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Ab initio study of solvent effects on reactant–modifier complexes in enantioselective hydrogenation

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Abstract

In order to investigate enantiodifferentiation mechanism on a molecular level one-to-one complexes between protonated cinchonidine and methyl pyruvate, ketopantolactone as well as 1-phenylpropane-1,2-dione with and without an acetic acid molecule were investigated computationally with ab initio quantum chemical method at the Hartree–Fock level using 6-31G* basis set. The stabilities of the diastereomeric complexes and the electronic structure of the reactants were examined in order to correlate molecular level properties and enantioselectivity with the solvent effect (acetic acid versus toluene). A correlation between the keto carbonyl orbital energies and the complex stability was found. However, the enantiodiscrimination could not solely be explained in these terms. Acetic acid was found to have a large influence on the keto carbonyl orbital energies.

Keywords: Ab initio calculations; Enantioselective hydrogenation; Electronic structure; Cinchonidine

1. Introduction

Due to the importance of asymmetric synthesis and catalysis in chemistry hydrogenation of activated ketones over cinchonidine (CD) modified Pt catalysts has been actively investigated [1] by groups working in the field of catalysis, organic chemistry, surface science and quantum chemistry. The main focus of today's research is in the understanding of enantiodifferentiation mechanism on catalytically active surfaces. In addition to advanced kinetics and in situ spectroscopic techniques theoretical methods have become an important tool in these mechanistic studies. Several mechanistic models have been proposed [1–4] for enantioselective hydrogenation over cinchonidine (CD) modified Pt catalyst, which account for the experimentally observed enantioselectivity. Molecular modeling has been utilized to confirm and quantify the substrate–modifier interactions central in these models and often a good correlation with experiments have been reported [2,3].

According to current knowledge, a one-to-one reactant–modifier complex is the source of enantiodifferentiation in catalytic hydrogenation reactions. Despite the apparent conformational flexibility of the modifier, CD, the experimental and theoretical results show that CD mainly exists in Open(3) conformation [5,6]. The most studied and widely accepted models postulate a hydrogen bond interaction between the reactant and the protonated quinuclidine nitrogen of CD. The protonation of the quinuclidine N is indeed very likely due to its high proton affinity (ca. 1000 kJ mol^{-1} [4]) as long as proton donors are available. These donors could be, e.g. traces of water as impurity in the solvent, adsorbed hydrogen on Pt or acidic sites on the Al_2O_3 or SiO_2 support. Therefore, complexes formed between reactants and the protonated Open(3) conformation of CD have been studied in this work.

The solvent has a considerable effect on the reaction rate [1,4] and the enantiomeric excess (ee), defined as ee (%) = 100 × ([*R*] − [*S*])/([*R*] + [*S*]), where [*R*] and [*S*] are the concentrations of (*R*)- and (*S*)-product enantiomers.

