

Perspectives on the Density Functional Theory of Chemical Reactivity

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Abstract. A brief perspective of the development of the density functional theory of chemical reactivity since the identification of the chemical potential with the electronegativity in 1978 is presented. The reactivity concepts are examined together with the chemical principles associated with them. Then, the interaction energy between a nucleophile and an electrophile is analyzed in order to illustrate the relevance of these concepts to characterize global reactivity and site selectivity trends.

Key words: Density functional theory, electronegativity, chemical potential, hardness, Fukui function, dual descriptor.

Resumen. Se presenta una breve perspectiva del desarrollo de la teoría de funcionales de la densidad de la reactividad química, a partir de la identificación del potencial químico con la electronegatividad en 1978. Se examinan los conceptos de reactividad junto con los principios químicos asociados con ellos. Posteriormente, se analiza la energía de interacción entre un nucleófilo y un electrófilo para ilustrar la relevancia de estos conceptos para caracterizar tendencias de reactividad tanto globales como de selectividad de sitios.

Palabras clave: Teoría de funcionales de densidad; electronegatividad, potencial químico, dureza, función de Fukui, descriptor dual.

1. Introduction

Density functional theory (DFT) has become the dominant tool in chemistry and physics for calculations of electronic structure [1,2]. Through the development of rather accurate approximations to the exchange-correlation energy functional [3], the Kohn-Sham (KS) method has been extensively and successfully applied to the study of simple and complex chemical systems [4]. Actually, by this approach it is possible to determine thermodynamic, kinetic and structural properties with a precision comparable to that of correlated *ab initio* methods, but at a much lower computational effort.

In addition, DFT has provided a very solid framework for the study of chemical reactivity [1,5-8]. Through this approach it has been possible to identify with fundamental variables of DFT chemically meaningful concepts that had been established intuitively, like the electronegativity and the chemical hardness. This identification has been very important to determine their absolute values and to understand the principles associated with them. Additionally, it has also been possible to derive new concepts, of global and local type, that contain very important information about the response of a chemical species when it interacts with different types of reagents.

Since the density functional theory of chemical reactivity may be considered to have been born three decades ago, with the work on electronegativity of Parr, Donnelly, Levy and Palke [9], the object of the present work is to provide a brief perspective of its development. Thus, we begin, in Sec. 2, with the analysis of the concepts that emerge from DFT and the principles associated with them. Then, in Sec. 3 we will discuss the interaction energy between a nucleophile and an electrophile through the concepts of DFT. Finally, in Sec. 4, some concluding remarks will be presented.

2. The concepts

The inherent chemical reactivity of a molecule may be discussed through response functions that describe the way in which the electronic structure of the reference state, which usually corresponds to that of the isolated species, is going to be affected by the presence of the other reagent.

In the initial stages of the interaction between a molecule and a reagent, when they are far apart from each other, one can observe basically two effects. One of them is concerned with the fact that the presence of the reagent changes the external potential felt by the electrons of the molecule, so that they are subject not only to the external potential due to its nuclei, but also to the external potential due to the nuclei and electrons of the reagent. The other effect comes from the possible electron transfer between the molecule and the reagent that may lead to a change in the total number of electrons of the molecule with respect to its value when it is isolated.

Thus, the description of the inherent chemical reactivity of a given species, through response functions, may be carried out in terms of the derivatives of the total energy with respect to the number of electrons, with respect to the external potential, or with respect to both.

It turns out that DFT provides a rather appropriate framework for the calculation of these derivatives. In DFT the ground state total energy for an N -electron system is expressed in terms of the three-dimensional ground-state electronic density $\rho(\mathbf{r})$ and the external potential $v(\mathbf{r})$ in the form [1]

$$E[\rho] = F[\rho] + \int d\mathbf{r} \rho(\mathbf{r}) v(\mathbf{r}), \quad (1)$$

where $F[\rho]$ is the universal functional of Hohenberg-Kohn given by the sum of the electronic kinetic energy functional and the electron-electron interaction energy functional, and

$$N = \int d\mathbf{r} \rho(\mathbf{r}), \quad (2)$$

guarantees the proper normalization of the electron density.

