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New Dual Descriptor for Chemical Reactivity

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In this paper, a new dual descriptor for nucleophilicity and electrophilicity is introduced. The new index is defined in terms of the variation of hardness with respect to the external potential, and it is written as the difference between nucleophilic and electrophilic Fukui functions, thus being able to characterize both reactive behaviors. It is shown that the new descriptor correctly predicts the site reactivity induced by different donor and acceptor groups in substituted phenyl molecules. Also, the Dunitz−Burgi attack on ketones and aldehydes has been revisited to illustrate the stereoselective capability of this new index. Finally, its predictive ability has been tested successfully on different series of conjugated and nonconjugated carbonyl compounds.

1. Introduction

Density functional theory (DFT) provides a powerful theoretical framework for the study of both reactivity and selectivity.[1] From the DFT equations, many concepts widely used by experimental chemists have found both mathematical basis and physical meaning.[2,3] Indeed, concepts such as the electronic chemical potential, μ, which characterizes the escaping tendency of electrons, and global hardness, η[4], which represents the resistance to charge transfer, have proven to be successful in the rationalization of chemical processes.[5] In this context, the principle of maximum hardness (PMH),[6] originally introduced by Pearson, has been very useful in characterizing reactants,[7] products, and transition states[8] of different kinds of chemical reactions. The PMH indicates that molecules tend to a maximum hardness value when they are at equilibrium, and the link between stability (energy) and hardness indicates that this latter principle is a good descriptor of the global reactivity of the system.[9] The PMH has been demonstrated[10,11] to be valid only when the external potential remains constant, although relaxations of this constraint have been encountered in different systems.[12,13] However, because during any chemical reaction there is structural and electronic reordering, the external potential hardly remains constant. Therefore, it becomes interesting to characterize the response of hardness when the chemical potential changes; and at the same time, this would be an interesting reactivity descriptor.

Chemical potential, hardness, and softness (the inverse of hardness: $S = {}^{1}/_{\eta}$) are global properties that are related to the reactivity of chemical systems, whereas local properties are basically related to the selectivity concept. These latter indexes are used to predict the selectivity and/or specificity of a chemical reaction. The key concepts in selectivity are the Fukui function and the local softness; a highly electrophilic/nucleophilic center is a site presenting a high value of the associated Fukui function. Local softness has been used to characterize soft−soft interactions within the context of a local hard−soft acid−base (HSAB) principle.[14−16] This empirical rule states that soft−soft and hard−hard interactions are energetically favorable over crossed hard−soft interactions. The local application of the HSAB rule requires reliable local reactivity descriptors. Unfortunately, Fukui functions and local softness are not always able to identify unambiguously the specific site where a reaction is favored or the site where it cannot take place.[17] The behavior of a system towards an electrophilic attack is quite well described through the use of the so-called electrophilic Fukui function; however, the behavior of the system towards a nucleophilic attack has not been unambiguously defined. There have been many attempts to characterize the nucleophilic power of atoms and molecules through the use of different descriptors.[18,19] Recently, Roy et al.[20] have proposed a nucleophilicity index based on the ratio of local electrophilic and nucleophilic softness; the index works reasonably well in many cases. More recently, Contreras et al.[21] have studied the relative nucleophilicity through the use of their solution-phase ionization potential. The problem of characterizing the nucleophilicity of atoms and molecules still exists.

In line with a recent paper by Chattaraj et al.[22] where a unique philicity descriptor was defined, in this paper we propose a new dual descriptor for nucleophilicity and electrophilicity in terms of the variation of hardness with respect to the variation of the external potential. An operational formula for this index is derived; it is defined as the difference between the nucleophilic and electrophilic Fukui functions. In this way, the new index is dual and can be used to detect simultaneously the nucleophile or electrophile behavior of a given atomic region in the molecule.

This article is organized as follows: In section 2, the master equations yielding the new reactivity/selectivity descriptor are presented. Section 3 describes the methodology and computational details. Section 4 provides examples in which the performance of the new descriptor is tested. Section 5 contains a few concluding remarks.

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2. Theory

2.1. General Definitions. A complete characterization of an N-particle wave function and energy requires a knowledge of the number of electrons N and the external potential $v(r)$. DFT provides the theoretical framework for rationalizing the reactivity of molecules in term of the response of the system towards the variation of N and $v(r)$.[23] The response to changes in the number of electrons, when the external potential remains constant, is measured at first order by the chemical potential and at second order by the hardness. Chemical potential is a global property that characterizes the electron transfer associated with any chemical process, and hardness can be seen as a resistance to charge transfer. The variation of the external potential, without charge transfer, is measured by the electronic density $\rho(r)$ at first order and by the Fukui function $f(r)$[24] at second order; both the electronic density and Fukui function are local quantities. The electronic density provides site-reactivity information about ionic systems, whereas the Fukui function is better suited to deal with neutral species.

