SOFTWARE REPORT

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Introducing a new bond reactivity index: Philicities for natural bond orbitals

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Abstract

In the present work, a new methodology defined for obtaining reactivity indices (philicities) is proposed. This is based on reactivity functions such as the Fukui function or the dual descriptor, and makes it possible to project the information from reactivity functions onto molecular orbitals, instead of onto the atoms of the molecule (atomic reactivity indices). The methodology focuses on the molecules' natural bond orbitals (bond reactivity indices) because these orbitals have the advantage of being localized, allowing the reaction site of an electrophile or nucleophile to be determined within a very precise molecular region. This methodology provides a "philicity" index for every NBO, and a representative set of molecules has been used to test the new definition. A new methodology has also been developed to compare the "finite difference" and the "frontier molecular orbital" approximations. To facilitate their use, the proposed methodology as well as the possibility of calculating the new indices have been implemented in a new version of UCA-FUKUI software. In addition, condensation schemes based on atomic populations of the "atoms in molecules" theory, the Hirshfeld population analysis, the approximation of Mulliken (with a minimal basis set) and electrostatic potential-derived charges have also been implemented, including the calculation of "bond reactivity indices" defined in previous studies.

Introduction

To understand some detailed reaction mechanisms such as regio-selectivity, besides global descriptors [1–11], local reactivity parameters to differentiate the reactive behavior of the atoms forming molecules are necessary. The Fukui function [12, 13] ($f(r)$) and the softness

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[14–16] ($s(r)$) are two of the most commonly used reactivity descriptors Eq.1

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{\nu} ; S = \left(\frac{\partial N}{\partial \mu}\right)_{\nu}$$
$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{\nu} = \left(\frac{\partial \rho(r)}{\partial N}\right)_{\nu} \cdot \left(\frac{\partial N}{\partial \mu}\right)_{\nu} = f(r) \cdot S \tag{1}$$

The Fukui function is primarily associated with the response of the density function of a system when changing the number of electrons (N) under the constraint of a constant external potential [$v(r)$]. The Fukui function can also represent the response of the electronic chemical potential [17] of a system when changing its external potential. Since the chemical potential is a measure of the intrinsic acidic or base strength, and softness incorporates global reactivity, they provide two indices that make it possible to determine, for example, the specific sites of interaction between two reagents.

Due to the discontinuity of the electron density with respect to N, finite difference approximation (FD) leads to three types of Fukui function for a system, namely: $f^+(r)$ Eq. (2), $f^-(r)$

Eq. (3), and $f^0(r)$ Eq. (4) for nucleophilic, electrophilic and radical attack, respectively. $f^+(r)$ is measured by the electron density change following the addition of an electron, and $f^-(r)$ by the electron density change upon removal of an electron. $f^0(r)$ is approximated to the average of the both previous terms, which are defined as follows:

$$f^+(r) = \rho_{N_0+1}(r) - \rho_{N_0}(r), \textit{for nucleophilic attack}, \quad (2)$$

$$f^-(r) = \rho_{N_0}(r) - \rho_{N_0-1}(r), \textit{for electrophilic attack}, \quad (3)$$

$$f^0(r) = \frac{1}{2}\left(\rho_{N_0+1}(r) - \rho_{N_0-1}(r)\right), \textit{for neutral (or radical) attack}. \quad (4)$$

The condensation of reactivity descriptors to atoms can be carried out in several ways, such as: the famous Yang–Mortier scheme [18] or other "population strategies", as can be seen in references [19, 20].

Frontier molecular orbital approximation

Considering the frozen orbital approximation (FOA) of Fukui [21–25], and neglecting the orbital relaxation effects, the Fukui function can be approximated as follows:

$$f^\alpha(r) \approx |\phi^\alpha(r)|^2 \quad (5)$$

where $\varphi^\alpha(r)$ is a particular frontier molecular orbital (FMO) chosen depending upon the value of $\alpha = +$ or $\alpha = -$. Eq. (5) can be used to develop an approximated definition of the Fukui function:

$$f^-(r) = \rho_{HOMO}(r), \textit{for electrophilic attack}, \quad (6)$$

$$f^+(r) = \rho_{LUMO}(r), \textit{for nucleophilic attack}, \quad (7)$$

$$f^0(r) = \frac{1}{2}(\rho_{LUMO}(r) + \rho_{HOMO}(r)), \textit{for neutral (or radical) attack}. \quad (8)$$

Expanding the FMO in terms of the atomic basis functions, the condensed Fukui function at the atom k is:

$$f_k^\alpha = \sum_{\nu \in k}\left[|C_{\nu\alpha}|^2 + \sum_{\chi \notin \nu} C_{\chi\alpha}{}^* C_{\nu\alpha}\, S_{\chi\nu}\right] \quad (9)$$

$$f_k^- = \sum_{\nu \in k}\left[|C_{\nu H}|^2 + \sum_{\chi \notin \nu} C_{\chi H}{}^* C_{\nu H}\, S_{\chi\nu}\right] (\textit{electrophilic attack}) (10)$$

$$f_k^+ = \sum_{\nu \in k}\left[|C_{\nu L}|^2 + \sum_{\chi \notin \nu} C_{\chi L}{}^* C_{\nu L}\, S_{\chi\nu}\right] (\textit{nucleophilic attack}) \quad (11)$$

$$f_k^0 = \frac{1}{2}\left(f_k^+ + f_k^-\right) (\textit{radical attack}) \quad (12)$$

where $C_{\nu\alpha}$ are the molecular frontier orbital coefficients, and $S_{\chi\nu}$ are the elements of the atomic orbital overlap matrix. The subscripts "H" and "L" in Eqs. (10, 11) are referenced to the HOMO and LUMO orbitals, respectively. This definition of the condensed Fukui function was pioneered by Pérez and

Chamorro [26, 27] and has been used in a variety of studies yielding reliable results [28–30].

Chemical reactions are mainly adjustment of valence electrons among the reactant orbitals. Fukui proposed his frontier orbital theory [31], which allows a chemical reaction to be understood in terms of HOMO and LUMO only. Fukui functions capture this concept of frontier orbital theory. The largest value of $f(r)$ at the reaction site will be preferable [32] since that will imply a large electronic-potential change. Since the hard species [33] are generally of small size and high charge and the soft species are large in size with a low charge, it is expected that in the *hard–hard* reactions ionic bonding would predominate [34, 35] and in the *soft–soft* reactions covalent bonding would predominate. For the soft species, the nuclear charge is adequately screened by the core electrons and the two soft species will mainly interact via frontier orbitals but the core orbitals are not just "spectators" for the hard-hard reactions, implying that soft-soft interactions are frontier-controlled (follow "through bond" interactions) while hard–hard interactions are charge-controlled (follow "through space" interactions) [34]. One should not expect FOT to work in the case of hard–hard interactions. While *soft–soft* interactions are controlled by $f(r)$, for *hard–hard* interactions the charges on each atom will decide the actual reaction site [36, 37]. It has also been shown [34] that for the interaction between a hard and a soft species the reactivity is generally very low and it cannot be identified as a charge/frontier-controlled reaction, vindicating the HSAB principle [36, 38–43].

