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QUANTITATIVE REPRESENTATION OF REACTIVITY, SELECTIVITY AND SITE ACTIVATION CONCEPTS IN ORGANIC CHEMISTRY@

Patricia Pérez [1], *Julia Parra-Mouchet* [2] *and Renato R. Contreras* [2]

[1] Departamento de Ciencias Químicas, Facultad de Ecología y Recursos Naturales, Universidad Andrés Bello, Santiago, Chile p.perez@unab.cl and
[2] Departamento de Química, Facultad de Ciencias, Universidad de Chile, Santiago, Chile.
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ABSTRACT

Reactivity, selectivity and site activation are classical concepts in chemistry which are amenable to quantitative representation, in terms of static global, local and non local density response functions. The use of these electronic indexes describing chemical interconversion is developed in this work along the perspective of the pioneering work conducted in Chile by the late Professor Fernando Zuloaga, to whom this article is dedicated in memoriam. While global responses, represented as derivatives of the electronic energy with respect to the total number of electrons quantitatively describe the propensity of a system to interconvert into another chemical species (chemical reactivity), the local counterparts assesses well those regions in the molecule where the reactivity pattern dictated by the global quantities is developed (selectivity). Site activation /deactivation may in turn be described by the variations in the local or regional patterns of reactivity, that may be induced by solvent effects or chemical substitution. These concepts are illustrated for a series of chemical reactions in Organic Chemistry, including electrocyclic processes, cycloadditions and electrophilic addition reactions. Some relationships between quantitative scales of reactivity and reaction mechanisms are discussed.

1. INTRODUCTION.

The description of chemical processes in terms of reactivity indexes has become a current approach in theoretical physical organic chemistry. From the dawn of Mulliken□s molecular orbital theory [1], the electronic structure of molecules has been the basis for the representation of static models of reactivity. These reactivity models were mainly framed on electron population analysis performed at each atomic center of the molecular system (gross and net atomic charges), as well as electron population at the internuclear regions (bond order indexes) [2]. An elegant formulation based on Huckel molecular orbital (HMO) theory was presented in a series of seminal papers by Coulson et al [3], to describe the electronic structure of conjugated systems (mobile electron theory). Several local and non local reactivity indexes defined in the form of static density response functions, namely, atomic and bond polarizability, where proposed within this context [3]. This generalization was formally introduced in the theory of chemical reactivity, first by Klopman and Salem [4-6], and subsequently by Fukui [7-10], within a theoretical framework known as the Frontier Molecular Orbital

(FMO) theory. Within this approach, most of the determining factors governing a chemical reaction involved the frontier molecular orbitals HOMO and LUMO of the electron donor and the electron acceptor pair. The basic quantities here are the molecular orbital coefficients and the intermolecular HOMO-LUMO gap.

Electronic polarizability has been rather recently related to Pearson´s concept of chemical softness [11-13], thereby incorporating non electrostatic forces in the reactivity models based on electronic indexes. Most of these ideas have been gathered in a compact form within the framework of density functional theory (DFT) [14,15]. Classical concepts like electronegativity, chemical hardness and softness have been given simple operational expressions, so that at present, it is possible to establish quantitative scales of chemical properties for atoms and molecules. They are currently used in connection with some empirical rules, namely, the electronegativity equalization (EEP), the maximum hardness (MHP) and the hard and soft acids and bases (HSAB) principles [16-17], to discuss chemical reactivity on a more quantitative basis. Besides these global quantities, local or regional reactivity indexes defined around specific regions of molecules have been proposed. The most important quantity is the Fukui function f(r), which condenses in a single number most of the information encompassed in the FMO theory. The Fukui function has been proposed as the natural descriptor of selectivity [18-20]. A high value of this index at a given region in a molecule is associated with a highest reactivity at that site. The Fukui function also has some additional mathematical properties, as most of the global properties are distributed within a molecule following the Fukui function. The local softness s(r) = f(r) S, is just an example that illustrates this property.

The use of the conceptual DFT to deal with reactivity and selectivity problems was pioneered in Chile by Zuloaga at the end of the 80´s [21]. This seminal work strongly stimulated the young theoretical chemist community in the country to incorporate these new concepts in the analysis of chemical reactivity. Several instructive applications, mainly devoted to the scrutiny of Diels-Alder cycloaddition reactions, were used by Fernando to illustrate the enormous potential of DFT to assist in the analysis of reactivity and selectivity of these processes [22,23]. In this work we intend to present an overview on the application of DFT based quantities to quantitatively describe the reactivity and selectivity patterns of cycloaddition reactions, electrocyclic processes, electrophilic addition to asymmetric alkenes and intermolecular hydrogen bonding, in the light of the fundamental and creative contributions made by Fernando Zuloaga in the field of theoretical physical organic chemistry.

2. Fundamentals of density functional theory.

In density functional theory, the ground state (GS) electronic energy E is a unique functional of the real space electron density r (r), a physical observable of atomic and molecular systems [24]. The electron density is in turn uniquely determined by the external potential u (r), due to the compensating positive (nuclear) charges. Since r (r) normalizes to the total number of electrons N in the system:

$$N = \int dr\, \rho(r) \qquad ; (1)$$

it becomes possible to write the electronic energy E as a function of the number of electrons, and a functional of the external potential: E = E[N, u (r)] [25]. The exact differential of E in this representation is [25]:

$$dE = \left[\frac{\partial E}{\partial N}\right]_{\upsilon(r)} dN + \int dr \left[\frac{\delta E}{\delta \upsilon(r)}\right]_N \delta\upsilon(r) \qquad (2)$$

$$= \mu\, dN + \int dr\, \rho(r)\, \delta\upsilon(r)$$

where

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{\upsilon(r)} \qquad (3)$$

is the electronic chemical potential of the system. This quantity is related to the amount and direction of the charge transfer during a chemical interaction. It flows from the highest to the lowest values, until an equilibrium regime is attained. For instance, if two interacting subsystems A and B say, are characterized by $\mu_A > \mu_B$, then the electron flux in the charge transfer process will take place from A towards B, until at the equilibrium where a complex A---B is formed, $\mu_A = m_B = \mu_{AB}$. Note that in addition, the relationship $\mu_A > \mu_B$ immediately entails that during the interaction A will act as nucleophile and B as electrophile. A more quantitative representation of electrophilicity and nucleophilicity will be given below.

