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Catalysis Today 107–108 (2005) 31–39
CATALYSIS TODAY
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The interaction between amines and methyl pyruvate involving protonated species

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Available online 24 August 2005

Abstract

The mechanism for enantioselective catalytic heterogeneous hydrogenation of α-ketoesters is still under debate. In the present paper, ab initio calculations were used to study the interaction between protonated amines and methyl pyruvate (MP), as well as between protonated MP and these amines. It has been suggested that interactions mediated by a proton between the pyruvic acid ester and the alkaloid are the main driving force leading to enantiodifferentiation in the hydrogenation of α-ketoesters. MP interacts with protonated amines preferentially in the *s-cis* conformation, with a proton making two hydrogen bonds to the carbonyl oxygens. This proton may be transferred to MP, forming a new complex in which the amines are bonded to the protonated MP. The last complex is approximately 10 kcal mol^{-1} less stable than the first one. However, this energy difference decreases to approximately 5 kcal mol^{-1} when solvent effects are included. This introduces new possibilities for the mechanism of MP hydrogenation.

Keywords: Heterogeneous catalysis; Reaction mechanisms; Ab initio calculations; Enantioselective hydrogenation

1. Introduction

Heterogeneous enantioselective catalysis has been described in the literature since 1932 [1]; however, high enantiomeric excesses (EES) for asymmetric hydrogenation on noble metal-supported catalysts were only obtained in 1979, when Orito et al. described the hydrogenation of α-ketoesters on a supported platinum catalyst modified by cinchonidine [2]. In fact, the application of supported platinum catalysts modified by cinchona alkaloids for the hydrogenation of ethyl pyruvate is a successful case of high optical yield. Under optimal conditions, EES of up to 95% have been reported [3,4].

Several models have been proposed to explain the origin of the enantiodifferentiation observed in hydrogenation of ethyl pyruvate [5–13]. Most frequently, interactions between the substrate and the cinchona moieties are invoked as the main origin of the forces inducing enantioselectivity. Although several molecular modelling approaches have been employed to study these interactions [5–10], the net mechanism for the type of interaction involved between the α-ketoester substrate and the cinchona modifier is not yet fully understood [14,15]. A reasonable proposal is that the

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doi:10.1016/j.cattod.2005.07.114

nucleophilic nitrogen atom of the quinuclidine moiety of the modifier would interact with the electrophilic ketonic carbon atom of pyruvate, thereby hindering one side of the substrate from further hydrogenation [10–12]. However, recent ab initio and semi-empirical quantum calculations do not support this hypothesis [16,17]. These calculations showed that the interaction between cinchonidine and methyl pyruvate, calculated by placing methyl pyruvate near the cinchonidine molecule in different orientations and fully optimising the resulting complex, revealed a stabilisation energy of less than 3.5 kcal mol^{-1}, predominantly due to van der Waal's non-covalent forces [16]. These interactions, therefore, cannot be responsible for the selective forces leading to enantiodifferentiation. Besides, in the final optimised complex, a clear differentiation between a pro-*R* and a pro-*S* complex was not possible, either from a geometric or from an energetic point of view [16].

On the other hand, Baiker and Bürgi [5,6] have proposed an alternative mechanism in which protonation of the modifier followed by its interaction with methyl pyruvate is the driving force for enantiodifferentiation. Protonation of the quinuclidine nitrogen atom resulted in a structure ready to preferentially interact with the *s-cis* conformer of methyl pyruvate. This complex, when adsorbed on the metallic surface, would also prevent one side of the substrate from hydrogenation. In this case, as well as in the neutral mechanism, steric hindrance of the anchoring quinoline moiety would result in preferential formation of the complex leading to the *R*-product.

A model complex between the ammonium ion and methyl pyruvate was computed and resulted in a much more stable complex than the corresponding one with the neutral ammonia molecule, due to favourable electrostatic interactions [5]. However, ab initio calculations at the Hartree–Fock level by Bürgi and Baiker for the interaction between methyl pyruvate and protonated cinchonidine did not reveal any preferential stabilisation of the pro-*R* over the pro-*S* complex, mainly when solvation effects were included in the calculations [6]. Indeed, these authors concluded that such complexes are quite flexible and that repulsions between methyl pyruvate and the quinoline ring play an important role in enantiodifferentiation [6]. Recent calculations by Vayner et al. [7] suggest the formation of a zwitterionic adduct between the cinchonidine and methyl pyruvate over the metal surface. The enantioselectivity is rationalised in terms of differences in stability of the two diastereoisomers of the intermediate zwitterion.

Protonation of the modifier may be promoted by the solvent. Experimental results show a clear solvent effect on the optical yield, especially when protic solvents are used. Higher EES values (97%) were obtained when acetic acid was used as the solvent [3,4]. Under the same conditions, toluene, the solvent used second most often, usually affords lower enantiomeric excess [3,4]. In a recent work by Bartók et al. using β-isocinchonidine as the modifier, different enantiomers were obtained depending on the solvent employed [18]. For acetic acid as solvent, the expected (*R*)-lactate was obtained. In contrast, when using toluene the (*S*)-lactate was preferentially formed. This was attributed to a change in the mechanism from hydrogen bonding in acetic acid to nucleophilic attack in toluene [18]. Therefore, any mechanism proposed for this catalytic reaction should also consider the relevant role played by the solvent.