Reactivity indices of natural bond orbitals

In a previous study [44], we proposed the FF_i^{NBO} reactivity index (Eq. 13) for NBO$_i$ (ST1 in the Supplementary Material shows a summary of the nomenclature and definitions),

$$FF_i^{NBO} = \sum_k |C_{i\alpha}|^2 f_{ki}^{(NBO)} \quad (13)$$

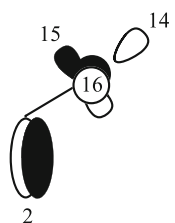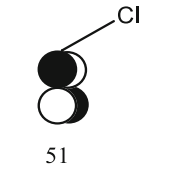which is based on the approximation:

$$f_k^\alpha = \sum_{\nu \in k}\left[|A_{\nu\alpha}|^2 + \sum_{\chi \notin \mu} A_{\chi\alpha}{}^* A_{\nu\alpha}\, S_{\chi\nu}\right] \approx \sum_i |C_{i\alpha}|^2 f_{ki}^{(NBO)}; (a = + or -) \quad (14)$$

where

$$f_{ki}^{(NBO)} = \sum_{\nu \in k}\left[\left|B_{\nu i}^{(NBO)}\right|^2 + \sum_{\chi \notin \nu} B_{\chi i}^{(NBO)}{}^* B_{\nu i}^{(NBO)}\, S_{\chi\nu}\right] \quad (15)$$

$A_{i\alpha}$ and B_{ij} represent the molecular orbital coefficients and χ_i the basis functions employed to develop $\varphi^{HOMO} = \sum_i A_i\chi_i$ and $\varphi_j^{NBO} = \sum_i B_{ij}\chi_i$. The subscripts "$i$" and "$k$" in Eqs. (13–15) are referenced to orbitals and atoms, respectively. The C_i coefficients of Eq. (16) were obtained by the least-squares

Table 1 $w_i^{-(NBO)}$, $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation, (HOMO and LUMO) for CH_2CHCl reagent

Schematic representations of NBOs	Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO)
	18	55	BD C2-Cl6	-0.00174	-0.00077	-0.00110
	17	51	BD C1-C2	0.00697	0.01487	0.01537
	Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO)
	16	2	BD C1-C2	0.01364	0.01295	-0.01451
	15	16	LP Cl6	0.00697	0.00678	-0.00630
	14	15	LP Cl6	0.00112	-0.00001	-0.00024
	8	14	LP Cl6	0.00092	0.00094	-0.00053

method by applying Eq. (17), which leads to the linear system of Eq. (18).

$$\int \left[\varphi^{(HOMO)} - \sum_i C_i \varphi_i^{(NBO)} \right]^2 d\tau = MINIMUM \qquad (17)$$

$$\varphi^{(HOMO)} \approx \sum_i C_i \varphi_i^{(NBO)} \qquad (16)$$

$$\sum_i \sum_l A_i B_{lj} S_{il} \approx \sum_k \sum_i \sum_l C_k B_{ik} B_{lj} S_{il} \qquad (18)$$

Table 2 $w_i^{-(NBO)}$ $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation (HOMO and LUMO) for CH_2CHCHO reagent

Schematic representations of NBOs	Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO: LUMO)
	19	65	BD C2-C6	-0.00167	-0.00109	-0.00117
	17	61	BD C1-C2	0.00240	0.00971	0.00961
	16	67	BD C6-O7	0.00792	0.01553	0.01723
	Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO: HOMO)
	15	15	LP O7	0.01410	0.02470	-0.02499
	14	2	BD C1-C2	0.00505	-0.00037	-0.00277
	13	8	BD C6-O7	0.00079	0.00080	-0.00169
	7	14	LP O7	-0.00298	0.00051	0.00015

Table 3 $w_i^{-(NBO)}$, $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation (HOMO and LUMO) for CH_2CHNO_2 reagent
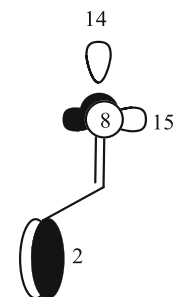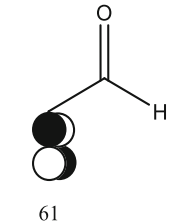
Schematic representations of NBOs

Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO: LUMO)
24	81	BD N6-O8	-0.00093	0.00008	0.00056
23	79	BD N6-O7	-0.00102	-0.00052	-0.00025
22	78	BD C2-N6	-0.00122	-0.00102	-0.00101
21	74	BD C1-C2	0.00314	0.00967	0.00949
20	80	BD N6-O7	0.00868	0.02067	0.02061
Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO: HOMO)
19	19	LP O8	-0.00195	-0.00063	0.00870
18	18	LP O8	0.00155	0.02044	-0.02045
17	165	LP O7	0.02000	0.02529	-0.02523
16	2	BD C1-C2	0.01005	-0.00006	-0.00237
15	8	BD N6-O7	-0.00226	-0.00180	-0.00102
10	17	LP O8	-0.00217	-0.00022	0.00178
9	15	LP O7	-0.00478	-0.00012	0.00178

Bond reactivity indices

NBO-based Fukui functions and related quantities have been previously studied in other works performed by different authors [45, 46], and the bond reactivity indices: $f_i^{+(NBO)}$ and $f_i^{-(NBO)}$ were defined in a previous own study [47] (table ST1 in the Supplementary Material shows a summary of the nomenclature and definitions). The main difference in the work performed in reference [45] regarding the proposed one in this paper is that it is the first one based on the partial occupations of the NBOs of the neutral molecule, the cation, and the anion (without considering possible changes in the NBOS set), while in the proposed work, the Fukui's functions are projected on the NBOs of the neutral molecule, and it is based on the approximation that states that NBOs do not change when the molecule loses or gains an electron, only their *effective* occupancies.

$\left\{f_i^{-(NBO)}\right\}$ and $\left\{f_i^{+(NBO)}\right\}$ sets, were estimated by using least-squares method, fitting Eq. (19).

$$\int\left(f^-\left(\overrightarrow{r}\right)-\sum_{i=1}^{all\ orbitals}f_i^{-(NBO)}\left|\varphi_i^{(NBO)}\left(\overrightarrow{r}\right)\right|^2\right)^2 d\overrightarrow{r} = MINIMUM$$
$$\int\left(f^+\left(\overrightarrow{r}\right)-\sum_{i=1}^{all\ orbitals}f_i^{+(NBO)}\left|\varphi_i^{(NBO)}\left(\overrightarrow{r}\right)\right|^2\right)^2 d\overrightarrow{r} = MINIMUM \quad (19)$$

The Lagrange multipliers [48] method was used to obtain the reactivity indices of Eq. (19), and finally, the following relations were obtained:

$$\int\left(f^-\left(\overrightarrow{r}\right)-\sum_{i=1}^{all\ orbitals}f_i^{-(NBO)}\left|\varphi_i^{(NBO)}\left(\overrightarrow{r}\right)\right|^2\right)^2 d\overrightarrow{r} \quad (20)$$
$$+ \lambda\left[\sum_{i=1}^{all\ orbitals}f_i^{-(NBO)}-1\right] = MINIMUM$$

$$\int \left(f^+\left(\overrightarrow{r}\right) - \sum_{i=1}^{all\ orbitals} f_i^{+(NBO)} \left| \varphi_i^{(NBO)}\left(\overrightarrow{r}\right)\right|^2 \right)^2 d\overrightarrow{r}$$

$$+ \lambda \left[\sum_{i=1}^{all\ orbitals} f_i^{+(NBO)} - 1 \right]$$

$$= MINIMUM \qquad (21)$$

$$\int \left(\Delta f\left(\overrightarrow{r}\right) - \sum_{i=1}^{all\ orbitals} \Delta f_i^{(NBO)} \left| \varphi_i^{(NBO)}\left(\overrightarrow{r}\right)\right|^2 \right)^2 d\overrightarrow{r}$$

$$+ \lambda \left[\sum_{i=1}^{all\ orbitals} \Delta f_i^{(NBO)} \right]$$

$$= MINIMUM \qquad (22)$$

Computational details

All the structures included in this study were optimized at B3LYP/6-31G(d) [49, 50] theory level by using the Gaussian 09 package [51]. For the FMO approximation, the electrophilic Fukui function was evaluated from a single point calculation in terms of molecular orbital coefficients and overlap integrals. For the FD approximation, the densities were calculated for the neutral molecule, the cation, and anion from a single-point calculation (the wave functions were obtained through Gaussian 09 software).

