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# Proposal of a Simple and Effective Local Reactivity Descriptor through a Topological Analysis of an Orbital-Weighted Fukui Function

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The prediction of reactivity is one of the long-standing objectives of chemistry, contributing to enforce the link between theory and experiment. In particular, the regioselectivity of aromatic molecules has motivated the proposal of different reactivity descriptors based on foundational theories, like Frontier Molecular Orbital (FMO) theory and density functional theory, to predict and rationalize such regioselectivity. This article examines cases where reactivity descriptors, based on FMO theories, are known to have failed, specifically on electrophilic

aromatic substitution reactions, through a simple but effective new reactivity model: the Orbital-weighted Fukui function ( $f_w^-(r)$ ) and its topological analysis. Interestingly, this descriptor proves to be effective in adequately predicting regioselectivities where other approximations failed. © 2017 Wiley Periodicals, Inc.

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## Introduction

In chemistry, different concepts and methods have been proposed for predicting qualitatively and semi-quantitatively how and where a reaction will take place. Among them, perhaps the most popular theoretical approximations are those based on the frontier molecular orbital (FMO) theory. Starting from the pioneering and visionary works of Kenichi Fukui<sup>[1]</sup> and Roald Hoffman<sup>[2,3]</sup> that showed that shapes (Fukui) and symmetries (Hoffman), of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), could successfully be used to indicate whether a reaction will occur or not. Most of this theory has been rationalized from the density functional theory (DFT) version of the electronic structure of the molecules,<sup>[4–8]</sup> which in principle avoids the primary limitation of the FMO approach by incorporating the effects of electron correlation and orbital relaxation.

In the DFT of chemical reactivity, the response of the system to a variation in the number of electrons and/or the external potential is analyzed as a perturbation series, where one of the main ingredients is the Fukui function, defined as the response of the chemical potential under a variation of the external potential at a fixed electron number

$$f(\vec{r}) = \left( \frac{\delta\mu}{\delta v(\vec{r})} \right)_N \quad (1)$$

As the chemical potential is the derivative of the energy with respect to the electron number, the Fukui function is a second derivative and, according to the Maxwell relationships, it can be expressed as follows:

$$f(\vec{r}) = \left( \frac{\partial \rho(\vec{r})}{\partial N} \right)_{v(\vec{r})} \quad (2)$$

where  $\rho(\vec{r})$  is the electron density. The last derivative evidences the discontinuity of the Fukui function at an integer number of electrons and, therefore, the derivative should be calculated from the left or right side of  $N$ . In this work, we will be interested in the case of an electron donor system, which corresponds to taking the derivative from the left side. Thus, in a finite difference approximation, the Fukui function will be calculated as

$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \quad (3)$$

However, many times the frozen orbital approximation<sup>[9,10]</sup> is used to get a simple expression for the Fukui function:

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$$f^-(\vec{r}) = |\phi_{\text{HOMO}}(\vec{r})|^2 \quad (4)$$

which is the square of the HOMO, clarifying the correspondence with the frontier orbital theory. Consequently, according to the Fukui function, the molecule should be more reactive where this function has the maximum values.<sup>[11]</sup>

Over time, several cases where FMO fails to predict reactivity, for example, electrophilic aromatic substitution reactions have been reported.<sup>[12–15]</sup> It has been recognized that the reactivity of these systems is not determined only by the HOMO or LUMO but one or more different orbitals take place in the response to the reagent (under perturbation).<sup>[16–18]</sup> This could be rationalized within the orbital perturbation theory. It is expected that orbitals couple differently to a given perturbation. An extreme case where it is impossible to uncouple the response of the systems to the particularities (details) of the perturbation is when the ground state of the system (or its vertical ions) is degenerate, or even pseudodegenerate.<sup>[19–21]</sup> Therefore, the correct way of introducing the contribution of non-frontier orbitals to the local reactivity is employing perturbation of (pseudo) degenerate states. However, its implementation is not necessarily easy.

Considering that the local reactivity description is a qualitative matter, the key aspect to be drawn from a local reactivity analysis is the relative intensity of the response more than its accurate value. Therefore, there is a need to develop easy-to-compute descriptors that include the contribution of “inner” orbitals. It is important to remark that these descriptors should contain the key features of the exact theory. The main feature is the fact that the deeper in energy an orbital is, the less relevant is its contribution to chemical reactivity. Descriptors with this characteristic have proved to be useful in describing the reactivity of solids and surfaces.<sup>[22–26]</sup> Geerlings and coworkers have also proposed a descriptor where the contribution of an inner orbital is weighted by the amplitude of each orbital rather than by its energy.<sup>[27]</sup>