To shed some light on interactions between the methyl pyruvate molecule and the cinchona modifier in a protic medium, we employed high-level ab initio methodologies to calculate the interactions between protonated model amines (ammonia, trimethylamine and quinuclidine) and methyl pyruvate. Calculations with model compounds that mimic the behaviour of the full system should give important information on the nature of the donor–acceptor interactions supposed to be present. In addition, we also investigated the reverse possibility, calculating the interactions between the model amines and protonated methyl pyruvate. Solvent effects were included, using an isodensity surface-polarised continuum model (IPCM from Gaussian 98) [19]. Based on these calculations, we propose a stepwise mechanism for hydrogenation of α-ketoesters that may help gather better understanding of the enantiodifferentiation mechanism at the molecular level, helping to elucidate the roles of the several players present in this catalytic reaction.

2. Methodology

The second-order Möller–Plesset perturbation (MP2) theory, with the 6-31G(d,p) basis set [20], was used to calculate the interaction between methyl pyruvate (MP) and the ammonium and trimethylammonium ions. Due to the size of the system, calculations involving the quinuclidinium ion were carried out at the MP2/6-31G(d) level. In each case, both the *s-cis* and *s-trans* conformers of methyl pyruvate were used. For these complexes, the starting geometries were designed in an arrangement favouring the formation of hydrogen bonds between the two species. The geometries of the complex and that of the individual units were fully optimised at the corresponding computational level.

Several forms of protonated MP were also optimised and their interaction with ammonia, trimethylamine [at MP2/6-31G(d,p)] and quinuclidine [at MP2/6-31G(d)] were calculated. In this case, the starting geometries were designed in two ways, either favouring the formation of hydrogen bonds between the two interacting species or favouring interactions between the nucleophilic amines and the electrophilic ketonic carbon atom of the protonated MP. Once again, the geometries of each complex and of the individual units were fully optimised. During the optimisation process, the amines either abstracted the hydrogen from protonated MP (when starting from a geometry favouring hydrogen bond) or directly added to it (when starting from a geometry favouring orbital interaction).

The energy of interaction between the two species forming a weak van der Waals' complex was corrected for the basis set superposition error (BSSE) using the method of counterpoise correction [21]. In this method, the energy of each subunit is calculated with ghost atoms replacing the atoms of the second subunit. This usually gives a lower energy than that calculated without the ghost atoms. As a consequence, the interaction energy is also reduced. The final interaction energy, corrected for BSSE, is calculated as the difference between the energy of the complex and that of the species at infinite separation.

Solvent effects were simulated using the isodensity surface polarised continuum model (IPCM) [19]. This method calculates the electric field analytically and defines a cavity in the solvent based on an isosurface of the total electron density of the solute, calculated at the level of theory being applied [19]. The solvent effects are thus derived from interaction of the potential isosurface with the dielectric continuum. As recommended for the simulation of water as the solvent, a dielectric constant of $\varepsilon = 78.39$ was used. For simulation of toluene, the dielectric constant $\varepsilon = 2.38$ was employed.

The GAUSSIAN98W software package [22] was used in all ab initio calculations.

3. Results and discussion

Protonation of the nitrogen atom of the quinuclidine moiety of cinchonidine has been described as the first step in the enantioselective hydrogenation mechanism proposed by Baiker and Bürgi [5,6]. The interaction between the protonated nitrogen and the oxygen of the ketonic group of MP, via hydrogen bonding, would promote enantiodifferentiation due to different steric hindrances with the aromatic quinoline moiety. It would also be responsible for the observed rate acceleration effect in the hydrogenation reaction [5].

At a first glance, both the modifier and the substrate could be protonated in a protic reaction environment. However, the basicity of the modifier is considerably higher than that of MP, probably precluding protonation of the latter. MP2/6-31G(d,p) calculations [MP2/6-31G(d) for quinuclidine] show that the proton affinity of ammonia, trimethylamine and quinuclidine is higher than that of MP by 16.1, 36.5 and 46.4 kcal mol^{-1}, respectively, as calculated by the isodesmic equations given in Table 1. These relative proton affinities reflect the increasing basicity of the amines.

Table 2
Solvation energies [MP2/6-31G(d,p)] (kcal mol^{-1}) of the neutral and cationic species, calculated as the energy difference between the species in the solvent and in the gas phase

	$\varepsilon = 2.38$	$\varepsilon = 78.39$
Neutral species		
NH_3	−2.37	−5.09
$N(CH_3)_3$	−0.90	−2.08
Quinuclidine	−1.22[a]	−2.99
MP	−3.01 (−6.81)[b]	−6.75 (−7.23)
Cationic species		
NH_4^+	−49.77	−84.78
$HN(CH_3)_3^+$	−34.39	−59.64
Quinuclidine ion	−30.50	−53.15
Protonated MP	−30.04 (−31.05)	−56.55 (−59.20)

[a] MP2/6-31G(d) for quinuclidine.
[b] The values in parentheses are related to the solvation energies at the MP2/6-31G(d) level.

