

*Research Article*

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# A New Set of Local Reactivity Indices within the Hartree-Fock-Roothaan and Density Functional Theory Frameworks

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**Abstract:** An overview of the origin of global and local reactivity indices arising from the Hartree-Fock-Roothaan (HFR) and Density Functional Theory (DFT) frameworks is presented. HFR provided us with atomic indices such as net charges, superdelocalizabilities, Fukui indices and density of states. DFT contributed with global indices such as electronic chemical potential, hardness, softness, electrophilicity and charge capacity. Staying within conceptual DFT, we present a new set of local atomic reactivity indices keeping the same units of measurement and maintaining a similar interpretation to the global ones. We discuss their use in molecular reactivity, and QSAR studies, and provide an example of their variation along the Intrinsic Reaction Coordinate for an intramolecular Diels-Alder reaction

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## 1. INTRODUCTION

A molecular descriptor (MD) is a numerical characterization of some structural feature of a molecule. Todeschini and Consonni defined MDs as “*the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment*” [1]. MDs can be sub-classified as coming from experimental measurements (log P, molar refractivity, dipole moment, polarizability, etc.), or from any theory or model describing molecular structure, reactivity, etc. Hansch and Hammett approaches are good examples of both [2-6]. This paper deals with the subset of MDs formed only by those reactivity indices developed from the eigenvalues and/or eigenvectors obtained from today’s two main quantum chemical sources: the Hartree-Fock-Roothaan (HFR) and the Density Functional Theory (DFT) approaches. By global we understand the whole molecular system and by local, atoms or groups of atoms (substituents for example) belonging to the molecular system. As my work deals with Quantum Pharmacology (model-based QSAR), all the material presented below corresponds to cases of closed-shell molecules. I have written only briefly about the history leading to quantum chemical reactivity indices avoiding the well-

known quantum mechanical equations because texts are full of them. At the end I propose a new way to localize the main reactivity indices coming from conceptual DFT.

Probably the final historical condition for the birth of Quantum Chemistry can be directly traced to the results of the work of Ernest Rutherford and others [7-14]. Niels Bohr summarized these results in these words: “*the characteristic feature of Rutherford's theory is the assumption of the existence of a positively charged nucleus inside the atom. A number of electrons are supposed to revolve in closed orbits around the nucleus, the number of these electrons being sufficient to neutralize the positive charge of the nucleus. The dimensions of the nucleus are supposed to be very small in comparison with the dimensions of the orbits of the electrons, and almost the entire mass of the atom is supposed to be concentrated in the nucleus*” [15]. He noted that “*the particles of the atom apparently could not be at rest in a state of stable equilibrium, and on the other hand we should have to expect that every motion which might be present would give rise to the emission of electromagnetic radiation which would not cease until all the energy of the system had been emitted and all the electrons had fallen into the nucleus*”. Making use of Planck's quantum idea, Bohr surmounted this problem proposing a planetary-like model for the atom and stating the rules that avoid the electron falling onto the nucleus [16]. Modern quantum mechanics was developed from two different lines of thought. Matrix mechanics abandoned the description of motion in terms of classical physics and replaced it by a description in terms of observable magnitudes. This was the work of Heisenberg, Born, Jordan, Wiener and Dirac [17-23]. The second line of thought is based on the problem of the nature of light and its main contributors are Schrödinger and de Broglie [24-31]. Schrödinger also provided proof of the intertranslatability of matrix and wave formalisms [32]. We may mention also the discovery of spin [33] and the Pauli Exclusion Principle for fermions [34].

## 2. THEORETICAL BACKGROUND

### 2.1. The First Path to Chemical Enlightenment: the Wave Function

Here we shall refer to the time-independent, non-relativistic, Born-Oppenheimer [35] Schrödinger equation and one of its by-products: the electron wave function. Although the Born-Oppenheimer approximation considerably reduces the complexity of the Schrödinger equation, the resulting electronic Schrödinger equation is still extremely complex to solve due to the electron-electron interactions. A satisfactory solution is to introduce the molecular orbital approximation, the simplest of which is the independent-particle, or Hartree approximation. The Hartree approximation assumes that each electron moves independently within its own orbital and sees only the *average* field generated by all the other electrons [36-40]. The Linear Combination of Atomic Orbitals (LCAO) was first introduced by Bloch<sup>41</sup>. In 1930 Fock pointed out that the Hartree wave function did not satisfy Pauli's Exclusion Principle, i.e., that the wave function must be antisymmetric with respect to electron interchange. Fock also showed that a Hartree product could be made antisymmetric by appropriately adding and subtracting all possible permutations of the Hartree product, thereby forming the Hartree-Fock (HF) wave function [42-44]. Later, Slater showed that the resulting wave function is simply the determinant of a matrix, called today a Slater determinant [45]. HF Theory assumes that an electron moves in a potential which is the average of the potentials due to all the other electrons and nuclei, so a trial wave function is required for the potential *before* the energy can be calculated. The HF method uses the variational wave function in the form of a single Slater determinant. The optimal wave function is then found by iteratively solving the Schrödinger equation. This initial guess must be close enough to the optimum wave function for the equations to

converge to the correct electronic state. If a unitary transformation is carried out on the orthonormal spinorbitals, then the new SOs are also orthonormal.

In the LCAO approximation, each MO ( $\varphi_i(\mathbf{r})$ ) is expressed as a Linear Combination of Atomic Orbitals,  $\chi_\mu(\mathbf{r})$ :

$$\varphi_i(\mathbf{r}) = \sum_{\mu=1}^N c_{\mu i} \chi_\mu(\mathbf{r}) \quad (1)$$

The set of functions  $\chi_\mu(\mathbf{r})$  is called a basis set. A natural choice is to employ as a basis set the atomic orbitals (AO) of the constituent atoms. These AOs can in turn be represented by several different mathematical functions. The coefficients  $c_{\mu i}$  are adjustable parameters.

A major breakthrough occurred when the Hartree-Fock method was formulated in the LCAO approximation (HFR method) [46-48]. The variational nature of the model guarantees that the energy eigenvalue solution for any approximate wave function is always greater than the energy obtained using the exact wave function. Therefore, the set of coefficients which minimize the energy of the resultant wave function will give the best approximation to the wave function from a given basis set. The variational constraint leads to a set of algebraic equations (Roothaan or Roothaan-Hall equations) for the coefficients  $c_{\mu i}$ , expressed in matrix form as:

$$\tilde{F}\tilde{C} = \tilde{S}\tilde{C}\tilde{\epsilon} \quad (2)$$

where  $\tilde{C}$  is the matrix of MO expansion coefficients (the  $c_{\mu i}$ ),  $\tilde{F}$  is the Fock matrix,  $\tilde{S}$  is the overlap matrix of basis functions and  $\tilde{\epsilon}$  is a diagonal matrix containing the one-electron energy of each MO.

At the beginning of the 1950's the numerical evaluation of the integrals appearing in HFR was the main barrier. The first basis sets were formed by Slater-Type-Orbitals (STO), but the numerical evaluation of the three- and four-center integrals remains very difficult. At that time this was possible for very small molecular systems. This procedure is called *ab initio*. The alternative methodology, called semi-empirical, is to apply the zero differential overlap approximation (ZDO, in which the product of atomic orbitals is neglected in most integrals), and to replace many integrals by parameters or experimental values. The Pariser-Parr-Pople method, treating  $\pi$  electrons in conjugated molecules, is the first example of this approach [49-52]. When all valence electrons were included CNDO/2, INDO, ZINDO/1 and similar methods began to appear in the 1960s [53-59]. All-electron Extended Hückel Theory was developed by Hoffmann since 1963 [60]. On the *ab initio* side, Boys showed in 1950 that by using Gaussian functions, and functions derived from these by differentiation with respect to the parameters, complete systems of functions can be constructed appropriate to any molecular problem, and that all the necessary integrals can be explicitly evaluated [61]. Today we have a plethora of Gaussian basis sets (minimal, split valence, polarized, diffuse, high angular momentum, etc.) and, with the arrival of faster and more powerful computers, the size of the molecular systems that can be studied has grown enormously.

## 2.2. Reactivity Indices in the HFR Framework: Fukui Indices and Superdelocalizabilities

At the end of the day (at the end of a calculation) we are in possession of a set of eigenvalues and a matrix containing the LCAO-MO coefficients as a starting material to extract useful information. A good framework to obtain reactivity indices is Mulliken Population Analysis (MPA) [62-66]. MPA is strongly dependent on the basis set and some orbital populations can be negative or greater than 2.0 (we have proposed an empirical way to correct this bad behavior [67]). There are several different other suggestions for a population analysis but here we shall use MPA. Two local atomic reactivity indices result directly

from this analysis: the total electronic population on an atom (and the atomic net charge) and the electron population of each MO on each atom. All the electron populations in each atom/MO form the complete set of Fukui indices,  $F_{\text{atom}}(\text{MO})$  (the Fukui indices of the HOMO and LUMO are the ones most used). Then, the Fukui index for MO  $i$  and atom  $k$  is (for the closed shell case):

$$F_k(i) = 2.0 \sum_r c_{i_k}^2 + 2.0 \sum_r \sum_{l \neq k} c_{i_k} c_{i_{s_l}} S_{i_k, s_l} \quad (3)$$

Aside from the error that arises from dividing the overlap populations equally between atoms of very different electronegativity, the Fukui indices for the frontier orbitals (HOMO and LUMO) are very good for comparing the reactivity of the atomic sites *within* a molecular system. Note also that within this scheme, the numerical values of Fukui indices must be zero or positive. They first appeared in 1952 under the name of frontier electron densities [68], and are an important part of the work on chemical reactivity of Kenichi Fukui *et al.* [68-74].

