# Heterogeneous Enantioselective Hydrogenation over Cinchona Alkaloid Modified Platinum: Mechanistic Insights into a Complex Reaction

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**ABSTRACT**

Modification of a metal surface by a strongly adsorbed chiral organic molecule has proven to be an interesting strategy for heterogeneous chiral catalysis. Platinum chirally modified by cinchona alkaloids, successfully applied for the enantioselective hydrogenation of α-ketoesters, is probably the most prominent catalyst based on this concept. Despite considerable research efforts toward understanding of this complex catalytic system, the proposed mechanistic models are still debated. Here we discuss how enantiodifferentiation can be induced on a catalytically active surface and validate the models proposed for the platinum−cinchona system in the light of the existing molecular knowledge.

## Introduction

The demand for optically active compounds in high enantiopurity has witnessed an explosion over the past decades, mainly driven by the awareness that application of the wrong enantiomer of a chiral product can have fatal consequences. Among the various methods applied in the production of chiral compounds,[1] asymmetric catalysis is unique in the sense that with a small amount of an optically active catalyst a large quantity of a chiral compound can be produced.[2] This aspect has been termed "chirality multiplication". In the past decades, homogeneous enantioselective catalysis has seen phenomenal progress, as reflected by the Nobel prizes in 2001 awarded to Sharpless, Noyori, and Knowles.[3−5] Many transition metal complexes with chiral ligands have been developed for various catalytic reactions important in the synthesis of optically pure compounds in the fine chemicals and pharmaceutical sectors. Heterogeneous enantioselective catalysis, that is, chiral catalysis at surfaces, is still lagging behind as concerns performance, mechanistic insight, and scope of reaction. Successful applications with synthetic potential are confined to a narrow range of asymmetric C=O and C=C hydrogenations.[6] Nevertheless, heterogeneous catalysis offers inherent practical advantages connected with separation, reuse, and stability of the catalyst and affords the opportunity for continuous process operation.[7] These technical advantages explain why research in heterogeneous asymmetric catalysis has gained considerable momentum in the past decade.

Various strategies have been applied in the development of heterogeneous chiral catalysts,[8,9] including the immobilization of successful homogeneous chiral transition metal complexes on a suitable support, imprinting of chiral templates, modification of active metals by an adsorbed chiral modifier, or the use of intrinsically chiral solids. Among these strategies, only the immobilization of homogeneous transition metal complexes and the chiral modification of metals show synthetic potential.[10] Particularly striking is the progress made in the chiral modification of supported metal catalysts,[11] among which platinum modified with cinchona alkaloids applied in the enantioselective hydrogenation of α-functionalized ketones and nickel modified with tartaric acid used in the asymmetric reduction of $\beta$-ketoesters are the most prominent examples.[12] Although the platinum−cinchona system has been successfully applied in the enantioselective hydrogenation of a variety of α-functionalized ketones, including α-ketoesters and α-ketoacids, α-ketoamides, α-diketones, α-keto acetals, α-ketoethers, trifluoromethyl ketones, ketopantolactone, and pyrrolidine-2,3,5-triones, most knowledge has been collected using the enantioselective hydrogenation of methyl or ethyl pyruvate, originally reported by Orito in 1979. The knowledge gathered since then on this catalytic system has been covered in various reviews.[6,12−15] Some important characteristic features of the platinum−cinchona system are summarized in Figure 1. The most striking characteristics are as follows: (i) the enantioselectivity is completely lost when the basic nitrogen at the quinuclidine moiety of the cinchona alkaloid is blocked by alkylation,[16] and (ii) the presence of the cinchona alkaloid results in significant rate acceleration, that is, the rate of the enantioselective hydrogenation is greatly enhanced compared to that of the racemic hydrogenation.[17]

The progress made in the mechanistic understanding of the platinum−cinchona system is the focus of this article. In the first part, we discuss briefly the principal possibilities how enantioselective catalysis can occur on a chirally modified metal surface. The second part is devoted to a critical analysis of the proposed mechanistic models for the enantioselective hydrogenation on platinum−cinchona systems.

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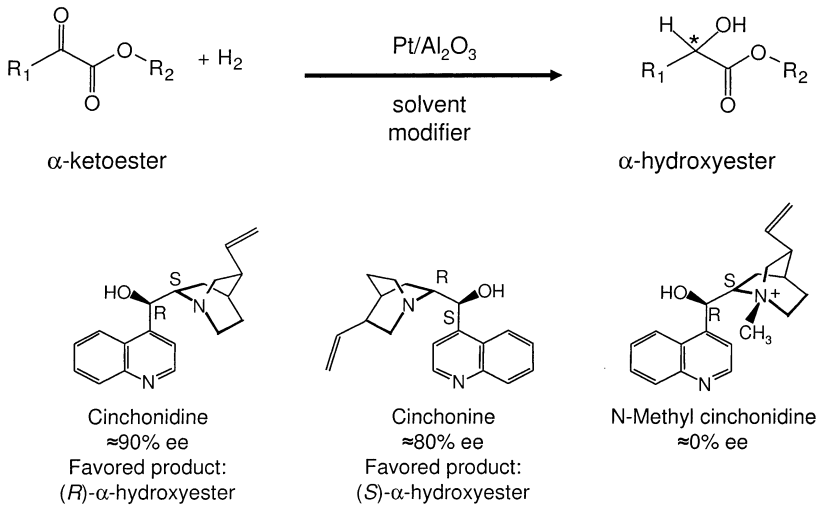


**FIGURE 1.** Heterogeneous enantioselective hydrogenation of α-ketoesters over cinchona alkaloid modified Pt. In the absence of the modifier, a racemic mixture of the α-hydroxyester is formed. Addition of cinchonidine (cinchonine) modifier leads to enantiomeric excess in favor of the (*R*)-α-hydroxyester ((*S*)-α-hydroxyester). Blocking of the quinuclidine N leads to complete loss of enantiodifferentiation.

