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Review Article

Philicity and Fugality Scales for Organic Reactions

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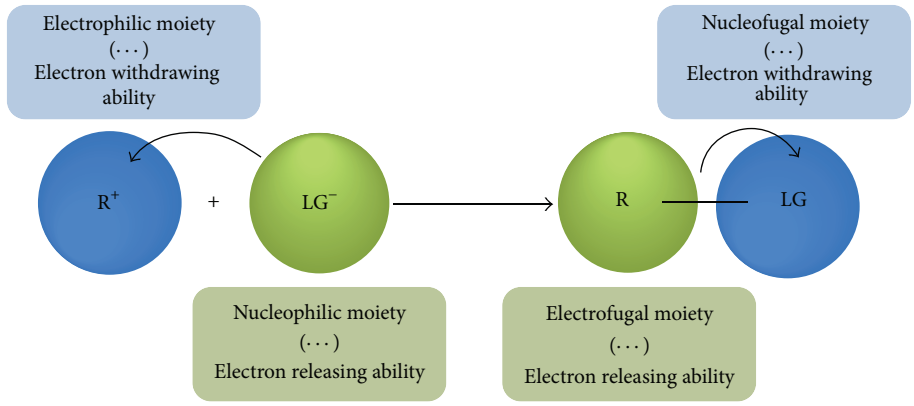
Theoretical scales of reactivity and selectivity are important tools to explain and to predict reactivity patterns, including reaction mechanisms. The main achievement of these efforts has been the incorporation of such concepts in advanced texts of organic chemistry. In this way, the modern organic chemistry language has become more quantitative, making the classification of organic reactions an easier task. The reactivity scales are also useful to set up a number of empirical rules that help in rationalizing and in some cases anticipating the possible reaction mechanisms that can be operative in a given organic reaction. In this review, we intend to give a brief but complete account on this matter, introducing the conceptual basis that leads to the definition of reactivity indices amenable to build up quantitative models of reactivity in organic reactions. The emphasis is put on two basic concepts describing electron-rich and electron-deficient systems, namely, nucleophile and electrophiles. We then show that the regional nucleophilicity and electrophilicity become the natural descriptors of electrofugality and nucleofugality, respectively. In this way, we obtain a closed body of concepts that suffices to describe electron releasing and electron accepting molecules together with the description of permanent and leaving groups in addition, nucleophilic substitution and elimination reactions.

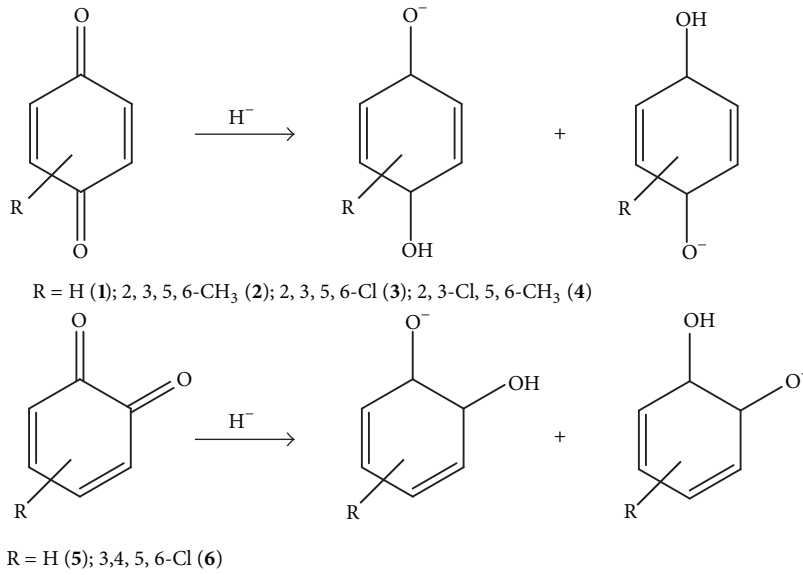
1. Introduction

The development of reactivity indices to describe organic reactivity has been an active area of research from the dawn of theoretical physical organic chemistry [1–4]. From the earlier semiempirical models proposed in Hückel molecular orbital (HMO) theory, reactivity was described with the aid of static first order reactivity descriptors like atomic charges, free valence index, and bond orders [5, 6]. These reactivity indices were formerly developed around the ground state of reactants. The next generation of reactivity indices began with the elegant theory proposed by Coulson and Longuet-Higgins, in a series of papers describing the response functions, including second order quantities like atomic and bond polarizabilities [7–9]. It is worth emphasizing that, at that time, HMO and Coulson-Longuet-Higgins theories were conceived not as methods to approximately solve the Schröedinger equation but as models of chemical bond. The third generation of reactivity indices started after the pioneering work of Gilles Klopman, who introduced the concept of charge and frontier controlled reactions, including solvation effects [4]. Nowadays, the treatment of chemical reactivity is mostly performed using the frame of the conceptual density functional theory developed by Parr et al. [10–14], Pearson [15–18] and Pearson and Songstad [19], and other authors [20–22]. This reactivity model converted classical chemical concepts like electronegativity, hardness, and softness into numbers. In this way, atoms, molecules, and charged system were classified into quantitative scales of reactivity. This historical description does not illustrate different and independent approaches to describing chemical reactivity on quantitative basis. As a matter of fact, those response functions defined within the Coulson-Longuet-Higgins theory can easily be cast into the form of response function of DFT [23, 24].

This brief review has been organized as follows: in the first section we introduce the basic definitions leading to the quantitative description of electronegativity, hardness, and softness. The key piece to achieve these definitions lies in the concept of electronic chemical potential and its derivatives introduced by Parr and Yang [13, 27] and Pearson and Songstad [19]. The electronic chemical potential μ is defined



Scheme 1: General heterolytic bond breaking process defining the nucleofuge (LG) and the electrofuge (PG). Adapted with permission from [25]. Copyright (2011) American Chemical Society.



