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Model of Reactant–Modifier Interaction in Enantioselective Hydrogenation of Ethyl Pyruvate on Platinum–Cinchona Catalysts: Extension to Synthetic Chiral Modifiers

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The previously proposed model for reactant–modifier interaction in the enantioselective hydrogenation of activated carbonyl compounds over platinum chirally modified by cinchona alkaloids has been extended to platinum modified by synthetic pyrrolidinyl–naphthyl–ethanol modifiers. As in the case of cinchonidine, the most used modifier, the model predicts enantiomeric excess in nearly quantitative agreement with experiment. Excellent agreement is achieved despite the fact that structural assumptions had to be made and the platinum surface was not explicitly taken into account. The one-to-one interaction between modifier and reactant was calculated at the ab initio level. A comparison of the results for different modifiers leads to the conclusion that steric repulsion caused by the anchoring group plays an important role in the enantiodifferentiating interaction. The favoured formation of the (*R*)-product is traced to the fact that the pro-(*S*) complex leading to the (*S*)-product upon hydrogenation is more destabilised due to repulsive interaction than the pro-(*R*) complex. The model calculations are a useful tool for designing effective modifiers and for gaining insight into the mechanism of enantiodifferentiation. © 2001 Academic Press

Key Words: **enantioselective hydrogenation; ethyl pyruvate; platinum; chiral modifier; pyrrolidinyl–naphthyl–ethanol; reactant–modifier complex; cinchona alkaloids; synthetic chiral modifiers.**

1. INTRODUCTION

The mechanism of enantiodifferentiation in the heterogeneous asymmetric hydrogenation of activated carbonyl compounds over chirally modified platinum metals has received much attention in recent years (1–3), mostly due to the increasing interest in enantio-pure chemicals and the technical advantages of a heterogeneous process. The hydrogenation of ethyl or methyl pyruvate to ethyl or methyl lactate over platinum in the presence of minute amounts of cinchona alkaloids is highly enantioselective and has served as a model reaction investigated by many groups. Systematic variation of the modifier structure lead to the conclusion (3) that a potential modifier is composed of (i) an anchoring group, through which the modifier is attached (adsorbed) to the platinum surface, (ii) a stereogenic region, and (iii) a nitrogen atom that is responsible for the interaction with the reactant. Based on this insight, synthetic modifiers were successfully designed (see **1** and **2** in Scheme 1) (4–10), which seems to support the view that a successful modifier is composed of the mentioned structural elements.

The structure of the synthetic modifiers in Scheme 1 is simplified with respect to the original cinchonidine. The quinoline group of cinchonidine, which is thought to act as the anchor, is substituted by a naphthyl group. The quinuclidine moiety is substituted by a pyrrolidinyl group and the number of stereogenic centers is reduced from 5 to 1. The unique stereogenic center that is left has an (*R*) absolute configuration for the molecules in Scheme 1, which is the same absolute configuration also present in the corresponding cinchonidine carbon atom. Recently, it became evident that the function of the three structural elements mentioned above cannot be considered independently of each other. For example, comparison of the three modifiers cinchonidine, deoxycinchonidine, and (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol (**1** in Scheme 1) shows that there is not one stereogenic center common to all three modifiers, although all of them give the same preferred chirality of the product with similar enantiomeric excess (ee). It is more the absolute arrangement of the anchoring group and amino group that is the common structural feature of the three modifiers. This arrangement is influenced by the anchoring group itself. Furthermore, repulsion with the anchoring group may be crucial in the enantiodifferentiating interaction (11).