The ground-state electronic density can be obtained from the solution of the Euler-Lagrange equation corresponding to the minimization of the energy given in eq (1), subject to the restriction given by eq (2), that is,

$$\mu = \left(\frac{\delta E}{\delta \rho(\mathbf{r})} \right)_v = v(\mathbf{r}) + \frac{\delta F}{\delta \rho(\mathbf{r})}, \quad (3)$$

where μ , the undetermined Lagrange multiplier, is the chemical potential that measures the escaping tendency of the electrons from a system. Electrons flow from places with higher chemical potential to places with lower chemical potential up to the point in which μ becomes constant throughout space.

a. Electronegativity and hardness

The basic relationship of the density functional theory of chemical reactivity is, precisely, the one established by Parr, Donnelly, Levy and Palke [9], that links the chemical potential of DFT with the first derivative of the energy with respect to the number of electrons, and therefore with the negative of the electronegativity χ ,

$$\mu = \left(\frac{\partial E}{\partial N} \right)_v = -\chi. \quad (4)$$

The next fundamental aspect comes from the identification of the concept of chemical hardness with the second derivative of the energy with respect to the number of electrons [10], that is,

$$\eta = \left(\frac{\partial^2 E}{\partial N^2} \right)_v = \left(\frac{\partial \mu}{\partial N} \right)_v. \quad (5)$$

The definitions of the chemical potential and the chemical hardness given by eqs (4) and (5) require from the knowledge of the energy as a function of the number of electrons. This one has been established through the extension of DFT to open systems with noninteger number of electrons, based on the grand canonical ensemble, that leads, in the limit of zero temperature, to a non smooth expression for the energy as a function of the number of electrons, given by a series of straight lines connecting the ground-state energies of the systems with integer number of electrons [11]. The joined straight line structure has also been shown to be required by any size consistent method, without invoking the grand canonical ensemble [12, 13]. Thus, a very important consequence of this behavior is that the left (μ^-) and right (μ^+) first derivatives are not equal, that is, for an N_0 -electron system, with N_0 being an integer, the straight line structure leads to [11]

$$\mu^+ = \left(\frac{\partial E}{\partial N} \right)_v^+ = E_{N_0+1} - E_{N_0} = -A, \quad (6)$$

and

$$\mu^- = \left(\frac{\partial E}{\partial N} \right)_v^- = E_{N_0} - E_{N_0-1} = -I, \quad (7)$$

where I and A are the vertical first ionization potential and the vertical electron affinity, respectively. It is remarkable that the average of the one-sided derivatives leads to the definition of electronegativity given by Mulliken [14],

$$\mu^0 = \left(\frac{\partial E}{\partial N} \right)_v^0 = \frac{1}{2}(\mu^- + \mu^+) = -\frac{1}{2}(I + A). \quad (8)$$

For the hardness, which is given by the second derivative, according to the straight line structure, is zero when evaluated from the left or from the right and it is not defined for integer number of electrons. However, Ayers and Parr [15] have shown that some information remains, namely [13]

$$\eta^{(N_0+x)} = (\mu^+ - \mu^-) \delta(x) = (I - A) \delta(x), \quad -1 \leq x \leq 1 \quad (9)$$

where $\delta(x)$ is the Dirac delta function.

Now, although from a chemical viewpoint, it makes sense to have different responses for charge removal and charge addition processes, the joint straight line structure destroys second order effects. Thus, in order to include them, an alternative approach is provided by the smooth quadratic interpolation around the reference point [10],

$$\Delta E = \mu \Delta N + \frac{1}{2} \eta (\Delta N)^2. \quad (10)$$

The finite differences approximations to the first and second derivatives, for an N_0 -electron system, that results from this smooth quadratic interpolation are^{1,10}

$$\mu = -\chi \approx -\frac{I + A}{2}, \quad (11)$$

and

$$\eta \approx I - A. \quad (12)$$

The relationships given by eqs (11) and (12) provide a strong support to the identifications established, because when one uses experimental information for I and A to calculate μ and η , one finds that, in general, the quantities obtained from eq (11) follow the same trends as those of the electronegativity concept of Pauling [16], while the quantities obtained from eq (12) show, in general, the same trends as those of the chemical hardness concept of Pearson [17].

Thus, in this case the energy and its derivatives are continuous functions of the number of electrons around N_0 , but the response functions for charge addition or removal processes are the same.

Now, in terms of orbital energies, the approximate, but conceptually useful expressions for the chemical potential and the chemical hardness are [1],

$$\mu = -\chi \approx \frac{1}{2}(\varepsilon_L + \varepsilon_H), \quad (13)$$

and

$$\eta \approx \varepsilon_L - \varepsilon_H, \quad (14)$$

where ε_H and ε_L are the eigenvalues of the highest occupied molecular spin-orbital (HOMO) and the lowest unoccupied molecular spin-orbital (LUMO), respectively.

In the case of the Kohn-Sham orbitals, the approximations involved in eqs (13) and (14), are related with the discontinuity of the exact exchange-correlation potential,^{11,18,19} and lead to larger values of μ and to lower values of η in comparison with the values obtained through the total vertical energy differences required to calculate them with eqs. (11) and (12).

