Journal of Catalysis 272 (2010) 140–150

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Substrate-controlled adsorption of cinchonidine during enantioselective hydrogenation on platinum

Erik Schmidt, Tamas Mallat, Alfons Baiker *

Institute of Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zürich, Hönggerberg, HCI, CH-8093 Zürich, Switzerland

ARTICLE INFO

Article history:
Received 5 January 2010
Revised 2 March 2010
Accepted 2 March 2010
Available online 28 March 2010

Keywords:
Cinchonidine adsorption
Asymmetric hydrogenation
Ligand acceleration
α-Ketoester

ABSTRACT

It is commonly accepted that the origin of enantioselection on chirally modified metals is the control of the adsorption and reactivity of the substrate by the chiral environment of the modifier. Here, we provide the first experimental evidence to a mutual process, namely, that the substrate controls the adsorption and reactivity of cinchonidine (CD) on the metal surface. Our approach is to follow the competing hydrogenation of the quinoline ring, the anchoring moiety of CD, in the presence or absence of an activated ketone substrate. On Pt/Al_2O_3 in the weakly interacting solvent toluene, CD (and 10,11-dihydro-CD) favors a C(4′) – pro(*S*) adsorption geometry and saturation of the heteroaromatic ring gives 1′,2′,3′,4′(*S*),10,11-hexahydro-CD {(*S*)-CDH_6} in excess. Addition of methyl benzoylformate, ketopantolactone, or ethyl pyruvate inverts the dominant conformation of CD to C(4′) – pro(*R*) as indicated by the major product (*R*)-CDH_6, and even the rate is higher by about 30% (“inverse ligand acceleration”). Acetic acid that interacts strongly with CD exerts a similar effect on quinoline hydrogenation. In contrast, the product α-hydroxyester interacts weakly with CD, decelerates the hydrogenation of the quinoline ring and the *de* of CDH_6 depends on the chirality of the α-hydroxyester. These unexpected observations provide a fundamentally new insight into the complexity of the surface conformation of CD and the origin of high enantioselectivity on cinchona–modified Pt.

© 2010 Elsevier Inc. All rights reserved.

1. Introduction

The concept of modifying a supported noble metal catalyst by adsorption of a chiral compound led to high enantioselectivities in the asymmetric hydrogenation of activated ketones [1–5]. The most successful catalytic system is platinum modified by cinchona alkaloids that afford up to 98% *ee* [6,7] even under very mild conditions [8].

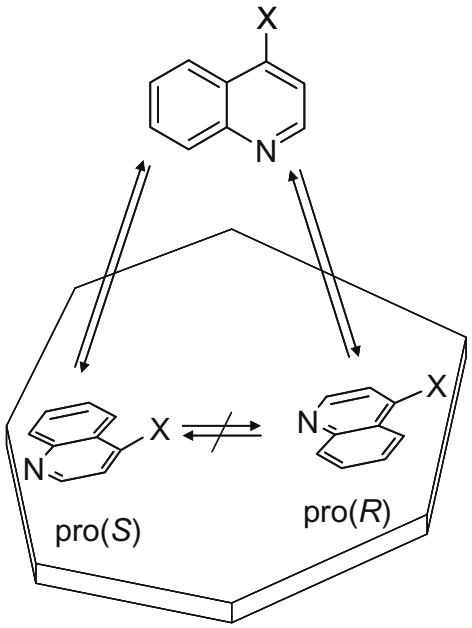
Significant progress in the understanding of the mechanistic details of this reaction has been achieved in the past years. Theoretical calculations as well as surface science studies focused on the adsorption of the modifier on the metal surface [9–20]. In case of cinchonidine (CD), spectroscopic investigations at the relevant solid–liquid interface revealed two major species: the alkaloid adsorbed via the quinoline ring π-bound nearly parallel to the metal surface and a tilted adsorption mode via the N-lone pair of the heteroaromatic ring. The relative amount of these structures depends strongly on the reaction conditions (concentration, pressure, temperature, solvent) and the structure of the metal surface [1,12,21–26], and even competition with strongly adsorbing molecules may have a remarkable influence on the adsorption geometry [27].

Asymmetric induction is a complex phenomenon that includes chiral recognition by intermolecular interaction of modifier and substrate, which concept is supported by complex formation in solution [28,29]. Most of the adsorption studies, however, focus on the behavior of the chiral modifier in the absence of the substrate. Recent attempts to overcome this shortcoming by theoretical calculations are highly demanding [30,31], while spectroscopic investigations are complicated by the intensive absorbance of the substrate being present in large excess to the alkaloid [32,33].

Numerous feasible conformations of the adsorbed modifier have been determined by DFT calculations [9,11,30]. The structures that are probable candidates for interacting with the ketone during hydrogen uptake can be divided into two major groups, which differ in the orientation of the quinoline ring at the metal surface, relative to the rest of the molecule (Scheme 1). Concerning the hydrogenation of the quinoline ring of the alkaloid (Scheme 2), in the first group CD is adsorbed pro(*S*) at C(4′) and in the other group pro(*R*). Importantly, inter-conversion of the structures belonging to the different groups is not possible on the Pt surface but requires desorption and re-adsorption. The possible rotation around the C(4′)–C(9) and C(9)–C(8) bonds gives rise to several different conformations which have been designated as surface open (SO), surface closed (SC), and surface quinuclidine bound (SQB), but all of them belong to either the pro(*R*) {SO(3), SC(2), SQB(2)} or the pro(*S*) group {SO(4), SC(1), SQB(1)} [11]. Experimental data that

* Corresponding author. Fax: +41 44 632 1163.
E-mail address: baiker@chem.ethz.ch (A. Baiker).

0021-9517/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcat.2010.03.003



Scheme 1. Two major adsorption modes of cinchonidine on Pt affording (*S*)- or (*R*)-CDH_6-A upon hydrogenation according to Scheme 2. X in the formula represents the non-aromatic part of the alkaloid.

could verify these theoretical predictions on the conformational structure of the modifier–substrate complex adsorbed on the Pt surface are not available, and thus the origin of chiral recognition is still a matter of debate, as summarized in some recent reviews [1,3,4,34].

Transformation of CD by hydrogenation of its aromatic anchoring unit has been observed spectroscopically [21,35] and was shown to be the most important side reaction limiting the performance of this catalytic system in terms of enantioselectivity [36–40]. The theoretical importance of this side reaction is that it allows us to study the adsorption behavior of the modifier indirectly by following its hydrogenation products [36,38,41,42]. It has been shown recently that Pt nanoparticles rich in Pt{1 0 0} face exhibit higher activity in this reaction, while the Pt{1 1 1} surface is more diastereoselective [40,41]. The selectivity depends remarkably on the presence of acids either as a solvent or surface residue [41]. Formation of 1′,2′,3′,4′(*S*),10,11-hexahydro-CD ((*S*)-CDH_6-A) is preferred in the weakly polar aprotic solvent toluene (Scheme 2). Assuming hydrogen uptake from the Pt surface, this observation indicates a pro(*S*) adsorption geometry of CD. On the other hand, predominantly 1′,2′,3′,4′(*R*),10,11-hexahydro-CD ((*R*)-CDH_6-A) with opposite absolute configuration at C(4′) is formed in the presence of acetic acid and poly(acrylic acid) capping agent [41], which is an evidence to the higher abundance of pro(*R*) CD species under these conditions.

Interestingly, the hydrogenation of α-ketoesters and α-ketolactones does not show such solvent dependency, i.e. always the same (*R*)-enantiomer is formed in the presence of CD [1,43]. Two possible conclusions might be drawn from these observations: (i) either both adsorption geometries of the modifier {pro(*S*) or pro(*R*) at C(4′)} favor the formation of the same enantiomer in the asymmetric hydrogenation of α-ketoesters and α-ketolactones, or (ii) the adsorption behavior of CD is controlled by the presence of the activated ketone substrate. To clarify this point, we studied the hydrogenation of CD under truly in situ conditions, during the hydrogenation of methyl benzoylformate (MBF), ethyl pyruvate (EP), and ketopantolactone (KPL, Scheme 3). This study provides direct evidence for the adsorption mode of CD on the Pt surface during ketone hydrogenation and offers a deeper understanding of the relevant surface interactions involved in enantioselection.

2. Experimental

2.1. Materials

In general, analytical grade reagents and solvents were used. Toluene (Fluka, >99.7%) was dried over activated mole sieve 4A; acetic acid (Acros organics, 99.8%), and CD (Fluka, >98% alkaloid) were used as received. Pt/Al_2O_3 (5 wt%) catalyst was purchased from Engelhard (Engelhard 4759).

Details on the synthesis and purification of the hydrogenation products of CD (Scheme 2) and their characterization by ^1H NMR spectroscopy (Bruker 200 MHz) can be found elsewhere [41].

