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Enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester using cinchonine-modified Pd/Al_2O_3 catalysts

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Abstract

The enantioselective hydrogenation of (*E*)-*N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester was investigated using cinchonine-modified Pd/Al_2O_3 catalysts. The catalysts were evaluated for this reaction using methanol as solvent with various cinchonine:NADPME molar ratios. Enantioselectivity was sensitive to this ratio as well as to the solvent, and in general, ee increased with the polarity of the solvent. The highest ee of 33% was observed with DMF/water as solvent, but attempts to improve upon this have been unsuccessful. We used combined structural modification of the reactant and alkaloid together with computer simulations to gain insight into why the low enantioselectivity persists. Using this approach, we propose a model in which NADPME interacts as a monomer with cinchonine via hydrogen bonding between the protonated quinuclidine-*N* of cinchonine and the hydrogen bond acceptor functional groups of NADPME, which induces enantioselection. DFT level calculations of these interactions show that N–H. . .O=C hydrogen bonding gives the most stable complexes and that the lowest pro-*S* and pro-*R* dimer forms are practically isoenergetic, although higher energy dimer pairs show discrimination, thereby helping to explain the disappointing ee obtained to date.

Keywords: Hydrogenation; Heterogeneous; Enantioselective; Computer modeling; Cinchonine

1. Introduction

Enantioselective hydrogenation of prochiral carbon–carbon double bonds in esters remains a difficult target for heterogeneous catalysis. The hydrogenation of (*E*)-*N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester is an example of this demanding class of reactions. NADPME and related prochiral molecules can be hydrogenated using chiral rhodium complexes, and ee in excess of 90% can be achieved [1–3]. However, immobilization of these complexes has not been particularly successful when such complex substrates, such as enamides, are used, because the immobilized catalysts tend to be unstable. Consequently, we have used a different approach in which we have tried to extend the use of cinchona-modified supported Pd catalysts for the enantioselective hydrogenation of NADPME. Previously, we showed [4,5] that Pd/TiO_2 and Pd/Al_2O_3 catalysts modified by cinchona alkaloids can induce low levels of enantioselection (ca. 30% ee) for NADPME hydrogenation. Furthermore, we also showed that enantioinversion can be seen when cinchonidine is used as the modifier [6]. In this paper, we extend these earlier studies and examine the hydrogenation of structural variations of NADPME, as well as the influence of solvent and modifier concentration. Even though we investigated an extensive range of experimental variables, we found that the ee remained disappointingly low. In view of this, we used computer simulation to consider the NADPME–modifier interaction. This coupled approach, combining theory with experiments, provides insight into the factors influencing enantioselectivity for this reaction.

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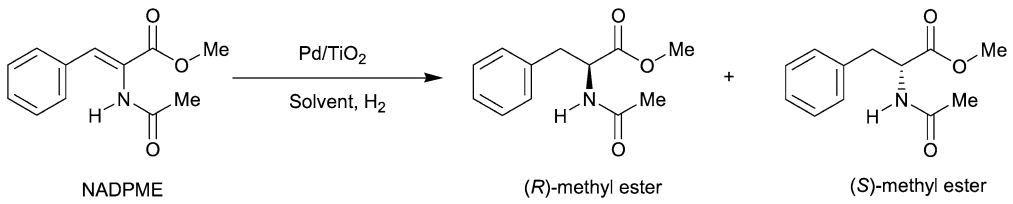


Scheme 1. The hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to the corresponding *R*- and *S*-enantiomers of *N*-acetyl phenylalanine methyl ester.

2. Experimental

2.1. Preparation of materials

Dehydrophenylalanine azlactone **5** (Fig. 8) and (*E*)-*N*-acetyl dehydrophenylalanine ethyl ester **2** were prepared as described previously [5]. Other materials were prepared as follows:

- Preparation of (*E*)-*N*-acetyl dehydrophenylalanine butyl ester **3**: Dehydrophenylalanine azlactone (15 g) was slurried in methanol (50 ml) at 25 °C for 1 h, after which 25% sodium butoxide in butanol was slowly added to form a brown solution, which was stirred for 1 h. The product was recovered by vacuum filtration, dried (50 °C, 16 h) and characterized by ^{1}H NMR (CD_3OD, 400 MHz), δ: 1.0 (multiplet, 2H), 1.1 (multiplet 2H), 1.4 (multiplet, 3H), 2.0 (singlet, 3H), 2.2 (singlet, 3H), 3.2 (multiplet, 2H), 6.0 (singlet, 1H), 7.2 (multiplet, 6H).
- Preparation of *N*-acetyl dehydrophenylalanine (NADP) **6**: Sodium hydroxide (10 ml, 46%) was added dropwise with stirring to dehydrophenylalanine azlactone (10 g, in deionized water 30 ml) while maintaining the pH at 12.5 and the temperature below 40 °C. The pH was then adjusted to pH 1.0 by adding hydrochloric acid, and the slurry was cooled to 5 °C. The product was recovered by vacuum filtration, dried (40 °C, 16 h), and characterized by ^{1}H NMR (CD_3OD, 400 MHz), δ: 2.2 (singlet, 3H), 6.9 (singlet, 1H), 7.5 (multiplet, 6H), 12.4 (singlet, 1H).
- Preparation of (*E*)-methyl cinnamic acid methyl ester **7**: Phenyl cinnamic acid (5 g, Fluka) was dissolved in methanol (50 ml) and concentrated hydrochloric acid (2 ml). After refluxing for 5 h, the reaction mixture was cooled, the solvent was removed by rotary evaporation, and the product was characterized by ^{1}H NMR (CD_3OD, 400 MHz), δ: 2.1 (singlet, 3H), 3.9 (singlet, 3H), 7.3 (multiplet, 5H), 7.6 (singlet, 1H).
- Preparation of NADPME hydrochloride salt **9**: NADPME (5 g) was dissolved in hydrochloric acid in toluene (0.5 mol l^{-1}) and refluxed using a Dean Stark procedure at 85 °C, the solvent was removed by rotary evaporation. The hydrochloride salt was characterized by ^{1}H NMR (CD_3OD, 400 MHz), δ: 2.1 (singlet, 3H), 2.2 (multiplet, 3H), 4.9 (singlet, 1H), 6.0 (multiplet, 5H).
- Preparation of alkaloid modifiers: Alkaloid modifiers were commercial samples used as supplied. 10,11-Dihydroderivatives were prepared by hydrogenation of the cinchona alkaloid (Pd/C, 25 °C, 3 h, 1 bar H_2) and recrystallized from ethanol prior to use. The quaternized cinchona alkaloids **17**, **18** were prepared by reaction of the cinchonine with methyl iodide or methyl chloride.

2.2. Hydrogenation reactions

The standard procedure for the hydrogenation of NADPME (Scheme 1), as has been described in detail previously, was used [5]. In this work, 5% Pd/Al_2O_3 (Johnson Matthey) was used as the catalyst throughout.

2.3. Computer simulation

All calculations were performed using the Gaussian03 code [7] with the ONIOM QM/MM method [8–11]. The system was divided into high (CD/CN and MP/NADPME) and low (surface modeled by graphite) regions. The high-level (QM) region was treated at the B3LYP/6-31G(d,p) level, and AMBER potentials [12] were used for the low-level (MM) region. The low-level (graphite) layer was frozen at the bulk coordinates for a graphitic sheet; all other degrees of freedom were allowed to fully relax. The open 3 conformer of CD or CN, as defined by Baiker [13], was used; input geometries for modifier and ketoester dimers were derived from the optimized gas-phase structures.

3. Results and discussion

3.1. Effect of chiral modifier

The enantioselective hydrogenation of NADPME using various cinchona, morphine, and strychnos alkaloids with methanol as solvent was investigated; the results are given in Table 1.

Table 1
Effect of modifier on the hydrogenation of NADPME using 5% Pd/Al_2O_3

Entry	Alkaloid type	Alkaloid modifier	ee (%)
1	Cinchona	Cinchonine	9.0 (*S*)
2	Cinchona	10,11-Dihydrocinchonine	9.5 (*S*)
3	Cinchona	Cinchonidine	3.5 (*R*)
4	Cinchona	10,11-Dihydrochinodinine	4.0 (*R*)
5	Cinchona	Quinine	0
6	Cinchona	Quinidine	0
7	Morphine	Oxycodone	3.5 (*S*)
8	Morphine	Codeine	1.5 (*R*)
9	Strychnos	Brucine	0

Note. Reaction conditions: methanol (20 ml), NADPME (500 mg), catalyst (100 mg), modifier (5 mg), H_2 pressure 10 bar, 25 °C, 1000 rpm, reaction time 6 h, all conversions 100%.