The first-order variation in the total energy is then expressed in terms of the simultaneous variation of the number of electrons N and external potential $v(r)$; this gives rise to the definition of global and local reactivity indexes.

$$\mathrm{d}E = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \mathrm{d}N + \int \left(\frac{\delta E}{\delta v(r)}\right)_N \mathrm{d}v(r)\,\mathrm{d}r \tag{1}$$

where

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \quad \text{and} \quad \rho(r) = \left(\frac{\delta E}{\delta v(r)}\right)_N \tag{2}$$

μ is the electronic chemical potential that appears as the Lagrange multiplier associated with the condition that $\rho(r)$ integrates to N. The chemical potential makes the link with classical chemistry through its relation to the electronegativity: $\mu = -\chi$.[25] The total differential of the chemical potential is

$$\mathrm{d}\mu = \left(\frac{\partial \mu}{\partial N}\right)_{v(r)} \mathrm{d}N + \int \left(\frac{\partial \mu}{\mathrm{d}v(r)}\right)_{v(r)} \mathrm{d}v(r)\,\mathrm{d}r \tag{3}$$

and the total differential of the electronic density is

$$\delta\rho(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r')} + \int\int \left(\frac{\delta \rho(r)}{\delta v(r')}\right)_N \mathrm{d}v(r')\,\mathrm{d}r \tag{4}$$

From eq 3, the molecular hardness is identified as

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{v(r)} \tag{5}$$

and from eq 4, the linear response is defined as

$$\left(\frac{\delta \rho(r)}{\delta v(r')}\right)_{v(r)} = \chi(r, r') \tag{6}$$

Because the crossed derivatives of μ and $\rho(r)$ must be equal, from eqs 3 and 4 the Fukui function can be defined as

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} = \left(\frac{\delta \mu}{\delta v(r)}\right)_N \tag{7}$$

2.2. Interaction of Two Molecules. When two molecules, A and B, approach each other, the up to second-order change in energy is for molecule A[26]

$$\Delta E_A = \mu_A^0 \Delta N_A + \int \rho_A(r)\,\Delta v_A(r)\,\mathrm{d}r + \frac{1}{2}\Big\{\eta_A(\Delta N_A)^2 + 2\Delta N_A \int f_A(r)\,\Delta v_A(r)\,\mathrm{d}r + \int\int \left[\frac{\delta \rho_A(r)}{\delta v_A(r')}\right] \Delta v_A(r)\,\Delta v_A(r')\,\mathrm{d}r\,\mathrm{d}r'\Big\} \tag{8}$$

and for molecule B

$$\Delta E_B = \mu_B^0 \Delta N_B + \int \rho_B(r)\,\Delta v_B(r)\,\mathrm{d}r + \frac{1}{2}\Big\{\eta_B(\Delta N_B)^2 + 2\Delta N_B \int f_B(r)\,\Delta v_B(r)\,\mathrm{d}r + \int\int \left[\frac{\delta \rho_B(r)}{\delta v_B(r')}\right] \Delta v_B(r)\,\Delta v_B(r')\,\mathrm{d}r\,\mathrm{d}r'\Big\} \tag{9}$$

Then the total energy change is $\Delta E = \Delta E_A + \Delta E_B$. A combination of eqs 8 and 9 and using the Sanderson principle[27,28] of electronegativity equalization leads to

$$\Delta N = \frac{(\mu_B^0 - \mu_A^0) + \int f_B(r)\,\Delta v_B(r)\,\mathrm{d}r - \int f_A(r)\,\Delta v_A(r)\,\mathrm{d}r}{(\eta_A + \eta_B)} \tag{10}$$

with $\Delta N = \Delta N_A = -\Delta N_B$. Using eq 10 in $\Delta E = \Delta E_A + \Delta E_B$ leads to

$$\Delta E = \Delta E_A + \Delta E_B = \Delta E_{\mathrm{int}} = \Delta E_c + \Delta E_e + \Delta E_p \tag{11}$$

with

$$\Delta E_c = -\frac{[(\mu_B^0 - \mu_A^0) + \int f_B(r)\,\Delta v_B(r)\,\mathrm{d}r - \int f_A(r')\,\Delta v_A(r')\,\mathrm{d}r]^2}{2(\eta_B + \eta_A)} \tag{12}$$

$$\Delta E_e = \int \rho_B(r)\,\Delta v_B(r)\,\mathrm{d}r + \int \rho_A(r')\,\Delta v_A(r')\,\mathrm{d}r' + \Delta V_{\mathrm{nn}} \tag{13}$$

$$\Delta E_p = \int\int \chi_A(r, r')\,\Delta v_A(r)\,\Delta v_A(r')\,\mathrm{d}r\,\mathrm{d}r' + \int\int \chi_B(r', r'')\,\Delta v_B(r')\,\Delta v_B(r'')\,\mathrm{d}r'\,\mathrm{d}r'' \tag{14}$$

where ΔV_{nn} is the nucleus−nucleus repulsion energy. The first term (ΔE_c) is the so-called covalent contribution;[1] it links frontier molecular orbital theory (FMO theory) to the HSAB principle. In this paper, attention will be focused on this term of the interaction energy because it becomes the dominant term when dealing with neutral and soft species. The second term (ΔE_e) is the electrostatic contribution that is the most important when the reaction involves two hard ionic species. The third term (ΔE_p) describes the polarization of electronic clouds of both molecules. This term might be important in hard−soft interactions, and we believe that it may help to rationalize the Fajan rules[29] for characterizing the partial covalent character in ionic compounds.

2.3. Analysis of the Covalent Contribution to ΔE_{int}. In this section, the covalent contribution to the interaction energy given by eq 12 is analyzed. Because hardness is a positive defined quantity, ΔE_c is always negative; it is a stabilizing energy. Although it is clear that the softest species (small amount of hardness) lead to the highest stabilization in energy, it is not entirely clear how the orbital control that appears in the second and third terms of the numerator influences the final value of ΔE_c. Although $(\eta_A + \eta_B)$ may change during the interaction process, the total net change is expected to be quite small because of canceling effects. The operational formula to obtain numerical hardness values involves the finite difference approximation and Koopman's theorem:

$$\eta = (\epsilon_L - \epsilon_H)$$

This leads to

$$\begin{aligned}(\eta_A + \eta_B) &= (\epsilon_L^A - \epsilon_H^A) + (\epsilon_L^B - \epsilon_H^B)\\ &= (\epsilon_L^A - \epsilon_H^B) + (\epsilon_L^B - \epsilon_H^A) \qquad (15)\end{aligned}$$

These expressions will be used in the next paragraphs to characterize the effect of the interaction on the denominator of eq 12. The analysis of the orbital control within the covalent contribution is the main goal of this section.