An interaction model for the enantiodifferentiating cinchonidine–ethyl (methyl) pyruvate complex has been proposed some time ago, which allowed one to rationalize the outcome of the absolute configuration of the product (3, 12–14). Very recently, we have shown that this model yields almost quantitative predictions for the enantiomeric excess

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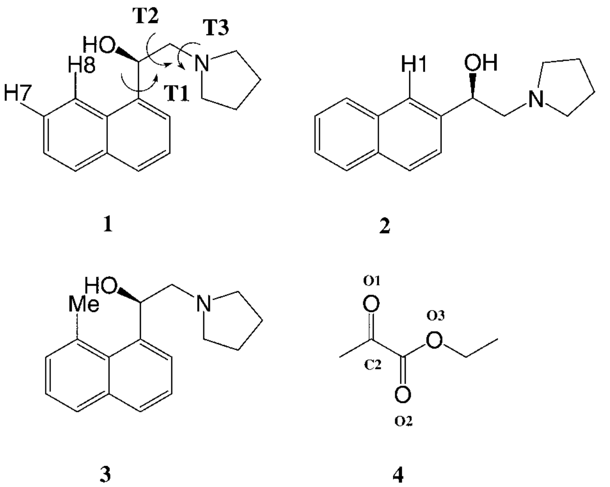

SCHEME 1. Synthetic modifiers: (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl) ethanol **1**, (*R*)-2-(1-pyrrolidinyl)-1-(2-naphthyl)ethanol **2**, and (*R*)-2-(1-pyrrolidinyl)-1-[1-(8-methyl-naphthyl)]ethanol **3**. Ethyl pyruvate **4**.

in the case of cinchonidine–methyl pyruvate, if the interaction is treated at the ab initio quantum chemical level (11).

In the present work we applied the same methodology to the synthetic modifiers shown in Scheme 1. The aim of the work was (i) to check whether the good agreement between experimental and calculated enantiomeric excess also holds for the synthetic modifiers, (ii) to rationalize the difference in enantiodifferentiating power of modifiers **1** and **2** (Scheme 1), and (iii) to gain better insight into the role of the anchoring group in the enantiodifferentiating interaction.

2. MODEL FOR ENANTIODIFFERENTIATION AND COMPUTATIONAL METHODS

The model calculations aimed at predicting the enantiomeric excess (ee) for the hydrogenation of ethyl pyruvate over platinum modified with a particular modifier. Due to the complexity of the reaction, several assumptions had to be made. It was assumed that the modifiers (Scheme 1) adsorb through π-bonding of the naphthyl moiety that lays flat on the metal surface. Also, ethyl pyruvate was assumed to adsorb flat on the Pt surface through the conjugated π-system. A one-to-one complex between ethyl pyruvate and the modifier is thought to be crucial for enantiodifferentiation. The two molecules interact via a hydrogen bond between the protonated N atom of the modifier and the keto carbonyl group of ethyl pyruvate.

