Reactivity indices for natural bond orbitals: a new methodology

Jesús Sánchez-Márquez

Abstract A new reactivity index has been defined; this parameter is focused on a molecule's natural bond orbitals (NBOs) and derives in a natural way from Fukui functions. NBOs have the advantage of being very localized, allowing the reaction site of an electrophile or nucleophile to be determined within a very precise molecular region. Finally, the indices for a representative set of organic molecules were calculated and their usefulness tested on some protonation reactions.

Keywords Condensed Fukui function · Natural bond orbital · Reactivity index

Introduction

The interpretation and prediction of organic reactions is often complicated by, amongst other things, the entanglement of electronic and steric effects. In 1963, Pearson [1] launched a unifying concept by which the chemical reactivities, selectivities, and stabilities of compounds could be rationalized readily. Chemical entities were categorized as "hard" or "soft" Lewis acids or bases. Complex stability, however, cannot be estimated adequately by considering only hardness; additional parameters have to be introduced.

Condensed Fukui functions and related local and global parameters are very useful in the study of chemical reactivity.

J. Sánchez-Márquez (✉)
Departamento de Química-Física, Facultad de Ciencias, Universidad de Cádiz, Campus Universitario Río San Pedro, 11510, Puerto Real Cádiz, Spain
e-mail: jesus.sanchezmarquez@uca.es

Several reactivity studies [2–6] have demonstrated the utility of these types of theoretical descriptors. In some publications, canonical orbitals are used to justify the reactivity of a system; these sometimes differ from the frontier molecular orbitals (HOMO-1, HOMO-2,…) [7–9]. Other kind of orbitals, such as natural bond orbitals (NBOs) could have some advantages over canonical orbitals. When we calculate the Fukui functions of the atoms in a molecule, we sometimes find that they possess a double behavior, i.e., they are simultaneously electrophilic and nucleophilic and that is inconsistent with Eq. (12) (see below), which can have only one value at each point in space. When we calculate indices for orbitals (such as for NBOs) this problem disappears because an occupied orbital does not exhibit electrophilic behavior (or at least its electrophilic behavior is negligible compared to its nucleophilic properties) and vice versa. Moreover, we have chosen to study NBOs because they are very localized, which allows the point of attack of an electrophile or nucleophile to be delimited to a very definite region of the molecule, and because of the comfort of Lewis' structure diagrams, which represent the complex problem of reactivity in very simple and visual terms. For example, consider the reaction:
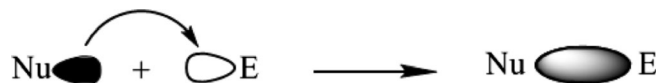
where 'Nu' is a nucleophile with one or more occupied NBO (lone pair, double-triple bond, …) and 'E' is an electrophile with one or more unoccupied NBO. To calculate the reactivity indices in such a case would be of great interest.

Theoretical background

In 1999, the concept of the electrophilicity index (ω) was quantitatively introduced by Parr et al. [10] as the stabilization

energy when atoms or molecules in their ground states acquire additional electronic charge from the environment.

At the second order, the energy change (ΔE) [11] due to the electron transfer (ΔN) satisfies Eq. 1:

$$\Delta E = \mu \, \Delta N + \frac{1}{2} \eta \, \Delta N^2 \tag{1}$$

where μ and η are the chemical potential (negative of the electronegativity) and chemical hardness, respectively, defined by Eqs. 2 and 3:

$$\mu = \left(\frac{\partial E}{\partial N} \right)_v \tag{2}$$

and

$$\eta = \left(\frac{\partial^2 E}{\partial N^2} \right)_v \tag{3}$$

with $\upsilon(r)$ as the external potential of the electrophile. According to Mulliken [12–16], using a finite difference method, working equations for the calculation of μ and η may be given as

$$\mu = -\frac{1}{2} (IP + EA) \tag{4}$$

and

$$\eta = (IP - EA) \tag{5}$$

where IP and EA are the first ionization potential and electron affinity, respectively. According to Koopmans' theorem [17] for closed-shell molecules, based on the finite difference approach, IP and EA can be expressed in terms of the highest occupied molecular orbital (HOMO) energy, $\in_H$, and the lowest unoccupied molecular orbital (LUMO) energy, $\in_L$, respectively, $IP \approx -\in_H$ and $EA \approx -\in_L$. Where $\in_H$ and $\in_L$ correspond to the Kohn-Sham [18] one-electron eigenvalues. Thus,

$$\mu = \frac{1}{2} (\in_L + \in_H) \tag{6}$$

and

$$\eta = (\in_L - \in_H) \tag{7}$$

If the electrophile environment provides enough charge, it will be become saturated with electrons according to Eq. 1

$$\left(\frac{dE}{dN} \right) = 0 \tag{8}$$

leading to the maximum amount of electron charge

$$\Delta N_{\max} = -\frac{\mu}{\eta} \tag{9}$$

and the total energy decrease

$$\Delta E_{\min} = -\frac{\mu^2}{2\eta} \tag{10}$$

The new density functional theory (DFT) reactivity index, global electrophilicity index or electrophilicity index (ω) [19] is proposed as

$$\omega \equiv \frac{\mu^2}{2\eta} \tag{11}$$

The electrophilicity index measures the stabilization energy when the system acquires an additional electronic charge $\Delta N_{\max} = -\mu/\eta$ from the environment, in terms of the electronic chemical potential μ and the chemical hardness η.

The electrophilicity index encompasses both the propensity of the electrophile to acquire an additional electronic charge driven by μ^2 (the square of electronegativity) and the resistance of the system to exchange electronic charge with the environment described by η. A good electrophile is, in this sense, characterized by a high value of μ and a low value of η.