Two additional reactivity indexes, one global the other local, may be defined by writing the exact differential for $\mu = \mu[N, \upsilon(r)]$, namely [25]:

$$d\mu = \left[\frac{\partial \mu}{\partial N}\right]_{\upsilon(r)} dN + \int dr \left[\frac{\delta \mu}{\delta \upsilon(r)}\right]_N \delta\upsilon(r) \qquad (4)$$

$$= \eta\, dN + \int dr\, f(r)\, \delta\upsilon(r)$$

While the quantity h has been associated with Pearson□s chemical hardness, the local quantity f(r) has been defined as Fukui function of the system. A hard species preferably establishes long range electrostatic interactions, and they currently participate in charge controlled processes. Its inverse, $S = 1/\eta$ is the chemical softness, a quantity related to the electronic polarizability of the system [26,27]. Soft species preferentially establishes covalent interactions with a significant amount of charge transfer. The Fukui function on the other hand, defined by [25] :

$$f(\mathbf{r}) \equiv \left[\frac{\delta\mu}{\delta v(\mathbf{r})}\right]_N = \left[\frac{\partial\rho}{\delta N}\right]_{v(\mathbf{r})} \qquad (5)$$

is one of the fundamental descriptors of selectivity [28,29]. As stated in the Introduction, the Fukui function has a remarkable mathematical property that allows most of the global properties to be distributed in space. This may be easily shown by using the definition of local softness [25] :

$$s(\mathbf{r}) \equiv \left[\frac{\partial\rho}{\partial\mu}\right]_{v(\mathbf{r})} = \left[\frac{\partial\rho(\mathbf{r})}{\partial N}\right]_{v(\mathbf{r})}\left[\frac{\partial N}{\partial\mu}\right]_{v(\mathbf{r})} = f(\mathbf{r})\,S \qquad (6)$$

Note that Eq (6) shows that the global softness S is distributed following the Fukui function f(r). The set of global indexes $\{\mu, \eta, \mathbf{S}\}$ and the local ones $\{\rho(r), f(r), s(r)\}$form a convenient representation for the discussion of the reactivity and selectivity concepts in Chemistry. Site activation on the other hand, may be described within a non local formalism [30-32], in terms of the first and second order static response functions $\chi(r,r')$ and $f(r,r')$, respectively. A non local DFT quantity is normally defined as the derivative of a local property at point r, with respect to another one at r' in space. For instance, the first order static density response function is defined by [33,25]:

$$\chi(\mathbf{r},\mathbf{r}') = \left[\frac{\partial\rho(\mathbf{r})}{\partial v(\mathbf{r}')}\right]_N \qquad (7)$$

for a fixed number of electrons. Note that the quantity $\chi(r,r')$ describes the changes in the electron density at point r, when the system is perturbed by a localized change in the external potential at a different point r'. This means that conformational changes, preferential solvation, and substituent effects at specific region of the molecule may induce local responses at a different site, thereby activating or deactivating that site at r towards a specific reaction. Site activation/deactivation may alternatively be described on a simpler frame. Consider for instance a first variation in s(r) defined in Eq (6). There we have [34]:

$$ds(\mathbf{r}) = f(\mathbf{r})\,dS + S\,df(\mathbf{r}) \qquad (8)$$

Eq (8) shows that a localized change in softness will be described by a global activation/deactivation contribution given by the first term, and a local activation/deactivation contribution given by the second one. This scheme has been used to rationalize the empirical Markovnikov regioselectivity rule [34].

The availability of global and local reactivity indexes opens the possibility of constructing theoretical reactivity scales that are to be validated against experimental

scales. Relevant examples are the kinetic scales of electrophilicity and nucleophilicity, which are recorded from rate coefficients involving electron donors and electron acceptors [35-40]. From a theoretical point of view, the electrophilic power of molecules has been cast into the form of a reactivity index w by Parr et al [41]. It is expressed in terms of the electronic chemical potential and the chemical hardness as :

$$\omega = \frac{\mu^2}{2\eta} \qquad (9)$$

Eq (9) indicates that a good electrophile will be characterized by a high electronegativity ($\chi = -\mu$), and a low value of chemical hardness. Note that the chemical hardness acts as a resistance to the exchange of electronic charge with the environment. The w index has been used to construct absolute scales of electrophilicity for a significant number of organic reagents participating in a wide variety of chemical processes [42-44]. The electrophilicity index has been found to be almost insensitive to solvation in neutral electron acceptors [45], so that gas phase calculations suffice to set up an electrophilicity hierarchy for atoms and molecules. It is also possible to generalize the electrophilicity index to define its local counterpart. This may be easily done by using the inverse relationship $1/\eta = S$ and the sum rule for the local softness, namely, $\mathbf{S} = \int \mathbf{dr\ s(r)}$. There results [42-44,46]:

$$\omega(\mathbf{r}) = \frac{\mu^2}{2} s(\mathbf{r}) = f(\mathbf{r})\omega \qquad (10)$$

Note that the most electrophilic site in the electron acceptor coincides with the softest site in the molecule, and that the more electrophilic site is the one corresponding to the highest value of the electrophilic Fukui function, i.e. the active site of the electrophile. The working formalism however, uses regional integrations so that the local quantities are usually described as condensed to atoms or group of atoms in the molecule. This scheme is easily implemented by condensing the Fukui function, within a single point calculation scheme as described elsewhere [47,48].

3. Applications

3.1 Cycloadditions. Diels-Alder Reactions.

Diels-Alder (DA) reactions are the largest family of cycloaddition processes [49,50]. In a DA reaction one p component, named the dienophile, adds to a 1,3-diene system to afford a six-membered ring product. By varying the nature of the diene and dienophile many different types of carbocyclic structures can be built up. However, not all possibilities take place easily. The most simple cycloaddition reaction is the DA reaction between butadiene and ethylene. This reaction must be forced to take place: after 17 hours at 165º C and 900 atmospheres, it does give a yield of 78% [51]. The presence of electron-releasing substituents in the diene and electron-withdrawing in the dienophile or vice versa can drastically accelerate the process.

In general, the DA reaction requires opposite electronic features in the substituents at the diene and the dienophile for being reasonably fast. Recent studies point out that this type of substitution on diene and dienophile favors the charge transfer along with an asynchronous mechanism [52]. Furthermore, the reaction mechanism changes progressively from a concerted, asynchronous to a polar stepwise pathway with increasing ability of the dienophile to stabilize a negative charge. At this point the 1,3-diene and the ene systems clearly behave as an nucleophile/electrophile pair.

