

This article was downloaded by:

On: 14 January 2011

Access details: Access Details: Free Access

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Molecular Simulation

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713644482>

Understanding the substituent effect on the acidity of alcohols and *para*-substituted phenols

Teodorico C. Ramalho^a; Douglas H. Pereira^a

^a Departamento de Química, Universidade Federal de Lavras, Lavras, MG, Brazil

To cite this Article Ramalho, Teodorico C. and Pereira, Douglas H.(2009) 'Understanding the substituent effect on the acidity of alcohols and *para*-substituted phenols', *Molecular Simulation*, 35: 15, 1269 – 1278

To link to this Article: DOI: 10.1080/08927020903015387

URL: <http://dx.doi.org/10.1080/08927020903015387>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Understanding the substituent effect on the acidity of alcohols and *para*-substituted phenols

Teodorico C. Ramalho* and Douglas H. Pereira

Departamento de Química, Universidade Federal de Lavras, Caixa Postal, CEP, Lavras, MG 37200-000, Brazil

(Received 19 November 2008; final version received 23 April 2009)

We carried out Hartree–Fock (HF) and density functional theory calculations on the conjugated bases of phenols and alcohols for 23 compounds and analysed their acid–base behaviour using molecular orbital (MO) energies and their dependence on solvent effects. Despite the well-known correlation between highest-occupied MO (HOMO) energies and their proton affinity (PA), we observed that HOMO energies are inadequate to describe the acid–base behaviour of these compounds. Therefore, we established a criterion to identify the best frontier MO for describing PA values and also to understand why the HOMO approach fails. The MO that fits our criterion provided very good correlations with PA values, much better than those obtained by the HOMO energies. Since the frontier MOs are those which drive the acid–base reactions in each compound, they were called frontier effective-for-reaction MOs, or FERMOs. By using the FERMO concept, the reactions that are HOMO driven, and those that are not, can be better explained, independent of the calculation method used, since both HF and Kohn–Sham methodologies lead to the same FERMO.

Keywords: acidity of alcohols; HOMO–LUMO; FERMO; molecular orbital

1. Introduction

The calculation of gas-phase acid–base parameters has been a well-established methodology. However, the theoretical calculation of acid–base parameters, especially in solution, is a great challenge for quantum chemists [1]. The proton affinity (PA) is the most useful acid–base parameter and a lot of work has shown how PA values correlate with quantum descriptors [2–6]. The PA of a molecule is a measure of its gas-phase basicity. Thus, the higher the PA, the stronger the base and the weaker the conjugate acid in the gas phase. In other words, PAs illustrate the role of hydration in aqueous-phase Brønsted acidity.

The relationships between the highest-occupied molecular orbital (HOMO) energies and PA are often present for families of compounds, such as phenols. However, for a large number of compounds, the HOMO energies do not show good correlation with PA values [$PA = A^*$ (orbital energy) + B , where A and B are the angular and linear coefficients, respectively]. Other quantum parameters, such as dipole moments, bond orders, atomic charges on hydrogens, and bond lengths, had to be included in multiple linear regression analysis in order to correlate them [3–6]. This procedure certainly weakens the familiar idea that donor–acceptor reactions are driven by frontier orbital energies. In line with that, a question arises from the results: why are the HOMO energies good acid–base descriptors for some compounds and not for others? A careful study is necessary to understand when the HOMO energy works and when

it does not, because there are clear limitations to the HOMO–lowest-unoccupied molecular orbital (LUMO) approach, and other concepts are needed to complement the HOMO–LUMO arguments. More recently, the frontier effective-for-reaction molecular orbital (FERMO) concept has emerged as a powerful approach for studying this situation [7–9].

In addition to that, there is a lack of studies concerning the most common and important classes of organic compounds, alcohols and phenols, and the relationship of their acid–base behaviour with their molecular orbital (MO) energies.

MOs and their properties such as energies and symmetries are very useful for chemists. Since Fukui and co-workers [10] used the frontier electron density for predicting the most reactive position in π -electron systems and Hoffmann and Woodward [11] set out orbital symmetry rules to explain several types of reactions in conjugated systems, the frontier MOs gained importance for the better understanding of chemical processes. Therefore, the knowledge of how the MOs would control a reaction is a central key for many answers in chemistry.

Although the MOs are very important to chemists, there are some theoretical issues concerning them. The MO comes from the Hartree–Fock (HF) approximation for solving the Schrödinger equation. Because of that, in the HF methods and post-HF methods (such as MP2), the MO idea is natural and their properties are widely used to explain many molecular properties and reaction mechanisms [12]. However, the HF method has a problem: the

*Corresponding author. Email: teo@ufla.br

lack of electron correlation. In the post-HF methods, the electron correlation is present, but another problem arises: the calculation time increases too much, and that type of calculation is restricted to small molecules. Because of these problems concerning the HF and post-HF methods, the density functional theory (DFT) became a very popular method for calculating the electronic structure of molecules, since it includes the electron correlation and the computer time spent is not as long as it is in the post-HF methods.

The DFT orbitals, named Kohn–Sham (KS) orbitals, and the MOs are sometimes treated as different quantum descriptors [12]. Another reason for that difference arises from the poor results given by the eigenvalues of the KS orbitals in the description of the ionisation potentials (IPs) of molecules (the Koopmans' theorem). Politzer and Abu-Awwad have analysed the behaviour of the HF and KS orbital energies in many molecules and compared the results with the experimental IP [13]. These results indicate that the KS orbitals are suitable to use in qualitative MO theory and that the problem with their energies comes from the poor asymptotic behaviour of the available functionals.

Thus, this work is devoted to investigating which is the best MO for describing the acid or base character for a collection of phenol and alcohol compounds in light of the FERMO concept at both the HF and DFT levels.

2. Theoretical approach

2.1 Computational details

All calculations were carried out with the Gaussian 98 package [14]. Each conjugated base from all 23 compounds was fully optimised using the DFT with the B3LYP functional [15,16] employing the 6-311G(d,p) basis set. No symmetry constraint was imposed during the optimisation process. No imaginary frequencies were found for the optimised geometries. These optimised geometries were used in all subsequent calculations. Furthermore, MP2 single-point energy calculations were computed using the 6-311G(d,p) basis set.

