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Journal of Molecular Catalysis A: Chemical 163 (2000) 205–220

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

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Transition state analogues — a guide for the rational design of enantioselective heterogeneous hydrogenation catalysts

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Received 18 February 2000; accepted 8 May 2000

Abstract

The present level of understanding the mechanism of the enantioselective hydrogenation of α-ketoesters over platinum, chirally modified by natural cinchona alkaloids is reviewed with special emphasis on the enantioselective hydrogenations of ethyl and methylpyruvate to the corresponding lactates. This knowledge is used in a combined experimental and theoretical approach to reveal the approximate structure of the crucial enantio-differentiating transition complexes formed by interaction of the reactant α-ketoester and the chiral modifier. The use of the concept of transition state analogues is shown to be a valuable guide for designing new efficient synthetic modifiers for this complex catalytic system.

Keywords: Asymmetric catalysis; α-ketoesters; Transition state analogues; Enantioselective hydrogenation; Ethyl- and methylpyruvate; Platinum; Chiral modifiers; Modeling; Mechanism; Catalyst design

1. Introduction

In the second half of the past century the design of solid catalysts has moved from purely empirical towards rational design. Some of these developments have been covered in recent reviews [1–5]. This progress has been spurred by major advances in several fields essential for catalysis such as surface analytical instrumentation, surface science, organometallic chemistry, theoretical techniques, solid-state chemistry, material science, and reaction engineering. Rational design as opposed to empirical design of a catalyst requires not only understanding of the reaction mechanism but also knowledge and control of the crucial structural and chemical properties of the solid catalyst under reaction conditions. Progress in analytical techniques has facilitated characterization of catalyst surfaces under reaction or near reaction conditions and revealed the nature of adsorbed surface species and their concentration. Dynamic techniques and isotope tracers make it possible to distinguish between catalytically important and spectator species. Surface science has greatly contributed to molecular-level understanding of the elementary processes on which catalytic reactions are based. Important relationships between structure and activity have been uncovered and confirmed on industrial catalysts, leading to detailed mechanistic insight of some reactions. Advances in synthetic organic chemistry and organometallic chemistry have broadened the scope and relevance of homogeneous catalysis and provided new opportunities in the design of catalytic processes for the production of fine chemicals. Quantum chemical techniques on both ab initio and semiempirical levels have been developed as a valuable tool aiding in understanding

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1381-1169/00/$ – see front matter
PII: S1381-1169(00)00387-3

molecular interactions relevant to the catalytic process and catalyst design. Progress in solid-state chemistry paved the way for synthesizing structurally and chemically tailored materials. Altogether these advances have led to a drastic reduction in the level of empiricism in catalyst design and moved it closer towards the ultimate goal of a rigorous rational design.

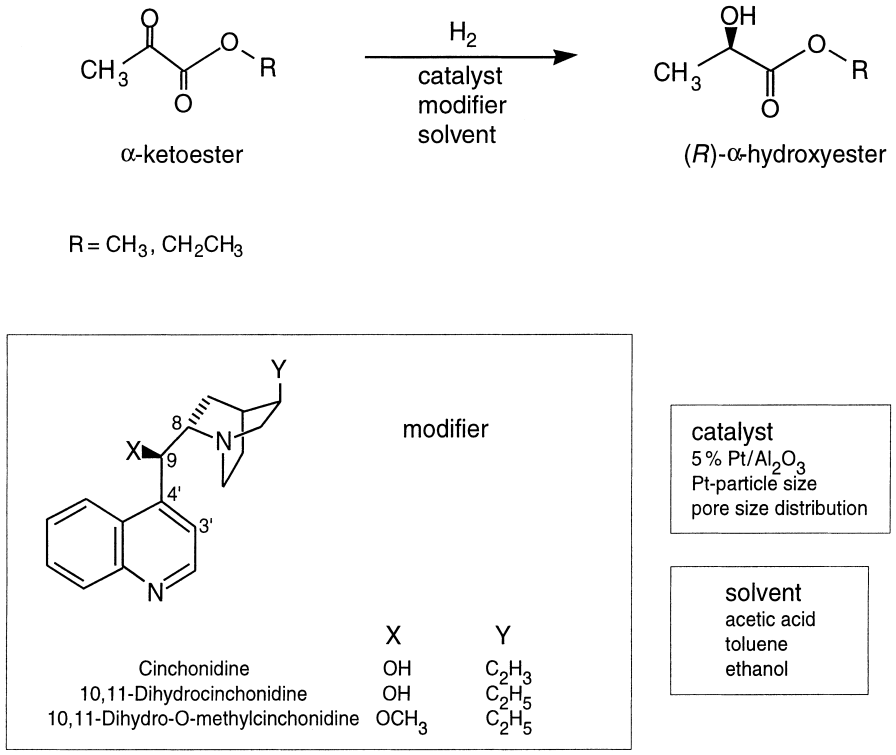
Exploitation of some of the paradigms of enzyme catalysis has triggered new ideas for the synthesis of catalytic materials. A powerful concept originating from studies of the functioning of enzymes is the design of catalytic materials that are based on mimicking reaction transition states. The discovery of catalytic antibodies by the groups of Lerner and co workers [6], and Schulz and coworkers [7] which relies on biological machinery for the production of the catalysts has been a milestone which fostered several other developments. The method involves the preparation of a large number of antibodies in the presence of an imprint molecule that is designed to approximate the transition state complex of a desired reaction. Subsequent to removal of the imprint, the antibodies are screened for imprint binding and/or catalytic activity. Both enzymes and antibodies are assumed to provide environments complementary to a conformationally restricted transition state analogue and to catalyze a reaction by stabilizing the same transition state as occurs in the uncatalyzed reaction. Conceptually, similar is the idea to use transition state analogue imprints to synthesize abiological catalytic materials such as polymers and amorphous metal oxides [5]. However, there is a dramatic difference in how catalytic antibodies and these materials are produced. With antibodies, a large number of different antibodies are prepared simultaneously and the successful ones selected by a screening procedure, whereas with the abiological imprinted materials only one catalytic material is formed. This renders the catalytic antibodies intrinsically more suitable for combinatorial approaches.

Another class of catalysts for which the concept of transition state analogues may be successfully applied in catalyst design are chirally modified metals for enantioselective hydrogenations [8–12]. Chiral modification of metal catalysts is generally achieved by a very small quantity (usually a sub-monolayer) of an adsorbed chiral modifier which by interacting with the reactant(s) can control the stereoselectivity of the catalytic process. Knowledge of the approximate structure of the enantio-differentiating diastereomeric transition state complexes, formed between reactant and chiral modifier can provide a valuable rational guide for the design of new modifiers. The basic strategy and the potential of this approach will be demonstrated using the example of chirally modified platinum catalysts for the enantioselective hydrogenation of α-ketoesters.

2. Chirally modified platinum for enantioselective hydrogenation — important features and reaction pathway

Following its discovery by Orito et al. [13–16] in 1979, several groups have investigated the platinum-cinchona alkaloid system and considerable knowledge has been collected concerning the crucial parameters of this catalytic system and its functioning. The progress made till 1996 is discussed in several reviews [8–12]. Some characteristic features of the catalytic system are summarized in Scheme 1. Chiral modification of the platinum catalyst is achieved by adsorbed cinchona alkaloid which is either simply added to the reactant mixture or deposited on the catalyst surface in a special pretreatment step before reaction. Even very small quantities of modifier (modifier: $Pt_{surf} \ll 1$) are sufficient to induce both enantio-differentiation and rate acceleration. The reaction is generally carried out at ambient temperature and a hydrogen pressure of 10–100 bar.

