



LETÍCIA SANTOS BRAGA

**Alternative theoretical model based on projection operators
of atomic orbitals for description of the basic behavior of
amines**

LAVRAS – MG

2019

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description of the basic behavior of amines**

Dissertation submitted to the Federal University of Lavras, as part of the requirements of the graduate program in agricultural chemistry, the area of concentration in computational chemistry, for obtaining the title of master.

Dr. Teodorico de Castro Ramalho
Advisor

Dr. Daniel Henriques Soares Leal
Co-Advisor

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Approved February 22, 2019.

Dr. Kátia Julia de Almeida

Dr. José Fernando Ruggiero Bachega

Dr. Teodorico de Castro Ramalho
Advisor

Dr. Daniel Henriques Soares Leal
Co-Advisor

LAVRAS – MG

2019

To my family and Renan, for all support, affection and patience at all stages.

To my friend Well, for being up there cheering for us,

I dedicate.

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To God, for being always by my side, for the opportunity granted, for health and strength.

My family for always being by my side, giving me support and strength not to give up. Especially my parents, Cleusa and Edilson, for my education and training, because I know how difficult those years have been. And for the love they put in me. To my brother Gabriel, for being this great partner at all times, for the moments of celebration, barbeques and always laughter of the bobearas moment.

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"Happiness is only real when shared"

H. David Thoreau.

RESUMO

O argumento HOMO-LUMO surgiu como mais uma interpretação da reatividade. Entretanto, este conceito pode não ser adequado para descrever a reatividade de certas reações químicas. Então, como a abordagem HOMO-LUMO tem certas limitações, há espaço para o surgimento de novas abordagens como o conceito de FERMO. Este novo conceito, baseado em intuição química e em critérios de composição e localização para determinação correta do orbital molecular de fronteira que regula reações químicas, pode ser entendido como um complemento ao argumento HOMO-LUMO. De modo que o HOMO só será o orbital que pode modular a reação se cumprir os requisitos para ser o FERMO. Assim, o objetivo pretendido com este trabalho é apresentar uma abordagem quantitativa do argumento FERMO, por meio da análise dos orbitais efetivos de reação de 17 aminas para determinar qual é o melhor orbital para descrever a reação química ácido/base. Para tanto, foi desenvolvido um método para quantificar a localização de um orbital molecular utilizando projetores, baseado no qual o Grau de Localização Γ_{FERMO} do orbital molecular $|\langle \Phi | \mu \rangle|$, que por sua vez é baseado na norma de um operador de projeção com base em orbitais atômicos do sítio ativo. 17 compostos foram na forma de base conjugada. Estes compostos foram totalmente otimizado com B3LYP/6-31G(d,p) com o software GAMESS. Em seguida, o algoritmo desenvolvido foi aplicado para geração de coeficientes que expressam o grau de localização dos diversos orbitais moleculares no espaço dos orbitais atômicos. Os dados quantitativos gerados pelo algoritmo apontaram que a abordagem do FERMO descreveu melhor o comportamento ácido-base dos compostos investigados em relação à abordagem HOMO-LUMO habitual. O conceito FERMO foi aplicado com sucesso para descrever o comportamento ácido-base de uma série de aminas, conforme demonstrado pelos valores dos coeficientes fornecidos pelo novo algoritmo.

Palavras-chave: orbital molecular de fronteira, FERMO, aminas.

ABSTRACT

The HOMO- LUMO argument emerged as another interpretation of the reactivity. However, this concept can not be appropriate to describe the reactivity of certain chemical reactions. So, as the HOMO-LUMO approach has certain limitations, there is space for the emergence of new approaches like the FERMO concept. This new concept, based on chemical intuition and on criteria of composition and localization for correct determination of the frontier molecular orbital that regulates chemical reactions, can be understood as a complement to the argument HOMO–LUMO. So that the HOMO only will be the orbital that can modulate the reaction if it meets the requirements to be the FERMO. Thus, the objective of this work is to present a quantitative approach of the FERMO argument, through the analysis of the effective orbital reaction of 17 amines to determine which is the best orbital to describe the acid/base chemical reaction. To do that, a method was developed to quantify the location of a molecular orbital using projectors, based on which the degree of localization Γ_{FERMO} of the molecular orbital $|\Phi\rangle$, which in turn is based on the standard of a projection operator based on atomic orbitals of the active site. 17 compounds were investigated in the form of a conjugated base. Those compounds were fully optimized with B3LYP/6-31g (d, p) with the Gamess software. Next, the developed algorithm was applied to generate coefficients that express the degree of localization of the various molecular orbitals in the space of the atomic orbitals. The quantitative data generated by the algorithm in point out that the FERMO approach describes better the acid-base behavior of the compounds investigated in relation to the usual HOMO-LUMO approach. In this line, the Fermo concept was successfully applied to describe the acid-base behavior of a series of amines, as demonstrated by the values of the coefficients provided by the new algorithm.

Keywords: frontier molecular orbital, FERMO, amines.

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LIST OF ACRONYMS AND ABBREVIATIONS

A.O- Atomic Orbital

DA- Diels-Alder cycloaddition reaction.

DFT- *Density Functional Theory.*

EEF- *External Electric Field.*

FERMO- *Frontier Effective for Reaction Molecular.*

FMO- *Frontier Molecular Orbital.*

GGA- *Generalized Gradient Approximation.*

HOMO- *Highest Occupied Molecular Orbital.*

LDA- *Local Density Approximation.*

LH- Bond Hydrogen

LUMO- *Lowest Unoccupied Molecular Orbital.*

OMs- Molecular Orbitals.

RHO- *Reactive Hybrid Orbital.*

TLV- Theory of Valence Bonding.

TOM- Molecular Orbitals Theory.

SUMMARY

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1 INTRODUCTION

The chemical reactions can be described mainly by the molecular orbitals, which explain the chemical reactivity at the atomic level. Lewis established the first concept of reactivity. According to him, the reactivity was linked to the availability of electrons, which would enable the formation of a chemical bond. In this theory, certain atoms could achieve stability by sharing electrons, becoming a stable structure, close to that of a noble gas. Such a theory became known as the Octet Rule.

In 1927, physicist Werner Heisenberg developed the Uncertainty Principle, a quantum concept whereby it is not possible to know simultaneously the position and velocity of the electron at the same time. Therefore, it is not possible for the electrons to be in circular orbits, since it would be possible to know where they are. From there, the concept of orbital emerged.

This fact brought a new perspective to the question, since it did not make sense to try to describe the values of the position and speed so exact of the electrons. Thus, in 1926, Erwin Schrödinger determined, by means of an infinity of mathematical operations, the regions in the space that would present maximum probability of finding an electron. In this way, wave quantum mechanics emerged, whose main result is the equation of stationary orbits of the hydrogen atom known as the Schrödinger equation, which describes the behavior of microscopic systems, considering the dualistic behavior of a particle moving in three dimensions.

Atomic orbitals (A.O) are steady states of the electronic wave function - the wave function (Ψ), which in this context is a mathematical tool that can be used to describe the space and momentum of the electron. However, because of the wave nature of the electron, the A.O do not represent the exact position of the electron in space, but only delimit a region of space in which the probability (Ψ^2) of finding it is high. Thus, the concept of orbital was created, or region of the most probable space of finding the electron. The orbitals are fundamental to understand chemical reactivity, electronic structure and many spectroscopic properties.

Through Max Born, molecular orbitals became the new energy levels and constituted properties of the molecules as a whole, such as bonding energy and bonding length. The wave functions of atomic orbitals are combined mathematically to produce the wave functions of the resulting molecular orbitals (OMs), that is, a new

set of energy levels corresponding to new electron cloud distributions (probability density).

In the quest for a quantitative relationship between reactivity and electronic configuration, the concept of border orbitals emerged. In a chemical reaction, the electrophile or electron acceptor and nucleophile (electron donor) are associated respectively with a species containing an empty molecular orbital that accommodates the pair of electrons donated from a occupied molecular orbital of the other species, being that the most accessible orbital is the one with the lowest energy between the unoccupied orbitals (ie, LUMO), and the most prone to losing its electrons is naturally the highest occupied orbital (ie HOMO). When molecules approach one another, the most favored configuration is the HOMO-LUMO overlap (Bittisti, 2007).

The *Frontier Molecular Orbital Theory* (FMO) arose through these concepts, with several intuitive postulates, generating rules for the interactions between the border orbitals, and the confirmation of the molecular orbitals as great rulers of the reactivity of the various compounds occurred by the study of the electrocyclic reactions (Pereira et al., 2016).

In 1965, B. Woodward and R. Hoffmann developed the Symmetry Conservation Theory, which was a great milestone for the development and use of theoretical models for the rationalization of mechanisms of organic reactions, such as for the cycloaddition reaction of Diels-Alder (Pauling, 1931; Rauk, 2001). In this reaction, the observation of symmetry patterns in all Hückel molecular orbitals in unsaturated systems containing $2n$ or $4n + 2 \pi$ electrons (being n an integer) makes it possible to predict whether or not a reaction will be allowed under thermal or photochemical conditions of according to the rules of conservation of orbital symmetry (Moraes, 2014).

By FMO, a simplification developed by Fukui from the method of Woodward and Hoffmann, when the two components, dieno and dienófilo approaches, the combination of all the molecular orbitals of these species occurs. The combination of HOMO of a species with LUMO is, therefore, according to this theory, the most significant for the stabilization of the system (Moraes, 2014)

However, HOMO and LUMO may not be adequate for understanding the mechanism of a given reaction, according to Fukui. But it may be the next orbital or any orbital that has energy very close to HOMO or LUMO. This concern was exposed in an article, which he wrote in commemoration of his Nobel Prize (Fukui, 1982).