2.2. Catalytic hydrogenations

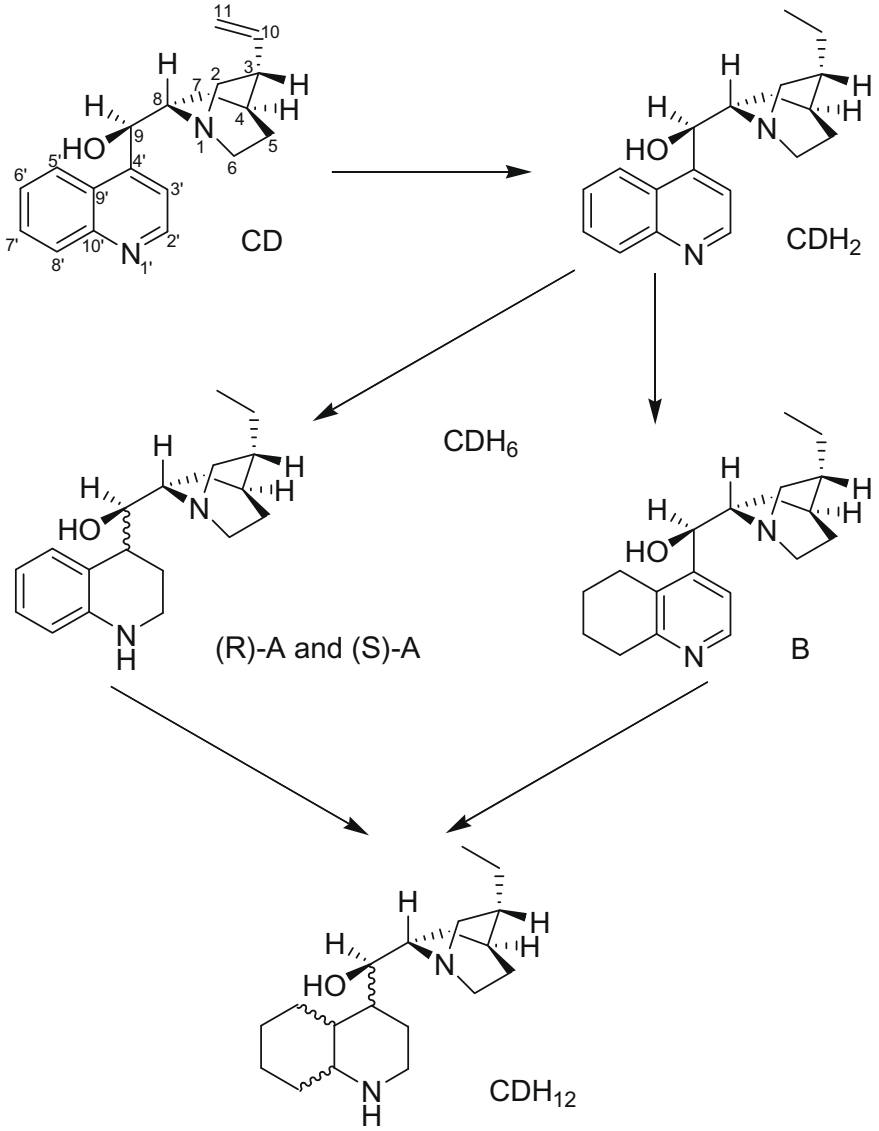
According to the standard procedure, hydrogenation of 3–6 mg (10–20 μmol) of CD in the absence of a ketone substrate was performed in 10 ml solvent (toluene or acetic acid) at 298 K and 2–50 bar hydrogen, in a 50-ml stainless steel reactor equipped with a glass-liner and magnetic stirrer (750 rpm). The pressure was controlled with a constant–volume constant–pressure system (Büchi BPC 9901). The amount of catalyst was 20 mg of 5 wt% Pt/Al_2O_3, which was pretreated in flowing H_2 at 400 °C (673 K) for 90 min prior to use, resulting in a Pt dispersion of 0.2 as determined by TEM [44].

Samples were taken regularly from the reaction mixture via syringe in order to follow the conversion and selectivity with time. In case of the solvent toluene, the samples were first washed with 0.5 M HCl in water. The pH of the separated aqueous phase was set to 12 with 0.5 M NaOH before repeated extraction with toluene. The combined organic phases were washed with 0.1 M NaOH saturated with NaCl. When the reaction was carried out in acetic acid solvent, the samples were first treated with excess aqueous 1 M NaOH before extraction with toluene three times. The organic phase was treated then analogously to the samples taken from the toluenic reaction mixture. Finally, the samples were filtered and analyzed by gas chromatography (Thermo Quest Trace 2000, HP-5 capillary column, FID). Details on the preparation and characterization of the hydrogenated CD derivatives are given in the supporting information of our former report [41].

Enantioselective hydrogenation of methyl benzoylformate (MBF, Acros organics, 99%) was carried out according to the standard procedure using 40 mg catalyst at 10 bar. MBF (4–20 mmol) was added either before starting the reaction or after a time delay of 30 min in the transient experiments. GC analysis of CD and its hydrogenation products was made analogously to the experiments in the absence of ketones. The conversion and enantioselectivity in the hydrogenation of MBF were followed by gas chromatography (Thermo Finnigan Trace 2000, CP-Chirasil-Dex CB capillary column, FID). Samples were taken regularly from the reaction mixture, the catalyst was filtered off, and the filtrate was diluted with ethyl acetate before analysis.

Hydrogenation of 540 mg (4.2 mmol) ketopantolactone (KPL, Hoffmann-La Roche, 99%) was investigated in the presence of 1 mg CD (3.5 μmol) at 50 bar H_2 pressure and 298 K using 5 mg catalyst in 10 ml toluene. Hydrogenation of 0.5 ml (4.5 mmol) ethyl pyruvate (EP, Acros organics, 98%, freshly distilled before use) was carried out using the standard procedure at 2 bar and 298 K in toluene. GC analysis of KPL or EP and their hydrogenation products was made after filtration and dilution of the samples, similarly to the experiments with MBF.

The standard procedure was applied also for the experiments on the hydrogenation of CD in the presence of the hydrogenation



Scheme 2. Stepwise hydrogenation of cinchonidine (CD) to CDH_{12} on Pt/Al_2O_3.

products of MBF. Therein 0.7 g (4.2 mmol) of either (*R*)-methyl mandelate (TCI Europe, >98%), (*S*)-methyl mandelate (ABCR, 99%), or *rac*-methyl mandelate (Fluka, >98%) has been added to the toluenic solution. The samples taken from the reaction mixture were treated and analyzed as described previously for MBF.

Hydrogenation of cyclohexene (Fluka, >99.5%) was investigated in the presence and absence of CD under the conditions used for ethyl pyruvate hydrogenation (20 mg catalyst, 3 mg CD, 4.5 mmol cyclohexene, 2 bar, 298 K). The products of cyclohexene hydrogenation were analyzed by gas chromatography (Thermo Quest Trace 2000, HP-FFAP capillary column, FID).

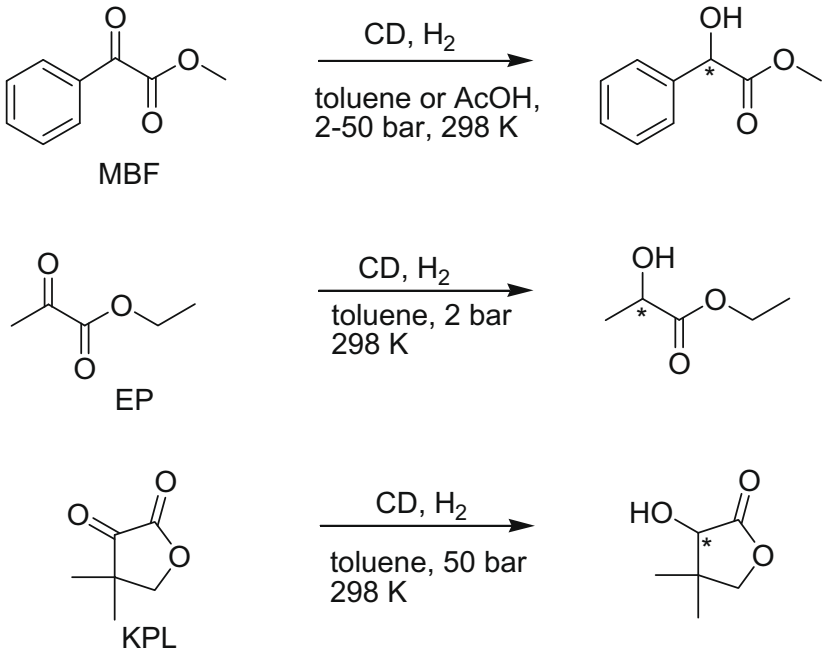
The estimated error in the determination of the diastereomeric excess (*de*) and the *ee* was about ±0.5% and that of the reaction rate (TOF) was in the range ±10%.