Most information has been gained by studying the asymmetric hydrogenation of methyl- or ethylpyruvate to the corresponding lactates. Parameters most crucial for the efficiency of the platinum-cinchona system are: (i) the structure and concentration of the modifier, (ii) the structural properties of the supported platinum, and (iii) the solvent used. Although, all of these parameters have to be optimized to achieve high optical yields, the structure of the modifier proves most important for enantio-differentiation. The most suitable chiral modifiers are cinchona alkaloids and their simple derivatives (Scheme 1), such as cinchonidine (CD), 10,11-dihydrocinchonidine (HCD), and 10,11-dihydro-*O*-methylcinchonidine (OH at C-9 in CD substituted by OCH_3). All these modifiers afford the *(R)*-α-hydroxyester product. Concerning the



Scheme 1. Main features of platinum-cinchona system for the enantioselective hydrogenation of α-ketoesters to corresponding α-hydroxyesters.

properties of the supported platinum catalyst, proper platinum dispersion [17], support material [18,19] and pore size distribution [20] are important. Suitable supports are alumina, silica and graphite [18], but zeolites [19] have been applied too. Another successful approach is the use of polymer-stabilized colloidal platinum [21,22].

The solvent can influence the catalytic behavior due to different solubility of reactants (α-ketoester and hydrogen), and interaction with the modifier, α-ketoester and platinum surface. Generally, a polar solvents with a dielectric constant (dc) in the range of 2–10 are applicable [23]. Most suitable solvents are acetic acid (dc = 6.2) and toluene. Acetic acid affords the highest enantiomeric excess (ee) reaching over 95% under optimized conditions [24,25]. In this medium the quinuclidine N-atom of cinchonidine is protonated [26]. Alcohols, such as ethanol and propanol, which are more polar (dc ≈ 30), also afford reasonably high ee, however, these solvents (in the presence of basic modifier) can undergo undesired side reactions with the reactant leading to hemiketal formation [27].

A very interesting characteristic feature of ethylpyruvate hydrogenation has been uncovered by kinetic studies which showed that the presence of cinchona modifier affords not only enantio-differentiation but also rate acceleration by a factor of 10–100 compared to the reaction over the unmodified catalyst [18,28].

Today, most authors agree that the enantioselective hydrogenation proceeds through a two-step, two-cycle mechanism [29–33] as presented in Fig. 1. In this mechanism, it is assumed that the active chiral sites associated with $[CD]_{ad}$ are formed by adsorption of the cinchona modifier (CD) on the platinum surface. Ethylpyruvate (EP) from the fluid phase adsorbs reversibly on these sites in its two enantiofacial configurations forming the diastereomeric intermediate complexes $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$, which upon hydrogenation afford the (*R*)- and (*S*)-ethyl

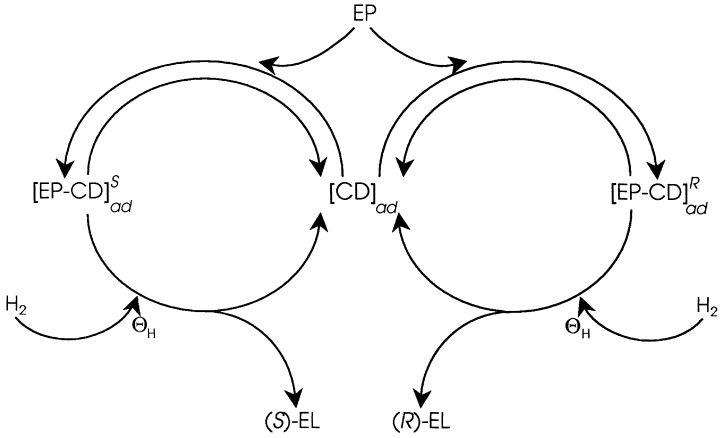


Fig. 1. Two-step, two-cycle mechanism suggested for enantioselective hydrogenation of ethylpyruvate (EP) over platinum modified by cinchonidine (CD). The $[CD]_{ad}$ represents an active chiral site on platinum surface formed by adsorbed CD, and $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$, represent diastereomeric intermediate complexes formed by interaction of chiral sites with EP, affording (*R*)- and (*S*)-ethyl lactate (EL), respectively, upon hydrogen addition.

lactate (EL), respectively. It has been suggested that the adsorbed cinchonidine modifier $[CD]_{ad}$ interacts with the adsorbed α-ketoester via hydrogen bonding between the quinuclidine N and the O atom of the α-carbonyl moiety [34,35]. The question as to whether the enantioselectivity is thermodynamically (stability of $[EP\text{-}CD]^{R}_{ad}$ versus $[EP\text{-}CD]^{S}_{ad}$) or kinetically controlled (different activation energies of hydrogenation of intermediate complexes) has not been definitively answered yet. Blaser et al. [33] suggested that for the hydrogenation on the unmodified catalyst, leading to racemic product mixtures, addition of the first hydrogen is rate-determining whereas for the hydrogenation to the major enantiomer occurring on modified chiral sites, the rate determining step is the addition of the second hydrogen. Albeit this scenario may be feasible, its experimental verification is still lacking. A major constraint of the kinetic studies available is that they do not allow any conclusions concerning the structures of the intermediate complexes $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$, which may be assumed to resemble the structure of the corresponding transition states leading to (*R*)- and (*S*)-products, respectively.

A different mechanism has been suggested by Margitfalvi and coworkers [36,37]. They assume that EP forms a complex with the aromatic part (shielding model) of the cinchonidine modifier in solution and that this activated complex is hydrogenated either via an Eley–Rideal [36] or Langmuir–Hinshelwood type mechanism [37]. Although substrate-modifier complex formation in solution is feasible, and may be fast, the concentration of this complex is limited by the extremely low modifier concentration. In EP hydrogenation 30 ppm HCD is sufficient to induce 95% ee [24]. Thus, the collision rate of these complexes with the hydrogen covered platinum surface (Eley–Rideal mechanism), and their adsorption rate (Langmuir–Hinshelwood mechanism) must be very low and would probably control the global hydrogenation rate in both suggested mechanisms. The observed rate enhancement in the enantioselective reaction compared to the racemic hydrogenation (10–100 times) cannot be explained reasonably on this ground. A more than 30,000 times lower reactant ([EP-CD] complex in solution) concentration in the enantioselective hydrogenation would imply an enhancement in the intrinsic reaction rate compared to the racemic hydrogenation by a factor of 3×10^6. In addition, the Eley–Rideal mechanism can be ruled out with considerable certainty due to the saturation effects observed at extremely low modifier concentration as well as at increasing EP concentration. Moreover, energetics favor adsorption of CD and EP compared to complex formation. The ground state diastereotopic interaction in H-bonded complexes, as have been suggested for [EP-CD] are of the order of

4–8 kcal/mol [38] and thus, considerably lower than expected adsorption binding energies of CD and EP. Although adsorption enthalpies of these compounds are not available, they must be much higher than the H-bond energies as emerges from a comparison of adsorption enthalpies of compounds which bind in an analogous mode (π-bonding) to platinum such as naphthalene (27 kcal/mol) [39] and ethene (32 kcal/mol) [40]. Thus, to date there seems to be no reasonable argument in favor of these mechanisms which assume that a complex [EP-CD] preformed in solution is hydrogenated on the platinum surface.

