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Generation of H_2 from 2-fluoroaziridine plus ammonia catalysed by an oriented external field

Generación de H_2 a partir de la 2-fluoroaziridina más amoniaco catalizado por un campo orientado eléctrico externo

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> *Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less*
>
> Marie Curie

Este trabajo ha sido posible gracias a la enorme ayuda proporcionada por varias personas.

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REPORT

CONTENTS

1. SUMMARY

In recent years, the use of oriented external electric fields (OEEF) has been investigated for its effect in reactivity and selectivity of chemical reactions. It is stated in the literature that orienting the electric field in reaction axis (axis where the electrons change from reactants-like to products-like) would catalyse or inhibit the reaction depending on the orientation along this axis. However, OEEF not only produces catalytic effects, but also has been reported it changes the mechanism of reactions, controls the selectivity of the reactions, and induce conformational rearrangements.

The main goal is to gain insight of the effects of OEEF in a specific organic reaction. The focus will be about the catalytic effects and therefore the method reported in the literature will be followed. To do so, first the reaction profile will be studied in an unperturbed state. The optimized structure of both reactants and product will be computed so this way the minima associated with the potential energy surface (PES) are obtained. The next step will be to find the corresponding TS of the reaction and finally carry out intrinsic reaction coordinate (IRC) calculations to build the reaction path.

The same procedure will be done, applying increasing values of strength field (negatives and positives) in the direction that corresponds to reaction axis. At this point the results obtained at each magnitude will be compared to the unperturbed state and in this way the main differences will be found and discussed.

The reaction selected for this work is an S_N2 of ammonia attacking a 2-fluoroaziridine where the nitrogen will be the leaving group. The ring opening of fluoroaziridines by nucleophiles is a method of great interest due to his applications in the synthesis of fluorinated organic compounds that are so important in industries such as pharmaceutical. This potential together with its size has made it suitable for this work.

The results have shown a more complex reaction than just an S_N2, that leads to unexpected products. Although the catalysis was the initial focus of this work, the rationalization of the

OEEF in chemical reactions under Valence Bond Theory will conduce to a more complex discussion of the effects computationally observed here.

Keywords: External electric field, 2-fluoroaziridine, energy barrier, reaction axis, catalysis, Valence Bond, S_N2

2. RESUMEN

En los últimos años el uso de campos orientados eléctricos externos (OEEF por sus siglas en inglés) se ha estado investigando activamente por sus efectos en la reactividad y la selectividad de las reacciones químicas. La bibliografía menciona que orientar el campo eléctrico en el eje de reacción (el eje por el cual los electrones pasan de configuración de reactivos a la de productos) cataliza o inhibe la reacción según el sentido en dicho eje. Sin embargo, los efectos de los OEEF no se limitan solamente a efectos de catálisis, sino que también se ha reportado cambios en el mecanismo de reacción, control de selectividad e incluso reordenamientos conformacionales.

El objetivo principal de este trabajo es llegar a comprender y visualizar los efectos de un OEEF sobre una reacción orgánica concreta. En concreto se centrará en los efectos de catálisis y para tal fin se seguirá la metodología reportada en la literatura. Primero se estudiará el perfil de la reacción sin perturbación. Se calculará la estructura optimizada de reactivos y de productos de forma que se obtenga los mínimos asociados a su superficie de energía potencial (SEP). El siguiente paso será encontrar el respectivo estado de transición de la reacción y finalmente realizar cálculos de coordenada intrínseca de reacción (IRC por sus siglas en inglés) para representar el camino de reacción.

Se seguirá el mismo procedimiento aplicando valores crecientes de magnitud del campo eléctrico (positivos y negativos) en la dirección del eje de reacción. Los resultados obtenidos serán comparados con el estado sin perturbar y se encontrarán las principales diferencias que posteriormente se discutirán.

La reacción seleccionada en este trabajo es una S_N2 en la que el amoniaco ataca una 2-fluoroaziridina donde el nitrógeno será el grupo saliente. La apertura de anillo de las fluoroaziridinas son un método de gran interés debido a sus aplicaciones en la síntesis de compuestos fluorados que son muy importantes en industrias como la farmacéutica. Las potenciales aplicaciones de esta reacción y el tamaño del sistema la han hecho idónea para este trabajo.

Los resultados han mostrado una reacción mas compleja que una S_N2 en la que los productos que se forman son inesperados. Aunque la catálisis fue el objetivo inicial de este trabajo, la racionalización de la interacción de los OEEF con las reacciones químicas según la Teoría de Enlace Valencia conducirá a una discusión mas compleja de las observaciones computacionales.

Palabras clave: campos orientados eléctricos externos, 2-fluoroaziridina, barrera energética, eje de reacción, catálisis, Enlace Valencia, S_N2

3. INTRODUCTION

Catalysis is an important field of interest and research in chemistry and in industry. Catalysts have enabled us to produce chemical products much faster, with less resources and minimizing the formation of undesired by-products. It is not surprising; therefore, they are present in the 75% of chemicals produced[1].

Different sort of catalysis has been discovered and studied, such as homogeneous and heterogeneous catalysis, photocatalysis, biocatalysis, etc. Recently, the application of external electric fields as catalysts has arisen interest in chemistry. It is known that external electric fields interact with atoms, molecules and materials and produces different kinds of effects. For instance, affects the spectroscopy of molecules[2], spin transitions[3], modifies the signals of spectroscopy[4], or induces spin-polarized electrical currents[5]. However, pioneering computational studies shows the great capability of oriented external electric fields (OEEF) for catalysing chemical reactions such as Menshutkin reaction[6], Diels Alder reactions, hydroboration reaction[7], electrocyclic reactions[8], electrophilic aromatic substitution reactions[9], hydrogenation reactions[10], Kemp elimination reaction[11], or proton transfer reactions[12]. Also, it can control the selectivity of the reactions[13–15], and even change the mechanism of the reaction[9,14].

Those findings have been supported by the experimental work of Aragones et al., where they designed a “surface model system to probe the Diels-Alder reaction and coupled it with a scanning tunnelling microscopy break-junction approach”[16]. This way in a single molecule experiment it was backed up the theoretical findings made time before by Shaik and co-workers[14].

For catalytic purposes, the literature mentions the direction where a great effect is expected that is the direction that corresponds to the reaction axis.

The rationalisation of the results will be made under Valence Bond theory (VB), as this offers a unique understanding of the ionicity that the field induces on bonds and transition states (TS) that are the reason behind the effects on reactivity[17].

It is also important to mention that recently a work of Bofill et al[18] has reported a manner to find the optimal OEEF (in both direction and magnitude) that induces a barrierless chemical reaction path. Although previously was mentioned that reaction axis is a direction where a great catalytic effect is expected, never was discussed whether this direction was the optimal one. It is important an optimal control as this allows to reduce the energy barrier in the most effective way yet using the minimum number of resources, and in this case, with the minimum strength field. The authors have applied that model to two reactions as an example, an S_N2 of the amine attack on chloromethane and the 1,3-Dipolar retro cycloaddition of isoxazole to fulminic acid plus acetylene. However, it was not possible to cover this topic in the reaction of this work so, as it is still under development, it will be briefly discussed the progress made and what would remain to be done.

The chemical reaction selected for this work is an S_N2 of the ammonia attack on 2-flouroaziridine, which is displayed in Figure 1. The reaction has been carefully selected for his potential applications in pharmacy or medicine. Fluorinated compounds present some useful properties, such as thermal, chemical, and light stability and oil and water repellency, what have made them profitable for different fields such as pharmacy, molecular biology, medicine or for designing functional materials[19]. In fact, fluorine is present in 25% of all market drugs[20]. Moreover, fluorinated amines are specially interesting as the presence of fluorine makes the amine less basic and, thus, increase the bioavailability of the drug molecule[21]. The aim is not only to gain insight about OEEF in a theoretical way, but at the same time to provide the work with a practical perspective by studying a reaction with much potential in the industry.

Also, the size of the system makes it suitable for the time available for this work as the number of atoms implied does not make it too computationally expensive.

Although the zwitterion as a product was expected in the beginning, the results reported that the reaction is taking place is more complex and the zwitterion here is an energetic intermediate. These findings led to find not only catalysis or inhibition, but even a change in the mechanism. The Valence Bond Theory will allow to explain all those results in qualitatively manner and the potential of the new reaction will be discussed as well in the conclusions.

This work is divided into three sections. The first one will provide a theoretical background that will enable to understand and rationalise what is happening with the reaction when OEEF is applied. The next section will comment the procedure followed and will discuss the results obtained. Finally, conclusions will be drawn about the results obtained.

The system used to perform the calculations was Linux based, the programme was Gamess[22] and all the calculations were carried out with B3LYP DFT method [23,24] and 6-311G(d,p) basis set[25].