Thus, the concept of *Molecular Orbital Effective Frontier for Reaction* (FERMO) arose in the face of the limitations imposed by the mentioned arguments of HOMO and LUMO. Such a concept, proposed by da Silva and Ramalho (2006), can be understood as a complement to HOMO-LUMO, in which HOMO will only be the orbital of reaction if it fulfills the requirements to be the FERMO. This idea has been well applied in the description of acid-base behavior, in organic and inorganic complexes, in pericyclic reactions and in the study of biological systems (La Porta et al., 2014).

The use of FERMO energy was successfully suggested and used by da Silva and colleagues in the paper entitled "On the Limits of Highest-Occupied Molecular Orbital Driven Reactions: the Frontier Effective-For-Reaction Molecular Orbital Concept", to correlate it with the pKa values of carboxylic acids, alcohols and phenols. It has been proposed that any occupied molecular orbital near the HOMO orbital or even the HOMO orbital itself may be responsible for the interaction of a particular molecule, tending to donate electrons, with another species predisposed to receive electrons, through HOMO-x nucleophile with the LUMO of the electrophile (da Silva et al., 2006).

2 GENERAL OBJECTIVE

To analyze both qualitatively and quantitatively the base acid-base behavior of amines in light of the FERMO concept.

2.1 Specifics objectives

- To calculate the energy at the point for each of these structures using different calculation bases.
- To analyze qualitatively and quantitatively the molecular orbitals involved in the acid-base behavior of amines.

3 THEORETICAL FRAMEWORK

3.1 Principles of reactivity

Some essential foundations to understand the concept of reactivity were established through Lewis' works. According to him, the reactivity is a result of the availability of electrons and the properties present in substances are directly correlated with the mobility of these electrons in the molecule (Lewis, 1913; Lewis, 1916).

The attempts to understand and classify a large quantity of chemical reactions and interactions with the purpose of predict them before the laboratory observations, led to the development of the theory of reactivity. The principal concepts of this theory, called "reactivity indices", can derive from the number of electrons, electronegativity, hardness and softness (Malek; Balawender, 2015) and have proved to be important prognostic tools for very different phenomena in contemporary chemical (Mineva, 2006).

Utilizing quantum chemical methods and molecular modeling techniques, it is possible to define a large number of atomic and molecular properties, characterizing properties related to the reactivity, form and mode of attachment of the fragments and molecular substituents. A quantum chemical descriptors category widely used is related to the energy of the frontier orbitals, with the HOMO and LUMO energies being utilized (Brook, 2010). Those energies provide information about the donor or acceptor character of the electrons of a compound, hence about the formation of a charge transfer complex (Honorius; Da Silva, 2003). The HOMO and LUMO energies have been used for some decades as indices of the chemical reactivity and they are commonly correlated with other indices, such as electron affinity and ionization energy (Arroyo et. al, 2010; Heaton et. Al, 2001).

The chemical concept of molecular hardness and softness has been formulated in accordance with the Lewis definitions of acids and bases (Shriver et al, 1994). Pearson presented the amounts of electron hardness and softness (not considering his acid-base concept, HSAB) in the initial stage of the theory of reactivity (Pearson, 1963). In the soft base case, the donor atom has high polarizability and low electronegativity and can be easily oxidized, in other words, it is associated with the Highest Occupied Molecular Orbital (HOMO), which makes the interaction with the LUMO, of soft acids, more effective (the energy difference between the HOMO and LUMO orbitals is small). On the interaction between a hard base and a hard acid, there is a large energy difference between the frontier molecular orbitals HOMO and LUMO, making the electron transition difficult (Brook, 2010).

Theoretically, the reactivity indices were introduced as descriptors of selectivity and reactivity (Mineva, 2006). The HOMO-LUMO argument emerged for another interpretation of the reactivity, led by the works of Kenichi Fukui and his collaborators.

3.2 The concept of frontier molecular orbitals: HOMO-LUMO

Initiating in the year of 1916, some fundamentals were established of what is known today about the chemical bond. Such concepts were established by Lewis, who correlated the availability of electrons with the reactivity. In 1926, Schrödinger had an extremely important role in quantum mechanics: the development of a new interpretation of the wave function (Ψ). A wave function can be understood to be an abstract mathematical representation of a system. It is an essential element to determine the molecular properties. In this sense, the Schrödinger equation (Equation 1), which is resolved to atoms and one-electron systems, is always used to determine the system's energy from the wave function:

$$\hat{H}\Psi = E\Psi \rightarrow$$

or

$$\left\{ \frac{-\hbar^2}{2m} \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) + V(\vec{r}) \right\} \Psi(\vec{r}, t) = i\hbar \frac{\partial \Psi(\vec{r}, t)}{\partial t}$$

Equation 1: Schrödinger equation.

where Ψ is the wave function which describes the system, subject to an external potential V . The Hamiltonian operator \hat{H} , which provides power to the system when applied to the wave function that describes it, that is, it is a mathematical structure that acts on a function to turn it into another function. As mentioned above, the Schrödinger equation can be solved analytically only for some simple problems, such as the hydrogen atom. For other atoms and molecules, only approximate solutions can be obtained. Such achievement is supported by the variational principle, according to which the energy of an approximate wave function is always greater than or equal to the energy of the exact solution (Atkins, 2009; Rauk, 2001).

The motion of the nuclei of the molecule can be disregarded and the equation can be solved only for the electrons, which are subject to a static potential generated by a particular arrangement of the nuclei, characterizing the commonly called Born-Oppenheimer approximation. Thus, the calculation can be repeated for different positions of the nuclei, generating a potential energy surface and allowing the identification of the lowest energy conformation (Atkins, 2009; Rauk, 2001).

From that perspective, Max Born proposed that to the square of Ψ could be given a precise physical meaning. According to him, Ψ^2 , for a particular location x , y and z of an electron, relates as shown in Equation 2:

$$p(x, t) = |\Psi(x, t)|^2$$

Equation 2: Probability density.

Ψ^2 expresses the probability of finding an electron in this position of the space, and this probability region generates, for example, the shape of the atomic orbitals s , p , d and f (Atkins, 2009; Rauk, 2001).

This is one of the models used to represent chemical bonds, known as the hybrid orbital model, which considers the reorganization of atomic orbitals to form hybrid orbitals, in order to decrease the energy of the system, by distancing groups in the molecule and therefore reducing the repulsion between them. Although this model is useful to represent chemical bonds and molecular geometry, it presents limitations, as the fact of not being able to explain the excited state of molecules. A modern model able to explain some phenomena, usually, difficult to understand by means of other theories, is the molecular orbital model.

In summary, the molecular orbitals can be defined, qualitatively, as linear combinations of atomic orbitals, that is, each atomic orbital has a coefficient (weight), that represents your contribution to the molecular orbital it composes (Freitas; Ramalho, 2013). Therefore, the molecular orbitals are important descriptors for the reactivity of compounds, since chemical reactions are governed by electrons (Da Silva, 2006; Parker et al., 2016).

Then, there was a great interest from the scientific community, since the orbitals could be calculated by approximate quantum mechanical methods, thus allowing a more quantitative understanding of how molecules are formed by combination of atomic orbitals, which originate the molecular orbitals (da Silva, 2006; da Silva, 2014).

The concept of HOMO and LUMO, introduced by a Japanese group led by Kenichi Fukui, became very important for the definition of reactivity. The HOMO exhibits electron-donating ability, and the smaller the LUMO energy, the lower the resistance to accept electrons (Yankova et al., 2016). These orbitals, also known as frontier orbitals, are used to determine the manner in which the molecule interacts with other species (Resmi et al., 2016). According to the frontier molecular orbital theory, the formation of a transition state is due to an interaction between the frontier orbitals (HOMO and LUMO) of the reactants (Latha et al.,

2017). The HOMO energy is directly related to the ionization potential, while the LUMO energy is directly related to the electron affinity (Srivastava et al., 2016).

A small energy difference ("gap") between the orbitals is associated with a high chemical reactivity (Sahin et al., 2016). This chemical reactivity can be explained by the global reactivity descriptors such as ionization potential, electron affinity, electronegativity and chemical potential (Resmi et al., 2016).

The physical interpretation of the orbital energies, was given by Koopmans (Koopmans et al., 1933). Fukui and his coworkers, in their studies on reactivity of aromatic hydrocarbons, proposed the use of frontier electron density to predict the most reactive position in these systems. Their calculations were in excellent agreement with experimental data. Afterwards, they established some postulates, based on the frontier orbitals, to predict the reactivity of electronic systems in various types of reactions (Fukui et al., 1952).

Thus, gathering the fundamentals of Lewis about reactivity and molecular orbitals, the reactivity of chemicals compounds became more understanding and qualitative (Liang et al., 2017).

3.3 Frontier Effective-for-Reaction Molecular Orbital (FERMO) and reactivity

The FERMO (Frontier Effective-for-Reaction Molecular Orbital) concept emerged as a tool to investigate the role of molecular orbitals applied to the description of the breaking and formation of chemical bonds. As noted by Fukui, HOMO and LUMO may not be suitable for a given reaction, but certainly the next or any other orbital, which has the amount of energy very close to the HOMO or LUMO, could be used. He cited as an example the protonation of the pyridine (Figure 1), process in which the HOMO is an orbital of the system π of the pyridine ring (Fukui, 1982). As is the hydrogen atom that binds to the nitrogen pair of electrons, the HOMO would not have any connection with this reaction in pyridine. Therefore, the orbital involved in the reaction is the third HOMO (or HOMO-2), which has the non-binding characteristic of the nitrogen pair of electrons (Pereira et al., 2016), as shown in Figure 2:

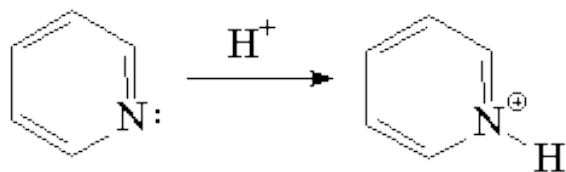


Figure 1 Protonation of the pyridine.