3. Results and discussion

3.1. Hydrogenation of CD in the absence of a ketone substrate

At first, the hydrogenation of cinchonidine (CD) was followed in the absence of any ketone. As previously shown [41], CD undergoes fast saturation of its vinyl group affording dihydrocinchonidine (CDH_2) (Scheme 2). Under standard conditions, all CD was converted to CDH_2 within 10 min. This facile transformation has barely any influence on the enantio-differentiating ability of the alkaloid [3]. The following hydrogenation of the quinoline moiety afforded hexahydrocinchonidines (CDH_6), i.e. no tetrahydrocinchonidines could be detected. The reaction was faster in acetic acid than in toluene in the whole conversion range (Fig. 1A). The corresponding turnover frequencies (TOF, Table 1) related to the conversion of CDH_2 were calculated based on the number of Pt surface atoms. The rate of the hydrogenation of CDH_2 is somewhat smaller compared to the recently published values [36,41], which is probably due to the different catalyst pretreatment procedure applied in the former work. The further reaction of CDH_6 to the fully hydrogenated diastereomers of dodecahydrocinchonidine (CDH_{12}) has recently been described [41] but was not followed in detail in the present work.

The chemo- and diastereoselectivity of the $CDH_2 \rightarrow CDH_6$ transformation depends strongly on the reaction conditions. Unless otherwise stated, the selectivity was determined at 40 ± 5% conversion of CDH_2. At this conversion, no CD was left in solution and the



Scheme 3. Hydrogenation of methyl benzoylformate (MBF), ethyl pyruvate (EP), and ketopantolactone (KPL) on CD-modified Pt/Al_2O_3.

selectivity to the fully saturated molecule CDH_{12} was always about 10%.

The favored hydrogenation of the heteroaromatic ring results in the formation of the two diastereomers (*R*)- and (*S*)-CDH_6-A with opposite absolute configuration at the new center of chirality at C(4′) (Scheme 2). The main product is (*S*)-CDH_6-A with a *de* of about 16% under standard conditions in toluene (Table 1). The diastereoselectivity was almost independent of the conversion of CDH_2 (Fig. 1B). Hydrogenation of the homoaromatic ring to give CDH_6-B was slow under the conditions applied as shown by the high A/B ratio in Table 1.

The most important solvent effect is the inversion of the major diastereomer in acetic acid compared to the dominant product in toluene (Fig. 1B) [41]. In addition, in acetic acid, the reaction was less selective to CDH_6-A (lower A/B ratio, Table 1), which is in good agreement with the literature data [36,41,45].

Acetic acid is able to form acid–base pairs with CD [36], and probably also with CDH_2, and this interaction may be the reason for the favored formation of (*R*)-CDH_6-A with a *de* of 55% under standard conditions (Table 1). This interaction is of fundamental importance in the enantioselective hydrogenation of unsaturated carboxylic acids on cinchona–modified Pd [1]. According to the latest spectroscopic and theoretical study [46], this interaction has a rather complex stoichiometry and interaction geometry (cyclic or acyclic) in solution and there is no in situ experimental evidence yet in favor of any of those structures on the surface of Pt [47] or Pd [48,49]. Note that CD can also be protonated by the Pt/H_2 system, as shown by spectroscopic investigations and theoretical calculations [10,50].

3.2. Hydrogenation of CD in the presence of methyl benzoylformate (MBF)

Hydrogenation of MBF under standard conditions in toluene gives more than 90% *ee* to (*R*)-methyl mandelate (Table 2). This value is in good agreement with the literature data [43,51], although 98% *ee* was achieved in the hydrogenation of the ethyl ester under carefully optimized conditions and with ultrasonicated Pt/Al_2O_3 [52,53]. No hydrogenation of the phenyl ring of MBF was observed under our conditions. Furthermore, the absence of an α-H atom in MBF prevents self-condensation catalyzed by the Pt surface and the basic quinuclidine N of the alkaloid, which makes this molecule – and also KPL – suitable substrates for mechanistic studies [5].

Hydrogenation of CD to CDH_2 was not affected by the addition of MBF. In the subsequent transformation of CDH_2 to CDH_6 in toluene, the main diastereomer was switched from (*S*)- to (*R*)-CDH_6-A and the selectivity to the homoaromatic product CDH_6-A decreased (Table 1). In general, the selectivities in toluene became very similar to those measured in acetic acid, while in the latter medium the selectivities were barely affected by the presence of MBF. From the similar selectivities we can conclude that the presence of MBF in toluene affects the adsorption geometry of CD molecules similar as acetic acid solvent does. This chiral switch is illustrated in Scheme 4, where two dominant conformations, the SO(4) and SO(3) are used to represent the C(4′) pro(*S*) and C(4′) pro(*R*) adsorption geometries, respectively [11]. The N–H–O type modifier–substrate interaction used here for illustration is based on our mechanistic model [1,32,54].

The rate of the aromatic hydrogenation of CDH_2 increased in the presence of MBF by about 30% in toluene and 5% in acetic acid (Table 1). The estimated error of the rate determination was in the range ±10%, so only the rate enhancement in toluene is significant.

The unexpected rate enhancement was confirmed by transient experiments. Hydrogenation of CD was started in the absence of MBF in toluene and the substrate was added only after 30 min. The *de* of about 16% for (*S*)-CDH_6-A at 20–30 min (Fig. 2B) and the initial rate of about 1.6 h^{-1}, calculated from the slope of the conversion–time plot (Fig. 2A) correspond well to the values given in Table 1. After 30 min, 8.4 mmol MBF was injected to the reaction mixture. The rate (TOF ≈ 3700 h^{-1}) and enantioselectivity (91% *ee*) of the hydrogenation of MBF were similar to the values obtained when starting the reaction in the presence of MBF (see Table 2). Addition of MBF increased the slope of the conversion–time plot (Fig. 2A) corresponding to an enhanced rate of CDH_2 hydrogenation (TOF ≈ 2.1 h^{-1}). Note that this value is almost identical to the rate observed when starting the reaction with MBF (Table 1), confirm-

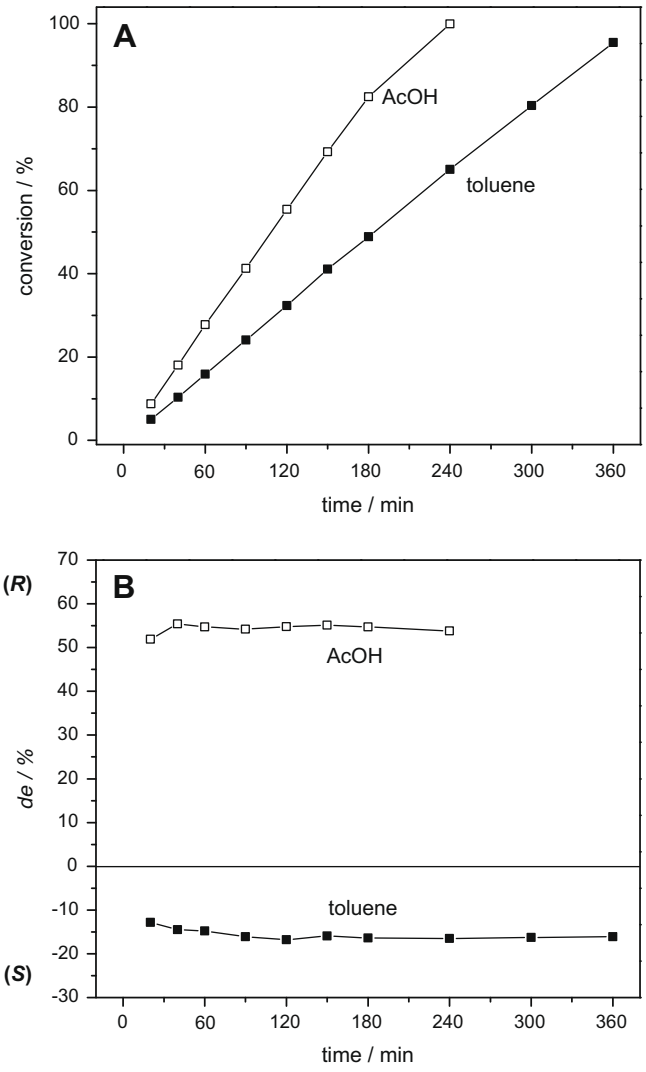


Fig. 1. Solvent effect on the rate of conversion of CDH_2 (A) and the diastereoselectivity of CDH_6-A (B); standard conditions, 10 bar, 3 mg CD in toluene and 6 mg CD in acetic acid.

ing that the higher rate of the saturation of the aromatic ring of CDH_2 is caused by the presence of the α-ketoester. The ratio of the two CDH_6-A diastereomers changed sharply after addition of MBF (Fig. 2B). The calculated differential *de* revealed that additional CDH_2 was hydrogenated with about 40–50% excess to (*R*)-CDH_6-A, in good agreement with the value observed when starting the reaction in the presence of MBF (Table 1). The amount of the heteroaromatic product CDH_6-B also increased (the A/B ratio decreased) immediately after addition of MBF (not shown). Obviously, the adsorption of CDH_2 on the Pt surface is strongly affected by the presence of MBF. The substrate–modifier interaction controlled the surface conformation of CD and thus the selectivity and reactivity in the hydrogenation of the quinoline ring.