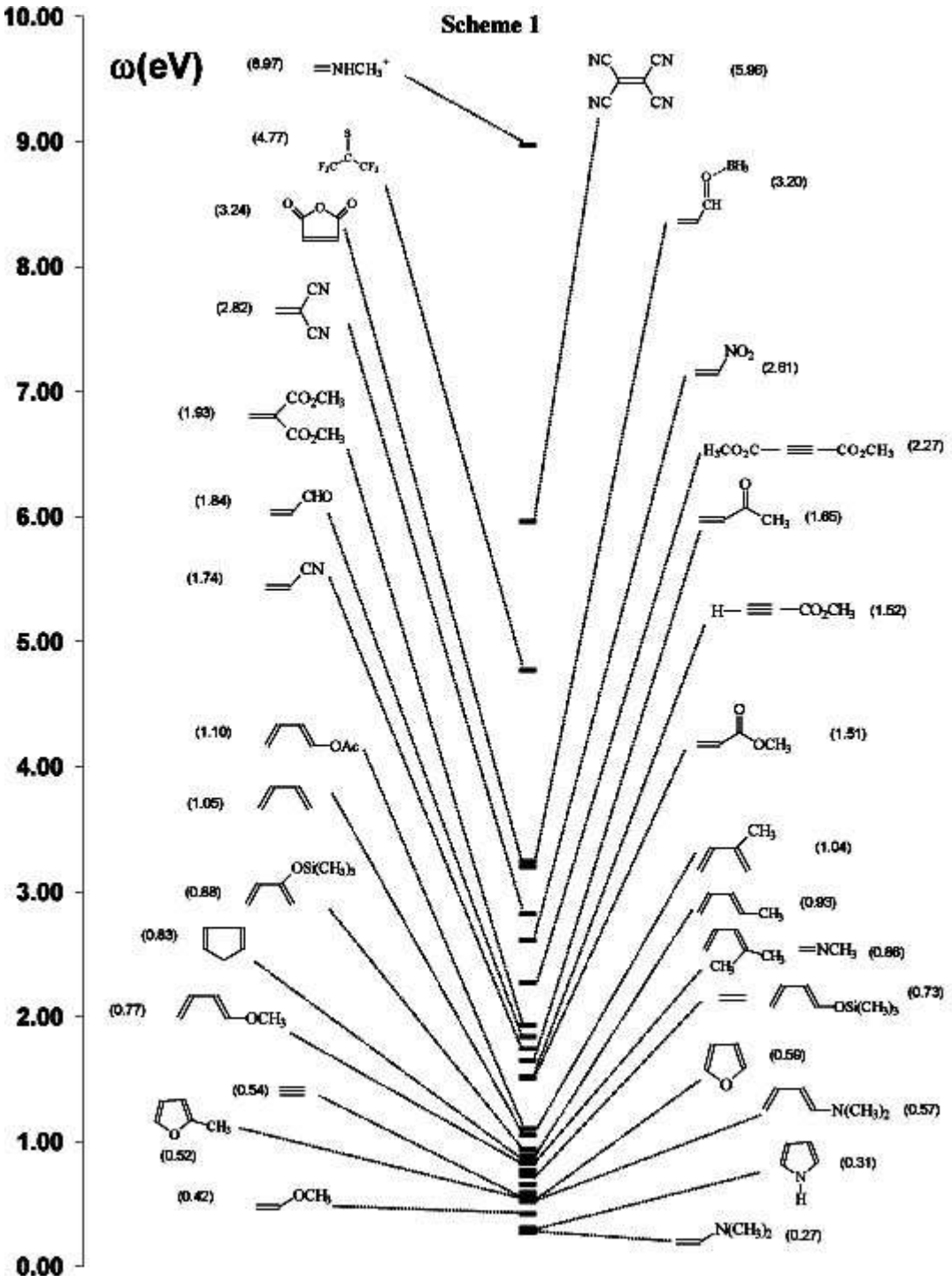
On the other hand, regioselectivity has been described in terms of a local hard and soft acids and bases (HSAB) principle, and some empirical rules have been proposed to rationalize the experimental regioselectivity pattern observed in some DA reactions [50c,53]. The local electrophilicity/nucleophilicity character of reagents may also be of significant utility to predict the regioselectivity patterns that can be expected for a given reaction, and to quantitatively assess the effects of electron-releasing and electron-withdrawing substituents in the electrophile/nucleophile interacting pair. This local electrophilic character may be seen as an extension of the global electrophilicity index, recently proposed by Parr et al. [41] to deal with the local or regional counterpart of this property.

The global electrophilicity power for a series of the most common dienes and dienophiles systems quoted in Scheme 1 was evaluated using Eq (9). The electronic chemical potential m , and chemical hardness h were evaluated in terms of the one electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO through $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $h \gg (e_L - e_H)$ respectively, at the ground state (GS) of the molecules using the B3LYP/6-31G(d) level of theory implemented in the GAUSSIAN98 package of programs [54].

In the absence of an accurate definition of nucleophilicity, we will assume that high nucleophilicity and high electrophilicity are opposite ends of a simple scale. Therefore, a molecule presenting a low electrophilicity power may be considered as a nucleophile, yet the inverse relationship between global electrophilicity and nucleophilicity has not been well-established [41]. Note that within our series of DA reagents one the most strong electrophiles is N-methylmethyleneammonium cation (ω = 8.97 eV). Moderate electrophilicity power is presented, for instance by 1-acetoxy-1,3-butadiene (ω= 1.10 eV) and cyclopentadiene (ω= 0.83 eV). Finally, dimethylvinylamine (ω= 0.27 eV) presents a marginal electrophilicity power, so that may be classified as nucleophile. Most of the structural and electronic features induced by chemical substitution are often reflected as responses in the global reactivity indexes [32]. In this sense, substituted ethylenes (dienophile) with electron withdrawing groups increase their electrophilic character. Compare for instance the electrophilicity index of ethylene (ω= 0.73 eV) and nitroethylene (ω= 2.61 eV). In a normal-electron-demand (NED) DA reaction, the ethylene component (dienophile) usually bears one or more electron-withdrawing groups that enhance both the reaction rate and the yield of the kinetic control product [51]. For instance, the reaction of 1,3-butadiene (ω= 1.05 eV) with acrolein (ω= 1.84 eV) takes place within half an hour in quantitative yield, compared to the 78% yield obtained in the ethylene/1,3-butadiene reaction under more extreme external conditions [49,50c].