However, the basicity of the amines is strongly affected by the solvent. While basicity in the gas phase increases in the order ammonia < trimethylamine < quinuclidine, in water this order is reversed, with ammonia being the strongest base [23]. This change in the relative basicity results from preferential solvation of the smaller NH_4^+ cation compared to the solvation of either the trimethylammonium or quinuclidinium ion. Calculated relative proton affinities in toluene and water are also given in Table 1. The higher proton affinity of the amines is stressed in both solvents. The stronger effect is calculated for ammonia, and the weaker one for quinuclidine. In toluene, the relative proton affinities increase to 36.5 kcal mol^{-1} ammonia, 43.0 kcal mol^{-1} trimethylamine and 51.5 kcal mol^{-1} quinuclidine, while in water they are all of the same magnitude, approximately 44–46 kcal mol^{-1}. The main effect of the solvents comes from the higher solvation energy of the cationic species (Table 2), with the smaller cations more strongly solvated than the larger ones. In addition, water (more polar solvent) solvates the cations more strongly than toluene (Table 2). Therefore, the relative proton affinity of ammonia increases by approximately 20.4 kcal mol^{-1} in toluene and by almost 30.0 kcal mol^{-1} in water (Table 1). In contrast, for the larger amine quinuclidine, the relative proton affinity in toluene increases by only 5.1 kcal mol^{-1}, while in water it even decreases by 1.8 kcal mol^{-1}.

For cinchonidine, a gas-phase proton affinity of the same magnitude as that calculated for quinuclidine could be foreseen. The effect of the solvent, however, should be less pronounced than on quinuclidine. Due to the higher size of

Table 1
MP2/6-31G(d,p) relative proton affinity as expressed by ΔE (kcal mol^{-1}) for the isodesmic equations below

Isodesmic equation	Gas phase $\varepsilon = 1.00$	Toluene $\varepsilon = 2.38$	Water $\varepsilon = 78.39$
$NH_3 + MPH^+ \rightarrow NH_4^+ + MP$	−16.08	−36.45	−45.96
$N(CH_3)_3 + MPH^+ \rightarrow HN(CH_3)_3^+ + MP$	−36.50	−42.96	−44.26
Quinuclidine + $MPH^+ \rightarrow$ quinuclidineH^+ + MP	−46.42[a]	−51.47	−44.62

[a] MP2/6-31G(d) for quinuclidine. For MP the most stable *s-trans* conformer was employed. For MPH^+ the most stable *s-cis* conformer was employed.

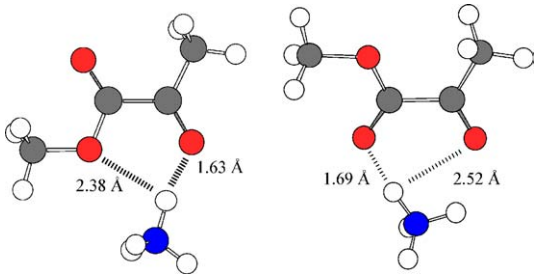

Fig. 1. Complexes [MP2/6-31G(d,p)] between MP and the ammonium ion.

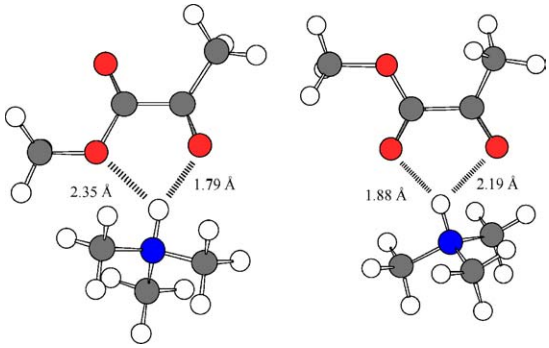

Fig. 2. Complexes [MP2/6-31G(d,p)] between MP and the trimethylammonium ion.

the protonated cinchonidine, it should have a lower solvation energy, so that the relative proton affinity of cinchonidine in water should be lower (less negative) than that of quinuclidine.

These results clearly indicate that protonation of the modifier, instead of protonation of the substrate, must be, thermodynamically, the most probable event. Thus, in the next step, we calculate the interaction between MP and three protonated model systems: ammonia, trimethylamine and quinuclidine.

3.1. Interaction between MP and protonated amines

Protonation of ammonia yields the tetrahedral ammonium ion, which interacts with MP by means of hydrogen bonds to the carbonyl oxygen atoms. Fig. 1 shows two optimised structures for the ammonium ion–MP complexes, taking both the *s-cis* and *s-trans* conformers of MP. The *s-cis* complex is more stable by 6.3 kcal mol^{-1}, which reverts the relative stability order of the *s-cis* versus the *s-trans* conformers of MP. In the gas phase, the *s-trans* conformer of MP is 1.6 kcal mol^{-1} more stable than the *s-cis* form [25]. In the complex with the *s-cis* conformer of MP, both carbonyl oxygens bind to hydrogens of the ammonium ion via hydrogen bonds (Fig. 1). The intermolecular N···C (C of the keto group) distance in the *s-cis* complex is approximately 3.6 Å, a value slightly higher than that found previously at the MP2/3-21G level [26]. The BSSE corrected interaction energy for the *s-cis* complex is 34.2 kcal mol^{-1}, while that for the *s-trans* complex is 26.3 kcal mol^{-1} (Table 3). These values are of the same magnitude as those calculated before with a smaller basis set [26], but significantly higher than those obtained for non-protonated complexes (approximately 3–4 kcal mol^{-1}) [13]. The higher stabilisation energy of the ionic complex is mainly due to the strong hydrogen bonds found in this case and to the dispersion of the positive charge of the ammonium ion into the MP molecule, as shown by the Mulliken charges of the NH_4^+ moiety, which adds up to only 0.922 e$^-$.