Using cinchonine-based modifiers gave the highest ee to *S*-*N*-acetyl phenylalanine methyl ester. Cinchonidine and 10,11-dihydrocinchonidine gave lower ee's to the *R*-*N*-acetyl phenylalanine methyl ester; thus, cinchonine was selected for further detailed study. Comparing the initial rates for the racemic and enantioselective reactions under the standard reaction conditions shows that the alkaloid modifier acted as a catalyst poison (initial rate, no cinchonine 48 mmol h^{-1} g(cat)$^{-1}$, with cinchonine 10 mmol h^{-1} g(cat)$^{-1}$). This is in contrast to the effect of cinchona modification on Pt/Al_2O_3 for alkyl pyruvate hydrogenation, for which a marked rate promotion for the enantioselective hydrogenation is observed [14,15], but is in agreement with cinchona modification of Pd/Al_2O_3 for the enantioselective hydrogenation of unsaturated carboxylic acids [16,17]. In addition, for pyruvate, polymerization of the reactant can lead to polymer formation on the surface; rate enhancement was recently attributed to the removal of this polymer by the basic modifier [18]. We would not expect polymerization to occur in the NADPME reaction; consequently, we would expect the same number of reaction centers to be available regardless of whether the modifier was present. The racemic and chiral reactions have similar rate expressions, determined from initial rate measurements:

$$\text{rate (racemic reaction)} = k[m_{\text{cat}}]^{1.5}\,[\text{NADPME}]^0\,[P_{H_2}]^{0.6} \quad (1)$$

and

$$\text{rate (chiral reaction)} = k[m_{\text{cat}}]^{1.2}\,[\text{NADPME}]^0\,[P_{H_2}]^{0.6}. \quad (2)$$

NADPME can react via a tautomeric form in which either a carbon–carbon or carbon–nitrogen double bond is hydrogenated. To investigate which of these processes is dominant, the reaction was carried out with D_2 using the standard reaction conditions. Analysis of the reaction products using ^1H NMR spectroscopy indicates that only the product of the hydrogenation of the carbon–carbon bond was observed. Hence, the tautomeric form of NADPME plays no significant part in the hydrogenation.

3.2. Effect of reaction conditions on enantioselectivity

The effect of H_2 pressure on enantioselectivity is shown in Fig. 1a. Clearly, under the standard reaction conditions, this parameter has a significant effect on ee, with a small increase in reaction pressure leading to a markedly enhanced ee. Similar effects were observed in previous studies using cinchona-modified Pt/Al_2O_3 for enantioselective hydrogenation of α-ketoesters [19–21]. In contrast, the ee is relatively insensitive to variation in temperature over the range −5 to 40 °C (Fig. 1b). In addition, the ee was independent of NADPME conversion (see Supplementary material, Fig. S.1), in agreement with the results of Huck et al. [22] for the enantioselective hydrogenation of methoxypyrone using cinchona-modified Pd. However, this effect is in contrast to the significantly enhanced ee observed with increasing conversion for the enantioselective hydrogenation of pyruvate esters using cinchona-modified Pt [23–25].

As expected, the cinchonine:NADPME molar ratio, the variation being achieved at constant NADPME concentration, also

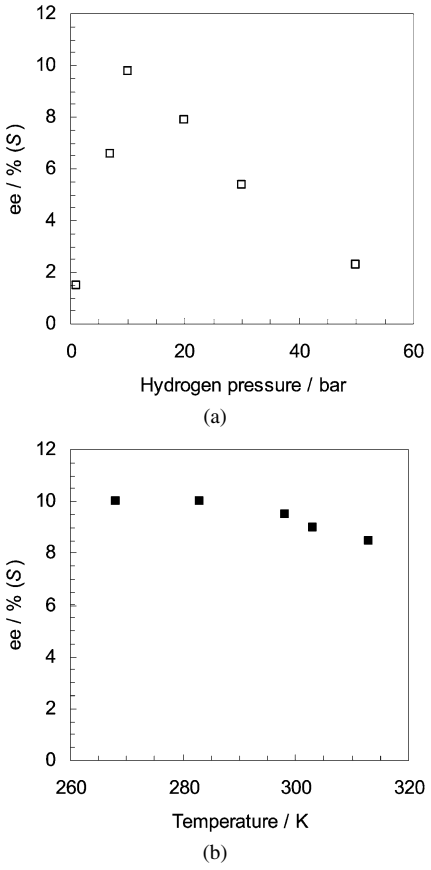


Fig. 1. Effect of (a) H_2 pressure and (b) temperature on ee observed for the enantioselective hydrogenation of NADPME.