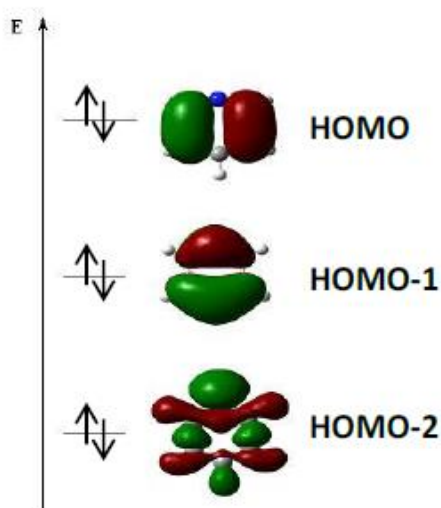


Figure 2 Shape of molecular orbitals of pyridine.

(Fukui, 1982).

Thus, it was possible to observe that, despite the progress, the frontier orbital theory had some limitations, enabling the emergence of new theories (Virk; Klein, 2014). One of these new theories was proposed in 1994 by Hiroshi Fujimoto (Fujimoto; Satoh, 1994), who worked with Fukui. In this theory, he proposed to recombine some molecular orbitals, chosen according to certain criteria, and locate the maximum of them in the reaction site. This procedure was named as Localized Reactive Orbital (Pereira et al., 2016).

Using this same argument, Hirao and Ohwada formulated the concept of *Reactive Hybrid Orbital* (RHO), according to which a reactive orbital well located is provided around a reaction center. They showed that the RHO is far superior than the HOMO to describe the attack in an aromatic system. They also applied the approach RHO to other systems, such as carbonyl compounds, cyclic amines and Diels-Alder reactions (Hirao; Ohwada, 2003). In all the mentioned reactions, the RHO approach described the reactivity of these compounds better than HOMO; However, a careful study is required to understand when the HOMO energy is appropriate or when it is not (da Silva et al., 2006a).

The FERMO concept is a simple, but very useful tool. With the FERMO concept, the reactions that were not understood on the basis of the HOMO-LUMO properties, ceased to be

exceptions. Among these reactions, it is worth emphasizing the acid-base behavior, the organic and inorganic complexes, the pericyclic reactions and the study of biological systems (La Porta et al, 2012; de Almeida et al., 2013; La Porta et al, 2011; Her Door et al., 2010).

According to da Silva (2006), for a given molecule, the choice of FERMO is made according to the following steps:

I. Check the shape of molecular orbitals.

II. To assess which of the molecular orbitals presents the greater assistance of the atom, or group of atoms, which is the reaction center. This is done by analyzing the value of the molecular orbitals' composition in terms of the expansion coefficients of the atomic orbitals.

The acid-base behavior may not be described by the HOMO energies in some acid-base reactions. In compounds such as alcohols and phenols, the orbital that describes the best acid-base behavior is not the HOMO (Figure 3), but the PxPy orbital (Figure 4), which is the FERMO for this reaction in each molecule, as illustrated in Figure 3 and 4 (da Silva et al., 2006).

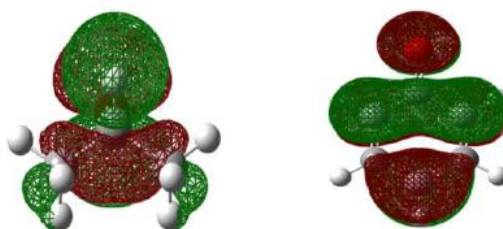


Figure 3 HOMO orbitals for the isopropoxide and phenoxide molecules.

(Fukui, 1982).

Through the FERMO concept, it is possible to analyze each shape and composition of the molecular orbitals in order to determine which of these orbitals will describe the reaction (Pereira et al., 2016).

The orbitals shown Figure 3 and 4 indicate that the HOMO-LUMO orbitals are not always responsible for all chemical reactions, as quoted by Fukui and his collaborators (1952; Parker et al., 2016).

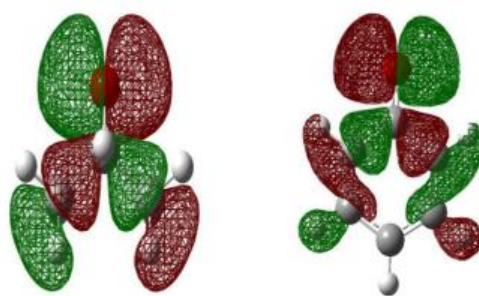


Figure 4 PxPy orbitals for the isopropoxide and phenoxide molecules.

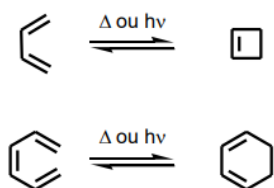
(Pereira et al., 2016).

This concept was also applied to a variety of amines to observe the acid-base behavior (La Door et al., 2010). It is known that the basicity is directly related to the availability of pairs of electrons (Kolpman, 1984). Therefore, the molecular orbitals and their properties, such as energy and symmetry, are very important to better understand your reactivity (Raczynska et al, 2017).

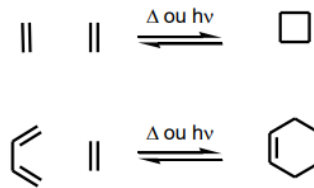
Regarding the organic and inorganic complexes, the FERMO also exhibited good results when used for certain types of ambidentate ligands correlating with the principle of hardness and a softness of Pearson. Pearson defined a more polarizable species as soft (acid or base) and a less polarizable species as hard (acid or base) (Vasconcellos, 2014). In the works of da Silva and his collaborators (da Silva et al., 2006b), the researchers affirmed that soft molecules have smaller HOMO-LUMO energy value when compared to hard sites. For this study, the authors used as ambidentate ligands the species SCN^- , NO_2^- , $\text{CH}_3\text{COCH}_2^-$ and dimethyl sulfoxide (DMSO), since there were many theoretical experimental works, in literature, with these molecules. Thus, it was possible to locate and form the FERMO for these ligands.

Another study involving FERMO was related to pericyclic reactions. These reactions can be defined as a concerted reorganization of chemical bonds by means of a cyclic arrangement of atoms continuously interconnected. The main types of pericyclic reactions are: electrocyclic reactions, cycloaddition reactions, sigmatropic rearrangement reactions and the Ene reactions (Solomons et al., 2004), as shown in Figure 5.

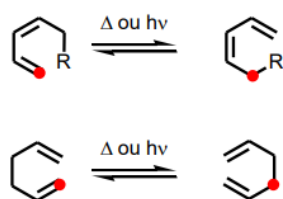
1) Eletrociclizações e aberturas eletrocíclicas



2) Ciclo-adições e retro-cicloadições



3) Sigmatrópicas



4) Enes e retro-enes

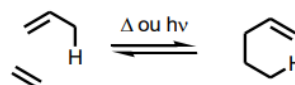


Figure 5 Main types of pericyclic reactions

The cycloaddition reactions are of great importance and interest in synthetic organic chemistry. In these reactions, two different molecules, which have π bonds, react to form a cyclic molecule by the rearrangement of the π electrons and two σ bonds (Domingo et al., 1998; Maksic and Vianello, 2006). Recently, in a work of La Porta and his collaborators (La Porta et al., 2011), the FERMO concept was applied with success in study of four 1.3-dipolar cycloaddition reactions, obtaining, as a result, better correlations of FERMO energy with the constants of basicity and acidity when compared to the HOMO energy. The reactions that are conducted by HOMO and those that are not, could be better explained, regardless of the method of calculation applied, because both, HF and Kohn-Sham, methodologies led to the same FERMO.

3.4 Amines

The amines are an important class of compounds resulting from the replacement of one or more hydrogen atoms, of the ammonia molecule, by alkyl and/or aryl groups. In nature, they occur between proteins, vitamins, alkaloids and hormones. In synthetic compounds, they occur in polymers, dyes and drugs (Peter, 2004).

As the ammonia, the nitrogen atom of amines is trivalent and contains an unshared pair of electrons. In amines, the orbitals of the nitrogen atom are, therefore, sp^3 hybridized and its geometry is pyramidal, with each one of the three sp^3 hybridized orbitals of nitrogen overlapping the orbitals of the hydrogen or carbon atoms, depending on the composition of

the amines, while the fourth sp^3 orbital of nitrogen, in all the amines, contains the unshared pair of electrons. This unshared pair of electrons causes the angle C-N-E (where E can be C or H) to be less than 109.5° ; for example, 108° in the case of trimethylamine, as shown in Figure 6 (Peter, 2004).

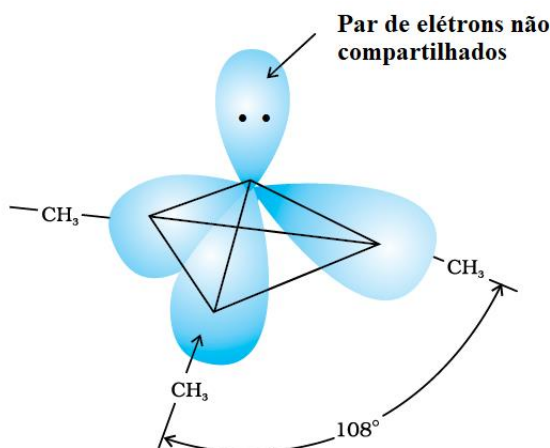


Figure 6 Pyramidal geometry of trimethylamine.

This class of compounds can be classified according to the number of hydrogen atoms replaced of by aryl and/or alkyl groups as primary, secondary and tertiary, as shown in Figure 7.