3. Key for design — approximate structure of enantio-differentiating transition state complexes

Although, the exact structures of the enantio-differentiating transition states are not amenable, neither experimentally nor theoretically, sufficient information seems to exist to gain knowledge of the approximate structure of the diastereomeric complexes $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$ (Fig. 1), which are assumed to resemble the structures of the corresponding transition states. In the case where the enantioselectivity is thermodynamically controlled, i.e. by the relative stabilities of the enantio-differentiating diastereomeric transition states, we may predict the sense of enantiodiscrimination by theoretical calculations. Considerable experimental and theoretical efforts have been expended to unravel the approximate structure of the enantio-differentiating diastereomeric transition states of methylpyruvate (MP) hydrogenation on platinum modified by cinchona alkaloids. For this purpose, it was necessary to consider all crucial interactions in the catalytic system and to analyze their effect on the structure of the transition state complexes formed between methylpyruvate and the cinchona modifier. Fig. 2 depicts schematically the interactions which can affect the structure and stability of the transition state complexes. Assuming that the transition state complex involves the adsorbed chiral modifier and the reactant molecule in a 1:1 stoichiometry, the structure of the transition state complex will mainly be determined by the conformations, the adsorption modes and the interaction of these species on the platinum surface. The present knowledge concerning these aspects will be considered next.

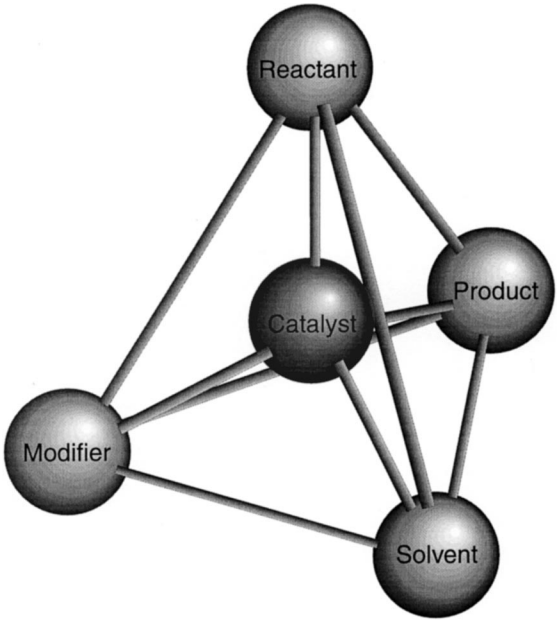


Fig. 2. Schematic illustration of important interactions to be considered in the enantioselective hydrogenation over chirally modified metals.

3.1. Cinchona modifier

3.1.1. Conformational behavior

Cinchona alkaloids show a rich conformational behavior. The most important degrees of freedom are the two torsional angles τ_1: $C_{3'}$–$C_{4'}$–C_9–C_8 and τ_2: $C_{4'}$–C_9–C_8–N, which determine the relative orientation of the quinoline and quinuclidine moieties (Scheme 1). Fig. 3 shows the major conformers of cinchonidine, Closed(1), Closed(2) and Open(3), coexisting at room temperature in different solvents as determined by NMR spectroscopy [41]. The terms "Open" or "Closed" are used to indicate whether the quinuclidine N points away or towards the heteroaromatic moiety (quinoline ring). The population of these conformers depends strongly on the polarity of the solvent, however, specific chemical interaction between cinchonidine and solvent can change this behavior. In a polar solvents as generally used in enantioselective hydrogenation, conformer Open(3) is most abundant as indicated by the dependence of its relative abundance on solvent polarity determined by NMR spectroscopy Fig. 4.

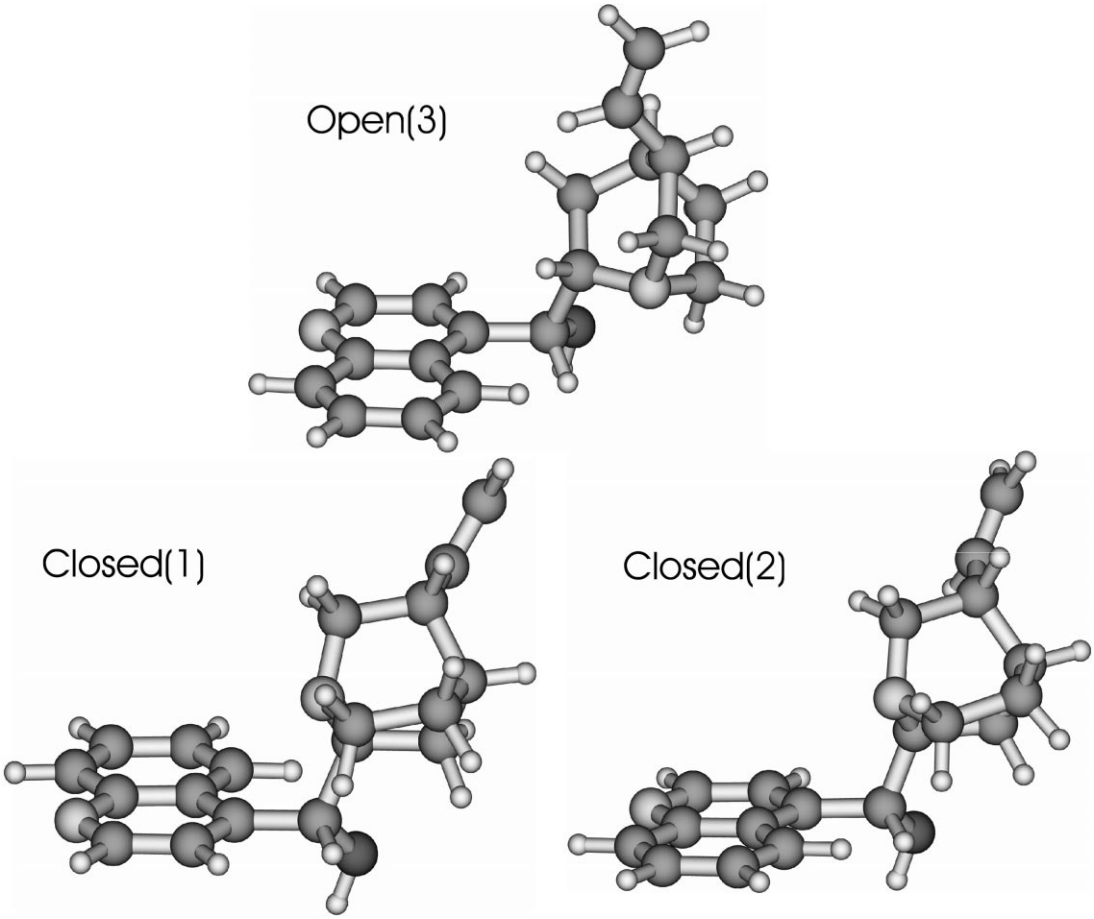


Fig. 3. Optimized structures of most stable conformers of cinchonidine at room temperature, Closed(1), Closed(2) and Open(3). All conformers have been identified by NMR spectroscopy [41].

Several theoretical studies ([41] and references therein) have focussed on the conformational behavior of cinchona alkaloids using various computational methods ranging from empirical potentials to ab initio calculations. In the two-dimensional conformational subspace, τ_1 and τ_2, six conformers exist on the potential energy surface. Ab initio and density functional reaction field calculations, using cavity shapes determined by an isodensity surface were applied to simulate the dependence of the population of conformer Open(3) from the polarity (dielectric constant) of the solvent (Fig. 4). The calculations can well describe the nonspecific interaction of the solvent with cinchonidine, i.e. interactions originating from polarization of the solvent due to the electrostatic potential associated with CD and the backpolarization of CD due to polarization of the solvent. However, the calculations fail when specific interactions between CD and the solvent occur as in the case of ethanol (Fig. 4). In ethanol, the experimentally derived relative abundance of conformer Open(3) is much higher than expected on the basis of its dielectric constant (Fig. 4). This behavior is attributed to hydrogen bonding of ethanol to the quinuclidine N atom which stabilizes Open(3) relative to the closed conformers.