While in the case of the Hartree-Fock orbitals, the approximations involved in eqs (13) and (14) are related with Koopmans theorem, and although the values thus obtained lie close to the values obtained from the Hartree-Fock vertical energy differences of eqs (11) and (12), they do not incorporate the correlation effects.

b. Electrophilicity, electroaccepting power and electrodonating power

The first ionization potential and the electron affinity measure the capability of a chemical species to donate and to accept one electron, respectively. However, many chemical interactions may be explained through charge transfer processes that may involve fractional amounts of charge.

In this context, Parr, Von Szentpály, and Liu [20] have defined an electrophilicity index that measures the energy change of an electrophile when it becomes saturated with electrons. For this purpose, they have considered a chemical species immersed in an idealized bath of electrons, with zero chemical potential. Thus, the species will accept electrons until the point in which its chemical potential becomes equal to that of the bath. From eq. (10), this condition implies that, at the minimum, $\Delta N_{\max} = -\mu/\eta > 0$, and the energy change is equal to $\Delta E = -\mu^2/2\eta < 0$, from which electrophilicity is defined as

$$\omega \equiv \mu^2/2\eta. \quad (15)$$

Recently, a quadratic interpolation for the energy as a function of the number of electrons, in which the response functions for the charge addition and the charge subtraction processes are differentiated, has been proposed [21]. In this case, it is assumed that for the interval between $N_0 - 1$ and N_0 eq. (10) adopts the form

$$\Delta E^- = \mu^- \Delta N + \frac{1}{2} \eta^- (\Delta N)^2, \quad (16)$$

while for the interval between N_0 and N_0+1 , it takes the form

$$\Delta E^+ = \mu^+ \Delta N + \frac{1}{2} \eta^+ (\Delta N)^2, \quad (17)$$

where μ^\mp are the chemical potentials and η^\mp are the chemical hardnesses, in their corresponding intervals. This procedure, together with the concept of a bath of electrons that represents the chemical environment in which a chemical species is immersed, and whose chemical potential may be adjusted to donate or accept charge, leads to the concepts of electrodonating (ω^-) and electroaccepting (ω^+) powers,

$$\omega^- = (\mu^-)^2/2\eta^- \quad \text{and} \quad \omega^+ = (\mu^+)^2/2\eta^+. \quad (18)$$

If $\mu^- = \mu^+ = \mu$ and $\eta^- = \eta^+ = \eta$ then one recovers the electrophilicity index $\omega^- = \omega^+ = \omega = \mu^2/2\eta$.

One can show that the definitions given by eq. (18) are not necessarily linked to the point at which the species becomes saturated with electrons. That is, eqs. (15) or (18) establish that the electrodonating or the electroaccepting powers may be quantified in terms of the chemical potential and the chemical hardness, independently of the fractional amount of charge donated or accepted. However, it is important to note that in the case of ω^+ , the charge acceptance process is such that it stabilizes the system, so that larger values imply a larger capability to accept electrons, while in the case of ω^- , the charge donating process is such that it destabilizes the system, so that smaller values imply a larger capability to donate electrons.

Thus, the electrodonating and the electroaccepting powers show a similar behavior to that of the first ionization potential and the electron affinity, respectively, although in the case of I and A one measures the capability of a chemical system to donate or to accept one electron, while in the case of ω^- and ω^+ one measures the capability of a chemical system to donate or to accept a small fractional amount of charge.

A simpler approach that also differentiates the response to charge donation from the response to charge acceptance, has also been proposed [21] by taking into account that the direction of flow of charge is fundamentally driven by the chemical potential, since in this context one may assume in eqs. (16) and (17) that $\eta^- = \eta^+ = \eta$, and that $\eta = \mu^+ - \mu^-$.

When these assumptions are combined with the energy differences for I and A , in eqs. (16) and (17), one finds that,

$$\eta = \frac{1}{2}(I - A), \quad \mu^- = -\frac{1}{4}(3I + A) \quad \text{and} \quad \mu^+ = -\frac{1}{4}(I + 3A). \quad (19)$$

Thus, by this procedure the hardness remains proportional to the difference of the first ionization potential and the electron affinity, while μ^- and μ^+ show differences related with the fact that they govern the charge donation and charge acceptance processes, respectively.

c. Fukui function, dual descriptor and linear response function

In the preceding section we have discussed the concepts that arise when one considers the derivatives of the energy with

respect to the number of electrons, so now we will consider the response functions that come up when one considers derivatives with respect to the external potential.

