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Journal of Catalysis 226 (2004) 69–82
JOURNAL OF CATALYSIS
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Adsorption of cinchonidine on platinum: a DFT insight in the mechanism of enantioselective hydrogenation of activated ketones

Angelo Vargas [a], Thomas Bürgi [b], Alfons Baiker [a,*]

[a] *Institute for Chemical and Bioengineering, Swiss Federal Institute of Technology, ETH-Hönggerberg, CH-8093 Zurich, Switzerland*
[b] *Institut de Chimie, Université de Neuchâtel, Av. de Bellevaux, CH-2007 Neuchâtel, Switzerland*

Received 12 January 2004; revised 4 May 2004; accepted 5 May 2004

Available online 15 June 2004

Abstract

The adsorption of cinchonidine on platinum has been calculated with relativistically corrected density-functional theory, by first studying the interaction of the 1(*S*)-(4-quinolinyl)ethanol with a platinum cluster of 31 metal atoms, and by successive addition and separate optimization of the quinuclidine moiety. The conformations of the alkaloid on the surface were analyzed and their possible interactions with a surface chemisorbed methylpyruvate and acetophenone are discussed. A chiral space that is able to selectively accommodate surface enantiomers and to promote their rapid hydrogenation in a ligand-accelerated fashion has been determined. The role of the O-alkylation of the alkaloid in the modulation of enantioselectivity has been rationalized within the new interaction model.

Keywords: Cinchonidine; Adsorption; DFT; Platinum; Enantioselective hydrogenation; DFT; Activated ketones; Mechanism

1. Introduction

The need to produce enantiopure compounds is steadily increasing, and so are synthetic approaches that minimize the amount of waste and are applicable on a large scale. Heterogeneous catalysis, combined with chiral modification of the catalyst surface, is a promising technique, because the presence of the catalyst in a different phase from that of the reactant and product allows easier separation. This procedure may become even more attractive if the reaction is carried out in a continuous flow reactor, as demonstrated for the enantioselective hydrogenation of ketopantolactone [1]. Unfortunately the number of enantioselective reactions that can be efficiently carried out using this methodology is still rather limited. Today the two most studied heterogeneous catalytic enantioselective hydrogenations are those of α-ketoesters on cinchona-modified platinum [2–7] and β-ketoesters on tartrate-modified nickel [8]. The former has been thoroughly studied from a mechanistic point of view and the scope of its applications is steadily broadening, including the enantioselective hydrogenation of α-ketoesters, α-ketolactones [1,5,7,9,10], α-diketones [11–15], α-ketoacetals [16,17], α,α,α-trifluoroketones [18–22], and linear and cyclic α-ketoamides [23–25]. Furthermore the modification of metal surfaces with cinchona alkaloids has been applied with success to palladium catalysts for the enantioselective hydrogenation of C–C double bonds [26]. The growing interest in cinchona alkaloid modification of metal catalysts has induced an increasing number of mechanistic studies that may help the rational extension of this synthetic route. The discovery of molecular level interactions that are responsible for the reactivity and for the selectivity would in fact help the design of tailored catalytic systems.

One of the first attempts to explain the enantioselectivity was made by Wells and co-workers, who proposed that the L-shaped modifier could generate a chiral surface, by adsorption on Pt in ordered non-close-packed arrays, allowing preferential adsorption on the metal surface of one of the faces of the prochiral substrate (template model) [27]. Later the first 1:1 interaction model was proposed by Baiker and co-workers, suggesting that modifier and reactant interact via hydrogen bonding [28,29]. The features of this model were discussed in detail in preceding articles [4,7]. A 1:1 in-

* Corresponding author.
E-mail address: baiker@tech.chem.ethz.ch (A. Baiker).

0021-9517/$ – see front matter
doi:10.1016/j.jcat.2004.05.011

teraction was also adopted in the revised model of Wells and co-workers [30]. A different model was proposed by Margitfalvi and co-workers [31] according to which enantioselectivity originates via a supramolecular complex between the cinchona alkaloid and the substrate that, successively stereoselectively reduced, should lead to the observed enantiodifferentiation. This model was based on the closed conformations of the alkaloid, and cannot explain the enantioselectivity achieved with modifiers with rigid open conformations as studied by Bartók et al. [32]. Recently Vayner et al. have revisited an interaction model proposed by Augustine et al. [33] which is based on the assumption that the quinuclidine nitrogen can make a nucleophilic attack to an activated carbonyl [34]. According to this model the two possible zwitterionic intermediates that can thus be formed have different energies, which leads to the selective formation of one of the two intermediates, and therefore to enantioselectivity after hydrogenolysis by surface hydrogen. This model nevertheless does not explain the enantiodifferentiation of nonbasic modifiers, such as the one reported by Marinas et al., that have no quinuclidine moiety, and no nitrogen atom, and thus no possibility to form zwitterionic intermediates [35]. Furthermore in situ spectroscopic evidence of hydrogen bond formation between the quinuclidine moiety of cinchonidine and ketopantolactone has been shown recently [36], which supports the hypothesis of the role of weak bond formation rather than that of the formation of intermediates such as those proposed by Vayner et al.

A striking deficiency of all model calculations performed so far is the lack of an explicit treatment of the role of the metal surface, though in some cases the geometrical constraints were inserted [37–39]. The objective of this work is to fill this gap by explicitly treating the adsorption of the chiral modifier and reactant on the platinum surface. Based on these calculations, on the in situ spectroscopic knowledge collected in the past years [40–45], and on the modeling of the adsorption of activated ketones on platinum [46], a possible scenario for enantiodifferentiation is proposed.

2. Computational methods

All calculations have been performed using the Amsterdam Density Functional program package [47]. The computational methods applied have already been described in detail in [46]. In the present contribution only the DZ basis set has been used, due to the larger adsorbates in study that currently still limit basis set size. It has been shown that this basis set is appropriate for the description of the systems in study, reaching very good agreement with experiments, for example, in the study of the adsorption modes of acetone on platinum [46].

3. Results and discussion

3.1. The adsorption of quinoline on platinum

The most widely accepted model for the role of cinchonidine in the enantioselective hydrogenation of activated ketones on cinchona-modified platinum identifies the quinoline moiety of the alkaloid as an *anchoring group*, i.e., the part of the molecule that is supposed to be the main cause for the binding of the modifier to the surface. The rest of the alkaloid would then be located in the space above the quinolinic moiety, promoting enantioselectivity through its interactions with the adsorbed activated ketone. The adsorption of quinoline and of cinchonidine has been thoroughly studied by means of FTIR in situ spectroscopy [40–45], by NEXAFS, variable temperature STM and TPR [48,49], and electrochemical methods [50,51]. The dominant role played by quinoline in the adsorption of cinchonidine, that had previously been proposed on the basis of isotope exchange experiments [52], was corroborated by spectroscopic investigations. The alkaloid was found adsorbed irreversibly on platinum in acidic aqueous solution [51], and in at least three different adsorption modes with increasing tilting angle to the surface, and with a relative population dependent on the concentration [40,41,48].

In order to investigate the adsorption of CD on Pt, the interaction of its anchoring part with platinum was considered first. Therefore the adsorption geometry of quinoline on a platinum 31 cluster was studied. With reference to previous investigations on the adsorption of benzene that indicated that bridge adsorption sites were energetically favored over other adsorption sites [53], the adsorption of quinoline was studied and two different adsorption modes were found, as shown in Fig. 1. The first showed a tilting angle to the surface of 28° (Figs. 1a and 1b), while the second was parallel to the metal surface (Figs. 1c and 1d). The calculated adsorption energy for the parallel adsorption was 47.7 kcal/mol, where both rings of the aromatic heterocycle could be adsorbed in a quasi-bridge mode, while the tilted one had a adsorption energy of 28.2 kcal/mol. Recent calculations using the same cluster and the same level of theory gave the value of 27.8 kcal/mol for the adsorption energy of benzene on a bridge site [46], which shows that the quinoline is able to adjust itself on the metal, almost doubling the adsorption heat of benzene. The parallel adsorption of quinoline on platinum had been calculated using a smaller cluster [54], but the existence of a tilted adsorption was in line with the FTIR experiments [41] that suggest the presence of different adsorption modes for quinoline on the surface. It should be pointed out that the literature dealing with the study of adsorption modes of cinchonidine investigated by IR spectroscopy [41] refers to tilted adsorption for N-lone pair-bonded species, i.e., species for which the quinoline moiety is almost perpendicular to the metal, while the present work uses the term tilted to refer to adsorbed species that are not parallel to the surface, but not necessarily bonded by the N-lone pair. The