To account for solvent effects from water, single-point energy calculations were performed using the polarizable continuum model (PCM) [17–19] and the conductor-like screening model (COSMO) [20,21] at both the DFT, with the B3LYP functional, and MP2 levels with the 6-311G(d,p) basis set. The orbital energies from these methods were fit to a linear model with experimental PA values and the determination coefficients (r^2) were analysed. The MO figures were prepared using the Gaussview 2.1 package [14] with a contour value of 0.020.

Furthermore, the theoretical IP of the orbitals can be obtained if the outer valence Green function (OVGF) method is used [22,23]. This method is state-of-the-art in ionisation calculations and was utilised by Ahmed on the

assignment of the photoelectron spectra of quinolines [24] and radiosensitiser in solution [25,26].

2.2 Orbital choice criteria

It is well known that Bronsted–Lowry acid–base reactions are localised phenomena, which take place between the proton and an atom (or group of atoms) in a molecule [27]. Therefore, the MO that drives those reactions must be centred in this atom or group of atoms. Thus, we carried out the investigation of these orbitals in two different ways: by looking at the orbital shapes [27] and by calculating the MO composition using the expansion coefficients.

2.3 Phenols and alcohols

Table 1 shows the 23 phenols and alcohols used in this work and their experimental values of the PA for the reaction.

3. Results and discussion

3.1 HOMO and chemical reactivity

Some works in the literature show that the HOMO energy (HOMOs) is related to the acid–base behaviour of some compounds [28]. Thus, in our work, we correlated the energy values of the HOMOs with their PA values.

Table 1. Phenols and alcohols and their experimental PA^a values.

Number	Molecules	PA (kJ mol ^{−1})
1	Methanol	1596 ^a
2	Ethanol	1583 ^a
3	Propanol	1572 ^a
4	Isopropanol	1569 ^a
5	Butanol	1570 ^a
6	Isobutanol	1567 ^a
7	Sec-butanol	1560 ^a
8	Hexanol	1565 ^a
9	2,2,2-Trifluoro-ethanol	1513 ^a
10	<i>p</i> -Amino phenol	1475 ^b
11	<i>p</i> -Methoxy-phenol	1466 ^b
12	<i>p</i> -Hydroxy-phenol	1466 ^b
13	<i>p</i> -Methyl-phenol	1465 ^b
14	Phenol	1454 ^b
15	<i>p</i> -Terc-phenol	1458 ^b
16	<i>p</i> -Dimethylamino-phenol	1470 ^b
17	<i>p</i> -Fluoro-phenol	1451 ^b
18	<i>p</i> -Chloro-phenol	1435 ^b
19	<i>p</i> -Trifluoromethyl-phenol	1410 ^b
20	<i>p</i> -Carboxi-phenol	1405 ^b
21	<i>p</i> -Cyano-phenol	1389 ^b
22	<i>p</i> -Ethanol-phenol	1393 ^b
23	<i>p</i> -Nitro-phenol	1371 ^b

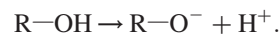
^aExperimental data, in NIST Chemistry WebBook, NIST MD, 20899 (<http://webbook.nist.gov>). ^bRef. [2]

The correlations between the energy values of the HOMO had been made with the conjugated bases of R—OH compounds and the results reported for both phenols and alcohols. From our calculations, we can observe that ionic groups (alkoxides and phenoxides) together provided very poor linear models (Table 2). The exception to that conclusion was the B3LYP/6-311G(d,p) methodology, because we can get acceptable determination coefficients. From these data, two doubts appear: (1) Can the two groups be correlated together? and (2) Will the HOMO be the best orbital to describe the reaction?

In order to find the answer to these questions, we separated our data into two groups: alcohols (alkoxides) and phenols (phenoxides).

Now we can analyse only the phenoxide group, whose results are presented in Tables 2 and 3. Whereas, the linear correlations for the HOMO in all the methodologies are good, except for the B3LYP/6-311G(d,p) methodology, the doubt still remains: will the HOMO be the same as the best orbital to describe the chemical reaction? In line with this, we expanded the correlations between PA and energy values for HOMO-1, HOMO-2 and HOMO-3 (Table 4). From Table 4, we can analyse the correlations between the

energy values of each orbital and the PA values. According to that, good correlations are also found, but none that indeed confirms which orbital could really describe the following chemical reaction:



With those correlations, it is not possible to distinguish which orbital is the best to describe the acid–base chemical reaction. At this point, we calculated the IPs for the compounds using the OGVF method [24], in order to get more accurate orbital energy values.

The results of the IP are presented in Table 5. Good correlations are obtained for all orbitals, thus it is not feasible to identify the best orbital that will describe the chemical reaction. Figure 1 shows the DFT and HF orbitals for the molecule 21 (*p*-cyano-phenoxide) and 13 (*p*-methyl-phenoxide) using the DFT or MP2 levels, respectively.

The results at all calculation levels for alkoxide ions were disappointing (Tables 2 and 3). It was found that none of those regressions could be considered as a linear

Table 2. Linear regression parameters for experimental PA values versus orbital energy of phenoxide and alkoxide ions.

Orbital/compound group	Methodology	r^2	A	B
HOMO/(phenoxide and alkoxide)	MP2/6-311G(d,p)	0.13	1497.12	−125.714
	B3LYP/6-311G(d,p)	0.63	1599.89	−268.75
HOMO/(phenoxides)	MP2/6-311G(d,p)	0.85	2012.98	246.17
	B3LYP/6-311G(d,p)	0.78	1362.34	132.43
HOMO/(alkoxides)	MP2/6-311G(d,p)	0.36	1683.00	−148.19
	B3LYP/6-311G(d,p)	0.34	1853.08	−194.99
FERMO/(phenoxide and alkoxide)	MP2/6-311G(d,p)	0.98	1734.00	−154.15
	B3LYP/6-311G(d,p)	0.94	1743.08	−189.49

r^2 (linear correlation); A, Angular coefficient; B, Linear coefficient.

Table 3. Linear regression parameters for experimental PA values versus orbital energy of phenoxide and alkoxide ions using the solvent effect.