## Chiral Recognition on a Metal Surface

It needs the combination of two basic functions that asymmetric catalysis can occur on a metal surface, namely, activity and stereochemical control. The nature of the active sites on chirally modified catalysts is the subject of ongoing debates and investigations. Principal possibilities on how chiral recognition and enantioselective catalysis can be induced are shown schematically in Figure 2. One possibility emerges from the fact that metal catalyst particles are not perfectly symmetric structures (Figure 2a). They contain defects such as kinks, some of which may be chiral. Such intrinsically chiral sites can be created deliberately by cutting a metal single crystal along certain high Miller index planes. Gellman and co-workers demonstrated that adsorption of chiral molecules is enantiospecific on such surfaces.[18] Attard found that intrinsically chiral Pt single-crystal surfaces exhibit enantioselectivity in the electrooxidation of D- and L-glucose.[19] In both examples mentioned above, the enantiospecificity of the metal surface is attributed to chiral kink sites. In a real catalyst sample containing supported metal particles, such sites may also exist. However, in the absence of additional chiral information, the amount of left- and right-handed kink sites (or other chiral structures) is equal. Hence such catalysts are racemic and do not yield enantiomeric excess.

A chiral modifier may however interact differently with chiral metal sites of opposite handedness (Figure 2b). As a consequence one enantiomer of the site can be selectively poisoned, leaving the other enantiomer preferentially exposed and accessible for the reactant. If this chiral site is catalytically active, enantiomeric excess can be induced. For the Pt−cinchona alkaloid system this is improbable based on several observations. Cinchonidine, which is the most efficient chiral modifier for platinum catalysts, and similar molecules are found to adsorb rather indiscriminately on Pt. For example, 1-(1-naphthyl)-ethylamine (NEA), a precursor of an efficient modifier, adsorbs indiscriminately at step and surface sites.[20] Furthermore, *R*- and *S*-NEA adsorption is the same on the chiral single-crystal surface Pt(643). From cyclic voltammetry, Attard concluded that adsorption of dihydrocinchonidine is structure-insensitive, since adsorption was very similar on various Pt single-crystal surfaces.[19] More importantly, a selective poisoning of sites of one handedness cannot explain the often-observed rate acceleration induced by the modifier. A selective poisoning diminishes the number of active sites and thus leads to an apparent rate deceleration with respect to the unmodified reaction.

The interaction of a chiral molecule with a (nonchiral) flat metal surface could in principle lead to a reconstruction of the metal surface and the generation of chiral sites with preferential handedness (Figure 2c). This was demonstrated by scanning tunneling microscopy (STM) for adsorption of 2,5,8,11,14,17-hexa(*tert*-butyl)decacyclene (HtBDC, $C_{60}H_{66}$) on Cu(110).[21] The driving force for such a process is the larger adsorption energy of the molecule on the reconstructed surface with respect to adsorption on the nonreconstructed surface, which overcompensates the energy for reconstruction. A net driving force is therefore only expected for large molecules with big adsorption energy. For cinchona alkaloids, such an adsorption-induced reconstruction has not been observed yet.

A somewhat similar idea was put forward by Raval and co-workers for the enantioselective hydrogenation of $\beta$-ketoesters over tartaric acid modified Ni catalysts.[22] Upon adsorption of a molecule, the surface metal atoms are slightly displaced from their equilibrium position in the absence of the adsorbate. In contrast to the reconstruction discussed above, the metal atoms are not removed from the lattice but are only slightly displaced. Raval and co-workers showed by calculations that adsorption of bitartrate displaces the neighboring Ni surface atoms, which leads to a "chiral footprint". This chiral ensemble of metal atoms may be the active catalytic site, combining catalytic activity and enantiodifferentiation. An important issue in this context is how much the surface atoms are displaced from the nonchiral unperturbed