Following the constructing criteria that inner orbitals contribute in some measure to the local reactivity, we introduce the Orbital-weighted Fukui Function,  $f_w(\vec{r})$ , and its topological analysis. Consequently, the main objective of this work is to extend our previous studies on the topological analysis of the Fukui function<sup>[28,29]</sup> with the aim of providing a set of theoretical tools to study reactivity of clusters and molecules.<sup>[30–32]</sup> The performance of this approximation is evaluated in a series of mono substituted benzene derivatives classified as *ortho/para*- and *meta-directing* (according to the nature of their substituents and empirical resonance rules). Additionally, we have included the isoquinoline, the 10-hydroxy-10,9-borazarophenanthrene and the 10-methyl-10,9-borazarophenanthrene, which were identified by Dewar as problematic molecules for FMO-based approximations,<sup>[12]</sup> and have been recently studied by Ayers et al. through the general-purpose reactivity descriptor.<sup>[33]</sup>

## Local Reactivity Descriptors through Topological Analysis

The topological analysis of molecular space has been historically applied in chemistry to analyze both, the electron density (AIM)<sup>[34]</sup> and the electron localization function (ELF)<sup>[35,36]</sup>

through the gradient field analysis of these two local functions. Some years ago, we proposed the use of this mathematically well-established method (gradient field analysis) to characterize the Fukui function.<sup>[28,29,37]</sup> This proposal is based on the fact that gradient field analysis can be applied to any well-defined local function, such as the electron density and derived functions. Although the ELF and the electrostatic potential are classic examples of these derived functions, the Fukui function also fulfills this condition. One clear deficiency of the frozen orbital approximation is that it eliminates the possibility of having negative values on the Fukui function.<sup>[38]</sup> The presence of these negative values has been recently proven algebraically in the works on the so-called Fukui matrix.<sup>[39]</sup> However, we have shown that, except for special cases, values condensed to atoms (according to the topological analysis) through frozen orbital approximation provides similar results as those obtained by finite difference approximation.<sup>[28,29,37]</sup> It is important to note that the topological analysis of the Fukui function does not guarantee the existence of an attractor at the nuclei position or that the number of basins coincides with the number of atoms. Then, to assign properties to atoms all the basins of the Fukui function that lies in the neighborhood of an atom where considered to “belong” to it. It is an empirical observation that attractors of the Fukui function are very close to the nuclear positions, or, at least, that was the case of all systems studied here. Moreover, condensation based on topological analysis avoids some ambiguities related with other condensation schemes, such as basis set dependence.<sup>[37,40,41]</sup> In this work, we will use the same procedure (topological analysis) to characterize an empirically-defined orbital-weighted Fukui function ( $f_w(\vec{r})$ ).

On purely practical grounds, the topological analysis of a given function ( $g(\vec{r})$ ) is used here to partition the molecular space into  $\Omega_k$  basins of chemical significance. Then, these functions are integrated into their basins according to:

$$g_k = \int_{\Omega_k} g(\vec{r}) d\vec{r} \quad (5)$$

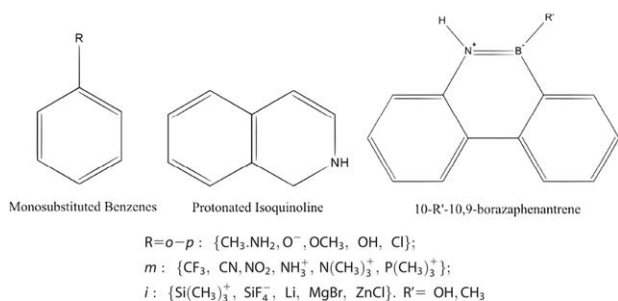
This analysis was applied to three functions. Two of them are approximations of the Fukui function, eqs. (3) and (4) and the third one is the orbital-weighted approximation,  $f_w^-(\vec{r})$ , whose analysis is the main objective of this work

$$f_w^-(\vec{r}) = \sum_i^{\text{HOMO}} w_i \rho_i(\vec{r}) \quad (6)$$

where  $w_i$  are the weighting factors and  $\rho_i(\vec{r})$  is the square of the  $i$ th molecular orbital,  $i$  runs over a set of MOs. The  $w_i$  are defined according to the Gaussian ansatz as follows:

$$w_i = \frac{\exp\left[-\left(\frac{\mu - \varepsilon_i}{\Delta}\right)^2\right]}{\sum_i^{\text{HOMO}} \exp\left[-\left(\frac{\mu - \varepsilon_i}{\Delta}\right)^2\right]} \quad (7)$$

where  $\mu$  is the chemical potential;  $\varepsilon_i$  is the energy of each orbital and  $\Delta$  is the width of the Gaussian function, which



Scheme 1. Schematic representation of the studied systems.