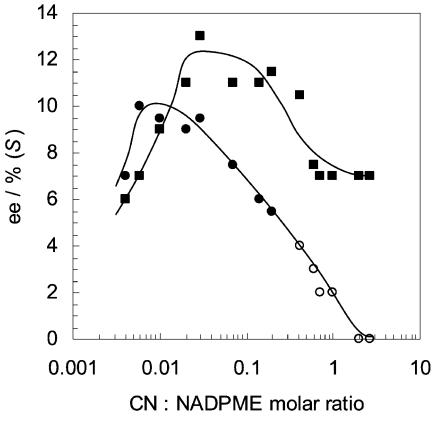


Fig. 2. Effect on ee of the cinchonine:NADPME mol ratio (NADPME 0.46 mmol). (●) Not buffered (○ represented solutions saturated with cinchonine), (■) buffered at pH 6.0.

influences the ee (Fig. 2); a broad maximum is observed. However, in general, the reaction tends toward being racemic at high cinchonine:NADPME molar ratios, where the cinchonine solutions are saturated. We considered that adding cinchonine, a base, would influence the pH of the reaction medium. Subsequently, we investigated the effect of pH at a constant cinchonine:NADPME ratio (see Supplementary material, Fig. S.2) with the pH varied by adding KOH or CH_3COOH. The ee is maximized (16%) at pH ca. 6. Consequently, we studied the effect of the cinchonine:NADPME molar ratio in buffered solu-

Table 2
Effect of solvent on the hydrogenation of NADPME over Pd/Al_2O_3

Entry	Cinchonine: NADPME mol ratio	ee (%) (*S*)			
		Methanol	Ethanol	DCM	DMF
1	0.006	7.0	4.0	0	7.0
2	0.02	9.0	5.0	2.5	13.0
3	0.07	8.0	6.0	3.0	18.0
4	0.2	5.0	4.0	2.0[a]	–[a]
5	0.4	4.0[a]	3.5[a]	–[a]	–[a]
6	1.0	2.0[a]	2.0[a]	–[a]	–[a]

[a] Cinchonine-saturated reaction medium, conversions too low to determine ee accurately.

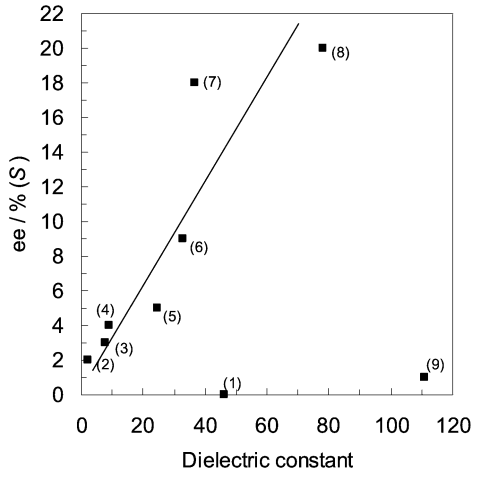


Fig. 3. Effect on ee of the dielectric constant of the solvent. Key: (1) dimethyl sulfoxide, (2) toluene, (3) THF, (4) dichloromethane, (5) ethanol, (6) methanol, (7) DMF, (8) water, (9) formamide.

tions at pH 6.0 (Fig. 2) and found a higher ee. However, at high pH there is no enhanced ee; this is again a significant difference from the enantioselective hydrogenation of pyruvate esters using cinchona-modified Pt.

3.3. Effect of solvent on enantioselectivity

We investigated the effect of variation in the solvent and the cinchonine:NADPME molar ratio with ethanol, dichloromethane (DCM), and *N*,*N*-dimethyl formamide (DMF). The results are compared with those for methanol in Table 2. It is clear that DMF gave much higher ee, but cinchonine had more limited solubility in this solvent. The maximum ee was observed with cinchonine:NADPME molar ratios of 0.02–0.07. A subsequent set of experiments was conducted using a range of solvents to investigate the effect of the dielectric constant of the medium on ee (Fig. 3). In general, the ee increased with dielectric constant, the exceptions being formamide and dimethyl sulfoxide, which appear to be unsuitable/impractical solvents for this reaction. The highest ee was observed in solvents in which the reaction proceeded rapidly (Fig. 4).

The highest ee and reaction rate were observed when water was used as solvent. However, cinchonine and other alkaloid modifiers exhibit poor solubility in water, and so we investigated mixed solvents in which water was added to methanol

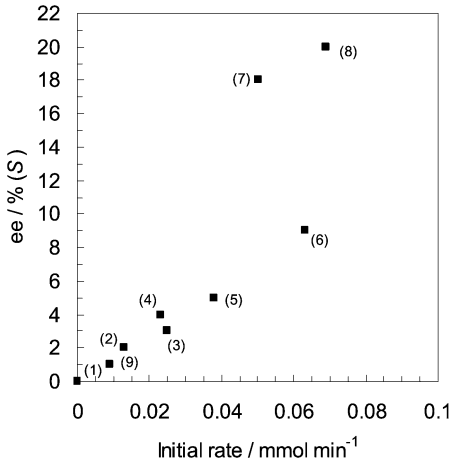


Fig. 4. Relationship between ee and initial rate (key as in Fig. 5).