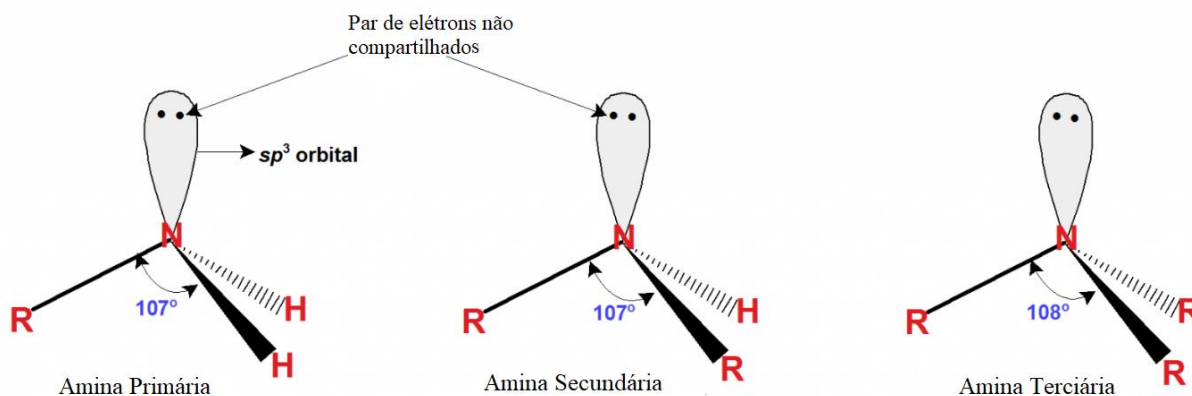


Figure 7 Classification of amines according to the number of hydrogen atoms replaced.

They can be further classified according to the nature of the carbon atom bonded to the nitrogen, aromatic (3) or aliphatic (1 and 2), as shown in Figure 8. If one of the carbon atoms bonded to the nitrogen atom is aromatic, the amine will be fragrant. In cyclic systems, the nitrogen atom can be in heterocyclic structures or, in the aromatic ring, aromatic heterocyclic structures (1) (Solomons, 2004).

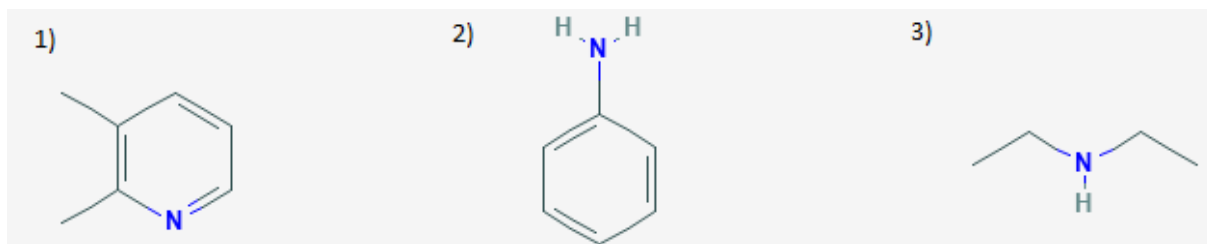


Figure 8 Classification of amines according to the number of hydrogen atoms replaced.

The presence of an unshared pair of electrons is responsible for the particular physical and chemical properties of amines. They are moderately polar substances and have boiling points higher compared to the alkanes, but generally lower compared to the alcohols of the same molar mass. Primary and secondary amine molecules can form hydrogen bonds with each other and with the water. Tertiary amine molecules cannot form hydrogen bonds with each other, but can form with the water and other hydroxylated solvents. As a result, tertiary amines come into boiling at temperatures lower than primary and secondary amines of comparable molecular weight (Solomons, 2004).

Finally, amines are excellent bases compared to the alcohols, because they present unshared pair of electrons more easily protonatable (Solomons, 2004).

3.5 Basic behavior of amines

It is known that acid-base behavior is one of the most important processes of transformation of organic molecules (Li et al., 2006). Knowing well the basicity of organic compounds in various solvents is fundamental to the study of reaction mechanisms in organic chemistry (Bruice, 2006).

However, before analyzing the relation between reactivity and the acid-base behavior, it is important to recall the current concept of Lewis, about acids and bases. From 1923, Lewis expanded this concept: he proposed that acid would be any chemical substance capable of receiving a pair of electrons, while the bases would be substances capable of donating a pair of electrons (Solomons, 2012).

The organic molecules have your reactivity linked to their acid or basic behavior. An example of these compounds are the amines (La Door et al., 2010). They are relatively weak bases, yet stronger than water, much weaker than the hydroxide and alkoxide ions. Their basicity can be provided by the basicity constant (pK_b), which is directly linked with the availability of unshared pairs of electrons. Therefore, as they are electron donor species, they serve as a base, since they can donate these electrons to a Lewis acid and establish a covalent

bond, as it was established by Lewis theory of acids and bases. Thus, the basicity is an important factor to adjust the reactivity of these transformations.

When there is the replacement of the hydrogen atom by an R group, there is a decrease in the value of pK_b , showing that the amine becomes more basic. This happens because the electron-withdrawing inductive effect of the R group is greater than that of a hydrogen atom. Although the R group is greater, the spatial arrangement of the carbon atoms in the structure favors the twist in carbon-carbon bond, which contributes to a reduction of the spatial block in the nitrogen pair of electrons (Solomons, 2012). The basic force can be reduced by the introduction of groups that remove electrons (-NO₂, -Cl, -Br) near the basic center.

The approach of the frontier orbitals HOMO-LUMO can be used to describe this acid-base behavior of the amines. However, for many compounds, the HOMO is not the MO that governs the reaction, since its energy does not describe properly the acid-base behavior, as it was presented by La Porta et al. (2010). La Porta and colleagues investigated which molecular orbitals would describe better the acid-base behavior of a set of 18 amines, where the approach FERMO could also be applied. As a result, the FERMO concept was successfully applied to describe the acid-base behavior of the set of amines studied, presenting better correlation with the pK_b compared to the HOMO. In this sense, the FERMO concept took into consideration each atomic shape and composition of molecular orbitals to determine which of them would be the orbital that would describe the reaction.

However, these results are still seen in a qualitative manner, since it is necessary to investigate the shape of the orbitals previously.

3.6 Theoretical calculations

The computational chemistry attracted much attention recently due to the large and growing interest in employing theoretical methods for analysis in general, as well as for the investigation of structural relations and complementation of experimental data. (Hehre et al., 1986). Theoretical approaches to calculate structural and electronic parameters are now implemented in packages of very efficient programs, that can be used in computing with increasing performance (Hehre et al., 1986).

The term "Computational Chemistry" became popular thanks to scientific, historical, cultural, and technological factors and its development occurred due to the greater processing power of modern computers, advanced software and better comprehension of the basic principles of science (Hehre et al., 1986).

The manipulation and the domain on a nanometric scale are currently indispensable, since they have useful applications in various fields of knowledge. And to simulate the behavior of matter at the atomic scale, computational chemistry methods based on the formalism of quantum mechanics are applied.

One of the ways used to represent the matter, in nanometric or macro scale, is the formulation in terms of the wave function represented by Schrödinger, who was responsible for the equation that correctly describes the movement of quantum systems. As previously explained, the solution of this equation is called wave function, which is a representation of a vector in a Hilbert space (Silva, 2013). This function can be complex, of real variable and can only be obtained for a restricted set of cases. For systems containing more than one electron, a sophisticated treatment is required.

For this reason, various approximation methods were proposed in order to find the electron orbitals for many-electron atoms. Among them are the Hartree-Fock method and Density Functional Theory (DFT), which are in constant development.

However, refined theoretical calculations, in the gaseous phase, revealed important information about the molecular interactions. Thanks to the remarkable development of computational chemistry, the calculations in the gaseous phase can have a good precision when compared to the experimental data. Besides that, some previous studies showed that the calculations in the gaseous phase have the same reliability that the liquid phase in the study of molecular orbitals, when it is based on the FERMO concept (La Porta et al. .2010; Santiago et al., 2010).

The calculations for the FERMO are based on Molecular Orbital Theory (MOT), according to which data are interpreted with the Valence Bond Theory of (VBT) (Pereira et al., 2016). In MOT, the electrons in a molecule occupy delocalized orbitals obtained from the linear combination of atomic orbitals (Bloom et al., 2007). However, it is necessary to emphasize that the TLV approach is quite useful to analyze the enzymatic reactivity (Nakamura; Truhlar, 2001; Truhlar, 2007), photochemistry (Brynda et al., 2006), chemical dynamics and the theories of conductivity, in which the localized representation is essential.

3.7 Density Functional Theory

The Schrödinger equation has an exact solution only for the hydrogen atom (Schrödinger, 1926) and for the hydrogen molecule ion H_2^+ with the exception of fixed

nuclei (Burrau, 1927). However, when the number of dynamic particles is greater than two, the problem of interacting electrons is still unmanageable accurately, as occurs with the cases of molecular system of two electrons of Helium (He) atom and hydrogen molecule H₂, for which only approximate analytical solutions can be obtained. Therefore, the case of many interacting bodies does not have an exact solution (Silva, 2013).

Several methods were proposed to treat this problem, as the Hartree-Fock method, post Hartree-Fock method (*Coupled Cluster* and *Configuration Interaction*), Density Functional Theory (DFT), among others.

