Update 1 of: Electrophilicity Index

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Contents

1. Introduction: Electrophilic and Nucleophilic Processes—Reaction Mechanisms, Thermodynamics, and Kinetics

Chemistry is the science of bond making and bond breaking. A thorough knowledge of these processes in the course of the chemical reaction lies at the heart of any reaction mechanism. In the heterolytic cleavage of a bond, the electron pair lies with one of the fragments, which becomes electron rich, while the other fragment becomes electron deficient. An electron-rich reagent gets attracted to the center of the positive charge and forms a bond with an electron-deficient species by donating electrons. The electron-rich species is known as a nucleophile, and the electron-deficient one, as an electrophile.[1−4]

Free radicals are generated through a corresponding homolytic process where an equal share of one electron is obtained by each fragment. Even radicals are designated as electrophilic/nucleophilic depending on their tendency to attack the reaction sites of relatively higher/lower electron density. Moreover, nucleophiles (electrophiles) are Lewis bases (acids) as well as reducing (oxidizing) agents since they donate (accept) electrons, implying a connection among electrophile−nucleophile chemistry, acid−base chemistry, and oxidation−reduction chemistry. Since the majority of the reactions can be analyzed through the electrophilicity/nucleophilicity of various species involved, a proper understanding of these properties becomes essential. Some related reviews on specific types of reactions are available,[5−13] albeit without a rigorous definition of electrophilicity.

The most important types of reactions we often encounter are substitution, addition (including pericyclic reactions), elimination (the opposite of addition reactions), and rearrangements. All these reactions are analyzed using thermodynamic and kinetic data. While the former determines how far a reaction will go (a large decrease in Gibbs free energy implies a large value of the equilibrium constant, K), the latter determines how fast it will take place (a smaller free energy of activation value implies a larger rate constant, k, at a given temperature, i.e., a faster reaction). Although the electrophilicity (nucleophilicity) and Lewis acidity (basicity) are related, the former is traditionally assumed to be a kinetic quantity and, hence, is estimated by relative k values whereas the latter is a thermodynamic quantity and is measured by relative K values.

The concept of electrophilicity has been known for several decades, although there has not been a rigorous definition of it until recently, when, inspired by the experimental findings of Maynard et al.,[13] Parr et al.[14] proposed a definition

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based on the energy lowering associated with a maximum amount of electron flow between two species. There resulted an upsurge of interest in understanding the utility of this quantity in analyzing several diverse areas of chemistry. Little did they[14] realize when they proposed this simple-looking index that it contains an enormous potential to connect the major facets of chemical sciences. It has been shown that electrophilicity possesses adequate information regarding structure, stability, reactivity, toxicity, bonding, interactions, and dynamics. Only the concept of electrophilicity index provided by Parr et al.,[14] its usefulness, and its various possible extensions will be reviewed in this article. Citations of the works related to the Maynard−Parr electrophilicity index are intended to be as exhaustive as possible with mention of and necessary comparison with all other known popular electrophilicity measures. Several papers related to this index appeared after the final submission of this article. They are cited in appropriate places in the References and Notes section. Section 2 introduces this global index, and its local variants are described in section 3. Existing electrophilicity scales are reported in section 4. Section 5 describes the use of the electrophilicity index in analyzing the reactivity patterns in various intramolecular and intermolecular physicochemical processes. Variation of this quantity during molecular vibrations, internal rotations, and chemical reactions is mentioned in section 6. Sections 7 and 8 report the dynamical and spin dependent variants of this index, respectively. Finally, section 9 contains some concluding remarks.

2. Global Electrophilicity Index

2.1. Genesis

Popular qualitative chemical concepts such as electronegativity[15,16] (χ) and hardness[17,18] (η) have been provided with rigorous definitions within the purview of conceptual density functional theory[19−26] (DFT). Electronegativity is the negative of chemical potential defined[29] as follows for an N-electron system with total energy E and external potential $v(\vec{r})$,

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \qquad (1)$$

μ is the Lagrange multiplier associated with the normalization constraint of DFT.[19,27,28] In DFT, the electron density ($\rho(\vec{r})$) is the basic variable instead of the many-particle wave function ($\Psi(\vec{x}_1,\vec{x}_2,...,\vec{x}_N)$).

Hardness (η) is defined[30] as the corresponding second derivative,

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

Sometimes a $^1/_2$ factor is included in the above definition. Softness (S) is the reciprocal of hardness; $S = 1/\eta$.

Complete characterization of an N-particle wave function needs only N and $v(\vec{r})$. While χ and η measure the response of the system when N varies at constant $v(\vec{r})$, the behavior of the system for a change in $v(\vec{r})$ at fixed N is given by the linear density response function.[19] The linear response of the electronic cloud of a chemical species to a weak external electric field is measured in terms of the static electric dipole polarizability (α). The electric dipole polarizability is a measure of the linear response of the electron density in the presence of an electric field F, and it represents a second-order variation in energy,

$$\alpha_{a,b} = -\left(\frac{\partial^2 E}{\partial F_a \partial F_b}\right); \quad a, b = x, y, z \qquad (3)$$

The polarizability (α) is then calculated as follows

$$\langle \alpha \rangle = {}^1/_3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \qquad (4)$$

These reactivity parameters are better appreciated by various associated electronic structure principles. According to the electronegativity equalization principle,[29,31−33] "All the constituent atoms in a molecule have the same electronegativity value given by the geometric mean of the electronegativities of the pertinent isolated atoms". Two hardness related principles are the hard−soft acids and bases (HSAB) principle[17,30,34−40] and the maximum hardness principle.[41−48] While the former states that, "Hard acids prefer to coordinate with hard bases and soft acids to soft bases for their thermodynamic and kinetic properties", the statement of the latter is, "There seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible". On the basis of the inverse relationship, $\eta \propto 1/\alpha^{1/3}$,[49−52] between hardness and polarizability, a minimum polarizability principle[53−56] has been proposed which states that,[53] "The natural direction of evolution of any system is toward a state of minimum polarizability". An inverse relationship between hardness and magnetizability has also been shown,[49b,c] which leads to a minimum magnetizability principle. A soft molecule is both polarizable and magnetizable.

Using a finite difference method, working equations for the calculation of χ and η may be given as[19]

$$\chi = \frac{I + A}{2} \tag{5}$$

$$1 = I - A \tag{6}$$

where I and A are the ionization potential and electron affinity, respectively. If ϵ_{HOMO} and ϵ_{LUMO} are the energies of the highest occupied and lowest unoccupied molecular orbitals, respectively, then the above equations can be rewritten[57] using Koopmans' theorem[58] as

$$\chi = -\frac{\epsilon_{\mathrm{HOMO}} + \epsilon_{\mathrm{LUMO}}}{2} \tag{7}$$

$$\eta = \epsilon_{\mathrm{LUMO}} - \epsilon_{\mathrm{HOMO}} \tag{8}$$

Maynard and co-workers[59] have shown that the reaction rates from the fluorescence decay studies on the human immunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 ($\mathrm{NC_P}$ 7) interacting with several electrophilic agents correlate strongly with the square of the electronegativity divided by its chemical hardness ($\chi^2/2\eta$). The $^1/_2$ factor arises due to the definition of hardness used here (eq 2). The quantity $\chi^2/2\eta$ is considered[13,59] to be related to the capacity of an electrophile to promote a soft (covalent) reaction. Prompted by this work of Maynard et al.,[13,59] an electrophilicity index (ω) has been defined as $\chi^2/2\eta$ by Parr et al.[14] They have shown[14] that ω measures the second-order energy of an electrophile when it gets saturated with electrons.

2.2. Prescription

To propose an electrophilicity index, Parr et al.[14] assumed a sea of free electron gas at zero temperature and zero chemical potential. When an electrophilic system (atom, molecule, or ion) would get immersed into the sea, there would be an electron flow of amount ΔN from the sea to the system until the chemical potential of the system becomes zero (cf. Sanderson's principle[29,31−33]). The resulting energy change (up to second order) associated with the electron-transfer process is

$$\Delta E = \mu \Delta N + \frac{1}{2}\eta(\Delta N)^2 \tag{9}$$

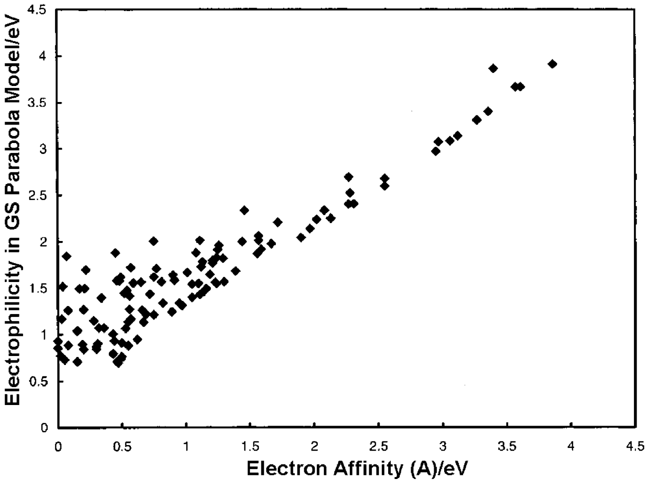

Figure 1. Correlation between electrophilicity index and electron affinity of some neutral atoms and simple molecules in the ground-state parabola model. Reprinted with permission from ref 14. Copyright 1999 American Chemical Society.

Considering the situation when the system becomes saturated by soaking up the maximum amount of electrons, ΔN_{max}, they set[14] ($\Delta E/\Delta N$) to be zero, implying

$$\Delta E = -\frac{\mu^2}{2\eta} \tag{10}$$

and

$$\Delta N_{\mathrm{max}} = -\frac{\mu}{\eta} \tag{11}$$

In eq 10, the numerator (μ^2) is quadratic and, hence, positive and the denominator (2η) is positive due to the convexity of the energy, and hence, ΔE is negative: the charge transfer is an energetically favorable process. Parr et al.[14] defined ω as

$$\omega = \frac{\mu^2}{2\eta} = \frac{\chi^2}{2\eta} \tag{12}$$

as a measure of electrophilicity of the ligand, just as was suggested by Maynard et al.[59]

This quantity ω is called[14] the "electrophilicity index" and is considered to be a measure of electrophilic power, just as, in classical electrostatics, power $= V^2/R$, and μ and η serve the purpose of potential (V) and resistance (R), respectively. It is transparent from Figures 1−3 that ω and A are not equal but they are correlated[14] and ω is more tightly correlated[60] with A than with χ, though all these quantities measure the propensity of electron intake. Since ω depends on both I and A, it is expected that A can provide similar qualitative trends as ω whenever the variation in I is not very significant. This is commonly observed for the elements belonging to the same group in the periodic table[60] and the functional groups containing them. It may be noted that A takes care of the energy change due to the addition of a single electron whereas the energy lowering associated with maximal electron flow is characterized by ω. Considering the discontinuity in the E vs N curve,[59b] separate definitions for electrophilicity have been proposed[59c] for the charge donation and charge acceptance processes, respectively, as $\omega^{\pm} = (\mu^{\pm})^2/2\eta$, where $\mu^{\pm}$ are the corresponding left and right derivatives obtained in the spirit of the Perdew, Parr, Levy, and Balduz prescription.[59b]

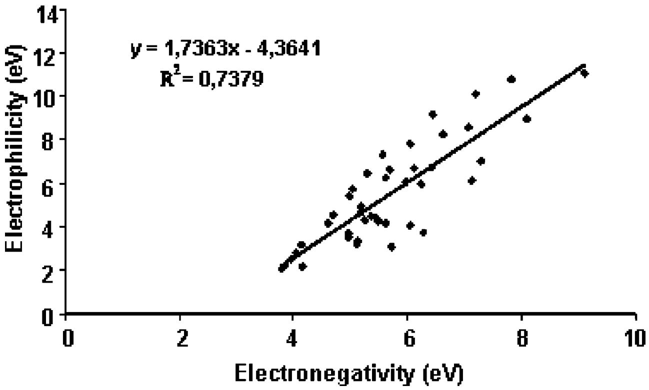

Figure 2. Correlation between electronegativities and electrophilicity indices for the functional groups XY_3 (X = C, Si, Ge, Sn, Pb, element 114; Y = CH_3, H, F, Cl, Br, I, At). Reprinted with permission from ref 60. Copyright 2005 American Chemical Society.

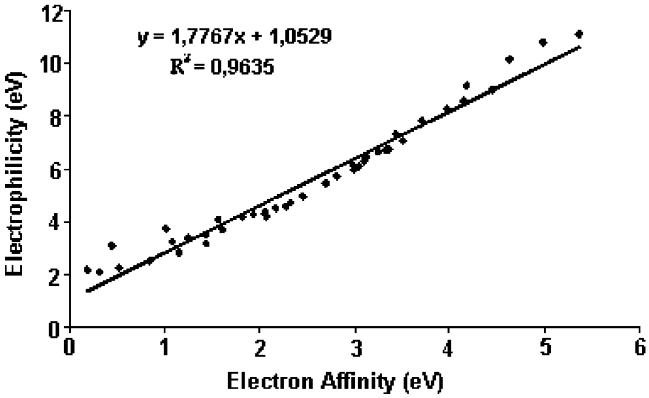

Figure 3. Correlation between electron affinities and electrophilicity indices for the functional groups XY_3 (X = C, Si, Ge, Sn, Pb, element 114; Y = CH_3, H, F, Cl, Br, I, At). Reprinted with permission from ref 60. Copyright 2005 American Chemical Society.

In the present review we will restrict ourselves to various ramifications of ω only. An update is provided here as a “Perennial Review” to the original article “Chattaraj, P. K.; Sarkar, U.; Roy, D. R. *Chem. Rev.* **2006**, *106*, 2065.”

3. Local Extensions and Site Selectivity

3.1. Local Electrophilicity

Global reactivity descriptors such as electronegativity, chemical potential, hardness, polarizability, and electrophilicity as introduced in the last section are defined for the system as a whole. To describe the site selectivity in a molecule, local descriptors of reactivity have also been proposed. An equivalent definition of hardness has been given by[61,62]

$$\eta = \frac{1}{N}\int\int \eta(\vec{r},\vec{r}')\, f(\vec{r}')\, \rho(\vec{r})\, d\vec{r}\, d\vec{r}' \qquad (13)$$

or its other variants[63−65] where $f(\vec{r})$ is the Fukui function[66−70] and the hardness kernel can be written as

$$\eta(\vec{r},\vec{r}') = \frac{1}{2}\frac{\delta^2 F[\rho]}{\delta\rho(\vec{r})\,\delta\rho(\vec{r}')} \qquad (14)$$

where $F[\rho]$ is the Hohenberg−Kohn−Sham[27,28] universal functional.

The Fukui function is by far the most important local reactivity index. It is defined as[69]

$$f(\vec{r}) \equiv (\delta\rho(\vec{r})/\partial N)_{\nu(\vec{r})} = (\delta\mu/\delta\nu(\vec{r}))_N \qquad (15)$$

Because of the discontinuities in slope of the $\rho(\vec{r})$ versus N curve,[59b,71] three types of Fukui functions can be written as follows[69]

for nucleophilic attack

$$f^+(\vec{r}) = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)^+_{\nu(\vec{r})} \approx \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \approx \rho_{\mathrm{LUMO}}(\vec{r}) \qquad (16a)$$

for electrophilic attack

$$f^-(\vec{r}) = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)^-_{\nu(\vec{r})} \approx \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \approx \rho_{\mathrm{HOMO}}(\vec{r}) \qquad (16b)$$

for radical attack

$$f^0(\vec{r}) = \frac{1}{2}[f^+(\vec{r}) + f^-(\vec{r})] \qquad (16c)$$

which capture the essence of Fukui’s frontier orbital theory. A gradient correction method[72,73] and a variational approach[74,75] for the calculation of $f(\vec{r})$ are known.

Other important local reactivity descriptors include $\nabla\rho(\vec{r})$ and $\nabla^2\rho(\vec{r})$ (as analyzed by Bader),[76,77] the molecular electrostatic potential,[78−81] and the quantum potential.[82,83] The quantum potential has been defined as

$$V_{\mathrm{qu}}(\vec{r},t) = -\frac{1}{2}\frac{\nabla^2\rho^{1/2}(\vec{r},t)}{\rho^{1/2}(\vec{r},t)} \qquad (17)$$

Two useful theories based on V_{qu} are quantum fluid dynamics (QFD)[82] and quantum theory of motion (QTM).[83] In the former, the dynamics of a quantum system is mapped onto that of a probability fluid under the guidance of a classical potential augmented by a quantum potential, while in QTM it is represented in terms of an ensemble of particle motions governed by forces originating from both classical and quantum potentials. In section 7 we will report the chemical reactivity dynamics by making use of these concepts.

