

1 Perspectives on the Role of Frontier Molecular Orbitals in the Study of 2 Chemical Reactivity: An Updated Review

3 Letícia S. Braga^a, Daniel H. S. Leal^b, Kamil Kuca^{c*#}, Teodorico C. Ramalho^{a,c†#}

4 ^aDepartment of Chemistry, Federal University of Lavras, Lavras, Brazil; ^bInstitute of Physics
5 and Chemistry, Federal University of Itajubá, Itajubá, Brazil; ^cDepartment of Chemistry,
6 Faculty of Science, University of Hradec Kralove, Hradec Kralove, Czech Republic.

7 *Authors for correspondence:
8 *teo@dqi.ufla.br and kamil.kuca@uhk.cz*

9
10 # TC Ramalho and K Kuca contributed equally to this work.

11 **Keywords: FMO; FERMO; HOMO-LUMO; theoretical calculations; reactivity..**

12 Abstract

13 Molecular orbitals are critical in the rationalization of several chemical reactions. Thus, the Frontier
14 molecular orbital theory, proposed by Fukui's group, postulated the importance of the highest
15 occupied molecular orbital (HOMO) and the unoccupied molecular orbital of lowest energy (LUMO)
16 for chemical reactions. It should be kept in mind, however, that there are limitations of this theory
17 and new perspectives about the chemical reactivity have recently been arisen based on composition
18 and location of other frontier molecular orbitals. In this review, we have reported the development of
19 the Frontier Effective-for-Reaction Molecular (FERMO) concept, which describes the breaking and
20 formation of new chemical bonds and can be in turn provide important clues that modulate chemical
21 reactivity of atoms and molecules.

22

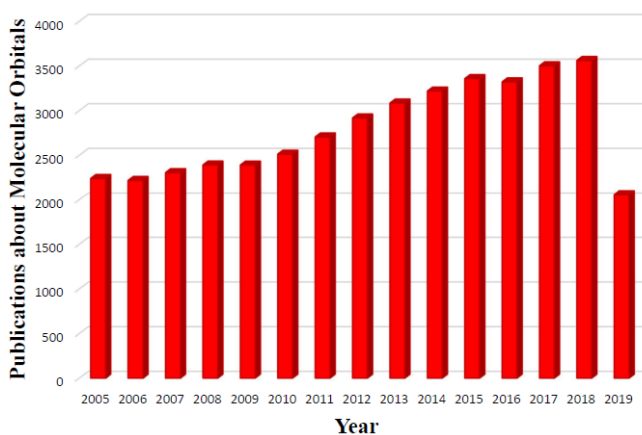
23 1 Introduction

24 In 1916, the famous chemist Gilbert N. Lewis set some fundamentals for what is known about
25 chemical bonding today (Lewis, 1913, 1916). According to Lewis, with a brilliant intuition, the
26 reactivity was due to availability of electrons, being that the difference of the properties presented by
27 substances was directly correlated to the mobility of the electrons of their molecules.

28 On the other hand, quantum mechanics emerged shortly after Lewis's pioneering work and played a
29 crucial role in this study (Chemistry: molecules, matter, and change by Atkins, P. W. (Peter
30 William), 1940-, Jones, Loretta L; Química Nova- Teoria do Funcional de Densidade Teoria do
31 Funcional de Densidade; Química Nova- Teoria do Funcional de Densidade Teoria do Funcional de
32 Densidade; Jensen, 1382; Schrödinger, 1926; Allinger, 1976; Atkins and Friedman, 1997; Hoffmann
33 et al., 2003). For a while, following Schrödinger's proposal in 1926, a precise physical interpretation
34 for the wave function (Ψ) challenged the early enthusiasts of quantum mechanics. It was up to Max
35 Born to show, a few months later, that the square of Ψ had a precise physical meaning. According to
36 Born, $|\Psi|^2$ for a position x, y, z expresses the probability of finding an electron in that space location.
37 This region of probability generates, for example, the form of the atomic orbitals s, p, d and f

38 (Chemistry: molecules, matter, and change by Atkins, P. W. (Peter William), 1940-, Jones, Loretta L;
39 Organic Chemistry - Livro - WOOK; Rauk, 2001). Since the importance of electron pairs for the
40 chemical reactivity of molecules had already been discussed previously by Lewis et al., the molecular
41 orbitals rapidly aroused great interest throughout the scientific community, because they could now
42 be calculated by approximate quantum mechanics methods, presenting a more quantitative
43 understanding. Therefore, for chemists in general, a great utility of atomic orbitals is related to the
44 understanding of how atoms combine to form molecules (Da Silva, R.R, 2006).

45 The great scientific interest in the subject can be easily verified by the expressive number of
46 publications that deals with the subject (Figure 1): a simple search in the ISI Web of Knowledge
47 (Web of Science), using the term “molecular orbital” as keyword, returns 2,000-2,500 papers by year
48 from 2005 to 2010. Since 2011, even more papers were annually published (reaching about 3,500 in
49 2018), showing the increasing importance of this theme. In this respect, the importance of molecular
50 orbitals for chemistry is undeniable. Understanding why reactions follow one path or another enables
51 greater planning and control of chemical phenomena at a more fundamental level. In this way,
52 molecular orbitals are important electronic parameters for description of the chemical reactivity of
53 compounds, since chemical reactions are modulated by electrons.



54

55 **Figure 1.** Number of papers retrieved with the keyword “molecular orbitals” in the ISI Web of
56 Knowledge database from 2005 to the middle of July 2019.

57 Understanding the processes involving breaking and formation of new chemical bonds is essential to
58 the rationalization of reaction mechanisms and represents a challenge that still intrigues and generates
59 many discussions. Furthermore, the knowledge about these processes also depends on understanding
60 the nature of chemical bonds. It is important to keep in mind that, since the early work of Linus
61 Pauling, the concept of chemical bonding has been changing substantially over the years (Pauling,
62 1931,1960). Thus, issues related to chemical bonding and molecular orbitals are always at the
63 forefront of chemistry research.

64 When a concept is solid enough, predictions can be made and tested, which will inevitably lead to
65 new discoveries. Molecular orbitals still pose a great challenge to chemists, holding some secrets that
66 can, nowadays, contribute significantly to advancements across all frontiers of chemistry. Thus,
67 attempting to understand chemical reactions, researchers turned their attention to the analysis of the
68 orbital molecules (Fukui et al., 1952, 1954; Hoffmann and Woodward, 1965c, 1965a, 1965b;
69 Woodward and Hoffmann, 1965; Bruice, 2004; La Porta et al., 2010a). So, in an update of a previous

70 paper (Pereira et al., 2016), we present in the present review some considerations about the
71 contributions of the frontier molecular orbitals approach to the understanding of chemical reactivity.

72 **2 Discussion**

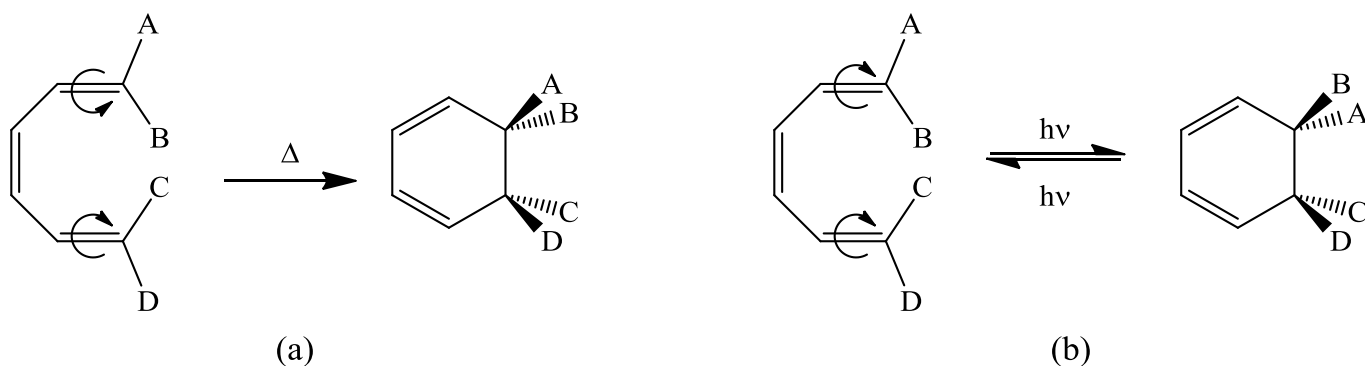
73 **2.1 The Frontier Molecular Orbital Theory**

74 The HOMO-LUMO (HOMO: Highest Occupied Molecular Orbital; LUMO: Lowest Unoccupied
75 Molecular Orbital) approach for the interpretation of chemical reactivity came up with a Japanese
76 research group headed by Kenichi Fukui, who was researching on the reactivity of aromatic
77 compounds (Fukui et al., 1952). The great difference between theirs and previous works from other
78 researchers was the attention given to the molecular orbitals from Fukui and colleagues. Instead of
79 interpreting only the energy or performing population analyzes, they analyzed the electron density
80 over each atom participating in the frontier orbitals. Fukui and his collaborators realized that the
81 HOMO electron density was very important for the reactivity of these compounds.

82 The HOMO electronic density was the strategy used by Fukui and his group to predict which the
83 reaction site for electrophilic substitutions in aromatic hydrocarbons. So, soon the concept of frontier
84 electrons became wider, leading to the Frontier Molecular Orbital Theory (FMO) (Fukui et al., 1954).
85 With a series of intuitive postulates, they proposed rules for the interactions between frontier orbitals.
86 Just as Lewis put the pair of electrons as a determinant of countless reactions, Fukui's group
87 established that certain chemical reactions, for instance Lewis acids and bases, would be governed by
88 the frontier orbitals. It was as if Lewis's pair of electrons occupied Fukui's frontier orbital. The two
89 concepts were equally simple and powerful in the interpretation of chemical reactions. Since then,
90 molecular orbitals have assumed a determining role in chemistry and the HOMO-LUMO approach
91 has been applied in several reactions with great success (Fukui et al., 1954; Fukui, 1982).

92 But it was by solving some challenges such as predicting the stereochemistry of electrocyclic
93 reactions that the molecular orbitals were confirmed as the great rulers of reactivity of several
94 compounds. Two very talented chemists, each with their own experience, explained the intriguing
95 behavior of pericyclic reactions. In 1965, Hoffmann and Woodward developed the theory of
96 conservation of orbital symmetry to explain the relationship between the structure and the
97 configuration of substrates and formation of the product under thermal and/or photochemical
98 conditions, in which the reactions occur (Hoffmann and Woodward, 1965c, 1965a, 1965b;
99 Woodward and Hoffmann, 1965; Bruice, 2004).

100 In these works, the authors postulated that, for a system like the formation of 1,3-cyclohexadiene
101 from 1,3,5-hexatriene, a disrotatory motion would be observed for thermal processes, as in Figure 2
102 (a), while a conrotatory motion would be observed for photochemical processes like Figure 2 (b).
103 The mystery about the exclusivity of one or another type of movement, depending on the process
104 involved, was intimately related to the HOMO symmetry. In this sense, the creation of a new
105 chemical bond would involve the superposition of different phases of the frontier molecular orbitals.
106 The conrotatory or disrotatory movement would be only a result of the orbitals seeking a constructive
107 overlap, which, in other words, would be the overlapping of equal phases. Another important aspect
108 about the contribution of the work of Hoffmann and Woodward, based on calculations using Hückel's
109 Extended Theory, is that they have obtained extremely useful results for the understanding of
110 fundamental aspects of the chemistry involved. Thus, the concept of conservation of orbitals
111 symmetry is a determinant of many chemical reactions.

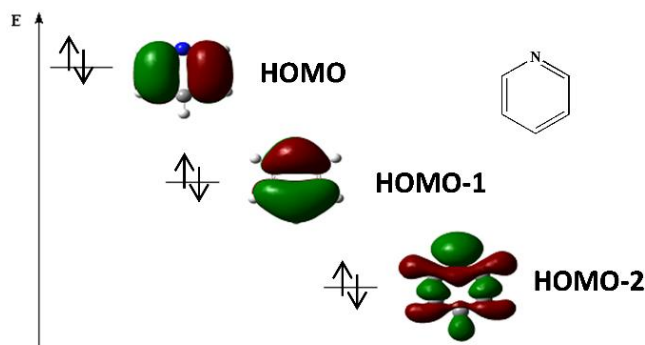


113 **Figure 2.** Thermal and photochemical conversion of hexatriene to cyclohexadiene. Disrotatory (a)
 114 and conrotatory (b) movement (adapted from reference (Pereira et al., 2016)).

115 Over the years, chemists have developed several processes in which molecular orbitals symmetry is
 116 responsible for controlling the reaction course (Klopman, 1968; Dewar, 1971; Pearson, 1986; Birney
 117 and Houk, 1990; Domingo et al., 1998; Svergun et al., 2000; Roque et al., 2002; Harnett et al., 2004;
 118 Polo et al., 2004; Berski et al., 2006; Rhyman et al., 2011). The recognition of the impact brought to
 119 science by the concept of molecular orbitals occurred in 1981, when the Nobel Prize in Chemistry
 120 was awarded to Kenichi Fukui and Roald Hoffmann. It could be said that, at that time, chemists were
 121 living the age of HOMO-LUMO, and molecular orbitals had already been accepted as a determinant
 122 of chemical reactions and sacred those who began to study the subject. However, despite the great
 123 success, the HOMO-LUMO approach was not unanimously accepted. Some wondered if only two
 124 orbitals would be responsible for the reactivity of molecules. Was it all dependent on HOMO and
 125 LUMO alone? Fukui exposed this concern in an article he wrote in commemoration of his Nobel
 126 Prize (Fukui, 1982). According to Fukui, the HOMO or LUMO orbitals could not be suitable for a
 127 given reaction, but, according to him, surely the next orbital or any orbital with energy very close to
 128 HOMO or LUMO could be used (Fukui, 1982). As an example of his argument, Fukui cited the case
 129 of pyridine protonation. In pyridine, the HOMO is clearly an orbital of the π -system of pyridine ring
 130 (Figure 3). Since the proton binds to the nitrogen electron pair, the HOMO would not be related to
 131 this reaction in pyridine. The orbital involved in the reaction would be the third highest occupied
 132 orbital or HOMO-2, which in fact has the typical shape of the nitrogen non-bonding pair, as seen in
 133 Figure 3. As it can be seen, the HOMO-LUMO approach has certain limitations, thus leaving a gap
 134 for the emergence of new theories.

135

136



137

138 **Figure 3.** Shapes of the three highest occupied molecular orbitals for pyridine (adapted from
 139 reference (Pereira et al., 2016)).