A previous study [20] presented a good linear correlation between the electrophilicity values obtained from the computed IPs and EAs of ethylene derivatives and those obtained from the HOMO and LUMO energies. The results from this study [20] allow us to confirm the use of accessible B3LYP/6-31G* HOMO and LUMO energies, $\in_H$ and $\in_L$, to obtain reasonable values for the global electrophilicity index of organic molecules, and thus make valuable electrophilicity scales.

Local reactivity descriptors: local parameters

To understand detailed reaction mechanisms such as regioselectivity, in addition to global properties, local reactivity parameters are necessary to differentiate the reactive behavior of atoms forming a molecule. The Fukui function [21] [$f(r)$] and local softness [22] [$s(r)$] are two of the most commonly used local reactivity parameters (Eq. 12).

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N} \right)_\nu$$
$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu} \right)_\nu = \left(\frac{\partial \rho(r)}{\partial N} \right)_\nu \cdot \left(\frac{\partial N}{\partial \mu} \right)_\nu = S \cdot f(r) \tag{12}$$

The Fukui function is associated primarily with the response of the density function of a system to a change in the number of electrons (N) under the constraint of a constant external potential [$v(r)$]. The Fukui function also represents the response of the chemical potential of a system to a change in external potential. As the chemical potential is a measure of the intrinsic acidic or base strength, and local softness incorporates global reactivity, both parameters provide a pair of indices with which to demonstrate, for example, the specific sites of interaction between two reagents.

Due to the discontinuity of the electron density with respect to N, finite difference (FD) approximation leads to three types of Fukui function for a system, namely $f^+(r)$ (Eq. 13), $f^-(r)$ (Eq. 14) and $f^0(r)$ (Eq. 15) for nucleophilic, electrophilic and radical attack, respectively. $f^+(r)$ is measured by the electron density change following addition of an electron, and $f^-(r)$ by the electron density change upon removal of an electron. $f^0(r)$ is approximated as the average of both previous terms, defined as follows:

$$f^+(r) = \rho_{N_0+1}(r) - \rho_{N_0}(r), \text{ for nucleophilic attack,} \quad (13)$$

$$f^-(r) = \rho_{N_0}(r) - \rho_{N_0-1}(r), \text{ for electrophilic attack,} \quad (14)$$

$$f^0(r) = \frac{1}{2}\left(\rho_{N_0+1}(r) - \rho_{N_0-1}(r)\right), \text{ for neutral (or radical) attack} \quad (15)$$

Frontier molecular orbital method

Equation 12 was used to develop another condensed form of the Fukui function that can be defined approximately as:

$$f^-(r) = \rho_{HOMO}(r), \text{ for electrophilic attack,} \quad (16)$$

$$f^+(r) = \rho_{LUMO}(r), \text{ for nucleophilic attack,} \quad (17)$$

$$f^0(r) = \frac{1}{2}(\rho_{LUMO}(r) - \rho_{HOMO}(r)), \text{ for neutral (or radical) attack,} \quad (18)$$

Under frozen orbital approximation (FOA) of Fukui, and neglecting the second-order variations in the electron density, the Fukui function can be approximated as

$$f^\alpha(r) \approx |\phi^\alpha(r)|^2 \quad (19)$$

where $\phi^\alpha(r)$ is a particular frontier molecular orbital (FMO) chosen depending upon the value of $\alpha=+$ or $\alpha=-$. Expanding the FMO in terms of the atomic basis functions, the condensed Fukui function at the atom k is:

$$f_k^\alpha = \sum_{\nu \in k} \left[|C_{\nu\alpha}|^2 + \sum_{\chi \notin \mu} C_{\chi\alpha}{}^* C_{\nu\alpha} S_{\chi\nu} \right] \quad (20)$$

$$f_k^- = \sum_{\nu \in k} \left[|C_{\nu H}|^2 + \sum_{\chi \notin \nu} C_{\chi H}{}^* C_{\nu H} S_{\chi\nu} \right] \text{ (electrophilic attack)} \quad (21)$$

$$f_k^+ = \sum_{\nu \in k} \left[|C_{\nu L}|^2 + \sum_{\chi \notin \nu} C_{\chi L}{}^* C_{\nu L} S_{\chi\nu} \right] \text{ (nucleophilic attack)} \quad (22)$$

$$f_k^0 = \frac{1}{2}\left(f_k^+ + f_k^- \right) \text{ (radicalary attack)} \quad (23)$$

Where $C_{\nu\alpha}$ are the molecular frontier orbital coefficients, and $S_{\chi\nu}$ are the atomic orbital overlap matrix elements. The subscripts "H" and "L" are referenced to the HOMO and LUMO orbitals. This definition of the condensed Fukui function (Eqs. 20–23) has been used in a variety of studies yielding reliable results [17–24].