Finally, we have to emphasize that the observed rate acceleration in the hydrogenation of CD does not contradict to the known high efficiency of the Pt–cinchona system. The key to understand this point is not the absolute but the relative rates of the hydrogenation of the ketone substrate and the quinoline ring of the alkaloid. In the best case, in the hydrogenation of ketopantolactone, a CD/substrate molar ratio of only 4 ppm was sufficient to achieve the highest *ee* at full conversion [55]. This ratio implies that the hydrogenation of the substrate was more than 250,000 times faster than that of the alkaloid, since at full conversion of ketopantolactone the Pt surface was still covered by (some) CD. Unfortunately, the usual CD/substrate molar ratio necessary under optimized conditions is orders of magnitude higher in the hydrogenation of some other substrates, for example of acetophenone derivatives [56,57].

3.3. Hydrogenation of CD in the presence of ethyl pyruvate (EP) and ketopantolactone (KPL)

We extended the study of the competing hydrogenation of CD during enantioselective hydrogenations on Pt involving EP and KPL as substrates. Hydrogenation of EP is the mostly used test reaction of the Pt–cinchona system, although extensive side reactions such as aldol-type self-condensation and decarbonylation [58,59] may distort the observations. KPL is an interesting model compound because of the higher rigidity of the lactone structure, and it does not undergo aldol condensation due to the absence of an H atom in α-position to the keto-carbonyl group, and also no decarbonylation was observed [32].

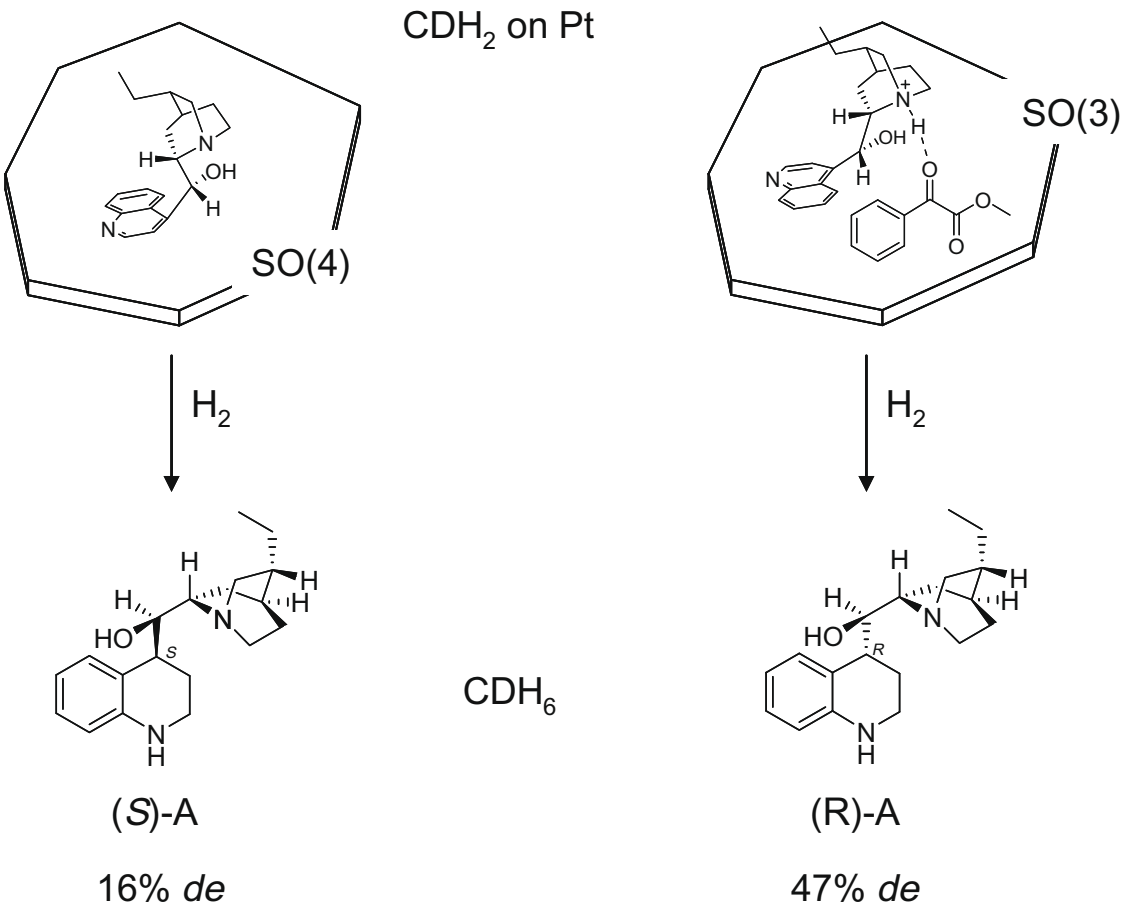
Generally, reasonable good *ee*'s were obtained in the hydrogenation of both substrates (Table 2) under slightly different reaction conditions compared to the experiments using MBF (see Section 2). The hydrogen pressure was adjusted to 50 bar for KPL and 2 bar for EP. In the absence of ketones, the reaction rate in the hydrogenation of CDH_2 increased with increasing H_2 pressure, but the effect on the chemo- and diastereoselectivities was minor (compare data in Tables 1 and 3). The presence of EP or KPL, however, changed the main diastereomer to (*R*)-CDH_6-A with 48% and 68% *de*, respectively. Also the A/B ratio decreased to 15 and 34, respectively, similar to the results in the hydrogenation of CDH_2 in the presence of MBF. In the presence of both ketones, the reactivity of CDH_2 increased by about 30%, in good agreement with the rate acceleration in the presence of MBF.

Obviously, all three substrates MBF, EP, and KPL have a very similar effect on the adsorption and hydrogenation of CDH_2 (Scheme 4). The significant enhancement of the activity in the hydrogenation of the aromatic anchoring unit of the modifier and the switch of the main product from (*S*)- to (*R*)-CDH_6-A indicate a strong interaction of modifier and substrate. The α-ketoester function, which is common for all three substrates, controls the conformation of CD on the Pt surface, its reactivity, and the product distribution in the hydrogenation of the quinoline ring. The structural differences in the three substrates, such as the steric bulkiness or molecular rigidity, play only a minor role in controlling CD hydrogenation. Interestingly, steric effects were found to be minor also in the hydrogenation of various α-ketoesters on cinchona–modified Pt [54,60].

3.4. Hydrogenation of CD in the presence of α-hydroxyesters

Addition of MBF to the slurry of Pt/Al_2O_3 and CD in toluene accelerated the hydrogenation of the quinoline ring and inverted the major product from (*S*)- to (*R*)-CDH_6-A (Scheme 4). Vice versa, the chiral modifier CD induced a sixfold rate enhancement in the hydrogenation of MBF and the preferred formation of (*R*)-methyl mandelate with 92% *ee* (Table 2). Obviously, the origin of these changes is the modifier–substrate interaction on the Pt surface. An important question is whether the product α-hydroxyester is involved in the interactions. To clarify this point, we investigated the hydrogenation of CD in the presence of methyl mandelate and a mixture of methyl mandelate and MBF.

No conversion of methyl mandelate, i.e. no phenyl ring hydrogenation or C–O bond hydrogenolysis was observed under the mild conditions applied. The presence of (*R*)-methyl mandelate inverted the absolute configuration of the dominant CDH_6 product at C(4′), compared to the transformation of CD alone (Table 4). The



Scheme 4. Adsorption and hydrogenation of CDH_2 in toluene (left) and the change of the dominant adsorption mode in the presence of MBF (right). (For the sake of simplicity, only the hydrogenation of the heteroaromatic ring is shown here.)

preferred formation of (*R*)-CDH_6-A is analogous to the influence of MBF on the hydrogenation of CD (Table 1), although the *de* is lower in the presence of methyl mandelate. Addition of (*S*)-methyl mandelate doubled the small excess of (*S*)-CDH_6-A measured in the hydrogenation of CD alone (Table 4). Another interesting effect of the addition of the (*R*)- or (*S*)-α-hydroxyesters is the deceleration of the saturation of the quinoline ring compared to the neat CD solution (Table 4). The decrease of the rate (TOF) was slightly bigger in the case of the (*S*)-enantiomer. These observations indicate that interaction of CD with the product methyl mandelate involves coordination to the hydroxyl group of mandelate; a feasible structure for this interaction is plotted in Scheme 5.