Scheme 2: Addition of H^- to quinones. Adapted with permission from [26]. Copyright (2009) Elsevier.

therein as the first derivative of the energy E with respect to the number of electrons N [27]:

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{\upsilon(\mathbf{r})} \approx -\frac{(I - A)}{2}. \quad (1)$$

In (1), the derivative is taken at constant external potential $\upsilon(\mathbf{r})$ (i.e., the potential due to the compensating nuclear charges in the system). I and A are the vertical ionization potential and electron affinity, respectively. The electronic chemical potential as given by (1) becomes the negative of Mulliken electronegativity, and therefore it becomes a natural description of the direction of the electronic flux during a chemical interaction [27]. For this reason, Parr et al. proposed the electronic chemical potential as a quantity measuring the tendency of electrons to escape from the system. This result is relevant for it gives a first appraisal of the global electron-donating/electron accepting pattern of an interacting pair of atoms or molecules. If the chemical potential of a species A, say, is greater than its partner B, then the electronic flux will take place from A to B, thereby suggesting that, during the interaction, A will act as nucleophile and B as electrophile. We will return to this point afterwards to introduce more refined models of electrophilicity and nucleophilicity.

A useful computational definition of the electronic chemical potential may be obtained using Koppmans's theorem [28] that leaves (1) in terms of the one-electron energy levels of the frontier molecular orbitals HOMO and LUMO:

$$\mu \cong \frac{(\epsilon_{\mathrm{HOMO}} + \epsilon_{\mathrm{LUMO}})}{2}. \quad (2)$$

The electronic chemical potential of stable species is a negative semidefinite quantity. This remark will be of importance later.

Another pertinent quantity is the chemical hardness, defined as the first derivative of the electronic chemical potential with respect to N (or the second derivative of the

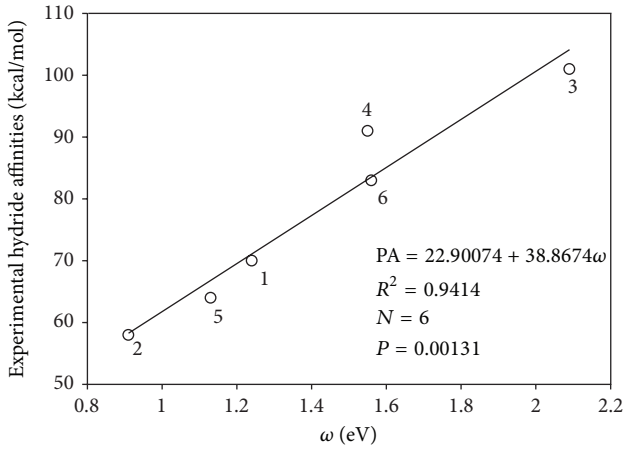


Figure 1: Comparison between the experimental hydride affinities of the quinone derivatives and their electrophilicity index (ω). Reprinted with permission from [26]. Copyright (2009) Elsevier.

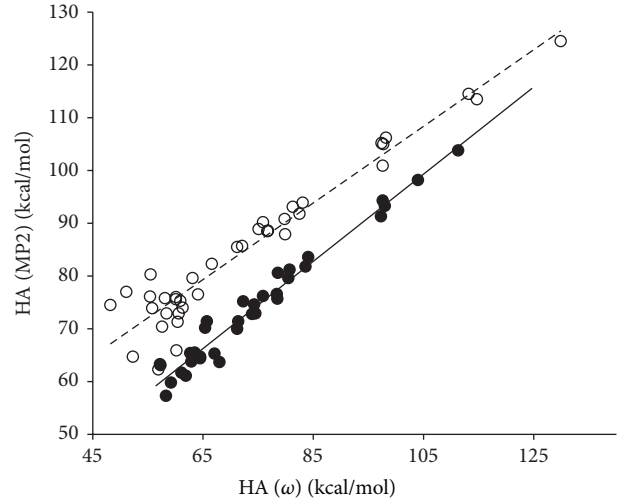


Figure 2: Comparison between hydride affinity of quinone derivatives from [29] and the hydride affinity obtained by electrophilicity index. The empty circles correspond to *ortho*-quinones derivatives (dashed line) and the full circles correspond to *para*-quinone derivatives (solid line). Reprinted with permission from [26]. Copyright (2009) Elsevier.

energy with respect to the number of electrons) [27]. Its finite difference version is as follows:

$$\eta \cong I - A \cong \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}. \quad (3)$$

Note that chemical hardness is a positive definite quantity. Its associated inverse is the chemical softness $S = 1/\eta$.

The functional derivative of the electronic chemical potential with respect to the external potential $v(\mathbf{r})$ at constant N defines a local response function called the Fukui function $f(\mathbf{r})$ [27]:

$$f(\mathbf{r}) = \left[\frac{\delta\mu}{\delta v(\mathbf{r})}\right]_N. \quad (4)$$

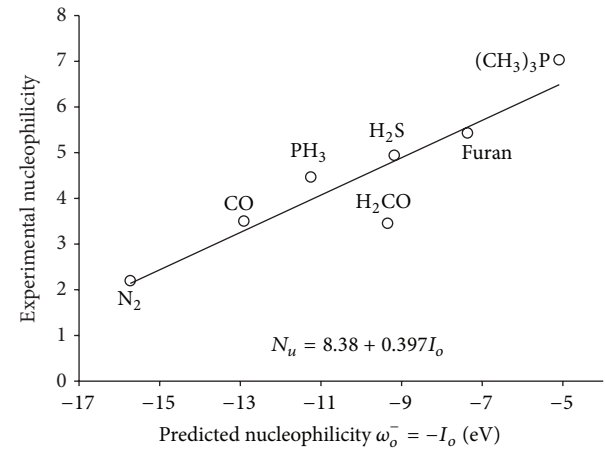


Figure 3: Comparison between experimental gas phase nucleophilicity and the negative of the gas phase ionization potential Io. Reprinted with permission from [30]. Copyright (2003) American Chemical Society.