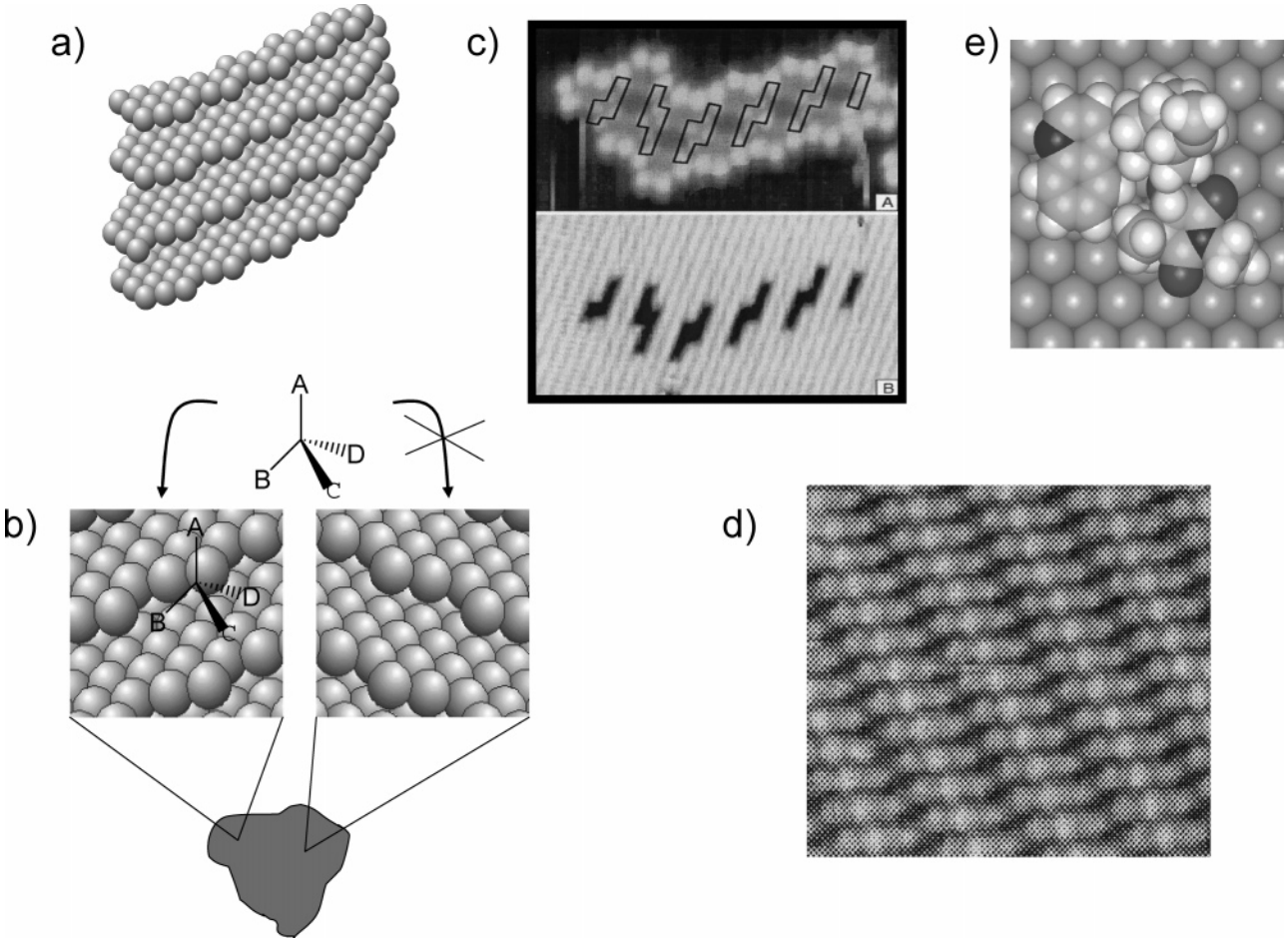


**FIGURE 2.** Principal possibilities for chiral induction on metal surfaces: (a) intrinsically chiral metal surfaces, kink sites on a high Miller index single-crystal surface;[18] (b) selective adsorption of a chiral molecule on chiral sites of one handedness (blocking) on a racemic surface of a metal particle; (c) creation of chiral sites on nonchiral terraces through adsorption induced reconstruction[21] (the example shows STM images of adsorbed 2,5,8,11,14,17-hexa(*tert*-butyl)decacyclene (HtBDC, $C_{60}H_{66}$) on Cu(110) (top), which results in the creation of chiral kink sites (bottom); even without reconstruction the adsorption of a chiral molecule may lead to a "chiral footprint");[22] (d) supramolecular chirality on nonchiral terraces by self-assembly of chiral molecules (the example shows adsorbed tartaric acid on Cu(110);[27] the adsorption pattern destroys all symmetry planes of the underlying metal surface; such adsorption patterns may leave shaped assemblies of surface atoms free (template));[28] (e) a chiral site on a metal surface can be generated by adsorption of a chiral molecule (modifier).

structure. The "footprint" can change from almost nonchiral, in the case that the displacement of the surface atoms is small, leaving a rather symmetric arrangement of surface atoms, to "very chiral" in the case of strong displacements from the symmetric arrangement. It is likely that such "chiral footprints" are also generated through adsorption of cinchona alkaloids on Pt, which could lead to enantioselection. To explain the observed rate acceleration in the Pt−cinchona alkaloid system, the chiral site ("chiral footprint") should also accelerate the reaction with respect to the nonreconstructed surface, which seems unlikely. Furthermore, the loss in enantioselectivity when blocking the quinuclidine N of the modifier would indicate that the quinuclidine N is involved in the formation of the "chiral footprint". However, in situ infrared[23,24] and Raman spectroscopies[25] of cinchonidine adsorption, as well as near edge X-ray absorption fine structure spectroscopy (NEXAFS), of 10,11-dihydrocinchonidine on Pt(111) in ultrahigh vacuum[26] indicate that the modifier is anchored via the quinoline ring. Thus in the light of currently available experimental findings a "chiral footprint" mechanism seems improbable for the Pt−cinchona alkaloid system.