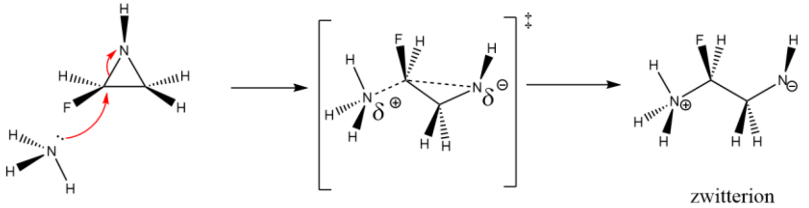

Figure 1. Reaction scheme of the S_N2 involving ammonia and 2-Fluoroaziridize.

4. OBJECTIVES

- Study of the profile reaction of ring opening of the 2-Fluoroaziridine by ammonia
- Understand and apply the current method of catalysis using OEEF in the previously mentioned reaction.
- Compare the results with the unperturbed case and observe the effects that has been produced by OEEF
- Rationalize the effects under VB theory and at the same time gain insight and become familiar with this method

5. THEORETICAL BACKGROUND

5.1. 1ST VALENCE BOND THEORY (VB)

Valence Bond Theory (VB) and Molecular Orbital Theory (MO) are the two general theories that were developed at about the same time. Although VB it has been in the past considered obsolete, principally due to “failures” in some of its predictions, for instance, the paramagnetic behavior of O_2, over time it has been demonstrated these failures are actually an incorrect application of VB. An accurate treatment shows that all those facts can be accurately rationalized. Nowadays, both are widely used in chemistry. VB is very intuitive, and one of his greatest contributions is its capability of expressing the wave function as a linear combination of chemically meaningful structures[26].

The effect of OEEF can be rationalized under both theories[27]. However, VB offers a unique comprehension about field-induced bond ionicity[17], as this becomes evident by constructing the bond wave function in absence and in presence of OEEF. Thus, a simple case of homonuclear molecule, X_2, will be treated as an example[17,26]. This study will allow understanding in a simple way how the OEEF induces ionicity in the bond and will allow introducing a general case of a chemical reaction, where bonds break and new ones are formed.

In absence of OEEF situation, the wave function that describes the bond X-X of Figure 2 has contributions of the covalent HL (**1**) and the two ionic structures (**2,3**). The covalent HL form is the superposition of the two biradical structures represented above, **a** and **b.** Both structures have each atom with one electron, which one is spin-up (α spin) and the other one is spin-down (β spin). The combination of these two structures is what produces the so-called “resonance energy” that explains the formation of the bond. For instance, for the H_2 molecule, this energy represents approximately the 75 % of the total bonding of the molecule [26]. However, there is still a small contribution of the ionic forms where one hydrogen would have the two electrons and would be charged negatively, and the other one would have none, being positively charged.

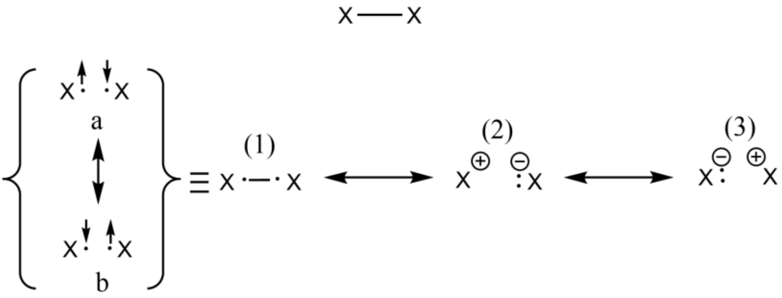

Figure 2. Representation of the structures that contributes to the bond.

The mixing of the structures is represented in Figure 3. As both ionic structures have the same symmetry of the covalent structure and therefore mix with it, it produces the bond to not have any static ionicity. Nevertheless, there is still a small ionic contribution. This small contribution will be important for the later discussion of the effect of OEEF along the reaction axis.

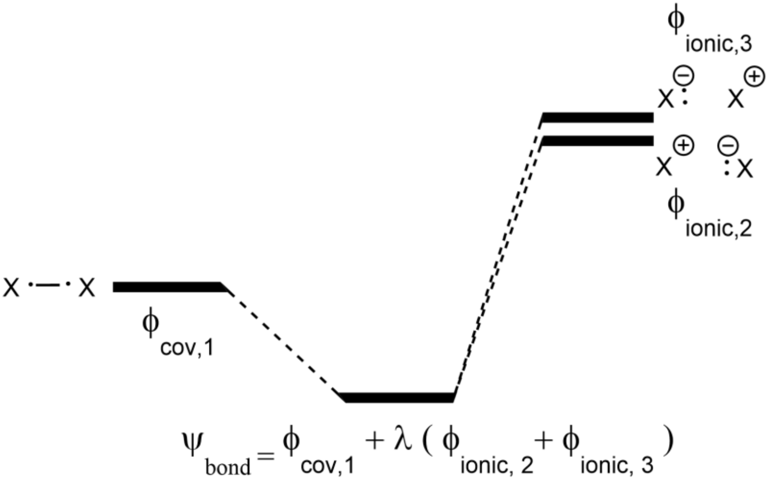

Figure 3. VB mixing of the degenerate ionic structures with the covalent structure to form the bond wave function.

Now, there is a basis to introduce the case of a chemical reaction. Figure 4 shows a general diagram for a polar reaction, that is, a reaction between a nucleophile and an electrophile. At the bottom of the diagram are represented R and P, which corresponds to the structures of reactants and products respectively in their ground state. Above, on the other hand, are represented R* and P*, which represent the structures of R and P respectively but in an excited state. If one start from R and will gradually deform the reactant system towards the structure of products, the system will be continuously increasing in energy until reaching the P* point that represents the product geometry, but conserving the same electronic structure of R. And the same situation is for the other curve, which starts from the excited state R* that represents the product geometry but with the same electronic structure of P. Note that both curves cross eventually at some point in the middle. However, the mixing of the two VB structures, that is represented with the blue curve, avoids that crossing and forms the reaction barrier that is so characteristically in chemical reactions. Therefore, in a chemical reaction, the bond scheme of products and reactants mix along the reaction path and are responsible for the energy barrier of the reaction.

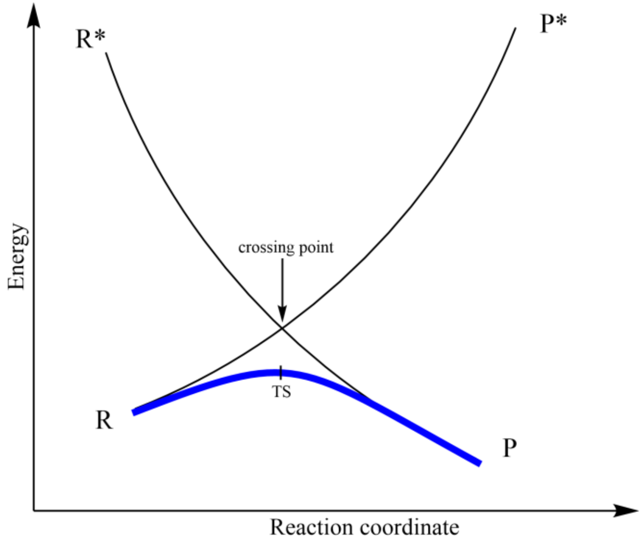

Figure 4. VB diagram of an example concerted reaction. The thick blue curve represents the reaction energy profile.

Notwithstanding, the reader will note not all chemical reactions goes in a concerted way, that is, in one step, especially in organic chemistry where multistep reactions with intermediates are common. In those situations, a simple case of a general VB diagram for two-step reaction is shown in Figure 5. Here we also have R and P and the respective excited structures R* and P*.

Nonetheless, there is a curve assigned as ψ_{int} that corresponds to the intermediate. In the situation displayed in Figure 5 that state lies below the crossing point and is considerably more stable than that point. In such case, it induces the formation of a reaction intermediate that provides an alternative energy pathway with lower energy. It is important to remark that although in most of the situations this is what happens, not always the intermediate curve lies below an intermediate is formed[26].

It is possible, too; the intermediate structure would be more energetic and would lie above the crossing point. This would imply the diagram would be like the one for Figure 4, that is, a concerted reaction and therefore it wouldn't be possible the formation of the intermediate.

In the example is only considered one intermediate structure. However, it is possible there exists more than one that contributes to the bond wave function. In those cases, the final curve will be the result of the mixing of all the possible structures and their respective weights in the wave function. It is necessary to study each reaction separately as the structures involved will be different. However, with the general examples represented in this introduction, it will be possible to have a basic understanding of VB representation of chemical reactions and to understand the changes in the diagram caused by the application of OEEF along the reaction axis.

