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Enantioselective hydrogenation of α-keto esters over cinchona-Pt/Al_2O_3 catalyst. Molecular modelling of the substrate–modifier interaction

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Abstract

The substrate–modifier interaction involved in the enantioselective hydrogenation of α-keto esters over cinchonidine-Pt/Al_2O_3 catalyst was investigated by molecular modelling. The model is based on our earlier kinetic and nuclear magnetic resonance (NMR) results as well as on analogies found in experimental organic chemistry. The model suggests the formation of a weak complex between the modifier and the substrate in the liquid phase. In the above complex, the modifier provides a specific shielding effect (SE). Due to the particular character of shielding, the α-keto ester can interact with the metal surface only by its unshielded site. If the reactivity of the substrate in the shielded [substrate–modifier] complex is higher than that of the free substrate, pronounced enantio-differentiation (ED) should be observed. In one of the shielded forms, the proper directionality of the quinuclidine nitrogen towards the keto carbonyl group provides the increased reactivity of the keto carbonyl group. The 'shielding effect' model can explain both the ED and the rate acceleration (RA) effect observed in the hydrogenation of methyl and ethyl pyruvate, methyl benzoylformate, pantolactone and trifluoroacetophenone (TFAP) over cinchonidine-Pt/Al_2O_3 catalyst. The 'shielding effect' model is the first model which can elucidate the substrate specificity of the above enantioselective hydrogenation reaction.

Keywords: α-Keto esters; Cinchonidine; Chiral modifiers; Enantioselective hydrogenation; Enantio-differentiation; Pt/Al_2O_3; Shielding effect

1. Introduction

1.1. General information

The enantioselective hydrogenation of α-keto esters over Pt/Al_2O_3 catalysts in the presence of different chiral modifiers, such as cinchona and other alkaloids [1–4], Troger's base [5], pyrrolidine [6] and *N*-ethyl-naphthylamine [7] derivatives, is intensively studied by different research groups. Despite these profound studies, the key feature of the above reaction, i.e., the rate acceleration (RA) phenomena and the origin of the enantio-differentiation (ED) steps is not really understood. The existing models cannot explain neither the substrate specificity nor the influence of solvent on the enantioselectivity.

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With respect to the origin of RA and ED steps, there are two possibilities: RA and ED are controlled either by (i) *modifier–active phase (Pt)* interaction [2,6–8] or (ii) *substrate–modifier* interactions [4,5,9] taking place in the liquid phase. It should also be mentioned that those who suggest *modifier–Pt* interaction in the RA and ED steps ignore one very important fact: cinchona alkaloids have been used by organic chemists to induce ED in a variety of organic reactions [10–12]. This is a very important issue indicating that in the reactions discussed, ED cannot exclusively be attributed to surface phenomena. We believe that ED, even in the presence of heterogeneous catalysts, is a phenomenon which should be controlled by general rules of organic chemistry.

In this work, based on our earlier results, such as catalytic experiments [3–5,13], kinetic studies [9,14] and NMR results [14], a new approach and concept are described by using methods of computational chemistry. This work can also be considered as a continuation of our previous studies in the field of molecular modelling [5,14]. We believe that this new approach can help to understand at molecular level the induction of ED in the presence of both chiral modifiers and heterogeneous catalysts. In this work, molecular modelling and methods of computational chemistry are used as tools to understand the nature of interactions involved in the ED step. We should like to emphasize that in none of the earlier studies the chemical nature of the substrate–modifier interaction was studied or discussed in such a detail. Probably, the lack of such kind of investigation is the reason that the substrate specificity of enantioselective hydrogenation reactions taking place over cinchona-Pt/Al_2O_3 catalysts is still not really well understood.

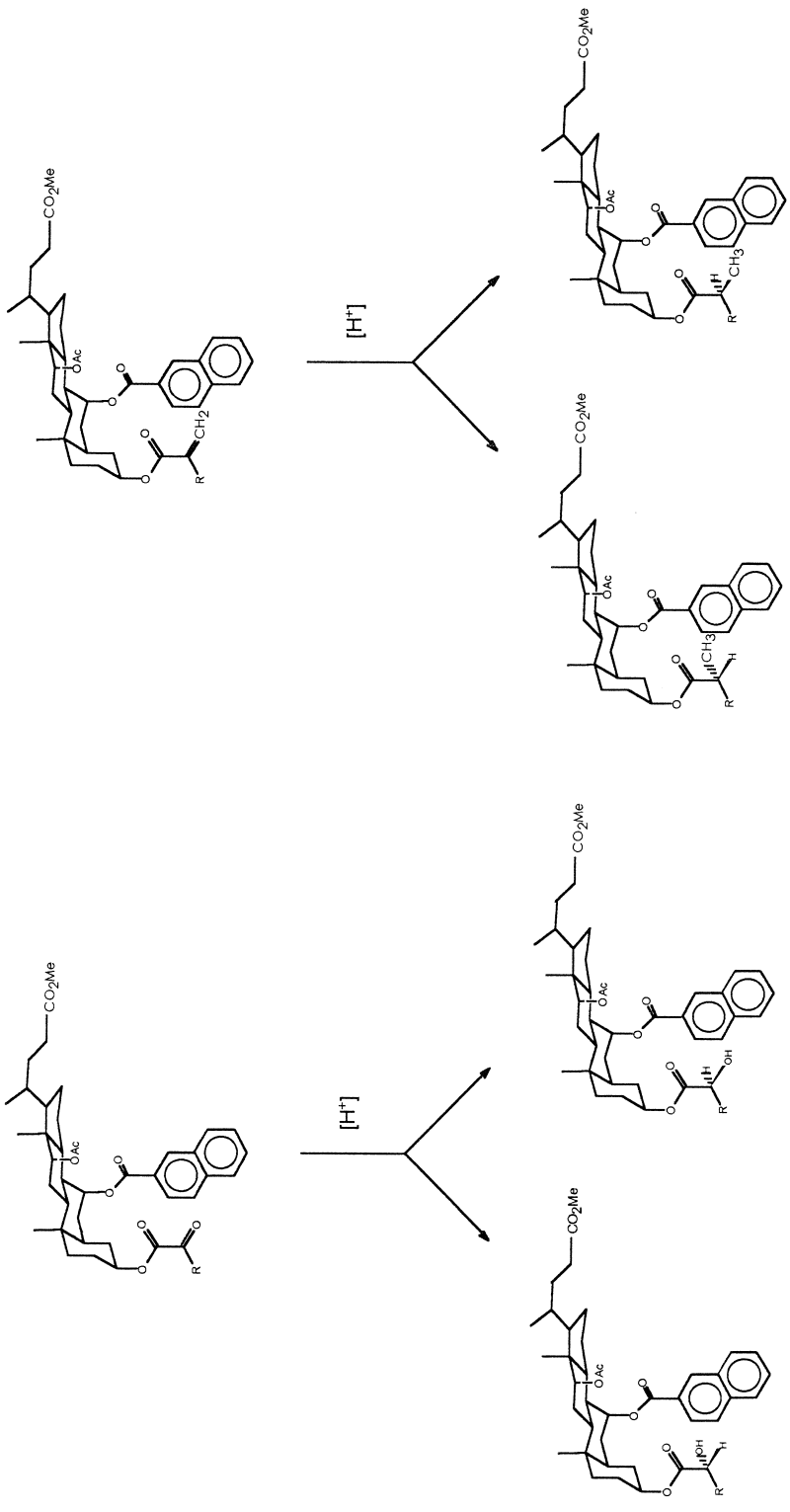
1.2. The principle of chemical shielding