Another important local reactivity descriptor is the electron localization function (ELF), which has been defined[84−87] for a single determinantal wave function in terms of various kinetic energy densities (Kohn−Sham, Weizsäcker and Thomas−Fermi) or, equivalently, the related local temperatures[87] as

$$\mathrm{ELF} = \frac{1}{1 + (t/t_{\mathrm{F}})^2} \qquad (18a)$$

where

$$t = \frac{1}{2}\sum_i |\nabla\Psi_i|^2 - \frac{1}{8}\frac{|\nabla\rho|^2}{\rho} \qquad (18b)$$

and

$$t_{\mathrm{F}} = \frac{3}{10}(3\pi^2)^{2/3}\rho^{5/3} \qquad (18c)$$

Sometimes it becomes difficult to analyze site selectivity using these local $\vec{r}$ dependent quantities. To tackle this problem, the related condensed-to-atom variants are written for the atomic site k of the molecule. For example, the corresponding Fukui functions (f_k^α, $\alpha = +, -, 0$) can be written[88] by replacing the associated electron densities by the respective electron populations (q_k); viz.,

for nucleophilic attack

$$f_k^+ = q_k(N+1) - q_k(N) \tag{19a}$$

for electrophilic attack

$$f_k^- = q_k(N) - q_k(N-1) \tag{19b}$$

for radical attack

$$f^0(\vec{r}) = \frac{1}{2}[f_k^+ + f_k^-] \tag{19c}$$

To tackle the hard−soft interactions better, local softnesses have been defined as[19,88]

$$s^\alpha(\vec{r}) = Sf^\alpha(\vec{r}) \tag{20a}$$

and

$$s_k^\alpha = Sf_k^\alpha \tag{20b}$$

where $\alpha = +, -$, and 0 refer to nucleophilic, electrophilic, and radical reactions, respectively. A local version of the HSAB principle has been proposed[89,90] in terms of these quantities.

On the other hand, a local electrophilicity has been introduced to analyze the electrophile−nucleophile reactions better. It is defined as[91,92]

$$\omega_k = \frac{\mu^2}{2}s_k^+ = \frac{\mu^2 S}{2}f_k^+ = \omega f_k^+ \tag{21}$$

A generalized version of this quantity has been termed as philicity, which has been defined through the resolution of the identity associated with the normalization of the Fukui function as[93]

$$\omega = \omega\int f(\vec{r})\,\mathrm{d}\vec{r} = \int \omega f(\vec{r})\,\mathrm{d}\vec{r} = \int \omega(\vec{r})\,\mathrm{d}\vec{r} \tag{22a}$$

where

$$\omega(\vec{r}) = \omega f(\vec{r}) \tag{22b}$$

Note that $\omega(\vec{r})$ can provide both ω (using eq 22a) and $f(\vec{r})$ (using eq 22b along with ω obtained from eq 22a) but $f(\vec{r})$ needs an explicit knowledge of ω to give $\omega(\vec{r})$. Moreover, $\omega(\vec{r})$ can provide $s(\vec{r})$, S, and η with an input of μ. The corresponding condensed-to-atom variants may be defined as[93]

$$\omega_k^\alpha = \omega f_k^\alpha; \quad \alpha = +, -, 0 \tag{22c}$$

Equations 20 and 21 dictate eq 22b to be the natural choice. In the place of $f(\vec{r})$, one may use other normalized-to-one quantities such as the shape function, $\sigma(\vec{r}) = \rho(\vec{r})/N$, which, however, may not be a better descriptor due to the lack of information regarding electron addition/removal. Prominent shell structures in the radial distribution of the philicity of halogen atoms are depicted in Figure 4. A strong rationale for the above definition of philicity has been provided recently by Gázquez et al.[59c] They have started[59c] from a functional Taylor expansion of the energy functional followed by the Ayers−Parr type minimization procedure[45] based on the Chattaraj−Cedillo−Parr variational principle[74] to obtain the above definition of philicity[93] and its generalization, $\omega_k^\pm = \omega^\pm f_k^\pm$, strengthening the original definition obtained through the resolution of identity associated with the normalization of $f(\vec{r})$. Of course, the two-parabola model[59c] may not be appropriate in all cases. It may be noted that the condition[59c] $\omega^+ = \omega^- = \omega$ is valid[59d] when there is a transfer of a fraction (noninteger number) of an electron, as is the case[14] with the electrophilicity as opposed to the electron affinity, which involves exactly one electron; hence, the former does not suffer[59d] from the derivative discontinuity problem.[59b]

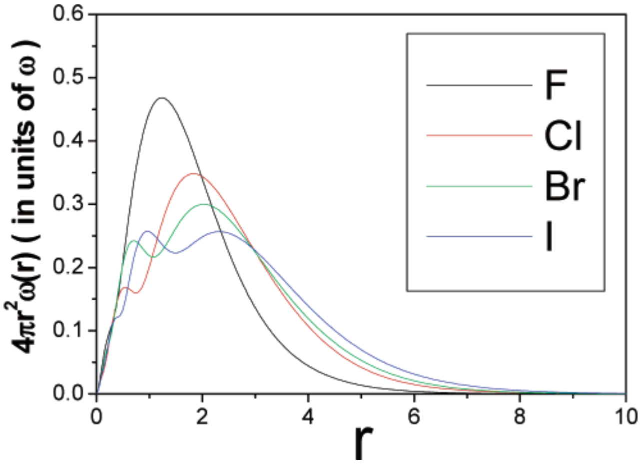

Figure 4. Radial distribution of philicity in the ground states of halogen atoms. Reprinted with permission from ref 93. Copyright 2003 American Chemical Society.

It is important to note that the Fukui function and the related quantities such as s_k^α and ω_k^α may not provide proper reactivity trends for hard−hard interactions,[94−96] as was long ago pointed out by Klopman.[97] Hard−hard interactions are charge-controlled since they are ionic in nature, whereas soft−soft interactions are frontier-controlled because of their covalent nature. The charge-based descriptors would be better suited to tackle the hard−hard interactions.[94−96] Although ambiguous,[63,64] a local hardness has been shown[65] to be a better descriptor of hard−hard reactions than the Fukui function.

3.2. Site Selectivity

An analysis of philicity (ω_k^α) provides the local information of a particular atomic site in a molecule being prone to elctrophilic, nucleophilic, or radical attack.[93] The global electrophilicity of a molecule is determined by these local properties,[91,93,98] as was suggested by Legon[99,100] in his electrostatic model.

The local reactivity of various atomic sites in a molecule can be understood equivalently by f_k^α, s_k^α, or ω_k^α (or its variants proposed by Gázquez et al.[59c]) because S and ω (or $\omega^\pm$) remain the same except for the cases where the molecule is undergoing an intramolecular process such as vibration, internal rotation, rearrangement, and/or interaction with a solvent or an external field where both the local and global descriptors change during the physicochemical process.

Philicity and local softness, respectively, would be better intermolecular reactivity indices (because they are products of global and local indices) than the Fukui function for analyzing electrophile−nucleophile interactions and hard−soft interactions. Recently, some of these aspects have been numerically verified.[101,102] Philicity and local softness essentially provide the same information that is provided by the Fukui function regarding intramolecular reactivity trends except for the intramolecular processes where ω and/or S also changes along with $f(\vec{r})$. However, for analyzing the intermolecular reactivity, f_k^α would be inadequate and s_k^α (or ω_k^α) should be used to compare the hard−soft (electrophilic−nucleophilic) behavior of a given atomic site in one molecule with that of another atomic site in another molecule. For the same molecule, f_k^α is adequate. While f_k^α will take care of reactivity variations on all atoms present in a molecule (and will not be able to differentiate between the reactivities of different molecules), the global quantities (S, ω, $\omega^\pm$, etc.) present in the definition will differentiate between the global reactivity behavior of two (or more) molecules, and hence, the product may be ideal for describing the intermolecular reactivity trends. Moreover, the global reactivity stems from the local reactivities, since $X = \sum_k x_k^a = \sum_k X f_k^a = X \sum_k f_k^a$, where $X = S$, ω, $\omega^\pm$, etc., which implies that a simple addition of reactivities at all atomic sites will provide the global reactivity. In most of the molecules, a single (or a few) atom(s) is (are) overwhelmingly more reactive (with comparatively very large f_k^α values) than the rest and hence will provide an estimate of the global reactivity. Of course, the domain of applicability of ω_k^α (or its variants proposed by Gázquez et al.[59c]) and s_k^α as intermolecular descriptors needs to be analyzed in detail.

During an electrophile−nucleophile interaction process, when two reactants approach each other from a large distance, they feel only the effect of the global electrophilicity of each other and not its local counterpart. The molecule with the larger ω value will act as an electrophile, and the other will behave as the nucleophile. The preferred interaction will be through the most electrophilic site of the former and the most nucleophilic site of the latter. The atom with the largest local electrophilicity value in the electrophile may not necessarily have this value larger than that of the nucleophile, especially when there is more than one active electro(nucleo)philic site present in a molecule. Similar situations arise during an analysis of the corresponding local and global softnesses, and the HSAB principle[34−40] can be at variance with its local counterpart[89,90] in those cases.

4. Electrophilicity Scales

4.1. Global Approach

Ever since Ingold[103] proposed an electrophilicity scale, various experimental and theoretically calculated quantities have been made use of in analyzing the electrophilicity behavior of a group of molecules. Both electrophilicity and nucleophilicity have been estimated[99,100] through hydrogen-bond stretching force constants measured from the rotational spectra of various hydrogen-bonded dimers. The hydrogen bond strength given by k_σ is related to nucleophilicities (N) and electrophilicities (E) as

$$k_\sigma = CNE \tag{23}$$

where C is a proportionality constant. It has been shown that $N \propto 1/E$ for a fixed value of k_σ, as expected. Here, the force constant is considered to be a measure of the binding strength between an electrophile and a nucleophile and is an alternative to the corresponding bond dissociation energy which is conventionally used to describe the electrophilic power. A comparison of E and ω has been made.[98] Activation hardness[104] and protonation energies[105] have been used to analyze electrophilic aromatic substitution reactions.

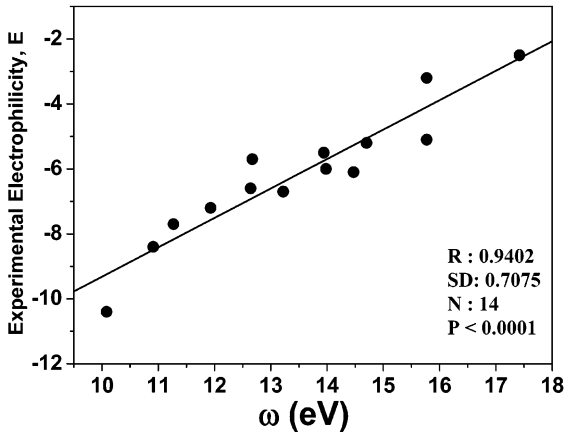

Figure 5. Correlation between experimental electrophilicity (E) and theoretical electrophilicity (ω) of a series of benzene diazonium ion and its derivatives containing a large variety of electron-releasing and electron-withdrawing groups in the *ortho*- and *para*-positions. Reprinted with permission from ref 128. Copyright 2003 American Chemical Society.

One of the most popular electrophilicity scales has been proposed and used to explain diverse types of reactions by Mayr and co-workers.[106−120] They[106−120] have demonstrated through studies on a series of electrophile−nucleophile combination reactions that the absolute rate constants of these reactions follow the following linear free energy relationship,

$$\log k(20\ ^\circ\mathrm{C}) = s(N + E) \tag{24}$$

where E and N are respectively the electrophilicity and nucleophilicity parameters and s is a nucleophile-specific slope parameter. This scale has been argued[121,122] to be the generalization of the Ritchie's scale[123,124] (eq 25) and is applicable to a larger domain

$$\log(k/k_0) = N_+ \tag{25}$$

where k_0 and N_+ are electrophile- and nucleophile dependent parameters, respectively. Mayr's scale is used[125] to analyze the HSAB principle. It has been used by other researchers as well.[91,126−128] Figure 5 shows[128] the linear correlation between E and ω for diazonium ions and their reactivity during interactions with π-nucleophiles.

The carbene-philicity scale (m_{CXY}) proposed by Moss[129−134] on the basis of kinetic data has been shown to be useful in categorizing carbenes[129−138] into electrophilic, ambiphilic, and nucleophilic varieties. There exists a linear free energy relationship between the carbene-philicity and the related Taft substituent parameters. These parameters have been made use of[139,140] in analyzing the connection between skin sensitization and electrophilicity. A comparison between m_{CXY} and ω has been made recently.[141]

The Swain−Scott free energy relationship[142] along with Legon's[99,100] electrophilicity scale have been made use of in analyzing[143] the kinetics and mechanism of oxidation by halogens and inter-halogens vis-à-vis their electrophilicity trends.

As discussed in the previous section, a theoretical electrophilicity index (ω) has been proposed by Parr et al.,[14] prompted by a qualitative finding by Maynard et al.[13,59,144] As electrophilicity and nucleophilicity are physically inverse of each other, the multiplicative inverse ($1/\omega$) (in the spirit of the definition of softness ($S = 1/\eta$)) and an additive inverse ($1 - \omega$) have been proposed[145] as possible definitions of nucleophilicity. Of course, C/ω and ($B - \omega$), where C and B are constants (B may be zero also) for a given series of molecules, may be considered as well. Similar inverse behaviors have been proposed by others.[99,100,146,147] The electrophilicity index (ω) obtained from several models for the charge dependence of the energy[148] within a broad framework of valence state atoms in molecules[149−151] has been reviewed recently.[148] In an interesting study on the nucleophilic substitution reaction of carbonyl compounds, it has been shown[152] that the concerted reaction mechanism will be associated with a large electrophilicity/nucleophilicity gap whereas the corresponding small gap will imply a stepwise reaction mechanism.

Several electrophilicity scales based on different physicochemical properties have been proposed prior to the introduction of the electrophilicity index (ω) rigorously defined by Parr et al.[14] In addition to the Ingold prescription,[103,153] solution phase ionization potentials,[154] ^{13}C NMR chemical shifts,[155−157] IR absorption frequencies,[155,156] charge decompositions,[158] LUMO energies,[159−162] ionization potentials,[163] redox potentials,[164] HPLC,[165] solid-state syntheses,[166] K_e values,[167] isoelectrophilic windows,[168] and the harmonic oscillator models of the aromaticity (HOMA) index[169] are some of the related quantities and subjects that have been used to understand the electrophilic/nucleophilic characteristics of chemical systems.

The various electrophilicity descriptors reported in this section may be broadly classified into three categories: viz., the kinetic descriptor that measures the rate at which an electrophilic attack takes place, the thermodynamic descriptor which measures the ease of such an attack, and a combination of these two approaches through a linear free energy relationship. Among the kinetic scales, the most important is that of Mayr and co-workers.[106−120] They have rank ordered various nucleophiles and electrophiles in terms of their N and E parameters respectively obtained from the associated experimental rate constants. Ritchie's parameters[123,124] or Swain−Scott parameters[142] are similar in spirit. Various quantum chemical and spectroscopic quantities such as LUMO energy,[159−162] ^{13}C NMR chemical shift, ν_{CO} frequencies,[155−157] and charge decomposition[158] have been correlated with the respective rates of the reaction. Thermodynamic electrophilic descriptors are based on the strength of the bond formed between the electrophilic and nucleophilic sites. They include the HOMA index as a measure of aromaticity[169] or other aromaticity indices,[252] bond force constants,[99,100] covalent bonding interaction via an HPLC assay,[165] solid-state synthesis,[166] K_e parameters,[167] LUMO energies,[159,167] hydrophobicities,[168] redox potentials,[164] maximum acceptor superdelocalizabilities,[159] and solution phase ionization potentials.[154] Uses of Hammett or Taft parameters in various linear free energy relationships have also been reported.[13,155,315,316] A linear correlation between the ionization and activation energies for electrophilic additions is also known.[163] Most of these descriptors are empirical in nature, and it is not always possible to transfer the parameters for one class of compounds to the other. The Maynard−Parr electrophilicity index is based on a firm footing. Originally, it was introduced by Maynard et al.[13] as $\omega = \chi^2/2\eta$, when they noticed that, compared to other descriptors, this quantity had a stronger correlation with the logarithm of the experimental rates of the reactions between HIV-1 nucleocapsid p7 zinc finger thiolates and different electrophilic ligands. It has been shown by Parr et al.[14] that the energy change associated with the process of an atom or a molecule in the gas phase becoming saturated with electrons from the environment is given by this quantity and, hence, can be legitimately considered to be a definition for electrophilicity. It may be noted that the basis of the definition given by Maynard et al. is kinetic in nature whereas the interpretation by Parr et al. is thermodynamic in nature.