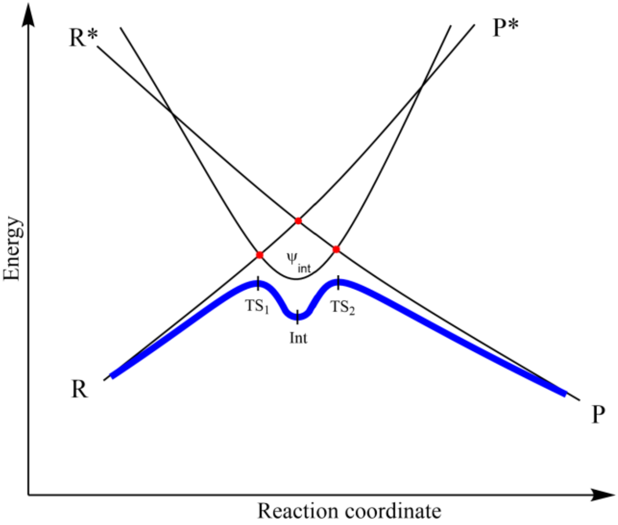

Figure 5. VB diagram of an example two-step reaction. The thick blue curve represents the energy profile. The red dots show the crossing points.

5.1. 2ND ORIENTED EXTERNAL ELECTRIC FIELD (OEEF)

Having been introduced basic concepts of VB theory now it is possible to discuss the effects of the OEEF in reactivity in a properly. The dissociation of the homonuclear diatomic molecule under OEEF will be addressed first. This will provide the understanding of how OEEF interacts with the diatomic molecule, and a similar principle will be applied to explain the catalytical/inhibitor effect in chemical reactions.

Starting with the homonuclear molecule X_2, it was remarked it the previous subsection that there is a small ionic contribution in the bond as the result of the combination of the degenerated ionic structures with the covalent state. When an electric field is applied along the z direction, the axis that contains both atoms, which will be called bond axis, one of the ionic structures becomes stabilized whereas the other ionic structure gets destabilized[17]. This fact produces the breakage of the initial degeneracy, and therefore the stabilized structure mixes preferentially with the covalent form. Hence, the new bond-wave-function will acquire a static ionicity. What structure will become favored will depend on the sense along the z axis of the OEEF. Figure 6 illustrates the situation where there is a positive orientation and the ionic structure referred as 2 is the one stabilized, whereas Figure 7 illustrates the opposite scenario.

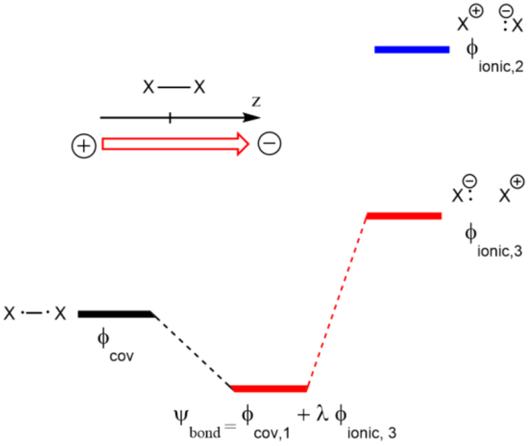

Figure 6. Modification of the VB-mixing diagram by the OEEF along the bond axis in positive direction. Electric field according to convention from physics.

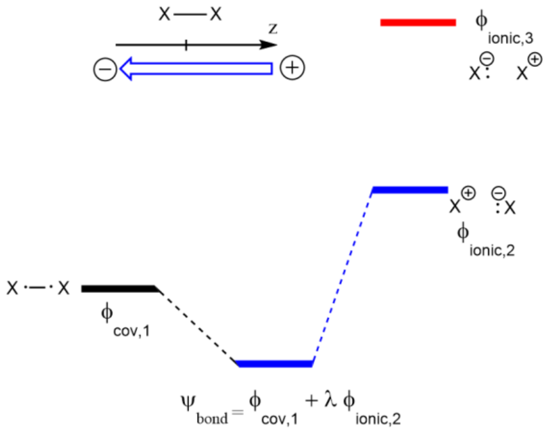

Figure 7. Modification of the VB-mixing diagram by the OEEF along the reaction axis in negative orientation. Electric field according to physics convention.

As the strength of the electric field becomes higher, the contribution of the ionic structure in will be further stabilized and this will lead to a higher contribution of this form in the bonding. It can be said then the bond is polarized, and the elongation of the bond is observed as the electric field drives apart both atoms. There will be one point where the favored structure has the same energy as the covalent one, and from then onwards, the weight of the ionic structure will be predominant, making the bond becomes ionic and dissociates in the respective ions barrierless in a heterolytically way. This point is called the critical point and to illustrate Table 1 shows the critical points for some homonuclear diatomic molecules [17].

H-H	0.1
F-F	0.14
Cl-Cl	0.06
I-I	0.04

Table 1. Critical points for some diatomic homonuclear molecules in atomic units (1 a.u. = $5.142207 \cdot 10^{11}$ V m^{-1} [22]).

To sum up, when an OEEF is applied along the bond axis, the stabilization of one ionic form induces the polarization of the bond and eventually the heterolytically dissociation occurs. Is the interaction with the ionic forms what also explains the effect on reactivity. In those cases, the direction in which the OEEF must be applied is the reaction axis.

Before entering to consider in detail the chemical reactions, it is important to talk about the reaction axis. This axis is taken as the one in which the reorganization of the electrons pairing from reactant-like to product-like takes place. To characterize this axis, the literature considers taking the dipole moment of the TS. So, once the dipole moment of the TS of the reaction is found, it will be known the direction of the reaction axis and consequently the direction in which to orient the electric field.

Figure 4 showed a situation of a concerted reaction in which there are no intermediates. How the barrier is lowered will depend on which structure is ionic. The nonionic structures will be not affected significantly by the OEEF.

For instance, looking at Figure 8 that illustrates the Menshutkin reaction, R* is an ionic structure as it has the same electronic structure of the product and P will be also an ionic structure, the curve that correlates them will be in consequence ionic. This curve will get affected by the presence of the field. The other curve, as it is involved nonionic electronic states, remains practically unaltered. Hence, the structures R* and P will go up or down in energy depending on the orientation of the OEEF along the reaction axis, making the curve that correlates them will be modified. Subsequently, the crossing point will change as well, and the TS will be displaced in consequence. The new TS will be closer to the geometry of products or reactants when is displaced by the OEEF.

The dipole moment that characterizes the reaction axis of this reaction is represented in the middle of Figure 8 as well as the positive and negative directions of the electric field. The convention followed for the electric field is from plus to minus, as this is the convention that follows the Gamess program[17,22]. Being like this, the catalysis will occur at negative fields and the inhibition at positive ones. However, what is important is that the electric field is opposed to the dipole moment, so when this notation is used, keep in mind that if the electric field would follow the same convention for the dipole moment the vectors would be parallel and opposed. Thus, whether the orientation in which the catalysis will occur will depend on the orientation of the dipole moment along the reaction axis.

The dipole moment will also increase in catalytic orientation and decrease in inhibition orientation. The reason is the more the contribution of ionic structures in the bond wave-function, the more ionicity of the molecule and in consequence the more dipole moment.

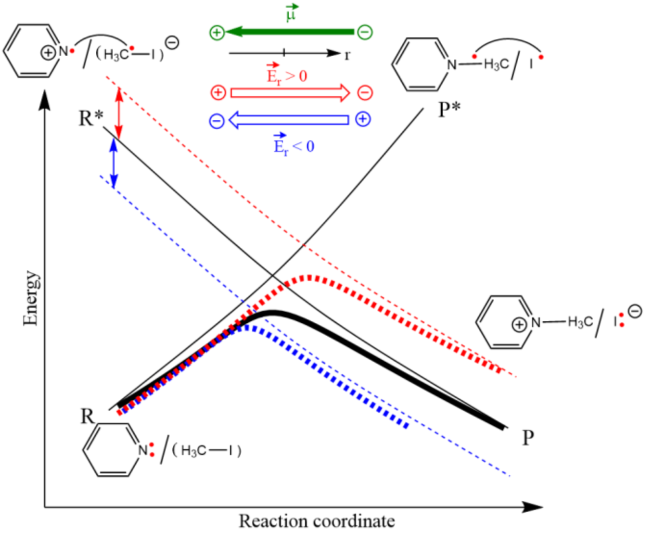

Figure 8. Modification of the VB-reaction diagram by OEEF applied in both orientations. The conventions of the vectors are represented in the middle of the Figure. The bold curve is the energy profile zero electric field. The thick-dashed lines, blue and red are the energy profiles with non-zero fields. The curve R*, P is ionic.