The calculation of the new indices and the new methodology defined in this study (see below) have been implemented in the new version of the UCA-FUKUI software (http://www2.uca.es/dept/quimica_fisica/software/UCA-FUKUI_v2.exe). A detailed description of all the improvements implemented in the new version of the program has been included in Appendix I of the Supplementary Material as well as several examples showing how to use them.

Results and discussion

In a previous paper [47] formula (23) was obtained, which allows us to relate the atomic reactivity indices, f_k^-, and those

Table 4 $w_i^{-(NBO)}$, $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation (HOMO and LUMO) for CH_2CHCN reagent

Schematic representations of NBOs

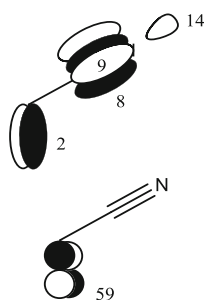| Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO: LUMO)
21	63	BD C2-C6	-0.00152	-0.00125	-0.00121
17	65	BD C6-N7	-0.00057	0.00075	0.00073
16	66	BD C1-C2	0.00258	0.00619	0.00773
15	59	BD C6-N7	0.00792	0.01704	0.01893
Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO: HOMO)
14	2	BD C1-C2	0.02436	0.02333	-0.02703
13	9	BD C6-N7	0.01090	0.01590	-0.01827
12	8	BD C6-N7	-0.00149	0.00046	-0.00129
11	14	LP N7	-0.00187	0.00063	-0.00034

Table 5 $w_i^{-(NBO)}$, $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation (HOMO and LUMO) for CH_2CHCH_3 reagent

Schematic representations of NBOs	Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO: LUMO)
	14	54	BD C2-C6	-0.00094	-0.00039	-0.00040
	13	50	BD C1-C2	0.00395	0.00913	0.00951
	Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO: HOMO)
	12	2	BD C1-C2	0.01210	0.01260	-0.01426

of the bond reactivity, $f_i^{-(NBO)}$, where the "k" subscript refers to atoms and the "i" subscript to orbitals.

$$f_k^- \approx \sum_i f_i^{-(NBO)} \cdot f_{ki}^{(NBO)} \qquad (23)$$

Furthermore, considering the relationship between the *atomic philicities* (w_k^-) and the global one (w) [52], by means of the condensed indices of Fukui $w_k^- = w \cdot f_k^-$ [30] and relating to the previous expression (23):

$$w_k^- \approx w \cdot \sum_i \left(f_i^{-(NBO)} \cdot f_{ki}^{(NBO)} \right) \qquad (24)$$

Since $w = \sum_k w_k^-$, then:

$$w \approx \sum_k \sum_i \left(w \cdot f_i^{-(NBO)} \cdot f_{ki}^{(NBO)} \right) \qquad (25)$$

or in other words:

$$w \approx \sum_i \left(w \cdot f_i^{-(NBO)} \cdot \sum_k f_{ki}^{(NBO)} \right) \qquad (26)$$

Table 6 $w_i^{+(NBO)}$, $w_i^{+(NBO)}$ and $\Delta w_i^{(NBO)}$ (Eqs. 28, 29, and 30) under FD approximation (electrophile and nucleophile attack) and FMO approximation (HOMO and LUMO) for CH_2CHOCH_3 reagent

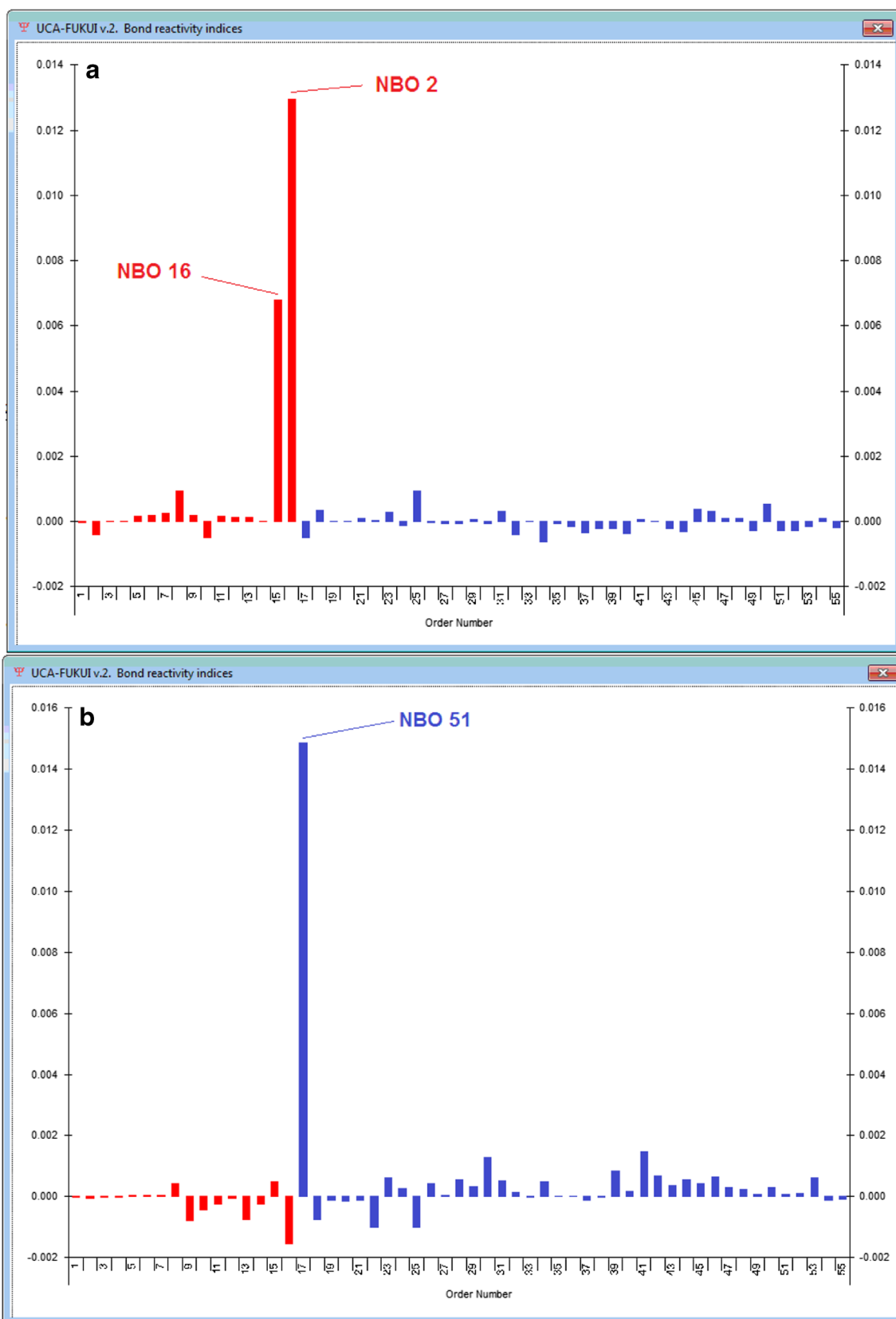| Schematic representations of NBOs	Level	NBO	Type	$w_i^{+(NBO)}$ (FD)	$w_i^{+(NBO)}$ (FMO: LUMO)	$\Delta w_i^{(NBO)}$ (FMO: LUMO)
	19	68	BD C2-O6	-0.00013	-0.00017	-0.00018
	18	69	BD O6-C7	-0.00007	-0.00005	0.00000
	17	63	BD C1-C2	0.00082	0.00261	0.00306
	Level	NBO	Type	$w_i^{-(NBO)}$ (FD)	$w_i^{-(NBO)}$ (FMO: HOMO)	$\Delta w_i^{(NBO)}$ (FMO: HOMO)
	16	16	LP O6	0.00091	0.00291	-0.00235
	15	1	BD C1-C2	0.00212	0.00227	-0.00380
	8	15	LP O6	-0.00005	0.00008	-0.00004