The second index is related to the comparison of the reactivity of two atoms belonging to different molecules. Let us consider molecules A and B composed by a ring (aromatic or not), with different substituents and having an atom  $x$ . We are interested in comparing the reactivity of atom  $x$  in A and B. The numerical value of  $F_x(\text{HOMO})$  is the same for both atoms (0.1), but the HOMO energy of A (-0.20 Ha) is higher than the HOMO energy of B (-0.37 Ha). Chemical intuition says that atom  $x$  of A can give frontier electrons more easily than atom  $x$  of B.

A good representation of this fact is an index obtained by dividing the Fukui index of an atom/MO by the corresponding MO energy. These indices are the superdelocalizabilities [68,71,74,75]. For atom  $x$  we define the electrophilic superdelocalizability (ESD) of the  $i$ -th occupied MO as:

$$S_x^E(i) = \frac{F_x(i)}{E_i} \quad (4)$$

We can obtain the total atomic electrophilic superdelocalizability (TSDE) of atom  $x$  by summing over all the terms corresponding to the occupied MOs:

$$S_x^E = \sum_{i=1}^{\text{HOMO}} \frac{F_x(i)}{E_i} \quad (5)$$

Given the structure of Eq. 5, it is clear that the last terms of the summation have higher numerical values, which is consistent with the fact that the HOMO and occupied MOs close to it are more important in chemical reactivity. The ESD and TSDE values are always negative (for most molecules with a closed shell). The interpretation of the TSDE is that, when comparing two or more sites for their feasibility to interact with an electrophile, the one having the most negative value of TSDE is more prone to that interaction. The same interpretation holds for the frontier occupied MO ESD. Notice that, when the HOMO is not localized over an atom, the frontier SDE value should be taken as the next occupied MO in which  $F_x(i)$  is not zero.

For the case of the empty MOs and for atom  $x$  we define the nucleophilic superdelocalizability (NSD) of the  $j$ -th MO as:

$$S_x^N(j) = \frac{F_x(j)}{E_j} \quad (6)$$

The total atomic nucleophilic superdelocalizability (TNDE) of atom  $x$  is obtained by summing over all the terms corresponding to the empty MOs:

$$S_x^N = \sum_{j=LUMO}^N \frac{F_x(j)}{E_j} \quad (7)$$

When the spectrum of the empty MO energies contains only positive values, as it is the case of the ZINDO/1 semiempirical method, the interpretation of Eqs. 6 and 7 is straightforward. A high value of  $S_x^N(j)$ , indicates more capacity of atom  $x$  to interact with nucleophiles through the  $j$ -th MO. The same holds for  $S_x^N$ . Unhappily, CNDO/2, HF and DFT methods (the last two with all the basis sets we have analyzed) present problems for the calculation of  $S_x^N$ . CNDO/2 is unsatisfactory because the empty MO eigenvalues it provides are highly dependent on the conformation [76]. HF and DFT calculations produce empty MOs with negative and positive eigenvalues leading to algebraic zeros around the Fermi Level which lead in turn to bad numerical results for the total atomic NSD. In this case, it is wise to use only  $S_x^N(LUMO)$ .

It is worth mentioning that the above reactivity indices can be properly called Local Atomic Reactivity Indices (LARI). Some LARIs, such as free valence, autopolarizability, Wheland's localization energies of, Brown's  $Z$  index and Dewar's reactivity number are not analyzed here. Nevertheless it seems important to mention that some of them were employed in the first applications of Quantum Chemistry to biological/pharmacological problems [77-82].

### 2.3. Reactivity Indices in the HFR Framework: Interactions between Molecular Orbitals

We may obtain a qualitative understanding of the great majority of, but not all, chemical phenomena employing a model based on the interaction between molecular orbitals. The historical roots of this approach can be traced to the work of Coulson and Longuet-Higgins [83-85], whose work was continued, enlarged and perfected by several scientists. We shall center our attention on the developments leading to the appearance of new LARIs. They are centered on the perturbation treatment of molecular orbital interactions [83,84].

In 1967 Klopman and Hudson published a general perturbation treatment of chemical reactivity, not restricted to  $\pi$ -conjugated molecules, in which allowance is made for ionic interactions [86-88]. According to this method, the change in electronic energy,  $\Delta E$ , associated with the interaction of atoms  $i$  (of molecule A) and  $j$  (of molecule B) is:

$$\Delta E = \sum_p \left[ Q_i Q_j / R_{ij} + (1/2)(\beta_{ij}^2) \sum_m \sum_n F_{mi} F_{nj} / (E_m - E_n) - (1/2)(\beta_{ij}^2) \sum_{m'} \sum_n F_{m'i} F_{nj} / (E_{m'} - E_n) \right] \quad (9)$$

where  $Q_i$  is the net charge of atom  $i$ ,  $F_{mi}$  is the Fukui index of atom  $i$  in the MO  $m$ ,  $\beta_{ij}$  is the resonance integral; and  $E_m$  ( $E_{m'}$ ) is the energy of the  $m$ -th ( $m'$ -th) occupied (virtual) MO of molecule A,  $n$  and  $n'$  standing for molecule B. The value of  $\beta_{ij}$  is kept independent of the kind of AO because the A-B complex does not involve covalent bonds. The summation on  $p$  is over all pairs of interacting atoms. This expression has been employed for different purposes [88,89]. Here we shall follow the time line leading to the appearance of new local atomic reactivity indices. As this theory represents the interaction energy in terms of atom-atom interactions it was only a question of time before the first papers applying it to the study of the interaction of biological molecules with different substrates appeared. As we have presented a detailed explanation of this model and its applications [90], we shall discuss only the most relevant parts. The central problem for the use of Eq. 9 in the study of the drug-receptor interaction is that the receptor

structure is not known. On the other hand, as we expect to study the variation of  $\Delta E$  in a family of drugs interacting with the same receptor, we need to reformulate Eq. 9 to separate the terms belonging to both molecular systems. The first attempt was made by Peradejordi *et al.* who replaced the occupied and empty MOs of the receptor by constants called “average values” [91]. This approximation permits the transformation of, for example,  $1/(E_m - E_{n'})$  into  $1/(E_m - k)$ , with  $k$  being a constant. With this procedure the following equation was obtained:

$$\Delta E = a + \sum_i \left[ e_i Q_i + f_i S_i^E + s_i S_i^N \right] \quad (10)$$

where  $S_i^E$  and  $S_i^N$  are, respectively, the total atomic superdelocalizability and the total atomic nucleophilic superdelocalizability of atom  $i$  (see Eqs. 5 and 7).

During the 1980s another way to separate the abovementioned denominator was employed by using a series expansion for  $1/1-x$ :

$$\frac{1}{1-x} = 1 + x + x^2 + x^3 + \dots \quad |x| < 1 \quad (11)$$

Below we shall work with a model in which all occupied MOs have negative energies and all empty MOs have positive energies. We are aware that almost all semiempirical (ZINDO/1 is the exception for neutral closed shell molecules), *ab initio* HF and DFT calculations produce empty MOs with negative energies. If we consider any pair of MOs, one belonging to A and the other to B, we have one of the following two possibilities:

If  $\left| \frac{E_m}{E_{n'}} \right| < 1$  then:

$$-\frac{1}{E_{n'}} \left( \frac{1}{1 - E_m/E_{n'}} \right) = -\frac{1}{E_{n'}} - \frac{1}{E_{n'}} \left( \frac{E_m}{E_{n'}} \right) - \frac{1}{E_{n'}} \left( \frac{E_m}{E_{n'}} \right)^2 + \dots + R \quad (12)$$

where  $R$  is the rest of the series expansion. With Eq. 9 at hand, we may appreciate that the first term of the right side of Eq. 12 corresponds to the product of the Fukui index of atom  $i$ /MO  $m$  belonging to A by the orbital nucleophilic superdelocalizability of atom  $j$ /MO  $n'$  belonging to B. The second term of the series expansion is the product of what we have called a second order orbital nucleophilic superdelocalizability of atom  $j$ /MO  $n'$  belonging to B with a term corresponding to the local density of states of atom  $i$ /MO  $m$  belonging to A. We use expansion 12 when we are dealing, for example, with the interaction of an empty MO (of B) having a high eigenvalue with an occupied MO of A having a low eigenvalue (case of the HOMO and nearby occupied MOs).