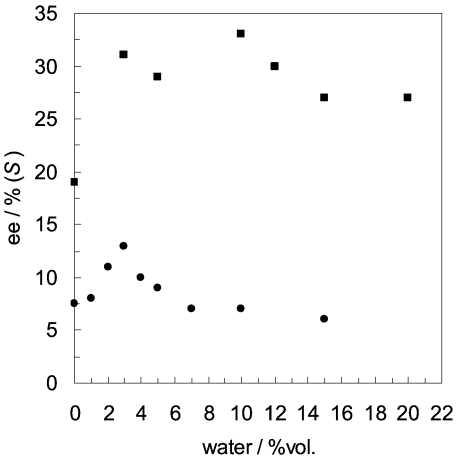


Fig. 5. Effect on ee of the addition of water to (●) methanol and (■) DMF.

and DMF (Fig. 5). In both cases, ee was enhanced by adding water, and in the case of DMF with 10% water, the ee increased to 33%, the highest enantioselection for this reaction that we have found in our studies to date. A similar effect has been observed for adding water to solvents for the enantioselective hydrogenation of ethyl pyruvate with cinchona-modified Pt/Al_2O_3 catalysts [25], and in this case the effect was shown to be caused by the hydrolysis of the ester, leading to an acid that protonated the cinchona alkaloid, leading to a change in its conformation.

3.4. Investigation of reactant–modifier interaction

To investigate the nature of the interaction between the chiral modifier and the reactant, derivatives of the substrate were prepared and reacted under standard conditions. The derivatives tested and ee's obtained are shown in Fig. 6; in all cases, 100% conversion was observed. Modification of the ester function of NADPME (**1**–**4**) gave lower ee with increasing substituent size. The azlactone **5** can be hydrogenated to form two chiral centers, one by hydrogenation of the carbon–carbon double bond and one from the hydrogenation of the carbon–nitrogen double bond. However, under the experimental conditions, the azlactone ring opened to form NADPME, which was subse-

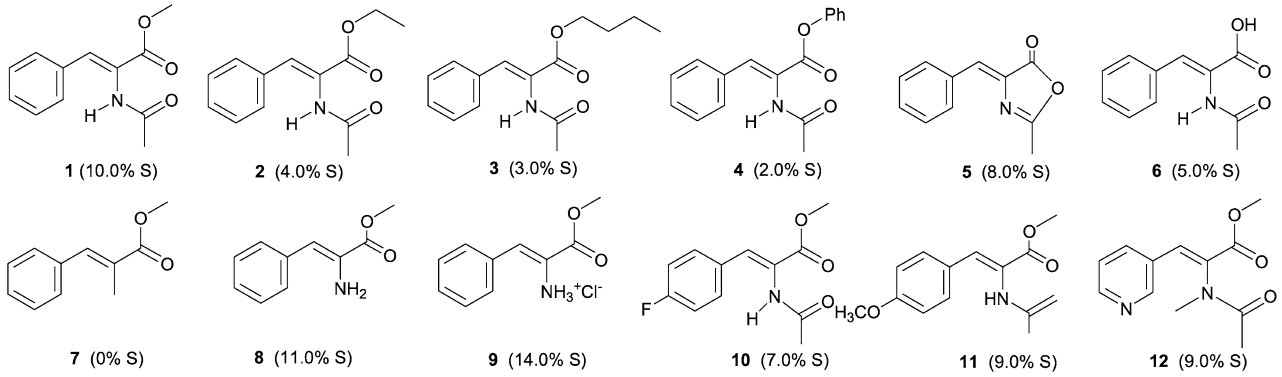
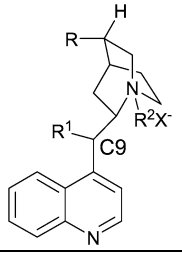


Fig. 6. Effect on ee of structural modification of the reactant (ee in parenthesis).