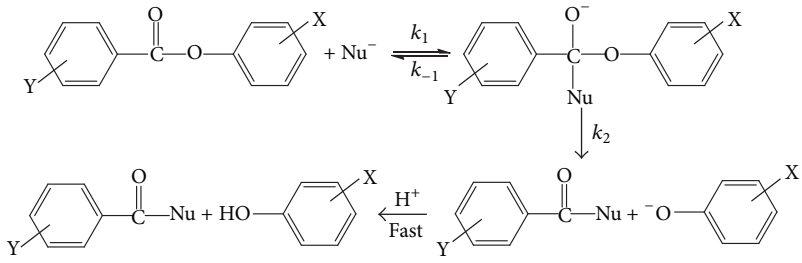
Table 1: Nucleophilic sites for electron donors and contributions to the regional nucleophilicity index. Adapted with permission from [30].

Species	Nucleophilic sites (k)	ω^-	f_k^-	ω_k^-
HO^-	O	−3.93	0.99	−3.89
HOO^-	O	−3.48	0.74	−2.58
N_3^{-a}	N_1	−5.79	0.49	−2.84
	N_2		0.02	−0.12
	N_3		0.49	−2.84
CH_3O^-	O	−3.99	0.73	−2.91
$CF_3CH_2O^-$	O	−4.91	0.75	−3.68
$C_6H_5S^-$	S	−5.45	0.62	−3.38
CN^-	C	−6.97	0.39	−2.72
	N		0.61	−4.25
NH_2OH	N	−3.72	0.71	−2.64
	O		0.27	−1.00
NH_3	N	−4.58	0.97	−4.44
$NH_2CONHNH_2$	O	−5.41	0.48	−2.60
H_2O	O	−6.65	0.98	−6.52
$CF_3CH_2NH_2$	N	−4.83	0.78	−3.77
CH_3ONH_2	O	−3.84	0.68	−2.61
	N		0.23	0.88
$CH_3CH_2CH_2S^-$	S	−3.46	0.94	−3.25
$CH_3CH_2S^-$	S	−3.43	0.95	−3.26
$OHCH_2CH_2S^-$	S	−3.15	0.94	−2.96
Piperidine	N	−4.32	0.66	−2.85
Morpholine	N	−4.46	0.49	−2.19
	O		0.13	−0.58

[a]N_2 is the central atom.

The Fukui function has a more workable operative form obtained after using a Maxwell relationship [27]:

$$f(\mathbf{r}) = \left[\frac{\delta\rho(\mathbf{r})}{\delta N}\right]_{v(\mathbf{r})}. \quad (5)$$



Scheme 3: General picture of the accepted reaction mechanism of aryl benzoates. Adapted with permission from [31]. Copyright (2010) Elsevier.

The Fukui function written as in (5) defines it as the change in the electron density at point **r** in space $\rho(\mathbf{r})$ after the system accepts or releases one electron unit. The Fukui function is a reactivity index itself (a normalized softness) [27]. However, the most relevant role of the Fukui function is to act as a distribution function that may be used to project any global quantity G [35]. The most useful form is however its condensed to atom version, f_k, obtained after a regional integration around the atomic center k in a molecule [36–38].

The condensed to atom Fukui function may be approached from a three-point interpolation finite difference formula, or using a single-point calculation using a Mulliken-like population analysis. Other approaches have also been proposed [39]. The finite difference approximation leads to the definition of electrophilic, nucleophilic, and radical Fukui functions that will play a key role in what follows [36, 37].

2. Philicity and Fugality Indices

Based on a proposal by Maynard et al. [40], Parr et al. derived global electrophilicity, defined as the stabilization in energy that an electron acceptor atom or molecule undergoes, when it is embedded in an electron bath at constant electronic chemical potential [12]. The global electrophilicity index was given the following working expression:

$$\omega = \frac{\mu^2}{2\eta} = \frac{\mu^2}{2} S. \tag{6}$$

Equation (6) shows that the best electrophile will be the species displaying a high value of the electronic chemical potential and a low value of chemical hardness or high electronegativity and high softness (or high polarizability). We have implemented Parr's global electrophilicity index in the form of reactivity scales for a series of classical reactions in organic chemistry [41] that include cycloaddition reactions [42], elimination reactions [43], nucleophilic reactions (both aromatic and aliphatic) [44, 45], addition reactions [46], epoxidation reactions [47], redox, and biochemical processes [46, 48], including the chemistry of carbenes [49].

Nucleophilicity on the other hand cannot be derived within the same model leading to the definition of the electrophilicity index [30, 50, 51]. This problem arises because, for the right-hand side of the parabola model used by Parr et al., the electronic chemical potential becomes positive semidefinite. This drawback of the philicity model is important for it is related to an empirical rule stating that big electrophilicity/nucleophilicity differences can be related to stepwise reaction mechanism with a high polar transition state, whereas small differences are related to nonpolar concerted mechanisms [52]. However, it is still possible to propose a nucleophilicity index based on the same energy expansion leading to the electrophilicity index. This index has been derived for the limit case where the charge released by the nucleophile is exactly equal to one electron unit. In this case the nucleophilicity index can be simply represented as the negative of the ionization potential; namely [30],

$$\omega^- = -I \approx \epsilon_{\mathrm{HOMO}}. \tag{7}$$

This definition can intuitively be justified for it suggests that the best nucleophile will be the species that destabilizes to a lowest extent in the process of releasing one electron unit of charge. In the following sections, we shall illustrate the reliability and usefulness of the electrophilicity and nucleophilicity indices for a series of classic organic reactions.

The definition of fugality indices requires the introduction of local reactivity indices, where the electrophilic (+) and nucleophilic (−) Fukui functions play a key role [25]. For instance, using (6) together with the additive property of global softness, one of us introduced the concept of semilocal or regional electrophilicity condensed to atom k as follows [43, 53]:

$$\omega_k = \omega f_k^+, \tag{8}$$

where f_k^+ is the condensed to atom k electrophilic Fukui function. In a similar way, the condensed to atom k nucleophilicity index can be expressed as [25]

$$\omega_k^- = \omega^- f_k^-, \tag{9}$$

where f_k^- is the condensed to atom k nucleophilic Fukui function.