If  $\left| \frac{E_{n'}}{E_m} \right| < 1$  then:

$$\frac{1}{E_m} \left( \frac{1}{1 - E_{n'}/E_m} \right) = \frac{1}{E_m} + \frac{1}{E_m} \left( \frac{E_{n'}}{E_m} \right) + \frac{1}{E_m} \left( \frac{E_{n'}}{E_m} \right)^2 + \dots + R' \quad (13)$$

Here, the first term of the right side of Eq. 13 corresponds to the product of the orbital electrophilic

superdelocalizability of atom  $i$ /MO  $m$  and the Fukui index of atom  $j$ /MO  $n'$ . The second term of the series expansion is the product of what we have called a second order orbital electrophilic superdelocalizability of atom  $i$ /MO  $m$  belonging to A with a term corresponding to the local density of states of atom  $j$  belonging to B. We use expansion 13 when we are dealing, for example, with the interaction of an occupied MO (of A) having a high eigenvalue (for example a core MO) with an empty MO of B having a low eigenvalue (case of the LUMO and nearby empty MOs).

For the third term of the right side of Eq. 9 we obtain analogous terms involving now the empty MOs of A and the occupied MOs of B. Now we consider the practical results obtained with Eq. 10. They all come from QSAR studies with a variety of ligands and receptors [91-93]. In these publications we find atomic net charges, total atomic ESD and NSDs inside the equations relating structure to biological activity. On the other hand, it is reasonable to accept that frontier molecular orbitals (HOMO and LUMO) and nearby MOs should play a more important role in weak interactions than the inner occupied and upper empty ones. Therefore, we have used R (the remainder of the series expansion) to add or subtract terms to obtain the following equation:

$$\Delta E = a + \sum_i \left[ e_i Q_i + f_i S_i^E + s_i S_i^N \right] + \sum_i \sum_m \left[ h_i(m) F_i(m) + j_i(m) S_i^E(m) \right] + \sum_i \sum_{m'} \left[ r_i(m') F_i(m') + t_i(m') S_i^N(m') \right] + \Phi \quad (14)$$

where  $a$ ,  $e$ ,  $f$ ,  $g$ ,  $h$ ,  $j$ ,  $r$  and  $t$  are constants to be determined, and  $\Phi$  stands for the new remaining series expansion terms. The third term of the right side of Eq. 14 contains the whole set of local atomic Fukui indices and the whole set of local atomic electrophilic superdelocalizabilities (see Eqs. 3-7). The last term of the right side of Eq. 14 contains similar terms but for the empty MOs. It is clear that the passage from Eq. 10 to Eq. 14 is neither straightforward nor absolutely formal but its success when applied to diverse systems (drug-receptor interactions) is splendid [94-101].

It is worth mentioning that from the remaining term of the series expansion it is possible to obtain some other reactivity indices. None of them appear to be used in model-based QSAR studies. The local atomic density of occupied states (LDOS) of atom  $i$ /MO  $m$ , is defined as:

$$\text{LDOS}_i^{\text{occ}}(m) = F_i(m) E_m \quad (15)$$

and the total atomic density (TDOS) of occupied states of atom  $i$ :

$$\text{LDOS}_i^{\text{occ}} = \sum_{m=1}^{\text{HOMO}} \text{LDOS}_i^{\text{occ}}(m) = \sum_{m=1}^{\text{HOMO}} F_i(m) E_m \quad (16)$$

The local atomic density of empty states of atom  $i$ /MO  $n'$  defined as:

$$\text{LDOS}_i^{\text{emp}}(n') = F_i(n') E_{n'} \quad (17)$$

and the total atomic density of empty states of atom  $i$ :

$$\text{LDOS}_i^{\text{emp}} = \sum_{n'=\text{LUMO}}^N \text{LDOS}_i^{\text{emp}}(n') = \sum_{n'=\text{LUMO}}^N F_i(n') E_{n'} \quad (18)$$

There are some higher order reactivity indices like the following ones:

$$S_i^{E(2)} = \sum_{m=1}^{\text{HOMO}} \frac{F_i(m)}{E_m^2} \quad (19)$$

and

$$S_i^{N(2)} = \sum_{n=\text{LUMO}}^N \frac{F_i(n)}{E_n^2} \quad (20)$$

The main conclusion of this section is that the HFR method provided us, over the course of time, with a set of local atomic reactivity indices which have shown their utility, from chemical reactivity to QSAR studies. In a review published in 1996 we find a list of all of them but DOS and LDOS [102].

#### 2.4. The Second Path to Chemical Enlightenment: the Electron Density

The historical roots of what today is called Density Functional Theory (DFT) go back to the idea of Paul Drude of treating the electrons in metals as an electron gas [103]. This line of thought continued with the works of Thomas [104], Fermi [105], Dirac [106] and von Weiszäcker [107] on the free electron gas. Next comes the work of Slater with the  $X_\alpha$  method [108-110]. When, in 1964, the Hohenberg and Kohn theorems were formulated DFT reached the status of a full theory [111,112]. There is a large number of books and reviews about DFT (for reviews see [113-119]). Here we shall follow the lines presented in the review of Geerlings, De Proft and Langenaeker because, in our opinion, it is conceptually very clear and delightful to read [119].

The central equation of DFT is:

$$v(r) + \frac{\delta F_{\text{HK}}}{\delta \rho(r)} = \mu \quad (21)$$

where  $v(r)$  is the external potential due to the nuclei,  $F_{\text{HK}}$  is the Hohenberg-Kohn functional,  $\rho(r)$  is the electron density and  $\mu$  the Lagrange multiplier. This is the DFT analogue of Schrödinger's time-independent equation. The problem here is that the electronic kinetic energy and the electron-electron interaction functionals are not known either completely or partly.

Kohn and Sham (KS) elaborated Eq. 21 in such a way that it shows a high analogy with the Hartree equations [120]. The KS equations are solved iteratively like the Hartree and Hartree-Fock ones. The implementation of the KS equations in quantum chemical software packages opened the way to use DFT as a tool for calculating molecular and atomic properties. Let us remember that the KS approach produces the appearance of the exchange correlation potential which has an unknown form. However, approximations exist which permit the calculation of certain physical quantities quite accurately. One of the most widely used approximations is the local-density approximation (LDA), where the functional depends only on the density at the coordinate where the functional is evaluated. Generalized gradient approximations (GGA) are still local but also take into account the gradient of the density at the same coordinate. Also, there are hybrid functionals, which are a class of approximations to the exchange-correlation energy functional that incorporate a portion of exact exchange from Hartree-Fock theory with exchange and correlation from other sources. One of the most used hybrid functionals in chemistry is B3LYP, in which the exchange energy, in this case from Becke's exchange functional, is combined with the exact energy from Hartree-Fock theory. Theoretical research on KS equations and the form of the functionals still continues.

The most important fact for our purposes is that KS equations introduce molecular orbitals in the working framework. Therefore, at the end of a calculation we have a matrix of eigenvectors and a 1D matrix (a



vector) with MO eigenvalues. With these two sets we may calculate all the HFR local atomic reactivity indices mentioned in section 2.3. I think that the obvious question of which, HF or DFT reactivity indices, correlate best with experimental results of any kind (let us remember that these indices are not observables in the quantum-mechanical sense) cannot be answered in a general way until extensive and comparative studies have been performed.

## 2.5. Conceptual Density Functional Theory

A very important area of research is what is termed “conceptual DFT” by Parr. Starting from the idea that the electron density is the basic quantity to describe molecular ground states, Parr, co-workers and later a large group of theoreticians built formal definitions for several chemical concepts, allowing their calculation and use [115,121-181]. The electronegativity ( $\chi$ , in Mulliken’s sense) has been identified as the negative of the electronic chemical potential,  $\mu$  (the Lagrange multiplier in the Euler-Lagrange equation 21):

$$\mu = \left( \frac{\partial E}{\partial N} \right)_{v(r)} = -\chi \quad (22)$$

where  $E$  is the total electronic energy,  $N$  is the number of electrons and  $v(r)$  is the external electrostatic potential an electron in  $r$  feels due to the nuclei. DFT chemical potential measures the tendency of electrons to escape from a system, so electrons flow from regions with higher chemical potential to areas with lower chemical potential until  $\mu$  becomes uniform throughout [121,125,182].

In the same way, the definition of the chemical hardness,  $\eta$ , has been shown to be [121,172,174,178,180,183]:

$$\eta = \left( \frac{\partial^2 E}{\partial N^2} \right)_{v(r)} = \left( \frac{\partial \mu}{\partial N} \right)_{v(r)} \quad (23)$$

Chemical hardness determines the resistance of the species to lose electrons. Both  $\mu$  and  $\eta$  are global properties at the ground state in the sense that they characterize the species as a whole, i.e., they are neither atomic nor orbital properties but molecular ones.