Entry	R	R^1	R^2	X^-	ee (%) (*S*)	Conversion (%)
13	C_2H_3	OH	–	–	9.0	100
14	C_2H_5	OH	–	–	9.5	100
15	C_2H_5	COC_6H_5Cl	–	–	9.5	100
16	C_2H_3	OH	H	Cl	14.0	42
17	C_2H_3	OH	CH_3	I	0	26
18	C_2H_3	OH	CH_3	Cl	0	40

Fig. 7. Effect on ee and conversion of structural modification of cinchonidine.

quently hydrogenated; therefore, similar ee's were observed with **5** and **1**. Hydrogenation of the free acid NADP **6** resulted in a lower ee. Modification of the *N*-acetyl function of NADPME (**7**–**9**) was instructive. Replacement of the *N*-acetyl group with a methyl group led to complete loss of enantioselection. This is consistent with previous reports that α,β-unsaturated esters are not enantioselectively hydrogenated using cinchona-modified Pd [25]. Hydrogenation of **8** and **9** gave ee's similar to that of NADPME. Modification of the phenyl group (**10**–**12**) had no significant affect on ee.

Five derivatives of cinchonine were investigated for the hydrogenation of NADPME under the standard reaction conditions (Fig. 7). The similar result for cinchonine **13** and dihydrocinchonine **14** confirms that under the reaction conditions, **13** rapidly hydrogenates to **14**, which is the active modifier in our experiments. Modification at the C9 position, **15**, 4-chlorobenzoate quinidine, does not affect the conversion or the ee. Protonation of the quinuclidine-*N* **16** leads to an enhanced ee with a lower conversion; however, quaternization of the quinuclidine-*N* of cinchonine, **17**, **18**, leads to complete loss of enantioselectivity.

3.5. Comments on the interaction of cinchonine and NADPME

The effects on ee of variations in solvent, reactant, and modifier can be used to gain an insight into the mechanism of the asymmetric hydrogenation. Cinchona alkaloids exhibit a range of conformations in solution due to rotation about the single bonds in the molecules; as a result, cinchonine is stable in four conformations (closed [1 and 2] and open [3 and 4]) [13]. The open 3 conformer has the quinuclidine nitrogen atom available for interaction with other adsorbates. This form is stabilized in solvents with low dielectric constants, and in general many enantioselective hydrogenations with cinchona-modified supported metal catalysts show a correlation between the concentration of the open 3 conformer in solution and the ee, and so higher enantioselectivity is observed in apolar solvents [13,26]. The closed 1 and 2 conformers have higher dipole moments and are stabilized in solvents that are more polar; in these conformations, the quinuclidine nitrogen atom is positioned over the quinoline ring system of the modifier and so is not as accessible as in the open conformations. The usual correlation of ee with dielectric constant, however, is not observed for the hydrogenation of NADPME, because the enantioselectivity increases with increasing dielectric constant (Fig. 3).

NADPME can exist as a monomer or a dimer in solution, via hydrogen bonding; the extent of the equilibrium will be influenced by the polarity of the solvent, with higher-polarity solvents favoring the monomer over the dimer. Hence, it is important to consider the potential interactions between the NADPME monomer and dimer with cinchonine. Interactions between the two are feasible if the cinchonine is in the open 3 form. As a monomer NADPME can interact with protonated cinchonine by hydrogen-bonding to the quinuclidine-*N*. This is analogous to the proposals of Nitta and Kobiro [27] for the enantioselective hydrogenation of (*E*)-phenyl cinnamic acid over cinchona-modified Pd. As a dimer, NADPME can also interact with cinchonine. For this to occur, both the quinuclidine-*N* and the hydroxyl group at C9 of cinchonine must participate in the interaction, which requires the formation of three hydrogen bonds: (a) between the quinuclidine-*N* of cinchonine and the NH of the acetyl group of one NADPME, (b) between the carbonyl group of one NADPME and the NH of the acetyl group of the second NADPME, and (c) between the carbonyl group of the second NADPME and the hydroxyl at C9 of cinchonine. This model is analogous to that proposed by Baiker et al. [28] for the hydrogenation of (*Z*)-2-methyl-but-2-enoic acid. They noted that the enantioselectivity was lost when either the quinuclidine-*N* was quaternized or the OH at C9 was

replaced by OMe, confirming that both functions of the modifier are required.