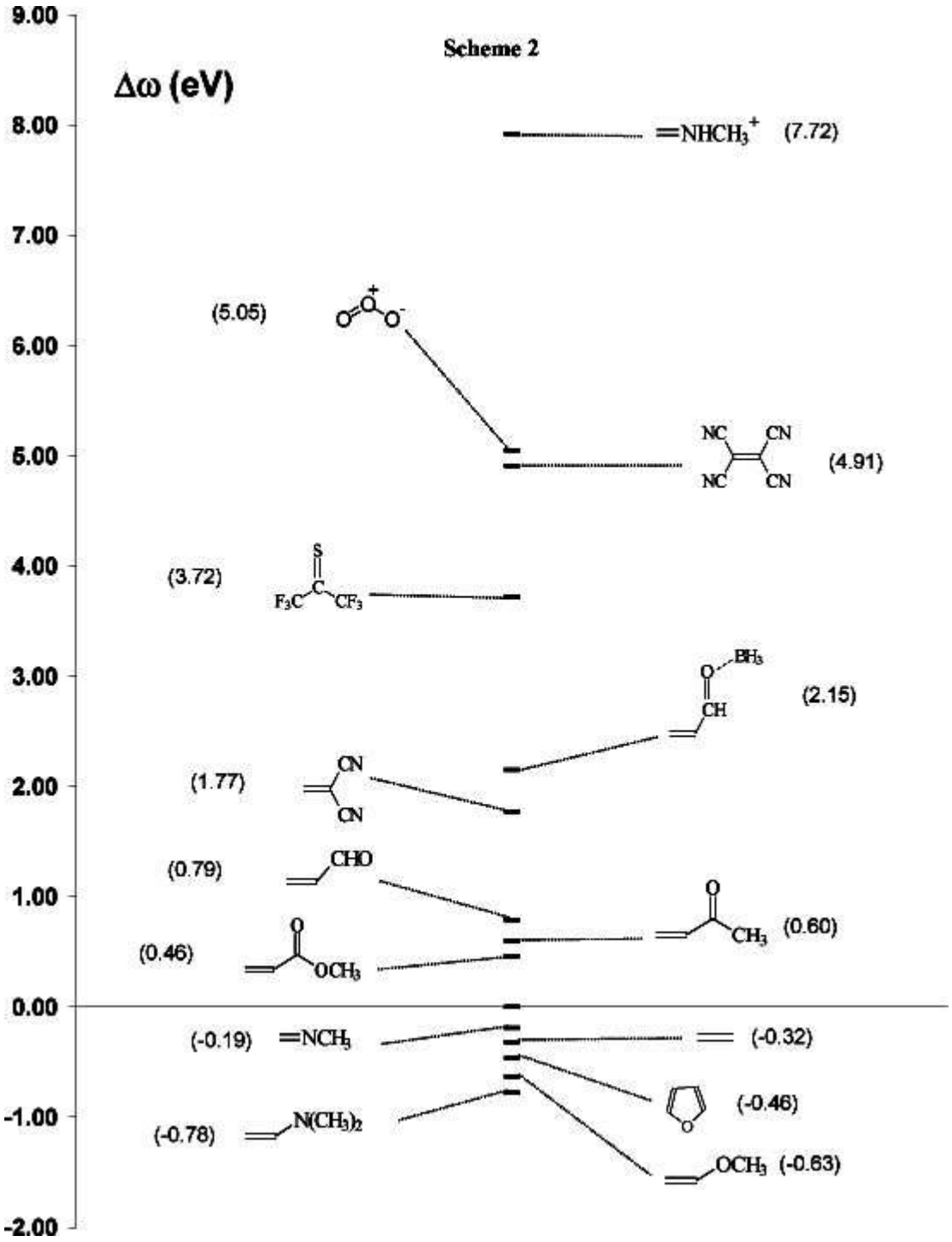
According to the electrophilicity scale of Scheme 1, nitroethylene is an electrophile which may be also regarded as heterodiene (in a NED-DA reaction, the diene is usually

the nucleophile), but in reaction with methyl vinyl ether or dimethylvinylamine it will act as nucleophile in inverse-electron demand (IED) process [55]. On the other hand, it is well know that the presence of Lewis Acids (LA) as catalysts increases both rate and regioselectivity. As a consequence, most of the LA catalyzed DA reactions take place at lower temperature that the uncatalyzed process. The effect of the LA catalyst on the DA reactions can be explained by an increase of the electrophilicity of the electron-poor DA component, which acts as the dienophile on a NED-DA reaction and as the diene in an IED-DA reaction. Compare w values of acrolein and acrolein-BH_3. It may be seen an enhance in the electrophilicity power in 1.54 eV relative to acrolein, in agreement with the more polar character of the LA catalyzed cycloaddition. The enhance in electrophilicity entails an increase of the ionicity of the process, which is usually accompanied by a decrease of the activation energy for the cycloaddition.



The difference in electrophilicity power of the dienophile/diene pair ($\Delta\,\omega$) has been shown to be an useful tool to describe the electronic pattern expected for the transition state structures involved in DA reactions, describing non polar ($\Delta\,\omega$small) or polar ($\Delta\,\omega$big) mechanisms [42]. Scheme 2 shows this behavior to selected dienophiles in reaction with 1,3-butadiene (ω= 1.05 eV) as reference. It is interesting to note that the DA reaction showing a$\Delta\,\omega > 0$ is characterized as a NED reaction i.e. diene is the

nucleophile and the dienophile is the electrophile. On the other hand, in a IED-DA reaction the difference in electrophilicity between diene/dienophile pair is negative, $\Delta\omega < 0$. In summary, the difference in the global electrophilicity of the diene/dienophile interacting pair gives information about the reaction polar pattern, being a useful quantity to classify the electrophilicity power of a series of dienes and dienophiles within a unique relative scale [42]. Thus, small electrophilicity differences can be related with non-polar (pericyclic process) mechanisms, while big electrophilicity differences can be related with polar (ionic process) mechanisms [35,36,56].