determines the energy range for orbitals that make a substantial contribution to the reactivity. By referencing to perturbation theory,  $\Delta$  could be interpreted as a measure of the strength of the coupling of the system with a perturbing reagent. A Gaussian model has been chosen, as a matter of convenience, because the numbers of orbitals and its contribution to reactivity can be controlled with a single parameter,  $\Delta$ . However, an extra support to this model is the empirical evidence that, in Møller–Plesset perturbation theory, within a given order of perturbation, the correction to the energy converge exponentially with the difference of energy between the orbitals and the chemical potential. We have tested different values of  $\Delta$  for the studied systems, shown in Tables S9 (in the Supporting Information), finding that a value of 0.1 a.u. is adequate to predict their regioselectivity. It is important to note that we have also analyzed a version of the superdelocalizability index<sup>[42–47]</sup> (which would be the classic orbital-weighted Fukui function) where the weighting factors are inversely proportional to the occupied orbital energy (for electrophilic superdelocalizability). The used function, as well as the results, is shown in Supporting Information Eqs. S1–S3 and Tables S1–S4, respectively. The use of these weighted factors does not substantially improve the regioselectivity prediction in the set of the analyzed systems, which justifies our proposal (of using adjusted  $\Delta$ s according to a Gaussian's distribution).

Condensed values of  $f^-(\vec{r})$  [eq. (3) and (4)] and  $f_w^-(\vec{r})$  [eq. (6)] were obtained according to their topological analysis [eq. (1)], and the results are labeled as  $M_I$ ,  $M_{II}$ , and  $M_{III}$  (Model I, Model II, and Model III) throughout the rest of the work, respectively.

## Computational Details

Geometry optimizations and electronic structure calculations of the systems were performed with the Gaussian 09 package of programs using DFT with the hybrid functional PBE0<sup>[48]</sup> and the 6-311g(d,p) basis set.<sup>[49]</sup> Next, we performed harmonic frequency calculations to verify that all molecules are true minima of the potential energy surface with all frequencies real. Finally, the topological analysis of  $f^-(\vec{r})$  [eq. (3) and (4)] and  $f_w^-(\vec{r})$  [eq. (6)], to obtain the condensed values was done. These calculations were carried out using the wave function obtained from the Gaussian calculation along with the Multiwfn 3.3.6 software.<sup>[50]</sup> This procedure is easy to perform

using a *pipeline* (TAFF),<sup>[51]</sup> which has been written as part of this work. Details are found in the supporting material (manual: installation, execution and examples).

## Results and Discussion

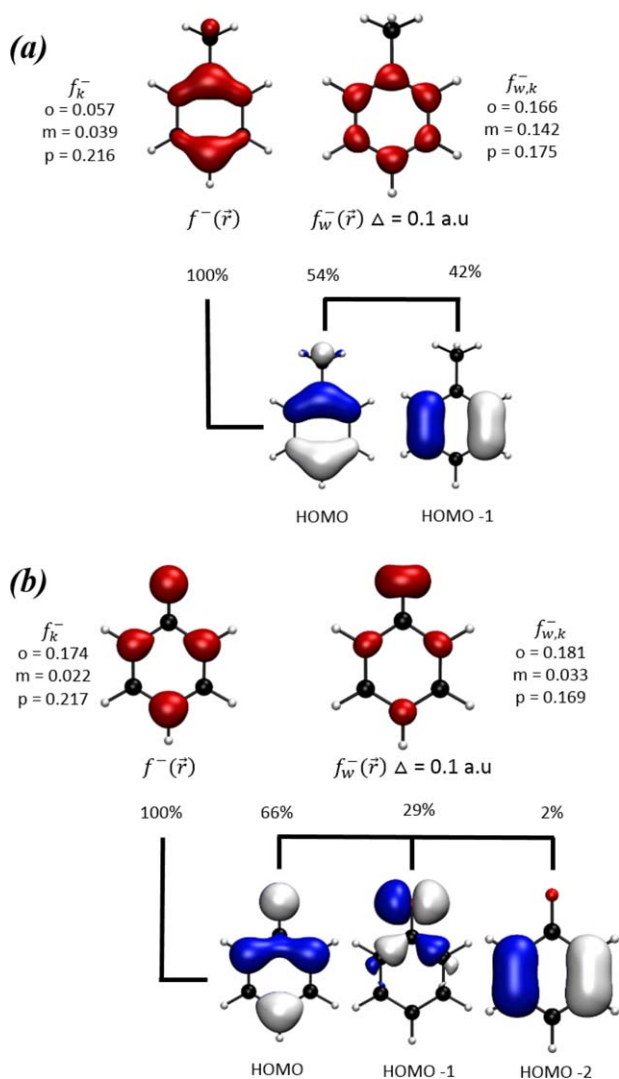
Scheme 1 depicts the twenty systems considered in the present work: a set of monosubstituted benzenes, the isoquinoline, the 10-hydroxy-10,9-borazarophenanthrene, and the 10-methyl-10,9-borazarophenanthrene. The optimized geometries of all these species are shown in Table-S5 of the Supporting Information. The local reactivity is analyzed according to the condensed values of the Fukui function,  $M_I$  (frozen core approximation) and  $M_{II}$  (finite differences), and the orbital weighted reactivity descriptor ( $M_{III}$ ). The condensed values were obtained by an integration of these functions into their basins (obtained from topological analysis) and have been compiled in Tables S6 to S8 of the Supporting Information.