The basis for this approach is the shielding effect (SE) known in organic chemistry. If a prochiral moiety is preferentially shielded, its further reaction can take place only from its unshielded site, resulting in ED. A chiral template molecule can induce SE in a similar way, i.e., it preferentially interacts with one of the prochiral sites of the substrate leaving the unshielded site free for the reaction.

Recently, intramolecular steric shielding of an α-keto ester moiety has been observed, resulting in ED in the hydrogenation of the α-keto group [15]. The ED was observed only in the presence of large aromatic substituent, such as naphthyl, and the ED was completely lost if the naphthyl ring was substituted for a phenyl one. Based on this finding, the ED was attributed to the SE induced by the large aromatic moiety. Similar phenomena were also described for the hydrogenation of an α,β-unsaturated ester moiety [16]. The above two reactions are shown in Scheme 1.

Surprisingly, similar results were recently observed in the enantioselective hydrogenation reactions in the presence of chiral modifiers and supported metal catalyst. It has been shown that cinchona alkaloids can also induce ED in the hydrogenation of α,β-unsaturated acids [17]. On the other hand, it was shown that in the hydrogenation of ethyl pyruvate over Pt/Al_2O_3 catalyst in the presence of new modifiers [derivatives of 2-(1-pyrrolidinyl)-1-(naphthyl)-ethanol], the ED was completely lost if the naphthyl ring was replaced by phenyl or pyridyl one [6]. It should also be mentioned that in the hydrogenation of α-keto esters over cinchonidine-Pt/Al_2O_3 catalysts, the ED was partially or fully lost if the quinoline ring of cinchonidine (CD) was partially or fully hydrogenated [18].

If results given in Scheme 1 are compared with those obtained in the heterogeneous hydrogenation experiments [6,18] described above, the following very important elements of similarity can be found: (i) ED can only be observed in the presence of large aromatic shielding groups; (ii) the reactive prochiral group (both the keto carbonyl and the C=C double bond) is activated by an electron-withdrawing carbonyl group; (iii) both double bonds (the keto and the



Scheme 1. Shielding effect in the hydrogenation of cholic acid derivatives (R = Me, Et, Ph).

olefinic one) of the reactive prochiral substrate are in a conjugation with the adjacent carbonyl group. The possible role of conjugation has already been mentioned in one of our earlier studies [9]. As emerges from these results, the presence of both a large aromatic substituent in the modifier and a conjugated double bond system in the substrate should play an important role in the induction of ED in these asymmetric hydrogenation reactions, i.e., these are the key elements resulting in the substrate specificity.

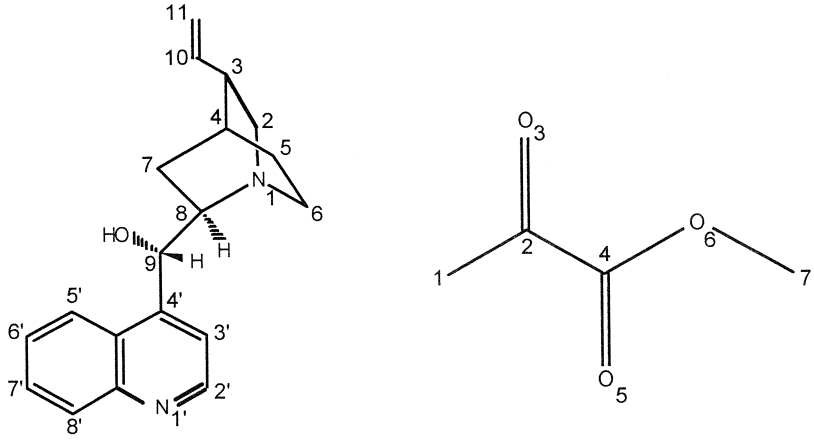
1.3. The aim of this work

The structural similarities described above inspired us to investigate further the role of substrate–modifier interaction and the role of SE in the enantioselective hydrogenation of different α-keto esters in the presence of cinchonidine-Pt/Al_2O_3 catalysts.

It has earlier been suggested that in heterogeneous catalytic asymmetric hydrogenation reactions, the surface of the metal is modified by the chiral modifier and the induction of ED is exclusively a surface phenomenon [1,2,6–8]. Contrary to that, we have proposed that 'host–guest' type interactions taking place between the substrate and modifier in the liquid phase are involved in the induction of ED [4,5,9]. The above 'host–guest' type interactions are considered as a specific case of *supramolecular* interactions.

The application of the SE model to the enantioselective hydrogenation of α-keto esters means that a chiral template molecule interacts with the prochiral substrate in such a way that one of the prochiral sites is *preferentially* shielded. If the substrate is shielded, then its adsorption onto the metal can only take place with its unshielded site, resulting in ED.

An organic molecule can induce both shielding and chiral induction if it has (i) an asymmetry center (A), (ii) an appropriate bulky functional group (B) for weak interaction with the substrate, (iii) relatively large planar group (C) to cause the steric shielding. If the above requirements are fulfilled, the modifier can form a weak complex with the substrate. In this complex, at least two different parts of the chiral modifier should interact with the substrate molecule, i.e., in the [substrate–modifier] complex, CD should behave like a bidentate ligand. We consider that in addition to the quinuclidine nitrogen, the aromatic ring can also be considered as a possible ligand site and a cooperative action of these two ligand sites is required to stabilize the α-keto ester molecule in its preferential orientation. The two-point stabilization of the substrate prevents the free rotation of the substrate either around the quinuclidine nitrogen or the (C2)–(C4) axis (the numeration of atoms in the substrate and modifier molecules is given in Scheme 2). However, CD can provide the



Scheme 2. Numeration of cinchonidine and methyl pyruvate molecules.

above-mentioned two-point stabilization effect only in its closed conformation.

We also suppose that in the [substrate–modifier] complex responsible for ED, the modifier should have an umbrella-like conformation with high extent of 'concavity' [5,9]. The role of 'concavity' in chemical shielding and chiral induction has been discussed earlier [19,20].