140 2.2 The Concept of Localized Reactive Orbital

141 One of the most intriguing theories involving molecular orbitals was developed by Hiroshi Fujimoto,
 142 who worked with Fukui (Fujimoto et al., 1986; Fujimoto, 1987; Fujimoto and Satoh, 1994; Roque et
 143 al., 2002). The main argument of Fujimoto and colleagues was that molecular orbitals were too
 144 delocalized and thus it was difficult to deal with certain reactions that were entirely localized. Their
 145 strategy was to recombine some molecular orbitals chosen according to certain criteria and locate
 146 their maximum at the reaction site. The procedure was called Localized Reactive Orbital (LRO)
 147 approach (Fujimoto et al., 1986; Fujimoto, 1987; Fujimoto and Satoh, 1994).

148 2.3 The Concept of Reactive Hybrid Orbital

149 The same kind of argument used by Fujimoto, according to which localized orbitals would be better
 150 to describe the reactivity of molecules, was employed by Hirao and Ohwada to formulate the concept
 151 of Reactive Hybrid Orbital (RHO) (Hirao and Ohwada, 2003, 2005; Nakamura et al., 2004; Ohwada
 152 et al., 2004). So, according to these authors, when an electron-donor orbital ϕ_{oc} is represented by a
 153 linear combination of canonical occupied molecular orbitals (Equation 1):

$$\phi_{oc} = \left(\sum_i^{oc} d_i \psi_i \right) / \left(\sum_i^{oc} d_i^2 \right)^{\frac{1}{2}} \quad (1)$$

154 the energy level λ_{oc} can be identified according to Equation 2:

$$\lambda_{oc} = \left(\sum_i^{oc} d_i^2 \varepsilon_i \right) / \left(\sum_i^{oc} d_i^2 \right) \quad (2)$$

155 the energy level λ_{oc} can be identified according to Equation 2:

$$\lambda_{oc} = \left(\sum_i^{oc} d_i^2 \varepsilon_i \right) / \left(\sum_i^{oc} d_i^2 \right) \quad (2)$$

156 where ε_i is the energy level of the canonical molecular orbital ψ_i obtained by solving a Hartree-
 157 Fock-Roothaan equation. The orbital ϕ_{oc} is represented by a linear combination of atomic orbitals
 158 like (Equation 3):

$$\phi_{oc} = \sum_{\mu} C_{\mu} \chi_{\mu} \quad (3)$$

159 By extracting from Equation 3 only the terms containing the atomic orbitals ϕ'_{oc} on the atom of the
 160 reaction center (named A), the Equation 4 can be defined:

$$\phi'_{oc} = \sum_{\mu \in A} C_{\mu} \chi_{\mu} \quad (4)$$

161 Then, similar functions can be defined for the frontier electron density f_{oc} and for an index ρ_{oc} ,
 162 respectively according to Equations 5 and 6:

$$f_{oc} = \langle \phi_{oc} / \phi'_{oc} \rangle \quad (5)$$

163 and

$$\rho_{oc} = -f_{oc} / \lambda_{oc} \quad (6)$$

164 The value $2f_{oc}$ corresponds to the electrons in the orbital ϕ_{oc} for the atom A. The formula for ρ_{oc} is
 165 similar to the superdelocalizability based on Hückel approximation. d_i values are obtained from
 166 Equation 1, which gives the maximum value of ρ_{oc} , by minimizing $1/\rho_{oc}$ numerically according to the
 167 Davidson-Fletcher-Powell method. The ϕ_{oc} orbital represented in Equation 1 with the d_i value
 168 optimization is specifically called RHO (Hirao and Ohwada, 2003).

169 2.4 The Triadic Analysis

170 Vianello and colleagues introduced the *triadic* formula (Vianello and Maksić, 2006), which also uses
 171 the concepts of frontier molecular orbitals, with the difference that such calculations are based on an
 172 equation with three terms like the Equation 7 for the interpretation of acidities:

$$PA(A^-)_{\alpha} = -IE(A^-)_n^{Koop} + E(ei)_{rex}^{(n)} + (BAE)_{\alpha} \quad (7)$$

$$+ 313.6 \text{ kcal/mol}$$

173 Equation 7 describes the protonation of the anionic conjugated base A^- , in which $PA(A^-)_{\alpha}$ is the
 174 proton affinity of A^- at the site α and $IE(A^-)_n^{Koop}$ determines the n^{th} Koopman's ionization energy of
 175 the anion A^- calculated in the approximate electronic density. Since ionization is not a sudden event,
 176 a reorganization of the nuclei-electrons system occurs, denoted by the relaxation energy term $E(ei)_{rex}^{(n)}$
 177 given by Equation 8:

$$E(ei)_{rex}^{(n)} = IE(A^-)_n^{Koop} - IE(A^-)_1^{ad} \quad (8)$$

178 in which $-IE(A^-)_1^{ad}$ is the first adiabatic ionization energy. The term $(BAE)_{\alpha}$ is the effect of the
 179 bond association energy between hydrogen and a cation radical. The electron affinity of the proton is
 180 313.6 kcal/mol. Thus, the proposal from Vianello et al. has a term related to the ionization energy,
 181 another one related to the relaxation energy and a third term related to association energy between the
 182 first ones. This methodology is currently widely used in the global description of deprotonation
 183 processes (Vianello and Maksić, 2006; Vianello et al., 2006, 2007).

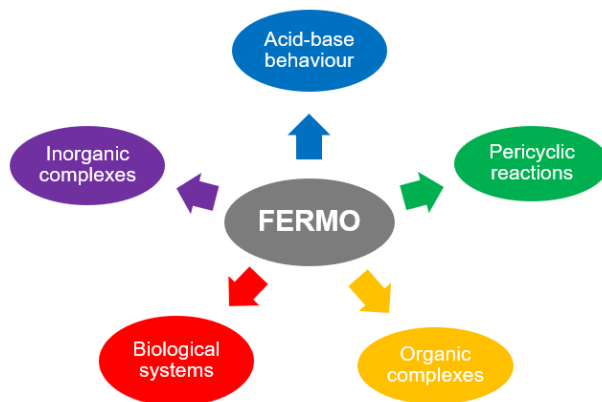
184 2.5 The Frontier Effective-for-Reaction Molecular Orbital

185 In line with that, the limitations of the arguments of HOMO-LUMO approach and the new
 186 approaches proposed in the literature to understand chemical reactivity, it became necessary to
 187 extend the role of molecular orbitals in chemistry. The FERMO (Frontier Effective-for-Reaction

188 Molecular Orbital) concept emerged as a tool to explore the role of molecular orbitals and chemical
189 reactivity as well as breaking and formation of chemical bonds (Da Silva et al., 2006a, 2006b,
190 2006c). As noted by Fukui, the HOMO and LUMO orbitals could not be suitable for a given reaction,
191 but certainly any close orbital with energy very close to those for HOMO or LUMO. The FERMO
192 concept was proposed by Da Silva and Ramalho (Da Silva et al., 2006a, 2006b, 2006c) and its
193 approach arose from composition and localization criteria, along with some chemical intuition, to
194 correctly determine the frontier molecular orbital that regulates chemical reactions. This theoretical
195 approach could be understood as a complement to the HOMO-LUMO approach, so the HOMO will
196 only be the orbital that rules a reaction if it fulfills the requisite to be the FERMO.

197 This concept has attracted attention and has been successfully applied in the description of chemical
198 processes as acid-base behavior, in organic and inorganic complexes, in pericyclic reactions and in
199 the study of biological systems (Figure 4) (Porta; Da Silva et al., 2006a, 2006c, 2006b; Ramalho and
200 Pereira, 2009; da Costa and Trsic, 2010; T. Santiago et al., 2010; La Porta et al., 2010a, 2011; A. La
201 Porta et al., 2012; De Almeida et al., 2013; Soleymani and Dashti Khavidaki, 2017; Soleymani,
202 2018). In this sense, this review will focus now in a quantitative and detailed description of the
203 FERMO in the understanding of chemical reactivity. The following discussion is divided into five
204 subsections. In the first one, it is described the acid-base behavior for some important classes of
205 compounds commonly used in organic chemistry. In the second subsection, the results obtained for
206 the understanding of some organic and inorganic compounds are presented. The third subsection
207 shows a detailed investigation on the reactivity and selectivity of pericyclic reactions. The fourth
208 subsection is related to the case of biological systems. Finally, the main conclusions are summarized
209 in the fifth subsection.

210



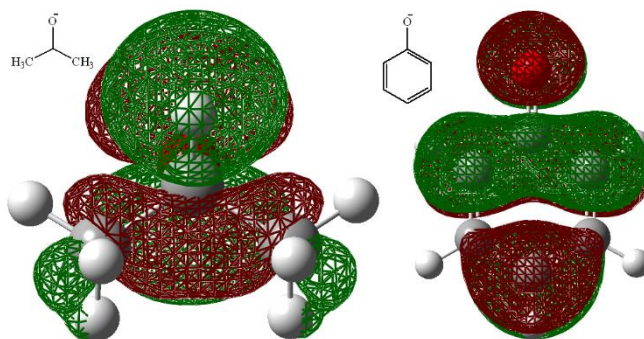
211

212 **Figure 4.** Some applications of the FERMO concept studied (adapted from reference (Pereira et al.,
213 2016)).

214 Despite the major advances in the understanding of the role of molecular orbitals in the study of
215 chemical reactivity, it is not easy yet to find didactic, well-founded and critical papers based on the
216 perspective of FERMO in scientific literature. So, we took it as motivation for preparing this review,
217 which aims to present the basic ideas of this concept as well as some of its applications in different
218 areas of chemistry. We hope that this study will be useful to the general public, providing the readers
219 (particularly students and researchers) interested in understanding this model.

220 2.5.1 Acid-base Behavior

221 Proton transfer is one of the most important processes of changing organic molecules. In this sense,
222 the acidity of organic compounds, measured in several solvents, is fundamental for the study of
223 reaction mechanisms in organic chemistry (Li et al., 2006). In this context, Da Silva and Ramalho
224 have shown in their works that the molecular orbitals responsible for acid-base reactions in phenols
225 and alcohols, in many cases, may not be rationalized in the light of the HOMO-LUMO approach (Da
226 Silva et al., 2006a, 2006b). In these same works, it was observed that the molecular orbital that best
227 described the acid-base behavior in the protonation reaction of the anionic conjugated bases for these
228 compounds was not the HOMO (Figure 5), but rather the $p_x p_y$ orbital, which was the FERMO for this
229 reaction in each molecule, as shown in Figure 6. In this sense, it is observed that the FERMO concept
230 take into account each shape as well as atomic composition of molecular orbitals to determine which
231 orbitals can describe a chemical reaction



232

233 **Figure 5.** HOMO orbitals for the anions isopropoxide (left) and phenoxide (right) (adapted from
234 reference (Da Silva et al., 2006a)).

235

236

237

238

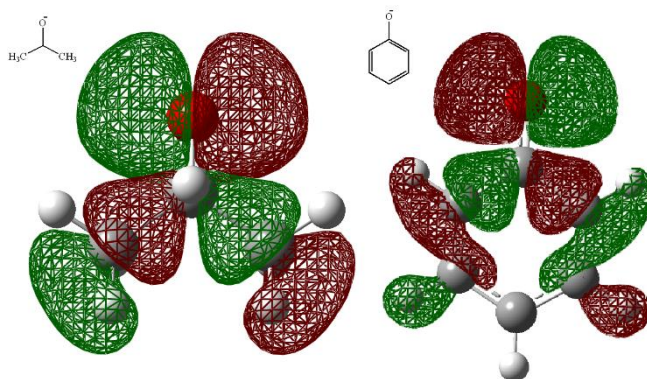
239

240

241

242

243

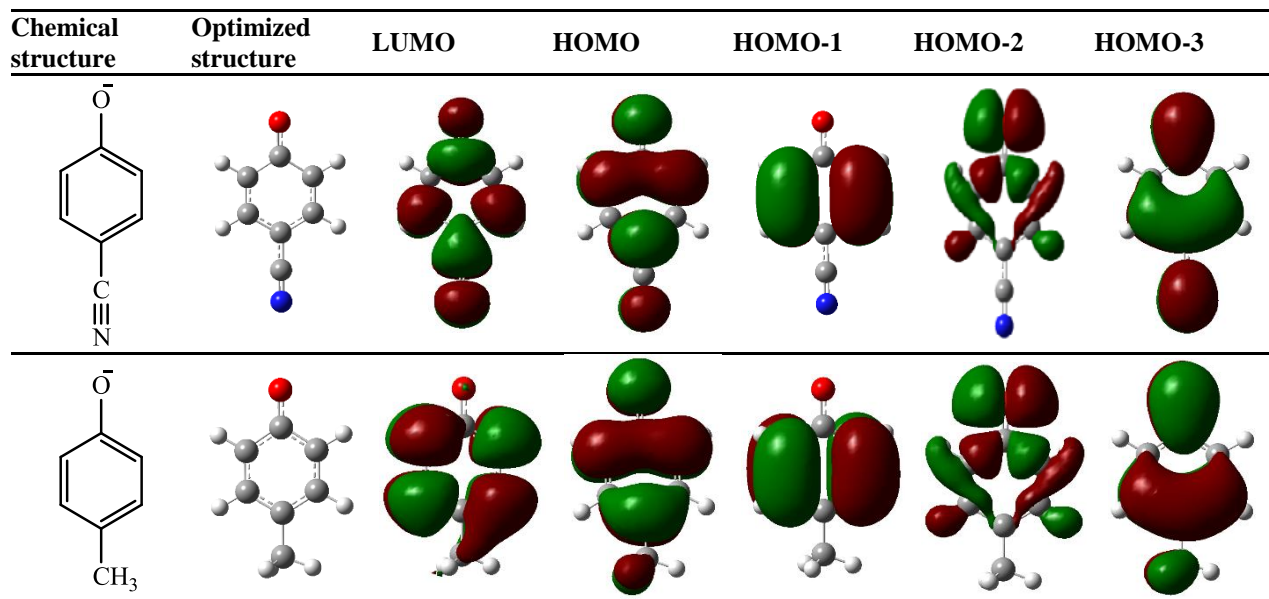


244 **Figure 6.** $p_x p_y$ orbitals for the anions isopropoxide (left) and phenoxide (right) (adapted from
245 reference (Da Silva et al., 2006a)).