Table 1 Parameters: f_k^- (Eq. 21), $f_k^{NBO,i}$ (Eq. 24) and $C_i^2 f_k^{NBO,i}$ (Eq. 33) for the CO molecule. *NBO* Natural bond orbital

k	Z		$f_k^{NBO\ 2}$ BD C2-O1	$f_k^{NBO\ 1}$ BD C2-O1	$f_k^{NBO\ 7}$ LP C2	$f_k^{NBO\ 6}$ LP O1		
1	8	$f_k^{NBO,i}$	0.7937	0.7937	0.0422	0.9303		
2	6	$f_k^{NBO,i}$	0.2063	0.2063	0.9578	0.0697		
		C_i^2	0.0000	0.0000	0.9088	0.0894	$\sum_i C_i^2 f_k^{NBO,i}$	f_k
1	8	$C_i^2 f_k^{NBO,i}$	0.0000	0.0000	0.0384	0.0831	0.1215	0.1331
2	6	$C_i^2 f_k^{NBO,i}$	0.0000	0.0000	0.8704	0.0062	0.8767	0.8669

Table 2   Parameters: f_k (Eq. 21), $f_k^{NBO,i}$ (Eq. 24) and $C_i^2 f_k^{NBO,i}$ (Eq. 33) for the F_2 molecule

k	Z		$f_k^{NBO\,6}$ LP F1	$f_k^{NBO\,8}$ LP F1	$f_k^{NBO\,9}$ LP F2	$f_k^{NBO\,2}$ LP F2	$f_k^{NBO\,5}$ LP F2	$f_k^{NBO\,7}$ LP F1	$f_k^{NBO\,4}$ LP F1		
1	9	$f_k^{NBO,i}$	0.0029	0.0029	0.9971	0.9971	0.9847	0.0153	0.0029		
2	9	$f_k^{NBO,i}$	0.9971	0.9971	0.0029	0.0029	0.0153	0.9847	0.9971		
		C_i^2	0.0000	0.4979	0.4979	0.0000	0.0000	0.0000	0.0000	$\sum_i C_i^2 f_k^{NBO,i}$	f_k
1	9	$C_i^2 f_k^{NBO,i}$	0.0000	0.0014	0.4965	0.0000	0.0000	0.0000	0.0000	0.4979	0.5000
2	9	$C_i^2 f_k^{NBO,i}$	0.0000	0.4965	0.0014	0.0000	0.0000	0.0000	0.0000	0.4979	0.5000

Computational methods

All the structures included in this study were optimized at the B3LYP/6-31G(d) [25, 26] level of theory using the Gaussian09 package [27]. The electrophilic Fukui function was evaluated from a single point calculation in terms of molecular orbital coefficients and overlap matrix. The wave functions were calculated with Gaussian09 and the condensed Fukui functions were obtained with a modified version of UCA-FUKUI [28] (URL: http://www2.uca.es/dept/quimica_fisica/software/UCA-FUKUI.zip).

Results and discussion

Condensed Fukui functions provide information related to the atomic reactivity in the molecule. The following section introduces a new reactivity index based on condensed Fukui functions, but which provides information about orbital rather than atomic reactivity. In this work, we chose to study NBOs, because they are very localized and allow the reaction site of an electrophile or nucleophile to be delimited to a relatively small region in the proximity of the atom. This can be an important advantage because it gives helpful information about the more reactive sites in the molecule.

Reactivity indexes for NBOs: theoretical justification

If canonical molecular orbital coefficients ($C_{\chi\alpha}$ and $C_{\nu\alpha}$) are substituted by NBO coefficients ($C_{\chi NBO}$ and $C_{\nu NNBO}$), Eq. 20 is transformed into Eq. 24. The values f_k^{NBO} used in this work were calculated using a modified version of UCA-FUKUI software [28].

$$f_k^{NBO} = \sum_{\nu \in k} \left[|C_{\nu NBO}|^2 + \sum_{\chi \notin \mu} C_{\chi NBO}^{\;*} C_{\nu NBO}\, S_{\chi\nu} \right] \quad (24)$$

Now, we will redefine the condensed functions in this way:

$$f_k^{\alpha} = \sum_{\nu \in k} \left[|A_{\nu\alpha}|^2 + \sum_{\chi \notin \mu} A_{\chi\alpha}^{\;*} A_{\nu\alpha}\, S_{\chi\nu} \right] \quad (25)$$

$$f_k^{NBO} = \sum_{\nu \in k} \left[|B_{\nu NBO}|^2 + \sum_{\chi \notin \mu} B_{\chi NBO}^{\;*} B_{\nu NBO}\, S_{\chi\nu} \right] \quad (26)$$

where $A_{i\alpha}$ and B_{ij} are molecular orbital coefficients and χ_i are basis functions.

$$\phi^{HOMO} = \sum_i A_i \chi_i \quad (27)$$

$$\phi_j^{NBO} = \sum_i B_{ij} \chi_i \quad (28)$$

If the HOMO is developed in a linear combination of NBOs, Eq. 29 is obtained,

$$\phi^{HOMO} \approx \sum_i C_i \phi_i^{NBO} \quad (29)$$

Table 3 FF^{NBOs} (Eq. 33) and related parameters: f_k (Eq. 21), $f_k^{NBO,i}$ (Eq. 24) and C_i (Eq. 29) for the CO molecule

Z	f_k^{-} CMO 7	$f_k^{NBO\,2}$ BD C2-O1	$f_k^{NBO\,1}$ BD C2-O1	$f_k^{NBO\,7}$ LP C2	$f_k^{NBO\,6}$ LP O1
8	0.1331	0.7937	0.7937	0.0422	0.9303
6	0.8669	0.2063	0.2063	0.9578	0.0697
C_i		0.0000	0.0000	0.9533	0.2989
FF^{NBO}		0.0000	0.0000	0.9088	0.0894

Table 4 FF^{NBOs} (Eq. 33) and related parameters: f_k (Eq. 21), $f_k^{NBO,i}$ (Eq. 24) and C_i (Eq. 29) for the F_2 molecule