The ionic structures, or also called charge transfer structures, will not be the same for all organic reactions. What structures will be ionic and the way they will interact with the field will be different for each reaction, so it will be essential to analyze each reaction separately.

It is possible there exists intermediate structures in the reaction under study, as Figure 5 represents. The number of intermediates can also be different for each reaction and whether they are charge transfer structures or not. This implies the rationalization of the catalysis in those reactions will be more difficult to perform.

Let's think about S_N2 reactions. S_N2 reactions coexists with S_N1 and with elimination reactions. For instance, when the conditions make favorable S_N1 this will be predominant over S_N2 and the reaction will be in two steps with one ionic intermediate. It is reasonable to think the VB diagram may be similar to the one presented in Figure 5. Otherwise, if the S_N2 is the one which is predominant, a diagram similar of Figure 4 would be expected but with the intermediate contribution lying above the crossing point. Whatever the situation is, the stabilization/destabilization of ionic structures will be the reason behind of the energy barrier and mechanism modification phenomena.

It is important to know for each scenario what structures are present and what is their weigh in the bond wave-function. To do that in a quantitative manner, a VB study must be performed. However, this is beyond the scope of this work. Only a qualitative analysis will be performed based on MO calculations.

Finally, and to conclude the theoretical background section, there is relevant to say two things. First, the effects in the stability of structures and the subsequently changes in the reaction diagram is not exclusively of OEEF. The presence of electronegative substituents, the solvent, etc. can also change remarkably the reaction diagram in a similar way.

Second, the selectivity of some reactions can be controlled when the OEEF is applied perpendicular to the reaction axis. This is an interesting topic that has been investigated in endo/exo selectivity of Diels Alder reactions, for instance.

6. STUDY OF THE REACTION PROFILE OF THE 2-FLUOROAZIRIDINE RING OPENING BY AMMONIA

Geometries of the molecules have been built in approximately in order to optimize them and this way find the equilibrium geometries of each product as well as their energies.

To build the input geometry for 2-fluoroaziridine the data of bond lengths and so on has been obtained from the work of Banks[28]. However, some angles were not mentioned in the work so to build the Z matrix some approximations were made to replace the lacking data.

The VdW structure, that corresponds to the pre-reactant system, could not be obtained directly. The obtaining of this result will be explained later. After those results, it was necessary to carry out calculations of frequencies to, in first place, check if minimums have been obtained and to dispose of the zero-point energies of each structure, so this way the energy reaction profile will be studied properly. The HOMO and LUMO orbitals of all the optimized participant molecules in the reaction are represented in Figures 9-14. The molecule of Figure 14 includes the numeration of the atoms. The next Figures will follow the same numeration displayed for Figures 13 and 14. Therefore, keep in mind the rest of atoms numbered will be referred to this disposition.

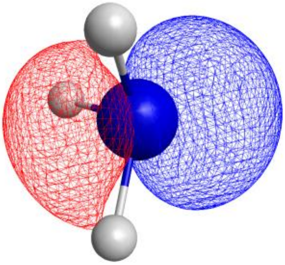

Figure 9. HOMO orbital of ammonia. The main contribution comes from the nitrogen atom.

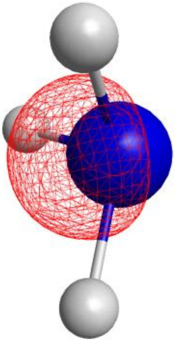

Figure 10. LUMO orbital of ammonia. The main contribution comes from the sigma bond H-N.

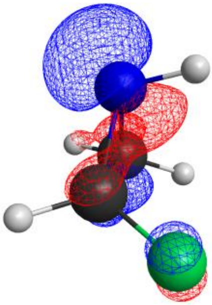

Figure 11. HOMO orbital of the 2-fluoroaziridine. There is a large contribution of the nitrogen. Its lone pair is described by this orbital. There is also a significant contribution in carbons and fluorine.

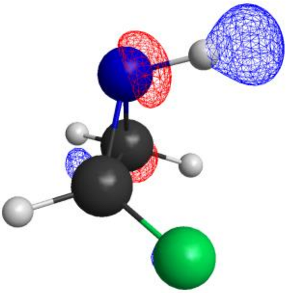

Figure 12. LUMO orbital of the 2-fluoroaziridine. The main contribution comes from the hydrogen bonded to the nitrogen.

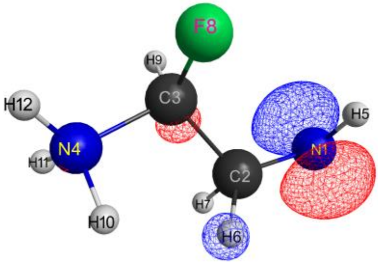

Figure 13. HOMO orbital of the zwitterion. The main contribution comes from the N1. Its lone pair of electrons is described by this orbital.

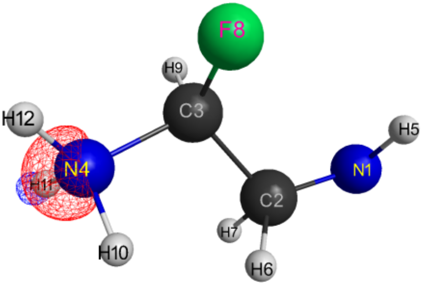

Figure 14. LUMO orbital of the zwitterion. The main contribution comes from the antibonding of N4 and the hydrogens bonded to it.

The next step was to find the TS. A sort of intermediate structure was proposed as input geometry to start the search with distance of N4. Once a result was obtained, a Hessian calculation were run in order to obtain the frequencies and to analyse if the TS was actually acquired. As the first frequency was imaginary, it can be assured it is indeed a TS. At this point, an analysis of orbitals were made. Figures 15 and 16 show both HOMO and LUMO of TS.

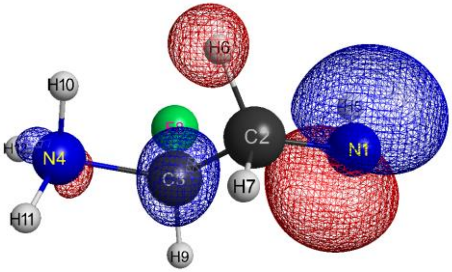

Figure 15. HOMO orbital of the TS. The largest contribution comes from the N1. The lone pair of N1 is described by this orbital.

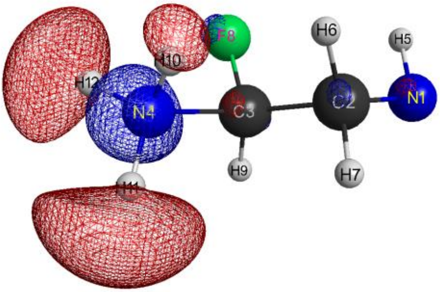

Figure 16. LUMO orbital of the TS. The largest contribution comes from the antibonding of N4 and the hydrogens bonded to it

An IRC calculation was performed with the aim to obtain the reaction profile. 5 points were necessary to arrive to product and 78 to arrive to reagent. This indicates the product have a similar geometry of TS and therefore, they will be close in energy as well. Using the geometry of the last point of the IRC trajectory that drives to reactants as an input, an optimization has been made and this way the optimized geometry for VdW complex has been obtained. Subsequently, a calculation of frequencies provided the zero-point vibrational energy. The HOMO and LUMO orbitals are not represented, as these are very similar to the orbitals displayed for the reactant molecules.

When the data was recollected to build the energy reaction profile it was observed something odd, the energy of the product when is corrected with the zero-point energy is higher than the corrected energy of the TS. As the electronic energy of both molecules are similar, is probable the selected base does not account enough correlation energy and displays these results. However, as the focus is on catalysis/inhibition, is enough studying the electronic energy and the next figures in which the energy is represented will be without zero-point vibrational corrections. Still, the frequencies will be calculated, in first place, to ensure the geometries obtained corresponds to minimums or TS and to comment whether the same behaviour is observed in the rest of the analysis. Figure 17 shows the reaction pathway of the reaction according to the calculations made to this point. It is relevant to remark this pathway, as in the next section will be found, is incomplete. The final product is different and significantly more stable. Although the discussion will be developed in the next section, here it is remarked a complete pathway is available in Figure 30.