Experimental evidence for the preferential flat adsorption of cinchonidine on Pt(111) under UHV conditions has recently been provided by a NEXAFS study (15). Analogous adsorption behavior was assumed for the synthetic modifiers in the study. The ethyl pyruvate, on the other hand, seems to exhibit more complex adsorption behavior. Its adsorption on Ni(111) has been investigated using IRRAS (16). It was concluded that adsorption occurs through the oxygen nonbonding electrons of the keto and ester carbonyl groups, in agreement with XPS, UPS (17), XANES (18), STM, and NEXAFS (19) measurements on Pt(111). In particular, the XANES study showed that the ethyl pyruvate molecular plane is tilted 72° with respect to the platinum surface. In the presence of coadsorbed hydrogen the ethyl pyruvate has a tendency to lie down (18). The hydrogen transfer that creates a stereogenic center is the one to the keto carbonyl C. To have access to activated hydrogen, this C atom has to be close to the surface, which is only possible when ethyl pyruvate is adsorbed flat or nearly flat during hydrogen transfer. The flat adsorption of ethyl pyruvate and the modifier on the platinum surface was taken into account by constraining the molecular plane of ethyl pyruvate coplanar to the naphthyl moiety of the modifier, without explicitly considering the platinum surface. The conformation of the modifiers has been assumed to be *open(3)*. According to a computational conformational analysis, *open(3)* proved to be the most stable conformer. A full conformational analysis concerning the two rotational angles T1 and T2 already used for the study of the conformations of cinchonidine (20) has been performed at a semiempirical level using the MNDO (21) and AM1 hamiltonians (22). The minima found on the resulting potential energy surface were further optimized at the HF-6-31G* level of theory. For modifier **1** this resulted in a stabilization energy of 1 kcal/mol of *open(3)* when compared to that of *open(4)*, the next more stable conformation. This result was similar to what was already found for cinchonidine both theoretically and experimentally (23). For modifier **2** the energies of *open(3)* and *open(4)* were similar ($\Delta E = 0.02$ kcal/mol), consistent with what would have been intuitively expected. The two conformations are less discriminated than those for **1** by the relative positions of pyrrolidine and the anchoring group. For **1** the major contribution to the discrimination of *open(3)* and *open(4)* comes from the steric interaction between the OH group and H_8, similar to that in cinchonidine but which is absent in **2**. For **2** the next more stable conformation is *open(6)*, with an energy difference of almost 2 kcal/mol. The structural features of the *open(3)* and *open(4)* conformations for modifier **2** are similar in the region where the interaction with the reactant occurs, and for the calculation of the interaction with *trans* and *cis* ethyl pyruvate *open(3)* was chosen. The conformational behaviour of the synthetic modifiers has shown remarkable similarities to that of cinchonidine, for which there exist solid evidence that *open(3)* plays a major role in the enantiodifferentiation process, both from the relative abundance of this conformation (23) and from the fact that rigid open conformers are able to induce high enantiomeric excesses (24). This is an additional reason for choosing *open(3)* as the preferred conformation for model calculations. For ethyl pyruvate both the *s-trans* and the *s-cis* conformations have been considered, although the model calculations afford a good prediction for ee only for the *s-trans* conformation, when cinchonidine is used as the surface modifier (11). For the *s-cis* conformer, which is according to IRRAS studies more abundant on Ni(111) (16), the model fails to predict reasonable enantiodifferentiation (11). The model furthermore assumes that the hydrogen approaches the keto carbonyl C from below, i.e., from the surface side, and that the enantiodifferentiation is determined by the relative stability of the complexes, which would yield (*R*)- and (*S*)-product, respectively, upon hydrogenation. These complexes will be designated pro-(*R*) and pro-(*S*) in the following.

Theoretical ee's were calculated from the relative abundance of the pro-(*R*) and pro-(*S*) complexes at 298°C, which was determined from the calculated relative energy of the complexes, thus neglecting differences in entropy. Calculations were performed at the Hartree–Fock (HF) level with the Gaussian 98 program (25) using the 6-31G* basis set of Pople and co-workers (26, 27). Binding energies were determined as the difference between the energy of the complex and the separated molecules without corrections for the basis set superposition error (BSSE). For hydrogen-bonded complexes calculated at the HF level using medium-sized basis sets, such as the one used in the present study, the BSSE and the correlation corrections (MP2) cancel quite evenly (28). All geometries have been optimized using the constraints for planarity described above. Molden (29) was used as the graphical interface.

3. RESULTS

Table 1 lists calculated energetic and structural data of the investigated complexes for the cases in which the ethyl pyruvate (EP) is adsorbed in the *trans* and in the *cis* conformations. Theoretical and experimental ee's are also compared. Figures 1–5 show the optimized structures of the pro-(*R*) and pro-(*S*) complexes for the investigated modifiers. The theoretical ee is in good agreement with experiment, with an overestimation of ca. 15% for both modifiers **1** and **2**, when the ethyl pyruvate is assumed to be bound in the *trans* conformation. The predicted loss in ee when going from modifier **1** to **2**, which differ only in the position of the pyrrolidinyl moiety, is calculated to be 28%, whereas it is 26% in the experiment. On the other hand, when the *cis* conformation is assumed for the ester, the predicted ee is much lower. Nevertheless, still the pro-(*R*) complex is more stable than the pro-(*S*), although the values found

