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Theoretical Modeling of the Interaction Chiral Modifier/Substrate as a Key Step in the Enantioselective Hydrogenation of α-ketoesters and Vicinal Diketones

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Abstract: This paper deals with the computational modeling of the chiral modifier/substrate interaction for chiral modifiers studied in our laboratory, different from those conventionally used in enantioselective hydrogenation reactions. (S)-(+)-1-Aminoindane and (R)-(-)-1-aminoindane were chosen as chiral modifiers and the selected substrates were methyl pyruvate, ethyl pyruvate and 1-ethyl-4,4-dimethyl-pyrrolidin-2,3,5-trione.

The geometry of each of the chiral modifier/substrate complexes was optimized using DFT calculations and a BLYP functional. The theoretical enantiomeric excess was calculated from the energy of each of the proposed complexes. The calculations were carried out considering different reaction solvents through the use of COSMO program.

It was found that this simple model allows predicting the experimental values of both the sense of enantiodifferentiation and the enantiomeric excess with a good approximation. It was also able to predict the *inversion of configuration* when using the (S)-(+)-1-aminoindane as chiral modifier in polar solvents such as acetic acid and 2-propanol.

Keywords: Theoretical modeling, Enantioselectivity, DFT, Hydrogenation, Chiral modifiers, Aminoindane.

INTRODUCTION

The use of chiral modifiers that are adsorbed onto metal surfaces has proven to be one of the most effective ways to transfer the chirality using heterogeneous catalysts. From the point of view of chemical composition, at present there are only three systems based on chirally modified metallic catalysts that allow obtaining enantiomeric excesses above 90%. These are the systems: Ni-tartaric acid for the hydrogenation of β-ketoesters [1, 2], Pt catalysts modified with alkaloid of the cinchona family for hydrogenation of α-ketoesters [3-6] and systems based on Pd using the same cinchona-derived modifiers, which are very efficient for the hydrogenation of α,β-unsaturated acids [7, 8].

The catalytic system consisting of Pt supported on a material of large specific area, such as SiO_2 or Al_2O_3, modified with alkaloids of the cinchona family has been one of the most extensively studied. This catalytic system was discovered in the late 70´s by Orito [9-12]. Although much progress has been made since then regarding the comprehension of the reaction mechanism, today it is still not fully elucidated.

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The hydrogenation of vicinal diketones can also be carried out enantioselectively with this same type of catalysts. Although the reaction mechanism has not been studied as extensively as in the case of α-ketoesters, obvious mechanistic similarities exist between the hydrogenation of α-ketoesters and vicinal diketones. The dependence on the properties of the catalyst (pretreatment, activation, structural properties, etc.), the solvent and concentration of the modifier is in some cases very similar.

In mechanistic studies of asymmetric heterogeneous metal catalysts, crucial questions are: which the nature of the chiral site is, and how enantiodifferentiation occurs on the metal surface. These questions are difficult to answer when the system involved is a three-phase system. The interrelationship of all the participating elements can be very complex as it involves the solid catalyst, the liquid phase (solvent, dissolved reactants and products and chiral modifier) and the gas phase [13].

The effect of the solvent has been extensively studied. Variations were observed in the activity, selectivity, and even in the stereoselectivity depending on the type of solvent used. However, the factors responsible for these variations can be various, for example the solubility of the liquid and gaseous reactants and their adsorption on the catalyst surface, competitive adsorption of solvent molecules, solvent interaction with both reagents in the bulk solution and at the surface of the catalyst and catalyst deactivation by the solvent. Moreover, complex organic molecules can exist in several conformations and the populations of the different con-