The calculated interaction energy between the MP and the trimethylammonium ion is 27.9 kcal mol^{-1} for the *s-cis* conformer and 20.7 kcal mol^{-1} for the *s-trans* conformer (Table 3). The *s-cis* complex is more stable than the *s-trans* form by 5.9 kcal mol^{-1}. The hydrogen bond distances are slightly increased when compared to the complex between the ammonium ion and MP (see Fig. 2). Lower interaction energies and longer hydrogen bonds for the complexes with the trimethylammonium ion compared to the ammonium ion may be due to the stronger repulsive interactions between the bulky methyl groups of the trimethylammonium ion and the MP molecule. The total Mulliken charge in the trimethylammonium moiety adds up to 0.933e$^-$.

For the complexes between MP and the quinuclidinium ion, the MP2/6-31G(d) interaction energy is 25.5 kcal mol^{-1} for the *s-cis* conformer of MP and 18.8 kcal mol^{-1} for the *s-trans* conformer (Table 3). The *s-trans* versus *s-cis* energy difference is reduced to 5.3 kcal mol^{-1}. The hydrogen bond distances are of the same order of magnitude (Fig. 3) as those calculated for complexes between the trimethylammonium ion and MP. The total Mulliken charge density in the quinuclidine moiety amounts to 0.939e$^-$.

The values for the interaction energy discussed above indicate that they are stronger for the smaller cation, decreasing gradually as the size of the cation increases, although the difference in the interaction energy of the complexes with the trimethylammonium ion and the quinuclidinium ion is of the order of only 2.0 kcal mol^{-1}. Higher charge concentration in the smaller cation, as well as

Table 3
Interaction energies (kcal mol^{-1}) of the complexes between MP and the ammonium ion, the trimethylammonium ion [MP2/6-31G(d,p)] and the quinuclidinium ion [MP2/6-31G(d)], corrected for BSSE

	s-cis			*s-trans*		
	$\varepsilon = 1.00$	$\varepsilon = 2.38$	$\varepsilon = 78.39$	$\varepsilon = 1.00$	$\varepsilon = 2.38$	$\varepsilon = 78.39$
NH_4^+	−34.18	−17.11	−7.04	−26.34	−11.41	−1.92
$HN(CH_3)_3^+$	−27.92	−18.65	−8.63	−20.68	−13.82	−6.36
Quinuclidine ion	−25.47	−18.45	−13.22	−18.82	−11.14	−10.52

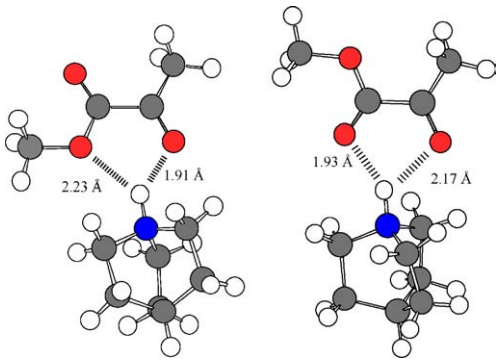

Fig. 3. Complexes [MP2/6-31G(d)] between MP and the quinuclidinium ion.

stronger steric repulsion in the larger ones, may explain the different behaviours of the protonated amines. As the cation increases in size, charges become more dispersed, leading to weaker interaction with MP. Steric repulsions may also play some role in reducing the interaction energy of the larger protonated amines.

Solvent effects strongly modify this picture. Due to the much higher solvation energy of the smaller protonated amines compared to the solvation energy of the complexes (Tables 2 and 4), the interaction energy in apolar (toluene) and polar (water) solvents is strongly reduced (Table 3). In toluene, the stabilisation energy is essentially constant for the three complexes, at approximately 18 kcal mol^{-1} for the *s-cis* complexes and approximately 11–13 kcal mol^{-1} for the *s-trans* complexes. In water, these values are reduced even further. However, in this case the complexes become stronger as the size of the amines increases. For the *s-cis* complexes, the stabilisation energy increases from 7.0 kcal mol^{-1} in the case of the ammonium ion to 8.6 kcal mol^{-1} for the trimethylammonium ion and to 13.2 kcal mol^{-1} for the quinuclidinium ion. Similarly, for the *s-trans* complexes, the interaction energy increases from 1.9 to 6.4 and to 10.5 kcal mol^{-1}, respectively. The solvent reduces the energy difference between the *s-cis* and *s-trans* complexes. The *s-cis* complexes are always more stable than the corresponding *s-trans* forms by at least 2.0 kcal mol^{-1}, with the only exception the complex between the quinuclidinium ion and MP in water, for which the *s-trans* complex is more stable by 1.3 kcal mol^{-1}.