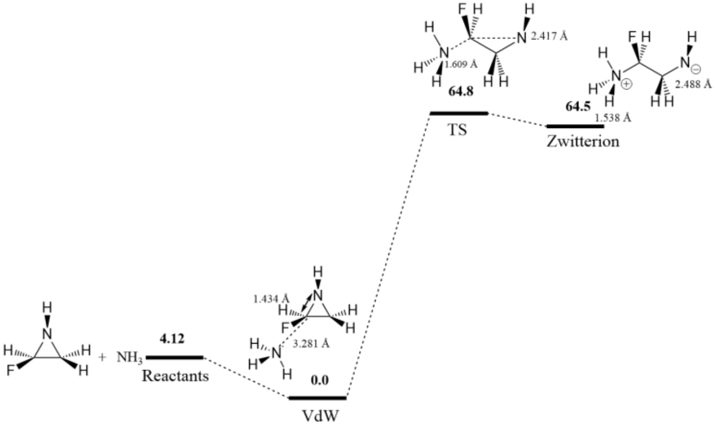

Figure 17. Reaction pathway of the S_N2 without the zero-point corrections. Energies are in kcal/mol units.

7. OEEF APPLIED IN THE RING OPENING OF THE 2-FLUOROAZIRIDINE REACTION. STUDY OF THE EFFECTS IN ENERGIES AND GEOMETRIES.

It is important to mention that not all the software packages follow the same convention for OEEF[17]. The convention followed by Gamess is from plus to minus, that is the convention from physics. However, other software packages follow a convention that is from minus to plus[17].

The first step is to find the reaction axis. So, the values of the dipole moment as well as its graphical representation are found in the calculation of frequencies of the TS. What is obtained is graphically illustrated in Figure 18. The convention for the electric field is illustrated, as well as the coordinate axes. The values of the components are represented in Table 2. The notation for the reaction axis will be "r", the direction in which the OEEF must be applied to observe catalysis or inhibition.

The range of the study was decided to be from -0.006 to +0.006 a.u. First, it was required to normalize the dipole moment vector to have the direction needed, and then each component was multiplied by the magnitude of the strength of the field. Doing so the components of the OEEF for each point were obtained.

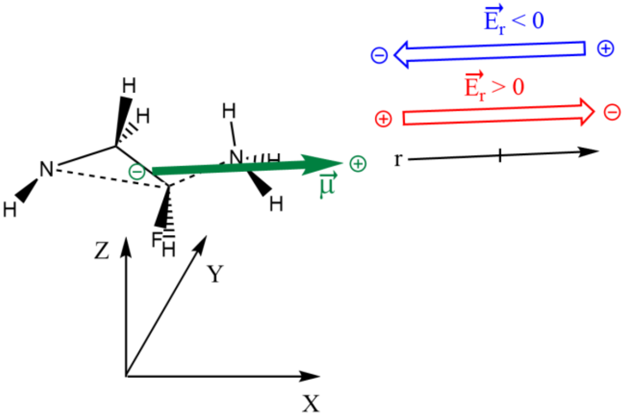

Figure 18. Representation of the reaction axis (r), the dipole moment of the TS ($\vec{\mu}$), and electric fields applied along r.

x	y	z	|D|
10.013087	3.229066	-1.051559	10.573295

Table 2. Components of dipole moment vector and his magnitude in Debyes.

For each point, it was followed a similar process than the one made for the unperturbed case. For the first magnitude of the strength field, +0.001 a.u., the optimized geometries of the molecules and TS were used as input, now including the corresponding components of electric field with the keyword "EFIELD". This returned the new optimized geometries for the new situation. Subsequently, calculations of frequencies were carried out. After checking all the results corresponded to a minimum or a TS, an IRC was performed for TS to obtain the reaction profile.

With all of those results, the energy barriers were calculated. Figures 19 and 20 shows clearly the catalytic effect when the OEEF points to the positive direction as both barriers, TS-zwitterion and TS-VdW, decrease. Also, on each point the magnitude of dipole moment has been set and, as it can be appreciated, this rises as the field becomes stronger.

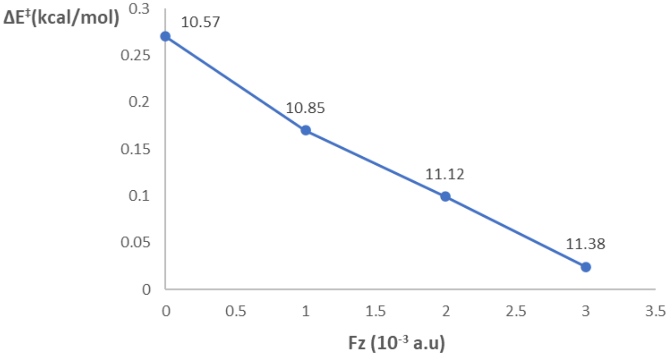

Figure 19. The energy barrier of TS-zwitterion. In each point is represented the value of the dipole moment

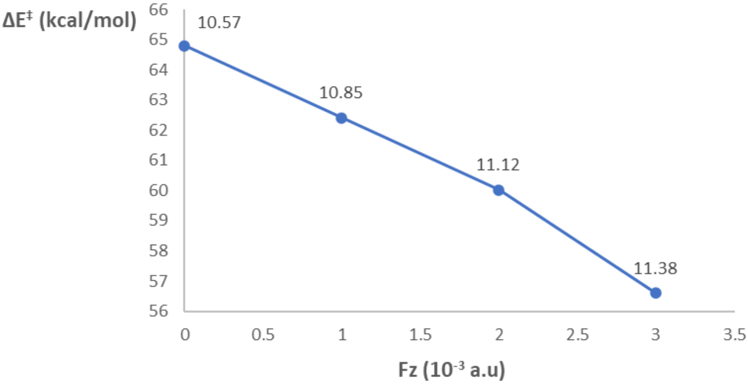

Figure 20. The energy barrier of TS-VdW. In each point is represented the value of the dipole moment.

For the barrier TS-prod the energy is represented, and it shows how the barrier is reduced due to the OEEF. Note that the energy at the third point is practically the same as the TS as the difference is considerably small (0.03 kcal/mol). The dipole moments have also been set. They increase with the field because they are related with the increasing of the ionicity of the system along the reaction axis[6].

The characteristic bond distances of this reaction correspond to N4-C3 and N1-C3 (Figure 14 numeration) that correlates to the attack of the nucleophile and the leaving group exit respectively. The energies of the TS (or the energy barrier) were represented in function of both distances, which results are represented in Figures 21 and 22. Here, it is observed that as the field increases, the new TS has distances that become similar to the distances the unperturbed product has. To put it plainly, the transition state gets a more similar geometry of products than reactants.

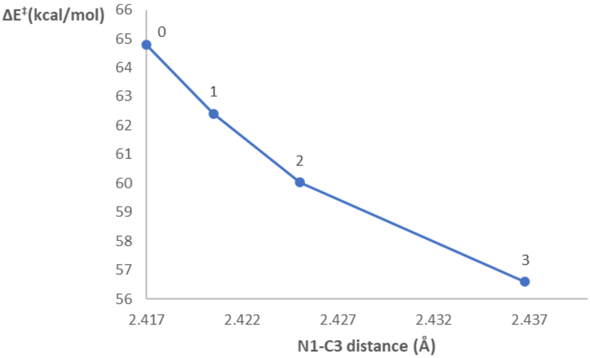

Figure 21. Representation of the variation of the N1-C3 distance of the different TS as the field increases. Above each point the magnitude of the strength field in $E_r \cdot 10^{-3}$ a.u. is represented.

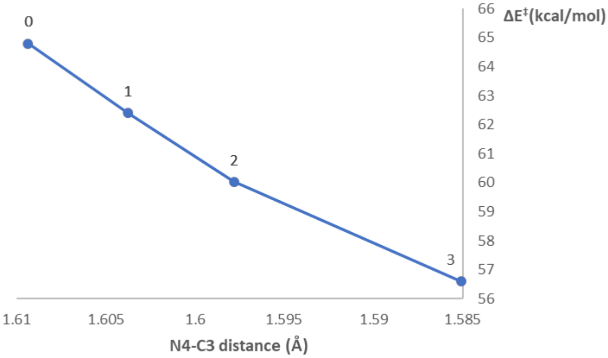

Figure 22. Representation of the variation of the N4-C3 distance of the different TS as the field increases. Above each point the magnitude of the strength field in $E_r 1 \cdot 0^{-3}$ a.u. is represented.

Points above +0.003 a.u. are not represented because further of that range it is not possible to find the same TS that has been found before.

The newfound TS with respect to zero field is different, and it is shown at Figure 23. Compared to the one for minor strength and in unperturbed state, here the bond between N4 and C3 is not already formed. It is also important to remark that this structure has a significantly a higher energy (74.2 kcal/mol at +0.004 a.u. vs 64.8 kcal/mol of the zero-field situation) and since then the energy only goes up. This odd result indicates that we are no longer in a catalytic case. To know what is happening, the same procedure is still being done. The results of the Hessian matrix calculation and analysis confirmed it was indeed a TS.