Another mechanism is based on a supramolecular chirality. The chiral modifier forms long-range ordered patterns on the metal surface, in such a way that the symmetry planes of the underlying metal surface are destroyed (Figure 2d). Raval and co-workers initially proposed that such a supramolecular chirality is responsible for enantiodifferentiation in the Ni−tartaric acid system. The proposal was based on STM experiments, which revealed ordered overlayers of tartaric acid on Cu(110).[27] A similar mechanism was proposed for the Pt−cinchona alkaloid system, albeit without experimental evidence.[28] An ordered adlayer of the alkaloid leaves chiral assemblies of surface Pt atoms exposed, which are catalytically active. Adsorption of the prochiral reactant on the two enantiofaces is unequal, which is assumed to be the origin of enantiodifferentiation. Such a "template model" is improbable for the Pt−cinchona alkaloid system due to the following reasons: Ordered overlayers of cinchona alkaloids or related compounds have not been found on

Pt by LEED studies.[29] Similar to the Ni−tartaric acid system, cinchonidine may form ordered overlayers on Cu(111).[30] On the latter surface, the lateral potential for adsorbates is usually smaller than for Ni(111) or Pt(111). Indeed no ordered overlayers of tartaric acid and cinchona alkaloids were found on Ni and Pt surfaces, respectively. Furthermore, the template model does not explain the rate acceleration due to the modification of the metal surface. Finally, very small Pt particles with 2 nm diameter were successfully used for the enantioselective hydrogenation of methyl pyruvate.[31] Such particles are too small to accommodate extended long-range ordered adsorbate layers of molecules of the size of cinchona alkaloids.

Finally, an interaction between the adsorbed modifier and the reactant (Figure 2e) could be at the origin of enantiodifferentiation. This scenario has been widely accepted for the platinum−cinchona system and will be examined in detail in the following.

## Proposed Model for Ethyl Pyruvate Hydrogenation

In 1994, Baiker and co-workers proposed a 1:1 interaction model based on quantum chemical calculations and the existing experimental knowledge to rationalize enantiodifferentiation in the heterogeneous enantioselective hydrogenation of ethyl pyruvate over cinchonidine-modified Pt.[32] The theoretical model assumed that enantiodifferentiation can be traced to the different stability of the diastereomeric complexes formed between cinchonidine anchored to the Pt catalyst surface and ethyl pyruvate adsorbed in its two enantiofacial forms (via *re*- and *si*-faces), leading to *S*- and *R*-ethyl lactate, respectively, upon hydrogenation. A structurally similar model was proposed by Wells and co-workers, albeit with unrealistically high-energy differences between the pro-*R* and pro-*S* activated complexes.[33] According to these models the chiral cinchonidine modifier adopts an "open" conformation, that is, a conformation where the basic quinuclidine nitrogen atom points away from the aromatic quinoline ring. Cinchonidine is anchored on the Pt catalyst surface via the quinoline moiety. In protic solvents (e.g., acetic acid), the protonated quinuclidine group interacts with the keto carbonyl oxygen of the adsorbed reactant molecule through a N−H···O hydrogen bond. In aprotic solvents (e.g., toluene), where the quinuclidine is not protonated, a N···H−O hydrogen bond involving a half-hydrogenated state of the reactant was envisaged. This intermolecular interaction combined with steric repulsion exerted by the anchoring group causes the preferential adsorption of the reactant on one enantioface (*re*- or *si*-face), and the product alcohol derived thereof is formed in excess. Note that the keto group was assumed to adsorb parallel to the Pt surface during hydrogenation. Support for this idea was provided by molecular mechanics and quantum chemical calculations modeling the modifier−reactant interaction assuming that the platinum surface only imposes some geometrical constrains. These calculations revealed first of all that the proposed interactions are feasible. More importantly they showed that with cinchonidine the complex, which would lead to the *R*-alcohol upon hydrogenation from the surface side, is more stable than its counterpart, whereas with cinchonine the pro-*S* complex was found to be more stable. The model calculations, despite the numerous assumptions and although neither catalyst surface nor solvent were explicitly considered, made a correct prediction of the absolute configuration of the major enantiomer. Figure 3 shows the essence of the initially proposed model.

## Validation of Model Assumptions

The 1:1 interaction model described above involves the quinuclidine N of the modifier, which is plausible in view of the observation that blocking of this function leads to a complete loss of enantiodifferentiation.[16] Other assumptions were less obvious at the time the model was proposed. These involve the adsorption mode and conformation of modifier and reactant. In this section, we will discuss what has been learned concerning these assumptions during the last years.

An important assumption concerns the conformation and adsorption mode of the cinchona alkaloid on the Pt catalyst surface. A refined conformational analysis using ab initio and density functional theory (DFT) reaction field calculations combined with NMR spectroscopy revealed that the population of the most stable conformer "open 3", assumed in the original model, depends on the polarity of the solvent.[34] Highest relative abundance of conformer "open 3" was observed in solvents that are apolar, whereas the population of the "closed" conformer was enhanced in polar solvents. This solvent-dependent conformational behavior is certainly an important factor for explaining the higher enantioselectivity achieved in apolar solvents. Further support for this contention comes from the fact that a synthetic cinchona derivative (α-isocinchonine) with fixed "open" conformation provides similar enantioselectivity to *S*-ethyl lactate as cinchonine itself.[35]

In the original model, the modifier was assumed to adsorb via the quinoline part with the latter being oriented parallel to the surface. The adsorption of 10,11-dihydrocinchonidine on Pt(111) under ultrahigh vacuum conditions was investigated by near-edge X-ray absorption fine structure spectroscopy (NEXAFS).[26] At room temperature, a mean angle of about zero was found between the quinoline plane and the surface, whereas at 323 K, the quinoline ring was more tilted away from the surface, forming a mean angle of about 60°. Quinoline itself was investigated by the group of Lambert and was also found to adsorb preferentially flat on Pt(111) at room temperature.[36] The studies just discussed reveal a tendency of the modifier to adsorb flat. However, the experiments were performed in a "clean" environment far from reaction conditions. Furthermore, due to the relatively broad transitions observed in NEXAFS only a mean orientation of the molecules could be determined.