Z	f_k^- CMO 9	$f_k^{NBO\,6}$ LP F1	$f_k^{NBO\,8}$ LP F1	$f_k^{NBO\,9}$ LP F2	$f_k^{NBO\,5}$ LP F2	$f_k^{NBO\,7}$ LP F2	$f_k^{NBO\,4}$ LP F1
9	0.5000	0.0029	0.0029	0.9971	0.9971	0.9847	0.0153
9	0.5000	0.9971	0.9971	0.0029	0.0029	0.0153	0.9847
C_i		0.0000	−0.7056	0.7056	0.0000	0.0000	0.0000
FF^{NBO}		0.0000	0.4979	0.4979	0.0000	0.0000	0.0000

then the HOMO (ϕ^{HOMO}) could be represented as in Eq. 30:

$$\phi^{HOMO} \approx \sum_i C_i \left(\sum_j B_{ji} \chi_j \right) = \sum_i \sum_j C_i B_{ji} \chi_j$$

$$= \sum_i \sum_j C_i B_{ji} \chi_j = \sum_j \left(\sum_i C_i B_{ji} \right) \chi_j \quad (30)$$

if we compare Eq. 30 and Eq. 27 we can deduce Eq. 31

$$A_j \approx \sum_i C_i B_{ji} \quad (31)$$

and by substituting Eq. 31 in Eq. 25 we obtain Eq. 32.

$$f_k^\alpha \approx \sum_i \left[|C_{i\alpha}|^2 f_k^{NBO,i} + \sum_j C_{i\alpha} C_{j\alpha} \left(\sum_{\substack{\nu \in k \\ \chi \neq \nu}} \sum_{\chi \in k} B_{\chi i} B_{\nu j} S_{\chi \nu} \right) \right]$$

$$(32)$$

In Eq. 32, two components can be distinguished, one of which being the elements $|C_{i\alpha}|^2 f_k^{NBO,i}$; this part could be considered the intrinsic participation of each NBO_i to f_k^α. The second contribution, $\sum_j C_{i\alpha} C_{j\alpha} \left(\sum_{\nu \in k} \sum_{\chi \in k} B_{\chi i} B_{\nu j} S_{\chi \nu} \right)$, is the sum of the crossed components (NBO_i with other NBOs). The parameters f_k^α and $f_k^{NBO,i}$ were calculated with a modified version of the UCA-FUKUI software, and the $C_{i\alpha}$ values were obtained by the least squares method. Thus, the term: $\sum_j C_{i\alpha} C_{j\alpha} \left(\sum_{\nu \in k} \sum_{\chi \in k} B_{\chi i} B_{\nu j} S_{\chi \nu} \right)$ can be calculated and we can determine if it is negligible. If $f_k^\alpha \approx \sum_i |C_{i\alpha}|^2 f_k^{NBO,i}$ is accepted, we obtain the distribution of the f_k^α coefficient taking into account the considered NBOs. This allows us to discuss what NBOs have influence on the f_k^α value. To compare different NBOs, we defined a global coefficient for each NBO, FF_i^{NBO}, as the sum of all terms: $|C_{i\alpha}|^2 f_k^{NBO,i}$, for all atoms in the molecule (Eq. 33), which summarizes the global reactivity of a NBO.

Fig. 1 *a* Fontier molecular orbital (FMO) of the Fukui approximation (Eq. 16) for the CO molecule. **b** Finite difference (FD) approximation (Eq. 14). **c** Main studied natural bond orbitals (NBOs) and FF^{NBOs} parameters. *d* NBO energy levels (a.u.)

Fig. 2 **a** FMO of the Fukui approximation (Eq. 16) for the F_2 molecule. **b** FD approximation (Eq. 14). **c** Main studied NBOs and FF^{NBOs} parameters. **d** NBO energy levels (a.u.)
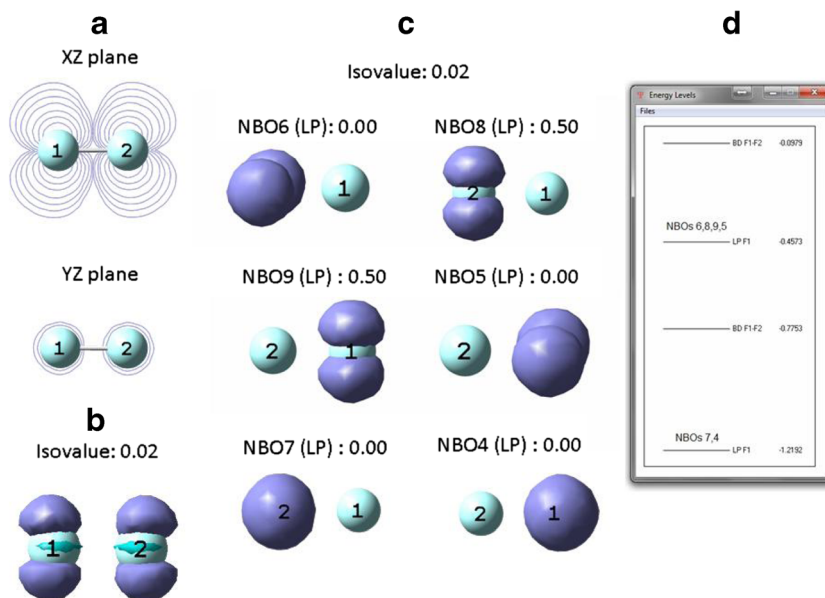
$$FF_i^{NBO} = \sum_k |C_{i\alpha}|^2 f_k^{NBO,i} \qquad (33)$$

Table 1 shows $|C_{i\alpha}|^2 f_k^{NBO,i}$ values (Eq. 32), calculated for the CO molecule. These values provide an approximate distribution of the f_k^α index in terms of NBOs. We can see that NBO 7 (lone pair centered on the carbon) contributes mainly to the condensed Fukui function of the C atom. The oxygen condensed Fukui function has a big contribution from NBO 6 (lone pair centered on the oxygen). Also, we can see that the sums $\sum_i |C_{i\alpha}|^2 f_k^{NBO,i}$ for oxygen and carbon atoms are approximately equal to

the corresponding f_k^- functions. In Table 2, $C_i^2 f_k^{NBO,i}$ values are shown for the F_2 molecule. The conclusions that can be drawn from the data in Table 2 are similar to the previous ones (Table 1). Finally, supplementary Tables S1–S3 show results for H_2O, CH_2O and NH_3 molecules.