Orbital/compound group	Methodology	r^2	A	B
HOMO/(phenoxide and alkoxide)	MP2/PCM/6-311G(d,p)	0.78	1367.17	−407.54
	MP2/COSMO/6-311G(d,p)	0.78	1385.78	−337.05
	B3LYP/PCM/6-311G(d,p)	0.75	1954.59	−628.43
	B3LYP/COSMO/6-311G(d,p)	0.74	1670.67	−824.77
HOMO/(phenoxides)	MP2/PCM/6-311G(d,p)	0.96	1418.33	125.67
	MP2/COSMO/6-311G(d,p)	0.96	1488.19	181.67
	B3LYP/PCM/6-311G(d,p)	0.92	1418.83	63.59
	B3LYP/COSMO/6-311G(d,p)	0.83	1345.89	123.76
HOMO/(alkoxides)	MP2/PCM/6-311G(d,p)	0.86	1394.65	−114.71
	MP2/COSMO/6-311G(d,p)	0.85	2112.89	−154.67
	B3LYP/PCM/6-311G(d,p)	0.78	1846.89	−193.41
	B3LYP/COSMO/6-311G(d,p)	0.80	1854.24	−204.15
FERMO/(phenoxide and alkoxide)	MP2/PCM/6-311G(d,p)	0.94	1694.63	−123.65
	MP2/COSMO/6-311G(d,p)	0.89	1967.89	−167.46
	B3LYP/PCM/6-311G(d,p)	0.89	1845.23	−194.35
	B3LYP/COSMO/6-311G(d,p)	0.89	1799.27	−197.48

r^2 (linear correlation); A, Angular coefficient; B, Linear coefficient.

Table 4. Correlation of energy of the MO HOMO-1, HOMO-2 and HOMO-3 with the experimental PA values for the phenoxides.

Methodology	r^2 / HOMO-1	r^2 / HOMO-2	r^2 / HOMO-3
<i>Ab initio</i>			
MP2/6-311G(d,p)	0.84	0.95	0.65
MP2/PCM/6-311G(d,p)	0.94	0.84	0.37
MP2/COSMO/6-311G(d,p)	0.94	0.84	0.37
DFT			
B3LYP/6-311G(d,p)	0.72	0.94	0.37
B3LYP/PCM/6-311G(d,p)	0.73	0.88	0.09
B3LYP/COSMO/6-311G(d,p)	0.69	0.85	0.08

Table 5. Results from the correlation of experimental PA values with the theoretical IP energy obtained using OVGF method.

Orbital	r^2	A	B
Homo	0.98	1642.56	62.20
Homo (-1)	0.98	1696.72	52.04
Homo (-2)	0.97	1320.85	29.43
Homo (-3)	0.86	1328.72	21.69

r^2 (linear correlation); A, Angular coefficient; B, Linear coefficient.

model. Thus, for both groups (alkoxides and phenoxides), it was not possible to rationalise the acid–base behaviour.

The HOMO problem arises from the influence of the aromatic π -electrons, and the solution would be finding a MO that does not have this influence. Thus, the orbital in the 'XY' aromatic ring plan became a natural choice to solve this problem [7]. Moreover, it also fits our orbital choice criterion, because they are common to all of the studied compounds and are mainly located, where the reaction takes place, in the oxygen atom. From this point of view, other concepts of chemical reactivity could be useful to understand reactions that were not driven by HOMO–LUMO properties. Recently, Silva and Ramalho proposed a simple and useful tool to explain this kind of situation (the FERMO concept) [7–9].

Thus, based on the FERMO idea, we expanded the correlations for the other frontier orbitals [HOMO-1, HOMO-2 and HOMO-3 (Table 4)]. Furthermore, in the FERMO concept, the MO composition and shape are taken into account to identify the MO that will actually be involved in a given reaction. A molecule could have as many FERMOs as it has reaction sites and it could be the HOMO or any other frontier MO. Reactions involving donation and acceptance of electrons are related to the MO energies, since electrons are occupying and will occupy a MO and a frontier one, as stated by Fukui. What we have done in this study is to build a criterion to determine the FERMO. In this concept, the FERMO provides the adequate orbital shape and composition to correlate with reactive indexes [7–9].

One should keep in mind that acid–base reactions are localised. Upon analysing the localisation and the composition of the orbitals more deeply, it can be observed that there is a MO with energy quite close to the HOMO energy value and with large oxygen contribution (Table 6). Thus, perhaps that orbital could better describe the acid–base behaviour than the HOMO. Therefore, this special orbital will be called the FERMO, which is localised in the XY plan, while the HOMO is localised in the Z-axis of the aromatic ring, which means that the plan of the aromatic ring is the 'XY plan'.

The HF orbitals found in the methodology MP2/6-311G(d,p) is very similar to the orbitals found in the methodology B3LYP/6-311G(d,p). These similarities also appear in other methodologies too. It is well known that the MO is extremely sensitive to the calculation method, base set, and the solvent effect, as previously described in the literature [7–9]. According to previous works, our findings in this paper indicated that the solvent effect can be rejected for the phenol group due to the higher hydrophobic character conferred by the aromatic ring.

Figure 2 describes the FERMO and HOMO of some selected molecules. It is worth noting that, comparing its form (shape) with the result of the atomic composition presented in Table 6, we observe that the FERMO receives a large contribution from the oxygen atom.

From Figure 2, it is clear that the HOMO is formed mainly by the atomic orbital in the 'Z' axis of the oxygen, while the FERMO has a high contribution of the atomic orbital of oxygen in the 'XY' plan (plan of the aromatic ring) of the hydroxyl group. A direct consequence of the different compositions of these orbitals is the position of their node plans in relation to the plan formed by hydroxyl atoms, where the HOMO presents two node plans in perpendicular orbital and the other coplanar. The FERMO is perpendicular to the plan formed by the aromatic ring. Observing the surface of the HOMO, we understand that it possesses a large contribution from the π system of the aromatic ring. While the FERMO is not under the influence of the π system of the phenoxide compounds, being then a frontier orbital with a high oxygen contribution. In line with that, one question arises: would it indeed be the FERMO of the phenoxides, which governs the chemical reaction of protonation?

In spite of the results obtained for phenol and alcohol conjugated bases as independent groups, they should be considered as only one group, as they have the same acid–base group, the OH/O^- . Having the same acid–base group implies that acid–base reactions will be driven by a MO common to both alkoxide and phenoxide ions. We have just shown that the HOMO is not this common orbital, since its energy cannot describe the acid–base behaviour of alcohols and phenols as a single group. The question now is which MO should be used to unify them into a single group?