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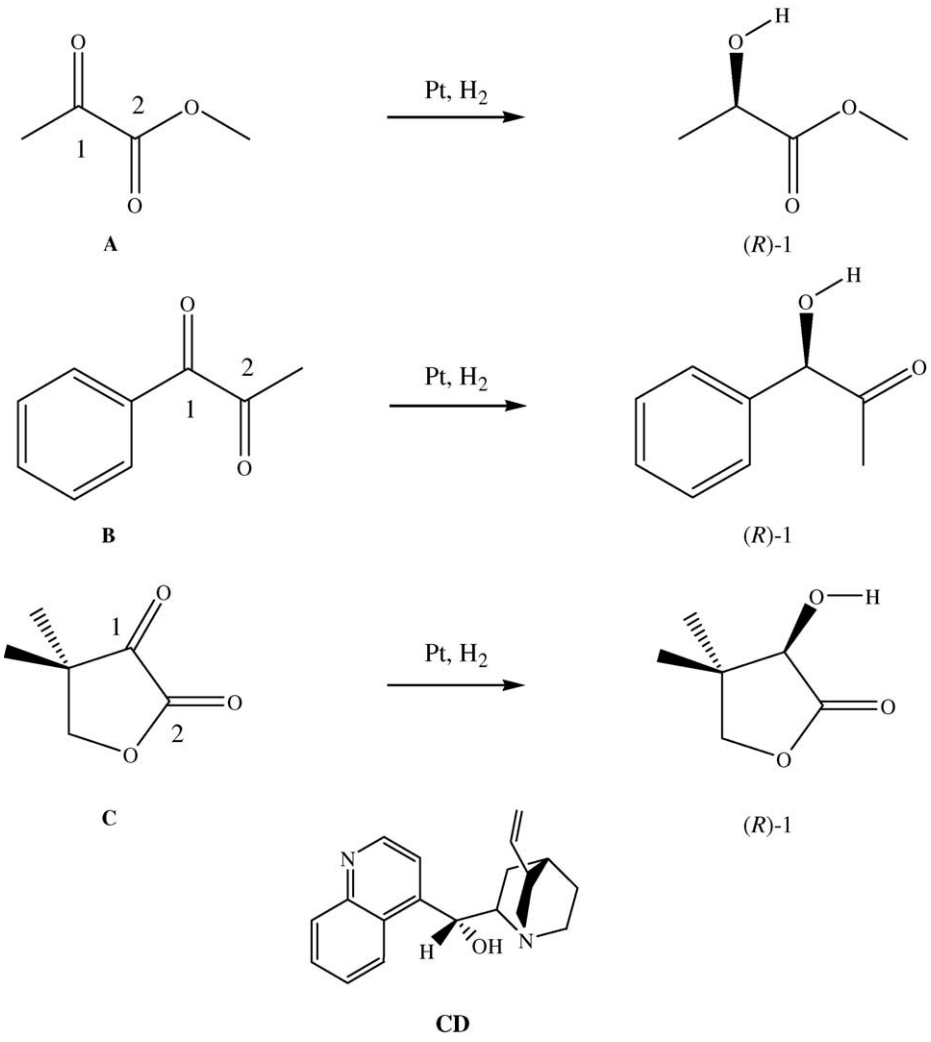

Fig. 1. Reactants and the excess enantiomers in the first hydrogenation reaction step over cinchonidine modified platinum surface. The reaction is regioselective meaning that the reaction takes place mainly at the C_1=O group.

Methyl pyruvate (**A**, an α-keto ester, Fig. 1) [2,7] reacts with higher ee in acetic acid [7] than in toluene, whereas 1-phenylpropane-1,2-dione (**B**) has a high ee = 65% in toluene and only a marginal 6% ee in acetic acid [4,8]. The negative effect of polar solvents, e.g. acetic acid and alcohols, on the enantioselectivity is characteristic not only of vicinal diones [4] but also of another α-keto ester, ketopantolactone (**C**), which has a very similar dependence on the solvent as **B** [3]. However, the dependence of enantiomeric excess on solvent cannot solely be explained in terms of solvent polarity since the dielectric constants for toluene and acetic acid are 2.4 and 6.2 at 20 °C, respectively, i.e. they do not differ that much in polarity. Therefore, e.g. the acidity of the solvent has to be considered, too.

As the dependence of the ee on solvent, particularly acetic acid, is not completely understood, the effects of an AcOH molecule on the properties of the diastereomeric reactant–modifier complexes were investigated computationally in the present work. **A**, **B** and **C** were used as model reactants (Fig. 1) because these compounds are among the frequently used substrates in the investigation of the enantioselective hydrogenation with chirally modified platinum catalysts and can be considered as representative ones. As mentioned above, they behave quite differently under the same reaction conditions. Furthermore, both reliable experimental and some molecular modeling results are available for these compounds in the literature. Thus these substrates provide an interesting basis for correlating theoretically obtained substrate–modifier interactions (thermodynamic or kinetic factors) with experiments.

