Origin of the rate acceleration in enantioselective hydrogenation of α-functionalised ketones over cinchona alkaloid modified platinum

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The origin of the rate acceleration in enantioselective hydrogenation of α-functionalised ketones over cinchona alkaloid modified platinum has been studied using a combined experimental and theoretical approach, and the rate acceleration is traced to a lowering of the energy of the carbonyl π orbitals in the diastereomeric complex formed between reactant and modifier.

Heterogeneous enantioselective hydrogenation of α-functionalised ketones on cinchona alkaloid modified platinum represents a promising route for the synthesis of chiral alcohols with high optical purity.[1–3] The reaction has received considerable attention in the last few years and the scope of the reaction is steadily broadening. On the other hand, its mechanism is still a matter of active debate.[4–6] A consistent model should be able to rationalise three characteristic features of the system: (*i*) enantiodiscrimination, (*ii*) the often observed rate acceleration induced by the modifier, and (*iii*) the effect of "activation" of the keto group through substituents.

A previously proposed mechanistic model[7,8] explains the first point by the different stability of the diastereomeric complexes, which would lead to *R* and *S* products, respectively, upon hydrogenation from the surface side. In this model an intermolecular interaction between the adsorbed modifier and the reactant leads to a discrimination for adsorption of the reactant on the two enantiofaces. Although simple, the model proved to be rather robust in predicting the absolute configuration of the reaction product and the enantiodifferentiating power of several synthetic modifiers.[2,9]

It is clear, however, that the relative rates of formation of *R* and *S* products depend not only on the relative stability of the interaction complexes but also on their intrinsic hydrogenation rate (reactivity). According to the Curtin–Hammett principle product distribution depends on the difference in the standard free energies of the respective transition states. The two (or more) complexes can be hydrogenated at different rates, independent of their thermodynamic stability. Depending on the relative value of the activation energies, E_S and E_R, we can distinguish three principal cases that are schematically shown in Fig. 1. The less stable complex (*S*) could in principle be hydrogenated faster (Fig. 1, case b).[10] The question whether the relative stability of the involved modifier-reactant complexes (thermodynamics) or their respective reactivity (kinetics) determines the relative apparent rates of reaction and enantiomeric excess is crucial for the understanding of the mechanism of enantiodiscrimination. This question will be addressed here. In the following we show that the same model proposed for enantioselection[2] also predicts rate acceleration with respect to the racemic reaction. The basis for this conclusion is the insight that the C=O group is activated towards hydrogenation through a lowering of the carbonyl π orbitals either by "electron withdrawing" substituents or hydrogen bonding with the modifier.

In order to gain insight into the relevant "activation" of the keto group we have studied the change in reactivity towards hydrogenation by (unmodified) platinum through substituent effects. The detailed experimental and theoretical results emerging from this study will be reported elsewhere.[11] Here we only focus on those results that are necessary to explain the origin of rate acceleration in the enantioselective hydrogenation. As a measure of the reactivity we chose the amount of reactant converted per time under fixed experimental conditions (solvent, temperature, pressure, catalyst). The thirteen investigated acetophenones showed differences in reactivity over a range of about two orders of magnitude. In parallel, *ab initio* electronic structure calculations were performed for all compounds. We have found that the experimentally determined reactivity is correlated with the stability of the keto carbonyl π orbitals. Fig. 2 shows a logarithmic plot of the measured reactivity (as defined above) in the hydrogenation catalysed by platinum *versus* the relative stability of the carbonyl π orbitals. A linear correlation is found, which resembles the classical Hammett relationship. A similar correlation was found for the energy of the bonding orbitals, whereas for the energy of the antibonding orbitals the correlation was less obvious.

The calculations show that the bonding carbonyl π orbital is delocalised over two MOs. One mixes in-phase with the aromatic π system, and the other mixes out-of-phase. For the analysis we considered the energy of the MO that had the biggest coefficient. In general this was the one that mixed not in-phase with the aromatic π system for the substituted acetophenones, and the other that mixes in-phase for substituted trifluoroacetophenones. This choice is justified within second-order pertur-

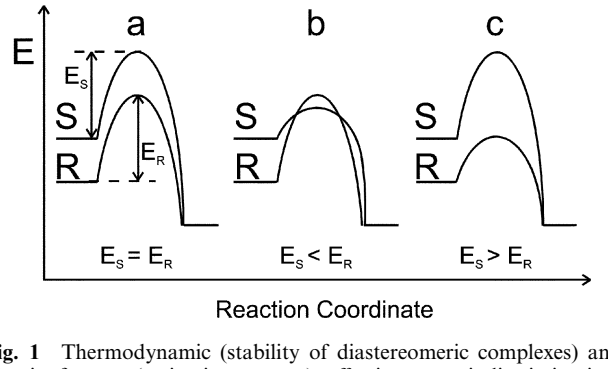


Fig. 1 Thermodynamic (stability of diastereomeric complexes) and kinetic factors (activation energy) affecting enantiodiscrimination. Three different cases can be distinguished: (a) $E_S = E_R$, (b) $E_S < E_R$, and (c) $E_S > E_R$. The initial state on the left in each case is the diastereomeric complex. The final state on the right in each case is the product after release from the chiral site.