4.2. Local Approach

The majority of the empirical electrophilicity scales introduced so far are global in nature. Their local variants were developed only recently, and most of them are based on the Fukui function.[66−70,170] An elegant recent review is obtainable in ref 20. Applications of these descriptors in understanding the substituent effects on the electrophilic processes[171−173] and related studies[174−177] highlight the power of these indices. Radical charge-transfer Fukui functions have been used[178] within an atoms-in-molecules (AIM) framework[179] for recognizing the electrophilic and nucleophilic centers in a molecule.

Relative electrophilicity and relative nucleophilicity are defined as s_k^+/s_k^- and s_k^-/s_k^+, respectively.[180] Although they perform better[101,102,180−182] than the Fukui function or local softness on certain occasions, they suffer from various drawbacks.[91,170,175,176,183] In light of the local HSAB principle,[89,90] a softness matching index has been defined[184−186] for analyzing the regioselectivity as

$$\Delta_{ij}^{kl} = (s_i^- - s_k^+)^2 + (s_j^- - s_l^+)^2 \tag{26}$$

when atoms i and j of a nucleophile form a cycloadduct through the atoms k and l of an electrophile. The corresponding philicity[93] related quantity was also reported recently.[187]

Novel reactivity and selectivity indices have been proposed as the integral[188] between the electrophilic Fukui function on one reactant and the nucleophilic Fukui function on the other or a difference[189] between two such functions. A similar integral index appears in quantum similarity studies also.[190] The effect of excess nucleophilicity over electrophilicity or vice versa (in a group sense) has been analyzed in the context of all-metal aromaticity/antiaromaticity and a possible molecular electronics.[189]

Local softness[19,88] and local electrophilicity[91−93] also perform well in analyzing regioselectivity. Figures 6 and 7 depict the beautiful correlations[91] between the experimental electrophilicity and respectively the global and local electrophilicities of a series of benzhydryl cations.

Li and Evans[191,192a] have restated the local HSAB principle[89,90] as, "For the soft−soft reactions the site with the maximum value of the Fukui function is preferred and the preferred site for the hard−hard interactions is that with the corresponding minimum value". The ambiguity in local hardness is felt in the local version of the HSAB principle.[89,90a] Minimization of a local grand potential is ad hoc.[90b] Even the minimization of energies of individual atoms does not necessarily lead to the minimization of the overall energy of the molecule. While the Gázquez−Méndez[89,90a] version considers similar Fukui function (FF) values for preferred interactions, the Li−Evans[191] principle dictates the preference of soft−soft interactions in the maximum FF site whereas the minimum FF site is the best for the hard−hard interactions.

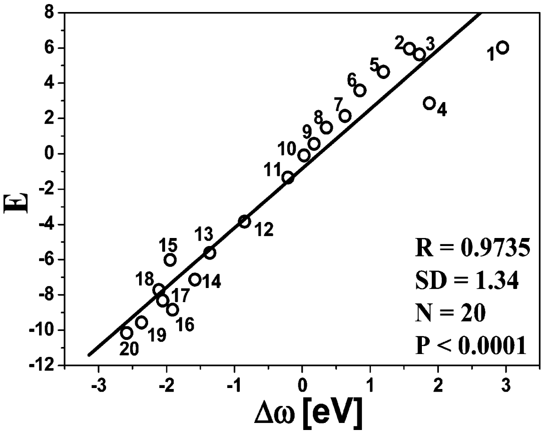

Figure 6. Correlation between the experimental electrophilicity (E) and the theoretical relative electrophilicity ($\Delta\omega$) of a series of benzhydryl cations. Reprinted with permission from ref 91. Copyright 2002 American Chemical Society.

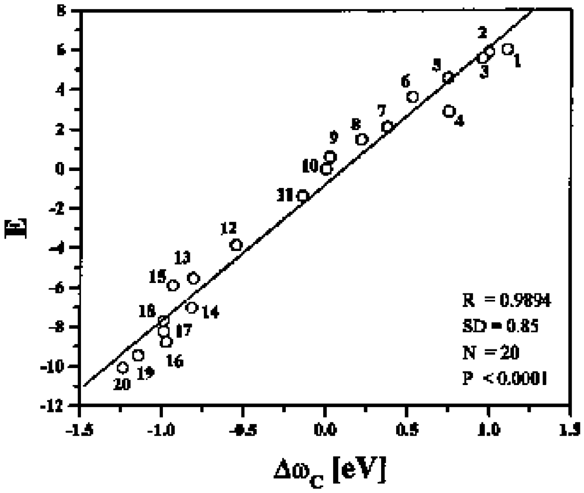

Figure 7. Correlation between the experimental electrophilicity (E) and the theoretical relative local electrophilicity ($\Delta\omega_C$) of a series of benzhydryl cations. Reprinted with permission from ref 91. Copyright 2002 American Chemical Society.

However, it has been argued[94,95] that the site with the minimum FF is the least reactive and, in the absence of a proper local hardness, hard reactions are to be analyzed in a different fashion at the local level. Of course, the minimum Fukui function condition may be used as a "tiebreaker" in some specific strongly electrostatically controlled reactions.[192b−d] Since hard interactions are electrostatic in nature, the Fukui function has been argued to be a poor descriptor for these reactions.[94] Charges[94−96,193] or associated quantities[65,194] such as molecular electrostatic potentials and local hardnesses are supposed to provide a better description for hard reactions.

Other quantities used for this purpose include the 1s electron energy of nitrogen in the substituted aniline,[195] the average local ionization energy,[196,197] pair-site nonlocal interactions,[198] electron localization functions,[199,200] etc. Nuclear Fukui functions[201−203] and electrofugality[204] have also been introduced.

5. Intramolecular and Intermolecular Reactivity Patterns

5.1. Periodicity

The concepts of atomic shell structure and chemical periodicity as proposed by Mendeleev form the cornerstone of chemical education. A periodic law may be stated as:[205] "The properties of chemical elements and their compounds are periodic functions of the atomic numbers of the elements". Atoms with completely filled shells and subshells are often relatively more stable and less reactive when compared with their open-shell counterparts. As expected from the principles of maximum hardness (MHP)[41−48] and minimum polarizability (MPP),[53−56] hardness increases along a period and decreases along a group whereas polarizability decreases along a period and increases along a group.[48,206,207] Alkali metals are the softest and the most polarizable while noble gases are the hardest and the least polarizable.[206,207] Electrophilicity also exhibits characteristic periodic oscillations with maxima on halogens, which are most electronegative and least nucleophilic as well.[206,207] As shown in Figure 8, the variation of $[\partial\omega/\partial N]$ for neutral atoms mimicks[207] that of μ because of the small values[208] of $\gamma = {}^1/_3[\partial\eta/\partial N]_{\upsilon(\vec{r})}$.

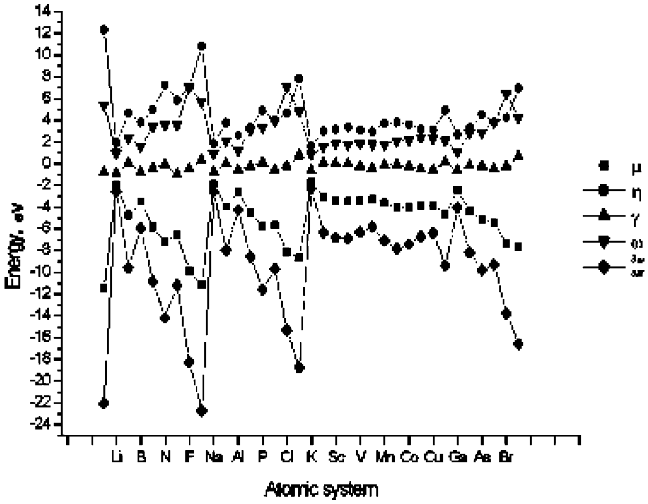

Figure 8. Variation of μ, η, γ, ω, and $\partial\omega/\partial N$ for neutral atoms from He to Kr. Reprinted with permission from ref 207. Copyright 2003 American Chemical Society.

5.2. Excited States

Through the excited-state DFT calculations on atoms and molecules in various electronic states which happen to be the lowest state of given symmetry[209−211] or in ensembles of states[212−215] (along with the related penalty-function-based formalisms[216]), it has been shown[217−220] that, "A system is harder and less polarizable in its ground state than in any of its excited states and an increase in the excited state contribution in a two state ensemble makes the system softer and more polarizable". This fact is in conformity with MHP and MPP, since an atom or a molecule is generally more reactive in its excited state. For example, the S (α) values (in au) of He atom in different electronic states are as follows:[218] (^{1}S, 1.51 (1.86); ^{1}P, 6.89 (117.92); ^{1}D, 13.09 (728.71); ^{1}F, 21.95 (3536.36)). And the α (η) values (in au (eV)) of HF molecule are as follows:[220] ($\sigma^2\pi^4$, $^1\Sigma^+$, 5.86 (10.8); $\sigma^2\pi^3\sigma^1$, $^3\Pi$, 38.4 (4.97); $\sigma^2\pi^3\sigma^1$, $^1\Pi$, 39.5 (3.91)). Even in time dependent situations[40,221−225] involving excited states including Rydberg states,[226−228] this fact remains valid.

Any system is generally less electronegative in its excited state.[145] The behavior of electrophilicity in the excited state in comparison to that in the ground state, however, will depend completely on the relative variations in χ and η upon electronic excitation, although both of them often decrease.

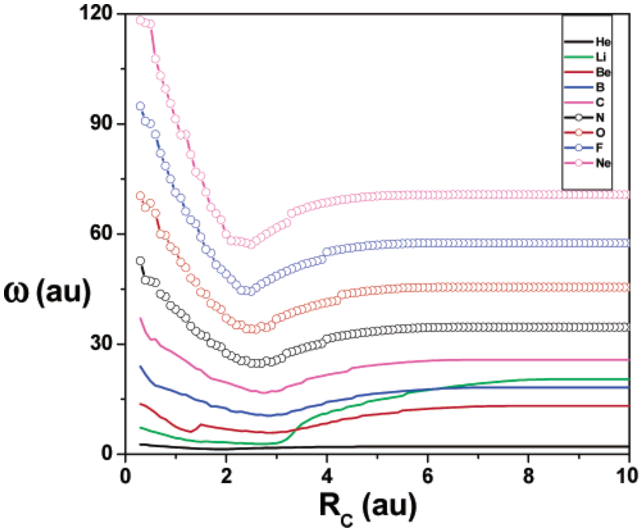

Figure 9. Plot of electrophilicity index (ω) versus cutoff radius (R_C) for atoms (He, Li, Be, B, C, N, O, F, Ne) confined in a spherical box. Reprinted with permission from ref 230. Copyright 2003 American Chemical Society.

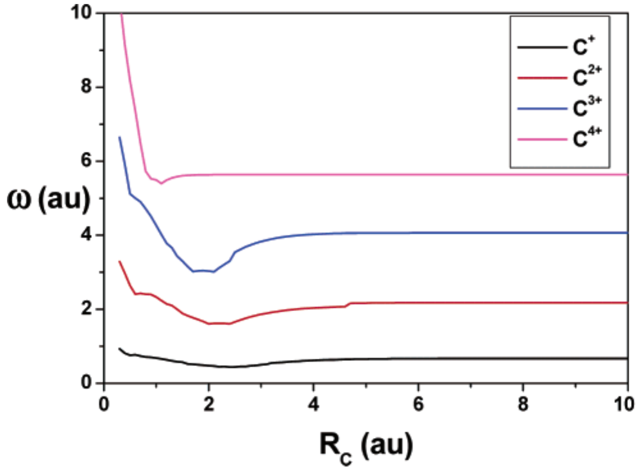

Figure 10. Plot of electrophilicity index (ω) versus cutoff radius (R_C) for ions (C^{n+}; $n = 1, 2, 3, 4$) confined in a spherical box. Reprinted with permission from ref 230. Copyright 2003 American Chemical Society.

For example, the χ (η, ω) values (in au) of He atom in different electronic states at the beginning of the process are as follows:[145] ($^1S(1s^2)$, 0.2591 (0.3920, 0.0856); $^1P(1s2p)$, 0.2044 (0.1315, 0.1589)).

5.3. Spherical Confinement

The concept of confined quantum mechanical systems stems from the idea of simulating the effect of pressure on atoms or molecules by confining them in impenetrable spherical boxes.[229] Numerical Hartree−Fock calculations with Dirichlet boundary conditions of various global reactivity descriptors of several atoms and ions have revealed[230−232] that all systems become harder and less polarizable with an increase in pressure. The inverse relationship $\eta \propto 1/\alpha^{1/3}$ remains valid when the confinement volume is decreased. Electrophilicity is not very sensitive[230] (Figures 9 and 10) to confinement except for very small cutoff radii, where it increases abruptly. Variations of ω with the atomic number (section 5.1) and degree of ionization (more positive charge implies more electrophilic) remain unaltered for all possible extents of confinement.

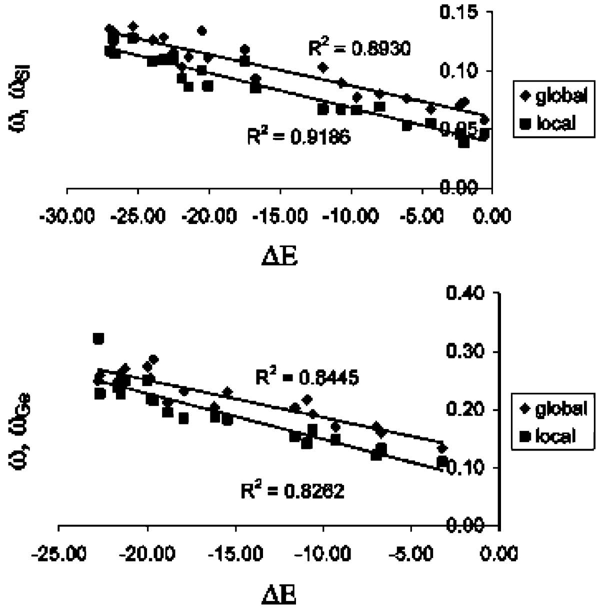

Figure 11. Plots of global (ω) and local (ω_{Si} and ω_{Ge}) electrophilicities of silylenes and germylenes versus their reaction energies (ΔE) with a Lewis base such as NH_3. Reprinted with permission from ref 147. Copyright 2005 American Chemical Society.

5.4. Chemical Processes

Both global and local electrophilicities have been found to be helpful in analyzing the reactivity and selectivity behavior of various chemical compounds as well as the reaction mechanisms of diverse classes of chemical processes. A plethora of systems have been studied including pentazolato complexes of the first row transition metals,[233] diazonium ions,[128] carbonyl carbons,[234] fluorine substituted disilanes,[235] carbenes,[141,236] Fischer-type chromium−carbene complexes,[237] copper clusters,[238] zeolites,[239] group-14 elements and related functional groups,[60] aliphatic amines,[240] alkanes,[241] silylenes and germylenes,[147] cobalt porphyrins and related aza derivatives,[242] highly hindered polyanionic chelating ligands,[243,244] organorhenium[245] and organoneodymium complexes,[246] and thiadiazolium salts.[187] Figure 11 clearly reveals[147] the power of global and local electrophilicities through beautiful linear variation of the reaction energy with these quantities associated with the complexation reactions of silylenes and germylenes with ammonia.

Intermolecular reactivity of carbonyl compounds has also been studied[247] using the group philicity. The importance of a theoretical analysis of the philicity−electrophilicity behavior in providing an effective synthetic protocol has been highlighted.[243,244] The connection between the electrophilicity[136,137] index and aromaticity[248−253] as well as superacidity[254−259] (superelectrophilicity) has been analyzed. Global electrophilicity values need not always correlate[253] with the nucleus independent chemical shift values,[260] which characterize the magnetic aspects of aromaticity.