The series of monosubstituted benzenes could be subclassified into three groups according to their regioselectivity (experimental evidence)<sup>[14,15]</sup>: *ortho-para* (*o-p*) directing (substituted with electron-releasing groups, ERGs), *meta* (*m*-) directing (substituted with electron withdrawing groups) and *ipso* (*i*-) directing (where the substituent is the leaving group). Consequently, it is expected that a good theoretical reactivity descriptor can adequately account for this regioselectivity.

In Table 1, a summary of the results obtained for the monosubstituted benzenes is reported; the numerical results are reported in Supporting Information Tables S6 to S8. We wrote a check (✓) when a certain descriptor predicts the expected regioselectivity, and a (X) mark when otherwise. As we can appreciate in the Table, all the evaluated descriptors adequately predict the regioselectivity of the *o-p*-directing systems. The effectiveness of the classical Fukui function approximations ( $M_I$  and  $M_{II}$ ) in these systems has also been discussed in earlier works.<sup>[28,29]</sup> For the *m*-directing systems,  $M_I$  and  $M_{II}$  fail in several cases (five of the six studied systems). This limitation has

Table 1. Summary of the regioselectivity prediction on monosubstituted benzenes according to the local reactivity descriptors ( $f^-(\vec{r})$  and  $f_w^-(\vec{r})$ ).

| R   | Position-directing | $M_I$ | $M_{II}$ | $M_{III}$ |
|---|--------------------|-------|----------|-----------|
| -CH <sub>3</sub>                                | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -NH <sub>2</sub>                                | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -O <sup>-</sup>                                 | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -OCH <sub>3</sub>                               | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -OH   | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -Cl   | <i>o-p</i>         | ✓     | ✓        | ✓         |
| -CF <sub>3</sub>                                | <i>m</i>           | ✓     | X        | ✓         |
| -CN   | <i>m</i>           | X     | X        | ✓         |
| -NO <sub>2</sub>                                | <i>m</i>           | X     | ✓        | ✓         |
| -NH <sub>3</sub> <sup>+</sup>                   | <i>m</i>           | X     | X        | ✓         |
| -N(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup>  | <i>m</i>           | X     | X        | ✓         |
| -P(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup>  | <i>m</i>           | X     | X        | ✓         |
| -Si(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup> | <i>i</i>           | ✓     | X        | ✓         |
| -SiF <sub>4</sub> <sup>+</sup>                  | <i>i</i>           | ✓     | ✓        | ✓         |
| -Li   | <i>i</i>           | ✓     | ✓        | ✓         |
| -MgBr   | <i>i</i>           | ✓     | ✓        | ✓         |
| -ZnCl   | <i>i</i>           | X     | X        | ✓         |



**Figure 1.** Isosurfaces of  $f^- (\vec{r})$  and  $f_w^- (\vec{r})$  ( $= 0.1 \text{ a.u.}$ ), their condensed values (according to the topological analysis) and the relevant orbital contribution for a) toluene and b) phenoxide. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

also been discussed in previous works.<sup>[18,52]</sup> Interestingly,  $M_{III}$  correctly predicts the regioselectivity of the *m*-directing systems, supporting the proposal that inner orbitals should necessarily be considered to adequately perform that task.

In the case of last subclass, consisting of the *i*-directing systems, the Fukui function fails in one or two systems, when  $M_I$  and  $M_{II}$  approximations are used, respectively. Whereas  $M_{III}$  successfully predicts the most reactive site in all cases. These results unequivocally show that the orbital-weighted model ( $M_{III}$ ), despite being empirically formulated, is an improved reactivity descriptor for regioselectivity prediction of monosubstituted benzenes. However, it is important to note that the quality of the descriptor is only being considered for its capability to adequately predict the order of the reactive centers. Another issue worth mentioning is the fact that a  $\Delta$  value of 0.1 a.u. has been adequate for all systems with the exception of the benzonitrile ( $R = \text{CN}$ ), where it is 0.3. This choice has been arbitrary and its dependency on the analyzed system remains to be studied in more detail.