Another useful expression is the Fukui function, defined as:

$$f(r) = \left( \frac{\partial \rho(r)}{\partial N} \right)_{v(r)} = \left( \frac{\delta \mu}{\delta v(r)} \right)_N \quad (24)$$

The question now is to find expressions for  $\mu$  and  $\eta$  allowing us to obtain numerical values for them. The method of finite difference yields an operational and approximate definition of  $\mu$  and  $\eta$ :

$$-\mu = (IP + EA) / 2 = \chi \quad (25)$$

$$\eta = (IP - EA) / 2 \quad (26)$$

where IP is the ionization potential and EA is the electron affinity of the system. Within the validity of Koopmans' theorem [184], the frontier orbital energies are given by:

$$IP = -\epsilon_{\text{HOMO}} \quad (27)$$

$$EA = -\epsilon_{\text{LUMO}} \quad (28)$$

where HOMO is the highest occupied MO, and LUMO the lowest unoccupied MO. Therefore, we can write the electronic chemical potential and the chemical hardness as:

$$\mu \cong (\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2 \quad (29)$$

$$\eta \cong (\epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}}) \quad (30)$$

Hardness is an exact quantity for which the HOMO-LUMO gap (or the band gap in solids) is an approximation. Hereafter we shall refer only to reactivity indices derived from Eqs. 29 and 30. These approximations are conceptually very important and useful to understand many aspects of chemical reactivity. Within this framework, three more reactivity indices can be generated. The global softness,  $S$ , is defined as the inverse of the hardness:

$$S = \frac{1}{\eta} \quad (31)$$

Note that the global softness is identified with the charge capacity,  $\kappa$ , defined as the ability to retain electronic charge once it has been acquired [185-189].

The electrophilic index,  $\omega$ , can be calculated by combining the hardness with the chemical potential:

$$\omega = \frac{\mu^2}{2\eta} \quad (32)$$

The electrophilic index accounts for a chemical's inherent electrophilicity.

The maximal amount of electronic charge that an electrophile may accept,  $Q^{\text{max}}$ , is defined as [157]:

$$Q^{\text{max}} = \frac{-\mu}{\eta} \quad (33)$$

## 2.6. Some Words about the Localization of Global Properties

The possibility of assigning numerical values for  $\mu$  and  $\eta$  (and the remaining global indices of Eqs. 31-33, and also for future reactivity indices derived from  $\mu$  and  $\eta$ ) for each atom of two or more interacting species would allow us to have a better microscopic insight on the whole interaction process and/or any of its steps (if such steps exist). This has been done within DFT for the electronic chemical potential [190-192], hardness and softness. We shall not comment on the procedures to do this but we point out that

there are still some controversies about the procedures to localize, and the use and the meaning of these LARISs.

### 3. NEW LOCAL ATOMIC REACTIVITY INDICES

Is there any other way to transform  $\mu$  and  $\eta$ , expressed using the finite difference method and Koopmans' theorem, from global indices to local atomic ones? [193]. If this can be done in a rational way, the remaining reactivity indices ( $S$ ,  $\omega$ ,  $Q^{\max}$  and any other similar index) can be also localized. Working with the hypothesis that only the frontier molecular orbitals (HOMO and LUMO) are important in weak intermolecular interactions we may localize any global reactivity index,  $G$ , by applying the following formula:

$$G_i = [F_i(\text{HOMO})G \pm F_i(\text{LUMO})G]^*K \quad (34)$$

where  $F_i(\text{HOMO})$  and  $F_i(\text{LUMO})$  are, respectively, the Fukui indices of atom  $i$  at the HOMO and LUMO.  $G_i$  is then a local atomic reactivity index of atom  $i$ .  $K$  and  $\pm$  are to be selected following our needs. If we chose  $K=1/2$  and the plus sign we get a local atomic electronic chemical potential. With  $K=1$  and the minus sign we get a local atomic hardness.

Now, let us look at the definitions of  $\mu$  and  $\eta$  as defined by Eqs. 29 and 30. As is well known,  $\mu$  is the middle point between the HOMO and LUMO, and  $\eta$  is the HOMO-LUMO gap. They are expressed in energy units (eV for example). Therefore I began searching for local (atomic) mathematical expressions for  $\mu$  (also called ECP) and  $\eta$  fulfilling the following two conditions: they must have the same or similar meaning as the global indices, and their numerical values must be expressed only in energy units. I discarded formulas based on Eq. 34 because their units are in  $\text{eV} \times e$  and therefore they do not have the same meaning as the global equivalents (for example, local  $\mu$  is not the middle point between HOMO and LUMO energies and local  $\eta$  is not the HOMO-LUMO gap). When I was analyzing the electronic structure of some molecules prior to a QSAR study, I created Figure 1 (a quite similar figure was recently published [90]). In this figure there are three atoms (A, B, C) belonging to the same molecule. The three highest occupied MOs (H, H-1, H-2) and the three first empty MOs (L, L+1, L+2) are shown. The circles indicate non-zero electron populations on one MO (for example, atom A contributes to the molecular HOMO but atoms B and C do not, etc.). It took some time to notice the simple fact that it was possible way to define immediately local atomic  $\mu$  and local atomic  $\eta$  indices as follows:

For atom A:

$$\mu_A = (\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})/2 \quad \text{and} \quad \eta_A = (\epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}}) \quad (35)$$

For atom B:

$$\mu_B = (\epsilon_{\text{HOMO}-2} + \epsilon_{\text{LUMO}})/2 \quad \text{and} \quad \eta_B = (\epsilon_{\text{HOMO}-2} - \epsilon_{\text{LUMO}}) \quad (36)$$

For atom C:

$$\mu_C = (\epsilon_{\text{HOMO}-1} + \epsilon_{\text{LUMO}+1})/2 \quad \text{and} \quad \eta_C = (\epsilon_{\text{HOMO}-1} - \epsilon_{\text{LUMO}+1}) \quad (37)$$

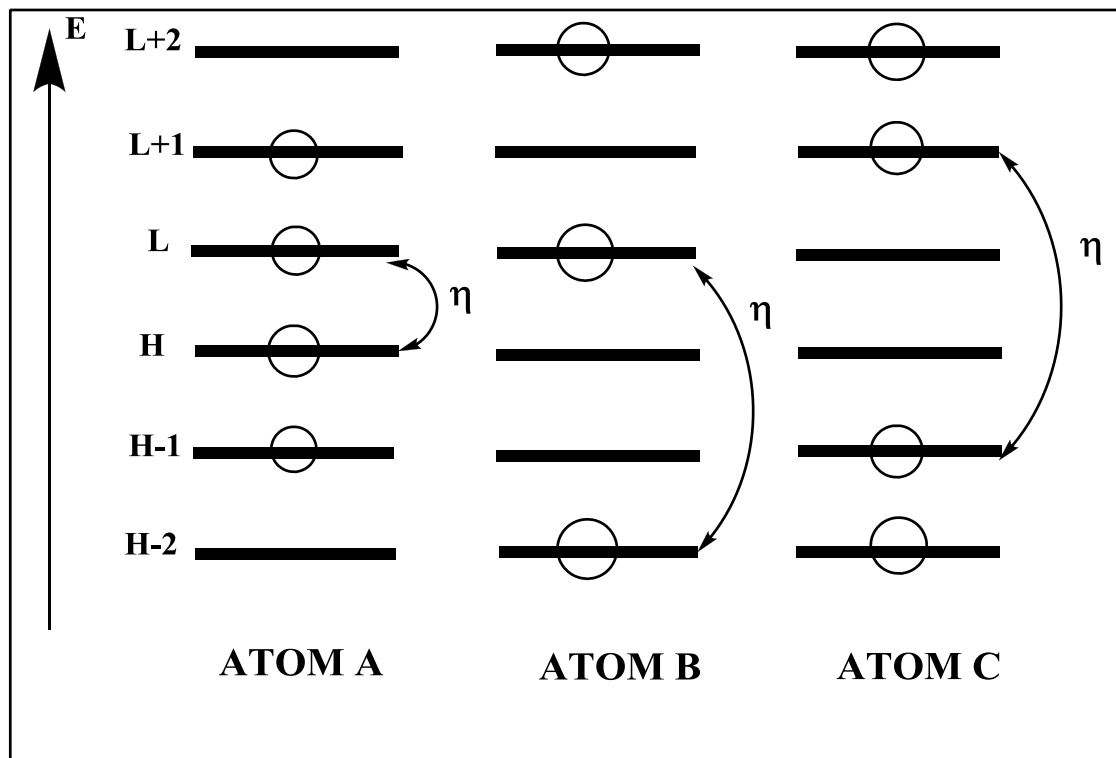
Eqs. 35 to 37 can be generalized for atom  $i$  as:

$$\mu_i = (\epsilon_{\text{HOMO}^*,i} + \epsilon_{\text{LUMO}^*,i})/2 \quad (38)$$

and

$$\eta_i = (\epsilon_{\text{HOMO}^*,i} - \epsilon_{\text{LUMO}^*,i}) \quad (39)$$

where  $\epsilon_{\text{HOMO}^*,i}$  and  $\epsilon_{\text{LUMO}^*,i}$  are, respectively, the energy of the highest occupied MO having a non-zero electron population on atom  $i$  (the local HOMO of atom  $i$ , HOMO\*), and the energy of the lowest empty MO having a non-zero electron population on atom  $i$  (the local LUMO of atom  $i$ , LUMO\*). The possible degeneracy of MO energies must not be forgotten in the calculations! Within this framework, a hard atom resists exchanging electrons with an approaching partner. In the same way we may localize any other reactivity indices.