2. Computational methods

The structures of the complexes were optimized without any constraints with conventional ab initio technique at the restricted Hartree–Fock (RHF) level [9] using the standard 6-31G* basis set and the GAUSSIAN 98 program package

[10]. No corrections were made for the basis set superposition error (BSSE). It was noted in the paper of Bürgi et al. [2] that for hydrogen-bonded complexes calculated at the HF level using medium-sized basis sets such as 6-31G(d,p), the BSSE and the correlation correction to the binding energy cancel quite evenly. All calculations were performed neglecting any possible complex solvation as if reactants were in the gas phase.

3. Results and discussion

3.1. Thermodynamic control

The origin of enantiodifferentiation has generally been proposed to be in the stability of different diastereomeric complexes (pro-*R* and pro-*S*, leading to (*R*)- and (*S*)-product enantiomers upon hydrogenation) between the modifier and the reactant (thermodynamic control). The crucial interaction is the hydrogen bond formed between the alkaloid and the substrate, which can be influenced by the solvent thus resulting into solvent dependent changes in the relative stability of the pro-*R* and pro-*S* complexes. The agreement of this ''thermodynamic'' model with the experimentally observed ee was investigated. First, minimum energy structures for complexes between protonated cinchonidine CDH^+ in Open(3) conformation and the reactant (**A**–**C**) were found. This represents the situation in toluene, or more exactly, in the gas phase. However, it is assumed here that toluene as a non-polar and aprotic solvent cannot bind to the positively charged complexes in a way, e.g. by hydrogen bond, which could change the relative stability of the diastereomeric complexes. In order to account for the effect of acetic acid, one AcOH molecule was placed near the reaction centre and the structures were fully optimized without restrictions. These complexes are shown in Figs. 2 and 3. The complexation energies and the values of the dihedral angles O=C–C=O in the reactants are given in Table 1.

In all optimized complexes the reactant and the quinoline ring of cinchonidine are nearly coplanar and consequently activated hydrogen on the Pt surface would have an easy access to the reactive C=O group. The reactants adopt s-*cis* conformation, which enables the formation of a bifurcated hydrogen bond between the N–H^+ proton and the two O atoms of both carbonyl groups of the reactants. On the contrary, the isolated optimized reactants are essentially in s-*trans* conformation (except for **C**).

Let us consider the complexation energies in Table 1. It is seen that the diastereomeric reactant-cinchonidine complexes are almost of equal energy, which does not explain enantioselectivity although the energies slightly favor the *R*-product with **A** and **B**. Bürgi and Baiker concluded [2] that the ee of **A** can only be rationalized by assuming that **A** adopts s-*trans* conformation in diastereomeric complexes, although it was reported that complexes where the reactant