Fitting a frontier orbital with a linear combination of NBOs

In the previous section, we replaced a frontier orbital with a linear combination of NBOs (Eq. 29). The coefficients of Eq. 29 were obtained by the least square method. For the HOMO frontier orbital, we chose the occupied NBOs with
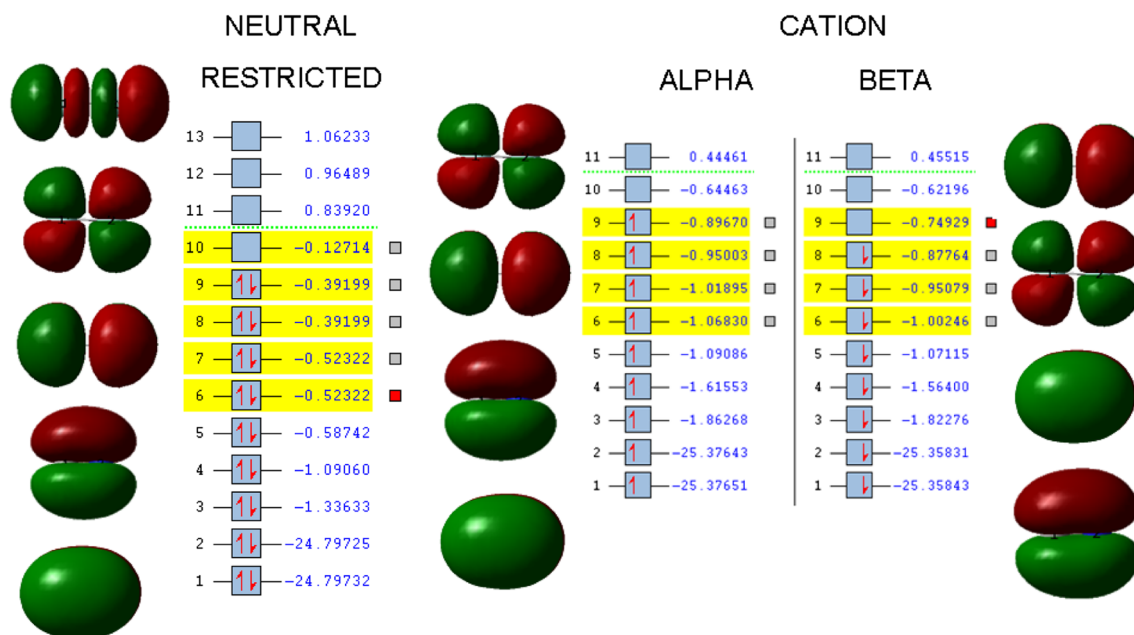

Fig. 3 Canonical-orbital energy levels for the F_2 molecule. *Left* Neutral-molecule energy levels, *right* cation-molecule energy levels

high energy (logically, for the LUMO we chose the unoccupied NBOs with low energy). Very stable sigma NBOs or core

NBOs were not included in Eq. 29. Fittings were obtained using a program we developed for this purpose.
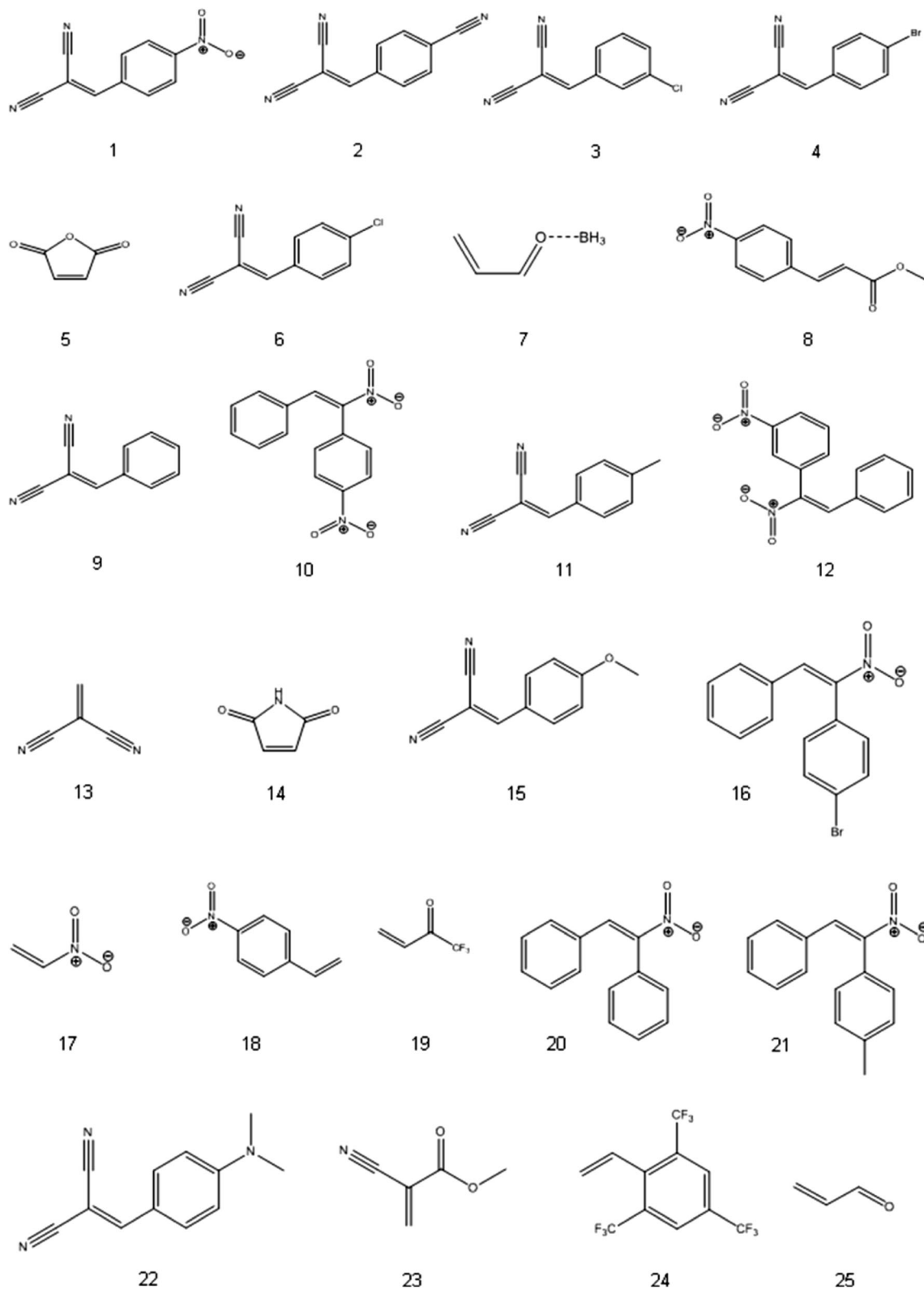