Fig. 1 Graphical representation of **a** $w_i^{-(NBO)}$ and **b** $w_i^{+(NBO)}$ parameters (28 and 29) calculated under frontier molecular orbital approximation for CH_2CHCl reagent. The NBOs are represented on the x-axis (sorted by energy); the *red color* means that the partial occupancy is greater than 1.92 and the *blue color* that the partial occupancy is less than 0.08

Fig. 2 Graphical representation of bond reactivity indices $\Delta w_i^{(NBO)}$ based on the *dual descriptor* function for CH_2CHCl reagent: **a** Frontier molecular orbital approximation and **b** finite difference approximation. The NBOs are represented on the *x*-axis (sorted by energy); the *red color* means that the partial occupancy is greater than 1.92 and the *blue color* that the partial occupancy is less than 0.08
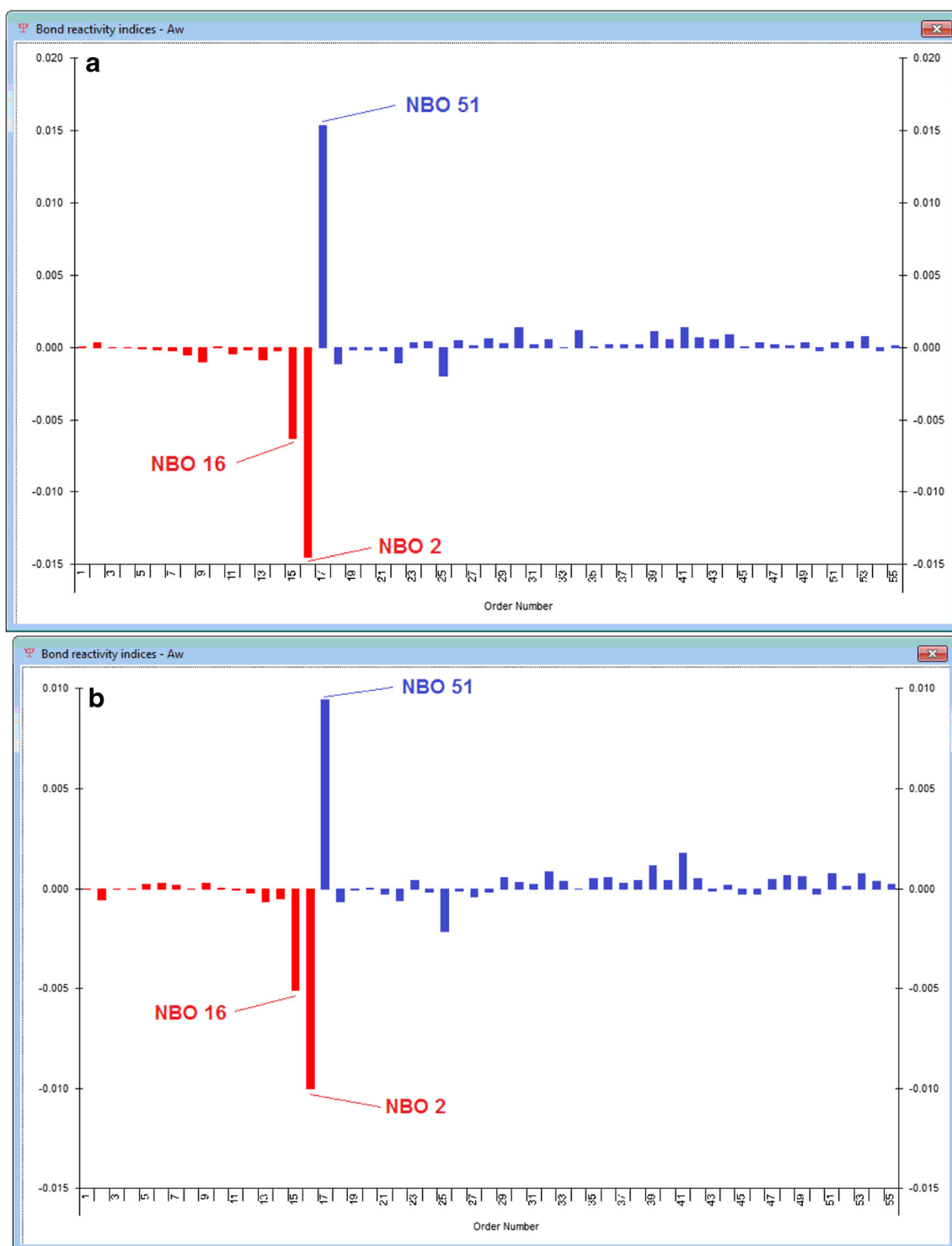
and since $\sum_k f_{ki}^{(NBO)} = 1; \forall i$, the following expression can be achieved:

$$w \approx \sum_i \left(w \cdot f_i^{-(NBO)} \right) = \sum_i w_i^{-(NBO)} \tag{27}$$

where $w_i^{-(NBO)}$ is defined as:

$$w_i^{-(NBO)} = w \cdot f_i^{-(NBO)} \tag{28}$$

Likewise, we can define (29) for the $f_i^{+(NBO)}$ index

$$w_i^{+(NBO)} = w \cdot f_i^{+(NBO)} \qquad (29)$$

In Eqs. (28, 29), we have obtained definitions of *philicity* in terms of orbitals instead of atoms. A *multiphilic descriptor* for chemical reactivity [53–57] can also be defined based on Eqs. (28, 29), as indicated below:

$$\Delta w_i^{(NBO)} = w_i^{+(NBO)} - w_i^{-(NBO)} = w \cdot \left(f_i^{+(NBO)} - f_i^{-(NBO)} \right) \quad (30)$$

Testing the new philicities in a sample set of representative molecules

The new definitions (28 and 29) have been implemented in software UCA-FUKUI v.2 [58] and the new indices were calculated for a representative molecules set. The molecules used in the test were: CH_2CHCl, CH_2CHCHO, CH_2CHNO_2, CH_2CHCN, CH_2CHCH_3, and CH_2CHOCH_3 in order to get a representative sample with diversity of functional groups (double bonds, halogen (Cl), nitro, ether and aldehyde). Also, the very simple molecules specially chosen for the example, allow achieving results easy to interpret.

The $w_i^{-(NBO)}$ and $w_i^{+(NBO)}$ indices are the maximum stabilizing energies (with opposite signs) when an NBO yields or takes a fraction of charge respectively. Hence, the $w_i^{-(NBO)}$ index can be used as an estimate of the nucleophile character of the orbital, and the $w_i^{+(NBO)}$ index, of the electrophilic character. On the other hand, the $\Delta w_i^{(NBO)}$ index (based on dual descriptor) takes positive and negative values. Positive corresponds to electrophilic character, and negative to nucleophilic one.

To obtain the indices presented in Tables 1, 2, 3, 4, 5 and 6, all NBOs have been used (as can be seen in Figs. 1 and 2). Tables 1, 2, 3, 4, 5 and 6 are an extract of the calculated indices. They include those with important values and some ones that are interesting for comparative purposes (for example, all of the Cl atom LPs of the CH_2CHCl reagent).