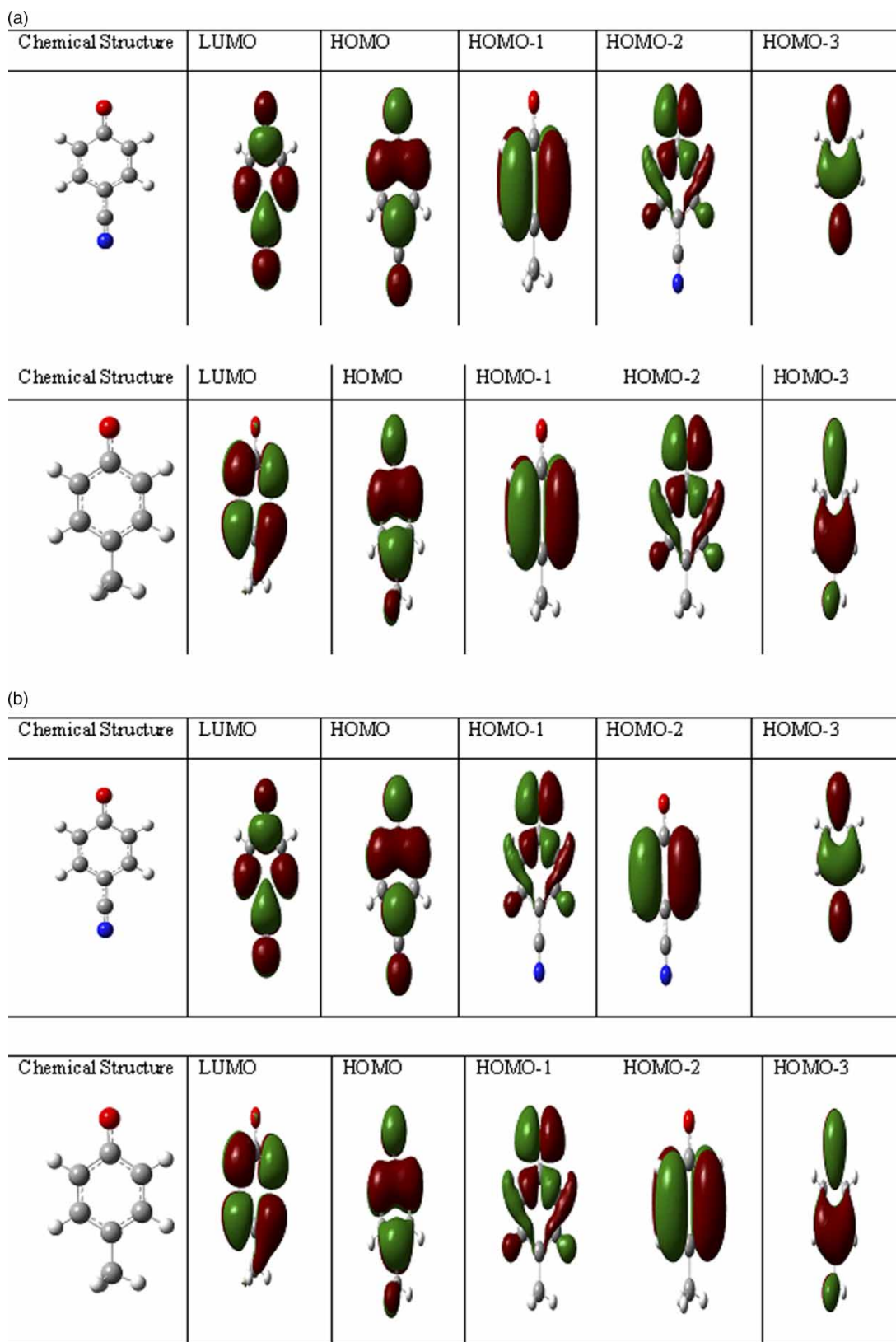


Figure 1. (a) Representation of the MO for the bases for the combined-cyano-phenoxides and *p*-methyl-phenoxides-level HF. (b) Representation of the MO for the bases for the combined-cyano-phenoxides and *p*-methyl-phenoxides-level DFT.

Table 6. Oxygen contribution (%) for the phenoxide and alkoxide ion using the methodology [B3LYP/6-311G(d,p)]. FERMO, in *italics*; HOMO, in **bold**.

Molecules	HOMO	HOMO-1	HOMO-2
1	68.34	69.20	26.31
2	65.40	67.35	30.04
3	58.20	62.43	37.27
4	59.40	61.29	78.02
5	57.30	60.06	62.18
6	53.86	58.60	12.86
7	56.36	63.10	35.40
8	59.08	70.03	49.63
9	62.30	64.28	0.00
10	66.23	0.00	69.36
11	65.01	0.00	72.49
12	68.06	0.00	72.31
13	65.46	0.00	58.40
14	67.64	0.00	57.32
15	64.04	0.00	70.30
16	69.40	0.01	80.94
17	67.47	0.27	68.15
18	66.61	65.26	80.40
19	62.71	0.00	73.40
20	58.27	0.00	69.65
21	62.85	0.81	100.00
22	59.26	0.00	69.46
23	56.74	0.02	64.38

Analysing the composition reported in Table 6 together with the MO shape, we can note that the best orbital to describe the chemical reaction is the FERMO. In line with this expectation, we correlated their energy values with PA values in order to show which is the best orbital to describe the chemical reaction. The graphs of the correlations are reported in Figure 3.

From the reported results of the correlation in Figure 3, we cannot conclude, for the phenoxide group, which orbital is preferentially reacting when analysing only the correlation coefficients; because, interestingly, all the correlation coefficients were good. Therefore, it is necessary to analyse the node plan, the specific forms for each orbital (shape) and the composition to determine which orbital will govern that chemical reaction.

Based on the idea that both phenol and alcohol groups have the hydroxyl group, i.e. effectively, the acid–base group (Figures 4 and 5), it is interesting to note that the FERMO of the phenoxides does not maintain a relation with the resonance effect (Figure 4) because it is perpendicular to the plan of the aromatic ring. In line with that, we can indeed consider that the FERMO could be the orbital responsible for the acid–base reaction in alcohols, aliphatic and aromatic (phenols). This certainly confirms recent findings in the literature [7–9].