From conventional first-order perturbation theory one can show that [1]

$$\left(\frac{\delta E}{\delta v(\mathbf{r})}\right)_N = \rho(\mathbf{r}), \quad (20)$$

so that using this expression and eqs. (4) and (5) one has that,

$$\left(\frac{\delta^2 E}{\delta v(\mathbf{r}') \delta v(\mathbf{r})}\right)_N = \left(\frac{\delta \rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right) = P(\mathbf{r}, \mathbf{r}'), \quad (21)$$

$$\left(\frac{\delta \mu}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v = f(\mathbf{r}), \quad (22)$$

and

$$\left(\frac{\delta \eta}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial N^2}\right)_v = \Delta f(\mathbf{r}), \quad (23)$$

where $P(\mathbf{r}, \mathbf{r}')$ is the conventional linear response function [1], $f(\mathbf{r})$ is known as the Fukui function [22], and $\Delta f(\mathbf{r})$ is known as the dual descriptor [23, 24].

The linear response function, eq. (21), measures the change in the electronic density at point \mathbf{r} due to a change in the external potential at point \mathbf{r}' , thus it provides information about the capacity of the electronic cloud of a molecule to polarize because of the presence of a reagent. Its evaluation may be carried out by means of second-order perturbation theory [1].

Now, in the case of the Fukui function, eq. (22), one needs first to establish the dependence of the electronic density in the number of electrons, through the extension of DFT to open systems with noninteger number of electrons, based on the grand canonical ensemble and in the limit of zero temperature. As in the case of the energy, one finds that the electronic density has slopes discontinuities at the integer numbers of electrons, due to the joint straight line structure of the electron density for noninteger number of electrons [11]. Therefore, the left ($f^-(\mathbf{r})$) and right ($f^+(\mathbf{r})$) derivatives are different, that is,

$$f^-(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v^- = \rho_{N_0}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r}), \quad (24)$$

and

$$f^+(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v^+ = \rho_{N_0+1}(\mathbf{r}) - \rho_{N_0}(\mathbf{r}), \quad (25)$$

while the arithmetic average of the one-sided derivatives leads to

$$f^0(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_v^0 = \frac{1}{2}(f^-(\mathbf{r}) + f^+(\mathbf{r})) = \frac{1}{2}(\rho_{N_0+1}(\mathbf{r}) - \rho_{N_0-1}(\mathbf{r})). \quad (26)$$

In eqs. (24)-(26), $\rho_{N_0-1}(\mathbf{r})$, $\rho_{N_0}(\mathbf{r})$, and $\rho_{N_0+1}(\mathbf{r})$ are the electronic densities of the $N_0 - 1$, N_0 , and $N_0 + 1$ -electron systems, calculated for the external potential of the ground-state of the N_0 -electron system.

Ayers and Parr [15] have made use of the variational principle for determining the Fukui function and the chemical hardness of an electronic system, derived by Chattaraj, Cedillo and Parr [25], to show that, from an energetic viewpoint, the best way to remove a fraction of an electron ΔN from a system, is to remove it from the place defined by the function $f^-(\mathbf{r})$, while the best way to add it is at the place defined by the function $f^+(\mathbf{r})$. This means that a molecule donates charge from the regions where $f^-(\mathbf{r})$ is large when it is attacked by an electrophilic reagent, and it accepts charge at the regions where $f^+(\mathbf{r})$ is large when it is attacked by a nucleophilic reagent, providing this way information of site reactivity within a molecule.

For the dual descriptor, eq. (23), which is given by the second derivative, according to the straight line structure, is zero when evaluated from the left or from the right and it is not defined for integer number of electrons. However, Ayers [13] has shown that, similarly to the case of the energy,

$$\Delta f^{(N_0+x)}(\mathbf{r}) = (f^+(\mathbf{r}) - f^-(\mathbf{r})) \delta(x), \quad -1 \leq x \leq 1. \quad (27)$$

Thus, in order to include the second derivative of the density with respect to the number of electrons, one can perform, as in the case of the energy, a smooth quadratic interpolation around the reference point,

$$\Delta \rho(\mathbf{r}) = f^0(\mathbf{r}) \Delta N + \frac{1}{2} \Delta f(\mathbf{r}) (\Delta N)^2. \quad (28)$$

The finite differences approximations to the first and second derivatives, for an N_0 -electron system, that results from this smooth quadratic interpolation are, eq. (26) for $f^0(\mathbf{r})$, and

$$\Delta f(\mathbf{r}) = f^+(\mathbf{r}) - f^-(\mathbf{r}). \quad (29)$$

Thus, according to the interpretation given to the Fukui functions, those sites where the sign of the dual descriptor is positive are favored for a nucleophilic attack, while those sites where the sign of the dual descriptor is negative are favored for an electrophilic attack.