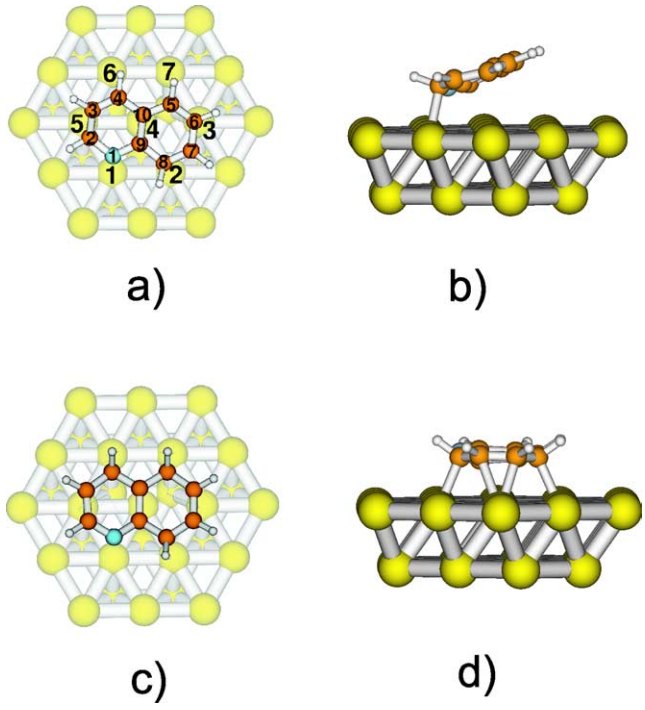

Fig. 1. Adsorption geometry of quinoline on Pt 31 cluster: (a) and (b) are the top view and side view, respectively, of the tilted adsorption mode, and (c) and (d) are the top view and side view, respectively, of the parallel adsorption mode.

tilting of quinoline shown in Fig. 1b is due to the effect of nitrogen that, through the formation of a σ bond to a platinum atom of the metal, as in the case of pyridine [55–57], competes with the parallel adsorption. In the tilted adsorption the N–Pt(1) bond distance was calculated to be 2.20 Å, but also the C(8)–Pt(2) bond length resulted in 2.22 Å, showing that C(8) is strongly bound to one Pt atom of the surface. The adsorption strength of cinchonidine might be tuned by substitution on this carbon, or by substitution on a conjugated carbon.

The geometrical parameters show that C(8) undergoes a rehybridization to sp^3 and that the other carbon atoms remain much closer to the original sp^2 hybridization. The most remarkable bond length variations with comparison to the free molecule are the ones including the nitrogen and C(8). The rest of the quinoline is rather distant from the platinum, reaching distances for C(3), C(10), and C(6) that make their contribution to binding negligible.

The parallel adsorption of quinoline shown in Figs. 1c and 1d on the other hand is characterized by the rehybridization of each carbon atom of the ring system. The C–C bond lengths are elongated more uniformly for the atoms that are more distant from the nitrogen, the bond distances from platinum are more uniform, and all the atoms contribute to the chemisorption. A measure of the rehybridization of the carbon atoms is the value of the dihedral angle formed by hydrogens with the ring carbons. Especially hydrogen atoms H(4), H(5), and H(8) show a strong deviation from planarity. Rehybridization of C(4) is particularly interesting because the quinuclidine moiety of cinchonidine is bound to this position, and therefore its coordinates in space will be influenced by the level of rehybridization of this carbon.

3.2. 1(S)-(4-quinolinyl)ethanol

The main element that differentiates the adsorption of quinoline and the adsorption of cinchonidine is the hydroxylic group on the quinolinic moiety of the alkaloid. Having calculated the structures of adsorbed quinoline, an ethanol moiety was added at quinoline C(4), resulting in 1(*S*)-(4-quinolinyl)ethanol (QUE). This molecule has only one stereogenic center, corresponding to the C(9) in cinchonidine. In QUE the absolute configuration of this carbon is S, while in cinchonidine it is R, due to the exchange of the quinuclidinyl moiety with a methyl group that changes the priorities within the Cahn–Ingold–Prelog rules. This does not change the relative position in space of the OH group with respect to cinchonidine. QUE on the Pt 31 cluster was fully reoptimized, and this addition completed the anchoring part of cinchonidine. Calculations were performed for both the tilted and the parallel structures found for quinoline, and the optimized geometries are shown in Fig. 2.

The molecule 1(*S*)-(4-quinolinyl)ethanol also adopted a tilted and a parallel adsorption mode, whose adsorption energies were calculated to be 36.3 and 52.6 kcal/mol, respectively. The tilted adsorption mode was almost identical to the one found for quinoline, and also had a tilting angle to the surface of 28°. The hydroxyl group had a binding interaction to the surface, responsible for the increase of adsorption energy. A recent study [49] showed that a methyl substituent in the C4 position of quinoline increases the tilting angle of adsorption. The present case does not show this behavior because the hydrogen bond to the surface acts as a constraint to further tilting. The hydroxylic hydrogen points to the middle of the Pt(6)–Pt(8) bond (Fig. 2a), with a distance to the surface of 2.3 Å.

The parallel adsorption (Figs. 2c and 2d) could have shown a high steric hindrance because of the addition of a substituent in position C(4), but the rehybridization of the C(4) that has been noted before for parallel adsorbed quinoline allows the substituent to point away from the surface, still allowing for rotation around the C(4)–C(1) bond. The hydroxyl can then adjust itself to interact with the surface in an optimal way. The rehybridization angle of C(4) was 24°. It must be pointed out that the angle formed by this C(1)–C(4) bond with the surface (Figs. 2d and 2b) is not due to steric hindrance, but to rehybridization.

The hydroxylic proton points to Pt(8) with a distance of 2.3 Å, as for the tilted adsorption (Fig. 2a). Similar to the tilted adsorption mode, geometrical parameters of the quinoline skeleton changed very little from the quinoline parallel adsorption, showing that the quinoline part dictates the adsorption also for QUE.

The adsorption energy of both tilted and parallel quinoline was increased by the presence of the new interaction of

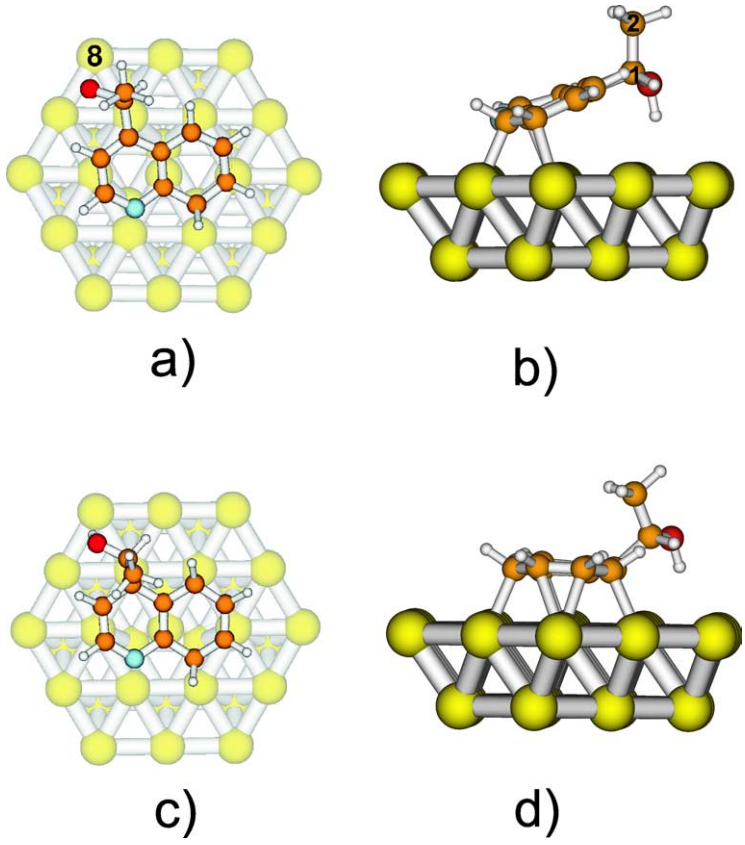

Fig. 2. Adsorption geometry of 1(*S*)-(4-quinolinyl)ethanol on a Pt 31 cluster: (a) and (b) are the top view and side view, respectively, of the tilted adsorption mode, and (c) and (d) are the top view and side view, respectively, of the parallel adsorption mode.