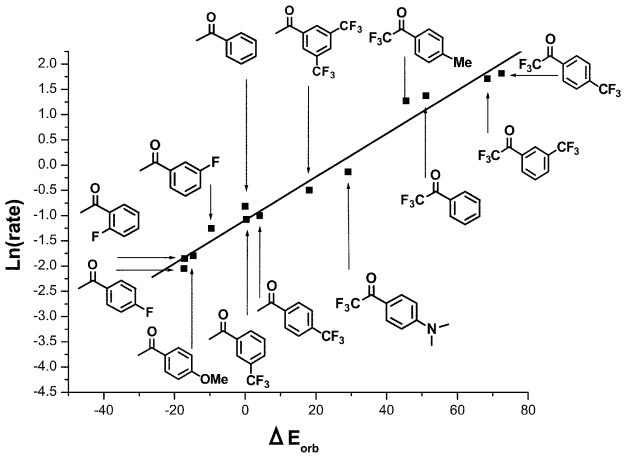


Fig. 2 Correlation between the relative orbital stabilisation ΔE_{orb} and the logarithm of the reaction rate (mmol h^{-1}).

bation theory[12] when considering that the contribution of the terms in the equation of the orbital controlled reaction is directly proportional to the product of the orbital coefficients. In detail, the values of ΔE_{orb} reported in Fig. 2 are the sums of two numbers: (*i*) the difference between the energy of the anti-bonding orbital of acetophenone (reference molecule) and the energy of the anti-bonding orbital of the respective substituted acetophenone or trifluoroacetophenone and (*ii*) the corresponding difference for the bonding orbitals. The orbital energies for the reference molecule acetophenone were calculated as 0.09344 Hartrees (anti-bonding) and −0.49134 Hartrees (bonding). Positive values of ΔE_{orb} denote more stable orbitals with respect to acetophenone. The larger is the value of ΔE_{orb}, the closer is the energy of the carbonyl orbitals to the energy of the hydrogen 1s orbital.

The correlation between reactivity and stability of the carbonyl π orbitals as shown in Fig. 2 can be rationalised using qualitative molecular orbital arguments. Upon transferring an H atom from the Pt surface to the carbonyl group the energy of the transition state is critically dependent on the energy gained by the formation of the new bond. It is here that the (rehybridised) carbonyl π orbitals play an important role. As a hydrogen atom approaches the carbonyl group the hydrogen 1s and carbonyl π and π* orbitals overlap. This leads to stabilisation of two-orbital three-electron and two-orbital one-electron interactions, as schematically shown in Fig. 3. A stabilisation of the carbonyl π orbitals, for example through substituents, decreases the energy gap to the hydrogen 1s orbital. This leads to an increased stabilising orbital interaction energy, to a lower hydrogenation barrier and a larger hydrogenation rate. This also explains why the sum of the relative orbital energies is a good measure for reactivity, since the overall orbital stabilisation depends on both the π and π* orbitals. Whether the first addition of hydrogen is on the oxygen or the carbon (as shown in Fig. 3) is still an open question. Since the π and π* orbitals have contributions from both atoms our discussion does not rely on any assumptions concerning this point.

It should be noted that the energy of the π orbitals could also influence the adsorption strength of the reactant, which would be reflected in an apparent hydrogenation rate having non-zero order kinetics with respect to the reactant. In our conditions the reaction rate is close to zero order, which was experimentally verified by comparison of the initial rate of hydrogenation of trifluoroacetophenone with different concentrations in the range of the applied standard reaction. Therefore, we conclude that differences in adsorption strengths cannot explain the large range, about two orders of magnitude, of observed reaction rates. Furthermore, earlier work suggested that electronic substituent effects do not have a large influence on the adsorption strengths of acetophenones.[13]