As can be seen in Figs. 1 and 2 and Tables 1, 2, 3, 4, 5 and 6, the most nucleophilic NBOs are those corresponding to double bonds and the non-shared pairs of the highest energy but with a high partial occupation of ≈ 2.0 (SF1 in the Supplementary Material shows some NBOs of CH_2CHCl reagent and their schematic representations). The most electrophilic NBOs correspond to double bonds (anti-bonding) with the lowest energy but with a low partial occupation (≈ 0.0). These conclusions coincide with those expected and, in addition, the two approaches used (FD and FMO), provide numerically different, but qualitatively equivalent results, leading to the same conclusions, with the exception of Table 3 (see the $\Delta w_i^{(NBO)}$ parameter) where very different results are shown. This is due to the orbital relaxation effects [58], which is treated in the following section. On the other hand, the conclusions obtained when analyzing the results of the $\Delta w_i^{(NBO)}$ index agree with those of the other indices. Examples of how to calculate this type of indices have been included in the Supplementary Material (EXAMPLE IV).

The proposed methodology (obtaining the indices based in the variation of the orbitals energy) can be employed as a tool for analyzing the atomic electrophilicities, that is, this approach allows determining the energetic contribution of each orbital of a concrete atom.

From the combination of Eqs. (24) and (28), the next expression is achieved:

$$w_k^- \approx \sum_i \left(w_i^{-(NBO)} \cdot f_{ki}^{(NBO)} \right) \qquad (31)$$

where the term $f_{ki}^{(NBO)}$ is the philicity fraction of the bonding orbital $\left(w_i^{-(NBO)} \right)$ which make its contribution to the philicity of atom "k" (w_k^-), keeping in mind that: $\sum_k f_{ki}^{(NBO)} = 1; \forall i$ and $0 \leq f_{ki}^{(NBO)} \leq 1; \forall i, \forall k$. Tables 7 and 8 show the $f_{ki}^{(NBO)}$ values for the reagents: CH_2CHCl and CH_2CHCHO (Tables S2-S5 in the Supplementary Material show the $f_{ki}^{(NBO)}$ values for the reagents: CH_2CHNO_2, CH_2CHCN, CH_2CHCH_3 and CH_2CHOCH_3). Tables 9 and 10 show the atomic philicities calculated per the relation: $w_k^\alpha = w \cdot f_k^\alpha; (\alpha = - or +)$ for the

Table 7 $f_{ki}^{(NBO)}$ values for the considered bond orbitals of the reagent: CH_2CHCl

Atom	NBO2 BD C1-C2	NBO16 LP Cl6	NBO15 LP Cl6	NBO14 LP Cl6	NBO51 BD C1-C2	NBO55 BD C2-Cl6
C1	0.4791	0.0002	0.0026	0.0035	0.5014	0.0068
C2	0.5165	0.0143	0.0226	0.0401	0.4952	0.5481
H3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0009
H4	0.0000	0.0000	0.0001	0.0004	0.0000	0.0018
H5	0.0000	0.0000	0.0010	0.0006	0.0000	0.0011
Cl6	0.0044	0.9855	0.9737	0.9554	0.0033	0.4413

Table 8 $f_{k\,i}^{(NBO)}$ values for the considered bond orbitals of the reagent: CH_2CHCHO

Atom	NBO14 LP O7	NBO8 BD C6-O7	NBO2 BD C1-C2	NBO15 LP O7	NBO67 BD C6-O7	NBO61 BD C1-C2	NBO65 BD C2-C6
C1	0.0006	0.0000	0.4636	0.0001	0.0000	0.4958	0.0082
C2	0.0023	0.0070	0.5265	0.0009	0.0098	0.4977	0.4897
H3	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0008
H4	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0038
H5	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010
C6	0.0879	0.3240	0.0098	0.0223	0.6116	0.0065	0.4876
O7	0.9078	0.6690	0.0001	0.9764	0.3786	0.0000	0.0040
H8	0.0009	0.0000	0.0000	0.0002	0.0000	0.0000	0.0048

example molecules disclosed therein. The Fukui (f_k^- and f_k^+) indices were obtained from the Hirshfeld population analysis. These atomic philicities are consistent with those obtained by using the new methodology proposed for the NBOs (shown in Tables 1, 2, 3, 4, 5 and 6). As an example, in the case of the reagent: CH_2CHCl, the highest value for w_k^- is the one corresponding to the Cl6 atom, which can be justified by the contributions of the NBOs: 14 (LP Cl6; $f_{Cl6\,NBO14}^{(NBO)} = 0.9554$, value obtained from Table 7), 15 (LP Cl6; $f_{Cl6\,NBO15}^{(NBO)} = 0.9737$) and 16 (LP Cl6; $f_{Cl6\,NBO16}^{(NBO)} = 0.9855$), since they have important $w_i^{-(NBO)}$ values. On the other hand, the NBO 2 (BD C1- C2) possesses the highest $w_i^{-(NBO)}$ value; however, it is distributed between C1 ($f_{C1\,NBO2}^{(NBO)} = 0.4791$) and C2 ($f_{C2\,NBO2}^{(NBO)} = 0.5165$) obtaining significant w_k^- values, but not as high as for the Cl6 atom. The higher w_k^+ values correspond to the C1 and C2 atoms, which can be justified by the contribution of the NBO 51 (BD C1-C2; $f_{C1\,NBO51}^{(NBO)} = 0.5014$; $f_{C2\,NBO51}^{(NBO)} = 0.4952$) that has the highest $w_i^{-(NBO)}$ value. For the case of the reagent: CH_2CHCHO, the most remarkable w_k^- value corresponds to

the O7 atom, due to the contribution of the NBO 14 (LP O7; $f_{O7\,NBO14}^{(NBO)} = 0.9078$) that has the most important $w_i^{-(NBO)}$ value. On the other hand, the highest values of the atoms: C1, C2, and O7 can be justified by the $w_i^{+(NBO)}$ contribution of the NBOs: 61 (BD C1-C2; $f_{C1\,NBO61}^{(NBO)} = 0.4958$; $f_{C2\,NBO61}^{(NBO)} = 0.4977$) and 67 (BD C6-O7; $f_{C6\,NBO67}^{(NBO)} = 0.6116$; $f_{O7\,NBO67}^{(NBO)} = 0.3786$). Similar conclusions can be reached for the rest of the reagents. Finally, Tables S6-S13 of the Supplementary Material show the atomic philicities w_k^- and w_k^+, calculated with the NPA, MBS, AIM populations and potential-derived charges for the same sample of molecules. The values obtained with these methodologies lead, qualitatively, to the same conclusions as those achieved by the Hirshfeld population analysis.

A new methodology to compare the frontier molecular orbital (FMO) and the finite difference (FD) approximations

A similar definition to Eq. (19) can be used to analyze the orbital relaxation effects [59] and how they affect the

Table 9 Atomic philicities w_k^- (a.u.) calculated by using Hirshfeld charges

CH2CHCl		CH2CHCHO		CH2CHNO2		CH2CHCN		CH2CHCH3		CH2CHOCH3	
k	w_k^-	k	w_k^-	k	w_k^-	k	w_k^-	k	w_k^-	k	w_k^-
C1	0.0047	C1	0.0049	C1	0.0064	C1	0.0084	C1	0.0038	C1	0.0025
C2	0.0032	C2	0.0021	C2	0.0020	C2	0.0062	C2	0.0031	C2	0.0014
H3	0.0015	H3	0.0023	H3	0.0031	H3	0.0027	H3	0.0011	H3	0.0008
H4	0.0014	H4	0.0017	H4	0.0021	H4	0.0024	H4	0.0011	H4	0.0007
H5	0.0012	H5	0.0017	H5	0.0019	H5	0.0023	H5	0.0010	H5	0.0006
Cl6	0.0075	C6	0.0046	N6	0.0035	C6	0.0048	C6	0.0009	O6	0.0017
		O7	0.0132	O7	0.0201	N7	0.0095	H7	0.0010	C7	0.0005
		H8	0.0047	O8	0.0113			H8	0.0005	H8	0.0004
								H9	0.0010	H9	0.0005
										H10	0.0005