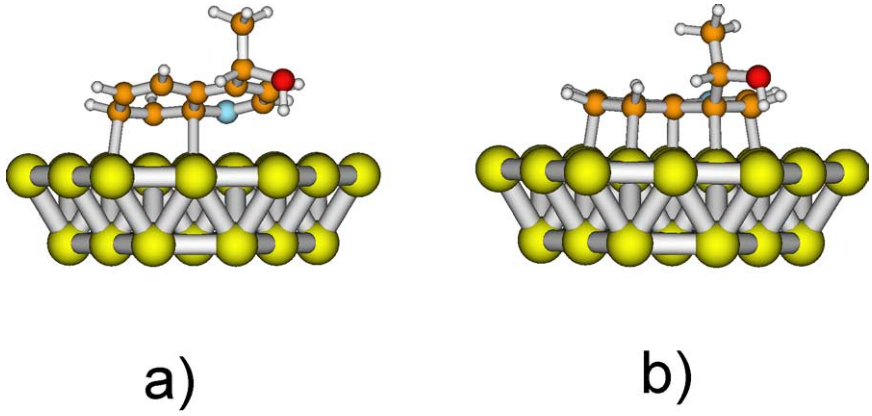

Fig. 3. Front view of the 1(*S*)-(4-quinolinyl)ethanol in (a) tilted mode and (b) parallel mode.

the hydroxyl hydrogen with the surface, which confirms the experimental findings on competitive adsorption between cinchona alkaloids that show that *O*-methoxycinchonidine is adsorbed less strongly than cinchonidine [58,59]. Furthermore it should be noted that the adsorption energy increases more for the tilted than for the parallel adsorption mode of QUE.

Fig. 3 shows a front view of the QUE adsorbed in the tilted (a) and in the parallel mode (b). The stability of the tilted adsorption and its probable equilibrium with the parallel adsorption mode, due to the nitrogen and hydroxyl interactions, may be the cause of the reported greater stability to hydrogenation of the cinchona modifiers compared to synthetic modifiers that have naphthalene instead of quinoline as anchoring group [60,61]. The short life (low resistance toward hydrogenation) of naphthalene-based modifiers is a serious limitation for their use compared to quinoline-based modifiers, because partial hydrogenation of the aromatic system leads to lower adsorption strength and consequently to desorption of the chiral modifier with concomitant loss of enantioselectivity of the catalyst.

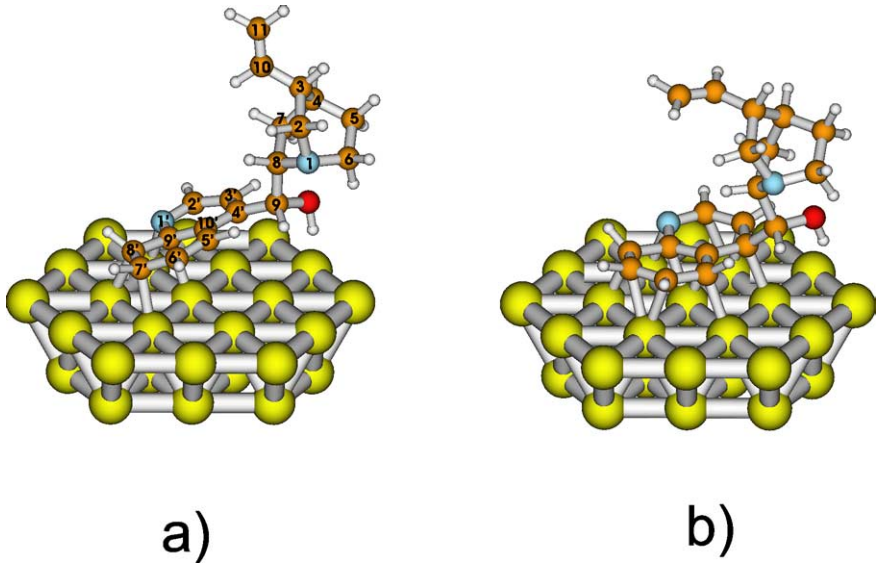

Fig. 4. Cinchonidine adsorption on platinum. The anchoring group is tilted with respect to the surface (a) or parallel to the surface (b). The quinuclidine has been optimized separately from the anchoring group and from the metal.

3.3. Cinchonidine

The 1(*S*)-(4-quinolinyl)ethanol was further modified by addition of the quinuclidine moiety. The geometry optimization of the quinuclidine moiety was achieved by freezing the coordinates of the 1(*S*)-(4-quinolinyl)ethanol and of the platinum cluster, by setting dummy atoms in place of the platinum atoms, and finally by optimizing the quinuclidine part. The basis functions were therefore only those of cinchonidine and the optimization could be rapidly achieved. The result is shown in Fig. 4, for the tilted adsorption (a) and for the parallel adsorption (b).

Both structures of adsorbed cinchonidine are consistent with the experimental evidence. Both conformations are very close to the Open(3) conformation that was found to be the most stable in apolar solvents [62]. The two structures in Fig. 4 will be named Tilted Surface-Open(3) (TSO(3)) and Parallel Surface-Open(3) (PSO(3)), respectively, in analogy to the names of the conformations in solution. Although the anchoring moiety changes position in the two cases, in both structures the quinuclidine moiety is above the anchoring part and forms a binding space that, according to a previously proposed model [4,7], could discriminate a pro-*R*- and a pro-*S*-adsorbed ketone. The position of the quinuclidine moiety in the space above the metal does not change too dramatically between TSO(3) and PSO(3) because of the compensating effects of tilting and rehybridization at C(4). In the case of TSO(3) the anchoring part is more distant from the surface but C(4) is not rehybridized, whereas in the case of PSO(3) the rehybridization has occurred but the anchor is closer to the surface. The C(10)–C(11) moiety is, in both conformations, distant from the surface and from the space where the reaction occurs, and its position is not relevant.

According to the model proposed by Baiker, the enantiodiscrimination involves the interaction of the nitrogen of the quinuclidine moiety with the adsorbed ketone. A study of the adsorption of ketones on platinum clusters [46] has allowed us to draw a picture of the possible interaction between an adsorbed ketone and the adsorbed cinchonidine. The cluster of Fig. 4 has been enlarged (graphically) and an adsorbed methylpyruvate (MP) has been adjusted using the coordinates found by separate optimization at the same level of theory [46]. For clarity it should be stressed that Fig. 5 was obtained by separate optimizations of the alkaloid and of the methylpyruvate on metal clusters, and that the structures were not further optimized since the resulting system is computationally too large. In Fig. 5 the distance between the hydrogen of the protonated quinuclidine moiety of cinchonidine and the keto-carbonyl oxygen of the activated surface MP is approximately 3.5 Å, in both cases. In the picture MP is pro-(*R*). If we indicate the adsorption of a ketone with two numbers, the first indicating the platinum atom that interacts with the oxygen and the second the platinum atom that interacts with the carbonyl carbon, then the adsorption of MP shown in Fig. 5a is 1-4.

The platinum atoms nearest to the quinuclidine nitrogen are those numbered in the figure. When the adsorption site of MP is 1-5 (not shown in the figures) the distance between the keto-carbonyl oxygen and the protonated quinuclidine is 3.5 Å, while other adsorption sites such as 5-4 or 1-3 would be either too far from the quinuclidine nitrogen, or too near to cinchonidine. Fig. 6 shows the part of the surface occupied by reactant and modifier.

