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Enantioselective hydrogenation of α-ketoesters over Pt/alumina modified with cinchonidine: theoretical investigation of the substrate–modifier interaction

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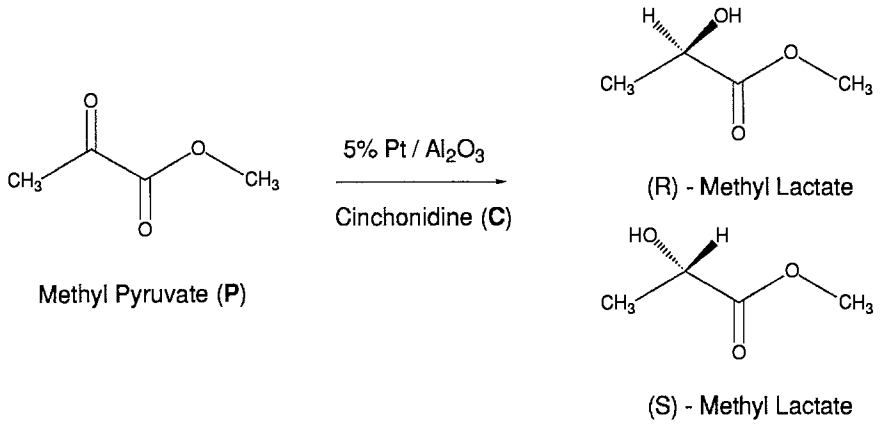
Enantio-differentiation in the asymmetric hydrogenation of α-ketoesters to α-hydroxyesters over platinum catalysts modified with cinchona-alkaloid modifiers occurs through interaction of the ketoester with the cinchona modifier. The structure of the probable transition complex has been calculated for the system methyl pyruvate (substrate)–cinchonidine (modifier) using molecular mechanics and quantum chemistry techniques at both ab initio and semi-empirical levels. The calculations suggest that protonated cinchonidine is energetically more likely to interact with the substrate and that the crucial interaction occurs via hydrogen bonding of the quinuclidine nitrogen and the oxygen of the α-carbonyl moiety of methyl pyruvate. In this complex the methyl pyruvate is transformed into a half-hydrogenated species which is adsorbed on the platinum surface and on hydrogenation yields the product methyl lactate. Theoretical studies indicate that adsorption of the complex leading to (R)-methyl lactate is energetically more favourable than that of the corresponding complex which yields (S)-methyl lactate, which may be the key for the enantio-differentiation.

Keywords: Enantioselective hydrogenation; α-ketoesters; α-hydroxyesters; cinchonidine; modifier; Pt/alumina; molecular modelling

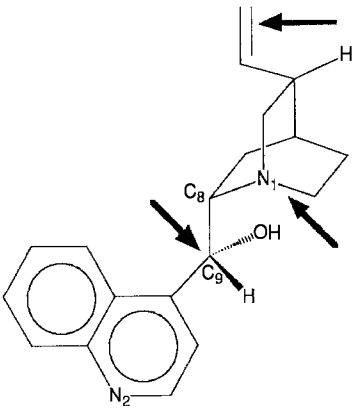
1. Introduction

Among the strategies available for the production of optically pure substances, asymmetric catalysis provides the unique advantage of multiplication of chirality. Although heterogeneous asymmetric catalysis has definite process engineering advantages compared to homogeneous catalysis, there are still only a few prochiral substances which can be converted with substantial yield into optically pure products at solid surfaces. Examples showing technically acceptable enantioselectivities are the extensively studied hydrogenation of β-ketoesters with tartrate modified nickel [1,2] and the hydrogenation of α-ketoesters with cinchona modified platinum catalysts, originally reported by Orito et al. [3]:



A prerequisite for the design of enantioselective catalysts is to gain information about the interaction of the chiral modifier with the substrate, solvent and platinum surface. In their original paper Orito et al. [3] reported that cinchona alkaloids with the same absolute configuration as cinchonidine induce preferentially the (R)-configuration of the α-hydroxyester, while the near-enantiomer cinchonine produces an excess of the (S)-enantiomer. These findings have been confirmed recently [4] by investigations of the influence of structural alterations of the modifier on its enantio-differentiating action.

Alterations of the cinchona alkaloids at the various positions indicated by arrows led to significant changes in the enantioselectivity of the hydrogenation of ethyl pyruvate:



Cinchonidine (**C**)

An important result which emerged from this study was that the enantioselectivity is lost when the quinuclidine nitrogen (N_1) in the cinchonidine modifier is alkylated, indicating that this nitrogen must be involved in the interaction complex leading to enantio-differentiation.