The 'shielding effect' model requires the retainment of the integrity of the above [substrate–modifier] complex even in the presence of heterogeneous catalysts. The maintenance requires the following prerequisites: (i) the supported metal catalyst should not hinder either the formation or the adsorption of the [substrate–modifier] complex; (ii) the modifier should not adsorb irreversible onto the catalyst; (iii) the metal should be inactive in the transformation of the modifier into a new derivative; (iv) the catalyst should be resistant towards poisoning by modifier, substrate, product or by-products.

2. Experimental

2.1. Molecular modelling

For the conformational analysis of the modifier, we used the Hypercube: HyperChem 3.1 program [21] with the MM + forcefield. The equilibrium conformations were calculated using the Polak–Ribiere (conjugate gradient) minimization algorithm. Also, the MM + forcefield was used when examining the 'reaction window' for the [CD_{closed}–methyl pyruvate] complex and the free rotation of the substrate in the [CD_{open}–methyl pyruvate] complex. The molecular docking calculations were performed with the InsightII program package of the MSI. We used the Discover module with the cvff forcefield (for details about the functional form of the bonding and non-bonding interactions, see Ref. [22]) and the Ampac/Mopac module with AM1 semiempirical method for optimizing the geometry of the complexes formed by the CD and one of the α-keto ester molecules. These calculations were performed for the whole systems from different initial positions of the examined complexes with the *transoid* conformations of the substrates.

The adsorption of the substrate–modifier complexes onto Pt (111) surface was investigated using the Solids–Docking module of the InsightII package, which performs a Monte-Carlo docking approach. The docking procedure is based on the random selection of positions and molecular orientations of the [substrate–modifier] complexes above the surface followed by the minimization of the flexible guest complex to optimize its interaction with the fixed host surface (for more details, see Ref. [23]).

The lowest unoccupied molecular orbitals (LUMOs) of the methyl pyruvate and trifluoroacetophenone (TFAP) molecules were obtained with the Turbomole module of the InsightII program. First, a full geometry optimization was made at ab initio Hartree–Fock level using the 3–21G basis set, then the contours of the LUMO were constructed.

3. Results and discussion

3.1. Conformational analysis of cinchonidine

The molecular modelling of the [substrate–modifier] interaction required detailed conformational analysis of CD. No similar detailed studies are available in the literature. The energy map of CD was calculated by changing the torsion angles (C3′)–(C4′)–(C9)–(C8) (phi) and (C4′)–(C9)–(C8)–(C7) (psi) using the MM + forcefield. (The numeration of substrate and CD molecules is given in Scheme 2).

In our previous study [5], the above analysis was done by using rigid quinoline and quinuclidine parts. As a result of earlier investigations, four stable conformations have been found. In the present study, all of these calculations were repeated in such a way that only the phi and psi torsion angles were forced to be constant for all

gridpoints of the map, and all the other degrees of freedom of the molecule were left to relax. The results are shown in Fig. 1.

The conformational analysis and full geometry optimization calculations (using other forcefields, too) indicate that CD can exist at least in nine different forms: A1, A2, A3, B1, B2, B3, C1, C2, and C3. (The notation of the conformations is the following: phi is near $-90°$, $90°$, and $20°$ for forms numbered 1, 2, and 3, respectively, and psi is near $-80°$, $60°$, and $180°$ for A, B, and C forms, respectively.) The calculated CD conformers are shown in Fig. 2. As emerges from Fig. 2, the main difference between the conformers of the CD molecule is in the direction of the lone pair orbital of the quinuclidine nitrogen. For the C1, C2, and C3 conformers, this orbital is directed towards the quinoline ring, while in other conformers, the nitrogen atom of the quinuclidine moiety and the quinoline ring are far away from each other. Hence, we will denote the C1, C2, and C3 forms as closed, while all the other forms as open conformations. The A2 conformer corresponds to the crystallographic form of CD.

The rotational barriers between the optimized structures are shown in Fig. 3a and b. These calculations were performed in such a way that only one torsion angle was restrained to keep a certain value and all the other degrees of freedom were left to relax. This way, the other torsion angle sets the value which minimizes the total energy with the other relaxed degrees of freedom. Fig. 3a shows the molecular mechanics energy as a function of psi along the path C1–A1–B1–C1 (solid line) and C2–A2–B2–C2 (dotted line). Along these paths, while psi changes its value from $-180°$ to $+180°$, the value of phi changes from $-120°$ to $-70°$ for C1–A1–B1–C1 path, and from $50°$ to $110°$ for C2–A2–B2–C2 path (see Fig. 1). Similar functions are shown in Fig. 3b, however, in this

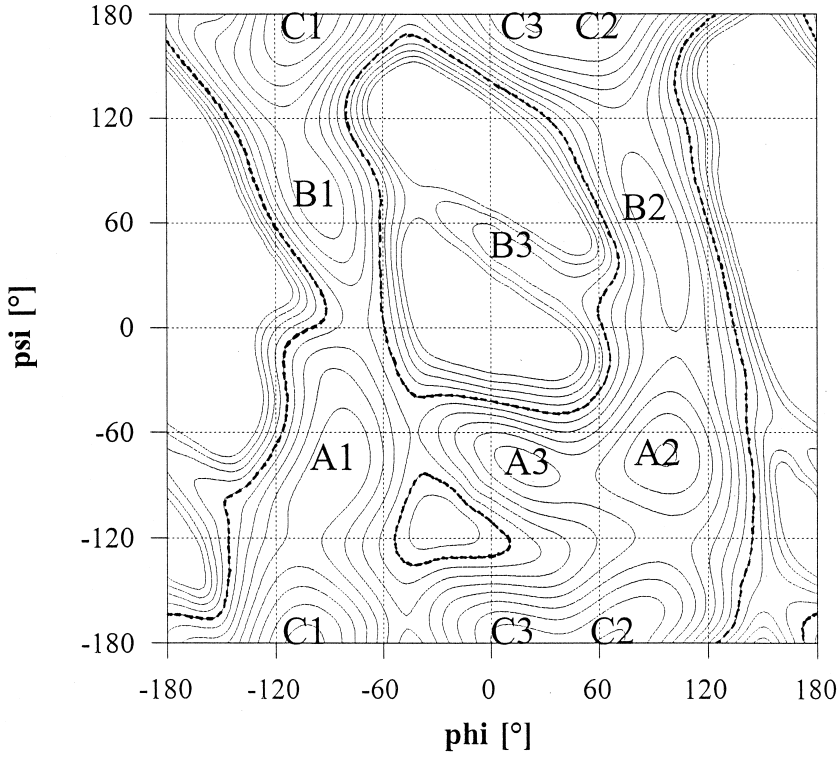


Fig. 1. Conformational analysis of cinchonidine. The calculated energy map obtained by changing the torsion angles (C3′)–(C4′)–(C9)–(C8) and (C4′)–(C9)–(C8)–(C7). The contours are given in steps 0.5 kcal/mol.