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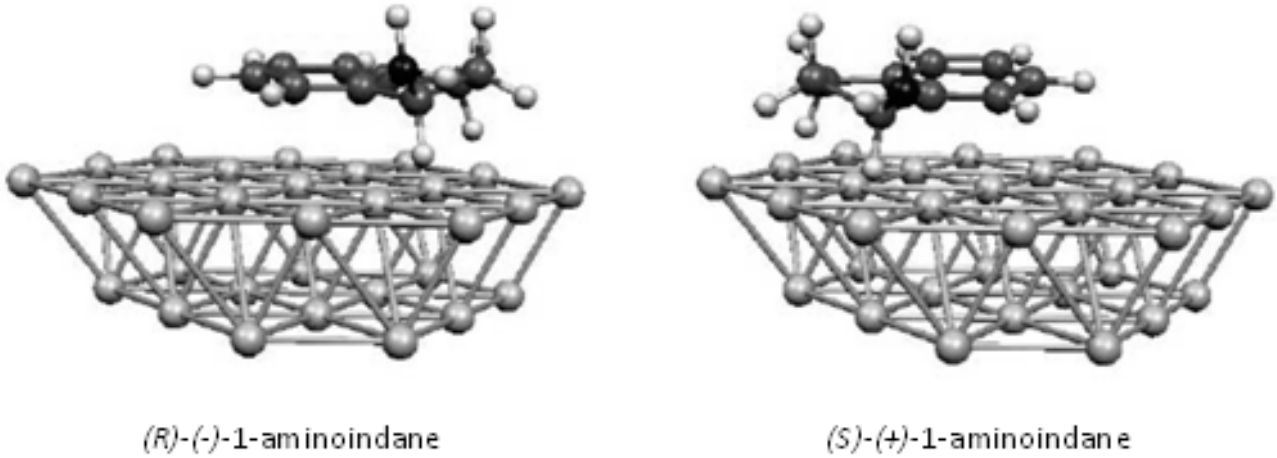

Fig. (1). 3D picture of (R)-(-)-1-aminoindane and (S)-(+)-1-aminoindane in a Pt surface. (Pt surface was not calculated, it´s only a representative scheme).

formers apparently may vary depending on the dielectric constant of the solvent and this would affect the selectivity. Thus, the phenomenon known as solvent effect is actually a combination of different physical and chemical phenomena, making it difficult to fully understand it. Attempts to generalize the results of heterogeneous catalysis in terms of solvent properties have not been successful [5].

With respect to the structure of chiral modifiers belonging to the cinchona family there are three key factors that appear to be responsible for the enantiodifferentiation. We can call these three structural factors that are present in all modifiers the anchor group, the group with a basic nitrogen atom near the stereogenic center and the chiral center [14].

From the knowledge of the structural requirements considered necessary to achieve positive results in enantioselective hydrogenation reactions of α-ketoesters, and with the intention of designing or finding an efficient catalyst for these reactions, we have studied the behavior of two chiral modifiers. These molecules are: (S)-(+)-1-aminoindane and (R)-(-)-1-aminoindane. These molecules have in their structure the three aforementioned characteristics necessary to generate enantiodifferentiation, however they are smaller, simpler and as rigid as cinchonidine and other chiral molecules used as modifiers belonging to the cinchona family [15].

With the aim of contributing to the understanding of the mechanism of enantiodifferentiation and finding a mechanistic model, we analyzed the substrate-modifier interaction, using the aforementioned modeling modifiers and different substrates in different solvents.

MOLECULAR MODELING AND THEORETICAL CALCULATIONS

Due to the complexity of the metal catalyst/chiral modifier/substrate/solvent system, to make the calculations several approximations were performed. Thus, the contribution of the metal was not explicitly considered in our calculations, since it involves a large computational demand. However, the presence of the catalytic surface was implicitly taken into account when considering the geometry of both the modifiers and the substrates. For the cinchonidine molecule there is experimental evidence, obtained from NEXAFS in UHV condition studies, demonstrating that this molecule is preferentially adsorbed in a parallel way on a Pt (111) surface [16].

Taking into account that aminoindanes behave similarly to the cinchonidine molecule, the classical chiral modifier employed in this type of catalytic systems, it was considered that the molecules of both modifiers (S)-(+)-1-aminoindane and (R)-(-)-1-aminoindane (Fig. **1**) would adsorbed onto the metal surface through a bond that involves their π-system, *i.e.* they remain practically parallel to the surface.

The conformational behavior of several α-ketoesters such as ethyl pyruvate, and vicinal diketones has been extensively studied in various solvents, both by IR spectroscopy and through theoretical calculations [17]. These studies revealed that the O=C-C=O bond is very flexible due to the small energy difference between both conformers; even at room temperature both of them coexist. In polar solvents, the *cis* conformer percentage increases and becomes comparable to that of the *trans*. The *cis* conformer percentage increases with the polarity of the solvent due to its higher dipole moment with respect to the *trans*. An increase in the fraction of *cis*-ethyl pyruvate with increasing solvent dielectric constant is a typical behavior of stabilization of a conformer through solvation, as predicted by Onsager´s law. From an energy point of view, the higher dipole moment of the *cis* conformation compared to that of the *trans* also favors the complex formation through hydrogen bonds with charged species of the type R_3N^+-H.