Fig. 4 Sample of molecules used to test the new index

Table 5 $FF^{NBO}s$ (Eq. 33) and related parameters: f_k^- (Eq. 21), $f_k^{NBO,\,i}$ (Eq. 24) and C_i (Eq. 29) for reagent 17

Z	f_k^- CMO 19	$f_k^{NBO\,17}$ LP O7	$f_k^{NBO\,16}$ LP O7	$f_k^{NBO\,19}$ LP O8	$f_k^{NBO\,2}$ BD C1-C2	$f_k^{NBO\,9}$ BD N6-O8	$f_k^{NBO\,15}$ LP O7	$f_k^{NBO\,18}$ LP O8
6	0.0282	0.0000	0.0005	0.0005	0.4386	0.0000	0.0026	0.0001
6	0.0083	0.0000	0.0004	0.0005	0.5520	0.0034	0.0076	0.0042
1	0.0009	0.0000	0.0005	0.0000	0.0000	0.0000	0.0003	0.0000
1	0.0084	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001
1	0.0035	0.0000	0.0000	0.0004	0.0000	0.0000	0.0002	0.0008
7	0.0068	0.0226	0.0283	0.0300	0.0093	0.3726	0.1036	0.0999
8	0.4289	0.9771	0.9674	0.0033	0.0000	0.0035	0.8820	0.0038
8	0.5150	0.0002	0.0030	0.9653	0.0000	0.6206	0.0038	0.8912
C_i		−0.0002	0.6089	−0.6830	0.0000	0.0001	−0.0713	0.0775
FF^{NBO}		0.0000	0.3708	0.4664	0.0000	0.0000	0.0051	0.0060

Testing the FF^{NBO} index in a sample of simple molecules

The new index (Eq. 33) was calculated for simple molecules: CO, F_2, H_2O, CH_2O and NH_3. The results can be seen in Tables 3 and 4 (see also supplementary Tables S4–S6). In Table 3, we can see the calculated parameters for the CO molecule: the column f_k^- / CMO 7 (canonical molecular orbital 7) corresponds to the condensed Fukui function for the HOMO (Eq. 21), the other columns are condensed functions of the NBOs (Eq. 24). In the row labeled C_i, the coefficients of