We got the worst results for linear correlation with the energy values of the HOMO, the best correlations being those, where the solvent effect is taken into consideration. In line with that, we concluded that the solvent effect for

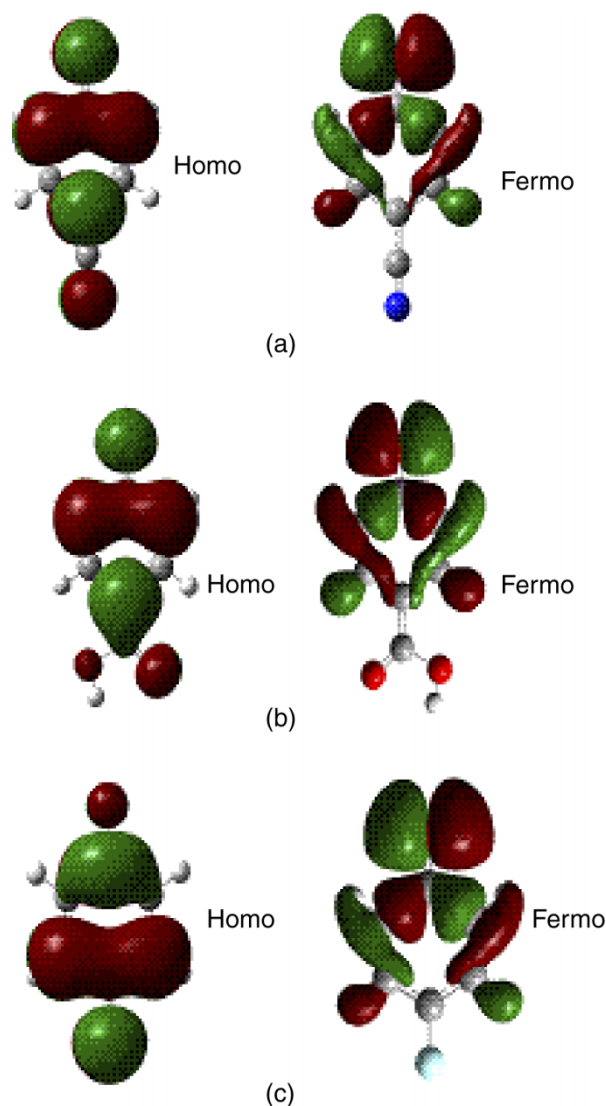


Figure 2. Representation of the MO HOMO and FERMO for the combined bases (a) *p*-cyano-phenoxides, (b) *p*-carboxy-phenoxides and (c) the *p*-fluoro-phenoxides at the HF level. The geometries were obtained at the MP2 level.

the aliphatic alcohols is significant when compared with the phenol group. The orbital correlations of the FERMO with PA of the alcohols are much better as shown in Table 2. Here, the solvent effect was also important and is just a theoretical prediction.

3.2 The orbital that governs the reaction

On the basis of the composition and localisation of the orbital, it is possible to get insights about the orbital that governs the reaction of the phenoxide and alkoxide. The composition of the orbital is an important indicator for discovering the adequate orbital. The MO shape and the atomic composition are very important parameters for analysing FERMO. Since the HOMO problem arises from

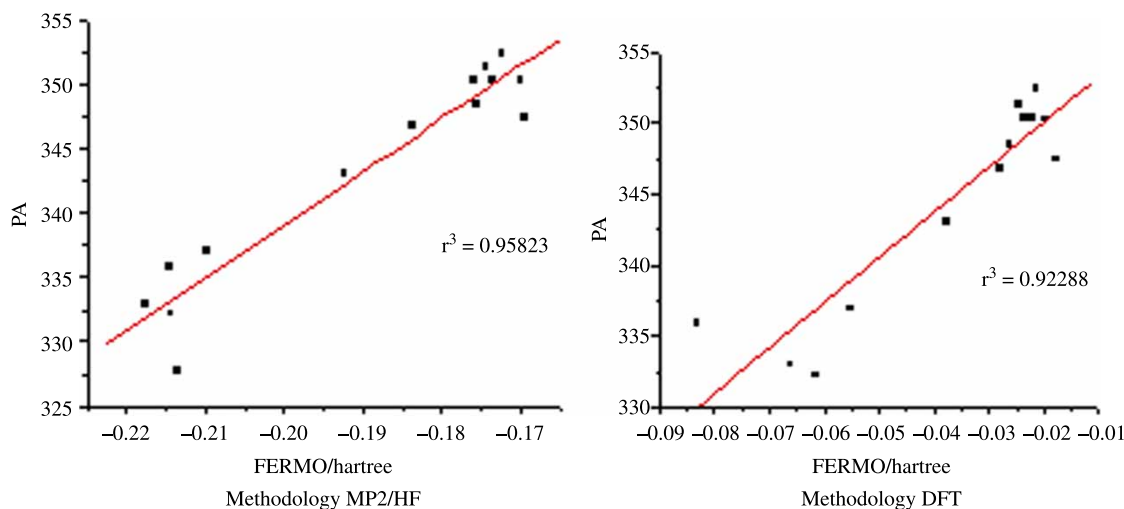


Figure 3. Graphics of the correlation energy of the FERMO with methodology for PA [B3LYP/6-31G(d,p)] and [MP2/6-31G(d,p)] methodology at the DFT and HF levels, respectively. The geometries were obtained at the MP2 level.

the influence of the aromatic π -electrons, the solution would be finding a MO that does not have this influence. Thus, the orbitals in the 'XY' plan became a natural choice to solve this problem [7]. Moreover, they also fit our orbital choice criterion, because they are common to all

the studied compounds and are mainly located, where the reaction takes place, at the oxygen atom.

It is well known that a reaction is governed by a frontier orbital, which is not necessarily a HOMO or LUMO. From this point of view, other concepts of chemical reactivity could be useful to understand the

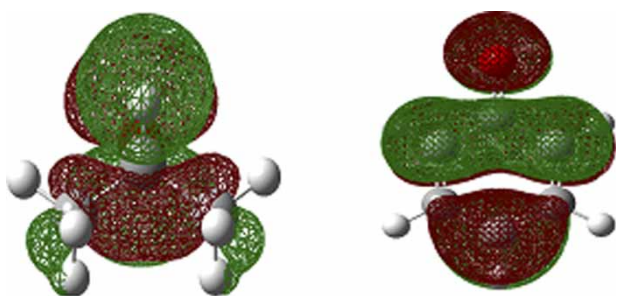


Figure 4. Comparison of the orbital HOMOs for molecules of isopropoxide phenoxides.