The complexes formed by the *cis* conformer of substrates such as ethyl pyruvate are between 4 and 7 kcal/mol more stable than those formed by the *trans* one. This has to do with the possibility of the *cis* conformer to interact with two hydrogen atoms of the RNH_3^+ group at a time, through its two C=O groups, since in this conformer these two groups are pointing to the same side [15]. Owing to the fact that the complexes formed by the modifier and substrates in their *cis* conformation are much more stable than those formed by the substrates in their *trans* conformation, only the former were taken into account when considering the complexes formed with the tested substrates.

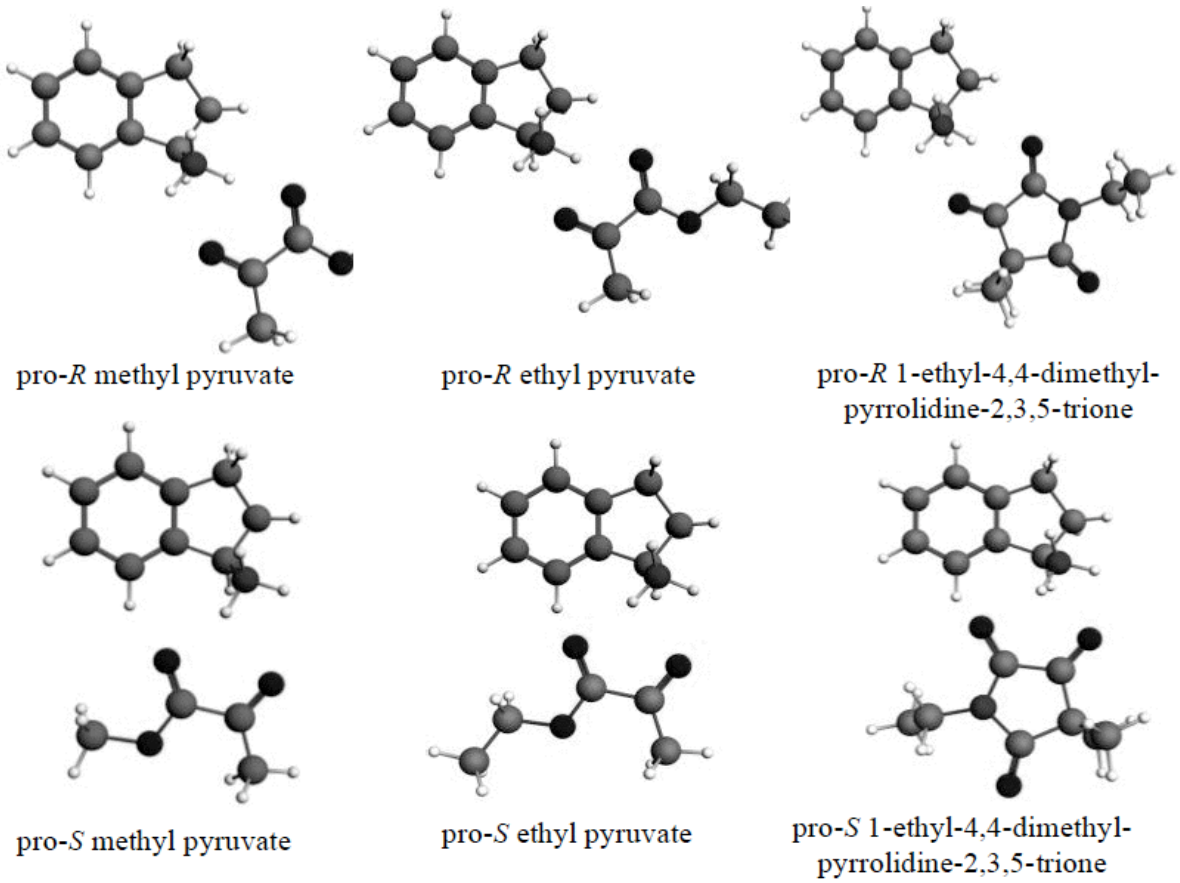

Fig. (2). Geometries of the complexes formed between R-(-)-aminoindane and each one of the substrates in both conformations.

In the present paper, besides considering a 1:1 interaction between the modifier and the substrate and a flat or nearly flat and parallel to the surface adsorption of the modifier, the mechanistic model selected proposes that the interaction responsible for the complex formation is always the same: the one existing between the quinuclidinic nitrogen atom of the modifier molecule and the carbonyl group of the substrate, regardless of the nature and polarity of the solvent.