The DFT is one of the techniques most utilized to treat the problem of many interacting electrons in molecular systems (Silva, 2013). The first ideas of this technique arose through Thomas and Fermi, who used the concepts of statistical mechanics to simplify the many-body problem with some postulates, which are based on the assumption that the electrons are uniformly distributed in space. It has emerged as an alternative to traditional *ab initio* and semi-empirical methods in the study of the ground-state properties of molecular systems. The great advantage of the DFT compared to the traditional *ab initio* methods (e.g., Hartree-Fock or post-Hartree-Fock) resides in the computational speed gain and memory space (Alcácer, 2007; Cramer; Truhlar, 2009; Morgon et al., 1994).

It was thus built an atomic theory based on electron density $\rho(r)$, contrary to the theory proposed by Schrödinger in 1926, which used the wave function as an object of description of atoms (Schrödinger, 1926). As a result, the Coulomb repulsion integral needs to be calculated only for the electron density, which is a three-dimensional function with N^3 , where N is the number of basis functions. On the other hand, the *ab initio* methods deal with functions that involve more dimensions, with N^4 or greater (Alcácer, 2007).

Therefore, the basic entity of the DFT is the electron density ($\rho(r)$), which describes the load distribution in a given molecule. The modern concepts of this theory were formulated by Khon and Sham in 1965 and are based on two theorems:

1. The ground-state wave function and, therefore, all the properties of that state are functional of the electron density, $\rho(r)$. Thus, the electron density of a system determines the external potential $v(r)$ and the number of electrons N and, therefore, the Hamiltonian of the system itself.

2. The ground-state energy of a multielectronic system under a given external potential $v(r)$ can be written as:

$$E_v[\rho(r)] = \int v(r) \rho(r) dr + F[\rho]$$

Equation 3: Electron density

where F is called universal functional of ρ , which is independent of the potential $v(r)$ (Alcácer, 2007; Jensen, 2007).

Thus, for an arbitrary atom, the ground-state energy depends only on the electron density, which describes the load distribution in a molecule, as shown in Equation 4:

$$E = K[\rho] - Z \int d^3r \frac{\rho(r)}{r} + \frac{1}{2} \int d^3r \int d^3r' \frac{\rho(r)\rho(r')}{|r-r'|}$$

Equation 4: Ground-state energy.

where $K[\rho]$ is the density functional, which is responsible for the contribution of the kinetic energy of the electrons to the total energy. The second term refers to the portion of energy due to the attraction of electrons by the core, and the last term corresponds to the energy due to electron-electron repulsion (Silva, 2013). The Fermi model was based on the division of the real space in small cubic boxes containing electrons, which do not interact with each other in different boxes and even in the same boxes.

In 1962, Edward Teller showed that, due to the kinetic energy functional approximation used in the Thomas-Fermi model, there was no stable bonds between atoms, that is, the sum of the isolated atoms energies is always less than the molecule energy (Teller, 1962). Dirac noticed another problem: the lack of exchange energy. Thus, he proposed a further term, presenting a new model, the Thomas-Fermi-Dirac model. However, the problem concerning the form of the kinetic energy functional still existed (Silva, 2013).

The Thomas-Fermi-Dirac model also suffered a correction, performed by Weizsäcker in 1935, using the electron density gradient to describe the kinetic energy, in the form $\left(\frac{1}{8} \int d^3r V \frac{\nabla \rho(r) V^2}{\rho(r)}\right)$ (Weizsäcker .1935). This correction allowed a much more precise calculation of the total energy of the hydrogen atom, drawing attention once again to the Density Functional Theory (Sarkar, 2013).

The exact resolution of the Schrödinger equation (Equation 3) presents a very high level of complexity. Thus, approximations are necessary for use it in real systems. One of the most important approximations is the Born-Oppenheimer approximation. Basically, this disregards the motion of the nuclei in the molecule, since the nuclear mass is many times

greater than the electron mass. Thus, the Schrödinger equation is solved only for the electrons, which are described by a purely electronic wave function in the presence of a potential produced by nuclei that assume fixed positions in space (Alcácer, 2007; Jensen, 2007).

In 1964, Walter Kohn and his student Pierre Hohenberg demonstrated a reformulation of quantum mechanics that used density functionals instead of wave functions (Hohenberg; Kohn, 1965). A functional is more generic, and maps a function into a number. In other words, a functional is a function whose variable is another function. Thus, to know any property of an atom, a molecule or a solid, it was necessary to know what is your electronic density. And, to find the ground state of the system, it was enough to minimize the total energy as a function of the density. This principle is equivalent to the Rayleigh-Ritz variational principle (Silva, 2013).

The first exchange-correlation functional was named as the Local Density Approximation (LDA), proposed by Kohn-Shan (Kohn; Sham, 1965), in which the inhomogeneous electron density is approximated as if every point in space was a result of a homogeneous density (Szabó, 1996). The following were referred to as Generalized Gradient Approximations (GGA) (Thomas, 1975) and meta GGA (Perdew et al, 2003). Subsequently, occurred the combination between the exchange-correlation functionals, forming the hybrid functionals. Such functionals use the exact exchange term of the HF method with the exchange-correlation functionals GGAs.

The B3LYP functional, of the DFT, is currently one of the most used and cited in literature (Musso et al., 2011; Nazarpour et al., 2012; Huang; Lee, 2012). It is a hybrid functional, that is, the combination of exchange-correlation functionals, which contains in their formulation GGA functionals, that includes a contribution from the HF method. It was developed by Becke (indicated by the letter B) and has a term of correlation developed by Lee, Yang and Parr (LYP), and still has three empirical parameters chosen to optimize its performance (indicated by the number 3) (Pereira, 2008).

A set of bases is a set of functions whose purpose is the creation of molecular orbitals. It can be understood as a primitive function used to represent each one of the orbitals in valence theory for the molecule treatment, that is, a function is provided for each atom of hydrogen, H, and helium, He (to simulate the 1s orbital), five functions for each atom of lithium, Li, or neon, Ne (for 1s, 2s and three 2p orbitals) and so on (Atkins et al., 2009).

There are two types of basis set used in calculations of electronic structure: Slater-Type Orbitals (STOs) and Gaussian-Type Orbitals (GTOs).

Slater has proposed the first basic functions to be used, which were similar to the atomic orbitals of the hydrogen atom (Arruda, 2009). These functions are appropriate for the calculation of physical properties of atomic or molecular systems, however, they do not allow a fast analytical and computational resolution of the two-electron multi-center integrals, or even the three-center nuclear attraction integrals (Arruda, 2009). They are given by the equation 5:

$$\chi_{\zeta,n,l,m}(r, \theta, \varphi) = NY_{l,m}(\theta, \varphi)r^{n-1}e^{-\zeta r}$$

Equation 5: Slater functions.

where N is a normalization constant, $Y_{l,m}$ are the usual spherical harmonic functions and $\zeta=(Z-W)/n$ is a constant. The Z-W term represents the effective nuclear charge, with W being a shielding constant. The ζ exponents are positive numbers and determines the characteristics of the functions (Arruda, 2009).

It was Boys (Boys; Egerton, 1950) who presented the Gaussian-Type Functions (GTFs), by means of which has been achieved the simplification of the computational calculations of multi-center integrals. They can be written in terms of cartesian or polar coordinates, respectively, as:

$$\chi_{\zeta,n,l,m}(r, \theta, \varphi) = NY_{l,m}(\theta, \varphi)r^{2(n-1)}e^{-\zeta r^2}$$

Equation 6: Polar Gaussian-Type Functions

or

$$\chi_{\zeta,l_x,l_y,l_z}(r, \theta, \varphi) = Nx^{l_x}y^{l_y}z^{l_z}e^{-\zeta r^2}$$

Equation 7: Cartesian Gaussian-Type Functions.

where the sum $L = l_x + l_y + l_z$ determines the orbital symmetry, since the cartesian Gaussian is from the s-type when L is 0; it is from the p-type when L is 1; it is from the d-type when L is 2, and so on (Jensen, 2007).

Due to the computational efficiency obtained through the use of GTOs, they are usually preferred and widely used as basic functions in electronic structure calculations (Jensen, 2007).

3.8 Degree of Localization FERMO

The atomic orbital basis can be used to create projection operators on a given subspace of the system. A projection operator can be regarded as the projection of a vector subspace in

another (or of a vector in particle on a subspace); it is the “component” that each vector of the first would have on the second (the " shadow "of one in another) (Silva, 2013).

The Degree of Localization, □FERMO (Frontier Effective-for-Reaction Molecular Orbital), of molecular orbital $|\Phi_\mu\rangle$ is based on a standard of a projection operator based on the atomic orbitals of active site. Since it is not possible to assign a physical meaning to the molecular orbitals, it was necessary the creation of localized molecular orbitals. The spatially localized orbitals are formed from the rotations of the molecular orbitals, according to various criteria (Silva, 2013).

The projection operator allows to build any subspace of atomic orbitals, and not necessarily of a single atom. In general, if G represents a set of atomic orbitals that belongs to a set of atoms, so Γ_G can be defined as shown in Equation 8 (Scott .2013).

$$\Gamma_G = \|\langle \Phi_\mu | \hat{P}_G | \Phi_\mu \rangle\| = \left[\sum_l \sum_{i \in G} \sum_{j \in G} \sum_k C_{l\mu} S_{li} S^{-1}_{ij} S_{jk} C_{k\mu} \right]^{\frac{1}{2}}$$

Equation 8: Molecular orbitals location.

where S_{li} , S^{-1} and S_{jk} are the overlap matrix and, $C_{l\mu}$ and $C_{k\mu}$ are the matrixes of molecular orbitals coefficients. The Equation 8 enables the calculation of molecular orbitals location in groups of atoms.