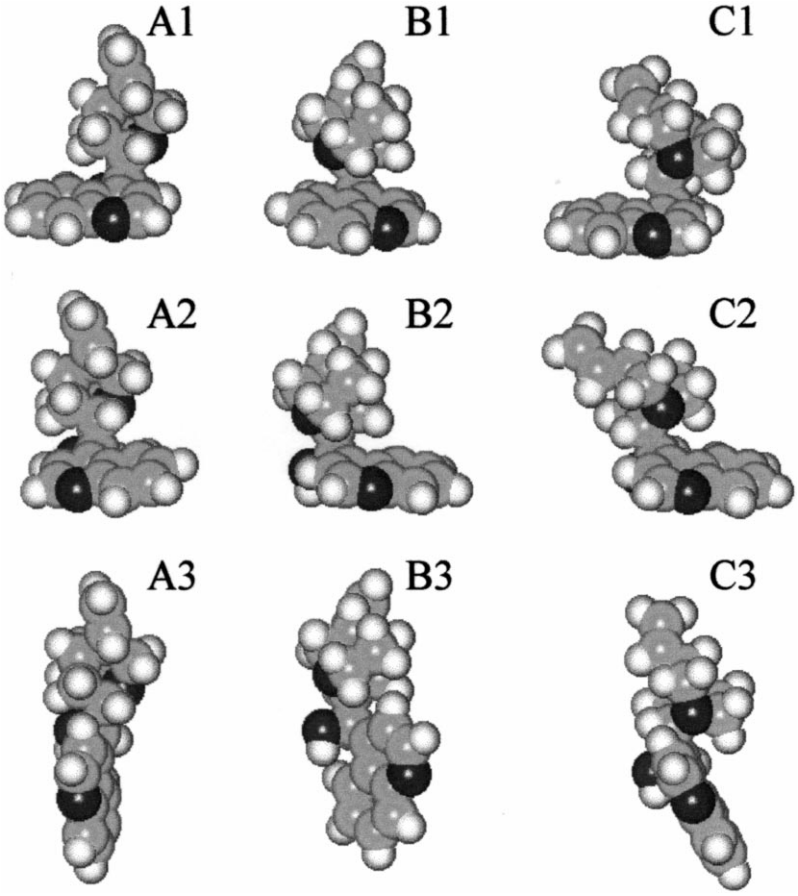


Fig. 2. Conformers of cinchonidine after geometry optimization.

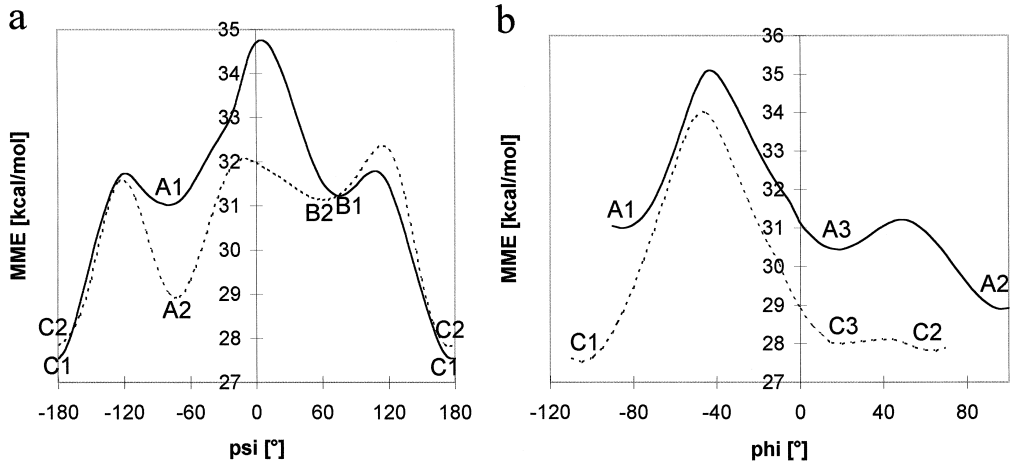


Fig. 3. Rotational barriers for the cinchonidine molecule; (a) rotations around the (C8)–(C9) bond, (b) rotations around the (C4′)–(C9) bond.

case, the total energy is the function of phi, and psi can change in order to minimize the total energy. Solid line shows the function along the A1–A3–A2 path, while dotted line demonstrates the C1–C3–C2 path. In these calculations, psi changes from −90° to −50° (for the A1–A3–A2 path) and from 170° to 200° (for the C1–C3–C2 path). It has to be added that there are no 'natural' C3–A3–B3–C3 and B1–B3–B2 paths along which the molecule can stably rotate (see Fig. 1), hence, these paths do not appear in Fig. 3a and b.

The conformational analysis indicates that there are only three stable conformers of CD, such as A2, C1 and C2. All of the other conformers are very unstable, hence around 1 kcal/mol energy is sufficient to transform A1, A3, B1, B2, and C3 conformers into another most stable conformer. The solid line in Fig. 1 gives the contour of the possible forms of CD within 8 kcal/mol energy. These results indicate how easy it is to rotate both the quinoline and quinuclidine moiety around the (C4′)–(C9) and (C9)–(C8) axes, respectively. The probability of free rotation increases with temperature, thus at high temperature, no preferential stabilization of CD can be expected. Probably, this fact is responsible for the loss of ED upon increasing reaction temperature above 35–40°C [2]. Please note that none of the earlier models can explain the loss of enantioselectivity observed at high temperature.

Due to the above discussion in this study, we shall use only the open A2 and the closed C1 and C2 forms for modelling. As it has already been mentioned, the A2 conformer corresponds to the crystallographic form of CD. The conformational change of CD from open A2 form to closed C2 one requires the rotation of the quinuclidine ring around the (C9)–(C8) axis, the energy needed for this change is less than 4 kcal/mol (see Fig. 3a). Similarly, the rotation of the molecule around the (C4′)–(C9) axis from the closed C2 conformation to the C1 is about 6 kcal/mol (see Fig. 3b). Thus, the conformational analysis strongly indicates that CD can exist both in open and closed forms and both forms of CD can be involved in the formation of [substrate–modifier] complex. It should be mentioned that in all of the previous modelling made by other research groups [24], only the open conformer of CD was used.

3.2. Modelling the methyl pyruvate–modifier complex with the involvement of the closed form of cinchonidine

The involvement of the closed C2 form of the modifier (CD_{closed}) in the formation of [substrate–modifier] complex was proposed in our recent studies [5,9]. In the closed conformer, the lone pair of electrons of the quinuclidine nitrogen is directed towards the quinoline ring and the geometries obtained from conformational analysis showed that CD in this conformation can provide the concave, umbrella-like form required for steric shielding [5,9]. The umbrella-like closed C2 form was used to model substrate–modifier interactions. The calculated [methyl pyruvate–CD_{closed}] complexes are shown in Fig. 4a and b.