The effect of the solvent on enantioselectivity differs for each of these models. Interactions involving the monomer are favored in polar solvents, whereas apolar solvents favor interaction via the dimer. We observe that ee increases with solvent polarity (Fig. 3) or when the polarity is enhanced by the addition of water (Fig. 5), indicating that the principal interaction is via the monomer. The structural changes of the cinchonine are also instructive. The observation that replacing the OH at C9 with a 4-chlorophenyl group does not affect the ee indicates that interaction by hydrogen bonding at the C9 position of cinchonine with NADPME is not essential for retention of enantioselectivity and that this is consistent only with the monomer interaction model. Hence, we can conclude that our results support a mechanism in which cinchonine interacts with the monomeric form of NADPME. The observation that the highest ee occurs when the pH is maintained at ca. 6 is also consistent with this model. At pH 6, the quinuclidine-*N* ($pK_a = 10$) will be preferentially protonated over the acetyl group of NADPME ($pK_a = 1.5$), which favors formation of the open 3 conformation of cinchonine [13]. Hence the solvent polarity and acidity require fine-tuning to minimize NADPME dimer formation while permitting formation of the open 3 conformer of cinchonine, because this conformation permits the interaction with NADPME, leading to enantioselective hydrogenation.

3.6. Computer modeling studies

Computer modeling using density functional theory (DFT) has already provided useful information on the preferred conformation of the cinchonidine modifier [13] and its interaction with reactant molecules. Our experimental investigations show that the highest ee for NADPME hydrogenation occurs when the modifier is present with the quinuclidine nitrogen atom protonated. This implies that the open 3 conformation [13] is the most relevant form of the modifier. We have also shown that NADPME is hydrogenated in its monomer form; thus, to better understand the selectivity, we consider open 3-NADPME dimer structures and their interaction with the surface. Unfortunately the size of the cinchonidine molecule makes the interaction with the metal surface extremely costly to consider at a quantum level because the system sizes required for either periodic or cluster models of the metal surface are prohibitively computationally expensive. Initial calculations involving representative molecules for sections of the molecule [29], and surface science experiments [30] have considered the adsorption mode of the modifier alone. This work suggests that at the low loadings used in catalysis, the alkaloid modifier is adsorbed through the interaction of the π-system of the quinoline group on Pd(111) so that this aromatic system is parallel to the surface plane. This mode of adsorption has also been recently observed for cinchonidine on Pt nanoclusters of catalyst particle dimensions using diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) [31]. Periodic DFT has been applied to simple dimer models on Pt(111), but the effective loading is high, resulting in a tilted adsorption mode for the modifier [32]. Previous calculations have assumed that the interaction between the alkaloid modifier and reactant is the most important factor in selectivity, and so the interaction with the surface can be ignored or included as an ad hoc constraint on the dimer system. Hence, the surface is considered a passive planar structure to which the modifier is anchored and from which the H atoms are delivered to the most accessible side of the prochiral double bond. Accordingly, most calculations on chiral selectivity involving cinchona alkaloid modifiers to date have simply omitted the surface [33] or used constraints to restrict the dimer geometry [34]. These approaches have yielded dividends when modeling the enantioselective hydrogenation of methyl pyruvate, for example [35]. The required energy difference between the pro-*R* and pro-*S* dimers to give an experimentally observable ee is small; based on a simple kinetic analysis, a 10 kJ mol^{-1} difference in dimer energy will give effectively 100% ee at room temperature [36]. Therefore, it is remarkable that the interaction with the surface does not appear to disturb the relative energies of the dimers, as evidenced by the success of modeling studies based on gas-phase dimers. However, NADPME contains an aromatic functionality that will be attracted to the surface in a manner similar to that of the anchoring quinoline ring system of the modifier and other aromatic systems, such as benzene [37]. This means that it is likely that the structure of the modifier-substrate dimer will be more strongly influenced by the interaction with the surface than in the alkyl pyruvate ester case. The affect of the attraction between a modifier and reactant dimer with the surface was recently considered in a study of the hydrogenation of 1-phenylpropane-1,2-dione [38]. It was found that DFT-level gas-phase dimer calculations did not give geometries in which the aromatic systems of the modifier and reactant are co-planar. Using a force field representation of the dimer and a model Pd(111) surface, co-planar geometries were found after considerable rearrangement of the gas-phase DFT geometries. We decided to directly combine the DFT description of the dimer structure with a force field representation of its interaction with the surface through a quantum mechanics/molecular mechanics (QM/MM) approach. Details of this model and its performance in the test case of methyl pyruvate hydrogenation are given in Supplementary material. Here we provide the results obtained for NADPME.

Three distinct dimer motifs with pro-*R* and pro-*S* forms were found; these are shown in order of increasing calculated energy in Fig. S.3, with the relevant data given in Table S.2. The stability of these species is affected by the proximity of the reactant to the modifier, the strength of the hydrogen bond, and the interaction between the terminal methyl groups and the quinoline ring. The most stable pair of related structures (Fig. 8) has a single principal hydrogen bond between either the ester carbonyl oxygen atom (1.87 Å, pro-*R*) or the amide carbonyl (1.82 Å, pro-*S*) and the protonated quinuclidene nitrogen. These structures are isoenergetic within the accuracy of our calculations, indicating that reaction via these structures would lead to a racemic product. The next most stable pair of dimers (Fig. S.3b) were destabilized by 15 and 7 kJ mol^{-1} (pro-*S* and pro-*R*, respectively) compared with the most stable structures.