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5 ARTICLE

Quantification of molecular orbitals based on projection operators: methodological development and applications to basicity prediction of amines in the gas phase

Leticia Santos Braga^a, Rodrigo A. Moreira^b, Daniel Henriques Soares Leal^c and Teodorico Castro Ramalho^{a,d,‡}

^a Chemistry Department, University Town, Federal University of Lavras, P. O. Box 3037, Minas Gerais, Brazil, leticia13santos@hotmail.com / teo@dqi.ufla.br

^b Department of Physics, Federal University of Pernambuco, 50670-901, Recife, Pernambuco, Brazil, rodrigoams@df.ufpe.br

^c Department of Health Sciences, Federal University of Espirito Santo, Sao Mateus, Espirito Santo, Brazil, daniel.leal@ufes.br

^d Center for Basic and Applied Research. University of Hradec Kralove. Hradec Kralove, Czech Republic

‡ Corresponding author: Teodorico C. Ramalho

e-mail: teo@dqi.ufla.br

Address: Chemistry Department, University Town, Federal University of Lavras, P. O. Box 3037, Lavras/MG, 37200-000, Brazil

Fax: 55 35 3829-1271

Tel: 55 35 3829-1522

Abstract

At present, acidity is a very important parameter with high impact both on biological systems and on technological problems. The HOMO-LUMO and FERMO theoretical approaches can describe the acid-base behavior of compounds such as amines. In the present work, a method, using the localization degree Γ_{FERMO} parameter based on projection operators to quantify the localization of molecular orbitals, was developed. This new method was employed for the analysis of the protonation reaction of 17 amines. The quantitative data from our findings point out that the FERMO approach could better describe the acid-base behavior of the investigated compounds.

Keywords

molecular orbital, HOMO-LUMO, FERMO, acid-base behaviour, localization degree, Γ_{FERMO}

Introduction

In recent decades, a large body of research has performed about chemical reactivity and Quantum Mechanics has arisen playing a vital role in this field [1-3]. It is well-known that wave functions of a molecule can be expressed using the framework of molecular orbitals (MO), in which a set of atomic orbitals (AO) is mathematically combined to produce new wave functions. Thenceforth, the use of atomic and molecular orbitals is intrinsically connected to our comprehension of how atoms unite for the formation of molecules [4]. In this sense, one of the most critical applications of MOs in chemical phenomena is related to the *highest occupied molecular orbital* (HOMO) and the *lowest unoccupied molecular orbital* (LUMO), whose energy difference is employed in the interpretation of the chemical reactivity [5].

Pioneers in this area, Fukui and coworkers realized that the HOMO energy was intrinsically related to the reactivity of molecules, where they used its electronic density to correctly predict which carbon atoms would be the reaction site for a series of electrophilic substitutions in aromatic hydrocarbons [6]. Moreover, in agreement with Lewis' ideas to use the electron pair as a determining part of many reactions, they also established that chemical reactions, such as those between Lewis's acids and bases, would be governed by the frontier orbitals [6]. In this context, the importance of frontier electrons became broader, evolving to the *frontier molecular orbital* (FMO) theory [7].

Attempts to understand and classify a large number of chemical interactions and reactions with the ultimate goal of predicting them before experimental observations led to the development of the *reactivity theory*, whose main concepts so-called "reactivity indexes" have proven to be important prognostic tools for apparently very different phenomena in contemporary chemistry [8]. For example, variations in HOMO-LUMO energy gaps can be used as reactivity indexes. Following the Pearson's principle, soft molecules have lower energy values for the HOMO-LUMO barrier when compared to hard sites [9].

However, even with the success of the HOMO-LUMO approach, many researchers wondered if these two orbitals would be the only responsible for molecules reactivity. Fukui has also exposed this concern in an article he wrote in commemoration of his Nobel Prize [10].

In the face of such limitations, another approach arose to understand the chemical reactivity: the FERMO (*Frontier Effective for Reaction Molecular Orbital*) concept, proposed by da Silva and Ramalho [4,11]. This approach arose from some chemical intuition, along with composition and localization criteria in order to correctly determine the FMO that modulates chemical reactions. This methodology can be understood as a complement to the HOMO-LUMO approach so that the HOMO could only be the MO that governs a reaction if it meets the requirements to be the FERMO. Such a concept has been successfully applied in the qualitative description for chemical reactivity parameters of phenomena like acid-base behavior, organic and inorganic complexes, pericyclic reactions and the study of biological systems [11-12].

Regarding the chemical reactivity, the acid-base behavior is one of the most important processes that affect the interconversion of organic molecules. The knowledge about acidity/basicity of organic compounds in various solvents is essential for the study of reaction mechanisms in organic chemistry. In this sense, a very useful acid-base parameter is the proton affinity (PA). The PA of a basic compound is defined as the negative of the enthalpy change for its protonation reaction: the higher the PA value, the most negative (and the more exergonic) is the enthalpy change for the formation of conjugated acids [13]. Thus, there is a correlation between PA values and stability of conjugate acids in the gas phase. In other words, PAs might also illustrate the role of hydration in aqueous-phase Brønsted-Lowry basicity. Whereas many articles have shown how PA values correlate with quantum descriptors [4-9,14], recent studies have revealed that the FERMO concept [15] can be more efficient to describe the acid-base behavior of molecules than the HOMO-LUMO argument [14]. It should be kept in mind, however, that so far the FERMO concept employs qualitative arguments to localize the reaction site.

Considering this scenario, our work is devoted to investigate which MO is the best for describing the acidity of amines as well as to develop a more quantitative approach for the identification of FERMOs in chemical reactions.

Methodology

Our strategy to quantify the FERMO localization is based on the use of projection operators as follows. The MOs θ_μ are constructed by a linear combination of AOs (the LCOA approach):

$$\theta_{\mu} = \sum C_{l\mu} \zeta_l(x) \quad (\text{Eq. 1})$$

where $C_{l\mu}$ is the matrix of MO coefficients and $\zeta_l(x)$ are gaussian AOs. They are constructed as an orthogonal set of vectors with components at each atomic orbital of a given molecule. However, the set of atomic orbitals $\zeta_l(x)$ form a non-orthogonal basis set, which defines the overlap matrix S_{ij} :

$$S_{ij} = \int \zeta_i(x) \zeta_j(x) dx \quad (\text{Eq. 2})$$

The overlap matrix can be used to construct a projection operator P_G , observing that, for a set of atomic orbitals G :

$$P_G = \sum_{i \in G} \sum_{j \in G} \zeta_i S_{ij}^{-1} \zeta_j \quad (\text{Eq. 3})$$

P_G is a projector and, namely, it is idempotent ($P_G P_G = P_G$).

Note that a projection operator can be intuitively understood as the projection of a “shadow” of a selected MO onto the subspace of an arbitrarily set of AOs [16], whereas its mathematical formulation becomes tricky due to the non-orthogonal character of the atomic orbitals. This property is precisely a quantitative characterization of the shape of given MO at a set of AOs, and consequently, a set of atoms.

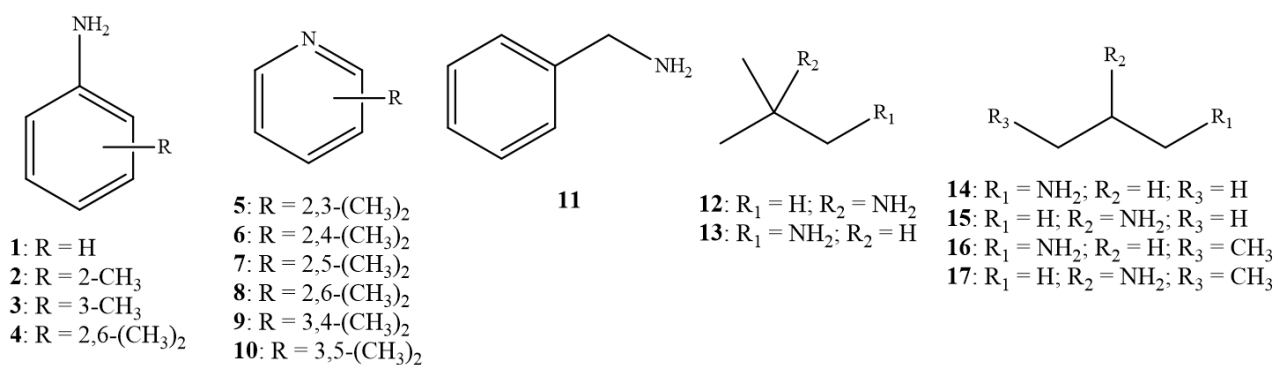
We define the degree of localization Γ_{FERMO} of a molecular orbital θ_{μ} as the norm of a projected MO onto the expected set of atomic orbitals that are relevant to the reaction center of a given compound. Thus, it is possible to calculate the localization of MOs in groups of atoms by a well-defined mathematical criterion using Equation 4 [16]:

$$\Gamma_{FERMO} = \sqrt{\sum_l \sum_{i \in G} \sum_{j \in G} \sum_k C_{l\mu} S_{li} S_{ij}^{-1} S_{jk} C_{k\mu}} \quad (\text{Eq. 4})$$

The choice of the set of atomic orbitals G relevant to reaction center will be discussed later in the text, when we describe the molecules characterized in this article.

For the current work, a total of 17 amines (whose structures are shown in Figure 1) were chosen for the study of the degree of localization, considering their protonation reactions. They were classified in aromatic (**1-4**), heterocyclic (**5-10**) and aliphatic (**11-17**). The *aliphatic* amines have a RNH₂-type structure (primary, with tetrahedral N and C atoms); the *heterocyclic* group own a pyridinic ring; and the *aromatic* amines have the ArNH₂ basic structure (Ar: aromatic group). We chose these compounds due to previous works, in which the reactivity of compounds was analyzed under the frontier orbitals approach [15]. Their experimental PA values are also shown in Table I.