Wells and coworkers [5] proposed a model for understanding the enantioselectivity of this reaction. Their model is based on the hypothesis that the cinchonidine molecules form an ordered array on the Pt surface which controls the stereochemistry of the hydrogen addition. This restriction of the role of the cinchonidine to that of a template took no account of the possibility that a specific interaction between the modifier and the substrate may be responsible for the enantiodifferentiation. Later the same group proposed that the enhancement of the hydrogenation rate occurring in the presence of the cinchonidine modifier is due to a stabilizing hydrogen bonding interaction between the methyl pyruvate substrate and the modifier [6]. However, hitherto the interaction of the modifier with the substrate has not been studied more thoroughly, neither theoretically nor experimentally.

The aim of the present theoretical study is to rationalize the interaction between the chiral cinchonidine modifier (**C**) and the methyl pyruvate substrate (**P**) and to explore whether the earlier experimental findings [4] and proposals [6] can be rationalized and possibly confirmed by calculations. For this purpose, molecular mechanics and quantum chemistry techniques at both ab initio and semiempirical levels, are used.

2. Theoretical calculations

The structures and energies of complexes formed upon interaction of the substrate **P** and simple models of the modifier have been calculated by performing ab initio and semiempirical calculations using reaction potentials. In the first case, to investigate the possible interaction of **P** with both unprotonated and protonated nitrogen centers of quinuclidine, the **P**–NH_3 and **P**–NH_4^+ systems were chosen as models. In the second case, to evaluate the propensity of **P** to behave as an electrophile or as an nucleophile, the **P**–H^- and **P**–H^+ model complexes were investigated. In addition, a semiempirical investigation of the regioselectivity of an electrophilic addition reaction to cinchonidine has been performed.

The ab initio calculations were carried out with the Gaussian 90 series of programs [7]. The geometries of the **P**–NH_3 and **P**–NH_4^+ systems were fully optimized using the 3-21G basis set at the SCF and MP2 levels and partially, i.e. with a pyruvate system frozen at its optimum geometry, with the 6-31++G basis set at the SCF level.

The semiempirical model is based on a local reactivity index consisting of the interaction energy $E_{int}(\boldsymbol{r})$ between a substrate and an incoming electrophilic or nucleophilic model reactant located in $\boldsymbol{r}$, which is expressed as

$$E_{int}(\boldsymbol{r}) = E_{es}(\boldsymbol{r}) + E_{ct}(\boldsymbol{r}) + E_{ex}(\boldsymbol{r}), \tag{1}$$

where E_{es}, E_{ct}, and E_{ex} are the electrostatic, charge-transfer and exchange-repulsion energy components, respectively, calculated using extended-Hückel

(EH) wavefunctions [8,9]. The reactivity index is such that negative (positive) values of E_{int} correspond to substrate–reactant attractive (repulsive) interactions. The regions where E_{int} is a minimum are, therefore, the most reactive sites of a substrate towards an attack by a reactant. To find E_{int} values which depend only on the position of a reactant and not on its orientation, two spherically symmetric model reactants have been chosen: a proton with a virtual 1s orbital for the electrophile and an H^- ion with two 1s electrons for the nucleophile. Being a local property depending on the position only of a reactant with respect to the substrate, E_{int} is conveniently represented in the form of isoenergy surfaces generated from a three-dimensional grid and represented as solid models. All the details relevant to the semiempirical calculations have been previously reported [10].

The molecular mechanics calculations on the **P–C** protonated complex have been performed using the Amber force field [11] as implemented in the MacroModel package [12]. In these calculations all the geometrical parameters of the complex have been optimized without any constraint.

All the calculations have been performed on a Silicon Graphics IRIS 4D/35 workstation.

3. Results and discussion

Fig. 1 presents the structural model of cinchonidine (**C**) together with semiempirical E_{int} selected low-energy grey-scaled contour maps displaying the propensity of the unprotonated modifier to bind with an electrophile. It is seen that, according to the semiempirical model, cinchonidine may behave as a nucleophile with a high regioselectivity for the addition reaction of an electrophile. In agreement with the experimental studies [4], it is seen that the quinuclidine nitrogen is a favorable site for the electrophilic attack, which is likely to be responsible for the crucial interaction leading to enantio-differentiation. Clearly, this center can therefore act either as a nucleophile through its nitrogen lone pair or as an electrophile after protonation in solution. The other two possible binding sites of **C** for electrophilic attack are discarded, as: (i) the nitrogen of the quinoline ring possesses considerably lower basicity than the tertiary nitrogen of the quinuclidine part; (ii) changes at the quinuclidine nitrogen were found to be most influential concerning the enantio-differentiation, while the substitution of the OH group by OCH_3 had relatively little influence [4].