To achieve this goal, we need to introduce analytic expressions for the external potential; following Parr and Ayers,[30] the external potential $\upsilon_A(r)$ is given by

$$\upsilon_A(r') = \upsilon_B^N(r') + \left[\int \frac{\rho_B(r)}{|r - r'|}\,dr + \upsilon_B^{XC}(r')\right] \qquad (16)$$

where $\nu_B^N(r')$ is the potential created in A by the nuclei of molecule B, $\nu_B^{XC}(r')$ is the exchange correlation potential, and $[\int\rho_B(r)/|r - r'|dr]$ is the electrostatic potential arising from electrons in B. Equation 16 gives the variation in the external potential that electrons in A feel when molecule B approaches; a similar expression can be obtained for $\upsilon_B(r)$. Putting eq 16 in eq 12, we can rewrite the covalent contribution as

$$\Delta E_c = \frac{\Big[(\mu_B^0 - \mu_A^0) + \int f_B(r)\left[\upsilon_A^N(r) + \left[\int \frac{\rho_A(r')}{|r - r'|}\,dr' + \upsilon_A^{XC}(r)\right]\right] dr}{2(\eta_A + \eta_B)} - \frac{\int f_A(r')\left[\upsilon_B^N(r') + \left[\int \frac{\rho_B(r)}{|r - r'|}\,dr + \upsilon_B^{XC}(r')\right]\right] dr'\Big]^2}{2(\eta_A + \eta_B)} \qquad (17)$$

Maximization of the numerator of eq 12 must enhance the efficiency of the covalent term. The algebraic development of eq 17 shows that the numerator can be decomposed into different terms, namely,

$$A = \mu_B^0 - \mu_A^0 = \Delta\mu^0 \qquad B = \int f_B(r)\,\upsilon_A^N(r)\,dr$$

$$C = \int\int \frac{f_B(r)\,\rho_A(r')\,dr\,dr'}{|r - r'|} \qquad D = \int f_B(r)\,\upsilon_A^{XC}(r)\,dr$$

There are complementary terms E, F, and G that are equivalent to the negatives of B, C, and D, respectively, but with exchanged A/B indexes. In the next paragraphs, the analysis and physical characterization of these terms will be performed. To do so, it is necessary to identify the reactive nature of the interactions. Let A be the electrophilic species, and let B the nucleophilic species; then $\mu_B^0 > \mu_A^0$, so $\Delta\mu > 0$. In this context, it is reasonable to use[31] $f_B(r) = f_B^-(r)$ and $f_A(r') = f_A^+(r')$. Moreover, under the frozen orbital assumption $f_B^-(r) \approx \rho_B^{HOMO}(r)$ and $f_A^+(r') \approx \rho_A^{LUMO}(r')$. It will possible to identify, at least qualitatively, the specific interactions that govern the different terms in eq 12.

Using the frontier orbital approximation for the Fukui functions, we give the terms B and E by

$$B = \int \rho_B^{HOMO}(r)\,\upsilon_A^N(r)\,dr \quad \text{and} \quad E = -\int \rho_A^{LUMO}(r')\,\upsilon_B^N(r')\,dr'$$

Note that they present opposite signs. The potential arising from the electric field created by the nuclei is given by

$$\upsilon_{A/B}^N = \sum_{N_A} -\frac{Z_{NA/B}}{|r - R_{NA/B}|}$$

which is always negative; $B < 0$ and $E > 0$ because $\rho_{A/B}(r)$ is positive. B and E represent the overlap integrals between the frontier orbital densities of one molecule and the electric potential created by the nuclei of the other molecule. Within the frozen density approximation used to estimate the energy of the frontier orbitals HOMO and LUMO, it can be shown that B and E represent the variation of the frontier orbital energies due to the electric field arising from the nuclei of the other molecule. As a result, the HOMO energy of the nucleophile decreases, whereas the LUMO energy of the electrophile increases. Equation 15 indicates that the net result is an increase in the value of the term $(\eta_A + \eta_B)$ in the denominator of eq 12, thus leading to a decreasing value of ΔE_c.

Terms D and G are now written as

$$D = \int \rho_B^{HOMO}(r)\,\upsilon_A^{XC}(r)\,dr \quad G = -\int \rho_A^{LUMO}(r')\,\upsilon_B^{xc}(r')\,dr'$$

A physical picture of these terms might be the distribution of the exchange correlation of one molecule projected through the frontier density of the other. Because the exchange correlation is a stabilizing potential ($\upsilon_{A/B}^{XC}(r) < 0$), D is negative whereas G is positive. Again, the HOMO energy of the nucleophile decreases, and the LUMO energy of the electrophile increases. The result due to D and G is a net increase of $(\eta_A + \eta_B)$ in the denominator of eq 12 (see eq 15), thus decreasing ΔE_c.