The relationship with fugality concepts is framed on the regional philicity concepts sketched in Scheme 1 [25].

First of all, fugality quantities are group properties of a molecule [25]. This means that the propensity of a fragment

Table 2: Electrophilicity index of X-substituted phenyl benzoated. Adapted with permission from [31].

Compound	ω (eV)	X	ω_{LG} (eV)	$\Delta\omega_{LG}$ (eV)	σ	k_N[a] ($M^{-1}s^{-1}$)
1	0.94	3,4-diNO_2	0.90	0.89	0.83	1.92
2	0.75	4-NO_2	0.72	0.71	0.78	0.231
3	0.61	4-CN	0.61	0.60	0.66	—
4	0.61	4-CHO	0.35	0.34	0.42	0.103
5	0.57	4-$COCH_3$	0.20	0.19	0.50	0.0768
6	0.56	4-CO_2Et	0.09	0.08	0.45	—
7	0.77	3-NO_2	0.77	0.76	0.71	0.141
8	0.56	3-$COCH_3$	0.21	0.20	0.38	0.0359
9	0.53	4-Cl	0.01	0.00	0.23	—
10	0.66	H	0.01	0.00	0.00	0.0102
11	0.47	4-CH_3	0.01	0.00	−0.17	0.00783
12	0.83	4-OCH_3	0.01	0.00	−0.27	0.00843

[a]Data from references [32–34].

Table 3: Experimental electrophilicity E of the benzhydryl cations; regional nucleophilicity at fragment R, N(R), and at fragment LG, N(LG), in the complex R-LG; experimental and predicted electrofugality of benzhydryl cations. Adapted with permission from [25].

Entry	E	N(R) (eV)	N(LG) (eV)	%N(R)	ω^{-}[b]
1	5.90	−8.67	−0.08	99.1	−6.05
2	3.63	−8.37	−0.06	99.3	−3.47
3	2.90	−8.29	−0.03	99.6	−3.55
4	2.11	−8.16	−0.03	99.7	−2.06
5	1.48	−8.10	−0.03	99.6	−1.29
6	0.61	−8.13	−0.05	99.3	−0.81
7	0.00	−8.03	−0.04	99.5	0.00
8	−0.56	−7.94	−0.03	99.6	0.33[c]
9	−1.36	−7.91	−0.04	99.5	0.60[c]
10	−3.14	−7.75	−0.03	99.6	2.05[c]
11	−3.89	−7.91	−0.03	99.6	0.63[c]
12[a]	−4.72	—	—	—	—
13	−5.53	−7.94	−0.03	99.6	0.36[c]
14	−5.89	−7.38	−0.02	99.7	5.46[c]
15	−7.02	−7.30	−0.02	99.7	6.22[c]
16	−7.69	−7.02	−0.02	99.7	8.78[c]
17	−8.22	−7.21	−0.02	99.7	6.99[c]
18	−8.76	−7.30	−0.02	99.7	6.22[c]
19	−9.45	−7.11	−0.02	99.7	7.91[c]
20	−10.04	−7.17	−0.02	99.7	7.34[c]

[a]For this compound the algorithm used to evaluate the nucleophilic Fukui function produces negative values. [b]Experimental electrofugality from [33]. [c]Predicted values using the empirical equation included in Figure 2(b).

to detach during a heterolytic bond breaking process may be safely described using a regional property of that fragment embedded in the chemical ambient of the remaining moiety of the molecule. It is important to stress this point that fugality quantities are not intrinsic properties of the isolated fragment [25, 43, 53]. With this model in mind, we can readily define nucleofugality, as the group electrophilicity evaluated on the whole molecule, where the highest values of group electrophilicity are expected to be mostly concentrated at the leaving group (LG) moiety. This is a reasonable representation of nucleofugality number, as the nucleofuge is the group that departs from the molecule bearing the bond electron pair during the heterolytic bond cleavage [53]. At the same time, the electrofuge (or permanent group R) is expected to act as an electron releasing fragment, and, therefore, electrofugality may reasonably be described by the group nucleophilicity [25]. The working formulae to quantify nucleofugality ν^{+} and electrofugality ν^{-} numbers are given by

$$\nu^{+} = \sum_{k\varepsilon G} \omega_k^{+}, \tag{10}$$

$$\nu^{-} = \sum_{k\varepsilon G} \omega_k^{-}, \tag{11}$$

respectively.

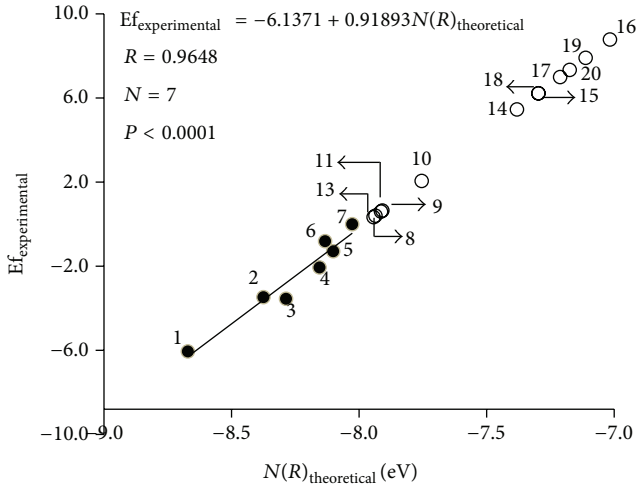


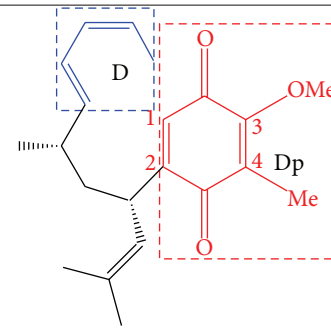
Figure 4: Comparison between experimental electrofugality (●) and the regional nucleophilicity of the permanent group R for a series of benzhydryl phenyl sulfinates derivatives. Predicted electrofugalities values are included (○). Reprinted with permission from [25]. Copyright (2011) American Chemical Society.

