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THEORETICAL MODELLI NG OF CHIRAL MODIFIER/SUBSTRATE INTERACTION FOR ENANTIOSELECTIVE HYDROGENATION OF p-ISOBUTYLACETOPHENONE

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Resumen
Se estudió a nivel DFT la interacción entre el modificador quiral y el sustrato para la reacción de hidrogenación enantioselectiva del tipo de Orito. Se realizó el modelado molecular a nivel DFT para estudiar la interacción entre el (R)-(-)-1-aminoindano y (S)-(+)-1-aminoindano como modificadores quirales y la p-isobutilacetofenona (intermediario en la síntesis del ibuprofeno). A partir de los cálculos teóricos e implementando un análisis de interacciones no covalentes, se demostró que la interacción responsable de la formación del complejo entre el modificador quiral y el sustrato es un enlace tipo puente de hidrógeno. Teniendo en cuenta las energías libres para la formación de cada complejo se calculó de forma teórica los excesos enantioméricos utilizando cada modificador quiral, encontrándose un exceso de alrededor del 30% del enantiómero R del producto cuando se utiliza el (R)-(-)-1-aminoindano, mientras que el exceso sería 30% pero para el enantiómero S del producto cuando se utiliza como modificador el (S)-(+)-1-aminoindano.

Abstract
DFT level calculations were carried out to study the interaction between chiral modifier and substrate for Orito type enantioselective hydrogenation. Molecular modelling on a DFT level was developed to study the interaction between (R)-(-)-1-aminoindane and (S)-(+)-1-aminoindane as chiral modifiers and p-isobutylacetophenone (intermediary the synthesis of Ibuprofen). Judging from theoretical calculations and implementing a non-covalent interaction analysis, it was shown that the interaction responsible for the formation of a complex between chiral modifier and substrate is a hydrogen bond. Taking into account the free energies of formation for each complex, a theoretical calculation was performed for the enantiomeric excess obtained from either chiral modifier, finding an excess of about 30% of the R enantiomer product when using (R)-(-)-1-aminoindane, while the excess would be of 30% for the S enantiomer product if the modifier is (S)-(+)-1-aminoindane.

Palabras Clave: Modelado molecular, DFT, enantioselectividad, hidrogenación
Keywords: Molecular DFT, enantioselectivity, hydrogenation

1. Introduction

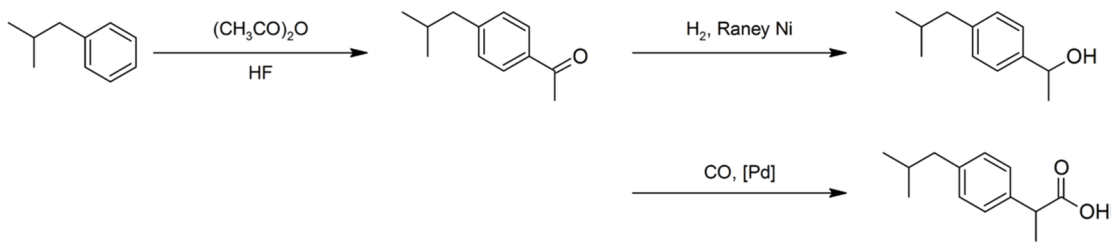
Using chiral modifiers that adsorb on metallic surfaces has proven to be one of the most effective ways to transfer chirality using heterogeneous catalysts. From a synthetic point of view there are nowadays only three systems of chirally modified metallic catalyst that lead to enantiomeric excess of over 90%. These are the Ni-tartaric acid for hydrogenation of β-ketoesters [1], Pt catalysts modified with alkaloids of the cinchona family for hydrogenation of α-ketoesters [2] and Pd based systems using the aforementioned modifiers, which are highly efficient in hydrogenation of α,β -unsaturated acids [3].

The system constituted by Pt supported over a material of great specific area, such as SiO_2 or Al_2O_3, modified by cinchona alkaloids, has been one of the most extensively studied. This catalytic system was discovered in the late 70's by Orito et al [4]. Despite the fact that there has been much progress regarding the comprehension of the reaction mechanism, it has not been elucidated up to date.

With regards to the structure of those chiral modifiers belonging to the cinchona family, three crucial factors seem to be responsible for the enantiomer differentiation. These structural factors, which occur in all of the modifiers, can be referred to as: an anchoring group, a group containing a basic nitrogen near the stereogenic center, and the chiral center [5].