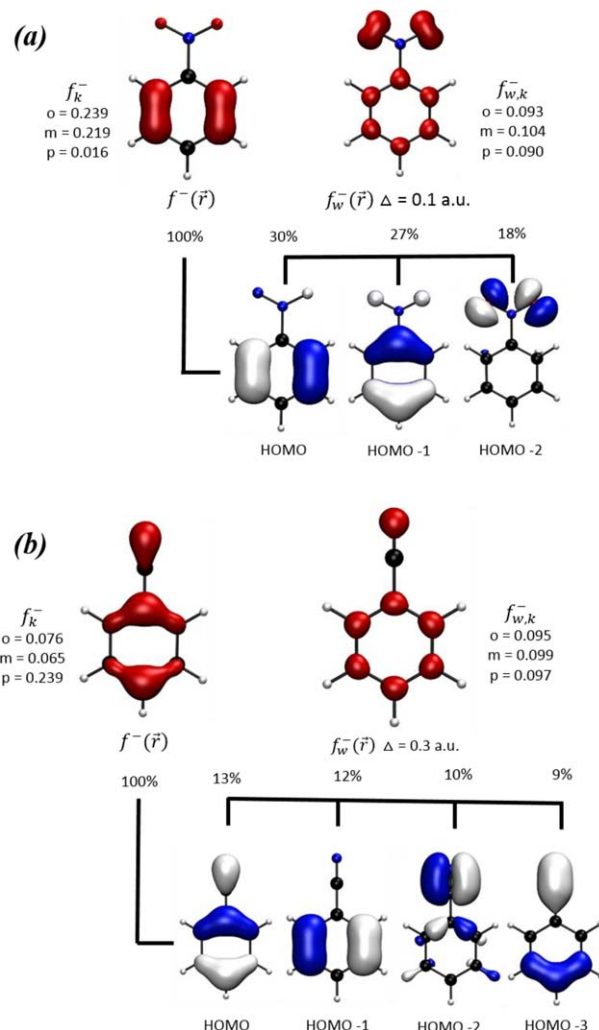
In the next paragraphs, the orbital's contribution to the  $f_w^- (\vec{r})$  function and its influence on the improvement of the regioselectivity prediction will be discussed for some representative systems.

Figures 1–3 show relevant information about both,  $f^- (\vec{r})$  (according to the frozen core approximation) and  $f_w^- (\vec{r})$  functions: isosurfaces of these functions, their condensed values (according to the topological analysis), as well as the relevant orbital contribution to them.

#### *ortho/para*-directing groups

Toluene and phenoxide systems were selected as representative cases of this series for the following reasons: on the one hand, the *para*-position is the most reactive site in the majority of the *o*-*p*-directing systems ( $p > o$ ), being represented by toluene; on the other hand, phenoxide is an exception where the most reactive site is the *ortho*-position ( $o > p$ ).

For the case of toluene,<sup>[53]</sup>  $f_k^-$  adequately predicts its regioselectivity, as it makes for the other *o*-*p*-directing analyzed



**Figure 2.** Isosurfaces of  $f^- (\vec{r})$  and  $f_w^- (\vec{r})$  ( $= 0.1$  and  $0.3 \text{ a.u.}$ ), their condensed values (according to the topological analysis) and the relevant orbital contribution for a) nitrobenzene and b) benzonitrile. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



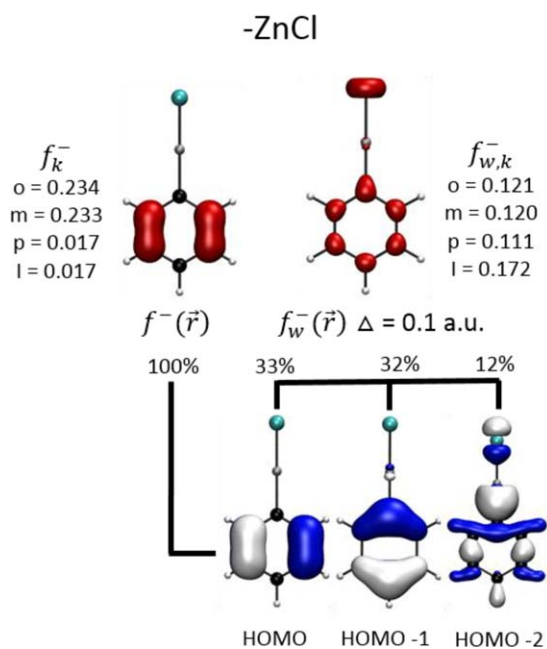


Figure 3. Isosurfaces of  $f_k^-(\vec{r})$  and  $f_{w,k}^-(\vec{r})$  ( $= 0.1 \text{ a.u.}$ ), their condensed values (according to the topological analysis) and the relevant orbital contribution for phenyl zinc chloride. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

systems (*vide supra*). This indicates that the relevant information on the reactivity of *o-p*-directing systems should be contained in the HOMO. However, although  $f_{w,k}^-$  is mainly conformed by HOMO and HOMO-1 (with contributions of 54% and 42%, respectively), the HOMO-1 contribution does not impoverish the regioselectivity prediction of this descriptor.