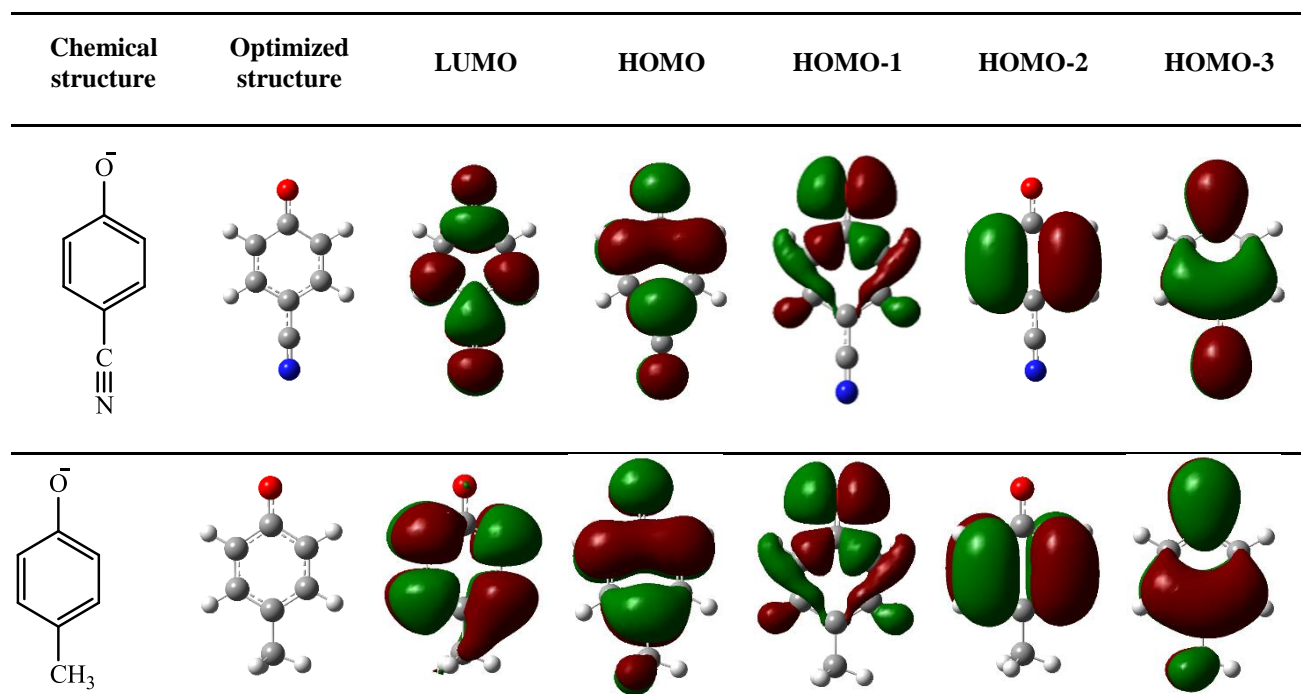
246

247 The orbitals of Figures 5 and 6 indicate that the HOMO-LUMO orbitals are not always responsible
248 for all chemical reactions, as previously quoted by Fukui (Fukui et al., 1952). Another important
249 consideration for employing the FERMO concept is that both Hartree-Fock (HF) or Kohn-Sham (KS)
250 orbitals lead to the same conclusions about chemical reactivity. This brings us back to the discussion
251 about the validity of the interpretation of KS orbitals. In Figures 7 and 8, there are two
252 representations of the HF and KS molecular orbitals for the *p*-cyanophenoxide and *p*-
253 methylphenoxide anions (Ramalho and Pereira, 2009). Moreover: based on these results, we can
254 observe that both calculation methodologies used (MP2 and DFT) point to the same molecular orbital
255 as the FERMO in the protonation reaction of these anions (HOMO-2 and HOMO-1 with MP2 and

256 DFT, respectively). Thus, this is a very intuitive concept, presenting the same molecular orbital shape
 257 for the same reactive site or class of compounds
 258



259 **Figure 7.** Representation of molecular orbitals of the anions *p*-cyanophenoxide and *p*-
 260 methylphenoxide calculated at MP2 level (adapted from reference (Ramalho and Pereira, 2009)).
 261



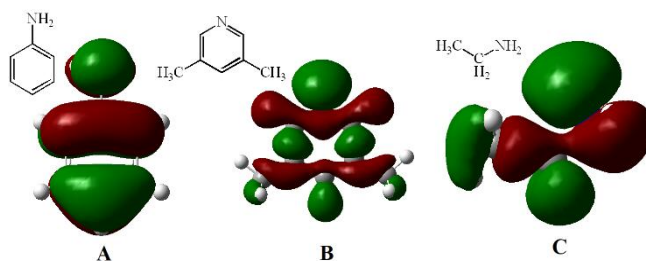
262 **Figure 8.** Representation of molecular orbitals of the anions *p*-cyanophenoxide and *p*-
 263 methylphenoxide calculated at DFT level (adapted from reference (Ramalho and Pereira, 2009)).
 264

265 It is important to keep in mind that, in spite of the physical and chemical meanings of some virtual
 266 orbitals being very dependent on the calculation method employed, the variation in the HOMO-
 267

268 LUMO or FERMO-LUMO energy barriers can be used as a reactivity index. For example, following
269 Pearson's principle, it is well-known that soft molecules will have lower energy values for the
270 HOMO-LUMO gap when compared to hard sites. In this way, the HOMO-LUMO energy can be
271 used.

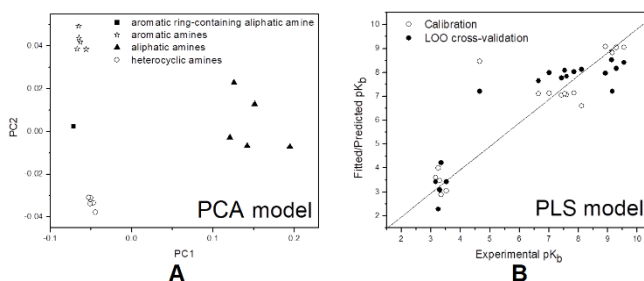
272 Thus, once again looking at the shape of molecular orbitals, based on the composition and location
273 criteria, the HOMO problem can be better understood.

274 The FERMO concept was also successfully applied in describing the acid-base behavior for a series
275 of amines, being pointed out the HOMO as the FERMO for aromatic and aliphatic amines but not for
276 heterocyclic amines, whose FERMO corresponded to the HOMO-2 (Figure 9) (La Porta et al.,
277 2010b). It is known that amines have great importance and play an essential role in organic
278 chemistry, and its basicity is directly related to the availability of the nitrogen electron pairs. In this
279 context, molecular orbitals and their properties, such as energy and symmetry, are very important to
280 better understand their reactivity and represent a fundamental step in the rational planning of some
281 important synthesis routes.



289 **Figure 9.** FERMO shapes for aromatic (A: aniline), heterocyclic (B: 3,5-dimethylpyridine) and
290 aliphatic (C: ethylamine) amines (adapted from reference (La Porta et al., 2010a)).

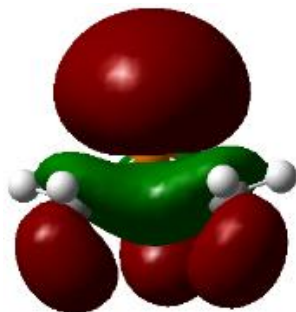
291 Another important contribution of this work was the use of Chemometrics which, through an
292 exploratory analysis using PCA and regression analysis using PLS, along with the FERMO approach,
293 allowed a more detailed analysis of data. So, in this quantitative description based on chemometric
294 methods and *ab initio* calculations, it was possible to correlate the energies of frontier orbitals with
295 pK_b values for the compounds classified into aliphatic, aromatic and heterocyclic amines (Figure 10)
296 (La Porta et al., 2010a). For this study, it was verified that the energy of the FERMO shows a better
297 correlation with basicity and acidity constants when compared to the HOMO energy. In addition, this
298 work showed that the B3LYP functional produces good results for the description of the acid-base
299 behavior, when the FERMO concept is used in the study of organic compounds.



309 **Figure 10.** PCA (A) and PLS (B) models employed in the study of aromatic, heterocyclic and
310 aliphatic amines (adapted from reference (La Porta et al., 2010a)).

312 In this same line of thought, the FERMO approach was applied with great success in describing the
313 acid-base behavior for a series of phosphines (T. Santiago et al., 2010). The HOMO-*n* and LUMO+*n*

314 ($n = 0-4$) energies were obtained from MP2 calculations in the form of an $a \times b$ matrix with a lines
 315 for phosphines and b columns for the energy of frontier molecular orbitals. It is remarkable that these
 316 results can be used to investigate the effect of the solvent on acid-base processes, using parameters
 317 from theoretical calculations of orbital energies. By analyzing more deeply the location and
 318 composition of the molecular orbitals of phosphines, it can be observed that the FERMO has great
 319 contribution of the phosphorus atom (above 54%; see Table 1). Thus, this orbital, shown in Figure 11
 320 for the compound trimethylphosphine, describes better the acid-base behavior.



321
 322

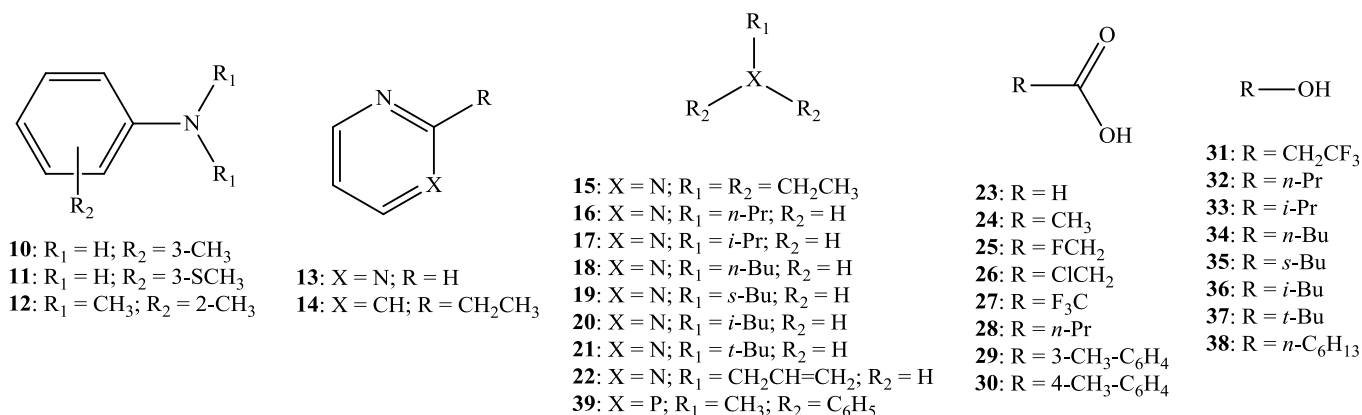
323 **Figure 11.** The FERMO shape of trimethylphosphine (adapted from reference (T. Santiago et al.,
 324 2010))

325 **Table 1.** Percentual contribution of the phosphorus atom for the FERMO and its orbital energy in
 326 studied phosphines through MP2/6-311G (d, p) in solution (adapted from reference (T. Santiago et
 327 al., 2010)).

Entry	Compounds	Contribution (%)	FERMO (Hartree)	Entry	Compounds	Contribution (%)	FERMO (Hartree)
1		81.25	-0.33033	6		71.68	-0.29692
2		80.87	-0.32209	7		67.90	-0.29729
3		81.62	-0.32574	8		53.90	-0.31453
4		81.17	-0.32392	9		81.38	-0.33617
5		64.96	-0.30515	-	-	-	-

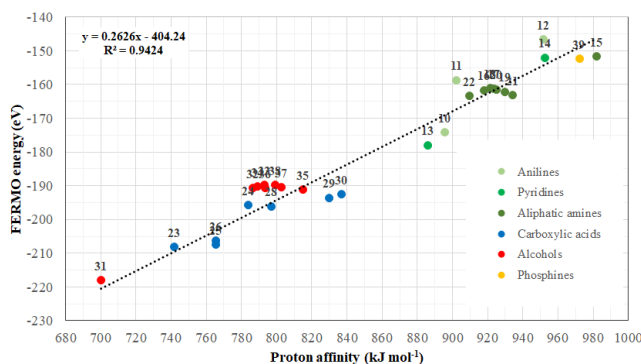
328 In these works, the FERMO argument was used in a qualitative manner. However, in a very recent
 329 paper (Braga et al., 2019), Braga and colleagues investigated, in a quantitative way, which molecular
 330 orbital would be better for the description of acidity in amines, carboxylic acids, alcohols and
 331 phosphines. For so, they developed a more quantitative methodology for the characterization of
 332 FERMO orbitals in chemical reactions based on projection operators. A projection operator could, in
 333 principle, be understood as the projection of a “shadow” of a selected molecular orbital in the
 334 subspace of an arbitrary set of atomic orbitals (Azevedo and Da Silva, 2013). This parameter is
 335 precisely a quantitative characterization of the shapes of molecular orbitals given in a set of atomic
 336 orbitals and, consequently, a set of atoms.

337 In this work, 30 different organic compounds were selected for studying their chemical reactivity,
 338 considering their protonation reactions to the corresponding cationic conjugated acids. They were
 339 grouped in anilines, pyridines, aliphatic amines, carboxylic acids, alcohols and phosphines, as shown
 340 in Figure 12.



341 **Figure 12.** Structures of the organic compounds selected for the study from Braga and colleagues
 342 (adapted from reference (Braga et al., 2019)).

343 Employing the FERMO energies instead of those for their HOMO orbitals, a correlation with a R^2
 344 value equal to 0.94 was obtained. This result indicates that the energy of the FERMO is proportional
 345 the proton affinity and, consequently, the basicity of the neutral forms of amines, carboxylic acids,
 346 alcohols and phosphines in the gas phase, as shown in Figure 13. Based on the localization degree of
 347 each molecular orbital, it was possible to infer that the orbital which governs the protonation reaction
 348 corresponded to that pointed out by the new quantitative algorithm proposed by the authors as the
 349 FERMO, showing again that the molecular orbital composition is also a critical parameter to
 350 investigate the appropriate orbital (Braga et al., 2019). So, both shapes and atomic composition of
 351 molecular orbitals were essential parameters for the determination and analysis of the FERMO.



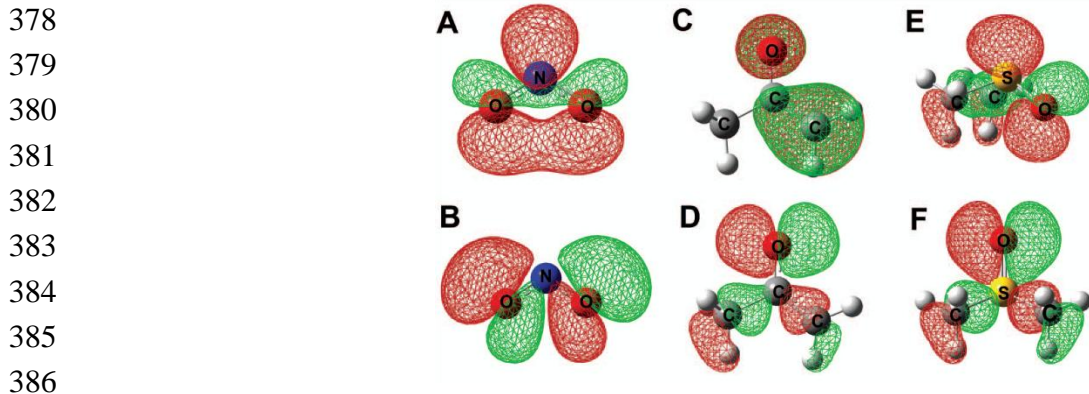
352
 353
 354
 355
 356
 357
 358
 359
 360
 361 **Figure 13.** PA values as well as FERMO energies for the selected compounds. The dotted line

362 corresponds to the linear fit (adapted from reference (Braga et al., 2019)).