Vibrational spectroscopy is usually less limited by overlapping bands and can be applied at or close to

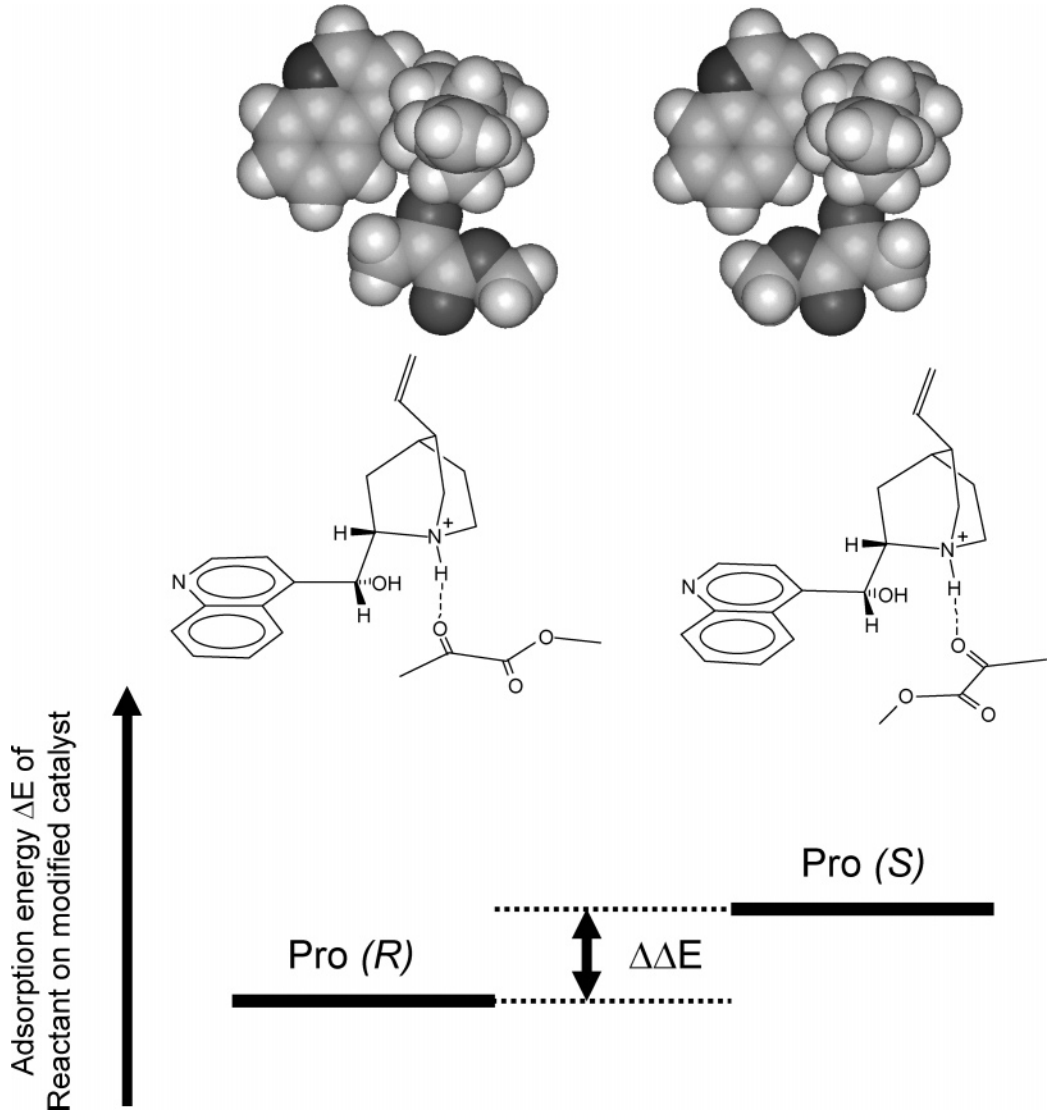


**FIGURE 3.** Original 1:1 interaction model proposed for the heterogeneous enantioselective hydrogenation of α-ketoesters over cinchonidine-modified Pt.[32] The reactant interacts with the adsorbed modifier through a hydrogen bond. This interaction leads to an energetic preference for adsorption on one enantioface of the reactant.

reaction conditions. The adsorption of cinchonidine was investigated by several groups using different techniques. Already the first report using attenuated total reflection (ATR) infrared spectroscopy to study cinchonidine adsorption on a $Pt/Al_2O_3$ model catalyst in the presence of $CH_2Cl_2$ solvent and hydrogen revealed that several differently adsorbed modifier species coexist on the Pt surface under hydrogenation conditions.[37] Later a detailed analysis of the spectra based on comparison with model compounds such as quinoline and pyridine and ab initio calculations were presented.[23] The orientation of the quinoline moiety with respect to the surface was determined from the orientation of the dynamic dipole moment associated with several vibrations of the molecule. This analysis lead to the following picture (Figure 4): At low concentrations, an adsorption mode prevails where the quinoline ring is oriented preferentially but not completely flat with respect to the surface. In this mode, cinchonidine is strongly attached to the Pt surface via the quinoline $\pi$-system. As the free Pt surface gets more