Figure 1. Structures of the seventeen amines selected for this study. (*SINGLE COLUMN IMAGE*)



All structures were fully optimized in the gas phase with the software GAMESS [15-16→17-18]. The DFT functional B3LYP and the basis set 6-31G(d,p) were employed. All systems were treated as closed shells. All optimized geometries were submitted to single-point calculations. Structures were considered converged when the maximum and the root-mean-square of the gradients fell below 10⁻⁴ and 3.3 x 10⁻⁵ kcal mol⁻¹ Å⁻¹, respectively.

The software Avogadro [19] was used for the analysis of shapes and coefficients of molecular orbitals and generation of figures, employing a contour value of 0.010.

Results and discussion

Searching for a way to make the argument FERMO more quantitative, we developed a method to quantify the location of a MO using the localization degree, as in Eq. 4. According to this new method, the optimized structures of the selected compounds are analyzed using the MOs eigenvectors and the overlap matrix. The localization degree of each MO as well as their respective energies were computed and analyzed.

The computation can be done considering all possible combinations of AOs. For example, it can evaluate the participation of one or more AOs as one of the three 2p orbitals of the heterocyclic nitrogen atom of pyridine or the whole three 2p orbitals plus the 2s orbital.

In this study, for all compounds, the projection operators were applied to the whole $2p_{x-z}$ orbitals of the nitrogen atom, considering that the proposed protonation reactions of these compounds involve the participation of non-ligand pairs.

For all optimized structures, the MOs shapes from HOMO to HOMO-2 were analyzed in order to determine which of them could best describe the protonation site in their acid-base reactions based on the criterion of a high density over the nitrogen atoms. After that, the Γ_{HOMO} and Γ_{FERMO} coefficients were calculated for comparison.

In Table I, the PA values are reported, Γ_{HOMO} and Γ_{FERMO} coefficients and HOMO and FERMO energies for the studied compounds as returned by the code. In Table II, it is shown the shapes from HOMO to HOMO-2 orbitals as calculated with B3LYP/6-31G(d,p).

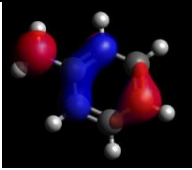
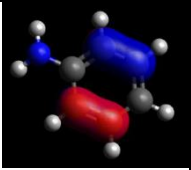
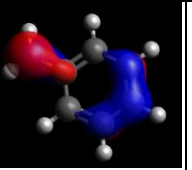
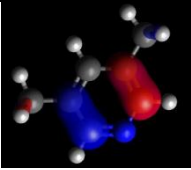
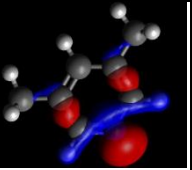
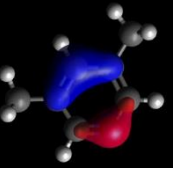
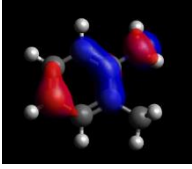
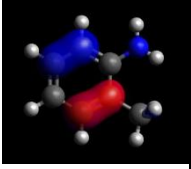
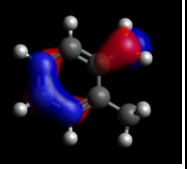
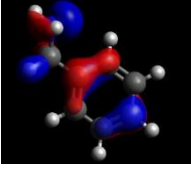
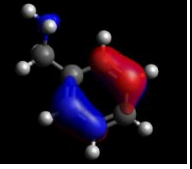
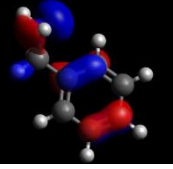
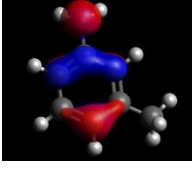
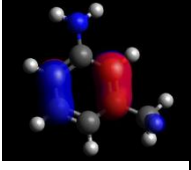
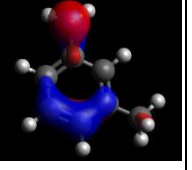
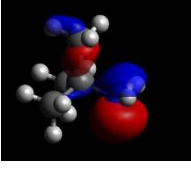
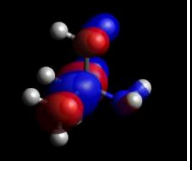
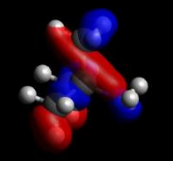
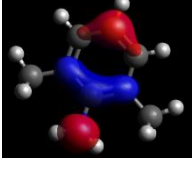
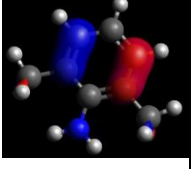
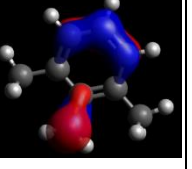
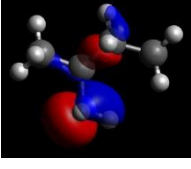
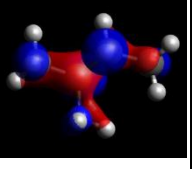
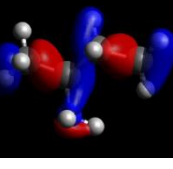
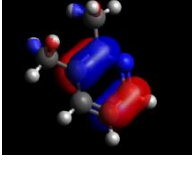
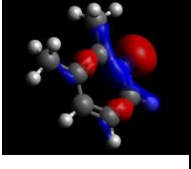
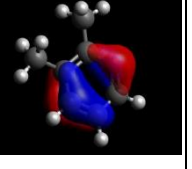
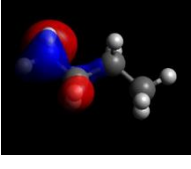
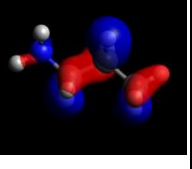
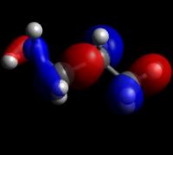
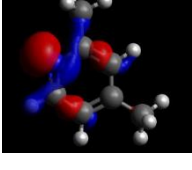
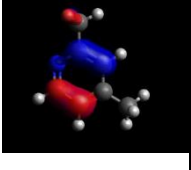
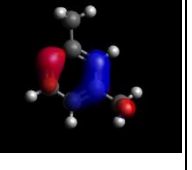
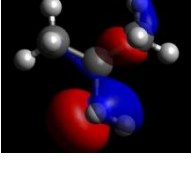
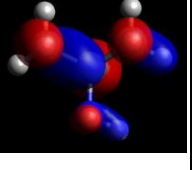
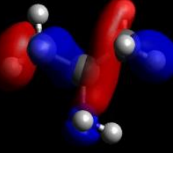
Table I: Comparison of physical properties and HOMO and FERMO coefficients and energies for the studied compounds. (*DOUBLE COLUMN TABLE*)

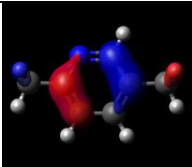
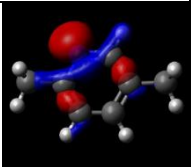
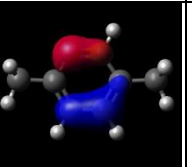
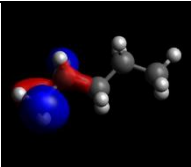
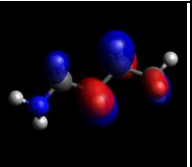
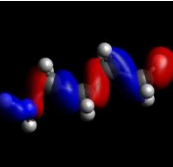
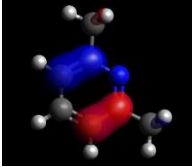
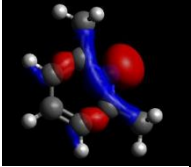

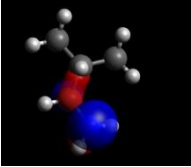
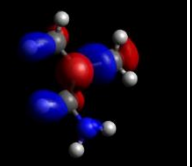
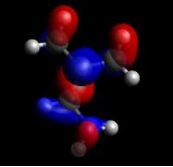
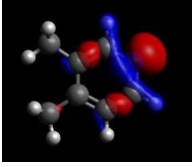
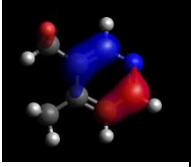
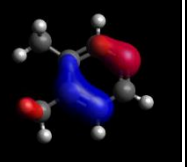
Number	Class	PA (kJ mol ⁻¹) [20]	HOMO		Shape-based FERMO		
			Γ_{HOMO}	Energy (eV)	Γ_{FERMO}	Relative Position	Energy (eV)
1	Aromatic	882.5	0.494426	-141.34236	0.562720	HOMO-2	-186.72888
2	Aromatic	890.9	0.476315	-135.27108	0.564633	HOMO-2	-211.75440
3	Aromatic	895.8	0.484538	-135.34512	0.541609	HOMO-2	-174.06804
4	Aromatic	901.7	0.464200	-129.27384	0.464200	HOMO	-129.27384
5	Heterocyclic	958.9	0.025289	-173.91996	0.725232	HOMO-1	-174.51228
6	Heterocyclic	962.9	0.729003	-173.62380	0.729003	HOMO	-173.62380
7	Heterocyclic	958.8	0.113857	-172.36512	0.724563	HOMO-1	-174.36420
8	Heterocyclic	963.0	0.001212	-174.58632	0.727060	HOMO-1	-174.66036
9	Heterocyclic	957.3	0.724800	-172.29108	0.724800	HOMO	-172.29108
10	Heterocyclic	955.4	0.000504	-173.62380	0.722908	HOMO-1	-174.58632
11	Aliphatic	913.3	0.489989	-142.52700	0.489989	HOMO	-142.52700
12	Aliphatic	924.8	0.776078	-161.40720	0.776078	HOMO	-161.40720

13	Aliphatic	934.1	0.778507	-163.11012	0.778507	HOMO	-163.11012
14	Aliphatic	917.8	0.792732	-161.62932	0.792732	HOMO	-161.62932
15	Aliphatic	923.8	0.784054	-161.18508	0.784054	HOMO	-161.18508
16	Aliphatic	921.5	0.791602	-161.11104	0.791602	HOMO	-161.11104
17	Aliphatic	929.7	0.776576	-162.07356	0.776576	HOMO	-161.4072

Table II: Composition and shape of molecular orbitals for some studied compounds.