Using the already-mentioned approximations, terms C and F, which read

$$C = \int\int \frac{\rho_B^{HOMO}(r)\,\rho_A(r')}{|r - r'|}\,dr\,dr' \quad \text{and}$$

$$F = -\int\int \frac{\rho_A^{LUMO}(r')\,\rho_B(r)}{|r - r'|}\,dr\,dr'$$

are local electrostatic energies, and the sum $C + F$ is the overlap of the frontier orbital density of one molecule with the global electronic density of the other molecule. These integrals represent the local reactivity of one molecule due to the presence of the electronic distribution of the other molecule. Because $\rho(r)$ is positive, C is positive and F is negative. This means that the HOMO energy of the nucleophile increases whereas the LUMO energy of the electrophile decreases, and the net result is that $(\eta_A + \eta_B)$ decreases with increasing ΔE_c. The effect of the above-described terms is summarized in Table 1.

Now, the problem is to maximize the absolute value of the numerator of eq 12. Parr and Yang proposed a way to achieve this goal by stating that for typical soft−soft interactions the frontier term in the numerator may overwhelm the electronegativity difference. Because charge transfer is proportional to $\Delta\mu$, a high value of $\Delta\mu$ is related mostly to ionic interactions,

TABLE 1: Characterization of the Different Terms Involved in Equation 12

terms	integral	sign	frontier orbital energy change	$\Delta(\eta_A + \eta_B)$
A	$\Delta\mu$	$+$		
B	$\int \rho_B^{\mathrm{HOMO}}(r)\, v_A^{\mathrm{nuclei}}(r)\, \mathrm{d}r$	$-$	$\Delta\epsilon_H^B < 0$	>0
C	$\int\int \frac{\rho_B^{\mathrm{HOMO}}(r)\, \rho_A(r')}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r'$	$+$	$\Delta\epsilon_H^B > 0$	<0
D	$\int \rho_B^{\mathrm{HOMO}}(r)\, v_A^{\mathrm{xc}}(r)\, \mathrm{d}r$	$-$	$\Delta\epsilon_H^B < 0$	>0
E	$-\int \rho_A^{\mathrm{LUMO}}(r')\, v_B^{\mathrm{nuclei}}(r')\, \mathrm{d}r'$	$+$	$\Delta\epsilon_L^A > 0$	>0
F	$-\int\int \frac{\rho_A^{\mathrm{LUMO}}(r')\, \rho_B(r)}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r'$	$-$	$\Delta\epsilon_L^A < 0$	<0
G	$-\int \rho_A^{\mathrm{LUMO}}(r')\, v_A^{\mathrm{xc}}(r')\, \mathrm{d}r'$	$+$	$\Delta\epsilon_L^A > 0$	>0

and covalent interactions are expected to present small values of $\Delta\mu$. In our particular case, where $\Delta\mu > 0$, all positive terms will increase the ionic character of the interaction. However, all negative terms tends to increase the covalent character of the interaction.

C and F should govern the selectivity of the reaction because they involve the interaction between the Fukui functions of a molecule with the whole density of the other. A closer analysis of these terms can be performed by assuming that

$$\rho(r) = \sum_{\mathrm{occ}} \rho_i(r)$$

Therefore, we obtain

$$C = \int\int \frac{\rho_B^{\mathrm{HOMO}}(r)[\sum_{1}^{\mathrm{HOMO}} \rho_i(r')]_A}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r' = \int\int \frac{\rho_B^{\mathrm{HOMO}}(r)\, \rho_A^{\mathrm{HOMO}}(r')}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r' + \int\int \frac{\rho_B^{\mathrm{HOMO}}(r)[\sum_{1}^{\mathrm{HOMO}-1} \rho_i(r')]_A}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r' = C_1 + C_2$$

Similarly, F can be written as $F = F_1 + F_2$ with

$$F_1 = -\int\int \frac{\rho_A^{\mathrm{LUMO}}(r')\, \rho_B^{\mathrm{HOMO}}(r)}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r'$$

and

$$F_2 = -\int\int \frac{\rho_A^{\mathrm{LUMO}}(r')[\sum_{1}^{\mathrm{HOMO}-1} \rho_i(r)]_B}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r'$$

C_2 represents the destabilization of the HOMO of the nucleophile due to the inner electronic density of the electrophile. Similarly, F_2 represents the stabilization of the LUMO energy of the electrophile due to the inner electronic density of the nucleophile. Both terms tend to decrease the hardness of both molecules. The overall result is that all four terms tend to decrease the energy gap between the HOMO of the nucleophile and the LUMO of the electrophile. Within the framework of frontier molecular orbital theory, we assume that the frontier interactions represented by C_1 and F_1 are the most important terms. Then the integral $C_1 + F_1$ becomes

$$C_1 + F_1 = \int\int \frac{\rho_B^{\mathrm{HOMO}}(r)\, \rho_A^{\mathrm{HOMO}}(r')}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r' - \int\int \frac{\rho_A^{\mathrm{LUMO}}(r')\, \rho_B^{\mathrm{HOMO}}(r)}{\lvert r - r'\rvert}\, \mathrm{d}r\, \mathrm{d}r' = -\left\{\int\int \frac{\rho_B^{\mathrm{HOMO}}(r)}{\lvert r - r'\rvert}[\rho_A^{\mathrm{LUMO}}(r') - \rho_A^{\mathrm{HOMO}}(r')]\, \mathrm{d}r\, \mathrm{d}r'\right\} \quad (18)$$

It is obvious that the term $C_1 + F_1$ is optimum when the overlapping quantity $\rho_A^{\mathrm{LUMO}}(r)$ and $\rho_B^{\mathrm{HOMO}}(r)$ is maximized whereas simultaneously the overlapping quantity $\rho_B^{\mathrm{HOMO}}(r)$ and $\rho_A^{\mathrm{HOMO}}(r)$ is minimized. The first term of $C_1 + F_1$ is equivalent to the Fukui overlap I^{mp} proposed by Clark, Ellis, and Snurr.[32] The above considerations indicate that the most favored site for nucleophilic attack is the one presenting the highest value of the density difference $\{\rho_A^{\mathrm{LUMO}}(r') - \rho_A^{\mathrm{HOMO}}(r')\}$ and the most favored site for an electrophilic attack will be the site with the greatest value of $\rho_B^{\mathrm{HOMO}}(r)$.