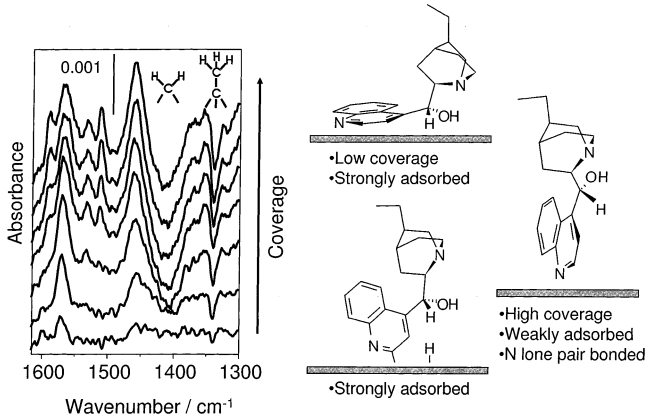


**FIGURE 4.** ATR-IR spectra (left) of cinchonidine on $Pt/Al_2O_3$ measured in situ while flowing solutions of the modifier at different concentrations in hydrogen-saturated dichloromethane over the sample. The spectrum strongly changes with increasing coverage. Negative bands are due to solvent decomposition products that are displaced from the surface by cinchonidine.[23] The right panel shows adsorbed cinchonidine species as deduced from ATR spectroscopy.

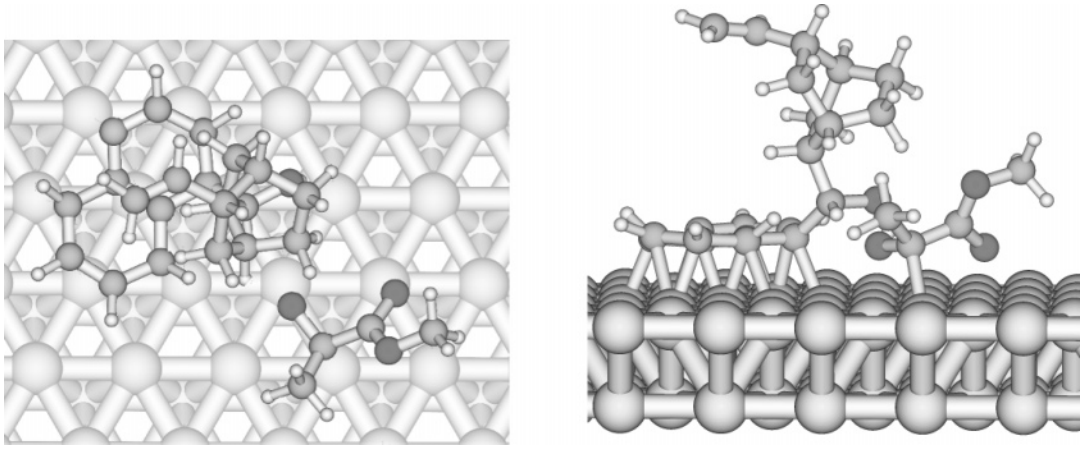

**FIGURE 5.** Model of the interaction between cinchonidine adsorbed on Pt and methyl pyruvate based on density functional theory (DFT) calculations.[39]

restricted, two additional adsorption modes are observed, where the quinoline part is tilted with respect to the surface. In one, the hydrogen in α-position to the quinoline N is abstracted, and the modifier is relatively strongly attached to the surface via a Pt−C bond. The abundance of this species depends on the coverage of hydrogen on the surface. Finally a species was observed that is weakly adsorbed via a quinoline N atom lone-pair bonding. Of course, the question remains, which of the observed species is responsible for enantiodifferentiation. The fact that enantioselectivity is observed already at very low modifier concentration supports the strongly anchored flat adsorption mode. More evidence should be provided by spectroscopic measurements and simultaneous determination of enantiomeric excess under different conditions. However, such information is challenging to obtain and still missing. The group of Zaera reported a study of cinchonidine adsorption on Pt using external reflection infrared spectroscopy.[24,38] The conclusions drawn from this analysis are in agreement with the ones derived from the ATR experiments discussed above.[24,38] Surface-enhanced Raman spectroscopy studies also lead to similar findings.[25]

The quite numerous spectroscopic data on the cinchonidine system supports the model assumption that the modifier is anchored via the quinoline moiety oriented preferentially parallel to the surface. This seems to be the most stable adsorption mode of the modifier under vacuum, in the presence of solvent, and under hydrogenation conditions. Recently the adsorption of cinchonidine on Pt was also studied theoretically by DFT methods. The Pt surface was modeled by a Pt cluster. These calculations confirmed the strong interaction between Pt surface and the quinoline $\pi$-system.[39]

As concerns the adsorption mode of the alkyl pyruvate reactant (methyl or ethyl pyruvate), ultrahigh vacuum studies on platinum single-crystal surfaces using X-ray and UV photoelectron spectroscopies (XPS and UPS),[40] NEXAFS,[41] and reflection/absorption infrared spectroscopy (RAIRS)[42] revealed that the alkyl pyruvate mainly adsorbs via lone pair−metal interaction of both carbonyl groups, that is, in *cis* conformation with the molecular plane oriented normal or tilted with respect to the surface. At high coverage, a minority species with a free carbonyl group was identified and assigned to an $\eta^1$-trans configuration.[42] Hydrogen coadsorption was found to have a significant influence on the alkyl pyruvate adsorption by lowering the tilting angle of the adsorbed species[43] and suppressing surface polymerization of the adsorbed enediolate species.[44] Recent in situ ATR infrared measurement on an alumina-supported platinum catalyst corroborated the existence of the adsorption modes previously found on single-crystal surfaces.[45]