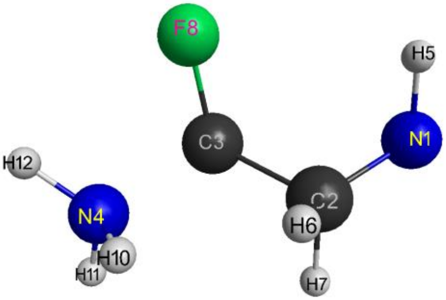

Figure 23. New TS found when the strength of the electric field is equal or superior to +0.004 a.u.

The next step was to run IRC forward and backward and to check what product will form. As Figure 24 shows, what it is obtained is completely different of what it would be expected. Here, there is not just one product but two, which are an imine on one side and H_2 on the other. To put it plainly, this means what we have here is another reaction different from the S_N2 that was expected. What it is observed here is H6 leaves as an “hydride” at the same time the double bond between C2 and N1 forms (always remind the same numeration is followed). Then, H6 attacks H10 and molecular hydrogen is generated. For now, it seems the OEEF change the reaction from +0.004 a.u. onwards. At this point there is no more reaction axis as the newfound transition state does not correspond to a S_N2 reaction and the corresponding dipole moment will be different as well. A more profound effect than just catalysis has been observed, that is, the alteration of the mechanism and the product of the reaction.

As what has been obtained as a product are two different molecules, to determine the energy of the system both molecules have been optimized separately, and then its frequencies have been calculated. The energy resultant show it is a product remarkably more stable than the zwitterion product and close in energy to the pre reactant system.

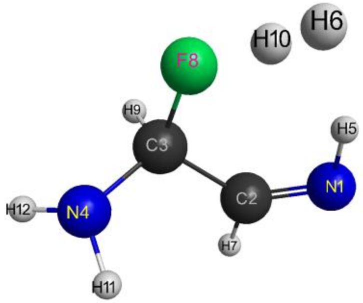

Figure 24. Structure of the new product formed when the strength is equal or superior to +0.004 a.u.

HOMO and LUMO have also been set in Figure 24 and 25. Both molecular orbitals are very alike to the HOMO and LUMO orbitals of the first TS.

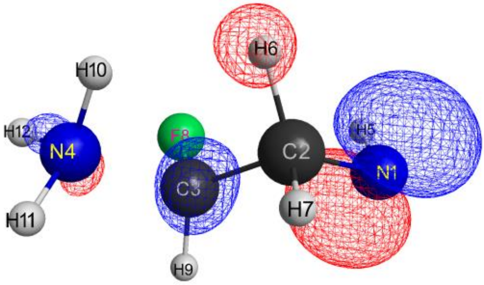

Figure 25. The HOMO orbital of the new TS found. There is a significant contribution of the N1 atom. The lone pair of the negative charge in this atom is described by this orbital.

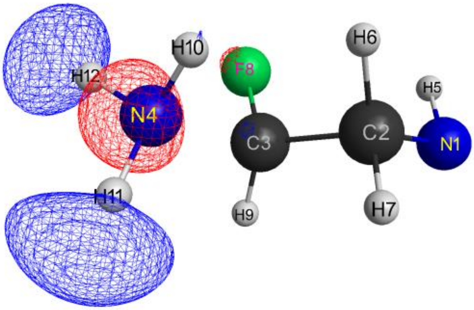

Figure 25. The LUMO orbital of the new TS found. The orbital is centred on N4 and both H12 and H11 bonded to it.

Having studied the catalysis at positive fields, the orientation was flipped in order to study the inhibition effect at negative fields.

Starting with -0.001 two things were observed. The first one was the confirmation of the inhibition as the energy barrier increased. The second one is the intermediate with the zero-point correction is already less energetic than the TS, that drives to a positive energy barrier TS-zwitterion (0.3 kcal/mol). Hence, when working at this magnitude, the zwitterion will be a relatively stable product. Also, in contrast to the opposite orientation, here the TS becomes closer to the geometry of reactants instead of the geometry of the zwitterion. Table 3 recollects the energy barriers of the unperturbed system and for the system at -0.001 a.u., and the characteristic distances for the last case.

Energy barrier TS-VdW. Nonelectric field	64.8 kcal/mol
Energy barrier TS-VdW. -0.001 a.u. field	66.6 kcal/mol
Distance N1-C3. Field: -0.001 a.u.	2.416 Å
Distance N4-C3. Field: -0.001 a.u.	1.610 Å

Table 3. Results obtained when the field is negative and with a magnitude of -0.001 a.u.

When the field is stronger than -0.001 a.u. the same product that was formed above +0.003 a.u. appears. This means is not possible to find the zwitterion as this does not exist at those fields. Therefore, the inhibition is restricted to a very narrow range (to -0.001 a.u.)

Also, we found the existence of the zwitterion, at least when the zero-point energy is not considered, is restricted to fields from -0.001 to +0.003 a.u. Outside this range it is not possible to find it and only the formation of the imine in a single kinetic step is observed.

To understand what is happening when the imine is formed IRC calculations were carried out, the visualization of the results in both directions enabled to understand what the movement of the electrons during the reaction was. Figure 26 shows the electronic movement.

The first pair to move is the lone pair of electrons of N4 that attacks C3 carbon. Subsequently, the electrons of the bond C3-N1 breaks homolytically and those electrons move first to N1 that is observed in the TS but later moves to form the double bond with C2. The third pair is those from the bond C2-H6 that breaks and goes to H6 forming an “hydride”. This movement takes place at the same time the second pair is forming the double bond. Finally, the last pair of electrons is from the bond of N4-H10 that goes to the nitrogen and thereby a no charged amine is formed.

The formation of the "hydride" indicates this hydrogen is remarkably basic. The reason behind this is due to the presence of a negative charged nitrogen that is looking to form a double bond with C2. The paper of the fluorine is suspected to be determinant in this process, as its highly electronegativity would attract the electronic density to it inductively, favouring the movement of the electrons of the negatively charged nitrogen to the C2 to form the double bond. Thus, when the electrons of the N1 are moving the electronic density from the C2 displaces to the H6 and this hydrogen is the one that leaves as an "hydride" to enable the formation of the imine. On the other hand, H10 is especially acid as it is bonded to a positively charged nitrogen. Moreover, the presence of the fluorine would make the withdrawing of the electronic density from H10 more pronounced. When the hydride is formed and as this form is not stable, rapidly attacks H10 to leave a neutral amine. Moreover, the formation of molecular hydrogen, a significantly stable molecule, makes the energy drops remarkably.

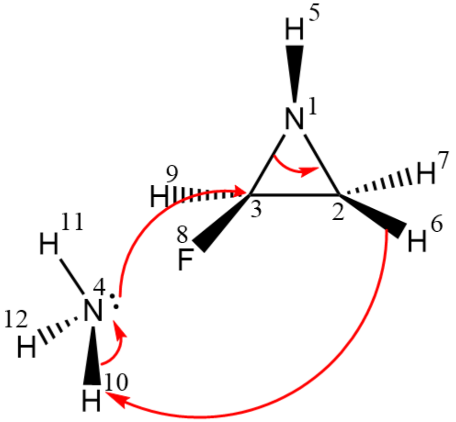

Figure 26. Movement of the 4 pair of electrons in the concerted reaction. The same numeration for the previous figures is followed.

At this point a new calculation was carried out using the geometry of the TS found for the new reaction as an input but without electric field. The aim of doing this was to test if this transition state converges to the initial geometry of TS found for S_N2 reaction. The result showed this is what indeed is happening. Therefore, the OEEF favours the formation of the new TS that connects the reactants with the imine in a single step.

In the last section, it was commented that when the zero-point vibrational energy was accounted, the energy of the zwitterion was higher than the TS. As the zwitterion was very energetic and close in geometry of the TS, it was possible it was a problem of correlation energy. However, when the field reached certain values, an imine and molecular hydrogen was formed, a considerably stable product. It is reasonable to think that the imine will also be formed at lower and even nonelectric fields. Then, there must exist a TS that connects the zwitterion structure with the imine.

Note that the IRC of the reaction when the field is equal or above of +0.003 a.u. and equal or below -0.002 a.u. showed the movement of the electrons that was discussed before. The movement of the first two electrons is practically the same that the one for the S_N2 that would form the zwitterion. So, it is reasonable to think that from the zwitterion to the imine the TS would correspond to the second part, the formation of the “hydride” that attacks the acid hydrogen and the formation of the double bond.

To test the hypothesis a calculation of saddle point was carried out with the optimized structure of the zwitterion but modifying the distance H6-H10 to 1.4 Å, an intermediate distance between the one they have when they form molecular hydrogen and what they have in the zwitterion.