The approximate expressions for the Fukui functions in terms of the Kohn-Sham orbitals may be established by approximating the electron densities of the $N_0 - 1$ - and the $N_0 + 1$ -electron systems with the orbitals set corresponding to the N_0 -electron system, because then, using eqs. (24) and (25), one finds that [22, 26]

$$f^-(\mathbf{r}) \approx \rho_H(\mathbf{r}) \quad \text{and} \quad f^+(\mathbf{r}) \approx \rho_L(\mathbf{r}), \quad (30)$$

where $\rho_H(\mathbf{r})$ and $\rho_L(\mathbf{r})$ are the densities of the highest occupied and lowest unoccupied molecular orbitals, respectively.

In the case of the dual descriptor, using eqs (29) and (30), one has that

$$\Delta f(\mathbf{r}) \approx \rho_L(\mathbf{r}) - \rho_H(\mathbf{r}). \quad (31)$$

Thus, one can see that the Fukui function is closely related to the frontier orbitals. However, for the case of the Kohn-Sham orbitals, the Fukui function, in contrast with frontier orbital theory, includes the orbital relaxation effects associated with electron addition or removal. In some cases these effects are very important.

The case of the Hartree-Fock orbitals is quite similar to that of the Kohn-Sham orbitals, except that in this case, the correlation effects are not considered.

d. The principles

Through the identifications established in this section for the concepts in terms of fundamental variables of DFT, it has been possible to achieve a better understanding of the principles associated with them, and to introduce new principles. This is a very important aspect, because these principles govern chemical interactions and therefore, through them, one can infer, in many cases, the course of a reaction.

Accordingly, as it was already mentioned before, the chemical potential measures the escaping tendency of the electrons from a system. Electrons flow from places with higher chemical potential to places with lower chemical potential up to the point in which μ becomes constant throughout the space. Thus, one can see that, from the identification of the electronegativity with the negative of the chemical potential, the principle of electronegativity equalization, proposed by Sanderson [27, 28], follows immediately.

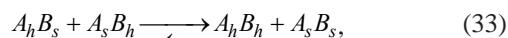
The hard and soft acids and bases (HSAB) principle proposed by Pearson [17], has been very important for the understanding of acid-base chemistry. The principle states that hard acids prefer to bind with hard bases, and that soft acids prefer to bind with soft bases.

The first DFT analysis of the HSAB principle were based on the acid-base reaction [29-31],



and were oriented to establish that the interaction between species of similar hardness were energetically favored.

Recently, Ayers et al [32-36] have considered the exchange reaction,



where A_h is a hard acid, A_s is a soft acid, B_h is a hard base, and B_s is a soft base. According to the HSAB principle the equilibrium in this reaction is displaced to the right. Thus, using a simple charge transfer model based on eq. (10), he was able to show that the reaction energy for this case is always less than zero. Thus, this result implies that the exchange reaction, eq. (33), is always exothermic in agreement with the HSAB principle. Because of the assumptions implicit in this approach, one can infer that electron transfer is the main contribution

in the HSAB principle, and that the exceptions to the rule are probably due to the fact that in some cases there may be other contributions that dominate the interaction.

The maximum hardness principle was first expressed by Pearson [37] who concluded that "there seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible." Later on, Parr and Chattaraj [38] provided a proof based on statistical mechanics that indeed, under conditions of constant chemical potential and temperature, a chemical system evolves toward the state of maximum hardness.

Other studies of this principle are based on approximate expressions for the energy difference between two states of a system, in terms of chemical potential differences and chemical hardness differences [30, 39, 40]. Through these expressions it has been shown that at constant chemical potential, as the total energy increases, the hardness decreases, and as the total energy decreases, the hardness increases. A maximum in the energy corresponds with a minimum in the hardness, and a minimum in the energy corresponds with a maximum in the hardness.

The HSAB principle may be interpreted as the result of two opposing tendencies, one related to the charge transfer process (chemical potential equalization principle), and the other one related to the reshuffling of the electronic density maximum hardness principle). In this framework a local version of the principle has been elucidated [41-43] by assuming that when two species interact, they do it through specific sites, so that the interaction energy is dominated by the local properties of these sites, rather than by the global properties of the species. Thus, as in the global HSAB principle, in the local HSAB principle one states that soft acids bind to soft bases through their softest sites, while hard acids bind to hard bases through their hardest sites.