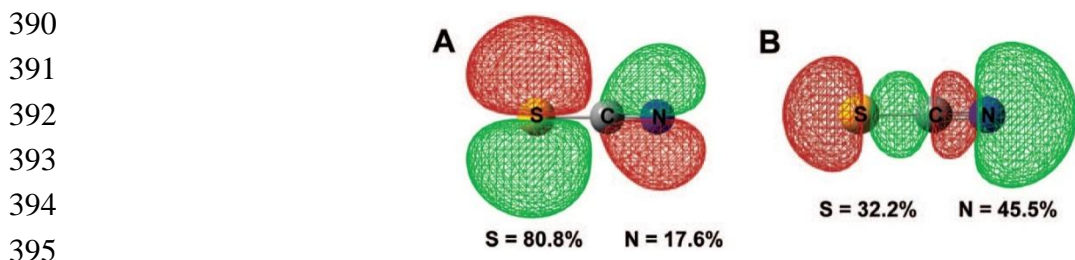
363 2.5.2 Organic and Inorganic Complexes

364 The FERMO concept and Pearson's principle of hardness and softness were also successfully
365 employed on four ambidentate ligands (that can bind to metals in two distinct ways). In this work, Da
366 Silva and Ramalho (Da Silva et al., 2006c), following Pearson's principle which states that soft
367 molecules have lower energy values for the HOMO-LUMO barrier when compared to hard sites,
368 reported that, in the light of the FERMO approach, it can be observed that a soft reaction site in a
369 molecule will have a lower FERMO-LUMO energy barrier than a harder. Clearly, the HOMO-
370 LUMO energy barrier cannot describe the hardness difference between these two binding sites on the
371 same molecule. Thus, a molecule can have as many FERMO orbitals as there are reaction sites,
372 which, in this case, could be the HOMO or any other frontier molecular orbital.

373 For this study, the authors used as ambidentate ligands the anions SCN^- , NO_2^- and $\text{CH}_3\text{COCH}_2^-$ and
374 the neutral molecule dimethylsulfoxide (DMSO). These ligands were chosen due to the great amount
375 of theoretical and experimental work reported in the literature. Thus, based on the location as well as
376 composition of molecular orbitals, it was possible to find the shape of the FERMO for these ligands
377 (Figures 14 and 15).



387 **Figure 14.** The FERMO shapes for NO_2^- , $\text{CH}_3\text{COCH}_2^-$ and DMSO. NO_2^- nitrogen-FERMO (A) and
388 oxygen-FERMO (B); $\text{CH}_3\text{COCH}_2^-$ carbon-FERMO (C) and oxygen-FERMO (D); DMSO sulfur-
389 FERMO (E) and oxygen-FERMO (F) (adapted from reference (Da Silva et al., 2006c)).



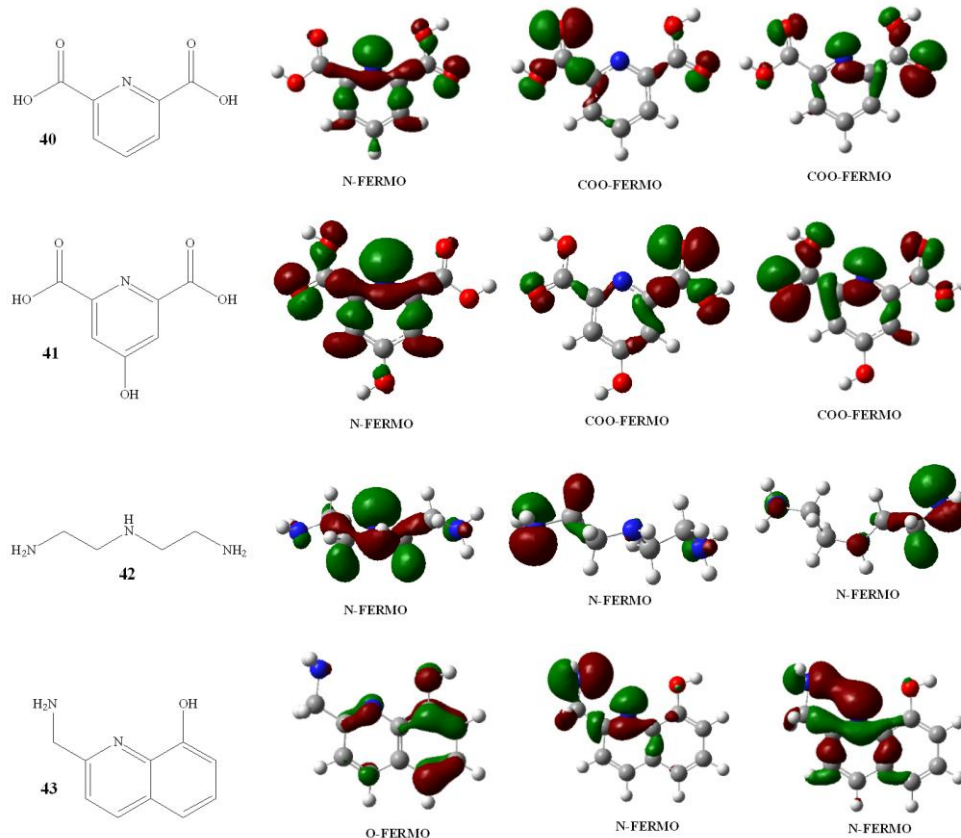
396 **Figure 15.** FERMO orbitals for the anion SCN^- at HF level. Sulfur-FERMO (A) and nitrogen-
397 FERMO (B) (adapted from reference (Da Silva et al., 2006c)).

398 The results obtained through the FERMO concept also explained the bond formation angle, because a
399 proper orbital orientation is required for the formation of a new bond. All results of this work are in
400 agree with experimental X-ray results.

401 Another interesting study involves the application of the FERMO concept to the description of
402 Pearson's principle of hardness and softness for four tridentate ligands (once they can bind metals in
403 three different ways). The shapes of the frontier orbitals that govern reactions of these ligands are

404 shown in
405 (A. La
406 al.,

Figure 16
Porta et
2012).



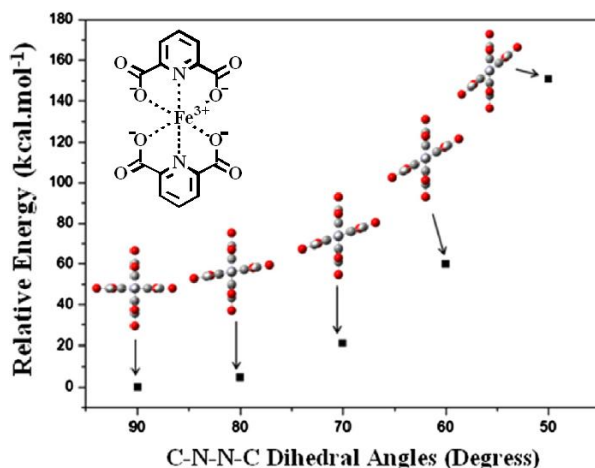
426 **Figure 16.** FERMO shapes for the studied tridentate ligands (adapted from reference (A. La Porta et
427 al., 2012)).

428 The complexation of metal ions with 2,6-pyridinedicarboxylic acid (PDC), corresponding to
429 compound **40** in Figure 16, has been extensively studied (Lainé et al., 1995; Chatterjee et al., 1998;
430 Wang et al., 2004; Gonzalez-Baró et al., 2005; Lima et al., 2005), since PDC is a very versatile
431 chelating agent, which acts as a bidentate, tridentate or bridged-bond ligand with different metal ions
432 (Hseu et al., 1991; La Porta et al., 2014). In addition, PDC has also other features such as low
433 toxicity and a biologically diversified activity, present in many natural products, such as oxidative
434 degradation products of vitamins, coenzymes and alkaloids (Crans et al., 2000; Khan et al., 2009). In
435 this way, we performed chemical reactivity studies between iron(III) ions and the ligand PDC in the
436 light of the FERMO concept.

437 The theoretical results indicated that the chemical bond between oxygen and iron atoms in the Fe-
438 PDC complex is predominantly electrostatic, and a small variation along the C-N-N-C dihedral is
439 favored (Figure 17) (La Porta et al., 2014). The use of iron complexes in catalysis has been
440 considered promising due to stabilization of iron in a wider pH range compared to the free ion in
441 solution. Another promising characteristic is that most chelating agents can be easily degraded by
442 microorganisms. This finding makes this organometallic complex an interesting material for catalytic
443 applications.

444

445



446
447
448
449
450
451
452
453
454

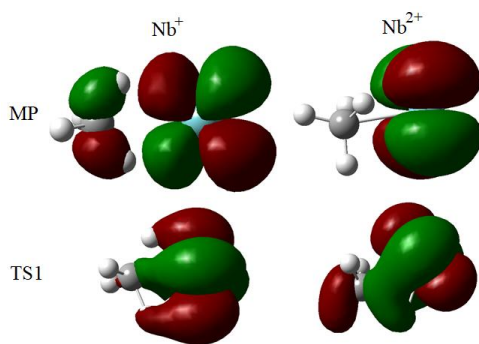
455 **Figure 17.** Potential energy surface for the C-N-N-C dihedral angles of the Fe-PDC complex
456 (structures visualized along the N-Fe-N bond) (adapted from reference (La Porta et al., 2014)).

457 Most of the complexes between Fe^{3+} and tridentate ligands are also octahedral, and the complex with
458 d^5 configuration can generate Jahn-Teller distortion. This observation is in very good agreement with
459 experimental studies (Daniele et al., 1997).

460 Molecular modeling of transition metal complexes is complicated because of the partially filled d
461 orbitals of metal ions which are responsible for both structures and multiplicity of coordination
462 compounds with a wide variety of coordination numbers and possible geometries. In this case, the
463 coordination geometry of a coordination compound always presents a relation between size and
464 electronic structure of the metal ion, and type, size, geometry and rigidity of coordinated ligands.
465 Thus, the structure of a coordination compound is strongly influenced by the linker structure
466 (Nakamura and Yamago, 2002; Comba et al., 2008).

467 In a recent study on methane dehydrogenation reactions with niobium ions (Nb^+ and Nb^{2+}) (De
468 Almeida et al., 2013), the FERMO concept was used to evaluate the process of charge transfer in the
469 reaction mechanisms involved. In this work, it was possible to observe that the FERMO of Nb^{2+} ion
470 has a higher contribution of C and Nb atoms (Figure 18), besides having lower energy than the
471 FERMO of Nb^+ ion. This can be evidenced by a factor that corresponds to the variation between the
472 energy values of FERMO for molecular precursor (MP) and transition state (TS1) structures in each
473 of the cases, due to Equation 9 below:

$$\Delta E_{\text{FERMO}} = |E_{\text{FERMO}}(\text{MP}) - E_{\text{FERMO}}(\text{TS1})| \quad (\text{Equation 9})$$



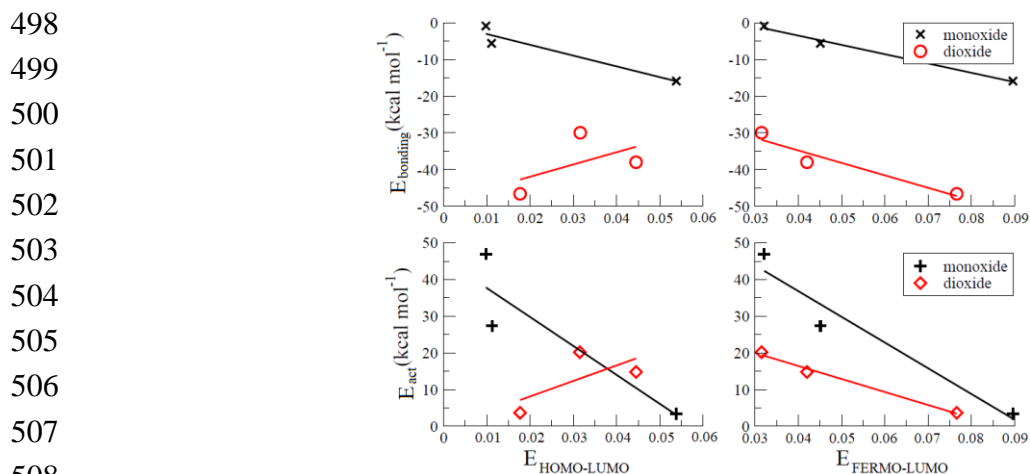
474 **Figure 18.** FERMO orbitals for molecular precursors (MP) and transition state (TS1) structures of
475 the studied methane dehydrogenation reactions by niobium ions (adapted from reference (De

476 Almeida et al., 2013)).

477 The obtained values were 0.03427 and 0.00424 a.u. (atomic units) for Nb^+ and Nb^{2+} , respectively.
478 These values showed a good correlation with Gibbs free energy values. Finally, it is worth to mention
479 that these results of molecular orbital analysis are in agreement with other analyzes also carried out
480 during the study involving structural and energetic parts and dehydrogenation mechanisms (De
481 Almeida et al., 2013).

482 Niobium compounds were again investigated in a related work (Almeida et al., 2016), in which
483 Almeida and collaborators reported the use of the HOMO-LUMO and FERMO-LUMO energy
484 differences to provide information about the methane C-H bond activation by niobium oxides (NbO ,
485 NbO^+ , NbO^{2+} , NbO_2 , NbO_2^+ and NbO_2^{2+}). The calculations for HOMO, LUMO and FERMO orbitals
486 were performed for all niobium oxides. The localized FERMO for the methane C-H bond activation
487 by niobium-oxo as well as for the niobium ions (De Almeida et al., 2013) were quite similar and
488 showed besides a major contribution of niobium *d* orbitals and a small participation of oxygen *s*
489 orbitals.

490 The energy gap between HOMO and LUMO orbitals ($E_{\text{HOMO-LUMO}}$) show a rather poor linear
491 correlation with E_{bonding} and E_{act} energies for the hydrogen abstraction from methane by niobium
492 oxides (Figure 19, left side). E_{bonding} and E_{act} are respectively the energy differences between isolated
493 structures of niobium oxides and methane and their adduct before activation (bonding energy) and
494 between transition states and reactant adducts (activation energy). These results can be explained by
495 the fact that in several cases, the HOMO-LUMO approach fails to rationalize the reactivity of the
496 chemical systems. However, the results show that the $E_{\text{FERMO-LUMO}}$ values have a good and strong
497 correlation with E_{bonding} and E_{act} (Figure 19, right side) (Almeida et al., 2016).