Fig. 5 **a** FD approximation (Eq. 14) of reagent 17. **b** FMO of Fukui approximation (Eq. 16). **c** NBOs 15, 16, 18, 19 and FF^{NBO} values
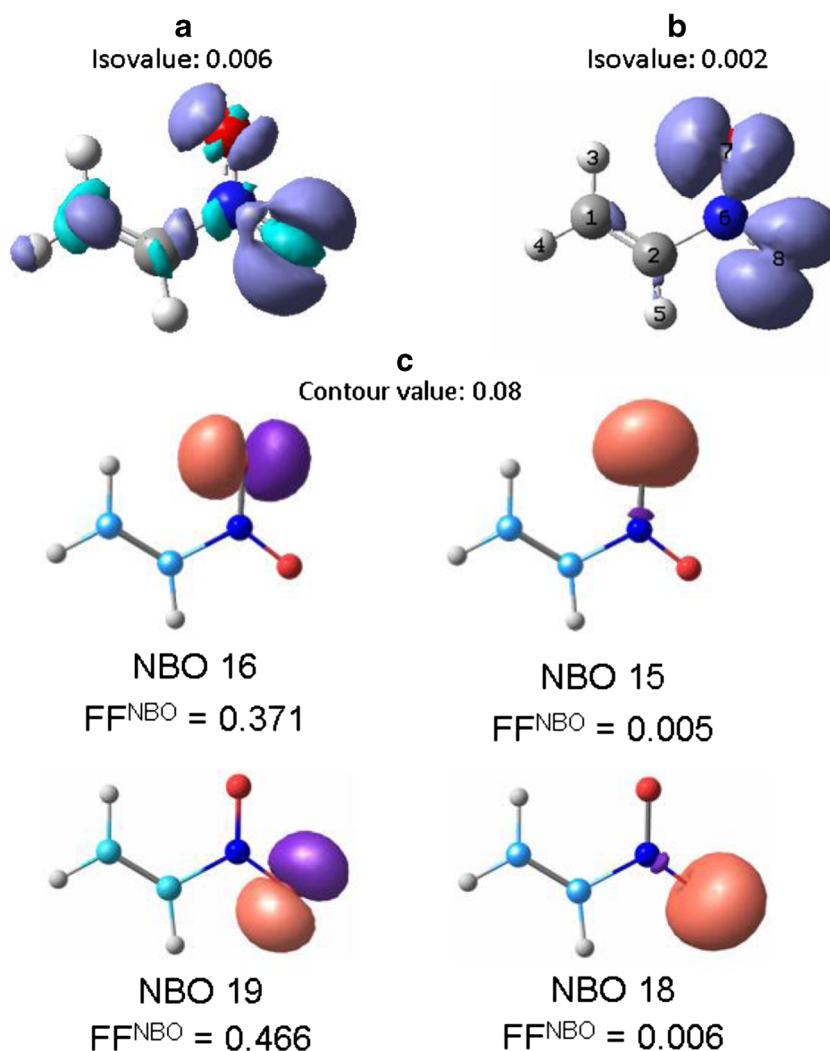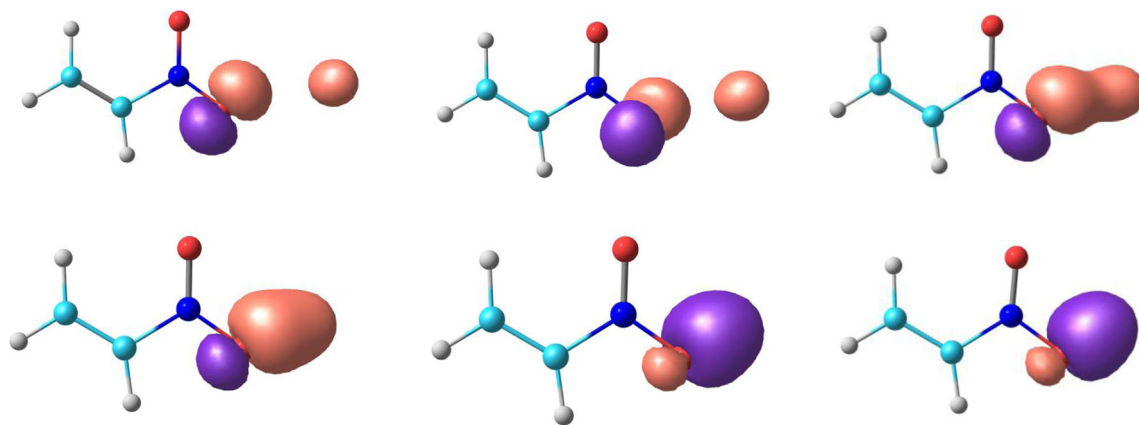
Fig. 6 Some images of the reaction path for the protonation of reagent 17

the least square method (Eq. 29) are shown, and in row FF^{NBO}, the new reactivity indices of the NBOs (Eq. 33). The f_k^- values for the CO molecule are 0.8669 (carbon) and 0.1331 (oxygen), and, as we can see in Table 1, the main contributor to the carbon parameter (100 % approximately) is NBO7 ($C^2_{NBO7} \cdot f^{NBO7}_{Carbon} = 0.8704$), for oxygen, NBO7 and NBO8 are the principal contributors of the f_k^- parameter (31 % and 68 % approximately: $C^2_{NBO6} \cdot f^{NBO6}_{Oxygen} = 0.0384$ and $C^2_{NBO7} \cdot f^{NBO7}_{Oxygen} = 0.0831$).

Figures 1 and 2c present graphical representations of the studied NBOs (Tables 3, 4) with their FF^{NBO} values (see also Figs. S1–S3 in the supplementary material). Also, we can see pictures of Fukui functions (Fig. 1a) calculated by means Eq. 16, and finite difference approximation (Fig. 1b) by Eq. 14. Figure 1a,b shows that both approximations are very

similar. In Fig. 1c, the NBO with the highest FF^{NBO} value is NBO 8, as we would expect if we compare the FMO of Fukui approximation images (Fig. 1a) with the NBO images (Fig. 1c). Something similar occurs in Fig. 2c: NBOs 8 and 9 have the highest FF^{NBO} values [compare the FMO of Fukui approximation images (Fig. 2a) with the NBOs images (Fig. 2c)]. Similar conclusions were also obtained for all the other studied NBOs (Figs. S1–S3). Note that Fig. 2a shows an unusual Fukui function because HOMO (CMO9) and HOMO−1 (CMO8) are degenerate orbitals (Fig. 3, left). Figure 3 (right) shows the F_2 cation and we also note that the lost electron belongs to BETA-CMO9. The CMO8 has the same shape as that of BETA-CMO9 and CMO9 is similar to a rotated BETA-CMO9. We have not changed this figure because it does not affect the discussion. The images in Figs. 1