**Figure 1.** A direct definition of the local atomic electronic chemical potential and the local atomic hardness. Arrows depict the local atomic hardness ( $\eta$ ).

We may also define similar expressions for the frontier ESD and NSD:

$$S_i^{E^*} = \frac{F_{i,\text{HOMO}^*}}{\epsilon_{\text{HOMO}^*}} \quad (40)$$

$$S_i^{N^*} = \frac{F_{i,\text{LUMO}^*}}{\epsilon_{\text{LUMO}^*}} \quad (41)$$

where  $\epsilon_{\text{HOMO}^*,i}$  and  $\epsilon_{\text{LUMO}^*,i}$  have the meanings just mentioned and  $F_{i,\text{HOMO}^*}$  and  $F_{i,\text{LUMO}^*}$  are the associated Fukui indices.

With Eqs. 38 and 39 we may calculate all the remaining LARIs defined in Eqs. 31-33 as follows:

The local atomic softness of atom  $i$ :

$$S_i = \kappa_i = \frac{1}{\eta_i} \quad (42)$$

The local atomic electrophilicity of atom  $i$ :

$$\omega_i = \frac{\mu_i^2}{2\eta_i} \quad (43)$$

The maximal charge atom  $i$  may accept:

$$Q_i^{\max} = -\frac{\mu_i}{\eta_i} \quad (44)$$

These definitions are expressed in the same units as their global counterparts and they also have similar meanings<sup>121,194</sup>. Note that in Eqs. 42-44, when  $\eta_i \rightarrow \infty$ ,  $S_i \rightarrow 0$ ,  $\omega_i \rightarrow 0$  and  $Q_i^{\max} \rightarrow 0$  as expected.

We need to keep in mind that these LARIs should work very well at least in two cases. Within a molecule, they serve to identify the most reactive sites. An erroneous interpretation is, for example, to say that in the case of a molecule in a fully stable state the different local atomic  $\mu$  values indicate that electrons will flow within the molecule. The second use is to analyze, within a model of atom-atom interaction (see Section 2.3), what the possible nature of an interaction partner could be. This is especially important for QSAR studies in which the exact molecular structure of the receptor is still not known.

Let us now consider a substituent or any group G of atoms within a molecule and composed of n atoms  $a_j$ . Then:

$$G = \{a_1, a_2, \dots, a_n\} \quad (45)$$

We may define the group electrophilicity,  $G^\omega$ , as:

$$G^\omega = \sum_1^n \omega_{a_i} \quad (46)$$

We may use this same procedure for defining any other group local reactivity index we need.

## 4. RESULTS AND DISCUSSION

### 4.1. Creating a Standard Set of Values

The next step is to verify if these local atomic reactivity indices can provide reasonable results when applied to concrete cases. As their numerical value is basis set-dependent, and inspired by the work of Pearson [124,195-198], a Table of “standard” values was created [193]. The B3LYP/6-31G(d) level of theory was employed to compute the energy of the highest occupied orbital (HOO) and the electron affinity of several atoms ( $-\epsilon_{\text{HOO}}=0.56+0.73\text{IP}$ ,  $R=0.98$ ,  $\text{SD}=0.57$ ). The electron affinity was calculated as the difference between the total energies of the neutral atom and its anion ( $E_{\text{neut}}-E_{\text{anion}}=-0.80+1.07\text{EA}$ ,  $R=0.76$ ,  $\text{SD}=1.16$ ). The results are shown in Table 1.

**Table 1.** Values of  $\mu$ ,  $\eta$ ,  $S$ ,  $\omega$  and  $Q^{\max}$  for atoms at the B3LYP/6-31G(d) level

Atom	Electron						
	$\epsilon_{\text{HOO}}$ (eV)	Affinity (eV)	$\mu$ (eV)	$\eta$ (eV)	$s$ (1/eV)	$\omega$ (eV)	$Q^{\max}$
H	-8.6034	-1.05	-4.83	7.55	0.13	1.54	0.64
Li	-3.6292	0.16	-1.73	3.79	0.26	0.4	0.46
B	-4.6763	-2.35	-3.51	2.33	0.43	2.65	1.51
C	-6.8769	-0.25	-3.56	6.63	0.15	0.96	0.54
N	-9.4951	-0.69	-5.09	8.81	0.11	1.47	0.58
O	-10.066	2.54	-3.76	12.61	0.08	0.56	0.3
F	-12.1409	1.08	-5.53	13.22	0.08	1.16	0.42
Na	-3.5095	0.44	-1.53	3.95	0.25	0.3	0.39
Al	-3.5715	-0.69	-2.13	2.88	0.35	0.79	0.74
Si	-5.2066	0.82	-2.19	6.03	0.17	0.4	0.36
P	-7.0352	0.76	-3.14	7.8	0.13	0.63	0.4
S	-7.5396	3.3	-2.12	10.84	0.09	0.21	0.2
Cl	-9.5849	3.19	-3.2	12.77	0.08	0.4	0.25
Br	-8.6217	2.86	-2.88	11.48	0.09	0.36	0.25

These values are not related to the experimental ones. From Table 1 we can make some qualitative statements. For example, the four best electron acceptors (a highly negative  $\mu$  value) are  $F > N > H > O$ . The four best electron donors are  $Na > Li > S \geq Al$ . The atomic hardness values indicate that the atoms more prone to change their electronic density (through a chemical reaction) are  $B > Al > Li > Na$ . In the case of halogens  $Q^{\max}$  indicates that fluorine is more prone to receive extra electronic charge than Cl and Br. Perhaps we may find some not-so-true relationships in Table I, but it was presented only to be used below as an example. For practical purposes, we do not need to rely on such kinds of Tables.

#### 4.2. Applications to Diatomic and Triatomic Molecules

All the calculations reported in this section were done at the B3LYP/6-31G(d) level of theory with full geometry optimization. Negative electron populations arising from Mulliken Population analysis were corrected as proposed [67]. A question that we need to comment on is the exact meaning of “zero” or “non-zero electron population” of an atom in a given MO. In any quantum-chemical calculation several results are sometimes given with too many digits in the fractional part of the number (in fact, as an anecdote, I have known two scientists that maintained the thesis that the total energies of optical enantiomers were different and another that obtained negative densities of states. The teaching of this anecdote is that it is not enough to buy commercial software and use it if you do not have a clear understanding of what you are doing). For the cases presented in this section we have considered as zero those Fukui indices having a value equal to or less than 0.01, unless another value is explicitly mentioned. The risk of using a very small value for small molecular systems is that no local atomic values will be obtained. In molecular systems composed of hundreds or thousands of atoms, in which a large or very large number of electrons are delocalized, a similar limit for the value of the Fukui index can be employed. This is because in such systems several of the large number of MOs become very similar in energy over a certain range, forming quasi-degenerate groups (at the limit they form bands). An ELF (electron localization function) analysis of the electron reorganization along the polar Diels-Alder reaction of cyclopentadiene with tetracyanoethylene at the B3LYP/6-31G(d) level was carried out by Domingo *et al.* [199]. They found charge transfer values ranging from 0.03 e up to 0.44 e. These results are in agreement with the cut-off value chosen for the Fukui index.

In the case of molecules in which all atoms are equivalent (homonuclear diatomic molecules for example), the DFT local atomic reactivity indices have the same numerical value as global ones. Table 2 shows the values of several LARIs for halogen homonuclear diatomic molecules.

**Table 2.** Local atomic reactivity indices of halogen homonuclear diatomic molecules at the B3LYP/6-31G(d) level of the theory

	F <sub>2</sub>	Cl <sub>2</sub>	Br <sub>2</sub>
$\mu$ (eV)	-7.06	-6.20	-5.76
$\eta$ (eV)	7.20	4.66	3.87
S (1/eV)	0.14	0.21	0.26
$Q^{\max}$	0.98	1.33	1.49
$\omega$ (eV)	3.46	4.13	4.29
$S^{E*}$ (e/eV)	-2.55	-3.19	-3.53
$S^{N*}$ (e/eV)	-7.86	-7.03	-7.11

Looking at Table 2 we may see that, *in comparison with the isolated atoms*, these molecules are better electron acceptors ( $\mu$ ), their resistance to change their electron density has diminished ( $\eta$ ) and their capacity to accept extra charge has increased ( $Q^{\max}$ ), a fact that is logical because electrons within molecules are not under the influence of only one nucleus.  $S^{N*}$  values show that the electron-accepting

capacities are in the order  $F_2 > Br_2 > Cl_2$ , in agreement with  $\mu$  values. Electron-donating capacities, given by  $S^{E*}$ , are in the order  $Br_2 > Cl_2 > F_2$ .  $Br_2$  is the molecule that can receive more extra charge than  $F_2$  and  $Cl_2$  ( $Q^{max}$ ) and has more ability to retain it once acquired (S). The local electrophilic index is associated with the electrophilic power and includes the tendency of the electrophile atom to receive extra electronic charge together with its resistance to exchange charge with the medium. This index can be viewed as a measure of the electrophilicity because it is an analogue of the classical electrostatic power,  $V^2/R$ , with  $\mu$  and  $\eta$  serving the purpose of potential (V) and resistance (R), respectively [116]. Within this definition  $Br_2$  is more electrophilic than the other two molecules.