It is important to mention that the hard and soft sites within a molecule may be obtained from the local softness, which is defined as [44]

$$s(\mathbf{r}) = \left(\frac{\partial \rho(\mathbf{r})}{\partial \mu} \right)_v = \left(\frac{\partial N}{\partial \mu} \right)_v \left(\frac{\partial \rho(\mathbf{r})}{\partial N} \right)_v = \frac{1}{\eta} f(\mathbf{r}) = S f(\mathbf{r}), \quad (34)$$

where eqs. (5) and (22) have been used. The quantity S is the global softness, the inverse of the chemical hardness. Thus, sites where the Fukui function is large are soft sites, while sites where the Fukui function is small are hard sites.

3. The interaction energy

In order to see how the concepts established in the previous section may lead to an understanding of reactivity trends, let us consider now the initial stages of the interaction between two chemical species, a nucleophile that is going to be attacked by an electrophile. In this case one may treat the presence of the electrophile as a perturbation on the nucleophile, and vice versa. Thus, one can perform [23, 24, 45, 46] a second order Taylor series expansion of the energy of the nucleophile, as a

function of the number of electrons and the external potential that leads, for the nucleophile, to

$$\begin{aligned} \Delta E_{nuc} &= \mu_{nuc} \Delta N_{nuc} + \frac{1}{2} \eta_{nuc} (\Delta N_{nuc})^2 \\ &+ \int d\mathbf{r} \rho_{nuc}(\mathbf{r}) \delta v_{nuc}(\mathbf{r}) + \Delta N_{nuc} \int d\mathbf{r} f_{nuc}^-(\mathbf{r}) \delta v_{nuc}(\mathbf{r}) \\ &+ \frac{1}{2} \iint d\mathbf{r} d\mathbf{r}' P_{nuc}(\mathbf{r}, \mathbf{r}') \delta v_{nuc}(\mathbf{r}) \delta v_{nuc}(\mathbf{r}'), \end{aligned} \quad (35)$$

while for the electrophile it leads to

$$\begin{aligned} \Delta E_{elec} &= \mu_{elec} \Delta N_{elec} + \frac{1}{2} \eta_{elec} (\Delta N_{elec})^2 \\ &+ \int d\mathbf{r} \rho_{elec}(\mathbf{r}) \delta v_{elec}(\mathbf{r}) + \Delta N_{elec} \int d\mathbf{r} f_{elec}^+(\mathbf{r}) \delta v_{elec}(\mathbf{r}) \\ &+ \frac{1}{2} \iint d\mathbf{r} d\mathbf{r}' P_{elec}(\mathbf{r}, \mathbf{r}') \delta v_{elec}(\mathbf{r}) \delta v_{elec}(\mathbf{r}'), \end{aligned} \quad (36)$$

where we have used eqs. (4), (5), (20), (21) and (22).

Now, in the case of eq. (35), the change in the external potential is due to the presence of the electrophile, thus

$$\begin{aligned} \delta v_{nuc}(\mathbf{r}) &= - \sum_{\beta \in elec} \frac{Z_\beta}{|\mathbf{r} - \mathbf{R}_\beta|} + \int d\mathbf{r}' \frac{\rho_{elec}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} + \Delta N \int d\mathbf{r}' \frac{f_{elec}^+(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \\ &= -v_{elec}^{es}(\mathbf{r}) + \Delta N \int d\mathbf{r}' \frac{f_{elec}^+(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}, \end{aligned} \quad (37)$$

where $\{Z_\beta\}$ the sets and $\{\mathbf{R}_\beta\}$ represent the nuclear charges and the positions of the nuclei of the electrophile, the first two terms corresponds to the negative of the electrostatic potential generated by the electrophile, $v_{elec}^{es}(\mathbf{r})$, and the third term corresponds to the modification of the electrostatic potential because of the charge transferred from the nucleophile to the electrophile,

$$\Delta N = \Delta N_{elec} = -\Delta N_{nuc}. \quad (38)$$

In the case of eq. (36), the change in the external potential is due to the presence of the nucleophile, therefore

$$\begin{aligned} \delta v_{elec}(\mathbf{r}) &= - \sum_{\alpha \in nuc} \frac{Z_\alpha}{|\mathbf{r} - \mathbf{R}_\alpha|} + \int d\mathbf{r}' \frac{\rho_{nuc}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} - \Delta N \int d\mathbf{r}' \frac{f_{nuc}^-(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \\ &= -v_{nuc}^{es}(\mathbf{r}) - \Delta N \int d\mathbf{r}' \frac{f_{nuc}^-(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}, \end{aligned} \quad (39)$$

where now the sets $\{Z_\alpha\}$ and $\{\mathbf{R}_\alpha\}$ represent the nuclear charges and the positions of the nuclei of the nucleophile, and, in a similar way, the first two terms of this relation represent the negative of the electrostatic potential generated by the nucleophile, $v_{nuc}^{es}(\mathbf{r})$, while the last term corresponds to the modification of the electrostatic potential because of the charge transferred from the nucleophile to the electrophile.

