	33	0–10	66
β-ICN	3.45	15.9	42[a]	50[a]	46[a]	–

[a] Inversion of enantioselection occurred.

4. Conclusion

In the hydrogenation of activated ketones the unexpected inversion of enantioselection has called attention to the significant influence of novel, so far unidentified factors on chiral induction, making further research in this field necessary and judicious. Because inversion was mostly observed in the case of the C9-ethers of the cinchona alkaloids we studied the effect of an ethereal derivative of Q (α-IQ), never used before as a chiral modifier in the Orito reaction. By the evidence of the results shown in Table 2, enantioselective hydrogenation of the four substrates was not associated with the inversion of enantioselection. Namely α-IQ induced enantioselection identical in direction with that induced by Q, i.e. (*R*)-alcohols were formed in excess.

Using the same experimental circumstances over the same catalyst in the reaction of the same substrate the extent of the ee is determined by the structure and adsorption mode of IC. It was identified that these are influenced by the following factors of the modifiers: (i) anchoring moiety for flat adsorption of the modifier, (ii) the chiral C8 and C9 atoms of modifier, (iii) basic N atom of modifier to interact with the substrate, (iv) H5′- and H6′ region of quinoline moiety interacting with the substrate, (v) anti open (open 3) conformation of modifier, (vi) spatial position of the N atom of quinuclidine.

In order to explain the differences in the enantioselectivities along the Q, α-IQ and β-ICN sequence, the relative adsorption properties and geometrical features were investigated by experimental and theoretical methods. Marked differences were found in the position and orientation of N-lone pair of the quinuclidine skeleton relative to the quinoline plain. According to the results obtained with α-IQ it is assumable that besides of the above factors the orientational angle of the N-lone pair in the quinuclidine moiety relative to the quinoline plain also has role in the enantioselection.

Thus, geometrical factors depending on the conformations of the substrate and the chiral modifier, i.e. a favorable geometrical fit between the anchor points of the two molecules adsorbed on the surface (substrate and modifier) play a determinant role in the formation of the IC responsible for enantioselection. If not only the chiral modifier, but also the substrate has rigid structure, interaction favourable for a single enantiomer is not established due to lack of a correct fit, enantioselection fails to happen (see Table 4 for KPL and α-IQ) and racemic hydrogenation takes place.

Our opinion related to the structure of the IC responsible for the enantioselection we have discussed in detailed in our previous works on the hydrogenation of EP, KPL [22,24,25]. For this reason this time on Fig. 6 we sketched only the IC of the reaction mechanisms based on electrophilic and nucleophilic interactions.

It is known from the literature that N-protonated cinchona appears on the Pt-surface under the conditions of the Orito-reaction. Although its role in the rate determining step has not been experimentally proven, N-protonation is considered as an essential step in course of the enantioselective hydrogenation [62–65]. Recent NMR study on cinchona alkaloid derivatives

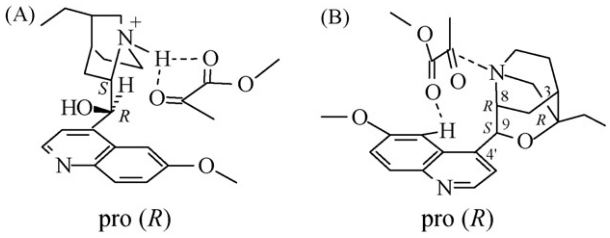


Fig. 6. The proposed structures of intermediate complexes in electrophilic (A) and nucleophilic-type (B) interactions.

(MeOCN, β-ICN) and KPL mixed in dry benzene revealed that the chiral modifiers and KPL readily form supramolecular complexes in solution, which are stabilized by direct interaction of nucleophilic nature between the quinuclidine N-lone pair and the C=O bonds [66]. The lone-pair orientation-dependence of the enantioselection revealed in the present work does not allow to decide upon a single mechanism. Nevertheless it may contribute to the understanding of the exact nature of the enantioselection step of the Orito-reaction.

Acknowledgements

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