For the case of the phenoxide<sup>[54]</sup> system, its regioselectivity shows to be a challenge for the assessed reactivity descriptors. Both,  $f_k^-$  and  $f_{w,k}^-$  predict *o-p*-preference. However, only  $f_{w,k}^-$  has been able to indicate the *o*-preference among them. This improvement, over that of  $f_k^-$ , can be explained by inspecting the orbitals' contribution: HOMO and HOMO-1 contribute with 66% and 29%, respectively. The former is distributed over the *o*-position and the oxygen, whereas the latter is mainly distributed over the *o*- and *m*-positions, with the total contribution enhancing the *o*-position. Regardless of the excellent results obtained from  $f_{w,k}^-$ , it is important to note that HOMO-1 is a sigma-orbital which is considered a non-reactive orbital under perturbative scheme.<sup>[18]</sup>

#### meta-directing groups

Nitrobenzene and benzonitrile systems have been selected to be analyzed in this series. The former's regioselectivity has been extensively studied by frontier orbital-based descriptors<sup>[18]</sup> and using reactivity indicators associated with conceptual DFT,<sup>[52]</sup> whereas the latter emerges as a problematic system in this work, as its regioselectivity was not adequately predicted using  $f_w^-(\vec{r})$  with a  $\Delta$  value of 0.1 a.u. (such value was the adequate one for the other studied monosubstituted benzenes). Only when a value of 0.3 a.u. is used, the regioselectivity is properly described.

According to experimental evidence, the regioselectivity of these systems shows the following trend  $m > o > p$ , with a clear preference for *m*-position. As we can see in Figure 2,  $f_k^-$  predicts the following reactivity patterns:  $o > m > p$  and  $p > o > m$  for nitrobenzene and benzonitrile, respectively. Whereas  $f_{w,k}^-$  predicts  $m > o > p$  and  $m > p > o$  for nitrobenzene and benzonitrile, respectively. The improved prediction of this descriptor is due to the fact that it includes inner  $\pi$ -orbital contributions: HOMO-1 (27%) in case of nitrobenzene and, HOMO-1 and HOMO-3 (12% and 9%, respectively) in case of benzonitrile.

#### ipso-directing groups

For this series, we have selected the phenylzinc chloride system.<sup>[55]</sup> As in the previously discussed cases,  $f_{w,k}^-$  greatly predicts *ipso* regioselectivity of phenylzinc chloride compound ( $i > o > m > p$ ); whereas  $f_k^-$  wrongly predicts that *ortho* and *meta* are the most reactive sites. As it happened in the previously discussed cases, the consideration of a second  $\pi$ -orbital (HOMO-1) in  $f_{w,k}^-$  improves its predictive capability as shown in Figure 3.

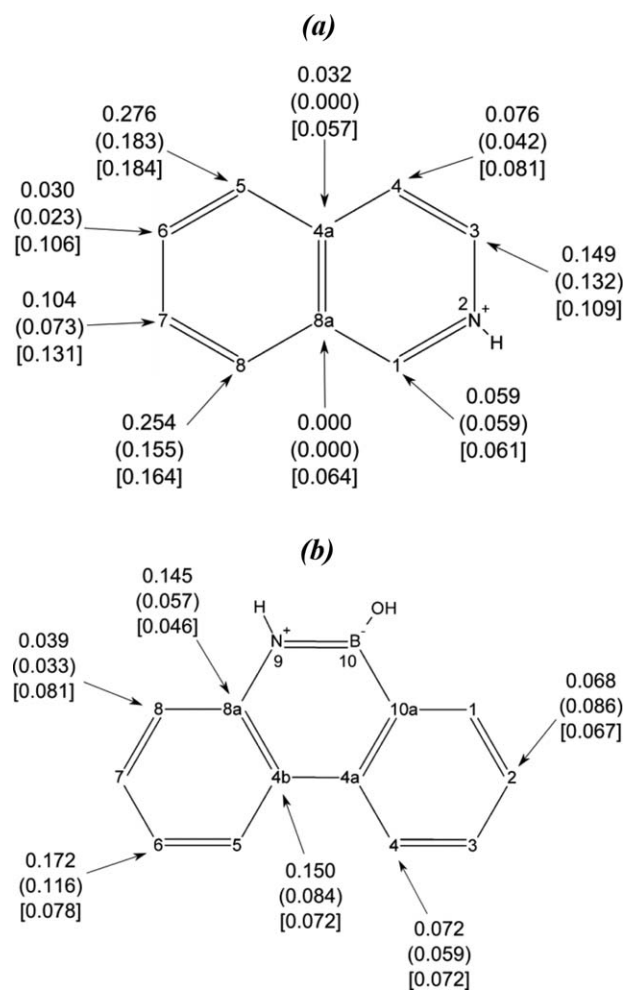


Figure 4. Condensed values of different reactivity descriptors for protonated isoquinoline a) and borazaphenanthrene b). The first two numbers correspond to  $f_k^-$  values obtained from both frozen core approximation and finite differences (in parenthesis), respectively. The last one (in brackets) corresponds to  $f_{w,k}^-$  values ( $\Delta = 0.15 \text{ a.u.}$ ).