3. Applications

The phenomenological reactivity theory described in the previous sections may be applied at the ground state of atoms and molecules as well as at the transition state stage of reactions. Note that, in doing so, both global and semilocal (regional) quantities may be used to build up "activation" properties. In what follows we present some of the applications that we and other authors have used to illustrate the reliability and usefulness of this theoretical model of reactivity that embodies reactivity, (regio)selectivity, and site activation [45, 54, 55].

3.1. The Electrophilicity Index. The electrophilicity index developed by Parr et al. (6) has been widely used to explain many organic reactions. The main purpose of these studies was traced to relate them to experimental data that include hydride affinity [26], rate coefficients [44, 56, 57], toxicity indexes [58–60], and many other applications [61–64]. For instance, Campodónico et al. demonstrated that the electrophilicity of quinones may be concisely used to deduce a hydride affinity (HA) scale in the gas phase [26]. The opportunity of having a global electrophilicity hierarchy related to HA is useful because experimental HA data are scarce. Because the measurement of HA is not direct, the electrophilicity-HA relationships provide a simple way to establish a sound HA scale. The gas phase hydride affinity may be obtained as the negative enthalpy change for the reaction $Q + H^- \rightarrow QH^-$, where Q is an oxidized molecule and QH^- is its reduced form. The hydride affinity has been considered as a descriptor for Lewis's acidity [65] since it may be a characteristic of the electron accepting capability of the electrophile [29]. Within this model, the ability of quinones to bind an H^- ion will be related to their electrophilic response and may be modulated by the presence of a series

Table 4: Global and regional indices for the IMDA reaction leading to diterpenoid elisabethin A.



μ	η	ω	ω^-	ω_{Dp}	ω_D	ω^-_{Dp}	ω^-_D
−0.1607	0.0940	3.65	3.46	3.64	0.00	0.00	3.44

of substituent R that can stabilize an extra negative charge, as illustrated in Scheme 2 [26].

The comparison between the experimentally observed hydride affinity and the electrophilicity index is shown in Figure 1. The regression is the result of the comparison of six experimentally obtained hydride affinities.

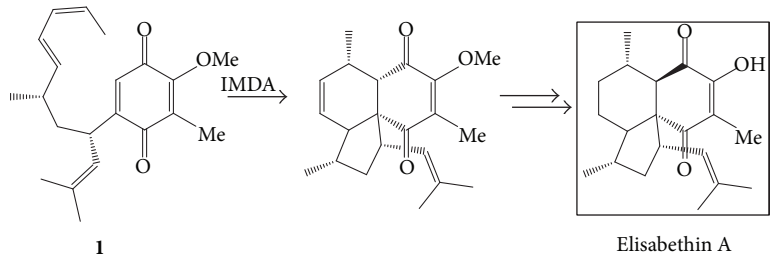
The empirical regression equation is

$$HA = 22.900 + 38.867\omega; \qquad R^2 = 0.94 \qquad (12)$$

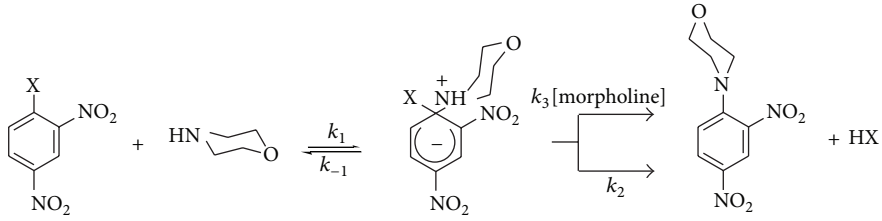
and is a suitable way to obtain the hydride affinity of quinones not established up to date. First of all, from the regression equation (12), it is possible to note that the hydride affinities are well correlated with the ω index. The relationship with the substituent effect is also described by ω in the sense that electron-donating groups enhance the hydride affinity of quinones, while electroattracting groups diminish the hydride affinity values. When the substituent is the CN or Cl groups (moderate electron-withdrawing groups), results in an electrophilic activation (ω = 2.09 eV and ω = 1.56 eV, resp.) with respect to the reference non-substituted quinone (ω = 1.24 eV). On the other hand, the presence of the marginal donating methyl group results in an electrophilic deactivation (ω = 0.91 eV) [26]. The regression between the electrophilicity index and the predicted hydride affinities [66] is presented in Figure 2.

The comparison in Figure 2 shows two families that cannot be accommodated in a single correlation line. The regression corresponds to the *ortho*-quinone derivatives (dashed line) and the *para*-quinone derivatives (solid line). These results represent another useful application of the ω index. The hydride attachment strongly depends on the relative position of the carbonyl groups on the quinine: in the *ortho*-like derivatives, the electrophilicity index well describes the alpha-like effect promoted in this system by the presence of an adjacent electron-rich atom [67, 68]. These systems are predicted as nucleophiles or marginal electrophiles [69, 70].

3.2. Nucleophilicity. The usefulness of the nucleophilicity index (7) is discussed here for a series of neutral and charged electron donors [30]. The series of neutral nucleophiles



Scheme 4: Synthesis of diterpenoid elisabethin A via an IMDA reaction.



X = F, Cl, Br, I

Scheme 5: General S_NAr reaction mechanism. Reprinted with permission from [45]. Copyright (2013) American Chemical Society.

relative to water include N_2, CO, PH_3, H_2CO, H_2S, furan, $(CH_3)_3P$, H_2O, NH_3, and CH_3OCH_3 [71, 72].