Further support for the outstanding role of conformer Open(3) was recently provided by Bartok et al. [42], who demonstrated that the rigid (no C_8–C_9 rotation) cinchona alkaloids, α-isocinchonine and α-isoquinidine which exist in the open conformation

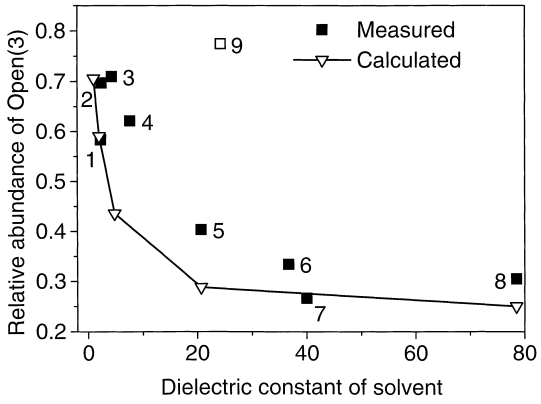


Fig. 4. Dependence of relative abundance of conformer Open(3) on solvent polarity determined by NMR spectroscopy (measured) and calculated using a reaction field model [41]. Solvents: (1) benzene, (2) toluene, (3) ethyl ether, (4) tetrahydrofuran, (5) acetone, (6) dimethylformamide, (7) dimethyl sulfoxide, (8) water, (9) ethanol. Note that the reaction field model does not take into account specific interaction such as the hydrogen bonding interaction between CD and ethanol, which explains the poor description of the NMR derived relative abundance of Open(3) for ethanol (open square 9).

afford high enantiomeric excesses. The enantio-differentiation achieved with α-isocinchonine as modifier cannot be explained by the "shielding model" suggested by Margitfalvi and coworkers [36,37], because this model is only conceivable when the cinchona alkaloid is in a closed conformation. Open conformations do not allow simultaneous interaction of the quinuclidine N atom and the aromatic quinoline ring (π-bond stacking) with the pyruvic acid ester.

3.1.2. Adsorption mode

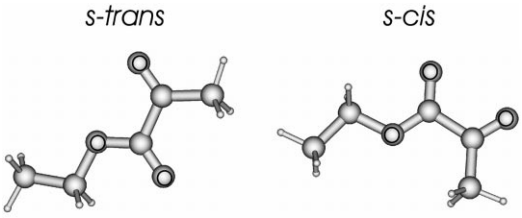
The two most feasible adsorption modes of cinchonidine are adsorption via the aromatic π-bonding system of the quinoline or adsorption via the quinoline N lone pair. The former results in a flat adsorption of the quinoline ring parallel to the platinum surface whereas the latter leads to an adsorption where the orientation of the quinoline ring is tilted or even perpendicular to the platinum surface. Although direct information concerning the adsorption mode of cinchonidine under reaction conditions is still not available, there exists considerable evidence to suggest that planar adsorption is prevalent, at least at lower surface coverages. This evidence emerges from NEXAFS studies [43], H/D exchange experiments [44] and a comparative study of the catalytic behavior of 2-phenyl-9-deoxy-10,11-dihydrocinchonidine (PDHCD), a cinchonidine derivative arylated in 2-position at the quinoline ring, and 9-deoxy-10,11-dihydrocinchonidine (DHCD) [45]. Adsorption via the quinoline nitrogen is not possible with PDHCD due to steric hindrance caused by the bulky phenyl group at C-2, whereas the interaction of the π-bonding system of quinoline is possible. The fact that both modifiers show similar enantio-differentiation corroborates parallel adsorption via the quinoline π-bonding under reaction conditions.

3.2. Alkyl pyruvate reactant

3.2.1. Conformational behavior

α-ketoesters such as methyl- and ethylpyruvate can adopt *s-cis*- and *s-trans*-conformation which can be interconverted by changing the dihedral angle O=C–C=O. The conformational behavior of several α-ketoesters has been investigated in different solvents using IR spectroscopy and ab initio calculations [46]. The studies revealed that EP is very flexible around the O=C–C=O torsional angle and the energy difference between *cis* and *trans* is relatively small. At room temperature, both conformers coexist with the *trans* conformer being predominant in apolar solvents. In polar solvents, the fraction of *cis*-EP becomes comparable to that of *trans*-EP. The stability of *cis*-EP increases with solvent polarity due to the larger dipole moment of this conformer compared to *trans*-EP. Fig. 5 illustrates the dependence of the relative abundance of the *trans* conformer of EP on the solvent polarity. The growth of the fraction of *cis*-EP with increasing dielectric constant is typical for solvent stabilization of a conformer with higher dipole moment as predicted by the Onsager model of solvation. Hydrogen bonding with alcoholic solvents also leads to a stabilization of the *cis* conformer. The greater dipole moment of *cis*- compared to *trans*-EP, energetically favors *cis*-conformation in intermolecular interactions with charged species such as R_3N^+–H.

Although *trans*-EP is the more stable isomer in the solvents generally used in enantioselective hydrogenation (acetic acid, toluene), the stability considerations available so far do not allow ruling out the participation of *cis*-EP in the formation of the transition complex. Adsorption on the platinum surface could have



Dielectric constant	ΔE(kcal/mol)	% *s-trans*
1.0	1.62	93.9
2.2	1.03	85.0
8.9	0.42	66.9
37.5	0.22	59.0

Fig. 5. Relative abundance of *s-trans* conformer of ethylpyruvate (EP) and relative energies, $\Delta E = E(s\text{-}cis) - E(s\text{-}trans)$, in solvents of different polarity [46]. Calculations were performed at the DFT level (B3PW91) using a 6–31++G(d,p) basis set in combination with a self consistent reaction field model. The dielectric constants correspond to *vacuum* (1.0), carbon tetrachloride (2.2), dichloromethane (8.9) and acetonitrile (37.5).

a prominent effect on the relative stability of *cis* and *trans* conformers due to interaction of the molecule's dipole moment with its image charge. This dipole induced dipole interaction is expected to be considerably stronger for *cis*-EP which has a larger dipole moment.

3.2.2. Adsorption mode

The bonding of the two model reactants, methyl- and ethylpyruvate is dominated by the two C=O groups which can give rise to bonding by the oxygen lone pairs or π-bonding of the C=O groups. In the lone pair binding mode, the C=O groups have a tendency to be oriented in an upright position (perpendicular or tilted adsorption) whereas with π-bonding, the C=O groups lie parallel to the platinum surface (parallel adsorption). Some insight into the adsorption of the model reactant, ethylpyruvate, on Pt(1 1 1) was gained recently by XPS and UPS [47]. The results of these investigations can be summarized as follows: upon chemisorption of EP at low temperature, the HOMO lone pair orbital is stabilized by about 0.7 eV with respect to the other orbitals, indicating that EP is predominantly lone pair bonded to the Pt surface under these conditions. Lone pair bonding is observed in the fully saturated chemisorption layer as well as far below saturation. As a consequence of the lone pair bonding EP is predominantly adsorbed in a tilted rather than a completely flat mode.

In situ XANES (X-ray absorption near edge structure) spectroscopy was applied to gain direct information about the orientation of adsorbed EP in the presence and absence of hydrogen [48]. The observed angular dependent shift of the π^* and σ^* resonances indicated the coexistence of differently adsorbed EP. Depending on the hydrogen and EP pressure, the C and O K edge spectra showed distinctly different angular dependence. Without hydrogen, the mean tilt angle of chemisorbed EP with respect to the surface was 72°, hinting towards bonding via the O lone pair, in agreement with the conclusions of XPS and UPS investigations [47]. In the presence of hydrogen, the mean tilt angle decreased to 58°. Thus, chemisorbed EP is oriented in a more upright position in the absence of hydrogen and more inclined towards the surface in the presence of hydrogen. This behavior could originate either from a change of the relative abundance of π-bonded and lone pair bonded EP or from a change of the adsorption geometry of lone pair bonded EP induced by coadsorbed hydrogen. An increased population of π-bonded species due to stabilization by partial hydrogenation of EP in the presence of hydrogen is also feasible.