In fact, solvation not only reduces the interaction energy between the two species, but also reverses the order for that interaction energy. As shown above, in the gas phase the order of interaction of the protonated amines with MP is ammonium ion > trimethylammonium ion > quinuclidinium ion. In solvent, however, this sequence changes. In toluene the three protonated amines interact with MP with almost the same intensity, while in water the order of interaction is quinuclidinium ion > trimethylammonium ion > ammonium ion. The origin of this reversal lies in the differential solvation of the cationic species. The smaller protonated amines are more strongly solvated than the corresponding complexes with MP. This differential solvation has the greatest effect in the case of the ammonium ion, for which the interaction energy becomes very low. For the larger quinuclidinium ion, the interaction energy increases again.

Table 4
Solvation energies [MP2/6-31G(d,p)] (kcal mol^{-1}) of the *s-cis* complexes between MP and protonated amines, calculated as the energy difference between the species in the solvent and in the gas phase

Complexes	$\varepsilon = 2.38$	$\varepsilon = 78.39$
NH_4^+ + MP	−34.97	−64.07
$HN(CH_3)_3^+$ + MP	−25.71	−45.10
Quinuclidine ion + MP	−23.96[a]	−42.26

[a] MP2/6-31G(d) for the quinuclidinium ion.

The discussion above indicates that although the gas-phase basicity of the amines increases in the order ammonia < trimethylamine < quinuclidine, this is not reflected in a stronger interaction of the protonated forms of the amines with MP. The main source of the interaction between the protonated amines and MP are the hydrogen bonds formed between the acidic hydrogen of the protonated amines and the oxygen lone pairs of MP. Due to the acid–base conjugated pair relationship, the acidity of the protonated forms increases in the reverse order of the basicity of the amines. Therefore, stronger interaction is found in the case of the more acidic ammonium ion, which is also reflected in shorter hydrogen bond distances. Weaker interactions are calculated for the less acidic quinuclidinium ion, with corresponding longer hydrogen bond distances. As solvation is stronger in smaller cations, it destabilises the complexes, thereby reducing the interaction energy and reversing the order of stability in the complexes.

In these complexes, the nitrogen atom of the amines moves to a position coplanar with the molecular plane of MP, where hydrogen bonds to the lone pair of the carbonyl oxygens of MP are stronger. This orientation of the protonated moiety is in clear contrast to that found in the case of neutral systems [16]. In the complex with MP, the neutral ammonia molecule occupies a position that is almost perpendicular to the molecular plane of MP, nearly equidistant from both carbonyl carbons [16]. In the neutral case, the interactions are much weaker and are mainly due to orbital interactions [16,17]. Therefore, in these two models of protonated and neutral complexes, the MP molecule assumes a distinctive orientation relative to the amines. Although the interactions are stronger in the protonated case, the rate acceleration effect observed in hydrogenation on the metallic surface is better interpreted in terms of orbital superposition, as indicated in the case of the neutral complexes [17].

3.2. Interaction between protonated MP and the amines

Despite the energetic advantage calculated for the protonation of amines compared to protonation of MP, an

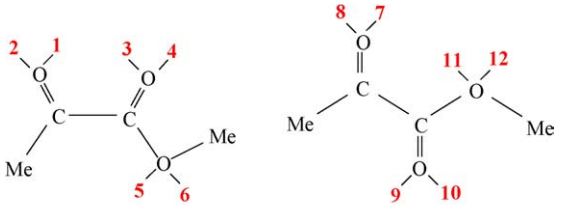

Fig. 4. Possible positions for protonation of MP.

Table 5
Relative energies [MP2/6-31G(d,p)] (kcal mol^{-1}) for isomeric protonated MP

Structure	ΔE	Structure	ΔE
1	3.57	7	6.36
2	12.46	8	11.90
3	0.00	9	10.06
4	12.64	10	12.53
5	29.24	11	17.26
6	31.06	12	23.49

interconversion involving protonated MP cannot be excluded a priori. Protonated MP may interact with the amines, forming a new covalent bond between the nitrogen atom of the amines and the carbon atom of MP, which could lead to a stabilised intermediate. Based on this hypothesis, we also calculated the interaction between protonated MP and the amines.

Protonation of MP can result in six isomeric structures for the *s-cis* and six for the *s-trans* conformers of MP. This occurs because any of the three oxygen atoms of MP can be protonated in at least two different positions (Fig. 4). The relative energies for the 12 conformers thereby obtained were calculated and are given in Table 5.

The most stable form of protonated MP (protonation in position 3, Fig. 4) is an *s-cis* conformer, resulting from protonation of the ester carbonyl oxygen. This conformation is stabilised by hydrogen bonding between the added hydrogen atom and the non-protonated carbonyl oxygen. It is also stabilised by the π-electron donor ability of the oxygen atom of the ester moiety, as depicted in Fig. 5. There are three resonance forms for the cation resulting from protonation of the ester carbonyl oxygen, in contrast to only two resonance forms when the ketonic carbonyl oxygen is protonated (protonation in position 1). The latter structure is the second most stable conformation. The most stable protonated *s-trans* conformation is that resulting from protonation in position 7 (Fig. 4), which exhibits a hydrogen bond between the added hydrogen and the oxygen atom of the ester moiety.