Using an extension of the global electrophilicity index it is possible to predict local (regional) electrophilicity at the active sites of the reagents involved in Diels-Alder processes on quantitative basis [46,47]. The model uses Eq (10), where f(r) corresponds to the electrophilic Fukui function f_k^+. The interaction between unsymmetrical dienes and dienophiles can give two isomeric adducts, depending upon the relative position of the substituent in the cycloadduct, head-to-head or head-to-tail (see Scheme 3a and 3b). The selectivity for the formation of one adducts over the

other is known as regioselectivity, and these isomers are called regioisomers. In this class of cycloadditions the degree of regioselectivity is often high, yet it is rather well established that the more powerful the electron-releasing (D) and electron-withdrawing (A) substituents on the diene/dienophile pair, the more regioselective is the reaction [50c]. Local parameters of reactivity are shown in Table 1. It may be seen that the whole series of dienophiles substituted with electron-withdrawing groups show local electrophilicity values in C2 greater than in C1 (see last column of Table 1), as a result of the higher values in the electrophilic Fukui function in C2, and corresponding global electrophilicity (see Eq (10)). Compound 8 may be classified as marginal electrophile [42].

Scheme 3.

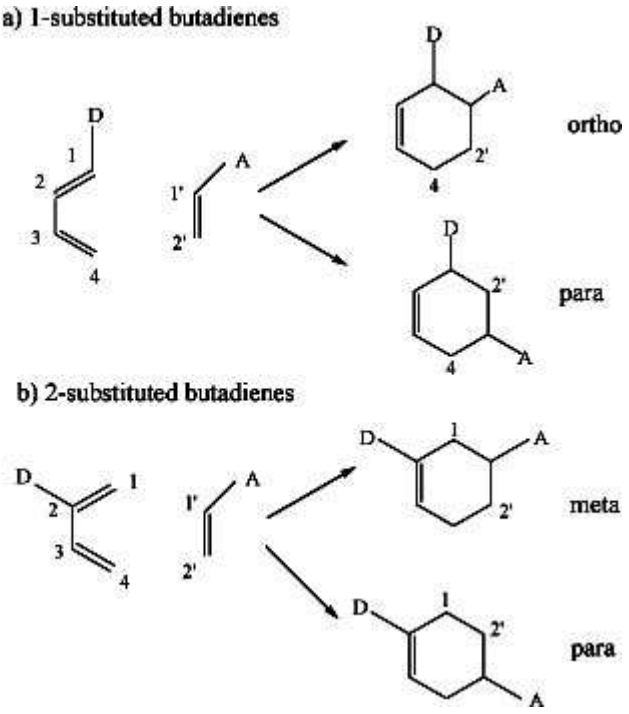
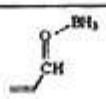
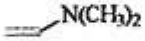
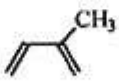
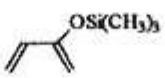
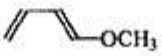
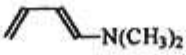
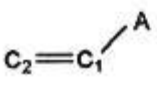
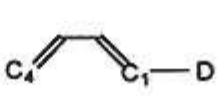
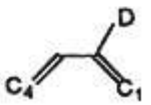


Table 1. Global an local properties of selected dienes an dienophiles used in DA reactions.

	a) Dienophiles		ω (eV)	Site (k)	f_k^-	f_k^+	ω_k (eV)
1	Acrolein-BH_3		3.20	C1	0.014	0.079	0.253
				C2	0.056	0.357	1.144
2	1,1-dicyanoethylene		2.82	C1	0.198	0.209	0.589
				C2	0.336	0.499	1.407
3	Nitroethylene		2.61	C1	0.010	0.077	0.200
				C2	0.006	0.279	0.726
4	Acrolein		1.84	C1	0.096	0.137	0.253
				C2	0.011	0.372	0.685
5	Acrylonitrile		1.74	C1	0.268	0.265	0.461
				C2	0.367	0.469	0.816
6	Ethylene		0.73	C1	0.500	0.500	0.365
				C2	0.500	0.500	0.365
7	Acetylene		0.54	C1	0.500	0.500	0.268
				C2	0.500	0.500	0.268
8	Dimethylvinylamine		0.27	C1	0.049	0.442	0.119
				C2	0.411	0.399	0.108
	b) Dienes						
9	1,3 butadiene		1.05	C1	0.338	0.332	0.355
				C4	0.338	0.332	0.355
10	2-methyl-1,3-butadiene		1.04	C1	0.380	0.304	0.316
				C4	0.289	0.341	0.354
11	2-trimethylsilyloxy-1,3-butadiene		0.88	C1	0.465	0.274	0.240
				C4	0.212	0.359	0.315
12	1-metoxy-1,3-butadiene		0.77	C1	0.217	0.312	0.240
				C4	0.290	0.326	0.251
13	N,N-dimethyl-1,3-butadiene-1-amine		0.57	C1	0.117	0.293	0.162
				C4	0.230	0.304	0.173







For instance, the interaction between acrolein (ω = 1.84 eV) and 1-methoxy-1,3-butadiene (w = 0.77 eV), shows an electrophilicity difference $\Delta\omega$ = 1.07 eV, indicating a polar pattern in according to our classification. This interaction corresponds

to a DA reaction of normal-electron-demand (NED) in which an electron-poor dienophile, the electrophile, reacts with a electron-rich diene, the nucleophile. The electrophilic site in acrolein is the C2 carbon, with a local electrophilicity value w_k = 0.685 eV (see Table 1). The highest value of ω_k in 1-methoxy-1,3-butadiene is located at the carbon atom C4. Therefore, the most interaction will take place between the C2 center of acrolein and the C4 center of 1-methoxy-1,3-butadiene leading to the formation of the ortho adduct (see Scheme 4a). The addition of 1-methoxy-1,3-butadiene to acrolein is experimentally known to preferentially afford the ortho regioisomer (80% yield, at 100ºC after 2 hours) [50c].

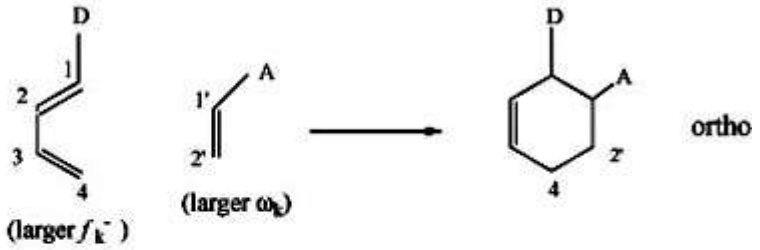
Ethylene (compound 6 in Table 1) presents a local electrophilicity value ω_k = 0.365 eV at the equivalent carbon atoms C1 and C2. Note that acetylene even having equivalent Fukui functions and , presents a lower local electrophilicity pattern as compared to that of ethylene (ω_k = 0.268 eV, at the equivalent carbon centers of acetylene). This result mainly comes from their difference in global electrophilicity due to the fact that ethylene is predicted to be softer than acetylene [42].