509 **Figure 19.** Correlation of the energy differences $E_{\text{HOMO-LUMO}}$ and $E_{\text{FERMO-LUMO}}$ with the E_{bonding} and
510 E_{act} values of the hydrogen abstraction from methane by niobium oxides (adapted from reference
511 (Almeida et al., 2016)).

512 There is an increase in $E_{\text{FERMO-LUMO}}$ compared to $E_{\text{HOMO-LUMO}}$, which is followed by a more favorable
513 initial electrostatic interaction between methane and charged niobium oxides, as well as a decrease in
514 E_{act} values. 0.08964 and 0.07661 atomic units are the highest $E_{\text{FERMO-LUMO}}$ values, calculated
515 respectively for doubly charged monoxide and dioxide, for which the best kinetic and
516 thermodynamic parameters were computed in the mentioned work. Methane is known to show a high
517 $E_{\text{HOMO-LUMO}}$, a fact that has been used to explain its high chemical inertia (Crabtree, 1995).

518 According to the hardness and softness acid base principles (HSAB), the inert methane is a hard acid

519 (high $E_{\text{HOMO-LUMO}}$ and $E_{\text{FERMO-LUMO}}$) and therefore should only react to hard species (those with high
520 $E_{\text{HOMO-LUMO}}$ or $E_{\text{FERMO-LUMO}}$). These characteristics are therefore in complete agreement with the
521 results obtained for niobium oxides (Almeida et al., 2016).

522 Therefore, the orbital FERMO analyses showed that the reactive molecular orbital is energetically
523 more stable in NbO^{2+} and NbO_2^{2+} , leading to the highest $E_{\text{FERMO-LUMO}}$ gaps. This feature is in
524 agreement with the HSAB principles since, in these cases, NbO^{2+} and NbO_2^{2+} can be considered as
525 hard species, like methane (Almeida et al., 2016).

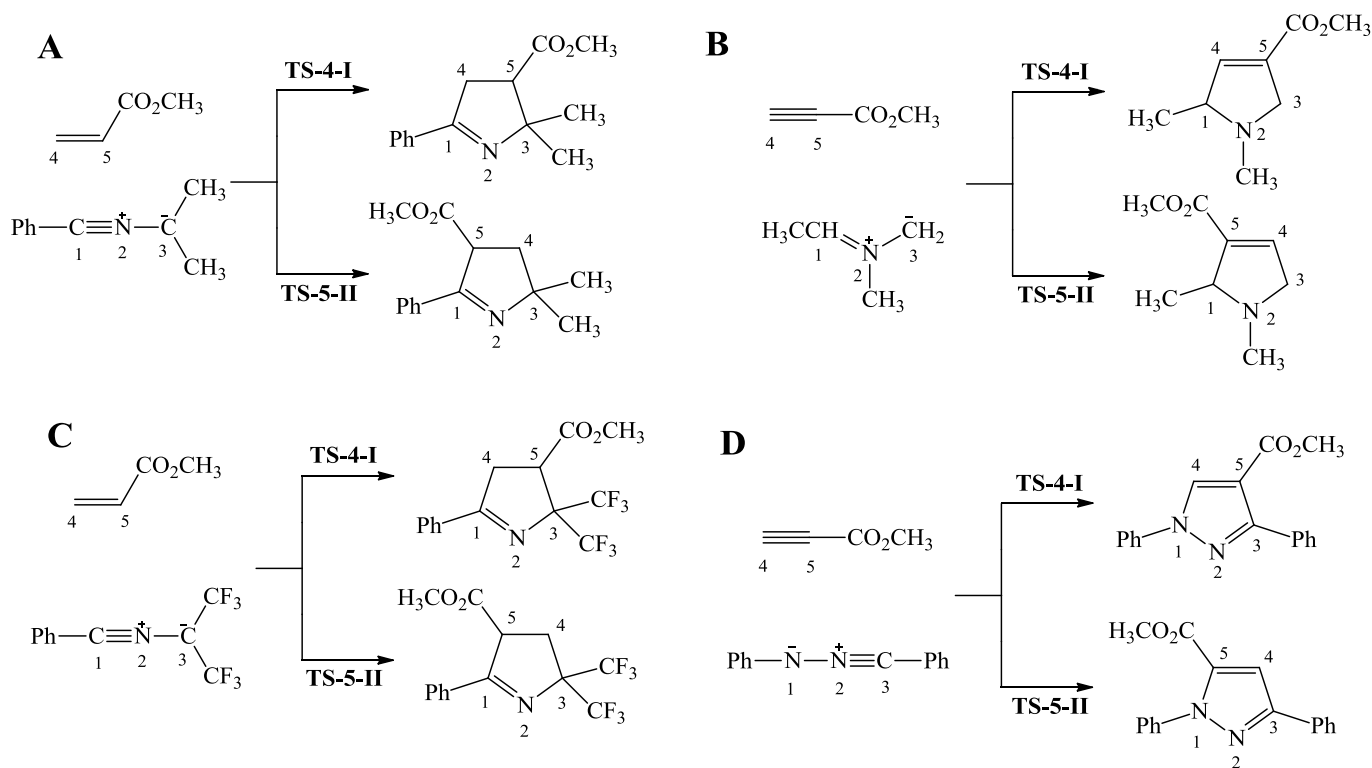
526 2.5.3 Pericyclic Reactions

527 Another subject that is worth mentioning is the study of pericyclic reactions, which can be defined as
528 a concerted reorganization of chemical bonds, through a cyclic arrangement of continuously
529 interconnected atoms ((PDF) Solomons Fryhle - Organic Chemistry - 10 Edition.pdf | Yasin Şenol -
530 Academia.edu). In this process, the reaction occurs through a conjugate transition state with usually
531 six atoms in the cyclic arrangement, but it may contain another number of atoms ((PDF) Solomons
532 Fryhle - Organic Chemistry - 10 Edition.pdf | Yasin Şenol - Academia.edu; Bruice, 2004). The main
533 kinds of pericyclic reactions are: a) electrocyclic; b) cycloaddition; c) sigmatropic rearrangement; d)
534 cheletropic; and e) "ene" reactions.

535 Cycloaddition reactions can be particularly considered as one of the most important and of great
536 interest in synthetic organic chemistry. In a cycloaddition reaction, two different molecules, both
537 containing π bonds, form a cyclic molecule by rearrangement of π electrons, in addition to creating
538 two new σ bonds. This interaction between two different π systems is usually intermolecular. The
539 cycloaddition reactions are classified according to the number of π electrons interacting in the
540 reaction, taking into account only the π electrons participating in the electronic rearrangement
541 (Jhaumeer-laulloo; Domingo et al., 1998; Gothelf and Jørgensen, 1998; Nakamura and Yamago,
542 2002; Aurell et al., 2004; Polo et al., 2004; Ess and Houk, 2008; La Porta et al., 2011).

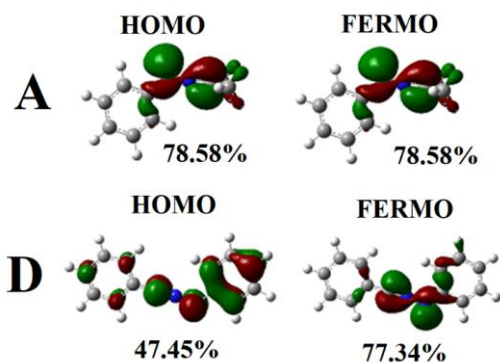
543 1,3-dipolar cycloaddition reactions are processed by a concerted [3+2] mechanism (Aurell et al.,
544 2004; La Porta et al., 2011). Their importance is related to the ease of formation of five-membered
545 heterocyclic compounds. Through the molecular orbital energies for each compound, we can also
546 calculate some global properties, which gives us an idea about their reactivities. In general, the
547 energy difference between reactants and products is not very high in 1,3-dipolar cycloaddition
548 reactions, and their activation energies are not usually very high. This allows these reactions to
549 proceed at room temperature. Thus, the HOMO-LUMO approach correctly describes pericyclic
550 reactions.

551 In a paper from La Porta et al. (La Porta et al., 2011), the FERMO concept was successfully
552 employed to the study of four different 1,3-dipolar cycloaddition reactions (named **A-D**) between
553 methyl acrylate or propiolate and substituted nitrilium or azomethine ylides or nitrilimine
554 compounds, proceeding through the corresponding **TS-4-I**-type or **TS-5-II**-type transition states
555 (Figure 20). Initially, calculations were made to obtain the minimum energy of the **A-D** studied
556 systems for fully relaxed molecules in gas phase. The H, CH_3 , CF_3 , and Ph substituents have been
557 selected in order to address small and huge groups, as well as electron-withdrawing and donating
558 effects in reactants.



559 **Figure 20.** Investigated 1,3-dipolar cycloaddition reactions between unsaturated esters and
 560 nitrogenated ylides or nitrilimine compounds (adapted from reference (La Porta et al., 2011)).

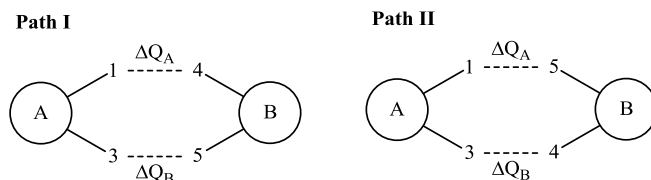
561 Through simple calculations, it was possible to identify the FERMO for all the studied cases. Based
 562 on composition and location of molecular orbitals, the FERMO was identified as the HOMO for A, B
 563 and C reactions, whereas, in D reaction, the FERMO was an orbital other than HOMO but with very
 564 close energy (Figure 21).



574 **Figure 21.** HOMO (left) and FERMO (right) shapes and their respective contributions in the reactive
 575 sites for the studied A (up) and D (down) system cycloaddition reactions (adapted from reference (La
 576 Porta et al., 2011)).

577 Chemical reactivity can be described in terms of long-range forces through the electrostatic potential
 578 (Marcus, 1993; Oliveira and De Araújo, 2007; Williams, 1991). The ΔQ charge transfer involved in
 579 the studied reactions (La Porta et al., 2011) could be calculated according to Equation 10 and Scheme
 580 1. In general, the charge transfer occurs by mean of the interaction between ligand orbitals of the
 581 charge donor molecule and anti-ligand orbitals of the proton donor species.

$$\Delta Q = \sum \Delta Q_{XY(Z \dots XY)} - \sum \Delta Q_Z \quad (10)$$



582 **Scheme 1.** Load transfer system between atoms 1 and 3 from unsaturated esters and atoms 4 and 5
 583 from nitrogenated ylides or nitrilimine compounds in the studied reactions (adapted from reference
 584 (La Porta et al., 2011)).

585 In this case, the charge is transferred from the atom Z to the species XY and $\Delta Q_{XY(Z \dots XY)}$ is the sum
 586 of point charges of the atoms X and Y, which represent the active site of this isolated molecule XY,
 587 ΔQ_Z (Williams, 1991).

588 It is important to point out that there are many methods that describe the molecular electron
 589 distribution in terms of atomic charges, such as Mülliken population analysis, GAPT dipolar model,
 590 AIM molecular partition and CHELPG charges (Oliveira and De Araújo, 2007; Williams, 1991). In
 591 this context, there is an appreciable number of papers applying these methodologies to the study of
 592 charge transfer and intermolecular stabilization energy phenomena (Marcus, 1993; Oliveira and De
 593 Araújo, 2007; Cormanich and Freitas, 2009; Oliveira, 2013; Williams, 1991)).

594 In addition, in this same work from La Porta and collaborators (La Porta et al., 2011), it is proposed
 595 the use of the difference between the sum of the module of charge transfers in the system as a new
 596 Δ_{FERMO} reactivity index, as described in Equation 11. This new reactivity index allows us to gather
 597 information about thermodynamic properties for these reactions with good correlation mainly with
 598 free energy values. The lower its value, the more effective is the charge transfer in the system, due to
 599 a greater interaction between orbitals.

$$\Delta_{FERMO} = \sum |\Delta Q_A - \Delta Q_B| \quad (11)$$

600 However, in order to calculate this electronic parameter, the implementation and interpretation of
 601 point charges is often used. An appropriate explanation for the concentration of atomic charges in
 602 donors can be demonstrated by the CHELPG charge transfer data and the Δ_{FERMO} index results,
 603 which explains very well the regioselectivity of these reactions (Table 2). A qualitative analysis of
 604 charge transfer allows us to gain important insights into the mechanism of 1,3-dipolar cycloaddition
 605 reactions (Marcus, 1993; Georgescu and Gérard, 1999; Aurell et al., 2004; Oliveira and De Araújo,
 606 2007; Cormanich and Freitas, 2009; Oliveira, 2013; Williams, 1991).

607

608

609

610

611

612 **Table 2:** ΔQ charge transfer values obtained from CHELPG method and Δ_{FERMO} index obtained for
 613 the studied reactions (adapeted from reference (La Porta et al., 2011)).

Model	ΔQ^{CHELPG}		Δ_{FERMO}		
	4-regioisomer	5-regioisomer	4-regioisomer	5-regioisomer	
A	ΔQ_{A}	0.178	0.125	0.033	0.041
	ΔQ_{B}	0.211	0.166	-	-
B	ΔQ_{A}	0.106	0.142	0.132	0.023
	ΔQ_{B}	0.238	0.165	-	-
C	ΔQ_{A}	0.022	0.008	0.106	0.168
	ΔQ_{B}	0.128	0.176	-	-
D	ΔQ_{A}	0.473	0.509	0.283	0.399
	ΔQ_{B}	0.190	0.110	-	-

614

615 Another important contribution from La Porta and collaborators (La Porta et al., 2011) was the use of
 616 the ADMP direct molecular dynamics method for calculations. The results obtained through this
 617 technique, in turn, provided detailed explanations at a molecular level for experimentally observed
 618 phenomena and are extremely useful for understanding fundamental aspects of chemistry. In
 619 addition, the shapes of frontier molecular orbitals were followed for the conformations obtained
 620 along the molecular dynamics simulations, showing that the reaction mechanism occurs through a
 621 concerted process (Figure 22). It is remarkable, however, that all these trajectories involved a
 622 concerted reaction path. In Table 3, the atomic contribution of frontier orbitals is presented along the
 623 mapped reaction path.

