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A theoretical investigation of the enantioselective hydrogenation mechanism of α -ketoesters

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Abstract

The enantioselective hydrogenation of α -ketoesters to α -hydroxyesters over Pt/Al₂O₃ catalysts modified by cinchona alkaloids is an interesting model reaction for the investigation of heterogeneous catalysis capable of producing optically active products. The aim of the present theoretical study is to rationalize the interaction between protonated cinchona alkaloids (modifiers) and methyl pyruvate (substrate) by investigating the possible weak complexes formed by these two species. For this purpose we use molecular mechanics and the AM1 semiempirical method. The optimization leads to two stable forms of the complexes, where the substrate is bound to the modifier via hydrogen bonding between the oxygen of the α -carbonyl of pyruvate and the quinuclidine nitrogen of the alkaloid. In such complexes the methyl pyruvate is transformed into a half-hydrogenated species which can be adsorbed on the platinum surface and, after hydrogenation, leads to methyl lactate product. The results show that adsorption of the complex leading to (*R*)-methyl lactate is more favorable than that of the corresponding system yielding (*S*)-methyl lactate, which may be the key for the enantio-differentiation.

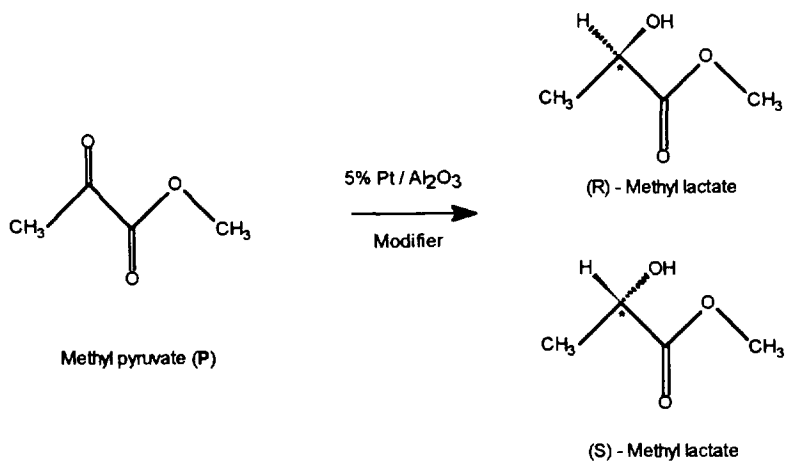
1. Introduction

The enantioselective hydrogenation of α -ketoesters to α -hydroxyesters using modified Pt/Al₂O₃ is an interesting model reaction for the investigation of heterogeneous catalysis capable of producing optically active products. By simply including cinchonidine, a chiral molecule, in the reaction mixture (cf. Scheme 1), it is possible to obtain an enantiomeric excess of up to 90% with a high conversion rate. In their original paper, Orto et al. [1] reported that cinchona alkaloids with the same absolute configuration as cinchonidine induce preferentially the (*R*)-configuration of

the α -hydroxyesters, while the near-enantiomer cinchonine produces an excess of the (*S*)-enantiomer (cf. Scheme 2).

The aim of the present theoretical study is to rationalize the interaction between the cinchonidine modifier (**C**) and the methyl pyruvate substrate (**P**) and to explore whether the earlier experimental findings [2] and proposals [3] can be rationalized and possibly confirmed by calculations. Ab initio and semiempirical calculations [4] were recently performed to evaluate the structure and energies of **P** interacting with small systems representative of both the unprotonated and protonated nitrogen center of quinuclidine. They have shown that a protonated form of cinchonidine is more likely to interact with methyl

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Scheme 1.