Finally, it should also be noted that EP can adsorb in *trans*- or *cis*-conformation. Lone pair bonding may favor the *cis* conformer because a bidentate species with both carbonyls bonded to the metal surface could be formed. The complexity of the adsorption behavior of EP demonstrates the difficulty in assessing the structure of the transition state complex formed between adsorbed EP and cinchonidine.

Clearly the available experimental results indicate that there are at least two different adsorption modes which should be taken into account at low temperature, lone pair and π-bonded EP. The population density of species bound via these adsorption modes as well as the conformation of adsorbed EP are expected to depend on various factors including surface coverage, temperature, and the presence of coadsorbed species. As a consequence of this behavior, the formation of several structurally different complexes $[EP\text{-}CD]_{ad}$ (Fig. 1) may be feasible, from which only the most stable is considered in the following section.

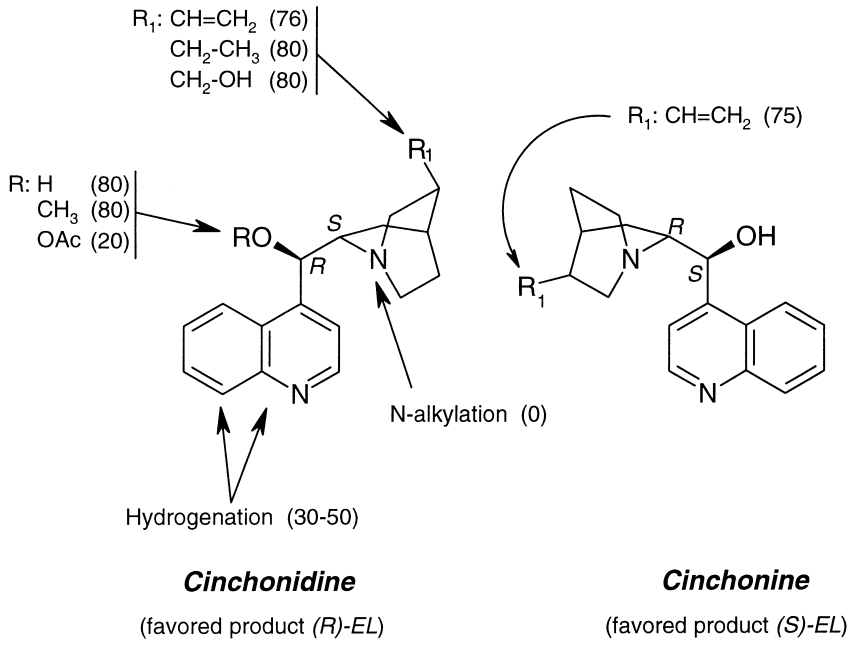


Fig. 6. Effect of changes in structure of cinchona alkaloid modifier on its behavior in enantioselective hydrogenation of ethylpyruvate (EP) to ethyl lactate (EL). Values given in parentheses indicate enantiomeric excesses (%) achieved under standard conditions.

3.3. Approximate structure of transition state complexes

As pointed out above, systematic variation of the cinchona alkaloid structure proved to be a valuable approach to shed light on the reaction mechanism. Fig. 6 illustrates schematically how structural changes of the cinchona alkaloids affect the enantiomeric excess in the hydrogenation of ethylpyruvate. Changing the absolute configuration at C-8 (*S*) and C-9 (*R*) of cinchonidine, i.e. substituting cinchonidine by the diastereomer cinchonine, alters the chirality of the product from (*R*)- to (*S*)-lactate. The fact that the use of 9-deoxy-10,11-dihydrocinchonidine (DHCD, C-9 is not chiral) as modifier affords the (*R*)-methyl lactate product in excess indicates that the sense of enantio-differentiation is mainly determined by the absolute configuration of C-8. Most important is the finding that the enantio-differentiation is completely lost upon alkylation of the quinuclidine nitrogen atom which indicates that this center plays a crucial role in the mechanism of enantioselection [20]. Partial hydrogenation of the quinoline ring causes a drop in ee to below 50%. The selectivity is only marginally influenced by *O*-methylation whereas replacing the OH by hydrogen (DHCD) or using the acylated derivative results in a significant decrease in ee. Interestingly, protonation of the quinuclidine nitrogen slightly increases ee, indicating a favorable interaction of N^+–H with the reactant EP in the enantio-differentiating complex.

Theoretical studies aimed at rationalizing the structure and stability of the reactant—modifier complex have been undertaken using quantum chemistry techniques, at both ab initio and semiempirical levels, and molecular mechanics [34,49,50]. The calculations provided feasible structures of the enantio-differentiating complexes which are supposed to resemble the corresponding transition complexes. It was assumed that the enantioselectivity is thermodynamically controlled, i.e. by the difference in the free energies of adsorption and complex formation $\Delta G^{o}_{ad,}$ of the pro-(*R*), $[EP\text{-}CD]^{R}_{ad}$ and pro-(*S*) $[EP\text{-}CD]^{S}_{ad}$ complexes (cf. Fig. 1). When adsorption equilibrium is established the relative surface coverages of $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$ can be expressed as

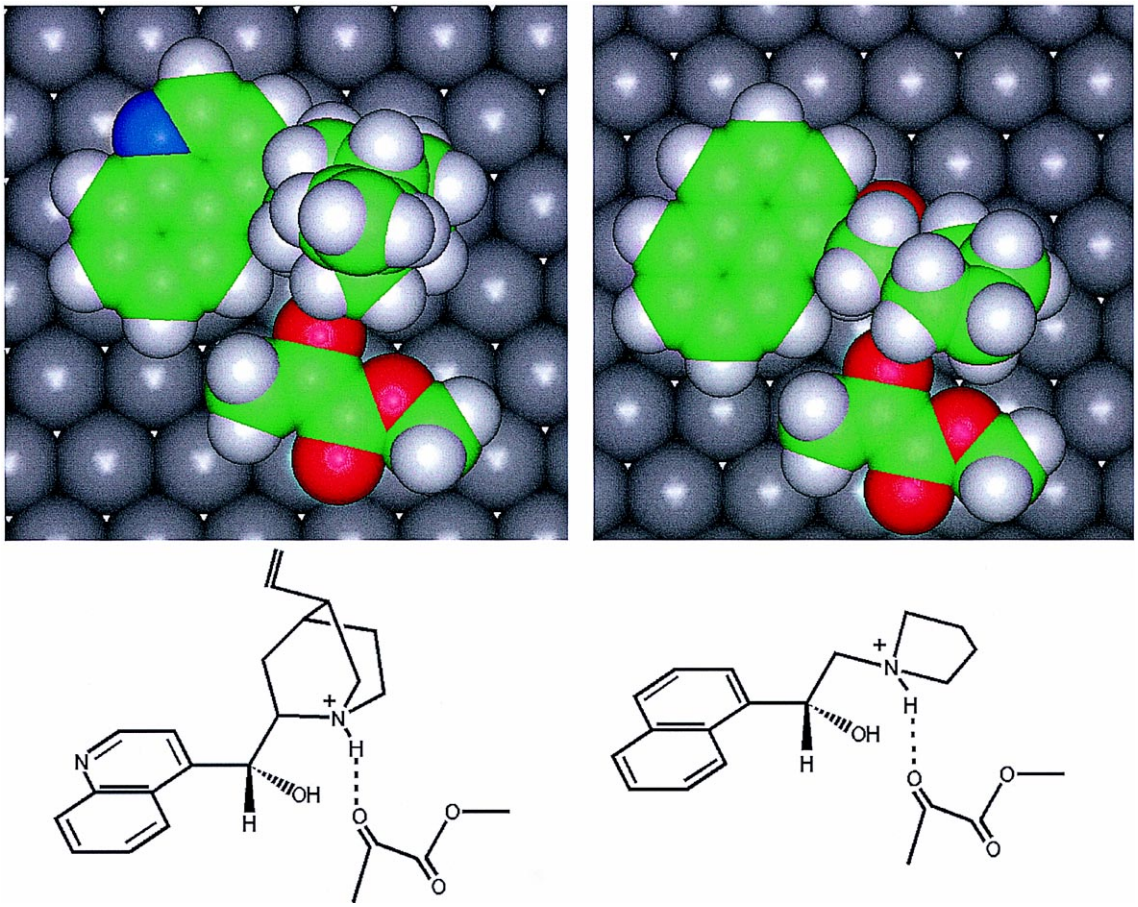


Fig. 7. Calculated structure of adsorbed transition complexes methylpyruvate — cinchonidine, $[MP\text{-}CD]^{R}_{ad}$ (left); and methylpyruvate — (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (PNE), $[MP\text{-}PNE]^{R}_{ad}$ (right), leading to (*R*)-methyl lactate upon hydrogenation. C is green, O is red, N is blue, H is white and Pt is grey.