Table 10 Atomic philicities w_k^+ (a.u.) calculated by using Hirshfeld charges

CH$_2$CHCl		CH$_2$CHCHO		CH$_2$CHNO$_2$		CH$_2$CHCN		CH$_2$CHCH$_3$		CH$_2$CHOCH$_3$	
k	w_k^+	k	w_k^+	k	w_k^+	k	w_k^+	k	w_k^+	k	w_k^+
C1	0.0053	C1	0.0075	C1	0.0096	C1	0.0087	C1	0.00360	C1	0.0023
C2	0.0045	C2	0.0042	C2	0.0050	C2	0.0063	C2	0.00300	C2	0.0021
H3	0.0018	H3	0.0030	H3	0.0040	H3	0.0032	H3	0.00130	H3	0.0008
H4	0.0019	H4	0.0025	H4	0.0031	H4	0.0029	H4	0.00130	H4	0.0009
H5	0.0018	H5	0.0021	H5	0.0028	H5	0.0027	H5	0.00120	H5	0.0008
Cl6	0.0042	C6	0.0061	N6	0.0058	C6	0.0043	C6	0.00080	O6	0.0006
		O7	0.0072	O7	0.0105	N7	0.0082	H7	0.00100	C7	0.0005
		H8	0.0026	O8	0.0095			H8	0.00050	H8	0.0005
								H9	0.00100	H9	0.0006
										H10	0.0005

comparison between the frontier molecular orbital (FMO) and the finite difference approximations (FD). This analysis of the Fukui function and the treatment of relaxation effects pursue a similar aim as the Fukui matrix decomposition proposed by Bultinck et al. [60, 61] but following a different methodology. The FMO approximation is in agreement with Eq. (6), which is based on assuming that MOs change very little when they lose or gain an electron. In other words:

$$\rho_{N-1}(r) \approx \left|\varphi^{HOMO}(r)\right|^2 + \sum_{i=1}^{\frac{N}{2}-1} 2\cdot\left|\varphi_i^{CMO}(r)\right|^2$$

$$\rho_{N+1}(r) \approx \left|\varphi^{LUMO}(r)\right|^2 + \sum_{i=1}^{\frac{N}{2}} 2\cdot\left|\varphi_i^{CMO}(r)\right|^2$$

(32)

where N is the number of electrons in the neutral molecule, and, by substituting (32) in $f^-(r) = \rho_N(r) - \rho_{N-1}(r)$ and $f^+(r) = \rho_{N+1}(r) - \rho_N(r)$, the expressions: $f^-(r) \approx \left|\varphi^{HOMO}(r)\right|^2$ and $f^+(r) \approx \left|\varphi^{LUMO}(r)\right|^2$ are achieved. However, this relation is not fulfilled for all cases due to the orbital relaxation effects. To study this effect, we have used the least-squares method and applied the condition (Eq. 33):

$$\int\left[f^\alpha(r) - \sum_{i=0}^{a} E_i\cdot\left|\varphi^{CMO_i}(r)\right|^2\right]^2 dr$$
$$= MINIMUM (with\, \alpha = -or +)$$

(33)

which leads to the Eq. (34):

$$\int f^-(r)\cdot\left|\varphi^{HOMO-j}(r)\right|^2 dr = \sum_{i=0}^{a} E_i\int\left|\varphi_i^{HOMO-i}(r)\right|^2\cdot\left|\varphi^{HOMO-j}(r)\right|^2 dr;\, j = 0, 1, 2, \ldots, a$$

$$\int f^+(r)\cdot\left|\varphi^{LUMO+j}(r)\right|^2 dr = \sum_{i=0}^{a} E_i\int\left|\varphi_i^{LUMO+i}(r)\right|^2\cdot\left|\varphi^{LUMO+j}(r)\right|^2 dr;\, j = 0, 1, 2, \ldots, a$$

(34)

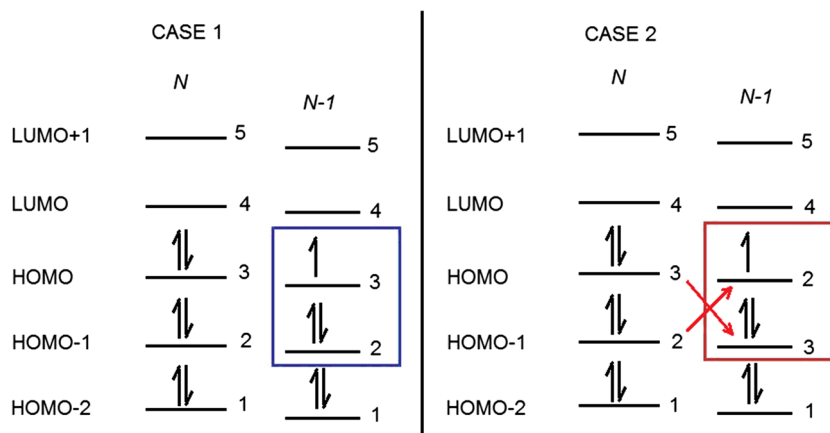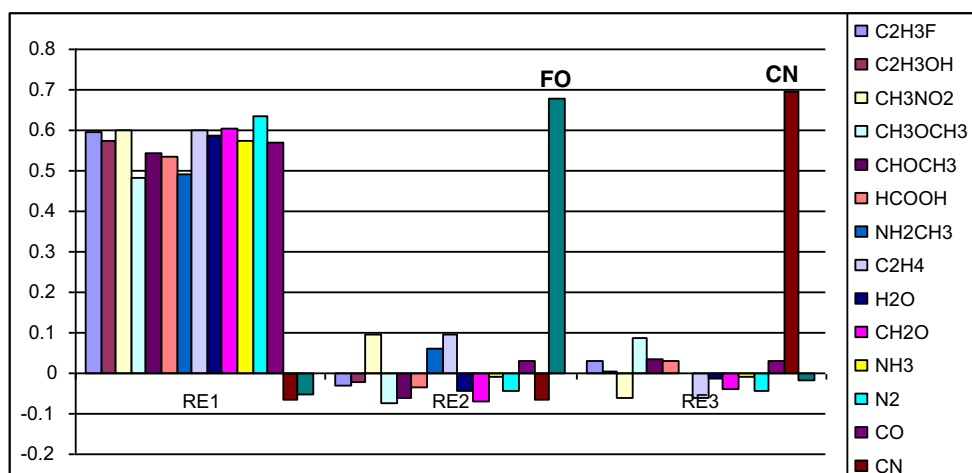**Fig. 3** *Left:* the lost electron belongs to the HOMO. *Right:* the lost electron belongs to the HOMO-1

where "a" is the number of orbitals to be considered in the analysis (e.g., all occupied orbitals) and "E_i" is a parameter that can help to study the orbital relaxation effects.

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \approx \sum_{i=0}^{a} E_i \left| \varphi^{HOMO-i}(r) \right|^2$$
$$f^+(r) = \rho_{N+1}(r) - \rho_N(r) \approx \sum_{i=0}^{a} E_i \left| \varphi^{LUMO+i}(r) \right|^2 \quad (35)$$

The systems of Eq. (34) provide the "E_i" coefficients of Eq. (35) that establish a relationship between the $f^\alpha(r)$ function (with $\alpha = -$ or $+$) and the canonical orbitals. This provides a very useful tool for comparing the FMO and FD approximations, so it has been added to the UCA-FUKUI v.2 package. It

is selectable from the "Additional Tools/FMO-FD Test" option in the menu bar of the main screen. To show the meaning of the E_i coefficients, the following example, considering the two cases of Fig. 3, is presented, where N represents the number of electrons of the neutral molecule.