In this figure the platinum atoms depicted in black are those occupied by the anchoring group of the alkaloid, while the numbered ones are the platinum atoms that can accommodate a keto-carbonyl bond. These platinum atoms form a surface-binding area where methylpyruvate can enter in contact with the quinuclidine moiety of the alkaloid. Although the adsorbed species are rather mobile on the surface, the

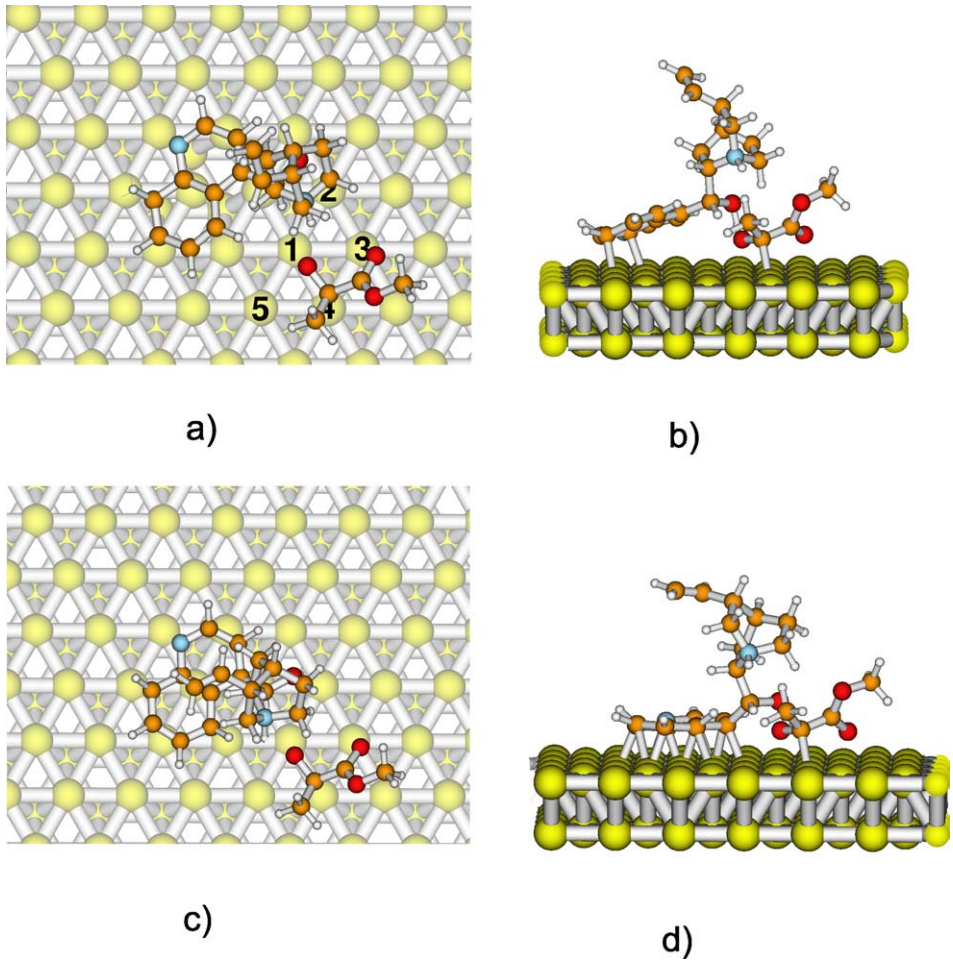

Fig. 5. Model of the interaction between cinchonidine and adsorbed *cis* pro-(*R*) methylpyruvate. The distance between the quinuclidine nitrogen and the keto-carbonyl moiety is ca. 3.5 Å.

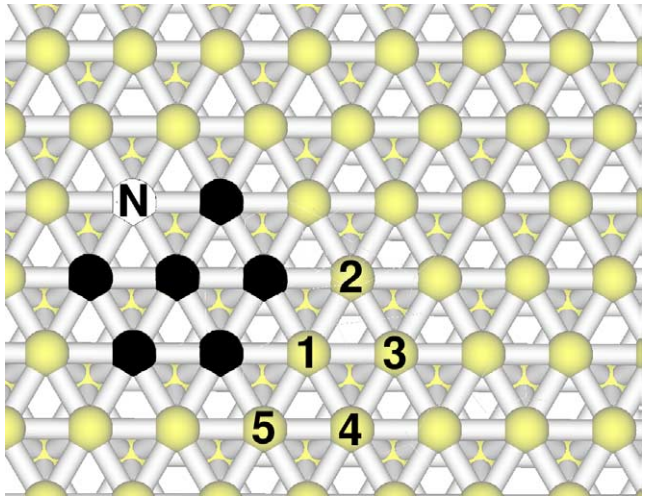

Fig. 6. Map of the surface atoms involved in the adsorption of the modifier (black) and in the adsorption of the ketone (numbered 1 to 5).

most populated adsorption sites are those where the C–O is forming bonds with two platinum atoms, leading to an η^2 adsorption mode [46]. The side views in Figs. 5b and 5d show that the relative positions also have three-dimensional constraints, that should contribute to determine the most suitable relative positions between adsorbed reactant and modifier. In Fig. 5 the MP is adsorbed pro-(*R*). From Figs. 5a and 5c it is evident that the pro-(*R*)-adsorbed MP fits to the interaction space better than the pro-(*S*)-adsorbed MP. For example, adsorption 1-5 is allowed for the pro-(*R*) MP, while for the pro-(*S*) such position would imply repulsive interactions between the ester group of MP and the anchoring part of the alkaloid. It should also be noted that the ester group can give repulsive interactions with the quinuclidine moiety of the alkaloid, which emerges from Figs. 5b and 5d. The ability of cinchonidine to discriminate between a pro-(*R*)- and a pro-(*S*)-adsorbed ketone is remarkable also in less evident cases. Trifluoroacetone, for example, is hydrogenated in the presence of CD, giving 20% ee, although the spacial asymmetry is mainly due to the difference between the C–H and the C–F bond lengths, the first being circa 1.1 Å and the second 1.4 Å [46].

In the preceding description of the interaction between surface modifier and adsorbed ketone, we have taken as critical parameter the distance between the protonated quinucli-

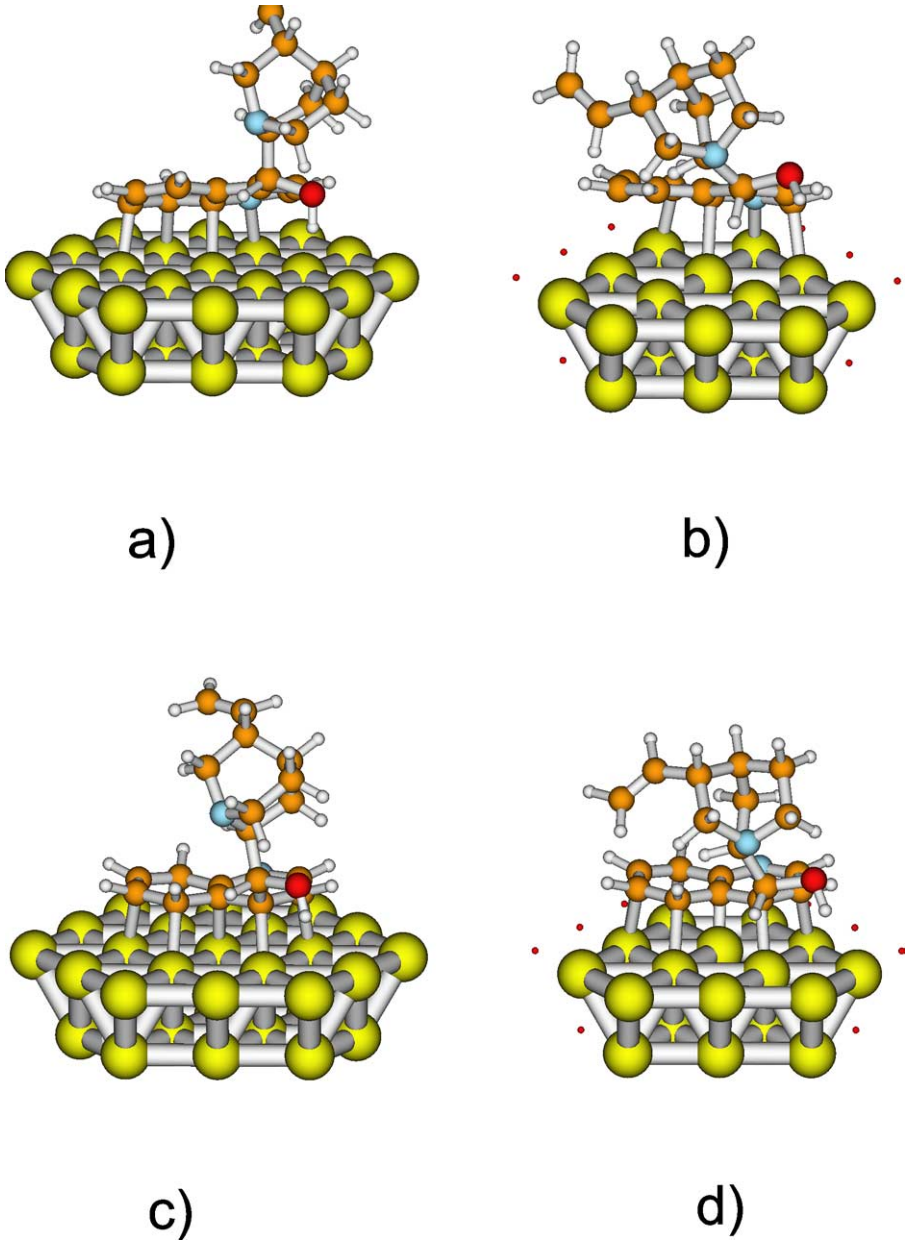

Fig. 7. Surface conformations of cinchonidine. (a) TSO(3), (b) TSO(5), (c) PSO(3), (d) PSO(5).

dine and the keto-carbonyl oxygen. The quinuclidine moiety of cinchonidine might in fact be protonated, in acidic medium. A recent publication [36] has shown that also under aprotic conditions a hydrogen-bonding interaction might occur between substrate and modifier. In the interaction model that we have just described the interaction between a protonated quinuclidine and the keto-carbonyl oxygen could be replaced by the interaction between the nonprotonated quinuclidine and the semihydrogenated ketone (semihydrogenated at the oxygen), without losing the concept, experimentally established, that the quinuclidine nitrogen plays a fundamental role in the reaction mechanism.