The stability and reactivity of azametallocenes have been studied[233] in terms of their global electrophilicity (ω) values, which corroborate the fact that the charge transfer from the ligand to the metal makes the aromatic pentazolato ligand more electrophilic. Similar studies on aza derivatives of cobalt porphyrin have revealed[242] that an increase in the number of aza-N atoms renders an electrophilicity enhancement at the cobalt center of the cobalt porphyrin complex. The presence of electron-withdrawing substituent groups on the carbonyl carbon atom in phenyl acetates has been shown[234] to drive the nucleophilic attack at those carbon centers through the enhancement of electrophilicity. Studies on Fischer-type chromium−carbene complexes have highlighted[237] that their electrophilicity is reduced due to the presence of π-donor substituents because the acceptor orbital in carbene gets occupied by π-donation. Similar behavior has been reported for silylenes and germylenes as well.[147] Among the pyridyl substituted bis-coumarins, the para-compound is the most electrophilic wheareas the ortho-isomer is the least electrophilic.[246] In the corresponding neodymium complexes, the carbonyl oxygen is the most favorable site for the electrophilic attack in comparison to the hydroxyl oxygen, the lactone oxygen, or the nitrogen atoms.[246] However, for metal coordination in the double-deprotonated compound, both carbonyl and hydroxyl oxygen sites become favorable sites for electrophilic attack.[246] Similar analysis on organorhenium complexes[245] shows that 2,2′-azobis(5-chloropyrimidine) ligand (L) is a better π-acceptor than the 2,2′-azobispyridine ligand (L) in the dinuclear radical anion complexes: $\{(\mu\text{-L})[\mathrm{Re(CO)_3Cl}]_2\}$. Electrophilicity remains more or less constant for most of the fluorine substituted disilanes.[235] Neutral copper clusters, on the other hand, exhibit odd−even oscillations,[238] as evidenced by experiments and theoretical calculations. Odd clusters are more electrophilic, are softer, and have the capacity to attain a closed shell configuration by accepting electrons. Adsorption of small molecules and cracking of hydrocarbons in zeolites are properly accounted for by the philicity.[239] Theoretical calculation of ω using spin−orbit interactions for halogens and group 14 atoms can reproduce the experimental trend of a monotonic decrease in electrophilicity by going down the group.[60] Global and local electrophilicities can properly reproduce the experimental electrophilicity/nucleophilicity patterns of diazonium ions,[128] aliphatic amines,[240] carbonyl compounds,[234,240] thiadiazolium salts,[187] etc. This is also true in most of the other cases described above. As is demonstrated in the case of highly hindered polyanionic chelating ligands, sometimes the theoretical values even suggest[243,244] possible efficient synthetic protocols.

The main classes of reactions for which the mechanisms have been analyzed in terms of global and local electrophilicities comprise 1,3-dipolar cycloaddition reactions,[261−267] specific cycloaddition reactions such as Diels−Alder reactions[183,268−275] with varied diene−dienophile pairs, and other cycloaddition reactions.[276−281] A typical Diels−Alder reaction will follow a nonpolar pericyclic mechanism if the electrophilicity difference between the diene and the dienophile is small whereas a polar mechanism will be followed for a large value of this difference.

Cycloaddition reactions constitute the most widely studied pericyclic processes where two π-components approach to form two new σ-bonds within a cyclic framework. In the Diels−Alder-type cycloaddition reactions, a diene and a dienophile interact to form a six-membered ring product. Considerable enhancement in the rates of these reactions has been noticed in the diene−dienophile pair with an electron-withdrawing substituent in one and an electron-releasing substituent in the other. It is expected that the difference in their global electrophilicity values will provide important insights into the associated reaction mechanism. Pericyclic processes with a nonpolar mechanism are characterized by a small electrophilicity difference of diene and dienophile whereas a large difference leads to a polar mechanism in the corresponding ionic processes. Use of the Maynard−Parr electrophilicity index and its local variant in understanding these aspects has been attempted mainly by Domingo and co-workers. In the normal electron demand reactions, the presence of electron-withdrawing groups in the dienophile increases the reaction rates of the associated Diels−Alder reactions. In these reactions, the charge transfer is from the diene−nucleophile to the dienophile−electrophile. However, in the inverse electron demand-type reactions, an electron-withdrawing substituent is present in the diene and/or an electron-releasing substituent is present in the dienophile, so that the charge gets transferred from the dienophile to the diene. Rank ordering of various dienes and dienophiles as electrophiles or nucleophiles has been done so that the reaction mechanism for a given pair may be ascertained at the beginning.[275] Cycloaddition reactions with large ionic character involving large electrophilicity differences include the reactions between 2-methylfuran and a masked *o*-benzoquinone,[277] substituted butadienes and ethylenes,[183] Lewis acid coordinated 2-(trimethylsilyloxy)acrolein and furan,[278] etc., whereas those with a nonpolar mechanism include the concerted [4+2] process between 2-azadiene and cyclopentene/propene,[272] the concerted [3+2] process between benzonitrile oxide and ethynyl/propynylboronate,[265] etc. This analysis allows one to devise a strategy so that the changes in the nature of the substituents in the dienes/dienophiles or changes of the reaction conditions, including the presence of a Lewis acid catalyst or a polar solvent, may change a nonpolar concerted process to a polar stepwise process. This causes an enhancement in the rate of the reaction and, in turn, of the yield of the corresponding kinetically controlled products. Several related experimental trends are understood through the electrophilicity analysis. They include Lewis acid catalyzed [4+2] and [4+3] cycloadditions between cyclopentadiene and arylidenoxazolones,[280] 1,3-butadienes and dimethyl acetylenedicarboxylate,[281] *N*-acyl-1-aza-1,3-butadienes and vinylamines,[273] nitroalkenes and aluminum derivatives of vinyl ethers,[274] butadiene derivatives and acetone,[270] and cyclopentadiene and cyanoethylenes.[269] Problems associated with this analysis in explaining inverse electron demand Diels−Alder reactions have also been reported.[271] It has been argued[271] that they are due to the inadequacy of the frontier molecular orbital theory.

Similar electrophilicity-based analysis has been extended to a variety of 1,3-dipolar cycloaddition reactions with a variety of dipole/dipolarophile pairs. Larger electrophilicity differences correspond to faster reactions.[264] Polar regioselective reactions between nitrile/azomethine ylide and methyl acrylate/propiolate have been properly accounted for by the relative global and local electrophilicities between dipoles and dipolarophiles.[267] The regio- and stereoselectivity of various 1,3-dipolar cycloaddition reactions, such as that between hindered thiocarbonyl ylides and tetracyanoethylene,[266] nitrile oxide and anthracene/acridine,[279] *C*-(methoxy carbonyl)-*N*-methyl nitrone and methyl acrylate/vinyl acelate,[263] 5-ethoxy-3-p-(S)-tolylsulfinyl furan-2(5H)-ones and diazoalkanes,[262] etc., have been shown to be in conformity with those predicted by the relative electrophilicity patterns. This approach is found to be more reliable[279] than the frontier molecular orbital theory.

Rank ordering of various dienes−dienophiles/dipoles−dipolarophiles may be summarized as in the following scheme.[264,275]

Large ω	Small ω
Strong electrophile (weak nucleophile): electron-poor dienophile (e.g. acrolein) and dipolarophile (e.g. nitroethylene) in a normal electron-demand (NED) reaction	*Weak electrophile (strong nucleophile): electron-rich diene (e.g. 1-methoxy-1,3-butadiene) and dipole (e.g. azides) in an NED reaction*
For inverse-electron-demand (IED) reactions: Local philicity (ω_k) or a group philicity would be a better descriptor to identify the electron releasing (withdrawing) substituent on the dienophile (diene)/ dipolarophile (dipole).	

The following scheme provides a guideline toward the possible reaction mechanism associated with a given Diels–Alder/1,3-dipolar cycloaddition reaction.[97,264,275]

$\Delta\omega$

(diene/ dienophile or dipole/ dipolarophile interacting pair)

Small	**Large**
Non polar, pericyclic, concerted process, frontier-controlled, soft-soft interactions e.g. Ethylene/1,3-butadiene reaction	***Polar, ionic, stepwise process, charge-controlled, hard-hard interactions e.g. N—methylmethylene ammonium cation/1,3-butadiene reaction***

For Lewis-acid catalyzed reactions: Increased ω of the electron-poor component: dienophile (NED reaction)/ diene (IED reaction)

Apart from these major types of reactions, the electrophilicity concept at both the global and the local levels has been used to analyze a wide variety of chemical processes. They include oxidation of thiophenes,[282] catalytic olefination of carbonyl compounds[283] and polyhaloalkanes,[284] reduction of formylchromones,[285] hydride transfer reaction in 1-methyl nicotinamide-lumiflavine,[286] formaldehyde decomposition,[287a] intermolecular ligand exchange in alkyltin trihalides,[287b] dissociation of HS$^-$ (HCN),[287c] discoloration of titanylporphyrin,[287d] nucleophilic addition to carbon–carbon double bonds,[288] Friedel–Crafts benzylation and acylation reactions,[289] metalation of oxazolines,[290] oxidation of thiols,[291] alkaline hydrolysis of *N*-phenylacetamides,[292] ene reactions of nitroso compounds,[293] aminolysis of thiocarbonates,[294] etc. The main theme of these studies is to identify a reactant which will act as an electrophile (larger ω value) or another to behave as a nucleophile (smaller ω value). Apart from the thermodynamic information content of ω as shown in Figure 11, it has been shown to possess enough kinetic information as well.[288,289,294]

Global ω values of nitroso compounds suggest that during their reactions, such as ene reactions, they behave[293] as good nucleophiles similar to singlet oxygen and triazolinediones. Their electrophilicity stems from the fact that their HOMOs are formed through high energy antibonding combination of lone pairs of N and O centers and are orthogonal to their low energy π^* LUMO. The energy change associated with the rate-determining step of the alkaline hydrolysis of *N*-phenylacetamides has been shown to decrease with an increase in their eletrophilicity values.[292] An electrophilicity analysis of oxidation of thiols by cobalt N$_4^-$ complexes reveals that azaporphyrins are very good electron acceptors during the oxidation process, which gets improved in the presence of polar solvents.[291] The behavior of chloromethyl derivatives toward metalation can be rationalized.[290] Quantitative linear relationships between the experimental rate constants and the Maynard–Parr electrophilicity index and/or its local counterpart have been obtained for the Friedel–Crafts reactions,[289] nucleophilic addition involving the C=C double bond,[288] and aminolysis of thiolcarbonates and dithiocarbonates.[294] The reactivity patterns associated with formaldehyde decomposition,[287] intermolecular ligand exchange in alkyltin trihalides,[287] hydride ion transfer,[286] etc. have been properly analyzed in terms of the electrophilicity index or its variants.

5.5. Solvent Effects

To understand the effect of a solvent on electrophilicity, a variation of ω (eq 12) up to first order has been written by Pérez et al.[295] as

$$\Delta\omega(1\rightarrow\epsilon) = (\mu/\eta)\Delta\mu - \frac{1}{2}(\mu/\eta)^2\Delta\eta = \Delta\omega^{(1)} + \Delta\omega^{(2)} \tag{27}$$

where ϵ is the dielectric constant of the medium and $\Delta\mu$ and $\Delta\eta$, respectively, describe the variation in μ and η when the system goes from the gas phase to the solution.

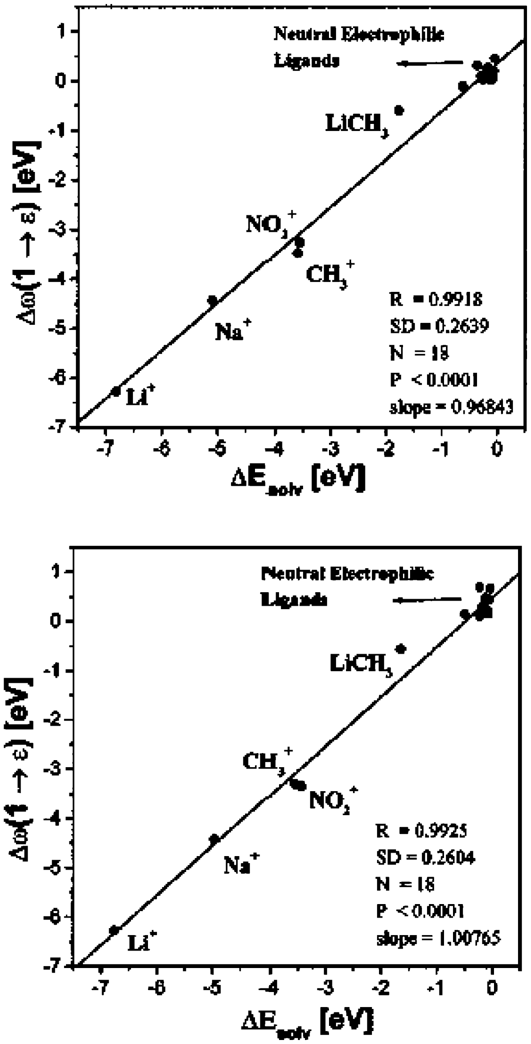

Figure 12. Plots of electrophilicity changes versus solvation energy of a series of both charged and neutral electrophilic ligands. Reprinted with permission from ref 295a. Copyright 2001 American Chemical Society.

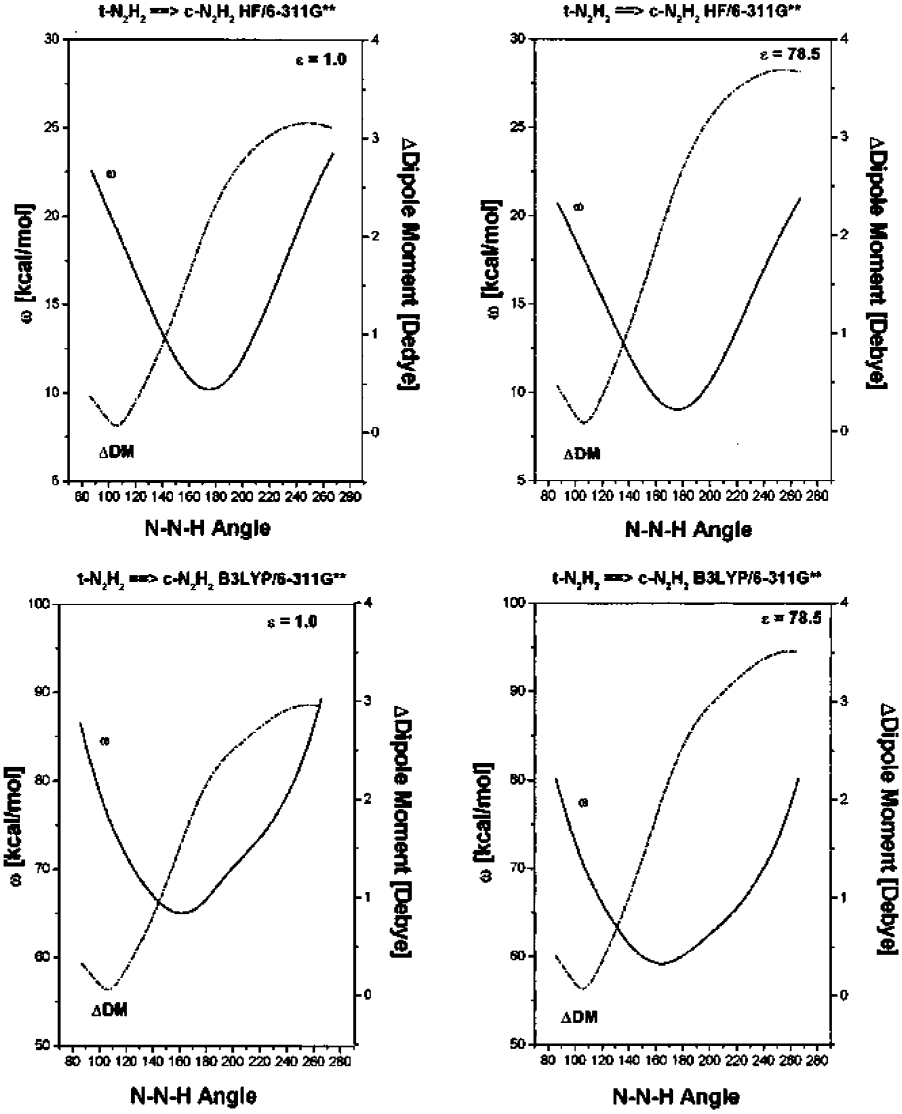

Figure 13. Variation of the electrophilicity index and the dipole moment in a vacuum and solvent along the reaction path of the intramolecular rearrangement reaction: *trans*-N_2H_2 → *cis*-N_2H_2. Reprinted with permission from ref 300. Copyright 2001 American Chemical Society.