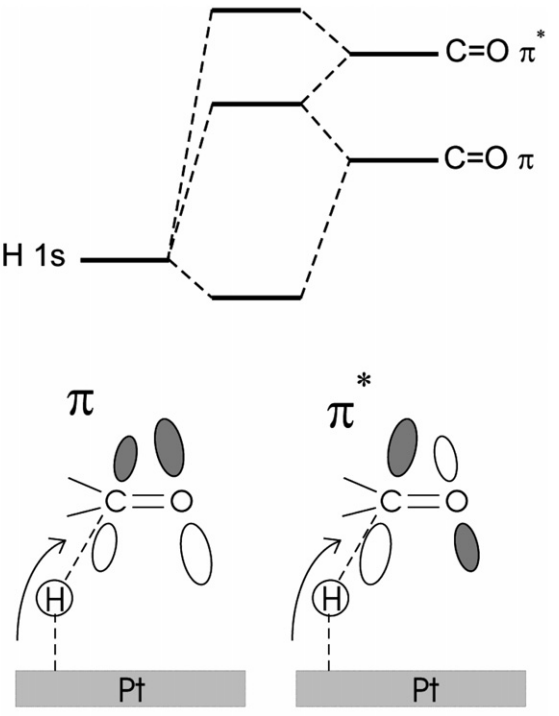


Fig. 3 Scheme of the orbital interactions that imply the participation of both the bonding and anti-bonding orbitals of the keto carbonyl moiety in the hydrogen uptake process.

The linearity of the correlation as depicted in Fig. 2 is explainable based on second-order perturbation theory, if we assume that the energy gap between the hydrogen 1s and the carbonyl orbitals of acetophenone, ΔE_{AP}, is much larger than the energy shift of the latter orbitals, ΔE_{orb}, due to substituent effects. The interaction energy $\Delta\varepsilon$ between orbitals is inversely proportional to the energy difference between the carbonyl orbital and the 1s hydrogen orbital. If ΔE_{AP} is the energy of an acetophenone π orbital with respect to the hydrogen 1s orbital, then we can write:

$$\Delta\varepsilon \propto \frac{1}{\Delta E} = \frac{1}{\Delta E_{AP} - \Delta E_{orb}} \propto \Delta E_{orb}$$

The result is that the more stabilised are the orbitals of the substituted acetophenones, the larger is ΔE_{orb}, and the larger is the predicted reactivity. The good quality of the correlation that has been found (correlation coefficient 0.99) shows that, at least for this system, the parameters used are able to describe the reactivity of the reactants. Similar arguments were used before for the interpretation of nucleophilic attack.[14]

On the other hand, the calculated charge at the carbonyl carbon did not correlate well with the reactivity. Upon substitution of the methyl group of acetophenone by the "electron-withdrawing" CF_3 group the Mulliken charge analysis showed that the electron density at the carbonyl carbon increased by circa 0.1 electron instead of decreasing, as might have been intuitively expected. The same trend was found when fitting atomic charges to the electrostatic potential derived from the *ab initio* calculations.[15] In addition, ^{13}C NMR experiments showed a shielding, instead of a deshielding, of the carbonyl carbon upon substitution of hydrogen by fluorine atoms in *n*-fluoroacetophenones ($n = 0$–3).

Given the correlation between activity and carbonyl π orbital energy the often observed rate acceleration induced by the cinchona alkaloid modifier in the hydrogenation reaction can

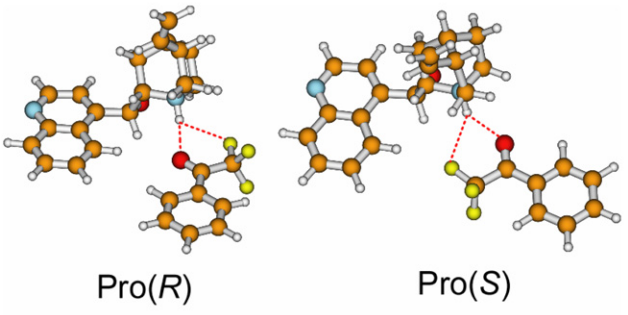


Fig. 4 Calculated pro(*R*) and pro(*S*) interaction complexes between cinchonidine and trifluoroacetophenone. Dashed lines indicate hydrogen bonding interactions. The complexes were optimised by leaving the aromatic moieties of cinchonidine and trifluoroacetophenone in a coplanar arrangement in order to consider the constraints imposed by the Pt surface.

be rationalised within the model proposed for enantiodifferentiation.[2,7,16] Quantum chemical calculations show that the hydrogen bond between the cinchonidine and the keto carbonyl group (Fig. 4) results in a stabilisation of the carbonyl orbitals and therefore in a rate acceleration with respect to a non-interacting carbonyl group. The calculated stabilisation of both the carbonyl bonding and anti-bonding π orbitals upon complex formation lies in the range of 50–100 kcal mol^{-1} for the compounds under study.