The complex (*R*) (see Fig. 4a), after subsequent hydrogenation over Pt, should result in (*R*)-lactate ester, while complex (*S*) (see Fig. 4b) should result in (*S*)-lactate. The major difference between complexes (*R*) and (*S*) is the mode of interaction between the lone pair of electrons of the quinuclidine nitrogen and the keto carbonyl group. In complex (*R*), the 'directionality' [25] of the nucleophilic attack by quinuclidine nitrogen towards the keto carbonyl group is very favourable to increase the reactivity of the keto carbonyl group because the electron-rich quinuclidine nitrogen and the O3 oxygen of the substrate are on the opposite sides of the C2 carbon atom (see Fig. 4a). According to the orbital steering theory [26], a proper 'reaction window' or 'reaction cone' can result in perturbation of the reacting group. In our case the proper 'reaction window' is determined by the relative position of the quinuclidine N1, pyruvate C2 and O3 atoms, i.e., by direct N1–C2

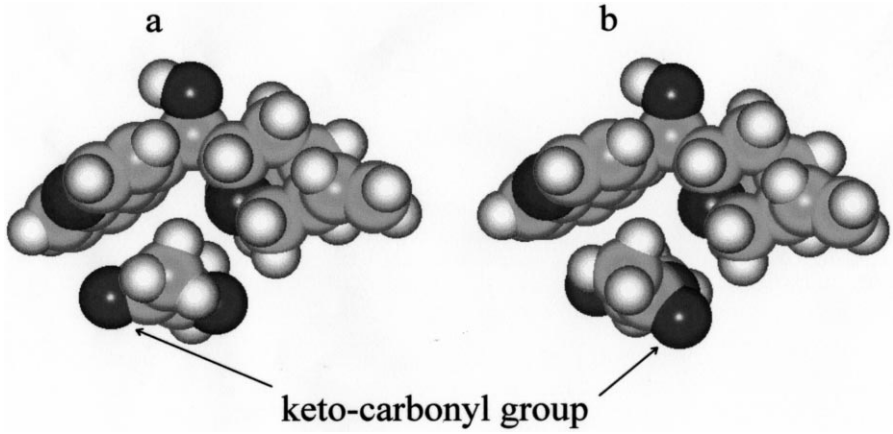


Fig. 4. [Methyl pyruvate–CD_{closed}] complexes; (a) complex leading to the formation of (*R*)-lactate, (b) complex leading to the formation of (*S*)-lactate.

interaction. The proper 'reaction window' also means that the overall reactivity of the keto group should increase. We suggest that the above perturbation leads to a pronounced rate increase both in the hydrogenation reaction and the formation of by-products, such as semi-ketal, transesterification and deuterium exchange products [3,4,14]. Thus, in complex (*R*), the

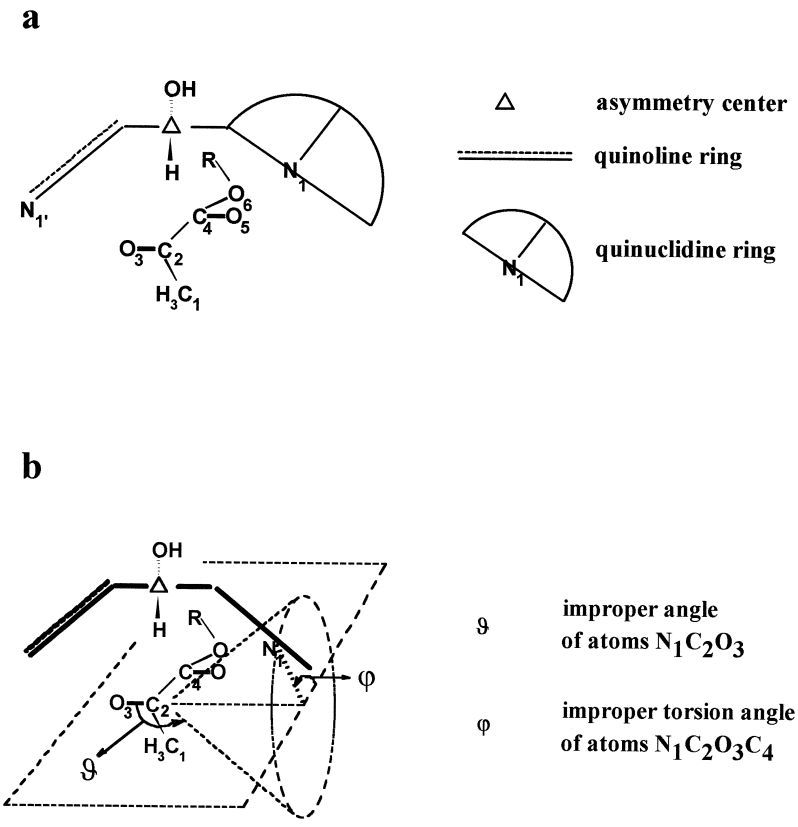


Fig. 5. (a) Simplified scheme for the [methyl pyruvate–CD_{closed}] complex; (b) the 'reaction window' for the substrate–modifier interaction in [methyl pyruvate–CD_{closed}] complex.

favourable directionality promotes the perturbation of the keto carbonyl group, resulting in the observed RA. Contrary to that in complex (*S*), due to the misalignment of the interacting groups, i.e., due to the lack of direct N1–C2 interaction, no RA can be expected, consequently, the hydrogenation of (*S*) complex is not accelerated.

The above discussed reaction window can also be determined by molecular mechanics calculations. The basis of these calculations is given in Fig. 5a and b. Fig. 5a shows the simplified arrangement of the substrate in the [methyl pyruvate–CD_{closed}] complex resulting in (*R*)-lactate. Fig. 5b shows the potential 'reaction cone' or 'reaction window' between the quinuclidine nitrogen (N1) and the (C2) carbon atom in the substrate. In order to perturbate the (C2) carbon atom in the substrate, the (N1) atom of the quinuclidine moiety should be within the 'reaction window'. The 'reaction window' can be characterized by three values: (i) the length between (N1) and (C2) (r); (ii) the angle of atoms (N1)–(C2)–(O3) (ϑ), and torsion angle of atoms (N1)–(C2)–(O3)–(C4) (φ). The key parameter is the angle ϑ which measures the position of the nucleophilic N1 and O3 atoms relative to the electrophilic C2 atom.