(DOUBLE COLUMN TABLE)

Entry	HOMO	HOMO-1	HOMO-2	Entry	HOMO	HOMO-1	HOMO-2
1				10			
2				11			
3				12			
4				13			
5				14			
6				15			

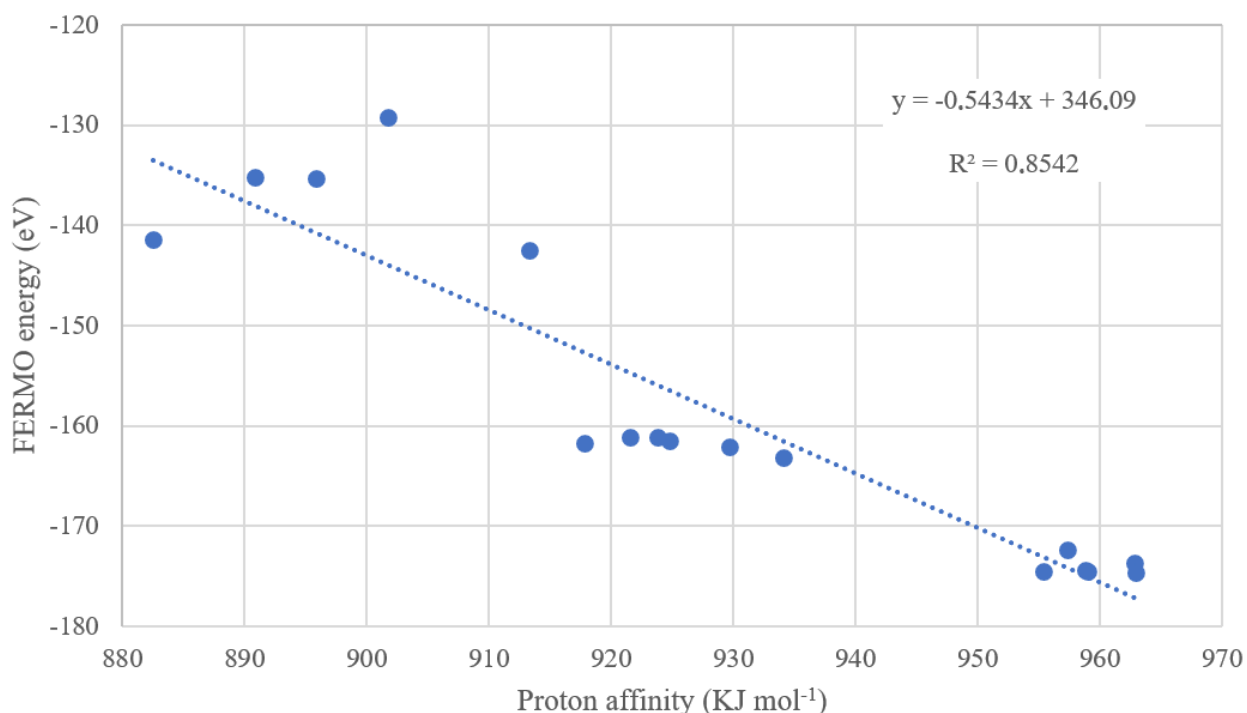
Entry	HOMO	HOMO-1	HOMO-2	Entry	HOMO	HOMO-1	HOMO-2
7				16			
8				17			
9				-	-	-	-

As it can be seen, the data from tables I and II show that there are compounds for which the HOMOs, as calculated with B3LYP/6-31G(d,p), does not spread over the nitrogen atoms (compounds **5**, **7**, **8** and **10**). So, they could not correspond to the FERMOs for the protonation reaction. In fact, their HOMO-1 MOs were pointed as FERMOs, since their shapes show the appropriate orientation for protonation and their energies are close to those for HOMOs. Their Γ_{HOMO} coefficients, as calculated through our new code, show very low values (0.025289, 0.113857, 0.001212 and 0.000504, respectively), while their $\Gamma_{\text{HOMO-1}}$ values were very high (0.725232, 0.724563, 0.727060 and 0.722908, respectively), leading us to the affirm that these HOMO-1 MOs would be their FERMOs.

For the compounds **1-4** and **11**, both HOMO and HOMO-2 MOs have shapes with great density over the nitrogen atoms. However, our code returned us different but close values of Γ_{HOMO} and $\Gamma_{\text{HOMO-2}}$ for compounds **1-3**: 0.494426 and 0.562720 (**1**), 0.476315 and 0.564633 (**2**) and 0.484538 and 0.541609 (**3**). For **4** and **11**, we got 0.464200 (**4**) and 0.489989 (**11**) for their HOMOs, higher than those for the other MOs. Based on this finding, we considered the HOMO-2 (in compounds **1-3**) and HOMO (in compounds **4** and **11**) as FERMOs.

For the compounds **6**, **9** and **12-17**, all HOMOs were pointed as FERMOs, according to their shapes and their Γ_{HOMO} values (all above 0.72). In Figure 2, it is shown the correlation between PA values and FERMO energies for the 17 studied amines.

Figure 2: PA values and FERMO energies for the studied compounds. The dotted line corresponds to the linear fit. (SINGLE COLUMN IMAGE)



It is known that, although the HOMO energies for families of compounds can be correlated with their PA values, there are many cases for which this correlation is not good, requiring other parameters for linear regression analysis. Using the FERMO energies instead of those for HOMOs, a correlation with a R^2 value equal to 0.85 was obtained, indicating a tendency to reduce the energy of the FERMO with the increase of the PA and, consequently, the basicity of the amines in the gas phase (Figure 2).

La Porta and collaborators [15] had previously employed the FERMO concept to describe the acid/base behavior of another set of amines, correlating their MO energies, shapes and atomic composition (including HOMOs) and pK_b values. They observed that, for many compounds, there were other MOs with energies very close to those for the HOMOs and with a significant contribution of nitrogen AOs. Thus, it was believed that these MOs could describe the acid/base behavior better than the HOMOs, so being considered as the FERMOs. Based on La Porta's approach, we chose to group the compounds according to their structure in aliphatic, heterocyclic and aromatic amines in order to search for a possible general understanding for all kinds of amines. As in the case of La Porta and collaborators [15], PA was chosen as the experimental data for comparison and search for possible correlations, since there was not yet established any direct relationship between PA and MOs energies.

In order to prove the effectiveness of our new code, we took into account both composition and shapes of MOs to identify which of these MOs would be involved in a specific reaction. Based on the localization degree of each MO, it was possible to infer that the orbital that governs the acid/base reaction corresponds to those pointed out by the new algorithm as the FERMO, showing that the MO composition is also an important indicator to determine which the appropriate orbital is. So, both shapes and atomic composition of MOs are essential parameters for the determination and analysis of the FERMO.

Conclusion

The developed method allowed us to obtain, with the application of the algorithm, different values of the localization degrees of MOs according to any combination of AOs. In this case, it can analyze each orbital individually or all at once, for a single atom or all of them. Intermediate orbital sets can also be analyzed. Since it returns as results not only the localization degree of the MOs in the subspace of one or more AOs as well as the energy of each of them, the code allows identifying the FERMOs based on the joint analysis of the localization coefficients and orbital energies.

Once again, the FERMO concept was successfully applied to describe the acid-base behavior for a series of amines, as demonstrated by the values of the coefficients provided by the new algorithm. The FERMO concept can be useful for explaining acid-based reactions in a wide range of applications. This concept provided chemical insights into which is the most related MO to acid-base reactions. It our the best knowledge, so far no first-principles approach has simultaneously reproduced the experimental results for aromatic, heterocyclic and aliphatic amines. Here we present substantial progress toward this goal.

Declaration of interest

The authors have no interests to declare.

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6 ATTACHMENT



REPÚBLICA FEDERATIVA DO BRASIL
MINISTÉRIO DA INDÚSTRIA, COMÉRCIO EXTERIOR E SERVIÇOS
INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL
DIRETORIA DE PATENTES, PROGRAMAS DE COMPUTADOR E TOPOGRAFIAS DE CIRCUITOS INTEGRADOS

Certificado de Registro de Programa de Computador

Processo Nº: BR512018052397-8

O Instituto Nacional da Propriedade Industrial expede o presente certificado de registro de programa de computador, válido por 50 anos a partir de 1º de janeiro subsequente à data de 27/02/2018, em conformidade com o §2º, art. 2º da Lei 9.609, de 19 de Fevereiro de 1998.

Título: MOLPROJ - Molecular Orbital Analysis by Projection Operators

Data de criação: 27/02/2018

Titular(es): UNIVERSIDADE FEDERAL DE LAVRAS

Autor(es): TEODORICO DE CASTRO RAMALHO; LETÍCIA SANTOS BRAGA; RODRIGO AZEVEDO MOREIRA DA SILVA; DANIEL HENRIQUES SOARES LEAL

Linguagem: LUA; MATLAB; OUTROS

Campo de aplicação: FQ-13; FQ-14; FQ-16

Tipo de programa: OS-05; TC-01; UT-01

Algoritmo hash: OUTROS

Resumo digital hash:
2659f8ae7a42471e744a6620ee4a639372663c5d9f34923fcc0b07f8740ba5fa99db7171ea949ed71a04fbb10f9fddf76196f855df1bb55d39104f8a9f0fd

Expedido em: 19/12/2018

Aprovado por:

Liane Elizabeth Caldeira Lage

Diretora de Patentes, Programas de Computador e Topografias de Circuitos Integrados