The distance of 3.5 Å between protonated quinuclidine and keto-carbonyl oxygen is large for an effective hydrogen-bonding interaction with the ketone. This distance could be shortened by the rotation of quinuclidine around C(4′)–C(9) (Fig. 4). An anticlockwise rotation along this bond would lead the quinuclidine system to a position nearer to the metal surface. The calculation of the whole system formed by cinchonidine and the Pt 31 cluster would be computationally too demanding, and in order to calculate the rotated structure, the number of metal atoms was reduced to 18 by setting the others as dummy atoms, as shown in Figs. 7b and 7d.

Figs. 7a and 7c show the TSO(3) and PSO(3) for comparison with the new structures. Both surface conformations 7b and 7d were obtained by freezing the coordinates of the platinum and of the anchoring moiety, and by partial optimization of the quinuclidine moiety and of the C(4′)–C(9)

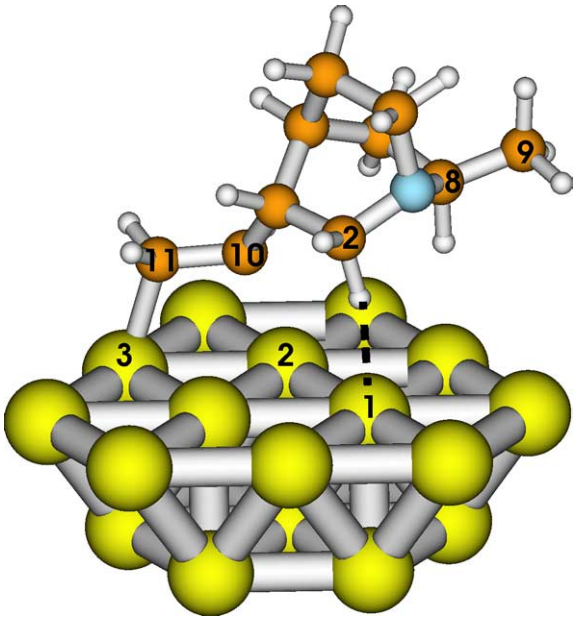

Fig. 8. Interaction of the quinuclidine moiety during cinchonidine adsorption on a Pt 19 cluster. The C(10)–C(11) double bond can undergo saturation by approaching the surface after rotation around the C(4′)–C(9) bond.

bond rotation. The minimization showed the existence of two energetically and geometrically very close states, where the hydrogen bound to C(9) and the hydroxylic hydrogen compete for the interaction with the platinum. The question of the dynamic transformation between the conformations will not be addressed in this work. For the moment it is sufficient to note that quinuclidine can, by rotation around a C–C bond, reach positions closer to the surface.

An experimental evidence in favor of the possibility of the rotation described above is the hydrogenation of the C(10)–C(11) double bond that occurs in correspondence to the adsorption of cinchonidine on a platinum surface. The quinuclidine moiety was calculated on a Pt 19 cluster and the resulting optimized geometry is shown in Fig. 8. A similar position of the quinuclidine moiety of the alkaloid could be reached by the noted rotation. The calculated C(11)–Pt(3) distance was 2.12 Å, while C(10)–Pt(2) was 2.20 Å, consistently with the values calculated for di-σ adsorbed ethylene [63]. Also the hydrogen at C(2) was very close to the surface (2.0 Å). Experimentally the quinuclidine double bond is saturated very fast. Once saturation has occurred quinuclidine might oscillate between the two other conformations described above. The saturation of the double bond is nevertheless an important clue for the flexibility of the quinuclidine moiety of the alkaloid, especially considering that adsorption of cinchonidine in solution has been found to be irreversible [51]. The resulting picture is that of an irreversible adsorption of the alkaloid through the aromatic anchoring moiety, and a flexibility of the quinuclidine moiety that is able to approach the surface more or less closely.

In analogy with the conformations of free cinchonidine, the structure in Fig. 7b will be named Tilted Surface Open(5) (TSO(5)), while the structure in Fig. 7d will be named Parallel Surface Open(5) (PSO(5)). Comparing conformation TSO(3) to TSO(5) (Figs. 7a and 7b, respectively), the dihedral angle O–C(9)–C(4′)–C(3′) of the latter (see Fig. 4 for the numbering) had undergone an anticlockwise rotation of 32°, and the dihedral angle O–C(9)–C(8)–N(1) also an anticlockwise rotation of 15°. Between PSO(3) and PSO(5) (Figs. 7c and 7d) the same angles varied by 32 and 24°.

Also for the surface Open (5) conformations the surface was graphically extended and MP accommodated in a position that allowed for interactions with the quinuclidine nitrogen. Fig. 9 shows the interaction geometries that were found.

For the TSO(5) the distance between protonated quinuclidine and keto-carbonyl oxygen was 2.5 Å, while for PSO(5) the same distance was only 2.2 Å. For both tilted and parallel conformations also the interaction between the hydroxylic proton and ester carbonyl oxygen is in reach. It should be noted that this double interaction is possible also for the pro-(*S*) adsorption mode of MP, but previous studies on the interaction of an ammonium ion with MP have shown that an ammonium ion has a stronger interaction energy with the keto-carbonyl than with the ester carbonyl [28], which would lead to an energy difference between pro-(*R*) and pro-(*S*) complexes that favors the pro-(*R*). The cited study on the interaction between an ammonium ion and MP was done for the free species, but related studies in our laboratory for adsorbed MP lead to similar results. Cinchonidine promotes the enantioselective hydrogenation of ethylpyruvate also when the hydroxy group is O-methylated. This behavior supports the shape discrimination rather than the participation of a guiding group that is able to produce a second interaction. Nevertheless it is also possible that the double interaction takes place when the hydroxy group is present, and when this becomes O-methylated the sole shape discrimination could act to differentiate the binding of a pro-(*R*)- and a pro-(*S*)-adsorbed species. At present this is only speculation, since the proposed interactions are consistent with both options, both leading to the same enantiomer.

The rotation of the quinuclidine moiety results in an approach of the skeleton of quinuclidine to the surface, with a subsequent increase of the repulsive interaction space in proximity of the nitrogen. Another important observation is that, unlike for the TSO(3) and PSO(3) cases, the position 1-5 for the ketone adsorption is completely hindered by the presence of the quinuclidine skeleton, and the repulsive interactions to the anchoring group can no longer take place. In other words, by rotation of the quinuclidine moiety the surface-binding space shown in Fig. 6 is more constrained to the 1-2 and 1-3 binding positions rather than to the 1-4 and 1-5. In the first case the anchoring moiety can play a role in deciding which surface species to accommodate, while in the second case it is the quinuclidine moiety that can hinder the approach of a pro-(*S*)-adsorbed ketone more efficiently.