624

625

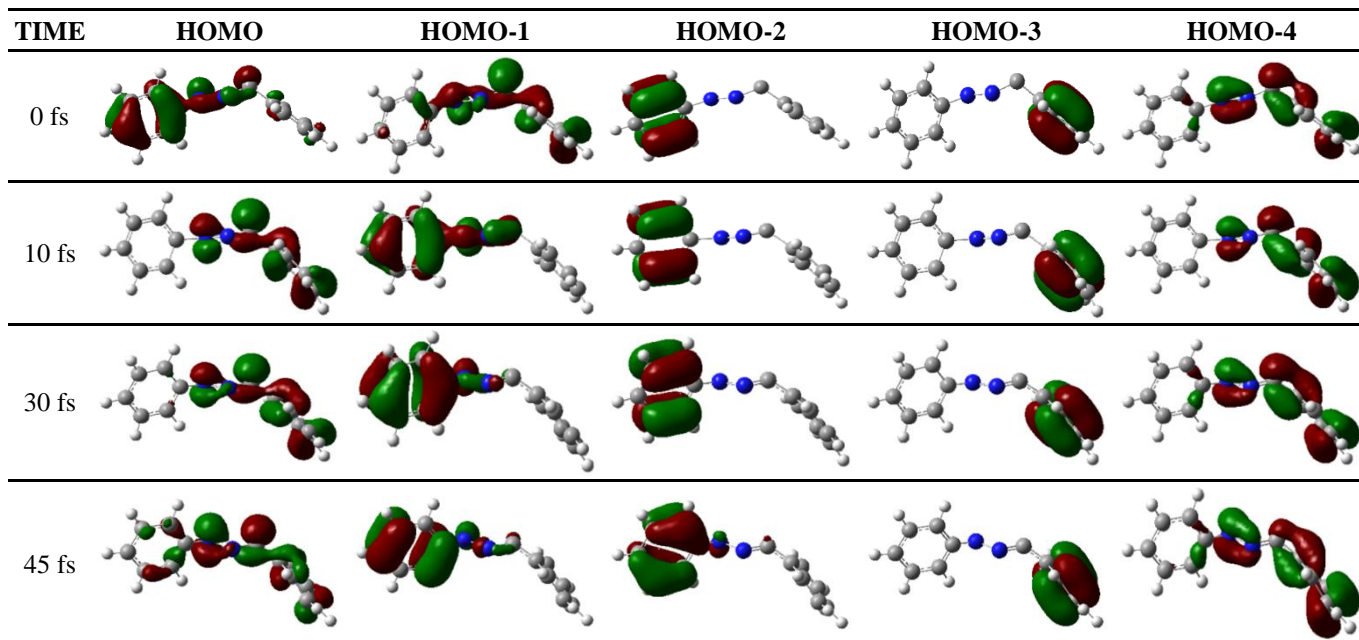
626

627

628

629

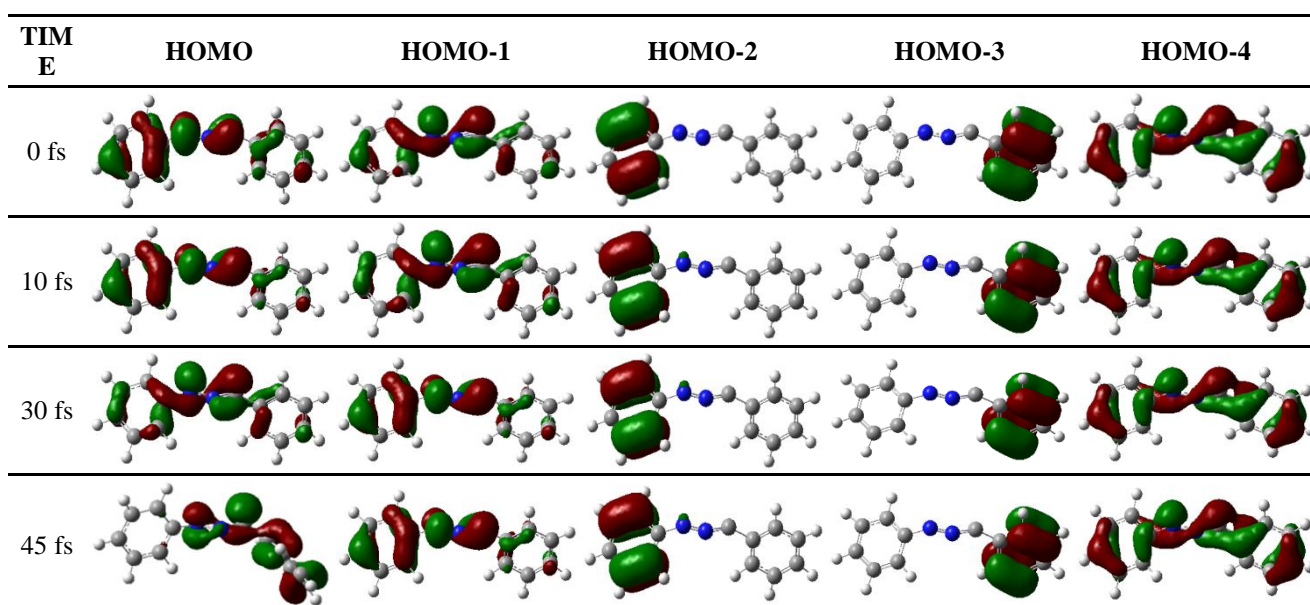
630



A

632

633



B

634

635 **Figure 22.** Representation of frontier molecular orbitals along the reaction path in the 4- (A) and 5-
 636 regioisomer (B) formation in the studied reaction D (adapted from reference (La Porta et al., 2011)).

637

638 **Table 3.** Percentual contribution of frontier orbitals of typical structures from trajectories for the
 639 formation of products in the reaction D (adapted from reference (La Porta et al., 2011)).

Molecular orbitals	FERMO percentual contribution							
	4-regioisomer				5-regioisomer			
	0 fs	10 fs	30 fs	45 fs	0 fs	10 fs	30 fs	45 fs
HOMO	40.13	60.41	55.05	63.23	57.22	58.16	59.17	73.84

HOMO-1	55.28	47.23	24.61	19.93	63.82	67.11	35.70	0.18
HOMO-2	0.02	0.25	0.26	9.18	0.15	3.55	0.40	14.79
HOMO-3	0.14	0.26	0.44	0.95	0.02	0.06	0.90	0.73
HOMO-4	51.58	39.84	46.94	32.21	41.23	34.95	55.07	26.35

640

641 In these results, it was showed that the molecular orbital responsible for describing the studied D
 642 reaction, the FERMO, becomes the HOMO (Figure 22). We believe that the effective molecular
 643 orbital for the reaction is the frontier molecular orbital that has electrons with highest kinetic energy.
 644 This fact explains the increase in the energy of the FERMO orbital, which is in agreement with the
 645 Virial Theorem (Georgescu and Gérard, 1999).

646 Another important aspect that we can notice is that the shape of the FERMO is maintained
 647 throughout the reaction. In this way, the FERMO concept removes the limitations of the HOMO-
 648 LUMO concept arguments and the new approaches proposed in the literature, and it can be
 649 considered as an innovative tool for studying the role of frontier molecular orbitals in chemical
 650 reactions.

651 In another work, also involving 1,3-dipolar cycloaddition reactions, the 1,3-dipolar double
 652 cycloaddition reaction between nitrilimine and allenolate was studied. This reaction had already been
 653 investigated experimentally by Liu and collaborators (Liu et al., 2017). However, in this work, it was
 654 studied theoretically at the computational levels B3LYP/6-311G(d,p) and wB97XD/6-311G(d,p) in
 655 both gas phase and dichloromethane solution. The author intended to elucidate global and local
 656 reactivity indices of reactants (Soleymani, 2018).

657 The mechanism was proposed, which was based on the interaction of nitrilimine with the C_{α} - C_{β}
 658 double bond of the allenolate in the first step to generate the dihydropyrazoline intermediate.
 659 Thereafter, the second nitrilimine molecule performs the cycloaddition to the C_{β} - C_{γ} double bond of
 660 the dihydropyrazoline intermediate to produce the corresponding spirobidihihydropyrazole (Figure 23)
 661 (Liu et al., 2017; Soleymani, 2018).

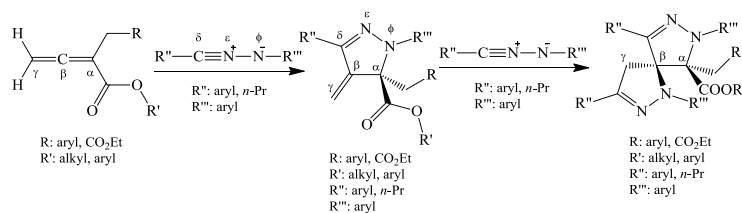
662

663

664

665

666



667 **Figure 23.** General scheme of the obtaining of spirobidihihydropyrazoles from nitrilimines and
 668 allenolates (adapted from (Liu et al., 2017; Soleymani, 2018)).

669 To determine how the molecular orbitals were interacting in this reaction, the energy differences
 670 between the frontier orbitals (HOMO / LUMO) of the electron donor (NI) and acceptor (Aln) groups
 671 were calculated. The FERMO concept was also used to describe the reactivity of pyrene active sites
 672 (Soleymani, 2018). Therefore, to determine the FERMO, the relative contribution of the active sites
 673 of NI (C_{δ} and N_{ϕ} atoms) in the three highest occupied molecular orbitals was calculated. Based on the
 674 composition and location of the molecular orbitals, it was found that the FERMO was once again the
 675 HOMO for the reaction, because the active sites of NI (C_{δ} and N_{ϕ} atoms) have a larger contribution
 676 for to HOMO compared to the other occupied molecular orbitals (Soleymani, 2018).

677 Their results showed that the formation of the experimentally described products can be clearly
 678 explained by Fukui function reactivity indices and transition states studies. Their analysis of the
 679 frontier molecular orbitals showed that the HOMO orbital of nitrilimine (acting as donor) is also the

680 FERMO (Soleymani, 2018).

681

682 2.5.4. Biological Systems

683 Heterocyclic aromatic compounds have great importance for medicinal chemistry due to their
684 biological activities, being mainly used as anticancer, antibacterial, antidepressants, anti-
685 inflammatories and herbicides, among other applications (Laber et al., 1999; Funakoshi et al., 2002;
686 Maccioni et al., 2002; Holla et al., 2003; Vicini et al., 2003; Harnett et al., 2004, Ingelman et al.,
687 2001). There are also compounds with excellent antitumor activities (Nicolaou et al., 1998; Bin and
688 Panek, 2000; Kamath and Jordan, 2003; Park et al., 2003; Storer et al., 2003), several compounds
689 that catalyze decarboxylation and condensation reactions (Svergun et al., 2000; Leonardi et al., 2003;
690 Melnick et al., 2003; Park et al., 2003) and others used in the fight against HIV virus (De Souza and
691 De Almeida, 2003). In addition, these compounds are often used as precursors in several reactions in
692 organic synthesis.

693 Arrang et al. discovered H₃ receptors in 1983 (Arrang et al., 1983). Recent studies have shown that,
694 in human brain, H₃ receptors are located in the cognition areas in the hippocampus. In these regions,
695 the neurotransmitter histamine is associated to other amines synthesized by human organism.
696 Investigating the role of histamine, it has been found that it inhibits its own release and synthesis in
697 the central nervous system (CNS) through interaction with H₃ receptors. For this reason, efforts have
698 been directed to the development of potent non-imidazole antagonists of the H₃ receptor (which, in
699 turn, belongs to the G-protein class), due to their potential therapeutic application in CNS disorders
700 such as memory and learning deficit, Alzheimer's, epilepsy, sleep disorders and obesity (Arrang et
701 al., 1985; Martinez-Mir et al., 1990; Haas and Panula, 2003; da Costa and Trsic, 2010).

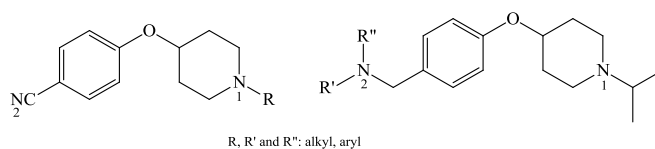
702 Da Costa and Trsic have evaluated, for a set of twenty-eight H₃ receptor antagonist compounds
703 (Figure 24), which theoretical parameters together would have a significant correlation with the
704 binding affinity to H₃ receptor (pK_i) (da Costa and Trsic, 2010), in order to assist the design of potent
705 H₃ antagonists. In this work, they used the FERMO energy along with reactivity descriptors such as
706 hardness, softness, electronegativity and electrophilicity indexes, chemical potential (all of them
707 calculated by substituting the energies of HOMO orbitals with the FERMO energies), and other
708 descriptors such as dipole moment, polarizability, hyperpolarizability, molecular volume, N¹ atom
709 charge (the nitrogen atom of piperidinic ring) and charge density in the N¹ atom in the FERMO
710 orbital ($\sum_{(FERMO)} c_i^2$), for the analysis of descriptors that influence the binding affinity values.

711

712

713

714



715 **Figure 24.** General structures of H₃ antagonists compounds investigated (adapted from (da Costa and
716 Trsic, 2010)).

717 Thus, in the statistical analysis for correlation with pK_i values, the FERMO energy correlated much
718 better with these experimental values than with the use of HOMO and LUMO orbitals energies. In
719 this research, the authors verified that four electronic descriptors, one of them being the FERMO
720 energy, were considered more appropriate to produce a satisfactory prediction for the theoretical pK_i
721 values. For the analysis of the descriptors that influence the binding affinity values, it was observed
722 that the FERMO energies behaved in a more pertinent way for the description of H₃ binding affinity
723 than the HOMO energies. Therefore, this result indicates that the energy value of the FERMO is a
724 critical parameter to be considered in quantitative studies of the structure-activity relationship.

725 The FERMO idea uses calculations based on the molecular orbital theory and interprets this data
726 according to the valence bond theory (Da Silva et al., 2006a, 2006b, 2006c). In molecular orbital
727 theory, electrons in a molecule occupy delocalized orbitals obtained from the linear combination of
728 atomic orbitals. However, it should bear in mind that the valence bond approach is very useful for
729 analyzing enzymatic reactivity (Nakamura and Truhlar, 2001; Truhlar, 2007), photochemistry
730 (Brynda et al., 2006; Truhlar, 2007), chemical dynamics (Brynda et al., 2006) and conductivity
731 theories where a localized representation is imperative.