Fig. 2 depicts the ab initio equilibrium geometries of the **P**–NH_3 and **P**–NH_4^+ complexes together with EH isoenergy surfaces calculated for a nucleophilic and electrophilic attack of **P**, respectively. Note that the zone of highest reactivity for nucleophilic attack is located between the ester- and keto-carbonyl groups, whereas the most favorable sites for electrophilic attack of **P** lie approximately in the regions of the lone pairs of the oxygen atoms. Interestingly, the zones of highest reactivity predicted by the semiempirical model correspond very well to the actual

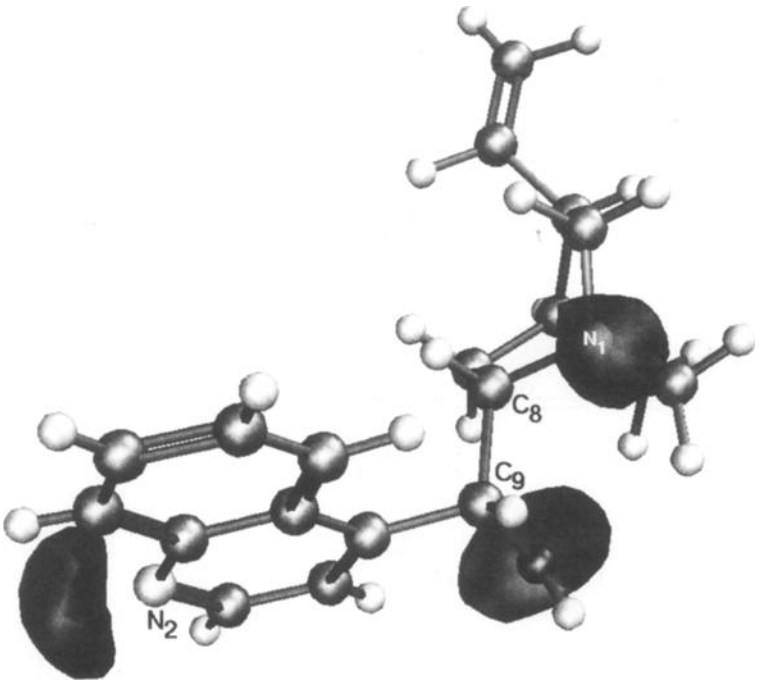


Fig. 1. Structural model of cinchonidine **C** represented together with isoenergy surfaces (black) corresponding to an interaction energy $E_{int} = -95$ kcal/mol calculated using the EH model for an electrophilic attack on **C**.

position of the reactants as predicted by the ab initio calculations for both **P**–NH_3 and **P**–NH_4^+ cases, which underlines the reliability of our reaction potentials model. Actually, docking of **P** to the protonated **C** via a hydrogen bond interaction seems to be energetically more favorable, according to a much more stabilizing complexation energy for the **P**–NH_4^+ complex (by 25 kcal/mol) predicted by ab initio calculations. This result indicates that such a complex is thermodynamically more stable and therefore likely to predominate under conditions where cinchonidine can be protonated. NMR studies on a possible protonation of **C** under standard reaction conditions [13] are currently being carried out. We suggest that the high enantioselectivity of ethyl pyruvate hydrogenation obtained in acetic acid [14] is mainly due to the enhanced affinity of the reactant for a protonated form of **C** existing in this medium.

Using these results as a model of the **P**–**C** interaction, we have investigated the possible conformations of the complex formed upon interaction of protonated **C** with **P** using molecular mechanics. Fig. 3 shows the side views of the most stable complexes formed upon interaction of protonated **C** and **P**, which upon hydrogenation would yield (R)-methyl lactate (fig. 3A) and (S)-methyl lactate (fig. 3B), respectively. The corresponding top views of the complexes are displayed in