Another interesting result follows from the comparison of site reactivity of acrolein and the acrolein-BH3 complex, representing the Lewis acid catalyzed processes (structures 4 and 1 in Table 1, respectively). On the basis of the Fukui function alone, the C2 carbon in acrolein is predicted to be slightly more electrophilic than in the Lewis acid coordinated species, in contrast with the significant enhancement in the rate constant experimentally observed for the Lewis catalyzed process (= 0.372 and 0.357 for 4 and 1, respectively). However, on the basis of the local electrophilicity index ω_k, the C2 carbon in acrolein-BH3 complex (ω_k = 1.144 eV) is approximately twice more electrophilic than the corresponding site in acrolein (ω_k = 0.685 eV).

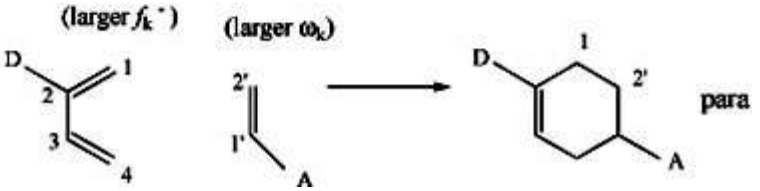
It is also interesting to examine the effect that the electron-releasing groups may have on the local electrophilicity pattern in ethylene. These systems have some importance in the inverse-electron-demand (IED) processes. Consider for instance the compound 8 in Table 1. On the basis of the Fukui function alone dimethylvinylamine displays nucleophilic activation at the C2 . Note that on the basis of the w index, this compound is predicted as marginally electrophilic, due to the low value in global electrophilicity. This compound is therefore predicted to react with electron-poor dienes, as for instance nitroethylene (ω= 2.61 eV), to afford the ortho regioisomer in an IED-DA reaction, acting as heterodiene [47] (see Scheme 4a). The interaction of with the electron-rich 2-substituted 1,3-butadienes such as compounds 10 and 11 on the other hand, would lead to the formation of the para regioisomer [50c] (see Scheme 4b). It is interesting to remark that although nitroethylene can act as dienophile or diene in DA reactions, it normally behaves as a strong electrophile, the C2 site being the most electrophilic position.

Scheme 4.

a) 1-substituted butadienes



b) 2-substituted butadienes



3.2 Electrocyclic processes.

The reaction mechanisms of the concerted stereospecific reactions are conveniently described through the well-known Woodward-Hoffmann rule, based on the conservation of the orbital symmetry [57]. In electrocyclic reactions, the reason for the observed stereospecificity is that the groups linked to the breaking bond all rotate in the same sense during the ring opening process. The motion, in which either all rotate clockwise or counter clockwise is called the conrotatory mode. If these groups rotate in the opposite direction during the ring formation process, the mode is called disrotatory.

One of the simplest electrocyclic concerted reactions explained by these rules is the thermolysis of cyclobutene to cis butadiene. From the MHP, we expect that the hardness value of the conrotatory transition state (TS) will be lower than both the hardness values of the cyclobutene and cis butadiene ground states. Furthermore, the disrotatory TS will have smaller hardness value in comparison to the hardness value of the corresponding conrotatory TS associated with the thermal isomerization of cyclobutene. In general, when the corresponding quantities of two possible TS´s are compared, the TS associated with a symmetry-allowed path is expected to display lower energy and larger hardness, whereas the TS associated with the symmetry forbidden pathway is expected to display higher energy and smaller hardness. In other words, we propose based on the MHP, that hardness is correlated with forbiddingness [58]. This hypothesis was tested for the thermolysis of cyclobutene to cis butadiene at the HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels of theory. The results of the calculations are shown in Table 2. The first striking feature revealed by this study, is that the planar C_{2v} structure is not a true minimum in the potential energy surface (PES). Note that this result is consistently found at both levels of theory used. Note also that the harmonic vibrational analysis of the disrotatory TS evaluated at the geometry reported by Breulet and Schaefer [59] reveals the presence of two imaginary frequencies, within the [1000i —1200i] range, the other at higher energy around 210i

cm^{-1} [58]. The MHP analysis consistently fails, as a consequence of the fact that the planar C_{2v} structure of cis butadiene is not a true minimum on the PES, leading to relative hardness values at the GS´s that contradicts the MHP: while cis butadiene is correctly predicted as more stable that cyclobutene, the hardness of butadiene is lower than the hardness value of cyclobutene. This result reveals the usefulness of the empirical MHP rule as an additional criterion to analyze the consistency between structure and stability. This textbook example illustrate well the fact that on the basis of a single energy criterion, the wrong C_{2v} structure would have been accepted, as it was in the major part of the Organic Chemistry textbooks. Theoretically obtained geometrical parameters for this molecule could not be compared with the corresponding experimental values, mainly because at that time (1999), there was no characterization of it, yet some indirect experimental evidence pointed out that this molecule was not planar [60]. In order to eliminate the imaginary frequency present in the spurious C_{2v} ground state of cis butadiene, we further explored the PES at both levels of theory. A lower symmetry structure (C2) resulted to be the true minimum with no imaginary frequencies. It is characterized by a non-planar arrangement with the terminal methylene groups c.a. 32º - 40º out of the molecular plane [58]. This GS structure is characterized by a hardness value 6.28 eV (HF/6-311G(d,p)) and 2.83 eV (B3LYP/6-311G(d,p)) respectively, in agreement this time with the MHP rule.

Table 2. Total energy (a.u.), number of imaginary frequencies (NIMAG), in i cm^{-1}, and hardness values (in eV) of the stationary points for the isomerization reaction of cyclobutene. HF/6-311G(d,p) (first entry) and B3LYP/6-311G(d,p) (second entry) calculations.