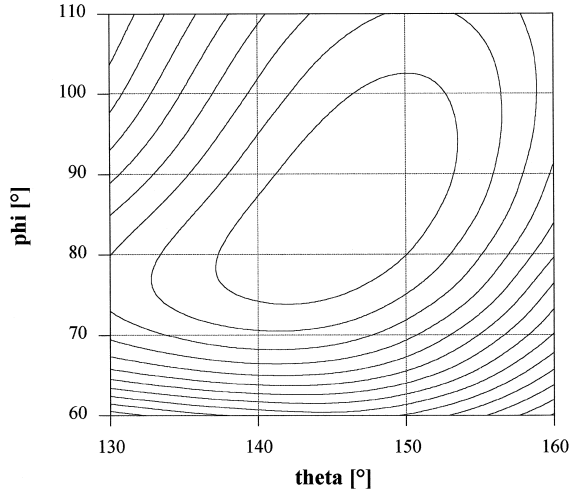


Fig. 6. Energy map for the 'reaction window' in the closed cinchonidine–methyl pyruvate complex. (The contours are given from $E = 26.1$ kcal/mol, in steps 0.1 kcal/mol.)

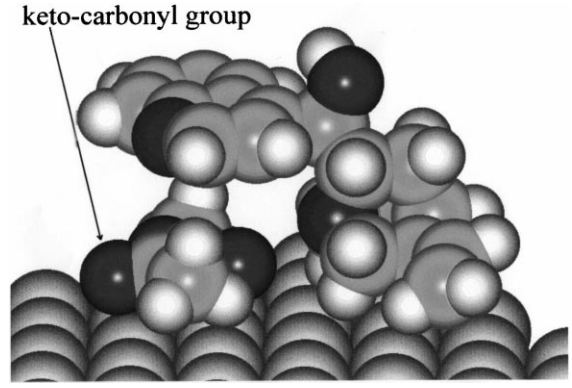


Fig. 7. Monte-Carlo simulation of the adsorption of the [methyl pyruvate–CD_{closed}] complex onto Pt (111) surface.

From the above, it is obvious that $\vartheta \sim 180°$ is optimal for the proper directionality.

Starting with the relaxed structure of the [methyl pyruvate–CD_{closed}] complex, the geometry optimization was done in such a way that the (N1) atom of the CD molecule and the (C2), (O3), and (C4) atoms of the methyl pyruvate molecule were fixed and all other atoms of the complex were left to relax. This way, for fixed (N1)–(C2) distance, the molecular mechanics energy can be expressed as a function of the (N1)–(C2)–(O3) angle and (N1)–(C2)–(O3)–(C4) dihedral (see Fig. 5b). This energy map for the calculated equilibrium value of r ($r = 4.24$ Å) is presented in Fig. 6. The energy minimum at $\vartheta = 145°$, $\varphi = 80°$ shows that the (C2) carbon atom in the keto group of the methyl pyruvate molecule is in a proper reaction window, so the (N1) atom can result in a perturbation of the reacting prochiral keto group. In order to generate a $\vartheta = 145°$, the methyl-pyruvate molecule has to be slightly twisted around the (C2)–(C4) bond, resulting in an increase in the torsion angle between the two carbonyl groups from 0° to 11°. On the other hand, the φ value is related to the rotation of the methyl-pyruvate molecule around its (C2)–(O3) bond (see Fig. 5b) which is prevented by the quinoline ring of CD. Thus, the minimum in the energy-φ function at fixed ϑ values (see Fig. 6) is caused by the steric shielding of the quinoline moiety of the CD molecule.

Monte-Carlo simulation method was used to investigate the interaction of the [methyl pyruvate–CD_{closed}] complex with Pt (111) surface. The result shown in Fig. 7 indicates that the shielded complex retains its entity even after adsorption. The above figure gives a good presentation of the SE provided by the large aromatic moiety.

3.3. Modelling the methyl pyruvate–modifier complex with the involvement of the open form of cinchonidine. Analysis of existing models

Recently, the interaction between CD and ethyl and methyl pyruvate has been reviewed and results obtained by using molecular modelling are presented [24]. In the above modelling, the open A2 form of protonated CD (CD_{open}) was used and in the [substrate–CD] complex, (N1)–(H^+)–(O3) interaction was proposed. It has also been suggested that the [substrate–CD] complex is formed at the Pt surface.

We have previously mentioned that in the open conformations, CD cannot provide the required steric SE [5,9]. In the open forms, only the quinuclidine moiety of CD can interact with the α-keto ester. It has already been shown that the quinuclidine moiety has a crucial role both in the RA and the induction of ED [2]. Experimental data indicate that the interaction of the keto group with the quinuclidine moiety is not sufficient to obtain high RA. In kinetic experiments, the quinuclidine provided 3–4-fold, while CD 10–15-fold rate increase [13]. Based on these results, we suggest that a cooperative effect, with the involvement both of the quinuclidine nitrogen and the quinoline ring, is needed for the RA and induction of ED.

In our modelling, we shall not use the protonated form of CD. We consider that a comprehensive model should reflect the general experimental observation, i.e., the high ee values obtained in aprotonic media, such as toluene or methyl-cyclohexane [5,8]. We consider that the exclusive use of protonated forms of CD in the modelling is one of the most serious disadvantages of the model presented by Baiker [24]. The investigation of the protonated forms of CD will be the subject of one of our forthcoming publications [27].

The results of modelling of the [methyl pyruvate–CD_{open}] complex are shown in Fig. 8a–c. In this complex, the quinuclidine nitrogen attacks the substrate in the similar way as in the [methyl pyruvate–CD_{closed}] complex. To maintain the right directionality between the (N1) nitrogen in the CD and the (C2) carbon in the substrate, similar theta ($\vartheta = 145°$) and phi ($\varphi = 80°$) values were used as obtained for the [methyl pyruvate–CD_{closed}] complex. In the complex shown in Fig. 8a, the substrate molecule upon subsequent hydrogenation will result in (*R*)-lactate. As emerges from Fig. 8a, in the [methyl pyruvate–CD_{open}] complex, there is no significant steric hindrance to prevent the free rotation of the substrate around the axis quinuclidine nitrogen (N1) and C(x), where C(x) is either the middle point between (C2) and (C4) carbon atoms or the center of mass in the substrate molecule. Similar free rotation of the substrate around the (C2)–(C4) axis cannot excluded either. Thus, in complex shown in Fig. 8a, there is no preferential stabilization of the substrate. The lack of stabilization is due to the fact that in this complex, CD acts as a monodentate ligand. The absence of preferential stabilization of the substrate indicates that the [methyl pyruvate–CD_{open}] complex cannot be responsible either for the ED or the RA.

The barrier for the rotation of the substrate in the [methyl pyruvate–CD_{open}] complex around the axis quinuclidine (N1) and C(x) was calculated and is shown in Fig. 9a and b for $r = 4$ Å and for $r = 3.5$ Å. In these calculations, the (C4) atom of the substrate was chosen as C(x), as (C4) is near the center of mass of the methyl pyruvate molecule. For all calculations, 3–3 atoms of the substrate and modifier molecules were fixed to define the rough relative position of both molecules and the position of the other atoms were left to change. The 0° for the rotation angle was defined as the initial structure.