This series was experimentally studied by Legon and Millen who proposed a spectroscopic scale of electrophilicity and nucleophilicity based on the intermolecular stretching force constant for the interaction of these neutral nucleophiles [71, 72] towards the hydrogen fluoride HF as probe. In the gas phase, the facile formation of a hydrogen bonded nucleophile-HF complex permits the intermolecular stretching of the nucleophile/HF moieties to be evaluated. The nucleophilicity scale is simply given by the ordered hierarchy of the respective force constants. The comparison between the experimental nucleophilicity numbers reported by Legon and Millen with those obtained from our model equation (7) for the whole series of neutral nucleophiles was fair, because ammonia and dimethyl ether strongly deviated from linearity. A deep sight to the available IR data for the complexes H_3N-HF and $(CH_3)_2O$-HF revealed that the normal mode assignments for these species were not as clean as desired. The calculated intermolecular stretching around the hydrogen bond was hardly contaminated by torsion and bond deformation (wagging) of the sp^3 groups attached to the heteroatoms N and O. However, when the regression was made with the 7 remaining nucleophiles, a reasonably good correlation was obtained. The comparison is shown in Figure 3.

It is worth mentioning that the model equation (7) also works reasonably well for ionization potential in solution phase [30].

As we will show later, the semilocal or regional nucleophilicity patterns of molecules become of great relevance to describe another property, namely, electrofugality, a group property describing permanent group abilities in heterolytic bond cleavage processes. The model equation describing regional or group nucleophilicity is that quoted as (9). Site reactivity is also useful for predicting regioselectivity, hydrogen bond basicity, and Lewis molecular basicity in polyfunctional species. In order to evaluate the regional nucleophilicity index given by (9), a series of charged and neutral nucleophiles in the gas phase were evaluated. The results are compiled in Table 1.

From the data collected in Table 1, it may be seen that the ω_k^- index consistently distributes the global nucleophilicity values on those atoms that are expected to be more nucleophilic. As expected, the most nucleophilic center is at the heteroatom (N, O, or S) site.

3.3. Nucleofugality. As defined at the beginning of this review, the nucleofugality index as stated in (10) may be used to quantitatively characterize the leaving group abilities of several fragments commonly present as nucleofuges in substitution and elimination reactions in organic chemistry. The basic ideas and concepts are those summarized in Scheme 1. In order to illustrate the reliability and usefulness of the nucleofugality index we have evaluated it for a series of aryl benzoates and discuss the usefulness of the resulting scales to assist in the rationalization of their reaction mechanism in nucleophilic substitution reactions [31]. The acyl group in aryl benzoates may react along stepwise or concerted nucleophilic substitution channels to yield the corresponding amide [32–34]. A general route is sketched in Scheme 3 [31].

In order to assess the effect of the leaving group on the reaction mechanism, we selected a series of reactions where the permanent group is kept fixed. The series is depicted in Table 2 [31].

From the data summarized in Table 2, it is possible to note that the electrophilicity index at the leaving group is mainly