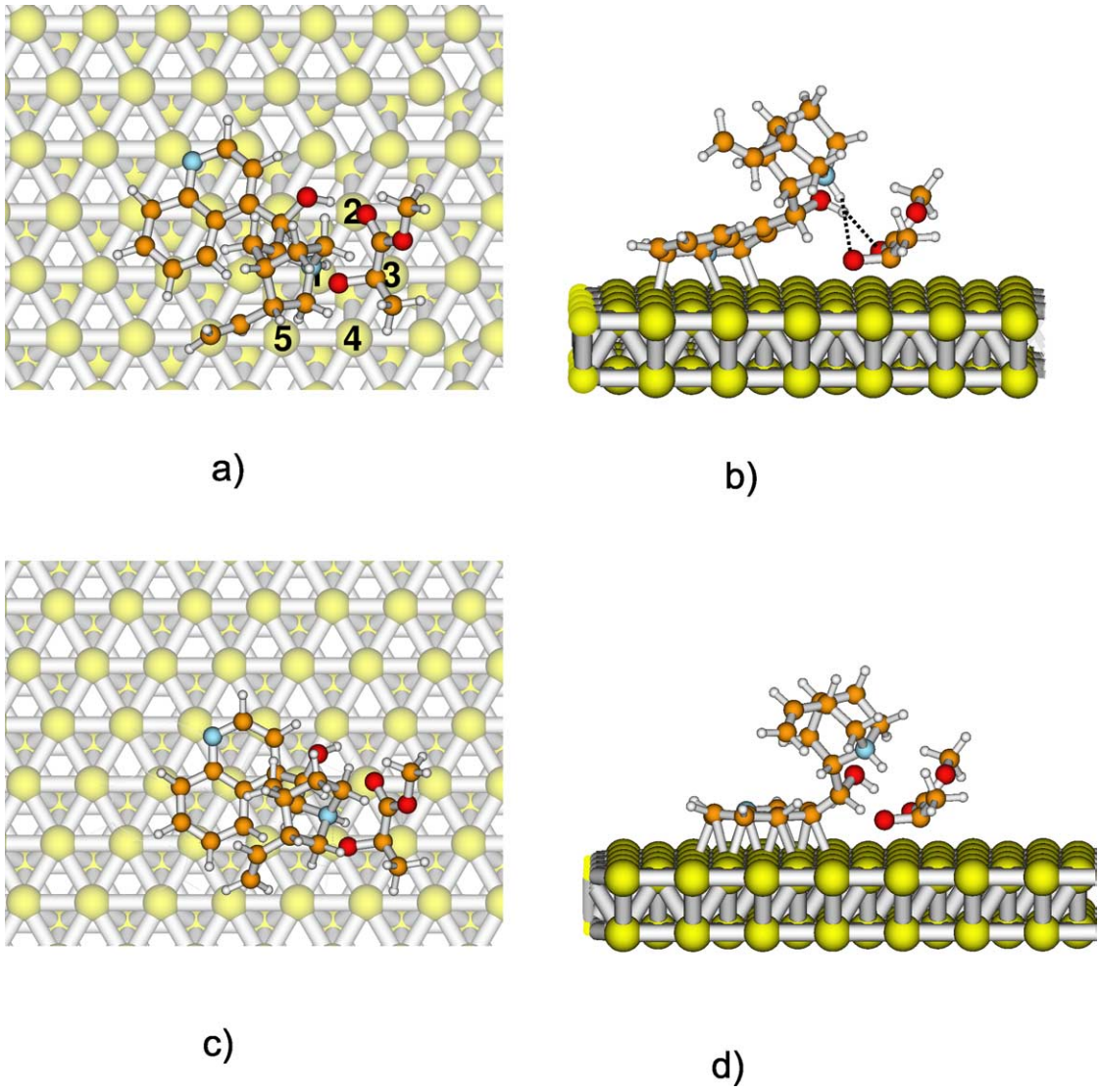

Fig. 9. Interaction of the TSO(5) (a and b) and PSO(5) (c and d) conformations of cinchonidine with an adsorbed *cis* pro-(*R*) methyl pyruvate. The distance between quinuclidine nitrogen and the adsorbed keto-carbonyl group is shorter than for the Surface Open(3) conformations.

3.4. The chiral pocket

In the previous discussion qualitative arguments have been used to describe the preference of an adsorbed pro-(*R*) MP to be accommodated in the space near to the adsorbed cinchonidine, while being at the same time near enough to the quinuclidine nitrogen to allow for hydrogen-bonding interactions. The resulting picture for the reaction of enantioselective hydrogenation of an activated prochiral ketone on cinchona-modified platinum is as follows: racemic hydrogenation of an activated ketone takes place on the platinum surface, but the interaction of the ketone with the quinuclidine nitrogen via a hydrogen bond accelerates the reaction. If the surface species that carries the quinuclidine is chiral, its interaction with the adsorbed ketone can differentiate between a pro-(*R*) and a pro-(*S*) species. As previously noted [46], the adsorbed ketone is already chiral, having undergone rehybridization, which intuitively enhances the enantiodiscriminating interactions. The surface enantiomer that reaches more easily the site near to the quinuclidine nitrogen is hydrogenated faster than the other enantiomer because the hydrogen bonding is weakened due sterical hindrance. The final outcome is then the production of a net ee in favor of the surface enantiomer that better reaches the hydrogen interaction with the quinuclidine nitrogen. In other words the reaction is ligand accelerated, and since the ligand is chiral a kinetic resolution can take place. Enantiodiscrimination is then the result of several factors, kinetic, enthalpic, and entropic, because they concern the relative population of surface complexes and their differential kinetics of hydrogenation. Furthermore it was already shown that both thermodynamic and kinetic factors favor the same enantiomer, because both factors are directly influenced in the same direction by the strength of the hydrogen-bonding interaction [38,39].

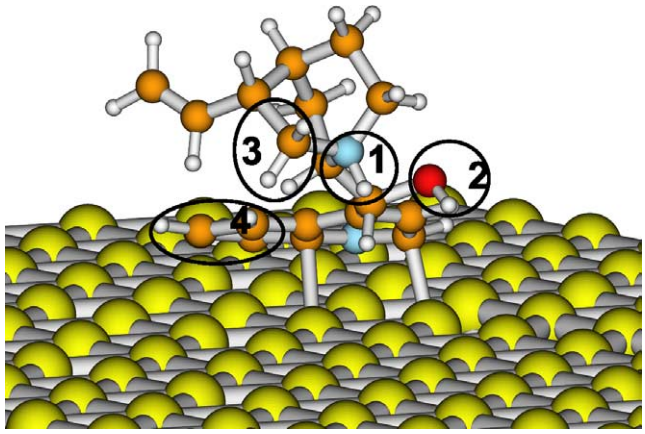

Fig. 10. Example of the chiral pocket for the Tilted Surface Open(5) conformation. Functional groups 1 and 2 are able to give bonding interactions, while the hydrocarbon skeleton of the alkaloid gives repulsive interactions, allowing only some molecular shapes to adjust themselves in the proximity of the quinuclidine nitrogen.

In analogy with many biological reactions that take place within a chiral binding space and in the presence of a transition metal, we can define also for this reaction a *chiral pocket*, i.e., a physical space that is able to accommodate, via bonding and repulsive interactions, a chiral adsorbate, and that is able to discriminate between its enantiomers. Fig. 10 shows the adsorbed cinchonidine in the conformation Tilted Surface-Open(5), and the main four elements of the chiral pocket.

(i) The quinuclidine nitrogen: whether or not protonated, it is able to interact with a surface species, either by promoting proton transfer or by stabilizing a semihydrogenated surface ketone. It has been shown that alkylation of this nitrogen leads to complete loss of selectivity [64].

(ii) The hydroxylic moiety: in the Surface-Open(5) and Tilted Surface Open(5) conformations the hydroxylic proton does not point toward the surface, but toward the space where the reaction takes place. The O–H can take part in hydrogen-bonding interactions with an adsorbed substrate, but can also regulate the equilibrium between surface conformations. The Surface-Open(3) and Tilted Surface Open(3) conformations have an O–H that is more closely interacting with the metal. O-Alkylation most probably tunes the equilibrium between the tilted and the parallel adsorption of the anchoring group, and the equilibrium between Surface Open(3) and Surface Open(5) conformers. Furthermore, any O-alkylation would induce the alkyl group to occupy the space where the reaction takes place, at a short distance from the quinuclidine nitrogen, and may have the effect of altering the selectivity or, if the space becomes too crowded, to reduce it, by hindering access to the quinuclidine nitrogen interaction and favoring therefore racemic hydrogenation. It has been shown, for example, that the O-methylation of the hydroxyl group is not detrimental for the enantioselectivity when ethylpyruvate [64] and ethyl-4,4,4-trifluoroacetoacetate [19] are hydrogenated, but it reduces it to zero for trifluoroacetophenone [21]. Studer et al. in a recent review [3] observed that in general groups larger than *O*-methoxy reduce enantioselectivity. Even inversion of enantioselectivity has been observed for ketopantolactone [65] when the *O*-phenyl cinchonidine was used, although inversion was followed by a drop of enantioselectivity from 80 to 50% ee. Evidently the binding space that could accommodate the pro-(*R*)-adsorbed species becomes hindered, and a new binding space, not quite as effective, is created by the presence of the new substituent. When also the ketone is bulky, as in the cited case of trifluoroacetophenone, loss of selectivity is complete if the O–H of the alkaloid is alkylated [21]. Overcrowding of the binding space on both sides of the modifier and of the substrate rules out contacts between the activated ketone and the quinuclidine nitrogen, and hydrogenation can only take place without the active participation of the modifier, leading to racemic hydrogenation.