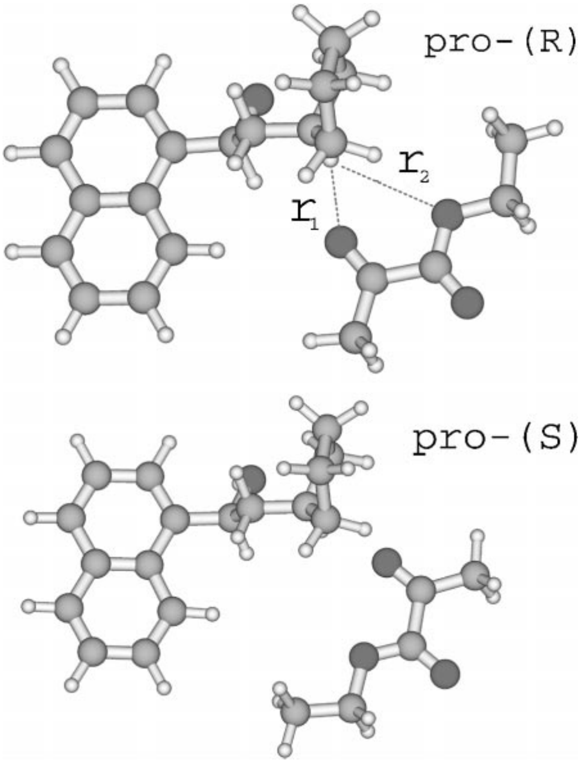

FIG. 1. Minimum energy structures of the pro-(*R*) and pro-(*S*) interaction complexes between (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol **1** and *trans* ethyl pyruvate. View perpendicular to the plane of the naphthyl group.

TABLE 1

Experimental and Theoretical Data for the Complexes Formed between the Modifiers 1, 2, and 3 and Ethyl Pyruvate (EP) (Scheme 1) (Energies Are Given in kcal/mol and Distances r_1 and r_2 in Å)

	Binding energy					r_1		r_2	
Complex	pro-(*R*)	pro-(*S*)	ΔE	e.e.(calc)	e.e.(exp)	pro-(*R*)	pro-(*S*)	pro-(*R*)	pro-(*S*)
1-*trans*-EP	14.7	13.2	1.45	84%	68%[a]	2.04	2.05	3.15	3.57
2-*trans*-EP	14.6	13.8	0.80	56%	42%[b]	1.99	2.01	3.28	3.49
1-*cis*-EP	20.1	19.9	0.16	13%	68%[a]	2.32	2.32	2.28	2.27
2-*cis*-EP	19.9	19.7	0.15	13%	42%[b]	2.21	2.49	2.45	2.17
3-*trans*-EP	14.2	12.8	1.49	85%		2.01	2.08	3.32	3.91

[a] Taken from Ref. (4).

[b] Taken from Ref. (7).

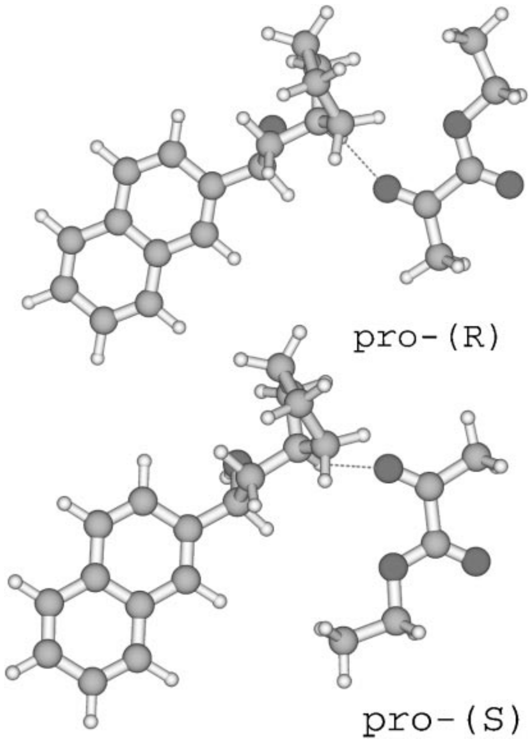

FIG. 2. Minimum energy structures of the pro-(R) and pro-(S) interaction complexes between (R)-2-(1-pyrrolidinyl)-1-(2-naphthyl)ethanol **2** and *trans* ethyl pyruvate. View perpendicular to the plane of the naphthyl group.