The relative energy (ΔE = 3.6 kcal mol^{-1}) between the two more stable *s-cis* conformers, 1 and 3, is not large enough to exclude the less stable conformer from interacting with other species. Therefore, we calculated the interaction of both these conformers, as well as of the most stable *s-trans* conformer of protonated pyruvate (structure 7), with ammonia, trimethylamine and quinuclidine. This interaction could, at least in principle, happen in two ways. It could either involve the formation of a hydrogen bond between the electron lone pair of the amine and the acidic hydrogen of protonated MP, or it could result from a direct interaction between the nucleophilic amine and the most electrophilic carbon atom of protonated MP.

When starting the optimisation with a geometry favouring the formation of a hydrogen bond as described above, the base abstracts the acidic hydrogen from protonated MP, converting it into a geometry in which the protonated base interacts with MP. The final structures are similar to those discussed in the previous section. Thus, they do not deserve any further discussion.

In the second arrangement, in which the lone pair of the amine interacts with the cationic carbon of protonated MP, the base adds directly to the protonated MP, with the formation of a covalent C–N bond. This occurs without any notable activation energy. The most stable species obtained after NR_3 addition to protonated MP are those with MP

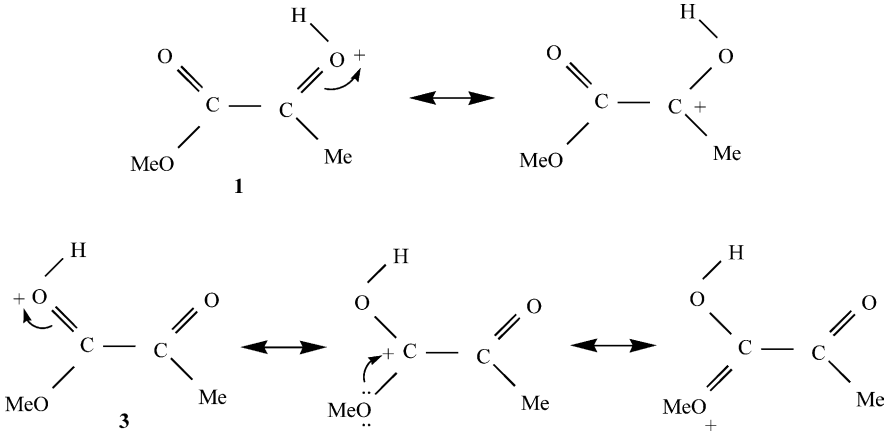

Fig. 5. Stabilization of protonated MP by the electron donor characteristic of the oxygen of the ester moiety.

Table 6
Relative energies (kcal mol^{-1}) of the structures formed by addition of ammonia, trimethylamine [MP2/6-31G(d,p)] and quinuclidine [MP2/6-31G(d)] to protonated MP

	Ammonia	Trimethylamine	Quinuclidine
1	0.78	0.00	0.00
3	20.43	14.22	14.70
7	0.00	1.00	1.02

Table 7
Interaction energies (kcal mol^{-1}) of complexes between protonated MP and the ammonia, trimethylamine [MP2/6-31G(d,p)] and quinuclidine [MP2/6-31G(d)]

	Ammonia	Trimethylamine	Quinuclidine
1	−42.99	−59.90	−68.12
3	−19.77	−42.10	−50.05
7	−46.56	−61.70	−69.93

protonated on the ketonic carbonyl oxygen—structures 1 and 7 (Table 6). The species obtained from protonation of the ester carbonyl oxygen (structure 3) has considerably lower stability. This may be ascribed not only to the lower number of hydrogen bonds formed in structure 3 compared to those in structures 1 and 7 (Fig. 6), but also to the higher degree of electronegative heteroatom substitution on the same carbon, as seen in structure 3. Thus, in the context of NR_3–protonated MP interaction, although MP protonation occurs preferably on the ester carbonyl, after interaction with the amines the favoured complexes are those obtained from protonation of the ketonic carbonyl moiety.

The interaction energies for the complexes between the amines and protonated MP are given in Table 7. As indicated, the interaction between protonated MP and the amines is considerably strong, especially for the species protonated on the carbonyl oxygen (positions 1 and 7). For quinuclidine this interaction energy may amount to 70 kcal mol^{-1}. This is of the same magnitude as the average bond enthalpy for a single carbon–nitrogen bond [24], showing that a true covalent bond was formed between the two species.

These interaction energies increase when going from ammonia to quinuclidine. This shows an opposite trend to that found in the case of the interaction between MP and the protonated amines, yet agreeing with the nucleophilicity scale of the amines. In addition, the larger amines have higher ability to disperse the positive charge of MP, therefore also contributing to the stronger interaction.