The interaction between cinchonidine-modified Pt and ketopantolactone substrate under hydrogenation conditions has been studied by modulation excitation ATR infrared spectroscopy.[46] The spectra showed characteristic bands associated with hydrogen-bonded N−H$^+$ and C=O groups thus indicating a hydrogen bond interaction between the quinuclidine nitrogen of the cinchonidine modifier and the oxygen of the α-carbonyl group of ethyl pyruvate. The bands were not observed for *N*-methyl cinchonidine, where the quinuclidine N is blocked (Figure 1). Shifted carbonyl vibrations were also observed by in situ ATR measurements of an alumina-supported platinum catalyst.[45] These in situ measurements strongly support the crucial role of the hydrogen bonding in the formation of the diastereomeric adducts between adsorbed modifier and α-ketoester, as implied in the original model.

Figure 5 provides a three-dimensional view on the interaction between the adsorbed cinchonidine and methyl pyruvate as it emerged from DFT calculations on a platinum cluster model.[39] It illustrates the crucial role of the three-dimensional structure of the modifier for enantiodifferentiation. Besides the main attractive interaction through hydrogen bonding, repulsive interactions are likely also necessary for enantiodifferentiation.[47]

## Origin of Rate Acceleration

A comprehensive model for the enantioselective hydrogenation of ethyl pyruvate should not only rationalize enantiodifferentiation but also provide a feasible explana-

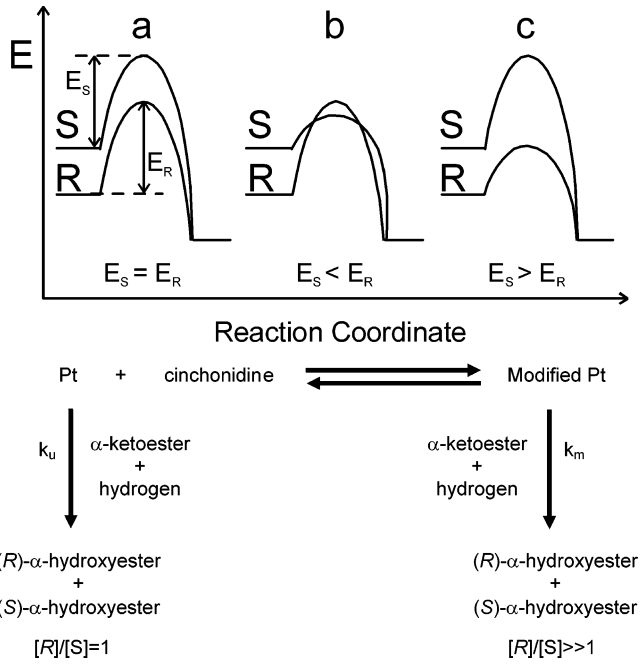


**FIGURE 6.** Thermodynamic (stability of diastereomeric complexes) and kinetic factors (activation energy) affecting enantiodiscrimination (top panel). Three different cases can be distinguished for two diastereomeric complexes with different energy that would lead to (*R*)- and (*S*)-product, respectively: (a) $E_S = E_R$; (b) $E_S < E_R$; (c) $E_S > E_R$. The initial state (left) represents diastereomeric complexes. The final state (right) represents product after release from the chiral site. The bottom panel shows the two-cycle mechanistic scheme.[17] Racemic hydrogenation on unmodified Pt proceeds with rate $k_u$, whereas on chirally modified Pt, the reaction proceeds with rate $k_m$.

tion for the observed rate enhancement. Generally, there are several possibilities how thermodynamic and kinetic factors can affect enantioselectivity and reaction rate, as schematically shown in Figure 6. In the previously discussed model, it was assumed that thermodynamics, that is, the stability of the adsorbed diastereomeric modifier−reactant adduct, controls enantioselectivity. Although, the model calculations showed excellent agreement with the experimental stereochemical outcome of the reaction, the model does not account for the rate acceleration of the enantioselective compared to the racemic reaction. For this purpose, kinetic factors, that is, preexponential factors and activation energies, have to be accounted for. The kinetic studies available so far indicate that the enantioselective hydrogenation can be described within the frame of a two-step, two-cycle scheme, as depicted in Figure 6.[17] Unfortunately, the absolute quantities of the relevant kinetic parameters are still unknown, but a general consideration is possible. It is clear that the number of active sites accessible for the α-ketoester and hydrogen on a platinum surface decreases upon adsorption of a chiral modifier (e.g., cinchonidine). Assuming that the activation entropy is similar for the nonmodified and modified site, we may conclude that the preexponential factor is considerably smaller for the enantioselective reaction on the modified sites. Hence, the rate acceleration of the enantioselective reaction has to originate from a lowering of the activation barrier. This has been demonstrated by a combined theoretical and experimental study where the relation between the electronic structure of substituted acetophenones in the racemic and enantioselective hydrogenation has been investigated.[48] A correlation between the keto carbonyl orbital energy and the hydrogenation rate was found, which rationalizes the effect of the substituent on the hydrogenation rate. The uncovered relationship between the keto carbonyl orbital energy and the hydrogenation rate provides a rational explanation for the observed rate acceleration. It could be shown that within the previously proposed 1:1 interaction model the more stabilized diastereomeric complex also undergoes a larger stabilization of the keto carbonyl orbitals, leading to the proposal that both thermodynamic and kinetic effects direct the reactivity toward the formation of the same enantiomer, as shown in Figure 6c. Interestingly, the activation of carbonyl compounds by hydrogen bonding is emerging as a tool in other asymmetric catalytic reactions.[49]