732

733 **CONCLUSION**

734 The shape and atomic composition of molecular orbitals are very important indicators for discovering
735 suitable orbitals for all reactions. Thus, in this review work, we seek to systematically present the
736 most recent advances in the study of chemical reactivity based on a deep understanding of the
737 physical properties of the Frontier Effective-for-Reaction Molecular Orbital, FERMO. We can notice
738 that the FERMO idea is an innovative concept that has been identified as quite promising in the study
739 of the importance of molecular orbitals for chemical reactivity, and which has been applied with
740 success for describing the acid-base behavior, chemical reactions of organic and inorganic
741 complexes, pericyclic reactions and biological systems. In this sense, in summary, the FERMO
742 concept is intuitive and based on simple calculations, emerging as a powerful tool that seeks to
743 describe breaking and formation of chemical bonds. In particular, a molecule can have as many
744 FERMOs as reaction sites. The results obtained using different approaches of theoretical calculations
745 reinforce the idea of the FERMO concept, leading to new perspectives on the role of frontier orbitals.
746 These evidences suggest that the molecular orbital that describes a reaction, being responsible for
747 bond formation, has electrons with higher kinetic energy. Another interesting factor that can observed
748 is that the FERMO shape is maintained throughout the reaction course. This evidence helps to
749 reinforce the idea of this concept and allows us to obtain insights about the orbital responsible for
750 describing the reaction. Thus, the FERMO concept removes the limitations of the HOMO-LUMO
751 approach and of the new approaches proposed in the literature. It and can be considered as a powerful
752 and innovative tool for the study of the role of frontier molecular orbitals. Maybe molecular orbitals
753 keep a few more secrets that still need to be discovered. Understanding the behavior of molecular
754 orbitals is fundamental to better understand chemistry. Therefore, these investigations lead to new
755 perspectives and new ideas about the reactivity of molecules.

756

757 **CONFLICT OF INTEREST**

758 All the authors declare no conflict of interest.

759

760 **ACKNOWLEDGEMENTS**

761 We thank the Brazilian agencies FAPEMIG, CNPq, and CAPES for the financial support. This
762 work was also supported by University of Hradec Kralove (Faculty of Science, VT2019-2021).

763

764

765

766

767

768 **REFERENCES**

- 769 Allinger, N.L. *Organic Chemistry*, 2nd ed.; Worth Publishers: New York, 1976.
- 770 Almeida, K.J.; Ramalho, T.C.; Neto, J.L.; Santiago, R.T.; Felicíssimo, V.C.; Duarte, H.A. Methane
771 Dehydrogenation by Niobium Ions: A First-Principles Study of the Gas-Phase Catalytic Reactions.
772 *Organometal.*, 2013, 32(4), 989-999.
- 773 Almeida, K.J.; Silva, T.C.; Neto, J.L.; Rocha, M.V.J.; Ramalho, T.C.; Miranda, M.N.; Duarte, H.A.
774 Methane C-H bond activation by niobium oxides: Theoretical analyses of the bonding and reactivity
775 properties of Nbon+m (m = 1, 2; n = 0, 1, 2). *J. Organomet. Chem.*, 2016, 802, 49-59.
- 776 Arrang, J.M.; Garbarg, M.; Schwartz, J.C. Auto-inhibition of brain histamine release mediated by a
777 novel class (H3) of histamine receptor. *Nature*, 1983, 302, 832-837.
- 778 Arrang, J.M.; Garbarg, M.; Schwartz, J.C. AUTOREGULATION OF HISTAMINE RELEASE IN
779 BRAIN BY PRESYNAPTIC H3-RECEPTORS. *Neurosci.*, 1985, 15(2), 553-562.
- 780 Atkins, P.W.; Friedman, R.S. *Molecular Quantum Mechanics*, 3rd ed.; Oxford University Press:
781 Oxford, 1997.
- 782 Atkins, P.W.; Jones, L. *Chemistry: Molecules, Matter and Change*, 3rd ed.; Freeman: New York,
783 1997.
- 784 Aurell, M.J.; Domingo, L.R.; Pérez, P.; Contreras, R. A theoretical study on the regioselectivity of
785 1,3-dipolar cycloadditions using DFT-based reactivity indexes. *Tetrahedron*, 2004, 60(50), 11503-
786 11509.
- 787 Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.S.; Sorensen, E.J.; Danishefsky, S.J. Total
788 Synthesis of (-)-Epothilone A. *Angew. Chem. Int. Ed.*, 1996, 35(23-24), 2801-2803.
- 789 Berski, S.; Andrés, J.; Silvi, B.; Domingo, L.R. New Findings on the Diels–Alder Reactions. An
790 Analysis Based on the Bonding Evolution Theory. [J. Phys. Chem. A](#), 2006, 110(51), 13939-13947.
- 791 Birney, D.M.; Houk, K.N. Transition Structures of the Lewis Acid Catalyzed Diels-Alder Reaction
792 of Butadiene with Acrolein. The Origins of Selectivity. [J. Am. Chem. Soc.](#), 1990, 112(11), 4127-
793 4133.
- 794 Braga, L.S.; Moreira, R.A.; Leal, D.H.S.; Ramalho, T.C. Quantification of molecular orbitals based
795 on projection operators: Methodological development and applications to basicity prediction of
796 organic compounds in the gas phase. *Chem. Phys. Lett.*, 2019, 726, 87-92.
- 797 Bruice, P.Y. *Organic Chemistry*, 4th ed.; Prentice Hall: Upper Saddle River, 2003.
- 798 Brynda, M.; Gagliardi, L.; Widmark, P.O.; Power, P.P.; Roos, B.O. A Quantum Chemical Study of
799 the Quintuple Bond Between Two Chromium Centers in [PhCrCrPh]: trans-Bent versus Linear
800 Geometry. *Angew. Chem. Int. Ed.*, 2006, 45(23), 3804-3807
- 801 Cane, D.E. Biosynthesis Meets Bioinformatics. *Science*, 2000, 287(5454), 818-819.

- 802 Chatterjee, M.; Maji, M.; Ghosh, S.; Mak, T.C.W. Studies of V(III) complexes with selected α -N-
803 heterocyclic carboxylato NO donor ligands: structure of a new seven-coordinated pentagonal
804 bipyramidal complex containing picolinato ligands. *J. Chem. Soc., Dalton Trans.*, 1998, 21, 3641-
805 3646.
- 806 Comba, P.; Hambley, T.W.; Martin, B.; *Molecular Modeling of Inorganic Compounds*, 3rd ed.;
807 Wiley-VCH: Weinheim, 2009.
- 808 Cormanich, R.A.; Freitas, M.P. A Theoretical View on the Conformer Stabilization of Butane. *J.*
809 *Org. Chem.*, 2009, 74(21), 8384-8387.
- 810 Correia, C.R.D.; Costa, P.R.R.; Ferreira, V.F. VINTE E CINCO ANOS DE REAÇÕES,
811 ESTRATÉGIAS E METODOLOGIAS EM QUÍMICA ORGÂNICA. *Quím. Nova*, 2002, 25(Supl.
812 1), 74-81.
- 813 Costa, E.B.; Trsic, M. A quantum chemical study on a set of non-imidazole H3 antihistamine
814 molecules. [J. Mol. Graph. Model.](#), 2010, 28(7), 657-663.
- 815 Crabtree, R.H. Aspects of Methane Chemistry. *Chem. Rev.*, 1995, 95(4), 987-1007.
- 816 Crans, D.C.; Yang, L.; Jakusch, T.; Kiss, T. Aqueous Chemistry of Ammonium
817 (Dipicolinato)oxovanadate(V): The First Organic Vanadium(V) Insulin-Mimetic Compound. *Inorg.*
818 *Chem.*, 2000, 39(20), 4409-4416.
- 819 Da Silva, R.R.; O Papel dos Orbitais Moleculares na Química: Sobre os Limites dos Argumentos
820 HOMO-LUMO para a Reatividade. MSc Dissertation, Instituto Militar de Engenharia: Rio de
821 Janeiro, 2006.
- 822 Da Silva, R.R.; Ramalho, T.C.; Santos, J.M.; Figueroa-Villar, J.D. On the Limits of Highest-
823 Occupied Molecular Orbital Driven Reactions: The Frontier Effective-for-Reaction Molecular
824 Orbital Concept. *J. Phys. Chem. A*, 2006, 110(3), 1031-1040.
- 825 Da Silva, R.R.; Ramalho, T.C.; Santos, J.M.; Figueroa-Villar, J.D. Reply to "Comment on the Paper
826 'On the Limits of Highest-Occupied Molecular Orbital Driven Reactions: The Frontier Effective-for-
827 Reaction Molecular Orbital Concept'". *J. Phys. Chem. A*, 2006, 110(36), 10653-10654.
- 828 Da Silva, R.R.; Santos, J.M.; Ramalho, T.C.; Figueroa-Villar, J.D. Concerning the FERMO Concept
829 and Pearson's Hard and Soft Acid-Base Principle. *J. Braz. Chem. Soc.*, 2006, 17(2), 223-226.
- 830 Daniele, P.G.; De Stefano, C.; Prenesti, E.; Sammartano, S. Copper (II) complexes of N-
831 (phosphonomethyl)glycine in aqueous solution: a thermodynamic and spectrophotometric study.
832 *Talanta*, 1997, 45(2), 425-431.
- 833 Dewar, M.J.S. Aromaticity and Pericyclic Reactions. [Angew. Chem. Int. Ed.](#), 1971, 10(11), 761-776.
- 834 Domingo, L.R.; Arno, M.; Andrés, J. Toward an Understanding of Molecular Mechanism of Domino
835 Cycloadditions. Density Functional Theory Study of the Reaction between Hexafluorobut-2-yne and
836 N,N'-Dipyrrolylmethane. *J. Am. Chem. Soc.*, 1998, 120(7), 1617-1618.

- 837 Ess, D.H.; Houk, K.N. Theory of 1,3-Dipolar Cycloadditions: Distortion/Interaction and Frontier
838 Molecular Orbital Models. *J. Am. Chem. Soc.*, 2008, 130(31), 10187-10198.
- 839 Fujimoto, H. Paired Interacting Orbitals: A Way of Looking at Chemical Interactions. *Acc. Chem.*
840 *Res.*, 1987, 20(12), 448-453.
- 841 Fujimoto, H.; Mizutani, Y.; Iwase, K. An Aspect of Substituents and Peripheral Structures in
842 Chemical Reactivities of Molecules. *J. Phys. Chem.*, 1986, 90(12), 2768-2772.
- 843 Fujimoto, H.; Satoh, S. Orbital Interactions and Chemical Hardness. *J. Phys. Chem.*, 1994, 98(5),
844 1436-1441.
- 845 Fukui, K. The Role of Frontier Orbitals in Chemical Reactions (Nobel Lecture). *Angew. Chem. Int.*
846 *Ed.*, 1982, 21(11), 801-809.
- 847 Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. Molecular Orbital Theory of Orientation in
848 Aromatic, Heteroaromatic, and Other Conjugated Molecules. [J. Chem. Phys.](#), 1954, 22(8), 1433-
849 1442.
- 850 Fukui, K.; Yonezawa, T.; Shingu, H. A Molecular Orbital Theory of Reactivity in Aromatic
851 Hydrocarbons. [J. Chem. Phys.](#), 1952, 20(4), 722-725.
- 852 Funakoshi, T.; Chaki, S.; Kawahima, N.; Suzuki, Y.; Yoshikawa, R.; Kumagai, T.; Nazakato, A.;
853 Kameo, K.; Goto, M.; Okuyama, S. In vitro and in vivo pharmacological profile of 5-{2-[4-(6-fluoro-
854 1H-indole-3-yl) piperidin-1-yl] ethyl}-4-(4-fluorophenyl) thiazole-2-carboxylic acid amide
855 (NRA0562), a novel and putative atypical antipsychotic. *Life Sci.*, 2002, 71(12), 1371-1384.
- 856 Georgescu, V.; Gérard, C. On the Virial Theorem in Quantum Mechanics. *Commun. Math. Phys.*,
857 1999, 208(2), 275-281.
- 858 Gonzalez-Baró, A.C.; Castellano, E.E.; Piro, O.E.; Parajón-Costa, B.S. Synthesis, crystal structure
859 and spectroscopic characterization of a novel bis (oxo-bridged) dinuclear vanadium(V)-dipicolinic
860 acid complex. *Polyhedron*, 2005, 24(1), 49-55.
- 861 Gothelf, K.V.; Jørgensen, K.A. Asymmetric 1,3-Dipolar Cycloaddition Reactions. *Chem. Rev.*, 1998,
862 98(2), 863-909.
- 863 Haas, H.; Panula, P. The role of histamine and the tuberomamillary nucleus in the nervous system.
864 *Nature Rev. Neurosci.*, 2003, 4, 121-130.
- 865 Harmet, J.J.; Veronique, R.; Dolo, C.; Charnet, C.; Spinnewyn, B.; Cornet, S.; Rolland, A.; Marin,
866 J.G.; Bigg, D.; Chabrier, P.E. Phenolic thiazoles as novel orally-active neuroprotective agents.
867 *Bioorg. Med. Chem. Lett.*, 2004, 14(1), 157-160.
- 868 Hirao, H.; Ohwada, T. Theoretical Revisit of Regioselectivities of Diels-Alder Reactions: Orbital-
869 Based Reevaluation of Multicentered Reactivity in Terms of Reactive Hybrid Orbitals. *J. Phys.*
870 *Chem. A*, 2006, 109(5), 816-824.
- 871 Hirao, H.; Ohwada, T. Theoretical Study of Reactivities in Electrophilic Aromatic Substitution
872 Reactions: Reactive Hybrid Orbital Analysis. *J. Phys. Chem. A.*, 2003, 107(16), 2875-2881.