Fig. 7 *Left* Average local ionization energy of reagent 17 (Eq. 35), *right* Fukui function (FD approximation, Eq. 14): electrophilic attack
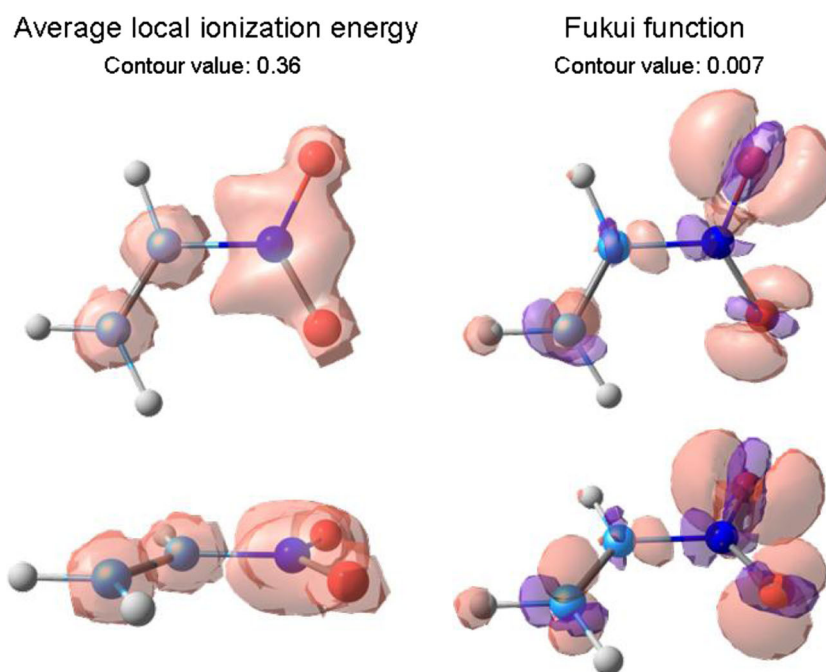
and 2 were generated with Gauss View [29] and UCA-FUKUI.

Testing the FF^{NBO} index in a representative sample of molecules

The molecules used to test the new index (Fig. 4) were taken from [30]. We chose this sample because it is representative and has a great diversity of functional groups: double bonds, triple bonds, halogens (F, Br, Cl), cyanide, nitro, ether, ester, amine, ketone, aldehyde, and aromatic rings.

Table 5 lists the calculated parameters for reagent 17. The column f_k^- / CMO 19 (canonical molecular orbital 19) corresponds to the condensed Fukui function for the HOMO (Eq. 21); the other columns are condensed functions of the NBOs (Eq. 24). The coefficients of the least square method (Eq. 29) are in row C and row FF^{NBO} shows the new reactivity indices of the NBOs (Eq. 33). Supplementary Tables S7–S31 present the parameters shown in Table 5 for the reagents shown in Fig. 4.

The most interesting thing in Table 5 is that two NBOs from the same atom have diverse values for the FF^{NBO} parameter. For example, NBO 19 and NBO 18 (Fig. 5): both are lone pairs centred in O8 but their FF^{NBO} values are very different. According to this index, a greater reactivity should be expected for NBO 19. To test the new reactivity index, we used a protonation reaction and calculated the reaction path for some reagents. The criteria for selection of the reaction site (the atom) was that it had to have a large nucleophile tendency and two or three NBOs (lone pairs) centred in the same atom. The highest FF^{NBO} value in reagent 17 was obtained for the lone pair NBO 19 (Table 5). Figure 5 (left) shows a representation of this orbital. To the right, we have NBO 18 (lone pair) but with a smaller FF^{NBO} value (Table 5). FD and FMO approximations are also illustrated in Fig. 5. FMO predicts the same reactivity for NBO16 and NBO19. However, FD approximation seems to indicate the largest reactivity for NBO19, as predicted by the FF^{NBO} index, but note that the FF^{NBO} is obtained from the FMO approximation. The images in Figs. 5 and 6 were produced using the software Chemcraft (http://www.chemcraftprog.com/).

Figure 6 shows the protonation of the O8 atom in reagent 17. Six points along the reaction path are represented. The NBO that interacts with the proton is NBO 19 (Fig. 5). Reagents in supplementary Figs. S4–S12 have the same characteristics of reagent 17 and we obtained the same conclusions in all cases.

Average local ionization energy and Fukui function

The average local ionization energy $I(r)$ is the energy necessary to remove an electron from point r in the space of a system. Its lowest values reveal the locations of the least tightly held electrons, and thus the favored sites for reaction with electrophiles or radicals. If $\rho_i(r)$ is the electronic density of the orbital $\varphi_i(r)$, having energy ε_i, and the total electronic density is $\rho(r)$, then the average orbital energy at point r is:

$$\overline{\varepsilon}_i = \frac{\sum_i \rho_i(r)\varepsilon_i}{\rho(r)}. \tag{34}$$

The summation is over all occupied orbitals. If $I_i \approx |\varepsilon_i|$ is assumed to be valid (where I_i is the ionization energy of an electron in an orbital and ε_i is the energy of an electron in ϕ_i), then Eq. 34 can be rewritten as:

$$\overline{I}(r) = \frac{\sum_i \rho_i(r)|\varepsilon_i|}{\rho(r)} \tag{35}$$

Where $\overline{I}(r)$ is the average local ionization energy at r [31].

Figure 7 (to the left) shows the average local ionization energy of reagent 17 and (to the right) the Fukui function for electrophilic attack (Eq. 14). These differ but both functions give complementary information about reactivity. On the one hand, the average local ionization energy describes the distribution of the energy necessary to extract an electron. On the other hand, the Fukui function (FD and FMO approximations) gives information about where an electron can be extracted with higher probability.

Conclusions

A new parameter that gives extra information about reactivity has been defined and a viable means of calculation has been identified for it. The parameter was calculated in a varied and representative group of molecules and the results compared with some protonation reactions to test the validity of the new index, obtaining satisfactory conclusions. The protonation reactions studied were coherent with the obtained values of FF^{NBO}.

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