2.4. New Nucleophilicity and Electrophilicity Index. The above considerations lead us to propose a new index of selectivity toward nucleophilic attack, but it can also be used to characterize an electrophilic attack. It is defined as

$$\Delta f(r) = [(f^{+}(r) - f^{-}(r))] \approx [\rho^{\mathrm{LUMO}}(r) - \rho^{\mathrm{HOMO}}(r)] \quad (19)$$

If $\Delta f(r) > 0$, then the site is favored for a nucleophilic attack, whereas if $\Delta f(r) < 0$, then the site could hardly be susceptible to undertake a nucleophilic attack but it may be favored for an electrophilic attack.

Because Fukui functions are positive ($0 \le f(r) \le 1$), $-1 \le \Delta f(r) \le 1$ and the normalization condition for $\Delta f(r)$ is

$$\int \Delta f(r)\, \mathrm{d}r = 0 \quad (20)$$

On the basis of these results, it is clear that numerical values of $\Delta f(r)$ are defined within the range $\{-1; 1\}$. This is an advantage with respect to other reactivity indexes that may present large values, thus leading to hard-to-interpret results. This point is important and might be considered to be a criterion to check the validity of calculations aimed at characterizing reactivity, especially the nucleophilic power.

To add physical meaning to the newly defined $\Delta f(r)$ index, let us consider the finite difference approximations that define the Fukui functions

$$f^{+}(r) = \left(\frac{\Delta\mu^{+}}{\Delta v(r)}\right)_N = -\left(\frac{\Delta A}{\Delta v(r)}\right)_N \quad (21)$$

$$f^{-}(r) = \left(\frac{\Delta\mu^{-}}{\Delta v(r)}\right)_N = -\left(\frac{\Delta I}{\Delta v(r)}\right)_N \quad (22)$$

where I and A are the ionization potential and the electronaffinity, respectively. Therefore,

$$\Delta f(r) = (f^{+}(r) - f^{-}(r)) = \left\{-\left(\frac{\Delta A}{\Delta v(r)}\right)_N + \left(\frac{\Delta I}{\Delta v(r)}\right)_N\right\} = \left(\frac{\Delta(I - A)}{\Delta v(r)}\right)_N \approx \left(\frac{\Delta\eta}{\Delta v(r)}\right)_N \quad (23)$$

Thus, $\Delta f(r)$ is the result of the variation of the hardness when the external potential changes. This result can be advanced from eq 7 by taking the Fukui function as a function of N and a functional of the external potential $f[N, \upsilon(r)]$.

2.5. $\Delta f(r)$ and the Principle of Maximum Hardness. The integral form of eq 23 in terms of Fukui functions is

$$\Delta\eta = \int \Delta f(r)\, \Delta\upsilon(r)\, dr \qquad (24)$$

It is now possible to follow the variations of hardness along the chemical path during the reaction process by monitoring the change in the nucleophilic and electrophilic Fukui functions along the charge transfer. Moreover, eq 24 relies directly on $\Delta f(r)$, with the PMH underlying the physical meaning of this latter descriptor. Using the variation of the cationic/anionic electrostatic potential as a model to describe the variation of the external potential that a molecule experience during an electrophile/nucleophile approach, we can qualitatively evaluate the variation of the molecular hardness. Let us consider a simple monoatomic ionic species. The external electrostatic potential at point r can be written as

$$\upsilon(r) = -\frac{(Z-N)}{r} \qquad (25)$$

where Z is the atomic number and N is the number of electrons. The variation of this potential is

$$\delta\upsilon(r) = \frac{(Z-N)}{r^2}\, dr \qquad (26)$$

When this species approaches a molecule $dr < 0$, the variation of the external potential that the molecule experience depends on the sign of $(Z - N)$. If $(Z - N) > 0$ (for cationic species), then $\delta\upsilon(r) < 0$; if $(Z - N) < 0$ (anionic species), then $\delta\upsilon(r) > 0$. If a cationic species approaches a site with $\Delta f(r) < 0$, then eq 24 indicates that the molecular hardness increases because $\delta\upsilon(r) < 0$. However, if an anionic species approaches a molecular site with $\Delta f(r) > 0$, then again the molecular hardness increases. These results are consistent with what is expected from the principle of maximum hardness. In this context, $\Delta f(r)$ might be thought of as a descriptor of the PMH.

3. Computational Details

The geometries of the studied molecules in sections 4.1 and 4.2 have been fully optimized at the HF/6-311G** level. We keep this level of theory because it gives a good description of the electron density and orbital energies of the compounds studied here.[20] Because the present analysis is based on the sign obtained from eq 23, the quality of $f(r)$ is crucial.[33] In this paper, the Fukui functions $f^+(r)/f^-(r)$ have been approximated by the spin density of the $(N + 1)/(N - 1)$ system, as suggested by Galvan, Gazquez, and Vela.[34] All of the calculations have been carried out using the Gaussian[35] 98/03 packages. We present in the next sections a few examples that illustrate the use and advantages of the newly defined dual index. The examples retained to make the comparison between the different condensed descriptors (section 4.3) are the ones used by Roy et al.[20] at the ROHF/D95* level of theory.