The insertion energy, ΔE_{ins}, of the solute going to solvent is defined as twice[296−298] the energy of solvation, ΔE_{solv}, i.e.

$$\Delta\omega^{(1)}(1\rightarrow\epsilon) = \left(\frac{\Delta E}{\Delta N}\right)_{\nu(\vec{r})}\left(\frac{\Delta N}{\Delta\mu}\right)_{\nu(\vec{r})}\Delta\mu \approx \Delta E_{\text{ins}} = E(\epsilon) - E(\mathbf{1}) = 2\Delta E_{\text{solv}} \quad (28)$$

The second term of eq 27 becomes

$$\Delta\omega^{(2)}(1\rightarrow\epsilon) = \frac{\mu}{\eta\Delta N}E_{\text{solv}} \quad (29)$$

A linear relation[295] between $\Delta\omega(1\rightarrow\epsilon)$ and ΔE_{solv} for a series of both neutral and charged electrophilic ligands as shown in Figure 12 highlights the authenticity of this approach.

A somewhat similar and related analysis has been presented in refs 299 and 300. In these papers, the effects of solvent on two intramolecular rearrangement reactions, viz., *trans*-N_2H_2 → *cis*-N_2H_2 and F_2S_2 → FSSF, have been studied.[299,300] It has been demonstrated that solvation makes the reactions more favorable both thermodynamically and kinetically. As shown in Figure 13 for the N_2H_2 rearrangement, ω passes through[300] an extremum at the transition state (TS) for both the reactions and both the phases although the dipole moment does not always pass through an extremum at the TS. In both the cases, the solvation decreases the electrophilicity.

The reactivity of several systems has been studied to gain insights into the solvation effects on both global and local electrophilicities. Charged peroxides,[301] cyclopropane ring opening in duocarmycin SA derivatives,[302] various electron donors,[154] aliphatic amines,[240] different organometallic compounds,[303] carbonyl compounds,[304] dye−redox mediator reactions,[305] etc. have been studied for this purpose. In general, the reactions become easier to perform in the solution phase, with some exceptions.[306] The effects of the solvent are more pronounced for the global electrophilicity than for its local variant.

5.6. External Field Effects

The reactivity of a chemical system changes drastically in the presence of an external field. This field may be an explicit external electromagnetic field or it may arise due to the presence of another molecule (reagent/reactant) and/or a solvent. The nuclear Coulomb potential in the parent molecule being experienced by its electrons would get augmented by the potentials generated due to the electrons and nuclei present in the reactant/reagent/solvent molecules in addition to the possible electron transfer between them. All these effects, including any external electromagnetic field, can be simulated by the presence of an external generic field. An explicit dynamical study on the variation of chemical reactivity in the presence of an external electric field will be discussed in section 7.

Changes in molecular reactivity and selectivity due to the presence of an applied uniform electric field are analyzed.[307] The internal electrostatic field of the molecule plays a crucial role in determining the chemical reactivity when the strength of the external field is low. However, at larger field strengths, significant variation in reactivity has been observed.[307]

Since any quantum system can be completely characterized by its number of electrons (N) and the external potential ($v(\vec{r})$), variation in any property of that system, including its chemical reactivity, may be analyzed by changing N and $v(\vec{r})$. For example, the change in chemical potential may be written as[19]

$$d\mu = \eta\, dN = \int f(\vec{r})\, dv(\vec{r})\, d\vec{r} \tag{30}$$

For a uniform electric field $E(\vec{r})$ it may be written as

$$d\mu = \eta\, dN - \int f(\vec{r})\, E(\vec{r}')\, d\vec{r}\, d\vec{r}' \tag{31}$$

Therefore, the changes in chemical potential would be directly proportional to the strength of the external field when there is no charge transfer. It has been shown[307] that μ and ω get significantly altered when the external field strength is increased. The effect of the external field is only marginal in the case of η, which implies that the second-order variation in the energy due to external perturbation is less than the corresponding first-order variation. A dynamical variant of this will be analyzed in section 7.

Local reactivity indices such as the Fukui function and the philicity have been shown[307] to change drastically in the presence of the external field. It may be noted that the variation of f_k^{α} and ω_k^{α} are not similar because the global electrophilicity also changes in this case. All these changes become more pronounced as the number of atoms in the molecule and the external field strength increase.

The effects of the external potential variation on reactivity and regioselectivity have been analyzed within variational[308] as well as perturbative[309,310] frameworks. A cooperative effect of the solvent and surface together to increase the reactivity has also been reported.[311]

5.7. Biological Activity and Toxicity

There has been a recent upsurge of interest in unraveling the connection between electrophilicity and biological activity, especially toxicity, mutagenicity, and carcinogenicity in different chemical, biological, and biochemical systems,[312,313] to broaden the applicability of the associated quantitative structure activity relationships (QSAR). Most of these analyses are qualitative in nature with more interpretive power and relatively less predictive potential. Based on these newly acquired ideas, strategies for rational drug designs have been developed. Relationships have been shown between electrophilicity and allergic contact dermatitis,[314] including skin sensitization,[315,316] the activity of phase 2 enzyme and glutathione in protecting mammalian cells from malignancy,[317] the toxicity of organic chemicals to *Tetrahymena pyriformis*[159] and *Chlorella vulgaris*,[318] glutathione S-transferase induction by *tert*-butylhydroquinone,[319] the mutagenicity and DNA damaging potential of *N*-acyloxy-*N*-alkoxymides,[320a] DNA alkylation of duocarmycins,[320b] the antioxidant activity of quercetin[321a] and catechin,[321b] the antitumor and antibacterial activity of kinamycins and lomaiviticin A,[322a] the antileukaemic activity of phenol,[322b] etc.

Similar studies have been performed in showing the importance of the electrophilicity concept in analyzing the role of methylidene imidazolone as an electrophilic prosthetic group,[323] aquatic toxicity,[160,161] polymeric surfactants as glutathione transferase mimics,[319,324] charged phenyl radical activity toward nucleic acid components,[325] in vitro trypanocidal activities of some typical heterocyclic quinones,[326] the importance of the standard-helix motif in biological hydrolysis,[327] the function of the Michaelis complex of pI258 arsenate reductase,[328] the behavior of zinc fingers related to retroviral activity,[164] suppression of breast cancer,[329] HIV-1 nucleocapsid protein p7,[59,144] *Escherichia coli* Ada protein,[144] etc.

The toxicity of polychlorinated biphenyls has been studied[330,331] through the profiles of electrophilicity and philicity in both gas and solution phases. Figure 14 depicts the variation of these quantities for 2,2′,5,5′-tetrachlorobiphenyl as a function of the torsional angle. High rotational energy barriers do not allow the toxin to rotate freely in a real environment so that it can interact with the cellular component of a living system.[330−333] Therefore, toxicity is related to the low rotational barrier. A comparison between the rotational energy profile and those of the hardness and the polarizability clearly delineates[330,331] that the high toxicity of PCBs is related to the minimum η value and the maximum α value, as expected from the MHP and the MPP. The electrophilicity is often maximum in those conformations. The most active toxic sites are identified through the philicity profiles.

The biological activities of various testosterone derivatives in terms of relative binding affinity (RBA), androgenic potency, relative androgenic activity, therapeutic index, TeBG affinity, relative competition indices, binding affinity for rat ventral prostate receptor protein, and myotrophic to androgenic potency in temporal as well as some estrogen derivatives quantified in terms of their RBA values have been shown[334] to correlate strongly with the electrophilicity index, suggesting it to be a suitable descriptor of the biological activity of these systems.

The toxicity of polychlorinated dibenzofurans (PCDFs) and dibenzo-p-dioxins (PCDDs) has been correlated with the electrophilicity index. The correlation is reasonably good.[335] However, a combination of electrophilicity and philicity drastically improves the situation,[336] as is authenticated by the analysis of the toxicity of various electron-donor- and electron-acceptor-type toxins, measured by their $pIGC_{50}$ data, toward *Tetrahymena pyriformis*. It also highlights the importance of charge transfer between a toxin and a biosystem for an overall understanding of toxicity. Experimental toxicity values (pIC_{50}) of a variety of polyaromatic hydrocarbons[337] such as PCDFs, PCDDs, and polychlorinated biphenyls (PCBs) as well as those of several aliphatic amines[336] correlate well with the corresponding toxicity values calculated using the HF energy along with the global and local electrophilicities.

To avoid collinearity and overfitting, pIC_{50} values of several electron acceptor toxins such as PCDFs and PCBs are correlated with only one parameter, ω, and for the donor

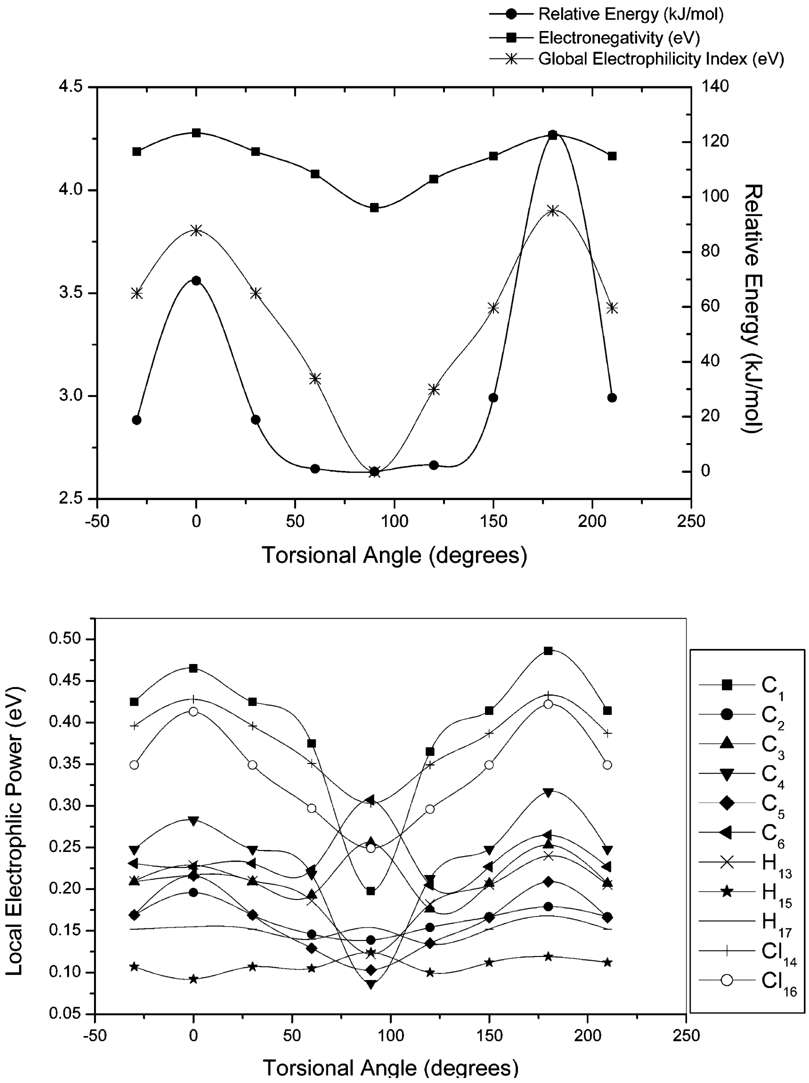

Figure 14. Variation of relative energy, electronegativity, global electrophilicity index, and local electrophilic power of 2,2′,5,5′-tetrachlorobiphenyl with the torsional angle. Reprinted with permission from ref 330. Copyright 2003 American Chemical Society.

toxins such as aliphatic amines and amino alcohols, the related pIGC$_{50}$ values are correlated with the related maximum local nucleophilicity values to obtain beautiful correlations.[336b] The regression model is more robust[336b] for acceptors than for donors. For example, the regression equations for 171 acceptors comprising saturated alcohols, diols and halogenated alcohols, mono and diesters, carboxylic and halogenated acids, aldehydes, and ketones and for 81 donors comprising unsaturated, α-acetylenic and amino alcohols and amines with toxicity toward *Tetrahymena pyriformis* are as follows:[289c]

Acceptors:

$$\text{predicted (pIGC}_{50}) = 1.000(0.020) \times \text{observed (pIGC}_{50}) - 1.708 \times 10^{-11}(0.019)$$

$$R^2 = 0.937, R_{\text{CV}}{}^2 = 0.936, \text{SD} = 0.241, N = 171$$

Donors:

$$\text{predicted (pIGC50)} = 1.000(0.036) \times \text{observed(pIGC}_{50}) - 1.044 \times 10^{-10}(0.039)$$

$$R^2 = 0.904, R_{\text{CV}}{}^2 = 0.899, \text{SD} = 0.232, N = 81$$

The number of carbon (non-hydrogenic) atoms, N_C (N_{NH}) may be considered to be a crude alternative[336c] to the *n*-octanol/water partition coefficient (corresponding log *P*, also correlated[336d] to N_C/N_{NH}) in developing QSAR/QSTR models which can be further improved[334b,336c] by adding ω and/or its local counterpart ($\omega_k{}^\alpha$) as well as charges on the relevant atoms (q_k). Of course, N_C/N_{NH} is lot more easy to obtain than log *P*. Several recent publications highlight the importance of electrophilicity in understanding biological processes and obtaining QSAR/QSTR models.[334,336a−k] Although N_C/N_{NH}/log *P* can be used for a broad spectrum of molecules, $\omega/\omega_k{}^\alpha/q_k$ depends on the electronic environment and hence should be applied to a group of congener molecules,[336l] as was done[336a] for nine acceptor groups and four donor groups separately.

In this section, the electrophilicity patterns related to chemical periodicity, the excited state reactivity, confined systems, and various intermolecular and intramolecular processes, including solvent and external field effects and biological activity, have been reviewed. The Maynard−Parr electrophilicity index and its local variants not only support the trends expected from chemical intuition but also provide new directions in analyzing reaction mechanisms of a diverse class of chemical reactions.

6. Variation of the Electrophilicity Index during Physicochemical Processes Such as Vibrations, Internal Rotations, and Chemical Reactions

6.1. Molecular Vibrations

It is important to know how the chemical reactivity of a molecule changes when it undergoes vibration, internal rotation, or chemical reaction. To analyze specifically the behavior of the electrophilicity index (ω, eq 12) in this regard, one starts from a first-order derivative of it as follows[207,338]

$$\frac{\partial\omega}{\partial\lambda} = \frac{\mu}{\eta}\left(\frac{\partial\mu}{\partial\lambda}\right) - \frac{1}{2}\left(\frac{\mu}{\eta}\right)^2\left(\frac{\partial\eta}{\partial\lambda}\right) \tag{32}$$

where λ may be a bond length (stretching), bond angle (bending), dihedral angle (internal rotation), or reaction coordinate (chemical reaction).

The extremal behavior of ω results from that of μ and η. If both μ and η are extrema (also constants or having inflection points), ω will be an extremum, and at that point the following condition will be satisfied:

$$\frac{\partial\mu}{\partial\lambda} = \frac{\mu}{2\eta}\left[\frac{\partial\eta}{\partial\lambda}\right] \tag{33}$$

So the extremum of electrophilicity will occur when the slopes of the changes in μ and η are of opposite signs, because $\mu < 0$ and $\eta > 0$, owing to the convexity in energy. Therefore, ω will be a minimum (maximum) when both μ and η are maxima (minima).[207,300,338]

Various global reactivity descriptors of water, ammonia, and ethane have been calculated[338] for their equilibrium geometries as well as the distorted geometries originating from displacements along normal coordinates of vibration. The extremal analysis made above has been found to be true. For H_2O and NH_3, the minimum energy−maximum hardness−minimum electrophilicity criteria for the equilibrium geometry have been shown[338] to be true when compared with corresponding quantities for displacements along all allowed normal modes. For C_2H_6, however, it is not true for a few normal modes because μ does not possess the maximum value where η is maximum in those cases.

6.2. Molecular Internal Rotations

It has been observed[339] during the internal rotation of the hydroxylic group of the enol form of guanine that the stable conformations are associated with minimum energy, maximum hardness, and minimum electrophilicity values, as would have been expected from the above analysis. The corresponding transition states have been shown to be the most electrophilic. This fact is confirmed[338] for the internal rotations of formamide, which is not obvious for hydrogen peroxide. Figure 15 depicts the profile of the maximum amount of charge transferred[339] during the internal rotation of the enol group of guanine, which mimicks the corresponding electrophilicity behavior, as expected. As shown[147] in Figure 11, energy and electrophilicity show a strong linear correlation in this case as well. Internal rotation of the phenyl group induces the reactivity in *trans*- and *cis*-phenyldiazene. For both isomers, the planar conformers are the most electrophilic and transition states are the least electrophilic (the cis-isomer has a maximum ω value in one of the TSs), which accounts for the extra electronic delocalization in the transition states.[340] This unexpected behavior may be rationalized[338] by the fact that both μ and η are maxima at the TS.