Table 3 shows the numerical values of several LARIs for some diatomic halogen heteronuclear molecules.

**Table 3.** Local atomic reactivity indices of halogen halide molecules at the B3LYP/6-31G(d) level of the theory

	BrCl	BrF	ClF
$\mu$ (eV)	-5.97	-5.86	-6.12
$\eta$ (eV)	4.17	4.86	5.63
S (1/eV)	0.24	0.21	0.18
$Q^{max}$	1.43	1.21	1.09
$\omega$ (eV)	4.28	3.53	3.33
$S^{E*}$ (e/eV)	Br = -4.33 Cl = -2.42	Br = -5.41 F = -1.16	Cl = -4.57 F = -1.52
$S^{N*}$ (e/eV)	Br = -7.99 Cl = -6.01	Br = -11.87 F = -4.01	Cl = -11.93 F = -4.54

Again, the local atomic reactivity indices are the same as the global ones. This is so because in small closed shell diatomic molecules the HOMO and LUMO have Fukui indices with high numerical values. But, on the other hand, frontier superdelocalizabilities, defined by Eqs. 40 and 41, provide chemically useful information.

When comparing the three molecules, the value of  $\mu$  indicates that, globally, ClF is a better electron acceptor than BrCl and BrF. But, as shown by the values of  $S^{E*}$  and  $S^{N*}$ , the Cl atom is a better electron donor and acceptor than the F atom. The same holds for BrF. In the case of BrCl the Br atom is a better electron donor and acceptor than the Cl atom but the difference between their SD indices values is less than in the other two molecules.

Table 4 shows the numerical values of the LARIs for  $H_2O$  and  $H_2S$ . In this case we have considered as zero those Fukui indices having a value equal to or less than 0.0001 to appreciate if we may get results that are chemically acceptable.

**Table 4.** Local atomic reactivity indices for  $H_2O$  and  $H_2S$  at the B3LYP/6-31G(d) level of theory

	O	H	S	H
$\mu$ (eV)	-1.95	-4.21	-3.29	-4.74
$\eta$ (eV)	11.95	11.83	7.65	10.55
S (1/eV)	0.84	0.85	0.13	0.95
$Q^{max}$	0.16	0.36	0.43	0.45
$\omega$ (eV)	0.16	0.75	0.71	1.07
$S^{E*}$ (e/eV)	-6.85	-0.31	-7.65	-0.58
$S^{N*}$ (e/eV)	1.41	11.59	56.64	22.81

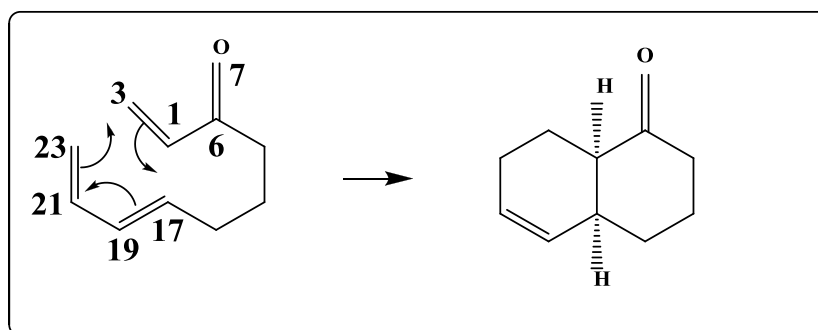
We may see from the  $S^{E*}$  values that the sulphur atom is a better electron donor than oxygen. The  $S^{N*}$

index informs us that the electron-acceptance ability order is  $S > H(H_2S) > H(H_2O) > O$ . The atoms of water are harder and they can accept less extra charge than hydrogen sulphide ones. H atoms from  $H_2S$  have greater electrophilicity. Looking at Table 1 we may see that the S atom has become a better electron acceptor compared with the isolated atom. On the contrary, the oxygen atom of water has diminished electron-accepting capacity.

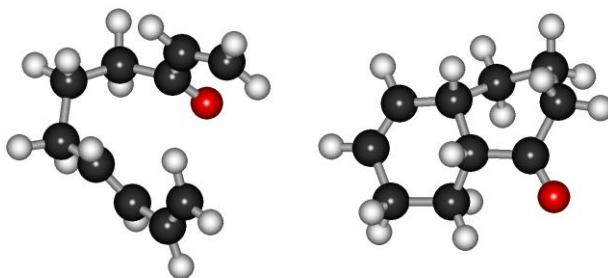
The examples presented above suggest that the local atomic reactivity indices derived from DFT can be of little use in small molecules. More systematic studies are needed to establish what “small” means exactly. Anyway, superdelocalizabilities derived within the HFR framework show their utility. Finally, systematic studies of small molecules with a variety of methods and basis sets may be carried out to compare the quality (and truthfulness) of the chemical information they can provide.

#### 4.3. An Example of the Variation of LARIs along the Intrinsic Reaction Coordinate (IRC)

Here we shall analyze the evolution of LARIs along the IRC for the case of one of the channels of the intramolecular Diels-Alder (IMDA) reaction of 1,3,9-decatrien-8-one [200,201]. Figures 2 and 3 show, respectively, the scheme of the reaction and the fully optimized structures of 1,3,9-decatrien-8-one and the final product. The goal of this study is to provide an example for finding any inconsistency for which there is no logical explanation. This should help to find a reliable value to consider that an atom has a non-zero electron population on its frontier orbitals. All IRC calculations were done at the B3LYP/6-31G(d,p) level of theory.



**Figure 2.** IMDA reaction of 1,3,9-decatrien-8-one



**Figure 3.** Fully optimized geometry of 1,3,9-decatrien-8-one and the final *endo* product of the IMDA reaction

The left side of Figure 2 shows the atoms included in the analysis shown below (atoms 1, 3, 6, 7, 17, 19, 21 and 23). Figure 4 shows the variation of the atomic net charges along the IRC for the selected atoms. Points marked 0 and 30 correspond, respectively, to the fully optimized 1,3,9-decatrien-8-one and the



final *endo* product. We may observe small net charge variations throughout the IRC. The O atom slightly raises its net charge after conjugation with atoms 1 and 3 is broken. The transition from  $sp^2$  to  $sp^3$  character produces different effects on the carbon atoms: while at atoms 3 and 23 the net charge diminishes its value, at atom 1 it does not change much. Atom 19, which has  $sp^2$  character at the beginning and the end of the IRC, reduces its net charge. In general we observe that, for this reaction, the variation of all net charges is smooth. At point 16 of the IRC we have  $d(3-23)=1.94\text{\AA}$ ,  $d(1-17)=2.57\text{\AA}$  and  $d(1-3)=1.42\text{\AA}$ . At point 18 of the IRC we have  $d(3-23)=1.77\text{\AA}$ ,  $d(1-17)=2.47\text{\AA}$  and  $d(1-3)=1.45\text{\AA}$ . At point 16 the 1-3 double bond still maintains its nature, but at point 18 it is much closer to atom 23. Therefore in this zone a slight rearrangement of net charges is expected.