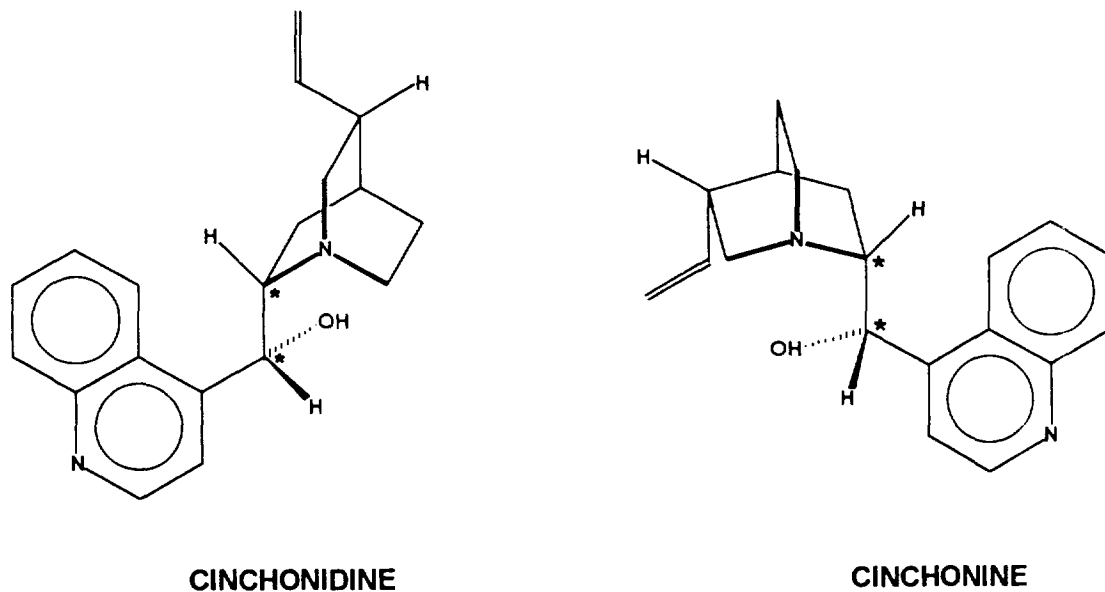
pyruvate. Therefore, possible structures of the complex formed by the whole protonated modifier and the substrate are investigated using molecular mechanics and the AM1 semiempirical method.

2. Methods

The molecular mechanics calculations on the P-protonated C complex have been performed using

the Amber force field [5] as implemented in the MACROMODEL [6] package and the semiempirical calculations were performed using the AM1 molecular orbital method [7] as implemented in the MOPAC (v. 5.10) program [8]. All the starting geometries for the AM1 calculations were obtained using the Amber force field. 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.



Scheme 2.

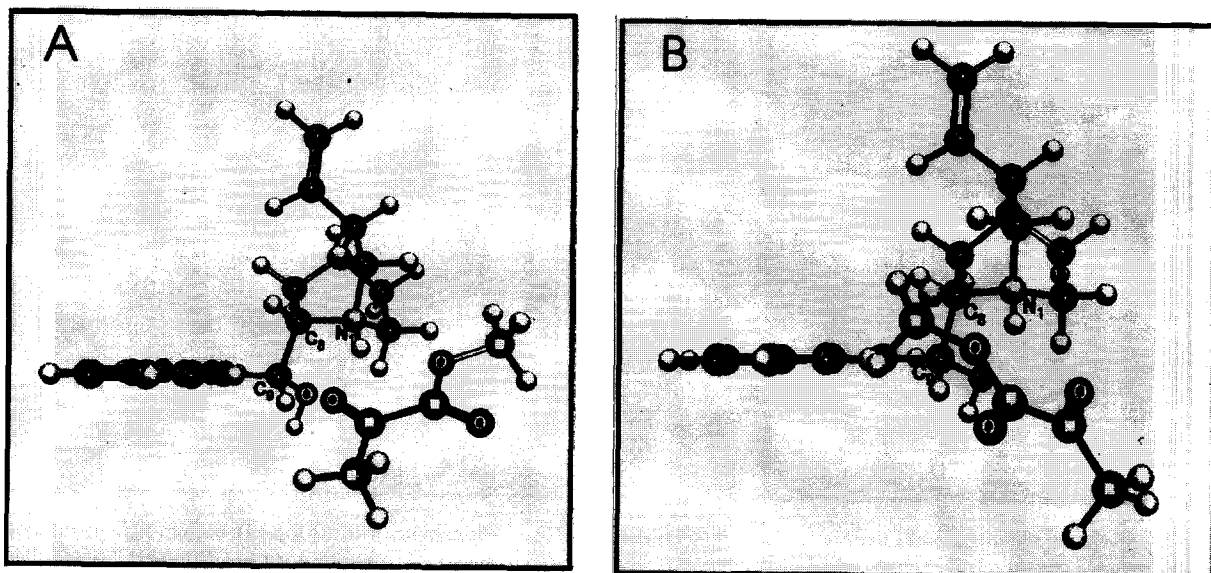


Fig. 1. Side view of the energetically most favorable complexes formed between protonated **C** and **P** which could yield (*R*)-methyl lactate (A) and (*S*)-methyl lactate (B), respectively, on hydrogenation. Note that the quinoline ring is placed perpendicular to the drawing plane. For the sake of clarity the carbon of the reactant **P** are marked with a white square and the oxygen atoms with an O.