The results file showed a new TS was obtained that is represented in Figure 27. There it can be observed how the H6 is as an “hydride” and is directing to H10.

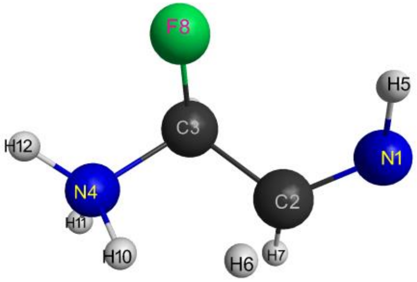

Figure 27. Representation of the TS that connects the zwitterion to the imine and H_2.

The HOMO and LUMO orbitals are represented in Figures 28 and 29.

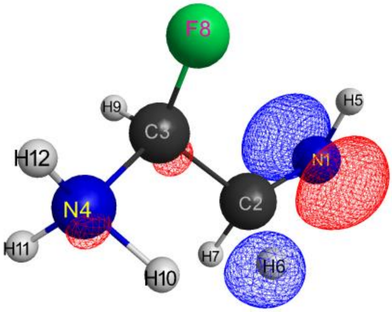

Figure 28. The HOMO orbital of the TS of Figure 27. The principal contribution comes from N1 atom. Its lone pair from the negative charge is described by this orbital.

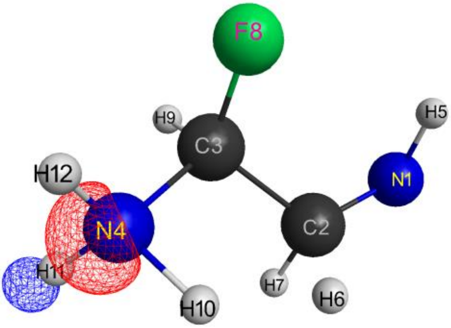

Figure 29. The LUMO orbital of the TS of Figure 27. The principal contribution is on sigma antibonding between N4, H11 and H12.

The calculation of frequencies confirmed it was a TS and IRC calculations correlated the zwitterion with the imine. These findings indicate that the imine will be the actual product of the reaction both when there is field applied and when there is not.

With these new findings, it is important to update the reaction profile that was illustrated in Figure 17, considering the structures and energies of the new TS and the imine + molecular hydrogen. The new reaction profile is illustrated in Figure 30.

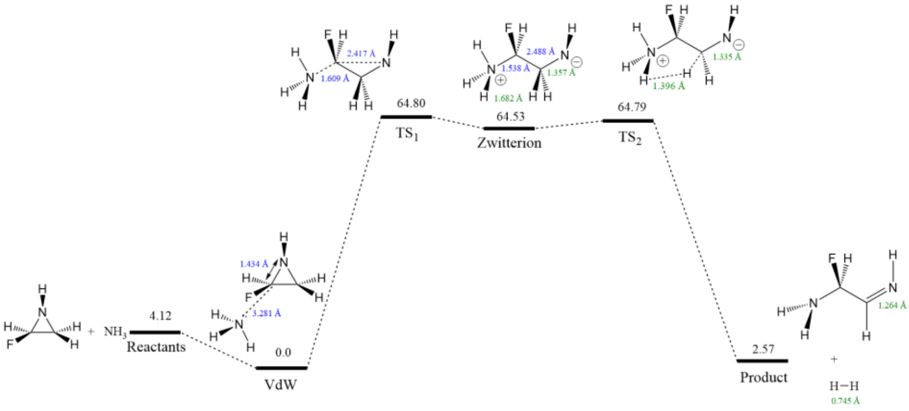

Figure 30. Complete reaction pathway at the unperturbed state with no zero-point vibrational energy corrections applied. The distances in blue are the characteristics distances of the S_N2 reaction and the green distances are the characteristic distances of the second reaction. The energies are represented in kcal/mol units

It is time to rationalise the results obtained during this section and the previous one. The treatment will be qualitative as it was not possible to extend in the study of the unexpected results and the revelation of the two steps reaction

To do so, let's first sum up the most relevant observations.

First, in the unperturbed situation, the zwitterion as a final product is observed when only the electronic energy is considered. Yet, performing the corrections of zero-point energies, it is found that this structure lies above of the TS.

Second, there is an effective range where the catalysis is possible, from 0 to +0.003 a.u.

Third, the inhibitor effect is only observed in a narrow range, from 0 to -0.001 a.u. Moreover, the zwitterion becomes lower in energy than the TS even when the energy is corrected.

Fourth, from a certain value of strength is not possible to locate the zwitterion and a new TS is found that drives to the formation of an imine in one step.

Fifth, in both directions when the change in the reaction occurs, the energy of the new TS is remarkably higher than the one for the previous point. From then onwards the energy will continue increasing as the strength of the field does it as well.

Sixth, only considering the electronic energy, the formation of the imine is the actual product in the range -0.001 to +0.003 a.u., although it is formed in two steps which the first one is an S_N2 that was characterized at the beginning.

Keeping that in mind, some conclusions can be drawn.

The first conclusion is that what happens when the OEEF is applied with a strength equal or superior to +0.004, or equal or inferior to -0.002 a.u., is that there is a process of coalescence between the intermediate and the second transition state, leading to only observe one TS and not two.

The second conclusion is that the intermediate structure interacts with OEEF and moves in a way that promotes the process of coalescence. However, as in both orientations the change in the mechanism occurs, the manner of how this structure moves in each situation must be different.

The third conclusion is that in a catalytic orientation, the TS moves to the right, so the intermediate structure must have a curve that displaces the TS to the products. In an inhibition situation, the curve must change in a way that moves the TS to the left as the geometry becomes closer to the geometry for reactants.

The last conclusion is that as both reactants and products are neutral, the respective excited structures R* and P* are not ionic. Thus, they won't be affected significantly by the OEEF and the main contribution to the changes observed will come from the intermediate structure that is ionic.

The VB reaction that takes into account the analysis made just before is represented in Figures 30 and 31. The first one shows the gradual change from the unperturbed state to the point in which the mechanism changes, passing through the points in which there is a catalytic effect. The intermediate structure moves in a way that produces the TS to move to the right in the direction of the products. The coalescence will be produced when the bulge moves outside the curve that correlates R* with P and onwards the energy will increase.

Figure 31, on the other hand, shows how the intermediate curve moves to the left as the magnitude of the field increases. This produces the geometry of the TS becomes similar to the one for the reactant, and the barrier energy increases. The bulge also is below the TS in energy, even when the zero-point energy is considered. Eventually the bulge will be out of the curve that correlates R with P* and a similar behaviour of increasing energy will be observed.

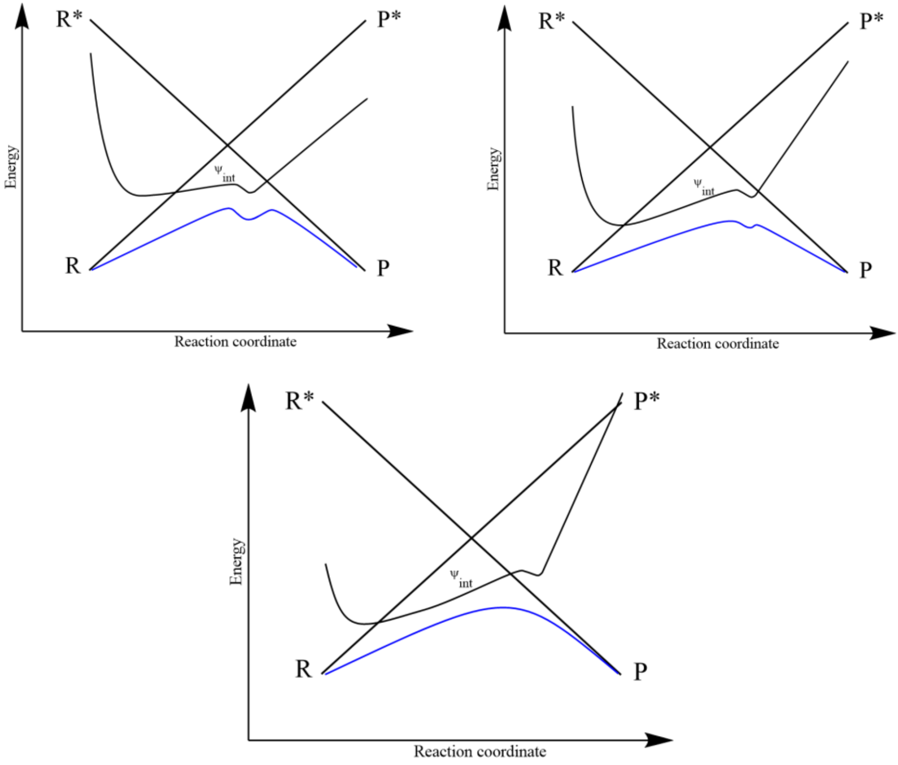

Figure 30. Upper left: VB bond diagram of the reaction when there is no OEEF. Upper right, VB diagram at field of +0.003 a.u. Bottom: VB diagram at field of +0.004 a.u.