Three different substrates were studied, two α-ketoesters (methyl pyruvate and ethyl pyruvate) and a vicinal diketone (1-ethyl-4,4-dimethyl-pyrrolidin-2,3,5-trione). The molecular structure of the latter is similar to that of a α-ketoester considering the two neighboring carbonyl groups, and therefore it is expected to interact in a similar way with the protonated N atom of the chiral modifier, through a hydrogen bond. All the potential complexes formed between the selected substrates and modifiers in different solvents were studied in order to determine whether there is any effect of the solvent polarity.

COMPUTATIONAL DETAILS

For each solvent considered, the two potential transition states for each modifier, (S)-(+)-1-aminoindane and (R)-(-)-1-aminoindane, were studied, without explicit consideration of the metal surface in the calculations. These states are called pro-(S) and pro-(R), respectively. As an example, Fig. (**2**) shows the initial geometry of the complexes formed between the (R)-(-)-1-aminoindane modifier and the three substrates. These geometries were optimized using the ADF (Amsterdam Density Functional) commercial software [18]. The DFT (Density Functional Theory) level optimizations were conducted using the BLYP functional [19] and a set of triple-Z quality bases plus a polarization function, called TZP.

As above-mentioned, another important factor when modeling this kind of system is the reaction solvent. The polarity of the solvent plays a significant role in the total energy of the system, especially in what concerns the solvation energies of the complexes proposed in this study.

One way to approach the model systems to the real systems would be to calculate their energy not in *vacuum*, but in a reaction medium that more closely resembles the solvents in which reactions were experimentally performed. To introduce this improvement into the modeling, each of the geometries previously optimized in *vacuum* were reoptimized using the solvation model provided by the ADF program called COSMO (Conductor-like Screening Model). This program allows determining the energy of the complexes in an environment of dielectric constant that simulates the reaction medium. COSMO is a dielectric model in which the solute molecule is included in a cavity having the molecular form of the solute, which in turn is surrounded by a medium of a given dielectric constant ε [20]. For these geometries optimization calculations, BLYP functionals and the TZP basis set were also used. All DFT level calculations were performed with the ADF program.

Table 1. Binding Energies of the Complexes and ee% Calculated in Acetic Acid.

Acetic Acid				
Modifier	**Substrate**	**BE (kcal/mol)**		**ee % (calc)**
		pro-*R*	**pro-*S***	
R-(-)-aminoindane	Methyl pyruvate	-5.150	-5.100	4.22 (*R*)
	Ethyl pyruvate	-7.053	-6.664	31.69 (*R*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-4.120	-3.170	66.55 (*R*)
S-(+)-aminoindane	Methyl pyruvate	-5.220	-5.020	16.74 (*R*)
	Ethyl pyruvate	-6.284	-6.126	13.29 (*R*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-4.420	-3.640	57.77 (*R*)

The binding energies (BE) were calculated as the difference between the energy of the complex formed and the energy of the molecules separated at an infinite distance.

$$BE = E_{complex} - [E_{substrate} + E_{modifier}] \quad (1)$$

Theoretical enantiomeric excesses ($ee_{calc.}$) were calculated from the relative abundance of the pro-(R) and pro-(S) complexes at 273 K for toluene and 2-propanol and at 293 K for acetic acid, from the total relative energies using a Maxwell-Boltzmann distribution. Entropy differences between isolated molecules and the transition complex formed were neglected.

$$\frac{N_i}{N} = \frac{e^{-\varepsilon_i/kT}}{\sum_i e^{-\varepsilon_i/kT}} \quad (2)$$

RESULTS AND DISCUSSION

Based on the data obtained for the energy of each studied system in each solvent, the percentage of each of the possible products was calculated using the Boltzmann equation. Then with the percentage of each enantiomer obtained, the enantiomeric excess was calculated from the following equation:

$$ee\% = \frac{[R] - [S]}{[R] + [S]} \times 100 \quad (3)$$

Table **1** presents the values of the BE of the complexes formed between the chiral modifiers and each one of the substrates, as well as the enantiomeric excesses calculated for acetic acid as solvent. As can be seen, all the calculated BEs for the complexes have values between *ca.* -3 and -7 kcal/mol. This means that the complexes are more stable than their isolated constituents.