Next, the hydrogenation of CDH_2 was followed in the presence of racemic methyl mandelate to clarify which enantiomer interacts stronger with the modifier. The results in terms of activity and selectivity are almost identical to the experiment using enantiomerically pure (*R*)-methyl mandelate (Table 4). The clear preference to the (*R*)-CDH_6-A diastereomer shows that the interaction of CD with (*R*)-methyl mandelate is stronger than the alternative interaction with the (*S*)-enantiomer.

Finally, the competition between MBF and methyl mandelate was investigated. Hydrogenation of CD was started in the presence of (*S*)-methyl mandelate and MBF was added to the reaction mixture after 30 min (Fig. 3). The initial TOF and *de* to (*S*)-CDH_6-A was controlled by the α-hydroxyester (compare Fig. 3 and Table 4). After injection of MBF, however, additional CDH_2 was hydrogenated preferentially to (*R*)-CDH_6-A and the calculated differential *de* of about 40% (Fig. 3B) was only slightly lower than the *de* observed in the absence of (*S*)-methyl mandelate, i.e. when starting the experiment in the presence of MBF (Table 1). The corresponding TOF of about 1.8 h^{-1} was very close to the value given in Table 1 for the absence of (*S*)-methyl mandelate, too.

The analogous experiment with (*R*)-methyl mandelate and MBF (Fig. 4) proved that MBF interacts stronger than the (*R*)-α-hydroxyester product, although in this case the replacement of the hydroxyester by the ketoester in the interacting complex was significantly slower, as indicated by the delayed changes in the differential *de* (Fig. 4B).

These transient experiments suggest that the α-ketoester substrate MBF interacts stronger with CDH_2 and controls its adsorption geometry and hydrogenation selectivity even in the presence of the α-hydroxyester product. The order of interaction strength is MBF > (*R*)-methyl mandelate > (*S*)-methyl mandelate.

3.5. "Ligand acceleration" and "inverse ligand acceleration"

Rate acceleration of ketone hydrogenation over the chirally modified Pt surface compared with that on unmodified Pt has some analogy to the ligand acceleration first described in homogeneous asymmetric catalysis [61]. Considerable experimental evidence has been collected in favor of this concept (for recent reports see Refs. [40,51,62,63]) and any mechanistic model for enantioselection on Pt has to rationalize this phenomenon. Note also that the term "ligand acceleration" is a good description for chiral metal complexes since the number of active sites remains unchanged by addition of the ligand, while on chirally modified metals an unknown fraction of the active surface sites are covered by the strongly adsorbing

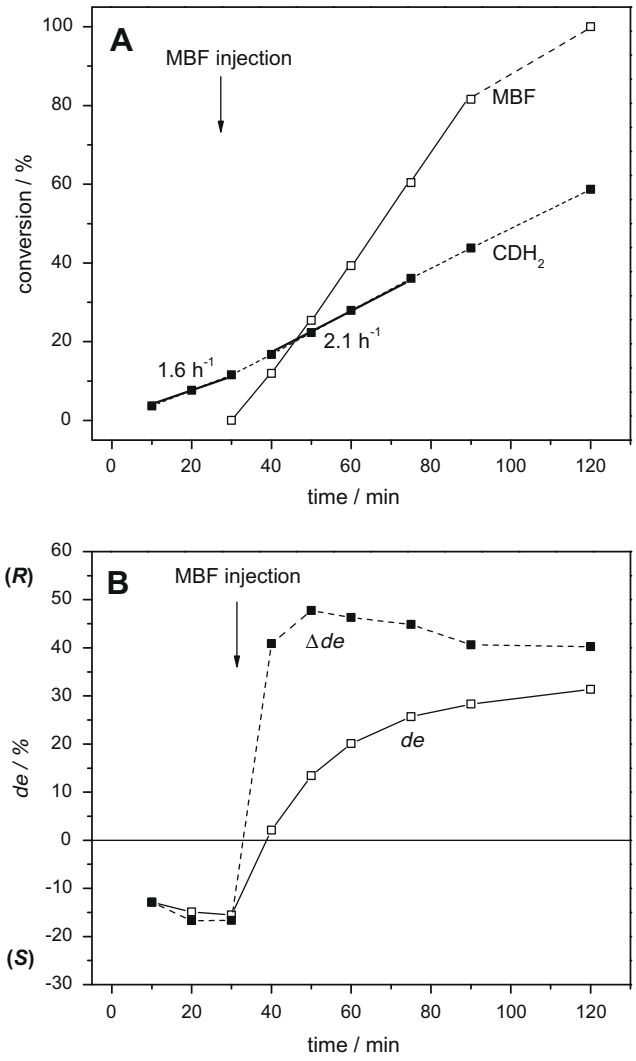


Fig. 2. Effect of methyl benzoylformate (MBF) addition after 30 min on the rate of CDH_2 conversion (A) and the diastereoselectivity of CDH_6-A (B); standard conditions, toluene, 10 bar. The numbers in the top part represent the TOF values of CDH_2 hydrogenation before and after addition of MBF.

Table 1
Effect of MBF on the hydrogenation of CDH_2 to CDH_6 (standard conditions, 10 bar).

Ketone substrate	Solvent	TOF (h^{-1})	Selectivity		
			de (%)		A/B
–	Toluene	1.7	16	(*S*)	39
MBF	Toluene	2.2	47	(*R*)	10
–	AcOH	6.1	55	(*R*)	7.9
MBF	AcOH	6.4	57	(*R*)	8.1

modifier and these sites are not available for the hydrogenation of the substrate.

In the hydrogenation of KPL and MBF, for which the reactions are not distorted by side reactions, rate acceleration by a factor of 4.7–6.1 was observed (Table 2). As mentioned earlier, the intrinsic rate acceleration related to the actual number of Pt surface sites available for ketone hydrogenation after CD adsorption is unknown. To estimate this value, we investigated the hydrogenation of cyclohexene in the presence and absence of the alkaloid. This simple unsaturated compound was chosen because its hydrogenation is a structure-insensitive, facile reaction [64], and no interaction between the substrate adsorbed via the C=C bond and the alkaloid is expected. Under standard conditions at 2 bar, the presence of CD diminished the reaction rate by a factor of 37 (Scheme 6). The missing interaction between CD and cyclohexene was confirmed by the analysis of the hydrogenation of CD: no significant change in the reaction rate or the chemo- and diastereoselectivities could be detected. This drop in reactivity of cyclohexene is in line with the expectation that the alkaloid covers a great part of the available Pt surface sites. Assuming a similar correlation in the hydrogenation of MBF and KPL, we propose that the chiral modifier may induce intrinsic rate acceleration by about two orders of magnitude. This estimate is supported by the 98% ee in the hydrogenation of ethyl benzoylformate [52,53], i.e. the (*R*)-mandelate may be produced 99 times faster than the (*S*)-enantiomer.

The study of the hydrogenation of CD under truly in situ reaction conditions revealed the inverse phenomenon, the accelerated hydrogenation of the modifier itself in the presence of the ketone substrate. Cinchona alkaloids are not stable under the conditions of ketone hydrogenation. The critical side reaction is the saturation of the quinoline ring, the so-called anchoring unit, that weakens the adsorption of the alkaloid on Pt and thus diminishes the enantioselectivity [36–40]. In the weakly interacting solvent toluene, addition of the activated ketone substrate induced a small but significant rate acceleration of the quinoline ring hydrogenation. The extent of the "inverse ligand acceleration" was very sim-

Table 2
Enantioselective hydrogenation of activated ketones; standard conditions.

Ketone substrate	Solvent	Pressure (bar)	CD	Activity		*ee* (%)
				TOF (h^{-1})	RE[a]	
MBF	Toluene	10	–	570	–	–
MBF	Toluene	10	+	3500	6.1	92
MBF	AcOH	10	–	530	–	–
MBF	AcOH	10	+	3200	6.0	85
KPL	Toluene	50	–	10,700	–	–
KPL	Toluene	50	+	50,000	4.7	82
EP	Toluene	2	–	335	–	–
EP	Toluene	2	+	870	2.6	78

[a] RE corresponds to rate enhancement, related to the unmodified reaction.