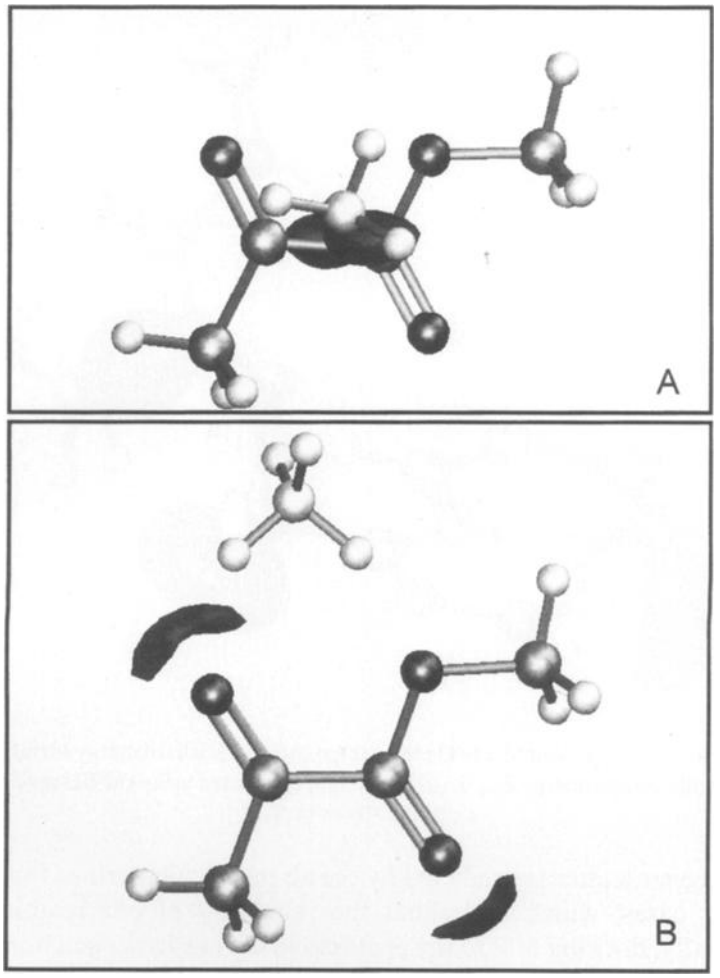


Fig. 2. Ab initio equilibrium geometries of the **P**–NH_3 and **P**–NH_4^+ complexes together with the EH isoenergy surfaces of E_{int} calculated for the nucleophilic attack on **P** (−6 kcal/mol, black) (A), and for electrophilic attack (−150 kcal/mol, black) (B).

figs. 4A and 4B. The complexes have been accommodated on a platinum (111) surface in order to illustrate the space requirements of the adsorbed complexes and no conclusions concerning the relative positions of platinum and complex atoms should be drawn from these pictures. Note that the complex with the *top-left, bottom-right* orientation of the carbonyl groups relative to the central C–C bond of **P** (figs. 3A and 4A), which is suggested to be the precursor to (R)-methyl lactate, can be adsorbed in a planar π-bonding mode on the platinum surface via the aromatic quinoline ring, without hindering the interaction of the carbonyl moieties of **P** with the platinum surface. This adsorption mode is impaired in the complex suggested to be the precursor to (S)-methyl lactate (figs. 3B and 4B) due to steric hindrance.

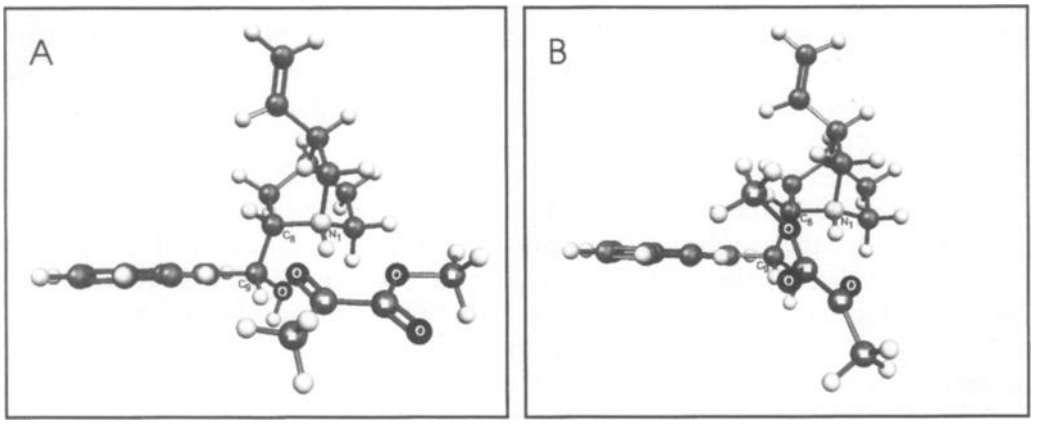


Fig. 3. Side view of the energetically most favorable complexes formed between protonated **C** and **P** which would yield (R)-methyl lactate (A) and (S)-methyl lactate (B), respectively, on hydrogenation. Note that the quinoline ring is placed perpendicular to the drawing plane. For the sake of clarity the carbon atoms of the reactant **P** are marked with a white square. Oxygen atoms in **P** and **C** are labelled with a white O. The corresponding top views of the complexes are presented in figs. 4A and 4B.