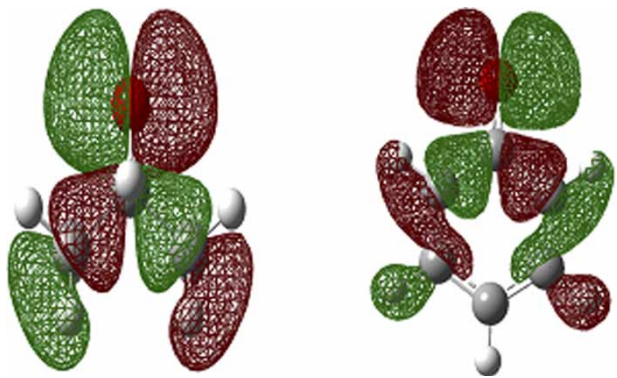


Figure 5. Comparison of the FERMO for molecules of isopropoxide phenoxides.

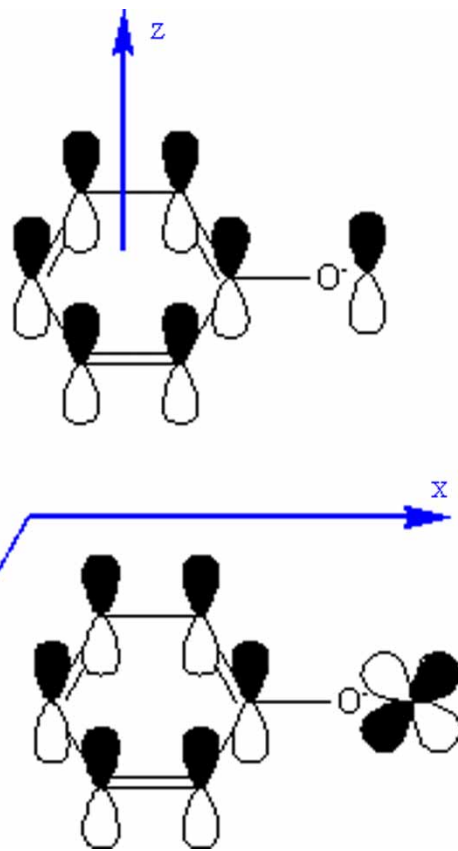


Figure 6. Molecular alignment of the HOMO in the Z-axis and FERMO in the Z-axis for the phenoxides.

acidity of alcohols and phenols. With the analyses performed in this work, it is possible to identify the FERMO for acid–base chemical reactions. In fact, many chemical reactions can be explained using the HOMO–LUMO arguments, however, there are many which cannot [7–9], which could easily be understood with the application of the FERMO concept. An important aspect is that the FERMO concept can be applied at the HF, post-HF or DFT level. This means that either the HF or KS orbitals lead to the same conclusions on the chemical reactivity. This again brings us to the discussion of the validity of the interpretation of the KS orbitals. Thus, we conclude that the FERMO concept embraces well the HOMO–LUMO argument and its exceptions.

3.3 The FERMO idea and the effect of resonance

From our theoretical results and correlation coefficients between orbital energy values and PA, it was not possible to identify, with precision, the FERMO for that reaction in the phenol group. Therefore, it became necessary to analyse the forms (shape) and the atomic composition of the orbital. Nevertheless, for the aliphatic alcohol group, the FERMO was easily identified mainly by the MP2/6-311G(d,p) and B3LYP/6-311G(d,p) methodologies, where the correlation coefficients had shown a great variation between the HOMO and the FERMO. Another question that appears at this moment is: what is the difference between the two compound groups? Why was the FERMO easily identified for one and not the other? To answer such a question, the energy differences (ΔE) between the HOMO and the FERMO were analysed. The results are reported in Table 7.

In order to get more accurate values for the orbital energies, we calculated IP with the OVGf method [28,29]. From Table 5, with the variation of the IP energy, we observe a large energy difference between the MO FERMO and the HOMO for the phenol group, while for the aliphatic alcohol group the energy variation was much smaller. This fact is curious, because the two compound groups present the same types of orbital (Figure 2). However, turning our attention to the phenol group, we can note that the HOMO has large influence from the π -system and this leads to the increase in energy. In fact, the alignment between the ‘p’ carbon orbital of the aromatic ring and the Pz atomic orbital of oxygen leads to strong interaction energy.

In the literature, a good correlation between the theoretical and experimental values for 10–23 molecules is observed. However, in the present work, we tried to understand the interrelationships among the acid–base behaviour of aliphatic alcohols and *para*-substituted phenols. Thus, it must be noticed that the aliphatic alcohol group (alkoxides) was not studied in combination with phenols. In fact, to our knowledge, the understanding of the substituent effect on the acidity of both alcohol groups (phenol and aliphatic) have not been investigated so far.

Table 7. Variation (ΔE) between the HOMO and the FERMO energies (Hartrees).

Molecule	E_{HOMO}	E_{FERMO}	ΔE
1	–	– 1.721	–
2	– 2.150	– 2.259	0.109
3	– 2.271	– 2.326	0.055
4	– 2.276	– 2.387	0.111
5	– 2.223	– 2.288	0.065
6	– 2.51	– 2.620	0.120
7	– 2.556	– 2.694	0.138
8	– 2.467	– 2.541	0.074
9	– 3.454	– 3.742	0.288
10	– 1.942	– 4.556	2.614
11	– 1.787	– 4.704	2.917
12	– 2.150	– 4.756	2.606
13	– 1.827	– 4.497	2.670
14	– 1.999	– 4.468	2.469
15	– 2.368	– 4.687	2.319
16	– 2.103	– 4.642	2.539
17	– 2.210	– 4.946	2.736
18	– 2.646	– 5.230	2.584
19	– 3.005	– 5.481	2.476
20	– 2.971	– 5.388	2.417
21	– 3.048	– 5.575	2.527
22	– 3.557	– 6.041	2.484
23	– 3.557	– 6.041	2.484

Using the HOMO–LUMO properties, phenoxide and alkoxide ions together provided very poor linear models. However, it is interesting to note that both groups (aliphatic and aromatic alcohols) have the same reactivity group, which is the hydroxyl group. Therefore, we could expect a similar behaviour for the acid–base chemical reaction. Our data reinforce this idea, because the alkoxides and phenoxides show the same FERMO.

However, it is also important to mention other interesting emerging methods used to better understand the role of the orbital in chemical reactions. For instance, the reactive bond orbital approach is an interesting perspective on the use of localised orbitals [30]. The Triadic analysis introduced by Professors R. Vianello and Z.B. Maksic provides a global description of the acidity behaviour. This methodology has been employed on different occasions [31–33].

It is important to note that the PA values are very useful parameters to monitor the chemical reactivity of species in gas phase. It should be kept in mind, however, that there are limitations in the PA calculation and a variety of high-level *ab initio* methods from the G3 family, including G3//B3LYP [34], G3(MP2) [35], G3(MP2)//B3LYP [34] and also the complete basis set (CBS) method, CBSQB3 [36,37], have been used.