Based on the knowledge of the structural requirements that are needed in order to obtain desirable results in enantioselective hydrogenation reactions of α-unsaturated ketones, and with the intention of designing or finding an efficient catalyst for this kind of reactions, the behavior of two chiral modifiers was studied. Such molecules are: (R)-(-)-1-aminoindane and (S)-(+)-1-aminoindane. In order to understand the enantiodifferentiation process and to find a model mechanism, substrate-modifier interaction was studied, using the previously mentioned modifiers.

This paper presents the results of studying the interaction between the molecules of the previously stated modifiers and p-isobutylacetophenone. The latter compound was chosen given that it is one of the intermediaries in the Ibuprofen® synthesis reaction. The Ibuprofen® molecule has a chiral center and therefore two enantiomers of it exist. The synthesis improved by **BHC Company** consists of only three steps. This scheme has been granted the "Presidential Green Chemistry Challenge Greener Synthetic Pathways" award in 1997[6].



Scheme 1: synthesis of Ibuprofen ® improved by BHC

The second step, as show in **Scheme 1**, the alcohol formation, is crucial given that it may lead to obtain an excess of the desired enantiomer or to the racemic mixture of both alcohols.

2. Molecular modelling and theoretical calculations

For each modifier, (S)-(+)-1-aminoindane and (R)-(-)-1-aminoindane, both possible transition states were studied: those corresponding to pro-(R) and pro-(S) conformations, respectively, without explicitly considering the metallic surface in the calculations. Different initial geometries were considered for each system, and optimization was performed by carrying out DFT calculations in three steps. The first optimization was run using a BP functional and a basis functions set of TZV(d) quality: the resulting geometries were further optimized with a TZV(2d) basis; and finally, vibrational frequencies were calculated so as to obtain thermodynamic parameters at 273 K using a TZV(2d) basis set of functions and a B3LYP functional. All calculations were performed by ORCA [7]. Bonding free energies (ΔG_B), were calculated as the difference between the energy of the complexes and that of the isolated molecules separated by an infinite distance, as show the **Equation 1**

$$\Delta G_B = G_{complex} - \left(G_{modifier} + G_{substract}\right) \qquad \textbf{(1)}$$

The theoretical enantiomeric excesses (ee_{calc}) were obtained from the relative abundance of pro-(R) and pro-(S) complexes at 298,15 K. For the relative abundance of each complex a Maxwell-Boltzmann statistical distribution was assumed, **Equation 2**:

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

In order to visualize the possible formation of hydrogen bonds responsible for the interaction between chiral modifier and substrate, the non-covalent interactions (NCI) technique was implemented [8]. The NCI analysis technique is based on the study of electronic densities and

their gradient in regions of low electronic densities and small reduced gradients. Those zones