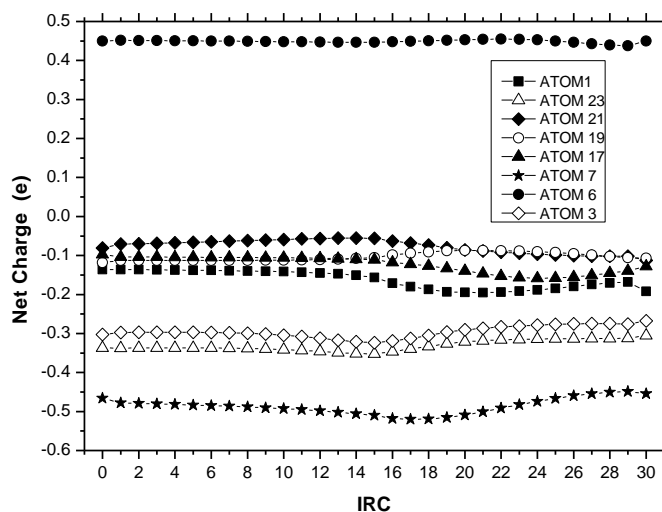


Figure 4. Variation of the net charges along the IRC

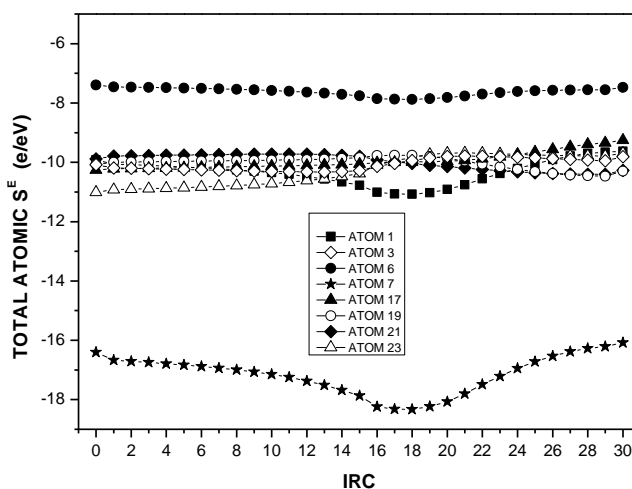
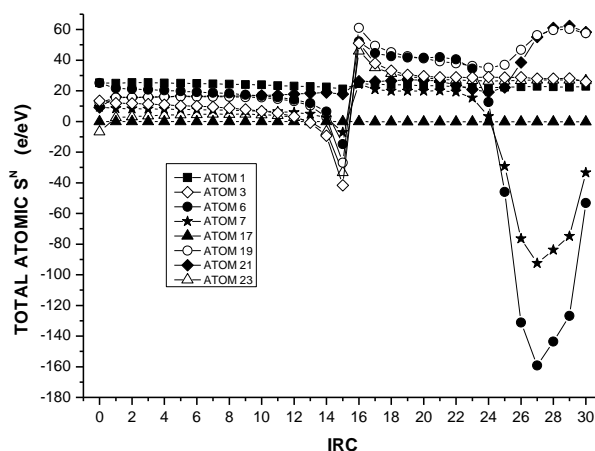
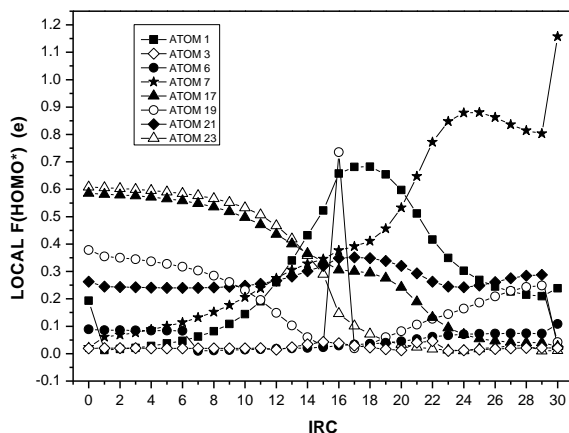


Figure 5. Variation of the total atomic electrophilic superdelocalizability along the IRC

Figure 5 shows the variation of the total atomic electrophilic superdelocalizability (TESD) along the IRC. Atom 21 (oxygen) has the highest electron-donating capacity while atom 6 (the C carbon attached to the O atom) shows the least electron-donating capacity, all this in agreement with chemical thinking and the particular composition of this system. Atoms 7 (oxygen), 6 (C) and 1 (C) slightly increase their electron donating capacities at points 16-18 of the IRC. Here the variation of the property along the IRC is also smooth. Figure 6 shows the variation of the total atomic nucleophilic superdelocalizability along the IRC. I have stated in another paper that the numerical values of this reactivity index are not reliable [90]. The reason is that this calculation, as I said above, produces algebraic zeros around the Fermi Level. This is the reason for the sudden changes of value and sign in Figure 6, which has been presented as an example to take into account when doing this kind of research.



**Figure 6.** Variation of the total atomic nucleophilic superdelocalizability along the IRC.



**Figure 7.** Variation of the local atomic Fukui index of HOMO\* along the IRC

Figure 7 shows the variation of the local atomic Fukui index of HOMO\* along the IRC. The first fact to notice is the sudden change of  $F_{19}(\text{HOMO}^*)$  at point 16 of the IRC. Close inspection of the results shows that the HOMO\* at points 15 and 17 for atom 19 corresponds to the molecular HOMO (MO 41) but in the

case of point 16 the local HOMO is MO 39 and the population of atom 19 at MOs 40 and 41 is close to zero. Therefore, this result is not an artifact coming from the cut-off value for the Fukui index. The HOMO\* of the other atoms displayed in Figure 7 do not present sudden changes. I think that if we work with a correct cut-off value for the Fukui index it would be possible to track points of interest in the IRC that could provide interesting chemical information. Another question, difficult to answer for the moment, is if the algorithm to generate the IRC points is completely reliable or not. Figure 8 shows the variation of the Fukui index of LUMO\* along the IRC. Again we find sudden changes for this index between points 8-12 of the IRC for atoms 17, 19, 21 and 23 that are not the product of a wrong choice of the cut-off value for the Fukui index. It is interesting to note that this sudden change of the Fukui index affects bonded atoms (17-19, 19-21 and 21-23), and that it could correspond to a change of localization of the LUMO.

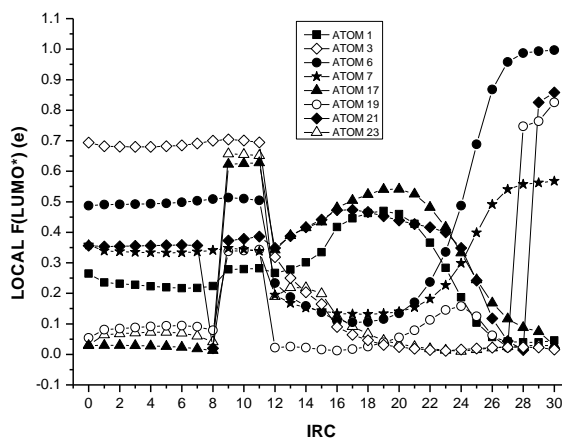


Figure 8. Variation of the local atomic Fukui index of LUMO\* along the IRC

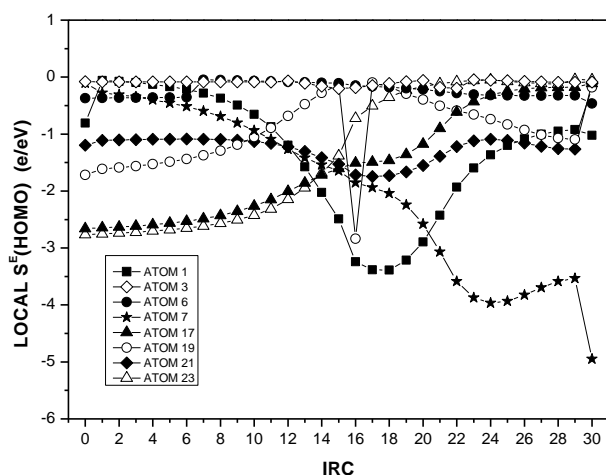
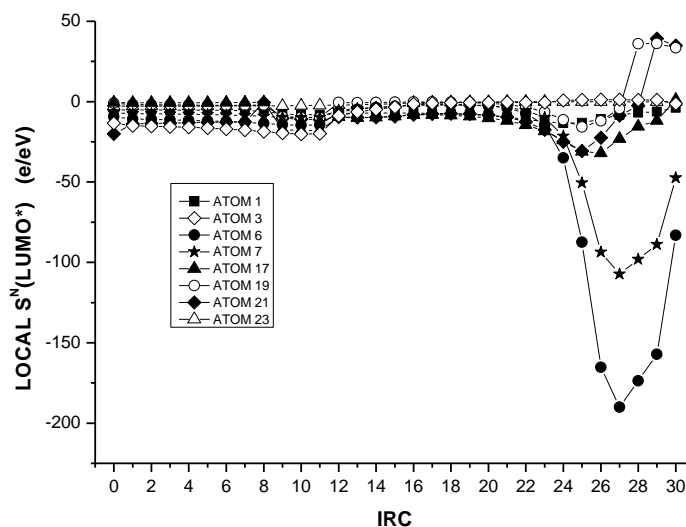


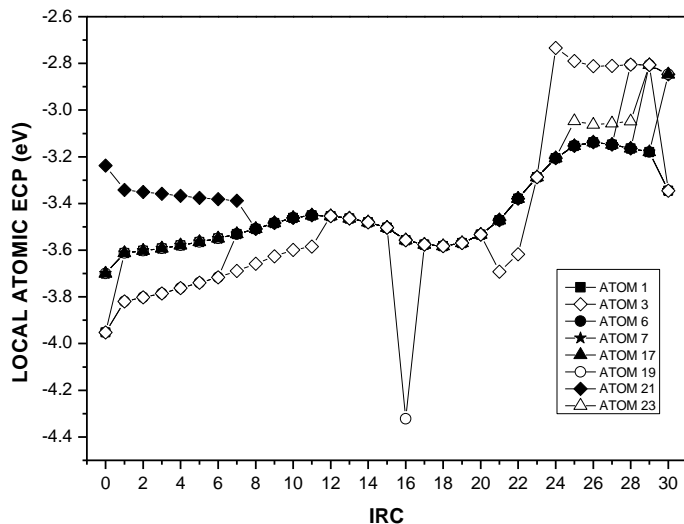
Figure 9. Variation of the local atomic HOMO\* electrophilic superdelocalizability along the IRC

Figure 9 shows the variation of the HOMO\* electrophilic superdelocalizability along the IRC. In correspondence with the value for  $F_{19}(\text{HOMO}^*)$ ,  $F_{19}(\text{LUMO}^*)$  presents a discontinuity. Here we may see

that the value for atom 19 (oxygen) diminishes continuously from left to right indicating that the disappearance of the conjugated double bond concentrates more charge on this atom. Figure 10 shows the variation of the local atomic LUMO nucleophilic superdelocalizability along the IRC. Knowing that the only empty MO with negative energy is the LUMO (MO 42) we may appreciate that at points 28-30 atoms 19 and 21 have a positive value for this index due to the fact that their local LUMOs are not the molecular one. Atom 6, attached to the oxygen atom, is more prone to interact with electron donors.