When analyzing the $ee_{calc.}$ values presented in Table **1**, it can be observed that in all cases, regardless of the chiral modifier and the substrate, the R-enantiomer is the product obtained. These data go in the same direction as those yet not published experimentally obtained in our research group for the enantioselective hydrogenation of ethyl pyruvate in acetic acid [21]. In the present paper ee_{calc} values of 31.69% and 13.29% were obtained when performing calculations with R-(-)-aminoindane and S-(+)-aminoindane as chiral modifiers, respectively, always yielding the (R) enantiomer as product. Calculated values properly reflect the experimental behavior of the catalytic systems, since in the ethyl pyruvate hydrogenation reaction in acetic acid conducted at 293 K, an enantiomeric excess of 53% towards the (R)-ethyl lactate and 10% towards the same conformer was obtained when using R-(-)-aminoindane and S-(+)-aminoindane as chiral modifiers, respectively. This behavior is commonly referred to as *inversion of configuration* [22].

That is wen the absolute configuration of a product in a reaction is unexpected if, in earlier reactions using a chiral catalyst of identical absolute configuration and substrates with not significantly different structures, the absolute configuration of the product was the opposite.

Besides, the ee_{calc} value obtained for methyl pyruvate as substrate and S-(+)-aminoindane as chiral modifier was 16.74%, close to the 10% enantiomeric excess experimentally obtained for ethyl pyruvate. This is a reasonable result due to the similarity between the two molecules.

Table **2** lists the results of the binding energies (BE) calculated for the optimized complexes, performed by simulating a medium having a dielectric constant equal to that of 2-propanol. In this case, it is observed that while all BEs are negative just as in the optimized complexes in an acetic acid medium, the values are lower and between -0.3 and -3.8 kcal/mol. The difference is due to the different dielectric constant of the medium surrounding the complexes. The solvent effect on enantioselective hydrogenation reactions has been widely studied since, up to the moment, the attempts to generalize results in terms of solvent properties did not succeed [23]. The solvent nature affects system characteristics such as the activity, the selectivity, and the stereoselectivity, and several factors may be responsible for these variations: solubility of reagents, hydrogen solubility, competitive adsorption of solvent and reagent molecules on the catalytic surface, etc. [5]. Besides, complex organic molecules usually coexist in several conformations and the population of each one of the different conformers may vary as a function of the solvent dielectric constant, affecting the reac-

Table 2. Binding Energies of the Complexes and ee% Calculated in 2-propanol

2-Propanol				
Modifier	**Susbtrate**	**BE (kcal/mol)**		**ee % (calc)**
		pro-*R*	**pro-*S***	
R-(-)-aminoindane	Methyl pyruvate	-2.160	-1.970	15.92 (*R*)
	Ethyl pyruvate	-3.653	-3.148	43.43 (*R*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-0.630	-0.340	24.02 (*R*)
S-(+)-aminoindane	Methyl pyruvate	-2.190	-2.100	7.59 (*R*)
	Ethyl pyruvate	-3.813	-3.026	61.99 (*R*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-1.110	-0.890	18.38 (*R*)

Table 3. Binding Energies of the Complexes and *ee*% Calculated in Toluene.

Toluene				
Modifier	**Susbtrate**	**BE (kcal/mol)**		**ee % (calc)**
		pro-*R*	**pro-*S***	
R-(-)-aminoindane	Methyl pyruvate	-11,320	-11,320	0.00
	Ethyl pyruvate	-13.701	-13.581	10.98 (*R*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-10.786	-10.320	23.22 (*R*)
S-(+)-aminoindane	Methyl pyruvate	-11.690	-11.670	1.69 (*R*)
	Ethyl pyruvate	-13.453	-13.604	13.8 (*S*)
	1-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione	-10.590	-10.610	1.69 (*S*)

tion selectivity [4]. Consequently, the solvent effect can be a combination of different physical and chemical phenomena and this makes difficult its complete explanation. Considering the $ee_{calc.}$ values, it can be seen that as in the case of the calculations in acetic acid medium, the systems present the phenomenon of *inversion of configuration*: both chiral modifiers give rise to the products with (R) conformation.

Yet not published experimental results for the ethyl pyruvate hydrogenation reaction carried out at 273 K in 2-propanol as solvent showed that when R-(-)-aminoindane was used as the chiral modifier, the product obtained had an enantiomeric excess of 45% of the (R) enantiomer and, when the S-(+)-aminoindane was the modifier used, an enantiomeric excess of 63% of the (R) enantiomer was obtained [21]. If these experimental data are compared with the theoretical results obtained in the present work, it is observed that the model used predicts those results with a very good approximation, both in value and in the sense of enantiodifferentiation. Thus, the calculated values are 43.43% for the complex formed with the R-(-)-aminoindane and 61.99% for the complex with the S-(+)-aminoindane, the (R)-ethyl lactate being the main product in both cases.