It is well known that in the MO theory, the electrons in a molecule are in the delocalised orbitals generated from linear combination of atomic orbitals. Nevertheless, sometimes these delocalised orbitals are quite diffuse, leading to a difficult rationalisation of the chemical

reactivity. In contrast, some chemical reactions, such as acid–base reaction, take place in specific regions of the molecule. Therefore, currently, the need for inexpensive computational techniques capable of reliably contributing to the prediction of the chemical reactivity based on chemical intuition is emerging. We believe that the FERMO idea could, in combination with other approaches, offer contributions in this sense.

Thus, we may notice that the FERMO idea is to use the MO calculations with a valence bond theory (VB) interpretation. In MO theory, the electrons in a molecule occupy delocalised orbitals made from linear combination of atomic orbitals. However, it should be kept in mind that the VB approaches are quite useful in analysing enzymatic reactivity [38,39], photochemistry [40–43], chemical dynamics [40] and theories of conductivity, where the localised representation seemed indispensable.

In fact, it is well known that the VB methods allow the generation of new ideas on chemical bonding. Recently, there has been an intense surge of concepts related to localised representation, e.g. multiple bonding between transition metals [44,45] and the development of natural resonance theory [46].

4. Conclusions

In this paper, we have demonstrated that the FERMO concept can be applied to understand the acid–base behaviour combining two important organic groups (alkoxides and phenoxides) in a very simple and chemically intuitive way. In this way, it is not necessary to introduce correction terms, in order to obtain reactivity properties of compounds in solution. In principle, the FERMO can be applied to understand reactions that the HOMO–LUMO [47,48] approach did and did not explain, thus making the role of the MO theory in chemistry stronger. However, further and still more accurate theoretical calculations in order to verify this hypothesis are necessities and now are in progress.

Acknowledgements

We are grateful to FAPEMIG, CAPES and CNPq Brazilian agencies for funding part of this work and CENAPAD-SP for the computational facilities.

References

- [1] W.J. Here, L. Random, P.P. Schleyer, and J.A. People, *Ab Initio Molecular Orbital Theory*, Wiley, New York, NY, 2006.
- [2] R. Vianello and Z.B. Makisić, *Triadic analysis of substituent effects – gas-phase acidity of para-substituted phenols*, *Tetrahedron* 62 (2006), pp. 3402–3410.
- [3] O. Pytela, M. Otyepka, J. Kulháněk, E. Otyepková, and T. Nevěšná, *Correlation of dissociation constants of 2- and 2,6-substituted anilines in water by methods based on the similarity principle and quantum-chemistry calculations*, *J. Phys. Chem. A* 107 (2003), pp. 11489–11498.
- [4] C. Gruber and V. Buss, *Quantum mechanically calculated properties for the development of quantitative structure–activity–relationships (QSARS) – pK_a values of phenol and aromatic and aliphatic carboxylic-acids*, *Chemosphere* 19 (1989), pp. 15–24.
- [5] M.J. Citra, *Estimating the pK_a of phenols, carboxylic acids and alcohols from semi-empirical quantum chemical methods*, *Chemosphere* 38 (1999), pp. 191–197.
- [6] E. Sorino, S. Cerdán, and P. Ballesteros, *Computational determination of pK_a values. A comparison of different theoretical approaches and a novel procedure*, *J. Mol. Struct. (Theochem)* 684 (2004), pp. 121–130.
- [7] R.R. Da Silva, T.C. Ramalho, J.M. Santos, and J.D. Figueroa-Villar, *On the limits of highest-occupied molecular orbital driven reactions: the frontier effective-for-reaction molecular orbital concept*, *J. Phys. Chem. A* 110 (2006), pp. 1031–1045.
- [8] R.R. Da Silva, T.C. Ramalho, J.M. Santos, and J.D. Figueroa-Villar, *Concerning the FERMO concept and Pearson's hard and soft acid–base principle*, *J. Braz. Chem. Soc.* 17 (2006), pp. 223–229.
- [9] R.R. Da Silva, T.C. Ramalho, and J.M. Santos, *Reply to 'comment on the paper' on the limits of highest-occupied molecular orbital driven reactions: the frontier effective-for-reaction molecular orbital concept*, *J. Phys. Chem. A* 110 (2006), pp. 10652–10653.
- [10] K. Fukui, T. Yonezawa, and H.J. Shingu, *A molecular orbital theory of reactivity in aromatic hydrocarbons*, *Chem. Phys.* 20 (1952), pp. 722–753.
- [11] R. Hoffmann and R. Woodward, *Orbital symmetries and endo–exo relationships in concerted cycloaddition reactions*, *J. Am. Chem. Soc.* 87 (1965), pp. 395–401.
- [12] W. Kohn, A.D. Becke, and R.G. Parr, *Density functional theory of electronic structure*, *J. Phys. Chem.* 100 (1996), pp. 12974–12982.
- [13] P. Politzer and F. Abu-Awwad, *A comparative analysis of Hartree–Fock and Kohn–Sham orbital energies*, *Theor. Chem. Acc.* 99 (1998), pp. 83–91.
- [14] M.J. Frisch, G.W. Trucks, H.B. Schlegel, and J.A. Pople, *Gaussian 98 (Revision A.11)*, Gaussian, Pittsburgh, 2001.
- [15] A.D. Becke, *Density-functional thermochemistry 3. The role of exact exchange*, *J. Chem. Phys.* 98 (1993), pp. 5648–5653.
- [16] C. Lee, W. Yang, and R.G. Parr, *Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density*, *Phys. Rev. B* 37 (1988), pp. 785–794.
- [17] S. Miertus, E. Scrocco, and J. Tomasi, *Electrostatic interaction of a solute with a continuum – a direct utilization of ab initio molecular potentials for the prevision of solvents effects*, *J. Chem. Phys.* 55 (1981), pp. 117–124.
- [18] S. Miertus, *Approximate evaluations of the electrostatic free-energy changes in solution processes*, *Chem. Phys.* 65 (1982), pp. 239–247.
- [19] M. Cossi, V. Barone, R. Cammi, and J. Tomasi, *Ab initio study of solvated molecules: a new implementation of the polarizable continuum model*, *Chem. Phys. Lett.* 225 (1996), pp. 327–335.
- [20] A. Klamt and G. Schuurmann, *COSMO – a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient*, *J. Chem. Soc., Perkins Trans. 2* (1993), pp. 799–810.
- [21] V. Barone and M. Cossi, *Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model*, *J. Phys. Chem. A* 102 (1998), pp. 1995–2004.
- [22] J.V. Ortiz, *Electron-binding energies of anionic alkali-metal atoms from partial 4th-order electron propagator theory calculations*, *J. Chem. Phys.* 89 (1988), pp. 6348–6352.
- [23] W. von Niessen, J. Schirmer, and L.S. Cederbaum, *Computational methods for the one-particle Green-function*, *Comp. Phys. Rep.* 1 (1984), pp. 57–125.
- [24] A.A. Ahmed, M. Julliard, F. Chanon, M. Chanon, F. Gracian, and G. Pfister-Guillouzo, *Photoelectron spectroscopy of quinoline derivatives. Correlation of experimental ionization potentials with calculated molecular energies*, *Spectrochim. Acta, Part A: Mol. Biomol. Spectrosc.* 53 (1997), pp. 335–343.
- [25] T.C. Ramalho, R.B. de Alencastro, M.A. La-Scalea, and J.D. Figueroa-Villar, *Theoretical evaluation of adiabatic and vertical electron affinity of some radiosensitizers in solution using FEP, ab initio and DFT methods*, *Biop. Chem.* 110 (2004), pp. 267–279.