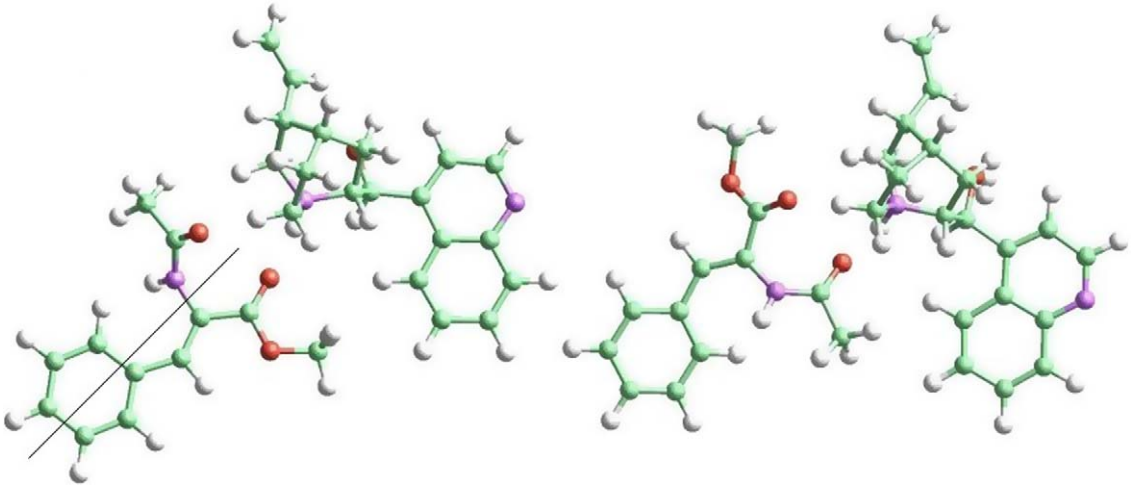


Fig. 8. The most favorable surface dimer species of NADPME and cinchonine. Left-hand side is pro-*R* species, right-hand side pro-*S*. Solid black line indicates approximate location of the pseudo-C_2 rotation axis as described in the text.

From the modeling results, one particular feature was noted for the reactant–modifier dimer interacting with the graphite model of the surface which may help explain the low enantioselectivity in this reaction. In the gas phase, the NADPME molecule is twisted with the plane of the phenyl group and the plane of the other atoms at an angle (a dihedral angle of approximately 50°). However, on interaction with the surface, the NADPME molecule becomes almost planar under the attractive force of the surface (Fig. S.4). The nature of the hydrogen bond between the $^{+}$N–H of the modifier and the two carbonyl oxygens means that an almost energetically, degenerate structure is formed by a 180° rotation around the pseudo-C_2 axis indicated in Fig. 8. This rotation also changes the facial attack of hydrogenation and so the enantiodifferentiation for this substrate is likely to be minimal. Based on the relative energies of all dimer structures optimized, we calculate an estimated ee of 9%, which compares well with the experimental values observed. In addition, it should be remembered that the enantioselective reaction is in competition with racemic hydrogenation on the unmodified regions of the catalyst particles. We have seen that an increased steric interaction between modifier and NADPME leads to destabilization of the dimer complex. Hence, experiments aimed at adding bulk to groups on one side of the pseudo-C_2 axis (Fig. 8) (e.g., substrate **4**, Fig. 6) may actually lead to a lower ee.

4. Conclusion

Cinchonine-modified Pd/Al_2O_3 catalysts are effective for the hydrogenation of NADPME to the *N*-acetyl phenylalanine methyl ester, but with only modest enantioselectivity. The ee is dependent on the polarity of the solvent and the pH, and the results are consistent with hydrogen bonding between the monomeric form of NADPME and cinchonine leading to the enantioselectivity. Using a detailed range of experiments, we have as yet been unable to increase the ee above 33%. Dimer models, including a parameterized model of the interaction with the surface, show that the low enantioselectivities observed may be due to the similarity in steric bulk of the acetyl and ester groups, so that the hydrogen-bonding arrangements for pro-*R* and pro-*S* structures have similar energies. Progress may be possible with modifiers designed to distinguish these groups.

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Supplementary material

The online version of this article contains additional supplementary information.

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