The opposite behaviour is found when the complexes formed upon interaction of protonated cinchonine (the near-enantiomer of **C**) with **P** are energetically optimized. The precursor complex resulting in (S)-methyl lactate upon hydrogenation can be adsorbed without significant steric hindrance, while the one yielding (R)-

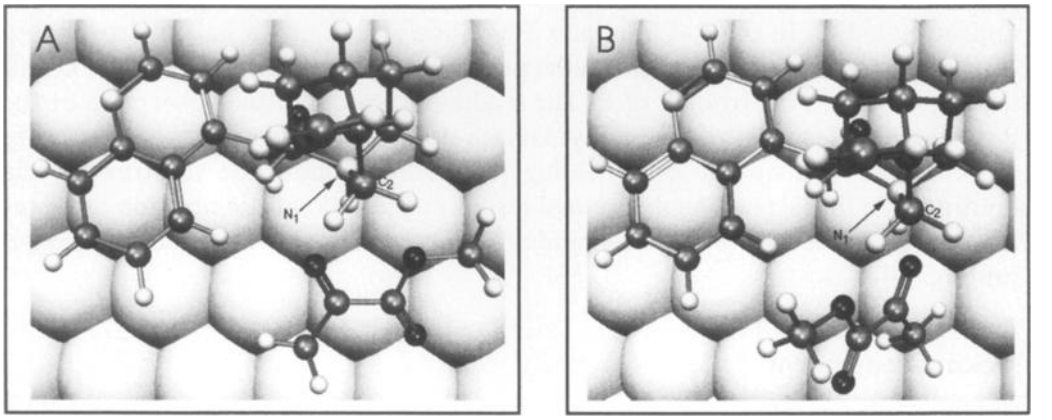


Fig. 4. Top view of the energetically most favourable complexes shown in fig. 3. The complex with the top-left, bottom-right orientation of the carbonyl groups relative to the central C–C bond of **P**, shown in (A), is suggested to be the precursor to (R)-methyl lactate, while complex (B) would yield (S)-methyl lactate. Note that an energetically feasible adsorption of complex (B) is unlikely due to strong steric hindrance (cf. fig. 3), making the adsorption of this complex and thus the formation of (S)-methyl lactate less likely. The complexes have been accommodated on a platinum (111) surface in order to illustrate the space requirements of the adsorbed complexes.

methyl lactate is strongly sterically hindered. Thus the conclusions which emerge from our theoretical considerations are in agreement with the experimental observation that the use of cinchonidine leads preferentially to (R)-methyl lactate, while the application of the near-enantiomer cinchonine yields (S)-methyl lactate in enantiomeric excess.

The molecular modelling approach, taking into account **P**, **C** and the steric constraints imposed by the adsorption on the platinum surface, leads to a reasonable explanation for the enantio-differentiation of this system. However, it is clear that our theoretical prediction of the complex formed between the methyl pyruvate substrate and the cinchonidine modifier has been made for an ideal case, since solvent effects and a quantum description of the interaction with the platinum surface atoms are not considered. Furthermore, the question of whether the **P**–**C** complex is formed in solution or by coadsorption of **P** and **C** on the platinum surface is still open. Nevertheless, the calculations provide undoubtedly further evidence for the crucial role of N_1 in the enantio-differentiating ability of cinchonidine and provide a feasible interpretation for the experimental observation that a change of the chirality of the stereogenic region (C_8, C_9) of the cinchona alkaloid used as modifier results in a corresponding change of the chirality of the product formed.

4. Conclusions

Our theoretical studies aimed at finding the structure of the complex formed upon interaction of methyl pyruvate (**P**) with cinchonidine (**C**) indicate that **C** protonated at the quinuclidine nitrogen forms a more stable complex with **P** than unprotonated **C**. In the **P**–**C** complex **P** is transformed into a half-hydrogenated state by hydrogen bonding between the protonated quinuclidine nitrogen of **C** and the oxygen at the α-carbonyl of **P**. The studies indicate that the adsorption of the **P**–**C** complex leading to (R)-methyl lactate upon hydrogenation is energetically more favorable than the one yielding (S)-methyl lactate due to strong steric hindrance in the latter. The theoretical results suggest a realistic reaction mechanism for the enantio-differentiation and are in agreement with earlier experimental findings [4].

Acknowledgement

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