Species, Point Group	NIMAG	-Energy	η	Frequency	
Cyclobutene, C_{2v}	0	154.9308	6.91	0	
	0	156.0113	3.61	0	
Cis-butadiene, C_{2v}	1	154.9516	5.70	160.2	i
	1	156.0313	2.57	255.7 i	
Conrotatory, C_2, TS	1	154.8523	5.43	922.7	i
	1	155.9532	2.42	780.2 i	
Disrotatory, C_s, TS	2	154.7564	3.27	1174.8	i
				208.7	i
	2	155.8828	0.91	1037.5	i
				212.5 i	

3.3 Electrophilic additions to asymmetric alkenes.

The regioselectivity of the electrophilic additions to alkenes depends on the substituent that the center C1 and C2 may bear. The selectivity in these processes has been proposed to follow the well-known empirical Markovnikov rule [61]. The original statement of this rule is as follows: the addition of an acidic proton to a double bond of an alkene yields a product where the proton is bound to the carbon atom bearing the largest number of hydrogen atoms. This rule proved to be more general, as it was

applied to electrophiles other that H^+[61]. In fact, the generalized version of it states that: in an addition reaction to alkenes, the electrophile adds in a form that leads to the formation of the most stable carbocation. Stated in either of the two forms, this empirical rule is essentially a selectivity rule, or as such, it is amenable to quantitative representation in terms of local descriptors of reactivity. Furthermore it may be conveniently described within the site activation model condensed in Eq (8). Site activation involves the transition state structure for the addition of the electrophile to the alkene, which is the rate-determining step in these processes [61]. Finite variations in the regional or condensed to atom softness with reference to the TS structure may be simply approached as the difference $\Delta f_k = f_k^{\neq} - f_k^0$ and $\Delta S = S^{\neq} - S^0$; with the local softness at site k at the transition state (TS) and ground state structures, respectively. Site activation ($\Delta s_k > 0$) or site deactivation ($\Delta s_k < 0$) may be further cast into a partitioned form by adding and subtracting the quantity $S^0 f_k^{\neq}$ to the expression, $\Delta s_k = s_k^{\neq} - s_k^0$ There results:

$$\Delta s_k = S^0 \Delta f_k + f_k^{\neq} \Delta S \qquad (11)$$

with

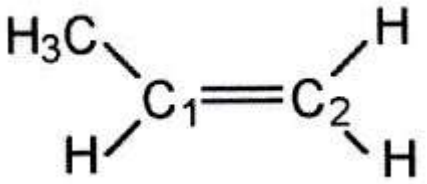
$$\Delta f_k = f_k^{\neq} - f_k^0 \text{ and } \Delta S = S^{\neq} - S^0 \qquad (12)$$

While the first term of Eq (11) assesses the local activation at the site, described by the contribution Δf_k, the second one takes into account the global activation of the whole system from the ground to the transition states. We will illustrate the model here by studying the addition of HCl to 2-propene [34]. Following the prescription described above, we first optimized the ground state of 2-propene at the B3LYP/6-311G(d,p) level of theory. We then localized two transition state structures at the same level of theory, one corresponding to the Markovnikov (M) channel, the other corresponding to the anti-Markovnikov (AM) channel. The resulting TS structures are characterized by a unique imaginary frequency of 1127 i and 1315 i cm^{-1}, respectively. The reactive modes are in both cases characterized by a C-H stretching concertedly occurring with a bending of the =CH2 moiety describing a sp^2 to sp^3 change of hybridization. The hardness of the TS of the M channel is less than the one corresponding to the AM channel, yet the activation energy is lower for the M process. This is an intriguing result, as it apparently contradicts the MHP rule. However, the fact that the preferred Markovnikov pathway is softer than the AM one seems to match better chemical intuition (the softest TS is expected to be the more reactive one).

With the ground state and transition state structures already at hand, we proceeded with the calculation of global and local reactivity indexes needed to perform the regioselectivity analysis using Eqs (11) and (12). The results of the calculations are displayed in Tables 3a and 3b. We first note in Table 3a that both TS(M) and TS(AM) have softness values higher than the ground state GS1 of 2-propene, as expected from the MHP rule. The local analysis reveals that the Markovnikov carbon atom (C1) shows

the highest value in regional Fukui function for an electrophilic attack by a proton. Note that at C1 is predicted to be higher than the corresponding anti-Markovnikov carbon center (C2), and greater than the corresponding f^{-} for nucleophilic attack at both the M and AM centers. These results may suggest that the addition of HCl takes place via an electrophilic attack at the Markovnikov center by a proton, prior to the nucleophilic attack of Cl^{-} to the most stable carbocation.

Table 3a. Local reactivity description for the electrophilic and nucleophilic addition to the Markovnikov (C1) and anti-Markovnikov (C2) sites in the reaction between HCl and 2-propene (GS1).



Structure	S	Site (k)	f_k^-	f_k^+
GS1	7.291	C1	0.499	0.471
		C2	0.399	0.460
TS (M)	16.978	C1	0.109	0.064
		C2	0.021	0.641
TS (AM)	15.102	C1	0.026	0.638
		C2	0.137	0.085

Table 3b. Global and local contributions to the electrophilic activation (deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) sites of the carbocations formed in the protonation of 2-propene.

Structure	Site (*k*)	Δs_k	$f_k^{\neq} \Delta S$	$S^o \Delta f_k$
TS (M)	C1	-2.347	0.620	-2.967
	C2	7.529	6.209	1.320
TS (AM)	C1	6.201	4.983	1.218

C2	-2.070	0.664	-2.734

The nucleophilic attack by Cl^- at the nucleophilic center is assumed to take place on the unprotonated carbon atom. From a static reactivity picture, the Fukui function, , at the GS1□s shows comparable values at the M and nucleophilic centers in propene. However, this ambiguity vanishes when the local reactivity analysis for the nucleophilic attack of Cl^- is performed at the TS structure, where the Markovnikov site is already bound to the proton. In other words, the interaction of the proton and the Markovnikov site is expected to activate the AM site towards the nucleophilic attack by the Cl^- species. Site nucleophilic activation may be evaluated at the Markovnikov TS channel using the model condensed in Eqs (11) and (12). The results are summarized in Table 3b. It can be observed that the interaction of the H^+ electrophile at the Markovnikov center significantly enhances the nucleophilic activity at the unprotonated carbon, as described by the variation in local softness at that site. For the Markovnikov carbocation, activation at the unprotonated center is dominated by the variation in global softness, while the change in the Fukui function represents the main contribution to the deactivation of the protonated site. The nucleophilic site activation at the unprotonated carbon is consistently predicted to be more significant than that associated to the protonated M site, which is in agreement with the observed reactivity pattern. It is also interesting to notice that upon the interaction with a proton at the transition state, the electrophilic site becomes systematically deactivated for both, the Markovnikov and anti Markovnikov channels.

3. 4. Gas phase protonation of amines: critical cases where the FMO fails.