## Other Proposed Models

Besides the 1:1 hydrogen bond model discussed in detail in this article, two distinctly different alternative models have been proposed (Figure 7). Margitfalvi and co-workers proposed a model that assumes that a supramolecular complex is stereoselectively reduced on the platinum surface.[50] The α-ketoester and cinchona alkaloid form a complex in which one side of the reactant is shielded by the cinchona alkaloid (shielding model), leaving the other side open for hydrogenation. A prerequisite of this model is that the cinchona alkaloid does complex in its "closed" conformation with the quinuclidine nitrogen pointing toward the aromatic quinoline ring. However, investigations with cinchona alkaloids bearing a rigid "open 3" conformation provide similar enantiodifferentiation as parent cinchona alkaloids,[35] indicating that the closed conformation does not play an important role in enantiodifferentiation. Furthermore, the rate enhancement of the enantioselective reaction cannot be explained with this model, as discussed in detail elsewhere.[13]

Another model implying nucleophilic catalysis involving the nitrogen of the chiral modifier and the ketone carbonyl has been proposed by Augustine and coworkers.[51] This nucleophilic addition scenario was recently studied by Vayner et al. using a variety of computational techniques.[52] They proposed that the key interaction between cinchonidine and pyruvate is a strong covalent bond joining the amine of cinchonidine to the pyruvate ketone carbonyl group (arrow in Figure 7). The zwitterionic adduct formed between cinchonidine and the ketone is adsorbed on the platinum through the quinoline ring and is subsequently reduced with inversion. However, at this time, the theoretical model clearly stands in contrast to some experimental observation and raises several unanswered questions. First of all, it has recently been shown that enantiodifferentiation is also observed with a

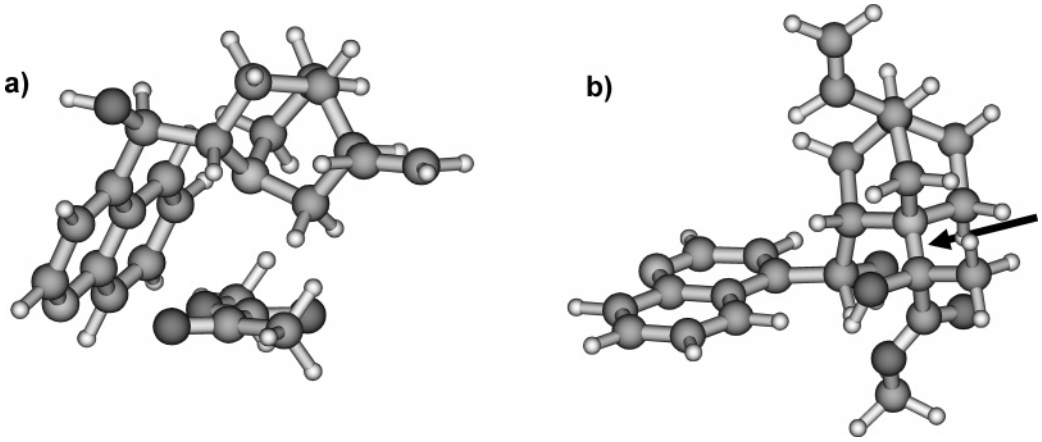


**FIGURE 7.** The left panel shows the shielding model proposed by Margitfalvi. One enantioface of the reactant is shielded by the modifier in closed conformation.[50] The right panel shows the model proposed by Augustine and co-workers[51] and refined by Vayner and co-workers:[52] A zwitterionic adduct is formed by nucleophilic addition (arrow). This adduct is reduced with inversion on the Pt surface.

structurally related diol, which possess no basic nitrogen and thus no possibility to form zwitterionic intermediates.[53] Formation of the zwitterionic adduct in acetic acid, in which the highest ee's are observed, is rather doubtful since the quinuclidine nitrogen will be protonated. For some cyclic ketones for which high ee's have been achieved, such as ketopantolactone, the formation of a zwitterionic adduct is sterically ruled out. Furthermore, there is no experimental evidence available so far that the hydrogenolysis of the zwitterionic adduct occurs over platinum under the mild conditions of enantioselective hydrogenation. Even if it would occur it seems likely that it is not selectively cleaving the C−N bond. Experimental work clarifying the above questions may help to finally assess the importance of this alternative model.

## Concluding Remarks

Although considerable progress has been made toward molecular level knowledge of the platinum−cinchona system a complete understanding is still out of reach. The fact that reactant and chiral modifier exist on the surface in different adsorption modes depending on surface coverage and composition of the adsorbed layer complicates the assessment of a particular adsorption geometry and thus structure of the transition state. As a result of this, we have to envision that the macroscopic stereochemical outcome of surface-catalyzed asymmetric reactions may reflect the superposition of several competing reaction pathways. This uncertainty has led to considerable debate as concerns the mechanism of this complex catalytic system. Nevertheless, the agreement between the 1:1 model and the experimental results is striking, lending some hope that we finally may reach a level of mechanistic understanding, which will greatly aid in the design of efficient asymmetric catalysts based on this concept.

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