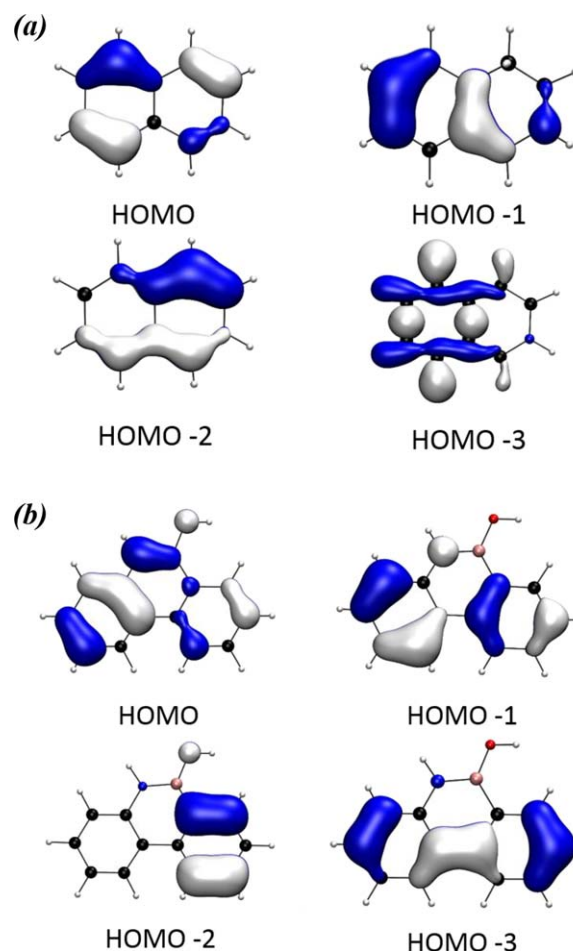
**Table 2.** Summary of the regioselectivity prediction on isoquinoline, 10-hydroxy-10,9-borazarophenanthrene, and 10-methyl-10,9-borazarophenanthrene according to the local reactivity descriptors ( $f_w^-(\vec{r})$  and  $f_w^-(\vec{r})$ ).

| Dewar problematic systems            | M <sub>I</sub> | M <sub>II</sub> | M <sub>III</sub> |
|--------------------------------------|----------------|-----------------|------------------|
| Isoquinoline                         | X              | X               | X                |
| Protonated isoquinoline              | ✓              | ✓               | ✓                |
| 10-hydroxy-10,9-borazarophenanthrene | X              | X               | ✓                |
| 10-methyl-10,9-borazarophenanthrene  | X              | X               | ✓                |

### Dewar problematic systems

Lastly, we will discuss the results obtained for three of the molecules (isoquinoline, 10-hydroxy-10,9-borazarophenanthrene, and 10-methyl-10,9-borazarophenanthrene) studied by Dewar as instances where FMO fails to properly describe regioselectivity.<sup>[12]</sup> More recently, Ayers used these systems to assess the predictive capability of his general-purpose reactivity indicator.<sup>[33]</sup> Along the same lines, we also analyzed them through the three tested models. Our results are depicted in Figure 4 and summarized in Table 2. For isoquinoline, all the tested descriptors fail in predicting its regioselectivity. Then, we calculated the protonated form according to the Ayers assumption that a more realistic model of this species should be protonated.<sup>[33]</sup> For this form, regioselectivity is correctly predicted by all the descriptors.

As we can see in Figure 4, the Fukui function adequately predicts the experimental reactivity trend for protonated isoquinoline C5 > C8 (according to frozen core approximation and finite differences). However, this descriptor fails in predicting regioselectivity in hydroxy-10,9-borazarophenanthrene, and 10-methyl-10,9-borazarophenanthrene. Interestingly,  $f_{w,k}^-$  values have the same pattern as the experimental regioselectivity in the three analyzed systems, C5 > C8 and C8 > C6 for



**Figure 5.** Canonical molecular orbitals with highest contributions to  $f_w^-(\vec{r})$ , see Table 2, for a) protonated isoquinoline and b) borazaphenanthrene. [Color figure can be viewed at wileyonlinelibrary.com]

**Table 3.** Highest reactive sites, according to  $f_{w,k}^-$ , with their respective condensed values (according to the topological analysis) for (a) isoquinoline (b) protonated isoquinoline and borazaphenanthrene derivatives: (c) R = OH and (d) CH<sub>3</sub>, respectively.