- [26] T.C. Ramalho, E.F.F. da Cunha, and R.B. De Alencastro, *Theoretical study of adiabatic and vertical electron affinity of radiosensitizers in solution part 2: analogues of tirapazamine*, J. Theor. Comp. Chem. 3 (2004), pp. 1–13.
- [27] T.C. Ramalho, E.F.F. da Cunha, and R.B. de Alencastro, *A density functional study on the complexation of ethambutol with divalent cations*, J. Mol. Struct. (Theochem) 676 (2004), pp. 149–154.
- [28] L.S. Cerdebaum and W. Domcke, *Theoretical aspects of ionization potentials and photoelectron spectroscopy: a Green's function approach*, Adv. Chem. Phys. 36 (1977), pp. 206–211.
- [29] R. Flores-Moreno, J. Melin, and J.V. Ortiz, *Efficient evaluation of analytic Fukui functions*, J. Chem. Phys. 129 (2008), pp. 224105–224111.
- [30] H. Hirao, *Reactive bond orbitals: A localized resonance–structure approach to charge transfer*, Chem. Phys. Lett. 443 (2007), pp. 141–146.
- [31] Z.B. Maksic and R. Vianello, *Quest for the origin of basicity: Initial vs final state effect in neutral nitrogen bases*, J. Phys. Chem. A 106 (2002), pp. 419–430.
- [32] Z. Maksic and R. Vianello, *Anionic versus neutral protonation-an ab initio analysis with a triadic formula*, ChemPhysChem 3 (2002), pp. 696–700.
- [33] R. Vianello and Z.B. Maksic, *Gas-phase acidity of para-substituted benzoic acids – a triadic analysis of substituent effects*, J. Phys. Org. Chem. 18 (2005), pp. 699–705.
- [34] J.W. Halley, Y. Duan, and L.A. Curtiss, *Lithium perchlorate ion pairing in a model of amorphous polyethylene oxide*, J. Chem. Phys. 111 (1999), pp. 3302–3308.
- [35] L.A. Curtiss, P.C. Redfern, and K. Raghavachari, *Gaussian-3 theory using reduced Moller–Plesset order*, J. Chem. Phys. 110 (1999), pp. 4703–4709.
- [36] J.A. Montgomery, M.J. Frisch, and J.W. Ochterski, *A complete basis set model chemistry. VI. Use of density functional geometries and frequencies*, J. Chem. Phys. 110 (1999), pp. 2822–2827.
- [37] T.L.C. Martins, T.C. Ramalho, J.D. Figueroa-Villar, A.F.C. Flores, and C.M.P. Pereira, *Theoretical and experimental C-13 and N-15 NMR investigation of guanyldiazones in solution*, Mag. Reson. Chem. 41 (2003), pp. 983–988.
- [38] R. Cimiraglia, J.P. Malrieu, M. Persco, and F. Spiegelman, *Quasi-adiabatic states and dynamical couplings from ab initio CI calculations-a new proposal*, J. Phys. B 18 (1985), pp. 3073–3381.
- [39] H. Nakamura and D.G. Truhlar, *The direct calculation of diabatic states based on configurational uniformity*, J. Chem. Phys. 115 (2001), pp. 10353–10358.
- [40] D.G. Truhlar, *Valence bond theory for chemical dynamics*, J. Comp. Chem. 28 (2007), pp. 73–85.
- [41] A.Th. van der Lugt and L.J. Oosterhoff, *Symmetry control and photoinduced reactions*, J. Am. Chem. Soc. 91 (1969), pp. 6042–6051.
- [42] G.J. Atchity and K. Ruedenberg, *Determination of diabatic states through enforcement of configurational uniformity*, Theor. Chem. Acc. 97 (1997), pp. 47–55.
- [43] M.A. Robb, M. Garavelli, M. Olivucci, and F. Bernardi, *A computational strategy for organic photochemistry*, Rev. Comp. Chem. 15 (2000), pp. 87–97.
- [44] M. Brynda, L. Gagliardi, P.-O. Widmark, P. P. Power, and B.O. Roos, *A quantum chemical study of the quintuple bond between two chromium centers in [PhCrCrPh]: Trans-bent versus linear geometry*, Angew. Chem., Int. Ed. 45 (2006), pp. 3804–3810.
- [45] F. Weinhold and C. Landis, *High bond orders in metal–metal bonding*, Science 316 (2007), pp. 61–66.
- [46] E.D. Glendening and F. Weinhold, *Natural resonance theory: I. General formalism*, J. Comp. Chem. 19 (1998), pp. 593–610.
- [47] T.C. Ramalho, E.F.F. da Cunha, and F.C. Peixoto, *Computational NMR investigation of radiosensitizer in solution*, J. Theor. Comp. Chem. 7 (2008), pp. 37–44.
- [48] E.F.F. da Cunha, R.B. de Alencastro, and T.C. Ramalho, *Theoretical study of adiabatic and vertical electron affinity of radiosensitizers in solution. Part 2: analogues of tirapazamine*, J. Theor. Comp. Chem. 3 (2004), pp. 1–2.