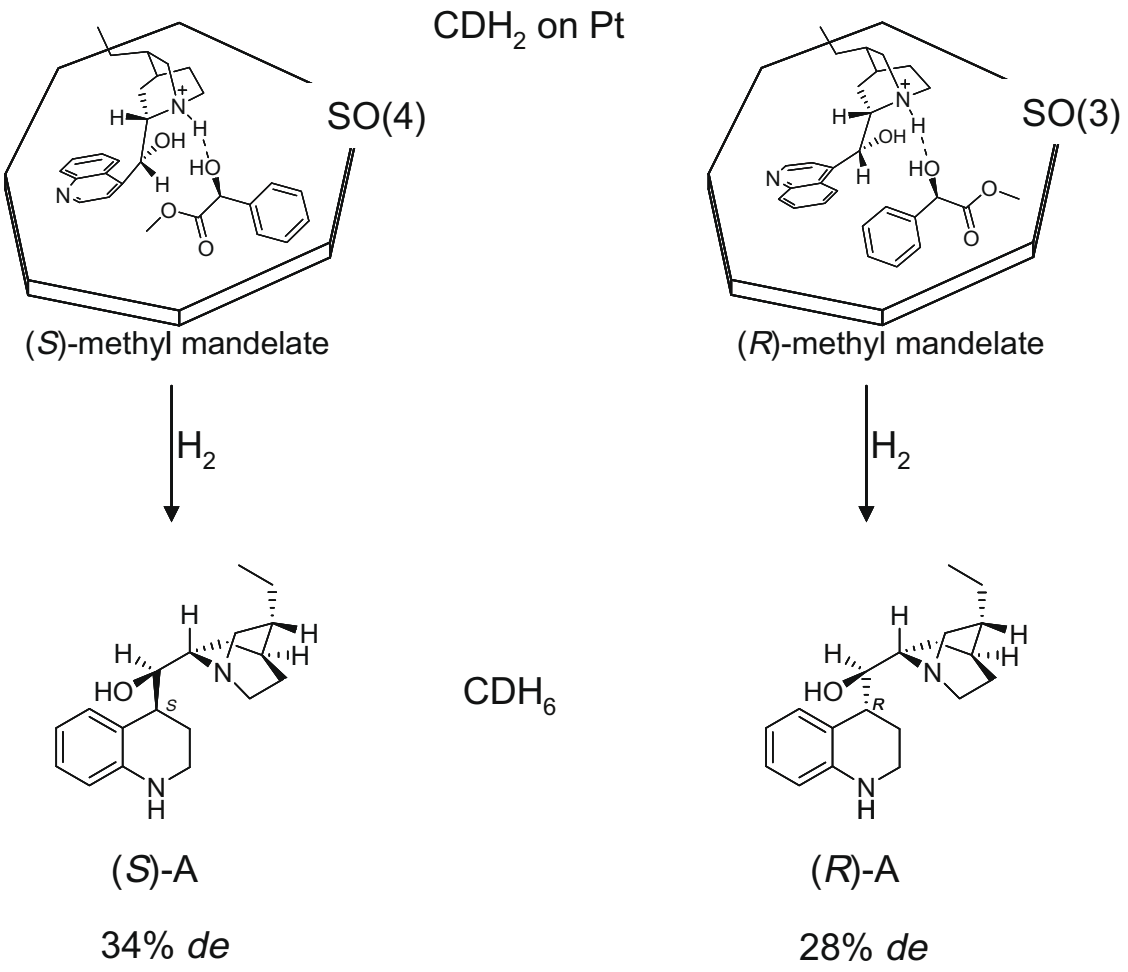
Table 3
Effect of KPL or EP on the hydrogenation of CDH_2 to CDH_6 in toluene; standard conditions.

Ketone substrate	H_2 pressure (bar)	CD hydrogenation		
		TOF (h^{-1})	*de* (%)	A/B
–	50	3.2	18 (*S*)	37
KPL	50	4.2	68 (*R*)	15
–	2	1.1	12 (*S*)	52
EP	2	1.5	48 (*R*)	34

Table 4
Effect of methyl mandelate on the hydrogenation of CDH_2 to CDH_6 in toluene (standard conditions, 10 bar).

Methyl mandelate additive[a]	CD hydrogenation		
	TOF (h^{-1})	*de* (%)	A/B
–	1.7	16 (*S*)	39
(*R*)	1.1	28 (*R*)	20
(*S*)	0.8	34 (*S*)	36
Racemic	1.1	27 (*R*)	22

[a] No conversion of methyl mandelate was detectable.



Scheme 5. Adsorption and hydrogenation of CDH_2 on Pt/Al_2O_3 in the presence of the products of MBF hydrogenation.

ilar in the hydrogenation of all three activated ketones, despite of their different structure and the partly different conditions (2–50 bar, Tables 1 and 3). In the presence of MBF, KPL, and EP, the rate of the quinoline ring hydrogenation increased by 29%, 31%, and 36%, respectively.

The "inverse ligand acceleration" effect may be related to the change in the adsorption mode of the alkaloid on the Pt surface. Most experimental studies revealed adsorption via the quinoline ring being in a tilted position relative to the Pt surface at sufficiently high concentration in solution [12–14]. In contrast, the majority of the mechanistic models developed for the hydrogenation of activated ketones assume that in the interacting CD–ketone complex, the quinoline ring is close to parallel to the metal surface (see [1,34] and references therein). This adsorption mode has also been supported by theoretical calculations. Thus, a plausible explanation would be that the higher rate of quinoline hydrogenation is due to the change in the adsorption geometry by interacting with the ketone. This explanation is based on the assumption that the hydrogenation rate increases when the quinoline ring is adsorbed close to parallel to the Pt surface and decreases in a tilted or perpendicular position.

Using the same logic, the rate deceleration by 35–47% in the hydrogenation of CD in the presence of the α-hydroxyester product (Table 4) may also be rationalized, assuming that the H-bonding interaction between the OH function of the product and the quinuclidine N of the alkaloid (Scheme 5) favors an adsorption geometry where the quinoline ring is more tilted relative to the Pt surface than in the case when CD is adsorbed alone. Note that these assumptions require independent confirmation by, for example, in situ spectroscopic measurements.

3.6. Conformation of cinchonidine on the Pt surface: mechanistic considerations

From a mechanistic point of view, the most important observation is the switch of the adsorption of CD from pro(*S*) to pro(*R*) upon addition of the activated ketone substrate (Schemes 1 and 2). The same chiral switch was observed in the hydrogenation of the alkaloid when the weakly interacting solvent toluene was replaced by acetic acid (Tables 1 and 3). A critical point is that hydrogenation of CDH_2 led to the same major diastereomer (*R*)-CDH_6-A during hydrogenation of the ketone substrate, independent of the solvent. This is a confirmation that the adsorption of the modifier in the presence of the substrate is controlled by the formation of a defined modifier–substrate complex whose structure is barely affected by the reaction conditions or the solvent. This interpretation is in good agreement with the observation of the preferred formation of the same α-hydroxyester enantiomer regardless of the solvent (toluene, acetic acid).

Several different models have been proposed for the origin of enantioselection in the hydrogenation of α-ketoesters and other activated ketones (see [1,34] and references therein). Most of these models include a direct 1:1 interaction of the chiral modifier and the substrate. A limitation of these concepts is that the exact con-

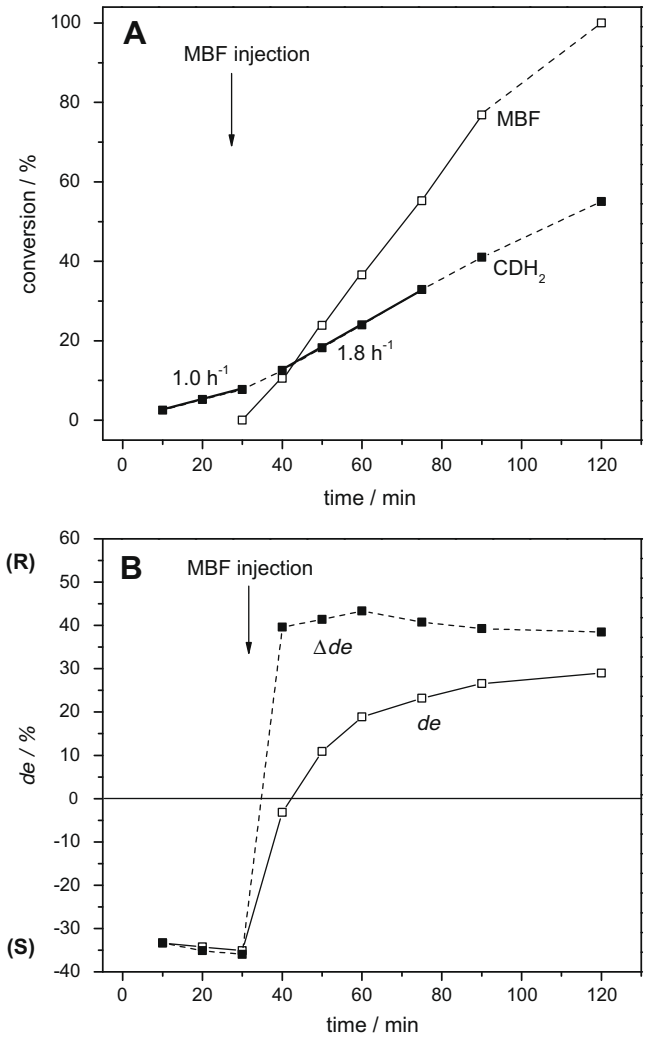


Fig. 3. Competition between (*S*)-methyl mandelate and methyl benzoylformate (MBF, added after 30 min) as indicated by the rate of CDH_2 conversion (A) and the diastereoselectivity of CDH_6-A (B); standard conditions, toluene, 10 bar.