$\Theta_{R^*}/\Theta_{S^*} = \exp(-\Delta\Delta G^{o}_{ad}/RT)$. If no kinetic factor controls, i.e. if activation energies and pre-exponential factors of the subsequent hydrogen additions are the same, the ratio of the product enantiomers is determined by the ratio of surface coverages $(R)/(S) = \Theta_{R^*}/\Theta_{S^*}$. Thus, under these conditions the sense of enantio-differentiation should be predictable by stability considerations of the intermediate complexes $[EP\text{-}CD]^{R}_{ad}$ and $[EP\text{-}CD]^{S}_{ad}$. Fig. 7 shows the optimized structure of the enantio-differentiating transition complex formed on interaction of protonated cinchonidine (acetic acid as solvent, or CD·HCl as modifier) and methylpyruvate (MP) which upon hydrogenation would yield (*R*)-methyl lactate. For the optimized structure of the corresponding complex leading to (*S*)-methyl lactate the reader is referred to a previous report [11]. Note that in the transition complexes the α-ketoester is stabilized in its half-hydrogenated form [51]. The pro (*R*)-methyl lactate complex was found to be energetically favored using different theoretical approaches [34,49,50]. Experimental evidence [43–45] suggests parallel adsorption of cinchonidine in a conformation similar to Open(3) on the Pt surface via π-bonding of the aromatic quinoline ring. This adsorption mode allows simultaneous interaction of the quinuclidine N with the α-carbonyl group of methylpyruvate. In the complex affording (*R*)-methyl lactate, both carbonyl moieties of the

reactant methylpyruvate lie in a plane parallel to the Pt surface providing optimal adsorptive interaction. This adsorption mode is sterically hindered in the pro (*S*)-methyl lactate complex [11]. The opposite behavior is found when the complexes formed between protonated cinchonine and methylpyruvate are optimized [11]. In this case, the complex leading to (*S*)-methyl lactate upon hydrogenation is energetically favored and can be adsorbed without significant steric hindrance while the one affording (*R*)-methyl lactate is sterically hindered. Thus, calculations showed that, in agreement with the experimental observations, a change in the chirality of the stereogenic region (C-8, C-9) of the cinchona alkaloid results in a change of the chirality of the product lactate.

The origin of the hydrogen responsible for the stabilizing interaction between the cinchona alkaloid and the ketoester is assumed to change depending on the solvent [11]. The hydrogen can either come from the solvent (protonation of basic nitrogen by acetic acid) or from dissociatively adsorbed hydrogen [11]. Fig. 8 depicts the two feasible mechanisms taking into account the knowledge gained on the adsorption states of cinchonidine modifier and EP reactant.

Considering the methyl-pyruvate — cinchona alkaloid interaction and the steric constraints imposed by the adsorption on the platinum surface, the molecular modeling approach leads to a reasonable explanation for the enantio-differentiation. Although the predictions of the complexes formed between methylpyruvate and the cinchona modifier have been made for an ideal case (calculation of ground state structures, neglecting quantum description of adsorptive interaction with platinum), this approach proved to be very useful in the search for new modifiers which will be considered next.

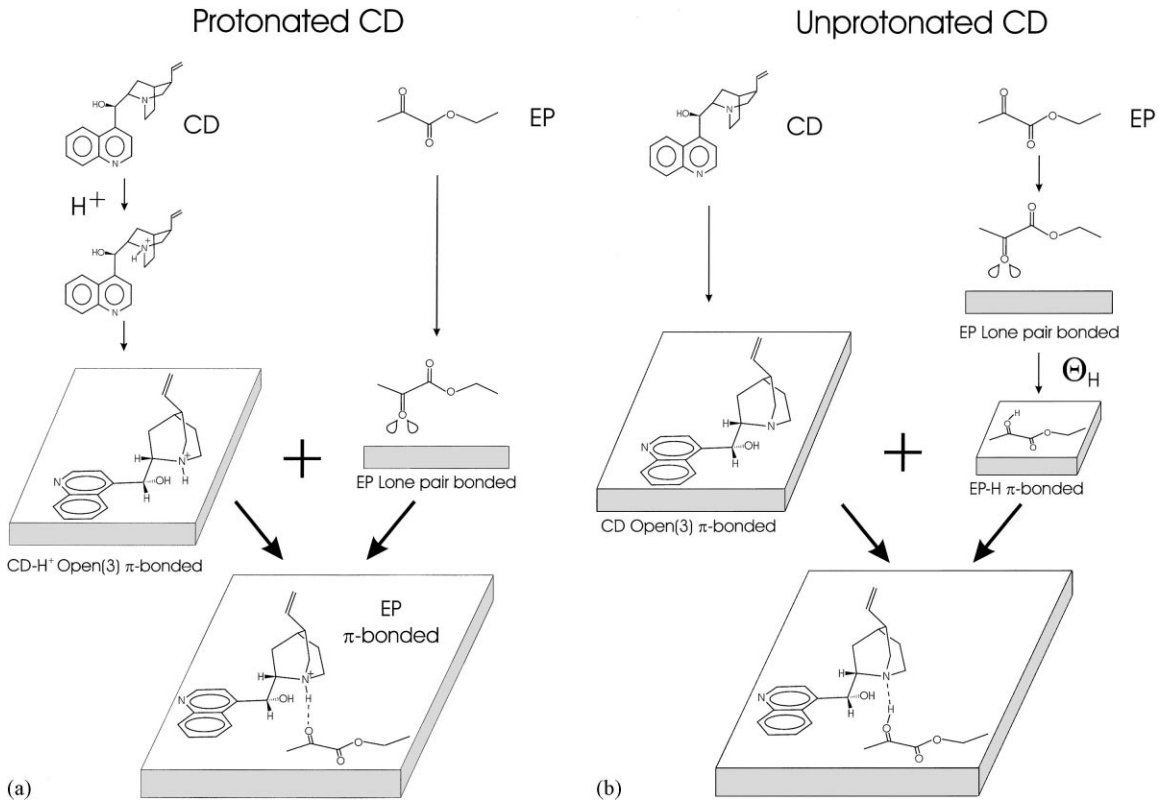


Fig. 8. (a) Reaction pathway proposed for enantioselective hydrogenation of EP with protonated CD (e.g. acetic acid as solvent). (b) Reaction pathway proposed for enantioselective hydrogenation of EP with unprotonated CD (e.g. toluene as solvent). Note that EP-H represents adsorbed half-hydrogenated state of EP.