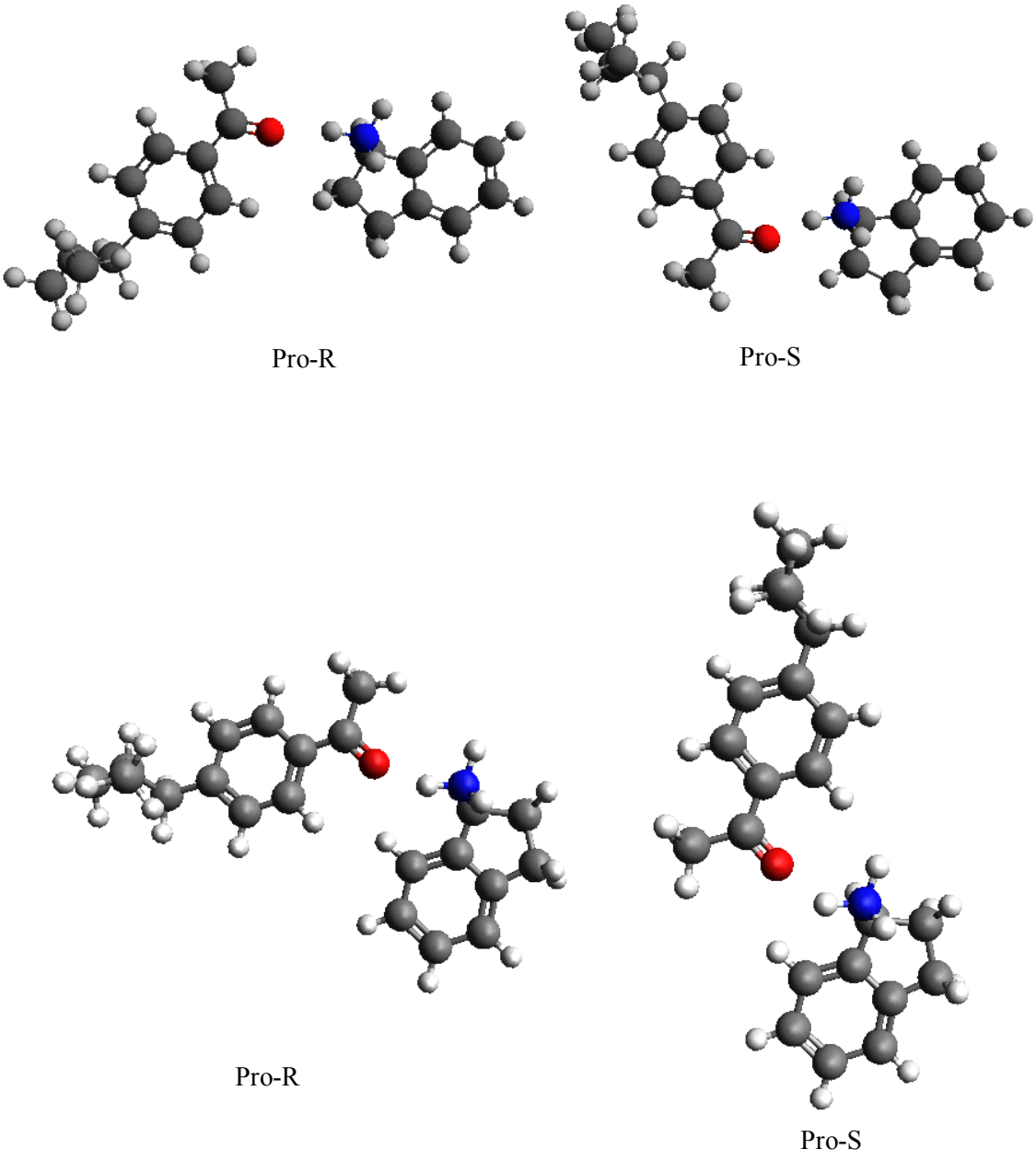


Figure 1: optimized geometries for (R)-(-)-1-aminoindane and (S)-(+)-1-aminoindane complex

where the reduced gradient s(ρ) is close to zero are characteristic of non-covalent interactions. To visualize this in a molecule, level surfaces were plotted and colored taking into account the sign of the second eigenvalue of the Hessian matrix, λ_2 (second derivative of the electronic density with respect to the nuclear coordinates). The blue zones of the isosurface correspond to positive λ_2 values, and represent regions in space where repulsive interactions are present. The red zones, which correspond to negative λ_2 values, allow the identification of regions where attractive non-covalent interactions, such as hydrogen bonds, exist. The green surfaces are zones

where the value of λ_2 is close to zero, and represent regions of weak, delocalized interactions [8-10]. From the electronic density and its gradients obtained with ORCA software, NCI analysis was performed using GABEDIT package. All molecular graphics of NCI analysis were realized using GABEDIT [11,12].

3. Results and discussion

Figure 1 shows the optimized geometries of the possible pro-R and pro-S transition states for each modifier (S)-(+)-1-aminoindane and (R)-(-)-1-aminoindane.

Table 1 summarizes the values of bond length between the oxygen atom in the substrate and hydrogen in the chiral modifier's protonated amine group, and bond angles between substrate oxygen, modifier hydrogen and nitrogen, for all complexes under study.

Table 1: Geometrical parameters of hydrogen bonding of the studied complexes

Complex		Bond length (A)	Bond angle (°)
R-(-)-aminoindane	Pro-R	1.56	166.14
	Pro-S	1.55	171.76
S-(+)-aminoindane	Pro-R	1.55	171.86
	Pro-S	1.55	166.13

As shown in Table 1, the calculated bond lengths between hydrogen and oxygen atoms presented a value of 1.55 A for all complexes, except for pro-R R-(-)-aminoindane, for which a value of 1.56 A was obtained. With regards to the calculated bond angles, it can be seen that for the studied complexes, these range between 166° and 172°. According to a classification proposed by Jeffrey [13] these parameters are in agreement with a moderate to strong hydrogen bond.

In Figure 2, the reduced gradient of the electronic density as a function of density multiplied by the sign of the second Hessian eigenvalue is plotted for the complex formed between R-(-)-1-aminoindane and the substrate in pro-R conformation. The graphics from 2D NCI analysis for the other complexes are similar to this. These type of graphics allow us to distinguish between binding (negative λ_2) from non-binding (positive λ_2) interactions. A noteworthy peak can be identified in the negative λ_2 region, around ρ=-0.068 a.u., which is indicative of the presence of a hydrogen bond type interaction.