3. Results and discussion

We have found that the AM1 structure of the protonated **C**–**P** complex is quite similar to that predicted by the Amber force field. Therefore, AM1 results only will be presented here. Fig. 1 displays 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. 1(A)) and (*S*)-methyl lactate (Fig. 1(B)), respectively. Note that these two complexes are practically equally stable, the AM1 energy difference between them being $1.4 \text{ kcal mol}^{-1}$ in favor of the (*R*)-methyl lactate. The corresponding top views of the complexes are displayed in Fig. 2(A) and 2(B). 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 1(A) and 2(A)), 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 1(B) and 2(B)) due to steric hindrance. The opposite behavior 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*)-methyl lactate is strongly sterically hindered. These conclusions are based on arguments which take account of steric interactions only and no energy difference can be reported at this moment to substantiate our model. However, they 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 modeling approach, taking into account **P**, **C** and the steric constraints imposed

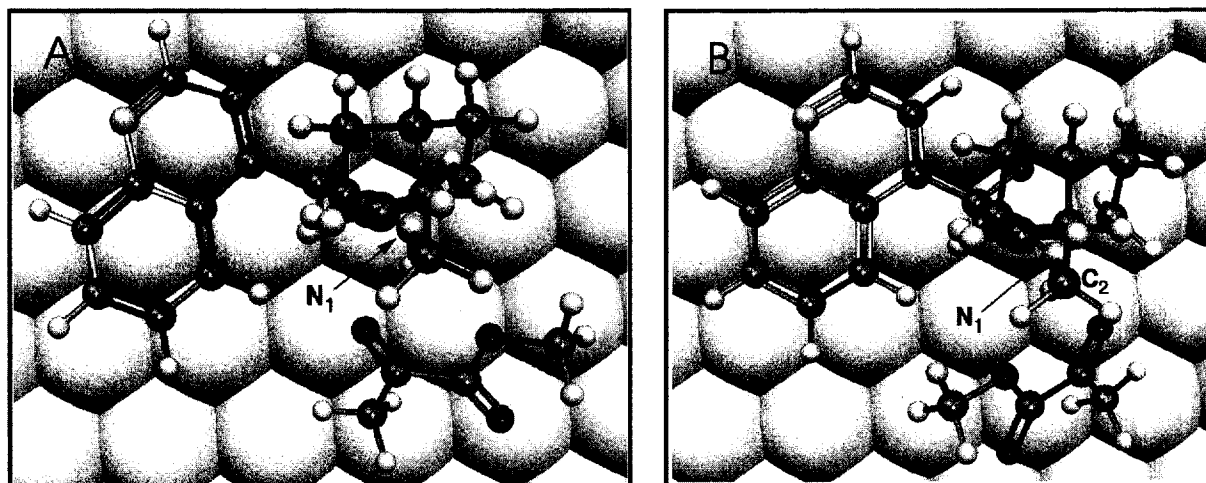


Fig. 2. Top view of the energetically most favorable complexes shown in Fig. 1. The complex with the top-left, bottom-right orientation of the carbonyl groups relative to the central C–C bond of **P**, shown in (A), is suggested to be precursor to (*R*)-methyl lactate, while complex (B) would yield (*S*)-methyl lactate. The complexes have been accommodated on a space-filling model of platinum (111) surface in order to illustrate the space requirements of the adsorbed complexes.

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**-protonated **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 , Fig. 1) of the cinchona alkaloid used as a modifier results in a corresponding change of the chirality of the product formed.

4. Conclusions

The present theoretical results show that in the protonated **C**–**P** complexes the substrate is

transformed to 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 [2].

Acknowledgments

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