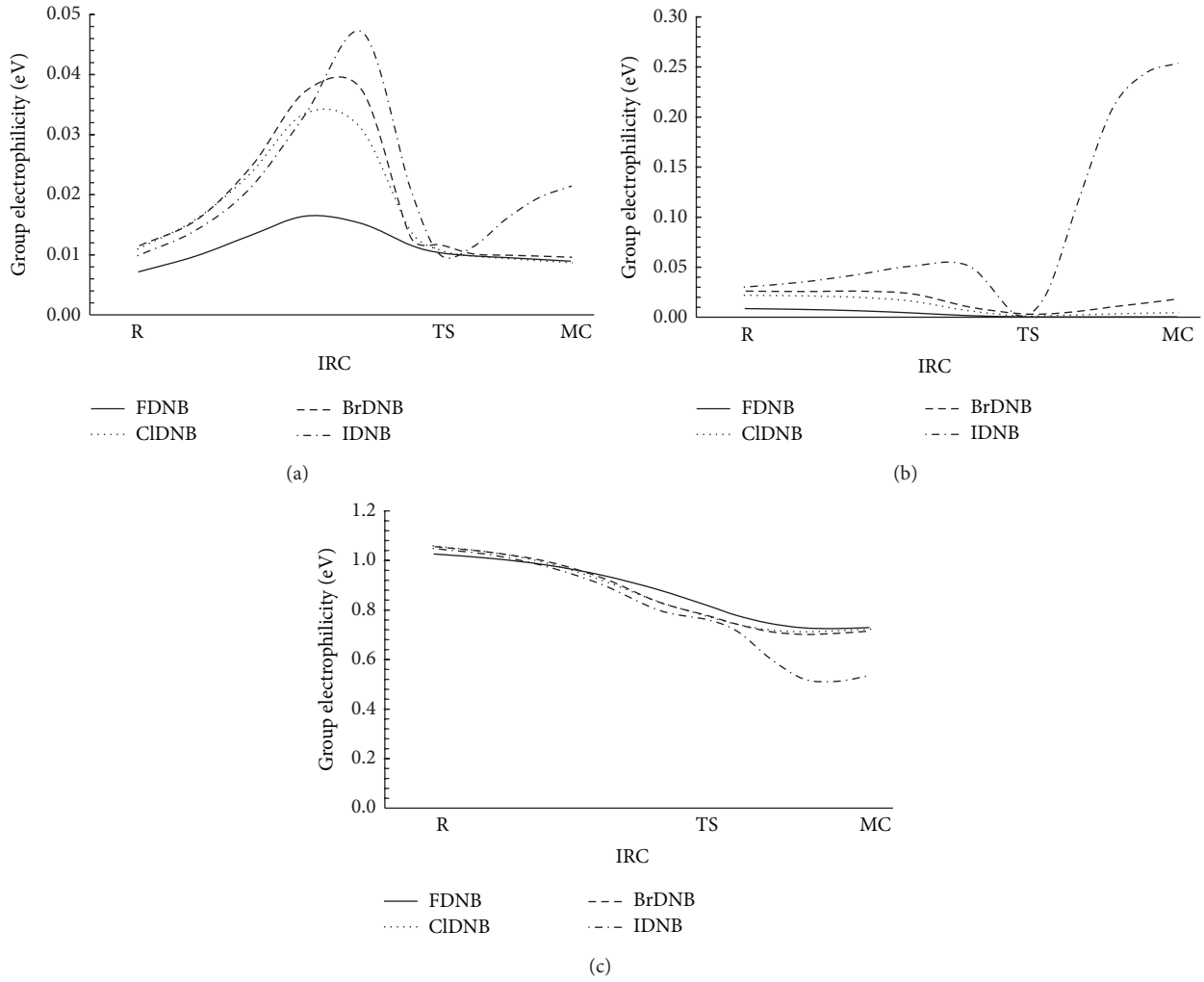


Figure 5: Profiles of group electrophilicity of the fragments centered in the moieties corresponding to (a) nucleophile, (b) leaving group, and (c) permanent group in the reaction between morpholine toward the XDNB series (X = F, Cl, Br, and I). Adapted with permission from [45].Copyright (2013) American Chemical Society.

driven by the presence of electron-withdrawing groups. The presence of these groups is related to an enhancement of the nucleofugality (leaving group ability) of this group. It is important to emphasize that the trends in nucleofugality coherently compare with the experimental rate coefficients measured by Um and coworkers [32–34]. The addition of electron-attracting groups on the leaving group may be responsible for the enhancement of the rate constant, since these groups contribute to the net destabilization of the intermediate from which the leaving group detaches.

3.4. Electrofugality. The electrofugality index given by (11) has been applied to a set of 20 benzhydryl sulfinates experimentally studied by Baidya et al. to establish a quantitative hierarchy of electrofugality [73]. According to Scheme 1, the best electrofuge is the fragment that displays the highest regional nucleophilicity [25]. During the bond cleavage the electrofuge is the fragment that releases the electron density, thereby acting as an electron donor. The results are summarized in Table 3.

Table 3 reveals that the regional nucleophilicity is mainly concentrated at fragment R which corresponds to the permanent group. It is important to remark that the electrofugality is fairly ordered in terms of inductive effects promoted by the substituents. The usefulness of this model is illustrated in Figure 4, in the perspective of the predictive potential of this tool: with known electrofugality data for a reduced set of molecules at hand, it becomes possible to anticipate the electrofugality number by simply evaluating the group nucleophilicity of the permanent group moiety at the intermediate complexes [25].

3.5. Site Activation: Fragment Reactivity Analysis. In equilibrium thermodynamics, the electronic chemical potential of density functional theory is a global response function, and therefore it is expected to have a uniform distribution