Furthermore, the calculations show that the carbonyl π orbitals are *differentially* stabilised in the diastereomeric complexes assumed in the previously proposed model.[2,7] In this model the aromatic moiety of the cinchonidine modifier and the reactant are assumed to be adsorbed parallel to the surface. The two molecules interact *via* a hydrogen bond between the protonated quaternary quinolinic amine of the modifier and the carbonyl oxygen of the reactant. Fig. 4 shows the optimised geometry of the pro(*R*) and pro(*S*) complexes between cinchonidine and trifluoroacetophenone. The differential stabilisation of the π orbitals leads to different intrinsic hydrogenation rates for the pathways to *R* and *S* products. The sum of the differential stabilisations of the carbonyl π orbitals is calculated to lie in the range of 1.0–5.0 kcal mol^{-1}. The calculations for acetophenone derivatives, for which experimental data measured under similar conditions are available,[17] show that in general within a couple of diastereomeric complexes, the more stabilised carbonyl π orbitals are associated with the more stable complex (Table 1) because both the stability of a complex and the stabilisation of the carbonyl π orbitals increase with the strength of the intermolecular hydrogen bond. Hence, while in general the most stable complex is not necessarily the one that is hydrogenated the fastest[10] (Fig. 1, case c), the calculations indicate that in this particular case this seems to hold. Table 1 summarises the results of these calculations and compares them with the experimental data. The calculations show that the pro(*R*) complexes have more stable carbonyl π orbitals, which is in line with the experimental observation that the *R* product is favoured.

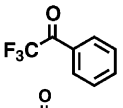
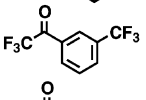
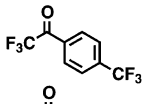
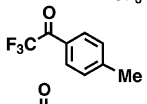
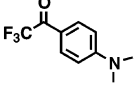
In conclusion, the mechanistic model previously proposed[2,7] to explain enantiodifferentiation in the enantioselective hydrogenation of carbonyl compounds over chirally modified platinum also predicts the often observed rate acceleration induced by the modifier. In addition, different rates are predicted for the pathways to *R* and *S* products. In general the more stable interaction complex within a diastereomeric couple is hydrogenated faster. The key feature of this insight is the observed correlation between hydrogenation rate and stability of the carbonyl π orbitals of the reactant.

Experimental and theoretical methods

All substrates were used as received (Fluka, Aldrich, Lancaster). Pt/Al_2O_3 catalyst (5 wt %) was pre-reduced as described elsewhere.[18] Under standard conditions 42 ± 2 mg of catalyst, 1.84 mmol of substrate, and 5 ml of toluene were stirred magnetically (1000 rpm) under a constant hydrogen pressure of 10 bar, at room temperature.[17] For the enantioselective hydrogenations 6.8 mmol of cinchonidine was added to the reaction mixture together with the substrate. Other parameters were the same as for the racemic reaction.

All calculations have been performed using the Gaussian[19] package, at the HF/6-31G* level of theory. For calculations of the free molecules all degrees of freedom were optimised and the orbital analysis was performed on the optimised structures. For the interaction complexes (such as those in Fig. 4) planar constraints were imposed on the reactant in order keep the quinoline part of the cinchonidine modifier and the reac-

Table 1 Calculated enantiomeric excess (ee), experimental ee (under standard conditions, see experimental) and calculated differential stabilisation of π orbitals

	Calcd		Exptal		Calcd
	Major enantiomer	ee[a]	Major enantiomer	ee	Differential stabilisation of π orbitals[b] /kcal mol^{-1}
	*R*	25%	*R*	36%	3.7
	*R*	69%	*R*	40%	3.5
	*R*	25%	*R*	11%	4.5
	*R*	25%	*R*	6%	3.4
	*R*	40%	*R*	27%	4.0

[a] Based only on the energy difference of the diastereomeric complexes, which would lead to *R* and *S* products, respectively. Calculated ee refer to 298 K. [b] Energy difference between carbonyl π orbitals in the pro(*R*) and pro(*S*) complexes. The sum of the energy differences of bonding and anti-bonding orbitals is given. For all diastereomeric couples the pro(*R*) complex has more stable carbonyl π orbitals.

tant coplanar. This simulates the constraints imposed by the catalyst surface on the adsorbed interaction complex.[9,20] All other degrees of freedom were optimised.

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