4. Representative Examples of the Use and Advantages of $\Delta f(r) < 0$

4.1. Aromatic Electrophilic Substitution. The molecules chosen to test the newly defined index of reactivity are phenol, aniline, benzaldehyde, and cyanobenzene because their reactivity and orientation are well known.[36] It is well known that OH and NH_2 are electron donors that orientate the aromatic electrophilic substitution (AES) in positions ortho and para to the phenyl moiety. However, it is difficult to predict how much of the product will be the ortho isomer and how much will be the para isomer.[37] A third possibility also arises from the activation of the ipso position. Indeed, an ipso attack followed by 1−2 migration and the loss of a proton will increase the proportion of the ortho isomer at the expense of the para isomer.[38] However, CHO and CN are electron-withdrawing groups that are meta-orienting groups and deactivate the aromatic ring.

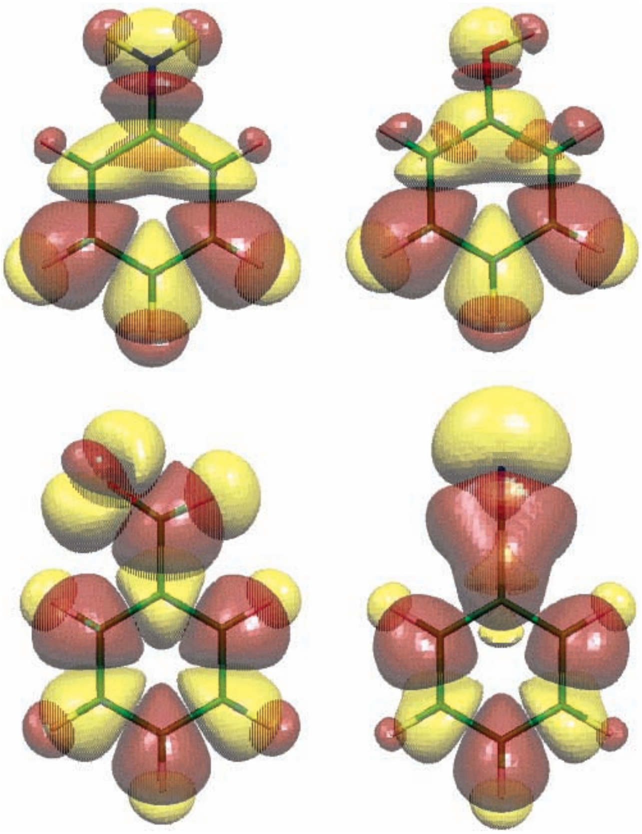
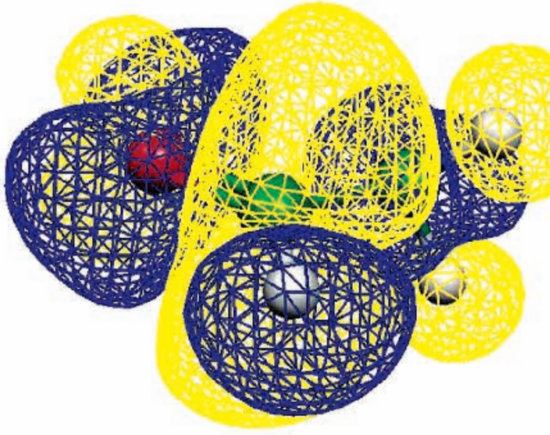
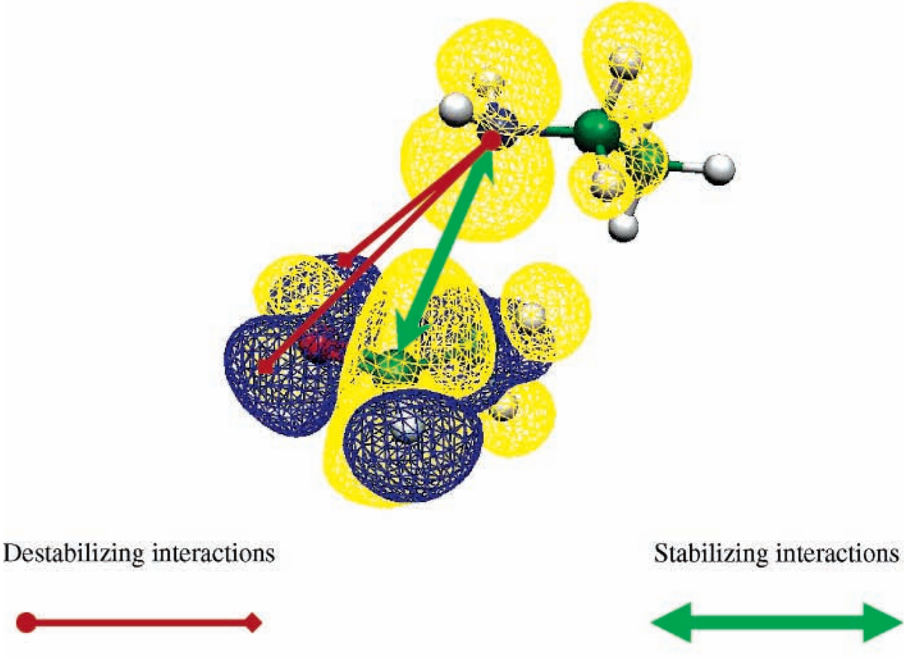


Figure 1. $\Delta f(r)$ calculated at HF/6-311G**.