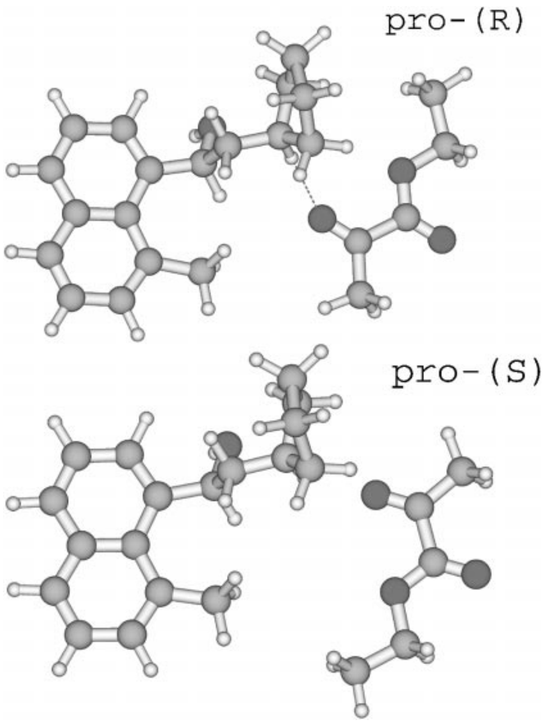

FIG. 3. Minimum energy structures of the pro-(R) and pro-(S) interaction complexes between (R)-2-(1-pyrrolidinyl)-1-[1-(8-methylnaphthyl)]ethanol **3** and *trans* ethyl pyruvate. View perpendicular to the plane of the naphthyl group.

in this case are far from quantitative. Binding energies are nearly identical for the *trans* pro-(R) complexes of modifiers **1** and **2**. On the other hand, the binding energies for the *trans* pro-(S) complexes are significantly different, indicating that the source of enantiodifferentiation is the destabilisation of the *trans* pro-(S) complex. The binding energies for the *cis* complexes are evidently higher than those for the *trans* complexes. The difference roughly lies between 5 and 6 kcal/mol. On the other hand, at the HF 6-31G* level of theory, in vacuo, the energy difference between the free *cis* and *trans* conformers is 2.0 kcal/mol in favour of the *trans*, corresponding to an equilibrium constant of ca. 30.

The calculated binding energy for modifier **3** with *trans* ethyl pyruvate is lower for both the pro-(R) and the pro-(S) complexes but the energy difference between them does not increase with respect to modifier **1**, showing that the additional methyl group in position 8 on the naphthyl group has a destabilising effect for both the pro-(R) and the pro-(S) complexes, in almost equal amounts.

In the complexes a bifurcated hydrogen bond is formed between the protonated N atom of the modifier and both the keto and the ester carbonyl oxygens. The hydrogen bond lengths for the keto and ester carbonyl oxygens are designated r_1 and r_2, respectively (see Fig. 1) and are listed in Table 1. Both modifiers **1** and **2** have a shorter r_1 in the