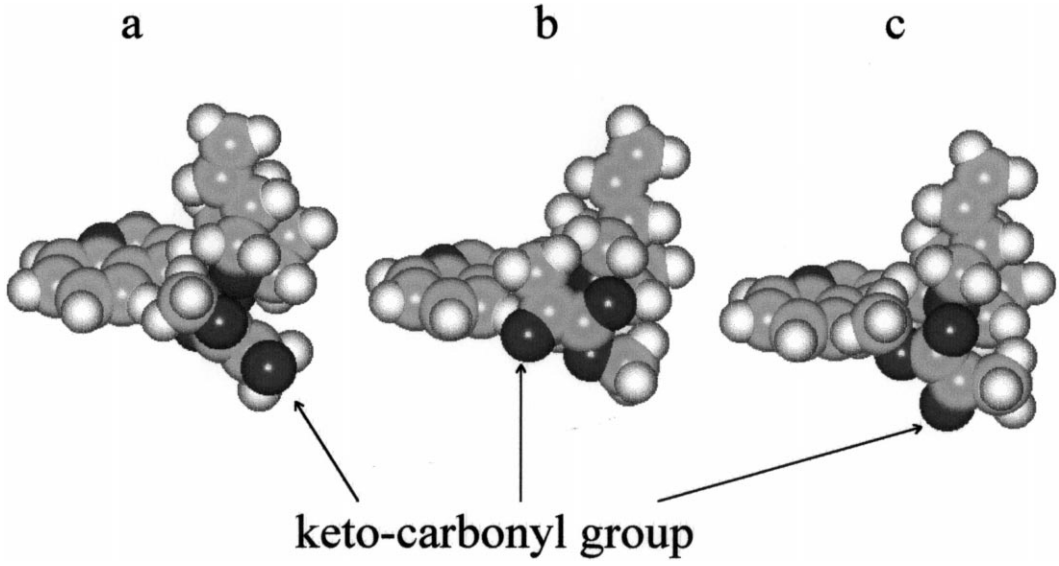


Fig. 8. [Methyl pyruvate–CD_{open}] complexes; (a) complex leading to the formation of (*R*)-lactate, (b) complex obtained by rotation of methyl pyruvate around the (N1)–(C4) axis, (c) complex obtained by rotation of methyl pyruvate around the (C2)–(C4) axis.

As far as in these calculations, the target of the geometry optimizations was not the total complex (six atoms were fixed), the minimum energies are not necessarily located at zero rotational angle. As emerges from Fig. 9a and b, the energy barrier required of free rotation around

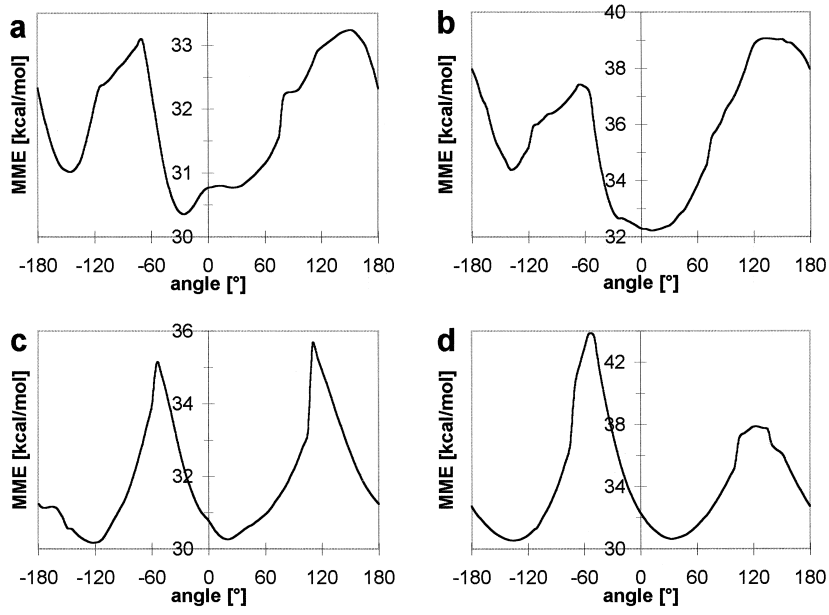


Fig. 9. Rotational barrier for the free rotation of methyl pyruvate in [methyl pyruvate–CD_{open}] complex. (a) Rotation around (N1)–(C4) axis, $r = 4$ Å. (b) Rotation around (N1)–(C4) axis, $r = 3.5$ Å. (c) Rotation around (C2)–(C4) axis, $r = 4$ Å. (d) Rotation around (C2)–(C4) axis, $r = 3.5$ Å.

the quinuclidine nitrogen is 3 kcal/mol (when $r = 4$ Å) and 7 kcal/mol (when $r = 3.5$ Å). In the latter case, the energy difference is only 5 kcal/mol for a 180° rotation. The resulted [methyl pyruvate–CD_{open}] complex is shown in Fig. 8b. However, the rotation of the substrate around (N1)–(C4) axis resulted in a complex, which upon hydrogenation should result in (*S*)-lactate.

The barrier for the free rotation around the (C2)–(C4) axis is shown in Fig. 9c and d. The above energy barriers are in the range of 5 kcal/mol for $r = 4$ Å and 13 kcal/mol for $r = 3.5$ Å, but the energy needed for a 180° rotation is only 7 kcal/mol. The resulted [methyl pyruvate–CD_{open}] complex is shown in Fig. 8c. In this complex, the orientation of the substrate is favourable for the formation of (*S*)-lactate. As emerges from the above calculations, the free rotation of the substrate either around the (N1)–(C4) or the (C2)–(C4) axis leads to the loss of ED.

Preliminary calculation shows if the protonated form of CD_{open} is used for calculation [27] due to the increased rotation axis, resulted in by addition of H^+ between (N1) and the (O3) carbonyl oxygen, the free rotation of the substrate will be sterically even more favourable. Based on these facts, we consider that the [methyl pyruvate–CD_{open}] complex cannot induce ED even in its protonated form. It is worth mentioning that the possibility of rotation of the substrate in the [methyl pyruvate–CD_{open}] complex was completely neglected in Ref. [24].