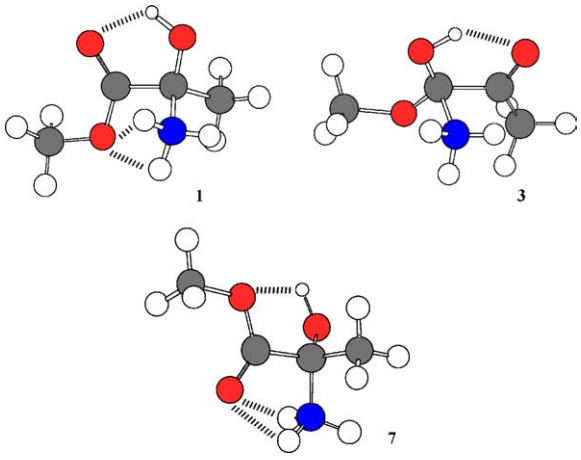

Fig. 6. MP2/6-31G(d,p) structures resulting from addition of ammonia to protonated MP.

3.3. Mechanism for substrate–protonated modifier interaction

The formation of an MP–R_3NH^+ complex has been suggested as the first step in the substrate–modifier interaction [5,6]. By means of further steps, this complex could thus evolve to other species, which would finally lead to the methyl-lactate. Fig. 7 shows a possible pathway for the hydrogenation process taking the ammonia molecule as a model for the modifier. After protonation of the modifier, a proton transfer may take place from the HNR_3^+ ion to the MP molecule. Although the NR_3 molecule is considerably more basic than MP (as discussed above), the formation of a cationic centre upon protonation of MP, which strongly interacts with the basic modifier, may compensate this basicity difference. This can be shown by the relative stability of species I and III of Fig. 7. In the case of ammonia, I is more stable than III by 10.0 kcal mol^{-1}, while for trimethylamine and quinuclidine, I is more stable than III by 9.7 and 9.1 kcal mol^{-1}, respectively. II is not a minimum on the potential energy surface, since the NR_3 molecule adds directly to the protonated MP without any energy barrier. Even when optimisation is started with a structure in which the protonated MP is far away from the amines, the final structure converges to one in which the nitrogen is chemically bonded to the cationic carbon. Therefore, the process of formation of III should occur in a concerted way. As soon as the proton is transferred to MP, the forming carbocation is stabilised by the addition of the NR_3 species, leading to III. The final step is hydride transfer from the metallic surface to the hydroxylic carbon, thereby releasing NR_3 and producing the α-hydroxyester. Complex III has a structure similar to that of the zwitterionic adduct proposed by Vayner et al. [7].

Calculation of solvent effects for the energy difference between complexes I and III indicates that in a polar solvent this process may be still more feasible. While complexes I and III in the case of ammonia have essentially the same solvation energy (Table 8), meaning that I is still considerably more stable than III (9.7 kcal mol^{-1} in toluene and 9.0 kcal mol^{-1} in water), for trimethylamine and quinuclidine, complexes III are more strongly solvated than complexes I by approximately 2.5 kcal mol^{-1} in toluene and 5.0 kcal mol^{-1} in water. This reduces the energy difference between complexes I and III to approximately 7.0 kcal mol^{-1} in toluene and 5.0 kcal mol^{-1} in water for both trimethylamine and quinuclidine. The

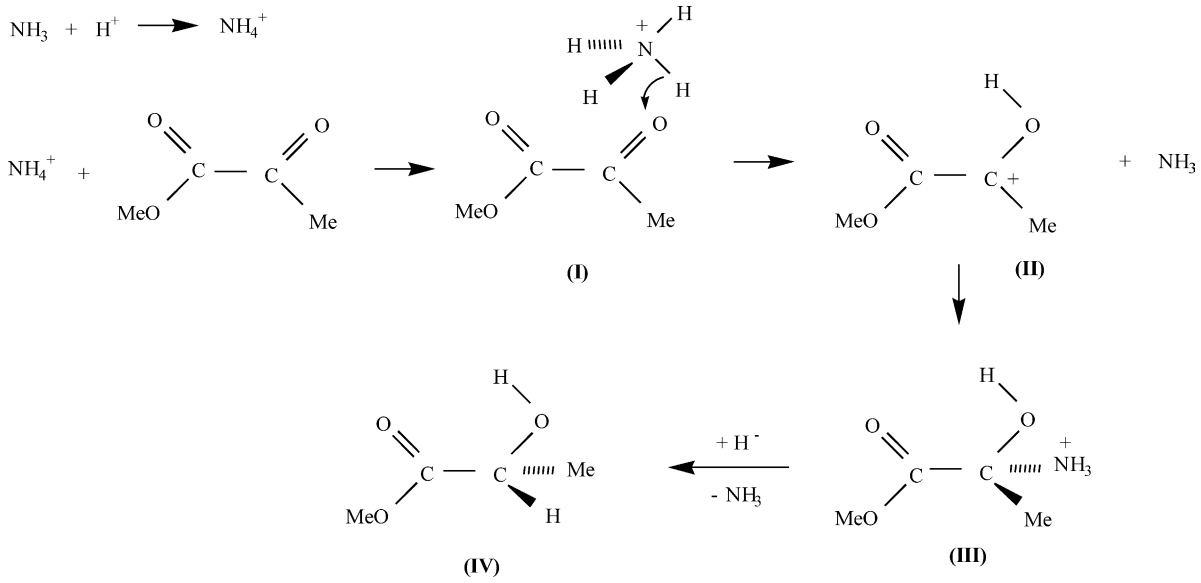

Fig. 7. Mechanism for proton transfer from the chiral modifier to the substrate.

above mechanism introduces new possibilities in the pathway for hydrogenation of α-ketoesters, in which intermediate III probably plays a relevant role.