4. Design guided by analogy of transition states

4.1. Strategy

Theoretical calculations aimed at elucidating the structure and stability of the diasteromeric transition complexes, leading to (*R*)- and (*S*)-products, proved to be a valuable guide for screening potential chiral modifiers. The search strategy was based on a systematic reduction of the cinchona alkaloid structure to the essential functional parts and rationalization of the structure and stability of the corresponding diastereomeric complexes formed between the new modifier and methylpyruvate. Molecular modeling indicated that simple chiral 2-hydroxy-2-aryl ethylamines should be promising substitutes for cinchona alkaloid modifiers. An example of an efficient modifier emerging from this search is (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol (PNE) [52] which is used for illustrating the strategy. The optimized structure of the enantio-differentiating diastereomeric complex $[\text{MP-PNE}]^{R}_{ad}$ yielding (*R*)-methyl lactate is compared to the corresponding complex formed between CD and MP, $[\text{MP-CD}]^{R}_{ad}$, in Fig. 7. The similarity of these complexes is striking, both complexes are stabilized by a N–H–O interaction and parallel adsorption (π-bonding) of the two carbonyl moieties is possible. This adsorption mode is sterically hindered in the corresponding pro (*S*)-complexes as shown elsewhere [11]. The pro-(*R*) complex was found to be energetically favored, indicating that the (*R*)-enantiomer product should prevail. Catalytic tests of ethylpyruvate hydrogenation corroborated these findings, PNE proved to be a remarkably efficient modifier inducing at low hydrogen pressures (1–10 bar) enantiomeric excesses as high as 75% of (*R*)-ethyl lactate which is comparable to that obtained with cinchonidine under these conditions. However, in contrast to CD which is more effective at higher pressure (70–100 bar), the enantioselectivity of PNE decreases at higher hydrogen pressures due to partial hydrogenation of the naphthalene ring and concomitant loss of the π-bonding. Replacing the naphthyl by a quinolyl anchoring group had no marked effect on the ee under otherwise similar conditions, indicating that the quinolyl nitrogen does not play an

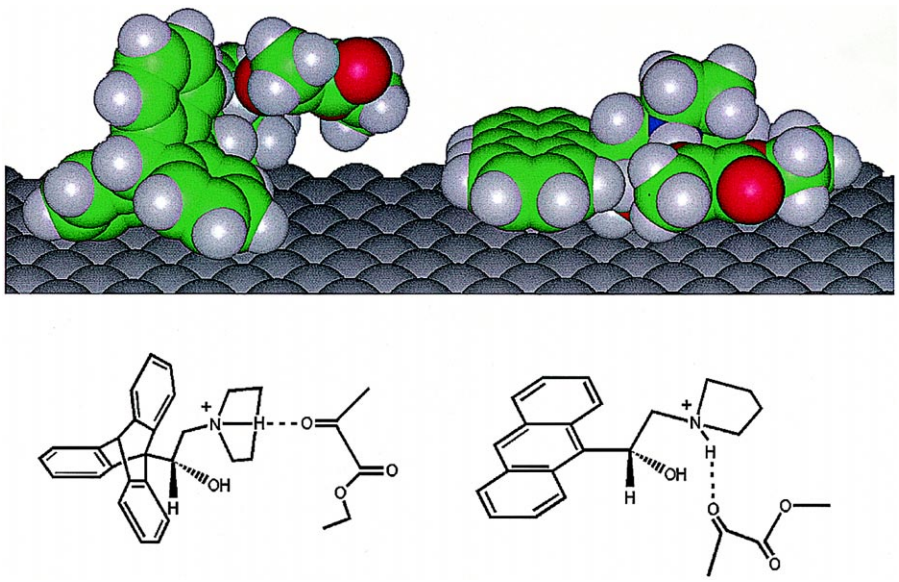


Fig. 9. Sterical constraints caused on the structure of transition complex by changing the anchoring group from 9-anthracenyl (APE) to 9-triptycenyl (TPE). Calculated minimum energy conformations of complexes $[\text{EP-TPE}]^{S}_{ad}$ (left) and $[\text{MP-APE}]^{S}_{ad}$ (right). Note that complex $[\text{EP-TPE}]^{S}_{ad}$ does not afford enantio-differentiation (ee = 0%), whereas $[\text{MP-APE}]^{S}_{ad}$ affords an ee of 87% favoring the (*S*)-product [55]. C is green, O is red, N is blue, H is white and Pt is grey.

important role, neither for adsorption nor for enantio-differentiation.

4.2. New modifiers

The rationally guided design strategy described for PNE was used to examine various 2-hydroxy-2-aryl ethylamines and other structurally related chiral compounds [53–55]. Using the Sharpless asymmetric dihydroxylation [56] as a key step, a series of enantiomerically pure 2-hydroxy-2-aryl ethylamines were synthesized from commercially available aromatic aldehydes or aryl-olefins (in cooperation with A. Pfaltz and coworkers) and tested in the enantioselective hydrogenation of ethylpyruvate [11,52–55]. The importance of the extended aromatic ring system for effective anchoring was demonstrated by comparing modifiers which only differ in the anchoring moiety [55]. Replacing the naphthyl anchoring moiety by quinoline had no significant effect on enantio-differentiation whereas benzene and pyridine analogues of PNE were ineffective (ee $\approx$ 0%). A remarkable increase in ee from 75 to 87% is achieved when the naphthyl anchoring moiety is substituted by an anthracenyl group resulting in 1-(9-anthracenyl)-2-(1-pyrrolidinyl)ethanol (APE). This behavior is mainly attributed to the higher adsorption strength of APE imposed by the anthracenyl anchoring group. Calculations suggested that the energy and geometry of the transition complexes, [MP-PNE] and [MP-APE], should be similar [55]. The different adsorption strength was not predictable by means of the model calculations because the electronic interaction of the anchoring group with the platinum surface is still out of reach of accurate quantum chemical calculations. The geometrical constraints imposed on the transition complex seem to be insufficient when a phenyl- or pyridyl-ring is used for anchoring. Substituting the 9-anthracenyl group by a 9-triptycenyl moiety (1-(9-triptycenyl)-2-(1-pyrrolidinyl)ethanol, TPE)

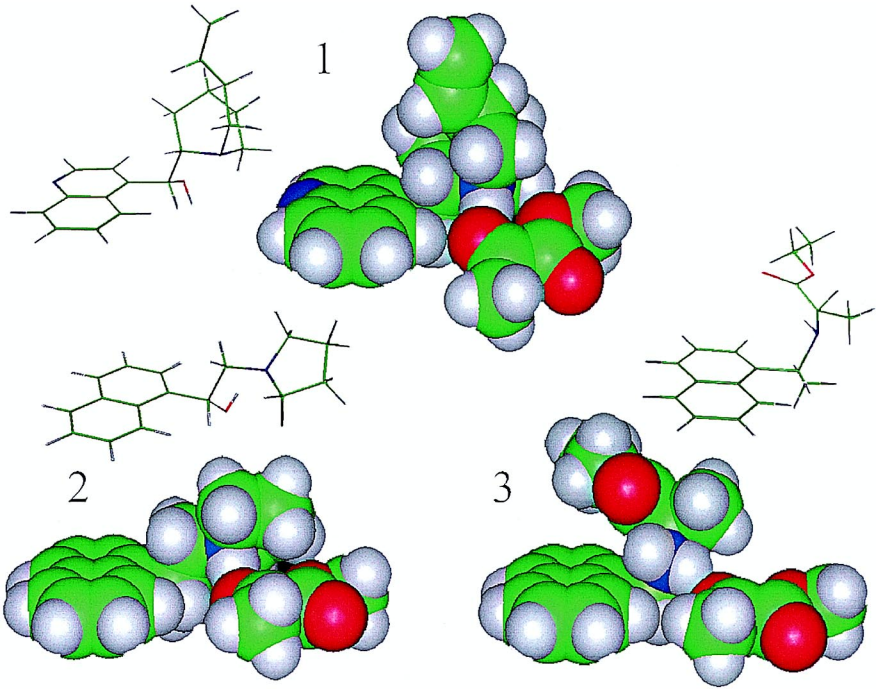


Fig. 10. Proposed structures of transition complexes formed by interaction of methylpyruvate (MP) with different modifiers, all leading to (*R*)-methyl lactate upon hydrogenation. (1): MP — cinchonidine (CD), (2): MP — (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol (PNE), (3): MP — (2*R*,1′*R*)-*N*-[1′-(1-napthyl)ethyl]-2-amino propionic acid methylester. Note that the modifier in case (3) is formed in situ by reductive alkylation of NEA with MP. Structures of modifiers are also represented by stick models. C is green, O is red, N is blue and H is white.