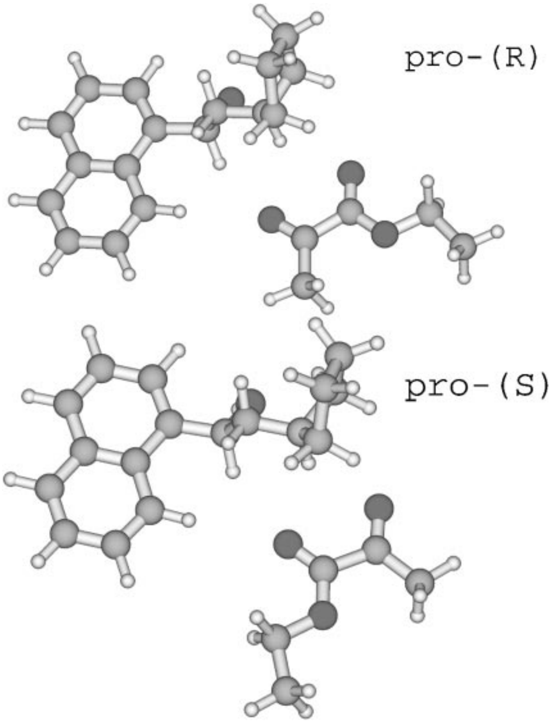

FIG. 4. Minimum energy structures of the pro-(R) and pro-(S) interaction complexes between (R)-2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol **1** and *cis* ethyl pyruvate. View perpendicular to the plane of the naphthyl group.

TABLE 2

HF/6-31G* Mulliken Charges of Free Ethyl Pyruvate (EP) and EP Complexes with Modifiers 1 and 2 (Atom Labelling According to Scheme 1)

			trans-EP-**1**		*trans*-EP-**2**		*cis*-EP-**1**		*cis*-EP-**2**	
Atom	*trans* EP free	*cis* EP free	pro-(R)	pro-(S)	pro-(R)	pro-(S)	pro-(R)	pro-(S)	pro-(R)	pro-(S)
C2	+0.44	+0.44	+0.47	+0.47	+0.47	+0.47	+0.46	+0.45	+0.46	+0.45
O1	−0.46	−0.46	−0.55	−0.55	−0.55	−0.55	−0.52	−0.51	−0.52	−0.51
O2	−0.52	−0.55	−0.52	−0.52	−0.51	−0.52	−0.58	−0.59	−0.58	−0.59
O3	−0.63	−0.60	−0.63	−0.62	−0.63	−0.62	−0.61	−0.61	−0.61	−0.61

pro-(R) complex, although the difference $(r_1)_{pro\text{-}(R)} - (r_1)_{pro\text{-}(S)}$ is larger for modifier **2**. The latter also has a shorter absolute value for $(r_1)_{pro\text{-}(R)}$, indicating a stronger hydrogen bond that does not reflect the bonding energy value. An interesting parameter to analyse is the sum $(r_1) + (r_2)$ for the various complexes. For the *trans* pro-(R) complex of modifier **1** this sum is 5.19 Å while in the pro-(S) case its value is 5.62 Å, with a difference Δ of 0.43 Å. For modifier **2** this difference amounts to 0.22, and it is 0.67 Å for modifier **3** due to the elongation of r_2 to 3.91 Å in the pro-(S) complex. Mulliken charges have been calculated and are reported in Table 2. We notice an increase in charge separation at the level of the reactive carbonyl group when passing from the free substrate to the bound substrate, which is slightly more pronounced for *trans* EP. The charge separation at the carbonyl passes from 0.90 to 1.02 in the case of the *trans* ethyl pyruvate and from 0.90 to 0.98–0.96 in the case of the *cis* ethyl pyruvate. In particular, for both modifers **1** and **2** the charge separation of the *cis*-EP-pro-(R) is 0.98 and the charge separation of the *cis*-EP-pro(S) is 0.96.