(iii) The C(4′)–C(9) and C(9)–C(8) bonds: these two bonds account for the flexibility of the quinuclidine moiety. It has already been shown that the conformational complexity of cinchonidine in solution is due to rotational freedom around these two bonds [66,67]. When cinchonidine is bound to the surface, rotation around their axes allows the flexibility of the quinuclidine moiety, and a dynamic variation of the size and position of the chiral pocket. The modifications of a cinchona alkaloid via O-alkylation probably also have the effect of changing the population of these angles, changing the shape of the pocket. For this reason the chiral pocket becomes “tunable,” via chemical substitution.

(iv) Finally, as shown in Fig. 10 with numbers 3 and 4, the skeleton of the alkaloid: the hydrocarbon structure of cinchonidine forms a space for repulsive interaction, either with the anchoring group or with the quinuclidine moiety. Repulsive interactions are more pronounced for bulky substituents, and therefore cinchonidine mostly produces *R*-alcohols. The repulsive interactions are all on the side where the bulkier group of a pro-(*S*)-adsorbed species should be accommodated, due to the anchoring moiety for the Surface Open(3) conformations, and due to the quinuclidine skeleton for the Surface Open(5) conformations. Note that acetophenone (ACPH) and substituted acetophenones lead on the contrary to the *S*-alcohols [68]. Trifluoroacetophenone (TFACPH) leads to the *R*-alcohol only as a consequence of nomenclature, because of the high priority of fluorine in the Cahn-Ingold-Prelog rules, but its pro-(*R*) arrangement on the surface geometrically corresponds to the pro-(*S*) arrangement of acetophenone. Recent studies on the adsorption of ACPH and TFACPH on a platinum cluster show that their aromatic moiety is adsorbed parallel to the surface in its η^2 (activated) adsorption mode [46].

Fig. 11 was drawn using the coordinates of η^2-adsorbed TFA as optimized using the same methods as those used for the present study [46]. It shows that TFACPH and ACPH are sufficiently close to the surface to accommodate the aromatic ring below the quinuclidine moiety that could trap the mobile adsorbed TFACPH or ACPH in prox-

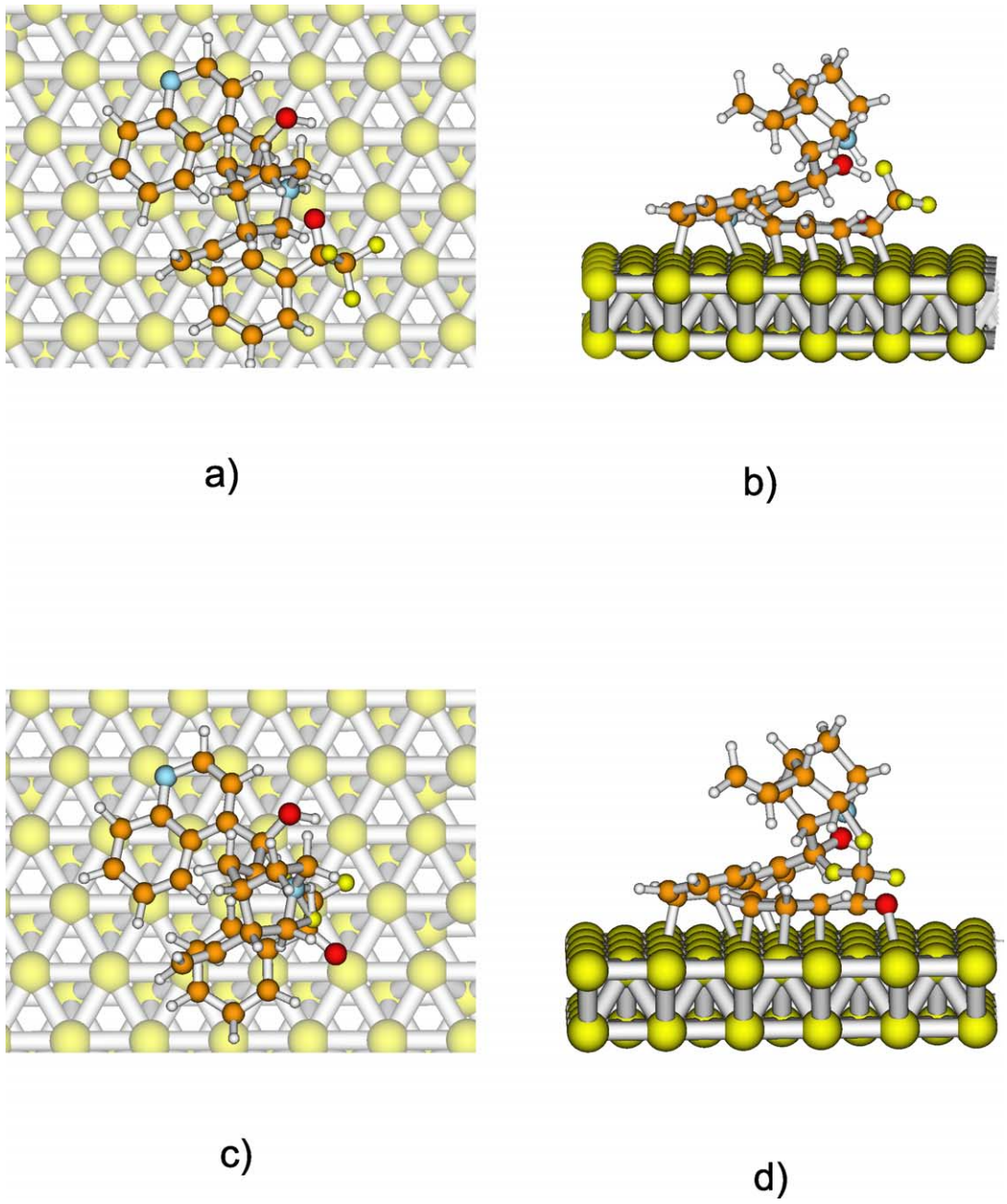

Fig. 11. Interaction of cinchonidine in a TSO(5) adsorption mode with trifluoroacetophenone pro-(*R*) (a and b) and pro-(*S*) (c and d).

imity of the modifier. ACHP and TFACPH have the peculiarity, compared to other nonaromatic substrates, that the bulky substituent, the benzene ring, unlike other substituents as, for example, the ester groups, is very close to the surface and occupies more space on the surface but less space above the surface. The element that can discriminate space above the surface is the methyl or trifluoromethyl group, in exactly the opposite way to the MP, for which the ester group is more bulky than the methyl, although both occupy space above the metal. Figs. 11a and 11b show that such an arrangement would allow interaction of the keto-carbonyl of the pro-(*R*) TFACPH (or pro-(*S*) ACPH) with the quinuclidine nitrogen, while Figs. 11c and 11d show that the relative position that leads to the opposite enantiomer has the keto-carbonyl oxygen pointing out of the chiral pocket.