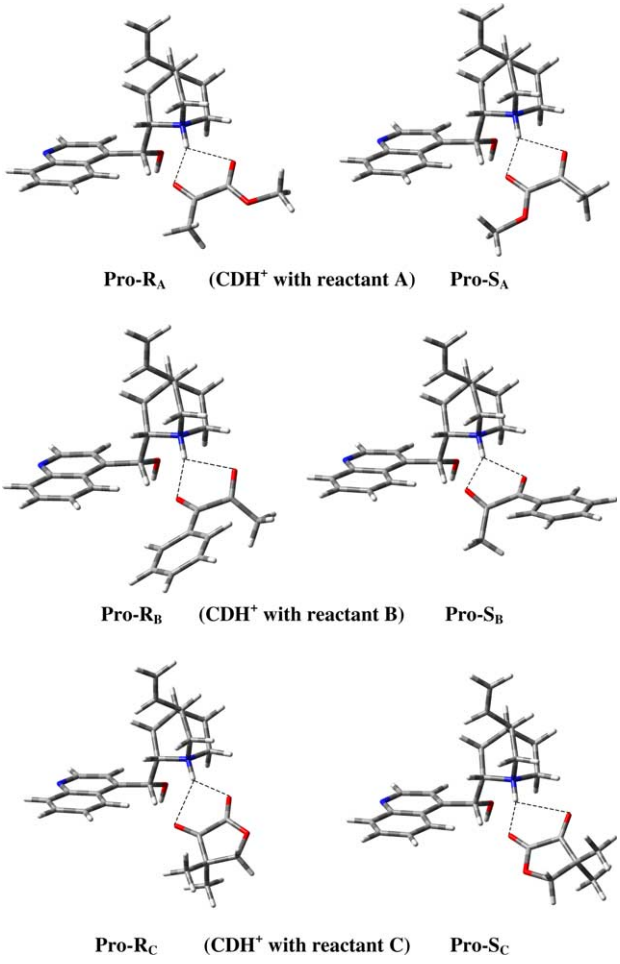

Fig. 2. Optimized CDH^+–reactant complexes for **A**, **B** and **C** without acetic acid. The dashed lines represent possible hydrogen bonds.

adopts s-*cis* are 9–17 kJ mol^{-1} more stable than s-*trans* forms. Our calculations are in agreement with these results. Detailed discussion about **B** in toluene can be found in [4]. The largest energy difference (6.3 kJ mol^{-1}) exists between the pro-*R* and pro-*S* complexes of **C** but it favors the formation of the pro-*S* complex, which would suggest the enantiomeric excess of the (*S*)-product. This is in contradiction with experiments and previous theoretical studies [3] carried out by using MM2 force field, which state that (*R*)-ketopantolactone is the major product. In the present work, electron correlation was taken into account in the complexes of **A** and **C** at the MP2/6-31G*//HF/6-31G* level but it was found to have only insignificant influence (<1 kJ mol^{-1}) on the relative stabilities of the complexes. The enlargement of the basis set from 6-31G* to 6-31G** to the complexes of methylpyruvate was also tested but it did not have any effect on the energy differences between pro-*S* and pro-*R* complexes, either.

The addition of an acetic acid molecule to reactant–cinchonidine complexes does not change the relative stability of the pro-*R* and pro-*S* complexes or the structure of the reactant considerably. Only in the case of the reactant

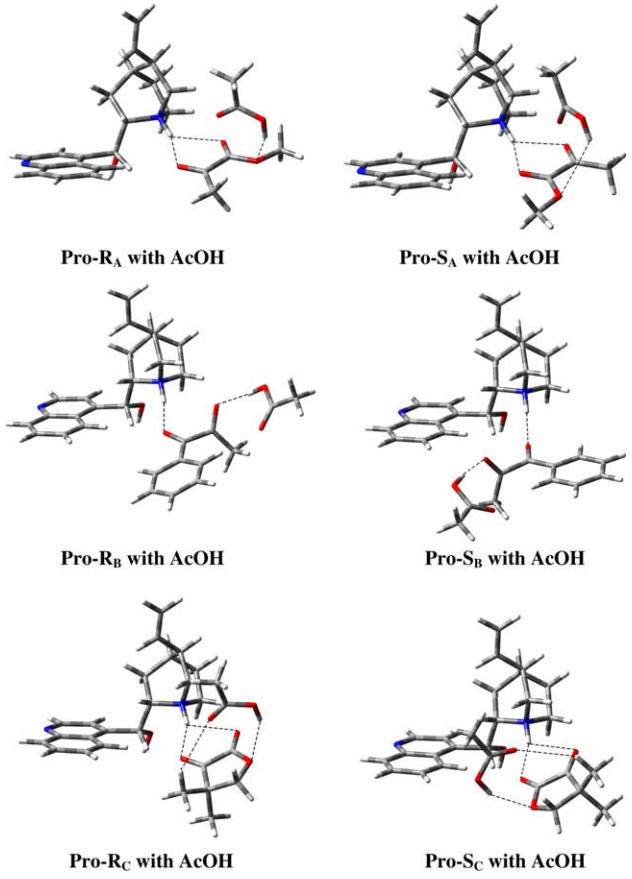

Fig. 3. Optimized CDH^+–reactant complexes for **A**, **B** and **C** with acetic acid. The dashed lines represent possible hydrogen bonds.