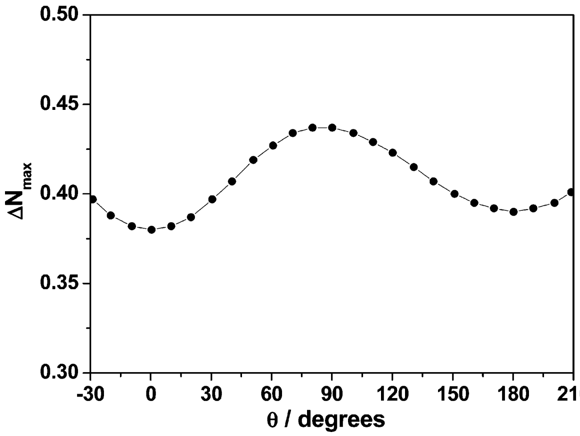

Figure 15. Profile of the maximum charge transferred during the internal rotation of the hydroxylic group of the enol form of guanine. Reprinted with permission from ref 339. Copyright 2003 American Chemical Society.

6.3. Chemical Reactions

In the intramolecular rearrangement reactions, *trans*-N_2H_2 → *cis*-N_2H_2 and F_2S_2 → FSSF, it has been shown that (μ, η, ω) values at the TS are respectively (maximum, minimum, minimum) and (minimum, minimum, maximum), as depicted in Figure 13. The behavior of the latter reaction is as expected. To gain further insights into the former reaction where μ is maximum and η is minimum, one needs to analyze[207] the following second derivative

$$\frac{\partial^2\omega}{\partial\lambda^2} = \frac{1}{\eta}\left(\frac{\partial\mu}{\partial\lambda}\right)^2 + \frac{\mu^2}{\eta^3}\left(\frac{\partial\eta}{\partial\lambda}\right)^2 - 2\frac{\mu}{\eta^2}\left(\frac{\partial\mu}{\partial\lambda}\right)\left(\frac{\partial\eta}{\partial\lambda}\right) + \frac{\mu}{\eta}\left(\frac{\partial^2\mu}{\partial\lambda^2}\right) - \frac{1}{2}\frac{\mu^2}{\eta^2}\left(\frac{\partial^2\mu}{\partial\lambda^2}\right) \tag{34}$$

Since the first derivatives are zero at the extremal points, the exact nature of the extremal (maximum or minimum) in ω at the TS would be governed by the relative magnitudes of the last two terms of the above equation for this type of reaction or where μ is minimum and η is maximum at the TS.

Figures 16−18 represent[207] some more interesting cases respectively in the CNH → HCN isomerization reaction, oxygen to oxygen proton transfer in HO−C(=O)−C(=S)−OH, and oxygen to sulfur proton transfer in HS−C(=O)−C(=S)−OH thioxalic acid derivatives, highlighting the validity of the above analysis. Similar findings on 1,3-intramolecular proton-transfer reactions in HXNY → XNYH (X, Y = O, S) have also been reported.[341a]

If μ^2 does not change significantly (or decreases) and η increases (cf. MHP), the minimum electrophilicity ($\omega = \mu^2/2\eta$) criterion may be attached to a favorable chemical process. In many exchange reactions, one of the products is the least electrophilic (among the reactants and the products) and the average product electrophilicity is less than the average reactant electrophilicity,[341b] which may be termed as the minimum electrophilicity principle, as suggested by the preceding analysis.[207,300,338] Even for various isomers, the hardest one would be the least electrophilic,[341c] when the μ^2 behavior is as mentioned above, and hence will be the most stable.

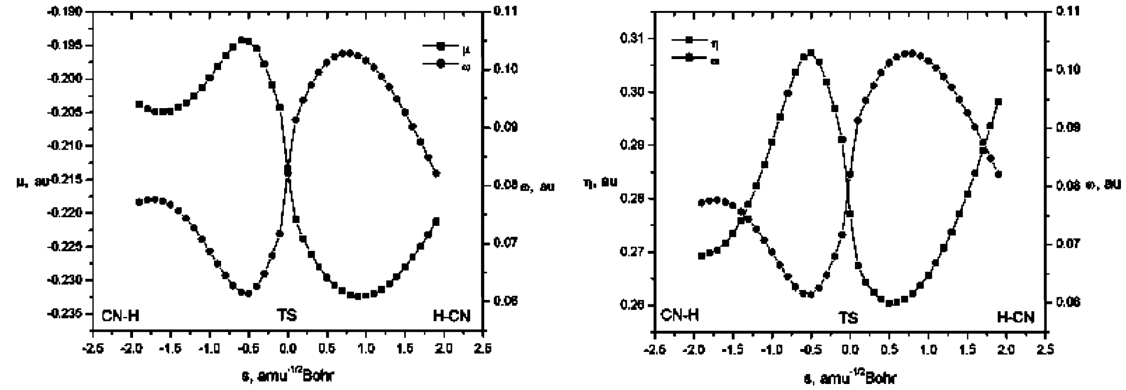

Figure 16. Variation of the chemical potential, hardness, and electrophilicity along the reaction path of the CNH → HCN isomerization reaction. Reprinted with permission from ref 207. Copyright 2003 American Chemical Society.

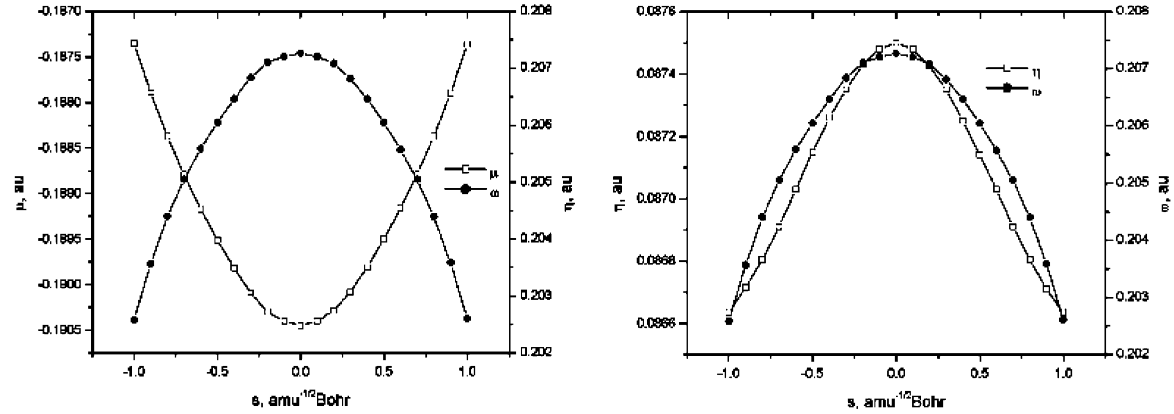

Figure 17. Variation of the chemical potential, hardness, and electrophilicity along the reaction path of the symmetric oxygen to oxygen proton-transfer reaction in the HO—C(=O)—C(=S)—OH system. Reprinted with permission from ref 207. Copyright 2003 American Chemical Society.

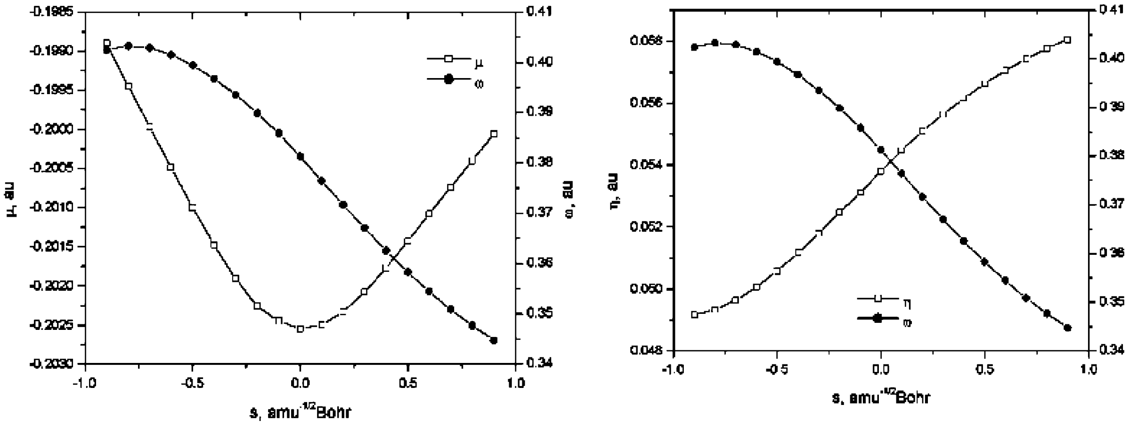

Figure 18. Variation of the chemical potential, hardness, and electrophilicity along the reaction path of the sulphur to oxygen proton transfer in the HS=C(=O)—C(=S)—OH system. Reprinted with permission from ref 207. Copyright 2003 American Chemical Society.

A thorough study has been performed to analyze the profiles of global and local reactivity descriptors during vibration, internal rotation, and chemical reaction.[342] Most of the characteristics discussed in this section are found to be valid. Variations in the Fukui functions and the atomic charges along the reaction path have also been studied.[96] This analysis[96] highlights the failure of the Fukui function and the usefulness of the charges in explaining hard−hard interactions.[94−97]

Figures 19 and 20 present the profiles of various local reactivity descriptors,[343] including $\omega_{F_a}{}^-$ and $\omega_{F_b}{}^-$, along the reaction path (IRC) of the gas-phase S_N2 substitution: $F_a^- + CH_3{-}F_b \rightarrow F_a{-}CH_3 + F_b^-$. In ref 343 the Mulliken charges were made use of. The corresponding populations are used in Figures 19 and 20. Local reactivity descriptors pass through a point of inflection in the transition state. This inflection point coincides with the saddle point of the reaction and provides a link between bonding and reactivity. For a thermoneutral reaction, similar profiles for the bond-making and the bond-breaking processes intersect at the transition state. The importance of these local descriptors is vindicated through a comparison with the profiles of standard indicators such as energy and bond order. Free F_a^- is more reactive to start with, and it gradually becomes less reactive as it

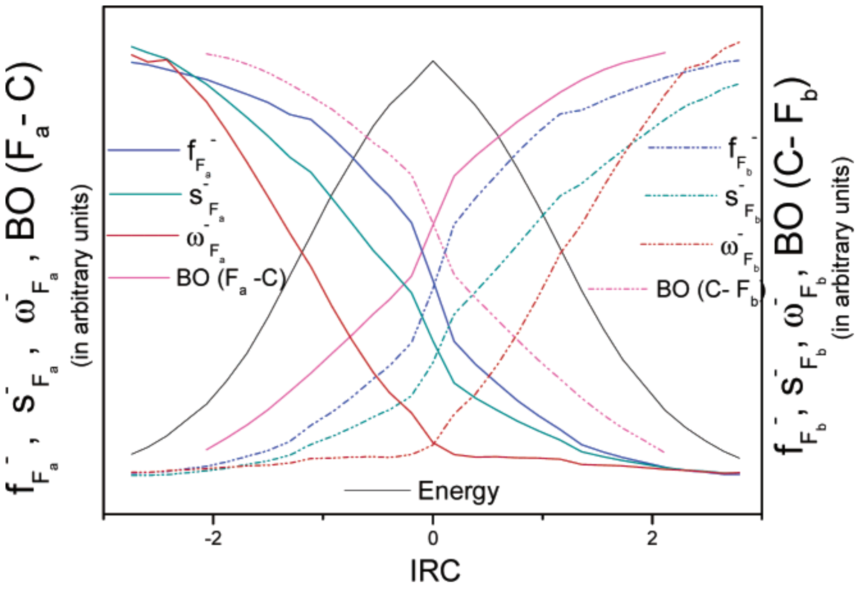

Figure 19. Profiles of f_{Fa}^- ($f = f, s, \omega$), f_{Fb}^- ($f = f, s, \omega$), the bond order (BO), and the energy along the reaction path of the gas-phase S_N2 substitution: $F_a^- + CH_3{-}F_b \rightarrow F_a\text{-}CH_3 + F_b^-$. Reprinted with permission from ref 343. Copyright 2005 American Chemical Society.

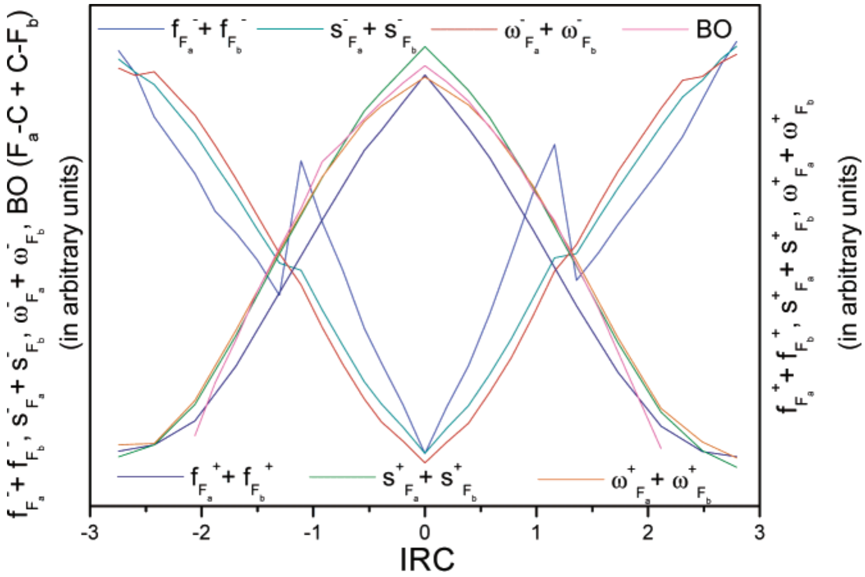

Figure 20. Profiles of $f_{Fa}^- + f_{Fb}^-$ ($f = f, s, \omega$), $f_{Fa}^+ + f_{Fb}^+$ ($f = f, s, \omega$), and the bond order (BO) along the reaction path of the gas-phase S_N2 substitution: $F_a^- + CH_3{-}F_b \rightarrow F_a{-}CH_3 + F_b^-$. Reprinted with permission from ref 343. Copyright 2005 American Chemical Society.

becomes bonded. On the other hand, bonded F_b^- is the least reactive at the beginning, and it becomes more and more reactive as it is released during the course of the reaction to have the most reactive free F_b^-. At the transition state, both F_a^- and F_b^- are equally reactive, as expected for a thermoneutral reaction.[343] Much work is needed in obtaining a more transparent view of how bonding, reactivity, and dynamics complement one another.