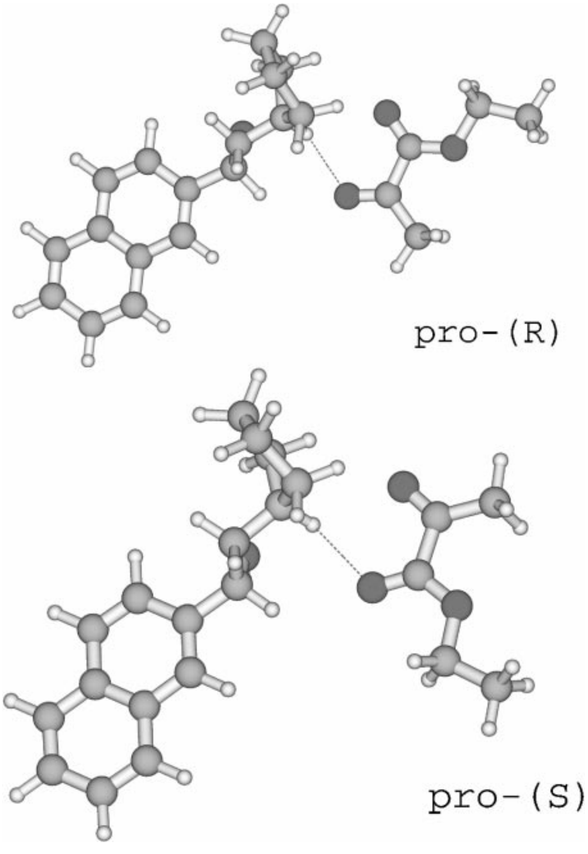

FIG. 5. Minimum energy structures of the pro-(R) and pro-(S) interaction complexes between (R)-2-(1-pyrrolidinyl)-1-(2-naphthyl)ethanol **2** and *cis* ethyl pyruvate. View perpendicular to the plane of the naphthyl group.

4. DISCUSSION

Modifiers **1** and **2** have been chosen in this study because the difference in their enantiodifferentiating ability allows one to test the hypothesis that the repulsion between ethyl (methyl) pyruvate and the anchoring group plays a crucial role in enantiodifferentiation (11). The two modifiers differ only in the position of the pyrrolidinyl moiety at the naphthyl anchoring group. Differences in adsorption energy and geometry are thus expected to be of minor importance and the experimentally observed significant difference in their enantiodifferentiating power has to be due to other reasons. A comparison between Figs. 1 and 2 shows that there is no steric hindrance between *trans* ethyl pyruvate and the naphthyl moiety in the pro-(R) complex for modifier **2** (Fig. 2). For the pro-(S) complexes of both modifiers, **1** and **2**, repulsion between *trans* ethyl pyruvate and the naphthyl moiety significantly influences the optimal hydrogen-bonding geometry. This distortion manifests itself in a larger r_2 value for the pro-(S) than for the pro-(R) complexes (Table 1), which is more pronounced for modifier **1**, leading to a larger energy difference between the pro-(R) and pro-(S) complexes for the latter. The bonding energy for the different *trans* complexes given in Table 1 indicates that destabilisation of the pro-(S) complex is more important for the ΔE than stabilisation of the pro-(R) complex. All of the above shows the importance of the repulsive interaction between the anchoring group and *trans* ethyl pyruvate. Within the pro-(R) complex of modifier **1** steric repulsion also occurs between the pyrrolidine ring and the ethyl ester moiety with a shortest H–H distance of 2.70 Å. The analogous distance is 2.83 Å for modifier **2**.

For *cis* ethyl pyruvate the calculations predict more stable complexes than those for *trans* ethyl pyruvate. On the other hand, the energy difference between pro-(R) and pro-(S) is lower than that for *trans* ethyl pyruvate. This leads to lower predicted ee for *cis*. Much better agreement between experimental and calculated ee for *trans* compared to *cis* was already found for the cinchonidine–methyl pyruvate system (11). Furthermore, the difference in enantiodifferentiating power of modifiers **1** and **2** is correctly predicted for *trans* EP but not for *cis* EP. As in the case of cinchonidine–methyl pyruvate, we face the situation where, according to the calculations, the thermodynamically less favorable *trans* complexes are predicted to result in ee in excellent agreement with experiment. This could be an indication that the hydrogenation route via the *trans* complexes is kinetically favored. A feasible explanation is the faster intrinsic hydrogenation rate of the *trans* complexes due to stronger activation by the modifier. The charge analysis supports such a contention. A different explanation is that the thermodynamic equilibrium between *cis* EP and *trans* EP is not established on the surface. Note that *trans* ethyl pyruvate is more abundant in the gas phase and apolar solvents (30). This situation would become important when hydrogenation is faster than *cis*–*trans* equilibration on the surface. Another possibility is that under reaction conditions the interactions of the coadsorbed species favor the *trans* conformation of EP. At the present time, these issues have not been clarified.