A the presence of AcOH changes the stability order of the diastereomeric complexes in the direction consistent with experiments, i.e. the pro-R_A complex is more stable with respect to the pro-S_A in acetic acid than in toluene. This would lead to an increased ee of the (*R*)-product in acetic acid. However, the energy difference between pro-R_A and pro-S_A in acetic acid (1.2 kJ mol^{-1}) is too small to explain high ee $\approx$ 98% in the hydrogenation reaction. Thus, the stability of the diastereomeric complexes (i.e. the thermodynamic control) does not explain enantiodiscrimination, at least within the framework of the present approach.

3.2. Kinetic control

Recently, Vargas et al. [11] proposed that kinetic factors may also play an important role in the enantioselective hydrogenation. They demonstrated that the stability of the keto carbonyl π-orbitals is a good measure for the reactivity of α-substituted ketones and also can be used to explain the observed enantioselectivity in the hydrogenation of some trifluoroacetophenone derivatives over cinchonidine-modified platinum. According to Vargas et al. [11], hydrogenation rates should depend on the energy differences between the carbonyl orbitals and the 1s orbital of the adsorbed hydrogen since these orbitals are strongly involved in the formation of the new bond. The 1s hydrogen orbital lies lower in energy than the reactive keto carbonyl orbitals of the reactant. Therefore, a stabilization of the keto carbonyl orbitals would induce an increase in orbital interaction, thus lowering the energy of the transition state and increasing the reaction rate. It was reported [11] that the sums of bonding and anti-bonding π-orbital energies are the most general, although not always the best parameters for reactivity. The HOMO–LUMO gap or carbonyl C atomic charge was not found to correlate with reactivity.

Table 1
The torsion angle D(O=C–C=O) (τ, °), complexation energies ($\Delta E_{complex}$, kJ mol^{-1}) and relative energies (kJ mol^{-1}) of the keto carbonyl anti-bonding π^*-orbital ($E_{A,B}$) and the two keto carbonyl bonding π-orbitals (E_{B1}, E_{B2})[a] in complexes formed by reactants (**A**–**C**) and protonated cinchonidine with and without acetic acid calculated at the HF/6-31G* level of theory

Complex	τ	$\Delta E_{complex}$[b]	$E_{A,B}$[c]	E_{B1}[d]	E_{B2}[e]	E_{sum}[f]
Pro-R_A	1.2	−85.8	0.0	0.0	0.0	0.0
Pro-S_A	7.8	−85.7	5.1	−17.1	14.2	2.3
Pure **A**	180.0	–	341.9	311.0	335.2	988.1
Pro-R_B	44.2	−70.9	0.0	0.0	0.0	0.0
Pro-S_B	−41.7	−69.5	2.7	8.0	1.8	12.5
Pure **B**	144.6	–	298.3	282.0	318.1	898.4
Pro-R_C	−7.1	−86.1	4.3	10.8	5.5	20.6
Pro-S_C	7.8	−92.4	0.0	0.0	0.0	0.0
Pure **C**	9.2	–	322.9	311.3	282.5	916.8
Complex with AcOH						
Pro-R_A	−5.0	−119.4	0.0	0.0	0.0	0.0
Pro-S_A	−2.5	−118.2	14.5	17.3	24.5	56.3
Pure **A**	180.0	–	303.5	313.6	316.2	933.3
Pro-R_B	53.3	−107.5	0.0	0.0	0.0	0.0
Pro-S_B	−84.5	−100.2	20.3	3.2	19.8	43.3
Pure **B**	144.6	–	274.4	264.3	303.3	842.1
Pro-R_C	−6.7	−129.6	2.5	14.1	4.6	21.3
Pro-S_C	5.4	−134.4	0.0	0.0	0.0	0.0
Pure **C**	9.2	–	292.5	302.3	267.7	862.4

[a] Energies relative to the energies of the corresponding orbitals in the most stable complex.
[b] Energies have been calculated as $\Delta E_{complex} = E_{complex} - E_{reactant} - E_{CDH^+}$ and $\Delta E_{complex} = E_{complex} - E_{reactant} - E_{CDH^+} - E_{AcOH}$ in complexes without and with AcOH, respectively.
[c] Anti-bonding π^*-orbital.
[d] Bonding π-orbital 1.
[e] Bonding π-orbital 2.
[f] $E_{sum} = E_{A,B} + E_{B1} + E_{B2}$.