However, based on these results, we cannot exclude that the [methyl pyruvate–CD_{open}] complex is involved in the hydrogenation reaction, but it produces only racemate. The rate of this racemic hydrogenation is probably slightly higher than the rate of racemic hydrogenation in

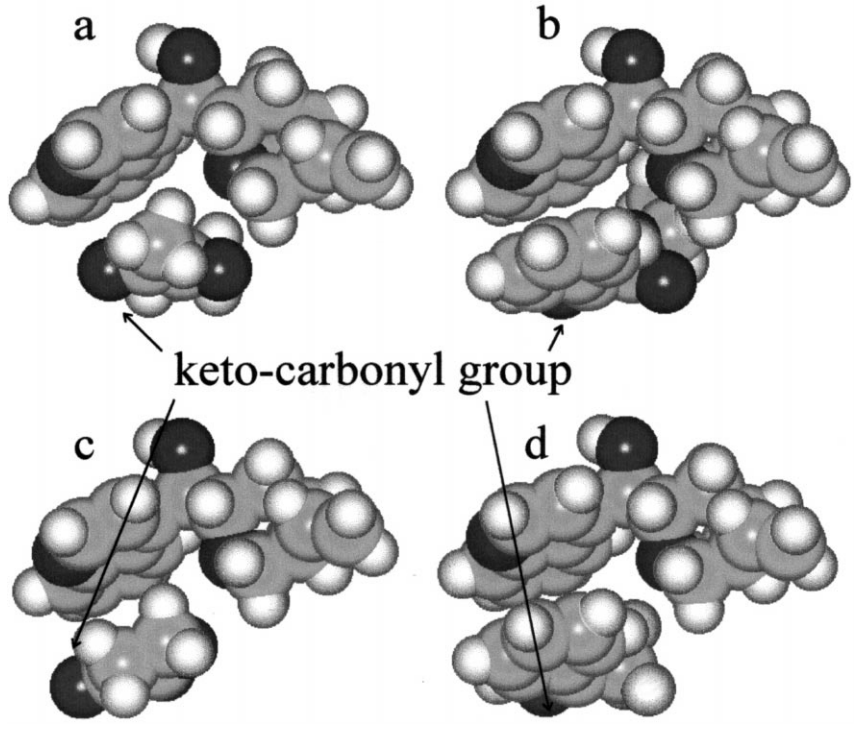


Fig. 10. [Substrate–CD_{closed}] complexes with different substrates; (a) ethyl pyruvate, (b) ethyl benzoylformate, (c) pantolactone, (d) trifluoroacetophenone.

Table 1
Measured r, ϑ and φ values for the calculated complexes of some substrates with the C1 and C2 conformations of the cinchonidine molecule

	Methyl pyruvate	Ethyl pyruvate	Ethyl mandalate	Pantolactone	TFAP
C1					
r	4.51	4.25	4.95	5.16	5.24
ϑ	149.10	130.63	158.65	125.92	154.19
φ	84.78	76.72	48.99	156.74	91.22
C2					
r	4.06	4.12	5.01	5.63	5.55
ϑ	146.50	147.81	157.47	158.70	160.47
φ	92.33	94.85	81.30	103.21	105.81

the absence of modifier. This racemic hydrogenation reaction has also been included into our overall kinetic model [5].

3.4. Modelling different substrate–modifier complexes with the involvement of the closed form of cinchonidine

Variety of other α-keto esters, such as ethyl pyruvate, methyl benzoylformate, dihydro-4,4-dimethyl-2,3-furanedione (pantolactone) were also used to calculate the shielded forms of [α-keto ester–CD_{closed}] complexes leading to the formation of (*R*) or (*S*) product, using the C1 and C2 conformations of the CD molecule. Fig. 10 shows the calculated [substrate–modifier] complexes of ethyl pyruvate (Fig. 10a), methyl benzoylformate (Fig. 10b) and dihydro-4,4-dimethyl-2,3-furanedione (pantolactone) (Fig. 10c), leading to the formation of corresponding (*R*)-lactate for the C2 form of CD. As emerges from these calculations, the favourable 'directionality' is maintained in the above complexes, even for dihydro-4,4-dimethyl-2,3-furanedione. The above defined r, ϑ and φ values of these complexes (see Fig. 5b) for both the C1 and C2 conformers of the CD molecule are presented in Table 1, which shows the proper directionality for the interaction between the (N1) nitrogen and the carbon atom of the corresponding keto compound.

The steric shielding provided by the quinoline ring can be seen for all substrates. Results given in Table 1 also indicate that the C2 conformation of CD provided better 'directionality' than the C1 conformation. As emerges from Table 1, the calculated r values are fairly long. This can be in relation with the point–point nature of the intermolecular interactions for the forcefield methods, which cannot take into consideration accurately the lone pair orbital of the quinuclidine nitrogen, the conjugated double bond system of the substrate and the aromatic nature of the quinoline ring.

The 'shielding' effect model can also be applied to model the substrate–modifier interactions involved between CD and other types of substrate. In this case, TFAP was used to demonstrate the validity of our model. TFAP was the first prochiral ketone, which could be hydrogenated in the presence of CD with high ee [28]. The [TFAP–CD_{closed}] complex is shown in Fig. 10d for the C2 form of CD.

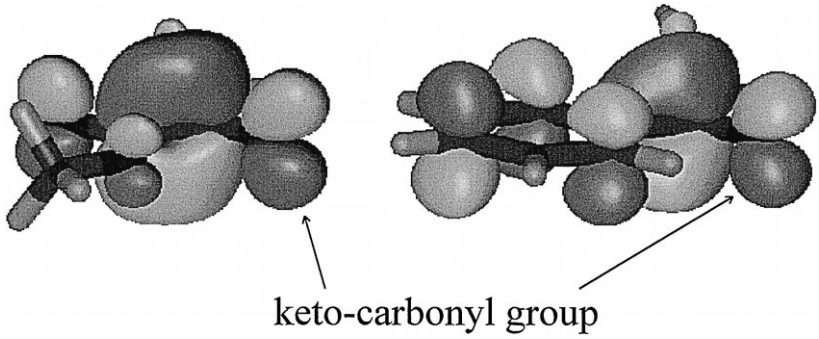


Fig. 11. The LUMOs of methyl pyruvate and trifluoroacetophenone.

Fig. 11 shows the LUMO for methyl pyruvate and TFAP. Fig. 11 clearly indicates the similarity between these two different substrates. In both substrates, the reacting prochiral keto carbonyl group forms a conjugated double bond system either with the ester carbonyl or the phenyl ring. Due to the above conjugation, both molecules are planar. In both substrates, the reacting prochiral keto group is activated by a strong electron-withdrawing group, i.e., either by an ester carbonyl or an CF_3-moiety. This activation can be responsible for the high activity of these ketones in the hydrogenation reaction.

4. Conclusions

A new model is proposed to understand the origin of ED in the hydrogenation of α-keto esters in the presence of a chiral modifier and heterogeneous catalysts. The shielding effect model was applied to explain both the RA and ED for the enantioselective hydrogenation of different α-keto esters. The model is based on the steric shielding provided by a large aromatic ring and the increased reactivity of the keto carbonyl. The latter was due to the nucleophilic attack of the quinuclidine nitrogen and the presence of an electron-withdrawing group near the keto group. The new model can explain the substrate specificity. The applicability of the model was shown for other types of substrate, such as TFAP. Our results demonstrate that molecular modelling with quantum chemical molecular mechanics calculations is a powerful tool to give qualitative explanations for the 'host–guest' type substrate–modifier interactions taking place in the liquid phase. In the next step, quantitative data should be presented for the above interactions. These calculations are in progress in our laboratories.

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