Figure 3 shows the most stable structures calculated for the complexes between R-(-)-1-aminoindane and S-(+)-1-aminoindane with the substrate, in both pro-R and pro-S conformations, together with the graphic for 3D NCI analysis. Just like Zenhacker et al. [14] a two colored isosurface is observed, which is typical of an intermolecular hydrogen bond.

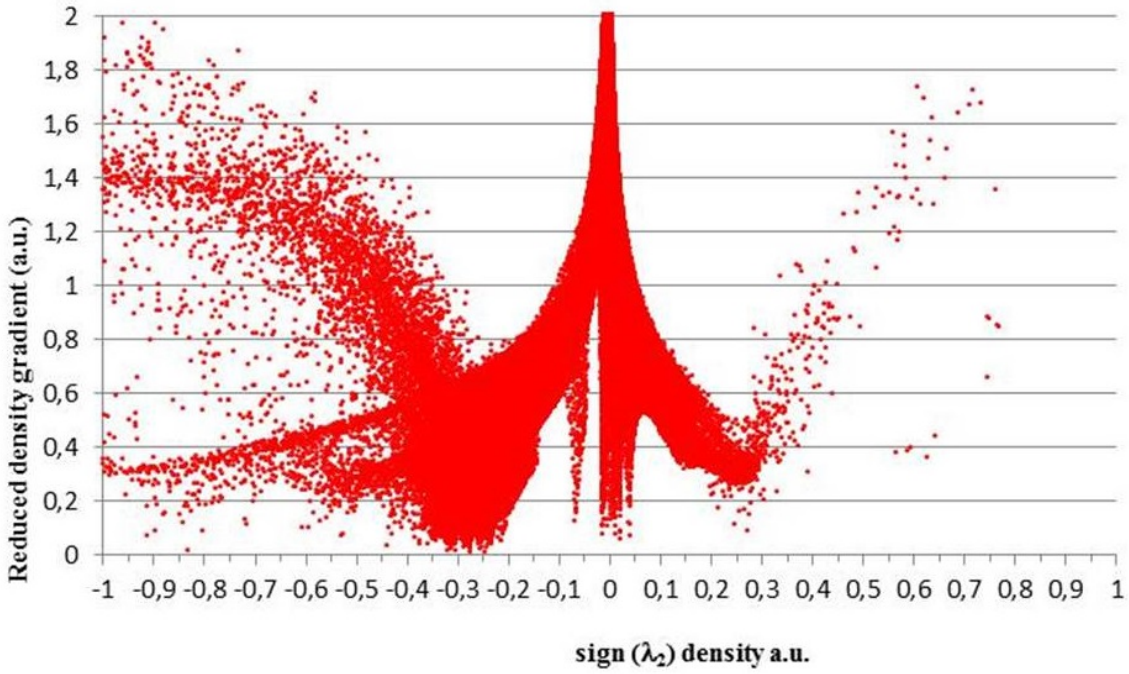


Figure 2: NCI 2D plot of R-(-)-1-aminoindane and the substrate in pro-R conformation