Consequently, assuming that the interaction energy is given by the sum of the energy change of the nucleophile and the energy change of the electrophile, one finds, using eqs. (35) - (37) and (39), and correcting for the double counting of the interactions, that

$$\Delta E_{int} = \Delta E_{cov} + \Delta E_{es} + \Delta E_{pol}, \quad (40)$$

where the quantity ΔE_{cov} is usually called the covalent contribution, and it is given by

$$\begin{aligned} \Delta E_{cov} &= (\mu_{elec} - \mu_{nuc}) \Delta N + \frac{1}{2} (\eta_{elec} + \eta_{nuc}) (\Delta N)^2 \\ &+ \Delta N \left\{ \int d\mathbf{r} f_{nuc}^-(\mathbf{r}) v_{elec}^{es}(\mathbf{r}) - \int d\mathbf{r} f_{elec}^+(\mathbf{r}) v_{nuc}^{es}(\mathbf{r}) \right\} - (\Delta N)^2 \iint d\mathbf{r} d\mathbf{r}' \frac{f_{elec}^+(\mathbf{r}) f_{nuc}^-(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}. \end{aligned} \quad (41)$$

The quantity ΔE_{es} is the electrostatic contribution, and it is given by

$$\Delta E_{es} = \int d\mathbf{r} \left[\sum_{\alpha \in nuc} Z_\alpha \delta(\mathbf{r} - \mathbf{R}_\alpha) - \rho_{nuc}(\mathbf{r}) \right] v_{elec}^{es}(\mathbf{r}), \quad (42)$$

and the quantity ΔE_{pol} is the polarization contribution, and it is given by

$$\begin{aligned} \Delta E_{pol} &= \frac{1}{2} \iint d\mathbf{r} d\mathbf{r}' P_{nuc}(\mathbf{r}, \mathbf{r}') \delta v_{nuc}(\mathbf{r}) \delta v_{nuc}(\mathbf{r}') \\ &+ \frac{1}{2} \iint d\mathbf{r} d\mathbf{r}' P_{elec}(\mathbf{r}, \mathbf{r}') \delta v_{elec}(\mathbf{r}) \delta v_{elec}(\mathbf{r}'). \end{aligned} \quad (43)$$

Note that in the electrostatic contribution we have included the nuclear-nuclear repulsion energy that results from the interaction of the nuclei of the nucleophile with the nuclei of the electrophile.

An analysis of eq. (40), together with eqs (41)-(43) reveals several aspects. First, it is important to mention that the interaction between the nucleophile and the electrophile is favored when the interaction energy is negative, thus, the lower ΔE_{int} , the greater the reactivity.

A very significant issue is related to the fact that the three terms contain integrals over functions, whose values depend on the position within the molecule. Since the value of the integral depends upon how the values of the integrand are distributed over the whole space, it means that these functions provide information about the reactivity of the different sites of the molecule.

Now, ΔE_{cov} is the main contribution when one considers the interaction between neutral and soft species. The second term, ΔE_{es} , is the dominant contribution when the interaction involves hard ionic species. Finally, ΔE_{pol} might be significant in hard-soft interactions.

The minimization of the interaction energy, eq (40), with respect to the charge transferred ΔN leads to

$$\Delta N = \frac{(\mu_{nuc} - \mu_{elec}) + \left\{ \int d\mathbf{r} f_{elec}^+(\mathbf{r}) v_{nuc}^{es}(\mathbf{r}) - \int d\mathbf{r} f_{nuc}^-(\mathbf{r}) v_{elec}^{es}(\mathbf{r}) \right\}}{\eta_{elec} + \eta_{nuc} - 2 J_f}, \quad (44)$$

where

$$J_f = \iint d\mathbf{r} d\mathbf{r}' \frac{f_{elec}^+(\mathbf{r}) f_{nuc}^-(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}. \quad (45)$$

Thus, one can see that a high overlap between $f_{elec}^+(\mathbf{r})$ and $f_{nuc}^-(\mathbf{r})$ will lead to a large value of the integral J_f and, consequently, to a large amount of charge transferred. This situation implies that the Fukui functions of the electrophile and the nucleophile provide information not only on site reactivity, but also on orientational selectivity, because of the directional properties of them. This can be seen also from the frontier orbital approximation to the Fukui function, which means that, using eq (30), $f_{elec}^+(\mathbf{r}) \approx \rho_{elec}^L(\mathbf{r})$ and $f_{nuc}^-(\mathbf{r}) \approx \rho_{nuc}^H(\mathbf{r})$. However, it is remarkable that this orientational selectivity may also be established using electronic density differences to determine the Fukui functions, through eqs. (24) and (25).