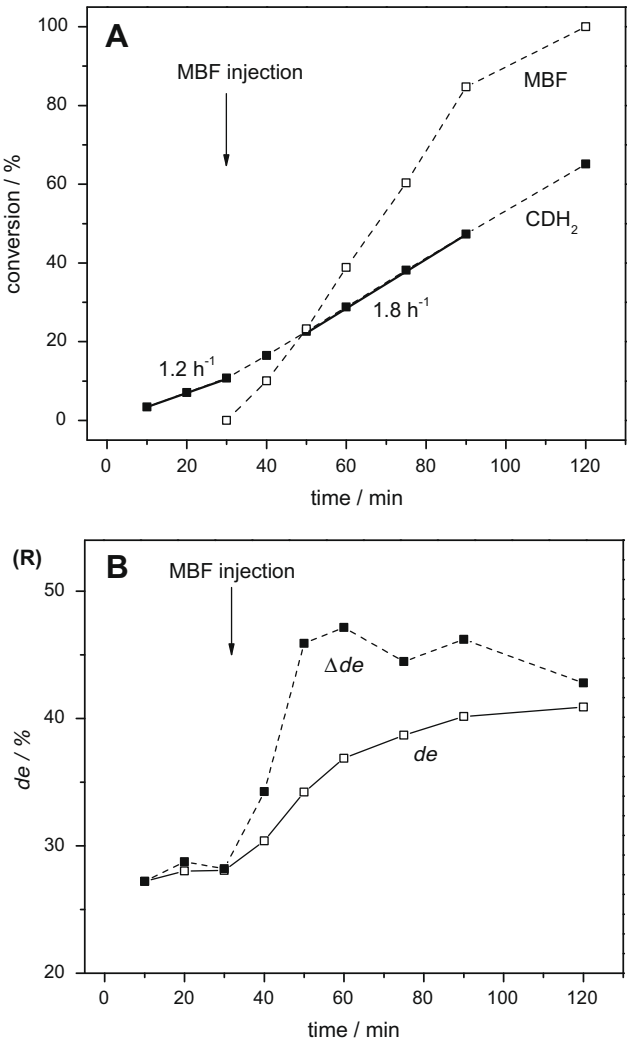
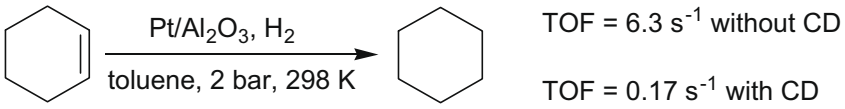


Fig. 4. Competition between (*R*)-methyl mandelate and methyl benzoylformate (MBF, added after 30 min) as indicated by the rate of CDH_2 conversion (A) and the diastereoselectivity of CDH_6-A (B); standard conditions, toluene, 10 bar.

formational structure of the modifier–substrate complex is mainly based on assumptions or theoretical calculations and only sparsely supported by direct in situ experimental observations [32]. The remarkable effect of the ketone substrate on the rate and diastereoselectivity of CD hydrogenation offers useful hints concerning the modifier–ketone interaction leading to enantioselection. The observation of a significant rate of aromatic hydrogenation of CD under these conditions, together with the "inverse ligand acceleration" phenomenon, clearly disproves mechanistic models that assume a modifier–substrate complex without adsorption of the quinoline unit of CD nearly parallel to the Pt surface. This is the case with Margitfalvi's "shielding model" [65–67]. According to this model the α-ketoester substrate forms an adduct with CD and this adduct is adsorbed on Pt, where the substrate is located between the Pt surface and the alkaloid modifier with the quinoline ring being in a strongly tilted position relative to Pt. Clearly, this fixed conformation of CD does not allow hydrogenation of the quinoline ring and the presence of the substrate should lead to rate deceleration, not rate acceleration. It is more likely that CD is adsorbed via its quinoline moiety being nearly parallel to the Pt surface (π-bound), a prerequisite for the aromatic hydrogenation (Scheme 4). Analogous arguments can be applied against any mechanistic concept that adopts tilted or perpendicular adsorption of the quinoline ring of the alkaloid [68].

Note that the preferred pro(*R*) adsorption of CD at C(4′) in the presence of ketones stands in contrast to recent results by DFT calculations, which suggested that the most stable modifier–substrate complex on Pt is an SO(4) conformation {C(4′) pro(*S*)} of the modifier [30]. This disagreement indicates the obvious limitation of theoretical calculations in a complex system where the interaction of five reaction components: substrate, modifier, metal surface, hydrogen, and solvent has to be determined.

The similar observations in the presence of three different substrates (MBF, EP, KPL) indicate that the conformational structure of this modifier–substrate complex is a general property, at least for the use of α-ketoester and α-ketolactone substrates. This interpretation is supported by the striking similarities of such substrates in terms of their hydrogenation activity and enantioselectivity, i.e. all substrates are hydrogenated with an enhanced rate to high excess of the (*R*)-alcohol in the presence of CD [51,54]. An extension of this work to other solvents and cinchona alkaloids, and also to structurally different substrates such as 1,1,1-trifluoromethyl ketones [69] is, however, necessary to evaluate the nature of the modifier–substrate interaction [34,70,71] more closely.



Scheme 6. Hydrogenation of cyclohexene on CD-modified Pt/Al_2O_3 and in the absence of CD.

4. Conclusions

We have shown that hydrogenation of CD, a well-known competing reaction during enantioselective hydrogenation on Pt-group metals, can be used as a "probe" to elucidate the conformation of the alkaloid on the metal surface during its interaction with the substrate. This experimental strategy was applied in the enantioselective hydrogenation of α-ketoesters and an α-ketolactone. The study revealed that the adsorption geometry of the chiral modifier is strikingly different in the presence or absence of the substrate, but the hydrogenation products and the solvent possessing a polar functional group may also induce conformational changes. Among these interactions, binding with the activated ketone substrate is clearly preferred, which relation is of fundamental importance in achieving high *ee* even at high conversion of the ketone.

As a result of the strong modifier–substrate interaction, both molecules are hydrogenated faster and with different selectivity than in the absence of their binding partner. From the point of view of the hydrogenation of the activated ketone such rate acceleration ("ligand acceleration") and the high *ee* up to 98% are well known. The concomitant hydrogenation of the aromatic anchoring unit of the modifier undergoes a rate acceleration by about 30% ("reverse ligand acceleration") and a remarkable inversion of the diastereoselectivity from (*S*)- to (*R*)-CDH_6-A (Scheme 4). We show that interaction of CD with the ketone substrate inverts the dominant adsorption mode of the modifier from pro(*S*) to pro(*R*) at C(4′) (Scheme 1). The probable origin of the "reverse ligand acceleration" is a change in the conformation of the quinoline ring relative to the Pt surface from tilted to nearly parallel (π-bonded) in a pro(*R*) conformation at C(4′) (most likely SO(3)).

The study revealed the formation of an almost identical modifier–substrate complex in case of three structurally different substrates (MBF, EP, KPL) and the conformational structure of this modifier–substrate adduct was not affected by the reaction conditions.

Another important conclusion emerging from this work is that investigation of the adsorption and interaction of modifier and substrate by theoretical calculations or spectroscopic methods under not truly in situ conditions has inherent limitations in providing a useful bases for mechanistic studies in such a complex system.

The approach of using the competing hydrogenation of the chiral modifier as a probe to characterize the adsorption of the modifier and its interaction with the substrate during reaction can probably be extended to other modifiers, substrates, and metals, and it may provide fundamentally new information for mechanistic considerations.

Acknowledgment

Financial support by the Swiss National Science Foundation is kindly acknowledged.