| $\Delta$ | Reactive C |        |        | % Orbital contribution |                |         |         |         |         |         |
|----------|------------|--------|--------|------------------------|----------------|---------|---------|---------|---------|---------|
|          | 5          | 8      | 4      | HOMO                   | HOMO -1        | HOMO -2 | HOMO -3 |         |         |         |
| (a)      |            |        |        |                        |                |         |         |         |         |         |
| 0.1      | 0.107      | 0.092  | 0.118  | 41.8                   | 27.7           | 20.6    | 6.9     |         |         |         |
| 0.15     | 0.092      | 0.086  | 0.104  | 26.4                   | 22.0           | 19.3    | 11.9    |         |         |         |
| 0.2      | 0.086      | 0.083  | 0.094  | 18.1                   | 16.3           | 15.2    | 11.6    |         |         |         |
| (b)      |            |        |        |                        |                |         |         |         |         |         |
| 0.1      | 0.184      | 0.164  | 0.081  | 59.4                   | 26.2           | 8.2     | 3.1     |         |         |         |
| 0.15     | 0.137      | 0.125  | 0.091  | 33.6                   | 23.3           | 13.9    | 9       |         |         |         |
| 0.2      | 0.115      | 0.107  | 0.09   | 21.3                   | 17.4           | 13      | 10.2    |         |         |         |
| $\Delta$ | 2          | 4      | 6      | 8                      | 8 <sup>a</sup> | 4b      | HOMO    | HOMO -1 | HOMO -2 | HOMO -3 |
| (c)      |            |        |        |                        |                |         |         |         |         |         |
| 0.1      | 0.072      | 0.076  | 0.1    | 0.095                  | 0.065          | 0.089   | 45.2    | 28.7    | 14.2    | 5.6     |
| 0.15     | 0.067      | 0.072  | 0.078  | 0.081                  | 0.046          | 0.072   | 24.4    | 20      | 14.6    | 9.6     |
| 0.2      | 0.062      | 0.065  | 0.067  | 0.069                  | 0.043          | 0.064   | 14.9    | 13.3    | 11.2    | 8.8     |
| (d)      |            |        |        |                        |                |         |         |         |         |         |
| 0.1      | 0.0793     | 0.0858 | 0.0897 | 0.0855                 | 0.0664         | 0.079   | 41.5    | 28.9    | 16.0    | 6.1     |
| 0.15     | 0.0696     | 0.0739 | 0.0716 | 0.0741                 | 0.0474         | 0.066   | 22.6    | 19.3    | 14.8    | 9.7     |
| 0.2      | 0.0621     | 0.0642 | 0.0627 | 0.064                  | 0.043          | 0.059   | 13.9    | 12.7    | 11.0    | 8.6     |

The condensed values have been estimated for different values of  $\Delta$ , and the main orbital contributions to  $f_w^-(\vec{r})$  are also reported.

isoquinoline and borazaphenanthrene derivatives, respectively. It is important to remark that the effectiveness of  $f_{w,k}^-$  as a reactivity descriptor is strongly dependent of the used  $\Delta$  value, being a 0.15 a.u. value the adequate one (see Table 3). Similar to what happened in all the analyzed systems, the improvement of this descriptor respect to the Fukui function is due to the fact that it considers contributions of inner orbitals. As we can see in Figure 5, for these systems,  $f_{w,k}^-$  is mainly conformed by  $\pi$ -symmetry orbitals (see Figs. 4 and 5).

Summarizing, our results supports the fact that, in cases where there is a degeneracy or quasi-degeneracy on the neutral, cation, or anion of the studied molecule, it seems reasonable to use the proposed orbital weighted Fukui function.

## Conclusions


In this work, we introduced the Orbital-weighted Fukui Function ( $f_w^-(\vec{r})$ ) and its topological analysis. The condensed values of this new descriptor ( $f_{w,k}^-$ ) prove to be superior to the classical expressions of the Fukui function. This is supported by the correct regioselectivity prediction of monosubstituted benzene derivatives classified as *ortho/para*-, *meta*-, and *ipso-directing* (according to the nature of their substituents and empirical resonance rules). Whereas, the condensed values of the classical approximations of the Fukui function erroneously identify the reactive centers, especially in the *meta*- and *ipso-directing* systems.

Additionally, three systems, identified by Dewar as problematic molecules for FMO-based approximations, have also been analyzed. For the first one (isoquinoline), the predictions based on  $f_{w,k}^-$  values are as poor as those obtained by traditional approximations of the Fukui function. Apparently, as Ayers suggested, it is not a problematic system for FMOs-based methods, but instead it needs to be simulated in the protonated form. For the last two cases (10-hydroxy-10,9-borazarophenanthrene and 10-methyl-10,9-borazarophenanthrene), regioselectivity is correctly predicted by  $f_{w,k}^-$  in contrast with what happens with other Fukui function approximations, where it fails.

The improved predictive capability of this new descriptor is due to the fact that it considers inner orbitals contribution, which in the present version have been chosen arbitrarily (according to a Gaussian distribution). Then, our results support the fact that, in cases where there is a degeneracy or quasi-degeneracy on the neutral, cation, or anion of the studied molecule, it seems reasonable to use the proposed orbital weighted Fukui function.

**Keywords:** chemical reactivity · topological analysis · electrophilic aromatic substitution

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