In case 1, the FMO approximation is fulfilled, ($f^-(r) \approx |\varphi^{HOMO}(r)|)^2$. However, in case 2, this approximation is not properly fulfilled, having to be replaced, in this case, by $f^-(r) \approx |\varphi^{HOMO-1}(r)|^2$. If the fit shown in Eq. (36) is performed for each one of those cases, E_1 will be the largest coefficient for case 1 while E_2 will be the largest one for case 2.

$$f^-(r) \approx E_1 \left| \varphi^{HOMO}(r) \right|^2 + E_2 \left| \varphi^{HOMO-1}(r) \right|^2 \quad (36)$$
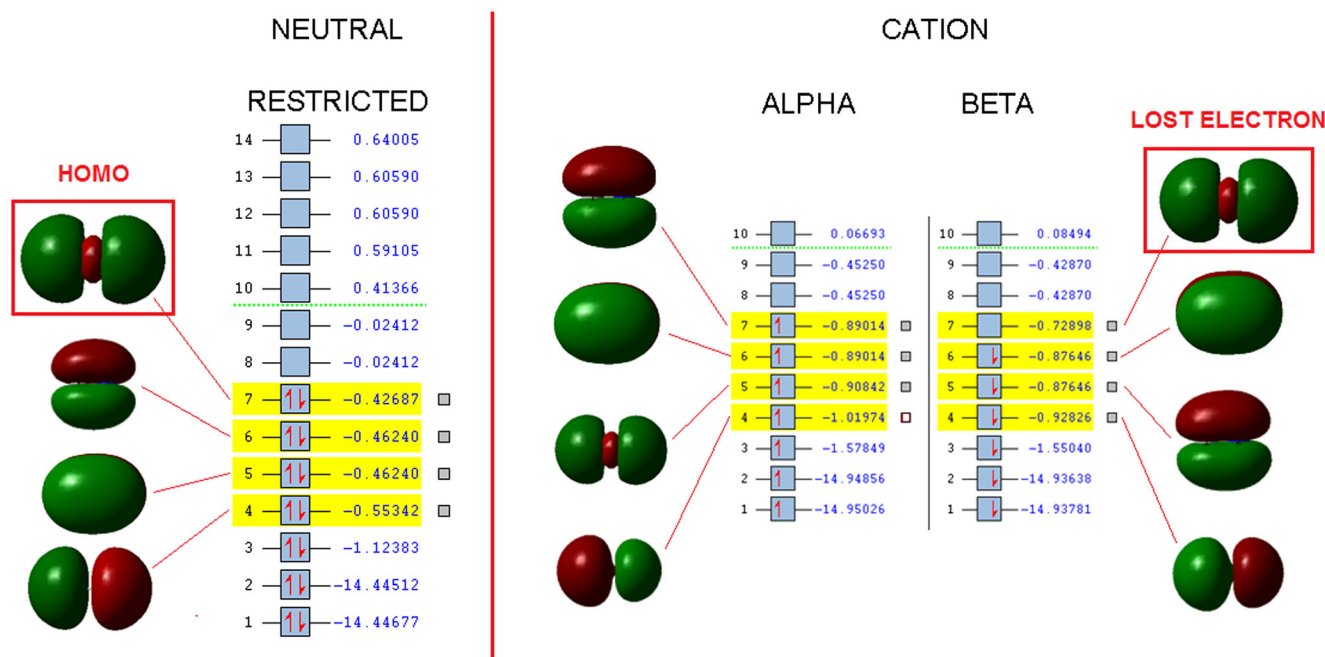

Fig. 5 Canonical-orbital energy levels for the N_2 molecule. *Left*: neutral-molecule energy levels. *Right:* those of the cation
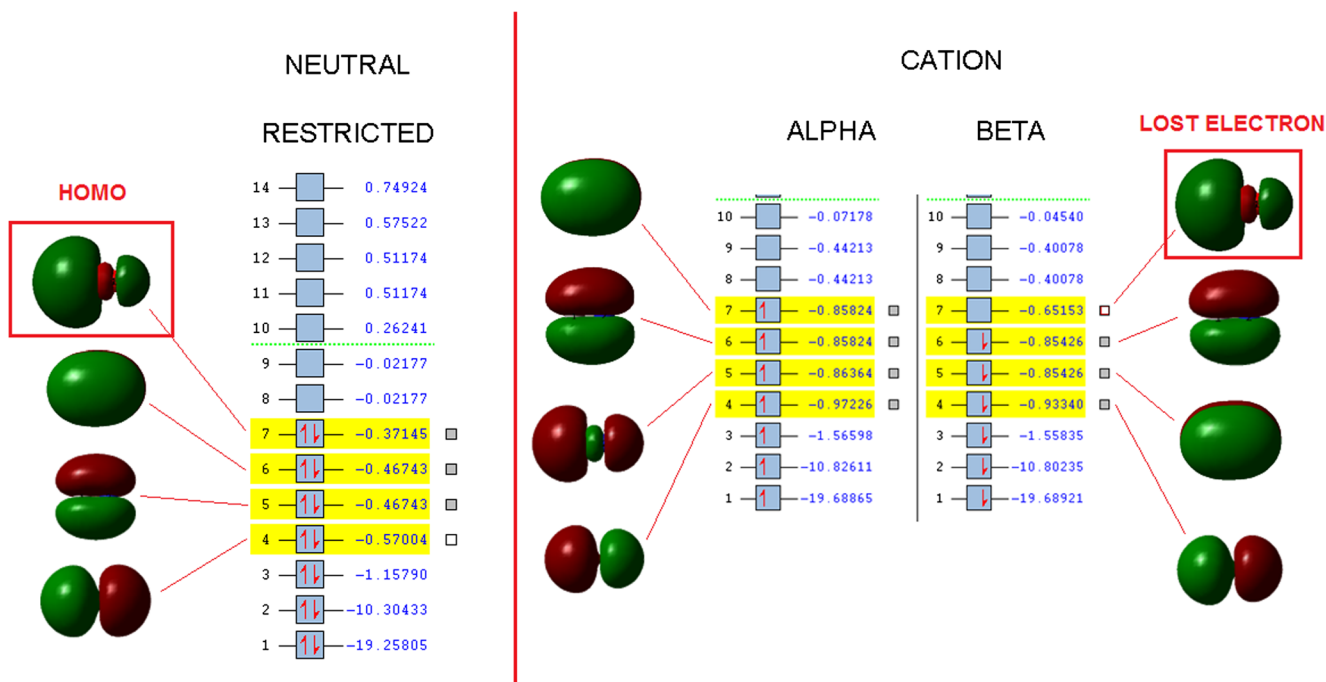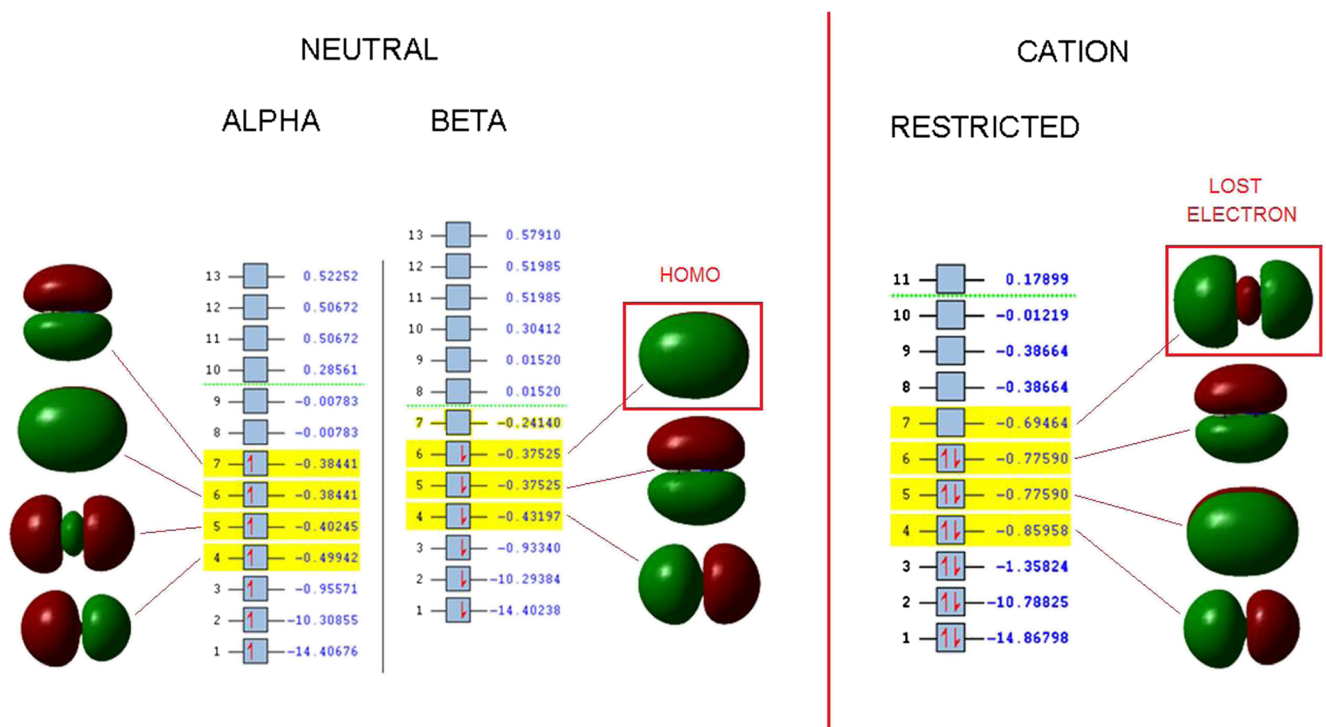
Fig. 6 Canonical-orbital energy levels for the CO molecule. *Left*: neutral-molecule energy levels. *Right*: those of the cation