- 873 Hoffmann, R.; Shaik, S.; Hiberty, P.C. A Conversation on VB vs MO Theory: A Never-Ending
874 Rivalry? *Acc. Chem. Res.*, 2003, 36(10), 750-756.
- 875 Hoffmann, R.; Woodward, R.B. Orbital Symmetries and endo-exo Relationships in Concerted
876 Cycloaddition Reactions. *J. Am. Chem. Soc.*, 1965, 87(19), 4388-4389.
- 877 Hoffmann, R.; Woodward, R.B. Orbital Symmetries and Orientational Effects in a Sigmatropic
878 Reaction. *J. Am. Chem. Soc.*, 1965, 87(19), 4389-4390.
- 879 Hoffmann, R.; Woodward, R.B. Selection Rules for Concerted Cycloaddition Reactions. *J. Am.*
880 *Chem. Soc.*, 1965, 87(9), 2046-2048.
- 881 Hoffmann, R.; Woodward, R.B. Selection Rules for Sigmatropic Reactions. *J. Am. Chem. Soc.*,
882 1965, 87(11), 2511-2513.
- 883 Holla, B. S.; Malini, K. V.; Rao, B. S.; Sarojini, B. F.; Kumari, N. S. Synthesis of some new 2,4-
884 disubstituted thiazoles as possible antibacterial and anti-inflammatory agents. *Eur. J. Med. Chem.*,
885 2003, 38(3), 313-318.
- 886 Hseu, J.F.; Chen, J.J.; Chuang, C.C.; Wei, H.H.; Cheng, M.C.; Wang, Y.; Yao, Y.D. Crystal
887 structure, magnetic property and Mössbauer spectra of bis(pyridine-2,6-dicarboxylato) iron (III)
888 dihydrate. *Inorg. Chim. Acta*, 1991, 184(1), 1-5.
- 889 Ingelman, S.M.; Simi, A.; Tindberg, N. Treatment of disorders mediated by p38 MAP kinase, e.g.,
890 inflammation or neurological disorders, using a thiazole derivative such as 5-(2-chloroethyl)-4-
891 methylthiazole. Canada Patent WO 0135959, CA 134:361399, 2001.
- 892 Jensen, F. *Introduction to Computational Chemistry*, 2nd ed.; Wiley & Sons: West Sussex, 2007.
- 893 Kamath, K.; Jordan, M.A. Suppression of Microtubule Dynamics by Epothilone B Is Associated with
894 Mitotic Arrest. *Cancer Res.*, 2003, 63(18), 6026-6031.
- 895 Khan, S.; Nami, S.A.A.; Siddiqi, K.S.; Husain, E.; Naseem, I. Synthesis and characterization of
896 transition metal 2,6-pyridinedicarboxylic acid derivatives, interactions of Cu (II) and Ni (II)
897 complexes with DNA in vitro. *Spectrochim. Acta A Mol. Biomol. Spectr.*, 2009, 72(2), 421-428.
- 898 Klopman, G. Chemical Reactivity and the Concept of Charge- and Frontier-Controlled Reactions. *J.*
899 *Am. Chem. Soc.*, 1968, 90(2), 223-224.
- 900 La Porta, F.A.; Ramalho, T.C.; Santiago, R.T.; Rocha, M.V.J.; Cunha, E.F.F. Orbital Signatures as a
901 Descriptor of Regioselectivity and Chemical Reactivity: The Role of the Frontier Orbitals on 1,3-
902 Dipolar Cycloadditions. *J. Phys. Chem. A*, 2011, 115(5), 824-833.
- 903 La Porta, F.A.; Ramos, P.H.; Resende, E.C.; Guerreiro, M.C.; Giacoppo, J.O.S.; Ramalho, T.C.;
904 Sambrano, J.R.; Andrés, J.; Longo, E. Structural, electronic and optical properties of Fe (III) complex
905 with pyridine-2,6-dicarboxylic acid: A combined experimental and theoretical study. *Inorg. Chim.*
906 *Acta*, 2014, 416, 200-206.

- 907 La Porta, F.A.; Santiago, R.T.; Ramalho, T.C.; Freitas, M.P.; Da Cunha, E.F.F. The role of the
908 Frontier orbitals in acid–base chemistry of organic amines probed by ab initio and chemometric
909 techniques. *Int. J. Quant. Chem.*, 2010, 110(11), 2015-2023.
- 910 La Porta, F.L.; Giacoppo, J.O.S.; Ramos, P.H.; Guerreiro, M.C.; Ramalho, T.C. Computational
911 Insights into the Role of the Frontiers Orbital in the Chemistry of Tridentate Ligands. *Am. J. Chem.*,
912 2012, 2(5), 255-262.
- 913 Laber, B.; Usunow, G.; Wiecko, E.; Franke, W.; Franke, H.; Köhn, A. Inhibition of Narcissus
914 pseudonarcissus Phytoene Desaturase by Herbicidal 3-Trifluoromethyl-1,1'-biphenyl Derivatives.
915 *Pest. Biochem. Physiol.*, 1999, 63(3), 173-184.
- 916 Lainé, P.; Gourdon, A.; Launay, J.P. Chemistry of Iron with Dipicolinic Acid. 1. Mononuclear
917 Complexes of Iron (II) or Iron (III). *Inorg. Chem.*, 1995, 34(21), 5129-5137.
- 918 Leonardi, R.; Fairhurst, S.A.; Kriek, M.; Lowe, D.J.; Roach, P.L. Thiamine biosynthesis in
919 *Escherichia coli*: isolation and initial characterisation of the ThiGH complex. *FEBS Lett.*, 2003,
920 539(1-3), 95-99.
- 921 Lewis, G.N. THE ATOM AND THE MOLECULE. *J. Am. Chem. Soc.*, 1916, 38(4), 762-785.
- 922 Lewis, G.N. VALENCE AND TAUTOMERISM. *J. Am. Chem. Soc.*, 1913, 35(10), 1448-1455.
- 923 Li, J.N.; Fu, Y.; Liu, L.; Guo, Q.X. First-principle predictions of basicity of organic amines and
924 phosphines in acetonitrile. *Tetrahedron*, 2006, 62(50), 11801-11813.
- 925 Lima, P.P.; Malta, O.L.; Júnior, S.A. ESTUDO ESPECTROSCÓPICO DE COMPLEXOS DE Eu³⁺,
926 Tb³⁺ E Gd³⁺ COM LIGANTES DERIVADOS DE ÁCIDOS DICARBOXÍLICOS. *Quím. Nova*,
927 2005, 28(5), 805-808.
- 928 Liu, H.; Jia, H.; Wang, B.; Xiao, Y.; Guo, H. Synthesis of Spirobidihydropyrazole through Double
929 1,3-Dipolar Cycloaddition of Nitrilimines with Allenates. *Org Lett.*, 2017, 19(18), 4714-4717.
- 930 Maccioni, E.; Cardia, M.C.; Bonsignore, L.; Plumitallo, A.; Pellerano, M.L.; De Logu, A. Synthesis
931 and anti-microbial activity of isothiosemicarbazones and cyclic analogues. *Il Farmaco*, 2002, 57(10),
932 809-817.
- 933 Marcus, R.A. Electron transfer reactions in chemistry. Theory and experiment. *Rev. Mod. Phys.*,
934 1993, 65(3), 599-610.
- 935 Martinez-Mir, M.I.; Pollard, H.; Moreau, J.; Arrang, J.M.; Ruat, M.; Traiffort, E.; Schwartz, J.C.;
936 Palacios, J.M. Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-
937 human primates. *Brain Res.*, 1990, 526(2), 322-327.
- 938 Melnick, J.S.; Sprinz, K.I.; Reddick, J.J.; Kinsland, C.; Begley, T.P. An Efficient Enzymatic
939 Synthesis of Thiamin Pyrophosphate. *Bioorg. Med. Chem. Lett.*, 2003, 13(22), 4139-4141.
- 940 Moreira, R. A. Eletrônica Molecular: Estudo ab initio da Separabilidade Eletrodo/Molécula Orgânica.
941 MSc Dissertation, Universidade Federal de Pernambuco: Recife, 2013.
- 942 Morgon, N.H.; Custodio, R. Teoria do Funcional de Densidade. *Quim. Nova*, 1995, 18(1), 44-55.

- 943 Nakamura, E.; Yamago, S. Thermal Reactions of Dipolar Trimethylenemethane Species. *Acc. Chem.*
944 *Res.*, 2002, 35(10), 867-877.
- 945 Nakamura, H.; Truhlar, D.G. The direct calculation of diabatic states based on configurational
946 uniformity. *J. Chem. Phys.*, 2001, 115(22), 10353-10372.
- 947 Nakamura, S.; Hirao, H.; Ohwada, T. Rationale for the Acidity of Meldrum's Acid. Consistent
948 Relation of C–H Acidities to the Properties of Localized Reactive Orbital. *J. Org. Chem.*, 2006,
949 69(13), 4309-4316.
- 950 Nicolau, K.C.; Roschangar, F.; Vourloumis, D. Chemical Biology of Epothilones. *Angew. Chem. Int.*
951 *Ed.*, 1998, 37(15), 2014-2045.
- 952 Ohwada, T.; Hirao, H.; Ogawa, A. Theoretical Analysis of Lewis Basicity Based on Local Electron-
953 Donating Ability. Origin of Basic Strength of Cyclic Amines. *J. Org. Chem.*, 2004, 69(22), 7486-
954 7494.
- 955 Oliveira, B.G. Structure, energy, vibrational spectrum, and Bader's analysis of $\pi \cdots H$ hydrogen bonds
956 and $H-\delta \cdots H+\delta$ dihydrogen bonds. [Phys. Chem. Chem. Phys.](#), 2013, 15(1), 37-79.
- 957 Oliveira, B.G.; Araújo, R.C.M.U. RELAÇÃO ENTRE TRANSFERÊNCIA DE CARGA E AS
958 INTERAÇÕES INTERMOLECULARES EM COMPLEXOS DE HIDROGÊNIO
959 HETEROCÍCLICOS. *Quím. Nova*, 2007, 30(4), 791-796.
- 960 Park, J.H.; Dorrestein, P.C.; Zhai, H.; Kinsland, C.; McLafferty, F.W.; Begley, T.P. Biosynthesis of
961 the Thiazole Moiety of Thiamin Pyrophosphate (Vitamin B1). *Biochem.*, 2003, 42(42), 12430-
962 12438.
- 963 Pauling, L. The Nature of the Chemical Bond and the Structure of Molecules and Crystals; An
964 Introduction to Modern Structural Chemistry, 3rd ed.; Cornell University Press: Ithaca, 1960.
- 965 Pauling, L. THE NATURE OF THE CHEMICAL BOND. APPLICATION OF RESULTS
966 OBTAINED FROM THE QUANTUM MECHANICS AND FROM A THEORY OF
967 PARAMAGNETIC SUSCEPTIBILITY TO THE STRUCTURE OF MOLECULES. *J. Am. Chem.*
968 *Soc.*, 1931, 53(4), 1367-1400.
- 969 Pearson, R.G. SYMMETRY RULES FOR CHEMICAL REACTIONS. *Comp. & Maths. with*
970 *Appls.*, 1976, 12(1-2 Part. B), 229-236.
- 971 Pereira, D.H.; La Porta, F.A.; Santiago, R.T.; Garcia, D.R.; Ramalho, T.C. Novas Perspectivas sobre
972 o Papel dos Orbitais Moleculares de Fronteira no Estudo da Reatividade Química: Uma Revisão.
973 *Rev. Virtual Quim.*, 2016, 8(2), 425-453.
- 974 Polo, V.; Andres, J.; Castillo, R.; Berski, S.; Silvi, B. Understanding the Molecular mechanism of the
975 1,3-Dipolar Cycloaddition between Fulminic Acid and Acetylene in Terms of the Electron
976 Localization Function and Catastrophe Theory. [Chem. A Eur. J.](#), 2004, 10(20), 5165-5172.
- 977 Ramalho, T.C.; Pereira, D.H. Understanding the substituent effect on the acidity of alcohols and
978 para-substituted phenols. *Mol. Simulat.*, 2009, 35(15), 1269-1278.

- 979 Rauk, A. *Orbital Interaction Theory of Organic Chemistry*, 2nd ed.; Wiley-Interscience: New York,
980 2000.
- 981 Rhyman, L.; Abdallah, H.H.; Jhaumeer-Laulloo, S.; Domingo, L.R.; Joule, J.A.; Ramasami, P. 1,3-
982 Dipolar cycloaddition of 1H-pyrazinium-3-olate and N1- and C-methyl substituted pyrazinium-3-
983 olates with methyl acrylate: a density functional theory study. *Tetrahedron*, 2011, 67(43), 8383-8391.
- 984 Sáez, J.A.; Arnó, M.; Domingo, L.R. A DFT study for the regioselective 1,3-dipolar cycloadditions
985 of nitrile N-oxides toward alkynylboronates. *Tetrahedron*, 2003, 59(46), 9167-9171.
- 986 Santiago, R.T.; La Porta, F.A.; Rocha, M.V.J.; Ramalho, T.C.; Freitas, M.P.; Cunha, E.F.F.
987 Description of the Acid/Base Behavior of Organic Phosphines Using ab initio and Chemometric
988 Approaches. *Lett. Org. Chem.*, 2010, 7(7), 552-556.
- 989 Schrödinger, E. [Quantizierung als Eigenwertproblem](#). *Annalen der Physik*, 1926, 384(4), 361-376.
- 990 Soleymani M. DFT study of double 1,3-dipolar cycloaddition of nitrilimines with allenates.
991 *Monatsh. Chem.*, 2018, 149(12), 2183-2193.
- 992 Soleymani, M.; Khavidaki, H.D. Inactivation possibility of pyrene by C 20 fullerene via
993 cycloaddition reactions: A theoretical study. *Comp. Theor. Chem.*, 2017, 1112, 37-45.
- 994 Solomons, T.W.G.; Fryhle, C.B. *Organic Chemistry*, 8th ed.; Wiley, 2003.
- 995 Souza, M.V.N.; Almeida, M.V. DROGAS ANTI-VIH: PASSADO, PRESENTE E PERSPECTIVAS
996 FUTURAS. *Quím. Nova*, 2003, 26(3), 366-372.
- 997 Storer, R.I.; Takemoto, T.; Jackson, P.S.; Ley, S.V. A Total Synthesis of Epothilones Using Solid-
998 Supported Reagents and Scavengers. *Angew. Chem. Int. Ed.*, 2003, 42(22), 2521-2525.
- 999 Svergun, D.I.; Petoukhov, M.V.; Koch, M.H.J.; Konig, S. Crystal Versus Solution Structures of
1000 Thiamine Diphosphate-dependent Enzymes. *J. Biol. Chem.*, 2000, 275(1), 297-302.
- 1001 Truhlar, D.G. Valence bond theory for chemical dynamics. *J. Comp. Chem.*, 2007, 28(1), 73-86.
- 1002 Vianello, R.; Maksić, Z.B. Triadic analysis of substituent effects – gas-phase acidity of para-
1003 substituted phenols. *Tetrahedron*, 2006, 62(14), 3402-3411.
- 1004 Vianello, R.; Peran, N.; Maksić, Z.B. Hydride Affinities of Some Substituted Alkynes: Prediction by
1005 DFT Calculations and Rationalization by Triadic Formula. *J. Phys. Chem. A*, 2006, 110(47), 12870-
1006 12881.
- 1007 Vianello, R.; Peran, N.; Maksić, Z.B. Hydride Affinities of Substituted Alkenes: Their Prediction by
1008 Density Functional Calculations and Rationalisation by Triadic Formula. *Eur. J. Org. Chem.*, 2007,
1009 2007(3), 526-539.
- 1010 Vicini, P.; Geronikaki, A.; Incerti, M.; Busonera, B.; Poni, G.; Cabras, C.A., La Colla, P. Synthesis
1011 and Biological Evaluation of Benzo[d]isothiazole, Benzothiazole and Thiazole Schiff Bases. *Bioorg.*
1012 *Med. Chem.*, 2003, 11(22), 4785-4789.

- 1013 Wang, X.L.; Chao, H.; Li, H.; Hong, X.L.; Ji, L.N.; Li, X.Y. Synthesis, crystal structure and DNA
1014 cleavage activities of copper (II) complexes with asymmetric tridentate ligands. *J. Inorg. Biochem.*,
1015 2004, 98(3), 423-429.
- 1016 Web of Science [v.5.33]. apps.webofknowledge.com (Accessed July 15, 2019)
- 1017 Williams, D.E. In: *Rev. Comput. Chem.*, Lipkowitz, K.B.; Boyd, D.B., Ed. Wiley-VCH: New York,
1018 1991; Vol. 2, pp 219-271.