In a previous study (10) a ΔE of 0.34 kcal/mol between the *trans* pro-(R) and pro-(S) complexes of modifier **1** was calculated using a force field approach (CFF91 version 2.0). Already at that level of theory, the sense of the product chirality could be predicted. However, the energy difference between the complexes is significantly smaller at the force field level. Larger computational resources render now the same computation feasible at an ab initio level with a medium size basis set. The number of basis functions used for the present study is 446, which gives an idea of the size of the calculation that can be routinely used for more accurate investigation.

Based on the insight that repulsion with the anchoring group is decisive for enantiodifferentiation, new modifiers might be designed that enhance this repulsion for the pro-(S) complexes. The results for modifier **3**, however, show that this may not be straightforward, as detailed in the following paragraph.

In modifier **1** (*trans* complexes) the repulsion is at the level of protons 7 and 8 (Scheme 1), whereas in modifier **2** the repulsive interaction is with proton 1 but only in the pro-(S) case, while in the pro-(R) complex the methyl group of ethyl pyruvate is sufficiently distant from proton 1 (4.8 Å) to rule out sterical hindrance. The spatial region occupied by ethyl pyruvate in the pro-(R) and pro-(S) complexes is quite similar for **1**. In other words, in the pro-(R) complex of modifier **1**, the methyl group in position α to the keto carbonyl causes sterical hindrance with the anchoring group in a fashion similar to that of the larger ethyl ester group in the corresponding pro-(S) complex. According to this, the presence of a methyl group in position 8 on the naphthalene ring (modifier **3**, Scheme 1, Fig. 3) should affect both the pro-(R) and the pro-(S) complexes. A comparison of the binding energies of **1** and **3** in Table 1 shows that this is indeed true and that the destabilisation induced by the additional methyl group is similar for the pro-(R) and the pro-(S) complex, leaving the theoretical ee basically unchanged.

It is worth noting that the natural modifier cinchonidine affords higher ee than the synthetic modifier **1** (3). One possible reason for this behavior could be the enhanced flexibility of modifier **1** as compared to that of cinchonidine. The pyrrolidinyl–naphthyl–ethanol modifiers have an additional degree of freedom, T3 (see Scheme 1), compared to those of cinchonidine, which allows the N atom (or the proton on the N atom) to point to different directions in space. This indicates that a fixed angle T3, and therefore a more rigid structure, is favourable for enantiodifferentiation. The calculated increase of charge separation at the level of the carbonyl upon complex formation could be important with respect to the experimentally observed hydrogenation rate acceleration in the presence of the modifier. The charge analysis indicates that the ethyl pyruvate within the complex is more activated compared to free ethyl pyruvate. In this respect the calculations indicate that the *cis* ethyl pyruvate complexes are less activated than the *trans*-EP complexes.

5. CONCLUSIONS

A striking quantitative agreement between calculated and experimental enantiomeric excess for the enantioselective hydrogenation of ethyl pyruvate over chirally modified platinum has been found for synthetic pyrrolidinyl–naphthyl–ethanol modifiers, assuming that ethyl pyruvate exists in the *trans* conformation in the adsorbed enantiodifferentiating complex. Although the model calculations were done without a quantum chemical consideration of the adsorption of the modifier and reactant, the good agreement with experiment suggests that the model accounts for the crucial factors determining the behavior of the complex catalytic system. The destabilising repulsive interaction between ethyl pyruvate and the anchoring group within the pro-(S) complex has been identified to be important for enantiodifferentiation.

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