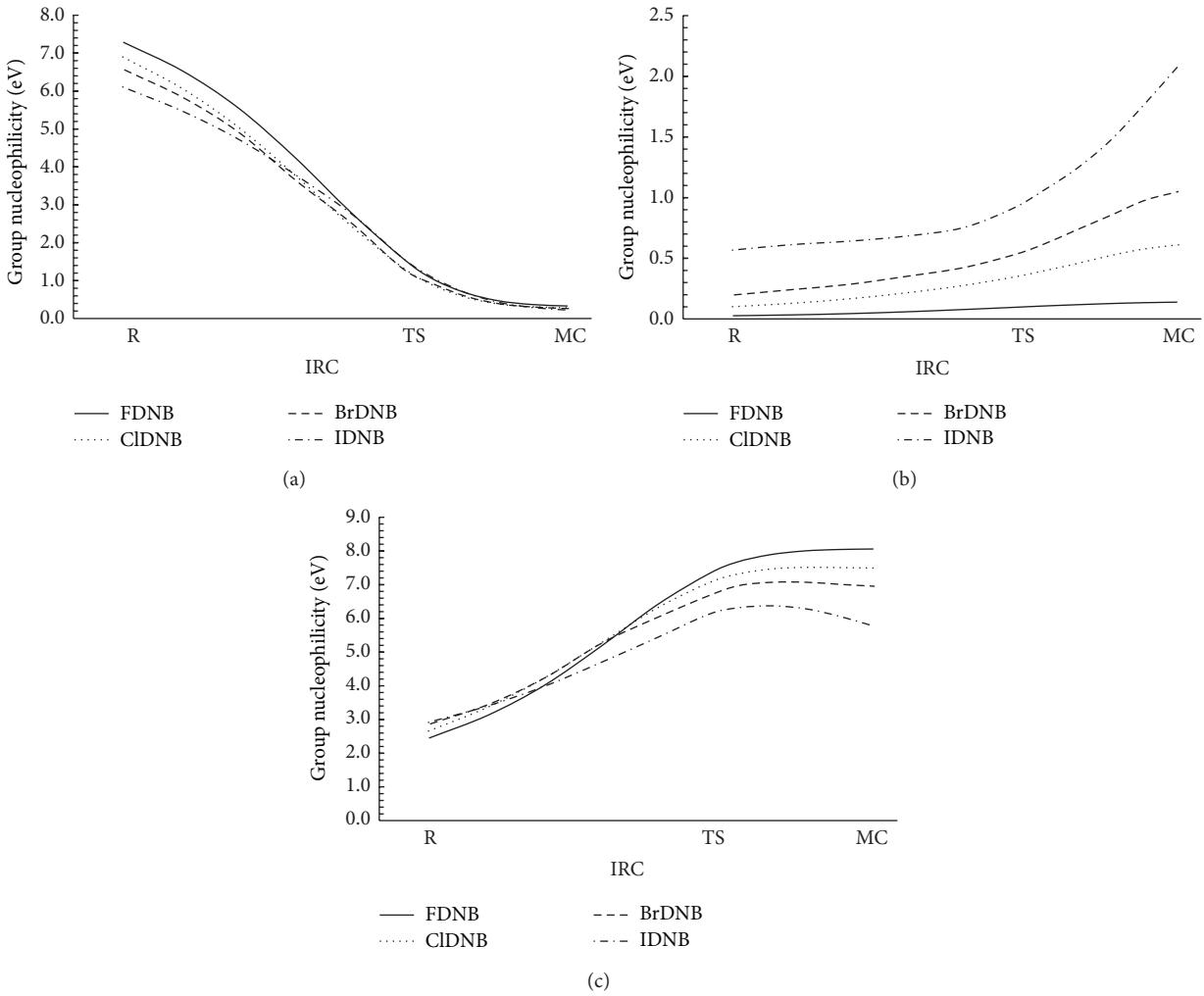


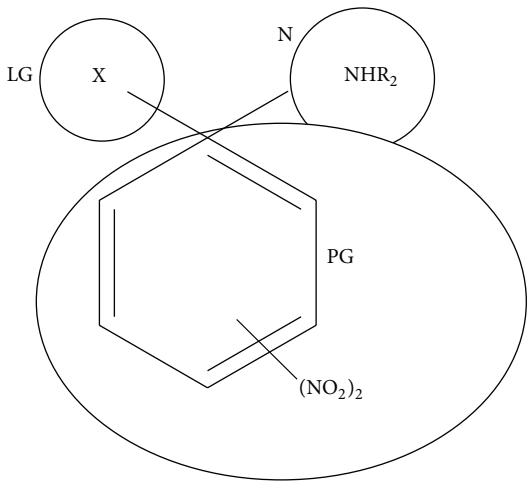
Figure 6: Group nucleophilicity profiles centered in the (a) nucleophile, (b) leaving group, and (c) permanent group for the reaction between morpholine towards 1-X-2,4-dinitrobenzene series (X = F, Cl, Br, and I). Adapted with permission from [45]. Copyright (2013) American Chemical Society.

within the whole molecular structure. However, intramolecular reactivity put a serious challenge for the application of electronic descriptors of reactivity, and some adaptations are to be introduced in order to account for how two or more fragments, within the same molecule, may interact to produce bond making/breaking processes. We proposed a model framed on nonequilibrium thermodynamics allowing two molecular fragments to be described by different electronic chemical potential, in such a way that they can exchange work, heat, or energy [74, 75]. We have used the intramolecular Diels-Alder (IMDA) reaction of Quinone systems to illustrate this model. The benchmark reaction used was the synthesis of the diterpenoid elisabethin A. The reaction is sketched in Scheme 4 [76].

The fragmentation scheme together with the global and regional indices associated with the diene (D) and Dienophile (Dp) fragments is summarized in Table 4.

The global electrophilicity of quinone **1** is within the range of strong electrophiles [69, 70]. The most electrophilic center of **1** that may react is the C1 carbon. Consequently, the favored IMDA reaction is that involving the diene fragment and the C1-C2 double bond. Note the remarkable resolution of the philicity patterns, a job that is performed by the Fukui function (see (8) and (9)). The fragmentation scheme used put over 98% of electrophilicity on the Dp fragment and over 99% of nucleophilicity on the D moiety.

3.6. Quasi-Static Approach: Reactivity Indices along a Reaction Pathway. A final word concerning the reactivity indices in organic reactions is a brief discussion on a nucleophilic aromatic substitution reaction, within a quasi-static scheme, obtained by following the changes in electrophilicity and nucleophilicity along the intrinsic reaction coordinates (IRC). The model reaction is that sketched in Scheme 5 [45, 55].



Scheme 6: General fragmentation model of the electrophile-nucleophile pair. LG, PG, and N stand for leaving group, permanent group, and nucleophile, respectively. Adapted with permission from [45]. Copyright (2013) American Chemical Society.

The model reaction is the S_NAr involving morpholine and 1-X-2,4-dinitrobenzenes (XDNB, X = F, Cl, Br, and I) [77, 78]. Figures 5 and 6 display the group electrophilicity and nucleophilicity profiles using the arbitrary fragmentation scheme below [25, 45].

As expected, the electrophilicity of the amine moiety (N) is marginal (Figure 5(a)). The electrophilicity condensed at the LG fragment shows a sudden enhancement for the iodine derivative. This result suggests that iodine may detach in the first stage of the reaction depicted in Scheme 5, in agreement with the experimental reports [77, 78]. Figure 5(c) shows the role of the permanent group on the reaction mechanism. In the region of the Meisenheimer complex (MC) all the substrates become electronically saturated. This result may be associated with the end of the charge transfer process, except for iodine which began to detach from the structure as iodide.

Figure 6 shows the nucleophilicity profile within the partitioning Scheme 6. When the index is condensed over the nucleophilic moiety, it seems that it dramatically diminishes downward the MC formation. This result suggests that the charge transfer reaches its minimum after the nucleophilic attack. It is important to note that the property condensed at the LG and PG reaches a maximum value near the MC: the charge is transferred from the nucleophile and accepted for the PG and then redirected to the LG. However, the maximum values for morpholine are different: 7.29, 6.91, 6.56, and 6.11 eV for X = F, Cl, Br, and I, respectively. These values suggest that the substrates interact in different way depending on the LG present. The results reported are in good agreement with the experimental observations, since the leaving group abilities are in the order F > Cl > Br > I when the nucleophile is morpholine [45, 55, 78].

4. Concluding Remarks and Perspectives

In this review, we have shown how conceptual aspects of density functional theory lead to the definition of reactivity indices amenable to build up quantitative models of reactivity in organic reactions. The emphasis has been put on two basic concepts describing electron-rich and electron-deficient systems, namely, nucleophile and electrophiles. We then show that the regional nucleophilicity and electrophilicity become the natural descriptors of electrofugality and nucleofugality, respectively. In this way, we have obtained a closed body of concepts that suffices to describe electron releasing and electron accepting molecules together with the ordering of leaving group ability of nucleofuges present in addition, nucleophilic substitution and elimination reactions. A natural perspective of these models is their use along a reaction coordinate following that result in an additional tool to rationalize reaction mechanisms in organic chemistry.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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