Based on the experimental observation that the stabilization of the keto carbonyl orbitals in substituted acetophenones leads to a higher hydrogenation rate, the anti-bonding π^*-orbital (corresponding to LUMO of the molecule) and the highest energy bonding π-orbital of the O=C–C=O group were taken into consideration. The bonding π-orbital mixes with the orbitals of the substituents attached to the O=C–C=O group and is split essentially into two molecular orbitals, here referred as bonding 1 and bonding 2 orbitals. The description of these three orbitals for **B** can be found in [4]. The relative energies of anti-bonding, bonding 1 and bonding 2 orbitals and sums of them for the reactants in the complexes with and without AcOH are given in Table 1.

In the pro-R_A complex without AcOH, the orbitals are 2.3 kJ mol^{-1} more stable in all than the corresponding orbitals of the pro-S_A complex. Although this energy difference is almost negligible, it suggests that the pro-R_A complex reacts slightly faster to the (*R*)-1 enantiomer than the pro-S_A complex to the (*S*)-1 enantiomer, thus leading to the excess of the (*R*)-1 enantiomer. The presence of an AcOH molecule increases the stability of the pro-R_A orbitals considerably with respect to the pro-S_A orbitals indicating that in acetic acid pro-R_A complexes react even faster compared to pro-S_A complexes. This is a plausible explanation for the increase of the ee in AcOH using **A** as the reactant.

Similar analysis does not seem to hold so well when applied to other complexes. The orbitals in **B** are 12.5 kJ mol^{-1} more stable in the pro-R_B than in the pro-S_B complex (Table 1) which is in good agreement with the ee in toluene, but addition of an AcOH molecule increases the energy difference, which is not consistent with experiments (ee decreases in AcOH). In the case of **C** both $\Delta E_{complex}$ and ΔE_{sum} (i.e. thermodynamic and kinetic effects) seem to direct the reactivity toward the formation of (*S*)-1 enantiomer, which is contradictory to experiments [3]. This suggests that the diastereomeric complexes used for **B** and **C** are not controlling enantiodifferentiation or, more likely, our relatively simple model is not sufficient for describing experimental ee.

Table 1 shows a qualitative correlation between the stabilities of the complexes and the orbitals: the more stable diastereomeric complex also has more stable keto carbonyl orbitals. This trend is mainly due to the fact that the orbital energy is affected by the strength and energy of the hydrogen bond(s), which on the other hand depend on the interaction geometries that are connected with the complexation energies.

4. Conclusions

The molecular model used in this study to explain dependence of enantioselectivity on solvent nature in Pt catalyzed hydrogenation of methyl pyruvate (**A**), 1-phenylpropane-1,2-dione (**B**) and ketopantolactone (**C**) took into account possible thermodynamic and kinetic control. Respectively, the stability of diastereomeric complexes (pro-*R* and pro-*S*) and keto carbonyl π-orbital stabilization were able to explain an increase of ee for hydrogenation of **A** in acetic acid compared to toluene. However, similar ab initio quantum chemical approach at the Hartree–Fock level using 6-31G* basis set could not predict correctly experimentally observed trends for **B** and **C**, e.g. a decrease of enantioselectivity to (*R*)-enantiomer in acetic acid, indicating that more sophisticated models are needed. Therefore, other interaction geometries as well as inclusion of the platinum surface and solvation should be taken explicitly into account in order to satisfactorily explain the behavior of the reactants studied, which is a challenging task for future studies.

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