The $\Delta f(r)$ functions calculated at the HF/6-311G** level are displayed in Figure 1. The sign of $\Delta f(r)$ is an important criterion of reactivity. As already shown, molecular sites with $\Delta f(r) > 0$ are expected to be electrophilic, whereas molecular centers with $\Delta f(r) < 0$ are expected to be nucleophilic. Seeking to identify unambiguously the reactivity behavior of the monosubstituted benzene rings, we have chosen to represent in yellow the zone with $\Delta f(r) > 0$ and in red the areas with $\Delta f(r) < 0$. Thus, Figure 1 can be seen as a map of the nucleophilic/electrophilic behavior of the different sites within the molecule. Indeed, regarding the AES, it is the zone with $\Delta f(r) < 0$ that we are interested in. For both phenol and aniline, the zones with $\Delta f(r) < 0$ where an electrophilic reaction should take place are located in positions ipso, ortho, and para. In both molecules, the meta position seems to be electrophilic. For benzaldehyde and cyanobenzene, the zones are totally exchanged. The zones with $\Delta f(r) < 0$ cover the meta positions in both cyanobenzene and benzaldehyde, whereas ortho and meta are positions with $\Delta f(r) > 0$. Thus, the $\Delta f(r)$ index indicates that, regarding the AES, ipso, ortho, and para are the activated sites in both aniline and



$\Delta f(r)$ calculated at HF/6-311G** level



Stabilizing and destabilizing Interactions between ethanal and ethanamine

Figure 2. Illustration of the Dunitz−Burgi attack.

phenol, whereas only meta zones are reactive in benzaldehyde and cyanobenzene. These conclusions are in good agreement with experimental results.

4.2. Stereoselectivity Capability of $\Delta f(r)$. To illustrate the stereoselectivity power of $\Delta f(r)$, we study the Dunitz−Burgi attack of carbonyl compounds. From crystallographic studies of amino-ketones, Burgi, Dunitz, and Shefter[39,40] have found that the angle of attack of a nucleophile on the carbonyl group should always be superior to 90°. The average angle is about 107°. Anh and Eisenstein have explained this amazing fact through the frontier molecular orbitals theory[41,42] using the asymmetry of the LUMO orbital of the carbonyl. Our purpose is to show how this attack can be explained through the use of $\Delta f(r)$. An illustration of the following discussion about interactions between ethanal and ethanamine is given in Figure 2.

The optimization of the term

$$C_1 + F_1 = -\left\{\int\int \frac{\rho_{\mathrm{B}}^{\mathrm{HOMO}}(r)}{|r - r'|}[\rho_{\mathrm{A}}^{\mathrm{LUMO}}(r') - \rho_{\mathrm{A}}^{\mathrm{HOMO}}(r')]\,\mathrm{d}r\,\mathrm{d}r'\right\}$$

involving Fukui functions leads us to expect a maximum overlap between $\rho_{\mathrm{nucleophile}}^{\mathrm{HOMO}}(r)$ and $\rho_{\mathrm{carbonyl}}^{\mathrm{LUMO}}(r)$ (yellow) and a minimum overlap between $\rho_{\mathrm{nucleophile}}^{\mathrm{HOMO}}(r)$ and $\rho_{\mathrm{carbonyl}}^{\mathrm{HOMO}}(r)$ (blue). The best way for a nucleophile to fulfill these two conditions is to increase the angle of attack. The main advantage of the use of $\Delta f(r)$ through eq 18 is the recovery of the stabilizing and destabilizing interactions, and then it gives information about the stereoselectivity of the interactions in contrast to the condensed DFT descriptors that are not suited to give information about stereoselectivity.

4.3. Comparison between Different Reactivity Descriptors. In this section, we compare different descriptors of nucleophilicity in order to find the most efficient one. For this purpose, the performance of three descriptors s_k^+, $s_k^r = (s_k^+/s_k^-)$, and $\Delta f(r)$ is going to be tested in the series of organic compounds investigated by Roy. Let us first define Δs_k as the condensed version of $\Delta f(r)$ multiplied by the molecular softness. An operational formula for this condensed descriptor is

$$\Delta s_k = S(f_k^+ - f_k^-) = (s_k^+ - s_k^-) \qquad (27)$$

Carbonyl Compounds. Carbonyl compounds are usually used to test the quality of the reactivity descriptors. Chattaraj et al.[43] have recently studied a set of these compounds in terms of their philicity index. For the sake of clarity, carbonyl compounds have been ordered into two different groups: nonconjugated and α,β-conjugated carbonyl compounds. Molecular structures with atomic numberings are displayed in Figure 3, and numerical results are listed in Table 2.

For the nonconjugated carbonyl compounds, the carbon atom bearing the carbonyl group ($C_{carbonyl}$) is expected to be the most reactive site to nucleophilic attack. Table 2 shows that all descriptors agree in that the higher value is assigned to the carbon atom bearing the carbonyl group. Nevertheless, the local softness of oxygen is roughly equivalent to the local softness of $C_{carbonyls}$, thus making it difficult to assess unambiguously the nucleophilic behavior of these atoms. Descriptor s_k^r gives a better discrimination between the carbon and the oxygen atoms concerning their electrophilic behavior. The Δs_k descriptor gives a highly positive value to the carbon of the carbonyl group and a negative value to the oxygen atom (−0.54), thus indicating that carbon is expected to be an electrophile whereas oxygen is expected to be a nucleophile. The electrophilc/nucleophilic behavior is then defined through the sign of Δs_k: when $\Delta s_k > 0$, atom k acts as an electrophile, and when $\Delta s_k < 0$, atom k acts as a nucleophile.