also results in a complete loss of enantio-differentiation [55]. This behavior can be traced to the steric constraints imposed in the complex [EP-TPE]. Fig. 9 compares the calculated minimum energy structures of the complexes [EP-APE] and [EP-TPE]. Note that adsorption of TPE and EP via π-bonding is excluded in the complex $[EP\text{-}TPE]_{ad}$, whereas in $[EP\text{-}APE]_{ad}$ these crucial interactions with platinum are possible. This behavior corroborates that the extended flat aromatic ring system is a crucial structural element of efficient modifiers for α-ketoester hydrogenation.

An attractive alternative to the novel aminoalcohol type modifiers is the use of 1-(1-naphthyl)ethylamine (NEA) and derivatives thereof as chiral modifiers [57–59]. Trace quantities of (*R*)- or (*S*)-1-(1-naphthyl) ethylamine induce up to 82% ee in the hydrogenation of ethylpyruvate over Pt/alumina. Note that naphthylethylamine is only a precursor of the actual modifier, a secondary amine which forms in situ by reductive alkylation of NEA with the reactant ethylpyruvate. This transformation which proceeds via imine formation and subsequent reduction of the C=N bond was found to be highly diastereoselective (d.e. >95%). Reductive alkylation of NEA with different aldehydes or ketones provides easy access to a variety of related modifiers [57–59]. The enantioselection achieved with the modifier derived from NEA could be rationalized with the same strategy of molecular modeling as demonstrated for the CD and PNE modifiers. Fig. 10 compares the proposed structures of the enantio-differentiating diastereomeric reactant — modifier complexes formed upon interaction of methyl-pyruvate (MP) with different modifiers (CD, PNE, NEA). Rationalizing the optimized structures of reactant — modifier complexes and comparing them to that of the well functioning reactant — cinchonidine pairs provided a powerful tool for pre-screening potential reactant — modifier pairs. Structural similarity of these complexes proved to be a strong indication for proper stereocontrol of the reaction system as the experimental tests summarized in Fig. 11 corroborate.

4.3. New reactants

Finally, it should be mentioned that the strategy used to search for new modifiers was also successfully applied to extend the scope of reactants as illustrated elsewhere for the enantioselective hydrogenation of ketopantolactone [60,61], 2,2,2-trifluoroacetophenone [62,63], α-ketoamides [64], and pyrrolidine-2,3,5-triones [65,66].

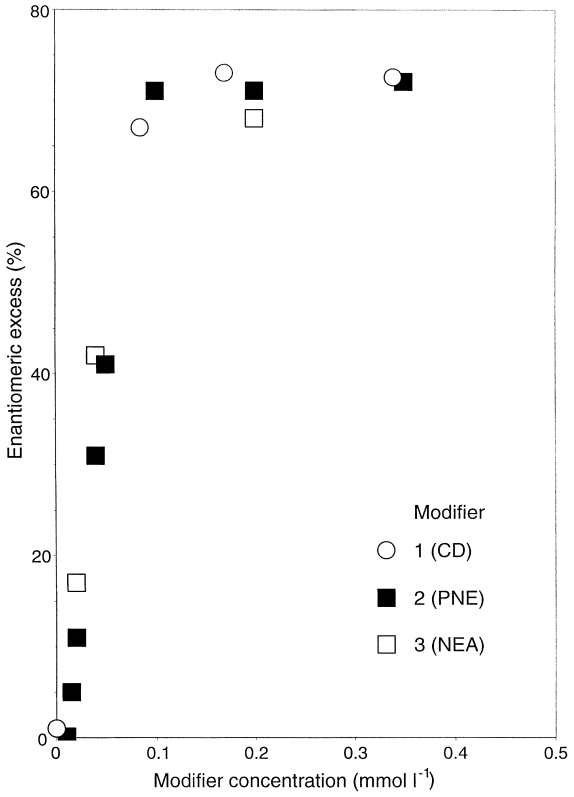


Fig. 11. Dependence of enantiodifferentiation in ethylpyruvate hydrogenation over supported platinum modified with (1): cinchonidine (CD) [11], (2): (R)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol, PNE [54], (3): (2*R*,1′*R*)-*N*-[1′-(1-napthyl) ethyl]-2-amino propionic acid ethylester (modifier formed in situ from NEA) [59]. Conditions: 100 mg catalyst, 10 ml (0.09 mol) ethylpyruvate, 20 ml acetic acid, 25°C, 10 bar.

5. Conclusions

In the past decade, considerable insight into the functioning of cinchona-modified platinum for the enantioselective hydrogenation of α-ketoesters has been gained. This knowledge paved the way for a rationally guided design of new efficient modifiers for this catalytic system. Computational methods, including ab initio, semiempirical and force field calculations were applied to rationalize the structure and stability

of various reactant — modifier complexes. The structures of these complexes are considered to resemble the structures of corresponding enantio-differentiating transition states and thereby provide a helpful criterion for judging the potential of a chiral compound to act as a suitable modifier. Steric constraints can be easily inspected and energetic considerations allow identification of the more stable diastereomeric complex favoring one of the enantiomers. Limitations of this approach arise mainly from the fact that binding energies and structures of large complexes adsorbed on metal surfaces are still out of reach for accurate quantum chemical calculations and the assumption that enantio-differentiation can be traced to different stability of the adsorbed transition complexes (thermodynamic control). Model predictions for such complex systems are only possible in conjunction with experimental verification of important boundary conditions (adsorption modes, conformations, interactions etc.) imposed on the model. Another limitation originates from the fact that the modeling approach focuses on the interaction of the substrate with the modifier in attempting to predict the transition state for the reaction of each enantiomer. Thus, minimum energy structures are compared whereas at the transition state, at least one of the degrees of freedom will be at a maximum and a choice has to be made as to the likely reaction pathway. Enantioselectivity is considered to come about by the different stability of the adsorbed diastereomeric reactant — modifier complexes, i.e. predictions of the sense of enantio-differentiation will fail if kinetics of hydrogen addition are different for the diastereomeric complexes affording the (*R*)- and (*S*)-products. In the case of enantioselective hydrogenation of α-ketoesters over chirally modified platinum, the predictability of the sense of enantio-differentiation by the modeling suggests that the assumptions made are reasonable.

The combined theoretical and experimental design strategy led to a series of new modifiers suitable for chiral modification of platinum. Two classes of suitable modifiers were found: 2-hydroxy-arylethylamine derivatives prepared from corresponding arylaldehydes or arylolefins using the Sharpless dihydroxylation as a key step, and modifiers prepared from a naphthylethylamine precursor by reductive alkylation with different carbonyl compounds. In some cases, the latter class of modifiers can be prepared in situ on the catalyst surface by reductive alkylation of naphthylethylamine with the reactant α-ketoester.

Acknowledgements

It is my pleasure to thank past and present coworkers for their valuable contributions, their enthusiasm and perseverance which have greatly stimulated our research. Financial support by the Swiss National Science Foundation is gratefully acknowledged.

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