Fig. 12 on the other hand shows another relative modifier/TFACPH geometry, in which the pro-(*R*) TFACPH can interact via the keto-carbonyl with the quinuclidine nitrogen, and via the fluorine with the hydroxyl group of the alkaloid. This second interaction is expected to be weak, but would be weaker for a pro-(*S*) than for a pro-(*R*)-adsorbed TFACPH, and would not occur with ACPH due to absence of the hydrogen bond with fluorine. The existence of a double interaction between hydroxy group of the modifier and fluorine could explain both the higher ee of TFACPH com-

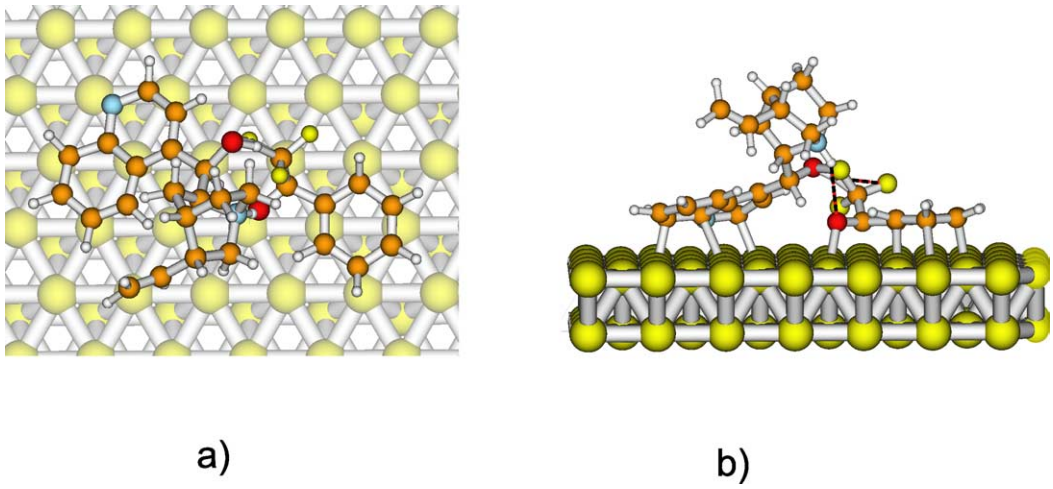

Fig. 12. Interaction of cinchonidine in a TSO(5) adsorption mode with trifluoroacetophenone pro-(*R*) with a double interaction between quinuclidine nitrogen and keto-carbonyl moiety and hydroxyl group of the alkaloid and fluorine.

pared to ACPH, and the loss of ee noted when *O*-methoxycinchonidine is used as modifier for the hydrogenation of TFACPH [21].

Although the preceding observations fit well to experimental results, it should be pointed out that the interaction space of cinchonidine is not simple, due to the flexibility of the modifier, and further studies with explicit calculation of all the interactions are needed to clarify and quantify the stabilizing effects that lead to enantiodiscrimination for different adsorbates.

3.5. *The conformations of cinchonidine on the surface*

The conformation in solution of cinchona alkaloids has been addressed in several studies [62,66,67,69–71], indicating that it can adopt six minimum energy conformations. The conformation with the lowest energy, indicated as Open(3), is generally considered responsible for the asymmetric induction, and most mechanistic studies (except [31]) published until now have used this conformation to model the reaction of enantioselective hydrogenation on cinchona-modified platinum. The conformational complexity was attributed to the possibility of the molecule to rotate around the bonds formed by C(4′)–C(9) and C(9)–C(8).

The effect of rotation around these axes was studied also for the cinchonidine adsorbed on platinum. Rotation around C(9)–C(8) in solution switches between Open and Closed conformations. The conformations produced on the surface due to rotation along this angle were addressed in the following way: for the Tilted Surface Open(3) conformation of Fig. 4a, dummy atoms were used instead of platinum atoms and the coordinates of the anchoring group and of the dummies were frozen, while the coordinates of the quinuclidine moiety were set free to optimize. The quinuclidine moiety was set in several closed conformations to sample the space, and a geometry optimization was run, in order to make a preliminary search of closed-type energy minima. The result was that cinchonidine always returned to the structures in Fig. 4a. Rotation around C(9)–C(8) did not produce minima in correspondence to closed structures, indicating that the conformational space of adsorbed cinchonidine when adsorbed tilted as in Fig. 4a was essentially different from that of cinchonidine in solution.

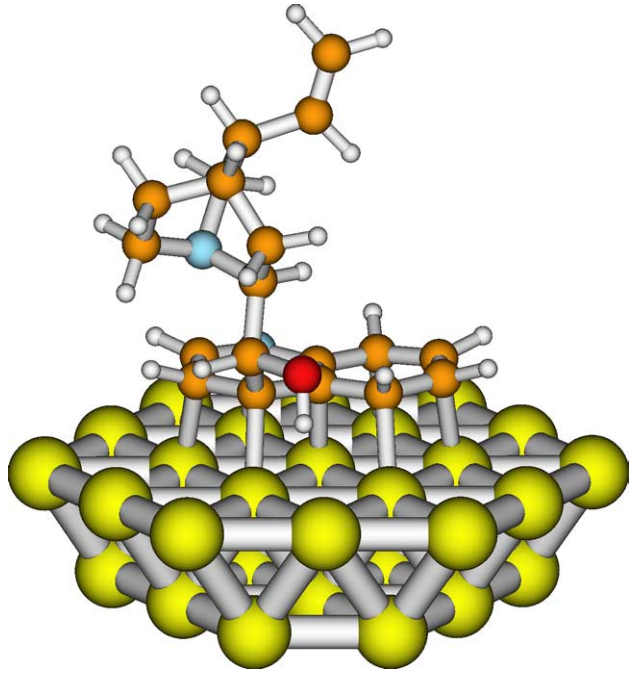

Fig. 13. A closed conformation of cinchonidine in the Parallel Surface adsorption mode of the anchoring group.

For the parallel adsorption mode of the alkaloid (Fig. 4b), on the other hand, one closed conformation was found, as shown in Fig. 13. The dihedral angle N(1)–C(8)–C(9)–C(4′) (numbering from Fig. 4a) in the conformations shown in Fig. 13 became 170°, showing that for this conformation the quinuclidine nitrogen points away from the space where a substrate could be adsorbed. A more complete study of the

conformational freedom of adsorbed cinchonidine requires further calculations, but both theoretical and experimental evidence are for now consistent with a major role played by Open conformations in the mechanism of enantiodifferentiation, in agreement with the hypotheses made for the interactions between modifier and substrate.

Rotation by 180° around the C(4′)–C(9) bond of the four conformations that have been described in the previous paragraphs can generate four other conformations, although their population on the surface might be limited by the equilibrium in solution that favors the Open(3) in apolar solvents with respect to the others [62]. Concerning the repulsive interactions between the surface species and the anchoring group, it is interesting to note that these can occur only when the ketone can be adsorbed on the 1-5 site (Fig. 5), therefore only when cinchonidine adopts a Surface Open(3) conformation, either tilted or parallel. By rotation of the anchoring group in the Surface Open(3) conformations, these repulsive interactions cannot take place. On the other hand for the Surface Open(5) conformation, either tilted or parallel, the rotation of the anchoring group, does not alter the chiral pocket, because the 1-5 adsorption of the ketone is hindered as shown in Fig. 9, and the contact with the anchoring group cannot take place. The selectivity in the interactions with a surface ketone remains therefore unaltered for the TSO(5) and PSO(5) conformations.

4. Conclusions

The adsorption of cinchonidine has been modeled by calculating the adsorption of the anchoring group (1(*S*)-(4-quinolinyl)ethanol) on a platinum cluster, and then by separately introducing and optimizing the quinuclidine moiety. The resulting structures of the adsorbed alkaloid are in good agreement with proposed structures based on experiments. By analyzing the minimum energy structures that resulted from the rotation of the C(9)–C(8) and C(4′)–C(9) bonds, four surface conformations were found, two of which, named Tilted Surface Open(5) and Parallel Surface Open(5), had the quinuclidine moiety sufficiently close to the surface to admit interactions with a chemisorbed ketone, while the other two, named Tilted Surface Open(3) and Parallel Surface Open(3), had the quinuclidine moiety more distant from the surface. Furthermore, for the two Surface Open(5) conformations the interactions with the reactant take place far from the anchoring group and thus the interaction between the latter and the reactant is unimportant and independent from the rotation around the C(4′)–C(9) bond. The alkaloid adsorbed on the platinum surface could form a tridimensional space within which the hydrogenation reaction can preferentially occur, due to a close interaction with the quinuclidine nitrogen. This space was called *chiral pocket* in analogy to biological systems that show high differentiation ability due to shape discrimination. The modulation of the chiral pocket, possible by O-alkylation of the hydroxylic moiety was found to be in line with the observed experimental variations of enantiodiscrimination when O-alkyl-modified cinchonidine was used as surface modifier.

Acknowledgments

Computing time has been provided by the ETH Zurich and by the Swiss Center for Scientific Computing (CSCS) in Manno. Financial support of the Swiss National Foundation is kindly acknowledged. Thanks are due to the technical staff of CSCS, and in particular to Carmelo Ponti and Claudio Redaelli.

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