References

[1] T. Mallat, E. Orglmeister, A. Baiker, Chem. Rev. 107 (2007) 4863.
[2] H.-U. Blaser, M. Studer, Acc. Chem. Res. 40 (2007) 1348.
[3] M. Bartók, Curr. Org. Chem. 10 (2006) 1533.
[4] D.Y. Murzin, P. Mäki-Arvela, E. Toukoniitty, T. Salmi, Catal. Rev. – Sci. Eng. 47 (2005) 175.
[5] M. von Arx, T. Mallat, A. Baiker, Top. Catal. 19 (2002) 75.
[6] X. Zuo, H. Liu, M. Liu, Tetrahedron Lett. 39 (1998) 1941.
[7] M. Sutyinszki, K. Szöri, K. Felföldi, M. Bartók, Catal. Commun. 3 (2002) 125.
[8] W.-R. Huck, T. Mallat, A. Baiker, Adv. Synth. Catal. 345 (2003) 255.
[9] S.R. Calvo, R.J. LeBlanc, C.T. Williams, P.B. Balbuena, Surf. Sci. 563 (2004) 57.
[10] A. Vargas, D. Ferri, A. Baiker, J. Catal. 236 (2005) 1.
[11] A. Vargas, A. Baiker, J. Catal. 239 (2006) 220.
[12] D. Ferri, T. Bürgi, J. Am. Chem. Soc. 123 (2001) 12074.
[13] J. Kubota, F. Zaera, J. Am. Chem. Soc. 123 (2001) 11115.
[14] W. Chu, R.J. LeBlanc, C.T. Williams, Catal. Commun. 3 (2002) 547.
[15] F. Zaera, J. Phys. Chem. C 112 (2008) 16196.
[16] M.A. Laliberte, S. Lavoie, B. Hammer, G. Mahieu, P.H. McBreen, J. Am. Chem. Soc. 130 (2008) 5386.
[17] C.J. Baddeley, Top. Catal. 25 (2003) 17.
[18] R.J. LeBlanc, W. Chu, C.T. Williams, J. Mol. Catal. A: Chem. 212 (2004) 277.
[19] I. Bakos, S. Szabó, M. Bartók, E. Kálmán, J. Electroanal. Chem. 532 (2002) 113.
[20] A. Kraynov, A. Suchopar, R. Richards, Catal. Lett. 110 (2006) 91.
[21] E. Schmidt, D. Ferri, A. Baiker, Langmuir 23 (2007) 8087.
[22] K.E. Simons, P.A. Meheux, S.P. Griffiths, I.M. Sutherland, P. Johnston, P.B. Wells, A.F. Carley, M.K. Rajumon, M.W. Roberts, A. Ibbotson, Recl. Trav. Chim. Pays-Bas 113 (1994) 465.
[23] T. Evans, A.P. Woodhead, A. Gutierrez-Soza, G. Thornton, T.J. Hall, A.A. Davis, N.A. Young, P.B. Wells, R.J. Oldman, O. Plashkevych, O. Vahtras, H. Agren, V. Caravetta, Surf. Sci. 436 (1999) L691.
[24] Z. Ma, F. Zaera, J. Phys. Chem. B 109 (2005) 406.
[25] Z. Ma, I. Lee, F. Zaera, J. Am. Chem. Soc. 129 (2007) 16083.
[26] A. Kraynov, A. Suchopar, L. D'Souza, R. Richards, Phys. Chem. Chem. Phys. 8 (2006) 1321.
[27] D.M. Meier, T. Mallat, D. Ferri, A. Baiker, J. Catal. 244 (2006) 260.
[28] T.A. Martinek, T. Varga, F. Fülöp, M. Bartók, J. Catal. 246 (2007) 266.
[29] M. Bartók, P.T. Szabó, T. Bartók, G. Szöllösi, Rapid Commun. Mass Spectrom. 14 (2000) 509.
[30] A. Vargas, G. Santarossa, M. Iannuzzi, A. Baiker, J. Phys. Chem. C 112 (2008) 10200.
[31] K.A. Avery, R. Mann, M. Norton, D.J. Willock, Top. Catal. 25 (2003) 89.
[32] N. Bonalumi, T. Bürgi, A. Baiker, J. Am. Chem. Soc. 125 (2003) 13342.
[33] M.S. Schneider, A. Urakawa, J.D. Grunwaldt, T. Bürgi, A. Baiker, Chem. Commun. (2004) 744.
[34] T. Bürgi, A. Baiker, Acc. Chem. Res. 37 (2004) 909.
[35] E. Schmidt, D. Ferri, A. Vargas, A. Baiker, J. Phys. Chem. C 112 (2008) 3866.
[36] W.-R. Huck, T. Bürgi, T. Mallat, A. Baiker, J. Catal. 216 (2003) 276.
[37] A. Baiker, H.-U. Blaser, in: G. Ertl, H. Knözinger, J. Weitkamp (Eds.), Handbook of Heterogeneous Catalysis, Wiley-VCH, Weinheim/Germany, 1997, p. 2422.
[38] G. Szöllösi, P. Forgó, M. Bartók, Chirality 15 (2003) S82.
[39] H.-U. Blaser, H.P. Jalett, W. Lottenbach, M. Studer, J. Am. Chem. Soc. 122 (2000) 12675.
[40] E. Schmidt, A. Vargas, T. Mallat, A. Baiker, J. Am. Chem. Soc. 131 (2009) 12358.
[41] E. Schmidt, W. Kleist, F. Krumeich, T. Mallat, A. Baiker, Chem. Eur. J. 16 (2010) 2181.
[42] M. Bartók, T. Bartók, G. Szöllösi, K. Felföldi, Catal. Lett. 61 (1999) 57.
[43] G. Szöllösi, S. Cserényi, F. Fülöp, M. Bartók, J. Catal. 260 (2008) 245.
[44] R. Hess, F. Krumeich, T. Mallat, A. Baiker, Catal. Lett. 92 (2004) 141.
[45] F.W. Vierhapper, E.L. Eliel, J. Org. Chem. 40 (1975) 2729.
[46] D.M. Meier, A. Urakawa, N. Turrà, H. Rüegger, A. Baiker, J. Phys. Chem. A 112 (2008) 6150.
[47] M. von Arx, T. Bürgi, T. Mallat, A. Baiker, Chem. Eur. J. 8 (2002) 1430.
[48] Y. Nitta, A. Shibata, Chem. Lett. 27 (1998) 161.
[49] K. Borszéky, T. Bürgi, Z. Zhaohui, T. Mallat, A. Baiker, J. Catal. 187 (1999) 160.
[50] I.C. Lee, R.I. Masel, J. Phys. Chem. B 106 (2002) 368.
[51] E. Tálas, J.L. Margitfalvi, O. Egyed, J. Catal. 266 (2009) 191.
[52] B. Török, K. Balázsik, M. Török, K. Felföldi, M. Bartók, Catal. Lett. 81 (2002) 55.
[53] M. Sutyinszki, K. Szöri, K. Felföldi, M. Bartók, Catal. Lett. 81 (2002) 281.
[54] S. Diezi, S. Reimann, N. Bonalumi, T. Mallat, A. Baiker, J. Catal. 239 (2006) 255.
[55] M. Schürch, N. Künzle, T. Mallat, A. Baiker, J. Catal. 176 (1998) 569.
[56] R. Hess, T. Mallat, A. Baiker, J. Catal. 218 (2003) 453.
[57] R. Hess, A. Vargas, T. Mallat, T. Bürgi, A. Baiker, J. Catal. 222 (2004) 117.
[58] J.M. Bonello, R.M. Lambert, N. Künzle, A. Baiker, J. Am. Chem. Soc. 122 (2000) 9864.
[59] D. Ferri, T. Bürgi, A. Baiker, J. Phys. Chem. B 108 (2004) 14384.
[60] K. Szöri, M. Sutyinszki, K. Felföldi, M. Bartók, Appl. Catal. A: Gen. 237 (2002) 275.
[61] M. Garland, H.-U. Blaser, J. Am. Chem. Soc. 112 (1990) 7048.
[62] D.M. Meier, D. Ferri, T. Mallat, A. Baiker, J. Catal. 248 (2007) 68.

[63] G. Szöllösi, S. Cserényi, K. Balázsik, F. Fülöp, M. Bartók, J. Mol. Catal. A: Chem. 305 (2009) 155.
[64] R.J. Madon, J.P. O'Connell, M. Boudart, AIChE J. 24 (1978) 904.
[65] J.L. Margitfalvi, M. Hegedüs, E. Tfirst, Stud. Surf. Sci. Catal. 101 (1996) 241.
[66] J.L. Margitfalvi, M. Hegedüs, E. Tfirst, Tetrahedron: Asymmetry 7 (1996) 571.
[67] J.L. Margitfalvi, E. Tfirst, J. Mol. Catal. A: Chem. 139 (1999) 81.
[68] R.L. Augustine, S.K. Tanielyan, L.K. Doyle, Tetrahedron: Asymmetry 4 (1993) 1803.
[69] A. Vargas, F. Hoxha, N. Bonalumi, T. Mallat, A. Baiker, J. Catal. 240 (2006) 203.
[70] K. Szöri, K. Balázsik, K. Felföldi, M. Bartók, J. Catal. 241 (2006) 149.
[71] S. Lavoie, G. Mahieu, P.H. McBreen, Angew. Chem., Intl. Ed. 45 (2006) 7404.