7. Dynamical Variants

7.1. Quantum Fluid Density Functional Theory

As discussed in section 3, two important time dependent density-based quantum mechanical theories are quantum fluid dynamics (QFD)[82] and the quantum theory of motion (QTM).[83] The quantum domain behavior of classically chaotic systems has been studied by using these theories.[344,345] Time dependent density functional theory (TDDFT)[346,347] strengthens them. According to TDDFT, which offers a time dependent extension to the original Hohenberg−Kohn theorems, the mapping between the time dependent external potential, $v(\vec{r},t)$, and the density, $\rho(\vec{r},t)$, is uniquely invertible up to an additive trivial time dependent function in the potential. This implies that all the properties of a system are functionals of $\rho(\vec{r},t)$ and the current density $j(\vec{r},t)$, whose time evolution for any many-electron system is governed by two basic QFD equations:[346,347] viz., the equation of continuity,

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \vec{j} = 0 \tag{35a}$$

and a Euler-type equation of motion

$$\frac{\partial \vec{j}}{\partial t} = P[\rho(\vec{r},t), \vec{j}(\vec{r},t)] \tag{35b}$$

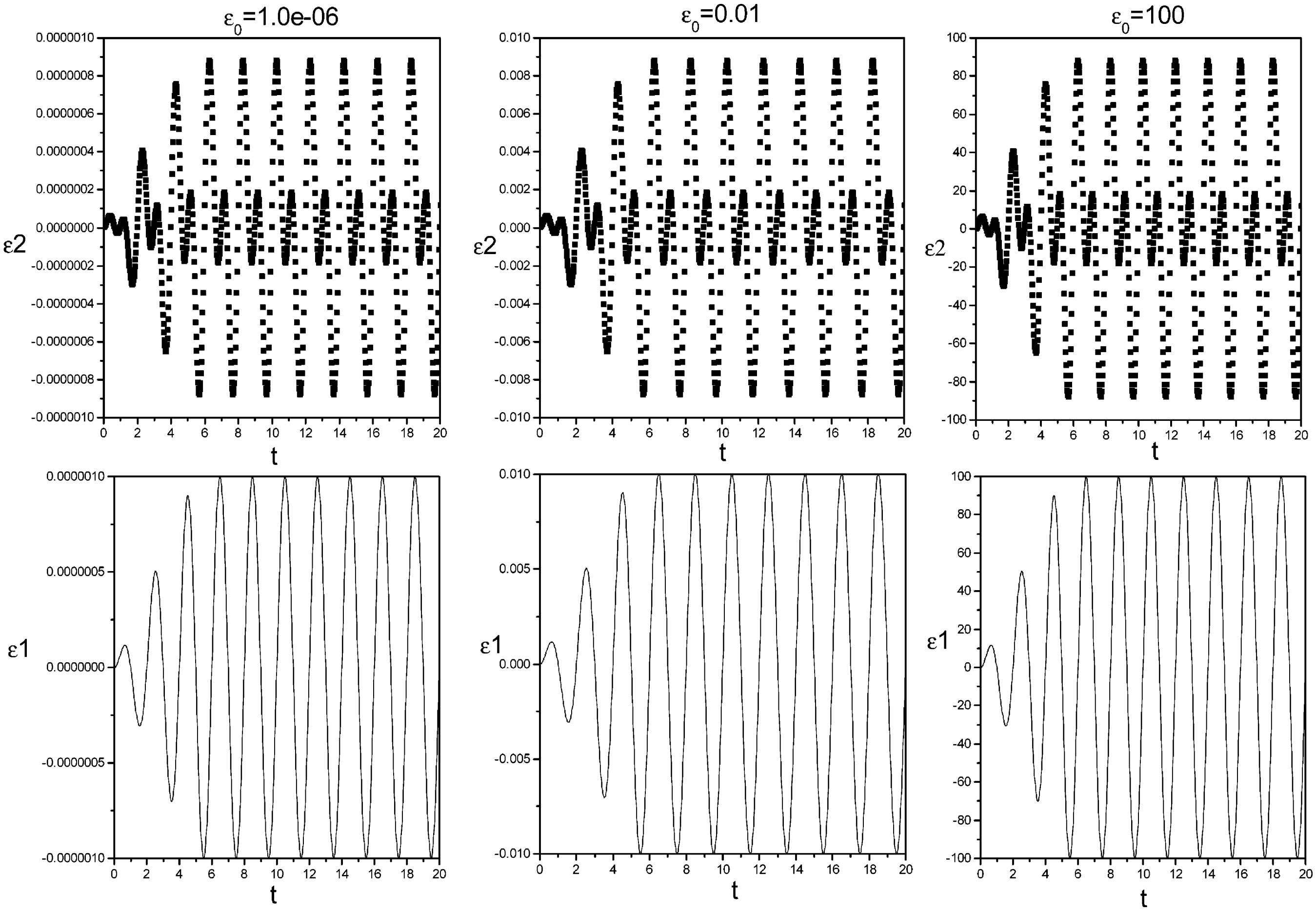

Figure 21. Time evolution of the external electric field with different colors and intensities. Reprinted with permission from ref 145. Copyright 2001 American Chemical Society.

where P is a functional whose form cannot be ascertained from TDDFT. To have an approximate form for P, a quantum fluid density functional theory (QFDFT)[222,224,348−351] has been proposed via an amalgamation of TDDFT and QFD. The basic equation in QFDFT is a generalized nonlinear Schrödinger equation (GNLSE) as follows (in a.u.),

$$\left[-\frac{1}{2}\nabla^2 + v_{\text{eff}}(\vec{r},t)\right]\Phi(\vec{r},t) = i\frac{\partial\Phi(\vec{r},t)}{\partial t} \qquad (36a)$$

where the effective potential may be written as

$$v_{\text{eff}}(\vec{r},t) = \frac{\partial T_{\text{NW}}}{\partial\rho} + \frac{\partial E_{\text{xc}}}{\partial\rho} + \int\frac{\rho(\vec{r}\,',t)}{[\vec{r} - \vec{r}\,']}\,\mathrm{d}\vec{r}\,' + v_{\text{ext}}(\vec{r},t) \qquad (36b)$$

where T_{NW} and E_{xc} are the non-Weizsäcker part of the kinetic energy and the exchange-correlation energy functional, respectively. The density and the current density are related to $\Phi(\vec{r},t)$ as follows

$$\rho(\vec{r},t)\ |\Phi(\vec{r},t)|^2 \qquad (37a)$$

and

$$\vec{j}(\vec{r},t) = [\Phi_{\text{re}}\nabla\Phi_{\text{im}} - \Phi_{\text{im}}\nabla\Phi_{\text{ie}}] \qquad (37b)$$

This GNLSE has been alternatively derived via a stochastic quantization[348] and has been solved to study ion−atom collisions[348,349] and atom−field interactions.[350,351] As discussed in section 5, these two processes may be considered to mimic the external perturbation a molecule experiences during a chemical reaction.

7.2. Atom−Field Interactions

The external potential, $v_{\text{ext}}(\vec{r},t)$ in GNLSE (eq 36b) of this problem has been written[145,350,351] for an atom in its ground and excited electronic states interacting with a z-polarized laser field of varying intensities and colors. Figure 21 presents the time dependence of the external field for three different field intensities for monochromatic and bichromatic pulses. The time evolution of μ and η shows that the in-phase oscillations are observed only when the external field intensity becomes appreciable. To start with, the electron density will have a spherical distribution due to the central nature of the nuclear Coulomb field. A tug-of-war between this and an axial laser field will begin once the latter is switched on. It has been shown[145] that η is less sensitive than μ. Only when the strength of the external laser field is large enough to overcome the effect of the nuclear field do the in-phase oscillations in the reactivity parameters start. The electron density becomes cylindrical, and an oscillating dipole results. Figures 22 and 23 clearly delineate[145] these aspects in the plots of time dependent ω and $1/\omega$, respectively. At the very large field intensity, the difference in response of μ and η is manifested in these plots. A corresponding analysis on the Rydberg states of hydrogen and helium atoms provides important insights into their chaotic ionization.[226−228]

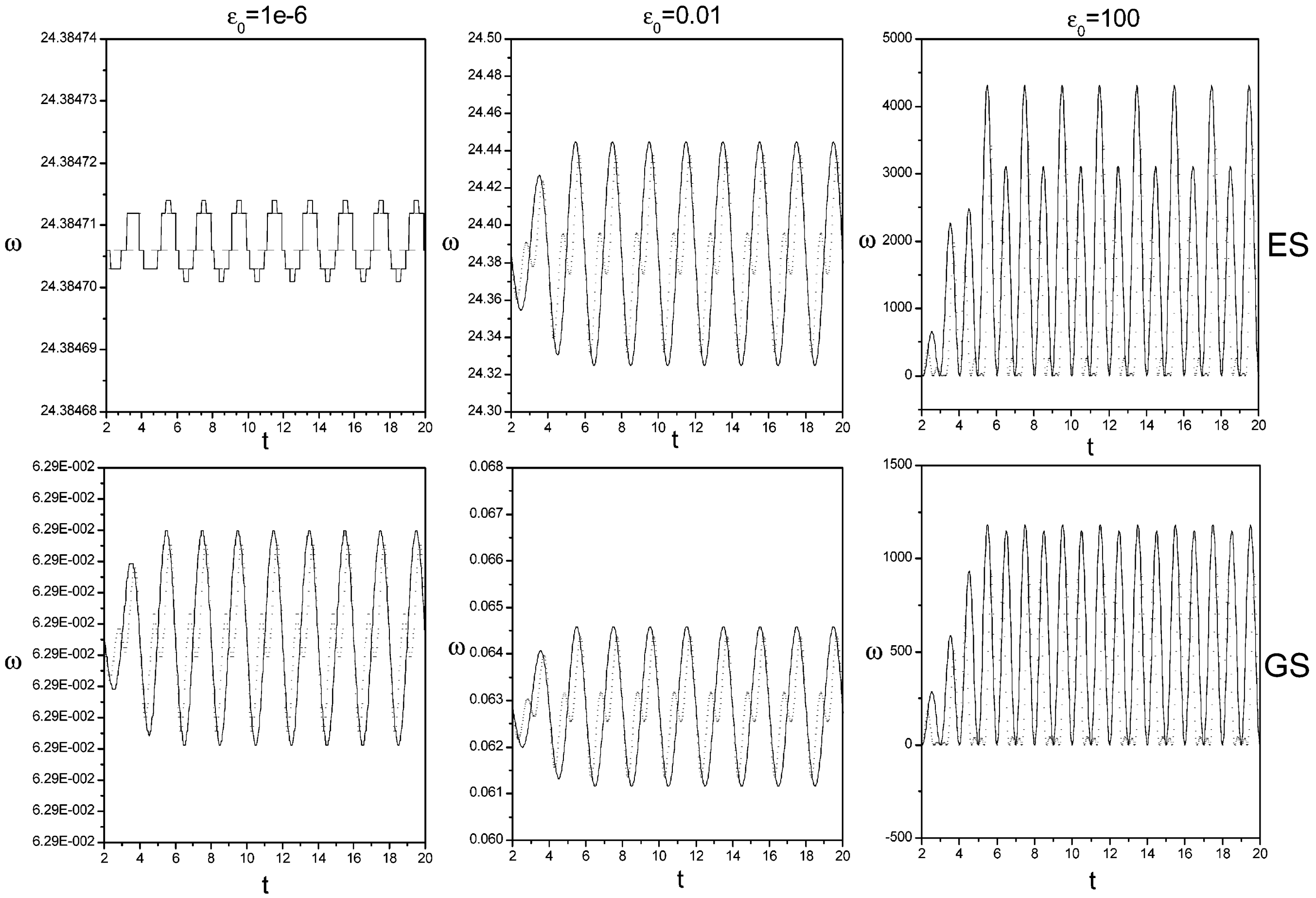

Figure 22. Time evolution of electrophlicity index (*ω*) of a helium atom in ground and excited states in the presence of external electric fields with different colors and intensities. Reprinted with permission from ref 145. Copyright 2001 American Chemical Society.

7.3. Ion–Atom Collisions

For the ion−atom collision problem, $v_{\mathrm{ext}}(\vec{r},t)$ comprises the electron−nuclear attraction potentials originating from the target and the projectile nuclei.[40,55,56,221−225,348,349] Figures 24−26 present the time evolution[40] of μ, η, and α, respectively, for a collision between a proton and an X-atom/ion (X = He, Li^+, Be^{2+}, B^{3+}, C^{4+}) in various electronic states. The dynamic μ profile has been shown to divide the whole collision process into three distinct regimes: viz., approach, encounter, and departure. In the encounter regime, the actual reaction takes place where η maximizes and α minimizes, showing the validity of the MHP and MPP in a dynamical situation. The HSAB principle also has revealed itself in action, and the associated regioselectivity of a reaction has been analyzed.[40,222] The dynamic ω profile resembles that of μ for different projectile velocities and impact parameters in both ground and excited states[232] and hence is not shown here.

7.4. Chemical Kinetics

Ever since Maynard et al.[13] pointed out the linear relationship between the logarithm of the rate coefficients and the electrophilicity index associated with the reactions between HIV-1 nucleocapsid protein p7 and several electrophilic reagents, there has been a renewed interest in analyzing this behavior for a variety of reactions. Hydrolysis of carbenium ions,[352] Friedel−Crafts reactions,[5,289] aminolysis of thiocarbonates,[294] etc. have been studied for this purpose. Figure 27 depicts a representative plot for a series of thiocarbonates reacting with piperidine.[294]

In general, these correlations are obtained for a set of molecules of similar chemical reactivity and often the outliers are to be removed for obtaining a meaningful correlation.[289b] A linear correlation between the rate constant and ω has also been proposed.[234] Both logarithmic[294,353] and linear[253,352] relations between the Hammett constant and the electrophilicity index have been reported. The experimental Hammett substituent constant correlates well[353] with its theoretically calculated electronic contribution for a series of substituted alkenes, as shown in Figure 28.

Some other related studies include those on reactivities of carbon-centered radicals,[354] dienophiles,[271] carbon−carbon double bonds,[288] metal polypyridyl complexes,[305] and some radicals toward hydrogen abstraction.[355] A slightly different version of Parr et al.'s definition has been used for the calculation of absolute rates of atom abstractions by radicals[356,357] as well as ultrafast excited-state proton transfer.[358] The quality of the leaving groups has been quantified[204a] in terms of electrofugality and nucleofugality, which help in analyzing the reactivities associated with electrophilic and nucleophilic processes. Electro- (nucleo)philicity may be considered to be a kind of inverse of nucleo- (electro)-fugality.[118,204] Although there have been some[204a−g] attempts in this regard, it needs to be analyzed whether we are

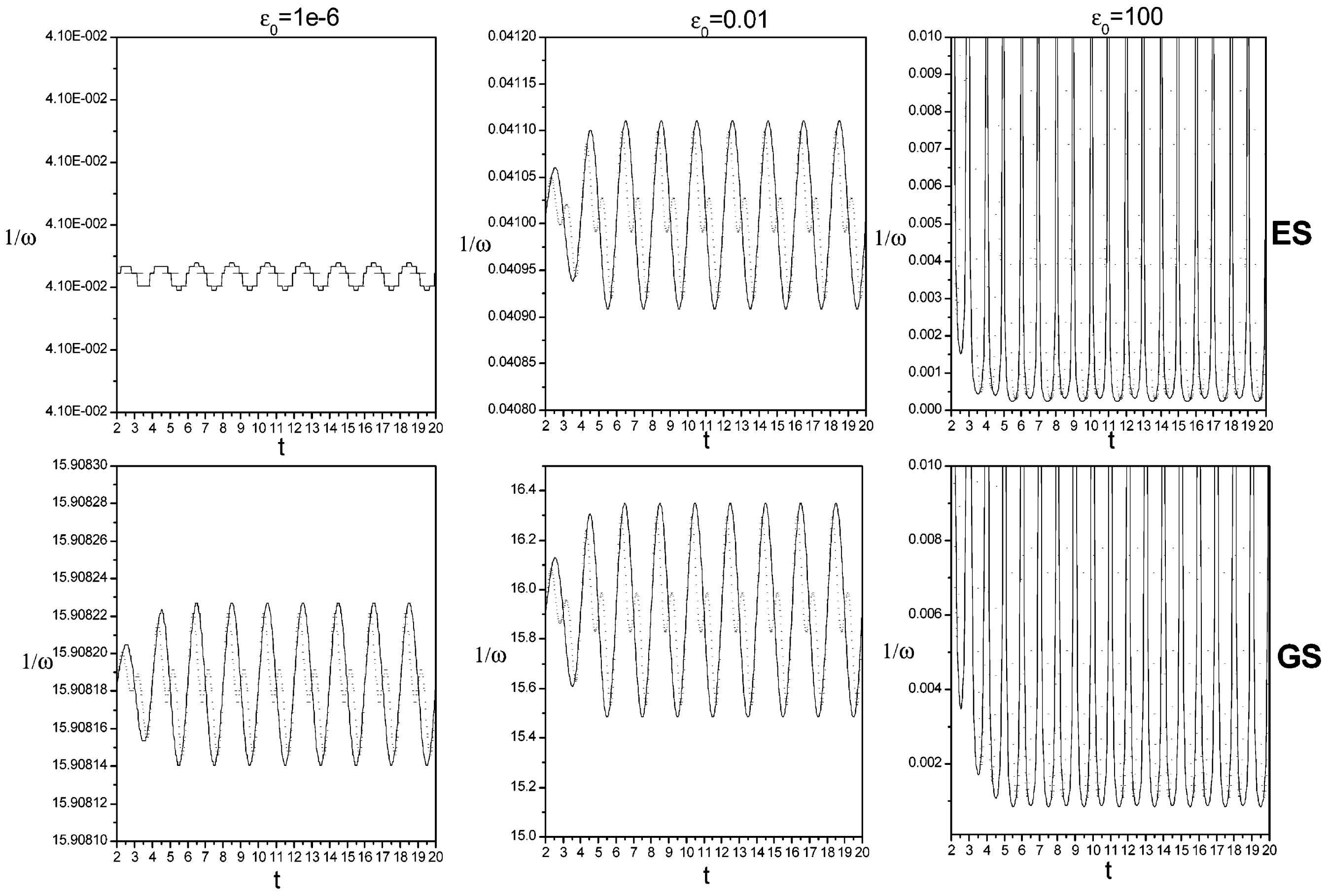

Figure 23. Time evolution of nucleophlicity index (1/*ω*) of a helium atom in ground and excited states in the presence of external electric fields with different colors and intensities. Reprinted with permission from ref 145. Copyright 2001 American Chemical Society.