It is important to mention that the relevance of eq. (45) was first established by Berkowitz [47], who formulated a model for the early stages of frontier controlled reactions between Lewis acids and bases. In this model it is assumed that the chemical potential that is already equalized for both the acid and the base, because they already form one system, remains equalized after the initial motion of the reactants along some reaction coordinate.

Recently, Ayers *et al.* [48] have shown that the Woodward-Hoffmann rules for pericyclic reactions may also be explained through electronic density differences, by making use of the dual descriptor.

In order to see the importance of this local reactivity indicator, from an energetic viewpoint, consider first eqs. (26) and (29) to express $f^+(\mathbf{r})$ and $f^-(\mathbf{r})$ in terms of $f^0(\mathbf{r})$ and $\Delta f(\mathbf{r})$, that is

$$f^+(\mathbf{r}) = f^0(\mathbf{r}) + \frac{1}{2} \Delta f(\mathbf{r}), \quad (46)$$

and

$$f^-(\mathbf{r}) = f^0(\mathbf{r}) - \frac{1}{2} \Delta f(\mathbf{r}). \quad (47)$$

If eqs. (46) and (47) are used in the last term of eq. (41), then there will be a term in the interaction energy corresponding to the Coulomb interaction between the dual descriptor of the nucleophile and that of the electrophile of the form [48],

$$(\Delta N)^2 \iint d\mathbf{r} d\mathbf{r}' \frac{\Delta f_{elec}(\mathbf{r}) \Delta f_{nuc}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|}. \quad (48)$$

Thus, if the positive regions of $\Delta f_{elec}(\mathbf{r})$ are aligned with the negative regions of $\Delta f_{nuc}(\mathbf{r})$, and vice versa, then the contribution to the interaction energy from the term expressed in eq. (48) is negative, indicating that in such case is favorable for the reaction to occur.

Now, since the dual descriptor is directly related with the changes in the chemical hardness produced by changes in the external potential, and since the dual descriptor seems to be able to provide rather precise information on site selectivity,

Morrell, Grand and Toro-Labbé [24] have concluded that the selectivity concept in chemistry could be a manifestation of the principle of maximum hardness.

4. Concluding remarks

In the preceding sections we have presented a brief perspective of the development of the density functional theory of chemical reactivity. We have seen that, essentially, it is constructed through response functions that are given by the derivatives of the energy and of the density with respect to the number of electrons.

On one hand, the identification of the derivatives of the energy with respect to the number of electrons with the chemical potential (electronegativity) and the chemical hardness is crucial, because it provides a link with fundamental concepts of chemistry.

On the other hand, the association of the response of the chemical potential and the chemical hardness to changes in the external potential with the derivatives of the density with respect to the number of electrons is also crucial, because it allows one to express the response of these fundamental concepts to the presence of a reagent in terms of electronic density differences.

The chemical potential and the chemical hardness, μ and η , are global type response functions that characterize the molecule as a whole, while the electronic density $\rho(\mathbf{r})$, the Fukui function $f(\mathbf{r})$, and the dual descriptor $\Delta f(\mathbf{r})$ are local type response functions whose values depend upon the position within the molecule. Thus, the global reactivity parameters allow one to characterize global reactivity trends, while the local reactivity parameters allow one to characterize site reactivity trends.

In the last three decades, after the work on electronegativity of Parr, Donnelly, Levy and Palke [9], there have been a rather large number of applications of these concepts to a wide variety of chemical systems, under many different circumstances. Thus, the DFT theory of chemical reactivity has been successfully applied, in general, to the understanding of Lewis acid-base chemistry, including the Brønsted-Lowry acidity and basicity, nucleophilic and electrophilic elimination and substitution reactions and redox reactions, among others.

In conclusion, we have seen that through the use of the electronic density as the basic variable, together with the identification of the chemical potential, the chemical hardness, the Fukui function and the dual descriptor, DFT grants a chemically meaningful language for the study of reactivity in terms of concepts and principles that have proven to be very useful to understand the behavior of a molecule when it interacts with different families of reagents.

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