The theoretical modeling of the substrate/chiral modifier systems in toluene as solvent was also carried out. The results of the BE calculated for the different proposed complexes and the corresponding theoretical enantiomeric excesses are presented in Table **3.** As in the case of the other two solvents, acetic acid and 2-propanol, also in the case of toluene, the values of the optimization calculations for all the BEs of the formed complexes were negative. In this solvent, the values are between -10 and -13 kcal/mol, *i.e.* the complex formed between the chiral modifier and the substrate is always more stable than the molecules separated at an infinite distance in a medium having a dielectric constant equal to that of toluene.

In contrast to the above-presented results, when toluene is the simulated solvent, *inversion of configuration* is observed neither for ethyl pyruvate nor for 1-ethyl-4,4-dimethyl-pyrrolidin-2 ,3,5-trione. That is, with the (R)-aminoindane chiral modifier, (R)-ethyl lactate or (R)-1-ethyl-3-hydroxy-4,4-dimethyl-pyrrolidin-2,5-dione are obtained as main products and with (S)-aminoindane, (S)-enantiomers are mainly obtained. The *inversion of configuration* was neither observed in the experimental tests conducted in our laboratory. When the enantioselective hydrogenation of ethyl pyruvate in toluene at 273K was studied, an enantiomeric excess of less than 5% of the (R)-ethyl lactate was obtained with R-(-)-aminoindane as the modifier, while the S-(+)-aminoindane modifier yielded 13% of the (S) enantiomer [22]. The theoretical model predicts both the sense and magnitude of the enantiomeric excess in the case of the complex of ethyl pyruvate with S-(+)-aminoindane. In the case of the R-(-)-aminoindane modifier, while the major

R-(-)-aminoindane modifier, while the major product is still the (R)-ethyl lactate, the calculated enantiomeric excess is significantly higher than the experimentally obtained.

For the other two studied substrates, very low (below 2%) theoretical enantiomeric excesses were obtained for the complexes involving the S-(+)-aminoindane modifier. Particularly, for the 1-ethyl-4,4-dimethyl-pyrrolidin-2 ,3,5-trione the model predicts that the (S)- configuration in the main product would be retained. The ee_{calc} for the complex formed between the R-(-)-aminoindane modifier and methyl pyruvate was zero, a value that goes in the same direction as that found for the enantiomeric excess obtained experimentally for ethyl pyruvate, which did not exceed 5%.

With respect to the tendency in the BE values of the different complexes as a function of the dielectric constants of the solvents modeled, it can be seen that there is an inverse relationship between them. As the dielectric constant of the medium increases (toluene, ε= 2.0; acetic acid, ε= 6.2 and 2-propanol, ε= 18.3), average BEs decrease: -11 kcal/mol in toluene, -5 kcal/mol in acetic acid and -2 kcal/mol in 2-propanol.

An analysis of the binding energy of the complexes formed by the vicinal diketone in each modeled solvent (see Tables **1**, **2** and **3**) allows observing that, regardless of the chiral modifier, the BE for 1-ethyl-4,4-dimethyl-pyrrolidin-2,3,5-trione has the lowest value. This is indicating that despite the structural similarities between the α-ketoesters and the 1-ethyl-4,4-dimethyl-pyrrolidin-2,3,5-trione, the interaction of the former with the chiral modifiers is higher, leading to more stable complexes.

CONCLUSIONS

New chiral modifiers for the enantioselective hydrogenation of α-ketoesters and vicinal diketones, different from the ones commonly used (alkaloids belonging to the cinchona family), were modeled. To do this, the structural features essential for creating an enantioselective environment were taken into account.

The model used for calculations of the interaction between the chiral modifier and the substrate, both for α-ketoesters and vicinal diketones, considers the formation of a hydrogen bridge bond between the carbonyl of the substrate and the protonated N atom of the modifier. Even though the metal surface was not explicitly taken into account, it was considered that both molecules (chiral modifier and substrate) should interact so as to remain in a position enabling them to adsorb flat and parallel to the metal surface.

The eecalc values obtained for ethyl pyruvate, which is the substrate for which experimental data were available, agreed quite accurately both in the sense of enantiodifferentiation and in the magnitude of the enantiomeric excess.

With a small computational cost, the simplicity of this model allows achieving theoretical results that can accurately predict the *ee* values for the enantioselective hydrogenation of various substrates, and even predict the occurrence of the phenomenon of *inversion of configuration*.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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