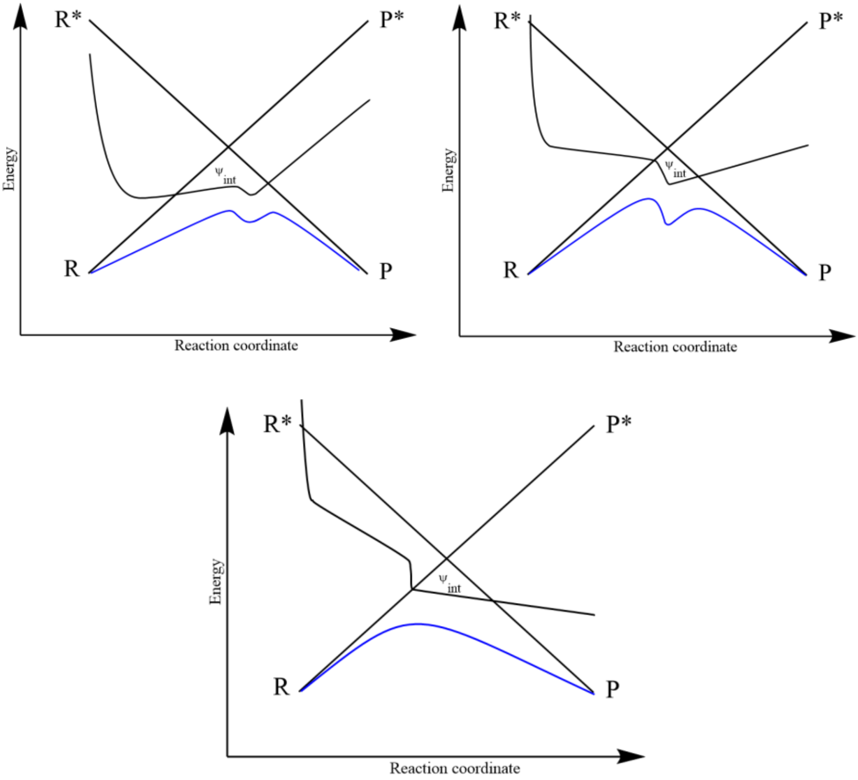

Figure 31. Upper left: VB diagram at zero field situation. Upper right: VB diagram at field of -0.001 a.u. Bottom: VB diagram at field of -0.002 a.u.

8. FINDING THE OPTIMAL OEEF FOR THE FORMATION OF THE IMINE PLUS H_2 FROM THE ATTACK OF AMMONIA TO 2-FLUOROAZIRIDINE

As the interest was addressed to the catalysis, finding the optimal oriented external electric field (optimal OEEF) would be the most important achievement around this topic. Some progress was made in this direction, though. However, finding an unexpected product made it difficult to advance in this matter, and it was not possible to obtain results that could be presented here. This part is still under development. Notwithstanding, a brief discussion of what is being done and the way of obtaining the optimal OEEF will be presented below.

Following the work of Bofill and co-workers[18], the first step is to obtain the potential energy surface (PES) by carrying out several optimizations with the characteristic bond distances as fixed parameters (N1-C3 and N4-C3 for our reaction). With these calculations, the dipole moments of each optimization are also obtained. Representing the direction of the unitary vector in each point gives us a dipole field. An example of a bidimensional dipole is illustrated in Figure 32. The y and x axes are the correspondent values of the dipole components.

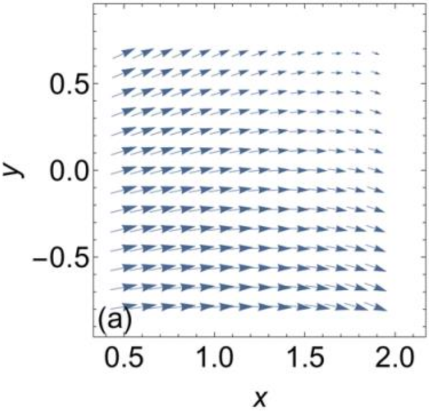

Figure 32. Dipole field of a certain reaction that only depends on x and y components. (Figure taken from Bofill et al., ref. 18). The arrows represent the direction of the unitary vector at each point.

From the dipole field is possible to drawn, by interpolation, the analytical function for the data obtained. The dipole moment that has been presented in Figure 18 and the Table 2 has three components, x, y and z. Its representation would be more complicated than the one is illustrated in Figure 32. However, once the analytical expression is found, the next step is to follow the procedure described in the work mentioned before[18], that is, to find the optimal bond breaking point (optimal BBP), by solving the equation 12 of the Bofill et al. work. The optimal BBP is defined as the point which defines the lowest electric field both in magnitude and direction that promotes the chemical reaction in a barrierless manner. That point corresponds to the one in which the value of the Hessian in the perturbed state is 0[18].

Once the optimal BBP is located, is possible to derive the corresponding optimal OEEF. Figure 33 illustrates the PES of a certain reaction when there is no electric field and when the OEEF is applied. There is also represented the optimal BBP in a green dot in the perturbed PES as this is the point that is located first and that enables to derive the optimal OEEF. Note how the perturbed PES shows no barrier and the process takes place in a plain pathway.

Then, the calculations made and presented before present a basis to continue the study around this topic that will show what is the optimal OEEF to catalyse the formation of the imine and molecular hydrogen.

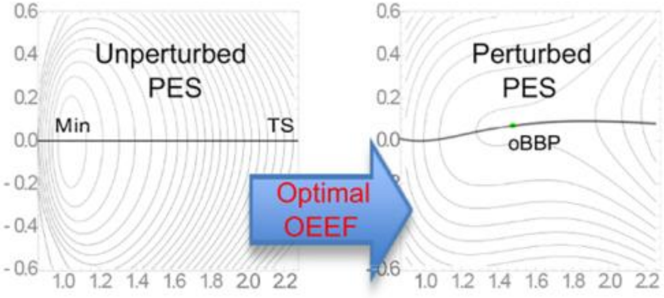

Figure 33. PES of a certain reaction when there is not perturbation and when the OEEF is applied. (Figure taken from Bofill et al., ref. 18).

10. CONCLUSIONS

The first objective was to study the reaction profile of the S_N2 attack of the 2-fluoroaziridine by ammonia. It has been found a more complex reaction and that the product in the beginning was thought to be the zwitterion was indeed an intermediate. It has been very instructive as a first approach in research to see how the findings can modify the initial hypothesis and how the investigation must be modified in line with the observations. This also produced to build a second profile that accounts for the second transition state and the formation of the actual product: imine and molecular hydrogen.

The second objective was to understand and apply the current method of catalysis in the chosen reaction. The literature concerning this topic has been reviewed and, with the information drawn, the introduction was done. Then the knowledge obtained has been tested in a chosen reaction that has not been addressed before. It was found the range in which the catalysis/inhibition works is from -0.001 to +0.003 a.u. The optimal catalysis according to this method must be situated between +0.003 and +0.004 a.u.

The third objective was to compare the differences found between the unperturbed case and when the OEEF is applied. Apart from the reduction or increasing of the energy barrier, there is also observed the modification of the geometry of the TS to become similar to products or reactants. Furthermore, the literature also mentions changes in reactivity and even in the mechanism of the reaction. Here it has been found this happens as well when the field increases above a critical value in positive (+0.004 a.u.) and in negative (-0.002 a.u.) orientations.

The last objective was to rationalise the observations under VB theory. This goal has also been achieved and, in a qualitative manner, the theoretical findings have been taken into account to represent the VB diagrams that show the behaviour of the system both without and with OEEF. How the intermediate structure affected the reactivity is shown as a curve in the middle of the diagram that endows with its characteristics the final bond curve. This structure has been found the responsible for the modifications observed with the electric field.

Despite the formation of a product different from the zwitterion, the imine molecule still contains a fluorinated amine, making it useful in the chemical industry. Moreover, the formation of the imine as well as the production of H_2 opens the window to find more possible applications that until now have not been addressed, such as a method of producing hydrogen or regenerating the initial aziridine.

11. REFERENCES AND NOTES

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12. ACRONYMS

MO: molecular orbitals theory

OEEF: Oriented external electric Field

PES: Potential energy surface

TS: Transition state

VB: Valence Bond theory

VDW: the pre reactant system.

BBP: Bond breaking point