Amines behave as nucleophile species due to the non-bonding lone pair electrons on the nitrogen atom. This electron pair may form an additional bond with an electrophile in addition reactions. The simplest process of this type is protonation. In gas phase, the basicity may be roughly described by the proton affinity (PA) which corresponds to the enthalpy change for the deprotonation reaction : $BH^+ \rightarrow B + H^+$ [61]. This quantity may be regarded as an intrinsic basicity, where solvent effects are not present. Intrinsic basicity has been normally rationalized in terms of inductive and resonance effects. For instance, electron releasing substituents at the—NR_2 group normally enhances the nucleophilicity of amines towards the electrophilic addition of a proton. On the other hand, resonance effects in aromatic amines cause the system to become less basic, due to the extra delocalization effects by resonance of the lone pair electrons of nitrogen.

The basicity of amines has been a challenge for the DFT descriptors of reactivity. For instance, the basicity of aliphatic amines has been studied by looking at the nucleophilic Fukui function $f^-_{\mathbf{N}}$ at the Nitrogen center [18,47,62]. The relationship found indicates that the highest PA was related to the lowest Fukui function at the N site. Moreover, the basicity of aromatic amines does not show any correlation with the nucleophilic Fukui function at the nitrogen atom evaluated at the frontier molecular orbital HOMO. Table 4 shows the experimental and theoretical PA values evaluated at the HF/6-31G(d) level of theory. The ratio PA_{theor}/PA_{exp} reveals that the intrinsic basicity pattern of these systems may be reliably described at this level of theory. In order to check whether or not the nucleophilic Fukui function at the nitrogen site, evaluated at the HOMO state may assess the intrinsic basicity pattern in these systems, we performed the calculation of the nucleophilic Fukui function $f^-_{\mathbf{N}}$, at the

same level of theory. The results are displayed in Table 4, fifth entry. It may be seen that only for Glycine and Alanine the nucleophilic Fukui function at nitrogen evaluated at the HOMO level shows a high value. For the remaining members of the series, all of them presenting a phenyl substituent, the Fukui function evaluated at the HOMO level markedly fails in predicting the basic site for protonation. Note that for Phenyl-alanine, Tyrosine, 2-Phenyl-ethylamine and Benzyl-amine, the Fukui function at nitrogen exactly vanishes, thereby indicating that the frontier molecular orbital presumably involved in the electrophilic addition of a proton has not contributions from the expected nucleophilic nitrogen site. This result prompted us to look at the more internal occupied MO that contains relevant contributions from the nitrogen site. We found that the HOMO-2, which corresponds to the MO localized essentially at the Nitrogen lone pair of electrons qualified for this criterion and we proceeded to evaluate the nucleophilic Fukui function $f_{\mathbf{N}}$ with the information encompassed in this molecular orbital. The results are also displayed in Table 4. Note that the basicity of aromatic amines is consistently accounted for by the nucleophilic Fukui function measured at the HOMO-2 for the same systems for which the same calculation performed at the HOMO level fails. Also the relative stabilization of the corresponding eigenvalue $E_{MO}(N:)$ decreases with increasing proton affinity (see Table 4). A possible explanation for this result may be traced to the fact that being in general the s molecular orbitals, as it is the case of the $-NR_2$ functionality, more stable than those having a π -symmetry involved in multiple bonds, as it is the case of the phenyl substituent, it is then expected that the highest occupied MO in these systems will have a more π character. Therefore, for those cases were the active site has σ -symmetry, one has to look at the more internal MO□s close to the frontier MO level involved in the reaction. Note in concluding that the Mulliken net charges at the Nitrogen site do not show any correlation with the intrinsic basicity, thereby indicating that the protonation process viewed as a charge controlled process can not either be explained by frontier molecular orbital theory arguments.

Table 4. Experimental proton affinities (PA, in kcal/mol), theoretical/experimental PA ratio; nucleophilic Fukui function at the HOMO and HOMO-2 levels , eigenvalue of the molecular orbital with highest N: component (in a.u.) and Mulliken net charges at nitrogen. Theoretical PA from HF/6-31G(d) calculations.

Species	Exp PA	PA Ratio	(HOMO)	$E_{MO}(N:)$[a)]	(HOMO-2)	Q_N
Glycine	212.1	1.05	0.73	-0.4053	0.00	-0.816
Alanine	215.7	1.05	0.71	-0.4025	0.00	-0.836
Phenyl-alanine	220.8	1.05	0.00	-0.4024	0.71	-0.825
Tyrosine	221.6	1.05	0.00	-0.4020	0.71	-0.826
Aniline	211.1	1.04	0.28	-0.4429	0.19	-0.889
Benzyl-amine	218.5	1.07	0.01	-0.3908	0.77	-0.846
2-phenyl-ethylamine	224.0	1.04	0.00	-0.3858	0.76	-0.847
N,N-dimethylaniline	225.1	1.06	0.21	-0.4025	0.39	-0.609

3,N,N-trimethylaniline	225.4	1.07	0.23	-0.3970	0.36	-0.671
2,N,N-trimethylaniline	227.7	1.06	0.08	-0.3594	0.56	-0.615

[a] $E_{MO}(N:)$ is the eigenvalue of the molecular orbital essentially localized at the Nitrogen lone pair of electrons

4. Concluding Remarks.

The usefulness of the global and local response functions defined within the context of density functional theory has been illustrated for a set of classical chemical reactions of Organic Chemistry. For instance, cycloadditions, usually classified as pericyclic processes, has been shown to display some polar character depending on the nature of electron releasing and electron withdrawing groups that the diene/dienophile pair may bear. The reaction mechanism changes from concerted (pericyclic reaction) to stepwise (polar process), and the electrophilicity difference between the diene/dienophile pair assesses well this feature. Normal or inverse electron demand process, as well as the effect of Lewis acids catalyst may be conveniently described within this model. Site activation effects become essential to discriminate between the DA and 1,3-DC mechanisms. Site activation is also an essential ingredient to explain the regioselectivity Markovnikov rule, based on the variation of local softness and electrophilicity indexes. The global response functions, like chemical hardness and polarizability seems to conveniently complement the symmetry based Woodward-Hoffmann rules of forbiddingness for electrocyclic processes. Finally, some examples where the FMO theory apparently fails have been examined. The generalization of the FMO theory of chemical reactivity seems to require the incorporation of additional information provided by the internal MO□s that are close in energy to the frontier molecular levels.

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