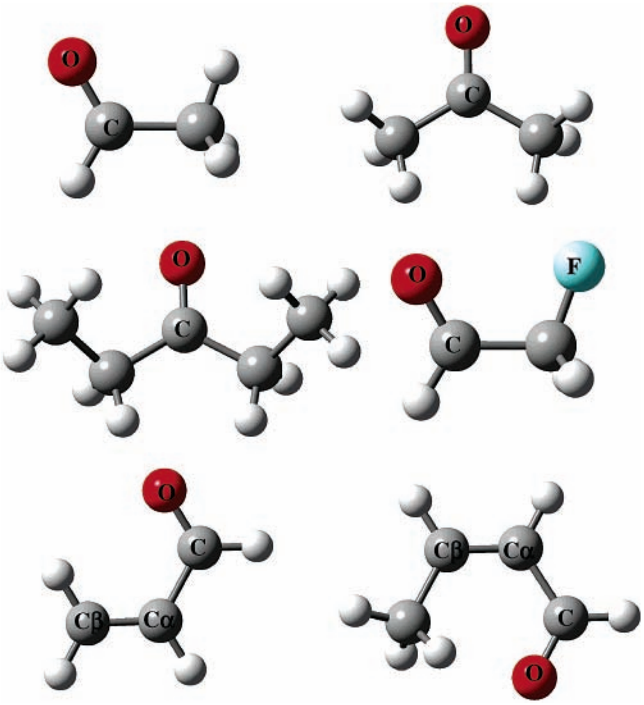


Figure 3. Molecules and numbering of atomic centers for carbonyl compounds.

TABLE 2: Local Softness ($s_k^+ = f_k^+S$, $s_k^- = f_k^-S$), Relative Softness ($s_k^r = s_k^+/s_k^-$), and $\Delta s_k = S\Delta f_k$ for Carbonyl Compounds

molecule		s_k^+	s_k^-	$s_k^r = (s_k^+/s_k)$	$\Delta s_k = (s_k^+ - s_k^-)$
CH_3CHO	C	0.9832	0.1468	6.6975	0.8364
	O	0.5284	1.0739	0.4920	−0.5455
CH_3COCH_3	C	0.7505	0.0882	8.5091	0.6623
	O	0.5167	1.0573	0.4887	−0.5406
$C_2H_5COC_2H_5$	C	0.6792	0.0925	7.3427	0.5867
	O	0.5209	1.0719	0.4860	−0.5510
CH_2FCHO	C	0.9557	0.2254	4.2400	0.7303
	O	0.5546	1.0765	0.5152	−0.5219
$CH_2{=}CHCHO$	C_β	0.7699	0.4427	1.7391	0.3272
	C	0.4194	0.1647	2.5464	0.2547
	O	0.4793	1.1759	0.4076	−0.6966
$CH_3CH{=}CHCHO$	C_β	0.5871	0.3806	1.5426	0.2065
	C	0.4405	0.1260	3.4960	0.3145
	O	0.4718	1.1758	0.4013	−0.7040

The α,β-conjugated carbonyl second family of compounds has been widely studied both experimentally and theoretically[44] because of the two reactive centers that they present. The first reactive site is the carbon of the carbonyl, and the second is the carbon in the β position. In such a case, the β carbon is activated because of the withdrawing mesomeric effect of the adjacent carbonyl group. As shown in Table 2, s_k^+ always indicates the conjugated carbon whereas s_k^r points out the carbon of the carbonyl as the most reactive site within the molecule. However, note that the oxygen atom still exhibit a high value. For instance, the values of the s_k^+ descriptor are 0.47 for the oxygen atom and 0.42 for the carbon atom of the carbonyl group of the $CH_2{=}CHCHO$ molecule, respectively. These are very close values that do not allow us to distinguish their reactive behavior. For the s_k^r descriptor, the values are 0.40 for the oxygen atom and 2.5 for the carbon atom, indicating that this latter descriptor is better than s_k^+ alone. The very same situation is found for all molecules studied. On the contrary, the descriptor Δs_k, once again, exhibits a high positive value on both carbons that are expected to be electrophilic, and it shows a negative value on the oxygen atom, thus underlying the nucleophilic character of this atom within the molecule. It is worth mentioning that the correct trends observed in Table 2 for Δs_k are reproduced when analyzing the effect of the basis set on this reactivity index.

Concluding Remarks

In this work, a new reactivity descriptor $\Delta f(r)$ has been proposed. It is shown that $\Delta f(r)$ provides useful information on both stabilizing and destabilizing interactions between a nucleophile and an electrophile and helps to identify the electrophilic/nucleophilic behavior of a specific site within a molecule. The index was tested on activated and deactivated monosubstituted benzene with good agreement with the experiment. The Dunitz−Burgi attack on carbonyl compounds was successfully rationalized, stressing the capability of the new index to handle stereoselectivity. Finally, a comparison between different reactivity descriptors has been carried out on a set of carbonyl compounds with promising results. The $\Delta f(r)$ index used to test nucleophilicity presents some advantages over local softness and relative electrophilicity.

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