The energetic behaviour of this mechanism may be summarised as follows. The formation of the MP–HNR_3^+ complex (I) from isolated MP and HNR_3^+ is exothermic by 34.2 kcal mol^{-1} in the case of ammonia, by 27.9 kcal mol^{-1} in the case of trimethylamine and by 25.5 kcal mol^{-1} in the case of quinuclidine. The proton transfer from HNR_3^+ to MP followed by NR_3 addition to the protonated MP (III) is endothermic by 10.0 kcal mol^{-1} in the case of ammonia, by 9.7 kcal mol^{-1} in the case of trimethylamine and by 9.1 kcal mol^{-1} in the case of quinuclidine. This picture changes when solvent effects are included. Solvation of the protonated amines varies considerably, being stronger for the smaller cations. This not only reduces the energy of interaction between MP and HNR_3^+, but also reverts the order of interaction, which becomes stronger for the less solvated quinuclidinium ion. However, the most relevant result is the reduction in the energy difference between complexes I and III. In a protic medium, the formation of protonated amines should be a fast process and the more basic amines should exist mainly in the protonated form.

Table 8
Solvation energies [MP2/6-31G(d,p)] (kcal mol^{-1}) of complexes I and complexes III

	$\varepsilon = 2.38$		$\varepsilon = 78.39$	
	I	III	I	III
NH_3	−64.07	−65.03	−34.97	−35.30
$N(CH_3)_3$	−45.10	−50.17	−25.71	−28.32
Quinuclidine	−42.26[a]	−47.62	−23.96	−26.32

[a] MP2/6-31G(d) for quinuclidine.

Therefore, following the mechanism proposed in the present work, a fundamental step would be proton transfer from the protonated amine to MP, leading to complex III. As shown above, the polar solvent preferably stabilises these complexes, reducing their relative energy to a value at which they may play a significant role. Of course, we assume that the last step in Fig. 7, hydride transfer followed by NR_3 elimination, is a fast step. In this manner, complex III should represent a transition state analogue for the entire mechanism. The present mechanism is also consistent with the observed rate-acceleration effect in the presence of the modifier. Protonation of MP as the rate-determining step is facilitated by the simultaneous addition of NR_3 to the forming protonated MP. This would stabilise the intermediate, thereby increasing the reaction rate.

A question that may arise is whether these results may be translated to the larger cinchonidine system. Although at a first sight there seems to be some steric effect due to the quinoline ring of cinchonidine, this should have only negligible effects on the above results. The potential energy surface for rotation around the C_4–C_9 and C_8–C_9 bond of cinchonidine is rather flat [16], so open conformations may always be adopted. In these conformations, after complexation with MP, low-energy interaction between the MP molecule and the quinoline ring may come into play. Either in complexes I or III, the results calculated above should be maintained in the case of interaction of MP and cinchonidine. This may also be a consequence of the relatively strong complex found in both cases. These results should be true not only in the case of a protic medium, but also in the case of a non-polar medium. In the latter case, our activated complex should correspond to the zwitterionic adduct of Vayner et al. [7] or to the half-hydrogenated state suggested by Wells et al. [12].

4. Conclusions

The protonation of either the modifier or the substrate in an acidic medium constitutes a plausible alternative for the enantioselective pyruvate hydrogenation process. The interaction energy between MP and the protonated modifier is substantially greater than that involving neutral species. This interaction occurs preferentially with the *s-cis* conformer of MP, being mainly stabilised by hydrogen bonds. Interactions of MP with protonated amines in the gas phase increase in the order ammonia > trimethylamirimethylamine > quinuclidine. This order, however, is reversed in a polar solvent, in which the larger quinuclidinium ion interacts more strongly.

Alternatively, protonation of MP may occur on the ester carbonyl oxygen of the *s-cis* conformer, which has greater electronic density. However, after interaction with the amines, the structure formed by protonation of the ketonic carbonyl oxygen has lower energy. Although this last complex (protonated MP + amine) is less stable than the first one (protonated amine + MP) by approximately 10 kcal mol^{-1}, it is preferentially stabilised in a polar solvent, thereby reducing its relative energy to approximately 5 kcal mol^{-1}.

These results suggest an alternative pathway for hydrogenation of MP, in which protonation of the modifier is followed by proton transfer to MP. The latter step may occur with the simultaneous addition of NR_3 amine to the protonated MP. The hydrogenation process may be concluded in a subsequent step involving hydride addition and NR_3 elimination.

Acknowledgements

J.W. de M.C., F.B.P., D.A.G.A. and O.A.C.A. are the recipients of research fellowships from CNPq. C. da S.B. de O. and P.R.N. de S. are the recipients of graduate fellowships from CNPq. Grant 62.0211/97-0 from PADCT III QEQ/ CNPq provided partial support for this work.

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