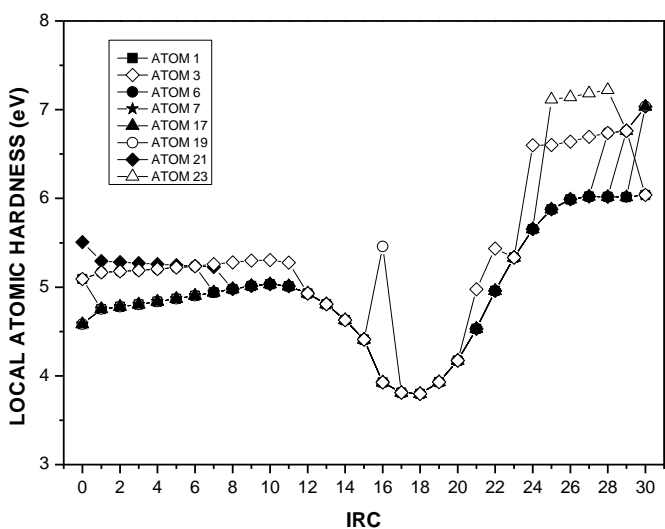


**Figure 10.** Variation of the local atomic LUMO nucleophilic superdelocalizability along the IRC

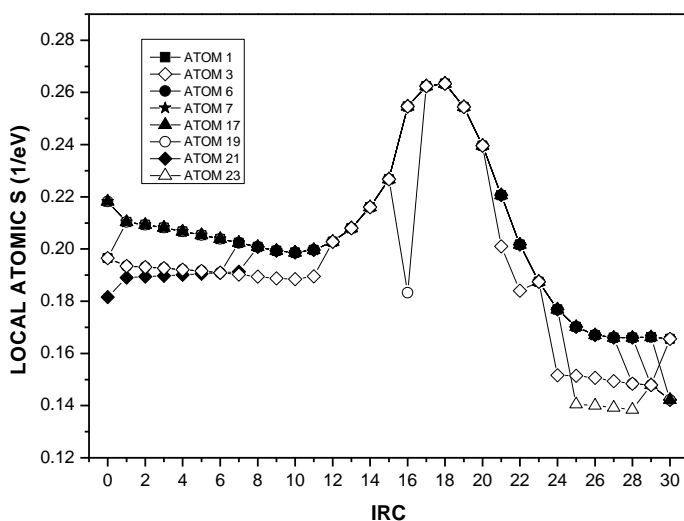


**Figure 11.** Variation of the variation of the local atomic electronic chemical potential along the IRC.

Figure 11 shows the variation of the local atomic electronic chemical potential along the IRC. We find the same discontinuity at point 16 for the reasons stated above. Figure 12 shows the variation of the local atomic hardness along the IRC. Apart from point 16, we may observe that atoms of the product are harder than atoms of the initial state.



**Figure 12.** Variation of the local atomic hardness along the IRC



**Figure 13.** Variation of the local atomic softness along the IRC.

Figure 13 shows the variation of the local atomic softness along the IRC. Here, the atoms of the product are softer than the atoms of the initial state. Given the definition of softness, this is expected. Figure 14 shows the variation of local atomic  $Q^{\max}$  along the IRC. In general, the atoms of the initial state can accept

more extra charge than the atoms of the final state. This is logical because in the initial state we have two areas of conjugation (remember that we are analyzing just these atoms), and in the final state only a double bond. Figure 15 shows the variation of the local atomic electrophilicity along the IRC. Here, again the atoms of the initial state have more electrophilic power than the atoms of the final state.

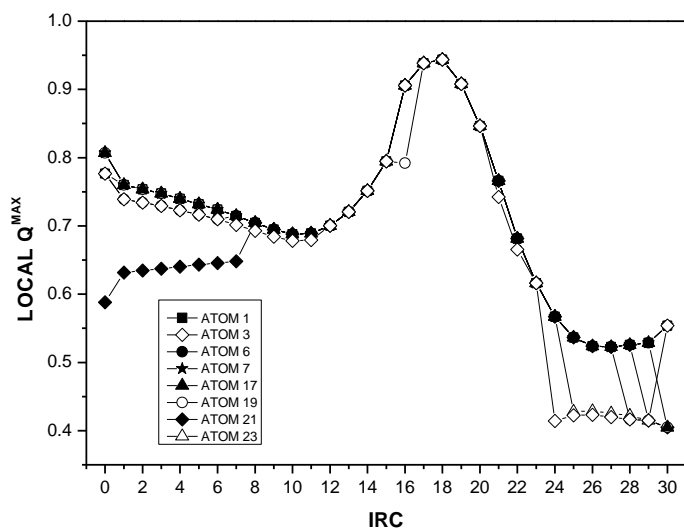


Figure 14. Variation of local atomic  $Q^{\max}$  along the IRC.

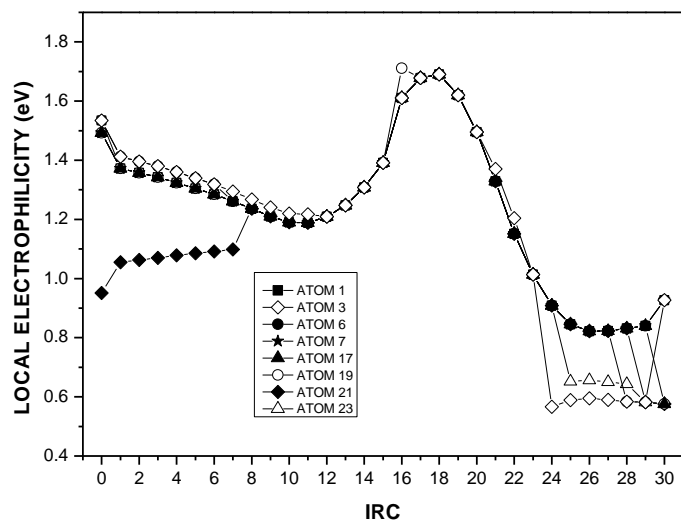


Figure 15. Variation of the local atomic electrophilicity along the IRC.

#### 4.4. The Use of LARIs in QSAR Studies

Perhaps the research area in which the above indices are showing their utility is model-based QSAR (for the definition of model-based see [90]). In a recent paper relating  $\mu$ ,  $\delta$  and  $\kappa$  opioid receptor binding affinity and molecular structure for a group of molecules having in common a morphine structural core we have obtained equations containing  $\eta_i$ ,  $\omega_i$  and  $Q_i^{\max}$  [90]. Recent results of the search for structure-activity relationships for two sets of molecules displaying inhibitory activity against some effects of HIV-1 and H1N1 viruses produced an equation containing a local atomic softness [202]. The appearance, in QSAR equations, of high values of local atomic  $\eta$  puzzled us until we noticed that these atoms could be interacting with hydrophobic areas of the partner (methylene groups of alkyl chains of aminoacids). As far as we know, this is the only quantum-chemical reactivity index giving an account of this kind of interaction.

## 5. CONCLUSIONS

The Hartree-Fock-Roothaan framework provided the first set of local atomic reactivity indices. Interestingly, at first sight (conceptual) Density Functional Theory generated an entirely different set of global and local reactivity indices. We have presented here a new way to create local atomic reactivity indices derived from conceptual Density Functional Theory using a series of approximations for the case of two interacting molecules. They differ from other sets of numerical values in that they keep their original physical meaning and units of measurement. The study of their variation along the IRC shows that they could be useful for a deeper study of some points presenting abrupt changes, but we need to carry out an extensive comparison with IRC results for a variety of reactions. In the field of model-based QSAR the use of these new indices provides information complementing that coming from the Hartree-Fock-Roothaan reactivity indices. My personal impression is that probably there should be a way to connect local atomic reactivity indices coming from DFT and HFR.

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