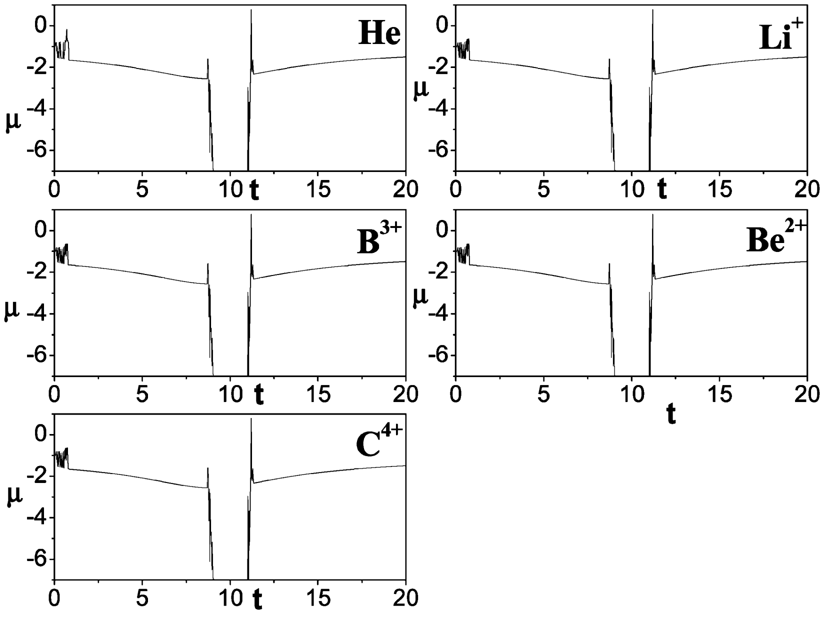

Figure 24. Dynamical chemical potential profile during a collision process between an X-atom/ion (X = He, Li^+, Be^{2+}, B^{3+}, C^{4+}) in its ground state and a proton. Reprinted with permission from ref 40. Copyright 2003 American Chemical Society.

comparing thermodynamic and/or kinetic properties.[1−3] It is also necessary to study whether a good electrophile or a poor nucleophile will be a good nucleofuge and vice versa. As was pointed out,[204a] it has been numerically verified that the definition is not always useful.[204f]

8. Spin Dependent Generalizations

8.1. $\{N, N_s, v(\vec{r})\}$ Representation

The reactivity and selectivity descriptors defined so far are inadequate in the study of reactions involving changes

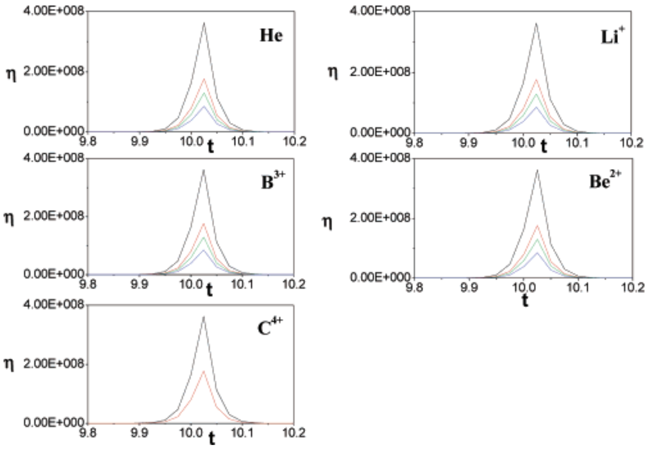

Figure 25. Dynamical hardness profile during a collision process between an X-atom/ion (X = He, Li^+, Be^{2+}, B^{3+}, C^{4+}) in various electronic states and a proton. Reprinted with permission from ref 40. Copyright 2003 American Chemical Society.

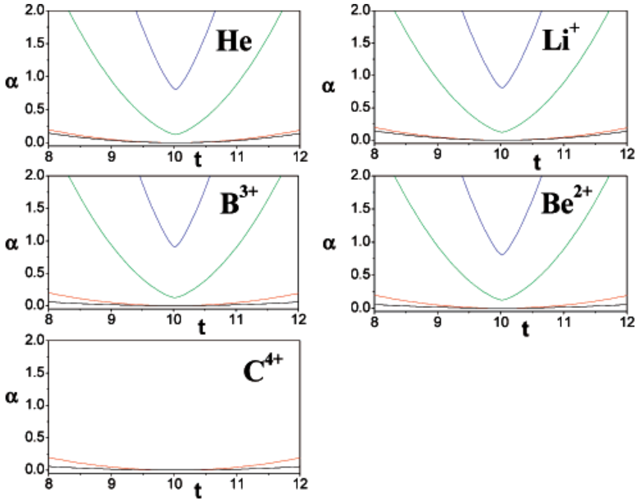

Figure 26. Dynamical polarizability profile during a collision process between an X-atom/ion (X = He, Li^+, Be^{2+}, B^{3+}, C^{4+}) and a proton. Reprinted with permission from ref 40. Copyright 2003 American Chemical Society.

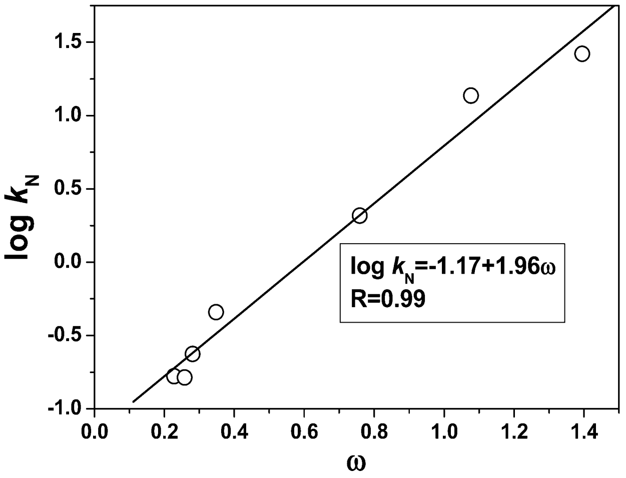

Figure 27. Plot of the experimental nucleophilic rate coefficient (k_N) for a series of thiolcarbonates reacting with piperidine, versus electrophilicity index. Reprinted with permission from ref 294. Copyright 2005 American Chemical Society.

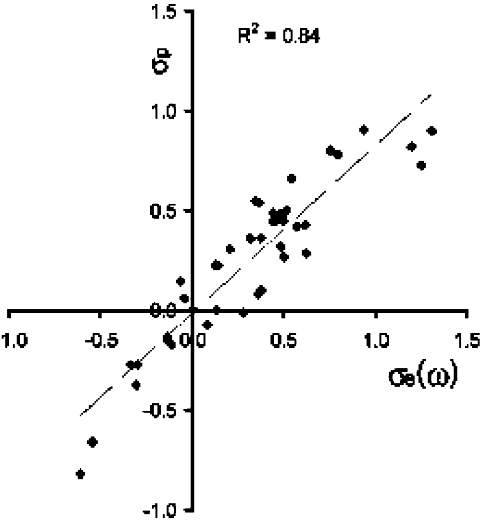

Figure 28. Plot of the experimental Hammett constant (σ_P) of a series of substituted ethylenes versus its theoretical counterpart ($\sigma_P(\omega)$). Reprinted with permission from ref 353. Copyright 2003 American Chemical Society.

in spin multiplicity, including spin catalysis. A spin polarized version of DFT has been developed for this purpose.[359−364] For a system with N_α and N_β numbers of α and β spins, respectively, with the corresponding densities ρ_α and ρ_β, the electron density, $\rho(\vec{r})$, the spin density, $\rho_s(\vec{r})$, the electron number, N, and the spin number, N_s, are defined as[359−364]

$$\rho(\vec{r}) = \rho_\alpha(\vec{r}) + \rho_\beta(\vec{r}) \tag{38a}$$

$$\rho_s(\vec{r}) = \rho_\alpha(\vec{r}) - \rho_\beta(\vec{r}) \tag{38b}$$

$$N = N_\alpha + N_\beta \tag{38c}$$

$$N_s = N_\alpha - N_\beta \tag{38d}$$

The corresponding chemical potential (μ_N) and spin potential (μ_S) are given by[359−364]

$$\mu_N = \left(\frac{\partial E}{\partial N}\right)_{N_s,v(\vec{r})} \tag{39a}$$

$$\mu_S = \left(\frac{\partial E}{\partial N_s}\right)_{N_s,v(\vec{r})} \tag{39b}$$

The related hardness parameters are defined as[359−364]

$$\eta_{NN} = \left(\frac{\partial \mu_N}{\partial N}\right)_{N_s,v(\vec{r})} \tag{40a}$$

$$\eta_{NS} = \left(\frac{\partial \mu_N}{\partial N_s}\right)_{N,v(\vec{r})} = \left(\frac{\partial \mu_s}{\partial N}\right)_{N_s,v(\vec{r})} = \eta_{SN} \tag{40b}$$

$$\eta_{SS} = \left(\frac{\partial \mu_s}{\partial N_s}\right)_{N,v(\vec{r})} \tag{40c}$$

Specific combinations[365] of the above quantities in the spirit of eq 12 will yield various spin dependent generalizations of the electrophilicity index. Spin philicity and spin donicity have been defined by Pérez et al.,[366] extended by Melin et al.,[367] and revised by Olah et al.[368,369] in this connection.

Spin dependent philicities can also be obtained[365] by knowing the above quantities and the various Fukui functions in this representation as described below:

$$f_{\mathrm{NN}}(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{N_{\mathrm{s}},v(\vec{r})} = \left(\frac{\partial \mu_{\mathrm{N}}}{\partial v(\vec{r})}\right)_{N,N_{\mathrm{s}}} \tag{41a}$$

$$f_{\mathrm{NS}}(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N_{\mathrm{s}}}\right)_{N,v(\vec{r})} = \left(\frac{\partial \mu_{\mathrm{s}}}{\partial v(\vec{r})}\right)_{N,N_{\mathrm{s}}} \tag{41b}$$

and similarly for $f_{\mathrm{SN}}(\vec{r})$ and $f_{\mathrm{SS}}(\vec{r})$. Some of these local quantities have been calculated[370] in analyzing the regioselectivity in the [2+2] photocycloaddition of enones to substituted alkenes.

8.2. $\{N_\alpha, N_\beta, v(\vec{r})\}$ Representation

An alternative representation may be developed[365] by defining various global and local reactivity descriptors explicitly for the spin up and spin down cases as follows:

Chemical potentials

$$\mu_\alpha = \left(\frac{\partial E}{\partial N_\alpha}\right)_{N_\beta,v(\vec{r})}; \quad \mu_\beta = \left(\frac{\partial E}{\partial N_\beta}\right)_{N_\alpha,v(\vec{r})} \tag{42a}$$

Hardness

$$\eta_{\alpha\alpha} = \left(\frac{\partial \mu_\alpha}{\partial N_\alpha}\right)_{N_\beta,v(\vec{r})}; \quad \eta_{\beta\beta} = \left(\frac{\partial \mu_\beta}{\partial N_\beta}\right)_{N_\alpha,v(\vec{r})} \tag{42b}$$

$$\eta_{\alpha\beta} = \left(\frac{\partial \mu_\alpha}{\partial N_\beta}\right)_{N_\alpha,v(\vec{r})} = \left(\frac{\partial \mu_\beta}{\partial N_\alpha}\right)_{N_\beta,v(\vec{r})} = \eta_{\beta\alpha} \tag{42c}$$

Fukui functions

$$f_{\alpha\alpha}(\vec{r}) = \left(\frac{\partial \rho_\alpha(\vec{r})}{\partial N_\alpha}\right)_{N_\beta,v(\vec{r})}; \quad f_{\beta\beta}(\vec{r}) = \left(\frac{\partial \rho_\beta(\vec{r})}{\partial N_\beta}\right)_{N_\alpha,v(\vec{r})} \tag{43a}$$

$$f_{\alpha\beta}(\vec{r}) = \left(\frac{\partial \rho_\alpha(\vec{r})}{\partial N_\beta}\right)_{N_\alpha,v(\vec{r})}; \quad f_{\beta\alpha}(\vec{r}) = \left(\frac{\partial \rho_\beta(\vec{r})}{\partial N_\alpha}\right)_{N_\beta,v(\vec{r})} \tag{43b}$$

Making use of the above quantities, the spin dependent variants of the electrophilicity index and the philicity may be easily derived.[365] The representation to be used would depend[365] on the nature of the spin multiplicity change in the given spin polarized process.

9. Conclusions

The tremendous power of the electrophilicity index proposed by Parr, Szentpaly, and Liu provides insight into almost every arena of chemistry and encompasses information about the structure, properties, stability, reactivity, interactions, bonding, toxicity, and dynamics of many-electron systems in ground and excited electronic states. The recurring theme of this review has been the electrophilicity concept in general, with the common thread being the Maynard−Parr electrophilicity index. The whole gamut of the conceptual density functional theory lends support toward the electrophilicity index and helps it realize its full potential. As is the case for most of the conceptual DFT-based reactivity/selectivity descriptors, the global and local electrophilicities possess strong interpretive power, which itself is important in understanding a diverse class of biophysicochemical processes. However, their predictive capacity has yet to be assessed. We conclude with the optimistic note that the electrophilicity will exhibit its tremendous predictive potential, which, along with its existing interpretive characteristics, together with those of the other descriptors, will be adequate in developing a complete theory of chemical reactivity.

10. Abbreviations and Symbols of Some Important Subjects/Quantities

A	electron affinity
α	polarizability
AIM	atoms-in-molecules
B3LYP	Becke three-parameter Lee−Yang−Parr functional
$[\partial\eta/\partial N]$	variation of hardness with electron number
ΔE_{ins}	insertion energy
ΔE_{solv}	energy of solvation
DFT	density functional theory
Δ_{ij}^{kl}	softness matching index
DNA	deoxyribonucleic acid
$[\partial\omega/\partial N]$	variation of electrophilicity with electron number
$\in_{\mathrm{HOMO}}$	highest occupied molecular orbital energy
ELF	electron localization function
$\in_{\mathrm{LUMO}}$	lowest unoccupied molecular orbital energy
E_{xc}	exchange-correlation energy functionals
FF	Fukui function
f_k^{α}	condensed Fukui function
$F[\rho]$	Hohenberg−Kohn−Sham universal functional
$f(\vec{r})$	Fukui function
η	hardness
GNLSE	generalized nonlinear Schrödinger equation
$\eta(\vec{r},\vec{r}')$	hardness kernel
HF	Hartree−Fock
HIV	human immunodeficiency virus
HOMA	harmonic oscillator model of aromaticity
HOMO	highest occupied molecular orbital
HSAB	hard and soft acids and bases
I	ionization potential
IC_{50}	50% inhibitory concentration
IGC_{50}	50% inhibitory growth concentration
IRC	intrinsic reaction coordinate
$j(\vec{r},t)$	current density
K	equilibrium constant
k	rate constant
k_σ	hydrogen bond strength
LUMO	lowest unoccupied molecular orbital
μ	chemical potential
m_{CXY}	carbene-philicity scale
MHP	maximum hardness principle
MPP	minimum polarizability principle
μ_{s}	spin potential
N	number of electrons
$v_{\mathrm{ext}}(\vec{r},t)$	time dependent external potential
NICS	nucleus independent chemical shift
NMR	nuclear magnetic resonance
NPA	natural population analysis
$v(\vec{r})$	external potential
N_{s}	spin number
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDF	polychlorinated dibenzofuran
QFD	quantum fluid dynamics
QSAR	quantitative structure−activity relationship
QTM	quantum theory of motion
RBA	relative binding affinity
$\rho(\vec{r})$	electron density
ρ_{s}	spin density
S	softness
s_k^{α}	condensed softness
$\mathrm{S_N2}$	substitution nucleophilic bimolecular
$s(\vec{r})$	local softness
TDDFT	time dependent density functional theory
TeBG	testosterone−estrogen binding globulin
t_{F}	Thomas−Fermi kinetic energy density

T_{NW}	non-Weizsäcker part of the kinetic energy
TS	transition state
V_{qu}	quantum potential
$V_{\mathrm{qu}}(\vec{r},t)$	time dependent quantum potential
$\Phi(\vec{r},t)$	3-D hydrodynamical wave function
χ	electronegativity
$\Psi(\vec{x}_1,\vec{x}_2,...,\vec{x}_N)$	many particle wave function for an N-electron system
ω	electrophilicity index
$\omega^{\pm}$	directional electrophilicity index
ω_k^{α}	condensed philicity
$\omega(\vec{r})$	philicity
$\omega^{\pm}(\vec{r})$	directional philicity

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