In any case, the E_i coefficient of largest magnitude should determine the orbital that has lost (or gained) the electron when the molecule is ionized.

To test this methodology, we have used, as a sample, a set of simple molecules: N_2, CO, CN, H2O, CH_2O, NH_3, C_2H_4, C_2H_3F, C_2H_3OH, CH_3NO_2, $CHOCH_3$,

Fig. 7 Canonical-orbital energy levels for the CN molecule. *Left*: neutral-molecule energy levels. *Right*: those of the cation
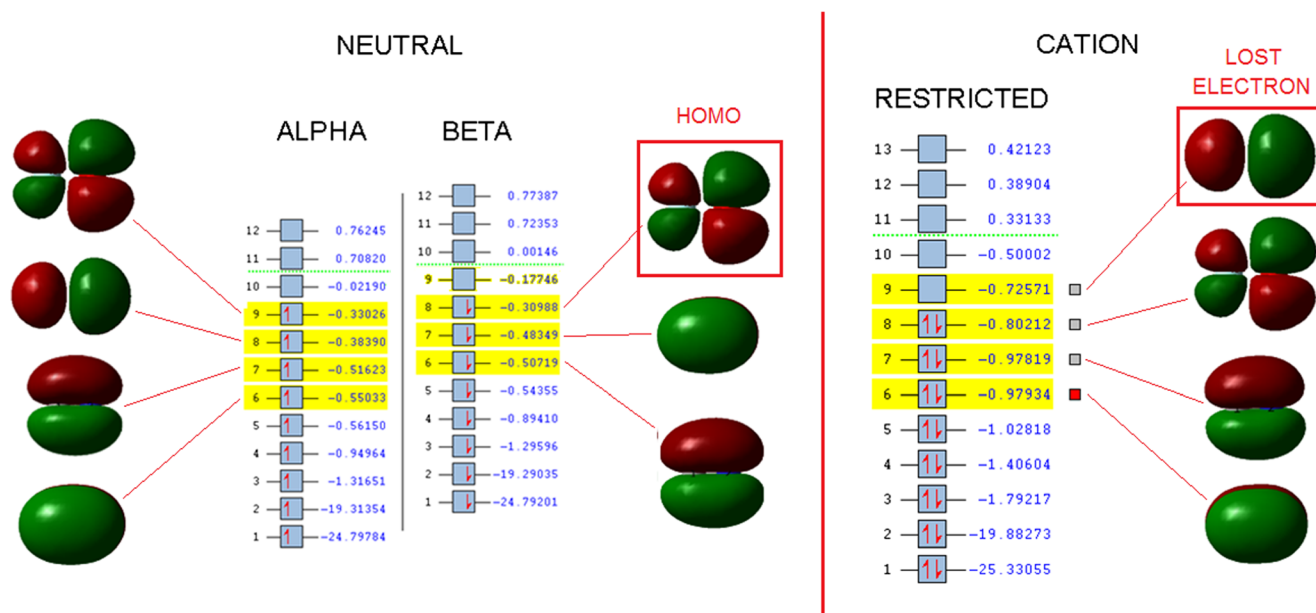
Fig. 8 Canonical-orbital energy levels for the FO molecule. *Left*: neutral-molecule energy levels. *Right:* those of the cation

HCOOH. For each molecule, the fit (37) has been applied by using Eq. (34).

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \approx E_1 \left| \varphi^{HOMO}(r) \right|^2 \qquad (37)$$

$$+ E_2 \left| \varphi^{HOMO-1}(r) \right|^2 + E_3 \left| \varphi^{HOMO-2}(r) \right|^2$$

Figure 4 shows the E_i coefficients (Eq. 34) calculated for the molecules of the sample. It is relevant to point out that, as expected, in most cases the E_1 parameter, corresponding to HOMO, is the largest of the three, while for the CN and FO molecules, this parameter is smaller than the rest (E_3 being the largest parameter for the CN molecule and E_2 the largest one for FO).

Figure 5 (for N_2 molecule) shows that the HOMO of the neutral molecule is CMO7 (FMO approximation), which matches the BETA-CMO7 orbital that has lost one electron in the cation (FD approximation). For the CO molecule (Fig. 6), the HOMO of the neutral molecule is CMO7, which matches with the BETA-CMO7 orbital.

However, a different situation is presented for the CN and FO molecules, as shown in Fig. 4. In those cases, FMO and FD approximations provide equivalent results by changing the HOMOs, where ALPHA-CMO5 and ALPHA-CMO8 should be the new HOMOs of the FMO approximation (probably, due to an orbital relaxation effect in the cation), as shown in Fig. 7 (for CN molecule) and Fig. 8 (for FO molecule). Finally, in the Supplementary Material, an example (EXAMPLE V) has been added showing how to perform this type of calculation.

Conclusions

A new methodology for obtaining reactivity indices (philicities) has been defined and subsequently used on a representative sample of organic molecules selected as an example. This methodology has been included in the new update of the UCA-FUKUI software (version 2.0). Also, condensation schemes based on atomic populations of the atoms in molecules theory, the Mulliken approximation (with a minimum basis) and electrostatic potential-derived charges have been implemented. In addition, the calculation of "bond reactivity indices", defined in previous studies, has been implemented. New "utilities" have also been included in this second version of the program, including a tool that allows the comparisons of finite difference and frontier molecular orbital approximations (described in detail in this paper) or a utility that automatically builds "* .cub" files with the ALIE (average local ionization energy) function. This could be very useful since the construction of this kind of functions can be very laborious. Finally, a set of commented examples that show the use of the program are also available in this new version.

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