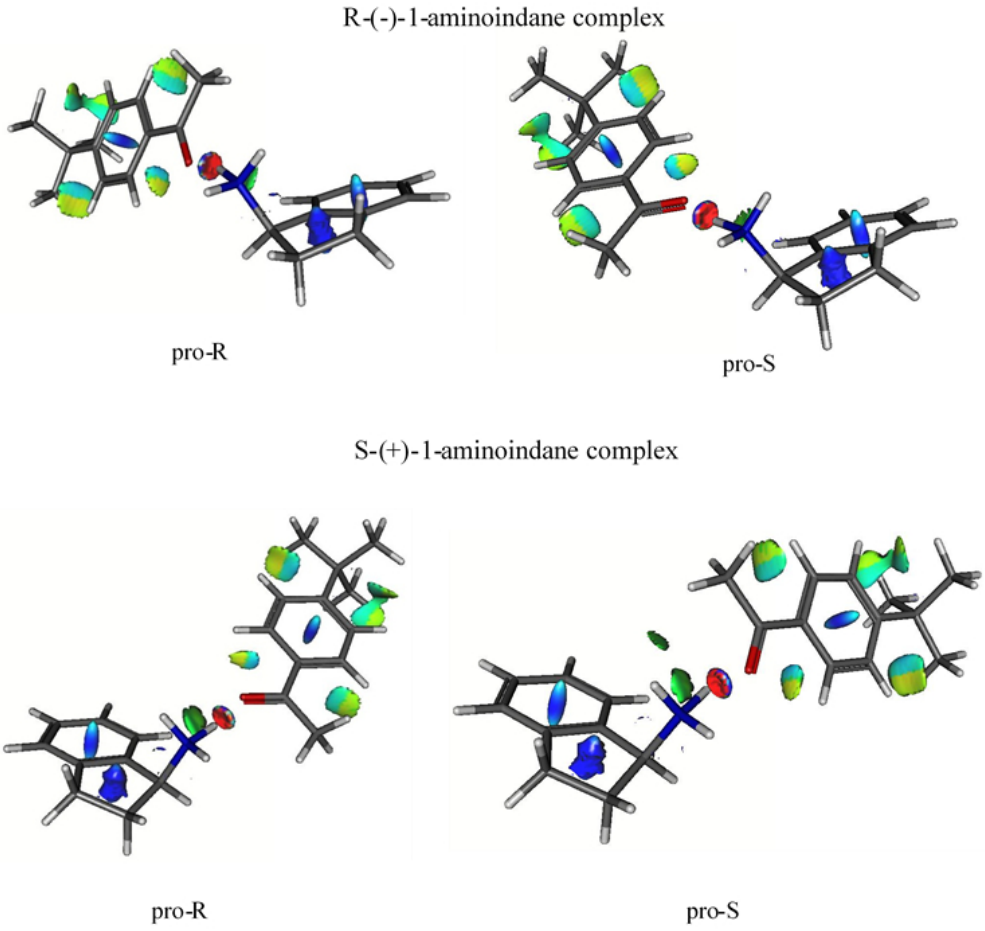


Figure 3: most stable structure and 3D NCI plots of R-(-)-1-aminoindane complex and S-(+)-1-aminoindane complex

The red level surface, which stands for a negative valued λ_2, between the oxygen in the substrate and the hydrogen in the chiral modifier's protonated amine group, can be interpreted as a clear evidence of the presence of this. On the other hand, the blue zones, where λ_2 has a positive sign, that are observed in the center of the modifier's two rings, as well as in the substrate molecule's ring, correspond to repulsive interactions, typical of the steric hindrance that arouses from cycle formation. The green level surface represents a zone in which the reduced gradient is close to zero. For both molecules it is observed between a hydrogen in the protonated amine group and another hydrogen bonded to a carbon in the aromatic ring. These regions of reduced gradient approximately null are characteristic of weak interactions of the van der Waals type. Parting from NCI analysis, either in 2D or 3D, it is possible to demonstrate the formation of an intermolecular hydrogen bond.

The percentage of each possible product was calculated from the output energies of the systems under study, by means of the Boltzmann equation. Afterwards, with the obtained percentages for each isomer, enantiomeric excess was calculated using the following equation:

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

In Table 2 the binding energies for each of complex, as well as the resulting enantiomeric excess are listed.

Table 2: energies and ee_{calc}

MODIFIER	BINDING ENERGY (kJ/mol)		%ee (calc)
	pro-*R*	pro-*S*	
R-(-)-aminoindano	-48,05	-46,16	33,85 (R)
S-(+)-aminoindano	-46,07	-47,57	-29,29 (S)

In the first place, it can be seen that the binding free energy data can be associated to a moderately strong hydrogen bond, which according to Jeffrey's classification [13] varies between 16 and 63 $kJ \cdot mol^{-1}$. This is in agreement with the geometric parameters found from this model for the hydrogen bond resulting from the optimized geometries presented in Table 1.

The binding energies for all of the possibly formed complexes enable us to calculate, using the Maxwell-Boltzmann distribution, the percentage of each complex. With each of these, ee_{calc} were theoretically calculated. In Table 2 it can be observed that the model predicts that with (R)-(-)-1-aminoindane as modifier an excess of about 30 % would be obtained for the (R) alcohol, while

using (S)-(+)-1-aminoindane as modifier would yield an excess of the same magnitude but of the (S) enantiomer of the corresponding alcohol.

4. Conclusions

With a simple model, in which the presence of the metallic surface was not explicitly considered for theoretical calculations, and with low computational cost, interaction between chiral modifier and substrate for enantioselective hydrogenation reactions of the Orito type can be described.

Both through geometric parameters, obtained from geometry optimization of the probable complexes, and through 2D and 3D NCI analysis, it is proven that the interaction between chiral modifier and substrate is a moderately intense hydrogen bond. Such interaction is responsible for the enantiodifferentiation mechanism in this type of reactions.

Enantiomeric excesses, calculated from the relative population of the different complexes, lead us to foresee that using (R)-(-)-1-aminoindane as chiral modifier would allow to obtain an excess of about 30 % for the (R) alcohol, while using (S)-(+)-1-aminoindane the most abundant product would be the (S) enantiomer of the alcohol, in a similar proportion.

Acknowledgements

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